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Stereoselective and efficient synthesis of (*S*)-pregabalin from D-mannitol

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Abstract—A straightforward synthesis of (*S*)-pregabalin in 28% overall yield starting from D-mannitol acetonide, as a primary source of chirality, is presented. The process is suitable for large-scale synthesis and involves simple and high-yielding chemical transformations as well as low-cost commercially available reagents.
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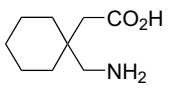
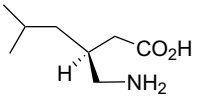
1. Introduction

(*S*)-Pregabalin (Lyrica®) **1** has been developed as a follow-up compound to gabapentin (Neurontin®) for the treatment of epilepsy, neuropathic pain, anxiety, and social phobia. (*S*)-Pregabalin displays a new mechanism of action and acts as a voltage-dependent calcium channel α2–δ subunit ligand. Both (*S*)-pregabalin and gabapentin are analogues of 4-aminobutyric acid (GABA), a neurotransmitter that is thought to play a major inhibitory role in the central nervous system. (*S*)-Pregabalin has been found to be useful in anticonvulsant therapy due to its activation of GAD (L-glutamic acid decarboxylase) promoting the production of GABA, which is released at 30% of the brain synapses.[1]



gabapentin



(*S*)-pregabalin, **1**

The pharmacological activity of **1** is primarily attributable to the (*S*)-enantiomer and thus, several methods have been developed to prepare (*S*)-pregabalin substantially free of the (*R*)-enantiomer.

The first methods, which were developed to prepare enantiomerically pure (*S*)-pregabalin **1**, involved the previous synthesis of a racemic mixture and subsequent resolution into the (*R*)- and (*S*)-enantiomers.[2] Different approaches using diastereomeric resolution have been described. One method starts with a Knoevenagel condensation of diethyl malonate with 3-methylbutanal, followed by the treatment with cyanide, decarboxylative hydrolysis, and hydrogenation to yield racemic pregabalin, which undergoes resolution with (*S*)-(+)-mandelic acid.[2,3] This route has the advantage of an inexpensive manufacturing process, but in this case undesired (*R*)-pregabalin cannot be efficiently recycled and is discarded as waste. Another procedure for the preparation of racemic pregabalin was patented by Warner–Lambert and comprises of the synthesis of 3-isobutylglutaric acid anhydride as a starting material. This compound is converted into racemic 3-carbamoylmethyl-5-methyl-hexanoic acid, which after resolution with (*R*)-(+)-1-phenylethylamine, yields the (*S*)-enantiomer. Finally, this compound undergoes a Hoffmann rearrangement to afford (*S*)-pregabalin, **1**.[4]

The current industrial process for the synthesis of (*S*)-pregabalin **1** was developed by Pfizer and involves an enzymatic resolution of racemic 2-(1-cyano-3-methylbutyl)malonic acid carried out by a lipase to give a mixture of the (*R*)-diester and the (*S*)-monoester potassium salt. The cyano group of the desired (*S*)-enantiomer is hydrogenated in water and the resulting compound is finally hydrolyzed and decarboxylated in water to afford **1**.[5]

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Alternatively, (*S*)-pregabalin **1** has been synthesized through different enantioselective routes that mostly comprise of the use of chiral auxiliaries or chiral catalysts. One approach to the preparation of **1** involves a chiral aluminum salen catalyst in the conjugate addition of trimethylsilyl cyanide to the corresponding precursor α,β-unsaturated imide.[6] While this route affords high enantiomeric purity, it shows practical limitations for large-scale synthesis because it employs expensive and sophisticated reagents. Another synthesis involves the asymmetric hydrogenation of 3-cyano-5-methylhexanoate with a rhodium Me–DuPHOS catalyst.[7] Other processes use chiral auxiliaries, such as (*S*)-phenylethyl amine[8] or Evans oxazolidinones[2] to obtain (*S*)-pregabalin in good enantiomeric excesses. Very recently, (*S*)-pregabalin has also been prepared via quinine-mediated desymmetrization of a cyclic anhydride,[9] and from a chiral γ-butyrolactone,[10] respectively.

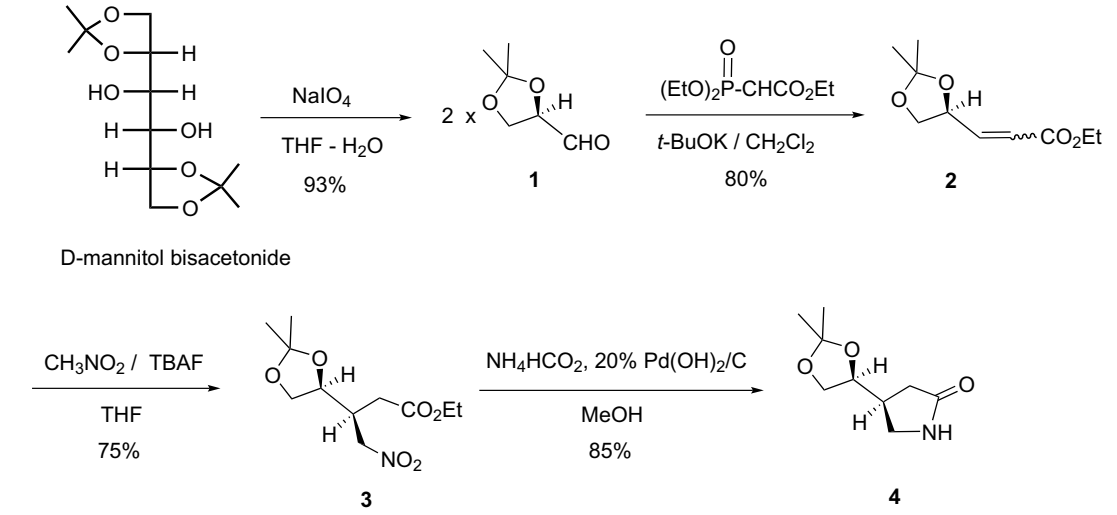
Nevertheless, despite the abundance of these processes to prepare (*S*)-pregabalin **1**, they are often unsuitable for multi-gram synthesis due to the high price of reagents and/or substrates, and the difficulty of some chemical manipulations regarding their intrinsic risk and the required equipment.[11]

Since (*S*)-pregabalin has been launched as a marketed pharmaceutical product, there is a need for an alternative, efficient, and cost effective process for its large-scale synthesis, which overcomes at least some of the disadvantages mentioned above.

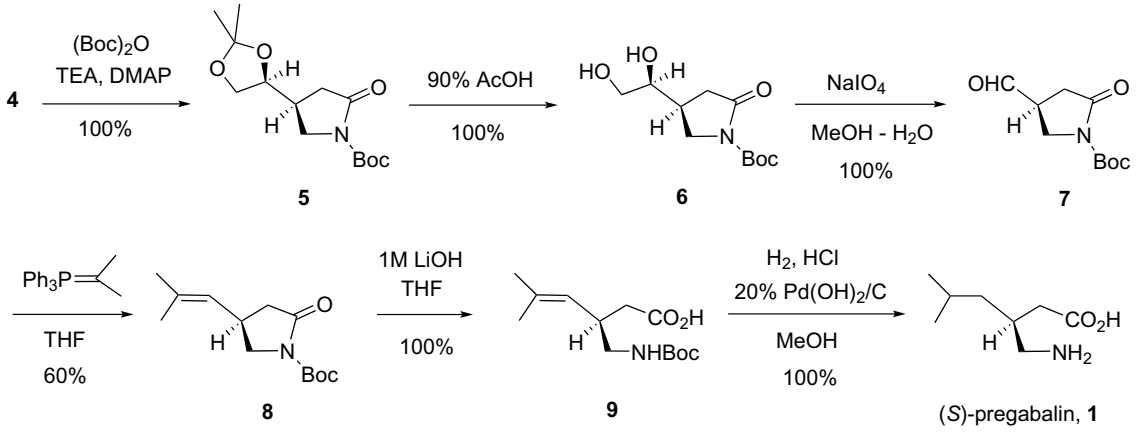
Herein, we report a new enantioselective process for the straightforward synthesis of (*S*)-pregabalin, **1**, starting from a polyfunctionalized oxazolidin-2-one prepared, in turn, from inexpensive D-mannitol acetonide. This compound is one of the components of the so-called chiral pool of natural products and has been widely used in the industrial synthesis of enantiomerically pure products.[12]

2. Results and discussion

Recently, Domingos et al. described the preparation of pyrrolidin-2-ones from a (*Z*)-enoate derived from D-mannitol. The key step was the stereoselective 1,4-addition of nitromethane to afford a nitroester that, upon reduction, gave lactam **4**.[13] In our laboratory, we have adapted this synthetic route in order to confer it with efficiency allowing the use of common reagents and simple processes. Thus,



Scheme 1.



Scheme 2.

the 1:9 (*Z*/*E*) mixture of enoates **2** was employed to prepare nitroester **3** that, once purified, was a single diastereoisomer obtained in 75% yield. Only trace amounts of a second diastereoisomer were detected in the ^{1}H NMR spectrum of the reaction crude. This excellent π-facial diastereoselectivity can be rationalized on the basis of the previously proposed models for the addition reactions of enoate **2** and related substrates with nucleophiles and diazoalkanes.[14] In turn, **2** was prepared by a Wadsworth–Emmons olefinization of D-glyceraldehyde acetonide, **1**, resulting from the oxidative cleavage of commercial D-mannitol acetonide (Scheme 1).[15] The nitro group was reduced by hydrogen transfer from ammonium formate using 20% $Pd(OH)_2$/C as a catalyst in refluxing methanol overnight.[14c] The formed amino ester cyclized in situ to provide lactam **4** in 85% yield.

In our synthesis of (*S*)-pregabalin, **1**, the intermediate lactam *N*-H was efficiently protected as a *N*-Boc derivative by the treatment of compound **4** with $(Boc)_2O$ in the presence of TEA and DMAP to quantitatively afford the *N*-Boc carbamate **5**, which is a novel compound (Scheme 2).

Subsequently, ketal protection was chemoselectively removed by the treatment of **5** with 90% AcOH providing diol **6** in 100% yield. The *N*-Boc protection was not altered under these mild conditions. Diol **6** was then oxidatively cleaved by $NaIO_4$ in MeOH–H_2O to give aldehyde **7**. The incorporation of the isopropyl group into the carbon backbone of the (*S*)-pregabalin precursors was achieved through a Wittig condensation of **6** with isopropylidenetriphenyl phosphorane leading to isobutenyl oxazolidin-2-one **8**. The lactam-ring was then opened by the reaction between **8** and 1 M LiOH in THF at room temperature, following the procedure described by Seebach et al. for a similar substrate[16] to quantitatively afford acid **9**, which is the direct precursor of (*S*)-pregabalin, **1**. The reduction of the C–C double bond and the hydrolysis of the *N*-Boc carbamate were carried out in one step by the hydrogenation of **9** over 20% $Pd(OH)_2$/C in ethanol, in the presence of aqueous HCl, under 6 atmospheres pressure at room temperature. In this way, enantiomerically pure (*S*)-pregabalin, **1**, $[\alpha]_D = +10.0$ (*c* 0.5, H_2O) {Lit.[2] $[\alpha]_D = +10.1$ (*c* 1.1 H_2O)} was obtained in six steps and 60% overall yield from oxazolidin-2-one **5**.

3. Conclusion

(*S*)-Pregabalin has been efficiently prepared in 10 synthetic steps from the chiral precursor D-mannitol acetonide. The performed reactions involve the use of inexpensive and commercially available reagents, as well as high-yield chemical transformations which are suitable for scaling-up the process.

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