95. Design and Synthesis of Potent Macrocyclic Benzolactam Growth Hormone Secretagogues

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Dedicated to the Memory of Professor *Wolfgang Oppolzer*[2])

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The synthesis of a variety of potent macrocyclic growth hormone secretagogues, *i.e.* **5**, **9**, **12**, and **20**–**22**, based on the known lead structure L-692,429 (**1**) is described. These conformationally constrained growth hormone secretagogues were prepared by joining the two essential pharmacophores, the amino-acid side chain at the 1*H*-1-benzazepine moiety and the 1,1′-biphenyl moiety with a variety of linkers. The most potent analog was found to be L-744,080 (**21**), a derivative in which a 2′-carboxamide moiety at 1,1′-biphenyl is *N*,*O*-joined to the OH group of the (2-hydroxypropyl)amino-acid side chain by a C_4 ester linker. This potent analog may be useful in determining the bound conformation of the benzolactam class of growth hormone secretagogues at the newly identified GHS receptor. L-744,080 (**21**) with an ED_{50} of 20 nM was up to fifty times more potent than the seco-acid precursor and 3-fold more potent than the parent 2′-tetrazole compound L-692,429 (**1**).

1. Introduction. – Growth-hormone secretagogues are novel mediators for the release of growth hormone (GH) from the pituitary. These agents whether peptidyl, such as GHRP-6 [1], or peptide mimetics, such as the benzolactam (= 1*H*-tetrahydro-1-benzazepin-2-one) L-692,429 (**1**; *Fig. 1*) [2] and the spiroindanylpiperidine MK-0677 [3], act as agonists at a newly identified pituitary/hypothalamus receptor (the GHS receptor) for which the native ligand has not been identified [4]. Binding at this G-protein coupled receptor causes release of intracellular calcium and ultimately release of GH from intracellular stores. During the medicinal chemistry effort on the benzolactam secretagogue, we sought to prepare conformationally constrained analogs to explore the effects on intrinsic potency and pharmacokinetic parameters for this class of compounds. Molecular modeling predicted a structure for L-692,429 in which two key pharmacophores, the primary-amino group of the amino-acid side chain and the tetrazolyl group at C(2′) of the 1,1′-biphenyl moiety are oriented toward each other [2b]. In earlier work, *Momany* and *Bowers* had also proposed that the active conformation of GHRP-6 was a structure, based on molecular modeling techniques, that placed the head and tail of the peptide in close proximity to each other [5]. We desired to prepare analogs of the non-peptidyl secretagogues which enforced this conformation in which the termini of the secreta-

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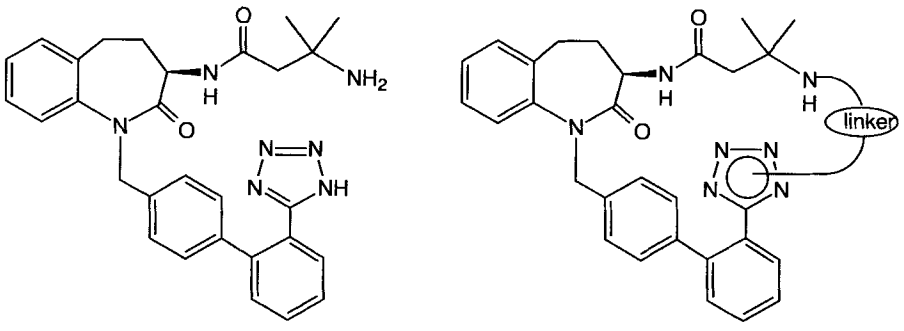
gogues were oriented toward one another. One approach to this end would be to join the key pharmacophores of L-692,429, the amino-acid side chain and the 2′-tetrazolylbiphenyl moiety, with a linking tether to form macrocyclic structures **2**. This strategy takes advantage of the fact that alkylation of either the 2′-tetrazolylbiphenyl moiety or the primary-amino group is tolerated, resulting in compounds of similar potency to L-692,429 [2c].



1 L-692,429 **2**

Fig. 1. *Structure of L-692,429* (**1**) *and proposed macrocyclic analog* **2**

We report in this paper the design and synthesis of several different macrocyclic benzolactam structures which possess equal or greater potency than the initial lead structure L-692,429 (**1**). The structure-activity relationships of this series of compounds were explored by varying the size of the ring as well as the nature of the linking groups. The important 2′-substituent at the biphenyl moiety was varied from 2′-tetrazolyl of L-692,429 to the synthetically more useful and equipotent 2′-carboxamide group [6]. These studies led to the identification of the macrocyclic ester L-744,080 (**21**) as a potent macrocyclic benzolactam GH secretagogue.

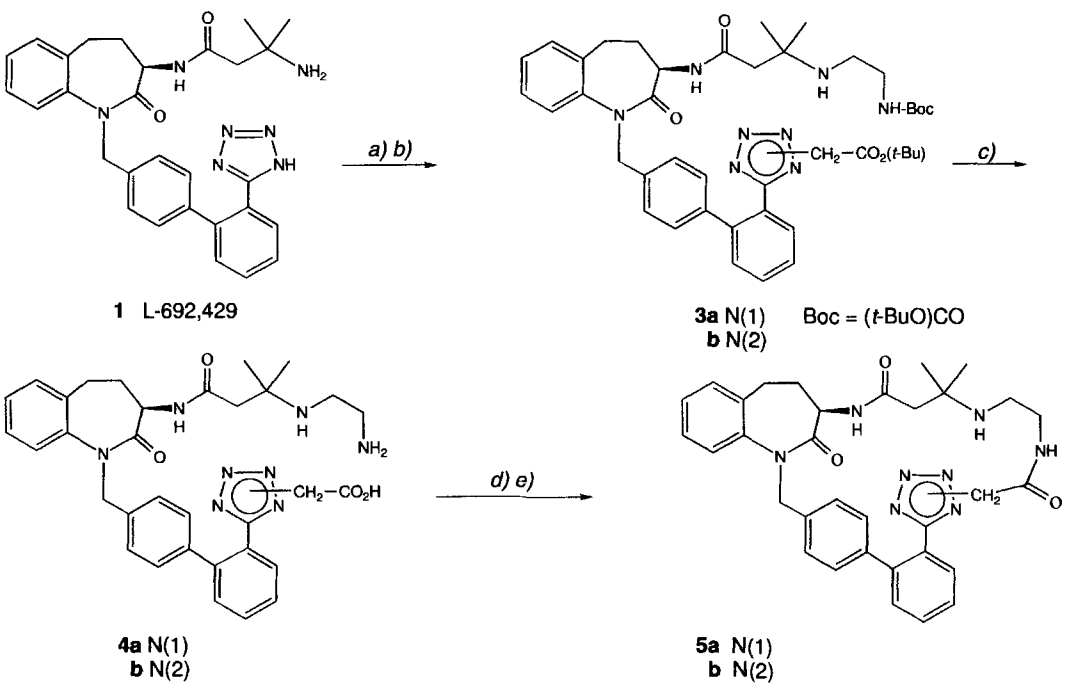
2. Results and Discussion. – 2.1. *Synthesis of Macrocyclic Benzolactam GH Secretagogues.* Macrocyclic benzolactam secretagogues containing the 2′-tetrazolyl group were synthesized from L-692,429 (**1**) as shown in *Scheme 1*. Reductive amination of the primary amino group of the amino-acid side chain [8] [9] with *N*-[(*tert*-butoxy)carbonyl]glycinal, then standard tetrazole alkylation under basic conditions with *tert*-butyl bromoacetate gave a separable mixture of *tert*-butyl of tetrazole-1- and -2-acetates **3a**, **b** (2:1 ratio of N(1) *vs.* N(2) alkylation) in modest yield (20–30% overall). Separate treatment of these protected intermediates with CF_3COOH in CH_2Cl_2 and anisole afforded the seco-amino acids **4a** and **4b**, respectively. Cyclization of the N(2) isomer **4b** was achieved by syringe-pump addition, under high-dilution conditions, to a solution of *Mukaiyama*'s salt [10] (= 2-chloro-1-methylpyridinium iodide) and Et_3N in CH_2Cl_2 at room temperature overnight. Mass-spectral analysis of the initial product isolated indicated the presence of a trifluoroacetyl group, presumably in the form of a trifluoroacetamide at the secondary amino group of the desired product **5b**. This precursor product is most likely formed from the trifluoroacetic acid salt of the starting amine **4b** which is activated under the reaction conditions and acylates the secondary amino group of the

cyclized product. Treatment of this trifluoroacetamide with K_2CO_3 in MeOH followed by reversed-phase chromatography afforded the desired N(2) macrocyclic tetrazole **5b** in 26% yield for the two steps. Conversion of the N(1) isomer precursor **4a** to the hydrochloride salt avoided the formation of the corresponding above-mentioned precursor product. Cyclization of the HCl salt of **4a** with *Mukaiyama*'s salt [10] afforded the desired N(1) isomer **5a** directly in 42% isolated yield. Mass-spectral and ^{1}H-NMR analysis confirmed the identity of the products. Most indicative of the macrocyclic structure was the large change in the chemical shifts of the CH_2 group between the biphenyl moiety and the benzazepine N-atom, resulting in a characteristic large difference for these diastereotopic H-atoms, one being shifted upfield and the other downfield upon macrocyclization, a pattern observed for all the macrocyclic compounds prepared.

In the starting seco-compounds, these diastereotopic benzylic H-atoms resonate at 4.79 and 5.32 ppm for **4a** and 4.92 and 5.22 ppm for **4b**, *i.e.*, with a $\Delta\delta$ of 0.53 and 0.30 ppm, respectively. These protons resonate at 4.37 and 5.79 ppm in the N(1) macrocyle **5a** and at 4.10 and 5.90 ppm for **5b**, *i.e.*, with a $\Delta\delta$ of 1.42 and 1.80 ppm, respectively, indicating a large anisotropic effect upon cyclization.

It was found that 2'-carboxamide groups were equipotent replacements for the 2'-tetrazolyl moiety in the benzolactam series of growth-hormone secretagogues, indicating

Scheme 1. *Synthesis of Macrocyclic Tetrazoles* **5a** *and* **5b**

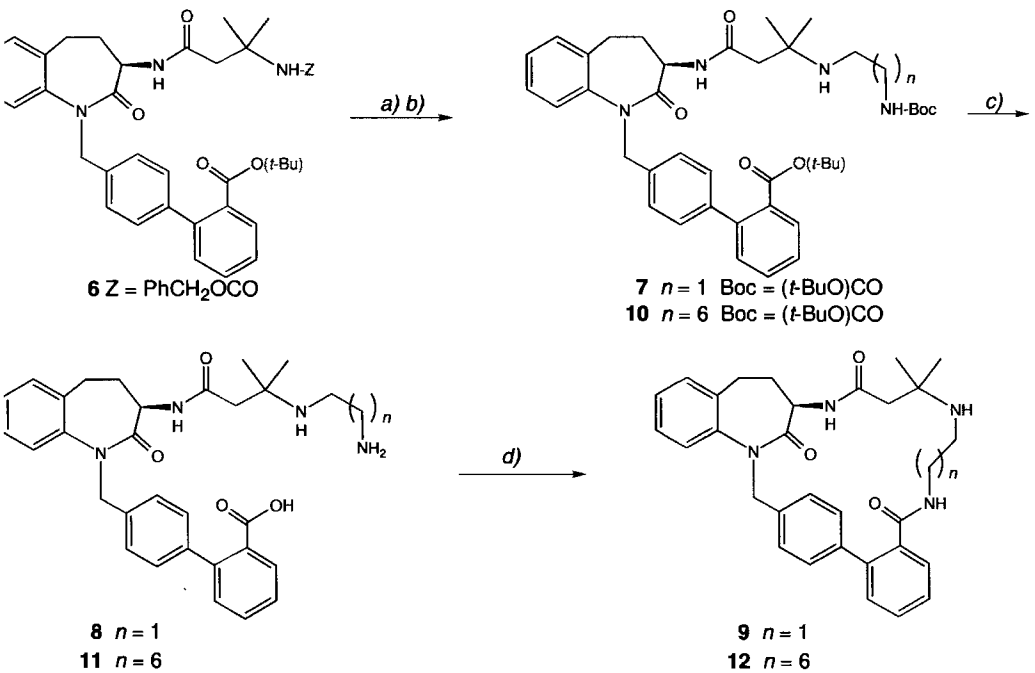


a) Boc-NHCH$_2$CHO, NaBH$_3$CN, 4 Å molecular sieves, MeOH, r.t., 16 h (54%). *b*) BrCH$_2$CO$_2$(*t*-Bu), Et$_3$N, CH$_2$Cl$_2$, r.t., 16 h (N(1), 55%; N(2), 39%). *c*) CF$_3$COOH, anisole, CH$_2$Cl$_2$, r.t., 3 h (63%). *d*) 2-Chloro-1-methylpyridinium iodide, 3 equiv. of Et$_3$N, 0.001M CH$_2$Cl$_2$, r.t., 24 h. *e*) Na$_2$CO$_3$, MeOH, r.t., 16 h, (N(1), 44%; N(2), 26%).

that the H-bonding capability of the 2′-pharmacophore was necessary for potency [6] [7]. This discovery simplified the macrocycle design by avoiding the regioisomeric alkylation of the tetrazole while expanding the choice of possible tethers. Substitution of the primary amino group of the amino-acid side chain with a tether containing an amino group would give a precursor which upon subsequent cyclization with a 2′-carboxylic acid to afford the desired macrocyclic 2′-carboxamide. This strategy was successfully employed as shown in *Scheme 2*.

The known [(benzyloxy)carbonyl]amino intermediate **6** [7], which contains the 2′-carboxylic acid *tert*-butyl ester, was deprotected to reveal the primary amino group. Again, reductive amination with *N*-[(*tert*-butoxy)carbonyl]glycinal gave the (2-aminoethyl)-amino derivative **7**. Treatment of this intermediate with CF_3COOH removed both the *N*-Boc group and the *tert*-butyl ester. Then, conversion to the HCl salt afforded the cyclization precursor **8** in good overall yield (79%, 3 steps). Cyclization proceeded smoothly using the superior conditions of *Boden* and *Keck* [11] to give the macrocyclic amide **9** (73%) which contains a C_2-linker between the secondary amino group and the 2′-carboxamide terminus of the benzolactam secretagogue. The analog which contains a C_7-linker was prepared similarly by utilizing 7-{[(*tert*-butoxy)carbonyl]amino}heptanal in the reductive amination step. The synthesis was completed *via* intermediates **10** and **11** (44%, 3 steps) to give, after cyclization, the desired macrocycle **12** ($n = 6$); however, the yield of the macrocyclization step was much lower (16%).

Scheme 2. *Synthesis of Macrocyclic Carboxamides by Cyclization of the 2′-Carboxylic Acid*



a) H_2 (1 atm), 5% (*w*/*w*) $Pd(OH)_2$ on C, MeOH, r.t., 4 h (97%). *b*) $Boc_1NH(CH_2)_nCHO$, $NaBH_3CN$, 4 Å molecular sieves, pH 5, MeOH, r.t., 16 h, then CF_3COOH, anisole, CH_2Cl_2, r.t., 3 h. *c*) 6N HCl ($n = 1$, 79%, 3 steps; $n = 6$, 44%), 3 steps. *d*) EDC, DMAP, DMAP · HCl, $CHCl_3$, reflux, 16 h ($n = 1$, 73%; $n = 6$, 16%).

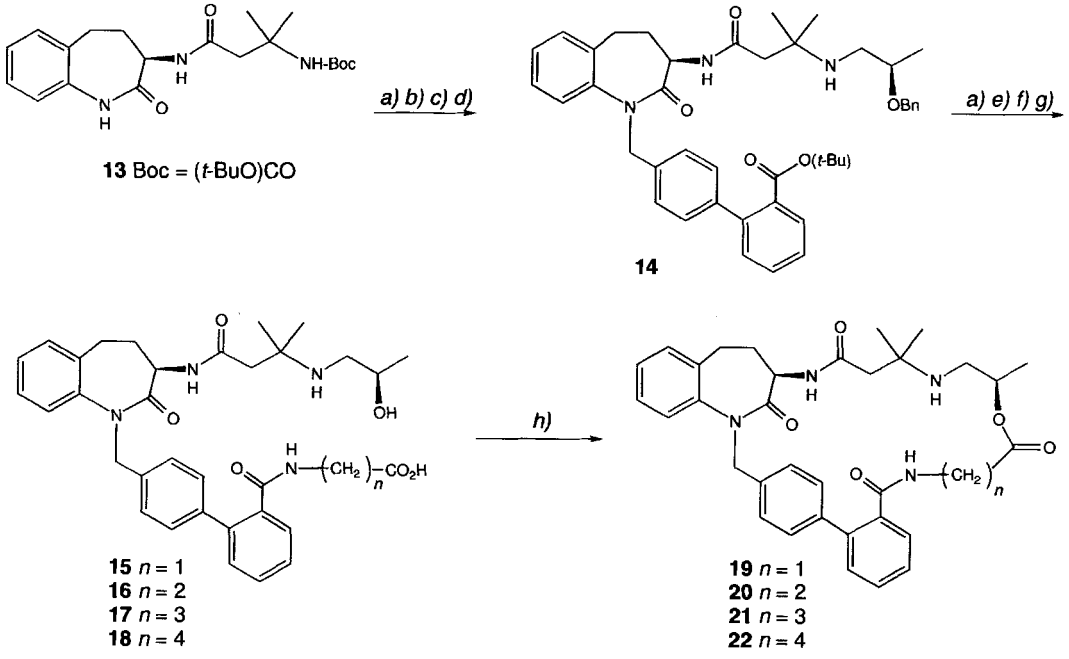
The third strategy utilized for the synthesis of macrocyclic benzolactams relied on the previously reported potency-enhancing [(2-hydroxypropyl)amino]-acid side chain [9] and a 2′-carboxamide group substituted at the N-atom with an alkanoic acid. Cyclization would give a macrocyclic product containing an ester in the linking group. The details of this approach are outlined in *Scheme 3*. The *N*-[(*tert*-butoxy)carbonyl] group of the known intermediate **13** [2a] was deprotected under acidic conditions. Reductive amination with the (*R*)-*O*-benzyllactaldehyde [9] followed by reversed-phase purification gave the [2-(benzyloxy)propyl]amino derivative as the trifluoroacetate salt. Formation of the free amino group followed by deprotonation of the lactam N-atom with NaH and then alkylation with 4′-(bromomethyl)-[1,1′-biphenyl]-2-carboxylic acid *tert*-butyl ester [2a] in dimethylformamide afforded intermediate **14** in good yield for the four steps (73%). Treatment of the *tert*-butyl ester with CF_3COOH in CH_2Cl_2 and anisole cleanly provided the 2′-carboxylic acid. Amide formation with the appropriate straight-chain benzyl ω-aminoalkanoates ($n = 1-4$) proceeded smoothly using the PyBOP reagent (= [(1*H*-benzotriazol-1-yl)oxy]tris(pyrrolidin-1-yl)phosphonium hexafluorophosphate) as previously described [7]. The appropriate benzyl ω-aminoalkanoates were available commercially ($n = 1, 2$) or were prepared from the amino acid ($n = 3, 4$) by treatment with oxalyl chloride to form the intermediate ω-aminoalkanoyl chloride hydrochloride salt followed by treatment with benzyl alcohol (see *Exper. Part*). Cleavage of the two benzyl groups under hydrogenolytic conditions and conversion to the hydrochloride salt gave the seco-acids **15**–**18** (overall yields 40–70%, 3 steps). Macrocyclization using the *Keck* conditions produced the desired macrocyclic esters **19**–**22** in variable yield (15–56%).

2.2. *Biological Data and Discussion.* The macrocycles were tested for their ability to release growth hormone from rat pituitary cells *in vitro* under the previously described assay conditions [2a] [12]. In general, all the ED_{50} values reported for the analogs were normalized to that of L-692,429 **1**; (ED_{50} 60 nM), run in the same experiment as a positive control.

Table 1 shows the data for the tetrazole-containing macrocycles **5a** and **5b** as well as corresponding acyclic analogs for comparison. The acyclic diamino acids **4a** and **4b** are over 30-fold less potent than L-692,429 (**1**). Similarly, decreases in potency are observed for the tetrazole-acetic acid analogs **23a** (17-fold) and **23b** (4-fold) or the diamine **24** (5-fold), demonstrating that these two modifications in combination are detrimental to GH-releasing activity. Unfortunately, the macrocyclic tetrazoles **5a** and **5b** are even more disappointing with an ED_{50} of 5 μM; however, we were gratified that these macrocycles are not completely devoid of GH-releasing activity. Indeed, the conformational freedom of the two key pharmacophores is greatly reduced by macrocyclization. *N*-Alkylation of the tetrazole moiety is most likely much more detrimental to activity since our previous work showed that *N*-substitution at the amino-acid side chain results in compounds of similar potency [8] [9], while tetrazole *N*-substitution generally results in much less potent compounds [6] as compared to the parent 1*H*-tetrazole.

At this time we discovered that carboxamide groups are equipotent replacements for the tetrazolyl moiety [7] indicating that the H-bonding capability of the tetrazole is important for potency and not its ability to act as a carboxylic-acid isostere. This allowed us to explore macrocyclic 2′-carboxamide derivatives as secretagogues with the advantage that *N*-substitution of the carboxamide function by certain groups is well tolerated. For example, the parent carboxamide **25** and *N*-ethylcarboxamide **26** are only slightly less

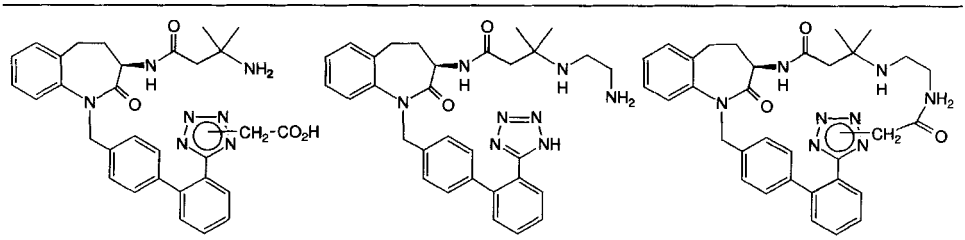
Scheme 3. *Synthesis of Macrocyclic Esters* **19–22**



a) CF_3COOH, CH_2Cl_2, r.t., 1 h (84%); or CF_3COOH, CH_2Cl_2, anisole, r.t., 1.5 h (98%). *b*) (*R*)-*O*-Benzyl-lactaldehyde, $NaBH_3CN$, 4 Å molecular sieves, pH 6, MeOH, r.t., 72 h (92%). *c*) aq. K_2CO_3 soln., CH_2Cl_2 (95%). *d*) NaH, DMF, 0°, then *tert*-butyl 4'-(bromomethyl)-[1,1'-biphenyl]-2-carboxylate (92%). *e*) $NH_2(CH_2)_nCO_2Bn$, PyBOP, Et_3N, CH_2Cl_2, r.t., 16 h. *f*) H_2 (50 psi), 10% PdC, MeOH, 24 h. *g*) 6N HCl (37–83%, 3 steps). *h*) EDC, DMAP, DMAP · HCl, $CHCl_3$, reflux, 16 h (15–56%).

Table 1. *GH-Releasing Activity of Macrocyclic Tetrazoles* **5** *and Related Analogs*

	4a (N(1))	**4b** (N(2))	**5a** (N(1))	**5b** (N(2))	**23a** (N(1))	**23b** (N(2))	**24**	**1**
ED_{50} [μM]	2	2	5	5	> 1	0.23	0.3	0.06



23a N(1)
b N(2)

24

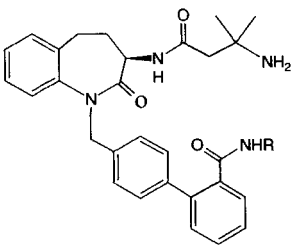
5a N(1)
5b N(2)

potent than L-692,429 (**1**) (*Table 2*). The macrocyclic carboxamide **9** containing an ethylene linker between the amino-acid side chain and the 2'-carboxamide group gives an ED_{50} of 1 μM. This compares favorably with the seco-compound **8** which is 5 times less

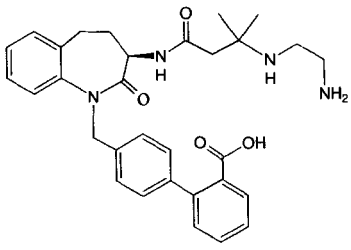
potent. However, 2′-carboxylic-acid derivatives are generally much less potent than the corresponding carboxamides (*ca.* 38-fold). A more appropriate comparison can be made between the tetrazole-containing macrocycles which are 5-fold less potent than the macrocyclic carboxamide **9**. This may be due to the important H-bond donating capability of the 2′-carboxamide group or the smaller ring size. In any event, we were pleased to note that we had marginally improved the potency of the macrocycles by replacing the tetrazole with a carboxamide group at the 2′-position of the biphenyl moiety.

Table 2. *GH-Releasing Activity of Macrocyclic Carboxamide Derivative* **9** *and Related Analogs*

	8	**9**	**25**	**26**	**1**
ED_{50} [μM]	5	1	0.08	0.09	0.06



25 R = H
26 R = Et



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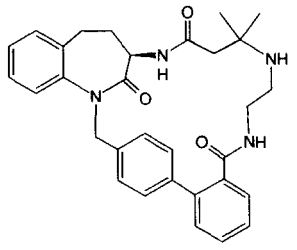

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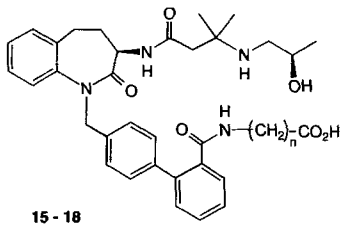
The macrocyclic esters (*Table 3*) were designed because these compounds would allow us to easily vary the ring size and provide intrinsically more potent seco-compounds in order to determine the effect of cyclization on GH-releasing activity. Immediately, we found potent seco-compounds such as **15** (ED_{50} 48 nM) derived from glycine and, upon cyclization, the equipotent macrocycle **19** (ED_{50} 48 nM, $n = 1$). Since the seco-compound is equipotent to the macrocycle, the possibility exists that the ester linker is hydrolyzed under the assay conditions. Fortunately, this trend was not observed for the other compounds in this series. The seco-acids **16** and **17** are 3-fold less potent than the corresponding macrocycle **20** ($n = 2$, ED_{50} 51 nM) and its homologue **21** ($n = 3$, ED_{50} = 21 nM). Indeed, **21** (L-744,080) is three fold *more* potent than L-692,429 (**1**), the parent benzolactam secretagogue, and 4-fold more potent than carboxamide **25**. Since these macrocyclic secretagogues are more potent than their acyclic precursors, it is unlikely that they are hydrolyzed under the assay conditions. The final macrocycle **22** ($n = 4$) is much less potent indicating that the ring can be too large, as observed for the tetrazole macrocycles **5**. This series shows that potent macrocyclic GH secretagogues can be prepared, and the optimal chain length between the carboxamide N-atom and the basic amino group is seven atoms.

To confirm the importance of this ring size and preclude the possibility of ring cleavage under the assay conditions, an analog containing the C_7 linker was prepared. Macrocycle **12** (ED_{50} 500 nM, *Table 4*) is 24-fold less potent than L-744,080 (**21**) and 8-fold less potent than the parent L-692,429 (**1**). However, the *N*-pentylcarboxamide **27**

Table 3. *GH-Releasing Activity of Macrocyclic Esters* **19–22**

	15	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**1**
n	1	2	3	4	1	2	3	4	
ED_{50} [nM]	48	161	72	75	48	51	21	> 5000	60



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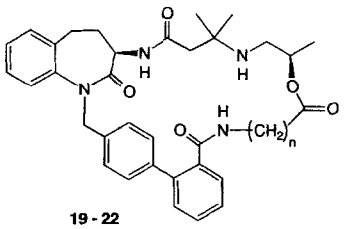
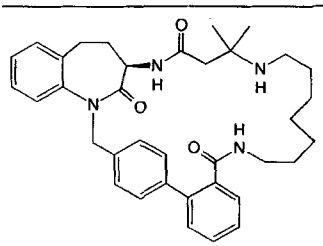


19 - 22

is at least 2-fold less potent than macrocycle **12**, indicating that this analog is adopting a more favorable conformation than the acyclic precursor without the possibility of cleavage of the linking tether. The large decrease in potency may be due to the loss of the ester moiety which may be capable to interact with the receptor. It was previously shown that the *N*-(4-hydroxybutyl)carboxamide **28** (ED_{50} 10 nM) is an extremely potent analog which may indicate the importance of heteroatoms in the macrocylic linker. A final possibility is that the ester moiety, which possesses the sp^2 carbonyl group, may be much less flexible than the straight C_7 alkanediyl linker, thereby allowing smaller changes in the conformation of the secretagogue termini.

Table 4. *GH-Releasing Activity of Macrocyclic Carboxamide* **12**, *L-744,080* (**21**) *and Related Analogs*

	12	**21** (L-744,080)	**27**	**28**	**1**
ED_{50} [nM]	500	21	> 1000	10	60



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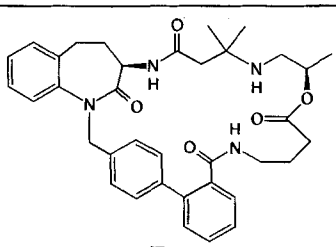

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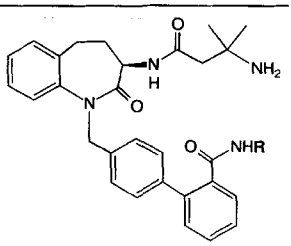

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3. Conclusion. – We have prepared a variety of macrocyclic growth-hormone secretagogues by cyclization of acyclic amino- or hydroxy-substituted carboxylic-acid precursors. Compounds possessing short (2 atoms) or long (> 8 atoms) tethers exhibit weaker GH releasing activity *in vitro*, while those of intermediate length ($n = 3-7$) are generally more potent. We identified L-744,080 (**21**, ED_{50} 21 nM) as the most potent macrocyclic analog which is 3-fold more potent than the parent benzolactam L-692,429 (**1**). The

macrocyclic secretagogue **21**, possessing a seven-atom ester linkage, indicates the importance of keeping the termini of the secretagogues oriented toward one another. The less potent analog **12** with a C_7 tether is 2-fold more potent than a similarly substituted acyclic carboxamide, indicating the importance of the macrocyclic linkage for activity without the possibility of ring cleavage under the assay conditions. Both macrocyclic GH secretagogues imply that the key pharmacophoric groups, the 2′-substituent at the biphenyl moiety and the basic amino group at the amino-acid side chain, are able to adopt a favorable conformation for activation of the receptor when they are constrained by macrocyclization and suggests that the preliminary molecular modeling of L-692,429 and GHRP-6 may be accurate. These macrocyclic GH secretagogues may provide insight on the bound conformation of non-peptidyl GH secretagogues at the newly identified GHS receptor. Further studies, including molecular modeling of macrocyclic GH secretagogues will be reported in the future.

We thank Dr. *Lawrence Colwell* and Ms. *Amy Bernick* for providing mass spectrometry services. Mr. *Glenn Reynolds* and Mr. *Joe Leone* provided several synthetic intermediates.

Experimental Part

1. *General.* All reactions were performed under anh. N_2 using dry solvents and reagents which were prepared by standard methods. All reagents were used as purchased and those not commercially available were prepared as described in the references provided. Column chromatography (CC): silica gel *60* (*Merck*, 70–230 mesh). Thin layer chromatography (TLC): pre-coated silica gel F_{254} *plates* (*E. Merck*), detection by UV and 12-phosphomolybdic acid stain and heating or I_2. Medium-pressure reversed-phase liquid chromatography (MPLC): prepacked columns *Lichroprep C-8* or *C-18* (*E. Merck*); elution with MeOH/0.1% aq. CF_3COOH soln. as indicated using refractive-index detection (*Waters*). ^{1}H-NMR Spectra: *Varian 200* or *400-MHz* spectrometers, chemical shifts in ppm rel. to the internal ref. Me_4Si or indirectly to $CHCl_3$ (7.27 ppm), coupling constants J in Hz. FAB-MS were performed by the Analytical Group of *Merck* Basic Chemistry Department.

2. *(12*R*,19*R*)-8,9,13,14,15,16,18,19,20,21-Decahydro-12,15,15-trimethyl-6*H*-28,31-etheno-19,26-methanodibenz[*l*,*t*][1,4,8,14,23]oxatetraazacycloheptacosine-5,10,17,34(7*H*,12*H*,27*H*)-tetrone Trifluoroacetate · CF$_3$COOH* (**21**; $n = 3$). 2.1. *3-Amino-3-methyl-*N*-[(3*R*)-2,3,4,5-tetrahydro-2-oxo-1*H*-1-benzazepin-3-yl]butanamide Trifluoroacetate.* To a soln. of 3-{[(*tert*-butoxy)carbonyl]amino}-3-methyl-*N*-[(3*R*)-2,3,4,5-tetrahydro-2-oxo-1*H*-1-benzazepin-3-yl]butanamide (**13**) [2a] (150 mg, 0.40 mmol) in CH_2Cl_2 (2 ml) at 0° was added CF_3COOH (2 ml). The mixture was stirred at r.t. for 1 h. All volatiles were removed under vacuum to give 130 mg (84%) of product. ^{1}H-NMR (200 MHz, CD_3OD): 1.33 (*s*, 3 H); 1.37 (*s*, 3 H); 2.12 (*m*, 1 H); 2.3–2.6 (*m*, 3 H); 2.6–3.9 (*m*, 2 H); 4.37 (*dd*, $J = 8$, 12, 1 H); 7.02 (*d*, $J = 8$, 1 H); 7.1–7.3 (*m*, 3 H). FAB-MS: 276 (100, $[M + H]^+$, $C_{15}H_{22}N_3O_2^+$).

2.2. *3-{[(2*R*)-2-(Benzyloxy)propyl]amino}-3-methyl-*N*-(3*R*)-[2,3,4,5-tetrahydro-2-oxo-1*H*-1-benzazepin-3-yl]-butanamide Trifluoroacetate.* To a soln. of 1.0 g (2.57 mmol) of product of *Exper. 2.1* in dry MeOH (25 ml was added dry powdered 3-Å molecular sieves (3.0 g) followed by a soln. of (prepared from ethyl D-lactate according to 2.5 g, 17 mmol) (*R*)-2-(benzyloxy)propanal [13] in dry MeOH (5 ml). The pH of the mixture was carefully adjusted to 6 by the addition of CF_3COOH and Et_3N. The mixture was stirred for 2 h at r.t. then 1.0M $NaBH_3CN$ (15.4 ml, 15.4 mmol) in THF was added by syringe. The mixture was stirred for 72 h and then filtered through a pad of *Celite*. To the filtrate was added CF_3COOH (5 ml) (*CAUTION*! evolution of HCN gas), and the resulting mixture was stirred for 3 h. The solvent was evaporated to afford a clear oil which was purified by MPLC (*C-8*, MeOH/0.1% aq. CF_3COOH soln. 6:4): 1.27 g (92%) of white solid. ^{1}H-NMR (200 MHz, CD_3OD): 1.31 (*d*, $J = 6$ H, 3 H); 1.40 (*s*, 3 H); 1.43 (*s*, 3 H); 2.17 (*m*, 1 H); 2.30 (*m*, 1 H); 2.6–3.1 (*m*, 5 H); 3.22 (*dd*, $J = 3$, 12, 1 H); 3.86 (*m*, 1 H); 4.48 (*dd*, $J = 8.12$, 1 H); 4.50 (*d*, $J = 1$ H); 4.70 (*d*, $J = 12$, 1 H); 7.11 (*d*, $J = 1$ H); 7.15–7.45 (*m*, 8 H). FAB-MS: 424 (100, $[M + H]^+$, $C_{25}H_{34}N_3O_3^+$).

2.3. *3-{[(2*R*)-2-(Benzyloxy)propyl]amino}-3-methyl-*N*-[(3*R*)-2,3,4,5-tetrahydro-2-oxo-1*H*-1-benzazepin-3-yl]butanamide.* To a soln. of 2.034 g (3.788 mmol) of the product of *Exper. 2.2* in CH_2Cl_2 (40 ml), H_2O (40 ml) was added. The mixture was stirred vigorously while sufficient solid K_2CO_3 was added to adjust the pH of the

aq. layer to 10–11. Stirring was discontinued and the layers allowed to separate. The aq. layer was extracted twice with CH_2Cl_2, the combined org. extract dried (K_2CO_3) and evaporated: 1.53 g (3.62 mmol, 95%) of white solid.

2.4. tert-*Butyl 4'-{{(3R)-3-{{3-{[(2R)-2-(benzyloxy)propyl]amino}-3-methyl-1-oxobutyl}amino}-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl}methyl}[1,1'-biphenyl]-2-carboxylate* (**14**). To a soln. of 600 mg (1.42 mmol) of the product of *Exper. 2.2* in DMF (10 ml) at 0° under N_2 was added 60% NaH/oil dispersion (59.5 mg, 1.49 mmol). After stirring for 5 min, a soln. of 450 mg (1.49 mmol) of *tert*-butyl 4'-(bromomethyl)-[1,1'-biphenyl]-2-carboxylate (prepared according to [14]) in DMF (4 ml) was added dropwise *via* cannula. The flask originally containing the *tert*-butyl 4'-(bromomethyl)-[1,1'-biphenyl]-2-carboxylate was rinsed with DMF (2 ml) which was added to the reaction mixture. The mixture was warmed to r.t. and stirred for 1.5 h, then diluted with AcOEt (300 ml), washed with H_2O (50 ml), sat. aq. $NaHCO_3$ soln. (50 ml), and brine (50 ml), dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatography (silica gel, $CHCl_3$/10% NH_4OH/MeOH, 93:7): 900 mg (92%) of product. ^{1}H-NMR (200 MHz, CD_3OD): 1.10 (*s*, 3 H); 1.12 (*s*, 9 H); 1.15 (*s*, 3 H); 1.25 (*d*, *J* = 7, 3 H); 2.15–2.70 (*m*, 7 H); 3.84 (*q*, *J* = 6, 1 H); 4.48–4.68 (*m*, 3 H); 4.82 (*d*, *J* = 15, 1 H); 5.31 (*d*, *J* = 15, 1 H); 7.08–7.48 (*m*, 16 H); 7.7 (*dd*, *J* = 2, 7, 1 H). FAB-MS: 690 (70, $[M + H]^+$, $C_{43}H_{52}N_3O_5^+$).

2.5. *4'-{{(3R)-3-{{3-{[(2R)-2-(Benzyloxy)propyl]amino}-3-methyl-1-oxobutyl}amino}-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl}methyl}[1,1'-biphenyl]-2-carboxylic Acid.* To a soln. of 900 mg (1.31 mmol) of **14** in dry CH_2Cl_2 (16 ml) anisole, (10 drops) was added, followed by CF_3COOH (10 ml). The mixture was stirred for 1.5 h at r.t. and then evaporated. The resulting oil was dissolved in CCl_4 (10 ml) and the soln. evaporated. The process was repeated with $CHCl_3$ (10 ml) followed by CH_2Cl_2 (10 ml) to give 959 mg (98% of product containing a minor amount of anisole) of off-white foam. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.20 (*d*, *J* = 7, 3 H); 1.31 (*s*, 3 H); 1.37 (*s*, 3 H); 1.6–1.8 (*m*, 2 H); 2.08–2.43 (*m*, 4 H); 2.55–3.29 (*m*, 4 H); 3.84–4.01 (*m*, 1 H); 4.36–4.59 (*m*, 3 H); 4.69 (*d*, *J* = 15, 1 H); 5.21 (*d*, *J* = 15, 1 H); 6.97–7.61 (*m*, 16 H); 7.95 (*d*, *J* = 8, 1 H); 8.23 (*d*, *J* = 8, 1 H). FAB-MS: 634 (65, $[M + H]^+$, $C_{39}H_{44}N_3O_5^+$).

2.6. *Benzyl 4-Aminobutanoate Hydrochloride.* To a soln. of 4-aminobutanoic acid (1.0 g) in CH_2Cl_2 (25 ml) at 0° under N_2 was added DMF (0.056 ml, 0.72 mmol), followed by oxalyl chloride (1.57 ml, 18.0 mmol). The mixture was warmed to r.t. and after 5 h, the solvent was evaporated and the residue dissolved in benzyl alcohol (25 ml). The soln. was stirred until it turned clear yellow, and then Et_2O (25 ml) was added. The desired product crystallized, was filtered, and triturated with a minimum of EtOH, giving 1.85 g (> 100%) of white crystals. ^{1}H-NMR (200 MHz, CD_3OD): 1.96 (*dt*, *J* = 8, 2 H); 2.51 (*t*, *J* = 8, 2 H); 2.97 (*t*, *J* = 8, 2 H); 5.12 (*s*, 2 H); 7.27–7.37 (*m*, 5 H). FAB-MS: 194 (100, $[M + H]^+$, $C_{11}H_{16}NO_2^+$).

2.7. N-*{3-[(Benzyloxy)carbonyl]propyl}-4'-{{(3R)-3-{{3-{[(2R)-2-(benzyloxy)propyl]amino}-3-methyl-1-oxobutyl}amino}-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl}methly}[1,1'-biphenyl]-2-carboxamide Hydrochloride.* To a soln. of 274 mg (0.367 mmol) of product of *Exper. 2.4* in CH_2Cl_2 (4 ml) was added Et_3N (0.169 ml, 1.21 mmol, 3.3. equiv.) and 210 mg of (1 H-benzotriazol-1-yloxy)tri(pyrrolidin-1-yl)phosphonium hexafluorophosphate (PyBOP; 0.404 mmol, 0.1 equiv.). The mixture was stirred for 10 min benzyl 4-aminobutanoate hydrochloride (*Exper. 2.5*; 92.6 mg, 0.404 mmol, 1.1 equiv.) was added and the mixture stirred at r.t. for 2 h. The mixture was added to AcOEt (150 ml) and washed with H_2O (50 ml), sat. aq. $NaHCO_3$ soln. (50 ml) and brine (50 ml). The org. layer was dried ($MgSO_4$) and evaporated and the residue purified by flash chromatography (silica gel, $CHCl_3$/10% NH_4OH in MeOH 93:7), to give 421 mg (> 100%) of a mixture of the product and a by-product, 1,1',1''-phosphinylidynetris(pyrrolidine), which co-eluted with the product on silica gel. The mixture was dissolved in 6N HCl (5 ml) and the soln. evaporated under high vacuum. This process was repeated once: 312 mg of hydrochloride salt. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.23 (*d*, *J* = 7, 3 H); 1.3–1.72 (*m*, 11 H); 1.8 (*m*, residual by-product); 2.21 (*t*, 2 H); 2.4–2.6 (*m*, 2 H); 2.7–3.0 (*m*, 4 H); 3.13 (*m*, residual by-product); 4.15–4.35 (*m*, 1 H); 4.35–4.55 (*m*, 1 H); 4.54 (*d*, *J* = 12, 1 H); 4.66 (*d*, *J* = 12, 1 H); 4.84 (*d*, *J* = 15, 1 H); 5.03 (*s*, 2 H); 5.09 (*d*, *J* = 15, 1 H); 5.22–5.38 (*m*, 1 H); 7.08–7.43 (*m*, 23 H); 7.59 (*dd*, *J* = 7, 2, 1 H); 7.77 (*m*, 1 H). FAB-MS: 809 (50, $[M + H]^+$, $C_{50}H_{57}N_4O_6^+$).

2.8. N-*(3-Carboxypropyl)-4'-{{[(3R)-2,3,4,5-tetrahydro-3-{{3-{[(2R)-2-hydroxypropyl]amino}-3-methyl-1-oxobutyl}amino}-2-oxo-1H-1-benzazepin-1-yl}methyl}[1,1'-biphenyl]-2-carboxamide Hydrochloride* (**17** · HCl). A soln. of 312 mg (0.369 mol) of product of *Exper. 2.6* in MeCN/H_2O 1:1 (5 ml) was hydrogenated at r.t. and 40 psi over 30% Pd/C (62.4 mg) for 24 h. The mixture was filtered through *Celite* and rinsed with MeCN and the filtrate evaporated. The residue was purified by MPLC (*C-18*) 0.1% CF_3COOH in MeCN/0.1% aq. CF_3COOH soln. (4:6), to give 183 mg (67% overall for *Exper. 2.6* and *2.7*) of white solid. The compound was dissolved in 6N HCl (5 ml) and the soln. evaporated under high vacuum. This process was repeated once: 126.5 mg of **17** · HCl. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.22 (*d*, *J* = 8, 3 H); 1.37 (*s*, 3 H); 1.38 (*s*, 3 H); 1.59 (*t*, *J* = 8, 2 H); 1.99–2.2 (*m*, 3 H); 2.38–3.05 (*m*, 7 H); 3.23 (*d*, *J* = 8, 2 H); 4.09–4.2 (*m*, 1 H); 4.39–4.5 (*m*, 1 H); 4.81 (*d*, *J* = 16, 1 H);

5.2 (*d*, *J* = 16, 1 H); 5.99–6.06 (*m*, 1 H); 7.13–7.8 (*m*, 13 H); 8.0–8.05 (*m*, 1 H); 8.69–8.8 (*m*, 1 H); 8.94–9.1 (*m*, 1 H). FAB-MS: 629 (100, $[M + H]^+$, $C_{36}H_{45}N_4O_6^+$).

2.9. *Macrocycle* **21** · *CF_3COOH*. A soln. of 4-(dimethylamino)pyridine (69.8 mg, 0.571 mmol), 4-(dimethylamino)pyridine hydrochloride (60.3 mg, 0.380 mmol), and dicyclohexylcarbodiimide (DCC; 78.4 mg, 0.380 mmol) in $CHCl_3$ (6.3 ml; EtOH-free; purified according to [15]) was heated to reflux while stirring. In a separate flask, **17** · HCl (127 mg, 0.19 mmol) was dissolved in $CHCl_3$ (1.8 ml) and treated with 4-(dimethylamino)pyridine (46.4 mg, 0.380 mmol). This soln. was placed in a 5-ml gas-tight syringe and added to the refluxing $CHCl_3$ soln. *via* syringe pump over 20 h. The syringe and the flask originally containing **17** · HCl and the 4-(dimethylamino)pyridine were rinsed with additional $CHCl_3$ (1.8 ml) which was then added *via* syringe pump over 2 h. The mixture was stirred under reflux 2 h more, cooled to r.t. and then dissolved in AcOEt (75 ml). The resulting soln. was washed with H_2O (30 ml), sat. aq. $NaHCO_3$ soln. (30 ml) and brine (30 ml). The org. layer was dried ($MgSO_4$) and evaporated. The residue was purified by MPLC (*C-18*, 0.1% CF_3COOH in MeCN/0.1% aq. CF_3COOH soln. 45:55): 77.2 mg (56%) of **21** · CF_3COOH. White solid. ^{1}H-NMR (400 MHz, CD_3OD): 1.3–1.4 (*m*, 3 H); 1.39–1.45 (*m*, 6 H); 1.55–1.68 (*m*, 1 H); 2.19–2.35 (*m*, 3 H); 2.37–2.48 (*m*, 1 H); 2.51 (*d*, *J* = 16, 1 H); 2.77–2.84 (*m*, 2 H); 2.9–3.05 (*m*, 2 H); 3.18–3.3 (*m*, 2 H); 3.5–3.6 (*m*, 1 H); 3.99 (*d*, *J* = 16, 1 H); 4.42 (*dd*, *J* = 4, 14, 1 H); 5.09–5.14 (*m*, 1 H); 5.98 (*d*, *J* = 16, 1 H); 6.81 (*d*, *J* = 9, 1 H); 7.14 (*t*, *J* = 9, 1 H); 7.25 (*t*, *J* = 7, 1 H); 7.32 (*d*, *J* = 9, 2 H); 7.4–7.53 (*m*, 8 H); 8.02 (*t*, *J* = 7, 1 H). FAB-MS: 611 (100, $[M + H]^+$, $C_{36}H_{43}N_4O_5^+$).

3. *(10*R*,17*R*)-11,12,13,14,16,17,18,19-Octahydro-10,13,13-trimethyl-6*H*-26,29-etheno-17,24-methanodibenz-[l, t] [1,4,8,14,23]oxatetraazocylopentacosine-5,8,15,32(7*H*,10*H*,25*H*)-tetrone Trifluoroacetate* (**19** · CF_3COOH; *n* = 1). 3.1. *N-{[(Benzyloxy)carbonyl]methyl}-4'-{{(3*R*)-3{{3-{[(2*R*)-2(benzyloxy)propyl]amino}-3-methyl-1-oxobutyl}amino}-2,3,4,5-tetrahydro-2-oxo-1*H*-1-benzazepin-1-yl}methyl}[1,1'-biphenyl]-2-carboxamide Hydrochloride*. The title compound (113 mg, 63%) was prepared from 156 mg (0.209 mmol) of product of *Exper. 2.4* and glycine benzyl ester hydrochloride (46.3 mg, 1.1 equiv.) according to *Exper. 2.6*. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.21 (*d*, *J* = 11, 3 H); 1.2 (*s*, 3 H); 1.22 (*s*, 3 H); 1.72–1.88 (*m*, 1 H); 2.08–2.7 (*m*, 7 H); 3.75–3.92 (*m*, 3 H); 4.48–4.67 (*m*, 3 H); 4.82 (*d*, *J* = 20, 1 H); 5.1 (*s*, 2 H); 5.22 (*d*, *J* = 20, 1 H); 5.72 (*t*, 1 H); 7.0–7.5 (*m*, 23 H); 7.64 (*dd*, *J* = 2, 7, 1 H); 9.1–9.3 (*m*, 1 H). FAB-MS: 781 (75, $[M + H]^+$, $C_{48}H_{53}N_4O_6^+$).

3.2. *N-(Carboxymethyl)-4'-{{(3*R*)-2,3,4,5-tetrahydro-3-{{3-{[(2*R*)-2-hydroxypropyl]amino}-3-methyl-1-oxobutyl}amino}-2-oxo-1*H*-1-benzazepin-1-yl}methyl}[1,1'-biphenyl]-2-carboxamide Hydrochloride* (**15** · HCl). Compound **15** · HCl (66 mg, 71%) was prepared from 120 mg, (0.147 mmol of product of *Exper. 3.1* by the procedure described in *Exper. 2.7* for **17** · HCl. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.37 (*d*, *J* = 7, 3 H); 1.41 (*s*, 3 H); 1.49 (*s*, 3 H); 1.88–2.02 (*m*); 2.2–2.45 (*m*, 6 H); 2.49–2.6 (*m*, 2 H); 2.7–3.2, 3.3–3.5 (2*m*, residual 1,1',1''-phosphinylidynetris(pyrrolidine)); 3.79 (*dd*, *J* = 4, 20, 1 H); 3.95 (*dd*, *J* = 4, 20, 1 H); 4.28–4.5 (*m*, 2 H); 4.64 (*d*, *J* = 15, 1 H); 5.16 (*d*, *J* = 15, 1 H); 5.83–5.91 (*m*, 1 H); 7.09 (*d*, *J* = 8, 1 H); 7.21–7.5 (*m*, 11 H); 7.7 (*dd*, *J* = 2, 7, 1 H); 8.65–8.9 (*m*, 2 H); 9.88 (*m*, 1 H). FAB-MS: 601 (75, $[M + H]^+$, $C_{34}H_{41}N_4O_6^+$).

3.3. *Macrocycle* **19** · *CF_3COOH*. Compound **19** · CF_3COOH (10 mg, 15%) was prepared from **15** · HCl (64 mg, 0.10 mmol) by the procedure described in *Exper. 2.8* for **21** · CF_3COOH. ^{1}H-NMR (400 MHz, CD_3OD): 1.29–1.40 (*m*, 6 H); 1.34 (*s*, 3 H); 2.2–2.31 (*m*, 1 H); 2.32–2.43 (*m*, 1 H); 2.49 (*d*, *J* = 16, 1 H); 2.77 (*d*, *J* = 16, 1 H); 2.78–2.85 (*m*, 1 H); 2.9–3.01 (*m*, 1 H); 3.1–3.2 (*m*, 1 H); 3.29–3.41 (*m*, 2 H); 3.96 (*d*, *J* = 17, 1 H); 4.22 (*d*, *J* = 16, 1 H); 4.39 (*dd*, *J* = 4, 14, 1 H); 4.42 (*d*, *J* = 17, 1 H); 5.42–5.51 (*m*, 1 H); 5.88 (*d*, *J* = 16, 1 H); 7.09 (*d*, *J* = 8, 1 H); 7.16–7.26 (*m*, 2 H); 7.32 (*d*, *J* = 7, 1 H); 7.41 (*d*, *J* = 8, 1 H); 7.52 (*d*, *J* = 8, 1 H); 7.56–7.6 (*m*, 2 H); 7.81 (*d*, *J* = 9, 2 H). FAB-MS: 583 (100, $[M + H]^+$, $C_{34}H_{39}N_4O_5^+$).

4. *(11*R*,18*R*)-7,8,12,13,14,15,17,18,19,20-Decahydro-11,14,14-trimethyl-27,30-etheno-18,25-methano-25*H*-dibenz[l, t][1,4,8,14,23]oxatetraazacyclohexacosine-5,9,16,33(6*H*,11*H*,26*H*)-tetrone Trifluoroacetate* (**20** · CF_3COOH; *n* = 2). 4.1. *N-{2-[(Benzyloxy)carbonyl]ethyl}-4'-{{(3*R*)-3-{{3-{[(2*R*)-2-(benzyloxy)propyl]amino}-3-methyl-1-oxobutyl}amino}-2,3,4,5-tetrahydro-2-oxo-1*H*-1-benzazepin-1-yl}methyl}[1,1'-biphenyl]-2-carboxamide Hydrochloride*. The title compound (375 mg) was prepared from 250 mg, (0.382 mmol) of product of *Exper. 2.4* and benzyl 3-aminopropanoate hydrochloride (153 mg, 1.1 equiv.) according to *Exper. 2.6*. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.11 (*s*, 3 H); 1.17 (*s*, 3 H); 1.22 (*d*, *J* = 7, 3 H); 1.76–1.9, 3.1–3.22 (2*m*, residual 1,1'1''-phosphinylidynetris(pyrrolidine)); 2.19–2.67 (*m*, 10 H); 2.5–3.1 (*m*, 1 H); 3.32 (*q*, *J* = 7, 2 H); 3.49 (*q*, *J* = 7, 1 H); 3.82 (*q*, *J* = 7, 1 H); 4.48–4.66 (*m*, 3 H); 4.79 (*d*, *J* = 20, 1 H); 5.01 (*s*, 1 H); 5.12 (*s*, 1 H); 5.22 (*d*, *J* = 20, 1 H); 5.72 (*t*, *J* = 6, 1 H); 7.04–7.47 (*m*, 22 H); 7.53 (*dd*, *J* = 2, 7, 1 H); 9.1–9.21 (*m*, 1 H).

4.2. *N-(2-Carboxyethyl)-4'-{{(3*R*)-2,3,4,5-tetrahydro-3-{{3-{[(2*R*)-2-hydroxypropyl]amino}-3-methyl-1-oxobutyl}amino}-2-oxo-1*H*-1-benzazepin-1-yl}methyl}[1,1'-biphenyl]-2-carboxamide Hydrochloride* (**16** · HCl). Compound **16** · HCl (232 mg, 83% 2 steps) was prepared from 375 mg of product of *Exper. 4.1* by the procedure described in *Exper. 2.7* for **17** · HCl. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.18–1.32 (*m*, 3 H); 1.3–1.6 (*m*, 6 H); 2.2–3.3 (*m*, 10 H); 3.35–3.55 (*m*, 2 H); 4.18–4.31 (*m*, 1 H); 4.4–4.55 (*m*, 1 H); 4.63 (*d*, *J* = 15, 1 H); 5.34 (*d*,

J = 15, 1 H); 6.18–6.27 (*m*, 1 H); 6.9–7.42 (*m*, 12 H); 7.48 (*t*, J = 7, 1 H); 7.61 (*d*, J = 8, 1 H); 8.8–9.0 (*m*, 1 H); 9.3–9.45 (*m*, 1 H). FAB-MS: 615 (100, $[M + H]^+$, $C_{35}H_{43}N_4O_6^+$).

4.3. *Macrocycle* **20** · *CF_3COOH*. Compound **20** (47 mg, 34%) was prepared from **16** · HCl (125 mg, 0.192 mmol) by the procedure described in *Exper. 2.8* for **21** · CF_3COOH, substituting 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDC) for DCC. ^{1}H-NMR (400 MHz, CD_3OD): 1.28 (*d*, J = 7, 1 H); 1.32–1.41 (*m*, 6 H); 1.42 (*s*, 3 H); 2.1–2.4 (*m*, 2 H); 2.4–2.51 (*m*, 1 H); 2.52–2.68 (*m*, 2 H); 2.7–2.82 (*m*, 2 H); 2.9–3.0 (*m*, 1 H); 3.13–3.22 (*m*, 1 H); 3.25–3.32 (*m*, 1 H); 3.51–3.59 (*m*, 1 H); 4.03 (*d*, J = 8, 1 H); 4.33–4.41 (*m*, 1 H); 4.42–4.65 (*m*, 1 H); 5.12–5.21 (*m*, 1 H); 5.99 (*d*, J = 8, 1 H); 6.88 (*d*, J = 8, 1 H); 7.12–7.27 (*m*, 3 H); 7.27–7.38 (*m*, 2 H); 7.38–7.52 (*m*, 6 H). FAB-MS: 597 (75, $[M + H]^+$, $C_{35}H_{41}N_4O_5^+$).

5. *(13*R*,20*R*)-7,8,9,10,14,15,16,17,19,20,21,22-Dodecahydro-13,16,16-trimethyl-29,32-etheno-20,27-methano-27*H*-dibenz[*l*, t][1,4,8,14,23]oxatetraazacyclooctacosine-5,11,18,35(6*H*,13*H*,28*H*)-tetrone Trifluoroacetate* (**22** · CF_3COOH; n = 4). 5.1. *Benzyl 5-Aminopentanoate Hydrochloride*. The title compound (343 mg, 43%) was prepared from 5-aminopentanoic acid (500 mg, 3.25 mmol) according to *Exper. 2.5*. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.6–1.8 (*m*, 4 H); 2.3–2.42 (*m*, 2 H); 2.9–3.1 (*m*, 2 H); 5.4 (*s*, 2 H); 7.2–7.38 (*m*, 5 H); 8.0–8.4 (*s*, 2 H). FAB-MS: 208 (100, $[M + H]^+$, $C_{12}H_{18}NO_2^+$).

5.2. *N-{[4-(Benzyloxy)carbonyl]butyl}-4′-{{(3*R*)-3-{{3-{[(2*R*)-2-(benzyloxy)propyl]amino}-3-methyl-1-oxobutyl}amino}-2,3,4,5-tetrahydro-2-oxo-1*H*-1-benzazepin-1-yl}methyl}[1,1′-biphenyl]-2-carboxamide Hydrochloride*. The title compound (380 mg) was prepared from 250 mg of product of *Exper. 2.4* and benzyl 5-aminopentanoate hydrochloride (243.5 mg, 1.1 equiv.) according to *Exper 2.6*. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.10 (*s*, 3 H); 1.17 (*s*, 3 H); 1.23 (*d*, J = 7, 3 H); 1.30–3.30 (very complex, difficult to interpret due to signals from residual 1,1′,1′-phosphinylidynetris(pyrrolidine)); 3.72–3.92 (*m*, 1 H); 4.48–4.69 (*m*, 3 H); 4.84 (*d*, J = 15, 1 H); 5.05 (*s*, 2 H); 5.11 (*d*, J = 15, 1 H); 5.22 (*t*, J = 7, 1 H); 7.07 (*m*, 23 H); 7.61 (*dd*, J = 2, 7, 1 H); 9.15 (*m*, 1 H). FAB-MS: 823 (85, $[M + H]^+$, $C_{51}H_{59}N_4O_6^+$).

5.3. *N-(4-Carboxybutyl)-4′-{{(3*R*)-2,3,4,5-tetrahydro-3-{{3-{[(2*R*)-hydroxypropyl]amino}-3-methyl-1-oxobutyl}amino}-2-oxo-1*H*-1-benzazepin-1-yl}methyl}[1,1′-biphenyl]-2-carboxamide Hydrochloride* (**18** · HCl). Compound **18** · HCl (108 mg, 37%, 2 steps) was prepared from 380 mg of *Exper. 5.2* according to the procedure described in *Exper. 2.7* for **17** · HCl. ^{1}H-NMR (400 MHz, CD_3OD): 1.05–1.45 (*m*, 12 H); 2.09 (*m*, 1 H); 2.17–2.27 (*m*, 2 H); 2.37–2.5 (*m*, 1 H); 2.5–2.7 (*m*, 3 H); 2.7–2.9 (*m*, 2 H); 2.92–3.06 (*m*, 1 H); 3.12–3.3 (*m*, 2 H); 4.07–4.2 (*m*, 1 H); 4.4–4.5 (*m*, 1 H); 4.9 (*d*, J = 15, 1 H); 5.14 (*d*, J = 15, 1 H); 5.93 (*m*, 1 H); 7.1–7.42 (*m*, 10 H); 7.46 (*t*, J = 9, 1 H); 7.54 (*d*, J = 9, 1 H); 7.9–8.02 (*m*, 1 H); 8.6–8.85 (*m*, 1 H); 8.85–9.3 (*m*, 3 H).

5.4. *Macrocycle* **22** · *CF_3COOH*. Compound **22** · CF_3COOH (35 mg, 38%) was prepared from **18** · HCl (84 mg, 0.124 mmol) by the procedure described in *Exper. 2.8* **21** · CF_3COOH, substituting EDC for DCC. ^{1}H-NMR (400 MHz, CD_3OD): 1.33 (*d*, J = 8, 3 H); 1.38 (*s*, 3 H); 1.4 (*s*, 3 H); 1.51–1.62 (*m*, 2 H); 2.18–2.42 (*m*, 4 H); 2.52 (*d*, J = 17, 1 H); 2.7–2.9 (*m*, 3 H); 3.15–3.32 (*m*, 6 H); 4.39–4.5 (*m*, 2 H); 4.78–5.2 (*m*, 1 H); 5.68 (*d*, J = 16, 1 H); 7.06 (*d*, J = 8, 1 H); 7.02–7.52 (*m*, 11 H). FAB-MS: 625 (100, $[M + H]^+$, $C_{37}H_{45}N_4O_5^+$).

6. *(*R*)-8,9,10,11,13,14,15,16-Octahydro-10,10-dimethyl-6*H*-23,26-etheno-14,21-methanodibenzo[l, t][1,4,8,14]-tetraazacyclododecosine-5,12,29(7*H*,22*H*)-trione Trifluoroacetate* (**9** · CF_3COOH). 6.1. *tert-Butyl 4′-{{(3*R*)-3-[(3-Amino-3-methyl-1-oxobutyl)[amino]-2,3,4,5-tetrahydro-2-oxo-1*H*-1-benzazepin-1-yl}methyl}[1,1′-biphenyl]-2-carboxylate Acetate*. To a soln. of 400 mg (0.592 mmol) of *tert*-butyl 4′-{{(3*R*)-3-{{3-{[(benzyloxy)carbonyl]amino}-3-methyl-1-oxobutyl}amino}-2,3,4,5-tetrahydro-2-oxo-1*H*-1-benzazepin-1-yl}methyl}[1,1′-biphenyl]-2-carboxylate (**6**; prepared according to [7]) in MeOH (10 ml) were added AcOH (0.034 ml, 0.59 mmol), $Pd(OH)_2$ (80 mg, 20% (*w*/*w*)). The resulting mixture was stirred under H_2 for 4 h. The catalyst was removed by filtration through *Celite* and the filtrate evaporated: 345 mg (97%) of white solid. ^{1}H-NMR (400 MHz, CD_3OD): 1.17 (*s*, 9 H); 1.37 (*s*, 3 H); 1.41 (*s*, 3 H); 1.92 (*s*, 3 H); 2.17 (*m*, 1 H); 2.35 (*m*, 1 H); 2.45–2.75 (*m*, 4 H); 4.41 (*dd*, J = 12, 8, 1 H); 4.93 (*d*, J = 15, 1 H); 5.37 (*d*, J = 16, 1 H); 7.12–7.52 (*m*, 11 H); 7.66 (*d*, J = 8, 1 H). FAB-MS: 542 (100, $[M + H]^+$, $C_{33}H_{40}N_3O_4^+$).

6.2. *2-{[(tert-Butoxy)carbonyl]amino}ethanol*. To a soln. of $NaHCO_3$ (2.8 g, 33 mmol) and di-*tert*-(butyl) dicarbonate (3.65 g, 16.7 mmol) in THF/H_2O 3:1 (32 ml) was added dropwise *via* syringe 2-aminoethanol (1.0 ml, 17 mmol). The mixture was stirred at r.t. for 4 h and then poured into AcOEt (100 ml). The org. phase was washed with H_2O (100 ml), sat. aq. NH_4Cl soln. (100 ml), and brine (100 ml), dried ($MgSO_4$), and evaporated, and the residue purified by flash chromatography (silica gel, AcOEt/hexanes 65:35): 2.27 g (85%) of clear oil. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.52 (*s*, 9 H); 3.34 (*t*, J = 4, 2 H); 3.76 (*t*, J = 4, 2 H).

6.3. *N-[(tert-Butoxy)carbonyl]glycinal*. To a soln. of 700 mg (4.34 mmol) of 2-{[(tert-butoxy)carbonyl]amino}ethanol in dry CH_2Cl_2 (35 ml) were added Et_3N (4.8 ml, 35 mmol) and dry DMSO (4.0 ml). To the resulting soln. was added in portions pyridine · SO_3 (2.8 g, 17 mmol). The resulting brown soln. was stirred at r.t. for 3 h. The mixture was diluted with Et_2O (500 ml), washed with 1N aq. HCl (2 × 50 ml), sat. aq. $NaHCO_3$ soln.

(100 ml), and brine (100 ml), dried ($MgSO_4$), and evaporated: 550 mg (80%) of oil. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.42 (*s*, 9 H); 4.04 (*d*, *J* = 4, 2 H); 5.18 (*s*, 1 H); 9.62 (*s*, 1 H).

6.4. *4'-{{(3R)-3-{{3-[(2-Aminoethyl)amino]-3-methyl-1-oxobutyl}amino}-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl}methyl}[1,1'-biphenyl]-2-carboxylic Acid Dihydrochloride* (**8** · 2 HCl). To a soln. of 345 mg (0.573 mmol) of product of *Exper. 6.1* in dry MeOH (10 ml) was added Et_3N (0.088 ml, 0.63 mmol) followed by powdered 4-Å molecular sieves (3.4 g, 10% (*w*/*w*)). To this mixture was added a soln. of *N*-[(*tert*-butoxy)carbonyl]-glycinal (540 mg, 3.4 mmol) in MeOH (5 ml). The pH of the mixture was adjusted to 6.5 by the addition of AcOH (4 drops) and then stirred at r.t. for 3 h at which time 1M $NaBH_3CN$/THF (3.4 ml, 3.4 mmol) was added dropwise *via* syringe. The mixture was stirred at r.t. for 16 h and then filtered through *Celite*. To the filtrate was added AcOH (2 ml; *CAUTION*! evolution of HCN gas). After stirring for 3 h, the solvent was evaporated, the residue dissolved in CH_2Cl_2 (5 ml), and anisole (5 drops) added followed by CF_3COOH (5 ml). The mixture was stirred at r.t. for 4 h and then evaporated. The residue was purified by MPLC (*C-8*, MeOH/0.1% aq. CF_3COOH 55:45). The resulting purified trifluoroacetate salt was dissolved in 6N HCl (10 ml) and the soln. evaporated. This was repeated twice more to afford 273 mg (73%) of **8** · 2 HCl. White solid. ^{1}H-NMR (200 MHz, CD_3OD): 1.44 (*s*, 3 H); 1.49 (*s*, 3 H); 2.05–2.45 (*m*, 2 H); 2.52–2.80 (*m*, 4 H); 3.35 (*m*, 4 H); 4.40 (*dd*, *J* = 11, 7, 1 H); 4.99 (*d*, *J* = 15, 1 H); 5.23 (*d*, *J* = 15, 1 H); 7.20–7.60 (*m*, 11 H); 7.80 (*d*, *J* = 8, 1 H). FAB-MS: 529 (100, $[M + H]^+$, $C_{31}H_{37}N_4O_4^+$).

6.5. *Macrocycle* **9** · *CF_3COOH*. Compound **9** (46 mg, 73%) was prepared from **8** · 2 HCl (61 mg, 0.10 mmol) as described in *Exper. 2.8* for **21** · CF_3COOH, substituting EDC for DCC. ^{1}H-NMR (200 MHz, CD_3OD): 1.39 (*s*, 3 H); 1.42 (*s*, 3 H); 2.13–2.45 (*m*, 2 H); 2.50 (*d*, *J* = 16, 1 H); 2.64 (*d*, *J* = 16, 1 H); 2.75–3.08 (*m*, 2 H); 3.13 (*m*, 2 H); 3.50 (*t*, *J* = 6, 1 H); 4.39 (*dd*, *J* = 12, 8, 1 H); 4.51 (*d*, *J* = 16, 1 H); 5.60 (*d*, *J* = 16, 1 H); 7.15–7.62 (*m*, 12 H). FAB-MS: 518 (100, $[M + Li]^+$).

7. *(29R)-17,18,19,20,21,22,23,24,25,26,28,29,30,31-Tetradecahydro-25,25-dimethyl-7,10-etheno-5,29-methano-5H-dibenzo[i,q][1,5,11,20]tetraazacycloheptacosine-15,27,32(6H,16H)-trione Trifluoroacetate* (**12** · CF_3COOH).

7.1. *7-{[(*tert*-Butoxy)carbonyl]amino}-N-methoxy-N-methylheptanamide*. To a soln. of 7-{[(*tert*-butoxy)-carbonyl]-amino}heptanoic acid (300 mg, 1.22 mmol) in dry CH_2Cl_2 (12 ml) under N_2 was added *N,O*-dimethylhydroxyl-amine hydrochloride (131 mg, 1.34 mmol), EDC (234 mg, 1.22 mmol), 4-(dimethylamino)pyridine (DMAP, 5.5 mg, 0.05 mmol) and $(i\text{-Pr})_2EtN$ (0.233 ml, 1.34 mmol). The mixture was stirred at r.t. for 16 h and then evaporated. The residue was dissolved in AcOEt (250 ml), the soln. washed with sat. aq. $NaHCO_3$ soln. (2 × 50 ml), H_2O (2 × 50 ml), 5% aq. citric acid soln. (2 × 50 ml), and brine (2 × 50 ml). The org. layer was dried ($MgSO_4$) and evaporated: 267 mg (76%) of clear oil. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.31 (*m*, 4 H); 1.40 (*s*, 9 H); 1.43 (*m*, 2 H); 1.57 (*m*, 2 H); 2.37 (*t*, *J* = 7.5, 2 H); 3.07 (*q*, 2 H); 3.14 (*s*, 3 H); 3.64 (*s*, 3 H); 4.48 (br. *s*, 1 H). FAB-MS: 289 (10, $[M + H]^+$, $C_{14}H_{29}N_2O_4^+$).

7.2. *7-{[(*tert*-Butoxy)carbonyl]amino}heptanal*. To a soln. of the product of *Exper. 7.1* (150 mg, 0.52 mmol) in dry THF (6 ml) under N_2 at 0° was added $LiAlH_4$ (51 mg, 1.35 mmol). After stirring for 1 h at 0°, Et_2O (50 ml) was added followed by 20% aq. citric acid soln. (50 ml). The mixture was stirred vigorously for 30 min. Then the aq. phase was extracted with Et_2O (2 × 50 ml), the combined org. phase washed with sat. aq. $NaHCO_3$ soln. (50 ml), 10% aq. citric acid soln. (50 ml), and brine (50 ml), dried ($MgSO_4$) and evaporated: 113 mg (95%) of clear oil which was used without purification. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.20–1.70 (*m*, 8 H); 1.38 (*s*, 9 H); 2.39 (*m*, 2 H); 3.06 (*m*, 2 H); 4.47 (*s*, 1 H); 9.72 (*m*, 1 H).

7.3. tert-*Butyl-4'-{{(3R)-3-{{3-{{7-{[(*tert*-Butoxy)carbonyl]amino}heptyl}amino}-3-methyl-1-oxobutyl}amino}-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl}methyl}[1,1'-biphenyl]-2-carboxylate* (**10**). Compound **10** was prepared from the product of *Exper. 6.1* and 7-{[(*tert*-butoxy)carbonyl]amino}heptanal according to the procedure of *Exper. 6.4* for **8**. The intermediate was purified by flash chromatography (silica gel, $CHCl_3$/2N NH_3 in MeOH 98:2); 187 mg (84%) of **10**. White solid. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.10–1.62 (*m*, 10 H); 1.10 (*s*, 12 H); 1.15 (*s*, 3 H); 1.39 (*s*, 9 H); 1.92 (*m*, 1 H); 2.18 (*m*, 1 H); 2.25–2.70 (*m*, 8 H); 3.05 (*m*, 2 H); 4.50 (*m*, 2 H); 4.70 (*m*, 1 H); 5.30 (*m*, 1 H); 7.05–7.25 (*m*, 10 H); 7.27–7.47 (*m*, 2 H); 7.68 (*dd*, 1 H); 8.90 (*m*, 2 H). FAB-MS: 755 (10, $[M + H]^+$, $C_{45}H_{63}N_4O_6^+$).

7.4. *4'{{(3R)-3-{{3[(7-Aminoheptyl)amino]-3-methyl-1-oxobutyl}amino}-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl}methyl}[1,1'-biphenyl]-2-carboxylic Acid Dihydrochloride* (**11** · 2 HCl). Compound **11** was prepared from **10** (187 mg, 0.248 mmol) according to the procedure for **9** (*Exper. 6.4*) to afford 93 mg (52%) of **11**. White solid. ^{1}H-NMR (200 MHz, CD_3OD): 1.30–1.47 (*m*, 4 H); 1.30 (*s*, 3 H); 1.37 (*s*, 3 H); 1.47–1.75 (*m*, 6 H); 2.00–2.42 (*m*, 2 H); 2.48–2.75 (*m*, 4 H); 2.82 (*t*, *J* = 8, 2 H); 2.93 (*t*, *J* = 8, 2 H); 4.37 (*dd*, *J* = 12, 8, 1 H); 5.00 (*d*, *J* = 16, 1 H); 5.15 (*d*, *J* = 16, 1 H); 7.18–7.35 (*m*, 9 H); 7.40 (*m*, 1 H); 7.50 (*m*, 1 H); 7.76 (*d*, *J* = 8, 1 H). FAB-MS: 599 (40, $[M + H]^+$, $C_{36}H_{47}N_4O_4^+$).

7.5. *Macrocycle* **12** · *CF_3COOH*. Compound **12** · CF_3COOH was prepared from **11** (50 mg, 0.074 mmol) by the procedure described in *Exper. 2.8* **21**, substituting EDC for DCC: 8 mg (16%) of **12**. White solid ^{1}H-NMR (400 MHz, CD_3OD): 1.0–1.22 (*m*, 2 H); 1.25–1.50 (*m*, 6 H); 1.39 (*s*, 3 H); 1.46 (*s*, 3 H); 1.65 (*m*, 2 H); 2.21

(*m*, 1 H); 2.37 (*m*, 1 H); 2.57 (*d*, *J* = 16, 1 H); 2.70–3.02 (*m*, 4 H); 3.10 (*m*, 1 H); 3.25 (*m*, 2 H); 4.39 (*dd*, *J* = 12, 8, 1 H); 4.41 (*d*, *J* = 16, 1 H); 5.81 (*d*, *J* = 16, 1 H); 7.04 (*d*, *J* = 8, 1 H); 7.23 (*m*, 2 H); 7.31 (*d*, *J* = 8, 1 H); 7.39–7.52 (*m*, 7 H); 8.05 (*m*, 1 H). FAB-MS: 581 (100, $[M+1]^+$, $C_{36}H_{45}N_4O_3^+$).

8. *(*R*)-7,8,9,10,11,12,14,15,16,17-Decahydro-11,11-dimethyl-23*H*-24,27-etheno-15,22-methano-5*H*-dibenz-*[o, w]*tetrazolo[5,1-y][1,4,7,11,17]pentaazacyclopentacosine-6,13,34-trione Trifluoroacetate* (**5a** · CF_3COOH). 8.1. *3-{{2-{[(*tert*-Butoxy)carbonyl]amino}ethyl}amino}-3-methyl-*N*-{(3*R*)-2,3,4,5-tetrahydro-2-oxo-1-{[2′-(1*H*-tetrazol-5-yl)[[1,1′-biphenyl]-4-yl]methyl}-1*H*-1-benzazepin-3-yl]butanamide Trifluoroacetate.* To a soln. of 3-amino-3-methyl-*N*-{(3*R*)-2,3,4,5-tetrahydro-2-oxo-1-{[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl}-1*H*-1-benzazepin-3-yl}butanamide trifluoroacetate (**1**, L-692,429; 485 mg, 0.833 mmol) [2a] in dry MeOH (8 ml) were added Et_3N (0.232 ml, 1.67 mmol) and dry powdered 4-Å molecular sieves (2.5 g) followed by a soln. of *N*-[(*tert*-butoxy)carbonyl]glycinal (200 mg, 1.25 mmol); see *Exper. 6.3* in dry MeOH (1 ml). The pH of the mixture was carefully adjusted to 6.5 with AcOH and, while stirring, 1.0M $NaBH_3CN$/THF (5 ml, 5.0 mmol) was added *via* syringe after 2 h. The mixture was stirred for 20 h and then filtered through a pad of *Celite*. To the filtrate was added AcOH (1.0 ml; *CAUTION*! evolution of HCN gas). The resulting mixture was stirred for 30 min and then evaporated. The clear oil was purified by reversed-phase HPLC (*C-18*, MeOH/0.1% aq. CF_3COOH soln. 65:35); 347 mg (54%) of white solid. ^{1}H-NMR (200 MHz, CD_3OD): 1.30 (*s*, 9 H); 1.35 (*s*, 3 H); 1.39 (*s*, 3 H); 2.10 (*m*, 1 H); 2.20–2.60 (*m*, 5 H); 3.10 (*m*, 2 H); 3.35 (*m*, 2 H); 4.39 (*dd*, *J* = 11, 8, 1 H); 4.95 (*d*, *J* = 15, 1 H); 5.21 (*d*, *J* = 15, 1 H); 7.05 (*m*, 2 H); 7.17–7.47 (*m*, 7 H); 7.45–7.70 (*m*, 3 H). FAB-MS: 653 (100, $[M+H]^+$, $C_{36}H_{45}N_8O_4^+$).

8.2. *5-{4′-{{(3*R*)-3-{{3-{{2-{[(*tert*-Butoxy)carbonyl]amino}ethyl}amino}-3-methyl-1-oxobutyl}amino}-2,3,4,5-tetrahydro-2-oxo-1*H*-1-benzazepin-1-yl}methyl}-1,1′-biphenyl]-2-yl}-1*H*-tetrazol-1-acetic Acid* tert-*Butyl Ester Trifluoroacetate* (**3a** · CF_3COOH) *and -2*H*-tetrazol-2-acetic Acid* tert-*Butyl Ester Trifluoroacetate* (**3b** · CF_3COOH). To a soln. of 124 mg (0.162 mmol) of the product of *Exper. 8.1* in acetone (1 ml), Et_3N (0.068 ml, 0.49 mmol) and then, dropwise, *tert*-butyl bromoacetate (0.040 ml, 0.24 mmol) were added. The mixture was stirred at r.t. for 4 h and then evaporated. The residue was dissolved in AcOEt (70 ml) the soln. washed with H_2O (25 ml) and then brine, dried ($MgSO_4$), and evaporated, and the residue purified by reversed-phase HPLC (*C-18*, MeOH/0.1% aq. CF_3COOH soln.): 39 mg (39%) of **3b** · CF_3COOH and 78 mg (55%) of **3a** · CF_3COOH.

3a · CF_3COOH: ^{1}H-NMR (200 MHz, $CDCl_3$): 1.24 (*s*, 9 H); 1.39 (*s*, 15 H); 2.18 (*m*, 1 H); 2.3–2.75 (*m*, 4 H); 2.90 (*m*, 1 H); 3.17 (*m*, 2 H); 3.52 (*m*, 2 H); 4.10 (*d*, *J* = 16, 1 H); 4.20 (*d*, *J* = 16, 1 H); 4.42 (*m*, 1 H); 4.87 (*d*, *J* = 15, 1 H); 5.19 (*d*, *J* = 15, 1 H); 6.15 (*s*, 1 H); 7.10–7.35 (*m*, 4 H); 7.40–7.70 (*m*, 4 H); 8.50 (*m*, 2 H); 8.95 (*s*, 2 H). FAB-MS: 767 (60, $[M+H]^+$, $C_{42}H_{55}N_8O_6^+$).

3b · CF_3COOH: ^{1}H-NMR (200 MHz, $CDCl_3$): 1.37 (*s*, 15 H); 1.44 (*s*, 9 H); 2.18 (*m*, 1 H); 2.3–2.7 (*m*, 4 H); 2.90 (*m*, 1 H); 3.15 (*m*, 2 H); 3.50 (*m*, 2 H); 4.43 (*m*, 1 H); 4.92 (*d*, *J* = 15, 1 H); 5.10 (*d*, *J* = 15, 1 H); 5.20 (*s*, 2 H); 6.20 (*s*, 1 H); 7.10 (*s*, 3 H); 7.14–7.35 (*m*, 5 H); 7.40–7.60 (*m*, 3 H); 7.80 (*m*, 1 H); 8.55 (*s*, 3 H). FAB-MS: 767 (60, $[M+H]^+$, $C_{42}H_{55}N_8O_6^+$).

8.3. *5-{4′-{{(3*R*)-3-{{3-[(2-Aminoethyl)amino]-3-methyl-1-oxobutyl}amino}-2,3,4,5-tetrahydro-2-oxo-1*H*-1-benzazepin-1-yl}methyl}[1,1′-biphenyl]-2-yl}-1*H*-tetrazol-1-acetic Acid Bistrifluoroacetate* (**4a** · CF_3COOH). To a soln. of **3a** · CF_3COOH (78 mg, 0.089 mmol) in dry CH_2Cl_2 (2 ml) was added anisole (10 drops), CF_3COOH (2 ml). The mixture was stirred at r.t. for 3 h and then evaporated. The residue was purified by MPLC (*C-8*, MeOH/0.1% aq. CF_3COOH soln. 1:1): 45 mg (63%) of **4a** · CF_3COOH. White solid. ^{1}H-NMR (200 MHz, CD_3OD): 1.38 (*s*, 3 H); 1.42 (*s*, 3 H); 2.0–2.7 (*m*, 6 H); 3.32 (*m*, 4 H); 4.37 (*dd*, *J* = 10, 8, 1 H); 4.48 (*s*, 2 H); 4.79 (*d*, *J* = 15, 1 H); 5.32 (*d*, *J* = 15, 1 H); 7.05 (*d*, *J* = 8, 2 H); 7.15–7.35 (*m*, 6 H); 7.55 (*m*, 3 H); 7.68 (*m*, 1 H). FAB-MS: 612 (20, $[M+2H]^+$, $C_{33}H_{40}N_8O_4^+$).

8.4. *5-{4′-{{(3*R*)-3-{{3-[(2-Aminoethyl)amino]-3-methyl-1-oxobutyl}amino}-2,3,4,5-tetrahydro-2-oxo-1*H*-1-benzazepin-1-yl}methyl}[1,1′-biphenyl]-2-yl}-1*H*-tetrazol-1-acetic Acid Dihydrochloride* (**4a** · 2 HCl). To a soln. of **4a** · $2CF_3COOH$ (0.05 mmol) in MeOH (1 ml) was added 6N aq. HCl (2 ml). Evaporation afforded 34 mg (100%) of **4a** · 2 HCl which was used in the next step without further purification.

8.5. *Macrocycle* **5a** · *CF_3COOH*. To a soln. of 2-chloro-1-methylpyridinium iodide (7.3 mg, 0.028 mmol) in CH_2Cl_2 (18 ml) under N_2 was added Et_3N (0.006 ml, 0.044 mmol). Then a soln. of **4a** · 2 HCl (15 mg, 0.022 mmol) and Et_3N (0.012 ml, 0.088 mmol) in CH_2Cl_2 (3 ml) was added by syringe within 3 h. After the addition, the syringe was rinsed with dry CH_2Cl_2 (1 ml) and the resulting soln. added by syringe to the mixture which was stirred at r.t. for 24 h. The reaction was quenched with H_2O (10 ml), the aq. layer extracted with CH_2Cl_2, the combined org. extract washed with brine (25 ml), dried (Na_2SO_4), and evaporated, and the residue purified by reverse-phase HPLC (*C-18*, MeOH/0.1% aq. CF_3COOH soln. 6:4): 6.9 mg (44%) of **5a** · CF_3COOH. White solid. ^{1}H-NMR (200 MHz, CD_3OD): 1.35 (*m*, 6 H); 2.2–2.50 (*m*, 2 H); 2.53–2.75 (*m*, 2 H); 2.76–3.20 (*m*, 3 H); 3.35

(*m*, 2 H); 3.65 (*m*, 1 H); 4.37 (*m*, 2 H); 5.18 (*s*, 2 H); 5.79 (*m*, 1 H); 7.00 (*m*, 1 H); 7.20–7.80 (*m*, 11 H). FAB-MS: 593 (100, $[M + H]^+$, $C_{33}H_{37}N_8O_3^+$).

9. *(R)-11,12,13,14,15,16,18,19,20,21-Decahydro-15,15-dimethyl-27H-28,31-etheno-19,26-methano-8,5-nitrilo-9H-dibenzo[q,y][1,2,3,6,9,13,19]heptaazacycloheptacosine-10,17,34-trione Trifluoroacetate* (**5b** · CF_3COOH). 9.1. *5-{4'-{{(3R)-3-{{3-[(2-Aminoethyl)amino]-3-methyl-1-oxobutyl}amino}-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl}methyl}[1,1'-biphenyl]-2-yl}-2H-2-acetic Acid Bistrifluoroacetate* (**4b** · $2CF_3COOH$). Compound **4b** · $2CF_3COOH$ (37 mg, 71%) was prepared from **3b** · CF_3COOH (55 mg, 0.062 mmol) as described in *Exper. 8.3*. ^{1}H-NMR (200 MHz, CD_3OD): 1.38 (*s*, 3 H); 1.42 (*s*, 3 H); 2.0–2.6 (*m*, 6 H); 3.32 (*m*, 4 H); 4.39 (*dd*, J = 7, 11, 1 H); 4.92 (*d*, J = 16, 1 H); 5.22 (*d*, J = 16, 1 H); 5.42 (*s*, 2 H); 7.04 (*d*, J = 8, 2 H); 7.17 (*d*, J = 8, 2 H); 7.2–7.4 (*m*, 4 H); 7.41–7.62 (*m*, 3 H); 7.75 (*m*, 1 H). FAB-MS: 611 (100, $[M + H]^+$, $C_{33}H_{39}N_8O_4^+$).

9.2. *Macrocycle* **5b** · *CF_3COOH*. To a soln. of 2-chloro-1-methylpyridinium iodide (8 mg, 0.031 mmol) in dry CH_2Cl_2 (20 ml) under N_2 was added Et_3N (0.007 ml, 0.048 mmol). Then **4b** · $2CF_3COOH$ (19 mg, 0.022 mmol) and Et_3N (0.017 ml, 0.088 mmol) in CH_2Cl_2 (4 ml) were added by syringe within 3 h. After the addition, the syringe was rinsed with dry CH_2Cl_2 (1 ml) and the resulting soln. added by syringe to the mixture which was stirred at r.t. for 24 h. The reaction was quenched with H_2O (10 ml), the aq. layer extracted with CH_2Cl_2, the combined org. extract washed with brine (25 ml), dried (Na_2SO_4), evaporated, and the residue purified by chromatography (silica gel, AcOEt) to afford 6 mg of a white solid. A soln. of this solid in MeOH (1 ml) was added to sat. aq. Na_2CO_3 soln. (0.5 ml), the mixture stirred at r.t. for 3 days and then evaporated, and the residue dissolved in sat. aq. NaCl soln. The aq. soln. was extracted with AcOEt (3 × 30 ml), the combined org. phase dried ($MgSO_4$), evaporated, and the residue purified by reversed-phase HPLC (*C-18*, MeOH/0.1% aq. CF_3COOH soln. 6:4): 4.1 mg (26%) of **5b** · CF_3COOH. White solid. ^{1}H-NMR (200 MHz, CD_3OD): 1.32 (*s*, 3 H); 1.40 (*s*, 3 H); 2.15–2.42 (*m*, 2 H); 2.65 (*m*, 2 H); 2.70–3.00 (*m*, 2 H); 3.20 (*m*, 2 H); 3.45 (*m*, 1 H); 3.70 (*m*, 1 H); 4.10 (*d*, J = 16, 1 H); 4.39 (*m*, 1 H); 5.50 (*s*, 2 H); 5.90 (*d*, J = 16, 1 H); 6.90 (*m*, 1 H); 7.10–7.40 (*m*, 8 H); 7.52 (*m*, 1 H); 7.65 (*m*, 2 H). FAB-MS: 593 (100, $[M + H]^+$, $C_{33}H_{37}N_8O_3^+$).

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