Chemoenzymatic synthesis of orthogonally protected (3R,4R)- and (3S,4S)-trans-3-amino-4-hydroxypyrrolidines

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ABSTRACT

Several orthogonally protected racemic *trans*-3-amino-4-hydroxypyrrolidines have been easily prepared from *N*-Cbz-3,4-epoxypyrrolidine. Resolution of each racemic compound was accomplished by means of lipase-catalyzed aminolysis, transesterification or hydrolysis reactions. In most cases, the corresponding remaining substrates and the products were obtained with very high enantiomeric excesses.

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1. Introduction

The synthesis of optically active vicinal amino alcohols is a very important task for organic chemists in view of the fact that these compounds have been successfully used as chiral auxiliaries, ligands, and building blocks for complex molecules.[1] Furthermore, non-racemic pyrrolidines constitute key structural units found in a variety of bioactive natural products and drugs.[2] An excellent representative example combining both a vicinal amino alcohol moiety and a pyrrolidine ring is Voreloxin (1, Fig. 1), a first-in-class anticancer quinolone derivative, that is, currently completing phase two clinical trials in acute myeloid leukemia and platinum-resistant ovarian cancer.[3] Compound 1 is easily obtained by the coupling of the selectively protected pyrrolidine (3S,4S)-2 (Fig. 1) with the appropriate 7-chloro-1,8-naphthyridine derivative.[3a]

Some synthetic approaches aimed at preparing optically active (3S,4S)-2 include the resolution of (±)-3 with mandelic acid,[4] or the enzymatic resolution of the azido derivative (±)-4[5] as key steps (Fig. 1). In addition, the chiral pool synthesis of (3S,4S)-2 from D-isoascorbic acid has also been described through a 10-step strategy.[6]
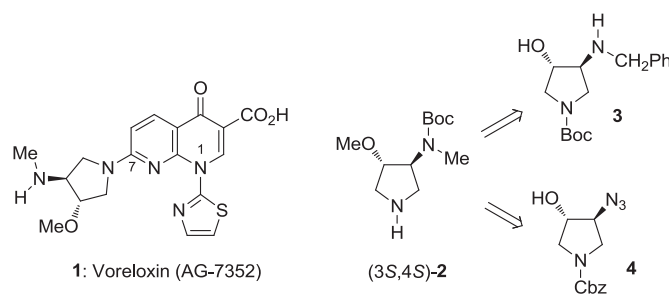

**Fig. 1.** Optically active pyrrolidine derivatives as precursors of Voreloxin.

As a part of our research on the chemoenzymatic synthesis of optically active functionalized heterocycles,[7] we planned the synthesis and enzymatic resolution of different orthogonally protected *trans*-3-amino-4-hydroxypyrrolidines[8] that can be used as precursors of the optically active pyrrolidine *trans*-2. The synthesis strategy reported here avoids the use of azide as a reagent and allows us to study the influence of the protecting group on the exocyclic nitrogen in the enzymatic resolution. Moreover, some of these optically active derivatives are also precursors of diastereomeric *cis*-4-amino-3-hydroxypyrrolidine,[9] which, in turn, has been used in the synthesis of biologically active pyrrolidine nucleotides.[10]

2. Results and discussion

2.1. Synthesis of orthogonally protected racemic *trans*-4-amino-3-hydroxypyrrolidine derivatives, and enzymatic aminolysis of (±)-7

We initially carried out the synthesis of racemic *trans*-3-(diallylamino)-4-hydroxypyrrolidine (±)-6 by opening the epoxide 5[7a] with diallylamine. The selection of diallylamine to incorporate the amine function at the 3-position of the pyrrolidine was based on the following reasons: (1) allyl groups are easily removed in the presence of other protecting groups, (2) the opening reaction affords a good yield, and (3) no side-products are formed.[11] Moreover, the presence of a bulky substituent adjacent to the secondary carbon bearing the hydroxyl group could favor the enzymatic resolution of this compound. As our aim in this study was also to investigate the influence of the protecting group on the exocyclic nitrogen, (±)-6 was converted into the unsubstituted amino alcohol (±)-7 by removal of the allyl groups with *N,N'*-dimethylbarbituric acid (NDMBA) in the presence of Pd(0)[11,12] (Scheme 1). In addition, (±)-7 was selectively *N*-acylated by treatment with vinyl acetate, and also converted into the *N*-Boc derivative (±)-9 by reaction with di-*tert*-butyl pyrocarbonate.
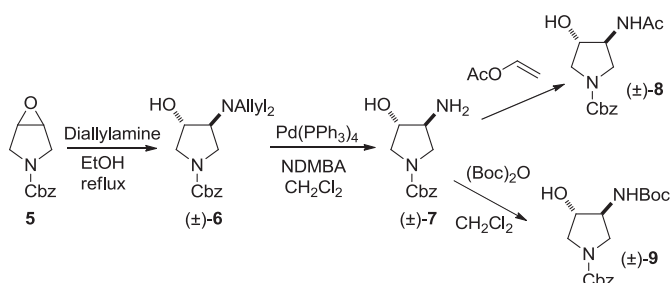
Scheme 1. Synthesis of some (±)-*trans*-3-amino-4-hydroxypyrrolidine derivatives.

Compound (±)-7 contains two groups—amino and hydroxyl—capable of being transformed by a lipase in aminolysis and transesterification reactions, respectively. Given that aminolysis requires less activated esters than transesterification, we started off by studying the aminolysis process. For this purpose, ethyl acetate was used as the acyl donor, and several enzymes [lipases A and B from *Candida antarctica* (CAL-A and CAL-B), lipase from *Burkholderia cepacia* (PSL-IM)], and solvents [*tert*-butyl methyl ether (TBME), toluene, and 1,4-dioxane] were tested. All the processes were carried out on a 25 mg scale monitoring the progress of each reaction by chiral-HPLC. Unfortunately, all the tested enzymes were poor catalysts. The best result is the one shown in Scheme 2. After 3 days of reaction at 30 °C, CAL-B catalyzed the selective acylation of the amino group of 7 (the degree of conversion was 45%), though with very low enantioselectivity (*E*=5).[13] In this process, the enzyme showed preference for the (3*S*,4*S*) enantiomer of the amino alcohol 7, contrary to what might be expected on the basis of Kazlauskas' rule.[14]
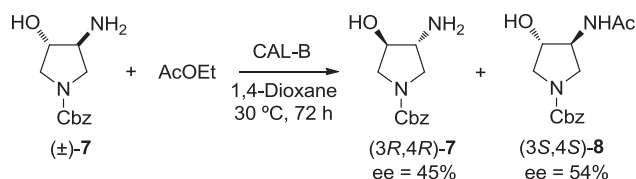

Scheme 2. CAL-B-catalyzed aminolysis of AcOEt with (±)-7.

2.2. Enzymatic transesterification of pyrrolidines (±)-6, (±)-8, and (±)-9

Resolution of the *N,N*-diallyl derivative (±)-6 via the transesterification reaction was attempted using vinyl acetate as the acyl donor and employing different lipase–solvent combinations. Initially, these reactions were carried out on a 25 mg scale; a selection of the results obtained is shown in Table 1. As can be seen, the solvent has a strong influence on both the enantioselectivity and the catalytic activity exhibited by CAL-B. This enzyme catalyzed the acetylation of 6 with very high enantioselectivity in TBME and 1,4-dioxane (Table 1, entries 2 and 8, respectively), though only the reaction in TBME was found to be of practical utility. Furthermore, PSL-IM showed very high enantioselectivity in all the tested solvents, and was found to be a more efficient catalyst than CAL-B in toluene and TBME. It is also of note the low catalytic activity exhibited by the PSL toward 6 in comparison with that shown in the transesterification, under analogues conditions, of (±)-*trans*-2-(diallylamino)cyclopentanol (after 3 h of reaction at 28 °C, the conversion degree was 50%; *E*>200).[11] This means that the benzyloxycarbonyl group on the pyrrolidinic nitrogen has a dramatical effect on the catalytic activity, but not on the enantioselectivity.

Table 1
Lipase-catalyzed transesterification of (±)-6[a]
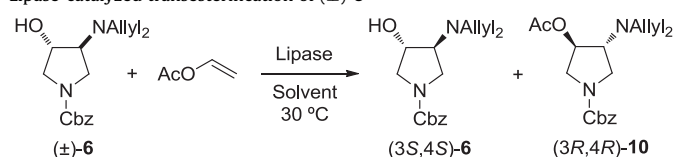
Entry	Enzyme	Solvent	t^b	ee$_S$ (%)[c]	ee$_P$ (%)[c]	c^d	E^e
1	CAL-A	TBME	1	4	29	12	2
2	CAL-B	TBME	3	57	99	37	>200
3	PSL-IM	TBME	3	92	99	48	>200
4	CAL-B	Toluene	5	18	91	17	26
5	PSL-IM	Toluene	5	42	>99	29	>200
6	CAL-B	THF	5	5	90	5	19
7	PSL-IM	THF	5	5	>99	5	>200
8	CAL-B	1,4-Dioxane	5	4	>99	4	>200
9	PSL-IM	1,4-Dioxane	5	4	>99	4	>200

[a] Reactions were carried out using 25 mg (entries 1, 2, 4–9) or 1.0 mmol (entry 3) of substrate. 5 equiv of vinyl acetate was employed in all cases.
[b] Reaction time (days).
[c] Determined by chiral-HPLC (see Section 4.12).
[d] The degree of conversion (%) was calculated from the enantiomeric excesses of the remaining substrate 6 (ee$_S$) and the product 10 (ee$_P$): c=ee$_S$/(ee$_S$+ee$_P$).
[e] See Ref. 13.

In view of the results included in Table 1, the best option to accomplish the resolution of (±)-6 is to use PSL-IM in TBME (Table 1, entry 3). In this case, both the remaining substrate (3*S*,4*S*)-6 and the product (3*R*,4*R*)-10 were isolated with very high enantiomeric excesses (ee≥92%) and yields (49 and 47%, respectively) after 3 days of reaction.

Some attempts to achieve the enantioselective transesterification of the acetamide derivative (±)-8 were unsuccessful. A drawback of these processes was the low solubility of the substrate in the usual organic solvents. After a screening of solvents, we decided to employ vinyl acetate both as acyl donor and solvent. Under these conditions, CAL-A and CAL-B catalyzed the reaction (a conversion degree of 20 and 39%, respectively, was obtained after 48 h of reaction at 30 °C), though with very low enantioselectivity (*E*=9). The reaction with PSL-IM was even less enantioselective. In these processes, CAL-A and CAL-B showed opposing enantiopreference,[15] although CAL-B preferentially catalyzed the acetylation of the (3*R*,4*R*) enantiomer (Scheme 3), as predicted by Kazlauskas' rule.