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ARTICLE

Total Asymmetric Synthesis of (+)-Asenapine.

Piotr Szcześniak,*[a] Olga Staszewska-Krajewska [b] and Jacek Mlynarski [b]

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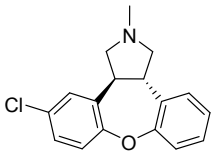
Total, asymmetric synthesis of (+)-Asenapine an atypical antipsychotic drug, used for treating schizophrenia and acute mania associated with bipolar disorder is reported. The key steps are organocatalytic Michael addition of aldehydes to *trans*-nitroalkenes and subsequent reductive cyclization.

Introduction

Schizophrenia and bipolar disorder (BD) are two potentially debilitating psychiatric illnesses that produce negative consequences in the lives of millions people all over the world, and an additional hundreds of thousands are diagnosed with the above-mentioned disorders every year.[1] Schizophrenia affects an estimated 1.1% of the world's population, and it is most commonly diagnosed between the ages of 16 to 25. Schizophrenia and its treatment has an enormous effect on the economy, costing between $32.5-$65 billion each year.[2] Bipolar disorder is another complex, multifaceted, multisystem psychiatric illness, affecting up to 1% of the world's population.[3] Characterized primarily by manic, hypomanic, and depressive mood episodes, it remains one of the most disabling illnesses worldwide.[4,5]

Asenapine **1** is an active ingredient of Saphris® (USA), Sycrest® (Europe), which is approved by FDA for treatment of schizophrenia and acute manic or mixed episodes associated with bipolar disorders.[6,7,8] The mechanism of asenapine action, as with other drugs having efficacy in schizophrenia and bipolar disorder, is unknown. It has been suggested that the efficacy of asenapine in schizophrenia is mediated through a combination of antagonist activity at D2 (dopamine) and 5-HT2A (serotonin) receptors, which has been shown to enhance dopamine (DA) and acetylcholine (Ach) efflux in rat brains.[9] Although it was approved for medical treatment in the U.S. and Europe in 2009, worldwide net sales strongly increase year by year. The sales of Saphris were estimated at $134.1 million in 2012. By 2022, GlobalData projects these sales to grow marginally to $154.9 million, with a compound annual growth rate (CAGR) of 1.45%.[10]



Asenapine **(1)**

Because of the medicinal importance of **1**, the synthesis of this pyrrolidine derivative has attracted many researchers at academia[11] as well as in industry.[12] Given that the FDA has approved the market launch of racemic asenapine, most patented and public domain protocols involve the total synthesis of asenapine in the racemic form. However, studies of the metabolism and pharmacokinetics of the individual enantiomers of asenapine revealed that (+)-isomer had shown a better plasma concentration in mice, rats, and rabbits compared to (–)-isomer.[13] For this reason, the development of an efficient and stereoselective strategy of the synthesis of enantiomerically pure (+)-asenapine is highly desirable. In 2016 Chandrasekhar and co-workers reported the first asymmetric synthesis of (+)-asenapine based on Julia olefination and the Ireland–Claisen rearrangement as the key steps.[14] The enantiopure product was obtained in overall 4.6% yield and 93.8% *ee*. The main drawback of this approache results from relatively long and complicated synthetic sequence requiring the use of reagents that are not acceptable in industrial production, such as diazomethane or osmium tetroxide. Since the strategies for asenapine preparation developed so far suffer from drawbacks, it is necessary to find an alternative and improved process for asenapine 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

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† Electronic Supplementary Information (ESI) available: Copies of ^{1}H, ^{13}C NMR, NOE, HPLC spectra. See DOI: 10.1039/x0xx00000x

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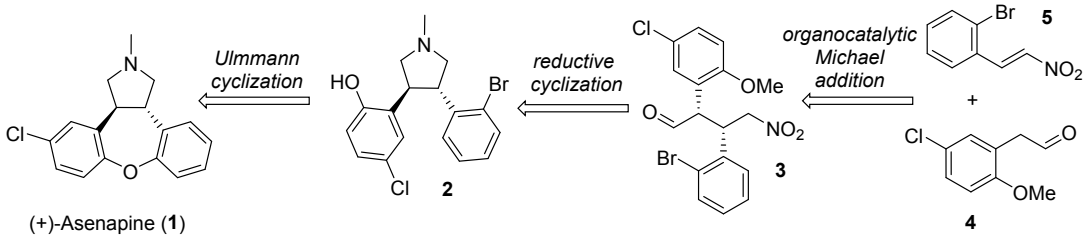
subsequent reductive cyclization.[15,16] The methodology was successfully applied to the first asymmetric synthesis of Methdilazine a phenothiazine compound with antihistaminic activity and BZN molecule exhibits interesting binding to HIV-1 protease.

Considering the chemical structure of (±)-asenapine as a tetracyclic framework, wherein the *N*-methylpyrrolidine ring fuses at the 3rd and 4th positions with chlorophenyl, phenyl ether in a trans geometry, conceptually, we visualized that the asenapine framework could be disconnected at the biaryl ether to synthon **2**, which could be built from **3** *via* reductive cyclization. In turn synthon **3** could be realised via organocatalytic Michael addition of aldehydes **4** to *trans*-nitroalkene **5** (Scheme 1).



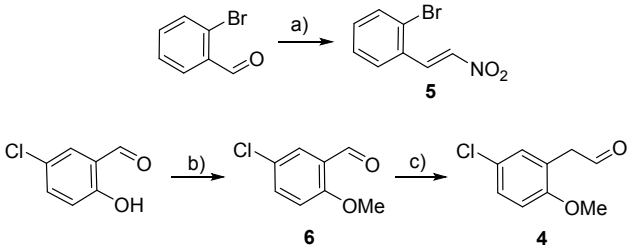
Scheme 1 Retrosynthetic Analysis of (+)-Asenapine (**1**).

With this strategy in mind, we thought of synthesizing one of the desired isomers (+) in an optically pure form. The application of the (S)-α,α-diphenylprolinol trimethylsilyl ether (Hayashi-Jørgensen catalyst **cat.I**) as a catalyst for Michael addition reaction should establish the correct configuration of the stereogenic center in (+)-asenapine. The successful execution of this strategy will naturally allow one to synthesize (–)-asenapine by simply switching of the catalyst.

Results and discussion

The study started with the preparation of nitroalkene **5** and aldehyde **4** – acceptor and donor in Michael addition reaction (Scheme 2). The corresponding nitroalkene **5** was obtained from commercially available 2-bromobenzaldehyde in a 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 **5** in good overall yield 86%. In turn, aldehyde **4** was prepared from commercially available 5-chlorosalicylaldehyde in three steps involves: protection of the phenolic hydroxyl group with a methyl group leading to aldehyde **6** in 98% yield. Then, a methylene-unit homologation of the aldehyde moiety was performed *via* Wittig reaction using phosphonium salt, followed by acidic hydrolysis, affording aldehyde **4** in 66% yield in two steps.

With the desired Michaele acceptor **5** and donor **4** in hand, we initiated the study of the organocatalytic Michaele addition reaction leading to γ-nitroaldehyde **3**. Based on our experience, the reaction between nitro olefin **5** and aldehyde **4** was performed in chloroform in the presence of 10 mol% of the Hayashi-Jørgensen catalyst **cat. I**. and benzoic acid (20 mol%) as an additive, at ambient temperature.



Scheme 2 *Reagents and condtions*: a) i. $MeNO_2$ (10 equiv), *N,N,N,N*-tetramethylguanidine (10 mol%), toluene, –10 ˚C, 90 min; ii. MsCl (1.5 equiv), Et_3N (1.5 equiv), –10˚C, 40 min, 86% (2 steps); b) K_2CO_3 (2.0 equiv), MeI (1.33 equiv), DMF, rt, 48 h, 98%; c) i. (methoxymethyl)triphenylphosphonium chloride (1.2 equiv), *n*-BuLi (1.6 M)(1.2 equiv), THF, 0˚C to rt, overnight; ii. HCl (5 M), THF, bp, 1 h, 66% (2 steps).

The reaction was complete within 4 h, providing γ-nitroaldehyde **3** in excellent yield (95%) and stereoselectivity (*syn*/*anti* ratio 8:1 and 96% *ee*.)(Scheme 5). The optimization attempts revealed that in order to maintain the high diastereomeric ratio (*syn*/*anti* 8:1), two equiv of the aldehyde **4** relatively to nitro olefin **5** should be used. Moreover the catalyst has to be removed from the reaction mixture after complete conversion of 5. These requirements arise from nature of α-substituted γ-nitroaldehydes, witch can undergo epimerization in the presence of the catalyst during Michael addtion reaction. The isomerization process occurs, when the product remains in contact with the catalyst for an extended period of time. The γ-nitroaldehyde with high *syn*:*anti* ratio

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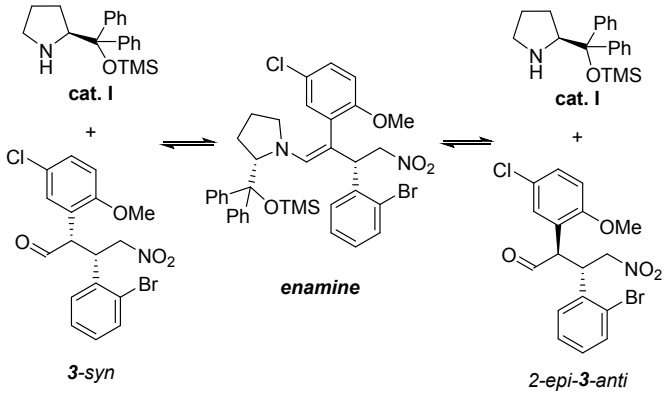
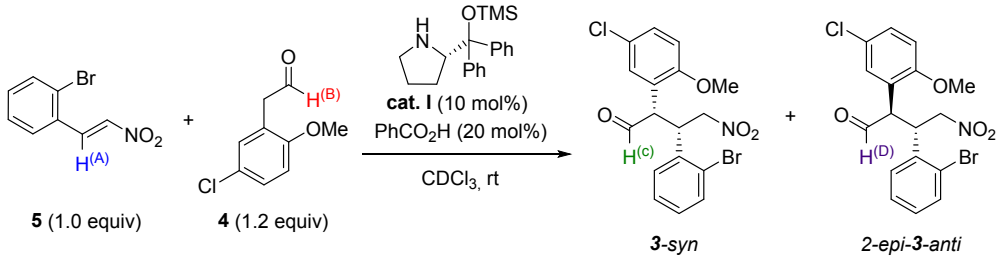
reacts with the catalyst, a low steady-state concentration of the enamine is rapidly established, and the equilibration beetwen *syn* and *anti* continues until thermodynamic ratio is reached (Scheme 3). This effect, has been intensively studied and explained by Blackmond.[17]

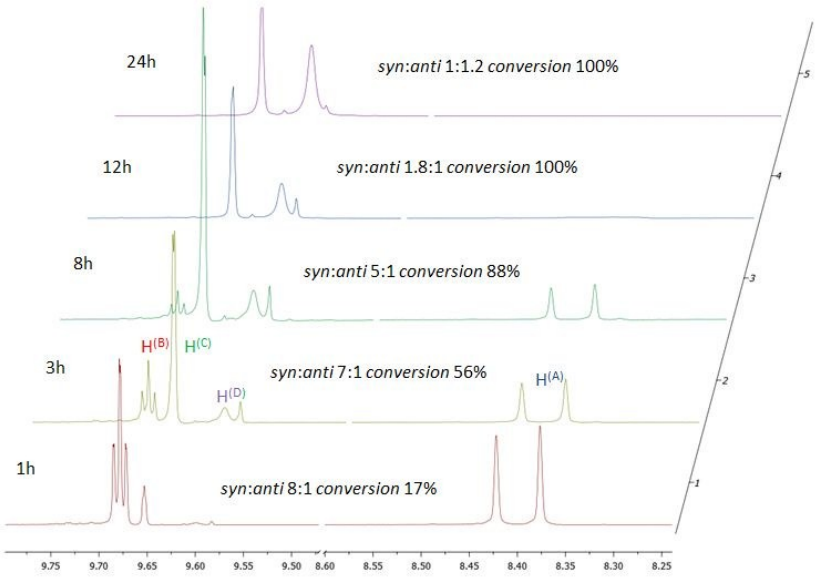


Scheme 3 Reversible enamine formation between **cat. 1**, **3**-*syn*, and 2-*epi*-**3**-*anti*.

An additional ^{1}H-NMR experiment in deuterated chloroform confirmed that the isomerization process of the γ-nitroaldehyde **3** occurs in the Michael addition of aldehyde **4** to nitro olefin **5** catalyzed by the Hayashi-Jørgensen catalyst **cat. I** (Scheme 4). The progress of the isomerization is very fast and difficult to control, when 1.2 equiv of the aldehyde **4** is used. This drawback was overcome by using the excess of the aldehyde **4**. We did not observe the diastereomeric ratio decrease significantly, when the reaction was performed with 2.0 equiv of the aldehyde **4**. Moreover the reaction was easy to monitor.

After finding the suitable conditions, we were ready to exploit the Michael reaction in the synthesis of (+)-asenapine **1**. Obtained γ-nitroaldehyde **3** with *syn*:*anti* ratio 8:1 was subjected reductive cyclizaton to pyrrolidine **7**.





Scheme 4 ^{1}H-NMR analysis of *syn*/*anti* equilibration in the Michael addition of aldehyde **4** (1.2 equiv) to nitro olefin **5** (2.0 equiv) catalyzed by 10 mol% of the Hayashi-Jorgensen catalyst **cat. I**.; selected signals are presented.

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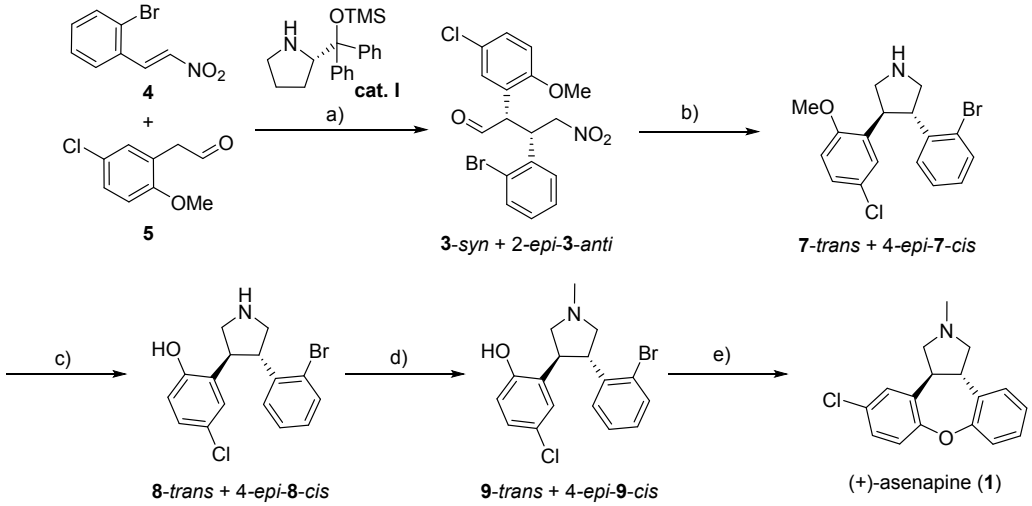
The reaction was performed with Zn powder (25 equiv) in a mixture of acetic acid and methanol (1:1) at 0 ˚C to room temperature over 12 h. After workup and further purification by column chromatography, isomeric mixture of pyrrolidine **7** (8:1 *trans*/*cis*) was obtained in 67% yield. The next step involving deprotection of phenolic group was carried out in the presence of 1M BBr_3 (5.0 equiv) in CH_2Cl_2 at -78 ˚C to room temperature over 4 h. A corresponding product **8** was isolated in yield (78%), as an inseparable mixture of *trans*/*cis* isomer in ratio 8:1. Next, compound **8** (8:1 *trans*/*cis*) was submitted to *N*-methylation, to furnish pyrrolidine **9**. For this purpose, pyrrolidine **8** was treated with formaldehyde followed by $NaCNBH_3$ in the presence of a catalytic amount of acetic acid in methanol at 0 ˚C to room temperature over 12 h. Aqueous workup and chromatography gave *N*-methyl-pyrrolidine **9** (8:1 *trans*/*cis*) in 67% yield. At this stage, the relative configuration of the isomer **9**-*trans* and 4-epi-**9**-*cis* was confirmed on the basis of the analysis of NOE experiments. The final step, intramolecular Ullmann condensation was carried out on the basis of a literature procedure.[14] The *N*-methyl-pyrrolidine **9** was subjected oxepine ring formation by exposure to Cs_2CO_3, catalytic amount of CuI and *N*,*N*-dimethylglycine in boiling 1,4-dioxane over 12 h. After purification by column chromatography, optical pure (+)-asenapine **1** was isolated as a single *trans* isomer in 71% yield and more than 94% *ee* (Scheme 5).



Scheme 5 *Reagents and Conditions:* a) nitro olefin **5** (1.0 equiv), aldehyde **4** (2.0 equiv), Hayashi-Jørgensen catalyst **cat. I** (10 mol%), $PhCO_2H$ (20 mol%), $CHCl_3$, rt, 4 h, 95%, *syn*/*anti* 8:1, ee (94.8%, **3**-*syn*), (94.6%, 2-*epi*-**3**-*anti*); b) Zn powder (25.0 equiv), AcOH:MeOH (1:1), 0˚C to rt , overnight, 67%; *trans*/*cis* 8:1; c) BBr_3 (1M in CH_2Cl_2)(6.0 equiv), CH_2Cl_2, –78˚C to rt, 2 h, 78%, *trans*/*cis* 8:1; d) formaldehyde (37% aq.)(1.5 equiv), $NaCNBH_3$ (2.0 equiv), AcOH (one drop), MeOH, 0 ˚C to rt , overnight, 90%; *trans*/*cis* 8:1; e) Cs_2CO_3 (1.2 equiv), *N*,*N*-dimethylglycine (25 mol%), CuI (25 mol%), 1,4-dioxane, bp, overnight, 71%, single *trans* isomer, 32% overall yield (5 steps started from Michael addition).

Conclusions

In summary, asymmetric total synthesis of (+)-asenapine involving organocatalytic Michael addition reaction and subsequent Zn-promoted reductive cyclization as the key steps has been reported. The target molecule was obtained with an overall yield of 32% (5 steps started from Michael addition) and >94% *ee*. Equally important advantage over so far developed asenapine synthesis methods lies in the simple route procedure employment readily available and inexpensive substrate. The easy availability of (*R*)-Hayashi-Jørgensen catalyst, will allow one to (-)-asenapine, respectively, by following the same synthetic transformations as presented here. The synthetic strategy presented above can be regarded as a general method for preparation of pyrrolidine derivatives. A change of substituent in aldehyde or nitroolefin should install different substituent at the 3rd and 4th positions, to provide other analogues of **1**.

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Experimental Section

(*E*)-2-bromo-β-nitrostyrene (5). To a solution of 2-bromobenzaldehyde (631 µL, 1 g, 5.4 mmol) in 15 mL of dry toluene, nitromethane (2.93 mL, 54 mmol, 10.0 equiv) and *N*,*N*,*N*,*N*-tetramethylguanidine (68 µL, 0.54 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 2-bromobenzaldehyde (TLC control, 1:6 AcOEt/hexanes). Then MsCl (627 µL, 8.1 mmol, 1.5 equiv) and Et_3N (1.13 mL, 8.1 mmol, 1.5 equiv) were added at 0 ˚C and the reaction mixture was stirred for additional 40 min at the same temperature (TLC control, 1:6 AcOEt/hexanes), the reaction mixture was quenched with sat. aq. $NaHCO_3$ (10 mL). and diluted with Et_2O (10 mL). After phase separation, the aqueous layer was washed with Et_2O (3×10 mL). The combined organic layers were dried over anhydr. 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 (1:15 AcOEt/hexanes) to give 1.085 g (86%) of nitroalkene **5** as a yellow solid. Rf = 0.37 (1:6 AcOEt/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40 (d, *J* = 13.7 Hz, 1H), 7.73–7.68 (m, 1H), 7.60–7.57 (m, 1H), 7.54 (d, *J* = 13.7 Hz, 1H), 7.43–7.31 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.5, 138.2, 134.7, 133.5, 131.0, 129.1, 128.7, 127.0; HRMS (ESI-TOF) m/z calcd for $C_8H_6BrNNaO_2$ [M+Na$^+$] 249.9480. Found 249.9474.

5-Chloro-2-methoxybenzaldehyde (6). To a solution of 5-chloro-2-hydroxybenzaldehyde (2.0 g, 12.77 mmol) in dry DMF (10 mL), potassium carbonate (3.5 g, 25.54 mmol, 2.0 equiv) and iodomethane (1 mL, 17.0 mmol, 1.33 equiv) were added under argon, the mixture was stirred at room temperature for 2 days. Then DMF was evaporated under reduced pressure. The resultant solid was dissolved in $CHCl_3$ (10 mL), and washed with 1 M aq. HCl (10 mL). After phase separation, the organic layer was dried over 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 (1:9 AcOEt/hexanes); to afford 2.131 g (98%) of aldehyde **6** as a white solid. Rf = 0.33 (1:6 AcOEt/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.42 (s, 1H), 7.79 (d, *J* = 2.8 Hz, 1H), 7.50 (dd, *J* = 8.9, 2.8 Hz, 1H), 6.96 (d, *J* = 8.9 Hz, 1H), 3.94 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.1, 160.9, 136.0, 128.6, 127.0, 126.3, 113.9, 56.6**;** HRMS (ESI-TOF) m/z calcd for $C_8H_8ClO_2$ [M+H$^+$] 171.0207. Found 171.0205.

5-Chloro-2-methoxyphenylacetaldehyd (4). To a solution of (methoxymethyl)triphenylphosphonium chloride (12.65 g, 36.9 mmol, 1.2 equiv) in 75 mL of dry THF, *n*-butyllithium solution (1.6M in hexanes)(23 mL, 36.9 mmol, 1.2 equiv) was added dropwise. The reaction mixture was stirred for 30 min at the same temperature, and then a solution of aldehyde **6** (5.246 g, 30.7 mmol) in dry THF (5 mL) was added dropwise. The resulting mixture was warmed gradually to room temperature and stirred overnight, until TLC analysis (1:9 AcOEt/hexanes) revealed consumption of the aldehyde **6**. The reaction was quenched with sat. aq. NH_4Cl (30 mL). The aqueous layer was washed with Et_2O (3x20 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure to give the residue, which was purified by silica gel column chromatography (1:9 AcOEt/hexanes); to afford enol ether, which was used directly for the next step. Obtained enol ether was dissolved in THF (75 mL) and 5M aq. HCl (35 mL) was added. The reaction mixture was refluxing until TLC analysis revealed complete hydrolysis of the enol ether (~1 hours). Then the reaction was cooled to room temperature, diluted with Et_2O (30 mL) and neutralized with sat. aq. $NaHCO_3$ (40 mL). After phase separation, the aqueous layer was washed with Et_2O (3x20 mL). The combined organic layers were washed with brine (50 mL), and then dried over 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 (1:15 AcOEt/hexanes); to afford 3.74 g (66%) of aldehyde **4** as a colorless oil. Rf = 0.41 (1:9 AcOEt/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.68 (t, *J* = 1.9 Hz, 1H), 7.26 (dd, *J* = 8.7, 2.6 Hz, 1H), 7.14 (d, *J* = 2.6 Hz, 1H), 6.84 (d, *J* = 8.7 Hz, 1H), 3.82 (s, 3H), 3.63 (d, *J* = 1.9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.7, 156.9, 131.6, 129.2, 126.1, 123.7, 112.3, 56.4, 45.7; HRMS (ESI-TOF) m/z calcd for $C_9H_9ClNaO_2$ [M+Na+] 207.0189. Found 207.0183.

2S,3S)-3-(2-Bromophenyl)-2-(5-chloro-2-methoxyphenyl)-4-nitrobutanal 3-*syn* and 2-epi-3-*anti*. To a solution of nitrostyrene **5** (100 mg, 0.439 mmol, 1.0 equiv) in 1 mL of $CHCl_3$, Hayashi-Jørgensen catalyst **cat.** I (14 mg, 0.0439 mmol, 10 mol%) and benzoic acid (11 mg, 0.0877 mmol, 20 mol%) were added, and the mixture was stirred at room temperature for 10 min, then solution of aldehyde **4** (162 mg, 0.877 mmol, 2.0 equiv) in 2 mL of $CHCl_3$ was added. The resulting mixture was stirred until complete conversion of **5** (reaction progress was monitored by TLC or ^{1}H-NMR, ~4 hours)(*in order to obtain the highest syn/anti ratio, the catalyst had to be immediately removed from the reaction mixture at the moment of complete conversion*). After that, solvent was evaporated under reduced pressure and the crude product was purified by silica gel column chromatography (1:3 AcOEt/hexanes) to afford 172 mg (95%) of the γ-nitroaldehydes **3**-*syn* and 2-epi-**3**-*anti*. Inseparable mixture of diastereomers; *syn*/*anti* 8:1 (determined by ^{1}H-NMR); for analysis some fraction was collected in pure form: major isomer **3**-*syn*: slightly yellow oil; Rf = 0.27 (1:3 AcOEt/hexanes); $[\alpha]_D^{19}$= +473.3 (c= 0.1; $CHCl_3$); *ee* 94.8% (determined by HPLC); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.66–9.65 (m, 1H), 7.42 (d, J 8.1 Hz, 1H), 7.19–7.11 (m, 3H), 7.05–6.96 (m, 2H), 6.69 (d, J 8.8 Hz, 1H), 5.09–4.95 (m, 2H), 4.90–4.79 (m, 1H), 4.52 (d, J 10.0 Hz, 1H), 3.77 (s, J 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.2, 156.5, 136.7, 134.1, 131.5, 130.1, 129.8, 128.0, 126.5, 123.5, 112.6, 56.3, 54.5; HRMS (ESI-TOF) m/z calcd for $C_{17}H_{15}BrClNNaO_4$ [M+Na$^+$] 433.9771. Found 433.9766; minor isomer 2-epi-**3**-*anti*: white solid; Rf = 0.28 (1:3 AcOEt/hexanes); $[\alpha]_D^{19}$= –580.1 (c= 0.13; CHCl3); *ee* 94.6% (determined by HPLC); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.62–9.59 (m, 1H), 7.64 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.32 (dd, *J* = 8.8, 2.6 Hz, 1H), 7.26 (td, *J* = 7.5, 1.2 Hz, 2H), 7.16 (td, *J* = 7.7, 1.7 Hz, 1H), 7.08–6.97 (m, 1H), 6.92–6.79 (m, 2H), 5.19–4.99 (m, 1H), 4.67 (s, 1H), 4.62–4.46 (m, 1H), 4.14 (s, 1H), 3.79 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.9, 156.6, 137.0, 134.4, 132.3, 130.6, 130.1, 128.5, 126.8, 123.8, 113.2, 76.5, 56.5; HRMS (ESI-TOF) m/z calcd for $C_{17}H_{15}BrClNNaO_4$ [M+Na$^+$] 433.9771. Found 433.9766. HPLC (Chiralcel OZ-H, 20% *i*-PrOH 80% *n*-hexane, flow rate: 1.0 mL min^{-1},λ = 210 nm, Tem. 21 ˚C); major isomer **3**-*syn* 11.8 min, 17.7 min; minor isomer 2-epi-**3**-*anti* 13.0 min, 40.2 min.

(3*S*,4*S*)-3-(2-Bromophenyl)-4-(5-chloro-2-methoxyphenyl) pyrrolidine 7-*trans* and 4-epi-7-*cis*. To a solution of γ-

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nitroaldehydes **3**-*syn* and 2-epi-**3**-*anti* (*syn*/*anti* 8:1)(172 mg, 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 (681 mg, 10.42 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 4M aq. NaOH to pH=12, and diluted with CH_2Cl_2 (5 mL). After phase separation, the aqueous layer was washed with CH_2Cl_2 (5x3 mL). The combined organic layers were dried over 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 (1:4 MeOH/AcOEt); to afford 103 mg (67%) of inseparable mixture of pyrrolidines **7**-*trans* and **4**-*epi*-**7**-*cis* in ratio~8:1 as an orange oil. Rf = 0.17 (1:2 MeOH/AcOEt); $[\alpha]_D^{24}$= +48.0 (c= 10.4; $CHCl_3$); major isomer **7**-*trans*: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.39 (d, *J* = 7.2 Hz, 1H), 7.28–7.21 (m, 1H), 7.18 (d, *J* = 2.4 Hz, 1H), 7.10 (dd, *J* = 8.7, 2.6 Hz, 1H), 7.02 (td, *J* = 7.6, 1.6 Hz, 1H), 6.72 (d, *J* = 8.7 Hz, 1H), 4.01 (dd, *J* = 17.8, 8.6 Hz, 1H), 3.85–3.76 (m, 1H), 3.74 (s, 3H), 3.72–3.63 (m, 1H), 3.63–3.54 (m, 1H), 3.18 (t, *J* = 10.0 Hz, 1H), 3.01 (t, *J* = 10.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.0, 140.3, 133.6, 130.4, 128.8, 128.7, 128.5, 128.3, 128.2, 126.3, 126.0, 112.4, 56.3, 53.8, 52.8, 49.6, 46.7; HRMS (ESI-TOF) m/z calcd for $C_{17}H_{18}BrClNO$ [M+H$^+$] 366.0260. Found 366.0244.

2-((3*S*,4*S*)-4-(2-Bromophenyl)pyrrolidin-3-yl)-4-chlorophenol 8-*trans* + 4-epi-8-*cis*. To a solution of pyrrolidines **7**-*trans* and **4**-*epi*-**7**-*cis* (100 mg, 0.27 mmol) in 2 mL of dry CH_2Cl_2, boron tribromide solution (1M in CH_2Cl_2)(1.62 mL, 1.62 mmol, 6.0 equiv) was added dropwise at –78 ˚C under argon. The reaction mixture was stirred for 15 min at the same temperature, and then warmed gradually to room temperature. After complete conversion of the starting pyrrolidines **7** (TLC control, 1:9 MeOH/AcOEt)(~2 hours), the reaction mixture was cooled to 0 °C, and quenched by slowly addition of MeOH. The resulting solution was warmed to room temperature and solvent was removed in *vacuo*. The remaining residue was dissolved in CH_2Cl_2 (5 mL) and washed with sat. aq. $NaHCO_3$ (5 mL). After phase separation, the aqueous layer was washed with CH_2Cl_2 (3x5 mL). The combined organic layers were dried over 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 (1:2 MeOH/AcOEt) to afford 74 mg (78%) of inseparable mixture of pyrrolidines **8**-*trans* and **4**-*epi*-**8**-*cis* in ratio~8:1 as a yellow oil. Rf = 0.35 (1:9 MeOH/CH_2Cl_2); $[\alpha]_D^{24}$= +34.9 (c= 5.1; $CHCl_3$); major isomer **8**-*trans*: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60–7.53 (m, 1H), 7.38–7.32 (m, 2H), 7.11 (ddd, *J* = 7.7, 5.3, 3.4 Hz, 1H), 7.05 (dd, *J* = 8.6, 2.6 Hz, 1H), 6.87–6.81 (m, 2H), 3.99 (ddd, *J* = 9.7, 8.2, 4.4 Hz, 1H), 3.80 (t, *J* = 7.8 Hz, 1H), 3.48–3.37 (m, 2H), 3.30 (dd, *J* = 6.5, 4.5 Hz, 1H), 2.89 (t, *J* = 9.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.2, 142.6, 134.0, 132.6, 130.2, 128.9, 128.9, 128.6, 128.6, 125.4, 123.2, 119.8, 55.2, 53.0, 51.4, 50.8; HRMS (ESI-TOF) m/z calcd for $C_{16}H_{16}BrClNO$ [M+H$^+$] 352.0096. Found 352.0096.

2-((3S,4S)-4-(2-Bromophenyl)-1-methylpyrrolidin-3-yl)-4-chlorophenol 9-*trans* + 4-epi-9-*cis*. To a solution of amines **8**-*trans* and **4**-*epi*-**8**-*cis* (72 mg, 0.2 mmol) in MeOH (2 mL), 37% aq. solution of formaldehyde (23 µl, 0.31 mmol, 1.5 equiv) and acetic acid (1 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 allowed to warm to room temperature and stirred overnight. After complete conversion of the starting amines **9** (TLC control, 1:9 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 over 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 (1:99 MeOH/CH_2Cl_2) to afford 66 mg (90%) of inseparable mixture of pyrrolidines **9**-*trans* and **4**-*epi*-**9**-*cis* in ratio~8:1 as a colorless oil. Rf = 0.11 (1:99 MeOH/CH_2Cl_2); $[\alpha]_D^{22}$= +59.9 (c= 4.0; $CHCl_3$); major isomer **9**-*trans*: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.52 (d, *J* = 7.8 Hz, 1H), 7.36–7.30 (m, 2H), 7.11–7.07 (m, 2H), 7.04 (dd, *J* = 8.6, 2.6 Hz, 1H), 6.81 (d, *J* = 8.6 Hz, 1H), 6.75 (d, *J* = 2.6 Hz, 1H), 4.06 (ddd, *J* = 10.1, 8.1, 4.4 Hz, 2H), 3.66 (t, *J* = 8.8 Hz, 1H), 3.29 (dd, *J* = 7.6, 4.5 Hz, 1H), 3.20 (d, *J* = 9.9 Hz, 1H), 2.89 (dd, *J* = 9.6, 8.1 Hz, 1H), 2.52 (s, 3H), 2.32 (t, *J* = 9.9 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 154.8, 141.9, 133.3, 131.8, 129.4, 128.3, 128.13, 128.00, 127.98, 124.7, 122.4, 119.1, 63.7, 61.7, 51.6, 50.6, 39.9; minor isomer **4**-*epi*-**9**-*cis* selected signals: 1H NMR (600 MHz, $CDCl_3$) δ 6.64 (d, *J* = 2.6 Hz, 1H), 6.47 (d, *J* = 8.6 Hz, 1H), 4.39–4.33 (m, 1H), 3.78 (dd, *J* = 9.6, 6.2 Hz, 1H), 3.54 (dd, *J* = 10.8, 4.3 Hz, 1H), 2.85–2.77 (m, 3H), 2.58 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 155.4, 139.0, 132.1, 131.8, 131.0, 127.8, 127.6, 127.0, 118.4, 60.2, 59.2, 48.4, 47.9, 40.1; HRMS (ESI-TOF) m/z calcd for $C_{17}H_{18}BrClNO$ [M+H$^+$] 366.0260. Found 366.0255.

(+)-Asenapine (1). To a solution of pyrrolidines **9**-*trans* and **4**-*epi*-**9**-*cis* (66 mg, 0.18 mmol, 1.0 equiv) in dry 1,4-dioxane (5 mL), cesium carbonate (70 mg; 0.216 mmol, 1.2 equiv), *N*,*N*-dimethylglycine (4.6 mg; 0.045 mmol, 0.25 equiv) and copper(I) iodide (8.6 mg; 0.045 mmol, 0.25 equiv) were added under argon at room temperature. The reaction mixture was heated to reflux and stirred overnight. After complete conversion of pyrrolidines **9** (TLC control, 1:9 MeOH/CH_2Cl_2), the reaction mixture was filtered through a pad of Celite, and washed with CH_2Cl_2 (3x5 mL). The combined filtrates were concentrated under reduced pressure to give the crude product, which was purified by silica gel column chromatography (1:4 MeOH/AcOEt) to afford 31 mg (71%) of single isomer of (+)-asenapine **1** as a yellow oil. Rf = 0.31 (1:4 MeOH/AcOEt); $[\alpha]_D^{26}$= +190.2 (c= 2.5; $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22–7.16 (m, 2H), 7.16–7.13 (m, 2H), 7.12–7.06 (m, 3H), 3.71–3.61 (m, 2H), 3.30–3.20 (m, 2H), 3.20–3.10 (m, 2H), 2.58 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.9, 154.8, 134.6, 132.5, 129.6, 128.3, 128.0, 127.44, 127.38, 124.8, 123.0, 121.6, 59.8, 59.7, 45.5, 45.4, 43.9; HRMS (ESI-TOF) m/z calcd for $C_17H_{17}ClNO$ [M+H$^+$] 286.0999. Found 286.0994; HPLC (Chiralcel OD-H, 20% *i*-PrOH 80% *n*-hexane, flow rate: 1.0 mL min^{-1},λ = 210 nm, Tem. 8˚C); 6.5 min.

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Notes and References

1 World Health Organisation Reports; 2017.

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2 www.who.int. https://www.onhealth.com/content/1/schizophrenia_treatmet
3 L. N. Yatham, S. H. Kennedy, S. V. Parikh, A. Schaffer, S. Beaulieu, M. Alda, C. O'Donovan, G. Macqueen, R. S. McIntyre, V. Sharma, A. Ravindran, L. T. Young, R. Milev, D. J. Bond, B. N. Frey, B. I. Goldstein, B. Lafer, B. Birmaher, K. Ha, W. A. Nolen, M. Berk, *Bipolar Disord.* **2013**, *15*, 1–44.
4 H. A. Whiteford, L. Degenhardt, J. Rehm, A. J. Baxter, A. J. Ferrari, H. E. Erskine, F. J. Charlson, R. E. Norman, A. D. Flaxman, N. Johns, R. Burstein, C. J. Murray, T. Vos T, *Lancet.* **2013**, *9*; 1575–1586.
5 S. Ratnasingham, J. Cairney, H. Manson, J. Rehm, E. Lin, P. Kurdyak, *Can J Psychiatry*. **2013** *58*, 529–537.
6 L. Citrome, Int. J. Clin. Pract., **2009**, *63*, 1762–1784.
7 T. Scheidemantel, I. Korobkova, S. Rej, M. Sajatovic, Neuropsychiatr Dis Treat. **2015**, *11*, 3007–3017.
8 C.M. Chwieduk, L.J. Scott, CNS Drugs, **2011** *25*, 251–267.
9 https://psychopharmacologyinstitute.com/antipsychotics/asenapine/mechanism-action-pharmacodynamics-asenapine/
10 GlobalData (2014). Saphris (Schizophrenia)– Forecast and Market Analysis to 2022, February 2014, GDHC356DFR.
11 H. A. Whiteford, L. Degenhardt, J. Rehm, A. J. Baxter, A. J. Ferrari, H. E. Erskine, F. J. Charlson, R. E. Norman, A. D. Flaxman, N. Johns, R. Burstein, C. J. Murray, T. Vos T, *Lancet.* **2013**, *9*; 1575–1586.
12 (a) W. J. van der Burg, US 4145434, **1979**. (b) G. J. Kemperman, J. J. M. Van der linden, M. R. Reeder, Organon Ireland Ltd.; PFIZER INC. EP1710241B1, **2006** (c) G. J. Kemperman, J. J. M. Van der linden, T. Stuk, N. V. Lee, ORGANON – *WO* 20083460A1, **2008**, (d) G. J. Kemperman, T. Stuk, N. V. Lee, J. J. M. Van der linden N. V., Organon – US20089619A1, **2008** (e) B. Synthon, J. Zhu, R. Keltjens, J. J. Firet, *WO*2008081010A1, **2008** (f) *CN* 102229613B, **2013** (g) G. J. Kemperman, J. J. M. Van der linden, M. R. Reeder, *EP* 2154134, **2006** (h) G. J. Kemperman, *US* 0227803, **2009**.
13 EMA/CHMP/583011/2010.
14 R. R. Anugu, P. S. Mainkar, B. Sridhar, S. Chandrasekhar, *Org. Biomol. Chem*. **2016**, *14*, 1332–1337.
15 P. Szcześniak, O. Staszewska-Krajewska, B. Furman, J. Mlynarski, *ChemistrySelect*, **2017**, *2*, 2670–2676.
16 P. Szcześniak, O. Staszewska-Krajewska, B. Furman, J. Mlynarski, *Tetrahedron Asymmetry*, **2017**, *28*, 1765–1773.
17 J. Bures, A. Armstrong, D. G. Blackmond, *J. Am. Chem. Soc*. **2012**, *134*, 6741–6750.

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