Antibacterial Amide-Macrocycles V

The invention relates to antibacterial amide macrocycles and methods for their preparation, their use for the treatment and/or prophylaxis of diseases, as well their use for the production of medicaments for the treatment and/or prophylaxis of diseases, in particular of bacterial infections.

WO 03/106480 and WO 04/012816 describe macrocycles of the biphenomycin B type which have antibacterial activity and have amide and ester substituents respectively.

US 3,452,136, thesis of R. U. Meyer, Stuttgart University, Germany 1991, thesis of V. Leitenberger, Stuttgart University, Germany 1991, Synthesis (1992), (10), 1025-30, J. Chem. Soc., Perkin Trans. 1 (1992), (1), 123-30, J. Chem. Soc., Chem. Commun. (1991), (10), 744, Synthesis (1991), (5), 409-13, J. Chem. Soc., Chem. Commun. (1991), (5), 275-7, J. Antibiot. (1985), 38(11), 1462-8, J. Antibiot. (1985), 38(11), 1453-61 describe the natural product biphenomycin B as having antibacterial activity. Some steps in the synthesis of biphenomycin B are described in Synlett (2003), 4, 522-526.

Chirality (1995), 7(4), 181-92, J. Antibiot. (1991), 44(6), 674-7, J. Am. Chem. Soc. (1989), 111(19), 7323-7, J. Am. Chem. Soc. (1989), 111(19), 7328-33, J. Org. Chem. (1987), 52(24), 5435-7, Anal. Biochem. (1987), 165(1), 108-13, J. Org. Chem. (1985), 50(8), 1341-2, J. Antibiot. (1993), 46(3), C-2, J. Antibiot. (1993), 46(1), 135-40, Synthesis (1992), (12), 1248-54, Appl. Environ. Microbiol. (1992), 58(12), 3879-8, J. Chem. Soc., Chem. Commun. (1992), (13), 951-3 describe a structurally related natural product, biphenomycin A, which has a further substitution with a hydroxy group on the macrocycle.

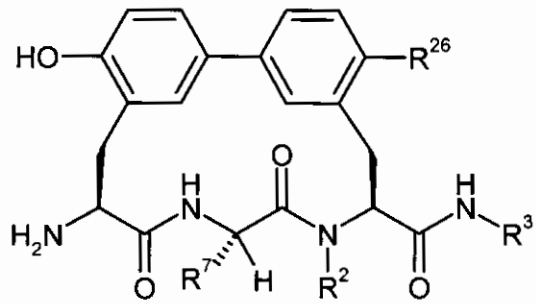
The natural products in terms of their properties do not comply with the requirements for antibacterial medicaments. Although structurally different agents with antibacterial activity are available on the market, the development of resistance is a regular possibility. Novel agents for a good and more effective therapy are therefore desirable.

One object of the present invention is therefore to provide novel and alternative compounds with the same or improved antibacterial activity for the treatment of bacterial diseases in humans and animals.

It has surprisingly been found that certain derivatives of these natural products in which the carboxy group of the natural product is replaced by an amide group which comprises a basic group have antibacterial activity against biphenomycin-resistant *S. aureus* strains (RN4220Bi^R and T17).

In addition, the derivatives show an improved spontaneous resistance rate for *S. aureus* wild-type strains and biphenomycin-resistant *S. aureus* strains.

The invention relates to compounds of formula

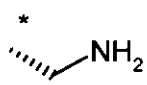
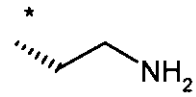
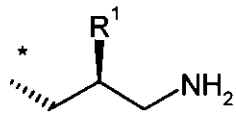
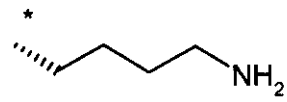


(I),

in which

R^{26} represents hydrogen, halogen, amino or methyl,

R^7 represents a group of formula




or


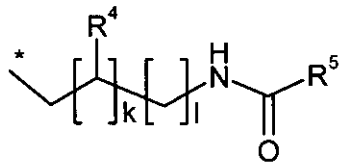
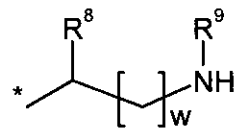
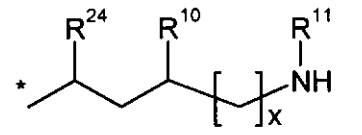
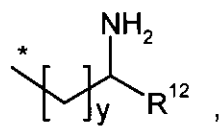
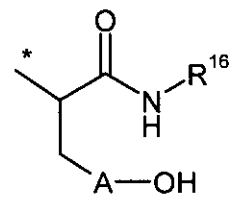
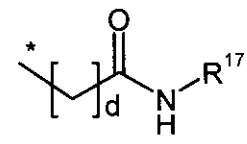
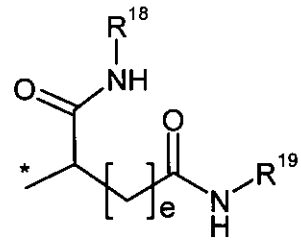
whereby

R^1 represents hydrogen or hydroxy,

* is the linkage site to the carbon atom,

R^2 represents hydrogen or methyl,

R^3 represents a group of formula







or


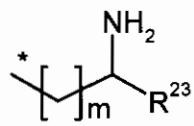
whereby

* is the linkage site to the nitrogen atom,

A represents a bond or phenyl,

R^4 represents hydrogen, amino or hydroxy,

R^5 represents a group of formula



wherein

* is the linkage site to the carbon atom,

R^{23} represents hydrogen or a group of formula *–$(CH_2)_n$-OH or *-$(CH_2)_o$-NH_2,

wherein

* is the linkage site to the carbon atom,

n and o independently of one another are a number 1, 2, 3 or 4,

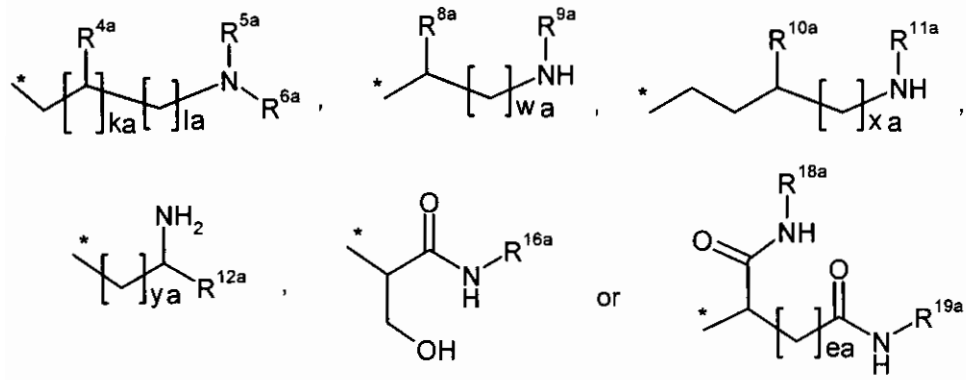
m is a number 0 or 1,

R^8 and R^{12} independently of one another represent a group of formula *–$CONHR^{14}$ or *-CH_2CONHR^{15},

wherein

* is the linkage site to the carbon atom,

R^{14} and R^{15} independently of one another represent a group of formula



wherein

* is the linkage site to the nitrogen atom,

R^{4a} represents hydrogen, amino or hydroxy,

R^{5a} represents hydrogen, methyl or aminoethyl,

R^{6a} represents hydrogen or aminoethyl,

or

R^{5a} and R^{6a} together with the nitrogen atom to which they are bonded form a piperazine ring,

R^{8a} and R^{12a} independently of one another represent *–$(CH_2)_{Z1a}$-OH, *-$(CH_2)_{Z2a}$-NHR^{13a}, *–$CONHR^{14a}$ or *-CH_2CONHR^{15a},

wherein

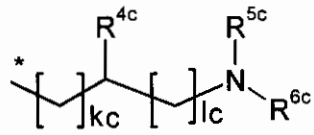
* is the linkage site to the carbon atom,

+Z1a and Z2a independently of one another are a number 1, 2 or 3,

R^{13a} represents hydrogen or methyl,

and

R^{14a} and R^{15a} independently of one another represent a group of formula



wherein

* is the linkage site to the nitrogen atom,

R^{4c} represents hydrogen, amino or hydroxy,

R^{5c} represents hydrogen, methyl or aminoethyl,

R^{6c} represents hydrogen or aminoethyl,

kc is a number 0 or 1,

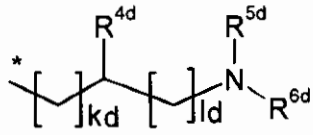
and

lc is a number 1, 2, 3 or 4,

R^{9a} and R^{11a} independently of one another represent hydrogen or methyl,

R^{10a} represents amino or hydroxy,

R^{16a} represents a group of formula



wherein

* is the linkage site to the nitrogen atom,

R^{4d} represents hydrogen, amino or hydroxy,

R^{5d} represents hydrogen, methyl or aminoethyl,

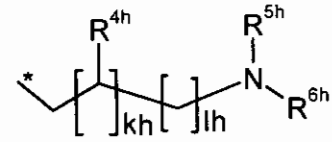
R^{6d} represents hydrogen or aminoethyl,

kd is a number 0 or 1,

and

ld is a number 1, 2, 3 or 4,

R^{18a} and R^{19a} independently of one another represent hydrogen or a group of formula



wherein

* is the linkage site to the nitogen atom,

R^{4h} represents hydrogen, amino or hydroxy,

R^{5h} represents hydrogen, methyl or aminoethyl,

R^{6h} represents hydrogen or aminoethyl,

or

R^{5h} and R^{6h} together with the nitogen atom to which they are bonded form a piperazine ring,

kh is a number 0 or 1,

and

lh is a number 1, 2, 3 or 4,

whereby R^{18a} and R^{19a} are not simultaneously hydrogen,

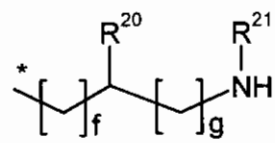
ka is a number 0 or 1,

ea is a number 1, 2 or 3,

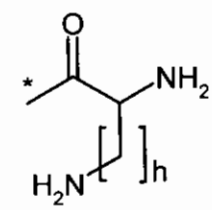
and

la, wa, xa and ya independently of one another are a number 1, 2, 3 or 4,

R^9 and R^{11} independently of one another represent hydrogen, methyl, *–$C(NH_2)$=NH or a group of formula



or



wherein

* is the linkage site to the nitrogen atom,

R^{20} represents hydrogen or *–$(CH_2)_i$-NHR^{22},

wherein

R^{22} represents hydrogen or methyl,

and

i is a number 1, 2 or 3,

R^{21} represents hydrogen or methyl,

f is a number 0, 1, 2 or 3,

g is a number 1, 2 or 3,

and

h is a number 1, 2, 3 or 4,

or

R^8 represents *–$(CH_2)_{Z1}$-OH,

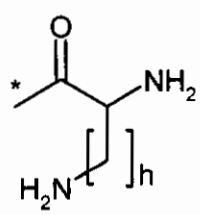
wherein

* is the linkage site to the carbon atom,

Z1 is a number 1, 2 or 3,

and

R^9 represents a group of formula



wherein

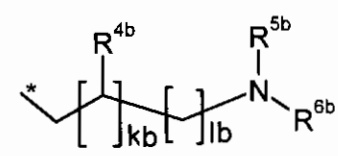
* is the linkage site to the nitrogen atom,

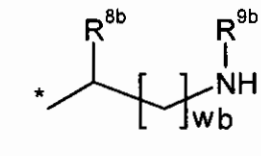
and

h is a number 1, 2, 3 or 4,

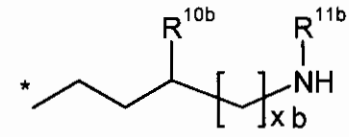
R^{10} represents amino or hydroxy,

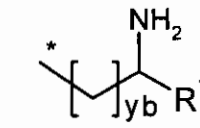
R^{16} and R^{17} independently of one another represent a group of formula



,


,



or


wherein

* is the linkage site to the nitrogen atom,

R^{4b} represents hydrogen, amino or hydroxy,

R^{5b} represents hydrogen, methyl or aminoethyl,

R^{6b} represents hydrogen or aminoethyl,

or

R^{5b} and R^{6b} together with the nitrogen atom to which they are bonded form a piperazine ring,

R^{8b} and R^{12b} independently of one another represent *-$(CH_2)_{Z1b}$-OH, *-$(CH_2)_{Z2b}$-NHR^{13b}, *-$CONHR^{14b}$ or *-CH_2CONHR^{15b},

wherein

* is the linkage site to the carbon atom,

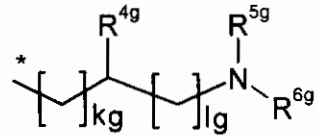
R^{13b} represents hydrogen or methyl,

and

Z1b and Z2b independently of one another are a number 1, 2 or 3,

and

R^{14b} and R^{15b} independently of one another represent a group of formula



wherein

* is the linkage site to the nitrogen atom,

R^{4g} represents hydrogen, amino or hydroxy,

R^{5g} represents hydrogen, methyl or aminoethyl,

R^{6g} represents hydrogen or aminoethyl,

kg is a number 0 or 1,

and

lg is a number 1, 2, 3 or 4,

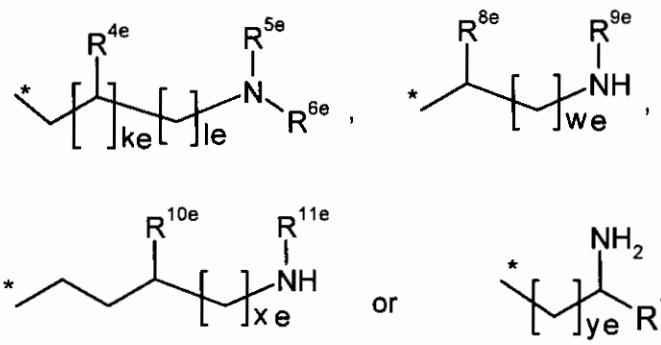
R^{9b} and R^{11b} independently of one another represent hydrogen or methyl,

R^{10b} represents amino or hydroxy,

kb is a number 0 or 1,

lb, wb, xb and yb independently of one another are a number 1, 2, 3 or 4,

R^{18} and R^{19} independently of one another represent hydrogen or a group of formula



wherein

* is the linkage site to the nitrogen atom,

R^{4e} represents hydrogen, amino or hydroxy,

R^{5e} represents hydrogen, methyl or aminoethyl,

R^{6e} represents hydrogen or aminoethyl,

or

R^{5e} and R^{6e} together with the nitrogen atom to which they are bonded form a piperazine ring,

R^{8e} and R^{12e} independently of one another represent *–$(CH_2)_{Z1e}$-OH or *-$(CH_2)_{Z2e}$-NHR^{13e},

wherein

* is the linkage site to the carbon atom,

R^{13e} represents hydrogen or methyl,

and

Z1e and Z2e independently of one another are a number 1, 2 or 3,

R^{9e} and R^{11e} independently of one another represent hydrogen or methyl,

R^{10e} represents amino or hydroxy,

ke is a number 0 or 1,

and

le, we, xe and ye independently of one another are a number 1, 2, 3 or 4,

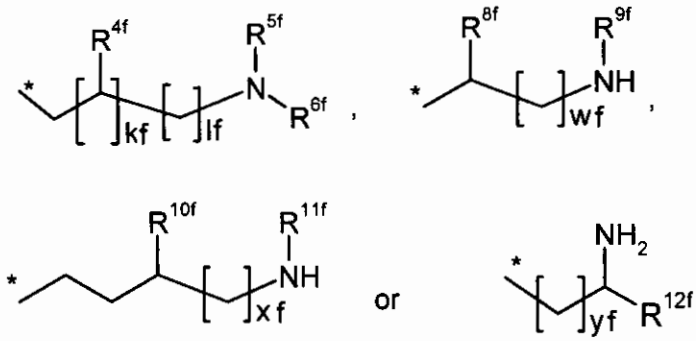
whereby R^{18} and R^{19} are not simultaneously hydrogen,

R^{24} represents a group of formula *–$CONHR^{25}$,

wherein

* is the linkage site to the carbon atom,

R^{25} represents a group of formula



wherein

* the linkage site to the nitrogen atom,

R^{4f} represents hydrogen, amino or hydroxy,

R^{5f} represents hydrogen, methyl or aminoethyl,

R^{6f} represents hydrogen or aminoethyl,

or

R^{5f} and R^{6f} together with the nitrogen atom to which they are bonded form a piperazine ring,

R^{8f} and R^{12f} independently of one another represent *–$(CH_2)_{z1f}$-OH or *-$(CH_2)_{z2f}$-NHR^{13f},

wherein

* is the linkage site to the carbon atom,

R^{13f} represents hydrogen or methyl,

and

Z1f and Z2f independently of one another are a number 1, 2 or 3,

R^{9f} and R^{11f} independently of one another represent hydrogen or methyl,

R^{10f} represents amino or hydroxy,

kf is a number 0 or 1,

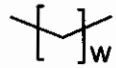
and

lf, wf, xf and yf independently of one another are a number 1, 2, 3 or 4,

d and e independently of one another are a number 1, 2 or 3,

k is a number 0 or 1,

l, w, x and y independently of one another are a number 1, 2, 3 or 4,



independently of one another may when w, x or y equals 3 carry a hydroxy group,

and their salts, their solvates and the solvates of their salts.

Compounds of the invention are the compounds of formula (I) and the salts, solvates and solvates of the salts thereof, as well as the compounds which are encompassed by formula (I) and are mentioned hereinafter as exemplary embodiment(s), and the salts, solvates and solvates of the salts thereof, insofar as the compounds which are encompassed by formula (I) and are mentioned hereinafter are not already salts, solvates and solvates of the salts.

The compounds of the invention may, depending on their structure, exist in stereoisomeric forms (enantiomers, diastereomers). The invention therefore relates to the enantiomers or diastereomers and their respective mixtures. The stereoisomerically pure constituents can be isolated from such mixtures of enantiomers and/or diastereomers in a known way by

known processes such as chromatography on a chiral phase or crystallization using chiral amines or chiral acids.

The invention also relates, depending on the structure of the compounds, to tautomers of the compounds.

Salts preferred for the purposes of the invention are physiologically acceptable salts of the compounds of the invention.

Physiologically acceptable salts of the compounds (I) include acid addition salts of mineral acids, carboxylic acids and sulfonic acids, e.g. salts of hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, toluenesulfonic acid, benzenesulfonic acid, naphthalenedisulfonic acid, acetic acid, propionic acid, lactic acid, tartaric acid, malic acid, citric acid, fumaric acid, maleic acid, trifluoroacetic acid and benzoic acid.

Physiologically acceptable salts of the compounds (I) also include salts of conventional bases such as, by way of example and preferably, alkali metal salts (e.g. sodium and potassium salts), alkaline earth metal salts (e.g. calcium and magnesium salts) and ammonium salts derived from ammonia or organic amines having 1 to 16 carbon atoms, such as, by way of example and preferably, ethylamine, diethylamine, triethylamine, ethyldiisopropylamine, monoethanolamine, diethanolamine, triethanolamine, dicyclohexylamine, dimethylaminoethanol, procaine, dibenzylamine, *N*-methylmorpholine, dihydroabietylamine, arginine, lysine, ethylenediamine and methylpiperidine.

Solvates for the purposes of the invention refer to those forms of the compounds which form a complex in the solid or liquid state through coordination with solvent molecules. Hydrates are a special form of solvates in which coordination takes place with water.

Halogen stands for fluorine, chlorine, bromine and iodine.

A symbol # on a carbon atom means that the compound is in enantiopure form with respect to the configuration at this carbon atom, meaning in the context of the present invention an enantiomeric excess of more than 90% (> 90% ee).

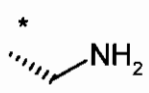
In the formulae of the groups which R^3 can represenst, the end point of the line beside which there is in each case an * does not represent a carbon atom or a CH_2 group but forms part of the bond to the nitrogen atom to which R^3 is bonded.

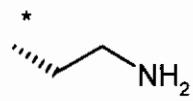
In the formulae of the groups which R^7 can respresent, the end point of the line beside which there is in each case an * does not represent a carbon atom or a CH_2 group but forms part of the bond to the carbon atom to which R^7 is bonded.

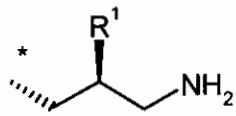
Preference is given in the context of the present invention to compounds of formula (I) in which

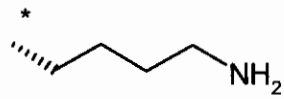
R^{26} represents hydrogen, halogen, amino or methyl,

R^7 represents a group of formula



,


,


or


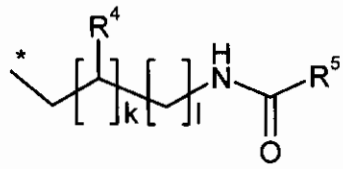
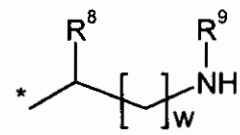
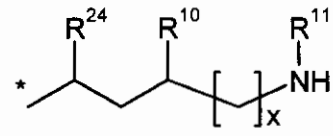
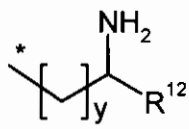
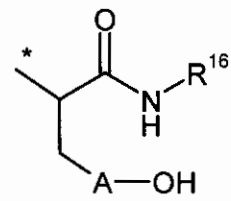
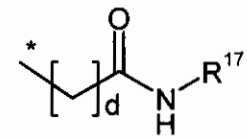
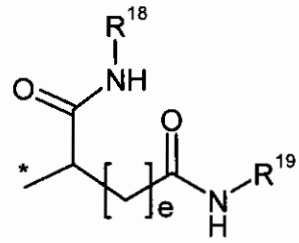
whereby

R^1 represents hydrogen or hydroxy,

* is the linkage site to the carbon atom,

R^2 represents hydrogen or methyl,

R^3 represents a group of formula







or


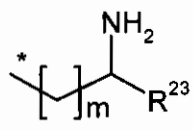
whereby

* is the linkage site to the nitrogen atom,

A represents a bond or phenyl,

R^4 represents hydrogen, amino or hydroxy,

R^5 represents a group of formula



wherein

* is the linkage site to the carbon atom,

R^{23} represents hydrogen or a group of formula *–$(CH_2)_n$-OH or *-$(CH_2)_o$-NH_2,

wherein

* is the linkage site to the carbon atom,

n and o independently of one another are a number 1, 2, 3 or 4,

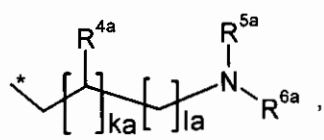
m is a number 0 or 1,

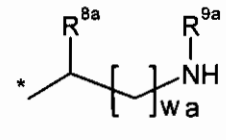
R^8 and R^{12} independently of one another represent a group of formula *–$CONHR^{14}$ or *-CH_2CONHR^{15},

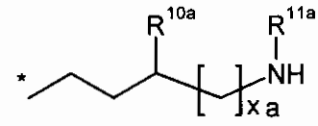
wherein

* is the linkage site to the carbon atom,

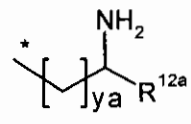
R^{14} and R^{15} independently of one another represent a group of formula

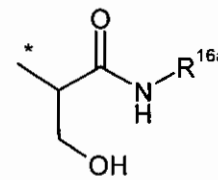


,


,


,



or


wherein

* is the linkage site to the nitrogen atom,

R^{4a} represents hydrogen, amino or hydroxy,

R^{5a} represents hydrogen, methyl or aminoethyl,

R^{6a} represents hydrogen or aminoethyl,

or

R^{5a} and R^{6a} together with the nitrogen atom to which they are bonded form a piperazine ring,

R^{8a} and R^{12a} independently of one another represent *–$(CH_2)_{Z1a}$-OH, *-$(CH_2)_{Z2a}$-NHR^{13a}, *–$CONHR^{14a}$ or *-CH_2CONHR^{15a},

wherein

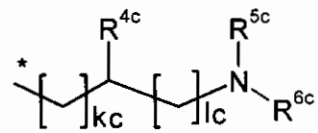
* is the point of the linkage to the carbon atom,

Z1a and Z2a independently of one another are a number 1, 2 or 3,

R^{13a} represents hydrogen or methyl,

and

R^{14a} and R^{15a} independently of one another represent a group of formula



wherein

* is the linkage site to the nitrogen atom,

R^{4c} represents hydrogen, amino or hydroxy,

R^{5c} represents hydrogen, methyl or aminoethyl,

R^{6c} represents hydrogen or aminoethyl,

kc is a number 0 or 1,

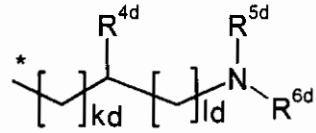
and

lc is a number 1, 2, 3 or 4,

R^{9a} and R^{11a} independently of one another represent hydrogen or methyl,

R^{10a} represents amino or hydroxy,

R^{16a} represents a group of formula



wherein

* is the linkage site to the nitrogen atom,

R^{4d} represents hydrogen, amino or hydroxy,

R^{5d} represents hydrogen, methyl or aminoethyl,

R^{6d} represents hydrogen or aminoethyl,

kd is a number 0 or 1,

and

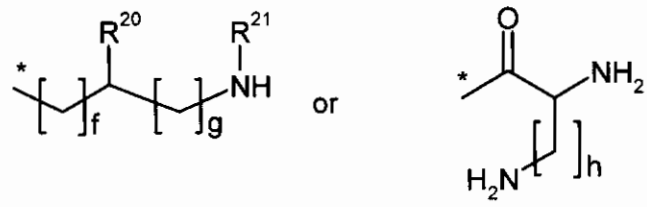
ld is a number 1, 2, 3 or 4,

ka is a number 0 or 1,

and

la, wa, xa and ya independently of one another are a number 1, 2, 3 or 4,

R^9 and R^{11} independently of one another represent hydrogen, methyl, *–$C(NH_2)$=NH or a group of formula



wherein

* is the linkage site to the nitrogen atom,

R^{20} represents hydrogen or *–$(CH_2)_i$-NHR^{22},

wherein

R^{22} represents hydrogen or methyl,

and

i is a number 1, 2 or 3,

R^{21} represents hydrogen or methyl,

f is a number 0, 1, 2 or 3,

g is a number 1, 2 or 3,

and

h is a number 1, 2, 3 or 4,

or

R^8 represents *–$(CH_2)_{Z1}$-OH,

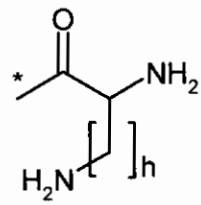
wherein

* is the linkage site to the carbon atom,

Z1 is a number 1, 2 or 3,

and

R^9 represents a group of formula



wherein

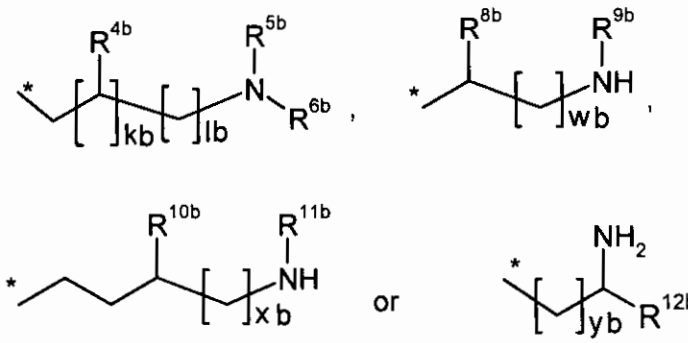
* is the linkage site to the nitrogen atom,

and

h is a number 1, 2, 3 or 4,

R^{10} represents amino or hydroxy,

R^{16} and R^{17} independently of one another represent a group of formula



wherein

* is the linkage site to the nitrogen atom,

R^{4b} represents hydrogen, amino or hydroxy,

R^{5b} represents hydrogen, methyl or aminoethyl,

R^{6b} represents hydrogen or aminoethyl,

or

R^{5b} and R^{6b} together with the nitrogen atom to which they are bonded form a piperazine ring,

R^{8b} and R^{12b} independently of one another represent *–$(CH_2)_{z1b}$-OH, *-$(CH_2)_{z2b}$-NHR^{13b}, *–$CONHR^{14b}$ or *–CH_2CONHR^{15b}

wherein

* is the linkage site to the carbon atom,

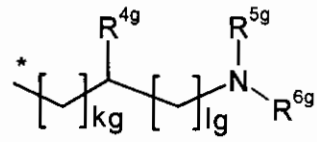
R^{13b} represents hydrogen or methyl,

and

Z1b and Z2b independently of one another are a number 1, 2 or 3,

and

R^{14b} and R^{15b} independently of one another represent a group of formula



wherein

* is the linkage site to the nitrogen atom,

R^{4g} represents hydrogen, amino or hydroxy,

R^{5g} represents hydrogen, methyl or aminoethyl,

R^{6g} represents hydrogen or aminoethyl,

kg is a number 0 or 1

and

lg is a number 1, 2, 3 or 4,

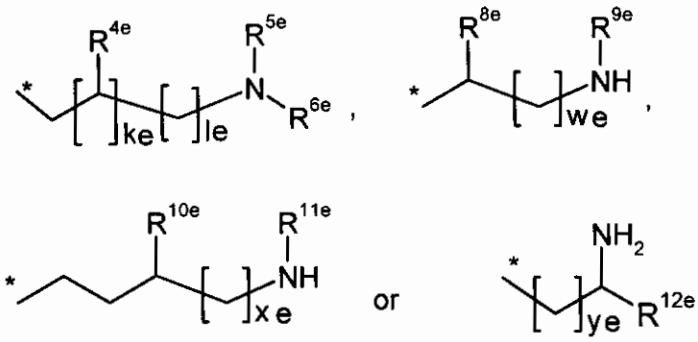
R^{9b} and R^{11b} independently of one another represent hydrogen or methyl,

R^{10b} represents amino or hydroxy,

kb is a number 0 or 1,

lb, wb, xb and yb independently of one another are a number 1, 2, 3 or 4,

R^{18} and R^{19} independently of one another represent hydrogen or a group of formula



wherein

* is the linkage site to the nitrogen atom,

R^{4e} represents hydrogen, amino or hydroxy,

R^{5e} represents hydrogen, methyl or aminoethyl,

R^{6e} represents hydrogen or aminoethyl,

or

R^{5e} and R^{6e} together with the nitrogen atom to which they are bonded form a piperazine ring,

R^{8e} and R^{12e} independently of one another represent *–$(CH_2)_{Z1e}$-OH or *-$(CH_2)_{Z2e}$-NHR^{13e},

wherein

* is the linkage site to the carbon atom,

R^{13e} represents hydrogen or methyl,

and

Z1e and Z2e independently of one another are a number 1, 2 or 3,

R^{9e} and R^{11e} independently of one another represent hydrogen or methyl,

R^{10e} represents amino or hydroxy,

ke is a number 0 or 1,

and

le, we, xe and ye independently of one another are a number 1, 2, 3 or 4,

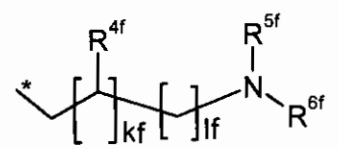
whereby R^{18} and R^{19} are not simultaneously hydrogen,

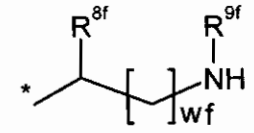
R^{24} represents a group of formula *–$CONHR^{25}$,

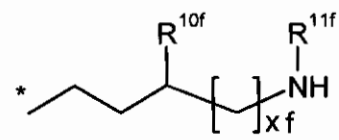
wherein

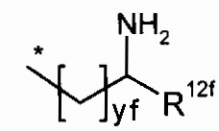
* is the linkage site to the carbon atom,

R^{25} represents a group of formula



,


,


or


wherein

* is the linkage site to the nitrogen atom,

R^{4f} represents hydrogen, amino or hydroxy,

R^{5f} represents hydrogen, methyl or aminoethyl,

R^{6f} represents hydrogen or aminoethyl,

or

R^{5f} and R^{6f} together with the nitrogen atom to which they are bonded form a piperazine ring,

R^{8f} and R^{12f} independently of one another represent *–$(CH_2)_{Z1f}$-OH or *-$(CH_2)_{Z2f}$-NHR^{13f},

wherein

* is the linkage site to the carbon atom,

R^{13f} represents hydrogen or methyl,

and

Z1f and Z2f independently of one another are a number 1, 2 or 3,

R^{9f} and R^{11f} independently of one another represent hydrogen or methyl,

R^{10f} represents amino or hydroxy,

kf is a number 0 or 1,

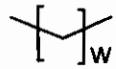
and

lf, wf, xf and yf independently of one another are a number 1, 2, 3 or 4,

d and e independently of one another are a number 1, 2 or 3,

k is a number 0 or 1,

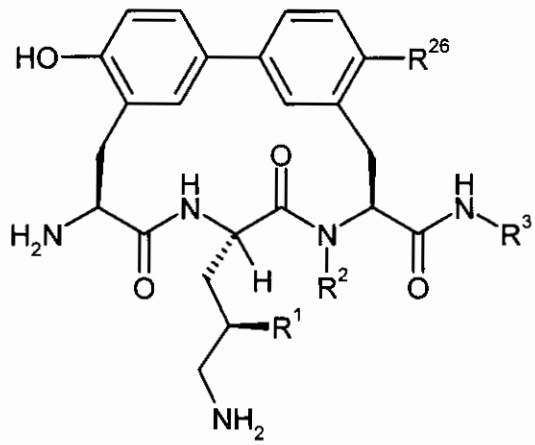
l, w, x and y independently of one another are a number 1, 2, 3 or 4,



independently of one another may when w, x or y equals 3 carry a hydroxy group,

and their salts, their solvates and the solvates of their salts.

Preference is also given in the context of the present invention to compounds of formula



(Ia),

in which

R^{26} represents hydrogen, halogen, amino or methyl,

R^1 represents hydrogen or hydroxy,

R^2 represents hydrogen or methyl,

R^3 is as defined above,

and their salts, their solvates and the solvates of their salts.

Preference is also given in the context of the present invention to compounds of formula (I) or (Ia) in which

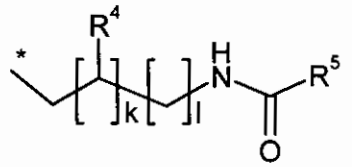
R^{26} represents hydrogen, chlorine or methyl.

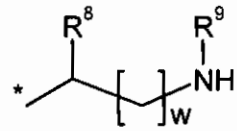
Preference is also given in the context of the present invention to compounds of formula (I) or (Ia) in which

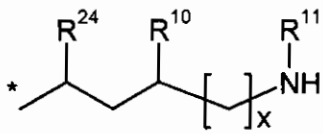
R^{26} represents hydrogen.

Preference is also given in the context of the present invention to compounds of formula (I) or (Ia) in which

R^3 represents a group of formula



,


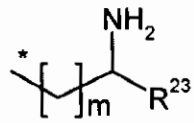
or


whereby

* is the linkage site to the nitrogen atom,

R^4 represents hydrogen, amino or hydroxy,

R^5 represents a group of formula



wherein

* is the linkage site to the carbon atom,

R^{23} represents hydrogen or a group of formula *–$(CH_2)_n$-OH or *-$(CH_2)_o$-NH_2,

wherein

* is the linkage site to the carbon atom,

n and o independently of one another are a number 1, 2, 3 or 4,

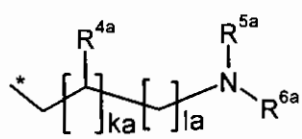
m is a number 0 or 1,

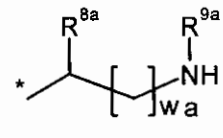
R^8 represents a group of formula *–$CONHR^{14}$ or *-CH_2CONHR^{15},

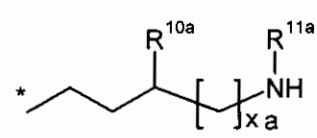
wherein

* is the linkage site to the carbon atom,

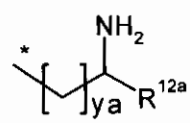
R^{14} and R^{15} independently of one another represent a group of formula

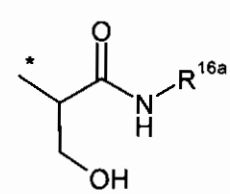


,


,


,



or


wherein

* is the linkage site to the nitrogen atom,

R^{4a} represents hydrogen, amino or hydroxy,

R^{5a} represents hydrogen, methyl or aminoethyl,

R^{6a} represents hydrogen or aminoethyl,

or

R^{5a} and R^{6a} together with the nitrogen atom to which they are bonded form a piperazine ring,

R^{8a} and R^{12a} independently of one another represent *-$(CH_2)_{Z1a}$-OH, *-$(CH_2)_{Z2a}$-NHR^{13a}, *-$CONHR^{14a}$ or *-CH_2CONHR^{15a},

wherein

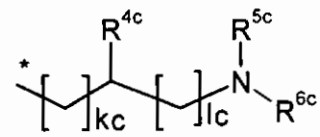
* is the linkage site to the carbon atom,

Z1a and Z2a independently of one another are a number 1, 2 or 3,

R^{13a} represents hydrogen or methyl,

and

R^{14a} and R^{15a} independently of one another represent a group of formula



wherein

* is the linkage site to the nitrogen atom,

R^{4c} represents hydrogen, amino or hydroxy,

R^{5c} represents hydrogen, methyl or aminoethyl,

R^{6c} represents hydrogen or aminoethyl,

kc is a number 0 or 1,

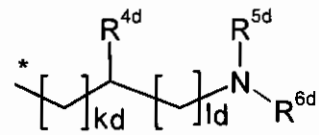
and

lc is a number 1, 2, 3 or 4,

R^{9a} and R^{11a} independently of one another represent hydrogen or methyl,

R^{10a} represents amino or hydroxy,

R^{16a} represents a group of formula



wherein

* is the linkage site to the nitrogen atom,

R^{4d} represents hydrogen, amino or hydroxy,

R^{5d} represents hydrogen, methyl or aminoethyl,

R^{6d} represents hydrogen or aminoethyl,

kd is a number 0 or 1,

and

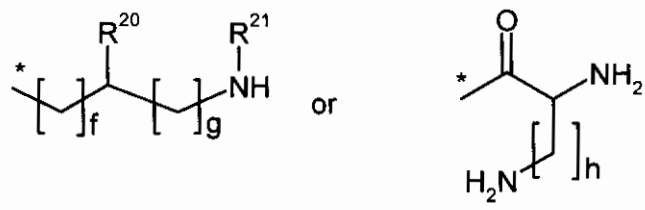
ld is a number 1, 2, 3 or 4,

ka is a number 0 or 1,

and

la, wa, xa and ya independently of one another are a number 1, 2, 3 or 4,

R^9 and R^{11} independently of one another represent hydrogen, methyl, *–$C(NH_2)$=NH or a group of formula



wherein

* is the linkage site to the nitrogen atom,

R^{20} represents hydrogen or *–$(CH_2)_i$-NHR^{22},

wherein

R^{22} represents hydrogen or methyl,

and

i is a number 1, 2 or 3,

R^{21} represents hydrogen or methyl,

f is a number 0, 1, 2 or 3,

g is a number 1, 2 or 3,

and

h is a number 1, 2, 3 or 4,

or

R^8 represents *–$(CH_2)_{Z1}$-OH

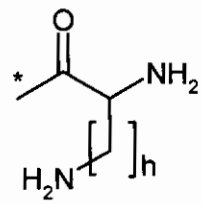
wherein

* is the linkage site to the carbon atom,

Z1 is a number 1, 2 or 3,

and

R^9 represents a group of formula



wherein

* is the linkage site to the nitrogen atom,

and

h is a number 1, 2, 3 or 4,

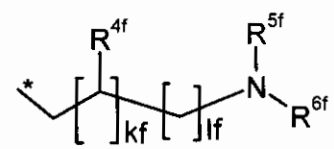
R^{10} represents amino or hydroxy,

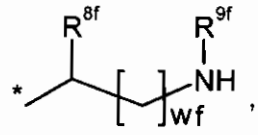
R^{24} represents a group of formula *–$CONHR^{25}$,

wherein

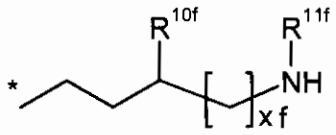
* is the linkage site to the carbon atom,

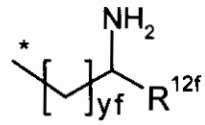
R^{25} represents a group of formula



,


,



or


wherein

* is the linkage site to the nitrogen atom,

R^{4f} represents hydrogen, amino or hydroxy,

R^{5f} represents hydrogen, methyl or aminoethyl,

R^{6f} represents hydrogen or aminoethyl,

or

R^{5f} and R^{6f} together with the nitrogen atom to which they are bonded form a piperazine ring,

R^{8f} and R^{12f} independently of one another represent *–$(CH_2)_{Z1f}$-OH or *-$(CH_2)_{Z2f}$-NHR^{13f},

wherein

* is the linkage site to the carbon atom,

R^{13f} represents hydrogen or methyl,

and

Z1f and Z2f independently of one another are a number 1, 2 or 3,

R^{9f} and R^{11f} independently of one another represent hydrogen or methyl,

R^{10f} represents amino or hydroxy,

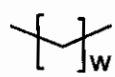
kf is a number 0 or 1,

and

lf, wf, xf and yf independently of one another are a number 1, 2, 3 or 4,

k is a number 0 or 1,

l, w and x independently of one another are a number 1, 2, 3 or 4,

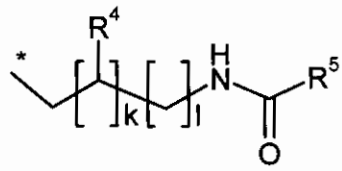


independently of one another may when w or x equals 3 carry a hydroxy group,

and their salts, their solvates and the solvates of their salts.

Particular preference is given in the context of the present invention to compounds of formula (I) or (Ia) in which

R^3 represents a group of formula

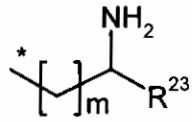


whereby

* is the linkage site to the nitrogen atom,

R^4 represents hydrogen, amino or hydroxy,

R^5 represents a group of formula



wherein

* is the linkage site to the carbon atom,

R^{23} represents hydrogen or a group of formula *–$(CH_2)_n$-OH or *-$(CH_2)_o$-NH_2,

wherein

* is the linkage site to the carbon atom,

n and o independently of one another are a number 1, 2, 3 or 4,

m is a number 0 or 1,

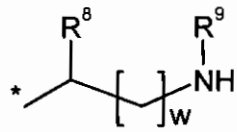
k is a number 0 or 1,

l is a number 1, 2, 3 or 4,

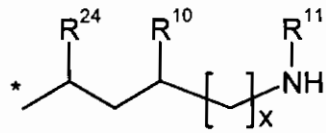
and their salts, their solvates and the solvates of their salts.

Particular preference is also given in the context of the present invention to compounds of formula (I) or (Ia) in which

R^3 represents a group of formula



or



whereby

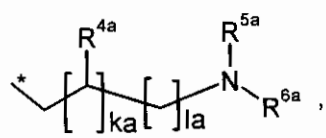
* is the linkage site to the nitrogen atom,

R^8 represents a group of formula *–CONHR^{14} or *-CH_2CONHR^{15},

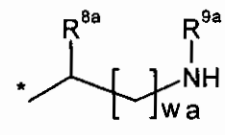
wherein

* is the linkage site to the carbon atom,

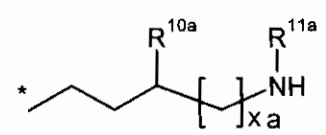
R^{14} and R^{15} independently of one another represent a group of formula



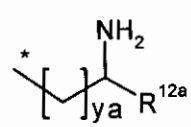
,



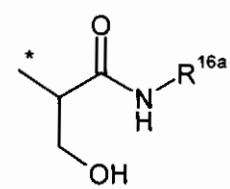
,



,



or



wherein

* is the linkage site to the nitrogen atom,

R^{4a} represents hydrogen, amino or hydroxy,

R^{5a} represents hydrogen, methyl or aminoethyl,

R^{6a} represents hydrogen or aminoethyl,

or

R^{5a} and R^{6a} together with the nitrogen atom to which they are bonded form a piperazine ring,

R^{8a} and R^{12a} independently of one another represent *–$(CH_2)_{Z1a}$-OH, *-$(CH_2)_{Z2a}$-NHR^{13a}, *–$CONHR^{14a}$ or *-CH_2CONHR^{15a},

wherein

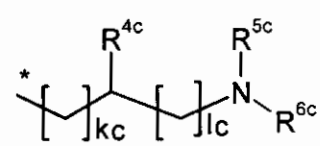
* is the linkage site to the carbon atom,

Z1a and Z2a independently of one another are a number 1, 2 or 3,

R^{13a} represents hydrogen or methyl,

and

R^{14a} and R^{15a} independently of one another represent a group of formula



wherein

* is the linkage site to the nitrogen atom,

R^{4c} represents hydrogen, amino or hydroxy,

R^{5c} represents hydrogen, methyl or aminoethyl,

R^{6c} represents hydrogen or aminoethyl,

kc is a number 0 or 1,

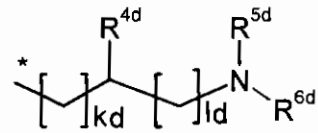
and

lc is a number 1, 2, 3 or 4,

R^{9a} and R^{11a} independently of one another represent hydrogen or methyl,

R^{10a} represents amino or hydroxy,

R^{16a} represents a group of formula



wherein

* is the linkage site to the nitrogen atom,

R^{4d} represents hydrogen, amino or hydroxy,

R^{5d} represents hydrogen, methyl or aminoethyl,

R^{6d} represents hydrogen or aminoethyl,

kd is a number 0 or 1,

and

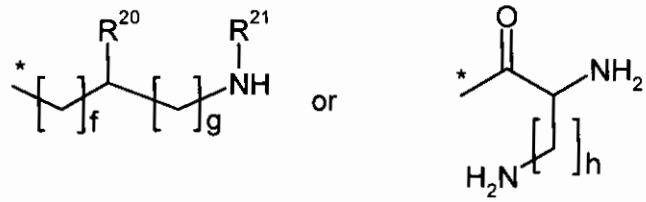
ld is a number 1, 2, 3 or 4,

ka is a number 0 or 1,

and

la, wa, xa and ya independently of one another are a number 1, 2, 3 or 4,

R^9 and R^{11} independently of one another represent hydrogen, methyl, *–$C(NH_2)$=NH or a group of formula



wherein

* is the linkage site to the nitrogen atom,

R^{20} represents hydrogen or *–$(CH_2)_i$-NHR^{22},

wherein

R^{22} represents hydrogen or methyl,

and

i is a number 1, 2 or 3,

R^{21} represents hydrogen or methyl,

f is a number 0, 1, 2 or 3,

g is a number 1, 2 or 3,

and

h is a number 1, 2, 3 or 4,

or

R^8 represents *–$(CH_2)_{Z1}$-OH,

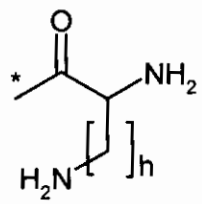
wherein

* is the linkage site to the carbon atom,

Z1 is a number 1, 2 or 3,

and

R^9 represents a group of formula



wherein

* is the linkage site to the nitrogen atom,

and

h is a number 1, 2, 3 or 4,

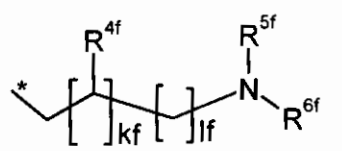
R^{10} represents amino or hydroxy,

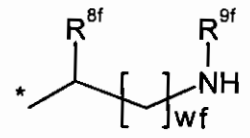
R^{24} represents a group of formula *–$CONHR^{25}$,

wherein

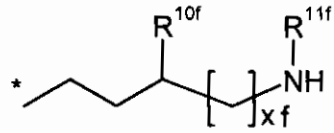
* is the linkage site to the carbon atom,

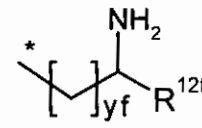
R^{25} represents a group of formula



,


,



or


wherein

* is the linkage site to the nitrogen atom,

R^{4f} represents hydrogen, amino or hydroxy,

R^{5f} represents hydrogen, methyl or aminoethyl,

R^{6f} represents hydrogen or aminoethyl,

or

R^{5f} and R^{6f} together with the nitrogen atom to which they are bonded form a piperazine ring,

R^{8f} and R^{12f} independently of one another represent *–$(CH_2)_{Z1f}$-OH or *-$(CH_2)_{Z2f}$-NHR^{13f},

wherein

* is the linkage site to the carbon atom,

R^{13f} represents hydrogen or methyl,

and

Z1f and Z2f independently of one another are a number 1, 2 or 3,

R^{9f} and R^{11f} independently of one another represent hydrogen or methyl,

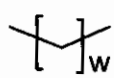
R^{10f} represents amino or hydroxy,

kf is a number 0 or 1,

and

lf, wf, xf and yf independently of one another are a number 1, 2, 3 or 4,

w and x independently of one another are a number 1, 2, 3 or 4,

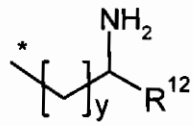


independently of one another may when w or x equals 3 carry a hydroxy group,

and their salts, their solvates and the solvates of their salts.

Preference is also given in the context of the present invention to compounds of formula (I) or (Ia) in which

R^3 represents a group of formula



whereby

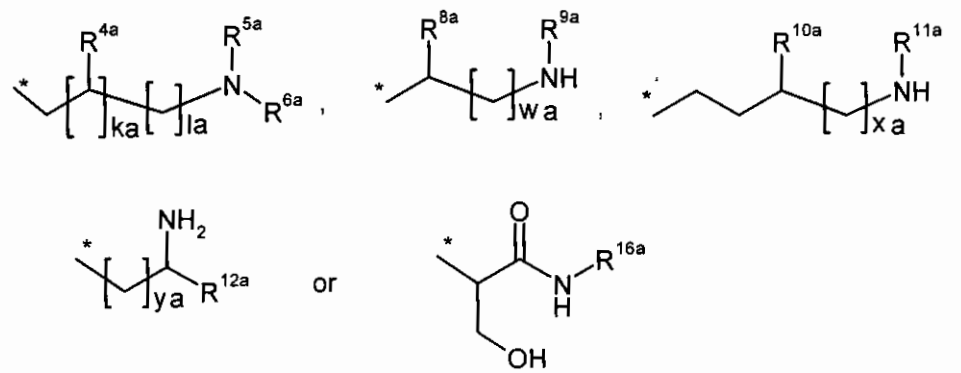
* is the linkage site to the nitrogen atom,

R^{12} represents a group of formula *–$CONHR^{14}$ or *-CH_2CONHR^{15},

wherein

* is the linkage site to the carbon atom,

R^{14} and R^{15} independently of one another represent a group of formula



wherein

* is the linkage site to the nitrogen atom,

R^{4a} represents hydrogen, amino or hydroxy,

R^{5a} represents hydrogen, methyl or aminoethyl,

R^{6a} represents hydrogen or aminoethyl,

or

R^{5a} and R^{6a} together with the nitrogen atom to which they are bonded form a piperazine ring,

R^{8a} and R^{12a} independently of one another represent *–$(CH_2)_{Z1a}$-OH, *-$(CH_2)_{Z2a}$-NHR^{13a}, *–$CONHR^{14a}$ or *-CH_2CONHR^{15a},

wherein

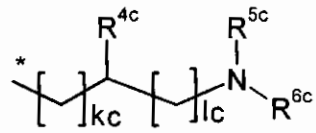
* is the linkage site to the carbon atom,

Z1a and Z2a independently of one another are a number 1, 2 or 3,

R^{13a} represents hydrogen or methyl,

and

R^{14a} and R^{15a} independently of one another represent a group of formula



wherein

* is the linkage site to the nitrogen atom,

R^{4c} represents hydrogen, amino or hydroxy,

R^{5c} represents hydrogen, methyl or aminoethyl,

R^{6c} represents hydrogen or aminoethyl,

kc is a number 0 or 1,

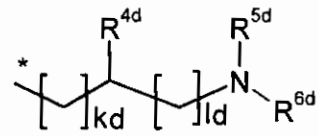
and

lc is a number 1, 2, 3 or 4,

R^{9a} and R^{11a} independently of one another represent hydrogen or methyl,

R^{10a} represents amino or hydroxy,

R^{16a} represents a group of formula



wherein

* is the linkage site to the nitrogen atom,

R^{4d} represents hydrogen, amino or hydroxy,

R^{5d} represents hydrogen, methyl or aminoethyl,

R^{6d} represents hydrogen or aminoethyl,

kd is a number 0 or 1,

and

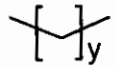
ld is a number 1, 2, 3 or 4,

ka is a number 0 or 1,

and

la, wa, xa and ya independently of one another are a number 1, 2, 3 or 4,

y is a number 1, 2, 3 or 4,

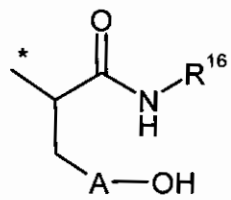


may when y equals 3 carry a hydroxy group,

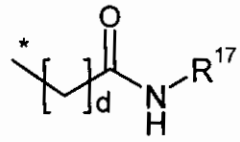
and their salts, their solvates and the solvates of their salts.

Preference is also given in the context of the present invention to compounds of formula (I) or (Ia) in which

R^3 represents a group of formula



or

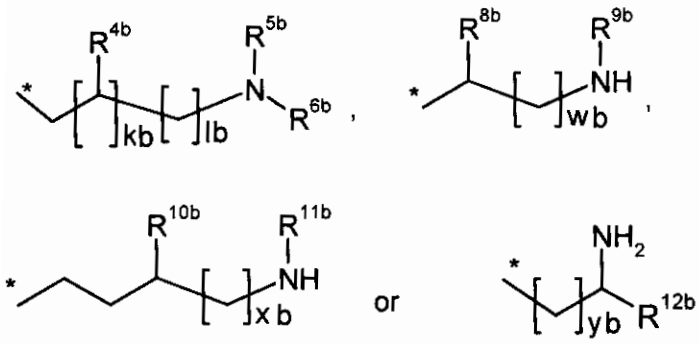


whereby

* is the linkage site to the nitrogen atom,

A represents a bond or phenyl,

R^{16} and R^{17} independently of one another represent a group of formula



wherein

* is the linkage site to the nitrogen atom,

R^{4b} represents hydrogen, amino or hydroxy,

R^{5b} represents hydrogen, methyl or aminoethyl,

R^{6b} represents hydrogen or aminoethyl,

or

R^{5b} and R^{6b} together with the nitrogen atom to which they are bonded form a piperazine ring,

R^{8b} and R^{12b} independently of one another represent *–$(CH_2)_{Z1b}$-OH or *-$(CH_2)_{Z2b}$-NHR^{13b},

wherein

* is the linkage site to the carbon atom,

R^{13b} represents hydrogen or methyl,

and

Z1b and Z2b independently of one another are a number 1, 2 or 3,

R^{9b} and R^{11b} independently of one another represent hydrogen or methyl,

R^{10b} represents amino or hydroxy,

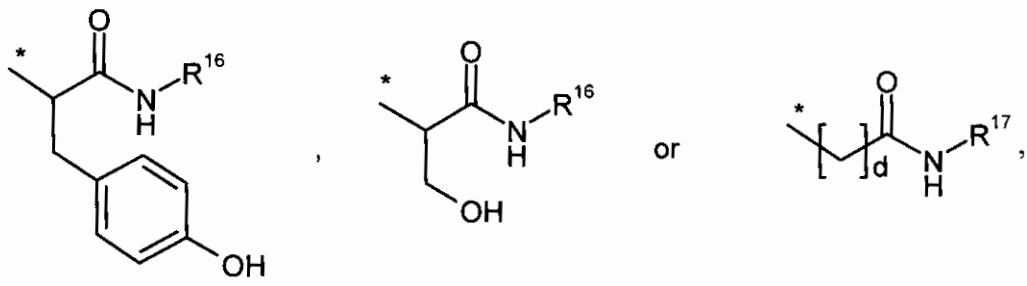
kb is a number 0 or 1,

lb, wb, xb and yb independently of one another are a number 1, 2, 3 or 4,

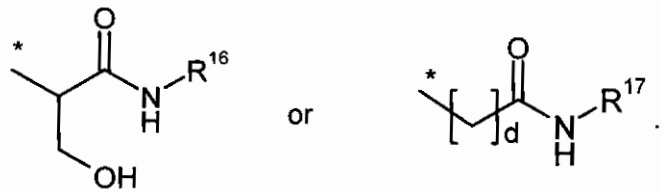
d is a number 1, 2 or 3,

and their salts, their solvates and the solvates of their salts.

Among these, particularly preferred compounds are those in which R^3 represents a group of formula

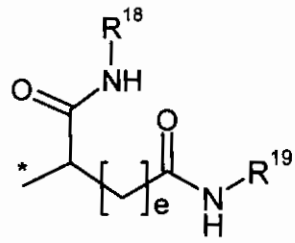


in particular a group of formula



Preference is also given in the context of the present invention to compounds of formula (I) or (Ia) in which

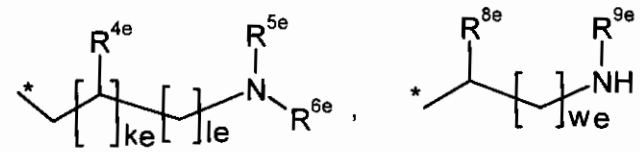
R^3 represents a group of formula

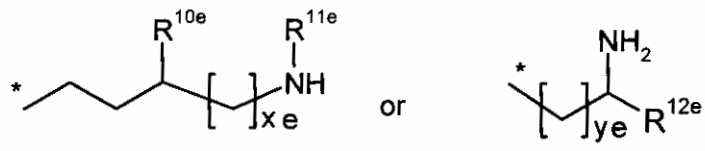


whereby

* is the linkage site to the nitrogen atom,

R^{18} and R^{19} independently of one another represent hydrogen or a group of formula





wherein

* is the linkage site to the nitrogen atom,

R^{4e} represents hydrogen, amino or hydroxy,

R^{5e} represents hydrogen, methyl or aminoethyl,

R^{6e} represents hydrogen or aminoethyl,

or

R^{5e} and R^{6e} together with the nitrogen atom to which they are bonded form a piperazine ring,

R^{8e} and R^{12e} independently of one another represent *–$(CH_2)_{Z1e}$-OH or *-$(CH_2)_{Z2e}$-NHR^{13e},

wherein

* is the linkage site to the carbon atom,

R^{13e} represents hydrogen or methyl,

and

Z1e and Z2e independently of one another are a number 1, 2 or 3,

R^{9e} and R^{11e} independently of one another represent hydrogen or methyl,

R^{10e} represents amino or hydroxy,

ke is a number 0 or 1,

and

le, we, xe and ye independently of one another are a number 1, 2, 3 or 4,

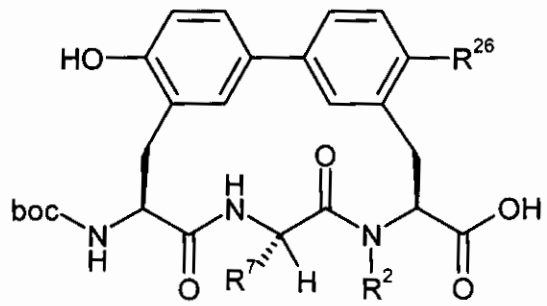
whereby R^{18} and R^{19} are not simultaneously hydrogen,

e is a number 1, 2 or 3,

and their salts, their solvates and the solvates of their salts.

The invention further relates to a method for preparing the compounds of formula (I) or their salts, their solvates or the solvates of their salts, whereby according to method

[A] compounds of formula



(II),

wherein R^2, R^7 and R^{26} have the meaning mentioned above, and boc is *tert*-butoxycarbonyl,

are reacted in a two-stage process firstly in the presence of one or more dehydrating reagents with compounds of formula

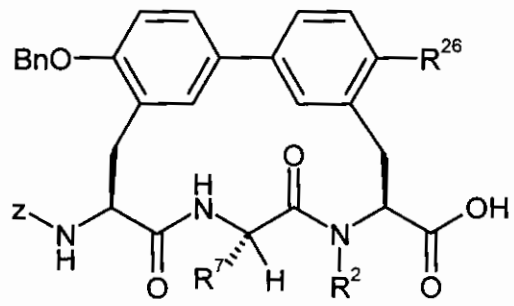
$$H_2NR^3 \qquad \text{(III)},$$

wherein R^3 has the abovementioned meaning,

and subsequently with an acid and/or by hydrogenolysis,

or

[B] compounds of formula



(IV),

wherein R^2, R^7 and R^{26} have the meaning mentioned above, and Z is benzyloxycarbonyl,

are reacted in a two-stage process firstly in the presence of one or more dehydrating reagents with compounds of formula

H_2NR^3 (III),

in which R^3 has the abovementioned meaning,

and subsequently with an acid or by hydrogenolysis.

The free base of the salts can be obtained for example by chromatography on a reversed phase column with an acetonitrile-water gradient with the addition of a base, in particular by using an RP18 Phenomenex Luna C18(2) column and diethylamine as base.

The invention further relates to a method for preparing the compounds of formula (I) or the solvates thereof according to claim 1 in which salts of the compounds or solvates of the salts of the compounds are converted into the compounds by chromatography with the addition of a base.

The hydroxy group on R^1 is where appropriate protected with a *tert*-butyldimethylsilyl group during the reaction with compounds of formula (III) which group is removed in the second reaction step.

Reactive functionalities in the radical R^3 of compounds of formula (III) are introduced into the synthesis already protected, with preference for acid-labile protecting groups (e.g. boc). After reaction has taken place to give compounds of formula (I), the protecting groups can be removed by a deprotection reaction. This takes place by standard methods of protecting group chemistry. Deprotection reactions under acidic conditions or by hydrogenolysis are preferred.

The reaction in the first stage of methods [A] and [B] generally takes place in inert solvents, where appropriate in the presence of a base, preferably in a temperature range from 0°C to 40°C under atmospheric pressure.

Examples of suitable dehydrating reagents in this connection are carbodiimides such as, for example, *N,N'*-diethyl-, *N,N'*-dipropyl-, *N,N'*-diisopropyl-, *N,N'*-dicyclohexylcarbodiimide, *N*-(3-dimethylaminoisopropyl)-*N'*-ethylcarbodiimide hydrochloride (EDC), *N*-cyclohexylcarbodiimide-*N'*-propyloxymethyl-polystyrene (PS-carbodiimide) or carbonyl compounds such as carbonyldiimidazole, or 1,2-oxazolium compounds such as 2-ethyl-5-phenyl-1,2-oxazolium 3-sulfate or 2-tert-butyl-5-methylisoxazolium perchlorate, or acylamino compounds such as 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline, or propanephosphonic anhydride, or isobutyl chloroformate, or bis(2-oxo-3-oxazolidinyl)phosphoryl chloride or benzotriazolyloxytri(dimethylamino)phosphonium hexafluorophosphate, or O-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HBTU), 2-(2-oxo-

1-(2H)-pyridyl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TPTU) or O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU), or 1-hydroxybenzotriazole (HOBt), or benzotriazol-1-yl-oxytris(dimethylamino)phosphonium hexafluorophosphate (BOP), or mixtures thereof, or mixtures thereof together with bases.

Examples of bases are alkali metal carbonates such as, for example, sodium or potassium carbonate, or sodium or potassium bicarbonate, or organic bases such as trialkylamines, e.g. triethylamine, *N*-methylmorpholine, *N*-methylpiperidine, 4-dimethylaminopyridine or diisopropylethylamine.

The condensation is preferably carried out with HATU in the presence of a base, in particular diisopropylethylamine, or with EDC and HOBt in the presence of a base, in particular triethylamine.

Examples of inert solvents are halohydrocarbons such as dichloromethane or trichloromethane, hydrocarbon such as benzene, or nitromethane, dioxane, dimethylformamide or acetonitrile. It is likewise possible to employ mixtures of the solvents. Dimethylformamide is particularly preferred.

The reaction with an acid in the second stage of methods [A] and [B] preferably takes place in a temperature range from 0°C to 40°C under atmospheric pressure.

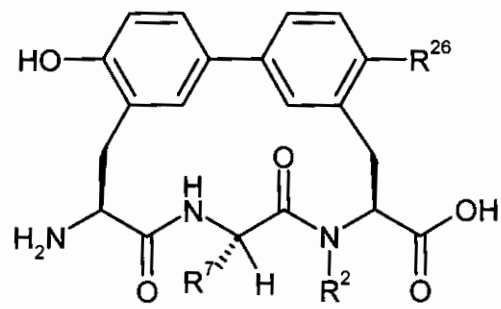
Suitable acids in this connection are hydrogen chloride in dioxane, hydrogen bromide in acetic acid or trifluoroacetic acid in methylene chloride.

The hydrogenolysis in the second stage of method [B] generally takes place in a solvent in the presence of hydrogen and palladium on activated carbon, preferably in a temperature range from 0°C to 40°C under atmospheric pressure.

Examples of solvents are alcohols such as methanol, ethanol, n-propanol or isopropanol, in a mixture with water and glacial acetic acid, with preference for a mixture of ethanol, water and glacial acetic acid.

The compounds of formula (III) are known or can be prepared in analogy to known methods.

The compounds of formula (II) are known or can be prepared by reacting compounds of formula



(V),

wherein R^2, R^7 and R^{26} have the meaning mentioned above,

with di(*tert*-butyl) dicarbonate in the presence of a base.

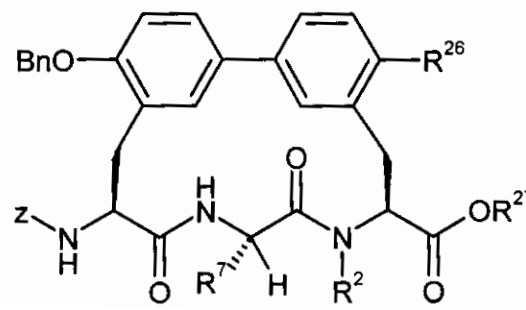
The reaction generally takes place in a solvent, preferably in a temperature range from 0°C to 40°C under atmospheric pressure.

Examples of bases are alkali metal hydroxides such as sodium or potassium hydroxide, or alkali metal carbonates such as cesium carbonate, sodium or potassium carbonate, or other bases such as DBU, triethylamine or diisopropylethylamine, with preference for sodium hydroxide or sodium carbonate.

Examples of solvents are halohydrocarbons such as methylene chloride or 1,2-dichloroethane, alcohols such as methanol, ethanol or isopropanol, or water.

The reaction is preferably carried out with sodium hydroxide in water or sodium carbonate in methanol.

The compounds of formula (V) are known or can be prepared by reacting compounds of formula



(VI),

wherein R^2, R^7 and R^{26} have the meaning mentioned above, and

R^{27} represents benzyl, methyl or ethyl,

with an acid or by hydrogenolysis as described for the second stage of method [B], where appropriate by subsequent reaction with a base to hydrolyse the methyl or ethyl ester.

The hydrolysis can for example take place as described for the reaction of compounds of formula (VI) to give compounds of formula (IV).

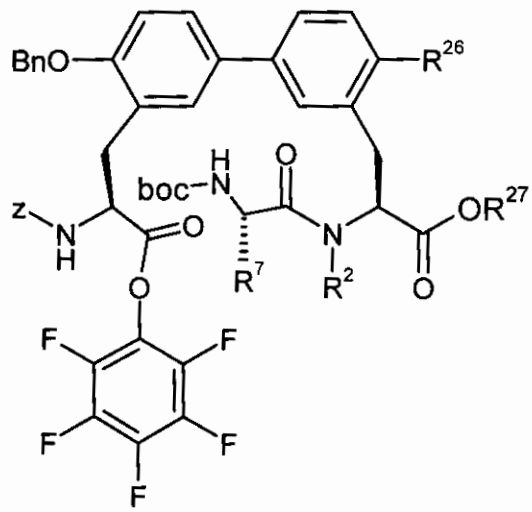
The compounds of formula (IV) are known or can be prepared by hydrolysing the benzyl, methyl or ethyl ester in compounds of formula (VI).

The reaction generally takes place in a solvent in the presence of a base, preferably in a temperature range from 0°C to 40°C under atmospheric pressure.

Examples of bases are alkali metal hydroxide such as lithium, sodium or potassium hydroxide, with preference for lithium hydroxide.

Examples of solvents are halohydrocarbons such as dichloromethane or trichloromethane, ethers, such as tetrahydrofuran or dioxane, or alcohols such as methanol, ethanol or isopropanol, or dimethylformamide. It is likewise possible to employ mixtures of the solvents or mixtures of the solvents with water. Tetrahydrofuran or a mixture of methanol and water are particularly preferred.

The compounds of formula (VI) are known or can be prepared by reacting compounds of formula



(VII),

wherein R^2, R^7, R^{26} and R^{27} have the meaning mentioned above,

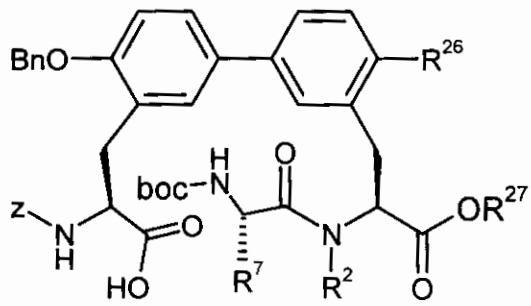
in the first stage with acids as described for the second stage of methods [A] and [B], and in the second stage with bases.

In the second stage the reaction with bases generally takes place in a solvent, preferably in a temperature range from 0°C to 40°C under atmospheric pressure.

Examples of bases are alkali metal hydroxides such as sodium or potassium hydroxide, or alkali metal carbonates such as cesium carbonate, sodium or potassium carbonate, or other bases such as DBU, triethylamine or diisopropylethylamine, with preference for triethylamine.

Examples of solvents are halohydrocarbons such as chloroform, methylene chloride or 1,2-dichloroethane, or tetrahydrofuran, or mixtures of the solvents, with preference for methylene chloride or tetrahydrofuran.

The compounds of formula (VII) are known or can be prepared by reacting compounds of formula



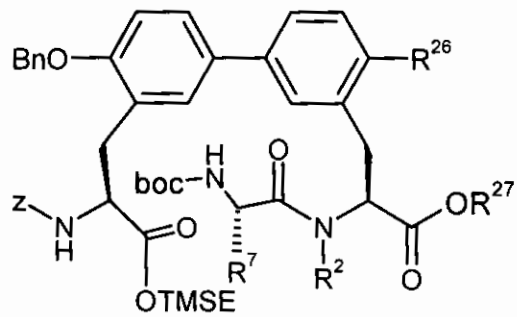
(VIII),

wherein R^2, R^7, R^{26} and R^{27} have the meaning mentioned above,

with pentafluorophenol in the presence of dehydrating reagents as described for the first stage of methods [A] and [B].

The reaction preferably takes place with DMAP and EDC in dichloromethane in a temperature range from -40°C to 40°C under atmospheric pressure.

The compounds of formula (VIII) are known or can be prepared by reacting compounds of formula



(IX),

wherein R^2, R^7, R^{26} and R^{27} have the meaning mentioned above,

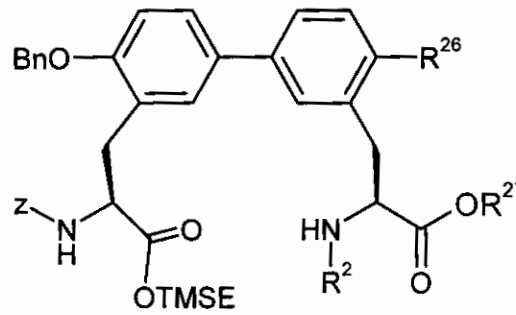
with fluoride, in particular with tetrabutylammonium fluoride.

The reaction generally takes place in a solvent, preferably in a temperature range from -10°C to 30°C under atmospheric pressure.

Examples of inert solvents are halohydrocarbons such as dichloromethane, or hydrocarbons such as benzene or toluene, or ethers such as tetrahydrofuran or dioxane, or dimethyl-

formamide. It is likewise possible to employ mixtures of the solvents. Tetrahydrofuran and dimethylformamide are preferred solvents.

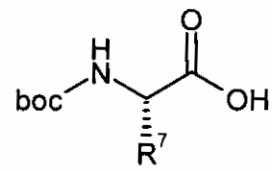
The compounds of formula (IX) are known or can be prepared by reacting compounds of formula



(X),

wherein R^2, R^{26} and R^{27} have the meaning mentioned above,

with compounds of formula



(XI),

wherein R^7 has the meaning mentioned above,

in the presence of dehydrating reagents as described for the first stage of methods [A] and [B].

The compounds of formula (X) are known or can be prepared in analogy to the methods described in the examples section.

The compounds of formula (XI) are known or can be prepared in analogy to known methods.

The compounds of the invention show a valuable range of pharmacological and pharmacokinetic effects which could not have been predicted.

They are therefore suitable for use as medicaments for the treatment and/or prophylaxis of diseases in humans and animals.

The compounds of the invention can, due to of their pharmacological properties, be employed alone or in combination with other active ingredients for the treatment and/or prophylaxis of infectious diseases, especially of bacterial infections.

For example, it is possible to treat and/or prevent local and/or systemic diseases caused by the following pathogens or by mixtures of the following pathogens:

gram-positive cocci, e.g. staphylococci (Staph. aureus, Staph. epidermidis) and streptococci (Strept. agalactiae, Strept. faecalis, Strept. pneumoniae, Strept. pyogenes); gram-negative cocci (neisseria gonorrhoeae) as well as gram-negative rods such as enterobacteriaceae, e.g. Escherichia coli, Haemophilus influenzae, Citrobacter (Citrob. freundii, Citrob. divernis), Salmonella and Shigella; furthermore klebsiellas (Klebs. pneumoniae, Klebs. oxytocy), Enterobacter (Ent. aerogenes, Ent. agglomerans), Hafnia, Serratia (Serr. marcescens), Proteus (Pr. mirabilis, Pr. rettgeri, Pr. vulgaris), Providencia, Yersinia, as well as the genus Acinetobacter. The antibacterial range additionally includes the genus Pseudomonas (Ps. aeruginosa, Ps. maltophilia) and strictly anaerobic bacteria such as Bacteroides fragilis, representatives of the genus Peptococcus, Peptostreptococcus, as well as the genus Clostridium; furthermore mycoplasmas (M. pneumoniae, M. hominis, M. urealyticum) as well as mycobacteria, e.g. Mycobacterium tuberculosis.

The above list of pathogens is merely by way of example and is by no means to be interpreted restrictively. Examples which may be mentioned of diseases which are caused by the pathogens mentioned or mixed infections and can be prevented, improved or healed by the topically applicable preparations of the invention, are:

infectious diseases in humans such as, for example, septic infections, bone and joint infections, skin infections, postoperative wound infections, abscesses, phlegmon, wound infections, infected burns, burn wounds, infections in the oral region, infections after dental operations, septic arthritis, mastitis, tonsillitis, genital infections and eye infections.

Apart from humans, bacterial infections can also be treated in other species. Examples which may be mentioned are:

Pigs: coli diarrhea, enterotoxemia, sepsis, dysentery, salmonellosis, metritis-mastitis-agalactiae syndrome, mastitis;

Ruminants (cattle, sheep, goats): diarrhea, sepsis, bronchopneumonia, salmonellosis, pasteurellosis, mycoplasmosis, genital infections;

Horses: bronchopneumonias, joint ill, puerperal and postpuerperal infections, salmonellosis;

Dogs and cats: bronchopneumonia, diarrhea, dermatitis, otitis, urinary tract infections, prostatitis;

Poultry (chickens, turkeys, quail, pigeons, ornamental birds and others): mycoplasmosis, E. coli infections, chronic airway diseases, salmonellosis, pasteurellosis, psittacosis.

It is likewise possible to treat bacterial diseases in the rearing and management of productive and ornamental fish, in which case the antibacterial spectrum is extended beyond the pathogens mentioned above to further pathogens such as, for example, Pasteurella, Brucella, Campylobacter, Listeria, Erysipelothris, corynebacteria, Borellia, Treponema, Nocardia, Rikettsie, Yersinia.

The present invention further relates to the use of the compounds of the invention for the treatment and/or prophylaxis of diseases, preferably of bacterial diseases, especially of bacterial infections.

The present invention further relates to the use of the compounds of the invention for the treatment and/or prophylaxis of diseases, especially of the aforementioned diseases.

The present invention further relates to the use of the compounds of the invention for the production of a medicament for the treatment and/or prophylaxis of diseases, especially of the aforementioned diseases.

The present invention further relates to a method for the treatment and/or prophylaxis of diseases, especially of the aforementioned diseases, using an antibacterially effective amount of the compounds of the invention.

The compounds of the invention may act systemically and/or locally. For this purpose, they can be administered in a suitable way such as, for example, orally, parenterally, pulmonarily, nasally, sublingually, lingually, buccally, rectally, dermally, transdermally, conjuctivally or otically or as an implant or stent.

For these administration routes the compounds of the invention can be administered in suitable administration forms.

Suitable for oral administration are administration forms which function according to the prior art and deliver the compounds of the invention rapidly and/or in modified fashion, and which contain the compounds of the invention in crystalline and/or amorphized and/or dissolved form, such as, for example, tablets (uncoated or coated tablets, for example having coatings which are resistant to gastric juice or dissolve with a delay or are insoluble and control the release of the compound of the invention), tablets or films/wafers, which disintegrate rapidly in the orale cavity, films/lyophilisates, capsules (for example hard or soft gelatin capsules), sugar-coated tablets, granules, pellets, powders, emulsions, suspensions, aerosols or solutions.

Parenteral administration can take place with avoidance of an absorption step (e.g. intravenous, intraarterial, intracardiac, intraspinal or intralumbar) or with inclusion of an absorption (e.g. intramuscular, subcutaneous, intracutaneous, percutaneous or intraperitoneal). Administration forms suitable for parenteral administration are, inter alia, preparations for injection and infusion in the form of solutions, suspensions, emulsions, lyophilisates or sterile powders.

Suitable for the other administration routes are, for example, pharmaceutical forms for inhalation (inter alia powder inhalers, nebulizers), nasal drops, solutions, sprays; tablets, films/wafers or capsules for lingual, sublingual or buccal administration, suppositories, preparations for the ears or eyes, vaginal capsules, aqueous suspensions (lotions, shaking mixtures), lipophilic suspensions, ointments, creams, transdermal therapeutic systems (such as, for example, patches), milk, pastes, foams, dusting powders, implants or stents.

The compounds of the invention can be converted into the stated administration forms. This can take place in a manner known per se by mixing with inert, nontoxic, pharmaceutically suitable excipients. These excipients include, inter alia, carriers (for example microcrystalline cellulose, lactose, mannitol), solvents (e.g. liquid polyethylene glycols), emulsifiers and dispersants or wetting agents (for example sodium dodecyl sulfate, polyoxysorbitan oleate), binders (for example polyvinylpyrrolidone), synthetic and natural polymers (for example albumin), stabilizers (e.g. antioxidants such as, for example, ascorbic acid), colors (e.g. inorganic pigments such as, for example, iron oxides) and taste and/or odor corrigents.

The present invention further relates to medicaments which comprise at least one compound of the invention, usually together with one or more inert, nontoxic, pharmaceutically suitable excipients, and to the use thereof for the aforementioned purposes.

It has generally proved advantageous on parenteral administration to administer amounts of about 5 to 250 mg/kg of body weight per 24 h to achieve effective results. The amount on oral administration is about 5 to 100 mg/kg of body weight per 24 h.

It may nevertheless be necessary where appropriate to deviate from the stated amounts, in particular as a function of the body weight, administration route, individual behavior towards the active ingredient, nature of the preparation and time or interval over which administration takes place. Thus, it may be sufficient in some cases to make do with less than the aforementioned minimum amount, whereas in other cases the stated upper limit must be exceeded. Where larger amounts are administered, it may be advisable to divide these into a plurality of single doses over the day.

The percentage data in the following tests and examples are percentages by weight unless otherwise indicated; parts are parts by weight. Solvent ratios, dilution ratios and concentration data for liquid/liquid solutions are in each case based on volume.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

A. Examples

Abbreviations used:

abs.	absolute
aq.	aqueous
Bn	benzyl
boc	*tert*-butoxycarbonyl
$CDCl_3$	chloroform
CH	cyclohexane
d	doublet (in ^{1}H-NMR)
dd	doublet of doublets (in ^{1}H-NMR)
DCC	dicyclohexylcarbodiimide
DIC	diisopropylcarbodiimide
DIEA	diisopropylethylamine (Hünig's base)
DMSO	dimethyl sulfoxide
DMAP	4-*N,N*-dimethylaminopyridine
DMF	dimethylformamide
EA	ethyl acetate (acetic acid ethyl ester)
EDC	*N'*-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide × HCl
ESI	electrospray ionization (in MS)
Ex.	example
Fmoc	9-fluorenylmethoxycarbonyl
HATU	*O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate
HBTU	*O*-(benzotriazol-1-yl)-*N,N,N'N'*-tetramethyluronium hexafluorophosphate
HOBt	1-hydroxy-1H-benzotriazole × H_2O
h	hour(s)
HPLC	high pressure, high performance liquid chromatography
LC-MS	coupled liquid chromatography-mass spectroscopy
m	multiplet (in ^{1}H-NMR)
min	minute
MS	mass spectroscopy
NMR	nuclear magnetic resonance spectroscopy
MTBE	methyl *tert*-butyl ether
Pd/C	palladium/carbon
PFP	pentafluorophenol
q	quartet (in ^{1}H-NMR)
R_f	retention index (in TLC)
RP	reverse phase (in HPLC)
RT	room temperature

R_t	retention time (in HPLC)
s	singlet (in ^{1}H-NMR)
sat	saturated
t	triplet (in ^{1}H-NMR)
TBS	*tert*-butyldimethylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMSE	2-(trimethylsilyl)ethyl
TPTU	2-(2-oxo-1(2H)-pyridyl)-1,1,3,3,-tetramethyluronium tetrafluoroborate
Z	benzyloxycarbonyl

LC-MS and HPLC methods:

Method 1 (LC-MS): Instrument: Micromass Quattro LCZ with HPLC Agilent series 1100; column: Phenomenex Synergi 2µ Hydro-RP Mercury 20 mm × 4 mm; eluent A: 1 l of water + 0.5 ml of 50% formic acid, eluent B: 1 l of acetonitrile + 0.5 ml of 50% formic acid; gradient: 0.0 min 90%A → 2.5 min 30%A → 3.0 min 5%A → 4.5 min 5%A; flow rate: 0.0 min 1 ml/min, 2.5 min/3.0 min/4.5 min 2 ml/min; oven: 50°C; UV detection: 208-400 nm.

Method 2 (LC-MS): MS instrument type: Micromass ZQ; HPLC instrument type: Waters Alliance 2795; column: Phenomenex Synergi 2µ Hydro-RP Mercury 20 × 4 mm; eluent A: 1 l of water + 0.5 ml of 50% formic acid, eluent B: 1 l of acetonitrile + 0.5 ml of 50% formic acid; gradient: 0.0 min 90%A → 2.5 min 30%A → 3.0 min 5%A → 4.5 min 5%A; flow rate: 0.0 min 1 ml/min, 2.5 min/3.0 min/4.5 min 2 ml/min; oven: 50°C; UV detection: 210 nm.

Method 3 (LC-MS): MS instrument type: Micromass ZQ; HPLC instrument type: HP 1100 series; UV DAD; column: Phenomenex Synergi 2µ Hydro-RP Mercury 20 mm × 4 mm; eluent A: 1 l of water + 0.5 ml of 50% formic acid, eluent B: 1 l of acetonitrile + 0.5 ml of 50% formic acid; gradient: 0.0 min 90%A → 2.5 min 30%A → 3.0 min 5%A → 4.5 min 5%A; flow rate: 0.0 min 1 ml/min, 2.5 min/3.0 min/4.5 min 2 ml/min; oven: 50°C; UV detection: 210 nm.

Method 4 (LC-MS): Instrument: Micromass Platform LCZ with HPLC Agilent series 1100; column: Grom-SIL120 ODS-4 HE, 50 mm × 2.0 mm, 3 µm; eluent A: 1 l of water + 1 ml of 50% formic acid, eluent B: 1 l of acetonitrile + 1 ml of 50% formic acid; gradient: 0.0 min 100%A → 0.2 min 100%A → 2.9 min 30%A → 3.1 min 10%A → 4.5 min 10%A; oven: 55°C; flow rate: 0.8 ml/min; UV detection: 208-400 nm.

Method 5 (LC-MS): MS instrument type: Micromass ZQ; HPLC instrument type: Waters Alliance 2795; column: Merck Chromolith SpeedROD RP-18e 50 × 4.6 mm; eluent A: water + 500 µl of 50% formic acid/l; eluent B: acetonitrile + 500 µl of 50% formic acid/l; gradient: 0.0 min 10%B → 3.0 min 95%B → 4.0 min 95%B; oven: 35°C; flow rate: 0.0 min 1.0 ml/min → 3.0 min 3.0 ml/min → 4.0 min 3.0 ml/min; UV detection: 210 nm.

Method 6 (LC-MS): MS instrument type: Micromass ZQ; HPLC instrument type: HP 1100 series; UV DAD; column: Grom-Sil 120 ODS-4 HE 50 mm × 2 mm, 3.0 µm; eluent A: water + 500 µl of 50% formic acid/l, eluent B: acetonitrile + 500 µl of 50% formic acid/l; gradient: 0.0 min 0%B → 2.9 min 70%B → 3.1 min 90%B → 4.5 min 90%B; oven: 50°C, flow rate: 0.8 ml/min, UV detection: 210 nm.

Method 7 (LC-MS): MS instrument type: Micromass ZQ; HPLC instrument type: Waters Alliance 2790; column: Grom-Sil 120 ODS-4 HE 50 mm × 2 mm, 3.0 µm; eluent A: water + 500 µl of 50% formic acid; eluent B: acetonitrile + 500 µl of 50% formic acid/l; gradient: 0.0 min 5%B → 2.0 min 40%B → 4.5 min 90%B → 5.5 min 90%B; oven: 45°C; flow rate: 0.0 min 0.75 ml/min → 4.5 min 0.75 ml/min 5.5 min → 5.5 min 1.25 ml/min; UV detection: 210 nm.

Method 8 (LC-MS): Instrument: Micromass Platform LCZ with HPLC Agilent series 1100; column: Thermo HyPURITY Aquastar, 3 µ 50 mm × 2.1 mm; eluent A: 1 l of water + 0.5 ml of 50% formic acid, eluent B: 1 l of acetonitrile + 0.5 ml of 50% formic acid; gradient: 0.0 min 100%A → 0.2 min 100%A → 2.9 min 30%A → 3.1 min 10%A → 5.5 min 10%A; oven: 50°C; flow rate: 0.8 ml/min; UV detection: 210 nm.

Method 9 (LC-MS): MS instrument type: Micromass ZQ; HPLC instrument type: Waters Alliance 2790; column: Grom-Sil 120 ODS-4 HE 50 × 2 mm, 3.0 µm; eluent B: acetonitrile + 0.05% formic acid, eluent A: water + 0.05% formic acid; gradient: 0.0 min 70%B → 4.5 min 90%B → 5.5 min 90%B; oven: 45°C; flow rate: 0.0 min 0.75 ml/min → 4.5 min 0.75 ml/min → 5.5 min 1.25 ml/min; UV detection: 210 nm.

Method 10 (LC-MS): Instrument: Micromass Platform LCZ with HPLC agilent series 1100; column: Thermo Hypersil GOLD-3µ 20 × 4 mm; eluent A: 1 l of water + 0.5 ml of 50% formic acid, eluent B: 1 l of acetonitrile + 0.5 ml of 50% formic acid; gradient: 0.0 min 100%A → 0.2 min 100%A → 2.9 min 30%A → 3.1 min 10%A → 5.5 min 10%A; oven: 50°C; flow rate: 0.8 ml/min; UV detection: 210 nm.

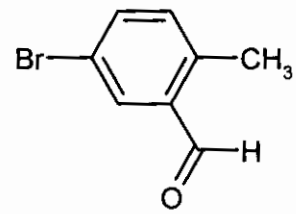
Method 11 (HPLC): Instrument: HP 1100 with DAD detection; column: Kromasil RP-18, 60 mm × 2 mm, 3.5 µm; eluent A: 5 ml of $HClO_4$/l of water, eluent B: acetonitrile; gradient: 0 min 2%B, 0.5 min 2%B, 4.5 min 90%B, 6.5 min 90%B; flow rate: 0.75 ml/min; oven: 30°C; UV detection: 210 nm.

Method 12 (HPLC): Instrument: HP 1100 with DAD detection; column: Kromasil RP-18, 60 mm × 2 mm, 3.5 µm; eluent A: 5 ml of $HClO_4$/l of water, eluent B: acetonitrile; gradient: 0 min 2%B, 0.5 min 2%B, 4.5 min 90%B, 15 min 90%B; flow rate: 0.75 ml/min; oven: 30°C; UV detection: 210 nm.

Starting compounds

Example 1A

5-Bromo-2-methylbenzaldehyde



77.7 g (583 mmol) of aluminum trichloride are suspended in 200 ml of dichloromethane and cooled to 0°C. 40.0 g (333 mmol) of 2-methylbenzaldehyde are added dropwise over the course of 30 min. Then, 53.2 g (333 mmol) of bromine are added over the course of 6 h at 0°C, the mixture is allowed to warm to RT and then stirred for 12 h. The reaction solution is added to 500 ml of ice-water. The aqueous phase is extracted a number of times with dichloromethane. The combined organic phases are washed successively with 2N hydrochloric acid, a saturated aqueous sodium bicarbonate solution and a saturated aqueous sodium chloride solution. The organic phase is dried over sodium sulfate and concentrated in vacuo. The residue is purified is silica gel chromatography and then via crystallization from cyclohexane. The precipitated product is collected by filtration.

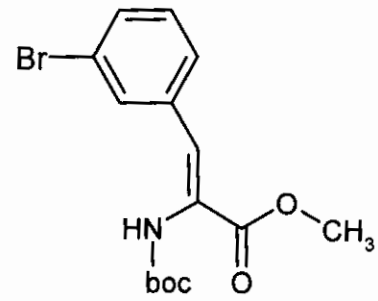
Yield: 3.2 g (5% of theory)

LC-MS (Method 7): R_t = 3.26 min

MS (EI): m/z = 199 $(M+H)^+$

Example 2A

Methyl (2Z)-3-(3-bromophenyl)-2-[(tert-butoxycarbonyl)amino]acrylate



7.48 ml (59.5 mmol) of *N,N,N,N*-tetramethylguanidine are added to a solution, cooled to -70°C, of 10 g (54.1 mmol) of 3-bromobenzaldehyde and 17.7 g (59.5 mmol) of methyl [(*tert*-butoxycarbonyl)amino](dimethoxyphosphoryl)acetate in 200 ml of anhydrous tetrahydrofuran. After stirring for 4 h at -70°C, the reaction mixture is stirred for 15 h at RT. 500 ml of water and 500 ml of ethyl acetate are added to the mixture. The organic phase is washed with water, dried over sodium sulfate and concentrated. The crude product is purified by column chromatography on silica gel (mobile phase cyclohexane:ethyl acetate 4:1).

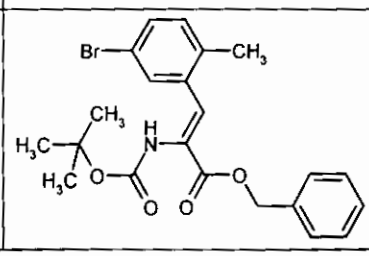
Yield: quant.

LC-MS (Method 3): R_t = 2.61 min.

MS (EI): m/z = 356 $(M+H)^+$.

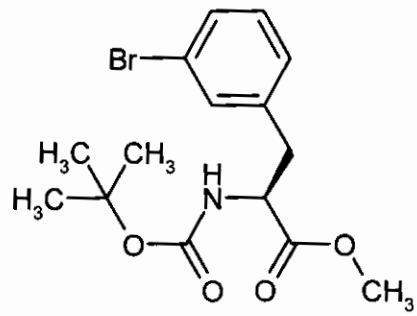
^{1}H-NMR (300 MHz, DMSO-d_6): δ = 1.40 (s, 9H), 3.73 (s, 3H), 7.15 (br.s, 1H), 7.48 (m, 1H), 7.56 (dd, 1H), 7.63 (dd, 1H), 7.86 (s, 1H), 8.82 (br.s, 1H).

Example 3A is prepared from the corresponding starting materials in analogy to the above procedure:

Example No.	Structure	Prepared in analogy to Example No.	Analytical Data
3A		2A from Ex. 1A and benzyl [(tert-butoxycarbonyl)-amino](dimethoxy-phosphoryl)acetate	LC-MS (Method 4): R_t = 3.38 min. MS (EI): m/z = 446 $(M+H)^+$ ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.35 (s, 9H), 2.28 (s, 3H), 5.30 (s, 2H), 6.21 (br. s, 1H), 7.04 (d, 1H), 7.21-7.46 (m, 7H), 7.10 (d, 1H).

Example 4A

Methyl 3-bromo-*N*-(*tert*-butoxycarbonyl)-*L*-phenylalaninate



10 g (28.1 mmol) of methyl-(2Z)-3-(3-bromophenyl)-2-[(*tert*-butoxycarbonyl)amino]acrylate (Example 2A) are dissolved in a mixture of 150 ml of ethanol and 100 ml of dioxane. Under an argon atmosphere, 100 mg (0.14 mmol) of hydrogenation catalyst [(+)-1,2-bis((2*S*,5*S*)-2,5-diethylphospholano)benzene(cyclooctadiene)rhodium(I) trifluoromethanesulfonate] are added, and argon is passed through the solution for 30 min. Hydrogenation is then carried out for 5 days under a hydrogen pressure of 3 bar. The mixture is filtered through silica gel, and careful afterwashing with ethanol is carried out. The filtrate is concentrated in vacuo and the crude product is dried under high vacuum.

Yield: 9.2 g (89% of theory)

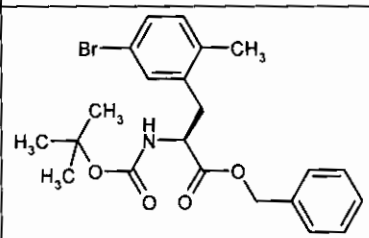
LC-MS (Method 3): R_t = 2.63 min.

MS (EI): m/z = 358 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 1.32 (s, 9H), 2.74 (m_c, 1H), 3.03 (m_c, 1H), 3.62 (s, 3H), 4.70 (m_c, 1H), 7.20-7.5 (m, 5H).

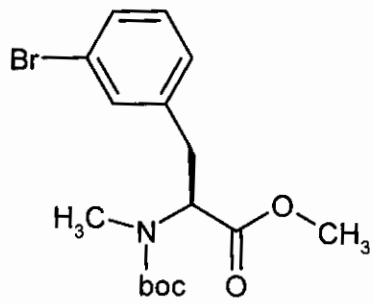
Example 5A is prepared from the corresponding starting materials in analogy to the above procedure:

Example No.	Structure	Prepared in analogy to Example No.	Analytical Data

Example No.	Structure	Prepared in analogy to Example No.	Analytical Data
5A		4A from Ex. 3A	LC-MS (Method 6): R_t = 3.81 min. MS (EI): m/z = 448 $(M+H)^+$ ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.39 (s, 9H), 2.24 (s, 3H), 2.83-3.15 (m, 2H), 4.57 (m_c, 1H), 5.00 (br. s, 1H), 5.09 (dd, 2H), 6.97 (d, 1H), 7.14-7.48 (m, 7H).

Example 6A

Methyl 3-bromo-*N*-(*tert*-butoxycarbonyl)-*N*-methyl-*L*-phenylalaninate



49.8 g (350.86 mmol) of iodomethane and 2.28 g (57.01 mmol) of sodium hydride are added to a solution of 16.5 g (43.86 mmol) of methyl 3-bromo-*N*-(*tert*-butoxycarbonyl)-*L*-phenylalaninate (Example 4A) in 220 ml of anhydrous tetrahydrofuran. The reaction mixture is stirred overnight at RT. 1000 ml of water and 1000 ml of ethyl acetate are added to the mixture. The organic phase is washed successively with water and a saturated sodium chloride solution, dried over sodium sulfate and concentrated. The crude product is purified by column chromatography on silica gel (mobile phase cyclohexane:ethyl acetate 3:1).

Yield: quant.

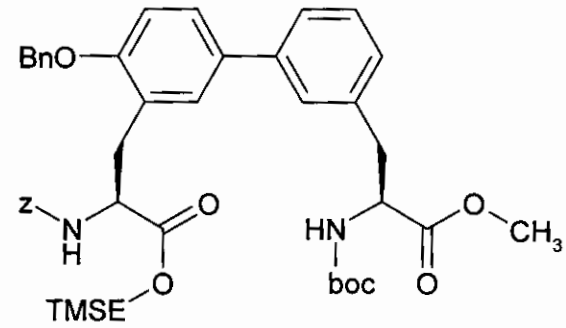
HPLC (Method 11): R_t = 5.1 min.

MS (DCI(NH_3)): m/z = 390 $(M+H)^+$.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.48 (d, 9H), 2.23 (d, 3H), 3.09 (dd, 1H), 3.30 (dd, 1H), 3.75 (s, 3H), 4.70 (ddd, 1H), 6.92 (dd, 1H), 7.30 (m, 2H).

Example 7A

Methyl (2*S*)-3-(4'-(benzyloxy)-3'-{(2*S*)-2-{[(benzyloxy)carbonyl]amino}-3-oxo-3-[2-(trimethylsilyl)ethoxy]propyl}biphenyl-3-yl)-2-[(*tert*-butoxycarbonyl)amino]propanoate



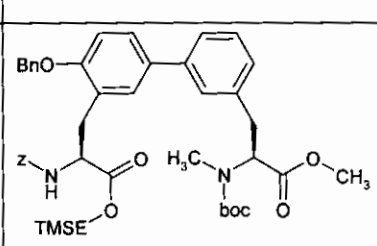
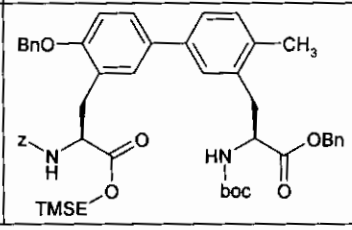
A solution of 6.0 g (16.8 mmol) of methyl 3-bromo-*N*-(*tert*-butoxycarbonyl)-*N*-methyl-*L*-phenylalaninate (Example 4A) and 11.7 g (18.4 mmol) of 2-(trimethylsilyl)ethyl-2-(benzyloxy)-*N*-[(benzyloxy)carbonyl]-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-*L*-phenylalaninate (Example 84A from WO03/106480) in 80 ml of 1-methyl-2-pyrrolidone and 4 ml of water is rendered inert and saturated with argon. 1.37 g (1.67 mmol) of bis(diphenylphosphino)ferrocenepalladium(II) chloride ($PdCl_2$(dppf)) and 11 g (34 mmol) of cesium carbonate are then added. Argon is gently passed over the reaction mixture, which is stirred for 10 h at 50°C. The mixture is cooled, taken up in dichloromethane and washed with water. The organic phase is dried over magnesium sulfate and the solvent is concentrated in vacuo. The residue is purified by column chromatography on silica gel (cyclohexane:ethyl acetate 15:1 → 7:1).

Yield: 6.82 g (52% of theory.).

LC-MS (Method 1): R_t = 3.41 min

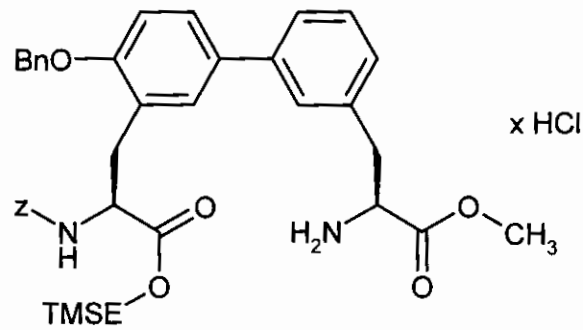
MS (EI): m/z = 783 $(M+H)^+$.

Examples 8A and 9A listed in the following table are prepared from the corresponding starting materials in analogy to the above procedure:

Example No.	Structure	Prepared in analogy to Example No.	Analytical Data
8A		7A from Ex. 4A and Ex. 84A from WO03/106480	HPLC (Method 12): R_t = 6.62 min. MS (ES): m/z = 819 $(M+Na)^+$
9A		7A from Ex. 5A and Ex. 84A from WO03/106480	LC-MS (Method 9): R_t = 4.01 min. MS (ES): m/z = 873 $(M+H)^+$

Example 10A

Methyl (2*S*)-2-amino-3-(4'-(benzyloxy)-3'-{(2*S*)-2-{[(benzyloxy)carbonyl]amino}-3-oxo-3-[2-(trimethylsilyl)ethoxy]propyl}biphenyl-3-yl)propanoate hydrochloride



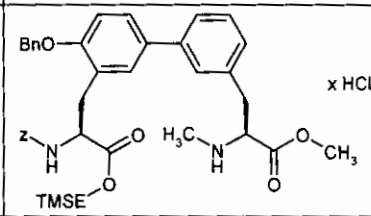
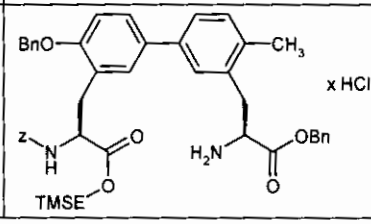
54 ml of a 4M hydrogen chloride-dioxane solution are added to a solution, cooled to 0°C, of 4.0 g (3.6 mmol) of the compound from Example 7A in 10 ml of anhydrous dioxane. After stirring for 3 h, the solvent is evaporated in vacuo, coevaporated several times with dichloromethane and dried to constant weight under high vacuum. The crude product is reacted without further purification.

Yield: quant.

LC-MS (Method 2): R_t = 2.24 min.

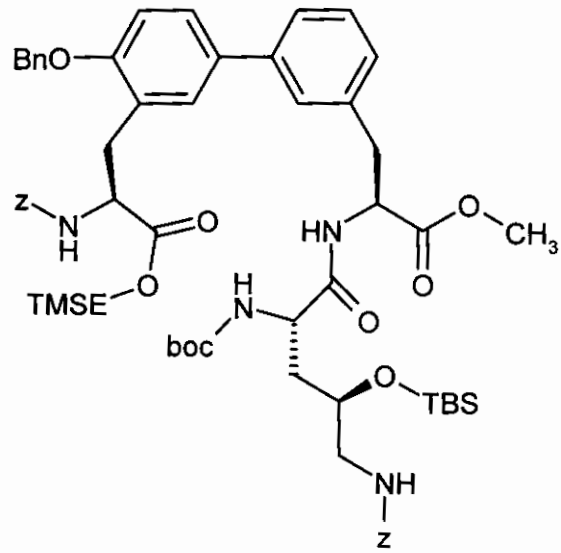
MS (EI): m/z = 683 $(M\text{-}HCl+H)^+$.

Examples 11A and 12A listed in the following table are prepared from the corresponding starting materials in analogy to the above procedure:

Example No.	Structure	Prepared in analogy to Example No.	Analytical Data
11A		10A from Ex. 8A	Crude product was reacted without further purification
12A		10A from Ex. 9A	LC-MS (Method 6): R_t = 3.10 min. MS (ES): m/z = 773 $(M\text{-}HCl+H)^+$

Example 13A

2-(Trimethylsilyl)ethyl (2*S*)-3-(4-(benzyloxy)-3'-{(2*S*)-2-[((2*S*,4R)-5-{[(benzyloxy)carbonyl]amino}-2-[(*tert*-butoxycarbonyl)amino]-4-{[*tert*-butyl(dimethyl)silyl]oxy}pentanoyl)amino]-3-methoxy-3-oxopropyl}biphenyl-3-yl)-2-{[(benzyloxy)carbonyl]amino}propanoate



At 0°C (bath temperature), 1.26 g (3.32 mmol) of HATU and 1.1 ml (6.2 mmol) of Hünig's base are added to a solution of 1.91 g (2.66 mmol) of the compound from Example 10A and 1.45 g (2.92 mmol) of (2*S*,4*R*)-5-{[(benzyloxy)carbonyl]amino}-2-[(*tert*-butoxycarbonyl)amino]-4-{[*tert*-butyl(dimethyl)silyl]oxy}pentanoic acid (Example 14A from WO03/106480) in 20 ml of abs. DMF. The mixture is stirred for 30 min at this temperature, then a further 0.55 ml (1.1 mmol) of Hünig's base are added and the temperature is allowed to rise to RT. After reaction overnight, everything is concentrated to dryness in vacuo and the residue is taken up in dichloromethane. The organic phase is washed with water and a saturated sodium chloride solution, dried over sodium sulfate and concentrated. The crude product is purified by chromatography on silica gel (mobile phase cyclohexane/ethyl acetate 5:1 → 3:1).

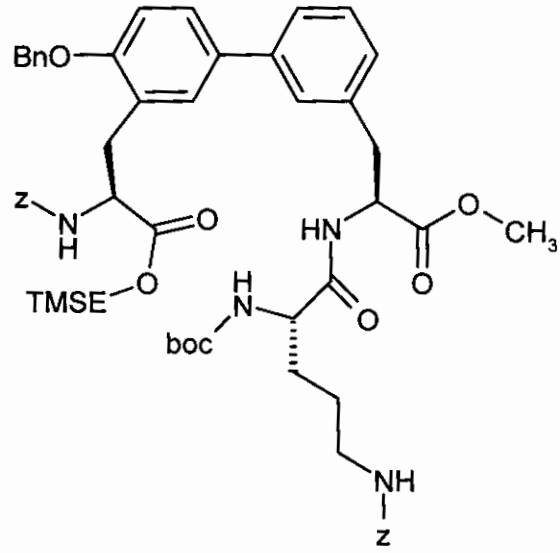
Yield: 1.89 g (61% of theory)

LC-MS (Method 3): R_t = 3.66 min.

MS (EI): m/z = 1161 $(M+H)^+$

Example 14A

2-(Trimethylsilyl)ethyl-(2*S*)-3-{4-(benzyloxy)-3'-[(2*S*)-2-({(2*S*)-5-{[(benzyloxy)carbonyl]amino}-2-[(*tert*-butoxycarbonyl)amino]pentanoyl}amino)-3-methoxy-3-oxopropyl]biphenyl-3-yl}-2-{[(benzyloxy)carbonyl]amino}propanoate



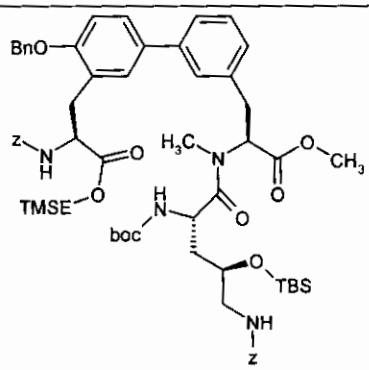
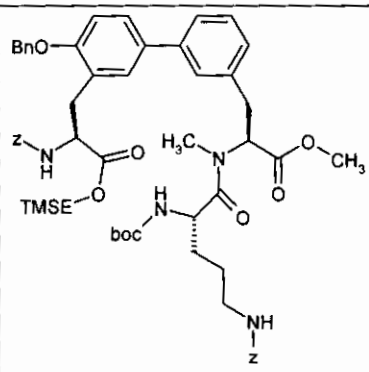
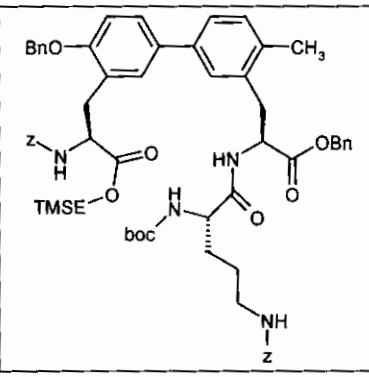
At 0°C (bath temperature), 1.03 g (2.7 mmol) of HATU and 1.1 ml (6.1 mmol) of Hünig's base are added to a solution of 1.55 g (2.16 mmol) of the compound from Example 10A and 0.95 g (2.59 mmol) of N^5-[(benzyloxy)carbonyl]-N^2-(*tert*-butoxycarbonyl)-*L*-ornithine in 28 ml of abs. DMF. The mixture is stirred for 30 min at this temperature, then a further 0.3 ml (1.5 mmol) of Hünig's base are added and the temperature is allowed to rise to RT. After reaction overnight, everything is concentrated to dryness in vacuo and the residue is taken up in dichloromethane. The organic phase is washed with water and a saturated sodium chloride solution, dried over sodium sulfate and concentrated. The crude product is purified by chromatography on silica gel (mobile phase dichloromethane/ethyl acetate 30:1 → 5:1).

Yield: 1.67 g (75% of theory)

LC-MS (Method 1): R_t = 3.40 min.

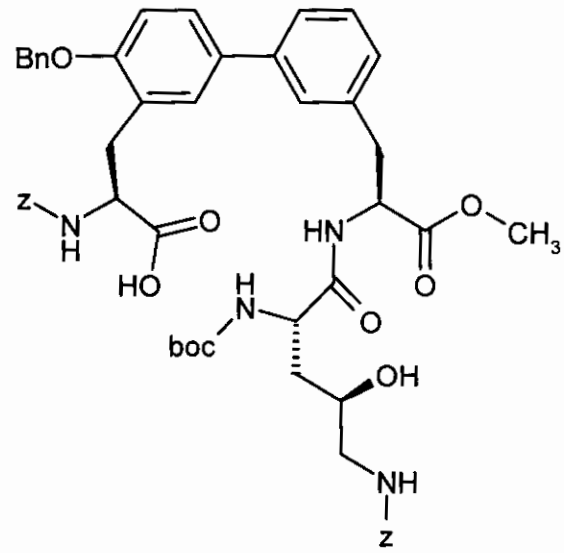
MS (EI): m/z = 1031 $(M+H)^+$

Examples 15A to 17A listed in the following table are prepared from the corresponding starting materials in analogy to the specified procedures:

Example No.	Structure	Prepared in analogy to Example No.	Analytical Data
15A		13A from Ex. 11A and Ex. 14A from WO03/106480	LC-MS (Method 5): R_t = 3.47 min. MS (ES): m/z = 1175 $(M+H)^+$
16A		14A from Ex. 11A and N^5-[(benzyl-oxy)carbonyl]-N^2-(*tert*-butoxy-carbonyl)-*L*-ornithine	LC-MS (Method 3): R_t = 3.52 min. MS (ES): m/z = 1045 $(M+H)^+$
17A		14A from Ex. 12A and N^5-[(Benzyl-oxy)carbonyl]-N^2-(*tert*-butoxy-carbonyl)-*L*-ornithine	LC-MS (Method 3): R_t = 3.54 min. MS (ES): m/z = 1121 $(M+H)^+$

Example 18A

(2*S*)-3-{4-(Benzyloxy)-3'-[(2*S*)-2-({(2*S*,4R)-5-{[(benzyloxy)carbonyl]amino}-2-[(*tert*-butoxycarbonyl)amino]-4-hydroxypentanoyl}amino)-3-methoxy-3-oxopropyl]-biphenyl-3-yl}-2-{[(benzyloxy)carbonyl]amino}propanoic acid



4.88 ml (4.88 mmol) of a 1N tetra-n-butylammonium fluoride solution in THF are added to a solution of 1.89 g (1.63 mmol) of the compound from Example 13A in 10 ml of abs. DMF with stirring. After 2 h at RT, the mixture is cooled to 0°C, and ice-water and some 0.5 N hydrochloric acid are added. The mixture is immediately extracted with ethyl acetate. The organic phase is dried over magnesium sulfate, concentrated in vacuo and dried under high vacuum. The crude product is reacted without further purification.

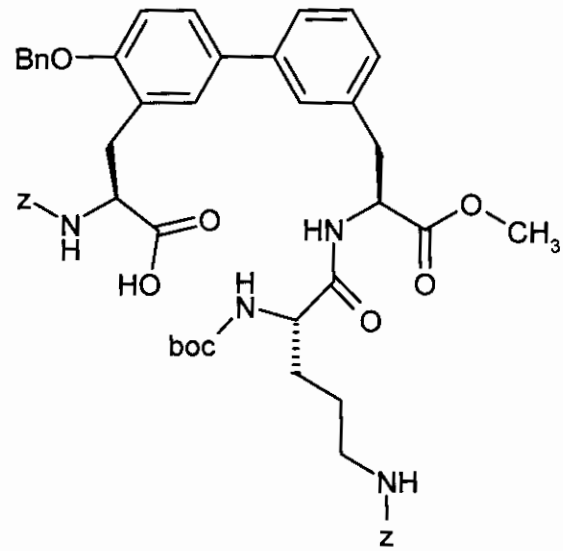
Yield: quant.

LC-MS (Method 3): R_t = 2.90 min

MS (EI): m/z = 947 $(M+H)^+$

Example 19A

(2*S*)-3-{4-(Benzyloxy)-3'-[(2*S*)-2-({(2*S*)-5-{[(benzyloxy)carbonyl]amino}-2-[(*tert*-butoxy-carbonyl)amino]pentanoyl}amino)-3-methoxy-3-oxopropyl]biphenyl-3-yl}-2-{[(benzyl-oxy)carbonyl]amino}propanoic acid



3.58 ml of a 1N tetra-n-butylammonium fluoride solution in THF are added dropwise to a solution of 2.38 g (1.79 mmol) of the compound from Example 14A in 35 ml of absolute DMF. After 2 h at RT, the mixture is cooled to 0°C, and ice-water and some 0.5 N hydrochloric acid are added. The mixture is immediately extracted with ethyl acetate. The organic phase is dried over magnesium sulfate, concentrated in vacuo and dried under high vacuum. The crude product is reacted without further purification.

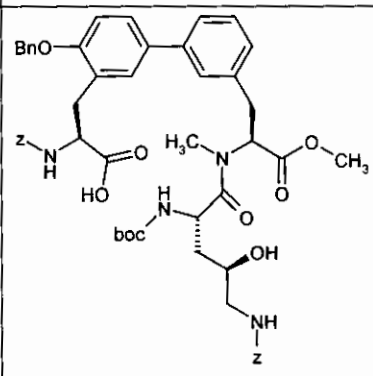
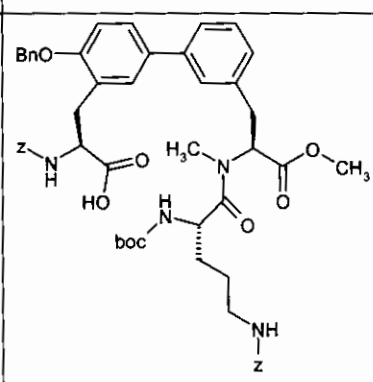
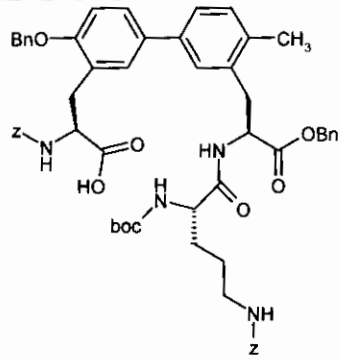
Yield: quant.

LC-MS (Method 2): R_t = 2.88 min.

MS (EI): m/z = 931 $(M+H)^+$.

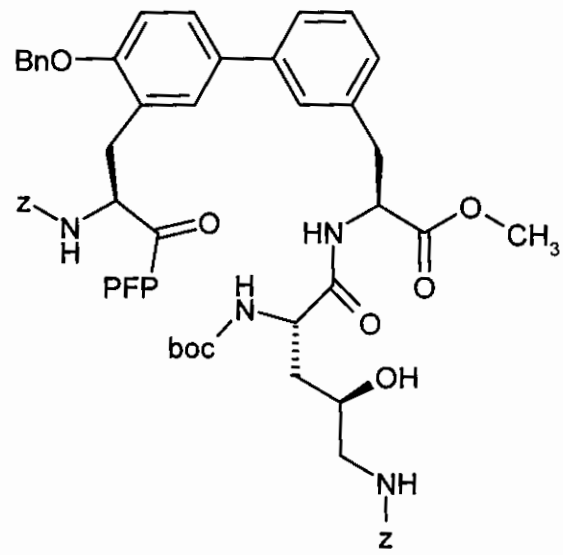
Examples 20A to 22A listed in the follwoing table are prepared from the corresponding starting materials in analogy to the specified procedures:

Example No.	Structure	Prepared in analogy to Example No.	Analytical Data

Example No.	Structure	Prepared in analogy to Example No.	Analytical Data
20A		18A from Ex. 15A	Crude product was reacted without further purification
21A		19A from Ex. 16A	Crude product was reacted without further purification
22A		19A from Ex. 17A	LC-MS (Method 6): R_t = 3.90 min MS (ES): m/z = 1021 $(M+H)^+$

Example 23A

Pentafluorophenyl (2*S*)-3-{4-(benzyloxy)-3'-[(2*S*)-2-({(2*S*,4R)-5-{[(benzyloxy)carbonyl]amino}-2-[(*tert*-butoxycarbonyl)amino]-4-hydroxypentanoyl}amino)-3-methoxy-3-oxopropyl]biphenyl-3-yl}-2-{[(benzyloxy)carbonyl]amino}propanoate



A solution of 1.54 g (1.63 mmol) of the compound from Example 18A in 50 ml of abs. dichloromethane is cooled to -20°C, and, with stirring, 1.2 g (6.52 mmol) of pentafluorophenyl, 0.02 g (0.16 mmol) of DMAP and 0.48 g (2.12 mmol) of EDC are added. The temperature is allowed to slowly rise to RT and the mixture is stirred overnight. The mixture is concentrated in vacuo and the crude product is dried to constant weight under high vacuum.

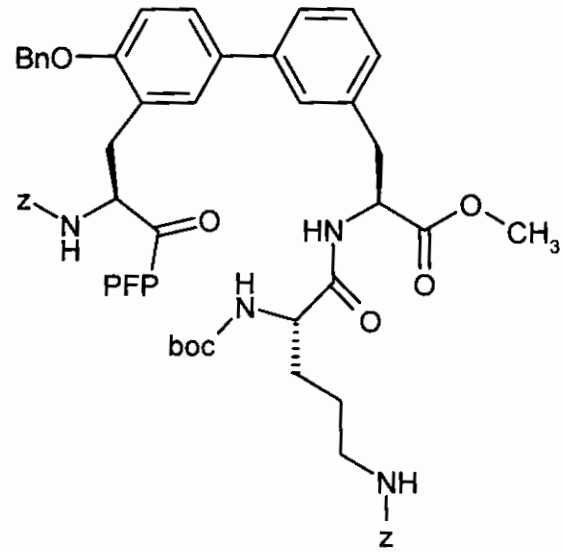
Yield: 1.8 g (99% of theory)

LC-MS (Method 2): R_t = 3.14 min

MS (EI): m/z = 1113 $(M+H)^+$

Example 24A

Pentafluorophenyl (2*S*)-3-{4-(benzyloxy)-3'-[(2*S*)-2-({(2*S*)-5-{[(benzyloxy)carbonyl]-amino}-2-[(*tert*-butoxycarbonyl)amino]pentanoyl}amino)-3-methoxy-3-oxopropyl]biphenyl-3-yl}-2-{[(benzyloxy)carbonyl]amino}propanoate



A solution of 1.67 g (1.79 mmol) of the compound from Example 19A in 70 ml of abs. dichloromethane is cooled to –20°C, and 1.65 g (8.95 mmol) of pentafluorophenyl, 0.025 g (0.18 mmol) of DMAP and 0.53 g (2.33 mmol) of EDC are added with stirring. The temperature is allowed to rise slowly to RT and the mixture is stirred overnight. The mixture is concentrated in vacuo and the crude product is dried to constant weight under high vacuum.

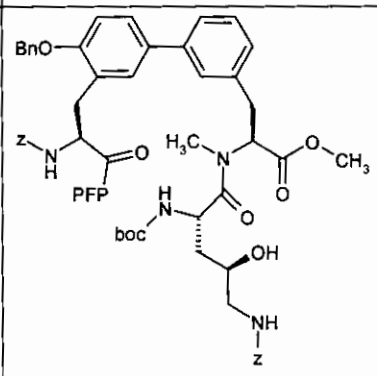
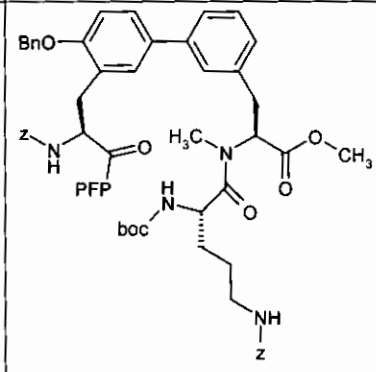
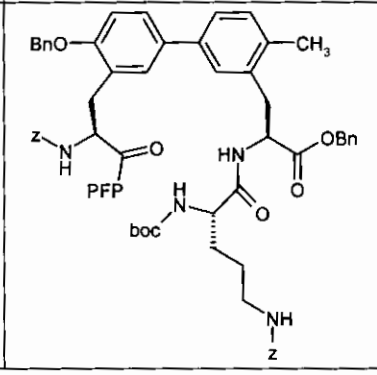
Yield: quant.

LC-MS (Method 3): R_t = 3.47 min

MS (EI): m/z = 1097 $(M+H)^+$

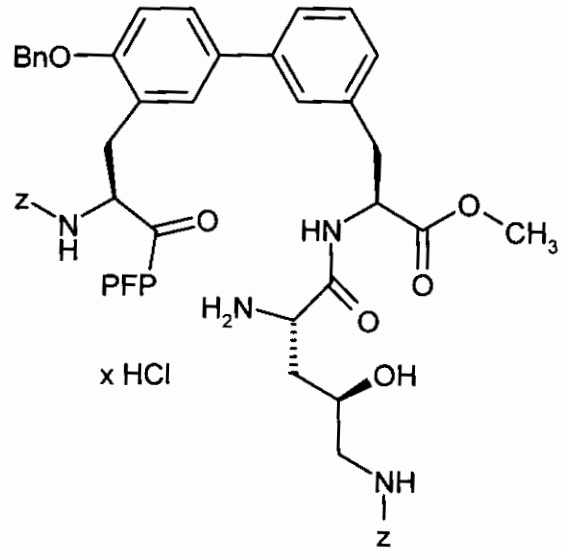
Examples 25A to 27A listed in the following table are prepared from the corresponding starting materials in analogy to the specified procedures:

Example No.	Structure	Prepared in analogy to Example No.	Analytical Data

Example No.	Structure	Prepared in analogy to Example No.	Analytical Data
25A		23A from Ex. 20A	Crude product was reacted without further purification
26A		24A from Ex. 21A	Crude product was reacted without further purification
27A		24A from Ex. 22A	LC-MS (Method 5): R_t = 3.32 min MS (ES): m/z = 1187 $(M+H)^+$

Example 28A

Methyl (2*S*)-2-[((2*S*,4R)-2-amino-5-{[(benzyloxy)carbonyl]amino}-4-hydroxypentanoyl)amino]-3-{4'-(benzyloxy)-3'-[(2*S*)-2-{[(benzyloxy)carbonyl]amino}-3-oxo-3-(pentafluorophenoxy)propyl]biphenyl-3-yl}propanoate hydrochloride



With stirring at 0°C, 20 ml of a 4N hydrogen chloride-dioxane solution are added to a solution of 1.81 g (1.63 mmol) of the compound from Example 23A in 10 ml of dioxane. The mixture is stirred for 30 min at 0°C, the temperature is allowed to rise to RT, the mixture is stirred for a further hour and then everything is evaporated to dryness in vacuo. After drying under high vacuum to constant weight the product is obtained.

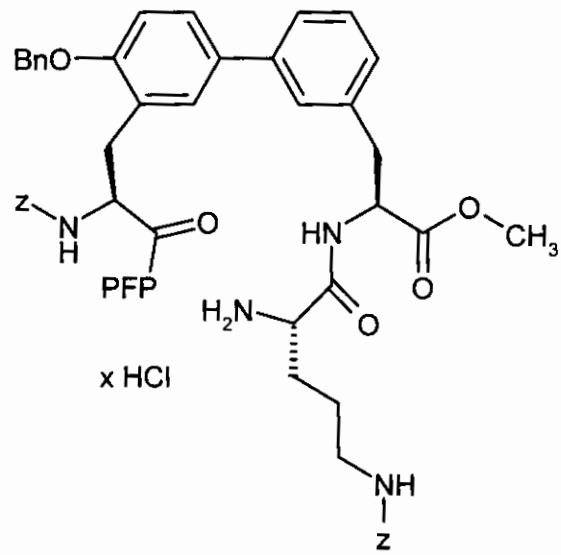
Yield: quant.

LC-MS (Method 3): R_t = 2.62 min

MS (EI): m/z = 1013 $(M\text{-}HCl+H)^+$

Example 29A

Methyl (2*S*)-2-[((2*S*)-2-amino-5-{[(benzyloxy)carbonyl]amino}pentanoyl)amino]-3-{4'-(benzyloxy)-3'-[(2*S*)-2-{[(benzyloxy)carbonyl]amino}-3-oxo-3-(pentafluorophenoxy)propyl]biphenyl-3-yl}propanoate hydrochloride



With stirring at 0°C, 60 ml of a 4N hydrogen chloride-dioxane solution are added to a solution of 1.96 g (1.79 mmol) of the compound from Example 24A in 20 ml of dioxane. The mixture is stirred for 60 min at 0°C, the temperature is allowed to rise to RT, the mixture is stirred for a further hour and then everything is evaporated to dryness in vacuo. After drying under high vacuum to constant weight the product is obtained.

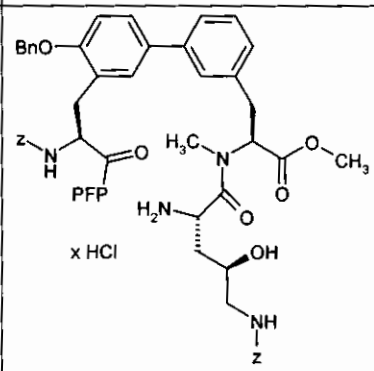
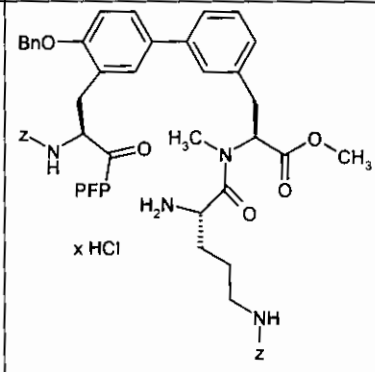
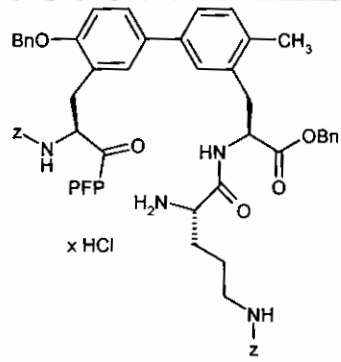
Yield: quant.

LC-MS (Method 1): R_t = 2.73 min

MS (EI): m/z = 997 $(M-HCl+H)^+$

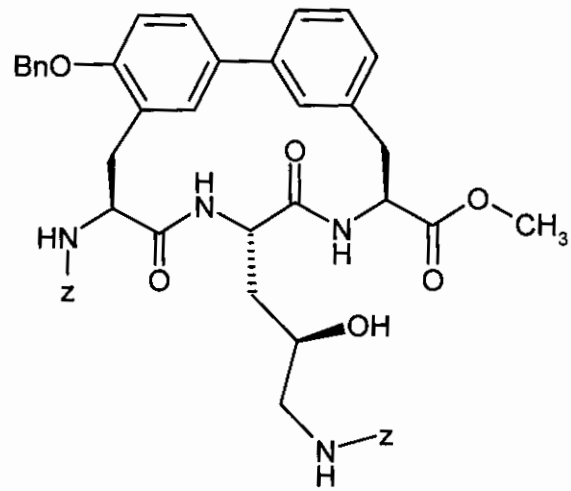
Examples 30A to 32A listed in the following table are prepared from the corresponding starting materials in analogy to the specified procedures:

Example No.	Structure	Prepared in analogy to Example No.	Analytical Data

Example No.	Structure	Prepared in analogy to Example No.	Analytical Data
30A		28A from Ex. 25A	Crude product was reacted without further purification
31A		29A from Ex. 26A	Crude product was reacted without further purification
32A		29A from Ex. 27A	LC-MS (Method 5): Rt = 3.32 min MS (ES): m/z = 1087 $(M\text{-}HCl+H)^+$

Example 33A

Methyl (8*S*,11*S*,14*S*)-17-(benzyloxy)-14-{[(benzyloxy)carbonyl]amino}-11-((2*R*)-3-{[(benzyloxy)carbonyl]amino}-2-hydroxypropyl)-10,13-dioxo-9,12-diazatricyclo [14.3.1.$1^{2,6}$]-henicosa-1(20),2(21),3,5,16,18-hexaene-8-carboxylate



A solution of 4.5 ml (32.6 mmol) of triethylamine in 150 ml of dichloromethane is added dropwise, with vigorous stirring, to a solution of 1.71 g (1.63 mmol) of the compound from Example 28A in 600 ml of abs. dichloromethane over the course of 20 min. The mixture is stirred further overnight and then everything is evaporated in vacuo (bath temperature about 40°C). The residue is stirred with acetonitrile and the remaining solid is collected by filtration and dried to constant weight under high vacuum.

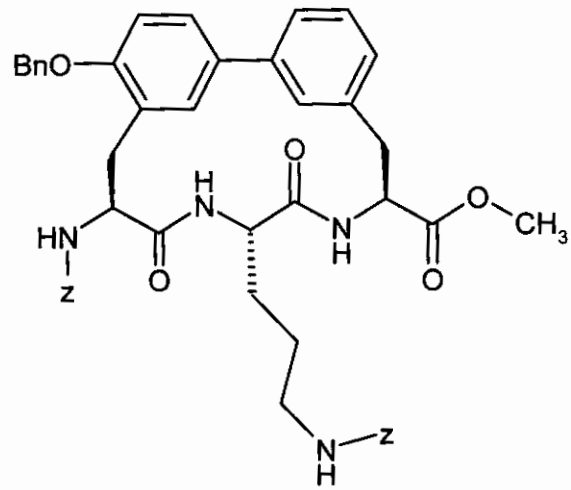
Yield: 0.611 g (45% of theory)

LC-MS (Method 3): R_t = 2.92 min

MS (EI): m/z = 829 $(M+H)^+$

Example 34A

Methyl (8*S*,11*S*,14*S*)-17-(benzyloxy)-14-{[(benzyloxy)carbonyl]amino}-11-(3-{[(benzyloxy)carbonyl]amino}propyl)-10,13-dioxo-9,12-diazatricyclo[14.3.1.$1^{2,6}$]henicosa-1(20),2(21),3,5,16,18-hexaene-8-carboxylate



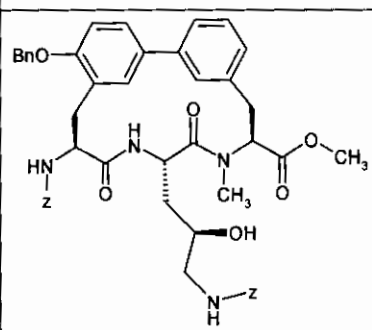
A solution of 5 ml (35.8 mmol) of triethylamine in 150 ml of chloroform is added drop-wise, with vigorous stirring, to a solution of 1.85 g (1.79 mmol) of the compound from Example 29A in 600 ml of abs. chloroform over the course of 20 min. The mixture is stirred further overnight and everything is evaporated in vacuo (bath temperature about 40°C). The residue is stirred with acetonitrile and the remaining solid is collected by filtration and dried to constant weight under high vacuum.

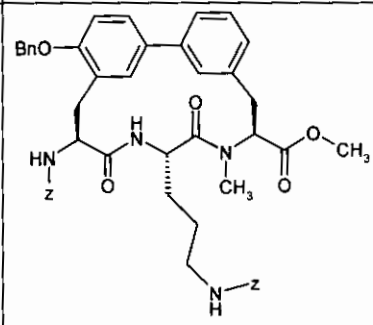
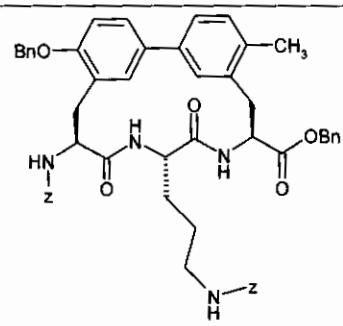
Yield: 1.21 g (83% of theory)

LC-MS (Method 1): R_t = 3.0 min

MS (EI): m/z = 813 $(M+H)^+$

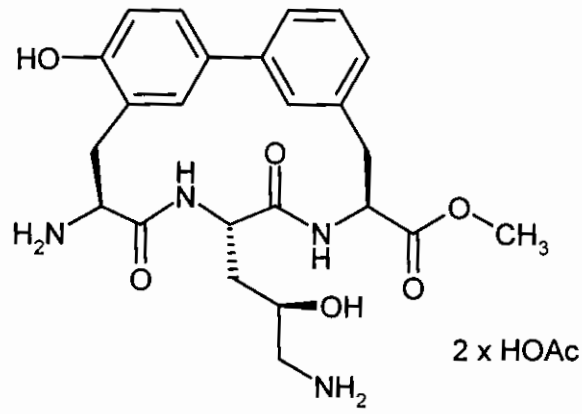
Examples 35A to 37A listed in the following table are prepared from the corresponding starting materials in analogy to the specified procedures:

Example No.	Structure	Prepared in analogy to Example No.	Analytical Data
35A		33A from Ex. 30A	LC-MS (Method 2): R_t = 2.83 min MS (EI): m/z = 843 $(M+H)^+$

Example No.	Structure	Prepared in analogy to Example No.	Analytical Data
36A		34A from Ex. 31A	LC-MS (Method 3): R_t = 3.23 min MS (EI): m/z = 827 $(M+H)^+$
37A		34A from Ex. 32A	LC-MS (Method 1): R_t = 3.23 min MS (EI): m/z = 903 $(M+H)^+$

Example 38A

Methyl (8*S*,11*S*,14*S*)-14-amino-11-[(2*R*)-3-amino-2-hydroxypropyl]-17-hydroxy-10,13-dioxo-9,12-diazatricyclo[14.3.1.1^{2,6}]henicosa-1(20),2(21),3,5,16,18-hexaene-8-carboxylate dihydroacetate



0.50 g (0.61 mmol) of the compound from Example 33A are added to a mixture of 60 ml of acetic acid/water/ethanol (4:1:1). 100 mg of palladium on activated carbon (10%) are added and the mixture is then hydrogenated for 36 h at RT under atmospheric pressure. The reaction mixture is filtered through prewashed kieselguhr, and washed with ethanol, and the filtrate is concentrated on a rotary evaporator in vacuo. The residue is dried to constant weight under high vacuum.

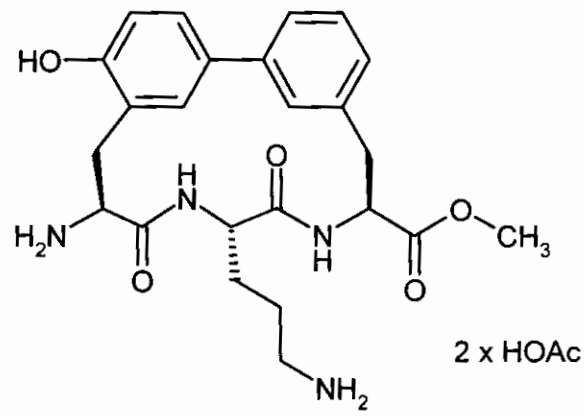
Yield: quant.

LC-MS (Method 2): R_t = 0.88 min

MS (EI): m/z = 471 $(M-2HOAc+H)^+$.

Example 39A

Methyl (8*S*,11*S*,14*S*)-14-amino-11-(3-aminopropyl)-17-hydroxy-10,13-dioxo-9,12-diazatricyclo[14.3.1.$1^{2,6}$]henicosa-1(20),2(21),3,5,16,18-hexaene-8-carboxylate dihydroacetate



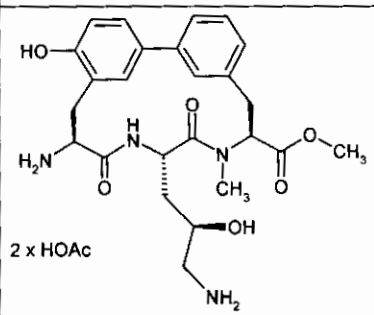
1.19g (1.46 mmol) of the compound from Example 34A are added to a mixture of 440 ml of acetic acid/water/ethanol (4:1:1). 200 mg of palladium on activated carbon (10%) are added and the mixture is then hydrogenated for 36h at RT under atmospheric pressure. The reaction mixture is filtered through prewashed kieselguhr, and washed with ethanol, and the filtrate is concentrated on a rotary evaporator in vacuo. The residue is dried to constant weight under high vacuum.

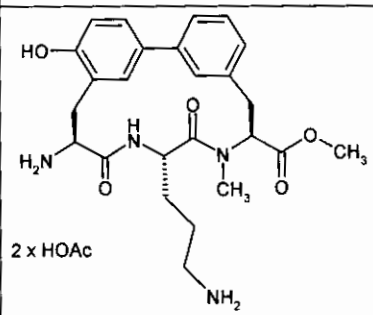
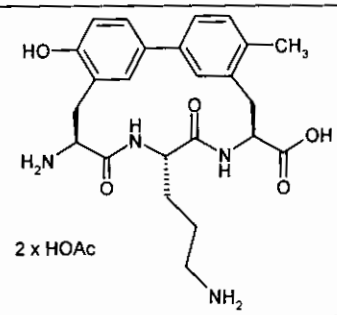
Yield: quant.

LC-MS (Method 8): R_t = 2.33 min

MS (EI): m/z = 455 $(M-2HOAc+H)^+$.

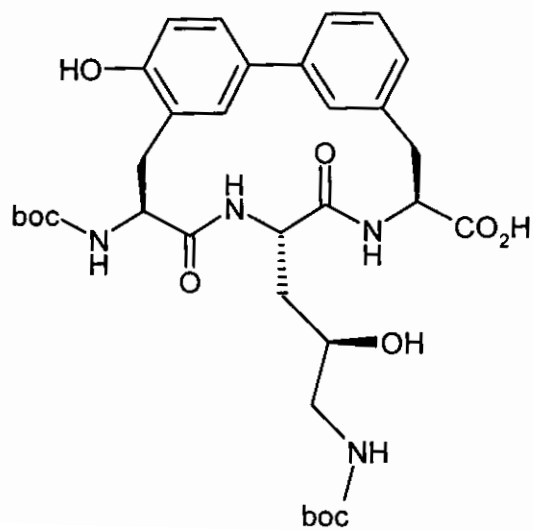
Examples 40A to 42A listed in the following table are prepared from the corresponding starting materials in analogy to the specified procedures:

Example No.	Structure	Prepared in analogy to Example No.	Analytical Data
40A		38A from Ex. 35A	LC-MS (Method 3): R_t = 1.22 min MS (EI): m/z = 485 $(M-2HOAc+H)^+$.

Example No.	Structure	Prepared in analogy to Example No.	Analytical Data
41A		39A from Ex. 36A	LC-MS (Method 10): R_t = 2.33 min MS (EI): m/z = 469 $(M-2HOAc+H)^+$.
42A		39A from Ex. 37A	LC-MS (Method 2): R_t = 0.96 min MS (EI): m/z = 455 $(M-2HOAc+H)^+$.

Example 43A

(8*S*,11*S*,14*S*)-14-[(*tert*-Butoxycarbonyl)amino]-11-{(2*R*)-3-[(*tert*-butoxycarbonyl)amino]-2-hydroxypropyl}-17-hydroxy-10,13-dioxo-9,12-diazatricyclo[14.3.1.$1^{2,6}$]-henicosa-1(20),2(21),3,5,16,18-hexaene-8-carboxylic acid



1.3 ml of a 1N sodium hydroxide solution is added to a solution of 150 mg (0.26 mmol) of the compound from Example 38A in 1 ml of water. With stirring, a solution of 170 mg (0.78 mmol) of di-*tert*-butyl dicarbonate in 0.5 ml of methanol is added at RT and the mixture is stirred for 4 h. The mixture is added to 15 ml of water, the pH of the mixture is adjusted to 3 using 0.1N hydrochloric acid and the mixture is extracted twice by shaking with ethyl acetate. The organic phases are combined, dried with magnesium sulfate and evaporated to dryness in vacuo. The remaining solid is purified by chromatography (Sephadex LH20, mobile phase methanol/acetic acid (0.25%)).

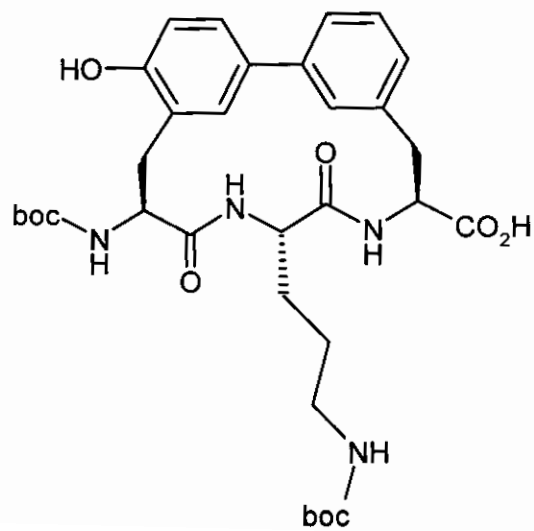
Yield: 137 mg (81% of theory)

LC-MS (Method 1): R_t = 1.94 min

MS (EI): m/z = 657 $(M+H)^+$

Example 44A

(8*S*,11*S*,14*S*)-14-[(*tert*-Butoxycarbonyl)amino]-11-{3-[(*tert*-butoxycarbonyl)amino]propyl}-17-hydroxy-10,13-dioxo-9,12-diazatricyclo[14.3.1.1^{2,6}]henicosa-1(20),2(21),3,5,16,18-hexaene-8-carboxylic acid



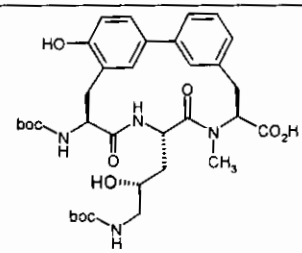
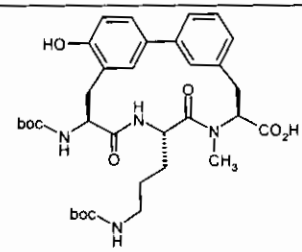
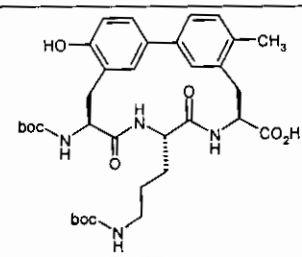
7.3 ml of a 1N sodium hydroxide solution are added to a solution of 0.85 g (1.45 mmol) of the compound from Example 39A in 5 ml of water. With stirring, a solution of 0.95 g (4.36 mmol) of di-*tert*-butyl dicarbonate in 2 ml of methanol is added at RT and the mixture is stirred for 6 h. The mixture is added to 25 ml of water, the pH of the mixture is adjusted to 3 using 0.1N hydrochloric acid and the mixture is extracted twice by shaking with ethyl actetate. The organic phases are combined, dried with magnesium sulfate and evaporated to dryness in vacuo. The remaining solid is purified to constant weight under high vacuum.

Yield: 0.75 g (81% of theory)

LC-MS (Method 1): R_t = 2.20 min

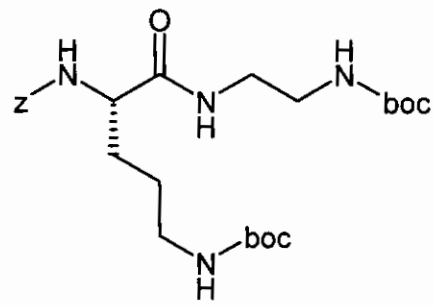
MS (EI): m/z = 641 $(M+H)^+$

Examples 45A to 47A listed in the following table are prepared from the corresponding starting materials in analogy to the specified procedures:

Example No.	Structure	Prepared in analogy to Example No.	Analytical Data
45A		43A from Ex. 40A	LC-MS (Method 2): R_t = 1.96 min MS (EI): m/z = 671 $(M+H)^+$
46A		44A from Ex. 41A	LC-MS (Method 2): R_t = 2.08 min MS (EI): m/z = 655 $(M+H)^+$
47A		44A from Ex. 42A	LC-MS (Method 2): R_t = 2.06 min MS (EI): m/z = 655 $(M+H)^+$

Example 48A

Benzyl {(1*S*)-4-[(*tert*-butoxycarbonyl)amino]-1-[({2-[(*tert*-butoxycarbonyl)amino]-ethyl}amino)carbonyl]butyl}carbamate



Under argon, 300 mg (0.82 mmol) of N^2-[(benzyloxy)carbonyl]-N^5-(*tert*-butoxycarbonyl)-*L*-ornithine and 171 mg (1.06 mmol) of *tert*-butyl-(2-aminoethyl)carbamate are dissolved in 6 ml of dimethylformamide. Then, at 0°C (ice bath), 204 mg (1.06 mmol) of EDC and 33 mg (0.25 mmol) of HOBt are added. The mixture is slowly warmed to RT and stirred at RT for 12 h. The solution is concentrated in vacuo and the residue is taken up with ethyl acetate. The organic phase is washed successively with saturated sodium bicarbonate and sodium chloride solutions, dried over magnesium sulfate and evaporated in vacuo. The remaining solid is dried under high vacuum.

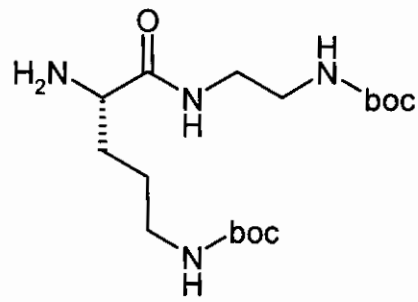
Yield: 392 mg (94% of theory)

LC-MS (Method 2): R_t = 2.36 min

MS (ESI): m/z = 509 $(M+H)^+$

Example 49A

N^5-(*tert*-Butoxycarbonyl)-*N*-{2-[(*tert*-butoxycarbonyl)amino]ethyl}-*L*-ornithinamide



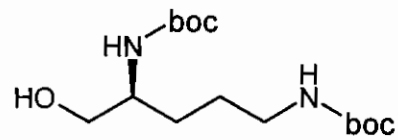
A solution of 390 mg (0.77 mmol) of benzyl {(1*S*)-4-[(*tert*-butoxycarbonyl)amino]-1-[({2-[(*tert*-butoxycarbonyl)amino]ethyl}amino)carbonyl]butyl}carbamate (Example 48A) in 50 ml of ethanol is hydrogenated after the addition of 40 mg of palladium on activated carbon (10%) at RT under atmospheric pressure for 4 h. The mixture is filtered through kieselguhr, and the residue is washed with ethanol. The filtrate is concentrated to dryness in vacuo. The product is reacted without further purification.

Yield: 263 mg (91% of theory)

MS (ESI): m/z = 375 $(M+H)^+$; 397 $(M+Na)^+$.

Example 50A

tert-Butyl [(1*S*)-4-[(*tert*-butoxycarbonyl)amino]-1-(hydroxymethyl)butyl]carbamate



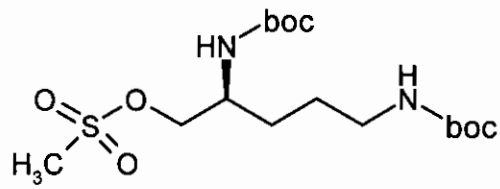
At -10°C, 91 mg (0.90 mmol) of 4-methylmorpholine and 98 mg (0.90 mmol) of ethyl chloroformate are added to a solution of 300 mg (0.90 mmol) of N^2,N^5-bis(*tert*-butoxycarbonyl)-*L*-ornithine in 10 ml of tetrahydrofuran, and the mixture is stirred for 30 min. At this temperature, 1.81 ml (1.81 mmol) of a 1M solution of lithium aluminium hydride in tetrahydrofuran are slowly added dropwise. The mixture is slowly warmed to RT and stirred at RT for 12 h. While cooling in ice, 0.1 ml of water and 0.15 ml of a 4.5% sodium hydroxide solution are cautiously added, and the mixture is stirred at RT for a further 3 h. The mixture is filtered and the filtrate is concentrated in vacuo. The residue is dissolved in ethyl acetate, washed with water, dried over magnesium sulfate and again concentrated to dryness in vacuo. The product is reacted without further purification.

Yield: 239 mg (83% of theory)

MS (ESI): m/z = 319 $(M+H)^+$; 341 $(M+Na)^+$.

Example 51A

(2*S*)-2,5-Bis[(*tert*-butoxycarbonyl)amino]pentyl methanesulfonate



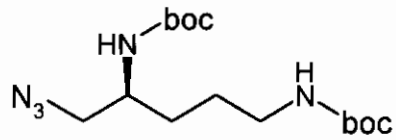
103 mg (0.90 mmol) of methanesulfonyl chloride and 0.21 ml (1.5 mmol) of triethylamine are added to a solution of 240 mg (0.75 mmol) of *tert*-butyl [(1*S*)-4-[(*tert*-butoxycarbonyl)amino]-1-(hydroxymethyl)butyl]carbamate (Example 50A) in 20 ml of dichloromethane, and the mixture is stirred at RT for 16 h. The mixture is diluted with dichloromethane and washed twice with 0.1N hydrochloric acid. The organic phase is dried over magnesium sulfate and concentrated to dryness in vacuo. The product is reacted without further purification.

Yield: 218 mg (73% of theory)

MS (ESI): m/z = 419 $(M+Na)^+$.

Example 52A

tert-Butyl-{(4*S*)-5-azido-4-[(*tert*-butoxycarbonyl)amino]pentyl}carbamate



36 mg (0.55 mmol) of sodium azide are added to a solution of 218 mg (0.55 mmol) of (2*S*)-2,5-bis[(*tert*-butoxycarbonyl)amino]pentyl methanesulfonate (Example 51A) in 15 ml of dimethylformamide and the mixture is stirred at 70°C for 12 h. Most of the solvent is distilled off in vacuo, and the residue is diluted with ethyl acetate. The mixture is washed

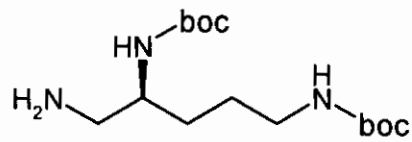
several times with a saturated sodium bicarbonate solution, dried over magnesium sulfate and concentrated to dryness in vacuo. The product is reacted without further purification.

Yield: 188 mg (99% of theory)

MS (ESI): m/z = 344 $(M+H)^+$.

Example 53A

tert-Butyl {(4*S*)-5-amino-4-[(*tert*-butoxycarbonyl)amino]pentyl}carbamate



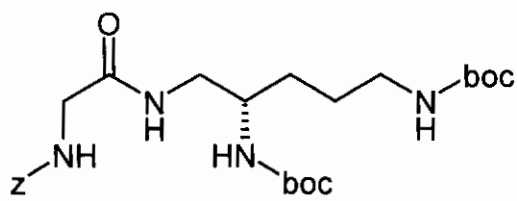
A solution of 188 mg (0.55 mmol) of *tert*-butyl {(4*S*)-5-azido-4-[(*tert*-butoxycarbonyl)-amino]pentyl}carbamate (Example 52A) in ethanol is hydrogenated after the addition of 20 mg of palladium on activated carbon (10%) at RT under atmospheric pressure for 12 h. The mixture is filtered through kieselguhr, and the residue is washed with ethanol. The filtrate is concentrated to dryness in vacuo. The product is reacted without further purification.

Yield: 102 mg (59% of theory)

MS (ESI): m/z = 318 $(M+H)^+$; 340 $(M+Na)^+$.

Example 54A

Benzyl [2-({(2*S*)-2,5-bis[(*tert*-butoxycarbonyl)amino]pentyl}amino)-2-oxoethyl]carbamate



Preparation takes place in analogy to Example 48A from 92 mg (0.44 mmol) of *N*-[(benzyloxy)carbonyl]glycine and 181 mg (0.57 mmol) of *tert*-butyl {(4*S*)-5-amino-4-[(*tert*-butoxycarbonyl)amino]pentyl}carbamate (Example 53A) in 6 ml of dimethylformamide with the addition of 110 mg (0.57 mmol) of EDC and 18 mg (0.13 mmol) of HOBt. The product is purified by preparative RP-HPLC (mobile phase water/ acetonitrile gradient: 90:10 → 5:95).

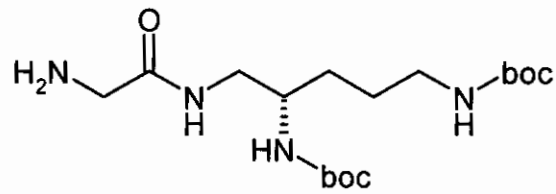
Yield: 105 mg (47% of theory)

LC-MS (Method 2): R_t = 2.12 min.

MS (ESI): m/z = 509 $(M+H)^+$

Example 55A

tert-Butyl {(4*S*)-5-[(aminoacetyl)amino]-4-[(*tert*-butoxycarbonyl)amino]pentyl}carbamate



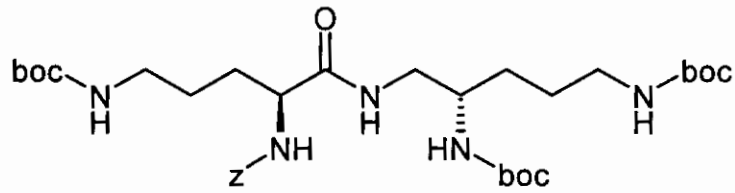
Preparation takes place in analogy to Example 49A from 105 mg (0.21 mmol) of benzyl [2-({(2*S*)-2,5-bis[(*tert*-butoxycarbonyl)amino]pentyl}amino)-2-oxoethyl]carbamate (Example 54A) in 50 ml of ethanol with the addition of 11 mg of palladium on activated carbon (10%). The product is reacted without further purification.

Yield: 64 mg (83% of theory)

MS (ESI): m/z = 375 $(M+H)^+$

Example 56A

Benzyl {(1*S*)-1-[({(2*S*)-2,5-bis[(*tert*-butoxycarbonyl)amino]pentyl}amino)carbonyl]-4-[(*tert*-butoxycarbonyl)amino]butyl}carbamate



Preparation takes place in analogy to Example 48A from 120 mg (0.33 mmol) of N^5-(*tert*-butoxycarbonyl)-N^2-[(benzyloxy)carbonyl]-*L*-ornithine and 136 mg (0.43 mmol) of *tert*-butyl {(4*S*)-5-amino-4-[(*tert*-butoxycarbonyl)amino]pentyl}carbamate (Example 53A) in 6 ml of dimethylformamide with the addition of 82 mg (0.43 mmol) of EDC and 13 mg (0.1 mmol) of HOBt. The product is purified by preparative RP-HPLC (mobile phase water/acetonitrile gradient: 90:10 → 5:95).

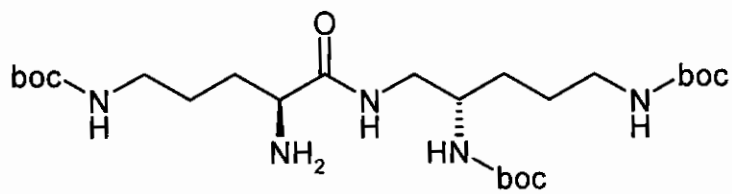
Yield: 132 mg (61% of theory)

LC-MS (Method 3): R_t = 2.68 min.

MS (ESI): m/z = 666 $(M+H)^+$

Example 57A

tert-Butyl [(4*S*)-4-amino-5-({(2*S*)-2,5-bis[(*tert*-butoxycarbonyl)amino]pentyl}amino)-5-oxopentyl]carbamate



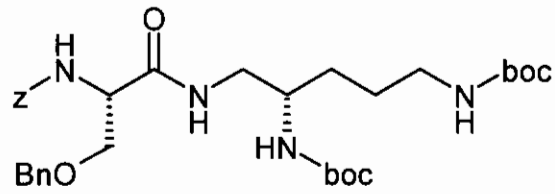
Preparation takes place in analogy to Example 49A from 132 mg (0.20 mmol) of benzyl {(1*S*)-1-[({(2*S*)-2,5-bis[(*tert*-butoxycarbonyl)amino]pentyl}amino)carbonyl]-4-[(*tert*-butoxycarbonyl)amino]butyl}carbamate (Example 56A) in 50 ml of ethanol with the addition of 13 mg of palladium on activated carbon (10%). The product is reacted without further purification.

Yield: quant.

MS (ESI): m/z = 532 $(M+H)^+$

Example 58A

Benzyl [(1*S*)-1-[(benzyloxy)methyl]-2-({(2*S*)-2,5-bis[(*tert*-butoxycarbonyl)amino]pentyl}-amino)-2-oxoethyl]carbamate



Preparation takes place in analogy to Example 48A from 150 mg (0.46 mmol) of *O*-benzyl-*N*-[(benzyloxy)carbonyl]-*L*-serine and 188 mg (0.59 mmol) of *tert*-butyl {(4*S*)-5-amino-4-[(*tert*-butoxycarbonyl)amino]pentyl}carbamate (Example 53A) in 6 ml of dimethylformamide with the addition of 114 mg (0.57 mmol) of EDC and 18 mg (0.13 mmol) of HOBt. The product is purified by preparative RP-HPLC (mobile phase water/acetonitrile gradient: 90:10 → 5:95).

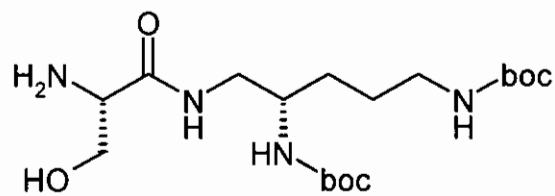
Yield: 129 mg (45% of theory)

LC-MS (Method 3): R_t = 2.81 min.

MS (ESI): m/z = 629 $(M+H)^+$

Example 59A

tert-Butyl {(4*S*)-5-{[(2*S*)-2-amino-3-hydroxypropanoyl]amino}-4-[(*tert*-butoxycarbonyl)-amino]pentyl}carbamate



A solution of 128 mg (0.77 mmol) of benzyl [(1*S*)-1-[(benzyloxy)methyl]-2-({(2*S*)-2,5-bis[(*tert*-butoxycarbonyl)amino]pentyl}amino)-2-oxoethyl]carbamate (Example 58A) in 50 ml of ethanol is hydrogenated after the addition of 13 mg of palladium on activated carbon (10%) at RT under atmospheric pressure for 48 h. The mixture is filtered through

kieselguhr and the residue is washed with ethanol. The filtrate is concentrated to dryness in vacuo. The product is purified by preparative RP-HPLC (mobile phase water/acetonitrile gradient: 90:10 → 5:95).

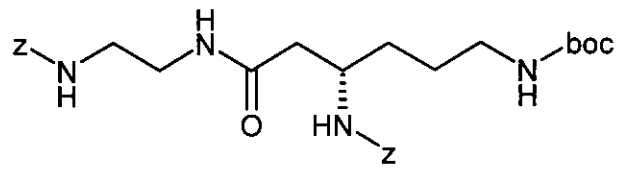
Yield: 22 mg (27% of theory)

LC-MS (Method 1): R_t = 1.43 min

MS (ESI): m/z = 405 $(M+H)^+$

Example 60A

Benzyl [2-({(3*S*)-3-{[(benzyloxy)carbonyl]amino}-6-[(*tert*-butoxycarbonyl)amino]-hexanoyl}amino)ethyl]carbamate



549.7 mg (1.446 mmol) of HATU and 339.7 mg (2.629 mmol) of *N,N*-diisopropylethylamine are added to a solution of 500 mg (1.31 mmol) of (3*S*)-3-{[(benzyloxy)carbonyl]-amino}-6-[(*tert*-butoxycarbonyl)amino]hexanoic acid in 25 ml of anhydrous DMF. After stirring at RT for 15 min, 333.5 mg (1.446 mmol) of benzyl (2-aminoethyl)carbamate hydrochloride are added. The reaction mixture is stirred at RT for 15 h. The solvent is then evaporated and the residue is taken up in dichloromethane. The organic phase is washed with water, dried over magnesium sulfate and concentrated. The crude product is purified by preparative HPLC.

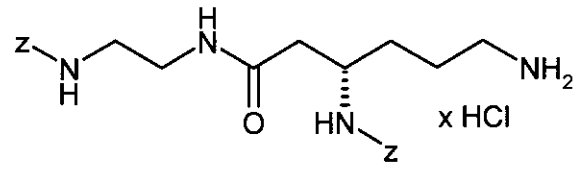
Yield 556.6 mg (44% of theory)

LC-MS (Method 3): R_t = 2.41 min

MS (ESI): m/z = 557 $(M+H)^+$.

Example 61A

Benzyl ((1*S*)-4-amino-1-{2-[(2-{[(benzyloxy)carbonyl]amino}ethyl)amino]-2-oxo-ethyl}butyl)carbamate hydrochloride



At 0°C, 8 ml of a 4M hydrogen chloride-dioxane solution are added to a solution of 320 mg (0.287 mmol) of benzyl [2-({(3*S*)-3-{[(benzyloxy)carbonyl]amino}-6-[(*tert*-butoxycarbonyl)amino]hexanoyl}amino)ethyl]carbamate (Example 60A) in 2 ml of dioxane. After 1 h at RT, the reaction solution is concentrated in vacuo, coevaporated several times with dichloromethane and dried under high vacuum. The crude product is reacted without further purification.

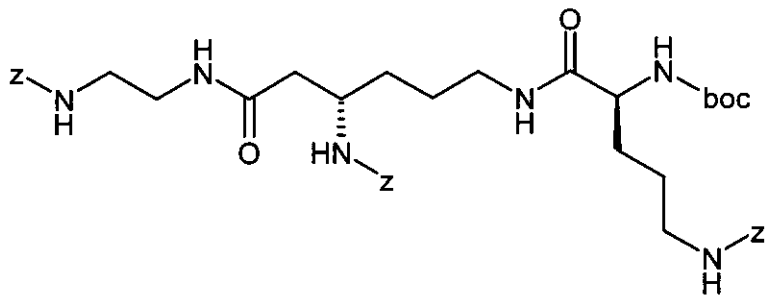
Yield: quant.

LC-MS (Method 2): R_t = 2.84 min.

MS (ESI): m/z = 457 $(M\text{-}HCl+H)^+$.

Example 62A

Benzyl {2-[((3*S*)-3-{[(benzyloxy)carbonyl]amino}-6-{[N^5-[(benzyloxy)carbonyl]-N^2-(*tert*-butoxycarbonyl)-*L*-ornithyl]amino}hexanoyl)amino]ethyl}carbamate



89.5 mg (0.235 mmol) of HATU and 55.3 mg (0.428 mmol) of *N,N*-diisopropylethylamine are added to a solution of 78.4 mg (0.214 mmol) of N^5-[(benzyloxy)carbonyl]-N^2-(*tert*-butoxycarbonyl)-*L*-ornithine in 5 ml of anhydrous DMF. After stirring at RT for 15 min, a solution of 116 mg (0.235 mmol) of benzyl ((1*S*)-4-amino-1-{2-[(2-{[(benzyloxy)-carbonyl]amino}ethyl)amino]-2-oxoethyl}butyl)carbamate hydrochloride (Example 61A) in 5 ml of anhydrous DMF is added. The reaction mixture is stirred at RT for 15 h. The solvent is then evaporated and the residue is taken up in dichloromethane. The organic phase is washed with water, dried over magnesium sulfate and concentrated. The crude product is purified by preparative HPLC.

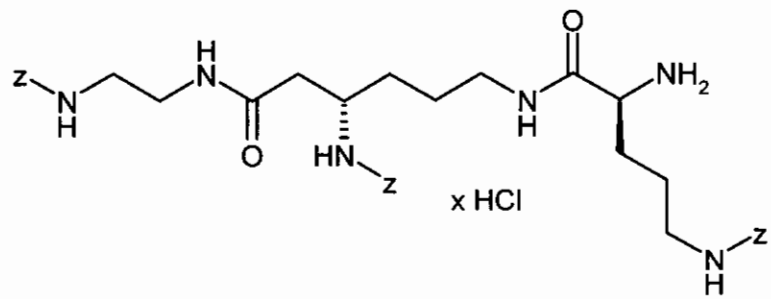
Yield 48 mg (28% of theory)

LC-MS (Method 2): R_t = 2.33 min

MS (ESI): m/z = 805 $(M+H)^+$.

Example 63A

Benzyl ((4*S*,10*S*)-4-amino-10-{[(benzyloxy)carbonyl]amino}-5,12,17-trioxo-19-phenyl-18-oxa-6,13,16-triazanonadec-1-yl)carbamate hydrochloride



At RT, 2.5 ml of a 4M hydrogen chloride-dioxane solution are added to a solution of 48 mg (0.060 mmol) of benzyl {2-[((3*S*)-3-{[(benzyloxy)carbonyl]amino}-6-{[N^5-[(benzyloxy)carbonyl]-N^2-(*tert*-butoxycarbonyl)-*L*-ornithyl]amino}hexanoyl)amino]-ethyl}carbamate (Example 62A) in 1 ml of dioxane. After 4 h at RT, the reaction solution is concentrated in vacuo, coevaporated several times with dichloromethane and dried under high vacuum. The crude product is reacted without further purification.

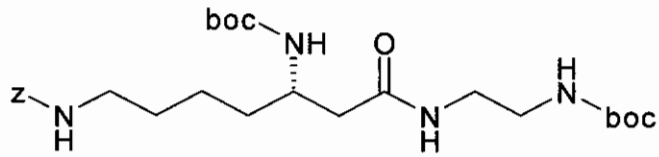
Yield: quant.

LC-MS (Method 2): R_t = 1.69 min

MS (ESI): m/z = 705 $(M-HCl+H)^+$.

Example 64A

Benzyl [(5*S*)-5-[(*tert*-butoxycarbonyl)amino]-7-({2-[(*tert*-butoxycarbonyl)amino]ethyl}-amino)-7-oxoheptyl]carbamate



Under argon, 1 g (2.54 mmol) of (3S)-7-{[(benzyloxy)carbonyl]amino}-3-[(*tert*-butoxy-carbonyl)amino]heptanecarboxylic acid, 406 mg (2.54 mmol) of *tert*-butyl (2-aminoethyl)-carbamate and 0.96 ml of triethylamine (6.85 mmol) are dissolved in 20 ml of dimethyl-formamide. Then, at 0°C (ice bath), 826 mg (4.3 mmol) of EDC and 113 mg (0.84 mmol) of HOBt are added. The mixture is slowly warmed to RT and stirred at RT for 12 h. The solution is concentrated in vacuo and the residue is taken up in ethyl acetate. The organic phase is washed successively with saturated sodium bicarbonate and sodium chloride solutions, dried over magnesium sulfate and concentrated in vacuo. The remaining solid is dried under high vacuum.

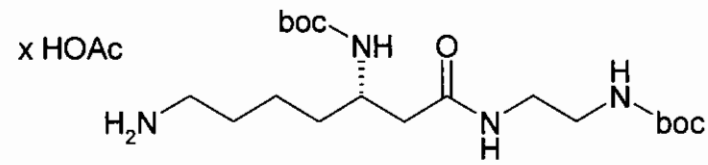
Yield: quant.

LC-MS (Method 2): R_t = 2.21 min.

MS (ESI): m/z = 537 $(M+H)^+$

Example 65A

tert-Butyl ((1*S*)-5-amino-1-{2-[(2-{[(benzyloxy)carbonyl]amino}ethyl)amino]-2-oxo-ethyl}pentyl)carbamate hydroacetate



1.3 g (2.42 mmol) of benzyl [(5*S*)-5-[(*tert*-butoxycarbonyl)amino]-7-({2-[(*tert*-butoxycarbonyl)amino]ethyl}amino)-7-oxoheptyl]carbamate (Example 64A) are dissolved in 100 ml of a glacial acetic acid/water mixture 4/1. 70 mg of palladium on activated carbon (10%) are added thereto, and the mixture is then hydrogenated under atmospheric pressure for 15 h. The reaction mixture is filtered through prewashed kieselguhr and the filtrate is concentrated on a rotary evaporator in vacuo. The crude product is reacted without further purification.

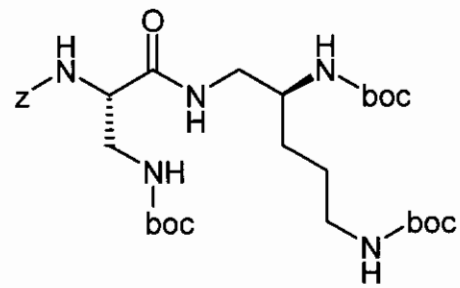
Yield: quant.

LC-MS (Method 1): R_t = 1.35 min.

MS (ESI): m/z = 403 $(M\text{-}HOAc+H)^+$

Example 66A

Benzyl *tert*-butyl[(2*S*)-3-({(2*S*)-2,5-bis[(*tert*-butoxycarbonyl)amino]pentyl}amino)-3-oxopropane-1,2-diyl]biscarbamate



Under argon, 0.127 g (0.37 mmol) of *N*-[(benzyloxy)carbonyl]-3-[(*tert*-butoxycarbonyl)amino]-*L*-alanine and 0.193 g (0.49 mmol) of *tert*-butyl {(4*S*)-5-amino-4-[(*tert*-butoxycarbonyl)amino]pentyl}carbamate (Example 53A) are dissolved in 6 ml of dimethylformamide. Then, at 0°C (ice bath), 0.093 g (0.49 mmol) of EDC and 0.015 g (0.11 mmol) of HOBt are added. The mixture is slowly warmed to RT and stirred at RT for 12 h. The solution is concentrated in vacuo and the residue is taken up in ethyl acetate. The organic phase is washed successively with saturated sodium bicarbonate and sodium chloride

solutions, dried over magnesium sulfate and evaporated in vacuo. The remaining solid is purified by preparative HPLC (Kromasil, mobile phase acetonitrile/0.25% aqueous trifluoroacetic acid 5:95 → 95:5).

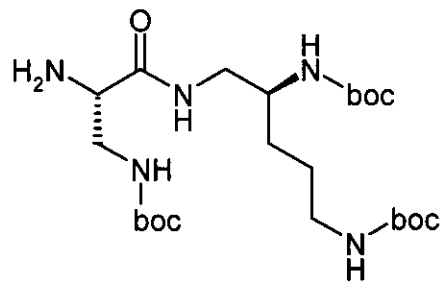
Yield: 0.126 g (53% of theory)

LC-MS (Method 1): R_t = 2.65 min.

MS (ESI): m/z = 638 $(M+H)^+$

Example 67A

tert-Butyl [(2*S*)-2-amino-3-({(2*S*)-2,5-bis[(*tert*-butoxycarbonyl)amino]pentyl}amino)-3-oxopropyl]carbamate



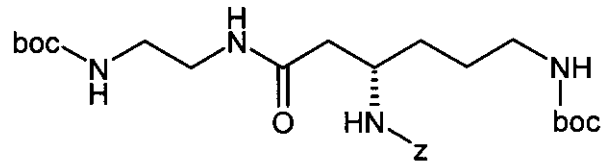
20 mg of palladium on activated carbon (10%) are added to a mixture of 0.122 g (0.19 mmol) of the compound from Example 66A in 50 ml of ethanol, and the mixture is then hydrogenated under atmospheric pressure for 4 h. The reaction mixture is filtered through kieselguhr, and the filtrate is concentrated in vacuo and dried under high vacuum. The crude product is reacted without further purification.

Yield: quant.

MS (ESI): m/z = 504 $(M+H)^+$

Example 68A

Benzyl {(1*S*)-4-[(*tert*-butoxycarbonyl)amino]-1-[2-({2-[(*tert*-butoxycarbonyl)amino]ethyl}-amino)-2-oxoethyl]butyl}carbamate



836.5 mg (2.2 mmol) of HATU and 517.0 mg (4 mmol) of *N,N*-diisopropylethylamine are added to a solution of 760.9 mg (2 mmol) of (3*S*)-3-{[(benzyloxy)carbonyl]amino}-6-[(*tert*-butoxycarbonyl)amino]hexanoic acid in 25 ml of anhydrous DMF. After stirring at RT for 15 min, 352.5 mg (2.2 mmol) of *tert*-butyl (2-aminoethyl)carbamate hydrochloride are added. The reaction mixture is stirred at RT for 15 h. The solvent is then evaporated and the residue is taken up in dichloromethane. The organic phase is washed with water, dried over magnesium sulfate and concentrated. The crude product is purified by preparative HPLC.

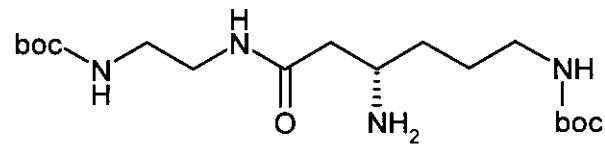
Yield 400 mg (38% of theory)

LC-MS (Method 1): R_t = 2.33 min

MS (EI): m/z = 523 $(M+H)^+$.

Example 69A

tert-Butyl [(4*S*)-4-amino-6-({2-[(*tert*-butoxycarbonyl)amino]ethyl}amino)-6-oxohexyl]-carbamate



400 mg (0.765 mmol) of benzyl {(1*S*)-4-[(*tert*-butoxycarbonyl)amino]-1-[2-({2-[(*tert*-butoxycarbonyl)amino]ethyl}amino)-2-oxoethyl]butyl}carbamate (Example 68A) are dissolved in 50 ml of ethanol. 80 mg of palladium on activated carbon (10%) are added thereto, and the mixture is then hydrogenated under atmospheric pressure for 15 h. The reaction mixture is filtered through prewashed kieselguhr, and the filtrate is concentrated on a rotary evaporator in vacuo. The crude product is reacted without further purification.

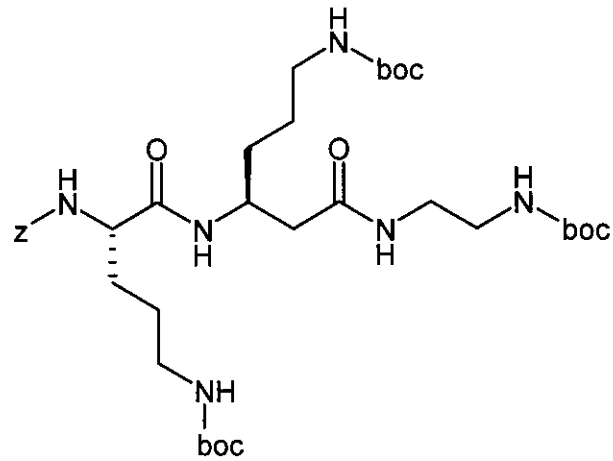
Yield: quant.

LC-MS (Method 3): R_t = 1.42 min

MS (ESI): m/z = 389 $(M+H)^+$.

Example 70A

Benzyl ((1*S*,4*S*)-1,4-bis{3-[(*tert*-butoxycarbonyl)amino]propyl}-13,13-dimethyl-2,6,11-trioxo-12-oxa-3,7,10-triazatetradec-1-yl)carbamate



Under argon, 72 mg (0.197 mmol) of N^2-[(benzyloxy)carbonyl]-N^5-(*tert*-butoxycarbonyl)-*L*-ornithine and 100 mg (0.26 mmol) of the compound from Example 69A are dissolved in 8 ml of dimethylformamide. Then, at 0°C (ice bath), 49 mg (0.26 mmol) of EDC and 8 mg (0.059 mmol) of HOBt are added. The mixture is slowly warmed to RT and stirred at RT for 12 h. The solution is concentrated in vacuo and the residue is taken up in ethyl acetate. The organic phase is washed successively with saturated sodium bicarbonate and sodium chloride solutions, dried over magnesium sulfate and concentrated in vacuo. The remaining solid is dried under high vacuum.

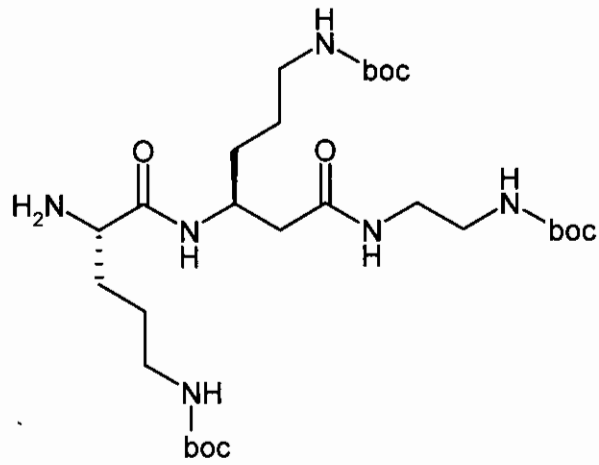
Yield 121 mg (83% of theory)

LC-MS (Method 1): R_t = 2.24 min

MS (ESI): m/z = 737 $(M+H)^+$.

Example 71A

tert-Butyl [(4*S*)-4-({(2*S*)-2-amino-5-[(*tert*-butoxycarbonyl)amino]pentanoyl}amino)-6-({2-[(*tert*-butoxycarbonyl)amino]ethyl}amino)-6-oxohexyl]carbamate



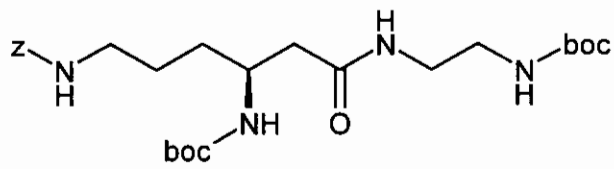
120 mg (0.16 mmol) of the compound from Example 70A are dissolved in 10 ml of ethanol. 15 mg of palladium on activated carbon (10%) are added thereto, and the mixture is then hydrogenated under atmospheric pressure for 15 h. The reaction mixture is filtered through prewashed kieselguhr and the filtrate is concentrated on a rotary evaporator in vacuo. The crude product is reacted without further purification.

Yield: quant.

MS (ESI): m/z = 603 $(M+H)^+$.

Example 72A

Benzyl [(4*S*)-4-[(*tert*-butoxycarbonyl)amino]-6-({2-[(*tert*-butoxycarbonyl)amino]ethyl}-amino)-6-oxohexyl]carbamate



Under argon, 100 mg (0.26 mmol) of (3*S*)-6-{[(Benzyloxy)carbonyl]amino}-3-[(*tert*-butoxycarbonyl)amino]hexanoic acid and 55 mg (0.34 mmol) of *tert*-butyl (2-aminoethyl)carbamate are dissolved in 6 ml of dimethylformamide. Then, at 0°C (ice

bath), 66 mg (0.34 mmol) of EDC and 11 mg (0.08 mmol) of HOBt are added. The mixture is slowly warmed to RT and stirred at RT for 12 h. The solution is concentrated in vacuo and the residue is taken up in ethyl acetate. The organic phase is washed successively with saturated sodium bicarbonate and sodium chloride solutions, dried over magnesium sulfate and concentrated in vacuo. The remaining solid is dried under high vacuum.

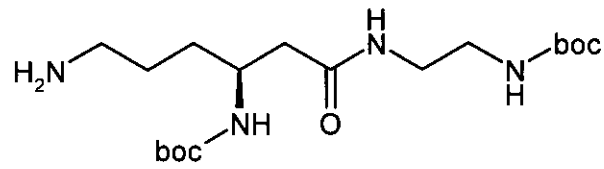
Yield: 71 mg (51% of theory)

LC-MS (Method 3): R_t = 2.43 min

MS (ESI): m/z = 523 $(M+H)^+$

Example 73A

tert-Butyl {(1*S*)-4-amino-1-[2-({2-[(*tert*-butoxycarbonyl)amino]ethyl}amino)-2-oxoethyl]butyl}carbamate



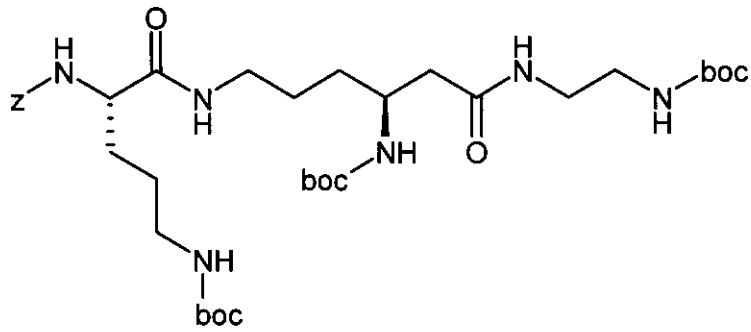
A solution of 71 mg (0.135 mmol) of the compound from Example 72A in 10 ml of ethanol is hydrogenated, after the addition of 15 mg of palladium on activated carbon (10%), for 12 h at RT under atmospheric pressure. The mixture is filtered through kieselguhr and the residue is washed with ethanol. The filtrate is evaporated to dryness in vacuo. The product is reacted without further purification.

Yield: quant.

MS (ESI): m/z = 389 $(M+H)^+$.

Example 74A

Benzyl ((1*S*,7*S*)-7-[(*tert*-butoxycarbonyl)amino]-1-{3-[(*tert*-butoxycarbonyl)amino]propyl}-16,16-dimethyl-2,9,14-trioxo-15-oxa-3,10,13-triazaheptadec-1-yl)carbamate



Under argon, 40 mg (0.11 mmol) of N^2-[(benzyloxy)carbonyl]-N^5-(*tert*-butoxycarbonyl)-*L*-ornithine and 55 mg (0.14 mmol) of the compound from Example 73A are dissolved in 8 ml of dimethylformamide. Then, at 0°C (ice bath), 27 mg (0.14 mmol) of EDC and 4.4 mg (0.033 mmol) of HOBt are added. The mixture is slowly warmed to RT and stirred at RT for 12 h. The solution is concentrated in vacuo and the residue is taken up in ethyl acetate. The organic phase is washed successively with saturated sodium bicarbonate and sodium chloride solutions, dried over magnesium sulfate and concentrated in vacuo. The remaining solid is dried under high vacuum.

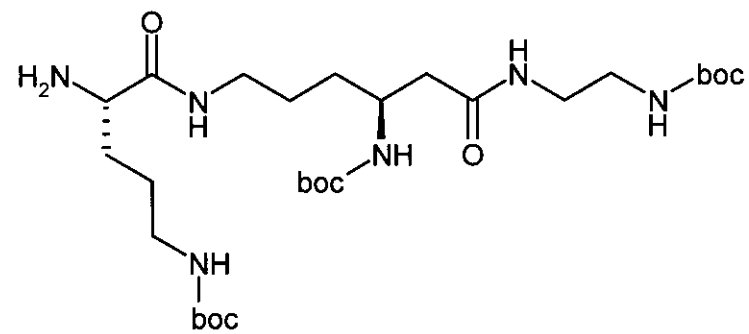
Yield: 72 mg (89% of theory)

LC-MS (Method 1): R_t = 2.2 min

MS (ESI): m/z = 737 $(M+H)^+$

Example 75A

tert-Butyl {(4*S*,10S)-4-amino-10-[(*tert*-butoxycarbonyl)amino]-19,19-dimethyl-5,12,17-trioxo-18-oxa-6,13,16-triazaicos-1-yl}carbamate



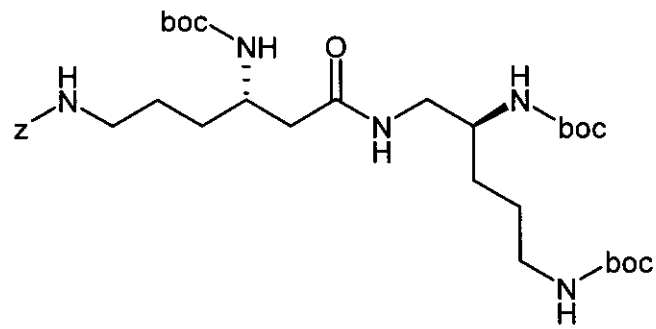
A solution of 72 mg (0.097 mmol) of the compound from Example 74A in 10 ml of ethanol is hydrogenated, after the addition of 10 mg of palladium on activated carbon (10%), for 12 h at RT under atmospheric pressure. The mixture is filtered through kieselguhr and the residue is washed with ethanol. The filtrate is concentrated to dryness in vacuo. The product is reacted without further purification.

Yield: quant.

MS (ESI): m/z = 603 $(M+H)^+$.

Example 76A

Benzyl {(4*S*)-6-({(2*S*)-2,5-bis[(*tert*-butoxycarbonyl)amino]pentyl}amino)-4-[(*tert*-butoxycarbonyl)amino]-6-oxohexyl}carbamate



Under argon, 0.1 g (0.263 mmol) of (3*S*)-6-{[(benzyloxy)carbonyl]amino}-3-[(*tert*-butoxycarbonyl)amino]hexanecarboxylic acid (*Bioorg. Med. Chem. Lett.* **1998**, *8*, 1477-1482) and 0.108 g (0.342 mmol) of *tert*-butyl {(4*S*)-5-amino-4-[(*tert*-butoxycarbonyl)-amino]pentyl}carbamate (Example 53A) are dissolved in 6 ml of dimethylformamide. Then, at 0°C (ice bath), 0.066 g (0.342 mmol) of EDC and 0.011 g (0.079 mmol) of HOBt are added. The mixture is slowly warmed to RT and stirred at RT for 12 h. The solution is concentrated in vacuo and the residue is taken up in ethyl acetate. The organic phase is washed successively with saturated sodium bicarbonate and sodium chloride solutions, dried over magnesium sulfate and concentrated in vacuo. The remaining solid is dried to constant weight under high vacuum.

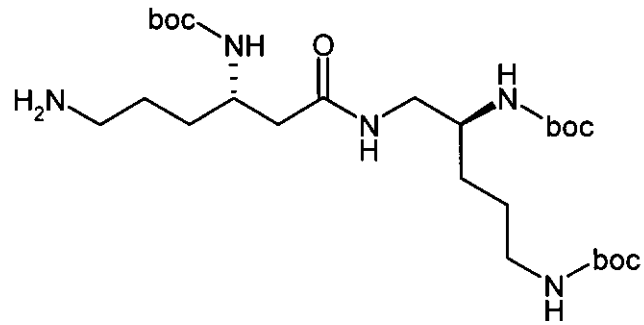
Yield: 0.127 g (71% of theory)

LC-MS (Method 1): R_t = 2.36 min

MS (ESI): m/z = 680 $(M+H)^+$

Example 77A

tert-Butyl {(1*S*)-4-amino-1-[2-({(2*S*)-2,5-bis[(*tert*-butoxycarbonyl)amino]pentyl}amino)-2-oxoethyl]butyl}carbamate



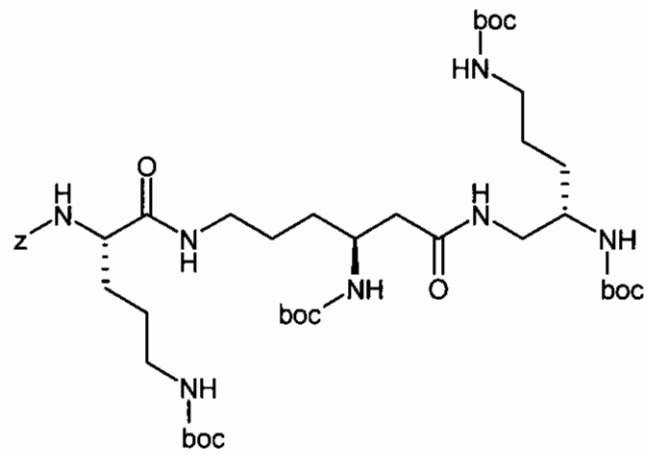
20 mg of palladium on activated carbon (10%) are added to a mixture of 0.127 g (0.19 mmol) of the compound from Example 76A in 10 ml of ethanol, and the mixture is then hydrogenated for 12 h under atmospheric pressure. The reaction mixture is filtered through kieselguhr, the filtrate is concentrated in vacuo and dried under high vacuum. The crude product is reacted without further purification.

Yield: quant.

MS (ESI): m/z = 546 $(M+H)^+$

Example 78A

Benzyl ((1*S*,7*S*,12*S*)-7,12-bis[(*tert*-butoxycarbonyl)amino]-1-{3-[(*tert*-butoxycarbonyl)amino]propyl}-19,19-dimethyl-2,9,17-trioxo-18-oxa-3,10,16-triazaicos-1-yl)carbamate



Under argon, 44 mg (0.12 mmol) of N^2-[(benzyloxy)carbonyl]-N^5-(*tert*-butoxycarbonyl)-*L*-ornithine and 85 mg (0.16 mmol) of the compound from Example 77A are dissolved in 8 ml of dimethylformamide. Then, at 0°C (ice bath), 30 mg (0.16 mmol) of EDC and 4.9 mg (0.036 mmol) of HOBt are added. The mixture is slowly warmed to RT and stirred at RT for 12 h. The solution is concentrated in vacuo and the residue is taken up in ethyl acetate. The organic phase is washed successively with saturated sodium bicarbonate and sodium chloride solutions, dried over magnesium sulfate and concentrated in vacuo. The remaining solid is dried under high vacuum.

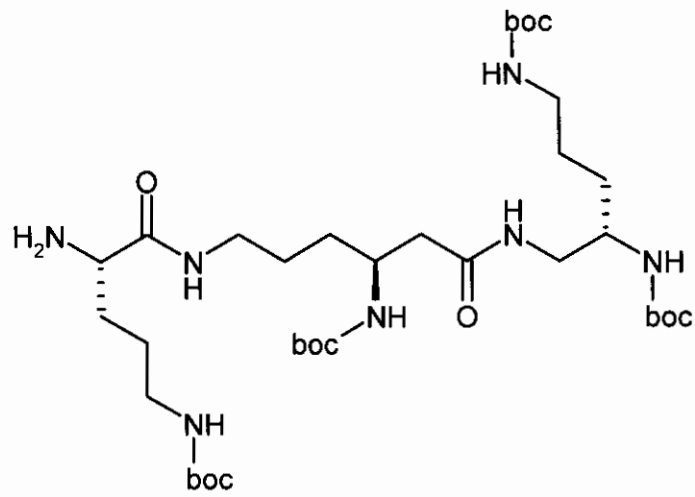
Yield: 91 mg (85% of theory)

LC-MS (Method 1): R_t = 2.35 min.

MS (ESI): m/z = 894 $(M+H)^+$

Example 79A

tert-Butyl {(4*S*,10*S*,15*S*)-4-amino-10,15-bis[(*tert*-butoxycarbonyl)amino]-22,22-dimethyl-5,12,20-trioxo-21-oxa-6,13,19-triazatricos-1-yl}carbamate



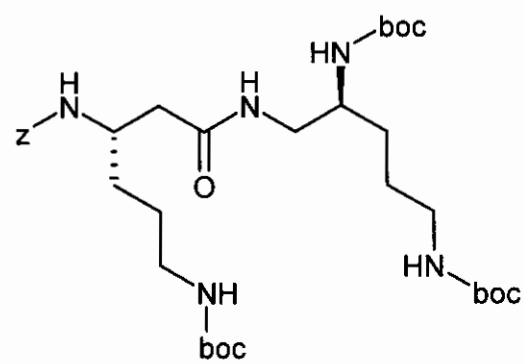
A solution of 91 mg (0.10 mmol) of the compound from Example 78A in 10 ml of ethanol is hydrogenated, after the addition of 10 mg of palladium on activated carbon (10%), for 12 h at RT under atmospheric pressure. The mixture is filtered through kieselguhr and the residue is washed with ethanol. The filtrate is concentrated to dryness in vacuo. The product is reacted without further purification.

Yield: quant.

MS (ESI): m/z = 760 $(M+H)^+$.

Example 80A

Benzyl {(1*S*)-1-[2-({(2*S*)-2,5-bis[(*tert*-butoxycarbonyl)amino]pentyl}amino)-2-oxoethyl]-4-[(*tert*-butoxycarbonyl)amino]butyl}carbamate



Under argon, 0.1 g (0.26 mmol) of (3*S*)-3-{[(benzyloxy)carbonyl]amino}-6-[(*tert*-butoxycarbonyl)amino]hexanoic acid (*J. Med. Chem.* **2002**, 45, 4246-4253) and 0.11 g (0.34 mmol) of *tert*-butyl {(4*S*)-5-amino-4-[(*tert*-butoxycarbonyl)amino]pentyl}carbamate (Example 53A) are dissolved in 6 ml of dimethylformamide. Then, at 0°C (ice bath), 0.065 g (0.34 mmol) of EDC and 0.011 g (0.079 mmol) of HOBt are added. The mixture is slowly warmed to RT and stirred at RT for 12 h. The solution is concentrated in vacuo and the residue is taken up in ethyl acetate. The organic phase is washed successively with saturated sodium bicarbonate and sodium chloride solutions, dried over magnesium sulfate and concentrated in vacuo. The remaining solid is dried to constant weight under high vacuum.

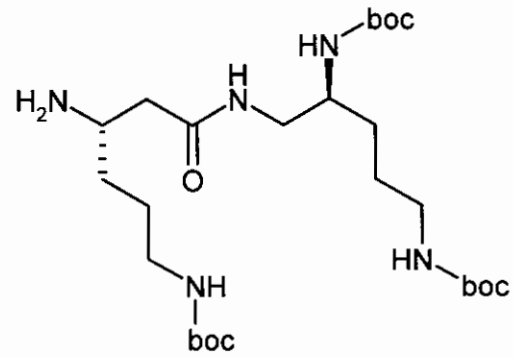
Yield: 0.146 g (82% of theory)

LC-MS (Method 2): R_t = 2.5 min

MS (ESI): m/z = 680 $(M+H)^+$

Example 81A

tert-Butyl [(4*S*)-4-amino-6-({(2*S*)-2,5-bis[(*tert*-butoxycarbonyl)amino]pentyl}amino)-6-oxohexyl]carbamate



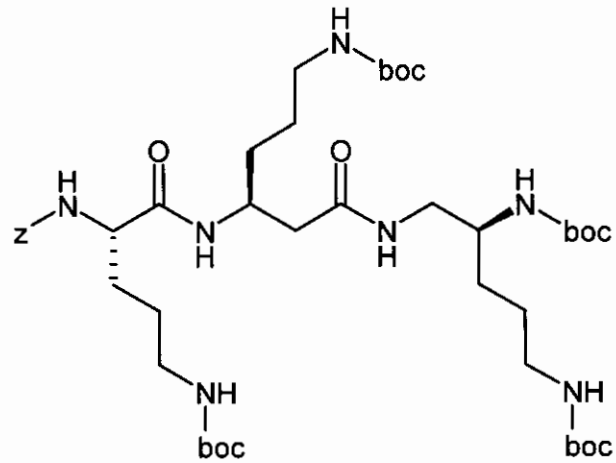
22 mg of palladium on activated carbon (10%) are added to a mixture of 0.146 g (0.22 mmol) of the compound from Example 80A in 10 ml of ethanol, and the mixture is then hydrogenated under atmospheric pressure for 12 h. The reaction mixture is filtered through kieselguhr, the filtrate is concentrated in vacuo and dried under high vacuum. The crude product is reacted without further purification.

Yield: quant.

MS (ESI): m/z = 546 $(M+H)^+$

Example 82A

Benzyl ((1*S*,4*S*,9*S*)-9-[(*tert*-butoxycarbonyl)amino]-1,4-bis{3-[(*tert*-butoxycarbonyl)-amino]propyl}-16,16-dimethyl-2,6,14-trioxo-15-oxa-3,7,13-triazaheptadec-1-yl)carbamate



Under argon, 40 mg (0.11 mmol) of N^2-[(benzyloxy)carbonyl]-N^5-(*tert*-butoxycarbonyl)-*L*-ornithine and 77 mg (0.14 mmol) of the compound from Example 81A are dissolved in 8 ml of dimethylformamide. Then, at 0°C (ice bath), 27 mg (0.14 mmol) of EDC and 4.4 mg (0.032 mmol) of HOBt are added. The mixture is slowly warmed to RT and stirred at RT for 12 h. The solution is concentrated in vacuo and the residue is taken up in ethyl acetate. The organic phase is washed successively with saturated sodium bicarbonate and sodium chloride solutions, dried over magnesium sulfate and concentrated in vacuo. The remaining solid is dried under high vacuum.

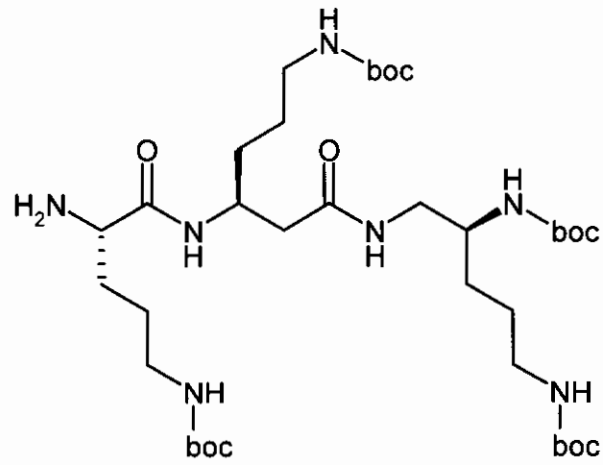
Yield: 78 mg (81% of theory)

LC-MS (Method 1): R_t = 2.43 min

MS (ESI): m/z = 894 $(M+H)^+$

Example 83A

tert-Butyl ((1*S*,6*S*,9*S*)-9-amino-1,6-bis{3-[(*tert*-butoxycarbonyl)amino]propyl}-16,16-dimethyl-4,8,14-trioxo-15-oxa-3,7,13-triazaheptadec-1-yl)carbamate



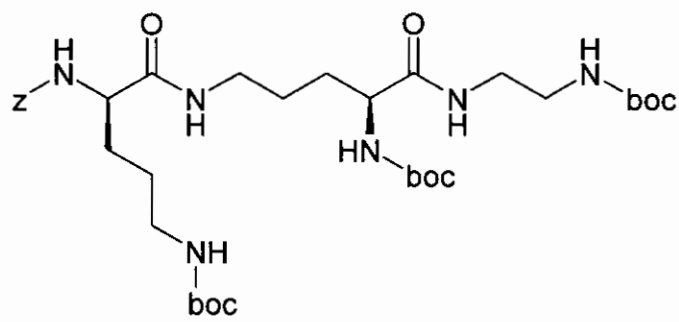
A solution of 78 mg (0.088 mmol) of the compound from Example 82A in 10 ml of ethanol is hydrogenated, after the addition of 10 mg of palladium on activated carbon (10%), for 12 h at RT under atmospheric pressure. The mixture is filtered through kieselguhr and the residue is washed with ethanol. The filtrate is concentrated to dryness in vacuo. The product is reacted without further purification.

Yield: quant.

MS (ESI): m/z = 760 $(M+H)^+$.

Example 84A

N^5-[N^2-[(Benzyloxy)carbonyl]-N^5-(*tert*-butoxycarbonyl)-*D*-ornithyl]-N^2-(*tert*-butoxycarbonyl)-*N*-{2-[(*tert*-butoxycarbonyl)amino]ethyl}-*L*-ornithinamide



Under argon, 286 mg (0.78 mmol) of N^2-[(benzyloxy)carbonyl]-N^5-(*tert*-butoxycarbonyl)-*D*-ornithine and 439 mg (1.17 mmol) of the compound from Example 104A are dissolved in 16 ml of dimethylformamide. Then, at 0°C (ice bath), 255 mg (1.33 mmol) of EDC and

106 mg (0.78 mmol) of HOBt are added. The mixture is slowly warmed to RT and stirred at RT for 48 h. The solution is concentrated in vacuo and the residue is taken up in dichloromethane and washed with a saturated aqueous sodium bicarbonate solution, 0.1 N hydrochloric acid and water. The combined organic phases are concentrated in vacuo and the solid obtained in this way is reacted further without purification.

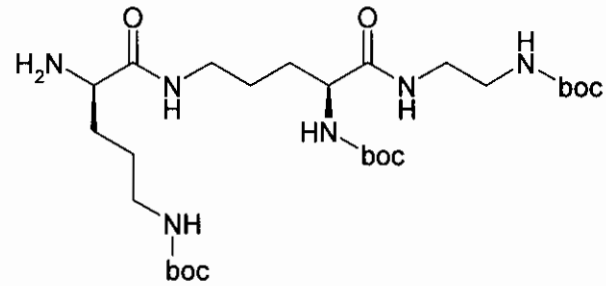
Yield: 0.58 g (quant.)

LC-MS (Method 3): R_t = 2.59 min.

MS (ESI): m/z = 723 $(M+H)^+$

Example 85A

N^5-[N^5-(*tert*-Butoxycarbonyl)-*D*-ornithyl]-N^2-(*tert*-butoxycarbonyl)-*N*-{2-[(*tert*-butoxycarbonyl)amino]ethyl}-*L*-ornithinamide



0.58 g (0.80 mmol) of the compound from Example 84A are dissolved in 27 ml of ethanol, and 0.06 g (0.06 mmol) of Pd/C are added. The mixture is hydrogenated under atmospheric pressure for 12 h and filtered through celite, and the filtrate is concentrated in vacuo. The solid obtained in this way is reacted further without purification.

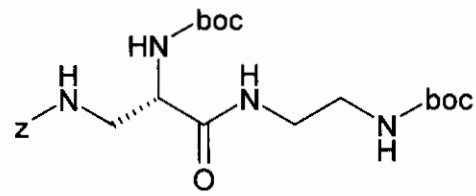
Yield: 0.47 g (97% of theory)

LC-MS (Method 1): R_t = 1.61 min.

MS (ESI): m/z = 589 $(M+H)^+$

Example 86A

Benzyl [(2*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-({2-[(*tert*-butoxycarbonyl)amino]ethyl}-amino)-3-oxopropyl]carbamate



Under argon, 0.50 g (0.96 mmol) of 3-{[(benzyloxy)carbonyl]amino}-*N*-(*tert*-butoxycarbonyl)-*L*-alanine - *N*-cyclohexylcyclohexanamine (1:1) and 0.154 g (0.96 mmol) of *tert*-butyl (2-aminoethyl)carbamate are dissolved in 10 ml of dimethylformamide and 0.5 ml of triethylamine. Then, at 0°C (ice bath), 0.314 g (1.64 mmol) of EDC and 0.043 g (0.32 mmol) of HOBt are added. The mixture is slowly warmed to RT and stirred at RT for 12 h. The solution is concentrated in vacuo and the residue is taken up in ethyl acetate. The organic phase is washed successively with saturated sodium bicarbonate and sodium chloride solutions, dried over magnesium sulfate and concentrated in vacuo. The remaining solid is dried to constant weight under high vacuum.

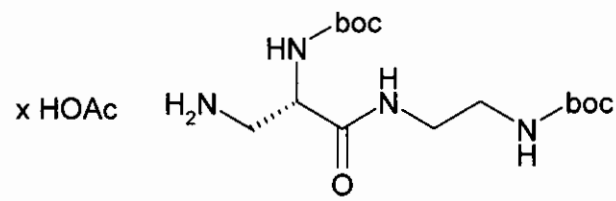
Yield: 0.41 g (88% of theory)

LC-MS (Method 2): R_t = 2.17 min

MS (ESI): m/z = 481 $(M+H)^+$

Example 87A

3-Amino-N^2-(*tert*-butoxycarbonyl)-*N*-{2-[(*tert*-butoxycarbonyl)amino]ethyl}-*L*-alaninamide hydroacetate



50 mg of palladium on activated carbon (10%) are added to a mixture of 0.41 g (0.847 mmol) of the compound from Example 86A in 80 ml of acetic acid/ethanol/water (4:1:1), and the mixture is then hydrogenated under atmospheric pressure for 12 h. The reaction mixture is filtered through kieselguhr, and the filtrate is concentrated in vacuo and dried under high vacuum. The crude product is reacted without further purification.

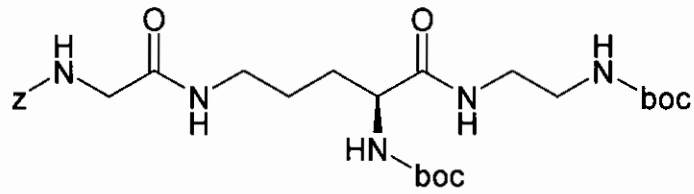
Yield: quant.

LC-MS (Method 2): R_t = 1.09 min

MS (ESI): m/z = 347 $(M\text{-}HOAc+H)^+$

Example 88A

N^5-{*N*-[(Benzyloxy)carbonyl]glycyl}-N^2-(*tert*-butoxycarbonyl)-*N*-{2-[(*tert*-butoxycarbonyl)amino]ethyl}-*L*-ornithinamide



Under argon, 300 mg (1.43 mmol) of *N*-[(benzyloxy)carbonyl]glycine and 830 mg (2.15 mmol) of the compound from Example 104A are dissolved in 28 ml of dimethylformamide. Then, at 0°C (ice bath), 467 mg (2.44 mmol) of EDC and 194 mg (1.43 mmol) of HOBt are added. The mixture is slowly warmed to RT and stirred at RT for 48 h. The solution is concentrated in vacuo and the residue is taken up in dichloromethane and washed with a saturated sodium bicarbonate solution, 0.1 N hydrochloric acid and water. The combined organic phases are concentrated in vacuo, and the solid obtained in this way is reacted further without purification.

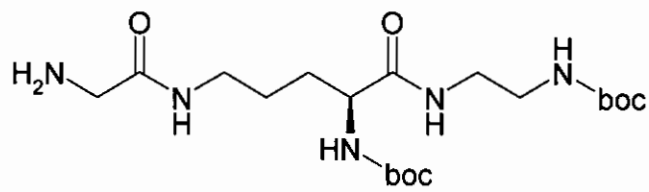
Yield: quant.

LC-MS (Method 2): R_t = 1.98 min.

MS (ESI): m/z = 566 $(M+H)^+$

Example 89A

N^5-Glycyl-N^2-(*tert*-butoxycarbonyl)-*N*-{2-[(*tert*-butoxycarbonyl)amino]ethyl}-*L*-ornithinamide



1.03 g (1.82 mmol) of the compound from Example 88A are dissolved in 60 ml of ethanol, and 100 mg (0.09 mmol) of Pd/C (10%) are added. The mixture is hydrogenated under atmospheric pressure overnight, and filtered through celite, and the filtrate is concentrated in vacuo. The solid obtained in this way is reacted further without purification.

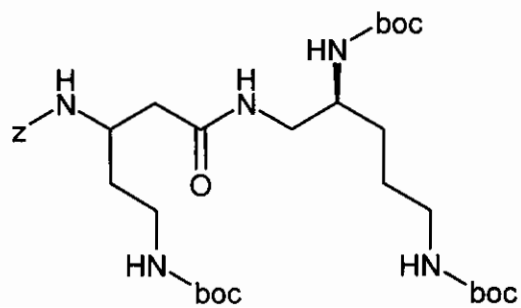
Yield: 693 mg (84% of theory)

LC-MS (Method 3): R_t = 1.41 min.

MS (ESI): m/z = 432 $(M+H)^+$

Example 90A

Benzyl *tert*-butyl-[5-({(2*S*)-2,5-bis[(*tert*-butoxycarbonyl)amino]pentyl}amino)-5-oxopentan-1,3-diyl]biscarbamate



0.146 g (0.40 mmol) of 3-{[(benzyloxy)carbonyl]amino}-5-[(*tert*-butoxycarbonyl)-amino]pentanoic acid (*Bioorg. Med. Chem.* **2003**, 13, 241-246) and 0.164 g (0.52 mmol) of *tert*-butyl {(4*S*)-5-amino-4-[(*tert*-butoxycarbonyl)amino]pentyl}carbamate (Example 53A) are dissolved in 8 ml of dimethylformamide under argon. Then, at 0°C (ice bath), 0.10 g (0.52 mmol) of EDC and 0.009 g (0.12 mmol) of HOBt are added. The mixture is slowly warmed to RT and stirred at RT for 12 h. The solution is concentrated in vacuo and the residue is taken up in ethyl acetate. The organic phase is washed successively with saturated sodium bicarbonate and sodium chloride solutions, dried over magnesium sulfate and concentrated in vacuo. The remaining solid is dried to constant weight under high vacuum.

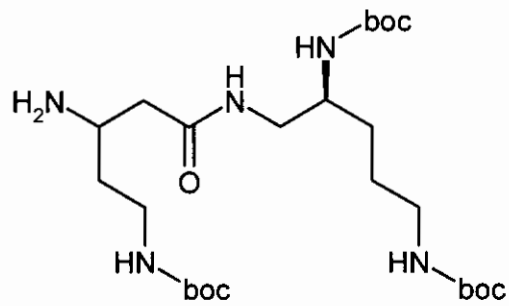
Yield: 0.232 g, (87% of theory)

LC-MS (Method 3): R_t = 2.73 min

MS (ESI): m/z = 666 $(M+H)^+$

Example 91A

tert-Butyl [3-amino-5-({(2*S*)-2,5-bis[(*tert*-butoxycarbonyl)amino]pentyl}amino)-5-oxopentyl]carbamate



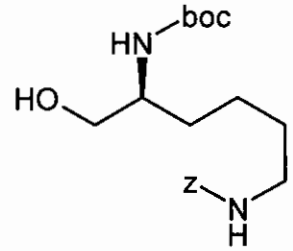
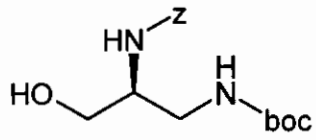
35 mg of palladium on activated carbon (10%) are added to a mixture of 0.232 g (0.35 mmol) of the compound from Example 90A in 10 ml of ethanol, and the mixture is then hydrogenated under atmospheric pressure for 12 h. The reaction mixture is filtered through kieselguhr, and the filtrate is concentrated in vacuo and dried under high vacuum. The crude product is reacted without further purification.

Yield: 0.175 g (94% of theory)

LC-MS (Method 3): R_t = 1.8 min

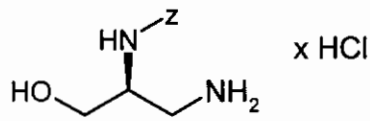
MS (ESI): m/z = 532 $(M+H)^+$

Examples 92A and 93A listed in the following table are prepared from the corresponding starting compounds in analogy to the procedure for Example 50A detailed above:

Ex. No.	Structure	Prepared from	Analytical Data
92A		N^6-[(Benzyloxy)-carbonyl]-N^2-(*tert*-butoxycarbonyl)-*L*-lysine	LC-MS (Method 2): R_t = 1.94 min MS (ESI): m/z = 367 $(M+H)^+$
93A		N-[(Benzyloxy)-carbonyl]-3-[(*tert*-butoxycarbonyl)-amino]-*L*-alanine	LC-MS (Method 1): R_t = 1.98 min MS (ESI): m/z = 325 $(M+H)^+$

Example 94A

Benzyl [(1*S*)-2-amino-1-(hydroxymethyl)ethyl]carbamate hydrochloride



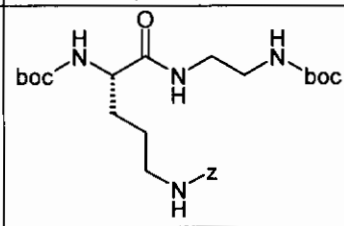
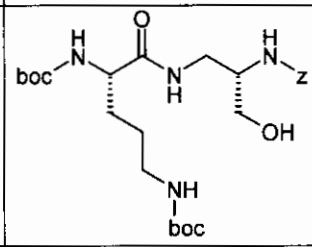
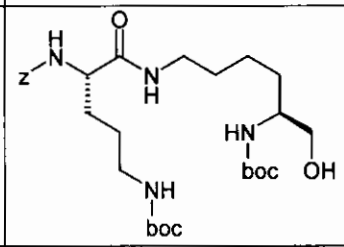
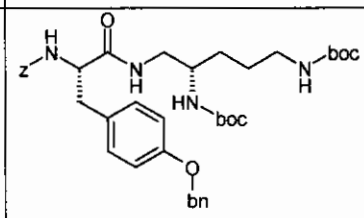
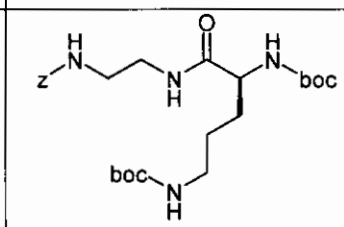
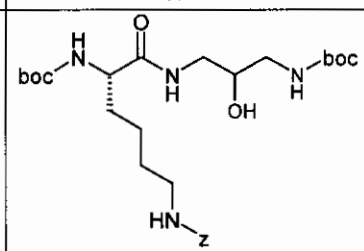
A mixture of 269 mg (0.83 mmol) of benzyl *tert*-butyl [(2*S*)-3-hydroxypropane-1,2-diyl]biscarbamate (Example 93A) and 5 ml of a 4M hydrogen chloride-dioxane solution is stirred at RT for 2 h. The reaction solution is concentrated, coevaporated several times with dichloromethane and dried under high vacuum. The crude product is reacted without further purification.

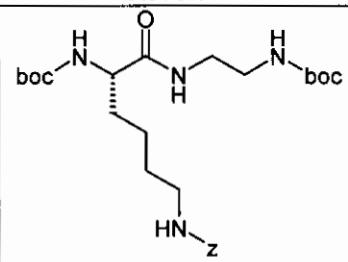
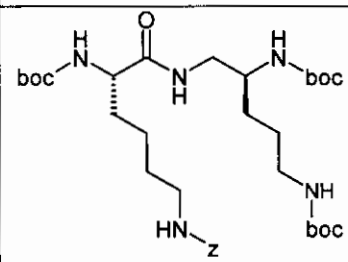
Yield: 212 mg (98% of theory)

LC-MS (Method 2): R_t = 0.55 min

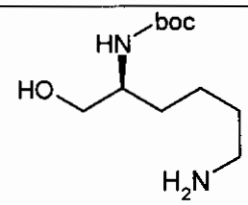
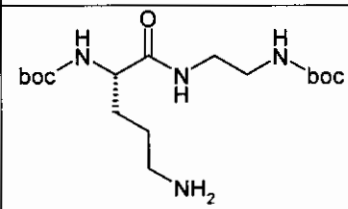
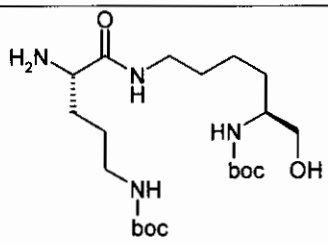
MS (ESI): m/z = 225 $(M-HCl+H)^+$.

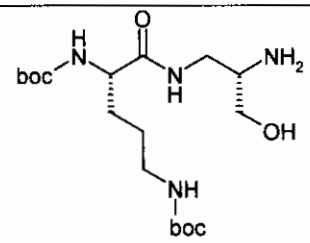
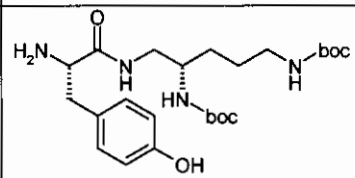
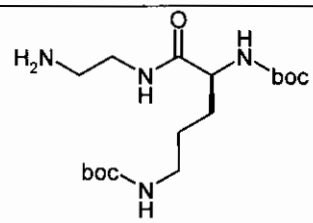
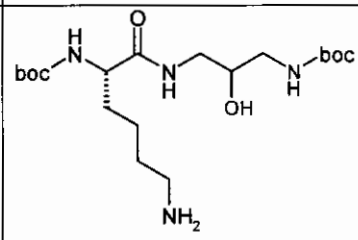
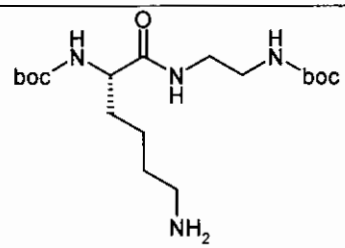
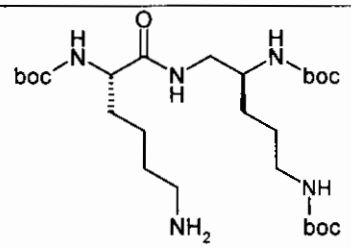
Examples 95A to 102A listed in the following table are prepared from the corresponding starting materials in analogy to the procedure of Example 48A detailed above:

Ex. No.	Structure	Prepared from	Analytical Data
95A		N^5-[(Benzyloxy)-carbonyl]-N^2-(*tert*-butoxycarbonyl)-*L*-ornithin and *tert*-butyl-(2-aminoethyl)carbamate	LC-MS (Method 1): R_t = 2.33 min MS (ESI): m/z = 509 $(M+H)^+$
96A		N^2,N^5-Bis(*tert*-butoxycarbonyl)-*L*-ornithine and Ex. 94A	LC-MS (Method 1): R_t = 2.20 min MS (ESI): m/z = 539 $(M+H)^+$
97A		N^2-[(Benzyloxy)-carbonyl]-N^5-(*tert*-butoxycarbonyl)-*L*-ornithine and Ex. 103A	LC-MS (Method 1): R_t = 2.31 min MS (ESI): m/z = 581 $(M+H)^+$
98A		*O*-Benzyl-*N*-[(benzyloxy)carbonyl]-*L*-tyrosine and Ex. 53A	LC-MS (Method 2): R_t = 2.79 min MS (ESI): m/z = 705 $(M+H)^+$
99A		N^2,N^5-Bis(*tert*-butoxycarbonyl)-*L*-ornithine and benzyl-(2-aminoethyl)carbamate	LC-MS (Method 2): R_t = 2.15 min MS (ESI): m/z = 509 $(M+H)^+$
100A		N^6-[(Benzyloxy)-carbonyl]-N^2-(*tert*-butoxycarbonyl)-*L*-lysine and *tert*-butyl (3-amino-2-hydroxypropyl)carbamate	LC-MS (Method 3): R_t = 2.4 min MS (ESI): m/z = 553 $(M+H)^+$

Ex. No.	Structure	Prepared from	Analytical Data
101A		N^6-[(Benzyloxy)-carbonyl]-N^2-(*tert*-butoxycarbonyl)-*L*-lysine and benzyl (2-amino-ethyl)carbamate	LC-MS (Method 3): R_t = 2.49 min MS (ESI): m/z = 523 $(M+H)^+$
102A		N^6-[(Benzyloxy)-carbonyl]-N^2-(*tert*-butoxycarbonyl)-*L*-lysine and Ex. 53A	LC-MS (Method 2): R_t = 2.55 min MS (ESI): m/z = 680 $(M+H)^+$

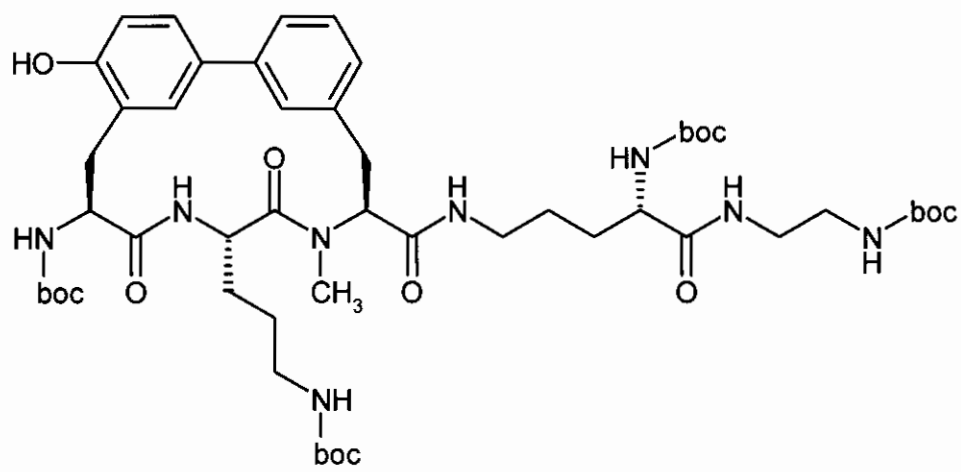
Examples 103A to 111A listed in the following table are prepared from the corresponding starting materials in analogy to the procedure of Example 49A detailed above:

Ex. No.	Structure	Prepared from Example	Analytical Data
103A		92A	MS (ESI): m/z = 233 $(M+H)^+$
104A		95A	MS (ESI): m/z = 375 $(M+H)^+$
105A		97A	MS (ESI): m/z = 447 $(M+H)^+$

Ex. No.	Structure	Prepared from Example	Analytical Data
106A		96A	MS (ESI): m/z = 405 $(M+H)^+$
107A		98A	LC-MS (Method 3): R_t = 1.67 min MS (ESI): m/z = 481 $(M+H)^+$
108A		99A	MS (ESI): m/z = 375 $(M+H)^+$
109A		100A	MS (ESI): m/z = 419 $(M+H)^+$
110A		101A	MS (ESI): m/z = 388 $(M+H)^+$
111A		102A	MS (ESI): m/z = 546 $(M+H)^+$

Example 112A

tert-Butyl (2-{[(2*S*)-2-[(*tert*-butoxycarbonyl)amino]-5-({[(8*S*,11*S*,14*S*)-14-[(*tert*-butoxycarbonyl)amino]-11-{3-[(*tert*-butoxycarbonyl)amino]propyl}-17-hydroxy-9-methyl-10,13-dioxo-9,12-diazatricyclo[14.3.1.1^{2,6}]henicosa-1(20),2(21),3,5,16,18-hexaen-8-yl]carbonyl}amino)pentanoyl]amino}ethyl)carbamate



50 mg (0.05 mmol) of (8*S*,11*S*,14*S*)-14-[(*tert*-butoxycarbonyl)amino]-11-{3-[(*tert*-butoxycarbonyl)amino]propyl}-17-hydroxy-9-methyl-10,13-dioxo-9,12-diazatricyclo[14.3.1.1^{2,6}]-henicosa-1(20),2(21),3,5,16,18-hexaene-8-carboxylic acid (Example 46A) and 34 mg (0.09 mmol) of N^2-(*tert*-butoxycarbonyl)-*N*-{2-[(*tert*-butoxycarbonyl)amino]ethyl}-*L*-ornithinamide (Example 104A) are dissolved in 2.5 ml of DMF and cooled to 0°C. 15 mg (0.08 mmol) of EDC and 6 mg (0.05 mmol) of HOBt are added and the mixture is stirred at room temperature for 12 h. The reaction mixture is concentrated on a rotary evaporator in vacuo. The crude product is reacted without further purification.

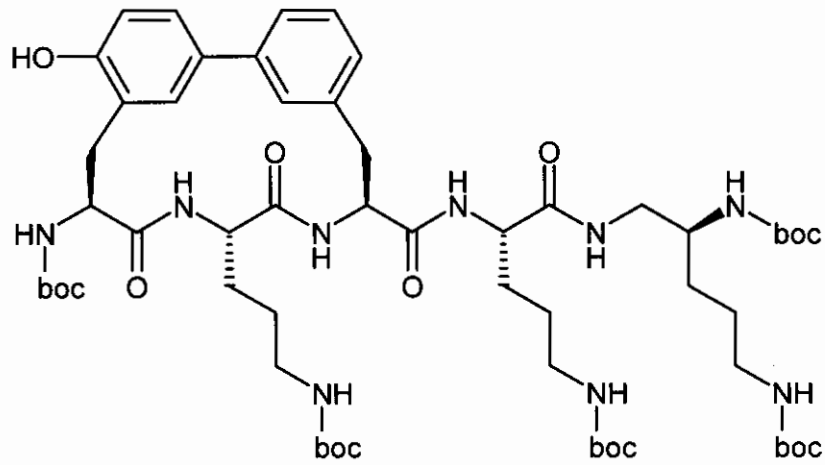
Yield: 215 mg (88% of theory)

LC-MS (Method 3): R_t = 2.70 min

MS (ESI): m/z = 1011 $(M+H)^+$

Example 113A

tert-Butyl [(4*S*)-5-({(2*S*)-2,5-bis[(*tert*-butoxycarbonyl)amino]pentyl}amino)-4-({[(8*S*,11*S*,14*S*)-14-[(*tert*-butoxycarbonyl)amino]-11-{3-[(*tert*-butoxycarbonyl)amino]propyl}-17-hydroxy-10,13-dioxo-9,12-diazatricyclo[14.3.1.1^{2,6}]henicosa-1(20),2(21),3,5,16,18-hexaen-8-yl]-carbonyl}amino)-5-oxopentyl]carbamate



29 mg (0.05 mmol) of (8*S*,11*S*,14*S*)-14-[(*tert*-butoxycarbonyl)amino]-11-{3-[(*tert*-butoxycarbonyl)amino]propyl}-17-hydroxy-10,13-dioxo-9,12-diazatricyclo[14.3.1.1^{2,6}]henicosa-1(20),2(21),3,5,16,18-hexaene-8-carboxylic acid (Example 44A) and 24 mg (0.05 mmol) of *tert*-butyl [(4*S*)-4-amino-5-({(2*S*)-2,5-bis[(*tert*-butoxycarbonyl)amino]pentyl}amino)-5-oxopentyl]carbamate (Example 57A) are dissolved in 2.0 ml DMF and cooled to 0°C. 15 mg (0.08 mmol) of EDC and 6 mg (0.05 mmol) of HOBt are added and the mixture is stirred at room temperature for 12 h. The reaction mixture is concentrated on a rotary evaporator in vacuo and purified by chromatography over Sephadex-LH20 (mobile phase methanol/acetic acid 0.25%).

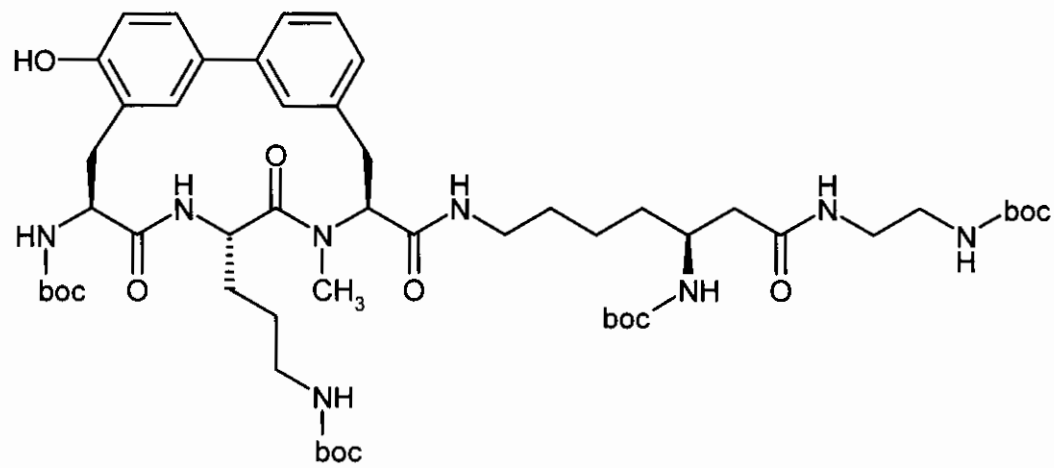
Yield: 53 mg (54% of theory)

LC-MS (Method 2): R_t = 2.68 min

MS (ESI): m/z = 1154 $(M+H)^+$

Example 114A

tert-Butyl (2-{[(3*S*)-3-[(*tert*-butoxycarbonyl)amino]-7-({[(8*S*,11*S*,14*S*)-14-[(*tert*-butoxycarbonyl)amino]-11-{3-[(*tert*-butoxycarbonyl)amino]propyl}-17-hydroxy-9-methyl-10,13-dioxo-9,12-diazatricyclo[14.3.1.1^{2,6}]henicosa-1(20),2(21),3,5,16,18-hexaen-8-yl]carbonyl}amino)heptanoyl]amino}ethyl)carbamate



40 mg (0.06 mmol) of (8*S*,11*S*,14*S*)-14-[(*tert*-butoxycarbonyl)amino]-11-{3-[(*tert*-butoxycarbonyl)amino]propyl}-17-hydroxy-9-methyl-10,13-dioxo-9,12-diazatricyclo-[14.3.1.1^{2,6}]henicosa-1(20),2(21),3,5,16,18-hexaene-8-carboxylic acid (Example 46A) and 46 mg (0.08 mmol) of *tert*-butyl {(1*S*)-5-amino-1-[2-({2-[(*tert*-butoxycarbonyl)-amino]ethyl}amino)-2-oxoethyl]pentyl}carbamate (Example 65A) are dissolved in 2.0 ml of DMF and cooled to 0°C. 15 mg (0.08 mmol) of EDC, 3 mg (0.02 mmol) of HOBt and 0.01 ml (0.08 mmol) of triethylamine are added and the mixture is stirred at room temperature for 12 h. The reaction mixture is concentrated on a rotary evaporator in vacuo and purified by a preparative HPLC.

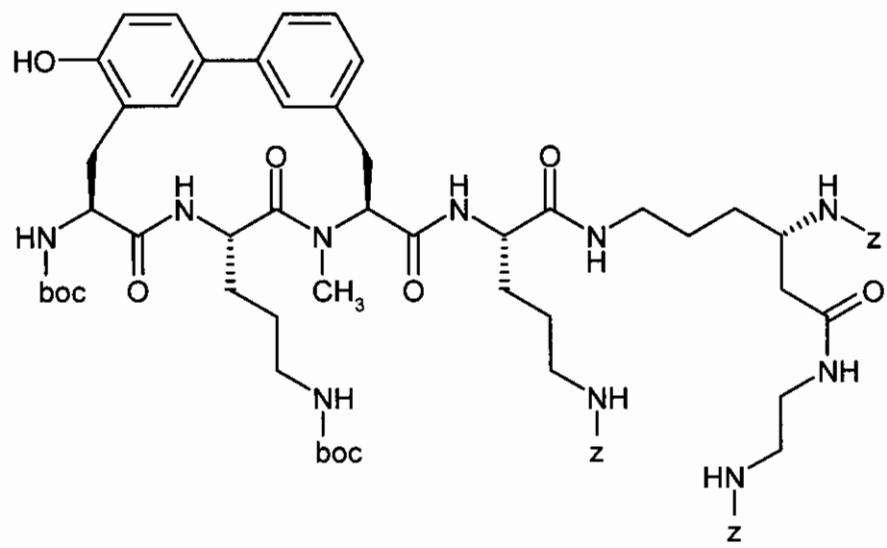
Yield: 6 mg (9% of theory)

LC-MS (Method 2): R_t = 2.47 min

MS (ESI): m/z = 1039 $(M+H)^+$

Example 115A

Benzyl ((1*S*)-4-{[(2*S*)-5-{[(benzyloxy)carbonyl]amino}-2-({[(8*S*,11*S*,14*S*)-14-[(*tert*-butoxy-carbonyl)amino]-11-{3-[(*tert*-butoxycarbonyl)amino]propyl}-17-hydroxy-9-methyl-10,13-dioxo-9,12-diazatricyclo[14.3.1.1^{2,6}]henicosa-1(20),2(21),3,5,16,18-hexaen-8-yl]-carbonyl}amino)pentanoyl]amino}-1-{2-[(2-{[(benzyloxy)carbonyl]amino}ethyl)amino]-2-oxoethyl}butyl)-carbamate



65 mg (0.06 mmol) of (8*S*,11*S*,14*S*)-14-[(*tert*-butoxycarbonyl)amino]-11-{3-[(*tert*-butoxycarbonyl)amino]propyl}-17-hydroxy-9-methyl-10,13-dioxo-9,12-diazatricyclo-[14.3.1.1^{2,6}]-henicosa-1(20),2(21),3,5,16,18-hexaene-8-carboxylic acid (Example 46A) and 120 mg (0.13 mmol) of benzyl ((5*S*,11*S*)-5-amino-11-{[(benzyloxy)carbonyl]amino}-6,13,18-trioxo-20-phenyl-19-oxa-7,14,17-triazaicos-1-yl)carbamate hydrochloride (Example 63A) are dissolved in 3.0 ml of DMF and cooled to 0°C. 25 mg (0.13 mmol) of EDC, 4 mg (0.03 mmol) of HOBt and 0.02 ml (0.13 mmol) of triethylamine are added and the mixture is stirred at room temperature for 12 h. The reaction mixture is concentrated on a rotary evaporator in vacuo and purified by preparative HPLC.

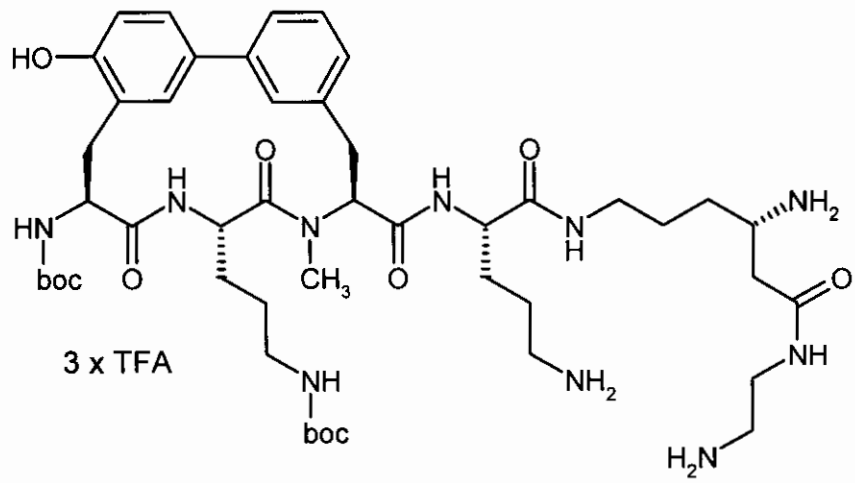
Yield: 50 mg (25% of theory).

LC-MS (Method 3): R_t = 2.92 min

MS (ESI): m/z = 1341 $(M+H)^+$

Example 116A

tert-Butyl {3-[(8*S*,11*S*,14*S*)-8-[({(1*S*)-4-amino-1-[({(4*S*)-4-amino-6-[(2-aminoethyl)amino]-6-oxohexyl}amino)carbonyl]butyl}amino)carbonyl]-14-[(*tert*-butoxycarbonyl)amino]-17-hydroxy-9-methyl-10,13-dioxo-9,12-diazatricyclo[14.3.1.1^{2,6}]henicosa-1(20),2(21),3,5,16,18-hexaen-11-yl]propyl}carbamate tris(hydrotrifluoracetate)



49 mg (0.04 mmol) of benzyl ((1*S*)-4-{[(2*S*)-5-{[(benzyloxy)carbonyl]amino}-2-({[(8*S*,11*S*,14*S*)-14-[(*tert*-butoxycarbonyl)amino]-11-{3-[(*tert*-butoxycarbonyl)amino]-propyl}-17-hydroxy-9-methyl-10,13-dioxo-9,12-diazatricyclo[14.3.1.1^{2,6}]henicosa-1(20),2(21),3,5,16,18-hexaen-8-yl]carbonyl}amino)pentanoyl]amino}-1-{2-[(2-{[(benzyloxy)-carbonyl]amino}ethyl)amino]-2-oxoethyl}butyl)carbamate (Example 115A) are dissolved in 10 ml of glacial acetic acid/water (4:1), 5 mg of Pd/C (10%) are added and the mixture hydrogenated under atmospheric pressure and a hydrogen atmosphere for 12 h. Suction filtration is carried out, and the reaction mxiture is concentrated in vacuo and purified by preparative HPLC (Kromasil 100 C18, 5 µm 250 mm × 20 mm; mobile phase acetonitrile/0.2% aqueous trifluoroacetic acid 5:95 → 95:5).

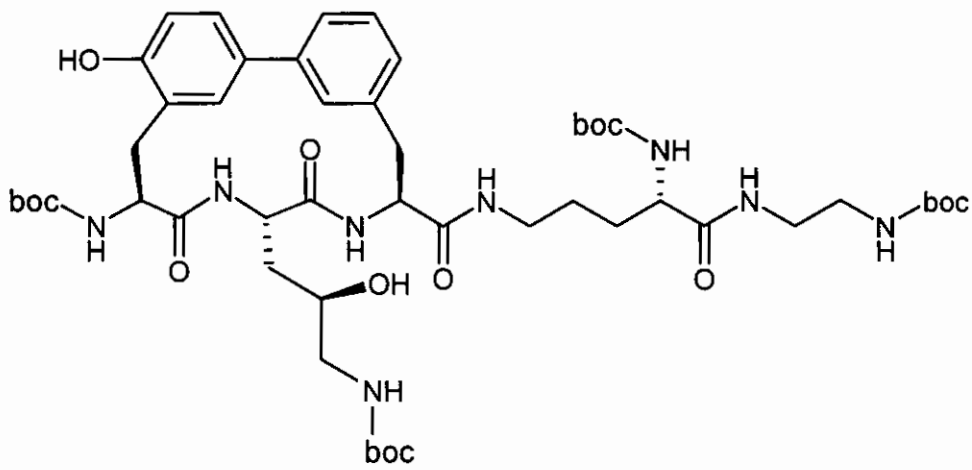
Yield: 9 mg (19% of theory)

LC-MS (Method 3): R_t = 1.45 min

MS (ESI): m/z = 939 $(M+H)^+$

Example 117A

tert-Butyl (2-{[(2*S*)-2-[(*tert*-butoxycarbonyl)amino]-5-({[(8*S*,11*S*,14*S*)-14-[(*tert*-butoxycarb-onyl)amino]-11-{(2*R*)-3-[(*tert*-butoxycarbonyl)amino]-2-hydroxypropyl}-17-hydroxy-10,13-dioxo-9,12-diazatricyclo[14.3.1.1^{2,6}]henicosa-1(20),2(21),3,5,16,18-hexaen-8-yl]carb-onyl}amino)pentanoyl]amino}ethyl)carbamate



Under argon, 50 mg (0.076 mmol) of the compound from Example 43A and 37 mg (0.1 mmol) of N^2-(*tert*-butoxycarbonyl)-*N*-{2-[(*tert*-butoxycarbonyl)amino]ethyl}-*L*-ornithinamide (Example 104A) are dissolved in 2 ml of dimethylformamide. Then, at 0°C (ice bath), 19 mg (0.1 mmol) of EDC and 3.1 mg (0.023 mmol) of HOBt are added. The mixture is slowly warmed to RT and stirred at RT for 12 h. The solution is concentrated in vacuo and the residue is stirred with water. The remaining solid is collected by suction filtration and purified via preparative HPLC.

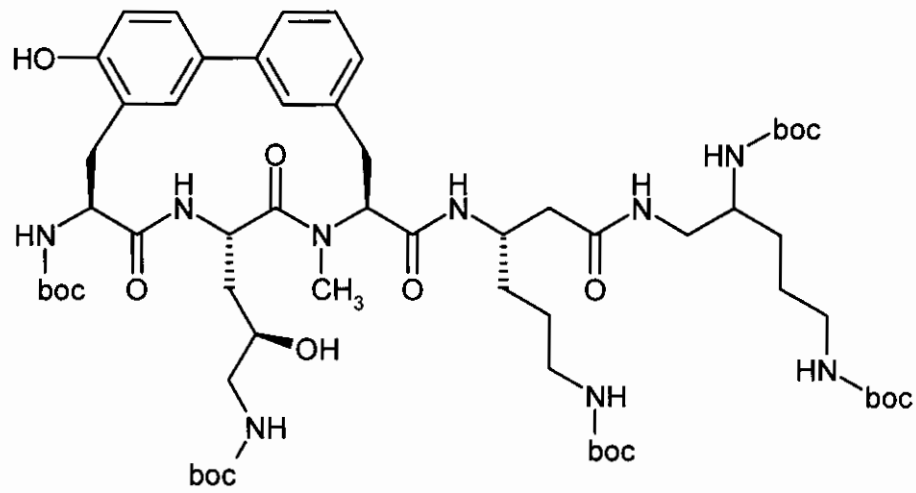
Yield: 6 mg (7% of theory)

LC-MS (Method 3): R_t = 2.49 min

MS (ESI): m/z = 1013 $(M+H)^+$

Example 118A

Di-*tert*-butyl (5-{[(3*S*)-6-[(*tert*-butoxycarbonyl)amino]-3-({[(8*S*,11*S*,14*S*)-14-[(*tert*-butoxycarbonyl)amino]-11-{(2*R*)-3-[(*tert*-butoxycarbonyl)amino]-2-hydroxypropyl}-17-hydroxy-9-methyl-10,13-dioxo-9,12-diazatricyclo[14.3.1.1^{2,6}]henicosa-1(20),2(21),3,5,16,18- hexaen-8-yl]carbonyl}amino)hexanoyl]amino}pentane-1,4-diyl)biscarbamate



30.7 mg (0.046 mmol) of (8*S*,11*S*,14*S*)-14-[(*tert*-butoxycarbonyl)amino]-11-{(2*R*)-3-[(*tert*-butoxycarbonyl)amino]-2-hydroxypropyl}-17-hydroxy-9-methyl-10,13-dioxo-9,12-diazatricyclo[14.3.1.1^{2,6}]henicosa-1(20),2(21),3,5,16,18-hexaene-8-carboxylic acid (Example 45A) and 30 mg (0.055 mmol) of the compound from Example 81A are dissolved in 2.0 ml of DMF and cooled to 0°C. 11.4 mg (0.06 mmol) of EDC and 2 mg (0.015 mmol) of HOBt are added and the mixture is stirred at room temperature for 12 h. The reaction mixture is concentrated on a rotary evaporator in vacuo and purified by chromatography over Sephadex-LH20 (mobile phase methanol/acetic acid 0.25%).

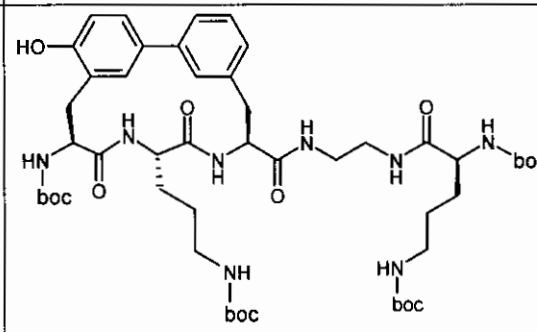
Yield: 13 mg (24% of theory)

LC-MS (Method 3): R_t = 2.84 min

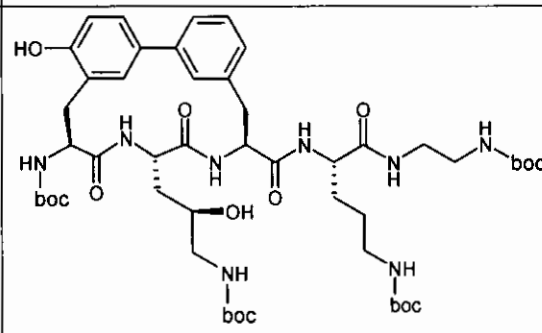
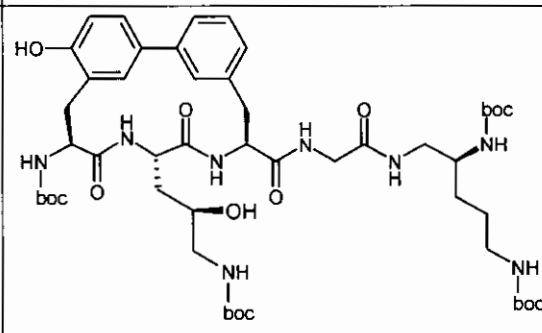
MS (ESI): m/z = 1198 $(M+H)^+$

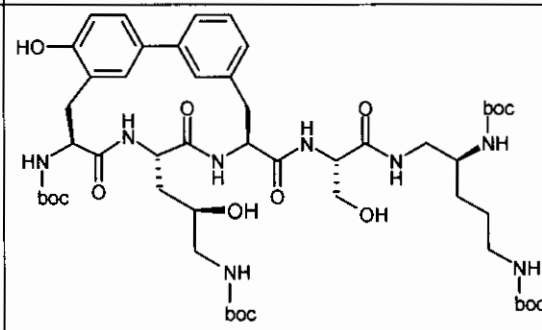
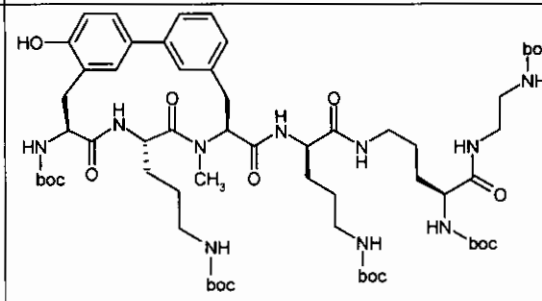
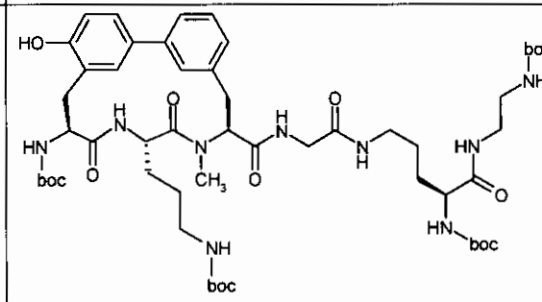
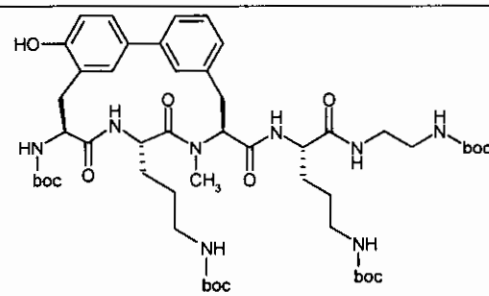
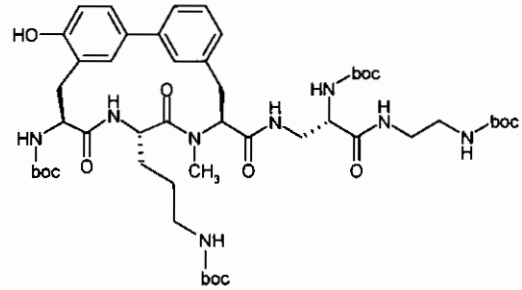
Example 119A listed in the following table is prepared in analogy to the procedure of Example 112A.

Example No.	Precursor Example	Structure	Analytical Data

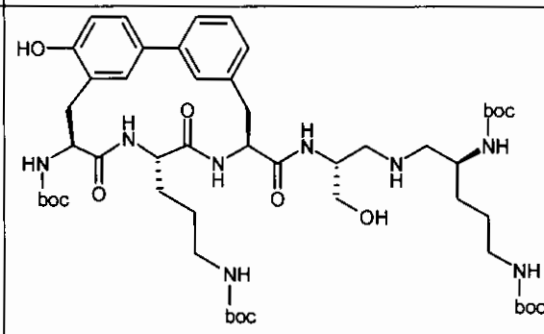
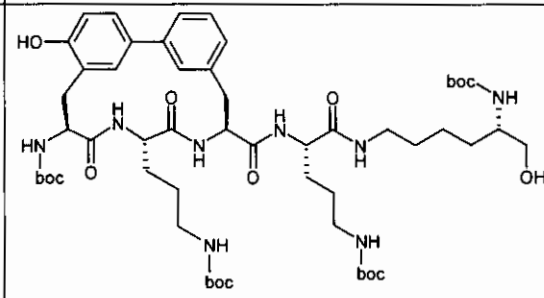
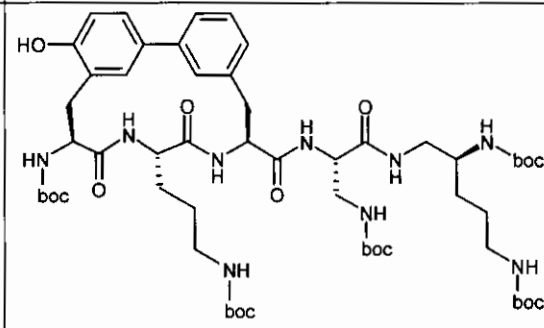
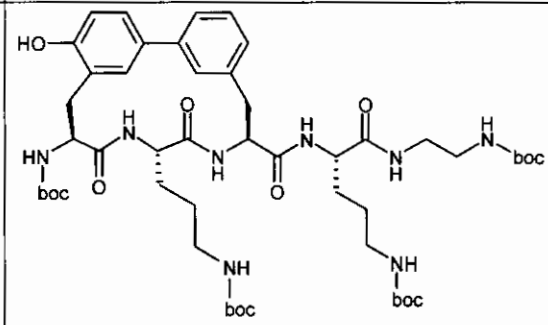
Example No.	Precursor Example	Structure	Analytical Data
119A	108A + 44A		LC-MS (Method 3): R_t = 2.57 min MS (ESI): m/z = 997 $(M+H)^+$.

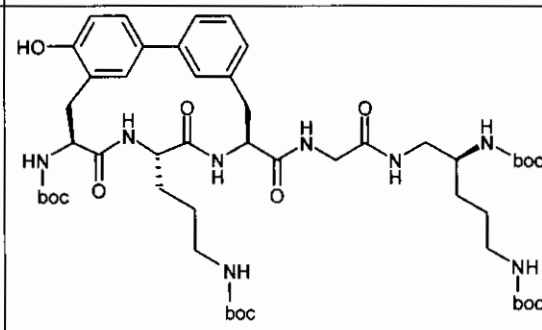
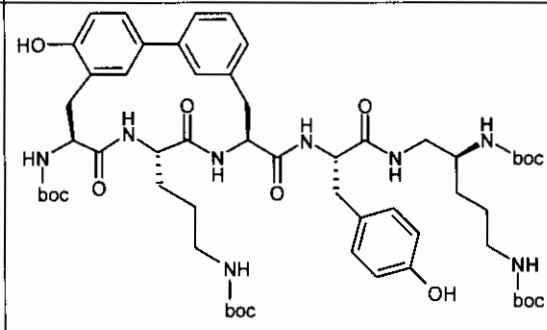
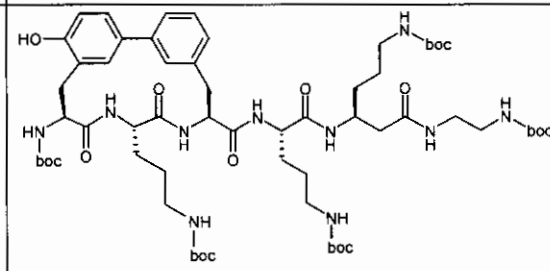
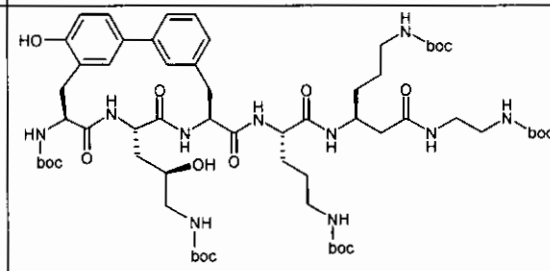
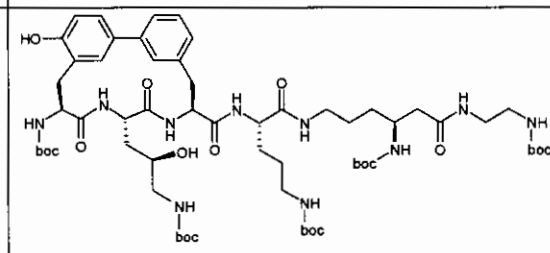
Examples 120A to 126A listed in the following table are prepared in analogy to the procedure of Example 117A.

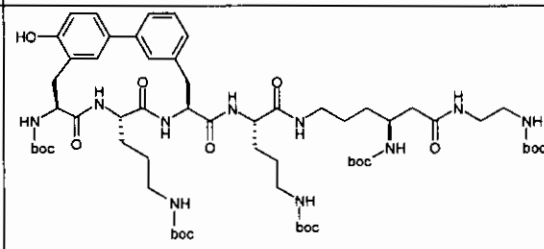
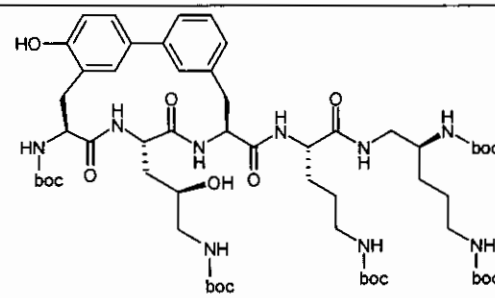
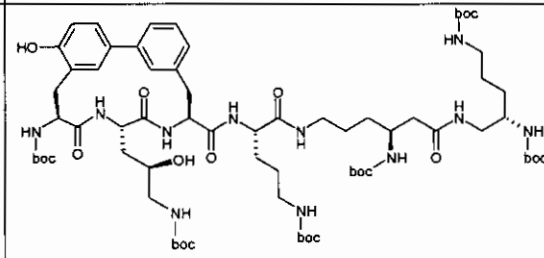
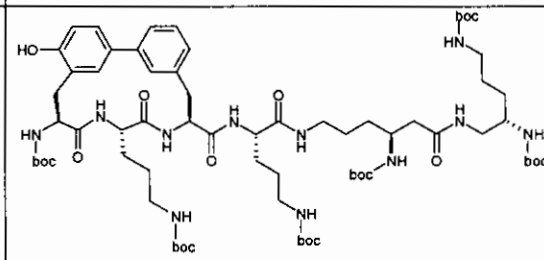
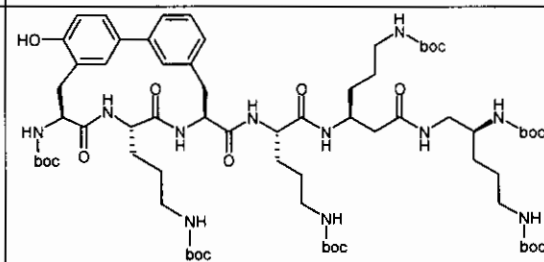
Example No.	Precursor Example	Structure	Analytical Data
120A	49A + 43A		LC-MS (Method 3): R_t = 2.57 min MS (ESI): m/z = 1013 $(M+H)^+$.
121A	55A + 43A		LC-MS (Method 1): R_t = 2.5 min. MS (ESI): m/z = 1013 $(M+H)^+$.

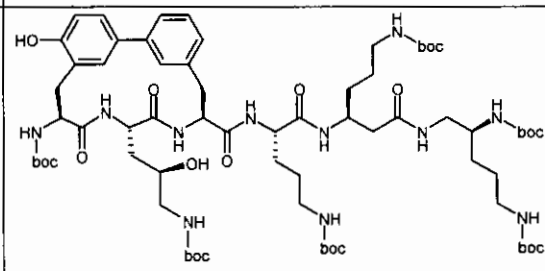
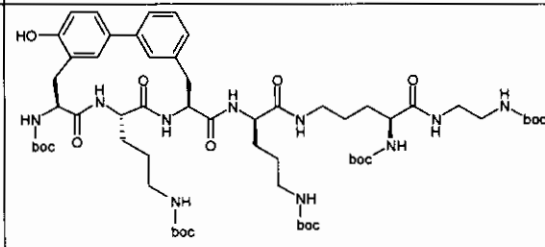
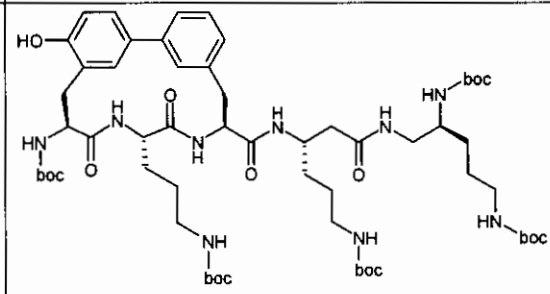
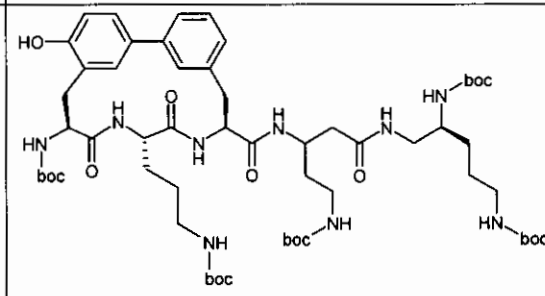
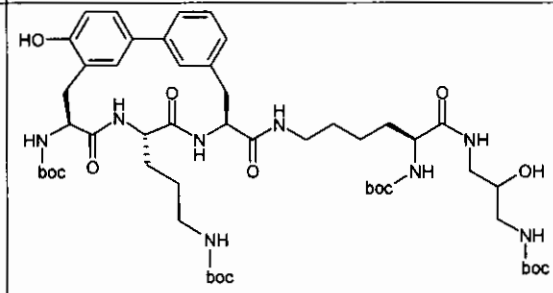
Example No.	Precursor Example	Structure	Analytical Data
122A	106A + 43A		LC-MS (Method 3): R_t = 2.46 min. MS (ESI): m/z = 1043 $(M+H)^+$.
123A	85A + 46A		LC-MS (Method 1): R_t = 2.71 min MS (ESI): m/z = 1225 $(M+H)^+$.
124A	89A + 46A		LC-MS (Method 1): R_t = 2.46 min MS (ESI): m/z = 1069 $(M+H)^+$.
125A	49A + 46A		LC-MS (Method 3): R_t = 2.74 min MS (ESI): m/z = 1011 $(M+H)^+$.
126A	87A + 46A		LC-MS (Method 2): R_t = 2.47 min MS (ESI): m/z = 983 $(M+H)^+$.

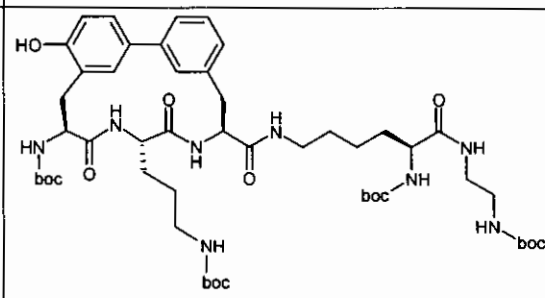
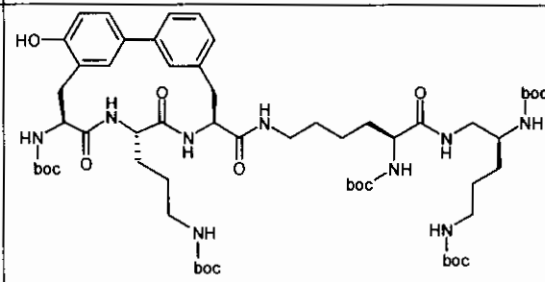
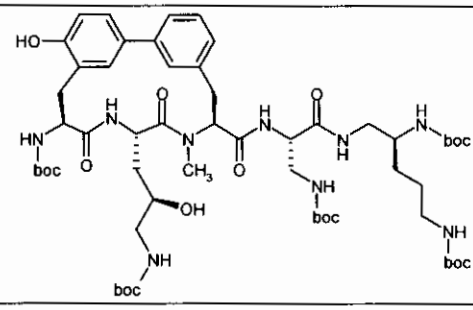
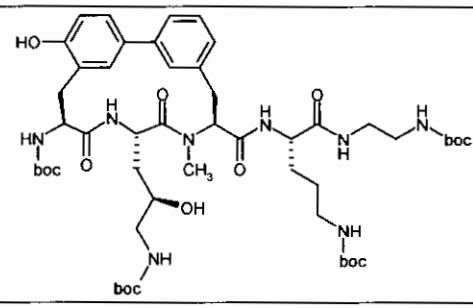
Examples 127A to 149A listed in the following table are prepared in analogy to the procedure of Example 113A.

Example No.	Precursor Example	Structure	Analytical Data
127A	59A + 44A		LC-MS (Method 3): R_t = 2.59 min MS (ESI): m/z = 1027 $(M+H)^+$.
128A	105A + 44A		LC-MS (Method 3): R_t = 2.65 min MS (ESI): m/z = 1069 $(M+H)^+$.
129A	67A + 44A		LC-MS (Method 3): R_t = 2.82 min MS (ESI): m/z = 1126 $(M+H)^+$.
130A	49A + 44A		LC-MS (Method 2): R_t = 2.41 min MS (ESI): m/z = 997 $(M+H)^+$.

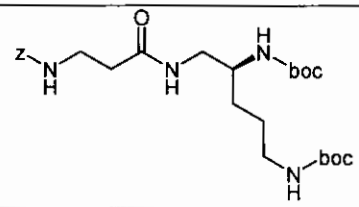
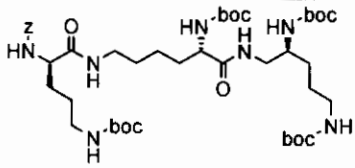
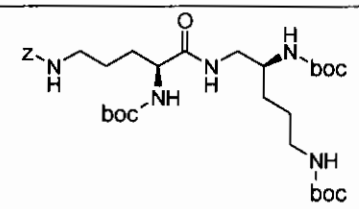
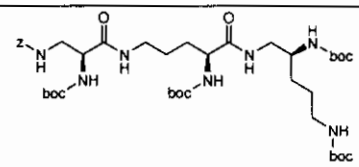
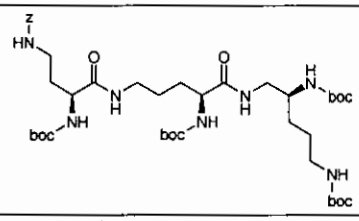
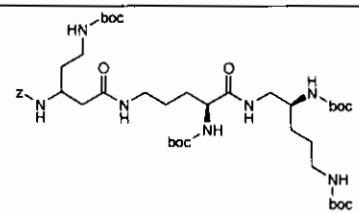
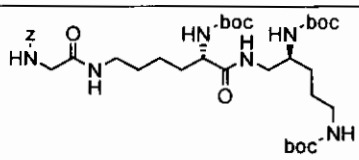
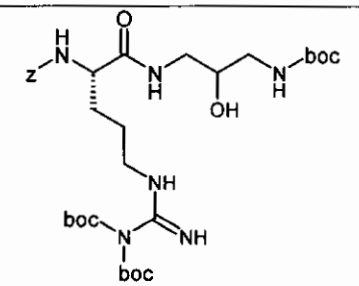
Example No.	Precursor Example	Structure	Analytical Data
131A	55A + 44A		LC-MS (Method 1): R_t = 2.56 min MS (ESI): m/z = 997 $(M+H)^+$.
132A	107A + 44A		LC-MS (Method 3): R_t = 2.67 min MS (ESI): m/z = 1103 $(M+H)^+$.
133A	71A + 44A		LC-MS (Method 2): R_t = 2.56 min MS (ESI): m/z = 1225 $(M+H)^+$.
134A	71A + 43A		LC-MS (Method 1): R_t = 2.64 min MS (ESI): m/z = 1241 $(M+H)^+$.
135A	75A + 43A		LC-MS (Method 2): R_t = 2.47 min MS (ESI): m/z = 1241 $(M+H)^+$.

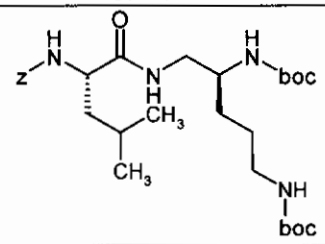
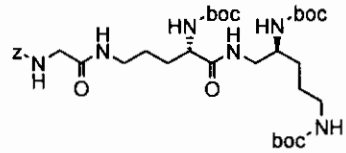
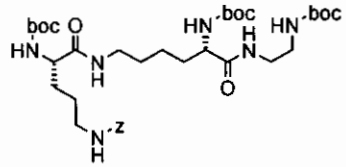
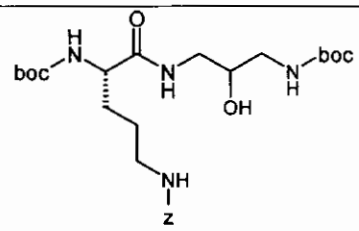
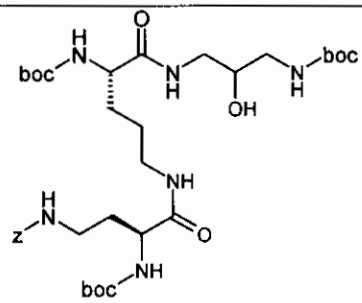
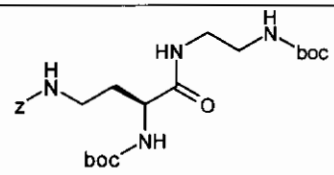
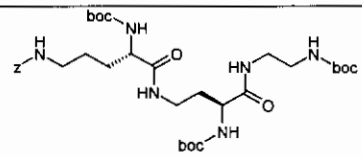
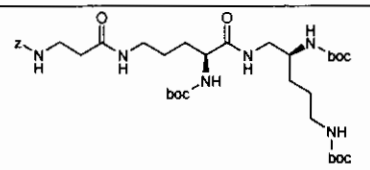
Example No.	Precursor Example	Structure	Analytical Data
136A	75A + 44A		LC-MS (Method 2): R_t = 2.52 min MS (ESI): m/z = 1225 $(M+H)^+$.
137A	57A + 43A		LC-MS (Method 3): R_t = 2.87 min MS (ESI): m/z = 1170 $(M+H)^+$.
138A	79A + 43A		LC-MS (Method 3): R_t = 2.92 min MS (ESI): m/z = 1398 $(M+H)^+$.
139A	79A + 44A		LC-MS (Method 2): R_t = 2.74 min MS (ESI): m/z = 1382 $(M+H)^+$.
140A	83A + 44A		LC-MS (Method 3): R_t = 2.95 min MS (ESI): m/z = 1382 $(M+H)^+$.

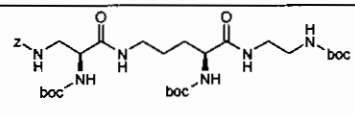
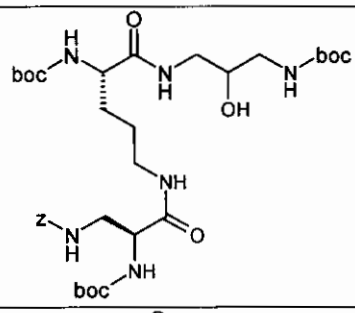
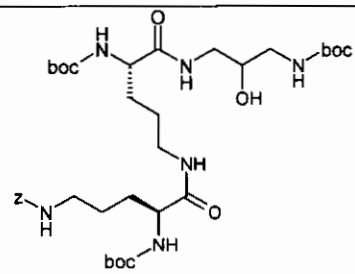
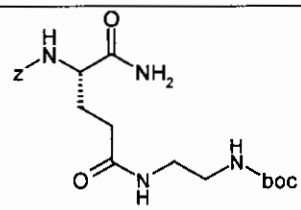
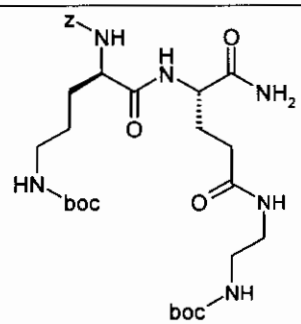
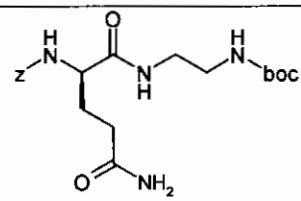
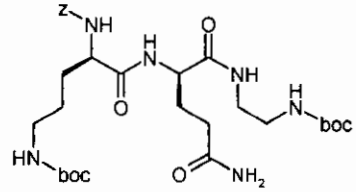
Example No.	Precursor Example	Structure	Analytical Data
141A	83A + 43A		LC-MS (Method 2): R_t = 2.72 min MS (ESI): m/z = 1398 $(M+H)^+$.
142A	85A + 44A		LC-MS (Method 1): R_t = 2.66 min MS (ESI): m/z = 1211 $(M+H)^+$.
143A	81A + 44A		LC-MS (Method 3): R_t = 2.82 min MS (ESI): m/z = 1168 $(M+H)^+$.
144A	91A + 44A		LC-MS (Method 2): R_t = 2.65 min MS (ESI): m/z = 1154 $(M+H)^+$.
145A	109A + 44A		LC-MS (Method 2): R_t = 2.3 min MS (ESI): m/z = 1041 $(M+H)^+$.

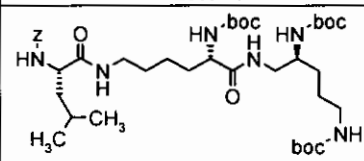
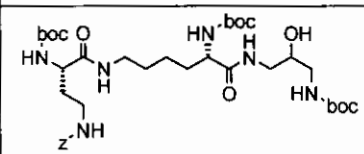
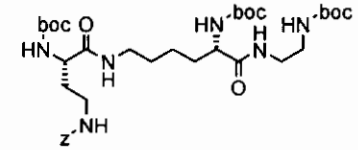
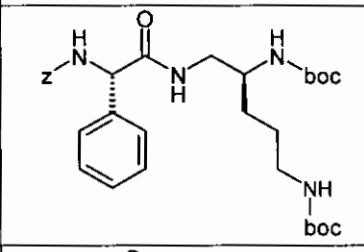
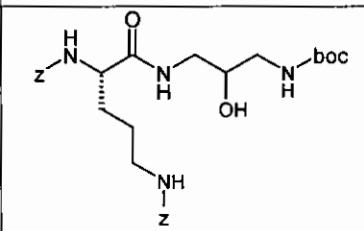
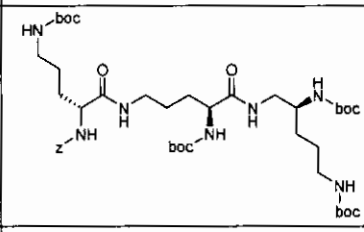
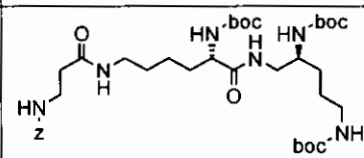
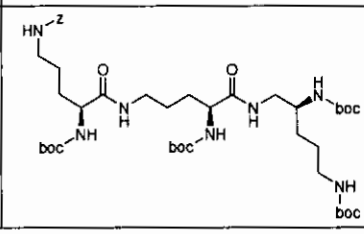
Example No.	Precursor Example	Structure	Analytical Data
146A	110A + 44A		LC-MS (Method 2): R_t = 2.38 min MS (ESI): m/z = 1011 $(M+H)^+$.
147A	111A + 44A		LC-MS (Method 2): R_t = 2.62 min MS (ESI): m/z = 1168 $(M+H)^+$.
148A	67A + 45A		LC-MS (Method 3): R_t = 2.88 min MS (ESI): m/z = 1156 $(M+H)^+$.
149A	49A + 45A		LC-MS (Method 3): R_t = 2.64 min MS (ESI): m/z = 1027 $(M+H)^+$.

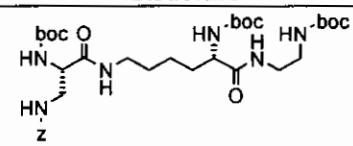
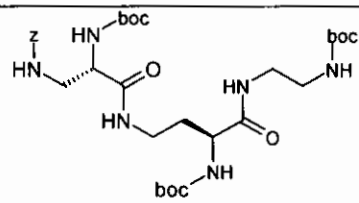
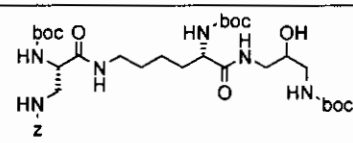
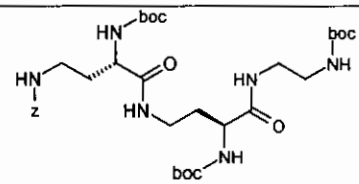
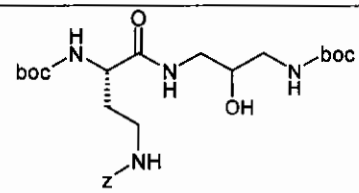
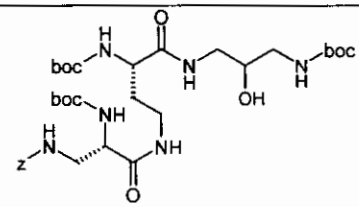
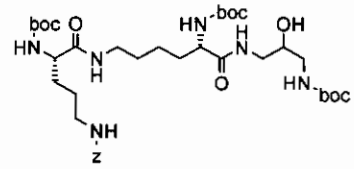
Examples 150A to 187A listed in the following table are prepared from the appropriate starting materials in analogy to the procedure of Example 48A.

Ex. No.	Structure	Prepared from	Analytical Data
150A		*N*-[(Benzyloxy)-carbonyl]-beta-alanine and Ex. 53A	LC-MS (Method 1): R_t = 2.19 min MS (ESI): m/z = 523 $(M+H)^+$
151A		N^2-[(Benzyloxy)-carbonyl]-N^5-(*tert*-butoxycarbonyl)-*D*-ornithine and Ex. 111A	LC-MS (Method 2): R_t = 2.62 min MS (ESI): m/z = 894 $(M+H)^+$
152A		N^5-[(Benzyloxy)-carbonyl]-N^2-(*tert*-butoxycarbonyl)-*L*-ornithine and Ex. 53A	LC-MS (Method 3): R_t = 2.68 min MS (ESI): m/z = 666 $(M+H)^+$
153A		3-{[(Benzyloxy)-carbonyl]amino}-*N*-(tert-butoxycarbonyl)- *L*-alanine and Ex. 190A	LC-MS (Method 3): R_t = 2.76 min MS (ESI): m/z = 852 $(M+H)^+$
154A		(2*S*)-4-{[(Benzyloxy)-carbonyl]amino}-2-[(*tert*-butoxycarbonyl)-amino]butanoic acid and Ex. 190A	LC-MS (Method 3): R_t = 2.75 min MS (ESI): m/z = 866 $(M+H)^+$
155A		3-{[(Benzyloxy)-carbonyl]amino}-5-[(tert-butoxycarbonyl)-amino]pentanoic acid and Ex. 190A	LC-MS (Method 3): R_t = 2.85 min MS (ESI): m/z = 880 $(M+H)^+$
156A		*N*-[(Benzyloxy)-carbonyl]glycine and Ex. 111A	LC-MS (Method 2): R_t = 2.32 min MS (ESI): m/z = 737 $(M+H)^+$
157A		N^2-[(Benzyloxy)carbonyl]-N^5-[[bis(*tert*-butoxy-carbonyl)amino]-(imino)methyl]-*L*-ornithine and *tert*-butyl (3-amino-2-hydroxy-propyl)carbamate	LC-MS (Method 2): R_t = 2.58 min MS (ESI): m/z = 681 $(M+H)^+$

Ex. No.	Structure	Prepared from	Analytical Data
158A		*N*-[(Benzyloxy)-carbonyl]-*L*-leucine and Ex. 53A	LC-MS (Method 2): R_t = 2.53 min MS (ESI): m/z = 565 $(M+H)^+$
159A		*N*-[(Benzyloxy)-carbonyl]glycine and Ex. 190A	LC-MS (Method 1): R_t = 2.45 min MS (ESI): m/z = 723 $(M+H)^+$
160A		N^5-[(Benzyloxy)-carbonyl]-N^2-(*tert*-butoxycarbonyl)-*L*-ornithine and Ex. 110A	LC-MS (Method 3): R_t = 2.53 min MS (ESI): m/z = 737 $(M+H)^+$
161A		N^5-[(Benzyloxy)-carbonyl]-N^2-(*tert*-butoxycarbonyl)-*L*-ornithine and *tert*-butyl (3-amino-2-hydroxy-propyl)carbamate	LC-MS (Method 3): R_t = 2.27 min MS (ESI): m/z = 539 $(M+H)^+$
162A		(2*S*)-4-{[(Benzyloxy)-carbonyl]amino}-2-[(*tert*-butoxycarbonyl) amino]butanoic acid and Ex. 199A	LC-MS (Method 3): R_t = 2.39 min MS (ESI): m/z = 739 $(M+H)^+$
163A		(2*S*)-4-{[(Benzyloxy)-carbonyl]amino}-2-[(tert-butoxycarbonyl) amino]butanoic acid and tert-butyl (2-amino-ethyl)carbamate	LC-MS (Method 3): R_t = 2.35 min MS (ESI): m/z = 495 $(M+H)^+$
164A		N^5-[(Benzyloxy)-carbonyl]-N^2-(*tert*-butoxycarbonyl)-*L*-ornithine and Ex. 201A	LC-MS (Method 2): R_t = 2.30 min MS (ESI): m/z = 709 $(M+H)^+$
165A		*N*-[(Benzyloxy)-carbonyl]-beta-alanine and Ex. 190A	LC-MS (Method 3): R_t = 2.60 min MS (ESI): m/z = 737 $(M+H)^+$

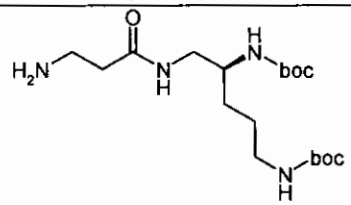
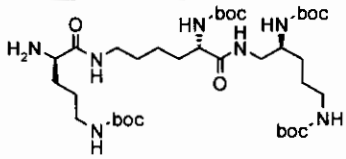
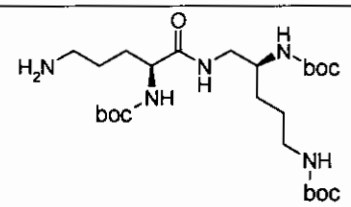
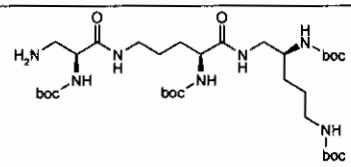
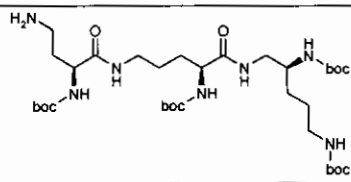
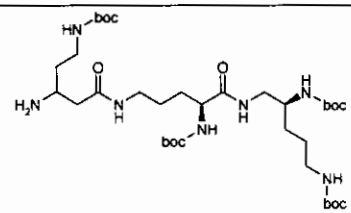
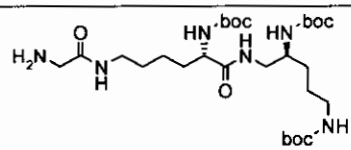
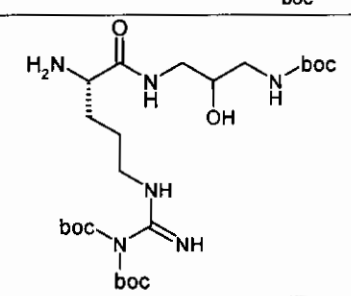
Ex. No.	Structure	Prepared from	Analytical Data
166A		3-{[(Benzyloxy)-carbonyl]amino}-*N*-(tert-butoxycarbonyl)-*L*-alanine and Ex. 104A	LC-MS (Method 3): R_t = 2.47 min MS (ESI): m/z = 695 $(M+H)^+$
167A		3-{[(Benzyloxy)-carbonyl]amino}-*N*-(tert-butoxycarbonyl)- *L*-alanine and Ex. 199A	LC-MS (Method 3): R_t = 2.39 min MS (ESI): m/z = 725 $(M+H)^+$
168A		N^5-[(Benzyloxy)-carbonyl]-N^2-(*tert*-butoxycarbonyl)-*L*-ornithine and Ex. 199A	LC-MS (Method 3): R_t = 2.40 min MS (ESI): m/z = 753 $(M+H)^+$
169A		N^2-[(Benzyloxy)-carbonyl]-L-alpha-glutamine and tert-butyl (2-aminoethyl)carbamate	LC-MS (Method 3): R_t = 1.93 min MS (ESI): m/z = 423 $(M+H)^+$
170A		N^2-[(Benzyloxy)-carbonyl]-N^5-(tert-butoxycarbonyl)-*D*-ornithine and Ex. 207A	LC-MS (Method 3): R_t = 2.26 min MS (ESI): m/z = 637 $(M+H)^+$
171A		N^2-[(Benzyloxy)-carbonyl]-*D*-glutamine and tert-butyl (2-aminoethyl)carbamate	LC-MS (Method 3): R_t = 1.94 min MS (ESI): m/z = 423 $(M+H)^+$
172A		N^2-[(Benzyloxy)-carbonyl]-N^5-(tert-butoxycarbonyl)-*D*-ornithine and Ex. 209A	LC-MS (Method 3): R_t = 2.25 min MS (ESI): m/z = 637 $(M+H)^+$

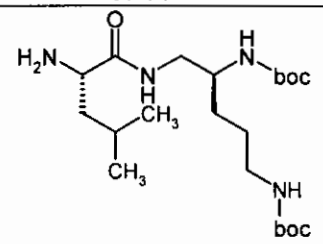
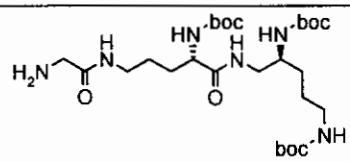
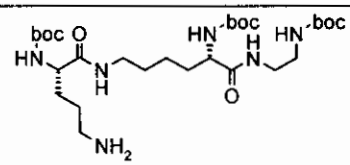
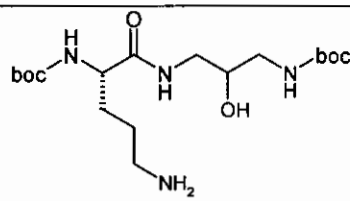
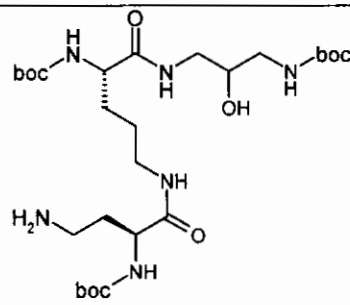
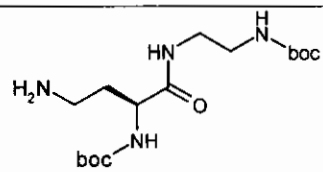
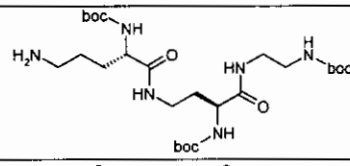
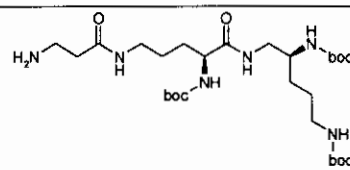
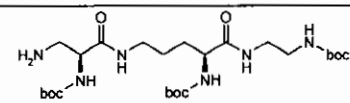
Ex. No.	Structure	Prepared from	Analytical Data
173A		*N*-[(Benzyloxy)-carbonyl]-*L*-leucine and Ex. 111A	LC-MS (Method 2): R_t = 2.82 min MS (ESI): m/z = 793 $(M+H)^+$
174A		(2*S*)-4-{[(Benzyloxy)-carbonyl]amino}-2-[(tert-butoxycarbonyl)-amino]butanoic acid and Ex. 109A	LC-MS (Method 3): R_t = 2.44 min MS (ESI): m/z = 753 $(M+H)^+$
175A		(2*S*)-4-{[(Benzyloxy)-carbonyl]amino}-2-[(tert-butoxycarbonyl)-amino]butanoic acid and Ex. 110A	LC-MS (Method 3): R_t = 2.52 min MS (ESI): m/z = 723 $(M+H)^+$
176A		(2*S*)-{[(Benzyloxy)-carbonyl]amino}-(phenyl)acetic acid and Ex. 53A	LC-MS (Method 2): R_t = 2.50 min MS (ESI): m/z = 585 $(M+H)^+$
177A		N^2,N^5-bis-[(Benzyloxy)-carbonyl]-*L*-ornithine and *tert*-butyl (3-amino-2-hydroxy-propyl)carbamate	LC-MS (Method 2): R_t = 2.15 min MS (ESI): m/z = 573 $(M+H)^+$
178A		N^2-[(Benzyloxy)-carbonyl]-N^5-(tert-butoxycarbonyl)-*D*-ornithine and Ex. 190A	LC-MS (Method 3): R_t = 2.88 min MS (ESI): m/z = 880 $(M+H)^+$
179A		*N*-[(Benzyloxy)-carbonyl]-beta-alanine and Ex. 111A	LC-MS (Method 3): R_t = 2.52 min MS (ESI): m/z = 751 $(M+H)^+$
180A		N^5-[(Benzyloxy)-carbonyl]-N^2-(tert-butoxycarbonyl)-*L*-ornithine and Ex. 190A	LC-MS (Method 3): R_t = 2.76 min MS (ESI): m/z = 880 $(M+H)^+$

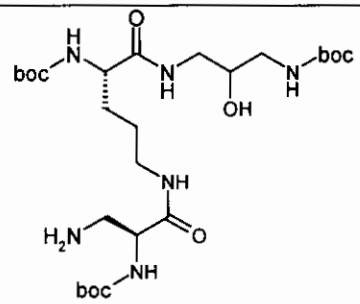
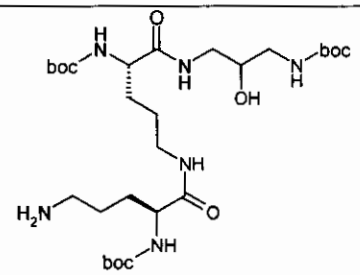
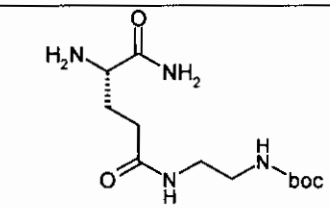
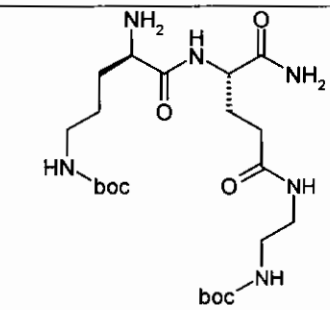
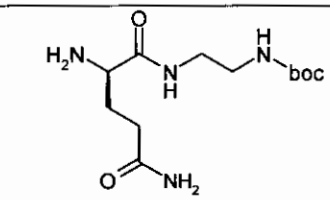
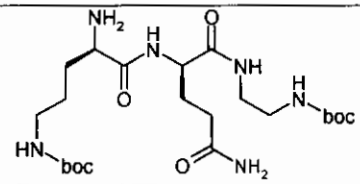
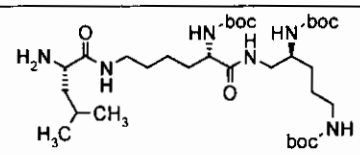
Ex. No.	Structure	Prepared from	Analytical Data
181A		3-{[(Benzyloxy)-carbonyl]amino}-*N*-(tert-butoxycarbonyl)- *L*-alanine and Ex. 110A	LC-MS (Method 1): R_t = 2.46 min MS (ESI): m/z = 709 $(M+H)^+$
182A		3-{[(Benzyloxy)-carbonyl]amino}-*N*-(tert-butoxycarbonyl)- *L*-alanine and Ex. 201A	LC-MS (Method 2): R_t = 2.31 min MS (ESI): m/z = 681 $(M+H)^+$
183A		3-{[(Benzyloxy)-carbonyl]amino}-*N*-(tert-butoxycarbonyl)- *L*-alanine and Ex. 109A	LC-MS (Method 1): R_t = 2.38 min MS (ESI): m/z = 739 $(M+H)^+$
184A		(2*S*)-4-{[(Benzyloxy)-carbonyl]amino}-2-[(tert-butoxycarbonyl)-amino]butanoic acid and Ex. 201A	LC-MS (Method 2): R_t = 2.29 min MS (ESI): m/z = 695 $(M+H)^+$
185A		(2*S*)-4-{[(Benzyloxy)-carbonyl]amino}-2-[(tert-butoxycarbonyl) amino]butanoic acid and *tert*-butyl (3-amino-2-hydroxypropyl) carbamate	LC-MS (Method 1): R_t = 2.38 min MS (ESI): m/z = 525 $(M+H)^+$
186A		3-{[(Benzyloxy)-carbonyl]amino}-*N*-(tert-butoxycarbonyl)- *L*-alanine and Ex. 223A	LC-MS (Method 1): R_t = 2.36 min MS (ESI): m/z = 711 $(M+H)^+$
187A		N^5-[(Benzyloxy)-carbonyl]-N^2-(tert-butoxycarbonyl)-*L*-ornithine and Ex. 109A	LC-MS (Method 3): R_t = 2.44 min MS (ESI): m/z = 767 $(M+H)^+$

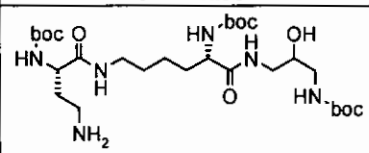
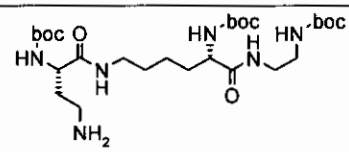
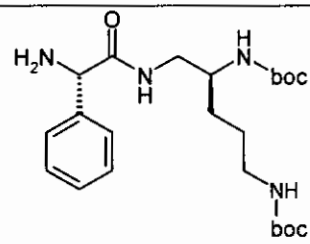
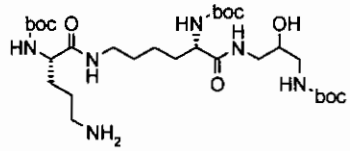
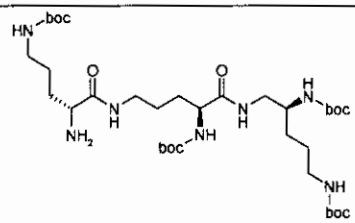
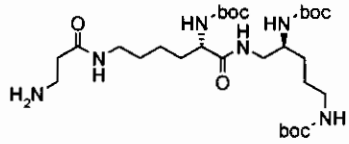
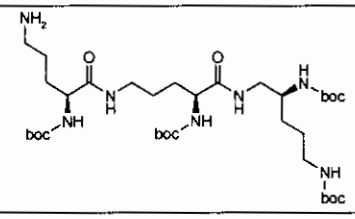
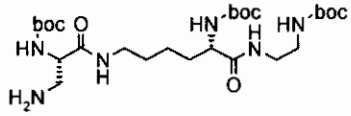
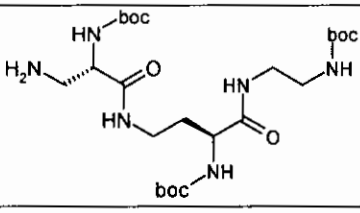
Examples 188A to 224A listed in the following table are prepared from the corresponding starting materials in analogy to the procedure of Example 49A.

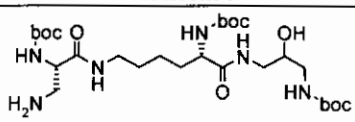
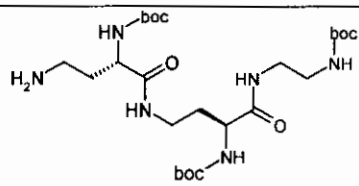
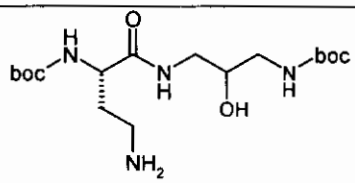
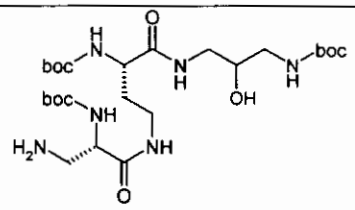
Ex. No.	Structure	Prepared from	Analytical Data

Ex. No.	Structure	Prepared from	Analytical Data
188A		Ex. 150A	MS (ESI): m/z = 389 $(M+H)^+$
189A		Ex. 151A	MS (ESI): m/z = 750 $(M+H)^+$
190A		Ex. 152A	MS (ESI): m/z = 532 $(M+H)^+$
191A		Ex. 153A	MS (ESI): m/z = 718 $(M+H)^+$
192A		Ex. 154A	MS (ESI): m/z = 732 $(M+H)^+$
193A		Ex. 155A	LC-MS (Method 2): R_t = 1.78 min MS (ESI): m/z = 746 $(M+H)^+$
194A		Ex. 156A	MS (ESI): m/z = 603 $(M+H)^+$
195A		Ex. 157A	MS (ESI): m/z = 547 $(M+H)^+$

Ex. No.	Structure	Prepared from	Analytical Data
196A		Ex. 158A	LC-MS (Method 2): R_t = 1.37 min MS (ESI): m/z = 431 $(M+H)^+$
197A		Ex. 159A	LC-MS (Method 1): R_t = 1.66 min MS (ESI): m/z = 589 $(M+H)^+$
198A		Ex. 160A	MS (ESI): m/z = 603 $(M+H)^+$
199A		Ex. 161A	MS (ESI): m/z = 405 $(M+H)^+$
200A		Ex. 162A	MS (ESI): m/z = 605 $(M+H)^+$
201A		Ex. 163A	MS (ESI): m/z = 361 $(M+H)^+$
202A		Ex. 164A	MS (ESI): m/z = 575 $(M+H)^+$
203A		Ex. 165A	LC-MS (Method 2): R_t = 1.56 min MS (ESI): m/z = 603 $(M+H)^+$
204A		Ex. 166A	MS (ESI): m/z = 561 $(M+H)^+$

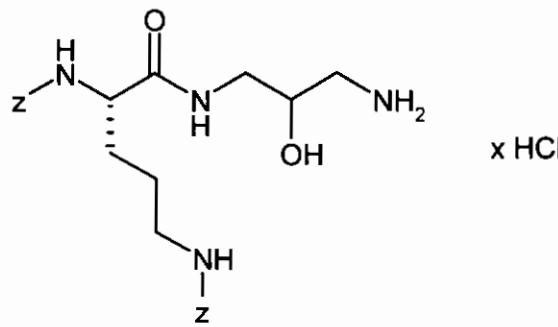
Ex. No.	Structure	Prepared from	Analytical Data
205A		Ex. 167A	MS (ESI): m/z = 591 $(M+H)^+$
206A		Ex. 168A	MS (ESI): m/z = 619 $(M+H)^+$
207A		Ex. 169A	LC-MS (Method 10): R_t = 2.23 min MS (ESI): m/z = 289 $(M+H)^+$
208A		Ex. 170A	LC-MS (Method 2): R_t = 1.11 min MS (ESI): m/z = 503 $(M+H)^+$
209A		Ex. 171A	LC-MS (Method 10): R_t = 2.20 min MS (ESI): m/z = 289 $(M+H)^+$
210A		Ex. 172A	LC-MS (Method 2): R_t = 1.10 min MS (ESI): m/z = 503 $(M+H)^+$
211A		Ex. 173A	MS (ESI): m/z = 659 $(M+H)^+$

Ex. No.	Structure	Prepared from	Analytical Data
212A		Ex. 174A	MS (ESI): m/z = 619 $(M+H)^+$
213A		Ex. 175A	MS (ESI): m/z = 589 $(M+H)^+$
214A		Ex. 176A	LC-MS (Method 2): R_t = 1.33 min MS (ESI): m/z = 451 $(M+H)^+$
215A		Ex. 187A	MS (ESI): m/z = 633 $(M+H)^+$
216A		Ex. 178A	LC-MS (Method 2): R_t = 1.79 min MS (ESI): m/z = 746 $(M+H)^+$
217A		Ex. 179A	MS (ESI): m/z = 617 $(M+H)^+$
218A		Ex. 180A	MS (ESI): m/z = 746 $(M+H)^+$
219A		Ex. 181A	MS (ESI): m/z = 575 $(M+H)^+$
220A		Ex. 182A	MS (ESI): m/z = 547 $(M+H)^+$

Ex. No.	Structure	Prepared from	Analytical Data
221A		Ex. 183A	MS (ESI): m/z = 605 $(M+H)^+$
222A		Ex. 184A	MS (ESI): m/z = 561 $(M+H)^+$
223A		Ex. 185A	MS (ESI): m/z = 391 $(M+H)^+$
224A		Ex. 186A	MS (ESI): m/z = 577 $(M+H)^+$

Example 225A

Benzyl ((4*S*)-5-[(3-amino-2-hydroxypropyl)amino]-4-{[(benzyloxy)carbonyl]amino}-5-oxopentyl)carbamate hydrochloride



At 0°C, 6.8 ml of a 4N hydrogen chloride-dioxane solution are added to a solution of 0.263 g (0.46 mmol) of the compound from Example 187A in 1 ml of dioxane. After 2 h at RT, the reaction solution is concentrated in vacuo and coevaporated several times with dichloromethane. The remaining solid is dried to constant weight under high vacuum.

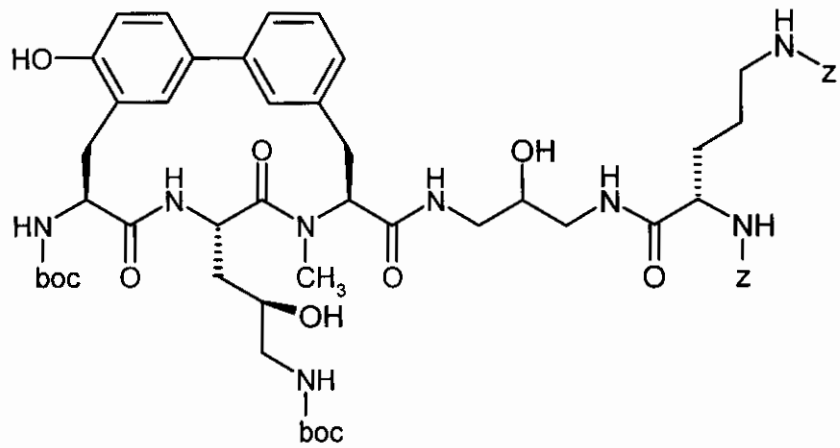
Yield: 0.205 g (88% of theory)

LC-MS (Method 2): R_t = 1.47 min

MS (EI): m/z = 473 $(M-HCl+H)^+$

Example 226A

Benzyl [(1S)-4-{[(benzyloxy)carbonyl]amino}-1-({[3-({[(8S,11S,14S)-14-[(tert-butoxycarbonyl)amino]-11-{(2R)-3-[(tert-butoxycarbonyl)amino]-2-hydroxypropyl}-17-hydroxy-9-methyl-10,13-dioxo-9,12-diazatricyclo[14.3.1.1^{2,6}]henicosa-1(20),2(21),3,5,16,18-hexaen-8-yl]carbonyl}amino)-2-hydroxypropyl]amino}carbonyl)butyl]carbamate



25 mg (0.037 mmol) of the compound from Example 45A are dissolved in 1.0 ml of DMF and cooled to 0°C. 21 mg (0.041 mmol) of PyBOP and 15 mg (0.11 mmol) of diisopropylamine are added. After 30 min, 24.7 mg (0.048 mmol) of the compound from Example 225A are added and the mixture is stirred for 12 h at room temperature. The reaction mixture is concentrated on a rotary evaporator in vacuo and purified by chromatography over Sephadex-LH20 (mobile phase methanol/acetic acid 0.25%).

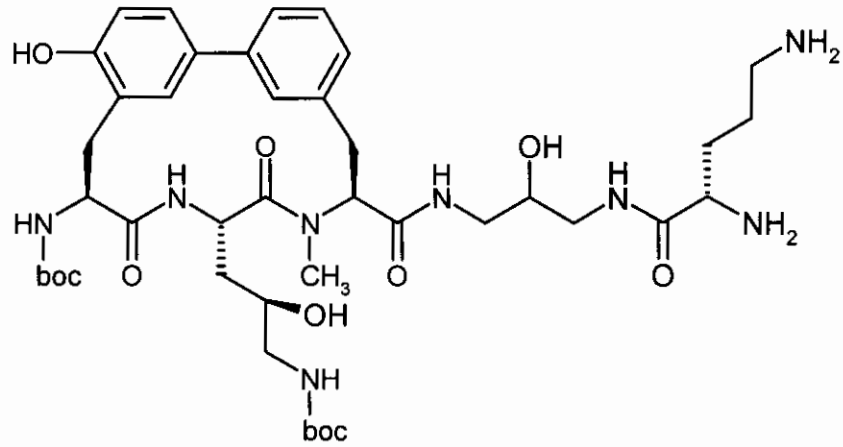
Yield: 12.7 mg (30% of theory)

LC-MS (Method 3): R_t = 2.61 min

MS (ESI): m/z = 1125 $(M+H)^+$

Example 227A

tert-Butyl {(2R)-3-[(8S,11S,14S)-14-[(tert-butoxycarbonyl)amino]-17-hydroxy-8-({[2-hydroxy-3-(*L*-ornithylamino)propyl]amino}carbonyl)-9-methyl-10,13-dioxo-9,12-diazatricyclo[14.3.1.1^{2,6}]henicosa-1(20),2(21),3,5,16,18-hexaen-11-yl]-2-hydroxy-propyl}carbamate



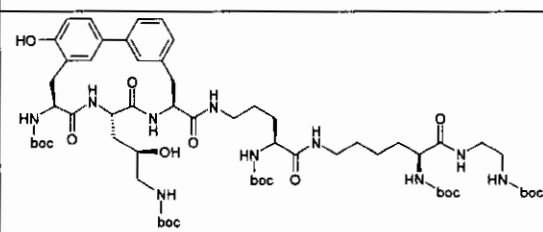
12.7 mg (0.011 mmol) of the compound from Example 226A are dissolved in 5 ml of ethanol, 5 mg of Pd/C (10%) ared added and the mixture is hydrogenated for 12 h under atmospheric pressure and a hydrogen atmosphere. Suction filtration is carried out, the reaction mixture is concentrated in vacuo and the crude product is used without further purification in the next step.

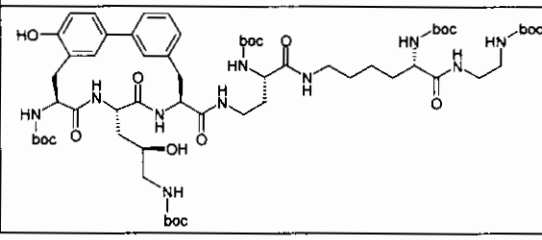
Yield: 11 mg (95% of theory)

LC-MS (Method 2): R_t = 1.26 min

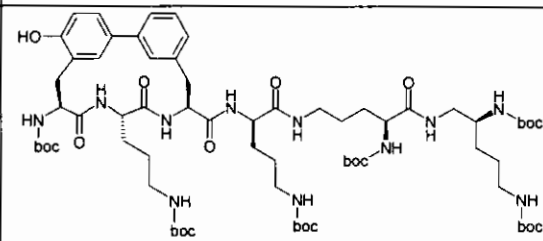
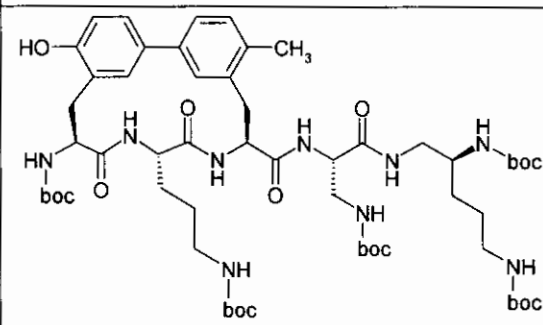
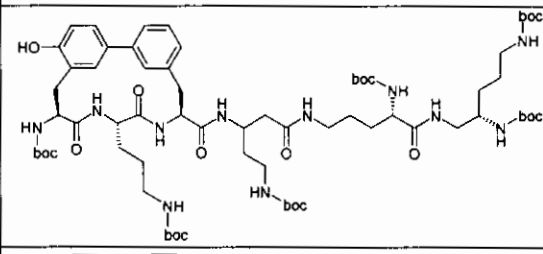
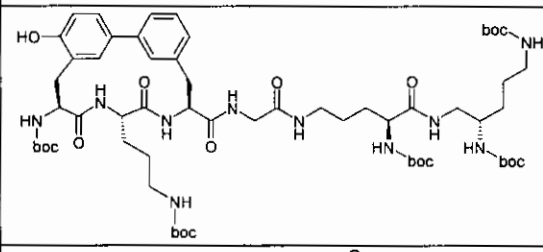
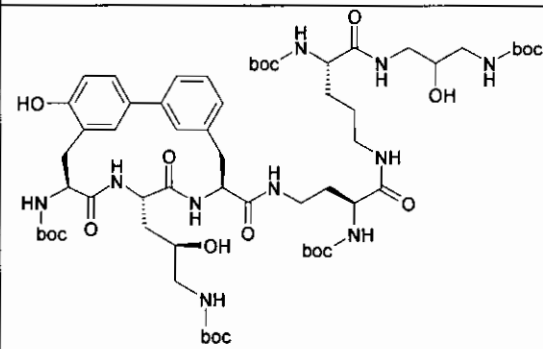
MS (ESI): m/z = 857 $(M+H)^+$

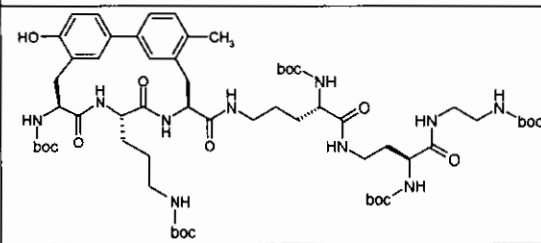
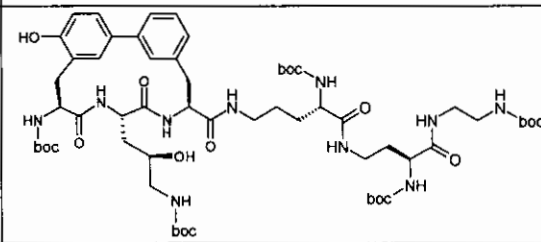
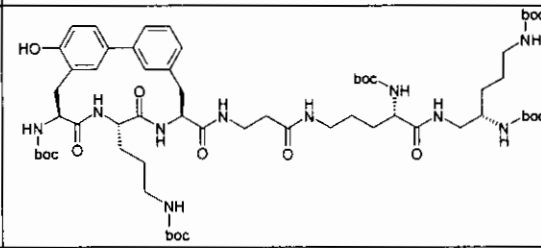
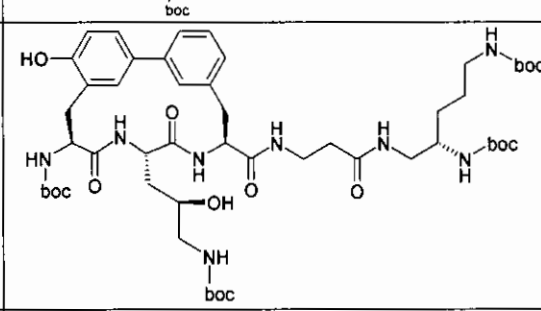
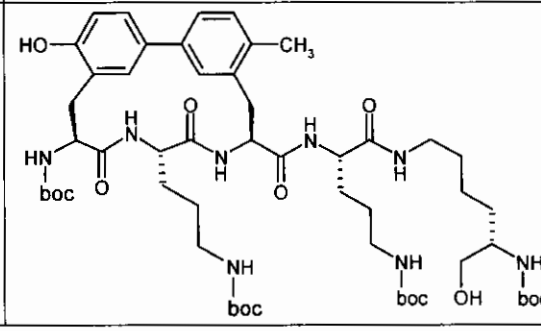
Examples 228A and 229A listed in the following table are prepared in analogy to the procedure of Example 112A.

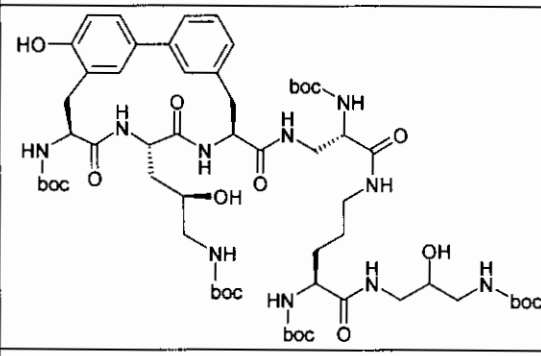
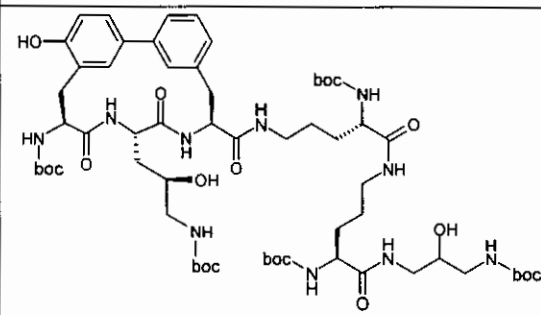
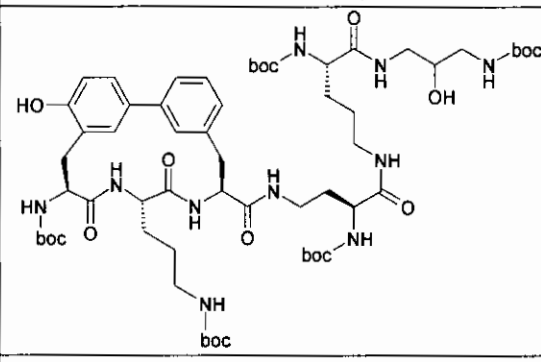
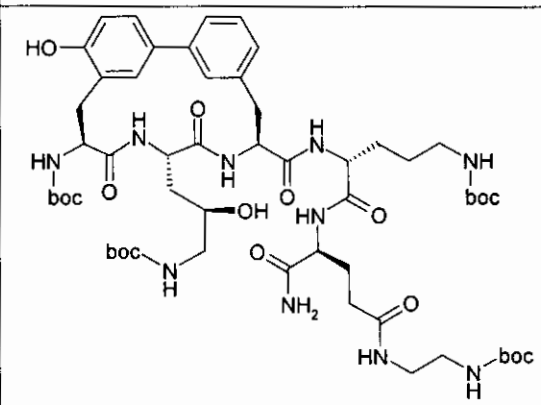
Example No.	Precursor Example	Structure	Analytical Data
228A	43A + 198A		LC-MS (Method 2): R_t = 2.41 min MS (ESI): m/z = 1241 $(M+H)^+$.

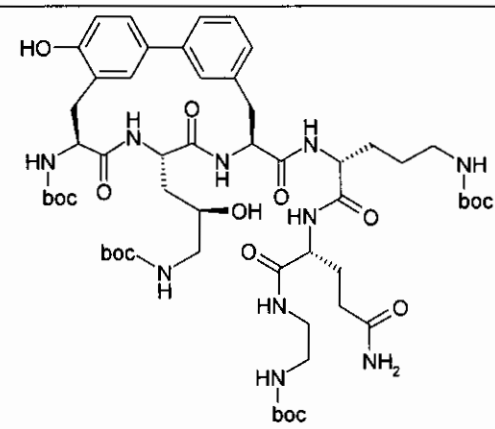
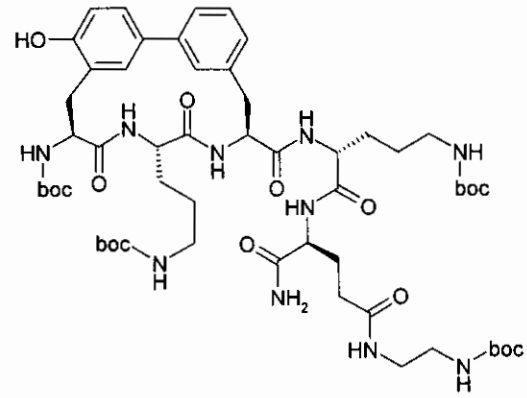
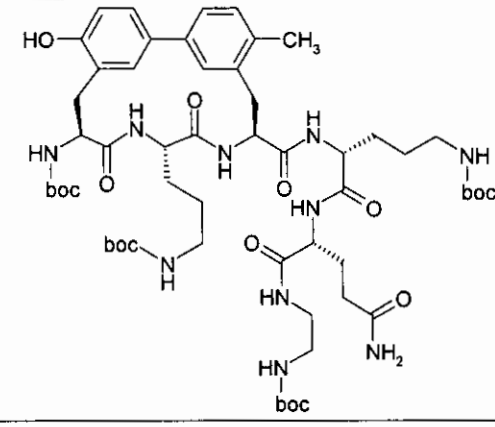
Example No.	Precursor Example	Structure	Analytical Data
229A	43A + 213A		LC-MS (Method 2): R_t = 2.41 min MS (ESI): m/z = 1227 $(M+H)^+$.

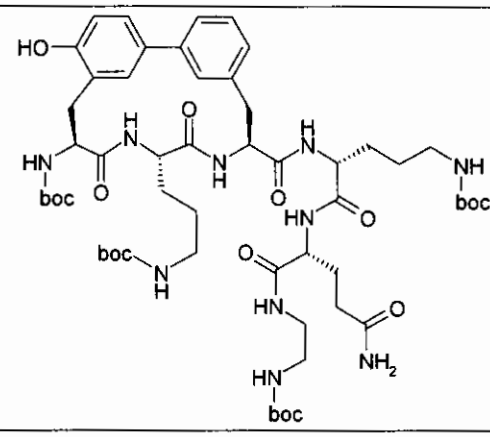
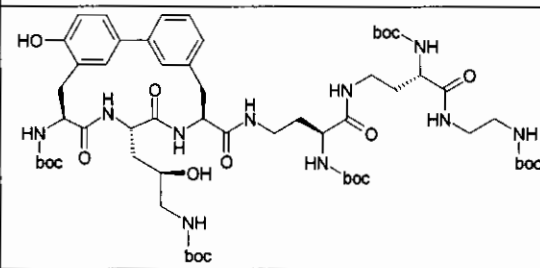
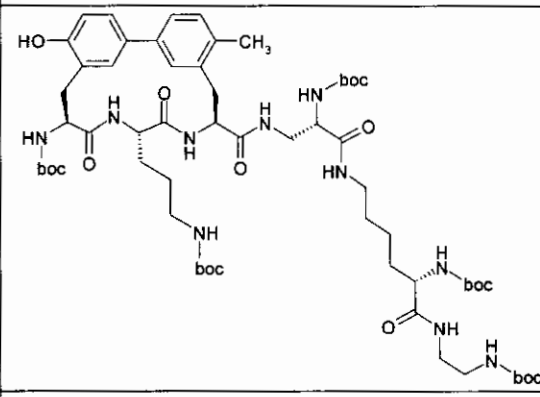
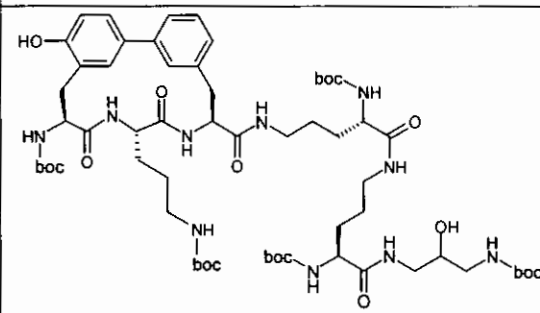
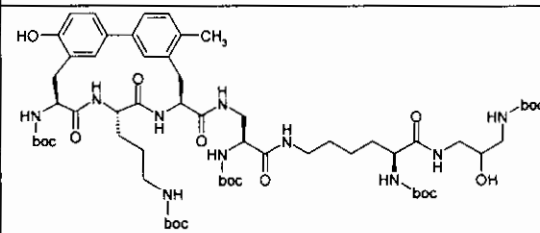
Examples 230A to 254A listed in the following table are prepared in analogy to the procedure of Example 117A.

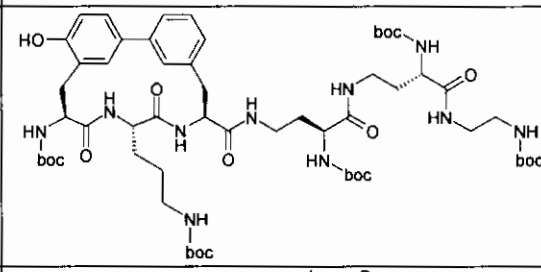
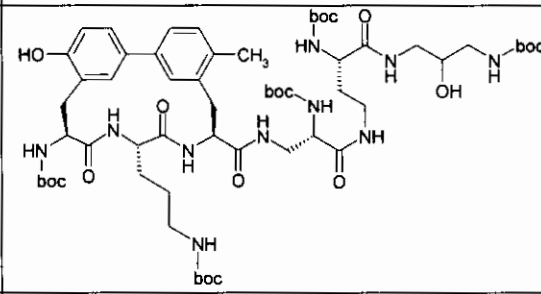
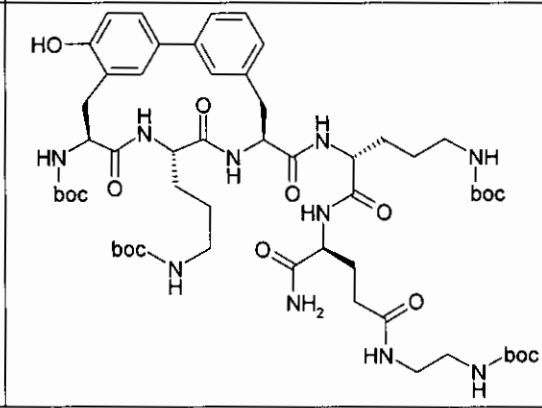
Example No.	Precursor Example	Structure	Analytical Data
230A	44A + 216A		LC-MS (Method 2): R_t = 2.76 min MS (ESI): m/z = 1368 $(M+H)^+$.
231A	47A + 67A		LC-MS (Method 2): R_t = 2.71 min MS (ESI): m/z = 1140 $(M+H)^+$.
232A	44A + 193A		LC-MS (Method 2): R_t = 2.72 min MS (ESI): m/z = 1368 $(M+H)^+$.
233A	44A + 197A		LC-MS (Method 2): R_t = 2.51 min MS (ESI): m/z = 1211 $(M+H)^+$.
234A	43A + 200A		LC-MS (Method 2): R_t = 2.61 min MS (ESI): m/z = 1243 $(M+H)^+$.

Example No.	Precursor Example	Structure	Analytical Data
235A	47A + 202A		LC-MS (Method 1): R_t = 2.65 min MS (ESI): m/z = 1211 $(M+H)^+$.
236A	43A + 202A		LC-MS (Method 2): R_t = 2.39 min MS (ESI): m/z = 1213 $(M+H)^+$.
237A	44A + 203A		LC-MS (Method 2): R_t = 2.51 min MS (ESI): m/z = 1225 $(M+H)^+$.
238A	43A + 188A		LC-MS (Method 2): R_t = 2.33 min MS (ESI): m/z = 1027 $(M+H)^+$.
239A	47A + 105A		LC-MS (Method 3): R_t = 2.63 min MS (ESI): m/z = 1083 $(M+H)^+$.

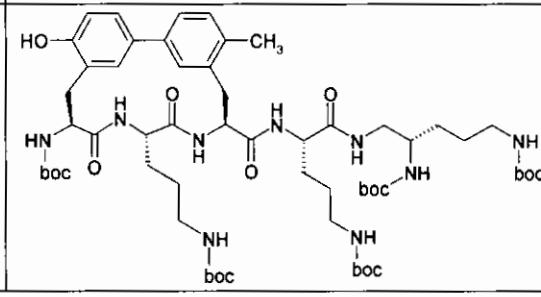
Example No.	Precursor Example	Structure	Analytical Data
240A	43A + 205A		LC-MS (Method 3): R_t = 2.64 min MS (ESI): m/z = 1229 $(M+H)^+$.
241A	43A + 206A		LC-MS (Method 3): R_t = 2.56 min MS (ESI): m/z = 1257 $(M+H)^+$.
242A	44A + 200A		LC-MS (Method 3): R_t = 2.67 min MS (ESI): m/z = 1227 $(M+H)^+$.
243A	43A + 208A		LC-MS (Method 3): R_t = 2.42 min MS (ESI): m/z = 1141 $(M+H)^+$.

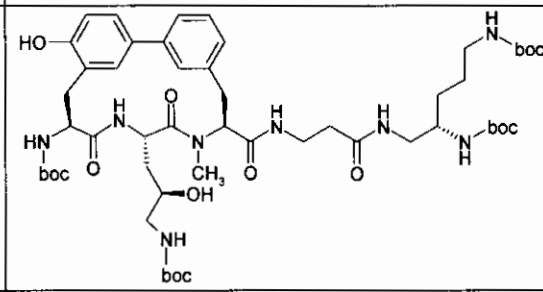
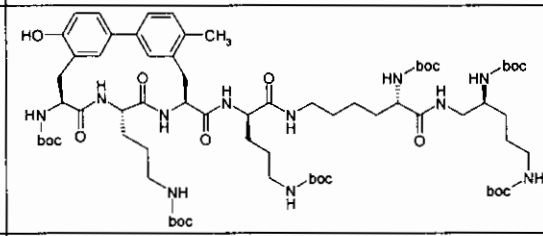
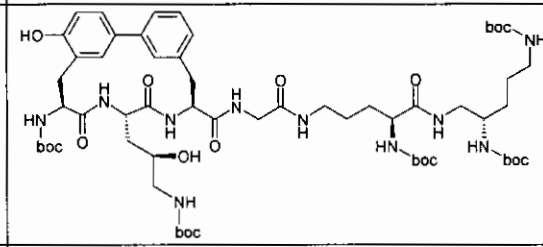
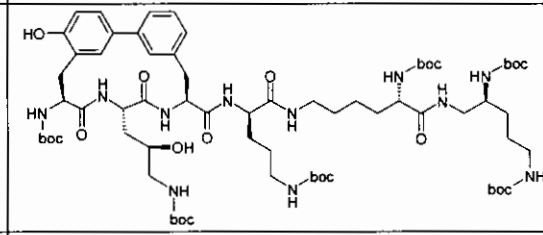
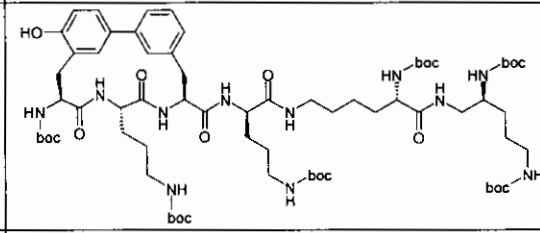
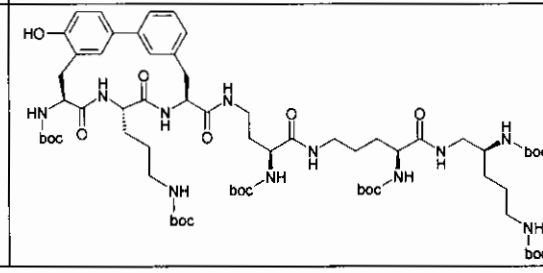
Example No.	Precursor Example	Structure	Analytical Data
244A	43A + 210A		LC-MS (Method 3): R_t = 2.42 min MS (ESI): m/z = 1141 $(M+H)^+$.
245A	47A + 208A		LC-MS (Method 3): R_t = 2.51 min MS (ESI): m/z = 1139 $(M+H)^+$.
246A	47A + 210A		LC-MS (Method 3): R_t = 2.51 min MS (ESI): m/z = 1139 $(M+H)^+$.

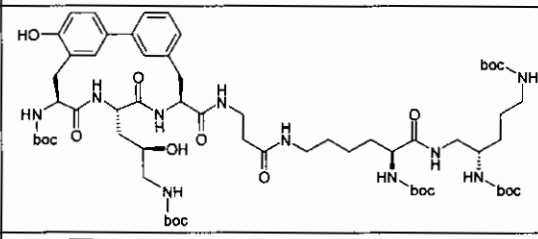
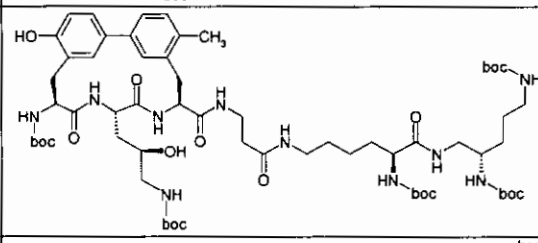
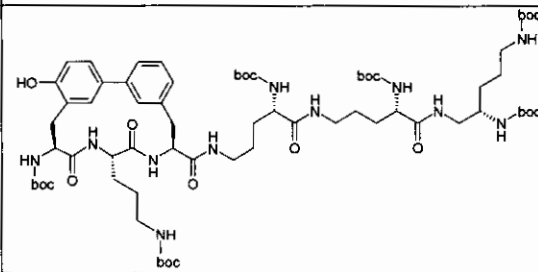
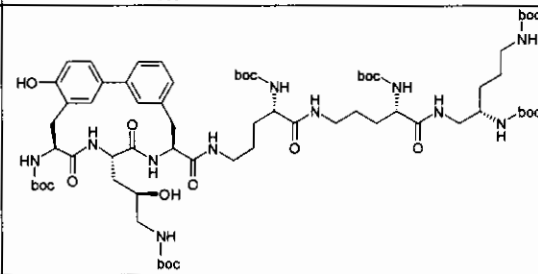
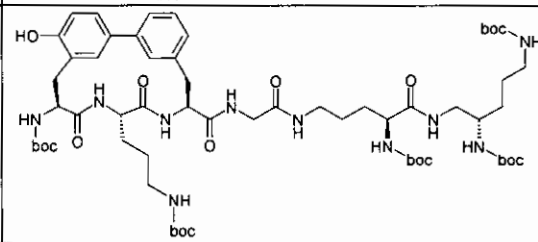
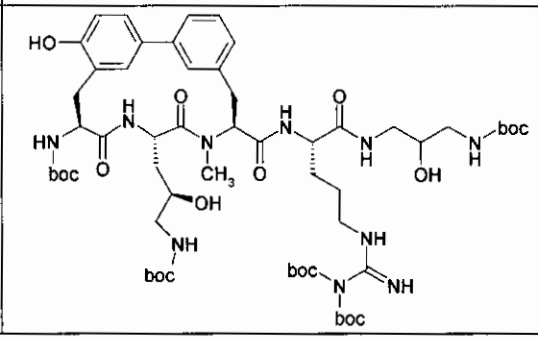
Example No.	Precursor Example	Structure	Analytical Data
247A	44A + 210A		LC-MS (Method 3): R_t = 2.46 min MS (ESI): m/z = 1125 $(M+H)^+$.
248A	43A + 222A		LC-MS (Method 3): R_t = 2.63 min MS (ESI): m/z = 1199 $(M+H)^+$.
249A	47A + 206A		LC-MS (Method 1): R_t = 2.72 min MS (ESI): m/z = 1211 $(M+H)^+$.
250A	44A + 206A		LC-MS (Method 3): R_t = 2.65 min MS (ESI): m/z = 1241 $(M+H)^+$.
251A	47A + 221A		LC-MS (Method 1): R = 2.61 min MS (ESI): m/z = 1241 $(M+H)^+$.

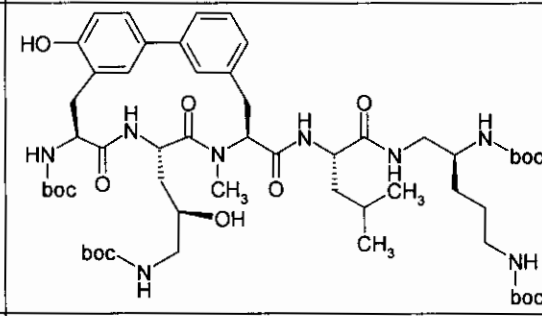
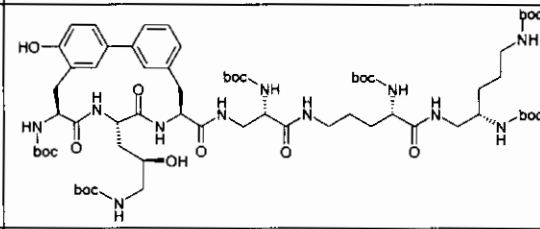
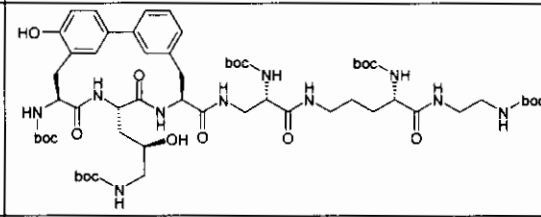
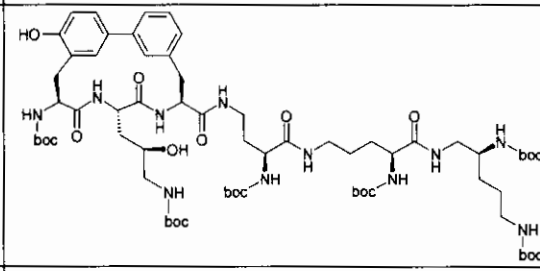
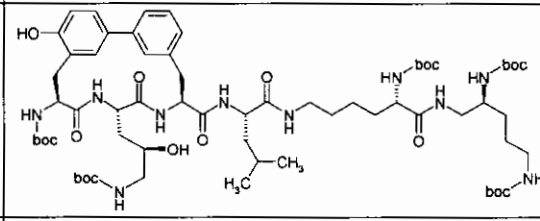
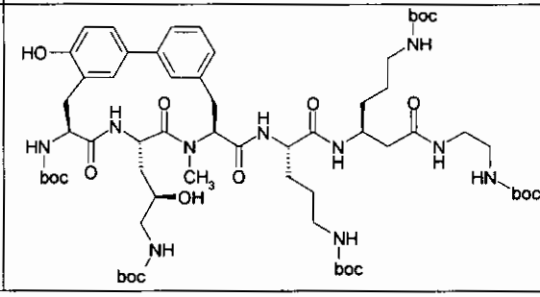
Example No.	Precursor Example	Structure	Analytical Data
252A	44A + 222A		LC-MS (Method 3): R_t = 2.71 min MS (ESI): m/z = 1183 $(M+H)^+$.
253A	47A + 224A		LC-MS (Method 1): R_t = 2.60 min MS (ESI): m/z = 1199 $(M+H)^+$.
254A	44A + 208A		LC-MS (Method 3): R_t = 2.45 min MS (ESI): m/z = 1125 $(M+H)^+$.

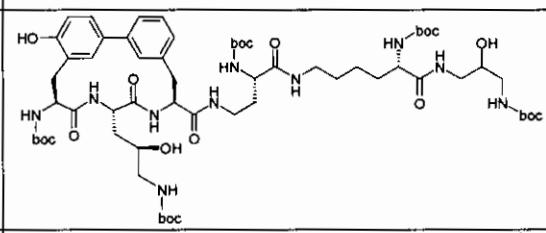
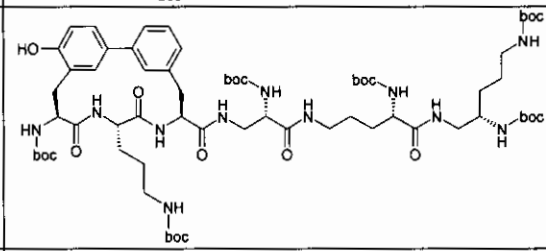
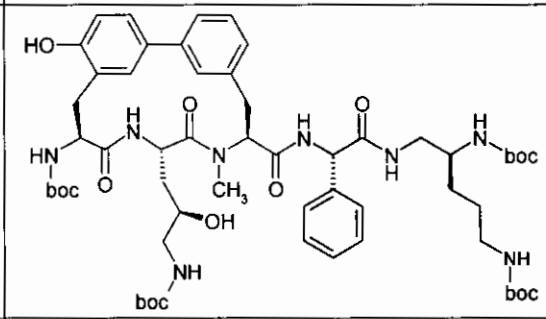
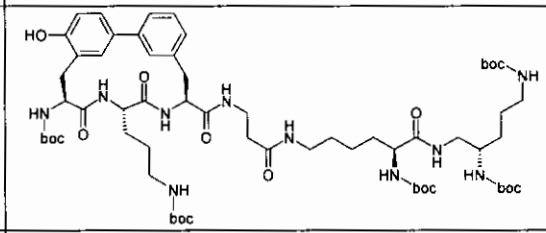
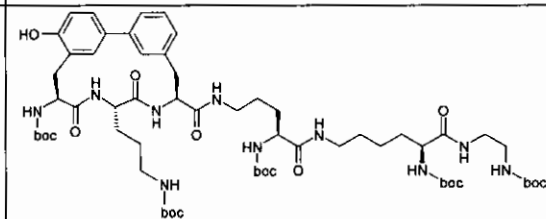
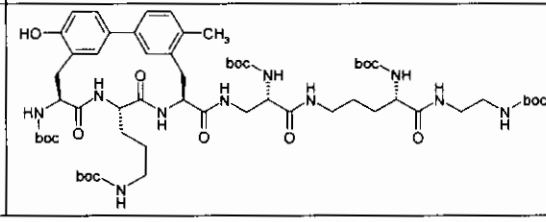
Examples 255A to 281A listed in the following table are prepared in analogy to the procedure of Example 113A.

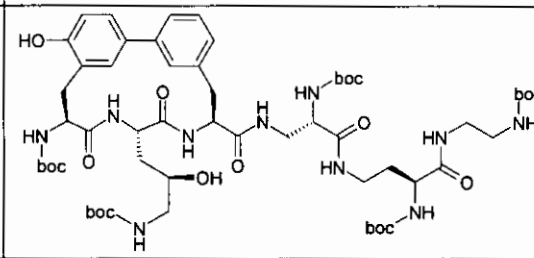
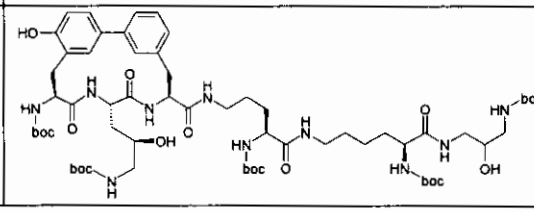
Example No.	Precursor Example	Structure	Analytical Data
255A	47A + 57A		LC-MS (Method 2): R_t = 2.73 min MS (ESI): m/z = 1168 $(M+H)^+$.

Example No.	Precursor Example	Structure	Analytical Data
256A	45A + 188A		LC-MS (Method 2): R_t = 2.42 min MS (ESI): m/z = 1041 $(M+H)^+$.
257A	47A + 189A		LC-MS (Method 3): R_t = 3.02 min MS (ESI): m/z = 1396 $(M+H)^+$.
258A	43A + 194A		LC-MS (Method 3): R_t = 2.65 min. MS (ESI): m/z = 1241 $(M+H)^+$.
259A	43A + 189A		LC-MS (Method 3): R_t = 2.90 min MS (ESI): m/z = 1398 $(M+H)^+$.
260A	44A + 189A		LC-MS (Method 3): R_t = 2.96 min MS (ESI): m/z = 1382 $(M+H)^+$.
261A	44A + 192A		LC-MS (Method 2): R_t = 2.67 min MS (ESI): m/z = 1354 $(M+H)^+$.

Example No.	Precursor Example	Structure	Analytical Data
262A	43A + 217A		LC-MS (Method 3): R_t = 2.63 min MS (ESI): m/z = 1255 $(M+H)^+$.
263A	47A + 217A		LC-MS (Method 2): R_t = 2.57 min MS (ESI): m/z = 1253 $(M+H)^+$.
264A	44A + 218A		LC-MS (Method 3): R_t = 2.95 min MS (ESI): m/z = 1368 $(M+H)^+$.
265A	43A + 218A		LC-MS (Method 3): R_t = 2.90 min MS (ESI): m/z = 1384 $(M+H)^+$.
266A	44A + 194A		LC-MS (Method 2): R_t = 2.52 min MS (ESI): m/z = 1225 $(M+H)^+$.
267A	45A + 195A		LC-MS (Method 3): R_t = 2.96 min MS (ESI): m/z = 1199 $(M+H)^+$.

Example No.	Precursor Example	Structure	Analytical Data
268A	45A + 196A		LC-MS (Method 3): R_t = 2.87 min MS (ESI): m/z = 1083 $(M+H)^+$.
269A	43A + 191A		LC-MS (Method 2): R_t = 2.66 min MS (ESI): m/z = 1356 $(M+H)^+$.
270A	43A + 204A		LC-MS (Method 3): R_t = 2.18 min MS (ESI): m/z = 1199 $(M+H)^+$.
271A	43A + 192A		LC-MS (Method 3): R_t = 2.88 min MS (ESI): m/z = 1370 $(M+H)^+$.
272A	43A + 211A		LC-MS (Method 3): R_t = 2.87 min MS (ESI): m/z = 1297 $(M+H)^+$.
273A	45A + 71A		LC-MS (Method 2): R_t = 2.56 min MS (ESI): m/z = 1255 $(M+H)^+$.

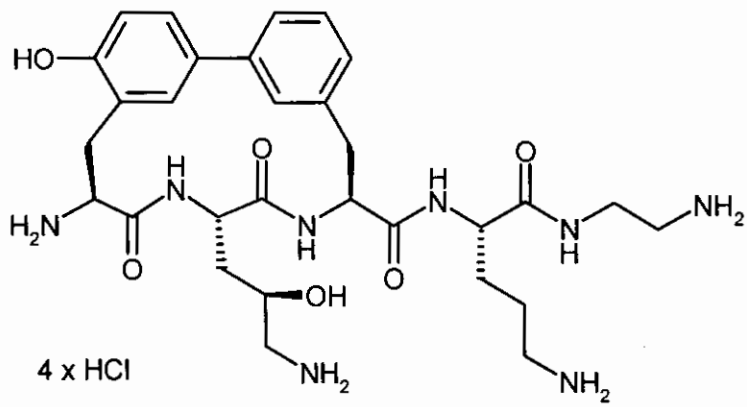
Example No.	Precursor Example	Structure	Analytical Data
274A	43A + 212A		LC-MS (Method 2): R_t = 2.35 min MS (ESI): m/z = 1257 $(M+H)^+$.
275A	44A + 191A		LC-MS (Method 2): R_t = 2.71 min MS (ESI): m/z = 1340 $(M+H)^+$.
276A	45A + 214A		LC-MS (Method 3): R_t = 2.81 min MS (ESI): m/z = 1103 $(M+H)^+$.
277A	44A + 217A		LC-MS (Method 2): R_t = 2.52 min MS (ESI): m/z = 1239 $(M+H)^+$.
278A	44A + 198A		LC-MS (Method 1): R_t = 2.61 min MS (ESI): m/z = 1225 $(M+H)^+$.
279A	47A + 204A		LC-MS (Method 2): R_t = 2.52 min MS (ESI): m/z = 1239 $(M+H)^+$.

Example No.	Precursor Example	Structure	Analytical Data
280A	43A + 220A		LC-MS (Method 1): R_t = 2.57 min MS (ESI): m/z = 1185 $(M+H)^+$.
281A	43A + 215A		LC-MS (Method 3): R_t = 2.52 min MS (ESI): m/z = 1271 $(M+H)^+$.

Exemplary Embodiments

Example 1

(8*S*,11*S*,14*S*)-14-Amino-*N*-((1*S*)-4-amino-1-{[(2-aminoethyl)amino]carbonyl}butyl)-11-[(2*R*)-3-amino-2-hydroxypropyl]-17-hydroxy-10,13-dioxo-9,12-diazatricyclo[14.3.1.1^{2,6}]-henicosa-1(20),2(21),3,5,16,18-hexaene-8-carboxamide tetrahydrochloride



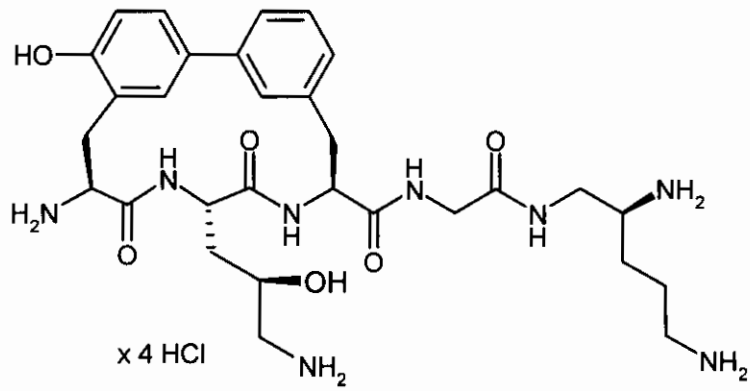
At 0°C, 0.084 ml of a 4N hydrogen chloride-dioxane solution are added to a solution of 5.7 mg (0.006 mmol) of the compound from Example 120A in 1 ml of dioxane. After 2 h at RT, the reaction solution is concentrated in vacuo and coevaporated several times with dichloromethane. The remaining solid is dried to constant weight under high vacuum.

Yield: 3.3 mg (77% of theory)

MS (ESI): m/z = 612 $(M-4HCl+H)^+$.

Example 2

(8*S*,11*S*,14*S*)-14-Amino-11-[(2*R*)-3-amino-2-hydroxypropyl]-*N*-(2-{[(2*S*)-2,5-diamino-pentyl]amino}-2-oxoethyl)-17-hydroxy-10,13-dioxo-9,12-diazatricyclo[14.3.1.1^{2,6}]-henicosa-1(20),2(21),3,5,16,18-hexaene-8-carboxamide tetrahydrochloride



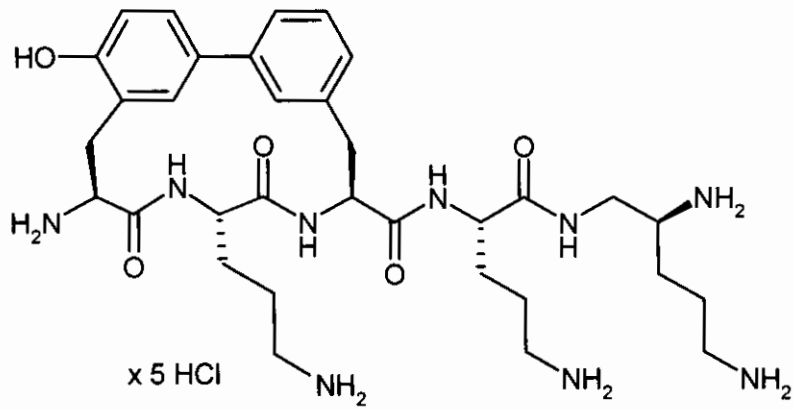
At 0°C, 0.062 ml of a 4N hydrogen chloride-dioxane solution are added to a solution of 4.2 mg (0.004 mmol) of the compound from Example 121A in 1 ml of dioxane. After 3 h at RT, the reaction solution is concentrated in vacuo and coevaporated several times with dichloromethane. The remaining solid is dried to constant weight under high vacuum.

Yield: 2 mg (64% of theory)

MS (ESI): m/z = 613 $(M-4HCl+H)^+$.

Example 3

(8*S*,11*S*,14*S*)-14-Amino-*N*-[(1*S*)-4-amino-1-({[(2*S*)-2,5-diaminopentyl]amino}carbonyl)-butyl]-11-(3-aminopropyl)-17-hydroxy-10,13-dioxo-9,12-diazatricyclo[14.3.1.$1^{2,6}$]-henicosa-1(20),2(21),3,5,16,18-hexaene-8-carboxamide pentahydrochloride



At 0°C, 0.4 ml of a 4N hydrogen chloride-dioxane solution are added to a solution of 22.8 mg (0.02 mmol) of the compound from Example 113A in 1 ml of dioxane. After 3 h

at RT, the reaction solution is concentrated in vacuo and coevaporated several times with dichloromethane. The remaining solid is dried to constant weight under high vacuum.

Yield: 15.3 mg (93% of theory)

MS (ESI): m/z = 654 $(M-5HCl+H)^+$.

^{1}H-NMR (400 MHz, D_2O): δ = 1.55-1.95 (m, 12H), 2.8-3.2 (m, 9H), 3.3-3.7 (m, 4H), 4.29 (m_c, 1H), 4.47 (m_c, 1H), 4.7-4.9 (m, 2H, under D_2O), 6.94 (d, 1H), 6.99 (s, 1H), 7.16 (d, 1H), 7.31 (s, 1H), 7.35 (t, 1H), 7.4-7.5 (m, 2H).

Example 4

(8*S*,11*S*,14*S*)-14-Amino-*N*-[(1*S*)-4-amino-1-({[(2*S*)-2,5-diaminopentyl]amino}carbonyl)-butyl]-11-(3-aminopropyl)-17-hydroxy-10,13-dioxo-9,12-diazatricyclo[14.3.1.1^{2,6}]-henicosa-1(20),2(21),3,5,16,18-hexaene-8-carboxamide penta(hydrotrifluoroacetate)

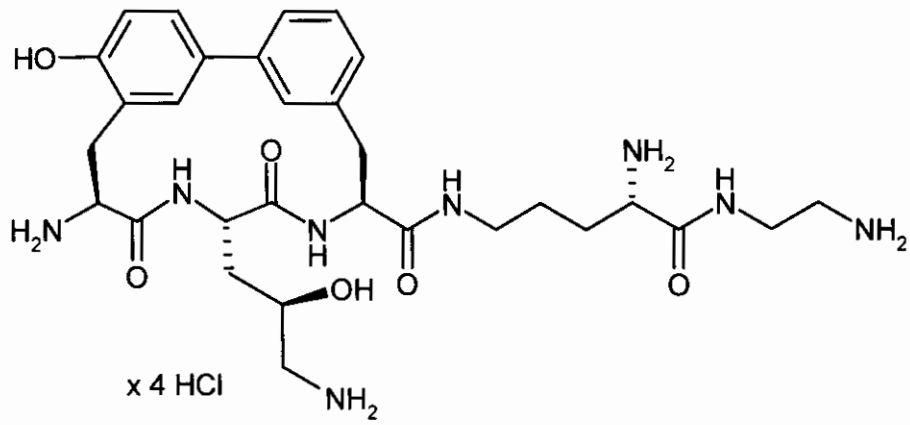
Example 3 as tetrahydrochloride salt is converted by preparative HPLC (Reprosil ODS-A, mobile phase acetonitrile/0.2% aqueous trifluoroacetic acid 5:95 → 95:5) into the tetra(hydrotrifluoroacetate).

LC-MS (Method 10): R_t = 2.21 min

MS (ESI): m/z = 654 $(M-5TFA+H)^+$.

Example 5

(8*S*,11*S*,14*S*)-14-Amino-*N*-{(4*S*)-4-amino-5-[(2-aminoethyl)amino]-5-oxopentyl}-11-[(2*R*)-3-amino-2-hydroxypropyl]-17-hydroxy-10,13-dioxo-9,12-diazatricyclo[14.3.1.1^{2,6}]-henicosa-1(20),2(21),3,5,16,18-hexaene-8-carboxamide tetrahydrochloride



At 0°C, 0.27 ml of a 4N hydrogen chloride-dioxane solution are added to a solution of 4.6 mg (0.005 mmol) of the compound from Example 117A in 1 ml of dioxane. After 3 h at RT, the reaction solution is concentrated in vacuo and coevaporated several times with dichloromethane. The remaining solid is dried to constant weight under high vacuum.

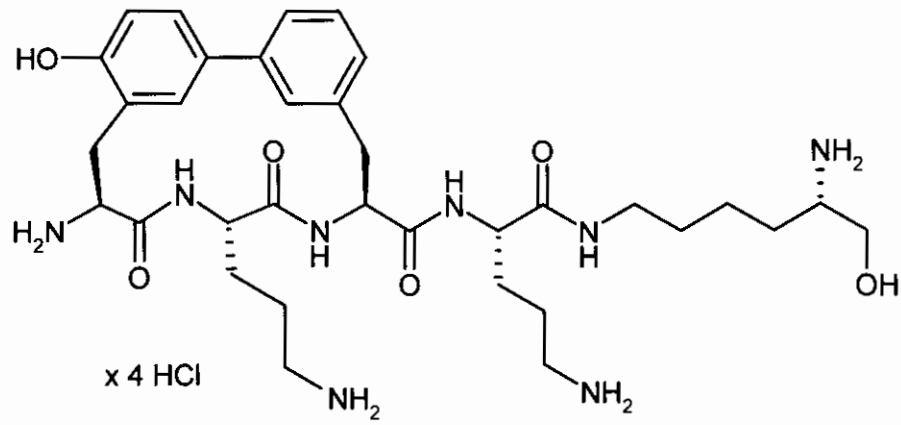
Yield: 3.4 mg (99% of theory)

MS (ESI): m/z = 613 $(M-4HCl+H)^+$.

^{1}H-NMR (400 MHz, D_2O): δ = 1.47-1.67 (m, 2H), 1.75-2.09 (m, 4H), 2.89 (m_c, 1H), 2.95-3.25 (m, 7H), 3.3 (m_c, 1H), 3.4 (m_c, 1H), 3.5-3.7 (m, 2H), 3.86 (m_c, 1H), 3.98 (m_c, 1H), 4.44 (m_c, 1H), 4.7-4.9 (m, 2H, under D_2O), 6.94 (d, 1H), 6.99 (s, 1H), 7.16 (d, 1H), 7.31 (s, 1H), 7.35 (t, 1H), 7.4-7.5 (m, 2H).

Example 6

(8*S*,11*S*,14*S*)-14-Amino-*N*-[(1*S*)-4-amino-1-({[(5*S*)-5-amino-6-hydroxyhexyl]amino}carbonyl)butyl]-11-(3-aminopropyl)-17-hydroxy-10,13-dioxo-9,12-diazatricyclo[14.3.1.1^{2,6}]henicosa-1(20),2(21),3,5,16,18-hexaene-8-carboxamide tetrahydrochloride



At 0°C, 0.87 ml of a 4N hydrogen chloride-dioxane solution are added to a solution of 62 mg (0.058 mmol) of the compound from Example 128A in 1 ml of dioxane. After 3 h at RT, the reaction solution is concentrated in vacuo and coevaporated several times with dichloromethane. The remaining solid is dried to constant weight under high vacuum.

Yield: 46 mg (97% of theory)

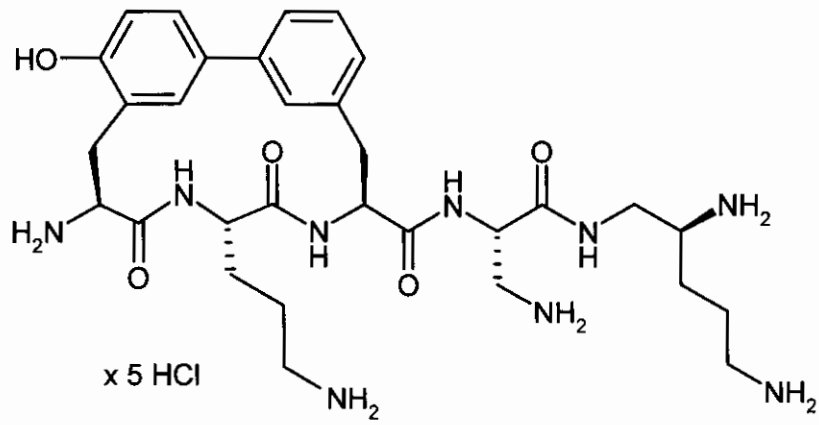
LC-MS (Method 10): R_t = 1.84 min

MS (ESI): m/z = 669 $(M-4HCl+H)^+$.

^{1}H-NMR (400 MHz, D_2O): δ = 1.25-1.95 (m, 14H), 2.9-3.3 (m, 10H), 3.5-3.8 (m, 3H), 4.19 (m_c, 1H), 4.46 (m_c, 1H), 4.7-4.9 (m, 2H, under D_2O), 6.94 (d, 1H), 6.99 (s, 1H), 7.16 (d, 1H), 7.31 (s, 1H), 7.35 (t, 1H), 7.4-7.5 (m, 2H).

Example 7

(8*S*,11*S*,14*S*)-14-Amino-*N*-((1*S*)-1-(aminomethyl)-2-{[(2*S*)-2,5-diaminopentyl]amino}-2-oxoethyl)-11-(3-aminopropyl)-17-hydroxy-10,13-dioxo-9,12-diazatricyclo[14.3.1.1^{2,6}]-henicosa-1(20),2(21),3,5,16,18-hexaene-8-carboxamide pentahydrochloride



At 0°C, 0.94 ml of a 4N hydrogen chloride-dioxane solution are added to a solution of 70 mg (0.062 mmol) of the compound from Example 129A in 1 ml of dioxane. After 3 h at RT, the reaction solution is concentrated in vacuo and coevaporated several times with dichloromethane. The remaining solid is dried to constant weight under high vacuum.

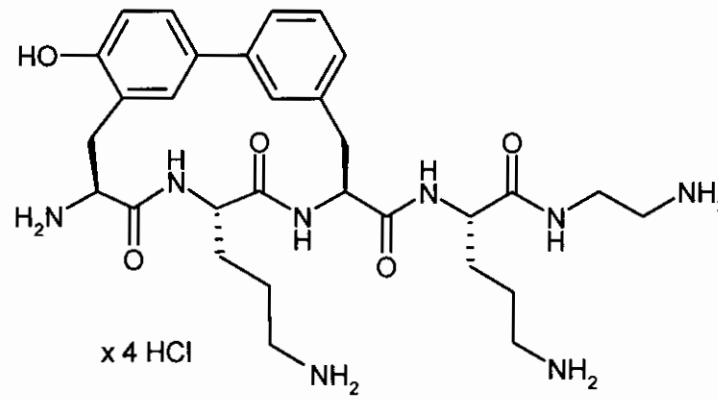
Yield: 50 mg (99% of theory)

MS (ESI): m/z = 626 $(M-5HCl+H)^+$.

^{1}H-NMR (400 MHz, D_2O): δ = 1.55-1.95 (m, 8H), 2.9-3.2 (m, 6H), 3.26 (m_c, 1H), 3.3-3.7 (m, 7H), 4.47 (m_c, 1H), 4.7-4.9 (m, 2H, under D_2O), 6.94 (d, 1H), 6.99 (s, 1H), 7.16 (d, 1H), 7.31 (s, 1H), 7.35 (t, 1H), 7.4-7.5 (m, 2H).

Example 8

(8*S*,11*S*,14*S*)-14-Amino-*N*-((1*S*)-4-amino-1-{[(2-aminoethyl)amino]carbonyl}butyl)-11-(3-aminopropyl)-17-hydroxy-10,13-dioxo-9,12-diazatricyclo[14.3.1.1^{2,6}]henicosa-1(20),2(21),3,5,16,18-hexaene-8-carboxamide tetrahydrochloride



At 0°C, 0.181 ml of a 4N hydrogen chloride-dioxane solution are added to a solution of 12 mg (0.012 mmol) of the compound from Example 130A in 1 ml of dioxane. After 3 h at RT, the reaction solution is concentrated in vacuo and coevaporated several times with dichloromethane. The remaining solid is dried to constant weight under high vacuum.

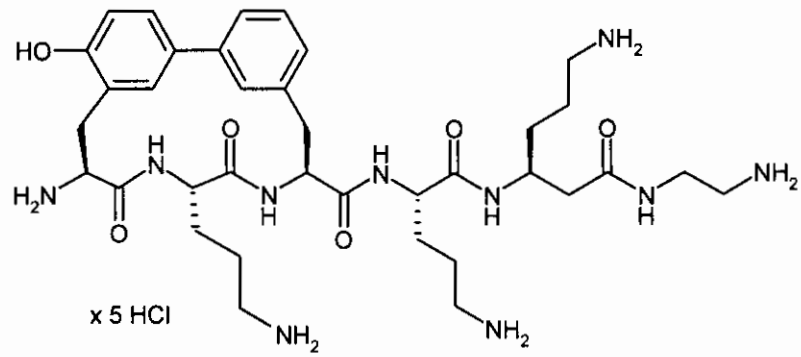
Yield: 8.8 mg (99% of theory)

MS (ESI): m/z = 597 $(M-4HCl+H)^+$.

^{1}H-NMR (400 MHz, D_2O): δ = 1.55-1.95 (m, 8H), 2.9-3.2 (m, 8H), 3.4-3.7 (m, 4H), 4.25 (m_c, 1H), 4.46 (m_c, 1H), 4.7-4.9 (m, 2H, under D_2O), 6.94 (d, 1H), 6.99 (s, 1H), 7.17 (d, 1H), 7.32 (s, 1H), 7.35 (t, 1H), 7.4-7.5 (m, 2H).

Example 9

(8*S*,11*S*,14*S*)-14-Amino-*N*-((1*S*)-4-amino-1-{[((1*S*)-4-amino-1-{2-[(2-aminoethyl)amino]-2-oxoethyl}butyl)amino]carbonyl}butyl)-11-(3-aminopropyl)-17-hydroxy-10,13-dioxo-9,12-diazatricyclo[14.3.1.1^{2,6}]henicosa-1(20),2(21),3,5,16,18-hexaene-8-carboxamide pentahydrochloride



At 0°C, 0.29 ml of a 4N hydrogen chloride-dioxane solution are added to a solution of 24 mg (0.02 mmol) of the compound from Example 133A in 1 ml of dioxane. After 3 h at RT, the reaction solution is concentrated in vacuo and coevaporated several times with dichloromethane. The remaining solid is dried to constant weight under high vacuum.

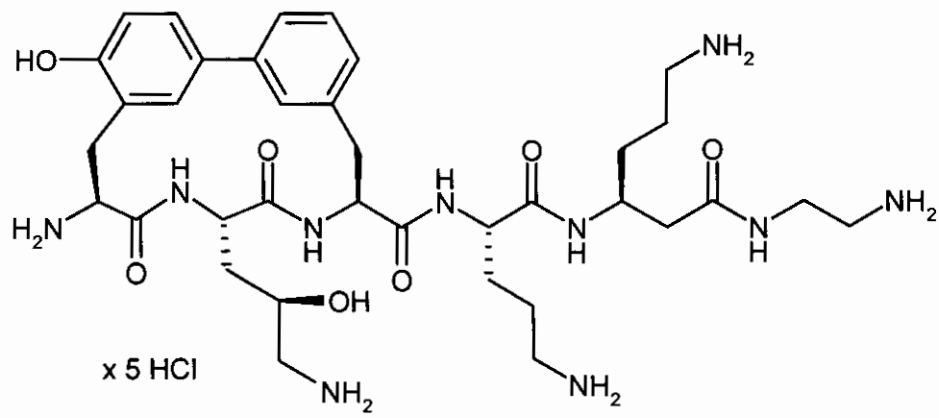
Yield: 17.5 mg (99% of theory)

MS (ESI): m/z = 725 $(M-5HCl+H)^+$.

^{1}H-NMR (400 MHz, D_2O): δ = 1.45-2.0 (m, 12H), 2.36 (m_c, 1H), 2.9-3.2 (m, 11H), 3.4-3.7 (m, 4H), 4.1-4.25 (m, 2H), 4.47 (m_c, 1H), 4.7-4.9 (m, 2H, under D_2O), 6.94 (d, 1H), 6.98 (s, 1H), 7.17 (d, 1H), 7.32 (s, 1H), 7.35 (t, 1H), 7.4-7.5 (m, 2H).

Example 10

(8*S*,11*S*,14*S*)-14-Amino-*N*-((1*S*)-4-amino-1-{[((1*S*)-4-amino-1-{2-[(2-aminoethyl)amino]-2-oxoethyl}butyl)amino]carbonyl}butyl)-11-[(2*R*)-3-amino-2-hydroxypropyl]-17-hydroxy-10,13-dioxo-9,12-diazatricyclo[14.3.1.1^{2,6}]henicosa-1(20),2(21),3,5,16,18-hexaene-8-carboxamide pentahydrochloride



At 0°C, 0.16 ml of a 4N hydrogen chloride-dioxane solution are added to a solution of 13 mg (0.01 mmol) of the compound from Example 134A in 1 ml of dioxane. After 3 h at RT, the reaction solution is concentrated in vacuo and coevaporated several times with dichloromethane. The remaining solid is dried to constant weight under high vacuum.

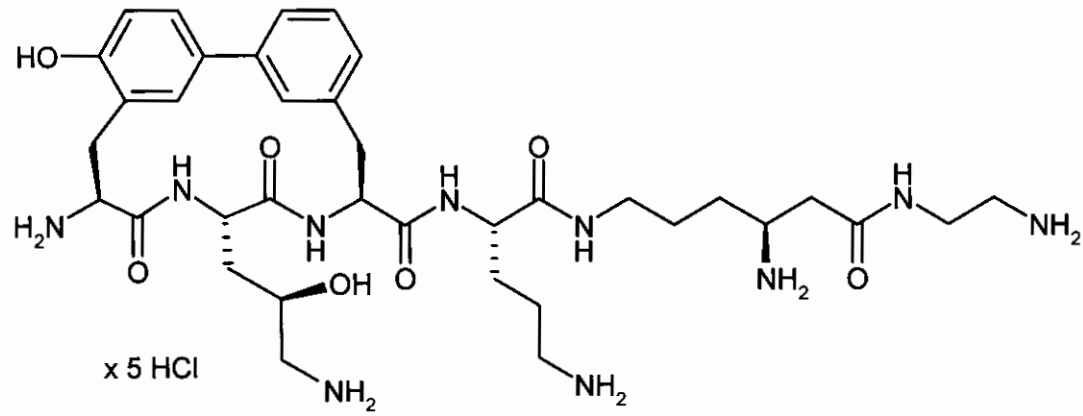
Yield: 9.5 mg (99% of theory)

MS (ESI): m/z = 741 $(M-5HCl+H)^+$.

^{1}H-NMR (400 MHz, D_2O): δ = 1.4-2.05 (m, 10H), 2.37 (m_c, 1H), 2.53 (m_c, 1H), 2.8-3.2 (m, 10H), 3.3-3.7 (m, 3H), 3.86 (m_c, 1H), 4.1-4.21 (m, 2H), 4.44 (m_c, 1H), 4.7-4.9 (m, 2H, under D_2O), 6.95 (d, 1H), 7.0 (s, 1H), 7.18 (d, 1H), 7.3-7.4 (m, 2H), 7.4-7.5 (m, 2H).

Example 11

(8*S*,11*S*,14*S*)-14-Amino-*N*-{(1*S*)-4-amino-1-[({(4*S*)-4-amino-6-[(2-aminoethyl)amino]-6-oxohexyl}amino)carbonyl]butyl}-11-[(2*R*)-3-amino-2-hydroxypropyl]-17-hydroxy-10,13-dioxo-9,12-diazatricyclo[14.3.1.1^{2,6}]henicosa-1(20),2(21),3,5,16,18-hexaene-8-carboxamide pentahydrochloride



At 0°C, 0.29 ml of a 4N hydrogen chloride-dioxane solution are added to a solution of 24 mg (0.02 mmol) of the compound from Example 135A in 1 ml of dioxane. After 3 h at RT, the reaction solution is concentrated in vacuo and coevaporated several times with dichloromethane. The remaining solid is dried to constant weight under high vacuum.

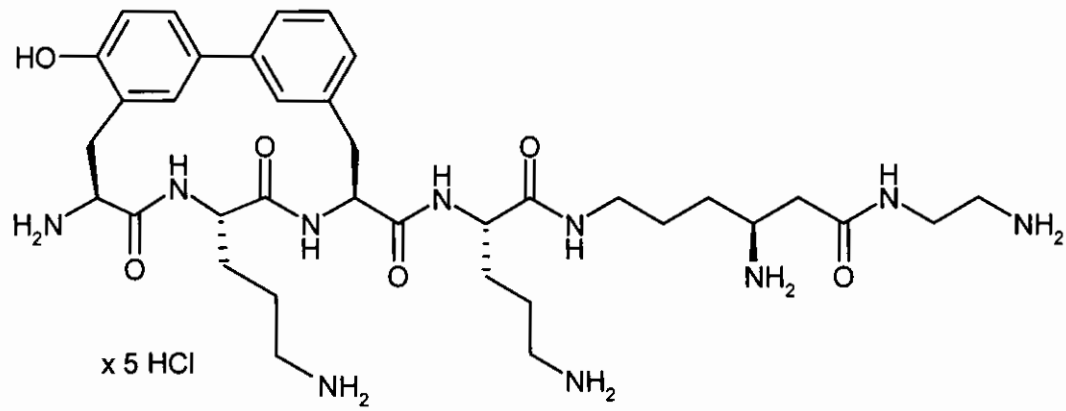
Yield: 17.5 mg (99% of theory)

MS (ESI): m/z = 741 $(M-5HCl+H)^+$.

^{1}H-NMR (400 MHz, D_2O): δ = 1.45-2.05 (m, 10H), 2.55 (m_c, 1H), 2.68 (m_c, 1H), 2.8-3.2 (m, 10H), 3.3-3.7 (m, 4H), 3.86 (m_c, 1H), 4.21 (m_c, 2H), 4.44 (m_c, 1H), 4.7-4.9 (m, 2H, under D_2O), 6.94 (d, 1H), 6.99 (s, 1H), 7.17 (d, 1H), 7.33 (s, 1H), 7.35 (t, 1H), 7.4-7.5 (m, 2H).

Example 12

(8*S*,11*S*,14*S*)-14-Amino-*N*-{(1*S*)-4-amino-1-[({(4*S*)-4-amino-6-[(2-aminoethyl)amino]-6-oxohexyl}amino)carbonyl]butyl}-11-(3-aminopropyl)-17-hydroxy-10,13-dioxo-9,12-diazatricyclo[14.3.1.1^{2,6}]henicosa-1(20),2(21),3,5,16,18-hexaene-8-carboxamide penta-hydrochloride



At 0°C, 0.26 ml of a 4N hydrogen chloride-dioxane solution are added to a solution of 21 mg (0.017 mmol) of the compound from Example 136A in 1 ml of dioxane. After 3 h at RT, the reaction solution is concentrated in vacuo and coevaporated several times with dichloromethane. The remaining solid is dried to constant weight under high vacuum.

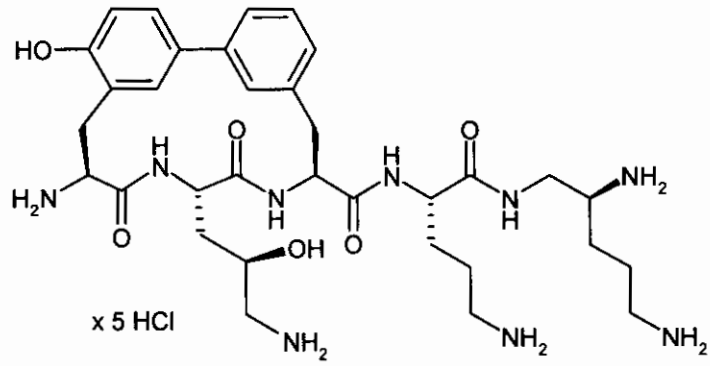
Yield: 15 mg (99% of theory)

MS (ESI): m/z = 716 $(M-5HCl+H)^+$.

^{1}H-NMR (400 MHz, D_2O): δ = 1.45-1.95 (m, 12H), 2.55 (m_c, 1H), 2.68 (m_c, 1H), 2.9-3.2 (m, 10H), 3.42 (m_c, 2H), 3.5-3.7 (m, 3H), 4.2 (m_c, 1H), 4.46 (m_c, 1H), 4.7-4.9 (m, 2H, under D_2O), 6.94 (d, 1H), 6.98 (s, 1H), 7.17 (d, 1H), 7.32 (s, 1H), 7.35 (t, 1H), 7.4-7.5 (m, 2H).

Example 13

(8*S*,11*S*,14*S*)-14-Amino-*N*-[(1*S*)-4-amino-1-({[(2*S*)-2,5-diaminopentyl]amino}carbonyl)-butyl]-11-[(2*R*)-3-amino-2-hydroxypropyl]-17-hydroxy-10,13-dioxo-9,12-diazatricyclo-[14.3.1.1^{2,6}]henicosa-1(20),2(21),3,5,16,18-hexaene-8-carboxamide pentahydrochloride



At 0°C, 0.256 ml of a 4N hydrogen chloride-dioxane solution are added to a solution of 20 mg (0.017 mmol) of the compound from Example 137A in 1 ml of dioxane. After 3 h at RT, the reaction solution is concentrated in vacuo and coevaporated several times with dichloromethane. The remaining solid is dried to constant weight under high vacuum.

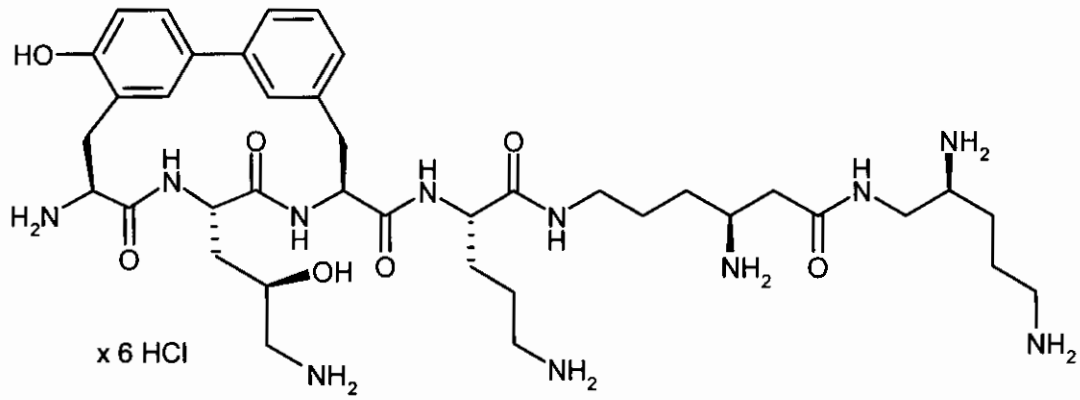
Yield: 13.5 mg (93% of theory)

MS (ESI): m/z = 670 $(M-5HCl+H)^+$.

^{1}H-NMR (400 MHz, D_2O): δ = 1.5-2.05 (m, 10H), 2.8-3.2 (m, 8H), 3.3-3.7 (m, 5H), 3.86 (m_c, 1H), 4.30 (m_c, 1H), 4.44 (m_c, 1H), 4.7-4.9 (m, 2H, under D_2O), 6.94 (d, 1H), 6.99 (s, 1H), 7.17 (d, 1H), 7.33 (s, 1H), 7.35 (t, 1H), 7.4-7.5 (m, 2H).

Example 14

(8*S*,11*S*,14*S*)-14-Amino-*N*-((1*S*)-4-amino-1-{[((4*S*)-4-amino-6-{[(2*S*)-2,5-diaminopentyl]-amino}-6-oxohexyl)amino]carbonyl}butyl)-11-[(2*R*)-3-amino-2-hydroxypropyl]-17-hydroxy-10,13-dioxo-9,12-diazatricyclo[14.3.1.1^{2,6}]henicosa-1(20),2(21),3,5,16,18-hexaene-8-carboxamide hexahydrochloride



At 0°C, 0.31 ml of a 4N hydrogen chloride-dioxane solution are added to a solution of 29 mg (0.021 mmol) of the compound from Example 138A in 1 ml of dioxane. After 3 h at RT, the reaction solution is concentrated in vacuo and coevaporated several times with dichloromethane. The remaining solid is dried to constant weight under high vacuum.

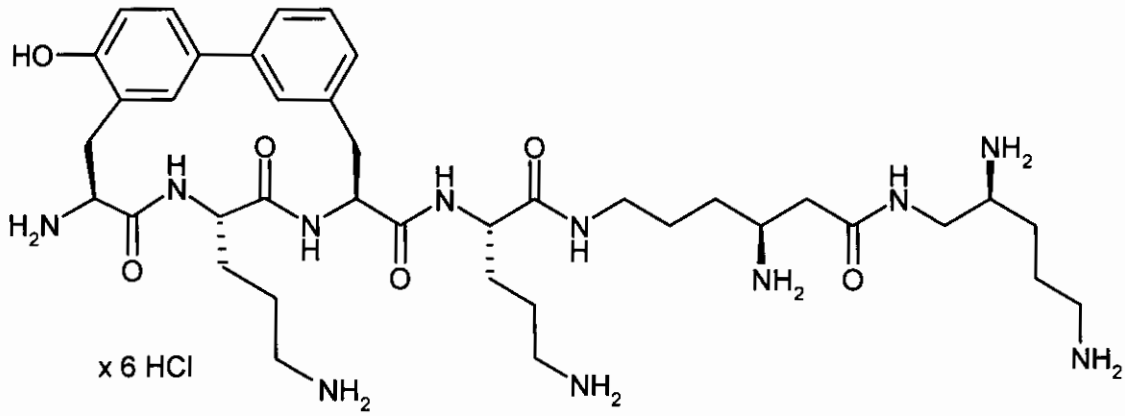
Yield: 16.5 mg (78% of theory)

MS (ESI): m/z = 798 $(M-6HCl+H)^+$.

^{1}H-NMR (400 MHz, D_2O): δ = 1.45-2.05 (m, 14H), 2.50 (m_c, 1H), 2.72 (m_c, 1H), 2.8-3.7 (m, 15H), 3.89 (m_c, 1H), 4.23 (m_c, 1H), 4.46 (m_c, 1H), 4.7-4.9 (m, 2H, under D_2O), 6.94 (d, 1H), 6.99 (s, 1H), 7.17 (d, 1H), 7.33 (s, 1H), 7.35 (t, 1H), 7.4-7.5 (m, 2H).

Example 15

(8*S*,11*S*,14*S*)-14-Amino-*N*-((1*S*)-4-amino-1-{[((4*S*)-4-amino-6-{[(2*S*)-2,5-diaminopentyl]-amino}-6-oxohexyl)amino]carbonyl}butyl)-11-(3-aminopropyl)-17-hydroxy-10,13-dioxo-9,12-diazatricyclo[14.3.1.1^{2,6}]henicosa-1(20),2(21),3,5,16,18-hexaene-8-carboxamide hexahydrochloride



At 0°C, 0.31 ml of a 4N hydrogen chloride-dioxane solution are added to a solution of 29 mg (0.021 mmol) of the compound from Example 139A in 1 ml of dioxane. After 3 h at RT, the reaction solution is concentrated in vacuo and coevaporated several times with dichloromethane. The remaining solid is dried to constant weight under high vacuum.

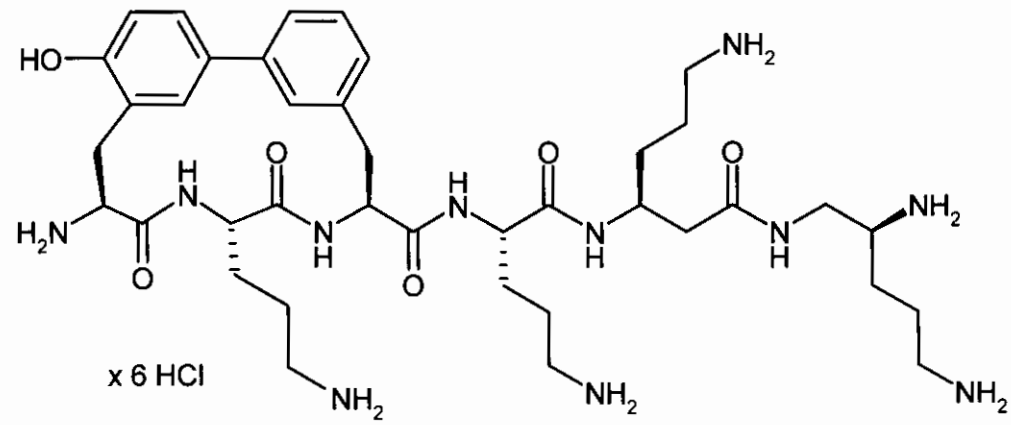
Yield: 16.5 mg (78% of theory)

MS (ESI): m/z = 782 $(M-6HCl+H)^+$.

^{1}H-NMR (400 MHz, D_2O): δ = 1.45-1.95 (m, 16H), 2.60 (m_c, 1H), 2.83 (m_c, 1H), 2.9-3.3 (m, 10H), 3.3-3.75 (m, 6H), 4.24 (m_c, 1H), 4.49 (m_c, 1H), 4.7-4.9 (m, 2H, under D_2O), 6.94 (d, 1H), 6.99 (s, 1H), 7.17 (d, 1H), 7.33 (s, 1H), 7.35 (t, 1H), 7.4-7.5 (m, 2H).

Example 16

(8*S*,11*S*,14*S*)-14-Amino-*N*-[(1*S*)-4-amino-1-({[(1*S*)-4-amino-1-(2-{[(2*S*)-2,5-diaminopentyl]-amino}-2-oxoethyl)butyl]amino}carbonyl)butyl]-11-(3-aminopropyl)-17-hydroxy-10,13-dioxo-9,12-diazatricyclo[14.3.1.1^{2,6}]henicosa-1(20),2(21),3,5,16,18-hexaene-8-carbox-amide hexahydrochloride



At 0°C, 0.3 ml of a 4N hydrogen chloride-dioxane solution are added to a solution of 28 mg (0.02 mmol) of the compound from Example 140A in 1 ml of dioxane. After 3 h at RT, the reaction solution is concentrated in vacuo and coevaporated several times with dichloromethane. The remaining solid is dried to constant weight under high vacuum.

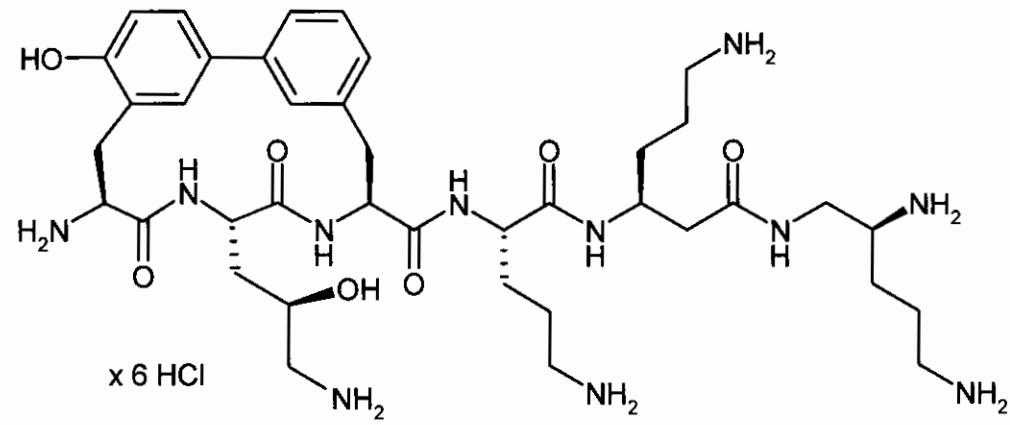
Yield: 20 mg (99% of theory)

MS (ESI): m/z = 782 $(M-6HCl+H)^+$.

^{1}H-NMR (400 MHz, D_2O): δ = 1.4-1.9 (m, 16H), 2.4 (m_c, 1H), 2.54 (m_c, 1H), 2.85-3.2 (m, 11H), 3.29 (m_c, 1H), 3.39 (m_c, 1H), 3.45-3.65 (m, 2H), 4.1-4.25 (m, 2H), 4.47 (m_c, 1H), 4.7-4.9 (m, 2H, under D_2O), 6.94 (d, 1H), 6.99 (s, 1H), 7.17 (d, 1H), 7.33 (s, 1H), 7.35 (t, 1H), 7.4-7.5 (m, 2H).

Example 17

(8*S*,11*S*,14*S*)-14-Amino-*N*-[(1*S*)-4-amino-1-({[(1*S*)-4-amino-1-(2-{[(2*S*)-2,5-diaminopentyl]-amino}-2-oxoethyl)butyl]amino}carbonyl)butyl]-11-[(2*R*)-3-amino-2-hydroxypropyl]-17-hydroxy-10,13-dioxo-9,12-diazatricyclo[14.3.1.1^{2,6}]henicosa-1(20),2(21),3,5,16,18-hexaene-8-carboxamide hexahydrochloride



At 0°C, 0.39 ml of a 4N hydrogen chloride-dioxane solution are added to a solution of 36 mg (0.026 mmol) of the compound from Example 141A in 1 ml of dioxane. After 3 h at RT, the reaction solution is concentrated in vacuo and coevaporated several times with dichloromethane. The remaining solid is dried to constant weight under high vacuum.

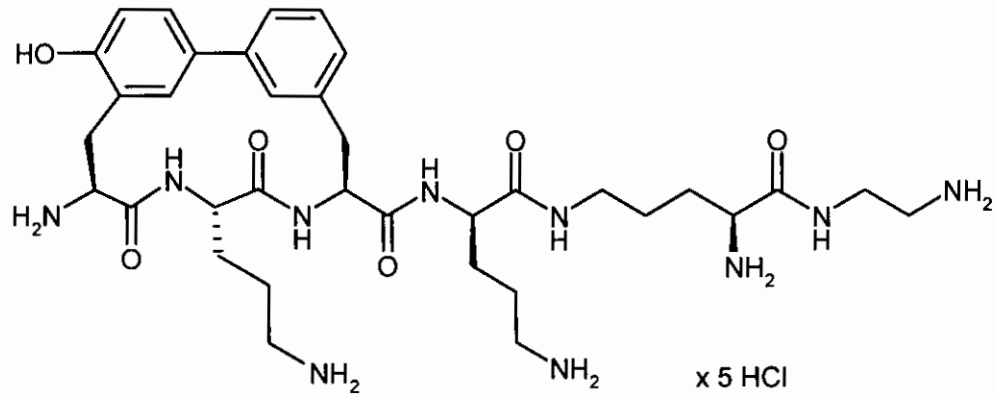
Yield: 26 mg (99% of theory)

MS (ESI): m/z = 798 $(M-6HCl+H)^+$.

^{1}H-NMR (400 MHz, D_2O): δ = 1.4-2.05 (m, 14H), 2.41 (m_c, 1H), 2.54 (m_c, 1H), 2.85-3.2 (m, 11H), 3.29 (m_c, 1H), 3.39 (m_c, 1H), 3.45-3.65 (m, 2H), 3.85 (m_c, 1H), 4.1-4.25 (m, 2H), 4.45 (m_c, 1H), 4.7-4.9 (m, 2H, under D_2O), 6.95 (d, 1H), 7.0 (s, 1H), 7.17 (d, 1H), 7.29-7.6 (m, 4H).

Example 18

N^5-(N^2-{[(8*S*,11*S*,14*S*)-14-Amino-11-(3-aminopropyl)-17-hydroxy-10,13-dioxo-9,12-diazatricyclo[14.3.1.1^{2,6}]henicosa-1(20),2(21),3,5,16,18-hexaen-8-yl]carbonyl}-*L*-ornithyl)-*N*-(2-aminoethyl)-*L*-ornithinamide pentahydrochloride



At 0°C, 0.58 ml of a 4N hydrogen chloride-dioxane solution are added to a solution of 47 mg (0.039 mmol) of the compound from Example 142A in 1 ml of dioxane. After 3 h at RT, the reaction solution is concentrated in vacuo and coevaporated several times with dichloromethane. The remaining solid is dried to constant weight under high vacuum.

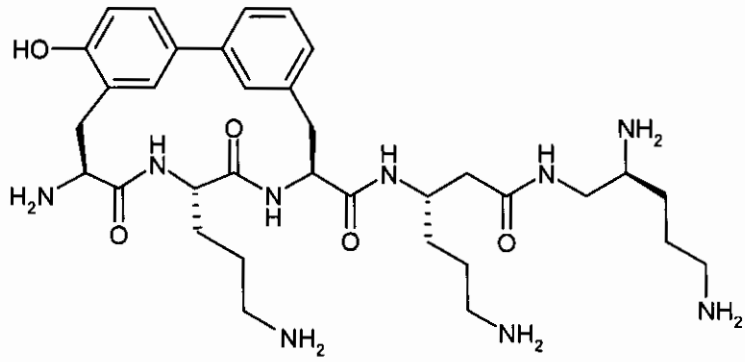
Yield: 34 mg (99% of theory)

MS (ESI): m/z = 711 $(M-5HCl+H)^+$.

^{1}H-NMR (400 MHz, D_2O): δ = 1.45-1.95 (m, 12H), 2.9-3.25 (m, 10H), 3.38 (m_c, 1H), 3.5-3.7 (m, 2H), 3.96 (m_c, 1H), 4.26 (m_c, 1H), 4.47 (m_c, 1H), 4.7-4.9 (m, 2H, under D_2O), 6.94 (d, 1H), 6.99 (s, 1H), 7.17 (d, 1H), 7.33 (s, 1H), 7.35 (t, 1H), 7.4-7.5 (m, 2H).

Example 19

(8*S*,11*S*,14*S*)-14-Amino-*N*-[(1*S*)-4-amino-1-(2-{[(2*S*)-2,5-diaminopentyl]amino}-2-oxo-ethyl)butyl]-11-(3-aminopropyl)-17-hydroxy-10,13-dioxo-9,12-diazatricyclo[14.3.1.1^{2,6}]-henicosa-1(20),2(21),3,5,16,18-hexaene-8-carboxamide penta(hydrotrifluoroacetate)



At 0°C, 0.19 ml of a 4N hydrogen chloride-dioxane solution are added to a solution of 15 mg (0.013 mmol) of the compound from Example 143A in 1 ml of dioxane. After 3 h at RT, the reaction solution is concentrated in vacuo and coevaporated several times with dichloromethane. The remaining solid is dried to constant weight under high vacuum. The crude product is converted by preparative HPLC (Reprosil ODS-A, mobile phase acetonitrile/0.2% aqueous trifluoroacetic acid 5:95 → 95:5) into the tetra(hydrotrifluoroacetate).

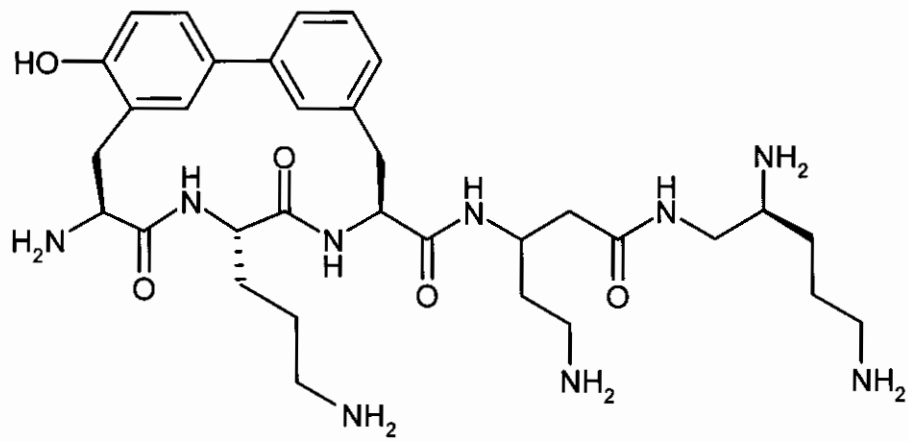
Yield: 5.4 mg (34% of theory)

MS (ESI): m/z = 668 $(M-5TFA+H)^+$.

^{1}H-NMR (400 MHz, D_2O): δ = 1.4-1.9 (m, 12H), 2.39 (m_c, 1H), 2.57 (m_c, 1H), 2.83-3.17 (m, 9H), 3.32 (m_c, 1H), 3.41 (m_c, 1H), 3.5-3.7 (m, 2H), 4.21 (m_c, 1H), 4.46 (m_c, 1H), 4.7-4.9 (m, 2H, under D_2O), 6.94 (d, 1H), 6.98 (s, 1H), 7.11 (d, 1H), 7.32 (s, 1H), 7.35 (t, 1H), 7.44-7.55 (m, 2H).

Example 20

(8*S*,11*S*,14*S*)-14-Amino-*N*-(1-(2-aminoethyl)-3-{[(2*S*)-2,5-diaminopentyl]amino}-3-oxopropyl)-11-(3-aminopropyl)-17-hydroxy-10,13-dioxo-9,12-diazatricyclo[14.3.1.1^{2,6}]henicosa-1(20),2(21),3,5,16,18-hexaene-8-carboxamide penta(hydrotrifluoroacetate)



x 5 TFA

At 0°C, 0.19 ml of a 4N hydrogen chloride-dioxane solution are added to a solution of 14.8 mg (0.013 mmol) of the compound from Example 144A in 1 ml of dioxane. After 3 h at RT, the reaction solution is concentrated in vacuo and coevaporated several times with dichloromethane. The remaining solid is dried to constant weight under high vacuum. The crude product is converted by preparative HPLC (Reprosil ODS-A, mobile phase acetonitrile/0.2% aqueous trifluoroacetic acid 5:95 → 95:5) into the tetra(hydrotrifluoroacetate).

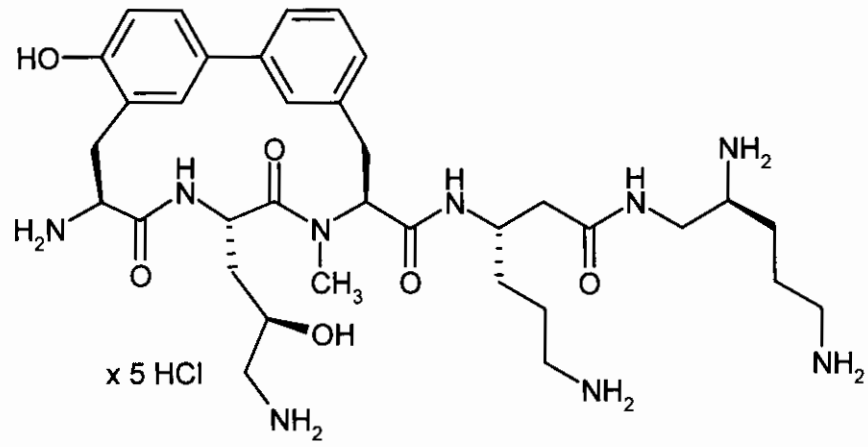
Yield: 8.9 mg (57% of theory)

MS (ESI): m/z = 654 $(M-5TFA+H)^+$.

^{1}H-NMR (400 MHz, D_2O): δ = 1.5-2.0 (m, 10H), 2.4-2.65 (m, 2H), 2.85-3.2 (m, 9H), 3.25-3.47 (m, 2H), 3.53-3.68 (m, 2H), 4.27 (m_c, 1H), 4.46 (m_c, 1H), 4.7-4.9 (m, 2H, under D_2O), 6.9-7.0 (m, 2H), 7.05-7.15 (m, 1H), 7.3-7.4 (m, 2H), 7.42-7.52 (m, 2H).

Example 21

(8*S*,11*S*,14*S*)-14-Amino-*N*-[(1*S*)-4-amino-1-(2-{[(2*S*)-2,5-diaminopentyl]amino}-2-oxoethyl)butyl]-11-[(2*R*)-3-amino-2-hydroxypropyl]-17-hydroxy-9-methyl-10,13-dioxo-9,12-diazatricyclo[14.3.1.1^{2,6}]henicosa-1(20),2(21),3,5,16,18-hexaene-8-carboxamide pentahydrochloride

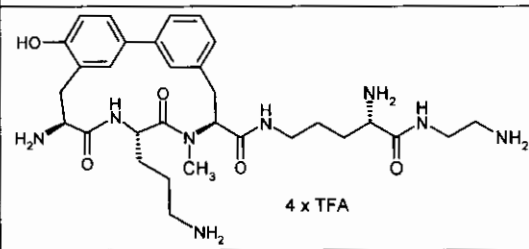
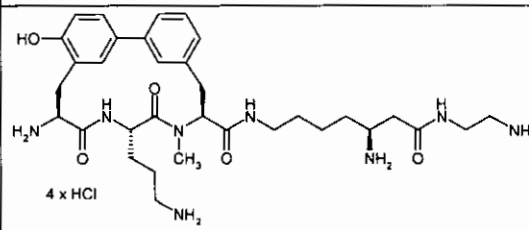


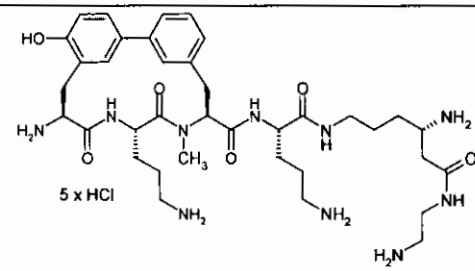
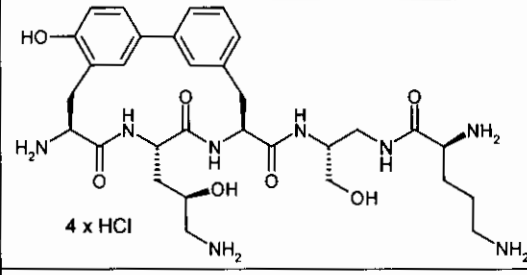
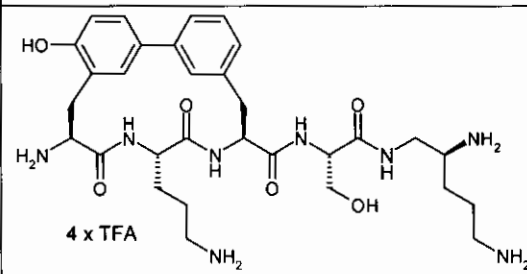
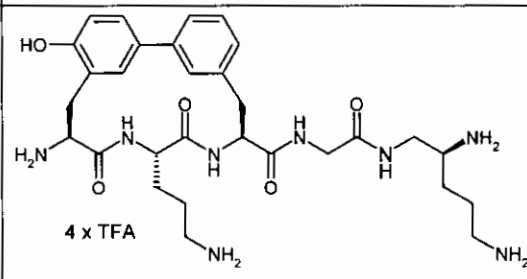
At 0°C, 0.161 ml of a 4N hydrogen chloride-dioxane solution are added to a solution of 12.9 mg (0.011 mmol) of the compound from Example 118A in 1 ml of dioxane. After 3 h at RT, the reaction solution is concentrated in vacuo and coevaporated several times with dichloromethane. The remaining solid is dried to constant weight under high vacuum.

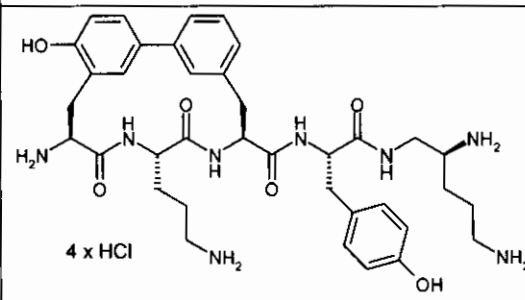
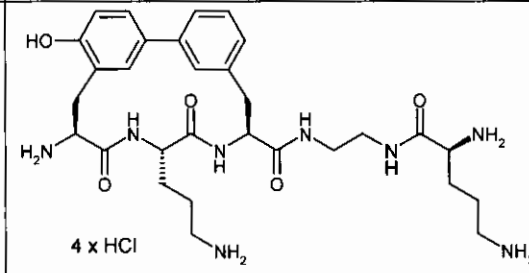
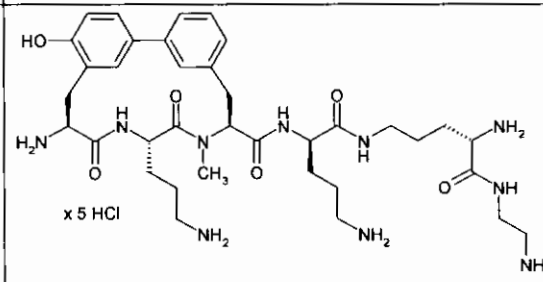
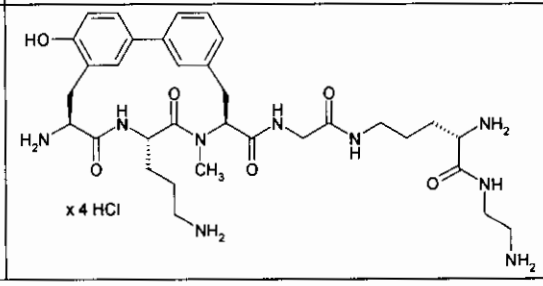
Yield: 9 mg (95% of theory)

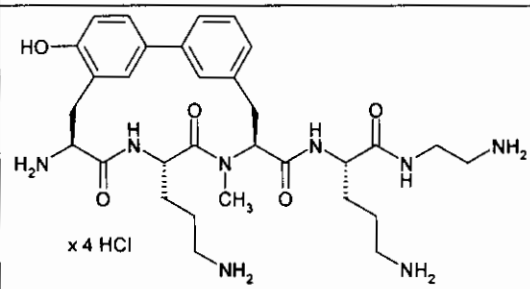
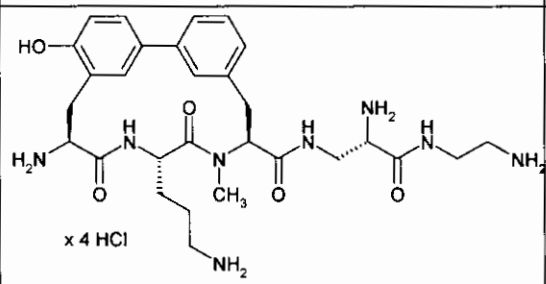
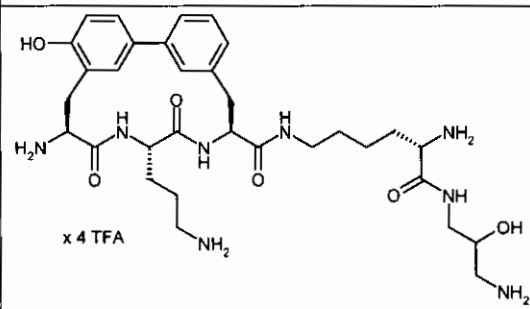
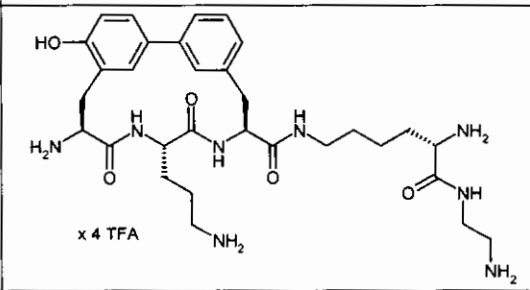
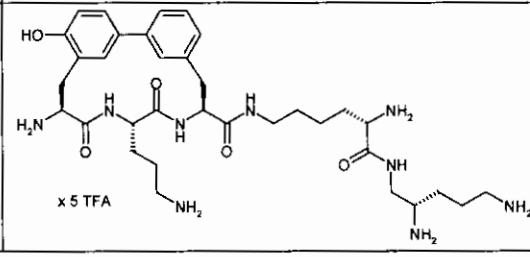
MS (ESI): m/z = 698 $(M-5HCl+H)^+$.

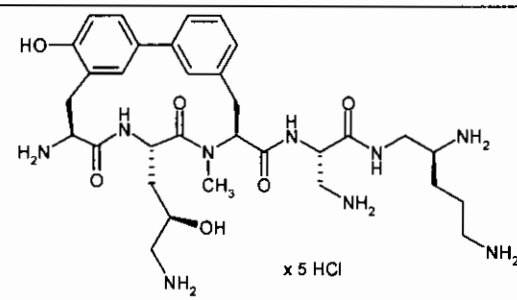
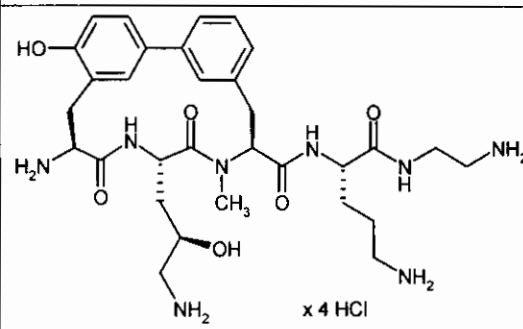
The examples listed in the following table are prepared in analogy to the procedure of Example 1, as hydrochloride or hydro(trifluoroacetate) salt according to the respective isolation method.

Example No.	Precursor Example	Structure	Analytical Data
22	112A		LC-MS (Method 10): R_t = 1.80 min MS (ESI): m/z = 654 $(M-4TFA+H)^+$.
23	114A		LC-MS (Method 10): R_t = 2.11 min MS (ESI): m/z = 639 $(M-4HCl+H)^+$.

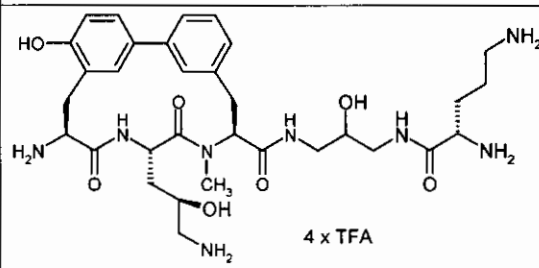
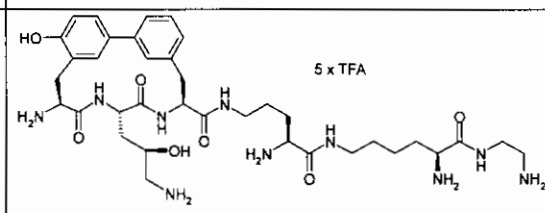
Example No.	Precursor Example	Structure	Analytical Data
24	116A		LC-MS (Method 10): R_t = 1.91 min MS (ESI): m/z = 739 $(M-5HCl+H)^+$
25	122A		MS (ESI): m/z = 643 $(M-4HCl+H)^+$
26	127A		MS (ESI): m/z = 613 $(M-4TFA+H)^+$ ^{1}H-NMR (400 MHz, D_2O): δ = 1.5-2.0 (m, 8H), 2.85-3.2 (m, 6H), 3.3-3.7 (m, 4H), 3.83 (m_c, 1H), 4.35-4.5 (m, 2H), 4.6 (m_c, 1H), 4.7-4.9 (m, 2H, under D_2O), 6.9-7.0 (m, 2H), 7.17 (d, 1H), 7.27-7.4 (m, 2H), 7.4-7.5 (m, 2H).
27	131A		MS (ESI): m/z = 597 $(M-4TFA+H)^+$ ^{1}H-NMR (400 MHz, D_2O): δ = 1.5-2.0 (m, 8H), 2.9-3.2 (m, 6H), 3.3-3.7 (m, 6H), 3.96 (m_c, 1H), 4.47 (m_c, 1H), 4.7-4.9 (m, 2H, under D_2O), 6.94 (d, 1H), 6.98 (s, 1H), 7.17 (d, 1H), 7.31 (s, 1H), 7.35 (t, 1H), 7.4-7.5 (m, 2H).

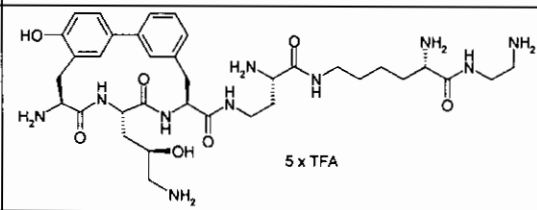
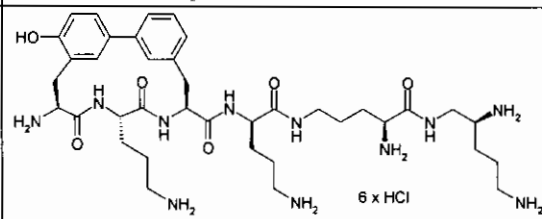
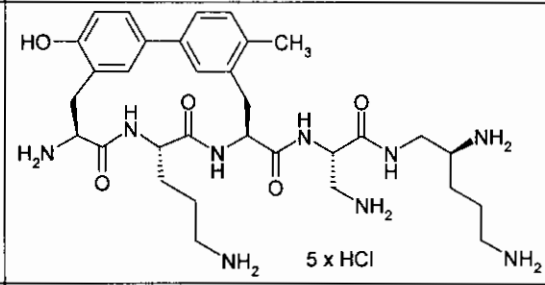
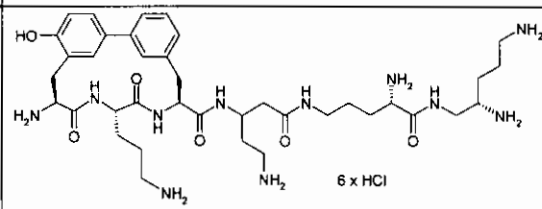
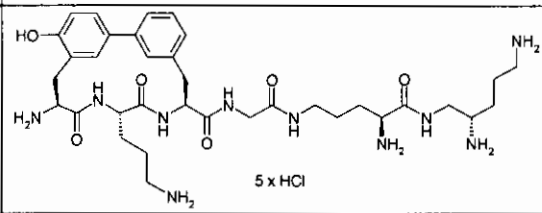
Example No.	Precursor Example	Structure	Analytical Data
28	132A		LC-MS (Method 17): R_t = 1.92 min MS (ESI): m/z = 703 $(M-4HCl+H)^+$ ^{1}H-NMR (400 MHz, D_2O): δ = 1.5-1.8 (m, 8H), 2.8-3.1 (m, 9H), 3.27 (m_c, 1H), 3.35-3.45 (m, 2H), 3.58 (m_c, 1H), 4.45-4.55 (m, 2H), 4.7-4.9 (m, 2H, under D_2O), 6.7-6.8 (m, 2H), 6.9-7.0 (m, 2H), 7.05-7.2 (m, 3H), 7.27 (s, 1H), 7.34 (t, 1H), 7.36-7.46 (m, 2H).
29	119A		MS (ESI): m/z = 597 $(M-4HCl+H)^+$ ^{1}H-NMR (400 MHz, D_2O): δ = 1.55-1.95 (m, 8H), 2.85-3.18 (m, 7H), 3.2-3.7 (m, 5H), 3.95 (m_c, 1H), 4.45 (m_c, 1H), 4.7-4.9 (m, 2H, under D_2O), 6.94 (d, 1H), 6.98 (s, 1H), 7.17 (d, 1H), 7.31 (s, 1H), 7.35 (t, 1H), 7.4-7.5 (m, 2H).
30	123A		LC-MS (Method 10): R_t = 1.77 min MS (ESI): m/z = 725 $(M-5HCl+H)^+$
31	124A		LC-MS (Method 10): R_t = 1.95 min MS (ESI): m/z = 668 $(M-4HCl+H)^+$

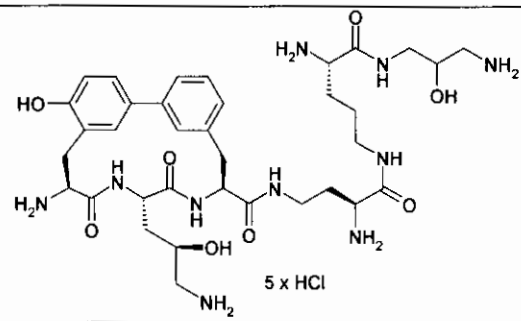
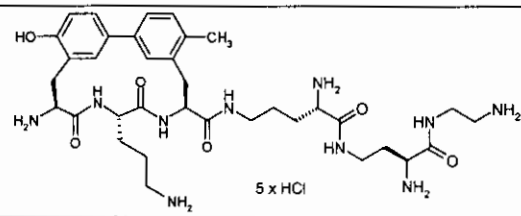
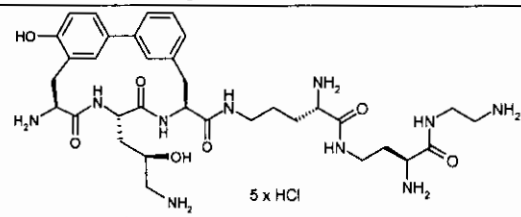
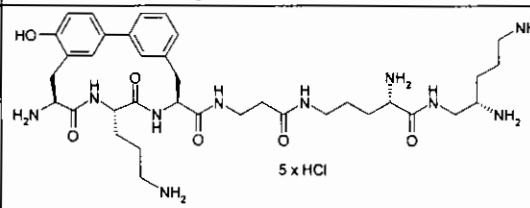
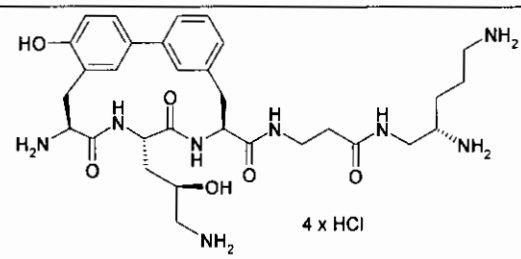
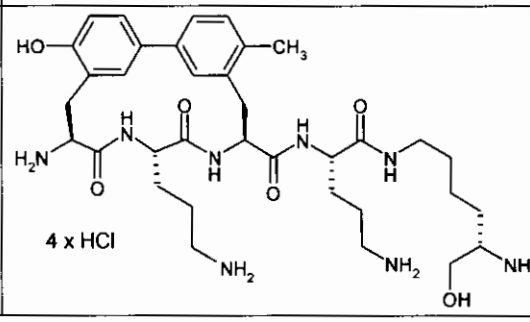
Example No.	Precursor Example	Structure	Analytical Data
32	125A		LC-MS (Method 10): R_t = 1.92 min MS (ESI): m/z = 611 $(M-4HCl+H)^+$
33	126A		LC-MS (Method 10): R_t = 1.81 min MS (ESI): m/z = 583 $(M-4HCl+H)^+$
34	145A		MS (ESI): m/z = 641 $(M-4TFA+H)^+$
35	146A		MS (ESI): m/z = 611 $(M-4TFA+H)^+$
36	147A		MS (ESI): m/z = 668 $(M-5TFA+H)^+$

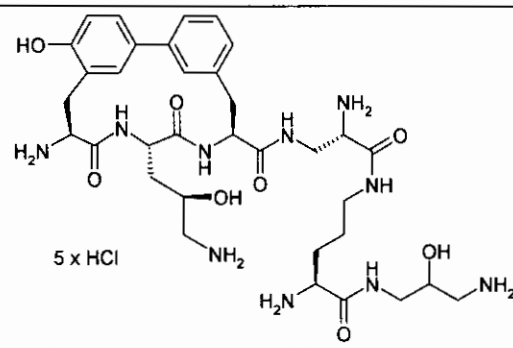
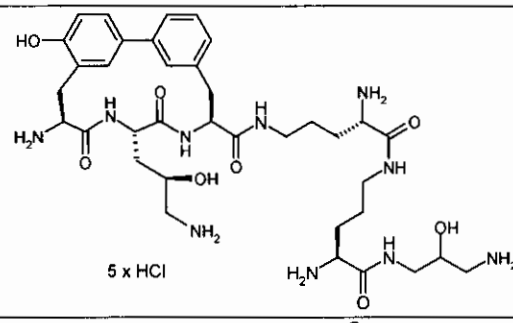
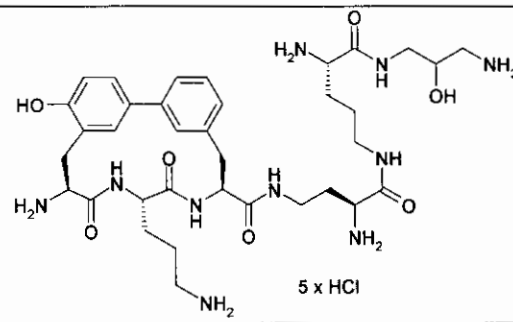
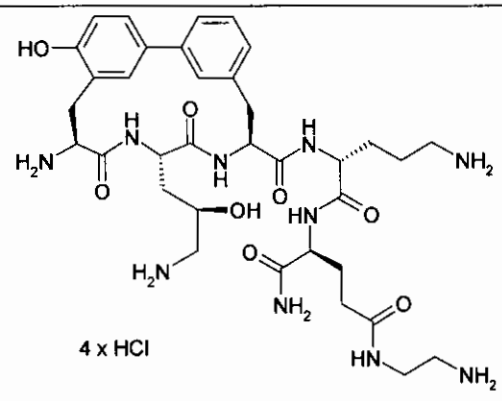
Example No.	Precursor Example	Structure	Analytical Data
37	148A	 x 5 HCl	MS (ESI): m/z = 655 (M-5HCl+H)$^+$.
38	149A	 x 4 HCl	MS (ESI): m/z = 627 (M-4HCl+H)$^+$.

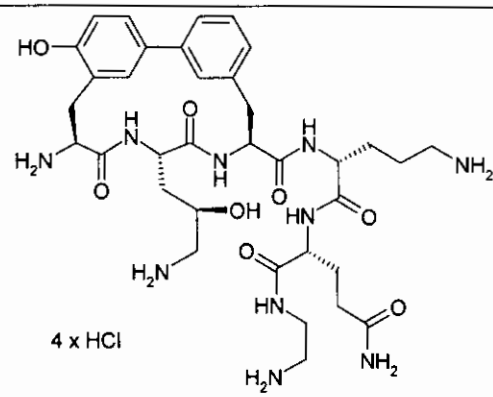
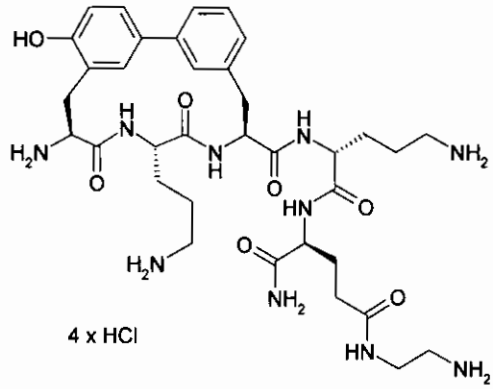
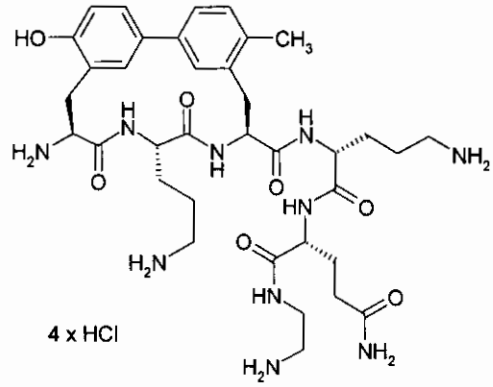
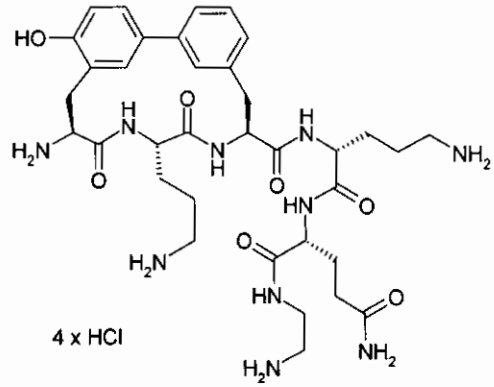
Examples 39 to 93 listed in the following table are prepared in analogy to the procedure of Example 1, as hydrochloride or hydro(trifluoroacetate) salt according to the respective isolation method.

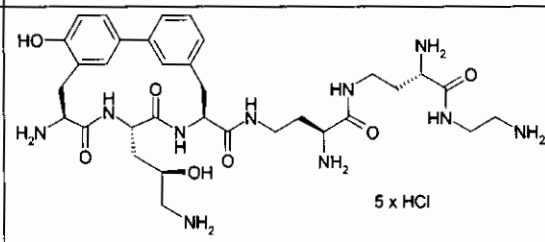
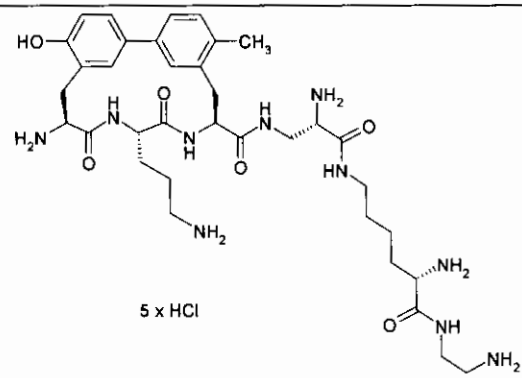
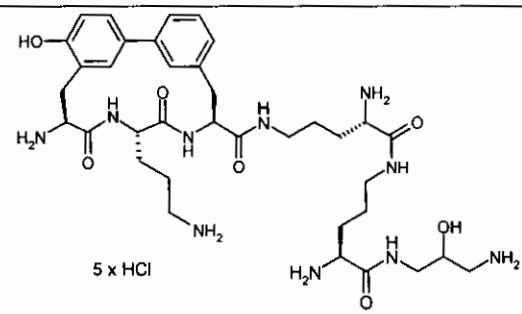
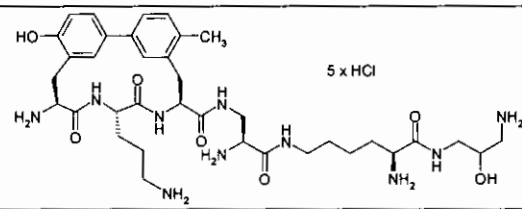
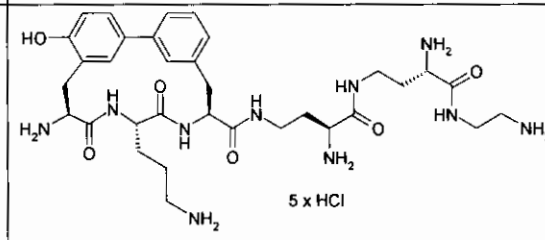
Example No.	Precursor Example	Structure	Analytical Data
39	227A	 4 x TFA	LC-MS (Method 2): R_t = 0.25 min MS (ESI): m/z = 657 (M-4TFA+H)$^+$.
40	228A	 5 x TFA	LC-MS (Method 10): R_t = 1.08 min MS (ESI): m/z = 741 (M-5TFA+H)$^+$.

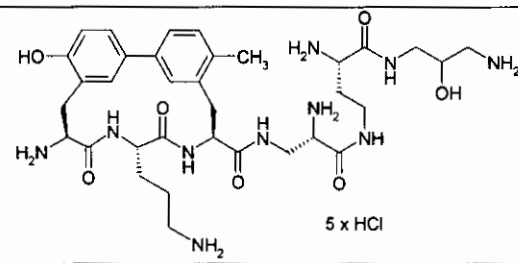
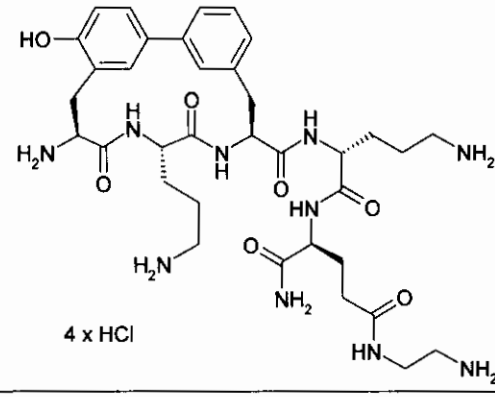
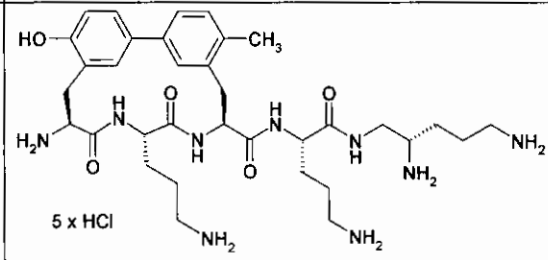
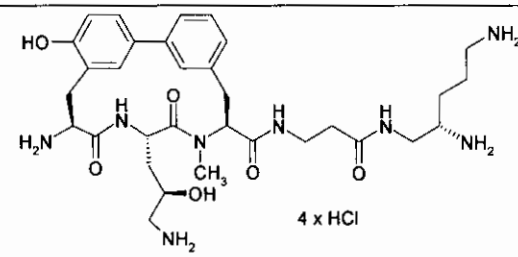
Example No.	Precursor Example	Structure	Analytical Data
41	229A		LC-MS (Method 10): R_t = 0.86 min MS (ESI): m/z = 727 $(M-5TFA+H)^+$.
42	230A		LC-MS (Method 1): R_t = 0.3 min MS (ESI): m/z = 768 $(M-6HCl+H)^+$. ^{1}H-NMR (400 MHz, D_2O): δ = 1.5-1.9 (m, 16H), 2.9-3.3 (m, 9H), 3.4-3.8 (m, 6H), 4.0 (m_c, 1H), 4.26 (m_c, 1H), 4.47 (m_c, 1H), 4.7-4.9 (m, 2H, under D_2O), 6.95 (d, 1H), 6.99 (s, 1H), 7.17 (d, 1H), 7.31 (s, 1H), 7.35 (t, 1H), 7.4-7.5 (m, 2H).
43	231A		LC-MS (Method 10): R_t = 0.46 min MS (ESI): m/z = 640 $(M-5HCl+H)^+$.
44	232A		LC-MS (Method 1): R_t = 0.31 min MS (ESI): m/z = 768 $(M-6HCl+H)^+$.
45	233A		LC-MS (Method 2): R_t = 0.26 min MS (ESI): m/z = 711 $(M-5HCl+H)^+$.

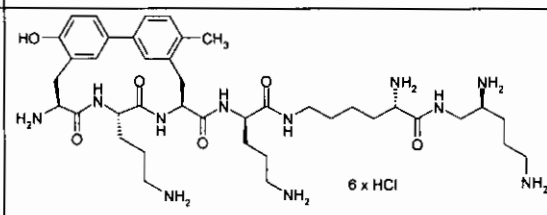
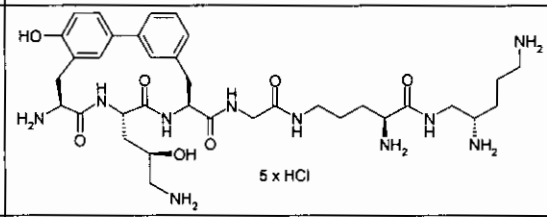
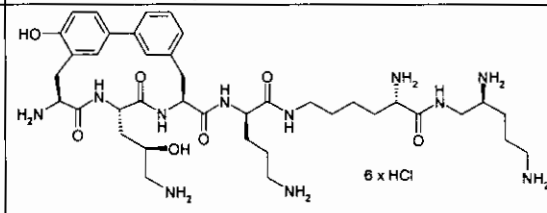
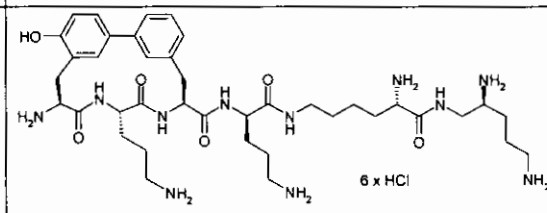
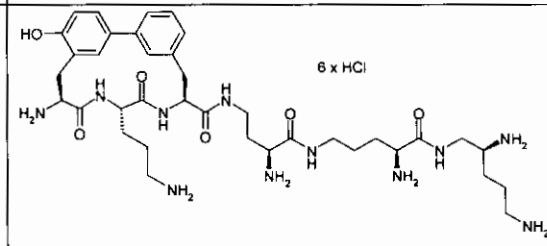
Example No.	Precursor Example	Structure	Analytical Data
46	234A		LC-MS (Method 2): R_t = 0.28 min MS (ESI): m/z = 743 (M-5HCl+H)$^+$.
47	235A		LC-MS (Method 1): R_t = 0.30 min MS (ESI): m/z = 711 (M-5HCl+H)$^+$.
48	236A		LC-MS (Method 1): R_t = 0.31 min MS (ESI): m/z = 713 (M-5HCl+H)$^+$.
49	237A		LC-MS (Method 1): R_t = 0.31 min MS (ESI): m/z = 725 (M-5HCl+H)$^+$.
50	238A		LC-MS (Method 1): R_t = 0.23 min MS (ESI): m/z = 627 (M-4HCl+H)$^+$.
51	239A		LC-MS (Method 10): R_t = 1.95 min MS (ESI): m/z = 683 (M-4HCl+H)$^+$.

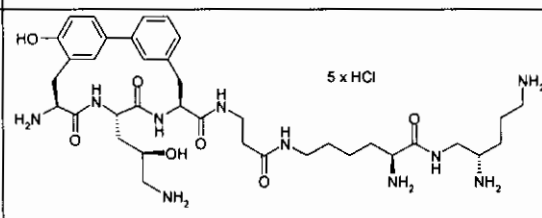
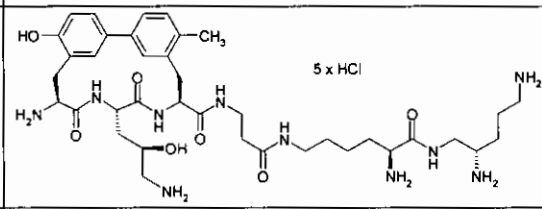
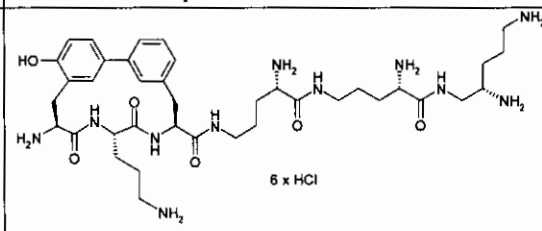
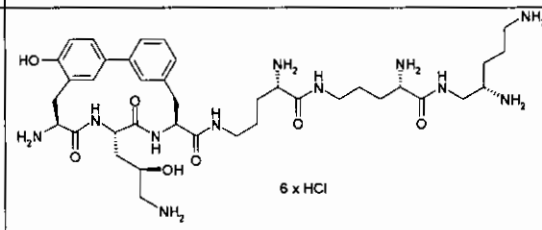
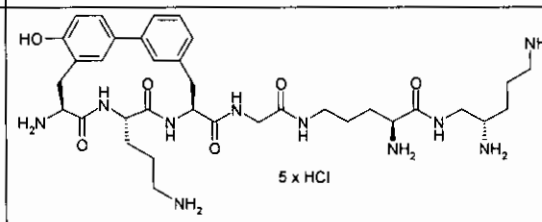
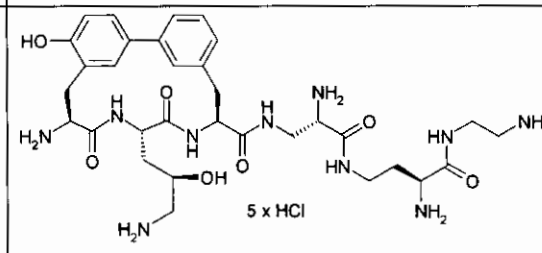
Example No.	Precursor Example	Structure	Analytical Data
52	240A		LC-MS (Method 2): R_t = 0.28 min MS (ESI): m/z = 729 $(M-5HCl+H)^+$.
53	241A		LC-MS (Method 3): R_t = 0.26 min MS (ESI): m/z = 757 $(M-5HCl+H)^+$.
54	242A		LC-MS (Method 2): R_t = 0.28 min MS (ESI): m/z = 727 $(M-5HCl+H)^+$.
55	243A		LC-MS (Method 10): R_t = 1.96 min MS (ESI): m/z = 741 $(M-4HCl+H)^+$. ^{1}H-NMR (400 MHz, D_2O): δ = 1.6-2.15 (m, 8H), 2.3 (m, 2H), 2.9-3.3 (m, 10H), 3.4-3.8 (m, 4H), 3.85 (m_c, 1H), 4.22 (m_c, 1H), 4.35 (m_c, 1H), 4.43 (m_c, 1H), 4.7-4.9 (m, 2H, under D_2O), 6.94 (d, 1H), 6.98 (s, 1H), 7.17 (d, 1H), 7.32 (s, 1H), 7.35 (t, 1H), 7.4-7.5 (m, 2H).

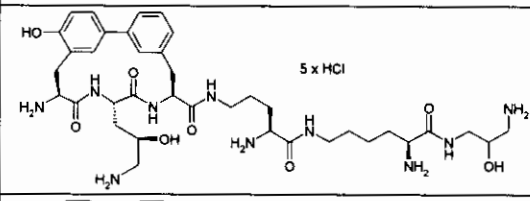
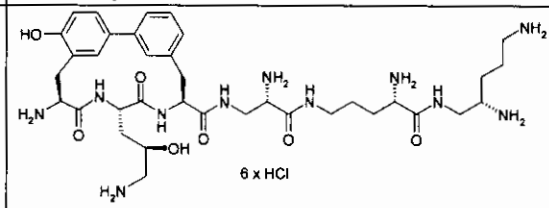
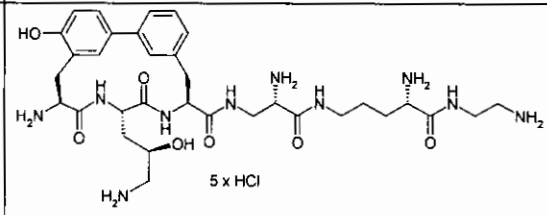
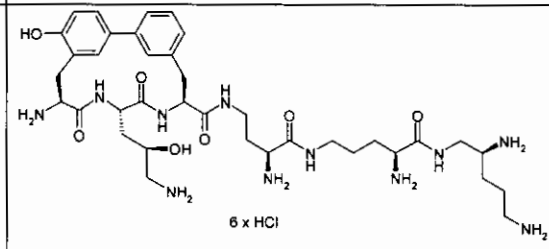
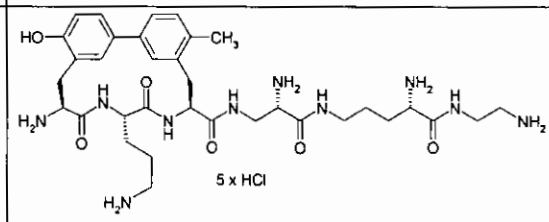
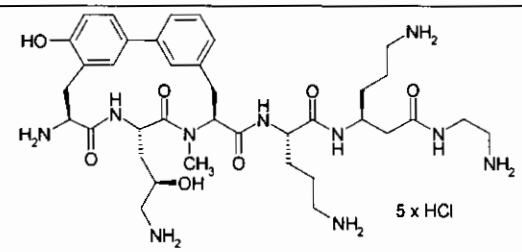
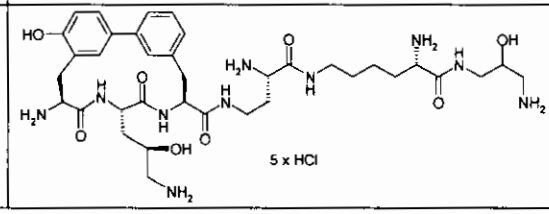
Example No.	Precursor Example	Structure	Analytical Data
56	244A		LC-MS (Method 10): R_t = 1.86 min MS (ESI): m/z = 741 $(M-4HCl+H)^+$.
57	245A		LC-MS (Method 10): R_t = 1.96 min MS (ESI): m/z = 739 $(M-4HCl+H)^+$.
58	246A		LC-MS (Method 10): R_t = 2.10 min MS (ESI): m/z = 739 $(M-4HCl+H)^+$.
59	247A		LC-MS (Method 10): R_t = 1.87 min MS (ESI): m/z = 725 $(M-4HCl+H)^+$.

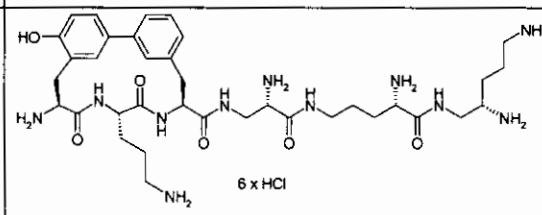
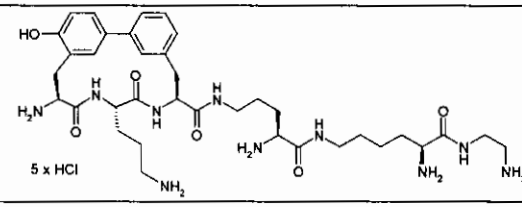
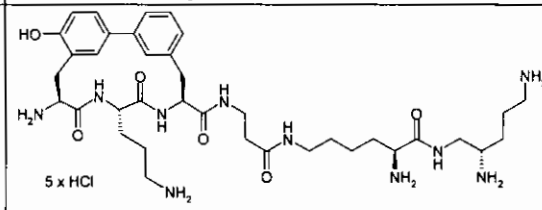
Example No.	Precursor Example	Structure	Analytical Data
60	248A		LC-MS (Method 3): R_t = 0.25 min MS (ESI): m/z = 699 (M-5HCl+H)$^+$.
61	249A		LC-MS (Method 2): R_t = 0.28 min MS (ESI): m/z = 711 (M-5HCl+H)$^+$.
62	250A		LC-MS (Method 2): R_t = 0.28 min MS (ESI): m/z = 741 (M-5HCl+H)$^+$.
63	251A		LC-MS (Method 2): R_t = 0.24 min MS (ESI): m/z = 741 (M-5HCl+H)$^+$.
64	252A		LC-MS (Method 2): R_t = 0.28 min MS (ESI): m/z = 683 (M-5HCl+H)$^+$.

Example No.	Precursor Example	Structure	Analytical Data
65	253A		LC-MS (Method 2): R_t = 0.28 min MS (ESI): m/z = 699 $(M-5HCl+H)^+$.
66	254A		LC-MS (Method 10): R_t = 1.88 min MS (ESI): m/z = 725 $(M-4HCl+H)^+$.
67	255A		LC-MS (Method 2): R_t = 0.29 min MS (ESI): m/z = 668 $(M-5HCl+H)^+$. ^{1}H-NMR (400 MHz, D_2O): δ = 1.55-1.95 (m, 12H), 2.24 (s, 3H), 2.8-3.2 (m, 9H), 3.3-3.7 (m, 4H), 4.33 (m_c, 1H), 4.46 (m_c, 1H), 4.63 (m_c, 1H), 4.94 (m_c, 1H), 6.94 (d, 1H), 7.07 (s, 1H), 7.25 (d, 1H), 7.30 (s, 1H), 7.45 (d, 1H), 7.55 (d, 1H)
68	256A		LC-MS (Method 2): R_t = 0.27 min MS (ESI): m/z = 641 $(M-4HCl+H)^+$. ^{1}H-NMR (400 MHz, D_2O): δ = 1.55-1.95 (m, 6H), 2.49 (m, 2H), 2.8-3.8 (m, 13H), 3.96 (m_c, 1H), 4.46 (m_c, 1H), 5.11 (m_c, 1H), 5.61 (m_c, 1H), 6.92-7.02 (m, 2H), 7.10 (s, 1H), 7.18 (d, 1H), 7.36 (t, 1H), 7.49 (d, 1H), 7.55 (d, 1H)

Example No.	Precursor Example	Structure	Analytical Data
69	257A		LC-MS (Method 2): R_t = 0.20 min MS (ESI): m/z = 796 (M-6HCl+H)$^+$. ^{1}H-NMR (400 MHz, D_2O): δ = 1.3-1.95 (m, 18H), 2.23 (s, 3H), 2.8-3.8 (m, 17H), 3.98 (m_c, 1H), 4.26 (m_c, 1H), 4.46 (m_c, 1H), 4.63 (m_c, 1H), 4.93 (m_c, 1H), 6.94 (d, 1H), 7.07 (s, 1H), 7.25 (d, 1H), 7.28 (s, 1H), 7.44 (td 1H), 7.54 (d, 1H).
70	258A		LC-MS (Method 2): R_t = 0.25 min MS (ESI): m/z = 741 (M-5HCl+H)$^+$.
71	259A		LC-MS (Method 10): R_t = 0.86 min MS (ESI): m/z = 798 (M-6HCl+H)$^+$.
72	260A		LC-MS (Method 2): R_t = 0.15 min MS (ESI): m/z = 782 (M-6HCl+H)$^+$. ^{1}H-NMR (400 MHz, D_2O): δ = 1.3-1.95 (m, 18H), 2.8-3.8 (m, 17H), 3.97 (m_c, 1H), 4.26 (m_c, 1H), 4.46 (m_c, 1H), 4.6-4.9 (m, 2H, under D_2O), 6.95 (d, 1H), 6.99 (s, 1H), 7.16 (d, 1H), 7.29-7.39 (m, 2H), 7.4-7.5 (m, 2H).
73	261A		LC-MS (Method 2): R_t = 0.15 min MS (ESI): m/z = 754 (M-6HCl+H)$^+$.

Example No.	Precursor Example	Structure	Analytical Data
74	262A		LC-MS (Method 2): R_t = 0.2 min MS (ESI): m/z = 755 (M-5HCl+H)$^+$.
75	263A		LC-MS (Method 2): R_t = 0.2 min MS (ESI): m/z = 753 (M-5HCl+H)$^+$.
76	264A		LC-MS (Method 2): R_t = 0.2 min MS (ESI): m/z = 768 (M-6HCl+H)$^+$.
77	265A		LC-MS (Method 2): R_t = 0.2 min MS (ESI): m/z = 784 (M-6HCl+H)$^+$.
78	266A		LC-MS (Method 2): R_t = 0.26 min MS (ESI): m/z = 725 (M-5HCl+H)$^+$.
79	280A		LC-MS (Method 2): R_t = 0.2 min MS (ESI): m/z = 685 (M-5HCl+H)$^+$.

Example No.	Precursor Example	Structure	Analytical Data
80	281A		LC-MS (Method 2): R_t = 0.2 min MS (ESI): m/z = 771 (M-5HCl+H)$^+$.
81	269A		LC-MS (Method 2): R_t = 0.2 min MS (ESI): m/z = 756 (M-6HCl+H)$^+$.
82	270A		LC-MS (Method 2): R_t = 0.2 min MS (ESI): m/z = 699 (M-5HCl+H)$^+$.
83	271A		LC-MS (Method 2): R_t = 0.2 min MS (ESI): m/z = 770 (M-6HCl+H)$^+$.
84	279A		LC-MS (Method 2): R_t = 0.2 min MS (ESI): m/z = 739 (M-5HCl+H)$^+$.
85	273A		LC-MS (Method 2): R_t = 0.26 min MS (ESI): m/z = 755 (M-5HCl+H)$^+$.
86	274A		LC-MS (Method 2): R_t = 0.2 min MS (ESI): m/z = 757 (M-5HCl+H)$^+$.

Example No.	Precursor Example	Structure	Analytical Data
87	275A		LC-MS (Method 2): R_t = 0.2 min MS (ESI): m/z = 740 (M-6HCl+H)$^+$.
88	278A		LC-MS (Method 2): R_t = 0.2 min MS (ESI): m/z = 725 (M-5HCl+H)$^+$.
89	277A		LC-MS (Method 2): R_t = 0.2 min MS (ESI): m/z = 739 (M-5HCl+H)$^+$.

Assessment of the physiological activity

Abbreviations used:

AMP	adenosine monophosphate
ATP	adenosine triphosphate
BHI medium	brain heart infusion medium
CoA	coenzyme A
DMSO	dimethyl sulfoxide
DTT	dithiothreitol
EDTA	ethylenediaminetetraacetic acid
KCl	potassium chloride
KH_2PO_4	potassium dihydrogen phosphate
$MgSO_4$	magnesium sulfate
MIC	minimum inhibitory concentration
MTP	microtiter plate
NaCl	sodium chloride
Na_2HPO_4	disodium hydrogen phosphate
NH_4Cl	ammonium chloride
NTP	nucleotide triphosphate
PBS	phosphate-buffered saline
PCR	polymerase chain reaction
PEG	polyethylene glycol
PEP	phosphoenolpyruvate
Tris	tris[hydroxymethyl)aminomethane

The *in vitro* effect of the compounds of the invention can be shown in the following assays:

In vitro transcription-translation with _E. coli_ extracts

In order to prepare an S30 extract logarithmically growing *Escherichia coli* MRE 600 (M. Müller; Freiburg University) are harvested, washed and employed it as described for the *in vitro* transcription-translation test (Müller, M. and Blobel, G. Proc Natl Acad Sci USA (1984) 81, pp. 7421-7425).

1 µl of cAMP (11.25 mg/ml) are additionally added per 50 µl of reaction mix to the reaction mix of the *in vitro* transcription-translation tests. The test mixture amounts to 105 µl, with 5 µl of the substance to be tested being provided in 5% DMSO. 1 µg/100 µl of mixture of the plasmid pBESTLuc (Promega, Germany) are used as transcription template. After incubation at 30°C for 60 min, 50 µl of luciferin solution (20 mM tricine, 2.67 mM $MgSO_4$, 0.1 mM EDTA, 33.3 mM DTT pH 7.8, 270 µM CoA, 470 µM luciferin, 530 µM ATP) are added, and the resulting bioluminescence is measured in a luminometer for 1 minute. The concentration of an inhibitor which leads to a 50% inhibition of the translation of firefly luciferase is reported as the IC_{50}.

In vitro transcription-translation with _S. aureus_ extracts

Construction of an _S. aureus_ luciferase reporter plasmid

For the construcktion of a reporter plasmid which can be used in an *in vitro* transcription-translation assay from *S. aureus* the plasmid pBESTluc (Promega Corporation, USA) is used. The *E. coli tac* promoter present in this plasmid in front of the firefly luciferase is replaced by the *capA1* promoter with corresponding Shine-Dalgarno sequence from *S. aureus*. The primers CAPFor 5'-CGGCCAAGCTTACTCGGATCC-AGAGTTTGCAAAATATACAGGGGATTATATATAATGGAAAACAAGAAAGGAA AATAG-GAGGTTTATATGGAAGACGCCA-3' and CAPRev 5'-GTCATCGTCGGGAAGACCTG-3' are used for this. The primer CAPFor contains the *capA1* promoter, the ribosome binding site and the 5' region of the luciferase gene. After PCR using pBESTluc as template it is possible to isolate a PCR product which contains the firefly luciferase gene with the fused *capA1* promoter. This is, after restriction with ClaI and HindIII, ligated into the vector pBESTluc which has likewise been digested with ClaI and HindIII. The resulting plasmid p1a can be replicated in *E. coli* and be used as template in the *S. aureus in vitro* transcription-translation test.

Preparation of S30 extracts from _S. aureus_

Six litres of BHI medium are inoculated with a 250 ml overnight culture of an S. aureus strain and allowed to grow at 37°C until the OD600 nm is 2-4. The cells are harvested by centrifugation and washed in 500 ml of cold buffer A (10 mM Tris acetate, pH 8.0, 14 mM magnesium acetate, 1 mM DTT, 1 M KCl). After renewed centrifugation, the cells are washed in 250 ml of cold buffer A with 50 mM KCl, and the resulting pellets are frozen at -20°C for 60 min. The pellets are thawed on ice in 30 to 60 min and taken up to a total volume of 99 ml in buffer B (10 mM Tris acetate, pH 8.0, 20 mM magnesium acetate, 1 mM DTT, 50 mM KCl). 1.5 ml portions of lysostaphin (0.8 mg/ml) in buffer B are provided in 3 precooled centrifuge cups and each mixed with 33 ml of the cell suspension. The samples are incubated at 37°C, shaking occasionally, for 45 to 60 min, before 150 µl of a 0.5 M DTT solution are added. The lysed cells are centrifuged at 30 000 × g and 4°C for 30 min. The cell pellet is taken up in buffer B and then centrifuged again under the same conditions, and the collected supernatants are combined. The supernatants are centrifuged again under the same conditions, and 0.25 volumes of buffer C (670 mM Tris acetate, pH 8.0, 20 mM magnesium acetate, 7 mM Na_3 phosphoenolpyruvate, 7 mM DTT, 5.5 mM ATP, 70 µM amino acids (complete from Promega), 75 µg of pyruvate kinase (Sigma, Germany)/ml are added to the upper 2/3 of the supernatant. The samples are incubated at 37°C for 30 min. The supernatants are dialysed against 2 l of dialysis buffer (10 mM Tris acetate, pH 8.0, 14 mM magnesium acetate, 1 mM DTT, 60 mM potassium acetate) in a dialysis tube with a 3500 Da cut-off with one buffer change at 4°C overnight. The dialysate is concentrated to a protein concentration of about 10 mg/ml by covering the dialysis tube with cold PEG 8000 powder (Sigma, Germany) at 4°C. The S30 extracts can be stored in aliquots at –70°C.

Determination of the IC_{50} in the *S. aureus in vitro* transcription-translation assay

The inhibition of protein biosynthesis of the compounds can be shown in an *in vitro* transcription-translation assay. The assay is based on the cell-free transcription and translation of firefly luciferase using the reporter plasmid p1a as template and cell-free S30 extracts obtained from *S. aureus*. The activity of the resulting luciferase can be detected by luminescence measurement.

The amount of S30 extract or plasmid p1a to be employed must be tested anew for each preparation in order to ensure an optimal concentration in the test. 3 µl of the substance to be tested, dissolved in 5% DMSO, are introduced into an MTP. Then 10 µl of a suitably concentrated plasmid solution p1a are added. Then 46 µl of a mixture of 23 µl of premix (500 mM potassium acetate, 87.5 mM Tris acetate, pH 8.0, 67.5 mM ammonium acetate, 5 mM DTT, 50 µg of folic acid/ml, 87.5 mg of PEG 8000/ml, 5 mM ATP, 1.25 mM of each NTP, 20 µM of each amino acid, 50 mM PEP (Na_3 salt), 2.5 mM cAMP, 250 µg of each *E. coli* tRNA/ml) and 23 µl of a suitable amount of *S. aureus* S30 extract are added and mixed. After incubation at 30°C for 60 min, 50 µl of luciferin solution (20 mM tricine, 2.67 mM $MgSO_4$, 0.1 mM EDTA, 33.3 mM DTT pH 7.8, 270 µM CoA, 470 µM luciferin, 530 µM ATP) are, and the resulting bioluminescence is measured in a luminometer for

1 min. The concentration of an inhibitor which leads to a 50% inhibition of the translation of firefly luciferase is reported as the IC_{50}.

Determination of the minimum inhibitory concentration (CLSI Standard)

The minimum inhibitory concentration (MIC) is the minimum concentration of an antibiotic with which the growth of a test microbe is inhibited over 18-24 h. The inhibitor concentration can in these cases be determined by standard microbiological methods (see, for example, The National Committee for Clinical Laboratory Standards. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard-fifth edition. NCCLS document M7-A5 [ISBN 1-56238-394-9]. NCCLS, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA, 2000). The test substances are thereby initially provided in 1:2 dilution series into 96-well round-bottom microtiter plates (Greiner) double-concentrated in 50 µl of test medium. The aerobically growing test microbes (e.g. staphylococci and enterococci), which are incubated overnight on Columbia blood agar plates (Becton-Dickinson), are, after resuspension in 0.9% NaCl, adjusted to a microbe count of about 5×10^7 microbes/ml and then diluted 1:150 in cation-adjusted MH medium (test medium). 50 µl of this suspension are pipetted onto the test preparations provided in the microtiter plates. The cultures are incubated at 37°C for 18-24 hours. For microaerophilically growing microbes (e.g. streptococci), 2% lysed horse blood in the final concentration is added to the medium and the cultures are incubated in the presence of 5% CO_2. The lowest substance concentration in each case at which no visible bacterial growth occurs any longer is defined as the MIC and is reported in µg/ml.

Determination of the minimum inhibitory concentration (MIC)

The minimum inhibitory concentration (MIC) is the minimum concentration of an antibiotic with which the growth of a test microbe is inhibited over 18-24 h. The inhibitor concentration can in these cases be determined by standard microbiological methods (see, for example, The National Committee for Clinical Laboratory Standards. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard-fifth edition. NCCLS document M7-A5 [ISBN 1-56238-394-9]. NCCLS, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA, 2000). The MIC of the compounds of the invention is determined in the liquid dilution test on the 96-well microtitre plate scale. The bacterial microbes are cultivated in a minimal medium (18.5 mM Na_2HPO_4, 5.7 mM KH_2PO_4, 9.3 mM NH_4Cl, 2.8 mM $MgSO_4$, 17.1 mM NaCl, 0.033 µg/ml thiamine hydrochloride, 1.2 µg/ml nicotinic acid, 0.003 µg/ml biotin, 1% glucose, 25 µg/ml of each proteinogenic amino acid with the exception of phenylalanine; [H.-P. Kroll; unpublished]) with the addition of 0.4% BH broth (test medium). In the case of *Enterococcus faecium* L4001, heat-inactivated fetal calf serum (FCS; GibcoBRL, Germany) is added to the test medium in a final concentration of 10%. Overnight cultures of the test microbes are diluted to an OD_{578} of 0.001 (to 0.01 in the case of enterococci) in fresh test medium, and incubated 1:1 with dilutions of the test substances (1:2 dilution

steps) in test medium (200 µl final volume). The cultures are incubated at 37°C for 18-24 hours; enterococci in the presence of 5% CO_2.

The lowest substance concentration in each case at which no visible bacterial growth occurs any longer is defined as the MIC.

Alternative method for determining the minimum inhibitory concentration (MIC)

The minimum inhibitory concentration (MIC) is the minimum concentration of an antibiotic with which the growth of a test microbe is inhibited over 18-24 h. The inhibitor concentration can in these cases be determined by standard microbiological methods with modified medium in an agar dilution test (see, for example, The National Committee for Clinical Laboratory Standards. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard-fifth edition. NCCLS document M7-A5 [ISBN 1-56238-394-9]. NCCLS, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA, 2000). The bacterial microbes are cultivated on 1.5% agar plates which contain 20% defibrinated horse blood. The test microbes, which are incubated overnight on Columbia blood agar plates (Becton-Dickinson), are diluted in PBS, adjusted to a microbe count of about 5×10^5 microbes/ml and placed dropwise (1-3 µl) on test plates. The test substances comprise different dilutions of the test substances (1:2 dilution steps). The cultures are incubated at 37°C in the presence of 5% CO_2 for 18-24 hours.

The lowest substance concentration in each case at which no visible bacterial growth occurs any longer is defined as the MIC and is reported in µg/ml.

Table A (with comparative example biphenomycin B)

Ex. No.	MIC *S. aureus* 133	MIC *S. aureus* T17	MIC *E. faecium* L4001	IC_{50} *S. aureus* 133 Translation
1	0.5	1.0	4.0	0.07
2	1.0	1.0	2.0	0.07
3	2.0	2.0	16.0	0.2
5	1.0	1.0	2.0	0.2
12	1.0	1.0	16.0	0.08
15	1.0	2.0	>32	0.1
19	1.0	1.0	16.0	0.1
67	1.0	1.0	16	0.1
68	1.0	1.0	8	0.2
Biphenomycin B	<0.03	>32	0.5	1.5

Concentration data: MIC in μg/ml; IC_{50} in μM.

Systemic infection with *S. aureus* 133

The suitability of the compounds of the invention for treating bacterial infections can be shown in various animal models. For this purpose, the animals are generally infected with a suitable virulent microbe and then treated with the compound to be tested, which is in a formulation which is adapted to the particular therapy model. The suitability of the compounds of the invention for the treatment of bacterial infections can be demonstrated specifically in a mouse sepsis model after infection with *S. aureus*.

For this purpose, *S. aureus* 133 cells are cultured overnight in BH broth (Oxoid, Germany). The overnight culture was diluted 1:100 in fresh BH broth and expanded for 3 hours. The bacteria which are in the logarithmic phase of growth are centrifuged and washed twice with a buffered physiological saline solution. A cell suspension in saline solution with an extinction of 50 units is then adjusted in a photometer (Dr Lange LP 2W). After a dilution step (1:15), this suspension is mixed 1:1 with a 10% mucine suspension. 0.2 ml of this infection solution is administered i.p. per 20 g of mouse. This corresponds to a cell count of about $1\text{-}2\times10^6$ microbes/mouse. The i.v. therapy takes place 30 minutes after the infection. Female CFW1 mice are used for the infection experiment. The survival of the animals is recorded for 6 days. The animal model is adjusted so that untreated animals die within 24 h after the infection. It was possible to demonstrate in this model a therapeutic effect of ED_{100} = 1.25 mg/kg for the compound of Example 2.

Determination of the rates of spontaneous resistance to *S. aureus*

The spontaneous resistance rates for the compounds of the invention are determined as follows: the bacterial microbes are cultivated in 30 ml of a minimal medium (18.5 mM Na_2HPO_4, 5.7 mM KH_2PO_4, 9.3 mM NH_4Cl, 2.8 mM $MgSO_4$, 17.1 mM NaCl, 0.033 μg/ml thiamine hydrochloride, 1.2 μg/ml nicotinic acid, 0.003 μg/ml biotin, 1% glucose, 25 μg/ml of each proteinogenic amino acid with the addition of 0.4% BH broth) at 37°C overnight, centrifuged at 6000×g for 10 min and resuspended in 2 ml of a phosphate-buffered physiological NaCl solution (about 2×10^9 microbes/ml). 100 μl of this cell suspension, and 1:10 and 1:100 dilutions, are plated out on predried agar plates (1.5% agar, 20% defibrinated horse blood, or 1.5% agar, 20% bovine serum in 1/10 Müller-Hinton medium diluted with PBS) which contain the compound of the invention to be tested in a concentration equivalent to 5×MIC or 10×MIC, and incubated at 37°C for 48 h. The resulting colonies (cfu) are counted.

Isolation of the biphenomycin-resistant *S. aureus* strains RN4220Bi^R and T17

The *S. aureus* strain RN4220Bi^R is isolated *in vitro*. For this purpose, 100 µl portions of an *S. aureus* RN4220 cell suspension (about 1.2×10^8 cfu/ml) are plated out on an antibiotic-free agar plate (18.5 mM Na_2HPO_4, 5.7 mM KH_2PO_4, 9.3 mM NH_4Cl, 2.8 mM $MgSO_4$, 17.1 mM NaCl, 0.033 µg/ml thiamine hydrochloride, 1.2 µg/ml nicotinic acid, 0.003 µg/ml biotin, 1% glucose, 25 µg/ml of each proteinogenic amino acid with the addition of 0.4% BH broth and 1% agarose) and on an agar plate containing 2 µg/ml biphenomycin B (10×MIC), and incubated at 37°C overnight. Whereas about 1×10^7 cells grow on the antibiotic-free plate, about 100 colonies grow on the antibiotic-containing plate, corresponding to a resistance rate of 1×10^{-5}. Some of the colonies grown on the antibiotic-containing plate are tested for the biphenomycin B MIC. One colony with an MIC of > 50 µM is selected for further use, and the strain is referred to as RN4220Bi^R.

The *S. aureus* strain T17 is isolated *in vivo*. CFW1 mice are infected intraperitoneally with 4×10^7 *S. aureus* 133 cells per mouse. 0.5 h after the infection, the animals are treated intravenously with 50 mg/kg biphenomycin B. The kidneys are removed from the surviving animals on day 3 after the infection. After homogenization of the organs, the homogenates are plated out as described for RN4220Bi^R on antibiotic-free and antibiotic-containing agar plates and incubated at 37°C overnight. About half the colonies isolated from the kidney show growth on the antibiotic-containing plates (2.2×10^6 colonies), demonstrating the accumulation of biphenomycin B-resistant *S. aureus* cells in the kidney of the treated animals. About 20 of these colonies are tested for the biphenomycin B MIC, and a colony with a MIC of > 50 µM is selected for further cultivation, and the strain is referred to as T17.

B. Exemplary embodiments of pharmaceutical compositions

The compounds of the invention can be converted into pharmaceutical preparations in the following way:

Solution which can be administered intravenously:

Composition:

1 mg of the compound of Example 1, 15 g of polyethylene glycol 400 and 250 g of water for injections.

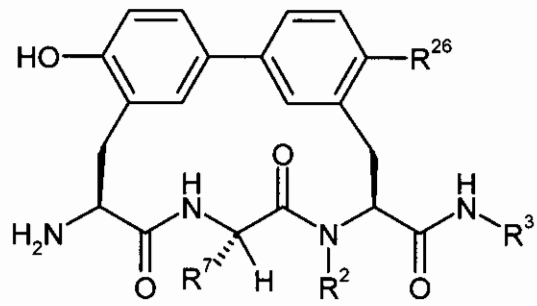
Preparation:

The compound of the invention is dissolved together with polyethylene glycol 400 in the water with stirring. The solution is sterilized by filtration (pore diameter 0.22 μm) and dispensed under aseptic conditions into heat-sterilized infusion bottles. These are closed with infusion stoppers and crimped caps.

WHAT IS CLAIMED IS:

CLAIMS

1. A compound of formula

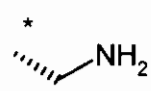


(I),

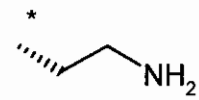
in which

R^{26} represents hydrogen, halogen, amino or methyl,

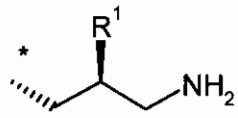
R^7 represents a group of formula



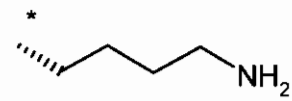
,



,



or



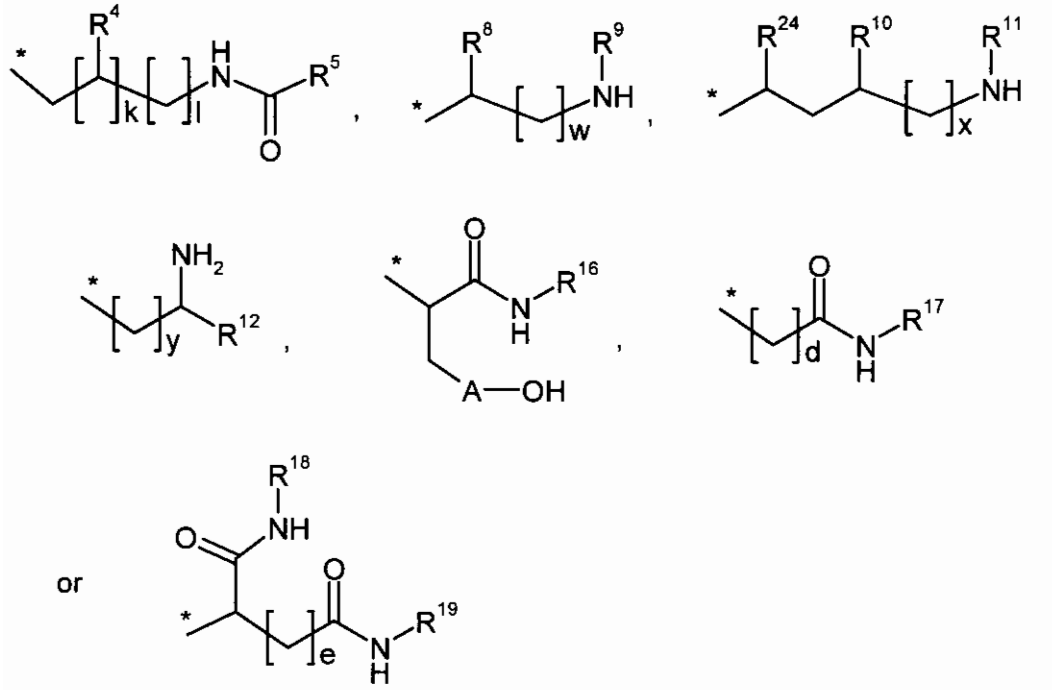
whereby

R^1 represents hydrogen or hydroxy,

* is the linkage site to the carbon atom,

R^2 represents hydrogen or methyl,

R^3 represents a group of formula



or

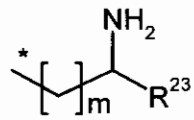
whereby

* is the linkage site to the nitrogen atom,

A represents a bond or phenyl,

R^4 represents hydrogen, amino or hydroxy,

R^5 represents a group of formula



wherein

* is the linkage site to the carbon atom,

R^{23} represents hydrogen or a group of formula *–$(CH_2)_n$-OH or *-$(CH_2)_o$-NH_2,

wherein

* is the linkage site to the carbon atom,

n and o independently of one another are a number 1, 2, 3 or 4,

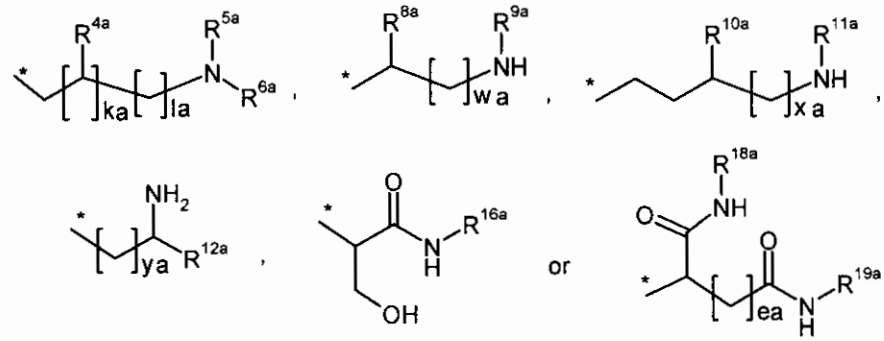
m is a number 0 or 1,

R^8 and R^{12} independently of one another represent a group of formula *–$CONHR^{14}$ or *-CH_2CONHR^{15},

wherein

* is the linkage site to the carbon atom,

R^{14} and R^{15} independently of one another represent a group of formula



wherein

* is the linkage site to the nitrogen atom,

R^{4a} represents hydrogen, amino or hydroxy,

R^{5a} represents hydrogen, methyl or aminoethyl,

R^{6a} represents hydrogen or aminoethyl,

or

R^{5a} and R^{6a} together with the nitrogen atom to which they are bonded form a piperazine ring,

R^{8a} and R^{12a} independently of one another represent *–$(CH_2)_{Z1a}$-OH, *-$(CH_2)_{Z2a}$-NHR^{13a}, *–$CONHR^{14a}$ or *-CH_2CONHR^{15a},

wherein

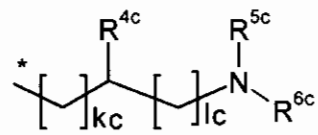
* is the linkage site to the carbon atom,

Z1a and Z2a independently of one another are a number 1, 2 or 3,

R^{13a} represents hydrogen or methyl,

and

R^{14a} and R^{15a} independently of one another represent a group of formula



wherein

* is the linkage site to the nitrogen atom,

R^{4c} represents hydrogen, amino or hydroxy,

R^{5c} represents hydrogen, methyl or aminoethyl,

R^{6c} represents hydrogen or aminoethyl,

kc is a number 0 or 1,

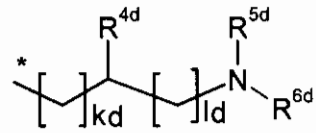
and

lc is a number 1, 2, 3 or 4,

R^{9a} and R^{11a} independently of one another represent hydrogen or methyl,

R^{10a} represents amino or hydroxy,

R^{16a} represents a group of formula



wherein

* is the linkage site to the nitrogen atom,

R^{4d} represents hydrogen, amino or hydroxy,

R^{5d} represents hydrogen, methyl or aminoethyl,

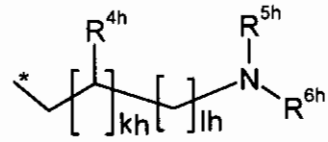
R^{6d} represents hydrogen or aminoethyl,

kd is a number 0 or 1,

and

ld is a number 1, 2, 3 or 4,

R^{18a} and R^{19a} independently of one another represent hydrogen or a group of formula



wherein

* is the linkage site to the nitrogen atom,

R^{4h} represents hydrogen, amino or hydroxy,

R^{5h} represents hydrogen, methyl or aminoethyl,

R^{6h} represents hydrogen or aminoethyl,

or

R^{5h} and R^{6h} together with the nitrogen atom to which they are bonded form a piperazine ring,

kh is a number 0 or 1

and

lh is a number 1, 2, 3 or 4,

whereby R^{18a} and R^{19a} are not simultaneously hydrogen,

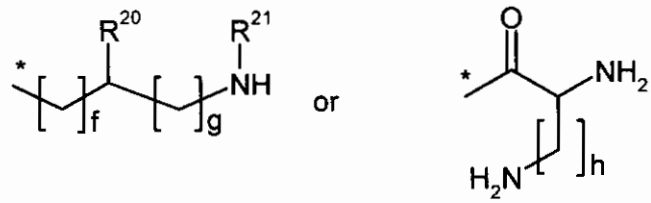
ka is a number 0 or 1,

ea is a number 1, 2 or 3,

and

la, wa, xa and ya independently of one another are a number 1, 2, 3 or 4,

R^9 and R^{11} independently of one another represent hydrogen, methyl, *–$C(NH_2)$=NH or a group of formula



wherein

* is the linkage site to the nitrogen atom,

R^{20} represents hydrogen or *–$(CH_2)_i$-NHR^{22},

wherein

R^{22} represents hydrogen or methyl,

and

i is a number 1, 2 or 3,

R^{21} represents hydrogen or methyl,

f is a number 0, 1, 2 or 3,

g is a number 1, 2 or 3,

and

h is a number 1, 2, 3 or 4,

or

R^8 represents *–$(CH_2)_{Z1}$-OH,

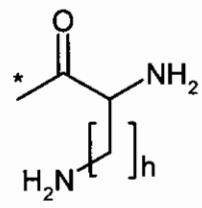
wherein

* is the linkage site to the carbon atom,

Z1 is a number 1, 2 or 3,

and

R^9 is a group of formula



wherein

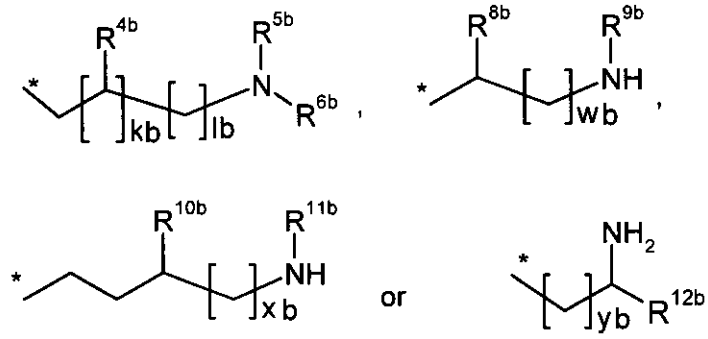
* is the linkage site to the nitrogen atom,

and

h is a number 1, 2, 3 or 4,

R^{10} represents amino or hydroxy,

R^{16} and R^{17} independently of one another represent a group of formula



wherein

* is the linkage site to the nitrogen atom,

R^{4b} represents hydrogen, amino or hydroxy,

R^{5b} represents hydrogen, methyl or aminoethyl,

R^{6b} represents hydrogen or aminoethyl,

or

R^{5b} and R^{6b} together with the nitrogen atom to which they are bonded form a piperazine ring,

R^{8b} and R^{12b} independently of one another represent *-$(CH_2)_{z1b}$-OH, *-$(CH_2)_{z2b}$-NHR^{13b}, *-$CONHR^{14b}$ or *-CH_2CONHR^{15b},

wherein

* is the linkage site to the carbon atom,

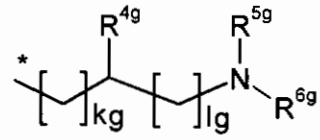
R^{13b} represents hydrogen or methyl,

and

Z1b and Z2b independently of one another are a number 1, 2 or 3,

and

R^{14b} and R^{15b} independently of one another represent a group of formula



wherein

* is the linkage site to the nitrogen atom,

R^{4g} represents hydrogen, amino or hydroxy,

R^{5g} represents hydrogen, methyl or aminoethyl,

R^{6g} represents hydrogen or aminoethyl,

kg is a number 0 or 1,

and

lg is a number 1, 2, 3 or 4,

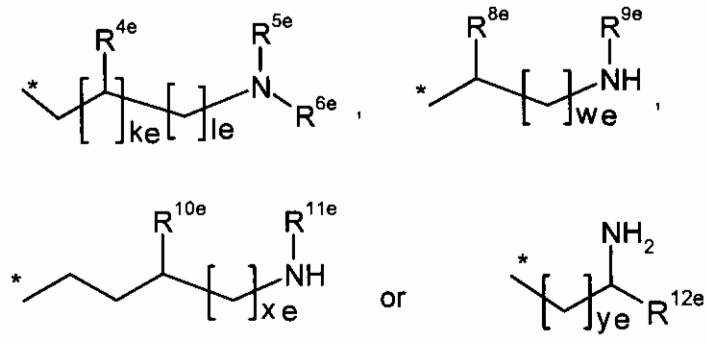
R^{9b} and R^{11b} independently of one another represent hydrogen or methyl,

R^{10b} represents amino or hydroxy,

kb is a number 0 or 1,

lb, wb, xb and yb independently of one another are a number 1, 2, 3 or 4,

R^{18} and R^{19} independently of one another represent hydrogen or a group of formula



wherein

* is the linkage site to the nitrogen atom,

R^{4e} represents hydrogen, amino or hydroxy,

R^{5e} represents hydrogen, methyl or aminoethyl,

R^{6e} represents hydrogen or aminoethyl,

or

R^{5e} and R^{6e} together with the nitrogen atom to which they are bonded form a piperazine ring,

R^{8e} and R^{12e} independently of one another represent *–$(CH_2)_{Z1e}$-OH or *-$(CH_2)_{Z2e}$-NHR^{13e},

wherein

* is the linkage site to the carbon atom,

R^{13e} represents hydrogen or methyl,

and

Z1e and Z2e independently of one another are a number 1, 2 or 3,

R^{9e} and R^{11e} independently of one another represent hydrogen or methyl,

R^{10e} represents amino or hydroxy,

ke is a number 0 or 1,

and

le, we, xe and ye independently of one another are a number 1, 2, 3 or 4,

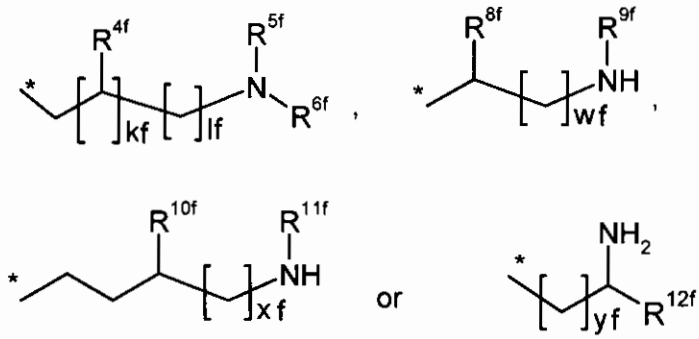
whereby R^{18} and R^{19} are not simultaneously hydrogen,

R^{24} represents a group of formula *–$CONHR^{25}$,

wherein

* is the linkage site to the carbon atom,

R^{25} represents a group of formula



wherein

* the linkage site to the nitrogen atom,

R^{4f} represents hydrogen, amino or hydroxy,

R^{5f} represents hydrogen, methyl or aminoethyl,

R^{6f} represents hydrogen or aminoethyl,

or

R^{5f} and R^{6f} together with the nitrogen atom to which they are bonded form a piperazine ring,

R^{8f} and R^{12f} independently of one another represent *–$(CH_2)_{Z1f}$-OH or *-$(CH_2)_{Z2f}$-NHR^{13f},

wherein

* is the linkage site to the carbon atom,

R^{13f} represents hydrogen or methyl,

and

Z1f and Z2f independently of one another are a number 1, 2 or 3,

R^{9f} and R^{11f} independently of one another represent hydrogen or methyl,

R^{10f} represents amino or hydroxy,

kf is a number 0 or 1,

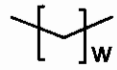
and

lf, wf, xf yf independently of one another are and a number 1, 2, 3 or 4,

d and e independently of one another are a number 1, 2 or 3,

k is a number 0 or 1,

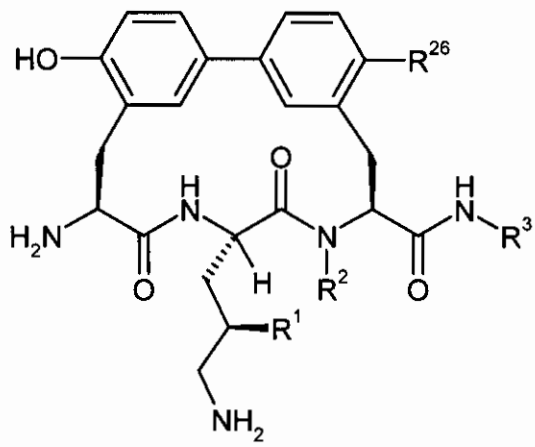
l, w, x and y independently of one another are a number 1, 2, 3 or 4,



independently of one another may when w, x or y equals 3 carry a hydroxy group,

or one of its salts, its solvates or the solvates of its salts.

2. The compound of claim 1, corresponding to formula



(Ia),

in which

R^{26} represents hydrogen, halogen, amino or methyl,

R^1 represents hydrogen or hydroxy,

R^2 represents hydrogen or methyl,

R^3 is as defined in claim 1,

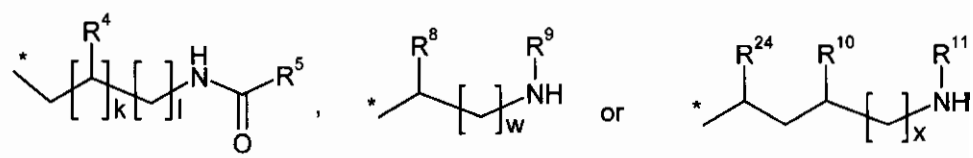
or one of its salts, its solvates or the solvates of its salts.

3. The compound of claim 1, wherein

R^{26} represents hydrogen, chlorine or methyl.

4. The compound according of claim 1, wherein

R^3 represents a group of formula

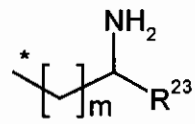


whereby

* is the linkage site to the nitrogen atom,

R^4 represents hydrogen, amino or hydroxy,

R^5 represents a group of formula



wherein

* is the linkage site to the carbon atom,

R^{23} represents hydrogen or a group of formula *–$(CH_2)_n$-OH or *-$(CH_2)_o$-NH_2,

wherein

* is the linkage site to the carbon atom,

n and o independently of one another are a number 1, 2, 3 or 4,

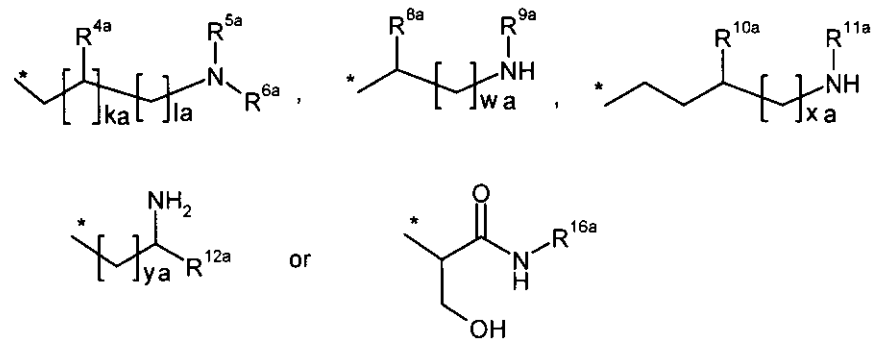
m is a number 0 or 1,

R^8 represents a group of formula *–$CONHR^{14}$ or *-CH_2CONHR^{15},

wherein

* is the linkage site to the carbon atom,

R^{14} and R^{15} independently of one another represent a group of formula



wherein

* is the linkage site to the nitrogen atom,

R^{4a} represents hydrogen, amino or hydroxy,

R^{5a} represents hydrogen, methyl or aminoethyl,

R^{6a} represents hydrogen or aminoethyl,

or

R^{5a} and R^{6a} together with the nitrogen atom to which they are bonded form a piperazine ring,

R^{8a} and R^{12a} independently of one another represent *-$(CH_2)_{z1a}$-OH, *-$(CH_2)_{z2a}$-NHR^{13a}, *-$CONHR^{14a}$ or *-CH_2CONHR^{15a},

wherein

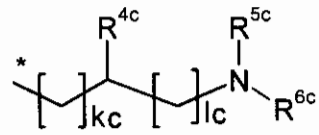
* is the linkage site to the carbon atom,

Z1a and Z2a independently of one another are a number 1, 2 or 3,

R^{13a} represents hydrogen or methyl,

and

R^{14a} and R^{15a} independently of one another represent a group of formula



wherein

* is the linkage site to the nitrogen atom,

R^{4c} represents hydrogen, amino or hydroxy,

R^{5c} represents hydrogen, methyl or aminoethyl,

R^{6c} represents hydrogen or aminoethyl,

kc is a number 0 or 1,

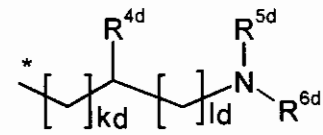
and

lc is a number 1, 2, 3 or 4,

R^{9a} and R^{11a} independently of one another represent hydrogen or methyl,

R^{10a} represents amino or hydroxy,

R^{16a} represents a group of formula



wherein

* is the linkage site to the nitrogen atom,

R^{4d} represents hydrogen, amino or hydroxy,

R^{5d} represents hydrogen, methyl or aminoethyl,

R^{6d} represents hydrogen or aminoethyl,

kd is a number 0 or 1,

and

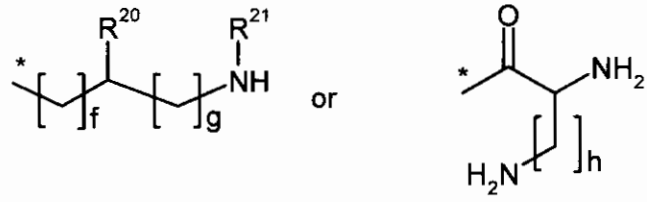
ld is a number 1, 2, 3 or 4,

ka is a number 0 or 1,

and

la, wa, xa and ya independently of one another are a number 1, 2, 3 or 4,

R^9 and R^{11} independently or one another represent hydrogen, methyl, *–$C(NH_2)$=NH or a group of formula



wherein

* is the linkage site to the nitrogen atom,

R^{20} represents hydrogen or *–$(CH_2)_i$-NHR^{22},

wherein

R^{22} represents hydrogen or methyl,

and

i is a number 1, 2 or 3,

R^{21} represents hydrogen or methyl,

f is a number 0, 1, 2 or 3,

g is a number 1, 2 or 3,

and

h is a number 1, 2, 3 or 4,

or

R^8 represents *–$(CH_2)_{Z1}$-OH

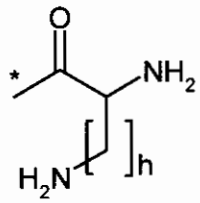
wherein

* is the linkage site to the carbon atom,

Z1 is a number 1, 2 or 3,

and

R^9 represents a group of formula



wherein

* is the linkage site to the nitrogen atom,

and

h is a number 1, 2, 3 or 4,

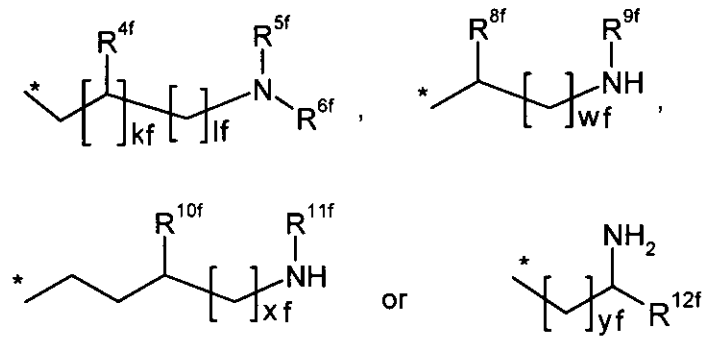
R^{10} represents amino or hydroxy,

R^{24} represents a group of formula *–$CONHR^{25}$,

wherein

* is the linkage site to the carbon atom,

R^{25} represents a group of formula



wherein

* is the linkage site to the nitrogen atom,

R^{4f} represents hydrogen, amino or hydroxy,

R^{5f} represents hydrogen, methyl or aminoethyl,

R^{6f} represents hydrogen or aminoethyl,

or

R^{5f} and R^{6f} together with the nitrogen atom to which they are bonded form a piperazine ring,

R^{8f} and R^{12f} independently of one another represent *–$(CH_2)_{Z1f}$-OH or *-$(CH_2)_{Z2f}$-NHR^{13f},

wherein

* is the linkage site to the carbon atom,

R^{13f} represents hydrogen or methyl,

and

Z1f and Z2f independently of one another are a number 1, 2 or 3,

R^{9f} and R^{11f} independently of one another represent hydrogen or methyl,

R^{10f} represents amino or hydroxy,

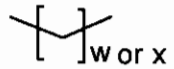
kf is a number 0 or 1,

and

lf, wf, xf and yf independently of one another are a number 1, 2, 3 or 4,

k is a number 0 or 1,

l, w and x independently of one another are a number 1, 2, 3 or 4,

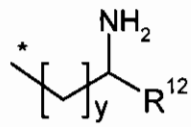


independently of one another may when w or x equals 3 carry a hydroxy group,

or one of its salts, its solvates or the solvates of its salts.

5. The compound of claim 1, wherein

R^3 represents a group of formula



whereby

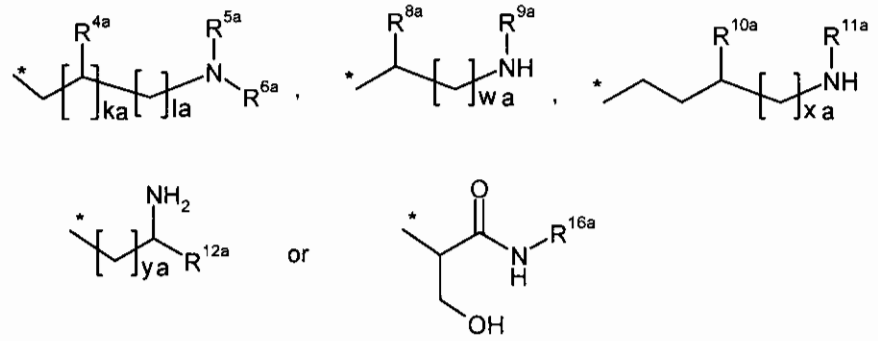
* is the linkage site to the nitrogen atom,

R^{12} represents a group of formula *–CONHR^{14} or *-CH_2CONHR^{15},

wherein

* is the linkage site to the carbon atom,

R^{14} and R^{15} independently of one another represent a group of formula



wherein

* is the linkage site to the nitrogen atom,

R^{4a} represents hydrogen, amino or hydroxy,

R^{5a} represents hydrogen, methyl or aminoethyl,

R^{6a} represents hydrogen or aminoethyl,

or

R^{5a} and R^{6a} together with the nitrogen atom to which they are bonded form a piperazine ring,

R^{8a} and R^{12a} independently of one another represent *–$(CH_2)_{Z1a}$-OH, *-$(CH_2)_{Z2a}$-NHR^{13a}, *–$CONHR^{14a}$ or *-CH_2CONHR^{15a},

wherein

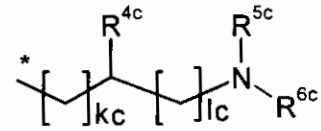
* is the linkage site to the carbon atom,

Z1a and Z2a independently of one another are a number 1, 2 or 3,

R^{13a} represents hydrogen or methyl,

and

R^{14a} and R^{15a} independently of one another represent a group of formula



wherein

* is the linkage site to the nitrogen atom,

R^{4c} represents hydrogen, amino or hydroxy,

R^{5c} represents hydrogen, methyl or aminoethyl,

R^{6c} represents hydrogen or aminoethyl,

kc is a number 0 or 1,

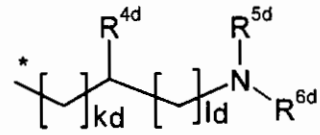
and

lc is a number 1, 2, 3 or 4,

R^{9a} and R^{11a} independently of one another represent hydrogen or methyl,

R^{10a} represents amino or hydroxy,

R^{16a} represents a group of formula



wherein

* is the linkage site to the nitrogen atom,

R^{4d} represents hydrogen, amino or hydroxy,

R^{5d} represents hydrogen, methyl or aminoethyl,

R^{6d} represents hydrogen or aminoethyl,

kd is a number 0 or 1,

and

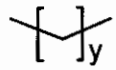
ld is a number 1, 2, 3 or 4,

ka is a number 0 or 1,

and

la, wa, xa and ya independently of one another are a number 1, 2, 3 or 4,

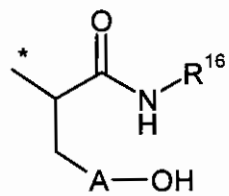
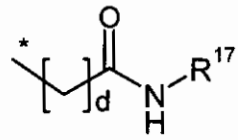
y is a number 1, 2, 3 or 4,

 may when y equals 3 carry a hydroxy group,

or one of its salts, its solvates or the solvates of its salts.

6. The compound of claim 1, wherein

R^3 represents a group of formula

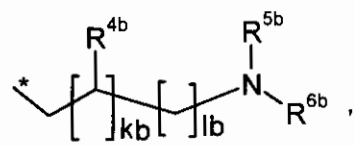
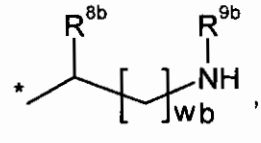
 or 

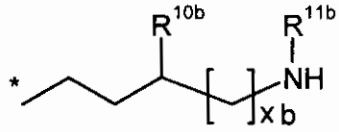
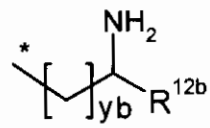
whereby

* is the linkage site to the nitrogen atom,

A represents a bond or phenyl,

R^{16} and R^{17} independently of one another represent a group of formula

 ,  ,

 or 

wherein

* is the linkage site to the nitrogen atom,

R^{4b} represents hydrogen, amino or hydroxy,

R^{5b} represents hydrogen, methyl or aminoethyl,

R^{6b} represents hydrogen or aminoethyl,

or

R^{5b} and R^{6b} together with the nitrogen atom to which they are bonded form a piperazine ring,

R^{8b} and R^{12b} independently of one another represent *–$(CH_2)_{Z1b}$-OH or *-$(CH_2)_{Z2b}$-NHR^{13b},

wherein

* is the linkage site to the carbon atom,

R^{13b} represents hydrogen or methyl,

and

Z1b and Z2b independently of one another are a number 1, 2 or 3,

R^{9b} and R^{11b} independently of one another represent hydrogen or methyl,

R^{10b} represents amino or hydroxy,

kb is a number 0 or 1,

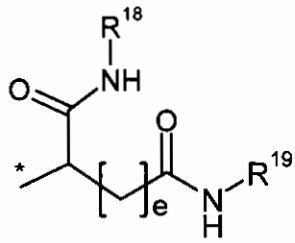
lb, wb, xb and yb independently of one another are a number 1, 2, 3 or 4,

d is a number 1, 2 or 3,

or one of its salts, its solvates or the solvates of its salts.

7. The compound of claim 1, wherein

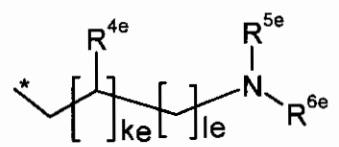
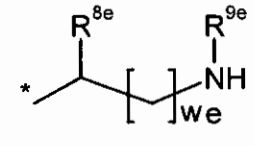
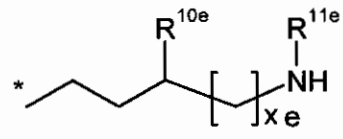
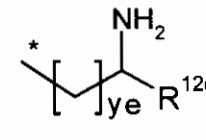
R^3 repesents a group of formula



whereby

* is the linkage site to the nitrogen atom,

R^{18} and R^{19} independently of one another represent hydrogen or a group of fomula


,

,

or


wherein

* is the linkage site to the nitrogen atom,

R^{4e} represents hydrogen, amino or hydroxy,

R^{5e} represents hydrogen, methyl or aminoethyl,

R^{6e} represents hydrogen or aminoethyl,

or

R^{5e} and R^{6e} together with the nitrogen atom to which they are bonded form a piperazine ring,

R^{8e} and R^{12e} independently of one another represent *–$(CH_2)_{Z1e}$-OH or *-$(CH_2)_{Z2e}$-NHR^{13e},

wherein

* is the linkage site to the carbon atom,

R^{13e} represents hydrogen or methyl,

and

Z1e and Z2e independently of one another are a number 1, 2 or 3,

R^{9e} and R^{11e} independently of one another represent hydrogen or methyl,

R^{10e} represents amino or hydroxy,

ke is a number 0 or 1,

and

le, we, xe and ye independently of one another are a number 1, 2, 3 or 4,

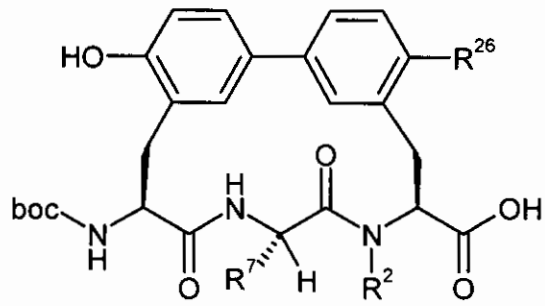
whereby R^{18} and R^{19} are not simultaneously hydrogen,

e is a number 1, 2 or 3,

or one of its salts, its solvates or the solvates of its salts.

8. A method for preparing a compound of formula (I) of claim 1 or one of its salts, solvates or solvates of its salts, wherein

[A] a compound of formula



(II),

wherein R^2, R^7 and R^{26} have the meaning indicated in claim 1, and boc is *tert*-butoxycarbonyl,

is reacted in a two-stage process firstly in the presence of one or more dehydrating reagents with a compound of formula

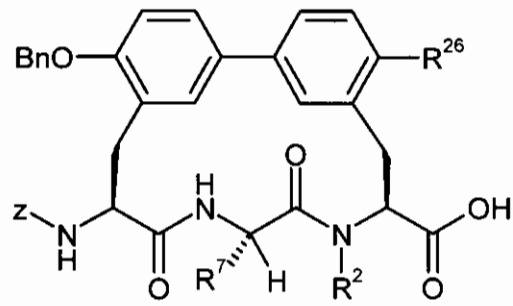
$$H_2NR^3 \qquad \text{(III)},$$

wherein R^3 has the meaning indicated in claim 1,

and subsequently with an acid, by hydrogenolysis, or with an acid and by hydrogenolysis

or

[B] a compound of formula



(IV),

wherein R^2, R^7 and R^{26} have the meaning indicated in claim 1, and Z is benzyloxycarbonyl,

is reacted in a two-stage process firstly in the presence of one or more dehydrating reagents with a compound of formula

$$H_2NR^3 \qquad \text{(III)},$$

wherein R^3 has the meaning indicated in claim 1,

and subsequently with an acid or by hydrogenolysis.

9. A method for preparing a compound of formula (I) of claim 1 or one of its solvates, wherein a salt of said compound or a solvate of a salt of said compound is converted into said compound by chromatography with the addition of a base.

10. The compound of claim 1 for the treatment and/or prophylaxis of diseases.

11. A method for the production of a medicament for the treatment, prophylaxis or treatment and prophylaxis of diseases using a compound of claim 1.

12. A method for the production of a medicament for the treatment, prophylaxis or treatment and prophylaxis of bacterial diseases using a compound of claim 1.

13. A medicament comprising at least one compound of claim 1 in combination with at least one inert, non-toxic, pharmaceutically suitable excipient.

14. The medicament of claim 13 for the treatment, prophylaxis or treatment and prophylaxis of bacterial infections.

15. A method for controlling bacterial infections in humans and animals by administering an antibacterially effective amount of at least one compound of claims1 or of a medicament of claim 13.