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

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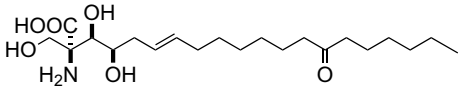
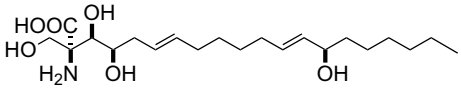
Abstract—Highly diastereoselective aldol additions of pure (2*R*,4*S*)-2-*tert*-butyloxazolidinone-3,4-dicarboxylic acid 3-*tert*-butyl ester 4-methyl ester **1** are reported. While achiral carbonyl compounds lead to mixtures of diastereomers, the double stereodifferentiation of chiral aldehydes gave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

In the course of our studies toward new synthetic routes for sphingosine[1] and structurally related but more elaborate metabolites like myriocin,[2] mycestericins,[3] and sphingofungins[4] we became interested in α-substituted β-hydroxy amino acids.[5] As a strategy to obtain these compounds stereoselectively, we chose to utilize the principle of self-regeneration of stereocenters (SRS).[6] 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 α-carbon of this particular amino acid, it is necessary to introduce a stereocenter transiently, which can be achieved by forming oxazolidines of type **1**.



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.[6,7] When isobutyraldehyde was added to the Li-enolate of an *N*-benzyl-protected *N,O*-acetal, the corresponding β-hydroxy amino ester was obtained in >98% diastereomeric purity and 51% yield after recrystallization.[8]

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

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).[7] Simple unbranched 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**[10] and **3**[11] 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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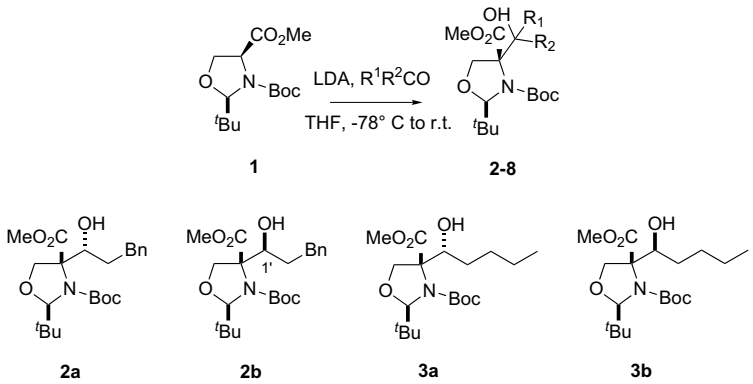


Scheme 1.

Table 1. Diastereoselectivity of aldol additions

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

[a] *dr*: Diastereomeric ratio pure *syn*- and *anti*-diastereomers **2**[10] and **3**[11] from aldol reaction with hydrocinnamaldehyde and valeraldehyde.

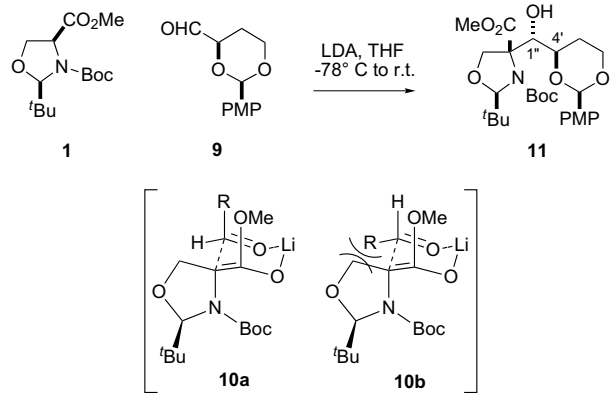
products according to NMR data, but traces of starting material (<10%) were usually present.

The ^{1}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.[12] 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**[13] less than 50% of the starting material was converted, but we obtained only the single *syn*-Felkin diastereomer **11**[14] in 25% yield (Scheme 2).[15] 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[16] 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_6 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,[17] and $J = 2.6$ Hz, which is characteristic for a long-range coupling in a fixed conformation in a condensed alicyclic system.[18]

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References and notes

1. (a) Koskinen, P. M.; Koskinen, A. M. P. *Synthesis* **1998**, 1075–1091; (b) Koskinen, P. M.; Koskinen, A. M. P. *Methods Enzymol.* **1999**, *311*, 458–479.
2. (a) Kluepfel, D.; Bagli, J.; Baker, H.; Charest, M.-P.; Kudelski, A.; Sehgal, S. N.; Vézina, C. *J. Antibiot.* **1972**, *25*, 109–115; (b) Aragozzini, F.; Manachini, P. L.; Craveri, R.; Rindone, B.; Scolastico, C. *Tetrahedron* **1972**, *28*, 5493–5498; (c) Fujita, T.; Inoue, K.; Yamamoto, S.; Ikumoto, T.; Sasaki, S.; Toyama, R.; Chiba, K.; Hoshino, Y.; Okumoto, T. *J. Antibiot.* **1994**, *47*, 208–215.
3. (a) Sasaki, S.; Hashimoto, R.; Kiuchi, M.; Inoue, K.; Ikumoto, T.; Hirose, R.; Chiba, K.; Hoshino, Y.; Okumoto, T.; Fujita, T. *J. Antibiot.* **1994**, *47*, 420–433; (b) Fujita, T.; Hamamichi, N.; Kiuchi, M.; Matsuzaki, T.; Kitao, Y.; Inoue, K.; Hirose, R.; Yoneta, M.; Sasaki, S.; Chiba, K. *J. Antibiot.* **1996**, *49*, 846–853.
4. (a) VanMiddlesworth, F.; Giacobbe, R. A.; Lopez, M.; Garrity, G.; Bland, J. A.; Bartizal, K.; Fromtling, R. A.; Polishook, J.; Zweerink, M.; Edison, A. M.; Rozdilsky, W.; Wilson, K. E.; Monaghan, R. L. *J. Antibiot.* **1992**, *45*, 861–867; (b) Horn, W. S.; Smith, J. L.; Bills, G. F.; Raghoobar, S. L.; Helms, G. L.; Kurtz, M. B.; Marrinan, J. A.; Frommer, B. R.; Thornton, R. A.; Mandala, S. M. *J. Antibiot.* **1992**, *45*, 1692–1696.
5. For recent reviews, see: (a) Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **1998**, *9*, 3517–3599; (b) Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2000**, *11*, 645–732.
6. Seebach, D.; Sting, A. R.; Hoffmann, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2708–2748.
7. (a) Seebach, D.; Aebi, J. D. *Tetrahedron Lett.* **1984**, *25*, 2545–2548; (b) Seebach, D.; Aebi, J. D.; Gander-Coquoz, M.; Naef, R. *Helv. Chim. Acta* **1987**, *70*, 1194–1216.
8. Corey, E. J.; Reichard, G. A. *J. Am. Chem. Soc.* **1992**, *114*, 10677–10678.
9. Loh, T.-P.; Chok, Y.-K.; Yin, Z. *Tetrahedron Lett.* **2001**, *42*, 7893–7897.
10. (1′*R*,2*R*,4*R*)-2-*tert*-Butyl-4-(1-hydroxy-3-phenylpropyl)-oxazolidine-3,4-dicarboxylic acid 3-*tert*-butyl ester 4-methyl ester (**2a**): **1** (203.0 mg, 0.70 mmol) afforded **2a** as a solid (76.0 mg, 25%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.29–7.15 (m, 5 arom. H), 5.05 (br s, 1H), 4.60–4.55 (br m, 2H), 4.10 (dd, $J = 8.4$ and 9.2 Hz, 1H), 3.76 (s, 3H), 3.59 (br s, 1H), 2.95 (br m, 1H), 2.66 (br m, 1H), 1.90 (br m, 1H), 1.49–1.23 (br m, 10H), 1.00 (s, 9H). ^{13}C NMR (benzene-d_6, 100 MHz) δ 174.6, 153.3, 142.5, 129.3–127.9, 126.2, 98.4, 80.9, 70.9, 70.4, 52.2, 39.8, 32.9, 32.1, 28.0, 26.9, 25.0. MS (EI) m/z 422 [M+H$^+$], 364, 322, 264 (100%), 231, 186, 130, 101, 91, 57. HRMS (EI) calcd: 420.2408 [M−H$^+$], found: 420.2385. R_f 0.43 (Hex/EtOAc 4/1). $[\alpha]_D^{20}$ +49 (c 1, $CHCl_3$).
(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%). ^{1}H NMR ($CDCl_3$, 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). ^{13}C NMR ($CDCl_3$, 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$^+$], 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$^+$], found: 444.2377. R_f 0.38 (Hex/EtOAc 4/1). $[\alpha]_D^{20}$ −25 (c 1, $CHCl_3$).
11. (1′*R*,2*R*,4*R*)-2-*tert*-Butyl-4-(1-hydroxypentyl)-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%). ^{1}H NMR ($CDCl_3$, 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). ^{13}C NMR ($CDCl_3$, 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$^+$], 300, 259, 242, 231, 217 (100%), 198, 186, 157, 145, 130, 101, 86, 69, 57. LCT-ES (g/mol) calcd: 396.2362 [M+Na$^+$], found: 396.2364. R_f 0.49 (Hex/EtOAc 4/1). $[\alpha]_D^{20}$ +13 (c 1, $CHCl_3$).
(1′*S*,2*R*,4*R*)-2-*tert*-Butyl-4-(1-hydroxypentyl)-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%). ^{1}H NMR ($CDCl_3$, 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). ^{13}C NMR ($CDCl_3$, 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$^+$], 300, 260, 231, 217 (100%), 198, 174, 156, 145, 113, 101, 85, 57. LCT-ES (g/mol) calcd: 396.2362 [M+Na$^+$], found: 396.2350. R_f 0.37 (Hex/EtOAc 4/1). $[\alpha]_D^{20}$ −45 (c 1, $CHCl_3$).
12. Van Draanen, N. A.; Arseniyadis, S.; Crimmins, M. T.; Heathcock, C. H. *J. Org. Chem.* **1991**, *56*, 2499–2506.
13. Blakemore, P. R.; Kim, S.-K.; Schulze, V. K.; White, J. D.; Yokochi, A. F. T. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1831–1847.
14. (1″*R*,2*R*,2′*R*,4′*R*,4*R*)-2-*tert*-Butyl-4-{hydroxy-[2-(4-methoxyphenyl)-[1,3]dioxan-4-yl]methyl}-oxazolidine-3,4-dicarboxylic acid 3-*tert* butyl ester 4-methyl ester (**11**): **1** (70.2 mg, 0.24 mmol) afforded **11** as a brown oil (25 mg, 20%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35 (d, $J = 4.2$ Hz, 2 arom. H), 6.83 (d, $J = 4.2$ Hz, 2 arom. H), 5.40 (s, 1H), 4.89 (br s, 1H), 4.55 (br s, 1H), 4.30 (br d, $J = 8.8$ Hz, 1H), 4.26 (ddd, $J = 11.4/4.6/1.0$ Hz, 1H), 4.14 (d, $J = 8.8$ Hz, 1H), 4.00–3.90 (m, $J = 12.0$ and 2.8 Hz, 2H), 3.77 (s, 6H), 2.10–1.80 (m, $J = 7.2$ Hz, 1H), 1.81 (d, $J = 8.0$ Hz, 1H), 1.28 (s, 9H), 0.95 (s, 9H). ^{13}C NMR (benzene-d_6, 100 MHz) δ 174.9, 161.2, 154, 132.5, 129.4–127.9, 114.2, 103.2, 99.0, 81.5, 78.4, 72.8, 71.3, 68.0, 55.4, 52.8, 40.1, 29.5, 28.7, 27.9. MS (EI) m/z 510 [M+H$^+$], 452, 436, 352 (100%), 318, 272, 216, 193, 137, 121, 109, 69, 57. LCT-ES (g/mol) calcd: 532.2523 [M+Na$^+$], found: 532.2523. R_f 0.49 (Hex/EtOAc 1/1). $[\alpha]_D^{20}$ +1 (c 0.33, $CHCl_3$).
15. (a) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, *9*, 2199–2204; (b) Nguyen, T. A.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61–70; (c) Nguyen, T. A. *Top. Curr. Chem.* **1980**, *88*, 145–162.
16. Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920–1923.
17. Karplus, M. *J. Chem. Phys.* **1959**, *30*, 11–15.
18. Pretsch, E.; Clerc, T. *Tabellen zur Strukturaufklärung organischer Verbindungen mit spektroskopischen Mitteln*; Springer: Berlin, 1990.