(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
27 November 2003 (27.11.2003)

PCT

(10) International Publication Number
WO 03/097668 A2

(51) International Patent Classification[7]: C07K 1/06, 1/113, 1/107, 5/087, 5/09, 7/06

(21) International Application Number: PCT/IN03/00160

(22) International Filing Date: 16 April 2003 (16.04.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
10/153,555 22 May 2002 (22.05.2002) US
460/MUM/2002 24 May 2002 (24.05.2002) IN

(71) Applicants and
(72) Inventors: **CHATURVEDI, Nishith, C.** [US/IN]; Wockhardt Limited, Wockhardt Towers, Bandra-Kurla Complex, Bandra (E), 400 051 MUMBAI (IN). **BERI, Suresh** [IN/IN]; Wockhardt Limited, Wockhardt Towers, Bandra-Kurla Complex, Bandra (E), 400 051 MUMBAI (IN). **YEOLE, Ravindra, D.** [IN/IN]; Wockhardt Limited, Wockhardt Towers, Bandra-Kurla Complex, Bandra (E), 400 051 MUMBAI (IN). **DE SOUZA, Noel, J.** [IN/IN]; Wockhardt Limited, Wockhardt Towers, Bandra-Kurla Complex, Bandra (E), 400 051 MUMBAI (IN).

(74) Agent: **DE SOUZA, Noel, J.**; Wockhardt Research Centre, D-4, MIDC, Chikalthana, 431 210 AURANGABAD (IN).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/097668 A2

(54) **Title:** NOVEL PROCESS FOR PRODUCTION OF THE SOMATOSTATIN ANALOG, OCTREOTIDE

(57) **Abstract:** The present invention relates to a process for commercial production of octreotide using solution peptide chemistry and inexpensive amino acid derivatives. Thus the hexapeptide (Boc) D-Phe-Cys(Acm)-Phe-D-Trp-Lys(Boc)-Thr-OMe is synthesised by condensation of two tripeptide fragments, saponified and condensed with Cys(Acm)-Thr-OL to give the linear octapeptide alcohol. The linear peptide alcohol is treated with iodine, after removal of Boc groups, to give the cyclic peptide octreotide. The linear octapeptide alcohol can alternately be made by condensation of the protected hexapeptide acid with the dipeptide Cys(Acm)-Thr-OMe, followed by reduction with sodium borohydride.

NOVEL PROCESS FOR PRODUCTION OF THE SOMATOSTATIN ANALOG, OCTREOTIDE

Field Of The Invention

The present invention relates to a process for the commercial production of the somatostatin analog, octreotide (I) and its pharmaceutically acceptable salts, using solution peptide chemistry, in high yield and purity.

H-(D)-Phe^1-Cys^2-Phe^3-(D)-Trp^4-Lys^5-Thr^6-Cys^7-Thr^8-OL

I

The present invention also relates to the intermediate compounds useful in the synthesis of octreotide.

Background Of The Invention

Octreotide is a highly potent and pharmacologically selective analog of somatostatin. It inhibits growth hormone for long duration and is therefore indicated for acromegaly to control and reduce the plasma level of growth hormone. The presence of D-Phe at the N-terminal and an amino alcohol at the C - terminal, along with D-tryptophan and a cyclic structure makes it very resistant to metabolic degradation.

The only solution synthesis reported in literature is by Bauer,W. and Pless, J. in Pat. No. U.S. 4,395,403 and EP029579.

Several solid phase syntheses have been subsequently described viz. Patent Nos. EP0953577A1 and U.S. 5,889,146 and in various research publications. Mergler et al (Proceedings of the 12th American Peptide Symposium) have used aminomethyl resin and Fmoc-butyl protection scheme for synthesis of octreotide. Alsina et al. Tetrahedron Letters, 38, 883, 1997) have used an active carbonate resin and Boc-Bzl protection scheme, necessitating the use of hydrogen fluoride/anisole for final

deprotection. Edwards et al (J. Med. Chem., 37, 3749, 1994) have described another synthesis using Fmoc-butyl protection and HMP resin, and Berta et al (EP 0 953 577A1) a synthesis using 2-chlorotrityl- type resin and Fmoc-butyl protection scheme.

All the solid phase syntheses described are useful only for the manufacture of small quantities of octreotide (100-300 mg). These procedures are not suitable for commercial manufacture of octreotide because they use costly resins and costly Fmoc-butyl protected amino acids in 2 to 4 times excess at every step. In one synthesis the final deprotection is carried out with hydrogen fluoride, a destructive and hazardous reagent.

The solution synthesis described by Bauer and Pless in Patent No. U.S. 4,395,403 and EP029579 uses BTFA/TFA to remove the methoxybenzyl group protecting the thiol group of cysteine, followed by cyclization. Decomposition of tryptophan is frequently known to occur during such harsh acid treatment for removal of protecting groups.

Summary Of The Invention

This invention describes a process for obtaining octreotide scalable upwards to kilogram quantities by solution chemistry methods using mild reagents and giving good yields. The process includes the following:

1) Cysteine thiol groups are protected by acetamidomethyl (Acm) groups. Treatment of the Cys(Acm)- containing linear novel octapeptide (XVI) of the invention with iodine, in one step removes the Acm groups and simultaneously effects cyclization to give octreotide (I) in 80-90 per cent yield.

H-(D)-Phe^1-Cys(Acm)^2-Phe^3-(D)-Trp^4-Lys^5-Thr^6-Cys(Acm)^7-Thr^8-OL. 2TFA

↓ XVI

H-(D)-Phe^1-Cys^2-Phe^3-(D)-Trp^4-Lys^5-Thr^6-Cys^7-Thr^8-OL.

I

2) The suitably protected octapeptide alcohol (XVI) of the invention is prepared by either of the following processes.

a) Sodium borohydride reduction of the novel C-terminal dipeptide methyl ester (X) to obtain the dipeptide alcohol (XI) (step 10). The Boc group is removed and the dipeptide (XII) on condensation with the hexapeptide acid (XIV), followed by deprotection, gives the novel intermediate (XVI) (Method 1-Steps 14 and 15)

b) Sodium borohydride reduction of the octapeptide XIX with methyl ester at C-terminal to give the novel intermediate XVI (Method 2-Step 19)

The novel hexapeptide fragment XIV is prepared by condensation of two appropriately protected novel tripeptide fragments V and IX followed by saponification (Steps 12 and 13).

Detailed Description Of The Invention

The process for the synthesis of

H-(D)-Phe-Cys-Phe-(D)-Trp-Lys-Thr-Cys-Thr-OL.

formula 1 comprises the synthesis of appropriate peptide fragments using the standard processes of peptide chemistry, known to the practitioners in the art. Thus amino functions of amino acids are protected with one of the commonly employed protecting groups like t-butyloxycarbonyl or benzyloxycarbonyl, and the carboxyl functions of amino acids are protected with alkyl groups like methyl, ethyl, or aralkyl groups like benzyl.

The condensation of the carboxyl group of the amino protected amino acid with the amino group of carboxyl protected amino acid is typically carried out by dissolving the respective appropriately protected amino acids in approximately equimolar quantities in a nonpolar solvent preferably like tetrahydrofuran, dichloromethane, chloroform, and adding a condensing agent such as N,N-dicyclocarbodiimide (DCCI), 1-hydroxy-benzotriazole (HOBt) or Benzotriazole-1-yl-oxy-tris-(dimethylamino) -phosphonium hexafluorophosphate (BOP) in approximately equimolar quantity at a temperature of –10°C to + 10°C and stirring at 20°C - 30°C for 4 to 24 hrs.

Alternately the carboxyl function of the amino protected aminoacid is activated as mixed anhydride by addition of an alkylchloro-formates wherein alkyl means methyl, ethyl, propyl, etc, preferably isobutylchloroformate, a tertiary amine such as TEA, DIEA, NMM, preferably NMM, in approximately equimolar quantities in a nonpolar solvent like dichloromethane, THF, chloroform, preferably THF at a temperature of –10°C to + 10°C following by addition of carboxyl protected amino acid carrying a free amino group and stirring at 20°C - 30°C for 4 to 24 hrs. The amino or the carboxyl protecting group is then selectively removed by the use of appropriate deprotecting agents known to those skilled in the art and condensed as desired with another amino acid derivative in an iterative procedure until the desired sequence is obtained.

The basic difference from other procedures already described is that a) the cysteine thiol groups are protected by acetamidomethyl (Acm) groups, b) the N-terminal hexapeptide has been synthesised by condensation of two tripeptide fragments, c) the C-terminal dipeptide alcohol is generated by sodium borohydride reduction of dipeptide methyl ester X instead of using threoninol as the starting material, d) treatment of the linear octapeptide alcohol XVI of the invention with iodine, in one step, removes the Acm groups and simultaneously effects cyclization to give octreotide in good yield, and e) the key intermediate octapeptide alcohol XVI could also be prepared by sodium borohydride reduction of octapeptide methyl ester XIX.

The Process for Producing OCTREOTIDE

H-(D)-Phe^1-Cys^2-Phe^3-(D)-Trp^4-Lys^5-Thr^6-Cys^7-Thr^8-OL

I

Step-1

Boc-Cys(Acm)-OH + H-Phe-OMe.HCl ⟶ Boc-Cys(Acm)-Phe-OMe

II

Step-2

Boc-Cys(Acm)-Phe-OMe ⟶ H-Cys(Acm)-Phe-OMe . TFA

III

Step-3

Boc-D-Phe-OH

+

H-Cys(Acm)-Phe-OMe .TFA ⟶ Boc-D-Phe-Cys(Acm)-Phe-OMe

IV

Step-4

Boc-D-Phe-Cys(Acm)-Phe-OMe ⟶ Boc-D-Phe-Cys(Acm)-Phe-OH

V

Step-5

Z-Lys(Boc)-OH + H-Thr-OMe.HCl ⟶ Z-Lys(Boc)-Thr-OMe

VI

Step-6

Z-Lys(Boc)-Thr-OMe ⟶ H-Lys(Boc)-Thr-OMe . AcOH

VII

Step-7

H-Lys(Boc)-Thr-OMe.AcOH

Z-D-Trp-OH + ⟶ Z-D-Trp-Lys(Boc)-Thr-OMe

VIII

Step-8

Z-D-Trp-Lys(Boc)-Thr-OMe ⟶ H-D-Trp-Lys(Boc)-Thr-OMe

IX

Step-9

Boc-Cys(Acm) + H-Thr-OMe.HCl ⟶ Boc-Cys(Acm)-Thr-OMe

X

Step-10

Boc-Cys(Acm)-Thr-OMe ⟶ Boc-Cys(Acm)-Thr-OL

XI

Step-11

Boc-Cys(Acm)-Thr-OL ⟶ H-Cys(Acm)-Thr-OL . TFA

XII

Step-12

Boc-D-Phe-Cys(Acm)-Phe-OH + D-Trp-Lys(Boc)-Thr-OMe

V IX

↓

Boc-D-Phe-Cys(Acm)-Phe-D-Trp-Lys(Boc)-Thr-OMe

XIII

Step-13

Boc-D-Phe-Cys(Acm)-Phe-D-Trp-Lys(Boc)-Thr-OMe

↓

Boc-D-Phe-Cys(Acm)-Phe-D-Trp-Lys(Boc)-Thr-OH

XIV

Preparation Of Novel Linear Octapeptide Alcohol Di Trifluoroacetate XVI

Method 1

Step-14

Boc-D-Phe-Cys(Acm)-Phe-D-Trp-Lys(Boc)-Thr-OH + H-Cys(Acm)-Thr.OL.TFA

XIV XII

↓

Boc-D-Phe-Cys(Acm)-Phe-D-Trp-Lys(Boc)-Thr-Cys(Acm)-Thr-OL

XV

Step-15

Boc-D-Phe-Cys(Acm)-Phe-D-Trp-Lys(Boc)-Thr-Cys(Acm)-Thr-OL

↓

H-D-Phe-Cys(Acm)-Phe-D-Trp-Lys-Thr-Cys(Acm)-Thr-OL . 2TFA

XVI

Method 2

Step-16

Boc-Cys(Acm)-Thr-OMe ⟶ H-Cys(Acm)-Thr-OMe . TFA

X XVII

Step-17

Boc-D-Phe-Cys(Acm)-Phe-D-Trp-Lys(Boc)-Thr-OH + H-Cys(Acm)-Thr-OMe.TFA

XIV XVII

↓

Boc-D-Phe-Cys(Acm)-Phe-D-Trp-Lys(Boc)-Thr-Cys(Acm)-Thr-OMe

XVIII

Step-18

Boc-D-Phe-Cys(Acm)-Phe-D-Trp-Lys(Boc)-Thr-Cys(Acm)-Thr-OMe

↓

H-D-Phe-Cys(Acm)-Phe-D-Trp-Lys-Thr-Cys(Acm)-Thr-OMe. 2TFA

XIX

Step-19

H-D-Phe-Cys(Acm)-Phe-D-Trp-Lys-Thr-Cys(Acm)-Thr-OMe . 2 TFA

↓

H-D-Phe-Cys(Acm)-Phe-D-Trp-Lys-Thr-Cys(Acm)-Thr-OL . 2 TFA

XVI

Preparation Of Octreotide From Novel Linear Octapeptide Alcohol Di Trifluoroacetate XVI

Step-20

H-(D)-Phe^1-Cys(Acm)^2-Phe^3-(D)-Trp^4-Lys^5-Thr^6-Cys(Acm)^7-Thr^8-OL . 2TFA

XVI

↓

H-(D)-Phe^1-Cys^2-Phe^3-(D)-Trp^4-Lys^5-Thr^6-Cys^7-Thr^8-OL. .AcOH

Abbreviations:

Acm = Acetamidomethyl

Boc = tert.-Butyloxycarbonyl

Bzl	=	Benzyl
BTFA	=	Boron-tris-trifluoroacetate
tBu	=	tert-Butyl
DCCI	=	Dicyclohexylcarbodiimide
DCM	=	Dichloromethane
DIEA	=	Diisopropylethylamine
DMAc	=	Dimethylacetamide
DMSO	=	Dimethylsulfoxide
ESMS	=	Electrospray Mass Spectrometry
EtOH	=	Ethanol
Fmoc	=	Flourenylmethoxycarbonyl
HF	=	Hydrogen fluoride
HOBt	=	1-Hydroxybenzotriazole
IBCF	=	Isobutylchloroformate
NMM	=	N-methylmorpholine
TEA	=	Triethylamine
TFA	=	Trifluoroacetic acid
THF	=	Tetrahydrofuran
Trt	=	Triphenyl methyl (Trityl)
Z	=	Benzyloxycarbonyl

The following preferred embodiment is described. As shown in step 9, cysteine carrying Boc group for N^{α} and Acm group for side chain SH protection may be treated with IBCF, NMM, H-Thr-OMe.HCl and TEA, all in approximately equimolar amounts in THF at – 10°C to give dipeptide methyl ester X. The C-terminal methyl ester is converted into alcohol function by reduction with sodium borohydride (2 equivalents) in 90% EtOH at 0°C to give dipeptide alcohol XI (step 10). The Boc group is removed by treatment with TFA at 0°C and the resultant compound XII is condensed with appropriately protected hexapeptide XIV, using DCC/HOBt as the condensing agents, in approximately equimolar amounts in THF/DMAc at 0°C, to give the protected octapeptide alcohol XV (step 14). Boc groups are removed by treatment with TFA at 0°C to give the novel octapeptide alcohol XVI (step 15)

which is cyclised with iodine (5-10 equivalents) in 90% MeOH to give octreotide I (Step 20).

Alternately as shown in step 17 (method 2) Boc protection is removed from dipeptide methyl ester X by treatment with TFA at 0°C and the resulting t dipeptide ester XVII is condensed with the hexapeptide XIV, using DCC/HOBt as the condensation agents in approximately equimolar amounts in THF at 0°C ,to give the protected octapeptide methyl ester XVIII. Boc groups are removed by treatment with TFA at 0°C and the octapeptide methyl ester XIX on reduction with sodium borohydride (5 to 6 equivalents), in 90% EtOH gives the novel octapeptide alcohol XVI (see steps 18 and 19) which is cyclized with iodine (5 to 10 equivalents) to octreotide I (Step 20).

The hexapeptide acid XIV of the invention is synthesised by condensation of two appropriately protected tripeptide fragments V and IX followed by saponification as shown in steps 12 and 13.

For synthesis of tripeptide fragment V, cysteine carrying Boc group for N^{α} and Acm group for side chain SH protection is treated with IBCF, NMM, H-Phe-OMe.HCl and TEA, all in approximately equimolar amounts in THF/DMSO at -10°C to give dipeptide II (step 1). The Boc group is removed from the protected dipeptide methyl ester II by treatment with TFA at 0°C to give III (step 2) which on condensation with (D)-phenyl-alanine carrying Boc group as N^{α} protection and using IBCF and NMM to make the mixed anhydride, in approximately equimolar amounts in THF at -10° gives protected tripeptide methyl ester IV (step 3). The saponification of IV gives the protected tripeptide acid V (step 4).

Similarly for synthesis of tripeptide fragment IX, lysine carrying Z and Boc group at N^{α} and N^{ε} respectively as protecting groups is treated with IBCF, NMM, H-Thr-OMe.HCl and TEA, all in approximately equimolar amounts in THF/DMSO at -10° to give dipeptide VI (step 5). The Z group is removed from dipeptide VI by hydrogenation over Pd/C to give VII (step 6) which on condensation with (D)-tryptophan carrying Z group as N^{α} protection and using IBCF and NMM in

approximately equimolar amounts in THF/DMSO to make the mixed anhydride, at -10°C gives protected tripeptide methyl ester VIII (step 7). Removal of Z group from VIII by hydrogenation over Pd/C provides the fragment IX (step 8).

The hexapeptide methyl ester XIII is then made by condensing the tripeptide V carrying the free carboxyl function and the tripeptide IX, carrying the free amino function and using DCCI and HOBt as the condensation reagents in approximately equimolar amounts in THF/DMA at 0° (step 12). The methyl ester group of XIII is removed by saponification to give the hexapeptide acid XIV (step 13).

Examples

H-(D)-Phe^1-Cys^2-Phe^3-(D)-Trp^4-Lys^5-Thr^6-Cys^7-Thr^8-OL.

I

A solution of linear octapeptide XVI H-(D)-Phe^1-Cys(Acm)^2-Phe^3-(D)-Trp^4-Lys ^{5}-Thr^6-Cys(Acm)^7-Thr^8-OL.2TFA(5.6g, 4mmol) in 90% methanol (200ml) is added dropwise to a solution of 90% methanol (1 lit) containing iodine (5.0g, 20mmol) over a period of an hour at 30°. The stirring is continued at 30° till the completion of reaction. The reaction mixture is cooled to 5°C, 20ml 1M sodium bisulphite is added followed by the addition of 40ml 1M sodium hydroxide and 2ml acetic acid. The solvent is evaporated under vacuum and the crude material is purified by column chromatography to give compound I. Yield 3.7g (84 %), $[\alpha]_D^{20}$ = -41.8° (c=1 in 95% acetic acid, Merck Index -42°), ESMS= 1019 (M+H).

The novel starting materials which also form an embodiment of this invention may be obtained as follows:

Boc-Cys(Acm)-Phe-OMe (II)

IBCF (13.0ml, 100mmol) is added to a solution of Boc-Cys(Acm)-OH (29.2, 100mmol) and NMM (11.0ml, 100mmol) in THF (300ml) at –10°C. To the reaction mixture is added slowly, after 5 mins, a cold solution of of H-Phe-OMe.HCl (21.5g, 100mmol) and TEA (14.0ml, 100mmol) in DMSO (10 ml) and THF (50ml). The stirring is continued at same temperature for one hour and then overnight at 30°C. The solvent is evaporated under vacuum at 40°C and diluted with ethyl acetate (300ml). The organic layer is washed with saturated sodium bicarbonate solution (3

x 100ml), 0.5M ice cold hydrochloric acid (3 x 100ml), brine (3x100ml), dried on sodium sulphate and evaporated to dryness to give compound II. Yield 43.0g (94%), m. p. = 99°C, $[\alpha]_D^{20}$ = -21.7° (c=1 in methanol), ESMS= 454.1 (M+H), 476.13 (M+Na).

H-Cys(Acm)-Phe-OMe. TFA (III)

The dipeptide II (40.8g, 90mmol) is suspended in DCM (40ml) and stirred at 0°C. TFA (160ml) is added and stirring continued for one hour. The TFA and DCM are evaporated under vacuum, ether (200ml) is added to the residue under stirring, the precipitate filtered, washed with diethyl ether and dried in vacuum to give compound III in 98% yield. ESMS= 354.1 (M+H).

Boc-(D)-Phe-Cys(Acm)-Phe-OMe (IV)

IBCF (11.8ml, 90mmol) is added to a solution of Boc-D-Phe-OH (24.0g, 90mmol) and NMM (9.9ml, 90mmol) in THF (100ml) at –10°C. To the reaction mixture is added ,after 5 mins, a cold solution of compound III (80mm, 38g) and TEA (12.7ml, 80mmol) in DMSO (25ml) and THF (50ml). The stirring is continued for one hour at same temperature and then overnight at 30°C. The reaction mixture is concentrated in vacuum, and the residue is dissolved in ethyl acetate (300ml). The organic layer is washed with saturated sodium bicarbonate solution (3 x 100ml), 0.5M ice cold hydrochloric acid (3 x 100ml), brine (3 x 100ml), dried on sodium sulphate and evaporated to dryness to give compound IV. Yield 48.8g (90%), m. p. = 134-135°C, $[\alpha]_D^{20}$ =-31.6° (c =0.5 in methanol), ESMS= 601 (M+H).

Boc-(D)-Phe-Cys(Acm)-Phe-OH (V)

1M sodium hydroxide solution (80.0ml) is added in 15 minutes to the cold solution of tripeptide methyl ester IV (48.0g, 80mmol) dissolved in methanol (300ml). The solution is stirred at 30° till the completion of reaction. pH is brought to 7 by addition of 1N hydrochloric acid, the solution is concentrated in vacuum, and acidified further with 1M hydrochloric acid (80ml) under cooling to pH 3, and ethyl acetate (300ml) is added. The organic layer is separated and water layer is re-extracted with ethyl acetate (200ml). The organic layers are combined, washed with brine (2 x 100ml), dried on sodium sulphate and evaporated to give compound V. Yield 43.5g (93%), m.p. = 141°- 145°C, $[\alpha]_D^{20}$ = -20.8° (c =1 in methanol), ESMS= 587 (M+H).

Z-Lys(Boc)-Thr-OMe (VI)

IBCF (26.0ml, 200mmol) is added to a solution of Z-Lys(Boc)-OH (76g, 200mmol) and NMM (22.0ml, 200mmol) in THF (400ml) at –10°C. To the reaction mixture is added, after 5 minutes, a cold solution of H-Thr-OMe.HCl (40.6g, 240mmol) and TEA (34.0ml, 240mmol) in DMSO (50 ml) and THF(100ml). The stirring is continued at same temperature for an hour and then overnight at 30°C. The solvent is evaporated under vacuum at 40°C and diluted with ethyl acetate(700ml). The organic layer is washed with saturated sodium bicarbonate solution(3 x 100ml), 0.5M ice cold hydrochloric acid (3 x 100ml, brine (3 x 100ml), dried on sodium sulphate and evaporated to dryness to give compound VI. Yield 83.0g (84%), m. p. = 77-78°C $[\alpha]_D^{20}$ = -10.2° (c=1 in DMF), ESMS= 496 (M+H).

H-Lys(Boc)-Thr-OMe. AcOH (VII)

The dipeptide VI (80.0g, 160mmol) is dissolved in methanol (500ml) and acetic acid (12.0ml) and hydrogen gas bubbled in the presence of Palladium on car bon (8.0g, 10%). When the hydrogenation is complete, the solution is filtered through celite bed, evaporated to dryness to yield compound VII in 96% Yield . ESMS= 362.1 (M+H).

Z-(D)-Trp-Lys(Boc)-Thr-OMe (VIII)

IBCF (20.8ml, 160mmol) is added to a solution of Z-(D)-Trp-OH (54.0g, 160mmol) and NMM (17.6ml, 160mmol) in THF (400ml) at –10°C. To the reaction mixture is added, after 5 minutes, a cold solution of compound VII (58g, 160 mm) and TEA (22.4ml, 160mmol) in DMSO (50ml) and THF(100ml). The stirring is continued for an hour at same temperature and then overnight at 30°C. The reaction mixture is concentrated in vacuum and the residue is dissolved in ethyl acetate (700ml). The organic layer is washed with saturated sodium bicarbonate solution (3 x 100ml), 0.5M ice cold hydrochloric acid (3 x 100ml, brine (3 x 100ml), dried on sodium sulphate and evaporated to dryness to give compound VIII. Yield 78g (70%), m. p. = 112-114°C, $[\alpha]_D^{20}$ = 3.0° (c=1 in DMF), ESMS= 682 (M+H).

H-(D)-Trp-Lys(Boc)-Thr-OMe (IX)

The tripeptide VIII (50.0g, 73mmol) is dissolved in methanol (500ml) and hydrogen gas bubbled through in the presence of Palladium on charcoal (6.0g, 10%). After the hydrogenation is complete, the solution is filtered through celite bed, evaporated to dryness to yield compound IX in 98% yield. ESMS= 548 (M+H), 570 (M+Na).

Boc-Cys(Acm)-Thr-OMe (X)

IBCF (39.0ml, 300mmol) is added to a solution of Boc-Cys(Acm)-OH (87.6, 300mmol) and NMM (33.0ml, 100mmol) in THF(400ml) at –10°C. To the reaction mixture is added, after 5 minutes, a cold solution of H-Thr-OMe.HCl (59.3g, 350mmol) and (TEA 49.4ml, 350mmol) in DMSO (30 ml) and THF (150ml). The stirring is continued at same temperature for an hour and then overnight at 30°C. The solvent is evaporated under vacuum at 40°C and diluted with ethyl acetate (700ml). The organic layer is washed with saturated sodium bicarbonate solution (3 x 100ml), 0.5M ice cold hydrochloric acid (3 x 100ml), brine (3 x 100ml), dried on sodium sulphate and evaporated to dryness to give compound X . Yield 110.0g (90%), ESMS= 408 (M+H).

Boc-Cys(Acm)-Thr-OL (XI)

$NaBH_4$ (7.4g, 200mmol) dissolved in 90% ethanol (50ml) is added dropwise to a solution of compound X (40.7g, 100mmol) in 90% ethanol (150ml) at 0°C. The stirring is continued for 3-4 hours till the reaction is complete as monitored by tlc. The solution is concentrated and desalted by HPLC to give compound XI in 95% yield . ESMS= 380 (M+H), 402(M+Na).

H-Cys(Acm)-Thr-OL. TFA (XII)

The dipeptide XI (7g, 18mmol)is dissolved in DCM (10ml) at 0°C under stirring. (TFA 30ml) is added and continue the stirring for an hour. The TFA and DCM are evaporated under vacuum, diethyl ether (100ml) is added to the residue under stirring, ether is decanted, repeated twice and dried in vacuum to give compound XII in 96% yield . ESMS= 280 (M+H), 302 (M+Na).

Boc-(D)-Phe-Cys(Acm)-Phe-(D)-Trp-Lys(Boc)-Thr-OMe (XIII)

The tripeptide acid V (38.0g, 65mmol) and HOBt (9.9g, 65mmol) is added to a solution of tripeptide IX (35.6g, 65mmol) in THF (200ml) and DMA (30ml). The solution is cooled to 0°C and DCCI (13.4g, 65mmol) is added. The reaction mixture is stirred at same temperature for 1-2 hours followed by overnight stirring at 30°C. Dicyclohexylurea is filtered, the filtrate is concentrated in vacuum and diluted with (500ml) ethyl acetate. The organic layer is washed with saturated sodium bicarbonate solution (3 x 100ml), 0.5M ice cold hydrochloric acid (3 x 100ml), brine (3 x 100ml), dried on sodium sulphate and evaporated to dryness to give

compound XIII: Yield 55.2g (76.3%), m. p. = 141-143°C , $[\alpha]_D^{20}$ = -29.8° (c=1 in in methanol), ESMS= 1116 (M+H), 1138(M+Na).

Boc-(D)-Phe-Cys(Acm)-Phe-(D)-Trp-Lys(Boc)-Thr-OH (XIV)

1M sodium hydroxide (45.0ml) solution is added in 15 minutes to the cold solution of hexapeptide methyl ester XIII (50.2g, 45mmol) in methanol (500ml). The solution is stirred at 30°C till the reaction is complete. pH is brought to 7 by addition of 1N hydrochloric acid, the solution is concentrated in vacuum, and acidified further with 1M hydrochloric acid (total 45ml) under cooling to pH 3, and ethyl acetate (300ml) is added. The organic layer is separated and water layer is re-extracted ethyl acetate (200ml). The organic layers are combined, washed with brine (2 x 100ml), dried on sodium sulphate and evaporated to give title compound XIV. Yield 46.1g (97%) m. p. = 134-135°C, $[\alpha]_D^{20}$ = -24.7° (c=1in methanol), ESMS= 1102 (M+1), 1124 (M+Na).

Preparation Of Novel Linear Octapeptide Alcohol XVI

Method 1

Boc-(D)-Phe-Cys(Acm)-Phe-(D)-Trp-Lys(Boc)-Thr-Cys(Acm)-Thr-OL (XV)

A solution of protected hexapeptide acid XIV (11.0g, 10mmol) and HOBt (1.5g, 10mmol) in DMAc (30 ml) is added to a solution of dipeptide alcohol TFA salt XII (7.0g, 18mmol) and TEA (2.5ml, 18mmol) in THF (50ml) and stirred at 0°C. DCCI (2.2g, 11mmol) is added at 0°C and the reaction mixture is stirred at 0°C for an hour followed by overnight stirring at 30°. Dicyclohexylurea is filtered and the filtrate concentrated in vacuum followed by addition of diethyl ether (50ml). The precipitate is filtered, washed with ethyl acetate, chloroform and dried in vacuum to give the title compound XV. Yield 12g (88%), ESMS= 1363.95 (M+H).

[0001] H-(D)-Phe-Cys(Acm)-Phe-(D)-Trp-Lys-Thr-Cys(Acm)-Thr-OL. 2TFA (XVI)

The protected octapeptide alcohol XV (16g) and anisole (2.3ml) and mercaptoethanol (2.0ml) are suspended in DCM (20ml) under N_2. The suspension is cooled to 0°C and TFA (80ml) is added. Stirring is continued for one and half hour at same temperature. The TFA and DCM are evaporated under vacuum at 30°C, ether (200ml) is added to the residue under stirring. The precipitate is filtered, washed with diethyl ether (300ml), dried in vacuum and purified by HPLC

to give compound XVI; Yield 9.7g (80%), m. p. = 161-163°C, $[\alpha]_D^{20}$ = -61.2° (c= 0.25 in methanol), ESMS= 1163 (M+H).

Method 2

H-Cys(Acm)-Thr-OMe. TFA (XVII)

The dipeptide methyl ester X (8.1g, 20mmol) is dissolved in DCM (10ml) at 0°C under stirring. TFA (30ml) is added and continue the stirring for an hour. The TFA and DCM are evaporated under vacuum, diethyl ether (50ml) is added to the residue under stirring, ether is decanted, repeated twice and dried in vacuum to give compound XVII in 97% yield . ESMS= 308 (M+H).

Boc-(D)-Phe-Cys(Acm)-Phe-(D)-Trp-Lys(Boc)-Thr-Cys(Acm)-Thr-OMe (XVIII)

To a solution of dipeptide XVII (8.1g, 20mmol) and TEA (2.8ml, 20mmol) in THF(50ml) is added, hexapeptide acid XIV (11.0g, 10mmol) and HOBt (1.5g, 10mmol). DCCI (2.2g, 11mmol) is added at 0°C . The reaction mixture is stirred at 0°C for an hour followed by overnight stirring at 30°C. Dicyclohexylurea is filtered and the filtrates are concentrated in vacuum followed by addition of ether (100ml). The precipitate is filtered, washed with ethyl acetate, water, diethyl ether and dried in vacuum to give the title compound. Yield 11 g (79%) . ESMS= 1391(M+H).

H-(D)-Phe-Cys(Acm)-Phe-(D)-Trp-Lys-Thr-Cys(Acm)-Thr-OMe. 2TFA (XIX)

The octapeptide ester XVIII (11g, 7.9mm anisole, 2 ml) and mercaptoethanol (2 ml,) are suspended in DCM (20ml) under N_2. The suspension is cooled to 0°C and TFA (80ml) is added. Stirring is continued for one and half hour at same temperature. The TFA and DCM are evaporated under vacuum at 30°C, ether (200ml) is added to the residue under stirring. The precipitates are filtered , washed with diethyl ether (300ml) and dried in vacuum to give compound XIX: Yield 10.0g (91%). ESMS= 1191 (M+H).

H-(D)-Phe-Cys(Acm)-Phe-(D)-Trp-Lys-Thr-Cys(Acm)-Thr-OL. 2TFA (XVI)

Sodiumborohydride (1.5g, 40mmol) dissolved in 90% ethanol (20ml) is added dropwise to crude compound XIX (10g, 7mm) dissolved in 90% ethanol (50ml at 0°C. The stirring is continued at same temperature till the reaction is complete. Acetic acid is added to the reaction mixture which is concentrated and purified on column chromatography to yield compound XVI. Yield 6.8g (69%), m. p. = 161-163°C, $[\alpha]_D^{20}$ = -60.6° (c= 0.25 in methanol), ESMS= 1163 (M+H).

CLAIMS:

1. A process for preparing octreotide from linear octapeptide H-D-Phe-Cys(Acm)-Phe-D-Trp-Lys-Thr-Cys(Acm)-Thr-OL.2 TFA comprising treating H-D-Phe-Cys(Acm)-Phe-D-Trp-Lys-Thr-Cys(Acm)-Thr-OL.2TFA (XVI) with iodine.

2. A process according to claim 1, wherein linear octapeptide H-D-Phe-Cys(Acm)-Phe-D-Trp-Lys-Thr-Cys(Acm)-Thr-OL.2 TFA is prepared by condensation of hexapeptide Boc-D-Phe-Cys(Acm)-Phe-D-Trp-Lys(Boc)-Thr-OH (XIV) with dipeptide H-Cys(Acm)-Thr-OL.2 TFA (XII) and removing the Boc groups.

3. The process according to claim 2, where dipeptide H-Cys(Acm)-Thr-OL. TFA (XII) is prepared by reducing Boc-Cys(Acm)-Thr-OMe with sodium borohydride and removing the Boc group.

4. The process according to claim 2, wherein hexapeptide Boc-D-Phe-Cys(Acm)-Phe-D-Trp-Lys(Boc)-Thr-OH (XIV) is prepared by condensing Boc-D-Phe-Cys(Acm)-Phe-OH (V) and H-D-Trp-Lys(Boc)-Thr-OMe followed by saponification.

5. The process according to claim 4, wherein Boc-D-Phe-Cys(Acm)-Phe-OH (V) is prepared starting from H-Phe-OMe-HCl, and condensing Boc-Cys(Acm) and Boc-D-Phe sequentially through mixed anhydride method, followed by saponification.

6. The process according to claim 4, wherein the tripeptide H-D-Trp-Lys(Boc)-Thr-OMe (IX) is prepared starting from H-Thr-OMe.HCl and condensing Z-Lys(Boc) and Z-D-Trp sequentially through mixed anhydride method, followed by removal of Boc group.

7. The process according to claim 1, where linear octapeptide H-D-Phe-Cys(Acm)-Phe-D-Trp-Lys-Thr-Cys(Acm)-Thr-OL obtained by condensation of hexapeptide Boc-D-Phe-Cys(Acm)-Phe-D-Trp-Lys(Boc)-Thr-OH with dipeptide H-Cys(Acm)-Thr-OL.TFA followed by removal of Boc groups.

8. The process according to claim 1, wherein H-D-Phe-Cys(Acm)-Phe-D-Trp-Lys-Thr-Cys(Acm)-Thr-OL is obtained by sodium borohydride reduction of linear octapeptide H-D-Phe-Cys(Acm)-Phe-D-Trp-Lys-Thr-Cys(Acm)-Thr-OMe.2TFA.

9. A process for preparing H - (D) - Phe^1 – Cys^2 - Phe^3 - (D) - Trp^4 - Lys^5 - Thr^6 - Cys^7 - Thr^8 -OL

comprising the steps of

a) Condensing Boc - Cys(Acm) - OH and H - Phe - OMe. HCl to obtain Boc - Cys(Acm) - Phe - OMe (II);
b) Condensing Boc - Cys(-Acm) - Phe - OMe and TFA to obtain H-Cys (Acm) - Phe - OMe. TFA;
c) Condensing Boc - D - Phe - OH and H-Cys(Acm) - Phe - OMe TFA to obtain Boc - D - Phe - Cys(Acm) - Phe - OMe;
d) saponifying Boc - D - Phe - Cys(Acm) - Phe - OMe to obtain Boc – D - Phe - Cys(Acm) - Phe - OH;
e) Condensing Z-Lys (Boc) - OH and H -Thr - OMe. HCl to obtain Z-Lys (Boc) - Thr - OMe (VI) where Z is benzyloxy carbonyl;
f) hydrogenating Z-Lys (Boc) - Thr - OMe (VI) to obtain H – Lys (Boc) - Thr - OMe. AcOH where Z is benzyloxy carbonyl;
g) condensing Z - (D) - Trp - OH and H - Lys (Boc) - Thr – OMe.AcOH (VII) to obtain Z - D - Trp - Lys (Boc) - Thr - OMe (VIII);
h) hydrogenating Z - D - Trp - Lys (Boc) - Thr - OMe to obtain H - D – Trp - Lys(Boc) - Thr - OMe (IX);
i) Condensing Boc - Cys(Acm) and H - Thr - OMe. HCl to obtain Boc - Cys (Acm) - Thr - OMe (X);

j) reducing Boc - Cys(Acm) - Thr Ome (X) with sodium borohydride to obtain Boc - Cys (Acm) - Thr - OL (XI);

k) treating Boc - Cys(Acm) - Thr- OL (XI) with TFA to obtain H – Cys(Acm) - Thr – OL.TFA (XII);

l) condensing Boc - D - Phe-Cys(Acm) - Phe - OH (V) and D – Trp – Lys (Boc) - Thr - OMe (IX) to obtain Boc - D - Phe Cys(Acm) - Phe - (D)- Trp - Lys(Boc) - Thr - Ome (XIII);

m) saponifying Boc - D - Phe - Cys(Acm) - Phe - D - Trp - Lys (Boc) – Thr - OMe (XIII) with a base to obtain Boc - (D) - Phe - Cys(Acm) - Phe - (D) - Trp - Lys(Boc) - Thr - OH (XIV);

n) condensing Boc - D - Phe - Cys(Acm) - Phe - D - Trp - Lys (Boc) – Thr – OH (XIV) and H-Cys(Acm) - Thr-OL. TFA (XII) to obtain Boc - D - Phe - Cys(Acm) - Phe - D - Trp- Lys(Boc) - Thr - Cys(Acm) - Thr - OL (XV);

o) treating Boc – (D) - Phe - Cys(Acm) - Phe - D - Trp - Lys (Boc) - Thr - Cys(Acm) - Thr - OL (XV) with TFA to obtain H – (D) - Phe - Cys (Acm) - Phe - D - Trp - Lys - Thr - Cys (Acm) - Thr - OL.2 TFA (XVI);

p) treating H - (D) - Phe^1 - $Cys(Acm)^2$ - Phe^2 - (D) - Trp^3 - Lys^5 - Thr^6 – $Cys(Acm)^7$ - Thr^8 - OL. 2 TFA (XVI) with iodine to obtain H - (D) - Phe^1 – Cys^2 - Phe^3 - (D) - Trp^4 - Lys^5 - Thr^6 - Cys^7 - Thr^8 - OL. AcOH

10. A process for preparing H - (D) - Phe^1 – Cys^2 - Phe^3 - (D) - Trp^4 - Lys^5 - Thr^6 - Cys^7 - Thr^8 -OL

comprising the steps of

a) Condensing Boc - Cys(Acm) - OH and H - Phe - OMe. HCl to obtain Boc - Cys (Acm) - Phe - OMe (II);

b) Condensing Boc - Cys(-Acm) - Phe - OMe and TFA to obtain H-Cys (Acm) - Phe - Ome. TFA;

c) Condensing Boc - D - Phe - OH and H-Cys(Acm) - Phe - OMe TFA to obtain Boc - D - Phe - Cys (Acm) - Phe - OMe;

d) saponifying Boc - D - Phe - Cys(Acm) - Phe - OMe to obtain Boc - D - Phe - Cys (Acm) - Phe - OH;

e) Condensing Z-Lys (Boc) - OH and H -Thr - OMe. HCl to obtain Z-Lys (Boc) - Thr - Ome (VI) where Z is benzyloxy carbonyl;

f) hydrogenating Z-Lys (Boc) - Thr - OMe (VI) to obtain H – Lys (Boc) - Thr - OMe. AcOH;

g) condensing Z - (D) - Trp - OH and H - Lys (Boc) - Thr – OMe.AcOH (VII) to obtain Z - D - Trp - Lys (Boc) - Thr - OMe (VIII);

h) hydrogenating Z - D - Trp - Lys (Boc) - Thr - OMe to obtain H – Trp - Lys(Boc) - Thr - OMe (IX);

i) Condensing Boc - Cys (Acm) and H - Thr - OMe. HCl to obtain Boc - Cys (Acm) - Thr - OMe (X);

j) reducing Boc - Cys(Acm) – Thr- OMe (X) with sodium borohydride to obtain Boc - Cys (Acm) - Thr - OL (XI);

k) treating Boc - Cys(Acm) - Thr- OL (XI) with TFA to obtain H - Cys(Acm) - Thr - OL (XII);

l) condensing Boc - D - Phe Cys(Acm) - Phe - OH (V) and D - Trp – Lys (Boc) - Thr - OMe (IX) to obtain Boc - D - Phe Cys(Acm) - Phe - (D)- Trp - Lys(Boc) - Thr - OMe (XIII);

m) saponifying Boc - D - Phe - Cys(Acm) - Phe - D - Trp - Lys (Boc) - Thr - OMe (XIII) with a base to obtain Boc - (D) - Phe - Cys(Acm) - Phe - (D) - Trp - Lys(Boc) - Thr - OH (XIV);

n) treating Boc - Cys(Acm) - Thr - OMe (X) with TFA to obtain H-Cys (Acm) - Thr - OMe. TFA (XVII);

o) condensing Boc - D - Phe - Cys(Acm) - Phe - D- Trp - Lys (Boc) - Thr – OH (XIV) and H - Cys(Acm) - Thr - OMe. TFA (XVII) to obtain Boc - D - Phe - Cys(Acm) - Phe - D - Trp - Lys (Boc) - Thr – Cys(Acm) - Thr - OMe (XVIII);

p) treating treating Boc - D - Phe - Cys(Acm) - Phe - D - Trp - Lys (Boc) - Thr – Cys(Acm) - Thr - OMe (XVIII) with TFA to obtain H - D - Phe - Cys(Acm) - Phe - D - Trp - Lys - Thr - Cys(Acm) - Thr - OMe. 2 TFA (XIX);

q) reducing H - D - Phe - Cys(Acm) - Phe - D - Trp - Lys - Thr - Cys (Acm) - Thr - OMe. 2 TFA (XIX) with sodium borohydride to obtain H - D - Phe - Cys (Acm) - Phe - D - Trp - Lys - Thr - Cys (Acm) - Thr - OL. 2 TFA (XVI);

r) treating H - (D) - Phe^1 - $Cys(Acm)^2$ - Phe^3 - (D) - Trp^4 - Lys^5 - Thr^6 – $Cys(Acm)^7$ - Thr^8 - OL. 2 TFA (XVI) with iodine to obtain H - (D) - Phe^1 –Cys^2 - Phe^3 - (D) - Trp^4 - Lys^5 - Thr^6 - Cys^7 - Thr^8 –OL

11. The process according to claim 9, wherein Boc - Cys(Acm) - Phe - OMe (II) is prepared by adding to Boc - Cys(Acm) OH, NMM, IBCF, H - Phe OMe. HCl and TEA in THF.

12. The process according to claim 9, wherein H - Cys(Acm) - Phe - OMe. TFA (III) is prepared by mixing Boc - Cys (Acm) - Phe - OMe and TFA.

13. The process according to claim 9, wherein Boc - (D) - Phe - Cys(Acm) Phe- Ome (IV) is prepared by adding IBCF to a solution of Boc - D - Phe - OH and NMM and adding H - Cys(Acm) - Phe OMe. TFA.

14. The process according to claim 9, wherein Boc - (D) - Phe - Cys(Acm) - Phe – OH (IV) is prepared by dissolving Boc - (D) - Phe - Cys(Acm) - Phe - OMe in alcohol and adding a base.

15. The process according to claim 9, wherein Z-Lys (Boc) - Thr - OMe (VI) is prepared by mixing IBCF, Z - Lys (Boc) - OH and NMM, and adding H - Thr - OMe. HCl and TEA.

16. The process according to claim 9, wherein H - (D) - Trp - Lys (Boc). Thr - OMe (VII) is prepared by hydrogenating Z – D – Trp - Lys (Boc) - Thr - OMe.

17. The process according to claim 9, wherein Boc - Cys(Acm) - Thr - OMe (VIII) is prepared by mixing IBCF, Boc - Cys(Acm) - OH and NMM, and adding H - Thr - OMe. HCl and TEA.

18. The process according to claim 9, wherein H - Cys(Acm) - Thr - OL. TFA (XII) is prepared by dissolving Boc - Cys(Acm) - Thr - OL in DCM and adding TFA.

19. The process according to claim 9, wherein Boc - (D) - Phe Cys(Acm) - Phe (D) – Trp - Lys (Boc) - Thr - OMe is prepared by condensation of Boc – D – Phe - Cys(ACM) – Phe - OH(IV) with H- (D) - Trp - Lys (Boc) - Thr - OMe (IX) in THF and DMA.

20. The process according to claim 9, wherein Boc (D) - Phe - Cys(Acm) - Phe - (D) - Trp - Lys (Boc) - Thr - OH is prepared by mixing Boc - D - Phe - Cys(Acm) - Phe - D - Trp - Lys (Boc) - Thr - OMe with a base and an alcohol.

21. The process according to claim 9, for preparing Boc - (D) - Phe - Cys (Acm) - Phe - (D) - Trp - Lys (Boc) - Thr - Cys(Acm) - Thr - OL (XV) wherein Boc - (D) - Phe - Cys(Acm) - Phe (D) - Trp - Cys (Boc) - Thr - OH (XIV) is mixed with DCC, HOBt, H - Cys(Acm) - Thr - OL. TFA (XII) and TEA.

22. The process according to claim 9, wherein H - (D) - Phe - Cys(Acm) - Phe - (D) – Phe - Cys(Acm) - Phe - (D) - Trp - Lys - Thr - Cys(Acm) - Thr - OL.2TFA (XVI) is prepared by mixing Boc - D - Phe - Cys(Acm) - Phe - D - Trp - Lys (Boc) - Thr - Cys(Acm) - Thr - OL with anisole and TFA.

23. The process according to claim 10, for preparing H - Cys(Acm) - Thr - OMe. TFA wherein Boc - Cys(Acm) - Thr - OMe is mixed with TFA.

24. The process according to claim 10, wherein Boc - (D) - Phe - Cys(Acm) - Phe - (D) - Trp - Lys (Boc) - Thr - Cys(Acm) - Thr - OMe (XVIII) is

prepared by mixing H - Cys(Acm) Thr - OMe. TFA and TEA with Boc - D - Phe - Cys(Acm) - Phe - D - Trp - Lys (Boc) - Thr - OH (XIV) and HOBt and DCCI.

25. The process according to claim 10, for preparing H - (D) - Phe - Cys (Acm) - Phe - (D) - Trp - Lys - Thr Cys(Acm) - Thr - OMe. 2TFA (XIX) wherein Boc - (D) - Phe - Cys(Acm) - Phe - (D) - Trp - Lys (Boc) - Thr - Cys(Acm) - Thr - OMe is suspended in DCM and TFA is added.

26. Boc - D - Phe - Cys (Acm) - Phe - D - Trp - Lys (Boc) - Thr - OH.

27. H - D - Phe - Cys (Acm) - Phe - D - Trp - Lys - Thr - Cys (Acm) - Thr - OL.2TFA.

28. Boc - D - Phe - Cys (Acm) - Phe - OH.

29. D - Trp - Lys (Boc) - Thr - OMe.

30. Boc - D - Phe - Cys (Acm) - Phe - OMe.