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Diastereoselective formation of highly functionalised α-substituted amino acid derivatives via aldol addition

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Abstract

Highly diastereoselective aldol additions of (2*R*,4*S*)-3-*tert*-butyl 4-methyl 2-*tert*-butyloxazolidine-3,4-dicarboxylate (**1**) are reported. The utility of the highly substituted oxazolidines of type **1** for diastereoselective α-addition of the fully protected amino acid L-serine with achiral and chiral carbonyl compounds is demonstrated and the relative and absolute configuration of the aldol products are discussed on the basis of NOESY data and solid state structures of selected examples. The aldol products represent highly useful intermediates in the syntheses of sphingosine-related metabolites.

Keywords: Aldol; Myriocin; Diastereoselectivity

1. Introduction

The search for versatile stereoselective syntheses of α-substituted amino acids is an important task in natural product synthesis [1]. Our studies on sphingosines [2] lead us towards new synthetic routes for sphingosine-related metabolites with an α-substituted amino acid moiety such as myriocin [3], mycestericins [4], and sphingofungins (Fig. 1) [6]. Conformational properties of related *N*,*O*-acetals derived from the well known Garner's aldehyde prompted us to the principle of self-regeneration of stereocentres (SRS) as the method of choice for stereoselective aldol additions at the α-carbon of L-serine [7]. The necessary transient stereocentre can be achieved by forming oxazolidines of type **1** [8]. Alkylations of these highly substituted *N*-Boc protected oxazolidines (**1a/b**) resulted in very good diastereoselectivities with regeneration and inversion of stereocentres, respectively (Fig. 2) [6].

Recently, aldol additions of the Li-enolate of *N*-formyl protected oxazolidines to acetone and benzaldehyde resulted in one single stereoisomer, while with the more hindered benzophenone no adduct was formed at all [7,9]. Similarly, when the Li-enolate of *N*-benzyl-protected oxazolidine was added to isobutyraldehyde, the corresponding β-hydroxy amino ester was obtained after recrystallisation in 51% yield and >98% diastereomeric purity [10] and, when added to its corresponding aldehyde, predominantly one single adduct was observed [11]. Herein, we report our results of the studies of highly diastereoselective aldol additions of oxazolidine **1a** with achiral and chiral carbonyl compounds.

2. Results and discussion

In our alkylation studies with oxazolidines **1**, we usually obtained only the corresponding diastereomers **2a** or **2b** as alkylation product. The yields of the **2a** series were systematically lower than of the ones of the **2b** series indicating a different behaviour of **1a** and **1b** upon deprotonation and enolisation (Fig. 2) [6].

We utilised diastereomer **1b** with the less hindered α-proton, where deprotonation under basic conditions is favoured, for our aldol reactions with aliphatic or aromatic carbonyl compounds under standard conditions (Scheme 1)

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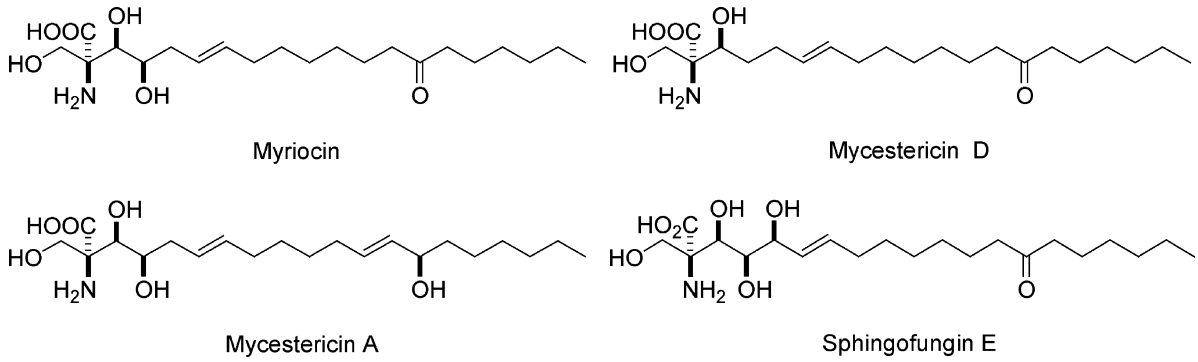


Fig. 1. Sphingosine-related metabolites.

[6,9]. Simple unbranched aldehydes such as valeraldehyde or hydrocinnamaldehyde reacted with high conversion (>90%) and low diastereoselectivity. We observed increased diastereomeric ratios (dr) accompanied by lowered conversion for isobutyraldehyde. Diastereoselectivity, but very low conversion, was also observed in the case of bulky pivalaldehyde.

The non-enolisable anisaldehyde, *p*-nitrobenzaldehyde, and benzaldehyde yielded the highest conversions and drs (Table 1). Aldol additions with long-chain aldehydes like 1-decanal, 1-octadecanal or ketones resulted in recovery of non-isomerised starting material.

Using specific conditions for reagent controlled stereoselection in the aldol addition of **1b** to hydrocinnamaldehyde did not improve the results: the product distribution **3a/b** changed only insignificantly [12]. A preference for the *syn* product **3b** was observed when we used alkali metal containing bases and best results were obtained with LDA and LICA, which may be explained with a minimally favoured five-membered ring transition state [13]. The diastereoselectivities were comparable, but clearly superior to the silazane bases such as NaHDMS or KHDMS. No selectivity was observed when we used Lewis acid/base tandems in CH_2Cl_2 (Table 2).

The pure *syn*- and *anti*-diastereomers of **3** and **4** were obtained in equimolar amounts after separation by chromatography, while **7a** was isolated as the sole product after recrystallisation according to NMR data. The corresponding crude mixtures did not contain further products, but traces of starting material were usually present. The relative structures of **3** and **4** were assigned from NOESY experiments and confirmed by an X-ray structure of the *anti*-diastereomer **3a** (Fig. 3). The ^{1}H NMR spectra of *syn*- and *anti*-diastereomers of both **3** and **4** show characteristic signals and the chemical shifts differ considerably. The β-methine proton at C1′ in the *syn*-isomer **3b** is shifted 0.67 ppm upfield.

When we used the reactive chiral aldehyde **10** [15] for the aldol addition to the chiral enolate of **1b**, we observed only the formation of one single product. Double stereodifferentiation gave the single *syn*-Felkin [16] diastereomer **12** in 20% yield while 50% of the starting material was consumed. The formed β-hydroxy ester is prone to retro-aldol reaction under the used conditions and slow decomposition of **12** was observed when storing at 5 °C (Scheme 2).

The relative configuration of **12** was assigned from NOESY experiments where we observed a correlation of the methyl protons of the Boc-groups and the methine proton at C1″. As predicted from the more favourable Zimmerman–Traxler [13] transition state **11a**, where the 1,3-dioxane ring of **10** adopts the axial position, this is only possible for

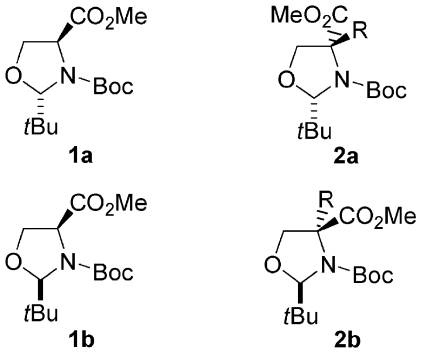
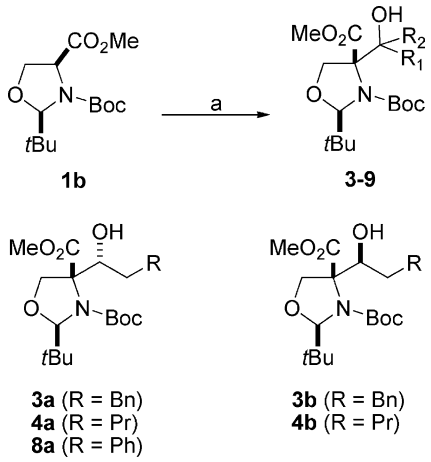


Fig. 2. Alkylation products (R = Me, allyl, benzyl, methyl bromoacetate).



Scheme 1.