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Substrate engineering: Effects of different *N*-protecting groups in the CAL-B-catalysed asymmetric *O*-acylation of 1-hydroxymethyl-tetrahydro-β-carbolines

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ABSTRACT

In the frame of substrate engineering, the steric effect of different *N*-protecting groups on the enantioselectivity and reaction rate of CAL-B-catalysed (*S*)-selective *O*-acylation of *N*-protected 1-hydroxymethyl-tetrahydro-β-carbolines was investigated. Excellent enantioselectivities ($E > 200$) were observed when the acylation of *N*-Boc [(±)-**1**], *N*-Cbz [(±)-**3**], and *N*-Fmoc-protected [(±)-**4**] substrates was performed with the use of CAL-B and acetic anhydride in toluene at 60 °C. The resolution of *N*-acetyl-protected substrate (±)-**2** showed excellent *E* (>200) after 30 min, but as the reaction progressed, *E* started decreasing after 2 days, because of $N \rightarrow O$ and $O \rightarrow N$ acyl migrations. Preparative resolutions of (±)-**3** and (±)-**4** resulted in unreacted amino alcohols (*R*)-**3** and (*R*)-**4** and esters (*S*)-**7a** and (*S*)-**8a** with good enantiomeric excesses (≥88%) and high yields (≥44%).

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1. Introduction

Tetrahydro-β-carboline alkaloids such as vincristine, vinblastine[1] or reserpine[2] are well known about their valuable therapeutic effects (Fig. 1). Because of their potential biological activity, attention is focused on the isolation and synthesis of compounds with the tetrahydro-β-carboline core. Cytotoxic activities of callophycine A from *Callophycus oppositifolius*[3] or (3*S*)-tetrahydro-β-carboline-3-carboxylic acid from *Cichorium endivia*[4] were described. The anticancer effects of synthetic tricyclic[5] and benzimidazole-substituted tetrahydro-β-carbolines were also demonstrated.[6]

Enzymatic resolution of amino alcohols is well known in the literature. For instance, lipase-catalysed chemoselective *N*- or *O*-acylations of unprotected amino alcohols[7–9] were investigated and proved that the type of the reaction product (amide or ester) highly depended on chain length between the primary amino and primary or secondary hydroxyl group.[10–12] When the primary amino group was protected, enantioselective enzymatic resolutions were described.[13–18] For example, *in situ* *N*-protection and selective *O*-acylation were achieved, when acid anhydrides were used as acyl donors in the *Burkholderia cepacia* lipase-catalysed resolution of 2-amino-1-phenylethanols.[19] Bulkier protecting groups, such as *N*,*N*-diallyl or *N*-Boc, were applied successfully in the stereoselective acylation of *trans*-3-amino-4-hydroxypyrrolidine.[20] Application of the *N*-alkoxycarbonyl protecting group for the resolution of 2-amino alcohols was also described.[21] Enzymatic acylation of amino alcohols containing a secondary amino group has been less often described in the literature and in many cases *N*-protection was applied.[20,22–24] Many activated esters used commonly could not be applied as acyl donors because of undesired background reactions. This was the case in the resolution of 1-methyl-tetrahydroisoquinoline or salsolidine and, therefore, their lipase-catalysed *N*-acylation was performed with carbonate type acyl donors.[25–28]

Note that protecting groups can also behave as docking groups in enzymatic processes,[29] which can extend the substrate specificity of the enzyme. This concept was applied by Raadt et al. to increase the selectivity of biohydroxylation reactions of carboxylic acids, ketones, aldehydes, and alcohols having achieved good results by the use of chiral docking and protecting groups.[29] Docking/protecting group design coupled with substrate engineering was also utilized for the preparation of (*S*)-2-hydroxy-2-methylbutyric

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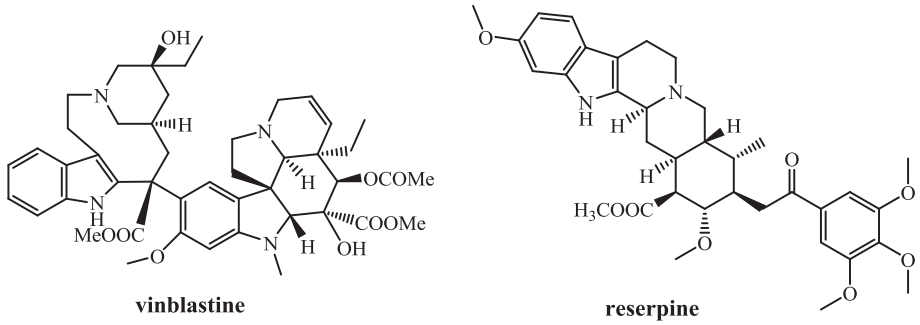


Fig. 1. Tetrahydro-β-carboline-core containing alkaloids.

acid in an enzymatic cyanohydrin reaction.[30] Substrate engineering supplemented with covalent immobilization was used to improve the catalytic activity and enantioselectivity (*E*) of the esterase enzyme in the hydrolytic resolution of (*R*,*S*)-mandelates.[31] The effect of the leaving alcohol moiety in CAL-B-catalysed transesterification of 2-bromobutyric esters was investigated by Silva et al.[32] They observed inversion of enantiopreference when ester-containing chiral alcohol moiety (*R*)-1-phenylethanol was applied instead of an achiral ordinary aliphatic alcohol. The effect of different *ortho*-, *meta*-, and *para*-substituted β-nitrostyrene derivatives on the Michael-type addition of acetaldehyde catalysed by 4-oxalocrotonate tautomerase was also investigated in the context of substrate engineering.[33] The substrate ketone was masked into enol to improve the stereoselectivity of hydroxynitrile lyase from *Hevea brasiliensis* for the preparation of 2-hydroxy-(4′-oxocyclohexyl)acetonitrile.[34] Enzyme and substrate engineering were used together for the synthesis of new fructooligosaccharides.[35] Results in a recently published article dealing with enzymatic hydrolysis of unactivated and activated β-lactams also underline the importance of substrate engineering.[36]

In this paper we aimed to investigate the stereochemical effect of different *N*-protecting groups [Boc (*tert*-butyloxycarbonyl), acetyl, Cbz (benzyloxycarbonyl), and Fmoc (9-fluoroenylmethyloxycarbonyl)] in the enzymatic *O*-acylation of 1-hydroxymethyl-1,2,3,4-tetrahydro-β-carboline [(±)-**10**]. This could allow us to develop a new approach for the enantioselective preparation of **10** through the use of the substrate engineering concept (Scheme 1).

2. Results and discussion

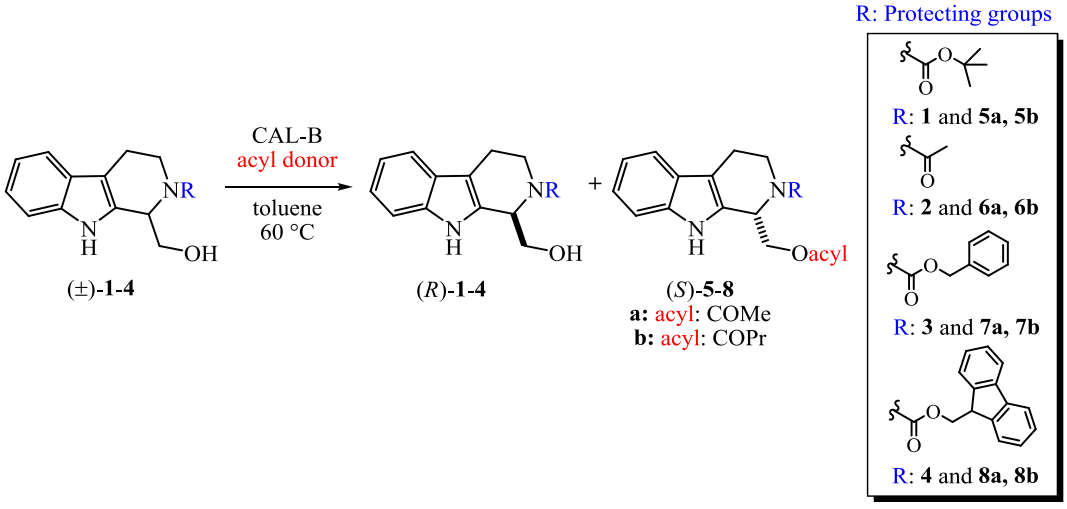
2.1. Synthesis of the starting compounds [(±)-*1*–(±)-*4*]

Racemic 1-hydroxymethyl-1,2,3,4-tetrahydro-β-carboline (±)-**10** was obtained by a Pictet–Spengler cyclisation of tryptamine hydrochloride and glycolaldehyde.[37] Besides Boc, three other commonly used protecting groups of different sizes, namely acetyl, Cbz, and Fmoc were selected for the protection of the secondary amino group of (±)-**10**. Derivatives of (±)-**10** with the *N*-Boc [(±)-**1**], *N*-acetyl [(±)-**2**],[38] *N*-Cbz [(±)-**3**], and *N*-Fmoc [(±)-**4**] protecting groups were synthesized by known methods (Experimental section).

2.2. Steric effects of various N-protecting groups on enzymatic O-acylation

2.2.1. Acylation of (±)-*1*

On the basis of our previous study on CAL-B-catalysed *O*-acylation of *N*-Boc-protected 1-hydroxymethyl-tetrahydro-β-carboline [(±)-**1**],[39] the resolution of (±)-**1** was first carried out with acetic anhydride as acyl donor in toluene at 60 °C (Table 1, entry 1). The relatively fast reaction (50% conversion after 30 min) afforded an excellent *E* (>200). Enantioselectivity (*E*) of an enzymatic transformation defines the changes of enantiomeric excesses (*ee*) of the remaining substrate (ee_s) and the product (ee_p) in function of conversion. Practically, it shows as how many times faster one enantiomer is transformed into product then the other one.[40,41] Next, vinyl acetate and 2,2,2-trifluoroethyl butyrate bearing a



Scheme 1. Effects of different *N*-protecting groups on the *O*-acylation of (±)-**1**-**4**.

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