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# Variety of natural products derived from tryptophan and stereoselective synthesis of tetrahydro-β-carboline derivatives of pharmacological importance

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**Abstract.** The use of chiral inductors belonging to different classes of compounds is elaborated. Tetrahydro-β-carboline derivatives were constructed stereoselectively by the use of (*R*)-1-arylethylamine and L-amino acids. Asymmetric transfer hydrogenation was proven highly effective in enantioselective synthesis of several alkaloids. 

*Keywords:* Alkaloids; Biomimetic synthesis; Chirality transfer; Stereocontrolled synthesis; Organocatalysis; Metal complexes; Secondary metabolites; L-tryptophan

## 1. Introduction

One of the most challenging topics in modern organic chemistry is the synthesis of natural products. Despite the considerable exploration within this field to date, there is still a need for further development of alternative, preferably biomimetic and/or catalytic ways for preparation of bioactive compounds.

Among the numerous families of natural products, isoquinoline and β-carboline alkaloids seem to attract the biggest attention due to their abundant presence in plants and even in the

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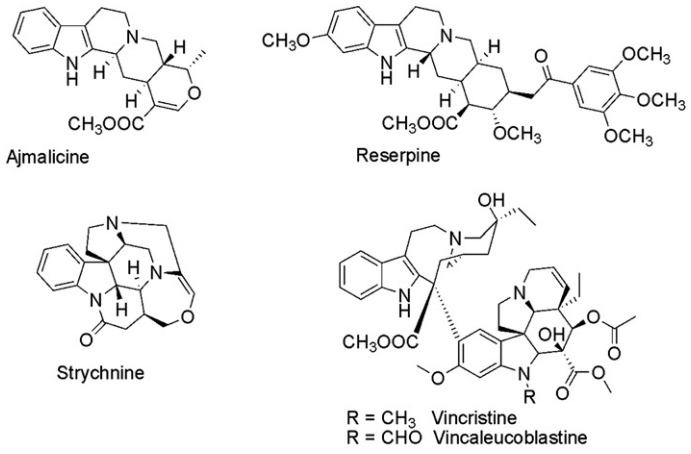
animal kingdom, along with their often important physiological activities [1]. Their bioactivity ranges from highly toxic, for example strychnine [2], to antihypertensive, for example ajmalicyne [3] and reserpine [4], and the cytotoxic activity shown by vincoleucoblastine and vincristine used for cancer chemotherapy [5,6]. All these medicinal alkaloids (Scheme 1) are basically indole derivatives formed from tryptamine provided by tryptophan and a terpenoid part provided by the iridoid glucoside secologanin. Tryptamine and secologanin are condensed to form stereoselectively strictosidine, which is the common precursor of all indole alkaloids [7]. The biodifferentiation of enantiomers together with clinical applications and regulatory pressure upon the pharmaceutical industry, constitute important reasons for the preparation of tetrahydroisoquinolines and of tetrahydro-β-carboline in their enantiomerically pure forms.

## 2. Stereoselective synthesis from popular chiral inductors

The tetrahydro-β-carboline skeleton is a common structural feature of numerous secondary metabolites, including *Vinca*-, *Rauwolfia*- and *Harman*-alkaloids. Many of these bases possess a tremendous value to pharmacology and were attractive synthetic targets for both academic and industrial research groups. In the synthesis of this class of compounds, the chirality on the C-1 carbon atom was often introduced by the use of chiral adjuvant in a stochiometric amount serving as a chiral building block or diastereoinducing auxiliary. All "classical" methods for tetrahydro-β-carboline framework formation were modified by the introduction of the stereochemistry source. The Pictet–Spengler, Bischler–Napieralski and the Pomeranz–Fritsch cyclizations gained the highest popularity [8]. Natural hydroxyacids constitute an important group of enantiopure compounds that have generated a tremendous impact on organic stereochemistry. Among them, tartaric and malic acids were most frequently used as cheap and relatively configurationally stable reagents available in both enantiomeric forms. They can be used as resolving agents, chiral building blocks, chiral auxiliaries and ligands for asymmetric transformations [9]. Surprisingly, the stereoselective synthesis of tetrahydroisoquinoline and β-carboline systems has not taken advantage of the




Scheme 1. Selected L-tryptophan secondary metabolites.