Synthesis of All Stereoisomers and Some Congeners of Isocytoxazone

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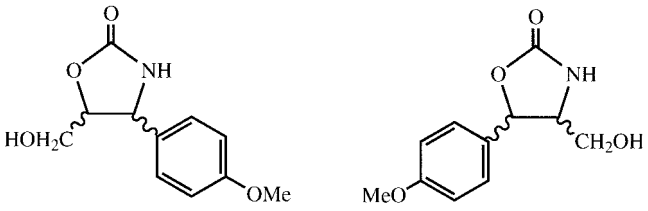
Abstract: *cis*-Isocytoxazone **2a** and *trans*-isocytoxazone **2b**, structural isomers of the antiasthmatic agent cytoxazone (–)-**1**, and their 5-substituted congeners **23**–**28** have been prepared. Aldol reaction of *para*-substituted benzaldehydes with 7-chloro-1-methyl-5-phenyl-1,4-benzodiazepin-2-one, followed by separation of diastereomeric racemates afforded **3**–**10**. Acid-catalyzed 1,4-benzodiazepine ring opening, and transformation of the methyl esters of β-aryl-β-hydroxy-α-amino acids (**11**–**16**) via 4-methoxycarbonyl derivatives of 1,3-oxazolidin-2-one (**17**–**22**) and their reduction afforded the target oxazolidin-2-one derivatives **23**–**28**. Racemic isocytoxazones **2a** and **2b** were prepared by an independent route starting from 4-methoxystyrene epoxide. Pure enantiomers of these diastereomeric racemates were separated by HPLC chromatography on chiral stationary phases. Their CD spectra, along with those of previously prepared enantiomers of *cis*-cytoxazone **1a** and *trans*-cytoxazone **1b** are discussed.

Key words: 1,4-benzodiazepines, ring opening, oxazolidin-2-ones, chiral HPLC

Following the finding that *Streptomyces sp*. exerts into fermentation broth a compound (4*R*,5*R*)-5-(hydroxymethyl)-4-(4-methoxyphenyl)-1,3-oxazolidine 2-one [(–)-**1**, generic name cytoxazone],[1] which was shown to posses high cytokine modulator activity by acting on the Th2 cells,[2] we,[3] and others,[4–7] have reported the preparation of (–)-**1** and its three stereoisomers in the optically pure form. Continuing this project, prompted by the first positive biological results, here we report the preparation of *cis*- and *trans*-isocytoxazones **2a**,**b**, structural isomers of cytoxazone **1a** and its *trans* epimer **1b**, and some congeners (Figure 1). Isomeric structures are characterized by the inverted position of the oxygen and nitrogen atom in the oxazolidin-2-one ring.



1a,b **2a,b**

Figure 1 Formula **1** and **2**

The reaction pathway for the synthesis of the diastereomeric racemic forms **23**–**28** is summarized in Scheme 1. Conventionally, all formula in this scheme represent only one enantiomer of the racemic form actually obtained.

In the first step, the aldol reaction between a 1,4-benzodiazepine derivative and a number of aliphatic and aromatic aldehydes is completed according to our recently reported protocol[8] to give easily separable mixtures of *cis* and *trans* diastereomeric racemic forms of **3**/**4**, **5**/**6**, **7**/**8**, and **9**/**10**. *Cis* and *trans* racemic diastereomers of **3**/**4** and **9**/**10** were separated by fractional crystallization from ethyl acetate, and further purified by flash chromatography, whereas the racemic diastereomers **5**/**6** and **7**/**8** were separated by chromatography.

After hydrolytic opening of the 1,4-benzodiazepine ring with concentrated aqueous hydrochloric acid in acetic acid as solvent, the ammonium salts of α-amino-β-hydroxy acids were obtained in high yield from all intermediary aldol products but from **9**/**10**, and were transformed without isolation into the corresponding methyl esters **11**–**16**. Diastereomers **9**/**10** were found to be unstable under all hydrolytic conditions attempted; a number of side products resulted on the acid-catalyzed cleavage of the 4-methoxybenzyl group via a stable carbenium ion. Therefore, a detour was needed to complete preparation of the stereoisomers **2a**,**b**. The best approach is the reaction sequence recently reported by Nicolaou et al. in the course of the total synthesis of vancomycine (Scheme 2).[9]

Acid-catalyzed ring opening of *trans*-epoxide **29** yielded a 7:3 mixture of *trans*/*cis* diols, with *trans*-**30** as the prevailing diastereomer. Under carefully controlled conditions [low temperature, slow addition of 4-nitrobenzene sulfonyl chloride (NsCl)] only the hydroxy group at C(2) of *trans*-diole **30** reacts selectively affording **31**. Azidolysis of *trans*-nosylate **31** furnished the *cis*-azide **32** in high yield with inversion of configuration at C(2). Carbobenzoxylation, ring closure to *cis*-**34**, and final reduction of the ester group afforded racemic *cis*-isocytoxazone **2a** in excellent yield.

To obtain the *trans* diastereomeric racemic form **2b**, epimerization of the oxazolidinone derivative **34** was completed under basic conditions and the *trans* diastereomer **35** was purified by column chromatography on silicagel. The assignment of the *cis* and *trans* configuration of oxazolidinones **34**/**2a** and **35**/**2b**, respectively, is based on the ^3J constants for C(4)-H/C(5)-H coupling in the ^{1}H

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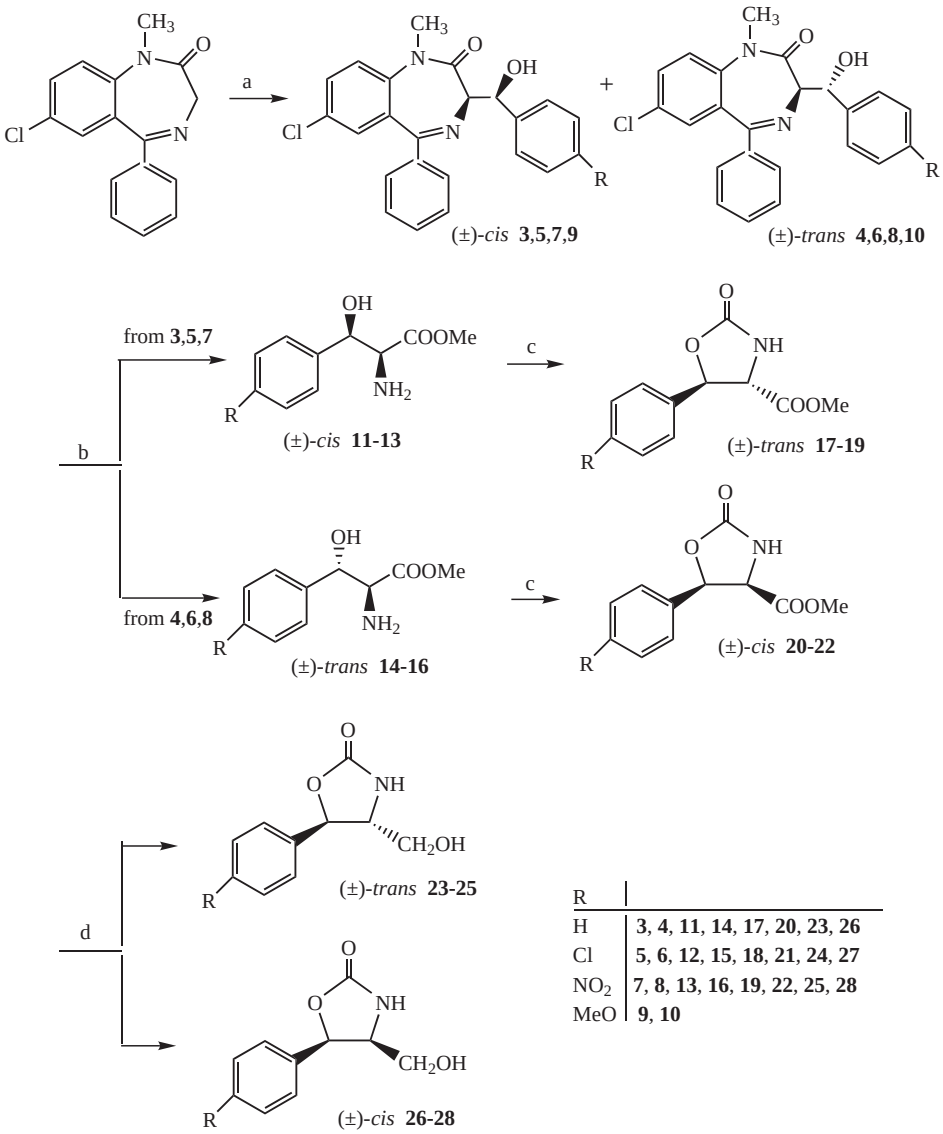


Scheme 1 Synthesis of congeners of epicytoxazone. *Reagents and conditions*: a) LDA/THF/Ar-CHO; b) *i*. concd HCl/AcOH, *ii*. aq NH_4OH, *iii*. TMSCl/MeOH; c) $(CCl_3)_2CO/Et_3N$/THF; d) $NaBH_4/CaCl_2$/THF

NMR spectra; for all oxazolidinones in the *cis* series ^3J is ca 8 Hz, while for the *trans* series ^3J is ca 5 Hz.

The racemic diastereomers **2a** and **2b** were separated by HPLC on the chiral columns Chiralcel OB-H and Chiralpak AS, respectively. Their CD spectra in MeCN, and those of the formerly prepared enantiomers of cytoxazone **1a** and epicytoxazone **1b**,[3] are presented in Figures 2 and 3.

The absolute configuration (4*R*,5*R*) of (–)-cytoxazone was elucidated by means of an X-ray structure analysis,[2] and of its *trans*-(–)-**1** epimer as (4*R*,5*S*) by chemical correlation.[6] Former structural and synthetic studies, and our completed synthesis of all four stereoisomers, have revealed for enantiomers of **1** that the sign of $[\alpha]_D$ is dictated by the absolute configuration at C(4); (+) for the (4*S*) stereoisomers and (–) for the (4*R*) stereoisomers. We expected to obtain some information from the CD spectra of

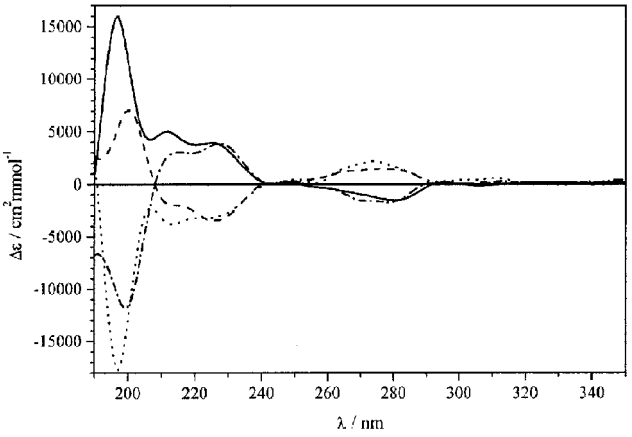
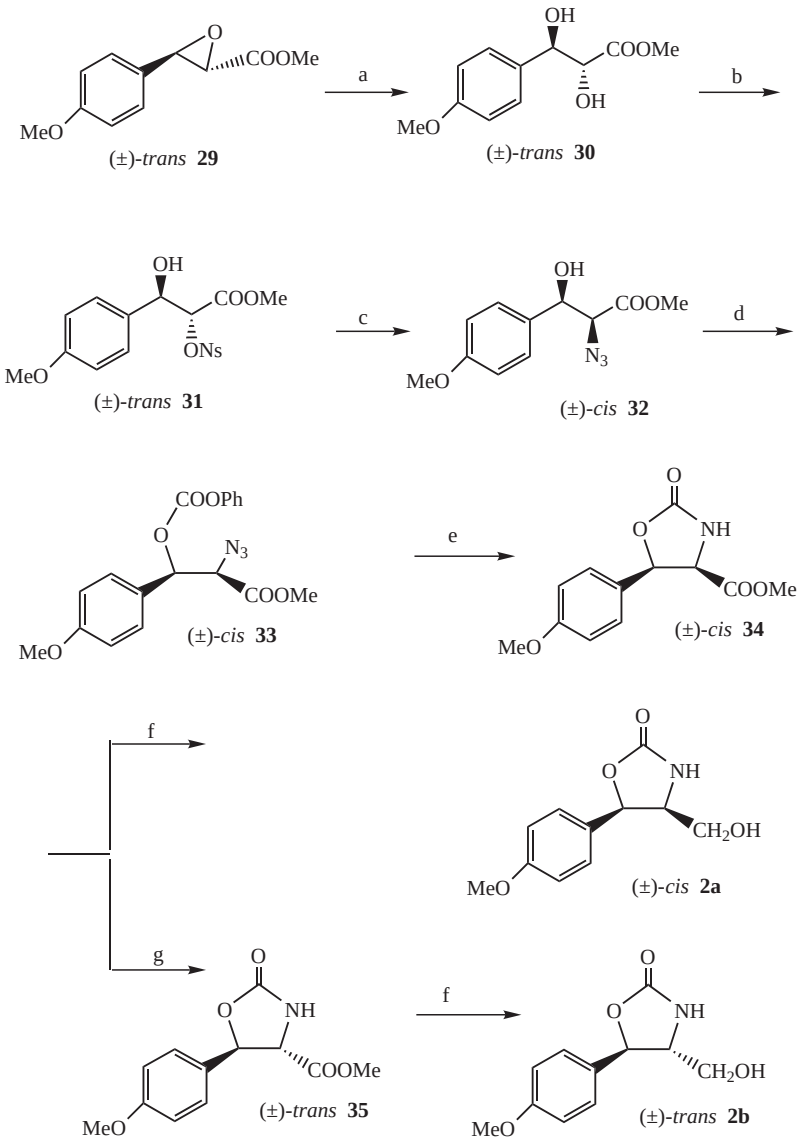


Figure 2 CD spectra of (+)-**1a** (——), (–)-**1a** (-.-.-.-), (+)-**1b** (- - - -) and (–)-**1b** (.....), measured in MeCN



Scheme 2 Synthesis of *cis*- and *trans*-epicytoxazones. *Reagents and conditions*: a) H^+/aq 1,4-dioxane; b) NsCl, Et_3N; c) NaN_3/DMF; d) $PhOCOCl/CH_2Cl_2$, –5 °C; e) PPh_3/aq THF, 50 °C; f) $NaBH_4/CaCl_2$/EtOH, r.t.; g) *i*. KOH/EtOH, reflux, *ii*. MeI/Na_2CO_2/DMF, r.t.

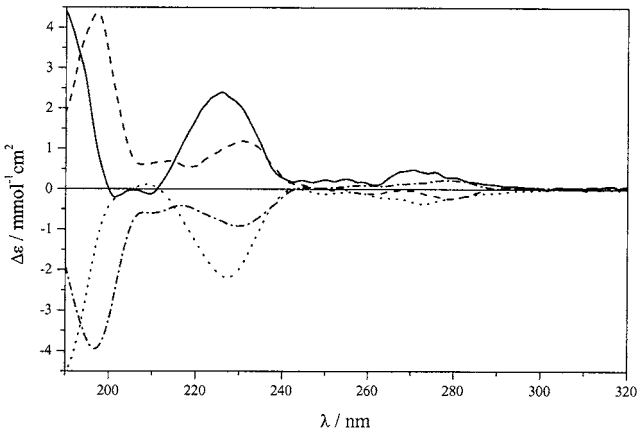


Figure 3 CD spectra of (+)-**2a** (——), (–)-**2a** (.....), (+)-**2b** (- - - -) and (–)-**2b** (-.-.-.-), measured in MeCN

compounds **2** that will allow the determination of the absolute configuration in the *iso* series.

In the CD spectra of **1a** and **1b**, a group of week bands (Δε ca 0.5) is observed between λ = 250–290 nm, two stronger bands (Δε = 1.5–2) in the region λ = 210–240 nm, and a third band (Δε = 6.5 for **1a** and 2.5 for **1b**) in the region λ = 195–200 nm. In the CD spectra of **2a** and **2b** the region of week bands (Δε > 0.5) extends between λ = 240–300 nm; stronger bands at λ ca 230 nm (Δε = 1–2.5), and between λ = 190–200 nm (Δε = 4–4.5) are observed. In the cytoxazine series the (+)-enantiomers of **1a** and **1b** exhibit a negative sign of the short- and medium-wavelength band at λ ca 200 nm and λ ca 220 nm, whereas in the *iso* series the (+)-enantiomers of **2a** and **2b** exhibit a positive sign of the two bands.

This nearly enantiomorphic relation of the strong CD bands of cytoxazone (**1a**) enantiomers and their isomers

(**2a**) is remarkable. Both isomers in the *epi*-(*trans*) series have the same sign of $[\alpha]_D$ and the same sign of CD extremes. However, all these data do not allow the assignment of the absolute configuration to the *trans* enantiomers. Namely, there is no suitable and clearly identifiable π–π^* transition that can serve as the second chromophore for excitation coupling with the aryl chromophore, since the UV properties of the HN–C(=O)–O-chromophore are not known. The application of a more sophisticated, recently developed method, based on the complexes with a porphyrin tweezer, is envisaged.[10,11]

IR spectra were recorded on a Perkin Elmer 297 spectrometer with KBr pallets. ^{1}H and ^{13}C NMR spectra were obtained with a Varian Gemini XL 300 spectrometer, with δ in ppm relative to TMS as internal reference, and *J* in Hz. CD spectra were recorded on a JASCO-810 spectropolarimeter (at 25 °C using 1 mm quartz cells in the concentration range 1×10^{-4} to 5×10^{-4} moldm^{-3}. HPLC chromatography was performed on a HP 1050 chromatograph with a Nucleosil C_{18} reversed phase column (250 × 4.6 mm); separation was monitored by a HP 1050 UV detector set up at λ = 235 nm and connected to a HP 3396A integrator. Melting points were determined on a Electrothermal Apparatus and are uncorrected. HRMS was performed on an Extrel-FTMS 2001 DD instrument; the HPLC purity of all analytical samples was >99.5%.

All commercial reagents were used as received; during usual workup all organic solutions were dried with Na_2SO_4 and evaporated in vacuo. Intermediates **3**–**10**,[8] and epoxide **29**[12] have been prepared as reported in the literature.

Hydrolytic Cleavage of the *cis*- and *trans*-Aldol Products 3–10; General Procedure

A solution of the racemic diastereomer (11.0 mmol) in a mixture of concd aq HCl (40 mL) and CH_3CO_2H (60 mL) was refluxed for 16 h. The solvent mixture was evaporated in vacuo azeotropically with *i*-PrOH (3 × 120 mL). The crude product was dissolved in H_2O (15 mL), adjusted to neutral pH with aq NH_4OH (5.0 mL) and the side product, 2-amino-5-chloro-benzophenone, was extracted with CH_2Cl_2 (4 × 10 mL). The aqueous layer was evaporated in vacuo azeotropically with *i*-PrOH (2 × 50 mL). The crude ammonium salt of the α-amino-β-hydroxy acid was dried at 0.1 mm Torr and used without purification in the next step.

To the suspension of the crude ammonium salt of the α-amino-β-hydroxy acid (8.0 mmol) in absolute MeOH (10 mL) chlorotrimethylsilane (TMSCl, 4.3 g, 5.0 mL, 40 mmol) was added, the reaction mixture (protected from moisture by P_2O_5) was stirred for 18 h at r.t. and then heated at reflux for 3 h. The solvent and TMSCl were evaporated at reduced pressure. The crude product was dissolved in EtOAc (15 mL), washed with a diluted aq solution of $NaHCO_3$ (10 mL), and the aqueous layer extracted with EtOAc (3 × 10 mL). After the usual workup the products were purified by chromatography or by crystallization.

Methyl (β*R*)-β-Hydroxy-l-phenylalaninate [(±)-11]

The pure product was obtained as thick oil after chromatography on silica gel (CH_2Cl_2–MeOH, 5.0:0.3), yield: 38%.

IR (film): 3280, 2940, 2215, 1735, 1435, 1345, 1200, 1010, 740, 700 cm^{-1}.

^{1}H NMR (acetone-d_6): δ = 3.69 (s, 3 H), 3.76 (d, *J* = 7.7 Hz, 1 H), 4.80 (d, *J* = 7.7 Hz, 1 H), 7.25–7.40 (m, 5 H).

^{13}C NMR (acetone-d_6): δ = 52.5, 69.0, 83.0, 127.1, 128.5, 129.1, 141.7, 172.7.

HRMS: *m*/*z* [M + H$^+$] calcd for $C_{10}H_{13}NO_3$, 196.0968; found, 196.0987.

Methyl (β*R*)-4-Chloro-β-hydroxy-l-phenylalaninate [(±)-12]

The pure product was crystallized from MeOH, yield: 41%.

Mp 102.5–103.0 °C.

IR (KBr): 3440, 3250, 1735, 1355, 1340, 1215, 1200, 1090, 990, 840, 800 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 3.53 (d, *J* = 4.4 Hz, 1 H), 3.65 (s, 3 H), 4.82 (d, *J* = 4.4 Hz, 1 H), 7.22–7.31 (m, 4 H).

^{13}C NMR ($CDCl_3$): δ = 52.1, 60.3, 73.2, 127.2, 128.3, 133.3, 139.2, 173.3.

HRMS: *m*/*z* [M + H$^+$] calcd for $C_{10}H_{12}ClNO_3$, 230.0578; found, 230.0557.

Methyl (β*R*)-β-Hydroxy-4-nitro-l-phenylalaninate [(±)-13]

The pure product was crystallized from MeOH, yield. 60%.

Mp 141.0–142.0 °C.

IR (KBr): 3330, 3280, 2900, 2830, 1725, 1615, 1510, 1345, 1215, 1010, 710 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 1.63 (br s, 2 H), 3.53 (d, *J* = 3.3 Hz, 1 H), 3.67 (s, 3 H), 4.98 (s, 1 H), 5.83 (d, *J* = 4.7 Hz, 1 H), 7.59 (d, *J* = 8.3 Hz, 2 H), 8.15 (d, *J* = 8.6 Hz, 2 H).

^{13}C NMR (DMSO-d_6): δ = 61.4, 70.1, 82.9, 132.5, 137.3, 156.1, 160.6, 183.6.

HRMS: *m*/*z* [M + H$^+$] calcd for $C_{10}H_{12}N_2O_5$, 241.0819; found, 241.0832.

Methyl (β*S*)-β-Hydroxy-l-phenylalaninate [(±)-14]

The pure product was crystallized from EtOAc–*n*-hexane, yield: 59%.

Mp 105.5–106.0 °C.

IR (KBr): 3080, 2860, 1725, 1580, 1435, 1285, 1210, 1170, 1040, 910, 770, 700 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 3.66 (s, 3 H), 3.76 (d, *J* = 5.5 Hz, 1 H), 4.91 (d, *J* = 5.5 Hz, 1 H), 7.24–7.34 (m, 5 H).

^{13}C NMR ($CDCl_3$): δ = 51.8, 59.8, 74.1, 126.1, 127.9, 128.1, 139.6, 173.3.

HRMS: *m*/*z* [M + H$^+$] calcd for $C_{10}H_{13}NO_5$, 196.0968; found, 196.0971.

Methyl (β*S*)-4-Chloro-β-hydroxy-l-phenylalaninate [(±)-15]

The pure product was crystallized from MeOH, yield: 23%.

Mp 119.5–120.0 °C.

IR (KBr): 3100, 2840, 1715, 1575, 1435, 1280, 1200, 1170, 1030, 915, 820 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 3.69 (s, 3 H), 3.81 (br s, 1 H), 4.94 (br s, 1 H), 7.23–7.30 (m, 4 H).

^{13}C NMR ($CDCl_3$): δ = 52.0, 59.5, 73.3, 127.5, 128.4, 133.7, 138.1, 173.2.

HRMS: *m*/*z* [M + H$^+$] calcd for $C_{10}H_{12}ClNO_3$, 230.0578; found, 230.0605.

Methyl (β*S*)-β-Hydroxy-4-nitro-l-phenylalaninate [(±)-16]

The pure product was crystallized from EtOAc, yield: 48%.

Mp 121.0–122.0 °C.

IR (KBr): 3350, 3100, 2840, 1700, 1500, 1350, 1215, 1015, 840 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 3.67 (s, 3 H), 3.88 (d, *J* = 4.7 Hz, 1 H), 5.07 (d, *J* = 4.8 Hz, 1 H), 7.47 (d, *J* = 8.5 Hz, 2 H), 8.19 (d, *J* = 8.3 Hz, 2 H).

^{13}C NMR ($CDCl_3$): δ = 51.5, 59.9, 78.0, 123.3, 127.1, 147.2, 147.5, 172.7.

HRMS: *m*/*z* [M + H$^+$] calcd for $C_{10}H_{12}N_2O_5$, 241.0819; found, 241.0797.

Cyclization of α-Amino-β-hydroxy Esters to 1,3-Oxazolidin-2-ones; General Procedure

The reaction was performed under an atmosphere of dry argon. To a cold (–10 °C to –15 °C) solution of *cis*-**11**–**13** or *trans*-**14**–**16** (1.5 mmol) and Et_3N (425 mg, 4.2 mmol) in absolute THF (10 mL) triphosgene (145 mg, 0.6 mmol) was added at once. The reaction mixture was stirred 60 min at –10 °C and 90 min at r.t., then Et_3N·HCl was filtered off and washed with THF (10 mL). The filtrate was evaporated and the crude product was dissolved in EtOAc (5 mL) and washed with a sat. aq solution of $NaHCO_3$ (5 mL). The aqueous layer was extracted with EtOAc (4 × 5 mL) and worked up as usual. The crude products were purified by chromatography on silica gel; the solvent mixtures used and the recrystallization solvent are indicated for any single product.

Methyl (4*S*,5*R*)-2-Oxo-5-phenyl-1,3-oxazolidin-4-carboxylate [(±)-17]

Starting from *cis*-**11**, the reaction was completed after 120 min at 0–5 °C. The crude product was purified by chromatography (12 g silica gel; TBME–EtOAc, 5.0:0.3) and recrystallized from TBME, yield: 211 mg (60%).

Mp 75.0–76.0 °C.

IR (KBr): 3250, 1750, 1710, 1300, 1220, 1190, 1215, 980, 930, 760, 730 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 3.86 (s, 3 H), 4.33 (d, *J* = 4.9 Hz, 1 H), 5.65 (d, *J* = 5.0 Hz, 1 H), 6.88 (s, 1 H), 7.35–7.50 (m, 5 H).

^{13}C NMR ($CDCl_3$): δ = 53.1, 61.2, 79.3, 125.2, 128.8, 129.0, 137.9, 158.4, 170.1.

HRMS: *m*/*z* [M$^+$] calcd for $C_{11}H_{11}NO_4$, 221.0682; found, 221.0658.

Methyl (4*S*,5*R*)-5-(4-Chlorophenyl)-2-oxo-1,3-oxazolidin-4-carboxylate [(±)-18]

The crude product was purified by chromatography (15 g silica gel; CH_2Cl_2–MeOH, 5.0:0.3) and recrystallized from CCl_4, yield: 77%.

Mp 90.5–91.0 °C.

IR (KBr): 3240, 3140, 2950, 2400, 1790, 1755, 1495, 1440, 1385, 1310, 1250, 1225, 1190, 1040, 1000, 905, 820, 745 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 3.89 (s, 3 H), 4.26 (d, *J* = 4.9 Hz, 1 H), 5.66 (d, *J* = 5.0 Hz, 1 H), 6.07 (s, 1 H), 7.37–7.44 (m, 4 H).

^{13}C NMR (CD_3OD): δ = 53.6, 62.7, 80.2, 128.5, 130.3, 136.1, 138.9, 171.9.

HRMS: *m*/*z* [M + H$^+$] calcd for $C_{11}H_{10}ClNO_4$, 256.0371; found, 256.0368.

Methyl (4*S*,5*R*)-5-(4-nitrophenyl)-2-oxo-1,3-oxazolidin-4-carboxylate [(±)-19]

Starting from *cis*-**13**, the reaction was completed in 2.5 h at r.t. After the usual workup the crude product was crystallized from EtOAc, yield: 86%.

Mp 125.0–126.0 °C.

IR (KBr): 3230, 3140, 1760, 1740, 1510, 1340, 1275, 1225, 1035, 840, 730 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 3.96 (s, 3 H), 4.62 (d, *J* = 5.1 Hz, 1 H), 6.00 (d, *J* = 4.7 Hz, 1 H), 7.61 (s, 1 H), 7.91 (d, *J* = 8.5 Hz, 2 H), 8.48 (d, *J* = 8.7 Hz, 2 H).

^{13}C NMR ($CDCl_3$): δ = 53.5, 60.8, 77.9, 124.2, 126.1, 144.7, 148.2, 157.2, 169.3.

HRMS: *m*/*z* [M + H$^+$] calcd for $C_{11}H_{10}N_2O_6$, 267.0612; found, 267.0604.

Methyl (4*R*,5*R*)-2-Oxo-5-phenyl-1,3-oxazolidin-4-carboxylate [(±)-20]

Starting from *trans*-**14**, the reaction was completed in 1 h at r.t. The product was purified by chromatography (15 g silica gel; TBME–MeOH, 5.0:0.3), yield: 85%.

Mp 160.0–161.0 °C.

IR (KBr): 3060, 1720, 1590, 1425, 1200, 995 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 3.17 (s, 3 H), 4.76 (d, *J* = 9 Hz, 1 H), 5.93 (d, *J* = 8.7 Hz, 1 H), 7.28 (d, *J* = 8.4 Hz, 2 H), 7.48 (d, *J* = 8.4 Hz, 2 H), 8.32 (s, 1 H).

^{13}C NMR (acetone-d_6): δ = 52.2, 60.6, 78.7, 129.0, 129.3, 135.1, 158.9, 170.4.

HRMS: *m*/*z* [M$^+$] calcd for $C_{11}H_{10}ClNO_4$, 255.0293; found, 255.0306.

Methyl (4*R*,5*R*)-5-(4-Chlorophenyl)-2-oxo-1,3-oxazolidin-4-carboxylate [(±)-21]

Starting from *trans*-**15**, the reaction mixture was stirred for 1 h at –10 °C, then 4 h at r.t. until completion. The crude product was purified by crystallization from EtOAc, yield: 83%.

Mp 151.0–152.0 °C.

IR (KBr): 3260, 1750, 1355, 1240, 1225, 1210, 1330, 1320, 1015, 760, 700 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 3.21 (s, 3 H), 4.71 (d, *J* = 9.1 Hz, 1 H), 5.85 (d, *J* = 9.1 Hz, 1 H), 6.69 (s, 1 H), 7.30–7.37 (m, 5 H).

^{13}C NMR ($CDCl_3$): δ = 52.0, 59.9, 79.1, 126.0, 128.2, 129.1, 133.8, 159.1, 169.0.

HRMS: *m*/*z* [M$^+$] calcd for $C_{11}H_{11}NO_4$, 221.0682; found, 221.0656.

Methyl (4*R*,5*R*)-5-(4-nitrophenyl)-2-oxo-1,3-oxazolidin-4-carboxylate [(±)-22]

Starting from *trans*-**16**, the reaction was completed in 30 min at r.t. After aqueous workup, the crude product was purified by crystallization from EtOAc, yield: 77%.

Mp 171.0–172.0 °C.

IR (KBr): 3330, 1765, 1725, 1510, 1340, 1215, 1130, 1095, 850, 740 cm^{-1}.

^{1}H NMR (acetone-d_6): δ = 3.31 (s, 3 H), 4.77 (d, *J* = 8.8 Hz, 1 H), 5.58 (s, 1 H), 5.96 (d; *J* = 9.1 Hz, 1 H), 7.56 (d, *J* = 8.5 Hz, 2 H), 8.28 (d, *J* = 8.5 Hz, 2 H).

^{13}C NMR (acetone-d_6): δ = 52.3, 60.5, 78.3, 124.3, 128.5, 143.4, 149.2, 158.6, 170.3.

HRMS: *m*/*z* [M$^+$] calcd for $C_{11}H_{10}N_2O_6$, 266.0533; found, 266.0512.

Reduction of Oxazolidincarboxylic Acid Esters to Hydroxymethyl Derivatives 23–28; General Procedure

In the solution of *trans*-**17**–**19** or *cis*-**20**–**22** (0.7 mmol) in absolute EtOH (10 mL) $CaCl_2$ (1.2 mmol) was slurried, then $NaBH_4$ (1.3 mmol) was added at once. The reaction mixture was stirred at r.t. for 1 h under dry argon atmosphere, then quenched with a sat. aq NH_4Cl solution (10 mL). EtOH was evaporated and the residue triturated with a sat. aq solution of NH_4Cl (5 mL). After extraction with

EtOAc (3 × 10 mL) and the usual workup, the crude product was purified by chromatography or by crystallization.

(4*R*,5*R*)-4-Hydroxymethyl-5-phenyl-1,3-oxazolidin-2-one [(±)-23]

The crude product was purified by chromatography (TBME–MeOH, 5.0:0.5) and recrystallized from CH_2Cl_2–*i*-Pr_2O, yield: 113 mg (83%).

Mp 109.0–109.5 °C.

IR (KBr): 3460, 3240, 1715, 1390, 1275, 1240, 1200, 1040, 1010, 755 cm^{-1}.

^1H NMR (acetone-d_6): δ = 3.70–3.81 (m, 3 H), 4.50 (br s, 1 H), 5.42 (d, *J* = 4.7 Hz, 1 H), 7.04 (s, 1 H), 7.34–7.45 (m, 5 H).

^{13}C NMR (acetone-d_6): δ = 62.7, 63.9, 80.0, 126.6, 129.3, 129.7, 141.2, 159.5.

HRMS: *m*/*z* [M + H^+] calcd for $C_{10}H_{11}NO_3$, 194.0812; found, 194.0839.

(4*R*,5*R*)-5-(4-Chlorophenyl)-4-(hydroxymethyl)-1,3-oxazolidin-2-one [(±)-24]

The crude product was purified by chromatography (CH_2Cl_2–MeOH, 5.0:0.5) and recrystallized from MeOH–TBME, yield: 120 mg (75%).

Mp 105.5–106.5 °C.

IR (KBr): 3310, 1725, 1395, 1290, 1205, 1085, 1025, 1010, 815, 805 cm^{-1}.

^1H NMR (acetone-d_6): δ = 3.67–3.77 (m, 3 H), 4.42 (br s, 1 H), 5.40 (d, *J* = 4.3 Hz, 1 H), 6.95 (s, 1 H), 7.44 (s, 4 H).

^{13}C NMR (acetone-d_6): δ = 61.8, 63.1, 78.6, 127.6, 128.9, 133.8, 139.3, 158.3.

HRMS: *m*/*z* [M + H^+] calcd for $C_{10}H_{10}ClNO_3$, 228.0422; found, 228.0416.

(4*R*,5*R*)-5-(4-Nitrophenyl)-4-(hydroxymethyl)-1,3-oxazolidin-2-one [(±)-25]

The pure product was obtained by crystallization from MeOH–TBME, yield: 160 mg (95%).

Mp 129.5–130.0 °C.

IR (KBr): 3350, 1740, 1500, 1340, 1035, 735 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 3.92 (s, 2 H), 4.29 (d, *J* = 5.2 Hz, 1 H), 5.80 (d, *J* = 5.2 Hz, 1 H), 6.39 (s, 1 H), 7.67 (d, *J* = 8.2 Hz, 2 H), 8.31 (d, *J* = 8.8 Hz, 2 H).

^{13}C NMR (acetone-d_6): δ = 62.4, 64.0, 78.9, 124.8, 127.6, 148.5, 148.7, 159.5.

HRMS: *m*/*z* [M + H^+] calcd for $C_{10}H_{10}N_2O_5$, 239.0662; found, 239.0655.

(4*S*,5*R*)-4-Hydroxymethyl-5-phenyl-1,3-oxazolidin-2-one [(±)-26]

The crude product was purified by chromatography (TBME–MeOH, 5.0:1.0) and recrystallized from MeOH–TBME, yield: 118 mg (87%).

Mp 97.5–98.0 °C.

IR (KBr): 3380, 1800, 1710, 1415, 1240, 1220, 1040, 1015, 930, 690 cm^{-1}.

^1H NMR (acetone-d_6): δ = 3.18–3.30 (m, 2 H), 3.94 (br s, 1 H), 4.28–4.35 (m, 1 H), 5.90 (d, *J* = 8.3 Hz, 1 H), 6.93 (s, 1 H), 7.46–7.56 (m, 5 H).

^{13}C NMR (acetone-d_6): δ = 58.4, 62.9, 79.5, 127.0, 129.1, 136.7, 159.4.

HRMS: *m*/*z* [M + H^+] calcd for $C_{10}H_{11}NO_3$, 194.0812; found, 194.0800.

(4*S*,5*R*)-5-(4-Chlorophenyl)-4-(hydroxymethyl)-1,3-oxazolidin-2-one [(±)-27]

The crude product was purified by chromatography (CH_2Cl_2–MeOH, 5.0:0.5) and recrystallization from MeOH–TBME, yield: 150 mg (95%).

Mp 106.5–107.5 °C.

IR (KBr): 3280, 1715, 1370, 1290, 1040, 1015, 1000, 790 cm^{-1}.

^1H NMR (acetone-d_6): δ = 3.09–3.22 (m, 2 H), 3.98 (s, 1 H), 4.15–4.22 (m, 1 H), 5.79 (d, *J* = 8.3 Hz, 1 H) 6.88 (s, 1 H), 7.43 (s, 4 H).

^{13}C NMR (acetone-d_6): δ = 57.5, 61.8, 78.3, 128.2, 128.5, 133.6, 135.0, 158.0.

HRMS: *m*/*z* [M + H^+] calcd for $C_{10}H_{10}ClNO_3$, 228.0422; found, 228.0409.

(4*S*,5*R*)-5-(4-Nitrophenyl)-4-(hydroxymethyl)-1,3-oxazolidin-2-one [(±)-28]

The pure product was obtained by crystallization from MeOH, yield: 158 mg (94%).

Mp 159.0–160.0 °C.

IR (KBr): 3200, 3110, 1735, 1500, 1340, 1225, 1200, 1090, 1030, 980 cm^{-1}.

^1H NMR (acetone-d_6): δ = 2.91 (s, 1 H), 3.11–3.27 (m, 2 H), 4.25–4.31 (m, 1 H), 5.96 (d, *J* = 8.3 Hz, 1 H), 6.95 (s, 1 H), 7.72 (d, *J* = 8.3 Hz, 2 H), 8.28 (d, *J* = 8.3 Hz, 2 H).

^{13}C NMR (acetone-d_6): δ = 58.1, 62.1, 78.8, 124.1, 128.5, 144.3, 148.8, 158.9.

HRMS: *m*/*z* [M + H^+] calcd for $C_{10}H_{10}N_2O_5$, 239.0662; found, 239.0675.

Methyl (2*R*,3*R*)-2,3-Dihydroxy-3-(4-methoxyphenyl)propanoate [(±)-30]

To the solution of *trans*-epoxide **29** (4.0 g, 19.0 mmol) in 1,4-dioxane–H_2O (80:20 mL), concd H_2SO_4 (0.5 mL) was added at r.t. The reaction mixture was stirred for 30 min, EtOAc (100 mL) was added and the organic layer was washed with sat. aq $NaHCO_3$ solution followed by H_2O. Upon usual workup, 3.7 g (85%) of a 7:3 mixture of *trans*/*cis*-**30** was obtained and used as such in the next step.

Methyl (2*R*,3*R*)-2-Nosyl-3-hydroxy-3-(4-methoxyphenyl)propanoate [(±)-31]

The crude mixture of *cis*/*trans*-**30** (3.0 g, 13.2 mmol) was dissolved in CH_2Cl_2 (40 mL). The solution was cooled to –10 °C, Et_3N (2.0 mL, 15 mmol) was added, followed by NsCl (2.5 g, 10 mmol), which was added in portions during 2 h. The reaction mixture was stirred for another 2 h at 10 °C, than was diluted with CH_2Cl_2 (50 mL) and washed with 0.5 M aq HCl, H_2O and aq bicarbonate solution. The crude product (4.1 g) was crystallized from EtOAc–*n*-hexane (25:75) to afford 1.4 g (28%) of stereochemically pure *trans*-nosylate **31** (96% pure by HPLC).

Mp 121.0–122.0 °C (dec.).

IR (KBr): 3510, 3100, 2960, 1730, 1610, 1350, 1175, 1000, 900 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 3.76 (s, 6 H), 4.99 (d, *J* = 3.5 Hz, 1 H), 5.20 (d, *J* = 3.5 Hz, 1 H), 6.71 (d, *J* = 8.7 Hz, 2 H), 7.13 (d, *J* = 8.7 Hz, 2 H), 7.81 (d, *J* = 8.3 Hz, 2 H), 8.21 (d, *J* = 8.3 Hz, 2 H).

^{13}C NMR ($CDCl_3$): δ = 53.0, 55.1, 70.5, 73.0, 80.6, 82.3, 113.7, 123.9, 127.1, 127.9, 129.0, 141.3, 150.3, 159.7, 166.8.

Methyl (2*S*,3*R*)-2-Azido-3-hydroxy-3-(4-methoxyphenyl)propanoate [(±)-32]

To a solution of *trans*-**31** (1.05 g, 2.3 mmol) in DMF (20 mL) NaN_3 (260 mg, 3.1 mmol) was added. The reaction mixture was heated to 45 °C for 15 h, then EtOAc (60 mL) was added. The solution was washed with H_2O and 5% aq $NaHCO_3$ solution. Upon usual workup the crude product was purified on a silica gel column (EtOAc–*n*-hexane, 3.0:7.0). Pure fractions yielded 455 mg (78%) of *cis*-**32**.

Mp 114.0–115.0 °C.

IR (KBr): 3420, 2900, 2110, 1720, 1605, 1220, 1020,780 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 3.79 (s, 3 H), 3.81 (s, 3 H), 4.10 (d, *J* = 7 Hz, 1 H), 4.96 (d, *J* = 7 Hz, 1 H), 6.85 (d, *J* = 8.5 Hz, 2 H), 7.31 (d, *J* = 8.5 Hz, 2 H).

^{13}C NMR ($CDCl_3$): δ = 52.7, 55.1, 66.7, 73.6, 113.9, 127.7, 130.8, 159.7, 169.3.

HRMS: *m*/*z* [M^+] calcd for $C_{11}H_{14}N_3O_4$, 252.0979; found, 252.1002.

Methyl (4*R*,5*R*)-5-(4-Methoxyphenyl)-2-oxo-1,3-oxazolidine-4-carboxylate [(±)-34]

To the solution of *cis*-**32** (60 mg, 0.25 mmol) in CH_2Cl_2 (2.0 mL) containing (50 μL, 1.0 mmol) of pyridine, phenylchloroformate (100 μL, 0.7 mmol) was added at –10 °C. After stirring overnight at r.t., the reaction mixture was poured on H_2O (20 mL) and extracted with EtOAc (3 × 30mL). The extracts were washed with H_2O, aq bicarbonate solution, and worked up as usual. Crude *cis*-**33** (160 mg) was dissolved in THF (2.0 mL), then triphenylphosphane (330 mg, 1.2 mmol) and H_2O (80 μL) were added. The reaction mixture was stirred at 50 °C for 1 h, the solvent was evaporated and the solid residue dissolved in EtOAc (50 mL), washed with 5% aq NaCl solution and dried. Crystallization of the crude product from *i*-Pr_2O yielded 50 mg (80%) of *cis*-**34** (98% pure by HPLC).

Mp 136.0–137.0 °C.

IR (KBr): 3420, 2930, 1730, 1600, 1500, 1240, 1090, 980 cm^{-1}.

^1H NMR (CD_3OD): δ = 3.33 (s, 3 H), 3.88 (s, 3 H), 4.79 (d, *J* = 9 Hz, 1 H), 5.96 (d, *J* = 9 Hz, 1 H), 7.01 (d, *J* = 9 Hz, 2 H), 7.33 (d, *J* = 9 Hz, 2 H).

^{13}C NMR (CD_3OD): δ = 52.8, 56.0, 61.7, 80.8, 115.0, 128.0, 129.1, 162.0, 171.5.

HRMS: *m*/*z* [M^+] calcd for $C_{12}H_{14}NO_5$, 252.0866; found, 252.0857.

(4*S*,5*R*)-4-Hydroxymethyl-5-(4-methoxyphenyl)-1,3-oxazolidin-2-one [(±)-2a]

Isocytoxazone **2a** was prepared by reduction of *cis*-**34** as described in the general procedure for the reduction of **17**–**22**; compound **2a** was obtained in 97% yield.

Mp 136.0–137.0 °C.

IR (KBr): 3460, 3220, 2910, 1730, 1310, 1230, 1015 cm^{-1}.

^1H NMR (CD_3OD): δ = 3.17–3.21 (m, 2 H), 3.89 (s, 3 H), 4.15–4.25 (m, 1 H), 5.80 (d, *J* = 8.5 Hz, 1 H), 7.03 (d, *J* = 8.5 Hz, 2 H), 7.35 (d, *J* = 8.5 Hz, 2 H).

^{13}C NMR (CD_3OD): δ = 50.1, 56.0, 59.5, 63.3, 81.1, 115.1, 128.4, 128.7, 161.6, 162.0.

HRMS: *m*/*z* [M + H^+] calcd for $C_{11}H_{13}NO_4$, 224.0917; found, 224.0936.

Enantiomers of **2a** were separated on the preparative scale on Chiralcel OB-H column (0.46 × 25 cm; EtOH–*n*-hexane, 20:80). First eluted enantiomer: ee >99.5%, $[\alpha]_D^{25}$ –120 (*c* = 0.2, MeOH); second eluted enantiomer: ee 94.5%, $[\alpha]_D^{25}$ +115 (*c* = 0.2, MeOH).

Methyl (4*S*,5*R*)-5-(4-methoxyphenyl)-2-oxo-1,3-oxazolidine-4-carboxylate [(±)-35]

Epimerization of *cis*-**34** (250 mg, 1.0 mmol) in EtOH (5.0 mL) was completed after heating for 1 h under reflux in the presence of KOH (70 mg, 1.2 mmol). Upon cooling, the pH was adjusted to acid medium by 10% aq HCl and the crude product was extracted with EtOAc. The combined extracts were worked up as usual, the crude product was dissolved in DMF (5 mL), K_2CO_3 (150 mg, 1.1 mmol) and MeI (200 mg, 1.40 mmol) were added. The reaction mixture was stirred overnight at r.t., H_2O (15 mL) and EtOAc (20 mL) were added and the organic layer was successively washed with H_2O. The crude product was purified by column chromatography on silica gel (TBME–*n*-hexane, 4.0:1.0). Pure fractions yielded 98 mg (40%) of *trans*-**35** as pale-yellow oil.

IR (neat): 3300, 2930, 1745, 1600, 1500, 1250, 1115, 820 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 3.82 (s, 3 H), 3.84 (s, 3 H), 4.32 (d, *J* = 5.5 Hz, 1 H), 5.58 (d, *J* = 5.5 Hz, 1 H), 6.81 (br s, 1 H), 6.92 (d, *J* = 8.5 Hz, 2 H), 7.34 (d, *J* = 8.5 Hz, 2 H).

^{13}C NMR ($CDCl_3$): δ = 53.0, 55.2, 61.2, 79.3, 114.2, 126.9, 129.7, 158.3, 160.0, 170.1.

HRMS: *m*/*z* [M^+] calcd for $C_{12}H_{14}NO_5$, 252.0866; found, 252.0878.

(4*R*,5*R*)-4-Hydroxymethyl-5-(4-methoxyphenyl)-1,3-oxazolidin-2-one [(±)-2b]

trans-Isocytoxazone **2b** was prepared in 62% yield as described for **2a**; the crude product was recrystallized from TBME–EtOAc (9.0:1.0),

Mp 131.5–133.0 °C.

IR (KBr): 3500, 2950, 1750, 1505, 1230, 1010, 815 cm^{-1}.

^1H NMR (CD_3OD): δ = 3.65–3.97 (m, 3 H), 3.89 (s, 3 H), 5.41 (d, *J* = 5.7 Hz, 1 H), 7.05 (d, *J* = 8.5 Hz, 2 H), 7.42 (d, *J* = 8.5 Hz, 2 H).

^{13}C NMR (CD_3OD): δ = 52.9, 60.5, 60.8, 78.5, 112.4, 125.6, 129.6, 158.7.

HRMS: *m*/*z* [M^+] calcd for $C_{11}H_{13}NO_4$, 223.0839; found, 223.0829.

Enantiomers of **2b** were separated on the preparative scale on Chiralpak AS column (1.0 × 25 cm; 2-PrOH–*n*-hexane, 50:50). First eluted enantiomer: ee >99.5%, $[\alpha]_D^{25}$ +70 (*c* = 0.4, MeOH); second eluted enantiomer: ee 98.2%, $[\alpha]_D^{25}$ –67.5 (*c* = 0.4, MeOH).

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