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Synthesis of functionalized phenylalanine derivatives by ring opening reactions of 3-arylaziridine-2-carboxylic esters

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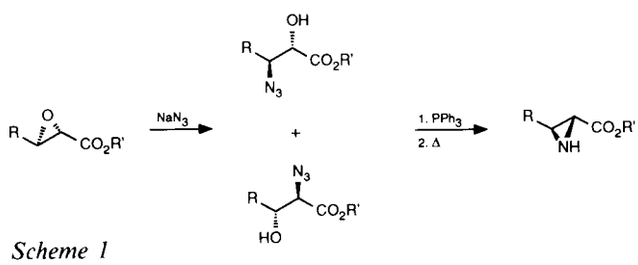
Abstract. Ring-opening reactions of 3-arylaziridine-2-carboxylic esters with various nucleophiles are described. Racemic methyl 3-(4-methoxyphenyl)-, 3-phenyl- and 3-(4-nitrophenyl)aziridine-2--carboxylate (**1a**, **1b** and **1c**, respectively) were selected as substrates. In the absence of acid, no ring opening occurred. On treatment with ethereal hydrogen chloride, **1a** gave a mixture of diastereomers **2a**, whereas **1b** and **1c** gave mixtures of regioisomers **2b**/**3b** and **2c**/**3c**, respectively. Boron-trifluoride etherate catalyzed reaction of **1a** with benzenethiol and indole also resulted in the formation of diastereomeric ring-opened products **4a** and **6a**, respectively, due to the electron-releasing properties of the p-methoxy group. Only C3 attack was observed. Under the same conditions, **1b** and **1c** gave a clean S_N2-type ring opening, leading to diastereomerically pure products **4b**, **4c**, **6b** and **6c**. Reaction of **1b** with acetic acid gave **7** in an S_N2-type ring opening at C3, followed by an O→N acyl shift. Treatment of enantiopure (+)-(2*S*,3*R*)-**1b** with benzenethiol, indole and acetic acid gave the corresponding enantiomerically pure β-functionalized α-amino acid derivatives. Functionalization of **1b** at nitrogen strongly increased the reactivity: *N*-acylaziridine **8** isomerized to *trans*-oxazoline **11** when treated with boron trifluoride etherate in acetonitrile.

Introduction

In recent reports[1], we have described a convenient synthetic method for aziridine-2-carboxylic esters **1** from the corresponding oxirane-2-carboxylic esters (Scheme 1). The



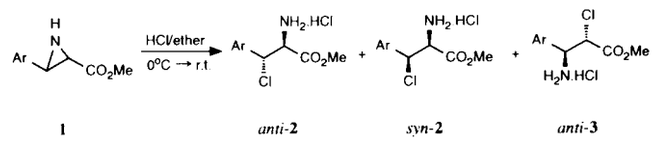
Scheme 1

chemistry of these *N-un*substituted aziridine carboxylic esters has received little attention. *Kyburz*[2] and *Wade*[3] have described the reaction of aziridine-2-carboxylic esters with hydrogen halides. Usually, mixtures of isomers were formed, depending on the reaction conditions. *Styngach*[4] reported the reaction of isopropyl *cis*-3-phenylaziridine-2-carboxylate with indole. *Hata* et al.[5] described ring opening of 3-methylaziridine-2-carboxylic acid with benzenethiol in aqueous solution. Regioisomeric mixtures were formed with the predominant product arising from C2-attack. *Marquet*[6] treated menthyl *trans*- and *cis*-3-phenylaziridine-2-carboxylate with 4-methoxyphenylmethanethiol in the presence of a Lewis acid and observed ring opening at C3. Several authors, however, reported ring opening of *N*-activated aziridine-carboxylic esters[7-12], usually with aliphatic substituents at C3.

This paper deals with the ring opening reactions of 3-aryl--substituted aziridine-2-carboxylic esters. Three substrates were selected for this study, *viz.* 3-(4-methoxyphenyl)-, 3-phenyl- and 3-(4-nitrophenyl)aziridine-2-carboxylic methyl esters **1a**, **1b** and **1c**, respectively.

Results and discussion

Treatment of the aziridine carboxylates **1** with hydrogen chloride in diethyl ether resulted in all three cases in ring-opened products, as shown in Scheme 2. With **1a**, only



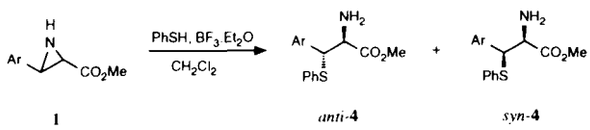
1 *anti*-**2** *syn*-**2** *anti*-**3**

1	Ar	Product	Yield(%)
1a	*p*-$MeOC_6H_4$	**2a** (*anti*/*syn* = 72:28)	77
1b	Ph	*anti*-**2b** + *anti*-**3b** (10:1)	85
1c	*p*-$O_2NC_6H_4$	*anti*-**2c** + *anti*-**3c** (65:35)	69

Scheme 2

attack of nucleophilic chloride at C3 was observed. The reaction is not stereospecific, because a 72 : 28 mixture of isomers *anti*- and *syn*-**2a** was formed[13]. The phenyl-substituted aziridine **1b** yielded a mixture of *anti*-**2b** and *anti*-**3b** resulting from attack of chloride at C3 and C2, respectively. The NMR spectrum of this product mixture was considerably different from that of the preceding experiment. From substrate **1c**, similar products were obtained, albeit in a different ratio. Comparison of the respective NMR spectra led to the conclusions that from **1a** a *anti/syn* mixture is formed and that **1b** and **1c** lead to a mixture of *anti* regioisomers (see Experimental). The initial reaction undoubtedly will be formation of aziridinium salt. This strongly activated aziridine derivative will then undergo nucleophilic ring opening by reaction with chloride anion. In the case of substrate **1a**, the *p*-methoxy substituent apparently assists C3-N bond cleavage to such an extent that the transition state of the nucleophilic reaction has considerable S_N1 character, with the consequence that a mixture of *anti*- and *syn*-**2a** is produced. When such a carbocation-stabilizing substituent is lacking, *e.g.*, as in **1b**, nucleophilic opening takes place by an S_N2-type reaction leading to either *anti*-**2b** or *anti*-**3b**, the attack at the benzylic C3 position being strongly favored. For aziridine **1c**, this preference for benzylic attack is suppressed by the electron-withdrawing *p*-nitro group.

Nucleophilic opening of **1a-c** with benzenethiol as the nucleophile (*cf.* ref. 6) could be accomplished using boron-trifluoride as the catalyst. Treatment of aziridines **1a-c** with two equivalents of benzenethiol in dichloromethane in the presence of 1.5 equivalents of boron-trifluoride etherate resulted in the products shown in Scheme 3. With the *p*-methoxy-

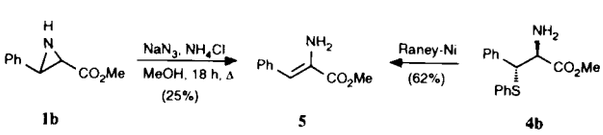


1 *anti*-**4** *syn*-**4**

1	Ar	Conditions	Product	*anti/syn*	Yield (%)
1a	*p*-$MeOC_6H_4$	room temp., < 15 min	**4a**	60:40	65
1b	Ph	room temp., 22h	**4b**	100:0	80
1c	*p*-$O_2NC_6H_4$	reflux, 9h	**4c**	100:0	65

Scheme 3

phenyl substituted substrate **1a**, the reaction is again not stereospecific, which points to a transition state for the attack at C3 that has a highly carbocationic character (*cf.*, Scheme 2). The other two substrates give a stereospecific reaction at C3, indicating that the nucleophile attacks in an S_N2 fashion. The regiochemistry of the products **4** was unequivocally established from the mass spectrum which exhibits the fragment $[XC_6H_4CHSPh]^+$ as the mass with the highest intensity. Furthermore, reduction of **4b** with Raney nickel (*cf.*, ref. 6) gave methyl 2-amino-3-phenyl-2-propenoate (**5**) in a yield of 62% (Scheme 4). The formation of this product was rather unexpected and can only be explained by elimination of benzenethiol from **4b**[14]. One other example of olefin formation during desulfurization has been reported (conversion of dithioacetals into olefins on treatment with Raney Ni)[15].

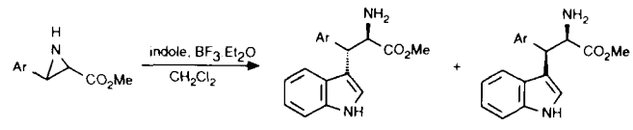


1b **5** **4b**

Scheme 4

Unexpectedly, the same unsaturated amino ester **5** was obtained from the reaction of aziridinecarboxylate **1b** on treatment with sodium azide in methanol, albeit in moderate yield (Scheme 4). No trace of the desired methyl 2-amino-3--azido-3-phenylpropanoate was found. Modification of the reaction conditions, *e.g.*, sodium azide in DMF (*cf.*, ref. 16), also did not give any azido product.

An interesting ring opening was observed upon reaction with indole in the presence of boron trifluoride etherate (*cf.*, ref. 17), *viz.*, the formation of α-amino-3-indolepropanoic esters **6** (Scheme 5). The best results were obtained with 2



1 *anti*-**6** *syn*-**6**

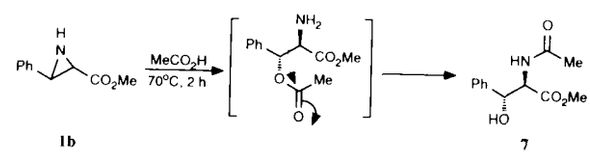
1	Ar	Conditions	Product	*anti/syn*	Yield (%)
1a	*p*-$MeOC_6H_4$	room temp., 1h	**6a**	55:45	68
1b	Ph	room temp., 2h	**6b**	100:0	53
1c	*p*-$O_2NC_6H_4$	room temp., 5d	**6c**	100:0	60

Scheme 5

equivalents of indole and 1.5 equivalents of Lewis-acid catalyst. With all three substrates, exclusive attack of the nucleophile at C3 was observed, for **1b** and **1c** with complete stereospecificity and for **1a** in a 55 : 45 ratio of *anti/syn*-**6a**. The regiochemistry of the reaction could readily be deduced from the mass spectrum[4] of the products **6a-c** and the ^1H NMR characteristics. Mechanistically, these reactions closely resemble those shown in Schemes 2 and 3, *viz.*, with an intermediate carbocation for **1a** and an S_N2 type ring opening for **1b** and **1c**.

Marquet et al.[6] showed that Lewis-acid-catalyzed ring opening reactions of *trans*- and *cis*-3-phenylaziridine-2-carboxylic esters with a thiol proceed with inversion of configuration at the benzylic center C3; for this reason, the reactions with indole and benzenethiol are also assumed to be of S_N2 type. Attempted reactions of **1a** and **1b** with an enamine, *viz.*, 1-(1-cyclopentenyl)pyrrolidine, and of **1b** with an enol silyl ether, *viz.*, (*Z*)-1-phenyl-2-(trimethylsilyloxy)propene, did not lead to the desired ring opening, not even in the presence of a Lewis- acid catalyst [boron-trifluoride etherate or titanium(IV) chloride]. The starting materials were recovered unchanged.

The acidolysis of substrate **1b** with acetic acid took an interesting course. After initial ring opening by attack of acetate anion at C3, acyl migration from oxygen to nitrogen, probably via a cyclic intermediate, takes place, to give the isolated product **7** in high yield (Scheme 6). This product



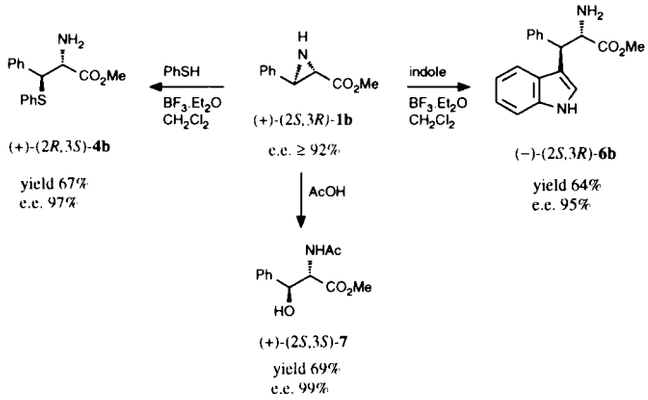
1b **7**

Scheme 6

could readily be identified by comparison of its physical data with those reported earlier[18]. Because **1b** leads to **7** as the sole product, this ring opening proceeds with complete inversion of configuration at C3; compound **12** (*vide infra*), which would have resulted from ring opening with retention of configuration at C3, was not found. Hence, the reaction

with acetic acid proceeds in an S_N2 fashion. Attempts to prepare the *N*-formyl product corresponding with **7**, failed, either by reaction with formic acid or by BF_3.DMF[20].

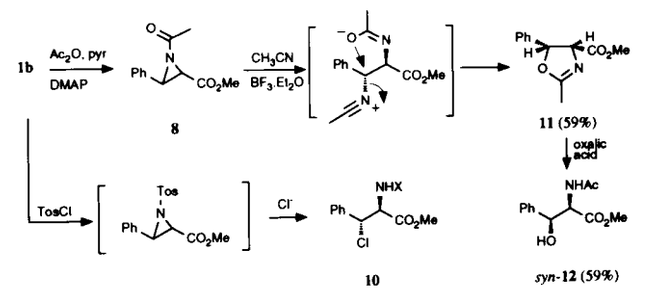
The results described above clearly demonstrate that, with 3-phenylaziridine-2-carboxylate **1b**, a regio- and stereospecific ring opening reaction can be accomplished with benzenethiol, acetic acid and indole as the nucleophiles. These reactions were, therefore, also carried out with substrate **1b** of high enantiomeric purity. Following the procedure described above, three ring opening reactions, *viz.*, that with indole, benzenethiol and acetic acid, gave the corresponding 3-substituted 2-amino-3-phenylpropanoates (+)-(2*R*,3*S*)-**4b**, (−)-(2*S*,3*R*)-**6b** and (+)-(2*S*,3*S*)-**7**, respectively, as shown in Scheme 7. The enantiomeric purity of the products was determined by 400-MHz ^{1}H NMR



Scheme 7

analysis of their Mosher derivatives. In the case of **7**, the optical rotation was compared with that reported earlier[18b]. These reactions represent an elegant method for the preparation of β-substituted phenylalanine derivatives with high enantiomeric purity.

Activation of the aziridine ring for nucleophilic ring opening reactions through *N*-acylation or *N*-tosylation was also considered. The *N*-acetyl derivative of **1b**, *viz.*, **8**, was readily prepared using acetic anhydride. The *N*-benzyloxycarbonyl derivative (**9**, formula not shown) was prepared simply by a standard procedure, although ring opened products (approximately 22%) were also formed. The preparation of a Mosher derivative of **1b** in the normal manner[1a] failed because a mixture of ring opened products was obtained. *N*-Tosylation of **1b** could also not be accomplished, because chloride anion readily opens the initially formed *N*-tosyl compound to give product **10** (Scheme 8).



Scheme 8

The *N*-acetyl derivative **8** underwent an interesting intramolecular ring-expansion reaction to produce five-membered *trans*-oxazoline **11** on treatment with a catalytic amount of boron-trifluoride etherate in acetonitrile (Scheme 8). This reaction resembles the isomerization of *N*-acylaziridines to oxazolines catalyzed by iodide[19]. It is assumed that iodide causes initial ring opening, which is followed by nucleophilic ring closure via S_N2 displacement of the iodide ion. This double inversion leads to net retention during the ring-expansion reaction. In the present case, acetonitrile serves as the nucleophile for the initial ring opening[22] (probably at C3) to give a zwitterionic intermediate, which then cyclizes to oxazoline **11** by expulsion of the nitrile unit. Oxazoline **11** has the *trans* configuration, as unambiguously established by its hydrolysis to methyl *syn*-2-(acetylamino)-3-hydroxy-3-phenylpropanoate **12**[19,23]. Hence, the conversion of **8** into **11** takes place with retention of configuration at both carbon atoms originally present in the three-membered ring. It is of interest to note that 3-aliphatically substituted *N*-acylaziridine-2-carboxylates show quite different behavior in acetonitrile in the presence of boron trifluoride etherate, *viz.*, they undergo ring expansion in which acetonitrile is a reaction partner[22].

From the results presented above, it is clear that nucleophilic ring opening of 3-arylaziridine-2-carboxylic esters is easy in the presence of either Lewis or Brönsted acids. In most cases, C3 attack is observed; only in the reaction with ethereal HCl mixtures of regioisomers are formed. In the presence of a strongly electron-releasing substituent on the aromatic ring, scrambling of stereochemical information at C3 is observed; in the other cases, however, clean S_N2-type ring opening takes place.

N-Acylation and *N*-tosylation makes the three-membered ring in methyl 3-phenylaziridine-2-carboxylate much more sensitive to ring opening reactions. In a forthcoming paper[21], it will be shown that, for aliphatically substituted aziridine-2-carboxylates, N activation by acylation or tosylation is a prerequisite for successful ring opening reactions.

Experimental section

General remarks

Mrs. *H. I. V. Amatdjais-Groenen* (elem. anal.), Mr. *P. M. van Galen* (MS) and Mr. *A. E. M. Swolfs* (non-routine NMR) provided most of the analytical data under the supervision of Mr. *F. P. van der Meer*.

Elemental analyses were standard carried out in triplicate.

^{1}H NMR spectra were recorded on a Varian EM 390 (90 MHz, CW), a Bruker WH 90 (90 MHz, FT) or a Bruker AM-400 (400 MHz, FT) spectrometer with TMS as internal standard. IR spectra were run on a Perkin-Elmer 298 spectrophotometer. For mass spectroscopy a double focussing VG 7070E was used.

Melting points were determined on a Reichert Thermopan microscope and are uncorrected.

GC was performed on a Hewlett-Packard 5710A instrument equipped with a packed Chrompack SE 30 (10%, 6′ × 1/8″) column, or on a Hewlett-Packard 5790A or 5890 instrument equipped with a capillary HP cross-linked methyl silicone (25 m x 0.31 mm) column, connected to a HP 3390 or HP 5890 calculating integrator.

Optical rotations were measured on a Perkin-Elmer 241 polarimeter.

For preparative chromatography, a slightly modified version of the "flash" chromatography technique as described by Still et al.[24] was used. The stationary phase was Silicagel 60H (Merck, art. no. 7736). A pressure of 1.5-2.0 bar was used to obtain the necessary flow rate. The column length was approximately 15 cm; column diameters varied between 2 and 5 cm.

Hexane was distilled from calcium hydride. Dichloromethane was distilled from phosphorus pentoxide. Diethyl ether was pre-dried over calcium chloride, then distilled from calcium hydride and once more from sodium hydride. Acetonitrile was distilled from phosphorus pentoxide. *N,N*-Dimethylformamide (DMF) was first purified by azeotropic distillation with benzene and after treatment

with barium oxide it was distilled at reduced pressure under nitrogen.

Reactions with HCl

Methyl (2R,3S*)/(2R*,3R*)-2-amino-3-chloro-3-(4-methoxyphenyl)-propanoate hydrochloride* (**2a**) *(general procedure).* A solution of **1a** (105 mg, 0.51 mmol) in ether (5 ml) was added dropwise to a pre-cooled ethereal HCl solution (0 °C) (5 ml). A precipitate was formed immediately. The cooling bath was then removed and the reaction mixture was stirred at room temperature for 18 h. The precipitate was filtered off, washed with ether and dried over P_2O_5. Yield 110 mg (77%) of a 72 : 28 mixture (according to NMR) of *anti*-(2*R**,3*S**)- and *syn*-(2*R**,3*R**)-**2a** as a yellowish solid. M.p. 128–135 °C. IR (KBr): ν 3600, 3300 (br), 3200-2400 (br), 1750/1735 (C=O), 1610, 1585, 1570, 1510, 1430, 1375, 1310, 1280, 1265, 1255, 1245, 1210, 1180, 1145, 1115, 1030, 840, 790 cm^{-1}. ^1H NMR (DMSO-d_6): δ 3.6 (s), 3.75 (s), 3.8 (s, 3H), 4.7 (d, 1H, *J* 7.6 Hz), 5.45 (d, 0.72H, *J* 8 Hz), 5.75 (d, 0.28H, *J* 5.6 Hz), 7.0 (d, 2H, C_6H_2), 7.45 (m, 2H, C_6H_2), 9.05 (br s, 3H, NH_3^+) ppm.

Methyl (2R,3S*)-2-amino-3-chloro-3-phenylpropanoate hydrochloride* (**2b**). Employing the general procedure, **1b** (100 mg, 0.56 mmol) gave a 10 : 1 mixture of *anti*-(2*R**,3*S**)-**2b** and *anti*-(2*R**,3*R**)-**3b** (120 mg, 85%) as a white solid. IR (KBr): ν 3700, 3300 (br), 3300-2400 (NH_3^+), 1745 (C=O), 1585, 1485, 1445, 1395, 1330, 1310, 1275, 1245, 1155, 1050, 945, 920, 880, 855, 820, 755, 705, 620 cm^{-1}. ^1H NMR (DMSO-d_6): δ 3.65 (s, 0.91 × 3H, CO_2Me), 3.70 (s, 0.09 × 3H, CO_2Me), 4.62 (d, 0.91 × 1H, *J* 5 Hz), 4.95 (d, 0.09 × 1H, *J* 5 Hz), 5.50 (d, 0.09 × 1H, *J* 5 Hz), 5.75 (d, 0.91 × 1H, *J* 5 Hz), 7.30 – 7.60 (m, 5H, Ph), 9.00 (br s, 3H, NH_3^+) ppm.

Methyl (2R,3S*)-2-amino-3-chloro-3-(4-nitrophenyl)propanoate hydrochloride* (**2c**) *and methyl (2R*,3R*)-3-amino-2-chloro-3-(4-nitrophenyl)propanoate hydrochloride* (**3c**). From **1c** (50 mg, 0.23 mmol) a 65 : 35 mixture of **2c** and **3c** (46 mg, 69%) was obtained as a white solid. IR (KBr): ν 3430 (br), 3200–2500, 1740/1725 (C=O), 1595, 1515, 1440, 1345, 1250, 1105, 1005, 940, 880, 865, 835, 745, 700 cm^{-1}. ^1H NMR (DMSO-d_6): δ 3.65 (s, 0.65 × 3H, CO_2Me), 3.70 (s, 0.35 × 3H, CO_2Me), 4.80 (d, 0.65H, *J* 5 Hz), 5.22 (d, 0.35H, *J* 5 Hz), 5.50 (d, 0.35H, *J* 5 Hz), 5.95 (d, 0.65H, *J* 5 Hz), 7.75 (d, 2H, C_6H_2, *J* 8 Hz), 8.25 (d, 2H, C_6H_2, J 8 Hz), 9.1 (br s, 3H, NH_3^+) ppm.

Reactions with benzenethiol

Methyl (2R,3S*)/(2R*,3R*)-2-amino-3-(4-methoxyphenyl)-3-(phenylthio)propanoate* (**4a**) *(general procedure).* Boron-trifluoride etherate (71.2 µl, 0.58 mmol) was gradually added to a solution of **1a** (120 mg, 0.58 mmol) and benzenethiol (118.9 µl, 1.16 mmol) in dichloromethane (5 ml) at room temperature under nitrogen. A yellow color was formed immediately. Within 15 min, all aziridine had reacted. After addition of satd. sodium bicarbonate solution (10 ml) the aqueous layer was extracted with dichloromethane. The combined organic layers were dried over Na_2SO_4 and then concentrated. The crude product was purified by chromatography (hexane/ethyl acetate 3 : 1 to 1 : 1), yielding 119 mg (65%) of **4a** as a 60 : 40 mixture of diastereomers (according to GC). IR (CCl_4): ν 3380, 3320, 3065, 3000, 2950, 2900, 2830, 1740 (C=O), 1605, 1505, 1465, 1435, 1300, 1245, 1175, 1040, 1025, 690 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.75 (br s, 2H, NH_2), 3.48 (s, 0.60 × 3H), 3.60 (s, 0.40 × 3H), 3.70 (s, 3H), 3.80 (0.6H, d, PhCHSPh, *J* 6 Hz), 3.84 (0.4H, d, PhCHSPh, *J* 6 Hz), 4.55 (d, 1H, $CHCO_2Me$, *J* 6 Hz), 6.7–7.4 (m, 9H, ArH) ppm. Exact mass determination on fragment MeO – Ph – CHSPh, calcd. for $C_{14}H_{13}OS$: 229.0687 amu; found: 229.0690 ± 0.0007.

Methyl (2R,3S*)-2-amino-3-phenyl-3-(phenylthio)propanoate* (**4b**). From **1b** (100 mg, 0.56 mmol) pure **4b** (129 mg, 80%) was obtained as a single isomer (according to GC and NMR). Reaction time 22 h. IR (CCl_4): ν 3390, 3320, 3060, 3030, 3000, 2950, 2840, 1740 (C=O), 1580, 1480, 1435, 1255, 1210, 1165, 1090, 1025, 700, 695 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.65 (br s, 2H, NH_2), 3.65 (s, 3H, CO_2Me), 3.9 (d, 1H, PhCHSPh, *J* 6 Hz), 4.55 (d, 1H, $CHCO_2Me$, *J* 6 Hz), 7.1 – 7.4 (m, 9H, ArH) ppm. MS (EI): *m/e* (%) 287 (4, M^+), 270 (2), 228 (22, $-CO_2Me$), 218 (18), 200 (100), 199 (100, $PhCH^+SPh$), 166 (40), 165 (41), 118 (72), 109 (26, PhS^+), 91 (61), 84 (27), 77 (26, Ph^+). Exact mass calcd. for $C_{16}H_{17}NO_2S$: 287.0980 amu; found 287.0977 ± 0.0008.

Methyl (2R,3S)-2-amino-3-phenyl-3-(phenylthio)propanoate (**4b**) From (2*S*,3*R*)-**1b** (251 mg, 1.41 mmol) pure (2*R*,3*S*)-**4b** (272 mg, 67%) was obtained as a very viscous oil. $[\alpha]_D^{20}$ + 192.3° (*c* = 1.2, $CHCl_3$). E.e. 97%, according to 400 MHz ^1H NMR analysis of the Mosher derivative (ratio OMe signals 98.3 : 1.7). IR and NMR as for the racemate.

Methyl (2R,3S*)-2-amino-3-(4-nitrophenyl)-3-(phenylthio)propanoate* (**4c**) From **1c** (50 mg, 0.23 mmol) diastereomerically pure **4c** (49 mg, 65%) was obtained as a yellow oil, after chromatography. IR (CCl_4): ν 3400, 3330, 3070, 3050, 3000, 2950, 2850, 1740 (C=O), 1595, 1520, 1480, 1435, 1345, 1215, 1170, 1110, 855, 700, 690 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.6 (br s, 2H, NH_2), 3.65 (s, 3H, CO_2Me), 4.0 (d, 1H, *J* 6 Hz), 4.6 (d, 1H, *J* 6 Hz), 7.0–7.5 (m + d, 7H, ArH), 8.1 (d, 2H, ArH) ppm. MS (EI): *m/e* (%) 332 (0.2, M^+), 273 (5, $-CO_2Me$), 245 (100, $O_2NC_6H_4$-CH^+-SPC_6H_4 + 1), 228 (39), 198 (24), 164 (8), 117 (8), 88 (19). Exact mass on fragment O_2N-C_6H_4-CH^+-SPh, calcd. for $C_{13}H_{10}NO_2S$: 244.0432 amu; found: 244.0431 ± 0.0005.

Reduction of **4b** *with Raney Ni.* A solution of **4b** (143 mg, 0.50 mmol) in methanol (40 ml) was treated with Raney Ni. The mixture was shaken for 24 h at room temperature. The mixture was then filtered and the filtrate concentrated and chromatographed, yielding 55 mg (62%) of methyl 2-amino-3-phenyl-2-propenoate (**5**) and 19 mg (35%) of diphenyl disulfide. Spectral data were identical with reported values[14] (see below).

Reaction of **1b** *with NaN_3/NH_4Cl in methanol.* Sodium azide (147 mg, 2.26 mmol) and ammonium chloride (121 mg, 2.26 mmol) were added to a solution of **1b** (100 mg, 0.56 mmol) in methanol (5 ml). The reaction mixture was heated under reflux for 18 h and the solvent was then evaporated. The residue was dissolved in water (10 ml) and the aqueous phase was extracted three times with ether. The combined organic layers were dried over Na_2SO_4 and concentrated, yielding 87 mg of crude product. IR analysis showed a very weak N3 signal. After chromatography (hexane/ethyl-acetate 10 : 1 to 1 : 1) 25 mg (25%) of **5** was obtained as the principal product, amongst various other unidentified products which did not contain an azide group. IR (CCl_4): ν 3470/3375 (NH_2), 3080, 3060, 3025, 2950, 1710 (C=O), 1635 (C=C), 1580, 1495, 1440, 1395, 1275, 1225, 1195, 1175, 1080, 990, 700 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.70 (s, 3H, CO_2Me), 4.10 (br s, 2H, NH_2), 6.35 (s, 1H, PhCH=C), 7.0–7.4 (m, 5H, Ph) ppm. These spectral data are identical with those reported earlier[14].

Reactions with indole

Methyl (2R,3S*)/(2R*,3R*)-2-amino-3-(indol-3-yl)-3-(4-methoxyphenyl)propanoate* (**6a**) *(general procedure).* Boron trifluoride etherate (89.0 µl, 0.72 mmol) was added dropwise to a solution of **1a** (97 mg, 0.47 mol) and indole (110 mg, 0.94 mmol) in dichloromethane (5 ml) at room temperature under nitrogen. An orange-yellow colour formed immediately. After 45 min, TLC showed the absence of starting aziridine. Satd. sodium bicarbonate solution was then added and the aqueous layer was extracted with dichloromethane (3 ×). The combined organic layers were dried over Na_2SO_4 and concentrated, yielding 230 mg of a pink-orange colored oil, which was chromatographed (hexane/ethyl acetate 1 : 1). Yield 103 mg (68%) of a 55 : 45 mixture of *anti*-(2*R**,3*S**)- and *syn*-(2*R**,3*R**)-**6a** as a colorless oil. IR (CCl_4): ν 3480 (NH-indole), 3400 (br), 3220 (br), 3060, 3040, 3000, 2950, 2840, 1730 (C=O), 1610, 1505, 1455, 1435, 1335, 1300, 1240 (br), 1175, 1110, 1040, 1010 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.75 (br s, 2H, NH_2), 3.45 (s, 0.55 × 3H, CO_2Me), 3.50 (s, 0.45 × 3H, CO_2Me), 3.65 (s, 3H, OMe), 4.10 (m, 1H), 4.60 (m, 1H), 6.6–7.4 (m, 9H, ArH), 8.45 (br d, indole-NH) ppm. MS (EI): *m/e* (%) 324 (1, M^+), 265 (14, $-CO_2Me$), 263 (17), 248 (17), 237 (100), 236 (100, $-NH_2$-CH-CO_2Me), 221 (26), 204 (15), 192 (59), 165 (14), 84 (94), 49 (100).

Methyl (2R,3S*)-2-amino-3-(indol-3-yl)-3-phenylpropanoate* (**6b**) *(general procedure).* From 1b (99 mg, 0.56 mmol) a crude product (210 mg) was obtained, which after chromatography (hexane/ethyl acetate 2 : 1) gave pure 6b (87 mg, 53%) as an oil. NMR indicated the presence of one single isomer. Reaction time 2 h. IR (CCl_4): ν 3490 (indole-NH), 3400 (NH_2), 3060, 3030, 2950, 1735 (C=O), 1580 (br), 1540 (br), 1455, 1435, 1415, 1335, 1235 (br), 1165, 1095, 1015, 1000, 705 cm^{-1}. ^1H NMR ($CDCl_3$) (400 MHz): δ 1.63 (br s, 2H, NH_2), 3.56 (s, 3H, CO_2Me), 4.23 (d, 1H, *J* 6.9 Hz), 4.68 (d,

1H, *J* 6.9 Hz), 6.99 (t, 1H, indole-H5, *J* 7.2 Hz), 7.10 (t, 1H, indole-H6, *J* 7.2 Hz), 7.14–7.34 (m, 7H, Ph, indole-H2, indole-H7), 7.37 (d, 1H, indole-H4, *J* 7.9 Hz), 8.39 (br s, 1H, indole-NH) ppm. ^{13}C NMR ($CDCl_3$): δ 46.9, 51.9, 111.0, 115.9, 119.0, 119.2, 121.9, 122.1, 126.7, 126.9, 128.4, 128.7, 136.0, 140.0, 174.9 ppm. MS (EI): *m/e* (%) 294 (4, M$^+$), 279 (4), 235 (14, $-CO_2Me$), 207 (99), 206 (100, $-NH_2$-CH-CO_2Me), 178 (31), 149 (19), 94 (100), 83 (100). Exact mass calcd. for $C_{18}H_{18}N_2O_2$: 294.1368 amu; found: 294.1365 ± 0.0009.

Methyl (2S,3R)-2-amino-3-(indol-3-yl)-3-phenylpropanoate (**6b**). From (2*S*,3*R*)-**1b** (200 mg, 1.13 mmol) pure **6b** (211 mg, 64%) was obtained as a very viscous oil. $[\alpha]_D^{20}$ −13.1° (*c* = 1.0, $CHCl_3$). E.e. 95%, according to a 400 MHz ^{1}H NMR analysis of the Mosher derivative (ratio OMe signal 97.6 : 2.4). IR and NMR, as for the racemic compound.

Methyl (2R,3S*)-2-amino-3-(indol-3-yl)-3-(4-nitrophenyl)propanoate* (**6c**). From **1c** (25 mg, 0.114 mmol) 52 mg of crude product was obtained as a yellow oil. Chromatography (hexane/ethyl acetate 1 : 2) gave pure **6c** (23 mg, 60%) as a yellow oil. IR (CCl_4): ν 3480 (indole-NH), 3400, 2960, 2930, 2860, 1740 (C=O), 1525, 1455, 1435, 1350, 1250, 1210, 1155, 1110, 1095, 1005, 980, 910 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.25–1.6 (br s, 2H, NH_2), 3.65 (s, 3H, CO_2Me), 4.33 (d, 1H, *J* 7 Hz), 4.87 (d, 1H, *J* 7 Hz), 6.81–7.64 (m, 7H, indole-CH, C_6H_2), 7.90–8.36 (m, 3H, C_6H_2, indole-NH) ppm.

Reaction with acetic acid

Methyl (2R,3R*)-2-(acetylamino)-3-hydroxy-3-phenylpropanoate* (**7**). A mixture of aziridine **1b** (100 mg, 0.56 mmol) and acetic acid (5 ml) was stirred at 70 °C for 2 h. Excess acetic acid was removed *in vacuo*, leaving **7** (136 mg, 100%) as a yellowish white solid, which was recrystallized from ethyl acetate. M.p. 120–120.5 °C (lit[18a] 120–122 °C, lit[18b] 118–119 °C). IR (KBr): ν 3320 (br, OH, NH), 3070, 3030, 2945, 2850, 1715 (OC=O), 1660 (NC=O), 1540, 1490, 1440, 1365, 1305, 1280, 1240, 1205, 1140, 1095, 1065, 1000, 970, 945, 775, 740, 700, 615 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 2.02 (s, 3H, $COCH_3$), 3.71 (s, 3H, CO_2Me), 4.47 (m, 1H, OH), 5.01 (dd, 1H, CHNAc, *J* 3.5 Hz, 7.2 Hz), 5.25 (m, 1H, CHO), 6.29 (d, 1H, NH, *J* 7 Hz), 7.30 (s, 5H, Ph) ppm; OH-decoupled: δ 5.25 (d, *J* 3.5 Hz) ppm; + D_2O: δ 5.01 (d, *J* 3.5 Hz), 5.25 (d, *J* 3.5 Hz) ppm.

Methyl (2S,3S)-2-(acetylamino)-3-hydroxy-3-phenylpropanoate (**7**). Following the procedure described for the synthesis of racemic **7**, 295 mg (100%) of crude product was obtained as a yellowish solid, starting from (2*S*,3*R*)-**1b** (217 mg, 1.22 mmol). Chromatography gave pure (2*S*,3*S*)-**7** (220 mg, 69%) as a white solid, which was recrystallized from ethyl acetate. M.p. 124.5–126 °C. $[\alpha]_D^{20}$ +140.2° (*c* 0.9, $CHCl_3$). $[\alpha]_D^{20}$ +63.0° (*c* 2.0, AcOH). Lit[18b] $[\alpha]_D^{25}$ +62.6° (*c* 2.0, AcOH), e.e. ≥98%; lit[18b] $[\alpha]_D^{25}$ −62.8° (*c* 2.0, AcOH), e.e. ≥98% for the enantiomer. IR and ^{1}H NMR as for the racemate. MS (CI): *m/e* (%) 238 (29, M + 1$^+$), 220 (35, OH), 188 (18), 178 (22, $-CO_2Me$), 131 (100, AcNH-CH-CO_2Me + 1$^+$), 107 (14, Ph-CH$^+$-OH), 99 (69), 89 (28), 79 (17), 77 (16), 57 (14), 43 (27, CH_3CO^+). Anal. calcd. for $C_{12}H_{15}NO_4$ (237.257): C 60.75, H 6.37, N 5.90; found: C 61.30, H 6.41, N 5.94%.

Synthesis of N-functionalized derivatives of **1b**

Methyl 1-acetyl-trans-*3-phenylaziridine-2-carboxylate* (**8**). Pyridine (460 µl, 5.64 mmol), acetic anhydride (400 µl, 4.20 mmol) and 4-(dimethylamino)pyridine (DMAP) (a few crystals) were added sequentially to a stirred solution of **1b** (500 mg, 2.82 mmol) in dichloromethane (5 ml). The mixture was stirred for 18 h at room temperature. The solvent was evaporated. The residue was then dissolved in water and extracted with ether (3 × 15 ml). The combined extracts were washed with 2N sulfuric acid and satd. sodium bicarbonate solutions, dried over $MgSO_4$ and concentrated, yielding 498 mg (81%) of crude product as a colorless oil. After chromatography, two fractions were obtained. The desired product **8** was obtained in 61% yield (375 mg). M.p. 51.5–52.5 °C (hexane). IR (KBr): ν 3045, 2960, 1735 (OC=O), 1695 (NC=O), 1460, 1440, 1365, 1345, 1320, 1230, 1205, 1165, 1025, 1000, 970, 920, 905, 780, 735, 700, 615 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 2.1 (s, 3H, $COCH_3$), 3.2 (d, 1H, $CHCO_2$, *J* 2 Hz), 3.8 (m, 3H, CO_2Me), 7.3 (s, 5H, Ph) ppm. MS (CI): *m/e* (%) 220 (24, M + 1$^+$), 188 (22, $-OCH_3$), 178 (98), 160 (4, $-CO_2Me$), 146 (11), 135 (6). Anal. calcd. for $C_{12}H_{13}NO_3$ (219.241): C 65.47, H 5.98, N 6.39; found: C 65.76, H 5.93, N 6.20%. The other fraction consisted of a mixture of oxazoline **11** and hydrolysis product **12** (18%, 111 mg).

Methyl 1-(benzyloxycarbonyl)-trans-*3-phenylaziridine-2-carboxylate* (**9**) At 0 °C benzyl chloroformate (600 µl, 4.23 mmol) and DMAP (a few crystals) were added sequentially to a solution of **1b** (500 mg, 2.82 mmol) in dichloromethane (10 ml) containing pyridine (457 µl, 5.60 mmol). The mixture was kept at 0 °C for 15 min and then stirred for 18 h at room temperature. The solvent was evaporated. The residue was dissolved in water and extracted with ether (3 ×). The combined extracts were washed with 2N sulfuric acid and satd. sodium bicarbonate solutions, dried ($MgSO_4$) and concentrated. The residue was purified by chromatography (hexane/ethyl-acetate 9 : 1), yielding 586 mg (67%) of **9**, together with 214 mg (22%) of a mixture of ring opening products. **9**: IR (CCl_4): ν 3065, 3035, 2955, 1735 (br, C=O), 1455, 1440, 1415, 1380, 1340, 1315, 1300, 1285, 1225, 1165, 1085, 1030, 905, 695 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 3.1 (d, 1H, *J* 2.2 Hz), 3.65 (s, 3H, CO_2Me), 3.85 (d, 1H, *J* 2.2 Hz), 5.2 (s, 2H, $PhCH_2$), 7.30 (s, 5H), 7.35 (s, 5H) ppm. MS (CI): *m/e* (%) 312 (50, M + 1$^+$), 280 (3, $-OCH_3$), 268 (82 (M + 1 − CO_2), 252 (7, $-CO_2CH_3$), 208 (37), 176 (94, $-CO_2CH_2Ph$), 117 (21), 91 (100, $PhCH_2^+$). Exact mass calcd. for $C_{18}H_{17}NO_4$: 311.1157 amu; found: 311.1157 ± 0.0009. Ring opening products: IR (CCl_4): ν 3430 (NH), 3065, 3030, 2950, 1735 (br, C=O), 1490, 1450, 1435, 1355, 1335, 1260, 1210, 1060, 1025, 910, 700 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 3.6 (s, 3H, CO_2Me), 4.95 (m, 1H), 5.05 (s, 2H, $PhCH_2$), 5.25 (d, 1H, NH, *J* 5.5 Hz), 5.5 (m, 1H), 7.3 (m, 10H, Ph) ppm.

Tosylation of **1b**. *p*-Toluenesulfonyl chloride (113 mg, 0.59 mmol) was added to a solution of **1b** (100 mg, 0.56 mmol), pyridine (91.4 µl, 1.12 mmol) and DMAP (a few crystals) in dichloromethane (1 ml). The reaction mixture was stirred for 16 h at room temperature. Water (10 ml) was then added and the aqueous layer was extracted twice with dichloromethane. The combined organic extracts were washed with a copper(II) sulfate solution (3 × 10 ml), dried over $MgSO_4$ and concentrated, yielding methyl (2*R**,3*S**)-3-chloro-3-phenyl-2-(tosylamino)-propanoate **10** (158 mg, 76%) as an off-white solid. The crude solid material was recrystallized from hexane/ethyl acetate. M.p. 141.5–143.5 °C. IR (KBr): ν 3290 (NH), 1730 (C=O), 1595, 1435, 1340 (NSO_2), 1230, 1160 (NSO_2), 1095, 910, 815, 760, 735, 720, 710, 695, 665 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 2.35 (s, 3H, CH_3C_6), 3.50 (s, 3H, CO_2Me), 4.40 (dd, 1H, $CHCO_2$, *J* 6 Hz, 10 Hz), 5.10 (d, 1H, $CHCCO_2$, *J* 6 Hz), 5.3 (d, 1H, NHTos, *J* 10 Hz), 7.05–7.30 (d + s, 7H, C_6H_2, Ph), 7.65 (d, 2H, C_6H_2, *J* 9 Hz) ppm. MS (CI): *m/e* (%) 370 [1.82, M + 1$^+$ (^{37}Cl)], 368 [5.42, M + 1$^+$ (^{35}Cl)], 332 (9, −Cl), 310 [2.77, $-CO_2Me$ (^{37}Cl)], 308 [7.75, $-CO_2Me$ (^{35}Cl)], 242 (100, TosNH-CH$^+$-CO_2Me), 176 (7), 155 (67, $TolSO_2^+$), 127 (3.23, PhCH$^+$-^{37}Cl), 125 (10.82, PhCH$^+$-^{35}Cl), 118 (11), 91 (44, $CH_3C_6H_4^+$), 65 (8). Anal. calcd. for $C_{17}H_{18}ClNO_4S$ (367.853): C 55.51, H 4.93, N 3.81, S 8.72; found: C 54.95, H. 4.91, N 3.81, S 9.17 %.

Methyl (4R,5S*)-2-methyl-5-phenyloxazoline-4-carboxylate* (**11**). Boron trifluoride etherate (5 mol%, 2.8 µl, 0.023 mmol) was added to a cooled solution (0 °C) of **11** (100 mg, 0.46 mmol) in acetonitrile (5 ml). The reaction mixture was stirred at room temperature for 18 h. After addition of satd. sodium bicarbonate solution the solvent was evaporated. The residue was diluted with water and extracted with ether (3x). The combined extracts were dried over $MgSO_4$ and concentrated, yielding product **11** (87 mg, 87%) as a colorless oil (93% pure according to GC). After chromatography (hexane/ethyl acetate 3 : 1), pure **11** (59 mg, 59%) was obtained as an oil which slowly crystallized on standing. IR (CH_2Cl_2): ν 2955, 1740 (C=O), 1615 (C=N), 1490, 1385, 1205, 995 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 2.1 (d, 3H, CH_3C=N, ^5J 1.5 Hz), 3.75 (s, 3H, CO_2Me), 4.55 (dm, 1H, C=N-CH, ^3J 8.1 Hz, ^5J 1.5 Hz), 5.7 (d, 1H, $CHCCO_2$, *J* 7.5 Hz), 7.3 (s, 5H, Ph) ppm. MS (CI): *m/e* (%) 220 (45, M + 1$^+$), 188 (4, −OMe), 178 (4, $-CH_3C$=N), 160 (91, $-CO_2Me$), 132 (9), 128 (10), 119 (25), 113 (100, CH_3-C=N-CH-CO_2Me^+), 105 (7), 91 (37), 85 (66, $NCHCO_2Me^+$), 77 (9, Ph^+), 43 (65). On recrystallization from petroleum ether/ethyl-acetate, beautiful small needles of hydrolysis product *syn*-**12** were obtained. M.p. 185–196 °C. IR (KBr): ν 3330/3210 (NH), 1715 (OC=O), 1645 (NC=O), 1530, 1435, 1370, 1345, 1295, 1265, 1095, 1065, 1005, 760, 710 cm^{-1}. Anal. calcd. for $C_{12}H_{15}NO_4$ (237.257): C 60.47, H 6.37, N 5.90; found: C 60.63, H 6.47, N 5.74%.

Methyl (2R,3S*)-2-(acetylamino)-3-hydroxy-3-phenylpropanoate* (**12**) Oxalic acid (100 mg, 1.11 mmol) was added to a solution of oxazoline 11 (41 mg, 0.19 mmol) in methanol (5 ml). The reaction mixture was heated under reflux for 18 h. After evaporation of the solvent, the residue was taken up in satd. sodium bicarbonate solution (5 ml). The aqueous solution was extracted with ether (3x15 ml). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated, yielding 12 (26 mg, 59%) as a white solid. IR (KBr): ν 3335 (NH), 3600–3000 (br, OH, NH), 2990, 2945, 2890, 1715 (OC=O), 1645 (NC=O), 1535, 1435, 1370, 1345, 1295, 1265, 1195, 1140, 1095, 1065, 1030, 1010, 930, 840, 790, 760, 710 (s), 630 cm^{-1}. ^1H NMR (DMSO-d_6): d 1.8 (s, 3H, $COCH_3$), 3.6 (s, 3H, CO_2Me), 4.55 (dd, 1H, $CHCO_2$, *J* 4 Hz, *J* 9 Hz), 5.05 (m, 1H, CHO), 5.75 (d, 1H, OH, *J* 4.5 Hz), 7.3 (m, 5H, Ph), 8.05 (d, 1H, NH, *J* 9 Hz) ppm.

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