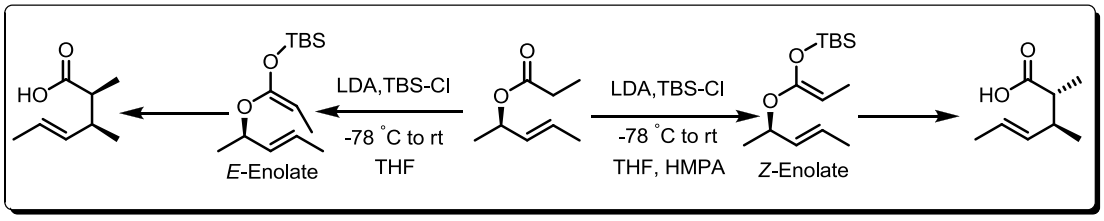
The thesis entitled "**Synthetic studies towards bioactives (+)-Asenapine and (-)-Englerin A**" is presented in three chapters.

General introduction of Ireland-Claisen rearrangement

In 1972, for first time Ireland-Claisen rearrangement was introduced and since then this reaction is widely used in the synthesis of natural products. The starting materials can be prepared easily by the coupling an allylic alcohol with carboxylic acid with excellent yields, product diastereoselectivity and atom economy.Ireland-Claisen rearrangement is a [3, 3]-sigmatropic shift of allylic ester which produce *γ, δ*-unsaturated acid. The rearrangement proceeds through chair like transition state. The allylic ester when subjected with base in presence of TBSCl initially forms an enolate which is stabilized by forming TBS ketene acetal. If there is a substitution at alpha positition of allylic ester, it can produce *E* and *Z* enolates which are responsible for the stereo chemical outcome. The formation of *E* and *Z* enolates are controlled by changing the reaction conditions.



Statement of problem

Chapter I: Total synthesis of (+)-Asenapine

This chapter describes the total synthesis of (+)-asenapine which is approved by FDA in 2009 for the treatment of schizophrenia. Asenapine is a synthetic drug which is developed by altering the structure of mianserin. Mianserin is an anti psychoactive drug which belongs to tetracyclic antidepressant (TeCA) therapeutic family. Asenapine is used for treatment of schizophrenia and acute manic or mixed episodes (bipolar disorders). This drug, when administered, enhances the extracellular dopamine concentration in the medial prefrontal Cortex (mPFC) and is also found to enhance the transmission of NMDA in the mFPC. The total synthesis of asenapine in racemic form is reported in the literature. The chemical structure of (±)-asenapine can be described as tetracyclic framework, where in *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 than (-)-isomer. 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. The synthetic challenges posed by the asenapine structure were influencial in taking up its total synthesis.

Chapter II: Synthesis of Asenapine analogues as neurotrophic agents

Schizophrenia is a disorder characterized to be both neuro-degenerative and neuro-developmental. Research in this area has identified the role of genes in the manifestation of this disease from what appears to be a normal childhood. In addition to genetic factors, environmental factors play a substantial role in the development of neurons. It has been thought that psychotropic drug molecules act through their neurotransmitter action. Bodnar *et al*. have reported that chronic activation of post synoptic 5-HTLA receptor may encourage neurite growth in hippocampus and regulation of BDNF. As asenapine is a 5-HT eceptor and we envisioned to explore the relation between BDNF and 5-HT receptor activity. To determine this some of the advanced intermediates, their derivative and asenapine analogues were screened for BDNF signaling.

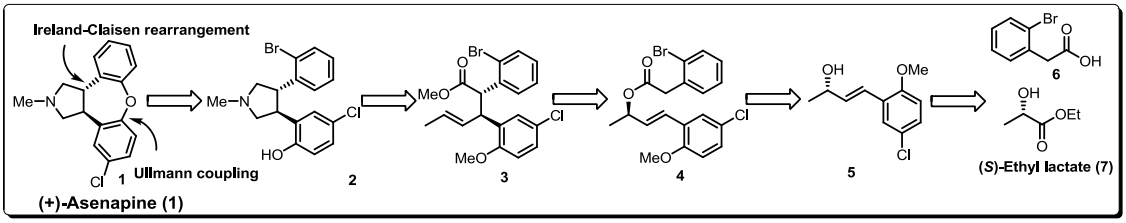
Chapter III: Synthetic efforts towards (-)-Englerin A

Beutler *et al*. isolated guanine sesquiterpene from the stem bark of *Phyllanthus* sp in 2009, and named them as englerin A **(1),** englerin B **(2)** and englerin B acetate **(3**). Englerin A (**1**) is characterized as a tricyclic (5-6-5) skeleton with ether bridge and it has cinnamic acid (C6) and glycolic acid (C9) residue. Englerin B (**2**) and englerin B acetate (**3**) showed significant loss of potency and selectivity toward renal cancer cells. Englerin A (**1**) has been used as a lead compound for drug discovery, due to its significant cytotoxic activity against six human cancer cell lines. It binds to TRPC protein tetramers (four cylinders) in a kidney cancer cell membrane. This opens the central ion channel, which allows Ca^{2+} into the cell and leads to cell death. Our group's interest in the total synthesis of natural products and the synthesis of bioactives of marine origin is the driving force which embarks on the total synthesis of Englerin A **(1**).

Methodology used

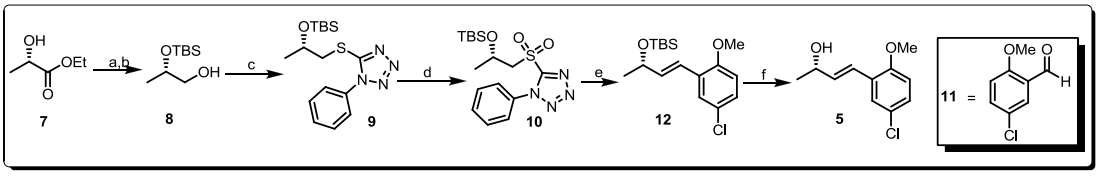
Chapter I: The total synthesis of (+)-asenapine

The retrosynthetic analysis of the (+)-asenapine framework could be obtained from synthon **(2)** through Ullmann coupling, 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 2-bromo phenyl acetic acid **(6).** Alcohol synthon **(5)** can be accessed from commercially available (*S*)-ethyl lactate **(7)** (Scheme 1).



Scheme 1

The synthetic plan was executed by choosing commercially available (*S*)-ethyl lactate **(7)**, which was protected with TBSCl and reduced to alcohol (**8**)**.** 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)** in 87% yield.

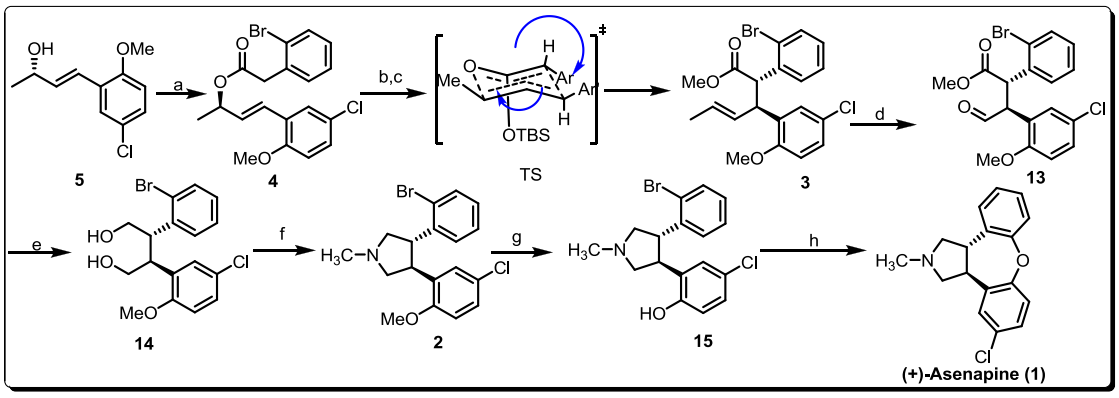


Scheme 2

Reagents and conditions: a) TBSCl, imidazole, DCM, 0 ^oC to rt, 2 h, 96%; b) DIBAL-*H*, DCM, 0 ^oC to rt, 4 h, 62%; c) TPP, DIAD, PTSH, THF, 0 ^oC to rt, 3 h, 92%; d) $(NH_4)_6Mo_7O_{24}$.$4H_2O$, 30% H_2O_2, EtOH, 0 ^oC to rt, 12 h, 87%; e) 5-chloro-2-methoxy benzaldehyde (**11**), KHMDS, THF, -78 ^oC, 2 h, 70%; f) TBAF, THF, 0 ^oC to rt, 6 h, 86%.

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 2). The Mitsunobu reaction between alcohol **(5)** and *o*-bromophenylacetic acid **(6)** was performed in presence of DIAD and PPh_3 at 0 ^oC to yield allyl acetate derivative **(4)** in 83% yield. The anionic Claisen rearrangement 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. The additive HMPA is known to stabilize the (*Z*)-transition state of enolate to furnish the *anti*-product in major ratio which can be separated by column chromatography. With The olefinic functionality in **(3)** was subjected to oxidative cleavage under OsO_4/ $NaIO_4$ conditions to obtain aldehyde **(13)** in 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. 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)** using Cs_2CO_3 and CuI resulted in (+) asenapine **(1)** in enantiopure form in 71% yield.



Scheme 3

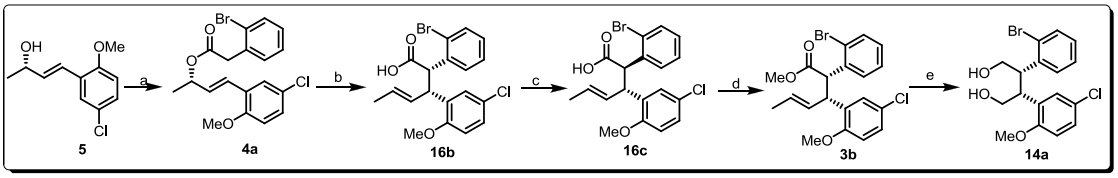
Reagents and conditions: a) DIAD, PPh_3, THF, 0 ^oC, 4 h, 83%; b) i) LDA, TBSCl, HMPA THF, -78 ^oC to rt 12 h; c) CH_2N_2, Et_2O, 0 ^oC 0.5 h, 85%; d) OsO_4 (cat), $NaIO_4$, THF/H_2O, (3:1), 0 ^oC, 12 h, 75%; e) DIBAL-*H*, CH_2Cl_2, 0 ^oC to rt, 6 h, 53%; f) i) TsCl, Pyridine, -15 ^oC to -10 °C, 12 h; ii) aq. 40% CH_3NH_2, CH_3CN 60 ^oC, 12 h, 57%; g) BBr_3, CH_2Cl_2, -78 ^oC to 0 ^oC to rt, 3 h, 83%; h) Cs_2CO_3, CuI, 1,4-dioxane, reflux, 12 h, 71%.

Conclusion

In summary, enantiopure (+)-asenapine has been synthesized employing Julia olefination and Ireland-Claisen rearrangement as key reactions. The synthesis was successfully completed utilizing commercially available (*S*)-ethyl lactate with 4.6% overall yield.

Chapter II: Synthesis of asenapine analogues as neurotrophic agents

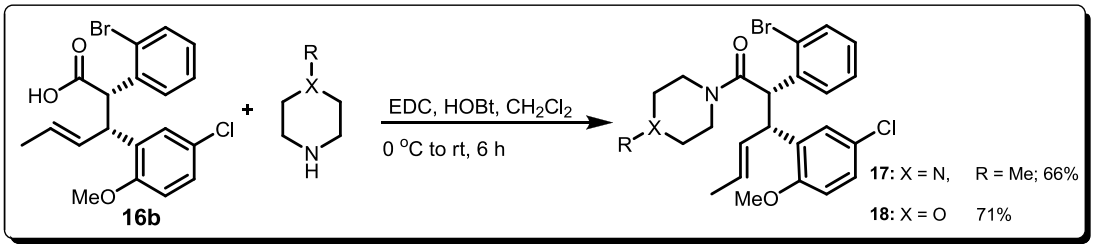
The synthetic plan was executed by choosing commercially available (*S*)-ethyl lactate **(7)**, which was converted to the alcohol derivative **(5)** in 28.6% overall yield. 2-bromophenylacetic acid **(6)** was coupled with chiral alcohol **(5)** in the presence of DCC/DMAP to furnish ester **(4a)**.



Scheme 4

Reagents and conditions: (a) 2-bromo phenylaceticacid (**6**), DCC, DMAP, CH_2Cl_2, 0 ^oC, 4 h, 88%; (b) LHMDS, TMSCl, THF, -78 ^oC to rt 12 h, 80%; (c) CH_2N_2, Et_2O, 0 ^oC, 0.5 h, 85%; (d) OsO_4 (cat), $NaIO_4$, THF/H_2O (3:1), 0 ^oC, 12 h; (e) DIBAL-*H*, CH_2Cl_2 0 ^oC to rt, 6 h, 51%.

Enolic ester **(4a)** was then subjected to sigmatropic rearrangement by using LiHMDS/TMSCl for a smooth reaction to give an acid **(16b)** with an excellent diastereoselectivity. The esterification of acid **16b** in the presence of CH_2N_2 afforded ester **(3b)** in 85% yield. Compound **(3b)** was dihydroxylated by using osmium tetroxide and NMO followed by oxidative cleavage using sodium periodate provided an aldehyde. The resultant aldehyde was subjected to DIBAL-H reduction to produce diol **(14a)** (Scheme 4). Free acid **(16b)** was coupled with two bases *N*-methyl piperidine and morpholine under EDC/HOBt conditions to get amide analogues (**17**) and (**18**) (Scheme 5). In addition to these compounds all advanced intermediates were screened for their neurotrophic activity (Figure 1).



Scheme 5

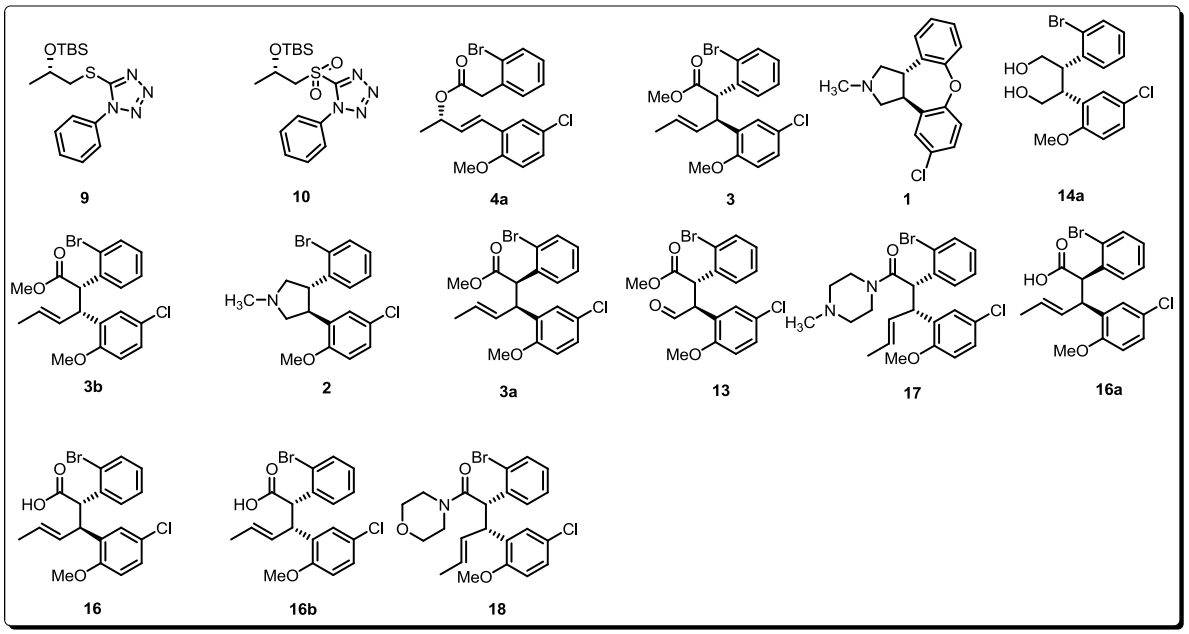


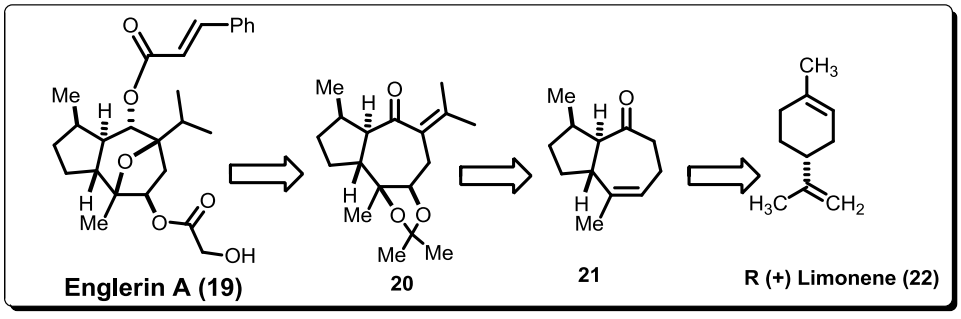
Figure 1

Conclusion

A set fifteen closely related compounds derived from asenapine were synthesized. Screening against 5-HT inhibition has been taken up. BDNF inhibitory studies on the fifteen compounds indicated that asenapine and intermediate **(3)** showed comparable activity.

Chapter III: Synthetic efforts towards (-)-Englerin A

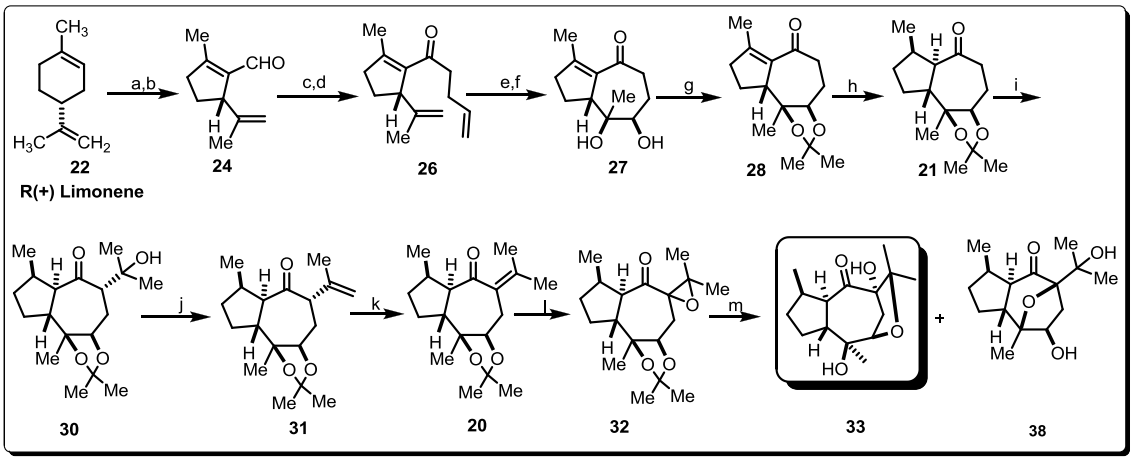
The retrosynthetic analysis of Englerine A (**19**) is depicted in scheme 6. The ether bridge could be accessed from intramolecular epoxide opening of compound (**20)**. The tetrasubstituted double bond of compound (**20)** could be derived from bicyclic compound (**21)** by aldol condensation. Compound (**21)** could be achieved from commercially available (*R*)-Limonene**.**



Scheme 6

The synthesis began with (*R*)-Limonene **(22)** as a chiral starting material. Thus, controlled ozonolysis of (*R*)-Limonene **(22)** followed by intromolecular aldol condensation of the resultant ketoaldehyde furnished the aldehyde **(24).** The aldehyde

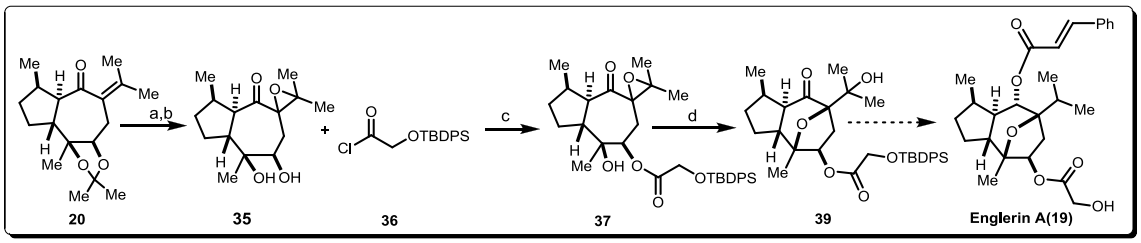
(24) on treating with 4-bromobut-1-ene yielded alcohol **(25)** which was oxidized with Dess-Martin periodinane (DMP) to give ketone **(26)**. The formation of bicyclic enone was mediated by RCM reaction using Grubbs 2nd generation catalyst which was further subjected to admix-*β* yielded diol (**27)**. This diol (**27)** was protected with 2,2-DMP to furnish compound **(28)**. The selective hydrogenation of the compound **(28)** with 10% palladium over charcoal as a catalyst in ethyl acetate furnished the saturated bycyclic enone **(21)** in 80% yield. The relative stereochemistry of compound **(21)** was established by NOESY correlations. The aldol condensation between bicyclic compound **(21)** and acetone in the presence of LDA and $ZnCl_2$ in THF at -78 ^oC afforded bicyclic alcohol **(30)**. Dehydration of alcohol **(30)** with Burgess reagent (MeO_2CN-SO_2NEt_3) gave alkene **(31)** in 95% yield**.** The migration of double bond was observed using K_2CO_3 in methanol under reflux condition to produce conjugated enone **(20)**. Epoxidation of **(20)** with hydrogen peroxide gave compound **(32)**. Unfortunately regioselective opening of epoxide **(32)** to give **(38)** was not successful; however formation of **(33)** was observed (Scheme 7).Deprotection of **(20)** with *p*-methyl sulphonic acid produced diol which on epoxidation with hydrogen peroxide gave compound (**35)** in 85% yield. Secondary alcohol **(35)** was coupled with acid chloride **(36)** in the presence of pyridine to furnish ester **(37)** in 86% yield. The etherification of compound **(37)** in presence of Lewis acid gave tricyclic alchohol **(39)** (Scheme 8).



Scheme 7

Reagents and conditions: (a) O_3, MeOH, -78 ^oC, 86%; (b) AcOH, piperidine, benzene, reflux, 85%; (c) Li, 4-bromobut-1-ene, THF, 0 ^oC 1 h, 71%; (d) IBX, DMSO, rt, 3 h, 85%; (e) $Ti(OiPr)_4$, Grubbs' catalyst (II), CH_2Cl_2; reflux, 3 h 79% (f) Admix-*β*, *t*BuOH/H_2O, 24 h, 73% (g) 2,2-DMP, CH_2Cl_2, rt, 4

h, 97% (h) Pd-C/H_2, EtOAc, 4 h, 81% (i) LDA, $ZnCl_2$, acetone, -78 ^oC, 4 h, 85% (j) Burgess reagent, $PhCH_3$, 110 ^oC, 1 h, 95% (k) K_2CO_3, MeOH, reflux, 6 h, 95% (l) 30% H_2O_2, 10% NaOH, CH_3OH 0 ^oC to r.t 6 h, 72% (m) $In(OTf)_3$, CH_3CN, H_2O (20:1), 80 ^oC, 4 h, 63%.



Scheme 8

Reagents and conditions: a) *p*TSA, MeOH, rt, 12 h, 92%; (b) 30% H_2O_2, MeOH, 0 °C to rt, 6 h 85% (c) **11**, pyridine, 0 °C to rt 1 h, 86% (d) $InCl_3$, $CHCl_3$, reflux, 4 h, 60%.

Conclusion

In conclusion enantioselective synthesis of fully functionalized tricyclic skeleton of (-)-Englerin A is completed.