

# Highly diastereoselective aldol additions to five-ring *N,O*-acetals

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**Abstract**—Highly diastereoselective aldol additions of pure (2*R*,4*S*)-2-*tert*-butyloxazolidinone-3,4-dicarboxylic acid 3-*tert*-butyl ester 4-methyl ester **1** are reported. While achiral carbonyl compounds lead to mixtures of diastereomers, the double stereodifferentiation of chiral aldehydes gave a single product isomer. The relative and absolute configurations of the aldol products were assigned by NOESY.

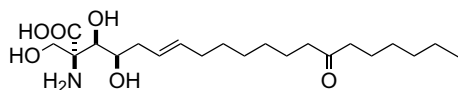
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In the course of our studies toward new synthetic routes for sphingosine<sup>1</sup> and structurally related but more elaborate metabolites like myriocin,<sup>2</sup> mycestericins,<sup>3</sup> and sphingofungins<sup>4</sup> we became interested in  $\alpha$ -substituted  $\beta$ -hydroxy amino acids.<sup>5</sup> As a strategy to obtain these compounds stereoselectively, we chose to utilize the principle of self-regeneration of stereocenters (SRS).<sup>6</sup> For our purposes, L-serine is the convenient starting material since it already contains all the necessary functionalities of the hydrophilic end of the above-mentioned metabolites. For stereoselective aldol addition at the  $\alpha$ -carbon of this particular amino acid, it is necessary to introduce a stereocenter transiently, which can be achieved by forming oxazolidines of type **1**.

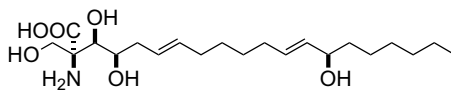
Recently, during synthetic studies for kaitocephalin, aldol reaction of the same compound with its corresponding aldehyde predominantly yielded one single adduct.<sup>9</sup>

We expected to obtain even better diastereoselectivities with highly substituted *N*-Boc protected *N,O*-acetals and, herein, report a new series of aldol products with regeneration of configuration at the original stereocenter.

The aldol reactions with *N,O*-acetal **1** and aliphatic or aromatic carbonyl compounds were carried out under standard conditions (Scheme 1).<sup>7</sup> Simple unbranched



Myriocin



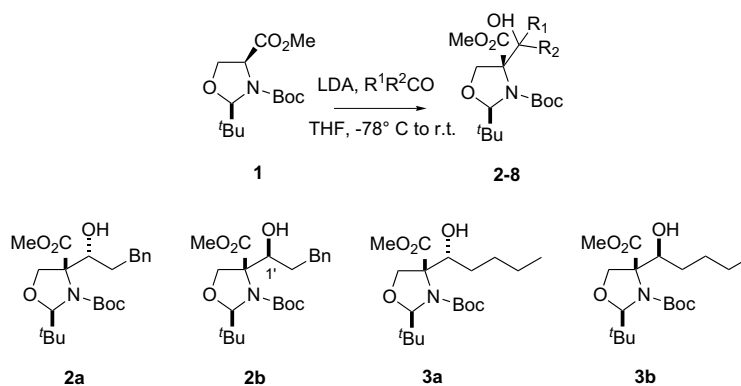
Mycestericin A

Aldol additions of the Li-enolate of *N*-formyl protected five-ring *N,O*-acetals to acetone and benzaldehyde resulted in one single isomer but with the more hindered benzophenone no adduct was formed at all.<sup>6,7</sup> When isobutyraldehyde was added to the Li-enolate of an *N*-benzyl-protected *N,O*-acetal, the corresponding  $\beta$ -hydroxy amino ester was obtained in >98% diastereomeric purity and 51% yield after recrystallization.<sup>8</sup>

aldehydes like valeraldehyde or hydrocinnamaldehyde reacted with high conversion (>90%) and low diastereoselectivity. We observed increased diastereomeric ratios (dr) for isobutyraldehyde, however, with lowered conversion. The more electrophilic anisaldehyde, *p*-nitrobenzaldehyde, and benzaldehyde yielded the highest drs (Table 1). Aldol additions with long-chain aldehydes like 1-octadecanal or ketones resulted in recovery of nonisomerized starting materials. The pure *syn*- and *anti*-diastereomers **2**<sup>10</sup> and **3**<sup>11</sup> from aldol reaction with hydrocinnamaldehyde and valeraldehyde were obtained in equimolar amounts after chromatographic separation. The crude mixtures did not contain further

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Scheme 1.

Table 1. Diastereoselectivity of aldol additions

Entry	Carbonyl compound	Conversion (%)	Product	<i>dr</i> <sup>a</sup>	
				<sup>1</sup> H NMR	HPLC
1	Hydrocinnamaldehyde	100	<b>2</b>	1/1	1/1
2	Valeraldehyde	95	<b>3</b>	3/2	1/1
3	Isobutyraldehyde	25	<b>4</b>	7/1	9/1
4	Pivalaldehyde	10	<b>5</b>	3/2	3/2
5	Anisaldehyde	95	<b>6</b>	10/1	—
6	Benzaldehyde	100	<b>7</b>	>23/1	1 isomer
7	<i>p</i> -Nitrobenzaldehyde	100	<b>8</b>	5/1	5/1

<sup>a</sup> *dr*: Diastereomeric ratio pure *syn*- and *anti*-diastereomers **2**<sup>10</sup> and **3**<sup>11</sup> from aldol reaction with hydrocinnamaldehyde and valeraldehyde.

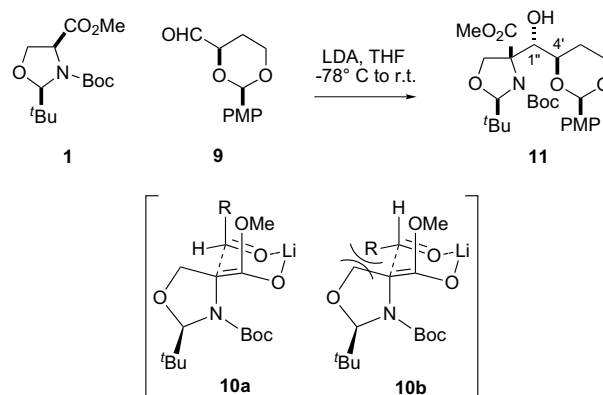
products according to NMR data, but traces of starting material (<10%) were usually present.

The <sup>1</sup>H NMR spectra of the *syn*- and *anti*-diastereomers of both **2** and **3** show characteristic signals and the chemical shifts differ considerably. The β-methine proton at C1' in the *syn*-isomer **2b** is shifted 0.67 ppm upfield.

Reagent controlled stereoselectivity is well known to direct product distributions.<sup>12</sup> However, diastereomeric ratios for *syn/anti*-products **2–8** improved only slightly when we used bases different from LDA. The increase in selectivity was often accompanied by a decrease in yield. Usually, a preference for the *syn*-product **2b** was observed when we used alkali metal containing bases, but for tin chloride the selectivity (*dr* 2/1) was in favor of the *anti*-product **2a**.

When we added the chiral enolate of **1** to the reactive chiral β-substituted aldehyde **9**<sup>13</sup> less than 50% of the starting material was converted, but we obtained only the single *syn*-Felkin diastereomer **11**<sup>14</sup> in 25% yield (Scheme 2).<sup>15</sup> The β-hydroxy ester **11** is prone to retro-aldol reaction under the reaction conditions used and slow decomposition of **11** was observed when stored at +5 °C.

The relative configuration of the *syn*-diastereomer **11** was assigned from NOESY experiments where an observed correlation of the methyl protons of the Boc-group and the methine proton at C1'' was indicative of



Scheme 2.

the 4*S*,1''*R*-configuration, the predicted product of the favorable Zimmerman–Traxler<sup>16</sup> transition state **10a**, although the 1,3-dioxane ring of **9** adopts the axial position. The close proximity of the aldehyde substituent and the methylene protons of **1** in **10a** favors the unusual conformation (Scheme 2).

In the aldol product **11**, the methine proton at C1'' splits in benzene-*d*<sub>6</sub> even at 60 °C into a doublet of doublets at δ 4.80 ppm with *J* = 7.0 Hz, which corresponds to a dihedral angle of ca. 30° for H–C4'–C1''–H,<sup>17</sup> and *J* = 2.6 Hz, which is characteristic for a long-range coupling in a fixed conformation in a condensed alicyclic system.<sup>18</sup>

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- (1'*S*,2*R*,4*R*)-2-*tert*-Butyl-4-(1-hydroxy-3-phenylpropyl)-oxazolidine-3,4-dicarboxylic acid 3-*tert*-butyl ester 4-methyl ester (**2b**): **1** (203.0 mg, 0.70 mmol) afforded **2b** as brown oil (79.0 mg, 26%). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 7.36–7.23 (m, 5H), 5.40 (br s, 1H), 5.23 (s, 1H), 4.38 (d, *J* = 9.6 Hz, 1H), 3.91 (m, 1H), 3.83 (s, 3H), 3.74 (d, *J* = 9.6 Hz, 1H), 3.05 (m, 1H), 2.80–2.68 (m, 1H), 2.07–1.86 (m, 2H), 1.53 (s, 9H), 0.96 (s, 9H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 171.2, 155.7, 141.9, 128.6, 128.5, 128.4, 128.3, 125.9, 99.4, 82.4, 75.2, 74.2, 52.6, 39.3, 32.7, 32.4, 28.2, 26.6. MS (EI) *m/z* 422 [M+H<sup>+</sup>], 364, 348, 322, 287, 265 (100%), 246, 231, 201, 186, 159, 145, 134, 101, 91, 79, 57. LCT-ES (g/mol) calcd: 444.2362 [M+Na<sup>+</sup>], found: 444.2377. *R*<sub>f</sub> 0.38 (Hex/EtOAc 4/1). [α]<sub>D</sub><sup>20</sup> –25 (*c* 1, CHCl<sub>3</sub>).
- (1'*R*,2*R*,4*R*)-2-*tert*-Butyl-4-(1-hydroxypropyl)-oxazolidine-3,4-dicarboxylic acid 3-*tert*-butyl ester 4-methyl ester (**3a**): **1** (100.9 mg, 0.35 mmol) afforded **3a** as brown oil (74.4 mg, 57%). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 5.00 (s, 1H), 4.51 (br s, 1H), 4.02 (dd, *J* = 8.8 and 1.0 Hz, 1H), 3.77 (s, 3H), 3.48 (br s, 1H), 1.39 (s, 9H), 1.60–1.20 (m, 6H), 0.97 (s, 9H), 0.86 (t, *J* = 7.6 Hz, 3H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 171.0, 153.1, 98.0, 81.1, 77.2, 71.3, 70.5, 52.6, 39.3, 28.9, 28.7, 26.5, 22.6, 14.1. MS (EI) *m/z* 316 [M–58<sup>+</sup>], 300, 259, 242, 231, 217 (100%), 198, 186, 157, 145, 130, 101, 86, 69, 57. LCT-ES (g/mol) calcd: 396.2362 [M+Na<sup>+</sup>], found: 396.2364. *R*<sub>f</sub> 0.49 (Hex/EtOAc 4/1). [α]<sub>D</sub><sup>20</sup> +13 (*c* 1, CHCl<sub>3</sub>).
- (1'*S*,2*R*,4*R*)-2-*tert*-Butyl-4-(1-hydroxypropyl)-oxazolidine-3,4-dicarboxylic acid 3-*tert*-butyl ester 4-methyl ester (**3b**): **1** (100.9 mg, 0.35 mmol) afforded **3b** as brown oil (40.2 mg, 31%). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ (rotamers) 5.20 (s, 1H), 4.41 (d, *J* = 9.6 Hz, 1H), 3.89–3.82 (m, 2H), 3.78 (s, 3H), 1.54 (m, 1H), 1.49 (s, 9H), 1.48–1.20 (m, 6H), 0.92 (s, 9H), 0.88 (t, *J* = 7.2 Hz, 3H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 171.5, 155.7, 99.5, 82.3, 78.0, 75.3, 74.5, 52.6, 39.4, 30.9, 30.1, 29.7, 26.6, 22.6, 13.9. MS (EI) *m/z* 316 [M–58<sup>+</sup>], 300, 260, 231, 217 (100%), 198, 174, 156, 145, 113, 101, 85, 57. LCT-ES (g/mol) calcd: 396.2362 [M+Na<sup>+</sup>], found: 396.2350. *R*<sub>f</sub> 0.37 (Hex/EtOAc 4/1). [α]<sub>D</sub><sup>20</sup> –45 (*c* 1, CHCl<sub>3</sub>).
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