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Multi-step synthesis strategies towards 1,2-amino alcohols with special emphasis on phenylpropanolamines

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ABSTRACT

Chiral vicinal amino alcohols are molecules with broad applications in the pharmaceutical as well as in the chemical industry. Due to their high potential, various multi-step chemical, chemo-enzymatic and enzymatic reaction synthesis strategies have been developed within the last decades. This review summarises the asymmetric synthetic routes towards vicinal amino alcohols in general and provides exemplary in-depth looks into multi-step phenylpropanolamine synthesis with special focus on recently published cascade approaches.

1. Introduction

The vast majority of pharmaceutical drugs and drug candidates contain amino groups or other functional groups which can be derived from amines. [1,2] These groups often introduce chirality which can have a major impact on the physiological functionality of these molecules. Since racemates are nowadays rated by the US Food and Drug Administration (FDA) as a composition of single isomers with independent physiological profiles, [3] there is a growing interest in the development of stereoselective synthesis strategies. [4–6]

A substantive subgroup within the broad field of amines is based on the functional motif of vicinal (often also referred to as 1,2-) amino alcohols. Those molecules can be found in a variety of different natural products and pharmaceutically active compounds. Currently, 82 compounds containing the amino alcohol motif are listed by the FDA as approved drugs. [7] Moreover, 119 are listed as "experimental drugs" meaning that although properties have been experimentally identified, the drug potential is not yet FDA approved. Another 23 amino alcohols are used as nutraceuticals e.g. in the food industry. [7] Selected examples are presented in Scheme 1.

In addition to the pharmaceutical interest, amino alcohols also find application as synthons and ligands or auxiliaries in organic synthesis. [8–11] Within SciFinder®, more than 350,000 reactions are currently listed with amino alcohols with secondary alcohols and primary amines function as reactants take place. This fact indicates the diverse potential of these compounds in the chemical industry.

In the following, different multi-step reaction strategies towards 1,2-amino alcohols are summarised. Enzyme catalysis, as part of the chemical platform, is nowadays used as a powerful tool for the synthesis of chiral compounds also in industrial scale applications. [12,13] Advantages of enzymatic catalysis, such as high regio-, chemo- and stereoselectivities and no protection and deprotection steps are well known and pointed out in many reviews. [13–16] Furthermore, enzymes are often active under mild reaction conditions, such as ambient temperature, atmospheric pressure, water as reaction media or physiological pH. However, if high selectivities can be reached, pure chemical reactions are often easily scalable. In this review on 1,2-aminoalcohol synthesis we distinguish between pure chemical, chemo-enzymatic and pure enzymatic multi-step reactions without rating one or the other method since advantages/disadvantages in e.g. purity, productivity, eco-efficiency or scalability need to be evaluated for the specific target. Exemplary, we present selected synthetic cascade reactions for all of these types on phenylpropanolamine synthesis in more detail.

2. General synthesis routes to vicinal amino alcohols

A number of chemical methods have been described for the synthesis of chiral vicinal amino alcohols (see Scheme 2). [8,9,17] Frequently used methods are for example based on functional group manipulation of molecules with two heteroatoms such as addition of nucleophiles to α-hydroxy imines or α-amino

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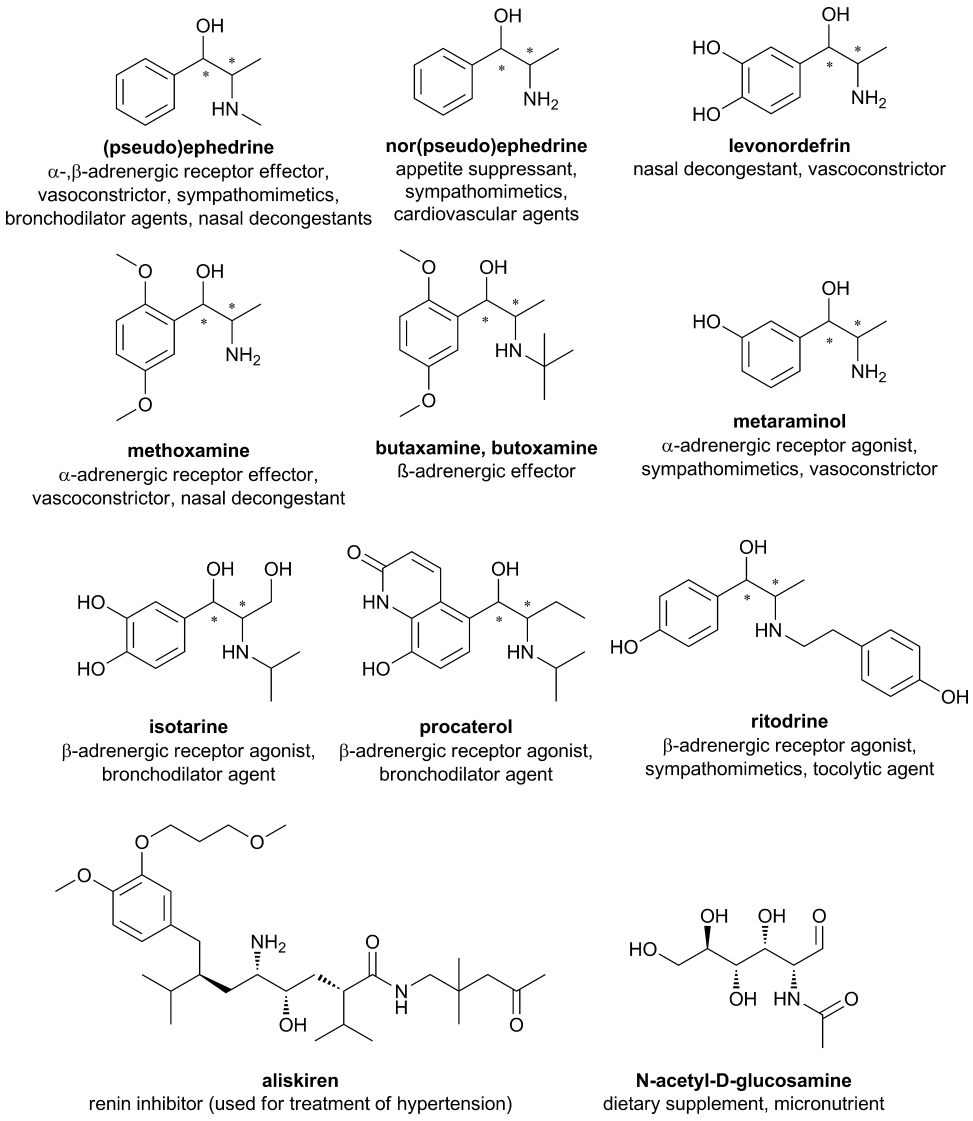
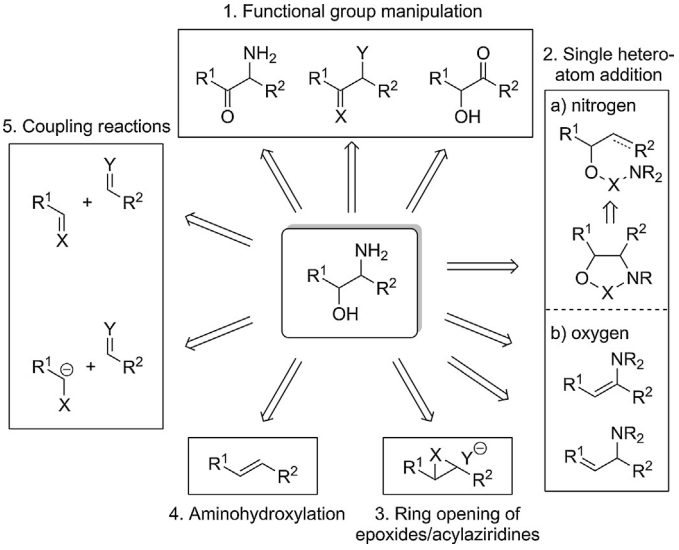


Scheme 1. Selected examples of pharmaceutically active compounds with vicinal amino alcohol motifs [7].



Scheme 2. Synthesis strategies for primary vicinal amino alcohols adapted from references [9,17].

aldehydes, reductive amination of α-hydroxy ketones and reduction of α-amino ketones (Scheme 2.1). Moreover, single heteroatom addition of nitrogen (Scheme 2.2.a – e.g. to allenyl carbamates or azidoformate) or of oxygen to α,β- and β,γ-unsaturated amines (Scheme 2.2.b) are known. In addition, ring opening of epoxides and acylaziridines (Scheme 2.3), Sharpless or Davies aminohydroxylation of olefins (Scheme 2.4) or coupling reactions (Scheme 2.5) have been described. [9,17]

Various enzymatic or chemo-enzymatic synthesis routes have also been published for the synthesis of chiral vicinal amino alcohols. In SciFinder, currently >38,000 syntheses towards products with a primary amino alcohol motif are listed containing at least one step referred to as "biotransformation". The strategies for such enzymatic or chemo-enzymatic 1,2-amino alcohol synthesis generally also follow the routes presented in Scheme 2. Some selected outstanding examples are described below in more detail.

The most famous amino alcohol synthesis strategy is probably the two-step synthesis of L-ephedrine which was patented by Hildebrandt and Klavehn in 1930 (Scheme 3). [18] In the initial reaction step, (*R*)-phenylacetylcarbinol is generated via fermentation with baker's yeast in the presence of benzaldehyde. Nowadays, it is known that a pyruvate decarboxylase is the responsible enzyme which catalyses the decarboxylation of pyruvate to acetaldehyde.