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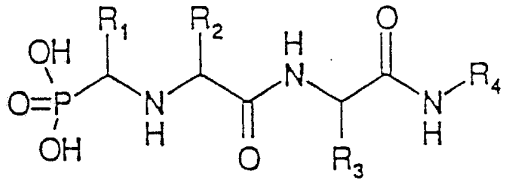

(I)

(57) Abstract

Phosphorus derivatives having structure (I), processes for their preparation and their use as collagenase inhibitors.

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Phosphonopeptides with collagenase inhibiting activity.

The present invention relates to novel phosphorus derivatives, processes for their preparation and their use in medicine. In particular, the present invention relates to their use as inhibitors of enzymes of the collagenase family of neutral metalloproteases, for treating arthritic and other diseases.

The mammalian collagenase family of enzymes comprises a number of proteases, exemplified by interstitial (type I) collagenase itself, the stromelysins (also known as proteoglycanases or transins), fibroblast and polymorphonuclear leucocyte gelatinases (also known as collagen-IV-ases), and 'pump-1' (putative metalloprotease 1, uterine metalloprotease) [Goldberg **et al**, J. Biol. Chem. **2610**, 6600, 1986; Whitham **et al**, Biochem. J. **240**, 913, 1986; Breathnach **et al**, Nucleic Acids Res., **15**, 1139, 1987; Muller **et al**, Biochem. J., **253**, 187, 1988; Collier **et al**, J. Biol. Chem., **263**, 6579, 1988; Murphy **et al**, Biochem. J., **258**, 463, 1989; Quantin **et al**, Biochem. (N.Y.), **28**, 5327, 1989; Birkedal-Hansen, J. Oral Pathol., **17**, 445, 1988; P. Basset **et al**, Nature **348**, 699, 1990]. Membership of the mammalian collagenase family of proteases is evident by possession of a number of highly characteristic and experimentally verifiable properties as described in EPA 401963 (Beecham Group), which can be adopted as criteria for allocation to this family of enzymes.

As a particular example of the therapeutic value of inhibitors of the collagenase family of enzymes, such as are disclosed in the present invention, chronic arthritic diseases leading to extensive loss of the collagen, proteoglycan and elastin components of the cartilage, bone and tendons within the joints, should be amenable to treatment with inhibitors of the collagenases, proteoglycanases (stromelysins) and gelatinases currently thought to be the major enzymes involved.

These enzymes have been detected in extracts of synovial and cartilage tissue, and have also been extensively studied in tissue cultures of a wide range of connective tissues. Apart from control of the biosynthesis, secretion and activation of the enzymes, the most important natural regulation of these enzymes in normal and diseased states, is considered to be the endogenous production of inhibitors such as the Tissue Inhibitor of Metalloproteinases and alpha-2 macroglobulin. An imbalance between the local levels of the proteolytic enzymes and of their natural inhibitors will allow destruction of connective tissue components to occur.

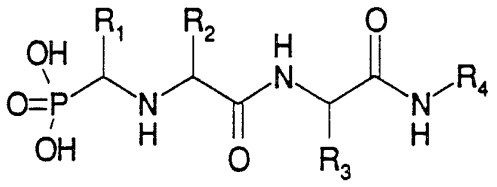
The compounds described in the present invention, being synthetic and low molecular weight inhibitors of this family of enzymes, offer a therapeutically useful way in which a more normal or non-pathological balance between inhibition and enzymic activity can be restored: they thus act to complement and supplement the endogenous enzyme inhibitors. Indeed, because these enzymes usually act only within restricted pericellular environments, before being inactivated by inhibitors circulating in the blood and present in most inflammatory exudates, the low molecular weight inhibitors disclosed here may be more effective than endogenous proteinaceous inhibitors that are excluded by their size from the localized regions of connective tissue destruction.

EPA-320118 (Beecham Group) discloses a class of phosphorus derivatives having activity as inhibitors of collagenase and utility in the treatment of rheumatoid arthritis and related diseases in which collagenolytic activity is a contributing factor.

Novel phosphorous derivatives have now been discovered, which are collagenase inhibitors and thus of potential

utility in the treatment of diseases in which collagenolytic activity and tissue remodelling is implicated.

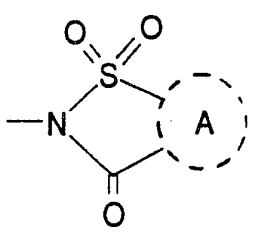
According to the present invention there is provided a compound of general formula (I), or a salt thereof:



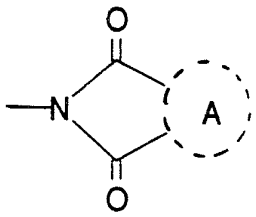
(I)

in which,

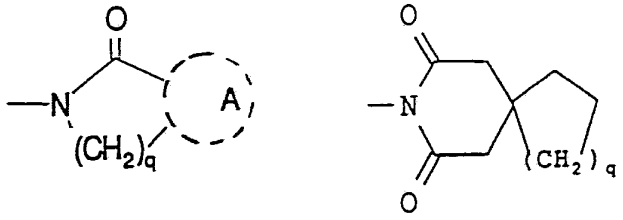
R_1 is $-(CH_2)_n-W$ where n is 0-6 and W is amino, optionally-substituted phenyl, $-CONR_5R_6$, $-NR_5COR_6$, $NR_5CO_2CH_2R_6$ or $NR_5CONR_5R_6$ where R_5 is hydrogen or C_{1-6} alkyl and R_6 is hydrogen, C_{1-6} alkyl, optionally-substituted phenyl or heteroaryl, or R_5 and R_6 together with the nitrogen atom to which they are bonded form a 5-, 6- or 7-membered ring with an optional oxygen or sulphur atom or an optionally substituted second nitrogen atom in the ring; or W is $-S(O)_p-R_7$ where p is 0, 1 or 2 and R_7 is C_{1-6}alkyl; or W is a group of sub-formula (a), (b), (c) or (d):



(a)



(b)

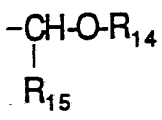


(c) (d)

where in sub-formula (a), (b) and (c) A represents an optionally-substituted mono or bicyclic aryl or heteroaryl ring, and in sub-formula (c) and (d) q is an integer from 1 to 3;

R_2 is C_{3-6} alkyl;

R_3 is hydrogen, C_{1-6}alkyl, $-CH_2-Z$ where Z is optionally substituted phenyl or heteroaryl, $-(CH_2)_rNR_8R_9$, $-(CH_2)_rNHCOR_{10}$, $-(CH_2)_rNR_{11}C(=NR_{12})NR_8R_9$, $-(CH_2)_rCONH(CH_2)_sNR_8R_9$ or $-(CH_2)_r-R_{13}$ where r is 1 to 6, s is 2 to 4, each of R_8 and R_9 is independently hydrogen or C_{1-6}alkyl or R_8 and R_9 together with the nitrogen atom to which they are bonded form a 5-, 6- or 7-membered ring with an optional oxygen or sulphur atom or an optionally substituted second nitrogen atom in the ring, R_{10} is C_{1-6}alkyl or $-(CH_2)_tNR_8R_9$ where t is 1 or 2 and R_8 and R_9 are as defined above, R_{11} is hydrogen or C_{1-6}alkyl or R_{11} and R_8, together with the nitrogen atoms to which they are bonded, form an optionally substituted 5-, 6- or 7-membered ring, R_{12} is hydrogen or C_{1-6}alkyl and R_{13} is an optionally substituted piperidyl ring or R_3 is a group:



where R_{14} is hydrogen, C_{1-6}alkyl or optionally substituted benzyl and R_{15} is hydrogen or C_{1-6}alkyl; and

R_4 is hydrogen, C_{1-6}alkyl or $-(CH_2)_rNR_8R_9$ in which r, R_8 and R_9 are as defined for R_3; or R_3 and R_4 are joined together as $-(CH_2)_m-$ where m is an integer from 4 to 12, or R_3 and R_4

are joined as $-(CH_2)_x-NR_{16}-(CH_2)_y-$ where x is an integer from 1 to 9, y is an integer from 2 to 10, and the moiety $-(CH_2)_x-$ is adjacent to the carbon atom bearing R_3 marked with an asterisk in formula (I), and R_{16} is selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkanoyl, C_{1-6}alkoxycarbonyl, aroyl, aralkyl or aralkyloxycarbonyl in each of which the aryl moiety is optionally substituted.

C_{1-6}alkyl groups (either alone or as part of another group), may be a straight chain or branched.

Optional substituents for aryl and heteroaryl groups may be selected from OH, C_{1-6} alkyl, C_{1-6} alkoxy, halogen, $-NHCO(C_{1-6})$alkyl, -NHCOPh and $-CONR_5R_6$, where Ph is optionally substituted phenyl and R_5 and R_6 are as defined above.

The term aryl includes phenyl and naphthyl.

It will be understood that the term heteroaryl includes aromatic heterocyclic groups containing one or more heteroatoms and includes 5- or 6-membered monocyclic and 9- or 10-membered bicyclic heteroaryl groups which preferably contain one or two heteroatoms selected from nitrogen, oxygen and sulphur. When Z is 9- or 10-membered bicyclic heteroaryl the two rings are fused with one 5- or 6-membered ring preferably containing a single heteroatom, for example indolyl.

When R_5 and R_6 or R_8 and R_9 groups combined with their appended nitrogen atom to form a heterocyclic ring, typical examples of a suitable ring structure are piperidine, or pyrrollidine, piperazine and morpholine. When such groups contain a second nitrogen heteroatom this may be optionally substituted, for example, by a C_{1-6}alkyl group.

Suitably R_1 is $-(CH_2)_n-W$ where n is 0, 1, 2 or 3.

Suitably W is amino, phenyl, N-phthalimido or 1,8-naphthalenedicarboxamido each of which may be optionally substituted, $NHCO_2CH_2R_6$ where R_6 is optionally substituted phenyl or $S(O)_pCH_3$ where p is 0, 1 or 2.

Preferably R_1 is 2-hydroxyphenyl, $-(CH_2)_n-W$ where n is 2 and W is amino, phenyl, 2-hydroxyphenyl, $NHCO_2CH_2Ph$, N-phthalimido, 4-bromo-1,8-naphthalenedicarboxamido, 7,9-dioxo-8-azaspiro[4,5]decyl, methylmercapto, methylsulphinyl or methylsulphonyl, or R_1 is $-(CH_2)_n-W$ where n is 1, 2 or 3 and W is a 1,8-naphthalenedicarboxamido group.

Suitably R_2 is a C_4 alkyl group, such as **n**-butyl, **iso**-butyl or **sec**-butyl. Preferably R_2 is **iso**-butyl.

Suitably R_3 is benzyl, C_{1-6}alkylamino, 4-hydroxybenzyl, C_{1-6}alkoxybenzyl such as 4-methoxybenzyl, or 9- or 10-membered fused bicyclic heteroarylmethyl such as 3-indolylmethyl. Preferably R_3 is benzyl, 4-methoxybenzyl, $-(CH_2)_4NH_2$ or 3-indolylmethyl.

Suitably R_4 is methyl, ethyl or $-(CH_2)_rNR^8R^9$. Preferably R_4 is methyl or $-(CH_2)_2NR^8R^9$ where R^8 and R^9 are both hydrogen or R^8 and R^9 together with the nitrogen atom to which they are bonded form a pyrrolidine or N-methylpiperazine group.

Suitably, when groups R_3 and R_4 are combined as $-(CH_2)_m-$ then m = 10, resulting in a lactam structure based on a 13-membered ring.

Suitably, when groups R_3 and R_4 are combined as $-(CH_2)_x-NR_{16}-(CH_2)_y-$ then x and y have values such that R_3 and R_4 form part of an 11- to 16-membered azalactam structure and R_{16} is hydrogen, methyl, benzyl, t-butoxy-carbonyl or benzyloxycarbonyl.

Preferably, when groups R_3 and R_4 are combined they form a group $-(CH_2)_{10}-$.

Particular compounds of this invention include:
N-[N-(1-phosphono-1-(2-hydroxyphenyl)methyl)-leucyl]-N,O-dimethyl-(S)-tyrosinamide,
N-[N-(1-phosphono-3-(1,8-naphthalenedicarboximide)propyl)-(S)-leucyl]-N,O-dimethyl-(S)-tyrosinamide,
N-[N-(1-phosphono-3-phthalimidopropyl)-(S)-leucyl]-(S)-phenylalanine-N-methylamide,
N-[N-(1-phosphono-4-(1,8-naphthalenedicarboximido)butyl)-(S)-leucyl]-(S)-phenylalanine-N-methylamide,
N-[N-(1-phosphono-2-(1,8-naphthalenedicarboximido)ethyl-(S)-leucyl]-(S)-phenylalanine-N-methylamide,
N-[N-(1-phosphono-3-(1,8-naphthalenedicarboximido)propyl)-(S)-leucyl]-(S)-phenylalanine-N-methylamide,
N-[N-(1-phosphono-3-phenylpropyl)-(S)-leucyl]-(S)-phenylalanine-N-methylamide,
N-[N-(1-phosphono-3-(4-bromo-1,8-naphthalene-dicarboximido)propyl)-(S)-leucyl]-(S)-phenylalanine methylamide,
N-[N-(1-phosphono-3-(benzyloxycarbonylamino)propyl)-(S)-leucyl]-(S)-phenylalanine methylamide,
N-[N-(1-phosphono-3-(2-hydroxyphenyl)propyl)-(S)-leucyl]-(S)-phenylalanine methylamide,
N-[N-(1-phosphono-3-(methylmercapto)propyl)-(S)-leucyl]-(S)-phenylalanine-N-methylamide,
N-[N-(1-phosphono-3-(methylsulphinyl)propyl)-(S)-leucyl]-(S)-phenylalanine-N-methylamide,
N-[N-(1-phosphono-3-(methylsulphonyl)propyl-(S)-leucyl]-(S)-phenylalanine-N-methylamide,
N-[N-(1-phosphono-3-(1,8-naphthalenedicarboximido)propyl)-(S)-leucyl]-(S) tryptophan-N-methylamide,
N-[N-(1-phosphono-3-(1,8-naphthalenedicarboximido)propyl)-(S)-leucyl-(S)-lysine-N-methylamide,
N-[N-(1-phosphono-3-(1,8-naphthalenedicarboximido)propyl)-(S)-leucyl]-(-)-aminoazacyclotridecan-2-one,

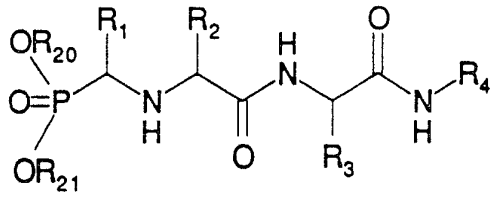
N-[N-(1-phosphono-3-(1,8-naphthalenedicarboximido)propyl)-(S)-leucyl]-(S)-lysine-N-(aminoethyl) amide,
N-[N-(1-phosphono-3-(1,8-naphthalenedicarboximido)propyl)-(S)-leucyl]-(S)-lysine-N-(ethylpyrrolidine) amide,
N-[N-(1-phosphono-3-(1,8-naphthalenedicarboximido)propyl)-(S)-leucyl]-(S)-lysine-N-(ethyl-N-methylpiperazine) amide,
N-[N-(1-phosphono-3-[8-(7,9-dioxo-8-azaspiro[4,5]decyl)]-propyl)-(S)-leucyl]-(S)-phenylalanine-N-methylamide, or
N-[N-(1-phosphono-3-[8-(7,9-dioxo-8-azaspiro[4,5]decyl)]-propyl)-(S)-leucyl]-(S)-lysine-N-methylamide,
and pharmaceutically acceptable salts thereof.

The compounds of formula (I) may form salts with bases e.g. sodium hydroxide. The compounds of formula (I) have a basic nitrogen atom and may form acid addition salts e.g. hydrochloride, hydrobromide, sulphate, phosphate, acetate, fumarate, maleate, citrate, lactate, tartrate, oxalate and similar acid addition salts. Such compounds form part of the present invention.

The compounds of formula (I) have at least two, and may have three or more asymmetric centres and therefore exist in more than one stereoisomeric form. The invention extends to all such forms and to mixtures thereof, including racemates, and diastereoisomeric mixtures.

Preferred isomers are those having the (S)- or (-)-configuration at the chiral centre bearing R_3 when R_3 is other than hydrogen, and those having the (S)-configuration at the chiral centre bearing R_2, both marked with an asterisk in formula (I).

The present invention also provides a process for the preparation of a compound of formula (I) which comprises cleaving a group R_{20} from a compound of formula (II):



(II)

wherein R_{20} is C_{1-6}alkyl, optionally substituted phenyl or optionally substituted benzyl and R_{21} is hydrogen, C_{1-6}alkyl or optionally substituted benzyl and R_1, R_2, R_3 and R_4 are as defined in formula (I), and where necessary, converting R_{21} to hydrogen by a further cleavage reaction.

Cleavage of R_{20} and, where necessary, R_{21}, may be carried out in aqueous acid or alkali or using a trimethylsilyl halide, preferably bromotrimethylsilane, in an inert solvent, for example dichloromethane. Benzyl esters may alternatively be removed by hydrogenolysis or other standard debenzylation procedures.

When both R_{20} and R_{21} are C_{1-6}alkyl, cleavage of R_{20} only, to give to a compound of formula (II) in which R_{20} is hydrogen and R_{21} is C_{1-6}alkyl, may be carried out by treatment with excess alkali under mild conditions, for example with aqueous sodium hydroxide in an alcoholic solvent at room temperature.

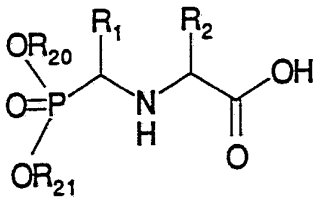
Similarly, where R_{20} is optionally substituted benzyl and R_{21} is C_{1-6}alkyl, the benzyl group only may be cleaved by hydrogenolysis to give a compound of formula (II) in which R_{20} is hydrogen and R_{21} is C_{1-6}alkyl.

Cleavage of an R_{21} C_{1-6}alkyl group may thereafter be carried out as described above to give the compound of formula (I).

When R_{21} is not hydrogen, then cleavage of both R_{21} and R_{20} is conveniently effected in a single reaction. Preferably R_{20} and R_{21} are both C_{1-6}alkyl, such as methyl or ethyl, or R_{20} and R_{21} are both benzyl.

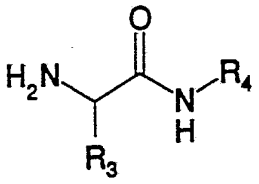
Compounds of formula (II) are believed to be novel and form a further aspect of the invention.

Compounds of formula (II) may be prepared by treating a compound of formula (III):



(III)

in which R_1, R_2, R_{20} and R_{21} are as defined in formula (II) (except that R_{21} is not H), with a compound of formula (IV):



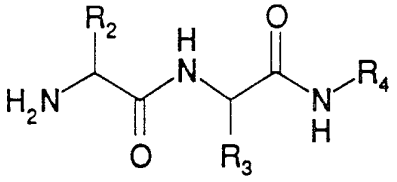
(IV)

in which R_3 and R_4 are as defined in formula (I).

The reaction is preferably carried out in the presence of a coupling agent, such as dicyclohexylcarbodiimide or 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride in the presence of 1-hydroxybenzotriazole, or using 1,1'-carbonyldiimidazole, in an inert solvent such as dichloromethane or acetonitrile.

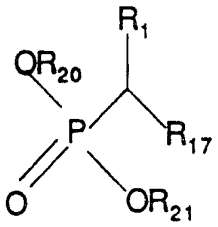
Selective cleavage of the group R_{21} may then be carried out using the procedures described above for the preparation of compounds of formula (I) to give compounds of formula (II) in which R_{21} is hydrogen.

Alternatively, compounds of formula (II) in which R_{20} and R_{21} are C_{1-6}alkyl or optionally substituted benzyl may be prepared by the reaction of a compound of formula (V):



(V)

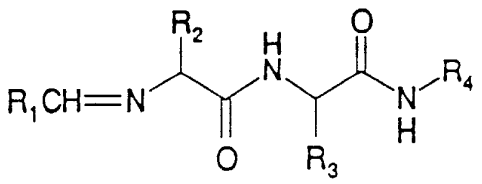
in which R_2, R_3 and R_4 are as defined in formula (I), with a compound of formula (VI):



in which R_1 is as defined in formula (I), R_{20} and R_{21} are C_{1-6}alkyl or optionally substituted benzyl and R_{17} is a leaving group such as halogen, methanesulphonyloxy or trifluoromethanesulphonyloxy, in the presence of a base such as triethylamine or Proton Sponge (1,8-bis(dimethylamino)-naphthalene), or using anhydrous potassium carbonate in an alcoholic solvent.

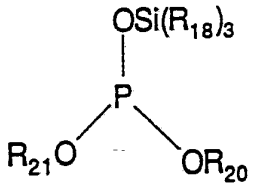
Where R_{17} is an oxygen-based leaving group, for example trifluoromethanesulphonyloxy, which is preferred, displacement of the leaving group is conveniently carried out in the presence of Proton Sponge in an inert solvent such as acetonitrile or dichloromethane, over a period of several days in the absence of light.

As a further alternative, compounds of formula (II) in which R_{20} and R_{21} are C_{1-6}alkyl, optionally substituted aryl or optionally substituted benzyl may be prepared by reaction of a compound of formula VII:



(VII)

in which R_1, R_2, R_3 and R_4 are as defined for formula (I) with a compound of formula (VIII):

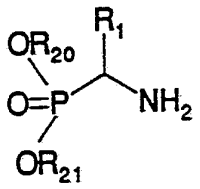


(VIII)

in which R_{18} is C_{1-6}alkyl and R_{20} and R_{21} are as defined for formula (II) provided that R_{21} is not hydrogen and thereafter removing the phosphonic acid protecting group.

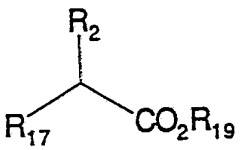
The reaction is suitably carried out in an organic solvent such as dichloromethane at reduced temperature, e.g. -10 to 5°C.

The intermediate compounds of formula (III) may be prepared by treating a compound of formula (IX) or a salt thereof:

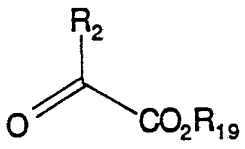


(IX)

in which R_1, R_{20} and R_{21} are as defined in formula (III), with a compound of formula (XA) or (XB) or a salt thereof:



(XA)



(XB)

in which R_2 is as defined in formula (I), R_{17} is as defined in formula (VI) and R_{19} is hydrogen or a carboxyl protecting group, and thereafter removing the R_{19} carboxyl protecting group.

When a compound of formula (XB) is used, the reductive amination may be carried out by hydrogenation over a noble metal catalyst such as palladium on carbon or by reaction with sodium cyanoborohydride at pH 6 to 7. Lower alkyl alcohol solvents such as methanol and ethanol are suitable for both reactions. These reactions may be carried out in the presence of molecular sieves.

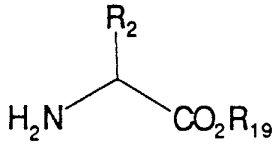
A hydrogenation reaction is preferred but this process precludes the use of compounds of formulae (IX) and (XB) in which any of R_{20}, R_{21} or R_{19} is benzyl. Preferably a carboxyl protecting group is a methyl or ethyl ester. Ester protecting groups may be removed under standard basic hydrolysis conditions using dilute base such as 1 Normal aqueous sodium hydroxide in methanol.

When the compound of formula (IX) is in the form of the free base, the compound of formula (XB) is suitably an α-keto ester (R_{19} = C_{1-6}alkyl).

When the compound of formula (IX) is a salt, such as the hydrochloride salt, the compound of formula (XB) is suitably a salt of an α-keto acid (R_{19} = H), for example the sodium salt.

The preparation of compounds of formula (III) using a compound of formula (XA) may be carried out under standard alkylation conditions. A halogen leaving group is preferably bromine and an oxygen-based leaving group is preferably trifluoromethanesulphonyloxy.

Compounds of formula (III) may alternatively be prepared by condensing a compound of formula (XI) or a salt thereof:

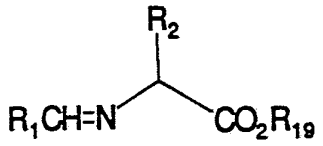


(XI)

in which R_2 is as defined in formula (I) and R_{19} is a carboxyl protecting group with an aldehyde, R_1-CHO in which R_1 is as defined in formula (I) and treating the condensation product with an appropriate phosphite, for example dimethyl phosphite, diphenyl phosphite or dibenzyl phosphite and thereafter removing the carboxyl protecting group. The carboxyl group is conveniently protected as an alkyl or benzyl ester which may be removed using standard hydrolysis or hydrogenation conditions.

As described above in connection with reductive amination of compounds of formula (XB), where a benzyl protecting group R_{19} is removed by hydrogenation then R_{20} and R_{21} are restricted to C_{1-6}alkyl.

As a further alternative, compounds of formula (III) may be prepared by treating a compound of formula (XII):



(XII)

in which R_1 and R_2 are as defined in formula (I) and R_{19} is a carboxyl protecting group as defined for formula (XI) with a compound of formula (VIII) as hereinbefore defined using conditions as described for the reaction of compounds of formulae (VII) and (VIII).

A further alternative preparation of compounds of formula (III) may be carried out by reacting a compound of formula (VI) as hereinbefore defined with a compound of formula (XI) as hereinbefore defined, using conditions as described for the reaction of compounds of formula (V) with compounds of formula (VI), and thereafter removing the protecting group R_{19}.

Suitable carboxyl protecting groups include alkyl, benzyl and trialkylsilyl groups. A trialkylsilyl protecting group,

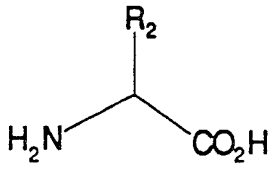
for example trimethylsilyl, is especially useful in that it may be readily incorporated, **in situ**, for example by addition of hexamethyldisilazane to the reactants in acetonitrile in the presence of triethylamine, and selectively removed in aqueous methanol, without imposing any limitations on the value of R_{20} and R_{21}. Other silylating agents include trimethylsilyl chloride and N,N-diethyltrimethylsilylamine.

An R_{19} alkyl carboxyl protecting group may be removed by base hydrolysis, for example using sodium hydroxide in aqueous methanol.

It will be appreciated that where the carboxyl protecting group R_{19} is alkyl, R_{20} and R_{21} may be alkyl or benzyl derivatives, but where R_{19} is a benzyl group, R_{20} and R_{21} are limited to alkyl.

When compounds of formula (III) are prepared by this route, it is preferred that R_{20} and R_{21} are benzyl and R_{17} is trifluoromethanesulphonyloxy in the compound of formula (VI) and R_{19} is trimethylsilyl or methyl in the compound of formula (XI).

Compounds of formula (V) may be prepared by treating a compound of formula (XIII):



(XIII)

in which R_2 is as defined in formula (I) and wherein the amino group is optionally protected, with a compound of formula (IV) as hereinbefore defined, in the presence of a coupling agent as hereinbefore described for the preparation of compounds of formula (II) from compounds of formulae (III) and (IV).

Compounds of formula (VII) may be prepared by reaction of an aldehyde R_1-CHO in which R_1 is as defined in formula (I) with an amine of formula (V) as hereinbefore defined in an organic solvent such as dichloromethane at reduced temperature (e.g. -10 to 5°C) in the presence of magnesium sulphate.

Compounds of formula (VIII) may be prepared by reaction of the corresponding phosphite, for example dimethylphosphite or dibenzylphosphite with a trialkylsilylhalide, for example trimethylsilyl chloride, in an inert solvent such as dichloromethane at reduced temperature (e.g. -10 to 5°C) in the presence of a base such as a trialkylamine.

Compounds of formula (VI) may be prepared from hydroxyalkylphosphonate derivatives by conversion of the hydroxyl group to the leaving group R_{17} by conventional methods. For example, where R_{17} is trifluoromethanesulphonyloxy, trifluoromethanesulphonic anhydride may be added to a solution of the hydroxyalkylphosphonate in an inert solvent such as dichloromethane, the reaction being carried out at reduced temperature under an inert atmosphere, according to the general method of E. Vedejs **et al.**, Journal of Organic Chemistry **50**, 2165, (1985).

Hydroxyalkylphosphonate compounds may in turn be prepared by reaction of the corresponding phosphite, for example dibenzylphosphite, with an aldehyde R_1-CHO in which R_1 is as defined in formula (I) according to the general method of F. Texier-Boullet and A. Foucaud, Synthesis, 916 (1982). Benzyl and alkyl phosphites are either commercially available compounds or can be prepared from commercially available starting materials by standard methods.

Intermediate compounds of formula (IX) are either known compounds or may be prepared from known aminoalkyl phosphonic acid derivatives using standard procedures to introduce the R_{20} and R_{21} as required. Protection of the

amine function during these reactions may be necessary. Introduction of an R_{20} or R_{21} methyl group may be effected by reaction with diazomethane in a suitable inert solvent.

Compounds of formula (IX) of fixed configuration may be prepared by the general method of R. Jacquier **et al.**, Phosphorus and Sulfur **36**, 73, 1983.

The compounds of formulae (IV) and (XIII) are either known amino acid derivatives or can be made from these derivatives by known methods. Compounds of formula (XA) and (XB) are either known compounds or may be prepared from known compounds by known methods.

Compounds of formula (XII) may be prepared from an aldehyde R_1-CHO as hereinbefore defined and a compound of formula (XI) as hereinbefore defined by a procedure analogous to that described for the preparation of compounds of formula (VII).

The intermediates of formulae (II), (III), and certain intermediates of formula (IX) disclosed herein are novel compounds and form an aspect of the present invention as do the described processes for their preparation.

Where obtainable, pharmaceutically acceptable salts of the compounds of formula (I) may be formed conventionally by reaction with the appropriate acid or base.

As mentioned previously, the compounds of formula (I) exist in more than one diastereoisomeric form. Where the processes of the invention produces mixtures thereof, the individual isomers may be separated one from another by chromatography e.g. column chromatography or HPLC.

Alternatively, separate diastereoisomeric compounds of formula (I) can be obtained by using stereoisomerically pure starting materials or by separating desired isomers of

intermediates at any stage in the overall synthetic process, and converting these intermediates to compounds of formula (I).

It will be appreciated that where a single diastereoisomer of a compound of formula (I) is prepared by more than one process variant as hereinbefore described, each of which allows a different chiral centre to be defined, it may be possible to deduce the configuration at a chiral centre which is not pre-determined using a particular process variant.

Furthermore, it will be appreciated that although the absolute configuration at a particular chiral centre may not be known, it is possible to characterise a given diastereoisomer relative to its epimer or to another diastereoisomer using MNR spectroscopy or optical rotation.

In a further aspect, the present invention provides compounds of formula (I) or pharmaceutically acceptable salts thereof for use as active therapeutic agents, particularly as agents for treatment of conditions in which degradation of connective tissue and other proteinaceous components of the body occurs, such as musculo-skeletal disorders resulting from collagenolytic activity, particularly rheumatism and/or arthritic conditions, and tissue remodelling.

Compounds of formula (I) also have potential utility in the treatment of cancer; for preventing myelin degradation in the central and peripheral nervous system; for the treatment or prevention of colonic damage such as irritable bowel disease; and in other conditions in which members of the collagenase family of neutral metalloproteases have pathological or other roles.

The present invention further provides a pharmaceutical composition, which comprises a compound of formula (I), or a

pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

A composition of this invention is useful in the treatment of musculo-skeletal disorders, particularly arthritic diseases and for modulation of tissue remodelling as well as having potential utility in the treatment of the diseases described above.

A composition of the invention, which may be prepared by admixture, may contain a diluent, binder, filler, disintegrant, flavouring agent, colouring agent, lubricant or preservative in conventional manner. These conventional excipients may be employed in conventional manner, for example as in the preparation of compositions of related peptide enzyme inhibitors, such as the ACE inhibitor enalapril.

A composition of the invention may be adapted for oral, topical, rectal or parenteral administration but oral administration is preferred. Parenteral compositions may be administered intravenously, intramuscularly, intra-articularly, intradermally, sub-cutaneously or into the cerebro-spinal fluid.

Preferably, a pharmaceutical composition of the invention is in unit dosage form and in a form adapted for use in the medical or veterinarial fields. For example, such preparations may be in a pack form accompanied by written or printed instructions for use as an agent in the treatment or prophylaxis of any of the disorders mentioned above.

The suitable dosage range for the compounds of the invention may vary from compound to compound and may depend on the condition to be treated. It will also depend, **inter alia**, upon the relation of potency to absorbability and the mode of administration chosen.

The compound or composition of the invention may be formulated for administration by any route, the preferred route depending upon the disorder for which treatment is required, and is preferably in unit dosage form or in a form that a human patient may administer to himself in a single dosage.

Compositions may, for example, be in the form of tablets, capsules, sachets, vials, powders, granules, lozenges, reconstitutable powders, or liquid preparations, for example solutions or suspensions, or suppositories.

The compositions, for example those suitable for oral administration, may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tableting lubricants, for example magnesium stearate; disintegrants, for example starch, polyvinylpyrrolidone, sodium starch glycollate or microcrystalline cellulose; or pharmaceutically acceptable wetting agents such as sodium lauryl sulphate.

Solid compositions may be obtained by conventional methods of blending, filling, tableting or the like. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. When the composition is in the form of a tablet, powder, or lozenge, any carrier suitable for formulating solid pharmaceutical compositions may be used, examples being magnesium stearate, starch, glucose, lactose, sucrose, rice flour and chalk. Tablets may be coated according to methods well known in normal pharmaceutical practice, in particular with an enteric coating. The composition may also be in the form of an ingestible capsule, for example of gelatin containing the compound, if desired with a carrier or other excipients. For example, in a hard gelatin capsule containing the required amount of a

compound of the invention in the form of a powder or granulate in intimate mixture with a lubricant, such as magnesium stearate, a filler, such as microcrystalline cellulose, and a disintegrant, such as sodium starch glycollate.

Compositions for oral administration as liquids may be in the form of, for example, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid compositions may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel, hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; aqueous or non-aqueous vehicles, which include edible oils, for example almond oil, fractionated coconut oil, oily esters, for example esters of glycerine, or propylene glycol, or ethyl alcohol, glycerine, water or normal saline; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid and, if desired, conventional flavouring or colouring agents.

The compounds of this invention may also be administered by a non-oral route. In accordance with routine pharmaceutical procedure, the compositions may be formulated, for example for rectal administration as a suppository or for parenteral administration in an injectable form. For injection, for example by intra-articular injection or by injection into the cerebro-spinal fluid or via other routes which will gain access to sites of demyelination, such as by intramuscular, intradermal or subcutaneous injection, as freely soluble solutions or as poorly dispersed depot stores, the compounds of the invention may be presented in an aqueous or non-aqueous solution, suspension or emulsion in a pharmaceutically acceptable liquid, e.g. sterile pyrogen-free water or a parenterally acceptable oil or a mixture of liquids, which may contain bacteriostatic agents,

anti-oxidants or other preservatives, buffers or solutes to render the solution isotonic with the blood, thickening agents, suspending agents or other pharmaceutically acceptable additives. Such forms will be presented in sterile unit dose form such as ampoules or disposable injection devices or in multi-dose forms such as a bottle from which the appropriate dose may be withdrawn or a solid form or concentrate which can be used to prepare an injectable formulation.

For topical and percutaneous administration, the preparations may also be presented as an ointment, cream, lotion, gel, spray, aerosol, wash, skin paint or patch.

A unit dose for treating diseases in which enzymes of the collagenase family are involved will generally contain from 10 to 1000 mg and preferably will contain from 10 to 500 mg, in particular 10, 50, 100, 150, 200, 250, 300, 350, 400, 450 or 500 mg. The composition may be administered one or more times a day, for example 2, 3 or 4 times daily, so that the total daily dose for a 70 kg adult will normally be in the range 10 to 3000 mg. Such a dosage corresponds to approximately 0.15 to 50 mg/kg per day. Alternatively, in particular for injection, the unit dose will contain from 2 to 200 mg of a compound of the invention and be administered in multiples, if desired, to give the desired daily dose.

The present invention additionally provides a method of treating conditions in which degradation of connective tissue and other proteinaceous components of the body occurs which comprises administering to the mammal in need of such treatment an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

The present invention also provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for use in the treatment

of conditions in which degradation of connective tissue and other proteinaceous components of the body occurs.

The following Descriptions and Examples illustrate the preparation of compounds of the invention. All temperatures are expressed in °C.

Description 1

N-[1-(Diethoxyphosphinyl)-1-(2-hydroxyphenyl)methyl]-leucine, benzyl ester (D1)

Salicylaldehyde (1.83g), leucine benzylester p-toluene sulfonate salt (5.9g) and triethylamine (2.1 ml) in toluene (100 ml) were heated at reflux for 2 h in a Dean-Stark apparatus. The solution was cooled and solvent removed **in vacuo**. Diethyl phosphite (3.2g) was added and the solution heated at 120°C for 24 h. The reaction mixture was cooled and column chromatography on silica gel, eluting with ethyl acetate, gave the title compound as a yellow oil (2.8g).

Description 2

N-[1-(Diethoxyphosphinyl)-1-(2-hydroxyphenyl)methyl]-leucine (D2)

The title compound (1.0g) was prepared from (D1) (1.4g) by hydrogenation at atmospheric pressure over 10% palladium on charcoal in ethanol.

Description 3

N-[N-(1-Diethoxyphosphinyl-1-(2-hydroxyphenyl)methyl)-leucyl]-N,O-dimethyl-L-tyrosinamide (D3)

A solution of N-[1-(diethoxyphosphinyl)-1-(2-hydroxyphenyl)methyl-leucine (D2) (0.5g) in dry acetonitrile was cooled to 0°C in an ice-bath and 1,1'-carbonyldiimidazole added. The mixture was kept at 0°C for 1 h and then O-methyl-(S)-tyrosine N-methylamide in the minimum volume of acetonitrile was added dropwise with stirring. The mixture was allowed to warm to room temperature and stirred for a further 2 days and then evaporated to dryness. The residue was taken up in chloroform and washed with dilute citric acid and water. The organic layer was dried with anhydrous

sodium sulphate, filtered and evaporated to dryness to give the crude product. Purification by column chromatography on silica gel with initially chloroform rising to 10% methanol/chloroform as eluant gave the title compound (0.43g).
Observed EI M^+563.

Description 4

3-(1,8-Naphthalenedicarboximido)propanol (D4)

3-Amino-1-propanol (3.75g) was dissolved in dichloromethane (500 ml) and dimethylformamide (50 ml) and naphthalic anhydride (9.9g) added, followed by triethylamine (6.9 ml). The solution was stirred at room temperature for 2h and 1-hydroxybenzotriazole (8.75g) and 1-ethyl-3(3-dimethylamino-propyl)carbodiimide hydrochloride (13.4g) added and the solution stirred at room temperature for 24h. The solution was filtered, washed with water, 1N hydrochloric acid, saturated sodium bicarbonate solution and dried with anhydrous sodium sulphate. The solution was filtered and the solvent evaporated **in vacuo** to give the title compound as a pale yellow solid (7.5g).

Description 5

3-(1,8-Naphthalenedicarboximido)propanal (D5)

A solution of oxalyl chloride (3.5 ml) in dichloromethane (100 ml) was cooled to -60°C and dimethylsulphoxide (5.95 ml) in dichloromethane (10 ml) added slowly over 15 min. The alcohol (9g) (D4) in dichloromethane (100 ml) was added dropwise over 30 min, and the solution stirred at -60°C for 15 min. The reaction mixture was allowed to warm to -15°C, cooled to -60°C and triethylamine (24.5 ml) added. The solution was allowed to warm to room temperature, washed with water, dilute hydrochloric acid, 10% sodium carbonate solution and dried with anhydrous sodium sulphate. The

solution was filtered and the solvent evaporated **in vacuo** to give the title compound as a white solid (8.3g).

δ ($CDCl_3$): 2.86 (2H, dt), 4.53 (2H, t), 7.75 (2H, t), 8.22 (2H, d), 8.56 (2H, d), 9.90 (1H, s).

Description 6

N-[N-(1-(Dibenzyloxyphosphinyl)-3-(1,8-naphthalene-dicarboximido)propyl)-(S)-leucyl]-N,O-dimethyl-(S)-tyrosinamide (D6)

3-(1,8-Naphthalenedicarboximido)propanal (3.2g) (D5) in dichloromethane (50 ml) was added to a solution of N-((S)-leucyl)-N,O-dimethyl-(S)-tyrosinamide (4.04g) in dichloromethane (50 ml) at 0°C. Magnesium sulphate was added and the reaction mixture stirred at 0°C for 15 min, then at room temperature for 15 min.

Dibenzyl trimethylsilylphosphite (4.25g), prepared by the method of J.I.G. Cadogan **et al.** [Tetrahedron 1990, **46**, 7175], was added via syringe to the above reaction mixture under nitrogen at 0°C. The solution was allowed to warm to room temperature and stirred for 18h, washed with water, 10% citric acid solution and saturated sodium chloride solution. The solution was dried with anhydrous sodium sulphate, filtered and the solvent evaporated **in vacuo** to give an orange oil.

Purification by column chromatography on silica gel, eluting with ethyl acetate, gave a single diastereoisomer.

Isomer D6A (0.9g)

δ ($CDCl_3$): 0.81 (6H, dd), 0.90-2.35 (6H, m), 2.77 (3H, d), 2.87 (2H, m), 3.22 (2H, m), 3.67 (3H, s), 4.12 (2H, t), 4.74 (1H, m), 4.95 (4H, m), 6.78 (2H, d), 7.10 (2H, d), 7.31

(10H, s), 7.60 (1H, d), 7.74 (3H, t), 8.22 (2H, d), 8.58 (2H, d).

Observed FAB $(M+H)^+$ 819. $C_{46}H_{51}N_4O_8P$ requires M 818.

Further elution gave a slower running single diastereoisomer.

Isomer D6B (1.8g)

δ ($CDCl_3$): 0.82 (6H, dd), 1.12-2.24 (6H, m), 2.69 (3H, d), 2.83 (1H, m), 3.13 (2H, m), 3.62 (1H, m), 3.68 (3H, s), 4.15 (1H, m), 4.27 (1H, m), 4.60 (1H, t), 4.95 (4H, m), 6.59 (1H, d), 6.76 (2H, d), 7.15 (2H, d), 7.30 (10H, m), 7.62 (1H, d), 7.76 (2H, t), 8.23 (2H, d), 8.60 (2H, d).

Observed FAB $(M+H)^+$ 819. $C_{46}H_{51}N_4O_8P$ requires M 818.

Description 7

3-(Phthalimido)propanol (D7)

3-Amino-1-propanol (7.5g) was dissolved in ethanol (200 ml), N-carbethoxyphthalimide (21.9g) was added and the solution stirred at room temperature for 24h. The solvent was evaporated **in vacuo** and the residue dissolved in chloroform and washed with water (2x). The chloroform solution was dried with sodium sulphate, filtered and the solvent evaporated **in vacuo** to give the title compound (12.7g).

Description 8

3-(Phthalimido)propanal (D8)

The title compound (11.5g) was prepared from 3-(phthalimido)propanol (D7) (12.7g) by the procedure described in Description 5.

δ ($CDCl_3$): 2.89 (2H, dt), 4.05 (2H, t), 7.74 (2H, m), 7.86 (2H, m), 9.83 (1H, s).

Description 9

N-[N-(1-(Dimethoxyphosphinyl)-3-phthalimidopropyl)-(S)-leucyl]-(S)-phenylalanine-N-methylamide (D9)

3-(Phthalimido)propanal (4.06g) (D8) in dichloromethane (50ml) was added to a solution of (S)-leucyl-(S)-phenylalanine-N-methylamide (5.82g) in dichloromethane (50ml) at 0°C. Magnesium sulphate was added and the reaction mixture stirred at 0°C for 15 min, then at room temperature for 15 min.

Dimethyl trimethylsilylphosphite (3.3g), prepared by the method of J.I.G. Cadogan **et al.** [Tetrahedron 1990, **46**, 7175] was added via syringe to the above reaction mixture under nitrogen at 0°C. The solution was allowed to warm to room temperature and stirred for 18h, washed with water, 10% citric acid solution and saturated sodium chloride solution. The solution was dried with anhydrous sodium sulphate, filtered and the solvent evaporated **in vacuo** to give an orange oil.

Purification by column chromatography on silica gel, eluting with ethyl acetate, followed by 10% methanol/ethyl acetate gave the title compound as a mixture of 2 diastereoisomers (8g) (D9).

δ ($CDCl_3$): 0.85 (6H, m), 0.95-2.18 (5H, m), 2.67 (1½H, d), 2.75 (1½H, d), 2.80-3.32 (3H, m), 3.55 (½H, t), 3.72 (8H, m), 3.84 (½H, m), 4.60 (½H, q), 4.75 (½H, m), 6.22 (½H,d) 7.22 (5½H, m), 7.53 (1H, t), 7.74 (3H, m), 7.85 (2H, m).

Observed FAB $(M+H)^+$ 587 $C_{29}H_{39}N_4O_7P$ requires M 586

The title compound was also prepared as a single diastereoisomer (D9A) (0.09g) from the acid (D24A) (0.1g) and (S)-phenylalanine-N-methylamide (0.05g) by the procedure described in Description 19.

δ ($CDCl_3$): 0.88 (6H, d), 1.28 (2H, m), 1.60 (2H, m), 1.84 (1H, m), 2.08 (1H, m), 2.67 (3H, d), 3.14 (2H, m), 3.55 (1H, t), 3.75 (8H, m), 3.84 (1H, m), 4.60 (1H, q), 6.26 (1H, d), 7.23 (5H, m),7.51 (1H, d), 7.73 (2H, m), 7.85 (2H, m)

Description 10

4-(1,8-Naphthalenedicarboximido)butanol (D10)

The title compound (4.5g) was prepared from 4-amino-1-butanol (4.45g) by the procedure described in Description 4.

Description 11

4-(1,8-Naphthalenedicarboximido)butanal (D11)

The title compound (3.96g) was prepared from 4-(1,8-naphthalenedicarboximido)butanol (D10) (4.38g) by the procedure described in Description 5.

δ ($CDCl_3$): 2.10 (2H, 2 overlapping t), 2.60 (2H, t), 4.20 (2H, t), 7.70 (2H, t), 8.17 (2H, d), 8.58 (2H, d, 9.83 (1H, s).

Description 12

N-[N-(1-(Dibenzyloxyphosphinyl)-4-(1,8-naphthalene-dicarboximido)butyl)-(S)-leucyl]-(S)-phenylalanine-N-methylamide (D12)

The title compound (3.33g) was prepared as a mixture of 2 diastereoisomers from 4-(1,8-naphthalenedicarboximido)-butanal D11) (3.96g), (S)-leucyl-(S)-phenylalanine-N-methylamide (4.32g) and dibenzyl trimethylsilylphosphite (4.99g) by the procedure described in Description 6.

δ ($CDCl_3$): 0.67 (3H, dd), 0.79 (3H, dd), 0.99-2.03 (8H, m), 2.56 (1½H, d), 2.74 (1½H, d), 2.70-3.69 (4H, m), 4.12 (2½H, m), 4.50 (½H, q), 4.93 (4H, m), 6.23 (½H, d), 7.23 (15H, m), 7.74 (3H, m), 8.22 (2H, m), 8.61 (2H, d).

Observed FAB $(M+H)^+$ 803. $C_{46}H_{51}N_4O_7P$ requires M 802.

Description 13

2-(1,8-Naphthalenedicarboximido)ethanol (D13)

The title compound (7g) was prepared from ethanolamine (3.05g) by the procedure described in Description 4.

Description 14

2-(1,8-Naphthalenedicarboximido)ethanal (D14)

The title compound (3.15g) was prepared from 2-(1,8-naphthalenedicarboximido)ethanol (D13) (3.21g) by the procedure described in Description 5.

δ ($CDCl_3$): 5.05 (2H, s), 7.73 (2H, t), 8.24 (2H, d), 8.60 (2H, d), 9.74 (1H, s).

Description 15

N-[N-(1-(Dibenzyloxyphosphinyl)-2-(1,8-naphthalene-dicarboximido)ethyl)-(S)-leucyl]-(S)-phenylalanine-N-methylamide (D15)

The title compound (3.0g) was prepared as a mixture of 2 diastereoisomers from 2-(1,8-naphthalenedicarboximido)-ethanal (D14) (3.13g), (S)-leucyl-(S)-phenylalanine-N-methylamide (3.81g) and dibenzyl trimethylsilylphosphite (4.4g) by the procedure described in Description 6.

δ ($CDCl_3$): 0.19 (1½H, d), 0.39 (1½H, d), 0.70 (3H, dd), 0.70-1.48 (3H, m), 2.22 (½H, dd), 2.68 (1½H, d), 2.74 (1½H, d), 2.74-3.65 (3½H, m), 4.30 (1H, m), 4.49 (1½H, m), 4.74 (½H, m), 4.98 (4H, m), 6.20 (½H, m), 6.78 (1H, dd), 6.86 (½H, d), 7.22 (15H, m), 7.76 (2H, t), 8.22 (2H, d), 8.57 (2H, d).

Observed FAB$(M+H)^+$ 775. $C_{44}H_{47}N_4O_7P$ requires M 774.

Description 16

N-[N-(1-(Dibenzyloxyphosphinyl)-3-(1,8-naphthalene-dicarboximido)propyl)-(S)-leucyl]-(S)-phenylanine-N-methylamide (D16)

The title compound (2.5g) was prepared from 3-(1,8-naphthalenedicarboximido)propanal (D5) (3.5g), (S)-leucyl-(S)-phenylalanine-N-methylamide (4.03g) and dibenzyl trimethylsilylphosphite (4.65g) by the procedure described in Description 6.

Purification by column chromatography on silica gel, eluting with a gradient of 0-5% methanol/ethyl acetate gave a single diastereoisomer.

Isomer D16A
δ ($CDCl_3$): 0.77 (6H, dd), 0.83-2.03 (5H, m), 2.17 (1H, m), 2.77 (3H, d), 2.77-3.37 (3H, m), 4.21 (2H, t), 4.78 (1H, m),

4.96 (4H, m), 7.24 (15H, m), 7.62 (1H, d), 7.76 (2H, t), 8.23 (2H, d), 8.57 (2H, d).
Observed FAB $(M+H)^+$ 789. $C_{45}H_{49}N_4O_7P$ requires M 788.

Analysis: $C_{45}H_{49}N_4O_7P$ requires C, 68.51; H, 6.26; N, 7.10%.
Found C, 68.44; H, 6.17; N, 7.55%.

Further elution gave a slower running diastereoisomer.

Isomer D16B
δ ($CDCl_3$): 0.79 (6H, dd), 1.05-2.28 (5H, m), 2.66 (3H, d), 2.78 (1H, m), 3.17 (2H, m), 3.58 (1H, t), 4.20 (2H, m), 4.63 (1H, m), 4.93 (4H, m), 6.63 (1H, d), 7.21 (15H, m), 7.65 (1H, d), 7.75 (2H, t), 8.21 (2H, d), 8.58 (2H, d).

Observed FAB $(M+H)^+$ 789. $C_{45}H_{49}N_4O_7P$ requires M 788.

Analysis: $C_{45}H_{49}N_4O_7P$ requires C, 68.51; H, 6.26; N, 7.10%.
Found C, 68.83; H, 6.18; N, 7.40%.

Description 17

N-[1-(Dibenzyloxyphosphinyl)-3-phenylpropyl]-(S)-leucine, methyl ester (D17)

Hydrocinnamaldehyde (4.62g) in dichloromethane (50 ml) was added to a solution of (S)-leucine methyl ester (5.0g) in dichloromethane (50 ml) at 0°C. Magnesium sulphate was added and the reaction mixture stirred at 0°C for 15 min, then at room temperature for 15 min.

Dibenzyl trimethylsilylphosphite (11.6g), prepared by the method of J.I.G. Cadogan **et al.** [Tetrahedron 1990, **46**, 7175], was added via syringe to the above reaction mixture under nitrogen at 0°C. The solution was allowed to warm to room temperature and stirred for 18h, washed with water, 10% citric acid solution and saturated sodium chloride solution. The solution was dried with anhydrous sodium sulphate,

filtered and the solvent evaporated **in vacuo** to give a yellow oil.

Purification by column chromatography on silica gel, eluting with a mixture of pentane:ether:acetone (10:9:1), gave a single diastereoisomer.

Isomer D17A (1.47g)

δ ($CDCl_3$): 0.88 (6H, dd), 1.40 (1H, m), 1.61-1.90 (2H, m), 2.10 (1H, m), 2.56-2.92 (5H, m), 3.63 (3H, s), 3.75 (1H, t), 4.97 (4H, m), 7.25 (15H, m).

Observed EI M^+ 524.

Further elution gave a slower running single diastereoisomer

Isomer D17B (0.61g)
δ ($CDCl_3$): 0.87 (6H, dd), 1.40 (2H, m), 1.75 (2H, m), 2.05 (1H, m), 2.66 (1H, m), 2.84 (2H, m), 3.42 (1H, t), 3.58 (3H, s), 4.93 (4H, m), 7.26 (15H, m).

Observed EI M^+ 524.

Analysis: $C_{30}H_{38}NO_5P$ requires C, 68.82; H, 7.73; N, 2.68%
Found C, 68.87; H, 7.23; N, 2.37%.

Description 18

N-[1-(Dibenzyloxyphosphinyl)-3-phenylpropyl]-(S)-leucine (D18)

The methyl ester (D17A) (1.35g) was dissolved in dioxan (30 ml) and water (15 ml). Sodium hydroxide (0.12g) was added and the solution was stirred at room temperature for 24h. The dioxan was evaporated **in vacuo** and the aqueous solution washed with ether, acidified with 2N hydrochloric acid and extracted with ethyl acetate (2x). The organic

extracts were dried with sodium sulphate and the solvent evaporated **in vacuo** to give the title compound, as a white solid (0.65g), as a single diastereoisomer (D18A).

δ ($CDCl_3$): 0.87 (6H, dd), 1.48 (2H, m), 1.77 (2H, m), 2.13 (1H, m), 2.86 (2H, m), 3.76 (1H, t), 5.02 (4H, m), 7.16 (5H, m), 7.33 (10H, s).

Observed EI M^+ 510

$[\alpha]_D^{22}$ = -12.08° (c=1% in methanol)

Analysis: $C_{29}H_{36}NO_5P.1/2H_2O$ requires C, 67.17; H, 7.19; N, 2.70%.
Found C, 67.13; H, 6.93; N, 2.79%.

Similarly, the title compound was prepared, as a pale yellow oil (0.22g), as a single diastereoisomer (D18B) from the methyl ester (D17B) (0.52g).

δ ($CDCl_3$): 0.88 (6H, t), 1.38 (1H, m), 1.62 (2H, m), 1.85 (1H, m), 2.10 (1H, m), 2.75 (3H, m), 3.37 (1H, t), 5.03 (4H, m), 7.16 (5H, m), 7.33 (10H, s).

Observed EI M^+ 510

Description 19

N-[N-(1-(Dibenzyloxyphosphinyl)-3-phenylpropyl)-(S)-leucyl]-(S)-phenylalanine-N-methylamide (D19)

The acid (D18A) (0.6g) was dissolved in dichloromethane (20 ml), cooled to 0°C and 1-hydroxybenzotriazole (0.23g) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.33g) were added. The solution was stirred at 0°C for 15 min, then at room temperature for 15 min, cooled to 0°C and (S)-phenylalanine-N-methylamide (0.24g) in dichloromethane (20 ml) added. The solution was stirred at room temperature

for 24h, washed with water, 10% citric acid solution and saturated sodium chloride solution. The organic solution was dried with anhydrous sodium sulphate and the solvent evaporated **in vacuo** to give a beige solid (0.69g).

Purification by column chromatography on silica gel, eluting with ethyl acetate gave the title compound, as a white solid (0.52g), as a single diastereoisomer (D19A).

δ ($CDCl_3$): 0.80 (6H, d), 1.20 (2H, m), 1.50 (1H, m), 1.73 (2H, m), 2.00 (1H, m), 2.54 (1H, m), 2.65 (3H, d), 2.73 (2H, m), 3.02 (2H, m), 3.57 (1H, t), 4.54 (1H, q), 4.97 (4H, m), 6.05 (1H, broad s), 7.19 (10H, m), 7.33 (10H, s).

Observed FAB $(M+H)^+$ 670. $C_{39}H_{48}N_3O_5P$ requires M 669.

$[\alpha]_D^{22} = -30.85°$ (c=0.98% in methanol)

Analysis: $C_{39}H_{48}N_3O_5P$ requires C, 69.94; H, 7.22; N, 6.27%. Found C, 70.05; H, 7.28; N, 6.38%.

Similarly, the title compound was prepared from the acid (D18B) (0.20g), as a pale yellow oil (0.23g), as a single diastereoisomer (D19B).

δ ($CDCl_3$): 0.78 (6H, dd), 1.02-1.32 (3H, m), 1.65-2.14 (3H, m), 2.60 (3H, m), 2.76 (3H, d), 2.92 (1H, dd), 3.14 (1H, dd), 3.32 (1H, dd), 4.80 (1H, m), 5.00 (4H, m), 7.00 (1H, d), 7.20 (10H, m), 7.33 (10H, m), 7.63 (1H, broad d).

Observed FAB $(M+H)^+$ 670. $C_{39}H_{48}N_3O_5P$ requires M 669.

Description 20

N-[1-(Dimethoxyphosphinyl)-3-(1,8-naphthalene dicarboximido)propyl]-(S)-leucine, benzyl ester (D20)

3-(1,8-Naphthalenedicarboximido)propanal (D5) (9.5g) was added to a solution of (S)-leucine benzyl ester, p-toluene sulphonate salt (14.75g) and triethylamine (5.8ml) in dichloromethane (100ml). Molecular sieves and magnesium sulphate were added and the mixture stirred under nitrogen for 18h. The solution was filtered and added dropwise to dimethyl trimethylsilylphosphite (7.5g), prepared by the method of J.I.G.Cadogan **et al** [Tetrahedron 1990, **46**, 7175], under nitrogen at 0°C. The solution was allowed to warm to room temperature and stirred for 18h, washed with water, 10% citric acid solution, saturated sodium bicarbonate solution and saturated sodium chloride solution. The solution was dried with anhydrous sodium sulphate, filtered and the solvent evaporated **in vacuo** to give a yellow oil.

Purification by column chromatography on silica gel, eluting with a mixture of ether:ethyl acetate (1:1) gave a single diastereoisomer (D20A) (5.51g).

δ ($CDCl_3$): 0.95 (6H, dd), 1.53 (2H, t), 1.75 - 2.00 (3H, m), 2.27 (1H, m), 2.98 (1H, m), 3.72 (3H, d), 3.80 (3H, d), 3.90 (1H, t), 4.20 (1H, m), 4.46 (1H, m), 5.65(2H,m), 7.35 (5H, m), 7.77 (2H, t), 8.23 (2H, d), 8.62 (2H, d).

^{31}P: δ ($CDCl_3$): 28.73

Observed CI $(M+H)^+$ 567, $C_{30}H_{35}N_2O_7P$ requires M 566

$[\alpha]_D^{22}$ = -14.94 (c=0.38, MeOH)

Analysis: $C_{30}H_{35}N_2O_7P$ requires C, 63.60; H, 6.23; N,4.94%
Found C, 63.28; H,6.20; N, 4.83%

Further elution gave a slower running single diastereoisomer.

Isomer D20B (5.23g)

δ ($CDCl_3$): 0.93 (6H, dd), 1.53 (2H, t), 1.80 (2H, m), 2.17 (1H, m), 3.10 (1H, m), 3.63 (1H, t), 3.71 (3H, d), 3.77 (3H, d), 4.29 (1H, m), 4.44 (1H, m), 5.15 (2H, m), 7.36 (5H, m), 7.75 (2H, t), 8.21 (2H, d), 8.59 (2H, d).

^{31}P: δ ($CDCl_3$): 29.65

Observed CI $(M+H)^+$ 567 $C_{30}H_{35}N_2O_7P$ requires M 566

$[\alpha]_D^{22}$ = -13.20 (c=0.44, MeOH)

Analysis: $C_{30}H_{35}N_2O_7P.H_2O$ requires C, 61.64; H, 6.38; N, 4.79%
Found C, 61.56; H, 6.35; N, 4.62%.

Description 21

N-[1-(Dimethoxyphosphinyl)-3-(1,8-naphthalene dicarboximido)propyl]-(S)-leucine (D21)

The benzyl ester (D20A) (3.7g) was dissolved in methanol (100ml) and hydrogenated over 10% palladium on charcoal at atmospheric pressure for 3h. The solution was filtered and the solvent evaporated **in vacuo** to give the title compound as a single diastereoisomer (2.7g) (D21).

δ ($CDCl_3$) : 0.96 (6H, t), 1.58 (2H, m), 1.89 (2H, m), 2.26 (1H, m), 3.12 (1H, m), 3.76 (3H, d), 3.83 (3H, d), 4.29 (1H, m), 4.47 (1H, m), 7.67 (2H, t), 8.14 (2H, d), 8.49 (2H, d)

^{31}P: δ ($CDCl_3$) : 29.22

Observed FAB $(M+H)^+$ 477 $C_{23}H_{29}N_2O_7P$ requires M 476

$[\alpha]_D^{22}$ = -1.50 (c = 1.00, MeOH)

Analysis: $C_{23}H_{29}N_2O_7P$. H_2O requires C, 55.87; H, 6.31; N, 5.66%
Found C, 55.67; H, 5.84; N, 5.66%

Description 22

N-[N-(1-(Dimethoxyphosphinyl)-3-(1,8-naphthalene dicarboximido)propyl)-(S)-leucyl]-(S)-phenylalanine-N-methylamide (D22)

The title compound (1.2g) was prepared from the acid (D21) (0.95g) and (S)-phenylalanine-N-methylamide (0.24g) by the procedure described in Description 19.

δ ($CDCl_3$) : 0.89 (6H, dd), 1.26 (2H, m), 1.62 (1H, m), 1.84 (2H, m), 2.11 (1H, brond s), 2.60 (3H, d), 2.85 (1H, m), 3.20 (2H, m), 3.55 (1H, t), 3.71 (3H, d), 3.78 (3H, d), 4.19 (1H, m), 4.33 (1H, m), 4.65 (1H, q), 6.56 (1H, d), 7.23 (5H, m), 7.71 (1H, d), 7.76 (2H, t), 8.23 (2H, d), 8.60 (2H, d).

Description 23

N-[1-(Dimethoxyphosphinyl)-3-phthalimidopropyl]-(S)-leucine, benzyl ester (D23)

The title compound was prepared from 3-(phthalimido-propyl)propanal (3.36g) and (S)-leucine benzyl ester, p-toluene sulphonate salt (6.51g) by the procedure described in Description 20.

Purification by column chromatography on silica gel, eluting with a mixture of ether:ethyl acetate (1:1) gave a single diastereoisomer.

Isomer D23A (1.62g)

δ ($CDCl_3$): 0.92 (6H, m), 1.38 - 1.92 (5H, m), 2.13 (1H, m), 2.93 (1H, m), 3.47 - 4.06 (3H, m), 3.73 (3H, d), 3.79 (3H, d), 5.13 (2H, m), 7.33 (5H, m), 7.70 (2H, m), 7.83 (2H, m).

Further elution gave a slower running single diastereoisomer.

Isomer D23B (1.52g)

δ ($CDCl_3$): 0.90 (6H, dd), 1.50 (2H, t), 1.70 - 2.20 (4H, m), 2.95 (1H, m), 3.53 (1H, t), 3.70 (3H, d), 3.75 (3H, d), 3.75 - 4.03 (3H, m), 5.14 (2H, m), 7.35 (5H, m), 7.70 (2H, m), 7.83 (2H, m)

Description 24

N-[1-(Dimethoxyphosphinyl)-3-phthalimidopropyl]-(S)-leucine (D24)

The title compound was prepared as a single diastereoisomer (D24A) (0.97g) from the benzyl ester (D23A) (1.52g) by the procedure described in Description 21.

δ ($CDCl_3$): 0.96 (6H, dd), 1.55 (2H, m), 1.85 (2H, m), 2.20 (1H, m), 3.03 (1H, dt), 3.78 (8H, m), 3.98 (1H, m), 7.70 (2H, m), 7.83 (2H, m)

Similarly, the title compound was prepared as a single diastereoisomer (D24B) (0.83g) from the benzyl ester (D23B) (1.4g)

δ ($CDCl_3$): 0.96 (6H, d), 1.55 (2H, m), 1.85 (2H, m), 2.15 (1H, m), 2.98 (1H, m), 3.44 (1H, m), 3.78 (8H, m), 7.73 (2H, m), 7.85 (2H, m)

^{31}P: δ ($CDCl_3$): 29.01

Description 25

3-(4-Bromo-1,8-naphthalenedicarboximido)propanol (D25)

A mixture of 4-bromophthalic anhydride and 3-amino-1-propanol (12g) in ethanol (200ml) was heated under reflux for 30 min. The solution was allowed to cool to room temperature and the solvent evaporated **in vacuo** to give a solid which was washed with ester to give the title compound (12.2g) (D25).

δ ($CDCl_3$): 2.00 (2H, dt), 3.60 (2H, t), 4.35 (2H, t), 7.88 (1H, t), 8.07 (1H, d), 8.44 (1H, d), 8.60 (1H, d), 8.70 (1H, d)

Description 26

3-(4-Bromo-1,8-naphthalenedicarboximido)propanal (D26)

The title compound (10.3g) (D26) was prepared from the alcohol (12.2g) (D25) by the procedure described in Description 5.

δ ($CDCl_3$): 2.90 (2H, dt), 4.54 (2H, t), 7.85 (1H, t), 8.04 (1H, d), 8.40 (1H, d), 8.59 (1H, dd), 8.66 (1H, dd), 9.90 (1H, s)

Description 27

N-[1-(Dimethoxyphosphinyl)-3-(4-bromo-1,8-naphthalene dicarboximido)propyl]-(S)-leucine, trimethylsilylethyl ester (D27)

The title compound (D27) was prepared from 3-(4-bromo-1,8-naphthalenedicarboxamido)propanal (D26) (3.0g) and (S)-leucine, trimethylsilylethyl ester (2.17g) by the procedure described in Description 20.

Purification by column chromatography on silica gel, eluting with 40 - 60° petrol, increasing to 20% ethyl acetate/40 - 60° petrol gave a single diastereoisomer

Isomer D27A (1.0g)

δ ($CDCl_3$): 0.96 (8H, m), 1.48 (2H, t), 1.82 (2H, m), 2.25 (1H, m), 2.94 (1H, m), 3.75 (8H, m), 4.15 (2H, m), 4.24 (1H, m), 4.52 (1H, dt), 7.81 (1H, t), 8.02 (1H, d), 8.39 (1H, d), 8.56 (1H, d), 8.63 (1H, d)

Further elution gave a slower running single diasterisomer.

Isomer D27B (0.95g)

δ ($CDCl_3$): 0.91 (8H, m), 1.47 (2H, t), 1.8 (2H, m), 2.13 (1H, m), 3.06 (1H, m), 3.51 (1H, t), 3.73 (3H, d), 3.79 (3H, d), 4.12 (3H, m), 4.26 (1H, m), 4.41 (1H, m), 7.80 (1H ,t), 8.00 (1H, d), 8.38 (1H, d), 8.54 (1H, d), 8.62 (1H, d)

Description 28

N-[1-(Dimethoxyphosphinyl)-3-(4-bromo-1,8-naphthalene dicarboximido)propyl]-(S)-leucine (D28)

The trimethylsilylethyl ester (1.0g) (D27A) was dissolved in tetrahydrofuran (50 ml) and the solution cooled to 0°C. A solution of 1M tetrabutylammonium fluoride (1.5ml) in tetrahydrofuran (10ml) was added dropwise under nitrogen and the solution stirred at room temperature for 24h. Water (20ml) was added and the solution cooled to 0°C and acidified with 2N hydrochloric acid. The solution was extracted with ethyl acetate (3x) and the combined organic extracts washed with water, dried with anhydrous sodium sulphate and the solvent evaporated **in vacuo** to give the title compound as a single diastereoisomer (0.8g) (D28A)

δ ($CDCl_3$): 1.04 (6H, m), 1.73 (2H, m), 2.00 - 2.60 (3H, m), 3.88 (7H, m), 4.21 (2H, m), 4.40 (2H, m), 7.55 (1H, t), 7.82 (1H, t), 8.05 (1H, d), 8.32 (2H, t)

Similarly the title compound was prepared as a single diastereoisomer (0.28g) (D28B) from the trimethylsilylethyl ester (0.33g) (D27B).

δ ($CDCl_3$): 0.98 (6H, d), 1.20 - 2.20 (5H, m), 3.07 (1H, m), 3.34 (1H, m), 3.50 (1H, t), 3.82 (6H, t), 4.34 (2H, t), 7.87 (1H, t), 8.06 (1H, t), 8.40 (1H, d), 8.60 (1H, d), 8.66 (1H, d)

Description 29

N-[N-(1-(Dimethoxyphosphinyl)-3-(4-bromo-1,8-naphthalenedicarboximido)propyl]-(S)-leucyl]-(S)-phenylalanine-N-methylamide (D29)

The title compound was prepared from the acid (1.0g) (D28A) and (S)-phenylalanine-N-methylamide (0.65g) by the method described in Description 19.

Purification by column chromatography on silica gel, eluting with 5% methanol/ethyl acetate gave the title compound as a single diastereoisomer (0.3g) (D29A)

δ ($CDCl_3$): 0.89 (6H, d), 1.27 (2H, m), 1.62 (1H, m), 1.69 (2H, m), 2.26 (1H, m), 2.70 (3H, d), 2.84 (1H, m), 2.93 - 3.25 (1H, m), 3.56 (1H, t), 3.72 (3H, t), 3.79 (3H, d), 4.17 (1H, m), 4.31 (1H, m), 4.58 (1H, m), 6.48 (1H, d), 7.23 (5H, m), 7.68 (1H, d), 7.87 (1H, t), 8.06 (1H, d), 8.42 (1H, d), 8.60 (1H, d), 8.68 (1H, d)

Similarly, the title compound was prepared as a single diastereoisomer (0.1g) (D29B) from the acid (0.28g) (D28B) and (S)-phenylalanine-N-methylamide (0.18g).

δ ($CDCl_3$): 0.85 (6H, dd), 1.13 (2H, m), 1.57 (2H, m), 1.90 - 2.24 (2H, m), 2.80 (3H, d), 3.00 (2H, m), 3.28 (2H, m), 3.70 (3H, d), 3.75 (3H, d), 4.27 (2H, t), 4.77 (1H, m), 7.23 (5H, m), 7.50 (1H, d), 7.62 (1H, d), 7.87 (1H, t), 8.05 (1H, d), 8.40 (1H, d), 8.60 (1H, d), 8.65 (1H, d)

Description 30

N-[N-(1-(Dibenzyloxyphosphinyl)-3-(2-benzyloxyphenyl)propyl)-(S)-leucyl]-(S)-phenylalanine-N-methylamide (D30)

The title compound (4.0g) was prepared from 3-(2-benzyloxyphenyl) propanol (4.8g), (S)-leucyl-(S)-phenylalanine-N-methylamide (5.82g) and dibenzyltrimethylsilyl phosphite (6.7g) by the procedure described in Description 6.

Observed FAB $(M+H)^+$ 776 $C_{46}H_{54}N_3O_6P$ requires M 775

Description 31

N-[N-(1-(Dimethoxyphosphinyl)-3-(methylmercapto)propyl)-(S)-leucyl]-(S)-phenylalanine-N-methylamide (D31)

The title compound (4.1g) (D31) was prepared from 3-(methylmercapto)propanal (2.08g), (S)-leucyl-(S)-phenylalanine-N-methylamide (5.82g) and dimethyltrimethylsilyl phosphite (3.3g) by the procedure described in Description 9.

Purification by column chromatography on silica gel, eluting with 3% methanol/ethyl acetate gave the title compound as a mixture of 2 diastereoisomers (4.1g) (D31)

$\delta(CDCl_3)$: 0.90 (6H, m), 0.90-1.95 (6H, m), 2.08 (1½H, s), 2.10 (1½H, s), 2.60 (2H, t), 2.73 (1½H, d), 2.76 (1½H, d), 2.82-3.12 (2H, m), 3.26 (1½H, m), 3.57 (½H, m), 3.74 (3H, d), 3.78 (3H, d), 4.55 (½H, q), 4.76 (½H, m), 6.14 (½H, broad s), 7.22 (5H, m), 7.38 (½H, broad s), 7.53 (½H, d), 7.64 (½H, d).

Observed FAB $(M+H)^+$ 488 $C_{22}H_{38}N_3O_5PS$ requires M 487

Description 32

N-[N-(1-(Dimethoxyphosphinyl)-3-(methylsulphinyl)propyl)-(S)-leucyl]-(S)-phenylalanine-N-methylamide (D32)

Sodium periodate (0.86g) in water (5ml) was added to a solution of N-[N-(1-(dimethoxyphosphinyl)-3-(methylmercapto)propyl)-(S)-leucyl]-(S)-phenylalanine-N-methylamide(0.98g) (D31) in methanol(50ml). The solution was stirred at room temperature for 2h and the solvent evaporated **in vacuo**. The residue was dissolved in chloroform, washed with water, saturated sodium chloride solution and dried with anhydrous sodium sulphate. The solution was filtered and the solvent evaporated **in vacuo** to give the title compound.

Purification by column chromatography on silica gel, eluting with 5% methanol/chloroform gave the title compound as a mixture of 2 diastereoisomers (0.63g) (D32)

$\delta(CDCl_3)$: 0.87 (6H, m), 1.03-2.35 (6H, m), 2.60 (1½H, d), 2.66 (1½H,d), 2.70 (1½H, d), 2.73 (1½H, d), 2.77-3.10 (4½H, m), 3.22 (1H, dd), 3.60(½H, m), 3.77(3H, d), 3.80(3H, d), 4.53-4.77(1H, m), 6.14(½H, broad s), 7.10(½H, broad s), 7.22(5H, m), 7.50(½H, d), 7.57(½H, d).

Observed FAB $(M+H)^+$ 504 $C_{22}H_{38}N_3O_6PS$ requires M 503

Description 33

N-[N-(1-(Dimethoxyphosphinyl)-3-(methylsulphonyl)propyl)-(S)-leucyl]-(S)-phenylalanine-N-methylamide (D33)

A solution of sodium periodate (4.26g) in water (20ml) was added to N-[N-(1-(dimethoxyphosphinyl)-3-(methylmercapto)propyl)-(S)-leucyl]-(S)-phenylalanine-N-methylamide(0.98g) (D31) in methanol(50ml). The solution was stirred at room temperature for 72h and the solvent evaporated **in vacuo**. The residue was dissolved in chloroform, washed with water, saturated sodium chloride solution and dried with anhydrous sodium sulphate. The solution was filtered and the solvent evaporated **in vacuo** to give the title compound.

Purification by column chromatography on silica gel, eluting with 10% methanol/ethylacetate gave the title compound as a mixture of 2 diastereoisomers (0.52g) (D33)

$\delta(CDCl_3)$: 0.84 (6H, m), 1.02-2.40 (7H, m), 2.70 (1½H, d), 2.74 (1½H, d), 2.93 (1½H, s), 3.01 (1½H, s), 3.03 (2H, m), 3.20 (2H, m), 3.40 (½H, m), 3.58 (½H, m), 3.78 (6H, m), 4.56 (1/2H, q), 4.66 (½H, m), 5.73 (½H, d), 6.80 (½H, d), 7.23 (5H, m), 7.44 (1H, t)

Observed FAB $(M+H)^+$ 520 $C_{22}H_{38}N_3O_7PS$ requires M 519

Description 34

N-[N-(1-(Dimethoxyphosphinyl)-3-(1,8-naphthalene dicarboximido) propyl)-(S)-leucyl]-(S)-phenylalanine-N-methylamide (D34)

The title compound (0.53g) was prepared as a single diastereoisomer (D34) from the acid (0.6g) (D21) and (S)-tryptophan-N-methylamide (0.31g) by the procedure described in Description 19.

$\delta(CDCl_3)$: 0.89 (6H, dd), 1.35 (2H, m), 1.72 (3H, m), 1.96 (1H, m), 2.71 (3H, d), 2.78 (1H, m), 3.27 (1H, dd), 3.44 (1H, dd), 3.55 (1H, m), 3.62 (3H, d), 3.75 (3H, d), 3.94 (1H, m), 4.17 (1H, m), 4.74 (1H, q), 6.42 (1H, d), 6.97 (2H, m), 7.14 (1H, d), 7.27 (1H, s), 7.62 (2H, dd), 7.77 (2H, t), 8.24 (2H, d), 8.43 (1H, broad s), 8.59 (2H, d)

Description 35

N-[N-(1-(Dimethoxyphosphinyl)-3-(1,8-naphthalene dicarboximido)propyl)-(S)-N_ε-benzyloxycarbonyllysine-N-methylamide (D35)

The title compound (1.4g) was prepared as a single diastereoisomer (D35) from the acid (0.95g) (D21) and (S)-N_ε-benzyloxycarbonyllysine-N-methylamide (0.42g) by the procedure described in Description 19.

$\delta(CDCl_3)$: 0.99 (6H, t), 1.32-2.04 (11H, m), 2.23 (1H, m), 2.74 (3H, d), 3.00 (1H, m), 3.73 (3H, d), 4.22-4.55 (3H, m), 5.09 (2H, s), 5.18 (1H, m), 6.50 (1H, d), 7.33 (5H, m), 7.57 (1H, d), 7.75 (2H, t), 8.23 (2H, d), 8.60 (2H, d)

^{31}P $\delta(CDCl_3)$: 29.96

m.p. 128-132°C

Observed FAB $(M+H)^+$ 742 $C_{38}H_{50}N_5O_9P$ requires M 751

$[\alpha]_D^{22}$ = -22.49 (c=0.98%,MeOH)

Analysis: $C_{38}H_{50}N_5O_9P$ requires C, 60.71; H, 6.70; N, 9.32%
Found C, 60.37; H, 6.47; N, 9.12%

Description 36

N-[N-(1-(Dimethoxyphosphinyl)-3-(1,8-naphthalene dicarboximido) propyl)-(S)-leucyl]-(-)-aminoazacyclo tridecan-2-one (D36)

The title compound (0.75g) was prepared as a single diastereoisomer (D36) from the acid (0.6g) (D21) and (-)-3-aminoazacyclotridecan-2-one (0.3g) ($[\alpha]_D^{20}$ = -63.6 (c=1% in methanol) by the procedure described in Description 19.

$\delta(CDCl_3)$: 0.95 (6H, dd), 1.28 (16H, m), 1.52 (2H, m), 1.65-2.11 (5H, m), 2.25 (1H, m), 2.85 (1H, m), 3.04 (1H, broad s), 3.62 (2H, m), 3.71 (3H, d), 3.79 (3H, d), 4.36 (2H, m), 4.54 (1H, m), 6.43 (1H, m), 7.63 (1H, d), 7.76 (2H, t), 8.22 (2H, d), 8.60 (2H, d)

Observed FAB $(M+H)^+$ 671 $C_{35}H_{51}N_4O_7P$ requires M 670

Description 37

(S)-N_α-t-Butyloxycarbonyl-N_ε-benzyloxycarbonyllysine-N-(benzyloxycarbonyl aminoethyl) amide (D37)

The title compound (7.2g) was prepared from N_α-t-butyloxycarbonyl-N_ε-benzyloxycarbonyllysine (5.3g) and 2-(benzyloxycarbonylamino) ethylamine(2.72g) by the procedure described in Description 19.

$\delta(CDCl_3)$: 0.90 (15H, m), 1.75 (1H, m), 3.17 (2H, q), 3.32 (4H, broad s), 4.00 (1H, q), 5.10 (4H, s), 5.39 (1H, d), 5.56 (1H, t), 6.76 (1H, broad s), 7.33 (10H, S)

Description 38

N-[N-(1-(Dimethoxyphosphinyl)-3-(1,8-naphthalene dicarboximido) propyl)-(S)-leucyl]-(S)-(N_ε-benzyloxy carbonyl)lysine-N-(benzyloxycarbonylaminoethyl)amide (D38)

N_α-t-Butyloxycarbonyl-N_ε-benzyloxycarbonyllysine-N-(benzyloxycarbonyl aminoethyl) amide (1.22g) (D37) was dissolved in dichloromethane (20ml) and trifluoroacetic acid (15ml) added. The solution was stirred at room temperature for 2h and the solvent evaporated **in vacuo**. The residue was dissolved in dichloromethane (25ml) and triethylamine added to pH10 to give N_ε-benzyloxycarbonyllysine-N-(benzyloxycarbonylaminoethyl) amide.

The title compound was prepared from the above amine (1.0g) and the acid (0.95g) (D21) by the procedure described in Description 19.

Purification by column chromatography on silica gel, eluting with 5% methanol/ethyl acetate gave the title compound as a single diastereoisomer (1.0g) (D38).

$\delta(CDCl_3)$: 0.93 (3H, d), 0.97 (3H, d), 1.30-2.10 (11H, m), 2.20 (1H, m), 3.15 (2H, m), 3.30 (4H, broad s), 3.64 (3H, d), 3.74 (3H, d), 4.32 (4H, m), 5.04 (4H, s), 5.15 (1H, broad s), 5.78 (1H, broad s), 7.08 (1H, broad s), 7.28 (10H, m), 7.65 (1H, d), 7.74 (2H, t), 8.22 (2H, d), 8.59 (2H, d).

Observed FAB $(M+H)^+$ 915 $C_{46}H_{59}N_6O_{11}P$ requires M 914

Description 39

N-[N-(1-(Dimethoxyphosphinyl)-3-(1,8-naphthalene dicarboximido) propyl)-(S)-leucyl]-(S)-(N_ε-benzyloxycarbonyl) lysine-N-(ethylpyrrolidine) amide (D39)

The title compound was prepared from (S)-(N_ε-benzyloxy-carbonyl) lysine-N-(ethylpyrrolidine) amide (0.73g) and the acid (0.83g.) (D21) by the procedure described in Description 19.

Purification by column chromatography on silica gel, eluting with 10% methanol/chloroform gave the title compound as a single diastereoisomer (1.2g) (D39)

$\delta(CDCl_3)$: 0.97 (6H, t), 1.34-1.66 (6H, m), 1.66-2.08 (9H, m), 2.25 (1H, m), 2.58 (6H, m), 3.03 (1H, m), 3.20 (2H, q), 3.30 (2H, q), 3.69 (1H, m), 3.72 (3H, d), 3.80 (3H, d), 4.21-4.44 (2H, m), 4.50 (1H, m), 5.09 (2H, s), 5.31 (1H, t), 6.78 (1H, broad s), 7.32 (5H, m), 7.54 (1H, d), 7.74 (2H, t), 8.22 (2H, d), 8.60 (2H, d).

^{31}P $\delta(CDCl_3)$: 30.05

Observed FAB $(M+H)^+$ 835 $C_{43}H_{59}N_6O_9P$ requires M 834

$[\alpha]_D^{22}$ = -17.21 (c=1.00, MeOH)

Description 40

(S)-N_α-t-Butyloxycarbonyl-N_ε-benzyloxycarbonyllysine-N-(ethyl-N-methylpiperazine) amide (D40)

The title compound (4.2g) was prepared from N_α-t-butyloxycarbonyl-N_ε-benzyloxycarbonyl lysine (3.8g) and 1-aminoethyl-4-methyl piperazine (1.43g) by the procedure described in Description 19.

$\delta(CDCl_3)$: 1.42 (9H, s), 1.50 (7H, m), 1.80 (1H, m), 2.30 (3H, s), 2.50 (10H, m), 3.19 (2H, q), 3.23 (2H, q), 4.05 (1H, m), 4.95 (1H, m), 5.08 (2H, s), 5.17 (1H, m), 6.55 (1H, m), 7.36 (5H, s).

Observed FAB $(M+H)^+$ 506 $C_{26}H_{43}N_5O_5$ requires M 505

Description 41

N-[N-(1-(Dimethoxyphosphinyl)-3-(1,8-naphthalene dicarboximido) propyl)-(S)-leucyl]-(S)-(N_ε-benzyloxycarbonyl)lysine-N-(ethyl-N-methylpiperazine) amide (D41)

The title compound was prepared from (D40) (1.1g) and the acid (0.92g) (D21) by the procedure described in Description (38).

Purification by colum chromatography on silica gel, eluting with 10% methanol/ethyl acetate gave the title compound as a single diastereoisomer (D41) (1.2g).

$\delta(CDCl_3)$: 0.93 (6H, t), 1.30-2.05 (12H, m), 2.26 (3H, s), 2.40 (10H, m), 3.00 (1H, m), 3.22 (4H, m), 3.67 (1H, m), 3.73 (3H, d), 3.80 (3H, d), 4.20-4.42 (2H, m), 4.50 (1H, m), 5.06 (2H, s), 5.25 (1H, m), 6.52 (1H, broad t), 7.30 (5H, s), 7.50 (1H, d), 7.70 (2H, t), 8.20 (2H, d), 8.58 (2H, d).

^{31}P $\delta(CDCl_3)$: 29.99

Observed FAB $(M+H)^+$ 864 $C_{44}H_{62}N_7O_9P$ requires M 863

$[\alpha]_D^{22}$ = -18.80 (c= 0.74, MeOH)

Description 42

3-[8-(7,9-dioxo-8-azaspiro[4,5]decyl)]propanol (D42)

3,3-Tetramethylene glutaric anhydride (8.4g) was dissolved in toluene (200ml) and 3-aminopropan-1-ol (4.5g) in toluene (50ml) added over 5 minutes. The solution was stirred at room temperature for 2h then heated at reflux for 3h. The solution was allowed to cool and solvent evaporated **in vacuo** to yield the title compound as a pale yellow oil (13.8g) (D42).

$\delta(CDCl_3)$: 1.53 (4H, m), 1.72 (6H, m), 2.65 (4H, s), 3.51 (2H, t), 3.92 (2H, t)

Description 43

3-[8-(7,9-dioxo-8-azaspiro[4,5]decyl)]propanal (D43)

The title compound (3.3g)(D43) was prepared from the alcohol (3.4g) (D42) by the procedure described in Description 5.

$\delta(CDCl_3)$: 1.50 (4H, m), 1.71 (4H, m), 2.60 (4H, s), 2.64 (2H, dt), 4.12 (2H, t), 9.75 (1H, s)

Observed CI M+H 224

Description 44

N-[1-(Dimethoxyphosphinyl)-3-[8-(7,9-dioxo-8-azaspiro[4,5]decyl)] propyl]-(S)-leucine, benzyl ester (D44)

The title compound was prepared from the aldehyde (3.2g) (D43), (S)-leucine, benzyl ester p-toluene sulphonate salt (5.7g) and dimethyl trimethylsilyl phosphite (2.6g) by the procedure described in Description 20.

Purification by colum chromatography on silica gel, eluting with a mixture of 2:1 ether: ethyl acetate, increasing to 1:1 ether:ethyl acetate, gave a single diastereoisomer.

Isomer D44A (2.14g)

$\delta(CDCl_3)$: 0.92 (6H, t), 1.37-1.87 (13H, m), 1.96 (1H, m), 2.57 (4H, s), 2.82 (1H, m), 3.71 (3H, d), 3.78 (3H, d), 3.83 (2H, m), 4.00 (1H, m), 5.13 (2H, m), 7.34 (5H, m)

^{31}P $\delta(CDCl_3)$: 28.74

Observed EI MH^+ 537

$[\alpha]_D^{22}$ = -13.33 (c=1.00, MeOH)

Analysis: $C_{27}H_{41}N_2O_7P.^1/_2H_2O$ requires C, 59.44; H, 7.76; N, 5.13%
Found: C, 59.42; H, 7.65; N, 4.99%

Further elution gave a mixture of 2 diastereoisomers (3.12g)
Further elution gave a slower running single diastereoisomer
Isomer D44B (0.70g)

$\delta(CDCl_3)$: 0.91 (6H, dd), 1.50 (6H, broad t), 1.70 (7H, m), 1.94 (1H, m), 2.59 (4H, s), 2.93 (1H, m), 3.53 (1H, t), 3.74 (6H, d), 3.84 (1H, m), 4.00 (1H, m), 5.16 (2H, s), 7.34(5H, m).

^{31}P $\delta(CDCl_3)$: 29.55

Observed EI MH^+ 537

$[\alpha]_D^{22}$ = -11.47 (c=0.78, MeOH)
Analysis: $C_{27}H_{41}N_2O_7P.^1/2H_2O$ requires C, 59.44; H, 7.76; N, 5.13%
Found C, 59.27; H, 7.58; N, 4.87%

Description 45

N-[1-(Dimethoxyphosphinyl)-3-[8-(7,9-dioxo-8-azaspiro[4,5]decyl)] propyl]-(S)-leucine (D45)

The title compound was prepared as a single diastereoisomer (D45A) (1.7g) from the benzyl ester (D44A) (2.1g) by the procedure described in Description 21.

$\delta(CDCl_3)$: 0.96 (6H, dd), 1.50 (6H, m), 1.70 (6H, m), 1.74 (1H, m), 2.06 (1H, broad s), 2.60 (4H, s), 2.98 (1H, m), 3.76 (3H, d), 3.81 (3H, d), 3.90 (2H, m), 4.03 (1H, m).

^{31}P $\delta(CDCl_3)$: 29.13

Observed FAB $(M+H)^+$ 447 $C_{20}H_{35}N_2O_7P$ requires M 446

$[\alpha]_D^{22}$ = -9.11 (c=0.48, MeOH)

Similarly, the title compound was prepared as a single diastereoisomer (D45B) (0.5g) from the benzyl ester (D44B) (0.7g)

$\delta(CDCl_3)$: 0.96 (6H, dd), 1.50 (6H, broad s), 1.60-1.90 (7H, m), 2.00 (1H, m), 2.59 (4H, s), 2.92 (1H, m), 3.41 (1H, t), 3.73 (1H, m), 3.80 (3H, d), 3.84 (3H, d), 3.92 (1H, m)

Description 46

N-[1-(Dimethoxyphosphinyl)-3-[8-(7,9-dioxo-8-azaspiro[4,5]decyl)] propyl)-(S)-leucyl]-(S)-phenylalanine-N-methylamide (D46)

The title compound was prepared as a single diasteroisomer (0.43g) (D46A) from the acid (D45A) and (S)-phenylalanine-N-methylamide (0.2g) by the procedure described in Description 19.

$\delta(CDCl_3)$: 0.87 (6H, dd), 1.20 (2H, m), 1.51 (5H, m), 1.73 (6H, broad s), 1.90 (1H, m), 2.61 (4H, s), 2.73 (3H, d), 3.12 (2H, m), 3.49 (1H, m), 3.72 (3H, d), 3.77 (3H, d), 3.74 (2H, m), 3.90 (1H, m), 4.57 (1H, q), 6.32 (1H, broad d), 7.25 (5H, m), 7.48 (1H, d).

^{31}P $\delta(CDCl_3)$: 30.10

Observed FAB $(M+H)^+$ 607 $C_{30}H_{47}N_4O_7P$ requires M 606

$[\alpha]_D^{22}$ = -25.38 (c=0.76,MeOH)

Analysis: $C_{30}H_{47}N_4O_7P^1/2H_2O$ requires C, 58.52; H, 7.86; N, 9.10%
Found C, 58.67; H, 7.50; N; 9.17%

Similarly, the title compound was prepared as a single diastereoisomer (D46B) (0.46g) from the acid (0.5g) (D45B) and (S)-phenylalanine-N-methylamide (0.22g)

$\delta(CDCl_3)$: 0.82 (6H, t), 1.00 (1,Hm), 1.16 (1H, m), 1.50 (5H, m), 1.70 (6H, m), 1.95 (1H, m), 2.60 (4H, s), 2.70 (3H, d), 2.98 (1H, dd), 3.10 (1H, m), 3.30 (1H, dd), 3.73 (3H, d), 3.78 (3H, d), 3.85 (3H, m), 4.77 (1H, m), 7.22 (5H, m), 7.34 (1H, broad d), 7.47 (1H, d)

Description 47

N-[N-(1-(Dimethoxyphosphinyl)-3-[8-(7,9-dioxo-8-azaspiro[4,5]decyl)] propyl)-(S)-leucyl]-(S)-benzyloxycarbonyllysine-N-methylamide (D47)

The title compound was prepared as a single diastereoisomer (0.5g) (D47) from the acid (0.45g) (D45A) and (S)-N_ε-benzyloxycarbonyllysine-N-methylamide (0.29g) by the procedure described in Description 19.

$\delta(CDCl_3)$: 0.96 (6H, dd), 1.47 (8H, m), 1.75 (11H, m), 1.98 (1H, m), 2.59 (4H, s), 2.75 (3H, d), 2.80 (1H, m), 3.20 (2H, m), 3.60 (1H, t), 3.72 (3H, d), 3.79 (3H, d), 3.85 (1H, m), 4.00 (1H, m), 4.30 (1H, q), 5.09 (2H, s), 5.17 (1H, broad s), 6.40 (1H, broad d), 7.34 (5H, s), 7.44 (1H, d).

^{31}P $\delta(CDCl_3)$: 30.01

Observed FAB $(M+H)^+$ 722 $C_{35}H_{56}N_5O_9P$ requires M 721

$[\alpha]_D^{22}$ = -28.87 (c=0.95,MeOH)

Analysis: $C_{35}H_{56}N_5O_9P^1/2H_2O$ requires C, 57.72; H, 7.86; N, 9.58%
Found C, 57.22; H.7.37; N, 9.54

Description 48

N-[N-(1-(Dimethoxyphosphinyl)-3-aminopropyl)-(S)-leucyl]-(S)-phenylalanine-N-methylamide (D48)

N-[N-(1-Dimethoxyphosphinyl)-3-phthalimidopropyl)-(S)-leucyl]-(S)-phenylalanine-N-methylamide (1g) (D9) was dissolved in a 0.2M methanol solution of hydrazine (50ml) and the solution stirred at room temperature for 24h. The solvent was evaporated **in vacuo** and the mixture treated with methanol, filtered and the solvent evaporated **in vacuo** to give the title compound as a mixture of 2 diastereoisomers (0.7g) (D48) which was used in the next stage without further purification.

Description 49

N-[N-(1-(Dimethoxyphosphinyl)-3-(benzyloxycarbonylamino) propyl)-(S)-leucyl]-(S)-phenylalanine-N-methylamide (D49)

N-[N-(1-(Dimethoxyphosphinyl)-3-aminopropyl)-(S)-leucyl]-(S)-phenylalanine-N-methylamide (4.5g) (D48) was dissolved in water (20ml) and dioxan (20ml). Benzyl chloroformate (1.8ml) was added and the pH maintained at 9 - 9.5 by the addition of 10% sodium hydroxide solution. After stirring at room temperature overnight, the solution was extracted with chloroform. The organic extracts were washed with water, dried with anhydrous sodium sulphate, filtered and the solvent evaporated **in vacuo** to give a colourless oil.

Purification by column chromatography on silica gel, eluting with 10% methanol/ethyl acetate gave the title compound as a mixture of 2 diastereoisomers (4.7g) (D49)

δ ($CDCl_3$): 0.87 (6H, m), 0.96 - 2.17 (6H,m), 2.59 (1½H, d), 2.62 (1½H ,d), 2.62 (1½H, d), 2.80 (1H, m), 3.00 (2H, m), 3.24 (2H, m), 3.44 (1H, m), 3.70 (6H, t), 4.66 (1H, m), 5.07

(2H, m), 5.36 (½H, broad t), 6.12 (½H, d), 6.41 (½H, broad t), 7.24 (11H, m), 7.60 (½H,d)

Observed FAB ($M+H^+$) 591 $C_{29}H_{43}N_4O_7P$ requires M 590

Example 1

N-[N-(1-Phosphono-1-(2-hydroxyphenyl)methyl)leucyl]-N,O-dimethyl-(S)-tyrosinamide (E1)

The diethyl ester (D3) (0.2g) was dissolved in dichloromethane (10ml) and treated with bromotrimethylsilane (0.5ml). The solution was stirred at room temperature for 4 days, methanol (20ml) was added and the solvent evaporated **in vacuo** to give the crude product. Column chromatography on reverse phase silica, eluting with a gradient of 5% to 30% methanol in water gave the title compound (0.16g) as a mixture of diastereoisomers.

Observed FAB $(M+H)^+$ 508. $C_{24}H_{34}N_3O_7P$ requires M 507.

Example 2

N-[N-(1-Phosphono-3-(1,8-naphthalenedicarboximide)propyl)-(S)-leucyl]-N,O-dimethyl-(S)-tyrosinamide (E2)

The dibenzyl ester (D6A) (0.5g) was dissolved in ethanol (100 ml) and hydrogenated over 10% palladium on charcoal at atmospheric pressure for 24h. The solution was filtered and the solvent evaporated **in vacuo** to give the title compound as a single diastereoisomer (E2A) (0.38g).

Observed FAB $(M+H)^+$ 639. $C_{32}H_{39}N_4O_8P$ requires M 638.

Similarly, the dibenzyl ester (D6B) gave the title compound as a single diastereoisomer (E2B).

Observed FAB $(M+H)^+$ 639. $C_{32}H_{39}N_4O_8P$ requires M 638.

Example 3

N-[N-(1-Phosphono-3-phthalimidopropyl)-(S)-leucyl]-(S)-phenylalanine-N-methylamide

The dimethyl ester (D9) (1g) was dissolved in dichloromethane (10ml) and bromotrimethylsilane (1.56g) added under nitrogen at room temperature. The solution was stirred at room temperature for 3h, then refluxed for 1.5h. The solution was allowed to cool and solvent evaporated **in vacuo** to give a colourless oil which was dissolved in dioxan (5ml) and water (0.5ml) and refluxed for 1h. The solvent was evaporated **in vacuo** to give the title compound as a white crystalline compound (0.7g) as a mixture of 2-diastereoisomers.

$\delta(CD_3OD)$: 0.98 (6H, m), 1.55-2.40 (5H, m), 2.65 (3H, s), 2.80-3.25 (3H, m), 3.68 (1½H, m), 3.84 (½H, m), 4.21 (½H, m), 4.43 (½H, t), 4.67 (1H, m), 7.27 (5H, m), 7.84 (4H, m)

Observed FAB $(M+H)^+$ 559 $C_{27}H_{35}N_4O_7P$ requires M 558

The dimethyl ester (D9A) (0.06g) was dissolved in dichloromethane (10ml) and the solution cooled to -20°C. Iodotrimethylsilane (0.1ml) was added under nitrogen at -20°C and the solution stirred for 30 min. The solution was allowed to warm to room temperature and stirred for 3h. The solvent was evaporated **in vacuo** and the residue dissolved in methanol (20ml) and stirred for 2h. Solvent was evaporated **in vacuo** to give the title compound (0.05g) as a single diastereoisomer.

$\delta(CD_3OD)$: 1.00 (6H, t), 1.70 (3H, m), 2.06 (1H, m), 2.42 (1H, m), 2.69 (3H, s), 2.83-3.20 (3H, m), 3.70 (1H, m), 3.86 (1H, m), 4.42 (1H, t), 4.68 (1H, dd), 7.30 (5H, m), 7.85 (4H, m)

Observed FAB $(M+H)^+$ 559 $C_{27}H_{35}N_4O_7P$ requires M 558

Example 4

N-[N-(1-Phosphono-4-(1,8-naphthalenedicarboximido)butyl)-(S)-leucyl]-(S)-phenylalanine-N-methylamide (E4)

The title compound (2.7g) was prepared from the dibenzyl ester (D12) (3.23g) by the procedure described in Example 2.

$\delta(CD_3OD)$: 0.68 (3H, dd), 0.83 (3H, dd), 1.06-1.90 (7H, m), 2.25-3.15 (4H, m), 2.53 (1½H, s), 2.60 (1½H, s), 3.94 (1½H, m), 4.24 (½H, t), 4.50 (1H, m), 7.06 (5H, m), 7.51 (2H, t), 8.14 (2H, d), 8.22 (2H, d).

Observed FAB $(M+Na)^+$ 645. $C_{32}H_{39}N_4O_7P$ requires M 622.

Example 5

N-[N-(1-Phosphono-2-(1,8-naphthalenedicarboximido)ethyl-(S)-leucyl]-(S)-phenylalanine-N-methylamide (E5)

The title compound (0.69g) was prepared from the dibenzyl ester (D15) (1.14g) by the procedure described in Example 2.

$\delta(CD_3OD)$: 0.27 (1½H, d), 0.42 (1½H, d), 0.96 (3H, d), 0.96-1.80 (3H, m), 2.46 (1½H, s), 2.74 (1½H, s), 2.50-3.30 (3H, m), 4.14 (½H, t), 4.50 (2H, m), 4.66 (1H, m), 4.81 (½H, m), 7.17 (5H, m), 7.76 (2H, t), 8.32 (2H, t), 8.50 (2H, d).

Observed FAB $(M+H)^+$ 595. $C_{30}H_{35}N_4O_7P$ requires M 594.

Example 6

N-[N-(1-Phosphono-3-(1,8-naphthalenedicarboximido)propyl)-(S)-leucyl]-(S)-phenylalanine-N-methylamide (E6)

The title compound (0.63g) was prepared as a single diastereoisomer (E6A) from the dibenzyl ester (D16A) by the procedure described in Example 2.

The title compound (0.4g) was also prepared as a single diastereoisomer (E6A) from the dimethyl ester (D22) by treatment with bromotrimethylsilane (1ml) in dichloromethane (50ml) at room temperature under nitrogen for 48h. The solvent was evaporated **in vacuo** and the residue dissolved in methanol (25ml) and water (5ml) and stirred for 2 h. The solvent was evaporated **in vacuo** to give the title compound (E6A) (0.4g) as a white solid.

$\delta(CD_3OD)$: 1.02 (6H, dd), 1.78 (4H, m), 2.14 (1H, m), 2.70 (3H, s), 2.96 (1H, dd), 3.12 (1H, dd), 3.99 (1H, m), 4.10 (1H, m), 4.34 (1H, m), 4.78 (1H, dd), 7.22 (5H, m), 7.78 (2H, t), 8.34 (2H, d), 8.53 (2H, d).

^{31}P: $\delta(CD_3OD)$: 18.47

Observed FAB $(M+H)^+$ 609 $C_{31}H_{37}N_4O_7P$ requires M 608

$[\alpha]_D^{22}$ = -25.39 (c=0.81, MeOH)

Similarly, the dibenzyl ester (D16B) gave the title compound as a single diastereoisomer (E6B).

$\delta(CD_3OD)$: 1.00 (6H, m), 1.76 (3H, m), 2.03 (1H, m), 2.41 (1H, m), 2.68 (3H, s), 2.95 (2H, m), 3.14 (1H, dd), 4.16 (2H, m), 4.46 (1H, t), 4.69 (1H, dd), 7.30 (5H, m), 7.75 (2H, t), 8.30 (2H, d), 8.46 (2H, d)

Observed FAB $(M+H)^+$ 609 $C_{31}H_{37}N_4O_7P$ requires M 608

Example 7

N-[N-(1-Phosphono-3-phenylpropyl)-(S)-leucyl]-(S)-phenylalanine-N-methylamide (E7)

The dibenzyl ester (D19A) (0.46g) was dissolved in ethanol (100 ml) and hydrogenated over 10% palladium on charcoal at atmospheric pressure for 24h. The solution was filtered and the solvent evaporated **in vacuo** to give the title compound, as a white solid, as a single diastereoisomer (E7A) (0.35g).

$\delta(CD_3OD)$: 0.95 (6H, dd), 1.66 (3H, m), 1.85 (1H, m), 2.14 (1H, m), 2.36 (1H, m), 2.50-2.84 (2H, m), 2.70 (3H, s), 2.92 (1H, dd), 3.07 (1H, dd), 4.40 (1H, t), 4.63 (1H, dd), 7.23 (10H, m).

$[\alpha]_D^{22}$ = -26.24° (c=1% in methanol)
m.p. = 147-150°C.

Observed FAB $(M+H)^+$ 490. $C_{25}H_{36}N_3O_5P$ requires M 489.

Analysis: $C_{25}H_{36}N_3O_5P.1/2H_2O$ requires C, 60.23; H, 7.48; N, 8.43%.
Found C, 59.84; H, 7.29; N, 8.43%.

Similarly, the title compound was prepared from the dibenzyl ester (D19B) (0.14g),as a white solid, as a single diastereoisomer (E7B) (0.10g).

$\delta(CD_3OD)$: 0.81 (6H, dd), 1.52 (3H, m), 1.78 (1H, m), 2.07 (1H, m), 2.52 (3H, s), 2.60 (1H, m), 2.65-3.04 (4H, m), 3.91 (1H, broad s), 4.49 (1H, t), 7.13 (10H, m).

$[\alpha]_D^{22}$ = -13.71° (c=1% in methanol).

Observed FAB $(M+H)^+$ 490. $C_{25}H_{36}N_3O_5P$ requires M 489.

Example 8

N-[N-(1-Phosphono-3-(4-bromo-1,8-naphthalenedicarboximido)-propyl)-(S)-leucyl]-(S)-phenylalanine-N-methylamide (E8)

The title compound was prepared as a single diastereoisomer (0.08g) (E8A) from the dimethyl ester (0.2g) (D29A) by the procedure described in Example 6.

$\delta(CD_3OD)$: 1.02 (6H, dd), 1.76 (3H, broad d), 2.02 (1H, broad s), 2.40 (1H, m), 2.68 (3H, s), 2.84 (1H, m), 2.94 (1H, dd), 3.11 (1H, dd), 4.04 (1H, m), 4.16 (1H, m), 4.47 (1H, t), 4.67 (1H, dd), 7.30 (5H, m), 7.79 (1H, t), 7.98 (1H, d), 8.20 (1H, d), 8.45 (2H, t).

Similarly, the title compound was prepared as a single diastereoisomer (E8B) from the dimethyl ester (D29B).

$\delta(CD_3OD)$: 0.97 (6H, dd), 1.78 (4H, m), 2.16 (1H, m), 2.94 (1H, dd), 3.08 (1H, dd), 3.20 (1H, m), 3.93 (1H, broad s), 4.05 (1H, broad s), 4.47 (1H, m), 4.70 (1H, t), 7.77 (1H, t), 7.95 (1H, d), 8.20 (1H, d), 8.42 (2H, t)

Example 9

N-[N-(1-Phosphono-3-(benzyloxycarbonylamino)propyl)-(S)-leucyl]-(S)-phenylalanine-N-methylamide (E9)

The title compound was prepared from the dimethyl ester (D49) by treatment with bromotrimethylsilane for 3h as described in Example 6.

$\delta(CD_3OD)$: 0.96 (6H, m), 1.55-2.30 (5H, m), 2.70 (3H, m), 2.88-3.21 (5H, m), 3.65 (1H, m), 4.05-4.45 (1H, m), 5.10 (2H, m), 7.30 (10H, m)

Observed FAB $(M+H)^+$ 563 $C_{27}H_{39}N_4O_7P$ requires M 562

Example 10

N-[N-(1-Phosphono-3-(2-hydroxyphenyl)propyl)-(S)-leucyl]-(S)-phenylalanine-N-methylamide (E10)

The title compound was prepared as a mixture of 2 diastereoisomers (2.5g) (E10) from the dibenzyl ester (4g) (D30) by the procedure described in Example 2.

Observed FAB$(M+H)^+$ 506 $C_{25}H_{36}N_3O_6P$ requires M 505

Example 11

N-[N-(1-Phosphono-3-(methylmercapto)propyl)-(S)-leucyl]-(S)-phenylalanine-N-methylamide (E11)

The title compound was prepared as a mixture of 2 diastereoisomers (0.15g) (E11) from the dimethyl ester (0.19g) (D31) by treatment with bromotrimethylsilane for 24h as described in Example 6.

Observed FAB $(M+H)^+$ 460 $C_{20}H_{34}N_3O_5PS$ requires M 459

Example 12

N-[N-(1-Phosphono-3-(methylsulphinyl)propyl)-(S)-leucyl]-(S)-phenylalanine-N-methylamide (E12)

The title compound was prepared as a mixture of 2 diastereoisomers (0.42g) (E12) from the dimethyl ester (0.52g) (D32) by treatment with bromotrimethylsilane for 24h as described in Example 6.

$\delta(CD_3OD)$: 0.99 (6H, m), 1.60-2.47 (5H, m), 2.70 (3H, m), 2.77-3.53 (8H, m), 4.36 (½H, m), 4.45 (½H, m), 4.70 (1H, m), 7.31 (5H, m)

Example 13

N-[N-(1-Phosphono-3-(methylsulphonyl)propyl)-(S)-leucyl]-(S)-phenylalanine-N-methylamide (E13)

The title compound was prepared as a mixture of 2 diastereoisomers (0.4g) (E13) from the dimethyl ester (0.5g) (D33) by treatment with bromotrimethylsilane for 48h as described in Example 6.

δ(DMSO) : 0.80 (6H, m), 1.22-1.54 (5H, m), 2.43 (1H, m), 2.50 (1½H, d), 2.57 (1½H, d), 2.84 (1H, m), 2.90 (1½H, s), 2.94 (1½H, s), 2.94-3.40 (4H, m), 4.50 (1H, m), 7.22 (5H, m), 8.06 (½H, d), 8.14 (½H, d), 8.33 (½H, d), 8.49 (½H, d)

Observed FAB $(M+H)^+$ 492 $C_{20}H_{34}N_3O_7PS$ requires M 491

Example 14

N-[N-(1-Phosphono-3-(1,8-naphthalenedicarboximido)propyl)-(S)-leucyl]-(S) tryptophan-N-methylamide (E14)

The title compound was prepared as a single diastereoisomer (0.4g) (E14) from the dimethyl ester (0.52g) (D34) by

treatment with iodotrimethylsilane as described in Example 3.

$\delta(CD_3OD)$: 0.65 (3H, d), 0.73 (3H, d), 1.20 (3H, m), 1.52 (1H, m), 1.72 (1H, m), 2.00 (1H, m), 2.45 (1H, m), 2.50 (3H, s), 2.58 (1H, m), 3.45 (1H, t), 4.06 (2H, m), 4.50 (1H, dd), 6.77 (2H, m), 7.07 (1H, s), 7.10 (1H, t), 7.45 (1H, d), 7.70 (2H, t), 8.23 (2H, d), 8.42 (2H, d)

^{31}P : $\delta(CD_3OD)$: 24.58

Observed FAB $(M+Na)^+$ 670 $C_{33}H_{38}N_5O_7P$ requires M 647

$[\alpha]_D^{22}$ = -20.41 (c=0.8%, MeOH)

Example 15

N-[N-(1-Phosphono-3-(1,8-naphthalenedicarboximido)propyl)-(S)-leucyl-(S)-lysine-N-methylamide hydrocholoride (E15)

The title compound was prepared as a single diastereoisomer (0.62g) (E15) from the dimethyl ester (1.0g) (D35) by treatment with bromotrimethylsilane for 48h as described in Example 6. The product was dissolved in methanol and treated with ether/HCl to give the hydrochloride salt.

$\delta(CD_3OD)$: 0.90 (6H, t), 1.44 (2H, m), 1.54-1.80 (7H, m), 2.08 (1H, m), 2.40 (1H, m), 2.60 (3H, s), 2.92 (2H, m), 3.26 (1H, m), 4.24 (2H, m), 4.34 (1H, m), 4.45 (1H, t), 7.73 (2H, t), 8.27 (2H, d), 8.45 (2H, d)

^{31}P $\delta(CD_3OD)$: 17.00

$[\alpha]_D^{22}$ = -9.03 (c=0.89, MeOH)

Observed FAB $(M+H)^+$ 590 $C_{28}H_{40}N_5O_7P$ requires M 589

Example 16

N-[N-(1-Phosphono-3-(1,8-naphthalenedicarboximido)propyl)-(S)-leucyl]-(-)-aminoazacyclotridecan-2-one, di-sodium salt (E16)

The title compound was prepared as a single diastereoisomer (0.6g) (E16) from the dimethyl ester (0.7g) (D36) by treatment with bromotrimethylsilane for 48h as described in Example 6. The product was dissolved in methanol/water and converted to the di-sodium salt by the addition of two equivalents of sodium hydroxide.

$\delta(CD_3OD)$: 0.98 (6H, m), 1.10-1.98 (22H, m), 2.18 (1H, broad s), 2.68 (2H, m), 3.63 (1H, q), 4.30 (3H, m), 7.75 (2H, q), 8.24 (2H, t), 8.46 (2H, t)

Observed FAB $(M+H)^+$ 687 $C_{33}H_{47}N_4O_7PNa_2$ requires M 686

Example 17

N-[N-(1-Phosphono-3-(1,8-naphthalenedicarboximido)propyl)-(S)-leucyl]-(S)-lysine-N-(aminoethyl) amide dihydrochloride (E17)

The dimethyl ester (0.4g) (D38) was dissolved in dichloromethane (40ml) and a 1.0M ether solution of hydrogen chloride (1.2ml) added. Bromotrimethylsilane (4ml) was added, the solution stirred at room temperature for 48h and the solvent evaporated **in vacuo**. The residue was dissolved in methanol (20ml) and the solution stirred for 2h. The addition of acetone gave the title compound (0.75g) as a single diastereoisomer (E17).

$\delta(CD_3OD)$: 1.02 (3H, d), 1.05 (3H, d), 1.47-2.03 (10H, m), 2.20 (1H, m), 2.54 (1H, m), 3.08 (4H, m), 3.37-3.63 (3H, m), 4.40 (2H, m), 4.58 (1H, t), 7.88 (2H, t), 8.41 (2H, d), 8.62 (2H, d)

Observed FAB $(M+H)^+$ 619 $C_{29}H_{43}N_6O_7P$ requires M 618

Example 18

N-[N-(1-Phosphono-3-(1,8-naphthalenedicarboximido)propyl)-(S)-leucyl]-(S)-lysine-N-(ethylpyrrolidine) amide dihydrochloride (E18)

The title compound was prepared as a single diastereoisomer (0.4g) (E18) from the dimethyl ester (0.6g) (D39) by the procedure described in Example 17.

$\delta(CD_3OD)$: 1.03 (3H, d), 1.06 (3H, d), 1.50-2.22 (13H, m), 2.55 (1H, m), 3.03 (2H, q), 3.12 (2H, m), 3.32 (4H, m), 3.54 (1H, m), 3.66 (1H, m), 3.75 (2H, m), 4.34 (2H, m), 4.62 (1H, t), 7.87 (2H, t), 8.40 (2H, d), 8.50 (2H, d)

^{31}P $\delta(CD_3OD)$: 15.71

Observed FAB $(M+H)^+$ 673 $C_{33}H_{49}N_6O_9P$ requires M 672

Example 19

N-[N-(1-Phosphono-3-(1,8-naphthalenedicarboximido)propyl)-(S)-leucyl]-(S)-lysine-N-(ethyl-N-methylpiperazine) amide trihydrochloride (E19)

The title compound was prepared as a single diastereoisomer (0.9g) (E19) from the dimethyl ester (1.1g) (D41) by the procedure described in Example 17.

$\delta(CD_3OD)$: 1.03 (6H, dd), 1.55 (2H, m), 1.69-2.03 (7H, m), 2.25 (1H, m), 2.53 (1H, m), 3.01 (1H, t), 3.05 (3H, s), 3.50 (4H, m), 3.65 (1H, m), 3.74 (1H, m), 3.81 (8H, broad s), 4.31-4.47 (4H, m), 4.55 (1H, t), 7.82 (2H, t), 8.35 (1H, d), 8.54 (1H, d)

^{31}P $\delta(CD_3OD)$: 17.45

Observed FAB $(M+H)^+$ 702 $C_{34}H_{52}N_7O_7P$ requires M 701

$[\alpha]_D^{22}$ = +1.79 (c=0.78, MeOH)

Example 20

N-[N-(1-Phosphono-3-[8-(7,9-dioxo-8-azaspiro[4,5]decyl)]-propyl)-(S)-leucyl]-(S)-phenylalanine-N-methylamide (E20)

The title compound was prepared as a single diastereoisomer (0.37g) (E20A) from the dimethyl ester (0.4g) (D46A) by treatment witn bromotrimethylsilane for 48h as described in Example 6.

$\delta(CD_3OD)$: 0.97 (6H, d), 1.50 (4H, m), 1.72 (8H, m), 2.17 (1H, m), 2.65 (4H, s), 2.69 (3H, s), 2.75 (1H, m) 2.98 (1H, m), 3.12 (1H, m), 3.77 (2H, m), 4.39 (1H, q), 4.68 (1H, q), 7.28 (5H, m).

^{31}P $\delta(CD_3OD)$: 18.54

Observed FAB $(M+H)^+$ 579 $C_{28}H_{43}N_4O_7P$ requires M 578

$[\alpha]_D^{22}$ = -23.45 (c=0.64, MeOH)

Similarly, the title compound was prepared as a single diastereoisomer (0.41g) (E20B) from the dimethyl ester (0.46g) (D46B)

Example 21

N-[N-(1-Phosphono-3-[8-(7,9-dioxo-8-azaspiro[4,5]decyl)]-propyl)-(S)-leucyl]-(S)-lysine-N-methylamide hydrochloride (E21)

The title compound was prepared as a single diastereoisomer (0.3g) (E21) from the dimethyl ester (0.5g) (D47) by the procedure described in Example 17.

$\delta(CD_3OD)$: 1.02 (6H, t), 1.55 (6H, m), 1.66-1.87 (11H, m), 1.95 (1H, m), 2.28 (1H, m), 2.72 (4H, s), 2.74 (3H, s), 3.00 (2H, t), 3.23 (1H, m), 3.90 (1H, m), 4.09 (1H, m), 4.42 (1H, q), 4.49 (1H, t)

^{31}P $\delta(CD_3OD)$: 18.04

Observed FAB $(M+H)^+$ 560 $C_{25}H_{46}N_5O_7P$ requires M 559

$[\alpha]_D^{22}$ = -16.72 (c=0.66, MeOH)

Example 22

Pharmaceutical compositions for oral administration may be prepared by combining the following:

1) **Solid Dosage Formulation**

	% w/w
Compound of formula 1	10%
Magnesium stearate	0.5%
Starch	2.0%
HPM cellulose	1.0%
Microcrystalline cellulose	86.5%

The mixture may be compressed to tablets, or filled into hard gelatin capsules.

The tablet may be coated by applying a suspension of film former (e.g. HPM cellulose), pigment (e.g. titanium dioxide) and plasticiser (e.g. diethyl phthalate) and drying the film by evaporation of the solvent. The film coat can comprise 2.0% to 6.0% of the tablet weight, preferably about 3.0%.

2) **Capsule**

	%w/w
Compound of formula 1	20%
Polyethylene glycol	80%

The medicinal compound is dispersed or dissolved in the liquid carrier, with a thickening agent added, if required. The formulation is then enclosed in a soft gelatin capsule by suitable technology.

Example 23

A pharmaceutical composition for parenteral administration may be prepared by combining the following:

	Preferred Level
Compound of formula 1	1.0%
Saline	99.0%

The solution is sterilised and sealed in sterile containers.

COLLAGENASE INHIBITOR ASSAY

The test is performed essentially as in Cawston and Barrett, Anal. Biochem. **99**, 340-345 (1979). Compounds for testing are dissolved in methanol by sonication and added to collagenase (purified from culture supernatants from the human lung fibroblast cell line, WI-38) in buffer. After a 5 min pre-incubation at 37°C, the assay tubes are cooled to 4°C and ^{3}H-acetylated rat skin type I collagen is added. The assay tubes are incubated at 37°C overnight. The ^{3}H-collagen forms insoluble fibrils, which are the substrate for the enzyme.

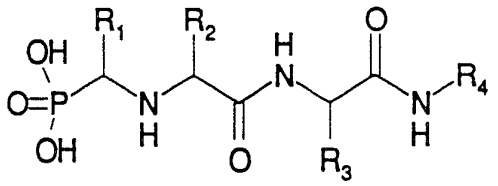
To terminate the assay, the assay tubes are spun at 12000 rpm for 15 minutes. Undigested ^{3}H-collagen is pelleted, while digested ^{3}H-collagen is found as soluble peptides in the supernatant. A sample of the supernatant is taken for liquid scintillation counting.

The activity of collagenase inhibitors (IC_{50}: 50% inhibitory concentration) is expressed as that concentration of compound that inhibits a known (standard) concentration of enzyme by 50%.

The compounds of Examples 2-12 had IC_{50} values in the range 2.3×10^{-6} - 1.3×10^{-8} M.

Claims:

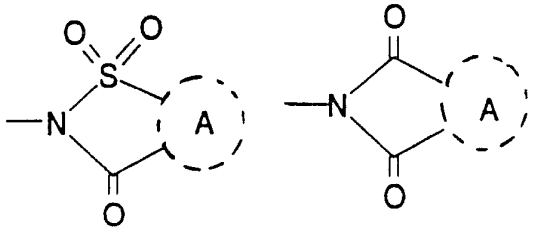
1. A compound of the formula (I) or a salt thereof:



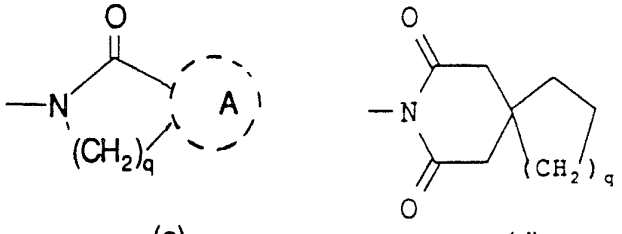
(I)

in which,

R_1 is $-(CH_2)_n-W$ where n is 0-6 and W is amino, optionally-substituted phenyl, $-CONR_5R_6$, $-NR_5COR_6$, $NR_5CO_2CH_2R_6$ or $NR_5CONR_5R_6$ where R_5 is hydrogen or C_{1-6} alkyl and R_6 is hydrogen, C_{1-6} alkyl, optionally-substituted phenyl or heteroaryl, or R_5 and R_6 together with the nitrogen atom to which they are bonded form a 5-, 6- or 7-membered ring with an optional oxygen or sulphur atom or an optionally substituted second nitrogen atom in the ring; or W is $-S(O)_p-R_7$ where p is 0, 1 or 2 and R_7 is C_{1-6}alkyl; or W is a group of sub-formula (a), (b), (c) or (d):



(a) (b)

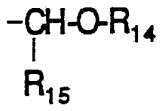


(c) (d)

where in sub-formula (a), (b) and (c) A represents an optionally-substituted mono or bicyclic aryl or heteroaryl ring, and in sub-formula (c) and (d) q is an integer from 1 to 3;

R_2 is C_{3-6} alkyl;

R_3 is hydrogen, C_{1-6}alkyl, $-CH_2-Z$ where Z is optionally substituted phenyl or heteroaryl, $-(CH_2)_rNR_8R_9$, $-(CH_2)_rNHCOR_{10}$, $-(CH_2)_rNR_{11}C(=NR_{12})NR_8R_9$, $-(CH_2)_rCONH(CH_2)_sNR_8R_9$ or $-(CH_2)_r-R_{13}$ where r is 1 to 6, s is 2 to 4, each of R_8 and R_9 is independently hydrogen or C_{1-6}alkyl or R_8 and R_9 together with the nitrogen atom to which they are bonded form a 5-, 6- or 7-membered ring with an optional oxygen or sulphur atom or an optionally substituted second nitrogen atom in the ring, R_{10} is C_{1-6}alkyl or $-(CH_2)_tNR_8R_9$ where t is 1 or 2 and R_8 and R_9 are as defined above, R_{11} is hydrogen or C_{1-6}alkyl or R_{11} and R_8, together with the nitrogen atoms to which they are bonded, form an optionally substituted 5-, 6- or 7-membered ring, R_{12} is hydrogen or C_{1-6}alkyl and R_{13} is an optionally substituted piperidyl ring or R_3 is a group:



where R_{14} is hydrogen, C_{1-6}alkyl or optionally substituted benzyl and R_{15} is hydrogen or C_{1-6}alkyl; and

R_4 is hydrogen, C_{1-6}alkyl or $-(CH_2)_rNR_8R_9$ in which r, R_8 and R_9 are as defined for R_3; or R_3 and R_4 are joined together as $-(CH_2)_m-$ where m is an integer from 4 to 12, or R_3 and R_4 are joined as $-(CH_2)_x-NR_{16}-(CH_2)_y-$ where x is an integer from 1 to 9, y is an integer from 2 to 10, and the moiety $-(CH_2)_x-$ is adjacent to the carbon atom bearing R_3 marked with an asterisk in formula (I), and R_{16} is selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkanoyl, C_{1-6}alkoxycarbonyl, aroyl, aralkyl or aralkyloxycarbonyl in each of which the aryl moiety is optionally substituted.

2. A compound according to claim 1 in which R_1 is 2-hydroxyphenyl, $-(CH_2)_n-W$ where n is 2 and W is amino, phenyl, 2-hydroxyphenyl, $NHCO_2CH_2Ph$, N-phthalimido, 4-bromo-1,8-naphthalenedicarboxamido, 7,9-dioxo-8-azaspiro[4,5]decyl, methylmercapto, methylsulphinyl or methylsulphonyl, or R_1 is $-(CH_2)_n-W$ where n is 1, 2 or 3 and W is a 1,8-naphthalenedicarboxamido group.

3. A compound according to claim 1 or 2 in which R_2 is n-butyl, iso-butyl or sec-butyl.

4. A compound according to any one of claims 1 to 3 in which R_3 is benzyl, C_{1-6}alkylamino, 4-methoxybenzyl, $-(CH_2)_4NH_2$ or 3-indolylmethyl and R_4 is methyl or $-(CH_2)_2NR_8R_9$ where R_8 and R_9 are both hydrogen or together with the nitrogen atom to which they are bonded, form a pyrrolidine or N-methylpiperazine group, or R_3 and R_4 are combined to form a group $-(CH_2)_{10}-$.

5. A compound according to any one of claims 1 to 5 in which the chiral centres marked with an asterisk in formula (I) have the (S)-configuration when R_3 is other than hydrogen.

6. A compound according to claim 1 which is:
N-[N-(1-phosphono-1-(2-hydroxyphenyl)methyl)-leucyl]-N,O-dimethyl-(S)-tyrosinamide,
N-[N-(1-phosphono-3-(1,8-naphthalenedicarboximide)propyl)-(S)-leucyl]-N,O-dimethyl-(S)-tyrosinamide,
N-[N-(1-phosphono-3-phthalimidopropyl)-(S)-leucyl]-(S)-phenylalanine-N-methylamide,
N-[N-(1-phosphono-4-(1,8-naphthalenedicarboximido)butyl)-(S)-leucyl]-(S)-phenylalanine-N-methylamide,
N-[N-(1-phosphono-2-(1,8-naphthalenedicarboximido)ethyl-(S)-leucyl]-(S)-phenylalanine-N-methylamide,
N-[N-(1-phosphono-3-(1,8-naphthalenedicarboximido)propyl)-(S)-leucyl]-(S)-phenylalanine-N-methylamide,

N-[N-(1-phosphono-3-phenylpropyl)-(S)-leucyl]-(S)-phenylalanine-N-methylamide,
N-[N-(1-phosphono-3-(4-bromo-1,8-naphthalene-dicarboximido)propyl)-(S)-leucyl]-(S)-phenylalanine methylamide,
N-[N-(1-phosphono-3-(benzyloxycarbonylamino)propyl)-(S)-leucyl]-(S)-phenylalanine methylamide,
N-[N-(1-phosphono-3-(2-hydroxyphenyl)propyl)-(S)-leucyl]-(S)-phenylalanine methylamide,
N-[N-(1-phosphono-3-(methylmercapto)propyl)-(S)-leucyl]-(S)-phenylalanine-N-methylamide,
N-[N-(1-phosphono-3-(methylsulphinyl)propyl)-(S)-leucyl]-(S)-phenylalanine-N-methylamide,
N-[N-(1-phosphono-3-(methylsulphonyl)propyl-(S)-leucyl]-(S)-phenylalanine-N-methylamide,
N-[N-(1-phosphono-3-(1,8-naphthalenedicarboximido)propyl)-(S)-leucyl]-(S) tryptophan-N-methylamide,
N-[N-(1-phosphono-3-(1,8-naphthalenedicarboximido)propyl)-(S)-leucyl-(S)-lysine-N-methylamide,
N-[N-(1-phosphono-3-(1,8-naphthalenedicarboximido)propyl)-(S)-leucyl]-(-)-aminoazacyclotridecan-2-one,
N-[N-(1-phosphono-3-(1,8-naphthalenedicarboximido)propyl)-(S)-leucyl]-(S)-lysine-N-(aminoethyl) amide,
N-[N-(1-phosphono-3-(1,8-naphthalenedicarboximido)propyl)-(S)-leucyl]-(S)-lysine-N-(ethylpyrrolidine) amide,
N-[N-(1-phosphono-3-(1,8-naphthalenedicarboximido)propyl)-(S)-leucyl]-(S)-lysine-N-(ethyl-N-methylpiperazine) amide,
N-[N-(1-phosphono-3-[8-(7,9-dioxo-8-azaspiro[4,5]decyl)]-propyl)-(S)-leucyl]-(S)-phenylalanine-N-methylamide, or
N-[N-(1-phosphono-3-[8-(7,9-dioxo-8-azaspiro[4,5]decyl)]-propyl)-(S)-leucyl]-(S)-lysine-N-methylamide,
and pharmaceutically acceptable salts thereof.

7. A process for the preparation of a compound according to claim 1 which process comprises cleaving a group R_{20} from a compound of formula (II):

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 92/01903

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[5]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC5: C 07 K 5/06, A 61 K 37/64

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
IPC5	A 61 K; C 07 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category *	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X	WO, A1, 9115506 (BEECHAM GROUP P.L.C.) 17 October 1991, see the whole document	1-10
X	WO, A1, 9115507 (BEECHAM GROUP PLC) 17 October 1991, see the whole document	1-10
X	EP, A1, 0401963 (BEECHAM GROUP P.L.C.) 12 December 1990, see the whole document	1-10

* Special categories of cited documents:[10]

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"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
28th December 1992	12.01.93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	Elisabeth Carlborg

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
X	EP, A2, 0320118 (BEECHAM GROUP PLC) 14 June 1989, see the whole document	1-10

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. PCT/GB 92/01903

SA 65498

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on 02/12/92
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Patent document cited in search report	Publication date	Patent family member(s)		Publication date
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		AU-D-	5315890	18/10/90
		JP-A-	3063294	19/03/91
EP-A2- 0320118	14/06/89	AU-D-	2507088	25/05/89
		JP-A-	1160992	23/06/89
		US-A-	4935404	19/06/90