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Regioselectivity of Ring-Opening Reactions of Optically Active N-Acetyl-2-Methoxycarbonylaziridine.

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Abstract: (S)-(–)-N-acetyl-2-methoxycarbonylaziridine **1** undergoes easy ring-opening by Brønsted acids or nucleophiles in the presence of a Lewis acid catalyst. The regioselectivity is not always exclusive, affording optically active α- and β-aminoacids.

Introduction

In recent years there has been an increasing interest in the use of aziridine-2-carboxylates as intermediates for the synthesis of biologically active compounds, such as α- and β-aminoacids or β-lactam antibiotics.[1]

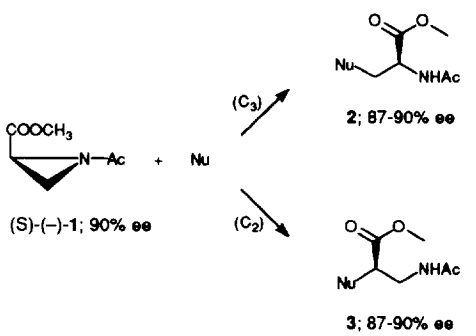
Aziridine-2-carboxylates can be obtained in enantiomerically pure forms by several procedures and their reactivity can be modified by a suitable choice of the substituent at the nitrogen atom: the introduction of an electron-withdrawing group, such as an acyl or sulphonyl group, is known to activate the compounds towards nucleophilic ring-opening reactions. Several examples of regio- and stereocontrolled ring-opening reactions are reported as providing a great number of useful synthetic intermediates, and many studies have been carried out on the effect of the ring substituents and of the nature of the nucleophile on the regioselectivity of the aziridine ring-opening process.[1,2] Relatively little is known about the regioselectivity of the reactions of monosubstituted aziridines.[3]

In this paper we report the regioselectivities observed when optically active (S)-(–)-N-acetyl-2-methoxycarbonylaziridine **1**, 90% enantiomeric excess (ee), was treated with Brønsted acids or nucleophiles in the presence of a Lewis acid catalyst.

Results and discussion

(S)-(–)-*N-acetyl-2-methoxycarbonylaziridine* **1**. – Racemic aziridine **1** was synthesized and resolved in highly optically active form (90% ee), following the procedure reported elsewhere.[4]

Nucleophilic ring-opening reactions.– The ring-opening of (S)-(–)-**1**, to afford non-natural α- and β-aminoacids, was performed by treatment with the Brønsted acids, hydrogen chloride, acetic acid and *p*.toluenesulphonic acid, or with the nucleophiles, methanol, benzyl thiol, sodium azide, indole or acetonitrile in the presence of a Lewis acid catalyst. The protonation or Lewis acid coordination to the N-acetylaziridine further increases the reactivity of the ring towards nucleophiles.[5] The ring-opening products indicate that the reactions occur with the nucleophilic attack at both the C_3 and C_2 ring-carbon atoms: two regioisomers, **2** and **3**, an α- and a β-aminoacid respectively, are obtained, Scheme 1.



Product	Nu
2a	CH_3COO
2b	*p*.TolSO$_3$
2c	CH_3O
2d,3d	Cl
2e,3e	$C_6H_5CH_2S$
2f, 3f	Indole
2g,3g	N_3
2h	CH_3CONH

Scheme 1

The optically active ring-opening products were identified by their mass-spectra or microanalyses and ^{1}H-NMR data. Enantiomeric excesses were determined by the analysis of the ^{1}H-NMR spectra recorded in C_6D_6 and in the presence of a 5-fold excess of the chiral solvating agent, (R)-(–)-2,2,2-trifluoro-1-(9-anthryl)ethanol, for the unknown products **2(a-c,e,g,h)** and **3(d-g)** and by comparison with the value reported in the literature for the known compounds **2(d,f)**. The chemical shift doublings (Table 1) refer in particular to methyl groups: the magnitudes of nonequivalence are high enough to allow the determination of nonequivalence senses and enantiomeric purities.

Absolute configurations were assigned by assuming that the ring-opening reactions occur with a S_N2-like mechanism, as verified for the reaction with sodium azide by chemical correlation.[4] So, α-aminoacids **2**, with the same configuration[6] as aziridine (S)-(–)-**1**, are expected from a nucleophilic attack at the C_3 carbon atom and β-aminoacids **3**, with opposite configuration, from a C_2 stereogenic centre nucleophilic attack. Nonequivalence senses of the carbomethoxy groups in α-aminoacids **2**, relating to the assigned configurations, agree well with the literature data: (S)-α-aminoesters are reported to exhibit a high field sense of nonequivalence when examined in the presence of (R)-(–)-2,2,2-trifluoro-1-phenylethanol.[7]

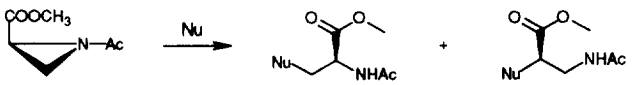
The results are summarized in Table 1. In particular, acetolysis of (S)-(–)-**1** for 15 h at room temperature afforded a single optically active product (87% ee) identified by ^{1}H-NMR spectroscopy as (+)-2-acetamido-3-acetoxypropanoic acid methyl ester **2a**, arising from the regiospecific attack of the nucleophile at the C_3 ring carbon atom.

The same C_3 nucleophilic attack was observed in the reaction with *p*.toluenesulphonic acid in methylene chloride at room temperature: after 20 min (+)-2-acetamido-3-*p*.tolylsulphonyloxypropanoic acid methyl ester **2b** was recovered in optically active form (90% ee) as the sole ring-opening product.

Methanolysis, in the presence of boron trifluoride etherate as catalyst, followed a similar chemical path yielding the nearly optically pure (+)-2-acetamido-3-methoxypropanoic acid methyl ester **2c**.

(S)-(–)-**1**, upon treatment with dry HCl in methylene chloride, yielded two optically active regioisomers, in 1:1 ratio, namely, (+)-2-acetamido-3-chloropropanoic acid methyl ester **2d** in 90% ee[8] and (–)-3-acetamido-2-chloropropanoic acid methyl ester **3d** in 90% ee, owing to nucleophilic attack at both the C_3 and C_2 ring carbon atoms, respectively.

Table 1. Ring-opening reactions of (S)-(–)-N-acetyl-2-methoxycarbonylaziridine **1**.



(S)-(–)-1; 90% ee **2** **3**

Product	Nu	Yield	$[\alpha]_D$[a]	ee (%)[b]	Abs. Conf.[c]	Nonequivalence,[b] Hz/sense[d]		
						$COOCH_3$	$NHCOCH_3$	Nu
2a	CH_3COO-	50	+60.1	87	S	3.2/H	13.6/H[e]	12.4/L[e]
2b	*p*.Tol.SO_3-	55	+45.0	90	S	8.8/H	-	-
2c	CH_3O-	55	+45.0	90	S	9.0/H	2.2/L	18.3/L
2d	Cl-	40	+73.2	90	R[f]	4.0/H	1.7/H	-
3d	Cl-	40	–13.9[g]	90	R	4.9/H	3.5/H	-
2e	$C_6H_5CH_2S$-	41	+34.2	90	R	2.6/H	6.7/H	-
3e	$C_6H_5CH_2S$-	10	+111.2	89	R	6.7/H	-	-
2f	Indole	40	+12.3[g]	89	S[f]	-	6.3/H	-
3f	Indole	20	+58.0	87	R	8.9/H	11.9/H	-
2g	N_3-	25	+74.2	90	S[h]	4.2/H	3.7/H	-
3g	N_3-	25	+81.6	90	R[h]	5.9/H	3.4/L	-
2h	CH_3CONH-	55	–7.4[g]	90	S[h]	23.4/H	20.0/L	13.1/L

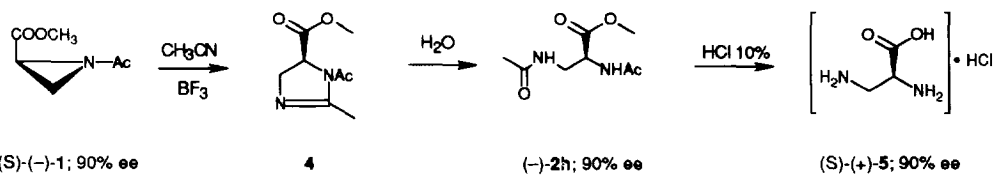
a) In $CHCl_3$ solution. b) Enantiomeric excesses and nonequivalences evaluated from the ^{1}H-NMR spectra recorded in C_6D_6 and in the presence of a 5-fold excess of (R)-(–)-2,2,2-trifluoro-1-(9-anthryl)ethanol. c) Absolute configurations assigned by assuming that the ring-opening reactions occur with a S_N2-like mechanism.[4] d) H refers to the high field position of the predominant enantiomer with respect to the other; L (low field position) indicates the converse. e) The signals were attributed by the analysis of the LIS effect on the spectrum recorded in C_6D_6 and in the presence of Yb(fod)$_3$, tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)ytterbium. f) Reported in the literature.[8,10] g) In methanol. h) By chemical correlation.

The reaction with benzyl thiol in methylene chloride and in the presence of boron trifluoride etherate, carried out at room temperature for 3 h, produced a mixture 6:1 of the two isomers, (+)-2-acetamido-3-benzylthiopropanoic acid methyl ester **2e** and (+)-3-acetamido-2-benzylthiopropanoic acid methyl ester **3e**, with 90% and 89% ee, respectively.

In the case of indole as nucleophile, zinc triflate in excess was used as Lewis acid: it affords higher yields than boron trifluoride as catalyst.[9] The reaction, carried out in chloroform solution at 60 °C for 2 h, afforded a mixture 2:1 of the isomers (+)-2-acetamido-3-(3-indolyl)propanoic acid methyl ester **2f** with 89% ee[10] and (+)-3-acetamido-2-(3-indolyl)propanoic acid methyl ester **3f** with 87% ee.

By treating (S)-(–)-**1** with sodium azide in DMF at 37 °C for 70 h, two ring-opening products, in 1:1 ratio, were isolated, namely, (+)-2-acetamido-3-azidopropanoic acid methyl ester **2g** and (+)-3-acetamido-2-azidopropanoic acid methyl ester **3g**, both with 90% ee.

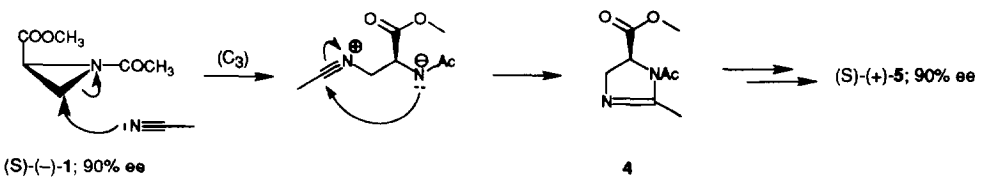
Finally, when aziridine (S)-(–)-**1** was treated with boron trifluoride etherate as catalyst in acetonitrile, a ring-expansion to N-acetyl-imidazoline **4** was observed, as already noted for N-activated-3-alkylaziridine-2-carboxylic esters,[2] Scheme 2.



(S)-(–)-**1**; 90% ee **4** (–)-**2h**; 90% ee (S)-(+)-**5**; 90% ee

Scheme 2

When left standing open to the air, imidazoline **4** gradually hydrolysed to the corresponding (–)-2,3-bisacetamidopropanoic acid methyl ester **2h**.[11] The stereochemistry of the reaction was elucidated by correlation of the derivative **2h** with the known compound 2,3-diaminopropanoic acid monohydrochloride **5**,[12] Scheme 2. By hydrolysis of (–)-**2h** in 10% hydrochloric acid, (S)-(+)-**5** was obtained in 90% ee and 70% chemical yield. The knowledge of the absolute S configuration of (+)-**5** enabled us to assign the absolute configuration to (–)-**2h**: since the hydrolysis reaction does not involve the C_2 stereogenic centre, compounds (–)-**2h** and (+)-**5** must have the same S configuration. This result allowed us to rationalize the acetonitrile nucleophilic attack by following the mechanistic pathway proposed for the aziridine ring-expansion with nitriles,[2] Scheme 3. Since the nucleophilic ring-opening reactions to aziridine **1** have been shown to take place *via* S_N2 displacement,[4] the S configuration common to the aziridine **1** and the derivative (–)-**2h** suggested that the initial attack of the nitrile nucleophile, which affords a nitrilium ion, must be at the C_3 carbon atom of the aziridine ring.

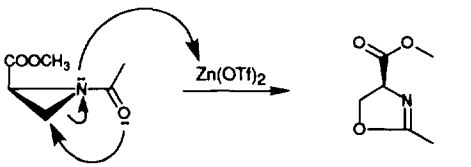


(S)-(–)-**1**; 90% ee **4**

Scheme 3

In many of the reported reactions an acid-catalyzed rearrangement-product of the aziridine **1**, oxazoline **6**, was observed as by-product, Scheme 4. This isomerisation was proved by treating aziridine (S)-(–)-**1** in chloroform solution with an equimolar amount of zinc triflate under reflux for 16 h: a quantitative conversion into the optically active (+)-2-methyl-4-methoxycarbonyloxazoline **6** was observed. Mass spectra and ^{1}H-NMR data, with particular reference to the presence of a long-coupling constant involving the C_2 methyl protons and the C_4 ring-proton,[2] are in close agreement with the reported structure. The rearrangement to oxazoline **6** seems

to indicate that the oxygen-nucleophilic attack of the N-acetyl substituent occurs at the C_3 ring carbon atom, Scheme 4.



(S)-(−)-**1**; 90% ee (+)-**6**; 90% ee

Scheme 4

As a rule, the literature reports total regioselectivity at the C_3 carbon atom for nucleophilic ring-opening reactions on 3-alkyl-2-methoxycarbonylaziridines[2] or N-acylaziridine-2-carboxylates;[5,9] the experimental data show that the steric and/or electrostatic effects determine preferential attack at the C_3 carbon atom, even if theoretical calculations, aimed at rationalizing the aziridine ring-opening regioselectivity, indicate the C_2 carbon atom of protonated N-acetylaziridine-2-carboxylate as the preferred site of attack by soft nucleophiles like indole.[5]

The results of Table 1 show that the ring-opening reactions on aziridine **1** occur exclusively at the aziridine C_3 ring carbon atom in the presence of methanol, acetic acid, *p*.toluenesulphonic acid or acetonitrile as nucleophiles, but no regioselectivity is observed in the reactions with benzyl thiol, sodium azide, hydrogen chloride or indole: in all these cases the attack is at both the C_3 and C_2 carbon atoms.

Conclusion

The present study shows that optically active N-acetyl-2-methoxycarbonylaziridine **1** undergoes easy ring-opening by Brønsted acids or nucleophiles in the presence of a Lewis catalyst. Regioselectivity is not exclusive, affording optically active α- and β-aminoacids. Therefore, aziridine **1** proved to be a very good chiral intermediate for the synthesis of D and L α- or β-aminoacids.

Experimental

^{1}H-NMR spectra were recorded in $CDCl_3$ solution on a Bruker AMX 400 WB spectrometer. Chemical shifts are reported in δ values from TMS as internal standard. Coupling constants (J) are given in Hz. Optical rotations were measured at 20 °C on a Perkin-Elmer 241 polarimeter and are in 10^{-1} deg cm^2 g^{-1}. Enantiomeric purities (ee%) were evaluated by analysis of the ^{1}H-NMR spectra recorded in C_6D_6 and in the presence of a 5-fold excess of the chiral solvating agent (CSA), (R)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol. Accuracy was within ±2%. Mass spectra were determined on a Hewlett-Packard 5970 mass selective detector. GLC analyses were performed on a Hewlett-Packard 5890 A gas chromatograph (capillary column DB-1, 5 μm, 30 m x 0.53 mm I.D.). Elemental analyses were performed with a Carlo Erba Elemental Analyzer mod. 1106. Chromatographic purifications of the compounds were performed on silica gel (ϕ 0.05-0.20 mm). (R)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol was purchased from Ega-Chemie. Tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)ytterbium was purchased from Janssen.

(S)-(–)-*N-acetyl-2-methoxycarbonylaziridine* **1**. – Compound **1** with $[\alpha]_D$ –70.4 (c 1.0, $CHCl_3$), 90% ee, was obtained as described elsewhere;[4] δ_H 2.16 (3H, s), 2.5 (1H, dd, *J* 5.5, 1.7), 2.58 (1H, dd, *J* 3.0, 1.7), 3.16 (1H, dd, *J* 3.0, 5.5), 3.8 (3H, s); MS *m/z* 144 ($M+1^+$).

Reaction with acetic acid. – A mixture of (S)-(–)-**1**, 90% ee, (100 mg, 0.7 mmol) and acetic acid (4 mL) was stirred at room temperature for 15 h. The excess of acetic acid was removed *in vacuo* and the residue treated with 30 mL of satd. $NaHCO_3$. The aqueous solution was repeatedly extracted with CH_2Cl_2 and the collected organic phases dried over Na_2SO_4. After removal of the solvent, the crude product, purified by column chromatography (ethyl acetate-hexane 80:20), provided (+)-2-acetamido-3-acetoxypropanoic acid methyl ester **2a** (58 mg, 50%) as a colourless oil, $[\alpha]_D$ +60.1 (c 1.1, $CHCl_3$), 87% ee; δ_H 2.057 (3H, s), 2.061 (3H, s), 3.78 (3H, s), 4.36 (1H, dd, *J* 11.4, 3.9), 4.45 (1H, dd, *J* 11.4, 3.9), 4.86 (1H, dt, *J* 7.9, 3.9), 6.37 (1H, br); MS *m/z* 204 ($M+1^+$).

Reaction with p.toluenesulphonic acid. – A crystal of 4-dimethylaminopyridine was added to a solution of (S)-(–)-**1**, 90% ee, (100 mg, 0.7 mmol) and *p*.toluenesulphonic acid hydrate (160 mg, 0.84 mmol), in CH_2Cl_2 (5 mL) and at room temperature. After 20 min the solution was washed with aqueous $NaHCO_3$ and dried (Na_2SO_4). The solvent was removed and the crude residue chromatographed (methylene chloride-diethyl ether 80:20) to afford (+)-2-acetamido-3-*p*.tolylsulphonyloxypropanoic acid methyl ester **2b** (120 mg, 55%), $[\alpha]_D$ +45.0 (c 0.64, $CHCl_3$), 90% ee, mp 66-67 °C; δ_H 1.94 (3H, s), 2.42 (3H, s), 3.68 (3H, s), 4.29 (1H, dd, *J* 10.3, 2.9), 4.36 (1H, dd, *J* 10.3, 2.9), 4.75 (1H, dt, *J* 7.6, 2.9), 6.28 (1H, br), 7.3-7.75 (4H, m); MS *m/z* 172 (M^+–143). *Anal.* Calcd for $C_{13}H_{17}NO_6S$: C, 49.52; H, 5.43; N, 4.44; S, 10.17. Found: C, 49.36; H, 5.45; N, 4.46; S, 10.20.

Reaction with methanol. – Boron trifluoride etherate (96 μL, 0.77 mmol) was added to a solution of (S)-(–)-**1**, 90% ee, (100 mg, 0.7 mmol) and methanol (84 μL, 2.1 mmol), in CH_2Cl_2 at –15 °C. The cooling bath was removed and the mixture allowed to react for 2 h at room temperature. The solution was washed with aqueous $NaHCO_3$, dried (Na_2SO_4) and the solvent removed *in vacuo*. The residue was purified by column chromatography (methylene chloride-diethyl ether 80:20) affording pure (+)-2-acetamido-3-methoxypropanoic acid methyl ester **2c** (92 mg, 70%) with $[\alpha]_D$ +45.0 (c 0.93, $CHCl_3$), 90% ee; δ_H 2.06 (3H, s), 3.35 (3H, s), 3.62 (1H, dd, *J* 9.5, 3.2), 3.77 (3H, s), 3.81 (1H, dd, *J* 9.5, 3.2), 4.74 (1H, dt, *J* 8.3, 3.2), 6.31 (1H, br). MS *m/z* 176 ($M+1^+$). *Anal.* Calcd for $C_7H_{13}NO_4$: C, 47.99; H, 7.48; N, 8.0. Found: C, 48.13; H, 7.50; N, 7.98.

Reaction with HCl. – Anhydrous HCl was gently bubbled for 5 min at –5 °C, through a solution of (S)-(–)-**1**, 90% ee, (200 mg, 1.4 mmol) in CH_2Cl_2. The cooling bath was removed and the reaction mixture allowed to react for 15 min. After removal of the solvent, the residue was purified by chromatography (ethyl acetate-diethyl ether 50:50) affording (+)-2-acetamido-3-chloropropanoic acid methyl ester **2d**, (97 mg, 40%), $[\alpha]_D$ +73.2 (c 0.74, $CHCl_3$), 90% ee;[8] m.p. 98-101 °C; δ_H 2.09 (3H, s), 3.83 (3H, s), 3.92 (1H, dd, *J* 11.4, 3.1), 3.99 (1H, dd, *J* 11.4, 3.1), 5.01 (1H, dt, *J* 7.5, 3.1), 6.39 (1H, br); MS *m/z* 182, 180 ($M+1^+$) and (–)-3-acetamido-2-chloropropanoic acid methyl ester **3d**, (94 mg, 40%) with $[\alpha]_D$ –13.9 (c 1.8, CH_3OH), 90% ee; δ_H 2.01 (3H, s), 3.73 (1H, dt, *J* 14.2, 6.3), 3.78 (1H, dt, *J* 14.2, 6.3), 3.81 (3H, s), 4.46 (1H, t, *J* 6.3), 5.98 (1H, br); MS *m/z* 182, 180 ($M+1^+$).

Reaction with benzyl thiol. – Boron trifluoride etherate (87 μL, 0.7 mmol) was gradually added to a solution of (S)-(–)-**1**, 90% ee, (100 mg, 0.7 mmol), and benzyl thiol (164 μL, 1.4 mmol) in dichloromethane (6 mL) at room temperature. After 3 h, the reaction mixture was poured into an aqueous solution of $NaHCO_3$ and

extracted twice with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by chromatography (ethyl acetate-hexane 80:20) to yield (+)-2-acetamido-3-benzylthiopropanoic acid methyl ester **2e** and (+)-3-acetamido-2-benzylthiopropanoic acid methyl ester **3e**. Compound **2e** (58 mg, 41%) showed $[\alpha]_D$ +34.2 (c 0.4, $CHCl_3$), 90% ee; δ_H 1.99 (3H, s), 2.87 (1H, dd, *J* 13.9, 5.2), 2.91 (1H, dd, *J* 13.9, 5.2), 3.70 (2H, s), 3.74 (3H, s), 4.81 (1H, dt, *J* 7.7, 5.2), 6.17 (1H, br), 7.22-7.33 (5H, m); MS *m/z* 267 (M^+). Compound **3e** (11 mg, 10%) showed $[\alpha]_D$ +111.2 (c 0.4, $CHCl_3$), 89% ee; δ_H 1.87 (3H, s), 3.38 (1H, dd, *J* 7.2, 6.3), 3.46 (1H, dt, *J* 13.9, 6.3), 3.57 (1H, dt, *J* 13.9, 7.2), 3.69 (3H, s), 3.82 (2H, s), 5.76 (1H, br), 7.21-7.33 (5H, m); MS *m/z* 267 (M^+).

Reaction with indole. – Indole (238 mg, 2.8 mmol) and zinc triflate (1.12 g, 3 mmol) were subsequently added at room temperature to a solution of (S)-(–)-**1**, 90% ee, (200 mg, 1.4 mmol), in $CHCl_3$ (5 mL). The temperature was gradually raised to a gentle reflux and the mixture allowed to react for 2 h. The solution was diluted with chloroform, washed with water and dried (Na_2SO_4). After removal of the solvent, the residue was chromatographed (methylene chloride-diethyl ether-methanol 70:20:10) to afford (+)-2-acetamido-3-(3-indolyl)propanoic acid methyl ester **2f** and (+)-3-acetamido-2-(3-indolyl)propanoic acid methyl ester **3f**. Compound **2f** (40 mg, 40%) showed $[\alpha]_D$ +12.3 (c 1.4, CH_3OH), 89% ee;[10] δ_H 2.03 (3H, s), 3.39 (1H, ddd, *J* 14.9, 5.4, 0.7), 3.42 (1H, ddd, *J* 14.9, 5.4, 0.7), 3.78 (3H, s), 5.04 (1H, dt, *J* 7.8, 5.4), 6.13 (1H, br), 7.03-7.64 (5H, m), 8.46 (1H, br); MS *m/z* 260 (M^+). Compound **3f** (21 mg, 20%) showed $[\alpha]_D$ +58.0 (c 2.1, $CHCl_3$), 87% ee; δ_H 1.95 (3H, s), 3.70 (3H, s), 3.82 (2H, dd, *J* 7.3, 6.3), 4.21 (1H, t, *J* 7.3), 5.93 (1H, br), 7.11-7.72 (5H, m), 8.41 (1H, br); MS *m/z* 260 (M^+).

Reaction wih NaN_3. – Boron trifluoride ethyl etherate (206 µL, 1.68 mmol) was gradually added to a solution of (S)-(–)-**1**, 90% ee, (200 mg, 1.4 mmol) and NaN_3 (272 mg, 4.2 mmol) in anhydrous DMF (5 mL) at 37 °C under nitrogen. After 70 h the reaction mixture was poured into water (40 mL), extracted with dichloromethane and dried (Na_2SO_4). After removal of the solvent, the chromatographed residue (ethyl acetate-hexane 80:20) afforded (+)-2-acetamido-3-azidopropanoic acid methyl ester **2g**, (67 mg, 25%) and (+)-3-acetamido-2-azidopropanoic acid methyl ester **3g**, (65 mg, 25%). Compound **2g** showed $[\alpha]_D$ +74.2 (c 1.4, $CHCl_3$), 90% ee; δ_H 2.07 (3H, s), 3.75 (1H, dd, *J* 12.6, 3.5), 3.77 (1H, dd, *J* 12.6, 3.5), 3.82 (3H, s), 4.76 (1H, dt, *J* 7.2, 3.5), 6.34 (1H, br); MS *m/z* 187 ($M+1^+$). Compound **3g** had $[\alpha]_D$ +81.6 (c 1.6, $CHCl_3$), 90% ee; δ_H 2.00 (3H, s), 3.51 (1H, dt, *J* 14.0, 6.7), 3.68 (1H, ddd, *J* 14.0, 6.1, 5.3), 3.82 (3H, s), 4.20 (1H, dd, *J* 6.7, 5.3), 5.90 (1H, br); MS *m/z* 187 ($M+1^+$).

Reaction with acetonitrile. – Boron trifluoride etherate (92 µL, 0.73 mmol) was added to a cooled solution at 0 °C of (S)-(–)-**1**, 90% ee, (100 mg, 0.7 mmol) in acetonitrile (3 mL). After 30 min the cooling bath was removed and the solution stirred for 24 h. After addition of a satd. sodium bicarbonate solution, the mixture was extracted with dichloromethane. The combined extracts were dried (Na_2SO_4) and concentrated to yield a colourless oil which was identified by GLC/MS as a mixture of compounds **4** [MS *m/z* 184 (M^+)] and **2h**. On being left to stand open to the air, a gradual conversion of **4** into **2h** was observed. After 24 h the GLC analysis of the mixture showed 93% of compound **2h**. From column chromatography (ethyl acetate-methanol 50:50), (–)-**2h**[11] was obtained (78 mg, 55%) with $[\alpha]_D$ –7.4 (c 1.2, CH_3OH), 90% ee; δ_H 1.99 (3H, s), 2.04 (3H, s), 3.62 (1H, dt, *J* 14.1, 6.8), 3.66 (1H, ddd, *J* 14.1, 5.6, 4.2), 3.78 (3H, s), 4.61 (1H, dt, *J* 6.8, 4.2), 6.09 (1H, br), 6.73 (1H, br); MS *m/z* 203 ($M+1^+$).

After hydrolysis in HCl 10% at 60 °C for 24 h, the reaction mixture was concentrated *in vacuo* and the residue crystallized from ethanol/water to afford (S)-(+)-2,3-diaminopropanoic acid mono hydrochloride **5**,[12] as

a white solid (46 mg), with $[\alpha]_D$ +21.7 (c 1.2, HCl 0.5 N), 90% ee, m.p. 236-237 °C (dec); δ_H (D_2O) 3.51 (2H, d, *J* 7.2), 4.06 (1H, t, *J* 7.2); MS *m/z* 105 ($M-Cl^+$).

Reaction with zinc triflate.– A solution of zinc triflate (280 mg, 0.77 mmol) and (S)-(–)-**1**, 90% ee, (100 mg, 0.7 mmol) in chloroform (5 mL) was refluxed for 16 h. The reaction mixture was washed with water and dried (Na_2SO_4). After removal of the solvent, the crude residue was purified by chromatography (ethyl acetate-hexane 80:20) to afford 2-methyl-4-methoxycarbonyloxazoline **6** (80 mg, 80%) $[\alpha]_D$ +89.1 (c 1.5, $CHCl_3$), 90% ee; δ_H 2.04 (3H, d, *J* 1.4), 3.80 (3H, s), 4.41 (1H, dd, *J* 10.6, 8.7), 4.49 (1H, dd, *J* 8.7, 7.9), 4.73 (1H, ddq, *J* 10.6, 7.9, 1.4); MS *m/z* 143 (M^+).

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