Diastereoselective functionalizations of enecarbamates derived from pipecolic acid towards 5-guanidinopipecolates as arginine mimetics†

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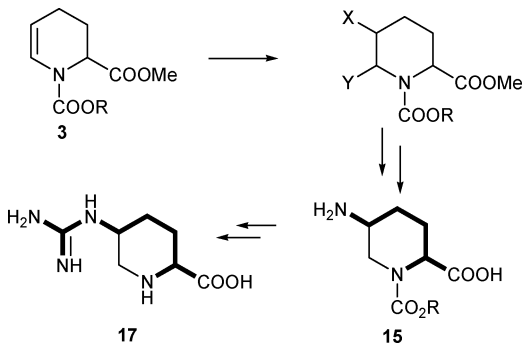
Various substituents could be diastereoselectively introduced into the 5-position of pipecolic acid *via* electrophilic or free-radical-initiated addition to the carbon–carbon double bond of endocyclic enecarbamates derived from pipecolic acid. This study allowed the diastereoselective synthesis of both *cis*- and *trans*-5-guanidino pipecolates, which were designed as constrained arginine mimetics and whose potential inhibition of nitric oxide synthase (NOS) was evaluated with three NOS isoforms.

Introduction

Pipecolic acid is an important noncoded cyclic amino acid, which is found in numerous microbial, plant and animal species, including humans; it is an intermediate in the major path of L-lysine degradation in the central nervous system.[1] Free L-pipecolic acid and many of its derivatives are found in nature.[2] In recent years it has been incorporated into several peptidic structures as a proline homologue.[3] In addition, some derivatives of substituted pipecolic acid were developed as β-turn mimetics,[4] and others were designed as constrained analogues of lysine[5] or phenylalanine,[6] or as *N*-methyl-D-aspartate receptor antagonists.[7] We have been working for some years on the chemistry of enecarbamates,[8] especially those derived from pipecolic acid.[9] As part of our study in this field, we required efficient access to 5-guanidinopipecolates **17** (Scheme 1), which we designed as arginine mimetics for their potential as NO synthase (NOS) inhibitors.[10] In connection with this project, we report here the results of our complete study on various regio- and stereoselective functionalizations of endocyclic enecarbamates **3**, in order to develop efficient access to both diastereomers of the target molecules **17** (Scheme 1).

Although there have been some studies describing reactions of enecarbamates with various electrophiles,[11] only a few have involved enecarbamates derived from pipecolic acid.[12] In this study, we used various reaction conditions that enabled us to prepare new pipecolate derivatives efficiently and diastereoselectively. The methodology employed was based on the reaction of 5,6-dehydropipecolate derivatives **3** with various electrophilic and radical species that led to selective functionalization at the C-5 position.



Scheme 1 5-Guanidinopipecolates from enecarbamates **3**.

Results and discussion

Substrate preparation

The starting materials, (*i.e.* racemic enecarbamates **3a–c**), were easily prepared from (±)-pipecolic acid on a multigram scale according to known procedures (Scheme 2).[13] The *N*-protected methylpipecolates **1a,b** were electrochemically oxidized into **2**, which underwent subsequent acid-catalyzed methanol elimination producing the corresponding compounds **3a** and **3b**. We have previously reported that addition of π-nucleophiles onto the iminiums derived from **2a** and **2c** yielded opposite diastereomers.[14] Consequently, we thought that due to its intrinsic strain, bicyclic enecarbamate **3c** might provide different diastereoselectivity from that expected with monocyclic substrates **3a,b**. Moderate yields of the bicyclic substrate **3c** were obtained by reductive cyclization of **3a**.[15] In order to improve the yield of **3c**, we investigated a different order of the oxidation–elimination–cyclization sequence used, by carrying out the oxazolidine ring formation prior to electromethoxylation and subsequent elimination of methanol (Scheme 2). Unfortunately, electromethoxylation of oxazolidinone **1c** selectively yielded the regioisomer **2′c** where the methoxy group was introduced at the ring junction position, as we have already observed with an analogous oxazolidinone derived from proline.[16]

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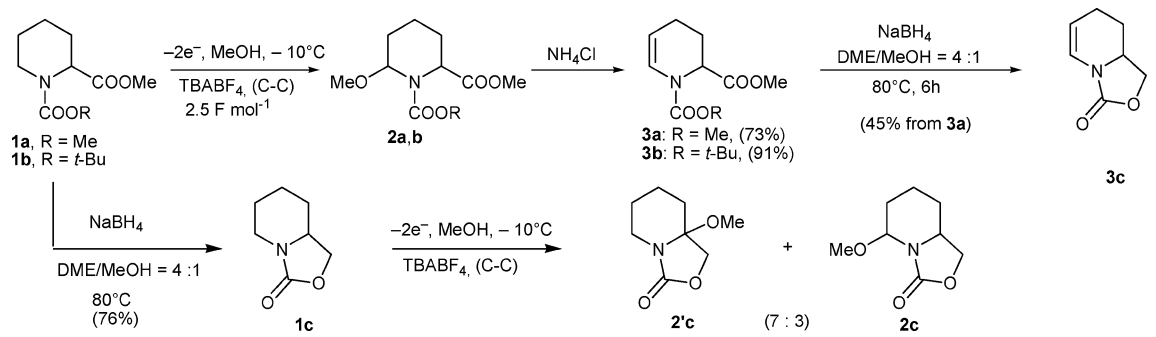
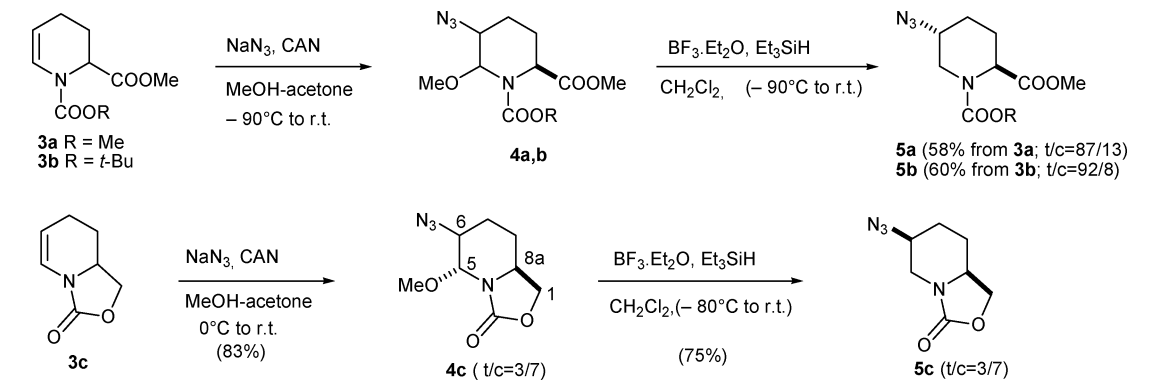


Scheme 2 Preparation of enecarbamates **3** from N-protected methylpipecolates.

Addition reactions of enecarbamates 3

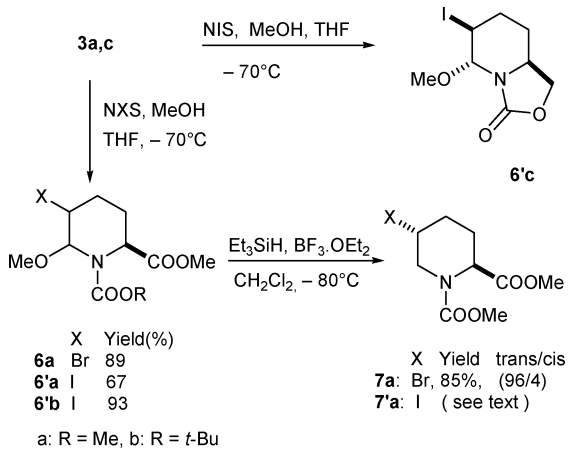
5-Azido-6-methoxylation. We devised the synthesis of the desired arginine analogues **17** by guanylation of the corresponding ornithine analogues, *i.e.* 5-aminopipecolates **15**, whose synthesis could be accomplished from enecarbamates **3** (Scheme 1). We first explored the β-hydroamination of the enecarbamates **3a** by reacting its crude hydroboration adduct with hydroxylamine-*O*-sulfonic acid,[17] which failed to provide the desired 5-aminopipecolate derivatives. We then planned to obtain the latter *via* the corresponding 5-azidopipecolates. To this end, we first examined direct regioselective introduction of this 5-azido substituent by oxidative-radical β-azido-α-methoxylation of the enecarbamate moiety. Preliminary attempts to perform this addition by electrochemical oxidation in a divided cell (Pt–Pt) according to a procedure described by Fujimoto *et al.*[18] led to low yields of the addition compounds **4**.[19] We then examined the conditions employed by Chavan *et al.*,[20] who performed azidomethoxylation of electron-rich olefins (including enol ethers), and more recently performed by Norton Matos *et al.*[21] with pyrrolidine and piperidine enecarbamates, by using cerium ammonium nitrate (CAN) as oxidizing agent, instead of anodic oxidation. Treatment of substrates **3a,b** with a combination of CAN/NaN_3 in the presence of methanol as the solvent thus led to the corresponding 5-azido-6-methoxypipecolates **4a,b** in good yields, albeit as mixtures of three diastereomers according to gas chromatography analysis (Scheme 3). Subsequent treatment of these mixtures of isomers with Et_3SiH and $BF_3{\cdot}OEt_2$ at low temperature resulted in the chemoselective reduction of the α-aminoether moieties, thus leading to the corresponding azido derivatives **5a,b** as mixtures of epimers at the C-5 position. The *trans*/*cis* ratio resulting from this sequence was highly dependent on the temperature of the first step, thus varying from approximately 1 : 1 at 0 °C to a 92 : 8 *trans*/*cis* mixture at −95 °C in acetone instead of acetonitrile as solvent for the azidomethoxylation step. Bicyclic substrate **3c** was less reactive towards azidomethoxylation, unlike **3a,b**, which reacted even at −95 °C (3–5 h at 1 mmol scale), the total conversion of substrate **3c** (1 mmol) required 16 h at room temperature. Under these conditions, **3c** led to **4c** as a 3 : 7 mixture of epimers at the C-6 position (oxazolidinone numbering). In both isomers the 5-methoxy group is *cis* to the hydrogen atom of the bicyclic junction (8*a*-H of the oxazolidinone **4c**), and is *trans* to the 6-azido group in the predominant epimer. Reductive treatment of this mixture with a $Et_3SiH/BF_3{\cdot}OEt_2$ combination led to the same 3 : 7 ratio of *trans*/*cis* isomers of **5c** (Scheme 3). Despite this interesting reverse selectivity that favours the *cis*- over the *trans*-isomer in the case of bicyclic enecarbamate **3c**, this method would require at least three steps to reach the *cis*-5-azido pipecolate from **5c**. In conclusion, the azido-methoxylation–reduction sequence seems suitable for the synthesis of *trans*-5-azidopipecolate when the first step is performed at a low temperature with monocyclic substrates **3a,b** (Scheme 3).

In order to obtain selectively the *cis*-5-azido pipecolate, we devised a two-step process in which the 5-azido substituent could be introduced by nucleophilic displacement of a suitable leaving group having a relative *trans* orientation to the C-2 substituent. Two types of leaving group, *i.e.* halides and sulfonic esters, were explored for this purpose.



Scheme 3 5-Azido pipecolate derivatives from **3**.

5-Halo-6-methoxylation. Treatment of enecarbamates **3a,b** with NBS/MeOH or NIS/MeOH at −70 °C in THF afforded good yields of the corresponding *O*-methyl halohydrines **6** with similar diastereoselectivity to that observed in the case of the azidomethoxylation reaction (Scheme 4). Under the same reaction conditions (*i.e.* NIS/MeOH) **3c** led to a single diastereomer of **6′c**, as shown in Scheme 4. Treatment of **6a** with triethylsilane in presence of boron trifluoride diethyl etherate at a low temperature afforded good yields of the demethoxylated derivative **7a** chemoselectively and with high diastereoselectivity (*trans*/*cis* = 96/4). Under the same conditions, 5-iodo-6-methoxy derivative **6′a** led to a 65 : 35 mixture of the expected 5-iodopipecolate **7′a** and compound **1a**. The formation of the latter was explained by the easy reduction of the carbon–iodine bond under the conditions required for the *N*,*O*-acetal moiety reduction (Scheme 4).

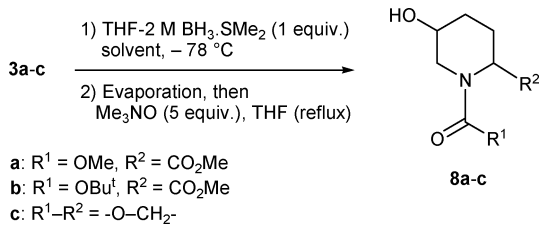


Scheme 4 Halomethoxylation of enecarbamates **3**.

Before discussing the halide substitution by azide, we describe the results for the preparation of 5-hydroxypipecolates, which need to be activated as sulfonates prior to substitution with azide *via* S_N2 displacement.

5-Hydroxypipecolate derivatives. Starting from substrates **3**, we explored three series of reactions aiming at the introduction of a 5-hydroxy substituent on the pipecolate ring, *i.e.* oxidative hydroboration, 5,6-dihydroxylation or 5-hydroxy-6-methoxylation followed by acetylation and subsequent chemoselective *N*,*O*-acetal reduction.

Oxidative hydroboration of 3. The best results were obtained with $BH_3{\cdot}SMe_2$ complex (Scheme 5). Generally, the hydroboration of enecarbamates **3** does not reach the trialkyl stage,[22] and moreover, this step is very slow in THF (15 h on a 1 mmol scale). Studying the effects of various solvents showed that improved rates were observed when the hydroboration step was performed in less basic solvents such as diethyl ether, toluene or, in particular, dichloromethane. Moreover, the best yields were obtained when the oxidative cleavage was achieved by removing all volatiles under vacuum, prior to oxidative treatment with trimethylamine *N*-oxide (TMO) in refluxing THF.[23a] Both monocyclic enecarbamates **3a,b** gave the corresponding alcohols *trans*-**8a,b**[12c,23b] selectively (Table 1, entries 1–5). Lower yields and almost no diastereoselectivity occurred with substrate **3c** (Table 1, entries 6–8).



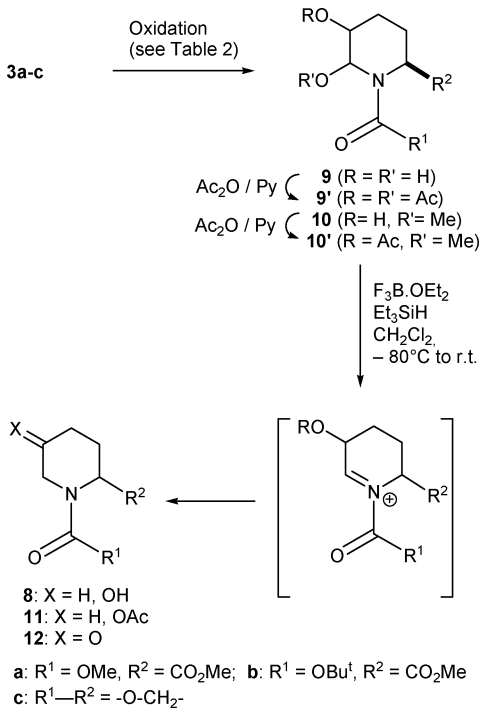
Scheme 5 Oxidative hydroboration of **3**.

Table 1 Diastereoselectivity of oxidative hydroboration of **3**

Entry	Substrate	Solvent	Alcohol (%)	*trans*/*cis*
1	**3a**	THF	**8a** (54)	84 : 16
2	**3a**	Et_2O	**8a** (45)	83 : 17
3	**3a**	CH_2Cl_2	**8a** (63)	85 : 15
4	**3a**	PhMe	**8a** (63)	75 : 25
5	**3b**	CH_2Cl_2	**8b** (63)	93 : 7
6	**3c**	Et_2O	**8c** (35)[a]	48 : 52
7	**3c**	CH_2Cl_2	**8c** (20)[a]	45 : 55
8	**3c**	PhMe	**8c** (35)[a]	55 : 45

[a] Up to 35% of compound **1c** was obtained.[23]

5,6-Dihydroxylation and 5,6-hydroxymethoxylation of 3. Besides the oxidative hydroboration method, we examined two other oxidation methods based on dihydroxylation or hydroxymethoxylation (Scheme 6). Dihydroxylation of substrates **3a,b** by using OsO_4/TMO[12b,24] or Oxone[25,12a] in an acetone–water mixture led to the expected 5,6-dihydroxypipecolates **9**,[24c] mainly as mixtures of two diastereomers. Attempts to selectively reduce the hemiaminal moieties selectively by using a $Et_3SiH/BF_3{\cdot}OEt_2$ combination resulted in poor yields of the expected 5-hydroxypipecolates **8**, along with the corresponding 5-oxopipecolates **12**. The latter were generated *via* the iminium intermediate which, instead of reduction by Et_3SiH, may also undergo deprotonation leading to the corresponding β-hydroxy enecarbamate which, in turn, tautomerizes into the corresponding 5-oxopipecolate **12**. To avoid such rearrangement, crude diols **9** were converted to diacetates **9′**,[12c] prior to *N*,*O*-acetal reduction with $Et_3SiH/BF_3{\cdot}OEt_2$ in dichloromethane (Scheme 6). By using such a sequence, we were able to isolate monoacetates **11a,b**[12c] in moderate to good overall yields (44–71%), and good selectivity in favour of the *trans* isomers, whatever the dihydroxylation reagent (Table 2, entries 1–4). Higher overall yields were obtained in the case of substrate **3c**; however, the diastereoselectivity depended on the dihydroxylation reagent (Table 2, entries 5 and 6). Thus, the OsO_4/TMO combination led to the *trans* isomer, although with lower selectivity than that reached with monocyclic substrates, while reverse stereoselectivity was observed when Oxone was employed as dihydroxylating agent. Workup of the vicinal diols **9** was generally difficult, because of their significant hydrosolubility. To avoid these difficulties, substrate **3a** was allowed to react with Oxone in methanol, thus producing the expected 5-hydroxy-6-methoxypipecolate derivative **10a**, which after acetylation and subsequent reduction afforded good overall yield of **11a**, albeit with almost no diastereoselectivity (Table 2, entry 7). When applied to **3c** (entry 8), the same three-step sequence led to **11c** with reverse selectivity (*trans*/*cis* = 3/7) as in the case of azidomethoxylation. It is of note that, when oxidized with Oxone, **3c** led to bicyclic compounds (**9c** or **10c**) whereas



Scheme 6 Monoacetates **11** from **3**.

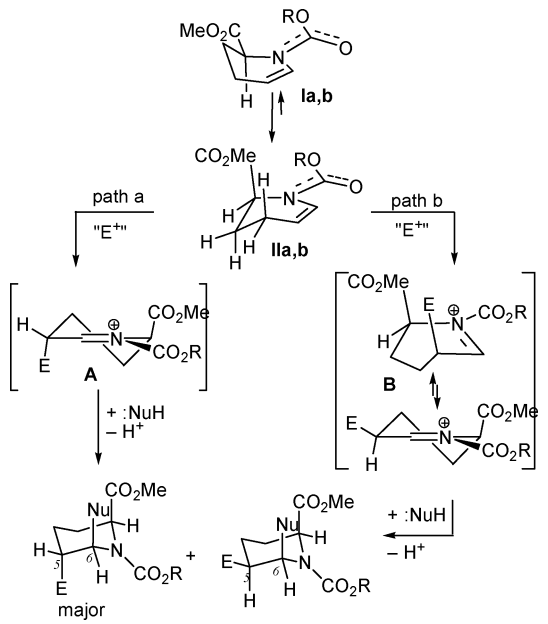
Table 2 Formation of monoacetates **11a-c** from **3a-c**

Entry	3	Oxidation conditions	11 (%)[a]	*trans*/*cis*
1	**3a**	OsO_4/TMO, H_2O	**11a** (69)	92 : 8
2	**3a**	Oxone/H_2O	**11a** (55)	85 : 15
3	**3b**	OsO_4/TMO, H_2O	**11b** (71)	92 : 8
4	**3b**	Oxone/H_2O	**11b** (44)	86 : 14
5	**3c**	OsO_4/TMO, H_2O	**11c** (60)	70 : 30
6	**3c**	Oxone/H_2O	**11c** (75)	37 : 63
7	**3a**	Oxone/MeOH	**11a** (58)	55 : 45
8	**3c**	Oxone/MeOH	**11c** (84)	30 : 70

[a] Overall yields starting from **3**.

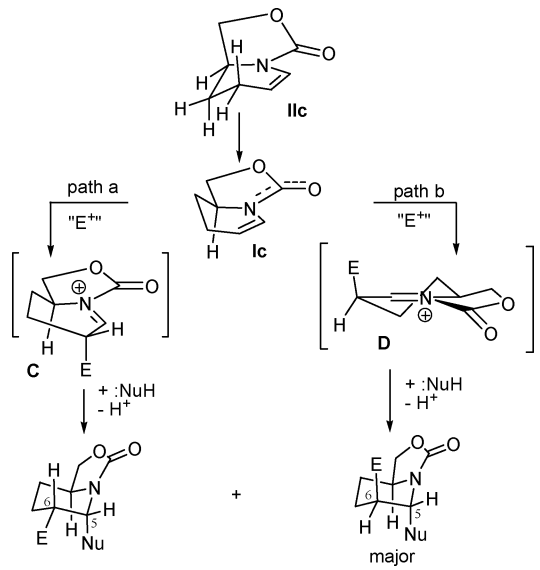
the C-5 substituents were always *syn* to the hydrogen atom of the bicyclic junction (8a-H), whatever the C-6 relative configuration. *m*-Chloroperbenzoic acid in methanol[26] was also employed as oxidizing agent with substrates **3c**; the expected hydroxymethoxypipecolate **10c** was obtained in moderate yield (30%), along with its corresponding 5-hydroxy-6-(*m*-chlorobenzoyloxy)pipecolate. The latter was isolated in 46% yield when the reaction was performed in absence of methanol and sodium bicarbonate.

Diastereoselectivity of the above additions. Some general comments regarding the observed diastereoselectivities in the additions performed on substrates **3** are necessary, before describing the functional conversion required at the C-5 position to synthesize the targeted 5-guanidinopipecolates. Some of the additions described above took place in a rather concerted manner (hydroboration and *syn*-dihydroxylation with osmium tetraoxide), and others (azidomethoxylation, halomethoxylation dihydroxylation or hydroxymethoxylation) involved multistep mechanisms. Generally, when performed on monocyclic substrates **3a,b**, all these additions and subsequent C-6 reduction provided selectively a *trans* relative orientation between the C-2 and C-5 substituents in the corresponding final monocyclic products (**5**, **7**, **8** and **11**), regardless of the mechanism involved in the addition step. However, additions to bicyclic enecarbamate **3c** appeared to be mechanism-dependent; *syn*-dihydroxylation with the OsO_4/TMO combination provided selectively the *trans* isomer (addition *anti* to the oxazolidinone methylene), while *syn*-hydroboration led to an approximately equimolar *cis*/*trans* mixture of alcohol **8c**. Other additions, which were multistep reactions, led selectively to final compounds (**5c**, **7c** and **11c**) in which the C-6 substituent was *trans* to the hydrogen atom of the ring junction (*i.e.* 8a-H). To explain the observed diastereoselectivities, we assume that, due to the partial double bond character of their exocyclic carbon–nitrogen bond, monocyclic enecarbamates **3a,b** preferentially adopt the envelope-like conformation **IIa,b**, owing to the 1,3-allylic strain present in conformation **Ia,b** where the 2-carbomethoxy substituent occupies a pseudo-equatorial position[27] (Scheme 7). Considering this conformational preference, two factors may account for the facial selectivity: (i) steric repulsion between the adding (electrophile or free radical) species and the 2-carbomethoxy group, and (ii) addition on the α-face (path a, Scheme 7) is expected to proceed *via* a half-chair transition state, while addition on the β-face (path b, Scheme 7) would proceed through a boat-like transition state. Then, for stereoelectronic reasons, both diastereomeric iminiums **A** and **B** would add nucleophiles (MeOH or H_2O) mainly *syn* to the 2-carbomethoxy substituent.[28]



Scheme 7 Possible explanation of the observed diastereoselectivity with **3a,b**.

Due to its bicyclic structure and resonance, enecarbamate **3c** is locked in conformation **Ic**. The first stage of stepwise additions takes place following path b (Scheme 8) preferentially *via* a half chair-like transition state leading to iminium ion **D**. For stereoelectronic reasons, addition of nucleophiles to both iminium intermediates **C** and **D** takes place exclusively on the α-face[14] (Scheme 8), thus leading to a mixture of epimers at the C-6-position (tetrahydrooxazolopyridin numbering). In both mono- and bicyclic enecarbamates, and unlike stepwise additions,

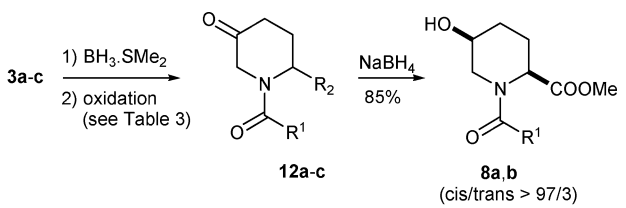


Scheme 8 Possible explanation of the observed diastereoselectivity with **3c**.

syn-dihydroxylation catalyzed with OsO_4 takes place selectively on the α-face, probably due to its concerted character and steric demand of the dihydroxylating osmium complex. However, both diasteromeric *syn*-diols derived from bicyclic substrate **3c** evolve into a mixture of C-6 epimers, due to epimerization at position C-5, which leads to the favoured *trans*-2,5 relative stereochemistry. Non-stereoselective *syn*-hydroboration of **3c** could be interpreted as a balance between steric and stereoelectronic factors.

5-Azidopipecolates *via* S_N2 reactions

Most of the oxidative methods examined above led selectively to the *trans* diastereomer; to obtain the *cis* 5-hydroxypipecolate selectively we decided to examine the reduction of its corresponding ketone **12**. This reduction was undertaken by assuming that ketones **12a,b** will be locked in a conformation with the 2-carbomethoxy substituent being axially oriented due, to the $A^{1,3}$ allylic interaction usually present in the α-substituted *N*-acylpiperidines.[27] Therefore, due to stereoelectronic control, treatment of such compounds with non-bulky hydride was expected to lead stereoselectively to the *cis* isomer of alcohol **8**, *via* an axial addition of hydride. Ketones **12**[29] were first obtained by oxidation of alcohols **8**; however, equivalent or slightly better yields were obtained following a one-pot procedure (Scheme 9) consisting of hydroboration of enecarbamates **3** and subsequent oxidative treatment with oxidants stronger than TMO or hydrogen peroxide (Table 3, entries 1–4). The best yields were obtained with



a: R^1 = OMe, R^2 = CO_2Me; **b**: R^1 = OBu^t, R^2 = CO_2Me; **c**: R^1—R^2 = -O–CH_2-

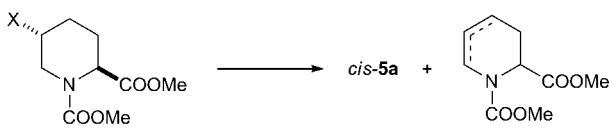
Scheme 9 Preparation of *cis* alcohols **8a,b** *via* ketones **12**.

Table 3 One-pot oxidation of **3a-c** to ketones **12**

Entry	Substrate	Conditions	Ketone (%)
1	**3a**	1) BH_3·SMe_2, 2) PCC	**12a** (45)
2	**3a**	1) BH_3·SMe_2, 2) IBX	**12a** (51)
3	**3b**	1) BH_3·SMe_2, 2) IBX	**12b** (40)
4	**3c**	1) BH_3·SMe_2, 2) IBX	**12c** (66)
5	**3c**	1) *m*-CPBA, PhMe; 2) PTSA (reflux)	**12c** (30)

2-iodoxybenzoic acid (IBX) as oxidant in refluxing acetonitrile. A lower yield of ketone **12c** was obtained *via* epoxydation of **3c** with *m*-CPBA and subsequent acid-catalyzed rearrangement (entry 5) as described by Matsumura *et al.*[29a] Reduction of ketones **12a,b** with sodium borohydride yielded the corresponding *cis* alcohols **8a,b** with high diastereoselectivity (Scheme 9).

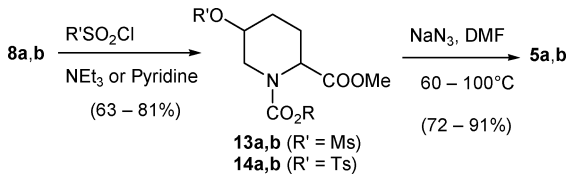
As mentioned above, azidomethoxylation of enecarbamates **3a,b** allowed selective formation of *trans*-5-azidopipecolates. To synthesise the *cis* isomers selectively, we considered nucleophilic displacement of a leaving group from either *trans*-5-halogeno- or *trans*-5-hydroxypipecolates with azide. Attempts to perform such nucleophilic substitution by reacting 5-halo-6-methoxy derivatives **6** (or **6′**) with sodium azide at 70 °C in DMF led to only partial elimination, which took place selectively at the C-4–C-5 position. Higher conversions were observed when substrates **6** were reacted with DBU or DABCO instead of sodium azide; this regioselective elimination was consistent with the *trans*-relationship between the 5-halogeno- and 6-methoxy substituents in derivatives **6**. This absence of nucleophilic substitution may be ascribed to the steric effect of the 6-methoxy substituent, which prevented the azide ion from reaching the electrophilic C-5 center. We therefore reacted demethoxylated compound **7a** with sodium azide at 70 °C in DMF, and obtained a 65 : 35 mixture of S_N2/E2 compounds. As anticipated, the elimination reaction with substrate **7a** was no longer regioselective. When using excess $TMSN_3$ in the presence of TBAF,[30] mainly nucleophilic substitution occurred (Scheme 10). A similar mixture was obtained from alcohol *trans*-**8a**, by using Mitsunobu conditions[31] (Scheme 10), albeit with low yields (<29%). Unfortunately, the major azide, *cis*-**5a**, was difficult to isolate from these mixtures in all cases.



Substrate	Conditions	S_N2/E_2
trans-**7a** (X = Br)	NaN_3, DMF (70°C)	65 / 35
trans-**7a** (X = Br)	$TMSN_3$/TBAF, THF (60°C)	85 / 15
trans-**7a** (X = Br)	$TMSN_3$/TBAF, THF (35°C)	96 / 4
trans-**8a** (X = OH)	DIAD/PPh_3/$(PhO)_2P(=O)N_3$	83 / 17

Scheme 10 Azide *cis*-**5a** from *trans*-**7a** and *trans*-**8a**.

Finally, we considered a two-step path, starting from alcohols **8a,b**, which were first activated as sulfonate esters, prior to reaction with sodium azide in DMF (Scheme 11). Indeed, mesylates **13** or tosylates **14** were efficiently converted to the corresponding azides *via* a clean S_N2 process. In addition, both diastereoisomers of alcohols **8a,b** could be successfully involved in this sequence. Thus, while *trans*-5-azides **5a,b** could be obtained either from the corresponding enecarbamates **3a,b** or from alcohol *cis*-**8a,b**, the *cis*



Scheme 11 Azides **5** from alcohols **8**.

isomers could only be reached *via* alcohols *trans*-**8a,b**. Eventually, both diastereoisomeric 5-azidopipecolates were prepared in pure form and with good yields.

5-Guanidinopipecolates

To reach the desired 5-guanidinopipecolates, each diastereomer of azide **5** had to be converted into the corresponding amine and then guanylated before final deprotection (Scheme 12). Azides **5** were submitted to hydrogenolysis in the presence of 10% palladium-on-charcoal in dichloromethane, and led efficiently to the corresponding primary amines **15**, which can be considered as ornithine analogues. To avoid intra- or inter-molecular amidation, amines **15** must be either stored as hydrochloride salts, or employed immediately in the following guanylation step.[32] To perform the latter, we tried two guanylation procedures[33] as shown in Table 4. The best yields of guanidine derivatives **16** were obtained by using *N*,*N*′-bisprotected-*S*-methylthiourea in the presence of triethylamine and mercury(II) chloride. We also performed the same hydrogenolysis/guanylation sequence starting from free acids **5**′. Isomer *trans*-**16**′**b** was obtained with 58% yield, while guanylation of *cis*-**5**′**b** led to lower yields of *cis*-**16**′**b** (Table 4). Finally, acid-catalyzed removal of the protecting groups yielded the arginine dihydrochloride mimetics **17**, which were purified by reverse-phase C-18 column chromatography. Under a high concentration of HCl (6 M), partial epimerization occurred at the C-2 position in the case of methyl carbamates **16a**. To avoid such epimerization, methyl carbamates **16a** were reacted with trimethylsilyl iodide[34] instead of aqueous HCl, leading to **17** in approximately 80% conversion, along with approximately 10% of its methylcarbamate with no detectable epimerization.

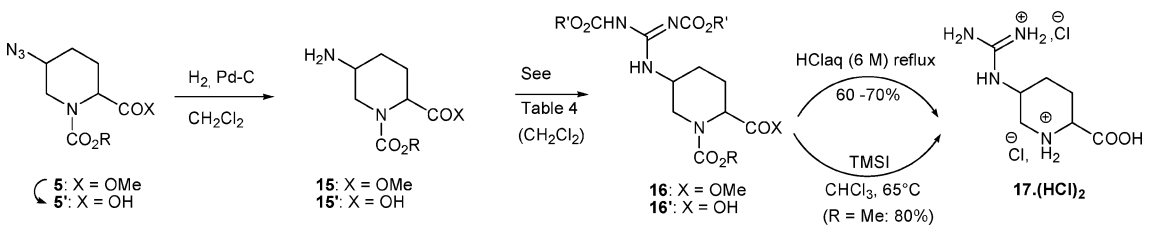
Table 5 NOS-inhibitory activity of **17**

	nNOS IC_{50}	iNOS IC_{50}	eNOS IC_{50}
(±)-*cis*-**17**	>1 mM	80 μM	200 μM
(±)-*trans*-**17**	>1 mM	160 μM	150 μM

The inhibition potency of the final arginine mimetics **17** was evaluated by examining their effects on the NOS-dependent oxidation of L-arginine to L-citrulline, according to the procedure previously described by Bredt *et al.*[35] The results of inhibition with three NOS isoforms (nNOS, iNOS and eNOS), are summarized in Table 5. Neither of the diastereomers of **17** showed inhibition towards the neuronal NOS. Although weak, some promising effects were observed in the case of inducible and endothelial isoforms. Moreover, some selectivity was observed: *cis*-**17** was more efficient in inhibiting iNOS, and *trans*-**17** was slightly more efficient in the case of the eNOS isoform (Table 5).

Conclusion

In summary, the reactivity of 5,6-dehydropipecolate derivatives **3** towards various electrophilic reagents was examined. This study allowed efficient and diastereoselective preparation of various 5-substituted pipecolates, which are valuable intermediates for the synthesis of potentially bioactive piperidine derivatives. The value of this reactivity study was illustrated by the synthesis of both diastereomers of 5-guanidinopipecolate, which we designed as constrained mimetics of arginine, and whose NOS-inhibitory activity towards three isoforms was evaluated. Weak to moderate inhibition was found and the development of less constrained



Scheme 12 Conversion of azides **5** into 5-guanidinopipecolates **17**.

Table 4 Guanylation conditions of amines **15**

Azide	Amine	Guanylation conditions	**16** (%)
trans-**5a**	*trans*-**15a**	$TfN{=}C(NHBoc)_2$, DIPEA	*trans*-**16a** (77)
trans-**5a**	*trans*-**15a**	$BocN{=}C(SMe)NHBoc$, $HgCl_2$, Et_3N	*trans*-**16a** (61)
trans-**5b**	*trans*-**15b**	$CbzN{=}C(SMe)NHCbz$, Et_3N	*trans*-**16b** (56)
trans-**5b**	*trans*-**15b**	$CbzN{=}C(SMe)NHCbz$, $HgCl_2$, Et_3N	*trans*-**16b** (80)
cis-**5a**	*cis*-**15a**	$TfN{=}C(NHBoc)_2$, DIPEA	*cis*-**16a** (68)
cis-**5a**	*cis*-**15a**	$BocN{=}C(SMe)NHBoc$, $HgCl_2$, Et_3N	*cis*-**16a** (85)
cis-**5b**	*cis*-**15b**	$CbzN{=}C(SMe)NHCbz$, Et_3N	*cis*-**16b** (52)
cis-**5b**	*cis*-**15b**	$CbzN{=}C(SMe)NHCbz$, $HgCl_2$, Et_3N	*cis*-**16b** (83)
trans-**5**′**b**	*trans*-**15**′**b**	$CbzN{=}C(SMe)NHCbz$, Et_3N	*trans*-**16**′**b** (58)
cis-**5**′**b**	*cis*-**15**′**b**	$TfN{=}C(NHCbz)_2$, Et_3N	*cis*-**16**′**b** (22)

pipecolate-based arginine mimetics is underway. The possibility of accessing these 5-substituted pipecolates efficiently is an important issue, as they can subsequently be included in peptidic structures. We are currently investigating several fundamental aspects of these compounds, such as their impact upon the conformation of peptides and their use as scaffolds[36] for the synthesis of small-molecule libraries.

Experimental

General remarks

IR spectra were recorded with a Perkin Elmer Spectrum one FT-IR spectrometer equipped with a MIRacleTM single reflection horizontal ATR unit (zirconium–selenium crystal). ^{1}H NMR spectra were recorded at 250 MHz on a Bruker AM 250 spectrometer, in $CDCl_3$ at 300 K (unless otherwise indicated); ^{13}C NMR spectra were recorded at 63 MHz on the same instrument. Chemical shifts are reported in parts per million (δ in ppm) and are referenced against solvent signals (δ_C 77.16 for chloroform) for ^{13}C spectra and solvent residual resonance (δ_H 7.26 for chloroform) for ^{1}H spectra. Coupling constants J are given in Hz. Multiplicity designation used are: s, d, t, q, dd, and m for singlet, doublet, triplet, quadruplet and double doublet respectively; broad signals are denoted by br. Mass spectra, chemical ionisation (CI) or fast atom bombardment (FAB) were recorded by the "Service de Spectrometrie de Masse" at Paris Descartes University. All reactions were carried out under an argon atmosphere, and were monitored by thin layer chromatography with Merck 60F-254 precoated (0.2 mm) on glass, and by gas chromatography (GC) analysis performed with an HP6890 apparatus equipped with DB1 capillary column (length: 25 m, diameter: 0.32 m) and an HP 3395 integrator. Dichloromethane (DCM) was distilled from CaH_2 under Ar. THF was distilled, under argon, from sodium/benzophenone ketyl radical immediately prior to use. Flash chromatography was performed with Merck kieselgel 60 (0.2–0.5 mm) or Bakerbond C-18 (0.04 mm); the solvent systems are given as v/v.

The effects of compounds **17** on the NOS-dependent oxidation of L-arginine to L-citrulline were determined according to a previously described protocol.[35] Briefly, enzymatic reactions were conducted at 37 °C for 5 min in 50 mM HEPES (pH 7.4) containing 5 mM dithiothreitol (DTT), 1 mM NADPH, 1 mM $CaCl_2$, 10 μg mL^{-1} calmoduline, 20 μM tetrahydrobiopterin (BH_4), 4 μM FAD, 4 μM FMN, 10 μM (about 500 000 cpm) [2,3,4,5-^{3}H]-L-arginine, and increasing concentrations of the tested compounds. Final incubation volumes were 100 μL. The reactions were started by the addition of protein and terminated by the addition of 500 μL cold stop buffer (20 mM sodium acetate pH 5.5, 1 mM L-citrulline, 2 mM EDTA and 0.2 mM EGTA). Samples (500 μL) were applied to columns containing 1 mL of Dowex AG 50W-X8 (Na^+ form, prepared from the H^+ form), pre-equilibrated with stop buffer and a total of 1.5 mL of stop buffer was added to eluate [^{3}H]-L-citrulline. Aliquots were then mixed with Pico-Fluor 40 (Packard) and counted on a Packard Tri-Carb 2300 liquid scintillation spectrometer. Control samples without NOS or NADPH were included for background determinations. Incubations in the presence of inducible NOS were performed similarly but $CaCl_2$ and calmoduline were omitted.

General methods for preparation of azides 5

Method A (from enecarbamates 3, by azidomethoxylation/reduction sequence). *Azidomethoxylation*. To a 0.08 M solution of enecarbamate **3a** (or **3b**) and NaN_3 (1.5 equiv.) in a 4 : 1 mixture of acetone–MeOH was added dropwise a 0.1 M solution of cerium ammonium nitrate (3 equiv.) in acetone at −95 °C. The mixture was stirred at *ca.* −90 °C until total conversion of **1** (as monitored by TLC), then diluted with H_2O and extracted with Et_2O. The combined organic layers were washed with water and brine, dried over $MgSO_4$ and concentrated *in vacuo*, prior to purification by flash column chromatography, affording adduct **4**. Azidomethoxylation of enecarbamate **1c** was performed in acetonitrile instead of acetone; the CAN solution was added at 0 °C and the reaction mixture was stirred at r.t. for 16 h.

Reduction. To a solution of the 5-azido-6-methoxy compound **4** in DCM were added $BF_3{\cdot}OEt_2$ (1.05 equiv.) and Et_3SiH (1.05 equiv.) at −90 °C. After allowing warming until r.t. for 8 h, the solution was diluted with DCM, and a saturated aqueous solution of $NaHCO_3$ was added. The aqueous phase was extracted twice with DCM; the combined organic layers were washed with water, dried over $MgSO_4$, and concentrated *in vacuo*. The final product **5** was purified by flash column chromatography.

Method B (from mesylates 13 or tosylates 14). To the mesylate or tosylate dissolved in DMF, was added NaN_3 (7–8 equiv.) and the mixture was heated at 65–100 °C; then DMF was removed *in vacuo*. Water (50 mL) was added and the mixture was extracted with DCM. The organic extracts were washed with water, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography afforded pure azido compound **5**.

(2*S,5*R**)-Dimethyl 5-azidopiperidine-1,2-dicarboxylate *trans*-5a.** Following Method A, from enecarbamate **3a** (275 mg, 1.38 mmol), NaN_3 (137 mg, 2.07 mmol) and CAN (2.27 g, 4.14 mmol), at −90 °C for 7 h. After workup, the crude azidomethoxylation compound **5a** was submitted to reduction with Et_3SiH (194 μL, 1.21 mmol) and $BF_3{\cdot}OEt_2$ (172 μL, 1.21 mmol). Flash column chromatography (cyclohexane–EtOAc 85 : 15) afforded a *trans*/*cis* (87 : 13) mixture of azido compounds **5a** (58%).

Following Method B, from mesylate *cis*-**13a** (380 mg, 1.29 mmol) and NaN_3 (620 mg, 9.54 mmol) in DMF (5 mL). Flash column chromatography (cyclohexane–EtOAc 7 : 3) afforded *trans*-**5a** as a colourless oil (220 mg, 72%).

Following Method B, from tosylate *cis*-**14a** (90 mg, 0.24 mmol) and NaN_3 (120 mg, 1.82 mmol) in DMF (2 mL). Flash column chromatography (cyclohexane–EtOAc 7 : 3) afforded *trans*-**5a** as a colourless oil (51 mg, 86%).

R_f = 0.26 (cyclohexane/AcOEt 7 : 3); δ_H (250 MHz, $CDCl_3$; Me_4Si) 5.05–4.94 (0.6 H, m, 2-H), 4.90–4.75 (0.4 H, m, 2-H), 4.35–4.00 (1 H, m, 6-H), 3.90–3.60 (7 H, m, 5-H, NCO_2CH_3, CO_2CH_3), 3.40–3.10 (1 H, m, 6-H), 2.15–2.00 (m, 2 H, 3-H), 1.95–1.45 (m, 2 H, 4-H); δ_C (63 MHz, $CDCl_3$) 171.4 (CO_2CH_3), 156.7, 156.2 (NCO_2CH_3), 54.8 (CH-5), 53.7, 53.4 (CH-2), 52.7 (NCO_2CH_3), 52.2 (CO_2CH_3), 44.1 (CH_2-6), 24.5 (CH_2-4), 20.8 (CH_2-3); MS (ESI): m/z = 265 [M + Na]$^+$ 100%; HRMS (ESI) m/z calcd for $C_9H_{14}N_4O_4Na$ [M + Na]$^+$ 265.0913, found 265.0910.

(2*S,5*S**)-Dimethyl 5-azidopiperidine-1,2-dicarboxylate *cis*-5a.** Following Method B, from mesylate *trans*-**13a** (380 mg, 1.29 mmol) and NaN_3 (620 mg, 9.54 mmol) in DMF (5 mL). Flash

column chromatography (cyclohexane–EtOAc 7 : 3) afforded *cis*-**5a** as a colourless oil (220 mg, 72%). R_f = 0.30 (cyclohexane–EtOAc 65 : 35); δ_H (250 MHz, $CDCl_3$; Me_4Si) 4.98–4.85 (0.6 H, m, 2-H), 4.83–4.70 (0.4 H, m, 2-H), 4.40–4.25 (0.4 H, m, 6-H), 4.23–4.05 (0.6 H, m, 6-H), 3.85–3.60 (6 H, m, CO_2CH_3), 3.50–3.20 (1 H, m, 5-H), 2.95–2.65 (1 H, s, 6-H), 2.45–2.20 (1 H, m, 3-H), 2.15–1.95 (1 H, m, 4-H), 1.85–1.60 (1 H, m, 3-H), 1.45–1.15 (1 H, m, 4-H); δ_C (63 MHz, $CDCl_3$) 171.2 (CO_2CH_3), 156.5, 156.1 (NCO_2CH_3), 56.4 (CH-5), 53.6, 53.3, 52.6 (CH-2, NCO_2CH_3, CO_2CH_3), 45.5, 45.3 (CH_2-6), 26.9 (CH_2-4), 25.5, 25.2 (CH_2-3); MS (ESI): m/z = 265 $[M + Na]^+$ 100%; HRMS (ESI) m/z calcd for $C_9H_{14}N_4O_4Na$ $[M + Na]^+$ 265.0913, found 265.0924.

(2*S,5*R**)-1-*tert*-Butyl 2-methyl 5-azidopiperidine-1,2-dicarboxylate *trans*-5b.** Following Method A, from enecarbamate **3b** (332 mg, 1.38 mmol), NaN_3 (137 mg, 2.07 mmol) and CAN (2.27 g, 4.14 mmol), at −90 °C for 1 h. Reduction step was performed by using $BF_3{\cdot}OEt_2$ (172 μL, 1.21 mmol) and Et_3SiH (194 μL, 1.21 mmol). Flash column chromatography (cyclohexane–EtOAc 85 : 15) afforded a *trans*/*cis* (92 : 8) mixture of azido compound **5b** (60%) from which isomer *trans* could be isolated as pure compound (155 mg, 47%).

Following Method B, from mesylate *cis*-**13b** (292 mg, 0.87 mmol) and NaN_3 (450 mg, 6.92 mmol) in DMF (3.5 mL). Flash column chromatography (cyclohexane–EtOAc 85 : 15) afforded pure *trans*-**5b** as a colourless oil (225 mg, 91%).

R_f = 0.23 (cyclohexane–EtOAc 8 : 2); ν_{max}(neat)/cm^{-1} 2981, 2945, 2108, 1726, 1679, 1416, 1364, 1243, 1147, 1013; δ_H (250 MHz, $CDCl_3$; Me_4Si) 5.05–4.85 (0.6 H, m, 2-H), 4.83–4.60 (0.4 H, m, 2-H), 4.25–4.00 (1 H, m, 6-H), 3.85–3.60 (4 H, m, 5-H, CO_2CH_3), 3.35–3.00 (1 H, m, 6-H), 2.10–1.95 (2 H, m, 3-H), 1.90–1.30 (11 H, m, 4-H, CMe_3); δ_C (63 MHz, $CDCl_3$) 171.9 (CO_2CH_3), 155.3 (CO_2tBu), 80.7 (CMe_3), 55.0 (CH-5), 54.2, 52.9 (CH-2), 52.2 (CO_2CH_3), 44.2, 43.7 (CH_2-6), 28.2 (CMe_3), 24.9 (CH_2-4), 21.0 (CH_2-3); MS (ESI): m/z = 307 $[M + Na]^+$ 100%; HRMS (ESI) m/z calcd for $C_{12}H_{20}N_4O_4Na$ $[M + Na]^+$ 307.1382, found 307.1374.

(2*S,5*S**)-1-*tert*-Butyl 2-methyl 5-azidopiperidine-1,2-dicarboxylate *cis*-5b.** Following method B, from mesylate *trans*-**13b** (1.48 g, 4.39 mmol) and NaN_3 (2.28 g, 35.12 mmol) in DMF (16 mL). Flash column chromatography (cyclohexane–EtOAc 85 : 15) afforded pure *cis*-**5b** as a colourless oil (1.11 g, 90%).

R_f = 0.32 (cyclohexane–EtOAc 8 : 2); ν_{max}(neat)/cm^{-1} 2971, 2868, 2098, 1741, 1695, 1403, 1364, 1245, 1147; δ_H (250 MHz, $CDCl_3$; Me_4Si) 4.95–4.80 (0.6 H, m, 2-H), 4.75–4.60 (0.4 H, m, 2-H), 4.35–4.17 (0.4 H, m, 6-H), 4.25–3.98 (0.6 H, m, 6-H), 3.72 (3 H, s, CO_2CH_3), 3.45–3.20 (1 H, m, 5-H), 2.85–2.55 (1 H, m, 6-H), 2.45–2.20 (1 H, m, 3-H), 2.10–1.90 (1 H, m, 4-H), 1.85–1.60 (1 H, m, 3-H), 1.55–1.15 (10 H, m, 4-H, CMe_3); δ_C (63 MHz, $CDCl_3$) 171.3 (CO_2CH_3), 155.1, 154.8 (CO_2-*t*-Bu), 80.8 (CMe_3), 56.4 (CH-5), 53.8, 52.5 (CH-2), 52.2 (CO_2CH_3), 45.7, 44.6 (CH_2-6), 28.2 (CMe_3), 26.8 (CH_2-4), 25.2, 25.0 (CH_2-3); MS (ESI): m/z = 307 $[M + Na]^+$ 100%; HRMS (ESI) m/z calcd for $C_{12}H_{20}N_4O_4Na$ $[M + Na]^+$ 307.1382, found 307.1367.

General method for hydroboration/oxidation sequences

Hydroboration. To a solution of the enecarbamate **3** in DCM at −80 °C was added dropwise a 2 M solution of $BH_3{\cdot}SMe_2$ (1 equiv.) in THF, and the mixture then warmed to room temperature. The reaction mixture was stirred at r.t. for 2.5 h (unless otherwise indicated), and then concentrated *in vacuo* to afford a borane compound, which was used in the oxidative steps.

*Oxidation with Me_3NO (for preparation of alcohols **8**)*. To the crude hydroboration compound were added THF and trimethylamine *N*-oxide and the heterogeneous mixture was refluxed at 70 °C for 15 min then concentrated *in vacuo*. Water was added and the organic layer was extracted with DCM, dried over $MgSO_4$, and then concentrated *in vacuo*. Purification by flash column chromatography afforded alcohols **8**.

*Oxidation with iodoxy benzoic acid (IBX) (for preparation of ketones **12**)*. To the crude hydroboration compound were added acetonitrile and IBX (4 equiv.) and the heterogeneous mixture was refluxed at 80 °C for 2.5 h. After filtration over Celite and washing with DCM, the filtrate was concentrated *in vacuo*. The residue was diluted with H_2O and the organic layer was extracted with DCM. Purification by flash column chromatography afforded ketones **12**.

(2*S,5*R**)-Dimethyl 5-hydroxypiperidine-1,2-dicarboxylate *trans*-8a[23b].** Prepared according to the above procedure, starting from enecarbamate **3a** (2.01 g, 10.1 mmol) in DCM (30 mL) and $BH_3{\cdot}SMe_2$ (2 M in THF, 5.0 mL, 10.1 mmol); then oxidation with triethylamine *N*-oxide (6.7 g, 60.6 mmol) in THF (30 mL). Flash column chromatography (EtOAc–cyclohexane 7 : 3) afforded a *trans*/*cis* (85 : 15) mixture of alcohol **8a** (63%) from which pure sample of the *trans* isomer could be isolated as a colourless oil (1.1 g, 50%): R_f = 0.20 (EtOAc–cyclohexane 7 : 3); ν_{max}(neat)/cm^{-1} 3451, 3016, 2955, 1738, 1686, 1447, 1252, 1123, 1017; δ_H (250 MHz, $CDCl_3$; Me_4Si) 4.98 (0.7 H, br s, 2-H), 4.84 (0.3 H, br s, 2-H), 4.15–3.85 (2 H, m, 6-H, 5-H), 3.73 (6 H, br s, CO_2CH_3, NCO_2CH_3), 3.30–3.13 (1 H, m, 6-H), 2.25–1.95 (2 H, m, 4-H), 1.85–1.40 (2 H, m, 3-H); δ_C (63 MHz, $CDCl_3$) 171.9 (CO_2CH_3), 157.5 (NCO_2CH_3), 63.4 (CH-5), 54.2, 53.8 (CH-2), 53.0, 52.3 (CO_2CH_3), 47.5, 42.6 (CH_2-6), 27.1, 26.7 (CH_2-4), 20.2 (CH_2-3); MS (ESI): m/z = 235 $[M + NH_4]^+$ 100%.

(2*S,5*R**)-1-*tert*-Butyl 2-methyl 5-hydroxypiperidine-1,2-dicarboxylate *trans*-8b.** Prepared according to the above procedure, starting from enecarbamate **3b** (5 g, 20.75 mmol) in DCM (100 mL), and $BH_3{\cdot}SMe_2$ (2 M in THF, 10.4 mL, 20.80 mmol), stirring at r.t. was maintained for 4 h, prior to oxidation with triethylamine *N*-oxide (12.5 g, 112.6 mmol) in THF (100 mL). Flash column chromatography (EtOAc–cyclohexane 6 : 4) afforded a *trans*/*cis* (93 : 7) mixture of alcohol **8b** (3.4 g, 63%) as colourless oil: R_f = 0.23 (EtOAc–cyclohexane 6 : 4); δ_H (250 MHz, $CDCl_3$; Me_4Si) 5.05–4.65 (1 H, m, 2-H), 4.15–3.80 (2 H, m, 5-H, 6-H), 3.70 (3 H, s, CO_2CH_3), 3.30–2.95 (1 H, m, 6-H), 2.30–1.60 (4 H, m, 3-H, 4-H), 1.42 (9 H, s, *t*-Bu); δ_C (63 MHz, $CDCl_3$) 172.5 (CO_2CH_3), 156.6 (CO_2-*t*-Bu), 80.8 (CMe_3), 63.9 (CH-5), 54.9, 53.7 (CH-2), 52.4 (CO_2CH_3), 48.2, 47.3 (CH_2-6), 28.6 (CMe_3), 27.3 (CH_2-4), 20.6 (CH_2-3); MS (ESI): m/z = 282 $[M + Na]^+$ 100%; HRMS (ESI) m/z calcd for $C_{12}H_{21}NO_5Na$ $[M + Na]^+$ 282.1317, found 282.1312.

(2*S,5*S**)-Dimethyl 5-hydroxypiperidine-1,2-dicarboxylate *cis*-8a[23b].** This stereoisomer was isolated in low yield from the oxidation–hydroboration of enecarbamate **3a**. It was also prepared, with higher yield, by reduction of ketone **12a** (2.58 g,

12.0 mmol) in ethanol (45 mL) by portionwise addition of sodium borohydride (910 mg, 23.9 mmol) at 0 °C, then the mixture was stirred at 0 °C for 15 min. The reaction mixture was portionned between DCM (50 mL) and 10% aqueous solution of citric acid (pH = 6). The aqueous layer was re-extracted with EtOAc (2 × 30 mL). The organic extracts were combined, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (EtOAc) afforded a *cis*/*trans* (99 : 1) mixture of alcohol **8a** (1.9 g, 74%): R_f = 0.26 (EtOAc–cyclohexane 7 : 3); ν_{max}(neat)/cm^{-1} 3418, 2953, 2866, 1736, 1682, 1446, 1237, 1212, 1151, 998; δ_H (250 MHz, $CDCl_3$; Me_4Si) 4.86 (0.6 H, br s, 2-H), 4.85 (0.4 H, br s, 2-H), 4.24 (0.4 H, d, *J* 11.0, 6-H), 4.12 (0.6 H, d, *J* 11.0, 6-H), 3.75–3.53 (7H, m, CO_2CH_3, NCO_2CH_3, 5-H), 2.83–2.64 (1 H, m, 6-H), 2.31–2.23 (1 H, m, 3-H), 2.00–1.91 (1 H, m, 4-H), 1.80–1.63 (1 H, m, 3-H), 1.31–1.10 (1 H, m, 4-H); δ_C (63 MHz, $CDCl_3$) 171.5 (CO_2CH_3), 157.3 (NCO_2CH_3), 66.5 (CH-5), 53.5, 53.2 (CH-2), 53.1, 52.4 (CO_2CH_3), 48.0 (CH_2-6), 30.3 (CH_2-4), 24.9 (CH_2-3); MS (ESI): *m*/*z* = 235 [M + NH_4]$^+$ 25%.

(2*S,5*S**)-1-*tert*-Butyl 2-methyl-*cis*-5-hydroxypiperidine-1,2-dicarboxylate *cis*-8b.** Obtained in higher quantities by reduction of ketone **12b** (832 mg, 3.24 mmol) in MeOH (17 mL), with sodium borohydride (129 mg 3.39 mmol) at 0 °C following the procedure employed in the case of ketone **12a**. Purification by flash column chromatography (EtOAc–cyclohexane 55 : 45) afforded a *cis*/*trans* (97 : 3) mixture of alcohol **8b** (712 mg, 85%) from which pure *cis*-**8b** could be isolated as colourless oil (630 mg, 75%): R_f = 0.21 (EtOAc–cyclohexane 55 : 45); ν_{max}(neat)/cm^{-1} 3416, 2971, 2868, 1739, 1692, 1403, 1238, 1209, 1142, 997; δ_H (250 MHz, $CDCl_3$; Me_4Si) 4.90–4.55 (1 H, m, 2-H), 4.30–3.95 (1 H, m, 6-H), 3.80–3.50 (4 H, m, CO_2CH_3, 5-H), 2.85–2.55 (1 H, m, 6-H), 2.35–2.15 (1 H, m, 3-H), 2.05–1.60 (3 H, m, 3-H, 4-H, OH), 1.43 (9 H, s, *t*-Bu), 1.30–1.10 (1 H, m, 4-H); δ_C (63 MHz, $CDCl_3$) 170.4 (CO_2CH_3), 155.5, 155.2 (CO_2-*t*-Bu), 80.6 (CMe_3), 66.4, 66.3 (CH-5), 54.0, 52.7 (CH-2), 52.2 (CO_2CH_3), 48.4, 47.6 (CH_2-6), 30.4, 29.8 (CH_2-4), 28.3 (CMe_3), 25.1, 24.9 (CH_2-3); MS (ESI): *m*/*z* = 282 [M + Na]$^+$ 100%; HRMS (ESI) *m*/*z* calcd for $C_{12}H_{21}NO_5Na$ [M + Na]$^+$ 282.1317, found 282.1327.

***rac*-Dimethyl 5-oxopiperidine-1,2-dicarboxylate 12a[29a].** Hydroboration of enecarbamate **3a** (1.1 g, 5.53 mmol) with BH_3·SMe_2 (2 M in THF, 2.76 mL, 5.52 mmol) in DCM (17 mL) then oxidative treatment with IBX (6.19 g, 22.1 mmol) in CH_3CN (75 mL), according to the procedure described above. Flash column chromatography (EtOAc–cyclohexane 5 : 5) afforded ketone **12a** as a yellow oil (600 mg, 51%): R_f = 0.34 (EtOAc–cyclohexane 6 : 4); ν_{max}(neat)/cm^{-1} 2958, 1737, 1694, 1441, 1203; δ_H (250 MHz, $CDCl_3$; Me_4Si) 4.85 (0.6 H, t, *J* 6.1, 2-H), 4.71 (0.4 H, t, *J* 6.1, 2-H), 4.46 (0.4 H, d, *J* 19.0, 6-H), 4.32 (0.6 H, d, *J* 19.0, 6-H), 3.93 (0.6 H, d, *J* 19.0, 6-H), 3.88 (0.4 H, d, *J* 19.0, 6-H), 3.76–3.72 (6 H, m, CO_2CH_3), 2.51–2.10 (4 H, m, 3-H, 4-H); δ_C (63 MHz, $CDCl_3$) 204.6 (C-5), 171.8 (CO_2CH_3), 156.3 (NCO_2CH_3), 53.7, 53.4 (CH-2), 53.2, 52.5 (CO_2CH_3), 51.9, 51.5 (CH_2-6), 35.6 (CH_2-4), 23.9, 23.5 (CH_2-3); MS (ESI): *m*/*z* = 233 [M + NH_4]$^+$ 100%.

***rac*-1-*tert*-Butyl 2-methyl 5-oxopiperidine-1,2-dicarboxylate 12b[29b].** Hydroboration of enecarbamate **3b** (438 mg, 1.82 mmol) with BH_3·SMe_2 (2 M in THF, 0.91 mL, 1.82 mmol) in DCM (9 mL), at r.t. for 4 h; and subsequent oxidative treatment with IBX (2.04 g, 7.82 mmol) in CH_3CN (10 mL), according to the procedure described above. Flash column chromatography (cyclohexane–EtOAc 7 : 3) afforded ketone **12b** as a yellow oil (187 mg, 40%): R_f = 0.24 (cyclohexane–EtOAc 7 : 3); ν_{max}(neat)/cm^{-1} 2971, 1736, 1695, 1392, 1150; δ_H (250 MHz, $CDCl_3$; Me_4Si) 4.85–4.75 (0.6 H, m, 2-H), 4.65–4.50 (0.4 H, m, 2-H), 4.38 (0.6 H, d, *J* 19.0, 6-H), 4.27 (0.4 H, d, *J* 19.0, 6-H), 3.97–3.80 (1 H, m, 6-H), 3.75 (3 H, s, CO_2CH_3), 2.50–1.95 (4 H, m, 3-H, 4-H), 1.43 (9 H, m, *t*-Bu); δ_C (63 MHz, $CDCl_3$) 205.6 (C-5), 172.6, 172.3 (CO_2CH_3), 154.9, 154.4 (CO_2-*t*-Bu), 81.4 (CMe_3), 54.6, 53.1 (CH-2), 52.5 (CO_2CH_3), 51.0 (CH_2-6), 36.0, 35.8 (CH_2-4), 28.3 (CMe_3), 23.8, 23.7 (CH_2-3); MS (ESI): *m*/*z* = 256 [M − H]$^+$ 100%.

(2*S,5*R**)-Dimethyl *trans*-5-(*N*,*N*′-bis(*tert*-butoxycarbonyl)-guanidino)piperidine-1,2-dicarboxylate *trans*-16a**

Method A. To a solution of the amino ester *trans*-**15a** (0.73 g, 2.89 mmol) in DCM (40 mL), were added *N*,*N*′-bis(*tert*-butoxycarbonyl)-*N*″-trifluoromethanesulfonylguanidine (3 g, 7.67 mmol) and DIPEA (1.41 mL, 8.69 mmol). The heterogeneous mixture was stirred at r.t. for 5 days and then concentrated *in vacuo*. Purification by flash column chromatography (DCM→DCM–MeOH 98 : 2) afforded the 5-guanidino compound *trans*-**16a** as a white solid (1.02 g, 77%).

Method B. To a solution of the amino ester *trans*-**15a** (103 mg, 0.41 mmol) in DCM (5 mL) was added *N*,*N*′-bis(*tert*-butoxycarbonyl)-*S*-methylisothiourea (277 mg, 0.96 mmol), triethylamine (157 μL, 1.13 mmol) and $HgCl_2$ (265 mg, 0.98 mmol). The mixture was stirred at r.t. for 30 h, then filtered through a pad of Celite, washed with DCM and the filtrate was concentrated *in vacuo*. Flash column chromatography (DCM→DCM–MeOH 98 : 2) afforded the 5-guanidino compound *trans*-**16a** as a white solid (115 mg, 61%). ν_{max}(neat)/cm^{-1} 2975, 1740, 1714, 1633, 1613, 1564, 1442, 1413, 1321, 1246, 1148; R_f = 0.42 (DCM/CH_3OH 98 : 2); m.p. = 64–68°C; δ_H (250 MHz, $CDCl_3$; Me_4Si) 11.42 (s, 1 H, N*H*Boc), 8.80 (1 H, br s, NH), 5.05–4.70 (1 H, m, 2-H), 4.55–4.26 (1 H, m, 5-H), 4.25–3.95 (1 H, m, 6-H), 3.73 (3 H, s, CO_2CH_3), 3.71 (3 H, s, NCO_2CH_3), 3.30–3.15 (1 H, m, 5-H), 2.22–2.07 (1 H, m, 3-H), 2.01–1.77 (2 H, m, 4-H), 1.51–1.44 (19 H, m, 2 × CMe_3, 3-H); δ_C (63 MHz, $CDCl_3$) 171.4 (CO_2CH_3), 163.6, 155.5, 153.1 (N-C=O, C=N), 83.2, 79.2 (2×CMe_3), 53.8 (CH-2), 53.0, 52.5 (CO_2CH_3, NCO_2CH_3), 45.7 (CH_2-6), 43.7 (CH-5) 28.3, 28.0 (2 × CMe_3), 24.9 (CH_2-4), 21.3 (CH_2-3); MS (ESI): *m*/*z* = 481 [M + Na]$^+$ 100%; HRMS (ESI) *m*/*z* calcd for $C_{20}H_{34}N_4O_8Na$ [M + Na]$^+$ 481.2274, found 481.2260.

(2*S,5*S**)-Dimethyl *trans*-5-(*N*,*N*′-bis(*tert*-butoxycarbonyl)-guanidino)piperidine-1,2-dicarboxylate *cis*-16a**

The amino ester *cis*-**15a** (580 mg, 2.29 mmol) was guanylated with *N*,*N*′-bis(*tert*-butoxycarbonyl)-*S*-methylisothiourea following the procedure described above for its *trans* isomer. Flash column chromatography (DCM→DCM–MeOH 98 : 2) afforded the 5-guanidino compound *cis*-**16a** as a white solid (898 mg, 85%). ν_{max}(neat)/cm^{-1} 2979, 1715, 1637, 1611, 1560,1446, 1411, 1368, 1335, 1309, 1242, 1137, 1052; δ_H (250 MHz, $CDCl_3$; Me_4Si) 11.48 (1 H, br s, NHBoc), 8.80 (1 H, d, *J* 7.8, *N*H), 4.98–4.88 (0.6 H,

m, 2-H), 4.82–4.70 (0.4 H, m, 2-H), 4.40–3.98 (2 H, m, 5-H, 6-H), 3.80–3.60 (6 H, m, CO_2CH_3, NCO_2CH_3), 2.85–2.60 (1 H, m, 6-H), 2.35–2.18 (1 H, m, 3-H), 2.10–1.92 (1 H, m, 4-H), 1.91–1.69 (1 H, m, 3-H), 1.65–1.35 (18 H, m, 2 × CMe_3), 1.30–1.05 (1 H, m, 4-H); δ_C (63 MHz, $CDCl_3$) 171.80 (CO_2CH_3), 163.8, 156.8, 156.5, 155.9, 153.4 (N-C=O, C=N), 83.6; 79.8, 79.6 (CMe_3), 53.7, 53.6, 53.3, 53.2, 52.6 (CH-2, CO_2CH_3, NCO_2CH_3), 46.1 (CH-5), 45.8 (CH_2-6) 28.4, 28.2 (CMe_3), 27.7, 27.6 (CH_2-3), 25.7, 25.4 (CH_2-4); MS (ESI): m/z = 481 [M + Na]$^+$ 100%; HRMS (ESI) m/z calcd for $C_{20}H_{34}N_4O_8Na$ [M + Na]$^+$ 481.2274, found 481.2256.

(2*S**,5*R**)-1-*tert*-Butyl 2-methyl-5-(*N*,*N*′-bis(benzyloxycarbonyl)-guanidino)piperidine-1,2-dicarboxylate *trans*-16b

To a solution of the amino ester *trans*-**15b** (80.5 mg, 0.33 mmol) in DCM (4 mL), were added *N*,*N*′-bis(benzyloxycarbonyl)-*S*-methylisothiourea (328 mg, 0.92 mmol), triethylamine (55 μL, 0.39 mmol) and mercury dichloride (255 mg, 0.94 mmol). The mixture was stirred at r.t. for 16 h then concentrated *in vacuo*. Purification by flash column chromatography (DCM→DCM–MeOH 97 : 3) afforded the 5-guanidino compound *trans*-**16b** as a colourless oil (150 mg, 80%). R_f = 0.46 (DCM–MeOH 99 : 1); ν_{max}(neat)/cm^{-1} 3322, 3291, 2950, 1798, 1728, 1695, 1633, 1617, 1566, 1452, 1423, 1377, 1364, 1336, 1300, 1240, 1199, 1124, 1046; δ_H (250 MHz, $CDCl_3$; Me_4Si) 11.67 (1 H, s, *N*HZ), 8.79 (1 H, d, *J* 7.0, *N*H), 7.44–7.08 (10 H, m, $H_{Ar.}$), 5.20–4.65 (5 H, m, 2 × OCH_2Ph, 2-H), 4.40–3.95 (2 H, m, 5-H, 6-H), 3.68 (3 H, s, CO_2CH_3), 3.22–2.93 (1 H, m, 6-H), 2.20–2.00 (1 H, m, 3-H), 1.98–1.72 (2 H, m, 3-H, 4-H), 1.63–1.16 (10 H, m, CMe_3, 4-H); δ_C (63 MHz, $CDCl_3$) 171.7 (CO_2CH_3), 163.8, 155.7, 155.4, 153.9 (N–C=O, C=N), 136.8, 134.7 ($C_{Ar.}$), 128.9, 128.7, 128.6, 128.5, 128.2, 128.0 ($CH_{Ar.}$), 80.9 (CMe_3), 68.3, 67.3 (2 × OCH_2Ph), 54.6, 53.1 (CH-2), 52.4 (CO_2CH_3), 45.5 (CH_2-6), 44.8, 44.5 (CH-5), 28.3 (CMe_3), 24.9 (CH_2-4), 21.4 (CH_2-3); MS (ESI): m/z = 591 [M + Na]$^+$ 100%; HRMS (ESI) m/z calcd for $C_{29}H_{36}N_4O_8Na$ [M + Na]$^+$ 591.2431, found 591.2402.

(2*S**,5*S**)-1-*tert*-Butyl 2-methyl -5-(*N*,*N*′-bis-(benzyloxycarbonyl)guanidino)piperidine-1,2- dicarboxylate *cis*-16b

Guanylation of the *cis*-amino ester compound *cis*-**15b** (93 mg, 0.38 mmol) was carried out as for its *trans* isomer. Flash column chromatography (DCM→DCM–MeOH 97 : 3) afforded the 5-guanidino compound *cis*-**16b** as a colourless oil (181 mg, 83%). R_f = 0.44 (DCM–MeOH 99 : 1); ν_{max}(neat)/cm^{-1} 3271, 2976, 1785, 1741, 1728, 1690, 1646, 1620, 1584, 1452, 1431, 1382, 1367, 1333, 1297, 1281, 1263, 1212, 1147, 1052; δ_H (250 MHz, $CDCl_3$; Me_4Si) 11.73 (1 H, s, *N*HZ), 8.16 (1 H, br s, *N*H), 7.46–7.17 (10 H, m, $H_{Ar.}$), 5.25–5.00 (4 H, m, 2 × OCH_2Ph), 4.95–4.62 (1 H, m, 2-H), 4.35–3.93 (2 H, m, 5-H, 6-H), 3.72 (3 H, s, CO_2CH_3), 2.70–2.53 (1 H, m, 6-H), 2.35–2.13 (1 H, m, 3-H), 2.06–1.90 (1 H, m, 4-H), 1.88–1.65 (1 H, m, 3-H), 1.41 (9 H, s, CMe_3), 1.28–1.05 (1 H, m, 4-H); δ_C (63 MHz, $CDCl_3$) 171.8 (CO_2CH_3), 163.8, 155.6, 155.3, 154.9, 153.9 (N–C=O, C=N), 136.7, 134.6 ($C_{Ar.}$), 128.9, 128.8, 128.5, 128.4, 128.2, 128.0 ($CH_{Ar.}$), 80.7 (CMe_3), 68.3, 67.3 (2 × OCH_2Ph), 53.9, 52.6 (CH-2), 52.3 (CO_2CH_3), 46.7 (CH-5), 45.7, 44.9 (CH_2-6), 28.3 (CMe_3), 27.6 (CH_2-4), 25.2 (CH_2-3); MS (ESI): m/z = 591 [M + Na]$^+$ 100%; HRMS (ESI) m/z calcd for $C_{29}H_{36}N_4O_8Na$ [M + Na]$^+$ 591.2431, found 591.2435.

5-guanidinopiperidine-2-carboxylic acids 17

Method A. Guanidino compound **16** (0.5 mmol scale) was heated at reflux in 6 M aqueous HCl (6 mL) for 4 days then concentrated *in vacuo*. The resulting powder was submitted to purification by C-18 reverse phase column chromatography (H_2O) to afford the final arginine mimetic **17** (69–79%).

Method B (for derivatives 16a). Guanidino compound **16a** (0.1–0.3 mmol scale) was refluxed in chloroform (1–3 mL) in the presence of trimethylsilyl iodide (16 equiv.) for 24 h. The reaction mixture was quenched by addition of 3 mL of saturated methanol with HCl(g) then concentrated under vacuum prior to purification by C-18 reverse phase column chromatography (H_2O) as in Method A.

(2*S,5*R**)-17 (*trans* isomer).** δ_H (250 MHz, D_2O) 3.95–3.77 (2 H, m, 2-H, 5-H), 3.76–3.62 (1 H, m, 6-H), 3.15–2.95 (1 H, m, 6-H), 2.58–2.41 (1 H, m, 3-H), 2.39–2.25 (1 H, m, 4-H), 2.05–1.65 (2 H, m, 3-H, 4-H); δ_C (63 MHz, D_2O) 174.2 (CO_2H), 159.1 (C=N), 59.4 (CH-2), 48.4 (CH_2-6), 48.1 (C-5) 31.1 (CH_2-4), 27.2 (CH_2-3); MS (FAB): m/z = 187 [M + H]$^+$ 100%; Anal. Calcd. for $C_7H_{16}Cl_2N_4O_2 \cdot 0.75H_2O$: C, 30.84; H, 6.47; N, 20.55. Found: C, 30.94; H, 6.39; N, 20.13.

(2*S,5*S**)-17 (*cis* isomer).** δ_H (250 MHz, D_2O) 4.17–3.97 (2 H, m, 2-H, 5-H), 3.58–3.39 (2 H, m, 6-H), 2.34–2.06 (3 H, m, 3-H, 4-H), 2.02–1.82 (1 H, m, 4-H); δ_C (63 MHz, D_2O) 173.8 (CO_2H), 159.2 (C=N), 58.3 (CH-2), 47.7 (CH_2-6), 46.9 (CH-5), 28.4 (CH_2-4), 24.3 (CH_2-3); MS (FAB): m/z = 187 [M + H]$^+$ 100%; Anal. Calcd. for $C_7H_{16}Cl_2N_4O_2 \cdot 1.75H_2O$: C, 28.93; H, 6.76; N, 19.28. Found: C, 28.39; H, 6.40; N, 19.81.

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