

NEW NPY ANTAGONISTS

Field of the Invention

5 This invention relates to new pharmaceutically-useful compounds, in particular antagonists of neuropeptide Y, the use of such compounds as medicaments, pharmaceutical compositions containing them and synthetic routes to their production.

10 Background

Neuropeptide Y (NPY) is a peptide consisting of 36 amino acids. In recent years it has been established that NPY is an important co-transmitter in the peripheral sympathetic nervous system.

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It has been postulated (see Pharmacological Reviews (1996) 48, 113) that the effects of sympathetic nerve activation are not only due to the neuronal release of noradrenaline but may also be the result of a simultaneous release of NPY from the sympathetic nerve terminal.

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Released NPY is known to elicit marked constriction of blood vessels in both the heart (coronary arteries) and in most peripheral organs. This vasoconstrictive effect of NPY is believed to be mediated by a receptor sub-type known as Y_1 .

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Released NPY may also act on autonomic nerve endings to inhibit the release of neurotransmitters and, in doing so, reduce the cardiac vagal tone as a result of decreased acetylcholine release. This effect of NPY is believed to be mediated by a receptor sub-type known as Y_2 .

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Other NPY-receptor sub-types, including the Y₃, Y₄, Y₅ and Y₆ sub-receptors, have been identified. The precise functions of these sub-receptors have not been identified in any detail, but the Y₅ sub-receptor is thought to be involved in feeding and eating regulation (see Exp. Opin. Invest. Drugs, 6, 437 (1997)).

Increased plasma concentrations of NPY have been found in several cardiovascular diseases including angina pectoris, myocardial infarction and hypertension. Further, emotional stress has been shown to cause a significant increase in plasma NPY levels (see Circulation (1994) 90, I-268, Abstract No. 1445). Such observations suggest a significant pathogenic role for NPY in myocardial ischemic heart disease and hypertension. Moreover, by causing coronary vasoconstriction and reduced vagal tone, NPY may predispose a patient to ventricular fibrillation and sudden cardiac death.

Effective NPY antagonists would therefore be expected to be useful in the treatment of *inter alia* cardiovascular diseases.

20 Prior Art

Non-peptide antagonists of NPY have been disclosed in European Patent Applications 614 911, 747 357, 747 356 and 747 378, International Patent Applications WO 94/17035, WO 97/19911, WO 97/19913, WO 97/19914, WO 96/22305, WO 96/40660, WO 96/12490, WO 97/09308, WO 97/20820, WO 97/20821, WO 97/20822 and WO 97/20823 and US Patents Nos. US 5,552,411 and US 5,567,714.

European Patent Applications 747 357, 747 356 and 747 378 disclose dihydropyridine derivatives as Y₁ sub-receptor antagonists.

International Patent Applications WO 96/12490, WO 97/09308 and US Patent No. 5,567,714 disclose benzothiophene and indole derivatives as Y₁ sub-receptor antagonists.

- 5 International Patent Application WO 96/40660 discloses benzylamine derivatives as Y₁ sub-receptor antagonists or partial Y₁ sub-receptor agonists.

US Patent No. US 5,552,411 discloses quinoline derivatives as Y₁ sub-receptor antagonists.

International Patent Applications WO 97/20820, WO 97/20821, WO 97/20822 and WO 97/20823 disclose quinazoline derivatives as Y₂ sub-receptor antagonists and are thus indicated for use in the treatment of eating disorders.

The compounds disclosed in International Patent Application WO 96/22305 are disclosed as Y₂ sub-receptor antagonists and are also indicated for use in the treatment of eating disorders. Amongst the compounds specifically disclosed are phenylalaninamide derivatives of N-(diphenylpropionyl)-arginine.

Whether the compounds disclosed in European Patent Application 614 911 and International Patent Application WO 94/17035 are Y₁ or Y₂ sub-receptor antagonists is not mentioned.

International Patent Application WO 94/17035 discloses certain amino acid derivatives, including (R)-N²-(diphenylacetyl)-N-[(4-hydroxyphenyl)-methyl]arginine amide, as antagonists of NPY. The presence of substituents on the carbon atom which is in the α -position relative to the (4-hydroxy)

substituted phenyl group in the above molecule is neither mentioned nor suggested.

Surprisingly we have found that novel analogues of the above compound,
5 containing substituents on the carbon atom which is in the α -position relative to the above-mentioned phenyl group are remarkably good antagonists of NPY.

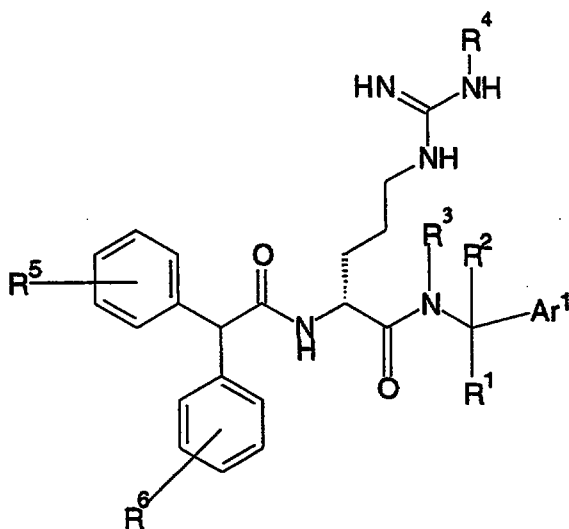
Disclosure of the Invention

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According to the invention there is provided a compound of formula I,

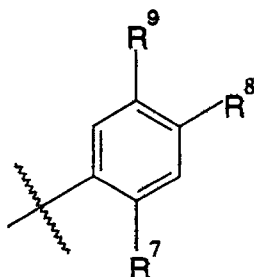
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wherein

25 Ar^1 represents a structural fragment of the formula



- or represents 1- or 2-naphthyl, which latter group is optionally substituted by one or more substituent selected from OH, halo or C_{1-7} alkoxy;
- 10 R^1 represents $C(O)NH_2$, C_{1-4} alkyl (optionally substituted or terminated by one or more substituent selected from hydroxy or amino), or, together with R^7 (in Ar^1), forms C_{2-3} alkylene;
- R^4 represents H, C_{1-7} alkyl or C_{1-4} alkylphenyl (in which latter group, the phenyl group is optionally substituted by one or more substituent
- 15 selected from OH or C_{1-4} alkoxy);
- R^5 and R^6 independently represent H, OH, C_{1-4} alkyl, C_{1-4} alkoxy or halo;
- R^7 represents H, OH or, together with R^1 , forms C_{2-3} alkylene;
- R^8 represents H, halo, OH, C_{1-7} alkoxy, phenyl, phenoxy, benzyloxy, $-(CH_2)_n C(O)N(R^{10})R^{11}$, $-(CH_2)_n N(H)C(O)N(R^{10})R^{11}$ or $-O(CH_2)_n C(O)OR^{10}$;
- 20 R^9 represents H, halo, OH or C_{1-7} alkoxy;
- R^2 , R^3 , R^{10} and R^{11} independently represent H or C_{1-7} alkyl; and
- n represents 1, 2, 3 or 4;
- or a pharmaceutically acceptable derivative thereof (hereinafter referred to together as "the compounds of the invention").

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Pharmaceutically acceptable derivatives includes solvates and salts. Particular salts which may be mentioned include those of hydrochloric, acetic and camphorsulphonic acid.

30 The compounds of the invention may exhibit tautomerism. All tautomeric

forms and mixtures thereof are included within the scope of the invention.

The compounds of the invention may also contain one or more asymmetric carbon atoms and may therefore exhibit optical and/or diastereoisomerism.

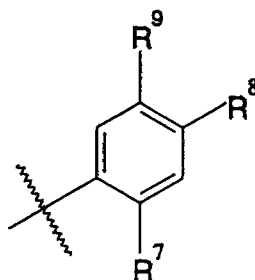
- 5 All diastereoisomers may be separated using conventional techniques, e.g. chromatography or fractional crystallisation. The various stereoisomers may be isolated by separation of a racemic or other mixture of the compounds using conventional, e.g. fractional crystallisation or HPLC, techniques. The desired optical isomers may be made by reaction of the
- 10 appropriate optically active starting materials under conditions which will not cause racemisation or epimerisation. Desired optical isomers may also be obtained by derivatisation, for example by reacting an intermediate with a homochiral acid, separating the diastereomeric derivatives by conventional means (e.g. HPLC, chromatography over silica) and
- 15 converting back to the optically pure intermediate. All stereoisomers are included within the scope of the invention.

- Alkyl groups which R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^{10} and R^{11} may represent may be linear or branched, may be cyclic or acyclic, may be saturated or
- 20 unsaturated and/or may be optionally interrupted by oxygen. Alkoxy groups which R^5 , R^6 , R^8 and R^9 may represent, and with which Ar^1 and R^4 may be substituted, may be linear or branched, may be cyclic or acyclic, may be saturated or unsaturated and/or may be optionally interrupted by oxygen. The alkylene part of alkylphenyl groups which R^4 may
- 25 represent may be linear or branched and/or may be saturated or unsaturated. Alkylene groups which R^1 and R^7 may together represent may be linear or branched and/or may be saturated or unsaturated.

- Halo groups which R^5 , R^6 , R^8 and R^9 may represent, and with which Ar^1
- 30 may be substituted, include fluoro, chloro, bromo and iodo.

The wavy line on the carbon atom in the structural fragment

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signifies the bond position of the fragment.

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Abbreviations are listed at the end of this specification.

Preferred compounds of formula I include those wherein:

R¹ represents C(O)NH₂, CH₂OH, ethyl or, especially, methyl;

15 R² represents H;

R³ represents H or methyl;

R⁴ represents H;

R⁵ represents OH, halo, methyl, methoxy or, especially, H;

R⁶ represents OH, halo, methyl, methoxy or, especially, H;

20 R⁷ represents H;

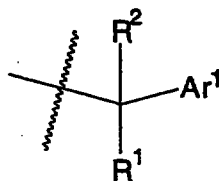
R⁸ represents OCH₃, bromo, -CH₂C(O)NH₂, -CH₂N(H)C(O)NH₂ or, especially, OH;

R⁹ represents H;

R¹⁰ represents H;

25 R¹¹ represents H.

Preferred compounds of formula I include those wherein the carbon atom which is in the α -position relative to Ar¹ in the fragment



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is in the:

- (a) R-configuration when R^1 represents C_{1-4} alkyl; and
- (b) S-configuration when R^1 represents $C(O)NH_2$ or CH_2OH .

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The wavy line on the carbon atom in the above fragment signifies the bond position of the fragment.

Preferred compounds of the invention include:

- 15 (R)-N²-(diphenylacetyl)-(R)-N-[1-(4-methoxyphenyl)ethyl]arginine amide;
- (R)-N²-(diphenylacetyl)-(R,S)-N-(1-phenylpropyl)arginine amide;
- (R)-N²-(diphenylacetyl)-(R,S)-N-[1-(4-hydroxyphenyl)ethyl]arginine amide;
- (R)-N²-(diphenylacetyl)-(R)-N-[1-(4-hydroxyphenyl)ethyl]arginine amide;
- 20 (R)-N²-(diphenylacetyl)-(S)-N-[1-(4-methoxyphenyl)ethyl]arginine amide;
- (R)-N²-(diphenylacetyl)-(S)-N-[1-(4-bromophenyl)ethyl]arginine amide;
- (R)-N²-(diphenylacetyl)-(R)-N-[1-(4-bromophenyl)ethyl]arginine amide;
- (R)-N²-(diphenylacetyl)-(R,S)-N-[1-(3-methoxyphenyl)ethyl]arginine amide;
- (R)-N²-(diphenylacetyl)-(R)-N-(1-phenylethyl)arginine amide;
- 25 (R)-N²-(diphenylacetyl)-(S)-N-(1-phenylethyl)arginine amide;
- (R)-N²-(diphenylacetyl)-(R,S)-N-[1-cyclopropyl-1-(4-methoxyphenyl)-methyl]-arginine amide;
- (R)-N²-(diphenylacetyl)-N-(1-methyl-1-phenylethyl)arginine amide;
- (R)-N²-(diphenylacetyl)-(R,S)-N-(1-indanyl)arginine amide;
- 30 (R)-N²-(diphenylacetyl)-(S or R)-N-(1-carbamoyl-phenylmethyl)arginine

amide;

(*R*)-*N*²-(diphenylacetyl)-(*R* or *S*)-*N*-[1-carbamoyl-(4-methoxyphenyl)-methyl]arginine amide;

(*R*)-*N*²-(diphenylacetyl)-(*S*)-*N*-(2-hydroxy-1-phenylethyl)arginine amide;

5 (*R*)-*N*²-(diphenylacetyl)-(*R*)-*N*-(2-hydroxy-1-phenylethyl)arginine amide;

(*R*)-*N*²-(diphenylacetyl)-(*R*)-*N*-[2-hydroxy-1-(4-methoxyphenyl)ethyl]-arginine amide;

(*R*)-*N*²-(diphenylacetyl)-(*S*)-*N*-[2-hydroxy-1-(4-methoxyphenyl)ethyl]-arginine amide;

10 (*R*)-*N*²-(diphenylacetyl)-(*S*)-*N*-[1-(4-hydroxyphenyl)ethyl]arginine amide;

(*R*)-*N*²-(diphenylacetyl)-(*R,S*)-*N*-[1-(4-methoxyphenyl)ethyl]arginine amide;

(*R*)-*N*²-(diphenylacetyl)-*N*-methyl-(*R*)-*N*-(1-phenylethyl)arginine amide;

(*R*)-*N*²-(diphenylacetyl)-*N*-methyl-(*S*)-*N*-(1-phenylethyl)arginine amide;

15 (*R*)-*N*²-(diphenylacetyl)-(*R,S*)-*N*-[1-(4-cyclopropylmethoxyphenyl)ethyl]-arginine amide;

(*R*)-*N*²-(diphenylacetyl)-(*R*)-*N*-[1-(4-benzyloxyphenyl)ethyl]arginine amide;

(*R*)-*N*²-(diphenylacetyl)-(*R,S*)-*N*-[1-(4-phenoxyphenyl)ethyl]arginine amide;

20 (*R*)-*N*²-(diphenylacetyl)-(*R,S*)-*N*-[1-(4-phenylphenyl)ethyl]arginine amide;

(*R*)-*N*²-(diphenylacetyl)-(*R,S*)-*N*-[1-(2-naphthyl)ethyl]arginine amide;

(*R*)-*N*²-(diphenylacetyl)-(*R*)-*N*-[1-(1-naphthyl)ethyl]arginine amide;

(*R*)-*N*²-[(*R,S*)-2-(4-methoxyphenyl)phenylacetyl]-(*R*)-*N*-[1-(4-hydroxyphenyl)ethyl]arginine amide;

25 (*R*)-*N*²-[(*R,S*)-2-(4-methylphenyl)phenylacetyl]-(*R*)-*N*-[1-(4-hydroxyphenyl)ethyl]arginine amide;

(*R*)-*N*²-[(*R,S*)-2-(4-chlorophenyl)phenylacetyl]-(*R*)-*N*-[1-(4-hydroxyphenyl)ethyl]arginine amide;

(*R*)-*N*²-(4,4'-dichlorodiphenylacetyl)-(*R*)-*N*-[1-(4-hydroxyphenyl)ethyl]-

30 arginine amide;

- (*R*)-N²-[(*R,S*)-2-(4-hydroxyphenyl)phenylacetyl]-(*R*)-N-[1-(4-hydroxyphenyl)ethyl]arginine amide;
- (*R*)-N^ω-(ethyl)-N²-(diphenylacetyl)-(*R*)-N-[1-(4-methoxyphenyl)ethyl]-arginine amide;
- 5 (*R*)-N^ω-(benzyl)-N²-(diphenylacetyl)-(*R*)-N-[1-(4-methoxyphenyl)ethyl]-arginine amide;
- (*R*)-N^ω-(1-(4-hydroxyphenyl)ethyl)-N²-(diphenylacetyl)-(*R*)-N-[1-(4-hydroxyphenyl)ethyl]arginine amide;
- (*R*)-N²-(diphenylacetyl)-(*R,S*)-N-[1-(4-(aminocarbonylmethyl)phenyl)ethyl]-
- 10 arginine amide;
- (*R*)-N²-(diphenylacetyl)-(*R,S*)-N-[1-(4-(aminocarbonylaminomethyl)phenyl)ethyl]arginine amide;
- (*R*)-N²-(4,4'-dichlorodiphenylacetyl)-(*R,S*)-N-[1-(4-(aminocarbonylmethyl)phenyl)ethyl] arginine amide; and
- 15 (*R*)-N²-(4,4'-dichlorodiphenylacetyl)-(*R,S*)-N-[1-(4-(aminocarbonylaminomethyl)phenyl)ethyl] arginine amide.

Particularly preferred compounds of the invention include:

- (*R*)-N²-(diphenylacetyl)-(*R*)-N-[1-(4-methoxyphenyl)ethyl]arginine amide;
- 20 (*R*)-N²-(diphenylacetyl)-(*R*)-N-[1-(4-hydroxyphenyl)ethyl]arginineamide;
- (*R*)-N²-[(*R,S*)-2-(4-chlorophenyl)phenylacetyl]-(*R*)-N-[1-(4-hydroxyphenyl)ethyl]arginine amide;
- (*R*)-N²-(4,4'-dichlorodiphenylacetyl)-(*R*)-N-[1-(4-hydroxyphenyl)ethyl]-arginine amide; and
- 25 (*R*)-N²-[(*R,S*)-2-(4-hydroxyphenyl)phenylacetyl]-(*R*)-N-[1-(4-hydroxyphenyl)ethyl]arginine amide.

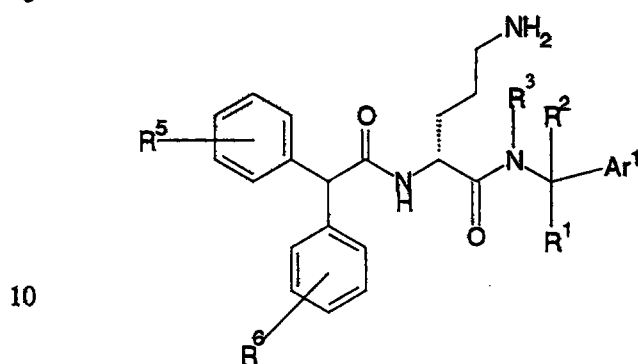
Preparation

- 30 According to the invention there is also provided a process for the

preparation of compounds of formula I which comprises:

(a) Preparation of a compound of formula I by reaction of a compound of formula II,

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wherein Ar^1 , R^1 , R^2 , R^3 , R^5 and R^6 are as hereinbefore defined with a compound of formula III,

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or a hydrogen sulphate salt thereof, wherein R^a represents C_{1-4} alkyl (e.g. methyl) and R^4 is as hereinbefore defined, for example at room temperature in the presence of a suitable base (e.g. DiPEA or triethylamine) and an appropriate organic solvent (e.g. DMF, THF or a mixture thereof).

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(b) Preparation of a compound of formula I, wherein R^4 represents H, by reaction of a compound of formula II as hereinbefore defined with 1H-pyrazole-1-carboxamidine, or a hydrohalide salt thereof, for example at room temperature in the presence of a suitable base (e.g. DiPEA or triethylamine) and an appropriate organic solvent (e.g. DMF).

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(c) Preparation of a compound of formula I by reaction of a compound of formula II as hereinbefore defined with a compound of formula IV,

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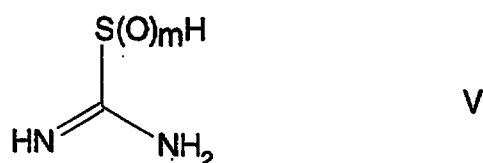


or a hydrogen sulphate salt thereof, wherein R^a and R^4 are as hereinbefore defined, for example between room temperature and 70°C in the presence of a suitable base (e.g. DiPEA or triethylamine) and an appropriate organic solvent (e.g. acetonitrile or DMF).

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(d) Preparation of a compound of formula I wherein R^4 represents H by reaction of a compound of formula II as hereinbefore defined with a compound of formula V,

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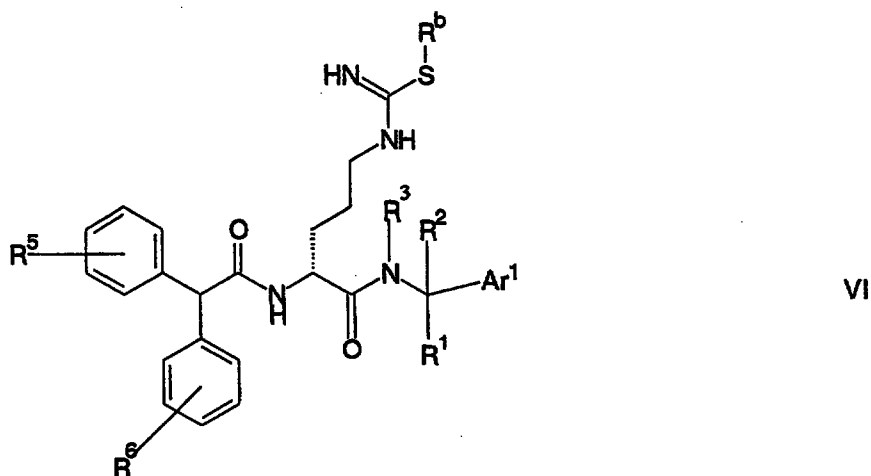
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wherein m represents 2 or 3, for example at room temperature to 70°C in the presence of a suitable base (e.g. DiPEA or triethylamine) and an appropriate organic solvent (e.g. acetonitrile or DMF).

(e) Preparation of a compound of formula I by reaction of a compound of formula VI,

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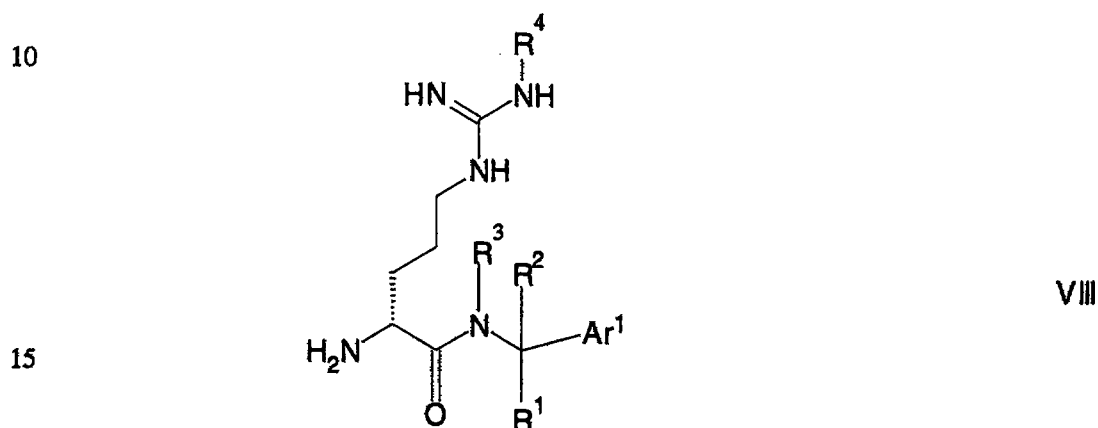
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wherein R^b represents C_{1-4} alkyl (e.g. methyl) and Ar^1 , R^1 , R^2 , R^3 , R^5 and R^6 are as hereinbefore defined with a compound of formula VII,

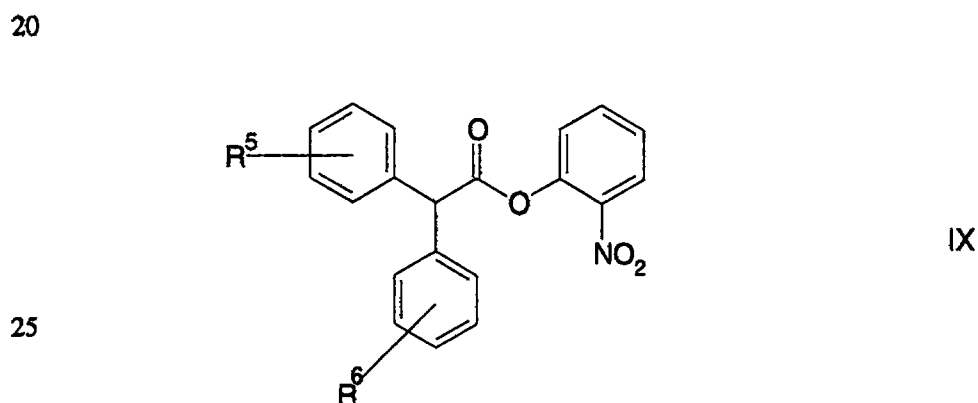


wherein R^4 is as hereinbefore defined, for example at room temperature in the presence of an appropriate solvent (e.g. DMF).

(f) Preparation of a compound of formula I by reaction of a compound of formula VIII,



wherein Ar^1 , R^1 , R^2 , R^3 and R^4 are as hereinbefore defined with a compound of formula IX,



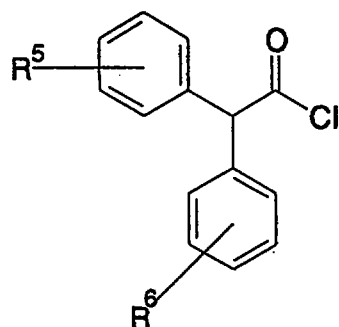
wherein R^5 and R^6 are as hereinbefore defined, for example between $-10^\circ C$ and reflux (e.g. -10 to $30^\circ C$) in the presence of a suitable base (e.g.

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triethylamine or DiPEA) and a suitable organic solvent (e.g. CH_2Cl_2).

(g) Preparation of a compound of formula I by reaction of a compound of formula VIII, as hereinbefore defined, with a compound of formula X,

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X

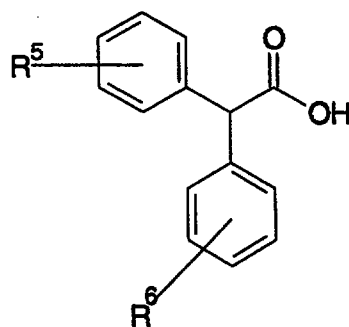
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wherein R^5 and R^6 are as hereinbefore defined, for example at or below room temperature in the presence of a suitable base (e.g. DiPEA, pyridine or sodium bicarbonate) and an appropriate organic solvent (e.g. THF, EtOAc or CH_2Cl_2 , with or without trace DMF).

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(h) Preparation of a compound of formula I by reaction of a compound of formula VIII, as hereinbefore defined, with a compound of formula XI,

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XI

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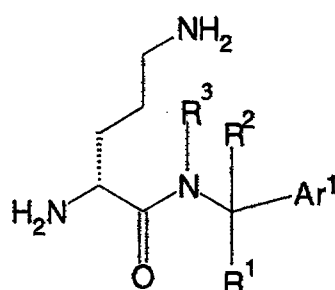
wherein R^5 and R^6 are as hereinbefore defined, for example at or below

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room temperature in the presence of a suitable peptide coupling system (e.g. BOP reagent), base (e.g. triethylamine) and a suitable organic solvent (e.g. acetonitrile).

- 5 Compounds of formula II may be prepared by reaction of a compound of formula XII,

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XII

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wherein Ar¹, R¹, R² and R³ are as hereinbefore defined with a compound of formula IX, as hereinbefore defined, for example under similar conditions to those described hereinbefore for compounds of formula I (process step (f)).

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Compounds of formula II may alternatively be prepared by reaction of a compound of formula XII, as hereinbefore defined, with a compound of formula X, as hereinbefore defined, for example under similar conditions to those described hereinbefore for compounds of formula I (process step (g)).

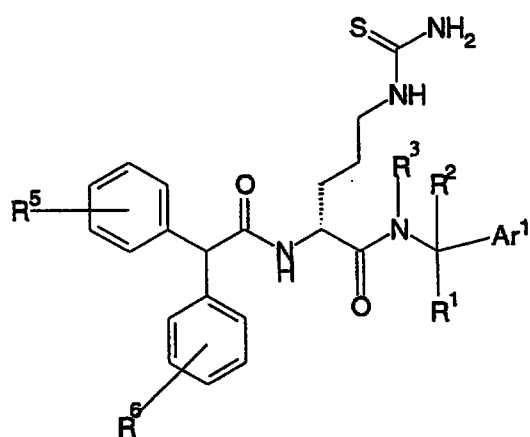
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Compounds of formula II may alternatively be prepared by reaction of a compound of formula XII, as hereinbefore defined, with a compound of formula XI, as hereinbefore defined, for example under similar conditions to those described hereinbefore for compounds of formula I (process step

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(h)).

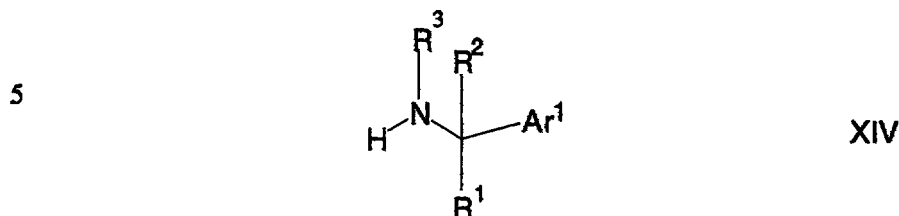
Compounds of formula VI may be prepared by reaction of a compound of formula XIII,



XIII

- 5 wherein Ar¹, R¹, R², R³, R⁵ and R⁶ are as hereinbefore defined, with the appropriate alkyl iodide, for example at room temperature in the presence of an appropriate solvent system (e.g. CH₂Cl₂ or MeOH or mixtures thereof).
- 10 Compounds of formula VIII may be prepared by reaction of a compound of formula XII, as hereinbefore defined, with a compound of formula III (or a hydrogen sulphate salt thereof), 1H-pyrazole-1-carboxamidine (or a hydrohalide salt thereof), or a compound of formula IV (or a hydrogen sulphate salt thereof), for example as described hereinbefore for the
- 15 synthesis of compounds of formula I (process steps (a), (b) and (c), respectively).

Compounds of formula XII may be prepared by reaction of a compound of formula XIV,



wherein Ar¹, R¹, R² and R³ are as hereinbefore defined with (*R*)-ornithine, or a derivative thereof, for example at room temperature in the presence of a suitable peptide coupling system (e.g. BOP reagent and HOBT or EDC), base (e.g. DiPEA, triethylamine or diisopropylamine) and an appropriate organic solvent (e.g. acetonitrile, CH₂Cl₂ or a mixture thereof).

15 Compounds of formula XII may alternatively be prepared by reaction of a compound of formula XIV or a hydrohalide salt thereof as hereinbefore defined with (*R*)-ornithine 2-nitrophenyl ester, for example at room temperature in the presence of an appropriate organic solvent (e.g. CH₂Cl₂) and, if the compound of formula XIV is a salt, a suitable base (e.g. triethylamine or DiPEA).

Compounds of formula XIII may be prepared by reaction of a compound of formula II as hereinbefore defined with isothiocyanate, or a derivative (e.g. the benzoyl derivative) thereof, for example at room temperature in the presence of an appropriate organic solvent (e.g. CH₂Cl₂), followed by, for example, treatment with aqueous base (e.g. potassium carbonate) in the presence of an appropriate solvent such as MeOH.

Compounds of formula XIV are either commercially available, are known in the literature or are available using known techniques. For example

compounds of formula XIV wherein R^2 and R^3 both represent H may be prepared by reductive amination of a corresponding compound of formula XV,

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10 wherein Ar^1 and R^1 are as hereinbefore defined under conditions which are well known to those skilled in the art.

Optically active compounds of formula XIV may be isolated in accordance with known techniques, and may subsequently be used in the synthesis of
15 corresponding compounds of formulae XII, II and I under conditions which will not cause racemisation or epimerisation such as those defined hereinbefore.

Compounds of formulae III, IV, V, VII, IX, X, XI, XV are either
20 commercially available, are known in the literature or are available using known techniques, for example as described hereinafter.

Substituents on the aromatic group in compounds of formulae I, II, III, IV, VI, VII, VIII, IX, X, XI, XII, XIII, XIV and XV may be interconverted
25 by techniques which are well known to those skilled in the art.

The compounds of the invention may be isolated from their reaction mixtures using conventional techniques.

30 It will be appreciated by those skilled in the art that, in the processes

described above, the functional groups of intermediate compounds may need to be protected by protecting groups.

Functional groups which it is desirable to protect include hydroxy, amino, amidino, guanidino and carboxylic acid. Suitable protecting groups for hydroxy include trialkylsilyl and diarylalkylsilyl groups (e.g. *tert*butyldimethylsilyl, *tert*butyldiphenylsilyl or trimethylsilyl) and tetrahydropyranyl. Suitable protecting groups for amino, amidino and guanidino include *tert*butyloxycarbonyl, 9-fluorenylmethoxycarbonyl or benzyloxycarbonyl. Amidino and guanidino nitrogens may be either mono- or diprotected. Suitable protecting groups for carboxylic acid include C₁₋₆ alkyl or benzyl esters.

The protection and deprotection of functional groups may take place before or after any of the reaction steps described hereinbefore.

Protecting groups may be removed in accordance with techniques which are well known to those skilled in the art and as described hereinafter.

Many protected derivatives of the intermediate compounds described hereinbefore are commercially available.

Persons skilled in the art will appreciate that, in order to obtain compounds of formula I in an alternative, and, on some occasions, more convenient, manner, the individual process steps mentioned hereinbefore may be performed in a different order, and/or the individual reactions may be performed at a different stage in the overall route (i.e. substituents may be added to and/or chemical transformations performed upon, different intermediates to those mentioned hereinbefore in conjunction with a particular reaction). This may negate, or render necessary, the need for

protecting groups. Accordingly, the order and type of chemistry involved will dictate the need, and type, of protecting groups as well as the sequence for accomplishing the synthesis.

- 5 The use of protecting groups is fully described in "Protective Groups in Organic Chemistry", edited by J W F McOmie, Plenum Press (1973), and "Protective Groups in Organic Synthesis", 2nd edition, T W Greene & P G M Wutz, Wiley-Interscience (1991).
- 10 It will also be appreciated by those skilled in the art that, although certain protected derivatives of compounds of formula I, which may be made prior to a final deprotection stage, may not possess pharmacological activity as such, they may be administered parenterally or orally and thereafter metabolised in the body to form compounds of the invention which are
- 15 pharmacologically active. Such derivatives may therefore be described as "prodrugs".

All prodrugs of compounds of formula I are included within the scope of the invention.

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Medical and pharmaceutical use

The compounds of the invention are useful because they possess pharmacological activity. They are therefore indicated as pharmaceuticals.

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According to a further aspect of the invention there is thus provided the compounds of the invention for use as pharmaceuticals.

- In particular, the compounds of the invention are potent antagonists of
- 30 NPY for example as demonstrated in the tests described below.

The compounds of the invention are thus expected to be useful in the treatment of diseases/disorders which are/may be mediated by NPY, such as cardiovascular diseases.

- 5 The compounds of the invention are thus indicated for use in the treatment of coronary heart diseases such as angina pectoris, myocardial infarction and syndrome X as well as high blood pressure, hypertension and chronic heart insufficiency.
- 10 According to a further aspect of the invention, there is provided a method of treatment of a cardiovascular disease, which method comprises administration of a therapeutically effective amount of a compound of the invention to a person suffering from, or susceptible to, such a condition.
- 15 The compounds of the invention are also indicated for use in the treatment of other diseases in which NPY is thought to play a pathogenic role, such as chronic kidney failure, tumour diseases such as phaeochromocytoma, infections, migraine, hyperthyroidism as well as obesity and diabetes.
- 20 Compounds of the invention have been found to be selective antagonists of the NPY sub-receptor Y_1 , for example as demonstrated in the tests described below.

25 The compounds of the invention thus find particularly utility in the inhibition of vasoconstriction and in disease states characterised thereby such as migraine, Horton's syndrome, Raynaud's disease, vasospasm after subarachnoid hemorrhage, angina pectoris, coronary infarction, heart failure, cardiac arrhythmias, hypertension, endotoxin shock and stroke.

- 30 According to a further aspect of the invention there is provided a method

of treatment of vasoconstriction, which method comprises administration of a therapeutically effective amount of a compound of the invention, or a pharmaceutically acceptable derivative thereof, to a person suffering from, or susceptible to, such a condition.

5

Pharmaceutical preparations

The compounds of the invention will normally be administered orally, intravenously, subcutaneously, buccally, rectally, dermally, nasally, 10 tracheally, bronchially, by any other parenteral route or *via* inhalation, in the form of pharmaceutical preparations comprising the active ingredient either as a free base, or a pharmaceutical acceptable non-toxic organic or inorganic acid addition salt, in a pharmaceutically acceptable dosage form. Depending upon the disorder and patient to be treated and the route of 15 administration, the compositions may be administered at varying doses.

The compounds of the invention may also be combined with other therapeutic agents which are useful in the treatment of cardiovascular disease, for example β -adrenoceptor antagonists, ACE-inhibitors, diuretics, 20 and calcium antagonists.

According to a further aspect of the invention there is thus provided a pharmaceutical formulation including a compound of the invention in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

25

Suitable doses of the compounds of the invention in therapeutic treatment of humans are about 0.1-1 mg/kg body weight per day at peroral administration and 0.001-0.1 mg/kg body weight per minute at parenteral administration.

30

Compounds of the invention have been observed to have the advantage that they produce fewer side effects than compounds known in the above-mentioned prior art.

- 5 Compounds of the invention may also have the advantage that they may be more efficacious, be less toxic, be longer acting, have a broader range of activity, be more potent, be more easily absorbed than, or that they may have other useful pharmacological properties over, compounds known in the prior art.

10

Biological Tests

Test A

Binding to NPY Y_1/Y_2 Receptors *in vitro*

15

(a) Preparation of Receptor Containing Membranes

(i) Y_1 receptors

The main portion of the rat brain cortex was used for this preparation.

- 20 The rats (male or female Sprague-Dawley rats, weighing 150-250 g) were killed using CO₂ followed by bleeding. The brains were excised, and put in ice cold buffer (0.3 M sucrose, 5mM Hepes; pH 7.4).

- 25 The material was diluted in 10 volumes of ice cold buffer, cut in smaller pieces, and homogenized first with a polytrone followed by 10 strokes at maximum speed with a Potter-Elvehjem homogenizer.

The homogenate was centrifuged at 650 x g at 4°C for 10 minutes. The supernatant was further centrifuged at 33 000 x g at 4°C for 19 minutes.

- 30 The pellets were washed once by resuspending them in buffer and repeating

the last centrifugation step. The final pellets were resolved in a small volume (0.3-1 mL per gram tissue) of buffer complemented with 10% (v/v) glycerol. Aliquots (~200 μ l) were quickly frozen in MeOH and dry ice, and stored at -80°C until further use.

5

The protein concentration was determined according to Bradford (Anal. Biochem. (1976) 72, 248), using the Bio-Rad kit. The Y_1 preparation contained approximately 70-80% Y_1 receptors.

10 (ii) Y_2 receptors

This preparation was performed using pig spleen from a local slaughter house (Farmek Ekonomisk, Förening, Varberg, Sweden). The preparative procedure was the same as for the Y_1 receptor above. The resulting membranes contained approximately 80-90% Y_2 receptors.

15

(b) Receptor Binding Assay

In a typical experiment, 300 μ g of Y_1 or Y_2 receptor containing membranes were mixed with 3 H-NPY and test compound in different concentrations. Membranes and ligands were diluted in the assay buffer
20 (137 mM NaCl, 2.7 mM KCl, 2.1 mM $MgCl_2$, 1.8 mM $CaCl_2$, 0.2% (w/v) bovine serum albumin, 20 mM Hepes; pH 7.4). The samples were incubated for 60 minutes at 30°C, and the binding reaction was stopped by putting the tubes on ice. The samples were filtered on glass fibre filters using a Millipore filtration manifold, to separate unbound and bound
25 isotope labelled ligand. The radioactivity collected on the filters was determined by liquid scintillation counting.

Non specific binding (non NPY related binding) was estimated in the presence of a high concentration (0.1 μ M) of unlabelled NPY. The
30 difference between total binding (in the absence of NPY/test compound)

and non specific binding was expressed as specific binding and is used at the maximal response in each experiment.

Test B

5 The Effects of Test Compounds on NPY in anaesthetised rats

Male Sprague-Dawley rats (300 - 450 g) from Charles River UK were used. The animals were initially anaesthetised with sodium pentobarbitone 70 mg/kg i.p. The anaesthesia was maintained by a continuous infusion in the tail artery (12-20 mg/kg/hour). Body temperature was measured by
10 a rectal probe and maintained by means of a heating pad and a heating lamp at 37.5-38.0°C. The rats were tracheotomised (PE 240) to facilitate spontaneous breathing. Catheters (PE 25) were inserted in the right and left jugular veins for infusions of NPY and test compound. In the tail artery a catheter (PE 25) was inserted for measurement of blood pressure
15 (BP) and for a continuous infusion of anaesthesia. Mean arterial pressure was measured with a transducer (156PC) and heart rate was measured from the pulsating arterial pressure signal with a rate-meter. The left renal artery was dissected free and a small probe was placed around the artery (Transonic 0.7 VB42) in order to measure renal blood flow.

20

All signals were recorded on a paper chart recorder (Grass Polygraph) and digitised using a standard PC. The sampling rate was 10 samples per second and the mean value was calculated and stored every 2 seconds. The computer program then calculated changes in mean arterial pressure,
25 heart rate and renal blood flow from control values measured before drug administration.

After completion of the surgical preparation above, and a stabilisation-period of 30 minutes, NPY (4 µg/kg/20sec.) was intravenously
30 administered at 20 minute intervals. After 2 stable readings following

NPY administration, test compound was intravenously administered in increasing doses (0.625 - 40 $\mu\text{g/kg/min.}$) over 20 minutes. After 10 minutes, further NPY was administered. A test compound was considered active if it attenuated the cardiovascular effect of further NPY treatment in a dose dependent manner.

The invention is illustrated by way of the following examples.

Examples

10

General

Thin layer chromatography utilized silica gel with the following eluent systems: CHCl_3 :MeOH:concentrated ammonium hydroxide (77:18:5) with EM Science No. 5714-3 plates (System A); MeOH: CH_2Cl_2 (1:9) with EM Science No. 5714-3 plates (System B); CH_2Cl_2 :MeOH:concentrated ammonium hydroxide (88.5:10:1.5) with Whatman No. 4420 222 plates (System C); CHCl_3 :MeOH:concentrated ammonium hydroxide (6:3:1) with Whatman No. 4420 222 plates (System D); [pyridine:HOAc:water (55:25:20)]:EtOAc (1:1) with Whatman No. 4420 222 plates (System E); [pyridine:HOAc:water (55:25:20)]:EtOAc (1:2) with Whatman No. 4420 222 plates (System F). Preparative TLC plates were Analtech Uniplate Silica Gel GF (20 x 20 cm, tapered layer; catalog #81013).

Example 1

25 (R)-N²-(Diphenylacetyl)-(R)-N-[1-(4-methoxyphenyl)ethyl]arginine amide hydrochloride

(a) (R)-N²-(Boc)-N⁵-(Cbz)-(R)-N-[1-(4-methoxyphenyl)ethyl]ornithine amide

30 To a magnetically stirred suspension of N^α-Boc-N^δ-Cbz-(R)-ornithine (3.6

g; 9.9 mmol), BOP reagent (4.4 g; 9.9 mmol) and HOBT (1.3 g; 9.9 mmol) in 200 mL of acetonitrile:CH₂Cl₂ (1:1) was added DiPEA (5.2 mL; 30 mmol) at room temperature under nitrogen. After 5 minutes, all the solids dissolved. To the resultant solution was added (*R*)-4-methoxy- α -methylbenzylamine (1.5 g; 9.9 mmol) in CH₂Cl₂ (5 mL). The solution was stirred at room temperature for 2 hours, then concentrated at reduced pressure to give a thick oil. The residue was dissolved in 500 mL of EtOAc and washed successively with 5% aqueous citric acid solution (2 x 300 mL), water (300 mL), saturated aqueous NaHCO₃ (2 x 300 mL) and brine (2 x 300 mL). The organic layer was dried (Na₂SO₄), filtered and evaporated at reduced pressure to give 5.0 g (100%) of the sub-title compound as a light yellow solid.

¹H NMR (CD₃OD) δ 1.39 (s, 9H), 1.40-1.75 (m, 7H), 3.03-3.18 (m, 2H), 3.72 (s, 3H), 4.00-4.10 (m, 1H), 4.89-5.00 (m, 1H), 5.03 (s, 2H), 6.83 (d, 2H), 7.22 (d, 2H), 7.25-7.35 (m, 5H).

(b) (*R*)-N⁵-(Cbz)-(*R*)-N-[1-(4-Methoxyphenyl)ethyl]ornithine amide hydrochloride

(*R*)-N²-(Boc)-N⁵-(Cbz)-(*R*)-N-[1-(4-methoxyphenyl)ethyl]ornithine amide (14.0 g; from step (a) above) in EtOAc (300 mL) was treated with EtOAc saturated with hydrogen chloride (HCl/EtOAc; 300 mL) at room temperature for 5 hours. The solution was concentrated to give the crude sub-title compound as a crushable foam (12.9 g) which was used without purification.

¹H NMR (CD₃OD) δ 1.45 (d, 3H), 1.70-1.90 (m, 4H), 3.08 (t, 2H), 3.74 (s, 3H), 3.87 (m, 1H), 5.01 (m, 1H), 5.06 (s, 2H), 6.87 (d, 2H), 7.27 (d, 2H), 7.30-7.48 (m, 5H).

(c) 2-Nitrophenyl diphenyl acetate

A solution of diphenylacetic acid (30.0 g; 141 mmol) and o-nitrophenol

(39.3 g; 282 mmol) in pyridine (250 mL) was cooled to 0°C. *N,N'*-dicyclohexylcarbodiimide (27.6 g; 134 mmol) was added at 0°C. The solution was stirred at 0°C for several hours, warmed to room temperature and stirred overnight. The resulting heterogeneous solution was diluted
5 with EtOAc and filtered. The filtrate was concentrated to afford a thick oil which was dissolved in a minimal amount of warm isopropanol. Upon cooling the sub-title compound began to crystallize from solution. The crystals were collected and dried under vacuum to afford the sub-title compound (37.3 g; 82%) as an off-white powder.

10 mp 83-85°C

¹H NMR (CDCl₃) δ 5.38 (s, 1H), 7.14 (d, 1H), 7.20-7.45 (m, 11H), 7.60 (t, 1H), 8.07 (d, 1H).

(d)(*R*)-N⁵-(Cbz)-N²-(Diphenylacetyl)-(*R*)-N-[1-(4-methoxyphenyl)ethyl]-
15 ornithine amide

(*R*)-N⁵-(Cbz)-(*R*)-N-[1-(4-methoxyphenyl)ethyl]ornithine amide

hydrochloride (12.9 g; 29.6 mmol; from step (b) above) and 2-nitrophenyl
diphenyl acetate (9.5 g; 29.6 mmol; from step (c) above) were combined
in CH₂Cl₂ (600 mL). Triethylamine (4.5 g; 44.4 mmol) was added. The
20 resulting yellow solution was stirred at room temperature for 60 hours.

When the coupling was complete, as determined by TLC, one volume of
0.5 N NaOH was added and the solution stirred for several minutes. The
organic layer was separated and the aqueous layer extracted twice more
with CH₂Cl₂. The combined organics were washed with brine, dried over
25 anhydrous sodium sulfate, filtered and concentrated under vacuum to give
the crude product as a light yellow solid (16.6 g). The product was
dissolved in a mixture of CH₂Cl₂, MeOH and EtOAc and concentrated
until solids formed. The solids were collected and dried to give pure
product as a white solid (3.2 g). The filtrate was concentrated to give a
30 solid which was chromatographed on silica gel using EtOAc:CH₂Cl₂ (1:3)

as eluent. Concentration of the appropriate fractions gave additional pure product as a white solid (8.8 g).

R_f 0.3 (EtOAc:CH₂Cl₂ (1:3); silica gel TLC plate)

¹H NMR (CDCl₃) δ 1.38 (d, 3H), 1.20-1.58 (m, 2H), 1.62-1.80 (m, 2H), 3.03 (m, 1H), 3.32 (m, 1H), 3.72 (s, 3H), 4.68 (m, 1H), 4.80-5.08 (m, 4H), 6.72 (d, 1H), 6.78 (d, 2H), 7.02-7.45 (m, 17H).

(e) (R)-N²-(Diphenylacetyl)-(R)-N-[1-(4-methoxyphenyl)ethyl]ornithine amide

10 A solution of (R)-N⁵-(Cbz)-N²-(Diphenylacetyl)-(R)-N-[1-(4-methoxyphenyl)ethyl]ornithine amide (5.7 g; 9.6 mmol; from step (d) above) and HCl (2 N; 6 mL) in MeOH (200 mL) was flushed with nitrogen prior to the addition of 10% Pd/C (w/w; 530 mg). The heterogeneous solution was briefly flushed with hydrogen and then stirred under 1 atmosphere of
15 hydrogen for 3 hours. When the deprotection was complete, as determined by TLC analysis, the solution was filtered through a pad of Celite to remove the catalyst. The filtrate was then evaporated at reduced pressure to give the crude product. The residue from evaporation of the filtrate was dissolved in water (300 mL) and washed with diethyl ether (2 x 50 mL).
20 The aqueous layer was adjusted to pH 12 with concentrated NH₄OH, then extracted with EtOAc (3 x 200 mL). The combined organic extracts were washed with brine (200 mL), then dried (Na₂SO₄) and filtered. The filtrate was evaporated at reduced pressure to give 4.2 g (95%) of the sub-title compound (free base) as a white solid.

25 ¹H NMR (CD₃OD) δ 1.30-1.48 (m, 2H), 1.35 (d, 3H), 1.50-1.80 (m, 2H), 2.52 (t, 2H), 3.72 (s, 3H), 4.32-4.42 (m, 1H), 4.85-4.95 (m, 1H), 5.05 (s, 1H), 6.82 (d, 2H), 7.18 (d, 2H), 7.20-7.30 (m, 10H).

(f) (R)-N^w,N^{w'}-bis(Cbz)-N²-(Diphenylacetyl)-(R)-N-[1-(4-methoxyphenyl)ethyl]arginine amide

(R)-N²-(Diphenylacetyl)-(R)-N-[1-(4-methoxyphenyl)ethyl]ornithine amide (free base from step (e) above; 3.26 g; 7.09 mmol) in DMF (35 mL) was
5 treated with N,N¹-bis(Cbz)-S-methylisothiourea (2.80 g, 7.80 mmol) and stirred for 60 hours. Concentration under vacuum gave the crude product (5.7 g of a crushable foam) which was chromatographed on silica gel eluting with CH₂Cl₂, then EtOAc to give pure sub-title compound as a white, crushable foam (5.4 g).

10 R_f 0.4 (CH₂Cl₂:EtOAc (3:1); silica gel TLC plate)

¹H NMR (CDCl₃) δ 1.34 (d, 3H), 1.25-1.68 (m, 3H), 1.78 (m, 1H), 3.12-3.45 (m, 2H), 3.78 (s, 3H), 4.47 (m, 1H), 4.88-5.10 (m, 4H), 5.18 (s, 2H), 6.67 (d, 1H), 6.83 (d, 2H), 6.95-7.45 (m, 22H), 8.30 (m, 1H).

15 (g) (R)-N²-(Diphenylacetyl)-(R)-N-[1-(4-methoxyphenyl)ethyl]arginine amide hydrochloride

(R)-N^w,N^{w'}-bis(Cbz)-N²-(diphenylacetyl)-(R)-N-[1-(4-methoxyphenyl)ethyl]-arginine amide (5.40 g; 7.10 mmol; from step (f) above) in HOAc (300 mL) was flushed with nitrogen prior to the addition of 10% Pd/C (w/w;
20 1.10 g). The heterogeneous solution was briefly flushed with hydrogen and then stirred under 1 atmosphere of hydrogen for 4 hours. When the deprotection was complete, as determined by TLC analysis, the solution was filtered through a pad of Celite to remove the catalyst. The filtrate was evaporated at reduced pressure to give the crude product. The crude
25 acetate salt was dissolved in HCl/MeOH, treated with activated carbon, filtered, concentrated, and dried under vacuum at 55-60°C for 5 hours to give the sub-title compound as an off-white solid (3.47 g).

mp 115-120°C

R_f 0.4 (System D)

30 [α]_D²⁵ = +53.2° (c = 0.98, MeOH)

^1H NMR (CD_3OD) δ 1.38 (d, 3H), 1.25-1.87 (m, 4H), 2.98-3.17 (m, 2H), 3.77 (s, 3H), 4.41 (m, 1H), 4.92 (m, 1H), 5.14 (s, 1H), 6.84 (d, 2H), 7.08-7.45 (m, 12H).

^{13}C NMR (CD_3OD) δ 23.8, 26.8, 30.5, 42.0, 49.8, 55.0, 56.2, 59.0,
5 115.2, 128.5, 129.8, 130.2, 137.2, 141.4, 158.8, 160.5, 173.0, 175.2.

Example 2

(R)-N²-(Diphenylacetyl)-(R,S)-N-(1-phenylpropyl)arginine amide
hydrochloride

10

(a) (R)-N²-(Boc)-N⁵-(Cbz)-(R,S)-N-(1-phenylpropyl)ornithine amide

Prepared according to the method described in Example 1(a) above from N^α-Boc-N^δ-Cbz-(R)-ornithine (4.1 g; 11 mmol), BOP reagent (4.9 g; 11 mmol), HOBT (2.9 g; 22 mmol) and DiPEA (12 mL; 67 mmol) in
15 acetonitrile (200 mL; instead of acetonitrile:CH₂Cl₂ (1:1)) followed by (R,S)-α-ethylbenzylamine (1.5 g; 11 mmol). Work up yielded the sub-title compound (5.4 g) as a thick oil which solidified upon standing.

^1H NMR (CDCl_3) δ 0.80-0.95 (m, 3H), 1.30-1.65 (m, 4H), 1.38 + 1.40 (s, 9H), 1.70-1.90 (m, 2H), 3.02-3.20 + 3.0-3.45 (m, 2H), 4.10-4.30 (m,
20 1H), 4.25-5.25 (m, 3H), 6.75-6.88 (m, 1H), 7.18-7.42 (m, 10H).

(b) (R)-N⁵-(Cbz)-(R,S)-N-(1-phenylpropyl)ornithine amide hydrochloride

(R)-N²-(Boc)-N⁵-(Cbz)-(R,S)-N-(1-phenylpropyl)ornithine amide (5.4 g; 11 mmol; from step (a) above) was suspended in EtOAc (30 mL) and
25 HCl/EtOAc (100 mL) was added. The mixture was magnetically stirred at room temperature for 1 hour, then evaporated at reduced pressure to give the crude sub-title compound as a thick oil, which was suitable for use in the next step without purification.

30

(c) (R)-N⁵-(Cbz)-N²-(Diphenylacetyl)-(R,S)-N-(1-phenylpropyl)ornithine amide

The crude (R)-N⁵-(Cbz)-(R,S)-N-(1-phenylpropyl)ornithine amide hydrochloride (from step (b) above) was dissolved in CH₂Cl₂ (100mL) and
5 diphenylacetyl chloride (2.5 g; 12 mmol) was added as a solid. The flask was cooled in an ice/water bath, magnetically stirred, and DiPEA (6.0 mL; 33 mmol) was added dropwise under nitrogen over 1 minute. The mixture was warmed to room temperature and stirred at that temperature for 1.5 hours. The solution was diluted with 100 mL of CH₂Cl₂ and washed
10 successively with aqueous saturated KHSO₄ (200 mL), water (200 mL), aqueous saturated NaHCO₃ (200 mL) and brine (150 mL), then dried (Na₂SO₄), filtered and evaporated at reduced pressure to give the sub-title compound (4.9 g; 77%) as a tan solid.

¹H NMR (CDCl₃) δ 0.72-0.89 (m, 3H), 1.25-1.90 (m, 6H), 2.92-3.15
15 + 3.25-3.44 (m, 2H), 4.58-5.12 (m, 4H), 6.50-6.70 (m, 1H), 7.00-7.40 (m, 20H).

(d) (R)-N²-(Diphenylacetyl)-(R,S)-N-(1-phenylpropyl)ornithine amide

Prepared according to the method described in Example 1(e) above from
20 (R)-N⁵-(Cbz)-N²-(diphenylacetyl)-(R,S)-N-(1-phenylpropyl)ornithineamide (2.5 g; from step (c) above), 10% Pd/C (150 mg), 50 mL of MeOH (no HCl was added), 2.5 hours reaction time, affording the sub-title compound (1.8 g; 95%; free base) as a pale white solid.

R_f 0.55 and 0.48 (System A)

¹H NMR (CD₃OD) δ 0.75-0.90 (m, 3H), 1.30-1.90 (m, 6H), 2.10-2.30
25 (br s, 2H), 2.50-2.70 (m, 2H), 4.35-4.50 (m, 1H), 4.60-4.72 (m, 1H), 5.00 + 5.10 (s, 1H), 7.10-7.40 (m, 15H).

(e) (R)-N²-(Diphenylacetyl)-(R,S)-N-(1-phenylpropyl)ornithine amide hydrochloride

A sample of (R)-N²-(diphenylacetyl)-(R,S)-N-(1-phenylpropyl)ornithine amide (from step (d) above) was treated with HCl/EtOAc then evaporated
5 at reduced pressure to constant weight to give a sample of the sub-title hydrochloride.

mp 170-180°C (dec.)

¹H NMR (CD₃OD) δ 0.75-0.90 (m, 3H), 1.45-1.95 (m, 6H), 2.75-2.95 (m, 2H), 4.35-4.52 (m, 1H), 4.62-4.75 (m, 1H), 5.03 + 5.10 (s, 1H), 7.10-
10 7.40 (m, 15H), 8.15-8.30 (m, 1H), 8.35-8.50 (m, 1H).

(f) (R)-N²-(Diphenylacetyl)-(R,S)-N-(1-phenylpropyl)arginine amide hydrochloride

The title compound was prepared analogously to a literature procedure (J.
15 Org. Chem., 57, 2497 (1992)). A mixture of (R)-N²-(diphenylacetyl)-(R,S)-N-(1-phenylpropyl)ornithine amide (0.78 g; 1.8 mmol; free base), 1H-pyrazole-1-carboxamide mono hydrochloride (0.27 g; 1.8 mmol) and DiPEA (1.2 mL; 7.0 mmol) in 3 mL of dry DMF was magnetically stirred under nitrogen for 18 hours. The resultant solution was diluted with 40
20 mL of CH₂Cl₂ and diethyl ether was added dropwise until the solution turned slightly cloudy. The solution was scratched to induce solid formation and the resultant solids were filtered, rinsed with CH₂Cl₂ and diethyl ether and then dried at 40°C under vacuum to give 300 mg (33%) of the title hydrochloride as a white solid.

25 mp 112-114°C

R_f = 0.24 (System A)

¹H NMR (CD₃OD) δ 0.75-0.90 (m, 3H), 1.40-1.90 (m, 6H), 3.06-3.10 + 3.10-3.20 (m, 2H), 4.40-4.50 (m, 1H), 4.60-4.70 (m, 1H), 5.05 + 5.10 (s, 1H), 7.15-7.88 (m, 15H).

Example 3(R)-N²-(Diphenylacetyl)-(R,S)-N-[1-(4-hydroxyphenyl)ethyl]arginine amide hydrochloride5 (a) (R)-N²-(Boc)-N⁵-(Cbz)-(R,S)-N-[1-(4-hydroxyphenyl)ethyl]ornithine amide

Prepared according to the method described in Example 1(a) above from N^α-Boc-N^δ-Cbz-(R)-ornithine (5.00 g, 13.6 mmol), (R,S)-4-hydroxy-α-methylbenzyl-amine (1.87 g, 13.6 mmol), BOP (9.0 g, 20.3 mmol) and
10 triethylamine (2.5 mL; instead of DiPEA) in acetonitrile (100 mL; instead of acetonitrile:CH₂Cl₂ (1:1)) to yield the sub-title compound (6.12 g) as a white foam. The NMR spectrum for this material was consistent with a mixture of diastereomers.

15 (b) (R)-N⁵-(Cbz)-(R,S)-N-[1-(4-Hydroxyphenyl)ethyl]ornithine amide hydrochloride

Prepared according to the method described in Example 1(b) above from (R)-N²-(Boc)-N⁵-(Cbz)-(R,S)-N-[1-(4-hydroxyphenyl)ethyl]ornithine amide (6.1 g; from step (a) above), EtOAc (150 mL) and HCl/EtOAc (150 mL)
20 yielding the sub-title compound (8.6 g) as a white foam. The NMR data for this compound was consistent with a mixture of diastereomers.

(c) (R)-N⁵-(Cbz)-N²-(Diphenylacetyl)-(R,S)-N-[1-(4-hydroxyphenyl)ethyl]-ornithine amide

25 (R)-N⁵-(Cbz)-(R,S)-N-[1-(4-hydroxyphenyl)ethyl]ornithine amide hydrochloride (6.0 g; 14.2 mmol; from step (b) above) was treated with diphenylacetic acid (3.32 g; 15.6 mmol), BOP (6.92 g; 15.6 mmol) and triethylamine (4.36 mL; 31.3 mmol) in 300 mL of acetonitrile. The reaction mixture was subjected to aqueous work up and the crude product
30 was chromatographed on 100 g of silica gel eluting with EtOAc:hexanes

(2:1), to afford the sub-title compound (4.1 g) as a white foam. The NMR for this compound was consistent with a mixture of diastereomers.

(d) (R)-N²-(Diphenylacetyl)-(R,S)-N-[1-(4-hydroxyphenyl)ethyl]ornithine
5 amide

Prepared according to the method described in Example 1(e) above from (R)-N⁵-(Cbz)-N²-(diphenylacetyl)-(R,S)-N-[1-(4-hydroxyphenyl)ethyl]-ornithine amide (4.1 g; from step (c) above), 10% Pd/C (1.2 g), MeOH (300 mL) and concentrated HCl (1 mL; instead of 2 N HCl), affording the
10 sub-title compound (1.9 g) as a white solid. The NMR of this material was consistent with a mixture of diastereomers.

(e) (R)-N²-(Diphenylacetyl)-(R,S)-N-[1-(4-hydroxyphenyl)ethyl]arginine
amide hydrochloride

15 Prepared according to the method described in Example 2(f) from (R)-N²-(diphenylacetyl)-(R,S)-N-[1-(4-hydroxyphenyl)ethyl]ornithine amide (free base; 150 mg; 0.311 mmol; from step (d) above), 1H-pyrazole-1-carboxamidine mono hydrochloride (45.6 mg, 0.311 mmol) and DiPEA (0.06 mL; 0.622 mmol) in 2 mL of dry DMF. The reaction mixture was
20 concentrated and the residue was applied to a preparative TLC plate and eluted with CH₂Cl₂:MeOH (90:10) to give the title compound (50 mg). The NMR of this material was consistent with a mixture of diastereomers.

¹H NMR (CD₃OD) δ 1.36 (d, 3H), 1.9-1.36 (m, 4H), 3.15 (m, 2H), 4.40 (m, 1H), 4.86 (m, 1H), 5.06 + 5.11 (s, 1H), 6.68 (d, 2H), 6.70 (d,
25 2H), 7.03 (d, 2H), 7.06 (d, 2H) 7.29 (m, 10H)

Example 4(R)-N²-(Diphenylacetyl)-(R)-N-[1-(4-hydroxyphenyl)ethyl]arginine amide hydrochloride5 (a) N^α-Boc-N^δ-Cbz-(R)-ornithine o-nitrophenyl ester

A solution N^α-Boc-N^δ-Cbz-(R)-ornithine (25.0 g; 68.2 mmol) and o-nitrophenol (19.0 g; 136.4 mmol) in pyridine (250 mL) was cooled to 0°C. Dicyclohexylcarbodiimide (13.4 g; 64.8 mmol) was added at 0°C. The solution was stirred at 0°C for several hours, warmed to room temperature and stirred overnight. The resulting heterogeneous solution was diluted with EtOAc and filtered. The filtrate was concentrated under reduced pressure to afford a thick oil. The oil was dissolved in a minimal amount of warm isopropanol and stirred. The resultant precipitate was collected via vacuum filtration and washed with isopropanol, then diethyl ether. Concentration of the isopropanol/ether filtrate and crystallization from isopropanol provided a second crop. The combined product was dissolved in EtOAc at room temperature and filtered. Concentration of the EtOAc gave the sub-title compound as a solid.

mp 96-98°C

20 ¹H NMR (CD₃OD) δ 1.48 (s, 9H), 1.60-1.90 (m, 4H), 2.00-2.15 (m, 1H), 3.22 (t, 2H), 4.35-4.42, (m, 1H), 5.08 (s, 2H), 7.20-7.38 (m, 6H), 7.49 (t, 1H), 7.76 (t, 1H), 8.12 (d, 1H).

25 (b) (R)-N²-(Boc)-N⁵-(Cbz)-(R)-N-[1-(4-hydroxyphenyl)ethyl]ornithine amide

N^α-Boc-N^δ-Cbz-(R)-ornithine o-nitrophenyl ester (33g; 66.8 mmol; from step (a) above) and (R)-4-hydroxy-α-methylbenzylamine (9.3 g; 68.2 mmol) were combined in CH₂Cl₂ (600 mL). The resulting yellow solution was stirred at room temperature for 4 hours. When the coupling was complete, as determined by TLC, the solution was concentrated under

vacuum to give the crude product. The crude material was dissolved in EtOAc, washed with 0.5N NaOH (2 x 300 mL), saturated KHSO₄ (2 x 300 mL), brine (2 x 300 mL), dried over Na₂SO₄, filtered and concentrated to yield 30.1 g (61.9 mmol; 93%) of the sub-title compound.

5 mp 64-105°C

$[\alpha]_D^{22} = +50.2^\circ$ (c = 1.0, MeOH)

R_f 0.29 (2:1 EtOAc/hexanes; silica gel TLC plate)

MS 486 m/z

¹H NMR (CD₃OD) δ 1.45 (s, 9H), 1.75-1.49 (m, 7H), 3.08 (m, 2H),
10 4.05 (m, 1H), 4.93 (m, 1H), 5.05 (m, 2H), 6.65 (m, 1H, NH), 6.72 (d, 2H), 6.95 (m, 1H, NH), 7.11 (d, 2H), 7.33 (m, 5H), 8.12 (d, 1H, NH)

(c) (R)-N⁵-(Cbz)-(R)-N-[1-(4-hydroxyphenyl)ethyl]ornithine amide hydrochloride

15 Prepared according to the method described in Example 1(b) above from (R)-N²-(Boc)-N⁵-(Cbz)-(R)-N-[1-(4-hydroxyphenyl)ethyl]ornithine amide (30.1 g; 61.98 mmol; from step (b) above), EtOAc (250 mL) and HCl/EtOAc (150 mL) yielding (after chromatography on silica gel, eluting with CH₂Cl₂:MeOH (80:20)) the sub-title compound (15.5 g; 60%).

20 mp 200-203°C

$[\alpha]_D^{21} +39.7^\circ$ (c = 1.0, MeOH)

MS 386 m/z

R_f 0.28 (CH₂Cl₂/MeOH (80:20))

¹H NMR (CD₃OD) δ 1.48 (d, 3H), 1.89-1.48 (m, 4H), 3.09 (t, 2H),
25 3.80 (m, 1H), 5.05 (s, 2H), 4.95 (m, 1H), 6.83 (d, 2H), 7.15 (d, 2H), 7.33 (m, 5H)

(d) (R)-N⁵-(Cbz)-N²-(Diphenylacetyl)-(R)-N-[1-(4-hydroxyphenyl)ethyl]-ornithine amide

30 (R)-N⁵-(Cbz)-(R)-N-[1-(4-hydroxyphenyl)ethyl]ornithine amide

hydrochloride (28.1 g; 66.6 mmol; from step (c) above) was dissolved in THF (500 mL) and solid sodium bicarbonate (22.4 g; 266.4 mmol; 4 eq.) was slowly added. A solution of diphenylacetylchloride (21.4 g; 66.60 mmol) in THF was then slowly added dropwise over 30 minutes. The reaction was monitored by TLC analysis. After the reaction was judged complete, the solvent was removed under vacuum and the residue was dissolved in a mixture of THF, EtOAc and MeOH and washed with saturated aqueous sodium bicarbonate, water, saturated KHSO₄ and brine. The organics were dried over Na₂SO₄, filtered and concentrated to dryness to yield 29.2 g (0.050 mol; 76%) of the sub-title compound.

mp 171-175°C

$[\alpha]_D^{22} + 15.1^\circ$ (c = 1.0, DMF)

R_f 0.68 (CH₂Cl₂:MeOH (80:20); silica gel TLC plate)

¹H NMR (CD₃OD) δ 1.35 (d, 3H), 1.42 (m, 2H), 1.60 (m, 1H), 1.74 (m, 1H), 3.03 (m, 2H), 4.39 (m, 1H), 4.95 (m, 1H), 5.02 (s, 2H), 5.08 (s, 1H), 6.71 (d, 2H), 6.80 (m, 1H, NH), 7.10 (d, 2H), 7.3 (m, 15H), 8.1 (d, 1H, NH)

(e) (R)-N²-(Diphenylacetyl)-(R)-N-[1-(4-hydroxyphenyl)ethyl]ornithine amide acetate

Prepared analogously to the method described in Example 1(e) above from (R)-N⁵-(Cbz)-N²-(diphenylacetyl)-(R)-N-[1-(4-hydroxyphenyl)ethyl]-ornithine amide (26.8 g; 46.23 mmol; from step (d) above), 10% Pd/C (2.5 g) and HOAc (1L; as opposed to HCl/MeOH) yielding 24.3 g of the sub-title compound (after azeotroping with toluene).

mp 120-145°C (with decomposition)

$[\alpha]_D^{23} + 57.1^\circ$ (c = 1.0, MeOH)

MS 446 m/z

R_f 0.11 (System B)

¹H NMR (CD₃OD) δ 1.35 (d, 3H), 1.61 (m, 3H), 1.80 (m, 1H), 1.95

(s, 3H, HOAc), 2.81 (t, 2H), 4.40 (m, 1H), 5.09 (s, 1H), 6.71 (d, 2H), 7.08 (d, 2H), 7.28 (m, 10H)

5 (f)(R)-N^w,N^{w'}-bis(Cbz)-N²-(Diphenylacetyl)-(R)-N-[1-(4-hydroxyphenyl)-ethyl]arginine amide

Prepared analogously to the method described in Example 1(f) above from (R)-N²-(diphenylacetyl)-(R)-N-[1-(4-hydroxyphenyl)ethyl]ornithine amide acetate (5.5 g; 11.8 mmol; from step (e) above) and N,N'-bis(Cbz)-S-methylisothiurea (6.14 g; 17.1 mmol), additionally using DiPEA (4.0 mL; 22.9 mmol) in 100 mL of DMF yielding 6.6 g of the sub-title compound as a white foam.

mp 58-74°C

$[\alpha]_D^{22} = +35.3^\circ$ (c = 1.0 in MeOH)

R_f 0.88 (EtOAc)

15 ¹H NMR (CD₃OD) δ 1.31 (d, 3H), 1.40 (m, 2H), 1.55 (m, 1H), 1.59 (m, 1H), 3.19 (m, 2H), 4.40 (m, 1H), 4.81 (q, 1H), 5.05 (s, 1H), 5.06 (s, 2H), 5.18 (s, 2H), 6.69 (d, 2H), 7.05 (d, 2H), 7.4-7.1 (m, 20H).

20 (g) (R)-N²-(Diphenylacetyl)-(R)-N-[1-(4-hydroxyphenyl)ethyl]arginine amide hydrochloride

Prepared according to the method described in Example 1(g) above from (R)-N^w,N^{w'}-bis(Cbz)-N²-(diphenylacetyl)-(R)-N-[1-(4-hydroxyphenyl)ethyl]-arginine amide (6.6 g; from step (f) above), HOAc (160 mL) and 10% Pd/C (w/w; 1.1 g) yielding 2.75 g of the title compound.

25 mp 150-153°C

$[\alpha]_D^{23} = +57.4^\circ$ (c = 1.0, MeOH)

R_f 0.44 (EtOAc:MeOH:concentrated ammonium hydroxide (47:47:6))

¹H NMR (CD₃OD) δ 1.38 (d, 3H), 1.50 (m, 2H), 1.69 (m, 1H), 1.79 (m, 1H), 3.09 (m, 2H), 4.39 (m, 1H), 4.86 (q, 1H), 5.11 (s, 1H), 6.71 (d, 2H), 7.09 (d, 2H), 7.25 (m, 10H), 8.15 (d, 1H, NH), 8.38 (d, 1H, NH).

Example 5(R)-N²-(Diphenylacetyl)-(S)-N-[1-(4-methoxyphenyl)ethyl]arginine amide hydrochloride5 (a) (R)-N²-(Boc)-N⁵-(Cbz)-(S)-N-[1-(4-methoxyphenyl)ethyl]ornithine amide

Prepared according to the method described in Example 4(b) above from N^α-Boc-N^δ-Cbz-(R)-ornithine o-nitrophenyl ester (14.0 g; 28.7 mmol) and (S)-4-methoxy-α-methylbenzylamine (5.0 g; 33.1 mmol) in CH₂Cl₂ (400 mL), 60 hours reaction time. The reaction mixture was submitted to aqueous work up using 0.5 N NaOH, brine, aqueous KHSO₄, and brine. The organic solution was dried, filtered and concentrated to give a solid (14.3 g) which was used without purification.

R_f 0.50 (hexanes:EtOAc (3:7); silica gel TLC plate)

15

(b) (R)-N⁵-(Cbz)-(S)-N-[1-(4-methoxyphenyl)ethyl]ornithine amide hydrochloride

Prepared according to the method described in Example 1(b) above from (R)-N²-(Boc)-N⁵-(Cbz)-(S)-N-[1-(4-methoxyphenyl)ethyl]ornithine amide (14.3 g; crude, from step (a) above), EtOAc (300 mL) and HCl/EtOAc (300 mL), 5 hours reaction time. The solution was concentrated to give the crude product as a crushable foam (13.3 g) which was used without purification.

¹H NMR (CD₃OD) δ 1.45 (d, 3H), 1.55-1.70 (m, 2H), 1.80-1.95 (m, 2H), 3.18 (t, 2H), 3.76 (s, 3H), 3.84 (m, 1H), 4.98 (m, 1H), 5.08 (s, 2H), 6.88 (d, 2H), 7.28 (d, 2H), 7.28-7.38 (m, 5H).

(c) (R)-N⁵-(Cbz)-N²-(Diphenylacetyl)-(S)-N-[1-(4-methoxyphenyl)ethyl]-ornithine amide

30 Prepared according to the method described in Example 1(d) above from

(*R*)-*N*⁵-(Cbz)-(*S*)-*N*-[1-(4-methoxyphenyl)ethyl]ornithine amide hydrochloride (13.3 g; 30.5 mmol; from step (b) above) 2-nitrophenyl diphenyl acetate (9.8 g; 30.5 mmol; see Example 1(c) above), triethylamine (4.6 g; 45.8 mmol) and CH₂Cl₂ (600 mL), 60 hours reaction
5 time. The reaction mixture was submitted to aqueous work up, dried, filtered and concentrated to give the crude product as a solid. The product was dissolved in CH₂Cl₂ and concentrated until solids began to form. Diethyl ether was added to precipitate more solids. The solids were collected and dried to give the sub-title compound as a white solid (13.5
10 g).

R_f 0.3 (EtOAc:CH₂Cl₂(1:3))

¹H NMR (CDCl₃) δ 1.38 (d, 3H), 1.35-1.62 (m, 2H), 1.72-1.80 (m, 2H), 3.09 (m, 1H), 3.34 (m, 1H), 3.78 (s, 3H), 4.58 (m, 1H), 4.75-5.12 (m, 4H), 6.56 (d, 1H), 6.78 (d, 2H), 6.90(d, 1H), 7.02-7.40 (m, 17H).

15

(d) (*R*)-*N*²-(Diphenylacetyl)-(*S*)-*N*-[1-(4-methoxyphenyl)ethyl]ornithine amide

Prepared according to the method described in Example 1(e) above from (*R*)-*N*⁵-(Cbz)-*N*²-(diphenylacetyl)-(*S*)-*N*-[1-(4-methoxyphenyl)ethyl]-
20 ornithine amide (6.3 g; 10.6 mmol; from step (c) above), 10% Pd/C (3.2 g), MeOH (500 mL) and concentrated HCl (20 mL) under hydrogen, 60 hours reaction time, to give the crude product as a solid (5.1 g). The solid was treated with ammonium hydroxide to afford the free base as a solid (4.7 g) which was chromatographed on silica gel eluting with
25 CH₂Cl₂:MeOH (80:20). Concentration of the product containing fractions gave pure sub-title compound as a solid (3.2 g).

R_f 0.4 (MeOH:ammonium hydroxide (30:1); silica gel TLC plate)

¹H NMR (CDCl₃) δ 1.08-1.47 (m, 5H), 1.62-1.88 (m, 2H), 2.47-2.72 (m, 2H), 3.78 (s, 3H), 4.48 (m, 1H), 4.92 (s, 1H), 4.97 (m, 1H), 6.78 (d,
30 2H), 6.95-7.45 (m, 12H).

(e) (R)-N^w,N^{w'}-bis(Cbz)-N²-(Diphenylacetyl)-(S)-N-[1-(4-methoxyphenyl)ethyl]arginine amide

Prepared according to the method described in Example 4(f) above from (R)-N²-(diphenylacetyl)-(S)-N-[1-(4-methoxyphenyl)ethyl]ornithine amide
5 (free base; 1.75 g; 3.81 mmol; from step (d) above), N,N'-bis(Cbz)-S-methylisothiourea (1.50 g; 4.19 mmol) and dimethyl formamide (15 mL), 18 hours reaction time. Concentration under vacuum gave the crude product which was chromatographed on silica gel eluting with CH₂Cl₂, then with EtOAc, to give pure sub-title compound as a white solid (2.3 g).

10 R_f 0.6 (hexane:EtOAc (3:7); silica gel TLC plate)

¹H NMR (CDCl₃) δ 1.15-1.72 (m, 3H), 1.37 (d, 3H), 1.85 (m, 1H), 3.15-3.40 (m, 2H), 3.77 (s, 3H), 4.49 (m, 1H), 4.85-5.07 (m, 4H), 5.18 (s, 2H), 6.68-6.82 (m, 3H), 6.95-7.45 (m, 22H), 8.32 (m, 1H).

15 (f) (R)-N²-(Diphenylacetyl)-(S)-N-[1-(4-methoxyphenyl)ethyl]arginine amide hydrochloride

Prepared according to the method described in Example 1(g) above from (R)-N^w,N^{w'}-bis(Cbz)-N²-(diphenylacetyl)-(S)-N-[1-(4-methoxyphenyl)ethyl]-arginine amide (2.8 g; from step (e) above), 10% Pd/C (1.5 g), and,
20 instead of HOAc, MeOH (225 mL) and concentrated HCl (21 mL) under hydrogen, 18 hours reaction time, which gave the crude product (1.8 g). Crystallization from MeOH:diethyl ether then from isopropanol:diethyl ether afforded the sub-title compound as a white solid (0.75 g).

mp 148-153°C

25 R_f 0.3 (System D)

[α]_D²⁵ = -9.7° (c = 1.0, MeOH)

¹H NMR (CD₃OD) δ 1.38 (d, 3H), 1.45-1.92 (m, 4H), 3.15 (t, 2H), 3.78 (s, 3H), 4.43 (t, 1H), 4.88 (m, 1H), 5.09 (s, 1H), 6.80 (d, 2H), 7.17 (d, 2H), 7.15-7.38 (m, 10H)

30 ¹³C NMR (CD₃OD) δ 23.0, 26.8, 30.4, 42.4, 55.0, 56.2, 59.0, 115.4,

128.4, 130.0, 130.4, 137.0, 141.2, 159.0, 160.6, 173.2, 175.4

Example 6

(R)-N²-(Diphenylacetyl)-(S)-N-[1-(4-bromophenyl)ethyl]arginine amide
5 hydrochloride

(a)(R)-N²-(Boc)-N⁵-(Cbz)-(S)-N-[1-(4-bromophenyl)ethyl]ornithine amide

Prepared according to the method described in Example 4(b) above from
N^α-Boc-N^δ-Cbz-(R)-ornithine o-nitrophenyl ester (4.4 g; 9.1 mmol; see
10 Example 1(c) above) and (-)-1-(4-bromophenyl)ethylamine (2.0 g; 10.0
mmol) in CH₂Cl₂, 18 hours reaction time. The product containing solution
was concentrated under vacuum to give a yellow solid which was used
without purification.

R_f 0.40 (hexanes:EtOAc (3:7); silica gel TLC plate)

15

(b) (R)-N⁵-(Cbz)-(S)-N-[1-(4-bromophenyl)ethyl]ornithine amide
hydrochloride

Prepared according to the method described in Example 1(b) above from
crude (R)-N²-(Boc)-N⁵-(Cbz)-(S)-N-[1-(4-bromophenyl)ethyl]ornithine
20 amide (9.1 mmol; from step (a) above), EtOAc (100 mL) and HCl/EtOAc
(75 mL), 2 hours reaction time. The solution was concentrated to give the
crude product as a yellow crushable foam (5.4 g) which was used without
purification.

¹H NMR (CD₃OD) δ 1.45 (d, 3H), 1.55-1.70 (m, 2H), 1.80-1.95 (m,
25 2H), 3.18 (t, 2H), 3.88 (t, 1H), 5.02 (m, 1H), 5.12 (s, 2H), 7.28 (d, 1H),
7.28-7.45 (m, 5H), 7.48 (d, 2H)

(c) (R)-N⁵-(Cbz)-N²-(Diphenylacetyl)-(S)-N-[1-(4-bromophenyl)ethyl]-
ornithine amide

30 Prepared according to the method described in Example 1(d) above from

(*R*)-N⁵-(Cbz)-(*S*)-N-[1-(4-bromophenyl)ethyl]ornithine amide hydrochloride (9.1 mmol; from step (b) above), 2-nitrophenyl diphenyl acetate (2.9 g; 9.1 mmol; see Example 1(c) above), triethylamine (3.7 g; 36.4 mmol) and CH₂Cl₂ (300 mL), 40 hours reaction time. The reaction mixture was submitted to aqueous work up, dried with Na₂SO₄ filtered and concentrated to give the crude product as a solid (6.1 g). The product was chromatographed on silica gel eluting with EtOAc:CH₂Cl₂ (1:3). Concentration of the appropriate fractions gave pure product as a white solid (4.2 g).

10 R_f 0.3 (EtOAc: CH₂Cl₂ (1:3); silica gel TLC plate)

¹H NMR (CDCl₃) δ 1.34 (d, 3H), 1.35-1.95 (m, 4H), 3.08 (m, 1H), 3.32 (m, 1H), 4.62 (m, 1H), 4.75-5.12 (m, 4H), 6.63 (d, 1H), 6.85-7.45 (m, 19H)

15 (d) (*R*)-N²-(Diphenylacetyl)-(*S*)-N-[1-(4-bromophenyl)ethyl]ornithine amide
(*R*)-N⁵-(Cbz)-N²-(diphenylacetyl)-(*S*)-N-[1-(4-bromophenyl)ethyl]ornithine amide (0.50 g; 0.78 mmol; from step (c) above) was suspended in CH₂Cl₂:acetonitrile (20 mL; 1:3) and was cooled to 0°C. Trimethylsilyl iodide (0.17 g, 0.86 mmol) was added at 0°C and the reaction stirred for
20 2 hours at 0°C (solids dissolving as the reaction proceeded). When the deprotection was complete, as determined by TLC analysis, the reaction was quenched with water and diluted with EtOAc. The organic layer was separated and washed with water (1X), 1 N sodium thiosulfate (1X) and brine (2X). The combined aqueous washings were extracted with CH₂Cl₂.
25 The organics were combined and triethylamine (5 mL) was added. The mixture was allowed to stand for 18 hours, transferred to a separating funnel, washed with brine (3X), dried over anhydrous sodium sulfate, filtered and concentrated to give the crude product as a yellow solid (0.40 g). The crude product was chromatographed on silica gel eluting with
30 MeOH:CH₂Cl₂ (3:7), then MeOH:CH₂Cl₂ (1:1), to give sub-title compound

(free base) as an off-white solid (0.25 g).

R_f 0.5 (System D)

¹H NMR (CDCl₃ + CD₃OD) δ 1.41 (d, 3H), 1.30-1.54 (m, 2H), 1.63 (m, 1H), 1.78 (m, 1H), 2.70 (t, 2H), 4.43 (m, 1H), 4.88 (m, 1H), 4.99 (s, 1H), 7.08 (d, 2H), 7.18-7.42 (m, 12H)

(e) (R)-N²-(Diphenylacetyl)-(S)-N-[1-(4-bromophenyl)ethyl]arginine amide hydrochloride

Prepared according to the method described in Example 2(f) above from (R)-N²-(diphenylacetyl)-(S)-N-[1-(4-bromophenyl)ethyl]ornithine amide (free base; 0.20 g; 0.39 mmol; from step (d) above), 1H-pyrazole-1-carboxamidine mono hydrochloride (0.06 g; 0.39 mmol), triethylamine (0.08 g; 0.78 mmol; instead of DiPEA) and dimethyl formamide (1 mL), 5 hours reaction time. The solution was concentrated under vacuum and the crude product chromatographed on silica gel eluting with MeOH:CHCl₃:ammonium hydroxide (3:6:1). Conversion of the eluted compound to the hydrochloride salt gave the title compound as a white solid (0.17 g).

mp 136-140°C

R_f 0.4 (System D)

[α]_D²⁵ = -15.3° (c = 1.0, MeOH)

¹H NMR (CD₃OD) δ 1.38 (d, 3H), 1.48-1.92 (m, 4H), 3.18 (t, 2H), 4.41 (m, 1H), 4.87 (m, 1H), 5.08 (s, 1H), 7.18 (d, 2H), 7.10-7.38 (m, 10H), 7.36 (d, 2H)

Example 7(R)-N²-(Diphenylacetyl)-(R)-N-[1-(4-bromophenyl)ethyl]arginine amide hydrochloride

- 5 (a) (R)-N²-(Boc)-N⁵-(Cbz)-(R)-N-[1-(4-Bromophenyl)ethyl]ornithine amide
Prepared according to the method described in Example 4(b) above from N^α-Boc-N^δ-Cbz-(R)-ornithine o-nitrophenyl ester (2.2 g; 4.5 mmol; see Example 4(a) above) and (+)-1-(4-bromophenyl)ethylamine (1.0 g; 5.0 mmol) in CH₂Cl₂ (75 mL), 18 hours reaction time. The product containing
10 solution was concentrated under vacuum to give a yellow solid which was used without purification.

R_f 0.40 (hexanes:EtOAc (3:7); silica gel TLC plate)

- 15 (b) (R)-N⁵-(Cbz)-(R)-N-[1-(4-Bromophenyl)ethyl]ornithine amide hydrochloride

- Prepared according to the method described in Example 1(d) above from crude (R)-N²-(Boc)-N⁵-(Cbz)-(R)-N-[1-(4-bromophenyl)ethyl]ornithine amide (2.46 g; 4.5 mmol; from step (a) above), EtOAc (75 mL) and HCl/EtOAc (50 mL), 2 hours reaction time. The solution was
20 concentrated to give the crude product as a yellow crushable foam (2.4 g) which was used without purification.

¹H NMR (CD₃OD) δ 1.48 (d, 3H), 1.65-1.90 (m, 4H), 3.12 (t, 2H), 3.90 (t, 1H), 5.00 (m, 1H), 5.08 (s, 2H), 7.25 (d, 2H), 7.25-7.40 (m, 5H), 7.48 (d, 2H).

25

- (c) (R)-N⁵-(Cbz)-N²-(Diphenylacetyl)-(R)-N-[1-(4-bromophenyl)ethyl]-ornithine amide

- Prepared according to the method described in Example 1(d) above from (R)-N⁵-(Cbz)-(R)-N-[1-(4-bromophenyl)ethyl]ornithine amide hydrochloride
30 (2.01 g; 4.5 mmol; from step (b) above) 2-nitrophenyl diphenyl acetate

(1.4 g; 4.5 mmol; see Example 1(c) above), triethylamine (1.8 g; 18.0 mmol) and CH_2Cl_2 (300 mL), 40 hours reaction time. The reaction mixture was submitted to aqueous work up, dried with Na_2SO_4 , filtered and concentrated to give the crude product as a solid (2.9 g). The product
5 was chromatographed on silica gel eluting with $\text{EtOAc}:\text{CH}_2\text{Cl}_2$ (1:3). Concentration of the product containing fractions gave the sub-title compound as a white solid (2.5 g).

R_f 0.3 ($\text{EtOAc}:\text{CH}_2\text{Cl}_2$ (1:3); silica gel TLC plate)

^1H NMR (CDCl_3) δ 1.35 (d, 3H), 1.20-1.98 (m, 4H), 3.03 (m, 1H),
10 3.32 (m, 1H), 4.71 (m, 1H), 4.80-5.12 (m, 4H), 6.68 (d, 1H), 7.05 (d, 2H), 7.12-7.50 (m, 17H)

(d) (R)-N²-(Diphenylacetyl)-(R)-N-[1-(4-bromophenyl)ethyl]ornithine amide

15 Prepared according to the method described in Example 6(d) above from (R)-N⁵-(Cbz)-N²-(diphenylacetyl)-(R)-N-[1-(4-bromophenyl)ethyl]ornithine amide (1.00 g; 1.56 mmol; from step (c) above), acetonitrile (30 mL), CH_2Cl_2 (10 mL) and trimethylsilyl iodide (0.34 g, 1.70 mmol), 1.5 hours reaction time, followed by additional trimethylsilyl iodide (0.14 g; 0.70
20 mmol), 0.5 hours reaction time. Work up using triethylamine (10 mL) gave the crude product as an oil (1.00 g). The product was chromatographed on silica gel eluting with MeOH, then with MeOH:ammonium hydroxide (30:1) to give pure sub-title compound (free base) as an off-white crushable foam (0.57 g).

25 R_f 0.5 (MeOH:ammonium hydroxide (30:1); silica gel TLC plate)

^1H NMR (CD_3OD) δ 1.22-1.45 (m, 2H), 1.40 (d, 3H), 1.52-1.83 (m, 2H), 2.58 (t, 2H), 4.38 (m, 1H), 4.91 (m, 1H), 5.07 (s, 1H), 7.11-7.35 (m, 12H), 7.43 (d, 2H)

(e) (R)-N²-(Diphenylacetyl)-(R)-N-[1-(4-bromophenyl)ethyl]arginine amide hydrochloride

Prepared according to the method described in Example 2(f) above from (R)-N²-(diphenylacetyl)-(R)-N-[1-(4-bromophenyl)ethyl]ornithine amide
5 (free base, 0.42 g; 0.83 mmol; from step (d) above), 1H-pyrazole-1-carboxamide mono hydrochloride (0.13 g; 0.83 mmol), triethylamine (0.17 g; 1.66 mmol; instead of DiPEA) and DMF (4 mL), 18 hours reaction time. The solution was concentrated under vacuum and the crude product chromatographed on silica gel using MeOH:CHCl₃:ammonium
10 hydroxide (3:6:1). Conversion to the hydrochloride salt afforded the title compound as a white solid (0.31 g).

mp 115-120°C

R_f 0.4 (System D)

[α]_D²³ = +49.8° (c=1, MeOH)

15 ¹H NMR (CD₃OD) δ 1.40 (d, 3H), 1.75-1.88 (m, 4H), 3.02-3.17 (m, 2H), 4.39 (m, 1H), 4.88 (m, 1H), 5.14 (s, 1H), 7.18 (d, 2H), 7.13-7.50 (m, 10H), 7.43 (d, 2H)

Example 8

20 (R)-N²-(Diphenylacetyl)-(R,S)-N-[1-(3-methoxyphenyl)ethyl]arginine amide hydrochloride

(a) (R)-N²-(Boc)-N⁵-(Cbz)-(R,S)-N-[1-(3-Methoxyphenyl)ethyl]ornithine amide

25 DiPEA (5.4 mL; 31 mmol) was added to a stirred mixture of EDC x HCl (6.0 g; 31 mmol), N-α-Boc-N-δ-Cbz-(R)-ornithine (7.7 g; 21 mmol), (±)-3-methoxy-α-methylbenzylamine (3.2 g; 21 mmol) in CH₂Cl₂ (100 mL). The mixture was stirred for 18 hours at room temperature, then diluted with CH₂Cl₂ (100 mL) and washed 3 times with brine. The organic layer
30 was separated and dried over sodium sulfate. After evaporation of the

solvent, there was obtained a colourless oil which was loaded onto a column of wet silica gel (column: 50 mm diameter by 100 mm height) and eluted with 20% EtOAc in hexanes (500 mL), then 50% EtOAc in hexane (500 mL) and finally 100% EtOAc (500 mL). Fractions (75 mL each) 10-13 were combined and concentrated to afford 10.1 g of product as a colourless glass (90%).

(b) (R)-N⁵-(Cbz)-(R,S)-N-[1-(3-methoxyphenyl)ethyl]ornithine amide hydrochloride

10 Prepared according to the method described in Example 1(b) above from (R)-N²-(Boc)-N⁵-(Cbz)-(R,S)-N-[1-(3-methoxyphenyl)ethyl]ornithine amide (10 g; 19.3 mmol; from step (a) above) which was deprotected using HCl/EtOAc (100 mL) yielding 7.7 g (100%) of sub-title compound.

15 (c) (R)-N⁵-(Cbz)-N²-(Diphenylacetyl)-(R,S)-N-[1-(3-methoxyphenyl)ethyl]ornithine amide

Prepared according to the method described in Example 4(d) above from (R)-N⁵-(Cbz)-(R,S)-N-[1-(3-methoxyphenyl)ethyl]ornithine amide hydrochloride (8.6 g; 19.3 mmol; from step (b) above) and diphenyl-
20 acetylchloride (4.85 g; 21 mmol), which were combined in THF (75 mL) and stirred at -5°C. A 1M solution of Na₂CO₃ (21 mL; 42 equivalents) was added and stirred vigorously, then warmed to room temperature over 3 hours. The mixture was poured into water and extracted with EtOAc. The organic extract was washed with 5% citric acid solution followed by
25 saturated NaHCO₃ solution, dried with Na₂SO₄ and concentrated to afford the sub-title compound (8.7 g; 73.7%).

(d) (R)-N²-(Diphenylacetyl)-(R,S)-N-[1-(3-methoxyphenyl)ethyl]ornithine amide hydrochloride

30 Prepared according to the method described in Example 1(e) above from

(*R*)-*N*⁵-(Cbz)-*N*²-(diphenylacetyl)-(*R,S*)-*N*-[1-(3-methoxyphenyl)ethyl]-ornithine amide (2.3 g; 3.76 mmol; from step (c) above), which was deprotected in HOAc (instead of MeOH). The compound was then dissolved in HCl/MeOH and concentrated to dryness to afford the sub-title compound (1.8 g; 94%) as the HCl salt from acetonitrile and EtOAc.

mp 173-175°C

¹H NMR (CD₃OD; mixture of diastereomers) δ 6.7-7.4 (m, 14H), 5.1 (s, 1H), 4.9 (m, 1H), 4.45 (m, 1H), 3.72 (s, 3H), 2.9 (m, 2H), 1.5-1.9 (m, 4H), 1.38 (d, 3H)

10 (e) (*R*)-*N*^ω,*N*^{ω'}-bis(Cbz)-*N*²-(Diphenylacetyl)-(*R,S*)-*N*-[1-(3-methoxyphenyl)ethyl]arginine amide

Prepared according to the method described in Example 4(f) above from (*R*)-*N*²-(diphenylacetyl)-(*R,S*)-*N*-[1-(3-methoxyphenyl)ethyl]ornithine amide hydrochloride (1.75 g; 3.4 mmol; from step (d) above), *N,N'*-bis(Cbz)-*S*-methylisothiourea (1.33 g; 3.7 mmol) in DMF (2.5 mL) and 1.5 equivalents of DiPEA. Reaction was over in 2 hours, based on TLC analysis. After chromatography, the sub-title product was used directly in the next step.

20 (f) (*R*)-*N*²-(Diphenylacetyl)-(*R,S*)-*N*-[1-(3-methoxyphenyl)ethyl]arginine amide hydrochloride

Prepared according to the method described in Example 1(g) above from (*R*)-*N*^ω,*N*^{ω'}-bis(Cbz)-*N*²-(diphenylacetyl)-(*R,S*)-*N*-[1-(3-methoxyphenyl)ethyl]arginine amide (1.7 g; 2.2 mmol; from step (e) above) in HOAc (100 mL) to afford 1.1 g of the title compound as the crude acetate salt. The salt was dissolved in MeOH and 1N HCl was added slowly to the cloud point. Crystals formed, which were collected and dried to afford 0.55 g (46%) of the title compound.

30 mp 103-108°C

¹H NMR (300 MHz) (CD₃OD) (mixture of diastereomers) δ 6.7-7.4 (m, 14H), 5.1 (s, 1H), 4.95 (m, 1H), 4.45 (m, 1H), 3.7 (s, 3H), 3.1 (m, 2H), 1.35-1.9 (m, 4H), 1.32 (d, 3H)

5 Example 9

(R)-N²-(Diphenylacetyl)-(R)-N-(1-phenylethyl)arginine amide hydrochloride

(a) (R)-N²-(Boc)-N⁵-(Cbz)-(R)-N-(1-phenylethyl)ornithine amide

Prepared according to the method described in Example 1(a) above from
10 *N^α*-Boc-*N^δ*-Cbz-(*R*)-ornithine (5.0 g; 13 mmol), BOP reagent (6.0 g; 13 mmol), HOBT (1.8 g; 13 mmol) and DiPEA (7.1 mL; 40.0 mmol) 100 mL of acetonitrile:CH₂Cl₂ (1:1), followed by 1.8 mL (13 mmol) of (*R*)-α-methylbenzylamine, then stirred overnight. After work up, the crude product was purified by passing it through a plug of silica gel with EtOAc
15 to give 5.9 g (92%) of the sub-title compound as a light yellow solid.

¹H NMR (CD₃OD) δ 1.3-1.8 (m, 16H); 3.2 (m, 2H), 4.05 (m, 1H) 5.0-5.1 (m, 3H), 7.1-7.4 (m, 10H).

(b) (R)-N⁵-(Cbz)-N²-(Diphenylacetyl)-(R)-N-(1-phenylethyl)ornithine
20 amide

Prepared according to the method described in Examples 2(b) and 2(c) above from (*R*)-N²-(Boc)-N⁵-(Cbz)-(R)-N-(1-phenylethyl)ornithine amide hydrochloride (5.9 g; 13 mmol; from step (a) above) EtOAc (30 mL) then HCl/EtOAc (100mL), 3.5 hours reaction time for the deprotection, then
25 CH₂Cl₂ (100 mL), diphenylacetyl chloride (2.9 g; 13 mmol) followed by pyridine (3.0 mL; 37 mmol; instead of DiPEA) over 1 min, overnight reaction time, diluted with CH₂Cl₂ (100 mL) for the work up procedure. The organic layer was partially concentrated at reduced pressure, upon which a precipitate formed, which was filtered to give 1.7 g (24%) of the
30 sub-title compound as a solid.

^1H NMR (CD_3OD) δ 1.4 (m, 5H), 1.6 (m, 1H), 1.75 (m, 1H), 3.05 (m, 2H), 4.4 (m, 1H), 4.75 (m, 1H), 5.02 (s, 2H), 5.08 (s, 1H), 6.9 (m (exchangeable), 1H), 7.1-7.4 (m, 20H), 8.25 (m (exchangeable), 1H)

5 (c) (R)-N²-(Diphenylacetyl)-(R)-N-(1-phenylethyl)ornithine amide hydrochloride

Prepared according to the method described in Example 1(e) above from (R)-N⁵-(Cbz)-N²-(diphenylacetyl)-(R)-N-(1-phenylethyl)ornithine amide (1.7g; 3.0 mmol; from step (b) above) 10% Pd/C (w/w; 100 mg), HOAc (75 mL), overnight reaction time. The crude acetate salt was converted to the sub-title compound and was used without further purification.

^1H NMR (CD_3OD) δ 1.38 (d, 3H), 1.6 (m, 3H), 1.8 (m, 1H), 2.85 (m, 2H), 4.45 (m, 1H), 4.95 (m, 1H), 5.1 (s, 1H), 7.2-7.4 (m, 15H).

15 (d) (R)-N^w,N^{w'}-bis(Cbz)-N²-(Diphenylacetyl)-(R)-N-(1-phenylethyl)-arginine amide

Prepared according to the method described in Example 4(f) above from (R)-N²-(diphenylacetyl)-(R)-N-(1-phenylethyl)ornithine amide (0.50 g; 1.0 mmol; from step (c) above), N,N'-bis(Cbz)-S-methylisothiourea (0.40 g; 1.1 mmol) and DiPEA (0.3 mL; 1.6 mmol) yielding 0.58 g (73%) of the sub-title compound as a solid.

(e) (R)-N²-(Diphenylacetyl)-(R)-N-(1-phenylethyl)arginine amide hydrochloride

25 Prepared according to the method described in Example 1(g) above from (R)-N^w,N^{w'}-bis(Cbz)-N²-(diphenylacetyl)-(R)-N-(1-phenylethyl)arginine amide (0.6 g; 0.8 mmol; from step (d) above), 10% Pd/C (w/w; 200 mg), HOAc (25 mL), overnight reaction time. The crude acetate salt was converted to the hydrochloride to give 0.4 g (99%) of title compound as a solid.

30

mp 111-116°C

R_f 0.46 (System D)

$[\alpha]_D^{24} = + 51.0^\circ$ (C = 0.65, MeOH)

¹H NMR (CD₃OD) δ 7.20-7.36 (m, 15H), 5.10 (s, 1H), 4.97 (q, 1H),
5 4.43 (t, 1H), 3.08 (m, 2H), 1.42-1.85 (m, 4H), 1.41 (d, 3H)

Example 10

(R)-N²-(Diphenylacetyl)-(S)-N-(1-phenylethyl)arginine amide hydrochloride

10

(a) (R)-N²-(Boc)-N⁵-(Cbz)-(S)-N-(1-Phenylethyl)ornithine amide

Prepared according to the method described in Example 1(a) above from
N^α-Boc-N^δ-Cbz-(R)-ornithine (5.0 g; 13 mmol), BOP reagent (6.0 g; 13
mmol), HOBT (1.8 g; 13 mmol) and DiPEA (7.1 mL; 40 mmol) 100 mL
15 of acetonitrile:CH₂Cl₂ (1:1), followed by (S)-α-methylbenzylamine (1.8
mL; 13 mmol), then stirred overnight. After work up, the crude product
was purified by passing it through a plug of silica gel with EtOAc to give
5.9 g (92%) of the sub-title as a light yellow solid.

¹H NMR (CD₃OD) δ 1.2-1.8 (m, 16H), 3.2 (m, 2H), 4.05 (m, 1H), 4.9-
20 5.1 (m, 3H), 7.1-7.4 (m, 10H)

(b) (R)-N⁵-(Cbz)-N²-(Diphenylacetyl)-(S)-N-(1-phenylethyl)ornithine amide

Prepared according to the method described in Example 2(b) and 2(c) from
(R)-N²-(Boc)-N⁵-(Cbz)-(S)-N-(1-phenylethyl)ornithine amide (5.9 g; 13
25 mmol; from step (a) above) EtOAc (30 mL) then HCl/EtOAc (100 mL),
3.0 hours reaction time for the deprotection, then CH₂Cl₂ (100 mL),
diphenylacetyl chloride (3.0 g; 13 mmol) followed by pyridine (3.0 mL;
37 mmol; instead of DiPEA) over 1 minute, overnight reaction time,
diluted with CH₂Cl₂ (100 mL) for the work up procedure. Crystallization
30 from CH₂Cl₂:EtOAc:MeOH gave 3.4 g (47%) of the sub-title compound

as a solid.

^1H NMR (CD_3OD) δ 1.35 (d, 3H), 1.45 (m, 2H), 1.65 (m, 1H), 1.8 (m, 1H), 3.2 (m, 2H), 4.45 (m, 1H), 4.85 (m, 1H), 5.02 (s, 1H), 5.08 (s, 2H), 7.1-7.4 (m, 20H)

5

(c) (R)-N²-(Diphenylacetyl)-(S)-N-(1-phenylethyl)ornithine amide hydrochloride

Prepared according to the method described in Example 1(e) above from (R)-N⁵-(Cbz)-N²-(diphenylacetyl)-(S)-N-(1-phenylethyl)ornithine amide (2.0 g; 3.5 mmol; from step (b) above), 10% Pd/C (w/w; 150 mg), HOAc (100 mL; instead of MeOH), overnight reaction time. The crude acetate salt was converted to the sub-title hydrochloride and was used without further purification.

^1H NMR (CD_3OD) δ 1.4 (d, 3H), 1.65 (m, 3H), 1.85 (m, 1H), 2.9 (m, 2H), 4.45 (m, 1H), 4.95 (m, 1H), 5.05 (s, 1H), 7.15-7.4 (m, 15H)

15

(d) (R)-N^w,N^{w'}-(bisCbz)-N²-(Diphenylacetyl)-(S)-N-(1-phenylethyl)arginine amide

Prepared according to the method described in Example 4(f) above from (R)-N²-(diphenylacetyl)-(S)-N-(1-phenylethyl)ornithine amide hydrochloride (0.50 g; 1.0 mmol; from step (c) above), N,N'-bis(Cbz)-S-methylisothiourea (0.40 g; 1.1 mmol) and DiPEA (0.3 mL; 1.6 mmol), yielding 0.59 g (74%) of sub-title compound as a solid.

20

(e) (R)-N²-(Diphenylacetyl)-(S)-N-(1-phenylethyl)arginine amide hydrochloride

Prepared according to the method described in Example 1(g) above from (R)-N^w,N^{w'}-bis(Cbz)-N²-(diphenylacetyl)-(S)-N-(1-phenylethyl)arginine amide (0.6 g; 0.8 mmol; from step (d) above), 10% Pd/C (w/w; 200 mg), HOAc (25 mL), overnight reaction time. The crude acetate salt was

30

converted to the hydrochloride to give 0.4 g (99%) of the title compound as a solid.

mp 112-118°C

R_f = 0.46 (System D)

5 $[\alpha]_D^{25} = -2.6^\circ$ (C = 1.1, MeOH)

^1H NMR (CD_3OD) δ 1.41 (d, 3H), 1.49-1.90 (m, 4H), 3.18 (m, 2H), 4.46 (t, 1H), 4.95 (q, 1H), 5.06 (s, 1H), 7.20-7.32 (m, 15H).

Example 11

10 (R)-N²-(Diphenylacetyl)-(R,S)-N-[1-cyclopropyl-1-(4-methoxyphenyl)-methyl]arginine amide hydrochloride

(a)(R)-N²-(Boc)-N⁵-(Cbz)-(R,S)-N-[1-Cyclopropyl-1-(4-methoxyphenyl)-methyl]ornithine amide

15 Prepared analogously to the method described in Example 4(b) above from N^α-Boc-N^δ-Cbz-(R)-ornithine o-nitrophenyl ester (6.25 g; 12.8 mmol; see Example 4(a) above), (R,S)-α-cyclopropyl-4-methoxybenzenemethanamine hydrochloride (3.01 g; 14.1 mmol) and DiPEA (1.99 g, 15.4 mmol) in CH_2Cl_2 (200 mL), 3 hours reaction time, followed by additional DiPEA (1
20 mL) and (R,S)-α-cyclopropyl-4-methoxybenzenemethanamine hydrochloride (0.50 g) and stirred for 15 minutes. The reaction mixture was concentrated and dissolved in EtOAc. The EtOAc was washed with water, saturated aqueous potassium hydrogen sulfate, water, saturated aqueous sodium carbonate, brine, and then dried. Concentration of the
25 organics afforded a yellow solid (7.40 g) as a mixture of diastereomers. The crude material was used without further purification. An analytical sample was prepared by crystallization from the EtOAc:diethyl ether:hexanes.

mp 122-125°C

30 R_f 0.50 (hexanes:EtOAc (3:7); silica gel TLC plate)

(b) (R)-N⁵-(Cbz)-(R,S)-N-[1-Cyclopropyl-1-(4-methoxyphenyl)methyl]-ornithine amide hydrochloride

Prepared according to the method described in Example 1(b) above from crude (R)-N²-(Boc)-N⁵-(Cbz)-(R,S)-N-[1-cyclopropyl-1-(4-methoxy-
5 phenyl)methyl]ornithine amide (5.6 g; from step (a) above), EtOAc (100 mL) and HCl/EtOAc (100 mL), 18 hours reaction time. The hydrochloride salt was precipitated by the addition of diethyl ether, collected and dried to give the sub-title compound as a greyish solid (3.8 g).

R_f 0.3 (CHCl₃:MeOH:HOAc (9.0:1.0:0.1); silica gel TLC plate)

10 ¹H NMR (CD₃OD; complex mixture of diastereomers) δ 0.28-0.42 (m), 0.52-0.65 (m), 0.88-0.98 (m), 1.15-1.98 (m), 3.02-3.20 (m), 3.72 (s), 3.74 (s), 3.75-3.95 (m), 4.20-4.30 (m), 5.02-5.13 (m), 6.83-6.90 (m), 7.18-7.40 (m)

15 (c) (R)-N⁵-(Cbz)-N²-(Diphenylacetyl)-(R,S)-N-[1-cyclopropyl-1-(4-methoxyphenyl)methyl]ornithine amide

Prepared according to the method described in Example 1(d) above from (R)-N⁵-(Cbz)-(R,S)-N-[1-cyclopropyl-1-(4-methoxyphenyl)methyl]ornithine
amide hydrochloride (2.0 g; 4.3 mmol; from step (b) above), 2-nitrophenyl
20 diphenyl acetate (1.4 g; 4.3 mmol; see Example 1(c) above), triethylamine (0.7 g; 6.5 mmol) and CH₂Cl₂ (150 mL), 18 hours reaction time at room temperature, and 4 hours reaction time at reflux. The reaction mixture was submitted to aqueous work up, dried, filtered and concentrated to give the crude product as a yellow solid (2.8 g). The product was chromatographed
25 on silica gel eluting with hexanes:EtOAc (1:1) then CH₂Cl₂:EtOAc (1:1). Concentration of the product containing fractions gave pure sub-title compound as a light yellow solid (2.2 g).

R_f 0.4 (hexanes:EtOAc (1:1), silica gel TLC plate)

¹H NMR (CD₃OD, complex mixture of diastereomers) δ 0.25-0.36 (m),
30 0.45-0.60 (m), 0.80-0.98 (m), 1.00-1.92 (m), 2.95-3.16 (m), 3.73 (s), 3.74

(s), 4.16-4.28 (m), 4.38-4.50 (m), 4.70-4.85 (m), 4.98-5.08 (m), 6.72-6.87 (m), 7.05-7.40 (m).

(d) (R)-N²-(Diphenylacetyl)-(R,S)-N-[1-cyclopropyl-1-(4-methoxy-phenyl)methyl]ornithine amide hydrochloride

Prepared according to the method described in Example 1(e) above from (R)-N⁵-(Cbz)-N²-(diphenylacetyl)-(R,S)-N-[1-cyclopropyl-1-(4-methoxy-phenyl)methyl]ornithine amide (2.0 g; 3.23 mmol; from step (c) above), 10% Pd/C (1.0 g), MeOH (250 mL) and concentrated HCl (5 mL) under hydrogen, 60 hours reaction time, to give the crude product. The free base was prepared to afford a solid (1.1 g) which was chromatographed on silica gel eluting with MeOH:ammonium hydroxide (15:1). Concentration of the product containing fractions gave pure sub-title compound as an off-white solid (0.6 g; R_f 0.4 (MeOH:ammonium hydroxide (30:1), silica gel TLC plate), which was treated with HCl/MeOH to give the sub-title hydrochloride salt as a white solid.

mp 190-197°C

¹H NMR (CD₃OD, mixture of diastereomers) δ 0.81-0.97 (m, 2H), 1.10-1.40 (m, 2H), 1.52-1.93 (m, 5H), 2.78-2.94 (m, 2H), 3.78 (s, 3H), 4.45 (m, 1H), 4.77 (m, 1H), 5.08 (s, 1H), 5.12 (s, 1H), 6.75-6.87 (m, 2H), 7.08-7.40 (m, 14H)

(e) (R)-N^ω,N^{ω'}-bis(Cbz)-N²-(Diphenylacetyl)-(R,S)-N-[1-cyclopropyl-1-(4-methoxyphenyl)methyl]arginine amide

Prepared according to the method described in Example 4(f) above from (R)-N²-(diphenylacetyl)-(R,S)-N-[1-cyclopropyl-1-(4-methoxyphenyl)-methyl]ornithine amide hydrochloride (0.46 g; 0.88 mmol; from step (d) above), N,N'-bis(Cbz)-S-methylisothiurea (0.35 g; 0.97 mmol), triethylamine (0.27 g; 2.64 mmol; instead of DiPEA) and THF (30 mL; instead of DMF), 18 hours reaction time. Concentration under vacuum

gave the crude product which was chromatographed on silica gel eluting with hexanes:EtOAc (1:1) to give pure sub-title compound (0.24 g).

R_f 0.3 (hexanes:EtOAc (1:1); silica gel TLC plate)

^1H NMR (CD_3OD , complex mixture of diastereomers) δ 0.77-0.90 (m),
5 1.08-1.94 (m), 3.12-3.42 (m), 3.77 (s), 3.78 (s), 4.38-4.55 (m), 4.73-4.87
(m), 4.88-5.22 (m), 6.62-6.87 (m), 6.90-7.48 (m), 8.22-8.40 (m).

(f) (R)-N²-(Diphenylacetyl)-(R,S)-N-[1-cyclopropyl-1-(4-methoxy-phenyl)methyl]arginine amide hydrochloride

10 Prepared according to the method described in Example 1(g) above from
(R)-N^w,N^{w'}-bis(Cbz)-N²-(diphenylacetyl)-(R,S)-N-[1-cyclopropyl-1-(4-methoxyphenyl)methyl]arginine amide (0.24 g; 0.30 mmol; from step (e) above), 10% Pd/C (0.12 g) and, instead of HOAc, MeOH (75 mL) and concentrated HCl (1 mL) under hydrogen, 15 hours reaction time, gave the
15 crude product which was chromatographed on silica gel eluting with MeOH:CHCl₃:ammonium hydroxide (3:6:1) to give the title compound as a solid (0.16 g).

mp 105-115°C

R_f 0.3 (System D)

20 ^1H NMR (CD_3OD , mixture of diastereomers) δ 0.80-0.93 (m), 1.07-1.92
(m), 3.03-3.20 (m), 3.78 (s), 4.35-4.47 (m), 4.62-4.95 (m), 5.13 (s), 5.16
(s), 6.25-6.88 (m), 7.08-7.45 (m), 8.10-8.26 (m)

^{13}C NMR (CD_3OD) δ 14.5, 21.0, 27.0, 30.5, 40.0, 42.2, 54.5, 55.2,
56.2, 59.0, 115.0, 128.4, 129.0, 129.8, 130.2, 136.2, 141.0, 158.8, 160.4,
25 173.2, 175.2.

Example 12(R)-N²-(Diphenylacetyl)-N-(1-methyl-1-phenylethyl)arginine amide hydrochloride5 (a) (R)-N²-(Boc)-N⁵-(Cbz)-N-(1-methyl-1-phenylethyl)ornithine amide

Prepared according to the method described in Example 4(b) above from N^α-Boc-N^δ-Cbz-(R)-ornithine o-nitrophenyl ester (5.0 g; 11.5 mmol; see Example 4(a) above) and cumylamine (1.55 g; 11.5 mmol) and 160 mL of CH₂Cl₂. The reaction mixture was heated to reflux for 2 hours. The
10 mixture was concentrated to dryness and dissolved in EtOAc and washed with saturated aqueous KHSO₄ and brine, dried with Na₂SO₄, filtered and concentrated to give 6.1 g of the sub-title compound as a yellow oil.

R_f 0.93 (System B)

15 (b) (R)-N⁵-(Cbz)-N-(1-methyl-1-phenylethyl)ornithine amide hydrochloride

Prepared according to the method described in Example 1(b) above from (R)-N²-(Boc)-N⁵-(Cbz)-N-(1-methyl-1-phenylethyl)ornithine amide (6.0 g; from step (a) above) treated with EtOAc (100 mL) and HCl/EtOAc (50 mL), 24 hours reaction time. The reaction mixture was concentrated to
20 dryness and triturated with ether to give 3.68 g of the sub-title compound as a white solid.

¹H NMR (CD₃OD) δ 1.95-1.5 (m, 4H), 1.64 (s, 3H), 1.66 (s, 3H), 3.14 (t, 2H) 3.89 (m, 1H), 5.06 (s, 2H), 7.45-7.1 (m, 10H).

25 (c) (R)-N⁵-(Cbz)-N²-(Diphenylacetyl)-N-(1-methyl-1-phenylethyl)-ornithine amide

Prepared according to the method described in Example 1(d) above from (R)-N⁵-(Cbz)-N-(1-methyl-1-phenylethyl)ornithine amide hydrochloride (3.6 g; 8.57 mmol; from step (b) above), 2-nitrophenyl diphenyl acetate
30 (3.44 g; 10.8 mmol; see Example 1(c) above), and triethylamine (1.5 mL;

10.8 mmol) in 100 mL of CH₂Cl₂. The reaction mixture was stirred for 12 hours and submitted to aqueous work up. The product was chromatographed eluting with EtOAc/hexanes on 250 mL of silica gel, yielding 4.26 g of sub-title compound.

5

(d) (R)-N²-(Diphenylacetyl)-N-(1-methyl-1-phenylethyl)ornithine amide hydrochloride

Prepared according to the method described in Example 1(e) above from (R)-N⁵-(Cbz)-N²-(diphenylacetyl)-N-(1-methyl-1-phenylethyl)ornithine
10 amide (4.21g; from step (c) above) using 10% Pd/C (200 mg) in 150 mL of MeOH and 1 mL of concentrated HCl, yielding 3.88 g of sub-title compound.

mp 126-128°C

MS(CI/Isobutane) 444 m/z

15 R_f 0.53 (EtOAc:MeOH:NH₄OH (47:47:6))

¹H NMR (CD₃OD) δ 1.48 (s, 3H), 1.58 (s, 3H), 1.78 (m, 2H), 1.55 (m, 2H), 2.61 (t, 2H), 4.41 (m, 1H), 5.05 (s, 1H), 7.4-7.05 (m, 15H)

20 (e) (R)-N²-(Diphenylacetyl)-(N^ω,N^{ω'})-bis(Cbz)-N-(1-methyl-1-phenylethyl)arginine amide

Prepared according to the method described in Example 4(f) above from (R)-N²-(diphenylacetyl)-N-(1-methyl-1-phenylethyl)ornithine amide hydrochloride (2.0 g; 4.2 mmol; from step (d) above), N,N'-bis(Cbz)-S-methylisothiourea (2.4 g; 6.2 mmol), 1 mL of DiPEA and 50 mL of DMF,
25 yielding 1.1 g of the sub-title compound as a white solid.

(f) (R)-N²-(Diphenylacetyl)-N-(1-methyl-1-phenylethyl)arginine amide hydrochloride

Prepared according to the method described in Example 1(g) above from
30 (R)-N²-(diphenylacetyl)-(N^ω,N^{ω'})-bis(Cbz)-N-(1-methyl-1-phenylethyl)-

arginine amide (0.5 g; from step (e) above), 10% Pd/C (0.1 g) and, instead of HOAc, concentrated HCl (0.4 mL) and MeOH (50 mL), yielding 62 mg of the title compound.

mp 140-143°C

5 R_f 0.43 (EtOAc:MeOH:conc. ammonium hydroxide (46:46:7))

^1H NMR (CD_3OD) δ 1.55 (s, 3H), 1.59 (s, 3H), 1.90-1.40 (m, 4H), 3.16 (m, 2H), 4.44 (m, 1H), 4.81 (m, 1H), 5.08 (s, 1H), 7.4-7.0 (m, 15H) 8.0 (s, 1H, NH), 8.38 (d, 1H, NH)

10 Example 13

(R)-N²-(Diphenylacetyl)-(R,S)-N-(1-indanyl)arginine amide hydrochloride

(a) (R)-N²-(Boc)-N⁵-(Cbz)-(R,S)-N-(1-indanyl)ornithine amide

Prepared according to the method described in Example 1(a) above from
15 N^{α} -Boc- N^{β} -Cbz-(R)-ornithine (3.7 g; 10 mmol), BOP reagent (4.4 g; 10 mmol), HOBT (2.7 g; 20 mmol) and DiPEA (5.0 mL; 30.0 mmol) in acetonitrile (200 mL; instead of acetonitrile: CH_2Cl_2 (1:1)), followed by (R,S)-1-indanamine (1.3 mL; 10 mmol). Work up gave 4.0 g (83%) of the sub-title compound as a solid.

20 ^1H NMR (CDCl_3) δ 1.30-1.90 (m, 7H), 1.40 (s, 9H), 2.45-2.62 (m, 1H), 2.75-3.05 (m, 2H), 3.05-3.22 + 3.25-3.50 (m, 2H), 4.15-4.32 (m, 1H), 4.82-5.00 (m, 2H), 5.18-5.33 (m, 1H), 5.35-5.55 (m, 1H), 6.60-6.70 (m, 1H), 7.05-7.40 (m, 9H)

25 (b) (R)-N⁵-(Cbz)-N²-(Diphenylacetyl)-(R,S)-N-(1-indanyl)ornithine amide

Prepared according to the method described in Example 2(b) and 2(c) above from (R)-N²-(Boc)-N⁵-(Cbz)-(R,S)-N-(1-indanyl)ornithine amide (1.6 g; 3.2 mmol; from step (a) above) EtOAc (10 mL) then HCl/EtOAc (125 mL), 1 hour reaction time for the deprotection, then CH_2Cl_2 (125
30 mL), diphenylacetyl chloride (0.74 g; 3.6 mmol), followed by DiPEA (1.7

mL; 9.7 mmol) over 1 minute, 1 hour reaction time, diluted with CH₂Cl₂ (125 mL) for the work up procedure, yielding 1.8 g (100%) of the sub-title compound.

¹H NMR (CDCl₃) δ 1.40-1.90 (m, 7H), 2.40-2.55 (m, 1H), 2.72-2.96 (m, 2H), 3.00-3.18 + 3.25-3.53 (m, 2H), 4.55-4.72 (m, 1H), 4.75-4.96 (m, 2H), 5.25-5.95 (m, 1H), 6.55-6.65 + 6.78-6.95 (m, 1H), 7.05-7.40 (m, 19H).

(c) (R)-N²-(Diphenylacetyl)-(R,S)-N-(1-indanyl)ornithine amide

Prepared according to the method described in Example 1(e) above from (R)-N⁵-(Cbz)-N²-(diphenylacetyl)-(R,S)-N-(1-indanyl)ornithine amide (1.2 g; 2.2 mmol; from step (b) above), 10% Pd/C (w/w; 500 mg), MeOH (100 mL; HCl was not added), and 2.5 hours reaction time, yielding 0.82 g (90%) of the sub-title compound as a pale white solid.

R_f 0.54 (System A)

¹H NMR (CDCl₃) δ 1.35-1.90 (m, 7H), 2.40-2.95 (m, 5H), 4.40-4.55 (m, 1H), 4.90 (s, 1H), 5.30-5.45 (m, 1H), 6.95-7.40 (m, 14 H).

(d) (R)-N²-(Diphenylacetyl)-(R,S)-N-(1-indanyl)ornithine amide

hydrochloride

A sample of (R)-N²-(diphenylacetyl)-(R,S)-N-(1-indanyl)ornithine amide (from step (c) above) was treated with HCl/EtOAc then evaporated at reduced pressure. Crystallization from MeOH:diethyl ether gave the sub-title hydrochloride.

mp 220-225°C (dec.)

¹H NMR (CD₃OD) δ 1.60-2.00 (m, 7H), 2.30-2.50 (m, 1H), 2.72-3.00 (m, 4H), 4.35-4.98 (m, 1H), 5.12 (s, 1H), 5.25-5.35 (m, 1H), 7.05-7.40 (m, 14H), 7.95-8.12 (m 1H), 8.45-8.55 (m, 1H).

(e) (R)-N²-(Diphenylacetyl)-(R,S)-N-(1-indanyl)arginine amide hydrochloride

Prepared according to the method described in Example 2(f) above from (R)-N²-(diphenylacetyl)-(R,S)-N-(1-indanyl)ornithine amide (0.54 g; 1.3 mmol; free base from step (c) above), 1H-pyrazole-1-carboxamide mono hydrochloride (0.20 g; 1.3 mmol), and DiPEA (0.8 mL; 5 mmol). The product was additionally rinsed with EtOAc to give 0.19 g (28%) of the title compound as a white solid.

mp 130-140°C

10 $R_f = 0.16$ (System A)

¹H NMR (CD₃OD) δ 1.50-1.95 (m, 7H), 2.35-2.52 (m, 1H), 2.75-3.00 (m, 2H), 3.08-3.20 (m, 2H), 4.35-4.45 (m, 1H), 5.10 (s, 1H), 5.28-5.38 (m, 1H), 7.05-7.40 (m, 14H).

15 Example 14

(R)-N²-(Diphenylacetyl)-(S or R)-N-(1-carbamoylphenylmethyl)arginine amide hydrochloride

20 (a) (R)-N²-(Boc)-N⁵-(Cbz)-(R or S)-N-(1-carbamoylphenylmethyl)ornithine amide and (R)-N²-(Boc)-N⁵-(Cbz)-(S or R)-N-(1-carbamoylphenylmethyl)-ornithine amide

Prepared according to the method described in Example 1(a) above from N²-Boc-N⁵-Cbz-(R)-ornithine (8.0 g; 22 mmol), BOP (9.7 g; 22 mmol), HOBT (3.0 g; 22 mmol) and DiPEA (11.3 mL; 65.0 mmol) in 160 mL of acetonitrile:CH₂Cl₂ (1:1), followed by racemic α -aminophenylacetamide (3.3 g; 22 mmol), then stirred overnight. After work up the crude product was purified by passing it through a plug of silica gel with EtOAc to give 8.0 g (73%) of a diastereomeric mixture of the sub-title compounds as a solid.

(b) (R)-N⁵-(Cbz)-N²-(Diphenylacetyl)-(R or S)-N-(1-carbamoylphenylmethyl)ornithine amide and (R)-N⁵-(Cbz)-N²-(Diphenylacetyl)-(S or R)-N-(1-carbamoyl-phenylmethyl)ornithine amide

Prepared according to the method described in Example 2(b) and 2(c) above from a mixture of (R)-N²-(Boc)-N⁵-(Cbz)-(R or S)-N-(1-carbamoyl-phenylmethyl)ornithine amide and (R)-N²-(Boc)-N⁵-(Cbz)-(S or R)-N-(1-carbamoylphenylmethyl)ornithine amide (8.0 g; 16 mmol; from step (a) above), EtOAc (250 mL) then HCl/EtOAc (60 mL), 2 hours reaction time for the deprotection, then CH₂Cl₂ (100 mL), diphenylacetyl chloride (3.7 g; 16 mmol) followed by pyridine (12 mL; 0.15 mol; instead of DiPEA) over 10 minutes, overnight reaction time, diluted with CH₂Cl₂ (100 mL) and some EtOAc to help with solubility for the work up procedure. The crude product was purified by dissolving the product in a mixture of MeOH:HOAc and filtering off the solids. Concentration of the filtrate at reduced pressure provided 6.0 g (63%) of a mixture of sub-title compounds as a solid.

¹H NMR (CD₃OD) δ 1.45 (m, 2H), 1.65 (m, 1H), 1.75 (m, 1H), 3.05 (m, 2H), 4.4 (m, 1H), 4.9-5.1 (m, 4H), 7.2-7.5 (m, 20H)

(c) (R)-N²-(Diphenylacetyl)-(R or S)-N-(1-carbamoylphenylmethyl)-ornithine amide acetate

Prepared according to the method described in Example 1(e) above from a mixture of (R)-N⁵-(Cbz)-N²-(diphenylacetyl)-(R or S)-N-(1-carbamoyl phenylmethyl)ornithine amide and (R)-N⁵-(Cbz)-N²-(diphenylacetyl)-(S or R)-N-(1-carbamoylphenylmethyl)ornithine amide (6.0 g; 10 mmol; from step (b) above) 10% Pd/C (w/w; 600 mg), HOAc (200 mL; instead of MeOH), overnight reaction time. The crude product mixture was crystallized from HOAc:EtOAc to give the sub-title compound (0.5 g; 94%).

(d) (R)-N²-(Diphenylacetyl)-(S or R)-N-(1-carbamoyl-phenylmethyl)-ornithine amide

The mother liquors from step (c) above were allowed to sit overnight, after which a second crop of crystals were obtained which was the sub-title
5 compound (0.42 g; 8%).

(e) (R)-N^ω,N^{ω'}-bis(Cbz)-N²-(Diphenylacetyl)-(S or R)-N-(1-carbamoyl-phenylmethyl)arginine amide

Prepared according to the method described in Example 4(f) above, with
10 the exception that THF (5 mL) was added as a co-solvent, from (R)-N²-(diphenylacetyl)-(S or R)-N-(1-carbamoyl-phenylmethyl)ornithine amide (0.4 g; 0.8 mmol; from step (d) above), N,N'-bis(Cbz)-S-methylisothiourea (0.3 g; 0.8 mmol) and DiPEA (0.2 mL; 1.1 mmol). The crude product was purified by crystallization from EtOAc, which gave 0.40 g (64%) of
15 the sub-title compound as a solid.

(f) (R)-N²-(Diphenylacetyl)-(S or R)-N-(1-carbamoylphenylmethyl)arginine amide hydrochloride

Prepared according to the method described in Example 1(g) above from
20 (R)-N^ω,N^{ω'}-bis(Cbz)-N²-(diphenylacetyl)-(S or R)-N-(1-carbamoylphenylmethyl)-arginine amide (0.25 g; 0.33 mmol; from step (e) above), 10% Pd/C (w/w; 100 mg), HCl/MeOH (50 mL), and overnight reaction time. The crude product was purified by column chromatography using CHCl₃:MeOH:concentrated ammonium hydroxide (6:3:1) to provide 0.16
25 g (91%) of the title compound.

mp 110-150°C

R_f = 0.58 (System D)

Example 15.(R)-N²-(Diphenylacetyl)-(R or S)-N-[1-carbamoyl-(4-methoxyphenyl)-methyl]arginine amide hydrochloride

- 5 (a) (R)-N²-(Boc)-N⁵-(Cbz)-(R or S)-N-[1-carbamoyl-(4-methoxyphenyl)-methyl]ornithine amide and (R)-N²-(Boc)-N⁵-(Cbz)-(S or R)-N-[1-carbamoyl(4-methoxy-phenyl)methyl]ornithine amide

Prepared according to the method described in Example 1(a) above from N^α-Boc-N^δ-Cbz-(R)-ornithine (5.0 g; 13 mmol), BOP reagent (6.0 g; 13 mmol), HOBT (1.8 g; 13 mmol) and DiPEA (7.1 mL; 40 mmol) in 100 mL of acetonitrile:CH₂Cl₂ (1:1), followed by a racemic mixture of 4-methoxy-α-aminophenylacetamide (2.5 g; 13 mmol), stirring overnight. After work up, the crude product was purified by crystallization from EtOAc:MeOH, yielding 4.5 g (62%) of a diastereomeric mixture of the sub-title compounds as a solid.

¹H NMR (CD₃OD) δ 1.43 (s, 9H), 1.49-1.85 (m, 4H), 3.12 (m, 2H), 3.76 and 3.79 (2s, 3H), 4.08 (m, 1H), 5.02 (s, 1H), 5.08 (s, 1H), 5.33 (m, 1H), 6.89 (d, 2H), 7.32 (m, 7H).

- 20 (b) (R)-N⁵-(Cbz)-(R or S)-N-[1-carbamoyl-(4-methoxyphenyl)methyl]-ornithine amide hydrochloride

A mixture of (R)-N²-(Boc)-N⁵-(Cbz)-(R or S)-N-[1-carbamoyl-(4-methoxyphenyl)methyl]ornithine amide and (R)-N²-(Boc)-N⁵-(Cbz)-(S or R)-N-[1-carbamoyl(4-methoxyphenyl)methyl]ornithine amide (4.5 g; 8.5 mmol) was dissolved in 25 mL of MeOH and 100 mL of HCl/EtOAc was added. The mixture was magnetically stirred at room temperature for 1 hour, then evaporated at reduced pressure to give a crude hydrochloride salt of the diastereomers of (R)-N⁵-(Cbz)-(R or S)-N-[1-carbamoyl-(4-methoxyphenyl)methyl]ornithine amide and (R)-N⁵-(Cbz)-(S or R)-N-[1-carbamoyl-(4-methoxyphenyl)methyl]ornithine amide hydrochloride. Crystallization

from MeOH:EtOAc provided 1.3 g of the more polar sub-title diastereomer (32%).

R_f 0.36 (System C)

^1H NMR (CD_3OD) δ 1.5 (m, 2H), 1.8 (m, 2H), 3.1 (m, 2H) 3.7 (s, 3H),
5 3.95 (m, 1H), 4.95 (d, 2H), 5.38 (s, 1H), 6.9 (d, 2H), 7.3 (m, 2H)

(c) (R)-N⁵-(Cbz)-N²-(Diphenylacetyl)-(R or S)-N-[1-carbamoyl-(4-methoxyphenyl)methyl]ornithine amide

To a mixture of (R)-N⁵-(Cbz)-(R or S)-N-[1-carbamoyl-(4-methoxyphenyl)-
10 methyl]ornithine amide hydrochloride (1.2 g; 2.6 mmol; from step (b) above) and pyridine (4 mL; 49 mmol) in CH_2Cl_2 (80 mL) and DMF (2.5 mL) was added diphenylacetyl chloride (0.59 g; 2.6 mmol) and the resultant mixture was stirred overnight. The solvents were evaporated under reduced pressure and the residue was partitioned between
15 MeOH:EtOAc (1:2) and dilute KHSO_4 solution. The organic layer was separated and concentrated under reduced pressure and the resulting solid was washed with water to remove inorganic salts. This provided 0.95 g (59%) of sub-title compound as a white solid.

^1H NMR (CD_3OD) δ 1.45 (m, 2H), 1.65 (m, 1H), 1.75 (m, 1H), 3.08
20 (m, 2H), 3.75 (s, 3H), 4.4 (m, 1H), 5.0-5.1 (s, s, m, 4H), 5.28 (s, 1H), 6.85 (d, 2H), 7.15-7.4 (17H)

(d) (R)-N²-(Diphenylacetyl)-(R or S)-N-[1-carbamoyl-(4-methoxyphenyl)-methyl]ornithine amide acetate

25 Prepared according to the method described in Example 1(e) above from (R)-N⁵-(Cbz)-N²-(diphenylacetyl)-(R or S)-N-[1-carbamoyl-(4-methoxyphenyl)methyl]ornithine amide (0.95 g; 1.4 mmol; from step (c) above) 10% Pd/C (w/w; 120 mg), HOAc (100 mL; instead of MeOH), overnight reaction time. The crude acetate salt was crystallized from MeOH:EtOAc
30 to give 0.84 g (99%) of the sub-title compound as a solid.

(e) (R)-N^w,N^{w'}-bis(Cbz)-N²-(Diphenylacetyl)-(R or S)-N-[1-carbamoyl-(4-methoxyphenyl)methyl]arginine amide

Prepared according to the method described in Example 4(f) above from (R)-N²-(diphenylacetyl)-(R or S)-N-[1-carbamoyl-(4-methoxyphenyl)-methyl]ornithine amide acetate (0.49 g; 1.0 mmol; from step (d) above),
5 *N,N'*-bis(Cbz)-*S*-methylisothiourea (0.35 g; 0.99 mmol) and DiPEA (0.25 mL; 1.4 mmol). The product was purified by crystallization from EtOAc:MeOH, which gave 0.43 g (70%) of the sub-title compound as a solid.

10

(f) (R)-N²-(Diphenylacetyl)-(R or S)-N-[1-carbamoyl-(4-methoxyphenyl)-methyl]-arginine amide hydrochloride

Prepared according to the method described in Example 1(g) above from (R)-N^w,N^{w'}-bis(Cbz)-N²-(diphenylacetyl)-(R or S)-N-[1-carbamoyl-(4-methoxyphenyl)methyl]arginine amide (0.42 g; 0.53 mmol; from step (e)
15 above) 10% Pd/C (w/w; 100mg), HOAc (75 mL) and overnight reaction time. The crude acetate salt was converted to the hydrochloride then triturated with MeOH:EtOAc to provide 0.15 g (52%) of the title compound.

20 mp 140-158°C

R_f = 0.56 (System E)

¹H NMR (CD₃OD) δ 1.42-1.91 (m, 4H), 3.12 (t, 2H), 3.79 (s, 3H), 4.41 (t, 1H), 5.08 (s, 1H), 5.31 (s, 1H), 6.82 (d, 2H), 7.18-7.35 (m, 12H)

25

30

Example 16(R)-N²-(Diphenylacetyl)-(S)-N-(2-hydroxy-1-phenylethyl)arginine amide hydrochloride5 (a) (R)-N²-(Boc)-N⁵-(Cbz)-(S)-N-(2-hydroxy-1-phenylethyl)ornithine amide

Prepared according to the method described in Example 4(b) above from N^α-Boc-N^δ-Cbz-(R)-ornithine o-nitrophenyl ester (4.0g; 9.22 mmol; see Example 4(a) above) and (S)-(+)-phenylglycinol (1.26 g; 9.22 mmol; 1 eq.)
10 and CH₂Cl₂ (160 mL). The reaction mixture was stirred overnight and then washed with saturated aqueous KHSO₄, saturated aqueous Na₂CO₃, brine, dried with Na₂SO₄, filtered and concentrated to dryness. The residue was triturated with ether to obtain 3.8 g of the sub-title compound as a white solid.

15 R_f 0.48 (CH₂Cl₂:MeOH (80:20); silica gel TLC plate)

¹H NMR (DMSO-d₆) δ 1.36 (s, 9H), 1.80-1.37 (m, 4H), 2.95 (q, 2H), 3.55 (m, 2H), 3.95 (m, 1H), 4.81 (m, 2H), 5.0 (s, 2H), 6.79 (d, 1H), 7.41-7.21 (m, 10H), 8.11 (d, 1H, NH)

20 (b) (R)-N⁵-(Cbz)-(S)-N-(2-hydroxy-1-phenylethyl)ornithine amide hydrochloride

Prepared according to the method described in Example 1(b) above from (R)-N²-(Boc)-N⁵-(Cbz)-(S)-N-(2-hydroxy-1-phenylethyl)ornithine amide (3.2 g; 6.6 mmol; from step (a) above), 25 mL of MeOH and 100 mL of
25 HCl/EtOAc, yielding 2.0 g of the sub-title compound as white crystals.

(c) (R)-N⁵-(Cbz)-N²-(Diphenylacetyl)-(S)-N-(2-hydroxy-1-phenylethyl)-ornithine amide

Prepared according to the method described in Example 1(d) above from
30 (R)-N⁵-(Cbz)-(S)-N-(2-hydroxy-1-phenylethyl)ornithine amide

hydrochloride (2.0 g, 4.74 mmol; from step (b) above), 2-nitrophenyl diphenyl acetate (1.67 g; 5.21 mmol; see Example 1(c) above) and triethylamine (0.726 mL; 5.21 mmol) in 150 mL of CH₂Cl₂. The reaction mixture was heated to reflux for 1 hour, followed by standard aqueous work up, yielding 1.78 g of the sub-title compound as a white solid.

¹H NMR (DMSO-d₆) δ 1.71-1.2 (m, 4H), 2.91 (m, 2H), 3.52 (m, 2H), 4.42 (m, 1H), 4.82 (m, 2H), 5.0 (s, 2H), 5.15 (s, 1H), 7.5-7.1 (m, 15H), 8.35 (m, 2H, NH).

10 (d) (R)-N²-(Diphenylacetyl)-(S)-N-(2-hydroxy-1-phenylethyl)ornithine amide

Prepared according to the method described in Example 1(e) above from a batch of (R)-N⁵-(Cbz)-N²-(diphenylacetyl)-(S)-N-(2-hydroxy-1-phenylethyl)ornithine amide (1.78 g; from step (c) above) and 10% Pd/C (200 mg) in 100 mL of MeOH and 1.0 mL of HCl (conc.), yielding 1.15 g of the sub-title compound as a white foam.

R_f 0.44 (EtOAc:hexanes (4:1))

¹H NMR (DMSO-d₆) δ 1.52 (m, 3H), 1.62 (m, 1H), 2.70 (m, 2H), 3.50 (m, 2H), 4.43 (m, 1H), 5.19 (s, 1H), 7.25 (m, 15H), 8.51 (d, 1H, NH), 8.61 (d, 1H, NH).

(e) (R)-N^ω.N^{ω'}-bis(Cbz)-N²-(Diphenylacetyl)-(S)-N-(2-hydroxy-1-phenylethyl)arginine amide

Prepared according to the method described in Example 4(f) above from (R)-N²-(diphenylacetyl)-(S)-N-(2-hydroxy-1-phenylethyl)ornithine amide (0.5 g; 1.12 mmol; from step (d) above), N,N¹-bis(Cbz)-S-methylisothiurea (0.603 g; 1.68 mmol), DiPEA (0.2 mL) and DMF (15 mL), yielding 0.386 g of the sub-title compound.

(f) (R)-N²-(Diphenylacetyl)-(S)-N-(2-hydroxy-1-phenylethyl)arginine
amide hydrochloride

Prepared according to the method described in Example 1(g) above from
(R)-N^ω,N^{ω'}-bis(Cbz)-N²-(diphenylacetyl)-(S)-N-(2-hydroxy-1-phenylethyl)-
5 arginine amide (0.250 g; from step (e) above), 10% Pd/C (200 mg) and,
instead of HOAc, 50 mL of MeOH with 1 mL of concentrated HCl,
yielding 78 mg of the title compound.

¹H NMR (CD₃OD) δ 1.57 (m, 2H), 1.71 (m, 1H), 1.86 (m, 1H), 3.14
(t, 2H), 3.70 (m, 2H), 4.53 (m, 1H), 5.08 (s, 1H), 7.35 (m, 15H)

10

Example 17

(R)-N²-(Diphenylacetyl)-(R)-N-(2-hydroxy-1-phenylethyl)arginine
amide hydrochloride

15 (a) (R)-N²-(Boc)-N⁵-(Cbz)-(R)-N-(2-Hydroxy-1-phenylethyl)ornithine
amide

Prepared according to the method described in Example 4(b) above from
N^α-Boc-N^δ-Cbz-(R)-ornithine o-nitrophenyl ester (5.0 g; 11.5 mmol; see
Example 4(a) above), (R)-(-)-phenylglycinol (1.58 g; 11.5 mmol) and 160
20 mL of CH₂Cl₂, yielding 3.9 g of the sub-title compound as a white solid.

R_f 0.60 (CH₂Cl₂:MeOH (80:20); silica gel TLC plate)

¹H NMR (DMSO-d₆) δ 1.66-1.25 (m, 4H), 1.40 (s, 9H), 2.95 (q, 2H),
3.56 (m, 2H), 3.96 (m, 1H), 4.82 (m, 2H), 5.05 (s, 2H), 6.85 (d, 1H, NH),
7.45-7.2 (m, 10H), 8.15 (d, 1H, NH).

25

(b) (R)-N⁵-(Cbz)-(R)-N-(2-hydroxy-1-phenylethyl)ornithine amide
hydrochloride

Prepared according to the method described in Example 1(b) above from
(R)-N²-(Boc)-N⁵-(Cbz)-(R)-N-(2-hydroxy-1-phenylethyl)ornithine amide
30 (3.8 g; 7.82 mmol; from step (a) above), 50 mL of MeOH and 100 mL of

HCl/EtOAc, isolating 2.68 g of the sub-title compound as white crystals.

(c) (R)-N⁵-(Cbz)-N²-(Diphenylacetyl)-(R)-N-(2-hydroxy-1-phenylethyl)-ornithine amide

- 5 Prepared according to the method described in Example 1(d) above from (R)-N⁵-(Cbz)-(R)-N-(2-hydroxy-1-phenylethyl)ornithine amide hydrochloride (2.6 g; 6.16 mmol; from step (b) above), 2-nitrophenyl diphenyl acetate (2.37 g; 7.39 mmol; see Example 1(c) above) and triethylamine (1.28 mL; 9.24 mmol) in 150 mL of CH₂Cl₂, yielding 2.5 g
10 of the sub-title compound as a white, crystalline material.

¹H NMR (DMSO-d₆) δ 1.38 (m, 2H), 1.51 (m, 1H), 1.67 (m, 1H), 2.99 (m, 2H), 3.52 (m, 2H), 4.38 (m, 1H), 4.81 (m, 2H), 5.02 (s, 2H), 5.10 (s, 1H), 7.40-7.05 (m, 15H), 8.2 (d, 1H, NH), 8.45 (d, 1H, NH)

- 15 (d) (R)-N²-(Diphenylacetyl)-(R)-N-(2-hydroxy-1-phenylethyl)ornithine amide hydrochloride

- Prepared according to the method described in Example 1(e) above from a batch of (R)-N⁵-(Cbz)-N²-(diphenylacetyl)-(R)-N-(2-hydroxy-1-phenylethyl)ornithine amide (2.5 g; from step (c) above), 10% Pd/C (200 mg),
20 100 mL of MeOH and 1.0 mL of concentrated HCl, yielding 1.8 g of the sub-title compound as a white foam.

R_f 0.52 (EtOAc:hexanes (4:1))

- ¹H NMR (DMSO-d₆) δ 1.52 (m, 3H), 1.72 (m, 1H), 2.73 (m, 2H), 3.52 (m, 2H), 4.41 (m, 1H), 4.75 (m, 2H), 4.85 (m, 1H), 5.11 (s, 1H), 7.25 (m,
25 15H), 8.45 (d, 1H, NH), 8.55 (d, 1H, NH)

(e) (R)-N^ω,N^{ω'}-bis(Cbz)-N²-(Diphenylacetyl)-(R)-N-(2-hydroxy-1-phenylethyl)arginine amide

- Prepared according to the method described in Example 1(f) above from
30 (R)-N²-(diphenylacetyl)-(R)-N-(2-hydroxy-1-phenylethyl)ornithine amide

hydrochloride (0.5 g; 1.12 mmol), *N,N'*-bis(Cbz)-*S*-methylothiourea (0.603 g; 1.68 mmol), DiPEA (0.2 mL) and DMF (15 mL) yielding 0.351 g of sub-title compound.

5 (f) (*R*)-N²-(Diphenylacetyl)-(*R*)-N-(2-hydroxy-1-phenylethyl)arginine amide hydrochloride

Prepared according to the method described in Example 1(g) above from (*R*)-N^ω,N^{ω'}-bis(Cbz)-N²-(diphenylacetyl)-(*R*)-N-(2-hydroxy-1-phenylethyl)-arginine amide (0.250 g; from step (e) above), 10% Pd/C (200 mg) and, instead of HOAc, 50 mL of MeOH with 1 mL of concentrated HCl, yielding 69 mg of the title compound.

¹H NMR (CD₃OD) δ 1.50 (m, 2H), 1.68 (m, 1H), 1.81 (m, 1H), 3.08 (m, 2H), 3.60 (m, 2H), 4.46 (m, 1H), 4.92 (m, 1H), 5.11 (s, 1H), 7.34 (m, 15H).

15

Example 18

(*R*)-N²-(Diphenylacetyl)-(*S*)-N-[2-hydroxy-1-(4-methoxyphenyl)ethyl]-arginine amide hydrochloride

20 (a) (*R*)-N²-(Boc)-N⁵-(Cbz)-(*S*)-N-[2-hydroxy-1-(4-methoxyphenyl)ethyl]-ornithine amide

Prepared according to the method described in Example 11(a) above from N^ω-Boc-N^δ-Cbz-(*R*)-ornithine *o*-nitrophenyl ester (4.83 g; 9.91 mmol; see Example 4(a) above) with (*S*)-4-methoxy- α -hydroxymethylbenzylamine hydrochloride (2.22 g; 10.90 mmol) and triethylamine (1.50 g; 14.87 mmol; instead of DiPEA) in CH₂Cl₂ (150 mL), 18 hours reaction time. The reaction mixture was submitted to aqueous work up using water, 1N HCl and brine. The organic solution was dried, filtered and concentrated to give the sub-title compound as a yellow solid (4.0 g) which was used without purification.

30

R_f 0.4 (CH₂Cl₂:MeOH (90:10); silica gel TLC plate)

(b) (R)-N⁵-(Cbz)-(S)-N-[2-hydroxy-1-(4-methoxyphenyl)ethyl]ornithine amide hydrochloride

- 5 Prepared according to the method described in Example 1(b) above from crude (R)-N²-(Boc)-N⁵-(Cbz)-(S)-N-[2-hydroxy-1-(4-methoxyphenyl)ethyl]-ornithine amide (4.0 g; from step (a) above), EtOAc (100 mL) and HCl/EtOAc (100 mL), 18 hours reaction time. The hydrochloride salt was precipitated by the addition of diethyl ether, collected and dried to give the
- 10 sub-title compound as a white solid (2.3 g).

¹H NMR (CD₃OD) δ 1.45-1.57 (m, 2H), 1.78-1.92 (m, 2H), 3.10 (t, 2H), 3.72 (s, 3H), 3.68-3.82 (m, 2H), 3.98 (t, 1H), 4.98 (m, 1H), 5.03 (s, 2H), 6.88 (d, 2H), 7.25 (d, 2H), 7.25-7.40 (m, 5H).

- 15 (c) (R)-N⁵-(Cbz)-N²-(Diphenylacetyl)-(S)-N-[2-hydroxy-1-(4-methoxyphenyl)ethyl]ornithine amide

- Prepared according to the method described in Example 1(d) above from (R)-N⁵-(Cbz)-(S)-N-[2-hydroxy-1-(4-methoxyphenyl)ethyl]ornithineamide hydrochloride (2.32 g, 5.13 mmol; from step (b) above), 2-nitrophenyl
- 20 diphenyl acetate (1.81 g; 5.65 mmol; see Example 1(c) above), triethylamine (0.78 g, 7.70 mmol) and CH₂Cl₂ (150 mL), 60 hours reaction time. The reaction mixture was submitted to aqueous work up, dried, filtered and concentrated to give the crude product as an off-white solid (3.39 g). The crude product was chromatographed on silica gel eluting
- 25 with CH₂Cl₂:MeOH (98:2). Concentration of the appropriate fractions gave pure sub-title compound as a white solid (2.85 g).

R_f 0.4 (CH₂Cl₂:MeOH (95:5); silica gel TLC plate)

- ¹H NMR (CD₃OD) δ 1.35-1.84 (m, 4H), 2.97-3.15 (m, 2H), 3.52-3.72 (m, 2H), 3.75 (s, 3H), 4.46 (m, 1H), 4.88 (m, 1H), 5.04 (s, 2H), 5.09 (s,
- 30 1H), 6.84 (d, 2H), 7.12-7.45 (m, 17H).

(d) (R)-N²-(Diphenylacetyl)-(S)-N-[2-hydroxy-1-(4-methoxyphenyl)-ethyl]ornithine amide hydrochloride

Prepared according to the method described in Example 1(e) above from (R)-N⁵-(Cbz)-N²-(diphenylacetyl)-(S)-N-[2-hydroxy-1-(4-methoxyphenyl)-ethyl]ornithine amide (2.85 g; from step (c) above), 10% Pd/C (1.40 g), MeOH (200 mL) and concentrated HCl (2 mL) under hydrogen for 6 hours to give the crude product as a solid (2.6 g). Pure sub-title compound was obtained by crystallization from MeOH:diethyl ether to give a white solid (1.58 g).

mp 202-205°C

R_f 0.50 (MeOH:ammonium hydroxide (30:1); silica gel TLC plate)

¹H NMR (CD₃OD) δ 1.52-1.95 (m, 4H), 2.86 (t, 2H), 3.62-3.75 (m, 2H), 3.78 (s, 3H), 4.47 (m, 1H), 4.88 (m, 1H), 5.15 (s, 1H), 6.86 (d, 2H), 7.18 (d, 2H), 7.15-7.43 (m, 10H).

(e) (R)-N^ω,N^{ω'}-bis(Cbz)-N²-(Diphenylacetyl)-(R)-N-[2-hydroxy-1-(4-methoxyphenyl)ethyl]arginine amide

Prepared according to the method described in Example 4(f) above from (R)-N²-(diphenylacetyl)-(S)-N-[2-hydroxy-1-(4-methoxyphenyl)ethyl]-ornithine amide hydrochloride (0.50 g; 0.98 mmol; from step (d) above), N,N¹-bis(Cbz)-S-methylisothiourea (0.38 g; 1.07 mmol) and triethylamine (0.15 g; 1.46 mmol; instead of DiPEA) and dimethyl formamide (10 mL), 18 hours reaction time. Concentration under vacuum gave the crude product, which was chromatographed on silica gel eluting with CH₂Cl₂:EtOAc (3:1) to give pure sub-title compound as a solid (0.66 g).

R_f 0.2 (CH₂Cl₂:EtOAc (3:1); silica gel TLC plate)

¹H NMR (CDCl₃) δ 1.15-1.88 (m, 4H), 2.62 (t, 1H), 3.17-3.42 (m, 2H), 3.61-3.85 (m, 2H), 3.77 (s, 3H), 4.54 (m, 1H), 4.89-5.24 (m, 6H), 6.82 (d, 2H), 7.02-7.54 (m, 22H), 8.32 (m, 1H).

(f) (R)-N²-(Diphenylacetyl)-(S)-N-[2-hydroxy-1-(4-methoxyphenyl)-ethyl]arginine amide hydrochloride

Prepared according to the method described in Example 1(g) above from (R)-N^α,N^{ω'}-bis(Cbz)-N²-(diphenylacetyl)-(S)-N-[2-hydroxy-1-(4-methoxyphenyl)-ethyl]arginine amide (0.58 g; from step (e) above), 10% Pd/C (0.25 g) and HOAc (50 mL) under hydrogen, 5 hours reaction time. The crude product (0.42 g) was chromatographed on silica gel eluting with MeOH:CHCl₃:ammonium hydroxide (3:6:1) to afford the title compound as a solid (0.15 g).

mp 80-90°C

R_f 0.4 (System D)

¹H NMR (CD₃OD) δ 1.42-1.93 (m, 4H), 3.01-3.18 (m, 2H), 3.66-3.72 (m, 2H), 3.78 (s, 3H), 4.46 (m, 1H), 4.87 (m, 1H), 5.17 (s, 1H), 6.84 (d, 2H), 7.17 (d, 2H), 7.20-7.38 (m, 10H).

Example 19

(R)-N²-(Diphenylacetyl)-(R)-N-[2-hydroxy-1-(4-methoxyphenyl)ethyl]-arginine amide hydrochloride

(a) (R)-N²-(Boc)-N⁵-(Cbz)-(R)-N-[2-hydroxy-1-(4-methoxyphenyl)ethyl]-ornithine amide

Prepared according to the method described in Example 11(a) above from N^α-Boc-N^δ-Cbz-(R)-ornithine o-nitrophenyl ester (3.11 g; 6.38 mmol; see Example 4(a) above), (R)-4-methoxy-α-hydroxymethylbenzylamine hydrochloride (1.43 g; 7.02 mmol) and triethylamine (0.97 g; 9.57 mmol; instead of DiPEA) in CH₂Cl₂ (100 mL), 18 hours reaction time. The reaction mixture was submitted to aqueous work up using water, 1N HCl and brine, then dried, filtered and concentrated to give a yellow solid (3.69 g) which was used without purification.

R_f 0.50 (System B)

(b) (R)-N⁵-(Cbz)-(R)-N-[2-hydroxy-1-(4-methoxyphenyl)ethyl]ornithine amide hydrochloride

Prepared according to the method described in Example 1(b) above from crude (R)-N²-(Boc)-N⁵-(Cbz)-(R)-N-[2-hydroxy-1-(4-methoxyphenyl)-ethyl]ornithine amide (3.7 g; from step (a) above), EtOAc (100 mL) and HCl/EtOAc (100 mL), 18 hours reaction time. The solution was concentrated to give the crude sub-title compound as a yellow crushable foam (3.3 g) which was used without purification.

10 (c) (R)-N⁵-(Cbz)-N²-(Diphenylacetyl)-(R)-N-[2-hydroxy-1-(4-methoxyphenyl)ethyl]ornithine amide

Prepared according to the method described in Example 1(d) above from (R)-N⁵-(Cbz)-(R)-N-[2-hydroxy-1-(4-methoxyphenyl)ethyl]ornithine amide hydrochloride (3.33 g; 7.37 mmol; from step (b) above), 2-nitrophenyl diphenyl acetate (2.60 g; 8.10 mmol; see Example 1(c) above), triethylamine (2.23 g; 22.11 mmol) and CH₂Cl₂ (200 mL), reaction time 60 hours. The resulting yellow solution was submitted to aqueous work up, dried, filtered and concentrated to give the crude product as an off-white solid (4.76 g). The crude product was chromatographed twice on silica gel eluting with CH₂Cl₂:MeOH (98:2). Concentration of the product containing fractions gave the sub-title compound as a white solid (0.63 g).

R_f 0.4 (CH₂Cl₂:MeOH (95:5); silica gel TLC plate)

¹H NMR (CD₃OD) δ 1.44-1.90 (m, 4H), 3.02-3.18 (m, 2H), 3.55-3.70 (m, 2H), 3.68 (s, 3H), 4.48 (m, 1H), 4.92 (m, 1H), 5.03 (s, 1H), 5.07 (s, 2H), 6.78 (d, 2H), 7.06-7.45 (m, 17H)

(d) (R)-N²-(Diphenylacetyl)-(R)-N-[2-hydroxy-1-(4-methoxyphenyl)ethyl]-ornithine amide hydrochloride

Prepared according to the method described in Example 1(e) above from (R)-N⁵-(Cbz)-N²-(diphenylacetyl)-(R)-N-[2-hydroxy-1-(4-methoxyphenyl)-

ethyl]ornithine amide (0.63 g; from step (c) above), 10% Pd/C (0.30 g), MeOH (100 mL) and concentrated HCl (1 mL) under hydrogen, 18 hours reaction time to give the crude sub-title compound as a solid (0.57 g) which was used without purification.

5 mp 208-212°C

R_f 0.5 (MeOH:ammonium hydroxide (30:1); silica gel TLC plate)

¹H NMR (CD₃OD) δ 1.58-1.97 (m, 4H), 2.95 (t, 2H), 3.58-3.82 (m, 2H), 3.78 (s, 3H), 4.52 (m, 1H), 4.87 (m, 1H), 5.06 (s, 1H), 6.80, (d, 2H), 7.15 (d, 2H), 7.12-7.42 (m, 10H)

10

(e) (R)-N^w,N^{w'}-bis(Cbz)-N²-(Diphenylacetyl)-(S)-N-[2-hydroxy-1-(4-methoxyphenyl)ethyl]arginine amide

Prepared according to the method described in Example 4(f) above from (R)-N²-(diphenylacetyl)-(R)-N-[2-hydroxy-1-(4-methoxyphenyl)ethyl]-
15 ornithine amide hydrochloride (0.57 g; 1.11 mmol; from step (d) above), N,N'-bis(Cbz)-S-methylisothiurea (0.44 g; 1.22 mmol), triethylamine (0.17 g; 1.67 mmol; instead of DiPEA) and dimethyl formamide (10 mL), 60 hours reaction time. Concentration under vacuum gave the crude product which was chromatographed on silica eluting with CH₂Cl₂:EtOAc (3:1),
20 then CH₂Cl₂:EtOAc (1:1), to give pure sub-title compound as a solid (0.48 g).

R_f 0.3 (CH₂Cl₂:EtOAc (3:1); silica gel TLC plate)

¹H NMR (CDCl₃) δ 1.42-1.98 (m, 4H), 2.85-3.02 (m, 1H), 3.15-3.37 (m, 2H), 3.55-3.86 (m, 2H), 3.77 (s, 3H), 4.56 (m, 1H), 4.82-5.23 (m,
25 6H), 6.78 (d, 2H), 6.92-7.54 (m, 22H), 8.36 (m, 1H)

(f) (R)-N²-(Diphenylacetyl)-(R)-N-[2-hydroxy-1-(4-methoxyphenyl)ethyl]arginine amide hydrochloride

Prepared according to the method described in Example 1(g) above from
30 (R)-N^w,N^{w'}-bis(Cbz)-N²-(diphenylacetyl)-(S)-N-[2-hydroxy-1-(4-methoxy-

phenyl)ethyl]arginine amide (0.48 g; from step (e) above), 10% Pd/C (0.25 g) and HOAc (50 mL) under hydrogen, 18 hours reaction time. The crude product (0.37 g) was chromatographed on silica gel eluting with MeOH:CHCl₃:ammonium hydroxide (3:6:1), to afford the title compound
5 as a solid (0.11 g).

mp 80-90°C

R_f 0.4 (System D)

¹H NMR (CD₃OD) δ 1.50-1.95 (m, 4H), 3.16 (t, 2H), 3.58-3.77 (m, 2H), 3.76 (s, 3H), 4.50 (t, 1H), 4.87 (m, 1H), 5.08 (s, 1H), 6.81 (d, 2H),
10 7.17 (d, 2H), 7.20-7.35 (m, 10H)

Example 20

(R)-N²-(Diphenylacetyl)-(S)-N-[1-(4-hydroxyphenyl)ethyl]arginine amide hydrochloride

15

(a) (R)-N²-(Boc)-N⁵-(Cbz)-(S)-N-[1-(4-hydroxyphenyl)ethyl]ornithine amide

Prepared according to the method described in Example 1(a) above from N^α-Boc-N^δ-Cbz-(R)-ornithine (5.34 g; 14.56 mmol), (S)-4-hydroxy-α-methylbenzylamine (2.0 g; 14.56 mmol), BOP reagent (9.67 g; 21.9
20 mmol), triethylamine (2.5 mL; instead of DiPEA) in acetonitrile (100 mL; instead of acetonitrile:CH₂Cl₂ (1:1)) to yield the sub-title compound (6.7g) as a white foam. The crude ¹H NMR was consistent with the structure.

25 (b) (R)-N⁵-(Cbz)-(S)-N-[1-(4-hydroxyphenyl)ethyl]ornithine amide hydrochloride

Prepared according to the method described in Example 1(b) above from (R)-N²-(Boc)-N⁵-(Cbz)-(S)-N-[1-(4-hydroxyphenyl)ethyl]ornithine amide (5.1 g; from step (a) above), ethyl acetate (100 mL) and HCl/EtOAc (100
30 mL) yielding, after isolation, 3.3 g of the sub-title compound as a tan

solid.

(c) (R)-N⁵-(Cbz)-N²-(Diphenylacetyl)-(S)-N-[1-(4-hydroxyphenyl)ethyl]-ornithine amide

- 5 Prepared according to the method described in Example 3(c) above from (R)-N⁵-(Cbz)-(S)-N-[1-(4-hydroxyphenyl)ethyl]ornithine amide hydrochloride (3.3 g; 7.8 mmol; from step (b) above), diphenylacetic acid (1.82 g, 8.6 mmol), BOP (3.79 g; 8.58 mmol) and triethylamine (4.0 mL; 1.1 eq.) in 300 mL acetonitrile, yielding 895 mg of the sub-title
10 compound.

¹H NMR (CD₃OD) δ 1.38 (d, 3H), 1.45 (m, 2H), 1.61 (m, 1H), 1.78 (m, 1H), 3.08 (m, 2H), 4.40 (m, 1H), 4.89 (q, 1H), 5.03 (s, 1H), 5.04 (s, 2H), 6.68 (d, 2H), 7.05 (d, 2H), 7.4 (m, 15H), 8.08 (d, 1H, NH)

- 15 (d) (R)-N²-(Diphenylacetyl)-(S)-N-[1-(4-hydroxyphenyl)ethyl]ornithine amide hydrochloride

- Prepared according to the method described in Example 1(e) above from (R)-N⁵-(Cbz)-N²-(diphenylacetyl)-(S)-N-[1-(4-hydroxyphenyl)ethyl]-ornithine amide (895 mg; from step (c) above), 10% Pd/C (300 mg) in
20 methanol (100 mL) with HCl (0.5 mL), yielding 65 mg of the sub-title compound.

R_f 0.66 (EtOAc:MeOH:conc. ammonium hydroxide (47:47:6))

- ¹H NMR (CD₃OD) δ 1.36 (d, 3H), 1.66 (m, 3H), 1.85 (m, 1H), 2.90 (m, 2H), 4.41 (m, 1H), 5.07 (s, 1H), 6.68 (d, 2H), 7.05 (d, 2H), 7.3 (m,
25 10H), 8.1 (d, 1H, NH), 8.40 (d, 1H, NH).

(e) (R)-N^ω.N^{ω'}-(bisCbz)-N²-(Diphenylacetyl)-(S)-N-[1-(4-hydroxyphenyl)-ethyl]arginine amide

- Prepared according to the method in Example 4(f) above from (R)-N²-(diphenylacetyl)-(S)-N-[1-(4-hydroxyphenyl)ethyl]ornithine
30 amide

hydrochloride (0.5 g; from step (d) above), *N,N'*-bis(Cbz)-*S*-methyisothioureia (0.4 g) and DiPEA (0.2 mL) in DMF (10 mL), yielding 0.526 g of the sub-title compound as a white foam.

R_f 0.90 (EtOAc)

5

(f) (*R*)-*N*²-(Diphenylacetyl)-(*S*)-*N*-[1-(4-hydroxyphenyl)ethyl]arginine amide hydrochloride

Prepared according to the method described in Example 1(g) above from (*R*)-*N*^ω,*N*^{ω'}-(bisCbz)-*N*²-(diphenylacetyl)-(*S*)-*N*-[1-(4-hydroxyphenyl)ethyl]-arginine amide (250 mg; from step (e) above), HOAc (10mL) and 10% Pd/C (0.2 g) treated with methanol and ethyl acetate saturated with HCl to give 125 mg of the title compound.

mp 146-148°C

R_f 0.18 (EtOAc:MeOH:concentrated ammonium hydroxide (47:47:6))

15 ¹H NMR (CD₃OD) δ 1.35 (d, 3H), 1.55 (m, 2H), 1.66 (m, 1H), 1.82 (m, 1H), 3.11 (m, 2H), 4.41 (q, 1H), 4.90 (q, 1H), 5.07 (s, 1H), 6.58 (d, 2H), 7.05 (d, 2H)

Example 21

20 (*R*)-*N*²-(Diphenylacetyl)-(*R,S*)-*N*-[1-(4-methoxyphenyl)ethyl]arginine amide hydrochloride

(a) (*R*)-*N*²-(Boc)-*N*⁵-(Cbz)-(*R,S*)-*N*-[1-(4-methoxyphenyl)ethyl]ornithine amide

25 Prepared according to the method described in Example 1(a) above from *N*^ω-Boc-*N*-δ-Cbz-(*R*)-ornithine (2.5 g; 6.7 mmol), BOP reagent (3.3 g; 7.4 mmol), HOBT (1.1 g; 7.4 mmol), DiPEA (5.8 mL; 33 mmol) and 100 mL of acetonitrile:CH₂Cl₂ (1:1) followed by (*R,S*)-4-methoxy-α-methylbenzylamine (1.0 g; 6.7 mmol; in 5 mL of acetonitrile). After work
30 up the crude product was used without further purification. The yield of

crude sub-title compound was 3.3 g (100%).

¹H NMR (CDCl₃) δ 1.38-1.72 (m, 5H), 1.49 + 1.51 (s, 9H), 1.72-2.00 (m, 2H), 3.10-3.28 + 3.35-3.55 (m, 2H), 3.28 + 3.33 (s, 3H), 4.18-4.40 (m, 1H), 4.82-5.25 (m, 3H), 6.68-6.80 (m, 1H), 6.82-6.95 (m, 2H), 7.22-
5 7.45 (m, 7H)

(b) (R)-N⁵-(Cbz)-N²-(Diphenylacetyl)-(R,S)-N-[1-(4-methoxyphenyl)ethyl]ornithine amide

Prepared analogously to the method described in Examples 2(b) and 2(c)
10 above from (R)-N²-(Boc)-N⁵-(Cbz)-(R,S)-N-[1-(4-methoxyphenyl)ethyl]-ornithine amide (3.3 g; 6.7 mmol; from step (a) above), HCl/EtOAc (75 mL), 30 minutes reaction time for the deprotection, then THF (200 mL; instead of CH₂Cl₂), diphenylacetyl chloride (1.7 g; 7.4 mmol) followed by DiPEA (4.7 mL; 27 mmol) over 5 min, 1 hour reaction time. The solvent
15 was evaporated at reduced pressure and the resultant residue dissolved in CH₂Cl₂ (300 mL) for the work up procedure. The crude material was purified to yield 2.0 g (51%) of the sub-title compound as a crushable foam.

20 (c) (R)-N²-(Diphenylacetyl)-(R,S)-N-[1-(4-methoxyphenyl)ethyl]ornithine amide hydrochloride

Prepared according to the method described in Example 1(e) above from (R)-N⁵-(Cbz)-N²-(diphenylacetyl)-(R,S)-N-[1-(4-methoxyphenyl)ethyl]-ornithine amide (2.0 g; 3.4 mmol; from step (b) above), 10% Pd/C (w/w;
25 500 mg), ethanol (150 mL; instead of methanol) and conc. HCl (1 mL), 2 hours reaction time, to yield the sub-title compound as a foam (1.5 g; 87%). A sample was crystallised from acetonitrile.

mp 198-201°C

(d) (R)-N^ω,N^{ω'}-bis(Cbz)-N²-(Diphenylacetyl)-(R,S)-N-[1-(4-methoxyphenyl)ethyl]arginine amide

Prepared according to the method described in Example 4(f) from (R)-N²-(diphenylacetyl)-(R,S)-N-[1-(4-methoxyphenyl)ethyl]ornithine amide

- 5 hydrochloride (1.08 g; 2.17 mmol; from step (c) above), N,N'-bis(Cbz)-S-methylisothiurea (0.780 g; 2.17 mmol) and triethylamine (0.6 mL; 4.35 mmol) in THF (40 mL), yielding 720 mg of the sub-title compound as a white solid.

10 (e) (R)-N²-(Diphenylacetyl)-(R,S)-N-[1-(4-methoxyphenyl)ethyl]arginine amide hydrochloride

- Prepared according to the method described in Example 1(g) from (R)-N^ω,N^{ω'}-bis(Cbz)-N²-(diphenylacetyl)-(R,S)-N-[1-(4-methoxyphenyl)ethyl]-arginine amide (440 mg; from step (d) above), 10% Pd/C (100 mg),
 15 ethanol (20 mL) and concentrated hydrochloric acid (0.2 mL) under hydrogen, 18 hours reaction time, yielding 174 mg of the title compound as a white solid.

$$[\alpha]_D^{20} = +21.8^\circ\text{C} (c=2.0; \text{methanol})$$

$$\text{mp} = 84-88^\circ\text{C}$$

- 20 $R_f = 0.47$ (CH₂Cl₂:MeOH (80:20))

¹H NMR (CD₃OD) 1.62 (d, 3H), 1.62 - 2.20 (m, 3H), 3.42 (m, 2H), 4.05 (s, 3H), 4.48 (m, 1H), 5.20 (q, 1H), 5.38 (s, 0.5H), 5.41 (s, 0.5H), 7.10 (d, 2H), 7.13 (d, 2H), 7.48 (d, 2H), 7.51 (d, 2H), 7.68 to 7.51 (m, 10H)

25

30

Example 22(R)-N²-(Diphenylacetyl)-N-methyl-(R)-N-(1-phenylethyl)arginine amide hydrochloride

- 5 (a) (R)-N²-(Boc)-N⁵-(Cbz)-N-methyl-(R)-N-(1-phenylethyl)ornithine amide

Prepared according to the method described in Example 1(a) above from N^α-Boc-N^δ-Cbz-(R)-ornithine (5.0 g; 13 mmol), BOP reagent (6.0 g; 13 mmol), HOBT (1.8 g; 13 mmol), DiPEA (7.1 mL; 40 mmol) and
10 acetonitrile:CH₂Cl₂ (1:1; 100 mL) followed by (R)-(+)-N,α-dimethylbenzylamine (2.0 mL; 13 mmol), then stirred overnight. After work up the crude product was purified by chromatography on silica gel with EtOAc to provide 6.0 g (91%) of the sub-title compound.

- 15 (b) (R)-N⁵-(Cbz)-N²-(Diphenylacetyl)-N-methyl-(R)-N-(1-phenylethyl)-ornithine amide

Prepared according to the method described in Examples 2(b) and 2(c) above from (R)-N²-(Boc)-N⁵-(Cbz)-N-methyl-(R)-N-(1-phenylethyl)-ornithine amide (5.0 g; 10 mmol; from step (a) above) EtOAc (75 mL)
20 then HCl/EtOAc (75 mL), 2 hours reaction time for the deprotection, then CH₂Cl₂ (50 mL), diphenylacetyl chloride (2.4 g; 10 mmol) followed by pyridine (3.0 mL; 37 mmol; instead of DiPEA) over 1 minute, overnight reaction time, diluted with CH₂Cl₂ (100 mL) for the work up procedure. The crude material was purified by chromatography on silica gel with
25 EtOAc:hexanes (1:1) to provide 1.6 g (26%) of the sub-title compound.

(c) (R)-N²-(Diphenylacetyl)-N-methyl-(R)-N-(1-phenylethyl)ornithine amide

Prepared according to the method described in Example 1(e) above from
30 (R)-N⁵-(Cbz)-N²-(diphenylacetyl)-N-methyl -(R)-N-(1-phenylethyl)ornithine

amide (1.6 g; 2.8 mmol; from step (b) above), 10% Pd/C (w/w; 100 mg), HOAc (75 mL), overnight reaction time. The crude acetate salt was purified by chromatography on silica gel with EtOAc, then CHCl₃:MeOH:concentrated ammonium hydroxide (6:3:1) to provide 1.2 g (98%) of the sub-title compound.

(d) (R)-N²-(Diphenylacetyl)-(N^ω,N^{ω'})-bis(Cbz)-N-methyl-(R)-N-(1-phenylethyl)arginine amide

Prepared according to the method described in Example 1(f) above from (R)-N²-(diphenylacetyl)-N-methyl-(R)-N-(1-phenylethyl)ornithine amide (0.50 g; 1.1 mmol; from step (c) above), N,N'-bis(Cbz)-S-methyl-isothiourea (0.40 g; 1.1 mmol), DiPEA (0.41 mL; 2.4 mmol) and THF (20 mL; instead of DMF). The crude product was purified by chromatography on silica gel with CH₂Cl₂, then EtOAc to provide 0.62 g (79%) of the sub-title compound as a solid.

(e) (R)-N²-(Diphenylacetyl)-N-methyl-(R)-N-(1-phenylethyl)arginine amide hydrochloride

Prepared according to the method described in Example 1(g) above from (R)-N²-(diphenylacetyl)-(N^ω,N^{ω'})-(bisCbz)-N-methyl-(R)-N-(1-phenylethyl)-arginine amide (0.62 g; 0.89 mmol; from step (d) above), 10% Pd/C (w/w; 100 mg), HOAc (50 mL), overnight reaction time. The crude acetate salt was converted to the hydrochloride then triturated with methanol to provide 0.12 g (25%) of the title compound as a solid.

mp 233-235°C

R_f 0.50 (System D)

[α]_D²¹=+109.7°(C=0.31, MeOH)

¹H NMR (CD₃OD) δ 1.46 and 1.66 (2d, 3H), 1.50-1.90 (m, 4H), 2.59 and 2.73 (2s, 3H), 3.16 (m, 2H), 4.88 (m, 1H), 5.03 and 5.10 (2s, 1H), 5.38 and 5.88 (2m, 1H), 7.15-7.37 (m, 10H)

Example 23(R)-N²-(Diphenylacetyl)-N-methyl-(S)-N-(1-phenylethyl)arginine amide hydrochloride5 (a) (R)-N²-(Boc)-N⁵-(Cbz)-N-methyl-(S)-N-(1-phenylethyl)ornithine amide

Prepared according to the method described in Example 1(a) above from N^α-Boc-N^δ-Cbz-(R)-ornithine (5.0 g; 13 mmol), BOP reagent (6.0 g; 13 mmol), HOBT (1.8 g; 13 mmol), DiPEA (7.1 mL; 40 mmol) and 100 mL of acetonitrile:CH₂Cl₂ (1:1) followed by (S)-(-)-N,α-dimethylbenzylamine
10 (2.0 mL; 13 mmol), then stirred overnight. After work up the crude product was purified by chromatography on silica gel with EtOAc to provide 5.5 g (83%) of the sub-title compound.

15 (b) (R)-N⁵-(Cbz)-N²-(Diphenylacetyl)-N-methyl-(S)-N-(1-phenylethyl)-ornithine amide

Prepared according to the method described in Examples 2(b) and 2(c) above from (R)-N²-(Boc)-N⁵-(Cbz)-N-methyl-(S)-N-(1-phenylethyl)-ornithine amide (5.3 g; 11 mmol; from step (a) above), EtOAc (75 mL), then HCl/EtOAc (75 mL), 2.5 hours reaction time for the deprotection,
20 then CH₂Cl₂ (50 mL), diphenylacetyl chloride (2.6 g; 11 mmol) followed by pyridine (3.0 mL; 37 mmol; instead of DiPEA) over 1 min, overnight reaction time, diluted with CH₂Cl₂ (100 mL) for the work-up procedure. The crude material was purified by chromatography on silica gel with EtOAc:hexane (1:1) to provide 1.9 g (30%) of the sub-title compound.

25

(c) (R)-N²-(Diphenylacetyl)-N-methyl-(S)-N-(1-phenylethyl)ornithine amide

Prepared according to the method described in Example 1(e) above from (R)-N⁵-(Cbz)-N²-(diphenylacetyl)-N-methyl-(S)-N-(1-phenylethyl)ornithine amide (1.9 g; 3.3 mmol; from step (b) above), 10% Pd/C (w/w; 100 mg),
30 HOAc (75 mL), overnight reaction time. The crude acetate salt was

purified by chromatography on silica gel with EtOAc, then CHCl_3 :MeOH:concentrated ammonium hydroxide (6:3:1) to provide 1.4 g (96%) of the sub-title compound.

5 (d) (R)-(N^w,N^{w'})-(bisCbz)-N²-(Diphenylacetyl)-N-methyl-(S)-N-(1-phenylethyl)arginine amide

Prepared according to the method described in Example 1(f) above from (R)-N²-(diphenylacetyl)-N-methyl-(S)-N-(1-phenylethyl)ornithine amide (0.50 g; 1.1 mmol; from step (c) above), N,N'-bis(Cbz)-S-methylisothiourea (0.40 g; 1.1 mmol), DiPEA (0.41 mL; 2.4 mmol) and THF (20 mL; instead of DMF). The crude product was purified by chromatography on silica gel with CH_2Cl_2 , then EtOAc to provide 0.71 g (91%) of the sub-title compound as a solid.

15 (e) (R)-N²-(Diphenylacetyl)-N-methyl-(S)-N-(1-phenylethyl)arginine amide hydrochloride

Prepared according to the method described in Example 1(g) above from (R)-(N^w,N^{w'})-bis(Cbz)-N²-(diphenylacetyl)-N-methyl-(S)-N-(1-phenylethyl)-arginine amide (0.70 g; 1.0 mmol; from step (d) above), 10% Pd/C (w/w; 20 100 mg), HOAc (50 mL), overnight reaction time. The crude acetate salt was converted to the hydrochloride then triturated with methanol to provide 0.15 g (28%) of the title compound as a solid.

mp 251-253°C

R_f 0.50 (System D)

25 $[\alpha]_{\text{D}}^{21} = -21.2^\circ (\text{C}=0.34; \text{MeOH})$

¹H NMR (CD₃OD) δ 1.40 and 1.51 (2d, 3H), 1.52-1.92 (m, 4H), 2.70 and 2.72 (2s, 3H), 3.03-3.24 (m, 2H), 4.90 (m, 1H), 5.05 and 5.08 (2s, 1H), 5.28 and 5.90 (2m, 1H), 7.17-7.39 (m, 10H)

Example 24

(R)-N²-(Diphenylacetyl)-(R,S)-N-[1-(4-cyclopropylmethoxyphenyl)ethyl]-
arginine amide hydrochloride

- 5 (a) (R)-N²-(Boc)-N⁵-(Cbz)-(R,S)-N-[1-(4-Cyclopropylmethoxyphenyl)-
ethyl]ornithine amide

A solution of N^α-Boc-N^δ-Cbz-(R)-ornithine-*o*-nitrophenyl ester (0.9 g; 1.86 mmol; see Example 4a above), (R,S)-[1-(4-cyclopropylmethoxyphenyl)-ethylamine (0.48 g, 1.86 mmol), triethylamine (0.39 mL, 2.79 mmol) in
10 CH₂Cl₂ (50 mL) was stirred for 5 h at room temperature. The resultant yellow solution was concentrated *in vacuo* and the residue chromatographed on silica eluting with CH₂Cl₂:CH₃OH (98:2). Fractions containing the desired product were combined and concentrated *in vacuo* to afford 0.67 g (67%) of the sub-title compound as a crushable foam.

- 15 R_f 0.5 (CH₂Cl₂:CH₃OH(95:5))

¹H NMR (CDCl₃) δ 0.28-0.38 (m, 2H), 0.58-0.68 (m, 2H), 1.26 (m, 1H), 1.34-1.88 (m, 16H), 3.14 (m, 1H), 3.42 (m, 1H), 3.71 and 3.78 (d, 2H), 4.22 (m, 1H), 4.78-5.27 (m, 5H), 6.68 (m, 1H), 6.79-6.87 (m, 2H), 7.21 (d, 2H), 7.26-7.41 (m, 5H)

20

- (b) (R)-N⁵-(Cbz)-(R,S)-N-[1-(4-Cyclopropylmethoxyphenyl)ethyl]-
ornithine amide

A solution of (R)-N²-(Boc)-N⁵-(Cbz)- (R,S)-N-[1-(4-cyclopropylmethoxyphenyl)ethyl]ornithine amide (0.67g, 1.30 mmol; from step (a) above) in
25 EtOAc was treated with HCl/EtOAc (10 mL). After stirring for 5 h, the reaction was concentrated *in vacuo* to provide 0.62 g (100%) as a crushable foam.

R_f 0.3 and 0.4 (CHCl₃:CH₃OH:AcOH(9:1:0.1))

¹H NMR (CD₃OD) δ 0.28-0.37 (m, 2H), 0.52-0.65 (m, 2H), 1.21 (m, 1H), 1.38-1.53 (m, 3H), 1.55-1.68 (m, 2H), 1.71-1.93 (m, 2H), 3.02-3.22
30

(m, 2H), 3.69-3.90 (m, 3H), 4.89-5.11 (m, 3H), 6.79-6.88 (m, 2H), 7.16-7.38 (m, 7H)

5 (c) (R)-N⁵-(Cbz)-N²-(Diphenylacetyl)-(R,S)-N-[1-(4-cyclopropylmethoxyphenyl)ethyl]ornithine amide

A solution of 2-nitrophenyl diphenyl acetate (0.42 g, 1.30 mmol; see Example 1(c) above), (R)-N⁵-(Cbz)-(R,S)-N-[1-(4-cyclopropylmethoxyphenyl)ethyl]ornithine amide (0.62 g, 1.30 mmol; from step (b) above) and triethylamine (0.54 mL, 3.90 mmol) in CH₂Cl₂ (50 mL) was stirred at
10 room temperature for 18 h. The resultant yellow solution was concentrated *in vacuo* and chromatographed on silica eluting with CH₂Cl₂:EtOAc (5:1). Fractions containing the desired product were combined and concentrated to afford 0.71 g (86%) of the sub-title compound.

R_f 0.5 (CH₂Cl₂:EtOAc (3:1))

15 ¹H NMR (CDCl₃) δ 0.27-0.39 (m, 2H), 0.57-0.68 (m, 2H), 1.24 (m, 1H), 1.32-1.90 (m, 7H), 3.08 (m, 1H), 3.37 (m, 1H), 3.70 and 3.76 (d, 2H), 4.63 (m, 1H), 4.79-5.12 (m, 5H), 6.53 (m, 1H), 6.79 (d, 2H), 6.88 (m, 1H) 7.13 (d, 2H), 7.14-7.41 (m, 15H)

20 (d) (R)-N²-(Diphenylacetyl)-(R,S)-N-[1-(4-cyclopropylmethoxyphenyl)ethyl]ornithine amide

To a solution of (R)-N⁵-(Cbz)-N²-(diphenylacetyl)-(R,S)-N-[1-(4-cyclopropylmethoxyphenyl)ethyl]ornithine amide (0.71 g, 1.12 mmol; from step (c) above) at 0°C in acetonitrile (40 mL) was added TMSI (0.21 mL, 1.46
25 mmol). The resultant solution was stirred for 1 h in the cold, then quenched with H₂O. EtOAc and NaHCO₃ solution were then added. The EtOAc layer was separated, washed with 1M Na₂S₂O₃ (once) and brine (twice), dried over Na₂SO₄ and concentrated *in vacuo*. The residue was chromatographed on silica eluting with CH₂Cl₂:CH₃OH:NH₄OH
30 (88.5:10:1.5). Fractions containing the desired product were combined and

concentrated *in vacuo* and converted to the hydrochloride salt, affording 0.17 g (30%) of the sub-title compound.

R_f 0.60 (System C)

¹H NMR (CD₃OD) δ 0.29-0.38 (m, 2H), 0.55-0.66 (m, 2H), 1.23 (m, 1H), 1.30-1.85 (m, 7H), 2.57 and 2.62 (t, 2H), 3.73-3.82 (m, 2H), 4.38 (m, 1H), 4.88 (m, 1H), 5.05 and 5.08 (s, 1H), 6.78 and 6.83 (d, 2H), 7.08-7.37 (m, 12H)

10 (e) (R)-N²-(Diphenylacetyl)-(R,S)-N-[1-(4-cyclopropylmethoxyphenyl)-ethyl]arginine amide hydrochloride

A solution of (R)-N²-(diphenylacetyl)-(R,S)-N-[1-(4-cyclopropylmethoxyphenyl)ethyl]ornithine amide (0.17 g; 0.34 mmol; from step (d) above), 1H-pyrazole-1-carboxamide hydrochloride (0.05 g; 0.34 mmol) and triethylamine (0.07 g; 0.68 mmol) in DMF (5 mL) was stirred for 24 h at room temperature. The solution was concentrated *in vacuo* and the residue chromatographed on silica eluting with CHCl₃:CH₃OH:NH₄OH (6:3:1). Fractions containing the desired compound were combined and concentrated *in vacuo* and then converted to the hydrochloride salt to afford 0.12 g (61%) of the title compound as a solid.

20 R_f 0.5 (System D)

¹H NMR (CD₃OD) δ 0.32-0.38 (m, 2H), 0.57-0.66 (m, 2H), 1.24 (m, 1H), 1.38 (d, 3H), 1.41-1.89 (m, 4H), 3.05-3.18 (m, 2H), 3.78 (d, 2H), 4.41 (m, 1H), 4.87 (m, 1H), 5.07 and 5.12 (s, 1H), 6.77 and 6.82 (d, 2H), 7.11-7.17 (m, 2H), 7.18-7.37 (m, 10H)

25

30

Example 25(R)-N²-(Diphenylacetyl)-(R)-N-[1-(4-benzyloxyphenyl)ethyl]arginine amide hydrochloride5 (a) (R)-N²-(Boc)-N⁵-(Cbz)-(R)-N-[1-(4-Benzyloxyphenyl)ethyl]ornithine amide

Prepared according to the method described in Example 4(b) above from N^α-Boc-N^δ-Cbz-(R)-ornithine-*o*-nitrophenyl ester (3.11 g; 6.37 mmol), (R)-4-benzyloxy- α -methylbenzylamine hydrochloride (1.68 g; 6.37 mmol),
10 TEA (1.94 g; 19.10 mmol) and CH₂Cl₂ (200 mL), 18 hours reaction time. The resultant yellow solution was concentrated to afford the crude sub-title compound which was used directly in the next step.

R_f 0.70 (System B)

15 (b) (R)-N⁵-(Cbz)-(R)-N-[1-(4-Benzyloxyphenyl)ethyl]ornithine amide hydrochloride

Prepared according to the method described in Example 1(b) above from crude (R)-N²-(Boc)-N⁵-(Cbz)-(R)-N-[1-(4-benzyloxyphenyl)ethyl]-ornithine amide (6.37 mmol; from step (a) above), EtOAc (200 mL) and
20 HCl/EtOAc (75 mL), 3 hours reaction time. The resultant heterogeneous solution was concentrated to 100 mL, slurried with Et₂O and the solids collected and dried to afford the sub-title compound as a white solid (2.5 g; 75%).

R_f 0.30 (CHCl₃, CH₃OH, AcOH (9:1:0.1))

25 ¹H NMR (CD₃OD) δ 1.38-1.58 (m, 2H), 1.47 (d, 3H), 1.72-1.90 (m, 2H), 3.08 (t, 2H), 3.87 (t, 1H), 4.88-5.12 (m, 5H), 6.95 (d, 2H), 7.17-7.43 (m, 12H)

(c) (R)-N⁵-(Cbz)-N²-(Diphenylacetyl)-(R)-N-[1-(4-benzyloxyphenyl)ethyl]ornithine amide

Prepared according to the method described in Example 1(d) above from (R)-N⁵-(Cbz)-(R)-N-[1-(4-benzyloxyphenyl)ethyl]ornithine amide

- 5 hydrochloride (2.5 g; 4.88 mmol; from step (b) above), 2-nitrophenyl diphenyl acetate (1.6 g; 4.88 mmol; see Example 1(c) above), TEA (1.5 g; 14.64 mmol) and CH₂Cl₂ (200 mL) at room temperature, 18 hours reaction time, followed by additional 2-nitrophenyl diphenyl acetate (0.6 g) and TEA (0.7 g) at reflux, 18 hours reaction time. The resulting
10 solution was concentrated and chromatographed on silica eluting with CH₂Cl₂:EtOAc (5:1) to afford the pure sub-title compound as a solid (2.9 g).

R_f 0.60 (CH₂Cl₂, EtOAc (3:1))

- ¹H NMR (CDCl₃) δ 1.27-1.59 (m, 6H), 1.75 (m, 1H), 3.04 (m, 1H),
15 3.40 (m, 1H), 4.68 (m, 1H), 4.78-5.06 (m, 6H), 6.58 (d, 1H), 6.87 (d, 2H), 6.95 (d, 1H), 7.16 (d, 2H), 7.18-7.43 (m, 20H)

(d) (R)-N²-(Diphenylacetyl)-(R)-N-[1-(4-benzyloxyphenyl)ethyl]ornithine amide

- 20 Prepared according to the method described in Example 6(d) above from (R)-N⁵-(Cbz)-N²-(diphenylacetyl)-(R)-N-[1-(4-benzyloxyphenyl)ethyl]-ornithine amide (1.0 g; 1.49 mmol; from step (c) above), trimethylsilyliodide (0.33 g; 1.64 mmol) and CH₃CN (35 mL) at 0°C, 2 hours reaction time. The resultant heterogeneous solution was submitted
25 to aqueous work up and chromatographed on silica eluting with CH₂Cl₂:MeOH:conc. NH₄OH (88.5:10:1.5) to afford the sub-title compound as a solid (0.7 g).

R_f 0.40 (System C)

- ¹H NMR (CDCl₃) δ 1.22-1.43 (m, 2H), 1.36 (d, 3H), 1.62-1.83 (m, 2H),
30 2.50-2.67 (m, 2H), 4.49 (q, 1H), 4.93 (s, 1H), 4.97 (t, 1H), 5.04 (s, 2H),

6.88 (d, 2H), 7.09-7.45 (m, 17H)

(e) (R)-N²-(Diphenylacetyl)-(R)-N-[1-(4-benzyloxyphenyl)ethyl]arginine amide hydrochloride

- 5 Prepared according to the method described in Example 6(e) above from (R)-N²-(diphenylacetyl)-(R)-N-[1-(4-benzyloxyphenyl)ethyl]ornithine amide (0.38 g; 0.71 mmol; from step (d) above), 1H-pyrazole-1-carboxamide monohydrochloride (0.10 g; 0.71 mmol), TEA (0.14 g, 1.42 mmol) and DMF (5 mL), 18 hours reaction time. The resulting solution was
10 concentrated and chromatographed on silica eluting with MeOH:CHCl₃:conc. NH₄OH (3:6:1) and converted to the hydrochloride salt to afford the title compound as a white solid (0.32 g).

mp 148-152°C

R_f 0.50 (System D)

- 15 ¹H NMR (CD₃OD) δ 1.38 (d, 3H), 1.41-1.87 (m, 4H), 3.02-3.18 (m, 2H), 4.41 (t, 1H), 4.92 (q, 1H), 5.06 (s, 2H), 5.11 (s, 1H), 6.92 (d, 2H), 7.17 (d, 2H), 7.18-7.46 (m, 15H)

Example 26

- 20 (R)-N²-(Diphenylacetyl)-(R,S)-N-[1-(4-phenoxyphenyl)ethyl]arginine amide hydrochloride

(a) (R)-N²-(Boc)-N⁵-(Cbz)-(R,S)-N-[1-(4-phenoxyphenyl)ethyl]ornithine amide

- 25 Prepared according to the method described in Example 4(b) above from N^α-Boc-N^δ-Cbz-(R)-ornithine-*o*-nitrophenyl ester (3.0 g; 6.15 mmol; see Example 4(a) above), (R,S)-4-phenoxy- α -methylbenzylamine (1.3 g; 6.15 mmol) and CH₂Cl₂ (150 mL), 24 hours reaction time. The resultant yellow solution was concentrated and chromatographed on silica eluting with
30 CH₂Cl₂:MeOH (98:2 then 95:5) to afford the sub-title compound as a

crushable foam (2.6 g).

R_f 0.60 (CH_2Cl_2 , MeOH (95:5))

(b) (R)-N⁵-(Cbz)-(R,S)-N-[1-(4-Phenoxyphenyl)ethyl]ornithine amide

5 hydrochloride

Prepared according to the method described in Example 1(b) above from (R)-N²-(Boc)-N⁵-(Cbz)-(R,S)-N-[1-(4-phenoxyphenyl)ethyl]ornithine amide (2.6 g; from step (a) above), EtOAc (100 mL) and HCl/EtOAc (50 mL), 22 hours reaction time. The resulting solution was concentrated to afford
10 the crude sub-title compound as a crushable foam (2.4 g) which was used directly in the next step.

R_f 0.30 and 0.40 (CHCl_3 :MeOH:AcOH (9:1:0.1))

¹H NMR (CD_3OD) δ 1.42-1.54 (m, 4H), 1.63 (m, 1H), 1.75-1.96 (m, 2H), 3.10 (t, 1H), 3.20 (t, 1H), 3.87 (m, 1H), 4.87-5.12 (m, 3H), 6.92-6.98
15 (m, 4H), 7.10 (m, 1H), 7.22-7.38 (m, 9H)

(c) (R)-N⁵-(Cbz)-N²-(Diphenylacetyl)-(R,S)-N-[1-(4-phenoxyphenyl)-ethyl]ornithine amide

Prepared according to the method described in Example 1(d) above from
20 (R)-N⁵-(Cbz)-(R,S)-N-[1-(4-phenoxyphenyl)ethyl]ornithine amide hydrochloride (2.4 g; 4.82 mmol; step (b) above), 2-nitrophenyl diphenyl acetate (1.5 g; 4.82 mmol; see Example 1(c) above), TEA (0.7 g, 7.23 mmol) and CH_2Cl_2 (250 mL), 18 hours reaction time. The resultant yellow solution was concentrated and chromatographed on silica eluting with
25 CH_2Cl_2 :EtOAc (5:1 then 3:1) to afford the sub-title compound as a solid (2.4 g).

R_f 0.50 (CH_2Cl_2 :EtOAc (3:1))

¹H NMR (CDCl_3) δ 1.12-1.63 (m, 6H), 1.78 (m, 1H), 3.07 (m, 1H), 3.31 (m, 1H), 4.65 (m, 1H), 4.78-5.13 (m, 4H), 6.67 (t, 1H), 6.82-7.43 (m,
30 24H)

(d) (R)-N²-(Diphenylacetyl)-(R,S)-N-[1-(4-phenoxyphenyl)ethyl]ornithine amide hydrochloride

Prepared according to the method described in Example 1(e) above from (R)-N⁵-(Cbz)-N²-(diphenyl acetyl)-(R,S)-N-[1-(4-phenoxyphenyl)ethyl]-
5 ornithine amide (2.4 g; from step (c) above), concentrated HCl (2 mL), MeOH (200 mL) and 10% Pd/C (w/w, 0.5 g) under 1 atmosphere of hydrogen, 4 hours reaction time. The resulting solution was filtered and concentrated to afford the crude sub-title compound as a crushable foam (2.1 g) which was used directly in the next step.

10 mp 190-195°C

R_f 0.50 (System C)

¹H NMR (CD₃OD) δ 1.35-1.45 (m, 3H), 1.54-1.95 (m, 4H), 2.82-2.97 (m, 2H), 4.44 (m, 1H), 4.93 (m, 1H), 5.08 and 5.15 (s, 1H), 6.78-6.98 (m, 4H), 7.02-7.41 (m, 15H)

15

(e) (R)-N²-(Diphenylacetyl)-(R,S)-N-[1-(4-phenoxyphenyl)ethyl]arginine amide hydrochloride

Prepared according to the method described in Example 6(e) above from (R)-N²-(diphenylacetyl)-(R,S)-N-[1-(4-phenoxyphenyl)ethyl]ornithine amide
20 hydrochloride (0.50 g; 0.90 mmol; from step (d) above), 1H-pyrazole-1-carboxamidine monohydrochloride (0.13 g; 0.90 mmol), TEA (0.36 g; 3.60 mmol) and DMF (7 mL), 18 hours reaction time. The resulting heterogeneous solution was concentrated and chromatographed on silica eluting with MeOH, CHCl₃, and concentrated NH₄OH (3:6:1) and
25 converted to the hydrochloride salt to afford the title compound as a white solid (0.35 g).

mp 87-95°C

R_f 0.50 (System D)

¹H NMR (CD₃OD) δ 1.41 (d, 3H), 1.47-1.90 (m, 4H), 3.08-3.19 (m, 2H), 4.42 (m, 1H), 4.94 (m, 1H), 5.10 and 5.17 (s, 1H), 6.82-6.98 (m,
30

4H), 7.04-7.38 (m, 15H)

Example 27

(R)-N²-(Diphenylacetyl)-(R,S)-N-[1-(4-phenylphenyl)ethyl]arginine amide
5 hydrochloride

(a) (R)-N²-(Boc)-N⁵-(Cbz)-(R,S)-N-[1-(4-Phenylphenyl)ethyl]ornithine
amide

Prepared according to the method described in Example 4(b) above from
10 N^α-Boc-N⁵-Cbz-(R)-ornithine-*o*-nitrophenyl ester (3.0 g; 6.15 mmol), (R,S)-
4-phenyl- α -methylbenzylamine (1.3 g; 6.77 mmol) and CH₂Cl₂ (150 mL),
18 hours reaction time. The resultant yellow solution was concentrated
and chromatographed on silica eluting with CH₂Cl₂:MeOH (95:5) to afford
the sub-title compound as a crushable foam (3.4 g).

15 R_f 0.50 (CH₂Cl₂, MeOH (95:5))

(b) (R)-N⁵-(Cbz)-(R,S)-N-[1-(4-Phenylphenyl)ethyl]ornithine amide
hydrochloride

Prepared according to the method described in Example 1(b) above from
20 (R)-N²-(Boc)-N⁵-(Cbz)-(R,S)-N-[1-(4-phenylphenyl)ethyl]ornithine amide
(3.4 g; from step (a) above), EtOAc (100 mL) and HCl/EtOAc (75 mL),
18 hours reaction time. The resultant solution was concentrated to afford
the crude sub-title compound as a crushable foam (3.2 g) which was used
directly in the next step.

25 R_f 0.30 and 0.40 (CHCl₃:MeOH:AcOH (9:1:0.1))

¹H NMR (CD₃OD) δ 1.43-1.57 (m, 4H), 1.65 (m, 1H), 1.77-1.98 (m,
2H), 3.11 (m, 1H), 3.20 (t, 1H), 3.88 (m, 1H), 4.99 (s, 1H), 5.03-5.14 (m,
2H), 7.23-7.48 (m, 10H), 7.54-7.62 (m, 4H)

(c) (R)-N⁵-(Cbz)-N²-(Diphenylacetyl)-(R,S)-N-[1-(4-phenylphenyl)ethyl]-ornithine amide

Prepared according to the method described in Example 1(d) above from (R)-N⁵-(Cbz)-(R,S)-N-[1-(4-phenylphenyl)ethyl]ornithine amide

- 5 hydrochloride (3.2 g; 6.53 mmol; from step (b) above), 2-nitrophenyl diphenyl acetate (2.1 g; 6.53 mmol; see Example 1(c) above), TEA (1.7 g; 16.33 mmol) and CH₂Cl₂ (250 mL), 60 hours reaction time. The resultant yellow solution was concentrated to give a solid. Digestion of the crude solids with hot CH₂Cl₂, EtOAc and MeOH afforded the sub-title
10 compound as a solid (1.2 g). Additional material was available by concentration of the resultant filtrate followed by chromatography on silica eluting with CH₂Cl₂:EtOAc (5:1 then 3:1) to afford additional sub-title compound as a solid (2.3 g).

R_f 0.50 (CH₂Cl₂, EtOAc (3:1))

- 15 ¹H NMR (CDCl₃) δ 1.33-1.68 (m, 6H), 1.78 (m, 1H), 3.02-3.23 (m, 2H), 4.48 (m, 1H), 4.93-5.11 (m, 4H), 7.18-7.49 (m, 24H)

(d) (R)-N²-(Diphenylacetyl)-(R,S)-N-[1-(4-phenylphenyl)ethyl]ornithine amide hydrochloride

- 20 Prepared according to the method described in Example 1(e) above from (R)-N⁵-(Cbz)-N²-(diphenylacetyl)-(R,S)-N-[1-(4-phenylphenyl)ethyl]-ornithine amide (1.2 g; from step (c) above), concentrated HCl (1 mL), MeOH (100 mL) and 10% Pd/C (w/w; 0.3 g) under 1 atmosphere of hydrogen, 18 hours reaction time. The resultant solution was filtered and
25 concentrated to afford the crude sub-title compound as a crushable foam (1.0 g) which was used directly in the next step.

mp 205-210°C

R_f 0.50 (System C)

- 30 ¹H NMR (CD₃OD) δ 1.44 (d, 3H), 1.58-1.97 (m, 4H), 2.84-2.98 (m, 2H), 4.48 (m, 1H), 4.98 (m, 1H), 5.13 and 5.19 (s, 1H), 7.12-7.61 (m,

19H)

(e) (R)-N²-(Diphenylacetyl)-(R,S)-N-[1-(4-phenylphenyl)ethyl]arginine amide hydrochloride

- 5 Prepared according to the method described in Example 6(e) above from (R)-N²-(diphenylacetyl)-(R,S)-N-[1-(4-phenylphenyl)ethyl]ornithine amide hydrochloride (0.50 g; 0.92 mmol; from step (d) above), 1H-pyrazole-1-carboxamide monohydrochloride (0.13 g; 0.92 mmol), TEA (0.37 g; 3.68 mmol) and DMF (7 mL), 18 hours reaction time. The resulting
10 heterogeneous solution was concentrated and chromatographed on silica eluting with MeOH:CHCl₃: conc. NH₄OH (3:6:1) and converted to the hydrochloride salt to afford the title compound as a white solid (0.22 g).

mp 100-105°C

R_f 0.50 (System D)

- 15 ¹H NMR (CD₃OD) δ 1.45 (d, 3H), 1.46-1.93 (m, 4H), 3.04-3.20 (m, 2H), 4.45 (m, 1H), 4.98 (m, 1H), 5.09 and 5.14 (s, 1H), 7.12-7.61 (m, 19H)

Example 28

- 20 (R)-N²-(Diphenylacetyl)-(R,S)-N-[1-(2-naphthyl)ethyl]arginine amide hydrochloride

(a) (R)-N²-(Boc)-N⁵-(Cbz)-(R,S)-N-[1-(2-naphthyl)ethyl]ornithine amide

- Prepared according to the method described in Example 4(b) above from
25 N^α-Boc-N^δ-Cbz-(R)-ornithine-o-nitrophenyl ester (3.0 g; 6.15 mmol; see Example 4(a) above), (R,S)-1-(2-naphthyl)ethylamine (1.2 g; 6.77 mmol) and CH₂Cl₂ (150 mL), 18 hours reaction time. The resultant yellow solution was concentrated and chromatographed on silica eluting with CH₂Cl₂:MeOH (95:5) to afford the sub-title compound as an oil (4.1 g).

- 30 R_f 0.40 (CH₂Cl₂:MeOH (95:5))

(b) (R)-N⁵-(Cbz)-(R,S)-N-[1-(2-Naphthyl)ethyl]ornithine amide hydrochloride

Prepared according to the method described in Example 1(b) above from (R)-N²-(Boc)-N⁵-(Cbz)-(R,S)-N-[1-(2-naphthyl)ethyl]ornithine amide (4.1 g; from step (a) above), EtOAc (100 mL) and HCl/EtOAc (75 mL), 18 hours reaction time. The resultant solution was concentrated to afford the crude sub-title compound as a crushable foam (3.6 g) which was used directly in the next step.

R_f 0.30 and 0.40 (CHCl₃:MeOH:AcOH (9:1:0.1))

10

(c) (R)-N⁵-(Cbz)-N²-(Diphenylacetyl)-(R,S)-N-[1-(2-naphthyl)ethyl]-ornithine amide

Prepared according to the method described in Example 1(d) above from crude (R)-N⁵-(Cbz)-(R,S)-N-[1-(2-naphthyl)ethyl]ornithine amide hydrochloride (3.6 g; 7.81 mmol; from step (b) above), 2-nitrophenyl diphenyl acetate (2.5 g; 7.81 mmol; see Example 1(c) above), TEA (2.0 g, 19.53 mmol) and CH₂Cl₂ (250 mL), 60 hours reaction time. The resultant yellow solution was concentrated and chromatographed on silica eluting with CH₂Cl₂ and EtOAc (5:1 then 3:1) to afford the sub-title compound as a solid (3.8 g).

20

R_f 0.50 (CH₂Cl₂:EtOAc (3:1))

¹H NMR (CDCl₃) δ 1.32-1.92 (m, 4H), 1.49 (d, 3H), 3.06 (m, 1H), 3.38 (m, 1H), 4.62-5.22 (m, 5H), 6.59 (m, 1H), 7.04-7.37 (m, 16H), 7.38-7.49 (m, 2H), 7.54-7.83 (m, 4H)

25

(d) (R)-N²-(Diphenylacetyl)-(R,S)-N-[1-(2-naphthyl)ethyl]ornithine amide hydrochloride

Prepared according to the method described in Example 1(e) above from (R)-N⁵-(Cbz)-N²-(diphenylacetyl)-(R,S)-N-[1-(2-naphthyl)ethyl]ornithine amide (3.8 g; from step (c) above), concentrated HCl (2 mL), MeOH (200

30

mL) and 10% Pd/C (w/w; 0.8 g) under 1 atmosphere of hydrogen, 18 hours reaction time. The resultant solution was filtered and concentrated to afford the crude sub-title compound as a crushable foam (3.3 g), which was used without further purification.

5 mp 65-75°C

R_f 0.50 (System C)

¹H NMR (CD₃OD) δ 1.47-1.53 (m, 3H), 1.54-1.96 (m, 4H), 2.82-2.97 (m, 2H), 4.48 (m, 1H), 5.03-5.18 (m, 2H), 7.08-7.49 (m, 13H), 7.68-7.85 (m, 4H)

10

(e) (R)-N²-(Diphenylacetyl)-(R,S)-N-[1-(2-naphthyl)ethyl]arginine amide hydrochloride

Prepared according to the method described in Example 6(e) above from (R)-N²-(diphenylacetyl)-(R,S)-N-[1-(2-naphthyl)ethyl]ornithine amide hydrochloride (0.50 g; 0.97 mmol; from step (d) above), 1H-pyrazole-1-carboxamide monohydrochloride (0.14 g, 0.97 mmol), TEA (0.39 g; 3.88 mmol) and DMF (7 mL), 18 hours reaction time. The resulting heterogeneous solution was concentrated and chromatographed on silica eluting with MeOH:CHCl₃: conc. NH₄OH (3:6:1) and converted to the hydrochloride salt to afford the title compound as a white solid (0.31 g).

20

mp 85-95°C

R_f 0.50 (System D)

¹H NMR (CD₃OD) δ 1.32-1.93 (m, 7H), 2.98-3.17 (m, 2H), 4.43 (m, 1H), 5.04-5.18 (m, 2H), 7.07-7.49 (m, 13H), 7.68-7.84 (m, 4H)

25

Example 29(R)-N²-(Diphenylacetyl)-(R)-N-[1-(1-naphthyl)ethyl]arginine amide hydrochloride5 (a) (R)-N²-(Boc)-N⁵-(Cbz)-(R)-N-[1-(1-Naphthyl)ethyl]ornithine amide

Prepared according to the method described in Example 4(b) above from N^α-Boc-N^δ-Cbz-(R)-ornithine-*o*-nitrophenyl ester (5.2 g; 10.6 mmol; see Example 4(a) above), (R)-1-(1-naphthyl)ethylamine hydrochloride (2.0 g; 11.7 mmol), and CH₂Cl₂ (150 mL), 48 hours reaction time. The resultant
10 yellow solution was concentrated to afford the crude sub-title compound as a solid (7.5 g) which was used directly in the next step.

R_f 0.40 (CH₂Cl₂:MeOH (95:5))

(b) (R)-N⁵-(Cbz)-(R)-N-[1-(1-Naphthyl)ethyl]ornithine amide hydrochloride

15 Prepared according to the method described in Example 1(b) above from crude (R)-N²-(Boc)-N⁵-(Cbz)-(R)-N-[1-(1-naphthyl)ethyl]ornithine amide (7.5 g; from step (a) above), EtOAc (150 mL) and HCl/EtOAc (75 mL), 6 hours reaction time. The resulting heterogeneous solution was diluted with Et₂O and the solids collected and dried to afford the sub-title
20 compound as a white solid (4.8 g).

R_f 0.40 (CHCl₃:MeOH:AcOH (9:1:0.1))

¹H NMR (CD₃OD) δ 1.36-1.52 (m, 2H), 1.58-1.90 (m, 5H), 2.92-3.10 (m, 2H), 3.91 (m, 1H), 4.74-5.02 (m, 3H), 5.88 (m, 1H), 7.18-7.37 (m, 4H), 7.38-7.61 (m, 5H), 7.76 (d, 1H), 7.87 (d, 1H), 8.08 (d, 1H)

25

(c) (R)-N⁵-(Cbz)-N²-(Diphenylacetyl)-(R)-N-[1-(1-naphthyl)ethyl]-ornithine amide

Prepared according to the method described in Example 1(d) above from (R)-N⁵-(Cbz)-(R)-N-[1-(1-naphthyl)ethyl]ornithine amide hydrochloride
30 (4.8 g; 10.46 mmol; from step (b) above), 2-nitrophenyl diphenyl acetate

(3.4 g; 10.46 mmol; see Example 1(c) above), TEA (2.7 g; 26.15 mmol) and CH_2Cl_2 (200 mL), 60 hours reaction time. The resultant heterogeneous solution was filtered. The filter cake was washed with Et_2O and dried to afford the sub-title compound as a white solid (3.4 g).

5 R_f 0.70 (CH_2Cl_2 :EtOAc (3:1))

^1H NMR (CDCl_3) δ 1.22-1.78 (m, 7H), 2.96 (m, 1H), 3.32 (m, 1H), 4.52-4.97 (m, 4H), 5.82 (m, 1H), 6.59 (d, 1H), 7.03 (d, 1H), 7.08-7.52 (m, 19H), 7.69 (d, 1H), 7.80 (d, 1H), 7.98 (d, 1H)

10 (d) (R)-N²-(Diphenylacetyl)-(R)-N-[1-(1-naphthyl)ethyl]ornithine amide

Prepared according to the method described in Example 6(d) above from (R)-N²-(Cbz)-N²-(diphenylacetyl)-(R)-N-[1-(1-naphthyl)ethyl]ornithine amide (1.0 g; 1.63 mmol; from step (c) above), trimethylsilyliodide (0.36 g, 1.79 mmol) and CH_3CN (60 mL) at 0°C, 3.5 hours reaction time. The resultant heterogeneous solution was submitted to aqueous work up and chromatographed on silica eluting with CH_2Cl_2 :MeOH:conc. NH_4OH (88.5:10:1.5) to afford the sub-title compound as a solid (0.5 g).

R_f 0.50 (System C)

20 ^1H NMR (CD_3OD) δ 1.25-1.43 (m, 2H), 1.52-1.81 (m, 2H), 1.58 (d, 3H), 2.47 (t, 2H), 4.42 (m, 1H), 5.08 (s, 1H), 5.78 (q, 1H), 7.17-7.33 (m, 10H), 7.40-7.54 (m, 4H), 7.78 (d, 1H), 7.88 (d, 1H), 8.06 (d, 1H)

(e) (R)-N²-(Diphenylacetyl)-(R)-N-[1-(1-naphthyl)ethyl]arginine amide hydrochloride

25 Prepared according to the method described in Example 6(e) above from (R)-N²-(diphenylacetyl)-(R)-N-[1-(1-naphthyl)ethyl]ornithine amide (0.42 g; 0.88 mmol; step (d) above), 1H-pyrazole-1-carboxamide mono-hydrochloride (0.14 g; 0.88 mmol), TEA (0.18 g; 1.76 mmol) and DMF (8 mL), 18 hours reaction time. The resultant solution was concentrated and chromatographed on silica eluting with MeOH: CHCl_3 :conc. NH_4OH

30

(3:6:1) to afford the title compound as a white solid (0.38 g).

mp 128-135°C

R_f 0.50 (System D)

¹H NMR (CD₃OD) δ 1.37-1.85 (m, 4H), 1.58 (d, 3H), 2.94-3.14 (m, 2H), 4.43 (t, 1H), 5.11 (s, 1H), 5.81 (q, 1H), 7.15-7.33 (m, 10H), 7.38-7.56 (m, 4H), 7.78 (d, 1H), 7.88 (d, 1H), 8.06 (d, 1H)

Example 30

(R)-N²-[(R,S)-2-(4-Methoxyphenyl)phenylacetyl]-(R)-N-[1-(4-hydroxy-phenyl)ethyl]arginine amide acetate

(a) (R)-N²-(Boc)-(R)-N-[1-(4-hydroxyphenyl)ethyl]ornithine amide

To a solution of (R)-N²-(Boc)-N⁵-(Cbz)-(R)-N-[1-(4-hydroxyphenyl)-ethyl]ornithine amide (66.26 g; 139 mmol; see Example 4(b) above) in methanol (400 mL) was added 10% Pd/C (w/w; 3.53 g). After stirring for 18 h under 1 atmosphere of hydrogen the reaction was filtered through Celite to remove the catalyst and the filtrate was concentrated under reduced pressure to afford the sub-title compound as a white foam (43.2 g, 123 mmol).

R_f 0.2 (System B)

(b) (R)-N^ω,N^{ω'}-bis(Cbz)-N²-(Boc)-(R)-N-[1-(4-Hydroxyphenyl)ethyl]-arginine amide

To a solution of (R)-N²-(Boc)-(R)-N-[1-(4-hydroxyphenyl)ethyl]ornithine amide (11.47 g; 0.33 mmol; from step (a) above) in DMF (50 mL) was added N,N'-bis(Cbz)-S-methylisothiourea (11.8 g; 0.33 mmol). The solution was stirred overnight at room temperature followed by removal of the solvent under reduced pressure. The resultant oil was chromatographed on a plug of silica gel (7.5 cm x 12.5 cm) eluting first with CH₂Cl₂ (800 mL) to remove the higher R_f impurities. The eluent was

switched to EtOAc (600 mL) to elute the sub-title compound as a white foam (14.67 g).

R_f 0.45 (EtOAc:hexanes (1:1))

5 (c) (R)-N^w,N^{w'}-bis(Cbz)-(R)-N-[1-(4-Hydroxyphenyl)ethyl]arginine amide hydrochloride

A solution of (R)-N^w,N^{w'}-bis(Cbz)-N²-(Boc)-(R)-N-[1-(4-hydroxyphenyl)-ethyl]arginine amide (11.2 g; 16.4 mmol, from step (b) above) in EtOAc (300 mL) was treated with HCl/EtOAc (300 mL) and stirred overnight at
10 room temperature. The product precipitated as a white residue from which the solvents were decanted. To the residue was added methanol (100 mL) followed by diethyl ether (50 mL). This mixture was slurried and then concentrated at reduced pressure to afford the sub-title compound as a white crushable foam (10.2 g; 100%).

15 R_f 0.89 (EtOAc, CH₃OH, conc. NH₄OH (47:47:6))

(d) (R)-N^w,N^{w'}-bis(Cbz)-N²-[(R,S)-2-(4-Methoxyphenyl)phenylacetyl]-(R)-N-[1-(4-hydroxyphenyl)ethyl]arginine amide

(R)-N^w,N^{w'}-bis(Cbz)-(R)-N-[1-(4-Hydroxyphenyl)ethyl]arginine amide x
20 hydrochloride (0.5 g; 0.848 mmol; from step (c) above) was treated with (R,S)-2-(4-methoxyphenyl)-phenylacetylchloride (0.933 mmol; 1.1 eq.) in EtOAc (25 mL) and saturated bicarbonate solution (25 mL). The reaction was stirred for 1.5 h at room temperature. The organic layer was separated and washed with KHSO₄ solution (25 mL) and brine (50 mL).
25 The organics were then dried with Na₂SO₄ and concentrated to afford the sub-title compound as a white foam (650 mg).

R_f 0.65 (EtOAc:hexanes (1:1))

(e) (R)-N²-[(R,S)-2-(4-Methoxyphenyl)phenylacetyl]-(R)-N-[1-(4-hydroxyphenyl)ethyl]arginine amide acetate

To a solution of (R)-N^ω,N^{ω'}-bis(Cbz)-N²-[(R,S)-2-(4-methoxyphenyl)-phenylacetyl]-(R)-N-[1-(4-hydroxyphenyl)ethyl]arginine amide (700 mg; 0.99 mmol; from step (d) above) in AcOH (50 mL) was added 10% Pd/C (w/w; 100 mg). The reaction was stirred for 18 h under 1 atmosphere of hydrogen, and then filtered through Celite to remove the catalyst. The filtrate was concentrated under vacuum. The title compound was isolated as an off white solid (560 mg, 0.97 mmol) after milling in EtOAc:Et₂O (100 mL; 3:1).

R_f 0.52 (EtOAc:CH₃OH:conc. NH₄OH (47:47:6))

mp 136-142°C

¹H NMR (CD₃OD) δ 1.38 (d, 3H), 1.41-1.89 (m, 4H), 1.90 (s, 3H), 3.09 (m, 2H), 3.80 (s, 3H), 4.39 (m, 1H), 4.87 (m, 1H), 5.05 (s, 1H), 6.69 (d, 2H), 6.82 (m, 2H), 7.15 (m, 2H), 7.18-7.37 (m, 7H)

Example 31

(R)-N²-[(R,S)-2-(4-Methylphenyl)phenylacetyl]-(R)-N-[1-(4-hydroxyphenyl)ethyl]arginine amide acetate

20

(a) (R)-N⁵-(Cbz)-N²-[(R,S)-2-(4-Methylphenyl)phenylacetyl]-(R)-N-[1-(4-hydroxyphenyl)ethyl]ornithine amide

A biphasic solution of (R)-N⁵-(Cbz)-(R)-N-[1-(4-hydroxyphenyl)ethyl]-ornithine amide hydrochloride (371 mg ; 0.880 mmol; from Example 1(b) above) in EtOAc (10 mL) and saturated bicarbonate solution (10 mL) was treated with (R,S)-2-(4-methylphenyl)phenylacetyl chloride (0.880 mmol; 1.0 eq.) and stirred for 2 h at room temperature. The organics were then separated and washed with KHSO₄ solution and brine. The organic layer was dried with Na₂SO₄ and concentrated. The residue was crystallized from hot ethyl acetate to give the sub-title compound as a white solid (163

30

mg).

R_f 0.48 (EtOAc:hexanes (1:1))

¹H NMR (CD₃OD) δ 1.33 (d, 3H), 1.41-1.81 (m, 4H), 2.25 (s, 3H),
3.01 (m, 2H), 4.40 (m, 1H), 4.87 (m, 1H), 5.05 (s, 1H), 6.71 (d, 2H), 6.9-
5 7.37 (m, 12H)

(b) (R)-N²-[(R,S)-2-(4-Methylphenyl)phenylacetyl]-(R)-N-[1-(4-hydroxy-phenyl)ethyl]ornithine amide hydrochloride

Prepared in a similar fashion to Example 1(e) above. To a solution of (R)-
10 N⁵-(Cbz)-N²-[(R,S)-2-(4-methylphenyl)phenylacetyl]-(R)-N-[1-(4-hydroxyphenyl)ethyl]ornithine amide (160 mg; 0.262 mmol; from step (a) above) in methanol (100 mL) was added 2N HCl (5 mL) and 10 % Pd/C (w/w, 100 mg). The reaction was stirred under 1 atmosphere of hydrogen for 18 h. The reaction mixture was filtered through Celite and the filtrate
15 concentrated to afford the sub-title compound as a white foam (120 mg; 0.262 mmol).

R_f 0.20 (System B)

(c) (R)-N^ω,N^{ω'}-bis(Cbz)-N²-[(R,S)-2-(4-Methylphenyl)phenylacetyl]-(R)-N-[1-(4-hydroxyphenyl)ethyl]arginine amide

Prepared in a similar fashion to Example 1(f) above. A solution of (R)-
N²-[(R,S)-2-(4-methylphenyl)phenylacetyl]-(R)-N-[1-(4-hydroxyphenyl)-ethyl]ornithine amide hydrochloride (120 mg; 0.262 mmol; from step (b) above) in DMF (15 mL) was treated with N,N'-bis(Cbz)-S-methylisothiourea (0.120 g; 0.335 mmol) and DiPEA (2 mL). The
25 reaction was stirred for 18 h at room temperature. The solvents were removed at reduced pressure and the resulting residue was chromatographed on silica gel. Eluting first with CH₂Cl₂ and then EtOAc afforded the sub-title compound as a white foam (160 mg).

30 R_f 0.65 (EtOAc:hexanes (1:1))

(d) (R)-N²-[(R,S)-2-(4-Methylphenyl)phenylacetyl]-(R)-N-[1-(4-hydroxyphenyl)ethyl]arginine amide acetate

To a solution of (R)-N^ω,N^{ω'}-bis(Cbz)-N²-[(R,S)-2-(4-methylphenyl)phenylacetyl]-(R)-N-[1-(4-hydroxyphenyl)ethyl]arginine amide (122 mg; 0.183 mmol; from step (c) above) in AcOH (50 mL) was added 10% Pd/C (w/w; 100 mg). The reaction was stirred for 18 h under 1 atmosphere of hydrogen, the reaction mixture was filtered through Celite and the filtrate concentrated to afford the title compound as a white foam (101 mg).

R_f 0.50 (EtOAc:CH₃OH:conc. NH₄OH (47:47:6))

mp 110-116°C

¹H NMR (CD₃OD) δ 1.33 (d, 3H), 1.41-1.89 (m, 4H), 1.90 (s, 3H), 2.26 (s, 3H), 3.09 (m, 2H), 4.38 (m, 1H), 4.87 (m, 1H), 5.02 (s, 1H), 6.69 (d, 2H), 6.9-7.37 (m, 11H)

Example 32

(R)-N²-[(R,S)-2-(4-Chlorophenyl)phenylacetyl]-(R)-N-[1-(4-hydroxyphenyl)ethyl]arginine amide hydrochloride

(a) (R)-N^ω,N^{ω'}-bis(Cbz)-N²-[(R,S)-2-(4-Chlorophenyl)phenylacetyl]-(R)-N-[1-(4-hydroxyphenyl)ethyl]arginine amide

(R)-N^ω,N^{ω'}-bis(Cbz)-(R)-N-[1-(4-Hydroxyphenyl)ethyl]arginine amide x hydrochloride (0.5 g; 0.848 mmol; see Example 30(c) above) was treated with (R,S)-2-(4-chlorophenyl)phenylacetylchloride (1.27 mmol; 1.5 eq.) in ethyl acetate (25 mL) and saturated bicarbonate solution (25 mL). The reaction was stirred for 1.5 h at room temperature. The organic layer was separated and washed with KHSO₄ (25 mL) and brine (50 mL). The organics were then dried with Na₂SO₄ and concentrated to afford the sub-title compound as a white foam (674 mg; 100%).

R_f 0.80 (System B)

(b) (R)-N²-[(R,S)-2-(4-Chlorophenyl)phenylacetyl]-(R)-N-[1-(4-hydroxyphenyl)ethyl]arginine amide hydrochloride

To a solution of (R)-N^w,N^{w'}-bis(Cbz)-N²-[(R,S)-2-(4-Chlorophenyl)phenylacetyl]-(R)-N-[1-(4-hydroxyphenyl)ethyl]arginine amide (670 mg; 0.84 mmol; from step (a) above) in CH₃OH (50 mL) was added 2N HCl (1.0 mL) and 10% Pd/C (w/w; 100 mg). The reaction was stirred for 18 h under 1 atmosphere of hydrogen, and then filtered through Celite to remove the catalyst and the filtrate was concentrated under vacuum. The title compound was isolated as a off white solid (400 mg, 0.72 mmol) after milling in EtOAc:Et₂O (100 mL; 3:1).

R_f 0.51 (EtOAc, CH₃OH, conc. NH₄OH (47:47:6))

mp 120-125°C

¹H NMR (CD₃OD) δ 1.33 (d, 3H), 1.41-1.89 (m, 4H), 3.08 (m, 2H), 4.39 (m, 1H), 4.90 (m, 1H), 5.08 (s, 1H), 6.70 (d, 2H), 7.05 (d, 2H), 7.1-7.4 (m, 9H)

Example 33

(R)-N²-(4,4'-Dichlorodiphenylacetyl)-(R)-N-[1-(4-hydroxyphenyl)ethyl]arginine amide hydrochloride

(a) (R)-N^w,N^{w'}-bis(Cbz)-N²-(4,4'-Dichlorodiphenylacetyl)-(R)-N-[1-(4-hydroxyphenyl)ethyl]arginine amide

To a biphasic solution of (R)-N^w,N^{w'}-bis(Cbz)-(R)-N-[1-(4-hydroxyphenyl)ethyl]arginine amide hydrochloride (1.26 g; 2.1 mmol; from Example 30(c) above) in EtOAc and saturated NaHCO₃ solution was added 4,4'-dichlorodiphenylacetyl chloride. The reaction mixture was stirred for 3.5 h at room temperature. The organics were separated, washed with KHSO₄ solution (100 mL) and brine (150 mL), dried with Na₂SO₄, filtered and concentrated to afford the sub-title compound as a white foam (920 mg; 1.15 mmol).

R_f 0.80 (System B)

(b) (R)-N²-(4,4'-Dichlorodiphenylacetyl)-(R)-N-[1-(4-hydroxyphenyl)ethyl]-arginine amide hydrochloride

- 5 To a solution of (R)-N^ω,N^{ω'}-bis(Cbz)-N²-(4,4'-dichlorodiphenylacetyl)-(R)-N-[1-(4-hydroxyphenyl)ethyl]arginine amide (800 mg; 1.00 mmol; from step (a) above) in CH₃OH (40 mL) was added 2N HCl (1 mL) and 10% Pd/C (w/w; 100 mg). The reaction was stirred for 18 h under 1 atmosphere of hydrogen. The reaction was filtered through Celite and the
10 filtrate concentrated to afford the title compound as an off white solid (436 mg; 0.735 mmol) after milling in EtOAc:Et₂O (100 mL; 3:1).

R_f 0.22 (EtOAc:CH₃OH:conc. NH₄OH (47:47:6))

mp 141-146°C

- ¹H NMR (CD₃OD) δ 1.32 (d, 3H), 1.41-1.89 (m, 4H), 3.08 (m, 2H),
15 4.35 (m, 1H), 4.90 (m, 1H), 5.11 (s, 1H), 6.71 (d, 2H), 7.1 (d, 2H), 7.15-7.4 (m, 8H).

Example 34

- (R)-N²-[(R,S)-2-(4-Hydroxyphenyl)phenylacetyl]-(R)-N-[1-(4-hydroxy-phenyl)ethyl]arginine amide hydrochloride
20

(a) N^ω,N^{ω'}-bis(Cbz)- N²-[(R,S)-2-(4-Hydroxyphenyl)phenylacetyl]-(R)-N-[1-(4-hydroxyphenyl)ethyl]arginine amide

- To a solution of (R)-N^ω,N^{ω'}-bis(Cbz)-(R)-N-[1-(4-hydroxyphenyl)ethyl]-arginine amide hydrochloride (0.821 g; 1.39 mmol; see Example 30(c) above) in THF (40 mL) was added (R,S)-2-(4-hydroxyphenyl)phenylacetic acid (0.188 g; 1.39 mmol), BOP (0.62 g; 1.39 mmol), HOBT (0.188 g; 1.39 mmol) and DiPEA (0.48 mL; 2.78 mmol). The reaction was stirred overnight at room temperature, followed by removal of the THF under
30 vacuum. The residues were taken up in ethyl acetate (100 mL) and

washed with KHSO₄ solution (100 mL) and brine (150 mL). The organics were dried with Na₂SO₄, filtered and concentrated to give the sub-title compound as a white foam (480 mg; 0.566 mmol).

R_f 0.60 (EtOAc:hexanes (1:1))

5

(b) (R)-N²-[(R,S)-2-(4-hydroxyphenyl)phenylacetyl]-(R)-N-[1-(4-hydroxyphenyl)ethyl]arginine amide hydrochloride

To a solution of (R)-N^ω,N^{ω'}-bis(Cbz)-N²-[(R,S)-2-(4-hydroxyphenyl)-phenylacetyl]-(R)-N-[1-(4-hydroxyphenyl)ethyl]arginine amide (480 mg; 0.566 mmol; from step (a) above) in methanol (50 mL) was added conc. HCl (5 drops) and 10% Pd/C (w/w; 40 mg). The reaction was stirred for 20 h under 1 atmosphere of hydrogen. The reaction mixture was then filtered through Celite and the filtrate concentrated to afford the title compound as an off white solid (305 mg; 0.565 mmol) after milling in EtOAc:Et₂O (70 mL; 3:1).

10
15

R_f 0.35 (EtOAc:CH₃OH:conc. NH₄OH (6:3:1))

mp 129-136°C

¹H NMR (CD₃OD) δ 1.34 (d, 3H), 1.41-1.85 (m, 4H), 3.08 (m, 2H), 4.38 (m, 1H), 4.85 (m, 1H), 5.11 (s, 1H), 6.71 (d, 2H), 7.05 (d, 2H), 7.15-7.4 (m, 9H)

20

Example 35

(R)-N^ω-(Ethyl)-N²-(diphenylacetyl)-(R)-N-[1-(4-methoxyphenyl)ethyl]-arginine amide hydrochloride

25

(a) (R)-N⁵-(Benzoylaminothiocarbonyl)-N²-(diphenylacetyl)-(R)-N-[1-(4-methoxyphenyl)ethyl]ornithine amide

To a solution of (R)-N²-(diphenylacetyl)-(R)-N-[1-(4-hydroxyphenyl)-ethyl]ornithine amide (2.0 g; 4.35 mmol; see Example 4(e) above) in CH₂Cl₂ (50 mL) was added benzoylisothiocyanate (0.59 mL; 4.35 mmol).

30

The reaction mixture was stirred for 24 h at room temperature. The reaction was then concentrated *in vacuo* and the residue dissolved in EtOAc. The precipitated product, produced by addition of Et₂O to the EtOAc solution, was collected and dried to afford 2.25 g (83%) of the sub-
5 title compound as a white solid. The resultant material was used without further characterization.

$R_f = 0.80$ (System B)

(b) (R)-N⁵-(Aminothiocabonyl)-N²-(diphenylacetyl)-(R)-N-[1-(4-
10 methoxyphenyl)ethyl]ornithine amide
(R)-N⁵-(Benzoylaminothiocabonyl)-N²-(diphenylacetyl)-(R)-N-[1-(4-methoxyphenyl)ethyl]ornithine amide (2.25 g; 3.6 mmol; from step (a) above), methanol (250 mL), water (250 mL) and K₂CO₃ (1.49 g; 10.8 mmol) were combined and stirred for 24 h at room temperature. The
15 reaction mixture was then partitioned between EtOAc (250 mL) and brine (250 mL). The EtOAc layer was separated and washed with brine, dried over Na₂SO₄ and concentrated *in vacuo* to afford 1.86 g (99%) of the sub-
title compound as a white foam.

R_f 0.55 (System B)

20 ¹H NMR (CD₃OD) δ 1.38 (d, 3H), 1.47 (m, 2H), 1.52 (m, 1H), 1.77 (m, 1H), 3.4 (m, 2H), 3.76 (s, 3H), 4.42 (m, 1H), 4.90 (q, 1H), 5.07 (s, 1H), 6.85 (d, 2H), 7.18 (d, 2H), 7.19-7.4 (m, 10H)

(c) (R)-N⁵-[Methylthio(iminomethyl)]-N²-(diphenylacetyl)-(R)-N-[1-(4-
25 methoxyphenyl)ethyl]ornithine amide hydroiodide

A solution of (R)-N⁵-(aminothiocabonyl)-N²-(diphenylacetyl)-(R)-N-[1-(4-methoxyphenyl)ethyl]ornithine amide (1.46g; 2.81 mmol; from step (b) above) and iodomethane (0.21 mL; 3.38 mmol) in CH₂Cl₂ (40 mL) and CH₃OH (40 mL) was stirred for 18 h at room temperature. The reaction
30 was concentrated *in vacuo* and the residue was dissolved in a minimal

amount of CH₃OH. To this solution was added EtOAc to initiate crystallization. 1.38 g (75%) of the sub-title compound was collected, which was used in the next step without further characterization.

R_f 0.15 (System B)

5

(d) (R)-N⁵-(Cbz)-N⁵-[Methylthio(Cbz-iminomethyl)]-N²-(diphenylacetyl)-
(R)-N-[1-(4-methoxyphenyl)ethyl]ornithine amide

(R)-N⁵-[Methylthio(iminomethyl)]-N²-(diphenylacetyl)-(R)-N-[1-(4-methoxyphenyl)ethyl]ornithine amide hydroiodide (1.38 g; 2.09 mmol; 10 from step (c) above), CH₂Cl₂ (100 mL), Cbz-Cl (0.75 mL; 5.22 mmol), water (100 mL) and K₂CO₃ (1.16 g; 8.36 mmol) were combined and stirred for 18 h at room temperature. The organic layer was separated and washed with KHSO₄ solution (twice), NaHCO₃ solution (twice) and brine (twice), dried over Na₂SO₄ and concentrated *in vacuo*. The residue was 15 chromatographed on silica column eluting with hexanes:EtOAc (3:1). Fractions containing the desired product were combined and concentrated *in vacuo* to afford 0.65 g (39%) of the sub-title compound. The material was used without further characterization.

R_f 0.85 (CH₂Cl₂:CH₃OH (9:1))

20

(e) (R)-N⁵-(Cbz)-N⁵-[Ethylamino(Cbz-iminomethyl)]-N²-(diphenyl-
acetyl)-(R)-N-[1-(4-methoxyphenyl)ethyl]ornithine amide

A solution of (R)-N⁵-(Cbz)-N⁵-[methylthio(Cbz-iminomethyl)]-N²-(diphenylacetyl)-(R)-N-[1-(4-methoxyphenyl)ethyl]ornithine amide (0.5 g; 25 0.63 mmol; from step (d) above) and ethylamine (70% wt. in water; 0.08 mL; 0.94 mmol) in DMF (10 mL) was stirred for 1 h at room temperature. The DMF was removed *in vacuo* and the residue dissolved in EtOAc. The EtOAc solution was washed with KHSO₄ solution, then 0.5 N NaOH solution and then brine, dried over Na₂SO₄ and concentrated *in vacuo* to 30 afford 0.33 g of the sub-title compound. The material was used directly

in the next step.

(f) (R)-N^ω-(Ethyl)-N²-(diphenylacetyl)-(R)-N-[1-(4-methoxyphenyl)-ethyl]arginine amide hydrochloride

- 5 To a solution of (R)-N⁵-(Cbz)-N⁵-[ethylamino(Cbz-imino)]-N²-(diphenylacetyl)-(R)-N-[1-(4-methoxyphenyl)ethyl]ornithine amide (0.21 g; 0.30 mmol; from step (e) above) in CH₃OH (30 mL) was added concentrated HCl (2 drops) and 10% Pd/C (w/w; 0.050 g). The reaction mixture was stirred for 18 h under 1 atmosphere of hydrogen at room temperature and
10 filtered through celite. The filtrate was concentrated *in vacuo* to afford 0.15 g (90%) of the title compound.

R_f 0.52 (EtOAc:CH₃OH:NH₄OH (47:47:6))

- ¹H NMR (CD₃OD) δ 1.17 (t, 3H), 1.38 (d, 2H), 1.50 (m, 2H), 1.59 (m, 1H), 1.80 (m, 1H), 3.11 (m, 2H), 3.17 (q, 2H), 3.75 (s, 3H), 4.40 (m, 1H),
15 4.85 (q, 1H), 5.13 (s, 1H), 6.81 (d, 2H), 7.19 (d, 2H), 7.22-7.38 (m, 10H)

Example 36

(R)-N^ω-(Benzyl)-N²-(diphenylacetyl)-(R)-N-[1-(4-methoxyphenyl)ethyl]-arginine amide hydrochloride

20

- (a) (R)-N⁵-(Cbz)-N⁵-[Benzylamino(Cbz-iminomethyl)]-N²-(diphenylacetyl)-(R)-N-[1-(4-methoxyphenyl)ethyl]ornithine amide

- A solution of (R)-N⁵-(Cbz)-N⁵-[methylthio(Cbz-iminomethyl)]-N²-(diphenylacetyl)-(R)-N-[1-(4-methoxyphenyl)ethyl]ornithine amide (0.25
25 g, 0.312 mmol; see Example 35(d) above) and benzylamine (0.05 mL; 0.476 mmol) in DMF (5 mL) was stirred overnight at room temperature. The DMF was removed *in vacuo* and the residue dissolved in EtOAc. The EtOAc solution was washed with KHSO₄ solution, 0.5 N NaOH solution and brine, dried over Na₂SO₄ and concentrated *in vacuo* to afford 0.25 g
30 of the sub-title compound. The material was used directly in the next step.

R_f 0.74 (EtOAc:hexanes (1:1))

¹H NMR (CD₃OD) δ 1.35 (d, 3H), 1.45-1.79 (m, 4H), 3.42 (m, 2H), 3.64 (m, 3H), 4.29 (s, 2H), 4.38 (m, 1H), 4.85 (m, 1H), 5.01 (s, 4H), 5.08 (s, 1H), 6.79 (d, 2H), 7.05 (d, 2H), 7.15-7.4 (m, 27H)

5

(b) (R)-N^ω-(Benzyl)-N²-(diphenylacetyl)-(R)-N-[1-(4-methoxyphenyl)-ethyl]arginine amide hydrochloride

To a solution of (R)-N⁵-(Cbz)-N⁵-[benzylamino(Cbz-iminomethyl)]-N²-(diphenylacetyl)-(R)-N-[1-(4-methoxyphenyl)ethyl]ornithine amide (0.248 g, 0.288 mmol; from step (a) above) in CH₃OH (50 mL) was added concentrated HCl (2 drops) and 10% Pd/C (w/w; 0.080 g). The reaction mixture was stirred overnight under 1 atmosphere of hydrogen at room temperature, filtered through Celite and the filtrate concentrated *in vacuo* to afford the title compound (0.168 g, 98%).

15 R_f 0.23 (EtOAc:CH₃OH:conc. NH₄OH (47:47:6))

mp 126-130°C

¹H NMR (CD₃OD) δ 1.32 (d, 3H), 1.41-1.89 (m, 4H), 3.11 (m, 2H), 3.71 (s, 3H), 4.31 (s, 2H), 4.35 (m, 1H), 4.90 (m, 1H), 5.10 (s, 1H), 6.81 (d, 2H), 7.15-7.4 (m, 17H)

20

Example 37

(R)-N^ω-(1-(4-hydroxyphenyl)ethyl)-N²-(diphenylacetyl)-(R)-N-[1-(4-hydroxyphenyl)ethyl]arginine amide

Hydrochloric acid (1 mL) and 10% Pd/C (w/w; 1.1 g) were added to a solution of (R)-N^ω,N^{ω'}-bis(Cbz)-N²-(diphenylacetyl)-(R)-N-[1-(4-hydroxyphenyl)ethyl]arginine amide (6.6 g; 8.7 mmol; see Example 4(f) above) in methanol. The reaction was stirred for 18 h under one atmosphere of hydrogen, filtered through Celite and the filtrate concentrated to afford an off-white foam. The material was applied to a column of silica (5 cm x 20 cm ht) and eluted with a mixture of CHCl₃:CH₃OH:conc. NH₄OH

30

(6:3:1). Fractions (5 mL each) were taken and analyzed by HPLC. Fractions containing the title compound were combined and concentrated to afford a white foam (12 mg). The HPLC method used above was conducted on a Microsorb MV Cyano column (25 cm x 4.6 mm) eluting
5 with water:CH₃CN:TFA (65:35:0.1) at a flow rate of 1 mL/min. While monitoring the eluent at 254 nm. The title compound was found to have a retention time of 9.16 min.

R_f 0.53 (System D)

mp 128-135°C

10 FAB MS m/z = 608

¹H NMR (CD₃OD) δ 1.35 (d, 3H), 1.45 (d, 3H), 1.51 (m, 2H), 1.60 (m, 1H), 1.72 (m, 1H), 3.10 (m, 2H), 4.38 (m, 1H), 4.62 (m, 1H), 4.90 (m, 1H), 5.12 (s, 1H), 6.71 (d, 2H), 6.78 (d, 2H), 7.08 (d, 2H), 7.12 (d, 2H), 7.2-7.4 (m, 18H)

15

Example 38

(R)-N²-(Diphenylacetyl)-(R,S)-N-[1-(4-(aminocarbonylmethyl)phenyl)-ethyl]arginine amide hydrochloride

20 (a) (R)-N⁵-(Cbz)-N²-(diphenylacetyl)-ornithine

1 N NaOH (75 mL) was added to a stirred suspension of (R)-N⁵-(Cbz)-ornithine hydrochloride (7.5 g; 25 mmol) in THF (114 mL). Once the starting material had dissolved, diphenylacetyl chloride (6.7 g; 26.3 mmol) was added. The reaction was stirred for 3 h at room temperature, then
25 made acidic with cold 1 N HCl and extracted with EtOAc (3 x 75 mL). The EtOAc extract was washed with brine, dried with Na₂SO₄, and concentrated to afford the crude product. Purification by flash chromatography on silica eluting with EtOAc:hexanes (1:1) afforded the sub-title compound (10.5 g; 91%).

30 R_f 0.22 (EtOAc:hexanes (1:1))

¹H NMR (CD₃OD) δ 1.53 (m, 2H), 1.71 (m, 1H), 1.79 (m, 1H), 3.09 (t, 2H), 4.40 (m, 1H), 5.05 (s, 2H), 5.09 (s, 1H), 7.12-7.45 (m, 15H).

(b) (R)-N⁵-(Cbz)-N²-(diphenylacetyl)-(R,S)-N-[1-(4-(aminocarbonylmethyl)phenyl)ethyl]ornithine amide

(R,S)-1-[4-(Aminocarbonylmethyl)phenyl]ethylamine (0.72 g; 4.04 mmol), BOP reagent (1.79 g; 4.04 mmol), HOBT (0.55 g; 4.04 mmol) and DiPEA (1.4 mL; 8.08 mmol) were added to a solution of (R)-N²-(diphenylacetyl)-N⁵-(Cbz)-ornithine (1.86 g; 4.04 mmol, from step (a) above) in THF (200 mL). The reaction was stirred overnight at room temperature and then concentrated *in vacuo*. The residue was dissolved in EtOAc (100 mL) and washed with KHSO₄ solution (100 mL), 0.5 N NaOH (100 mL) and brine (100 mL). The organics were separated dried with Na₂SO₄ and concentrated. The resulting crude product was crystallized from EtOAc to afford the sub-title compound as a white crystalline solid (0.560 g; 0.90 mmol; 22 %).

R_f 0.69 (System B)

(c) (R)-N²-(Diphenylacetyl)-(R,S)-N-[1-(4-(aminocarbonylmethyl)phenyl)ethyl]ornithine amide acetate

Acetic acid (3.2 mL; 56.6 mmol) and 10% Pd/C (w/w; 70 mg) were added to a stirred solution of (R)-N⁵-(Cbz)-N²-(diphenylacetyl)-(R,S)-N-[1-(4-(aminocarbonylmethyl)phenyl)ethyl]ornithine amide (0.56 g; 0.90 mmol; from step (b) above) in methanol (20 mL). The reaction was stirred for 4 h under one atmosphere of hydrogen, filtered through Celite to remove the catalyst and the filtrate was concentrated to afford the sub-title compound as a white solid (0.48 g; 0.84 mmol; 39%).

R_f 0.10 (System B)

(d) (R)-N²-(Diphenylacetyl)-(R,S)-N-[1-(4-(aminocarbonylmethyl)-phenyl)ethyl]arginine amide hydrochloride

A solution of (R)-N²-(diphenylacetyl)-(R,S)-N-[1-(4-(aminocarbonylmethyl)phenyl)ethyl]ornithine amide acetate (0.48 g; 0.88 mmol; from step 5 (c) above), 1H-pyrazole-1-carboxamidine x HCl (0.14 g; 0.97 mmol) and triethylamine (0.50 mL; 3.52 mmol) in DMF (15 mL) was stirred for 24 hours at room temperature. The reaction was concentrated *in vacuo* and the residue chromatographed on silica eluting with CHCl₃:methanol:conc. NH₄OH (6:3:1). Fractions containing the desired compound were 10 combined and concentrated to afford the title compound as a white solid (0.34 g; 0.60 mmol; 68%).

R_f 0.36 (System D)

¹H NMR (CD₃OD) δ 1.39 (m, 3H), 1.55-1.74 (m, 4H), 3.05 (m, 1H), 3.11 (m, 1H), 3.55 (m, 2H), 4.42 (q, 1H), 5.01 (s, 0.5H), 5.11 (s, 0.5), 15 7.15-7.45 (m, 14H)

Example 39

(R)-N²-(Diphenylacetyl)-(R,S)-N-[1-(4-(aminocarbonylaminomethyl)-phenyl)ethyl]arginine amide hydrochloride

20

(a) (R)-N⁵-(Cbz)-N²-(diphenylacetyl)-(R,S)-N-[1-(4-(aminocarbonylaminomethyl)phenyl)ethyl]ornithine amide

(R,S)-1-[4-(Aminocarbonylaminomethyl)phenyl]ethylamine (0.73 g; 3.77 mmol), BOP reagent (1.67 g; 3.77 mmol), HOBT (0.51 g; 3.77 mmol), 25 DiPEA (1.3 mL; 67.54 mmol) and DMF (15 mL) were added to a solution of (R)-N²-(diphenylacetyl)-N⁵-(Cbz)-ornithine (1.74 g; 3.77 mmol; see Example 38(a) above) in THF (200 mL). The reaction was stirred overnight at room temperature and then concentrated *in vacuo*. The residues were dissolved in EtOAc (100 mL) and washed with KHSO₄ solution (100 mL), 0.5 N NaOH (100 mL) and brine (100 mL). The 30

organics were separated, dried with Na_2SO_4 and concentrated to afford the sub-title compound as a pale yellow solid (1.24 g; 1.95 mmol; 52%).

R_f 0.59 (System B)

^1H NMR (CD_3OD) δ 1.45 (dd, 3H), 1.57 (m, 2H), 1.71 (m, 2H), 2.64 (m, 1H), 3.08 (m, 2H), 4.25 (s, 2H), 4.90 (q, 1H), 5.11 (s, 1H), 5.45 (s, 2H), 7.0-7.4 (m, 19H)

(b) (R)-N²-(Diphenylacetyl)-(R,S)-N-[1-(4-(aminocarbonylaminomethyl)-phenyl)ethyl]ornithine amide hydrochloride

10 TMSI (0.36 mL; 2.54 mmol) was added to a stirred solution of (R)-N⁵-(Cbz)-N²-(diphenylacetyl)-(R,S)-N-[1-(4-(aminocarbonylaminomethyl)-phenyl)ethyl]ornithine amide (1.24 g; 1.95 mmol; from step (a) above) in CH_3CN (20 mL) and CH_2Cl_2 (20 mL). The resultant solution was stirred at room temperature for 1.5 h and then quenched with 1 N HCl (10 mL).
15 The sub-title compound crystallized from the solution as a white solid (0.52 g; 1.04 mmol; 53%).

R_f 0.10 (System B)

(c) (R)-N²-(Diphenylacetyl)-(R,S)-N-[1-(4-(aminocarbonylaminomethyl)-phenyl)ethyl]arginine amide hydrochloride

20 A solution of (R)-N²-(diphenylacetyl)-(R,S)-N-[1-(4-(aminocarbonylaminomethyl)phenyl)ethyl]ornithine amide hydrochloride (0.52 g; 1.04 mmol; from step (b) above), 1H-pyrazole-1-carboxamidine x HCl (0.152 g; 1.04 mmol) and triethylamine (0.58 mL; 4.15 mmol) in DMF (8 mL) was stirred for 24 hours at room temperature. The reaction was concentrated *in vacuo* and the residue chromatographed on silica eluting with $\text{CHCl}_3:\text{CH}_3\text{OH}:\text{conc. NH}_4\text{OH}$ (6:3:1). Fractions containing the desired compound were combined and concentrated to afford the title compound as a white solid (0.17 g; 0.30 mmol; 29%).

30 R_f 0.44 (System D)

¹H NMR (CD₃OD) δ 1.37 (m, 3H), 1.55-1.74 (m, 4H), 3.05 (m, 1H), 3.15 (m, 1H), 4.25 (s, 2H), 4.39 (q, 1H), 5.05 (s, 0.5H), 5.09 (s, 0.5), 7.0-7.4 (m, 14H)

5 Example 40

(R)-N²-(4,4'-Dichlorodiphenylacetyl)-(R,S)-N-[1-(4-(aminocarbonylmethyl)-phenyl)ethyl]arginine amide hydrochloride

(a) (R)-N⁵-(Cbz)-N²-(4,4'-Dichlorodiphenyl)-ornithine

10 2 N NaOH (200 mL) and 4,4'-dichlorodiphenylacetyl chloride (14.2 mmol) were added to a stirred solution of (R)-N⁵-(Cbz)-ornithine hydrochloride (4.73 g; 15.6 mmol) in THF (250 mL). After stirring for 18 h, the organic layer was separated and concentrated. The resultant residue was dissolved in EtOAc and washed with 1 N HCl (125 mL) and brine (125 mL). The
15 organics were separated, dried with Na₂SO₄ and concentrated to afford the sub-title compound as a yellow foam (4.79 g; 9.05 mmol; 64%).

R_f 0.10 (System B)

(b) (R)-N⁵-(Cbz)-N²-(4,4'-dichlorodiphenylacetyl)-(R,S)-N-[1-(4-(amino-
20 carbonylmethyl)phenyl)ethyl]ornithine amide

(R,S)-1-[4-(aminocarbonylmethyl)phenyl]ethylamine (0.72 g; 4.04 mmol), BOP reagent (1.79 g; 4.04 mmol), HOBt (0.55 g; 4.04 mmol) and DiPEA (1.4 mL; 8.08 mmol) were added to a solution of (R)-N²-(4,4'-dichlorodiphenylacetyl)-N⁵-(Cbz)-ornithine (2.14 g; 4.04 mmol; from step
25 (a) above) in THF (200 mL). The reaction was stirred overnight at room temperature and then concentrated *in vacuo*. The residue was dissolved in EtOAc (100 mL) and washed with KHSO₄ solution (100 mL), 0.5 N NaOH (100 mL) and brine (100 mL). The organics were separated, dried with Na₂SO₄, and concentrated. The crude product was crystallized from
30 EtOAc to afford the sub-title as a white crystalline solid (0.88 g; 1.27

mmol, 34%).

R_f 0.69 (System B)

5 (c) (R)-N²-(4,4'-Dichlorodiphenylacetyl)-(R,S)-N-[1-(4-(aminocarbonylmethyl)phenyl)ethyl]ornithine amide acetate

Acetic acid (3.2 mL; 56.6 mmol) and 10% Pd/C (w/w; 70 mg) were added to a stirred solution of (R)-N⁵-(Cbz)-N²-(4,4'-dichlorodiphenylacetyl)-(R,S)-N-[1-(4-(aminocarbonylmethyl)phenyl)ethyl]ornithine amide (0.88 g; 1.27 mmol; from step (b) above) in methanol (20 mL). The reaction mixture
10 was stirred for 4 h under one atmosphere of hydrogen, filtered through Celite to remove the catalyst and the filtrate was concentrated *in vacuo* to afford the sub-title compound as a white solid (0.56 g; 0.98 mmol; 44%).

R_f 0.10 (System B)

15 (d) (R)-N²-(4,4'-Dichlorodiphenylacetyl)-(R,S)-N-[1-(4-(aminocarbonylmethyl)phenyl)ethyl]arginine amide hydrochloride

A solution of (R)-N²-(4,4'-dichlorodiphenylacetyl)-(R,S)-N-[1-(4-(aminocarbonylmethyl)phenyl)ethyl]ornithine amide acetate (0.55 g; 0.89 mmol; from step (c) above), 1H-pyrazole-1-carboxamide x HCl (0.14 g; 0.98 mmol) and triethylamine (0.50 mL; 3.56 mmol) in DMF (15 mL) was
20 stirred for 24 hours at room temperature. The reaction was concentrated *in vacuo* and the residue chromatographed on silica eluting with CHCl₃:methanol:conc. NH₄OH (6:3:1). Fractions containing the desired compound were combined and concentrated to afford the title compound
25 as a white solid (0.31 g; 0.49 mmol; 55%).

R_f 0.30 (System D)

¹H NMR (CD₃OD) δ 1.39 (m, 3H), 1.49-1.74 (m, 4H), 3.06 (m, 1H), 3.15 (m, 1H), 3.50 (m, 2H), 4.41 (q, 1H), 5.08 (s, 0.5H), 5.12 (s, 0.5), 7.20-7.37 (m, 12H)

Example 41

(R)-N²-(4,4'-Dichlorodiphenylacetyl)-(R,S)-N-[1-(4-(aminocarbonylamino-methyl)phenyl)ethyl]arginine amide hydrochloride

- 5 (a) (R)-N⁵-(Cbz)-N²-(4,4'-dichlorodiphenylacetyl)-(R,S)-[1-(4-(amino-carbonylaminomethyl)phenyl)ethyl]ornithine amide
(R,S)-1-[4-(Aminocarbonylaminomethyl)phenyl]ethylamine (0.73 g; 3.77 mmol), BOP reagent (1.67 g; 3.77 mmol), HOBT (0.51 g; 3.77 mmol), DiPEA (1.3 mL, 67.54 mmol) and DMF (20 mL) were added to a solution
10 of (R)-N²-(4,4'-dichlorodiphenylacetyl)-N⁵-(Cbz)-ornithine (1.99 g; 3.77 mmol; see Example 40(a) above) in THF (200 mL). The reaction was stirred for 18 h at room temperature and then concentrated *in vacuo*. The residues were dissolved in EtOAc (100 mL) and washed with KHSO₄ solution (100 mL), 0.5 N NaOH (100 mL) and brine (100 mL). The
15 organics were separated, dried with Na₂SO₄ and concentrated to give the sub-title compound as a pale yellow solid (1.60 g; 2.27 mmol; 60%).

R_f 0.55 (System B)

¹H NMR (CD₃OD) δ 1.45 (dd, 3H), 1.55 (m, 2H), 1.74 (m, 2H), 2.6 (m, 1H), 3.04 (m, 2H), 4.22 (s, 2H), 4.90 (q, 1H), 5.01 (s, 1H), 5.50 (s,
20 2H), 7.0-7.4 (m, 17H)

(b) (R)-N²-(4,4'-Dichlorodiphenylacetyl)-(R,S)-N-[1-(4-(aminocarbonyl-aminomethyl)phenyl)ethyl]ornithine amide hydrochloride

- TMSI (0.42 mL; 2.95 mmol) was added to a stirred solution of (R)-N⁵-(Cbz)-N²-(4,4'-dichlorodiphenylacetyl)-(R,S)-N-[1-(4-(aminocarbonyl-aminomethyl)phenyl)ethyl]ornithine amide (1.6 g; 2.27 mmol; from step
25 (a) above) in CH₃CN (20 mL) and CH₂Cl₂ (20 mL). The reaction was stirred at room temperature for 1.5 h. and then quenched with 1 N HCl (10 mL). The sub-title compound crystallized from the solution as a white
30 solid (0.52 g, 0.91 mmol, 41%).

R_f 0.10 (System B)

(c) (R)-N²-(4,4'-Dichlorodiphenylacetyl)-(R,S)-N-[1-(4-(aminocarbonylaminomethyl)phenyl)ethyl]arginine amide hydrochloride

- 5 A solution of (R)-N²-(4,4'-dichlorodiphenylacetyl)-(R,S)-N-[1-(4-(aminocarbonylaminomethyl)phenyl)ethyl]ornithine amide x HCl (0.52 g; 0.91 mmol; from step (b) above), 1H-pyrazole-1-carboxamidine x HCl (0.134 g; 0.91 mmol) and triethylamine (0.51 mL; 3.64 mmol) in DMF (8 mL) was stirred for 24 h at room temperature. The reaction was concentrated
10 *in vacuo* and the residue chromatographed on silica eluting with CHCl₃:methanol:conc. NH₄OH (6:3:1). Fractions containing the desired compound were combined and concentrated to afford the title compound as a white solid (0.142 g; 0.218 mmol; 24%).

R_f 0.43 (System D)

- 15 ¹H NMR (CD₃OD) δ 1.39 (m, 3H), 1.50-1.77 (m, 4H), 3.05 (m, 1H), 3.15 (m, 1H), 4.26 (s, 2H), 4.41 (q, 1H), 4.90 (q, 1H), 5.01 (s, 0.5H), 5.11 (s, 0.5), 7.0-7.4 (m, 12H)

Example 42

- 20 The title compounds of Examples 1 to 41 were tested in Test A above and were all found to exhibit an IC₅₀ value of less than 5.0 μM (Y₁ receptors).

Abbreviations

- 25 ACE = angiotensin-converting enzyme
Boc = t-butoxycarbonyl
BOP = 1-benzotriazolyloxytris(dimethylamino)phosphonium
 hexafluorophosphate
Cbz = benzyloxycarbonyl
30 dec. = decomposed

	DiPEA =	diisopropylethylamine
	DMF =	<i>N,N</i> -dimethylformamide
	DMSO =	dimethylsulphoxide
	EDC =	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
5	Et ₂ O =	diethyl ether
	EtOAc =	ethyl acetate
	HCl =	hydrochloric acid
	x HCl =	hydrochloride salt
	HCl/EtOAc =	EtOAc saturated with hydrogen chloride
10	HCl/MeOH =	MeOH saturated with hydrogen chloride
	HOAc =	acetic acid
	HOBT =	<i>N</i> -hydroxybenzotriazole
	MeOH =	methanol
	NMR =	nuclear magnetic resonance
15	NPY =	neuropeptide Y
	Pd/C =	palladium on carbon
	PE =	polyethylene
	TEA =	triethylamine
	TLC =	thin layer chromatography
20	THF =	tetrahydrofuran
	TMSI =	trimethylsilyl iodide

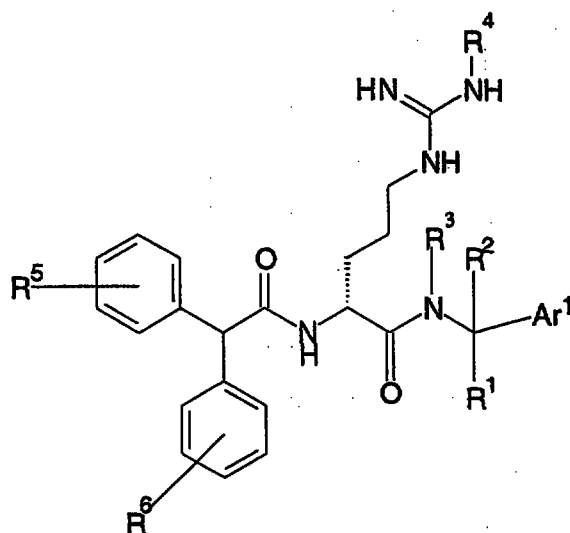
Claims



1. A compound of formula I,

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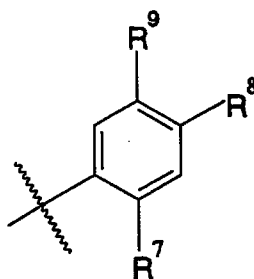


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wherein

Ar¹ represents a structural fragment of the formula

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25 or represents 1- or 2-naphthyl, which latter group is optionally substituted by one or more substituent selected from OH, halo or C₁₋₇ alkoxy;

R¹ represents C(O)NH₂, C₁₋₄ alkyl (optionally substituted or terminated by one or more substituent selected from hydroxy or amino), or, together with R⁷ (in Ar¹), forms C₂₋₃ alkylene;

30 R⁴ represents H, C₁₋₇ alkyl or C₁₋₄ alkylphenyl (in which latter group,



the phenyl group is optionally substituted by one or more substituent selected from OH or C₁₋₄ alkoxy);

R⁵ and R⁶ independently represent H, OH, C₁₋₄ alkyl, C₁₋₄ alkoxy or halo;

R⁷ represents H, OH or, together with R¹, forms C₂₋₃ alkylene;

5 R⁸ represents H, halo, OH, C₁₋₇ alkoxy, phenyl, phenoxy, benzyloxy, -(CH₂)_nC(O)N(R¹⁰)R¹¹, -(CH₂)_nN(H)C(O)N(R¹⁰)R¹¹ or -O(CH₂)_nC(O)OR¹⁰;

R⁹ represents H, halo, OH or C₁₋₇ alkoxy;

R², R³, R¹⁰ and R¹¹ independently represent H or C₁₋₇ alkyl; and

n represents 1, 2, 3 or 4;

10 or a pharmaceutically acceptable derivative thereof.

2. A compound of formula I as claimed in Claim 1, wherein R¹ represents C(O)NH₂, CH₂OH, ethyl or methyl.

15 3. A compound of formula I as claimed in Claim 2, wherein R¹ represents methyl.

4. A compound of formula I as claimed in any one of the preceding claims, wherein R² represents H.

20

5. A compound of formula I as claimed in any one of the preceding claims, wherein R³ represents H or methyl.

6. A compound of formula I as claimed in any one of the preceding
25 claims, wherein R⁴ represents H.

7. A compound of formula I as claimed in any one of the preceding claims, wherein R⁵ represents H, OH, halo, methyl or methoxy.

30 8. A compound of formula I as claimed in Claim 7, wherein R⁵ represents



H.

9. A compound of formula I as claimed in any one of the preceding claims, wherein R^6 represents H, OH, halo, methyl or methoxy.

5

10. A compound of formula I as claimed in Claim 9, wherein R^6 represents H.

11. A compound of formula I as claimed in any one of the preceding
10 claims, wherein R^7 represents H.

12. A compound of formula I as claimed in any one of the preceding claims, wherein R^8 represents OCH_3 , bromo, $-CH_2C(O)NH_2$, $-CH_2N(H)C(O)NH_2$ or OH.

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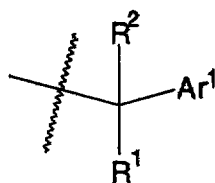
13. A compound of formula I as claimed in Claim 12, wherein R^8 represents OH.

14. A compound of formula I as claimed in any one of the preceding
20 claims, wherein R^9 represents H.

15. A compound of formula I as claimed in any one of the preceding claims, wherein R^{10} represents H.

25 16. A compound of formula I as claimed in any one of the preceding claims, wherein R^{11} represents H.

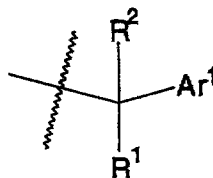
17. A compound of formula I as claimed in any one of the preceding claims, wherein the carbon atom which is in the α -position relative to Ar^1
30 in the fragment



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is in the R-configuration when R^1 represents C_{1-4} alkyl.

- 10 18. A compound of formula I as claimed in any one of Claims 1 to 16, wherein the carbon atom which is in the α -position relative to Ar^1 in the fragment



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is in the S-configuration when R^1 represents $C(O)NH_2$ or CH_2OH .

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19. A compound as claimed in Claim 1 which is:

- (*R*)- N^2 -(diphenylacetyl)-(*R*)-N-[1-(4-methoxyphenyl)ethyl]arginine amide;
 (*R*)- N^2 -(diphenylacetyl)-(*R,S*)-N-(1-phenylpropyl)arginine amide;
 (*R*)- N^2 -(diphenylacetyl)-(*R,S*)-N-[1-(4-hydroxyphenyl)ethyl]arginine amide;
 25 (*R*)- N^2 -(diphenylacetyl)-(*R*)-N-[1-(4-hydroxyphenyl)ethyl]arginine amide;
 (*R*)- N^2 -(diphenylacetyl)-(*S*)-N-[1-(4-methoxyphenyl)ethyl]arginine amide;
 (*R*)- N^2 -(diphenylacetyl)-(*S*)-N-[1-(4-bromophenyl)ethyl]arginine amide;
 (*R*)- N^2 -(diphenylacetyl)-(*R*)-N-[1-(4-bromophenyl)ethyl]arginine amide;
 30 (*R*)- N^2 -(diphenylacetyl)-(*R,S*)-N-[1-(3-methoxyphenyl)ethyl]arginine amide;



- (*R*)-*N*²-(diphenylacetyl)-(*R*)-*N*-(1-phenylethyl)arginine amide;
(*R*)-*N*²-(diphenylacetyl)-(*S*)-*N*-(1-phenylethyl)arginine amide;
(*R*)-*N*²-(diphenylacetyl)-(*R,S*)-*N*-[1-cyclopropyl-1-(4-methoxyphenyl)-methyl]-arginine amide;
5 (*R*)-*N*²-(diphenylacetyl)-*N*-(1-methyl-1-phenylethyl)arginine amide;
(*R*)-*N*²-(diphenylacetyl)-(*R,S*)-*N*-(1-indanyl)arginine amide;
(*R*)-*N*²-(diphenylacetyl)-(*S* or *R*)-*N*-(1-carbamoyl-phenylmethyl)arginine amide;
(*R*)-*N*²-(diphenylacetyl)-(*R* or *S*)-*N*-[1-carbamoyl-(4-methoxyphenyl)-methyl]arginine amide;
10 (*R*)-*N*²-(diphenylacetyl)-(*S*)-*N*-(2-hydroxy-1-phenylethyl)arginine amide;
(*R*)-*N*²-(diphenylacetyl)-(*R*)-*N*-(2-hydroxy-1-phenylethyl)arginine amide;
(*R*)-*N*²-(diphenylacetyl)-(*R*)-*N*-[2-hydroxy-1-(4-methoxyphenyl)ethyl]-arginine amide;
15 (*R*)-*N*²-(diphenylacetyl)-(*S*)-*N*-[2-hydroxy-1-(4-methoxyphenyl)ethyl]-arginine amide;
(*R*)-*N*²-(diphenylacetyl)-(*S*)-*N*-[1-(4-hydroxyphenyl)ethyl]arginine amide;
(*R*)-*N*²-(diphenylacetyl)-(*R,S*)-*N*-[1-(4-methoxyphenyl)ethyl]arginine amide;
20 (*R*)-*N*²-(diphenylacetyl)-*N*-methyl-(*R*)-*N*-(1-phenylethyl)arginine amide;
(*R*)-*N*²-(diphenylacetyl)-*N*-methyl-(*S*)-*N*-(1-phenylethyl)arginine amide;
(*R*)-*N*²-(diphenylacetyl)-(*R,S*)-*N*-[1-(4-cyclopropylmethoxyphenyl)ethyl]-arginine amide;
(*R*)-*N*²-(diphenylacetyl)-(*R*)-*N*-[1-(4-benzyloxyphenyl)ethyl]arginine amide;
25 (*R*)-*N*²-(diphenylacetyl)-(*R,S*)-*N*-[1-(4-phenoxyphenyl)ethyl]arginine amide;
(*R*)-*N*²-(diphenylacetyl)-(*R,S*)-*N*-[1-(4-phenylphenyl)ethyl]arginine amide;
(*R*)-*N*²-(diphenylacetyl)-(*R,S*)-*N*-[1-(2-naphthyl)ethyl]arginine amide;
(*R*)-*N*²-(diphenylacetyl)-(*R*)-*N*-[1-(1-naphthyl)ethyl]arginine amide;
30 (*R*)-*N*²-[(*R,S*)-2-(4-methoxyphenyl)phenylacetyl]-(*R*)-*N*-[1-(4-hydroxy-



- phenyl)ethyl]arginine amide;
 (R)-N²-[(R,S)-2-(4-methylphenyl)phenylacetyl]-(R)-N-[1-(4-hydroxy-phenyl)ethyl]arginine amide;
 (R)-N²-[(R,S)-2-(4-chlorophenyl)phenylacetyl]-(R)-N-[1-(4-hydroxy-phenyl)ethyl]arginine amide;
 5 (R)-N²-(4,4'-dichlorodiphenylacetyl)-(R)-N-[1-(4-hydroxyphenyl)ethyl]-arginine amide;
 (R)-N²-[(R,S)-2-(4-hydroxyphenyl)phenylacetyl]-(R)-N-[1-(4-hydroxy-phenyl)ethyl]arginine amide;
 10 (R)-N^ω-(ethyl)-N²-(diphenylacetyl)-(R)-N-[1-(4-methoxyphenyl)ethyl]-arginine amide;
 (R)-N^ω-(benzyl)-N²-(diphenylacetyl)-(R)-N-[1-(4-methoxyphenyl)ethyl]-arginine amide;
 (R)-N^ω-(1-(4-hydroxyphenyl)ethyl)-N²-(diphenylacetyl)-(R)-N-[1-(4-
 15 hydroxyphenyl)ethyl]arginine amide;
 (R)-N²-(diphenylacetyl)-(R,S)-N-[1-(4-(aminocarbonylmethyl)phenyl)ethyl]-arginine amide;
 (R)-N²-(diphenylacetyl)-(R,S)-N-[1-(4-(aminocarbonylaminomethyl)-phenyl)ethyl]arginine amide;
 20 (R)-N²-(4,4'-dichlorodiphenylacetyl)-(R,S)-N-[1-(4-(aminocarbonylmethyl)-phenyl)ethyl] arginine amide; or
 (R)-N²-(4,4'-dichlorodiphenylacetyl)-(R,S)-N-[1-(4-(aminocarbonylamino-methyl)phenyl)ethyl] arginine amide.
- 25 20. A compound as claimed in Claim 1 which is:
 (R)-N²-(diphenylacetyl)-(R)-N-[1-(4-methoxyphenyl)ethyl]arginine amide;
 (R)-N²-(diphenylacetyl)-(R)-N-[1-(4-hydroxyphenyl)ethyl]arginineamide;
 (R)-N²-[(R,S)-2-(4-chlorophenyl)phenylacetyl]-(R)-N-[1-(4-hydroxy-phenyl)ethyl]arginine amide;
 30 (R)-N²-(4,4'-dichlorodiphenylacetyl)-(R)-N-[1-(4-hydroxyphenyl)ethyl]-



arginine amide; or

(*R*)-N²-[(*R,S*)-2-(4-hydroxyphenyl)phenylacetyl]-(*R*)-N-[1-(4-hydroxyphenyl)ethyl]arginine amide.

- 5 21. A pharmaceutical formulation including a compound as defined in any one of Claims 1 to 20, or a pharmaceutically acceptable derivative thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.
- 10 22. A compound as defined in any one of Claims 1 to 20, or a pharmaceutically acceptable derivative thereof, for use as a pharmaceutical.
23. A compound as defined in any one of Claims 1 to 20, or a pharmaceutically acceptable derivative thereof, for use in the treatment of
- 15 a disorder which is mediated by neuropeptide Y.
24. A compound as defined in any one of Claims 1 to 20, or a pharmaceutically acceptable derivative thereof, for use in the treatment of cardiovascular disease.
- 20 25. The use of a compound as defined in any one of Claims 1 to 20, or a pharmaceutically acceptable derivative thereof, in the manufacture of a medicament for use in the treatment of a disorder which is mediated by neuropeptide Y.
- 25 26. The use of a compound as defined in any one of Claims 1 to 20, or a pharmaceutically acceptable derivative thereof, in the manufacture of a medicament for use in the treatment of cardiovascular disease.
- 30 27. A method of treatment of a cardiovascular disease, which method



comprises administration of a therapeutically effective amount of a compound as defined in any one of Claims 1 to 20, or a pharmaceutically acceptable derivative thereof, to a person suffering from, or susceptible to, such a condition.

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28. A compound as defined in any one of Claims 1 to 20, or a pharmaceutically acceptable derivative thereof, for use in the treatment of a disorder which is mediated by neuropeptide Y sub-receptor Y_1 .

10 29. A compound as defined in any one of Claims 1 to 20, or a pharmaceutically acceptable derivative thereof, for use in the treatment of vasoconstriction.

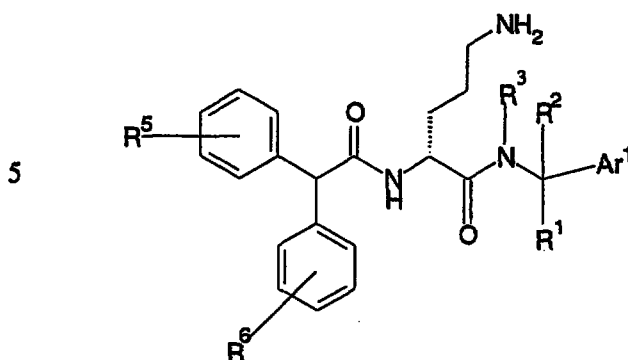
15 30. The use of a compound as defined in any one of Claims 1 to 20, or a pharmaceutically acceptable derivative thereof, in the manufacture of a medicament for use in the treatment of a disorder which is mediated by neuropeptide Y sub-receptor Y_1 .

20 31. The use of a compound as defined in any one of Claims 1 to 20, or a pharmaceutically acceptable derivative thereof, in the manufacture of a medicament for use in the treatment of vasoconstriction.

25 32. A method of treatment of a vasoconstriction, which method comprises administration of a therapeutically effective amount of a compound as defined in any one of Claims 1 to 20, or a pharmaceutically acceptable derivative thereof, to a person suffering from, or susceptible to, such a condition.

30 33. A process for the preparation of compounds of formula I which comprises:

(a) reaction of a compound of formula II,



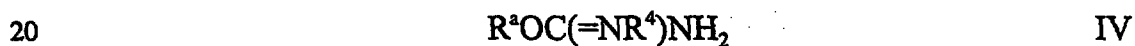
10 wherein Ar^1 , R^1 , R^2 , R^3 , R^5 and R^6 are as defined in Claim 1 with a compound of formula III,



or a hydrogen sulphate salt thereof, wherein R^a represents C_{1-4} alkyl and R^4 is as defined in Claim 1;

15 (b) for compounds of formula I in which R^4 represents H, reaction of a compound of formula II as defined above with 1H-pyrazole-1-carboxamidine, or a hydrohalide salt thereof;

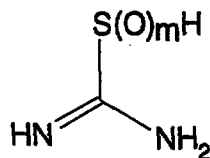
(c) reaction of a compound of formula II as defined above with a compound of formula IV,



or a hydrogen sulphate salt thereof, wherein R^a is as defined above and R^4 is as defined in Claim 1;

(d) for compounds of formula I in which R^4 represents H, reaction of a compound of formula II as defined above with a compound of formula V,

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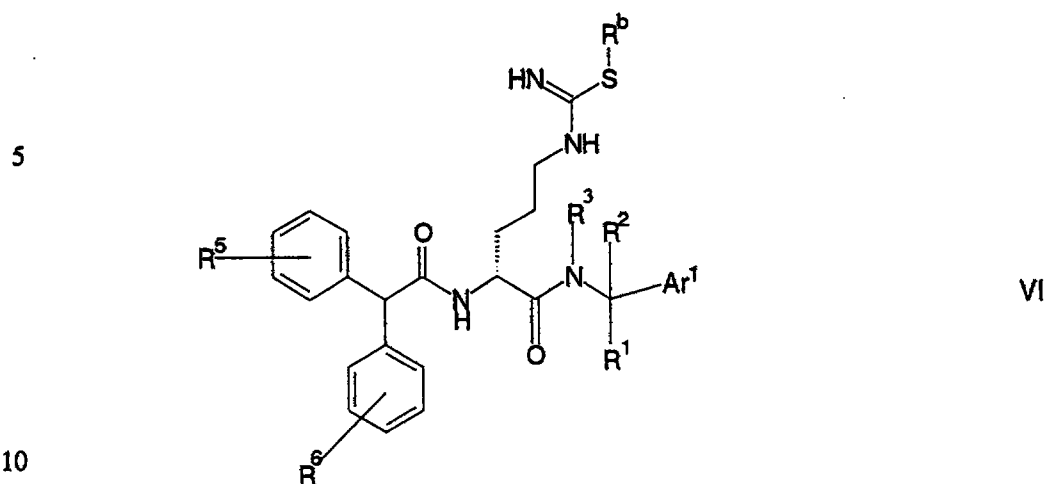


V

30 wherein m represents 2 or 3;



(e) reaction of a compound of formula VI,

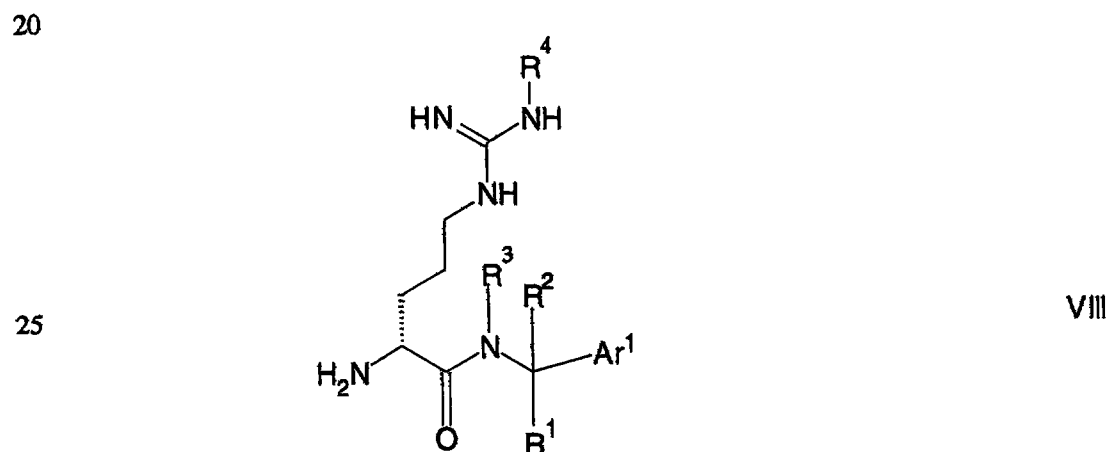


wherein R^b represents C_{1-4} alkyl and Ar^1 , R^1 , R^2 , R^3 , R^5 and R^6 are as defined in Claim 1 with a compound of formula VII,



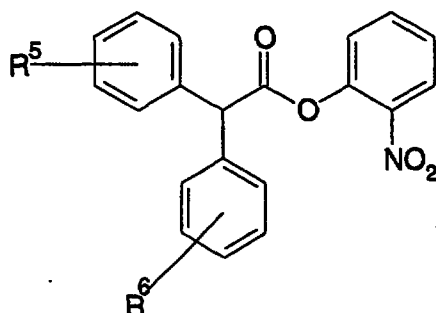
wherein R^4 is as defined in Claim 1;

(f) reaction of a compound of formula VIII,



wherein Ar^1 , R^1 , R^2 , R^3 and R^4 are as defined in Claim 1 with a compound of formula IX,

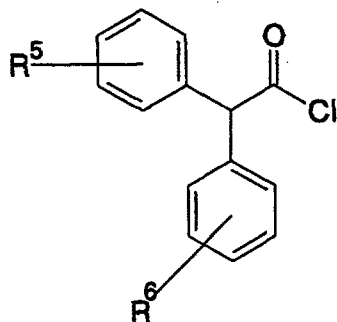
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IX

10 wherein R^5 and R^6 are as defined in Claim 1;

(g) reaction of a compound of formula VIII, as defined above, with a compound of formula X,



X

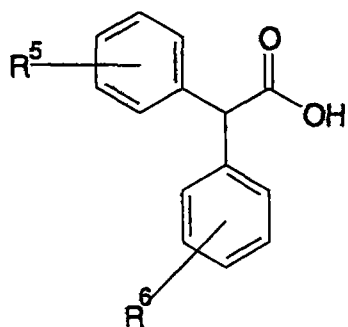
20 wherein R^5 and R^6 are as defined in Claim 1; or

(h) reaction of a compound of formula VIII, as defined above, with a compound of formula XI,

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XI

10 wherein R⁵ and R⁶ are as defined in Claim 1.