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FORMIC ACID-INDUCED π-CYCLIZATION OF GLYCINE CATION EQUIVALENTS TO SUBSTITUTED PIPECOLIC ACID DERIVATIVES

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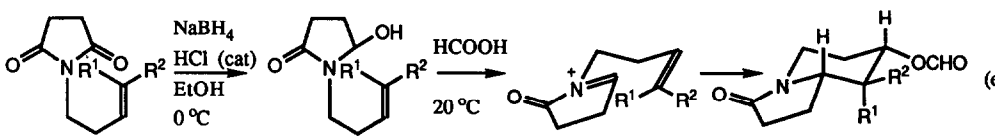
Summary: Formic acid-mediated cyclization reactions of *N*-(3-alkenyl)-*N*-(methoxycarbonyl)-acetoxyglycine esters are described. The major reaction products are 4-formyloxypipecolic acid derivatives, formed with low stereoselectivity at C-4. The several subtle features of the cyclization process are satisfactorily explained by a mechanism involving (1) a rapid cationic aza-Cope rearrangement of the incipient iminium ion and (2) participation of the ester moiety through formation of a relatively stable bicyclic dioxycarbenium cation as pivotal intermediate.

INTRODUCTION

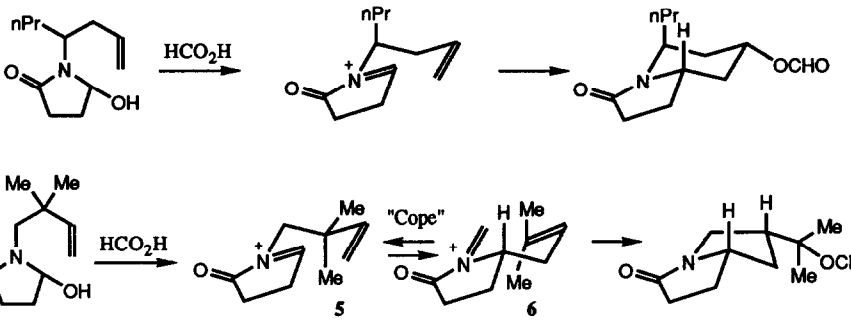
N-Acyliminium ions are highly useful intermediates for the preparation of *N*-heterocycles.[1] The intramolecular reactions with alkenes have proved particularly suited for the total synthesis of several alkaloids.[2] These applications arose from the fundamental work of the late seventies on the formic acid induced cyclizations of *cyclic* *N*-acyliminium ions derived from *N*-substituted succinimides (eq 1). Such reactions usually proceed best in neat formic acid and are attended with virtually complete regio- and stereocontrol, leading to six-membered rings via chair-like transition states with stereospecific *trans*-addition to the alkene double bond. Thus, hydroxylactams **1** and **2** exclusively give **3** and **4**, respectively.[3]



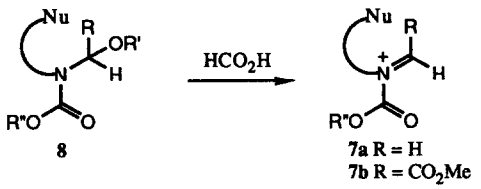
1 R^1 = H, R^2 = Me
2 R^1 = Et, R^2 = H

3 R^1 = H, R^2 = Me
4 R^1 = Et, R^2 = H

Later work on molecules bearing substituents on the chain connecting nitrogen and double bond have revealed additional relevant information about the mechanistic details. Thus, a substituent homoallylic with respect to the alkene ends up in an axial position, in order to avoid allylic 1,3-strain caused by the *N*-acyl group (eq 2).[4,5] Furthermore, the presence of certain allylic substituents leads to five-membered ring formation (eq 3).[6] This result proves the occurrence of a fast cationic aza-Cope equilibrium between iminium ions **5** and **6**. Such equilibria are likely also present in the reactions of eq 1 and 2, but do not show up, because both "Cope" isomers lead to the same cyclization product. In eq 3, however, iminium ion **6** contains a more nucleophilic double bond than **5**, while the electronic bias of the double bond in **6** is such that only 5-membered ring formation occurs.[6]



In this paper similar cyclization reactions of *acyclic* iminium ions **7** are described, generated from **8** in neat formic acid (eq 4). This work parallels our studies of Lewis acid-induced cyclizations of the same type.[7] Few examples of formic acid-induced cyclizations of **7** with simple alkenes as nucleophiles are known in the literature and stereochemical aspects have received little attention.[8] The main theme of this paper is the cyclization of glycine cation equivalents **7b**, leading to cyclic α-amino acid derivatives.[7]

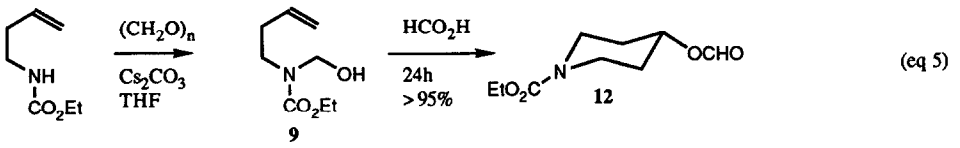


8

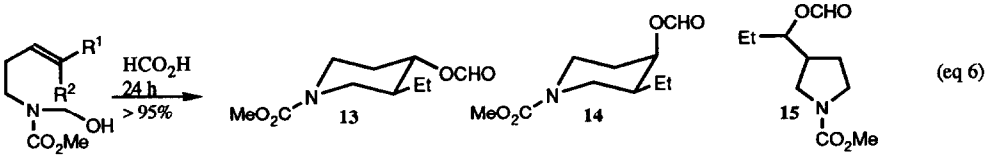
7a R = H
7b R = CO_2Me

RESULTS

The simple iminium ions **7a** were generated from *N*-hydroxymethylcarbamates **9-11** (eq 5, 6). These latter compounds were prepared from the corresponding NH-carbamates by treatment with paraformaldehyde in the presence of cesium carbonate,[9] and were stable enough to be purified by flash chromatography. When these iminium ion precursors **9-11** were stirred in formic acid at room temperature for 24 h complete cyclization occurred. The parent **9** gave 4-formyloxypiperidine **12** as the sole product (eq 5).



9 **12**



13 **14** **15**

10 R^1 = Et, R^2 = H	88	:	4	:	8	
11 R^1 = H, R^2 = Et	18	:	73	:	9 (20:80 mixture)	

The (*E*)- and (*Z*)-alkenes **10** and **11** gave mixtures of the same three products **13-15** albeit in completely different ratios (eq 6). The stereochemistry of **13** and **14** could be readily inferred from their ^{1}H NMR spectra. The hydrogen adjacent to the formyloxy function showed the characteristic splitting pattern for an axial, respectively equatorial disposition (Table I). The pyrrolidine byproduct **15** was obtained as a mixture of stereoisomers.

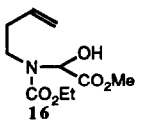
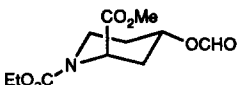
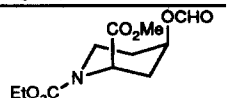
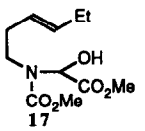
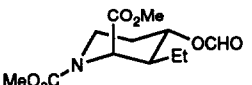
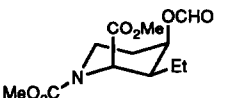
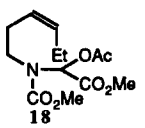
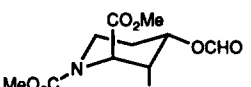
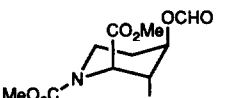
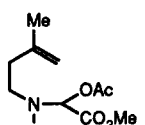
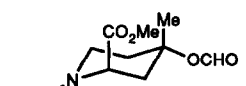
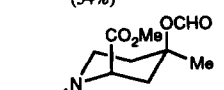
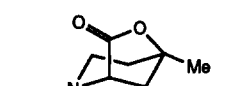
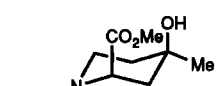
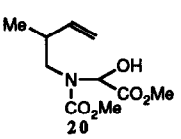
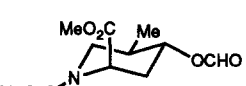
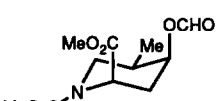
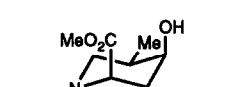
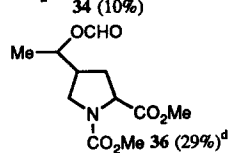
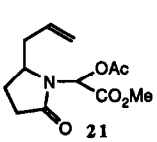
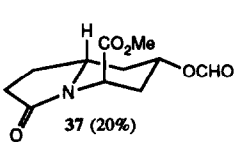
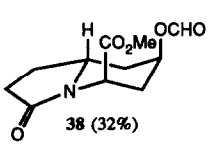
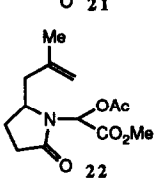
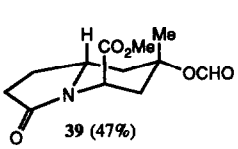
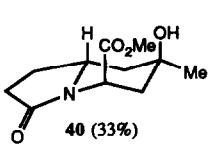
Table I Selected ^{1}H NMR data (ppm)

compound	N-C<u>H</u>CO$_2$R	HC-OCHO	C-C<u>H</u>$_3$
12	-	5.07 (tt, *J* = 7.8, 3.9 Hz)	-
13	-	4.79 (td, *J* = 8.4, 4.1 Hz)	-
14	-	5.27 (bs)	-
15	-	4.90-5.05 (m)	-
23	4.90, 5.07 (bs)	4.87 (tt, *J* = 11.5, 4.3 Hz)	-
24	4.78, 4.88 (bs)	5.21 (bt, *J* = 2.7 Hz)	-
25	4.95, 5.10 (bs)	5.12 (td, *J* = 10.7, 4.6 Hz)	-
26	4.70, 4.87 (d, *J* = 5.9 Hz)	5.25 (bs)	-
27	---4.8-5.1 (m)[a]---		-
28	4.60, 4.78 (s)	5.03 (bd, *J* = 2.7 Hz)	-
29	4.74, 4.89 (d, *J* = 6.2 Hz)	-	1.57 (s)
30	obscured	-	1.50 (s)
31	4.85 (bs)	-	1.53 (s)
32[b]	4.72, 4.89 (d, *J* = 6.6 Hz)	-	1.25 (s)
33	4.91, 5.07 (bd, *J* = 6.4 Hz)	4.62 (td, *J* = 11.0, 4.3 Hz)	0.90 (d, *J* = 6.5 Hz)
34	4.72, 4.88 (d, *J* = 6.7 Hz)	5.08 (bs)	0.87 (d, *J* = 6.7 Hz)
35[b]	4.68, 4.85 (d, *J* = 6.6 Hz)	3.75 (obsc)	0.94, 0.95 (d, *J* = 6.9 Hz)
36	4.30-4.50 (m)	4.97 (m)	1.26 (d, *J* = 6.3 Hz)
37	---4.8-5.0 (m)[a]---		-
38	4.74 (d, *J* = 7.1 Hz) 5.25 (bs)	-	-
39	4.84 (d, *J* = 6.5 Hz) -	1.50 (s)	-
40	4.73 (d, *J* = 5.9 Hz) -	1.26 (s)	-
41	3.94 (dd, *J* = 11.7, 3.8 Hz)	4.26 (quintet, *J* = 3.1 Hz)	-

[a] Signals of H-2 and H-4 overlapped. [b] See reference 7.

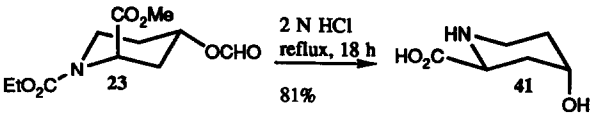
Glycine cation equivalents were generated from α-hydroxy or α-acetoxycarbamates **16-22** (Table II).[6] The cyclization reactions were performed by stirring these precursors in formic acid at room temperature for 1-3 days. The products could be purified by flash chromatography in most cases. The stereochemical assignments were mainly based on ^{1}H NMR data (Table I). A key element for the assignment was the axial orientation of the ester function α to nitrogen in all cases. This conformation is imposed by the methoxycarbonyl substituent on nitrogen to avoid allylic 1,3-strain.[5,10] The hydrogens adjacent to nitrogen often showed broad signals due to slow rotation on the NMR timescale around the CN bond of the carbamate moiety. The α-ester hydrogens usually gave different signals for the two rotamers (see Table I). The coupling constant, when visible, was less than 8 Hz, which points to an equatorial orientation of H-2. This was further confirmed by its chemical shift of ca. 4.90 ppm. Exhaustive hydrolysis (eq 7) of **23** gave α-amino acid **41**, a naturally occurring compound.[11] The C-2 hydrogen now absorbed at 3.94 ppm, ca. 1 ppm

Table II Results of the formic acid induced cyclizations of **16-22**

entry	cyclization precursor	products (yield)[a]	
1	 **16**	 **23** (39%)	 **24** (48%)
2	 **17**	 **25** (16%)	 **26** (59%)
3	 **18**	 **27** (43%)	 **28** (34%)[b]
4	 **19**	 **29** (36%)[c]	 **30** (6%)[c]
		 **31** (15%)	 **32** (13%)
5	 **20**	 **33** (35%)	 **34** (10%)
		 **35** (5%)	 **36** (29%)[d]
6	 **21**	 **37** (20%)	 **38** (32%)
7	 **22**	 **39** (47%)	 **40** (33%)

[a] Isolated yields; [b] This product was contaminated with 4% of **26**; [c] Compounds **29** and **30** could not be seperated; [d] mixture of stereoisomers.

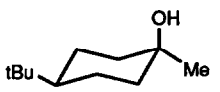
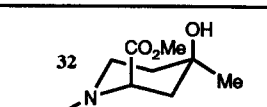
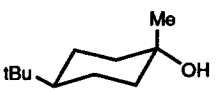
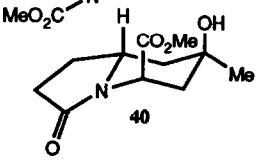
upfield compared to **23**, and the splitting pattern (Table I) clearly indicated an axial orientation.



(eq 7)

The signals of the hydrogens adjacent to the formyloxy function were also very diagnostic. Axial hydrogens showed well resolved multiplets with ax-ax couplings of ca. 11 Hz, whereas equatorial hydrogens gave narrower signals without much resolution (Table I). Treatment of **24**, **26**, and **28** with methanolic ammonia led to the corresponding axial alcohols, which have been characterized before.[7] Also alcohols **32** and **35** were described in our previous paper.[7] The stereochemistry of **32** and **40** could be inferred from the ^{13}C NMR chemical shifts of their quaternary methyl groups (Table III). The formation of a five-membered ring in one case (entry 5, Table II) was apparent from the deviating chemical shift of H-2 of **36** (see Table I) and the low field methyl doublet (cf. products **33-35**). A COSY-spectrum provided conclusive evidence for the structure of **36**.

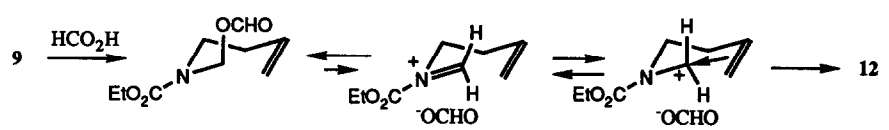
Table III Selected ^{13}C NMR chemical shift data (ppm)

compound	δ(C-$\underline{C}H_3$)	compound	δ(C-$\underline{C}H_3$)
	31.5[a]		30.9
	25.3[a]		30.3

[a] See reference 12.

DISCUSSION

The mechanistic events during cationic cyclization of **9** to **12** involve, successively, formation of a formate, reversible formation of an iminium ion, reversible formation of a π-complex between the cationic carbon atom and the alkene in a chair-like conformation, and irreversible trapping of this π-complex by back-side attack of formate at the most positively charged carbon of the original double bond. This usual sequence of events in cationic olefin cyclization[13] (to a six-membered ring) is shown in eq 8.

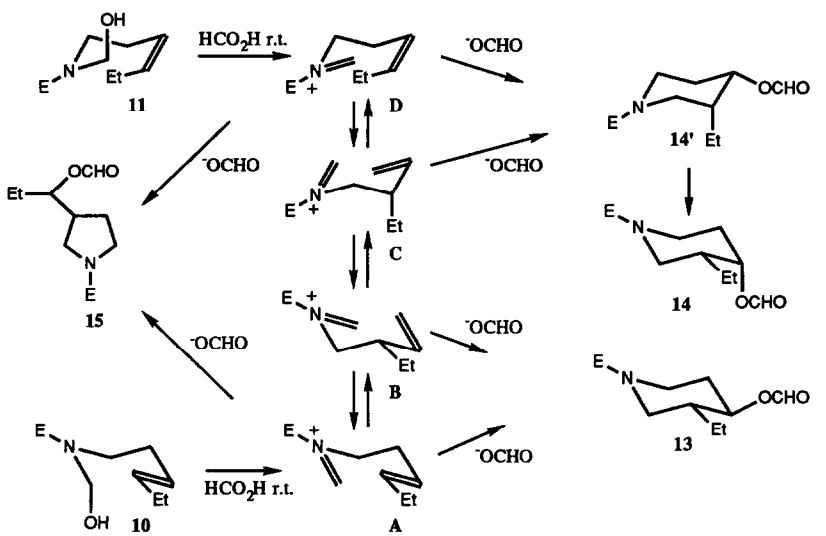


(eq 8)

Stereochemical details of such a process are revealed in the ring closures of **10** and **11** (eq 6). From (*E*)-alkene **10** iminium ion **A** arises, which will be in a fast cationic aza-Cope rearrangement with **B** (Scheme I).[14] Cyclization of both **A** and **B** preferably leads to piperidine derivative **13**. Similarly, (*Z*)-alkene **11** produces **14** (initially in a less favourable conformation **14'**), which is isomeric to **13** at C-3. The

minor 5-membered ring product **15** from both **10** and **11**, arising from **A** and **D**, respectively, indicates that with an electronically and sterically unbiased alkene 5-ring formation can compete to some extent with 6-ring formation. Five-membered ring formation does not occur if the iminium moiety is endocyclic in a pyrrolidinone ring (eq 1).[3] Moreover, cyclizations of **A** and **D**, mediated by $SnCl_4$, also exclusively give 6-membered rings.[7] A point of similarity between the formic acid and $SnCl_4$ induced ring closure is the stereochemical leakage, being more serious for the (*Z*)- than for the (*E*)-alkene.[7] As discussed earlier this can be readily explained by invoking an equilibrium between **B** and **C**, which favours **B** due to the pseudo-equatorial disposition of the ethyl group in **B** versus a pseudo-axial orientation in **C**.

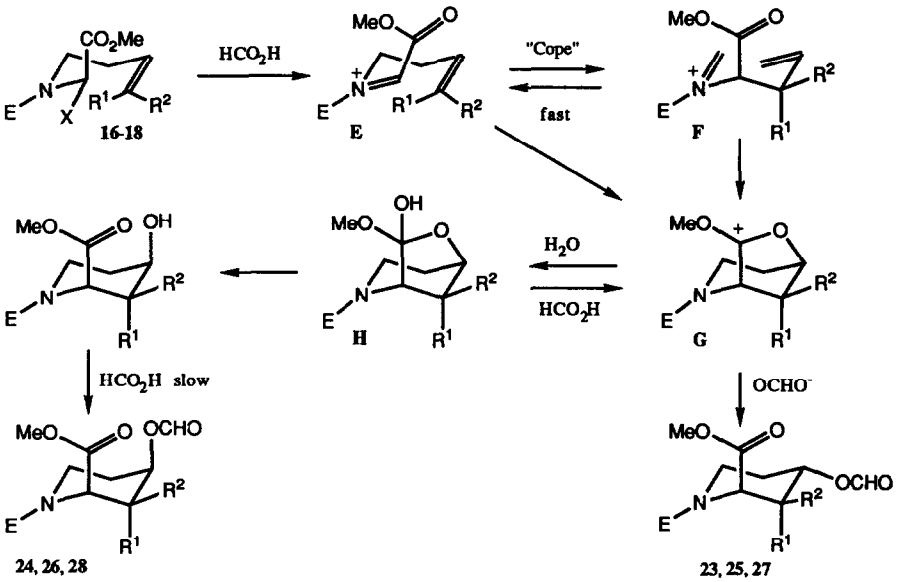
Scheme I (E = CO_2Me)



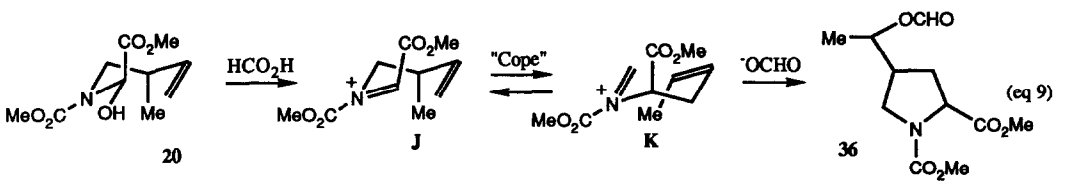
Application of the mechanism of eq 8 to the cyclizations of glycine cations shown in Table II well explains the formation of the equatorial formates (e.g. **23**, **25**, **27** and **37**). The axial orientation of the α-amino ester function could then be the result of the avoidance of allylic 1,3-strain.[4,5] However, the mechanism of eq 8 does not account for the presence of axial formates in most reaction mixtures. Importantly, product ratios are kinetically controlled in most cases. This was proved for entry 1, because stirring of both **23** and **24**, separately, in formic acid for 24 h did not give a trace of epimerization. The results of Table II can be understood by invoking a mechanism (illustrated for precursors **16-18** in Scheme II) similar to that put forward for the $SnCl_4$-induced cyclizations.[7] First, a rapid equilibrium is established between the incipient iminium ion **E** and its isomer **F**. From either of these species the more stable dioxycarbenium ion **G** is formed irreversibly via *cis*-addition of carbon and oxygen to the double bond.[7] Formate attack by an S_N2 mechanism at C-4 of the piperidine ring leads to the equatorial formates. Alternatively, **G** can capture a water molecule[15] to give **H**, which opens to an axial alcohol. This latter alcohol is then esterified by formic acid to an axial formate. Where applicable, the cyclization process may

also go via a tertiary cation (entries 4,7). The isolation of an axial alcohol in certain cases (entries 4, 5, 7) can be explained by assuming slow esterification in these more sterically hindered systems. Formation of lactone **31** probably arises from attack of formate on the methoxy function in **G**. Finally, the pyrrolidine **36** might be formed by direct cyclization of (Z)-alkene **K** to a five-membered ring (eq 9), whereby **K** is in equilibrium with iminium ion **J** with an axial methyl group (cf. a similar cyclization in reference 7). The remaining cyclization products from **20** arise via **G** with an equatorial C-5 methyl substituent.

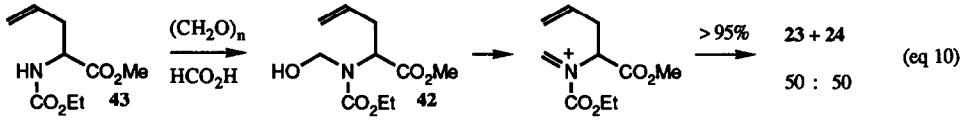
Scheme II (E = CO_2R)



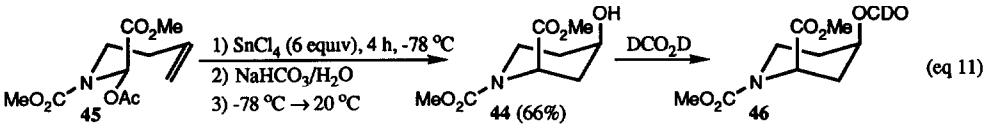
With the mechanism of Scheme II the products of Table II can be satisfactorily explained. The ratios of axial and equatorial 4-oxy products is not so readily understood. It cannot be excluded that equatorial formates are (also) formed by direct cyclization of iminium ions without the intermediacy of a dioxycarbenium ion of type **G**.



Experimental proof for the details of Scheme II was gathered as follows. Evidence for the occurrence of the cationic aza-Cope rearrangement was obtained by carrying out a cyclization reaction starting from iminium precursor **42**. This compound was prepared *in situ* (see eq 10) from allylglycine derivative **43**,[16] by stirring with paraformaldehyde in formic acid, and cyclized under the same conditions to a 50:50 mixture of **23** and **24**. This ratio is within experimental error of the ratio obtained from iminium precursor **16** (Table II, entry 1) and confirms that Cope equilibration is fast compared to cyclization.

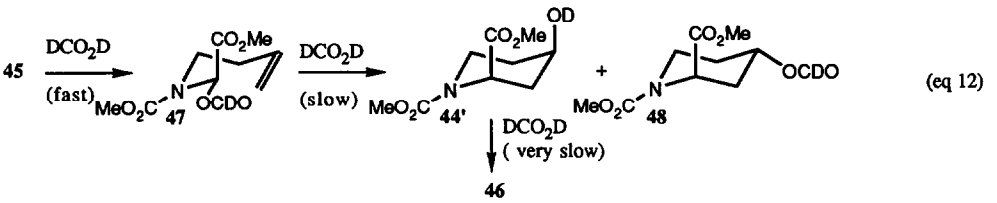


(eq 10)



(eq 11)

The formation of the axial formates by slow formylation of axial alcohols was proved by using ^1H NMR spectroscopy. To this end axial alcohol **44** was synthesized by $SnCl_4$-induced cyclization of **45** followed by aqueous quench at -78 °C (eq 11).[7] A solution of alcohol **44** in deuteroformic acid (DCO_2D) was monitored by ^1H NMR. The signal of H-4 of alcohol **44** at 4.33 ppm slowly disappeared, while at the same time the signal of H-4 of formate **46** at 5.28 ppm grew. After 18 h this conversion was virtually complete. Then acetate **45** was dissolved in DCO_2D and the resulting events were monitored by ^1H NMR. First a very fast conversion to formate **47** was observed (eq 12). At a slower rate **44'** and **48** appeared in the spectrum, in a ca. 1:1 ratio, easily visible by the H-4 hydrogens at 4.33 and 4.96 ppm, respectively. The signal of **48** remained growing, while at a certain time the signal of **44'** began to decrease because of slow conversion of **44'** to formate **46**.



(eq 12)

In conclusion, this paper provides fundamental information about the formic acid mediated cyclization of the cationic 2-aza-1,5-hexadiene entity. The cationic aza-Cope rearrangement is an essential part of the mechanistic scheme describing the cyclization process. A methoxycarbonyl substituent at the 1- (or 3-) position drastically intervenes in the normal cyclization mechanism to give bicyclic dioxycarbenium ion **G** as the pivotal intermediate. This intermediate is responsible for the formation of mixtures of isomeric pipecolic esters as cyclization products.

EXPERIMENTAL

General information. See reference 7.

General procedure for the methylol synthesis.[9] To a solution of the carbamate in 15 mL of THF was added, successively, paraformaldehyde (1.1 equiv) and Cs_2CO_3 (2 equiv). The reaction mixture was stirred at room temperature for 24 h. The excess Cs_2CO_3 was filtered off and the filtrate was concentrated *in vacuo*. The residue was chromatographed.

Ethyl *N*-(3-butenyl)-*N*-(hydroxymethyl)carbamate (9). Ethyl *N*-(3-butenyl)carbamate[7] (386 mg, 2.70 mmol) was treated with paraformaldehyde (90 mg, 3.0 mmol) and Cs_2CO_3 (1.7 g, 5.22 mmol) in 15 mL of THF to give **37**

OCH_2CH_3), 2.60 (bs) and 3.20 (bs, two rotamers, 1 H, OH), 2.34 (q, J = 7.1 Hz, 2 H, =CHCH_2), 3.41 (t, J = 7.1 Hz, 2 H, CH_2CH_2N), 4.17 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 4.74 (bs) and 4.78 (bs, two rotamers, 2 H, CH_2OH), 5.00-5.15 (m, 2 H, $=CH_2$), 5.65-5.90 (m, 1 H, =CH-).

Methyl *N*-[(*E*)-3-hexenyl]-*N*-(hydroxymethyl)carbamate (10). Methyl *N*-[(*E*)-3-hexenyl]carbamate[7] (127 mg, 0.812 mmol) was treated with paraformaldehyde (25 mg, 0.83 mmol) and Cs_2CO_3 (530 mg, 1.63 mmol) in 15 mL of THF to give **38** (62 mg, 0.33 mmol, 41%) as a colourless oil. R_f 0.23 (EtOAc/hexanes: 1/2). IR 3590 (s) and 3440 (b, OH), 1690 (NC=O). ^{1}H NMR (200 MHz) 0.95 (t, J = 7.4 Hz, 3 H, CH_2CH_3), 1.99 (quintet, J = 7.3 Hz, 2 H, CH_2CH_3), 2.24 (bq, J = 6.7 Hz, 2 H, NCH_2CH_2), 3.20-3.45 (m, 2 H, NCH_2CH_2), 3.72 (s, 3 H, OCH_3), 4.75 (s, 2 H, CH_2OH), 5.25-5.40 (m, 1 H, -CH=), 5.40-5.60 (m, 1 H, -CH=).

Methyl *N*-[(*Z*)-3-hexenyl]-*N*-(hydroxymethyl)carbamate (11). Methyl *N*-[(*Z*)-3-hexenyl]carbamate[7] (305 mg, 1.94 mmol) was treated with paraformaldehyde (60 mg, 2.0 mmol) and Cs_2CO_3 (1.20 g, 3.68 mmol) in 15 mL of THF to give **39** (280 mg, 1.49 mmol, 77%) as a colourless oil. R_f 0.23 (EtOAc/hexanes: 1/2). IR 3590 (s) and 3440 (b, OH), 1690 (NC=O). ^{1}H NMR (200 MHz) 0.95 (t, J = 7.5 Hz, 3 H, CH_2CH_3), 2.03 (quintet, J = 7.4 Hz, 2 H, CH_2CH_3), 2.31 (bq, J = 7.2 Hz, 2 H, NCH_2CH_2), 3.25-3.50 (m, 2 H, NCH_2CH_2), 3.73 (s, 3 H, OCH_3), 4.74 (bs) and 4.77 (bs, two rotamers, 2 H, CH_2OH), 5.20-5.40 (m, 1 H, -CH=), 5.40-5.60 (m, 1 H, -CH=).

Cyclization of 9. Methylol **9** (78 mg, 0.45 mmol) was dissolved in 1 mL of formic acid and stirred for 24 h at room temperature. The reaction mixture was evaporated *in vacuo*. The residue was diluted with 2 mL of toluene and evaporated *in vacuo*. This was repeated twice to give **4-formyloxy-1-piperidinecarboxylic acid ethyl ester (12)** (89 mg, 0.44 mmol, 100%) as a colourless oil. R_f 0.51 (EtOAc/hexanes: 1/2). IR 1720 (HC=O), 1680 (NC=O). ^{1}H NMR (200 MHz) 1.24 (t, J = 7.1 Hz, 3 H, CH_3), 1.55-1.75 (m, 2 H), 1.75-2.00 (m, 2 H), 3.31 (ddd, J = 13.6, 8.3, 3.8 Hz, 2 H, H^{2ax} and H^{6ax}), 3.65-3.80 (m, 2 H, H^{2eq} and H^{6eq}), 4.12 (q, J = 7.1 Hz, 2 H, OCH_2), 5.07 (tt, J = 7.8 3.9 Hz, 1 H, H^{4ax}), 8.04 (s, 1 H, OCHO).

Cyclization of 10. According to the procedure used for the cyclization of **9**, methylol compound **10** (49 mg, 0.26 mmol) was stirred in 2 mL formic acid to give a 88:4:8 mixture of **13:14:15** in quantitative yield.

Cyclization of 11. According to the procedure used for the cyclization of **9**, methylol compound **11** (240 mg, 1.26 mmol) was stirred in 5 mL formic acid to give a 18:73:9 mixture of **13:14:15** in quantitative yield. This mixture was chromatographed to give two fractions. The first fraction consisted of a 22:78 mixture of ***trans*-3-ethyl-4-formyloxy-1-piperidinecarboxylic acid methyl ester (13)** and ***cis*-3-ethyl-4-formyloxy-1-piperidinecarboxylic acid methyl ester (14)** (217 mg, 1.01 mmol, 80%) as a colourless oil. R_f 0.60 (EtOAc/hexanes: 1/1). IR 1715 (C=O), 1680 (NC=O). ^{1}H NMR (200 MHz) **13**: 0.91 (t, J = 7.3 Hz, 3 H, CH_2CH_3), 1.05-1.30 (m, 1 H), 1.40-1.65 (m, 3 H), 1.88-2.00 (m, 1 H), 2.75-2.95 (m, 1 H), 3.05-3.20 (m, 1 H), 3.66 (s, 3 H, OCH_3), 3.75-4.05 (m, 2 H), 4.79 (td, J = 8.4, 4.1 Hz, 1 H, H^{4ax}), 8.05 (s, 1 H, OCHO); **14** (characteristic signals): 5.27 (bs, 1 H, H^{4eq}). ^{13}C NMR (63 MHz) **13**: 10.9 (CH_3), 22.0 (CH_2), 29.5 (C-5), 41.4 (C-6), 41.5 (C-3), 45.3 (C-2), 52.5 (OCH_3), 73.4 (C-4), 155.7 (NC=O), 160.2 (HC=O); **14**: 10.8 (CH_3), 21.0 (CH_2), 29.3 (C-5), 39.0 (C-6), 40.5 (C-3), 44.0 (C-2), 52.5 (OCH_3), 69.1 (C-4), 155.9 (NC=O), 160.2 (HC=O). The second fraction consisted of **3-(1-formyloxypropyl)-1-pyrrolidinecarboxylic acid methyl ester (15)** (24 mg, 0.11 mmol, 9%) as a colourless oil. R_f 0.45 (EtOAc/hexanes: 1/1). IR 1715 (C=O), 1680 (NC=O). ^{1}H NMR (250 MHz, a 20:80 mixture of diastereoisomers) 0.91 (t, J = 7.4 Hz, 3 H, CH_2CH_3), 1.45-1.75 (m, 3 H), 1.85-2.10 (m, 1 H), 2.30-2.55 (m, 1 H), 2.85-3.70 (m, 4 H, CH_2NCH_2), 3.67 (s, 3 H, OCH_3), 4.90-5.05 (m, 1 H, C*H*OCHO), 8.10 and 8.12 (s, 1 H, OCHO).

Cyclization of 16. Hydroxy compound **16**[7] (93.5 mg, 0.405 mmol) was dissolved in 1 mL of formic acid and stirred for 3 days at room temperature. The formic acid was evaporated *in vacuo*. The residue was diluted with 2 mL of toluene and evaporated *in vacuo*. The residue was chromatographed to give two fractions. The first fraction consisted of ***trans*-4-formyloxy-1,2-piperidinedicarboxylic acid 1-ethyl, 2-methyl ester (23)** (40.8 mg, 0.157 mmol, 39%) as a colourless oil. R_f 0.27 (EtOAc/hexanes: 1/2). IR 1735 (C=O), 1720 (HC=O), 1685 (NC=O). ^{1}H NMR (200 MHz) 1.15-1.35 (m, 3 H, CH_2CH_3), 1.53 (qd, J = 12.7, 5.0 Hz, 1 H, H^{5ax}), 1.78 (td, J = 12.5, 6.3 Hz, 1 H, H^{3ax}), 1.95-2.10 (m, 1 H, H^{5eq}), 2.50 (bd, J = 12.9 Hz, 1 H, H^{3eq}), 2.95-3.20 (m, 1 H, H^{6ax}), 3.75 (s, 3 H, OCH_3), 4.00-4.20 (m, 1 H,

1.15-1.35 (m, 3 H, CH_2CH_3), 1.53 (qd, J = 12.7, 5.0 Hz, 1 H, H^{5ax}), 1.78 (td, J = 12.5, 6.3 Hz, 1 H, H^{3ax}), 1.95-2.10 (m, 1 H, H^{5eq}), 2.50 (bd, J = 12.9 Hz, 1 H, H^{3eq}), 2.95-3.20 (m, 1 H, H^{6ax}), 3.75 (s, 3 H, OCH_3), 4.00-4.20 (m, 1 H, H^{6eq}), 4.15 (q, J = 7.1 Hz, 2 H, CH_2O), 4.87 (tt, J = 11.5, 4.3 Hz, 1 H, H^{4ax}), 4.90 (bs) and 5.07 (bs, two rotamers, 1 H, H^{2eq}), 8.00 (s, 1 H, OHCO). ^{13}C NMR (63 MHz) 14.5 (CH_3), 30.4, 31.7, 39.8 (C-6), 52.5 (OCH_3), 53.8 (C-2), 61.9 (OCH_2), 68.1 (C-4), 155.9 (NC=O), 160.0 (HC=O), 171.1 (C=O). Accurate mass 259.1088 (calcd for $C_{11}H_{17}NO_6$ 259.1056). The second fraction consisted of ***cis*-4-formyloxy-1,2-piperidinedicarboxylic acid 1-ethyl, 2-methyl ester (24)** (49.9 mg, 0.193 mmol, 48%) as a colourless oil. R_f 0.36 (EtOAc/hexanes: 1/2). IR 1735 (C=O), 1720 (HC=O), 1685 (NC=O). ^1H NMR (200 MHz) 1.15-1.30 (m, 3 H, CH_2CH_3), 1.60-2.00 (m, 3 H, H^{3ax} and H^{5ax} and H^{5eq}), 2.59 (bd, J = 13.6 Hz, 1 H, H^{3eq}), 3.15-3.45 (m, 1 H, H^{6ax}), 3.71 (s, 3 H, OCH_3), 3.85-4.10 (m, 1 H, H^{6eq}), 4.15 (q, J = 7.1 Hz, 2 H, OCH_2), 4.78 (bs) and 4.88 (bs, two rotamers, 1 H, H^{2eq}), 5.21 (bt, J = 2.7 Hz, 1 H, H^{4eq}), 7.92 (s, 1 H, OCHO). ^1H NMR (C_6D_6, 200 MHz) 0.95-1.45 (m, 6 H, CH_2CH_3 and H^{3ax} and H^{5ax} and H^{5eq}), 2.40 (ddt, J = 14.6, 3.3, 2.1 Hz, 1 H, H^{3eq}), 3.32 (s, 3 H, OCH_3), 3.30-3.55 (m, 1 H, H^{6ax}), 3.80 (bd, J = 13.6 Hz) and 4.10-4.30 (m, two rotamers, 1 H, H^{6eq}), 4.68 (bd) and 5.06 (bd, J = 6.9 Hz, two rotamers, 1 H, H^{2eq}), 4.80 (t, J = 2.9 Hz, 1 H, H^{4eq}), 7.47 (s, 1 H, OCHO). ^{13}C NMR (50 MHz) 14.5 (CH_3), 28.5, 30.3, 36.0 (C-6), 50.7 (C-2), 52.1 (OCH_3), 61.8 (OCH_2), 66.2 (C-4), 156.0 (NC=O), 159.7 (HC=O), 171.6 (C=O). Accurate mass 259.1042 (calcd for $C_{11}H_{17}NO_6$ 259.1056).

Cyclization of 17. Hydroxy compound **17**[7] (207 mg, 0.845 mmol) was dissolved in 2 mL of formic acid and stirred for 3 days at room temperature. The reaction mixure was concentrated *in vacuo*. The residue was diluted with 2 mL of toluene and evaporated *in vacuo*. This procedure was repeated twice. The residue was chromatographed to give two fractions. The first fraction consisted of ***rel*-(2*R*,3*R*,4*R*)-3-ethyl-4-formyloxy-1,2-piperidinedicarboxylic acid dimethyl ester (25)** (35.0 mg, 0.128 mmol, 15%) as a colourless oil. R_f 0.51 (EtOAc/hexanes: 1/2). IR 1735 (C=O), 1720 (HC=O), 1690 (NC=O). ^1H NMR (250 MHz) 0.98 (t, J = 7.4 Hz, 3 H, CH_2CH_3), 1.10-1.35 (m, 1 H), 1.40-1.80 (m, 3 H), 2.05-2.15 (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}), 4.95 (bs) and 5.10 (bs, two rotamers, 1 H, H^{2eq}), 5.12 (td, J = 10.7, 4.6 Hz, 1 H, H^{4ax}), 8.04 (s, 1 H, OCHO). ^{13}C NMR (63 MHz) 11.3 (CH_3), 20.7 (CH_2), 30.9 (C-5), 39.5 (C-6), 44.3 (C-3), 51.9 (OCH_3), 53.0 (OCH_3), 56.0 (C-2), 71.4 (C-4), 155.3 (NC=O), 160.3 (HC=O), 170.0 (C=O). Accurate mass 273.1204 (calcd for $C_{12}H_{19}NO_6$ 273.1212). The second fraction consisted of ***rel*-(2*R*,3*R*,4*S*)-3-ethyl-4-formyloxy-1,2-piperidinedicarboxylic acid dimethyl ester (26)** (135.6 mg, 0.497 mmol, 59%) as a colourless oil. R_f 0.43 (EtOAc/hexanes: 1/2). IR 1735 (C=O), 1720 (HC=O), 1690 (NC=O). ^1H NMR (250 MHz) 0.99 (t, J = 7.4 Hz, 3 H, CH_2CH_3), 1.45 (septet, J = 7.2 Hz, 1 H), 1.60-2.00 (m, 4 H), 3.40-3.60 (m, 1 H, H^{6ax}), 3.69 (s, 3 H, OCH_3), 3.71 (s, 3 H, OCH_3), 3.91 (dd) and 4.04 (dd, J = 13.8, 4.8 Hz, 1 H, two rotamers, H^{6eq}), 4.70 (d) and 4.87 (d, J = 5.9 Hz, 1 H, two rotamers, H^{2eq}), 5.25 (bs, 1 H, H^{4eq}), 7.99 (s, 1 H, OCHO). ^{13}C NMR (50 MHz) 11.7 (CH_3), 22.2 and 22.3 (CH_2), 29.3 and 29.5 (C-5), 36.2 and 36.3 (C-6), 44.2 and 44.3 (C-3), 51.6 (OCH_3), 52.9 (OCH_3), 54.2 and 54.5 (C-2), 68.2 and 68.4 (C-4), 156.1 and 156.8 (NC=O), 160.0 (HC=O), 171.0 and 171.1 (C=O). Accurate mass 273.1221 (calcd for $C_{12}H_{19}NO_6$ 273.1212).

Cyclization of 18. Acetoxy compound **18**[7] (341 mg, 1.19 mmol) was dissolved in 2 mL of formic acid and stirred for 2 days at room temperature. The formic acid was evaporated *in vacuo*. The residue was diluted with 2 mL of toluene and evaporated *in vacuo*. The residue was chromatographed to give two fractions. The first fraction consisted of ***rel*-(2*R*,3*S*,4*R*)-2-ethyl-4-formyloxy-1,2-piperidinedicarboxylic acid dimethyl ester (27)** (139 mg, 0.512 mmol, 43%) as a colourless oil. R_f 0.31 (EtOAc/hexanes: 1/2). IR 1735 (C=O), 1720 (HC=O), 1690 (NC=O). ^1H NMR ($CDCl_3$, 200 MHz) 1.00 (t, J = 7.3 Hz, 3 H, CH_2CH_3), 1.20-1.45 (m, 1 H), 1.55-1.90 (m, 3 H), 2.35-2.45 (m, 1 H, H^{3eq}), 3.18 (bs, 1 H, H^{6ax}), 3.72 (s, 3 H, OCH_3), 3.77 (s, 3 H, OCH_3), 4.00-4.30 (m, 1 H, H^{6eq}), 4.80-5.10 (m, 2 H, H^{2eq} and H^{4ax}), 8.02 (s, 1 H, OCHO). ^1H NMR (C_6D_6, 250 MHz) 0.70-1.00 (m, 3 H, CH_2CH_3), 1.05-1.70 (m, 4 H), 2.40-2.50 (m, 1 H, H^{3eq}), 3.00 -3.30 (m, 1 H, H^{6ax}), 3.23 (s, 3 H, OCH_3), 3.41 (s, 3 H, OCH_3), 3.85 (bd, J = 9.7 Hz) and 4.25-4.40 (m, two rotamers, 1 H, H^{6eq}), 4.89 and 5.31 (bs, two rotamers, 1 H, H^{2eq}), 4.95-5.05 (m, 1 H, H^{4ax}), 7.43 (s, 1 H, OCHO) ^{13}C NMR (50 MHz) 12 1 (CH_3), 17.4 (CH_2), 25.1 (C-5), 39.8 (C-6), 40.8 (C-3), 52.5

(OCH_3), 53.1 (OCH_3), 56.4 (C-2), 70.3 (C-4), 156.9 (NC=O), 160.0 (HC=O), 171.3 (C=O). Accurate mass 273.1199 (calcd for $C_{12}H_{19}NO_6$ 273.1212). The second fraction consisted of a 17:83 mixture (109 mg, 0.396 mmol, 34%) of **26** and ***rel*-(2*R*,3*S*,4*S*)-3-ethyl-4-formyloxy-1,2-piperidinedicarboxylic acid dimethyl ester (28)** as a colourless oil. R_f 0.26 (EtOAc/hexanes: 1/2). IR 1740 (C=O), 1720 (HC=O), 1690 (NC=O). ^{1}H NMR (200 MHz) 1.02 (t, J = 7.3 Hz, 3 H, CH_2CH_3), 1.45 (quintet, J = 7.7 Hz, 2 H, CH_2CH_3), 1.60-1.95 (m, 2 H, H^{5ax} and H^{5eq}), 2.43 (bd, J = 4.6 Hz, 1 H, H^{3eq}), 3.20-3.45 (m, 1 H, H^{6ax}), 3.70 (s, 3 H, OCH_3), 3.72 (s, 3 H, OCH_3), 3.90 (dd) and 4.05 (dd, two rotamers, J = 13.4, 5.0 Hz, 1 H, H^{6eq}), 4.60 (s) and 4.78 (s, two rotamers, 1 H, H^{2eq}), 5.03 (bd, J = 2.7 Hz, 1 H, H^{4eq}), 7.91 (s, 1 H, OCHO). ^{13}C NMR (63 MHz) 11.9 (CH_3), 23.2 (CH_2), 24.1 and 24.3 (C-5), 36.0 and 36.2 (C-6), 40.9 (C-3), 52.1 (OCH_3), 52.9 (OCH_3), 54.2 and 54.6 (C-2), 70.0 (C-4), 156.7 and 157.3 (NC=O), 159.5 (HC=O), 171.6 (C=O). Accurate mass 273.1205 (calcd for $C_{12}H_{19}NO_6$ 273.1212).

Cyclization of 19. Acetoxy compound **19**[7] (95.3 mg, 0.349 mmol) was dissolved in 4 mL of formic acid and stirred at room temperature for 40 h. The reaction mixture was concentrated *in vacuo*. The residue was chromatographed to give three fractions. The first fraction consisted of a 86:14 mixture of ***trans*-4-formyloxy-4-methyl-1,2-piperidinedicarboxylic acid dimethyl ester (29)** and ***cis*-4-formyloxy-4-methyl-1,2-piperidinedicarboxylic acid dimethyl ester (30)** (33 mg, 0.126 mmol, 36%) as a colourless oil. R_f 0.25 (EtOAc/hexanes: 1/2). IR 1750 (C=O), 1730 (HC=O), 1705 (NC=O). ^{1}H NMR (200 MHz) **29**: 1.35-1.60 (m, 1 H), 1.57 (s, 3 H, CH_3), 1.74 (dd, J = 14.9, 7.0 Hz, 1 H, H^{5eq}), 2.38 (bd, J = 14.3 Hz, 1 H), 2.82 (dt, J = 14.6, 2.1 Hz, 1 H), 3.10-3.45 (m, 1 H, H^{6ax}), 3.68 (s) and 3.71 (s) and 3.73 (s, 6 H, 2 × OCH_3), 3.80-4.10 (m, 1 H, H^{6eq}), 4.74 (d) and 4.89 (d, two rotamers, J = 6.2 Hz, 1 H, H^{2eq}), 7.87 (s, 1 H, OCHO); **30** (isolated signals): 1.50 (s, 3 H, CH_3), 2.12 (dd, J = 13.6, 6.8 Hz, 1 H), 2.68 (bd, J = 13.6 Hz, 1 H), 7.95 (s, 1 H, OCHO). ^{13}C NMR (63 MHz) **29**: 25.9 (CH_3), 34.5, 36.9, 37.0, 51.5 and 51.8 (C-2), 52.0 (OCH_3), 52.9 (OCH_3), 79.2 (C-4), 156.8 (NC=O), 159.5 (HC=O), 171.5 (C=O); **30** (isolated signals) 22.2 (CH_3), 35.7, 38.9, 80.1 (C-4), 159.8 (HC=O), 171.8 (C=O). The second fraction consisted of ***rel*-(2*R*,5*S*)-5-methyl-7-oxo-6-oxa-2-azabicyclo[3.2.1]nonane-2-carboxylic acid methyl ester (31)** (10 mg, 0.05 mmol, 15%) as a colourless oil. R_f 0.16 (EtOAc/hexanes: 1/2). IR 1795 (C=O), 1710 (NC=O). ^{1}H NMR (200 MHz) 1.53 (s, 3 H, CH_3), 1.70-2.15 (m, 4 H), 3.05-3.30 (m, 1 H, H^{3endo}), 3.74 (s, 3 H, OCH_3), 4.00-4.25 (m, 1 H, H^{3exo}), 4.85 (bs, 1 H, H^1). Accurate mass 199.0875 (calcd for $C_9H_{13}NO_4$ 199.0845). The third fraction consisted of ***rel*-(2*R*,4*S*)-4-hydroxy-4-methyl-1,2-piperidinedicarboxylic acid dimethyl ester (32)** (11 mg, 0.05 mmol, 13%) as a colourless oil (for spectral data see ref. 7).

Cyclization of 20. Hydroxy compound **20**[7] (297.1 mg, 1.286 mmol) was dissolved in 6 mL of formic acid and stirred for 18 h at room temperature. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in 2 mL of benzene and concentrated *in vacuo*. The residue was chromatographed to give 4 fractions. The first fraction consisted of ***rel*-(2*R*,4*S*,5*S*)-4-formyloxy-5-methyl-1,2-piperidinedicarboxylic acid dimethyl ester (33)** (117.1 mg, 0.4521 mmol, 35%) as a colourless oil. R_f 0.43 (EtOAc/hexanes: 1/2). IR 1740 (C=O), 1720 (HC=O), 1695 (NC=O). ^{1}H NMR (200 MHz) 0.90 (d, J = 6.5 Hz, 3 H, CH_3), 1.72 (dd, J = 11.7, 6.4 Hz, 1 H, H^3), 1.80 (dd, J = 11.7, 6.4 Hz, 1 H, H^3), 2.45-2.60 (m, 1 H, H^{5ax}), 2.74 (dd) and 2.83 (dd, two rotamers, J = 13.5, 12.2, H^{6ax}), 3.70 (s) and 3.74 (s) and 3.77 (s, 6 H, 2 × OCH_3), 4.03(dd) and 4.18 (dd, two rotamers, J = 12.6, 3.7 Hz, H^{6eq}), 4.62 (td, J = 11.0, 4.3 Hz, 1 H, H^{4ax}), 4.91 (bd) and 5.07 (bd, J = 6.4 Hz, two rotamers, 1 H, H^{2eq}), 8.08 (s, 1 H, OCHO). ^{13}C NMR (50 MHz) 14.6 (CH_3), 31.6 and 31.8 (C-3), 35.4 and 35.5 (C-5), 46.4 (C-4), 52.5 (OCH_3), 53.0 (OCH_3), 53.8 and 53.9 (C-2), 72.8 (C-4), 156.0 and 156.3 (NC=O), 160.2 (HC=O), 170.9 (C=O). Accurate mass 259.1068 (calcd for $C_{11}H_{17}NO_6$ 259.1056). The second fraction consisted of ***rel*-(2*R*,4*R*,5*S*)-4-formyloxy-5-methyl-1,2-piperidinedicarboxylic acid dimethyl ester (34)** (33.5 mg, 0.129 mmol, 10%) as a colourless oil. R_f 0.33 (EtOAc/hexanes: 1/2). IR 1740 (C=O), 1720 (HC=O), 1690 (NC=O). ^{1}H NMR (200 MHz) 0.87 (d, J = 6.9 Hz, 3 H, CH_3), 1.80-2.00 (m, 2 H, H^{3eq} + H^{3ax}), 2.55-2.75 (m, 1 H, H^{5ax}), 2.96 (dd) and 3.04 (dd, J = 13.0, 12.6 Hz, 1 H, H^{6ax}), 3.72 (s) and 3.69 (s) and 3.68 (s, 6 H, 2 × OCH_3), 3.80 (dd) and 3.95 (dd, two rotamers, J = 13.4, 4.9 Hz, 1 H, H^{6eq}), 4.72 (d) and 4.88 (d, two rotamers, J = 6.7 Hz, 1 H, H^{2eq}), 5.08 (bs, 1 H, H^{4eq}), 7.96 (s, 1 H, OCHO). ^{13}C NMR (63 MHz) 14.6 and 14.9 (CH_3), 30.9 and 31.1 (C-3), 33.1 and 33.2 (C-5), 42.4 and 42.7 (C-6), 50.3 and

50.6 (C-2), 52.1 (OCH_3), 52.9 (OCH_3), 69.8 and 69.9 (C-4), 156.1 and 156.6 (NC=O), 159.9 (HC=O), 171.4 (C=O). Accurate mass 259.1042 (calcd for $C_{11}H_{17}NO_6$ 259.1056). The third fraction consisted of **4-(1-formyloxyethyl)-1,2-pyrrolidinedicarboxylic acid dimethyl ester (36)** (96.2 mg, 0.371 mmol, 29%) as a colourless oil. R_f 0.24 (EtOAc/hexanes: 1/2). IR 1740 (C=O), 1720 (HC=O), 1695 (NC=O). ^{1}H NMR (200 MHz) 1.26 (dd, J = 6.3, 1.7 Hz, 3 H, CH_3), 1.90-2.20 (m, 2 H, 2 × H^3), 2.40-2.65 (m, 1 H, H^4), 3.07 (d) and 3.18 (d, two rotamers, J = 10.3 Hz, 1 H, H^5), 3.60-3.80 (m, 7 H, 2 × OCH_3 + H^5), 4.30-4.50 (m, 1 H, H^2), 4.97 (bquintet, J = 5.7 Hz, 1 H, CHO_2CH), 8.02 (s, 1 H, OCHO). ^{13}C NMR (50 MHz) 18.7 (CH_3), 31.6 and 32.9 (C-3), 41.3 and 42.2 (C-4), 47.8 and 48.3 (C-5), 52.2 (OCH_3), 52.5 (OCH_3), 58.6 and 58.8 (C-2), 70.7 and 71.0 (CHO_2CH), 154.9 and 155.3 (NC=O), 160.2 (HC=O), 172.7 (C=O). Accurate mass 259.1042 (calcd for $C_{11}H_{17}NO_6$ 259.1056). The fourth fraction consisted of ***rel*-(2*R*,4*R*,5*S*)-4-hydroxy-5-methyl-1,2-piperidinedicarboxylic acid dimethyl ester (35)** (15.3 mg, 0.0662 mmol, 5%) as a colourless oil (for spectral data see ref. 7).

Cyclization of 21. Acetoxy compound **21**[7] (69.2 mg, 0.271 mmol) was dissolved in 2 mL of formic acid and stirred for 17 h at room temperature. The reaction mixture was concentrated *in vacuo*. The residue was diluted with 2 mL of toluene and evaporated *in vacuo*. The residue was chromatographed to give two fractions. The first fraction consisted of ***rel*-(5*R*,7*R*,8a*S*)-7-formyloxy-octahydro-3-oxoindolizine-5-carboxylic acid methyl ester (37)** (17.7 mg, 0.0734 mmol, 27%) as a colourless oil. R_f 0.40 (CH_2Cl_2/acetone: 2/1). IR 1740 (C=O), 1720 (HC=O), 1680 (NC=O). ^{1}H NMR (200 MHz) 1.23 (q, J = 11.7 Hz, 1 H), 1.50-1.80 (m, 2 H), 2.10-2.50 (m, 5H), 3.69 (s, 3 H, OCH_3), 3.65-3.90 (m, 1 H, H^{8a}), 4.80-5.00 (m, 2 H, H^5 + H^7), 7.95 (s, 1 H, OCHO). ^{13}C NMR (50 MHz) 25.1 (C-1), 29.8 (C-8), 31.1 (C-6), 38.0 (C-8), 49.6 (C-5), 52.5 (OCH_3), 52.8 (C-8a), 67.5 (C-7), 159.8 (HC=O), 170.2 (C=O), 174.0 (C^3). The second fraction consisted of ***rel*-(5*R*,7*S*,8a*S*)-7-formyloxy-octahydro-3-oxoindolizine-5-carboxylic acid methyl ester (38)** (25.5 mg, 0.106 mmol, 39%) as white crystals, mp 86-87 °C (ether/hexanes). R_f 0.30 (CH_2Cl_2/acetone: 2/1). IR 1740 (C=O), 1720 (HC=OO), 1675 (NC=O). ^{1}H NMR (200 MHz) 1.30-1.65 (m, 2 H), 1.75-1.95 (m, 1 H), 2.05-2.65 (m, 5 H), 3.66 (s, 3 H, OCH_3), 3.85-4.05 (m, 1 H, H^{8a}), 4.74 (d, J = 7.1 Hz, H^5), 5.25 (bs, 1 H, H^7), 7.88 (s, 1 H, OCHO). ^{13}C NMR (50 MHz) 25.7 (C-1), 29.7, 29.9, 36.0 (C-8), 47.8 (C-5), 49.1 (C-8a), 52.3 (OCH_3), 66.8 (C-7), 159.5 (HC=OO), 170.6 (C=O), 174.6 (C-3).

Cyclization of 22. Acetoxy compound **22**[7] (0.649 g, 3.04 mmol) was dissolved in 14 mL of formic acid and stirred for 50 h at room temperature. The reaction mixture was poured out slowly in 300 mL of saturated aq $NaHCO_3$ and stirred for 10 min. The mixture was extracted (4 ×) with 150 mL of CH_2Cl_2. The collected organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed to give two fractions as oils which crystallized on standing. The first fraction consisted of ***rel*-(5*R*,7*S*,8a*S*)-7-formyloxy-octahydro-7-methyl-3-oxoindolizine-5-carboxylic acid methyl ester (39)** (0.364 g, 1.42 mmol, 47%) as white needles, mp 92-93 °C (ether/hexanes). R_f 0.40 (CH_2Cl_2/acetone: 2/1). IR 1740 (C=O), 1720 (HC=O), 1680 (NC=O). ^{1}H NMR (200 MHz) 1.45-1.75 (m, 2 H), 1.50 (s, 3 H, CH_3), 2.03 (dd, J = 13.5, 7.5 Hz, 1 H), 2.20-2.55 (m, 4 H), 2.79 (d, J = 13.5 Hz, 1 H), 3.73 (s, 3 H, OCH_3), 3.70-3.95 (m, 1 H, H^{8a}), 4.84 (d, J = 6.5 Hz, 1 H, $CHCO_2Me$), 7.92 (s, 1 H, OCHO). ^{1}H NMR (200 MHz, C_6D_6) 0.75-1.15 (m, 2H), 1.33 (s, 3 H, CH_3), 1.30-1.55 (m, 1 H), 1.62 (dd, J = 13.5 Hz, J = 7.5 Hz, 1 H), 1.85-2.10 (m, 3 H), 2.61 (bd, J = 13.5 Hz, 1 H), 3.15 (s, 3 H, OCH_3), 3.20-3.50 (m, 1 H, H^{8a}), 4.88 (d, J = 6.5 Hz, 1 H, H^5), 7.47 (s, 1 H, OCHO). ^{13}C NMR (50 MHz) 21.8 (CH_3), 25.6 (C-1), 29.9 (C-2), 36.3 (C-6), 43.5 (C-8), 49.2 (C-5), 51.8 (C-8a), 52.5 (OCH_3), 80.8 (C-7), 159.7 (HC=OO), 171.0 (C=O), 174.2 (C-3). Accurate mass 255.1106 (calcd for $C_{12}H_{17}NO_5$ 255.1107). The second fraction consisted of ***rel*-(5*R*,7*R*,8a*S*)-octahydro-7-hydroxy-7-methyl-3-oxoindolizine-5-carboxylic acid methyl ester (40)** (0.230 g, 1.02 mmol, 33%) as white crystals, mp 132-134 °C (ether/hexanes). R_f 0.20 (CH_2Cl_2/acetone: 2/1). IR 3600, 3400 (OH), 1725 (C=O), 1675 (NC=O). ^{1}H NMR (200 MHz) 1.15-1.30 (m, 1 H, H^{8ax}), 1.26 (s, 3 H, CH_3), 1.45-1.65 (m, 1 H, H^1), 1.68 (dd, J = 14.1, 6.9 Hz, 1 H, H^{6ax}), 1.80-1.95 (m, 1 H, H^{8eq}), 2.05 (bs, 1 H, OH), 2.10-2.50 (m, 4 H, H^1 + 2 × H^2 + H^{6eq}), 3.69 (s, 3 H, OCH_3), 3.95-4.15 (m, 1 H, H^{8a}), 4.73 (d, J = 5.9 Hz, 1 H, H^{5eq}). ^{13}C NMR (50 MHz) 25.4 (C-1), 30.3 (C-2), 30.6 (CH_3), 38.3 (C-6), 44.8 (C-8), 48.7 (C-5), 50.6 (C-8a), 52.2 (OCH_3), 68.3 (C-7), 171.7 (C=O), 174.5 (C-3). Accurate mass

227.1177 (calcd for $C_{11}H_{17}NO_4$ 227.1158).

***trans*-4-Hydroxy-2-piperidinecarboxylic acid (41).** Formate **23** (25.8 mg, 0.100 mmol) was dissolved in 2 mL of 2 N aqueous HCl and refluxed for 18 h. The reaction mixture was evaporated *in vacuo*. The residue was chromatographed using an ion exchange column as described[7] to give **41** (11.6 mg, 0.080 mmol, 81%) as a thick oil. ^{1}H NMR (200 MHz, D_2O) 1.85-2.10 (m, 3 H), 2.20-2.35 (m, 1 H), 3.30-3.40 (m, 2 H, H^{6eq} + H^{6ax}), 3.94 (dd, J = 11.7, 3.8 Hz, H^{2ax}), 4.26 (quintet, J = 3.1 Hz, H^{4eq}). ^{13}C NMR (50 MHz, D_2O) 29.9 (C-5), 34.7 (C-3), 40.5 (C-6), 55.9 (C-2), 63.7 (C-4), 176.2 (CO_2H).

Cyclization of 43 with paraformaldehyde in formic acid. Paraformaldehyde (23 mg, 0.77 mmol) was added to 1 mL of formic acid. The mixture was heated until all paraformaldehyde had dissolved and then cooled to room temperature. This solution was added to **43**[16] (111 mg, 0.553 mmol) and stirred for 24 h. The reaction mixture was concentrated *in vacuo*, treated with 1 mL of benzene, and concentrated *in vacuo* (this procedure was repeated twice). The residue (142 mg, 5.49 mmol) was a 50:50 mixture of **23** and **24**.

Acetoxy[*N*-(3-butenyl)-*N*-(methoxycarbonyl)amino]acetic acid methyl ester (45). According to procedure A described in ref. 7, methyl *N*-(acetoxymethyl)carbamate[7] (302.5 mg, 2.058 mmol) was treated with allyltrimethylsilane (0.4 mL, 2.51 mmol) and BF_3•OEt_2 (0.38 mL, 3.1 mmol) in 5 mL CH_2Cl_2 to give methyl *N*-(3-butenyl)carbamate (207.8 mg, 1.611 mmol, 78%) as a colourless oil. R_f 0.60 (EtOAc/hexanes: 1/2). IR 3450 (NH), 1715 (NC=O). 1H NMR (250 MHz) 2.22 (q, J = 6.7 Hz, 2 H, CH_2CH=), 3.22 (q, J = 6.3 Hz, 2 H, NCH_2), 3.63 (s, 3 H, OCH_3), 4.75 (bs, 1 H, NH), 5.00-5.15 (m, 2 H, =CH_2), 5.60-5.80 (m, 1 H, -CH=). According to procedure F described in ref. 7, this product (1.20 g, 9.30 mmol) was treated with methyl glyoxylate hydrate (6.4 g, 72.8 mmol) in 80 mL of benzene to give [*N*-(3-butenyl)-*N*-(methoxycarbonyl)amino]hydroxyacetic acid methyl ester (1.64 g, 7.56 mmol, 81%) as a colourless oil. R_f 0.33 (EtOAc/hexanes: 1/2). IR 3520 (OH), 1740 (C=O), 1690 (NC=O). 1H NMR (200 MHz) 2.33 (q, J = 7.0 Hz, 2 H, =CHCH_2), 3.35 (dt, J = 7.3, 2.9 Hz, 2 H, CH_2N), 3.71 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 4.20 (bs, 1 H, OH), 5.00-5.15 (m, 2 H, =CH_2), 5.24 (bs, 1 H, NCHO), 5.65-5.90 (m, 1 H, -CH=). According to procedure G described in ref. 7, the methyl glyoxylate adduct (1.02 g, 4.69 mmol) was treated with DMAP (40 mg, 0.33 mmol) and acetic anhydride (0.55 mL, 5.83 mmol) in 10 mL of pyridine to give **45** (1.09 g, 4.22 mmol, 90%) as a colourless oil. R_f 0.50 (EtOAc/hexanes: 1/2). IR 1745 and 1715 (3 × C=O). 1H NMR (200 MHz) 2.17 (s, 3 H, C=OCH_3), 2.25-2.45 (m, 2 H, =CHCH_2), 3.20-3.35 (m, 1 H, CHN), 3.40-3.60 (m, 1 H, CHN), 3.76 (s, 3 H, OCH_3), 3.79 (s, 3 H, OCH_3), 5.00-5.15 (m, 2 H, =CH_2), 5.65-5.90 (m, 1 H, -CH=), 6.51 (s, 1 H, NCHO).

Cyclization of 45 at -78 °C with $SnCl_4$. Under a nitrogen atmosphere, a 1.2 M solution of $SnCl_4$ in CH_2Cl_2 (3.50 mL, 4.20 mmol) was slowly added to a solution of **45** (183 mg, 0.707 mmol) in 2 mL of CH_2Cl_2 at -78 °C. The reaction mixture was stirred for 4 h at -78 °C and then 5 mL of saturated aq $NaHCO_3$ was added. The reaction mixture was allowed to warm up to room temperature and after extraction (3 ×) with 20 mL of $CHCl_3$, the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed to give ***cis*-4-hydroxy-1,2-piperidinedicarboxylic acid dimethyl ester (44)** (101 mg, 0.466 mmol, 66%) as a colourless oil. R_f 0.22 (EtOAc/hexanes: 1/1). IR 3600 (s) and 3480 (b, OH), 1730 (C=O), 1685 (NC=O). ^{1}H NMR (200 MHz) 1.55-1.80 (m, 2 H, H^{5ax} and H^{5eq}), 1.87 (ddd, J = 14.3, 6.7, 2.2 Hz, 1 H, H^{3ax}), 2.38 (bs, 1 H, OH), 2.43 (bd, J = 14.2 Hz, 1 H, H^{3eq}), 3.30-3.55 (m, 1 H, H^{6ax}), 3.72 (s, 6 H, 2 × OCH_3), 3.75-4.05 (m, 1 H, H^{6eq}), 4.14 (b quintet, J = 2.7 Hz, 1 H, H^{4eq}), 4.70 and 4.82 (bs, two rotamers, 1 H, H^{2eq}). ^{1}H NMR (250 MHz, DCOOD) 1.70-1.95 (m, 2 H), 2.05 (ddd, J = 14.8, 6.8, 2.1 Hz, 1 H), 2.45-2.55 (m, 1 H), 3.30-3.55 (m, 1 H, H^{6ax}), 3.79 (s, 6 H, 2 × OCH_3), 3.90-4.00 (m, 1 H, H^{6eq}), 4.33 (bs, 1 H, H^{4eq}), 4.85-5.00 (m, 1 H, H^2). ^{13}C NMR (50 MHz) 30.9, 33.2, 35.6, 50.7 and 50.9 (C-2), 52.1 (OCH_3), 52.7 (OCH_3), 62.7 (C-4), 156.5 and 156.9 (NC=O), 172.8 (C=O). Accurate mass 217.1003 (calcd for $C_9H_{15}NO_5$ 217.0950).

***cis*-4-Formyloxy-*d*-1,2-piperidinedicarboxylic acid dimethyl ester (46).** Precursor **44** (30 mg, 0.138 mmol) was dissolved in 0.5 mL of DCOOD. The formylation reaction was monitored by ^{1}H NMR. ^{1}H NMR (250 MHz, DCOOD) 1.75-2.00 (m, 2 H), 2.13 (ddd, J = 15.0, 6.8, 2.1 Hz, 1 H), 2.55-2.70 (m, 1 H), 3.20-3.45 (m, 1 H, H^{6ax}),

3.80 (s, 6 H, 2 × OCH_3), 4.90-5.05 (m, 1 H, H^2), 5.28 (bt, J = 2.7 Hz, 1 H, H^{4eq}).

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