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Asymmetric Synthesis of Anti-Convulsive Drug (*S*)-Vigabatrin®

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Abstract: An asymmetric synthesis of fully protected (*S*) - Vigabatrin® is described using Sharpless asymmetric aminohydroxylation and reductive elimination of α-oxy-β-amino carbonylhydrazone as key steps.

4-Aminobutanoic acid (γ-aminobutyric acid, GABA, **1**) is an important neurotransmitter in mamallian systems [1]. Several important neurological disorders such as Parkinson's disease [2], epilepsy [1] and Huntington's chorea [3] have been associated to a deficiency of GABA. The biochemical mechanisms responsible for these diseases, characterised by convulsive seizures, occur when GABA levels diminish below a certain threshold level in the brain [4], however, peripheral adminstration of GABA is ineffective due to it's low lipophilicity [5]. Alternatively, a more lipophilic compound that selectively inhibits GABA-transminase (GABA-T), the enzyme which degrades GABA to succinic semialdehydes [6], would block the degradation of GABA. One of the most effective and selective inhibitors of GABA-T is 4-amino-5-hexenoic acid (γ-vinyl GABA, Vigabatrin®) [7] **2** which is an important anticonvulsive drug marketed in racemic form as Sabril® [8]. Since the (*S*)-enantiomer is pharmacologically active [7a], the asymmetric synthesis of this drug is of current interest. Until now several syntheses of this compound have been published, most of them starting from natural amino acids [9].

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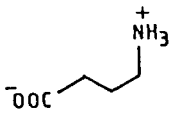
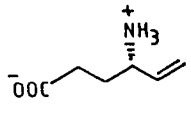
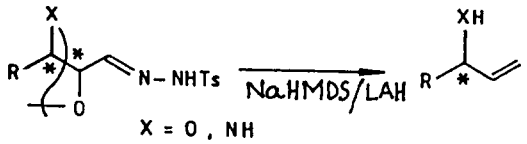


GABA 1



(S)-Vigabatrin 2

We have reported earlier an efficient methodology [10] for the preparation of enantiopure chiral allyl alcohols based on the reduction of α-oxy carbonyl hydrazones (equation-1).

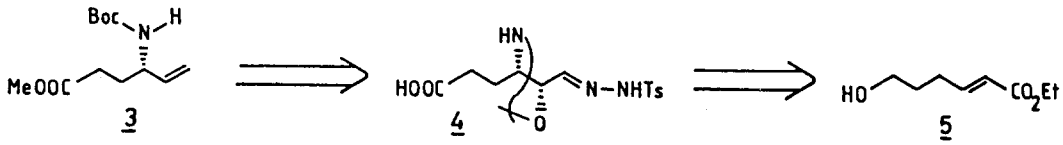


X = O, NH

(equation 1)

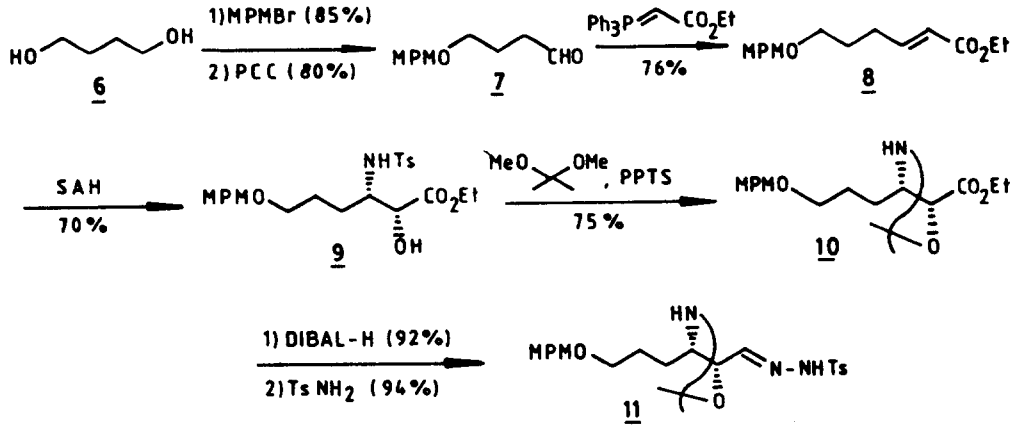
We would like to report now an asymmetric synthesis of fully protected enantiopure (*S*)-Vigabatrin®**2**, where the allyl amine moiety is obtained from α-oxy-β-amino carbonyl tosylhydrazone using our previously reported procedure and the carboxylic acid functionality could arise from the oxidation of primary alcohol as shown in scheme 1.

Scheme-1

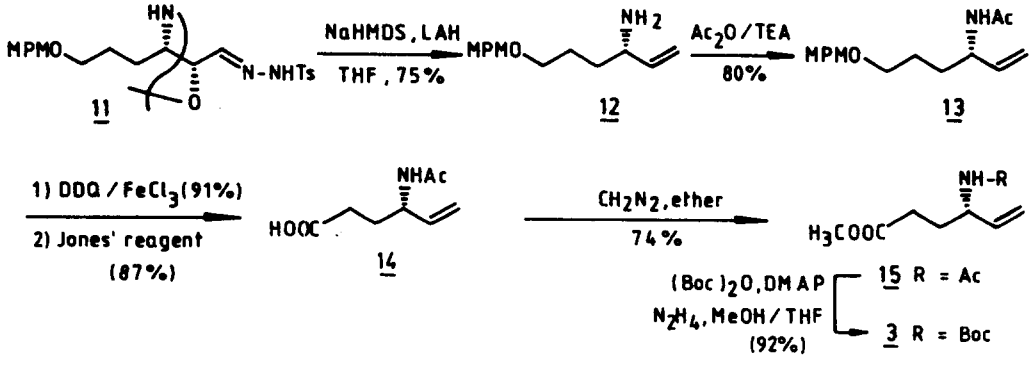


3 **4** **5**

In the present instance, the α,β-unsaturated *trans* ester **5** was prepared in 80 % yield from commercially available butane-1,4-diol **6**. Diol **6** was monoprotected with methoxy benzyl bromide which on oxidation with PCC gave aldehyde **7**. Aldehyde **7** was converted to the olefinic ester **8** by Wittig reaction with carboethoxymethylenetriphenylphosphorane in benzene. Optically enriched aminol **9** was obtained on employing the recently described Sharpless aminohydroxylation procedure [11] which shows an improvement of ee of the product up to 85 % after a single recrystallisation from petroleum ether : ether (8:2) mixture. Aminol **9** when treated with 2,2-dimethoxypropane and catalytic PPTS in toluene, resulted in the simultaneous cleavage of the *N*-Ts group as well as acetonation with the neighbouring hydroxy group, the reaction being recently explored by us [12]. The β-amino carbonylhydrazone **11** was obtained from **10** on DIBAL-H reduction of the ester to the corresponding aldehyde and its derivatisation with *p*-toluene sulphonylhydrazine.



The chiral hydrazone **11** was treated with NaHMDS and $LiAlH_4$ to obtain the allyl amine **12** in 75 % yield which was protected as acetate **13**. At this stage, the MPM group was deprotected using cat. DDQ/$FeCl_3$ [13] to the corresponding alcohol which on oxidation with Jones' reagent gave acid **14** in 60 % yield. The acid was esterified using ethereal diazomethane to furnish the fully protected (*S*)-Vigabatrin **15**. The enantiomeric purity was calculated by converting *N*-acetyl derivative to *N*-Boc Vigabatrin methyl ester [14] **3** having $[\alpha]_D$ = + 10.8° (c 1.5 in $CHCl_3$), $[\alpha]_D$ lit[9g] + 11.4° (c 1 in $CHCl_3$).



In conclusion, an asymmetric synthesis of (*S*)-Vigabatrin® has been realised using the Sharpless asymmetric aminohydroxylation as the source of chirality for the first time. The route described would also allow the synthesis of various stereoisomers by simple modifications.

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