2-Iminopyrrolidines as Potent and Selective Inhibitors of Human Inducible Nitric Oxide Synthase[‖]

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A series of substituted 2-iminopyrrolidines has been prepared and shown to be potent and selective inhibitors of the human inducible nitric oxide synthase (hiNOS) isoform versus the human endothelial nitric oxide synthase (heNOS) and the human neuronal nitric oxide synthase (hnNOS). Simple substitutions at the 3-, 4-, or 5-position afforded more potent analogues than the parent 2-iminopyrrolidine **1**. The effect of ring substitutions on both potency and selectivity for the different NOS isoforms is described. Substitution at the 4- and 5-positions of the 2-iminopyrrolidine yielded both potent and selective inhibitors of hiNOS. In particular, (+)-*cis*-4-methyl-5-pentylpyrrolidin-2-imine, monohydrochloride **(20)**, displayed potent inhibition of hiNOS (IC_{50} = 0.25 μM) and selectivities of 897 (heNOS IC_{50}/hiNOS IC_{50}) and 13 (hnNOS IC_{50}/hiNOS IC_{50}). Example **20** was shown to be an efficacious inhibitor of NO production in the mouse endotoxin assay. Furthermore, **20** displayed in vivo selectivity, versus heNOS isoform, by not elevating blood pressure at multiples of the effective dose in the mouse.

Introduction

Nitric oxide (NO) is an endogenously produced inorganic free radical that has been implicated in a number of biological actions. Nitric oxide synthase (NOS) catalyzes the oxidation of arginine to citrulline and nitric oxide. There have been several recent reviews on the subject of NOS and the biological activity of NO.[1−8] There are three isoforms of NOS: type I or nNOS (neuronal), type II or iNOS (inducible), and type III or eNOS (endothelial). Both the endothelial and neuronal isoforms are constitutive. The endothelial isoform is responsible for blood pressure regulation and platelet aggregation. The induced isoform is found predominately in activated macrophages as well as other cell types in which nitric oxide plays a role in host defense mechanisms. Selective inhibitors of the induced isoform of NOS are postulated to be useful in the treatment of numerous disease states that are mediated by the overproduction of NO.[1−8]

It was recently reported that 2-iminoazaheterocycles are potent inhibitors of human NOS.[9] The ring sizes ranged from five- to nine-membered rings, with the most potent compounds being iminopiperidine and iminohomopiperidine, 1.0 and 2.0 μM for hiNOS inhibition, respectively. The he/hi selectivity[10] was reported to be 8 and the hn/hi selectivity[10] was reported to be 1.8 for the iminohomopiperidine ring. The parent iminopyrrolidine ring was a modest (26 μM) inhibitor of hiNOS with the he/hi selectivity being 3.6 and the hn/hi selectivity being 0.8. It seemed apparent that the potency and selectivity, as the ring size progressed from five to seven, depended on increasing steric bulk. If the iminopyrrolidine ring was used as a scaffold, functionality could be directed into the desired spatial and steric regions, realizing potent and selective iminopyrrolidine inhibitors of the isoforms of human NOS.

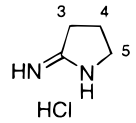

Figure 1. Numbering system for 2-iminopyrrolidines.

Chemistry

Several synthetic methods were used to synthesize the iminopyrrolidine rings. Most analogues were synthesized from the corresponding lactams (Scheme 3). There are numerous synthetic routes to form pyrrolidin-2-ones. The methods used in this paper can be divided into two categories: the radical ring cyclization of Itoh that produced predominately the trans isomers[11] and reduction/cyclization of a γ-nitro ester. The γ-nitro esters could be readily prepared from the Michael addition of a nitro alkyl derivative and an acrylate. The routes are represented in Schemes 1 and 2.

The disubstituted lactams prepared according to Scheme 1 were predominately the trans diastereomers, while the lactams prepared according to the method described in Scheme 2 were nearly equimolar mixtures of cis and trans diastereomers. In most cases, the cis and trans diastereomers were separated by column chromatography. The lactams were converted to the

[‖] Abbreviations: NO, nitric oxide; NOS, nitric oxide synthase; hiNOS, human inducible NOS; heNOS, human endothelial NOS; hnNOS, human neuronal NOS; LPS, lipopolysaccharide; L-NMA, N^G-monomethyl-L-arginine; L-NNA, N^G-nitro-L-arginine.

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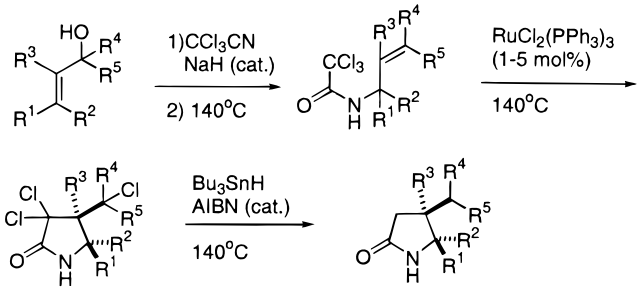
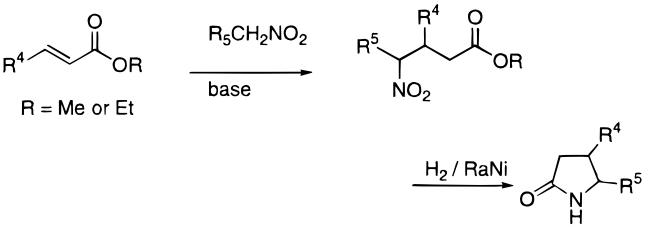
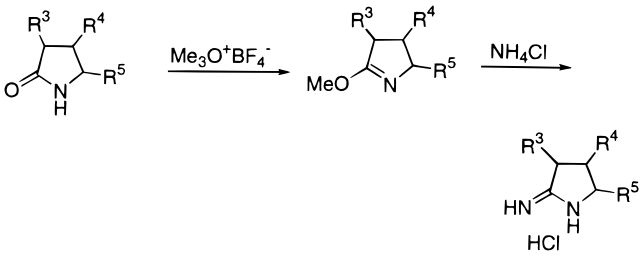
Scheme 1



Scheme 2



Scheme 3



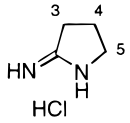
amidine via the iminoether, as illustrated in Scheme 3. The lactam was reacted with trimethyloxonium tetrafluoroborate ($Me_3O^+BF_4^-$) in dichloromethane to form the iminoether, which was reacted with ammonium chloride in refluxing methanol to prepare the desired iminopyrrolidines. The single enantiomers were isolated by chiral HPLC chromatography of an intermediate, by chromatographic separation of a diastereomeric ureide,[12] or by resolution as a diastereomeric salt.

The relative stereochemistry of the pyrrolidin-2-ones was determined by NMR spectroscopy. When possible, comparisons were made to examples or intermediates from the literature.[11] The stereochemistry of the ring substituents was determined by a comparison of the ^{13}C NMR chemical shifts of methyl and methylene groups attached to the ring in the lactam precursors of **9**−**11** and **16**. In the more crowded cis isomers, the ^{13}C NMR shifts are 5−6 ppm upfield relative to the corresponding shifts of the trans isomers. The assignment of the ^{13}C NMR shifts of the methylenes was determined from $^{13}C-^{1}H$ heterocorrelation spectra. The stereochemical assignments of related compounds were based on a comparison of the coupling patterns and chemical shifts of the ring methine protons.

Results and Discussion

Structure−Activity Relationships. Substitution of a simple methyl group at the 3-, 4-, or 5-position of the iminopyrrolidine ring resulted in increased potency compared to the parent compound **1**; the results are summarized in Table 1. The 4-methyl analogue **3** was the most potent inhibitor of hiNOS (IC_{50} = 1.4 μM),

Table 1. Comparison of IC_{50} Values for Inhibition of Human NOS Isoforms of Monosubstituted Iminopyrrolidines



		IC_{50} (μM)			SEL	
compd	R	hiNOS	heNOS	hnNOS	heNOS[a]	hnNOS[b]
1	none	26	93	20	3.65	0.78
2	3-Me	11.3	9.1	3.0	0.81	0.26
3	4-Me	1.4	14.2	4.7	11	4
4	5-Me	10.2	24.9	9.8	2.44	0.96
5	4-Et	3.4	29.8	5.46	8.91	1.6
L-NMA[9]		14	5.9	10	0.4	0.7
L-NNA[9]		7.6	0.5	0.5	0.066	0.066

[a] heNOS selectivity = IC_{50} heNOS/IC_{50} hiNOS. [b] hnNOS selectivity = IC_{50} hnNOS/IC_{50} hiNOS.

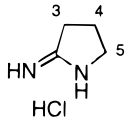
while the 3- or 5-methyl compounds **2** and **4** (IC_{50}'s = 7.0 and 8.8 μM, respectively) were more potent than the parent compound **1** (IC_{50} = 26 μM). The 4-ethyl compound **5** was also more potent at inhibiting hiNOS (3.35 μM) than **1** but less potent than the 4-methyl analogue **3**. In addition, IC_{50} values for two commonly used inhibitors, N^G-monomethyl-L-arginine (L-NMA) and N^G-nitro-L-arginine (L-NNA), are included in Table 1 to facilitate comparison of the data in this paper with our earlier published work and with other work in the literature.

Disubstitution at the 4- and 5-positions resulted in very potent inhibitors of hiNOS; the results are summarized in Table 2. The 4-methyl-5-ethyl analogue **6** was the most potent inhibitor of hiNOS, with IC_{50} = 0.17 μM. Increasing the steric bulk in the 5-position resulted in compounds that retained potency and increased selectivity as the size of the substituent in the 5-position increased. The heNOS/hiNOS selectivity progressed from 10 to 153 in the series of *trans*-iminopyrrolidines as the substituent increased from ethyl (**6**) to *n*-pentyl (**9**) and benzyl (**11**). A similar increase in selectivity for 7-substituted iminohomopiperidines and 6-substituted iminopiperidines has been reported.[13,14]

There is a dramatic increase in potency and selectivity in going from the *trans*-4-methyl-5-pentyliminopyrrolidine **9** to the *cis*-4-methyl-5-pentyliminopyrrolidine **10**, with hiNOS IC_{50}'s of 0.9 versus 0.36 μM, respectively. The potency for the cis analogues **10** and **14** is 12−15-fold greater than the potency of the corresponding trans analogues **9** and **13**. There is a corresponding 14-fold increase in selectivity for the cis analogues **10** and **14** versus the corresponding trans analogues **9** and **13**. The heNOS/hiNOS selectivity of the trans analogue **9** is 53, while that of the cis analogue **10** is 750. This trend is reversed in the 5-benzyliminopyrrolidines; the trans analogue **11** is both more potent and selective than the cis analogue **16**.

The 4-position could also be substituted with a trifluoromethyl group. The potent and most selective analogues are **14** and **10**, with IC_{50}'s of 0.81 and 0.36 μM for hiNOS inhibition and selectivities of 484 he/hi and 6.7 hn/hi and 671 he/hi and14.8 hn/hi. The results of the 5-benzyl-substituted iminopyrrolidines are summarized in Table 3. The 5-benzyliminopyrrolidine **15,** which lacks a substituent in the 4-position, does not

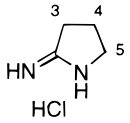
Table 2. Comparison of IC_{50} Values for Inhibition of Human NOS Isoforms of Substitued Iminopyrrolidines



			IC_{50} (μM)			SEL	
compd	R^4	R^5	hiNOS	heNOS	hnNOS	heNOS[a]	hNNOS[b]
6	Me	ethyl (*trans*)	0.17	1.6	0.17	10	1
7	Me	propyl (*trans*)	0.30	3.5	0.39	12	1
8	Me	butyl (*trans*)	0.66	23.6	0.85	36	2
9	Me	pentyl (*trans*)	0.91	47.5	1.31	53	1
10	Me	pentyl (*cis*)	0.36	243	5.37	671	15
11	Me	benzyl (*trans*)	3.0	458	8.29	153	3
12	$(Me)_2$	pentyl	64% @ 100 μM[c]	17% @ 100 μM[c]	46% @ 100 μM[c]	ND	ND
13	CF_3	pentyl (*trans*)	10	336	9.05	32.3	1
14	CF_3	pentyl (*cis*)	0.81	392	5.44	484	7

[a] heNOS selectivity = IC_{50} heNOS/IC_{50} hiNOS. [b] hnNOS selectivity = IC_{50} hnNOS/IC_{50} hiNOS. [c] Percent inhibition of nitrite formation at indicated concentration. ND, not done.

Table 3. Comparison of IC_{50} Values for Inhibition of Human NOS Isoforms of Benzyl-Substituted Iminopyrrolidines



			IC_{50} (μM)			SEL	
compd	R^4	R^5	hiNOS	heNOS	hnNOS	heNOS[a]	hnNOS[b]
15	H	benzyl	26% @ 100 μM[c]	16% @ 100 μM[c]	47% @ 100 μM[c]	ND	ND
11	Me	benzyl (*trans*)	3	458	8.29	153	3
16	Me	benzyl (*cis*)	14	639	11.2	46	0.8
17	CF_3	benzyl (*trans*)	22	1010	12.1	45	0.5
18	CF_3	benzyl (*cis*)	74	2920	38.3	39	0.5
19	$(Me)_2$	benzyl	12% @ 100 μM[c]	3% @ 100 μM[c]	17% @ 100 μM[c]	ND	ND

[a] heNOS selectivity = IC_{50} heNOS/IC_{50} hiNOS. [b] hnNOS selectivity = IC_{50} hnNOS/IC_{50} hiNOS. [c] Percent inhibition of nitrite formation at indicated concentration. ND, not done.

retain the potency that is observed in the 4,5-disubstitued analogues **11** and **16**. In addition, the analogues that have a 4,4-dimethyl substition, **19** and **12**, are far less potent than the corresponding 4-methyl analogues **3**, **10**, **11**, and **16**. These results stress the importance of 4,5-disubstituted iminopyrrrolidines as NOS inhibitors.

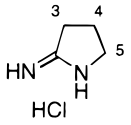
Furthermore, the enantiomers of **14** were separated via chiral HPLC to yield the (−)-isomer **23** and the (+)-isomer **22**. The results obtained for the enantiomers are summarized in Table 4. The (+)-isomer **22** was both more potent and more selective; hiNOS $IC_{50} = 0.23\ \mu M$ and selectivity of 916 he/hi and 10.9 hnc/hi. The enantiomers of **10** were also separated into their single enantiomers to give the (−)-isomer **21** and the (+)-isomer **20**. Again the most active analogue was the (+)-isomer **20** with hiNOS $IC_{50} = 0.25\ \mu M$ and selectivities of 897 he/hi and 12.7 hnc/hi. In addition, the single enantiomer of **20** could be prepared on a large scale via resolution as its L-tartrate salt as illustrated in Scheme 4. The racemic iminoether was reacted with diammonium L-tartrate in methanol. Selective crystallization from ethanol yielded **20B**, while recrystallization from water yielded the other diasteromeric salt **21B**.

In Vivo Results. Compound **20** is a selective, potent inhibitor of iNOS in vivo. It inhibits LPS-induced plasma nitrite/nitrate 75% at 10 mg/kg and has an ED_{50} of approximately 3 mg/kg following oral administration in the mouse low-endotoxin assay. Following iv administration of up to 10 mg/kg, it had no effect on mean arterial pressure in the conscious, restrained mouse (Figure 2).

Conclusions

The synthesis of substituted iminopyrrolidines has led to potent inhibitors of the human inducible isoform of NOS. The most potent analogue is **6** with an IC_{50} of 0.17 μM. Analogues in this series also possess potency

Table 4. Comparison of IC_{50} Values for Inhibition of Human NOS Isoforms of Enantiomers of Selected Substituted Iminopyrrolidines



			IC_{50} (μM)			SEL	
compd	R^4	R^5	hiNOS	heNOS	hnNOS	heNOS[a]	hnNOS[b]
(+)-isomer **20**	Me	pentyl (*cis*)	0.25	226	3.2	897	13
(−)-isomer **21**	Me	pentyl (*cis*)	4.5	578	20.6	130	5
(+)-isomer **22**	CF_3	pentyl (*cis*)	0.23	212	2.53	916	11
(−)-isomer **23**	CF_3	pentyl (*cis*)	7.5	1680	45.7	226	6

[a] heNOS selectivity = IC_{50} heNOS/IC_{50} hiNOS. [b] hnNOS selectivity = IC_{50} hnNOS/IC_{50} hiNOS.

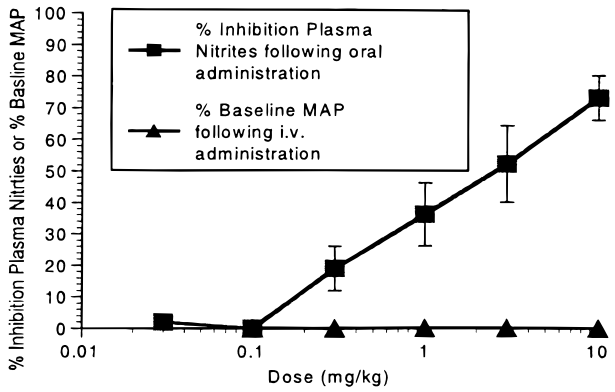
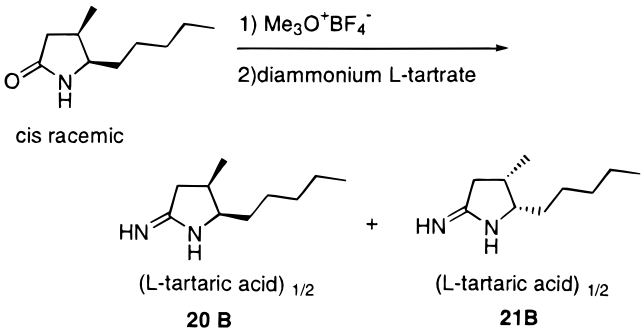


Figure 2. In vivo selectivity of **20** in the mouse.

Scheme 4



and selectivity for hiNOS. The 4-methyl-5-pentyl analogue **10** has a selectivity of 671 versus heNOS and 15 versus hnNOS, while retaining potency for hiNOS with an IC_{50} = 0.36 μM. The relative stereochemistry is important, with the cis diastereomers generally being more selective and potent than the trans diastereomers. The absolute stereochemistry is critical with the (+)-isomer (**20**) being more active and selective than the (−)-isomer (**21**). The analogues **20** and **22** are highly potent and selective inhibitors of hiNOS, with IC_{50}'s of 0.25 and 0.23 μM, selectivities versus heNOS greater than 800, and selectivities versus hnNOS greater than 10. Furthermore, **20** is potent in vivo in mouse models of nitric oxide synthase inhibition and exhibits marked selectivity as demonstrated by the lack of an elevation in blood pressure. The use of **20** and other analogues will be pivotal in determining the effectiveness of potent and selective inhibitors of hiNOS in human diseases in which hiNOS is theorized to play a role.

Experimental Section

Chemicals and reagents were purchased from Aldrich Chemical Co. (Milwaukee, WI) or Sigma (St. Louis, MO) unless otherwise noted. L-[2,3-^{3}H]arginine was purchased from DuPont NEN (Boston, MA); (6*R*)-tetrahydro-L-biopterin was from Research Biochemicals, Inc. (Natick, MA); frozen rat cerebella were from Pel-Freez (Rogers, AR). Purification of synthesized compounds was performed using a Delta Pak C-18 column or crystallization. ^{1}H NMR spectra were obtained at 300 or 400 MHz on a QE300 or Varian VXR-400 spectrometer in D_2O, DMSO-d_6, or $CDCl_3$ (δ units). ^{13}C NMR spectra were obtained at 125 MHz on a Varian VXR-500 spectrometer in D_2O, DMSO-d_6, or $CDCl_3$. Mass spectra were obtained on either a VG model 250 or a Finnigan MAT 90 spectrometer. Elemental analyses were performed on a Carlo Erba model 1106 elemental analyzer. Male Lewis rats (150−200 g) were purchased from Harlan Sprague−Dawley (Indianapolis, IN) and were housed and cared for in accordance with the guidelines of the Institutional Animal Care and Use Committee and in accordance with NIH guidelines on laboratory animal welfare. *Escherichia coli* lipopolysaccharide (serotype 0111:B4, Westphal extract) (LPS, endotoxin) was purchased from Sigma Chemical Co. (St. Louis, MO). Ultrafree-MC filter units were from Millipore (Bedford, MA).

Assay of NOS Activity. NOS activity was measured by monitoring the conversion of L-[2,3-^{3}H]arginine to L-[2,3-^{3}H]-citrulline.[14,16] Human inducible NOS (hiNOS), human endothelial constitutive NOS (heNOS), and human neuronal constitutive NOS (hnNOS) were each cloned from RNA extracted from human tissue. The cDNA for hiNOS was isolated from a λcDNA library made from RNA extracted from a colon sample from a patient with ulcerative colitis; heNOS was isolated from a λcDNA library made from RNA extracted from human umbilical vein endothelial cells (HUVEC); and hnNOS was isolated from a λcDNA library made from RNA extracted from human cerebellum obtained from a cadaver. The recombinant enzymes were expressed in Sf9 insect cells using a baculovirus vector. Enzyme activity was isolated from soluble cell extracts and partially purified by DEAE-Sepharose chromatography.[14] The K_m values for L-arginine for hiNOS, heNOS, and hnNOS were 7, 4, and 6 μM, respectively.[9] To measure NOS activity, 10 μL of enzyme was added to 40 μL of 50 mM Tris (pH 7.6) and the reaction initiated by the addition of 50 μL of a reaction mixture containing 50 mM Tris (pH 7.6), 2.0 mg/mL bovine serum albumin, 2.0 mM DTT, 4.0 mM $CaCl_2$, 20 μM FAD, 100 μM tetrahydrobiopterin, 0.4 mM NADPH, and 60 μM L-arginine containing 0.9 mCi of L-[2,3-^{3}H]arginine. For constitutive NOS, calmodulin was included at a final concentration of 40 nM. Following incubation at 37 °C for 15 min, the reaction was terminated by addition of 300 μL of cold buffer containing 10 mM EGTA, 100 mM HEPES (pH 5.5), and 1.0 mM L-citrulline. The [^{3}H]citrulline was separated by chromatography on Dowex 50W X-8 cation-exchange resin and radioactivity quantified with a liquid

scintillation counter. All assays were performed at least in duplicate; standard deviations were 10% or less. Production of [^{3}H]citrulline was linear with time over the course of the assay.

In Vivo Selectivity. Male BALB/c mice (BALB/cAnHsd, Harlan Sprague−Dawley, Inc., Indianapolis, IN), weighing 28−32 g, were anesthetized with metofane (Mallinckrodt Veterinary Inc., Mundelein, IL), and the femoral artery and vein were cannulated using PE-10 intramedic polyethylene tubing (Becton Dickinson and Co., Sparks, MD). The mice were allowed to recover from the anesthesia and restrained. The arterial cannula was connected to a Cobe disposable pressure transducer (Cobe Laboratories, Inc., Lakewood, CO), and hemodynamic parameters (i.e., mean arterial, systolic, and diastolic pressures, as well as heart rate) were measured using a Gould transducer signal conditioner (model 13-6615-50) and a Gould TA recording system (Gould Instrument Systems Inc., Valley View, OH). Baseline data were collected for 30 min prior to administration of iNOS inhibitors dissolved in PBS, administered as iv bolus injections. For 5 h following the oral dose hemodynamic parameters were recorded. The iv bolus injections were given at regular intervals through the venous cannula such that doses were cumulative. Parameters were recorded during the injections and for a period of time following the last dose (∼20 min). The dose of compound resulting in a >10% change from baseline mean arterial pressure was considered to be a nonselective effect of the compound on eNOS in the conscious BALB/c mouse.

Low-Endotoxin Assay. Male BALB/c mice were treated with an intraperitoneal injection of 12.5 mg/kg endotoxin (LPS) to induce systemic expression of inducible nitric oxide synthase, resulting in markedly elevated plasma nitrite/nitrate levels. Compounds were administered orally by gavage 30 min prior to LPS administration, and plasma nitrite/nitrate levels were determined 5 h following LPS administration using a fluorescence assay.[16] Data are expressed as the percent inhibition of the induced nitrite/nitrate production.

General Procedure A: Synthesis of Iminoethers from Lactams. To a stirred solution of the lactam (1 equiv) in CH_2Cl_2 was added trimethyloxonium tetrafluoroborate ($Me_3O^+BF_4^-$) (1.2 equiv, Lancaster) under argon. The mixture was stirred for 12 h, diluted with CH_2Cl_2, extracted with $KHCO_3$ or $NaHCO_3$ and brine, dried (Na_2SO_4), filtered, and stripped of all solvent to provide the crude iminoether.

General Procedure B: Synthesis of Iminopyrrolidines from Iminoethers. To a stirred solution of the iminoether in MeOH was added ammonium chloride (NH_4Cl), and the resulting mixture was refluxed for 4−12 h. After cooling to room temperature the solution was filtered and stripped of all solvent to provide the crude iminopyrrolidine hydrochloride. The material was dissolved in water and extracted with EtOAc, and the aqueous phase was chromatographed via RPHPLC eluting with ACN/H_2O (gradient). The iminopyrrolidine product was lyophilized.

2-Iminopyrrolidine Hydrochloride (1). The title compound was prepared according to literature method.[18] Anal. ($C_4H_8N_2$·HCl·0.25H_2O) C, H, N.

3-Methylpyrrolidin-2-imine Hydrochloride (2). The title compound was prepared according to literature method.[18] ^{1}H NMR (D_2O, 300 MHz): 1.15 (d, J = 7 Hz, 3H), 1.71 (m, 1H), 2.25 (m, 1H), 3.00 (m, 1H), 3.42 (m, 1H), 3.51 (m, 1H).

4-Methylpyrrolidin-2-imine Hydrochloride (3). 4-Methylpyrrolidin-2-one was prepared from 3,3-dichloro-4-(chloromethyl)pyrrolidin-2-one.[11] A mixture of 3,3-dichloro-4-(chloromethyl)pyrrolidin-2-one (3 g, 15 mmol), tributyltin hydride (14.3 mL), and AIBN (25 mg) was heated at 140 °C for 8 h. The product was chromatographed to yield 900 mg (61%) of 4-methylpyrrolidin-2-one as a solid.

The 4-methylpyrrolidin-2-one (500 mg, 5 mmol) was reacted with trimethyloxonium tetrafluoroborate (890 mg, 6 mmol) according to general procedure A to yield, after chromatography, 610 mg of the iminoether. The iminoether (610 mg, 5 mmol) was reacted with ammonium chloride (200 mg, 4 mmol) according to general procedure B to yield the title material **3**, 500 mg (70%, from the lactam). HRMS: m/z M^+ 98.0844; $C_5H_{10}N_2$ requires 98.0844. ^{1}H NMR (D_2O, 400 MHz): 1.13 (d, J = 7 Hz, 3H), 2.53 (dd, 1H), 2.71 (m, 1H), 3.03 (dd, 1H), 3.28 (dd, 1H), 3.80 (dd, 1H). Anal. ($C_5H_{10}N_2$·HCl· 0.25H_2O·0.75NH_4Cl) C, H, N, Cl.

5-Methylpyrrolidin-2-imine Hydrochloride (4). The title compound was prepared according to literature method.[18] HRMS: m/z M^+ 98.0844; $C_5H_{10}N_2$ requires 98.0844. ^{1}H NMR (D_2O, 300 MHz): 1.13 (d, J = 7 Hz, 3H), 1.63 (m, 1H), 2.22 (m, 1H), 2.69 (m, 1H), 2.77 (m, 1H), 3.97 (hextet, 1H).

4-Ethyl-4-pyrrolidin-2-imine Hydrochloride (5). 4-Ethyl-4-pyrrolidin-2-one was prepared from 2-buten-1-ol and trichloroacetonitrile[10] in a manner similar to the method described for the lactam of **3**. A solution of 3-buten-2-ol (8.7 mL, 100 mmol) in THF (50 mL) was added to potassium hydride (KH; 600 mg, 15 mmol) over 15 min. The resulting alkoxide solution was added to a stirred solution of trichloroacetonitrile (10 mL, 100 mmol) in ether (100 mL) at −10 °C. The solution was stirred at 0 °C for 3 h, followed by removal of solvent under reduced pressure (temperature < 25 °C); pentane (400 mL) and methanol (1 mL) were added, and the mixture was filtered. Concentration afforded a yellow oil (17.4 g). The oil was dissolved in xylene (450 mL) and refluxed for 2.5 h. The solvent was removed to yield 16.8 g of *N*-(2-butenyl)-2,2,2-trichloroacetamide as a white solid. The *N*-(2-butenyl)-2,2,2-trichloroacetamide was converted to 4-ethylpyrrolidin-2-one by the method described for the lactam of **3**. ^{1}H NMR ($CDCl_3$, 300 MHz): 0.93 (t, J = 7 Hz, 3H), 1.50 (p, J = 7 Hz, 2H), 2.02 (m, 1H), 2.31−2.50 (m, 2H), 3.03 (dd, J = 9, 7 Hz, 1H), 3.50 (dd, J = 9, 8 Hz, 1H), 5.84 (br s, 1H).

4-Ethylpyrrolidin-2-one (750 mg, 6.6 mmol) was reacted with trimethyloxonium tetrafluoroborate (1.18 g, 8 mmol) according to general procedure A to yield, after chromatography, the iminoether. The iminoether was reacted with ammonium chloride (394 mg, 16 mmol) according to general procedure B to yield the title material **5**, 535 mg (64%, from the lactam). ^{1}H NMR ($CDCl_3$, 300 MHz): 0.95 (t, J = 7.5 Hz, 3H), 1.53 (pentet, J = 7.5 Hz, 2H), 2.49 (heptet, J = 7.5 Hz, 1H), 2.60 (dd, J = 18, 7.5 Hz, 1H), 3.12 (dd, J = 18, 8 Hz, 1H), 3.28 (dd, J = 11, 7 Hz, 1H), 3.75 (dd, J = 11, 8 Hz, 1H), 8.78 (br s, 1H), 9.36 (br s, 2H). Anal. ($C_6H_{12}N_2$·HCl·0.8H_2O) C, H, N, Cl.

***trans*-5-Ethyl-4-methylpyrrolidin-2-imine Hydrochloride (6).** 5-Ethyl-4-methylpyrrolidin-2-one was prepared from *cis*-2-penten-1-ol and trichloroacetonitrile[10] in a manner similar to the method described for lactam **3**. The 5-ethyl-4-methylpyrrolidin-2-one was flash chromatographed (EA) and then recrystallized (*n*-hexane). ^{1}H NMR ($CDCl_3$, 300 MHz): 0.97 (t, J = 7 Hz, 3H), 1.13 (d, J = 7 Hz, 3H), 1.45 (m, 1H), 1.62 (m, 1H), 1.99 (dd, J = 17, 8 Hz, 1H), 2.11 (m, 1H), 2.53 (dd, J = 17, 8 Hz, 1H), 3.12 (dt, J = 8, 6 Hz, 1H), 6.23 (br s, 1H).

5-Ethyl-4-methylpyrrolidin-2-one (625 mg, 5 mmol) was reacted with trimethyloxonium tetrafluoroborate (800 mg, 5.5 mmol) according to general procedure A to yield, after chromatography, 704 mg of the iminoether. The iminoether (704 mg, 5 mmol) was reacted with ammonium chloride (279 mg, 5.6 mmol) according to general procedure B to yield the title material **6**, 560 mg (59%, from the lactam). ^{1}H NMR ($CDCl_3$, 300 MHz): 1.02 (t, J = 7 Hz, 3H), 1.18 (d, J = 7 Hz, 3H), 1.57 (m, 1H), 1.70 (m, 1H), 2.22 (heptet, J = 7 Hz, 1H), 2.57 (dd, J = 18, 7.5 Hz, 1H), 3.21 (dd, J = 18, 8 Hz, 1H), 3.42 (q, J = 7 Hz, 1H), 8.51 (br s, 1H), 9.53 (br s, 1H), 9.76 (br s, 1H). Anal. ($C_7H_{14}N_2$·HCl·H_2O) C, H, N, Cl.

***trans*-5-Propyl-4-methylpyrrolidin-2-imine Hydrochloride (7).** 5-Propyl-4-methylpyrrolidin-2-one was prepared from *trans*-2-hexen-1-ol and trichloroacetonitrile[11] in a manner similar to the method described for the lactam in **3**. ^{1}H NMR ($CDCl_3$, 300 MHz): 0.96 (t, J = 7 Hz, 3H), 1.12 (d, J = 7 Hz, 3H), 1.23−1.65 (m, 4H), 1.98 (dd, J = 16, 7.5 Hz, 1H), 2.08 (m, 1H), 2.52 (dd, J = 16, 8 Hz, 1H), 3.18 (m, 1H), 6.91 (br s, 1H).

5-Propyl-4-methylpyrrolidin-2-one (700 mg, 5 mmol) was reacted with trimethyloxonium tetrafluoroborate (800 mg, 5.5

mmol) according to general procedure A to yield, after chromatography, 760 mg of the iminoether. The iminoether (760 mg, 5 mmol) was reacted with ammonium chloride (290 mg, 5.4 mmol) according to general procedure B to yield the title material **7**, 500 mg (57%, from the lactam). ^{1}H NMR (DMSO-d_6, 400 MHz): 0.92 (t, J = 7 Hz, 3H), 1.07 (d, J = 7 Hz, 3H), 1.20−1.63 (m, 4H), 2.17 (septet, J = 7 Hz, 1H), 2.43 (dd, J = 17, 7 Hz, 1H), 2.97 (dd, J = 17, 9 Hz, 1H), 3.44 (q, J = 6 Hz, 1H). Anal. ($C_8H_{10}N_2$·0.33H_2O·1.1HCl) C, H, N, Cl.

***trans*-5-Butyl-4-methylpyrrolidin-2-imine Hydrochloride (8).** 5-Butyl-4-methylpyrrolidin-2-one was prepared from *trans*-2-hepten-1-ol and trichloroacetonitrile[11] in a manner similar to the method described for the lactam in **3**. ^{1}H NMR ($CDCl_3$, 300 MHz): 0.92 (t, J = 7 Hz, 3H), 1.13 (d, J = 7 Hz, 3H), 1.25−1.7 (m, 6H), 1.97 (dd, J = 16, 7.5 Hz, 1H), 2.08 (m, 1H), 2.52 (dd, J = 16, 8 Hz, 1H), 3.16 (m, 1H), 7.05 (br s, 1H).

5-Butyl-4-methylpyrrolidin-2-one (1.0 g, 6.43 mmol) was reacted with trimethyloxonium tetrafluoroborate (1.15 g, 7.78 mmol) according to general procedure A to yield, after chromatography, 660 mg of the iminoether. The iminoether (660 mg, 3.9 mmol) was reacted with ammonium chloride (231 mg, 4.3 mmol) according to general procedure B to yield the title material **8**, 432 mg (35%, from the lactam). ^{1}H NMR (DMSO-d_6, 400 MHz): 0.89 (t, J = 6.7 Hz, 3H), 1.06 (d, J = 6.8 Hz, 3H), 1.22−1.60 (m, 6H), 2.13 (heptet, J = 7 Hz, 1H), 2.41 (dd, J = 17.5, 7.5 Hz, 1H), 2.98 (dd, J = 17.5, 8 Hz, 1H), 3.76 (q, J = 7 Hz, 1H), 9.3 (br s, 3H). ^{13}C NMR (DMSO-d_6, 125 MHz): 169.6 (C-2), 66.3 (C-5), 37.2 (C-3), 35.0 (C-4), 33.2 (C-7), 27.4 (C-8), 21.9 (C-9), 17.9 (C-6), 13.7 (C-10). Anal. ($C_9H_{18}N_2$·HCl) C, H, N.

***trans*-5-Pentyl-4-methylpyrrolidin-2-imine Hydrochloride (9).** *cis*- and *trans*-5-pentyl-4-methylpyrrolidin-2-one were prepared from nitrohexane and methyl crotonate. A suspension of methyl crotonate (7.6 g, 76 mmol), 1-nitrohexane (10.0 g, 76 mmol), K_2CO_3 (10.5 g), and Aliquat 336 (10 drops) was sonicated for 6 h. To the reaction was added Et_2O (200 mL). The reaction mixture was filtered, acidified with 0.5 N HCl, extracted with brine, dried over Na_2SO_4 (anhydrous), filtered, and concentrated under reduced pressure to give 13 g of yellow liquid. The product was purified by column chromatography to give 6.0 g (34%) of methyl 3-methyl-4-nitrononanoate.

A solution of methyl 3-methyl-4-nitrononanoate (5.0 g) in MeOH was reduced under catalytic hydrogenation conditions (60 psi, 55 °C) using Raney nickel. The reaction was heated for 16 h to effect cyclization after reduction of the nitro group. After concentration of the reaction mixture under reduced pressure, the residue was purified by column chromatography to give 3.3 g of a light-yellow liquid. A second column was run to separate the *cis*- and *trans*-5-pentyl-4-methylpyrrolidin-2-one.

***trans*-5-Pentyl-4-methylpyrrolidin-2-one:** GC t_R = 14.7 min.[20] ^{1}H NMR ($CDCl_3$, 400 MHz): 0.89 (t, J = 6 Hz, 3H), 1.11 (d, J = 7 Hz, 3H), 1.22−1.60 (m, 6H), 1.95 (dd, J = 16, 7.5 Hz,1H), 2.07 (heptet, J = 7 Hz,1H), 2.50 (dd, J = 16, 8 Hz,1H), 3.14 (q, J = 6 Hz,1H), 6.43 (br s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): 13.9, 19.3, 22.5, 25.9, 31.7, 35.5, 35.6, 38.7, 62.0, 177.5.

***cis*-5-Pentyl-4-methylpyrrolidin-2-one:** GC t_R = 15.15 min.[20] ^{1}H NMR ($CDCl_3$, 400 MHz): 0.89 (t, J = 6 Hz, 3H), 1.00 (d, J = 7 Hz, 3H), 1.20−1.50 (m, 6H), 1.98 (dd, 1H), 2.54 (heptet, 1H), 2.43 (dd, 1H), 3.55 (m, 1H), 6.37 (br s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): 13.8, 14.4, 22.3, 26.0, 30.2, 31.6, 32.5, 38.5, 57.5, 177.6.

trans-5-Pentyl-4-methylpyrrolidin-2-one (1.0 g, 5.9 mmol) was reacted with trimethyloxonium tetrafluoroborate (1.05 g, 7.14 mmol) according to general procedure A to yield, after chromatography, 790 mg of the iminoether. The iminoether (740 mg, 4 mmol) was reacted with ammonium chloride (238 mg, 4.45 mmol) according to general procedure B to yield the title material **9**, 650 mg (66%, from the lactam). ^{1}H NMR (DMSO-d_6, 400 MHz): 0.88 (t, J = 6.8 Hz, 3H), 1.06 (d, J = 6.8 Hz, 3H), 1.2−1.6 (m, 8H), 2.13 (heptet, J = 7 Hz, 1H), 2.41 (dd, J = 17.5, 7.5 Hz), 2.97 (dd, J = 17.5, 8.5), 3.39 (q, J = 8 Hz, 1H), 9.3 (br s, 3H). ^{13}C NMR (DMSO-d_6, 125 MHz): 13.7, 17.8 (CH_3's); 21.8, 24.6, 30.9, 33.2, 37.1 (CH_2's); 34.9, 66.4 (CH's); 169.3 (C═N). Anal. ($C_{10}H_{18}N_2$·HCl) C, H, N, Cl.

***cis*-5-Pentyl-4-methylpyrrolidin-2-imine Hydrochloride (10).** *cis*-5-Pentyl-4-methylpyrrolidin-2-one (700 mg, 4.5 mmol) was reacted with trimethyloxonium tetrafluoroborate (806 mg, 5.5 mmol) according to general procedure A to yield, after chromatography, 610 mg of the iminoether. The iminoether (610 mg, 4.5 mmol) was reacted with ammonium chloride (200 mg, 4 mmol) according to general procedure B to yield the title material **10**, 441 mg (70%, from the lactam). ^{1}H NMR (D_2O, 400 MHz): 0.88 (distorted t, J = 7 Hz, 3H), 1.02 (d, J = 7.1 Hz, 3H), 1.3−1.6 (m, 8H), 2.54 (dd, J = 17.1, 6.8 Hz, 1H), 2.70 (apparent sept., J = 7 Hz, 1H), 2.97 (dd, J = 17.2, 7.9 Hz, 1H), 3.92 (dt, J = 7.9, 6.8 Hz, 1H). ^{13}C NMR (D_2O, 125 MHz): 15.8, 16.2, 24.7, 28.0, 31.5, 33.9, 35.7, 40.2, 66.0, 178.3. Anal. ($C_{10}H_{18}N_2$·HCl) C, H, N, Cl.

***trans*-5-Benzyl-4-methylpyrrolidin-2-imine Hydrochloride (11) and *cis*-5-Benzyl-4-methylpyrrolidin-2-imine Hydrochloride (16).** Methyl crotonate (6.4 g, 64 mmol) was mixed with β-nitroethylbenzene[19] (9.7 g, 64 mmol), potassium carbonate (8.9 g, 64 mmol), and Aliquat 336 (20 drops). The mixture was sonicated at room temperature. When the reaction, monitored by GC, was complete, the mixture was acidified with HCl (1 N) and the aqueous phase extracted with ether. Purification by chromatography on silica gel yielded methyl 3-methyl-4-nitrobenzenepentanoate (14.7 g, 91%). The methyl 3-methyl-4-nitrobenzenepentanoate (5 g, 20 mmol) in absolute MeOH was hydrogenated over RaNi at 55 °C and 60 psi for 24 h. The reaction product was purified by column chromatography to yield *cis*,*trans*-5-benzyl-4-methylpyrrolidin-2-one (2.35 g, 62%) as a mixture of diastereomers.

The material *cis*,*trans*-5-benzyl-4-methylpyrrolidin-2-one (1.35 g, 7 mmol) was reacted with trimethyloxonium tetrafluoroborate according to general procedure A to yield, after chromatography, 610 mg of the iminoether as a mixture of diastereomers. The iminoether (610 mg, 5 mmol) was reacted with ammonium chloride (200 mg, 4 mmol) according to general procedure B to yield the title materials **11** and **16**, followed by chromatography on reverse-phase HPLC to generate the cis and trans title materials, **11** (300 mg) and **16** (220 mg).

11: ^{1}H NMR (D_2O, 400 MHz) 1.05 (d, J = 6.7 Hz, 3H), 2.40 (m, 1H), 2.45 (dd, J = 17.5, 6.4 Hz, 1H), 2.85 (dd, J = 17.5, 8.2 Hz, 1H), 2.90 (dd, J = 14.1, 6.8 Hz, 1H), 3.01 (dd, J = 14.1, 5.7 Hz, 1H), 3.89 (apparent q, J = 6 Hz, 1H), 7.25−7.5 (m, 1H), 7.32 (complex d, J = 8 Hz, 2H), 7.35 (complex t, J = 8 Hz, 1H), 7.42 (complex t, J = 8 Hz, 2H). Anal. ($C_{10}H_{18}N_2$·HCl).

16: DSC 142.08 °C (sharp). ^{1}H NMR (D_2O, 400 MHz): 1.17 (d, J = 7.0 Hz, 3H), 2.54 (dd, J = 17, 8 Hz, 1H), 2.74 (dd, J = 14, 10 Hz, 1H), 2.81 (septet, J = 7 Hz, 1H), 2.99 (dd, J = 14, 3 Hz, 1H), 2.99 (dd, J = 17, 8 Hz, 1H), 4.25 (m, 1H), 7.29−7.45 (m, 5H). Anal. ($C_{10}H_{18}N_2$·HCl) C, H, N, Cl.

5-Pentyl-4,4-dimethylpyrrolidin-2-imine Hydrochloride (12). The ethyl 3,3-dimethylacrylate (4.9 g, 38 mmol) was mixed with nitrohexane (5.0 g, 38 mmol) and 1 M tetrabutylammonium fluoride (38 mL) and heated at 40 °C for 24 h. The reaction mixture was diluted with diethyl ether and washed with brine, followed by water. Purification by chromatography on silica gel yielded methyl 3,3-dimethyl-4-nitrononanoate (6.6 g, 67%).

The methyl 3,3-dimethyl-4-nitrononanoate (5.6 g, 24 mmol) in absolute MeOH was hydrogenated over RaNi at 55 °C and 60 psi for 24 h. The reaction product was purified by column chromatography to yield 5-pentyl-4,4-dimethylpyrrolidin-2-one (2.63 g, 60%).

The 5-pentyl-4,4-dimethylpyrrolidin-2-one (2.6 g, 14.3 mmol) was reacted with trimethyloxonium tetrafluoroborate according to general procedure A to yield, after chromatography, 2.0 g of the iminoether. The iminoether (2.0 g, 10 mmol) was reacted with ammonium chloride (529 mg, 10 mmol) according to general procedure B to yield **12** (1.67 g). ^{1}H NMR (D_2O, 400 MHz): 0.88 (distorted t, J = 7 Hz, 3H), 1.04 (s, 3H), 1.17

(s, 3H), 1.27−1.63 (m, 8H), 2.64 (d, J = 17.3 Hz, 1H), 2.70 (d, J = 17.3 Hz, 1H), 3.57 (dd, J = 9.4, 4.0 Hz, 1H). ^{13}C NMR (D_2O, 125 MHz): 16.2, 23.8, 28.6 (CH_3's); 24.7, 28.6, 31.8, 33.8, 46.9 (CH_2's); 42.5 (C), 71.8 (CH), 172.7 (C=NH). Anal. ($C_{11}H_{20}N_2$·HCl) C, H, N, Cl.

***trans*-5-Pentyl-4-(trifluoromethyl)pyrrolidin-2-imine Hydrochloride (13).** A suspension of ethyl 4,4,4-trifluorocrotonate (10.0 g, 59 mmol), 1-nitrohexane (7.86 g, 60 mmol), K_2CO_3 (4.1 g), and Aliquat 336 (6 drops) was sonicated for 5 h. To the reaction was added Et_2O (200 mL). The reaction mixture was filtered, extracted with brine, dried over Na_2SO_4 (anhydrous), filtered, and concentrated under reduced pressure to give a yellow liquid. The product was purified by column chromatography to give 13.8 g (77%) of methyl 3-(trifluoromethyl)-4-nitrononanoate.

A solution of methyl 3-(trifluoromethyl)-4-nitrononanoate (13.0 g) in MeOH was reduced under catalytic hydrogenation conditions (60 psi, 55 °C) using Raney nickel. The reaction was heated for 8 h to effect cyclization after reduction of the nitro group. After concentration of the reaction mixture under reduced pressure, the residue was purified by column chromatography to give 9.0 g of a light-yellow liquid. A second column was run to separate the *cis*- and *trans*-5-pentyl-4-(trifluoromethyl)pyrrolidin-2-one.

***trans*-5-Pentyl-4-(trifluoromethyl)pyrrolidin-2-one:** R_f = 0.5 (silica gel; EA). ^{1}H NMR ($CDCl_3$, 400 MHz): 0.90 (t, J = 6 Hz, 3H), 1.22−1.41 (m, 6H), 1.53 (m, 1H), 1.65 (m, 1H), 2.49 (dd, J = 17.5, 6.1 Hz, 1H), 2.62 (dd, J = 17.5, 10.0 Hz, 1H), 2.75 (dqdd, J = 10.0, 8.8, 6.1, 4.4 Hz, 1H), 3.75 (dt, J = 7.5, 4.4 Hz, 1H) 6.50 (br s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz, HETCOR): 13.8 (C-11), 22.3 (C-10), 25.0 (C-8), 30.3 (q, J_{CF} = 3 Hz, C-3), 31.3 (C-9), 36.7 (C-7), 43.6 (q, J_{CF} = 29 Hz, C-4), 54.2 (C-5), 126.7 (q, J_{CF} = 277 Hz, C-6), 174.8 (C-2). Anal. ($C_{10}H_{16}NOF_3$·0.1EA) C, H, N.

***cis*-5-Pentyl-4-(trifluoromethyl)pyrrolidin-2-one:** R_f = 0.4 (silica gel; EA). ^{1}H NMR ($CDCl_3$, 400 MHz): 0.90 (t, J = 6, 3H), 1.22−1.45 (m, 6H), 1.54 (m, 1H), 1.66 (m, 1H), 2.50 (dd, J = 17.0, 9.1 Hz, 1H), 2.57 (dd, J = 17.0, 9.1 Hz, 1H), 3.20 (qtd, J = 9.4, 9.1, 7.6 Hz, 1H), 3.79 (ddd, J = 10.7, 7.6, 3.4 Hz, 1H) 6.48 (br s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz, HETCOR): 13.9 (C-11), 22.4 (C-10), 26.2 (C-8), 30.2 (q, J_{CF} = 2 Hz, C-3), 30.7 (q, J_{CF} = 2 Hz, C-7), 31.5 (C-9), 42.1 (q, J_{CF} = 29 Hz, C-4), 54.5 (C-5), 126.0 (q, J_{CF} = 278 Hz, C-6), 174.7 (C-2). Anal. ($C_{10}H_{16}NOF_3$) C, H, N.

trans-5-Pentyl-4-methylpyrrolidin-2-one (1.05 g, 4.7 mmol) was reacted with trimethyloxonium tetrafluoroborate (770 mg, 5.2 mmol) according to general procedure A to yield, after chromatography, 1.12 g of the iminoether. The iminoether (1.12 g, 4.64 mmol) was reacted with ammonium chloride (250 mg, 4.64 mmol) according to general procedure B to yield the title material **13**, 410 mg (34%, from the lactam). ^{1}H NMR (D_2O, 300 MHz): 0.9 (t, J = 6 Hz, 3H), 1.15−1.7 (m, 6H), 1.95 (dd, J = 16, 7.5 Hz, 1H), 2.40−2.83 (m, 3H), 3.72 (m, 1H). Anal. ($C_{10}H_{16}NOF_3$·HCl) C, H, N, Cl.

***cis*-5-Pentyl-4-(trifluoromethyl)pyrrolidin-2-imine Hydrochloride (14).** *cis*-5-Pentyl-4-(trifluoromethyl)pyrrolidin-2-one (500 mg, 5 mmol) was reacted with trimethyloxonium tetrafluoroborate (890 mg, 6 mmol) according to general procedure A to yield, after chromatography, 610 mg of the iminoether. The iminoether (610 mg, 5 mmol) was reacted with ammonium chloride (200 mg, 4 mmol) according to general procedure B to yield the title material **14**, 500 mg (70%, from the lactam). ^{1}H NMR (DMSO-d_6, 400 MHz): 0.88 (t, J = 6 Hz, 3H), 1.20−1.65 (m, 6H), 3.01 (dd, J = 17, 7 Hz, 1H), 3.17 (dd, J = 17, 9 Hz, 1H), 3.74 (m, 1H), 4.12 (apparent q, J = 7 Hz, 1H). Anal. ($C_{10}H_{17}N_2F_3$·1HCl·0.15NH_4Cl) C, H, N, Cl.

5-Benzylpyrrolidin-2-imine Hydrochloride (15). The methyl acrylate (2.84 g, 33 mmol) was mixed with β-nitroethylbenzene[19] (5.0 g, 33 mmol), potassium carbonate (4.6 g, 33 mmol), and Aliquat 336 (10 drops), in a manner similar to the method described in **11**. Purification by chromatography on silica gel yielded methyl 4-nitrobenzenepentanoate (4.0 g, 55%). The methyl 4-nitrobenzenepentanoate (4.0 g, 18 mmol) was hydrogenated over Pd/C (4%) at 55 °C and 5 psi for 40 h. The reaction product was purified by column chromatography to yield 5-benzylpyrrolidin-2-one (0.61 g, 29%).

The 5-benzylpyrrolidin-2-one (0.54 g, 3.1 mmol) was reacted with trimethyloxonium tetrafluoroborate (550 mg, 3.7 mmol) according to general procedure A to yield, after chromatography, 460 mg of the iminoether. The iminoether (460 mg, 2.4 mmol) was reacted with ammonium chloride (144 mg, 2.7 mmol) according to general procedure B to yield the title material **15**, 310 mg (48%, from the lactam). ^{1}H NMR (D_2O, 400 MHz): 1.96 (dddd, J = 13.2, 9.6, 6.3, 5.1 Hz, 1H), 2.29 (dddd, J = 13.2, 10.0, 7.9, 6.4 Hz, 1H), 2.63 (ddd, J = 17.9, 9.6, 6.4 Hz, 1H), 2.77 (ddd, J = 17.9, 10.0, 6.3 Hz, 1H), 2.91 (dd, J = 13.9, 6.5 Hz, 1H), 2.95 (dd, J = 13.9, 6.2 Hz, 1H), 4.32 (dq, J = 8, 6 Hz, 1H), 7.31 (complex d, J = 7.5 Hz, 2H), 7.36 (tt, J = 7, 2 Hz, 1H), 7.42 (complex t, J = 7.5 Hz, 2H). ^{13}C NMR (D_2O, 125 MHz): 28.4, 32.5, 43.0 (CH_2's); 64.3 (CH); 129.9, 131.7, 132.5 (=CH's); 139.9 (=C); 174 (C=N). Anal. ($C_{11}H_{14}N_2$·HCl) C, H, N, Cl.

***trans*-5-Benzyl-4-(trifluoromethyl)pyrrolidin-2-imine Hydrochloride (17) and *cis*-5-Benzyl-4-(trifluoromethyl)pyrrolidin-2-imine Hydrochloride (18).** The ethyl 4,4,4-(trifluoromethyl)crotonate (5.5 g, 33 mmol) and β-nitroethylbenzene[19] (5.0 g, 33 mmol) were reacted with potassium carbonate (4.6 g, 33 mmol) and Aliquat 336 (10 drops), in a manner similar to the method described in **11.** Purification by chromatography on silica gel yielded the methyl 3-(trifluoromethyl)-4-nitrobenzenepentanoate (4.4 g, 42%).

The methyl 3-(trifluoromethyl)-4-nitrobenzenepentanoate (4.3 g, 13.5 mmol) in absolute MeOH was hydrogenated over RaNi at 55 °C and 60 psi for 16 h. The reaction product was purified by column chromatography to yield *cis*,*trans*-5-benzyl-4-(trifluoromethyl)pyrrolidin-2-one (2.33 g, 71%) as a mixture of diastereomers.

The *cis*,*trans*-5-benzyl-4-(trifluoromethyl)pyrrolidin-2-one (0.74 g, 3 mmol) was treated with trimethyloxonium tetrafluoroborate (0.54 g, 3.7 mmol) in DCM (20 mL) by general method A, to yield the iminoether (0.58 g, 76%) as a mixture of diastereomers. A solution of the iminoethers (0.58 g, 2.3 mmol) in MeOH (20 mL) was reacted with ammonium chloride (134 mg, 2.3 mmol) by general method B, followed by chromatography on reverse-phase HPLC to generate the cis and trans title materials, *trans*-5-benzyl-4-(trifluoromethyl)pyrrolidin-2-imine (240 mg) and *cis*-5-benzyl-4-(trifluoromethyl)pyrrolidin-2-imine (250 mg).

***trans*-5-Benzyl-4-(trifluoromethyl)pyrrolidin-2-imine (17):** ^{1}H NMR (D_2O, 400 MHz) 2.93 (dd, J = 18.6, 9.6 Hz, 1H), 3.00 (dd, J = 14.0, 6.6 Hz, 1H), 3.02 (dd, J = 18.6, 4.5 Hz, 1H), 3.12 (dd, J = 14.0, 5.3 Hz, 1H), 3.28 (m, 1H), 4.58 (m, 1H), 7.32 (complex d, 2H), 7.38 (complex t, 1H), 7.43 (complex t, 2H). ^{13}C NMR (D_2O, 125 MHz): 32.8, 42.4, 45.0 (q, J_{CF} = 29 Hz), 63.9, 129.1 (q, J_{CF} = 277 Hz), 130.4, 131.9, 132.7, 138.2, 171.3. Anal. ($C_{12}H_{13}N_2F_3$·1HCl·1.1NH_4Cl·0.67H_2O) C, H, N.

***cis*-5-Benzyl-4-(trifluoromethyl)pyrrolidin-2-imine (18):** ^{1}H NMR (D_2O, 400 MHz) 2.91 (br t, J = 13 Hz, 1H), 3.22 (br dd, J = 14, 2 Hz, 1H), 3.28 (dd, J = 18, 9 Hz, 1H), 3.36 (dd, J = 18, 8.5 Hz, 1H), 3.72 (heptet, J = 8 Hz, 1H), 4.60 (m, 1H), 7.34 (complex d, J = 8 Hz, 2H), 7.37 (complex t, J = 7 Hz, 1H), 7.44 (complex t, J = 8.5 Hz, 2H). ^{13}C NMR (D_2O, 125 MHz): 33.0, 38.4, 44.4 (q, J_{CF} = 29 Hz), 63.9, 128.6 (q, J_{CF} = 278 Hz), 131.9, 132.0, 132.2, 139.7, 171. Anal. ($C_{12}H_{13}N_2F_3$·1HCl·0.1AcOH) C, H, N, Cl.

4,4-Dimethyl-5-benzylpyrrolidin-2-imine Hydrochloride (19). Ethyl dimethyl acrylate (10.75 g, 84 mmol) was mixed with β-nitroethylbenzene[19] (12.68 g, 84 mmol) in tetra-*n*-butylammonium fluoride in THF (84 mL, 1 M) and heated at 40 °C. When the reaction, monitored by GC, was complete, the mixture was treated with brine (saturated) and the aqueous phase was extracted with ether. Purification by chromatography on silica gel yielded the product ethyl 3,3-dimethyl-4-nitrobenzenepentanoate (9.04 g, 34%). Anal. ($C_{15}H_{21}NO_4$).

The above product (3.5 g, 12.5 mmol) in absolute MeOH was

hydrogenated over Ra Ni at 55 °C and 60 psi for 6 h. The reaction product was purified by column chromatography to yield 4,4-dimethyl-5-benzylpyrrolidin-2-one (2.41 g, 95%).

The above product (1.04 g, 5.1 mmol) was treated with trimethyloxonium tetrafluoroborate (0.91 g, 6.2 mmol) in DCM (25 mL) by general method A, to yield the iminoether (0.83 g, 75%). A solution of the iminoether (0.8 g, 3.5 mmol) in MeOH (60 mL) was reacted with ammonium chloride (187 mg, 3.5 mmol) by general method B followed by chromatography on reverse-phase HPLC to generate the title material **19** (570 mg, 68%). ^{1}H NMR (DMSO, 400 MHz): 1.06 (s, 3H), 1.07 (s, 3H), 2.66 (s, 2H), 2.70 (dd, J = 14, 10 Hz, 1H), 2.88 (dd, J = 14, 5 Hz, 1H), 3.92 (dd, J = 10, 5 Hz, 1H), 7.27 (t, J = 8 Hz, 1H), 7.29 (d, J = 8 Hz, 2H), 7.35 (t, J = 8 Hz, 2H), 8.30 (br s, 1H), 9.12 (br s, 2H). Anal. ($C_{13}H_{18}N_2$·1HCl) C, H, N, Cl.

(+)-*cis*-4-Methyl-5-pentylpyrrolidin-2-imine, Monohydrochloride (20). A solution of 5-pentyl-4-methylpyrrolidin-2-one (4.29 g, 25.0 mmol) and (*R*)-(−)-1-(1-naphthyl)ethyl isocyanate (5.00 g, 25.3 mmol) in 200 mL of benzene was heated at reflux for 24 h. Additional isocyanate (5.00 g, 25.3 mmol) was added. After an additional 24 h of heating, the reaction mixture was concentrated under reduced pressure. The resulting diastereomeric ureide mixture was separated by column chromatography to yield 2.0 g of ureide A (R_f = 0.5) and 2.1 g of ureide B (R_f = 0.33) [TLC solvent system (9:1 EA/MeOH), EM silica gel 60 F_{254} plates].

To NaH (0.28 g, 11.9 mmol) was added *n*-BuOH (40 mL). After stirring for 10 min, a solution of ureide B (1.87 g, 5.1 mmol) in 10 mL of *n*-BuOH was added to *n*-BuONa. After heating for 18 h, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in EtOAc. The organic solution was washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography to give 0.23 g of (+)-*cis*-5-pentyl-4-methylpyrrolidin-2-one ([α]$_D$ = +29.6, $CHCl_3$).

(+)-*cis*-5-Pentyl-4-methylpyrrolidin-2-one (210 mg, 1.2 mmol) was reacted with trimethyloxonium tetrafluoroborate (220 mg, 1.5 mmol) according to general procedure A to yield, after chromatography, 180 mg of the iminoether. The iminoether (180 mg) was reacted with ammonium chloride (74 mg, 1.4 mmol) according to general procedure B to yield the title material **20**, 102 mg (54%, from the lactam). ^{1}H NMR (D_2O, 400 MHz): 0.88 (t, J = 7 Hz, 3H), 1.02 (d, J = 7.2 Hz, 3H), 1.23−1.43 (m, 6H), 1.43−1.60 (m, 2H), 2.13 (m, 1H), 2.53 (dd, J = 17.2, 6.7 Hz, 1H), 2.70 (sep., J = 7.2 Hz, 1H), 2.96 (dd, J = 17.2, 7.9 Hz, 1H), 3.92 (td, J = 7.8, 6.4 Hz, 1H). ^{13}C NMR (D_2O, 125 MHz): 15.8, 16.2 (CH_3's); 24.7, 28.0, 31.5, 33.8, 40.2 (CH_2's); 35.7, 66.0 (CH's); 173.2 (C=N). [α]$_D$ = +42.6, MeOH. Anal. ($C_{10}H_{18}N_2$·HCl) C, H, N.

(−)-*cis*-4-Methyl-5-pentylpyrrolidin-2-imine, Monohydrochloride (21). To NaH (0.28 g, 11.9 mmol) was added *n*-BuOH (40 mL). After stirring for 10 min, a solution of ureide A (1.87 g, 5.1 mmol) in 10 mL of *n*-BuOH was added to *n*-BuONa. After heating for 18 h, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in EtOAc. The organic solution was washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography to give 0.23 g of (−)-*cis*-5-pentyl-4-methylpyrrolidin-2-one ([α]$_D$ = −36.5, $CDCl_3$).

(−)-*cis*-5-Pentyl-4-methylpyrrolidin-2-one (210 mg, 1.2 mmol) was reacted with trimethyloxonium tetrafluoroborate (220 mg, 1.5 mmol) according to general procedure A to yield, after chromatography, 180 mg of the iminoether. The iminoether (180 mg) was reacted with ammonium chloride (74 mg, 1.4 mmol) according to general procedure B to yield the title material **21**, 102 mg (54%, from the lactam). ^{1}H NMR (D_2O, 400 MHz): 0.88 (t, J = 6 Hz, 3H), 1.02 (d, J = 7.0 Hz, 3H), 1.23−1.44 (m, 6H), 1.44−1.62 (m, 2H), 2.53 (dd, J = 17.1, 6.7 Hz, 1H), 2.70 (septet, J = 7 Hz, 1H), 2.97 (dd, J = 17.1, 7.9 Hz, 1H), 3.92 (q, J = 7 Hz, 1H). ^{13}C NMR (D_2O, 125 MHz): 15.8, 16.2 (CH_3's); 24.7, 28.0, 31.5, 33.8, 40.2 (CH_2's); 35.7, 66.0 (CH's); 173.2 (C=N). [α]$_D$ = −34.7, $CHCl_3$. Anal. ($C_{10}H_{18}N_2$·HCl) C, H, N.

(+)-*cis*-5-Pentyl-4-(trifluoromethyl)pyrrolidin-2-imine, Monohydrochloride (22). The title compound was isolated from **14** by chiral HPLC on a Chirobiotic V column with 20:80:0.1 EtOH/HEP/TFA as the mobile phase. ^{1}H NMR (400 MHz, DMSO-d_6): 0.89 (t, 3H), 1.2−1.7 (m, 8H), 3.02 (dd, 1H), 3.17 (dd, 1H), 3.63 (m, 1H), 4.13 (m, 1H), 8.8 (s, 1H), 9.4 (s, 1H), 10.3 (s, 1H). [α]$_D$ = +30.0, MeOH. Anal. ($C_{10}H_{17}N_2F_3$·1HCl·1.5H_2O·0.025TFA) C, H, N.

(−)-*cis*-5-Pentyl-4-(trifluoromethyl)pyrrolidin-2-imine, Monohydrochloride (23). The title compound was isolated from **14** by chiral HPLC on a Chirobiotic V column with 20:80:0.1 EtOH/HEP/TFA as the mobile phase. ^{1}H NMR (400 MHz, DMSO-d_6): 0.89 (t, 3H), 1.2−1.7 (m, 8H), 3.02 (dd, 1H), 3.17 (dd, 1H), 3.63 (m, 1H), 4.13 (m, 1H), 8.8 (s, 1H), 9.4 (s, 1H), 10.3 (s, 1H). [α]$_D$ = −33.8, MeOH. Anal. ($C_{10}H_{17}N_2F_3$·1HCl·0.9H_2O) C, H, N.

***cis*-5-Pentyl-4-methylpyrrolidin-2-imine, Semitartrate (20B).** *cis*-5-Pentyl-4-methylpyrrolidin-2-one (19.0 g, 111 mmol) was reacted with trimethyloxonium tetrafluoroborate (35.2 g, 166 mmol) according to general procedure A to yield, after chromatography, 21.7 g of the iminoether. To a suspension of diammonium L-tartrate (14.40 g, 78 mmol) in 110 mL of dry methanol was added 16.8 g (70.6 mmol, by GC analysis) of the crude methyl iminoether. The mixture was refluxed for 5 h, the reaction was cooled to room temperature, 50 mL of MTBE was added, and the mixture was stirred for an additional 15 min. The excess diammonium L-tartrate was filtered, washed with two portions of 1:1 MTBE−MeOH (50 mL total), and dried.

The solvent was removed from the mother liquor via rotary evaporation and azeotroping with hexane. The resulting solids were triturated with MTBE (250 mL) for 90 min, filtered, and washed with 2 × 50 mL of MTBE. The solids were filtered to yield 17.3 g, 101%, of a white solid. Elemental analysis and ^{1}H NMR ($CDCl_3$) show this salt to be the bis-amidine tartrate.

Crude tartrate (14.3 g) was then dissolved in 118 mL of hot absolute ethanol (100%), giving a cloudy solution which was filtered while hot, rinsed down with approximately 30 mL of ethanol, and the now clear solution concentrated to approximately 100-mL volume, cooled to room temperature, seeded, and cooled in the refrigerator (2−4 °C) overnight. The product was then collected in a fritted glass filter funnel, washed with approximately 60 mL of 3:1 MTBE−EtOH, and filtered to yield 8.6 g of fluffy, white solid. HPLC analysis showed approximately 29% of the opposite isomer to be present. These solids were then redissolved in 68 mL of hot absolute ethanol (100%) and cooled to room temperature, at which point crystals began to form without additional seeding. The mixture solidified, necessitating the addition of 10 mL of ethanol. After standing at room temperature for a total of 90 min, the slushy mixture was filtered, and the solids were washed with approximately 30 mL of 3:1 MTBE−EtOH, yielding 3.50 g of white crystals. DSC 205.28 °C (sharp). ^{1}H NMR (D_2O, 400 MHz): 0.88 (t, J = 6.4 Hz, 3H), 1.02 (d, J = 7.0 Hz, 3H), 1.24−1.44 (m, 6H), 1.44−1.52 (m, 2H), 2.53 (dd, J = 17.1, 6.7 Hz, 1H), 2.70 (sep., J = 7 Hz, 1H), 2.96 (dd, J = 17.1, 7.9 Hz, 1H), 3.92 (q, J = 7 Hz,1H), 4.32 (s, 1H). ^{13}C NMR (D_2O, 125 MHz): 18.7, 19.1, 27.6, 30.9, 34.4, 36.7, 38.5, 43.1, 68.8, 79.6, 176.0, 184.1. [α]$_D$ = +42.6, MeOH. Anal. ($C_{24}H_{46}N_4O_6$) C, H, N.

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