Stereocontrolled α-Alkylation of Fully Protected L-Serine

Martin Brunner,[a] Pauli Saarenketo,[b] Thomas Straub,[a] Kari Rissanen,[b] and Ari M. P. Koskinen*[a]

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Diastereoselective alkylation of the (2*S*,4*S*) and (2*R*,4*S*) diastereomers of 3-*tert*-butyl 4-methyl 2-*tert*-butyl-1,3-oxazolidine-3,4-dicarboxylate (**1a/b**) is reported. Formation of both diastereomers of these oxazolidines was achieved by changing the order of protection steps, and their relative and absolute configurations were determined by NOESY spectroscopy. The use of the bulky ring substituent *t*Bu together with Boc as the *N*-protecting group led to the exclusive formation of only one alkylated diastereomer.

Introduction

Myriocin,[1] mycestericins,[2] and sphingofungins[3] are sphingosine-related metabolites with strong antifungal and immunosuppressive activity (Figure 1). In the course of our studies[4] to obtain these derivatives of L-serine stereoselectively, we became interested in α-substituted amino acids.[5] Stereoselective α-alkylation according to the principle of self-regeneration of stereocentres (SRS)[6,7] is a particularly convenient methodology for our purposes. The necessary transient stereocentre can be introduced by forming oxazolidines of type **1**. Although such oxazolidines have been prepared previously, we report herein a new series of alkylation products where the variation of the ring substituent influences the preference for diastereoselection. In contrast to recent literature reports, we have not only regenerated the configuration at the defined stereocentre, but we have also prepared the products of inversion.[8]

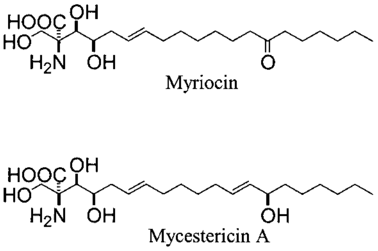

Figure 1. Sphingosine-related metabolites

Results and Discussion

Oxazolidines derived from serine esters are prone to ring-chain tautomerism, and equilibrium studies of methyl and ethyl esters with aromatic aldehydes in $CDCl_3$ showed three-component tautomeric mixtures where the open-chain, Schiff-base intermediate was typically predominating.[9] Among the two ring forms the amount of the *cis* epimer was always higher than the *trans* epimer and, unlike for the thiazolidines,[10] no reaction condition could be found to obtain predominantly the *trans* product.[9] Both diastereomers of the oxazolidines used in our alkylation studies were prepared according to standard methods (**1a**) or using a slightly modified literature procedure (**1b**).[11,12]

Compound **1a** was isolated from a 3:1 mixture together with **1b**, while **1b** was obtained in diastereomerically pure form in three steps (Scheme 1).[8] In fact, **1a** was a 9:1 mixture of rotamers while **1b** was observed in only one rotameric form.[13] We deduced the relative configurations of **1a/b** from NOESY experiments where correlation was observed for the acetal proton at C2 with *t*Bu at C2 and with H_{eq} at C5 only in **1a**.[14] An ORTEP-3[15] plot of **1a** confirmed the *trans* configuration of the C2 and C4 ring substituents from the NOESY observations. The X-ray structure of **1a** shows that bulky ester and *t*Bu groups shield the five-membered ring of the oxazolidine and that the large ring substituent on C2 shields one face of the oxazolidine (Figure 2). The nitrogen atom of the oxazolidine ring is almost planar and is found to be 0.25(0.01) Å above the plane defined by carbon atoms C2, C4 and C6.[16] The observed planarity of the nitrogen is probably due to delocalized elec-

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[a] Laboratory of Organic Chemistry, Helsinki University of Technology,
P. O. Box 6100, 02150 Espoo, Finland
Fax: +358-9-451-2538
E-mail: ari.koskinen@hut.fi
[b] X-ray crystallography: Laboratory of Organic Chemistry, University of Jyväskylä,
40351 Jyväskylä, Finland
Fax: +358-14-260-2672
E-mail: kari.rissanen@jyu.fi

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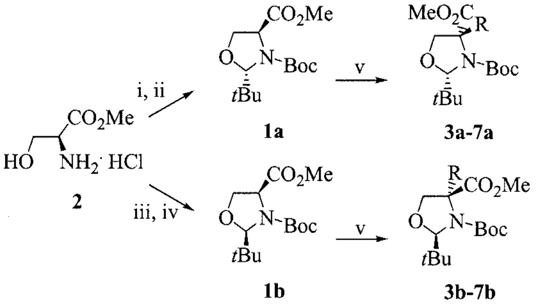
tron density of the conjugated p-orbitals of the carbamate moiety. Adaptation of the ring conformation and orientation of the C4-ester substituent for better overlap of the p-orbitals is seen in the torsion angles C2−N3−C6−O7 [12.8(6)°] and C4−N3−C6−O8 [−22.3(5)°].



Scheme 1. Conditions: i) $(Boc)_2O$, CH_2Cl_2/MeOH, room temp.; ii) pivalaldehyde, PPTS, toluene, reflux; iii) 2,2-dimethylpropanal, pentane/TEA, reflux; iv) $(Boc)_2O$, TEA/ THF, room temp.; v) LDA, RX (see Table 1), THF, −78 °C

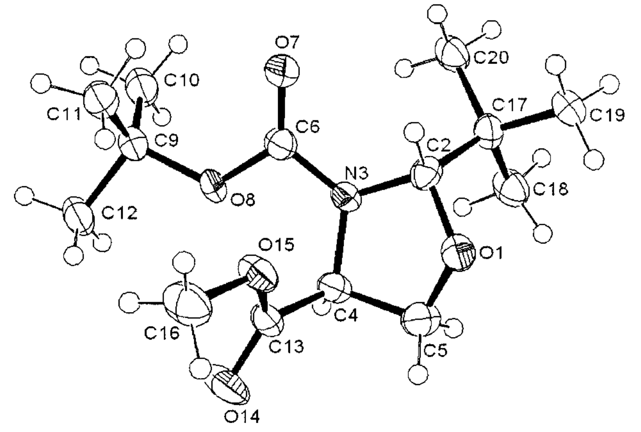


Figure 2. ORTEP-3 plot of **1a**

Subsequent alkylation reactions of the ester enolates of **1a** and **1b** were performed under standard conditions (Scheme 1).[8] Addition of 110 mol % of LDA was sufficient to deprotonate **1b** but not **1a**, where H4 is sterically more hindered. However, the alkylation yields were only modest. Increasing the amount of base to 200 mol % led to improved yields for all alkylated products **3**−**7**. In each case only one diastereomer was obtained as the sole alkylation product (^1H NMR spectroscopy and HPLC). However, the alkylation products of the **a** series gave systematically lower yields, indicating a more hindered electrophilic attack to the enolate of **1a**, which was also observed upon deuteration of the enolates of **1a/b**. We also observed different side products. While **3b** was accompanied only by starting material, an additional product from protonation with inversion of configuration was observed for **3a**. The yields for alkylations with more hindered electrophiles decreased rapidly, and benzylation (products **6a/b)** was accompanied by significant amounts of 1-bromo-1,2-diphenylethane.[17] In contrast to literature reports,[8a] the use of DMPU as a cosolvent did not improve the situation.[18]

The relative and, by inference, absolute configurations of **3a/b** were obtained from NOESY experiments and confirmed by NMR data of **1a/b** and the crystal structure of **1a**. The correlation in the NOESY spectrum of **1b** between the methyl protons of the *t*Bu and the acetal proton at C2 as well as the H_{eq} at C5 is observed in **4b**, too (Figure 3). Therefore, the newly introduced substituent is necessarily *trans* to the *t*Bu ring substituent. We assigned compounds **5** to **7** in an analogous manner. Product pairs **3a/b** to **7a/b** are enantiomers, as confirmed by their identical NMR spectra and opposite signs of optical rotation. The yields and selectivities of the reactions are shown in Table 1.

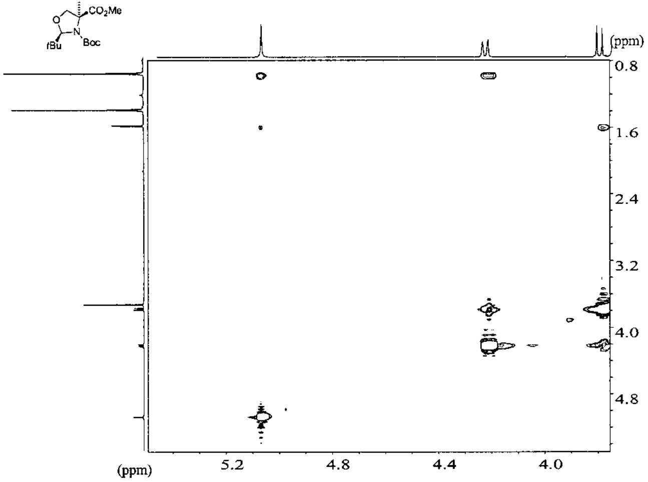


Figure 3. NOESY spectrum of **4b**

Table 1. Diastereoselective alkylation of diastereomers **1a** and **1b**

Entry	1	RX	Product	Yield[a]	*dr*[b]
1	**a**	D_2O	**3a**	n.d.	mixture
2	**a**	MeI	**4a**	87	99:1
3	**a**	Allyl bromide	**5a**	30 (67)	99:1
4	**a**	BnBr	**6a**	11	one isomer
5	**a**	$BrCH_2CO_2Me$	**7a**	20	one isomer
6	**b**	D_2O	**3b**	(64)	99:1
7	**b**	MeI	**4b**	92	99:1
8	**b**	Allyl bromide	**5b**	45 (79)	99:1
9	**b**	BnBr	**6b**	(25)	99:1
10	**b**	$BrCH_2CO_2Me$	**7b**	(67)	99:1

[a] Yields after chromatography; crude yields in parentheses. [b] Diastereomeric ratio (*dr*) determined by ^1H NMR spectroscopy.

Conclusion

In summary, formation of both diastereomers of 3-*tert*-butyl 4-methyl 2-*tert*-butyl-1,3-oxazolidine-3,4-dicarboxylate (**1a/b**) was achieved by two different routes where the reversal of the order of protection steps is the directive tool. The stereoelectronic properties cause the ring nitrogen atom in **1a** to be nearly planar, as shown by an X-ray structure. The observed structural and conformational properties of

1a/b were utilized to achieve diastereoselective alkylation reactions with high *dr*s and good yields. Further examples of the SRS principle and practical applications in the synthesis of natural compounds will be reported in due course.

Experimental Section

General Remarks: All reactions with moisture-sensitive compounds 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. Allyl bromide, benzyl bromide and methyl bromoacetate were passed through a short column of basic Al_2O_3 prior to use. Melting points are uncorrected and were determined with recrystallized samples. NMR spectra were recorded from $CDCl_3$ solutions at room temp. with an instrument operating at 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 a direct inlet probe in EI mode at 50 V. Elemental analysis was performed with a Perkin−Elmer Elemental Analyser 2400CHN. Optical rotations were measured with a Perkin−Elmer Polarimeter 343.

(2*R*,4*S*)-3-*tert*-Butyl 4-Methyl 2-*tert*-Butyl-1,3-oxazolidine-3,4-dicarboxylate (1a): A 100 mL flask was charged with *N*-(1,1-dimethylethoxycarbonyl)-L-serine methyl ester[19] (1.1 g, 5.0 mmol, 100 mol %), toluene (20 mL), PPTS (63 mg, 0.25 mmol, 5 mol %), 2,2-dimethylpropanal (2.2 mL, 20.0 mmol, 400 mol %) and trimethyl orthoformate (0.83 mL, 8.0 mmol, 150 mol %). The reaction mixture was stirred for 4 d at 90 °C. After cooling to room temp. and subsequent extraction with a solution of 10% $NaHCO_3$ (2 × 20 mL) and then brine (20 mL), the organic layer was dried over Mg_2SO_4. Evaporating the solvent and drying in vacuo gave the crude product, which contained a 3:1 mixture of diastereomers. Separation by flash chromatography (hexane/EtOAc, 4:1) gave **1a** (0.85 g, 60%). $[\alpha]_D^{20} = -57$ ($c = 0.5$, MeOH). $R_f = 0.17$ (hexane/EtOAc, 4:1). m.p. 64−65 °C (Hex). ^1H NMR (major rotamer): $\delta =$ 5.17 (br. s, 1 H), 4.33 (m, 2 H), 4.00 (d, $J = 7.2$ Hz, 1 H), 3.73 (s, 3 H), 1.43 (br. s, 9 H), 0.93 (s, 9 H) ppm. ^{13}C NMR (major rotamer): $\delta =$ 172.0, 154.0, 96.8, 81.0, 70.4, 60.5, 52.3, 39.0, 28.1, 26.0 ppm. MS (EI): *m*/*z* (%) = 288 [M^+], 272, 232, 214, 200, 188, 174, 172, 160, 146 (100), 130, 128, 112, 102, 86, 70, 57. $C_{14}H_{25}NO_5$: calcd. C 58.46, H 8.77, N 4.88; found C 58.04, H 8.72, N 4.66.

(2*S*,4*S*)-3-*tert*-Butyl 4-Methyl 2-*tert*-Butyl-1,3-oxazolidine-3,4-dicarboxylate (1b): NEt_3 (5.75 mL, 41.3 mmol, 110 mol) was added to a suspension of **2** (5.83 g, 37.5 mmol, 100 mol %) and pentane (50 mL). The reaction mixture was boiled at reflux until no further water was collected in a Dean−Stark trap. The $Et_3N{\cdot}HCl$ salt was filtered, washed with Et_2O (3 × 30 mL) and the organic layer dried over Mg_2SO_4. Evaporating the solvent and drying in vacuo gave a coloured oil (8.87 g) containing a 1:1 mixture of epimers. A 100 mL flask was charged with the epimer mixture (7.0 g, 37.5 mmol, 100 mol %) and THF (20 mL). The solution was cooled to 0 °C and $(Boc)_2O$ (17.4 mL, 75.0 mmol, 200 mol %) was added dropwise while the formed CO_2 was passed through a silicon trap. The reaction mixture was allowed to warm to room temp. overnight, and then poured onto a mixture of ice (ca. 10 g) and saturated $NaHCO_3$ solution (50 mL). Et_2O (50 mL) was added and the organic layer was washed with saturated $NaHCO_3$ solution (4 × 20 mL) and dried over Mg_2SO_4. Evaporation of the solvent and drying in vacuo gave the crude product. The excess of $(Boc)_2O$ was distilled to give **1b** (9.7 g, 90 mol %) as the only product. $[\alpha]_D^{20} = -30$ ($c = 0.3$, MeOH). $R_f = 0.19$ (hexane/EtOAc, 4:1). ^1H NMR: $\delta =$ 5.00 (s, 1 H), 4.67 (br. m, 1 H), 4.24 (dd, $J = 5.6$, 8.6 Hz, 1 H), 4.11 (t, $J =$ 8.6 Hz, 1 H), 3.73 (s, 3 H), 1.45 (s, 9 H), 0.91 (s, 9 H) ppm. ^{13}C NMR: $\delta =$ 170.9, 155.1, 97.6, 81.3, 68.3, 59.7, 52.2, 37.7, 28.2, 25.8 ppm. HRMS ($C_{14}H_{26}NO_5$): calcd. 288.1810 [M^+]; found 288.1823.

General Procedure for Alkylation: A 50 mL flask was placed under Ar and charged with THF (35 mL) and diisopropylamine (DIPA) with a syringe. The solution was cooled to −78 °C (isopropanol/dry ice) and *n*BuLi was added dropwise. The colorless reaction mixture was stirred at 0 °C for 15 min, then cooled to −78 °C and **1** in THF (5 mL) was slowly added to the solution. After stirring for 45 min at −78 °C, the electrophile was added. The reaction mixture was allowed to warm up to room temp. overnight and then poured into a mixture of a semisaturated solution of NH_4Cl (30 mL) and Et_2O (80 mL). The organic layer was separated, washed with distilled water (4 × 50 mL) and dried over Mg_2SO_4. Evaporating the solvent and drying in vacuo gave the crude product, which was purified by flash chromatography (FC) using mixtures of hexane/EtOAc, or hexane/acetone as eluent.

(2*R*,4*R*)-3-*tert*-Butyl 4-Methyl 2-*tert*-Butyl-4-deuterio-1,3-oxazolidine-3,4-dicarboxylate (3a): DIPA (0.11 mL, 0.8 mmol, 210 mol %), *n*BuLi (1.96 M in *n*-hexanes, 0.39 mL, 0.8 mmol, 210 mol %), **1a** (110.0 mg, 0.38 mmol, 100 mol %), D_2O (0.02 mL, 1.1 mmol, 290 mol %). FC (hexane/EtOAc, 8:1) gave an inseparable mixture of **3a**, **1a** and D-serine derivative *ent*-**1b**.

(2*S*,4*S*)-3-*tert*-Butyl 4-Methyl 2-*tert*-Butyl-4-deuterio-1,3-oxazolidine-3,4-dicarboxylate (3b): DIPA (0.13 mL, 0.9 mmol, 190 mol %), *n*BuLi (2.10 M in *n*-hexanes, 0.44 mL, 0.9 mmol, 190 mol %), **1b** (133.8 mg, 0.47 mmol, 100 mol %), D_2O (0.02 mL, 1.1 mmol, 235 mol %). FC (hexane/EtOAc, 8:1) gave pure **3b** (35.3 mg, 26%) as a brown oil accompanied by a side product identified as the product of β-elimination. $[\alpha]_D^{20} = -29$ ($c = 1$, $CHCl_3$). $R_f = 0.20$ (hexane/EtOAc, 8:1). ^1H NMR: $\delta =$ 5.03 (s, 1 H), 4.26 (d, $J = 8.6$ Hz, 1 H), 4.13 (d, $J = 8.6$ Hz, 1 H), 3.75 (s, 3 H), 1.47 (s, 9 H), 0.92 (s, 9 H) ppm. ^{13}C NMR: δ 171.4, 155.5, 98.0, 81.7, 68.7, 60.1, 52.7, 38.2, 28.6, 26.2 ppm.

(2*R*,4*R*)-3-*tert*-Butyl 4-Methyl 2-*tert*-Butyl-4-methyl-1,3-oxazolidine-3,4-dicarboxylate (4a): DIPA (0.06 mL, 0.4 mmol, 115 mol %), *n*BuLi (2.08 M in *n*-hexanes, 0.20 mL, 0.41 mmol, 115 mol %), **1a** (100.4 mg, 0.35 mmol, 100 mol %), methyl iodide (0.07 mL, 1.1 mmol, 315 mol %). FC (hexane/EtOAc, 8:1) gave pure **4a** (25.5 mg, 25%) as a brown oil. $[\alpha]_D^{20} = +4$ ($c = 0.4$, $CHCl_3$). ^1H NMR: $\delta =$ 5.09 (s, 1 H), 4.25 (d, $J = 8.0$ Hz, 1 H), 3.80 (d, $J =$ 8.0 Hz, 1 H), 3.75 (s, 3 H), 1.62 (s, 3 H), 1.43 (s, 9 H), 1.00 (s, 9 H) ppm. ^{13}C NMR: $\delta =$ 172.9, 154.1, 97.4, 81.2, 77.5, 66.8, 52.8, 39.6, 28.5, 26.9, 21.7 ppm. MS (EI): *m*/*z* (%) = 302 [$M + H^+$], 296, 228, 214, 202, 186, 160 (100), 114, 100, 84, 69, 58. HRMS ($C_{15}H_{28}NO_5$): calcd. 302.1967 [$M + H^+$]; found 302.1977.

(2*S*,4*S*)-3-*tert*-Butyl 4-Methyl 2-*tert*-Butyl-4-methyl-1,3-oxazolidine-3,4-dicarboxylate (4b): DIPA (0.11 mL, 0.8 mmol, 215 mol %), *n*BuLi (2.1 M in *n*-hexane; 0.37 mL, 0.78 mmol, 210 mol %), **1b** (110.0 mg, 0.37 mmol, 100 mol %), methyl iodide (0.06 mL, 1.0 mmol, 270 mol %). Pure **4b** (103.0 mg, 92%) was obtained as a brown oil. $[\alpha]_D^{20} = -5$ (c = 0.4, $CHCl_3$). R_f = 0.58 (hexane/EtOAc, 1:1).

(2*R*,4*R*)-3-*tert*-Butyl 4-Methyl 4-Allyl-2-*tert*-butyl-1,3-oxazolidine-3,4-dicarboxylate (5a): DIPA (0.10 mL, 0.7 mmol, 200 mol %), *n*BuLi (2.03 M in *n*-hexane, 0.35 mL, 0.71 mmol, 200 mol %), **1a** (100.7 mg, 0.35 mmol, 100 mol %), allyl bromide (0.08 mL, 1.0 mmol, 290 mol %). FC (hexane/EtOAc, 18:1) gave pure **5a** (33.8 mg, 30%) as a brown oil. $[\alpha]_D^{20} = -15$ (c = 1.0, $CHCl_3$). R_f = 0.10 (hexane/EtOAc, 9:1). ^1H NMR: δ = 5.86 (m, 1 H), 5.20 (m, 2 H), 5.09 (s, 1 H), 4.26 (dd, J = 8.6, 1.6 Hz, 1 H), 4.09 (d, J = 8.6 Hz, 1 H), 3.78 (s, 3 H), 3.16 (br. s, 1 H), 2.74 (dd, J = 6.0 Hz, 1 H), 1.47 (s, 9 H), 1.01 (s, 9 H) ppm. ^{13}C NMR: δ = 172.6, 153.5, 132.4, 120.0, 98.4, 81.3, 75.7, 69.0, 52.8, 39.9, 31.3, 28.6, 26.9 ppm. MS (EI): m/z (%) = 328 [M + H$^+$], 300, 285, 270, 254, 242, 228, 212, 198, 186, 171 (100), 130, 110, 82, 69, 57. HRMS ($C_{17}H_{30}NO_5$): calcd. 328.2133 [M + H$^+$]; found 328.2096.

(2*S*,4*S*)-3-*tert*-Butyl 4-Methyl 4-Allyl-2-*tert*-butyl-1,3-oxazolidine-3,4-dicarboxylate (5b): DIPA (0.11 mL, 0.8 mmol, 210 mol %), *n*BuLi (2.10 M in *n*-hexane, 0.37 mL, 0.78 mmol, 205 mol %), **1b** (110.3 mg, 0.38 mmol, 100 mol %), allyl bromide (0.08 mL, 1.0 mmol, 265 mol %). FC (hexane/EtOAc, 18:1) gave pure **5b** (55.9 mg, 45%) as a brown oil. $[\alpha]_D^{20} = +12$ (c = 1, $CHCl_3$). R_f = 0.58 (hexane/EtOAc, 4:1).

(2*R*,4*R*)-3-*tert*-Butyl 4-Methyl 4-Benzyl-2-*tert*-butyl-1,3-oxazolidine-3,4-dicarboxylate (6a): DIPA (0.08 mL, 0.6 mmol, 210 mol %), *n*BuLi (2.10 M in *n*-hexane, 0.29 mL, 0.58 mmol, 200 mol %), **1a** (80.0 mg, 0.28 mmol, 100 mol %), benzyl bromide (0.09 mL, 0.8 mmol, 290 mol %). Crude product: 180 mg, containing an inseparable mixture of **6a** (11%) and 1-bromo-1,2-diphenylethane (89%).

(2*S*,4*S*)-3-*tert*-Butyl 4-Methyl 4-Benzyl-2-*tert*-butyl-1,3-oxazolidine-3,4-dicarboxylate (6b): DIPA (0.15 mL, 1.1 mmol, 220 mol %), *n*BuLi (2.10 M in *n*-hexane, 0.50 mL, 1.05 mmol, 210 mol %), **1b** (149.9 mg, 0.51 mmol, 100 mol %), benzyl bromide (0.15 mL, 1.3 mmol, 250 mol %). FC (hexane/EtOAc, 18:1) gave **6b** (48.0 mg, 25%) as a brown oil. $[\alpha]_D^{20} = +73$ (c = 1, $CHCl_3$). R_f = 0.51 (hexane/EtOAc, 1:1). ^1H NMR (major rotamer): δ = 7.32−7.27 (m, 4 H), 7.23 (m, 2 H), 4.65 (s, 1 H), 4.18 (dd, J = 8.8, 0.8 Hz, 2 H), 3.83 (s, 3 H), 3.69 (m, 1 H), 3.39 (d, J = 14.2 Hz, 1 H), 1.55 (s, 9 H), 1.01 (s, 9 H) ppm. ^{13}C NMR (major rotamer): δ = 172.7, 153.5, 136.4, 130.7, 128.7, 127.3, 98.0, 81.5, 74.2, 70.0, 52.9, 39.9, 28.7, 27.0, 25.3 ppm. HRMS ($C_{21}H_{32}NO_5$): calcd. 378.2280 [M + H$^+$]; found 328.2273.

(2*R*,4*R*)-3-*tert*-Butyl 4-Methyl 4-Methoxycarbonyl-2-*tert*-butyl-1,3-oxazolidine-3,4-dicarboxylate (7a): DIPA (0.04 mL, 0.5 mmol, 200 mol %), *n*BuLi (2.03 M in *n*-hexane, 0.23 mL, 0.5 mmol, 200 mol %), **1a** (75.8 mg, 0.26 mmol, 100 mol %), methyl bromoacetate (0.06 mL, 0.7 mmol, 270 mol %). FC (hexane/acetone, 18:1) gave a 3:1 mixture of **1a** and **7a**. R_f = 0.12 (hexane/EtOAc, 8:1).

(2*S*,4*S*)-3-*tert*-Butyl 4-Methyl 4-Methoxycarbonyl-2-*tert*-butyl-1,3-oxazolidine-3,4-dicarboxylate (7b): DIPA (0.10 mL, 0.7 mmol, 190 mol %), *n*BuLi (2.03 M in *n*-hexane, 0.35 mL, 0.71 mmol, 190 mol %), **1b** (107.5 mg, 0.37 mmol, 100 mol %), methyl bromoacetate (0.09 mL, 1.0 mmol, 270 mol %). FC (hexane/acetone, 18:1) gave **7b** (89.4 mg, 67% yield). $[\alpha]_D^{20} = +51$ (c = 1, $CHCl_3$). R_f = 0.22 (hexane/EtOAc, 9:1). ^1H NMR: δ = 4.98 (s, 1 H), 4.41 (br. d, J = 8.6 Hz, 1 H), 4.27 (d, J = 8.6 Hz, 1 H), 3.77 (s, 3 H), 3.68 (s, 1 H), 3.20−3.00 (br. s, 1 H), 2.97 (d, J = 14.1 Hz, 1 H), 1.46 (s, 9 H), 1.01 (s, 9 H) ppm. ^{13}C NMR: δ = 170.9, 170.7, 153.1, 97.4, 81.3, 74.1, 67.5, 52.7, 51.9, 39.1, 37.7, 36.9, 28.1, 26.6 ppm. MS (EI): m/z (%) = 360 [M + H$^+$], 302, 286, 272, 260, 246, 202, 186, 170, 157, 142 (100), 110, 82, 69, 57. HRMS ($C_{17}H_{28}NO_7$): calcd. 358.1865 [M − H$^+$]; found 358.1793.

X-ray Crystallographic Study of 1a: The data were recorded on a Nonius Kappa CCD diffractometer using graphite-monochromated Mo-K_α radiation (λ = 0.71073 Å). The data were processed using Denzo-SMN.[20] The structure was solved by direct methods (SHELXS-97)[21] and refined on F^2 by full-matrix least-squares techniques (SHELXL-97).[22] The hydrogen atoms were calculated at their ideal positions and refined as riding atoms with isotropic temperature factors 1.2 (CH and CH_2) or 1.5 (CH_3) times the corresponding carbon temperature factor. The absolute configuration of **1a** was not defined, as shown by the meaningless value of Flack's x parameter [0.1(2.5)]. An absorption correction was not applied. Crystal data: $C_{14}H_{25}NO_5$, M_r = 287.35, orthorhombic, space group $P2_12_12_1$, a = 5.9326(2), b = 10.1145(7), c = 26.3519(17) Å, V = 1581.25(16) Å^3, Z = 4, T = 173(2) K, $F(000)$ = 624, μ = 0.091 mm^{-1}. Data collection: crystal size 0.38 × 0.13 × 0.13 mm^3, 173(2) K, index ranges $-7 \le h \le 7$, $-13 \le k \le 10$, $-34 \le l \le 34$, Θ range 3.07−27.51°, 10166 measured reflections, 3627 unique (R_{int} = 0.1295), $R(F^2)$ = 0.0974, $wR(F^2)$ = 0.2099 for 2167 observed reflections [$F_o > 4\sigma(F_o)$].
CCDC-230045 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; Fax: +44-1223-336033; E-mail: deposit@ccdc.cam.ac.uk.

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