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Vigabatrin Synthesis By Thermal Rearrangements

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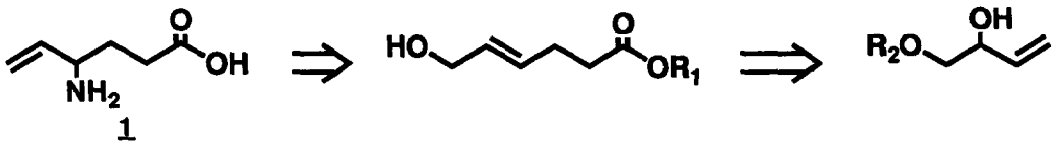
Abstract: Successive thermal reactions based on a Claisen and an Overman rearrangements furnish an original access to vigabatrin starting from erythritol.

Epilepsy is a disease characterized by convulsive seizures and may affect as much as one percent of the world population.[1] Low levels of the inhibitory neurotransmitter 4-aminobutanoic acid (GABA) in brain is a major factor linked with the epileptic phenomena.[2] Irreversible inhibition of GABA-transaminase (GABA-T, EC 2.6.1.19), the enzyme mainly responsible for GABA catabolism, led to the development of the very promising anticonvulsant drug, Sabril® **1**(R,S-4-amino-5-hexenoic acid, vigabatrin).[3]

Several synthesis of vigabatrin have been described so far based on either a Michael addition of propargylic anions followed by catalytic hydrogenation [3,4] or biscondensation of malonate anion on 1,4-dichloro-2-butene and aminolysis.[5] More recently asymmetric syntheses of the active enantiomer of vigabatrin starting from L-glutamic acid were described but they are unlikely to be acceptable for large scale production[6]. Therefore a short sequence based on successive thermal rearrangements would appear to be an attractive tool for scale up synthesis of the drug. A retrosynthetic analysis based on an Overman rearrangement to introduce the allylamine function and a Claisen rearrangement to introduce the carboxylic function, lead to 1,2-dihydroxy-3-butene as a starting material as shown below:



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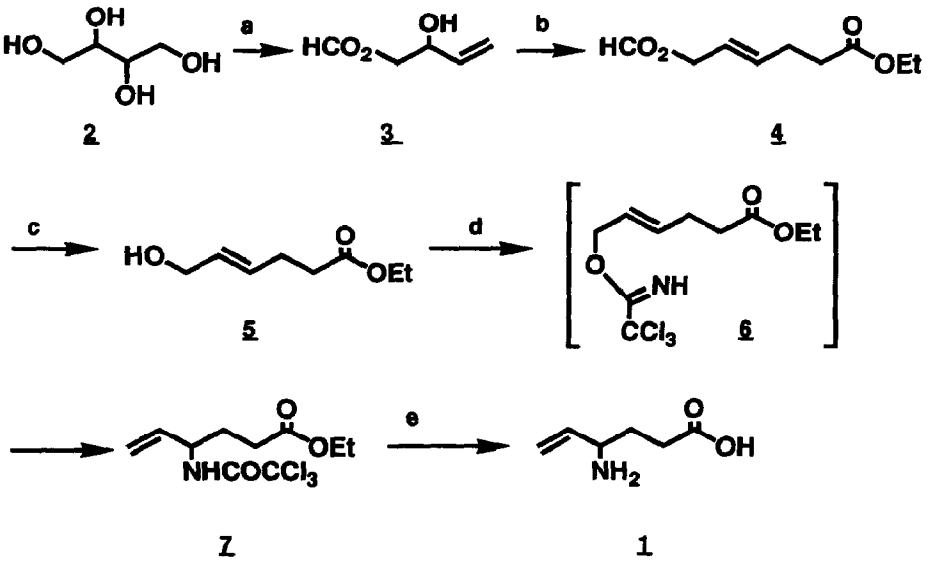
Among the various possibilities to form 3-butene-1,2-diol derivatives, the one using erythritol **2**, which could be obtained by periodate-oxidation followed by Raney nickel hydrogenation of potato starch in 55% yield[7], fulfils the requirement of a low cost starting material. The desired double bond of **3** was formed by reductive elimination (heating **2** in formic acid) and by distillation of the 1-formyloxy-2-hydroxy-3-butene (**3**) as described by Prévost.[8]

Subsequently the double bond was moved along the chain by a Claisen rearrangement concomitantly with the introduction of the ester function by heating **3** in ethyl orthoacetate[9] to give 6-formyloxy-4-hexenoic acid ethyl ester (**4**). This compound could be used for the next step without further purification.

The 6-formyl ester of **4** was hydrolysed in ethanol in the presence of a catalytic amount of HCl gas to give quantitatively the 6-hydroxy derivative **5** which was used immediately for the next step.

The amino function was then introduced by an Overman rearrangement[10] by heating the intermediate trichloromethyl imidate **6**, (obtained by in situ treatment of **5** with trichloroacetonitrile in the presence of a catalytic amount of NaH) to give the trichloroacetamido ethyl ester of vigabatrin **7** .

The vigabatrin hydrochloride was obtained by hydrolysis of the ester and the trichloroacetamide functions of **7** by heating in 6 N HCl. Chromatography on a resin column finally afforded the free aminoacid **1**.



a) 75% aq. HCO_2H, 12h 100°C then distillation, bp : 90°C/10mm Hg, 68%. b) excess $CH_3C(OEt)_3$ cat.propionic acid, 130°C, 2h, 58%. c) EtOH, cat. HCl gas, quanti. d) 0.1 eq.NaH CCl_3CN, ether, 0°C, 1h then 48h reflux in xylene, 65%. e) 6N HCl, reflux, 12h, quanti., then Dowex H^+, NH_4OH 1N and recristallisation in EtOH-H_2O, mp : 187°C[11].

In conclusion this thermal synthesis of vigabatrin offers an original alternative process to produce this drug in 25% overall yield starting from erythritol, using inexpensive reagents and reaction conditions.

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