Discovery of 4-Substituted Pyrrolidone Butanamides as New Agents with Significant Antiepileptic Activity

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Received June 2, 2003

(*S*)-α-ethyl-2-oxopyrrolidine acetamide **2** (levetiracetam, Keppra, UCB S.A.), a structural analogue of piracetam, has recently been approved as an add-on treatment of refractory partial onset seizures in adults. This drug appears to combine significant efficacy and high tolerability due to a unique mechanism of action. The latter relates to a brain-specific binding site for **2** (LBS for levetiracetam binding site) that probably plays a major role in its antiepileptic properties. Using this novel molecular target, we initiated a drug-discovery program searching for ligands with significant affinity to LBS with the aim to characterize their therapeutic potential in epilepsy and other central nervous system diseases. We systematically investigated the various positions of the pyrrolidone acetamide scaffold. We found that (i) the carboxamide moiety on **2** is essential for affinity; (ii) among 100 different side chains, the preferred substitution α to the carboxamide is an ethyl group with the (*S*)-configuration; (iii) the 2-oxopyrrolidine ring is preferred over piperidine analogues or acyclic compounds; (iv) substitution of positions 3 or 5 of the lactam ring decreases the LBS affinity; and (v) 4-substitution of the lactam ring by small hydrophobic groups improves the in vitro and in vivo potency. Six interesting candidates substituted in the 4-position have been shown to be more potent antiseizure agents in vivo than **2**. Further pharmacological studies from our group led to the selection of (2*S*)-2-[(4*R*)-2-oxo-4-propylpyrrolidin-1-yl]butanamide **83α** (ucb 34714) as the most interesting candidate. It is approximately 10 times more potent than **2** as an antiseizure agent in audiogenic seizure-prone mice. A clinical phase I program has been successfully concluded and **83α** will commence several phase II trials during 2003.

Introduction

Epilepsy, a common neurological disorder characterized by recurrent spontaneous seizures, is a major health problem that affects ∼1% of the population worldwide.[1] Despite progress in understanding the pathogenesis of epileptic seizures[2], the cellular basis of human epilepsy remains a mystery and, in the absence of specific etiological comprehension, approaches to drug therapy are still directed toward the control of symptoms, i.e., suppression of seizures. Chronic administration of antiepileptic drugs (AEDs) is the treatment of choice in epilepsy.[3] The goal of current therapy with an AED is to keep the patient free of seizures without inducing significant adverse effects. However, while the prognosis for seizure control is acceptable in at least 60% of the patients, up to 40% of individuals suffer from intractable pharmacoresistant epilepsy.[4,5] Furthermore, clinical use of most older AEDs is hampered by their limited tolerability, most commonly consisting of central nervous system (CNS)-related adverse effects and idiosyncratic reactions such as skin rashes.[6] For these reasons, a major goal in epilepsy research is to develop new AEDs combining improved seizure control with better tolerability.[7]

The past decade witnessed considerable progress in the pharmacotherapy of epilepsy, including the introduction of several new AEDs and improved formulations of older, "first-generation" drugs, such as phenytoin, carbamazepine, phenobarbital, and valproate.[8,9] Newer "second-generation" drugs include lamotrigine, vigabatrin, tiagabine, topiramate, oxcarbazepine, zonisamide, gabapentin, and levetiracetam.[8,9] However, only a minority of patients refractory to first-generation AEDs are reported to be seizure-free with second-generation AEDs.[9] This indicates that progress in epilepsy therapy with second-generation drugs is mainly due to an improvement in drug tolerability.[7,9] The promising therapeutic potential of the newer AEDs also appears to exist in CNS diseases beyond epilepsy. Indeed, several reports suggest a beneficial outcome in the treatment of neuropathic pain, bipolar disorders, migraine, and anxiety disorders, which to varying degrees appear to reflect hyperexcitability within specific CNS structures.[9]

Levetiracetam, **2** (Keppra, Chart 1), recently obtained marketing authorization in the US (2000) and EU (2001) for add-on treatment of refractory partial-onset seizures in adults and reached the 200 000 patient/year milestone at the end of 2002.[10,11] It was originally synthesized as a structural analogue of piracetam, **1**

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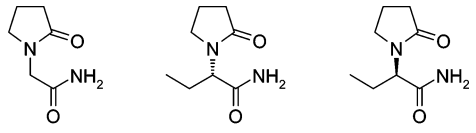
10.1021/jm030913e CCC: $27.50
Published on Web 12/25/2003

Chart 1



1 Piracetam Nootropil®

2 Levetiracetam Keppra®

3

(Nootropil),[12] but its antiepileptic properties were discovered by random screening. Indeed, it clearly differs from **1** by its potent ability to protect against seizure activity in sound-sensitive mice.[13] Levetiracetam possesses a unique pharmacological profile in animal models of seizure and epilepsy[13] that appears to be linked to a novel mechanism of action.[14] Within a series of close analogues of levetiracetam (**2**), there is a strong correlation between LBS (levetiracetam binding site) affinity and seizure protection.[15] This suggests a functional role of LBS in the antiepileptic properties of levetiracetam (**2**).

Given the promising clinical profile of levetiracetam as an AED, we decided to initiate a drug-discovery program focusing on LBS as a novel molecular target. The aim was to identify a new generation of antiepileptic drugs by screening for ligands with a higher affinity for LBS than levetiracetam. These compounds were then carefully characterized in the audiogenic seizure mouse model of epilepsy with respect to their antiseizure potency. This paper describes the medicinal chemistry efforts of this drug-discovery program.

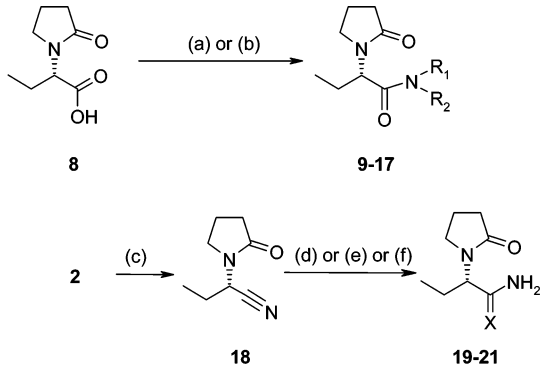
Chemistry

At the beginning of the program, there was only limited information about the structure−activity relationship around the LBS. We therefore systematically investigated the importance of the primary carboxamide and its side chain. In addition, all positions around the pyrrolidone scaffold were analyzed by placing (functionalized)alkyl groups or by disconnecting the C3−C4 bond to generate acyclic derivatives.

Modulation of the Carboxamide Function. Analogues of **2**, with changes to the carboxamide moiety, have been synthesized using conventional methods starting either from the carboxylic acid **8**[16] or the nitrile **18**,[17] easily obtained by dehydration of levetiracetam **2**[18] in the presence of tosyl chloride (Scheme 1). The various amides **9**−**12** and **15**−**17** were obtained by reaction of an amine with either a mixed anhydride between **8** and ethyl chloroformate,[19,20] a pentafluorophenyl ester,[20]or an ethyl ester **22**.[16] The carboxylic acid derivatives **8**, **10**−**20**, and **22** had high enantiomeric purity (ee > 95%). When the absolute stereochemistry was unknown, stereoisomers were characterized by the sign of their specific rotation [levo (*l*) or dextro (*d*) isomers]. Carboxamide **21** was racemic due to epimerization during the aminolysis reaction (see Experimental Section).

De Novo Synthesis of Substituted 2-Oxopyrrolidinyl Carboxamides. Conventional methods for the synthesis of γ-lactams were used for the preparation of substituted levetiracetam analogues (generically shown as **23**, Scheme 2).[20] Briefly, this involved (i) alkylation of an α-bromo acid derivative (amide or ester) **24** by the pyrrolidone **25** (method A) or (ii) construction of the

Scheme 1[a]



9 : R_1 : Ph; R_2 : H. **10** : R_1,R_2 : n-Hex. **11** : R_1 : Me; R_2 : H. **12** : R_1 : $PhCH_2$-; R_2 : H. **13** : R_1 : Me; R_2 : OMe. **14** : R_1 : OH; R_2 : H. **15** : R_1 : Me; R_2 : OH. **16** : R_1 : OMe; R_2 : H. **17** : R_1 : NH_2; R_2 : H. **19** : X : S. **20** : X : NHOH. **21** : X : NH.

[a] Reagents and solvents: (a) $ClCO_2Et$, Et_3N then R_1NHR_2. (b) C_6F_5OH, DCC then R_1NHR_2. (c) TsCl, pyridine, CH_2Cl_2. (d) X = NH: MeOH, HCl then NH_3. (e) X = NOH: NH_2OH, AcOK. (f) X = S: H_2S, Et_3N.

2-oxopyrrolidine ring by reductive amination or alkylation of an α-amino acid derivative **26** followed by an acid- or base-catalyzed cyclization of the corresponding γ-amino ester intermediate (methods B, C, and D). The compounds were synthesized as mixtures of stereoisomers (racemic or diastereoisomeric mixtures). They were used as such, or separated by preparative HPLC on silica gel and/or chiral phases. The synthetic routes used and the stereochemical information are included in Tables 1−5.

Method A. One of the classical methods for the synthesis of lactams such as **34**−**41** involves the alkylation of the sodium salt of **33a**−**g** by a bromoacetate derivative **24f**−**h** in refluxing acetonitrile, followed by aminolysis (Scheme 3).[20] The 2-oxopyrrolidones **33a**−**c** substituted in the 4-position were conveniently prepared in two steps by base-catalyzed Michael addition of a nitromethane derivative[21] to an α,β-unsaturated ester **31a**−**c** with subsequent nitro group reduction/lactamization.[22] The reduction was preferably conducted in the presence of a stoichiometric amount of HCl in order to avoid any cyclization of the intermediate hydroxylamine prior to full reduction. The 2-oxopyrrolidines **33d**,[23] **33e**,[24,25] **33f**,[3]and **33g**[27] were synthesized using known methods. Method A proved to be robust but was not stereoselective and only afforded the pure enantiomers after purification by preparative HPLC on a chiral phase.

Method B. The tandem two-step procedure of reductive amination/lactamization[28] had the main advantage of using readily available enantiomerically pure α-amino acid derivatives. As shown in Scheme 4 (method B-1) (*S*)-2-aminobutyramide **49,** borohydrides ($NaBH_3CN$ or $NaBH(OAc)_3$), and aldehyde esters **45a**−**f** afforded the intermediate γ-amino esters, which were directly cyclized to the corresponding lactams **50**−**55**.

The intermediate 3-substituted aldehyde esters **45** (R_3, R'_3 = H) were conveniently prepared from the aldehyde **43** via alkylation of the enamine **44** with a bromoacetate derivative (Scheme 4).[29,30] Substituted aldehyde esters **45** (R_4 = H) were prepared by ozonolysis of pent-5-enoic derivatives starting from **42**.[31] The

Scheme 2. Synthetic Routes to Substituted 2-Oxopyrrolidinyl Acetamides 23

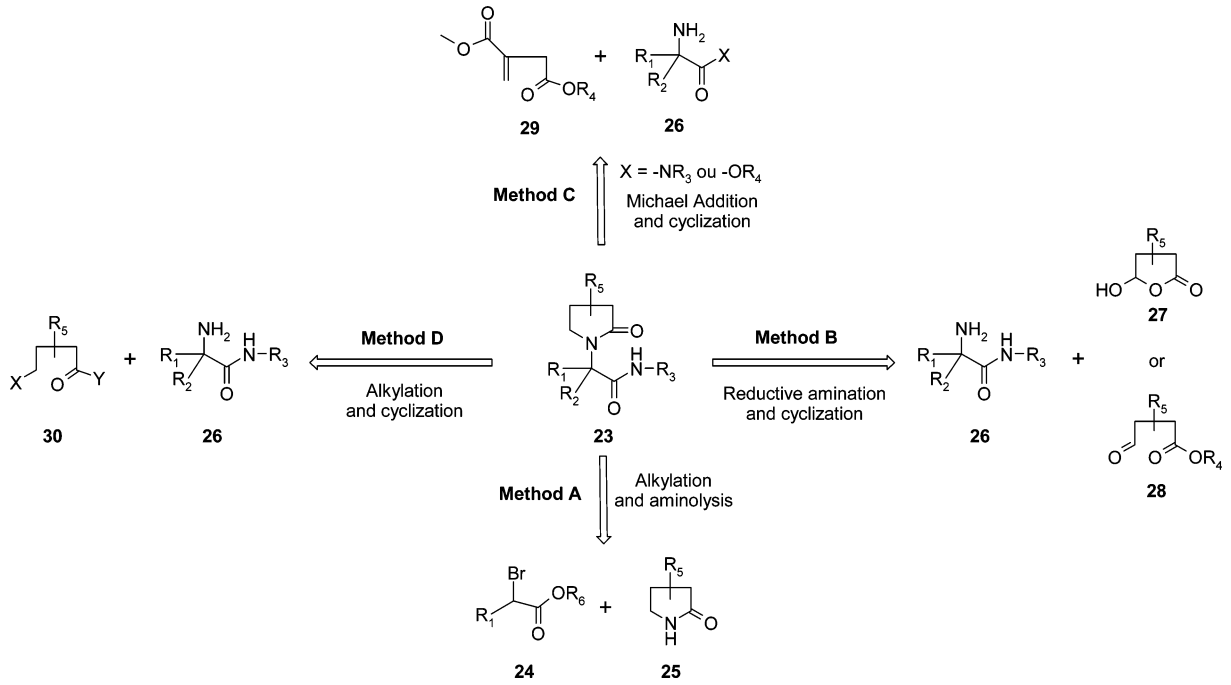
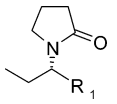


Table 1. In Vitro and in Vivo Pharmacological Data for Analogues of Levetiracetam on the Carboxamide Function



compd	R_1	LBS[a] (pIC_{50})	ED_{50} (μmol/kg)[b] audiogenic mouse
2	$CONH_2$	6.1	180 (143-283)
8	COOH[c]	(<20%)	3200*
9[d]	CONHPh	(<20%)	560*
10	CON(*n*-Hex)$_2$	(<20%)	560 (no limits)
11	CONHMe	4.9	1800 (no limits)
12	CONHBn	(<30%)	560*
13	CONMeOMe	(<20%)	1000*
14	CONHOH	5.7	1000*
15	CONMeOH	4.7	1000*
16	CONHOMe	(<20%)	1000*
17	$CONHNH_2$[e]	5.2	1000*
19	$CSNH_2$	(<20%)	1000 (MAD)
20	$C(NOH)NH_2$	(<20%)	1000*
21	$C(NH)NH_2$[e]	4.9	1000*
22[c]	COOEt[c]	(<20%)	n.d.

[a] $pIC_{50} = -\log$ of the unlabeled drug concentration that inhibits the [^{3}H]-(2*S*)-2-[4-(3-azidophenyl)-2-oxopyrrolidin-1-yl]butanamide-specific binding by 50%. All the values represent the mean of two independent determinations. Each pIC_{50} value lies within 0.2 log unit of the mean. Figures in parentheses relate to the percentage of displacement of the radioligand at 10^{-5} M as described in the biological section. [b] Dose protecting 50% of audiogenic seizure prone mice against clonic convulsions. Figures in parentheses are the 95% confidence limit. An asterisk signifies inactive up to the indicated dose (maximum dose tested). MAD: minimal active dose; i.e., the first dose revealing a statistically significant seizure protection vs control group ($p < 0.05$ Fisher test). [c] Compounds synthesized using the methods described.[16] [d] Compound tested as a racemic mixture. [e] Obtained as an hydrochloride

5-hydroxy lactones such as **48** (Scheme 4) were later found to be useful alternatives to the aldehyde esters **45** because of their greater stability and accessibility. Morpholine-catalyzed condensation[32,33] of aldehyde **43a** and glyoxylic acid **46** afforded the 5-hydroxyfuranone **47**, which was then reduced under nickel catalysis to provide **48**.

Table 2. In Vitro and in Vivo Pharmacological Data for Analogues of Levetiracetam Alpha to the Carboxamide

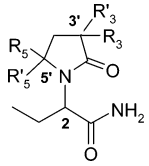
no.	R_1	R_2	stereo-chem	method	LBS[a] (pIC_{50})	ED_{50} (μmol/kg)[b] audiogenic mouse
1[c]	H	H			4.4	10 000*
2[d]	Et	H	*S* (*l*)		6.1	180 (143−283)
3[e]	Et	H	*R* (*d*)		<3.0	1000*
39α	*n*-Pr	H	(*l*)	A	5.3	190 (59−281)
39*β*	*n*-Pr	H	(*d*)	A	3.0	1000*
40α	*i*-Pr	H	(*l*)	A	4.7	890 (no limits)
56	$(CH_2)_3NH_2$	H	*R*,*S*	B-2	(<20%)	nd
84	Me	H	(*l*)	D-1	5.5	504 (102−715)
85	*t*-Bu	H	S	D-2	(<20%)	nd
93	Me	Me		D-2	(<20%)	nd

[a] See footnote *a* of Table 1. [b] See footnote *b* of Table 1. [c] Compounds synthesized using the methods described.[66] [d] Compounds synthesized using the methods described.[16] [e] Compounds synthesized using the methods described.[36]

The reductive lactamization of aldehydes **28** (Method B-2) or 5-hydroxy lactone **48** (Method B-3) with α-amino amides **26** was successfully applied to solid-phase methodology using 91 different commercially available enantiomerically pure α-amino acids **26** linked onto a Rink resin (Scheme 5). Enantiomerically pure α-amino acids derivatives (ee > 99%) were generally used and, under our conditions, no racemization was observed. The reductive lactamization was not stereoselective, affording diastereoisomeric mixtures. The stereochemically pure compounds were obtained by preparative HPLC (silica gel or chiral phase).

Method C. The tandem two-step Michael addition/lactamization reaction[34] between (*S*)-2-aminobutyramide **49** and methyl itaconate **41** produced up to kilogram quantities of the 1/1 diastereoisomeric mixture of esters **57α** and **57*β***, which were easily separated by chromatography (Scheme 6).

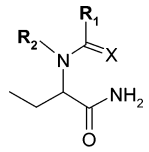
Table 3. In Vitro and in Vivo Pharmacological Data for 3′ or 5′-Substituted-2-oxo-pyrrolidinyl Derivatives



no.	R_5	R_5	R_3	R_3	stereochem[a]	method	LBS[b] (pIC_{50})	ED_{50} (μmol/kg)[c] audiogenic mouse
2[d]	H	H	H	H	2*S*		6.1	180 (143−283)
38	Me	Me	H	H	2[e]	A	4.2	1000*
51α	H	H	$PhCH_2$	H	2*S*,3	B-1	(<20%)	320*
52α	H	H	Me	Et	2*S*,3	B-1	(<20%)	1000*
90	*n*-pentyl	H	H	H	*f*	D-2	(<20%)	nd
91α	H	H	Me	H	2*S*,3	D-2	4.7	1000*
92[g]	Me	H	H	H	2*S*,5	D-2	5.6	100 (54−194)
96α	H	H	CH_2OH	H	2*S*,3	E	(<20%)	nd

[a] The number refers to the chiral center that is defined. Absolute stereochemistry (*R* or *S*) is set next to the number when known. For enantiomerically pure compounds, ee are superior to 99%. [b] See footnote *a* of Table 1. [c] See footnote *b* of Table 1. [d] Compounds synthesized using the methods described.[16] [e] Levo enantiomer. [f] A mixture of four stereoisomers. [g] Racemic mixture of a single diastereoisomer, relative stereochemistry unknown.

Table 4. In Vitro and in Vivo Pharmacological Data for Open Compounds **99**



99

no.	R_1	R_2	X	stereochem[g]	method	LBS[a] (pIC_{50})	ED_{50} (μmol/kg)[b] audiogenic mouse
2[c]	$-(CH_2)_3-$	O	S			6.1	180 (143 −283)
105	$-(CH_2)_3-$	S	S	*d*		6.3[e]	144 (93−249)
106	$-(CH_2)_4-$	O	nd[d]	*d*		5.2[e]	1000*
99aα	4-$ClC_6H_4CH_2$	*n*-Oct	O	nd[d]	F-1	5.7	1000*
99b	Et	*n*-Oct	O	*rac*	F-1	5.4	nd
99c[e]	Me	*n*-Pr	O	*rac*	F-1	(<20%)	nd
99d	Me	Me	O	S	F-2	4.8[d]	1800 (no limits)
99e	Et	*n*-Bu	O	S	F-2	5.0	nd
99f	Et	*n*-Pent	O	*rac*	F-4	5.7	nd
99g	4-$MeOC_6H_4CH_2$	*n*-Hept	O	*rac*	F-4	5.6	nd

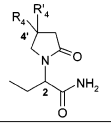
[a] See footnote *a* of Table 1. [b] See footnote *b* of Table 1. [c] Compounds synthesized using the methods described.[16] [d] Data taken from the literature.[15] [e] Levo isomer.

Transformation of the ester function of **57α** into the mesylate **64** using standard conditions allowed the introduction of fluoride or azide functionalities. Hydrogenolysis of the azide **66** afforded the aminomethyl derivatives **74**−**76**. The iodide **70**, obtained directly from the alcohol **63**, was also a useful precursor for the sulfide **71**, the amine **72**, and the nitrate **73**. Curtius rearrangement of the acid **59** in the presence of diphenylphosphorazidate[35] and trapping of the intermediate isocyanate afforded carbamates **60α** (42%) and **60*β*** (9%) with partial retention of configuration. Hydrogenation on Pd/C led to the 4-amino lactam **62**. The stereochemical configuration of the compounds obtained by method C was assigned by chemical correlation from **66** for which an X-ray crystal structure was obtained (see Supporting Information).

Method D. A large number of 2-oxopyrrolidine acetamide derivatives **83**−**93** have been synthesized[20] by alkylation of the 4-halobutanoic acid derivatives **82a**−**h** with an amino acid derivative **26** (Scheme 7). Method D-1 uses optically pure 2-aminoalkylamides **26**. To avoid racemization during the alkylation/cyclization procedure, we developed a two-phase method using powdered potassium hydroxide and tetra-*n*-butylammonium bromide (TBAB) as the phase-transfer catalyst.[36] The method permitted the synthesis of 2-oxopyrrolidone acetamides on a large scale with no significant racemization (<1%), provided that the reaction temperature was maintained below 0 °C. However, on large scale, a major drawback with this method was the need to eliminate the TBAB from the crude product pyrrolidone. This could be avoided with method D-2,[36] where the amino acid derivative **26** was condensed with the 4-bromobutyrate **82g**−**h**. The intermediate γ-amino ester (which could be isolated and recrystallized as a salt) directly cyclized in the presence of acetic acid or 2-hydroxypyridine (Scheme 7).

Both 4-halobutanoic acid derivatives **82a**−**d** (Z = Cl) and **82e**−**f** (Z = OR) were available in good yields by ring opening of the γ-lactones **81** using respectively $SOCl_2/ZnCl_2$ (X = Cl)[37] or $TMSI/SOCl_2$ (X = I),[38,39] or HBr or HCl in an alcohol (Scheme 7). Monosubstituted 4-alkylbutyrolactones (R_3, R'_4, R_5 = H) **81** were conveniently obtained by carbocupration of the 2(5*H*)-furanone **80** by a lithium (or magnesium) dialkyl cuprate. As described,[40] addition of trimethylchlorosilane before **80** greatly improved the yields, leading to a 1/1 mixture of C/O silylated lactones that were directly hydrolyzed

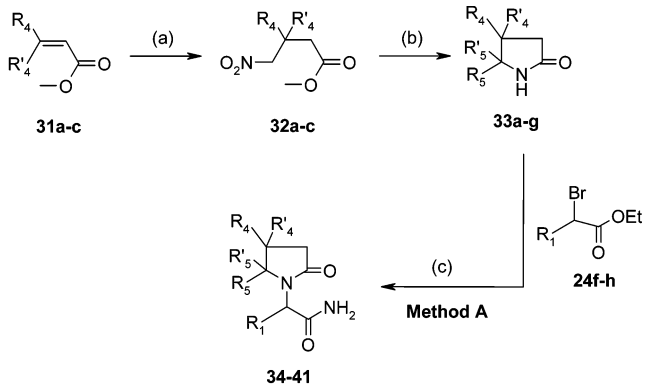
Table 5. In Vitro and in Vivo Pharmacological Data for 4′-Substituted-2-oxopyrrolidinyl Derivatives



Compound	R_4	R'_4	Stereochemistry[a]	Method	LBS[b] (pIC_{50})	ED_{50} (μmol/kg)[c] Audiogenic mouse
2[d]	H	H	2S	--	6.1	180 (143 – 283)
34α	$-CF_3$	H	2,4'	A	(<20%)	#1000
35α	$-CH_2OMe$	H	2,4'	A	5.8	400 (236 – 894)
36α	n-Pent	H	2,4'	A	5.9	n.d.
37	$-(CH_2)_4-$		Racemate	A	5.7	#1000
41α	OH	H	2,4'R	A	(<20%)	#1000
50α	$-CH_2$-*t*-Bu	H	2S,4'	B-1	6.1	1000 (MAD)
53α	Et	H	2S,4'	B-1	5.9	87 (52 – 134)
54α	$-CH_2Ph$	H	2S,4'	B-1	5.6	1000 (MAD)
55α	*i*-Pr	H	2S,4'	B-1	5.4'	360 (271 – 468)
57α	$-CO_2Me$	H	2S,4'R	C	(<20%)	#1000
58	$-CONH_2$	H	2S,4'R	C	(<20%)	#1000
59	$-CO_2H$	H	2S,4'R	C	(<20%)	#1000
61	$-NHCO_2Me$	H	2S,4'	C	5.8	540 (311 – 1641)
62	$-NH_2$	H	2S,4'	C	(<20%)	n.d.
63	$-CH_2OH$	H	2S,4'R	C	(<20%)	n.d.
65	Me	H	2S,4'	C	5.9	110 (78 – 204)
66	$-CH_2N_3$	H	2S,4'R	C	7.1	3.6 (2.6 – 5.1)
67	$-CH_2F$	H	2S,4'R	C	5.9	370 (245 – 757)
68	$-CH_2Cl$	H	2S,4'R	C	6.7	25 (16 – 41)
69	$-CH_2Br$	H	2S,4'R	C	6.6	180 (108 – 297)
70	$-CH_2I$	H	2S,4'R	C	6.8	13 (7.4 – 21)
71	$-CH_2SMe$	H	2S,4'R	C	6.9	160 (111 – 208)
72		H	2S,4'R	C	(<20%)	#320
73	$-CH_2ONO_2$	H	2S,4'R	C	7.0	25 (16 – 39)
75	$-CH_2NHSO_2Ph$	H	2S,4'R	C	(<20%)	#1000
76		H	2S,4'R	C	4.6	#1000
83α	*n*-Pr	H	2S,4'R	D-1	7.0	14 (6.6 – 24)
83β	*n*-Pr	H	2S,4'S	D-1	6.6	44 (30 – 59)
86	n-But	H	2,4'	D-1	6.4	480 (415 – 576)
87α		H	2S,4'	D-1	6.9	33 (20 – 57)
88α	*n*-Pr	Me	2S,4'	D-1	6.4	400 (298 – 688)
89	*n*-Pr	*n*-Pr	2S,4'	D-1	(<30%)	#1000

[a] See footnote *a* of Table 3. [b] See footnote *a* of Table 1. [c] See footnote *b* of Table 1. [d] Compounds synthesized using the methods described in ref 16.

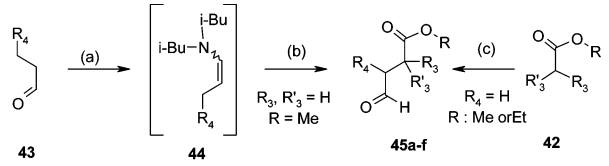
Scheme 3. [a] Alkylation of α-Bromo Esters by 2-Oxopyrrolidines Derivatives (Method A)



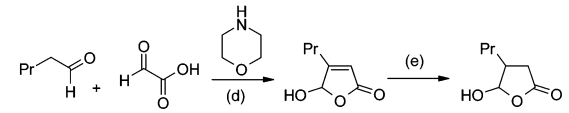
a : R_4,R'_4 : H, n-Pentyl; R_5,R'_5 : H; **b** : R_4,R'_4 : H, $-CF_3$; R_5,R'_5 : H; **c** : R_4,R'_4 : H, $-CH_2OMe$; R_5,R'_5 : H; **d** : R_4,R'_4 : $-(CH_2)_4-$; R_5,R'_5 : H; **e**: R_4,R'_4 : H; R_5,R'_5 : Me; **f** : R_1 : i-Pr; **g** : R_1 : n-Pr; **h** : R_1 : Et

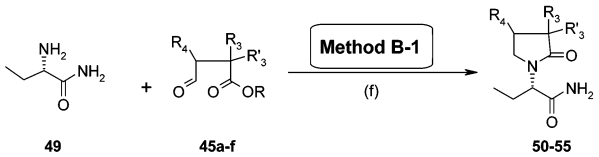
[a] Reagents and solvents: (a) $MeNO_2$, 1,8-diazabicyclo[5.4.0]undec-7-ene. (b) (i) H_2, Pd/C, HCl, EtOH; (ii) AcOH, Δ. (c) (i) NaH, DMF or MeCN; (ii) NH_3, MeOH or (ii) NaOH then $SOCl_2$ then NH_4OH.

Scheme 4. [a] Synthesis and Reductive Amination of Aldehydic Esters 24 (Method B)



a : R_4 : Et; **b** : R_4 : t-Bu; **c** : R_4 : i-Pr; **d** : R_4 : $PhCH_2$-; **e** :R_3, R'_3 = H; $PhCH_2$-; **f** : R_3, R'_3 = Me, Et



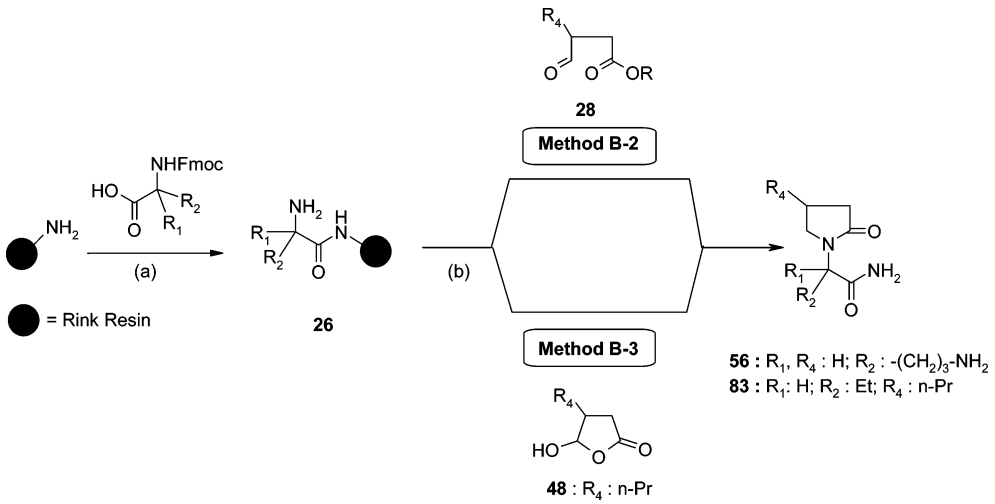


[a] Reagents and solvents: (a) (i) $(i\text{-Bu})_2NH$, PhMe; (b) $BrCH_2$-CO_2Me, MeCN then H_2O (c) (i) LDA,THF then allylBr (ii) O_3, CH_2Cl_2 then Ph_3P. (d) EtOH. (e) $NaBH_4$, $NiCl_2$, EtOH. (f) (i) MeOH, 40°C; (ii) $NaBH_4$ or $NaBH_3CN$, MeOH, 20°C; (iii) HOBt, PhMe, reflux or CH_3CO_2H, reflux.

with TBAF. For unstable organocuprates such as lithium dicyclopropylmethylcuprate or disubstituted 4-alkylbutyrolactones **81** (R'_4 = alkyl), we preferred the $CaBH_4$[41]-induced reduction/cyclization of the hemisuccinate **79b**–**d**, conveniently prepared by alkylation of the lithium enolate of either **77**[42] or **78**.[31]

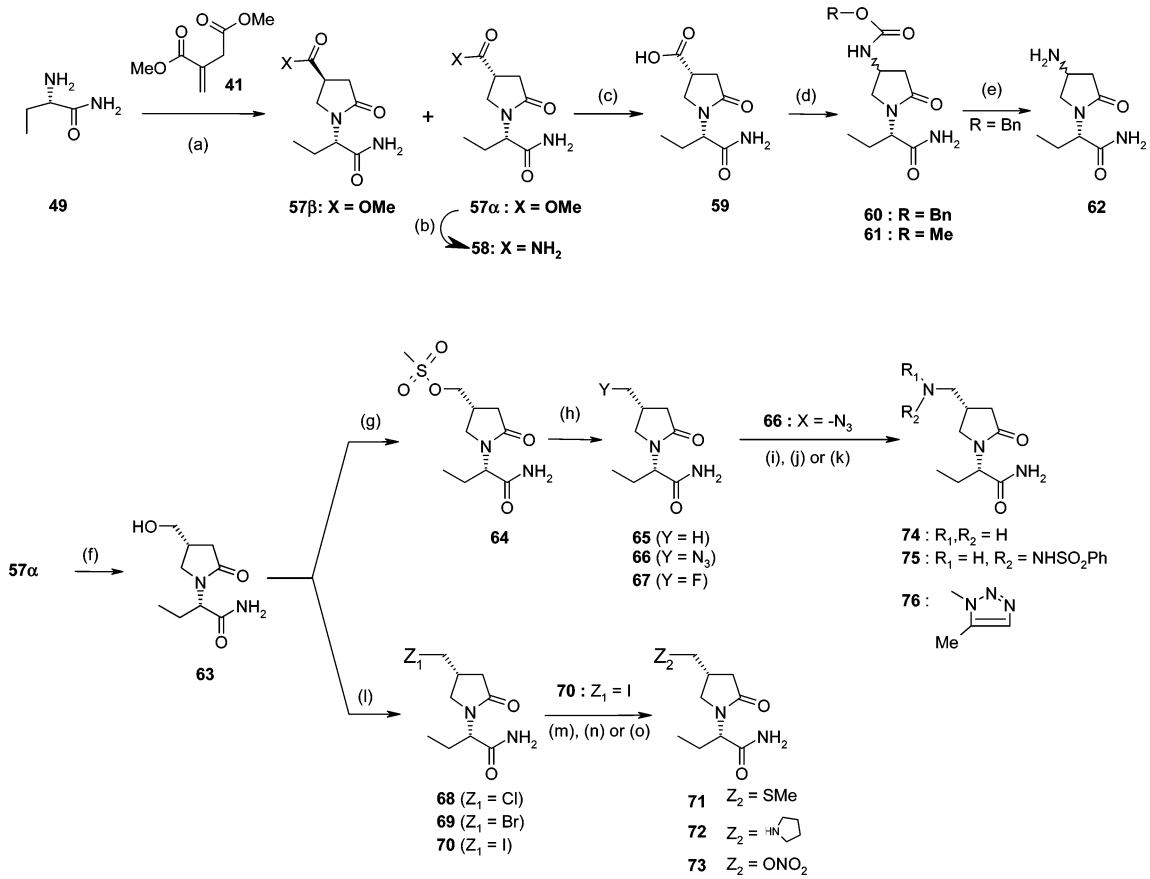
Synthesis of 96α (Method E). These compounds were synthesized by homoconjugate[43] ring opening of the spiro acylal **94**[44] with amine **49** followed by intramolecular cyclization (Scheme 8). Classical functional group transformations of **95** is partially racemizing and led to the diastereoisomers **96α** and **96*β***.

Scheme 5. [a] Solid Phase Synthesis of Substituted 2-Oxopyrrolidinyl Acetamides by Reductive Amination of Aldehydic Esters (Method B-3 and B-2)



[a] Reagents and solvents: (a) (*i*-Pr-N)$_2$=C, DMF then piperidine. (b) NaBH(OAc)$_3$ then TFA/CH_2Cl_2.

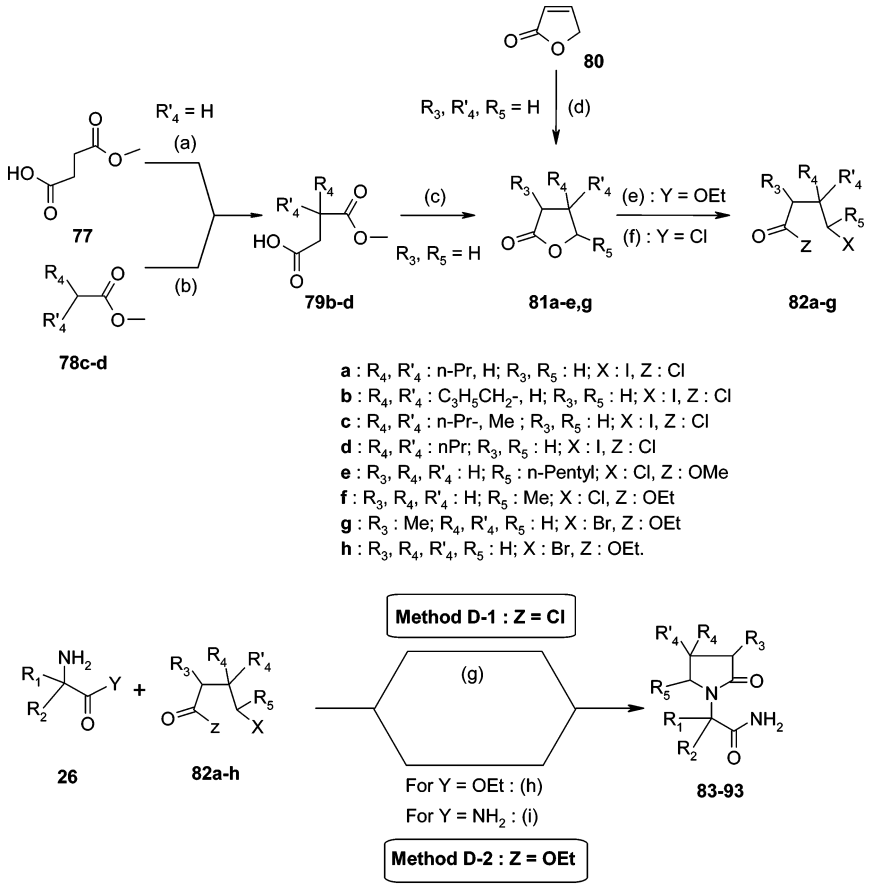
Scheme 6. [a] Michael Addition to Methyl Itaconate and Further Derivatization (Method C)



[a] Reagents and solvents: (a) MeOH, reflux. (b) NH_3, MeOH. (c) NaOH, MeOH then HCl. (d) $(PhO)_2PON_3$, Et_3N, MeCN then ROH. (e) H_2, Pd/C, EtOH. (f) $NaBH_4$, EtOH. (g) MsCl, Et_3N, CH_2Cl_2. (h) X = H: Zn, NaI, DME/MeOH; X = N_3: NaN_3, MeCN; X = F: *n*-Bu_4NF. (i) H_2, Pd/C, EtOH. (j) Et_3N, $PhSO_2Cl$, CH_2Cl_2. (k) Ph_3P=CHCOMe, PhMe. (l) Z_1 = I: Ph_3P, I_2, MeCN; Z_1 = Cl: Ph_3P, C_2Cl_6, MeCN; Z_1 = Br: Ph_3P, CBr_4, MeCN. (m) MeSNa, THF. (n) pyrrolidine, EtOH. (o) $AgNO_3$, MeCN.

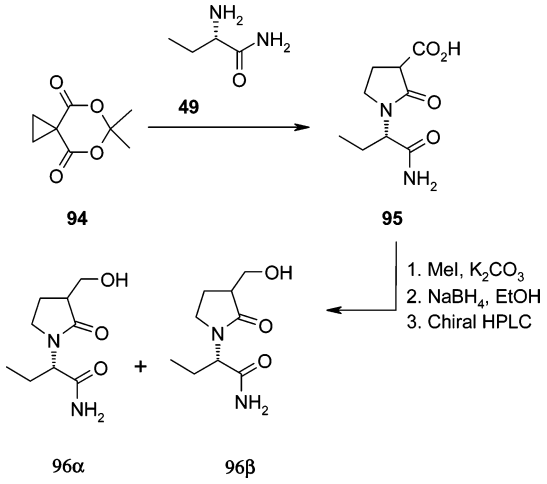
Synthesis of Acyclic Compounds (Method F). To generate the acyclic or open-chain compounds **99**, we employed liquid-phase parallel methodology (Scheme 9). Three precursors were used based on well-known chemistry, an α-acylamino ester **98** or **104** (methods F-1 and F-4), the amine **100** (method F-2), and an α-acylamino nitrile **101** (method F-3). The α-acylamino esters **98** were easily obtained from α-bromo esters **97** by nucleophilic substitution with amines followed by acylation with a set of acid chlorides (method F-1). After automated liquid−liquid extraction, aminolysis in pressure tubes was applied to generate the acyclic compounds **99**, which were purified by liquid chromatography (purity > 75%). This methodology generated a library of 278 compounds but suffered from three drawbacks: the small diversity of α-bromo ester, the need for liquid−

Scheme 7. [a,b] Synthesis and Alkylation of γ-Halogeno Acid 30 Derivatives by 2-Aminoalkanoic Acid 26 (Method D)



[a] Reagents and solvents: (a) LDA, THF then R_4CH_2Br, HMPA. (b) (i) LDA, THF then $BrCH_2CO_2t$-Bu; (ii) TFA, CH_2Cl_2. (c) (i) KOH, MeOH; (ii) $NaBH_4$, $CaCl_2$, EtOH. (d) (i) $R_4R'_4CuLi$, TMSCl, THF; (ii) $(n\text{-}Bu)_4NF$, THF. (e) HBr, EtOH. (f) $ZnCl_2/SOCl_2$ or (i) TMSI, CH_2Cl_2; (ii) $SOCl_2$, PhMe. (g) KOH (powder), $n\text{-}Bu_4NBr$, Na_2SO_4, CH_2Cl_2. (h) (i) Et_3N, CH_2Cl_2; (ii) 2-hydroxypyridine, Δ; (iii) NaOH, H_2O then HCl; (iv) $SOCl_2$, C_6H_6; (v) NH_3; (i) (i) K_2CO_3, NaI, DMF; (ii) AcOH, MeOH, Δ. [b]For the structure of compounds **83**−**93**, see Tables 3 and 5.

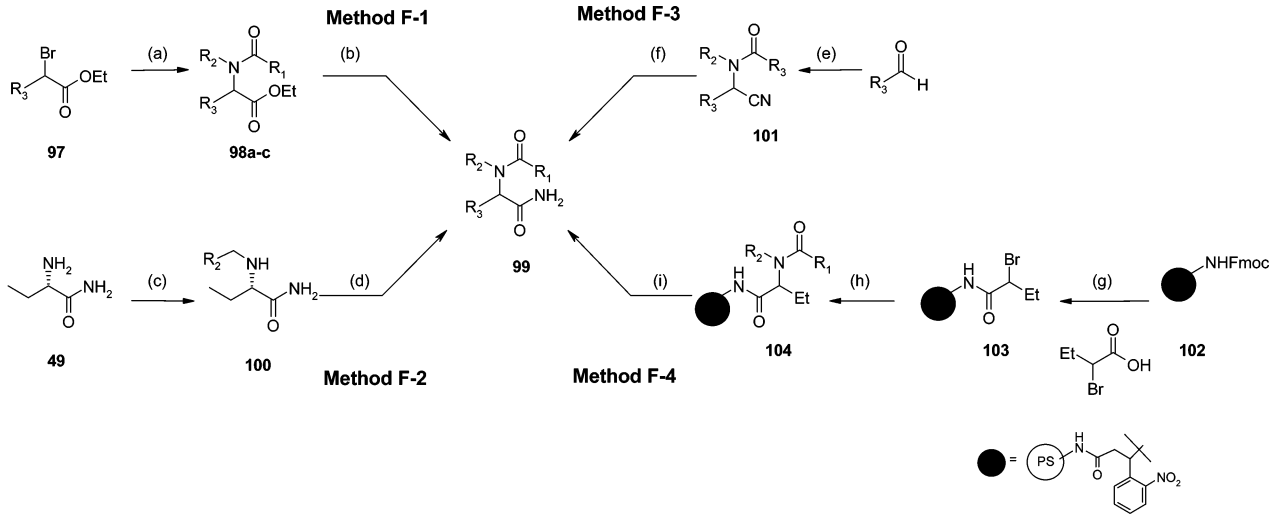
Scheme 8. Synthesis of 96 (Method E)



liquid extraction, and the aminolysis reaction. Method F-2 was also used on several occasions. However, it provided a limited diversity of compounds **99**, since the synthetic intermediate **100** is obtained by reductive amination of **49**. To improve the throughput, we developed another pathway that included a one-pot synthesis of open-chain Reissert compounds **101** (method F-3).[45] A biphasic system was used to carry out the acylation step directly in the organic phase, where the intermediate **101** is stable. Oxidation by hydrogen peroxide in basic DMSO converted the nitrile into a primary amide. By combining different sets of amines, aldehydes, and acid chlorides, a library of 1169 compounds was generated in 4 months (purity > 75%). The remaining problems were linked to some manual operations (liquid−liquid extraction). We also developed a second chemical methodology using solid-phase parallel synthesis (method F-4) similar to the liquid phase one (method F-1). Use of the Rink amide resin provided mixtures of the acid corresponding to ester **98** and the final amides **99** (data not shown). Using Geysen's photolabile linker, the release of **99** from the solid phase was performed under very mild conditions by irradiation in DCM/MeOH.[46] This method allowed the production of 496 compounds in 15 days (purity of crude material > 90%).

Biological Methods. The aim of this drug discovery program was to prepare ligands with a higher affinity to LBS than **2** in an attempt to improve antiseizure potency. The primary in vitro screen employed a binding assay with tritiated **2** in order to characterize the analogue affinities for LBS. Ligands with a $pIC_{50} > 4$ were then tested in vivo in audiogenic seizure-prone mice. In this model, seizures are evoked by exposing animals to high-frequency sonic stimulation.[47] This induces three phases of seizure activity, successively wild running and clonic and tonic convulsions. Effective dose (ED_{50} value) abolishing clonic convulsions in 50% of the animals was used as the parameter to estimate

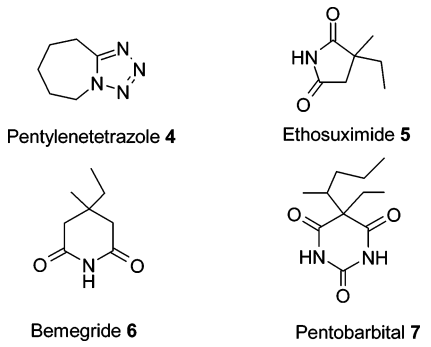
Scheme 9. [a] Synthetic Methods for Acyclic Compounds 99 (Method F)



a : R_1 : $ClC_6H_4CH_2$-; R_2 : n-octyl; **b** : R_1 : Et; R_2 : n-octyl; **c** : R_1 : Me, R_2 : n-Pr; **d** : $R_1 = R_2$: Me; **e** : R_1 : n-Bu; R_2 : Et

[a] Reagents and solvents: (a) (i) R_2NH_2, DMF, Et_3N; (ii) R_1COCl then liquid−liquid extraction. (b) MeOH/NH_3 then chiral chromatography. (c) R_2CHO, $NaBH_3CN$. (d) R_2COCl, Et_3N. (e) (i) H_2O, $NaHSO_3$; (ii) R_2NH_2,CH_2Cl_2; (iii) NaCN, H_2O; (iv) R_1COCl then liquid−liquid extraction. (f) (i) H_2O_2, K_2CO_3, DMSO then liquid−liquid-extraction. (g) (i) Piperidine, DMF; (ii) (*i*-Pr-N)$_2$=C. (h) (i) R_2NH_2, DMSO; (ii) R_1COCl, Et_3N, CH_2Cl_2. (i) hν, CH_2Cl_2–MeOH.

Chart 2



the potency of seizure protection (see Experimental Section for details).

Results and Discussions

At the beginning of the program, we were aware that **2** ($pIC_{50} = 6.1$) had an affinity superior to its enantiomer **3** ($pIC_{50} < 3.0$) (Chart 1) and that the commonly known anti- or proconvulsant drugs do not bind to the LBS or bind with only moderate affinity. This is the case for ethosuximide ($pIC_{50} = 3.5$), pentylenetetrazole ($pIC_{50} = 4.1$), pentobarbital ($pIC_{50} = 3.8$), and bemegride ($pIC_{50} = 5.0$) (Chart 2).[15] Pharmacological data on some of these compounds have been published elsewhere but are incorporated in the following tables for completeness.[15] When more than one stereoisomer has been biologically tested, only the most active one (the "α" isomer) is included in the tables and the others (stereoisomers β, γ, δ) are described in Supporting Information.

The Carboxamide Moiety of 2 is Essential for Affinity. The primary carboxamide moiety of **2** is probably responsible for the excellent water solubility and low lipophilicity (log *D* (pH 7.4) = −0.65). Mono- or disubstitution by alkyl or heteroatoms on the amide nitrogen considerably lower in vitro affinity and in vivo activity (Table 1). Moderate affinity ($4.9 < pIC_{50} < 5.7$) only remains with secondary amides bearing small

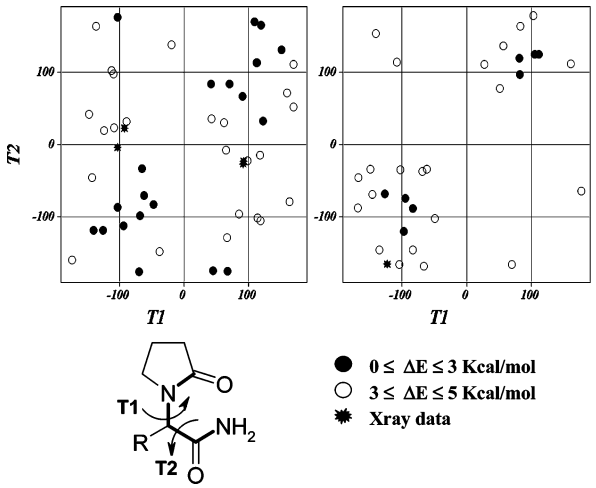


Figure 1. Conformational map of piracetam (**1**) (left) and levetiracetam (**2**) (right).

substituents such as methyl (**11**: $pIC_{50} = 4.9$), hydroxyl (**14**: $pIC_{50} = 5.7$), or amino (**17**: $pIC_{50} = 5.2$). Other functions such as ester (**22**), acid (**8**), thioamide (**19**), or amidine (**21**) are not active.

To define all the positions of the carboxamide toward the γ-lactam scaffold, a conformational analysis was undertaken. The conformational map (Figure 1) revealed two zones of low energy ($\Delta E \leq 3.0$ kcal/mol) centered on the conformations characterized by either T1 = 90° and T2 = 120° or T1 = −90° and T2 = −120°, each one being stabilized by an intramolecular hydrogen bond. The crystal packing of **83α**, a 4-substituted analogue of **2**, emphasizes the high hydrogen-bonding ability of the compound (Figure 2). In the crystalline state, **2** (not shown) and **83α** adopt torsion angles of T1 ≅ −120° and T2 ≅ −160° (Figure 1) with the formation of an intermolecular H-bond. In comparison with the minimum of the conformational map, the X-ray conformation is 4.8 kcal/mol higher in energy. This corresponds to the energy that is necessary to break the intramolecular hydrogen bond but it is offset in the

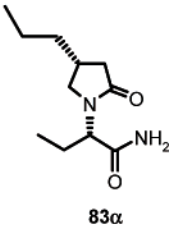


Figure 2. X-ray structure of **83α**.

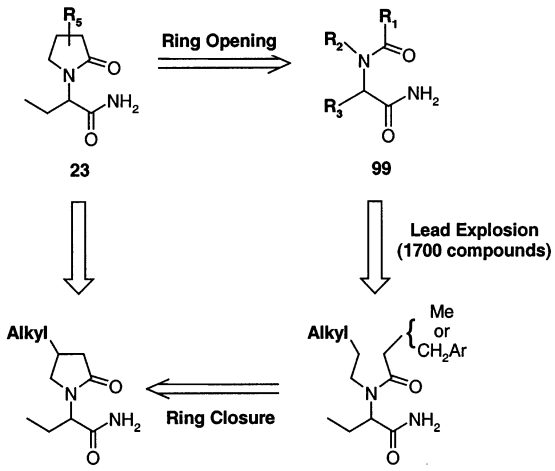
crystal cells by the energy released by the intermolecular hydrogen binding. Indeed, the two hydrogens of the carboxamide moiety of **83α** take part in hydrogen bonding with the carbonyl of either the carboxamide side chain, or the γ-lactam of the other molecules, within the crystal (Figure 2). In conclusion, the bioactive conformation of **2** should be closely related to one of these three stable conformations previously mentioned.

The Preferred Substitution α to the Carboxamide Is an Ethyl Group with the *S Configuration*. We have published that piracetam (**1**), the unsubstituted 2-oxopyrrolidone acetamide used to treat cognitive deficits in the elderly,[48] only recognizes LBS with modest affinity (Table 2).[15] Methyl and *ethyl* substitution on position 2 dramatically increase the LBS affinity and also the in vivo activity in a proportional manner.[15] Furthermore, the ligand binding pocket would appear to be very limited in size, since sterically more demanding substituents such as isopropyl, *tert*-butyl, phenyl, or dimethyl substitutions (like **93**) are not tolerated. This observation proved to be the general rule, since 91 compounds bearing a variety of different side chains [starting from commercially available amino acid derivatives (Scheme 5)] and a broad diversity of functional groups have now been tested without improving the affinity of the corresponding ethyl derivative (e.g. **56**). Stereoselectivity is always observed among the analogues, with a strong preference for the "*S*" over the "*R*" enantiomer.[15] The absolute stereochemistry of **39α**, **39*β***, **40α**, **84**, and **85** have not been determined, but it is always the levo isomer that binds to the LBS more strongly.

In conclusion, the introduction of a single short alkyl chain α to the carboxamide leads to an increase in affinity. We think that this increase is due to a conformational effect (see the conformational maps of **1** and **2** in Figure 1) that stabilizes the compound in the bioactive conformation. The strong preference for LBS binding of the "*S*" over the "*R*" enantiomer shows that available space is limited to a single direction. Such a proposal is supported by the inactivity of the disubstituted derivative (**93**) to bind the LBS.

Substitution of Positions 3 or 5 of the Lactam Ring Leads to Less Active Compounds. The following order of LBS affinity is observed among the various substituents: H > Me > CH_2OH ~ $PhCH_2$ ~ Me, Et (Table 3). For the LBS, the substitution is thus limited

Chart 3



to hydrogen in this region of space. The seizure protection obtained in vivo with **92** correlates with the in vitro affinity for the LBS. For some of the 3-alkyl-substituted derivatives (e.g. **51α**), we observed severe toxic effects (mortality at 1000 μmol/kg). This is in sharp contrast to the usual excellent tolerability of most of the pyrrolidone acetamide derivatives. Recently, Covey and coworkers have described several 3-alkyl-substituted 2-oxopyrrolidines and 2-oxopiperidines devoid of the acetamide moiety that induce seizure protection[31,49−51]either by direct potentiation of the $GABA_A$-receptor-mediated chloride channel[31,49] or by modulation of the sodium currents[50,51] in a voltage- and concentration-dependent manner. This contrasts with recent findings on levetiracetam (**2**) where *direct* modulation of the GABA-gated chloride channel[14] and sodium channel[52] was not demonstrated. We are currently testing another close analogue of **2** (**83α**) for its capacity to modulate $GABA_A$-receptor-gated currents and/or Na channels. The low potency of the 3-alkyl-substituted compounds in epilepsy models further distinguished them from the compounds described by Covey et al.[31,49−51]

The 2-Oxopyrrolidine Ring Is Preferred over Acyclic Compounds. Replacement of the cyclic amide by a thioamide leads to a slight increase in affinity (**105**: $pIC_{50} = 6.3$) and similar in vivo activity, while 2-oxopiperidine **106**[15] has a lower affinity than **2** (Table 4). Disconnection of the ring into the open compound **99d** decreases both the in vitro ($pIC_{50} = 4.8$) and in vivo activities. However, this observation was interesting and it finally boosted our lead explosion program. For a long time, we were unsuccessful with the development of a high-throughput combinatorial synthesis of the 2-oxopyrrolidinyl acetamide derivatives, whereas a plethora of methods have been described for acyclic amino acid derivatives **99**.[45,53]As a novel strategy, we embarked on the high-throughput synthesis of acyclic compounds **99** that can be considered as 2-oxopyrrolidinyl mimics (Chart 3), and the most active of these were then "reclosed" into the cyclic derivatives. In total, more than 1700 analogues of **99** with diverse substituents have been synthesized and screened in vitro. A set of the most active compounds is presented in Table 4. The 2(*S*)-aminobutyramides derivatives, as stated before, always show the highest affinity. The best tertiary amides are either a propanamide or more complex

substituted arylacetamides. The most interesting observation was at position R_2, where linear alkyl chains longer than propyl always resulted in the most active compounds. Cyclization of the best compounds **99e**, **99f**, and **99b** into the corresponding 2-oxopyrrolidines derivatives and knowing that 3′- and 5′-substitution was disfavored indicated that hydrophobic substitution of the 4-position of the lactam ring by alkyl chains (or any other hydrophobic substituents) was the strategy of choice for improving the LBS affinity of our ligands (Chart 3). A systematic investigation of this position was thus initiated.

4-Substitution of the Lactam Ring by Size-Limited Hydrophobic Groups Improves the in Vitro and in Vivo Potency. Hydrophobic groups are clearly needed in the 4-position, and polar substituents such as amino, hydroxyl, amides, esters, carboxylic acids, amines, and alcohols are not tolerated (pIC_{50} < 5.0; Table 5). A systematic investigation of the influence of the alkyl chain length on LBS affinity produced a bell-shaped curve (Me ∼ Et < *n*-Pr > *n*-Bu > *n*-Pent), with a maximum for the *n*-propyl chain and a 10-fold increase in the affinity compared to **2**. Both *n*-propyl-substituted diastereoisomers **83α** and **83*β*** bind the LBS with a preference for the 4′*R*-stereoisomer (**83α**, pIC_{50} = 7.1; **83*β***, pIC_{50} = 6.8). The better affinity of the 4′*R*-stereoisomer over 4′*S* proved to be a general finding in this series. By comparing the ethyl-substituted **53α** (pIC_{50} = 5.9) with the isopropyl derivative **55α** (pIC_{50} = 5.4) or the trifluoromethylated **34α** (pIC_{50} < 5.0), it was concluded that the carbon atom α to the lactam ring is preferably monosubstituted. Attachment of various heteroatoms to this 4′-methylene was systematically investigated for the 4′*R* stereoisomer. The following affinity order was observed, ONO_2 > I ∼ SMe > Br > Cl > F > Ph, suggesting that LBS binding is extremely size-sensitive, as observed previously in the alkyl series. Again, apolar substituents are preferred as exemplified by the differences in affinity between **35α** (R_4 = CH_2-OMe, pIC_{50} = 5.8) and **71** (R_4 = CH_2SMe, pIC_{50} = 6.9). Basic tertiary amines are not tolerated (e.g., **72**: pIC_{50} < 5.0) and dialkyl substitution on the 4-position strongly decreases LBS affinity (compare **83α**, pIC_{50} = 7.1; **88α**, pIC_{50} = 6.4; see Figure 2 for relative stereochemistry).

As already described,[15] a gain in LBS affinity clearly influences the potency of the observed seizure protection in vivo. Most of the ligands in the highest affinity range (pIC_{50} = 6.8−7.1) have effective doses (ED_{50} = 13−33 μmol/kg) lower than levetiracetam **2**. As expected, outliers are present (e.g. compounds **66**, **69**, **71**, **86**, and **88α**) and this is probably due to differences in pharmacodynamic (e.g. multiple cellular mechanisms) and/or pharmacokinetic parameters (high plasma clearance, low blood−brain barrier penetration, etc.) between these compounds. For example, the low potency observed in vivo with **71** (pIC_{50} = 6.9; ED_{50} = 160 μmol/kg) can probably be explained by a rapid clearance, since it was found to be very rapidly metabolized in vitro in rat microsomes (data not shown).

Selection of 83α as a Potential Drug Candidate. The most potent compounds in the audiogenic seizure test in mice, e.g. **66**, **68**, **70**, **73**, **83α**, and **87α**, were evaluated further in additional pharmacological models. These revealed that **83α** induces the most potent and complete seizure suppression in animal models at doses devoid of side effects.[54a] Likewise, further testing of **83α** in animal models mimicking several other CNS diseases, such as neuropathic pain and essential tremor, also confirmed promising pharmacological activities.[54b,c] A preclinical development program was initiated with **83α** enabling the start of phase I clinical studies at the end of 2001. Several phase II trials focusing on multiple disease areas are scheduled to begin during 2003.

Table 6. Pharmacokinetics (rat) and Physicochemical Parameters for 4′-Substituted-2-oxopyrrolidinyl Derivatives

no.	physicochemisry		in vivo pharmacokinetic (rat)				
	log *D*[a]	solubility[b] (mg/mL)	dose (mg/kg)	$T_{1/2}$ (h)	T_{max} (h)	Cl (mL/min/kg)	F_{oral} (%)
70	0.51	65	1	2.0	0.8	4.80	∼100
83α	1.00	681	10	1.7	0.5	4.67	∼100

[a] log *P* octanol/water, buffer PBS (pH 7.4). [b] In pure water.

Preliminary Pharmacokinetic Parameters. The two most studied pyrrolidone acetamides, **83α** and **70**, have very similar physicochemical parameters to **2** and are characterized by high water solubility and relatively modest lipophilicity (Table 6). In vitro, both are metabolically stable with low intrinsic clearance on NADPH-fortified liver microsomes (Cl_{int} < 5 μL/min mg of protein).[55] On Caco-2 cells, the compounds show good permeability (Papps > 10^{-6} cm/s).[56] In vivo, pharmacokinetic studies in rats confirmed the high bioavailability (>80%) together with a low total clearance and half-life values in the range of levetiracetam (**2**) (Table 6).[57]

Conclusions

Given the clinical promise of **2** as an AED and the apparent involvement of LBS as the novel molecular target responsible for its antiseizure activity, we systematically investigated the effects of substitutions at various positions of the pyrrolidone acetamide scaffold on LBS affinity. We found that (i) the carboxamide moiety on **2** is essential for LBS affinity; (ii) among 100 different side chains, the optimal substitution α to the carboxamide is an ethyl group in the *S* configuration; (iii) the 2-oxopyrrolidine ring is preferred over piperidine or acyclic analogues and a thiocarbonyl is acceptable for LBS; (iv) substitution at positions 3 or 5 of the lactam ring decrease LBS affinity; and (v) 4-substitution of the lactam ring by small-sized hydrophobic groups improves activity. Six candidates substituted in the 4-position were shown to induce more potent seizure protection than **2** in vivo, and further pharmacological studies have identified (2*S*)-2-[(4*R*)-2-oxo-4-propylpyrrolidin-1-yl]butanamide, **83α** (ucb 34714), as the most interesting candidate.[54a] This study shows that **83α** is approximately 10 times more potent than levetiracetam (**2**) in audiogenic seizure-prone mice. Further studies from our group have shown that **83α** possesses significant efficacy in several animal models of chronic epilepsy.[54a] Finally, testing in animal models mimicking a variety of other CNS diseases revealed a promising therapeutic potential beyond epilepsy in diseases such as neuropathic pain and essential tremor.[54b,c] The compound **83α** has successfully completed a clinical phase I program and will enter several phase II trials during 2003. Substitution of the 4-position of the lactam ring by other

substituents such as aryl[54d] and alkenes as well as other heterocycles replacing the pyrrolidone moiety will be the subject of a future publication.

Experimental Section

Chemistry. NMR spectra were recorded on a BRUKER AC 250 Fourier Transform NMR spectrometer fitted with an Aspect 3000 computer and a 5 mm $^1H/^{13}C$ dual probehead or BRUKER DRX 400 FT NMR fitted with a SG Indigo^2 computer and a 5 mm inverse geometry $^1H/^{13}C/^{15}N$ triple probehead. Samples were studied in DMSO-d_6 (or $CDCl_3$) solutions at a probe temperature of 313 K and at a concentration of 20 mg/mL. The instrument was locked on the deuterium signal of DMSO-d_6 (or $CDCl_3$). Chemical shifts are given in ppm downfield from TMS taken as internal standard and coupling constants are in hertz. Mass spectrometric measurements in LC/MS mode were performed as follows. HPLC conditions: Analyses were performed using a WATERS Alliance HPLC system mounted with an INERTSIL ODS 3, DP 5 mm, 250 × 4.6 mm column. The gradient ran from 100% solvent A (acetonitrile, water, TFA (9.9/90/0.1, v/v/v)) to 100% solvent B (acetonitrile, water, TFA (90/10/0.1, v/v/v)) in 7 min with a hold of 4 min at 100% B. The flow rate was set at 2.5 mL/min and a split of 1/10 was used just before the API source. The chromatography was carried out at 30 °C. MS conditions: Samples were dissolved in acetonitrile/water 70/30 (v/v) at the concentration of about 250 mg/mL. API spectra were performed using a FINNIGAN (San Jose, CA) LCQ ion trap mass spectrometer. APCI source operated at 450 °C and the capillary heater at 160 °C. The ESI source operated at 3.5 kV and the capillary heater at 210 °C. Mass spectrometric measurements in DIP/EI mode were performed as follows: samples were vaporized by heating the probe from 50 to 250 °C in 5 min. EI (Electron Impact) spectra were recorded using a FINNIGAN (San Jose, CA) TSQ 700 tandem quadrupole mass spectrometer. The source temperature was set at 150 °C. Specific rotation was recorded on a Perkin-Elmer MC241 or 341 polarimeter. The angle of rotation was recorded at 25 °C on 1% solutions in MeOH. For some molecules, the solvent was CH_2Cl_2 or DMSO, due to solubility problems. Water content was determined using a Metrohm microcoulometric Karl Fischer titrator. Preparative chromatographic separations were performed on silica gel 60 Merck, particle size 15−40 mm, ref 1.15111.9025, using in-house modified Jobin Yvon-type axial compression columns (80 mm i.d.), flow rates between 70 and 150 mL/min. The mount of silica gel and solvent mixtures are described in individual procedures. Preparative chiral chromatographic separations were performed on a DAICEL Chiralpak AD 20 mm, 100 × 500 mm column using an in-house build instrument with various mixtures of lower alcohols and C5−C8 linear, branched, or cyclic alkanes at ±350 mL/min. Solvent mixtures as described in individual procedures. Melting points were determined on a Büchi 535 Totolitype fusionometer, and were not corrected, or by the onset temperature on a Perkin-Elmer DSC 7. Full experimental details were given for representative examples of the various synthetic steps. Photolysis were carried out with a 365 nm lamp (100W) (Cole-Parmer). Purity of the sample by HPLC under acid conditions: Xterra MS C18 column (5 μm, 4.6 × 150 mm) and MeCN/H_2O/TFA (from 9.9/89.9/2 to 89.9/9.9/2 after 11 min) at 2.5 mL/min. Purity of the sample by HPLC under basic conditions: Inertsil ODS3 column (5 μm, 4.6 × 150 mm), MeCN/H_2O/NH_5CO_3 at pH 8 (from 9.9/89.9/2 to 89.9/9.9/2 after 11 min) at 2.5 mL/min. Full spectral and analytical data may be found in the Supporting Information.

2-(2-Oxopyrrolidin-1-yl)-*N*-phenylbutanamide (9). In a 250-mL, three-necked flask fitted with a magnetic stirrer, under inert atmosphere, Na (0.115 g, 5 mmol) is added by portion to a solution of **22** (6.96 g, 35 mmol) and aniline (15 mL) in MeOH (3 mL) at room temperature and warmed 1 h at 60 °C. After cooling at room temperature, the brown residue is diluted with Et_2O, washed carefully with water, treated with Norite, dried over Na_2SO_4, and concentrated in vacuo. The crude amide is recrystallized with AcOEt and the precipitate is washed with hexane to afford **9** (1.5 g, 17%) as a white powder. Anal. ($C_{14}H_{18}N_2O_2$): C, H, N, S.

(2*S*)-*N*,*N*-Dihexyl-2-(2-oxopyrrolidin-1-yl)butanamide (10). In a 250-mL, three-necked flask fitted with a magnetic stirrer, under inert atmosphere, ethyl chloroformate (2.45 mL, 23 mmol) is added to a stirred solution of **8** [36](4.0 g, 23 mmol) and Et_3N (3.9 mL, 28 mmol) in dry CH_2Cl_2 (40 mL) at −10 °C. After 0.5 h, (*n*-Hex)$_2$NH (5.45, 23 mmol) is added at −10 °C. The reaction mixture is warmed to room temperature, quenched with HCl (0.5 N), extracted with CH_2Cl_2, and the organic layer is dried over $MgSO_4$ and concentrated in vacuo. The crude amide is purified by column chromatography on silica gel (CH_2Cl_2–MeOH−NH_3 (97/2.7/0.3 (v/v)), to give **10** (4.35 g, 55%). HPLC: 100%.

(2*S*)-*N*-Methyl-2-(2-oxopyrrolidin-1-yl)butanamide (11). As for **10**, **8** (4 g, 23 mmol) and CH_3NH_2 (1.5 g, 46.8 mmol) give **11** (2.38 g, 55%). HPLC: >99%.

(2*S*)-*N*-Benzyl-2-(2-oxopyrrolidin-1-yl)butanamide (12). As for **10**, **8** (76.95 g, 0.45 mol) and $PhCH_2NH_2$ (49 mL, 0.45 mol) give **12** (98.5 g, 84%). HPLC: >99%.

(2*S*)-*N*-Methoxy-*N*-methyl-2-(2-oxopyrrolidin-1-yl)butanamide (13). As for **10**, **8** (6 g, 35 mmol) and $CH_3ONMeH\cdot$HCl (3.42 g, 35 mmol) give **13** (1.8 g, 24%). HPLC: >99%.

***N*-Hydroxy-2-(2-oxopyrrolidin-1-yl)butanamide (14).** In a 250-mL, three-necked flask fitted with a magnetic stirrer, under inert atmosphere, DCC (6.63 g, 32 mmol) is added to pentafluorophenol (5.91 g, 32 mmol) and **8** (5 g, 29 mmol) in THF (75 mL) at 0 °C. After 1 h at this temperature, the solid is filtrated and the filtrate is concentrated in vacuo. In a 50-mL, three-necked flask fitted with a magnetic stirrer, under inert atmosphere, the crude ester is dissolved in THF (50 mL) at 0 °C, and $(NH_2OH)_2\cdot H_2SO_4$ (2.4 g, 14.6 mmol) and Et_3N (4 mL, 29 mmol) are added successively. After 1 h at 0 °C and 20 h at room temperature, the white precipitate is filtered off and purified by column chromatography on silica gel (CH_2Cl_2−MeOH−AcOH (92.3/7/0.7 (v/v)) to give the crude hydroxamate which is successively lyophilized in water (20 mL) and recrystallized from acetonitrile (20 mL) give **14** (0.85 g, 16%). Anal. ($C_8H_{14}N_2O_3$): C, H, N.

(2*S*)-*N*-Hydroxy-*N*-methyl-2-(2-oxopyrrolidin-1-yl)butanamide (15). As for **10**, **8** (5 g, 29 mmol) and HONHMe·HCl (2.44 g, 29 mmol) give **15** (2.7 g, 46%). HPLC: >99%.

(2*S*)-*N*-Methoxy-2-(2-oxopyrrolidin-1-yl)butanamide (16). As for **10**, **8** (5 g, 29 mmol) and $CH_3ONH_2\cdot$HCl (2.44 g, 29 mmol) give **16** (1.24 g, 21%). HPLC: >99%.

(2*S*)-2-(2-Oxopyrrolidin-1-yl)butanohydrazide (17). As for **10**; **8** (5 g, 29 mmol) and $NH_2NH_2\cdot H_2O$ (14 mL, 290 mmol) give the hydrazide as a free base (3.5 g, 64%) but partially racemized (ee: 65%). A solution of HCl in MeOH (5.3 M) is added to the crude hydrazide at room temperature and after 0.2 h, the reaction mixture is concentrated in vacuo, dissolved in water, lyophilized and finally recrystallized 3 times from EtOH (in order to obtain the enantiomerically pure compound) to give **17** (1.81 g, 43%). Anal. ($C_8H_{15}N_3O_2\cdot$HCl): C, H, N,Cl.

(2*S*)-2-(2-Oxo-1-pyrrolidinyl)butanenitrile (18). In a 500-mL, three-necked flask fitted with a magnetic stirrer, under inert atmosphere, pyridine (57 mL, 704 mmol) is added to a solution of **2** (30 g, 176 mmol) and *p*-toluenesulfonyl chloride (84.1 g, 440 mmol) in dry CH_2Cl_2 (300 mL). The mixture is stirred at room temperature (20 h) and concentrated in vacuo and the crude nitrile is purified by column chromatography on silica gel [CH_2Cl_2–MeOH from 99.5/0.5 to 97/3 (v/v)] to give **18** (25 g, 93%). δ_H (250 MHz, C_2D_6SO): 0.88 (3H, t, *J* 8.4), 1.63−2.09 (4H, m), 2.30 (2H, t, *J* 7.3), 3.31−3.52 (2H, m), 4.95 (1H, t, *J* 8.4). MS *m*/*z* (EI): 152 ($M^{+\bullet}$), 123, 112. $[\alpha]_D^{25}$ (*c* = 1, MeOH): −77.3°.

(2*S*)-2-(2-Oxopyrrolidin-1-yl)butanethioamide (19). In a 4-L, three-necked flask fitted with a mechanical stirrer, under inert atmosphere, Et_3N (167.6 mL, 1.2 mol) is added to a solution of **18** (182.4 g, 1.2 mol) in dry $CHCl_3$ (1810 mL) at 0 °C. The mixture is saturated in gaseous H_2S (yellow solution). After 7 h, the excess H_2S is removed by bubbling with nitrogen, and 500 mL of the water is added. The organic layer is separated, dried over sodium sulfate, and concentrated

in vacuo to afford **19** after recrystallization from AcOEt (137.9 g, 61.7%). Anal. ($C_8H_{14}N_2OS$): C, H, N, S.

(2*S*)-*N*′-Hydroxy-2-(2-oxopyrrolidin-1-yl)butanimidamide (20). In a 500-mL, three-necked flask fitted with a magnetic stirrer, NH_4Cl (18.3 g, 218 mmol) in H_2O (100 mL) is added to **18** (22.24 g, 146 mmol) in EtOH (220 mL) at room temperature. After 24 h, the solid is filtered and the filtrate is concentrated in vacuo. The crude imide is purified by column chromatography on silica gel (CH_2Cl_2–methyl *tert*-butyl ether–EtOH (47/47/3 (v/v)) and recrystallized from acetonitrile give **20** (8.55 g, 32%). Anal. ($C_8H_{15}N_3O_2$): C, H, N.

2-(2-Oxopyrrolidin-1-yl)butanimidamide (21). In a 250-mL, three-necked flask fitted with a mechanical stirrer, under inert atmosphere, HCl is bubbled into a solution of **18** (9.4 g, 61.8 mmol) in dry MeOH (100 mL) at 10 °C. After 4 h, the residue is concentrated in vacuo and dissolved in MeOH (100 mL). NH_3 is bubbled into the solution at 0 °C and the temperature is increased up to 25 °C. After 48 h at 0 °C, the crude amidine is concentrated in vacuo, dissolved in *i*-PrOH (100 mL), filtered to remove the NH_4Cl, and concentrated in vacuo. Several attempts to recrystallize the crude amidine as a salt or to purify it by chromatography on silica gel lead to partial racemization of the compound. It is then fully racemized. In a 100-mL, three-necked flask fitted with a magnetic stirrer, under inert atmosphere, the crude amidine (4.2 g, 0.025 mol) is refluxed in MeOH for 8 h, cooled at room temperature overnight, and concentrated in vacuo. The residue is recrystallized from *i*-PrOH to afford **21** (1.4 g, 10%). Anal. ($C_8H_{15}N_3O$·HCl·H_2O): C, H, N.

4-(Trifluoromethyl)pyrrolidin-2-one (25b). In a 250-mL pressure jar, under inert atmosphere, 336 mg (1.5 mmol) of **32b** is dissolved in 10 mL of ethanol. A suspension of 40 mg of predried (3×, ethanol) Raney nickel in ethanol is added and the mixture hydrogenated on a Parr hydrogenator at a maximum of 20 psi of H_2 pressure (**Caution:** strongly exothermic reaction, ice/water cooling required). The mixture is degassed, filtered on a Celite/Norite pad, and the filtrate concentrated in vacuo, to give 150 mg of the crude amino ester used as such in the next step. In a 500-mL flask fitted with a reflux condenser and a magnetic stirrer, 150 mg of ethyl 4-amino-3-(3-trifluoromethyl)butanoate is dissolved in 10 mL of toluene, and the mixture is refluxed for 0.5 h. The solution is concentrated to dryness to give 121 mg of **25b** (54%). δ_H (250 MHz, $CDCl_3$): 2.41–2.58 (2H, m), 3.04–3.25 (1H, m), 3.41–3.60 (2H, m), 6.50 (1H, s (broad)).

4-Pentylpyrrolidin-2-one (25a) is synthesized (54%) by following the same procedure as for **25b** starting from **32a** (0.34 g, 1.5 mmol). MS *m*/*z* (APCI): 156 (MH^+).

4-(Methoxymethyl)pyrrolidin-2-one (25c) is synthesized (60%) by following the same procedure as for **25b** starting from **32c** (23.5 g, 0.123 mol). δ_H (250 MHz, $CDCl_3$): 2.09 (1H, dd, *J* 17.1; 8.1), 2.39 (1H, dd, *J* 17.1; 10.0), 2.66–2.78 (1H, m), 3.15 (1H, dd, *J* 6.9; 10.0), 3.15–3.40 (5H, m, at 3.32 ppm (3H, s)), 3.46 (1H, d, *J* 9.0), 6.12 (1H, s (broad)). *m*/*z* (EI): 129 ($M^{+\bullet}$), 101, 87, 69.

5-Hydroxy-4-propyldihydrofuran-2-one (27). 5-Hydroxy-4-propyl-5*H*-furan-2-one (**47**)[32,33] (15 g, 0.1 mol), ethyl acetate (260 mL), and Pd/C 5% are placed in a Parr apparatus. The mixture is degassed, and hydrogen is introduced at a pressure of 35 psi. This mixture is then stirred vigorously at 25 °C for 2 h. After filtration on Celite, the solvent is removed under reduced pressure at 50 °C to give **27** as a crude product (100% yield). MS *m*/*z* (APCI): 145 (MH^+).

4,4,4-Trifluoro-3-(nitromethyl)butyric Acid Ethyl Ester (32b). In a 50-mL, three-necked flask fitted with a reflux condenser, a magnetic stirrer, and a dropping funnel under inert atmosphere, 1 g (6 mmol, 1 equiv) of ethyl 3-(trifluoromethyl)-2-propenoate (**31b**) is dissolved in 1.6 mL (30 mol, 5 equiv) of nitromethane. Diazabicycloundecene (0.915 mL, 6 mmol, 1 equiv) is then added dropwise under efficient stirring, keeping the temperature below 25 °C (ice/water bath). The deep red mixture is stirred overnight at room temperature. The mixture is diluted with diethyl ether and washed with 1 N HCl, and the aqueous phase is reextracted twice with diethyl ether. The combined organic phases are dried over magnesium sulfate, filtered, and concentrated to dryness to give 0.34 g of crude **32b**, 24% yield, used as such in the next step. δ_H (250 MHz, $CDCl_3$): 1.27 (3H, t, *J* 7.3), 2.56 (1H, dd, *J* 9.0; 12.5), 2.79 (1H, dd, *J* 4.2; 12.5), 3.54–3.70 (1H, m), 4.16 (1H, q, *J* 7.3), 4.58 (1H, dd, *J* 11.0; 5.2), 4.66 (1H, dd, *J* 11.0; 5.2).

3-Nitrooctanoic acid methyl ester (32a) is synthesized (6.5 g, 94%) by following the same procedure as for **32b** starting from methyl *trans*-2-octenoate (**31a**) (5 g, 32 mmol). δ_H (250 MHz, C_2D_6SO): 0.89 (3H, t, *J* 7.3), 1.18–1.49 (9H, m), 2.45 (2H, d, *J* 5.5), 3.59 (3H, s), 4.58 (2H, d, *J* 6.6).

3-(Methoxymethyl)-4-nitrobutyric acid methyl ester (32c) is synthesized (23.6 g, 68%) by following the same procedure as for **32b** starting from 4-methoxybut-2-enoic acid methyl ester (**31c**)[58](23.7 g, 182 mmol). δ_H (250 MHz, $CDCl_3$): 2.45–2.50 (2H, m), 2.84 (1H, m), 3.40 (2H, d, *J* 7.0), 3.60 (3H,s), 4.63 (2H, d, *J* 7.0). MS *m*/*z* (EI): 192 ($M^{+\bullet}$), 160, 129, 71.

Method A. 2-[2-Oxo-4-(trifluoromethyl)-1-pyrrolidinyl]-butanamide (34α and 34*β*). Step 1: Condensation. In a 100-mL, three-necked flask fitted with a reflux condenser, magnetic stirrer, and dropping funnel under an inert atmosphere, 1 g (6.5 mmol, 1 equiv) of **25b** is dissolved in 35 mL of acetonitrile. Then, 2.36 g (13 mmol, 2 equiv) of methyl 2-bromobutanoate (**24h**) is added and the temperature raised to 50 °C. Sodium hydride (0.313 g, 13 mmol, 2 equiv) is added in portions, the temperature raising to 65 °C. The mixture is stirred one more hour at 50 °C. The mixture is concentrated to dryness, the residue suspended in ethyl acetate and washed with water, and the aqueous phase reextracted with ethyl acetate. The combined organic phases are dried over magnesium sulfate, filtered, and concentrated to dryness. The residue is purified by chromatography on silica gel (pet. ether–EtOAc 70/30) to give 1.76 g (42%) of pure 2-(2-oxo-4-(trifluoromethyl)-pyrrolidin-1-yl)butyric acid methyl ester. δ_H (250 MHz, $CDCl_3$): 0.91 (3H, t, *J* 7.3), 1.58–1.79 (1H, m), 1.93–2.12 (1H, m), 2.54–2.70 (2H, m), 3.00–3.20 (1H, m), 3.37–3.56 (1H, m), 3.60–3.83 (4H, m + s at 3.66 ppm), 4.64 and 4.68 (1H, dd for the two diastereoisomers, *J* 5.2; 10.4).

Step 2: Aminolysis. In a 250-mL, three-necked flask fitted with a reflux condenser and a magnetic stirrer, 4.0 g (2.76 mmol) of the ester are dissolved in 5 mL of methanol. Gaseous ammonia is bubbled through the solution, and the saturated solution kept at room temperature for 5 days, while occasionally resaturating with ammonia. After completion of the reaction, the solution is concentrated to dryness. The residue is purified by Prep LC (1 kg SiO_2, CH_2Cl_2–MeOH 98/2) to give 1.15 g of the first eluted diastereoisomer **34α** (32%, recrystallized from AcOEt) and 1.41 g of the second eluted diastereoisomer **34*β***[59] (39%, recrystallized from EtOH). **34α** HPLC: >99%.

2-[4-(Methoxymethyl)-2-oxo-1-pyrrolidinyl]butanamide (35)α is synthesized following the same procedure as for **34α** starting from **25c** (9.3 g, 72 mmol) and **24h** to give, after HPLC on chiral phase, **35α** (1.28 g, 8%, recrystallized from *i*-Pr_2O), **35*β*** (1.98 g, 13%, recrystallized from *i*-Pr_2O), **35*γ*** (1.43 g, 9%, recrystallized from *i*-Pr_2O), and its stereoisomer **35*δ*** (1.31 g, 8%, recrystallized from *i*-Pr_2O). **35α** Anal. ($C_{10}H_{18}N_2O_3$) C, H, N: calcd, 13.07; found, 13.60.

2-(2-Oxo-4-pentylpyrrolidin-1-yl)butyramide (36α and 36*β*) is synthesized following the same procedure as for **34α** starting from **25a** (0.5 g, 3.2 mmol) and **24h** to give **36α** (3.3%) and its stereoisomer **36*β***.[59] **36α** HPLC: 97%.

2-(3-Oxo-2-azaspiro[4.5]dec-2-yl)butyramide (37) is synthesized by following the same procedure as **34α** starting from **25d**[23] (0.43 g, 2.8 mmol) and **24h** to give the racemic **37** (43%, recrystallized from $PhCH_3$). Anal. ($C_{13}H_{22}N_2O_2$) C, N, H: calcd, 9.30; found, 10.75.

2-(2,2-Dimethyl-5-oxopyrrolidin-1-yl)butyramide (38) is synthesized following step 1 of the method for **34α** starting from **25e**[24] and **24h**. The ester is ammonified using the same method as for **93** to give **38** (recrystallized from AcOEt). Anal. ($C_{10}H_{18}N_2O_2$): C, H, N

2-(2-Oxopyrrolidin-1-yl)pentanamide (39α and 39*β*) is synthesized following the same procedure as for **34α** starting

from 2-pyrrolidone and methyl 2-bromopentanoic ester **24g**. The racemic pentanamide is separated by HPLC on chiral phase to give **39α** (levo isomer, recrystallized from AcOEt) and its stereoisomer **39*β***[59] (dextro isomer, recrystallized from AcOEt). **39α** Anal. ($C_9H_{16}N_2O_2$) N, C: calcd, 58.67; found, 59.23. H: calcd, 15.21; found, 15.75.

3-Methyl-2-(2-oxopyrrolidin-1-yl)butyramide (40α and 40*β*) is synthesized following the same procedure as for **34α** starting from 2-pyrrolidone and methyl 2-bromo-3-methylbutanoic ester (**24f**). The racemic pentanamide is separated by HPLC on chiral phase to give **40α** (levo isomer, recrystallized from *i*-PrOH) and its stereoisomer **40*β***[59] (dextro isomer, recrystallized from *i*-PrOH). **40α** Anal. ($C_9H_{16}N_2O_2$): C, H, N

2-(4-Hydroxy-2-oxopyrrolidin-1-yl)butyramide (41α and 41*β*). In a 100-mL, three-necked flask fitted with a reflux condenser, a magnetic stirrer, and a dropping funnel under inert atmosphere, 12.8 g (59.4 mmol, 1 equiv) of (*R*)-4-((*tert*-butyldimethylsilanyl)oxy)pyrrolidinone (**25f**)[5] is dissolved in 300 mL of acetonitrile. Methyl 2-bromobutanoate (**24h)** (23.18 g, 118.8 mmol, 2 equiv) is added and the temperature raised to 50 °C. Sodium hydride (2.85 g (118.8 mmol, 2 equiv) is added by portions, the temperature raising to 65 °C. The mixture is stirred one more hour at 50 °C. The mixture is concentrated to dryness, the residue suspended in ethyl acetate and washed with water, the aqueous phase reextracted with ethyl acetate. The combined organic phases are dried over magnesium sulfate, filtered, and concentrated to dryness. The residue is purified by chromatography on silica gel (pet. ether−EtOAc 70/30) to give 5.5 g (28%) of 2-[(3*R*)-3-((*tert*-butyldimethylsilanyl)oxy)pyrrolidin-1-yl]butyric acid ethyl ester. δ_H (250 MHz, $CDCl_3$): 0.06 (6H, s), 0.87 (9H, s), 0.96 (3H, t, *J* 7.7), 1.27 (3H, t, *J* 7.3), 1.60−1.80 (1H, m), 1.90−2.10 (1H, m), 2.30−2.45 (1H, m), 2.60 and 2.68 (1H, dd, for one diastereoisomer *J* 6.2; 1.5; for the other one diastereoisomer *J* 7.0; 1.8), 3.15 (1H, dd, *J* 10.5; 2.2 for one diastereoisomer), 3.35 (1H, dd, *J* 10.5; 3.5 for one diastereoisomer), 3.53 (1H, dd, *J* 10.5; 7.5 for one diastereoisomer), 3.72 (1H, dd, *J* 10.5; 6.1 for one diastereoisomer), 4.15 (2H, m), 4.42−4.56 (1H, m), 4.69 and 4.71 (1H, m for the two diastereoisomers). In a 50-mL, three-necked flask fitted with a magnetic stirrer, under inert atmosphere, a solution of *n*-Bu_4NF (10.6 g, 0.036 mol) and the previous ester (5.5 g, 0.016 mol) in THF (100 mL) is stirred overnight at room temperature and concentrated in vacuo, and the residue is diluted with water and extracted with CH_2Cl_2. The organic layer is dried over $MgSO_4$, filtered, and evaporated to dryness, and the residue is purified by chromatography on silica gel (CH_2Cl_2–MeOH 90/10 (v/v)) to give 2-((3*R*)-3-hydroxypyrrolidin-1-yl)butyric acid ethyl ester (2.6 g, 72%). MS *m*/*z* (APCI): 230 (MH^+), 170. In a 250-mL, three-necked flask fitted with a reflux condenser and a magnetic stirrer, 2.23 g (0.01 mmol) of the ester is dissolved in 10 mL of methanol. Gaseous ammonia is bubbled through the solution, and the saturated solution is kept at room temperature for 5 days, while occasionally resaturating with ammonia. After completion of the reaction, the solution is concentrated to dryness. The residue is purified by Prep LC (0.4 kg SiO_2, CH_2Cl_2–MeOH 98/2) to give 0.47 g of the first eluted diastereoisomer **41α** (24%, recrystallized from AcOEt) and 0.92 g of the second eluted diastereoisomer **41*β*** (48%, recrystallized from AcOEt). **41α** HPLC: >99%.

5,5-Dimethyl-3-formylhexanoic Acid Methyl Ester (45b). In a three-necked flask fitted with a Dean−Stark apparatus under argon, a solution of diisobutylamine (4.62 mL from Acros) and 4,4-dimethylpentanal (43**b**)[60](2.5 g, 0.021 mol) in toluene (20 mL) is heated at 130 °C for 2 h and water is extracted. The yellow solution is cooled to room temperature and methyl bromoacetate (3.7 g, 0.024 mol) is added in one portion. The pink solution is stirred at room temperature overnight and 1 h at 90 °C. Water (10 mL) is added at this temperature, and after 1 h, the solution is cooled to room temperature. The organic layer is washed with 1 N HCl and saturated aqueous sodium bicarbonate, dried over magnesium sulfate, filtered, and evaporated to afford an oil which is distilled under reduced pressure (1 mmHg) to afford **45b** as a liquid (1.1 g, 0.05 mol, T_{eb} (1 mmHg): 69−71 °C). Alternatively, alkylation with ethyl bromoacetate can be conducted in the presence of toluene−acetonitrile 1/1 (v/v) as solvent. δ_H (250 MHz, $CDCl_3$): 0.94 (9H, s), 1.22 (1H, dd, *J* 3.1; 12.5), 1.79 (1H, dd, *J* 12.5; 7.3), 2.41 (1H, dd, *J* 15.6; 5.2), 2.66 (1H, dd, *J* 15.6; 9.3), 2.77−2.90 (1H, m), 3.72 (3H, s), 9.73 (1H, s).

3-Formyl-4-phenylbutyric acid methyl ester (45d) (T_{eb} (1 mmHg) = 95−100 °C, 22%) is prepared from 3-formyl-4-phenylbutyric acid methyl ester (20.4 g, 0.15 mol) using the method for **45b**. δ_H (250 MHz, $CDCl_3$): 2.40 (1H, dd, *J* 5.2; 15.6), 2.66 (1H, dd, *J* 7.3; 15.6), 2.66−2.79 (1H, m), 3.0−3.16 (2H, m), 3.70 (3H, s), 7.10−7.39 (5H, m + solvent signal), 9.80 (1H, s).

2-Ethyl-2-methyl-4-oxobutyric Acid Methyl Ester (45f). In a 150-mL, three-necked flask fitted with a magnetic stirrer, under inert atmosphere, methyl 2-methyl-butanoate (8.0 g, 0.069 mol) is added to a solution of LDA (2 M in THF, 30 mL, 0.076 mol) cooled at −78 °C. After 1 h, the allyl bromide (9.99 g, 0.083 mol) diluted in THF (20 mL) is added dropwise. The reaction mixture is stirred at −78 °C (1 h) and room temperature (4 h), quenched with ice water, and extracted with ether. The organic layer is dried on $MgSO_4$, filtered, and concentrated in vacuo to give 2-ethyl-2-methylpent-4-enoic acid ethyl ester (18.43 g) which is used in the next step without further purification. In a 250-mL, three-necked flask fitted with a magnetic stirrer, under inert atmosphere, ozone is bubbled into the crude ester (13.2 g in CH_2Cl_2 (70 mL) at −78 °C until a blue color appears, and Ph_3P (27.1 g, 0.103 mol) is added. The reaction mixture is warmed to room temperature and concentrated to dryness, and the residue is purified by chromatography on silica gel (hexanes−AcOEt 90/10 (v/v)) to give **45f** (7.87 g, 72%). δ_H (250 MHz, $CDCl_3$): 0.86 (3H, t, *J* 7.5), 1.29 (3H, s), 1.66 (2H, q, *J* 7.25), 2.46 (1H, d, *J* 16.56), 2.81 (1H, d, *J* 16.56), 3.70 (3H, s), 9.72 (1H, t, *J* 2.5).

Method B. (2*S*)-2-(4-Neopentyl-2-oxo-1-pyrrolidinyl)-butanamide (50α and 50*β*). In a three-necked flask fitted with a reflux condenser, under argon, a suspension of the aldehyde **45b** (1.7 g, 0.09 mol), (*S*)-2-aminobutanamide (1.58 g, 0.15 mol), and molecular sieves (3 Å from Aldrich) in MeOH is heated at 60 °C for 0.5 h. The suspension is cooled to 0 °C and sodium borohydride (0.55 g, 0.015 mol) is added in portions. After 1 h at room temperature, the reaction mixture is diluted with ether, washed with water, dried over magnesium sulfate, filtered, and evaporated to afford a yellow oil. Methyl 4-{[((1*S*)-1-aminocarbonyl)propyl]amino}butanoate is used directly in the next step without any further purification. In a three-necked flask fitted with a reflux condenser, under argon, the amino ester is dissolved in a 1/1 mixture of toluene and 1,2-dichloroethane (25 mL each) in the presence of hydroxybenzotriazole (2.05 g) and the solution is heated at 90 °C for 2 h and cooled to room temperature. The organic phase is washed successively with saturated aqueous sodium bicarbonate and water, dried over magnesium sulfate, filtered, and evaporated to afford a brown solid (1.8 g) which is purified by column chromatography on silica gel (CH_2Cl_2–MeOH 95/05 (v/v)) to afford (2*S*)-2-(4-neopentyl-2-oxo-1-pyrrolidinyl)butanamide (0.89 g, 0.0036 mol) as a 1/1 mixture of diastereoisomers. Separation of the two isomers is realized by chromatography on a chiral stationary phase (EtOH−hexane 1/1 (v/v)) to afford, after recrystallization in toluene, **50α** and its stereoisomer **50*β***[59] (0.35 g, 7.4% and 0.37 g, 7.8%). **50α** Anal. ($C_{13}H_{24}N_2O_2$): C, H, N.

(2*S*)-2-(3-Benzyl-2-oxo-1-pyrrolidinyl)butanamide (51α and 51*β*). As described for the preparation of **50α**, **45e**[31](4 g, 19 mmol) and **49** (1.98 g, 19 mmol) react to give **51α** (0.818 g, 16%) and **51*β*** (0.772 g, 15%) as white solids. **51α** Anal. ($C_{15}H_{20}N_2O_2$): C, H, N.

(2*S*)-2-(3-Ethyl-3-methyl-2-oxo-1-pyrrolidinyl)butanamide (52α and 52*β*). As described for the preparation of **50α**, **49** (5.08 g, 50 mmol) and **45f** (7.87 g, 50 mmol) react to give **52α** (0.877 g, 8%) and its stereoisomer **52*β***[59] (0.986 g, 9%) as white solids. **52α** Anal. ($C_{11}H_{20}N_2O_2$) N, H, C: calcd, 62.3; found, 63.17.

(2*S*)-2-(4-Ethyl-2-oxo-1-pyrrolidinyl)butanamide (53α and 53*β*). As described for the preparation of **50α**, **49** (866

mg, 8.5 mmol) and **45a**[61] (1 g, 7 mmol) react to give **53α** (130 mg, 1.5%) and its stereoisomer **53*β***[59] (200 mg, 2.3%). **53α** Anal. ($C_{10}H_{18}N_2O_2$): C, H, N.

(2*S*)-2-(4-Benzyl-2-oxo-1-pyrrolidinyl)butanamide (54*β* and 54*β*). As described for the preparation of **50α**, **49** (1.36 g,13.4 mmol) and **43d** (2.75 g, 13.4 mmol) react to give **54α** (0.2 g, 3%) and its stereoisomer **54*β***[59] (0.91 g, 12%). **54α** Anal. ($C_{15}H_{20}N_2O_2$) N, H, C: calcd, 69.20; found, 68.78.

(2*S*)-2-(4-Isopropyl-2-oxo-1-pyrrolidinyl)butanamide (55α and 55*β*). As described for the preparation of **50α**, **49** (3.87 g, 38 mmol) and **45c**[62] (6 g, 38 mmol) react to give **55α** (2.03 g, 25%) and its stereoisomer **55*β***[59] (2.15 g, 27%). **55α** Anal. ($C_{11}H_{20}N_2O_2$) N,H,C: calcd, 53.98; found, 54.43.

Method B-2. 5-Amino-2-(2-oxopyrrolidin-1-yl)pentanoic Acid Amide (56). Rink amide resin (100 g, 0.51 mequiv/g, 100−200 mesh) is placed in a glass vessel and stirred in 20% v/v piperidine/DMF (40 mL) for 0.5 h. The resin is drained and the entire deprotection repeated. The resin is filtered, washed (6 × DMF), and dried. The resin (0.84 g) is suspended in DMF (5 mL) and treated with 9-fluorenylmethoxycarbonyl-*N*-ϵ-*tert*-butyloxycarbonyl-L-ornithine (1.00 g, 1.76 mmol), followed by a solution of 1,3-diisopropyl carbodiimide (5 equiv, 277.6 mg) and 5 equiv of HOBt (297.3 mg) in DMF (5 mL). The reaction is stirred for 1 h at room temperature and then filtered and washed (DMF), and the coupling process is repeated. The resin is filtered, washed (6 × DMF, 6 × CH_2Cl_2), dried, and used as it stands in the next steps. Amide resin (150 mg, 0.051 mmol) is contained within a fritted polypropylene syringe. Removal of the Fmoc group is achieved using 20% piperidine in DMF. To the amino resin is added 4-oxobutyric acid 4-methoxybenzyl ester[63] (0.066 g, 0.3 mmol) in $(MeO)_3CH$ (2 mL). The resin is stirred for 48 h and then fitrered, washed with CH_2Cl_2, and treated with sodium triacetoxyborohydride (19 mg, 0.09 mmol). The reaction is stirred for 18 h at room temperature and then filtered; washed in the solvent sequence MeOH, 3 × CH_2Cl_2, 3 × MeOH; and dried. The resin is suspended in trifluoroacetic acid/H_2O (95/5) with 5% of triisopropylsilane for 4 h with vortex agitation and then filtered and washed (CH_2Cl_2 × 2). The filtrate is concentrated and the residue is dissolved in CH_2Cl_2 (2 mL) and concentrated once more. The desired compounds are purified by LC/MS (Micromass-Gilson, LCZ-Platform, RP-18 column, gradient elution, CH_3CN-H_2O−1% TFA) to afford **56** (0.002 g). HPLC: 65%.

Method B-3. (2*S*)-2-[-2-Oxo-4-propylpyrrolidin-1-yl]butanamide (83α and 83*β*) (1/1 Mixture). *N*-Fmoc-2-aminobutyric amide resin (100 mg, 0.051 mmol; see method B-2) is contained within a fritted polypropylene syringe. Removal of the Fmoc group is achieved using 20% piperidine in DMF. To the amino resin is added 5-hydroxy-4-propylfuran-2-one (from 36.72 mg, 0.25 mmol) in DCE (2 mL). The resin is then treated with acetic acid (15 μL) and sodium triacetoxyborohydride (54 mg, 0.25 mmol). The reaction is stirred for 18 h at room temperature and then filtered; washed with the solvent sequence H_2O/DMF (1:1), DMF, CH_2Cl_2, MeOH; and dried. The resin is suspended in trifluoroacetic acid/CH_2Cl_2 mixture (1/1) for 4 h with vortex agitation, filtered, and washed (CH_2Cl_2 × 2). The filtrate is concentrated, and the residue is dissolved in CH_2Cl_2 (2 mL) and concentrated once more. The desired compounds are purified by LC/MS (Micromass-Gilson, LCZ-Platform, RP-18 column, gradient elution, CH_3CN-H_2O−1% TFA).

Method C Methyl (1-[(1*S*)-1-(Aminocarbonyl)propyl]-5-oxo-3-(3R)-pyrrolidinecarboxylate (57α and 57*β*). In a 10-L, three-necked flask fitted with mechanical stirrer and reflux condenser, under inert atmosphere, 1226 g (12 mol, 1 equiv) of (2S)-2-aminobutanamide and 1912 mL (2150 g, 13.2 mol, 1.1 equiv) of dimethyl itaconate **41** are dissolved in 6.13 L of MeOH. The mixture is brought to reflux for 10 h and cooled slowly to 20 °C over 4 h. It is filtered, the precipitate is washed with MeOH, and the combined organic phases are concentrated to dryness to give 3.283 g of crude intermediate (74%). In a 20-L, three-necked flask fitted with a mechanical stirrer, Rashig column, and distillation arm, under inert atmosphere, the crude intermediate and 84.7 g (891 mmol, 0.1 equiv) of 2-hydroxypyridine are dissolved in 11.6 L of toluene. The mixture is brought to reflux and the methanol formed is distilled off for 8 h, until 480 mL is collected. The temperature in the pot reached 112 °C. The mixture is cooled and concentrated to dryness to give 2187 g of crude amide ester as a mixture of diastereoisomers in a 57.5/42.5 ratio. The two diastereoisomers are separated by preparative LC on a Chiral Phase (Chiralpak AD 100 × 500 mm, EtOH−H_2O 99.9/0.1) column, the eluate is concentrated to dryness to give 968 g of crude **57*β*** (first eluted) and 1052 g of crude **57α** (second eluted). Crude **57*β*** did not crystallize; it is dissolved in 1.5 L of EtOH and kept as such, for further use. Crude **57α** is recrystallized from 2 L of AcOEt to give 676 g of pure **57α**. HPLC: >99%.

1-[(1*S*)-1-(Aminocarbonyl)propyl]-5-oxo-3-pyrrolidinecarboxamide (58). In a 0.5-L, three-necked flask fitted with reflux condenser, magnetic stirrer, and an addition gas tube dipping in the solution, 10 g (0.035 mol) of **57α** is dissolved in 100 mL of methanol. Gaseous ammonia is then bubbled through the solution, and the saturated solution is kept at room temperature for 1 day, while occasionally resaturating with ammonia. After completion of the reaction, the solution is concentrated in vacuo to afford the crude amide **58** (9.6 g, 100%). Anal. ($C_9H_{15}N_3O_3$) N, H, C: calcd, 50.70; found, 50.25.

1-[(2*S*)-1-(aminocarbonyl)propyl]-5-oxo-(3S)-3-pyrrolidinecarboxylic Acid (59). In a three-necked flask, under argon, a solution of 1 N NaOH (126 mL) is added to a solution of the enantiomerically pure ester **57α** (22.62 g, 0.1 mol.) in MeOH cooled at 0 °C. After 1.5 h at this temperature, the reaction is acidified by HCl (1 N, 109 mL), and the solvents are evaporated under vacuum. The residue is extracted with *i*-PrOH and filtered and the filtrate is concentrated in vacuo to afford the crude acid (17.82 g) which is recrystallized from MeCN to produce the enantiomerically pure **59**. Anal. ($C_9H_{14}N_2O_4$): C, H, N

[1-(1-Carbamoylpropyl)-5-oxopyrrolidin-3-yl]carbamic Acid Benzyl Ester (60α and 60*β*). In a three-necked flask, under argon, a solution of the enantiomerically pure **59** (19.06 g, 0.089 mol.), diphenylphosphoryl azide (26.9 g, 0.097 mol), and Et_3N (13.5 mL) in MeCN (225 mL) is heated at 55 °C with formation of N_2. The temperature is kept at 55 °C for 0.5 h and at 70 °C for 2 h and cooled to room temperature. Benzyl alcohol (9.25 mL) is added and the solution is refluxed for 4 h, cooled to room temperature, and concentrated in vacuo. The crude carbamate is purified by chromatography on silica gel (AcOEt−MeOH−NH_4OH 95/04/01 (v/v)) to afford the two diasteroisomeric carbamates **60*β*** (2.64 g, 9.3%) and its stereoisomer **60α** (11.9 g, 42%). **60α** and **60*β*** Anal. ($C_{15}H_{19}N_3O_4$): C, H, N.

[1-(1-Carbamoylpropyl)-5-oxopyrrolidin-3-yl]carbamic Acid Methyl Ester (61). In a 50-mL, three-necked flask fitted with a magnetic stirrer, under inert atmosphere, $(PhO)_2PON_3$ (2.37 mL, 11 mmol) is added to a solution of **59** (2.14 g, 10 mmol) and Et_3N (1.53 mL, 11 mmol) at room temperature. After 1 h at 60 °C, the reaction is cooled to room temperature, quenched with MeOH (12.5 mL), refluxed for 4 h, and stirred overnight at room temperature. The reaction mixture is concentrated in vacuo and the residue is purified by column chromatography on silica gel (CH_2Cl_2−*i*-PrOH−NH_4OH 89/10/1 (v/v)) to give the major (0.7 g) and the minor (0.18 g) diastereoisomer. The major diastereoisomer is lyophilized and dried in vacuo (0.01 mmHg) but always contains residual *i*-PrOH. The residue is dissolved in PhMe−H_2O, concentrated to dryness, and lyophilized to give **61** (0.5 g, 21%). Anal. ($C_{10}H_{17}N_3O_4$) H, C: calcd, 49.37; found, 48.37. N: calcd, 17.28; found, 16.81.

2-[4-Amino-2-oxo-1-pyrrolidinyl]butanamide (62). In a 0.25-L pressure jar, under inert atmosphere, 11.9 g (0.0037 mmol) of **60α** and Pd on charcoal (10% w/w, 0.2 g) are dissolved in EtOH (300 mL), and the mixture is hydrogenated on a Parr hydrogenator at a maximum of 20 psi H_2 pressure. After 20 h, the mixture is degassed and filtered on a Celite/Norite pad, and the filtrate is concentrated in vacuo, to give the crude

fluoro alkane which is recrystallized from PhMe to afford **62** (6.99 g, quantitative). HPLC: >99%.

(2*S*)-2-[4-((4*R*)-Hydroxymethyl)-2-oxo-1-pyrrolidinyl]-butanamide (63). In a 2-L three-necked flask fitted with mechanical stirrer and reflux condenser, under inert atmosphere, a solution of 133 g (583 mmol, 1 equiv) of **57α** in 200 mL of EtOH is added to 300 mL of EtOH, and the mixture is cooled to 0 °C. Solid $NaBH_4$ (66.2 g, 1.74 mol, 12 equiv) is then added by portions over 1.5 h, all the while the temperature being maintained between 2 and 4 °C. After 2 h, the temperature is raised to 12 °C for 1 h and lowered again to 2−4 °C. Then, 240 mL of a saturated solution of NH_4Cl is added dropwise over 1 h, followed by 120 mL of acetone, and the mixture is left overnight at room temperature. The mixture is filtered and the precipitate washed with 3 × 70 mL of EtOH, and the combined organic fractions are concentrated to dryness to give 148 g of crude **63**. It is suspended in 300 mL of CH_2Cl_2, stirred for 0.5 h, filtered, washed with 2 × 100 mL of CH_2Cl_2, and dried to give 114 g of pure **63** (98%). Anal. ($C_9H_{16}N_2O_3$) N, H, C: calcd, 53.98; found, 54.43.

{1-[(1*S*)-1-(Aminocarbonyl)propyl]-5-oxo-3((3*R*)-pyrrolidinyl}methylmethanesulfonate (64). In a 4-L, three-necked flask fitted with mechanical stirrer, dropping funnel, and reflux condenser under inert atmosphere, 114 g (569 mmol, 1 equiv) of **63** is dissolved in 2 L of CH_2Cl_2 and cooled to 0 °C. Dry triethylamine (158.5 mL, 115 g, 2 equiv) is added in one portion, followed by dropwise addition of a solution of 66.3 mL (96.2 g, 1.5 equiv) of methanesulfonyl chloride in 190 mL of CH_2Cl_2 over 1 h, all the while the temperature being maintained below 4 °C. After 4 h, 7.5 mL of methanesulfonyl chloride and 15 mL of triethylamine are added, and the mixture is kept overnight in the refrigerator. The mixture is filtered, the residue is washed with CH_2Cl_2, and the combined organic phases are concentrated to dryness to give 216 g of crude **64**. It is purified by Prep LC in several batches (1 kg SiO_2, CH_2Cl_2–EtOH 100/0 → 96/4) to give 109 g of pure **64** (69%). Anal. ($C_{10}H_{18}N_2O_5S$): C, H, N, S.

2-(4-Methyl-2-oxopyrrolidin-1-yl)butyramide (65). In a 2-L, three-necked flask fitted with mechanical stirrer and reflux condenser, under inert atmosphere, 109 g (390 mmol, 1 equiv) of **64** is dissolved in 700 mL of DME−MeOH (6/4 (v/v)). Sodium iodide (87.6 g, 590 mmol, 1.5 equiv), followed by zinc (383 g, 5.83 mol), is added in one portion. The mixture is brought to reflux in 0.3 h and stirred overnight. Sodium iodide (29.2 g, 196 mmol, 0.5 equiv) is added and reflux continued for a total of 44 h. After cooling to 40 °C, the mixture is filtered, the precipitate is washed with EtOH, and the combined organic fractions are concentrated to dryness. The residue is purified by chromatography on silica gel (CH_2Cl_2–MeOH 98/02 (v/v)) and recrystallized from AcOEt to give 63 g of pure **65** (83%). Anal. ($C_9H_{16}N_2O_2$) N, H; C: calcd, 58.67; found, 59,23.

(2*S*)-2-[(4*R*)-4-(Azidomethyl)-2-oxo-1-pyrrolidinyl]butanamide (66). In a 3-L, three-necked flask fitted with mechanical stirrer and reflux condenser, under inert atmosphere, 89.7 g (322 mmol, 1 equiv) of **64** is dissolved in 300 mL of acetonitrile. Sodium azide (27.3 g, 419 mmol, 1.3 equiv) is added in one portion, with 150 mL of acetonitrile. The mixture is brought to reflux in 0.3 h and stirred overnight. Sodium azide (3.1 g, 48 mmol, 0.2 equiv) is added and reflux continued for a total of 44 h. After cooling to 10 °C, the mixture is filtered, the precipitate is washed with 3 × 50 mL of acetonitrile, and the combined organic fractions are concentrated to dryness to give 77.3 g of crude **66**. It is crystallized from 150 mL of AcOEt at 10 °C to give 60 g of pure **66** (82%). Anal. ($C_9H_{15}N_5O_2$): C, H, N.

(2*S*)-2-[(4*R*)-4-(Fluoromethyl)-2-oxo-1-pyrrolidinyl]butanamide (67). In a 25-mL, three-necked flask fitted with a magnetic stirrer and reflux condenser, under inert atmosphere, neat $(^nBu)_4NF(H_2O)_3$ is heated at 55 °C under vacuum (0.5 mmHg) for 11 h. It is cooled to room temperature and 0.85 g (3.0 mmol, 1 equiv) of **64** is added. After 8 h at 60 °C, the reaction is quenched with brine (30 mL) and extracted with CH_2Cl_2. The organic layer is dried with $MgSO_4$, filtered, and evaporated in vacuo to afford, after purification by HPLC on silica gel (CH_2Cl_2–MeOH 95/5 (v/v)) and recrystallization (AcOEt/*i*-Pr_2O 1/2), **67** (0.25 g, 55%). Anal. ($C_9H_{15}FN_2O_2$): C, H, N.

(2*S*)-2-[(4*R*)-4-(Chloromethyl)-2-oxo-1-pyrrolidinyl]butanamide (68). In a 3-L, three-necked vessel, fitted with mechanical stirrer and reflux condenser under inert atmosphere, 84.4 g (0.42 mol, 1 equiv) of **63** is dissolved in 1680 mL of acetonitrile. C_2Cl_6 (150 g, 0.63 mol, 1.2 equiv) is added, followed by triphenylphosphine (166.8 g, 1.2 equiv). The mixture is heated to 70 °C for 2 h, cooled to room temperature, and concentrated in vacuo. The residue, suspended in Et_2O, is extracted with water and the aqueous layer is concentrated in vacuo. The crude chloride is purified two times by HPLC on silica gel (first elution, CH_2Cl_2–MeOH 95/5 (v/v); second elution, MeO*t*Bu−CH_2Cl_2–*i*-PrOH 45/45/1 (v/v)). Recrystallization from toluene and removal of the residual solvent by solid−liquid extraction in Et_2O give **68** (42.93 g, 47%). Anal. ($C_9H_{15}ClN_2O_2$): C, H, N.

(2*S*)-2-[(4*R*)-4-(Bromomethyl)-2-oxo-1-pyrrolidinyl]butanamide (69). In a 100-mL, three-necked vessel, fitted with a magnetic stirrer and reflux condenser under inert atmosphere, 2.30 g (0.011 mol, 1 equiv) of **63** is dissolved in 50 mL of acetonitrile. Triphenylphosphine (3.31 g, 1.1 equiv) is added followed by the addition in 0.2 h of 4.19 g of CBr_4 (0.012 mol, 1.1 equiv) at 0 °C. The mixture is heated to 80 °C for 1 h and cooled to 0 °C, and a second portion of triphenylphosphine (3.31 g, 1.1 equiv) and 4.19 g of CBr_4 (0.012 mol, 1.1 equiv) are added. After 1 h at 80 °C, the reaction mixture is cooled to room temperature and concentrated in vacuo. The residue suspended in Et_2O and water (1/1 (v/v)) is filtrated and the organic layer is discarded. The precipitate and the aqueous layer are combined and extracted with CH_2Cl_2 (2×). The organic layer is concentrated in vacuo and the residue is triturated with Et_2O until completed elimination of Ph_3PO. The residue is recrystallized three times (*i*-PrOH, AcOEt, and then MeCN) to afford **69** (0.31 g, 20%). Anal. ($C_9H_{15}BrN_2O_2$): C, H, N.

(2*S*)-2-[4-((4*R*)-Iodomethyl)-2-oxo-1-pyrrolidinyl]butanamide (70). In a 10-L, three-necked vessel, fitted with mechanical stirrer and reflux condenser under inert atmosphere, 400 g (2 mol, 1 equiv) of (2*S*)-2-[4-(hydroxymethyl)-2-oxo-1-pyrrolidinyl]butanamide (**63**) is dissolved in 3 L of acetonitrile. Then, 629 g (2.4 mol, 1.2 equiv) of triphenylphosphine is added, followed by 608 g (2.4 mol, 1.2 equiv) of iodine in three portions over 0.1 h. The mixture is heated to 60 °C in 0.5 h and stirred at that temperature for 5 h. After cooling, the mixture is concentrated to dryness, and the residue is suspended in a solution of 750 g of $Na_2S_2O_3$ in 10 L of water and stirred at 50 °C for 4 h. The precipitate is filtered off and washed with 3 × 1 L of water. The combined aqueous phases are treated with 1 kg of NaCl and extracted with 6 × 1 L of CH_2Cl_2. The combined organic phases are dried over $MgSO_4$, filtered, and concentrated to dryness to give 482 g of crude **70**. It is crystallized from toluene. Several crops are recrystallized together from ethyl acetate to give 425 g of pure **70** (68%). Anal. ($C_9H_{15}IN_2O_2$): C, H, N.

(2*S*)-2-{(4*R*)-4-[(Methylsulfanyl)methyl]-2-oxo-1-pyrrolidinyl}butanamide (71). In a 50-mL, three-necked flask, fitted with a magnetic stirrer under inert atmosphere, 0.5 g (1.6 mmol, 1 equiv) of **70** is dissolved in 15 mL of THF. MeSNa (0.226 g, 3.2 mmol, 2 equiv) is added at −40 °C. The reaction mixture raised to −10 °C and additional THF (5 mL) is added to allow a good stirring of the white suspension. After 5 h at −10 °C, the reaction mixture is allowed to warm to room temperature, poured in water, and extracted with AcOEt. The organic phase is dried with $MgSO_4$, filtered, and concentrated in vacuo. The crude thioether is purified by chromatography on silica gel (CH_2Cl_2–MeOH 95/05) to give **71** (0.23 g, 62%) as an oil. HPLC: 98%.

(2*S*)-2-[2-Oxo-4-(1-pyrrolidinylmethyl)-1-pyrrolidinyl]-butanamide (72). In a 25-mL, three-necked flask, fitted with mechanical stirrer and reflux condenser under inert atmosphere, 0.5 g (1.6 mmol, 1 equiv) of **70** is dissolved in 10 mL of EtOH. Pyrrolidine (0.28 mL, 3.38 mmol, 2.1 equiv) is added

and the mixture is brought to reflux for 8 h and stirred overnight at room temperature. The mixture is concentrated to dryness, purified by Prep LC (400 g SiO_2, CH_2Cl_2–MeOH–NH_4OH 94/5/1) and crystallized hexanes–ethyl acetate to give 90 mg of pure **72** (34%). Anal. ($C_{13}H_{23}N_3O_2$): C, H, N.

{1-[(1*S*)-1-(Aminocarbonyl)propyl]-5-oxo-3-pyrrolidinyl}methyl nitrate (73). In a 500-mL, three-necked flask, fitted with mechanical stirrer and reflux condenser under inert atmosphere, 8.10 g (26 mmol, 1 equiv) of **70** is dissolved in 250 mL of acetonitrile. Silver nitrate (4.86 g, 28.6 mmol, 1.1 equiv) is added and the mixture is brought to reflux. After 2 h, 440 mg (2.8 mmol, 0.1 equiv) of silver nitrate is added, and reflux is continued for a total of 4 h. After cooling, the mixture is concentrated to dryness and purified by Prep LC (200 g SiO_2, CH_2Cl_2–MeOH–NH_4OH 96/5.4/0.6) to give 5.7 g of crude **73**. It is crystallized from 50 mL of ethyl acetate to give 4.13 g of pure **73** (65%). Anal. ($C_9H_{15}N_3O_5$): C, H, N.

(2*S*)-2-(2-Oxo-(4*R*)-4-{[(phenylsulfonyl)amino]methyl}-1-pyrrolidinyl)butanamide (75). In a 500-mL pressure jar, under inert atmosphere, 900 mg of 10% Pd adsorbed on charcoal is suspended in 100 mL of ethanol. A solution of 8.7 g (38 mmol) of (2*S*)-2-[4-(azidomethyl)-2-oxo-1-pyrrolidinyl]-butanamide (**66**) in 150 mL of ethanol is added and the mixture hydrogenated on a Parr hydrogenator at a maximum of 30 psi H_2 pressure for 2 h. The mixture is degassed and filtered on a Celite/Norite pad, the residue is washed with 2 × 100 mL EtOH, and the combined filtrates are concentrated to dryness, to give 7.93 g of crude of (2*S*)-2-[4-(aminomethyl)-2-oxo-1-pyrrolidinyl]butanamide hydrochloride (**74**, 100% yield), used as such in the next step. In a 25-mL, three-necked flask, fitted with a magnetic stirrer under inert atmosphere, 1 g (4.24 mmol, 1 equiv) of **74** is suspended in 10 mL of CH_2Cl_2. Triethylamine (1.3 mL, 940 mg, 2.2 equiv) is added and the mixture cooled to 0 °C. A solution of 0.60 mL (820 mg, 1.1 equiv) of benzenesulfonyl chloride in 2 mL of CH_2Cl_2 is added dropwise over 0.25 h, and the mixture is stirred for 3 h at room temperature. The mixture is diluted with 20 mL of CH_2Cl_2 and washed with 2 × 15 mL of brine, dried over $MgSO_4$, and concentrated to dryness, and the residue is purified by Prep LC (350 g of SiO_2, CH_2Cl_2–MeOH–NH_4OH 95.6/4/0.4 → 93.4/6/0.6) to give 1.1 g of pure **75** (75%). It is crystallized from 30 mL of acetonitrile. Anal. ($C_{15}H_{21}N_3O_4S$): C, H, N.

(2*S*)-2-{(4*R*)-4-[(5-Methyl-1*H*-1,2,3-triazol-1-yl)methyl]-2-oxo-1-pyrrolidinyl}butanamide (76). In a 50-mL, three-necked flask, fitted with a magnetic stirrer and reflux condenser under inert atmosphere, 1 g (4.44 mmol, 1 equiv) of **66** is suspended in 20 mL of toluene. 1-(Triphenylphosphoranylidene)acetone (1.55 g, 4.88 mmol, 1.1 equiv) is added, and the mixture is heated to 80 °C for 24 h. After cooling, the mixture is concentrated to dryness and purified by Prep LC (1 kg SiO_2, CH_2Cl_2–MeOH–NH_4OH 94.5/5/0.5) It is suspended in 15 mL of water and lyophilized to give 240 mg of pure **76** as a clear oil (42%). HPLC: >99%.

2-Methyl-2-propylsuccinic Acid 1-Methyl Ester (79c). In a 150-mL, three-necked flask fitted with a magnetic stirrer, under inert atmosphere, methyl 2-methylpentanoate (**78c**) (7.0 g, 0.054 mol) is added to a solution of LDA (2 M in THF, 30 mL, 0.059 mol) cooled at −78 °C. After 1 h, the *tert*-butyl bromoacetate (12.58 g, 0.065 mol) diluted in THF (20 mL) is added dropwise. The reaction mixture is stirred at −78 °C (1 h) and room temperature (4 h), quenched with ice water, and extracted with ether. The organic layer is dried on $MgSO_4$, filtered, and concentrated in vacuo to give 2-methyl-2-propylsuccinic acid 4-*tert*-butyl ester 1-methyl ester (15.21 g) which is used in the next step without further purification. In a 250-mL, three-necked flask fitted with a magnetic stirrer, under inert atmosphere, the crude ester (13.2 g) is stirred in TFA (70 mL) and CH_2Cl_2 (100 mL) for 48 h at room temperature. The reaction mixture is concentrated to dryness to give **79c** (13.07 g). δ_H (250 MHz, $CDCl_3$): 0.90 (3H, t, *J* 7.5), 1.20−1.40 (5H, m + s at 1.29), 1.51−1.67 (2H, m), 2.46 (1H, d, *J* 13.8), 2.70 (1H, d, *J* 13.8), 3.69 (3H, s), 6.78 (1H, s (broad)).

2,2-Dipropylsuccinic acid 1-methyl ester (79d) is synthesized using the same method as for **79c** starting from 2-propyl-pentanoic acid methyl ester **78d**. δ_H (250 MHz, $CDCl_3$): 0.90 (6H, t, *J* 7.5), 1.10−1.36 (4H, m), 1.65 (4H, t, *J* 7.5), 2.67 (2H, s), 3.69 (3H, s), 6.92 (1H, s (broad)).

2-(Cyclopropylmethyl)succinic Acid 1-Methyl Ester (79b). In a 250-mL, three-necked flask fitted with a magnetic stirrer, under inert atmosphere, monomethyl succinate (7.5 g, 0.057 mol) in THF (100 mL) cooled at −78 °C is added dropwise via cannula to a solution of LDA (2 M in THF, 62.7 mL) and HMPA (51 g, 0.285 mol) in THF (220 mL) at −78 °C. After 1 h, $C_3H_5CH_2Br$ (10.0 g, 0.074 mol) is added dropwise and the solution turned from red to yellow. After 2 h at −78 °C, the reaction is quenched carefully by adding HCl (3 M) in Et_2O, warmed to room temperature, and filtered. The filtrate is concentrated in vacuo and the residue purified by chromatography on silica gel (CH_2Cl_2–EtOH–AcOH 96/3.6/0.4 (v/v)) to give **79b** (7.77 g, 73%). δ_H (250 MHz, C_2D_6SO): 0.0−0.1 (2H, m), 0.32−0.48 (2H, m), 0.57−0.78 (1H, m), 1.44 (2H, t, *J* 8.4), 2.37−2.9 (3H, m + solvent signal), 3.62 (3H, s). The crude is contaminated by 50% of the starting materiel (NRM).

4-(Cyclopropylmethyl)dihydrofuran-2-one (81b). In a 500-mL, three-necked flask fitted with a magnetic stirrer, KOH (2.4 M, 17 mL) is added dropwise to **79b** (7.77 g, 0.041 mol) in MeOH (20 mL) at 0 °C. The reaction mixture is concentrated in vacuo and the residue dissolved in EtOH and cooled to 0 °C. Powdered $CaCl_2$ (11.58 g, 0.11 mol) and $NaBH_4$ (6.3 g, 0.16 mol dissolved with KOH (1.12 g) in EtOH (80 mL)) are added successively at 0 °C. The reaction mixture is stirred overnight at room temperature and quenched with HCl (6 M, 100 mL), and the organic solvents are evaporated carefully. The residue is diluted in water and extracted with CH_2Cl_2, and the organic layer is dried on $MgSO_4$, filtrated, and evaporated to give **81b** (3.76 g, 64%) which is used without further purification. δ_H (250 MHz, C_2D_6SO): 0.0−0.1 (2H, m), 0.27−0.44 (2H, m), 0.54−0.73 (1H, m), 0.94−1.38 (2H, m), 2.03−2.71 (3H, m + solvent signal), 3.84 (1H, dd, *J* 8.4; 8.4), 4.34 (1H, dd, *J* 8.8; 8.8). The crude is contaminated by 28% (NMR) of γ-butyrolactone.

4-Methyl-4-propyldihydrofuran-2-one (81c) is synthesized using the same method as for **81b** starting from **79c**. δ_H (250 MHz, $CDCl_3$): 0.94(3H, t, *J* 6.25), 1.16 (3H, s), 1.21−1.51 (4H, m), 2.23 (1H, d, *J* 17.5), 2.36 (1H, d, *J* 17.5), 3.94 (1H, d, *J* 10.0), 4.02 (1H, d, *J* 10.0).

4,4-Dipropyldihydrofuran-2-one (81d) is synthesized using the same method as for **81b** starting from **79d**. δ_H (250 MHz, $CDCl_3$): 0.94 (6H, t, *J* 5.0), 1.14−1.55 (8H, m), 2.32 (2H, s), 4.01 (2H, s).

4-*n*-Propylbutyrolactone (81a). In a 2-L, three-necked flask under argon, *n*-PrMgBr (2.0 M in ether, 820 mL, 1.64 mol) is added dropwise to a suspension of CuI (159.4 g, 0.82 mol) in dry Et_2O (450 mL) cooled at −20 °C. After 0.5 h, the solution is cooled to −40 °C, and TMSCl (89.09 g, 0.82 mol) is added dropwise followed by 2,3-furanone **80** (68.9 g, 0.82 mol) dissolved in dry Et_2O (addition time: 0.5 h). The suspension is allowed to warm to room temperature and hydrolyzed with saturated ammonium chloride. The aqueous layer is extracted with AcOEt (3×), washed with water, dried over magnesium sulfate, and evaporated to dryness to afford the 4-*n*-propylbutyrolactone (**81a**, 103 g). It is used in the next step without further purification (distillation led to partial decomposition of the compound). δ_H (250 MHz, $CDCl_3$): 0.98 (3H, t, *J* 8.2), 1.22−1.57 (4H, m), 2.15 (1H, dd, *J* 5.4; 16.1), 2.45−2.67 (2H, m), 3.89 (1H, dd, *J* 8.7; 8.7), 4.41 (1H, dd, *J* 8.7; 8.7).

4-Chlorononanoic Acid Methyl Ester (82e). To a solution of γ-nonalactone **81e** (0.32 mL, 2 mmol) in thionyl chloride (164 μL, 2.25 mmol) is added zinc chloride (12 mg, 0.088 mmol) at room temperature and the mixture is stirred for 24 h. Excess methanol is added and the reaction mixture is stirred for 0.2 h and then concentrated under reduced pressure to give **82e** used as such. MS *m*/*z* (EI): 175 ($M^{+\bullet}$),130, 96, 74.

Method D-1. (2*S*)-2-[2-Oxo-4-propylpyrrolidin-1-yl]butanamide (83β and 83α). In a three-necked flask, under argon, TMSI (51 mL) is added to a solution of the crude **81a** (103.04 g, 0.805 mol) in CH_2Cl_2 (820 mL) cooled at 0 °C. The solution is stirred for 2 h at room temperature and hydrolyzed

with 1 N HCl (870 mL) and then $Na_2S_2O_3$ (10% w/w, 300 mL). The aqueous layer is extracted with CH_2Cl_2, and the combined organic phase is washed with brine, dried over magnesium sulfate, and concentrated in vacuo to afford the crude 3-(iodomethyl)hexanoic acid (148.48 g). It is used in the next step without further purification. δ_H (250 MHz, $CDCl_3$): 1.80−2.05 (2H, m), 2.20 (2H, t), 2.40−2.60 (2H, t), 5.10−5.20 (2H, m), 5.15−5.80 (1H, m). In a three-necked flask fitted with a reflux condenser, under argon, a solution of thionyl chloride (138 g, 1.16 mol) and the crude 3-iodomethyl-hexanoic acid (148.48 g) in benzene (150 mL) is stirred for 24 h at room temperature. The solvents are evaporated in vacuo and the residue is distilled (0.32 mmHg, T_{eb} = 85−90 °C) to afford the crude 3-(iodomethyl)hexanoic acid chloride **82a** (120 g) contaminated by iodine. δ_H(250 MHz, $CDCl_3$): 0.92 (3H, t, *J* 5.2), 1.90−2.05 (2H, m), 2.15 (2H, t), 2.90−3.10 (2H, m), 3.25 (1H, dd), 3.35 (1H, dd), 5.10−5.20 (2H, m), 5.15−5.80 (1H, m). In a three-necked flask, under argon, the acid chloride **82a** (119.5 g, 0.43 mol) in CH_2Cl_2 (640 mL) is added dropwise to a mechanically stirred suspension of molecular sieves (72 g), powdered KOH (72.8 g), anhydrous Na_2SO_4 (72.8 g), tetra-*n*-butylammonium bromide (7.0 g, 0.02 mol), and *S*-2-aminobutyramide ($[\alpha]^{25}_D$ = +19.35°) (66.6 g, 0.65 mol) in CH_2Cl_2 (1500 mL) cooled at 0 °C. The solution is stirred for 5 h at −5 °C, powdered KOH is added (15.6 g), and the stirring is continued overnight at −5 °C. The reaction mixture is filtered on Hyflocel and the solvent is evaporated in vacuo. The crude reaction mixture is purified successively by chromatography on silica gel (AcOEt−*i*-PrOH 97/03 (v/v)) and preparative chromatography on a chiral stationary phase (hexanes−EtOH) to afford the two isomers of **83*β*** (36.26 g) and **83α** (39.37 g) after recrystallization in *i*-Pr_2O. **83α** and **83*β*** Anal. ($C_{11}H_{20}N_2O_2$): C, H, N.

(2*S*)-2-(2-Oxopyrrolidin-1-yl)propionamide (84) is synthesized using the same procedure as for **83α**. (2*S*)-2-Aminopropionamide[64] reacts with 4-chlorobutyryl chloride to give **84** (recrystallized from AcOEt). HPLC: 100%.

(2*S*)-2-[2-Oxo-4-butylpyrrolidin-1-yl]butanamide (86) is synthesized using the same procedure as for **83α** starting from *n*-BuLi without separation of the two diastereoisomers. Anal. ($C_{12}H_{22}N_2O_2$) N, H: calcd, 9.80; found, 9.32. N: calcd, 63.69; found, 63.09.

2-[4-(Cyclopropylmethyl)-2-oxo-1-pyrrolidinyl]butanamide (87α and 87*β*) is synthesized using the same procedure as for **83α** starting from **81b**. **87α** Anal. ($C_{12}H_{20}N_2O_2$) C, N, H: calcd, 8.99; found, 9.58.

(2*S*)-2-(4-Methyl-2-oxo-4-propyl-1-pyrrolidinyl)butanamide (88 α and 88*β*) is synthesized using the same procedure as for **83α** starting from **81c** leading after HPLC on a chiral phase to **88*β***[59] (first eluted, an oil) and its stereoisomer **88α** (second eluted, recrystallized from *i*-Pr_2O). **88α** Anal. ($C_{12}H_{22}N_2O_2$) C, H: calcd, 9.72; found, 10.19. N: calcd, 12.37; found, 12.79.

(2*S*)-2-(2-Oxo-4,4-dipropyl-1-pyrrolidinyl)butanamide (89) (recrystallized from *i*-Pr_2O) is synthesized using the same procedure as for **83α** starting from **81d**. Anal. ($C_{14}H_{26}N_2O_2$): C, H, N.

3,3-Dimethyl-2-(2-oxopyrrolidin-1-yl)butanamide (85) is synthesized using the same procedure as for **83α** starting from the *tert*-butylglycinamide and the 4-chlorobutyryl chloride.

Method D-2. (2*S*)-2-(5-Nonyl-2-oxo-1-pyrrolidinyl)butanamide (90). To a solution of **82e** (2 mmol) in DMF (2 mL) are successively added (2*S*)-2-aminobutyramide (1 g, 10 mmol), 300 mg of sodium iodide (2 mmol), and 276 mg of potassium carbonate (2 mmol). The mixture is stirred overnight at 60 °C. The solids are filtered and washed by CH_2Cl_2 (2 × 2 mL). The filtrate is concentrated under reduced pressure to give 4-(1-carbamoylpropylamino)nonanoic acid methyl ester used as such for the cyclization. In a 50-mL, three-necked flask fitted with a magnetic stirrer, under inert atmosphere, the amino ester is heated at 80 °C in 1/1 MeOH−AcOH for 10 h and concentrated in vacuo. The residue is purified by chromatography on silica gel (CH_2Cl_2–MeOH 98/02 (v/v)) to afford **90** (3.4 mg, 7%). HPLC: >90%.

(2*S*)-2-(3-Methyl-2-oxopyrrolidin-1-yl)butyramide (91α and 91*β*) is synthesized using the same procedure as for **90** starting from (2*S*)-2-aminobutyramide and 4-bromo-2-methylbutyric acid ethyl ester.[65] The diastereoisomers are separated by chromatography on silica gel (CH_2Cl_2–MeOH−NH_4OH 96/3.8/02 (v/v)) leading to **91α** and its stereoisomer **91*β***[59]**. 91α** Anal. ($C_9H_{16}N_2O_2$) N, H, C: calcd, 58.67; found, 59.08.

2-(2-Methyl-5-oxopyrrolidin-1-yl)butyramide (92) is synthesized using the same procedure as for **90**. (2*S*)-2-Aminobutyramide and 4-bromopentanoic acid ethyl ester **82f** [66] react to give the two stereochemically pure diastereoisomeric 4-(1-carbamoyl-propylamino)pentanoic acid ethyl ester separation by chromatography on silica gel (CH_2Cl_2–MeOH−NH_4OH 96/3.8/02 (v/v)). Cyclization of the second-eluted isomer in MeOH−AcOH leads to **92** after lyophilization**.** HPLC: >99%.

2-(2-Oxopyrrolidin-1-yl)isobutyramide (93). In a 500-mL, three-necked flask fitted with a magnetic stirrer, under inert atmosphere, a solution of 2-amino-2-methylpropionic acid methyl ester (24.35 g, 0.208 mol), Et_3N (39 mL), and 4-bromobutyrate ethyl ester [67] (40.56 g, 0.208 mol) is heated at 80 °C for 10 h, cooled, and filtered, and the filtrate is evaporated to dryness. The amino diester (39.5 g) is directly cyclized without further purification. In a 100-mL, three-necked flask fitted with a magnetic stirrer, under inert atmosphere, 2-hydroxypyridine (1.61 g, 0.017 mol) and the amino ester (33.5 g) are heated at 120 °C overnight. The reaction mixture is distilled in a Kugelrhör apparatus (T_{eb} = 150−210, 0.001 mmHg) and the main fraction is recrystallized from Et_2O−hexane to give 2-methyl-2-(2-oxopyrrolidin-1-yl)propionic acid methyl ester (18.03 g, 57%) as a white solid. MS *m/z* (EI): 185 ($M^{+\bullet}$). In a 100-mL, three-necked flask fitted with a magnetic stirrer, under inert atmosphere, a solution of 2-methyl-2-(2-oxopyrrolidin-1-yl)propionic acid methyl ester (14.6 g, 0.079 mol) and NaOH (3.4 g, 0.0084 mol) is heated at 80 °C for 1.5 h, cooled to room temperature, acidified with HCl (12 N, 7.5 mL), and extracted with CH_2Cl_2, and the organic layer is dried on $MgSO_4$ and concentrated in vacuo. The residue is recrystallized from *i*-PrOH to give 2-methyl-2-(2-oxopyrrolidin-1-yl)-propionic acid (8.7 g). MS *m/z* (EI): 171 ($M^{+\bullet}$). In a three-necked flask fitted with a reflux condenser, under argon, a solution of thionyl chloride (6.66 g, 0.056 mol) and 2-methyl-2-(2-oxopyrrolidin-1-yl)propionic acid (8.7 g) in benzene (50 mL) is stirred for 24 h at room temperature. The solvents are evaporated in vacuo and the crude acid chloride is used in the next step without further purification. In a 50-mL, three-necked flask fitted with a magnetic stirrer, under inert atmosphere, a solution of NH_4OH (40 mL) is added carefully at room temperature to 2-methyl-2-(2-oxopyrrolidin-1-yl)-propionyl chloride (1.91 g) dissolved in PhMe (50 mL). After 2.5 h, the solvents are evaporated, and the residue is purified by chromatography on silica gel (CH_2Cl_2–MeOH 95/5 (v/v)) to give **93** (0.8 g, 42%). HPLC: >99%.

Method E. 1-((1*S*)-1-Carbamoylpropyl)-2-oxopyrrolidine-3-carboxylic Acid (95). In a 4-L, three-necked flask fitted with a mechanical stirrer, under inert atmosphere, a solution of 6,6-dimethyl-5,7-dioxaspiro[2.5]octane-4,8-dione (**94**) (167.9 g, 0.98 mol) and (2*S*)-2-aminobutanamide (**49**) (165.5, 1.65 mol) in MeCN (2.5 l) is warm to 65 °C for 2 h. Another portion of **94** (16.8 g, 0.098 mol) is added. After 3.5 h at 60 °C, the reaction mixture is left overnight at room temperature and the precipitate is filtered, dissolved in water, and purified on ion-exchange resin (AG50W-X4) with water, and the acidic fractions (pH <2) are collected to afford **95** (150 g, 71%). δ_H (250 MHz, DMSO): 0.8 (3H, t, *J* 8.3), 1.46−1.79 (2H, m, *J* 7.3), 2.04−2.38 (2H, m, *J* 8.3), 3−3.67 (3H, m + H_2O signal), 4.34 (1H, dd, *J* 6.2), 6.97 (1H, s (broad)), 7.13 and 7.44 (1H, 2s (broad)),12.00 and 12.90 (1H, s (broad)).

(2*S*)-2-(3-Hydroxymethyl-2-oxopyrrolidin-1-yl)butyramide (96α and 96*β*). In a 6-L, three-necked flask fitted with a mechanical stirrer, under inert atmosphere, CH_3I (447 g, 3.15 mol) is added dropwise to a suspension of K_2CO_3 (132 g, 0.954 mol) and **95** (135 g, 0.63 mol) in acetone (3900 mL) at room temperature. The mixture is refluxed for 2 h, and a second portion of CH_3I (447 g, 3.15 mol) is added dropwise.

The reaction mixture is left overnight at room temperature, refluxed 4 h, cooled to room temperature, and concentrated in vacuo. The filtrate is extracted with AcOEt and evaporated to dryness to afford the crude methyl ester (150 g) which is used without further purification. In a 2-L, three-necked flask fitted with a magnetic stirrer, under inert atmosphere, $NaBH_4$ (30.9 g, 0.82 mol) is added to a mixture of the crude methyl ester (50 g, ~0.22 mol) in *t*-BuOH at room temperature. After 2 h at 80 °C, the reaction is cooled to room temperature and quenched with water (1 l), and *t*-BuOH is removed in vacuo (bath temperature 30 °C). The aqueous layer is saturated with NaCl, lowered to pH 6.8, extracted with $CHCl_3$–MeOH (80/20 (v/v)), and concentrated to dryness to afford the crude alcohol. The two diastereoisomers are separed by three successive HPLC on silica gel (CH_2Cl_2–MeOH 92/08 (v/v)). **96α** (1.01 g, 2.3%) is recrystallized from EtOH (below 50 °C) and **96*β*** from MeCN (0.75 g, 1.7%). **96α** Anal. ($C_9H_{16}N_2O_3$): C, H, N.

Method F-1. 2-{[2-(4-Chlorophenyl)acetyl]octylamino}-butyramide (99aα). In a 500-mL, three-necked flask fitted with a magnetic stirrer, under inert atmosphere, $EtCHBrCO_2$-Me **97** (15.4 g, 0.085 mol) dissolved in DMF (85 mL) is added dropwise to a solution of *n*-$OctNH_2$ (11.0 g, 0.085 mol) and Et_3N (8.5 g, 0.85 mol) in DMF (100 mL) at room temperature. After 5 h at room temperature, successively Et_3N (8.5 g, 0.85 mol) and parachlorophenyl acetyl chloride (16.07, 0.085 mol) are added dropwise to the reaction mixture (**Caution:** exothermic!). After 24 h at room temperature, the reaction mixture is diluted with water, extracted with AcOEt, dried on $MgSO_4$, and concentrated in vacuo. The crude ester **97a** is directly ammonified. In a 250 mL Parr vessel under inert atmosphere, the crude ester (5.23 g) is dissolved in MeOH (30 mL) and the vessel is charged with NH_3. After 20 h at 40 °C, the reaction mixture is cooled to room temperature and degassed. The residue is purified by chromatography on silica gel (CH_2Cl_2–MeOH 98/02 (v/v)) and the two enantiomers are separed by chiral chromatography. Upon standing at room temperature, **99aα** is crystallize (0.37 g) and **99a*β*** remains a liquid. **99aα** Anal. ($C_{20}H_{31}ClN_2O_2$) N, H, C: calcd, 65.47; found, 66.15.

2-((Octylpropionyl)amino)butyramide (99b). The same procedure as for **99aα** is used without chiral chromatography. HPLC: 87%.

2-((Acetylpropyl)amino)butyramide (99c). The same procedure as for **99aα** is used without chiral chromatography. HPLC: >99%.

Method F-2. 2-((Butylpropionyl)amino)butyramide (99e). In a 50-mL, three-necked flask fitted with a magnetic stirrer, under inert atmosphere, butanal (0.72 g, 0.01 mol) is added to a mixture of (2*S*)-2-aminobutyramide (**49)** (1.02 g, 0.01 mol) and $(MeO)_3CH$ (15 mL). After 0.75 h, the $NaBH_3CN$ (0.63 g, 0.01 mol) is added in three portions (temperature raised to 40 °C). The reaction mixture is quenched with saturated NH_4Cl, evaporated to dryness, dissolved in CH_2Cl_2, and washed with $NaHCO_3$, and the organic layer is dried on $MgSO_4$, filtrated, and concentrated in vacuo. The residue is dissolved in HCl (1 N) and the aqueous layer is extracted with Et_2O, basicified with solid K_2CO_3, and extracted with CH_2Cl_2. The organic layer is dried on $MgSO_4$, filtrated, and concentrated in vacuo, and the residue is purified by chromatography on silica gel (CH_2Cl_2–MeOH−NH_4OH 96.7/3/0.3 (v/v)). The crude amine **100d** is directly engaged into the next step: In a 50-mL, three-necked flask fitted with a magnetic stirrer, under inert atmosphere, C_3H_7COCl (24 μL) is added to a solution of pyridine (23 μL) and the crude amine (0.042 g) in CH_2Cl_2 at room temperature. After 24 h at room temperature, the reaction mixture is quenched with HCl (1 N), diluted with water, extracted with AcOEt, dried on $MgSO_4$, and concentrated in vacuo. The crude amide is purified by chromatography on silica gel (CH_2Cl_2–MeOH 97/03 (v/v)) to afford **99e** (0.014 g). HPLC: 97%.

(2*S*)-2-[Acetyl(methyl)amino]butanamide (99d). The same procedure as for **99e** is used. Anal. ($C_7H_{14}N_2O_2$): C, H, N.

Method F-4. 2-((Pentylpropionyl)amino)butyramide (99f). Amide resin **102** (16 g, 0.76 mequiv/g, 100−200 mesh) is placed in a glass vessel and stirred in 20% v/v piperidine/DMF (40 mL) for 0.5 h. The resin is drained and the entire deprotection repeated. The resin is filtered, washed (6 × DMF), and dried. The resin is suspended in DMF (150 mL) and treated with 2-bromobutyric acid (24.3 g, 145 mmol), followed by a solution of 1,3-diisopropylcarbodiimide (18.41 g, 145 mmol) in DMF (200 mL). The reaction is stirred for 1 h at room temperature, filtered, and washed (DMF) and the coupling process repeated. The resin is filtered, washed (6 × DMF, 6 x CH_2Cl_2), dried, and used as it stands in the next steps. 2-Bromobutyric amide resin **103** (1.32 g, 0.91 mmol) is contained within a fritted polypropylene syringe and amylamine (3.179 g, 36.4 mmol) is added. The reaction is stirred for 18 h at room temperature, filtered, and washed with the following solvent sequence: MeOH, CH_2Cl_2, DMF, and DMSO. 2-Pentylaminobutyric amide resin (0.06 g, 0.038 mmol) and Et_3N (53 μL) are contained within a fritted polypropylene syringe, and propyonyl chloride (0.035 g, 0.38 mmol) is added. The reaction is stirred for 18 h at room temperature, filtered, and washed with the following solvent sequence: DMF, CH_2Cl_2, and MeOH. Deprotection of the resin **104f** is performed by suspending the resin in a 1/1 CH_2Cl_2–MeOH mixture and irradiation (ν 350 nm) using a 365-nm lamp (100W) (Cole-Parmer) during 8 h to afford **99f**. HPLC: 70%.

2-{Heptyl-[2-(4-methoxyphenyl)acetyl]amino}butyramide (99g). The same procedure as for **99f** is used.

Biological Methods. Animal Model of Sound-Susceptible Mice (Audiogenic Seizure-Prone Mice).[11] Male or female genetically sound-sensitive mice (14−28 g; $N = 10$), derived from a DBA strain originally selected by Dr. Lehmann of the Laboratory of Acoustic Physiology (Paris, France) and bred in the UCB Pharma Sector husbandry unit since 1978, are used. The experimental design consisted of several groups, one group receiving the vehicle control and the other groups different doses of the test compound. The compounds are administered intraperitoneally 60 min before the induction of audiogenic seizures. The range of the doses administered had a logarithmic progression, generally between 1.0×10^{-5} and 1.0×10^{-3} mol/kg, but lower or higher doses are tested if necessary. For testing, the animals are placed in small cages, one mouse per cage, in a sound-attenuated chamber. After a period of orientation of 30 s, the acoustic stimulus (90 dB, 10−20 kHz) is delivered for 30 s via loudspeakers positioned above each cage. During this interval, the mice are observed and the presence of the three phases of the seizure activity, namely wild running and clonic and tonic convulsions, is recorded. The proportion of mice protected against wild running and clonic and tonic convulsions, respectively, is calculated. For active compounds, an ED_{50} value, i.e., the dose producing 50% protection relative to the control group, together with 95% confidence limits, is calculated using a Probit Analysis (SAS/STAT Software, version 6.09, PROBIT procedure) of the proportions of protected mice for each of the three phases of the seizure activity.

LBS measurement has been described elsewhere.[15] Briefly, cerebral cortex from 200−250-g male Sprague−Dawley rats are homogenized using a Potter S homogenizer (10 strokes at 1000 rpm; Braun, Germany) in 20 mmol/L Tris-HCl (pH 7.4) and 250 mmol/L sucrose (buffer A); all operations are performed at 4 °C. The homogenate is centrifuged at 30 000 g for 15 min. The crude membrane pellet obtained is resuspended in 50 mmol/L Tris-HCl (pH 7.4) (buffer B), incubated 15 min at 37 °C, centrifuged at 30000*g* for 15 min, and washed twice with the same buffer. The final pellet is resuspended in buffer A at a protein concentration ranging from 15 to 25 mg/mL and stored in liquid nitrogen. Membranes (150−200 mg of protein/assay) are incubated at 4 °C for 120 min in 0.5 mL of a 50 mmol/L Tris-HCl buffer (pH 7.4) containing 2 mmol/L $MgCl_2$, 1− to 2×10^{-9} mol/L of [^{3}H]-2-[4-(3-azidophenyl)-2-oxo-1-pyrrolidinyl]butanamide, and increasing concentrations of the test substance. The nonspecific binding (NSB) is defined as the residual binding observed in the presence of a concentra-

tion of reference substance (e.g. 10^{-3} mol/L levetiracetam) that binds essentially all the receptors. Membrane-bound and free radioligands are separated by rapid filtration through glass-fiber filters (equivalent to Whatman GF/C or GF/B; VEL, Belgium) presoaked in 0.1% polyethyleneimine and 10^{-3} mol/L levetiracetam to reduce nonspecific binding. Samples and filters are rinsed by at least 6 mL of 50 mmol/L Tris-HCl (pH 7.4) buffer. The entire filtration procedure does not exceed 10 s per sample. The radioactivity trapped onto the filters is counted by liquid scintillation in a β-counter (Tri-Carb 1900 or TopCount 9206, Camberra Packard, Belgium, or any other equivalent counter). Data analysis is performed by a computerized nonlinear curve-fitting method using a set of equations describing several binding models assuming populations of independent noninteracting receptors that obey to the law of mass.

Acknowledgment. The author are grateful to Mrs. L. Archen, C. Gotteaux, Z. Povegliano, A. Gallisz, C. Chaussée, M-F. Deltent, M. Grossman, and T. Phan and Mr. M. Van Thuyne, Y. Evrard, F. Perl, J. Mercier, M. Legrand, and M. Callaert, for their skillful assistance; Dr. A. Ducarme, Dr. E. Schenkel, Dr. L. Quere, and Mrs. L. Ellens, for lipophilicity and solubility measurements; Dr. G. Bodson, Dr. F. Lurquin, and Dr. O. Diouf, for helpful discussions on the synthetic strategies; Ir E. Cavoy, for chromatographic purifications; Dr. R. Dieden, Dr. B. Mathieu, and Mr. A. Fauconnier, for analytical assistance; Dr. E. Baltes, Dr. J-M. Nicolas, Dr. L. Maier, and Ir P. Collart, for in vivo and in vitro PK measurements; and Prof. F. Durant and Ms B. Norberg (FUNDP, Namur), for the X-ray crystal structures. We thank Dr. R. Massingham and Dr. E. Schwartz for careful reading of the manuscript.

Supporting Information Available: Analytical and physicochemical properties of the new compounds and data for the X-ray crystal structure determination of **83α** and **66**. This material is available free of charge via the Internet at http://pubs.acs.org.

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JM030913E