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Full Papers

Synthesis of functionalized amino acids by ring-opening reactions of aliphatically substituted aziridine-2-carboxylic esters

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Abstract. Nucleophilic ring-opening reactions of 3-alkylaziridine-2-carboxylic esters are described. Without ring activation at nitrogen, ring opening could only be accomplished with ethereal hydrogen chloride. Introduction of electron-withdrawing activating groups at the nitrogen atom was necessary. Three types of activating groups were used, *viz.* acyl, alkoxycarbonyl and sulfonyl groups. In the presence of a Lewis-acid catalyst, ring opening with two nucleophiles, namely indole and benzenethiol, could be accomplished. S_N2-type attack at C3 was observed exclusively. With Brönsted acids (hydrogen chloride, formic acid, acetic acid), ring opening could also be effected. 3-Formyloxy derivatives could also be prepared by reaction of the activated aziridines with *N*,*N*-dimethylformamide in the presence of boron trifluoride etherate. Reaction with sodium azide caused some difficulties; complex product mixtures were usually obtained. *N*-Sulfonylaziridine-2-carboxylic esters gave a mixture of the two possible regioisomers, resulting from attack at C2 and C3. Treatment of *N*-sulfonylaziridine-2-carboxylic esters with trimethylsilyl azide, however, gave products exclusively ring-opened at C2. On reaction of the activated aziridines with acetonitrile in the presence of boron trifluoride etherate, a ring-expansion reaction was observed, leading to imidazolines. On standing, these heterocyclic compounds slowly hydrolyzed to α,β-diamino carboxylic acid derivatives.

Introduction

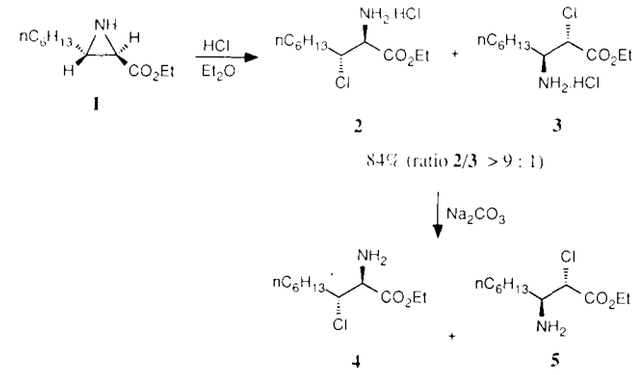
Aziridine-2-carboxylic acids may be regarded as α- and β-amino acids at the same time. Because of the known intrinsic high reactivity of the three-membered aziridine ring, it is plausible to consider these aziridine derivatives as precursors of a variety of functionalized amino acids.

Both β-functionalized α-amino acids and α-functionalized β-amino acids are important classes of compounds[1-7]. Especially, the hydroxy derivatives appear in several biologically important naturally occurring compounds, *e.g.*, bestatin[1], amastatin[2] and cyclosporin[3]. In the last decade, several approaches to optically active functionalized amino acids have been reported[4-7]. In this paper, we report the synthesis of various functionalized amino acid derivatives by ring-opening reactions of aliphatically 3-substituted aziridine-2-carboxylic esters.

Little attention has so far been given to the chemistry of aziridine-2-carboxylic esters[8]. *Kyburz*[9] and *Wade*[10] described the reaction of aziridine-2-carboxylic esters with hydrogen halides. Mixtures of isomers were usually formed, depending on the reaction conditions. *Styngach*[11] reported the reaction of isopropyl *cis*-3-phenylaziridine-2-carboxylate with indole. *Hata* et al.[12] described ring opening of cis-3-methylaziridine-2-carboxylic acid with benzenethiol in aqueous solution. Regioisomeric mixtures were formed with the predominant product arising from attack at C2. *Marquet*[13] treated menthyl 3-phenylaziridine-2-carboxylate (both *cis* and *trans*) with (4-methoxyphenyl)methanethiol in the presence of a Lewis acid. Several authors, however, described ring opening of N-activated aziridinecarboxylic esters[14-19], usually with aliphatic substituents at C3. *Okawa* et al.[14,15] reported a number of ring-opening experiments with esters of *N*-(benzyloxycarbonyl)aziridine-2-carboxylic acid and *N*-(benzyloxycarbonyl)-*cis*-3-methylaziridine-2-carboxylic acid, derived from serine and threonine, respectively. The same type of N-activation was used by *Sato*[16] and *Shima*[17] in their synthesis of tryptophan derivatives from serine[16] and threonine[17]. *Baldwin*[18,19] described ring opening of *N*-tosylated aziridinecarboxylic esters with Wittig reagents[18] and organometallics[19]. *Tanner*[20] also used *N*-tosyl activation in ring-opening reactions of diethyl aziridine-2,3-dicarboxylate. Recently[21], we have reported the convenient preparation of racemic and optically active aziridine-2-carboxylic esters from the corresponding oxirane-2-carboxylic esters. For the study presented in this paper, ethyl *trans*-3-hexylaziridine-2-carboxylate will be used as the model substrate for 3-aliphatically substituted aziridine-2-carboxylic esters.

Results and discussion

Ring opening of the model substrate **1** could readily be accomplished by treatment with hydrogen chloride in ether, as could be expected[9]. This reaction leads to the predomi-

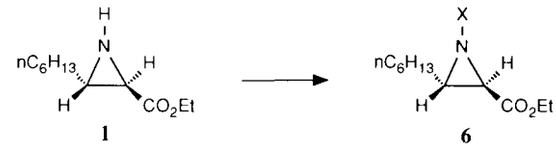


Scheme 1

nant formation of the regioisomer **2** resulting from nucleophilic attack of chloride anion at C3 of the initially formed aziridinium salt. Compound **2** consists of single diastereomer, implying that ring opening takes place in an S_N2 fashion.

For 3-aryl-substituted aziridine-2-carboxylic esters, we

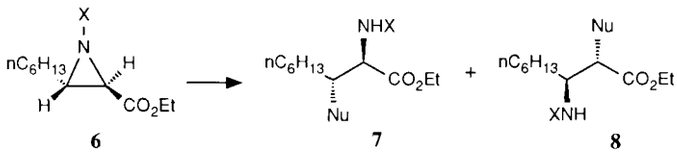
Chart 1 N-Functionalization of **1**.



Reagent	Product	X	Yield (%)
Ac_2O, pyr, DMAP[a]	**6a**	Ac	90
$(CF_3CO)_2O$, pyr, DMAP	**6b**	$C(=O)CF_3$	30 (95)[d]
Z-ONSu[b], Et_3N, MeCN	**6c**	CO_2CH_2Ph	82
TEOC-Cl[c], pyr	**6d**	$CO_2CH_2CH_2SiMe_3$	84
$MeSO_2Cl$, Et_3N	**6e**	SO_2Me	85
p-$TolSO_2Cl$, Et_3N	**6f**	SO_2Tol-*p*	51 (100)[d]
$PhCH_2SO_2Cl$, pyr	**6g**	SO_2CH_2Ph	65
$C_6Me_5SO_2Cl$, pyr	**6h**	$SO_2C_6Me_5$	38 (65)[d]

[a] DMAP: 4-(dimethylamino)pyridine. [b] Z-ONSu: *N*-(benzyloxycarbonyloxy)succinimide. [c] TEOC-Cl: 2-(trimethylsilyl)ethyl chloroformate. [d] Numbers in parentheses refer to crude product yields.

Chart 2 Ring-opening reactions of N-activated substrates **6a-g**.



Entry	Substrate	X	Reagent	Product	Nu	Yield (%)
A	**6a**	Ac	HCl/ether	**7aa**	Cl	71
B	**6f**	Tos	HCl/ether	**7fa** + **8fa**[a]	Cl	97
C	**6a**	Ac	PhSH, $BF_3 \cdot Et_2O$	**7ab**	PhS	38
D	**6c**	Z	PhSH, $BF_3 \cdot Et_2O$	**7cb**	PhS	95
E	**6d**	TEOC	PhSH, $BF_3 \cdot Et_2O$	**7db** + **8dg**[b]	PhS	70
F	**6e**	Ms	PhSH, $BF_3 \cdot Et_2O$	**7eb**	PhS	40
G	**6f**	Tos	PhSH, $BF_3 \cdot Et_2O$	**7fb**	PhS	63 (90)[c]
H	**6g**	$BzlSO_2$	PhSH, $BF_3 \cdot Et_2O$	**7gb**	PhS	63 (90)[c]
I	**6a**	Ac	indole, $BF_3 \cdot Et_2O$	**7ac**	Ind	27
J	**6a**	Ac	HCO_2H (neat)	**7ad**	HCOO	91
K	**6a**	Ac	DMF, $BF_3 \cdot Et_2O$	**7ad** + ...[d]	HCOO	mixt.[d]
L	**6c**	Z	HCO_2H (neat)	**7cd**	HCOO	86
M	**6c**	Z	DMF, $BF_3 \cdot Et_2O$	**7cd**	HCOO	100[e]
N	**6d**	TEOC	HCO_2H (neat)	**7dd**	HCOO	75
O	**6d**	TEOC	DMF, $BF_3 \cdot Et_2O$	**7dd**	HCOO	45[f]
P	**6f**	Tos	HCO_2H (neat)	**7fd**	HCOO	85
Q	**6f**	Tos	DMF, $BF_3 \cdot Et_2O$	**7fd**	HCOO	49[g] (93)[c]
R	**6a**	Ac	AcOH	**7ae**	AcO	78
S	**6c**	Z	AcOH	**7ce**	AcO	90
T	**6d**	TEOC	AcOH	**7de**	AcO	100
U	**6a**	Ac	NaN_3, $BF_3 \cdot Et_2O$, DMF	**7af** + **8af** + ...[h]	N_3	32[h]
V	**6e**	Ms	NaN_3, DMF	**7ef** + **8ef** + ...[i,j]	N_3	[i,j]
W	**6e**	Ms	Me_3SiN_3, EtOH, DMF	**8ef**	N_3	88
X	**6f**	Tos	NaN_3, DMF	**7ff** + **8ff** + ...[i,k]	N_3	[i,k]
Y	**6f**	Tos	Me_3SiN_3, EtOH, DMF	**8ff**	N_3	56
Z	**6g**	$BzlSO_2$	NaN_3, DMF	**7gf** + **8gf**[l]	N_3	60

[a] Ratio **7fa**/**8fa** = 2:3. [b] Ratio **7db**/**8dg** = 3:2, the nucleophile in **8dg** was F. [c] Numbers in parentheses refer to crude product yields. [d] A mixture of three products was obtained, among which formyloxy derivative **7ad**. The mixture was not separated (see experimental). [e] Purity 86%. [f] Purity 93%. [g] Purity 100%. [h] Ratio **7af**/**8af** = 93:7 after chromatography. [i] Both isomers were present in a complex mixture. [j] Ratio **7ef**/**8ef** > 1. [k] Ratio **7ff**/**8ff** > 1. [l] Ratio **7gf**/**8gf** = *ca.* 1:2.

showed[22] that nucleophilic opening can be realized with benzenethiol and indole in the presence of boron trifluoride etherate as catalyst, and also with acetic acid. Attempts to accomplish similar ring-opening reactions with substrate **1** failed, despite the fact that various experimental conditions were tried. It was, therefore, concluded that an activating group at nitrogen is necessary to facilitate the desired ring-opening reactions. For this purpose, three different types of N-functional groups were selected, *viz.*, acyl, alkoxycarbonyl and sulfonyl groups. These activating functions were introduced using standard procedures, as shown in Chart 1. The *N*-(trifluoroacetyl) derivative **6b** was difficult to purify due to its intrinsic instability. Therefore, this derivative is not suitable as a substrate in ring-opening reactions. For introduction of the benzyloxycarbonyl group, benzyl chloroformate was used; however, the yield of **6c** was much lower than that obtained with *N*-(benzyloxycarbonyloxy)succinimide. Pyridine was the base of choice for the formation of **6d**; with triethylamine, the reaction with chloroformate was not complete. The reactions with various sulfonyl chlorides were dependent on the base. For the preparation of **6e** and **6f**, triethylamine gave good results, whereas for **6g** and **6h** pyridine was preferred. When pyridine was used for tosylation of **1**, considerable ring opening was observed. Derivative **6h** was difficult to purify and was, therefore, not further studied in ring-opening experiments. It should be noted that 3-arylaziridine-2-carboxylic esters could not be tosylated because of concomitant ring-opening reactions[22]. This observation substantiates the fact that the aliphatically substituted aziridine carboxylates are much more reluctant to undergo ring-opening reactions than the corresponding 3-aryl compounds.

The different N-activated aziridine-2-carboxylic esters were subjected to several nucleophilic reagents in order to achieve a ring-opening reaction. The results are collected in Chart 2. *N*-Acyl compound **6a** gave, upon treatment with HCl in ether, a single diastereomer arising from nucleophilic reaction at C3. The reaction with the *N*-tosyl aziridine **6f** is not regiospecific because a mixture of C2 and C3 ring-opened products was obtained. In the reaction with *N*-acyl derivative **6a**, effective H^+ catalysis by protonation of N or O will cause regiospecific attack at C3. At C2, the positive charge cannot be stabilized due to the presence of an electron-withdrawing ester group. In the reaction with *N*-tosyl derivative **6f**, however, no initial protonation can occur. For this reason, the attack of chloride is fully governed by the electron-withdrawing effect of the SO_2Tol group, thus causing the formation of a mixture of products.

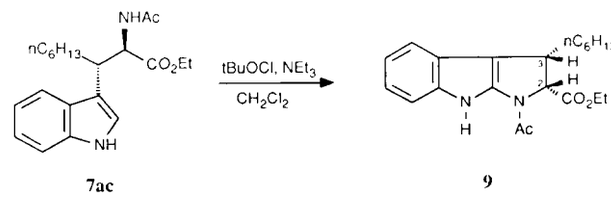
The reaction with benzenethiol was tested with all N-activated aziridinecarboxylates studied. In all cases, the phenylthio group was introduced at C3 in a stereospecific manner. With **6a**, product **7db** was obtained in a rather low yield; however, *N*-(benzyloxycarbonyl) substrate **6c** gave an almost quantitative yield. For **6d**, a 3-fluoro product **8dg**, arising from attack of fluoride at C3, was isolated as an important by-product. The reasons for the differences in behaviour between **6c** and **6d** are obscure. The sulfonyl derivatives **6e**, **6f** and **6g** all gave products in moderate yields, exclusively ring-opened at C3.

The reaction with indole, which was very successful for the 3-aryl substituted aziridine-2-carboxylic esters[22], gave a disappointing yield of ring-opened product **7ac** when prepared from the *N*-acyl substrate **6a**. Attempted reaction with tin(IV) chloride as the Lewis acid catalyst gave no **7ac**, only **7aa** was isolated, resulting from ring opening by chloride ion. Treatment with formic acid gave smooth ring-opening reactions for *N*-acetyl (**6a**), *N*-alkoxycarbonyl (**6c,d**) and *N*-tosyl (**6f**) substrates. The same formyl products could be obtained by treatment with *N,N*-dimethylformamide (DMF) in the presence of boron trifluoride etherate, albeit less pure and in poor yields. Mechanistically, it is assumed that DMF acts as a nucleophile, giving rise to an *O*-iminium salt which, during work-up, hydrolyzes to the formyl compounds **7ad**, **7cd**, **7dd** and **7gd**, respectively (*cf.*, ref. 23). 3-Acetoxy derivatives were readily produced on treatment of **6a**, **6c** and **6d**, respectively, with acetic acid. Unexpectedly, *N*-tosyl substrate **6f** did not give the expected acetoxy product when treated with acetic acid. However, a considerable amount of starting material was recovered, even after prolonged reaction times at 100°C. Ring opening is seriously hampered because no protonation can occur (*cf.*, reaction with hydrogen chloride in ether).

The reaction of *N*-acyl substrate **6a** with sodium azide in DMF[24] using boron trifluoride etherate as catalyst gave a moderate yield of azide product **7af**, which contained a small amount of regioisomer **8af** as by-product. In the absence of catalyst no reaction was observed. With **6c** and **6d**, sodium azide in DMF also gave no reaction, even at elevated temperatures (90°C) and prolonged reaction times (7 d). With sulfonyl activated substrates (**6e**, **6f** and **6g**) reaction with sodium azide in DMF could be accomplished; however, a mixture of regioisomers was obtained, along with some other unidentified products. For **6g**, the regioisomeric ratio amounted to 1 : 2. An interesting observation was made when **6e** and **6f** were treated with azidotrimethylsilane in DMF containing one equivalent of ethanol. These conditions, originally used by *Saito* et al.[25,26], caused ring opening exclusively at C2; no attack at C3 was observed. Thus, 2-azido-3-(sulfonylamino) esters **8ef** and **8ff** were obtained in good yields as single isomers.

The presence of a 3-substituted 2-amino ester in most cases could be deduced from the presence of a doublet of doublets in the ^1H NMR spectrum between δ 4 and δ 5 ppm, arising from C2–H coupling with C3–H and NHX. 2-Substituted 3-amino esters like **7eb**, **7fb** and **7gb** exhibited a doublet arising from C2–H coupling with C3–H. The presence of regioisomers and their ratio could usuallly be deduced easily from the number and ratio of NHX signals in the ^1H NMR spectrum.

The various ring-opening reactions are assumed to proceed with inversion of configuration at the center of nucleophilic attack. This is exemplified by the relative stereochemistry of **7ac**, which could be established as follows: Cyclization of **7ac** with *tert*-butyl hypochlorite, following a procedure reported by *Witkop*[27] and *Turchin*[28], gave 2,3-dihydropyrrolo[2,3-b]indole **9** (Scheme 2). The ^1H NMR spectrum

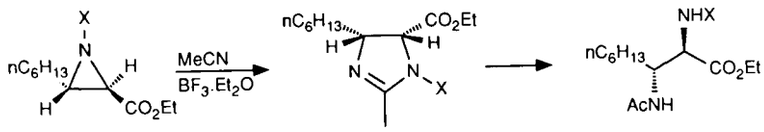


7ac **9**

Scheme 2

of this heterocycle clearly showed the *cis* relationship of C2–H and C3–H (^3J 9.7 Hz); the stereochemistry of **7ac** must, therefore, be *anti*, resulting from S_N2-type ring opening of *N*-acylaziridine **6a**. There is no reason to believe that the stereochemical course of the other ring-opening reactions is different (*cf.* refs. 19, 20, 29 and 30). Because *trans*-aziridines were used throughout this study, all amino acid derivatives described above thus have the *anti* configuration. Finally, the *N*-activated aziridines were subjected to a reaction with acetonitrile using boron trifluoride etherate as Lewis acid catalyst (*cf.*, ref. 31). An interesting ring

Chart 3 Ring-expansion reactions of **6** *with acetonitrile.*



6 **10** **11**

Entry	Substrate	X	Reagent	Product	Yield (%)	Amide[a]
A	**6a**	Ac	MeCN, $BF_3 \cdot Et_2O$, r.t., $1\frac{1}{2}$ h	**10a**[b]	91	**11a**
B	**6c**	Z	MeCN, $BF_3 \cdot Et_2O$, r.t., $1\frac{1}{2}$ h	**10c**	85	**11c**
C	**6d**	TEOC	MeCN, $BF_3 \cdot Et_2O$, r.t., $1\frac{1}{2}$ h	**10d**	93	**11d**
D	**6e**	Ms	MeCN, $BF_3 \cdot Et_2O$, r.t., 20 h	**10e**	92	**11e**
E	**6f**	Tos	MeCN, $BF_3 \cdot Et_2O$, r.t., 20 h	**10f**	65	**11f**

[a] Amides **11** were formed by slow hydrolysis of imidazolines **10** on standing, due to air moisture. [b] After reaction at reflux temperature, amide **11a** was isolated.

expansion to *N*-substituted imidazolines **10** was observed. The results are shown in Chart 3. The structures of these products were established on the basis of their spectral data. The IR and ^{1}H NMR spectra both clearly show the absence of any NH group. In the IR spectrum, a C=N absorption peak was present at about 1660 cm^{-1}. Furthermore, in the NMR spectrum, a doublet was present at δ 4.8 ppm (*J* 10.5 Hz), indicating the presence of two hydrogens (*viz.* C4–H and C5–H) in a *cis* relationship. The methyl signal at δ 2.3 ppm showed long-range coupling (^5J 1.5 Hz) across the C=N double bond with C5–H which proves the regiochemistry of the reaction.

Because of the stereochemical relationship between the hexyl and ester group, which is *cis*, the formation of this ring expansion product proceeds via initial attack of acetonitrile at C3 of the epoxide with inversion of configuration, followed by ring closure involving a reaction of the nitrogen atom, which was originally in the three-membered ring, with the nitrilium group. On continued exposure to moisture, the imidazolines gradually hydrolyzed to the corresponding 2-[acyl (or sulfonyl)amino]-3-(acetylamino) esters **11**. We assume that the stereochemical relationship around the chiral centres is not altered during this hydrolysis. These compounds were usually present in the crude imidazolines to a small extent, as was evident from IR and NMR spectra.

For the protected amino acid derivatives prepared above, several deprotection methods are available. A broad survey is given by *Greene*[32] and various other methods have recently been published. *N*-Acetyl derivatives may be cleaved mildly and selectively with triethyloxonium tetrafluoroborate (Meerwein's reagent) as described by *Hanessian*[33]. *N*-Benzyloxycarbonyl derivatives may be deprotected by hydrogenolysis in some cases (in the absence of sulfur atoms in the molecule), but some alternatives have been reported, *e.g.* treatment with trimethylsilyl iodide as published by *Lott* et al.[34]. *N*-[2-(Trimethylsilyl)ethoxycarbonyl] derivatives may be easily deprotected with fluoride[35]. Finally, *N*-sulfonyl derivatives may be deprotected reductively or with acid.

The results presented above clearly demonstrate that N-activated 3-alkyl-substituted aziridine-2-carboxylic esters undergo nucleophilic ring opening by reaction of the nucleophile at C3 in almost all cases. Exceptions are the reactions of *N*-sulfonylaziridinecarboxylates **6e,f,g** with hydrogen chloride and sodium azide, which gave mixtures of regioisomers, and with azidotrimethylsilane/ethanol in dimethylformamide, which showed ring opening exclusively at C2. The chemistry presented above demonstrates the versatility of aziridine ring-opening reactions and, therefore, easy access to functionalized amino acid derivatives.

Experimental

General remarks

Mrs. H. I. V. *Amatdjais-Groenen* (el. anal.), Mr. *P. M. van Galen* (m.s.) 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 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.[36] 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 predried on 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. Ethyl acetate p.a. (Janssen Chimica or Merck) was used as such. Azidotrimethylsilane was purchased from Janssen Chimica.

Reactions of ethyl trans*-3-hexylaziridine-2-carboxylate* (**1**)

Ethyl (2R,3S*)-2-amino-3-chlorononanoate hydrochloride* (**2**) *and ethyl (2R*,3R*)-3-amino-2-chlorononanoate hydrochloride* (**3**). A solution of **1**[21] (207 mg, 1.04 mmol) in ether (5 ml) was slowly added to a cooled (0°C) ethereal HCl solution. Immediately, the aziridinium chloride precipitated, which gradually dissolved when the cooling bath was removed. Later, a precipitate of the product was formed. After stirring at room temperature for 18 h, the mixture

was cooled and filtered. The collected product was washed well with ether and dried over P_2O_5. Yield 226 mg (84%) of a white solid, mainly consisting of **2** and the by-product being regioisomer **3** (ratio **2** : **3** > 9 : 1). IR (KBr): ν 3440 (br), 3300–2500 (br, NH_3^+), 1750 (C=O), 1600, 1570, 1495, 1460, 1375, 1365, 1300, 1180, 1165, 1090, 1025 cm^{-1}. ^1H NMR (*DMSO-d_6*): δ 0.9 [t, 3H, $C\underline{H}_3(CH_2)_5$], 1.1–1.8 [m, 13H, $CH_3(C\underline{H}_2)_5$, $OCH_2C\underline{H}_3$], 3.75 (m, 1H, $C\underline{H}CHCO_2Et$), 4.25 (q, 2H, $OC\underline{H}_2CH_3$), 5.4 (m, 1H, $C\underline{H}CO_2Et$), 8.8 (br s, 3H, $N\underline{H}_3^+$) ppm. ^1H NMR (DMSO-d_6 + D_2O): δ 5.2 (d, 1H, $C\underline{H}CO_2Et$, *J* 3 Hz) ppm.

*Ethyl (2*R*,*3*S*)-2-amino-3-chlorononanoate* (**4**). Hydrochloride **2** (48 mg, 0.176 mmol) was stirred at room temperature in a two-phase system of ether and aqueous sodium carbonate solution. After 1½ h, the layers were separated and the aqueous layer was extracted twice with ether. The combined organic layers were dried over Na_2SO_4 and concentrated. Yield 45 mg (100%) of **4** as an oil. IR (CCl_4): ν 3400 (w, NH_2), 2955, 2920, 2855, 1740 (C=O), 1460, 1370, 1260, 1205, 1175, 1160, 1025 cm^{-1}. ^1H NMR (CCl_4): δ 0.9 [t, 3H, $C\underline{H}_3(CH_2)_5$], 1.2–1.7 [m, 13H, $CH_3(C\underline{H}_2)_5$, $OCH_2C\underline{H}_3$], 2.3 (br s, 2H, $N\underline{H}_2$), 3.1 (m, 1H, $C\underline{H}CHCO_2Et$), 3.95–4.35 (m, 3H, $C\underline{H}CO_2Et$, $OC\underline{H}_2CH_3$) ppm. ^1H NMR (CCl_4 + D_2O): δ 3.95 (d, 1H, $C\underline{H}CO_2Et$, *J* 7 Hz), 4.2 (q, 2H, $OC\underline{H}_2CH_3$) ppm.

Synthesis of activated aziridines

*Ethyl (2*R*,*3*S*)-1-acetyl-3-hexylaziridine-2-carboxylate* (**6a**). A solution of acetic anhydride (2.15 ml, 22.8 mmol) in dichloromethane (2 ml) was added to a cooled mixture (0°C) of aziridine-2-carboxylate **1** (3.02 g, 15.2 mmol), pyridine (2.45 ml, 30.3 mmol) and a few crystals of 4-(dimethylamino)pyridine (DMAP). After 10 min, the cooling bath was removed and the reaction mixture was stirred for 18 h at room temperature. After addition of water, the aqueous layer was extracted with ether (4 x 30 ml). The combined organic layers were washed with 2N HCl and satd. sodium bicarbonate solution, dried over $MgSO_4$ and concentrated. Yield 3.25 g (89%) of pure **6a** as an oil. IR (CCl_4): ν 2960, 2930, 2860, 1735 (OC=O), 1710 (NC=O), 1440, 1365, 1305, 1205, 1165, 1120, 1040 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.9 (t, 3H, $C\underline{H}_3(CH_2)_5$), 1.2–1.7 [m, 13H, $(CH_2)_5$, $OCH_2C\underline{H}_3$], 2.05 (s, 3H, $COC\underline{H}_3$), 2.8 (m, 1H, $C\underline{H}CHCO_2Et$), 2.9 (d, 1H, $CHC\underline{H}CO_2Et$, *J* 2.5 Hz), 4.2 (q, 2H, $OC\underline{H}_2CH_3$) ppm. MS (CI): *m/e* (%) 242 (100, M + 1$^+$), 228 (11), 196 (23, – OEt), 183 (18), 168 (99, – CO_2Et), 126 (59). Exact mass calcd. for $C_{13}N_{23}NO_3$: 242.1678 amu; found: 241.1677 ± 0.0005.

*Ethyl (2*R*,*3*S*)-1-(trifluoroacetyl)-3-hexylaziridine-2-carboxylate* (**6b**). Employing the procedure described for **6a**, crude **6b** (1.44 g, 97%) was obtained from **1** (1.00 g, 5.0 mmol) (reaction time 7½ h) as a yellowish oil. After flash chromatography only 30% of pure **6b** could be isolated. IR (CCl_4): ν 2960, 2925, 2855, 1745 (C=O), 1440, 1370, 1335, 1255, 1160, 1110, 1040, 925 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.9 (t, 3H, $C\underline{H}_3$), 1.1–1.8 [m, 13H, $(C\underline{H}_2)_5$, $OCH_2C\underline{H}_3$], 2.95 (m, 1H, $C\underline{H}CHCO_2Et$), 3.2 (d, 1H, $CHC\underline{H}CO_2Et$, *J* 3 Hz), 4.2 (q, 2H, $OC\underline{H}_2CH_3$) ppm.

*Ethyl (2*R*,*3*S*)-3-hexyl-1-(benzyloxycarbonyl)aziridine-2-carboxylate* (**6c**). *N*-(benzyloxycarbonyloxy)succinimide (4.70 g, 18.8 mmol) was added to a solution of **1** (2.50 g, 12.5 mmol) and triethylamine (3.50 ml, 25 mmol) in acetonitrile (50 ml) at 0°C. After removal of the cooling bath, the reaction mixture was stirred for 15 h at room temperature. The solvent was then evaporated. The residue was taken up in water and extracted with ether. The ether extract was washed with 2N HCl and satd. sodium bicarbonate solution, dried over $MgSO_4$ and concentrated. The crude product was chromatographed (hexane/ethyl acetate 13 : 1), yielding pure **6c** (3.28 g, 82%) as an oil. IR (CCl_4): ν 3060, 3030, 2955, 2925, 2855, 1740 (C=O), 1730 (C=O), 1445, 1375, 1335, 1300, 1215, 1175, 1070, 1040, 1025, 695 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.9 [t, 3H, $C\underline{H}_3(CH_2)_5$], 1.1–1.6 [m, 13H, $(C\underline{H}_2)_5$, $OCH_2C\underline{H}_3$], 2.8 (m, 2H, $C\underline{H}C\underline{H}CO_2Et$), 4.1 (q, 2H, $OC\underline{H}_2CH_3$), 5.1 (s, 2H, $PhC\underline{H}_2$), 7.3 (s, 5H, Ph) ppm. MS (EI): *m/e* (%) 333 (0.5, M$^+$), 260 (3, – CO_2Et), 242 (2, – $PhCH_2$), 227 (7), 216 (12), 198 (100, – CO_2Bzl), 184 (35, – NCO_2Bzl), 170 (20), 124 (44), 107 (22), 91 (100, $PhCH_2^+$), 65 (35), 55 (58). Exact mass calcd. for $C_{19}H_{27}NO_4$: 333.1940 amu; found: 333.1945 ± 0.0007.

*Ethyl (2*R*,*3*S*)-3-hexyl-1-[2-(trimethylsilyl)ethoxycarbonyl]aziridine-2-carboxylate* (**6d**). Pyridine (1.20 ml, 15 mmol), a few crystals of DMAP and a solution of 2-(trimethylsilyl)ethyl chloroformate (1.90 g, 11.3 mmol) in dichloromethane (10 ml) were sequentially added to a cooled solution of **1** (1.50 g, 7.5 mmol) in dichloromethane (50 ml). After 5 min, the solvent was evaporated. The residue was dissolved in ether and washed with 2N sulfuric acid and satd. sodium bicarbonate solution. The ethereal solution was dried over $MgSO_4$ and concentrated. The crude product was chromatographed with hexane/ethyl acetate 12 : 1, giving **6d** (2.10 g, 84%) as a yellowish oil. IR (CCl_4): ν 2955, 2930, 2855, 1740 (C=O), 1725 (C=O), 1445, 1380, 1370, 1300, 1250, 1220, 1175, 1065, 1040, 860, 840 cm^{-1}. ^1H NMR ($CDCl_3$): δ (*vs.* Me_3Si) 0.00 (s, 9H, Me_3Si), 0.85 (t, 3H, $C\underline{H}_3(CH_2)_5$), 1.0–1.6 [m, 15H, $CH_3(C\underline{H}_2)_5$, $OCH_2C\underline{H}_3$, $C\underline{H}_2SiMe_3$], 2.5–2.8 (m, 2H, $C\underline{H}C\underline{H}CO_2Et$), 3.9–4.2 (m, 4H, $OC\underline{H}_2CH_3$, $OC\underline{H}_2CH_2SiMe_3$) ppm. MS (CI): *m/e* (%) 344 (12, M + 1$^+$), 316 (45), 300 (33), 272 (44), 256 (34), 242 (28, – $CH_2CH_2SiMe_3$), 226 (13, – $OCH_2CH_2SiMe_3$), 198 (23, – $CO_2CH_2CH_2SiMe_3$), 147 (30), 101 (38, $Me_3SiCH_2CH_2^+$), 73 (100, Me_3Si^+), 59 (46).

*Ethyl (2*R*,*3*S*)-3-hexyl-1-(methylsulfonyl)aziridine-2-carboxylate* (**6e**). Triethylamine (1.40 g, 10.0 mmol), a few crystals of DMAP and methanesulfonyl chloride (570 µl, 7.5 mmol) were added sequentially to a solution of **1** (1.00 g, 5.00 mmol) in dichloromethane (25 ml) at 0°C. The mixture was stirred for 2 h at room temperature. The solvent was then evaporated and the residue was dissolved in water. After extraction with ether, the combined organic layers were dried over $MgSO_4$ and concentrated, yielding **6e** (1.32 g, 84%) (purity *ca.* 86%) which was not purified further. IR (CCl_4): ν 2960, 2920, 2855, 1740 (C=O), 1465, 1445, 1370, 1335 (NSO_2), 1195, 1170 (NSO_2), 1130, 1035, 965, 920, 625 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.9 (t, 3H, $C\underline{H}_3(CH_2)_5$), 1.2–1.7 [m, 11H, $CH3(C\underline{H}_2)_4$, $OCH_2C\underline{H}_3$], 1.7-2.2 [m, 2H, $CH_3(CH_2)_4C\underline{H}_2$], 2.9–3.3 (m + s + d, 5H, $C\underline{H}CHCO_2Et$, $C\underline{H}_3SO_2$, $CHC\underline{H}CO_2Et$, $J_{doublet}$ 3.5 Hz), 4.2 (q, 2H, $OC\underline{H}_2CH_3$) ppm. MS (CI): *m/e* (%) 278 (67, M + 1 +), 232 (11, – OEt), 204 (100, – CO_2Et), 198 (87, – CH_3SO_2), 183 (64), 109 (80).

*Ethyl (2*R*,*3*S*)-3-hexyl-1-(4-tolylsulfonyl)aziridine-2-carboxylate* (**6f**). Employing the procedure described for **6e**, crude **6f** (3.58 g, 100%) was obtained from aziridine **1** (2.00 g, 10.0 mmol), triethylamine (2.20 ml, 15.0 mmol) and 4-toluenesulfonyl(tosyl) chloride (2.00 g, 10.5 mmol) (reaction time 18 h). It still contained a trace of tosyl chloride. Two recrystallization steps from hexane gave 1.81 g (51%) of **6f** as white crystals. M.p. 63.5–64°C. IR (CCl_4): ν 3060, 3030, 2955, 2925, 2855, 1740 (C=O), 1595, 1460, 1445, 1380, 1370, 1335 (NSO_2), 1305, 1290, 1185, 1165 (NSO_2), 1090, 1035, 920, 705, 690, 685, 635 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.9 [t, 3H, $C\underline{H}_3(CH_2)_5$], 1.1–1.7 [t + m, 11H, $OCH_2C\underline{H}_3$, $CH_3(C\underline{H}_2)_4$], 1.95 (m, 2H, $CH_3(CH_2)_4C\underline{H}_2$), 2.4 (s, 3H, $C\underline{H}_3C_6H_5$), 3.05 (m, 1H, $C\underline{H}CHCO_2Et$), 3.25 (d, 1H, $CHC\underline{H}CO_2Et$, *J* 3.5 Hz), 4.15 (q, 2H, $OC\underline{H}_2CH_3$), 7.3 (d, 2H, $C_6\underline{H}_2$, *J* 7.5 Hz), 7.85 (d, 2H, $C_6\underline{H}_2$, *J* 7.5 Hz) ppm. MS (CI): *m/e* (%) 354 (19, M + 1$^+$), 308 (6, – OEt), 280 (100, – CO_2Et), 256 (13), 224 (5), 198 (63, – $TolSO_2$), 183 (54), 172 (8), 155 (11, $TolSO_2^+$), 137 (9), 124 (10), 109 (13), 91 (3, $CH_3C_6H_4^+$), 55 (15), 43 (41). Calcd. for $C_{18}H_{27}NO_4S$ (353.482): C 61.16, H 7.70, N 3.96; found: C 61.42, H 7.72, N 4.02%.

*Ethyl (2*R*,*3*S*)-1-(benzylsulfonyl)-3-hexylaziridine-2-carboxylate* (**6g**). Employing the procedure described for **6e**, compound **6g** (560 mg, 65%) was obtained from aziridine **1** (500 mg, 2.5 mmol), pyridine (420 µl, 5.0 mmol) and phenylmethanesulfonyl chloride (500 mg, 2.63 mmol). (Reaction time 2 h.) It was sufficiently pure for further experiments. IR (CCl_4): ν 3060, 3035, 2955, 2925, 2855, 1745 (C=O), 1455, 1370, 1335 (NSO_2), 1235, 1190, 1155 (NSO_2), 1125, 1030, 920, 695 cm^{-1}. ^1H NMR (CCl_4): δ 0.9 [t, 3H, $C\underline{H}_3(CH_2)_5$], 1.1–2.1 [m, 13H, $OCH_2C\underline{H}_3$, $CH_3(C\underline{H}_2)_5$], 2.4 (s, 3H, $C\underline{H}_3C_6H_4$), 2.7–2.9 (m, 2H, $C\underline{H}C\underline{H}CO_2Et$, *J* 1.5 Hz), 4.05 (q, 2H, $OC\underline{H}_2CH_3$), 4.35 (s, 2H, $PhC\underline{H}_2$), 7.3 (m, 5H, $\underline{Ph}$) ppm.

*Ethyl (2*R*,*3*S*)-3-hexyl-1-(pentamethylphenylsulfonyl)aziridine-2-carboxylate* (**6h**). Employing the procedure described for **6e**, compound **6h** (76 mg, 38%) was obtained from aziridine **1** (100 mg, 0.50 mmol), pyridine (84 µl, 1.0 mmol) and pentamethylbenzenesulfonyl chloride (185 mg, 0.75 mmol) as a white solid, after chromatography (hexane/ethyl acetate 25 : 1) (reaction time 18 h). M.p. 77.5°C. IR (CCl_4): ν 2960, 2925, 1745/1735 (C=O),

1445, 1370, 1325 (NSO_2), 1280, 1220, 1190, 1155 (NSO_2), 1035, 945, 915, 655, 640 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.9 [t, 3H, $C\underline{H}_3(CH_2)_5$], 1.1–1.6 [m, 11H, $CH_3(C\underline{H}_2)_4$, $OCH_2C\underline{H}_3$], 1.95 [m, 2H, $CH_3(CH_2)_4C\underline{H}_2$], 2.2 [s + s, 9H, $Ph(C\underline{H}_3)_3$], 2.6 [s, 6H, $Ph(CH_3)_2$], 3.0 (m, 1H, $C\underline{H}CHCO_2Et$), 3.25 (d, 1H, $CHC\underline{H}CO_2Et$, *J* 4 Hz), 4.1 (q, 2H, $OC\underline{H}_2CH_3$) ppm. Calcd. for $C_{22}H_{35}NO_4S$ (409.584): C 64.51, H 8.61, N 3.42, S 7.83; found: C 64.29, H 8.61, N 3.42, S 7.87%.

Reactions with ethereal HCl

Ethyl (2R,3S*)-2-(N-acetyl)amino-3-chlorononanoate* (**7aa**). A solution of **6a** (107 mg, 0.44 mmol) in ether (5 ml) was gradually added to a cooled ethereal HCl solution. After stirring for 65 h at room temperature, the solvent was evaporated. The residue was redissolved in ether and washed with satd. sodium bicarbonate solution. Drying ($MgSO_4$) and evaporation of the solvent gave **7aa** (115 mg, 93%) as an oil. The crude product was chromatographed (hexane/ethyl acetate 3 : 1). Yield 87 mg (71%) of pure **7aa** as an oil. IR (CCl_4): ν 3430 (NH), 2955, 2925, 2860, 1740 (OC=O), 1685 (NC=O), 1490, 1465, 1375, 1215, 1195, 1145, 1020 cm^{-1}. ^1H NMR (CCl_4): δ 0.9 [t, 3H, $C\underline{H}_3(CH_2)_5$], 1.1–1.7 [m, 11H, $CH_3(C\underline{H}_2)_4$, $OCH_2C\underline{H}_3$], 1.7–2.1 [m, 2H, $CH_3(CH_2)_4C\underline{H}_2$], 2.0 (s, 3H, $COC\underline{H}_3$), 3.9–4.4 (m, 3H, $OC\underline{H}_2CH_3$, $C\underline{H}CHCO_2Et$), 4.75 (dd, 1H, $CHC\underline{H}CO_2Et$, *J* 4.5 Hz, 8 Hz), 6.95 (d, 1H, N<u>H</u>, *J* 8 Hz) ppm. Exact mass calcd. for $C_{13}H_{24}ClNO_3$: 277.1445 amu; found: 277.1439 ± 0.0008.

Ethyl (2R,3S*)-3-chloro-2-[(4-tolylsulfonyl)amino]nonanoate* (**7fa**) *and ethyl (2R*,3R*)-2-chloro-3-[4-tolylsulfonyl)amino]nonanoate* (**8fa**).

Employing the procedure described for **7aa**, from **6f** (55 mg, 0.156 mmol) a mixture of **7fa** and **8fa** (59 mg, 97%) (ratio *ca.* 2 : 3 according to NMR) was obtained. IR (CCl_4): ν 3360/3260 (NH), 2950, 2925, 2860, 1735 (C=O), 1460, 1420, 1370, 1350/1165 (NSO_2), 1095, 1020, 905, 665 cm^{-1}. ^1H NMR (CCl_4): δ 0.9 [t, 3H, $C\underline{H}_3(CH_2)_5$], 1.0–1.9 [m, 13H, $CH_3(C\underline{H}_2)_5$, $OCH_2C\underline{H}_3$], 2.4 (s, 3H, $C\underline{H}_3C_6H_4$), 3.8–4.4 (m, 4H, $OC\underline{H}_2CH_3$, $C\underline{H}CHCO_2Et$), 5.5 (d, 0.4H, N<u>H</u>Tos, *J* 9 Hz), 5.75 (d, 0.6H, N<u>H</u>Tos, *J* 9 Hz), 7.1–7.8 (m, 4H, $CH_3C_6\underline{H}_4$) ppm.

Reactions with benzenethiol

Ethyl (2R,3S*)-2-(acetylamino)-3-(phenylthio)nonanoate* (**7ab**). Boron trifluoride etherate (210 µl, 1.7 mmol) was added to a cooled solution (0°C) of **6a** (500 mg, 2.1 mmol) and benzenethiol (420 µl, 4.1 mmol) in dichloromethane (10 ml). The reaction mixture was stirred at room temperature for 1 h. After addition of satd. sodium bicarbonate solution, the aqueous layer was extracted twice with dichloromethane. The combined organic layers were dried over $MgSO_4$ and concentrated. The crude product was chromatographed to remove excess benzenethiol. Yield 270 mg (38%) of **7ab** as a yellowish oil. IR (CCl_4): ν 3450 (NH), 3060, 2955, 2925, 2855, 1730 (OC=O), 1675 (NC=O), 1490, 1480, 1465, 1440, 1375, 1205, 1145, 1025, 810, 690 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.85 [t, 3H, $C\underline{H}_3(CH_2)_5$], 1.1–1.8 [m, 13H, $OCH_2C\underline{H}_3$, $CH_3(C\underline{H}_2)_5$], 1.8 (s, 3H, $COC\underline{H}_3$), 3.45 (m, 1H, $C\underline{H}CHCO_2Et$), 4.15 (q, 2H, $OC\underline{H}_2CH_3$), 4.75 (dd, 1H, $CHC\underline{H}CO_2Et$, *J* 3 Hz, 7.5 Hz), 6.25 (d, 1H, NH, *J* 7.5 Hz), 7.1–7.4 (m, 5H, <u>Ph</u>S) ppm. Exact mass calcd. for $C_{19}H_{29}NO_3S$: 351.1868 amu; found: 351.1871 ± 0.0007.

Ethyl (2R,3S*)-2-[(benzyloxycarbonyl)amino]-3-(phenylthio)-nonanoate* (**7cb**). Employing the procedure described for **7ab**, from **6c** (50 mg, 0.16 mmol) 66 mg (95%) of **7cb** were obtained as a yellowish oil after chromatography (hexane/ethyl-acetate 9 : 1). IR (CCl_4): ν 3435 (NH), 3060, 3030, 2960, 2930, 2855, 1725 (C=O), 1490, 1455, 1435, 1370, 1330, 1195, 1055, 1025, 695 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.9 [t, 3H, $C\underline{H}_3(CH_2)_5$], 1.1–1.7 [m, 13H, $CH_3(C\underline{H}_2)_5$, $OCH_2C\underline{H}_3$], 3.4 (m, 1H, $C\underline{H}CHCO_2Et$), 4.15 (m, 2H, $OC\underline{H}_2CH_3$), 4.65 (dd, 1H, $CHC\underline{H}CO_2Et$, *J* 9.0 Hz, 3.5 Hz), 5.05 (s, 2H, $PhC\underline{H}_2$), 5.4 (d, 1H, N<u>H</u>, *J* 9.0 Hz), 7.1–7.5 (m, 10H, <u>Ph</u>CH_2, <u>Ph</u>S) ppm. Exact mass calcd. for $C_{25}H_{33}NO_4S$: 443.2129 amu; found: 443.2134 ± 0.0009.

Ethyl (2R,3S*)-3-(phenylthio)-2-[2-(trimethylsilyl)ethoxycarbonyl]-amino]nonanoate* (**7db**). Boron trifluoride etherate (23 µl, 0.19 mmol) was added to a solution of **6d** (100 mg, 0.30 mmol) and benzenethiol (60 µl, 0.60 mmol) in dichloromethane (10 ml) at 0°C. The reaction mixture was stirred for 6 h at room temperature. After addition of satd. sodium bicarbonate solution, the aqueous layer was extracted with ether. The combined organic layers were dried over $MgSO_4$ and concentrated. The crude product was chromatographed (hexane/ethyl acetate 12 : 1), giving a mixture of 3-(phenylthio) and 3-fluoro ring-opened products **7db** and **8dg** (91 mg, 70%), which could not be separated. The mixture was analyzed by GC/MS (CI). Major component (**7db**): *m/e* (%) 454 (6, $M + 1^+$), 426 (38), 410 (26, $M + 1^+ - CO_2$), 352 (6, $-CH_2CH_2SiMe_3$), 336 (8, $-OCH_2CH_2SiMe_3$), 316 (12), 293 (24, –NHTEOC), 219 (31), 207 (100, $C_6H_{13}CH^+SPh$), 73 (36, Me_3Si^+). Minor component (**8dg**): *m/e* (%) 364 (2, $M + 1^+$), 336 (13), 320 (24, $M + 1^+ - CO_2$), 292 (8), 262 (9, $-CH_2CH_2SiMe_3$), 218 (13, –TEOC), 200 (13), 174 (5), 146 (4), 126 (10), 101 (40, $CH_2CH_2SiMe_3^+$), 73 (100, Me_3Si^+). IR (CCl_4) of mixture: ν 3440 (NH), 3070, 2955, 2930, 2860, 1725 (C=O), 1495, 1470, 1370, 1320, 1250, 1195, 1065, 1025, 940, 860, 840, 695 cm^{-1}. ^1H NMR ($CDCl_3$; Me_3Si 0.00 ppm): δ 0.7–2.0 [m, $C\underline{H}_3(C\underline{H}_2)_5$, $C\underline{H}_2SiMe_3$, $OCH_2C\underline{H}_3$], 3.35 (m, CHSPh), 3.9–4.2 (m, $OC\underline{H}_2CH_2SiMe_3$, $OC\underline{H}_2CH_3$), 4.5 (m, $C\underline{H}CO_2Et$), 4.8 (m, C<u>H</u>F), 5.15 (d, N<u>H</u>, *J* 9 Hz), 5.4 (d, N<u>H</u>, *J* 9 Hz), 7.05–7.4 (m, S<u>Ph</u>) ppm.

Ethyl (2R,3S*)-2-[(methylsulfonyl)amino]-3-(phenylthio)nonanoate* (**7eb**). Boron trifluoride etherate (96.7 µl, 0.79 mmol) was added dropwise to a cooled solution (0°C) of **6e** (200 mg, 0.72 mmol) and benzenethiol (148 µl, 1.44 mmol) in dichloromethane (15 ml). The reaction mixture was then stirred for 4 h at room temperature. After work-up as described for **7db** [chromatography with petroleum-ether-(60–80)/ethyl-acetate 3 : 1], compound **7eb** (112 mg, 40%) was obtained as a colorless oil. IR (CCl_4): ν 3330/3280 (br, NH), 3040, 2955, 2925, 2855, 1735 (C=O), 1525 (br), 1465, 1435, 1365, 1340, 1325, 1250, 1200, 1155, 1130, 1100, 1025, 970, 910, 855, 695 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.9 [t, 3H, $C\underline{H}_3(CH_2)_5$], 1.1–1.8 [m, 13H, $CH_3(C\underline{H}_2)_5$, $OCH_2C\underline{H}_3$], 3.0 (s, 3H, SO_2CH_3), 3.45 (m, 1H, $C\underline{H}CHCO_2Et$), 4.05–4.4 (m, 3H, $OC\underline{H}_2CH_3$, $CHC\underline{H}CO_2Et$), 5.25 (d, 1H, N<u>H</u>, *J* 8 Hz), 7.2–7.6 (m, 5H, <u>Ph</u>S) ppm. MS (CI) *m/e* (%) 388 (22, $M + 1^+$), 314 (10, $-CO_2Et$), 293 (32, –NHMs), 207 (100, $C_6H_{13}CH^+SPh$).

Ethyl (2R,3S*)-3-(phenylthio)-2-[(4-tolylsulfonyl)amino]nonanoate* (**7fb**). Employing the procedure described for the synthesis of **7db**, from **6f** (500 mg, 1.40 mmol), benzenethiol (285 µl, 2.78 mmol) and boron trifluoride etherate (100 µl, 0.81 mmol) crude **7fb** (576 mg, 90%) was obtained, which slowly solidified on cooling. Recrystallization from hexane gave 405 mg (63%) of **7fb** as white crystals. M.p. 45–57°C. IR (CCl_4): ν 3360/3265 (NHTos), 3060, 3030, 2950, 2920, 1735 (C=O), 1595, 1465, 1440, 1420, 1370, 1350 (NSO_2), 1305, 1185, 1165 (NSO_2), 1115, 1090, 1025, 910, 865, 705, 690, 665 cm^{-1}. ^1H NMR ($CDCl_3$) (400 MHz): δ 0.86 [t, 3H, $C\underline{H}_3(CH_2)_5$, *J* 7.0 Hz], 1.11 (t, 3H, $OCH_2C\underline{H}_3$, *J* 7.00 Hz), 1.17–1.75 [m, 10H, $CH_3(C\underline{H}_2)_5$], 2.41 (s, 3H, $C\underline{H}_3C_6H_5$), 3.24 (dt, 1H, $C\underline{H}CHCO_2Et$, *J* 8.80 Hz, 4.51 Hz), 3.85–3.97 (m, 2H, $OC\underline{H}_2CH_3$), 4.09 (dd, 1H, $CHC\underline{H}CO_2Et$, *J* 5.04 Hz, 9.70 Hz), 5.35 (d, 1H, N<u>H</u>, *J* 9.68 Hz), 7.26 (m, 5H, PhS), 7.35 (m, 2H, $CH_3C_6\underline{H}_2$), 7.67–7.78 (m, 2H, $C_6\underline{H}_2SO_2$) ppm. MS (CI): *m/e* (%) 464 (18, $M + 1^+$), 390, 3, $-CO_2Et$), 293 (38, –NHTos), 219 (15), 207 (100, $C_6H_{13}CH^+SPh$), 183 (6), 155 (6, SO_2Tol^+), 123 (17), 110 (6), 97 (9), 91 (12, $C_6H_4CH_3+$), 55 (13). Calcd. for $C_{24}H_{33}NO_4S_2$ (463.661): C 62.17, H 7.17, N 3.02; found: C 61.72, H 7.17, N 3.07%.

Ethyl (2R,3S*)-2-[(benzylsulfonyl)amino]-3-(phenylthio)nonanoate* (**7gb**). Employing the procedure described for the synthesis of **7db**, from **6g** (100 mg, 0.28 mmol), benzenethiol (57 µl, 0.56 mmol) and boron trifluoride etherate (5 µl, 0.04 mmol) 115 mg (90%) of **7gb** was obtained after chromatography. It was recrystallized from hexane twice, yielding 80 mg (63%) of **7gb** as white crystals. M.p. 68–69°C. IR (CCl_4): ν 3520, 3370, 3320 (br), 3060, 3030, 2955, 2925, 1735 (C=O), 1455, 1435, 1405, 1370, 1345 (NSO_2), 1260, 1200, 1155, 1130, 1070, 1025, 925, 855, 695 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.9 [m, 3H, $C\underline{H}_3(CH_2)_5$], 1.1–1.6 [m, 13H, $OCH_2C\underline{H}_3$, $(C\underline{H}_2)_5$], 3.3 (m, 1H, $C\underline{H}CHCO_2Et$), 4.0–4.3 (m, 3H, $OC\underline{H}_2CH_3$, $CHC\underline{H}CO_2Et$), 4.3 (s, 2H, $PhC\underline{H}_2$), 4.95 (d, 1H, N<u>H</u>, *J* 9 Hz), 7.1–7.5 (m, 10H, <u>Ph</u>CH_2, <u>Ph</u>S) ppm. MS (CI): *m/e* (%) 464 (48, $M + 1^+$), 400 (100, $M + 1^+ - SO_2$), 390 (6, $-CO_2Et$), 293 (85, $-NHSO_2Bzl$), 207 (100, $C_6H_{13}CH^+SPh$), 200 (98), 183 (12), 123 (23), 109 (5, PhS^+), 91 (68, $PhCH_2^+$), 55 (15), 41 (72).

Reaction with indole

Ethyl (2R,3S*)-2-(acetylamino)-3-(indol-3-yl)nonanoate* (**6ac**). Boron trifluoride etherate (155.2 µl, 1.26 mmol) was added dropwise to a cooled solution of **6a** (203 mg, 0.84 mmol) and indole (200 mg, 1.68 mmol) in dichloromethane (15 ml). The reaction mixture was stirred at 0°C for 2 h and then at room temperature for another 2 h. Satd. sodium bicarbonate solution (5 ml) was then added and the aqueous layer was extracted with dichloromethane (3 x 10 ml). The combined organic layers were dried over $MgSO_4$ and concentrated. The crude product was chromatographed, giving **7ac** (82 mg, 27%) as an oil, amongst several indole derivatives. IR (CCl_4): ν 3480 (indole-NH), 3430 (NH), 3320 (br, NH), 3055, 2955, 2925, 2855, 1730 (OC=O), 1675 (NC=O), 1495, 1455, 1375, 1335, 1190, 1140, 1095, 1025 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.85 [t, 3H, $C\underline{H}_3(CH_2)_5$], 1.05 (t, 3H, OCH_2CH_3, *J* 7.5 Hz), 1.1–1.5 [m, 8H, $CH_3(C\underline{H}_2)_4$], 1.7–2.0 [m + s, 5H, $CH_3(CH_2)_4C\underline{H}_2$, $COC\underline{H}_3$], 3.35 (m, 1H, $C\underline{H}CHCO_2Et$), 4.0 (q, 2H, $OC\underline{H}_2CH_3$, *J* 7.5 Hz), 4.95 (dd, 1H, $CHC\underline{H}CO_2Et$, *J* 6 Hz, 8.5 Hz), 6.15 (d, 1H, NHAc, *J* 8.5 Hz), 6.85–7.65 (m, 5H, indole-H), 8.7 (br s, 1H, indole-N$\underline{H}$) ppm. MS (CI): *m/e* (%) 359 (15, M + 1$^+$), 313 (5, – OEt), 285 (9, – CO_2Et), 214 (100, $C_6H_{13}CH^+$Ind), 130 (39).

Ethyl cis-*1-acetyl-3-hexyl-2,3-dihydropyrrolo[2,3-b]indole-2-carboxylate* (**9**). *tert*-Butyl hypochlorite (13.5 µl, 0.12 mmol) was added to a cooled solution (0°C) of **7ac** (44 mg, 0.12 mmol) and triethylamine (69 µl, 0.48 mmol) in dichloromethane (7 ml). The reaction mixture was stirred in the dark for 2 h at 0°C and then overnight at room temperature. The reaction mixture was then washed with cold water (2 x 5 ml), dried (Na_2SO_4) and concentrated. After addition of ether/petroleum ether (1 : 4), the precipitated product was filtered off. Yield 6 mg (14%) of **9** as a pale orange solid. M.p. 182–185°C (subl. 170°C). IR (KBr): ν 3320 (br, NH), 2955, 2920, 2855, 1735 (OC=O), 1655 (NC=O), 1610, 1580, 1525, 1450, 1410, 1370, 1340, 1260, 1190, 1025, 800, 735, 660 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.90 [t, 3H, $C\underline{H}_3(CH_2)_5$], 1.25–1.80 [m, 13H, $CH_3(C\underline{H}_2)_5$, $OCH_2C\underline{H}_3$], 2.08 (s, 3H, $COC\underline{H}_3$), 4.00 (m, 1H, $C_6H_{13}C\underline{H}$), 4.30 (q, 2H, $OC\underline{H}_2CH_3$), 5.27 (d, 1H, $C\underline{H}CO_2Et$, *J* 9.7 Hz), 7.09 (m, 2H, ArH), 7.31 (m, 1H, ArH), 7.39 (m, 1H, ArH), 9.24 (br s, 1H, indole-N$\underline{H}$) ppm. Exact mass calcd. for $C_{21}H_{28}N_2O_3$: 356.2100 amu; found: 356.2094 ± 0.0007.

Reactions with $DMF/BF_3 \cdot Et_2O$

Reaction of **6a** *with $DMF/BF_3 \cdot Et_2O$.* Boron trifluoride etherate (21 µl, 0.17 mmol) was added to a solution of **6a** (25 mg, 0.11 mmol) in DMF (3 ml). The reaction mixture was stirred for 18 h at 60°C. The solvent was then evaporated. The residue was taken up in satd. sodium bicarbonate solution and extracted with ether (3x). The combined organic layers were dried over $MgSO_4$ and concentrated. The crude product (100%) consisted of three compounds, according to GC. One of them was the formyloxy compound **7ad**, as deduced from NMR (*cf.*, the ring-opened product with formic acid).

Ethyl (2R,3R*)-2-[(benzyloxycarbonyl)amino]-3-(formyloxy)nonanoate* (**7cd**). Boron trifluoride etherate (15 µl, 0.122 mmol) was added to a solution of **6c** (25 mg, 0.073 mmol) in DMF (3 ml). The mixture was stirred at 90°C for 40 h. After 24 h, an additional amount of boron trifluoride etherate (15 µl) was added. After completion of the reaction, the solvent was evaporated. Satd. sodium bicarbonate solution was added and the aqueous solution was extracted with ether. The combined extracts were dried over $MgSO_4$ and concentrated. Yield 34 mg (100%) of crude **7cd** (86% pure on GC). IR (CCl_4): ν 3430 (NH), 3060, 3030, 2955, 2925, 1725 (C=O), 1490, 1465, 1455, 1370, 1280, 1190, 1160, 1055, 1025, 695 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.85 [t, 3H, $C\underline{H}_3(CH_2)_5$], 1.1–1.9 [m, 13H, $(C\underline{H}_2)_5$, OCH_2CH_3], 4.2 (q, 2H, $OC\underline{H}_2CH_3$), 4.65 (m, 1H, $CHC\underline{H}CO_2Et$), 5.2 (s, 2H, $PhC\underline{H}_2$), 5.25 (m, 1H, $C\underline{H}CHCO_2Et$), 7.3 (s, 5H, $\underline{Ph}$), 8.0 (s, 1H, $\underline{H}COO$) ppm.

Ethyl (2R,3R*)-3-(formyloxy)-2-[[(2-trimethylsilyl)ethoxycarbonyl]-amino]nonanoate* (**7dd**). Employing the procedure described above for the reaction of **6a**, from **6d** (200 mg, 0.60 mmol) crude **7dd** (217 mg) was obtained (reaction time 48 h), which after chromatography gave **7dd** (100 mg, 45%) as a yellowish oil, gas chromatographically 96% pure. IR (CCl_4): ν 3435 (NH), 2950, 2925, 2855, 1725 (C=O), 1490, 1465, 1380, 1370, 1320, 1245, 1190, 1165, 1055, 1025, 950, 935, 860 cm^{-1}. ^1H NMR ($CDCl_3$): δ (*vs.* $SiMe_3$), 0.00 (s, 9H, $SiMe_3$), 0.8 [t, 3H, $C\underline{H}_3(CH_2)_5$], 1.0–1.8 [m, 15H, $C\underline{H}_2SiMe_3$, OCH_2CH_3, $CH_3(C\underline{H}_2)_5$], 3.95–4.3 (m, 4H, $OC\underline{H}_2CH_3$, $OC\underline{H}_2CH_2SiMe_3$), 4.55 (dd, 1H, $CHC\underline{H}CO_2Et$, *J* 9 Hz, 4 Hz), 5.15 (m, 1H, $C\underline{H}CHCO_2Et$), 5.4 (d, 1H, N$\underline{H}$, *J* 9 Hz), 7.95 (s, 1H, $\underline{H}COO$) ppm. MS (CI): *m/e* (%) 390 (4, M + 1$^+$), 362 (14), 344 (8, – OEt or – HCOO), 316 (42, – CO_2Et), 300 (14), 272 (10, – $OCH_2CH_2SiMe_3$), 244 (15, – TEOC), 219 (9), 200 (14), 101 (13, $Me_3SiCH_2CH_2^+$), 73 (42, Me_3Si^+), 41 (100).

Reaction of **6f** *with $DMF/BF_3 \cdot Et_2O$.* Employing the procedure described above for the reaction of **6a**, from **6f** (200 mg, 0.57 mmol) a yellowish oil (110 mg, 49%) was obtained after chromatography, mainly consisting of the 3-formyloxy isomer **7fd** (reaction time 4 days). IR (CCl_4): ν 3430/3360 (NH), 2960, 2925, 2855, 1730 (C=O), 1445, 1430, 1370, 1355 (NSO_2), 1165 (NSO_2), 1095, 1020, 910, 665 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.9 [t, 3H, $C\underline{H}_3(CH_2)_5$], 1.0–1.8 [m, 13H, $OCH_2C\underline{H}_3$, $CH_3(C\underline{H}_2)_5$], 2.4 (s, 3H, $CH_3C_6H_4$), 4.0 (q, 2H, $OC\underline{H}_2CH_3$), 4.2 (dd, 1H, $CHC\underline{H}CO_2Et$, *J* 4.5 Hz, 9.5 Hz), 5.1 (m, 1H, $C\underline{H}CHCO_2Et$), 5.55 (d, 1H, N$\underline{H}$, *J* 9 Hz), 7.3 (d, 2H, $C_6\underline{H}_2$, *J* 7.5 Hz), 7.75 (d, 2H, $C_6\underline{H}_2$, *J* 7.5 Hz), 8.0 (s, 1H, $\underline{H}COO$) ppm.

Reactions with formic acid

Ethyl (2R,3R*)-2-(acetylamino)-3-(formyloxy)nonanoate* (**7ad**). Formic acid (5 ml) was mixed with **6a** (139 mg, 0.58 mmol). Within 1 min, the reaction was completed in a clean fashion. After evaporation of excess formic acid, pure **7ad** (150 mg, 91%) was obtained. IR (CCl_4): ν 3435 (NH), 2955, 2925, 2855, 1730 (OC=O), 1685 (NC=O), 1490, 1465, 1370, 1285, 1190, 1165, 1020 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.9 [t, 3H, $C\underline{H}_3(CH_2)_5$], 1.1–1.5 [m, 11H, $OCH_2C\underline{H}_3$, $CH_3(C\underline{H}_2)_4$], 1.8 [m, 2H, $CH_3(CH_2)_4C\underline{H}_2$], 2.05 (s, 3H, $COC\underline{H}_3$), 4.2 (q, 2H, $OC\underline{H}_2CH_3$), 4.85 (dd, 1H, $CHC\underline{H}CO_2Et$, *J* 3.5 Hz, 8 Hz), 5.2 (m, 1H, $C\underline{H}CHCO_2Et$), 6.7 (d, 1H, N$\underline{H}$, *J* 8 Hz), 8.0 (s, 1H, $\underline{H}COO$) ppm. MS (CI): *m/e* (%) 288 (96, M + 1$^+$), 270 (6), 260 (15), 242 (100, – HCOO), 228 (7), 214 (6, – CO_2Et), 200 (12), 196 (15), 168 (26), 145 (28, $AcNHCH^+CO_2Et$), 99 (18).

Reaction of **6c** *with formic acid.* Employing the procedure described for **7ad**, from **6c** (25 mg, 0.075 mmol) 94% pure **7cd** (27 mg, 100%) was obtained as a yellowish oil. IR and NMR as above.

Reaction of **6d** *with formic acid.* Employing the procedure described for **7ad** from **6d** (110 mg, 0.34 mmol) compound **7dd** (94 mg, 75%) was obtained as a yellowish oil. IR and NMR as above.

Reaction of **6f** *with formic acid.* A mixture of aziridine **6f** (92 mg, 0.26 mmol) and formic acid (4 ml) was stirred at 0°C for 10 min and then at room temperature for 1 h. Excess formic acid was removed in vacuo. Yield 88 mg (85%) of pure **7fa** as a colorless oil. IR (CCl_4): ν 3330/3270 (br, NH), 3060, 2955, 2925, 2855, 1740 (C=O), 1730 (C=O), 1465, 1430, 1370, 1355, 1305, 1165, 1095, 1020, 930, 855, 665 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.9 [t, 3H, $C\underline{H}_3(CH_2)_5$], 1.0–1.9 [m, 13H, $CH_3(C\underline{H}_2)_5$, $OCH_2C\underline{H}_3$], 2.4 (s, 3H, $C_6H_4C\underline{H}_3$), 4.0 (q, 2H, $OC\underline{H}_2CH_3$, *J* 7.5 Hz), 4.2 (dd, 1H, $CHC\underline{H}CO_2Et$, *J* 4.5 Hz, *J* 10 Hz), 5.1 (m, 1H, $C\underline{H}CHCO_2Et$), 5.65 (d, 1H, N$\underline{H}$, *J* 10 Hz), 7.35 (d, 2H, $C_6\underline{H}_2$, *J* 8.5 Hz), 7.7 (d, 2H, $C_6\underline{H}_2$, *J* 8.5 Hz), 7.95 (s, 1H, $\underline{H}COO$) ppm. MS (CI): *m/e* (%) 400 (20, M + 1$^+$), 382 (53), 354 (21, – OEt or – HCOO), 326 (17, – CO_2Et), 280 (29), 256 (11, $TosNHCH^+CO_2Et$), 244 (5), 198 (7), 183 (15), 155 (19, Tos^+), 139 (10), 102 (100, $H_2NCH^+CO_2Et$), 91 ($C_6H_4CH_3^+$).

Reactions with acetic acid:

Ethyl (2R,3R*)-3-acetoxy-2-(acetylamino)nonanoate* (**7ae**). A stirred solution of aziridine **6a** (205 mg, 0.85 mmol) in acetic acid (5 ml) was heated at 65°C for 2 h. Excess acetic acid was then evaporated, yielding crude **7ae** (277 mg, 100%) as an oil. Crystallization from hexane/ethyl-acetate gave pure **7ae** (200 mg, 78%) as a white solid. M.p. 67–68.5°C. IR (CCl_4): ν 3430 (NH), 2955, 2930, 2860, 1740 (OC=O), 1685 (NC=O), 1490, 1370, 1225, 1190, 1155, 1025 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.9 [t, 3H, $C\underline{H}_3(CH_2)_5$], 1.1–1.8 [m, 13H, $CH_3(C\underline{H}_2)_5$, $OCH_2C\underline{H}_3$], 2.05 (s, 6H, $OCOC\underline{H}_3$, $NHCOC\underline{H}_3$), 4.25 (q, 2H, $OC\underline{H}_2CH_3$), 4.85 (dd, 1H, $CHC\underline{H}CO_2Et$, *J* 8 Hz, 4 Hz), 5.05 (m, 1H, $C\underline{H}CHCO_2Et$), 6.4 (d, 1H, NH, *J* 8 Hz) ppm. MS (CI): *m/e* (%) 302 (10, M + 1$^+$), 242 (18, – OAc), 187 (21), 168 (12), 145 (100, AcNHCHCO$_2$Et + 1$^+$),

127 (12), 103 (11), 99 (30), 43 (41, CH_3CO^+). Calcd. for $C_{15}H_{27}NO_5$ (301.384): C 59.78, H 9.03, N 4.65; found: C 59.64, H 9.07, N 4.73%.

Ethyl (2R,3R*)-3-acetoxy-2-[(benzyloxycarbonyl)amino]nonanoate* (**7ce**). Following the procedure described for the synthesis of **7ae**, from **6c** (204 mg, 0.61 mmol) pure **7ce** (218 mg, 90%) was obtained as an oil after chromatography. Reaction time 20 h. IR (CCl_4): ν 3430 (NH), 3090, 3065, 3030, 2955, 2925, 2860, 1730 (C=O), 1495, 1465, 1455, 1370, 1220, 1060, 1030, 700 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.9 [t, 3H, $C\underline{H}_3(CH_2)_5$], 1.1–1.8 [m, 13H, $CH_3(C\underline{H}_2)_5$, $OCH_2C\underline{H}_3$], 2.0 (s, 3H, $OCOC\underline{H}_3$), 4.2 (q, 2H, $OC\underline{H}_2CH_3$), 4.65 (dd, 1H, $CHC\underline{H}CO_2Et$, *J* 9 Hz, 3.5 Hz), 5.0–5.2 (m + s, 3H, $C\underline{H}CHCO_2Et$, $PhC\underline{H}_2$), 5.65 (d, 1H, N<u>H</u>, *J* 9 Hz), 7.35 (s, 5H, <u>Ph</u>) ppm. MS (CI): *m/e* (%) 394 (42, M + 1$^+$), 350 (15, $-CH_3CO$), 334 (20, −AcO), 320 (1, $-CO_2Et$), 290 (5), 286 (2, $-OCH_2Ph$), 279 (21), 260 (4), 244 (8), 237 (34, $ZNHCHCO_2Et + 1^+$), 176 (60), 164 (5), 146 (6), 102 (12), 91 (100, $PhCH_2^+$), 65 (6), 43 (38, CH_3CO^+).

Ethyl (2R,3R*)-3-acetoxy-2-[[(2-trimethylsilyl)ethoxycarbonyl]amino]nonanoate* (**7de**). Following the procedure described for the synthesis of **7ae**, from **6d** (170 mg, 0.49 mmol) compound **7de** (209 mg, 100%) was obtained as an oil. Reaction time 10 h. IR (CCl_4): ν 3430 (NH), 2950, 2925, 2860, 1725 (C=O), 1495, 1370, 1220, 1055, 1025, 860 cm^{-1}. ^1H NMR ($CDCl_3$): δ (*vs.* $SiMe_3$) 0.00 (s, 9H, $SiMe_3$), 0.85 [t, 3H, $C\underline{H}_3(CH_2)_5$], 1.0–1.7 [m, 15H, $CH_3(C\underline{H}_2)_5$, $OCH_2C\underline{H}_3$, $C\underline{H}_2SiMe_3$], 2.0 (s, 3H, $OCOC\underline{H}_3$), 4.1 (m, 4H, $OC\underline{H}_2CH_3$, $OCH_2C\underline{H}_2SiMe_3$), 4.65 (dd, 1H, $CHC\underline{H}CO_2Et$, *J* 8 Hz, 3.5 Hz), 5.0 (m, 1H, $C\underline{H}CHCO_2Et$), 5.4 (d, 1H, NH, *J* 8 Hz) ppm. MS (CI): *m/e* (%) 404 (2, M + 1$^+$), 388 (15), 376 (77), 360 (6, $-CH_3CO$), 358 (3, −OEt), 330 (3, $-CO_2Et$), 316 (100), 300 (10), 272 (5), 256 (13), 247 (9, $TEOCNHCHCO_2Et + 1^+$), 244 (12), 219 (26), 198 (7), 175 (11), 173 (9), 146 (5), 133 (8), 126 (6), 117 (6, $OCH_2CH_2SiMe_3^+$), 101 (11, $CH_2CH_2SiMe_3^+$), 73 (78, Me_3Si^+).

Introduction of azide

Ethyl (2R,3R*)-3-azido-2-(acetylamino)nonanoate* (**7af**). A solution of **6a** (1.00 g, 4.2 mmol), sodium azide (820 mg, 12.6 mmol) and boron trifluoride etherate (620 µl, 5.0 mmol) in *N,N*-dimethylformamide (DMF) (30 ml) was heated at 90°C for 5 h. The solvent was evaporated and the residue was treated with satd. sodium bicarbonate solution. The aqueous solution was extracted twice with ether. The combined extracts were dried over $MgSO_4$ and concentrated, yielding a yellow oil (0.86 g). According to GC, this consisted of 60% of azide-containing product, 12% of another product and 10% of starting material. Chromatography gave 93% pure **7af** (385 mg, 32%). On NMR, a small amount of isomer **8af** could be seen. IR (CCl_4): *v* 3425 (NH), 3330 (br), 2955, 2925, 2855, 2120 (N_3), 1730 (OC=O), 1680 (NC=O), 1485, 1440, 1440, 1375, 1340, 1235, 1195, 1150, 1020, 860 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.9 [t, 3H, $C\underline{H}_3(CH_2)_5$], 1.2–1.8 [m, 13H, $OCH_2C\underline{H}_3$, $CH_3(C\underline{H}_2)5$], 2.0 (s, 3H, $COC\underline{H}_3$), 3.65 (m, 1H, $C\underline{H}CHCO_2Et$), 4.2 (q, 2H, $OC\underline{H}_2CH_3$), 4.72 (dd, 1H, $CHCHCO_2Et$, *J* 4 Hz, 8.5 Hz), 6.68 (d, 1H, N<u>H</u>, *J* 8.5 Hz) ppm.

Ethyl (2R,3R*)-2-azido-3-[(methylsulfonyl)amino]nonanoate* (**8ef**). A mixture of azidotrimethylsilane (170 µl, 1.28 mmol) and ethanol (74 µl, 1.28 mmol) was added to a solution of **6e** (200 mg, 0.64 mmol) in DMF (10 ml). The mixture was stirred at 60°C for 6 h. The solvent was then evaporated. The residue taken up in water and extracted with ether. The combined organic layers were dried over $MgSO_4$ and concentrated. The crude product (269 mg) was purified by chromatography (hexane/ethyl acetate 7 : 1 (v/v)), to give **8ef** (200 mg, 88%) as an oil. IR (CCl_4): ν 3375 (NH), 3275 (NH), 2955, 2930, 2115 (N_3), 1740 (C=O), 1465, 1445, 1425, 1410, 1370, 1330 (NSO_2), 1270, 1195, 1155 (NSO_2), 1025, 970, 860 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.9 (t, 3H, $C\underline{H}_3$), 1.1–1.5 [m, 13H, $OCH_2C\underline{H}_3$, $CH_3(C\underline{H}_2)_5$], 3.0 (s, 3H, $C\underline{H}_3SO_2$), 3.8 (m, 1H, $C\underline{H}CHCO_2Et$), 4.1–4.4 (q + d, 3H, $OC\underline{H}_2CH_3$, $CHC\underline{H}CO_2Et$, $J_{doublet}$ 3.0 Hz), 5.0 (d, 1H, N<u>H</u>, *J* 9 Hz) ppm. MS (CI): *m/e* (%) 321 (100, M + 1$^+$), 293 (93), 278 (9), 247 (13, $-CO_2Et$), 214 (75), 192 (92, $C_6H_{13}CH^+NHMs$), 142 (15), 114 (11), 102 (17), 41 (22).

Ethyl (2R,3R*)-2-azido-3-[(4-tolylsulfonyl)amino]nonanoate* (**8ff**). Employing the procedure described for **8ef**, from **6f** (200 mg, 0.57 mmol) pure **8ff** (127 mg, 56%) was obtained after recrystallization from hexane. Reaction time 15 h. M.p. 77.5–78.5°C. IR (CCl4): ν 3375/3280 (NH), 2955, 2925, 2855, 2110 (N_3), 1735 (C=O), 1455, 1415, 1370, 1340 (NSO_2), 1270, 1190, 1160 (NSO_2), 1090, 1025, 910, 855, 665 cm^{-1}. ^1H NMR ($CDCl_3$) (400 MHz): δ 0.83 [t, 3H, $C\underline{H}_3(CH_2)_5$, *J* 7.17 Hz], 0.90–1.25 [m, 10H, $CH_3(C\underline{H}_2)_5$], 1.30 (t, 3H, $OCH_2C\underline{H}_3$, *J* 7.13 Hz), 2.44 (s, 3H, $C\underline{H}_3C_6H_4$), 3.69 (m, 1H, $C\underline{H}CHCO_2Et$), 4.20 (d, 1H, $CHC\underline{H}CO_2Et$, *J* 3.51 Hz), 4.24 (m, 2H, $OC\underline{H}_2CH_3$, ABM_3), 4.81 (d, 1H, N<u>H</u>Tos, *J* 9.34 Hz), 7.32 (d, 2H, $CH_3C_6\underline{H}_2$, *J* 8.0 Hz), 7.79 (d, 2H, $CH_3C_6\underline{H}_2$, *J* 8.0 Hz) ppm; NH decoupled: δ 3.69 (dt, 1H, $CH_2C\underline{H}CHCO_2Et$, *J* 10.3 Hz, 3.3 Hz) ppm. MS (CI): *m/e* (%) 397 (34 (M + 1$^+$), 369 (24), 323 (4, $-CO_2Et$), 268 (100, $C_6H_{13}CH^+NHTs$), 214 (36), 155 (49, $CH_3C_6H_4SO_2^+$), 139 (23), 107 (17), 91 (42, $CH_3C_6H_4^+$), 41 (32). Calcd. for $C_{18}H_{28}N_4O_4S$ (396.510): C 54.53, H 7.12, N 14.13; found: C 54.49, H 7.14, N 14.21%.

Ethyl (2R,3R*)-2-azido-3-[(benzylsulfonyl)amino]nonanoate* (**7gf**) *and ethyl (2R*,3R*)-3-azido-2-[(benzylsulfonyl)amino]nonanoate* (**8gf**). Sodium azide (55 mg, 0.84 mmol) was added to a solution of **6g** (100 mg, 0.28 mmol) in DMF (5 ml). After stirring for 2 h at room temperature, the solvent was evaporated. The residue was dissolved in water and extracted with ether. The combined extracts were dried over $MgSO_4$ and concentrated. The crude product (110 mg) was purified by chromatography (hexane/ethyl acetate 9 : 1), giving a mixture of **7gf** and **8gf** (60 mg, 60%) as a yellowish oil (ratio *ca.* 1 : 2). IR (CCl_4): ν 3380/3270 (NH), 3060, 3035, 2955, 2925, 2855, 2115 (N_3), 1735 (C=O), 1455, 1415, 1370, 1340 (NSO_2), 1260, 1195, 1155 (NSO_2), 1130, 1030, 930, 695 cm^{-1}. ^1H NMR: δ 0.9 [t, 3H, $C\underline{H}_3(CH_2)_5$], 1.1–1.6 [13H, $CH_3(C\underline{H}_2)_5$, $OCH_2C\underline{H}_3$], 3.4 (m, $C_6H_{13}C\underline{H}N_3$), 3.75 [m, $C_6H_{13}C\underline{H}(NHTs)$], 3.95 [d, $C\underline{H}(N_3)CO_2Et$], 4.0-4.35 [m, $OC\underline{H}_2CH_3$, $C\underline{H}(NHTs)CO_2Et$, $PhC\underline{H}_2$], 4.5 (d, 0.67H, N<u>H</u>, *J* 9 Hz), 5.25 (d, 0.33H, N<u>H</u>, *J* 8 Hz), 7.2–7.5 (m, 5H, <u>Ph</u>) ppm.

Reactions with acetonitrile/$BF_3 \cdot Et_2O$

Ethyl (4R,5R*)-1-acetyl-4-hexyl-2-methylimidazoline-5-carboxylate* (**10a**). Boron trifluoride etherate (105 µl, 1.05 equiv.) was added to a solution of **6a** (200 mg, 1.50 mmol) in acetonitrile (8 ml) at 0°C. After 10 min, the cooling bath was removed and the reaction mixture was stirred at room temperature for 1½ h. The solvent was then evaporated and the residue was taken up in satd. sodium bicarbonate solution. After extraction with ether (3x), the combined extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Yield 214 mg (91%) of **10a** as a colorless oil. According to GLC a single isomer. IR (CCl_4): ν 2955, 2925, 2860, 1740 (OC=O), 1695, 1680, 1640, 1375, 1335, 1245, 1190, 1030 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.9 [t, 3H, $C\underline{H}_3(CH_2)_5$], 1.2–1.9 [m, 11H, $CH_3(C\underline{H}_2)_4$, $OCH_2C\underline{H}_3$], 2.0 (m, 2H, $C\underline{H}_2CHCHCO_2Et$), 2.2 (s, 3H, $COC\underline{H}_3$), 2.4 (d, 3H, $C\underline{H}_3C{=}N{-}CH$, ^5J 1.5 Hz), 4.0–4.4 (q + m, 3H, $OC\underline{H}_2CH_3$, $C\underline{H}CHCO_2Et$), 4.7 (d, 1H, $CHC\underline{H}CO_2Et$, *J* 10 Hz) ppm.

Reaction of **6a** *with acetonitrile/$BF_3 \cdot Et_2O$ at reflux temperature.* Boron trifluoride etherate (25 µl, 0.2 mmol) was added to a solution of **6a** (250 mg, 1.1 mmol) in acetonitrile (10 ml). The reaction mixture was heated at reflux for 4 days. The solvent was then evaporated *in vacuo*. The residue was taken up in satd. sodium bicarbonate solution and extracted with chloroform (3x). The combined organic layers were dried over $MgSO_4$ and concentrated. Yield 350 mg (100%) of crude product as a solid. Recrystallization from hexane/ethyl acetate gave a white crystalline product (125 mg, 40%), which was shown to be the hydrolysis product (*2R*,3R**)-**11a**. M.p. 151.5–152.5°C. IR (KBr): ν 3260, 3070, 2920, 2855, 1735 (OC=O), 1650 (NC=O), 1550, 1465, 1445, 1370, 1305, 1260, 1185, 1120, 1035, 950 cm^{-1}. ^1H NMR ($CDCl_3$) (400 MHz): δ 0.87 (t, 3H, $C\underline{H}_3$, *J* 7.0 Hz), 1.2–1.4 [m, 11H, $OCH_2C\underline{H}_3$, $CH_3(C\underline{H}_2)_4$], 1.48 (m, 2H, $C\underline{H}_2CHCHCO_2Et$), 2.01 (s, 3H, $COC\underline{H}_3$), 2.04 (s, 3H, $COC\underline{H}_3$), 4.23 (q, 2H, $OC\underline{H}_2CH_3$, *J* 7.1 Hz), 4.31 (m, 1H, $C\underline{H}CHCO_2Et$), 4.56 (dd, 1H, $CHC\underline{H}CO_2Et$, *J* 2.7 Hz, 6.7 Hz), 6.10 [d, 1H, N<u>H</u> (C3), *J* 8.6 Hz], 6.78 [d, 1H, N<u>H</u> (C2), *J* 6.5 Hz] ppm; NH (6.78 ppm) decoupled: δ 4.56 (d, 1H, $CHCHCO_2Et$, *J* 2.7 Hz); NH (6.1 ppm) decoupled: δ 4.31 (m, 1H, $C\underline{H}CHCO_2Et$). MS (CI): *m/e* (%) 301 (94, M + 1$^+$), 283 (4), 255 (10, −OEt), 241 (13), 227 (9, $-CO_2Et$), 196 (3), 156 (24, $C_6H_{13}CH^+NHAc$), 114 (16), 60 (3), 41 (100). Calcd. for $C_{15}H_{28}N_2O_4$ (300.399): C 59.98, H 9.39, N 9.33; found: C 59.97, H 9.31, N 9.25%.

Ethyl (4R,5R*)-1-(benzyloxycarbonyl)-4-hexyl-2-methylimidazoline-5-carboxylate* (**10c**). Following the procedure described for the synthesis of **10a**, from **6c** (500 mg, 1.50 mmol), compound **10c** (470 mg, 85%) was obtained as a colorless oil, which slowly solidified in the refrigerator. IR (CCl_4): ν 3065, 3035, 2960, 2930, 2860, 1735 (C=O), 1655 (C=N), 1455, 1385, 1350, 1230, 1185, 1125, 1090, 1025, 700 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.9 [t, 3H, $C\underline{H}_3(CH_2)_5$], 1.15 (t, 3H, $OCH_2C\underline{H}_3$, *J* 7.5 Hz), 1.1–1.7 [m, 10H, $CH_3(C\underline{H}_2)_5$], 2.35 (d, 3H, $C\underline{H}_3C{=}N{-}CH$, *J* 1.5 Hz), 3.9–4.2 (m, 3H, $OC\underline{H}_2CH_3$, $C\underline{H}CHCO_2Et$), 4.65 (d, 1H, $CHC\underline{H}CO_2Et$, *J* 10.5 Hz), 5.1 (d, 2H, $PhC\underline{H}_2$, *J* 3.0 Hz), 7.25 (s, 5H, Ph) ppm. MS (CI): *m/e* (%) 375 (100, M + 1$^+$), 359 (12), 331 (64, $-CO_2$), 301 (33, $-CO_2Et$), 257 (29), 91 (95, $PhCH_2^+$).

Ethyl (4R,5R*)-4-hexyl-2-methyl-1-[(2-trimethylsilyl)ethoxycarbonyl]imidazoline-5-carboxylate* (**10d**). Following the procedure described for the synthesis of **10a**, from **6d** (100 mg, 0.30 mmol) compound **10d** (124 mg, 100%) was obtained as a colorless oil. GC analysis showed 93% purity, without a trace of an isomer. IR (CCl_4): ν 2955, 2925, 2855, 1730 (C=O), 1650 (C=N), 1450, 1435, 1385, 1340, 1250, 1190, 1175, 1120, 1080, 1040, 860 cm^{-1}. ^1H NMR ($CDCl_3$): δ (*vs.* Me_3Si) 0.00 (s, 9H, Me_3Si), 0.85 [t, 3H, $C\underline{H}_3(CH_2)_5$], 1.1–1.7 [m, 15H, $OCH_2C\underline{H}_3$, $CH_3(C\underline{H}_2)_5$, $OCH_2C\underline{H}_2SiMe_3$] 2.3 (d, 3H, $C\underline{H}_3C{=}N{-}CH$, *J* 1.5 Hz), 3.9–4.3 (m, 5H, $OC\underline{H}_2CH_3$, $OC\underline{H}_2CH_2SiMe_3$, $C\underline{H}CHCO_2Et$), 4.6 (d, 1H, $CHC\underline{H}CO_2Et$, *J* 10.5 Hz) ppm. MS (CI): *m/e* (%) 385 (64, M + 1$^+$), 375 (24), 357 (21), 341 (54, $-CO_2$), 313 (35), 311 (19), 297 (14), 283 (8), 267 (34), 241 (37), 239 (39), 156 (13), 101 (23, $Me_3SiCH_2CH_2^+$), 73 (86, Me_3Si^+).

Ethyl (4R,5R*)-4-hexyl-2-methyl-1-(methylsulfonyl)imidazoline-5-carboxylate* (**10e**). Following the procedure described for the synthesis of **10a**, from **6e** (50 mg, 0.18 mmol) compound **10e** (60 mg, 100%) was obtained as a colorless oil, which was 92% pure according to GC, without a trace of an isomer. IR (CCl_4): ν 2955, 2925, 2855, 1740 (C=O), 1660 (C=N), 1465, 1435, 1360 (NSO_2), 1325, 1200, 1160 (NSO_2), 1095, 1070, 1025, 965, 930 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.9 [t, 3H, $C\underline{H}_3(CH_2)_5$], 1.1–1.7 [m, 13H, $OCH_2C\underline{H}_3$, $CH_3(C\underline{H}_2)_5$], 2.3 (d, 3H, $C\underline{H}_3C{=}N{-}CH$, *J* 1.5 Hz), 3.2 (s, 3H, $C\underline{H}_3SO_2$), 4.0–4.4 (m, 3H, $OC\underline{H}_2CH_3$, $C\underline{H}CHCO_2Et$), 4.85 (d, 1H, $CHC\underline{H}CO_2Et$, *J* 10.5 Hz) ppm.

Ethyl (4R,5R*)-4-hexyl-2-methyl-1-(4-tolylsulfonyl)imidazoline-5-carboxylate* (**10f**). At 0°C boron trifluoride etherate (115 μl, 0.93 mmol) was added to a solution of **6f** (210 mg, 0.59 mmol) in acetonitrile (8 ml) at 0°C. The reaction mixture was stirred at 0°C for 1 h and then at room temperature for 2 h. Satd. sodium bicarbonate solution (5 ml) was added and excess acetonitrile was evaporated. The residue was diluted with water and extracted with ether (3x). The combined extracts were dried over $MgSO_4$ and concentrated, yielding **10f** (217 mg, 93%) as a yellowish oil, which slowly solidified. It was recrystallized from hexane. M.p. 57.5–58.5°C. IR (CCl_4): ν 3065, 2955, 2855, 1745 (OC=O), 1665, 1655, 1370, 1350, 1240, 1195, 1170, 1095, 670 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.9 [t, 3H, $C\underline{H}_3(CH_2)_5$], 1.1–1.7 [m, 13H, $OCH_2C\underline{H}_3$, $CH_3(C\underline{H}_2)_5$], 2.2 (d, 3H, $C\underline{H}_3C{=}N{-}CH$, *J* 1.5 Hz), 2.45 (s, 3H, $C\underline{H}_3C_6H_4$), 4.0–4.3 (m, 3H, $OC\underline{H}_2CH_3$, $C\underline{H}CHCO_2Et$), 4.75 (d, 1H, $CHC\underline{H}CO_2Et$, *J* 10.5 Hz), 7.3 (d 2H, $C_6\underline{H}_2$, *J* 8 Hz), 7.8 (d, 2H, $C_6\underline{H}_2$, *J* 8 Hz) ppm. MS (CI): *m/e* (%) 395 (100, M + 1$^+$), 365 (8, −EtH), 354 (6, M + 1 − CH_3CN), 321 (26, $-CO_2Et$), 280 (9, $-CO_2Et-CH_3CN$), 239 (79, $-SO_2Tol$), 169 (10), 167 (14), 156 (17), 155 (12), 114 (10), 91 (24, $C_6H_4CH_3^+$), 41 (18, CH_3CN^+).

Ethyl (2R,3R*)-2,3-bis(acetylamino)nonanoate* (**11a**). On standing, imidazoline **10a** gradually hydrolyzed to diamino acid derivative **11a**, which was recrystallized from hexane/ethyl acetate. M.p. 149–151°C. IR and ^1H NMR as above. MS (CI): *m/e* (%) 301 (M + 1$^+$), 255 (10, −OEt), 241 (18), 227 (12, $-CO_2Et$), 156 (100, $C_6H_{13}CHNHAc^+$), 114 (94).

Ethyl (2R,3R*)-2-[(benzyloxycarbonyl)amino]-3-(acetylamino)-nonanoate* (**11c**). On standing, imidazoline **10c** gradually hydrolyzed to diamino acid derivative **11c**, which was recrystallized from hexane/ethyl acetate. M.p. 86–87°C. IR (KBr): ν 3375, 3345 (br), 3060, 2945, 2860, 1720/1710 (OC=O), 1640 (NC=O), 1560, 1525, 1465, 1370, 1335, 1315, 1235, 1225, 1205, 1165, 1065, 1025, 960, 755, 720, 700, 610 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.9 [t, 3H, $C\underline{H}_3(CH_2)_5$], 1.1–1.6 [m, 13H, $CH_3(C\underline{H}_2)_5$, $OCH_2C\underline{H}_3$], 2.0 (s, 3H, $COC\underline{H}_3$), 4.1–4.5 (q + m, 4H, $OC\underline{H}_2CH_3$, $C\underline{H}C\underline{H}CO_2Et$), 5.1 (s, 2H, $PhC\underline{H}_2$), 5.75–6.05 (d + d, 2H, $N\underline{H}Ac$, $N\underline{H}CO_2Bzl$), 7.3 (s, 5H, Ph) ppm. Calcd. for $C_{21}H_{32}N_2O_5$ (392.500): C 64.26, H 8.22, N 7.14; found: C 64.20, H 8.12, N 7.14%.

Ethyl (2R,3R*)-2-[[(2-trimethylsilyl)ethoxycarbonyl]amino]-3-(acetylamino)-nonanoate* (**11d**). On standing, imidazoline **10d** gradually hydrolyzed to diamino acid derivative **11d**. IR (CCl_4): ν 3420, 3360 (br), 2960, 2925, 2855, 1725 (OC=O), 1680 (NC=O), 1500, 1465, 1370, 1345, 1245, 1200, 1060, 865, 835, 695 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.0 (s, 9H, Me_3Si), 0.7–1.5 [m, 18H, $C\underline{H}_3(C\underline{H}_2)_5$, $OCH_2C\underline{H}_3$, $OCH_2C\underline{H}_2SiMe_3$], 2.0 (s, 3H, $COC\underline{H}_3$), 4.0–4.4 (m, 6H, $OC\underline{H}_2CH_3$, $OC\underline{H}_2CH_2SiMe_3$, $C\underline{H}C\underline{H}CO_2Et$), 5.15 (br d, 1H, $N\underline{H}$, *J* 7 Hz), 6.05 (br d, 1H, $N\underline{H}$, *J* 8 Hz) ppm.

Ethyl (2R,3R*)-2-[(methylsulfonyl)amino]-3-(acetylamino)nonanoate* (**11e**). On standing, imidazoline **10e** gradually hydrolyzed to diamino acid derivative **11e**, which was recrystallized from hexane/ethyl-acetate. M.p. 112–113°C. IR (KBr): ν 3300, 3220, 3090, 2955, 2920, 2860, 1730 (OC=O), 1655 (NC=O), 1550, 1465, 1375, 1335, 1315, 1250, 1220, 1200, 1160, 1120, 985, 955, 920, 860, 770, 725, 630, 610 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.85 [t, 3H, $C\underline{H}_3(CH_2)_5$], 1.1–1.4 [m, 13H, $OCH_2C\underline{H}_3$, $CH_3(C\underline{H}_2)_5$], 2.0 (s, 3H, $COC\underline{H}_3$), 2.9 (s, 3H, $C\underline{H}_3SO_2$), 4.15–4.55 (m, 4H, $OC\underline{H}_2CH_3$, $C\underline{H}C\underline{H}CO_2Et$), 5.5 (d, 1H, $N\underline{H}$, *J* 9 Hz), 5.9 (d, 1H, $N\underline{H}$, *J* 9 Hz) ppm.

Ethyl (2R,3R*)-2-[(4-tolylsulfonyl)amino]-3-(acetylamino)nonanoate* (**11f**). On standing, imidazoline **10f** gradually hydrolyzed to diamino acid derivative **11f**, which was recrystallized from hexane/ethyl acetate. M.p. 151.5–152°C. IR (KBr): ν 3300, 3235, 3070, 2955, 2920, 2860, 1725 (OC=O), 1655 (NC=O), 1600, 1545, 1445, 1370, 1335 (NSO_2), 1315, 1205, 1165 (NSO_2), 1090, 1020, 950, 915, 815, 745, 710, 690, 630, 610 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.85 [t, 3H, $C\underline{H}_3(CH_2)_5$], 1.0–1.4 [m, 13H, $OCH_2C\underline{H}_3$, $CH_3(C\underline{H}_2)_5$], 2.05 (s, 3H, $COC\underline{H}_3$), 2.45 (s, 3H, $CH_3C_6H_4$), 3.9–4.1 (m, 3H, $OC\underline{H}_2CH_3$, $C\underline{H}NH$), 4.3 (m, 1H, $C\underline{H}NH$), 5.4 (d, 1H, $N\underline{H}$, *J* 8.5 Hz), 5.75 (d, 1H, $N\underline{H}$, *J* 8.5 Hz), 7.15–7.75 (m, 4H, $C_6\underline{H}_4$) ppm.

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