Regioselective Reactions of Mesyloxymethylazetidinones with Nucleophiles I. Cleavage of the Azetidinone Ring, Azetidinone-aziridine Ring Transformations

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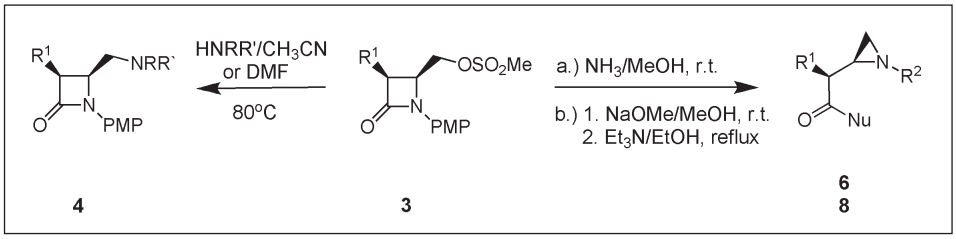

The reaction of 4-mesyloxymethylazetidin-2-one derivatives **3** with ammonia and sodium methoxide was investigated. The two electrophilic centers of the substrate reacted successively, resulting in cleavage of the lactam bond and formation of a new aziridine ring. The resulting type **6** and **8** aziridinylacetic acid derivatives are related to the novel 2-(aziridin-2-yl)-3-phenylpropionic acid type carboxypeptidase A inhibitors and, as such, potential drug candidates.

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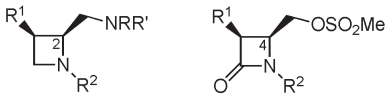
Introduction.

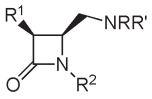
Recently [1] the synthesis of 2-(*N*,*N*-disubstituted aminomethyl)azetidines (**1**) by reaction of 4-(methanesulfonyloxymethyl)azetidin-2-ones **3** with secondary amines, followed by $LiAlH_4/AlCl_3$ reduction of the resulting 4-(*N*,*N*-disubstituted aminomethyl)azetidin-2-ones (**4**) was described.

In extension of this study, the preparation of analogues **2** of the compounds **1** carrying unsubstituted aminomethyl groups in position 2 was attempted by replacing the secondary amines with ammonia in the reactions with the compounds **3**.



1: R, R'≠H
2: R=R'=H

3



4: R, R'≠H
5: R=R'=H

While reactions of compounds **3a-c** with secondary amines smoothly afforded the desired 4-(*N*,*N*-disubstituted aminomethyl)azetidinones **4a-c**, application of ammonia as the nucleophilic agent led, in the case of compounds **3a-d** to a completely different, unexpected result, *viz.* to the formation of aziridin-2-ylacetamides **6a-d** (see Scheme 2). A similar transformation (formation of esters **8a-c**) could be brought about by reacting the compounds **3a-d** with methanolic sodium methoxide followed by refluxing with ethanolic triethylamine.

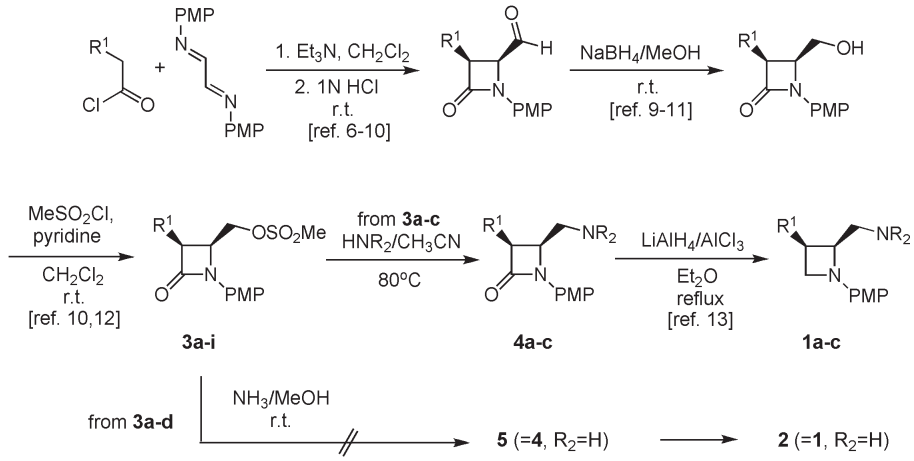
Since, in contrast to the aziridinecarboxylic acids which have been extensively studied [2-4], the homologous azetidinylacetic acids and their derivatives, such as the amides **6a-d** and the esters **8a-c** remain a less well known group of compounds, we have decided to study the transformations **3** → **6** or **3** → **8** in more detail, seeing that compounds **6** and **8** may be regarded as analogues of the 2-(aziridin-2-yl)-3-phenylpropionic acid type novel carboxypeptidase A inhibitors [5].

Results and Discussion.

Nine variously substituted 4-(methylsulfonyloxymethyl)azetidinones (**3a-i**) were synthesised as shown in Scheme 1[†].

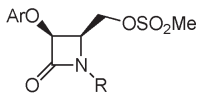
In addition, compounds **3j** and **3k** were prepared by CAN-induced demethoxyphenylation of compound **3b** and by silylation of compound **3j**, respectively.

Scheme 1



	R^1		R^1		R^1	PMP=4-MeOC$_6$H$_4$
a	4-F-C$_6$H$_4$O	**d**	PhCH$_2$O	**g**	Et	
b	4-Cl-C$_6$H$_4$O	**e**	C$_6$H$_4$(CO)$_2$N	**h**	H	
c	4-MeO-C$_6$H$_4$O	**f**	PhCH$_2$OC(O)NH	**i**	Cl	

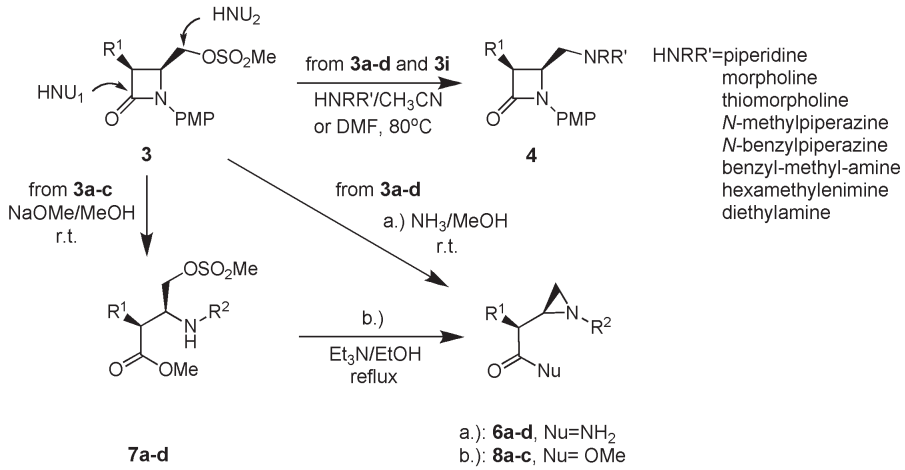
Synthesis of 2-(*N*,*N*-disubstituted aminomethyl)azetidines **1** and attempted synthesis of 2-(*N*-unsubstituted aminomethyl)azetidines **2**.



	R	OAr= 4-Cl-C$_6$H$_4$O
3b	4-MeO-C$_6$H$_4$	
3j	H	
3k	t-BuMe$_2$Si	

While the reaction of compounds **3a-c** with secondary amines in acetonitrile or DMF at 80 °C afforded the 4-(*N*,*N*-disubstituted aminomethyl)azetidinones **4a-c** in good to excellent yields [1], replacement of the secondary amines by methanolic ammonia‡ brought about ring transformation of compounds **3a-d** even at room temperature to afford the 2-(aziridin-2-yl)acetamides **6a-d** in 72-92% yields, see Scheme 2 and Table 1.

Scheme 2



Reaction of azetidinones **3** with secondary amines, ammonia and sodium methoxide.

Table 1

Reaction of Compounds **3a-k** with Ammonia in Methanol

3	R^1	R^2	Time [h]	Result
a [1]	4-FC_6H_4O	4-$MeOC_6H_4O$	24	90% **6a**
b [1]	4-ClC_6H_4O	4-$MeOC_6H_4O$	72	75% **6b**
c [1]	4-$MeOC_6H_4O$	4-$MeOC_6H_4O$	70	91% **6c**
d	$PhCH_2O$	4-$MeOC_6H_4O$	168	92% **6d**
e [10]	$C_6H_4(CO)_2N$	4-$MeOC_6H_4O$	0.5	R^1 cleavage
f [10]	$PhCH_2OC(O)NH$	4-$MeOC_6H_4O$	90	14% **6f**, *p*-anisidine + other products
g [12]	Et	4-$MeOC_6H_4O$	90	no reaction
h [12]	H	4-$MeOC_6H_4O$	90	no reaction
i	Cl	4-$MeOC_6H_4O$	28	no product isolated
j	4-ClC_6H_4O	H	36	**6j** in traces, aziridine cleavage and other products
k	4-ClC_6H_4O	Bu^tMe_2Si	3	R^2 cleavage

The reactions of azetidinones **3e-k** with methanolic ammonia were also briefly studied. The tentative results are included into Table 1.

Good yields of aziridinylacetamides **6** were obtained only in the **a**-**d** series, the rate of the reaction being considerably lower in the benzyloxy (**d**) than in the aryloxy series (**a**-**c**). The reaction of the acylamino derivatives (**3e**, **3f**) is complicated by the formation of several by-products arising partly as a result of R^1 cleavage but **6f** was isolated in low yield. Compounds **3g** and **3h** did not react at all. Compound **3i** reacted readily with ammonia, but no products could be isolated.

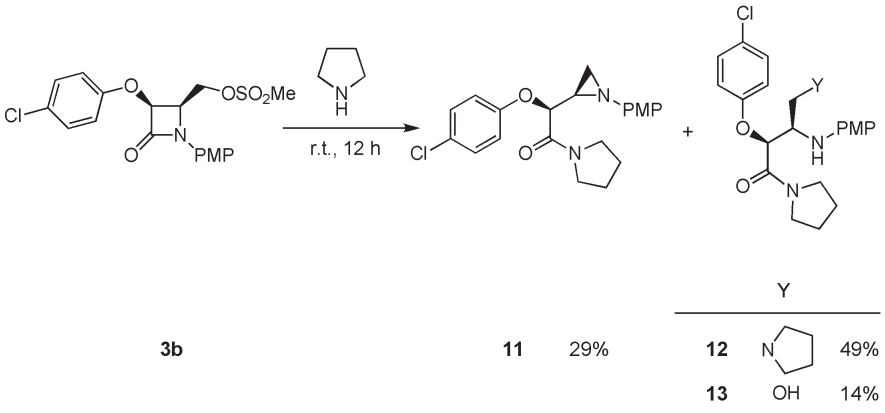
Compound **3k** reacted with ammonia by R^2 cleavage, giving **3j** as a product, which then reacted with methanolic ammonia at a much lower rate of reaction than **3a-c**, giving aziridinylacetamide **6j** in low yield accompanied by the formation of other products.

The only secondary amine, which, in contrast to all other secondary amines studied, was able to bring about the azetidinone-aziridine ring transformation was pyrrolidine. Thus compound **3b** with neat pyrrolidine at room temperature afforded the aziridinylacetamide **9** together with compounds **10** and **11** resulting by exchange of the mesyloxy or mesyl group, respectively.

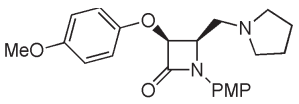
Interestingly, when compound **3c** was allowed to react instead of neat pyrrolidine with pyrrolidine in refluxing acetonitrile, pyrrolidinomethylazetidinone **12** was obtained in low yield (27%).

In contrast, the reaction of **3a** with piperidine proved insensitive to the conditions applied: in all cases piperidinomethylazetidinone **13** was obtained (conditions, yields: MeCN, r.t., 200h, 58%; MeCN, reflux, 20h, 98%; EtOH, r.t., 200h, 57%; EtOH, reflux, 90h, 11%; neat, r.t., 200h, 52%, neat, ~80 °C, 3h, 78%) [2].

Scheme 3



Reaction of compound **3b** with neat pyrrolidine.



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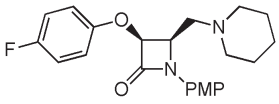

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The solvent dependence of the reaction with ammonia was also investigated. In this case, no reaction took place when using DMF as a solvent.

To give an explanation for these results, the nucleophilicities of the reagents, determined by their basicity and steric requirements, have to be considered [14-17]. Thus the hard nucleophile methoxide anion in every case reacts at the harder electrophilic lactam carbonyl, while the nucleophilicity of piperidine, a quite strong base, is restricted by the steric hindrance allowing only an attack at the side chain electrophilic center. Pyrrolidine being an intermediate (stronger base with lower steric requirements) between piperidine and ammonia, can react at both centers. The regioselectivity in this case is probably determined by the activation energy requirements, being lower in the reaction with the lactam carbonyl, and higher with the side chain center.

Although, considering its low steric requirements, ammonia should also be able to react on both centers, as a result of its week basicity and since the reaction was carried out at room temperature, the reaction occurred exclusively at the lactam carbonyl, the center with the lower energy barrier.

Similar ring transformations were brought about by treatment of compounds **3a-d** with methanolic sodium methoxide at room temperature, followed by refluxing with ethanolic triethylamine. In the first step the lactam carbonyl was selectively attacked by the nucleophile to afford the open-chain esters **7a-c** (60-90% yields of the isolated esters) which in the second step underwent intramolecular nucleophilic substitution to afford the aziridinylacetic esters **8a-c** (50-90% yield).

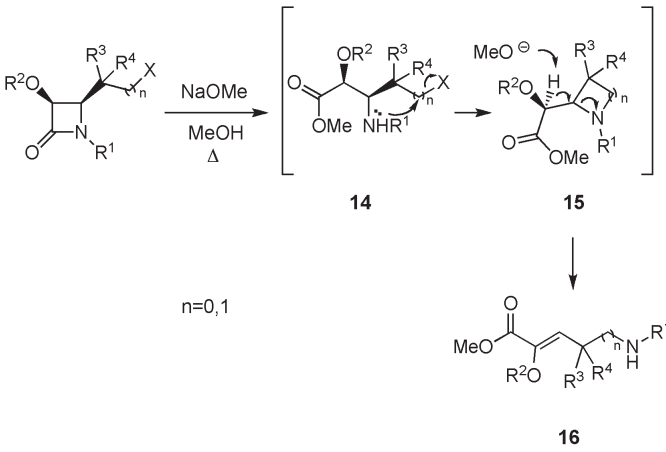
Similar azetidinone-aziridine ring transformations have been reported in three cases.

Santer and Ongania investigated the synthesis of benzanellated carbacepham derivatives [18]. They found that in the case of 4-substituted azetidinones containing two electrophilic centers, the same nucleophile may react, depending on the substituents of the starting material, with either of the two reaction centers to afford different products. The authors explain this observation on the basis of the principle of hard and soft nucleophiles and electrophiles, the hard nucleophile reacting in both cases with the harder electrophilic center.

A further azetidinone-aziridine ring transformation was reported in the case of 3-chloroazetidinones [19]. Here the cleavage of the β-lactam ring was followed by the intramolecular nucleophilic attack of the N atom at the former C3, resulting in the formation of an aziridinyl carboxylic acid product.

Quite recently Dejaegher and Kimpe reported the synthesis of methyl-ω-alkylaminoalkenoates **16** by ring opening of the appropriate azetidinone derivatives [20], followed by intramolecular nucleophilic substitution and ring opening of the cyclic intermediate **15** by β-elimination (Scheme 4). Since their original goal was to investigate the ring transformation of 4-(1-haloalkyl)-2-azetidinones to the cyclic intermediate, these authors studied the conditions needed to interrupt the reaction before the elimination. However, although working with the same reagent than we (NaOMe/MeOH), they never succeeded to isolate the expected aziridinyl or azetidinyl derivatives under basic conditions. However, the desired aziridinyl and azetidinyl derivatives could be obtained from the appropriate azetidin-2-ones in two steps, *viz*. by acidic hydrolysis followed by triethylamine induced ring closure [20].

Scheme 4



14 **15** **16**

Suggested pathway of formation of methyl ω-alkylaminobut-2-enoates and pent-2-enoates from 4-(1- and 2-haloalkyl)azetidin-2-ones, respectively [20] (X=Cl, Br).

The initial steps of the pathways suggested for the formation of the methyl ω-alkylaminoalk-2-enoates [20] (Scheme 4) and for the 2-(aziridin-2-yl)acetates **8a-c** (Scheme 2) are similar. The difference in the final outcome of the two transformations is probably the result of the difference of the reaction conditions (ice cooling in our experiments and reflux temperature in those described in

ref. 20). A further factor may be the difference in the type of the azetidinone *N*-substituent (4-methoxyphenyl in our experiments and mostly alkyl or alkenyl in those described in ref. 20).

A possible explanation for the different results can be the difference in the reaction conditions, *viz.* at higher temperature the reaction cannot be interrupted at the intermediate stage.

Conclusions.

Ammonia and sodium methoxide induced ring transformations of 4-(1-mesyloxymethyl)azetidin-2-ones **3a-d** to (aziridin-2-yl)acetic acid derivatives **6a-d** and **8a-c**, respectively, were effected in good yields. Transformations **3** → **8** were shown to take place *via* the open-chain compounds **7**. Almost all secondary amines react, in another way different from that in the case of ammonia. The difference is caused by the different regioselectivities of the attack of the nucleophilic reagents.

EXPERIMENTAL

Abbreviations: CAN: cerium ammonium nitrate, DMF: dimethylformamide, mesyl: methanesulfonyl, PMP: 4-methoxyphenyl, TBDMS: tert-butyl-dimethylsilyl, Tos: toluenesulfonyl, FC: flash column chromatography. *Techniques*: All reactions were monitored by TLC (DC-Alufolien 60 F_{254}, Merck; visualized by UV_{254}, and/or UV_{366} irradiation and/or by dipping into phosphormolybdic acid soln., followed by heating), and allowed to go to completion. Separations of product mixtures by FC were carried out using Kieselgel 60 G (Merck) as the adsorbent unless otherwise stated (pressure differences between the two ends of the columns 67-75 kPa). For preparative TLC separations 20x20 cm glass plates coated with Kieselgel $PF_{254+366}$ (Merck; thickness of adsorbent layer 2.0 mm) were used (home-made ones, except when otherwise noted). The solvents are given in parentheses. The purity of the products was checked in combination with IR spectroscopy, by TLC on DC-Alufolien 60 F_{254} (Merck); the individual compounds were detected by UV irradiation. Evaporations to dryness were carried out at reduced pressure. Reaction of mesyloxymethyl azetidinones **3a-k** with methanolic ammonia were carried out with a solution containing 107 g ammonia in 500 ml methanol. All new compounds described in the present paper were colourless crystals, unless otherwise stated. Melting point values were determined on a Kofler hot-stage melting point apparatus and are uncorrected. IR spectra were recorded on a Specord-75 or Specord M-80 spectrometers (Zeiss, Jena), measured as film or KBr pellets, absorption bands are in cm^{-1}. NMR spectra were obtained with a Varian XL-400 (^1H: 400 MHz, ^{13}C: 100 MHz) spectrometer; chemical shifts (δ–values) are reported in ppm with respect to Me_4Si (δ= 0 ppm) as the internal standard, coupling constants (J) are given in Hz. Relative configuration of the chirality centers were determined on the basis of the coupling constants. Exact molecular mass determinations were made at 70 eV with a Finnigan-MAT 95 SQ hybride – tandem instrument using a heated direct inlet system and perfluorokerosene as the reference.

(3*RS*,4*SR*)-3-Chloro-4-(hydroxymethyl)-1-(4-methoxyphenyl)-azetidin-2-one.

To a stirred solution of (3*RS*,4*SR*)-3-chloro-4-formyl-1-(4-methoxyphenyl)azetidin-2-one [9] (54.37 mmol) in methanol (160 ml) was added $NaBH_4$ (65.25 mmol) in small portions with vigorous stirring and external ice-cooling. The resulting mixture was stirred at room temperature for 4 h. After evaporation of the solvent at reduced pressure, the residue was washed with water (200 ml) and extracted with CH_2Cl_2 (3x70 ml). The combined organic layers were dried on $MgSO_4$ and evaporated yielding the title compound which was recrystallized from EtOAc. Yield: 90 %, m.p.: 91 °C; IR ν_{max}(KBr)/cm^{-1} 1752 (CO) and 3448 (OH); ^1H NMR ($CDCl_3$): δ_ 2.02 (dd, 1H, OH, J= 6.5), 3.78 (s, 3H, methoxy protons), 4.10 (ddd, 1H, C_α-H, Jg=12.4, Jv=4.5, $J_{v(OH)}$=6.5), 4.14 (ddd, 1H, C_α-H, J_g=12.4, J_v=5.5, $J_{v(OH)}$=6.0), 4.41 (ddd, 1H, C_4-H, J_{cis}=5.2, J_v=5.5, J_v=4.5), 5.07 (d, 1H, C_3-H, J_{cis}=5.2), 6.88 (m, 2H, aromatic $C_{3'}$- and $C_{5'}$-H), 7.42 (m, 2H, aromatic $C_{2'}$- and $C_{6'}$-H); HRMS *m/z* (EI) 241.0507 ($M^{\bullet+}$ $C_{11}H_{12}NO_3Cl$ requires 241.0500).

General Procedure for the Synthesis of 4-(Methanesulfonyloxymethyl)azetidin-2-ones (**3d** and **3i**).

Methanesulfonyl chloride (62.66 mmol) was added dropwise to solutions of compounds **2** (52.22 mmol) in pyridine (52 ml) with continuous stirring and external ice-cooling. The mixture was stirred at room temperature for 2 h then poured onto ice to obtain the pure crystalline products **3**.

(3*RS*,4*SR*)-3-Benzyloxy-1-(4-methoxyphenyl)-4-(methanesulfonyloxymethyl)azetidin-2-one (**3d**).

This compound was obtained in 94 % yield, m.p. 103 °C; IR ν_{max}(KBr)/cm^{-1} 1744 (CO) and 1352 & 1176 ($ROSO_2R'$); ^1H NMR ($CDCl_3$): δ 2.88 (s, 3H, mesyl protons), 3.78 (s, 3H, methoxy protons), 4.47-4.59 (m, 3H, C_4-H and C_α-H_2), 4.76 & 4.91 (2d, each, 1H, benzyl CH_2, J_g=11.5), 4.89 (d, 1H, C_3-H, J_{cis}=4.5), 6.38 (m, 2H, aromatic (PMP) $C_{3'}$- and $C_{5'}$-H), 7.40 (m, 2H, aromatic (PMP) $C_{2'}$- and $C_{6'}$-H), 7.3 (m, 2H, aromatic (benzyl) $C_{3'}$- and $C_{5'}$-H), 7.45 (m, 2H, aromatic (benzyl) $C_{2'}$- and $C_{6'}$-H); HRMS *m/z* (EI) 391.1076 ($M^{\bullet+}$ $C_{19}H_{21}NO_6S$ requires 391.1084).

(3*RS*,4*SR*)-3-Chloro-1-(4-methoxyphenyl)-4-(methanesulfonyloxymethyl)azetidin-2-one (**3i**).

This compound was obtained in 95 % yield, m.p. 126 °C; IR ν_{max}(KBr)/cm^{-1} 1756 (CO) and 1360 & 1176 ($ROSO_2R'$); ^1H NMR ($CDCl_3$): δ 3.01 (s, 3H, mesyl protons), 3.8 (s, 3H, methoxy protons), 4.56-4.69 (m, 3H, C_4-H and C_α-H_2), 5.16 (d, 1H, C_3-H, J_{cis}=4.5), 6.92 (m, 2H, aromatic $C_{3'}$- and $C_{5'}$-H), 7.40 (m, 2H, aromatic $C_{2'}$- and $C_{6'}$-H); HRMS *m/z* (EI) 319.0264 ($M^{\bullet+}$ $C_{12}H_{14}NO_5SCl$ requires 319.0276).

(3*RS*,4*SR*)-3-(4-Chlorophenoxy)-4-(methanesulfonyloxymethyl)azetidin-2-one (**3j**).

To a solution of **3b** (10 mmol) in acetonitrile (120 ml) was added dropwise a solution of CAN (25 mmol) in water (120 ml) at -5 °C in 10 min. The reaction mixture was extracted with EtOAc (100 and 3x25 ml), with cc Na_2CO_3 (30 ml), with 10 % $NaHSO_3$ (2x30 ml), and finally with cc Na_2CO_3 (30 ml), then was dried on $MgSO_4$ and evaporated *in vacuo*. The residue was recrystallized from ethanol to give product **3j** in 92 % yield. M.p. 147 °C (EtOH); IR ν_{max}(KBr)/cm^{-1} 3240 (NH); 1760 (CO) and 1320 & 1168 ($ROSO_2R'$); ^1H NMR ($CDCl_3$): δ 3.03 (s, 3H,

mesyl protons), 4.24 (ddd, 1H, C_4-H, J_{cis}=4.9, J_v=5.1, J_v=7.0), 4.39 (dd, 1H, C_α-H, J_g=10.7, J_v=7.0), 4.47 (dd, 1H, C_α-H, J_g=10.7, J_v=5.1), 5.34 (dd, 1H, C_3-H, J_{cis}=4.9, J_{NH}=2.4),), 7.04 (m, 2H, aromatic $C_{2'}$- and $C_{6'}$-H), 7.26 (m, 2H, aromatic $C_{3'}$- and $C_{5'}$-H), 8.51 (br s, 1H, NH); HRMS *m/z* (EI) 305.01198 ($M^{\bullet+}$ $C_{11}H_{12}NClO_5S$ requires 305.0119).

(3*RS*,4*SR*)-1-(t-Butyldimethylsilyl)-3-(4-chlorophenoxy)-4-(methanesulfonyloxymethyl)-azetidin-2-one (**3k**).

To a solution of **3j** (2.62 mmol) in acetonitrile (10 ml) was added 3.2 mmol Et_3N, and 6.4 mmol $^tBuMe_2SiCl$ in two portions at 0 °C. The reaction mixture was stirred at room temperature for 7 h then evaporated *in vacuo*. The residue was dissolved in CH_2Cl_2 and washed with water (10 ml). The suspension was filtered, extracted with CH_2Cl_2 (2x10 ml), and evaporated *in vacuo*. The residue was purified by FC (Hex-EtOAc= 8:1) to give pure product **3k** in 78 % overall yield. Yellow oil; IR ν_{max}(KBr)/cm^{-1} 1752 (CO) and 1180 & 1360 ($ROSO_2R'$). ^{1}H NMR ($CDCl_3$): δ 0.30 & 0.32 (2s, each, 3H, silyl methyl protons), 1.00 (s, 9H, t-butyl protons), 2.93 (s, 3H, mesyl protons), 4.20 (ddd, 1H, C_4-H, J_{cis}=5.4, J_v=5.3, J_v=6.0), 4.40 (dd, 1H, C_α-H, J_g=10.8, J_v=5.3), 4.51 (dd, 1H, C_α-H, J_g=10.8, J_v=6.0), 5.32 (d, 1H, C_3-H, J_{cis}=5.4) 7.02 (m, 2H, aromatic $C_{2'}$- and $C_{6'}$-H), 7.25 (m, 2H, aromatic $C_{3'}$- and $C_{5'}$-H); HRMS *m/z* (EI) (decomposed under the conditions of the measurement) 362.01848 ($M^{\bullet+}$ $C_{13}H_{17}NClO_5SSi$ requires 362.0280).

General Procedure for the Synthesis of Substituted Aziridinyl-acetamides **6a-d**, **f**, **j**.

To 2.43 mmol of compounds **3** were added solutions of ammonia in methanol (17 ml, 6.29 mol/500 ml). The reaction mixture was stirred at room temperature until complete reaction (TLC). After evaporation of the solvent, the residue was washed with methanol to give crystalline products **6**.

(2*RS*)-2-(4-Fluorophenoxy)-2-[(2*SR*)-1-(4-methoxyphenyl)-aziridin-2-yl]acetamide (**6a**).

Reaction time: 24 h. Yield: 90 %, m.p. 142 °C; IR ν_{max}(KBr)/cm^{-1} 1676 (CO). ^{1}H NMR ($CDCl_3$): δ 2.14 (dd, 1H, aziridine CH_2, J_g~1, J_v=6.5), 2.55 (dd, 1H, aziridine CH_2, J_g~1, J_v=3.3), 2.63 (ddd, 1H, aziridine CH, J_v= 5.0, J_v=6.5, J_v=3.3), 3.73 (s, 3H, methoxy protons), 4.54 (d, 1H, C_2-H, J_v=5.0), 6.69 & 6.27 (2 br s, each, 1H, NH_2), 6.74 (m, 2H, aromatic (PMP) $C_{3'}$-H and $C_{5'}$-H), 6.91 (m, 2H, aromatic (PMP) $C_{2'}$-H and $C_{6'}$-H), 6.98 (m, 4H, aromatic (4-fluorophenoxy) protons); HRMS *m/z* (EI) 316.1217 ($M^{\bullet+}$ $C_{17}H_{17}N_2O_3F$ requires 316.1218).

Anal. Calcd. for $C_{17}H_{17}N_2O_3F$: C, 64.55; H, 5.42; N, 8.86; F, 6.01. Found: C, 64.47; H, 5.42; N, 8.86; F, 5.87.

(2*RS*)-2-(4-Chlorophenoxy)-2-[(2*SR*)-1-(4-methoxyphenyl)-aziridin-2-yl]acetamide (**6b**).

Reaction time: 72 h. Yield: 75 %, m.p. 157 °C; IR ν_{max}(KBr)/cm^{-1} 1644 (CO) and 3400 & 3200 (NH_2). ^{1}H NMR ($CDCl_3$): δ 2.16 (dd, 1H, aziridine CH_2, J_g~1, J_v=6.6), 2.55 (dd, 1H, aziridine CH_2, J_g~1, J_v=3.4), 2.63 (ddd, 1H, aziridine CH, J_v= 5.0, J_v=6.6, J_v=3.4), 3.74 (s, 3H, methoxy protons), 4.57 (d, 1H, C_2-H, J_v=5.0), 5.78 & 6.55 (2 br s, each, 1H, NH_2), 6.75 (m, 2H, aromatic (PMP) $C_{3'}$-H and $C_{5'}$-H), 6.92 (m, 2H, aromatic (PMP) $C_{2'}$-H and $C_{6'}$-H), 6.97 (m, 2H, aromatic (4-chlorophenoxy) $C_{2'}$-H and $C_{6'}$-H), 7.28 (m, 2H, aromatic (4-chlorophenoxy) $C_{3'}$-H and $C_{5'}$-H); HRMS *m/z* (EI) 332.0912 ($M^{\bullet+}$ $C_{17}H_{17}N_2O_3Cl$ requires 332.0922).

(2*RS*)-2-(4-Methoxyphenoxy)-2-[(2*SR*)-1-(4-methoxyphenyl)-aziridin-2-yl]acetamide (**6c**).

Reaction time: 70 h. Yield: 91 %, m.p. 138 °C; IR ν_{max}(KBr)/cm^{-1} 1676 (CO) and 3408 & 3200 (NH_2). ^{1}H NMR ($CDCl_3$): δ 2.13 (dd, 1H, aziridine CH_2, J_g~1, J_v=6.6), 2.56 (dd, 1H, aziridine CH_2, J_g~1, J_v=3.4), 2.63 (ddd, 1H, aziridine CH, J_v= 5.0, J_v=6.6, J_v=3.4), 3.74 & 3.79 (2s, each, 3H, methoxy protons), 4.53 (d, 1H, C_2-H, J_v=5.0), 5.88 & 6.65 (2 br s, each, 1H, NH_2), 6.55 (m, 2H, aromatic (PMP) $C_{3'}$-H and $C_{5'}$-H), 6.97 (m, 2H, aromatic (PMP) $C_{2'}$-H and $C_{6'}$-H), 6.83 (m, 2H, aromatic (PMP^2) $C_{2'}$-H and $C_{6'}$-H), 6.86 (m, 2H, aromatic (PMP^2) $C_{3'}$-H and $C_{5'}$-H);. HRMS m/z (EI) 328.1435 ($M^{\bullet+}$ $C_{18}H_{20}N_2O_4$ requires 328.1418).

Anal. Calcd. for $C_{18}H_{20}N_2O_4$: C, 65.84; H, 6.14; N, 8.53. Found: C, 65.91; H, 6.08; N, 8.35.

(2*RS*)-2-Benzyloxy-2-[(2*SR*)-1-(4-methoxyphenyl)aziridin-2-yl]-acetamide (**6d**).

Reaction time: 7 days. Yield: 92 %, m.p. 102-104 °C; IR ν_{max}(KBr)/cm^{-1} 1664 (CO) and 3384 & 3184 (NH_2). ^{1}H NMR ($CDCl_3$): δ 2.07 (dd, 1H, aziridine CH_2, J_g~1, J_v=6.3), 2.48 (dd, 1H, aziridine CH_2, J_g~1, J_v=3.3), 2.46 (ddd, 1H, aziridine CH, J_v= 5.5, J_v=6.3, J_v=3.3), 3.74 (s, 3H, methoxy protons), 3.88 (d, 1H, C_2-H, J_v=5.5), 4.71 & 4.76 (2d, each, 1H, benzyloxy CH_2, Jg=11.5), 5.74 & 6.70 (2 br s, each, 1H, NH_2), 6.77 (m, 2H, aromatic (PMP) $C_{3'}$-H and $C_{5'}$-H), 6.96 (m, 2H, aromatic (PMP) $C_{2'}$-H and $C_{6'}$-H), 7.3 & 7.4 (2m, each, 2H, aromatic (benzyloxy protons); HRMS *m/z* (EI) 312.1456 ($M^{\bullet+}$ $C_{18}H_{20}N_2O_3$ requires 312.1468).

(2*RS*)-(*N*-Benzyloxycarbonylamino)-2-[(2*SR*)-1-(4-methoxyphenyl)aziridin-2-yl]acetamide (**6f**).

Reaction time: 90 h. Yield: 14 %, m.p. 162-164 °C; IR ν_{max}(KBr)/cm^{-1} 1680 (CO) and 3350 & 3150 (NH_2). ^{1}H NMR ($CDCl_3$): δ 2.02 (dd, 1H, aziridine CH_2, J_g~1, J_v=6.,5), 2.14 (dd, 1H, aziridine CH_2, J_g~1, J_v=3.4), 2.82 (ddd, 1H, aziridine CH, J_v~3, J_v=6.5, J_v=3.4), 3.75 (s, 3H, methoxy protons), 4.59 (dd, 1H, C_2-H, J_v~3, $J_{2,NH}$=8), 5.14 (s, 2H, benzyloxy CH_2), 5.73 (br d, 1H, C_2-NH, J_v=8), 5.61 & 6.58 (2 br s, each, 1H, NH_2), 6.76 (m, 2H, aromatic (PMP) $C_{3'}$-H and $C_{5'}$-H), 6.92 (m, 2H, aromatic (PMP) $C_{2'}$-H and $C_{6'}$-H), 7.3-7.4 (m, 5H, aromatic (Ph) protons); HRMS *m/z* (EI) 355.1528 ($M^{\bullet+}$ $C_{19}H_{21}N_3O_4$ requires 355.1527).

(2*RS*)-2-[(2*SR*)-(Aziridin-2-yl)]-2-(4-chlorophenoxy)acetamide (**6j**).

Reaction time: 36 h. Yield: 5%, m.p. 132-134 °C; IR ν_{max}(KBr)/cm^{-1} 1680 (CO) . ^{1}H NMR ($CDCl_3$): δ 1.55 (dd, 1H, aziridine CH_2, J_g<1, J_c=6.4), 1.94 (ddd, 1H, aziridine CH, J_c=6.4, J_{tr}=3.3, $J_{2,3}$=6.5), 2.08 (dd, 1H, aziridine CH_2, J_g<1, J_{tr}=3.3), 4.14 (d, 1H, C_2-H, J_v=6.5), 6.98 (br s, 2H, NH_2), 6.87 (m, 2H, aromatic (4-chlorophenoxy) $C_{2'}$-H and $C_{6'}$-H), 7.12 (m, 2H, aromatic (4-chlorophenoxy) $C_{3'}$-H and $C_{5'}$-H); HRMS *m/z* (EI) Title compound decomposed under conditions of the measurement, characterization was based on the spectroscopic data.

General Procedure for the Synthesis of Substituted 3-Amino-4-(methanesulfonyloxy)butyric Esters **7a-c**.

To solutions of sodium (6.06 mmol) in methanol (12 ml) were added 2.43 mmol of compounds **3** with vigorous stirring and

external ice-cooling. The reaction mixture was stirred at room temperature for 1.5 h and again cooled in an ice bath to give crystalline products **7**.

Methyl (2*RS*,3*SR*)-2-(4-Fluorophenoxy)-3-[(4-methoxyphenyl-)amino]-4-(methanesulfonyloxy)butanoate (**7a**).

Yield: 69 %, m.p. 120 °C; IR ν_{max}(KBr)/cm^{-1} 1760 (CO) and 1356 & 1176 ($ROSO_2R'$). ^{1}H NMR ($CDCl_3$): δ_ 3.34 (s, 3H, mesyl protons), 3.50 & 3.60 (m, 2H, C_4-H_2), 3.63 (s, 3H, ester methyl protons), 3.74 (s, 3H, methoxy protons), 3.90 (br s, 1H, NH), 4.14 (m, 1H, C_3-H), 4.91 (d, C_2-H, J_v=2.3), 6.66 (m, 2H, aromatic (PMP) $C_{3`}$-H and $C_{5`}$-H), 6.77 (m, 2H, aromatic (PMP) $C_{2`}$-H and $C_{6`}$-H), 6.88 (m, 2H, aromatic (4-fluorophenoxy) $C_{2`}$-H and $C_{6`}$-H), 6.96 (m, 2H, aromatic (4-fluorofenoxy) $C_{3`}$-H and $C_{5`}$-H); HRMS *m/z* (EI) 427.1103 ($M^{\bullet+}$ $C_{19}H_{22}NO_7SF$ requires 427.1096).

Methyl (2*RS*,3*SR*)-2-(4-chlorophenoxy)-3-[(4-methoxyphenyl)-amino]-4-(methanesulfonyloxy)butanoate (**7b**).

This compound was obtained in 90 % yield, m.p. 127 °C; IR ν_{max}(KBr)/cm^{-1} 3336 (NH), 1756 (CO) and 1356 & 1184 ($ROSO_2R'$). ^{1}H NMR ($CDCl_3$): δ_ 2.94 (s, 3H, mesyl protons), 3.63 (s, 3H, ester methyl protons), 3.74 (s, 3H, methoxy protons), 4.29 (dd, 1H, C_4-H_2, J_g=9.5, J_v=8.5), 4.42 (dd, 1H, C_4-H_2, J_g=9.5, J_v=4.0), 4.35 (m, 1H, C_3-H), 4.94 (d, C_2-H, J_v=2.4), 6.68 (m, 2H, aromatic (PMP) $C_{3`}$-H and $C_{5`}$-H), 6.79 (m, 2H, aromatic (PMP) $C_{2`}$-H and $C_{6`}$-H), 6.87 (m, 2H, aromatic (4-chlorophenoxy) $C_{2`}$-H and $C_{6`}$-H), 7.26 (m, 2H, aromatic (4-chlorofenoxy) $C_{3`}$-H and $C_{5`}$-H); HRMS *m/z* (EI) 443.07879 ($M^{\bullet+}$ $C_{19}H_{22}NO_7SCl$ requires 443.0800).

Methyl (2*RS*,3*SR*)-2-(4-Methoxyphenoxy)-3-[(4-methoxyphenyl)amino]-4-(methanesulfonyloxy)butanoate (**7c**).

This compound was obtained in 59 % yield, m.p. 91-92 °C; IR ν_{max}(KBr)/cm^{-1} 3336 (NH);1756 (CO) and 1344 & 1172 ($ROSO_2R'$). ^{1}H NMR ($CDCl_3$): δ _2.93 (s, 3H, mesyl protons), 3.62 (s, 3H, ester methyl protons), 3.74 & 3.76 (2s, each, 3H, methoxy protons), 3.75 (br s, 1H, NH), 4.28 & 4.47 (m, 3H, C_4-H_2 and C_3-H) 4.88 (d, 1H, C_2-H, J_v=2.1), 6.67 (m, 2H, aromatic (PMP) $C_{3`}$-H and $C_{5`}$-H), 6.78 (m, 2H, aromatic (PMP) $C_{2`}$-H and $C_{6`}$-H), 6.82 (m, 2H, aromatic (PMP^2) $C_{3`}$-H and $C_{5`}$-H), 6.90 (m, 2H, aromatic (PMP^2) $C_{2`}$-H and $C_{6`}$-H); HRMS *m/z* (EI) (decomposed under the conditions of the measurement) 343.1403 ($M^{\bullet+}$ $C_{19}H_{21}NO_5$ requires 343.1414).

General Procedure for the Synthesis of Substituted Aziridinylacetic Acid Derivatives **8a-c**.

To solutions of compounds **7a-c** (0.45 mmol) in ethanol (2 ml) was added triethylamine (0.2 ml) at room temperature. The reaction mixtures were refluxed for 20 min and then evaporated *in vacuo*. The residues were washed with water (10 ml) and extracted with CH_2Cl_2 (3x4 ml). The combined organic layers were dried on $MgSO_4$ then evaporated. The resulting oils crystallized from isopropyl alcohol or methanol to yield the corresponding products **8a-c**.

Methyl (2*RS*)-2-(4-Fluorophenoxy)-2-[(2*SR*)-1-(4-methoxyphenyl)aziridin-2-yl]acetate (**8a**).

This compound was obtained in 89 % yield, m.p. 81 °C (iPrOH); IR ν_{max}(KBr)/cm^{-1} 1760 (CO). ^{1}H NMR ($CDCl_3$): δ 2.18 (dd, 1H, aziridine CH_2, J_g~1, J_v=6.4), 2.49 (dd, 1H, aziridine CH_2, J_g~1, J_v=3.4), 2.59 (m, 1H, aziridine CH), 3.76 (s, 3H, ester methyl protons), 3.81 (s, 3H, methoxy protons), 4.44 (d, 1H, C_2-H, J_v=7.0), 6.78 (m, 2H, aromatic (PMP) $C_{3`}$-H and $C_{5`}$-H), 6.95 (m, 2H, aromatic (PMP) $C_{2`}$-H and $C_{6`}$-H), 6.97 (m, 4H, aromatic (4-fluorofenoxy) protons).

Anal. Calcd. for $C_{18}H_{18}NO_4F$: C, 62.25; H, 5.48; N, 4.23; F, 5.73. Found: C, 62.33; H, 5.57; N, 4.34; F, 5.83.

Methyl (2*RS*)-2-(4-Chlorophenoxy)-2-[(2*SR*)-1-(4-methoxyphenyl)aziridin-2-yl]acetate (**8b**).

This compound was obtained in 81 % yield: 81 %, m.p. 74-75 °C; IR ν_{max}(KBr)/cm^{-1} 1756 (CO). ^{1}H NMR ($CDCl_3$): δ 2.17 (dd, 1H, aziridine CH_2, J_g~1, J_v=6.5), 2.48 (dd, 1H, aziridine CH_2, J_g~1, J_v=3.5), 2.60 (m, 1H, aziridine CH), 3.74 (m, 3H, ester methyl protons), 3.80 (s, 3H, methoxy protons), 4.49 (d, 1H, C_2-H, J_v=7.1), 6.77 (m, 2H, aromatic (PMP) $C_{3`}$-H and $C_{5`}$-H), 6.95 (m, 2H, aromatic (PMP) $C_{2`}$-H and $C_{6`}$-H), 6..96 (m, 2H, aromatic (4-chlorophenoxy) $C_{2`}$-H and $C_{6`}$-H), 7.25 (m, 2H, aromatic (4-chlorophenoxy) $C_{3`}$-H and $C_{5`}$-H); HRMS *m/z* (EI) 347.0910 ($M^{\bullet+}$ $C_{18}H_{18}NO_4Cl$ requires 347.0919).

Methyl (2*RS*)-2-(4-methoxyphenoxy)-2-[(2*SR*)-1-(4-methoxyphenyl)aziridin-2-yl]acetate (**8c**).

This compound was obtained in 51 % yield, yellow oil; IR ν_{max}(film)/cm^{-1} 1760 (CO). ^{1}H NMR ($CDCl_3$): δ 2.16 (dd, 1H, aziridine CH_2, J_g~1, J_v=6.6), 2.48 (dd, 1H, aziridine CH_2, J_g~1, J_v=3.4), 2.58 (m, 1H, aziridine CH), 3.75 & 3.80 (3s, each, 3H, methoxy and ester methyl protons), 4.43 (d, 1H, C_2-H, J_v=7.0), 6.77 (m, 2H, aromatic (PMP) $C_{3`}$-H and $C_{5`}$-H), 6.96 (m, 2H, aromatic (PMP) $C_{2`}$-H and $C_{6`}$-H), 6.81 (m, 2H, aromatic (PMP^2) $C_{3`}$-H and $C_{5`}$-H), 6.96 (m, 2H, aromatic (PMP^2) $C_{2`}$-H and $C_{6`}$-H); HRMS *m/z* (EI) 343.1403 ($M^{\bullet+}$ $C_{19}H_{21}NO_5$ requires 343.1414).

Anal. Calcd. for $C_{19}H_{21}NO_5$: C, 66.46; H, 6.16; N, 4.08. Found: C, 66.37; H, 6.15; N, 4.12.

Reaction of **3b** with Pyrrolidine.

Suspension of **3b** (0.72 mmol) in pyrrolidine (2 ml) was stirred at room temperature for 12 hours. The reaction mixture was then evaporated *in vacuo* and the residue chromatographed (CH_2Cl_2:Aceton=10:0.5_→10:1 →7:3) to give crystalline products **9-11**.

(2*RS*)-2-(4-Chlorophenoxy)-2-[(2*SR*)-1-(4-methoxyphenyl)-aziridin-2-yl]-1-(pyrrolidin-1-yl)ethan-1-one (**9**).

This compound was obtained in 29 % yield, m.p. 132-133°C; IR ν_{max}(KBr)/cm^{-1} 1650 (CO). ^{1}H NMR ($CDCl_3$): δ 1.7-1.9 (m, 4H, pyrrolidine C_3- and C_2-H), 2.17 (dd, 1H, aziridine CH_2, J_g<1, J_c=6.5), 2.49 (dd, 1H, aziridine CH_2, J_g<1, J_{tr}=3.4), 2.64 (ddd, 1H, aziridine CH, J_c= 6.5, J_{tr}=3.4, $J_{2,3}$=6.2), 3.3-3.9 (m, 4H, pyrrolidinyl C_2- and C_5-H), 3.75 (s, 3H, methoxy protons), 4.63 (d, 1H, C_2-H, $J_{2,3}$=6.2), 6.76 (m, 2H, aromatic (PMP) $C_{3`}$-H and $C_{5`}$-H), 6.89 (m, 2H, aromatic (PMP) $C_{2`}$-H and $C_{6`}$-H), 6.98 (m, 2H, aromatic (4-chlorophenoxy) $C_{2`}$-H and $C_{6`}$-H), 7.24 (m, 2H, aromatic (4-chlorophenoxy) $C_{3`}$-H and $C_{5`}$-H); HRMS *m/z* (EI) 386.1387 ($M^{\bullet+}$ $C_{21}H_{23}N_2O_3Cl$ requires 386.1392).

(2*RS*,3*SR*)-2-(4-Chlorophenoxy)-3-[(4-methoxyphenyl)amino]-1,4-di(pyrrolidin-1-yl)butan-1-one (**10**).

This compound was obtained in 49 % yield, m.p. 112-115 °C; IR ν_{max}(KBr)/cm^{-1} 1610 (CO) and 3425 (NH). ^{1}H NMR ($CDCl_3$): δ 1.3-1.8 (m, 8H, pyrrolidinyl C_3-H and C_4-H), 2.45-

2.85 (3m, each, 2H, C_4-H_2 and 4-pyrrolidinyl C_2-H and C_5-H), 3.05&3.4&3.84 (3m, 1H+2H+1H, 1-pyrrolidinyl C_2-H and C_5-H), 3.73 (s, 3H, methoxy protons), 4.07 (br, 1H, NH), 4.11 (m, 1H, C_3-H), 4.91 (d, C_2-H, J_v=2.0), 6.64 (m, 2H, aromatic (PMP) $C_{3`}$-H and $C_{5`}$-H), 6.75 (m, 2H, aromatic (PMP) $C_{2`}$-H and $C_{6`}$-H), 6.85 (m, 2H, aromatic (4-chlorophenoxy) $C_{2`}$-H and $C_{6`}$-H), 7.22 (m, 2H, aromatic (4-chlorophenoxy) $C_{3`}$-H and $C_{5`}$-H); HRMS *m/z* (EI) 457.2129 ($M^{\bullet+}$ $C_{25}H_{32}N_3O_3Cl$ requires 459.2127).

(2*RS*,3*SR*)-2-(4-Chlorophenoxy)-4-hydroxy-3-[(4-methoxyphenyl)amino]-1-(pyrrolidin-1-yl)butan-1-one (**11**).

This compound was obtained in 14 % yield, m.p. 118-124 °C; IR ν_{max}(KBr)/cm^{-1} 1620 (CO) and 3300-3500 (OH). ^{1}H NMR ($CDCl_3$): δ 1.65-1.80 (m, 4H, pyrrolidinyl C_3-H and C_4-H), 3.2 & 3.6 (2m, each, 2H, pyrrolidinyl C_2-H and C_5-H), 3.74 (s, 3H, methoxy protons), 3.74 (dd, 2H, C_4-H, J_g=11.3, J_v=5.3), 3.92 (ddd, 1H, C_3-H, J_v=5.3, J_v=3.9, $J_{2,3}$=4.5), 4.06 (dd, 1H, C_4-H, J_g=11.3, J_v=3.9), 4.97 (d, C_2-H, $J_{2,3}$=4.5), 6.67 (m, 2H, aromatic (PMP) $C_{3`}$-H and $C_{5`}$-H), 6.78 (m, 2H, aromatic (PMP) $C_{2`}$-H and $C_{6`}$-H), 6.82 (m, 2H, aromatic (4-chlorophenoxy) $C_{2`}$-H and $C_{6`}$-H), 7.24 (m, 2H, aromatic (4-chlorophenoxy) $C_{3`}$-H and $C_{5`}$-H). HRMS *m/z* (EI) 404.1504 ($M^{\bullet+}$ $C_{21}H_{25}N_2O_4Cl$ requires 404.1497).

(3*RS*,4*SR*)-3-(4-Methoxyphenoxy)-1-(4-methoxyphenyl)-4-[(pyrrolidin-1-yl)methyl]azetidin-2-one (**12**).

To a solution of **3c** (1 mmol) in acetonitrile (4 ml) was added pyrrolidine (2,2 mmol). The reaction mixture was refluxed for 50 h and then evaporated *in vacuo*. The residue was treated with water and 1 *N* NaOH solution (2 ml), to give a crystalline product, which was then purified by flash chromatography (CH_2Cl_2:acetone=7:3). Yield: 27%, m.p.: 133 °C; IR ν_{max}(film)/cm^{-1} 1760 (CO). ^{1}H NMR ($CDCl_3$): δ 2.60+1.76 (m, 8H, pyrrolidine protons), 3.03 (d, 2H, C_α–H_2, J_v=5.4), 3.78 & 3.8 (2 s, each 3H, methoxy protons), 4.46 (dt, 1H, C_4-H, J_{cis}=5.1, J_v=5.4), 5.26 (d, 1H, C_3-H, J_{cis}=5.1), 6.84 & 6.9 (2 m, each 2H, aromatic $C_{3'}$- and $C_{5'}$-H), 7.08 & 7.5 (2 m, each 2H, aromatic $C_{2'}$- and $C_{6'}$-H); HRMS *m/z* (EI) 382.1891 ($M^{\bullet+}$ $C_{22}H_{26}N_2O_4$ requires 382.18926).

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† All chemical compounds discussed in the present paper are racemic and only one enantiomer is shown.

‡ Reactions of compounds **3** with primary amines is also in process.

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