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A protecting group free and scalable approach towards total synthesis of (-)-venlafaxine

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A protecting group free asymmetric total synthesis of (-)-venlafaxine is reported. Strategy employs Sharpless epoxidation and regio-selective epoxide ring opening by *in situ* generated Gilman reagent as key steps. This paper reports 53% overall yield in 6 steps for total synthesis of (-)-venlafaxine.

Development of a number of nontricyclic antidepressants with reduced or completely diminished cardiovascular or anticholinergic liability has been reported[1] and they have provided impetus to treat depression.

Among those one of the most prescribed antidepressants is venlafaxine **1**, which is a unique drug with well documented efficacy and safety in the acute treatment of major depressive disorder.[2] It was first time released for clinical trials in 1994 by Wyeth, now part of Pfizer and is globally marketed as Effexor R®. It has now become widely recognised as an effective first line agent in the treatment of major depressive disorder (MDD), generalised anxiety disorders and comorbid indications in certain anxiety disorders for depression. It was a top selling drug from 2006 to 2008 and sixth most prescribed antidepressant in US in the year 2007. In 2010 it was 25th in top 200 brand name drugs by total US prescriptions.

Venlafaxine **1** is marketed in recemic form, although both *R* and *S* enantiomers show different bioactivities i.e. *S*-enantiomer is a selective serotonin reuptake inhibitor, while *R*-enantiomer is more selective towards the nor epinephrine transporter.[3] Also, it has no or little activity on a variety of neuroreceptors.[4]

In literature there are a number of syntheses of venlafaxine **1** reported[5] including few reports from this group[6] but for asymmetric total synthesis of either *R* or *S* venlafaxine there are only three reports available. Davies *et al*.[7] have reported an asymmetric synthesis of (+)-venlafaxine by efficient use of Rh-catalysed Mannich reaction as a key chirality inducing step while

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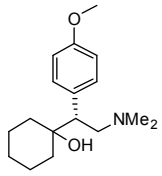
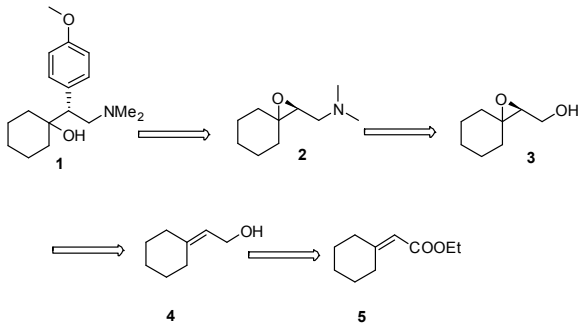


Figure1. Structure of (-)-venlafaxine

Nanda *et al*.[8] used enzymatic resolution as the key step for the synthesis of both *R* and *S* venlafaxine along with some of its analogs. Also Kochetkov *et al*.[9] have reported resolution of (±)-venlafaxine. Recently, we have reported a concise and novel route for asymmetric synthesis of (-)-venlafaxine **1** using environment friendly organocatalyst.[10]

In continuation of our interest in the development of newer synthetic methodologies towards venlafaxine **1**, we thought to synthesize an optically pure venlafaxine **1** by a more efficient, simple and practical approach by using Sharpless asymmetric epoxidation reaction as a chirality inducing tool. Literature survey also led us to think that there is a need of more concise and viable asymmetric route for venlafaxine **1**. The use of Sharpless asymmetric epoxidation reaction was taken advantage of, as both *R*-venlafaxine **1** as well as *S*-venlafaxine could be accessed by just switching tartarate ester ligands from D to L. More importantly, in the present work we have successfully avoided the use of protection-deprotection sequence, making the approach

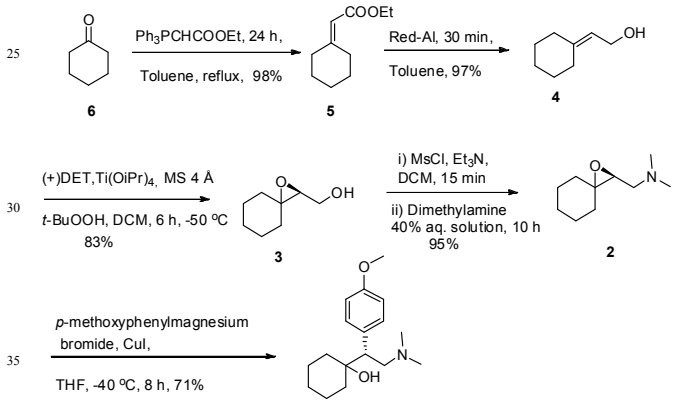


Scheme 1. Retrosynthetic analysis of (-)-venlafaxine.

more efficient with significant improvement in overall yield. In

view of potential use of venlafaxine in medicinal chemistry, we devised a novel synthetic route for the total synthesis of (+) and (-) venlafaxine **1** as outlined in retrosynthetic scheme 1.

In our retrosynthetic analysis, we envisioned that required stereochemistry for target molecule **1** can be generated by Sharpless asymmetric epoxidation reaction, followed by opening of epoxide **2** with Grignard reagent and hence inversion of stereogenic center to obtain target molecule **1**. The required epoxy alcohol **3** could be accessed from allyl alcohol **4**, which in turn can be obtained from commercially available *α,β*-unsaturated ester **5** or two-carbon Wittig product of cyclohexanone by selective ester reduction. Though unsaturated ester **5** is commercially available, the synthesis of (-)-venlafaxine **1** began from commercially available, inexpensive cyclohexanone **6**. Accordingly, carbonyl of cyclohexanone **6** was homologated with two carbons to convert it in to *α, β*-unsaturated ester **5** in 98% yield. This ester was subjected for the selective ester reduction. The reduction of unsaturated ester to allyl alcohol **4** was carried out by treatment with Red-Al (commercially known as vitride) in 97% yield. The crude allyl alcohol **4** obtained as very pure, was directly subjected for Sharpless asymmetric epoxidation reaction at -50 ^{o}C.[11]



Scheme 2 Total Synthesis of (-)-venlafaxine 1.

The asymmetric epoxidation gave 83% yield of epoxide and 85% ee, determined by chiral GC.[12] The epoxide **3** obtained was treated with methanesulphonyl chloride and triethyl amine at 0 ^{o}C for 15 min to obtain crude mesylate, which was subsequently subjected for amination in 40% aqueous dimethyl amine solution for 8-10 h at room temperature. The epoxy amine **2** was obtained in 95% yield over two steps and was subjected to nucleophilic epoxide opening.[13] This conversion was carried out by treatment with *p*-methoxyphenylmagnesium bromide in the presence of catalytic copper iodide at -40 ^{o}C for 8 h to afford (-)-venlafaxine **1** in 71% yield with ≥99% *ee*[14] after recrystallization in ethyl acetate. Spectral data and optical rotation for (-)-venlafaxine **1** were in good agreement with the data reported in literature.[3]

Present synthetic approach provides asymmetric synthesis of venlafaxine **1**, in a high overall yield (53%) in 6 steps from readily available, inexpensive starting material. In our approach, Sharpless asymmetric epoxidation reaction is a key chirality inducing step. Epoxide opening with Gilman reagent and selective ester reduction are other important reactions.

In conclusion, we have achieved a short, practical and scalable asymmetric total synthesis of (-)-venlafaxine **1** in a very efficient manner from commercially easily available, cheap starting material. In present synthesis column chromatographic purification can be avoided in all steps except at epoxidation and can be carried out at gram scale.

By using different enantiomers of tartarate ester in Sharpless asymmetric epoxidation reaction both the enantiomers of venlafaxine are accessible in a very concise manner.

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