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

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Abstract: The S_N2-like mechanism of the nucleophilic attack of sodium azide on (S)-(–)-N-acetyl-2-methoxycarbonylaziridine was verified through the chemical correlation of the ring-opening products with (S)-(+)- or (R)-(–)-2,3-diaminopropanoic acid monohydrochloride.

Introduction.

Aziridines, like epoxides and cyclopropanes, have high ring-strain, which makes for easy ring-opening in the presence of nucleophiles. They can therefore be used as useful intermediates for the synthesis of biologically and pharmacologically active compounds. Ring-opening occurs even more readily in aziridines when an electron-withdrawing group, such as an acyl or sulphonyl substituent, is introduced on the ring-nitrogen atom. There are many reports in the literature about the stereochemical and regiochemical control exhibited by aziridine-ring substituents and nucleophiles and about the conditions pertaining to the ring-opening reactions.[1-4]

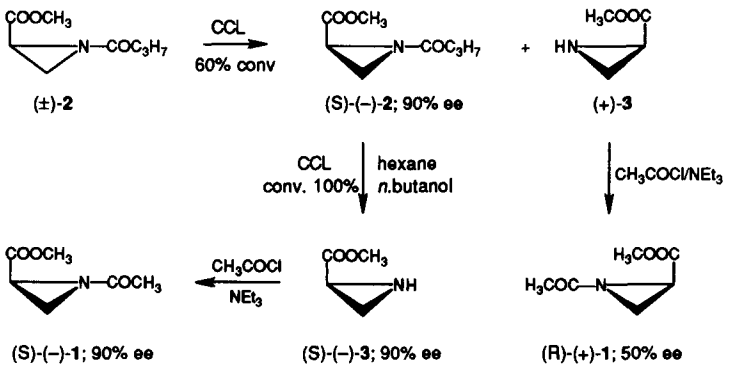
In this work we perform a detailed study of the mechanism by which sodium azide induces an acid-catalyzed ring-opening reaction of optically active N-acetyl-2-methoxycarbonylaziridine **1**. (S)-(–)-N-acetyl-2-methoxycarbonylaziridine **1** was treated with sodium azide in the presence of boron trifluoride etherate as Lewis acid catalyst. The ring-opening products were correlated with the enantiomerically and configurationally known[5] 2,3-diaminopropanoic acid monohydrochloride, which is commercially available. This correlation allowed us to define unequivocally the stereochemical course of the nucleophilic attack on the aziridine ring.

Results and discussion.

(S)-(–)-*N-acetyl-2-methoxycarbonylaziridine* **1**: *resolution*.-- Resolution of **1** through stereoselective enzymatic hydrolysis, catalyzed by *Candida cylindracea* lipase (CCL), is reported to afford only 50-60% enantiomeric excess (ee).[6] Enantiomerically pure aziridine **1** was obtained here in good chemical yield from the corresponding N-butyryl-2-methoxycarbonylaziridine **2**, which can be resolved in 90% ee by CCL-enzymatic hydrolysis, following Scheme 1.

Racemic aziridine **2** was synthesized and resolved by CCL-catalysed hydrolysis, following the procedure reported in the literature.[6] The resolution was performed in phosphate buffer (0.1 mol dm^{-3} and NaCl 0.1 mol dm^{-3}; pH 7.5) at 37 °C using an enzyme /aziridine ratio (w/w) of 1:60. After 30 min, at 60% conversion, the reaction mixture revealed the presence of N-H aziridine **3**, as hydrolysis product, together with unchanged aziridine **2**. The mixture was extracted with methylene chloride and directly acetylated with acetyl chloride in the

presence of triethylamine to convert the unstable and volatile aziridine **3** into the corresponding N-acetylaziridine **1**. Aziridine (S)-(–)-**2**, in a nearly enantiomerically pure form (90% ee), and aziridine (R)-(+)-**1** with 50% ee were isolated by chromatography.

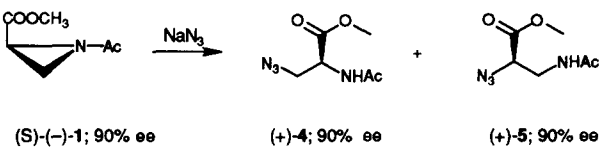


Scheme 1

Enzymatic deacylation of enantiomerically pure aziridine **2** in hexane, using a CCL/aziridine ratio of 1:1 at 37 °C for 45 min in the presence of an equimolar amount of *n*.butanol and water in trace, gave the derivative **3** in quantitative yield. After removal of the enzyme by filtration, the solution was acylated to afford (S)-(–)-**1** in 70 % chemical yield and 90% ee.

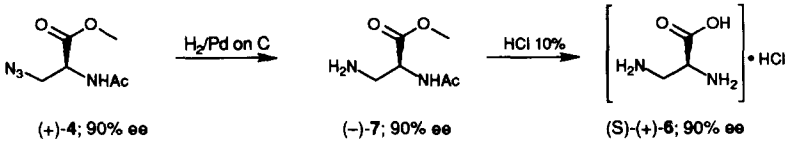
The enantiomeric purities of aziridines **1** and **2** were determined by analysis of the ^{1}H-NMR spectra recorded in $CDCl_3$ and in the presence of the chiral shift-reagent, Eu(hfc)$_3$, tris [3-(heptafluoropropyl-hydroxymethylene)-(+)-camphorato]europium-(III). The absolute configurations of **1** and **2** are known from the literature.[6]

Ring-opening of (S)-(–)-**1** *by sodium azide.*– Treating (S)-(–)-**1** with sodium azide in DMF and in the presence of boron trifluoride ethyl etherate, as Lewis acid catalyst, at 37 °C for 3 days, two ring-opening products were obtained in a ratio of 1:1 in 50% total chemical yield. ^{1}H-NMR and mass data confirm that the nucleophilic attack occurred at both the C_3 and C_2 ring-carbon atoms, thus affording two regioisomers, namely, (+)-2-acetamido-3-azidopropanoic acid methyl ester **4** and (+)-3-acetamido-2-azidopropanoic acid methyl ester **5**, respectively. Moreover, the ^{1}H-NMR spectra recorded in C_6D_6 and in the presence of the chiral solvating agent (R)-(–)-2,2,2-trifluoro-1-(9-anthryl)ethanol showed that the enantiomeric purities of **4** and **5** were not less than 90%, Scheme 2.



Scheme 2

Chemical correlations.– In order to verify the mechanism of the aziridine-ring nucleophilic attack we correlated the unknown compounds **4** and **5** with the known compound (S)-(+)- or (R)-(–)-2,3-diaminopropanoic acid monohydrochloride **6**.[5] Catalytic hydrogenation of azide (+)-**4** in methanol, with Pd 10% on carbon as catalyst, afforded (–)-2-acetamido-3-aminopropanoic acid methyl ester **7**; the hydrolysis of (–)-**7** in aqueous HCl 10% afforded (S)-(+)-**6** with 90% ee, Scheme 3.

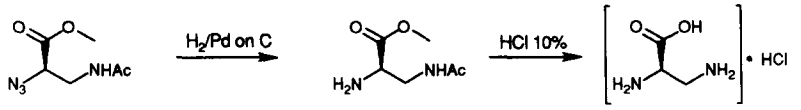


(+)-**4**; 90% ee (–)-**7**; 90% ee (S)-(+)-**6**; 90% ee

Scheme 3

Similarly, the catalytic hydrogenation of (+)-**5** provided (–)-3-acetamido-2-aminopropanoic acid methyl ester **8**, which gave, by hydrolysis in HCl 10%, (R)-(–)-**6** with 90% ee, Scheme 4.

Since reduction and hydrolysis do not involve the carbon stereogenic centre of azido-derivatives, compounds (+)-**4** and (–)-**7** must have the same S configuration at the stereogenic centre of (+)-**6**. At the same time, compounds (+)-**5** and (–)-**8** must have the same R configuration at the stereogenic centre of (–)-**6**.

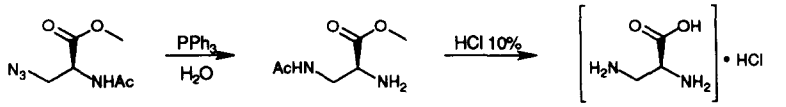


(+)-**5**; 90% ee (–)-**8**; 90% ee (R)-(–)-**6**; 90% ee

Scheme 4

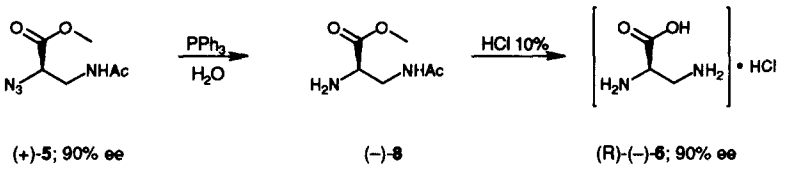
This result unambiguously indicates that, when the nucleophilic attack is at the C_3 ring-carbon atom of aziridine (S)-(–)-**1**, the ring-opening product (+)-**4** has the same configuration as the aziridine **1**. On the other hand, when the nucleophilic attack occurs at the C_2 stereogenic carbon atom of (S)-(–)-**1**, a ring-opening product (+)-**5** of opposite configuration with respect to aziridine **1** is recovered. Clearly, nucleophilic attack on aziridine (S)-(–)-**1** occurs by a S_N2-like mechanism with total inversion.

It is also noteworthy that the same correlation, effected by reduction of the azides (+)-**4** and (+)-**5** with triphenylphosphine[7] in THF, surprisingly provided only the derivative **8** in both the enantiomeric forms, (+) and (–)-**8**, respectively. Acidic hydrolysis of (+)-**8** and (–)-**8** afforded (S)-(+)-**6** and (R)-(–)-**6**, respectively, thus confirming the above correlation, Scheme 5a,b.



(+)-**4**; 90% ee (+)-**8** (S)-(+)-**6**; 90% ee

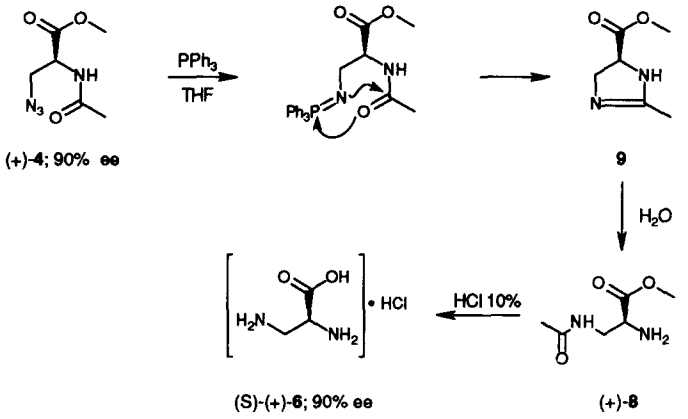
Scheme 5a



(+)-**5**; 90% ee (–)-**8** (R)-(–)-**6**; 90% ee

Scheme 5b

The recovery of (+)-**8** from (+)-**4**, as reduction product, seems to indicate that reduction proceeds through the formation of an iminophosphoranic intermediate which spontaneously cyclizes to the imidazoline **9** by an aza-Wittig intramolecular reaction, as already reported for ω-azido ketones,[7] Scheme 6.



(+)-**4**; 90% ee **9**

(S)-(+)-**6**; 90% ee (+)-**8**

Scheme 6

Easy imidazoline hydrolysis would produce derivative (+)-**8**. Since hydrolysis and phosphorane rearrangement do not involve the azide-stereogenic centre, we can deduce that (+)-**8** and (+)-**4** must again have the same S configuration as the correlated compound (+)-**6**.

Conclusion.

Nucleophilic ring-opening attack of sodium azide on monosubstituted N-activated aziridine (S)-(–)-**1**, under acid catalysis, occurs at both the C_2 and C_3 aziridine carbon atoms and with a S_N2-like mechanism with total inversion to the C_2 stereogenic centre. This agrees with reports in the literature[1,3] regarding the parent compounds. Thus, α-aminoacids with the same configuration and β-aminoacids with opposite configuration can be synthesized from aziridine (S)-(–)-**1** by C_3- and C_2-nucleophilic attack, respectively, at the aziridine ring.

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 (s singlet, d doublet, m multiplet, t triplet, br broad signal). Coupling constants (J) are given in Hz. Optical rotations were measured at 20 °C on a Perkin-Elmer 241 polarimeter in chloroform solutions and are in 10^{-1} deg cm^2 g^{-1}. Enantiomeric purities (ee's) were evaluated

from the ^{1}H-NMR spectra recorded in $CDCl_3$ and in the presence of the chiral lanthanide shift-reagent (CLSR) Eu(hfc)$_3$, tris [3-(heptafluoropropyl-hydroxymethylene)-(+)-camphorato]europium (III), in the CLSR/compound molar ratio 0.5-1, or 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.). Chromatographic purification of the compounds was performed on silica gel (ϕ 0.05-0.20 mm). Eu(hfc)$_3$ and (R)-(–)-2,2,2-trifluoro-1-(9-anthryl)ethanol were purchased from Ega-Chemie and used without purification. The enzyme *Candida cylindracea* lipase (type VII) was purchased by Aldrich and used without purification. (S)-(+)-2,3-diaminopropanoic acid monohydrochloride was furnished by Fluka.

Racemic N-acetyl-2-methoxycarbonylaziridine **1** and N-butyryl-2-methoxycarbonylaziridine **2** were synthesized as described in the literature.[6]

(S)-(–)-N-Butyryl-2-methoxycarbonylaziridine 2: Following the procedure described elsewhere,[6] racemic aziridine **2** (3 g) was added to 0.1 mol dm^{-3} potassium phosphate buffer [120 mL containing NaCl (0.1 mol dm^{-3})], pH 7.5 at 37 °C and treated with *Candida cylindracea* lipase (CCL, 50 mg) with vigorous stirring. Hydrolysis was followed by GLC and TLC and stopped after 30 min at 60% conversion. The reaction-mixture, containing the unchanged aziridine **2** and the N-unsubstituted aziridine **3**, was extracted with dichloromethane; the organic extracts were dried over Na_2SO_4 and treated with acetyl chloride and triethylamine at 0 °C to convert the volatile aziridine **3** into the aziridine **1**. The mixture was stirred for 1 h, washed with water, dried (Na_2SO_4) and concentrated. The residue was chromatographed on column (diethyl ether-light petroleum 50:50) to afford (S)-(–)-**2** (1.1 g, 37%), $[\alpha]_D$ –76.1 (c 0.9), 93% ee; δ_H 0.91 (3H, t), 1.70 (2H, m), 2.39 (2H, m), 2.50 (1H, dd, *J* 1.7, 5.5), 2.57 (1H, dd, *J* 1.7, 3.0), 3.12 (1H, dd, *J* 3.0, 5.5), 3.80 (3H, s); MS *m/z* 171 (M^+). (R)-(+)-**1** (1.2 g, 48%) was obtained with $[\alpha]_D$ +34.5 (c 1.1), 50% ee; 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 ($M+1^+$).

(S)-(–)-N-acetyl-2-methoxycarbonylaziridine 1: *n*.Butanol (1.1 mL, 12 mmol) and CCL (1.76 g) were added to a solution of (S)-(–)-N-butyryl-2-methoxycarbonylaziridine **2**, (1.76 g, 10 mmol), 90% ee, in hexane (25 mL) previously saturated with water, and the suspension was vigorously stirred at 37 °C. After 45 min, GLC analysis revealed complete conversion of compound **2** into **3**. The enzyme was removed by filtration and the solution treated at 0 °C with triethylamine (12 mmol) and acetyl chloride (11 mmol). After 30 min, the mixture was washed with water, dried (Na_2SO_4) and the solvent removed under reduced pressure. Column chromatography (diethyl ether-light petroleum 50:50), afforded compound **1** as a colourless oil (1.05 g, 70%) showing $[\alpha]_D$ –70.4 (c 1.0), 90% ee; 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 ($M+1^+$).

Methyl (+)-2-acetamido-3-azidopropanoate 4 and methyl (+)-3-acetamido-2-azido propanoate 5: Boron trifluoride ethyl etherate (206 μL, 1.7 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 in water (40 mL), extracted with dichloromethane and dried (Na_2SO_4). After removal of the solvent, the residue was chromatographed (ethyl acetate-hexane 80:20) to isolate compounds **4** and **5**. Compound **4** showed $[\alpha]_D$ +74.2 (c 1.4), 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 **5** had $[\alpha]_D$ +81.6 (c 1.6), 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 ($M+1^+$).

General procedure for catalytic hydrogenation of the azido derivatives (+)-4 and (+)-5: A solution of each azido-derivative in methanol, at room temperature, was stirred with Pd 10% on carbon, as catalyst, under 1 atm of hydrogen until TLC analysis (ethyl acetate-hexane 80:20) showed that no azide remained. The catalyst was removed by filtration and the solution concentrated *in vacuo*. The identity of the reduction products was confirmed by ^{1}H-NMR and mass spectroscopies.

Methyl (S)-(–)-2-acetamido-3-aminopropanoate 7: From (+)-**4** (0.13 g), 90% ee, after 2 h, compound **7** (95%) was obtained with $[\alpha]_D$ –22.6 (c 2.3, CH_3OH), 90% ee; δ_H 1.20 (2H, br), 2.06 (3H, s), 3.06 (1H, dd, *J* 13.2, 4.4), 3.11 (1H, dd, *J* 13.2, 4.4), 3.78 (3H, s), 4.61 (1H, dt, *J* 8.8, 4.4), 6.53 (1H, br); MS *m/z* 161 ($M+1^+$). The absolute configuration of (–)-**7** was assigned by conversion into (S)-(–)-2,3-diaminopropanoic acid monohydrochloride **6**. The hydrolysis of (–)-**7** in aqueous HCl 10% at 60 °C for 12 h afforded (S)-(+)-**6**, m.p. 235-238 °C (dec), with $[\alpha]_D$ + 21.6 (c 0.67, HCl 0.5 N), 90% ee.

Methyl (R)-(–)-3-acetamido-2-aminopropanoate 8: From (+)-**5**, (0.1 g), 90% ee, after 1.30 h, product **8** (93%) was obtained with $[\alpha]_D$ – 27.3 (c 0.65, CH_3OH), 90% ee; δ_H 1.89 (2H, br), 2.01 (3H, s), 3.34 (1H, ddd, *J* 13.1, 6.5, 5.0), 3.61 (1H, dd, *J* 6.5, 5.0), 3.66 (1H, ddd, *J* 13.1, 6.5, 5.0), 3.76 (3H, s), 6.09 (1H, br); MS *m/z* 131 ($M-OCH_3^+$). Hydrolysis of (–)-**8** in aqueous HCl 10% afforded (R)-(–)-**6**, $[\alpha]_D$ – 22.0 (c 0.75, HCl 0.5 N), 90% ee.

General procedure for reduction of (+)-4 and (+)-5 with triphenylphosphine: PPh_3 (1 mmol) was added to a solution of (+)-**4** or (+)-**5** (1 mmol) in THF at room temperature with vigorous stirring. After 25 h, water (1.5 mmol) was added and the solution refluxed for 38 h until the disappearance of the azide was verified by TLC analysis (ethyl acetate-hexane 80:20). After the removal of the solvent, the residue was chromatographed on column to afford (+)-**8** or (–)-**8** in no more than 70% chemical purity: further purification attempts failed. (+)-**8** was obtained from (+)-**4** and (–)-**8** from (+)-**5**. The hydrolysis in HCl 10% of (+)-**8** and (–)-**8** afforded, respectively, (S)-(+)-**6** and (R)-(–)-**6** with 90% ee.

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