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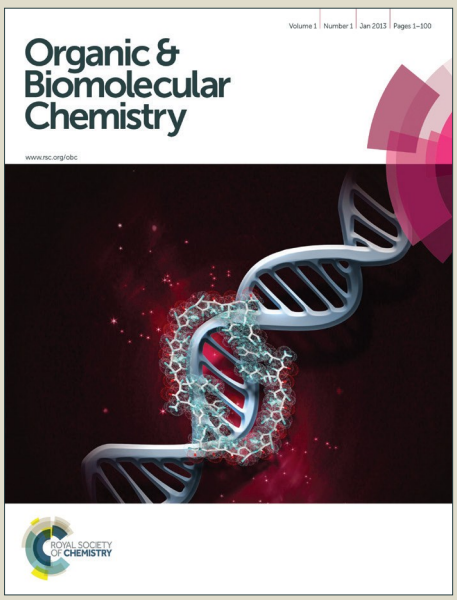

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ARTICLE

Ireland-Claisen Rearrangement Strategy towards the Synthesis of Schizophrenia Drug, (+)-Asenapine

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(±)-Asenapine, sold in the market as Saphris/Sycrest for the treatment of bipolar disorders is synthesized in optically pure form involving Ireland-Claisen rearrangement as the key step. This approach allows access to all diastereomers.

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Introduction

The sigmatropic rearrangement involves multiple bond migrations, cleavages and allows one to access functional synthons in perfect enantio- and stereo-control. Various versions of these rearrangements in the applications of total synthesis of bioactives are recently reviewed.[1,2] Even though these reactions are extensively used in the total synthesis of natural products, there are not many reported uses documented in the preparation of pharmaceutically useful approved synthetic drugs.

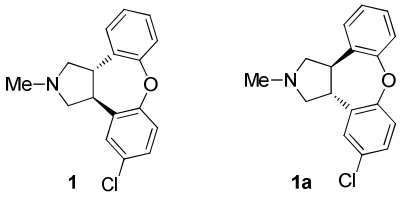


Fig. 1 Structure of asenapine

(±) Asenapine (Fig. 1, **1 & 1a**) is approved by FDA for treatment of Schizophrenia and acute manic or mixed episodes (bipolar disorders). This drug, when administered, enhances the extracellular dopamine concentration in the mPFC (medial prefrontal Cortex) and is also found to enhance the transmission of NMDA in the mFPC. The total synthesis of Asenapine in racemic form is reported in both patented and public domain.[3-8] The chemical structure of (±)-Asenapine can be described as tetracyclic framework, wherein *N*-methylpyrrolidine ring fuses at 3rd and 4th positions with chlorophenyl, phenyl ether in a *trans* geometry. Interestingly, the (+)-isomer has exhibited better plasma concentration.[9] However, based on preclinical data, the FDA has approved the market launch with the racemic version. It would be worthy an effort to develop a strategy which enables one to synthesise any of the possible four isomers by choosing the appropriate starting materials albeit the same synthetic sequence.

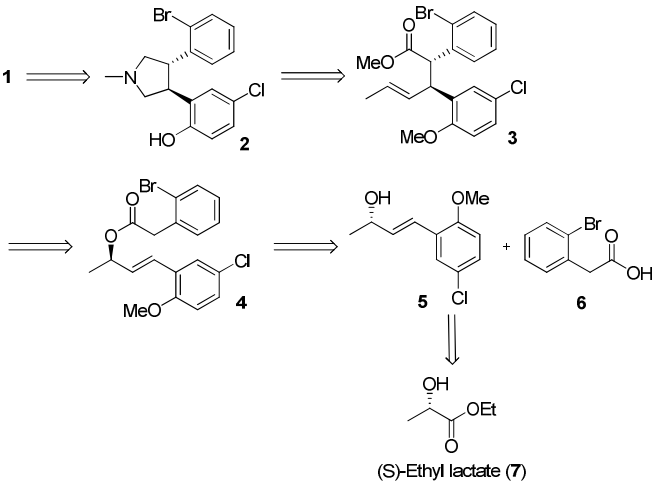
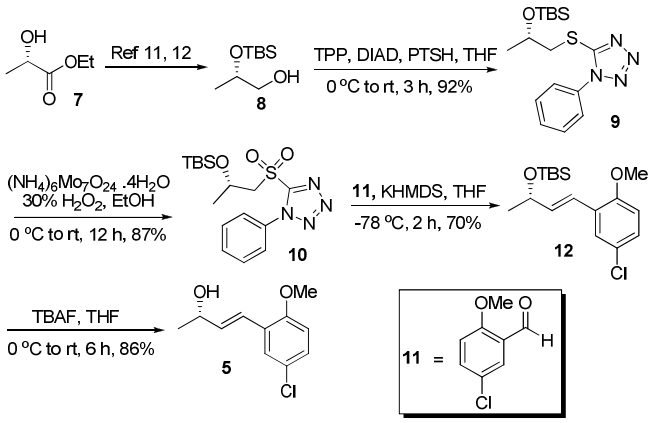


Fig. 2 Retrosynthetic analysis

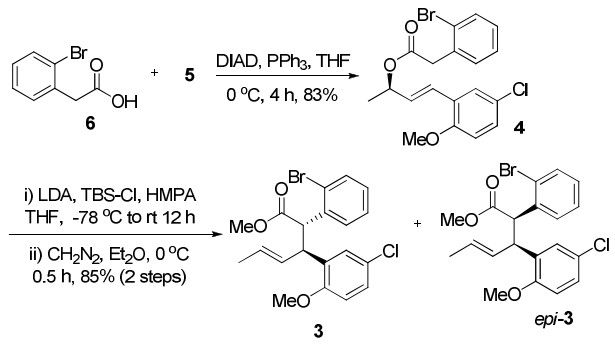
Results and discussion

Our group has been engaged in developing newer synthetic strategies for the approved drugs in CNS related disorders *viz*., Sertraline,[10] and Galanthamine.[11] Conceptually, we visualized the Asenapine framework could be disconnected at the biaryl ether to synthon **2,** which could be built from **3,** which in turn could be realised from ester **4** *via* Ireland-Claisen rearrangement. The intermediate **4** could be built from alcohol **5** and acid **6** (Fig. 2).



Scheme 1 Synthesis of intermediate **5**

With this strategy in mind, it was thought to synthesize one of the desired isomers in optically pure form rather than a racemate to prove the hypothesis. The successful execution of this strategy will naturally allow one to synthesize either the racemate or the other isomers by simply switching one starting material *i.e*, lactic acid ester **7**, skipping inversion in the Mitsunobu reaction or by altering the Claisen conditions (avoiding HMPA) for other stereoisomers through non-stabilized enolate.



Scheme 2 Synthesis of Ireland-Claisen rearrangement product

Moving forward, commercially available (*S*)-ethyl lactate, **7**, was converted to 1,2 propanediol derivative **8** following literature procedure.[12-13] The alcohol in compound **8** was converted to thiotetrazole **9** under Mitsunobu conditions in 92% yield. A smooth oxidation of **9** with ammonium molybdate and H_2O_2 yielded sulfone **10**,[14] the Julia-Kocienski olefination partner, in 87% yield. The olefination between 2-methoxy-4-chloro benzaldehyde **11** and sulfone **10** was accomplished with KHMDS as base to isolate the (*E*)-styrene derivative **12** in 70% yield. The silyl ether in **12** was unmasked to alcohol **5** with TBAF (Scheme 1).

With this, the platform was set to build the key synthon **4,** having the mandatory functionalities *viz*, olefin, hetero atom (*O*) and active methylene for triggering the Ireland-Claisen rearrangement. The Mitsunobu reaction[15] between alcohol **5** and *o*-bromophenylacetic acid **6** was performed in presence of DIAD and PPh_3 at 0 °C to yield allyl acetate derivative **4** in 83% yield. The anionic Claisen rearrangement[16-19] was enforced on **4** with LDA, TBSCl and HMPA as additive, in THF and subsequent esterification (after CH_2N_2 reaction) provided a diastereomeric mixture of esters **3** and *epi*-**3** (9:1 ratio), in 85% yield (Scheme 2). The additive HMPA is known to stabilize the (*Z*)-transition state of enolate to furnish the *anti*-product (Fig. 3) in major ratio which can be separated by column chromatography.

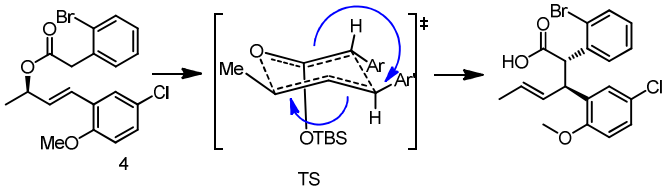


Fig. 3 Transition state Ireland-Claisen rearrangement

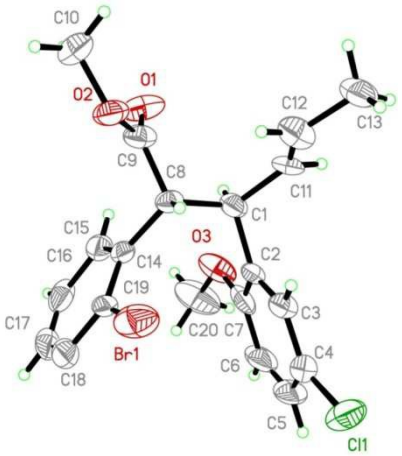
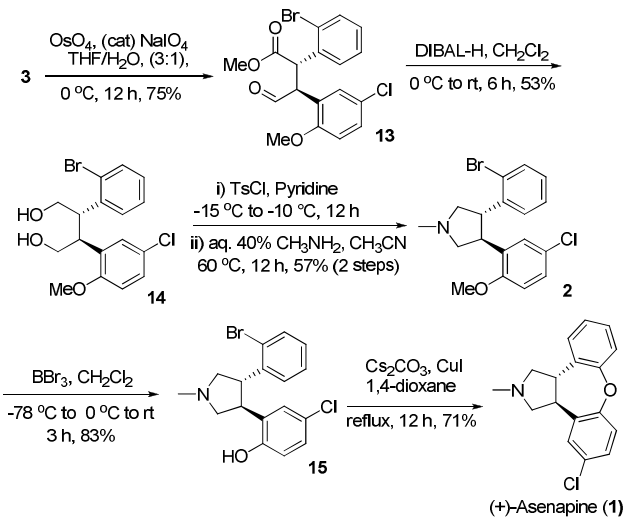


Fig. 4 ORTEP diagram of compound **3**

With The olefinic functionality in **3** was subjected to oxidative cleavage under OsO_4/ $NaIO_4$ conditions to obtain aldehyde **13** (75% yield) which was further reduced with excess of DIBAL-H to diol **14** in 53% yield. The *N*-methylpyrrolidine ring was constructed *via* tosylation followed by treatment with aqueous methylamine in acetonitrile to generate the tricyclic core **2** in 57% yield over two steps.[20] Demethylation was achieved with BBr_3 in CH_2Cl_2 to provide phenol derivative **15** in 83% yield. The oxepine ring was constructed from **15** following a known procedure,[21] where exposure to $CsCO_3$ and CuI resulted in (+) Asenapine in 71% yield with 93.8% *ee* (Scheme 3).



Scheme 3 Synthesis of (+)-Asenapine from **3**

Conclusions

In conclusion, enantiopure (+)-Asenapine has been synthesized involving Julia olefination and Ireland-Claisen rearrangement as key steps starting from commercially available (*S*)-ethyl lactate in overall 4.6% yield. The easy availability of (±)-lactic acid and *R*-lactic acid, in principle, will allow to synthesize (±)-Asenapine (Saphris) and (-)-Asenapine, respectively, by following the same synthetic transformations as presented here.

Experimental

General

All the reagents and solvents were reagent grade and used without purification unless specified otherwise. All the dry reactions were performed under an atmosphere of nitrogen in flame-dried or oven-dried glassware with magnetic stirring. When used as a reaction solvent, THF was freshly distilled from sodium benzophenone ketyl. Technical grade ethyl acetate and hexanes used for column chromatography were distilled prior to use. Column chromatography was carried out using silica gel (60–120 mesh and 100–200 mesh) packed in glass columns. Optical rotations were measured with a digital polarimeter using a 2 mL cell with a 1 dm path length. ^{1}H and ^{13}C NMR spectra were recorded at 300, 400, 500 and 75, 100, 125 MHz, respectively. Chemical shifts (δ) are reported in ppm, using the residual solvent peak in $CDCl_3$ (H: δ = 7.26 and C: δ = 77.0 ppm) as internal standard, and coupling constants (J) are given in Hz. High-resolution mass spectra (HRMS) were obtained by electron spray ionization using a ESI-TOF mass spectrometer in positive ion mode (M + H or M + Na) as indicated.

X-ray Crystallography: The intensity data were collected at room temperature using a Bruker Smart Apex CCD diffractometer with graphite monochromated MoKα radiation (λ=0.71073Å) by the ω-scan method. Preliminary lattice parameters and orientation matrices were obtained from four sets of frames. Integration and scaling of intensity data were accomplished using the program SAINT. The structures were solved by direct methods using SHELXS97 and refinement was carried out by full-matrix least-squares technique using SHELXL97. Anisotropic displacement parameters were calculated for all non-hydrogen atoms. All other H atoms were positioned geometrically and treated as riding on their parent C atoms [C-H = 0.93-0.97 Å and U_{iso}(H) = 1.5U_{eq}(C) for methyl H or 1.2U_{eq}(c) for other H atoms]. The methyl groups were allowed to rotate but not to tip.

(*S*)-5-(2-(*tert*-Butyldimethylsilyloxy)propylthio)-2-phenyl-2*H*-tetrazole (9): DIAD (1.18 mL, 6.3 mmol) was added to a solution of **8** (1 g, 5.2 mmol), triphenylphosphine (1.65 g, 6.3 mmol) and 1-phenyl-1*H*-tetrazole-5-thiol (1.12 g, 6.3 mmol) in THF (10 mL) at 0 °C. After stirring for 1 h, the reaction was quenched with water (10 mL) and the aqueous layer was extracted with EtOAc (2 x 20 mL), organic layer was dried over Na_2SO_4 and concentrated. Purification by flash silica gel column chromatography (10% ethyl acetate in hexanes) yielded sulphide **9** (1.7 g, 92%) as a clear oil. R_f = 0.45 (10% ethyl acetate in hexanes). $[\alpha]_D^{20}$ = +18.8 (c = 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69-7.64 (m, 2H), 7.62-7.55 (m, 3H), 4.63-4.54 (m, 1H), 4.03 (dd, J = 14.7, 7.1 Hz, 1H), 3.78 (dd, J = 14.7, 4.4 Hz, 1H), 1.36 (d, J = 6.2 Hz, 3H), 0.82 (s, 9H), 0.05 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.7, 133.7, 130.1, 129.8, 123.8, 66.9, 42.1, 25.8, 23.1, 18.1, -4.5, -4.8; IR (thin film): ν_{max} 2955, 2930, 2857, 1500, 1254, 1597, 1387, 1254, 1135, 1090, 987, 837, 775 cm^{-1}; HRMS (ESI): *m/z* calculated for $[M+H]^+$ $C_{16}H_{27}N_4OSSi$ 351.1664; found 351.1664.

(*S*)-5-(2-(*tert*-Butyldimethylsilyloxy)propylsulphonyl)-2-phenyl-2*H*-tetrazole (10): To a stirred solution of **9** (1.5 g, 4.2 mmol) in ethanol (15 mL) at 0 ºC was added a solution of ammonium molybdate (1.58 g, 1.2 mmol) in 30% aq. H_2O_2 (1.2 g, 2 mmol). The reaction mixture was allowed to warm to room temperature. After 24 h, the reaction mixture was diluted with saturated ammonium chloride (15 mL) and H_2O (15 mL), partitioned between ethyl acetate (25 ml) and water (25 mL). The organic phase was washed with brine (15 mL) and dried over Na_2SO_4. Concentration and flash chromatography (20% ethyl acetate in hexanes) afforded **10** (1.5 g, 87% yield) as a colourless solid. R_f = 0.5 (20% ethyl acetate in hexanes). m.p.: 53 °C; $[\alpha]_D^{20}$ = +22.5 (c = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.73-7.59 (m, 5H), 4.66-4.55 (m, 1H), 4.06 (dd, J = 14.7, 7.1 Hz, 1H), 3.81 (dd, J = 14.7, 4.5 Hz, 1H), 1.38 (d, J = 6.2 Hz, 1H), 0.85 (s, 9H), 0.08 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.3, 132.9, 131.0, 129.4, 125.2, 63.8, 63.4, 25.7, 24.1, 17.8, -4.6, -5.1; IR (thin film): ν_{max} 2956, 2932, 2858, 1498, 1348, 1257, 1158, 1070, 985, 838, 772 cm^{-1};

HRMS (ESI): *m/z* calculated for $[M+Na]^+$ $C_{16}H_{26}O_3N_4NaSSi$ 405.1387; found 405.1394.

(*R,E*)-*tert*-Butyl (4-(5-chloro-2-methoxyphenyl)but-3-en-2-yloxy)dimethylsilane (12): To a solution of compound **10** (3.7 g, 9.8 mmol) in THF (30 mL) was added KHMDS (0.5 M in THF, 24 mL, 12.3 mmol) at –78 ºC. After 45 min, 2-methoxy-4-chlorobenzaldehyde (1.4 g, 8.2 mmol) in THF (7 mL) was added to the reaction at –78 ºC. After 3 h at –78 ºC, the mixture was quenched with aqueous NH_4Cl solution (15 mL), allowed to warm to room temperature and extracted with EtOAc (20 mL). The organic phase was washed with water (20 mL) and brine (20 mL), then dried over Na_2SO_4. Concentration of organic layer and column chromatography (5% ethyl acetate in hexanes) afforded **12** (1.9 g, 70% yield, *E*/*Z* >98:2, 99% *ee*) as a colorless oil. R_f = 0.5 (5% ethyl acetate in hexanes). $[\alpha]_D^{20}$ = -68.5 (*c* = 0.9, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28 (d, *J* = 2.6 Hz, 1H), 7.04 (dd, *J* = 8.7, 2.6 Hz, 1H), 6.72-6.64 (m, 2H), 6.12 (dd, *J* = 16.0, 5.5 Hz, 1H), 4.43-4.32 (m, 1H), 3.72 (s, 3H), 1.21 (d, *J* = 6.4 Hz, 3H), 0.84 (s, 9H), 0.001 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.3, 136.3, 128.0, 127.6, 126.4, 125.7, 121.7, 112.1, 69.5, 55.8, 25.9, 24.6, 18.3, -4.5, -4.7; IR (thin film); ν_{max} 2956, 2931, 2857, 1485, 1435, 1248, 1218, 1148, 1124, 1081, 1034, 972, 909, 835,805,772 cm^{-1}; Analysis calculated for ($C_{17}H_{27}ClO_2Si$) C 62.45, H 8.32; found C 62.40, H 8.23.

(*S,E*)-4-(5-Chloro-2-methoxyphenyl)but-3-en-2-ol (5): To a solution of **12** (1.6 g, 4.9 mmol) in 16 mL of THF at 0 ºC was added 5 mL (9.8 mmol, 1.0 M) of TBAF in THF. The reaction mixture was stirred at ambient temperature for 16 h and then concentrated under *vacuo*. The crude was purified by flash chromatography (20% ethyl acetate in hexanes) as the eluant to give alcohol **5** (900 mg, 86%) as a colourless oil: R_f = 0.55 (20% ethyl acetate in hexanes). $[\alpha]_D^{20}$ = -12.7 (*c* = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31 (d, *J* = 2.5 Hz, 1H), 7.08 (dd, *J* = 8.8, 2.6 Hz, 1H), 6.76-6.68 (m, 2H), 6.18 (dd, *J* = 16.0, 6.4 Hz, 1H), 4.48 – 4.33 (m, 1H), 3.74 (s, 3H), 1.78 (brs, 1H), 1.28 (t, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.2, 135.5, 128.1, 127.3, 126.5, 125.7, 123.0, 112.0, 69.1, 55.7, 23.3; IR (thin film): ν_{max} 3359, 2969, 1593, 1485, 1248, 1124, 1030, 972, 907, 804, 773 cm^{-1}; Analysis calculated for ($C_{11}H_{13}ClO_2$) C 62.12, H 6.16; found C 62.54, H 6.21.

(*R,E*)-4-(5-Chloro-2-methoxyphenyl)but-3-en-2-yl 2-(2-bromophenyl)acetate (4): A stirred suspension of alcohol (*S,E*)-**5** (2 g, 9.43 mmol), triphenylphosphine (2.88 g, 1.32 mmol) and 3-bromophenylacetic acid (2.41 g, 1.32 mmol) in dichloromethane (20 mL) at 0 °C and under nitrogen, was treated dropwise with neat diisopropyl azodicarboxylate (2.16 mL, 2.22 g, 1.32 mmol). The reaction was allowed to reach room temperature overnight and quenched with water (10 mL) and then extracted with dichloromethane (25 mL). The organic phase was washed with water (25 mL) and brine (20 mL), then dried over Na_2SO_4. Concentration and column chromatography (10% ethyl acetate in hexanes) afforded **4** (3.2 g, 83% yield, 97% *ee*) as a colorless oil. R_f = 0.7 (10% ethyl acetate in hexanes). $[\alpha]_D^{20}$ = +23.0 (*c* = 0.95, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50 (d, *J* = 7.9 Hz, 1H), 7.31 – 7.20 (m, 3H), 7.08 (td, *J* = 8.9, 2.7 Hz, 2H), 6.79-6.68(m, 2H), 6.12 (dd, *J* = 16.1, 6.5 Hz, 1H), 5.50-5.45 (m, 1H), 3.86 – 3.61 (m, 5H), 1.34 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 169.7, 155.5, 134.4, 132.8, 131.5, 130.4, 128.8, 128.4, 127.5, 127.0, 126.7, 125.7, 125.3, 125.1, 112.1, 71.9, 55.8, 42.0, 20.3; IR (thin film): ν_{max} 3510, 3060, 2981, 2932, 1735, 1485, 1249, 1167, 1029, 806, 759 cm^{-1}; HRMS (ESI): *m/z* calculated for $[M+Na]^+$ $C_{19}H_{18}O_3BrClNa$ 431.0020; found 431.0059.

(*2S,3S,E*)-Methyl 2-(2-bromophenyl)-3-(5-chloro-2-methoxyphenyl)hex-4-enoate (3): To a stirred solution of **4** (1 g, 2.45 mmol) in THF (95 mL) and HMPA (20 mL) was added TBSCl (735 mg, 4.9 mmol) in THF (5 mL). After allowing the reaction mixture to -78 °C, LDA (4.1 mL, 0.5 M in THF) was slowly added dropwise. The reaction mixture was slowly warmed to room temperature and stirred for 15 h. It was acidified to *p*H 2-3 with 1N HCl aqueous solution (15 mL) and extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with brine (15 mL), dried over Na_2SO_4 and concentrated. The crude acid **12** was taken to next step without purification. The acid was dissolved in dry ether (10 mL) and treated with ethereal solution of diazomethane (1.2 g, 12.25 mmol) at 0 °C. After stirring the mixture for 0.5 h, aqueous NH_4Cl solution (15 mL) was added and extracted with ether (20 mL). The combined organic layers were dried over Na_2SO_4 filtered and concentrated under *vacuo*. The residue was purified by column chromatography on silica gel to give **3** (850 mg, 85% over two steps). Diastereomeric excess (*de*) was determined by LC-MS [Waters X select CSH column 150 x 4.6 mm x 5µ column with 70% acetonitrile and 30% water as mobile phase, at 210 nm] retention times were observed at 22.034 and 23.896 min respectively for the 2 diastereomers. R_f =0.65 (10% ethyl acetate in hexanes). m.p.: 191 °C; $[\alpha]_D^{20}$ = +13.6 (*c* = 0.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.57 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.35 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.14 (td, *J* = 7.7, 1.2 Hz, 1H), 7.11 (d, *J* = 2.6 Hz, 1H), 6.95 (dd, *J* = 8.7, 2.5 Hz, 2H), 6.94-6.91 (m, 1H), 6.54 (d, *J* = 8.7 Hz, 1H), 5.76 -5.70 (m, 1H), 5.66 -5.58 (m, 1H), 4.75 (d, *J* = 11.4 Hz, 1H), 4.48 (dd, *J* = 11.3, 8.3 Hz, 1H), 3.70 (s, 3H), 3.66 (s, 3H), 1.66 (dd, *J* = 6.3, 1.3 Hz, 3H). IR (thin film): ν_{max} 1737, 1219, 1027, 772 cm^{-1}. R_f =0.65; ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.0, 155.3, 136.1, 132.6, 130.9, 130.5, 129.8, 129.1, 128.5, 127.8, 127.1, 127.0, 125.2, 111.6, 55.6, 53.6, 52.0, 45.7, 18.1; HRMS (ESI) calculated for $[M+Na]^+$ $C_{20}H_{20}BrClO_3Na$ 445.0177; found 445.0181.

Crystal Data:[22-24] $C_{20}H_{19}BrClO_3$ (*M* =422.71): monoclinic, space group $P2_1/c$ (no. 14), *a* = 8.241(3) Å, *b* = 9.598(4) Å, *c* = 25.276(10) Å, β = 99.148(6)°, *V* = 1973.8(13) Å^3, *Z* = 4, *T* = 294.15 K, µ(MoKα) = 2.233 mm^{-1}, *Dcalc* = 1.422 g/mm^3, 14919 reflections measured (3.264 ≤ 2Θ ≤ 49.996), 3470 unique (R_{int} = 0.0691) which were used in all calculations. The final R_1 was 0.1232 (I > 2σ(I)) and wR_2 was 0.3589 (all data). CCDC 1407428 contains supplementary Crystallographic data for the structure. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/data_request/cif.

(*2S,3S*)-Methyl 2-(2-bromophenyl)-3-(5-chloro-2-methoxyphenyl)-4-oxobutanoate (13): To a stirred solution of **3** (750 mg 1.77 mmol) and *N*-methylmorpholine *N*-oxide (828 mg, 7.08 mmol) in THF/water (7:3, 7.5 mL) was added OsO_4 (1.6 mL in toluene, 0.01mmol) at room temperature. After 12 h, sodium bisulfite (353 mg, 3.40 mmol) was added. After stirring for 5 min, the mixture was extracted with EtOAc (2 x 10 mL). The combined organic layers were dried over $NaSO_4$, filtered and concentrated under *vacuo*. The residue was then dissolved in a mixture of THF/H_2O (7:3, 8 mL) and treated with $NaIO_4$ (828 mg, 7.08 mmol). After 15 min, the mixture was poured into saturated aqueous solution of $NaHCO_3$ (10 mL) and extracted with EtOAc (15 mL). The combined organic layers were dried over $NaSO_4$, filtered and concentrated under *vacuo*. The residue was then purified by flash chromatography (10% ethyl acetate in hexanes) on silica gel to afford **13** as a white solid (550 mg, 75%). R_f =0.7 (10% ethyl acetate in hexanes). m.p.: 102 ^oC; $[\alpha]_D^{20}$ = +42.4 (*c* = 1, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 9.67 (s, 1H), 7.39 -7.33 (m, 2H), 7.21-7.16 (m, 1H), 7.09 (dd, *J* = 8.8, 2.6 Hz, 1H), 7.00-6.95 (m, 1H), 6.90 (d, *J* = 2.6 Hz, 1H), 6.62 (d, *J* = 8.8 Hz, 1H), 4.98 (d, *J* = 11.1 Hz, 1H), 4.66 (d, *J* = 11.1 Hz, 1H), 3.73 (s, 3H), 3.69 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 198.0, 173.0, 156.1, 135.5, 133.0, 131.5, 129.2, 128.9, 127.3, 125.4, 125.1, 122.7, 111.7, 56.1, 55.5, 52.7, 48.1; IR (thin film): ν_{max} 2952, 1731, 1491, 1255, 1219, 1025, 772 cm^{-1}; HRMS (ESI): *m/z* calculated for $[M+Na]^+$ $C_{18}H_{16}BrClO_4Na$ 432.9813; found 432.9837.

(2*S*,3*S*)-2-(2-Bromophenyl)-3-(5-chloro-2-methoxyphenyl)butane-1,4-diol (14): Diisobutylaluminium hydride (2.2 mL of a 25% solution in toluene, 3.90 mmol) was added dropwise to a stirred solution of **13** (400 mg, 0.9 mmol) in dry dichloromethane (4 mL) at 0 °C under nitrogen. The resulting mixture was stirred at room temperature for 12 h, then quenched with saturated sodium potassium tartrate (4 mL). The reaction mixture was diluted with dichloromethane (5 mL). The layers were separated and aqueous layer was extracted with dichloromethane (2 x10 mL). The combined organic portions were dried over Na_2SO_4, filtered and concentrated under *vacuo*. The residue was purified by column chromatography on silica gel to afford **14** (200 mg, 53%) as a colourless oil. R_f = 0.45 (30% ethyl acetate in hexanes). $[\alpha]_D^{20}$ = -5.9 (*c* = 1.1, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 7.37-7.34 (m, 1H), 7.29 (s, 1H), 7.19 (s, 1H), 7.06-7.00 (m, 1H), 6.93-6.91 (m, 2H), 6.87 (ddd, *J* = 8.0, 6.5, 2.5 Hz, 1H), 6.55 (d, *J* = 8.6 Hz, 1H), 3.96-3.89 (m, 2H), 3.88-3.75 (m, 4H), 3.68 (s, 3H), 2.26 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.4, 140.2, 132.8, 131.0, 129.0, 128.4, 128.0, 127.2, 127.0, 125.5, 111.6, 65.3, 55.7, 47.8, 43.1; IR (thin film): ν_{max} 3392, 2954, 2931, 2856, 1488, 1468, 1247, 1056, 1025, 809, 771 cm^{-1}; HRMS (ESI): *m/z* calculated for $[M+Na]^+$ $C_{17}H_{18}BrClO_3Na$ 407.0020; found 407.0030.

(3*S*,4*S*)-3-(2-Bromophenyl)-4-(5-chloro-2-methoxyphenyl)-1-methylpyrrolidine (2): Anhydrous pyridine (3.3 mL, 28.5 mmol) was added slowly to a mixture of diol **14** (600 mg, 1.5 mmol) and *p*-toluenesulfonyl chloride (1.2 g, 6.2 mmol) at -15 °C. The mixture was stirred at -10 °C for 4 h and at 0 °C for 24 h. After pouring the reaction mixture into ice-water, the di-tosylate product solidified in 0.5 h. It was filtered and washed consecutively with H_2O (5 ml), 2% HCl (5 mL), 2% aqueous NaOH solution (5 mL), and H_2O (5 mL). Yield of the crude was 900 mg (83%). It was further purified by recrystallization from benzene/hexane. A mixture containing di-tosylate (800 mg, 0.1 mmol), acetonitrile (60 mL) and methylamine (2.2 mL, 40% aq. methylamine) was sealed in a pressure reactor and stirred for 24 h at 80 °C. After completion, the reaction mixture was concentrated under *vacuo* and re-dissolved in dichloromethane (25 mL). After washing with water (25 mL), brine (10 mL), the organic layer was dried and concentrated *in vacuo* and the residue was purified by column chromatography on silica gel to afford **2** (300 mg, 69%) as a colourless oil. R_f = 0.65 (10% MeOH in CH_2Cl_2). $[\alpha]_D^{20}$ = +5.4 (*c* = 0.95, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.57 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.46 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.31-7.26 (m, 2H), 7.11 (dd, *J* = 8.7, 2.6 Hz, 1H), 7.02 (ddd, *J* = 8.0, 7.4, 1.7 Hz, 1H), 6.70 (d, *J* = 8.7 Hz, 1H), 4.08 (dt, *J* = 7.1, 8.3 Hz, 1H), 3.88 (q, *J* = 8.2 Hz, 1H), 3.64 (s, 3H), 3.23 (dt, *J* = 15.3, 8.9 Hz, 2H), 2.87-2.78 (m, 2H), 2.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.1, 132.5, 128.2, 127.9, 127.8, 127.2, 125.6, 124.8, 111.7, 63.8, 62.6, 55.4, 49.1, 46.1, 42.5; IR (thin film): ν_{max} 2929, 2840, 2780, 1489, 1245, 1125, 1026, 880, 809, 756 cm^{-1}; HRMS (ESI): *m/z* calculated for $[M+H]^+$ $C_{18}H_{20}BrClNO$ 380.0411; found 380.0423.

2-((3*S*,4*S*)-4-(2-Bromophenyl)-1-methylpyrrolidin-3-yl)-4-chlorophenol (15): To a solution of compound **2** (250 mg, 0.6 mmol) in dry dichloromethane (4 mL) at -78 °C under nitrogen atmosphere was added boron tribromide (2.6 mL, 2.6 mmol, 1M in CH_2Cl_2) drop wise. After 30 min, the reaction was quenched by the saturated aqueous solution of $NaHCO_3$ (5 mL), dichloromethane (3 mL) was then added, the layers were separated and aqueous layer was extracted with dichloromethane (2 x 5 mL). The combined organic portions were dried over Na_2SO_4, filtered and the residue was purified by column chromatography on silica gel (5% MeOH in CH_2Cl_2) to afford **15** (200 mg, 83%) as a colourless oil. R_f = 0.65 (5% MeOH in CH_2Cl_2). $[\alpha]_D^{20}$ = +11.00 (*c* = 0.2, $CHCl_3$). ^1H NMR (300 MHz, CD_3OD): δ 7.5-7.39 (m, 2H), 7.27 (t, *J* = 7.6 Hz, 1H), 7.014-6.97 (m, *J* = 7.6 Hz, 1H), 6.92-6.84 (m, 2H), 6.625-6.60 (m, 1H), 4.65-4.49 (m, 1H), 4.06 (dd, *J* = 16.6, 8.1 Hz, 1H), 3.54 (dd, *J* = 12.4, 7.5 Hz, 1H), 3.38 (t, *J* = 8.9 Hz, 1H), 3.08-2.90 (m, 2H), 2.50-2.45 (m, 1H), 2.43 (s, 3H); IR (thin film): ν_{max} 2925, 2853, 1480, 1258, 1219, 1023, 772 cm^{-1}; ^{13}C NMR (75 MHz, CD_3OD): δ 155.8, 142.8, 134.0, 132.0, 129.8, 129.5, 129.3, 128.6, 125.8, 124.4, 118.7, 64.5, 62.9, 50.8, 50.1, 41.3; HRMS (ESI): *m/z* calculated for $[M+H]^+$ $C_{17}H_{18}BrClNO$ 366.0255; found 366.0270.

***trans*-(5-Chloro-2-methyl-2,3,3a,12b-tetrahydro-1*H*-dibenz[2,3:6,7]oxepine-[4,5-c]pyrrole (1):** To a stirred solution of compound **15** (100 mg; 0.273 mmol) in dioxane (10 ml) was added cesium carbonate (106 mg; 1.2 eq), *N,N*-dimethylglycine (7 mg; 0.25 eq) and copper iodide (13 mg; 0.25 eq) under a nitrogen atmosphere at room temperature. The reaction mixture was heated to reflux and stirred for 12 hours. The reaction mixture was filtered over celite and washed with

dioxane (3 x 10 ml). The organic solvent was concentrated under *vacuo* and residue was then purified by column chromatography (5% MeOH in CH_2Cl_2) to afford Asenapine **1** (50 mg, 71% yield, 93.8% *ee*, Overall yield 4.6%) as a slightly yellow oil. R_f = 0.4 (5% MeOH in CH_2Cl_2). $[\alpha]_D^{20}$ = +31.1 (*c* = 0.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.18-6.93 (m, 7H), 3.85-3.73 (m, 2H), 3.70-3.55 (m, 2H), 3.52-3.35 (m, 2H), 2.82 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.3, 154.2, 130.2, 129.7, 129.3, 128.9, 128.6, 128.3, 126.8, 124.9, 123.0, 121.5, 58.5, 58.4, 43.6, 43.5, 43.2; HRMS (ESI): *m/z* calculated for $[M+H]^+$ $C_{17}H_{17}ClNO$ 286.0990; found 286.1012.

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Notes and references

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† Electronic supplementary information (ESI) available: [The copies of ^{1}H & ^{13}C NMR spectra for all new compounds and single crystal X-ray data. CCDC 1407428. For ESI and crystallographic data in CIF]. See DOI: 10.1039/b000000x/

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24. CCDC-1407428 (**3**) contains the supplementary crystallographic data for this paper†. This data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0) 1223 336 033; email: deposit@ccdc.cam.ac.uk.

Graphical Abstract

Ireland-Claisen Rearrangement Strategy towards the Synthesis of Schizophrenia Drug, (+)-Asenapine

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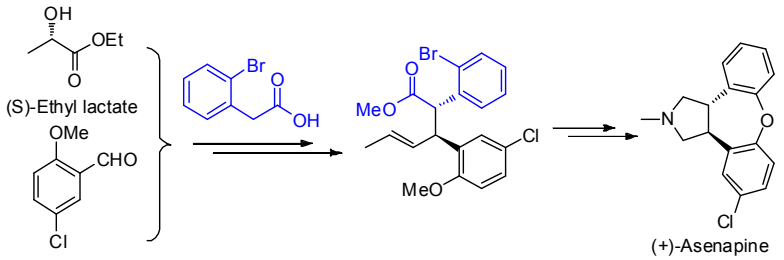

(±)-Asenapine, sold in the market as Saphris/Sycrest for the treatment of bipolar disorders is synthesized in optically pure form involving Ireland-Claisen rearrangement as the key step. This approach allows access to all diastereomers