United States Patent [19]

Wenger

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[54] **NOVEL CYCLOSPORINS**

[75] Inventor: **Roland Wenger**, Riehen, Switzerland

[73] Assignee: **Sandoz Ltd.**, Basel, Switzerland

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Related U.S. Application Data

[63] Continuation of Ser. No. 932,760, Nov. 19, 1986, abandoned, which is a continuation of Ser. No. 713,259, Mar. 19, 1985, abandoned.

[51] **Int. Cl.**[4] **A61K 37/02**; C07K 5/12

[52] **U.S. Cl.** **514/11**; 530/317

[58] **Field of Search** 530/321; 514/11

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,108,985	8/1978	Ruegger et al.	514/11
4,210,581	7/1980	Ruegger et al.	530/321
4,220,641	9/1980	Traber et al.	514/11

Primary Examiner—Delbert R. Phillips

Attorney, Agent, or Firm—Gerald D. Sharkin; Robert S. Honor; Thomas O. McGovern

[57] **ABSTRACT**

Cyclosporins wherein the amino acid residue at the 8-position is a (D)-acyloxy-α-amino acid residue, typically of formula

X-Y-Sar-MeLeu-Z-MeLeu-Ala-Q-MeLeu-MeLeu-MeVal

wherein X=—MeBmt— or —dihydro—MeBmt—, Y=—αAbu—, —Ala—, —Thr—, —Val— or —Nva—, Z=—Val— or —Nva— and Q=R_1—CO—O—CH(R_2)—CH(CO—)—NH— wherein R_1=H, C_{1-4}alkyl or phenyl and R_2=H or CH_3, possess immunosuppressive, anti-inflammatory and anti-parasitic activity.

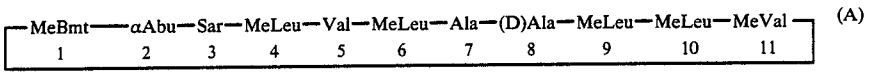
6 Claims, No Drawings

NOVEL CYCLOSPORINS

This is a continuation of application Ser. No. 932,760, filed Nov. 19, 1986, which in turn is a continuation of application Ser. No. 713,259, filed Mar. 19, 1985, both now abandoned.

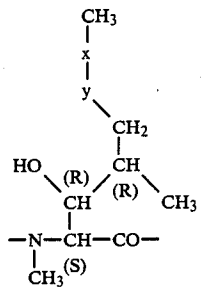
The present invention relates to novel cyclosporins, processes for their production, their use as pharmaceuticals and pharmaceutical compositions comprising them.

The cyclosporins comprise a class of structurally distinctive, cyclic, poly-N-methylated undecapeptides commonly possessing pharmacological, in particular immunosuppressive, anti-inflammatory and anti-parasitic activity. The first of the cyclosporins to be isolated and the "parent" compound of the class, was the naturally occurring fungal metabolite Cyclosporine, also known as cyclosporin A, of formula A



(A)

wherein —MeBmt— represents the N-methyl-(4R)-4-but-2E-en-1-yl-4-methyl-(L)threonyl residue of formula B



(B)

in which —x—y— is —CH=CH— (trans).

Since the original discovery of Cyclosporine a wide variety of naturally occurring cyclosporins have been isolated and identified and many further non-natural cyclosporins have been prepared by total- or semi-synthetic means or by the application of modified culture techniques. The class comprised by the cyclosporins is thus now substantial and includes for example the naturally occurring cyclosporins A through Z [c.f. Kobel et al. European Journal of applied Microbiology and Biotechnology 14, 237–240 (1982) and poster presented by Traber et al., 24th. Interscience Conference on Antimicrobial Agents and Chemotherpy, Washington, Oct. 8–10, (1984)]; as well as various non-natural or artificial cyclosporins, including dihydro-cyclosporins (in which the group —x—y— of the —MeBmt— residue—see formula B above—is saturated, e.g. as disclosed in U.S. Pat. Nos. 4,108,985; 4,210,581 and 4,220,641), cyclosporins in which the —MeBmt— residue is present in isomeric or N-desmethyl form [c.f. European Pat. No. 0 034 567 and "Cyclosporin A", Proc. Internat. Conference on Cyclosporin A, Cambridge (U.K.) September 1981, Ed. D. J. G. White, Elsevier Press (1982)—both describing the total-synthetic method for the production of cyclosporins developed by R. Wenger] and cyclosporins in which incorporation of variant amino acids at specific positions within the peptide sequence is effected (c.f. European Pat. No. 0 056 782). Examples of such cyclosporins as disclosed in the above art references include e.g. [Thr]^2—, [Val]^2—, [Nva]^2— and [Nva]^2—[Nva]^5—Cyclosporine (also known as cyclosporins C, D, G and M respectively), [Dihydro-MeBmt-]^1—[Val]^2—Cyclosporine (also known as dihydrocyclosporin D) and [(D)Ser]^8— and [Dihydro-MeBmt-]^1—[(D)-Ser]^8—Cyclosporine.

[In accordance with now conventional nomenclature for the cyclosporins, these are defined throughout the present specification and claims by reference to the structure of Cyclosporine (i.e. cyclosporin A). This is done by first indicating those residues in the molecule which differ from those present in Cyclosporine and then applying the term "Cyclosporine" to characterise the remaining residues which are identical to those present in Cyclosporine. At the same time the term —dihydro—MeBmt— is employed to designate the residue of formula B above in which —x—y— is —CH$_2$—CH$_2$—. Thus [Dihydro—MeBmt]^1—[Val]^2—Cyclosporine is the cyclosporin having the sequence shown in formula A, but in which —MeBmt— [formula B, —x—y—=—CH=CH— (trans)] at the 1-position is replaced by —dihydro—MeBmt— [formula B, —x—y—=—CH$_2$—CH$_2$—] and —αAbu— at the 2-position is replaced by —Val—. Similarly [(D)Ser]^8—Cyclosporine is the cyclosporin having the sequence shown in formula A, but in which —(D)Ala— at the 8-position is replaced by —(D)Ser—.

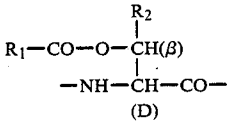
In addition, amino acid residues referred to by abbreviation, e.g. —Ala—, —MeVal— etc . . . are, in accordance with conventional practice, to be understood as having the (L)-configuration unless otherwise indicated. Residue abbreviations preceded by "Me", as in the case of —MeLeu— represent N-methylated residues. The individual residues of the cyclosporin molecule are numbered, as in the art, clockwise and starting with the residue —MeBmt— or —dihydro—MeBmt— in position 1. The same numerical sequence is employed throughout the present specification and claims.]

In accordance with the present invention it has now been found that novel cyclosporins may be obtained having pharmaceutical utility, in which the residue at the 8-position comprises an acyloxy α-amino acid residue having the (D)-configuration.

Accordingly, in its broadest aspect, the present invention provides: a cyclosporin wherein the amino acid residue at the 8-position is a (D)-acyloxy-α-amino acid residue, i.e. the residue of an α-amino acid of the (D)-series wherein the side chain attaching to the α-carbon atom is acyloxy-substituted.

Preferably the amino acid residue at the 8-position is a (D)-β-acyloxy-α-amino acid residue, i.e. the residue of an α-amino acid of the (D)-series having an acyloxy group attached at the β-carbon atom.

Preferred (D)-β-acyloxy-α-amino acid residues are those of formula II



(II)

wherein

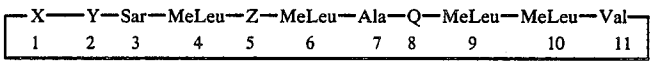
R_1 is hydrogen, C_{1-4}alkyl or phenyl and
R_2 is hydrogen or methyl.

Especially preferred cyclosporins in accordance with the present invention are those wherein the amino acid residue at the 8-position is an O-acyl-(D)-seryl or O-acyl-(D)-threonyl residue, in particular an O-acyl-(D)seryl or O-acyl-(D)-threonyl residue of formula II above.

In one group of cyclosporins in accordance with the present invention, the amino acid residue at the 8-position is an O-acyl-(D)-seryl residue, especially an O-acyl-(D)-seryl residue wherein the acyl moiety has the formula R_1—CO— in which R_1 has the meaning given above.

In a second group of cyclosporins in accordance with the present invention, the amino acid residue at the 8-position is a (D)-β-acyloxy-α-amino acid residue, especially an O-acyl-(D)-seryl residue, more especially an O-acyl-(D)-seryl residue wherein the acyl moiety has the formula R_1—CO— in which R_1 is hydrogen or C_{1-4}alkyl, and the residue at the 5-position is an (L)-norvalyl residue.

Most preferred are cyclosporins of formula I



(I)

wherein
X is —MeBmt— or —dihydro—MeBmt—,
Y is —αAbu—, —Ala—, —Thr—, —Val— or —Nva—
Z is —Val— or —Nva—, and
Q is a residue of formula II as defined above.

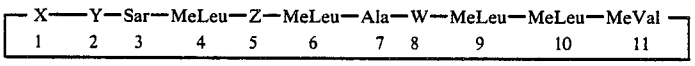
In formula I, Q is preferably an O-acyl-(D)-seryl or O-acyl-(D)-threonyl residue wherein the acyl moiety has the formula R_1—CO— in which R_1 has the meaning given for formula II. Y is preferably —αAbu—, —Thr—, —Val— or —Nva—.

A group of cyclosporins in accordance with the present invention are those of formula I as defined above, wherein Y is —αAbu— or —Nva—, Z is —Val— and R_2 is hydrogen.

A further group of cyclosporins in accordance with the present invention are those of formula I as defined above, wherein Y is —αAbu— or —Nva—, Z is —Nva—, R_1 is hydrogen or C_{1-4}alkyl and R_2 is hydrogen.

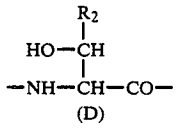
The present invention also provides a process for the production of a cyclosporin wherein the amino acid residue at the 8-position is a (D)-acyloxy-α-amino acid residue, for example a (D)-β-acyloxy-α-amino acid residue, e.g. for the production of a cyclosporin of formula I as defined above, which process comprises:

(a) Acylating a cyclosporin wherein the amino acid residue at the 8-position is a (D)-hydroxy-α-amino acid residue, for example a (D)-β-hydroxy-α-amino acid residue, e.g. acylating a cyclosporin of formula III



(III)

wherein X, Y and Z have the meanings given above for formula I and W is a residue of formula IV


(IV)

wherein R_2 has the meaning given above for formula II, to introduce a group R_1—CO—, wherein R_1 has the meaning given above for formula II, at the B-position of said residue IV; or

(b) Reducing a cyclosporin wherein the amino acid residue at the 1-position is —MeBmt— and the residue at the 8-position is a (D)-acyloxy-α-amino acid residue, for example a (D)-β-acyloxy-α-amino acid residue, to produce the corresponding cyclosporin wherein the residue at the 1-position is —dihydro—MeBmt—, e.g. reducing a cyclosporin of formula I as hereinbefore defined, wherein X is —MeBmt—, to produce the corresponding cyclosporin wherein X is —dihydro—MeBmt—.

Process step (a) above may be carried out in accordance with standard procedures for the acylation of hydroxy groups, for example by reaction with (preferably 2 equivalents or, when Y=—Thr—, 1 equivalent) of an appropriate acyl—, e.g. C_{1-5}alkanoyl— or benzoyl-halide, or corresponding -anhydride or, for formylation, by reaction with e.g. acetic-formic anhydride, at a temperature of e.g. from about −10° to 50° C. The reaction is carried out under anhydrous conditions, suitably in the presence of an inert solvent or diluent such as methylene chloride, and in the presence of a condensation agent such as 4-dimethyl-amino-pyridine. In this connection it is to be noted that the reaction proceeds with acylation occurring at the OH group of the amino acid residue at the 8-position, in preference to the hydroxy group of the amino acid residue at the 1-position.

Process step (b) may be carried out analogously to known methods for reducing naturally-occurring cyclosporins to the corresponding dihydrocyclosporins, for example by catalytic hydrogenation, e.g. in accordance with the general methods disclosed in U.K. Patent Specification No. 1,567,201.

Hydrogenation is suitably effected under neutral pH conditions at temperatures of from about 20° to about 30° C. and at atmospheric or slightly elevated pressure, in the presence of a catalyst such as platinum or, preferably, palladium (e.g. palladium on charcoal) in the presence of an inert solvent or diluent such as ethyl acetate or lower aliphatic alkanols such as methanol or isopropanol.

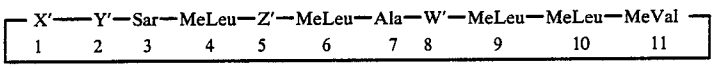
Cyclosporins having a β-hydroxy-α-amino acid residue at the 8-position, in particular [(D)Ser]^8-Cyclosporine and [Dihydro-MeBmt]^1-[(D)Ser]^8-Cyclosporine, suitable for use as starting materials in process step (a) above are known and have been described together with processes for their production, e.g. in the afore-

mentioned European Pat. No. 0 056 782. Other cyclosporins having a hydroxy-α-amino acid residue at the 8-position and required as starting materials for process step (a), may be prepared analogously or in accordance with the general procedures of the cyclosporin total-synthetic method described in European Pat. No. 0 034 567 to which publication 0 056 782 cross-refers, or in accordance with the procedures hereinunder described in particular in the accompanying examples.

The cyclosporins starting materials for use in process step (b) above are obtainable in accordance with the method of process step (a).

Although the cyclosporin starting materials of formula III above specifically disclosed in the accompanying examples are embraced by the broad disclosure of the aforementioned European Pat. No. 0 056 782, certain of these cyclosporins are formally novel over the teachings of that publication, i.e. have never previously been described as such. In accordance with the present invention it has also been found that these cyclosporins possess especially interesting or advantageous biological activity or profile, in particular in relation to immunosuppressive activity, and especially in relation to prevention of transplant, e.g. organ transplant, rejection, e.g. as compared with known cyclosporins of formula III, i.e. cyclosporins of formula III specifically disclosed in European Pat. No. 0 056 782.

Accordingly in a further aspect the present invention also provides a cyclosporin of formula IIIa



(IIIa)

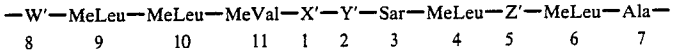
wherein
Y′ is —αAbu—, —Thr—, —Val— or —Nva—,
Z′ is —Val— or, when Y′ is —αAbu— or —Nva—, —Nva—
W′ is —(D)Ser— or, when Y′ is —αAbu— and Z′ is —Val—, —(D)Thr—, and
X′ is —MeBmt— or, when Y′ is —Thr—, —Val— or —Nva—, Z′ is —Val— and W′ is 13 (D)Ser—, —dihydro—MeBmt—.

Specific cyclosporins of formula IIIa are:
(a) [(D)Thr]^{8}-Cyclosporine
(b) [Thr]^{2}-[(D)Ser]^{8}-Cyclosporine
(c) [Dihydro-MeBmt]^{1}-[Thr]^{2}-[(D)Ser]^{8}-Cyclosporine
(d) [Val]^{2}-[(D)Ser]^{8}-Cyclosporine
(e) [Dihydro-MeBmt]^{1}-[Val]^{2}-[(D)Ser]^{8}-Cyclosporine
(f) [Nva]^{2}-[(D)Ser]^{8}-Cyclosporine
(g) [Dihydro-MeBmt]^{1}-[Nva]^{2}-[(D)Ser]^{8}-Cyclosporine
(h) [Nva]^{5}-[(D)Ser]^{8}-Cyclosporine; and
(i) [Nva]^{2}-[Nva]^{5}-[(D)Ser]^{8}-Cyclosporine

Of the above listed cyclosporins, (a), (b), (e), (f) and (i), and in particular (a), (f) and (i) are of especial interest, having regard to their activity (e.g. immunosuppressive activity)/activity profile, e.g. in relation to cyclosporins specifically disclosed in European Pat. No. 0 056 782.

In addition to the foregoing the present invention also provides a process for the production of a cyclosporin of formula IIIa as defined above, which process comprises: (c) Deprotecting a cyclosporin of formula III as defined above which is in O-protected form;

(d) Cyclising a straight chain undecapeptide comprising the sequence



wherein Y′, Z′, W′ and X′ have the meanings given above for formula IIIa, said undecapeptide being in unprotected or O-protected form and, when required, carrying out process step c;

(e) For the production of a cyclosporin of formula IIIa wherein
Y′ is —Thr—, —Val— or —Nva—,
Z′ is —Val— or, when Y′ is —Nva—, —Nva—,
W′ is —(D)Ser—
and X′ is —MeBmt—,
cultivating a [Thr]^{2}-Cyclosporine, [Val]^{2}-Cyclosporine, [Nva]^{2}-Cyclosporine or [Nva]^{2}-[Nva]^{5}-Cyclosporine producing fungus strain in contact with a nutrient medium containing (D)-Serine and isolating the cyclosporin of formula IIIa from the obtained culture medium;

(f) For the production of a cyclosporin of formula IIIa wherein X′ is -dihydro-MeBmt, reducing the corresponding cyclosporin of formula IIIa wherein X′ is —MeBmt—.

Undecapeptides suitable for use in process step (d) above may be obtained analogously to the general methods described in the above mentioned European Pat. No. 0 056 782, e.g. in relation to the flow chart to Example 1*a* thereof, by combination of the peptide sequence comprising residues 8 through 11 of the cyclosporin molecule with the sequence comprising residues 1 through 7 but with the required substitution of residues at positions 2 and/or 5 and/or 8. Suitably the —(D)Ser— or —(D)Thr— residue at the 8-position is in O-protected form, e.g.in the form of the O-t-butyl derivative. Cyclisation is carried out using the particular techniques described in the said European Patent, with final removal of O-protecting groups when present [process step (c)] in accordance with techniques known in the art of peptide chemistry.

The preferred fungus strain for use in the method of process step (e) is the strain NRRL 8044 of the species *Tolypocladium inflatum* (Gams), a culture of which has been deposited with the United States Department of Agriculture (Northern Research and Development Division), Peoria, Ill., USA and is freely available to the public. A further culture of this strain has been deposited with the Fermentation Research Institute, Inage, Chiba City, Japan, under the code number FRI FERM-p No. 2796. The morphological characteristics of said strain, originally classified as belonging to the species *Trichoderma polysporum* (Link ex Pers.), as well as methods for the preparation and maintainance of pre- and sub-cultures are fully described e.g. in UK patent specification No. 1,491,509.

In accordance with process step (e) the selected strain [e.g. *Tolypocladium inflatum* (Gams)] is suitably maintained for a period of ca. 2 weeks at a temperature of ca. 27° C. in a culture medium such as described in the

following examples, in the presence of added (D)- or (D,L)-serine. The amino acid precursor is suitably added in an amount of from about 1 to about 15 g, more preferably from about 4 to about 10 g/liter culture medium. Suitably the culture medium also contains added amino acid precursor for the residue present in the desired cyclosporin at position 2, e.g. in amounts of from about 6.0 to about 10.0, preferably about 8.0 g/liter culture medium. Following incubation the culture is harvested and the obtained cyclosporin of formula IIIa extracted in accordance with known techniques, e.g. by comminution of conidia and mycelia, followed by extractive and/or absorptive isolation. The initially obtained, raw cyclosporin may thereafter be purified e.g. chromatographically and/or by recrystallisation, in particular to effect separation from other cyclosporin contaminants in particular "natural cyclosporin" contaminants.

Process step (f) above may be carried out e.g. using the same methods hereinbefore described in relation to process step (b).

The following examples are illustrative of the processes of the present invention.

EXAMPLE 1

Synthesis of [(O-acetyl)-(D)Ser]^8-Cyclosporine [Formula I: X=—MeBmt—, Y=—αAbu—, Z=—Val—, Q=—O—acetyl—(D)Ser—]

20 mg 4-dimethylaminopyridine are added to 47 mg [(D)Ser^8]-Cyclosporine (prepared in accordance with the method described in Example 1 or 3 of the above mentioned European Pat. No. 0 056 782) dissolved in 3 ml methylene chloride. 6.1 mg of freshly distilled acetylchloride in 1 ml methylene chloride are then added and the obtained reaction mixture is stirred for 1 hour at room temperature. The reaction mixture is diluted with 50 ml methylene chloride and shaken with 30 ml H_2O. The organic phase is separated, dried over Na_2SO_4, filtered off and evaporated. The residue is filtered on 60 g silica gel (0.062–0.20 mm) using methylene chloride/5% methanol as eluant and collected in 25 ml fractions. The title compound is recovered from fractions 4 to 8 by thin layer chromatography using $CHCl_3$/5 % methanol as carrier phase: $[\alpha]_D^{20}=-202°$ (c=0.92 in $CHCl_3$).

EXAMPLE 2

The following compounds may be prepared analogously to example 1 starting from the corresponding non-acylated cyclosporin:

2.1 [(O-benzoyl-(D)Ser]^8-Cyclosporine [Formula I: X=—MeBmt—, Y=—αAbu—, Z=—Val—, Q=—O—benzoyl—(D)Ser-]: $[\alpha]_D^{20}=-220°$ (c=1.0 in $CHCl_3$);

2.2 [O-acetyl-(D)Thr]^8-Cyclosporine Formula I: X=—MeBmt—, Y=—αAbu—, Z=—Val—, Q=—O-acetyl-(D)-Ser-]: $[\alpha]_D^{20}=-219°$ (c=1.0 in $CHCl_3$);

2.3 [Nva]^2-[O-acetyl-(D)Ser]8-Cyclosporine [Formula I: X=—MeBmt—, Y=—Nva—, Z=—Val—, Q=-O-acetyl-(D)Ser-]: $[\alpha]_D^{20}=-240°$ (c=1.0 in $CHCl_3$)/−233° (c=0.8 in $CHCl_3$)/−177° (c=0.76 in CH_3OH): m.p.=143°–147° C.

2.4 [Val]^2-[O-acetyl-(D)Ser]^8-Cyclosporine [Formula I: X=—MeBmt—, Y=—Val—, Z=—Val—, Q=-O-acetyl-(D)Ser-]: $[\alpha]_D^{20}=-219°$ (c=0.9 in $CHCl_3$);

2.5 [Nva]^5-[O-acetyl-(D)Ser]^8-Cyclosporine [Formula I: X=—MeBmt—, Y=—αAbu—, Z=—Nva—, Q=-O-acetyl-(D)Ser-]: $[\alpha]_D^{20}=-215°$ (c=1.0 in $CHCl_3$);

2.6 [Nva]^2-[Nva]^5-[O-acetyl-(D)Ser]^8-Cyclosporine [Formula I: X=—MeBmt—, Y=—Nva—, Z=—Nva—, Q=-O-acety-(D)Ser-]: $[\alpha]_D^{20}=-196.9°$ (c=1.0 in $CHCl_3$); and

2.7 [Thr]^2-[O-acetyl-(D)Ser]^8-Cyclosporine [Formula I: X=—MeBmt—, Y=—Thr—, Z=—Val— Q=-O-acetyl-(D)Ser-]: $[\alpha]_D^{20}=-251°$ (c=0.86 in $CHCl_3$)/−174° (c=0.81 in CH_3OH): m.p.=143°–146° C.

EXAMPLE 3

Synthesis of [Dihydro-MeBmt]^1—[O-acetyl-(D)Ser]^8-Cyclosporine [Formula I: X=—dihydro—MeBmt—, Y=—αAbu—, Z=—Val—, Q=-O-acetyl-(D)Ser-]

54 mg of [(O-acetyl)-(D)Ser^8]-Cyclosporine in 10 ml ethanol are hydrogenated using 10 mg palladium/charcoal (10%) at room temperature and under normal pressure. After 20 hours the obtained reaction solution is filtered through a thin layer of talc and the ethanol is evaporated off under vacuum. After further drying under high vacuum, the title compound is obtained: $[\alpha]_D^{20}=-205.8°$ (c=1.02 in $CHCl_3$).

EXAMPLE 4

The following compounds may be prepared either analogously to example 1, starting from the corresponding non-acylated cyclosporin or analogously to example 3, by hydrogenation of the corresponding cyclosporin described in example 2:

4.1 [Dihydro-MeBmt]^1-[Nva]^2-[O-acetyl-(D)Ser]^8-Cyclosporine [Formula I: X=—dihydro—MeBmt13 , Y=—Nva—, Z=—Val—, Q=-O-acetyl-(D)Ser-]: m.p.=139°–141° C.; $[\alpha]_D^{20}=-225°$ (c=0.88 in $CHCl_3$)/−163° (c=0.76 in CH_3OH);

4.2 [Dihydro-MeBmt]^1-[Val]^2-[O-acetyl-(D)Ser]^8-Cyclosporine [Formula I: X=—dihydro—MeBmt—, Y=—Val—, Z=—Val—, Q=-O-acetyl-(D)Ser-]: $[\alpha]_D^{20}=-210°$ (c=0.85 in $CHCl_3$); and

4.3 [Dihydro-MeBmt]^1-[Thr]^2-[O-acetyl-(D)Ser]^8-Cyclosproine [Formula I: X=—dihydro—MeBmt—, Y=—Thr—, Z=—Val—, Q=O-acetyl-(D)Ser-]: $[\alpha]_D^{20}=-241°$ (c=1.0 in $CHCl_3$)/−162° (c=1.0 in CH_3OH): m.p.=148°–150° C.

Preparation of starting materials

EXAMPLE 5

The following compounds required as starting materials for the production of the compounds of examples 2.2 through 2.7 may be prepared analogously to the known compound [(D)Ser]^8-Cyclosporine, the preparation of which is described in Example 1 of European Pat. No. 0 056 782, with substitution of the appropriate residues at positions 2 and/or 5 and/or 8 in the process sequence set forth in the flow chart to Example 1*a* of said patent:

5.1 [(D)Thr]^8-Cyclosporine [Formula IIIa: X'=—MeBmt—, Y'=—αAbu—, Z'=—Val—, W'=—(D)-Thr—]: $[\alpha]_D^{20}=-248.7°$ (c=1.0 in $CHCl_3$);

5.2 [Nva]^2-[(D)Ser]^8-Cyclosporine [Formula IIIa: X'=—MeBmt—, Y'=—Nva—, Z'=—Val—, W'=—(D)Ser—]: m.p.=150°–153° C.; $[\alpha]_D^{20}=-262°$ (c=0.71 in $CHCl_3$)/−191° (c=0.73 in CH_3OH);

5.3 [Val]^2-[(D)Ser]^8-Cyclosporine [Formula IIIa: X'=—MeBmt—, Y'=—Val—, Z'=—Val—,

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