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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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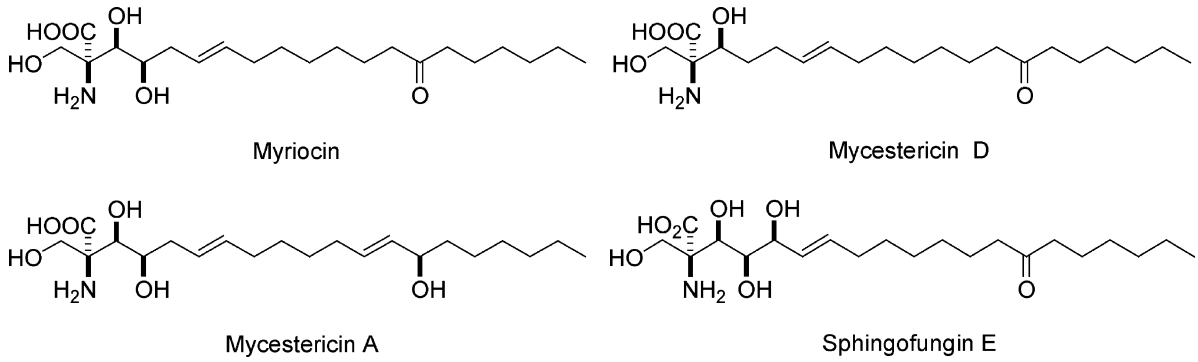


Fig. 1. Sphingosine-related metabolites.

[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

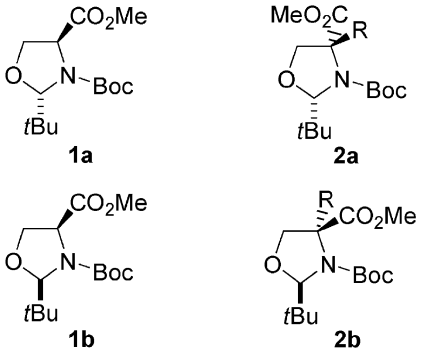
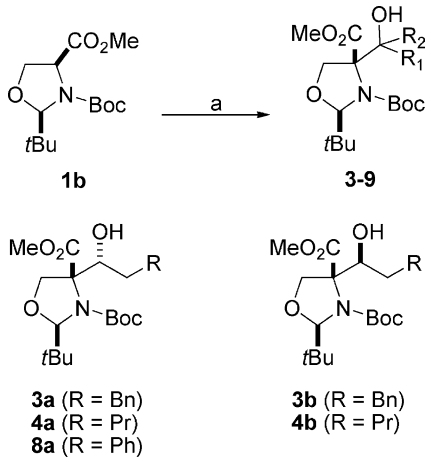


Fig. 2. Alkylation products (R = Me, allyl, benzyl, methyl bromoacetate).



Scheme 1.

Table 1
Diastereoselectivities of aldol additions

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

dr, diastereomeric ratio.

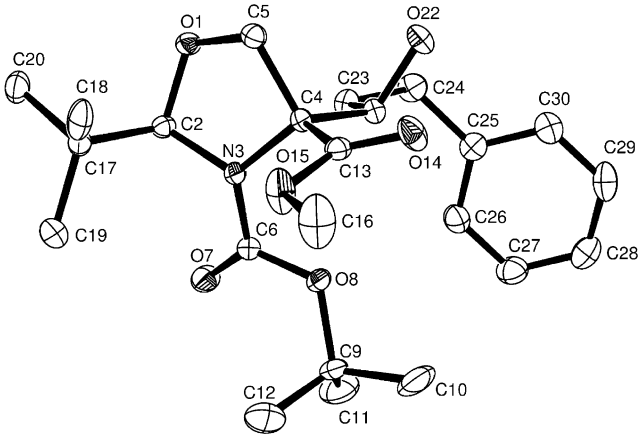


Fig. 3. *ORTEP* [14]—plot of *anti*-diastereomer **3a**.

the product with 4*R*,1″*R*-configuration. The methine proton of C1″ is in benzene-d_6 *even at 60 °C 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 of condensed alicyclic systems (Fig. 4) [18].

X-ray analysis of the obtained crystal structure of *anti*-diastereomer **3a** was not only useful for the assignment of the relative configuration of the stereoisomers, but revealed interesting conformational properties, too. The crystal structure of the highly rigid oxazolidine **1a** [6a,b] and the alkylated derivative **13** (Figs. 5 and 6) with very spacious ring substituents represent further examples where a powerful allylic 1,3-strain ($A^{1,3}$-strain) directs the reaction outcome [19,20]. *N*-protecting groups in five-membered *N*,*O*-acetals are known to influence the reactivity and selectivity and are not only spectators in reactions. The higher stability of *N*-formylated *N*,*O*-acetals is explained with the more electron-withdrawing formyl group and less $A^{1,3}$-strain in the corresponding enolates than for *N*-carbamoyl *N*,*O*-acetals [21]. Accordingly, the high selectivities in alkylation and aldol reactions of **1a/b** may be influenced by the $A^{1,3}$-effect.

Table 2
Reagent controlled Aldol reaction

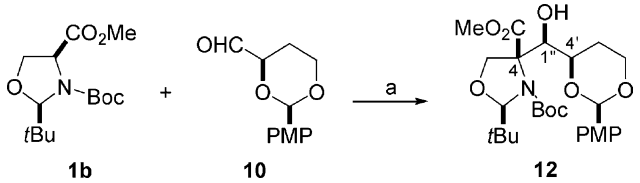
Entry	Reagent[a]/solvent	dr[b] **3a/b** (NMR)	dr **3a/b** (HPLC)
1	LDA/THF	1:2	1:2
2	LICA/THF	2:3	2:3
3	$TiCl_4$/TEA/CH_2Cl_2	1:1	1:1
4	$SnCl_4$/DIPEA/CH_2Cl_2	1:1	1:1
5	NaHDMS/THF	2:5	1:1
6	KHDMS/THF	SM	SM

SM, starting material.
[a] Conditions: 100 mol% of **1a**, 200 mol% of the reagent, 250 mol% of hydrocinnamaldehyde, 50 ml solvent per mol of **1a**, −78 °C.
[b] dr, diastereomeric ratio.

The five-membered rings in the crystal structures of **1a**, **3a**, and **13** adopt puckered envelope conformations and the protected nitrogen atom, which is in the same plane with three of the five ring atoms, is close to planar. The ring-oxygen in **1a** lies out of plane while the bulky substituents of the ring-carbon atoms take untypical quasi-axial positions. The methyl ester group at C4 is nearly perpendicular to the above-mentioned ring plane and the twisted Boc group forms with the *t*Bu–C2 a dihedral angle of 13.4°. The *Re*-face of the enolate of **1a** and, therefore, also its corresponding enolate is completely shielded by both the *t*Bu ring substituent and the Boc group to relieve extra $A^{1,3}$-strain.

The two α-substituted compounds **3a** and **13** on the other hand are puckered envelopes with slightly twisted five-membered rings where C5 is out of the plane. The *t*Bu–C2 substituents and the spacious substituent at C4 in each compound are in quasi-axial position. The dihedral angles of the *t*Bu–C2 and the Boc groups are 24° for **3a** and 2° for **13**. The high angle value for **3a** indicates a strongly distorted Boc group (Fig. 6).

In summary, diastereoselective formation of aldol products from the chiral enolate of **1a** and achiral carbonyl compounds resulted in the expected statistical mixtures of 1″-diastereomers while the utilisation of chiral electrophiles such as reactive aldehyde **10** gave exclusively diastereomer **12**. The alkylation and aldol reactions of **1a/b** represent further examples where a powerful $A^{1,3}$-strain may direct the reaction outcome and the crystal structures of **1a**, **3a** and **13** show interesting conformational properties.



Scheme 2.

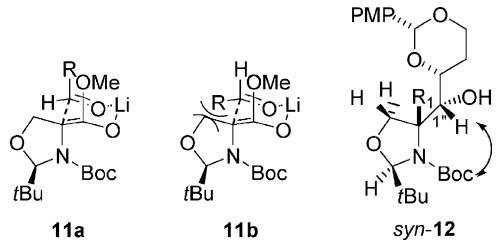


Fig. 4. Zimmerman–Traxler-transitions states **11a** and **11b** (R = 2-methoxyphenyl-1,3-dioxane) and observed NOE of aldol adduct *syn*-**12** ($R_1 = CO_2Me$).

Further examples of this methodology and careful structural analysis of the highly substituted *N*,*O*-acetals will be reported in due course.

3. Experimental

General methods. All reactions were conducted in flame-dried glassware under an atmosphere of argon. Solvents were dried by distillation from $LiAlH_4$ (THF) or from Na (toluene) or used as purchased (pentane, CH_2Cl_2). *n*-Butyllithium solution in hexanes (2.5 M) was purchased from Aldrich in Sure-Seal containers. Starting materials that were commercially available were used without purification. Melting points are uncorrected and were determined using recrystallized samples. NMR spectra were recorded from $CDCl_3$ or benzene-d_6 *solutions at r.t. with a Bruker Avance 400 instrument operating at approximately 400 MHz/100 MHz ($^1H/^{13}C$). Analytical thin-layer chromatography (TLC) was performed on SiO_2 60 F_{254} plates and visualization was accomplished with a 254 nm UV light or by staining with ninhydrin (0.3 g ninhydrin, 100 ml 1-butanol) or acidic PMA (1.0 g phosphomolybdic acid hydrate, 5% H_2SO_4, 100 ml EtOH) followed by heating. Flash-Chromatography was performed using the indicated solvent system on MERCK silica gel 60 (particle size 0.040–0.063 mm; 230–400 mesh ASTM). Low- and high-resolution mass spectra were obtained with a JEOL-DX303 Mass Spectrometer with direct inlet probe and EI at 50 V. Elemental Analysis was performed with a Perkin–Elmer Elemental Analyser 2400CHN. Optical rotations were measured with a Perkin–Elmer Polarimeter 343.*

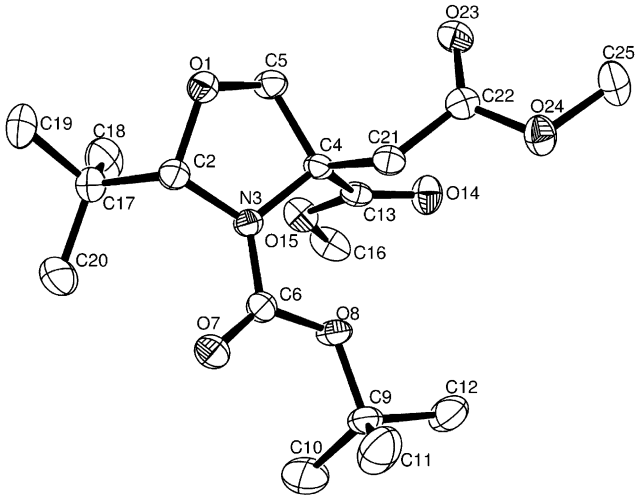


Fig. 5. *ORTEP* [14]—plot of **13**.

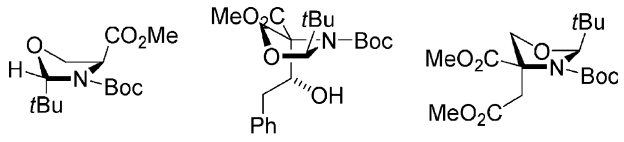


Fig. 6. Conformations of **1a**, **3a** and **13**.

The X-ray crystallographic data were recorded with a Nonius Kappa CCD diffractometer using graphite monochromatised Mo K_α radiation [λ(Mo K_α) = 0.71073 Å] and temperature of 173.0 ± 0.1 K. The CCD data were processed with Denzo-SMN v0.93.0 [22] and the structures were solved by direct methods (SHELXS-97 [23]) and refined on F^2 by full-matrix least-squares techniques (SHELXS-97 [24]). The hydrogen atoms were calculated to their idealised positions and refined as riding atoms (1.5 or 1.2 times the carbon temperature factor). Other experimental data is presented in Table 3. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC-241330 and 241331. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (Fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

General method for aldol reaction. A 100 ml flask was charged with THF (35 ml) and DIPA (0.20 ml, 1.4 mmol, 200 mol%). After cooling the solution to −78 °C, *n*-BuLi (2.0 M in Hex, 0.72 ml, 1.4 mmol, 200 mol%) was added dropwise. The colourless reaction mixture was stirred at

Table 3
Experimental data for the X-ray diffraction studies on **3a** and **13**

	3a	**13**
Formula	$C_{23}H_{35}NO_6$	$C_{17}H_{29}NO_7$
Formula weight	421.52	359.41
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1$ (no. 4)	$P2_1$ (no. 4)
a (Å)	10.7690 (4)	9.9746 (7)
b (Å)	9.5194 (4)	8.0158 (6)
c (Å)	11.6423 (5)	13.094 (1)
β (deg)	105.435 (2)	108.993 (3)
V (Å^3)	1150.46 (8)	989.9 (1)
Z	2	2
μ (Mo K_α) (mm^{-1})	0.087	0.093
No. of refl. measured	5488	4697
No. of independent refl.	3727	3181
R_{int}	0.022	0.048
$R(\%)/R_w(\%)$ ($I > 2\sigma I$)	3.92/7.77	5.43/9.15
GOF	1.033	1.097

0 °C for 20 min, then cooled to −78 °C. **1b** (203.0 mg, 0.7 mmol, 100 mol%) in THF (5 ml) was slowly added and after stirring for 1 h at −78 °C, the aldehyde (1.8 mmol, 250 mol%) was added dropwise. The reaction mixture was stirred for 3 h at −78 °C, AcOH (0.14 ml, 2.5 mmol, 350 mol%) in Et_2O (2 ml) was added and the reaction mixture allowed to warm up to r.t. overnight. The reaction mixture was poured into a mixture of a semi-saturated solution of NH_4Cl (50 ml) and Et_2O (100 ml) and separated. After drying the organic layer over Mg_2SO_4 and evaporating of the solvents the crude product was purified by FC using mixtures of Hex/EtOAc or Isooctane/EtOAc.

(1′R,2R,4R)-2-*tert*-Butyl-4-(1-hydroxy-3-phenylpropyl)-oxazolidine-3,4-dicarboxylic acid 3-*tert*-butyl ester 4-methyl ester (**3a**). 76.0 mg, 25%. ^{1}H-NMR ($CDCl_3$) 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) 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. LRMS-EI *m/z* 422 ($M+H^+$), 364, 322, 264 (BP), 231, 186, 130, 101, 91, 57. HRMS-EI (g/mol) calc.: 420.2408 $M-H^+$; found: 420.2385. R_f 0.43 (Hex/EtOAc 4/1). $[\alpha]_D^{20}=+49$ (*c 1 g/100 ml, $CHCl_3$*).

(1′S,2R,4R)-2-*tert*-Butyl-4-(1-hydroxy-3-phenylpropyl)-oxazolidine-3,4-dicarboxylic acid 3-*tert*-butyl ester 4-methyl ester (**3b**). 79.0 mg, 26%. ^{1}H-NMR ($CDCl_3$) 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 ($CDCl_3$) 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. LRMS-EI *m/z* 422 ($M+H^+$), 364, 348, 322, 287, 265 (BP), 246, 231, 201, 186, 159, 145, 134, 101, 91, 79, 57. LCT-ES (g/mol) calc.: 444.2362 $M+Na^+$, found: 444.2377. R_f 0.38 (Hex/EtOAc 4/1). $[\alpha]_D^{20}=-25$ (*c 1 g/100 ml, $CHCl_3$*).

(1′R,2R,4R)-2-*tert*-Butyl-4-(1-hydroxypentyl)-oxazolidine-3,4-dicarboxylic acid 3-*tert*-butyl ester 4-methyl ester (**4a**). 74.4 mg, 57%. ^{1}H-NMR ($CDCl_3$) 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 ($CDCl_3$) 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. LRMS-EI *m/z* 316 (M-58), 300, 259, 242, 231, 217 (BP), 198, 186, 157, 145, 130, 101, 86, 69, 57. LCT-ES (g/mol) calc.: 396.2362 $M+Na^+$; found: 396.2364. R_f 0.49 (Hex/EtOAc 4/1). $[\alpha]_D^{20}=+13$ (*c 1 g/100 ml, $CHCl_3$*).

(1′S,2R,4R)-2-*tert*-Butyl-4-(1-hydroxypentyl)-oxazolidine-3,4-dicarboxylic acid 3-*tert*-butyl ester 4-methyl ester (**4b**). 40.2 mg, 31%. ^{1}H-NMR ($CDCl_3$) 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 ($CDCl_3$) 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. LRMS-EI *m/z* 316 (M-58), 300, 260, 231, 217 (BP), 198, 174, 156, 145, 113, 101, 85, 57. LCT-ES (g/mol) calc.: 396.2362 $M+Na^+$; found: 396.2350. R_f 0.37 (Hex/EtOAc 4/1). $[\alpha]_D^{20}=-45$ (*c 1 g/100 ml, $CHCl_3$*).

(1″R,2R,4R)-2-*tert*-Butyl-4-(1-hydroxyphenylmethyl)-oxazolidine-3,4-dicarboxylic acid 3-*tert*-butyl ester 4-methyl ester (**8a**). Recrystallisation from hexane, yield: 138.2 mg, 90%. ^{1}H-NMR ($CDCl_3$) δ 7.38–7.25 (m, 5 arom. H), 5.60 (br s, 1H), 4.62 (d, J=9.0 Hz), 4.35 (br s, 1H), 4.11 (s, 1H), 4.03 (dd, J=9.0 and 1.2 Hz), 3.85 (s, 3H), 1.51 (s, 9H), 0.86 (s, 9H). ^{13}C-NMR ($CDCl_3$) δ 174.1, 152.3, 137.8, 128.0, 126.9, 97.5, 81.7, 71.5, 69.5, 52.8, 39.3, 30.9, 28.3, 26.8. LRMS-EI *m/z* 394 ($M+H^+$), 336, 320, 294, 287, 252, 236, 218, 204, 186 (BP), 158, 129, 107, 79, 57. *EA* calc.: C 64.10, H 7.94, N 3.56; found: C 64.18, H 8.05, N 3.34. R_f 0.35 (Hex/EtOAc 1/1). $[\alpha]_D^{20}=+73$ (*c 1 g/100 ml, $CHCl_3$*).

(1″R,2R,2′R,4′R,4R)-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 (**12**). 25 mg, 20%. ^{1}H-NMR ($CDCl_3$) δ 7.35 (d, J=4.2 Hz, 2H), 6.83 (d, J=4.2 Hz, 2H), 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) 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. LRMS-EI *m/z* 510 ($M+H^+$), 452, 436, 352 (BP), 318, 272, 216, 193, 137, 121, 109, 69, 57. LCT-ES (g/mol) calc.: 532.2523 $M+Na^+$; found: 532.2523. R_f 0.49 (Hex/EtOAc 1/1). $[\alpha]_D^{20}=+1$ (*c 0.33 g/100 ml, $CHCl_3$*).

Aldol reaction with NaHDMS or KHDMS. A 100 ml flask was charged with NHDMS (ca. 1 M in THF, 0.72 ml, 0.7 mmol, 200 mol%) or KHDMS (ca. 0.5 M in toluene, 1.44 ml, 0.7 mmol, 200 mol%) in THF (35 ml) at −78 °C and **1b** (103.2 mg, 0.35 mol, 100 mol%) in THF (5 ml) was added dropwise. After stirring the clear colourless reaction mixture for 1 h at −78 °C hydrocinnamaldehyde (0.12 ml, 0.9 mmol, 250 mol%) was added dropwise and the clear colourless solution was stirred for 3 h at −78 °C. AcOH (0.1 ml, 1.7 mmol, 450 mol%) diluted in Et_2O (2 ml) was added and the reaction mixture was allowed to warm up to r.t. The clear solution was poured into a mixture of semi-saturated solution of NH_4Cl (50 ml) and Et_2O (100 ml) and separated. The organic layer was dried over Mg_2SO_4 prior to evaporation to yield a mixture of **3a/b**.

Aldol reaction with $SnCl_4$/DIPEA or $TiCl_4$/TEA. A 100 ml flask was charged with **1b** (109.5 mg, 0.4 mol, 100 mol%) in CH_2Cl_2 (20 ml) and the solution was cooled to −78 °C. $SnCl_4$ or $TiCl_4$ (0.09/0.08 ml, 0.7 mmol, 190 mol%) was added dropwise and stirred for 2 min. Then, TEA (0.11 ml, 0.8 mmol, 200 mol%) was slowly

added whereupon a red precipitate was immediately formed. After stirring for 1.5 h between −78 and −65 °C, hydrocinnamaldehyde (0.18 ml, 1.4 mmol, 350 mol%) was added dropwise and the deep red mixture was stirred for an additional 1.5 h. A saturated solution of NH_4Cl (2 ml) was added and a white solid instantly precipitated. The heterogeneous reaction mixture was allowed to warm up to r.t. and subsequent addition of dist. H_2O re-dissolved the precipitate. The aqueous layer was extracted with Et_2O (50 ml) and the combined organic layers were dried over Mg_2SO_4. Evaporating the solvent and drying in vacuum gave a mixture of **3a/b**.

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Appendix. Supplementary material

Supplementary data associated with this article can be found, in the online version, at 10.1016/j.molstruc.2004.09.020

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