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Highly enantioselective synthesis of terutroban key intermediate via asymmetric hydrogenation☆

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ABSTRACT

A chiral (*R*) key intermediate of the biologically active form of terutroban has been prepared by asymmetric hydrogenation. The catalysts are based on very easily accessible ruthenium complexes modified by chiral phosphorous ligands. The use of the chiral catASium®T ligands family allowed us to realize this transformation efficiently in terms of yield and enantioselectivity (ee up to 92%) with high substrate/catalyst ratios.

RÉSUMÉ

Un intermédiaire clé chiral de configuration (*R*) correspondant à la forme biologiquement active du térutroban a été préparé par hydrogénation asymétrique. Les catalyseurs sont formés à partir de complexes du ruthénium aisément accessibles modifiés par des ligands phosphorés chiraux. L'utilisation des ligands chiraux de la famille des catASium®T permet de réaliser cette transformation très efficacement en termes d'activité et d'énantiosélectivité (ee jusqu'à 92 %), avec de hauts rapports substrat/catalyseur.

1. Introduction

Optically active amine scaffolds such as 2-aminotetraline derivatives are found in many biologically active molecules. This family of compounds provides very important intermediates for organic synthesis and members are present in drug candidates and pharmaceutical compounds (Fig. 1) [1]. Indeed, 2-aminotetraline derivatives have been reported to exhibit, for example, anti-inflammatory activity [2]. More, ST1214 [3] has been developed as a potent drug for cerebral ischemia and stroke. 7-OH-DPAT [4] was found to be a selective dopamine D3 receptor antagonist and CHF-1024 [5] is a compound endowed with DA2-dopaminergic/α2-adrenergic receptor antagonist activity in myocardial ischemia/reperfusion damage. Terutroban [6] is a thromboxane/prostaglandin endoperoxide receptor antagonist. The racemic sodium salt of terutroban (S18204) was described first in 1995 [7]. The synthesis includes a Diels–Alder reaction between the appropriate 2-pyrone and a properly substituted alkyne (Scheme 1) [8]. The optically pure (*R*) sodium salt of terutroban (S18886), which is the biologically active enantiomer, was obtained by chiral HPLC separation of enantiomers [8a].

Synthesis of optically pure 2-aminotetralines via asymmetric hydrogenation is a powerful and straightforward

☆ Thematic issue dedicated to François Garin.

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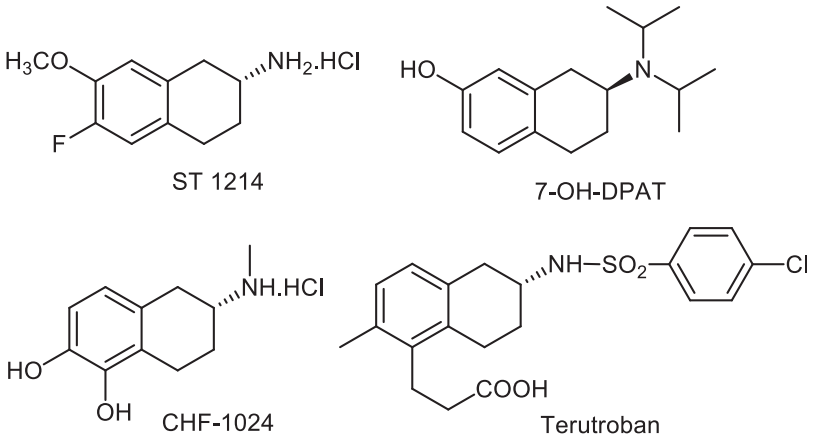
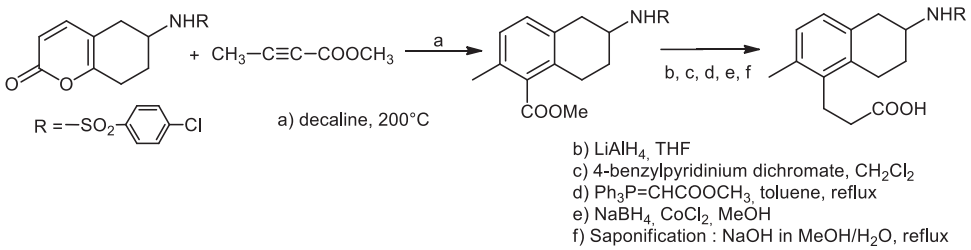


Fig. 1. Examples of chiral 2-aminotetralines based pharmaceutical compounds.



Scheme 1. Synthesis of racemic terutroban.

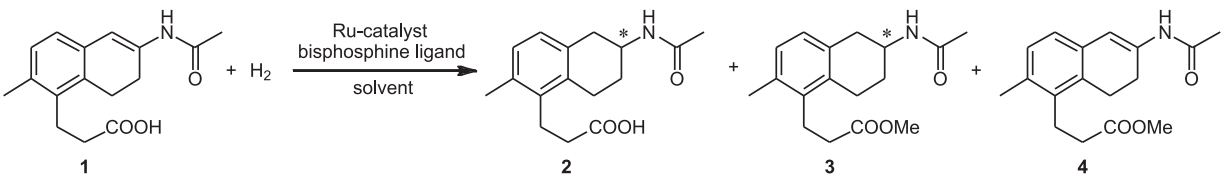
methodology. Different precursors to optically enriched 2-aminotetralines can be used such as imines [9], iminiums [10], enamines [11], enecarbamates [12], and enamides [13], in the presence of a large variety of catalysts based mainly on chiral organometallic complexes of rhodium, ruthenium, and iridium.

In order to obtain the optically enriched 2-aminotetraline scaffold of terutroban, direct asymmetric hydrogenation of a key intermediate is the most direct method. An enecarbamate precursor has been hydrogenated for that purpose as reported by Bruneau and Dixneuf (substrate/ruthenium catalyst = 100, 70% yield, 92% ee) [12]. In spite of this interesting result, the methodology suffers from low substrate/catalyst ratio, which limits its potential application.

As part of our ongoing research toward the use of catalyzed asymmetric transformations for the synthesis of biologically relevant targets [14], previously, we have also reported on the enantioselective access to chiral 2-aminotetraline derivatives and disclosed a highly selective synthesis of Amibregeon (SR58611A), a potent selective β3 adrenergic receptor agonist [15]. We thought to explore further the asymmetric hydrogenation of enamides to prepare a (*R*) optically enriched intermediate of terutroban.

2. Results and discussion

The enamide 3-(6-acetamido-2-methyl-7,8-dihydro-naphthalen-1-yl)propanoic acid **1** has been selected as substrate (Scheme 2). The latter was synthesized following a classical procedure by the condensation of acetamide with the corresponding cyclic ketone in the presence of *para*-toluenesulfonic acid as catalyst [12a,13b]. Then, in a typical hydrogenation experiment, either a commercially available ruthenium precatalyst was used or the catalyst precursor was prepared easily by mixing a ruthenium complex and the desired chiral phosphorous ligand in 15 mL of methanol under an inert atmosphere. In the latter case, the mixture was stirred at room temperature for 1 h before transfer into a double walled 50 mL stainless steel autoclave, which contained already substrate **1**. Then, the



Scheme 2. Hydrogenation of the 3-(6-acetamido-2-methyl-7,8-dihydronaphthalen-1-yl)-propanoic acid **1**.