*Tetrahedron* Vol 47, No 24, pp 4039-4062, 1991
Printed in Great Britain

0040-4020/91 $3.00+.00


# TIN TETRACHLORIDE-INDUCED π-CYCLIZATIONS OF GLYCINE CATION EQUIVALENTS TO SUBSTITUTED PIPECOLIC ACID DERIVATIVES

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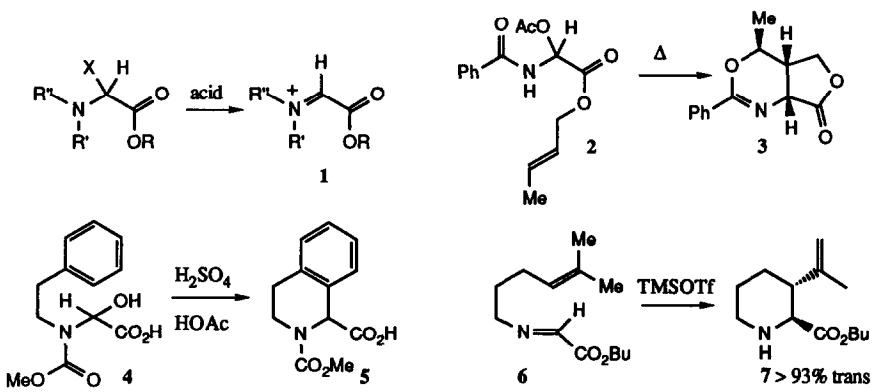
(*Received in UK* 8 *January* 1991)

*Summary*: Cationic π-cyclization reactions of *N*-(3-alkenyl)-*N*-(methoxycarbonyl)acetoxyglycine esters induced by tin tetrachloride in dichloromethane are described. Reactions started and quenched with water at -78 °C mainly yield *cis*-4-hydroxypipecolic esters, whereas reactions quenched after warm-up to room temperature provide *trans*-4-chloropipecolic esters as major products. A mechanistic scheme is advanced which adequately explains these results. The essentials are a rapid cationic aza-Cope equilibrium of the incipient iminium cation, and participation of the ester moiety through formation of a relatively stable bicyclic dioxycarbenium cation as pivotal intermediate.

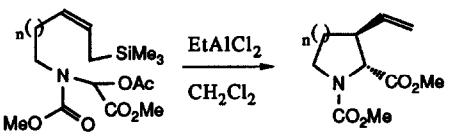
## INTRODUCTION

The synthesis of α-amino acids through *intermolecular* coupling of a carbon nucleophile with glycine cation equivalent **1** draws increasing attention in recent years,[1] in particular the asymmetric version.[2,3] We have recently published the successful use of allyl- and enolsilanes for this purpose leading to γ,δ-unsaturated α-amino acids and γ-oxo-α-amino acids, respectively.[4]



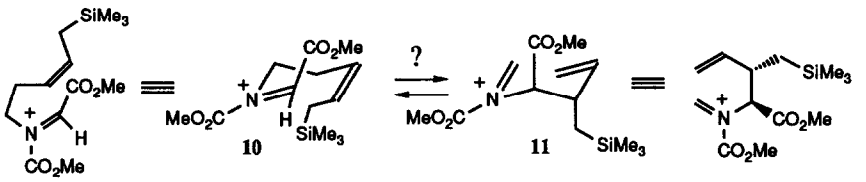

The corresponding *intramolecular* CC bond formation has received only scant attention. Acetate **2** bearing a nucleophilic olefin in the ester function, has been shown to furnish cycloaddition product **3**.[5] If the nucleophile is located in the *N*-substituent, normal CC bond formation takes place, as appears from the following examples. When a phenyl ring is used as nucleophile as in **4**, aromatic amino acid derivatives like **5** are formed.[6] With a trisubstituted alkene as nucleophile in **6** pipecolic acid derivative **7** is obtained.[7] We have utilized the allylsilane function as nucleophile in this fashion and obtained from **8** the cyclic amino acid

derivatives **9** in excellent yield.[8] The preponderant formation of the *trans*-product **9a** from **8a** was explained by assuming, that the chair-like conformation **10** with an (*E*)-iminium geometry leads to the most favourable transition state.



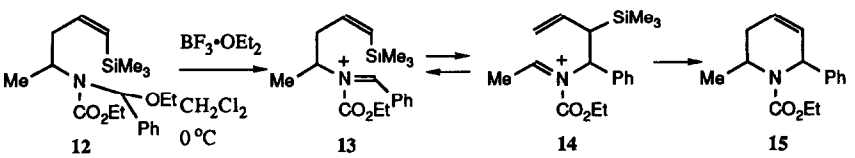
**8a** n = 1
**8b** n = 2

**9a** n = 1 *trans*:*cis* = 78:22
**9b** n = 2 *trans*:*cis* = 54:46



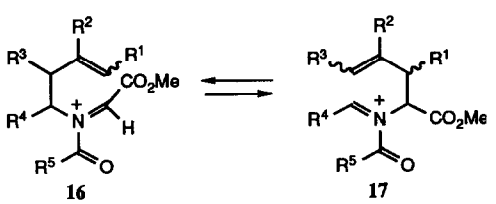
**10** **11**

The above examples show that cyclic α-amino acids can be prepared via glycine cations. However, the scope of this methodology and some mechanistic details remain to be established. In this respect, the nature of iminium ion **10** intrigued us, because this type of iminium ion with a 1,5-relationship between the unsaturated bonds is known to be prone to rearrange in a cationic 2-aza-Cope rearrangement.[9] Overman and coworkers have proved that upon acid treatment of carbamate **12** the equilibration between **13** and **14** is much faster than cyclization to **15**.[10] Rearrangement of **10** would lead to **11**. Cyclization of **11** is expected to give a product different from **9a**. Apparently, cyclization of **10** is much faster than either the rearrangement of **10** to **11** or cyclization of **11**. That **10** cyclizes faster than **11** is not unreasonable, because the iminium cation in **10** is probably more electrophilic than that of **11** and, perhaps more important, the allylsilane in **10** is more nucleophilic than the monosubstituted olefin in **11**.



**12** **13** **14** **15**

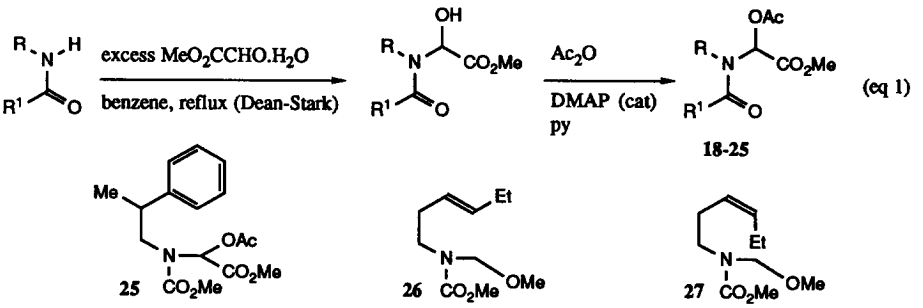
In this paper we report a detailed study of the Lewis acid-induced cyclization of glycine cations of type **16**. This study was undertaken for two reasons, namely (1) to establish the value of this methodology for the synthesis of substituted prolines or pipecolic acids,[11] and (2) to elucidate the stereochemical details of the cyclization process, including the relevance of the cationic aza-Cope rearrangement to **17**.[12] The following paper in this issue will deal with formic acid-induced cyclization of the same substrates.[13]

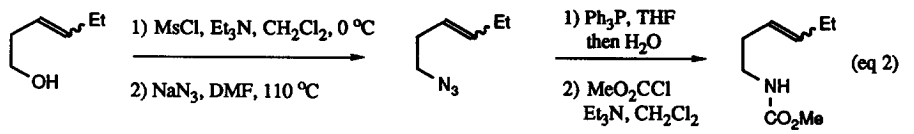


**16** **17**

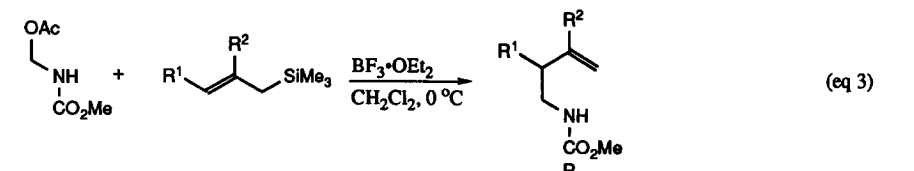
RESULTS

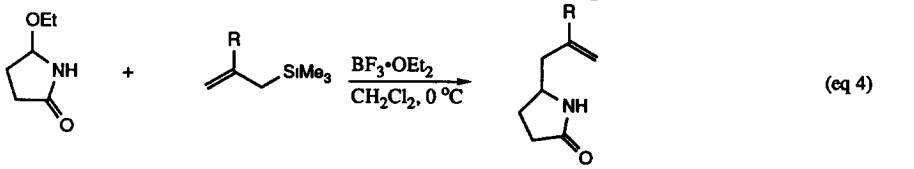
The iminium ions **16** were generated from the *N,O*-acetals **18-24** (see Table I) and **25**. These compounds were prepared from carbamates or 2-pyrrolidinones as shown in eq 1. Both, the intermediate hydroxy compounds and the acetates were easily purified by using flash chromatography, and the overall yields over two steps were usually above 65%.



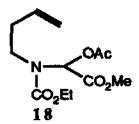
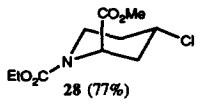
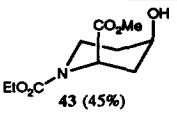
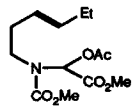
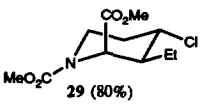
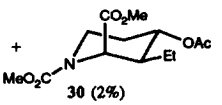
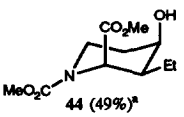
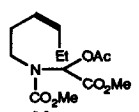
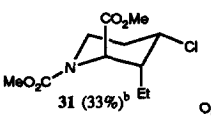
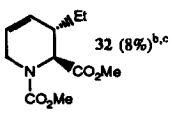
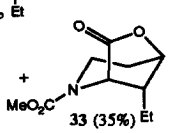
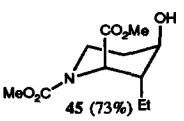
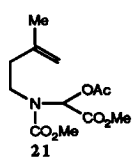
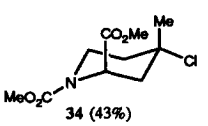
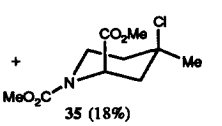
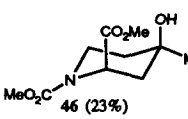
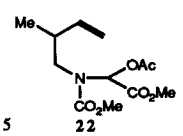
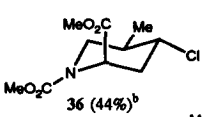
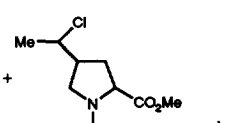
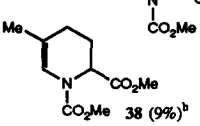
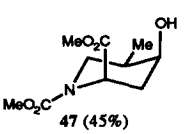
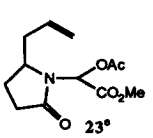
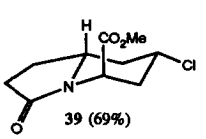
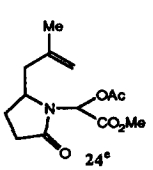
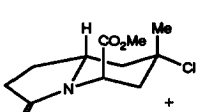
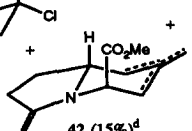
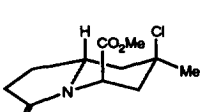

The methoxy compounds **26** and **27** used for comparing the cyclization behaviour of **16** with iminium ions lacking the ester function arose from treatment of the NH carbamates with chloromethyl methyl ether in DMF and NaH as base. These latter carbamates, also required for entries 2 and 3 (Table I), were prepared as shown in eq 2 from the commercial alcohols. The homoallylic carbamates and pyrrolidinones required for entries 1, 4, 5, 6 and 7 were prepared as detailed in eq 3 and 4 by *N*-acyliminium ion chemistry using allyl-, methallyl- and crotylsilane as nucleophiles.[14] These syntheses are further detailed in the Experimental.



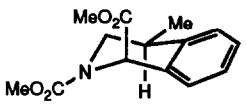

The cyclizations of precursors **18-27** were effected by adding 2 equiv of $SnCl_4$ to solutions in $CH_2Cl_2$ at -78 °C, followed by warm-up to room temperature. The reactions were stopped by adding excess aqueous $NaHCO_3$. In a separate series of experiments (entries 1-6) the same reaction mixtures were not allowed to warm up but were stirred at -78 °C for a prolonged period of time and then quenched at this temperature with excess aqueous $NaHCO_3$. Table I shows the products and isolated yields starting from **18-24** obtained after work-up and flash chromatographic separation and purification. In some cases products could

**Table I** Results of the $SnCl_4$-induced cyclizations of **18-24**

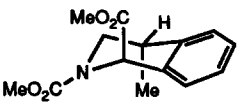
| entry | cyclization precursor | Products (yields) hydrolytic quench at 20 °C | hydrolytic quench at -78 °C |
|---|---|---|---|
| 1 |  **18** |  **28** (77%) |  **43** (45%) + **18** (41%) |
| 2 |  **19** |  **29** (80%) +  **30** (2%) |  **44** (49%)[a] + **19** (34%) |
| 3 |  **20** |  **31** (33%)[b] +  **32** (8%)[b,c] +  **33** (35%) + **29** (8%)[b] |  **45** (73%) + **44** (8%) |
| 4 |  **21** |  **34** (43%) +  **35** (18%) |  **46** (23%) + **34** (32%) + **35** (42%) |
| 5 |  **22** |  **36** (44%)[b] +  **37** (12%)[d] +  **38** (9%)[b] |  **47** (45%) + **37** (11%) + **22** (37%) |
| 6 |  **23**[e] |  **39** (69%) | **23** (>90%) |
| 7 |  **24**[e] |  **40** (46%) +  **42** (15%)[d] +  **41** (21%) | n.d.[f] |

[a] With 6 equiv of $SnCl_4$ the yield rose to 85%. [b] This compound could not be separated from one or more other products. [c] Stereochemistry not proved but follows from mechanism in Scheme I. [d] Mixture of inseparable isomers. [e] $SnCl_4$ was added at 0 °C instead of at -78 °C. [f] This experiment was not carried out.

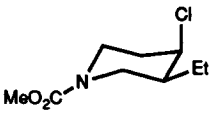
not be separated. Yields are then based on $^1$H NMR integration values. Cyclization of precursor **25** at 0 °C to room temperature furnished a 75:25 mixture of **48** and **49** in 83% yield. Precursors **26** and **27** were cyclized at -78 °C to room temperature to give in quantitative yield a mixture of **50** and **51** in ratios of 5:95 and 67:33, respectively.



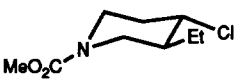

**48**




**49**




**50**



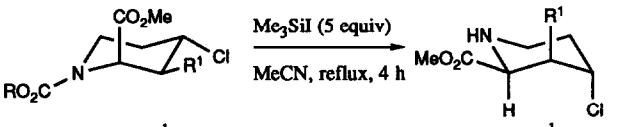

**51**

The structural and stereochemical assignments of the products is based on NMR data in most cases. Essential for the interpretation of the $^1$H NMR spectra is the knowledge that the α-amino ester function occupies an axial position in a chair-like piperidine ring. This axial orientation is imposed by the presence of the *N*-carbonyl funtion which would cause excessive allylic 1,3-strain[15] in the case of an equatorial ester function.[16] The hydrogen adjacent to the ester function usually showed two broad signals (see Table II) in a ratio between 1:1 and 2:1. This doubling of signals is the result of slow rotation on the NMR timescale in the carbamate moiety and severely hampered the interpretation of several $^1$H and $^{13}$C NMR spectra. This problem is, of course, not present in **39-42**, which showed sharp signals.

**Table II** Selected $^1$H NMR data (ppm)

| compound | N-C<u>H</u>CO$_2$R | <u>H</u>-C-Cl | <u>H</u>-C-O- | C-C<u>H</u>$_3$ |
|---|---|---|---|---|
| **28** | 4.88, 5.00 (bs) | 3.82 (tt, *J* = 12.0, 4.1 Hz) | - | - |
| **29** | 4.95, 5.10 (bs) | 4.18 (td, *J* = 11.4, 4.4 Hz) | - | - |
| **30** | 4.95, 5.10 (bs) | - | 4.97 (td, *J* = 10.8, 4.6 Hz) | - |
| **31** | obscured | 4.05 (dt, *J* = 11.8, 4.3 Hz) | - | - |
| **32** | 4.74, 4.92 (s) | - | - | - |
| **33** | 4.58, 4.75 (bs) | - | 4.75 (bs) | - |
| **34** | 4.67, 4.71 (d, *J* = 4.6 Hz) | - | - | 1.55 (s) |
| **35** | 4.73, 4.89 (d, *J* = 6.9 Hz) | - | - | 1.60 (s) |
| **36** | 4.81, 4.87 (d, *J* = 6.2 Hz) | 3.70 (obscured) | - | 1.00 (d, *J* = 6.4 Hz) |
| **37** | 4.35-4.55 (m) | 3.90-4.05 (m) | - | 1.52 (d, *J* = 6.6 Hz) |
| **38** | 4.75 (d, *J* = 3.8 Hz) | - | - | 1.59 (s) |
| **39** | 4.87 (dd, *J* = 6.5, 1.4 Hz) | 3.88 (tt, *J* = 12.2, 3.9 Hz) | - | - |
| **40** | 4.82 (d, *J* = 7.5 Hz) | - | - | 1.53 (s) |
| **41** | 4.78 (d, *J* = 6.8 Hz) | - | - | 1.63 (s) |
| **43** | 4.70, 4.79 (bs) | - | 4.10 (obscured) | - |
| **44** | 4.71, 4.87 (bs) | - | 3.93 (bs) | - |
| **45** | 4.55, 4.74 (bs) | - | 3.71 (dt, *J* = 2.9, 2.8 Hz) | - |
| **46** | 4.72, 4.89 (d, *J* = 6.6 Hz) | - | - | 1.25 (s) |
| **47** | 4.68, 4.85 (d, *J* = 6.6 Hz) | - | 3.75 (obscured) | 0.94, 0.95 (d, *J* = 6.9 Hz) |
| **48** | 5.58, 5.64 (s) | - | - | 1.34 (d, *J* = 6.9 Hz) |
| **49** | 5.57, 5.66 (s) | - | - | 1.28 (d, *J* = 7.0 Hz) |
| **50** | - | 4.41 (bq, *J* = 2.8 Hz) | - | - |
| **51** | - | 3.79 (td, *J* = 8.7, 3.9 Hz) | - | - |
| **52** | 3.83 (dd, *J* = 9.1, 3.7 Hz) | 4.43 (quintet, *J* = 4.3 Hz) | - | - |
| **53** | 4.02 (d, *J* = 3.4 Hz) | 4.46 (q, *J* = 3.8 Hz) | - | - |
| **54** | 3.67 (dd, *J* = 12.9, 3.3 Hz) | - | 3.97 (tt, *J* = 11.0, 4.4 Hz) | - |
| **55** | 3.84 (d, *J* = 3.3 Hz) | - | 4.21 (dt, *J* = 11.0, 4.7 Hz) | - |
| **56** | 3.51 (d, *J* = 9.9 Hz) | - | 3.87 (td, *J* = 9.8, 4.2 Hz) | - |

The shape of the signal of the hydrogen adjacent to the ester function was usually a broad singlet or doublet with a coupling constant of less than 8 Hz, pointing to the absence of ax-ax couplings. Its chemical shift of ca. 4.75 ppm was also a strong indication of an equatorial position. Removal of the *N*-carbomethoxy function[17] (eq 5) led via a chair-chair interconversion to an equatorial ester function in **52** and **53**. This was evident from the chemical shift of H-2 which shifted ca. 1.0 ppm upfield. Compound **52** showed an ax-ax coupling for H-2 of 9.1 Hz. In going from **28** and **29** to **52** and **53** the hydrogens adjacent to chlorine went 0.3-0.6 ppm downfield and lost their ax-ax couplings of ca. 12.0 Hz (Table II). For many compounds in Table I the splitting pattern of the $^1$H NMR signal of the hydrogen adjacent to chlorine was very diagnostic for the stereochemistry of the product.



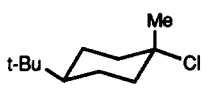
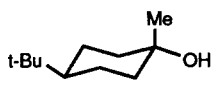
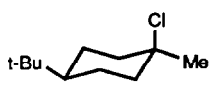

(eq 5)

**28** R = Et, $R^1$ = H
**29** R = Me, $R^1$ = Et

**52** $R^1$ = H
**53** $R^1$ = Et

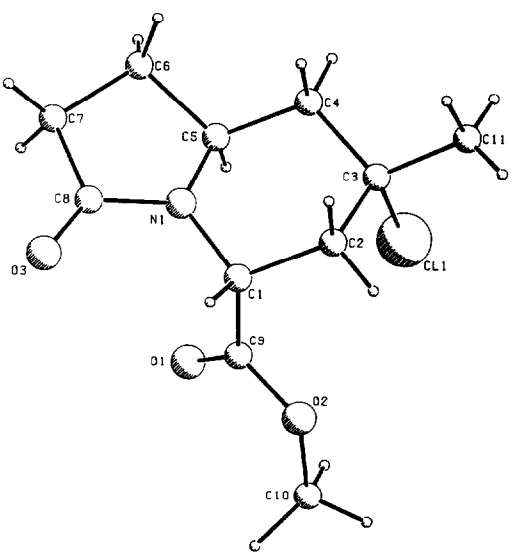
The stereochemistry of the quaternary centres in chlorides **34**, **35**, **40**, and **41** and in alcohol **46** is partly based on the $^{13}$C NMR chemical shift of the methyl carbon atoms. Literature data of *cis*- and *trans*-4-*tert*-butyl-1-chloro-1-methylcyclohexane[18] and the corresponding alcohols indicate that this chemical shift value is very diagnostic for either an axial or equatorial orientation of the methyl group (Table III). The stereochemistry of **41** was proved beyond doubt by determining the X-ray crystal structure (Figure I). Both the chlorine atom and the ester function are axially disposed, as expected from NMR data.

**Table III** $^{13}$C NMR chemical shifts of ring methyl carbons

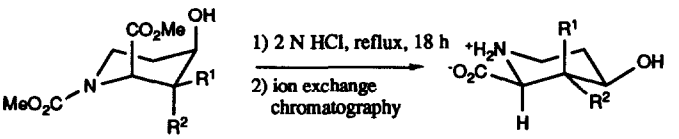
| compound | δ ($CH_3$), ppm |
|---|---|
|  | 28.1[a] |
| **34** | 28 4 |
| **40** | 25.4 |
|  | 25.3[a] |
|  | 34.2[a] |
| **35** | 33 6 |
| **41** | 33 6 |
|  | 31 5[a] |
| **46** | 30.9 |

[a] see ref 18.

**Figure I** Crystal structure of compound **41**



The stereochemistry of alcohols **43-45** was further proved by hydrolysis to the free amino acids **54-56** (eq 6). This transformation led to an upfield shift for H-2 of ca. 1.0 ppm (see Table II). The vicinal coupling constants of H-2 in **54-56** provided conclusive evidence for their structures. Furthermore, the spectral data of **54** were in agreement with those reported in the literature.[19] α-Amino acid **54** is a natural product isolated from *Acacia* species[20] and from *Calliandra pittieri*.[21]

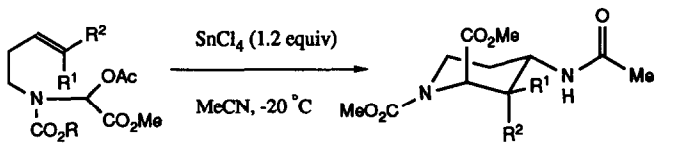



(eq 6)

**43** $R^1 = R^2 = H$
**44** $R^1$ = Et, $R^2 = H$
**45** $R^1 = H$, $R^2$ = Et

**54** $R^1 = R^2 = H$
**55** $R^1$ = Et, $R^2 = H$
**56** $R^1 = H$, $R^2$ = Et

The general features of the cyclization reactions studied here can be summarized as follows. If the reaction is commenced and quenched at -78 °C the major product is usually the *cis*-4-hydroxypipecolic acid derivative. However, if the reaction mixture is warmed up to room temperature before quenching the *trans*-4-chloropipecolic acid derivative is the preponderant product in most cases. Furthermore, we found that if the reaction was carried out with **18-20** in acetonitrile as solvent[22] the *trans*-4-(acetylamino)pipecolic acid derivatives **57-59**, respectively, were obtained in good yield and with complete stereoselectivity (eq 7).




(eq 7)

**18-20**

**57** R = Et, $R^1 = R^2 = H$
**58** R = Me, $R^1$ = Et, $R^2 = H$
**59** R = Me, $R^1 = H$, $R^2$ = Et

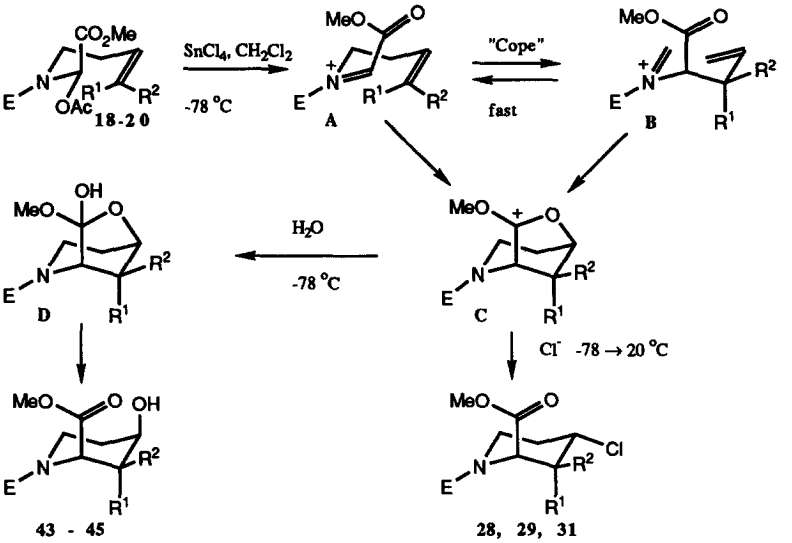
## DISCUSSION

The cyclization results (Table I) can be satisfactorily explained with the mechanistic picture of Scheme I, applicable to starting materials **18-20**. Heterolysis induced by $SnCl_4$ leads to the glycine cation **A** which is in a fast equilibrium with iminium ion **B** in a cationic aza-Cope rearrangement. Either **A** or **B** then gives **C** in a process which is characterized by a stereospecific formation of a CC and a CO bond. Dioxycarbenium ion **C** is a stable species at -78 °C. Treatment of **C** with water at -78 °C leads to the axial alcohols **43-45** via intermediate **D**. On raising the temperature, **C** starts to react with chloride via $S_N2$ substitution at C-4 to give the equatorial chlorides **28, 29** and **31**.

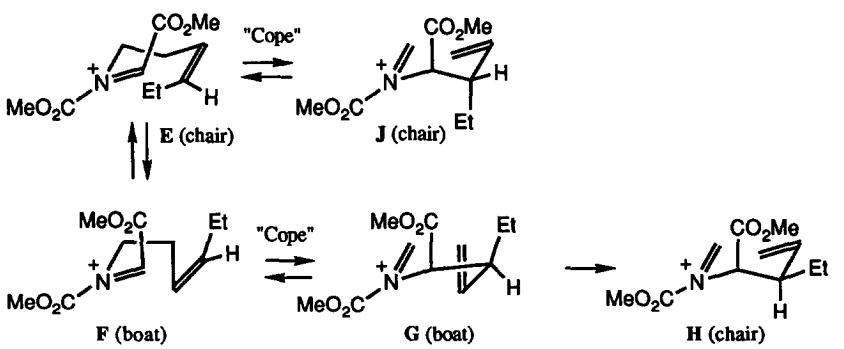
By postulating **C** as crucial intermediate, most other products of Table I can also be readily explained. In entry 2 acetate can compete with chloride as nucleophile to open up **C** to **30**. In entry 3 chloride apparently has difficulty to react with **C**, probably due to the steric hindrance caused by the axial ethyl substituent. Proton abstraction at C-5 and chloride attack at the methoxy group are side reactions leading to olefin **32** and lactone **33**, respectively. The third byproduct **29** points to some stereochemical leakage. Interestingly, this phenomenon is also found in the low temperature quench reaction. This means that species **C** is formed with some loss of stereochemistry. In the light of literature precedent, this can

best be explained by assuming that the cationic aza-Cope rearrangement takes place to some extent via a boat transition state (see Scheme II, **F** → **G**).[23] Probably, the usual rearrangement **E** → **J** via chair geometries is somewhat hampered by the presence of the (*Z*)-ethyl group. Cyclizations of precursors **21** and **24** (entries 4 and 7) proceed at least partly through tertiary carbocations, because mixtures of chlorides are produced, even at -78 °C, but **46** still must arise from a dioxycarbenium ion.

**Scheme I** (E = $CO_2R$)

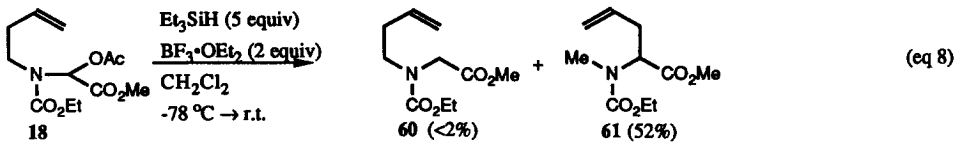


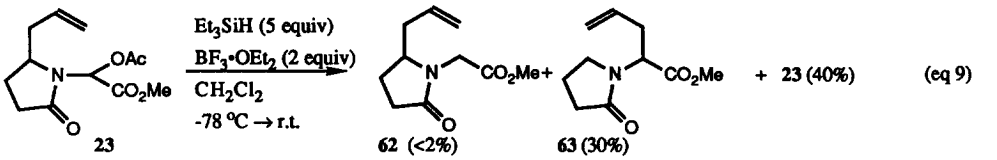

**Scheme II**

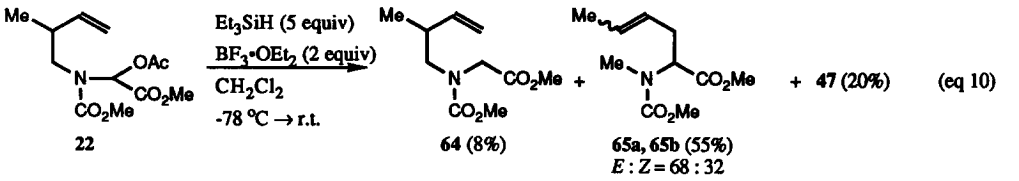



The occurrence of a cationic aza-Cope rearrangement was proved in three cases by trapping the rearranged iminium ion **B** (Scheme I) through reduction.[24,25] Best results were obtained by using triethylsilane as reducing agent in the presence of $BF_3$•$OEt_2$ as Lewis acid. Thus, when a mixture of **18** and 5 equiv of $Et_3SiH$ in $CH_2Cl_2$ was treated with $BF_3$•$OEt_2$ only the reduction product **61** of the rearranged iminium ion was isolated (eq 8), no trace of **60** being detectable. Similarly, from **23** only **63** and no **62** was isolated in addition to starting material (eq 9). Recovery of starting material in the latter case shows that heterolysis of **23** and **24** is less facile than in the acyclic cases **18-22**. This was confirmed by

treating **23** with $SnCl_4$ at -78 °C, followed by aqueous quench (entry 7, Table I) which gave back starting material. Apparently, heterolysis of **23** and **24** needs higher temperatures, but these compounds otherwise followed the mechanistic picture of Scheme I.

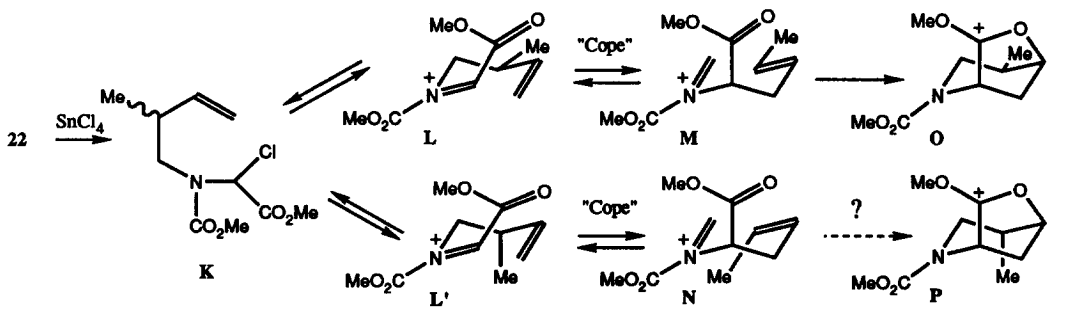


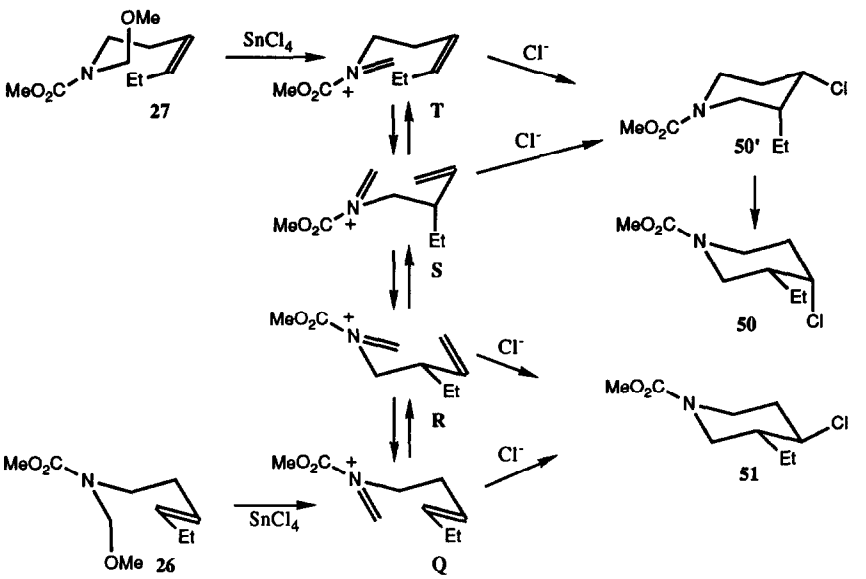

Reductive trapping of the iminium ions derived from **22** (entry 5, Table I) provided interesting additional information (eq 10). The formation of **47** shows that the reduction is not so fast that cyclization is completely prevented. Furthermore, reduction products **64** and **65** from, respectively, the original (**L**) and the rearranged iminium ions (**M**, **N**) were obtained (see Scheme III). Reduction product **65** showed an *E*/*Z* ratio of 68:32, indicating that rearrangement occurred to a considerable extent from the iminium ion with an axial methyl group (**L'**). The main products of cyclization (**36**, **47**) originate from dioxycarbenium ion **O**. Enecarbamate **38** can also arise from **O** by proton abstraction and isomerization (cf. **32** and **42**). The origin of **37** is not clear. A possible explanation is as follows. Due to steric hindrance by the axial or (*Z*)-methyl group in **L'** or **N**, cyclization to dioxycarbenium ion **P** is so slow, that, besides going via **K** to **L** and **M**, iminium ion **N** cyclizes in a 5-*exo* fashion to chloride **37**.

**Scheme III**

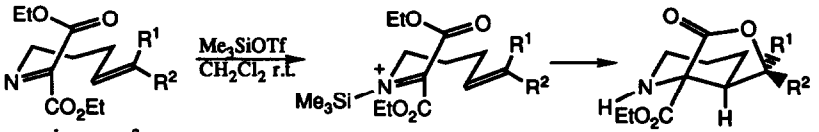


Three types of cyclization precursors which are fundamentally different from the previous ones are **25**-**27**. In the case of the phenyl nucleophile (**25**), the cationic aza-Cope rearrangement will probably not compete with cyclization (cf. **4** → **5**).[6] The result with respect to the methyl stereochemistry is in agreement with literature precedent.[26] Iminium ions derived from **26** and **27**, and lacking the C-ester function are clearly subject to aza-Cope equilibration (Scheme IV). The (*E*)-olefin **26** gives cation **Q** which is in equilibrium with **R**. Both ions cyclize to **51** after attack of chloride on the intermediate π-complexes.[27] That the cyclization of **26** is not completely stereospecific is the result of chair-chair interconversion of **R** to **S**. Species **S** is in "Cope"-equilibrium with (*Z*)-alkene **T**. Both **S** and **T** cyclize after chloride attack to **50'** which interconverts to the more stable conformer **50**. When starting from (*Z*)-alkene **27** the same ionic intermediates are formed. The eventual ratio of products **50** and **51** formed is the result of a subtle competition between rates of cyclization and ion isomerization. The fact that the equilibrium between **R** and **S** favours **R** renders cyclization of **27** less stereospecific than cyclization of **26**.[28]

**Scheme IV**




Returning to the the mechanistic picture of Scheme I, the key step is the low temperature (-78 °C) formation of **C** from **A** and/or **B**. It was independently proved that **C** does not arise from a cyclized secondary chloride, because treatment of **29** at -78 °C for 6 h with 6 equiv of $SnCl_4$, followed by aqueous quench, resulted in complete recovery of **29**. Species **C** thus, presumably, results from initial formation of a π-complex through interaction of the iminium cation with the olefin, followed by front side attack of the carbonyl oxygen on this π-complex.[27] The overall result is a cationic *syn*-addition which is quite unusual.[29] A recent paper of Tietze and coworkers reports a similar process (eq 11).[30] Treatment of imine **66** with $Me_3SiOTf$ leads to iminium ion **67**, which cyclizes with participation of the pseudo-axial ester substituent to lactone **68**. The stereochemistry of the olefin is completely retained in this process.




**66a** $R^1$ = Me, $R^2$ = H
**66b** $R^1$ = H, $R^2$ = Me

**67a, b**

**68a, b**

(eq 11)

In conclusion, we have shown that the nature of the products obtained from $SnCl_4$ induced π-cyclization of *N*-(3-alkenyl)glycine cation equivalents depends on manifold subtle factors such as the presence and nature of substituents on the alkene and on the chain connecting alkene and nitrogen, the temperature of aqueous quench, and the solvent. Our mechanistic picture provides a satisfactory explanation for the influences of these reaction variables. Pivotal intermediate is the bicyclic dioxycarbenium ion for which we hope to report spectroscopic evidence in the near future. Judicious choice of substrates and reaction conditions should now make possible the directed synthesis of several pipecolic acid derivatives.

## EXPERIMENTAL

**General information** Infrared (IR) spectra were obtained from $CHCl_3$ solutions using a Perkin Elmer 298 or a Perkin Elmer 1310 spectrophotometer and are reported in $cm^{-1}$. Proton nuclear magnetic resonance ($^1H$ NMR) spectra were determined in $CDCl_3$ (unless indicated otherwise) as solvent using a Varian XL-100 (100 MHz), a Bruker AC 200 (200 MHz) or a Bruker WM 250 (250 MHz) instrument. The latter two machines were also used for the $^{13}C$ NMR (ATP) spectra (50.3 MHz and 62.9 MHz) in $CDCl_3$ solution (unless indicated otherwise). Chemical shifts are given in ppm downfield from tetramethylsilane. Accurate mass measurements were carried out using a Varian MAT 711 or a VG Micromass ZAB-2HF instrument. $R_f$ values were obtained by using thin-layer chromatography (TLC) on silica gel-coated plastic sheets (Merck silica gel 60 $F_{254}$) with the indicated solvent (mixture). Chromatographic purification refers to flash chromatography using the same solvent as for TLC and Merck silica gel 60 (230-400 mesh) or Janssen Chimica silica gel (0.030-0.075 mm). Melting and boiling points are uncorrected. CH2Cl2 was distilled from $P_2O_5$ and kept under an atmosphere of dry nitrogen. $SnCl_4$ was distilled and stored under a dry nitrogen atmosphere as a 1.2 M solution in $CH_2Cl_2$. Dry THF was distilled under an atmosphere of dry nitrogen from sodium benzophenone ketyl prior to use. Dry DMF was distilled from $CaH_2$ and stored under an atmosphere of dry nitrogen. Reactions under a dry nitrogen atmosphere were performed in flame-dried glassware. Standard syringe techniques were applied for transfer of Lewis acids, dry solvents and reagents.

**General procedure A.** (eq 3,.4) *Reaction of allylsilanes with methyl N-(acetoxymethyl)carbamate or 5-ethoxy-2-pyrrolidinone.* Under a nitrogen atmosphere, the allylsilane (1.2 equiv) and $BF_3{\cdot}OEt_2$ (1.5-2.0 equiv) were successively added to a 0.5 M solution of methyl *N*-(acetoxymethyl)carbamate[32] or 5-ethoxy-2-pyrrolidinone[33] in $CH_2Cl_2$ at 0 °C. After 15 min the reaction mixture was allowed to warm up to room temperature and stirred for 18 h. The reaction mixture was poured into water and extracted (3 ×) with $CHCl_3$. The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed.

**General procedure B.** (eq 2) *Mesylation of alcohols.* At 0 °C, 1.2 equiv of $Et_3N$ was added to a stirred 1 M solution of the alcohol in $CH_2Cl_2$ under a nitrogen atmosphere. After 15 min, 1.1 equiv of mesyl chloride was added dropwise and the reaction mixture allowed to warm up to room temperature. After 30 min the reaction mixture was poured out into water and extracted with $CH_2Cl_2$ (3 ×). The combined organic extracts were dried ($K_2CO_3$) and concentrated *in vacuo*. The crude mesylate was used without purification.

**General procedure C.** (eq 2) *Azide synthesis.* Under a nitrogen atmosphere, $NaN_3$ (ca. 8 equiv) was added to a 0.4 M solution of the mesylate in DMF. The reaction mixture was heated at 110 °C for 1.75 h. After the mixture was cooled to room temperature it was poured into water (ca. 4 × the DMF volume). After extraction with pentane/ether (1:1) (4 ×), the combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude azide was used in the next step.

**General procedure D.** (eq 2) *Amine synthesis.* Triphenylphosphine (1.05 equiv) was added to a 0.3 M solution of the azide in

THF and stirred for 1.5 h at room temperature. Then water (3 equiv) was added and the reaction mixture was stirred for 18 h at room temperature. The solvent was removed by distillation and the residue was taken up in little $Et_2O$. The resulting mixture was first heated and if necessary diluted with ether until a homogeneous solution was obtained, then cooled to allow the triphenylphosphine oxide to crystallize. The triphenylphosphine oxide was filtered off and washed with $Et_2O$. The combined ether fractions were extracted (3 ×) with 100 mL of 10% aq $NaHSO_4$. The combined water fractions were washed with 20 mL of $Et_2O$ (2 ×) and then basefied with 150 mL of 2 N aq NaOH. After extraction with 40 mL of $Et_2O$ (5 ×), the combined organic layers were dried ($MgSO_4$). The solvent was removed by distillation, and the crude product was distilled under reduced pressure.

**General procedure E.** (eq 2) *Methoxycarbonylation of amines.* Under a nitrogen atmosphere, $Et_3N$ (1.1 equiv) was added to a 0.5 M solution of the amine in $CH_2Cl_2$. At 0 °C, methyl chloroformate (1.1 equiv) was added dropwise. After 10 min the reaction mixture was allowed to warm up to room temperature and stirred for 18 h. The reaction mixture was poured into water and extracted with $CH_2Cl_2$ (3 ×). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. In most cases, the crude carbamate was pure enough for futher use. It can be purified by chromatography.

**General procedure F.** (eq 1) *Reaction of carbamates and pyrrolidinones with methyl glyoxylate hydrate.* Powdered dimethyl L-tartrate (Aldrich, 7.1 g, 39.6 mmol) was suspended in 80 mL of ether. Over a 1 h period, powdered periodic acid (Merck, 9.1 g, 39.9 mmol) was added in five portions to the solution. After the last portion, the reaction mixture was stirred for 0.5 h till a white powder had precipitated and the solution was clear. The solid was filtered off and the ether was removed *in vacuo*. The crude methyl glyoxylate hydrate was distilled (bulb to bulb, 150 °C/15 mmHg) to give methyl glyoxylate hydrate (5.5 g, 62.5 mmol, 79%) as a light brown oil. Methyl glyoxylate hydrate was used immediately for reactions with carbamates and pyrrolidinones.
Methyl glyoxylate hydrate (ca. 10 equiv) was added to a 0.5 M solution of the carbamate or pyrrolidinone in benzene. The reaction mixture was refluxed for 3 h in a Dean-Stark apparatus and stirred for 18 h at room temperature. The reaction mixture was concentrated *in vacuo*, taken up in ether/pentane (1:1), and washed (3 ×) with aq NaCl. The combined aq NaCl fractions were washed with ether. The combined ether fractions were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed.

**General procedure G.** (eq 1) *Acetylation of alcohols.* Under a dry nitrogen atmosphere, DMAP (ca. 0.1 equiv) was added to a 0.5 M solution of the α-hydroxyester in pyridine. At 0 °C, acetic anhydride (1.2-1.5 equiv) was added dropwise. After 10 min, the reaction mixture was allowed to warm up to room temperature and stirred for 18 h. The reaction mixture was concentrated *in vacuo*, treated with benzene, and concentrated *in vacuo* (this procedure was repeated 3 times). The residue was chromatographed.

**Acetoxy[*N*-(3-butenyl)-*N*-(ethoxycarbonyl)amino]acetic acid methyl ester (18).** Potassium carbonate (15.5 g, 112 mmol) and paraformaldehyde (1.80 g, 60 mmol) were added to a solution of ethyl carbamate (5.00 g, 56.2 mmol) in 125 mL of benzene. The mixture was heated for 3.5 h at 70-75 °C and then cooled to room temperature. The $K_2CO_3$ was filtered off and the filtrate concentrated *in vacuo* to give crude ethyl *N*-(hydroxymethyl)carbamate (6.80 g, 100%) as a colourless oil. $^1$H NMR (200 MHz) 1.23 (t, $J$ = 7 Hz, 3 H, $CH_3$), 4.13 (q, $J$ = 7 Hz, 2 H, $OCH_2CH_3$), 4.69 (s, 2 H, $CH_2OH$). This crude product (6.80 g) was dissolved in 50 mL of MeOH and 25 drops of concentrated sulfuric acid were added. The reaction mixture was stirred for 2 h and then poured out into aq saturated $NaHCO_3$. After extraction with 100 mL of $CH_2Cl_2$ (3 ×), the combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give crude ethyl *N*-(methoxymethyl)carbamate (7.50 g, 56.3 mmol, 100%) as a colourless oil. $^1$H NMR (200 MHz) 1.26 (t, $J$ = 7 Hz, 3 H, $OCH_2CH_3$), 3.33 (s, 3 H, $OCH_3$), 4.18 (q, $J$ = 7 Hz, 2 H, $OCH_2CH_3$), 4.61 (bd, $J$ = 7 Hz, 2 H, $MeOCH_2N$), 5.43 (bs, 1 H, NH). Allyltrimethylsilane (0.45 mL, 2.83 mmol) was added to a solution of ethyl *N*-(methoxymethyl)carbamate (117 mg, 0.880 mmol) in 8 mL of $CH_2Cl_2$ under a nitrogen atmosphere. At 0 °C, $BF_3$•$OEt_2$ (0.25 mL, 20.3 mmol) was added. After 15 min, the reaction mixture was allowed to warm up to room temperature and stirred for 18 h. The reaction mixture was poured out into water and extracted with $CH_2Cl_2$ (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed to give ethyl *N*-(3-butenyl)carbamate (90 mg, 0.643 mmol, 72%) as a light yellow oil. $R_f$ 0.80 (EtOAc). IR 3450 (NH), 1705 (NC=O). $^1$H NMR (200 MHz) 1.24 (t, $J$ = 7.1 Hz, 3 H, $CH_3$), 2.25 (q, $J$ = 6.7 Hz, 2 H, $CH_2CH$=), 3.15-3.35 (m, 2 H, $CH_2N$), 4.11 (q, $J$ = 7.1 Hz, 2 H, $OCH_2$), 4.66 (bs, 1 H, NH), 4.95-5.20 (m, 2 H, =$CH_2$), 5.60-5.90 (m, 1 H, -CH=). According to procedure F, ethyl *N*-(3-butenyl)carbamate (700 mg, 4.90 mmol) was treated with methyl glyoxylate hydrate (6.8 g, 77.3 mmol) in 80 mL of benzene to give the glyoxylate adduct (906 mg, 3.92 mmol, 80%) as a colourless oil. $R_f$ 0.37 (EtOAc/hexanes: 1/2). IR 3530 (OH), 1750 (C=O), 1690 (NC=O). $^1$H NMR (200 MHz) 1.25 (t, $J$ = 7.1 Hz, 3 H, $OCH_2CH_3$), 1.60 (bs, 1 H, OH), 2.34 (q, $J$ = 7.3 Hz, 2 H, =$CHCH_2$), 3.37 (t, $J$ = 7.3 Hz, 2 H, $CH_2N$), 3.80 (s, 3 H, $OCH_3$), 4.05-

4.25 (m, 2 H, $OCH_2$), 5.00-5.15 (m, 2 H, $=CH_2$), 5.19 (bs, 1 H, NCHO), 5.65-5.90 (m, 1 H, -CH=). According to procedure G, the glyoxylate adduct (733 mg, 3.46 mmol) was treated with DMAP (40 mg, 0.33 mmol) and acetic anhydride (0.40 mL, 4.24 mmol) in 5 mL of pyridine to give **18** (880 mg, 3.22 mmol, 93%) as a colourless oil. $R_f$ 0.54 (EtOAc/hexanes: 1/2). IR 1745 and 1705 (3 x C=O). $^1$H NMR (200 MHz) 1.20-1.30 (m, 3 H, $OCH_2CH_3$), 2.16 (s, 3 H, $O=CCH_3$), 2.25-2.45 (m, 2 H, $=CHCH_2$), 3.15-3.35 (m, 1 H, CHN), 3.40-3.60 (m, 1 H, CHN), 3.78 (s, 3 H, $OCH_3$), 4.19 (q, $J$ = 7.1 Hz, 2 H, $OCH_2$), 5.00-5.10 (m, 2 H, $=CH_2$), 5.65-5.85 (m, 1 H, -CH=), 6.49 (s, 1 H, NCHO).

**Acetoxy[*N*-(3-(*E*)-hexenyl)-*N*-(methoxycarbonyl)amino]acetic acid methyl ester (19).** According to procedure B, (*E*)-3-hexen-1-ol (Aldrich, 4.15 g, 41.4 mmol) was treated with $Et_3N$ (7.00 mL, 50.2 mmol) and mesyl chloride (3.60 mL, 46.6 mmol) in 40 mL of $CH_2Cl_2$ to give the mesylate (7.05 g, 39.6 mmol, 96%) as a light brown oil. IR 1350 and 1175 ($SO_3$). $^1$H NMR (200 MHz) 0.96 (t, $J$ = 7.5 Hz, 3 H, $CH_3$), 2.01 (dq, $J$ = 7.5, 7.5 Hz, 2 H, $CH_3CH_2$), 2.42 (q, $J$ = 6.5 Hz, 2 H, $CH_2CH_2OMs$), 2.98 (s, 3 H, $SO_2CH_3$), 4.20 (t, $J$ = 6.5 Hz, 2 H, $CH_2O$), 5.25-5.45 (m, 1 H, -CH=), 5.50-5.70 (m, 1 H, -CH=). According to procedure C, this mesylate (7.00 g, 39.3 mmol) was treated with $NaN_3$ (20.0 g, 308 mmol) in 100 mL of DMF to give 1-azido-3-(*E*)-hexene (4.17 g, 33.4 mmol, 85%) as a light yellow oil. IR 2090 ($N_3$). $^1$H NMR (200 MHz) 0.98 (t, $J$ = 7.5 Hz, 3 H, $CH_3$), 2.03 (dq, $J$ = 7.5, 7.5 Hz, 2 H, $CH_3CH_2$), 2.29 (q, $J$ = 7.0 Hz, 2 H, $CH_2CH_2N$), 3.26 (t, $J$ = 7.0 Hz, 2 H, $CH_2N_3$), 5.30-5.45 (m, 1 H, -CH=), 5.50-5.70 (m, 1 H, -CH=). According to procedure D, 1-azido-3-(*E*)-hexene (4.15 g, 33.4 mmol) was treated with triphenylphosphine (9.60 g, 36.7 mmol) and water (1.8 mL, 100 mmol) in 250 mL of THF to give 1-amino-3-(*E*)-hexene (1.12 g, 11.3 mmol, 34%) as a colourless liquid (bulb to bulb, bp 50-70 °C/30 mmHg). IR 3480 (s) and 3180 (b) ($NH_2$). $^1$H NMR (200 MHz) 0.96 (t, $J$ = 7.5 Hz, 3 H, $CH_3$), 1.35 (s, 2 H, $NH_2$), 1.90-2.20 (m, 4 H), 2.69 (t, $J$ = 6.6 Hz, 2 H, $CH_2N$), 5.20-5.40 (m, 1 H, -CH=), 5.40-5.60 (m, 1 H, -CH=). According to procedure E, 1-amino-3-(*E*)-hexene (1.10 g, 11.1 mmol) was treated with $Et_3N$ (1.75 mL, 12.6 mmol) and methyl chloroformate (0.95 mL, 12.3 mmol) in 20 mL of $CH_2Cl_2$ to give methyl *N*-(3-(*E*)-hexenyl)carbamate (1.75 g, 11.1 mmol, 88%) as a yellow liquid. IR 3450 (NH), 1715 (NC=O). $^1$H NMR (200 MHz) 0.95 (t, $J$ = 7.5 Hz, 3 H, $CH_2CH_3$), 1.99 (dq, $J$ = 7.0, 7.0 Hz, $CH_2CH_3$), 2.16 (q, $J$ = 7.0 Hz, 2 H, $CH_2CH_2N$), 3.15-3.25 (m, 2 H, $CH_2N$), 3.64 (s, 3 H, $OCH_3$), 4.68 (bs, 1 H, NH), 5.20-5.40 (m, 1 H, -CH=), 5.45-5.60 (m, 1 H, -CH=). According to procedure F, methyl *N*-(3-(*E*)-hexenyl)carbamate (951 mg, 6.06 mmol) was treated with methyl glyoxylate hydrate (5.0 g, 56.8 mmol) in 120 mL of benzene to give [*N*-(3-(*E*)-hexenyl)-*N*-(methoxycarbonyl)amino]hydroxyacetic acid methyl ester (1.35 g, 5.52 mmol, 91%) as a colourless oil. $R_f$ 0.55 (EtOAc/hexanes: 1/1). IR 3530 (OH), 1750 (C=O), 1700 (NC=O). $^1$H NMR (250 MHz) 0.93 (t, $J$ = 7.4 Hz, 3 H, $CH_2CH_3$), 1.97 (quintet, $J$ = 7.1 Hz, 2 H, $CH_2CH_3$), 2.24 (q, $J$ = 7.1 Hz, 2 H, $CH_2CH_2N$), 3.15-3.40 (m, 2 H, $CH_2N$), 3.69 (s, 3 H, $OCH_3$), 3.78 (s, 3 H, $OCH_3$), 5.19 (bs, 1 H, NCHO), 5.15-5.40 (m, 1 H) and 5.45-5.60 (m, 1 H, CH=CH). According to procedure G, the gloxylate adduct (1.073 g, 4.38 mmol) was treated with DMAP (50 mg, 0.41 mmol) and acetic anhydride (0.50 mL, 5.30 mmol) in 10 mL of pyridine to give **19** (1.099 g, 3.83 mmol, 87%) as a colourless oil. $R_f$ 0.53 (EtOAc/hexanes: 1/2). IR 1710 and 1745 (3 x C=O). $^1$H NMR (250 MHz) 0.93 (t, $J$ = 7.4 Hz, 3 H, $CH_2CH_3$), 1.97 (quintet, $J$ = 7.1 Hz, 2 H, $CH_2CH_3$), 2.14 (s, 3 H, $O=CCH_3$), 2.10-2.35 (m, 2 H, $CH_2CH_2N$), 3.10-3.25 (m, 1 H, CHN), 3.30-3.45 (m, 1 H, CHN), 3.72 (s, 3 H, $OCH_3$), 3.76 (s, 3 H, $OCH_3$), 5.20-5.35 (m, 1 H, -CH=), 5.45-5.60 (m, 1 H, -CH=), 6.47 (bs, 1 H, NCHO).

**Acetoxy[*N*-(3-(*Z*)-hexenyl)-*N*-(methoxycarbonyl)amino]acetic acid methyl ester (20).** According to procedure B, (*Z*)-3-hexen-1-ol (Aldrich, 10.24 g, 0.102 mol) was treated with $Et_3N$ (16.0 mL, 0.115 mol) and mesyl chloride (8.75 mL, 0.113 mmol) in 110 mL of $CH_2Cl_2$ to give the mesylate (17.6 g, 98.9 mmol, 97%) as a light brown oil. IR 1355 and 1175 ($SO_3$). $^1$H NMR (200 MHz) 0.96 (t, $J$ = 7.5 Hz, 3 H, $CH_2CH_3$), 2.05 (dq, $J$ = 7.5, 7.5 Hz, 2 H, $CH_2CH_3$), 2.46 (q, $J$ = 7.0 Hz, 2 H, $CH_2CH_2SO_3$), 2.99 (s, 3 H, $SO_2CH_3$), 4.19 (t, $J$ = 7.0 Hz, 2 H, CHO), 5.20-5.35 (m, 1 H, -CH=), 5.50-5.65 (m, 1 H, -CH=). According to procedure C, this mesylate (17.6 g, 98.9 mmol) was treated with $NaN_3$ (50.0 g, 770 mmol) in 250 mL of DMF to give 1-azido-3-(*Z*)-hexene (12.0 g, 96.0 mmol, 97%) as a yellow liquid. IR 2100 ($N_3$). $^1$H NMR (200 MHz) 0.99 (t, $J$ = 7.5 Hz, 3 H, $CH_3$), 2.08 (quintet, $J$ = 7.5 Hz, 2 H, $CH_2CH_3$), 2.35 (q, $J$ = 7.0 Hz, 2 H, $CH_2CH_2N_3$), 3.27 (t, $J$ = 7.0 Hz, 2 H, $CH_2N_3$), 5.20-5.40 (m, 1 H, -CH=), 5.45-5.65 (m, 1 H, -CH=). According to procedure D, 1-azido-3-(*Z*)-hexene (12.0 g, 96.0 mol) was treated with triphenylphosphine (26.0 g, 99.2 mmol) and water (5.2 mL, 289 mmol) in 250 mL of THF to give 1-amino-3-(*Z*)-hexene (6.15 g, 62.1 mmol, 64%) as a colourless liquid (bp 58-65 °C/100 mmHg). IR 3480(s) and 3180(b) ($NH_2$). $^1$H NMR (200 MHz) 0.94 (t, $J$ = 7.5 Hz, 3 H, $CH_3$), 1.38 (s, 2 H, $NH_2$), 1.95-2.25 (m, 4 H), 2.69 (t, $J$ = 6.7 Hz, 2 H, $CH_2N$), 5.20-5.35 (m, 1 H, -CH=), 5.35-5.50 (m, 1 H, -CH=). According to procedure E, 1-amino-3-(*Z*)-hexene (6.10 g, 61.6 mmol) was treated with $Et_3N$ (9.50 mL, 68.2 mmol) and methyl chloroformate (5.30 mL, 68.6

mmol) in 125 mL of $CH_2Cl_2$ to give methyl *N*-(3-(*Z*)-hexenyl)carbamate (8.96 g, 57.1 mmol, 93%) as a light yellow oil. IR 3460 (NH), 1715 (NC=O). $^1$H NMR (200 MHz) 0.93 (t, $J$ = 7.5 Hz, 3 H, $CH_2CH_3$), 2.02 (quintet, $J$ = 7.3 Hz, 2 H, $CH_2CH_3$), 2.21 (q, $J$ = 7.0 Hz, 2 H, $CH_2CH_2N$), 3.17 (bq, $J$ = 6.4 Hz, 2 H, $CH_2N$), 3.63 (s, 3 H, $OCH_3$), 4.75 (bs, 1 H, NH), 5.15-5.30 (m, 1 H, -CH=), 5.40-5.55 (m, 1 H, -CH=). According to procedure F, methyl *N*-(3-(*Z*)-hexenyl)carbamate (750 mg, 4.78 mmol) was treated with methyl glyoxylate hydrate (5.5 g, 62.5 mmol) in 80 mL of benzene to give [*N*-(3-(*Z*)-hexenyl)-*N*-(methoxycarbonyl)amino]hydroxyacetic acid methyl ester (957 mg, 3.91 mmol, 82%) as a colourless oil. $R_f$ 0.50 (EtOAc/hexanes:1/1). IR 3530 (OH), 1750 (C=O), 1700 (NC=O) $^1$H NMR (200 MHz) 0.96 (t, $J$ = 7.5 Hz, 3 H, $CH_2CH_3$), 2.06 (quintet, $J$ = 7.3 Hz, 2 H, $CH_2CH_3$), 2.34 (q, $J$ = 7.5 Hz, 2 H, $CH_2CH_2N$), 3.20-3.35 (m, 2 H, $CH_2N$), 3.73 (s, 3 H, $OCH_3$), 3.82 (s, 3 H, $OCH_3$), 5.20-5.55 (m, 3 H, CH=CH and NCHO). According to procedure G, the methyl glyoxylate adduct (933 mg, 3.81 mmol) was treated with DMAP (60 mg, 0.49 mmol) and acetic anhydride (0.45 mL, 4.77 mmol) in 5 mL of pyridine to give **20** (1.039 g, 3.62 mmol, 95%) as a colourless oil. $R_f$ 0.57 (EtOAc/hexanes: 1/2). IR 1745 and 1715 (3 x C=O). $^1$H NMR (200 MHz) 0.95 (t, $J$ = 7.5 Hz, 3 H, $CH_2CH_3$), 1.95-2.10 (m, 2 H, $CH_2CH_3$), 2.15 (s, 3 H, C=$OCH_3$), 2.20-2.40 (m, 2 H, $CH_2CH_2N$), 3.05-3.25 (m, 1 H, CHN), 3.30-3.50 (m, 1 H, CHN), 3.75 (s, 3 H, $OCH_3$), 3.77 (s, 3 H, $OCH_3$), 5.20-5.30 (m, 1 H, -CH=), 5.40-5.50 (m, 1 H, -CH=), 6.52 (s, 1 H, NCHO).

**Acetoxy[*N*-(3-methyl-3-butenyl)-*N*-(methoxycarbonyl)amino]acetic acid methyl ester (21).** According to procedure A, methyl *N*-(acetoxymethyl)carbamate[32] (1.458 g, 9.919 mmol) was treated with methallyltrimethylsilane[14] (2.05 g, 15.6 mmol) and $BF_3$•$OEt_2$ (1.90 mL, 15.5 mmol) to give methyl *N*-(3-methyl-3-butenyl)carbamate (0.978 g, 6.84 mmol, 69%) as a yellow oil. $R_f$ 0.60 (EtOAc/hexanes: 1/2). IR 3450 (NH) 1710 (NC=O). $^1$H NMR (200 MHz) 1.73 (s, 3 H, $CH_3$), 2.21 (t, $J$ = 6.7 Hz, 2 H, $CH_2C$=), 3.30 (q, $J$ = 6.6 Hz, 2 H, $NCH_2$), 3.66 (s, 3 H, $OCH_3$), 4.68 (bs, 1 H, NH), 4.73 (bs, 1 H, =CH), 4.82 (bs, 1 H, =CH). According to procedure F, methyl *N*-(3-methyl-3-butenyl)carbamate (979.1 mg, 6.85 mmol) was treated with methyl glyoxylate hydrate (5.3 g, 60.3 mmol) in 90 mL of benzene to give hydroxy[*N*-(3-methyl-3-butenyl)-*N*-(methoxycarbonyl)amino]acetic acid dimethyl ester (1.328 g, 4.86 mmol, 71%) as a colourless oil. $R_f$ 0.42 (EtOAc/hexanes: 1/2). IR 3520 (OH), 1750 (C=O), 1700 (NC=O). $^1$H NMR (250 MHz) 1.70 (s, 3 H, $CH_3$), 2.15-2.40 (m, 2 H, $CH_2C$=), 3.36 (td, $J$ = 8.3, 1.7 Hz, 2 H, $NCH_2$), 3.68 (s, 3 H, $OCH_3$), 3.76 (s, 3 H, $OCH_3$), 4.20 (bs, 1 H, OH), 4.66 (s, 1 H, =CH), 4.73 (s, 1 H, =CH), 5.25 (bs, 1 H, NCHO). According to procedure G, the methyl glyoxylate adduct (248.0 mg, 1.074 mmol) was treated with acetic anhydride (0.15 mL, 1.6 mmol) and DMAP (6 mg, 0.05 mmol) in 6 mL of pyridine to give **21** (280 mg, 1.03 mmol, 96%) as a colourless oil. $R_f$ 0.52 (EtOAc/hexanes: 1/2). IR 1745 and 1715 (3 × C=O). $^1$H NMR (200 MHz) 1.71 (s, 3 H, $CH_3$), 2.13 (s, 3 H, C=$OCH_3$), 2.10-2.40 (m, 2 H, $CH_2C$=), 3.20-3.35 (m, 1 H, CHN), 3.40-3.60 (m, 1 H, CHN), 3.72 (s, 3 H, $OCH_3$), 3.76 (s, 3 H, $OCH_3$), 4.66 (s, 1 H, =CH), 4.74 (s, 1 H, =CH), 6.49 (bs, 1 H, NCHO).

**Acetoxy[*N*-(2-methyl-3-butenyl)-*N*-(methoxycarbonyl)amino]acetic acid methyl ester (22).** According to procedure A, methyl *N*-(acetoxymethyl)carbamate[32] (1.089 g, 7.410 mmol) was treated with crotyltrimethylsilane[14] (1.135 g, 8.870 mmol) and $BF_3$•$OEt_2$ (1.80 mL, 14.6 mmol) to give methyl *N*-(2-methyl-3-butenyl)carbamate (0.9042 g, 6.323 mmol, 85%) as a colourless oil. $R_f$ 0.54 (EtOAc/hexanes: 1/2). IR 3460 (NH), 1715 (NC=O). $^1$H NMR (200 MHz) 0.99 (d, $J$ = 6.8 Hz, 3 H, $CH_3$), 2.30 (septet, $J$ = 6.9 Hz, 1 H, CHMe), 2.90-3.05 (m, 1 H, CHN), 3.10-3.25 (m, 1 H, CHN), 3.63 (s, 3 H, $OCH_3$), 4.77 (bs, 1 H, NH), 4.95-5.10 (m, 2 H, $=CH_2$), 5.55-5.75 (m, 1 H, -CH=). According to procedure F, *N*-(2-methyl-3-butenyl)carbamate (878.7 mg, 6.145 mmol) was treated with methyl glyoxylate hydrate (5.7 g, 64.8 mmol) in 90 mL of benzene to give hydroxy[*N*-(2-methyl-3-butenyl)-*N*-(methoxycarbonyl)amino]acetic acid dimethyl ester (1.120 g, 4.847 mmol, 79%) as a colourless oil. $R_f$ 0.38 (EtOAc/hexanes: 1/2). IR 3515 (OH), 1750 (C=O), 1700 (NC=O). $^1$H NMR (200 MHz, mixture of diastereoisomers) 1.00 (d, $J$ = 6.8 Hz, 3 H, $CH_3$), 2.40-2.65 (m, 1 H, CHMe), 3.10-3.45 (m, 2 H, $CH_2$), 3.68 (s, 3 H, $OCH_3$), 3.78 (S, 3 H, $OCH_3$), 4.20 (bs, 1 H, OH), 4.90-5.20 (m, 3 H, $=CH_2$ + NCHO), 5.60-5.85 (m, 1 H, -CH=). According to procedure G, the methyl glyoxylate adduct (725.8 mg, 3.142 mmol) was treated with acetic anhydride (0.36 mL, 3.8 mmol) and DMAP (20 mg, 0.16 mmol) in 15 mL of pyridine to give **22** (820.9 mg, 3.007 mmol, 96%) as a colourless oil. $R_f$ 0.60 (EtOAc/hexanes: 1/2). IR 1740 and 1710 (3 × C=O). $^1$H NMR (200 MHz, mixture of diastereoisomers) 0.96 (d, $J$ = 6.7 Hz) and 0.99 (d, $J$ = 6.7 Hz, 3 H, $CH_3CH$), 2.14 (s, 3 H, C=$OCH_3$), 2.40-2.60 (m, 1 H, $CH_3CH$), 3.00-3.20 (m, 1 H, CHN), 3.25-3.50 (m, 1 H, CHN), 3.71 (s, 3 H, $OCH_3$), 3.75 (s , 3 H, $OCH_3$), 4.90-5.10 (m, 2 H, $=CH_2$), 5.50-5.80 (m, 1 H, -CH=), 6.37 (bs, 1 H, NCHO).

**α-Acetoxy-2-oxo-5-(2-propenyl)-1-pyrrolidineacetic acid methyl ester (23).** According to procedure A, 5-ethoxy-2-pyrrolidinone[33] (1.28 g, 9 92 mmol) was treated with allyltrimethylsilane (1.90 mL, 12.0 mmol) and $BF_3$•$OEt_2$ (1.35 mL, 11.0

mmol) in 30 mL of $CH_2Cl_2$ to give 5-(2-propenyl)-2-pyrrolidinone (1.09 g, 8.72 mmol, 88%) as a colourless oil. $R_f$ 0.35 (EtOAc/hexanes: 1/4). IR 3430 and 3220 (NH), 1680 (NC=O). $^1$H NMR (200 MHz) 1.65-1.85 (m, 1 H), 2.10-2.50 (m, 5 H), 3.70 (q, $J$ = 6.3 Hz, 1 H, NCH), 5.00-5.20 (m, 2 H, $=CH_2$), 5.60-5.90 (m, 1 H, -CH=), 6.43 (bs, 1 H, NH). According to procedure F, 5-(2-propenyl)-2-pyrrolidinone (2.02 g, 16.1 mmol) was treated with methyl glyoxylate hydrate (6.4 g, 72.8 mmol) in 250 mL of benzene to give α-hydroxy-2-oxo-5-(2-propenyl)-1-pyrrolidineacetic acid methylester (2.95 g, 13.8 mmol, 86%) as a light yellow oil. $R_f$ 0.25 (EtOAc). IR 3520 (OH), 1745 (C=O), 1685 (NC=O). $^1$H NMR (200 MHz, mixture of diastereoisomers ) 1.75-1.95 (m, 1 H), 2.05-2.55 (m, 5 H), 3.82 (s, 3 H, $OCH_3$), 3.80-4.30 (m, 1 H, NC*H*$(CH_2)_2$), 4.30 (bs, 1 H, OH), 5.00-5.20 (m, 2 H, $=CH_2$), 5.40 (bs) and 5.55 (bs, 1 H, NCHO), 5.60-5.90 (m, 1 H, -CH=). According to procedure G, the methyl glyoxylate adduct (2.75 g, 12.9 mmol) was treated with DMAP (150 mg, 1.2 mmol) and acetic anhydride (1.8 mL, 15 mmol) in 25 mL of pyridine to give **23** (2.89 g, 11.0 mmol, 85%) as a colourless oil. $R_f$ 0.40 (EtOAc). IR 1750 and 1705 (3 × C=O). $^1$H NMR (250 MHz, mixture of diastereoisomers) 1.75-1.95 (m, 1 H), 2.05-2.55 (m, 5 H), 2.14 (s) and 2.15 (s, 3 H, $C{=}OCH_3$), 3.65-3.95 (m, 1 H, NC*H*$(CH_2)_2$), 3.76 (s) and 3.79 (s, 3 H, $OCH_3$), 5.05-5.20 (m, 2 H, $=CH_2$), 5.55-5.85 (m, 1 H, -CH=), 6.42 (s) and 6.56 (s, 1 H, NCHO).

**α-Acetoxy-2-(2-methyl-2-propenyl)-5-oxo-1-pyrrolidineacetic acid methylester (24).** According to procedure A, 5-ethoxy-2-pyrrolidinone[33] (129 mg, 1.00 mmol) was treated with methallyltrimethylsilane (154 mg, 1.20 mmol) and $BF_3{\cdot}OEt_2$ (135 μL, 1.10 mmol) in 3 mL of $CH_2Cl_2$ to give 5-(2-methyl-2-propenyl)-2-pyrrolidinone (129 mg, 0.928 mmol, 93%) as a colourless oil. $R_f$ 0.30 (EtOAc). IR 3430 and 3220 (NH), 1680 (NC=O). $^1$H NMR (200 MHz) 1.60-1.90 (m, 1 H), 1.69 (s, 3 H, $CH_3$), 2.00-2.50 (m, 5 H), 3.65-3.90 (m, 1 H, NCH), 4.69 (bs, 1 H, =CH), 4.79 (bs, 1 H, =CH), 6.61 (bs, 1 H, NH). According to procedure F, 5-(2-methyl-2-propenyl)-2-pyrrolidinone (1.05 g, 7.55 mmol) was treated with methyl glyoxylate hydrate (6.4 g, 72.8 mmol) in 80 mL of benzene to give α-hydroxy-2-(2-methyl-2-propenyl)-5-oxo-1-pyrrolidineacetic acid methylester (1.07 g, 4.76 mmol, 63%) as a colourless oil. $R_f$ 0.30 ($CHCl_3$). IR 3520 (OH), 1745 (C=O), 1685 (NC=O). $^1$H NMR (250 MHz, mixture of diastereoisomers ) 1.73 (s, 3 H, $CH_3$), 1.50-2.70 (m, 6 H), 3.82 (s, 3 H, $OCH_3$), 3.80-4.30 (m, 1 H, NC*H* $(CH_2)_2$), 4.25 (bs, 1 H, OH), 4.76 (s, 1 H, -CH=), 4.84 (s, 1 H, -CH=), 5.30 (s) and 5.33 (s, 1 H, NCHO). According to procedure G, the glyoxylate adduct (403 mg, 1.77 mmol) was treated with DMAP (20 mg, 0.16 mmol) and acetic anhydride (0.25 mL, 2.65 mmol) in 5 mL of pyridine to give **24** (287 mg, 1.07 mmol, 60%) as a colourless oil. $R_f$ 0.45 (EtOAc). IR 1750 and 1705 (3 × C=O). $^1$H NMR (200 MHz, mixture of diastereoisomers) 1.60-2.70 (m, 6 H), 1.73 (s, 3 H, $CH_3$), 2.16 (s) and 2.18 (s, 3 H, $C{=}OCH_3$), 3.79 (s) and 3.81 (s, 3 H, $OCH_3$), 3.70-4.20 (m, 1 H, NC*H*$(CH_2)_2$), 4.76 (bs, 1 H, -CH=), 4.86 (bs, 1 H, -CH=), 6.43 (s) and 6.56 (s, 1 H, NCHO).

**Acetoxy[*N*-(methoxycarbonyl)-*N*-(2-phenylpropyl)amino]acetic acid methyl ester (25).** According to procedure E, β-methylphenetylamine (Aldrich, 3.26 g, 24.11 mmol) was treated with $Et_3N$ (3.70 mL, 26.5 mmol) and methyl chloroformate (2.00 mL, 25.9 mmol) in 50 mL of $CH_2Cl_2$ to give methyl *N*-(2-phenylpropyl)carbamate (4.55 g, 23.58 mmol, 98%) as a light yellow oil. $R_f$ 0.36 (EtOAc/hexanes: 1/4). IR 3420 (NH), 1700 (NC=O). $^1$H NMR (200 MHz) 1.27 (d, $J$ = 6.9 Hz, 3 H, $CHCH_3$), 2.80-3.05 (m, 1 H, $CHCH_3$), 3.10-3.30 (m, 1 H, CHN), 3.30-3.55 (m, 1 H, CHN), 3.63 (s, 3 H, $OCH_3$), 4.63 (bs, 1 H, NH), 7.10-7.40 (m, 5 H, $-C_6H_5$). According to procedure F, methyl *N*-(2-phenylpropyl)carbamate (1.56 g, 8.08 mmol) was treated with methyl glyoxylate hydrate (5.7 g, 53.8 mmol) in 90 mL benzene to give starting compound (0.630 g, 3.36 mmol, 40%) and hydroxy[*N*-(methoxycarbonyl)-*N*-(2-phenylpropyl)amino]acetic acid methyl ester (0.850 g, 3.02 mmol, 37%) as a colourless oil. $R_f$ 0.19 (EtOAc/hexanes: 1/4). IR 3530 (OH), 1745 (C=O), 1700 (NC=O). $^1$H NMR (200 MHz, mixture of diastereoisomers) 1.31 (d, $J$ = 6.9 Hz, $CHCH_3$), 3.00-3.25 (m, 1 H, $CHCH_3$), 3.35-3.90 (m, 8 H, 2 x $OCH_3$ + $CH_2N$), 4.24 (bs, 1 H, OH), 4.70-5.15 (m, 1 H, NC*H*OH), 7.10-7.40 (m, 5 H, $C_6H_5$). According to procedure G, the glyoxylate adduct (594 mg, 2.11 mmol) was treated with acetic anhydride (0.40 mL, 4.24 mmol) in 10 mL of pyridine to give **25** (514 mg, 1.59 mmol, 75%) as a colourless oil. $R_f$ 0.25 (EtOAc/hexanes: 1/4). IR 1740 and 1710 (3 x C=O). $^1$H NMR (200 MHz, mixture of diastereoisomers) 1.27 (d) and 1.29 (d, $J$ = 6.9 Hz, 3 H, $CHCH_3$), 2.12 (s, 3 H, $C{=}OCH_3$), 3.00-3.85 (m, 9 H, 2 x $OCH_3$ + $CH_2N$ + $CHCH_3$), 6.34 (bs, 1 H, NCHO), 7.10-7.40 (m, 5 H, $C_6H_5$).

**Methyl *N*-((*E*)-3-hexenyl)-*N*-(methoxymethyl)carbamate (26).** A sodium hydride dispersion (55-60% in mineral oil, 55 mg, 1.20 mmol) was washed (3 ×) with 1 mL of hexane under a dry nitrogen atmosphere and then 2 mL of DMF were added. A solution of methyl *N*-((*E*)-3-hexenyl)carbamate (180 mg, 1.15 mmol) in 2 mL of DMF was added dropwise at 0 °C. The mixture was stirred for 1 h and then a solution of chloromethyl methyl ether (0.12 mL, 1.6 mmol) in 3 mL of DMF was added dropwise. After 20 min the reaction mixture was allowed to warm up to room temperature and stirred for 18 h. The mixture was poured out into water and

extracted with $CCl_3CH_3$ (3 ×) and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed to give **26** (61.5 mg, 0.306 mmol, 27%) as a colourless oil. $R_f$ 0.35 (EtOAc/hexanes: 1/4). IR 1695 (NC=O). $^1H$ NMR (200 MHz) 0.94 (t, $J$ = 7.5 Hz, 3 H, $CH_3$), 1.98 (quintet, $J$ = 7.3 Hz, 2 H, $CH_2CH_2N$), 2.15-2.35 (m, 2 H, $CH_3CH_2$), 3.27 (bs, 5 H, $CH_2OCH_3$ and $CH_2N$), 3.71 (s, 3 H, $OCH_3$), 4.66 (bs) and 4.71 (bs, two rotamers, 2 H, $NCH_2O$), 5.25-5.40 (m, 1 H, -CH=), 5.40-5.60 (m, 1 H, -CH=).

**Methyl *N*-((*Z*)-3-hexenyl)-*N*-(methoxymethyl)carbamate (27).** According to the procedure used for the preparation of **26**, methyl *N*-((*Z*)-3-hexenyl)carbamate (500 mg, 3.18 mmol) was treated with sodium hydride (55-60% dispersion in mineral oil, 170 mg, 3.70 mmol) and chloromethyl methyl ether (0.36 mL, 4.7 mmol) in 7 mL of DMF to give **27** (276.2 mg, 1.37 mmol, 43%) as a colourless oil. $R_f$ 0.40 (EtOAc/hexanes: 1/4). IR 1700 (NC=O). $^1H$ NMR (200 MHz) 0.96 (t, $J$ = 7.5 Hz, 3 H, $CH_3$), 2.05 (quintet, $J$ = 7.3 Hz, 2 H, $CH_2CH_2N$), 2.20-2.45 (m, 2 H, $CH_3CH_2$), 3.29 (bs, 5 H, $CH_2OCH_3$ and $CH_2N$), 3.73 (s, 3 H, $OCH_3$), 4.69 (bs) and 4.74 (bs, two rotamers, 2 H, $NCH_2O$), 5.20-5.40 (m, 1 H, -CH=), 5.40-5.55 (m, 1 H, -CH=).

**Cyclization of 18 at -78 °C to room temperature.** To a solution of **18** (209 mg, 0.765 mmol) in 5 mL of $CH_2Cl_2$ was added at -78 °C a 1.2 M solution of $SnCl_4$ in $CH_2Cl_2$ (1.3 mL, 1.56 mmol) under a nitrogen atmosphere. The reaction mixture was allowed to warm up to room temperature in a period of 2 hours. After stirring for 30 min at room temperature, the white reaction mixture was poured out into aq $NaHCO_3$ (25 mL) and extracted (3 ×) with chloroform (20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The residue (190.2 mg) was chromatographed to give ***trans*-4-chloro-1,2-piperidinedicarboxylic acid 1-ethyl, 2-methyl ester (28)** (147.1 mg, 0.590 mmol, 77%) as a colourless oil. $R_f$ 0.56 (EtOAc/hexanes: 1/2). IR 1740 (C=O), 1690 (NC=O). $^1H$ NMR (250 MHz) 1.15-1.30 (m, 3 H, $CH_2CH_3$), 1.71 (qd, $J$ = 12.9, 4.9 Hz, 1 H, $H^{5ax}$), 1.92 (td, $J$ = 12.7, 6.2 Hz, 1 H, $H^{3ax}$), 2.05-2.15 (m, 1 H, $H^{5eq}$), 2.65 (bd, $J$ = 13.0 Hz, 1 H, $H^{3eq}$), 2.90-3.15 (m, 1 H, $H^{6ax}$), 3.72 (s, 3 H, $OCH_3$), 3.82 (tt, $J$ = 12.0, 4.1 Hz, 1 H, $H^{4ax}$), 4.00-4.20 (m, 1 H, $H^{6eq}$), 4.13 (q, $J$ = 7.1 Hz, 2 H, $OCH_2$), 4.88 (bs) and 5.00 (bs, two rotamers, 1 H, $H^{2eq}$). $^1H$ NMR ($C_6D_6$, 200 MHz) 0.96 (t, $J$ = 7.1 Hz, 3 H, $CH_2CH_3$), 1.37 (qd, $J$ = 12.5, 4.8 Hz, 1 H, $H^{5ax}$), 1.50-1.70 (m, 2 H, $H^{3ax}$ and $H^{5eq}$), 2.48 (bd, $J$ = 13.3 Hz, 1 H, $H^{3eq}$), 2.65-3.00 (m, 1 H, $H^{6ax}$), 3.17 (s, 3 H, $OCH_3$), 3.53 (bt, $J$ = 12.0 Hz, 1 H, $H^{4ax}$), 3.80 (bd) and 4.17 (bd, $J$ = 13.6 Hz, two rotamers, 1 H, $H^{6eq}$), 4.68 (bs) and 5.08 (bd, $J$ = 4.8 Hz, two rotamers, 1 H, $H^{2eq}$). $^{13}C$ NMR (63 MHz) 14.5 ($CH_3$), 35.5, 36.7, 41.3 (C-6), 52.4, 53.4, 54.7 (C-2), 62.0 ($OCH_2$), 156.0 (b, NC=O), 171.0 (C=O). Accurate mass 249.0773 (calcd for $C_{10}H_{16}NO_4{}^{35}Cl$ 249.0768).

**Cyclization of 19 at -78 °C to room temperature.** To a solution of **19** (425 mg, 1.48 mmol) in 5 mL of $CH_2Cl_2$ was added at -78 °C, a 1.2 M solution of $SnCl_4$ in $CH_2Cl_2$ (2.5 mL, 3.00 mmol) under a nitrogen atmosphere. The reaction mixture was allowed to warm up to room temperature over a period of 4 hours. After stirring for 1 hour (-40 °C) the reation mixture was white, after 2.5 hours (-10 °C) the reaction mixture was clear again. The reaction mixture was poured out into excess aq $NaHCO_3$ and extracted (3 ×) with $CH_2Cl_2$ (20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The residue (393 mg) was chromatographed to give two fractions. The first fraction consisted of ***rel*-(2*R*,3*R*,4*R*)-4-chloro-3-ethyl-1,2-piperidinedicarboxylic acid dimethyl ester (29)** (314 mg, 1.19 mmol, 80%) as a colourless oil. $R_f$ 0.45 (EtOAc/hexanes: 1/4). IR 1730 (C=O), 1690 (NC=O). $^1H$ NMR (200 MHz) 1.00 (t, $J$ = 7.3 Hz, 3 H, $CH_2CH_3$), 1.05-1.55 (m, 1 H), 1.60-1.95 (m, 2 H), 2.00-2.15 (m, 1 H), 2.24 (bd, $J$ = 10.4 Hz, 1 H, $H^{3ax}$), 3.15-3.45 (m, 1 H, $H^{6ax}$), 3.69 (s, 3 H, $OCH_3$), 3.70 (s, 3 H, $OCH_3$), 3.80-4.15 (m, 1 H, $H^{6eq}$), 4.18 (td, $J$ = 11.4, 4.4 Hz, 1 H, $H^{4ax}$), 4.95 (bs) and 5.10 (bs, two rotamers, 1 H, $H^{2eq}$). $^{13}C$ NMR (50 MHz) 11.3 ($CH_3$), 22.0 ($CH_2$), 36.3 (C-5), 40.7 (C-6), 47.8 (C-3), 51.8 ($OCH_3$), 53.0 ($OCH_3$), 56.5 (C-2), 59.3 (C-4), 155.8 (NC=O), 170.3 (C=O). Accurate mass 263.0908 (calcd for $C_{11}H_{18}NO_4{}^{35}Cl$ 263.0924). The second fraction consisted of ***rel*-(2*R*,3*R*,4*R*)-4-acetoxy-3-ethyl-1,2-piperidinedicarboxylic acid dimethyl ester (30)** (10 mg, 0.023 mmol, 2%) as a colourless oil. $R_f$ 0.25 (EtOAc/hexanes: 1/4). IR 1735 (2 × OC=O), 1690 (NC=O). $^1H$ NMR (250 MHz) 0.99 (t, $J$ = 7.4 Hz, 3 H, $CH_2CH_3$), 1.10-1.35 (m, 1 H), 1.40-1.80 (m, 3 H), 2.03 (s, 3 H, C=$OCH_3$), 2.00-2.15 (m, 1 H, $H^{3ax}$), 3.25-3.50 (m, 1 H, $H^{6ax}$), 3.70 (s, 6 H, 2 × $OCH_3$), 3.90-4.20 (m, 1 H, $H^{6eq}$), 4.97 (td, $J$ = 10.8, 4.6 Hz, 1 H, $H^{4aq}$), 4.95 (bs) and 5.10 (bs, two rotamers, 1 H, $H^{2eq}$). Accurate mass 287.1365 (calcd for $C_{13}H_{21}NO_6$ 287.1369).

**Cyclization of 20 at -78 °C to room temperature.** To a solution of **20** (177 mg, 0.618 mmol) in 3 mL of $CH_2Cl_2$ was added at -78 °C, a 1.2 M solution of $SnCl_4$ in $CH_2Cl_2$ (1.0 mL, 1.2 mmol) under a nitrogen atmosphere. The reaction mixture was allowed to warm up to room temperature over a period of 2 hours. The reaction mixture was poured out into excess aq $NaHCO_3$ and extracted (3 ×) with $CH_2Cl_2$ (30 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The residue

was chromatographed to give two fractions. The first fraction (66 mg, $R_f$ 0.60 (EtOAc/hexanes: 1/2)) consisted of a 4:1:1 mixture of ***rel*-(2*R*,3*R*,4*R*)-4-chloro-3-ethyl-1,2-piperidinedicarboxylic acid dimethyl ester (31)** ($^1$H NMR (200 MHz) characteristic signal: 4.05 (dt, $J$ = 11.8, 4.3 Hz, 1 H, $H^{4ax}$)), elimination product **3-ethyl-1,2,3,6-tetrahydro-1,2-pyridinedicarboxylic acid dimethyl ester (32)** ($^1$H NMR (200 MHz) characteristic signals: 4.74 (s) and 4.92 (s, two rotamers, 1 H, $H^{2eq}$), 5.61 (tt, $J$ = 10.5, 3.1 Hz, $H^4$), 5.70-5.85 (m, 1 H, $H^5$)) and chloride **29**. The second fraction consisted of ***rel*-(1*R*,5*S*,8*S*)-8-ethyl- 2-methoxycarbonyl-6-oxa-2-azabicyclo[3.2.1]octan-7-one (33)** (46 mg, 0.215 mmol, 35%) as a colourless oil. $R_f$ 0.30 (EtOAc/hexanes: 1/2). IR 1785 (C=O), 1695 (NC=O). $^1$H NMR 0.96 (t, $J$ = 7.4 Hz, 3 H, $CH_2CH_3$), 1.35-1.65 (m, 2 H, $CH_2CH_3$), 1.75-1.95 (m, 2 H, $H^{4exo}$ and $H^{4endo}$), 2.15-2.30 (m, 1 H, $H^8$), 3.05-3.25 (m, 1 H, $H^{3endo}$), 3.70 (s, 3 H, $OCH_3$), 3.90-4.25 (m, 1 H, $H^{3exo}$), 4.58 (bs) and 4.75 (bs, two rotamers, 1 H, $H^1$), 4.75 (bs, 1 H, $H^5$). $^{13}$C NMR (50 MHz) 11.4 (b, $CH_3$), 18.1 ($CH_2$), 23.2 (C-4), 38.0 (C-3), 45.8 (C-8), 53.1 ($OCH_3$), 55.6 (b, C-1), 79.0 (b, C-5), 155.6 (NC=O), 173.0 (C-7).

**Cyclization of 21 at -78 °C to room temperature.** Under a nitrogen atmosphere, a 2.0 M solution of $SnCl_4$ in $CH_2Cl_2$ (1.0 mL, 2.0 mmol) was added to a solution of **21** (261.7 mg, 0.959 mmol) in 10 mL of $CH_2Cl_2$ at -78 °C. The reaction mixture was allowed to warm up to room temperature over a 4 h period. After stirring for 30 min at room temperature, the reaction mixture was poured out into 15 mL of saturated aq $NaHCO_3$. After extraction (3 ×) with 50 mL of $CHCl_3$, the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed to give two fractions The first fraction consisted of ***trans*-4-chloro-4-methyl-1,2-piperidinedicarboxylic acid dimethyl ester (34)** (103.2 mg, 0.414 mmol, 43%) as a colourless oil. $R_f$ 0.60 (EtOAc/hexanes: 1/2). IR 1740 (C=O), 1695 (NC=O). $^1$H NMR (200 MHz) 1.55 (s, 3 H, $CH_3$), 1.45-1.60 (m, 1 H), 1.85-2.20 (m, 2 H), 2.32 (dd, $J$ = 13.9, 6.7 Hz, 1 H), 2.52 (bdd, J = 13.9, 6.7 Hz, 1 H), 3.20-3.50 (m, 1 H, $H^{6ax}$), 3.72 (s, 3 H, $OCH_3$), 3.75 (s, 3 H, $OCH_3$), 3.80-4.00 (m, 1 H, $H^{6eq}$), 4.67 (d) and 4.71 (d, $J$ = 4.6 Hz, 1 H, $H^{2eq}$). $^{13}$C NMR (50 MHz) 28.4 ($CH_3$), 40.0, 40.5, 41.7, 52.2 ($OCH_3$), 52.9 ($OCH_3$), 54.0 (C-2), 66.2 (C-4), 156.0 (NC=O), 171.4 (C=O). Accurate mass 249.0765 (calcd for $C_{10}H_{16}NO_4{}^{35}Cl$ 249.0768). The second fraction consisted of ***cis*-4-chloro-4-methyl-1,2-piperidinedicarboxylic acid dimethyl ester (35)** (42.3 mg, 0.170 mmol, 18%) as a colourless oil. $R_f$ 0.45 (EtOAc/hexanes: 1/2). IR 1740 (C=O), 1690 (NC=O). $^1$H NMR (200 MHz) 1.60 (s, 3 H, $CH_3$), 1.55-1.75 (m, 1 H), 1.80-1.95 (m, 1 H), 1.93 (dd, $J$ = 14.7, 7.0 Hz, 1 H), 2.60-2.75 (m, 1 H), 3.30-3.55 (m, 1 H, $H^{6ax}$), 3.72 (s, 3 H, $OCH_3$), 3.73 (s, 3 H, $OCH_3$), 3.90-4.20 (m, 1 H, $H^{6eq}$), 4.73 (d) and 4.89 (d, $J$ = 6.9 Hz, 1 H, $H^{2eq}$). $^{13}$C NMR (50 MHz) 33.6 ($CH_3$), 37.8 and 37.9, 39.5 and 39.7, 40.6 and 40.8, 51.8 ($OCH_3$), 52.2 ($OCH_3$), 53.0 (C-2), 67.1 and 67.2 (C-4), 156.2 and 156.7 (NC=O), 171.3 and 171.4 (C=O). Accurate mass 249.0773 (calcd for $C_{10}H_{16}NO_4{}^{35}Cl$ 249.0768).

**Cyclization of 22 at -78 °C to room temperature.** Under a nitrogen atmosphere, a 1.2 M solution of $SnCl_4$ in $CH_2Cl_2$ (2.2 mL, 2.6 mmol) was added to a solution of **22** (361.5 mg, 1.324 mmol) in 5 mL of $CH_2Cl_2$ at -78 °C. The reaction mixture was allowed to warm up to room temperature over a 2 h period. After stirring for 30 min at room temperature, the reaction mixture was poured out into 15 mL of saturated aq $NaHCO_3$. After extraction (3 ×) with 50 mL of $CHCl_3$, the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed to give two fractions. The first fraction (171 mg) contained ***rel*-(2*R*,4*S*,5*S*)-4-chloro-5-methyl-piperidine-1,2-dicarboxylic acid dimethyl ester (36)** (145 mg, 0.584 mmol, 44%) as a colourless oil. $R_f$ 0.58 (EtOAc/hexanes: 1/2). IR 1730 (C=O), 1680 (NC=O). $^1$H NMR (200 MHz) 1.00 (d, $J$ = 6.4 Hz, 3 H, $CH_3$), 1.50-1.85 (m, 1 H), 1.97 (td, $J$ = 13.2, 5.7 Hz, 1 H, $H^{3ax}$), 2.50-2.75 (m, 1 H, $H^5$), 3.43 (td, $J$ = 12.1, 3.1 Hz, $H^{6ax}$), 3.60-3.80 (m, 1 H, $H^{4ax}$), 3.66 (s) and 3.67 (s) and 3.69 (s, 6 H, 2 × $OCH_3$), 3.97 (dd) and 4.11 (dd, two rotamers, $J$ = 13.4, 5.1 Hz, $H^{6eq}$), 4.81 (d) and 4.87 (d, two rotamers, $J$ = 6.2 Hz, 1 H, $H^{2eq}$). $^{13}$C NMR (50 MHz) 16.3 ($CH_3$), 36.8 and 36.9 (C-3), 39.4 (C-5), 47.6 (C-6), 52.5 ($OCH_3$), 53.0 ($OCH_3$), 54.7 and 54.9 (C-2), 60.9 (C-4), 156.2 (NC=O), 170.9 (C=O). Accurate mass 249.0756 (cacld for $C_{10}H_{16}NO_4{}^{35}Cl$ 249.0768). This fraction was contaminated with **5-methyl-1,2,3,4-tetrahydro-1,2-pyridinedicarboxylic acid dimethyl ester (38)** (9%). $^1$H NMR (200 MHz, isolated signals) 1.59 (s, 3 H, $CH_3$), 4.75 (d, one rotamer, $J$ = 3.8 Hz, $H^{2eq}$), 6.53 (bs) and 6.65 (bs, two rotamers, 1 H, $H^6$) The second fraction contained **4-(1-chloroethyl)-1,2-pyrrolidinedicarboxylic acid dimethyl ester (37)** (39.5 mg, 0.158 mmol, 12%, mixture of diastereoisomers) as a colourless oil. $R_f$ 0.30 (EtOAc/hexanes: 1/2). IR 1740 (C=O), 1695 (NC=O). $^1$H NMR (200 MHz) 1.52 (d, $J$ = 6.6 Hz, 3 H, $CH_3$), 2.00-2.25 (m, 2 H), 2.50-2.75 (m, 1 H, $H^4$), 3.10-3.40 (m, 1 H, $H^5$), 3.72 (s, 3 H, $OCH_3$), 3.75 (s, 3 H, $OCH_3$), 3.60-3.75 (m, 1 H, $H^5$), 3.90-4.05 (m, 1 H, ClCH), 4.35-4.55 (m, 1 H, $H^2$). $^{13}$C NMR (63 MHz) 23.9 ($CH_3$), 32.8 and 33.2 and 34.1 (C-3), 44.4 and 44.7 and 45.5 (C-4), 49.1 and 49.3 (C-5), 52.3 ($OCH_3$), 52.6 ($OCH_3$), 58.8 and 58.9 and 59.1 and 59.4 (C-2 and ClCH), 156.0 (b, NC=O), 172.7 (C=O). Accurate mass 249.0775 (cacld for $C_{10}H_{16}NO_4{}^{35}Cl$ 249.0767).

**Cyclization of 23 at 0 °C.** Under a nitrogen atmosphere, a 1.2 M solution of $SnCl_4$ in $CH_2Cl_2$ (7.90 mL, 9.48 mmol) was added dropwise to a solution of **23** (1.09 g, 4.27 mmol) in 40 mL of $CH_2Cl_2$ at 0 °C. The reaction mixture was stirred for 3 h at 0 °C and then poured out into 150 mL saturated aq $NaHCO_3$. After extraction with $CHCl_3$ (4 × 100 mL), the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed to give ***rel*-(5*R*,7*R*,8a*S*)-7-chloro-octahydro-3-oxoindolizine-5-carboxylic acid methyl ester (39)** (0.580 g, 2.96 mmol , 69%) as a light yellow oil. $R_f$ 0.30 ($CH_2Cl_2$/aceton: 2/1). IR 1740 (C=O), 1680 (NC=O). $^1$H NMR (200 MHz) 1.45 (q, $J$ = 12.1 Hz, 1 H, $H^{8ax}$), 1.50-1.70 (m, 1 H, $H^1$), 1.88 (td, $J$ = 12.6, 6.5 Hz, 1 H, $H^{6ax}$), 2.15-2.50 (m, 4 H, ), 2.55-2.70 (m, 1 H, $H^{6eq}$), 3.71 (s, 3 H, $OCH_3$), 3.65-3.80 (m, 1 H, $H^{8a}$), 3.88 (tt, $J$ = 12.2, 3.9 Hz, 1 H, $H^{7ax}$), 4.87 (dd, $J$ = 6.5 , 1.4 Hz, 1 H, $H^{5ax}$). $^1$H NMR (200 MHz, $C_6D_6$) 0.75-1.05 (m, 2 H), 1.35-1.80 (m, H), 1.95-2.10 (m, 2 H), 2.35-2.50 (m, 1 H, $H^{6eq}$), 3.15 (s, 3 H, $OCH_3$), 3.25-3.50 (m, 1 H, $H^{8a}$), 3.61 (tt, $J$ = 12.2, 3.9 Hz, 1 H, $H^{7ax}$), 4.86 (d, $J$ = 6.5 Hz, 1 H, $H^{5eq}$). $^{13}$C NMR (63 MHz) 25.0 (C-1), 29.7 (C-2), 35.9 (C-6), 42.9 (C-8), 50.6 (C-5), 52.2 (C-7), 52.5 ($OCH_3$), 54.0 (C-8a), 170.0 (C=O), 173.9 (C-3).

**Cyclization of 24 at 0 °C to room temperature.** To a solution of **24** (970 mg, 3.60 mmol) in 15 mL of $CH_2Cl_2$ was added at 0 °C, a 1.2 M solution of $SnCl_4$ in $CH_2Cl_2$ (6.6 mL, 7.9 mmol) under a nitrogen atmosphere. The reaction mixture was allowed to warm up to room temperature. After stirring for 1.5h, the reaction mixture was poured out into half saturated aq $NaHCO_3$ (50 mL) and extracted (3 ×) with $CH_2Cl_2$ (30 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed to give two fractions. The first fraction consisted of a 3:1 mixture of ***rel*-(5*R*,7*S*,8a*S*)-7-chloro-octahydro-7-methyl-3-oxoindolizine-5-carboxylic acid methyl ester (40)** and **42** (520 mg). Crystallization (hexane/ether) gave **40** (410 mg, 1.67 mmol, 46%) as a white solid. $R_f$ 0.30 (EtOAc). IR 1740 (C=O), 1680 (NC=O). $^1$H NMR (200 MHz) 1.53 (s, 3 H, $CH_3$), 1.60-1.85 (m, 3 H), 2.20-2.55 (m, 4 H), 2.68 (ddd, $J$ = 13.8, 1.9 Hz, 1.9 Hz, 1 H), 3.74 (s, 3 H, $OCH_3$), 3.70-3.95 (m, 1 H, $H^{8a}$), 4.82 (d, $J$ = 7.5 Hz, 1 H, $H^5$). $^{13}$C NMR (50 MHz) 25.4 (C-1), 27.4 ($CH_3$), 29.8 (C-2), 41.1 (C-6), 48.7 (C-8), 50.0 (C-5), 52.3, 52.5, 65.7 (C-7), 170.8 (C=O), 174.3 (C-3). The second fraction consisted of ***rel*-(5*R*,7*R*,8a*S*)-7-chloro-octahydro-7-methyl-3-oxoindolizine-5-carboxylic acid methyl ester (41)** (190 mg, 0.700 mmol, 21%) as white crystals, mp 102-104 °C (hexanes/ether). $R_f$ 0.20 (EtOAc). IR 1740 (C=O), 1680 (NC=O). $^1$H NMR (200 MHz) 1.37 (dd, $J$ = 13.7, 11.2 Hz, 1 H, $H^{8ax}$), 1.50-1.75 (m, 1 H, $H^1$), 1.63 (s, 3 H, $CH_3$), 1.88 (dd, $J$ = 14.8, 7.3 Hz, 1 H, $H^{6ax}$), 2.10-2.25 (m, 1 H, $H^{8eq}$), 2.25-2.60 (m, 3 H, 2 × $H^2$ + $H^1$), 2.70 (d, $J$ = 14.8 Hz, 1 H, $H^{6eq}$), 3.72 (s, 3 H, $OCH_3$), 4.05-4.25 (m, 1 H, $H^{8a}$), 4.78 (d, $J$ = 6.8 Hz, 1 H, $H^5$). $^{13}$C NMR (50 MHz) 24.9 (C-1), 30.0 (C-2), 33.6 ($CH_3$), 40.0 (C-6), 47.0 (C-8), 48.8 (C-5), 50.9 (C-8a), 52.3 ($OCH_3$), 67.1 (C-7), 170.3 (C=O), 174.5 (C-3). Accurate mass 245.0824 (calcd for $C_{11}H_{16}NO_3$ 245.0819). Crystallographic data: monoclinic, $P2_1/a$; $a$ 9.732(2) Å, $b$ 13.903(3) Å, $c$ 9.116(2) Å; $\beta$ = 99.99(1) °; $V$ = 1215 Å$^3$; $Z$ = 4; 1172 reflections; Mo-α-radiation, $\lambda$ = 0.71069 Å; $R$ = 0.43; $R_w$ = 0.43.

**Cyclization of 18 and aq quench at -78 °C.** Under a nitrogen atmosphere, a 1.2 M solution of $SnCl_4$ in $CH_2Cl_2$ (0.60 mL, 0.72 mmol) was added to a solution of **18** (102 mg, 0.373 mmol) in 3 mL of $CH_2Cl_2$ at -78 °C. The reaction mixture was stirred for 2.5 h at -78 °C, then treated all at once with excess aq $NaHCO_3$, and warmed up to room temperature. After extraction (3 ×) with 20 mL of $CHCl_3$, the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The residue (84 mg) was chromatographed to give starting compound **18** (35 mg, 0.13 mmol, 35%) and ***cis*-4-hydroxy-1,2-piperidinedicarboxylic acid 1-ethyl, 2-methyl ester (43)** (39.1 mg, 0.169 mmol, 45%) as a colourless oil. $R_f$ 0.30 (EtOAc/hexanes: 1/1). IR 3600(s) and 3480(b) (OH), 1730 (C=O), 1685 (NC=O). $^1$H NMR (250 MHz) 1.15-1.35 (m, 3 H, $CH_2CH_3$), 1.60-1.80 (m, 2 H, $H^{5ax}$ and $H^{5eq}$), 1.87 (ddd, $J$ = 13.4, 4.7, 2.1 Hz, 1 H, $H^{3ax}$), 2.38 (bs, 1 H, OH), 2.41 (bd, $J$ = 14.2 Hz, 1 H, $H^{3eq}$), 3.30-3.45 (m, 1 H, $H^{6ax}$), 3.69 (s, 3 H, $OCH_3$), 3.75-4.00 (m, 1 H, $H^{6eq}$), 4.00-4.20 (m, 3 H, $OCH_2$ and $H^{4eq}$), 4.70 and 4.79 (bs, two rotamers, 1 H, $H^{2eq}$). $^{13}$C NMR (50 MHz) 14.5 ($CH_3$), 31.1, 33.3, 35.6(b, C-6), 50.8(b, C-2), 52.2 ($OCH_3$), 61.6 ($OCH_2$), 63.0 (C-4), 156.5(b, NC=O), 173.0 (C=O).

**Cyclization of 19 and aq quench at -78 °C.** Under a nitrogen atmosphere, a 1.2 M solution of $SnCl_4$ in $CH_2Cl_2$ (1.60 mL, 1.92 mmol) was added to a solution of **19** (277 mg, 0.966 mmol) in 5 mL of $CH_2Cl_2$ at -78 °C. The reaction mixture was stirred for 2 h at -78 °C and treated all at once with excess aq $NaHCO_3$. The mixture was allowed to warm up to room temperature and then extracted (3 ×) with 20 mL of $CH_2Cl_2$. The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The residue (238 mg) was chromatographed to give starting compound **19** (94 mg, 0.33 mmol, 34%) and ***rel*-(2*R*,3*R*,4*S*)-3-ethyl-4-hydroxy-1,2-piperidinedicarboxylic acid dimethyl ester (44)** (117 mg, 0.478 mmol, 49%) as a colourless oil. $R_f$ 0.26 (EtOAc/hexanes: 1/2). IR 3600 (s) and 3480 (b) (OH), 1730 (C=O), 1690 (NC=O). $^1$H NMR (250 MHz) 0.98 (t, $J$ = 7.3 Hz, $CH_2CH_3$), 1.54 (quintet, $J$ = 7.2 Hz, 2 H, $CH_2CH_3$), 1.60-1.75 (m, 2 H, $H^{5ax}$ and $H^{5eq}$), 1.80-1.90 (m, 1 H, $H^{3ax}$), 2.50 (bs, 1 H, OH), 3.35-3.55 (m, 1 H, $H^{6ax}$), 3.68

(s, 3 H, $OCH_3$), 3.70 (s, 3 H, $OCH_3$), 3.80-4.05 (m, 1 H, $H^{6eq}$), 3.93 (bd, $J$ = 2.6 Hz, $H^{4eq}$), 4.71 (bs) and 4.87 (bs, 1 H, two rotamers, $H^{2eq}$). $^{13}C$ NMR (50 MHz) 11.6 ($CH_3$), 21.9 ($CH_2$), 32.6 (C-5), 35.6 (C-6), 43.9 (C-3), 52.2 ($OCH_3$), 52.9 ($OCH_3$), 55.3(b, C-2), 65.3 (C-4), 156.5(b, NC=O), 173.7(b, C=O). Accurate mass 245.1261 (calcd for $C_{11}H_{19}NO_5$ 245.1263).

**Cyclization of 20 and aq quench at -78 °C.** Under a nitrogen atmosphere, a 1.2 M solution of $SnCl_4$ in $CH_2Cl_2$ (2.80 mL, 3.36 mmol) was added to a solution of **20** (409 mg, 1.43 mmol) in 15 mL of $CH_2Cl_2$ at -78 °C. The reaction mixture was stirred for 2.25 h at -78 °C and treated all at once with excess aq $NaHCO_3$. After extraction (3 ×) with 50 mL of $CHCl_3$, the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The residue (340 mg) was chromatographed to give alcohol **44** (27 mg, 0.11 mmol, 8%) and ***rel*-(2*R*,3*S*,4*S*)-3-ethyl-4-hydroxy-1,2-piperidinedicarboxylic acid dimethyl ester (45)** (255 mg, 1.04 mmol, 73%) as a crystalline solid, mp 95-96 °C (benzene). $R_f$ 0.17 (EtOAc/hexanes: 1/1). IR 3600 (s) and 3480 (b) (OH), 1730 (C=O), 1690 (NC=O). $^1H$ NMR (250 MHz) 1.01 (t, $J$ = 7.2 Hz, 3 H, $CH_2CH_3$), 1.41 (quintet, $J$ = 7.2 Hz, 2 H, $CH_2CH_3$), 1.50-1.60 (m, 1 H), 1.70-1.90 (m, 2 H), 2.25-2.40 (m, 1 H, $H^{3eq}$), 3.41 (bq, $J$ = 14 Hz, 1 H, two rotamers, $H^{6ax}$), 3.68 (s, 3 H, $OCH_3$), 3.71 (s, 3 H, $OCH_3$), 3.75-4.00 (m, 1 H, $H^{6eq}$), 3.71 (dt, $J$ = 2.9, 2.8 Hz, 1 H, $H^{4eq}$), 4.55 (bs) and 4.74 (bs, 1 H, two rotamers, $H^{2eq}$). $^{13}C$ NMR (63 MHz) 12.1 ($CH_3$), 23.0 ($CH_2$), 26.4 and 26.5 (C-5), 35.5 and 35.7 (C-6), 44.2 (C-3), 51.9 ($OCH_3$), 52.7 ($OCH_3$), 53.9 and 54.2 (C-2), 67.1 (C-4), 157.2 and 157.3 (NC=O), 172.7 (C=O). Accurate mass 245.1263 (calcd for $C_{11}H_{19}NO_5$ 245.1263).

**Cyclization of 21 and aq quench at -78 °C.** Under a nitrogen atmosphere, a 2.0 M solution of $SnCl_4$ in $CH_2Cl_2$ (1.2 mL, 2.4 mmol) was added to a solution of **21** (108.8 mg, 0.399 mmol) in 5 mL of $CH_2Cl_2$ at -78 °C. The reaction mixture was stirred for 4 h at -78 °C and poured out into 5 mL of saturated aq $NaHCO_3$. After extraction (3 ×) with 30 mL of $CHCl_3$, the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed to give three fractions. The first two fractions consisted of **34** (31.8 mg, 0.128 mmol, 32%) and **35** (41.4 mg, 0.166 mmol, 42%) as a colourless oils. The third fraction consisted of ***cis*-4-hydroxy-4-methyl-1,2-piperidinedicarboxylic acid dimethyl ester (46)** (21.6 mg, 0.094 mmol, 23%) as a colourless oil. $R_f$ 0.07 (EtOAc/hexanes: 1/2). IR 3590 and 3500 (OH), 1740 (C=O), 1685 (NC=O). $^1H$ NMR (200 MHz) 1.25 (s, 3 H, $CH_3$), 1.35-1.60 (m, 2 H), 1.77 (dd, $J$ = 14.1, 6.7 Hz, 1 H), 2.25-2.45 (m, 1 H), 3.25-3.50 (m, 1 H, $H^{6ax}$), 3.69 (s, 3 H, $OCH_3$), 3.72 (s, 3 H, $OCH_3$), 3.60-4.10 (m, 1 H, $H^{6eq}$), 4.72 (d, $J$ = 6.6 Hz) and 4.89 (d, $J$ = 6.6 Hz, 1 H, $H^{2eq}$). $^{13}C$ NMR (50 MHz) 30.9 ($CH_3$), 36.9 and 37.3, 37.1 and 37.4, 38.8 and 39.0, 51.9 and 52.2, 52.3, 52.9, 67.4 ($C^4$), 156.9 (NC=O), 172.8 (C=O). Accurate mass 231.1104 (calcd for $C_{10}H_{17}NO_5$ 231.1107).

**Cyclization of 22 and aq quench at -78 °C.** Under a nitrogen atmosphere, a 1.2 M solution of $SnCl_4$ in $CH_2Cl_2$ (0.7 mL, 0.84 mmol) was added to a solution of **22** (119.5 mg, 0.438 mmol) in 5 mL of $CH_2Cl_2$ at -78 °C. The reaction mixture was stirred for 4 h at -78 °C and treated all at once with excess aq $NaHCO_3$. After extraction (3 ×) with 30 mL of $CHCl_3$, the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed to give three fractions. The first fraction consisted of starting compound **22** (45.6 mg, 0.167 mmol, 38%). The second fraction consisted of ***rel*-(2*R*,4*R*,5*S*)-4-hydroxy-5-methyl-1,2-piperidinedicarboxylic acid dimethyl ester (47)** (45.3 mg, 0.196 mmol, 45%) as a colourless oil. $R_f$ 0.15 (EtOAc/hexanes: 1/2). IR 3600 and 3500 (OH), 1740 (C=O), 1690 (NC=O). $^1H$ NMR (200 MHz) 0.94 (d) and 0.95 (d, two rotamers, $J$ = 6.9 Hz, 3 H, $CH_3$), 1.60-1.80 (m, 1 H, $H^{3eq}$), 1.80-2.00 (m, 1 H, $H^{3ax}$), 2.40-2.60 (m, 1 H, $H^{5ax}$), 3.01 (dd) and 3.09 (dd, two rotamers, $J$ = 13.0, 12.7 Hz, 1 H, $H^{6ax}$), 3.72 (s) and 3.73 (s, 6 H, 2 × $OCH_3$), 3.60-3.90 (m, 2 H, $H^{6eq}$ + $H^{4eq}$), 4.68 (d) and 4.85 (d, $J$ = 6.6 Hz, 1 H, $H^{2eq}$). $^{13}C$ NMR (50 MHz) 14.8 ($CH_3$), 34.1 (C-5), 34.5 (C-3), 41.7 and 41.9 (C-6), 50.2 and 50.5 (C-2), 52.2 ($OCH_3$), 52.8 ($OCH_3$), 67.2 and 67.3 (C-4), 156.3 and 156.7 (NC=O), 173.0 (C=O). Accurate mass 231.1112 (calcd for $C_{10}H_{17}NO_5$ 231.1107). The third fraction consisted of **37** (12 mg, 0.047 mmol, 11%, mixture of diastereoisomers) as a colourless oil.

**Cyclization of 25 at -78 °C to room temperature.** Under a nitrogen atmosphere, a 1.2 M solution of $SnCl_4$ in $CH_2Cl_2$ (2.0 mL, 2.4 mmol) was added to a solution of (380.4 mg, 1.180 mmol) in 5 mL of $CH_2Cl_2$ at -78 °C. The reaction mixture was allowed to warm up to room temperature in a 3 h period. The reaction mixture was poured out into 20 mL of aq $NaHCO_3$ and extracted (3 ×) with 30 mL of $CHCl_3$. The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed to give an inseparable 75:25 mixture of ***cis*-3,4-dihydro-4-methyl-*1H*-isoquinoline-1,2-dicarboxylic acid dimethyl ester (48)** and ***trans*-3,4-dihydro-4-methyl-*1H*-isoquinoline-1,2-dicarboxylic acid dimethyl ester (49)** (257.7 mg, 0.9798 mmol, 83%) as a colourless oil. $R_f$ 0.36 (EtOAc/hexanes: 1/4). IR 1740 (C=O), 1690 (NC=O). $^1H$ NMR (200 MHz) **48**: 1.34 (d, $J$ = 6.9 Hz, 3 H, $CHCH_3$), 2.90-3.15 (m, 1 H, $H^4$), 3.27 (dd, minor rotamer, $J$ = 13.0, 10.1 Hz) and 3.38 (dd, major rotamer, $J$ = 13.1, 9.4 Hz, 1 H, $H^{3ax}$), 3.74 (s, 3 H, $OCH_3$), 3.75 (s, 3 H, $OCH_3$), 3.99 (dd, major rotamer, $J$ = 13.1, 5.2 Hz) and 4.20 (dd, minor rotamer,

$J$ = 13.0, 5.2 Hz, 1 H, $H^{3eq}$), 5.58 (s, minor rotamer) and 5.64 (s, major rotamer, 1 H, $H^{1eq}$), 7.10-7.40 (m, 3 H), 7.45-7.60 (m, 1 H); **49** (isolated signals): 1.28 (d, $J$ = 7.0 Hz, 3 H, $CHCH_3$), 3.55 (dd, rotamer, $J$ = 12.8, 6.4 Hz, $H^{3ax}$), 5.57 (s, minor rotamer) and 5.66 (s, major rotamer, 1 H, $H^{1eq}$). $^{13}C$ NMR (50 MHz) **48**: 17.5 and 17.9 ($CH_3$), 32.1 (C-4), 46.1 and 46.5 (C-3), 52.4 ($OCH_3$), 52.9 ($OCH_3$), 57.9 (C-1), 126.2, 126.8, 127.7, 127.8, 129.2 and 129.4 (C-8a), 139.4 and 139.6 (C-4a), 155.9 and 156.4 (NC=O), 171.3 (C=O); **49**: 8.6 and 19.4 ($CH_3$), 31.7 (C-4), 46.4 and 46.8 (C-3), 52.4 ($OCH_3$), 52.9 ($OCH_3$), 57.9 (C-1), signals of C-5-C-8 not clear, 129.3 and 129.8 (C-8a), 140.0 and 140.2 (C-4a), 156.3 and 157.0 (NC=O), 171.4 (C=O).

**Cyclization of 26 at -78 °C to room temperature.** Under a nitrogen atmosphere, a 1.2 M solution of $SnCl_4$ in $CH_2Cl_2$ (0.50 mL, 0.60 mmol) was added dropwise to a solution of (50.8 mg, 0.253 mmol) in 1.5 mL of $CH_2Cl_2$ at -78 °C. The reaction mixture was allowed to warm up to room temperature over a 2 h period and then poured out into excess aq $NaHCO_3$. After extraction with $CHCl_3$ (4 × 10 mL), the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to give almost pure **51** (5% of **50**) in quantitative yield. ***trans*-4-Chloro-3-ethyl-1-piperidinecarboxylic acid methyl ester (51)** $R_f$ 0.40 (EtOAc/hexanes: 1/2). IR 1685 (NC=O). $^1H$ NMR (200 MHz) 0.91 (t, $J$ = 7.4 Hz, 3 H, $CH_3$), 1.15-1.40 (m, 1 H), 1.50-1.85 (m, 3 H), 2.05-2.20 (m, 1 H), 2.70-2.95 (m, 1 H), 2.95-3.20 (m, 1 H), 3.67 (s, 3 H, $OCH_3$), 3.79 (td, $J$ = 8.7, 3.9 Hz, 1 H, $H^{4ax}$), 3.85-4.10 (m, 2 H). $^{13}C$ NMR (50 MHz) 10.8 ($CH_3$), 23.3 ($CH_2$), 34.5 (b, C-5), 42.5 (C-6), 45.2 (C-3), 46.3 (b, C-1), 52.8 ($OCH_3$), 61.8 (C-4), 155.5 (NC=O).

**Cyclization of 27 at -78 °C to room temperature.** According to the procedure used for the cyclization of **61**, methoxymethyl compound **62** (256 mg, 1.27 mmol) was treated with a 1.2 M solution of $SnCl_4$ in $CH_2Cl_2$ (2.10 mL, 2.52 mmol) in 5 mL of $CH_2Cl_2$ to give a inseparable 67:33 mixture of **50** and **51** in quantitative yield. ***cis*-4-Chloro-3-ethyl-1-piperidinecarboxylic acid methyl ester (50)** $^1H$ NMR (200 MHz) characteristic signals: 4.41 (bq, $J$ = 2.8 Hz, 1 H, $H^{4eq}$). $^{13}C$ NMR (50 MHz) 10.6 ($CH_3$), 22.9 ($CH_2$), 33.6 (C-5), 38.6 (C-6), 42.5 (C-3), 43.4 (C-1), 52.4 ($OCH_3$), 60.7 (C-4), 155.7 (NC=O).

***trans*-4-Chloro-2-piperidinecarboxylic acid methyl ester (52).** NaI (230 mg, 1.53 mmol) was added to a solution of **28** (94 mg, 0.38 mmol) in 5 mL of $CH_3CN$. At room temperature trimethylsilyl chloride (0.20 mL, 1.58 mmol) was added to the stirred solution. The reaction mixture became brown and was stirred for 1 h at room temperature and subsequently refluxed for 3 h. The reaction mixture was allowed to cool to room temperature. Then 2 mL of a solution of aq $Na_2S_2O_5$ (0.5 M) was added and the mixture was concentrated *in vacuo*. The residue was taken up in 15 mL of 2N HCl and extracted with 20 mL of $CH_2Cl_2$. The organic layer consisted of starting material (37 mg, 0.15 mmol, 39%). The aqueous layer was basified with $Na_2CO_3$ to pH 10, and extracted (3 ×) with 15 mL of $CH_2Cl_2$. The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to give **52** (25 mg, 0.14 mmol, 25%) as a light yellow oil. IR 3340 (NH), 1735 (C=O). $^1H$ NMR (200 MHz) 1.75-2.30 (m, 4 H), 2.92 (dt, $J$ = 12.5, 4.5 Hz, 1 H, $H^{6eq}$), 3.11 (ddd, $J$ = 12.7, 9.3, 3.6 Hz, 1 H, $H^{6ax}$), 3.72 (s, 3 H, $OCH_3$), 3.83 (dd, $J$ = 9.1, 3.7 Hz, 1 H, $H^{2ax}$), 4.43 (quintet, $J$ = 4.3 Hz, 1 H, $H^{4eq}$). Accurate mass 177.0564 (calcd for $C_7H_{12}NO_2{}^{35}Cl$ 177.0557).

***rel*-(2*R*,3*R*,4*R*)-4-Chloro-3-ethyl-2-piperidinecarboxylic acid methyl ester (53).** According to the procedure used for the preparation of **52**, carbamate **29** (175 mg, 0.663 mmol) was treated with NaI (400 mg, 2.67 mmol) and trimethylsilyl chloride (0.35 mL, 2.76 mmol) in 5 mL of $CH_3CN$ to give **53** (97 mg, 0.47 mmol, 71%) as a light yellow oil. IR 3340 (NH), 1730 (C=O). $^1H$ NMR (200 MHz) 0.92 (t, $J$ = 7.3 Hz, 3 H, $CH_2CH_3$), 1.20-1.45 (m, 1 H), 1.50-1.80 (m, 2 H), 1.92 (bs, 1 H, NH), 1.95-2.15 (m, 2 H), 2.94 (dt, $J$ = 12.0, 4.2 Hz, 1 H, $H^{6eq}$), 3.07 (td, $J$ = 11.4, 3.2 Hz, 1 H, $H^{6ax}$), 3.72 (s, 3 H, $OCH_3$), 4.02 (d, $J$ = 3.4 Hz, $H^{2ax}$), 4.46 (q, $J$ = 3.8 Hz, 1 H, $H^{4eq}$). $^{13}C$ NMR (50 MHz) 11.9 ($CH_3$), 21.0 ($CH_2$), 30.0 (C-5), 40.3 (C-6), 45.7 (C-3), 51.6 ($OCH_3$), 56.8 (C-2), 59.8 (C-3), 173.0 (C=O).

***cis*-4-Hydroxy-2-piperidinecarboxylic acid (54).** Compound **43** (36.3 mg, 0.157 mmol) was dissolved in 5 mL of 2 N aqueous HCl and refluxed for 18 h. The reaction mixture was evaporated *in vacuo* to give a light yellow foam (HCl salt). A column (2 × 20 cm) ofAmberlite CG-120 ($H^+$) (Fluka) was eluted successively with 1000 mL of distilled water, 1000 mL of 5% aq HCl and 1000 mL of distilled water. The HCl salt was dissolved in 2 mL of distilled water and brought on the column. The column was eluted with ca. 1 bedvolume of distilled water and checked with a 5% $AgNO_3$ solution in EtOH until no $Cl^-$ came off anymore. The column was eluted with ca. 4 bedvolumes of distilled water. Finally, the column was eluted with 5% aq $NH_3$ under a light pressure and fractions of 10 mL were combined. The ninhydrin positive frations were combined and evaporated *in vacuo* to give **54** (21.2 mg, 0.146 mmol, 93%) as a thick gum. $^1H$ NMR (250 MHz, $D_2O$) 1.60 (td, $J$ = 13.2, 11.0 Hz, 1 H, $H^{3ax}$), 1.63 (tdd, $J$ = 13.6, 11.1, 4.6 Hz, 1 H, $H^{5ax}$), 2.12-2.21 (m, 1 H, $H^{5eq}$), 2.46-2.56 (m, 1 H, $H^{3eq}$), 3.05 (td, $J$ = 13.3, 3.2 Hz, 1 H, $H^{6ax}$), 3.51 (ddd, $J$ = 13.2, 4.5, 2.6 Hz, 1 H, $H^{6eq}$), 3.67 (dd, $J$ = 12.9, 3.3 Hz, 1 H, $H^{2ax}$), 3.97 (tt, $J$ = 11.0, 4.4 Hz, 1 H, $H^{4ax}$). $^{13}C$ NMR (50 MHz, $D_2O$) 31.9 (C-5), 36.7

(C-3), 43.4 (C-6), 59.9 (C-2), 67.5 (C-4), 175.3 ($CO_2H$).

***rel*-(2*R*,3*R*,4*S*)-3-Ethyl-4-hydroxy-2-piperidinecarboxylic acid (55).** Compound **44** (77.2 mg, 0.315 mmol) was dissolved in 5 mL of 2 N aqueous HCl and refluxed for 18 h. The reaction mixture was evaporated *in vacuo* to give a colourless thick oil. This salt was neutralized and purified on a ion-exchange column as described for **54** to give **55** (54.5 mg, 0.315 mmol, 100%) as a colourless thick gum. $^1$H NMR (200 MHz, $D_2O$) 1.12 (t, $J$ = 7.4 Hz, 3 H, $CH_3$), 1.42 (septet, $J$ = 6.5 Hz, 1 H, $H^{3eq}$), 1.65-2.15 (m, 3 H, $H^{5ax}$ + $CH_2$), 2.40-2.55 (m, 1 H, $H^{5eq}$), 3.16 (td, $J$ = 12.9, 4.2 Hz, 1 H, $H^{6ax}$), 3.57 (ddd, $J$ = 13.1, 4.4, 3.0 Hz, 1 H, $H^{6eq}$), 3.84 (d, $J$ = 3.3 Hz, 1 H, $H^{2ax}$), 4.21 (dt, $J$ = 11.0, 4.7 Hz, 1 H, $H^{4ax}$). $^{13}$C NMR (50 MHz, $D_2O$) 16.1 ($CH_3$), 17.5 ($CH_2CH_3$), 27.0 (C-5), 43.4 (C-6), 44.5 (C-3), 63.5 (C-2), 70.7 (C-4), 174.9 ($CO_2H$).

***rel*-(2*R*,3*S*,4*S*)-3-Ethyl-4-hydroxy-2-piperidinecarboxylic acid (56).** Compound **45** (36.6 mg, 0.149 mmol) was dissolved in 3 mL of 2 N aqueous HCl and refluxed for 18 h. The reaction mixture was evaporated *in vacuo* to give colourless crystalline solid (mp 160-165 °C). This salt was neutralized and purified on a ion-exchange column as described for **54** to give **56** (21.2 mg, 0.112 mmol, 82%) as a white powder (mp > 360 °C). $^1$H NMR (200 MHz, $D_2O$) 0.97 (t, $J$ = 7.3 Hz, 3 H, $CH_3$), 1.50-2.00 (m, 4 H), 2.15-2.30 (m, 1 H,), 3.12 (td, $J$ = 12.9, 3.4 Hz, $H^{6ax}$), 3.40-3.55 (m, 1 H, $H^{6eq}$), 3.51 (d, $J$ = 9.9 Hz, 1 H, $H^{2ax}$), 3.84 (td, $J$ = 9.8, 4.2 Hz, 1 H, $H^{4ax}$). $^{13}$C NMR (50 MHz, $D_2O$) 10.6 ($CH_3$), 21.3 ($CH_2CH_3$), 31.7 (C-5), 43.0 (C-6), 46.5 (C-3), 63.8 (C-2), 68.7 (C-4), 175.1 ($CO_2H$).

**General procedure for cyclization of 18-20 in acetonitrile.** To a 0.2 M solution of the acetoxy compound in acetonitrile at -20 °C was added a 1.2 M solution of $SnCl_4$ (1.2 equiv) in $CH_2Cl_2$ under a nitrogen atmosmphere. The reaction mixture was stirred for 2.5 h at -25/-15 °C and then poured out into excess aq $NaHCO_3$. After extraction with chlorofom (3 ×) the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed

***trans*-4-Acetylamino-1,2-piperidinedicarboxylic acid 1-ethyl, 2-methyl ester (57).** Acetoxy compound **18** (334 mg, 1.22 mmol) was treated with a 1.2 M solution of $SnCl_4$ (1.2 mL, 1.44 mmol) in 5 mL of acetonitrile give **57** (250 mg, 0.918 mmol, 75%) as a colourless oil. $R_f$ 0.15 (EtOAc). IR 3440 (NH), 1740 (C=O), 1685 and 1675 (2 x NC=O). $^1$H NMR (200 MHz) 1.15-1.35 (m, 3 H, $CH_2CH_3$), 1.50 (td, $J$ = 12.3, 6.3 Hz, $H^{3ax}$), 1.65-1.85 (m, 2 H), 1.94 (s, 3 H, $C=OCH_3$), 2.40-2.55 (m, 1 H, $H^{3eq}$), 2.95-3.25 (m, 1 H, $H^{6ax}$), 3.73 (s, 3 H, $OCH_3$), 3.70-3.90 (m, 1 H, $H^{6eq}$), 4.00-4.25 (m, 3 H, $OCH_2$ and $H^{4ax}$), 4.85 (bd) and 5.03 (bd, $J$ = 5.5 Hz, 1 H, $H^{2eq}$), 5.32 (bd, $J$ = 7.0 Hz, 1 H, NH). $^{13}$C NMR (50.3 MHz) 14.4 ($CH_3$), 23.2($C=OCH_3$), 31.3 and 31.5, 32.5 and 32.7, 40.4 (C-6), 44.0 (C-4), 52.4 ($OCH_3$), 53.8 and 54.1 (C-2), 61.8 ($OCH_2$), 155.7 and 156.2 (NC=O), 169.3 ($C=OCH_3$), 171.1 (C=O)

***rel*-(2*R*,3*S*,4*R*)-4-Acetylamino-3-ethyl-1,2-piperidinedicarboxylic acid dimethyl ester (58).** Acetoxy compound **19** (185 mg, 0.643 mmol) was treated with a 1.2 M solution of $SnCl_4$ (0.65 mL, 0.78 mmol) in 3 mL of acetonitrile to give **58** (167 mg, 0.585 mmol, 91%) as a colourless oil. $R_f$ 0.22 (EtOAc). IR 3440 (NH), 1735 (C=O), 1690 (2 x NC=O). $^1$H NMR (250 MHz) 0.95-1.10 (m, 3 H, $CH_2CH_3$), 1.20-1.45 (m, 2 H), 1.50-1.65 (m, 2 H), 1.95 (s, 3 H, $NCOCH_3$), 2.30-2.45 (m, 1 H, $H^{3eq}$), 3.05-3.30 (m, 1 H, $H^{6ax}$), 3.70 (s, 3 H, $OCH_3$), 3.75 (s, 3 H, $OCH_3$), 3.85-4.25 (m, 2 H, $H^{4ax}$ and $H^{6eq}$), 4.80 (bs) and 4.97 (bs, two rotamers, 1 H, $H^{2eq}$), 5.48 (bd, $J$ = 6.1 Hz, 1 H, NH). $^{13}$C NMR (50 MHz) 12.3(b, $CH_3$), 17.5(b, $CH_2$), 23.3 ($C=OCH_3$), 25.7(b, C-5), 40.4 (C-3), 40.5 (C-6), 46.8 (C-4), 52.4 ($OCH_3$), 53.0 ($OCH_3$), 56.2 (C-2), 156.5(b, NC=O), 169.2 ($C=OCH_3$), 171.5 (C=O).

***rel*-(2*R*,3*R*,4*R*)-4-Acetylamino-3-ethyl-1,2-piperidinedicarboxylic acid dimethyl ester (59).** Acetoxy compound **20** (141 mg, 0.492 mmol) was treated with a 1.2 M solution of $SnCl_4$ (0.5 mL, 0.60 mmol) in 3 mL of acetonitrile to give **59** (110 mg, 0.385 mmol, 78%) as a colourless oil. $R_f$ 0.20 (EtOAc). IR 3430 (NH), 1740 (C=O), 1680 (2 x NC=O). $^1$H NMR (200 MHz) 0.92 (t, $J$ = 7.3 Hz, 3 H, $CH_2CH_3$), 1.10-1.75 (m, 4 H), 1.85-2.00 (m, 1 H, $H^{3ax}$), 1.92 (s, 3 H, $NCOCH_3$), 3.25-3.50 (m, 1 H, $H^{6ax}$), 3.65 (s, 6 H, 2 x $OCH_3$), 3.80-4.15 (m, 2 H, $H^{4ax}$ and $H^{6eq}$), 4.88 (bs) and 5.01 (bs, 1 H, two rotamers, $H^{2eq}$), 6.07 (d, $J$ = 9.1 Hz, 1 H, NH). $^{13}$C NMR (50 MHz) 11.5 ($CH_3$), 20.9 ($CH_2$), 23.1 ($C=OCH_3$), 32.2 (C-5), 40.1 (C-6), 45.4 (C-4), 46.9 (C-3), 51.7 ($OCH_3$), 52.8 ($OCH_3$), 55.8 (C-2), 156.2 (NC=O), 169.6 ($C=OCH_3$), 170.3 (C=O).

**Trapping experiment with 18.** Triethylsilane (0.4 mL, 2.5 mmol) was added to a solution of **18** (139 mg, 0.508 mmol) in 2 mL of $CH_2Cl_2$ under a nitrogen atmosphere. At -78 °C, $BF_3$•$OEt_2$ (0.125 mL, 1.02 mmol) was added. The reaction mixture was allowed to warm up to room temperature over 5 h period. The reaction mixture was poured out into water and extracted (3 ×) with 30 mL of $CH_2Cl_2$. The combined organic layers wre dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed to give **[*N*-(ethoxycarbonyl)-*N*-methylamino]allylacetic acid methyl ester (61)** (57 mg, 0.26 mmol, 52%) as a colourless oil. IR 1740 (C=O), 1685 (NC=O). $^1$H NMR (200 MHz) 1.26 (t, $J$ = 7.1 Hz, 3 H, $CH_2CH_3$), 2.35-2.60 (m, 1 H, =CHC*H*), 2.65-2.90 (m, 1

H, =CHC*H*), 2.83 (s(b), 3 H, $NCH_3$), 3.83 (s, 3 H, $OCH_3$), 4.15 (q, $J$ = 7.1 Hz, 2 H, $OCH_2$), 4.62 (dd) and 4.89 (dd, $J$ = 5.6, 5.1 Hz, two rotamers, 1 H, $NCHCO_2Me$), 5.00-5.20 (m, 2 H, $=CH_2$), 5.60-5.80 (m, 1 H, -CH=). $^{13}C$ NMR (50 MHz, 50°C) 14.5 ($CH_3$), 30.7(b), 33.4(b), 52.0, 53.0, 61.6 ($OCH_3$), 117.7 (CH=), 133.7 ($=CH_2$), 156.0 (NC=O), 171.5 (C=O). Accurate mass 215.1153 (calcd for $C_{10}H_{17}NO_4$ 215.1158).

**Trapping experiment with 23.** Under a nitrogen atmosphere, $BF_3{\cdot}OEt_2$ (0.13 mL, 1.06 mmol) was added to a stirred solution of **23** (128 mg, 0.500 mmol) and $Et_3SiH$ (0.40 mL, 2.51 mmol) in 3 mL of $CH_2Cl_2$ at -78 °C. The reaction mixture was allowed to warm up to room temperature in a 3 hour period. The reaction mixture was poured out in water and extracted (3 ×) with 15 mL of $CH_2Cl_2$. The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed to give starting compound **23** (51 mg, 0.20 mmol, 40%) and **2-oxo-α-(2-propenyl)-1-pyrrolidineacetic acid methylester (63)** (30 mg, 0.15 mmol, 30%) $R_f$ 0.45 (EtOAc). IR 1740 (C=O), 1675 (NC=O). $^1H$ NMR (200 MHz) 1.90-2.20 (m, 2 H, $NCH_2CH_2$), 2.30-2.55 (m, 3 H, $CH_2CH$= + C=OCH), 2.60-2.80 (m, 1 H, C=OCH), 3.25-3.55 (m, 2 H, $NCH_2$), 3.69 (s, 3 H, $OCH_3$), 4.86 (dd, $J$ = 10.1 Hz, $J$ = 5.1 Hz, $NCHCO_2$), 5.00-5.15 (m, 2 H, $=CH_2$), 5.55-5.80 (m, 1 H, -CH=). $^{13}C$ NMR (50 MHz) 18.2 (C-4), 30.7 (C-3), 33.2 ($CH_2CH$=), 43.6 (C-5), 52.1 ($OCH_3$), 53.0 (NCH), 117.9 ($=CH_2$), 133.3 (-CH=), 170.9 (C=OO), 175.7 (C-2). Accurate mass 197.1083 (calcd for $C_{10}H_{15}NO_3$ 197.1052).

**Trapping experiment with 22.** Triethylsilane (0.31 mL, 1.9 mmol) was added to a solution of **22** (105 mg, 0.385 mmol) in 2 mL of $CH_2Cl_2$ under a nitrogen atmosphere. At -78 °C, $BF_3{\cdot}OEt_2$ (0.09 mL, 0.73 mmol) was added. The reaction mixture was allowed to warm up to room temperature over 5 h period. The reaction mixture was poured out into water and extracted (3 ×) with 30 mL of $CH_2Cl_2$. The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed to give alcohol **47** (17.8 mg, 0.077 mmol, 20%) and an inseparable 59:28:13 mixture (52.4 mg, 0.244 mmol, 63%) of (*E*)- and (*Z*)-[*N*-**methyl-*N*-(methoxycarbonyl)amino]-2-butenylacetic acid dimethyl ester (65a, 65b)** and ***N*-(2-methyl-3-butenyl)-*N*-(methoxycarbonyl)glycine methyl ester (64).** $R_f$ 0.57 (EtOAc/hexanes: 1/2). IR 1740 (C=O), 1685 (NC=O). $^1H$ NMR (250 MHz) 0.95 (d, $J$ = 6.7 Hz, 3 H, $CH_3$ **64**), 1.59 (s) and 1.62 (s, 3 H, $CH_3$ **65a, 65b**), 2.25-2.70 (m, 2 H, $CH_2CH$=, **65a, 65b**), 2.79 (s) and 2.83 (s, 3 H, $NCH_3$ **65a, 65b**), 3.00-3.25 (m, 2 H, $CH_2N$, **64**), 3.68 (s) and 3.69 (s, 6 H, 2 × $OCH_3$), 3.91 (s) and 3.79 (s, two rotamers, 2 H, $NCH_2CO_2Me$, **64**), 4.45-4.60 (m, 1 H, $NCHCO_2Me$, **65b**), 4.70-4.85 (m, 1 H, $NCHCO_2Me$ **65a**), 4.85-5.05 (m, 2 H, $=CH_2$), 5.15-5.35 (m, 1 H, -CH=, **65a, 65b**), 5.40-5.60 (m, 1 H, -CH= **65a, 65b**), 5.45-5.80 (m, 1 H, -CH=, **64**). $^{13}C$ NMR (63 MHz) 12.8 ($CH_3$ **65b**), 17.8 ($CH_3$ **65a**), 26.5 ($NCH_2$ **64**), 30.4 ($NCH_3$, **65a, 65b**), 32.1 ($CH_2CH$= **65a**), 32.4 ($CH_2CH$= **65b**), 48.9 and 49.1 ($NCH_2CO_2$, **64**), 52.0 ($OCH_3$), 52.8 ($OCH_3$), 58.5 ($NCHCO_2$, **65a, 65b**), 115.3 ($=CH_2$, **64**), 125.0 ($CH_3CH$=, **64b**), 125.9 ($CH_3CH$=, **65a**), 127.0 ($CH_3CH$=$CH$, **65b**), 128.4 ($CH_3CH$=$CH$, **65a**), 141.8 (-CH=, **64**), 156.0 (NC=O), 170.2 (C=O, **64**), 171.7 (C=O, **65a, 65b**). Accurate mass 215.1122 (calcd for $C_{10}H_{17}NO_4$ 215.1157).

## ACKNOWLEDGEMENTS

K. Goubitz, and D. Heijdenrijk (Department of Crystallography, University of Amsterdam) are gratefully acknowledged for the X-ray crystal structure determination. We thank C. Kruk and his staff for their help in obtaining and interpreting the NMR spectra, and M. J. Moolenaar and M. J. Wanner for the preparation of some essential starting materials. This work was supported by the Netherlands Foundation for Chemical Research (SON) with financial aid from the Netherlands Organization for Advancement of Pure Research (NWO).

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