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Asymmetric synthesis of both the enantiomers of antidepressant venlafaxine and its analogues

Rajib Bhuniya, Samik Nanda *

Department of Chemistry, IIT-Kharagpur, Kharagpur 721302, India

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ABSTRACT

Chemoenzymatic asymmetric synthesis of antidepressant agent venlafaxine and its analogue have been reported in this communication. The main highlight of the reported synthesis is the stereoselective synthesis of cyanohydrins by (*S*)-hydroxynitrile lyase (*Hevea brasiliensis*) followed by lipase catalyzed kinetic resolution.

Venlafaxine hydrochloride belongs to a class of well known antidepressant agents generally known as SNRIs (serotonin-norepinephrine reuptake inhibitor). It is widely known by its brand name EffexorXR®, which was first introduced by Wyeth and now marketed globally by Pfizer, is approved for the effective treatment of major depressive disorder (MDD) and generalized anxiety disorder (GAD). Effexor XR® made history when it became Wyeth's largest selling drug accounting for 16–18% of net revenue from 2006 to 2008. The reported synthetic routes for racemic venlafaxine mainly involve the condensation of cyclohexanones with 4-methoxyphenyl acetic acids or 4-methoxyphenyl acetonitriles followed by functional group manipulation.[1] There is also another report which involves an efficient HDA (Hetero Diels–Alder) reaction of an azadiene followed by transketalization and hydroxymethylation reaction.[2] Recently an efficient enzymatic resolution of (±)-venlafaxine has been reported by Kochetkov et al.[3] We are interested to develop an asymmetric synthetic route for both the enantiomers of venlafaxine, as both the enantiomers have a role in its antidepressant activity [(+)-enantiomer inhibiting serotonin reuptake and the (−)-enantiomer inhibiting norepinephrine reuptake]. We thought that cyanohydrins generated from cyclohexanones and its analogues can be synthetically manipulated to both the enantiomers of venlafaxine (**1**). Our retrosynthetic scheme is outlined below (Scheme 1). The cyanohydrins are easily synthesized from the corresponding ketone by an enzymatic route applying (*S*)-hydroxynitrile lyase (HNL) from *Hevea brasiliensis* (*HbHNL*).[4] We have also decided to synthesize two venlafaxine analogues (**2** and **3**) by the same strategy.

For the synthesis of (*R*)-venlafaxine (**1**) we have started from cyclohexanone. Cyclohexanone is converted to its corresponding cyanohydrin (**4**) by an enzymatic transcyanation reaction with acetone cyanohydrin and *HbHNL* as the enzyme. Chemistry of the cyanohydrin formation by similar HNL is well established in our laboratory and elsewhere.[5,6] By applying a transcyanation protocol with acetone cyanohydrins as a cyanide source cyclohexanone cyanohydrin is synthesized on a 10 g scale by using crude the enzymatic extract of HNL from rubber tree (*Hevea brasiliensis*). The role of enzyme in this particular reaction is unique as the biocatalytic reaction is very fast and high yielding (almost quantitative conversion is achieved) than the corresponding chemical reaction. The biocatalytic reaction is also highly stereoselective in the case of cyanohydrins' formation from 4-methyl cyclohexanone (for synthesis of **3**), as it yields only one diastereomer (*syn* addition of CN ion; Me is equatorial). *Syn* addition of CN ion to cyclohexanone analogue by similar (*S*)-HNL is reported by Effenberger co-workers.[7] This fixes the alcohol functionality in axial and CN group in the equatorial position of the cyclohexane ring in the case of 4-methylcyclohexanone. The free hydroxyl group in compound **4** was protected as its EOM ether by treatment with EOM-Cl (ethoxymethyl chloride) with DIPEA (diisopropyl ethyl amine) to afford EOM-protected cyanohydrin **7** in a 90% yield. Addition of Grignard reagent (generated from 4-bromo anisole) on compound **7** followed by acidic work-up afforded ketone **10** in an 85% yield. Wittig reaction with ketone **10** and triphenylphosphonium methyl iodide in the presence of KOtBu afforded the olefin **13** in an 82% yield. Asymmetric hydroboration reaction with (−)-Ipc$_2$BH was

* Corresponding author.
E-mail address: snanda@chem.iitkgp.ernet.in (S. Nanda).

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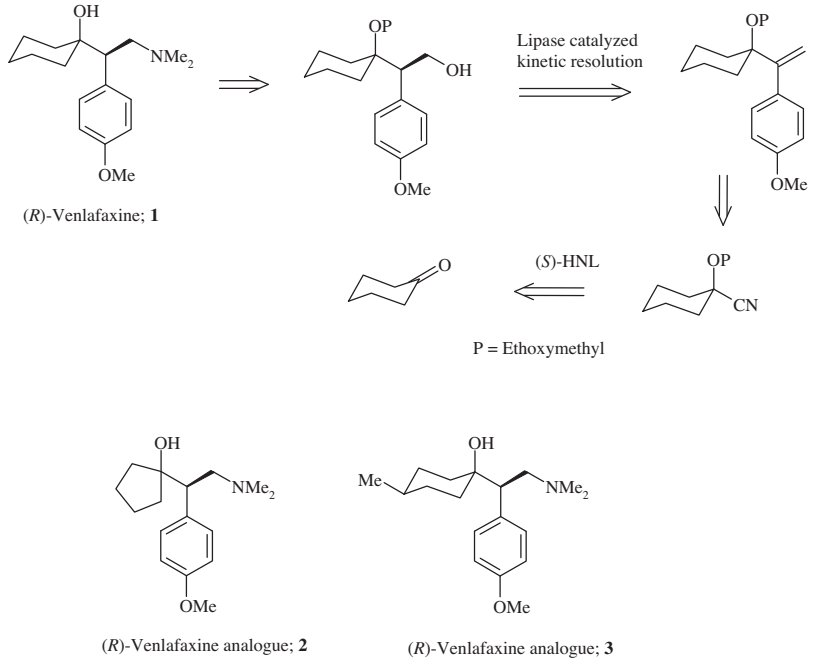
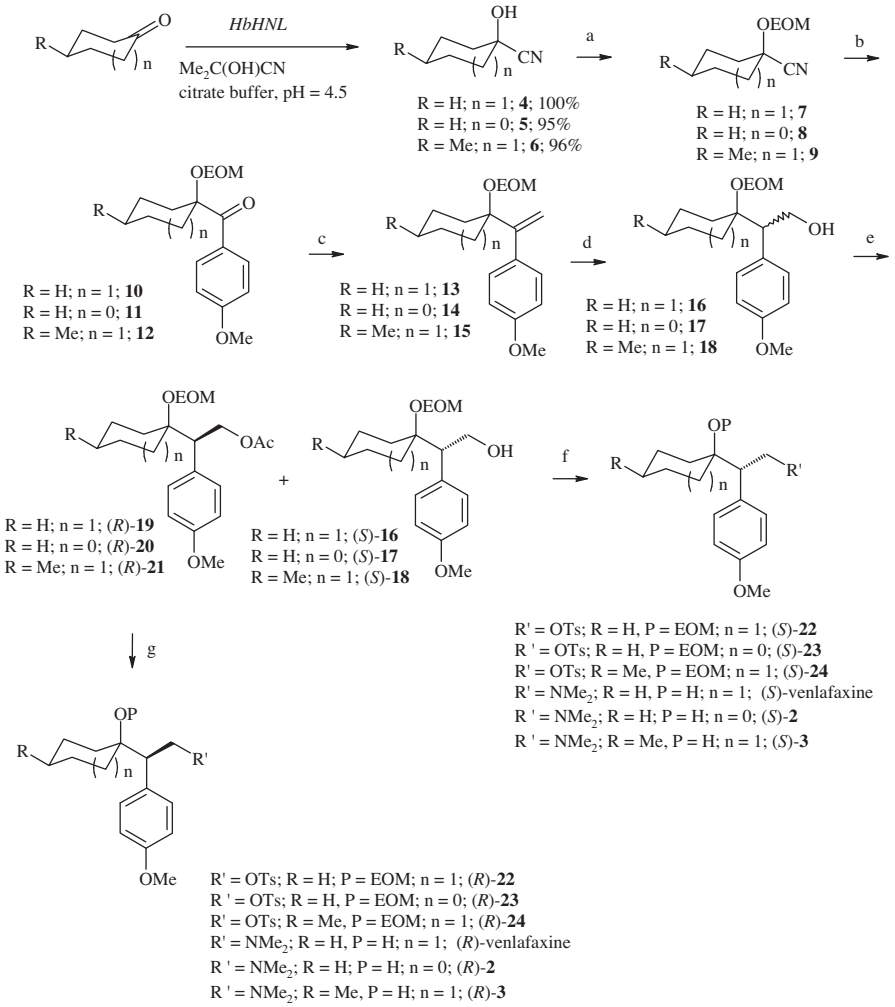


Scheme 1. Retrosynthetic analysis for (*R*)-venlafaxine and two of its structural analogues.



Scheme 2. Asymmetric synthesis of venlafaxine and its analogues: Reagents and conditions: (a) EOM-Cl, DIPEA, 90%; (b) *p*-$MeOC_6H_4MgBr$, 85%; (c) Ph_3P^+MeI, KOtBu, 82%; (d) $BH_3{\cdot}SMe_2$, KOH, H_2O_2, 84%; (e) $CH_2{=}CHOAc$, Lipase PS-D, MS 4 Å, 48%; (f) (i) *p*-TSCl, Et_3N, DMAP, 88%; (ii) Me_2NH, 80 °C, 48 h; (iii) PTSA, MeOH, 65% (over two steps); (g) (i) K_2CO_3, MeOH; then same reaction sequences as in f.

attempted at the beginning, to our dismay the enantioselectivity in the product alcohol was found to be very poor (only 20%).[8] In general none of the chiral boranes developed to date are efficient for the enantioselective hydroboration of 1,1-disubstituted olefins such as compound **13–15**. At this point we have decided to change our strategy and we thought to opt for the enzymatic kinetic resolution (EKR) strategy, which will allow the synthesis of both the enantiomers of venlafaxine in a straightforward way. Hydroboration of olefinic compound **13** with $BH_3{\cdot}SMe_2$ afforded the corresponding racemic hydroxymethylated compound **16** in an 84% yield. Compound **16** was subjected to lipase catalyzed EKR (transesterification with active ester) with vinyl acetate. Lipase PS-D (*Burkholderia cepacia*, lipase immobilized on diatomaceous earth) was found to be the best lipase in terms of enantioselectivity.[9] Subsequently the fast reacting enantiomer of compound **16** was converted to its (*R*)-acetate **19** (ee = 94%; yield = 48%) and the slow reacting enantiomer (ee = 95%; yield = 46%; *S*) was recovered after chromatographic separation. The absolute configuration was predicted by Kazlauskas empirical rule.[10]

Once the stereocenter has been fixed, the remaining steps in achieving the target molecules seem to be a routine affair. Compound (*S*)-**16** is converted to its corresponding tosylate derivative (*S*)-**22** by treatment with *p*-TsCl and Et_3N in an 88% yield. Reaction of (*S*)-**22** with dimethyl amine (Me_2NH, 40% aq solution)[11] in a closed vessel for 48 h at 80 °C followed by the removal of EOM group with PTSA (*para*-toluene sulfonic acid), afforded (*S*)-venlafaxine in a 65% yield (two steps, overall yield = 14% from cyclohexanone. Overall yield of venlafaxine analogue **2** is 10.2% from cyclopentanone and **3** is 12.8% from 4-methyl cyclohexanone). The optical rotation value of our synthesized venlafaxine matches well with the literature value, and that establishes the absolute configuration of our synthesized venlafaxine.[12] Deacetylation with K_2CO_3–MeOH and the similar reaction sequences as described above afforded (*R*)-venlafaxine from the (*R*)-acetate **19**. The venlafaxine analogues have also been synthesized by following similar reaction sequences from (*S*)-**17**/**18** and (*R*)-**20**/**21** (Scheme 2).

In conclusion, asymmetric synthesis of both enantiomers of antidepressant agent venlafaxine and two of its analogues has been reported here. The main highlight of our synthetic strategy was (*S*)-HNL catalyzed synthesis of cyanohydrins from cyclic ketones and lipase-PS catalyzed kinetic resolution for creation of the stereocenter. Novel synthetic studies for structurally similar analogues are currently underway in our laboratory.

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Supplementary data

Supplementary data (^1H and ^{13}C NMR spectra for all new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2012.02.025.

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