



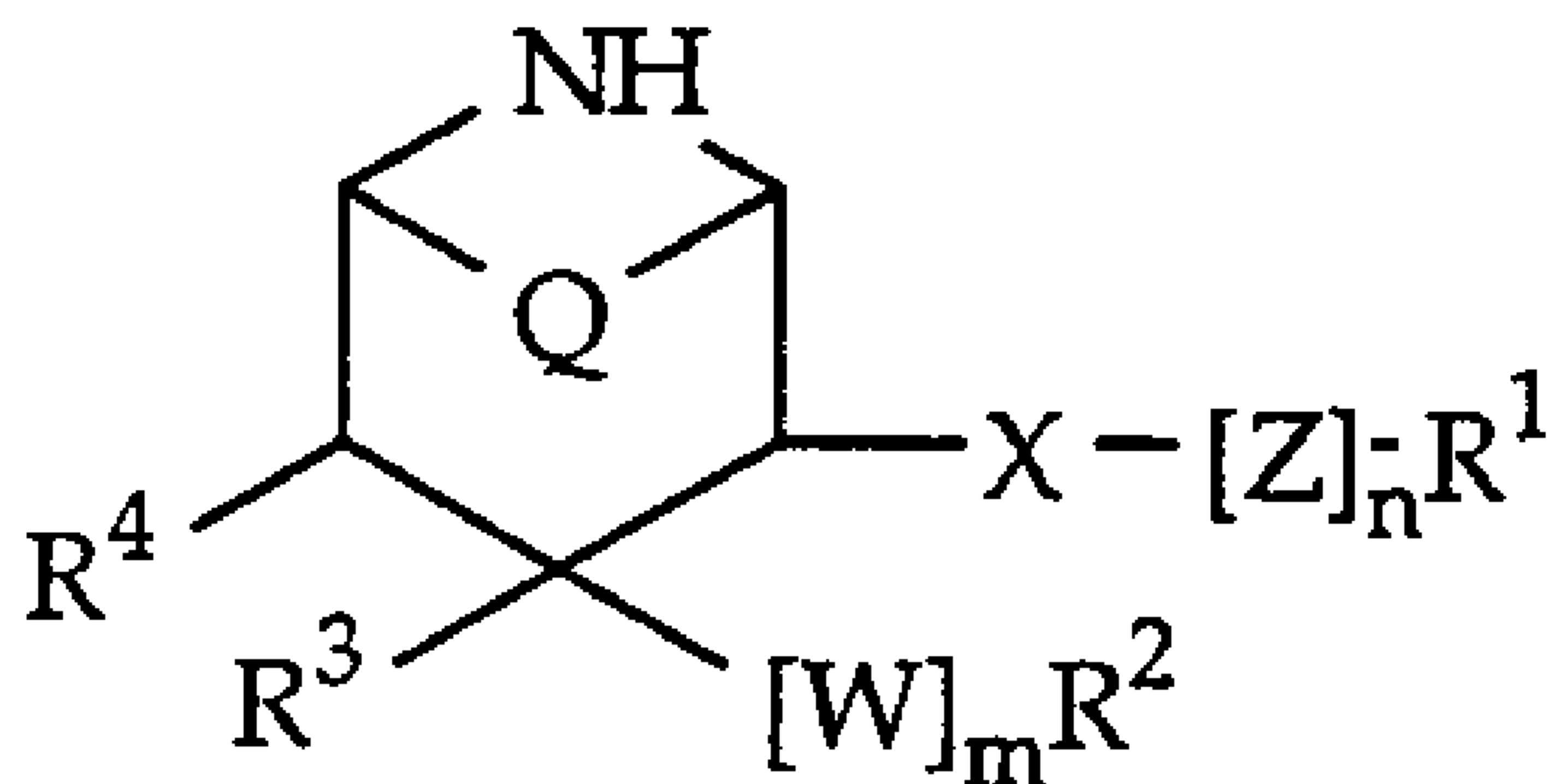
(86) Date de dépôt PCT/PCT Filing Date: 1996/08/29
(87) Date publication PCT/PCT Publication Date: 1997/03/13
(45) Date de délivrance/Issue Date: 2009/05/19
(85) Entrée phase nationale/National Entry: 1998/03/02
(86) N° demande PCT/PCT Application No.: EP 1996/003803
(87) N° publication PCT/PCT Publication No.: 1997/009311
(30) Priorités/Priorities: 1995/09/07 (CH2548/95-1);
1996/07/26 (CH1876/96)

(51) Cl.Int./Int.Cl. *C07D 211/42* (2006.01),
A61K 31/435 (2006.01), *A61K 31/495* (2006.01),
A61K 31/535 (2006.01), *A61K 31/54* (2006.01),
C07D 401/04 (2006.01), *C07D 401/06* (2006.01),
C07D 401/12 (2006.01), *C07D 401/14* (2006.01),
C07D 405/00 (2006.01), *C07D 409/00* (2006.01),
C07D 413/00 (2006.01), ...

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(54) Titre : NOUVELLES 4-(OXYALCOXYPHENYL)-3-OXY-PIPERIDINES UTILES POUR TRAITER L'INSUFFISANCE
CARDIAQUE ET RENALE

(54) Title: 4-(OXYALKOXYPHENYL)-3-OXY-PIPERIDINES FOR TREATING HEART AND KIDNEY INSUFFICIENCY



I

(57) Abrégé/Abstract:

The invention relates to novel piperidine derivatives of the general formula I (see formula I) wherein R¹, R², R³, R⁴, Q, W, X, Z, m and n have the meaning given in the specification. The novel piperidine derivatives can be used as renin inhibitors in the control or prevention of high blood pressure and cardiac insufficiency, as well as glaucoma, cardiac infarct, kidney insufficiency and restenosis.



(51) Cl.Int./Int.Cl. (suite/continued) *C07D 417/00* (2006.01), *C07D 471/08* (2006.01), *C07D 521/00* (2006.01),
C07F 7/10 (2006.01)

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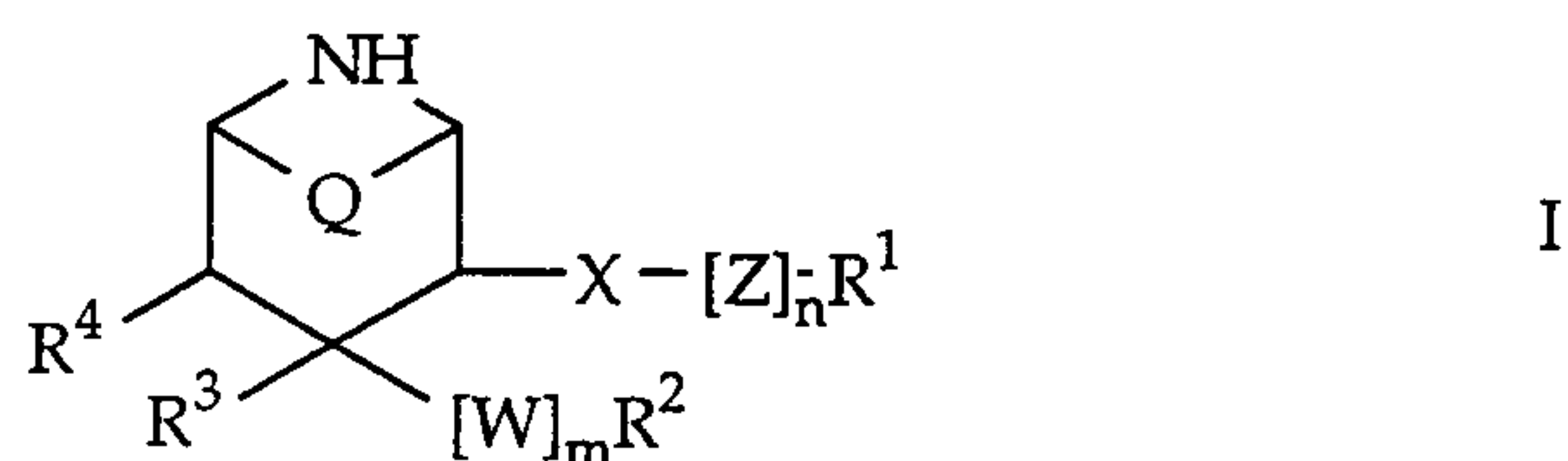
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RAN 4019/135Abstract

- 5 The invention relates to novel piperidine derivatives of the general formula I



- 10 wherein R¹, R², R³, R⁴, Q, W, X, Z, m and n have the meaning given in the specification. The novel piperidine derivatives can be used as renin inhibitors in the control or prevention of high blood pressure and cardiac insufficiency, as well as glaucoma, cardiac infarct, kidney insufficiency and restenosis.

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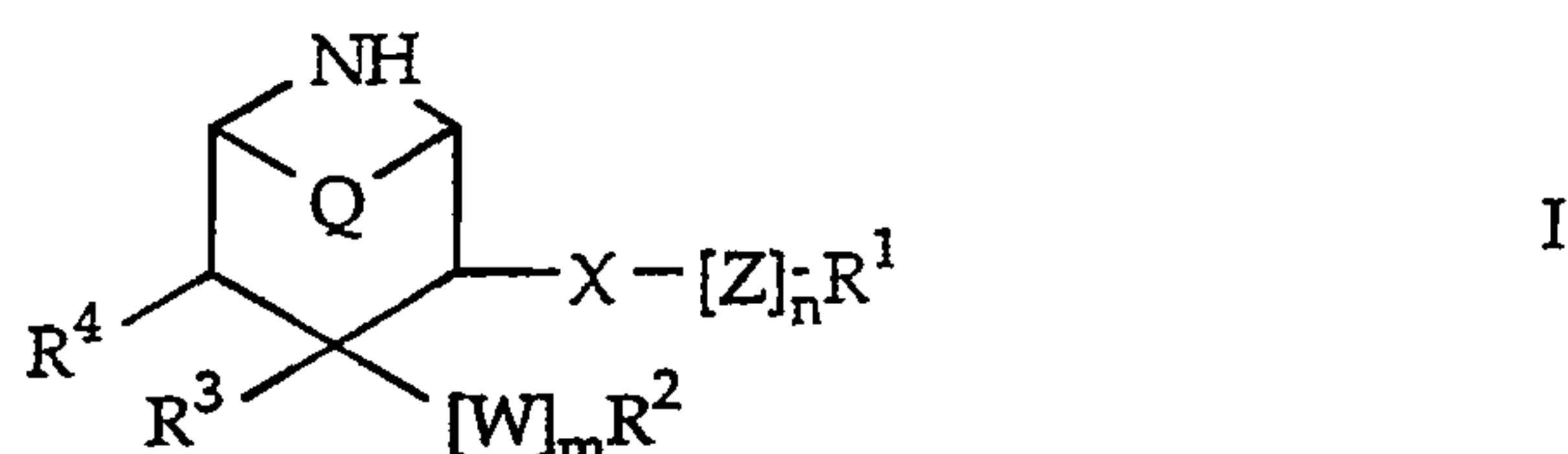
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THIS IS VOLUME 1 OF 2

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4-(Oxyalkoxyphenyl)-3-oxy-piperidines for Treating Heart and Kidney Insufficiency

The present invention is concerned with novel piperidine derivatives, their manufacture and use as medicaments. In particular, the invention is concerned with the novel piperidine derivatives of general formula I



wherein

R¹ represents aryl or heterocyclyl;

R² represents phenyl, naphthyl, acenaphthyl, cyclohexyl, pyridyl, pyrimidinyl, pyrazinyl, oxo-pyridinyl, diazinyl, triazolyl, thienyl, oxazolyl, oxadiazolyl, thiazolyl, pyrrolyl or furyl, which groups can be substituted by 1-3 halogen, hydroxy, cyano, trifluoromethyl, lower-alkyl, halo-lower-alkyl, hydroxy-lower-alkyl, lower-alkoxy-lower-alkyl, cyano-lower-alkyl, carboxy-lower-alkyl, lower-alkanoyloxy-lower-alkyl, lower-alkoxy-carbonyloxy-lower-alkyl, lower-alkoxycarbonyl, or lower-alkoxy groups, or by lower-alkylenedioxy, and/or by a group L¹-T¹-L²-T²-L³-T³-L⁴-T⁴-L⁵-U;

L¹, L², L³, L⁴ and L⁵ independently of one another represent a bond, C₁-8-alkylene, C₂-8-alkenylene or C₂-8-alkynylene or are absent;

T¹, T², T³ and T⁴ independently of one another represent

- (a) a bond or are absent or represent one of the groups
- (b) -CH(OH)-
- (c) -CH(OR⁶)-
- (d) -CH(NR⁵R⁶)-
- (e) -CO-

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- (f) -CR⁷R⁸-
- (g) -O- or -NR⁶-
- (h) -S(O)₀₋₂ -
- (i) -SO₂NR⁶ -
- 5 (j) -NR⁶ SO₂-
- (k) -CONR⁶ -
- (l) -NR⁶ CO-
- (m) -O-CO-
- (n) -CO-O-
- 10 (o) -O-CO-O-
- (p) -O-CO-NR⁶-
- (q) -NR⁶ -CO-NR⁶-
- (r) -NR⁶ -CO-O-

and the bonds emanating from (b), (d), (e) and (g)-(r) join to a C
 15 atom of the adjacent group and this C atom is saturated when the
 bond emanates from a hetero atom, and not more than two groups
 (b)-(f), three groups (g)-(h) and one group (i)-(r) are present;

R³ represents hydrogen, hydroxy, lower-alkoxy or lower-
 20 alkenyloxy; and

R⁴ represents hydrogen, lower-alkyl, lower-alkenyl, lower-
 alkoxy, hydroxy-lower-alkyl, lower-alkoxy-lower-alkyl, benzyl,
 oxo or a group

25 R^{4a}-Z¹-X¹- in which R^{4a} represents

- (a) H-
- (b) lower-alkyl-
- (c) lower-alkenyl-
- (d) hydroxy-lower-alkyl-
- 30 (e) polyhydroxy-lower-alkyl-
- (f) lower-alkyl-O-lower-alkyl-
- (g) aryl-
- (h) heterocyclyl-
- (i) arylalkyl-
- 35 (j) heterocyclylalkyl-
- (k) aryloxyalkyl-
- (l) heterocyclyloxyalkyl-

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(m) (R⁵R⁶)-N-(CH₂)₁₋₃-(n) (R⁵R⁶)-N-(o) lower-alkyl-S(O)₀₋₂-(p) aryl-S(O)₀₋₂-5 (q) heterocyclyl-S(O)₀₋₂-(r) HO-SO₃- or salt thereof(s) H₂N-C(NH)-NH-

(t) NC-,

and the bonds emanating from (n)-(t) join to a C atom of the
 10 adjacent group and this C atom is saturated when the bond
 emanates from a hetero atom;

Z¹ represents

(a) a bond, is absent or represents one of the groups

15 (b) lower-alkylene-

(c) lower-alkenylene-

(d) -O-, -N(R¹¹)-, -S(O)₀₋₂-

(e) -CO-

(f) -O-CO-

20 (g) -O-CO-O-

(h) -O-CO-N(R¹¹)-,(i) -N(R¹¹)-CO-O-(j) -CO-N(R¹¹)-(k) -N(R¹¹)-CO-25 (l) -N(R¹¹)-CO-N(R¹¹)-(m) -CH(OR⁹)-,

and the bonds emanating from (d) and (f)-(m) join to a C atom of
 the adjacent group and this C atom is saturated when the bond
 emanates from a hetero atom;

30

X¹ represents

(a) a bond, is absent or represents one of the groups

(b) -O-

(c) -N(R¹¹)-,35 (d) -S(O)₀₋₂-(e) -(CH₂)₁₋₃-

or R³ and R⁴ together represent a bond;

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R⁵ and R⁶ represent hydrogen, lower-alkyl, lower-alkenyl, aryl-lower-alkyl or acyl or together with the N atom to which they are attached represent a 5- or 6-membered heterocyclic ring which
 5 can contain an additional N atom or an O or S atom or a SO or SO₂ group and the additional N atom can be optionally substituted by lower-alkyl;

R⁷ and R⁸ together with the C atom to which they are attached
 10 represent a 3-7 membered ring which can contain one or two O or S atoms or SO or SO₂ groups;

R⁹ represents hydrogen, lower-alkyl, acyl or arylalkyl;

15 R¹⁰ represents carboxyalkyl, alkoxycarbonylalkyl, alkyl or hydrogen;

R¹¹ represents hydrogen or lower-alkyl;

U represents hydrogen, lower-alkyl, cycloalkyl, cyano, optionally
 20 substituted cycloalkyl, aryl or heterocyclyl;

Q represents ethylene or is absent;

X represents a bond, oxygen, sulphur or a group -CH-R¹¹-,
 25 -CHOR⁹-, -O-CO-, -CO- or C=NOR¹⁰-with the bond emanating from an oxygen or sulphur atom joining to a saturated C atom of group Z or to R¹;

W represents oxygen or sulphur;

30

Z represents lower-alkylene, lower-alkenylene, hydroxy-lower-alkylidene, -O-, -S-, -O-Alk-, -S-Alk-, -Alk-O- or -Alk-S-, in which Alk represents lower alkylene; provided that

35 a) X is -CH-R¹¹- and either R² contains a substituent L¹-T¹-L²-T²-L³-T³-L⁴-T⁴-L⁵-U or R⁴ is a substituent defined above other than hydrogen when Z represents -O- or -S-;

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b) X is $-\text{CH-R}^{11}-$ when Z represents $-\text{O-Alk-}$ or $-\text{S-Alk-}$; and

c) Z represents lower-alkenylene, $-\text{Alk-O-}$ or $-\text{Alk-S-}$ when X represents a bond;

5

n is 1 or, when X represents $-\text{O-CO-}$, 0 or 1; and

m is 0 or 1;

10 and pharmaceutically usable salts thereof;

with the exception of the compound 4-(4-fluorophenyl)-3-(3,4-methylenedioxybenzyloxy)piperidine and its hydrochloride.

15

The term "lower" used here denotes groups with 1-6, preferably 1-4, C atoms. Examples of lower alkyl and alkoxy groups are methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec.-butyl, tert-butyl, pentyl, hexyl and, respectively, methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec.-butoxy and
 20 tert-butoxy. Lower-alkylenedioxy groups are preferably methylenedioxy, ethylenedioxy and propylenedioxy. Acetyl, propionyl and butyryl are examples of lower-alkanoyl groups. Cycloalkyl signifies a saturated, cyclic hydrocarbon group with 3-6 carbon atoms, i.e. cyclopropyl, cyclobutyl, cyclopentyl and
 25 cyclohexyl. C_{1-8} -Alkylene groups are e.g. methylene, ethylene, propylene, 2-methyl-propylene, tetra-, penta- and hexamethylene; C_{2-8} -alkenylene groups are e.g. vinylene and propenylene; C_{2-8} -alkynylene groups are e.g. ethynylene. Acyl groups are alkanoyl groups, preferably lower-alkanoyl groups, or aroyl groups such as
 30 benzoyl. Aryl denotes mono-nuclear or poly-nuclear aromatic groups which can carry one or more substituents, such as, for example, phenyl, substituted phenyl, naphthyl, substituted naphthyl, tetrahydronaphthyl or substituted tetrahydronaphthyl. Examples of substituents on such aryl groups are lower-alkyl,
 35 trifluoromethyl, nitro, amino, lower-alkenyl, lower-alkoxy, lower-alkylcarbonyloxy, hydroxy, halogen, cyano, carbamoyl and lower-alkylenedioxy, as well as optionally halo-, lower-alkyl-, lower-alkoxy- or dihydroxy-lower-alkylaminocarbonyl-

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substituted phenyl, phenoxy, phenylthio, phenyl-lower-alkyl or phenyl-lower-alkoxy. Further examples of substituents on aryl groups are lower-alkoxycarbonylphenyl, hydroxy-lower-alkyl-phenyl, benzyloxy, pyridylcarbonylamino-lower-alkyl, lower-alkenyloxy, lower-alkoxy-lower-alkoxy, methoxybenzyloxy, hydroxybenzyloxy, phenethyloxy, methylenedioxybenzyloxy, dioxolanyl-lower-alkoxy, cyclopropyl-lower-alkoxy, hydroxy-lower-alkoxy, carbamoyloxy-lower-alkoxy, pyridyl-carbamoyloxy-lower-alkoxy, benzoyloxy-lower-alkoxy; as well as optionally halo-, lower-alkyl-, lower-alkoxy- or dihydroxy-lower-alkylaminocarbonyl-substituted pyridyl, pyridyloxy, pyridylthio, pyridylamino, pyridyl-lower-alkyl, pyridyl-lower-alkoxy, pyrimidinyl, pyrimidinyloxy, pyrimidinylthio, pyrimidinylamino, pyrimidinyl-lower-alkyl, pyrimidinyl-lower-alkoxy, thienyl, thienyl-lower-alkyl, thienyl-lower-alkoxy, furyl, furyl-lower-alkyl and furyl-lower-alkoxy.

The term heterocyclyl denotes monocyclic or bicyclic, saturated and unsaturated heterocyclic groups with 1 to 4 nitrogen atoms and/or 1 or 2 sulphur or oxygen atoms, which can be mono- or multiply-substituted, especially by (in the case of unsaturated heterocyclyl groups) alkyl, hydroxy, alkoxy, nitro or halogen or by substituents as defined above for aryl groups or (in the case of saturated heterocyclyl groups) by alkyl or alkoxy. Examples of heterocyclyl groups are pyridyl, thienyl, pyrazinyl, triazolyl, imidazolyl, benzthiazolyl, furyl, pyrimidinyl, morpholinyl, quinazolinyl, quinolyl, quinoxalinyl, isoquinolyl, benzo[b]thienyl, isobenzofuranyl, benzimidazolyl, 2-oxo-benzimidazolyl or thiazolyl. Examples of substituted heterocyclyl groups are nitrobenzthiazolyl, phenyl-tetrazolyl, phenyl-oxadiazolyl, phenyl-oxadiazolyl, thienyl-oxadiazolyl, furanyl-oxadiazolyl, benzyl-oxadiazolyl and phenyl-oxazolyl. Examples of saturated heterocyclyl groups are dioxolanyl, dioxanyl, dithiolanyl, dithianyl, pyrrolidinyl, piperidinyl, piperazinyl, 4-methylpiperazinyl, morpholinyl, thiomorpholinyl, 2-hydroxymethylpyrrolidinyl, 3-hydroxypyrrolidinyl, 3,4-dihydroxypyrrolidinyl, 4-hydroxypiperidinyl, 4-oxopiperidinyl, 3,5-dimethylmorpholinyl, 4,4-dioxothio-

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morpholinyl, 4-oxothiomorpholinyl, 2,6-dimethylmorpholinyl, 2-oxo-imidazolidinyl, 2-oxo-oxazolidinyl, 2-oxo-pyrrolidinyl, 2-oxo-[1,3]oxazinyl, 2-oxo-tetrahydro-pyrimidinyl and the like.

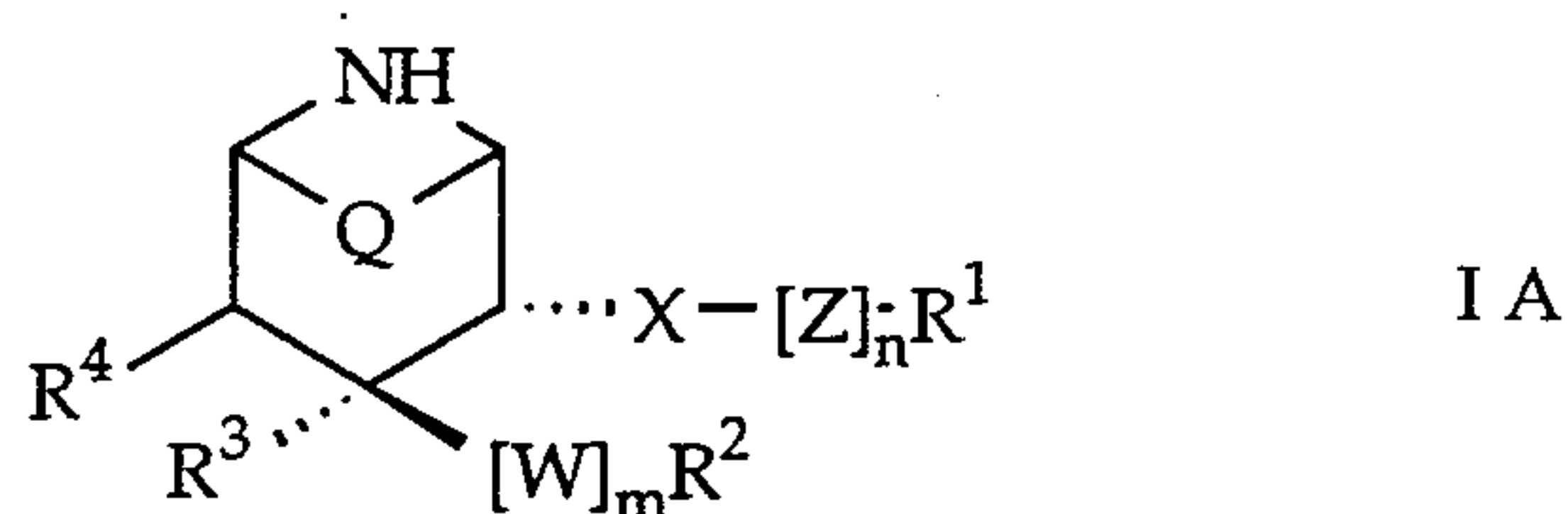
5 In the case of R¹, R^{4a} and R⁹ the aryl, aroyl and heterocyclyl groups can be additionally substituted by heterocyclylalkyl, heterocyclylalkoxy or heterocyclylalkoxyalkyl, such as, for example, piperidinoalkyl, piperidinoalkoxy, piperidinoalkoxyalkyl, morpholinoalkyl, morpholinoalkoxy, morpholinoalkoxyalkyl, 10 piperazinoalkyl, piperazinoalkoxy, piperazinoalkoxyalkyl or N-methylpiperazinoalkyl, N-methylpiperazinoalkoxy, N-methylpiperazinoalkoxyalkyl, as well as alkylaminoalkyl, alkylaminoalkoxy, alkylaminoalkoxyalkyl, mono- and polyhydroxy-alkyl, -alkoxy, -alkoxyalkyl and -alkoxyalkoxy, carbamoylalkyloxy, 15 lower-alkoxy, amino-lower-alkoxy, hydroxy-lower-alkoxy or by the -O-CH₂CH(OH)CH₂NR^x group, in which NR^x represents a mono- or di-lower-alkyl-amino, piperidino, morpholino, piperazino or N-methylpiperazino group. Examples of 5- and 6-membered heterocyclic rings denoted by NR⁵R⁶ are pyrrolidinyl, piperidinyl, 20 piperazinyl, morpholinyl, thiomorpholinyl, 2-hydroxymethylpyrrolidinyl, 3-hydroxypyrrolidinyl, 3,4-dihydroxypyrrolidinyl, 4-hydroxypiperidinyl, 4-oxopiperidinyl, 3,5-dimethylmorpholinyl, 4,4-dioxothiomorpholinyl, 4-oxothiomorpholinyl, 2,6-dimethylmorpholinyl, 2-oxo-imidazolidinyl, 2-oxo-oxazolidinyl, 2-oxo-pyrrolidinyl, 2-oxo-[1,3]oxazinyl, 2-oxo-tetrahydro-pyrimidinyl and the like. Cyclopentyl, cyclohexyl, cycloheptyl, 1,3-dioxolanyl, 1,3-dioxanyl, 1,3-dithiolanyl and 1,3-dithianyl are examples of 3-7 membered rings denoted by CR⁷R⁸. The term polyhydroxy-alkyl denotes C₁-C₇-alkyl groups which can be substituted by 2-6 25 hydroxy groups, such as e.g. glyceryl, arabityl, sorbityl etc.

The compounds of formula I have at least two asymmetric carbon atoms and can accordingly exist in the form of optically pure diastereomers, diastereomer mixtures, diastereomeric 35 racemates or mixtures of diastereomeric racemates or as meso forms. The invention embraces all of these forms. Diastereomeric mixtures, diastereomeric racemates or mixtures of diastereomeric racemates can be separated according to usual methods, e.g. by

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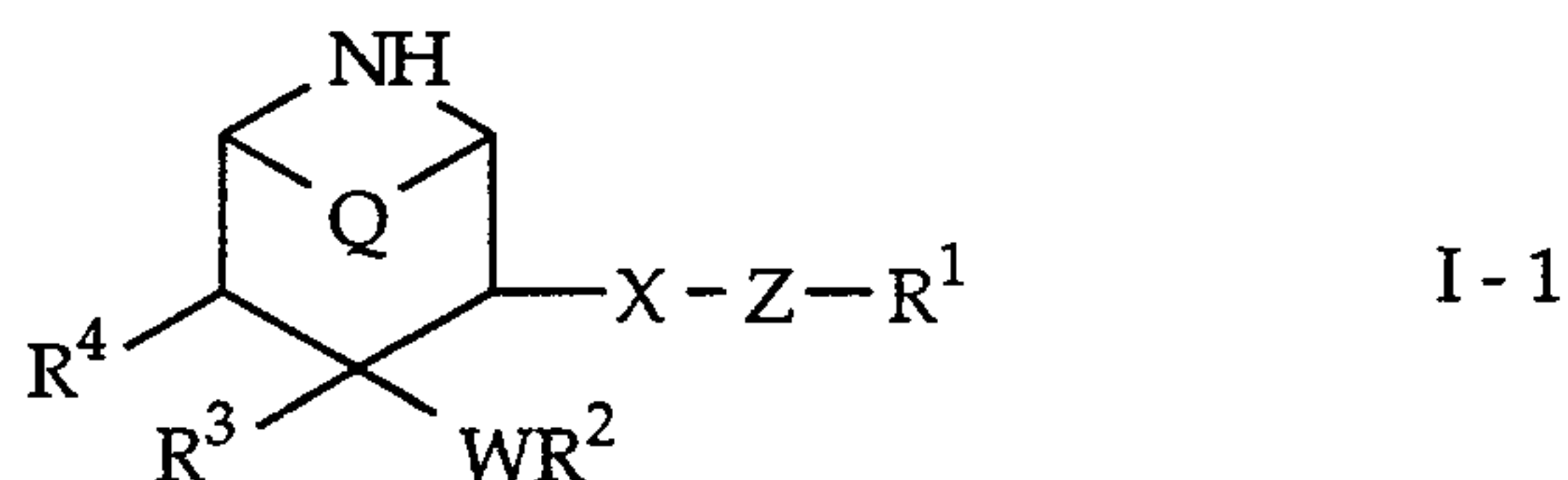
column chromatography, thin-layer chromatography, HPLC and the like.

Preferred compounds in accordance with the invention are
5 those of the general formula



10 wherein R¹-R⁴, Q, W, X, Z, n and m have the significance given above.

A further preferred group of compounds of formula I comprises compounds of the formula



15

wherein

R¹ represents aryl or heterocyclyl;

20

R² represents phenyl, cyclohexyl, phenyl or cyclohexyl substituted by halogen, hydroxy, cyano, trifluoromethyl, lower-alkyl, halo-lower-alkyl, hydroxy-lower-alkyl, lower-alkoxy-lower-alkyl, cyano-lower-alkyl, carboxy-lower-alkyl, lower-alkanoyloxy-lower-alkyl, lower-alkoxycarbonyloxy-lower-alkyl, lower-alkoxycarbonyl, lower-alkoxy or lower-alkylenedioxy or by
25 a group L¹-T¹-L²-T²-L³-T³-L⁴-T⁴-L⁵-U; or naphthyl or acenaphthyl;

30 L¹, L², L³, L⁴ and L⁵ independently of one another represent a bond, C₁-8-alkylene, C₂-8-alkenylene or C₂-8-alkynylene or are absent;

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T¹, T², T³ and T⁴ independently of one another represent

- (a) a bond or are absent or represent one of the groups
- (b) -CH(OH)-
- (c) -CH(OR⁶)-
- 5 (d) -CH(NR⁵R⁶)-
- (e) -CO-
- (f) -CR⁷R⁸-
- (g) -O- or -NR⁶-,
- (h) -S(O)₀₋₂ -
- 10 (i) -SO₂NR⁶ -
- (j) -NR⁶ SO₂-
- (k) -CONR⁶ -
- (l) -NR⁶CO-
- (m) -O-CO-
- 15 (n) -CO-O-
- (o) -O-CO-O-
- (p) -O-CO-NR⁶-,

with the bonds emanating from (b), (d), (e) and (g)-(p) joining to a C atom of the adjacent group and this C atom being saturated
 20 when the bond emanates from a hetero atom, and not more than two groups (b)-(f), three groups (g)-(h) and one group (i)-(p) being present;

R³ represents hydrogen, hydroxy, lower-alkoxy or lower-
 25 alkenyloxy;

R⁴ represents hydrogen, lower-alkyl, lower-alkenyl, lower-alkoxy, hydroxy-lower-alkyl, lower-alkoxy-lower-alkyl or benzyl;

30 R⁵ and R⁶ are hydrogen, lower-alkyl or acyl or together with the N atom to which they are attached represent a 5- or 6-membered heterocyclic ring which can contain an additional N atom or an O or S atom;

- 10 -

R⁷ and R⁸ together with the C atom to which they are attached represent a 3-7 membered ring which can contain one or two oxygen or sulphur atoms;

- 5 U represents hydrogen, lower-alkyl, cycloalkyl, cyano, aryl or heterocyclyl;

Q represents ethylene or is absent;

- 10 X represents oxygen, sulphur or a group -CH₂-, -CHOR⁹- or -OCO- and R⁹ represents hydrogen, lower-alkyl, acyl or arylalkyl;

W is absent; or can represent oxygen or sulphur when R³ represents hydrogen; and

15

Z represents lower-alkylene or is absent;

and pharmaceutically usable salts thereof;

- 20 with the exception of the compound 4-(4-fluorophenyl)-3-(3,4-methylenedioxybenzyloxy)piperidine and its hydrochloride.

Furthermore, compounds of formulae I and IA in which W is absent and those in which Q is absent are preferred. X is
25 preferably oxygen, sulphur or -CO-; Z is preferably methylene.

Preferred groups R¹ are phenyl and phenyl substituted by lower-alkyl, lower-alkenyl, lower-alkoxy, lower-alkylthio, halogen, hydroxy, hydroxy-lower-alkoxy, lower-alkoxy-lower-alkoxy, lower-alkylsulphinyl, lower-alkylsulphonyl, cyano,
30 trifluoromethyl, trifluoromethoxy, carboxy, cyclobutylmethoxy-lower-alkyl, lower-alkylenedioxy, phenyl, phenoxy, lower-alkoxycarbonylphenyl, hydroxy-lower-alkylphenyl, 2,3-dihydroxy-propylaminocarbonylphenyl, benzyloxy, benzoyl, pyridyl-lower-alkoxy-lower-alkyl or nicotinoylamino-lower-alkyl.
35

Other preferred groups R¹ are naphthyl, naphthyl substituted by hydroxy, oxo, lower-alkoxy, lower-alkenyloxy,

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lower-alkoxy-lower-alkoxy, di-lower-alkylamino, 2,3-dihydroxypropoxy, 2,3-dihydroxypropoxy-lower-alkoxy, 2,3-dimethoxypropoxy, lower-alkoxycarbonyl-lower-alkoxy, carbamoyl-lower-alkoxy, methoxybenzyloxy, hydroxybenzyloxy, phenethyloxy, methylenedioxybenzyloxy, dioxolanyl-lower-alkoxy, cyclopropyl-lower-alkoxy, hydroxy-lower-alkoxy, carbamoyloxy-lower-alkoxy, pyridyl-carbamoyloxy-lower-alkoxy, morpholino-lower-alkoxy, 3-morpholino-2-hydroxypropoxy, N-methylpiperazino-N-lower-alkoxy, benzoyloxy-lower-alkoxy or picolyloxy; tetrahydronaphthyl or methyl-substituted tetrahydronaphthyl, or indanyl.

Likewise preferred groups R¹ are pyridyl, benzimidazolyl, di-lower-alkoxypyrimidinyl or 2- and 5-benzo[b]thienyl, 6- and 7-quinolyl, 6- and 7-isoquinolyl, 6- and 7-tetrahydroquinolyl, 6- and 7-tetrahydroisoquinolyl, 6-quinoxalyl, 6- and 7-quinazolinyl, as well as 6- and 7-quinolyl, 6- and 7-isoquinolyl, 6- and 7-tetrahydroquinolyl, 6- and 7-tetrahydroisoquinolyl, 6-quinoxalyl or 6- and 7-quinazolinyl substituted by hydroxy, oxo, lower-alkoxy, lower-alkenyloxy, lower-alkoxy-lower-alkoxy, di-lower-alkylamino, 2,3-dihydroxypropoxy, 2,3-dihydroxypropoxy-lower-alkoxy, 2,3-dimethoxypropoxy, lower-alkoxycarbonyl-lower-alkoxy, carbamoyl-lower-alkoxy, methoxybenzyloxy, hydroxybenzyloxy, phenethyloxy, methylenedioxybenzyloxy, dioxolanyl-lower-alkoxy, cyclopropyl-lower-alkoxy, hydroxy-lower-alkoxy, carbamoyloxy-lower-alkoxy, pyridyl-carbamoyloxy-lower-alkoxy, morpholino-lower-alkoxy, 3-morpholino-2-hydroxypropoxy, N-methylpiperazino-N-lower-alkoxy, benzoyloxy-lower-alkoxy or picolyloxy.

30

Preferred groups R² are phenyl and phenyl substituted by halogen, hydroxy, cyano, trifluoromethyl, lower-alkyl, halo-lower-alkyl, hydroxy-lower-alkyl, lower-alkoxy-lower-alkyl, cyano-lower-alkyl, carboxy-lower-alkyl, lower-alkanoyloxy-lower-alkyl, lower-alkoxycarbonyloxy-lower-alkyl, lower-alkoxycarbonyl, lower-alkoxy or lower-alkylenedioxy.

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Likewise preferred groups R^2 are phenyl substituted by a group $L^1-T^1-L^2-T^2-L^3-T^3-L^4-T^4-L^5-U$ in which L^1 and L^2 are preferably absent or are C_{1-8} -alkylene and L^3 is absent and U represents hydrogen, lower-alkyl, cyclo-lower-alkyl, phenyl, phenyl substituted by lower-alkyl, lower-alkoxy, lower-alkylthio, lower-alkylsulphinyl, lower-alkylenedioxy, halogen, benzoyl-lower-alkyl, halo-lower-alkyl, lower-alkanoyloxy or hydroxy; or naphthyl; or pyridyl, thienyl, pyrazinyl, triazolyl, imidazolyl, phenyl-oxadiazolyl, thienyl-oxadiazolyl, furyl-oxadiazolyl, phenyl-oxazolyl, benzthiazolyl, furyl, pyrimidinyl, nitrobenz-thiazolyl, phenyltetrazolyl or morpholinyl.

In groups T^1-T^4 the meanings (a)-(c), (e)-(h), (m) and (n) are preferred.

Examples of especially preferred groups R^2 are phenyl or phenyl substituted by

2-benzothiazolyl-thio-lower-alkyl,
 2-benzyloxy-3-methoxypropoxy,
 2-benzoyloxy-3-methoxypropoxy,
 2,3-dihydroxypropoxy,
 2-hydroxy-3-benzylamino-propoxy,
 2-hydroxy-3-phenoxypropoxy,
 2-hydroxy-3-phenylthiopropoxy,
 2-methoxy-3-phenoxypropoxy,
 2-methoxy-3-benzyloxypropoxy,
 2-methyl-3-fluoro-phenylbutyryloxy-lower-alkoxy,
 2-lower-alkenyloxy-4-phenylbutyl,
 3,4,5-trimethoxyphenyl-oxadiazolyl-lower-alkoxy,
 6-nitro-2-benzothiazolyl-thio-lower-alkyl,
 benzamido-lower-alkoxy,
 benzamido-lower-alkyl,
 benzoyl-lower-alkoxy and ketals thereof,
 benzoyl-lower-alkyl and ketals thereof,
 benzoyl-lower-alkyl-aminocarbonyl-lower-alkyl,
 benzoyl-lower-alkoxycarbonyl-lower-alkyl,
 benzoyl-lower-alkylaminocarbonyl,

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benzoyloxy,
benzoyloxy-lower-alkyl-benzoyloxy-lower-alkoxy,
benzoyloxy-lower-alkoxy,
benzoyloxy-lower-alkyl,
5 benzthiazolylthio-lower-alkoxy,
benzthiazolylthio-lower-alkyl,
benzylcarbamoyl-lower-alkoxy,
benzyloxy-lower alkylcarbonyloxy-lower-alkyl,
benzyloxy-lower-alkoxy,
10 benzylthio-lower-alkoxy,
carbamoyloxy-lower-alkoxy,
carbamoyloxy-lower-alkyl,
carboxy-lower-alkoxy,
carboxy-lower-alkyl,
15 cyano,
cyano-lower-alkoxy,
cyano-lower-alkyl,
cyanophenyl-lower-alkoxy,
cyclohexylcarbonyloxy-lower-alkyl,
20 cyclopropylcarbonyloxy-lower-alkyl,
cyclopropyloxy-benzyloxy-lower-alkoxy,
dioxolanyl-lower-alkoxy,
furyl-oxadiazolyl-lower-alkoxy,
furoyloxy-lower-alkoxy,
25 halo-phenoxy-lower-alkyl,
halobenzoyl-lower-alkoxy,
halobenzoyloxy-lower-alkyl,
halobenzoyloxy-lower-alkoxy,
halobenzyloxy-lower-alkoxy,
30 halogen,
halogen-lower-alkyl,
halophenoxy,
halophenyl-oxadiazolyl-lower-alkoxy,
hydroxy,
35 hydroxy-benzoyloxy-lower-alkyl,
hydroxy-benzyloxy-lower-alkoxy,
hydroxy-lower-alkoxy,
hydroxy-lower-alkyl,

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imidazolylcarbonyloxy-lower-alkyl,
methoxybenzoyl-lower-alkyl,
methoxybenzyloxy-lower-alkoxy,
methylenedioxybenzoyl-lower-alkoxy,
5 morpholino-lower-alkoxy,
morpholinocarbonyloxy-lower-alkoxy,
morpholinocarbonyloxy-lower-alkyl,
N-methylaminophenyl-carbonyloxy-lower-alkyl,
N-methyl-benzylamino-lower-alkoxy,
10 N-methylpyrrolylcarbonyloxy-lower-alkoxy,
N-lower-alkylbenzamido-lower-alkyl,
naphthyl-lower-alkoxy,
nicotinoyloxy-lower-alkoxy,
nicotinoyloxy-lower-alkyl,
15 lower-alkanoylbenzoyloxy-lower-alkyl,
lower-alkanoyloxy-lower-alkoxy
lower-alkanoyloxy-lower-alkyl,
lower-alkenyl-benzyloxy-lower-alkoxy,
lower-alkenyloxy,
20 lower-alkenyloxy-benzyloxy-lower-alkoxy,
lower-alkoxy,
lower-alkoxy-benzoyloxy-lower-alkyl,
lower-alkoxy-carbonyl,
lower-alkoxy-lower-alkyl,
25 lower-alkoxybenzoylamino-lower-alkyl,
lower-alkoxybenzylcarbonyloxy-lower-alkyl,
lower-alkoxy-benzyloxy-lower-alkoxy,
lower-alkoxy-benzylthio-lower-alkoxy,
lower-alkoxycarbonyl,
30 lower-alkoxycarbonyl-lower-alkoxy,
lower-alkoxycarbonyl-lower-alkyl,
lower-alkoxyphenyl-oxadiazolyl-lower-alkoxy,
lower-alkyl,
lower-alkylbenzyloxy-lower-alkoxy,
35 lower-alkylenedioxy,
lower-alkylenedioxybenzyloxy-lower-alkoxy,
lower-alkylsulphonylbenzoyl-lower-alkoxy,
lower-alkylthiobenzoyloxy-lower-alkoxy,

- 15 -

lower-alkylthio-benzyloxy-lower-alkoxy,
benzoyloxybenzyl-lower-alkoxy,
hydroxybenzyl-lower-alkoxy,
lower-alkoxybenzyl-lower-alkoxy,
5 lower-alkoxybenzylcarbonyloxy-alkoxy,
phenoxy-benzyloxy-lower-alkoxy,
phenoxycarbonyl-lower-alkyl,
phenoxy-lower-alkenyloxy,
phenoxy-lower-alkynyloxy,
10 phenyl-lower-alkanoylamino-lower-alkyl,
phenyl-lower-alkenyloxy,
phenyl-lower-alkoxy,
phenoxy-lower-alkyl,
phenyl-lower-alkylaminocarbonyl,
15 phenoxy-lower-alkylcarbonyl-lower-alkoxy,
phenyl-lower-alkylaminocarbonyl-lower-alkyl,
phenylaminocarbonyloxy-lower-alkoxy,
phenylaminocarbonyloxy-lower-alkyl,
phenyl-hydroxy-lower-alkyl,
20 phenyl-oxadiazolyl-lower-alkoxy
phenyl-oxadiazolyl-lower-alkoxy,
phenyl-oxadiazolyl-lower-alkyl,
phenyl-oxazolyl-lower-alkoxy,
phenyloxy-lower-alkoxy,
25 phenylsulphamoyl-lower-alkyl,
phenylsulphinyl-lower-alkyl,
phenylsulphonyl-lower-alkoxy,
phenylsulphonyl-lower-alkyl,
phenyltetrazolyl-thio-lower-alkyl,
30 phenylthio-lower-alkoxy,
phenylthio-lower-alkyl,
pyrazinylcarbonyloxy-lower-alkyl,
pyridylaminocarbonyloxy-lower-alkoxy
pyridylaminocarbonyloxy-lower-alkyl,
35 pyridylcarbamoyloxy,
pyridyl-lower-alkoxy-lower-alkoxy,
pyridyl-lower-alkoxy-lower-alkyl,
pyridyl-oxadiazolyl-lower-alkoxy,

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pyridylthio-lower-alkyl,
 pyrimidinyloxy-lower-alkoxy,
 pyrimidinylthio-lower-alkyl,
 thenoyloxy-lower-alkoxy,
 5 thenoyloxy-lower-alkyl,
 thienyl-oxadiazolyl-lower-alkoxy,
 triazolyl-lower-alkoxy,
 trifluoromethylbenzyloxy-lower-alkoxy or
 trifluoromethyl.

10

Preferred groups R⁴ are

2-oxo-imidazolidin-1-yl-lower-alkyl,
 4-hydroxy-piperidin-1-yl-lower-alkoxy,
 15 4-hydroxy-piperidin-1-yl-lower-alkoxy-lower-alkyl,
 4-methyl-piperazin-1-yl-lower-alkoxy,
 4-methyl-piperazin-1-yl-lower-alkoxy-lower-alkyl,
 4-methyl-piperazin-1-yl-lower-alkyl-carbamoyloxy-lower-
 alkyl,
 20 1,2,4-triazolyl-lower-alkyl,
 amino,
 amino-lower-alkyl,
 amino-lower-alkyl-amino
 amino-lower-alkyl-amino-lower-alkyl,
 25 amino-lower-alkoxy,
 amino-lower-alkoxy-lower-alkyl,
 aminocarbonyloxy-lower-alkyl,
 benzyloxy or benzyloxy substituted by lower-alkyl, lower-
 alkenyl, lower-alkoxy, trifluoromethoxy, lower-alkylthio, hydroxy
 30 or halogen,
 benzyloxy-lower-alkyl or benzyloxy-lower-alkyl substituted by
 lower-alkyl, lower-alkenyl, lower-alkoxy or halogen,
 carbamoyloxy-lower-alkyl,
 cyano-lower-alkyl,
 35 di-lower-alkyl-amino,
 di-lower-alkyl-amino-lower-alkyl,
 di-lower-alkyl-amino-lower-alkyl-(N-lower-alkyl)-amino-
 lower-alkyl,

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di-lower-alkyl-amino-lower-alkyl-amino
di-lower-alkyl-amino-lower-alkyl-amino-lower-alkyl,
di-lower-alkyl-amino-lower-alkoxy
di-lower-alkyl-amino-lower-alkoxy-lower-alkyl,
5 dihydroxy-lower-alkoxy,
dihydroxy-lower-alkoxy-lower-alkyl
dihydroxy-lower-alkyl-amino,
dihydroxy-lower-alkyl-amino-lower-alkyl
guanidinyllower-alkoxy-lower-alkyl,
10 guanidinyllower-alkyl,
hydroxy,
hydroxy-lower-alkyl,
sulphooxy-lower-alkyl,
hydroxy-lower-alkoxy,
15 hydroxy-lower-alkoxy-lower-alkyl,
morpholin-4-yl-lower-alkoxy,
morpholin-4-yl-lower-alkoxy-lower-alkyl,
morpholin-4-yl-lower-alkyl-carbamoyloxy-lower-alkyl,
naphthyl-alkoxy or naphthyl-alkoxy substituted by lower-alkoxy,
20 lower-alkoxy,
lower-alkoxy-lower-alkoxy
lower-alkoxy-lower-alkoxy-lower-alkyl,
lower-alkoxy-lower-alkyl,
lower-alkyl,
25 lower-alkylsulphonylamino-lower-alkyl,
phenoxy-lower-alkyl or phenoxy-lower-alkyl substituted by
lower-alkyl, lower-alkoxy,
phenyl-thio-lower-alkyl or phenyl-thio-lower-alkyl substituted
by lower-alkyl, lower-alkoxy,
30 piperazin-4-yl-lower-alkoxy,
piperazin-4-yl-lower-alkoxy-lower-alkyl,
piperidin-1-yl-lower-alkyl-carbamoyloxy-lower-alkyl,
piperidin-4-yl-lower-alkoxy,
piperidin-4-yl-lower-alkoxy-lower-alkyl,
35 pyridyl-lower-alkoxy,
pyridyl-lower-alkoxy-alkyl,
pyridylthio-lower-alkyl,

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pyrimidinyloxy-lower-alkyl or pyrimidinyloxy-lower-alkyl
 substituted by lower-alkoxy,
 tetrazolyl-lower-alkyl,
 trifluoromethylsulphonylamino-lower-alkyl or
 5 hydrogen.

Other preferred groups of compounds of formula I are those in
 which R² represents cyclohexyl or benzoyloxymethylcyclohexyl;
 those in which R² represents naphthyl, tetrahydronaphthyl or
 acenaphthyl; those in which R² represents pyridyl or oxopyridyl or
 10 pyridyl or oxopyridyl substituted by 3H-2-thioxo-benzthiazolyl,
 lower-alkoxyphenyl-lower-alkoxy-lower-alkoxy, phenyl-lower-
 alkoxy-lower-alkoxy, phenyl-lower-alkyl, cyclohexyl-lower-alkoxy,
 phenoxy-lower-alkyl or phenyl-lower-alkoxy-lower-alkyl; those in
 which R² represents pyrimidinyl or pyrimidinyl substituted by
 15 benzodioxanyl-lower-alkoxy, biphenyloxy, biphenyl-lower-
 alkoxy, cyclohexyl-lower-alkoxy, cyclohexyloxy-lower-alkoxy,
 halophenyl-lower-alkoxy, halophenyl-oxadiazolyl-lower-alkoxy,
 indanyl-lower-alkoxy, naphthyl-lower-alkoxy, phenyl-lower-alkyl,
 N-lower-alkyl-phenyl-lower-alkoxy-lower-alkylamino, N-lower-
 20 alkyl-phenyl-lower-alkylamino, lower-alkylthio, lower-alkoxy,
 lower-alkoxyphenyl-lower-alkoxy-lower-alkoxy, lower-
 alkoxyphenyl-lower-alkylamino, halophenyl-lower-alkylamino,
 halophenoxy-lower-alkoxy, lower-alkylpyridyl-lower-alkoxy,
 phenyl-lower-alkoxy-lower-alkoxy, phenyl-lower-alkoxy-lower-
 25 alkylthio, phenyl-lower-alkoxy-lower-alkylamino, phenoxy-phenyl-
 lower-alkoxy, phenoxy-phenoxy, phenyl-lower-alkynyloxy, lower-
 alkoxy-phenyl-lower-alkoxy-lower-alkoxy, phenylthio-lower-
 alkoxy, phenyl-oxazolyl-lower-alkoxy, phenyl-lower-alkenyloxy,
 phenyl-lower-alkylamino, phenyl-pyridyl-lower-alkoxy or phenyl-
 30 pyridyl-lower-alkylamino; and finally those in which R² represents
 halobenzoyloxy-lower-alkyl-triazolyl, phenyl-lower-alkoxy-lower-
 alkyl-triazolyl or phenyl-lower-alkoxy-lower-alkoxy-lower-alkyl-
 triazolyl.

Especially preferred are the following compounds:
 35 4-[2-[7-[(3R,4R)-4-[4-(3-benzyloxy-propoxy)-phenyl]-piperidin-3-
 yloxymethyl]-naphthalen-2-yloxy]-ethyl]-morpholine
 (R)-3-[7-[(3R,4R)-4-[4-(3-benzyloxy-propoxy)-phenyl]-piperidin-3-
 yloxymethyl]-naphthalen-2-yloxy]-propane-1,2-diol

- (S)-3-[7-[(3R,4R)-4-[4-(3-benzyloxy-propoxy)-phenyl]-piperidin-3-yloxymethyl]-naphthalen-2-yloxy]-propane-1,2-diol
- (R)-3-[2-[7-[(3R,4R)-4-[4-(3-benzyloxy-propoxy)-phenyl]-piperidin-3-yloxymethyl]-naphthalen-2-yloxy]-ethoxy]-propane-1,2-diol
- 5 (S)-3-[2-[7-[(3R,4R)-4-[4-(3-benzyloxy-propoxy)-phenyl]-piperidin-3-yloxymethyl]-naphthalen-2-yloxy]-ethoxy]-propane-1,2-diol
- 1-[2-[7-[(3R,4R)-4-[4-(3-benzyloxy-propoxy)-phenyl]-piperidin-3-yloxymethyl]-naphthalen-2-yloxy]-ethyl]-4-methyl-piperazine
- 10 1-[(3R,4S)-4-[4-(3-benzyloxy-propoxy)-phenyl]-piperidin-3-yl]-2-naphthalen-2-yl-ethanone
- (3R,4S,5S)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-(1,4-dimethoxy-naphthalen-2-ylmethoxy)-piperidin-5-ol
- 15 (3R,4R)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-[7-[(R)-2,3-dihydroxy-propoxymethyl]-naphthalen-2-ylmethoxy]-piperidine
- (3R,4R)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-[7-[(S)-2,3-dihydroxy-propoxymethyl]-naphthalen-2-ylmethoxy]-piperidine
- (3R,4R)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-[6-[(R)-2,3-dihydroxy-propoxymethyl]-naphthalen-2-ylmethoxy]-piperidine
- 20 (3R,4R)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-[6-[(S)-2,3-dihydroxy-propoxymethyl]-naphthalen-2-ylmethoxy]-piperidine
- 4-[(3R,4S,5S)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidin-5-yloxy]-butan-1-ol
- 25 3-[(3R,4S,5S)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidin-5-yloxy]-propan-1-ol
- 1-{2-[(3R,4R,5S)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidin-5-yloxy]-ethyl}-4-methyl-piperazine
- 30 (3R,4R,5R)-4-[2-[4-[4-(3-benzyloxy-propoxy)-phenyl]-5-(naphthalen-2-ylmethoxy)-piperidin-3-ylmethoxy]-ethyl]-morpholine
- (3R,4S,5S)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-(4-methoxy-benzyloxy)-piperidin-5-ol
- 35 (3R,4s,5S)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3,5-bis-(4-methoxy-benzyloxy)-piperidine

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- (3S,4R,5R)-4-[2-[4-[4-(3-benzyloxy-propoxy)-phenyl]-5-(naphthalen-2-ylmethoxy)-piperidin-3-ylmethoxy]-ethyl]-morpholine
- (3S,4R,5R)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-methoxymethyl-5-(naphthalen-2-ylmethoxy)-piperidine
- (3S,4R,5R)-4-[4-(3-benzyloxy-propoxy)-phenyl]-5-(naphthalen-2-ylmethoxy)-piperidin-3-ylmethyl [3-(4-methyl-piperazin-1-yl)-propyl]-carbamate
- (3S,4R,5R)-4-[4-[4-(3-benzyloxy-propoxy)-phenyl]-5-(naphthalen-2-ylmethoxy)-piperidin-3-ylmethanolsulphanyl]-pyridine
- 2-(4-cyclohexyl-butoxy)-5-[(3R,4R)-3-(1,4-dimethoxynaphthalen-2-ylmethoxy)-piperidin-4-yl]-pyrimidine
- (3'R,4'R)-6-(3-cyclohexyl-propoxy)-3'-(1,4-dimethoxynaphthalen-2-ylmethoxy)-1',2',3',4',5',6'-hexahydro-[3,4']bipyridine
- (3S,4R,5R)-[4-[4-(3-benzyloxy-propoxy)-phenyl]-5-(naphthalen-2-ylmethoxy)-piperidin-3-yl]-methanol
- (3S,4R,5R)-N-[4-[4-(3-benzyloxy-propoxy)-phenyl]-5-(naphthalen-2-ylmethoxy)-piperidin-3-ylmethyl]-N,N',N'-trimethyl-ethane-1,2-diamine
- (3S,4R,5R)-[4-[4-(3-benzyloxy-propoxy)-phenyl]-5-(naphthalen-2-ylmethoxy)-piperidin-3-ylmethyl]-diethyl-amine
- 1-[(3R,4S,5S)-4-[4-(3-benzyloxy-propoxy)-phenyl]-5-(2-morpholin-4-yl-ethoxymethyl)-piperidin-3-yl]-2-naphthalen-2-yl-ethanone
- (3R,4R)-3-(1,4-dimethoxynaphthalen-2-ylmethoxy)-4-[4-[3-(2-methoxy-phenoxy)-propoxy]-phenyl]-piperidine
- (3R,4s,5S)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3,5-bis-(3,4,5-trimethoxy-benzyloxy)-piperidine
- (3R,4R,5S)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-5-[1,2,4]triazol-1-ylmethyl-piperidine
- (3R,4R)-4-[4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl]-3-(quinolin-7-ylmethoxy)-piperidine
- 2-(7-[(3R,4R)-4-[4-(3-benzyloxy-propoxy)-phenyl]-piperidin-3-yloxymethyl]-naphthalen-2-ylmethoxy)-ethanol
- 7-[(3R,4R)-4-[4-(3-benzyloxy-propoxy)-phenyl]-piperidin-3-yloxymethyl]-naphthalen-2-ylmethyl)-dimethyl-amine

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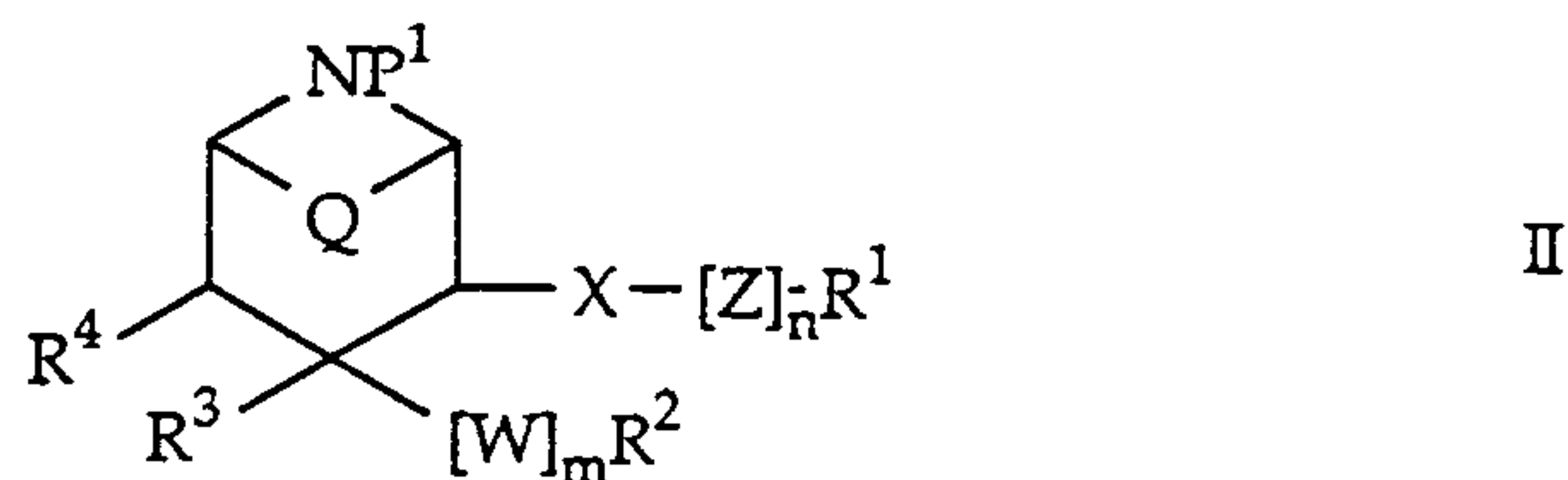
- (3R,4R)-3-(4-benzyloxy-naphthalen-2-ylmethoxy)-4-(4-fluorophenyl)-piperidine
 (3'R,4'R)-3'-(1,4-dimethoxy-naphthalen-2-ylmethoxy)-6-[3-(2-methoxybenzyloxy)-propoxy]-1',2',3',4',5',6'-hexahydro-
- 5 [3,4']bipyridine
 (3R,4R)-3-(1,4-dimethoxy-naphthalen-2-ylmethoxy)-4-[4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl]-piperidine
 (3S,4R,5R)-1-[4-[4-(3-benzyloxy-propoxy)-phenyl]-5-(naphthalen-2-ylmethoxy)-piperidin-3-ylmethyl]-imidazolidin-2-
- 10 one
 (3R,4R)-4-[4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl]-3-(2-oxo-1,2-dihydro-quinolin-7-ylmethoxy)-piperidine,
 (3R,4R)-3-(isoquinolin-7-ylmethoxy)-4-[4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl]-piperidine,
- 15 (3R,4R)-4-[4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl]-3-(1,2,3,4-tetrahydro-quinolin-7-ylmethoxy)-piperidine,
 1-[2-[7-[(3R,4R)-4-[4-[3-(2-methoxy-benzyloxy)-propoxy]-piperidin-3-yloxymethyl]-naphthalin-2-yloxy]-ethyl]-4-methyl-piperazine,
- 20 1-[2-[7-[(3R,4S,5S)-5-hydroxy-4-[4-[3-(2-methoxy-benzyloxy)-propoxy]-piperidin-3-yloxymethyl]-naphthalin-2-yloxy]-ethyl]-4-methyl-piperazine,
 (3R,4S,5S)-3-(1,4-dimethoxy-naphthalin-2-ylmethoxy)-4-[4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl]-piperidin-5-ol,
- 25 (3R,4R,5S)-3-(1,4-dimethoxy-naphthalin-2-ylmethoxy)-4-{4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl}-5-(1H-tetrazol-5-ylmethyl)-piperidine and
 (3'S,4'S)-3'-(1,4-dimethoxy-naphthalen-2-ylmethoxy)-4-[3-(2-methoxy-benzyloxy)-propoxy]-1',2',3',4',5',6'-hexahydro-
- 30 [1,4']bipyridin-2-one.

The term "pharmaceutically usable salts" embraces salts with inorganic or organic acid such as hydrochloric acid, hydrobromic acid, nitric acid, sulphuric acid, phosphoric acid,

35 citric acid, formic acid, maleic acid, acetic acid, succinic acid, tartaric acid, methanesulphonic acid, p-toluenesulphonic acid and the like.

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The compounds of formula I can be manufactured in accordance with the invention by cleaving off the protecting group(s) from a compound of formula II



in which P¹ represents a protecting group and the remaining symbols have the significance given in claim 1 and hydroxy groups which may be contained in R¹, R² and R⁴ may be present in protected form,

10 if desired, functionally modifying reactive groups in the thus-obtained compound of formula I and/or converting the compound of formula I into a pharmaceutically usable salt, with the manufacture of 4-(4-fluorophenyl)-3-(3,4-methylenedioxy-

15 benzyloxy)piperidine and its hydrochloride being excluded.

The cleavage of a protecting group P¹ and hydroxy protecting groups which may be present can be carried out in a manner known per se. Examples of protecting groups P¹ are usual

20 amino protecting groups such as tert-butoxycarbonyl, benzyloxycarbonyl, vinyloxycarbonyl, alkylsilylalkyloxycarbonyl such as 2-(trimethylsilyl)ethoxycarbonyl, and trichloroethoxycarbonyl. Examples of hydroxy protecting groups are ether protecting groups such as tetrahydropyranyl, allyl, 2-(trimethylsilyl)ethoxy-

25 methyl, trityl, tert-butyldimethylsilyl or ester protecting groups such as acetyl.

The cleavage of these protecting groups is effected by acidic or basic hydrolysis, by hydrogenolysis, by reductive

30 methods or by means of Lewis acids. A solution of a mineral acid such as hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid and the like in an inert solvent or solvent mixture is advantageously used for the acidic hydrolysis. Suitable solvents are alcohols such as methanol or ethanol, ethers such as

35 tetrahydrofuran or dioxan, chlorinated hydrocarbons such as

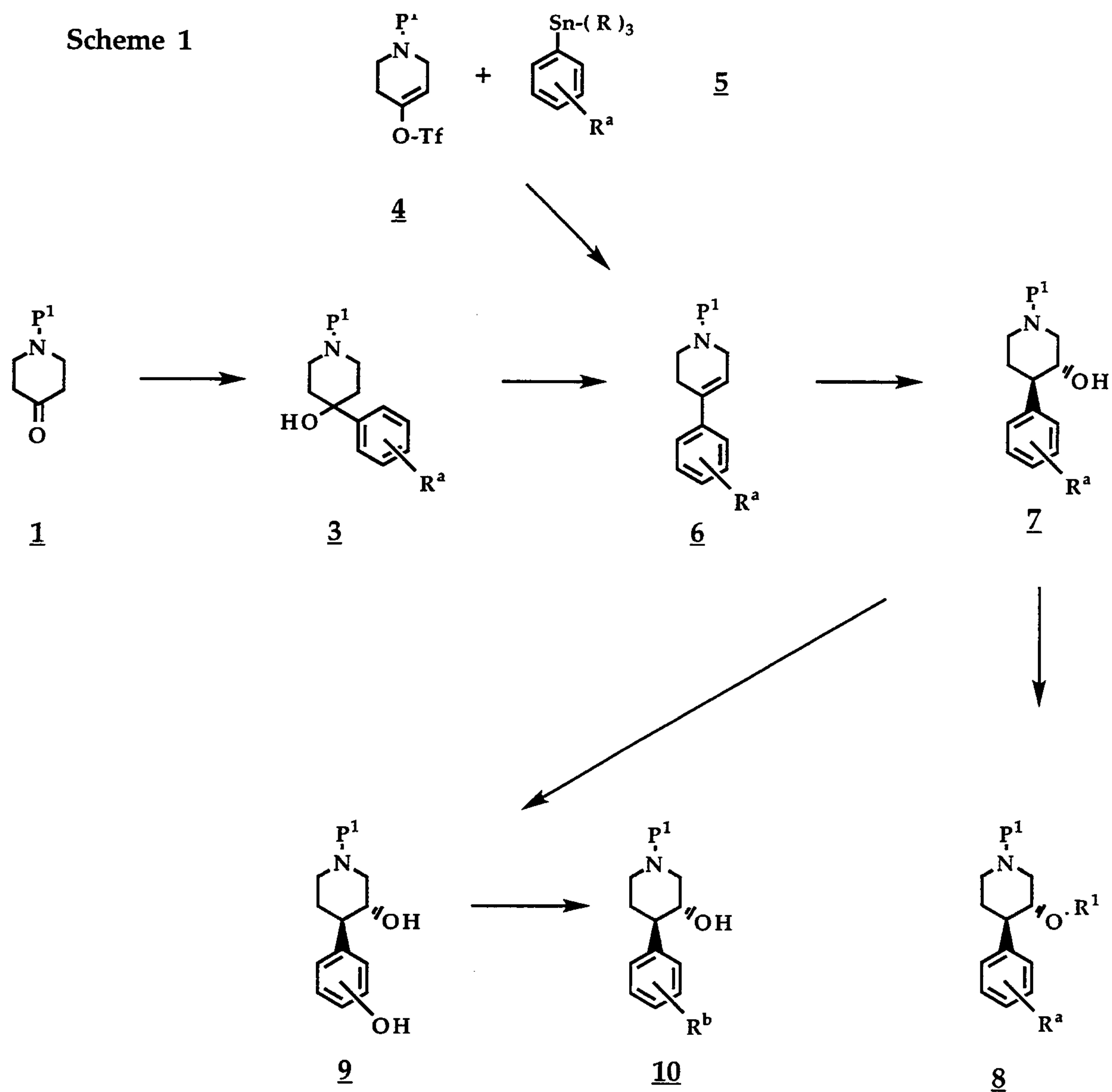
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methylene chloride, and the like. Alkali metal hydroxides and alkali metal carbonates such as potassium hydroxide or sodium hydroxide or potassium carbonate or sodium carbonate, organic amines such as piperidine, and the like can be used for the basic hydrolysis. Inert organic solvents as referred to above for the acidic hydrolysis can be used as solubilizers. The reaction temperature for the acidic and basic hydrolysis can be varied in a range from 0°C to the reflux temperature, with the reaction preferably being carried out at between about 0°C and room temperature. The tert-butoxycarbonyl group is conveniently cleaved off with hydrochloric acid, hydrogen chloride, trifluoroacetic acid or formic acid in the presence or absence of an inert solvent. Furthermore, the tert-butoxycarbonyl group can be cleaved off by means of anhydrous zinc bromide in the presence of an inert solvent, preferably methylene chloride. The cleavage of the trichloroethoxycarbonyl group can be advantageously effected reductively with zinc in glacial acetic acid. The reaction temperature can lie in a range of 0°C to 40°C, with the reaction preferably being carried out at room temperature. The cleavage of the 2-(trimethylsilyl)ethoxycarbonyl group can be effected by means of fluoride ions in the presence of an inert solvent such as acetonitrile, dimethyl sulphoxide, dimethylformamide or tetrahydrofuran, preferably by means of tetrabutylammonium fluoride in tetrahydrofuran, at temperatures from about 0°C to about room temperature.

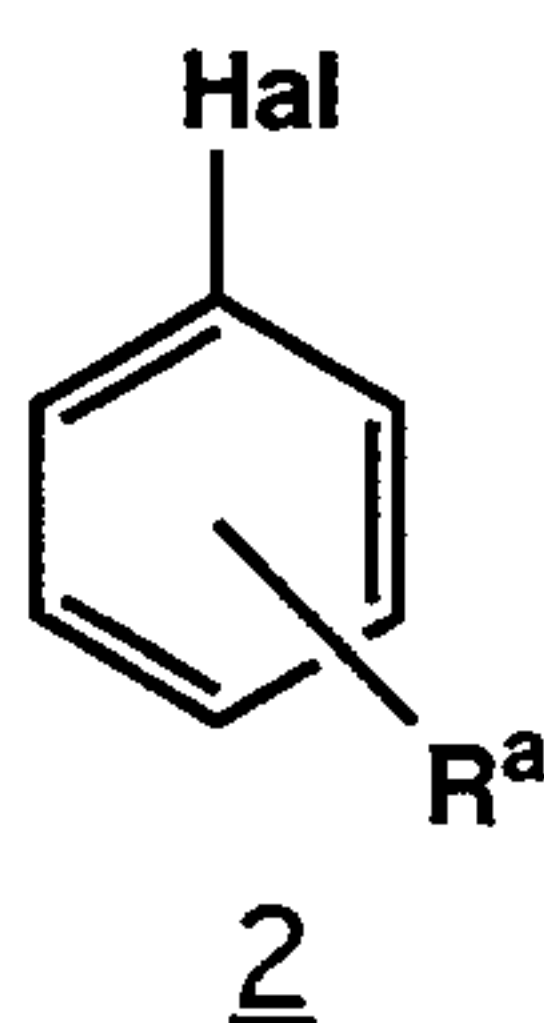
The compounds of formula II are novel and are also an object of the invention. Their preparation is described in more detail hereinafter in Schemes 1-15 and in the Examples.

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Scheme 1



In accordance with Scheme 1 compounds of general formula **3** can be obtained by reacting compounds of general formula **1** in a manner known per se with metal-organic derivatives, preferably lithium or magnesium derivatives, prepared from compounds of general formula **2**



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wherein R^a represents hydrogen or a substituent which is inert under the reaction conditions or in which reactive groups are present in protected form. Preferably, compounds 2 in which R^a represents halogen, lower-alkoxy or benzyloxy are used and these
5 substituents are utilized for the synthesis of another desired substituent at an appropriate later stage of the reaction sequence.

The reaction with such a metal-organic compound is
10 effected according to methods known per se, for example in a solvent which is inert under the reaction conditions, such as an ether, at a temperature between about -78°C and 75°C . The compounds of general formula 6 can be obtained therefrom in the presence of an acid or another water-cleaving reagent, optionally
15 in the presence of a base, in an organic solvent. As acids there come into consideration e.g. hydrochloric acid, trifluoroacetic acid or p-toluenesulphonic acid, and as the water-cleaving reagent there can be used e.g. phosphorus oxytrichloride in pyridine. The reaction temperature lies between $0-120^{\circ}\text{C}$; as
20 solvents there can be used e.g. toluene, dimethylformamide or alcohols.

Compounds of general formula 6 can also be obtained directly starting from a compound of general formula 4 in which
25 Tf is an activating group such as trifluoromethylsulphonyl (triflate) by reaction with a metal-organic compound, especially a tin derivative of general formula 5 in which R is lower-alkyl, e.g. butyl, or a corresponding arylboric acid derivative using a suitable catalyst such as e.g. tetrakis-triphenylphosphine-
30 palladium in an inert solvent such as dioxan, dimethoxyethane or dimethylformamide at temperatures between room temperature and 150°C .

Compounds of general formula 7 can be obtained from
35 compounds of general formula 6 by hydroboration and subsequent basic oxidative working-up. The hydroboration can be effected according to methods known per se, for example in a solvent which is inert under the reaction conditions, such as an ether, e.g.

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1,2-dimethoxyethane, at a temperature between about 0°C and 70°C, and with a diborane-containing or diborane-liberating reagent such as e.g. borane in tetrahydrofuran or a mixture of sodium borohydride and boron trifluoride etherate. The carbo-
 5 boranes which are formed as intermediates can be converted into the secondary alcohols of general formula 7 by reaction with bases, e.g. potassium hydroxide, and an oxidizing agent, e.g. hydrogen peroxide, at a temperature between about room temperature and 120°C.

10

Compounds of general formula 8 in which R^a is halogen, cyano, trifluoromethyl, lower-alkyl, lower-alkoxy-lower-alkyl, lower-alkoxy or lower-alkylenedioxy can be obtained from 7 by alkylation with a compound which yields the group R¹. The
 15 alkylation of the secondary alcohol is effected according to methods known per se, for example in a solvent which is inert under the reaction conditions, such as an ether, e.g. tetrahydrofuran or 1,2-dimethoxyethane, or dimethylformamide, with the aid of an alcoholate-forming base, e.g. sodium hydride, at a
 20 temperature between about 0°C and 40°C and using a halide, preferably chloride or bromide, or a sulphonic acid ester, e.g. a mesylate or tosylate, as the compound which yields R¹.
 Compounds of formula 7 in which R^a is lower-alkoxy can be converted into compounds of general formula 9 by an alkyl-aryl
 25 ether cleavage. The ether cleavage is effected according to methods known per se by, preferably starting from compounds in which R^a has the meaning methoxy, reacting the alkyl-aryl ether with mineral acids such as hydrobromic acid or hydroiodic acid or preferably with Lewis acids such as boron trichloride or boron
 30 tribromide in a solvent which is inert under the reaction conditions, such as e.g. a halogenated hydrocarbon, at a temperature between about -10°C and room temperature.

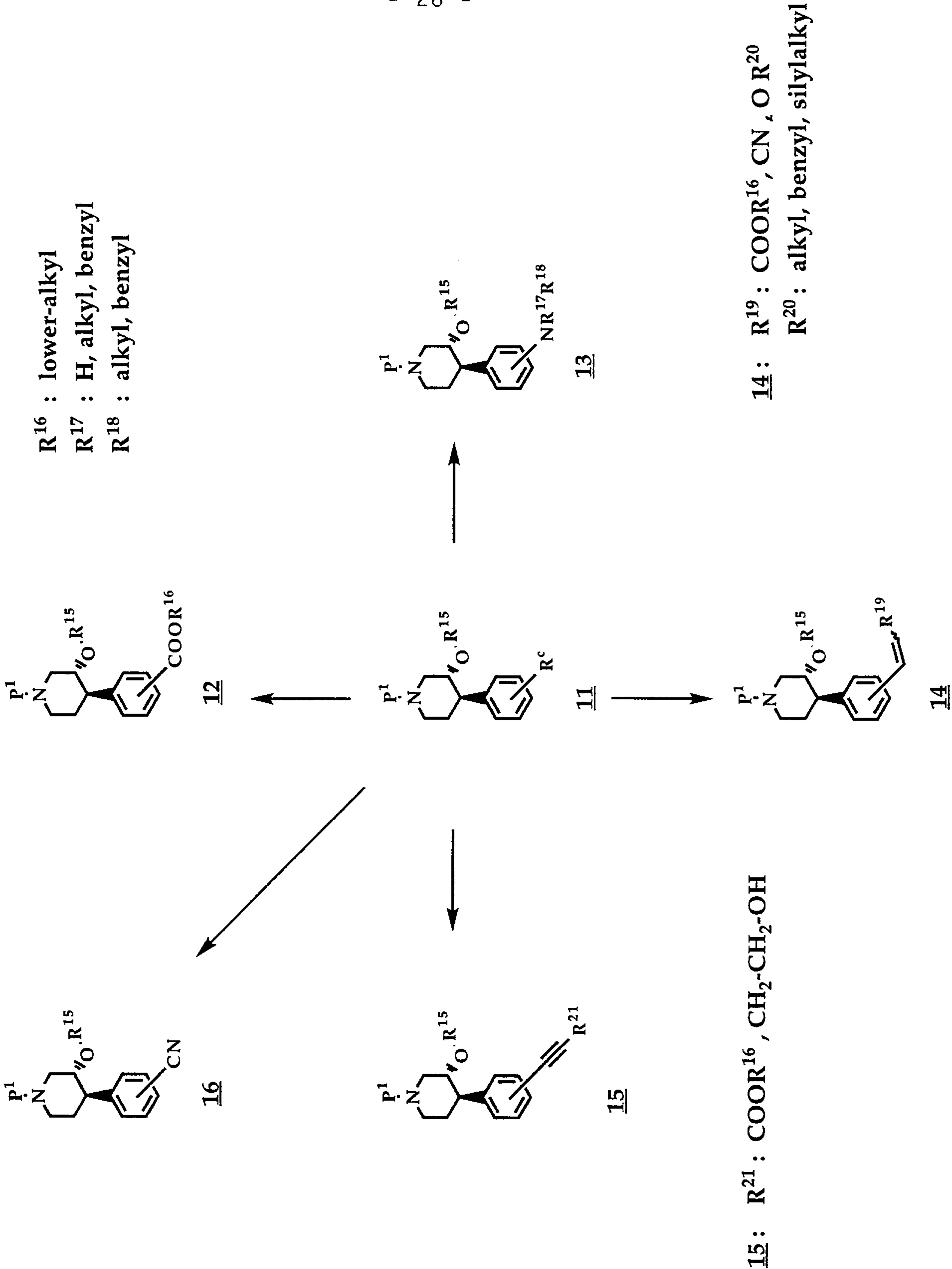
Compounds of general formula 9 can be used as starting
 35 materials for the preparation of compounds of general formula 10 in which R^b is a group -T¹-L²-T²-L³-T³-L⁴-T⁴-U, T¹ is oxygen, (m), (o) or (p) and the remaining symbols L^{2,3,4}, T^{2,3,4} and U can have the meanings referred to earlier. The linkage of the group

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-L²-T²-L³-T³-L⁴-T⁴-U can be effected selectively by reaction with a derivative of the group to be introduced which carries a suitable leaving group, although the desired group can also be built up stepwise. The selective linkage with the phenolic
5 alcohol is effected according to alkylation or acylation methods which are known per se in the presence of a base such as potassium carbonate. Chlorides, bromides, iodides, tosylates or mesylates come into consideration as alkylating agents. The reaction is effected in a solvent which is inert under the reaction
10 conditions, such as e.g. an ether such as tetrahydrofuran or an aromatic hydrocarbon such as e.g. toluene, pyridine, acetone or methyl ethyl ketone, at a temperature between about 0°C and 100°C. Suitable acylating agents are activated derivatives such as optionally activated esters, acid halides, acid anhydrides or
15 mixed acid anhydrides. The reaction is effected in a solvent which is inert under the reaction conditions, such as e.g. an ether such as tetrahydrofuran, an aromatic hydrocarbon such as e.g. toluene, a chlorinated hydrocarbon such as methylene chloride or chloroform, and the like at a temperature between about 0°C and
20 50°C.

Reactive groups such as keto or hydroxy groups contained in addition to the leaving group in the group to be introduced are preferably present in a form which is protected in a suitable
25 manner, e.g. in the form of acetals, esters, carbamates, silyl derivatives and the like. After cleavage of these protecting groups a stepwise synthesis of the group -T¹-L²-T²-L³-T³-L⁴-T⁴-U can be continued. The thus-obtained compounds containing a hydroxy group in the piperidine ring can be alkylated as described
30 above for the conversion of 7 into 8.

Scheme 2



29

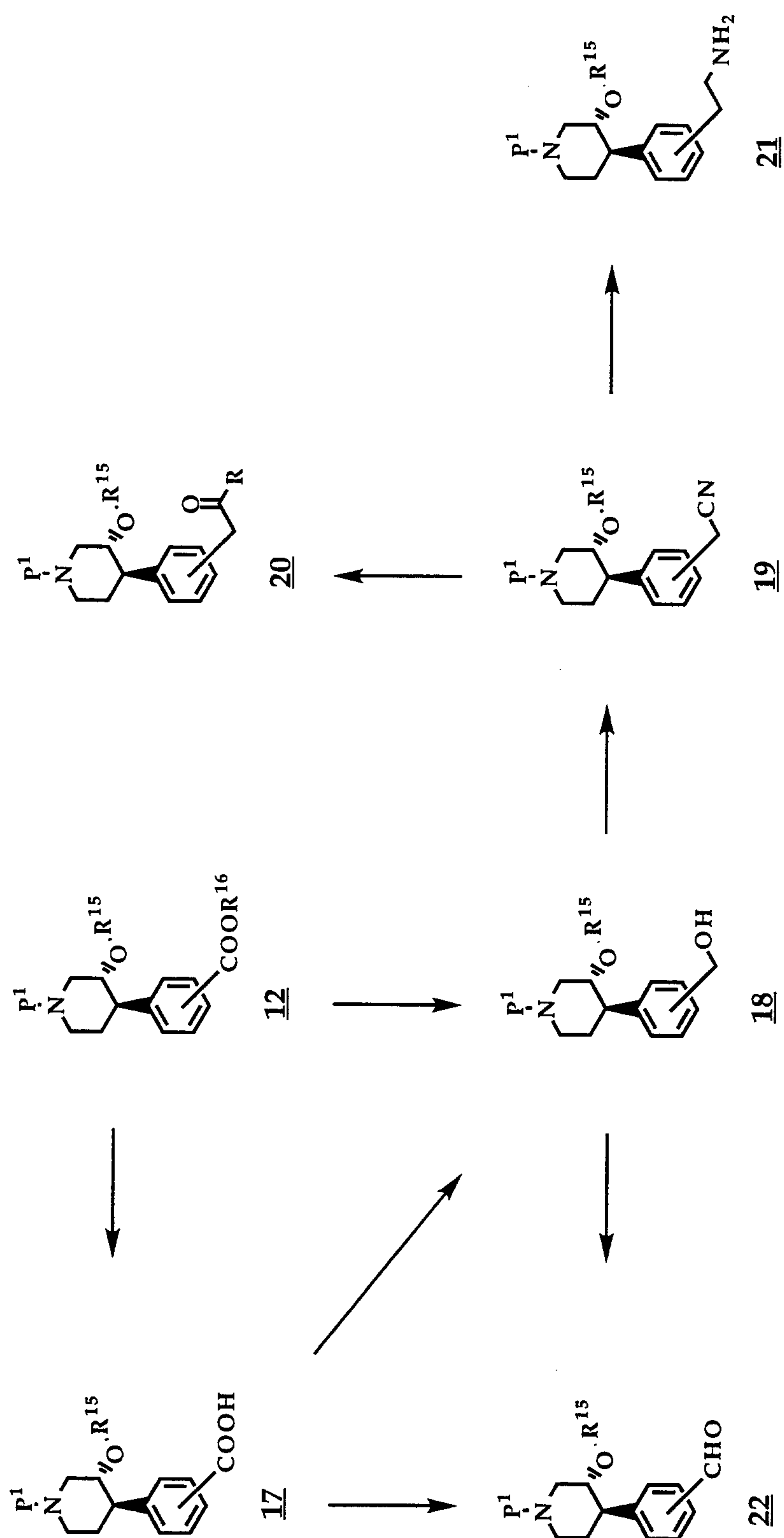
Compounds of formulae 12-16 can be prepared in accordance with Scheme 2 starting from compounds of general formula 11 in which R^c is chlorine, bromine, iodine as well as hydroxy in the form of an activated derivative such as e.g. the triflate and R¹⁵ is hydrogen or a group which is inert under the reaction conditions by carrying out palladium-catalyzed couplings in a manner known per se with carbon monoxide, cyanides, amines or compounds of the general formulae



wherein R¹⁹ is -COOR¹⁶, -CN or -OR²⁰.

As palladium catalysts there can be used complexes, prepared in situ, of e.g. PdCl₂(CH₃CN)₂ or Pd(OAc)₂ with 1,1'-bis(diphenylphosphino)ferrocene, 1,3-bis(diphenylphosphino)propane or tri(o-tolyl)phosphine. The group -HC=CH-R¹⁹ or -C≡C-R¹⁹ in the thus-obtained compounds can be derivatized for a further stepwise synthesis of a substituent L¹-T¹-L²-T²-L³-T³-L⁴-T⁴-U. A C≡C triple bond can be converted into a double bond and the latter can be converted into a single bond. A cyano group can be converted into an amide, an aldehyde, an acid, an ester or an amine. Compounds of formula 13 with R^{17,18} = benzyl can be debenzylated and the thus-formed sec. or prim. amino group can also be utilized for a further derivatization. All of these transformations or derivatizations, which are presented in a non-limiting manner in Schemes 3-9, can be undertaken according to methods known per se.

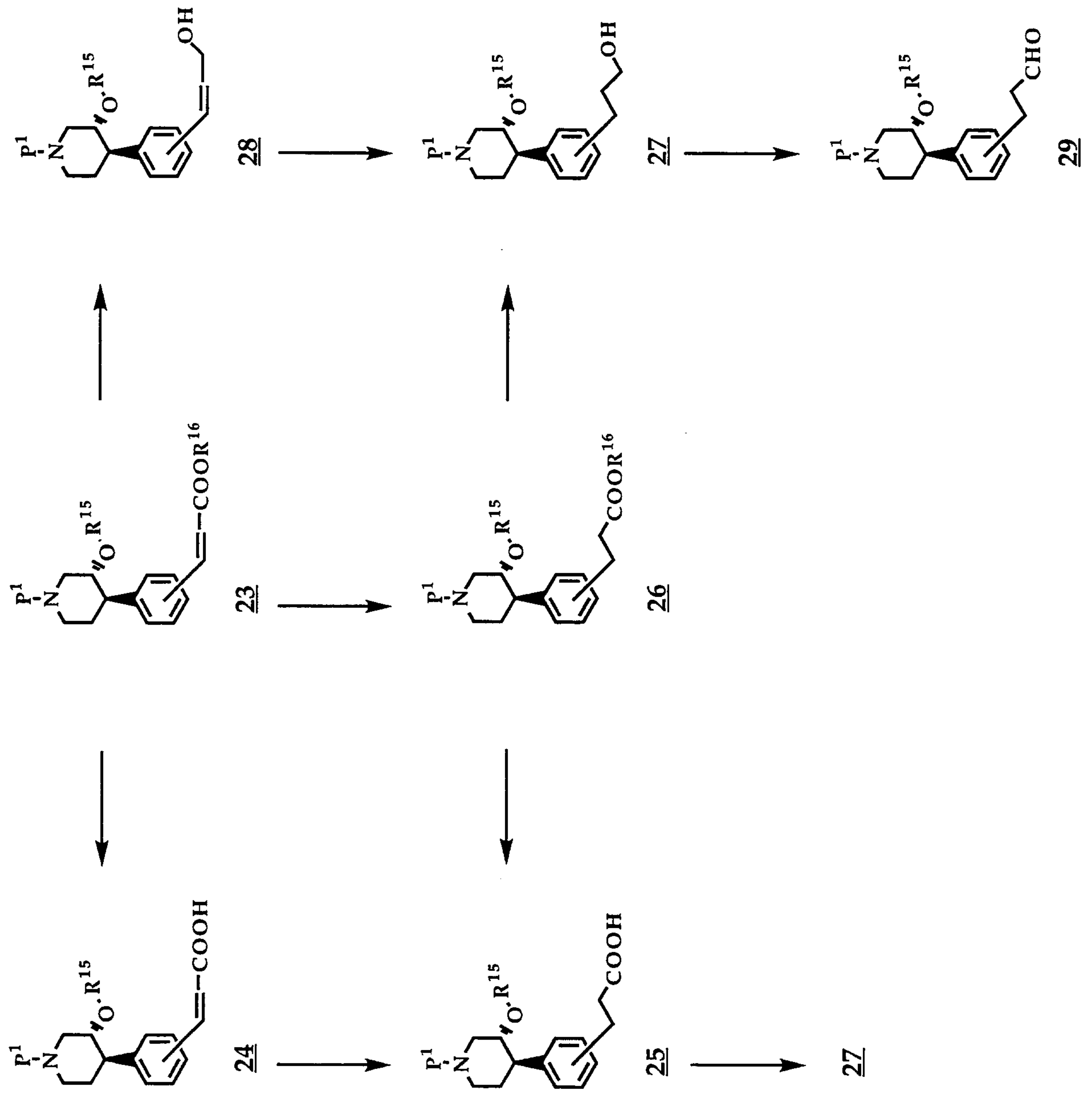
Scheme 3



- 31 -

Compounds of general formulae 17-22 can be obtained in accordance with Scheme 3 from compounds of general formula 12, obtained by reaction of compounds of general formula 11 with carbon monoxide by means of palladium catalysis.

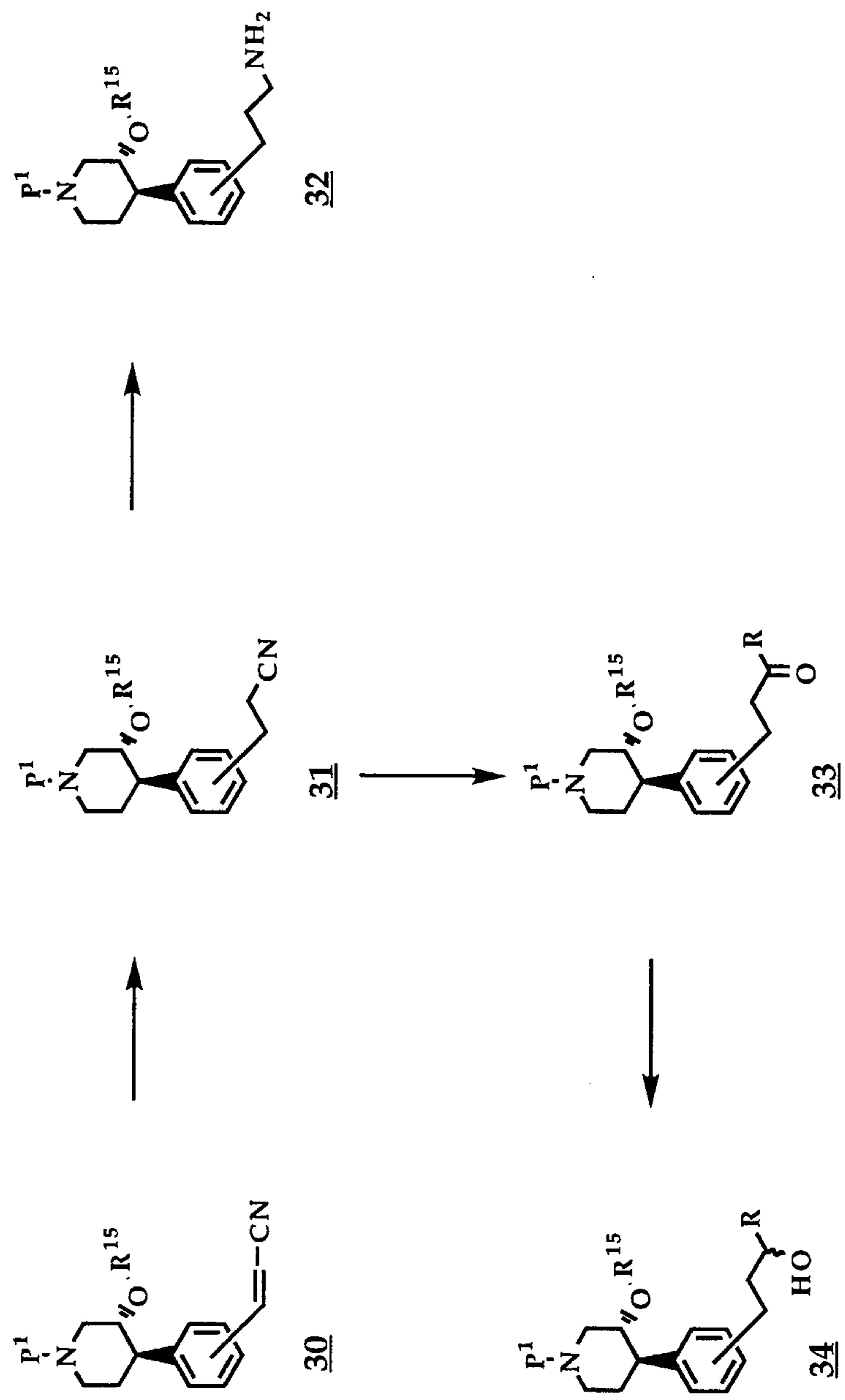
Scheme 4



- 33 -

Compounds of general formulae 24-29 can be obtained in accordance with Scheme 4 from compounds of general formula 23, obtained by reaction of compounds of general formula 11 with acrylic acid esters by means of palladium catalysis.

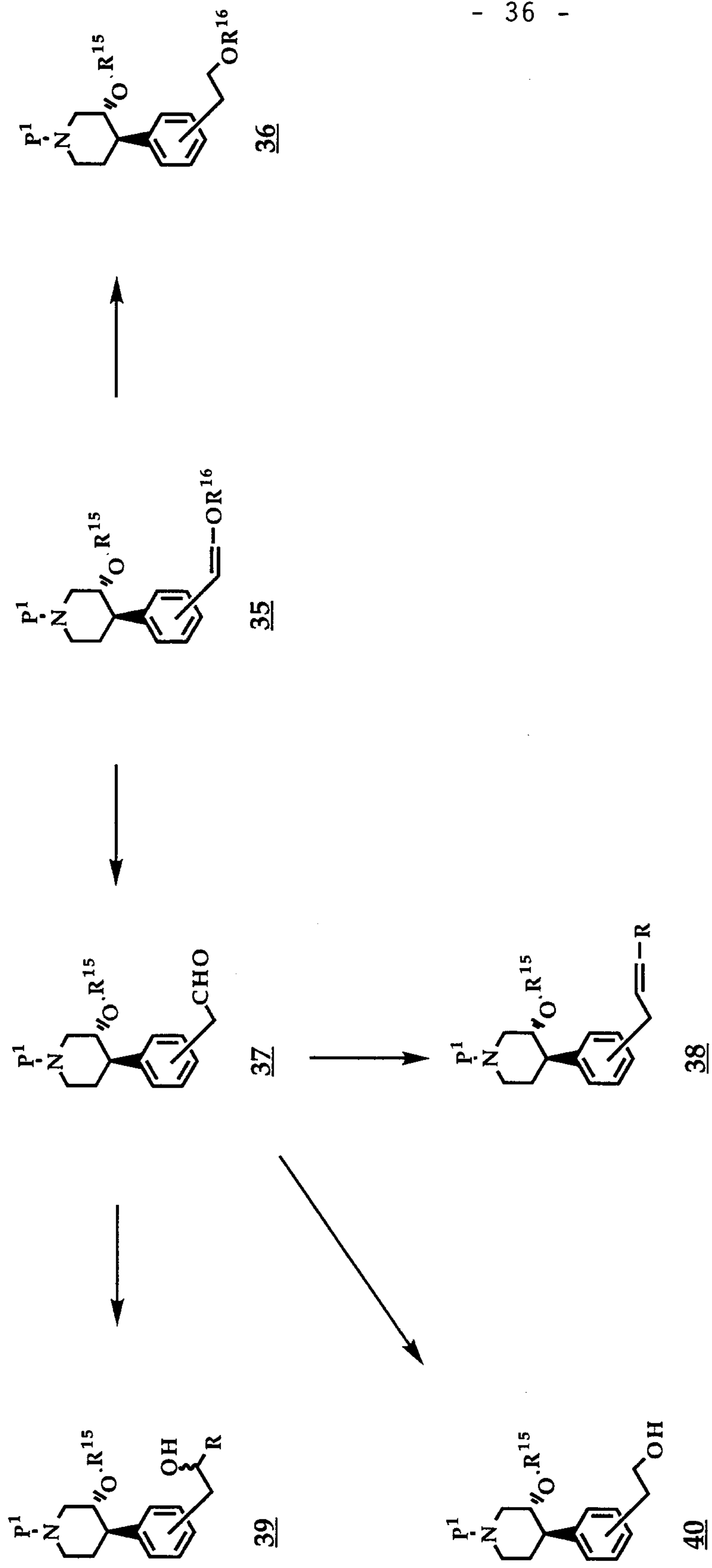
Scheme 5



- 35 -

Compounds of general formulae 31-34 can be obtained in accordance with Scheme 5 from compounds of general formula 30, obtained by reaction of compounds of general formula 11 with acrylonitrile by means of palladium catalysis.

Scheme 6



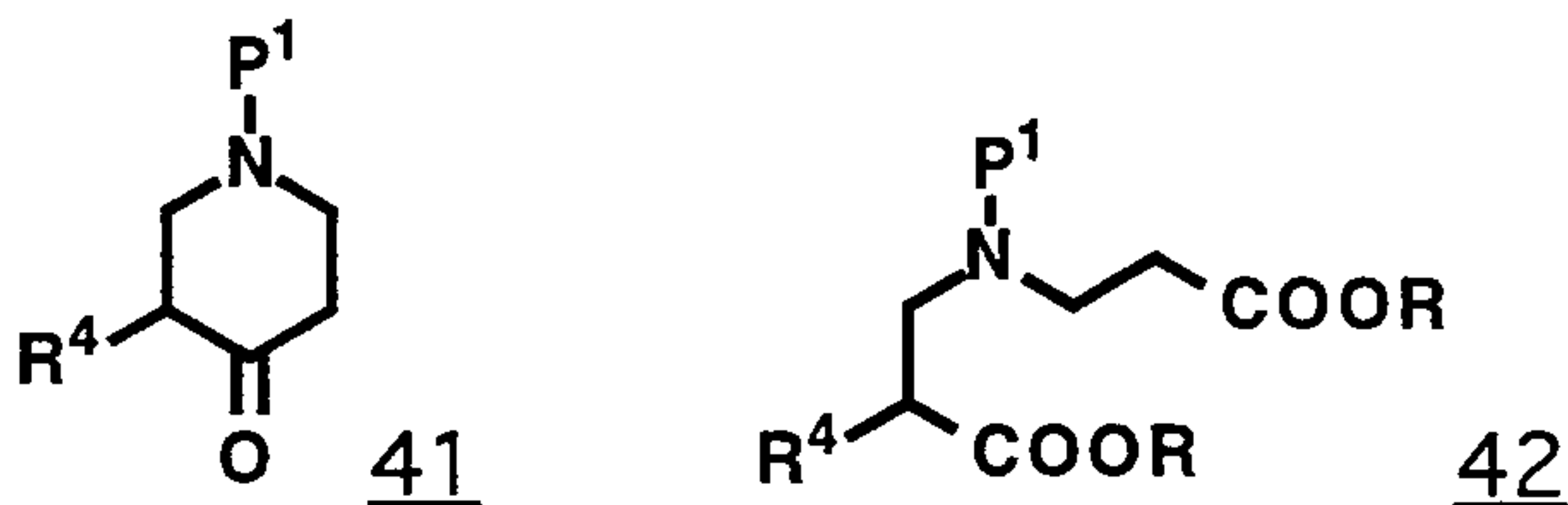
- 37 -

Compounds of general formulae 36-40 can be obtained in accordance with Scheme 6 from compounds of general formula 35, obtained by reaction of compounds of general formula 11 with vinyl ethers by means of palladium catalysis.

5

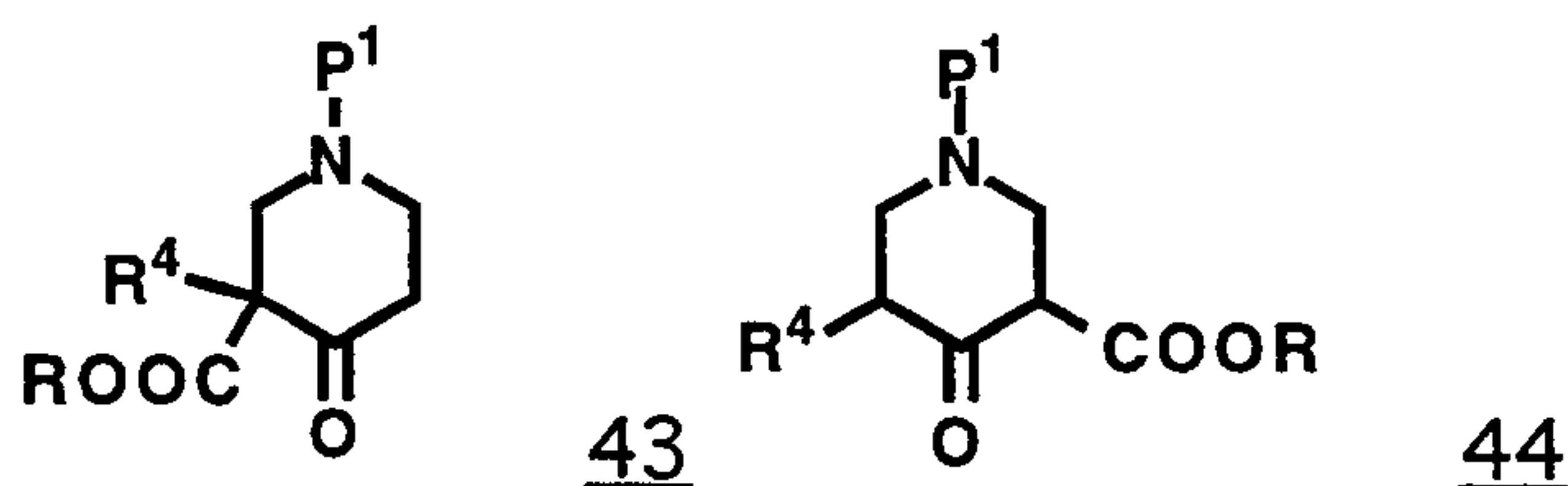
The piperidones of general formula 41 can be used as starting materials for the synthesis of the piperidine derivatives I analogously as described for the piperidone 1. They can be obtained analogously to the process of A.H. Beckett et al described in the Journal of Medicinal and Pharmaceutical Chemistry Vol 1(1), 37-58 (1959). The piperidones of general formula 41 can be obtained by intramolecular ring-closure of a propionic acid derivative of general formula 42,

15



in which R⁴ is as defined earlier or represents a substituent, which is inert under the reaction conditions or wherein reactive groups are present in an appropriately protected form. Preferably, R⁴ is chosen in a manner to make it possible to optionally construe another desired substituent at an appropriate later stage of the reaction sequence. P¹ has the meaning of methyl or benzyl. The ring closure is carried out in the presence of a base such as e.g. sodium alcoholate, sodium hydride or sodium dispersion in xylene. The subsequent decarboxylation of a thus-obtained compound of general formula 43 or 44

25

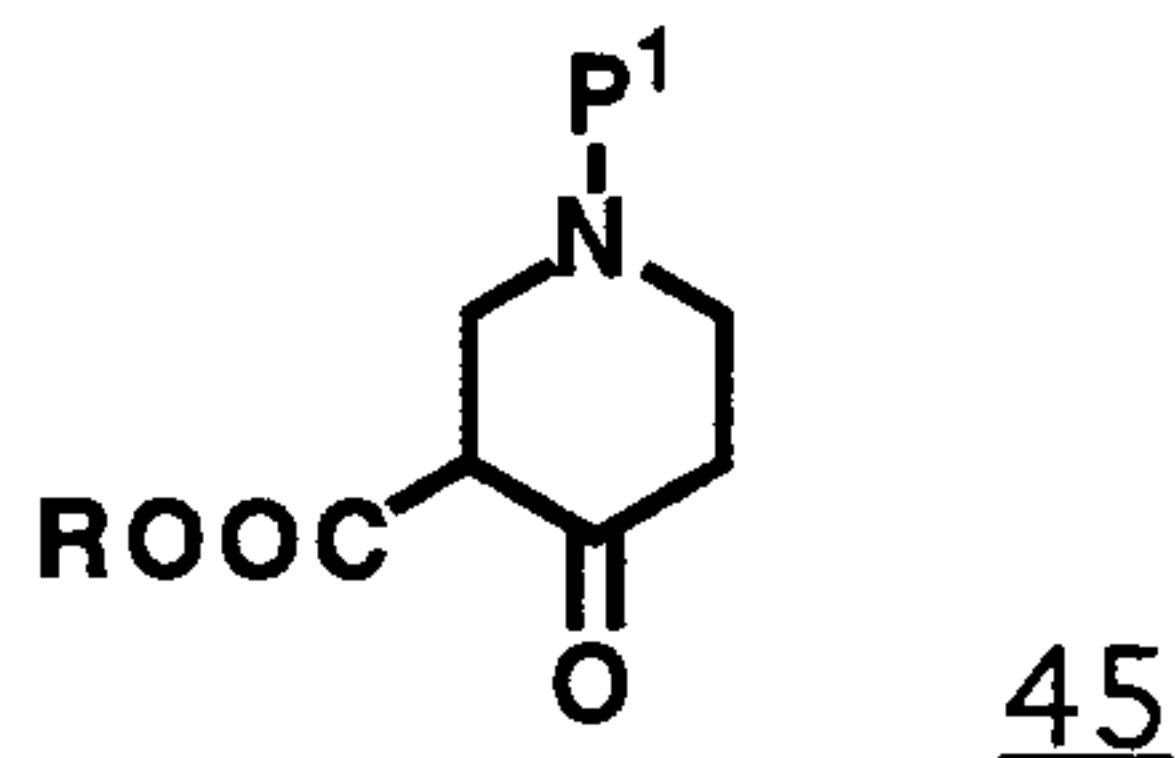


by means of hydrochloric acid leads to compounds of general formula 41.

30

- 38 -

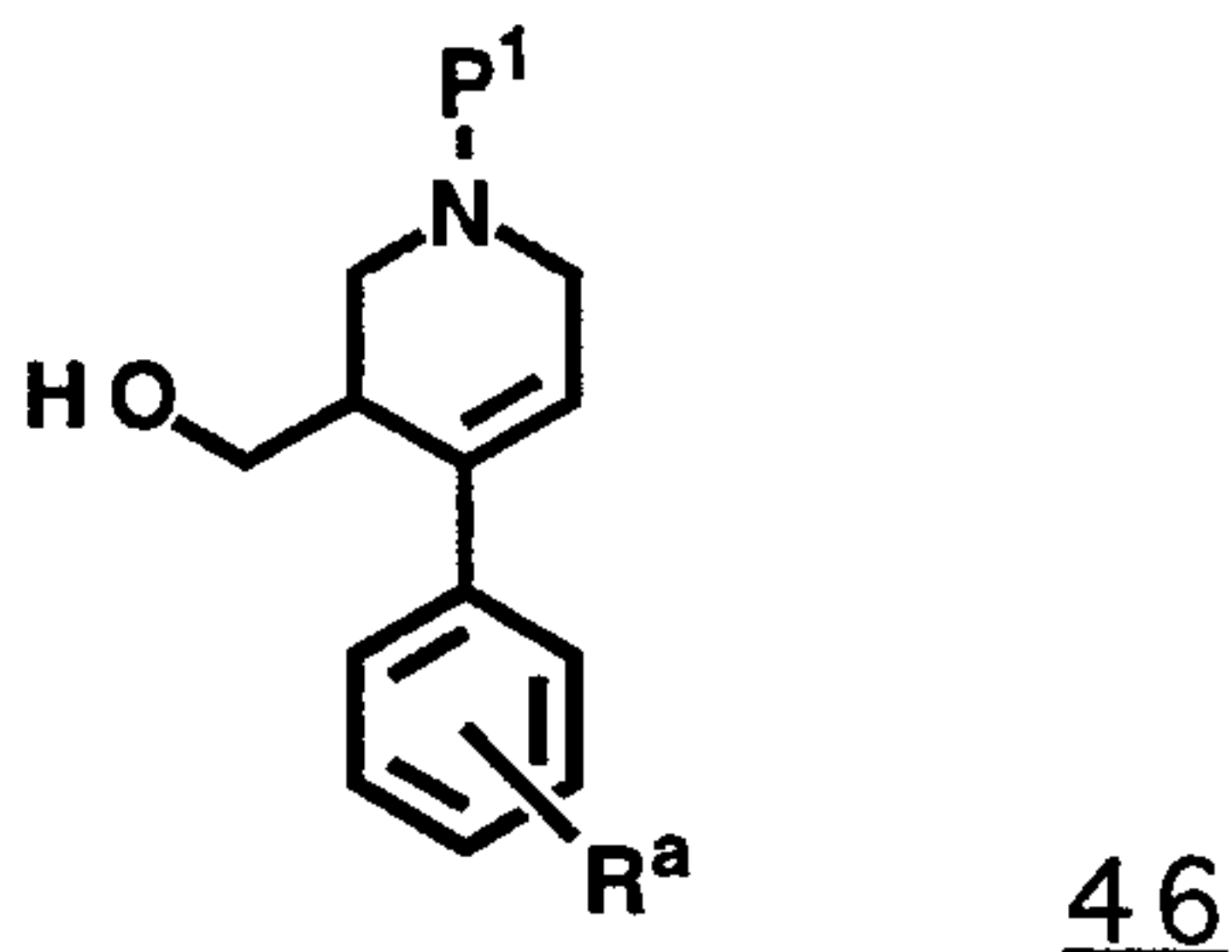
Derivatives of general formula 43 in which R⁴ signifies allyl or benzyl can also be prepared in a direct manner by C-alkylation of the sodium salt of a compound of general formula 45



by means of allyldimethylanilinium bromide or benzyldimethylanilinium bromide analogously to the process described by A.H.Beckett et al. (see above).

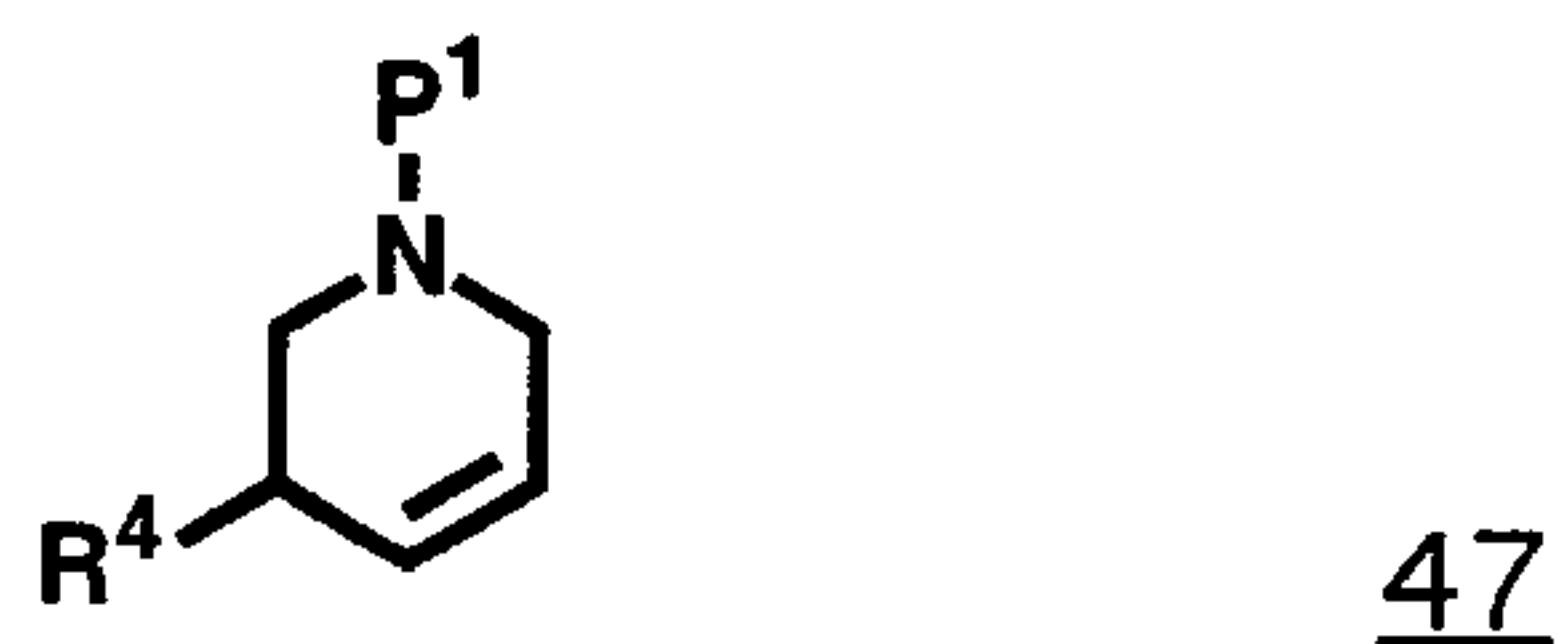
Derivatives of general formula 41 in which R⁴ signifies hydroxymethyl which is suitably protected at the hydroxy function can also be obtained from the compound of general formula 45 by reduction to the diol analogously to the process described by E.Jaeger und J.H.Biel in J.Org.Chem. 30(3), 740-744 (1965), introduction of a suitable protecting group for the primary alcohol, e.g. trityl, and oxidation of the secondary alcohol obtained.

Furthermore, derivatives of general formula 46 can be prepared by hydroxymethylating compounds of general formula 6 analogously to the process of K. Willcocks et al. described in the Journal of Labelled Compounds and Radiopharmaceuticals Vol. XXXIII, No.8, 783-794 (1993).



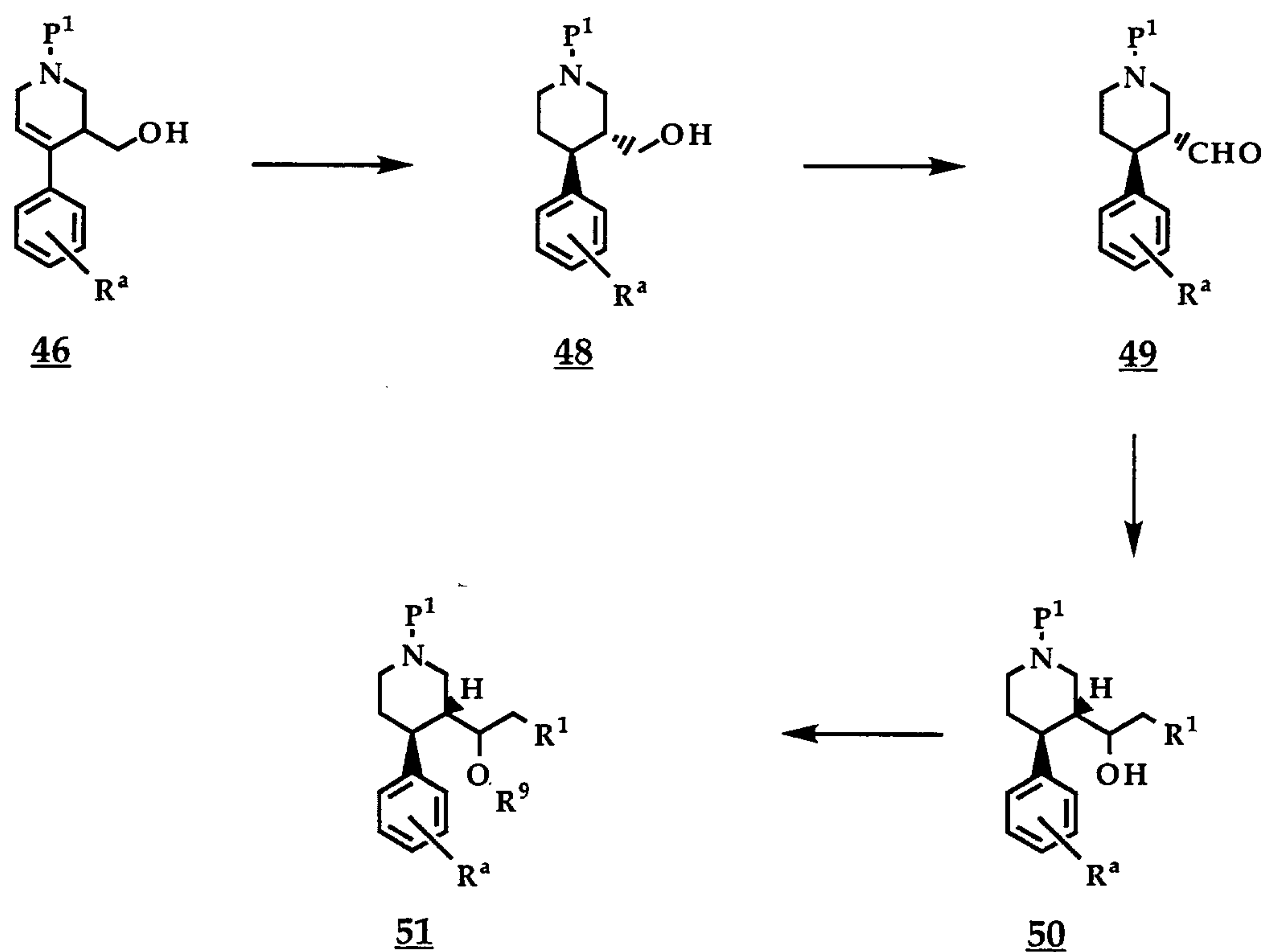
Compounds of general formula II in which R³ has the meaning hydrogen and W has the meaning oxygen or sulphur can be obtained starting from compounds of general formula 47

- 39 -



by epoxidation. Compounds of general formula 47 can be prepared
 5 according to the process described by M.Ferles and M.Jankovsky in
 Coll.Czechoslov.Chem.Comm. Vol, 35, 2802-2809 (1970). The
 epoxides can then be opened by reaction with suitable thio-
 phenolates and phenolates as described by R. Paioni in German
 Offenlegungsschrift 2738477. The further synthesis to
 10 compounds of formula II can be effected as described previously.

Scheme 7



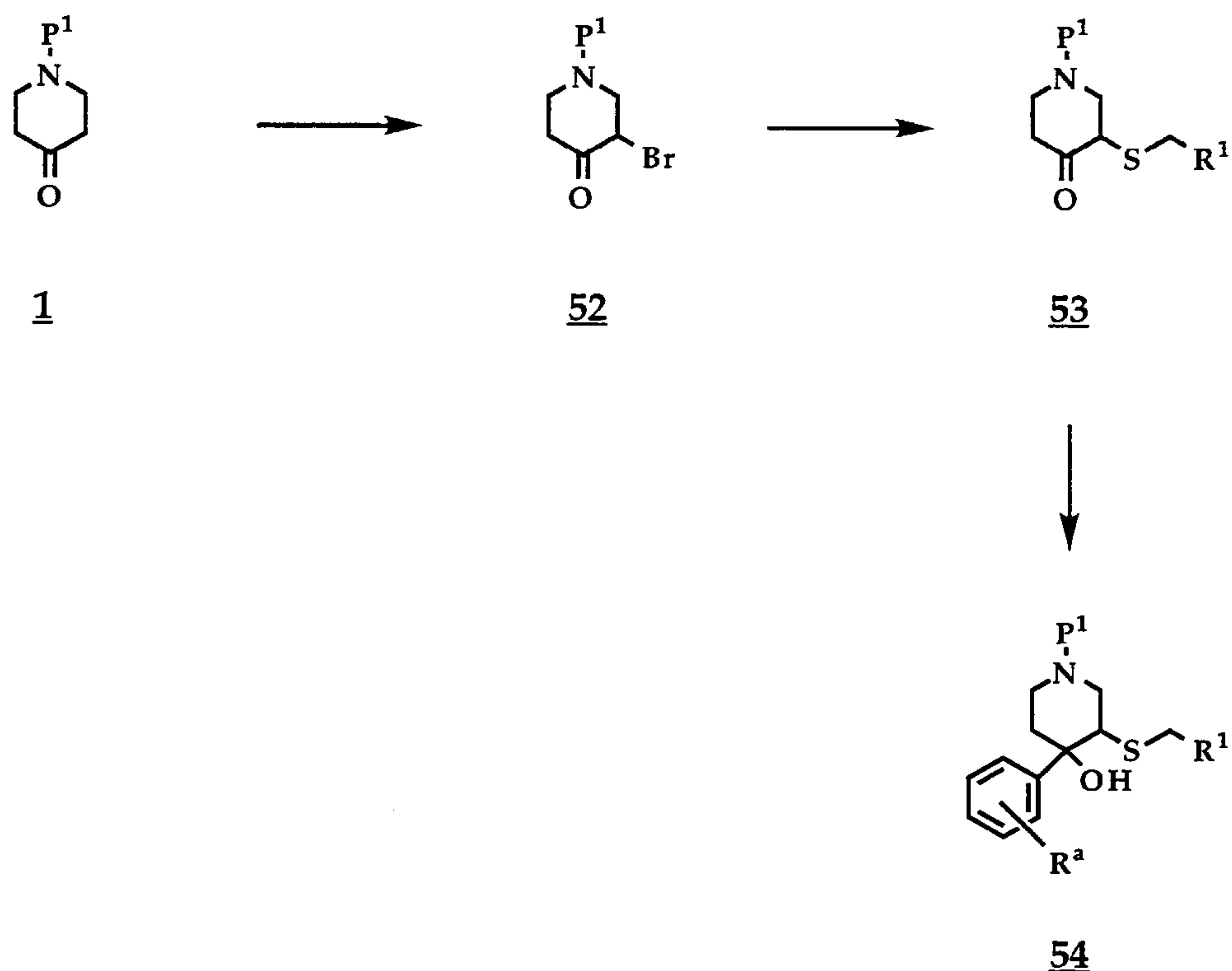
In accordance with Scheme 7 compounds of general formula
 15 51 can be obtained from compounds of general formula 46 by
 firstly reducing the double bond using complex hydrides such as
 lithium aluminium hydride as described by J.M. Lundbeck et al. in
 European Patent Application E.P. 0 374 674 or sodium dihydrido-
 bis-(2-methoxyethoxy)aluminate in a solvent which is inert under

- 40 -

the reaction conditions, such as tetrahydrofuran, dioxan or toluene, at temperatures between room temperature and 110°C or hydrogenating the double bond with hydrogen using a catalyst, with compounds of general formula 48 being obtained. Compounds
 5 of general formula 48 can be converted into the corresponding aldehydes of general formula 49 by a usual oxidation process, e.g. using oxalyl chloride and dimethyl sulphoxide as described by A.J. Mancuso and D. Swern in Synthesis 1981, 165.

10 The condensation of aldehydes of general formula 49 with Grignard or lithium compounds in a solvent which is inert under the reaction conditions, such as ether, tetrahydrofuran or dioxan, at temperatures between -80°C and room temperature leads to
 15 compounds of general formula 50 which can be converted according to known processes into the corresponding ester or ether compounds of general formula 51.

Scheme 8

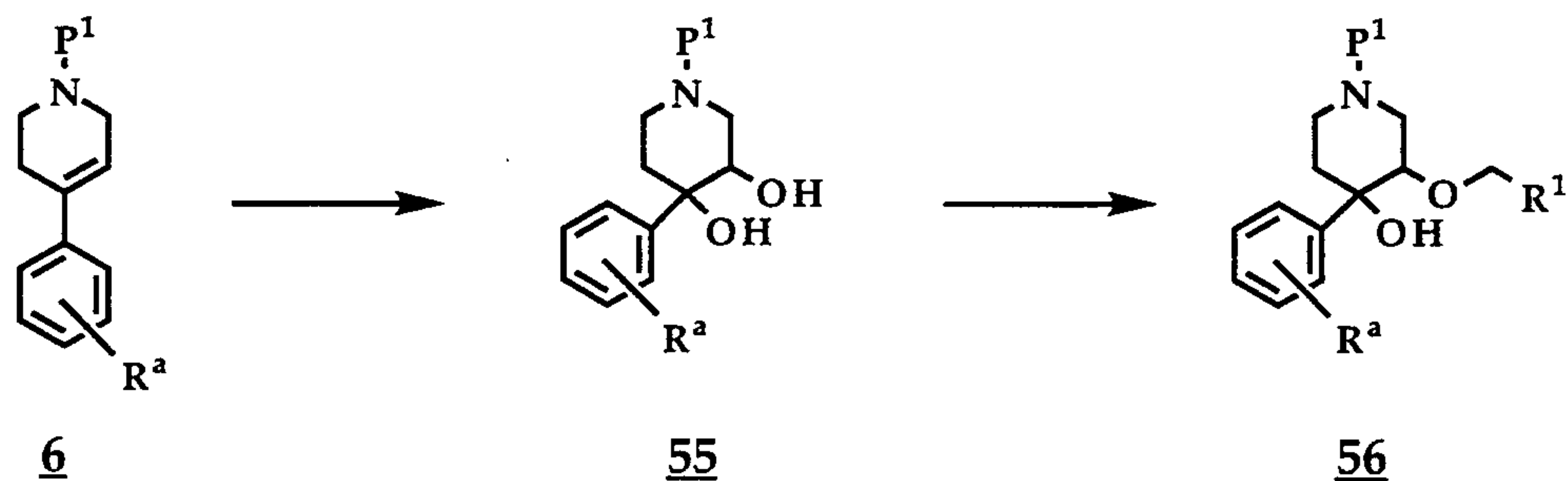


20 In accordance with Scheme 8 compounds of general formula 54 are obtained by brominating compounds of general formula 1 in

- 41 -

a solvent which is inert under the reaction conditions, such as chloroform or methylene chloride, and using a buffer salt such as disodium hydrogen phosphate at temperatures between 0°C and 50°C to firstly form compounds of general formula 52, reaction of
 5 which with an alkali metal salt of a thiol in a solvent such as acetone, acetonitrile or dimethylformamide at temperatures between room temperature and 100°C gives compounds of general formula 53. Condensation of these with Grignard or lithium compounds in inert solvents such as ether, tetrahydrofuran or
 10 dioxan at temperatures between -80°C and room temperature then yields compounds of general formula 54.

Scheme 9



15 In accordance with Scheme 9 compounds of general formula 56 can be obtained by dihydroxylating compounds of general formula 6 to compounds of general formula 55. Alkylation of these yields, according to previously described processes, compounds of general formula 56. The dihydroxylation can be
 20 effected according to processes known per se, for example in a solvent which is inert under the reaction conditions, such as acetone or tert-butanol, at a temperature between 0°C and 50°C, preferably at room temperature, with a hydroxylating reagent such as e.g. a mixture of osmium tetroxide and hydrogen peroxide.

25

The compounds prepared in Schemes 2-9 can, moreover, be used as described above as starting materials for a further synthesis of a substituent

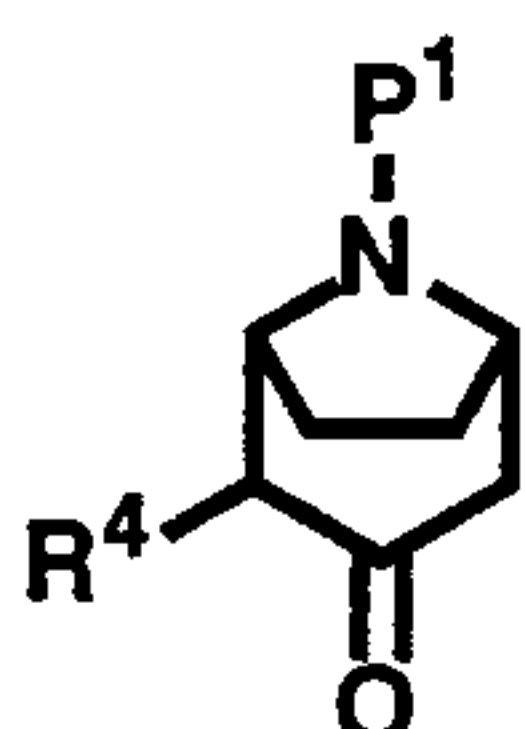
30

-L¹-T¹-L²-T²-L³-T³-L⁴-T⁴-U

- 42 -

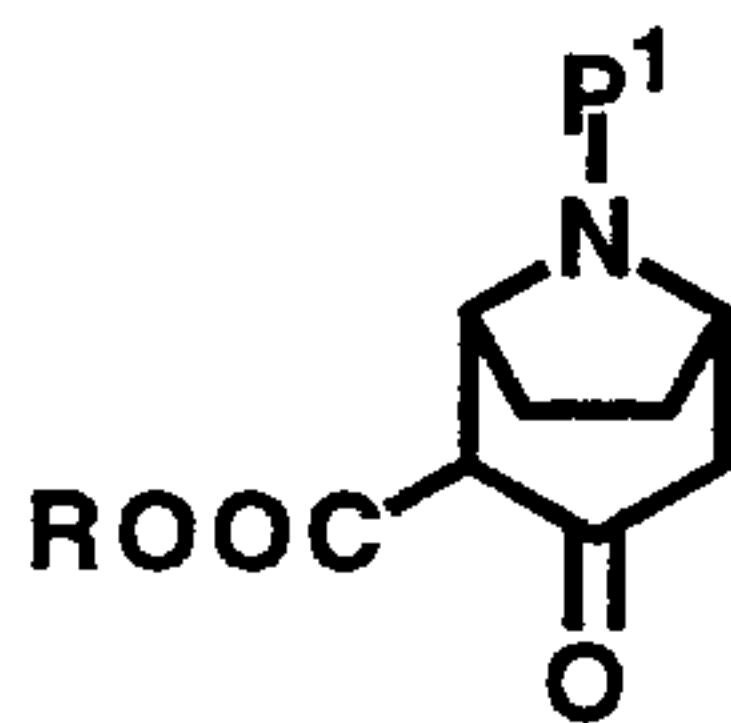
optionally present in R².

Furthermore, compounds of general formula II in which an ethylene bridge Q is present can be prepared in accordance with
 5 the processes described in Schemes 1-9 as well as the processes described hereinbefore and in more detail in the Examples.

57

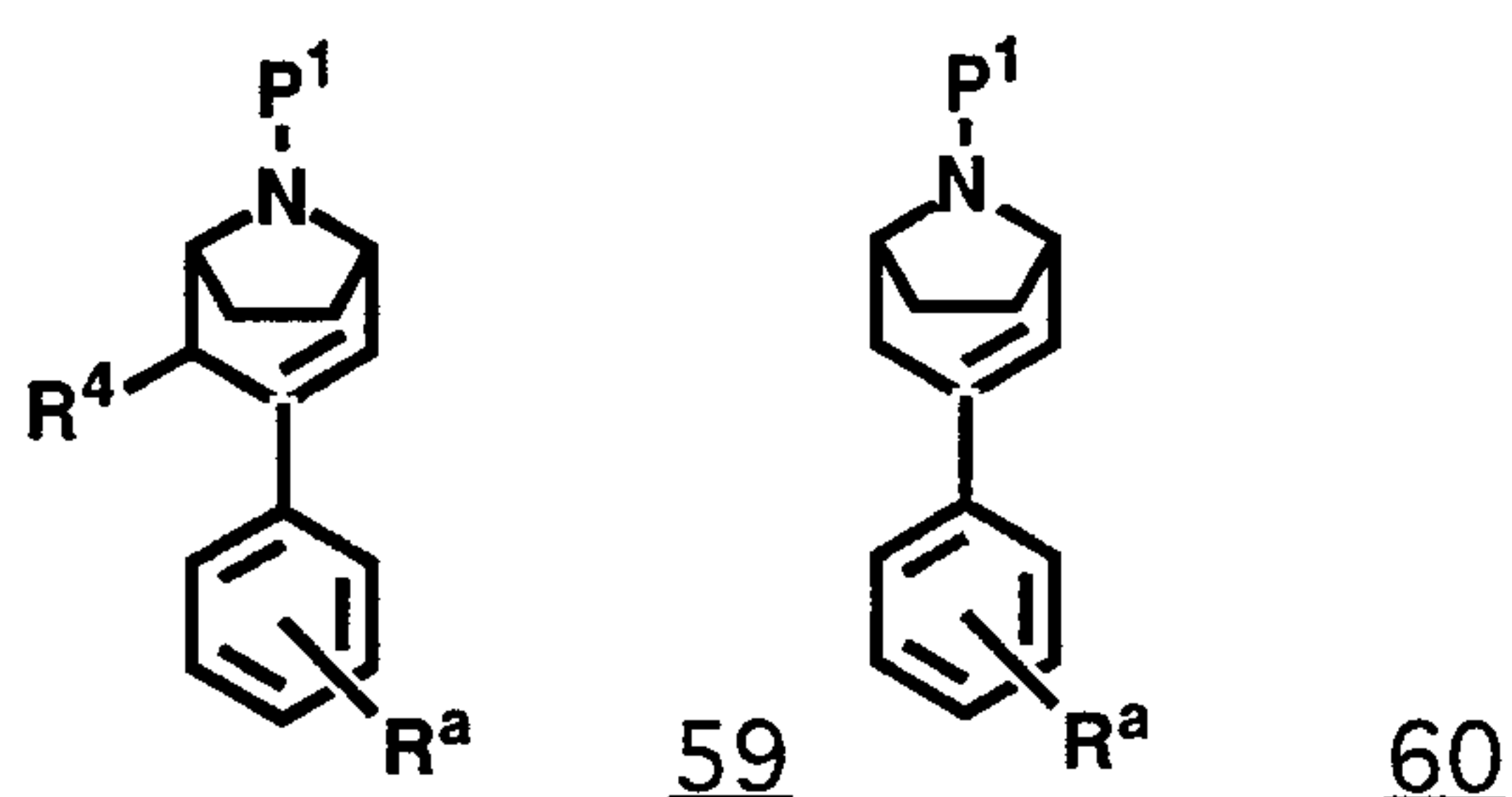
10 The tropinones of general formula 57 usable as starting materials can be prepared, inter alia, according to the processes described by M.Lounasmaa and C.J.Johansson in Tetrahedron Letters, No.29, 2509 (1974) or Ö.Kovács et al. in Helv.Chim.Acta Vol. XXXVII, 802 (1954).

15

58

Derivatives of general formula 57 can be obtained from the compound of general formula 58 according to the process
 20 described by Ö.Kovács et al. in Helv.Chim.Acta Vol. XXXVII, 802 (1954) by reduction to the diol, introduction of a suitable protecting group for the primary alcohol, e.g. trityl, and oxidation of the secondary alcohol obtained. Herein, R⁴ is as defined earlier or is a substituent which is inert under the reaction conditions or
 25 wherein any reactive groups are present in protected form and are preferably chosen in a manner to make the construction of another desired substituent at an appropriate, later stage of the reaction sequence possible.

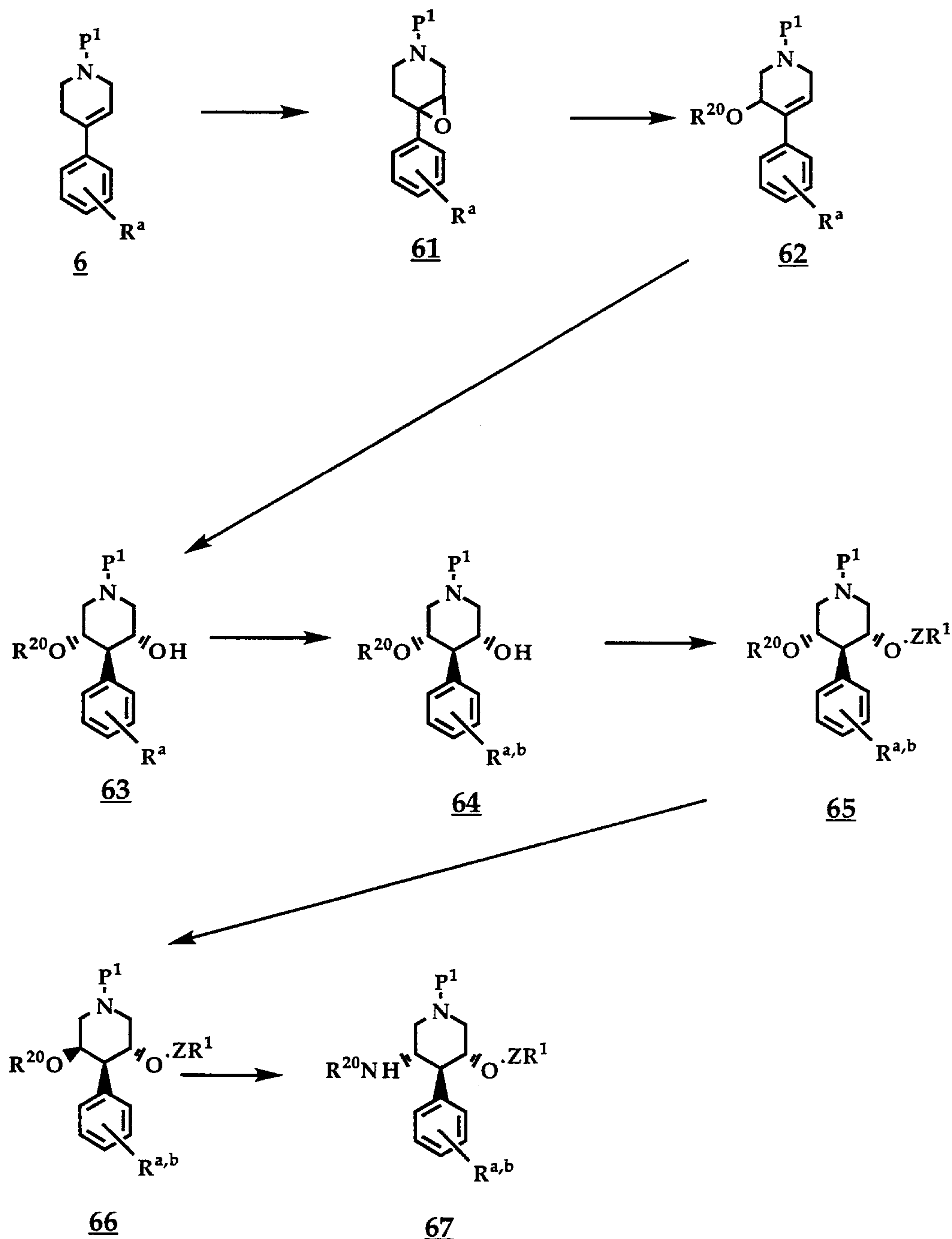
- 43 -



Furthermore, derivatives of general formula 59 in which R^4 signifies hydroxymethyl can be prepared by hydroxymethylating
 5 compounds of general formula 60 analogously to the process of K. Willcocks et al. described in Journal of Labelled Compounds and Radiopharmaceuticals Vol. XXXIII, No.8, 783-794 (1993).

Furthermore, there exists the possibility of preparing
 10 derivatives of general formula 57 starting from correspondingly substituted acetonedicarboxylic acid derivatives by a reaction with succindialdehyde and an amine analogously to procedures known in the literature, with the corresponding tropinone derivative being synthesized. The substituted acetone-
 15 dicarboxylic acid derivatives used as starting materials can be prepared according to the procedures described by I. Ito and S. I. Nagai in Chem. Pharm. Bull. 22(9) 2131 (1974) or T. Arslan and S. A. Benner in J. Org. Chem. 58, 2260 (1993).

Scheme 10

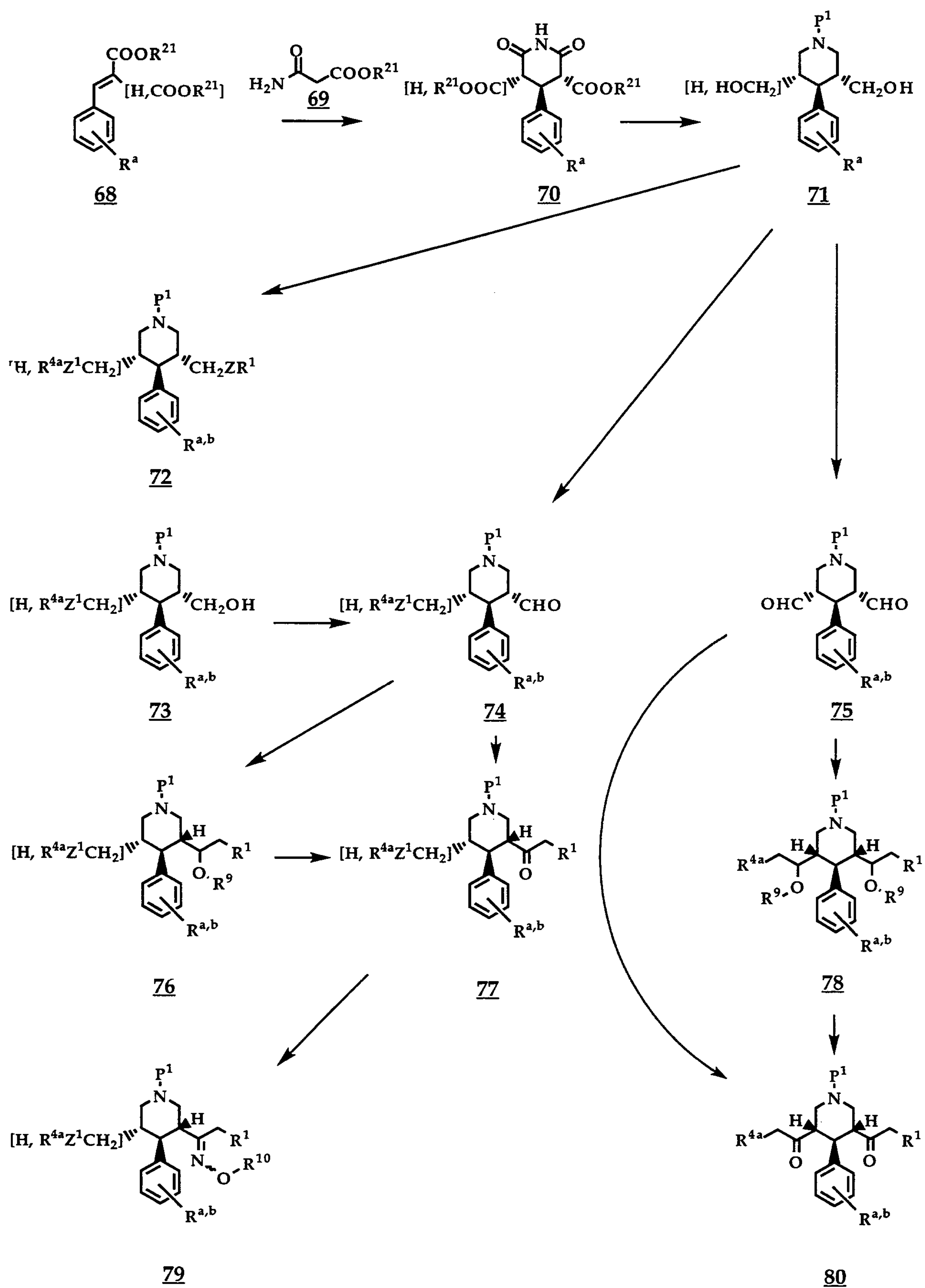


One possible synthetic route to 4-aryl-piperidines which are substituted in each of positions 3 and 5 with O or N atoms is shown in Scheme 10. Oxirane compounds of general formula LXI can be formed from olefins 6, for example, via a bromohydrin which is formed as an intermediate and which can be obtained by the addition of bromine in aqueous dioxan. Subsequently, the bromohydrin can be ring-closed to the epoxide **61** by the addition

- 45 -

of aqueous sodium hydroxide solution. Treatment of such an oxirane with methyllithium, butyllithium or a lithium amide in aprotic solvents such as ether or tetrahydrofuran at temperatures between -80°C and $+60^{\circ}\text{C}$ leads to allyl alcohols 62 which, with a
5 free OH or after the introduction of an ether function R^{20} , can be further processed. Hydroboration of these allyl alcohol derivatives 62, as described earlier for the preparation of compounds of general formula 7, yields the free or monofunctionalized dihydroxy derivatives 63. For the structural variation of
10 the group R^{20} (R^{4a}Z^1 - or H), $-\text{ZR}^1$ and R^a , depending on the target molecule being prepared, groups R^{20} and $-\text{ZR}^1$ can be introduced in a different sequence and group R^a can be modified to R^b , a group of the general formula $-\text{T}^1-\text{L}^2-\text{T}^2-\text{L}^3-\text{T}^3-\text{L}^4-\text{T}^4-\text{U}$. It can be advisable to provide one of the two OH functions intermediately
15 with a protecting group and to cleave this off at a later stage of the synthesis or to choose the groups $-\text{ZR}^1$ and R^{20} such that, if desired, it is possible to synthesize another desired substituent at a suitable later stage of the reaction sequence. Starting from monoether-protected derivatives 65 the free OH function can, for
20 example, be stereochemically inverted by reaction with formic acid, triphenylphosphine and an azodicarboxylic acid ester in an inert solvent such as tetrahydrofuran according to Mitsunobu [Synthesis 1981, 1], with compounds of general formula 66 being obtained. The use of diphenylphosphoryl azide in place of formic
25 acid under similar conditions provides a possibility of introducing, starting from compounds 66 by a renewed inversion at the same centre, an azido function which can be converted into a primary amino function, for example, by reduction with
30 triphenylphosphine/water in tetrahydrofuran at temperatures between room temperature and 80°C [Synth. Commun. 17, 377 (1987)]. There are thus obtained compounds of general formula 67, which can be subsequently alkylated or acylated.

Scheme 11

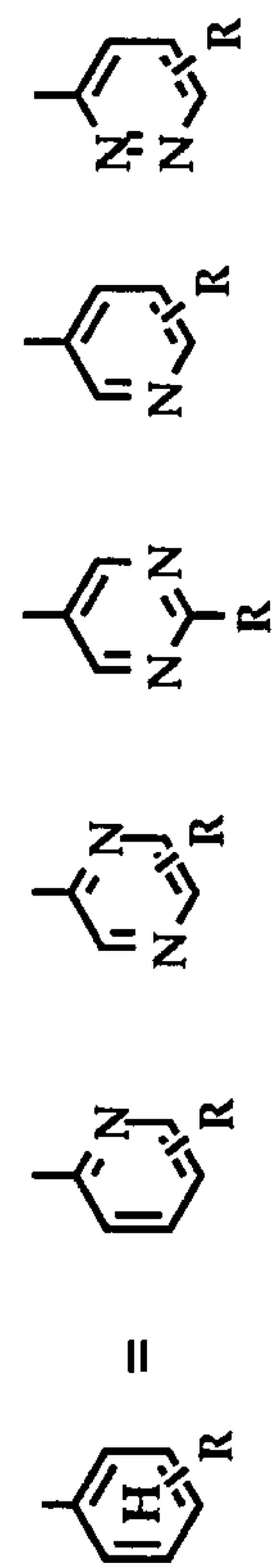
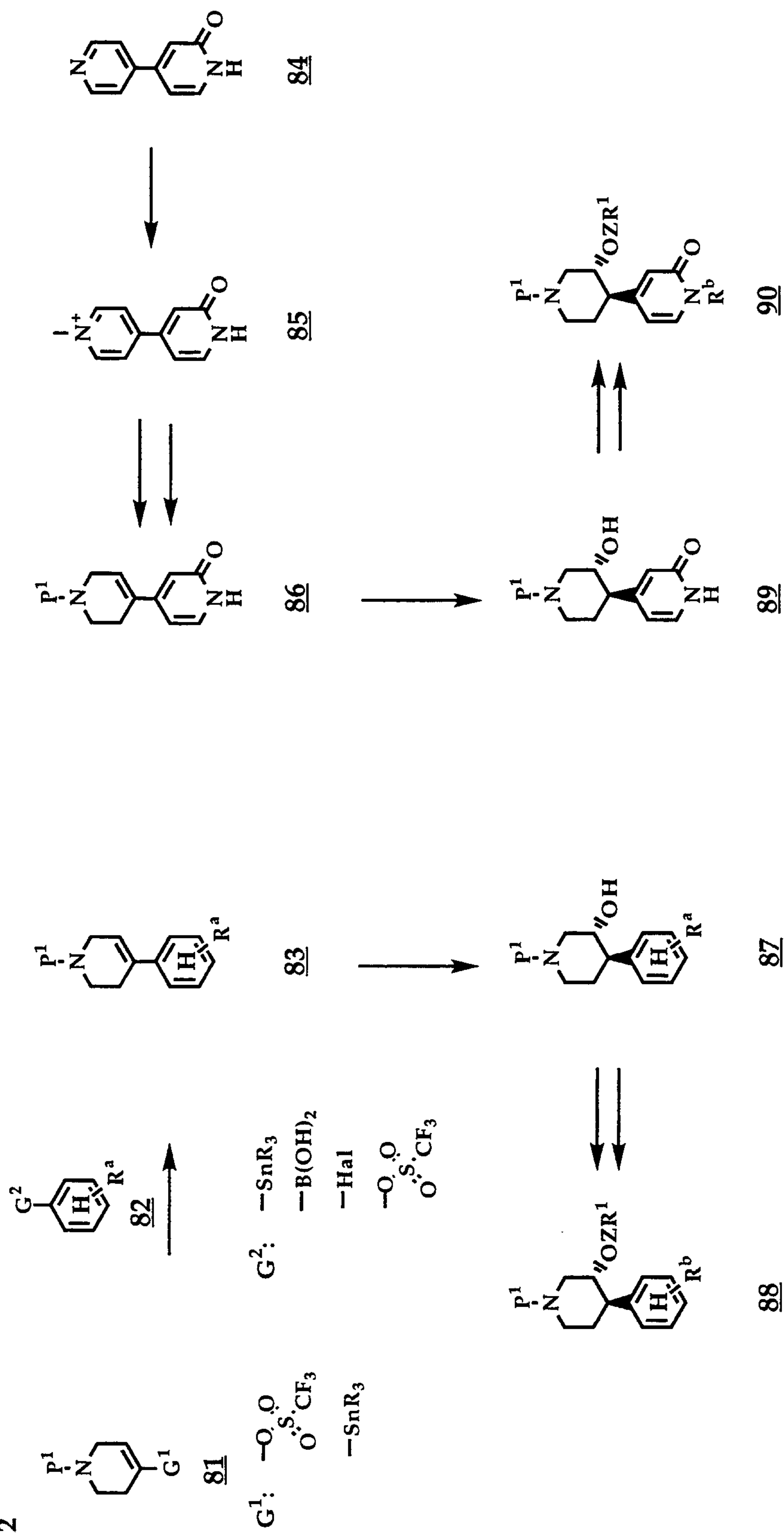


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In accordance with Scheme 11 cinnamic acid derivatives 68, which are known from the literature, can be converted with malonic acid monoester monoamides 69 in protic solvents such as ethanol or methanol or aprotic solvents such as N,N-dimethyl-
5 formamide, dimethyl sulphoxide, tetrahydrofuran or acetonitrile using bases such as, for example, potassium tert-butyrate or sodium hydride at temperatures between room temperature and 130°C into cyclic imides 70. Reduction of these imides 70 with
10 hydride reducing reagents such as lithium aluminium hydride, diisobutyl aluminium hydride or sodium dihydrido-bis-(2-methoxyethoxy)aluminate in aprotic solvents such as ethers, tetrahydrofuran or dioxan at temperatures between room temperature and 120°C yields the piperidine mono- and dimethanols 71, which can be provided at the piperidine nitrogen
15 with a suitable protecting groups. Mono- and dihydroxy compounds of general formula 71 can now be selectively functionalized stepwise in an analogous manner to that described earlier for mono- and dihydroxy compounds 7, 10, 62, 63, 64 or by conversion into the corresponding bromo, chloro or iodo
20 compounds or aryl- or alkylsulphonic acid esters and subsequent nucleophilic substitution with alcoholates, phenolates or thiophenolates according to conventional methods. Thereby, ZR¹, Z¹R^{4a} can represent substituents as defined earlier in general formula I or suitable precursors, which are inert under the
25 reaction conditions or in which reactive groups are present in appropriately protected form, preferably chosen such that, if desired, it is possible to synthesize another desired substituent at a suitable later stage of the reaction sequence. R^a and R^b correspond to the definitions set forth above. Alternatively,
30 monohydroxy compounds 71, dihydroxy compounds 71 or derivatives 73 of the dihydroxy compounds 71, the hydroxy function of which has been structurally modified, can be converted into the aldehydes 74 by oxidation, for example according to Swern (dimethyl sulphoxide, oxalyl chloride) [J. Org.
35 Chem. 43, 2480 (1978)]. Addition of a Grignard compound or lithium compound according to known methodology in an inert solvent such as tetrahydrofuran or 1,2-dimethoxyethane at temperatures between -78°C and room temperature then yields

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the alcohols 76 ($R^9 = H$), which can be optionally alkylated, acylated or again oxidized, for example according to Swern, and thus give derivatives 76 (R^9 other than H) or, respectively ketones 77. Compounds of general formula 78 and 80 can be
5 obtained starting from dihydroxy compounds 71 by simultaneous conversion of both hydroxy functions analogously to that described above via dialdehydes 75. The transformation of aldehydes 74, 75 into ketones 77, 80 can also be effected via an oxidation to the acids [for example with sodium chlorite,
10 amidosulphonic acid and isopropenyl acetate in a solvent such as acetone/water at 0°C to room temperature according to J. Am. Chem Soc. 110, 2242 (1988)], subsequent amide coupling to N-methyl-N-methoxy amides with N,O-dimethylhydroxylamine according to known methods as well as reaction thereof with
15 organolithium or organomagnesium compounds in an inert solvent such as tetrahydrofuran or 1,2-dimethoxyethane at temperatures between -78°C and room temperature as described, for example, in [Synthesis 1986, 944]. Ketones 77 can be converted into oximes 79 in which R^{10} can have the significance defined in
20 general formula I by reaction with optionally substituted hydroxylamine derivatives in a solvent such as pyridine in the presence of catalytic or stoichiometric amounts of a strong acid at temperatures between room temperature and 120°C.



- 50 -

Compounds of general formulae 88 and 90, which contain heterocyclic substituents in the 4-position of the piperidine ring, can be synthesized stepwise in accordance with Scheme 12, e.g. as described hereinafter.

5

4-Heteroaryl-1,2,3,6-tetrahydro-pyridine derivatives 83 can be obtained, for example, from 1,2,3,6-tetrahydro-pyridine derivatives 81 activated in the form of an enol triflate by condensation with suitable functionalized heteroaromatic compounds activated, for example, in the form of tin compounds. Coupling reactions of this type are preferably carried out in an inert solvent such as 1,2-dimethoxyethane, tetrahydrofuran or N,N-dimethylformamide using a catalyst such as tetrakis-(triphenylphosphine)-palladium at temperatures up to 130°C. In place of tin compounds there can also be used analogous boric acid derivatives 82 under comparable reaction conditions or a vinyl-tin compound 81 which is analogous to the enol triflate 81, can be reacted with heterocyclic halo compounds or triflates 82, likewise under comparable conditions; in both cases the reactions lead to the same products. 4-Heteroaryl-1,2,3,6-tetrahydro-pyridine derivatives 86 can, however, also be obtained from pyridyl-heteroaryl-biaryl derivatives such as 84 according to known methods: N-methylation, partial hydrogenation of the methylated pyridine ring with a suitable hydride reagent such as sodium borohydride and subsequent conversion of the N-methyl function into a suitable protecting group by demethylating carbamoylation [as described, for example, in J. Org. Chem. 49, 2081 (1984)].

30 Compounds of general formulae 87 and 89 can be obtained by hydroboration and subsequent basic oxidative working-up of compounds of general formulae 83 and 86. The hydroboration can be effected according to methods known per se, for example in a solvent which is inert under the reaction conditions, such as an ether, e.g. 1,2-dimethoxyethane, at a temperature between about 0°C and 70°C, and with a reagent which contains or liberates diborane, such as e.g. borane in tetrahydrofuran, borane-dimethyl sulphide or a mixture of sodium borohydride and boron trifluoride

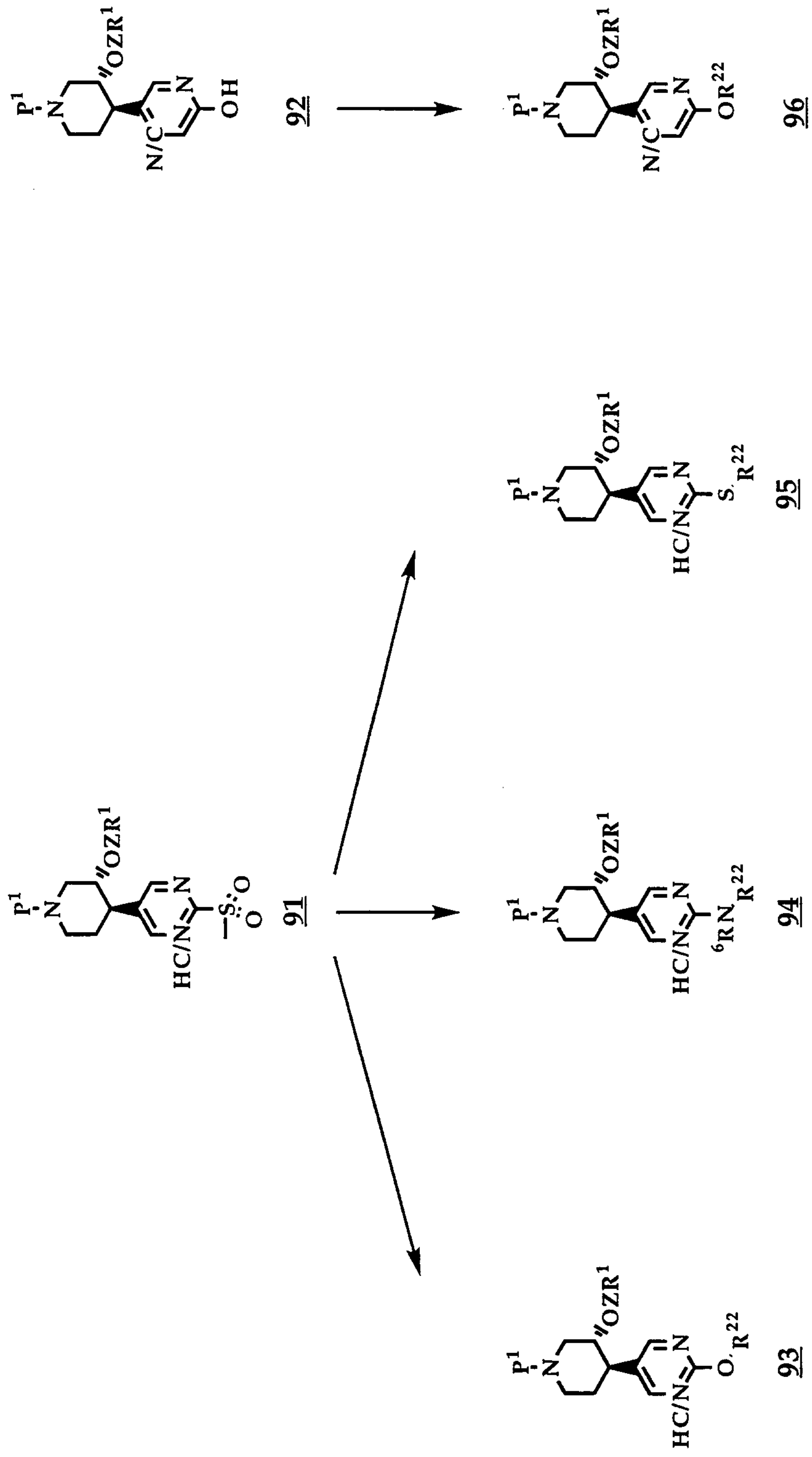
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- 51 -

etherate. The carboboranes which are formed as intermediates can be converted into the secondary alcohols of general formula 87 and 89 by reaction with bases, e.g. potassium hydroxide, and an oxidizing agent, e.g. hydrogen peroxide, sodium perborate or sodium percarbonate, with a combination of base and oxidizing agent or with trimethylamine N-oxide without the addition of base at a temperature between about room temperature and 120°C.

10 Compounds of general formulae 88 and 90 in which -ZR¹ represents a substituent containing an aryl or heteroaryl function can be obtained from compounds of general formulae 87 and 89 by alkylation with a compound which yields the group -ZR¹. Alkylation of the secondary alcohol is effected according to
15 methods known per se, for example in a solvent which is inert under the reaction conditions, such as an ether, e.g. tetrahydrofuran or 1,2-dimethoxyethane, or dimethylformamide, with the aid of an alcoholate-forming base, e.g. sodium hydride, at a temperature between about 0°C and 40°C and using a halide,
20 preferably a chloride or bromide, or a sulphonic acid ester, e.g. a mesylate or tosylate, as the compound which yields -ZR¹. The group R^a can be structurally modified prior to or after the alkylation described above. Modification reactions of group R^a to R^b, a group of the general formula -T¹-L²-T²-L³-T³-L⁴-T⁴-U,
25 include usual transformation reactions such as removal and re-introduction of a functional group, alkylation and acylation of alcohol and amine functions, oxidations of sulphides to sulphoxides and sulphones as well as other transformation reactions which are well documented in the literature. Examples
30 of specific structural transformations of group R^a to group R^b are compiled in Scheme 13:

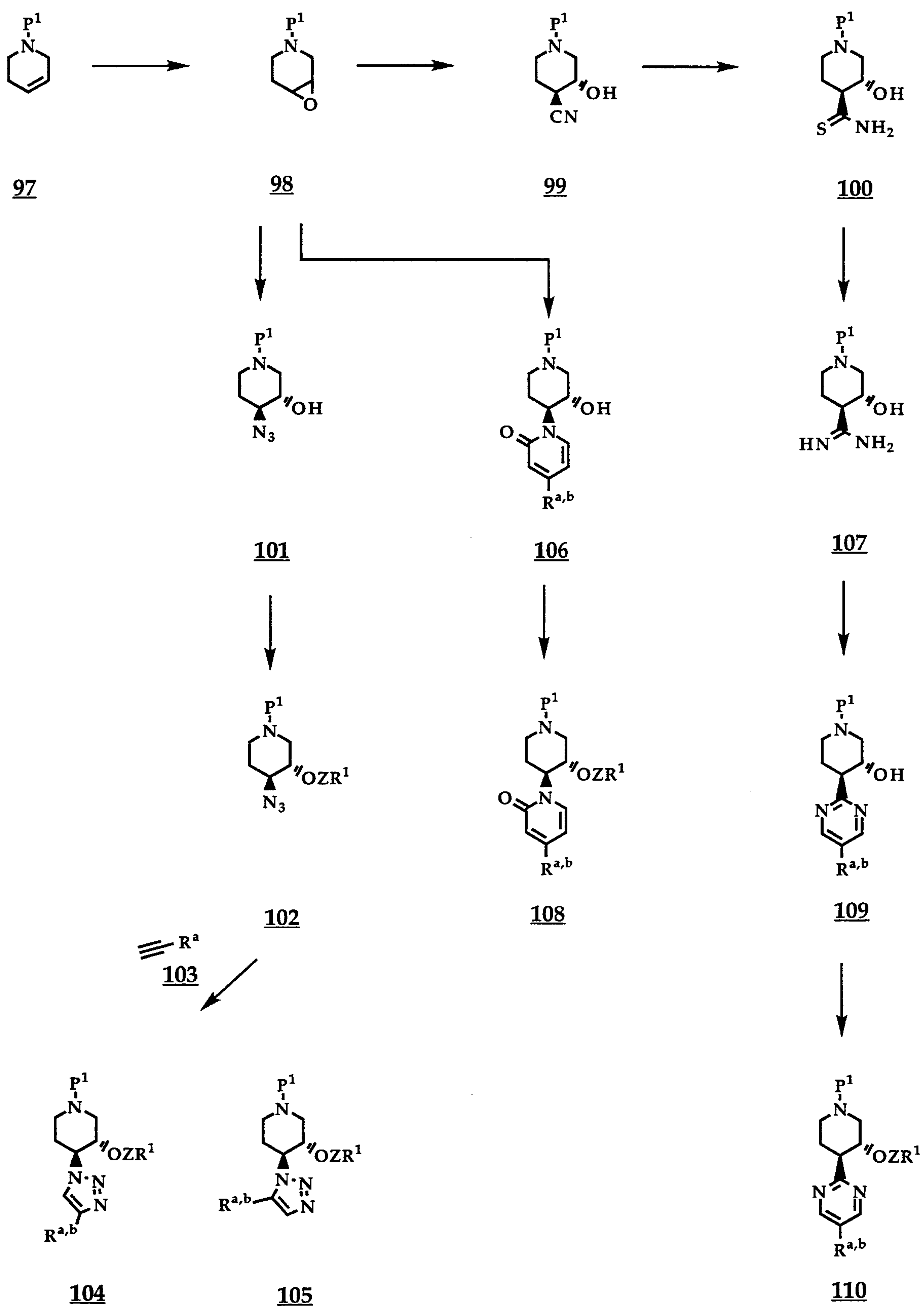
Scheme 13



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2-Methylsulphonyl pyridine and pyrimidine derivatives 91, which are already appropriately substituted in the 3-position of the piperidine, can be converted into the correspondingly substituted heteroaryl compounds with alcoholates, thiolates and
5 amines in tetrahydrofuran, 1,2-dimethoxyethane, dimethylformamide or dimethyl sulfoxide at temperatures between room temperature and about 150°C. Phenolic pyridine or pyrazine derivatives 92, which have a OH or OZR¹ function in the 3-position of the piperidine, can be alkylated at the phenolic O
10 function using a base and an alkylating agent according to known methods, in which case varying amounts of N-alkylation products can result. On the other hand, when the reaction is carried out with an alcohol in the presence of triphenylphosphine and an azodicarboxylic acid ester in a solvent such as tetrahydrofuran or
15 1,2-dimethoxyethane according to Mitsunobu [Synthesis 1981, 1], then O-alkylation products are formed almost exclusively. Accordingly, in the reaction products of general formulae 93-96 -OR²², -R⁶NR²² and -SR²² each represent a group -T¹-L²-T²-L³-T³-L⁴-T⁴-U, in which T¹ = oxygen, nitrogen or sulphur.

Scheme 14



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Compounds of general formulae 104, 105 as well as 108 to 110 can be obtained from oxirane compounds 98 in accordance with Scheme 14. Oxirane compounds 98 can be obtained by oxidation of the corresponding olefins by means of peracids such as peracetic acid or perbenzoic acid, preferably 3-chloro-perbenzoic acid. They can be converted into azido compounds 101 with azide anions in protic solvents such as ethanol or methanol or in aprotic solvents such as N,N-dimethylformamide, acetonitrile or dimethyl sulphoxide with or without the addition of Lewis acids such as lithium perchlorate or magnesium sulphate at temperatures between 50°C and 150°C, with varying amounts of epoxide-opened products having the azido function in the 3-position and the OH function in the 4-position of the piperidine ring being formed. The undesired isomeric compounds having the azido function in the 3-position of the piperidine ring can be separated, for example, by chromatography on silica gel. After the introduction of a suitable ether function in the 3-position the azido compounds can be converted by condensation with a suitable acetylene compound 103, such as, for example, propargyl alcohol in an apolar solvent such as toluene or xylene at temperatures between 60°C and 160°C, into the two isomeric N-triazolyl compounds of general formulae 104 and 105. Both give potent renin inhibitors after the introduction of a suitable side-chain on the substituents of the triazole ring using specific modification reactions of group R^a to R^b such as removal and re-introduction of a functional group, alkylation and acylation of alcohol and amine functions, oxidations of sulphides to sulfoxides and sulphones as well as other transformations which are well documented in the literature and after cleavage of the protecting group on the nitrogen atom of the piperidine ring. Compounds of general formula 106 can be synthesized by the nucleophilic opening of oxiranes of general formula 98 with an anion obtained from the substituted pyridone. The nucleophilic opening can be effected according to methods known per se, for example in a solvent which is inert under the reaction conditions, such as e.g. acetonitrile, 1,2-dimethoxyethane or N,N-dimethylformamide, at a temperature between about room temperature and 120°C and using a catalyst, e.g. ammonium chloride or lithium perchlorate,

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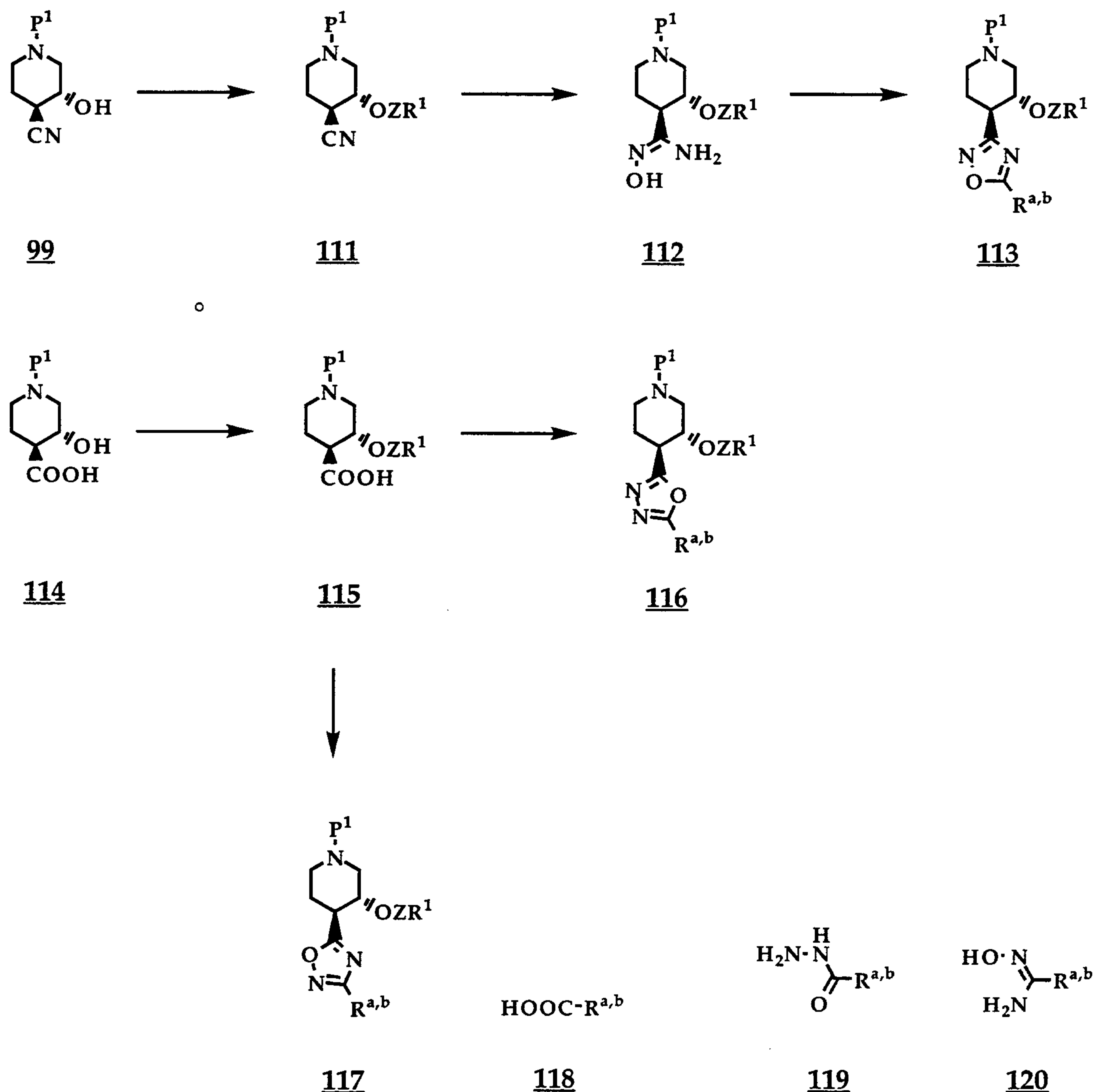
with the isomeric epoxide-opened product which occurs in varying amounts conveniently being separated by chromatography on silica gel. Compounds of general formula 109 can be obtained starting from compounds of general formula 98 by firstly
5 performing a nucleophilic opening of the oxiranes by means of cyanide ions to give compounds of formula 99. The nucleophilic opening can be effected according to methods known per se, for example in a solvent which is inert under the reaction conditions, such as e.g. acetonitrile, 1,2-dimethoxyethane or N,N-dimethyl-
10 formamide, at a temperature between about room temperature and 120°C and using a catalyst, e.g. ammonium chloride, zinc trifluoroacetate or lithium tetrafluoroborate, especially lithium perchlorate, with the isomeric epoxide-opened product which occurs in varying amounts conveniently being separated by
15 chromatography on silica gel. Compounds of general formula 107 can be obtained from compounds of general formula 99 by the direct addition of ammonia or via the corresponding thioamides of general formula 100. The addition can be effected according to methods known per se, for example by reacting the nitrile under
20 pressure with ammonia and ammonium chloride or by reacting sulphuretted hydrogen, preferably in the form of a hydrogen sulphide, with the nitrile to give the thioamide of general formula 100. This can be further converted, e.g. according to the procedure described in Helv.Chim.Acta Vol. 69, 1224 (1986), by
25 alkylation with methyl iodide or ethyl iodide into the corresponding sulphonium derivative, ammonolysis of which, e.g. with ammonium chloride, leads to the amidine of general formula 107. Compounds of general formula 109 can be prepared by a ring-closure reaction of the amidine of general formula 107 with a
30 corresponding malondialdehyde. The synthesis of the pyrimidine unit can be effected according to procedures known per se, for example by reaction of the amidine with a diacetal or enamine of the 2-substituted malondialdehyde in a solvent which is inert under the reaction conditions, such as e.g. methanol, at a
35 temperature between about room temperature and 120°C.

Depending on the target molecule under preparation, starting from compounds 106 and 109 firstly -ZR¹ can be

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introduced and subsequently group R^a can be modified to R^b or a reversed synthetic route can be used.

Scheme 15



5

Compounds of general formula **113** can be obtained from compounds of general formula **99** in accordance with Scheme 15 by firstly alkylating the secondary alcohol with a compound which yields the group $Z-R^1$, whereby, if desired, the further synthesis of the desired substituents can be effected at a later stage of the reaction sequence. The alkylation of the secondary

10

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alcohol is effected according to procedures known per se, for example in a solvent which is inert under the reaction conditions, such as an ether, e.g. tetrahydrofuran or 1,2-dimethoxyethane, or dimethylformamide, with the aid of an alcoholate-forming base, e.g. sodium hydride, at a temperature between about 0°C and 40°C and using a halide, preferably a chloride or bromide, or a sulphonic acid ester, e.g. a mesylate or tosylate, as the compound which yields Z-R¹.

The reaction of compounds of general formula 111 with hydroxylamine in the presence of a base such as e.g. sodium methylate, conveniently at temperatures between 40°C and 100°C, gives amidoxines of general formula 112. Compounds of general formula 113 are obtained by reacting a reactive functional derivative of a carboxylic acid of general formula 118 with an amidoxime of formula 112. The reaction is conveniently effected by heating for several hours to about 70°C to 130°C in an inert solvent, e.g. in dimethylformamide. The non-cyclized condensation product which is formed as an intermediate cyclizes spontaneously under the given reaction conditions. As reactive functional derivatives of carboxylic acids of general formula 118 there can be used the corresponding imidazolides, which can be prepared from the corresponding free carboxylic acids according to procedures known per se, e.g. by reaction with 1,1'-carbonyldiimidazole in an inert organic solvent, e.g. in dimethylformamide. Furthermore, as reactive functional derivatives of the carboxylic acids there can also be used carboxylic acid chlorides which can be prepared from the corresponding free carboxylic acids by means of thionyl chloride or oxalyl chloride.

Compounds of general formula 116 can be obtained from compounds of general formula 114 firstly, as mentioned above, by alkylating compounds of general formula 115. These are then converted into reactive, functional derivatives of the carboxylic acid and reacted with hydrazides of general formula 119. The reaction is conveniently effected at room temperature to 50°C in an inert organic solvent, e.g. in dimethylformamide. The non-cyclized condensation product which thereby results can be

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isolated and then cyclized to compounds of general formula 116 by heating for several hours with polyphosphoric acid at about 100°C.

5 Compounds of general formula 117 can be obtained from compounds of general formula 115 in accordance with Scheme 15 by reacting reactive, functional derivatives of the carboxylic acids with amidoximes of general formula 120. The reaction is conveniently effected by heating for several hours to about 70°C
10 to 130°C in an inert solvent, e.g. in dimethylformamide. The non-cyclized condensation product which is formed as an intermediate cyclises spontaneously under the given reaction conditions.

 The compounds of general formulae 114 and 118 - 120
15 belong to generally known classes of compound and will therefore be readily accessible to any person skilled in the art.

 Furthermore, compounds of general formula II in which R² has the meaning of a 5-membered aromatic group can also be
20 prepared very similarly to the synthesis route described in Scheme 12, in which the specifically functionalized 6-membered aromatic synthon 82 must be replaced by a corresponding 5-membered aromatic synthon.

25 Piperidines of general formula I can also exist in optically pure form. Separation into antipodes can be effected according to methods known per se, either preferably at an early stage of the synthesis by salt formation with an optically active acid such as, for example, (+)- or (-)- mandelic acid and separation of the
30 diastereomeric salts by fractional crystallization or preferably at a later stage by derivatization with a chiral auxiliary substance such as, for example, (+)- or (-)- camphamoyl chloride and separation of the diastereomeric products by chromatography and/or crystallization and subsequent cleavage of the bond to the
35 chiral auxiliary substance. In order to determine the absolute configuration of the piperidine obtained, the pure diastereomeric salts and derivatives can be analyzed by conventional spectro-

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scopic methods, with X-ray spectroscopy on single crystals being an especially suitable method.

The compounds of formula I and their pharmaceutically
5 usable salts have an inhibitory activity on the natural enzyme
renin. The latter passes from the kidneys into the blood and there
brings about the cleavage of angiotensinogen with the formation
of the decapeptide angiotensin I which is then cleaved in the
lungs, the kidneys and other organs to the octapeptide angiotensin
10 II. Angiotensin II increases blood pressure not only directly by
arterial constriction, but also indirectly by the liberation of the
sodium ion-retaining hormone aldosterone from the adrenal gland,
with which is associated an increase in the extracellular fluid
volume. This increase is attributed to the action of agiotensin II
15 itself or to the hepapeptide angiotensin III which is formed
therefrom as a cleavage product. Inhibitors of the enzymatic
activity of renin bring about a decrease in the formation of
angiotensin I and as a consequence of this the formation of a
smaller amount of angiotensin II. The reduced concentration of
20 this active peptide hormone is the direct reason for the blood
pressure-lowering activity of renin inhibitors.

The in-vivo potency of renin inhibitors can, as described
by W.Fischli et al. in Hypertension, Vol. 18 (1), 22-31 (1991) or
25 Hypertension Vol. 22 (1), 9-17 (1993) be demonstrated
experimentally by means of the tests described hereinafter. The
tests can be carried out in analogy to those described by D.T.Pals
et al. in Hypertension Vol 8, 1105-1112 (1986) or J.Boger et al. in
J.Med.Chem. 28, 1779-1790 (1985) or J.F.Dellaria et al. in
30 J.Med.Chem. 30, 2137-2144 (1987) or T.Kokubu et al. in
Biochem.Biophys.Res.Comm. 118, 929-933 (1984).

In vitro test with pure human renin

35 The test is carried out in Eppendorf test tubes. The
incubation mixture consists of (1) 100 μ l of human renin in
buffer A (0.1M sodium phosphate solution, pH 7.4, containing 0.1%
bovine serum albumin, 0.1% sodium azide and 1 mM ethylene-

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diaminetetraacetic acid), sufficient for a renin activity of 2-3 ng of angiotensin I/ml/hr.; (2) 145 μ l of buffer A: (3) 30 μ l of 10 mM human tetradecapeptide renin substrate (hTD) in 10 mM hydrochloric acid: (4) 15 ml of dimethyl sulphoxide with or
5 without inhibitor and (5) 10 μ l of a 0.03 molar solution of hydroxyquinoline sulphate in water.

The samples are incubated for three hours at 37°C and, respectively, 4°C in triplicate. 2 x 100 μ l samples per test tube
10 are used in order to measure the production of angiotensin I via RIA (standard radioimmunoassay; clinical assay solid phase kit). Cross reactivities of the antibody used in the RIA are: angiotensin I 100%; angiotensin II 0.0013%; hTD (angiotensin I-Val-Ile-His-Ser-OH) 0.09%. The production of angiotensin I is determined by
15 the difference between the test at 37°C and that at 4°C.

The following controls are carried out:

- (a) Incubation of hTD samples without renin and without
20 inhibitor at 37°C and 4°C. The difference between these two values gives the base value of the angiotensin I production.
- (b) Incubation of hTD samples with renin, but without inhibitor at 37°C and 4°C. The difference between these values gives the
25 maximum value of the angiotensin I production.

In each sample the base value of the angiotensin I production is subtracted from the angiotensin I production which is determined. The difference between the maximum value and
30 the base value gives the value of the maximum substrate hydrolysis (= 100%) by renin.

The results are given as IC₅₀ values which denote that concentration of the inhibitor at which the enzymatic activity is
35 inhibited by 50%. The IC₅₀ values are determined from a linear regression curve from a logit-log plot.

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The results obtained in this test are compiled in the following Table:

Table

5	<u>Compound</u>	<u>IC₅₀ values in μMol/l</u>
	A	0.011
	B	0.026
	C	0.070
	D	0.040
10	E	0.041
	F	0.057
	G	0.033
	H	0.073
	I	0.317
15	J	0.017
	K	2.600
	L	3.080
	M	0.008
	N	0.012
20	O	0.017
	P	0.006
	Q	0.005
	R	0.003
	S	0.002
25	T	0.005
	U	0.024
	V	0.002
	W	0.002
	X	0.003
30	Y	0.003
	Z	0.001
	AA	0.001
	BB	0.003
	CC	0.002
35	DD	0.001

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	EE	0.0004
	FF	0.0006
	GG	0.001
	HH	0.006
5	II	0.002
	JJ	0.002
	KK	0.012
	LL	0.001
	MM	0.0005
10	NN	0.001
	OO	0.006
	PP	0.002
	QQ	0.002
	RR	0.270
15	SS	132
	TT	0.0005
	UU	0.0001
	VV	0.002
	WW	0.009
20	XX	0.0008
	YY	0.0005
	ZZ	0.00003

25 A = (3RS,4RS)-2-[4-(3-Naphthalen-2-ylmethoxy-piperidin-4-yl)-phenoxy]-ethyl thiophene-2-carboxylate hydrochloride
(Example 58-4)

B = (3RS,4RS)-2-[4-(3-Naphthalen-2-ylmethoxy-piperidin-4-yl)-phenoxy]-ethyl 2-chloro-benzoate hydrochloride (Example 54-2)

30 C = (3RS,4RS)-2-[4-[3-[4-(2-methoxy-benzyloxy)-naphthalen-2-ylmethoxy]-piperidin-4-yl]-phenoxy]-ethyl benzoate hydrochloride (Example 55-2)

35 D = (3RS,4RS)-4-[4-(3-Benzyloxy-propoxy)-phenyl]-3-(2,3-dihydro-benzo[1,4]dioxin-6-ylmethoxy)-piperidine (Example 86-54)

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- E = (3RS,4RS)-3-(Naphthalen-2-ylmethoxy)-4-[4-(3-phenyl-[1,2,4]oxadiazol-5-ylmethoxy)-phenyl]-piperidine trifluoroacetate (Example 86-34)
- F = (3RS,4RS)-3-(Naphthalen-2-ylmethoxy)-4-[4-(3-phenyl-
5 isoxazol-5-ylmethoxy)-phenyl]-piperidine trifluoroacetate (Example 86-36)
- G = (3RS,4RS)-3-(Naphthalen-2-ylmethoxy)-4-[4-(3-phenylsulphanyl-propyl)-phenyl]-piperidine (Example 86-19)
- H = (3RS,4RS)-3-[4-[4-[2-(Benzothiazol-2-ylsulphanyl)-ethyl]-phenyl]-piperidin-3-yloxymethyl]-naphthalen-1-ol
10 (Example 86-23)
- I = (3RS,4RS,5SR)-3-(4-Benzyloxy-naphthalen-2-ylmethoxy)-4-(4-fluoro-phenyl)-5-propyl-piperidine (Example 64)
- J = (3SR,4RS,5RS)-4-(4-Benzyloxymethyl-phenyl)-3-
15 methoxymethyl-5-(naphthalen-2-ylmethoxy)-piperidine (Example 86-60)
- K = (SR)- or (RS)-1-[(3RS,4SR)-4-(4-fluoro-phenyl)-piperidin-3-yl]-2-naphthalen-2-yl-ethyl benzoate hydrochloride (Example 75 b)
- 20 L = (1RS,2RS,3RS,5SR)-2-(4-Benzyloxy-naphthalen-2-ylmethoxy)-3-(4-fluoro-phenyl)-8-aza-bicyclo[3.2.1]octane (Example 84 e)
- M = (3RS,4RS)-4-[4-(3-Benzyloxy-propoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine
- 25 N = 4-[2-[7-[(3RS,4RS)-4-[4-(3-Benzyloxy-propoxy)-phenyl]-piperidin-3-yloxymethyl]-naphthalen-2-yloxy]-ethyl]-morpholine hydrochloride (1:2) (Example 90-07)
- O = Mixture of (RS)- and (SR)-3-[7-[(3RS,4RS)-4-[4-(3-benzyloxy-propoxy)-phenyl]-piperidin-3-yloxymethyl]-naphthalen-2-yloxy]-propane-1,2-diol (Example 90-08)
- 30 P = Mixture of (RS)- and (SR)-3-[2-[7-[(3RS,4RS)-4-[4-(3-benzyloxy-propoxy)-phenyl]-piperidin-3-yloxymethyl]-naphthalen-2-yloxy]-ethoxy]-propane-1,2-diol hydrochloride(1:1) (Example 98)
- 35 Q = 1-[2-[7-[(3RS,4RS)-4-[4-(3-Benzyloxy-propoxy)-phenyl]-piperidin-3-yloxymethyl]-naphthalen-2-yloxy]-ethyl]-4-methyl-piperazine hydrochloride (1:3) (Example 90-13)

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- R = 1-[(3RS,4SR)-4-[4-(3-Benzoyloxy-propoxy)-phenyl]-piperidin-3-yl]-2-naphthalen-2-yl-ethanone hydrochloride (1:1) (Example 100)
- S = (3RS,4SR,5SR)-4-[4-(3-Benzoyloxy-propoxy)-phenyl]-3-(1,4-dimethoxy-naphthalen-2-ylmethoxy)-piperidin-5-ol (Example 109-04)
- T = Mixture of (3RS,4RS)- and (3SR,4SR)-4-[4-(3-benzoyloxy-propoxy)-phenyl]-3-[7-[(RS)-2,3-dihydroxy-propoxymethyl]-naphthalen-2-ylmethoxy]-piperidine (Example 106-02)
- 10 U = Mixture of (3RS,4RS)- and (3SR,4SR)-4-[4-(3-benzoyloxy-propoxy)-phenyl]-3-[6-[(RS)-2,3-dihydroxy-propoxymethyl]-naphthalen-2-ylmethoxy]-piperidine (Example 106-01)
- V = 4-[(3RS,4SR,5SR)-4-[4-(3-Benzoyloxy-propoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidin-5-yloxy]-butan-1-ol (Example 110-08)
- 15 W = 3-[(3RS,4SR,5SR)-4-[4-(3-Benzoyloxy-propoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidin-5-yloxy]-propan-1-ol (Example 110-07)
- X = 1-{2-[(3RS,4RS,5SR)-4-[4-(3-Benzoyloxy-propoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidin-5-yloxy]-ethyl}-4-methyl-piperazine (Example 110-02)
- 20 Y = 4-{2-[(3RS,4RS,5SR)-4-[4-(3-Benzoyloxy-propoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidin-5-yloxy]-ethyl}-morpholine (Example 110-09)
- 25 Z = (3RS,4SR,5SR)-4-[4-(3-Benzoyloxy-propoxy)-phenyl]-3-(4-methoxy-benzoyloxy)-piperidin-5-ol (Example 109-28)
- AA = (3R,4s,5S)-4-[4-(3-Benzoyloxy-propoxy)-phenyl]-3,5-bis-(4-methoxy-benzoyloxy)-piperidine (Example 109-27)
- BB = (3SR,4RS,5RS)-4-[2-[4-[4-(3-Benzoyloxy-propoxy)-phenyl]-5-(naphthalen-2-ylmethoxy)-piperidin-3-ylmethoxy]-ethyl]-morpholine (Example 149-04)
- 30 CC = (3SR,4RS,5RS)-4-[4-(3-Benzoyloxy-propoxy)-phenyl]-3-methoxymethyl-5-(naphthalen-2-ylmethoxy)-piperidine (Example 148)
- 35 DD = (3SR,4RS,5RS)-4-[4-(3-Benzoyloxy-propoxy)-phenyl]-5-(naphthalen-2-ylmethoxy)-piperidin-3-ylmethyl [3-(4-methyl-piperazin-1-yl)-propyl]-carbamate (Example 150-01)

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- EE = (3SR,4RS,5RS)-4-[4-[4-(3-Benzoyloxy-propoxy)-phenyl]-5-(naphthalen-2-ylmethoxy)-piperidin-3-ylmethylsulphanyl]-pyridine (Example 149-02)
- FF = 2-(4-Cyclohexyl-butoxy)-5-[(3RS,4RS)-3-(1,4-dimethoxy-naphthalen-2-ylmethoxy)-piperidin-4-yl]-pyrimidine (Example 139-03)
- GG = (3'RS,4'RS)-6-(3-Cyclohexyl-propoxy)-3'-(1,4-dimethoxy-naphthalen-2-ylmethoxy)-1',2',3',4',5',6'-hexahydro-[3,4']-bipyridine (Example 140-01)
- 10 HH = (3SR,4RS,5RS)-[4-[4-(3-Benzoyloxy-propoxy)-phenyl]-5-(naphthalen-2-ylmethoxy)-piperidin-3-yl]-methanol hydrochloride (Example 149-01)
- II = (3SR,4RS,5RS)-N-[4-[4-(3-Benzoyloxy-propoxy)-phenyl]-5-(naphthalen-2-ylmethoxy)-piperidin-3-ylmethyl]-N,N',N'-15 trimethyl-ethane-1,2-diamine (Example 149-06)
- JJ = (3SR,4RS,5RS)-[4-[4-(3-Benzoyloxy-propoxy)-phenyl]-5-(naphthalen-2-ylmethoxy)-piperidin-3-ylmethyl]-diethyl-amine (Example 149-05)
- KK = 1-[(3RS,4SR,5SR)-4-[4-(3-Benzoyloxy-propoxy)-phenyl]-5-20 (2-morpholin-4-yl-ethoxymethyl)-piperidin-3-yl]-2-naphthalen-2-yl-ethanone (Example 101)
- LL = (3RS,4RS)-3-(1,4-Dimethoxy-naphthalen-2-ylmethoxy)-4-[4-[3-(2-methoxy-phenoxy)-propoxy]-phenyl]-piperidine (Example 123-27)
- 25 MM = (3R,4s,5S)-4-[4-(3-Benzoyloxy-propoxy)-phenyl]-3,5-bis-(3,4,5-trimethoxy-benzoyloxy)-piperidine (Example 109-29)
- NN = (3RS,4RS,5SR)-4-[4-(3-Benzoyloxy-propoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-5-[1,2,4]triazol-1-ylmethyl-piperidine hydrochloride (Example 149-07)
- 30 OO = (3RS,4RS)-4-[4-[3-(2-Methoxy-benzoyloxy)-propoxy]-phenyl]-3-(quinolin-7-ylmethoxy)-piperidine (Example 120-07)
- PP = 2-(7-[(3RS,4RS)-4-[4-(3-Benzoyloxy-propoxy)-phenyl]-piperidin-3-ylloxymethyl]-naphthalen-2-ylmethoxy)-ethanol (Example 106-03)
- 35 QQ = 7-[(3RS,4RS)-4-[4-(3-Benzoyloxy-propoxy)-phenyl]-piperidin-3-ylloxymethyl]-naphthalen-2-ylmethyl)-dimethyl-amine (Example 106-03)

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- RR = (3R,4R)-3-(4-Benzyloxy-naphthalen-2-ylmethoxy)-4-(4-fluoro-phenyl)-piperidine (Example 154-06)
- SS = (3S,4S)-3-(4-Benzyloxy-naphthalen-2-ylmethoxy)-4-(4-fluoro-phenyl)-piperidine (Example 154-07)
- 5 TT = (3'RS,4'RS)-3'-(1,4-Dimethoxy-naphthalen-2-ylmethoxy)-6-[3-(2-methoxybenzyloxy)-propoxy]-1',2',3',4',5',6'-hexahydro-[3,4']bipyridine (Example 140.02)
- UU = (3RS,4RS)-3-(1,4-Dimethoxy-naphthalen-2-ylmethoxy)-4-[4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl]-piperidine
- 10 (Example 123.32)
- VV = (3SR,4RS,5RS)-1-[4-[4-(3-Benzyloxy-propoxy)-phenyl]-5-(naphthalen-2-ylmethoxy)-piperidin-3-ylmethyl]-imidazolidin-2-one (Example 149.08)
- WW = (3RS,4RS)-4-[4-[3-(2-Methoxy-benzyloxy)-propoxy]-phenyl]-3-(2-oxo-1,2-dihydro-quinolin-7-ylmethoxy)-piperidine
- 15 (Example 120.10)
- XX = (3RS,4RS)-3-(Isoquinolin-7-ylmethoxy)-4-[4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl]-piperidine (Example 120.11)
- 20 YY = (3RS,4RS)-4-[4-[3-(2-Methoxy-benzyloxy)-propoxy]-phenyl]-3-(1,2,3,4-tetrahydro-quinolin-7-ylmethoxy)-piperidine (Example 120.12)
- ZZ = (3RS,4SR,5SR)-3-(1,4-Dimethoxy-naphthalin-2-ylmethoxy)-4-[4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl]-piperidin-5-ol (Example 112-11)
- 25

The compounds of formula I as well as their pharmaceutically usable salts can be used as medicaments, e.g. in the form of pharmaceutical preparations. The pharmaceutical

30 preparations can be administered enterally such as orally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions, nasally, e.g. in the form of nasal sprays, or rectally, e.g. in the form of suppositories. However, the administration can also be effected

35 parenterally such as intramuscularly or intravenously, e.g. in the form of injection solutions.

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The compounds of formula I as well as their pharmaceutically usable salts can be processed with pharmaceutically inert, inorganic or organic excipients for the production of tablets, coated tablets, dragées and hard gelatine capsules.

5 Lactose, corn starch or derivatives thereof, talc, stearic acid or its salts etc can be used e.g. as such excipients for tablets, dragees and hard gelatine capsules.

Suitable excipients for soft gelatine capsules are e.g.
10 vegetable oils, waxes, fats, semi-solid and liquid polyols etc.

Suitable excipients for the production of solutions and syrups are e.g. water. polyols, sucrose, invert sugar, glucose etc.

15 Suitable excipients for injection solutions are e.g. water, alcohols, polyols, glycerol, vegetable oils bile acids, lecithin etc.

Suitable excipients for suppositories are e.g. natural or hardened oils, waxes, fats, semi-liquid or liquid polyols etc.
20

Moreover, the pharmaceutical preparations can contain preservatives, solubilizers, viscosity-increasing substances, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers,
25 masking agents or antioxidants. They can also contain still other thereapeutically valuable substances.

In accordance with the invention the compounds of general formula I as well as their pharmaceutically usable salts can be
30 used in the control or prevention of high blood pressure and cardiac insufficiency, as well as glaucoma, cardiac infarct, kidney insufficiency and restenosis.

The compounds in accordance with the invention can also be
35 administered in combination with one or more agents having cardiovascular activity, e.g. α - and β -blockers such as phentolamine, phenoxybenzamine, prazosin, terazosin, tolazine, atenolol, metoprolol, nadolol, propranolol, timolol, carteolol etc.; vaso-

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dilators such as hydralazine, minoxidil, diazoxide, nitroprusside, flosequinan etc.; calcium antagonists such as amrinone, bencyclane, diltiazem, fendiline, flunarizine, nicardipine, nimodipine, perhexilene, verapamil, gallopamil, nifedipine etc.;
5 ACE inhibitors such as cilazapril, captopril, enalapril, lisinopril etc.; potassium activators such as pinacidil; anti-serotonergics such as ketanserin; thromboxane synthetase inhibitors; angiotensin II antagonists; as well as diuretics such as hydrochlorothiazide, chlorothiazide, acetazolamide, amiloride, bumetanide,
10 benzthiazide, ethacrynic acid, furosemide, indacrinone, metolazone, spironolactone, triamterene, chlorthalidone etc.; sympatholytics such as methyldopa, clonidine, guanabenz, reserpine; and other agents which are suitable for the treatment of high blood pressure, cardiac insufficiency or vascular
15 disorders in humans and animals associated with diabetes or kidney disorders such as acute or chronic kidney failure. Such combinations can be used separately or in preparations which contain several components.

20 The dosage can vary within wide limits and will, of course, be fitted to the individual requirements in each particular case. In general, in the case of oral administration a daily dosage of about 3 mg to about 3 g, preferably about 10 mg to about 1 g, e.g. approximately 300 mg per adult person (70 kg), divided into
25 preferably 1-3 individual doses which e.g. can be of equal amount, should be sufficient, although the upper limit given can also be exceeded when this is found to be indicated. Usually, children receive a reduced dose appropriate to their age and body weight.

30 The following Examples are intended to illustrate the present invention, but they are not intended to be limiting in any manner. All temperatures are given in degrees Celsius. The following abbreviations are used:

35 BOC : tert-Butoxycarbonyl
DME : 1,2-Dimethoxyethane
DMF : Dimethylformamide

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TBAF : Tetrabutylammonium fluoride

EDC : N-Ethyl-N'-(3-dimethylaminopropyl)-carbodiimide
hydrochloride

THP : Tetrahydropyranyl

5 TROC : Trichloroethoxycarbonyl.

TPTU: O-(1,2-Dihydro-2-oxo-1-pyridyl)-N,N,N'N'-
tetramethyluronium-tetrafluoroborate10 HBTU: O-(1H-Benzotriazol-1-yl)-N,N,N'N'-
tetramethyluronium-hexafluorophosphate

SEM: 2-(Trimethylsilyl)-ethoxymethyl

15 Example 1

(a) A solution of 23.6 g (100 mmol) of 1,3-dibromobenzene in 250 ml of absolute ether was cooled to -75°C. A solution of 62.5 ml (100 mmol) of n-butyllithium (1.6M in hexane) was
20 added dropwise within 45 minutes. The resulting suspension was stirred at -75°C for 2.5 hours. Subsequently, a solution of 19.0 g (100 mmol) of 1-benzyl-4-piperidone in 100 ml of absolute ether was added dropwise within 30 minutes at -70°C to -75°C and thereafter the mixture was stirred for 2 hours.
25 Subsequently, the mixture was partitioned between ether and saturated ammonium chloride solution, the organic phase was dried over magnesium sulphate and finally the solvent was removed under reduced pressure. The crude product was purified by chromatography on silica gel with a 1:1 mixture of methylene
30 chloride and hexane as the eluent. There were obtained 28.3 g (82% of theory) of 1-benzyl-4-(3-bromophenyl)-piperidin-4-ol as a yellow oil; MS: 345, 347 (M)+.

(b) A solution of 28.2 g (81.4 mmol) of 4-(3-bromophenyl)-
35 piperidin-4-ol in 600 ml of toluene was treated with 30 g (157 mmol) of p-toluenesulphonic acid monohydrate and heated to reflux on a water separator for 4 hours. Subsequently, the reaction mixture was cooled to room temperature and adjusted to pH 10 with 3N sodium hydroxide solution. Thereafter, it was

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firstly extracted three times with 500 ml of methylene chloride. The combined organic phases were washed three times with 200 ml of water each time, dried over magnesium sulphate and then evaporated under reduced pressure. The crude product was
5 purified by chromatography on silica gel with a 1:1 mixture of methylene chloride and hexane as the eluent. There were obtained 9.5 g (36% of theory) of 1-benzyl-4-(3-bromophenyl)-1,2,3,6-tetrahydro-pyridine as a light yellow oil; MS: 327, 329 (M+H)+.

10 (c) 3.15 g (83.3 mmol) of sodium borohydride were added portionwise at room temperature to a suspension of 9.5 g (28.9 mmol) of 1-benzyl-4-(3-bromophenyl)-1,2,3,6-tetrahydro-pyridine in 65 ml of absolute dimethoxyethane (DME). Thereafter, a solution of 17.7 ml (20.0 g 140.9 mmol) of boron trifluoride
15 etherate in 11 ml of DME was added dropwise at 15-20°C and the mixture was stirred at room temperature for 2 hours. Subsequently, a solution of 18.3 g (326 mmol) of potassium hydroxide in 100 ml of water was added dropwise within 30 minutes at 20-25°C. Finally, 55 ml of 30% hydrogen peroxide
20 solution were added dropwise within 30 minutes at 20-25°C. The mixture was stirred at room temperature for 30 minutes and heated to reflux for 3 hours. After cooling the reaction mixture the separated boric acid was filtered off. Subsequently, the filtrate was partitioned between methylene chloride and water,
25 the organic phase was dried over magnesium sulphate and the solvent was removed under reduced pressure. The crude product was purified by chromatography on silica gel with a 1:1 mixture of ethyl acetate and methylene chloride as the eluent. There were obtained 6.3 g (63% of theory) of (3RS,4RS)-1-benzyl-4-(3-bromophenyl)-piperidin-3-ol as a colourless oil. MS: 345,
30 347 (M)+.

(d) A solution of 691 mg (2.00 mmol) of (3RS,4RS)-1-benzyl-4-(3-bromophenyl)-piperidin-3-ol in 3 ml of absolute tetrahydro-
35 furan was treated with 163 mg (2.20 mmol) of lithium carbonate and cooled to -50°C. A solution of 722 mg (4.00 mmol) of β -trimethylsilylethyl chloroformate [Synthesis 346 (1987)] in 4 ml of toluene was added dropwise thereto at -50°C. The reaction

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mixture was warmed to room temperature and stirred for 24 hours. Subsequently, the mixture was partitioned between methylene chloride and water, the organic phase was dried over magnesium sulphate and finally the solvent was removed under reduced pressure. The crude product (0.8 g) was purified by chromatography on silica gel with methylene chloride as the eluent. There were obtained 470 mg (43% of theory) of 2-trimethylsilylethyl (3RS,4RS)-4-(3-bromophenyl)-3-(2-trimethylsilyl-ethoxycarbonyloxy)-piperidine-1-carboxylate as a light yellow oil, which was used directly in the next step.

(e) A solution of 470 mg (0.863 mmol) of 2-trimethylsilylethyl (3RS,4RS)-4-(3-bromophenyl)-3-(2-trimethylsilyl-ethoxycarbonyloxy)-piperidine-1-carboxylate in 3 ml of absolute tetrahydrofuran was treated with 2.65 ml (2.91 mmol) of tetrabutylammonium fluoride solution (1.1M in THF) and stirred at room temperature for 2.5 hours. Subsequently, the mixture was partitioned between methylene chloride and saturated sodium carbonate solution, the organic phase was dried over magnesium sulphate and finally the solvent was removed under reduced pressure. The crude product (440 mg) was purified by chromatography on silica gel with a 6.5:1:0.1 mixture of methylene chloride, MeOH and 25% ammonia as the eluent. There were obtained 180 mg (81% of theory) of (3RS,4RS)-4-(3-bromophenyl)-piperidin-3-ol as a light yellow oil. MS: 255, 257 (M)+.

(f) A solution of 180 mg (0.702 mmol) of (3RS,4RS)-4-(3-bromophenyl)-piperidin-3-ol in 1 ml of absolute dimethylformamide was treated at 0°C with 0.1 ml (73 mg, 0.72 mmol) of triethylamine. A solution of 167 mg (76.5 mmol) of di-tert-butyl dicarbonate in 0.5 ml of dimethylformamide was added thereto at 0°C. The mixture was warmed to room temperature and stirred for 20 hours. The solvent was distilled off at 50-55°C at 0.1 mm Hg. Subsequently, the residue obtained was partitioned between methylene chloride and water, the organic phase was dried over magnesium sulphate and finally the solvent was removed under reduced pressure. The crude product was purified by chromatography on silica gel with a 4:1 mixture of methylene

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chloride and ethyl acetate. There were obtained 220 mg (92% of theory) of tert-butyl (3RS,4RS)-4-(3-bromophenyl)-3-hydroxy-piperidine-1-carboxylate as a colourless solid; MS: 299, 301 (M-C₄H₈)⁺.

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(g) A solution of 168 mg (0.47 mmol) of tert-butyl (3RS,4RS)-4-(3-bromophenyl)-3-hydroxy-piperidine-1-carboxylate and 157 mg (0.71 mmol) of 2-bromomethylnaphthalene in 2 ml of dimethylformamide was treated with 28 mg (0.7 mmol) of sodium hydride (60% dispersion in refined oil) and the mixture was stirred at room temperature for 3 hours. Subsequently, the reaction mixture was partitioned between ethyl acetate and water, the organic phase was dried over magnesium sulphate and finally the solvent was removed under reduced pressure. The crude product was purified by chromatography on silica gel with a 1:4 mixture of ethyl acetate and hexane as the eluent. There were obtained 173 mg (74% of theory) of tert-butyl (3RS,4RS)-4-(3-bromophenyl)-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a light yellow oil; MS: 439, 441 (M-C₄H₈)⁺.

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(h) A solution of 173 mg (0.35 mmol) of tert-butyl (3RS,4RS)-4-(3-bromophenyl)-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate in 6 ml of methanol was treated with 6 ml of a 2N solution of hydrogen chloride in MeOH and stirred at 50°C for 4 hours. Subsequently, the mixture was partitioned between ethyl acetate and a 5% sodium hydrogen carbonate solution, the organic phase was dried over magnesium sulphate and finally the solvent was removed under reduced pressure. The crude product was purified by chromatography on silica gel with a 10:1:0.1 mixture of methylene chloride, MeOH and 25% ammonia and the eluent. There were obtained 126 mg (91% of theory) of (3RS,4RS)-4-(3-bromophenyl)-3-(naphthalen-2-ylmethoxy)-piperidine as a light yellow oil. MS: 396, 398 (M+H)⁺.

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Example 2

The following compounds were obtained by cleavage of the BOC group in an analogous manner to that described in Example

5 1 (h):

1) - (3RS,4RS)-3-(4-Methoxy-benzyloxy)-4-phenyl-piperidine as a light yellow oil, MS: 298 (M+H)⁺, from tert-butyl (3RS,4RS)-3-(4-methoxy-benzyloxy)-4-phenyl-piperidine-1-carboxylate;

10

2) - (3RS,4RS)-4-(4-bromophenyl-3-(4-methoxy-benzyloxy)-piperidine as a colourless oil, MS: 376, 378 (M+H)⁺, from tert-butyl (3RS,4RS)-4-(4-bromophenyl-3-(4-methoxy-benzyloxy)-piperidine-1-carboxylate;

15

3) - (3RS,4RS)-3-(4-methoxy-benzyloxy)-4-(3-trifluoromethylphenyl)-piperidine as a colourless oil, MS: 366 (M+H)⁺, from tert-butyl (3RS,4RS)-3-(4-methoxy-benzyloxy)-4-(3-trifluoromethylphenyl)-piperidine-1-carboxylate;

20

4) - (3RS,4RS)-3-(4-methoxy-benzyloxy)-4-p-tolyl-piperidine as a colourless solid, MS: 312 (M+H)⁺, from tert-butyl (3RS,4RS)-3-(4-methoxy-benzyloxy)-4-p-tolyl-piperidine-1-carboxylate;

25

5) - (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-phenyl-piperidine as a light yellow oil, MS: 318 (M+H)⁺, from tert-butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-phenyl-piperidine-1-carboxylate;

30

6) - (3RS,4RS)-4-(4-bromophenyl)-3-(naphthalen-2-ylmethoxy)-piperidine as a colourless solid, MS: 396, 398 (M+H)⁺, from tert-butyl (3RS,4RS)-4-(4-bromophenyl)-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate;

35

7) - (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-(3-trifluoromethyl-phenyl)-piperidine as a colourless oil, MS: 386 (M+H)⁺, from tert-butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-(3-trifluoromethyl-phenyl)-piperidine-1-carboxylate;

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- 8) - (3RS,4RS)-4-cyclohexyl-3-(naphthalen-2-ylmethoxy)-
piperidine as a light yellow oil, MS: 324 (M+H)⁺, from tert-butyl
(3RS,4RS)-4-cyclohexyl-3-(naphthalen-2-ylmethoxy)-piperidine-
5 1-carboxylate;
- 9) - (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-p-tolyl-
piperidine as a colourless solid, MS: 332 (M+H)⁺, from tert-butyl
(3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-p-tolyl-piperidine-1-
10 carboxylate;
- 10) - (3RS,4RS)-4-naphthalen-2-yl-3-(naphthalen-2-yl-
methoxy)-piperidine as a colourless oil, MS: 367 (M)⁺, from tert-
butyl (3RS,4RS)-4-naphthalen-2-yl-3-(naphthalen-2-ylmethoxy)-
15 piperidine-1-carboxylate;
- 11) - (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-(5,6,7,8-
tetrahydro-naphthalen-2-yl)-piperidine as a colourless oil,
MS: 372 (M+H)⁺, from tert-butyl (3RS,4RS)-3-(naphthalen-2-
20 ylmethoxy)-4-(5,6,7,8-tetrahydro-naphthalen-2-yl)-piperidine-
1-carboxylate;
- 12) - (3RS,4RS)-4-naphthalen-1-yl-3-(naphthalen-2-yl-
methoxy)-piperidine as a colourless solid, MS: 367 (M)⁺, from
25 tert-butyl (3RS,4RS)-4-naphthalen-1-yl-3-(naphthalen-2-
ylmethoxy)-piperidine-1-carboxylate;
- 13) - (3RS,4RS)-4-(3,4-dimethoxy-phenyl)-3-(naphthalen-2-yl-
methoxy)-piperidine as a colourless resin, MS: 377 (M)⁺, from
30 tert-butyl (3RS,4RS)-4-(3,4-dimethoxy-phenyl)-3-(naphthalen-
2-ylmethoxy)-piperidine-1-carboxylate;
- 14) - (3RS,4RS)-4-acenaphthen-5-yl-3-(naphthalen-2-yl-
methoxy)-piperidine as a colourless solid, MS: 394 (M+H)⁺, from
35 tert-butyl (3RS,4RS)-4-acenaphthen-5-yl-3-(naphthalen-2-
ylmethoxy)-piperidine-1-carboxylate;

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15) - (3RS,4RS)-4-(4-chlorophenyl)-3-(3-phenoxy-benzyloxy)-piperidine as a colourless solid, MS: 394, 396 (M+H)⁺, from tert-butyl (3RS,4RS)-4-(4-chlorophenyl)-3-(3-phenoxy-benzyloxy)-piperidine-1-carboxylate;

5

16) - (3RS,4SR)-3-(naphthalen-2-ylmethoxy)-4-phenyl-piperidine hydrochloride as a colourless powder, MS: 318 (M+H)⁺, from tert-butyl (3RS,4SR)-3-(naphthalen-2-ylmethoxy)-4-phenyl-piperidine-1-carboxylate.

10

The BOC compounds used as the starting materials were prepared as follows:

The following compounds were obtained in an analogous manner to that described in Example 1 (b)-(c) and (f)-(g):

(a) From 4-phenyl-piperidin-4-ol there was obtained by elimination 4-phenyl-1,2,3,6-tetrahydro-pyridine as a light yellow oil; MS: 159 (M)⁺. Subsequent hydroboration gave
20 (3RS,4RS)-4-phenyl-piperidin-3-ol as a colourless solid; MS: 177 (M)⁺. Introduction of the BOC group yielded tert-butyl (3RS,4RS)-3-hydroxy-4-phenyl-piperidine-1-carboxylate as a colourless solid; MS: 277 (M)⁺. After alkylation with 4-methoxybenzyl bromide there was obtained tert-butyl (3RS,4RS)-3-(4-methoxy-
25 benzyloxy)-4-phenyl-piperidine-1-carboxylate as a colourless solid; MS: 340 (M-C₄H₉)⁺.

(b) From 4-(4-bromophenyl)-piperidin-4-ol there was obtained by elimination 4-(4-bromophenyl)-1,2,3,6-tetrahydro-pyridine as
30 a light yellow solid; MS: 237, 239 (M)⁺. Subsequent hydroboration gave (3RS,4RS)-4-(4-bromophenyl)-piperidin-3-ol as a colourless solid; MS: 255, 257 (M)⁺. Introduction of the BOC group yielded tert-butyl (3RS,4RS)-4-(4-bromophenyl)-3-hydroxy-piperidine-1-carboxylate as a colourless solid; MS: 299, 301 (M-C₄H₈)⁺.
35 After alkylation with 4-methoxybenzyl bromide there was obtained tert-butyl (3RS,4RS)-4-(4-bromophenyl)-3-(4-methoxy-benzyloxy)-piperidine-1-carboxylate as a light yellow oil; MS: 418, 420 (M-C₄H₉)⁺.

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(c) From 4-(3-trifluoromethylphenyl)-piperidin-4-ol there was obtained by elimination 4-(3-trifluoromethylphenyl)-1,2,3,6-tetrahydro-pyridine as a colourless solid; MS: 227 (M)⁺. Subsequent hydroboration gave (3RS,4RS)-4-(3-trifluoromethylphenyl)-piperidin-3-ol as a colourless solid; MS: 245 (M)⁺. Introduction of the BOC group yielded tert-butyl (3RS,4RS)-3-hydroxy-4-(3-trifluoromethylphenyl)-piperidine-1-carboxylate as a colourless solid; MS: 289 (M-C₄H₈)⁺. After alkylation with 4-methoxybenzyl bromide there was obtained tert-butyl (3RS,4RS)-3-(4-methoxybenzyloxy)-4-(3-trifluoromethylphenyl)-piperidine-1-carboxylate as a light yellow oil; MS: 408 (M-C₄H₉)⁺.

(d) From 1-benzyl-4-(p-tolyl)-piperidin-4-ol there was obtained by elimination 1-benzyl-4-(p-tolyl)-1,2,3,6-tetrahydro-pyridine as a light yellow solid; MS: 263 (M)⁺. Subsequent hydroboration gave (3RS,4RS)-1-benzyl-4-(p-tolyl)-piperidin-3-ol as a colourless solid; MS: 281 (M)⁺.

(e) A solution of 2.5 g (8.9 mmol) of (3RS,4RS)-1-benzyl-4-(p-tolyl)-piperidin-3-ol in 100 ml of methanol was hydrogenated at 5 bar at room temperature for 18 hours using a palladium (10%)-carbon catalyst. For the working up, the catalyst was filtered off, washed with methanol and the solution obtained was evaporated under reduced pressure. For purification, the residue was chromatographed on silica gel using a 5:1:0.1 mixture of methylene chloride, methanol and ammonia as the eluent. There were obtained 1.15 g (68% of theory) of (3RS,4RS)-4-(p-tolyl)-piperidin-3-ol as a colourless solid; MS: 191 (M)⁺.

(f) From (3RS,4RS)-4-(p-tolyl)-piperidin-3-ol by introduction of the BOC group there was obtained tert-butyl (3RS,4RS)-3-hydroxy-4-(p-tolyl)-piperidine-1-carboxylate as a colourless solid; MS: 291 (M)⁺. After alkylation [with] 4-methoxybenzyl bromide there was obtained tert-butyl (3RS,4RS)-3-(4-methoxybenzyloxy)-4-(p-tolyl)-piperidine-1-carboxylate as a colourless oil; MS: 354 (M-C₄H₉)⁺.

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The following compounds were obtained in an analogous manner to that described in Example 1 (g):

- 5 (g) By alkylating tert-butyl (3RS,4RS)-3-hydroxy-4-phenyl-piperidine-1-carboxylate with 2-bromomethylnaphthalene there was obtained tert-butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-phenyl-piperidine-1-carboxylate as a light yellow oil; MS: 417 (M)⁺.
- 10 (h) By alkylating tert-butyl (3RS,4RS)-4-(4-bromophenyl)-3-hydroxy-piperidine-1-carboxylate with 2-bromomethyl-naphthalene there was obtained tert-butyl (3RS,4RS)-4-(4-bromophenyl)-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a colourless solid; MS: 495, 497 (M)⁺.
- 15 (i) By alkylating tert-butyl (3RS,4RS)-3-hydroxy-4-(3-trifluoromethylphenyl)-piperidine-1-carboxylate with 2-bromomethylnaphthalene there was obtained tert-butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-(3-trifluoromethyl-phenyl)-piperidine-1-carboxylate as a light yellow oil; MS: 485 (M)⁺.
- 20 (j) A solution of 4.0 g tert-butyl (13.8 mmol) of tert-butyl (3RS,4RS)-3-hydroxy-4-phenyl-piperidine-1-carboxylate in 100 ml of methanol was hydrogenated at 150 bar at 100°C for 18 hours using a rhodium(5%)-aluminium oxide catalyst. For the working up, the catalyst was filtered off, washed with methanol and the solution obtained was evaporated under reduced pressure. For purification, the residue was chromatographed on silica gel using a 4:1 mixture of hexane and ethyl acetate as the eluent.
- 30 There were obtained 2.32 g (59% of theory) of tert-butyl (3RS,4RS)-4-cyclohexyl-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a colourless solid; MS: 283 (M)⁺.
- 35 (k) By alkylating tert-butyl (3RS,4RS)-4-cyclohexyl-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate with 2-bromomethylnaphthalene there was obtained tert-butyl

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(3RS,4RS)-4-cyclohexyl-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a light yellow oil; MS: 423 (M)⁺.

5 (l) By alkylating tert-butyl (3RS,4RS)-3-hydroxy-4-(p-tolyl)-piperidine-1-carboxylate with 2-bromomethylnaphthalene there was obtained tert-butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-p-tolyl-piperidine-1-carboxylate as a colourless oil; MS: 431 (M)⁺.

10 The remaining starting materials were obtained as follows:

(m) From 2-bromonaphthalene and 1-benzyl-4-piperidone there was obtained in an analogous manner to Example 1(a) 1-benzyl-4-naphthalen-2-yl-piperidin-4-ol as a light yellow oil; MS: 317
15 (M)⁺. Elimination in an analogous manner to that described in Example 1(b) yielded 1-benzyl-4-naphthalen-2-yl-1,2,3,6-tetrahydro-pyridine as a light brown oil; MS: 299 (M)⁺. Subsequent cleavage of the benzyl group analogously to Example 1(d) gave 2-trimethylsilylethyl 4-naphthalen-2-yl-1,2,3,6-tetra-
20 hydro-pyridine-1-carboxylate as a colourless solid; 4-MS: 325 (M-C₂H₄)⁺. By treatment with tetrabutylammonium fluoride in tetrahydrofuran analogously to Example 1(e) there was obtained 4-naphthalen-2-yl-1,2,3,6-tetrahydro-pyridine as a colourless solid; MS: 209 (M)⁺. Subsequent hydroboration in an analogous
25 manner to that described in Example 1(c) gave (3RS,4RS)-naphthalen-2-yl-4-piperidin-3-ol as a colourless solid; MS: 227 (M)⁺. Introduction of the BOC group in analogy to Example 1(f) yielded tert-butyl (3RS,4RS)-3-hydroxy-4-naphthalen-2-yl-piperidine-1-carboxylate as a colourless oil; MS: 327 (M)⁺. After
30 alkylation with 2-bromomethylnaphthalene in an analogous manner to the procedure described in Example 1(g) there was obtained tert-butyl (3RS,4RS)-4-naphthalen-2-yl-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a colourless oil; MS: 467 (M)⁺.

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(n) In an analogous manner to that described in Example 2(e), by catalytically hydrogenating (3RS,4RS)-1-benzyl-4-naphthalen-2-yl-piperidin-3-ol there was obtained (3RS,4RS)-4-(5,6,7,8-

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tetrahydro-naphthalen-2-yl)-piperidin-3-ol as a colourless solid; MS: 231 (M)⁺. Introduction of the BOC group in an analogous manner to that described in Example 1(f) yielded tert-butyl (3RS,4RS)-3-hydroxy-4-(5,6,7,8-tetrahydro-naphthalen-2-yl)-piperidine-1-carboxylate as a colourless oil; MS: 331 (M)⁺. After alkylation with 2-bromomethylnaphthalene in an analogous manner to the procedure described in Example 1(g) there was obtained tert-butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-(5,6,7,8-tetrahydro-naphthalen-2-yl)-piperidine-1-carboxylate as a colourless oil; MS: 471 (M)⁺.

(o) From 1-benzyl-4-naphthalen-1-yl-1,2,3,6-tetrahydro-pyridine (EP-A-372 776) by hydroboration in an analogous manner to Example 1(c) there was obtained (3RS,4RS)-1-benzyl-4-naphthalen-1-yl-piperidin-3-ol as a colourless solid; MS: 317 (M)⁺. The benzyl group was removed by catalytic hydrogenation [palladium (10%)-charcoal, ethanol, 80°C, 24 hours, 50 bar, 21% of theory] in an analogous manner to that described in Example 2(e). (3RS,4RS)-4-Naphthalen-1-yl-piperidin-3-ol was obtained as a beige solid; MS: 227 (M)⁺. Introduction of the BOC group in an analogous manner to that described in Example 1(f) yielded tert-butyl (3RS,4RS)-3-hydroxy-4-naphthalen-1-yl-piperidine-1-carboxylate as a colourless solid; MS: 327 (M)⁺. After alkylation with 2-bromomethylnaphthalene, in analogy to the procedure described in Example 1(g) there was obtained tert-butyl (3RS,4RS)-4-naphthalen-1-yl-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a colourless solid; MS: 467 (M)⁺.

(p) From 1-benzyl-4-(3,4-dimethoxy-phenyl)-1,2,3,6-tetrahydro-pyridine (JP 60 146 872) by hydroboration in an analogous manner to that described in Example 1(c) there was obtained (3RS,4RS)-1-benzyl-(3,4-dimethoxy-phenyl)-piperidin-3-ol as a colourless solid; MS: 327 (M)⁺. The benzyl group was removed by catalytic hydrogenation [palladium (10%)-charcoal, methanol, room temperature, 18 hours, 5 bar, 81% of theory] in an analogous manner to that described in Example 2(e). (3RS,4RS)-4-(3,4-Dimethoxy-phenyl)-piperidin-3-ol was obtained as a colourless solid; MS: 237 (M)⁺. Introduction of the

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BOC group in an analogous manner to that described in Example 1(f) yielded tert-butyl (3RS,4RS)-3-hydroxy-4-(3,4-dimethoxy-phenyl)-piperidine-1-carboxylate as a light yellow oil; MS: 337 (M)⁺. After alkylation with 2-bromomethylnaphthalene in analogy
5 to the procedure described in Example 1(g) there was obtained tert-butyl (3RS,4RS)-4-(3,4-dimethoxy-phenyl)-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a light yellow oil; MS: 477 (M)⁺.

10 (q) From 5-bromo-acenaphthene and 1-benzyl-4-piperidone there was obtained in an analogous manner to Example 1(a) 4-acenaphthen-5-yl-1-benzyl-piperidin-4-ol as a yellow oil; MS: 343 (M)⁺. Elimination in an analogous manner to that described in Example 1(b) yielded 4-acenaphthen-5-yl-1-benzyl-
15 1,2,3,6-tetrahydro-pyridine as a light brown oil; MS: 325 (M)⁺. Subsequent hydroboration in an analogous manner to that described in Example 1(c) gave (3RS,4RS)-1-benzyl-acenaphthen-5-yl-4-piperidin-3-ol as a yellow oil; MS: 343 (M)⁺. The benzyl group was removed by catalytic hydrogenation [palladium (10%)-
20 charcoal, methanol, room temperature, 18 hours, 5 bar, 95% of theory] in an analogous manner to that described in Example 2(e). (3RS,4RS)-4-Acenaphthen-5-yl-piperidin-3-ol was obtained as a colourless solid; MS: 253 (M)⁺. Introduction of the BOC group in an analogous manner to that described in Example 1(f) yielded
25 tert-butyl (3RS,4RS)-4-acenaphthen-5-yl-3-hydroxy-piperidine-1-carboxylate as a colourless solid; MS: 353 (M)⁺. After alkylation with 2-bromomethylnaphthalene in analogy to the procedure described in Example 1(g) there was obtained tert-butyl (3RS,4RS)-4-acenaphthen-5-yl-3-(naphthalen-2-yl-
30 methoxy)-piperidine-1-carboxylate as a yellow solid; MS: 493 (M)⁺.

(r) From 4-(4-chlorophenyl)-piperidin-4-ol by elimination in an analogous manner to that described in Example 1(b) there was
35 obtained 4-(4-chlorophenyl)-1,2,3,6-tetrahydro-pyridine as a light yellow solid; MS: 193, 195 (M)⁺. Hydroboration in an analogous manner as Example 1(c) gave (3RS,4RS)-4-(4-chlorophenyl)-piperidin-3-ol as a colourless solid; MS: 211, 213 (M)⁺.

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- Introduction of the BOC group in an analogous manner to that described in Example 1(f) yielded tert-butyl (3RS,4RS)-4-(4-chlorophenyl)-3-hydroxy-piperidine-1-carboxylate as a colourless solid; MS: 255, 257 (M-C₄H₈)⁺. After alkylation with 4-phenoxybenzyl chloride in analogy to the procedure described in Example 1(g) there was obtained tert-butyl (3RS,4RS)-4-(4-chlorophenyl)-3-(4-phenoxy-benzyloxy)-piperidine-1-carboxylate as a colourless oil; MS: 437, 439 (M-C₄H₉)⁺.
- (s) From (3RS,4SR)-4-phenyl-piperidin-3-ol [J.A.Gauthier et al., US 4132710] by introduction of the BOC group there was obtained tert-butyl (3RS,4SR)-3-hydroxy-4-phenyl-piperidine-1-carboxylate as a colourless solid; m.p.: 134-134.5°C. Subsequent alkylation with 2-bromomethylnaphthalene gave tert-butyl (3RS,4SR)-3-(naphthalen-2-ylmethoxy)-4-phenyl-piperidine-1-carboxylate as a colourless solid; MS: 417 (M)⁺.

Example 3

130 mg (0.31 mmol) of tert-butyl (3RS,4RS)-4-(4-fluorophenyl)-3-(4-methoxy-benzyloxy)-piperidine-1-carboxylate were dissolved in 5 ml of methanol, treated with 5 ml of a 2N solution of hydrogen chloride in methanol and stirred at 50°C for 4 hours. Subsequently, the mixture was partitioned between ethyl acetate and aqueous 5% sodium hydrogen carbonate solution, the organic phase was dried over magnesium sulphate and finally the solvent was distilled off under reduced pressure. For purification, the crude product was chromatographed on silica gel with a 10:1:0.1 mixture of methylene chloride, methanol and ammonia as the eluent. There were obtained 76 mg (78% of theory) of (3RS,4RS)-4-(4-fluorophenyl)-3-(4-methoxy-benzyloxy)-piperidine as a colourless oil. MS: 316 (M+H)⁺.

The tert-butyl (3RS,4RS)-4-(4-fluorophenyl)-3-(4-methoxy-benzyloxy)-piperidine-1-carboxylate used as the starting material was prepared as follows:

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(a) 20.0 g (93.6 mmol) of (3RS,4RS)-4-(4-fluorophenyl)-1,2,3,6-tetrahydropyridine hydrochloride were suspended in 160 ml of absolute dimethoxyethane. 10.6 g (280 mmol) of sodium borohydride were added portionwise at room temperature. 5 Thereafter, a solution of 62 ml (500 mmol) of boron trifluoride etherate in 30 ml of dimethoxyethane was added dropwise at 15-20°C and the mixture was stirred at room temperature for 2.5 hours. Subsequently, a solution of 65 g (1.16 mmol) of potassium hydroxide in 340 ml of water was added dropwise at 10 20-25°C within 60 minutes. 55 ml of hydrogen peroxide solution (30%) were then added dropwise at 20-25°C within 30 minutes. The mixture was stirred at room temperature for 30 minutes and boiled under reflux for 3 hours. After cooling the reaction mixture the precipitated boric acid was filtered off. Subse- 15 quently, the filtrate was partitioned between methylene chloride and water, the organic phase was dried over magnesium sulphate and the solvent was distilled off under reduced pressure. The crude product was purified by chromatography on silica gel with a 3:1:0.1 mixture of methylene chloride, methanol and ammonia as 20 the eluent. There were obtained 9.1 g (50% of theory) of (3RS,4RS)-4-(4-fluorophenyl)-piperidin-3-ol as a colourless oil. MS: 195 (M)+.

(b) 4.10 g (21.0 mmol) of (3RS,4RS)-4-(4-fluorophenyl)- 25 piperidin-3-ol were dissolved in 35 ml of absolute dimethyl-formamide. Thereto there were added at 0°C 3.2 ml (23.0 mmol) of triethylamine and subsequently dropwise a solution of 5.04 g (23.1 mmol) of di-tert-butyl dicarbonate in 15 ml of dimethyl-formamide. The mixture was warmed to room temperature and 30 stirred for 20 hours. The solvent was distilled off at 0.1 mm Hg at 50-55°C. Subsequently, the residue obtained was partitioned between methylene chloride and water, the organic phase was dried over magnesium sulphate and finally the solvent was removed under reduced pressure. The crude product (7.09 g) was 35 purified by chromatography on silica gel with a 2:3 mixture of ethyl acetate and hexane as the eluent. There were obtained 5.45 mg (88% of theory) of tert-butyl (3RS,4RS)-4-(4-fluoro-

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phenyl)-3-hydroxy-piperidine-1-carboxylate; MS: 239
(M - C₄H₈)⁺.

(c) 200 mg (0.68 mmol) of tert-butyl (3RS,4RS)-4-(4-fluorophenyl)-3-hydroxy-piperidine-1-carboxylate and 159 mg (1.01 mmol) of 4-methoxybenzyl chloride were dissolved in 3 ml of dimethylformamide. 40 mg (1.01 mmol) of a 60% sodium hydride suspension were added and the mixture was stirred at room temperature for 3 hours. Subsequently, the reaction mixture was partitioned between ethyl acetate and water, the organic phase was dried over magnesium sulphate and finally the solvent was removed under reduced pressure. The crude product was purified by chromatography on silica gel with a 1:3 mixture of ethyl acetate and hexane as the eluent. There were obtained 250 mg (90% of theory) of tert-butyl (3RS,4RS)-4-(4-fluorophenyl)-3-(4-methoxy-benzyloxy)-piperidine-1-carboxylate as a light yellow oil; MS: 358 (M - C₄H₉)⁺.

Example 4

20

The following compounds were prepared in an analogous manner to that described in Example 3:

- 1) (3RS,4RS)-4-(4-fluorophenyl)-3-(naphthalen-2-yl-methoxy)-piperidine as a colourless oil, MS: 336 (M+1)⁺, from tert-butyl (3RS,4RS)-4-(4-fluorophenyl)-3-(naphthalen-2-yl-methoxy)-piperidine-1-carboxylate;
- 2) (3RS,4RS)-3-(3-benzyloxy-benzyloxy)-4-(4-fluorophenyl)-piperidine as a colourless solid, MS: 392 (M+1)⁺, from tert-butyl (3RS,4RS)-3-(3-benzyloxy-benzyloxy)-4-(4-fluorophenyl)-piperidine-1-carboxylate;
- 3) (3RS,4RS)-4-(4-fluorophenyl)-3-(4-methoxy-quinazolin-2-ylmethoxy)-piperidine as a colourless solid, MS: 368 (M+1)⁺, from tert-butyl (3RS,4RS)-4-(4-fluorophenyl)-3-(4-methoxy-quinazolin-2-ylmethoxy)-piperidine-1-carboxylate;

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- 4) (3RS,4RS)-3-(benzo[b]thiophen-5-ylmethoxy)-4-(4-fluorophenyl)-piperidine as a colourless solid, MS: 342 (M+1)⁺, from tert-butyl (3RS,4RS)-3-(benzo[b]thiophen-5-ylmethoxy)-4-(4-fluorophenyl)-piperidine-1-carboxylate;
5
- 5) (3RS,4RS)-4-(4-fluorophenyl)-3-(indan-5-ylmethoxy)-piperidine as a colourless solid, MS: 326 (M+1)⁺, from tert-butyl (3RS,4RS)-4-(4-fluorophenyl)-3-(indan-5-ylmethoxy)-piperidine-1-carboxylate,
10
- 6) (3RS,4RS)-4-(4-fluorophenyl)-3-(5,6,7,8-tetrahydronaphthalen-2-ylmethoxy)-piperidine as a colourless solid, MS: 340 (M+1)⁺, from tert-butyl (3RS,4RS)-4-(4-fluorophenyl)-3-(5,6,7,8-tetrahydronaphthalen-2-ylmethoxy)-piperidine-1-carboxylate;
15
- 7) (3RS,4RS)-4-(4-fluorophenyl)-3-(isoquinolin-6-ylmethoxy)-piperidine as a colourless solid, MS: 337 (M+1)⁺, from tert-butyl (3RS,4RS)-4-(4-fluorophenyl)-3-(isoquinolin-6-ylmethoxy)-piperidine-1-carboxylate.
20

The BOC derivatives used as the starting materials were obtained as follows in an analogous manner to the alkylation procedure described in Example 3 (c):
25

- tert-Butyl (3RS,4RS)-4-(4-fluorophenyl)-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a light yellow oil, MS: 436 (M+1)⁺, from tert-butyl (3RS,4RS)-4-(4-fluorophenyl)-3-hydroxy-piperidine-1-carboxylate and 2-naphthylmethyl bromide;
30
- tert-butyl (3RS,4RS)-3-(3-benzyloxy-benzyloxy)-4-(4-fluorophenyl)-piperidine-1-carboxylate as a colourless solid, MS: 492 (M+1)⁺, from tert-butyl (3RS,4RS)-4-(4-fluorophenyl)-3-hydroxy-piperidine-1-carboxylate and 3-benzyloxy-benzyl chloride [J. Med. Chem. 31(3), 606 (1988)];
35

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- tert-butyl (3RS,4RS)-4-(4-fluorophenyl)-3-(4-methoxy-quinazolin-2-ylmethoxy)-piperidine-1-carboxylate as a colourless solid, MS: 492 (M+1)⁺, from tert-butyl (3RS,4RS)-4-(4-fluorophenyl)-3-hydroxy-piperidine-1-carboxylate and 2-bromo-
5 methyl-4-methoxy-quinazoline;
- tert-butyl (3RS,4RS)-3-(benzo[b]thiophen-5-ylmethoxy)-4-(4-fluoro-phenyl)-piperidine-1-carboxylate as a light yellow resin, MS: 442 (M+1)⁺, from tert-butyl (3RS,4RS)-4-(4-fluorophenyl)-3-
10 hydroxy-piperidine-1-carboxylate and 5-bromomethyl-benzo[b]-thiophene [J. Med. Chem. 34(1), 65(1991)];
- tert-butyl (3RS,4RS)-4-(4-fluorophenyl)-3-(indan-5-ylmethoxy)-piperidine-1-carboxylate as a colourless solid, MS: 426
15 (M+1)⁺, from tert-butyl (3RS,4RS)-4-(4-fluorophenyl)-3-hydroxy-piperidine-1-carboxylate and 5-chloromethylindane [Recl. Trav. Chim. Pays-Bas 77, 792 (1988)];
- tert-butyl (3RS,4RS)-4-(4-fluorophenyl)-3-(5,6,7,8-tetra-
20 hydro-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a light yellow resin, MS: 440 (M+1)⁺, from tert-butyl (3RS,4RS)-4-(4-fluorophenyl)-3-hydroxy-piperidine-1-carboxylate and 6-chloromethyl-1,2,3,4-tetrahydro-naphthalene [J. Chem. Soc. 684(1941)];
- tert-butyl (3RS,4RS)-4-(4-fluoro-phenyl)-3-(isoquinolin-6-ylmethoxy)-piperidine-1-carboxylate as a light yellow resin, MS: 437 (M+1)⁺, from tert-butyl (3RS,4RS)-4-(4-fluorophenyl)-
3-hydroxy-piperidine-1-carboxylate and 6-bromomethyliso-
30 quinoline hydrobromide.

2-Bromomethyl-4-methoxy-quinazoline

- (a) By brominating 2-methyl-4-methoxy-quinazoline [Recl.
35 Trav. Chim. Pays-Bas 76, 401 (1957)] with N-bromosuccinimide in carbon tetrachloride in an analogous manner to the procedure described for the preparation of 6-bromomethylquinoxaline [J. Het. Chem. 11, 595(1974)] from 6-methylquinoxaline there was

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obtained 2-bromomethyl-4-methoxy-quinazoline as a light yellow solid; MS: 252, 254 (M)⁺.

6-Bromomethyl-isoquinoline hydrobromide

5

(b) From isoquinoline-6-carboxylic acid [J.Am.Chem.Soc. 61, 183(1939)] by esterification with ethanol/sulphuric acid there was obtained ethyl isoquinoline-6-carboxylate as a colourless solid; MS: 201 (M)⁺. Subsequent reduction yielded 6-isoquinoline-
10 methanol as a yellow solid which was used directly in the next step.

(c) A solution of 190 mg (1.19 mmol) of 6-isoquinoline-methanol in 1 ml of glacial acetic acid was treated with 2 ml of
15 30% HBr in glacial acetic acid and the mixture was heated at 70°C for 45 minutes. The reaction mixture was cooled, treated with 20 ml of diethyl ether and stirred at 0°C for 30 min. The resulting solid was filtered off, washed with diethyl ether and dried in a high vacuum. There was obtained 6-bromomethyl-
20 isoquinoline hydrobromide (73% of theory) as a light brown solid; MS: 221, 223 (M)⁺.

Example 5

25 70 mg (0.141 mmol) of β -trimethylsilylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-(4-hydroxy-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate were dissolved in 1.0 ml of tetrabutyl-ammonium fluoride solution (1M in tetrahydrofuran) and stirred at room temperature for one hour. Subsequently, the mixture was
30 partitioned between methylene chloride and aqueous 5% sodium hydrogen carbonate solution, then the organic phase was dried over magnesium sulphate and finally the solvent was distilled off under reduced pressure. The crude product (72 mg) was purified by chromatography on silica gel with a 10:1:0.1 mixture of
35 methylene chloride, methanol and ammonia as the eluent. There were obtained 41 mg (83% of theory) of (3RS,4RS)-4-(4-fluorophenyl)-3-(4-hydroxy-naphthalen-2-ylmethoxy)-piperidine as a colourless solid. MS: 352 (M+H)⁺.

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The β -trimethylsilylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-(4-hydroxy-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate used as the starting material was prepared as follows:

- 5 (a) 17.87 g (82.64 mmol) of ethyl 4-hydroxy-naphthalene-2-carboxylate [J.Agric.Chem Soc.Japan 24, 313 (1950)] were suspended in 900 ml of methylene chloride, the suspension was cooled to 0-5°C and subsequently treated with 17.9 ml
10 (91.02 mmol) of 2-(trimethylsilyl)-ethoxymethyl chloride (SEM chloride) and 28.3 ml (165.31 mmol) of N-ethyldiisopropylamine. The yellow solution was warmed to room temperature and stirred for 2 hours. The solvent was distilled off under reduced pressure and the crude product (58 g), without further purification, was
15 chromatographed on silica gel using a 3:2 mixture of methylene chloride and hexane as the eluent. There were obtained 15.81 g (99% of theory) of ethyl 4-(2-trimethyl-silylethoxy-methoxy)-naphthalene-2-carboxylate as a light yellow oil; MS: 322, 324 (M)⁺.
- 20 (b) A solution of 28.31 g (81.70 mmol) of ethyl 4-(2-trimethyl-silylethoxy-methoxy)-naphthalene-2-carboxylate in 480 ml of diethyl ether was added dropwise within 90 minutes at -5 to 0°C under argon to a suspension of 3.29 g (86.69 mmol)
25 of lithium aluminium hydride in 230 ml of diethyl ether. The reaction mixture was warmed to room temperature and stirred for 2 hours. For the working-up, the mixture was cooled to 0°C, treated dropwise with 25 ml of ethyl acetate and with 50 ml of saturated potassium sodium tartrate solution. A light yellowish
30 solution containing a white precipitate resulted. The solution was warmed to room temperature [and] decanted off from the precipitate. The residue was suspended three times with diethyl ether and the solvent was decanted off each time. The combined organic phases were washed with water, the organic phase was
35 dried over magnesium sulphate and finally the solvent was removed under reduced pressure. The crude product (26.4 g) was chromatographed on silica gel using a 3:7 mixture of ethyl acetate and hexane. There were obtained 23.72 g (95% of theory)

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of [4-(2-trimethylsilyl-ethoxymethoxy)-naphthalen-2-yl]-methanol as a light yellow oil; MS: 304 (M)⁺.

(c) 23.72 g (77.91 mmol) of [4-(2-trimethylsilyl-ethoxy-
5 methoxy)-naphthalen-2-yl]-methanol were dissolved in 350 ml of carbon tetrachloride and the solution was cooled to 0°C. Thereupon, 350 ml of acetonitrile and 26.54 g (1.012 mmol) of triphenylphosphine were added. The light yellow solution was stirred at 0°C for 30 minutes, warmed to room temperature and
10 stirred for a further 2 hours. A further 10.14 g (38.7 mmol) of triphenylphosphine were added and the reaction mixture was stirred at room temperature for 90 minutes. Subsequently, the mixture was partitioned between methylene chloride and water, the organic phase was dried over magnesium sulphate and finally
15 the solvent was removed under reduced pressure. The crude product was chromatographed on silica gel using a 3:7 mixture of methylene chloride and hexane as the eluent. There were obtained 15.81 g (63% of theory) of 2-chloromethyl-4-(β-trimethylsilyl-ethoxymethoxy)-naphthalene as a light yellow oil; MS: 322, 324
20 (M)⁺.

(d) A solution of 4.00 g (20.5 mmol) of (3RS,4RS)-4-(4-fluorophenyl)-piperidin-3-ol in 150 ml of ethanol was treated with 2.80 g (26.4 mmol) of sodium carbonate and refluxed. A
25 solution of 2.50 ml (21.1 mmol) of benzyl bromide in 50 ml of ethanol was added dropwise within one hour and thereafter the mixture was held at reflux temperature for 2 hours. The pale brownish suspension was filtered and the filtrate was concentrated under reduced pressure. Subsequently, the residue
30 was partitioned between methylene chloride and water, the organic phase was dried over magnesium sulphate and finally the solvent was distilled off under reduced pressure. The crude product was chromatographed on silica gel using a 2:3 mixture of ethyl acetate and hexane as the eluent. There were obtained
35 4.34 g (74% of theory) of (3RS,4RS)-1-benzyl-4-(4-fluorophenyl)-piperidin-3-ol as a colourless solid; MS: 285 (M)⁺.

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(e) In an analogous manner to that described in Example 1 (g), by alkylating (3RS,4RS)-1-benzyl-4-(4-fluoro-phenyl)-piperidin-3-ol with 2-chloromethyl-4-(β -trimethylsilylethoxymethoxy)-naphthalene there was obtained (3RS,4RS)-1-benzyl-4-(4-fluoro-phenyl)-3-[4-(2-trimethylsilyl-ethoxymethoxy)-naphthalen-2-ylmethoxy]-piperidine as a light yellow oil; MS: 572 (M+H)⁺.

(f) In an analogous manner to that described in Example 1(d) by cleavage of the benzyl group by means of β -trimethylsilylethyl chloroformate from (3RS,4RS)-1-benzyl-4-(4-fluoro-phenyl)-3-[4-(2-trimethylsilyl-ethoxymethoxy)-naphthalen-2-ylmethoxy]-piperidine there was obtained β -trimethylsilylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-[4-(2-trimethylsilyl-ethoxymethoxy)-naphthalen-2-yl-methoxy]-piperidine-1-carboxylate as a light yellow oil; MS: 626 (M+H)⁺.

(g) 4.65 g (7.43 mmol) of β -trimethylsilylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-[4-(2-trimethylsilyl-ethoxymethoxy)-naphthalen-2-ylmethoxy]-piperidin-1-carboxylate were dissolved in 40 ml of methanol, treated with 40 ml of a 2N solution of hydrogen chloride in methanol and stirred at 50°C for 90 minutes. Subsequently, the mixture was partitioned between methylene chloride and aqueous 5% sodium hydrogen carbonate solution, the organic phase was dried over magnesium sulphate and finally the solvent was distilled off under reduced pressure. The crude product (6.8 g) was purified by chromatography on silica gel with a 3:7 mixture of ethyl acetate and hexane. There were obtained 2.93 g (80% of theory) of β -trimethylsilylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-(4-hydroxy-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a colourless solid; MS: 496 (M+H)⁺.

Example 6

The following compounds were obtained in an analogous manner to that described in Example 5:

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- 1) - 4-(4-Fluoro-phenyl)-3-(1-hydroxy-naphthalen-2-yl-methoxy)-piperidine as a light brown solid, MS: 351 (M)⁺, from β -trimethylsilylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-(1-hydroxy-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate;
- 5 2) - 4-(4-fluoro-phenyl)-3-(5-hydroxy-naphthalen-2-yl-methoxy)-piperidine as a colourless solid, MS: 351 (M)⁺, from β -trimethylsilylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-(5-hydroxy-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate;
- 10 3) - 4-(4-fluoro-phenyl)-3-(6-hydroxy-naphthalen-2-yl-methoxy)-piperidine as a colourless solid, MS: 351 (M)⁺, from β -trimethylsilylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-(6-hydroxy-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate;
- 15 4) - 4-(4-fluoro-phenyl)-3-(7-hydroxy-naphthalen-2-yl-methoxy)-piperidine as a light brown solid, MS: 351 (M)⁺, from β -trimethylsilylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-(7-hydroxy-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate;
- 20 5) - 4-(4-fluoro-phenyl)-3-(8-hydroxy-naphthalen-2-yl-methoxy)-piperidine as a light yellow resin, MS: 352 (M+H)⁺, from β -trimethylsilylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-(8-hydroxy-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate.

25

The trimethylsilylethyl carbamates used as the starting materials were obtained as follows in analogy to the procedure described in Example 5 (a)-(f):

30

(a) From methyl 1-hydroxy-naphthalene-2-carboxylate [J. Chem. Soc. 309 (1948)] by introducing the protecting group there was obtained methyl 1-(2-trimethylsilylethoxymethoxy)-naphthalene-2-carboxylate as a light yellow oil, MS: 333 (M+H)⁺.

35

(b) Reduction of methyl 1-(2-trimethylsilyl-ethoxymethoxy)-naphthalene-2-carboxylate gave [1-(2-trimethyl-silylethoxy-methoxy)-naphthalen-2-yl]-methanol as a light yellow oil, MS: 305 (M+H)⁺.

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(c) Chlorination of [1-(2-trimethylsilylethoxy-methoxy)-naphthalen-2-yl]-methanol yielded 2-chloro-methyl-1-(β -trimethylsilylethoxymethoxy)-naphthalene as a colourless oil,
5 MS: 322, 324 (M)+.

(d) Alkylation of (3RS,4RS)-1-benzyl-4-(4-fluoro-phenyl)-piperidin-3-ol with 2-chloromethyl-1-(β -trimethylsilylethoxy-methoxy)-naphthalene yielded (3RS,4RS)-1-benzyl-3-(4-fluoro-phenyl)-3-[1-(2-trimethylsilylethoxy-methoxy)-naphthalen-2-ylmethoxy]-piperidine as a light yellow oil, MS: 572 (M+H)+.
10

(e) Cleavage of the N-benzyl group from (3RS,4RS)-1-benzyl-3-(4-fluorophenyl)-3-[1-(2-trimethylsilylethoxy-methoxy)-naphthalen-2-ylmethoxy]-piperidine with β -trimethylsilylethyl chloroformate gave β -trimethylsilylethyl (3RS, 4RS)-4-(4-fluorophenyl)-3-[1-(2-trimethylsilyl-ethoxymethoxy)-naphthalen-2-ylmethoxy]-piperidine-1-carboxylate as a colourless oil, MS: 626 (M+H)+.
15

(f) Cleavage of the SEM group from β -trimethylsilylethyl (3RS, 4RS)-4-(4-fluorophenyl)-3-[1-(2-trimethylsilyl-ethoxy-methoxy)-naphthalen-2-ylmethoxy]-piperidine-1-carboxylate yielded β -trimethylsilylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-(1-hydroxy-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a colourless oil, MS: 494 (M-H)-.
20
25

(g) From 5-hydroxy-naphthalene-2-carboxylic acid [Bull. Soc. Chim. Fr., 857 (1953)] there was obtained firstly by
30 esterification with methanol/sulphuric acid methyl 5-hydroxy-naphthalene-2-carboxylate as a light yellow solid, MS: 202 (M)+. By introducing the protecting group there was obtained methyl 5-(2-trimethylsilyl-ethoxymethoxy)-naphthalene-2-carboxylate as a light yellow oil, MS: 333 (M+H)+.

35
(h) Reduction of methyl 5-(2-trimethylsilyl-ethoxymethoxy)-naphthalene-2-carboxylate gave [5-(2-trimethylsilyl-ethoxy-

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methoxy)-naphthalen-2-yl]-methanol as a light yellow oil, MS: 305 (M+H)⁺.

5 (i) Chlorination of [5-(2-trimethylsilyl-äthoxymethoxy)-naphthalen-2-yl]-methanol yielded 2-chloro-methyl-5-(β -trimethyl-silylethoxy-methoxy)-naphthalene as a colourless oil, MS: 322, 324 (M)⁺.

10 (j) Alkylation of (3RS,4RS)-1-benzyl-4-(4-fluoro-phenyl)-piperidin-3-ol with 2-chloromethyl-5-(β -trimethyl-silylethoxy-methoxy)-naphthalene yielded (3RS,4RS)-1-benzyl-3-(4-fluoro-phenyl)-3-[5-(2-tri-methylsilyl-ethoxymethoxy)-naphthalen-2-ylmethoxy]-piperidine as a light yellow oil, MS: 572 (M+H)⁺.

15 (k) Cleavage of the N-benzyl group from (3RS,4RS)-1-benzyl-3-(4-fluoro-phenyl)-3-[5-(2-trimethylsilyl-ethoxymethoxy)-naphthalen-2-ylmethoxy]-piperidine with β -trimethylsilylethyl chloroformate gave β -trimethylsilylethyl (3RS,4RS)-4-(4-fluoro-phenyl)-3-[5-(2-trimethylsilyl-ethoxymethoxy)-naphthalen-2-ylmethoxy]-piperidine-1-carboxylate as a colourless oil, MS: 626 (M+H)⁺.

25 (l) Cleavage of the SEM group in β -trimethylsilylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-[5-(2-trimethylsilyl-ethoxy-methoxy)-naphthalen-2-ylmethoxy]-piperidine-1-carboxylate yielded β -trimethylsilylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-(5-hydroxy-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a colourless oil, MS: 494 (M-H)⁻.

30 (m) From ethyl 6-hydroxy-naphthalene-2-carboxylate [J. Chem. Soc. 123, 1654 (1923)] by introducing the protecting group there was obtained ethyl 6-(2-trimethylsilyl-ethoxymethoxy)-naphthalene-2-carboxylate as a light yellow oil, MS: 346 (M)⁺.

35 (n) Reduction of ethyl 6-(2-trimethylsilyl-ethoxymethoxy)-naphthalene-2-carboxylate gave [6-(2-trimethylsilyl-ethoxy-methoxy)-naphthalen-2-yl]-methanol as a colourless solid, MS: 304 (M)⁺.

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- (o) Chlorination of [6-(2-trimethylsilyl-ethoxy-methoxy)-naphthalen-2-yl]-methanol yielded 6-chloromethyl-1-(β -trimethylsilylethoxymethoxy)-naphthalene as a colourless oil,
5 MS: 322, 324 (M)⁺.
- (p) Alkylation of (3RS,4RS)-1-benzyl-4-(4-fluoro-phenyl)-piperidin-3-ol with 6-chloromethyl-1-(β -trimethylsilyl-ethoxymethoxy)-naphthalene yielded (3RS,4RS)-1-benzyl-3-(4-fluorophenyl)-3-[6-(2-trimethyl-silylethoxy-methoxy)-
10 naphthalen-2-ylmethoxy]-piperidine as a light yellow oil, MS: 572 (M+H)⁺.
- (q) Cleavage of the N-benzyl group from (3RS,4RS)-1-benzyl-
15 3-(4-fluorophenyl)-3-[6-(2-trimethyl-silylethoxy-methoxy)-naphthalen-2-ylmethoxy]-piperidine with β -trimethylsilylethyl chloroformate gave β -trimethylsilylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-[6-(2-trimethylsilylethoxy-methoxy)-naphthalen-2-yl-methoxy]-piperidine-1-carboxylate as a
20 colourless oil, MS: 626 (M+H)⁺.
- (r) Cleavage of the SEM group from β -trimethylsilylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-[6-(2-trimethylsilylethoxy-methoxy)-naphthalen-2-yl-methoxy]-piperidine-1-carboxylate
25 yielded β -trimethylsilylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-(6-hydroxy-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a colourless resin, MS: 495 (M)⁺.
- (s) From 7-hydroxy-naphthalene-2-carboxylic acid [Bull. Soc.
30 Chim. Fr., 573 (1952)] there was firstly obtained by esterification with methanol/sulphuric acid methyl 7-hydroxy-naphthalene-2-carboxylate as a colourless solid, MS: 202 (M)⁺. Introduction of the protecting group yielded methyl 7-(2-trimethylsilyl-ethoxymethoxy)-naphthalene-2-carboxylate as a
35 light yellow oil, MS: 332 (M)⁺.
- (t) Reduction of methyl 7-(2-trimethylsilyl-ethoxymethoxy)-naphthalene-2-carboxylate gave [7-(2-trimethylsilyl-ethoxy-

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methoxy)-naphthalen-2-yl]-methanol as a light yellow oil, MS: 304 (M)+.

5 (u) Chlorination of [7-(2-trimethylsilyl-ethoxy-methoxy)-naphthalen-2-yl]-methanol yielded 2-chloromethyl-7-(β -trimethyl-silylethoxymethoxy)-naphthalene as a light yellow oil, MS: 322, 324 (M)+.

10 (v) Alkylation of (3RS,4RS)-1-benzyl-4-(4-fluoro-phenyl)-piperidin-3-ol with 2-chloromethyl-7-(β -trimethyl-silylethoxy-methoxy)-naphthalene yielded (3RS,4RS)-1-benzyl-3-(4-fluoro-phenyl)-3-[7-(2-trimethylsilyl-ethoxymethoxy)-naphthalen-2-ylmethoxy]-piperidine as a light yellow oil, MS: 572 (M+H)+.

15 (w) Cleavage of the N-benzyl group from (3RS,4RS)-1-benzyl-3-(4-fluoro-phenyl)-3-[7-(2-trimethylsilyl-ethoxymethoxy)-naphthalen-2-ylmethoxy]-piperidine with β -trimethylsilylethyl chloroformate yielded β -trimethylsilylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-[7-(2-trimethylsilyl-ethoxymethoxy)-naphthalen-2-ylmethoxy]-piperidine-1-carboxylate as a
20 colourless oil, MS: 626 (M+H)+.

(x) Cleavage of the SEM group from β -trimethylsilylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-[7-(2-trimethylsilyl-ethoxy-methoxy)-naphthalen-2-ylmethoxy]-piperidine-1-carboxylate
25 yielded β -trimethylsilylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-(7-hydroxy-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a light yellow oil, MS: 495 (M)+.

30 (y) From 8-hydroxy-naphthalene-2-carboxylic acid [Bull. Soc. Chim. Fr., 857 (1953)] there was firstly obtained by esterification with methanol/sulphuric acid methyl 8-hydroxy-naphthalene-2-carboxylate as a light yellow solid, MS: 202 (M)+. Introduction of the protecting group yielded methyl 8-(2-trimethylsilyl-ethoxymethoxy)-naphthalene-2-carboxylate as a
35 colourless solid, MS: 274 [M-(C₂H₄+CH₂O)]+.

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(z) Reduction of methyl 8-(2-trimethylsilyl-ethoxymethoxy)-naphthalene-2-carboxylate gave [8-(2-trimethylsilyl-ethoxymethoxy)-naphthalen-2-yl]-methanol as a colourless oil, MS: 304 (M)⁺.

5

(aa) Chlorination of [8-(2-trimethylsilyl-ethoxymethoxy)-naphthalen-2-yl]-methanol yielded 2-chloromethyl-8-(2-trimethylsilylethoxy-methoxy)-naphthalene as a light yellow oil, MS: 322, 324 (M)⁺.

10

(bb) Alkylation of (3RS,4RS)-1-benzyl-4-(4-fluoro-phenyl)-piperidin-3-ol with 2-chloromethyl-8-(2-trimethylsilylethoxy-methoxy)-naphthalene yielded (3RS,4RS)-1-benzyl-3-(4-fluoro-phenyl)-3-[8-(2-trimethylsilylethoxy-methoxy)-naphthalen-2-ylmethoxy]-piperidine as a light yellow oil, MS: 572 (M+H)⁺.

15

(cc) Cleavage of the N-benzyl group from (3RS,4RS)-1-benzyl-3-(4-fluoro-phenyl)-3-[8-(2-trimethylsilylethoxy-methoxy)-naphthalen-2-ylmethoxy]-piperidine with β -trimethylsilylethyl chloroformate gave β -trimethylsilylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-[8-(2-trimethylsilyl-ethoxymethoxy)-naphthalen-2-yl-methoxy]-piperidine-1-carboxylate as a colourless oil, MS: 626 (M+H)⁺.

20

(dd) Cleavage of the SEM group from β -trimethylsilylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-[8-(2-trimethylsilyl-ethoxymethoxy)-naphthalen-2-yl-methoxy]-piperidine-1-carboxylate yielded β -trimethylsilylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-(8-hydroxy-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a colourless oil, MS: 494 (M-H)⁻.

30

Example 7

The following compounds were prepared in an analogous manner to that described in Examples 3 and 5:

35

1) (3RS,4RS)-4-(4-Fluorophenyl)-3-(3-hydroxy-naphthalen-2-ylmethoxy)-piperidine

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In an analogous manner to that described in Examples 3 and 5 (g), by cleaving off the two protecting groups with methanolic hydrochloric acid from tert-butyl (3RS,4RS)-4-(4-fluorophenyl)-
5 3-[3-(2-trimethylsilyl-ethoxymethoxy)-naphthalen-2-yl-methoxy]-piperidine-1-carboxylate there was obtained (3RS,4RS)-4-(4-fluorophenyl)-3-(3-hydroxy-naphthalen-2-yl-methoxy)-piperidine as a colourless solid, MS: 351 (M)⁺.

10 The tert-butyl (3RS,4RS)-4-(4-fluorophenyl)-3-[3-(2-trimethylsilyl-ethoxymethoxy)-naphthalen-2-ylmethoxy]-piperidine-1-carboxylate used as the starting material was prepared as follows:

15 (a) In an analogous manner to that described in Example 5 (a), from methyl 3-hydroxy-naphthalene-2-carboxylate by introducing the protecting group there was obtained methyl 3-(2-trimethylsilyl-ethoxy-methoxy)-naphthalene-2-carboxylate as a light yellow oil, MS: 274 (M-(C₂H₄+CH₂O))⁺.

20

(b) In an analogous manner to that described in Example 5(b), reduction of methyl 3-(2-trimethylsilyl-ethoxy-methoxy)-naphthalene-2-carboxylate gave [3-(2-trimethylsilylethoxy-methoxy)-naphthalen-2-yl]-methanol as a light yellow oil, MS:
25 304 (M)⁺.

(c) 400 mg (1.30 mmol) of [3-(2-trimethylsilylethoxy-methoxy)-naphthalen-2-yl]-methanol and 462 mg (1.81 mmol) of carbon tetrabromide were dissolved in 5 ml of absolute
30 acetonitrile and the solution was cooled to 0°C. A solution of 446 mg (1.68 mmol) of triphenylphosphine in 6 ml of absolute acetonitrile was added dropwise thereto at 0°C within 10 minutes and thereafter the mixture was stirred at 0°C for a further 30 minutes. Subsequently, the solvent was distilled off
35 under reduced pressure and, for purification, the crude product was chromatographed, without further working up, on silica gel using a 2:3 mixture of methylene chloride and hexane as the eluent. There were obtained 314 mg (65% of theory) of 2-bromo-

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methyl-3-(2-trimethylsilylethoxymethoxy)-naphthalene as a light yellow oil; MS: 366, 368 (M)⁺.

(d) In an analogous manner to that described in Example 3 (c),
5 by alkylating tert-butyl (3RS,4RS)-4-(4-fluorophenyl)-3-hydroxy-piperidine-1-carboxylate with 2-bromomethyl-3-(2-trimethylsilylethoxy-methoxy)-naphthalene there was obtained tert-butyl (3RS,4RS)-4-(4-fluorophenyl)-3-[3-(2-trimethylsilylethoxy-methoxy)-naphthalen-2-ylmethoxy]-piperidine-1-
10 carboxylate as a light yellow oil; MS: 523 [M-(C₂H₄ + CH₂O)]⁺.

2) (3RS,4RS)-4-(4-Fluorophenyl)-3-(1-methoxy-naphthalen-2-yl-methoxy)-piperidine

15 In an analogous manner to that described in Example 3, by cleavage of the BOC protecting group from tert-butyl (3RS,4RS)-4-(4-fluorophenyl)-3-[1-methoxy-naphthalen-2-ylmethoxy]-piperidine-1-carboxylate there was obtained (3RS,4RS)-4-(4-fluorophenyl)-3-(1-methoxy-naphthalen-2-yl-methoxy)-
20 piperidine as a light yellow oil; MS: 365 (M)⁺.

The tert-butyl (3RS,4RS)-4-(4-fluorophenyl)-3-[1-methoxy-naphthalen-2-ylmethoxy]-piperidine-1-carboxylate used as the starting material was obtained as follows:

25

(e) In an analogous manner to that described in Example 5 (b), by reducing methyl 1-methoxy-naphthalene-2-carboxylate [J. Chem. Soc. 121,1657 (1922)] there was obtained [1-methoxy)-naphthalen-2-yl]-methanol as a colourless solid; MS: 188 (M)⁺.

30

(f) In an analogous manner to that described in Example 7 (c), by brominating [1-methoxy)-naphthalen-2-yl]-methanol there was obtained 2-bromomethyl-1-methoxy-naphthalene as a colourless solid; MS: 250, 252 (M)⁺.

35

(g) In an analogous manner to that described in Example 3 (c), by alkylating tert-butyl (3RS,4RS)-4-(4-fluorophenyl)-3-hydroxy-piperidine-1-carboxylate [Example 3 (b)] with 2-bromo-

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methyl-1-methoxy-naphthalene there was obtained tert-butyl (3RS,4RS)-4-(4-fluorophenyl)-3-[1-methoxy-naphthalen-2-yl-methoxy]-piperidine-1-carboxylate as a colourless resin; MS: 465 (M)+.

5

3) (3RS,4RS)-4-(4-Fluorophenyl)-3-(3-methoxy-naphthalen-2-yl-methoxy)-piperidine

10 In an analogous manner to that described in Example 3, by cleavage of the BOC protecting group from tert-butyl (3RS,4RS)-4-(4-fluorophenyl)-3-[3-methoxy-naphthalen-2-ylmethoxy]-piperidine-1-carboxylate there was obtained (3RS,4RS)-4-(4-fluorophenyl)-3-(3-methoxy-naphthalen-2-yl-methoxy)-piperidine as a light yellow oil; MS: 365 (M)+.

15

The tert-butyl (3RS,4RS)-4-(4-fluorophenyl)-3-[3-methoxy-naphthalen-2-ylmethoxy]-piperidine-1-carboxylate used as the starting material was obtained as follows:

20 (h) In an analogous manner to that described in Example 5 (b), by reducing methyl 3-methoxy-naphthalene-2-carboxylate [J. Chem. Soc. 2351 (1950)] there was obtained [3-methoxy)-naphthalen-2-yl]-methanol as a colourless solid; MS: 188 (M)+.

25 (i) In an analogous manner to that described in Example 7 (c), by brominating [3-methoxy)-naphthalen-2-yl]-methanol there was obtained 2-bromomethyl-3-methoxy-naphthalene as a colourless solid; MS: 250, 252 (M)+.

30 (j) In an analogous manner to that described in Example 3 (c), by alkylating tert-butyl (3RS,4RS)-4-(4-fluorophenyl)-3-hydroxy-piperidine-1-carboxylate [Example 3 (b)] with 2-bromo-methyl-3-methoxy-naphthalene there was obtained tert-butyl (3RS,4RS)-4-(4-fluorophenyl)-3-[3-methoxy-naphthalen-2-yl-methoxy]-piperidine-1-carboxylate as a colourless resin; MS: 465 (M)+.

35

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Example 8

- (a) To 1.46 g of magnesium shavings, which had previously been covered with tetrahydrofuran, was added dropwise a
5 solution of 12.06 g (60 mmol) of 5-bromo-benzo[1,3]dioxol in
30 ml of absolute tetrahydrofuran, followed by 11.35 g
(60 mmol) of 1-benzyl-4-piperidone. The reaction mixture was
stirred at 50°C for 1 hour, then poured on to ice and ammonium
chloride solution. The 4-benzo[1,3]dioxol-5-yl-1-benzyl-
10 piperidin-4-ol formed was extracted with ethyl acetate and
crystallized upon concentration of the solution. There were
obtained 10.85 g (58% of theory) of white crystals; m.p.: 144°C.
- (b) In an analogous manner to that described in Example 2(e),
15 from 4-benzo[1,3]dioxol-5-yl-1-benzyl-piperidin-4-ol by
catalytic hydrogenation at normal pressure within 4 hours there
was obtained 4-benzo[1,3]dioxol-5-yl-piperidin-4-ol as a
colourless solid in quantitative yield; MS: 221 (M)+.
- (c) In an analogous manner to that described in Example 1(b),
20 from 4-benzo[1,3]dioxol-5-yl-piperidin-4-ol by elimination there
was obtained 4-benzo[1,3]dioxol-5-yl-1,2,3,6-tetrahydro-
pyridine as a beige coloured solid; MS: 203 (M)+.
- (d) In an analogous manner to that described in Example 1(f),
25 from 4-benzo[1,3]dioxol-5-yl-1,2,3,6-tetrahydro-pyridine by
introducing the BOC group there was obtained tert-butyl
4-benzo[1,3]dioxol-5-yl-3,6-dihydro-2H-pyridine-1-carboxylate
as a colourless oil; MS: 304 (M+H)+.
- (e) In an analogous manner to that described in Example 1(c), by
hydroborating tert-butyl 4-benzo[1,3]dioxol-5-yl-3,6-dihydro-
2H-pyridine-1-carboxylate there was obtained tert-butyl
(3RS,4RS)-4-benzo[1,3]dioxol-5-yl-3-hydroxy-piperidine-1-
35 carboxylate as white crystals; m.p.: 112°C.
- (f) In an analogous manner to that described in Example 1(g), by
alkylating tert-butyl (3RS,4RS)-4-benzo[1,3]dioxol-5-yl-3-

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hydroxy-piperidine-1-carboxylate with 2-bromomethyl-naphthalene there was obtained tert-butyl (3RS,4RS)-4-benzo-[1,3]dioxol-5-yl-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as white crystals after crystallization from hexane;
5 m.p.: 128-129°C.

(g) A solution of 190 mg (0.41 mmol) of tert-butyl (3RS,4RS)-4-benzo[1,3]dioxol-5-yl-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate in a mixture of 5 ml of methanol and 25% aqueous
10 hydrochloric acid was heated under reflux for 1 hour. Subsequently, the solvent mixture was distilled off under reduced pressure. After recrystallization of the residue from a mixture of methanol and ether there were obtained 130 mg (73% of theory) of (3RS,4RS)-4-(1,3-benzodioxol-5-yl)-3-naphthalen-2-ylmethoxy-piperidine hydrochloride as a white powder; MS: 362
15 (M+H)⁺.

Example 9

20 The following compounds were obtained in an analogous manner to that described in Example 8(g) by cleavage of the BOC group using acid:

- 1) - Pyridine-3-carboxylic acid (3RS,4RS)-2-(4-phenyl-piperidin-3-yloxymethyl)-benzylamide hydrochloride as a beige
25 coloured powder, MS: 402 (M+H)⁺, from tert-butyl (3RS,4RS)-4-phenyl-3-(2-{[(pyridine-3-carbonyl)-amino]-methyl}-benzyloxy)-piperidine-1-carboxylate;
- 30 2) - (3RS,4RS)-2-(4-[1,3]benzodioxol-5-yl-piperidin-3-yloxymethyl)-benzamide hydrochloride as a white powder, MS: 355 (M+H)⁺, from tert-butyl (3RS,4RS)-4-benzo[1,3]dioxol-5-yl-3-(2-carbamoyl-benzyloxy)-piperidine-1-carboxylate.

35 The BOC derivatives used as the starting materials were prepared as follows:

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(a) In an analogous manner to that described in Example 1(g), by alkylating tert-butyl (3RS,4RS)-3-hydroxy-4-phenyl-piperidine-1-carboxylate [Example 2(a)] with 2-bromomethylbenzonitrile there was obtained tert-butyl (3RS,4RS)-3-(2-cyano-benzyloxy)-4-phenyl-piperidine-1-carboxylate as a colourless oil; MS: 393 (M+H)⁺.

(b) 528 mg (1.35 mmol) of tert-butyl (3RS,4RS)-3-(2-cyano-benzyloxy)-4-phenyl-piperidine-1-carboxylate were reduced with 0.3 ml of borane-dimethyl sulphide complex in analogy to the process described by H.C.Brown et al. in Synthesis 1981, 605. There were obtained 480 mg (90% of theory) of tert-butyl (3RS,4RS)-3-(2-aminomethyl-benzyloxy)-4-phenyl-piperidine-1-carboxylate as a colourless solid; 397 (M+H)⁺.

(c) A solution of 150 mg (0.38 mmol) of tert-butyl (3RS,4RS)-3-(2-aminomethyl-benzyloxy)-4-phenyl-piperidine-1-carboxylate in 2 ml of methylene chloride was treated with 229 mg (2.26 mmol) of triethylamine, 139 mg (1.05 mmol) of nicotinic acid, 216 mg (1.13 mmol) of EDC and 10 mg (0.08 mmol) of 4-dimethylaminopyridine and the mixture was stirred at room temperature for 24 hours. Thereafter, the reaction solution was diluted with methylene chloride and washed with a saturated sodium hydrogen carbonate solution. The organic phase was separated, dried over sodium sulphate and evaporated under reduced pressure. The residue was chromatographed on silica gel using ethyl acetate as the eluent. There were obtained 100 mg (53% of theory) of tert-butyl (3RS,4RS)-4-phenyl-3-(2-[(pyridine-3-carbonyl)-amino]-methyl)-benzyloxy)-piperidine-1-carboxylate as a colourless solid; MS: 502 (M+H)⁺.

(d) In an analogous manner to that described in Example 1(g), by alkylating tert-butyl (3RS,4RS)-4-benzo[1,3]dioxol-5-yl-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate [Example 8(f)] with 2-bromomethyl-benzonitrile there was obtained tert-butyl (3RS,4RS)-4-benzo[1,3]dioxol-5-yl-3-(2-cyano-benzyloxy)-piperidine-1-carboxylate as colourless crystals; MS: 455 (M+H)⁺.

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(e) 0.5 ml of hydrogen peroxide (33%) and 0.2 ml of 2N sodium hydroxide solution were added to a solution of 236 mg (0.54 mmol) of tert-butyl (3RS,4RS)-4-benzo[1,3]dioxol-5-yl-3-(2-cyano-benzyloxy)-piperidine-1-carboxylate in 5 ml of methanol. The reaction solution was heated under reflux for 2 hours. Subsequently, the same amounts of hydrogen peroxide and sodium hydroxide solution were again added and the solution was heated for a further 2 hours. Thereafter, the solution was cooled and evaporated under reduced pressure. For purification, the residue was chromatographed on silica gel using a 9:1 mixture of methylene chloride and ether as the eluent. There were obtained 140 mg (57% of theory) of tert-butyl (3RS,4RS)-4-benzo[1,3]dioxol-5-yl-3-(2-carbamoyl-benzyloxy)-piperidine-1-carboxylate as a colourless solid; MS: 455 (M+H)⁺.

Example 10

(a) In an analogous manner to that described in Example 1(g), by alkylating tert-butyl (3RS,4RS)-4-(4-fluorophenyl)-3-hydroxy-piperidine-1-carboxylate with 6-chloromethyl-2,3-dihydro-benzo[1,4]dioxin [Brit. Pat. 566732 (1943)] there was obtained tert-butyl (3RS,4RS)-3-(2,3-dihydro-benzo[1,4]dioxin-6-ylmethoxy)-4-(4-fluorophenyl)-piperidine-1-carboxylate as a colourless solid; MS: 444 (M+H)⁺;

(b) A solution of 280 mg (0.63 mmol) of tert-butyl (3RS,4RS)-3-(2,3-dihydro-benzo[1,4]dioxin-6-ylmethoxy)-4-(4-fluorophenyl)-piperidine-1-carboxylate in 5 ml of dry methylene chloride was treated with 808 mg (1.89 mmol) of anhydrous zinc bromide and the mixture was stirred at room temperature for 5 hours. Subsequently, the solvent was distilled off under reduced pressure, the residue was taken up in 10 ml of methanol, treated with 2 ml of 2N sodium hydroxide solution and the solid was separated. The filtrate was evaporated under reduced pressure and the residue was partitioned between methylene chloride and water. The organic phase was separated and evaporated under reduced pressure. There were obtained 220 mg

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(98% of theory) of (3RS,4RS)-3-(2,3-dihydrobenzo[1,4]dioxin-6-yl-methoxy)-4-(4-fluorophenyl)-piperidine as a yellowish solid; MS: 344 (M+H)⁺.

5

Example 11

In an analogous manner to that described in Example 10(b), from tert-butyl (3RS,4RS)-3-(benzo[b]furan-5-ylmethoxy)-4-(4-fluoro-phenyl)-piperidine-1-carboxylate there was obtained
10 (3RS,4RS)-3-(benzo[b]furan-5-ylmethoxy)-4-(4-fluorophenyl)-piperidine as a colourless solid; MS: 326 (M+1)⁺;

The tert-butyl (3RS,4RS)-3-(benzo[b]furan-5-ylmethoxy)-4-(4-fluoro-phenyl)-piperidine-1-carboxylate used as the
15 starting material was obtained as a colourless solid, MS: 426 (M+H)⁺, analogously to the procedure described in Example 1(g) by alkylating tert-butyl (3RS,4RS)-4-(4-fluorophenyl)-3-hydroxy-piperidine-1-carboxylate.

20 The 5-bromomethyl-benzo[b]furan used as the alkylating agent was prepared as follows:

By brominating 5-methyl-benzo[b]furan [Synth. Commun. 19, 257(1989)] with N-bromosuccinimide in carbon tetrachloride in
25 an analogous manner to the procedure for the preparation of 5-bromomethyl-benzo[b]thiophene [J. Med. Chem. 34(1), 65(1991)] from 5-methyl-benzo[b]thiophene there was obtained 5-bromo-methyl-benzo[b]furan as a light yellow solid; MS: 210, 212 (M)⁺.

30

Example 12

(a) In an analogous manner to that described in Example 1(c), from 4-(4-chloro-phenyl)-1-methyl-1,2,3,6-tetrahydropyridine [US Pat. 3 320 265] by hydroboration using borane in tetra-
35 hydrofuran there was obtained (3RS,4RS)-4-(4-chloro-phenyl)-1-methyl-piperidin-3-ol which, after recrystallization from a mixture of methylene chloride and hexane, formed colourless crystals of m.p.: 99-100°C.

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(b) A solution of 1.12 g (5 mmol) of (3RS,4RS)-4-(4-chloro-phenyl)-1-methyl-piperidine-3-ol in 5 ml of tetrahydrofuran was added dropwise to a suspension of 0.264 g (5 mmol) of sodium hydride (50% dispersion in refined oil) in 8 ml of tetrahydrofuran and the mixture was stirred at 50°C for 60 minutes. Subsequently, it was cooled to room temperature and treated with 1.10 g (5 mmol) of 2-bromomethyl-naphthalene in 5 ml of tetrahydrofuran. After 2 hours at 50°C the reaction solution was poured into 60 ml of ice-water and extracted three times with 25 ml of ethyl acetate each time. The organic phases were washed with saturated sodium chloride solution, dried over magnesium sulphate, filtered and evaporated. The residue was chromatographed on silica gel using a 95:5 mixture of methylene chloride and ethanol as the eluent. There was obtained 0.53 g (28% of theory) of (3RS,4RS)-4-(4-chloro-phenyl)-1-methyl-3-(naphthalen-2-ylmethoxy)-piperidine as a pale yellow oil; MS: 366 (M)⁺.

(c) A solution of 0.526 g (1.43 mmol) of (3RS,4RS)-4-(4-chloro-phenyl)-1-methyl-3-(naphthalen-2-ylmethoxy)-piperidine in 12 ml of toluene was treated with 100 mg of potassium carbonate and heated to 100°. Subsequently, 0.423 g (0.288 ml, 2 mmol) of 2,2,2-trichloroethyl chloroformate was added thereto and the mixture was stirred at 100° for 12 hours. The reaction solution was evaporated, taken up in 50 ml of ethyl acetate and washed with 20 ml of water and 20 ml of saturated sodium hydrogen carbonate solution. Drying over magnesium sulphate, filtration (sic) and evaporation yielded a colourless oil which was chromatographed on silica gel using a 3:2 mixture of hexane and ethyl acetate as the eluent. There was obtained 0.426 g (57% of theory) of 2,2,2-trichloroethyl 4-(4-chloro-phenyl)-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a colourless oil; R_f: 0.31 (silica gel, hexane/ethyl acetate: 3/2).

35

(d) A suspension of 0.420 g (0.8 mmol) of 2,2,2-trichloroethyl 4-(4-chloro-phenyl)-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate and 300 mg of zinc in 10 ml of acetic acid was

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stirred at room temperature for 12 hours. The reaction solution was diluted with 40 ml of water and extracted four times with 30 ml of methylene chloride. The organic phase was washed twice with 40 ml of 1N sodium hydroxide solution each time,
5 dried over sodium sulphate, filtered and evaporated. The residue was chromatographed on silica gel using a 9:1 mixture of methylene chloride and methanol as the eluent. There was obtained 0.210 g (74% of theory) of (3RS,4RS)-4-(4-chloro-phenyl)-3-(naphthalen-2-ylmethoxy)-piperidine, MS: 210 (M - C₁₁H₉)⁺,
10 which was converted into the hydrochloride of m.p. 159-161°C (dec.) with a solution of hydrogen chloride in methanol.

Example 13

15 The following compounds were prepared in an analogous manner to that described in Example 12(b)-(d) by alkylation and subsequent cleavage of the N-methyl group:

1) - from (3RS,4RS)-4-(4-chloro-phenyl)-1-methyl-piperidin-3-ol and 1-bromomethylnaphthalene, (3RS,4RS)-4-(4-chloro-phenyl)-3-(naphthalene-1-ylmethoxy)-piperidine, MS: 210 (M-C₁₁H₉)⁺, which was converted with a solution of hydrogen chloride in ethanol into the hydrochloride of m.p. 210-213°C (dec.).

25 2) - from (3RS,4RS)-4-(4-chloro-phenyl)-1-methyl-piperidin-3-ol and 1-bromomethyl-4-tert-butylbenzene, (3RS,4RS)-3-(4-tert.butyl-benzyloxy)-4-(4-chloro-phenyl)-piperidine, MS: 358 (M)⁺, which was converted with a solution of hydrogen chloride in
30 ethanol into the hydrochloride of m.p. 164-166°C (dec.).

3) - from (3RS,4RS)-4-(4-chloro-phenyl)-1-methyl-piperidin-3-ol and 5-chloromethyl-benzo[1.3]dioxol, (3RS,4RS)-3-(benzo[1.3]dioxol-5-yl-methoxy)-4-(4-chloro-phenyl)-piperidine,
35 MS: 210 (M-C₈H₇O₂)⁺, which was converted with methanesulphonic acid in a mixture of dioxan and water and subsequent lyophilization into the corresponding methanesulphonate; R_f: 0.45 (silica gel, methylene chloride/methanol: 9/1).

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- 4) - from (3RS,4RS)-4-(4-chloro-phenyl)-1-methyl-piperidin-3-ol and 1,2-dichloro-4-chloromethylbenzene, (3RS,4RS)-4-(4-chloro-phenyl)-3-(3,4-dichlorobenzyloxy)-piperidine, MS: 370 (M)⁺, which was converted with a solution of hydrogen chloride in ethanol into the hydrochloride of m.p. 156-158°C (dec.).
- 5) - from (3RS,4RS)-4-(4-chloro-phenyl)-1-methyl-piperidin-3-ol and 2,4-dichloro-1-chloromethylbenzene, (3RS,4RS)-4-(4-chloro-phenyl)-3-(2,4-dichloro-benzyloxy)-piperidine of m.p. 83-84°C; MS: 370 (M)⁺.
- 6) - from (3RS,4RS)-4-(4-chloro-phenyl)-1-methyl-piperidin-3-ol and 1-chloro-4-chloromethylbenzene, (3RS,4RS)-3-(4-chlorobenzyloxy)-4-(4-chloro-phenyl)-piperidine, MS: 210 (M-C₇H₆Cl)⁺, which was converted with a solution of hydrogen chloride in ethanol into the hydrochloride of m.p. 128-130°C (dec.).
- 7) - from (3RS,4RS)-4-(4-chloro-phenyl)-1-methyl-piperidin-3-ol and 1-chloromethyl-3-methoxy-benzene, (3RS,4RS)-4-(4-chloro-phenyl)-3-(2-methoxy-benzyloxy)-piperidine, MS: 332 (M)⁺, which was converted with a solution of hydrogen chloride in ethanol into the hydrochloride of m.p. 116-118°C (dec.).
- 8) - from (3RS,4RS)-4-(4-chloro-phenyl)-1-methyl-piperidin-3-ol and 1-chloro-2-chloromethyl-benzene, (3RS,4RS)-3-(2-chlorobenzyloxy)-4-(4-chloro-phenyl)-piperidine, MS: 210 (M-C₇H₆Cl)⁺, which was converted with a solution of hydrogen chloride in ethanol into the hydrochloride of m.p. 145-147°C (dec.).
- 9) - from (3RS,4RS)-4-(4-chloro-phenyl)-1-methyl-piperidin-3-ol and 4-chloromethyl-biphenyl, (3RS,4RS)-3-(biphenyl-4-ylmethoxy)-4-(4-chloro-phenyl)-piperidine, MS: 210 (M-C₁₃H₁₁)⁺, which was converted with a solution of hydrogen chloride in ethanol into the hydrochloride of m.p. 177-180°C (dec.).

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- 10) - from (3RS,4RS)-4-(4-chloro-phenyl)-1-methyl-piperidin-3-ol and 2-chloromethyl-quinoline, (3RS,4RS)-2-[4-(4-chloro-phenyl)-piperidin-3-yloxy-methyl]quinoline, MS: 353 (M)⁺ of m.p. 109-110°C.
- 5 11) - from (3RS,4RS)-4-(4-chloro-phenyl)-1-methyl-piperidin-3-ol and 3-chloromethyl-benzofuran [J.Am. Chem. Soc. 73, 4400 (1951)], (3RS,4RS)-3-(benzofuran-2-ylmethoxy)-4-(4-chloro-phenyl)-piperidine, MS: 341 (M)⁺, which was converted with a
10 solution of hydrogen chloride in ethanol into the hydrochloride of m.p. 144-146°C (dec.).
- 12) - from (3RS,4RS)-4-(4-chloro-phenyl)-1-methyl-piperidin-3-ol and 2-chloromethyl-benzo[b]thiophene [J. Am.Chem. Soc. 71,
15 2856 (1949)], (3RS,4RS)-3-(benzo[b]thiophen-2-ylmethoxy)-4-(4-chloro-phenyl)-piperidine, MS: 210 (M-C₈H₇S)⁺, which was converted with a solution of hydrogen chloride in ethanol into the hydrochloride of m.p. 141-144°C (dec.).
- 20 13) - from (3RS,4RS)-4-(4-chloro-phenyl)-1-methyl-piperidin-3-ol and methyl 4'-bromomethyl-biphenyl-2-carboxylate [J. Med. Chem. 34, 2525 (1991)], methyl (3RS,4RS)-4'-[4-(4-chloro-phenyl)piperidin-3-yloxy-methyl]-biphenyl-2-carboxylate,
25 MS: 436 (M)⁺, which was converted with hydrochloric acid in ethanol into the hydrochloride of m.p. 95-99°C (dec.).
- 14) - from (3RS,4RS)-4-(4-chloro-phenyl)-1-methyl-piperidin-3-ol and 3-chloromethyl-pyridine [J. Am. Chem. Soc. 77, 1054 (1955)], (3RS,4RS)-3-[4-(4-chloro-phenyl-piperidin-3-yloxy-methyl)-pyridine, MS: 303 (M)⁺, which was converted with a
30 solution of hydrogen chloride in ethanol into the hydrochloride of m.p. 78-81°C (dec.).
- 15) - from (3RS,4RS)-4-(4-chloro-phenyl)-1-methyl-piperidin-3-ol and 6-chloromethyl-1,1,4,4,-tetramethyl-1,2,3,4-tetra-
35 hydronaphthalene, (3RS,4RS)-4-(4-chloro-phenyl)-3-(5,5,8,8,-tetramethyl-5,6,7,8-tetrahydronaphthalene-2-ylmethoxy)-piperidine, MS: 412 (M)⁺, which was converted with a solution of

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hydrogen chloride in ethanol into the hydrochloride of m.p. 118-121°C (dec.).

- 16) - from (3RS,4RS)-4-(3-chloro-phenyl)-1-methyl-piperidin-3-ol [US Pat. 4 132 710 (1976)] and 4-methoxybenzyl chloride, (3RS,4RS)-3-(4-methoxy-benzyloxy)-4-(3-chloro-phenyl)-piperidine; MS: 332 (M)+.

Example 14

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The following compounds were prepared in analogy to the procedure described in Example 1 (e) by cleavage of the 2-trimethylsilyl-ethoxycarbonyl group with tetrabutylammonium fluoride in tetrahydrofuran:

15

- 1) - (3RS,4RS)-4-(4-fluorophenyl)-3-(4-methoxy-naphthalen-2-ylmethoxy)-piperidine as a colourless solid, MS: 365 (M)+, from β -trimethyl-silylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-(4-methoxy-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate;

20

- 2) - (3RS,4RS)-4-(4-fluorophenyl)-3-(5-methoxy-naphthalen-2-ylmethoxy)-piperidine as a colourless solid, MS: 365 (M)+, from β -trimethyl-silylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-(5-methoxy-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate;

25

- 3) - (3RS,4RS)-4-(4-fluorophenyl)-3-(6-methoxy-naphthalen-2-ylmethoxy)-piperidine as a colourless solid, MS: 365 (M)+, from β -trimethyl-silylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-(6-methoxy-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate;

30

- 4) - (3RS,4RS)-4-(4-fluorophenyl)-3-(7-methoxy-naphthalen-2-ylmethoxy)-piperidine as a colourless solid, MS: 365 (M)+, from β -trimethyl-silylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-(7-methoxy-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate;

35

- 5) - (3RS,4RS)-4-(4-fluorophenyl)-3-(8-methoxy-naphthalen-2-ylmethoxy)-piperidine as a colourless resin, MS: 366 (M+H)+,

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from β -trimethyl-silylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-(8-methoxy-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate;

6) - (3RS,4RS)-4-(4-fluorophenyl)-3-[4-(pyridin-2-yl-methoxy)-naphthalen-2-ylmethoxy]-piperidine as a colourless solid, MS: 442 (M)⁺, from β -trimethyl-silylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-[4-(pyridin-2-ylmethoxy)-naphthalen-2-yl-methoxy]-piperidine-1-carboxylate;

7) - (3RS,4RS)-4-(4-fluorophenyl)-3-[4-(pyridin-3-yl-methoxy)-naphthalen-2-ylmethoxy]-piperidine as a colourless solid, MS: 443 (M+H)⁺, from β -trimethyl-silylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-[4-(pyridin-3-ylmethoxy)-naphthalen-2-yl-methoxy]-piperidine-1-carboxylate;

8) - (3RS,4RS)-4-(4-fluorophenyl)-3-[4-(pyridin-4-yl-methoxy)-naphthalen-2-ylmethoxy]-piperidine as a colourless solid, MS: 442 (M)⁺, from β -trimethyl-silylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-[4-(pyridin-4-ylmethoxy)-naphthalen-2-yl-methoxy]-piperidine-1-carboxylate;

9) - (3RS,4RS)-3-(4-allyloxy-naphthalen-2-ylmethoxy)-4-(4-fluorophenyl)-piperidine as a colourless solid, MS: 391 (M)⁺, from β -trimethyl-silylethyl (3RS,4RS)-3-(4-allyloxy-naphthalen-2-ylmethoxy)-4-(4-fluorophenyl)-piperidine-1-carboxylate;

10) - (3RS,4RS)-3-(6-allyloxy-naphthalen-2-ylmethoxy)-4-(4-fluorophenyl)-piperidine as a colourless solid, MS: 391 (M)⁺, from β -trimethyl-silylethyl (3RS,4RS)-3-(6-allyloxy-naphthalen-2-ylmethoxy)-4-(4-fluorophenyl)-piperidine-1-carboxylate;

11) - (3RS,4RS)-4-(4-fluorophenyl)-3-(4-isobutyloxy-naphthalen-2-ylmethoxy)-piperidine as a colourless solid, MS: 407 (M)⁺, from β -trimethyl-silylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-(4-isobutoxy-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate;

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- 12) - (3RS,4RS)-3-(1-benzyloxy-naphthalen-2-ylmethoxy)-4-(4-fluorophenyl)-piperidine as a light yellow oil, MS: 441 (M)⁺, from β -trimethyl-silylethyl (3RS,4RS)-3-(1-benzyloxy-naphthalen-2-ylmethoxy)-4-(4-fluorophenyl)-piperidine-1-carboxylate;
5
- 13) - (3RS,4RS)-3-(4-benzyloxy-naphthalen-2-ylmethoxy)-4-(4-fluorophenyl)-piperidine as a colourless solid, MS: 441 (M)⁺, from β -trimethyl-silylethyl (3RS,4RS)-3-(4-benzyloxy-naphthalen-2-ylmethoxy)-4-(4-fluorophenyl)-piperidine-1-carboxylate;
10
- 14) - (3RS,4RS)-3-(5-benzyloxy-naphthalen-2-ylmethoxy)-4-(4-fluorophenyl)-piperidine as a light yellow oil, MS: 442 (M+H)⁺, from β -trimethyl-silylethyl (3RS,4RS)-3-(5-benzyloxy-naphthalen-2-ylmethoxy)-4-(4-fluorophenyl)-piperidine-1-carboxylate;
15
- 15) - (3RS,4RS)-3-(7-benzyloxy-naphthalen-2-ylmethoxy)-4-(4-fluorophenyl)-piperidine as a colourless solid, MS: 441 (M)⁺, from β -trimethyl-silylethyl (3RS,4RS)-3-(7-benzyloxy-naphthalen-2-ylmethoxy)-4-(4-fluorophenyl)-piperidine-1-carboxylate;
20
- 16) - (3RS,4RS)-3-(8-benzyloxy-naphthalen-2-ylmethoxy)-4-(4-fluorophenyl)-piperidine as a light yellow resin, MS: 442 (M+H)⁺, from β -trimethyl-silylethyl (3RS,4RS)-3-(8-benzyloxy-naphthalen-2-ylmethoxy)-4-(4-fluorophenyl)-piperidine-1-carboxylate;
25
- 17) - (3RS,4RS)-4-(4-fluorophenyl)-3-[4-(2-methoxy-ethoxy)-naphthalen-2-ylmethoxy]-piperidine as a colourless solid, MS: 410 (M+H)⁺, from β -trimethyl-silylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-[4-(2-methoxy-ethoxy)-naphthalen-2-ylmethoxy]-piperidine-1-carboxylate;
30
35
- 18) - 4-(4-fluorophenyl)-3-[4-(3-methoxy-propoxy)-naphthalen-2-ylmethoxy]-piperidine as a light yellow solid,

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MS: 424 (M+H)⁺, from β -trimethyl-silylethyl 4-(4-fluorophenyl)-3-[4-(3-methoxy-propoxy)-naphthalen-2-ylmethoxy]-piperidine-1-carboxylate;

5 19) - (3RS,4RS) 3-(4-butoxy-naphthalen-2-ylmethoxy)-4-(4-fluorophenyl)-piperidine as a colourless solid, MS: 408 (M+H)⁺, from β -trimethyl-silylethyl (3RS,4RS) 3-(4-butoxy-naphthalen-2-ylmethoxy)-4-(4-fluorophenyl)-piperidine-1-carboxylate;

10 20) - (3RS,4RS)-4-(4-fluorophenyl)-3-(4-(2-methoxy-benzyl-oxy)-naphthalen-2-ylmethoxy)-piperidine as a colourless resin, MS: 472 (M+H)⁺, from β -trimethyl-silylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-(4-(2-methoxy-benzyloxy)-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate;

15 21) - (3RS,4RS)-4-(4-fluorophenyl)-3-(4-(3-methoxy-benzyl-oxy)-naphthalen-2-ylmethoxy)-piperidine as a colourless solid, MS: 471 (M)⁺, from β -trimethyl-silylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-(4-(3-methoxy-benzyloxy)-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate;

20 22) - (3RS,4RS)-4-(4-fluorophenyl)-3-(4-(2-methoxy-benzyl-oxy)-naphthalen-2-ylmethoxy)-piperidine as a colourless oil, MS: 471 (M)⁺, from β -trimethyl-silylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-(4-methoxy-benzyloxy)-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate;

23) - (3RS,4RS)-4-(4-fluorophenyl)-3-(1-phenethyloxy-naphthalen-2-ylmethoxy)-piperidine as a light yellow oil, MS: 456 (M+H)⁺, from β -trimethyl-silylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-(1-phenethyloxy-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate;

30 24) - (3RS,4RS)-4-(4-fluorophenyl)-3-(4-phenethyloxy-naphthalen-2-ylmethoxy)-piperidine as a colourless solid, MS: 456 (M+H)⁺, from β -trimethyl-silylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-(4-phenethyloxy-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate;

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- 25) - (3RS,4RS)-3-[4-(2-[1,3]dioxolan-2-yl-ethoxy)-naphthalen-2-ylmethoxy]-4-(4-fluorophenyl)-piperidine as a light yellow oil, MS: 451 (M)⁺, from β -trimethyl-silylethyl (3RS,4RS)-
5 3-[4-(2-[1,3]dioxolan-2-yl-ethoxy)-naphthalen-2-ylmethoxy]-4-(4-fluorophenyl)-piperidine-1-carboxylate;
- 26) - (3RS,4RS)-3-[1-(2-[1,3]dioxolan-2-yl-ethoxy)-naphthalen-2-ylmethoxy]-4-(4-fluorophenyl)-piperidine as a light
10 yellow oil, MS: 452 (M+H)⁺, from β -trimethyl-silylethyl (3RS,4RS)-3-[1-(2-[1,3]dioxolan-2-yl-ethoxy)-naphthalen-2-ylmethoxy]-4-(4-fluorophenyl)-piperidine-1-carboxylate;
- 27) - (3RS,4RS)-3-[4-(benzo[1,3]dioxol-5-ylmethoxy)-naphthalen-2-ylmethoxy]-4-(4-fluorophenyl)-piperidine as a colourless
15 resin, MS: 485 (M)⁺, from β -trimethyl-silylethyl (3RS,4RS)-3-[4-(benzo[1,3]dioxol-5-ylmethoxy)-naphthalen-2-ylmethoxy]-4-(4-fluorophenyl)-piperidine-1-carboxylate;
- 28) - (3RS,4RS)-3-[4-(2-cyclopropyl-ethoxy)-naphthalen-2-ylmethoxy]-4-(4-fluorophenyl)-piperidine as a colourless solid,
20 MS: 419 (M)⁺, from β -trimethyl-silylethyl (3RS,4RS)-3-[4-(2-cyclopropyl-ethoxy)-naphthalen-2-ylmethoxy]-4-(4-fluorophenyl)-piperidine-1-carboxylate;
- 29) - (3RS,4RS)-4-(4-fluorophenyl)-3-[4-(2-hydroxy-ethoxy)-naphthalen-2-ylmethoxy]-piperidine as a colourless solid,
25 MS: 395 (M)⁺, from β -trimethyl-silylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-[4-(2-hydroxy-ethoxy)-naphthalen-2-ylmethoxy]-piperidine-1-carboxylate;
30

The compounds used as starting materials were prepared as follows:

- 35 (a) 99 mg (0.20 mmol) of β -trimethyl-silylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-(4-hydroxy-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate were dissolved in 1 ml of dimethylformamide, treated with 69 mg (0.50 mmol) of anhydrous

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potassium carbonate and 19 μ l (43 mg, 0.30 mmol) of methyl iodide and stirred at room temperature for 4 hours. Subsequently, the mixture was partitioned between methylene chloride and water, the organic phase was dried over magnesium sulphate and finally the solvent was distilled off under reduced pressure. For purification, the crude product was chromatographed on silica gel with a 4:1 mixture of hexane and methylene chloride as the eluent. There were obtained 85 mg (83% of theory) of β -trimethyl-silylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-(4-methoxy-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a light yellow oil; MS: 509 (M)+.

The following compounds were prepared in an analogous manner to the previously described procedure:

- 15 - from β -trimethylsilylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-(5-hydroxy-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate and methyl iodide, β -trimethylsilylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-(5-methoxy-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate, which was used in crude form in the next step;
- from β -trimethylsilylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-(6-hydroxy-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate and methyl iodide, β -trimethylsilylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-(6-methoxy-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a light yellow oil; MS: 509 (M)+;
- 25 - from β -trimethylsilylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-(7-hydroxy-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate and methyl iodide, β -trimethylsilylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-(7-methoxy-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate, which was used in crude form in the next step;
- 30 - from β -trimethylsilylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-(8-hydroxy-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate and methyl iodide, β -trimethylsilylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-(8-methoxy-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate, which was used in crude form in the next step;

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- 5 - from β -trimethylsilylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-(4-hydroxy-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate and 2-pyridylmethyl chloride, β -trimethylsilylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-[4-(pyridin-2-ylmethoxy)-naphthalen-2-ylmethoxy]-piperidine-1-carboxylate as a light yellow oil; MS: 587 (M+H)⁺;
- 10 - from β -trimethylsilylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-(4-hydroxy-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate and 3-pyridylmethyl chloride, β -trimethylsilylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-[4-(pyridin-3-ylmethoxy)-naphthalen-2-ylmethoxy]-piperidine-1-carboxylate, which was used in crude form in the next step;
- 15 - from β -trimethylsilylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-(4-hydroxy-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate and 4-pyridylmethyl chloride, β -trimethylsilylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-[4-(pyridin-4-ylmethoxy)-naphthalen-2-ylmethoxy]-piperidine-1-carboxylate as a light yellow oil; MS: 587 (M+H)⁺;
- 20 - from β -trimethylsilylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-(4-hydroxy-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate and allyl bromide, β -trimethylsilylethyl (3RS,4RS)-3-(4-allyloxy-naphthalen-2-ylmethoxy)-4-(4-fluorophenyl)-piperidine-1-carboxylate, which was used in crude form in the next step;
- 25 - from β -trimethylsilylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-(6-hydroxy-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate and allyl bromide, β -trimethylsilylethyl (3RS,4RS)-3-(6-allyloxy-naphthalen-2-ylmethoxy)-4-(4-fluorophenyl)-piperidine-1-carboxylate, which was used in crude form in the next step;
- 30 - from β -trimethylsilylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-(4-hydroxy-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate and iso-butyl bromide, β -trimethylsilylethyl (3RS,4RS)-4-(4-fluoro-

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phenyl)-3-(4-isobutoxy-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate, which was used in crude form in the next step;

5 - from β -trimethylsilylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-(1-hydroxy-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate and benzyl bromide, β -trimethylsilylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-(1-benzyloxy-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate, which was used in crude form in the next step;

10 - from β -trimethylsilylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-(4-hydroxy-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate and benzyl bromide, β -trimethylsilylethyl (3RS,4RS)-3-(4-benzyloxy-naphthalen-2-ylmethoxy)-4-(4-fluorophenyl)-piperidine-1-carboxylate as a light yellow oil; MS: 586 (M+H)⁺;

15 - from β -trimethylsilylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-(7-hydroxy-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate and benzyl bromide, β -trimethylsilylethyl (3RS,4RS)-3-(7-benzyloxy-naphthalen-2-ylmethoxy)-4-(4-fluorophenyl)-piperidine-1-carboxylate as a light yellow oil; MS: 585 (M)⁺;

20 - from β -trimethylsilylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-(5-hydroxy-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate and benzyl bromide, 2-trimethylsilanyl-ethyl (3RS,4RS)-3-(5-benzyloxy-naphthalen-2-ylmethoxy)-4-(4-fluorophenyl)-piperidine-1-carboxylate as a colourless oil; MS: 585 (M)⁺;

25 - from β -trimethylsilylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-(8-hydroxy-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate and benzyl bromide, β -trimethylsilylethyl (3RS,4RS)-3-(8-benzyloxy-naphthalen-2-ylmethoxy)-4-(4-fluorophenyl)-piperidine-1-carboxylate, which was used in crude form in the next step;

30 - from β -trimethylsilylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-(4-hydroxy-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate and 2-methoxyethyl bromide, 2-trimethylsilanyl-ethyl (3RS,4RS)-4-(4-fluorophenyl)-3-[4-(2-methoxy-ethoxy)-

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naphthalen-2-ylmethoxy]-piperidine-1-carboxylate, which was used in crude form in the next step;

5 - from β -trimethylsilylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-(4-hydroxy-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate and 3-methoxypropyl chloride [J. Org. Chem. 16, 704(1951)], 2-trimethylsilanyl-ethyl (3RS,4RS)-4-(4-fluoro-phenyl)-3-[4-(3-methoxy-propoxy)-naphthalen-2-ylmethoxy]-piperidine-1-carboxylate, which was used in crude form in the next step;

10

- from β -trimethylsilylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-(4-hydroxy-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate and butyl bromide, 2-trimethylsilanyl-ethyl (3RS,4RS)-3-(4-butyl-naphthalen-2-ylmethoxy)-4-(4-fluoro-phenyl)-piperidine-1-carboxylate, which was used in crude form in the next step;

15

- from β -trimethylsilylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-(4-hydroxy-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate and 2-methoxybenzyl chloride, 2-trimethylsilanyl-ethyl (3RS,4RS)-4-(4-fluoro-phenyl)-3-[4-(2-methoxy-benzyloxy)-naphthalen-2-ylmethoxy]-piperidine-1-carboxylate, which was used in crude form in the next step;

20

- from β -trimethylsilylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-(4-hydroxy-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate and 3-methoxybenzyl chloride, 2-trimethylsilanyl-ethyl (3RS,4RS)-4-(4-fluoro-phenyl)-3-[4-(3-methoxy-benzyloxy)-naphthalen-2-ylmethoxy]-piperidine-1-carboxylate as a light yellow oil; MS: 615 (M)+;

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- from β -trimethylsilylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-(4-hydroxy-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate and 4-methoxybenzyl chloride, 2-trimethylsilanyl-ethyl (3RS,4RS)-4-(4-fluoro-phenyl)-3-[4-(4-methoxy-benzyloxy)-naphthalen-2-ylmethoxy]-piperidine-1-carboxylate as a light yellow oil; MS: 616 (M+H)+;

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- from β -trimethylsilylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-(4-hydroxy-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate and phenethyl bromide, β -trimethylsilylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-(4-phenethyloxy-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate, which was used in crude form in the next step;
- from β -trimethylsilylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-(1-hydroxy-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate and phenethyl bromide, 2-trimethylsilanyl-ethyl (3RS,4RS)-4-(4-fluoro-phenyl)-3-(1-phenethyloxy-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a light yellow oil; MS: 600 (M+H)+;
- from β -trimethylsilylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-(4-hydroxy-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate and 2-(2-bromoethyl)-1,3-dioxolan, 2-trimethylsilanyl-ethyl (3RS,4RS)-3-[4-(2-[1,3]dioxolan-2-yl-ethoxy)-naphthalen-2-ylmethoxy]-4-(4-fluoro-phenyl)-piperidine-1-carboxylate, which was used in crude form in the next step;
- from β -trimethylsilylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-(1-hydroxy-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate and 2-(2-bromoethyl)-1,3-dioxolan, β -trimethylsilylethyl (3RS,4RS)-3-[1-(2-[1,3]dioxolan-2-yl-ethoxy)-naphthalen-2-ylmethoxy]-4-(4-fluorophenyl)-piperidine-1-carboxylate, which was used in crude form in the next step;
- from β -trimethylsilylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-(4-hydroxy-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate and 3,4-methylenedioxybenzyl chloride, β -trimethyl-silylethyl (3RS,4RS)-3-[4-(benzo[1,3]dioxol-5-ylmethoxy)-naphthalen-2-ylmethoxy]-4-(4-fluorophenyl)-piperidine-1-carboxylate, which was used in crude form in the next step;
- from β -trimethylsilylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-(4-hydroxy-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate and 2-cyclopropyl-ethyl chloride [Justus Liebigs Ann. Chem. 759, 132 (1972)], β -trimethylsilylethyl (3RS,4RS)-3-[4-(2-cyclopropyl-

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ethoxy)-naphthalen-2-ylmethoxy]-4-(4-fluorophenyl)-piperidine-1-carboxylate as a light pink coloured oil; MS: 564 (M+H)⁺;

- from β -trimethylsilylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-(4-hydroxy-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate and 2-(2-bromoethoxy)-tetrahydropyran, a mixture of β -trimethylsilylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-{4-[2-[(RS)- and (SR)-tetrahydro-pyran-2-yloxy]-ethoxy]-naphthalen-2-ylmethoxy}-piperidine-1-carboxylate as a colourless oil; MS: 624 (M+H)⁺.

Subsequent cleavage of the THP protecting group with a 1M solution of hydrogen chloride in methanol (10 minutes, room temperature) yielded β -trimethyl-silylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-[4-(2-hydroxy-ethoxy)-naphthalen-2-ylmethoxy]-piperidine-1-carboxylate as a colourless solid; MS: 540 (M+H)⁺.

Example 15

(a) A solution of 63 mg (0.116 mmol) of β -trimethyl-silylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-[4-(2-hydroxy-ethoxy)-naphthalen-2-ylmethoxy]-piperidine-1-carboxylate in 2 ml of methylene chloride was treated with 38 mg (0.58 mmol) of sodium cyanate. 44 μ l (67 mg, 0.58 mmol) of trifluoroacetic acid were added to this suspension at 0°C and the reaction mixture was stirred at room temperature for 2 hours. Subsequently, the mixture was partitioned between methylene chloride and a 5% sodium hydrogen carbonate solution, the organic phase was dried over magnesium sulphate and finally the solvent was distilled off under reduced pressure. The crude β -trimethyl-silylethyl (3RS,4RS)-3-[4-(2-carbamoyloxy-ethoxy)-naphthalen-2-ylmethoxy]-4-(4-fluorophenyl)-piperidine-1-carboxylate obtained was used in the following step without further purification and characterization.

(b) From the crude β -trimethyl-silylethyl (3RS,4RS)-3-[4-(2-carbamoyloxy-ethoxy)-naphthalen-2-ylmethoxy]-4-(4-fluoro-

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phenyl)-piperidine-1-carboxylate there was obtained by cleavage of the protecting group with tetrabutylammonium fluoride in tetrahydrofuran in analogy to the procedure described in Example 1(e) (3RS,4RS)-3-[4-(2-carbamoyloxy-ethoxy)-naphthalen-2-ylmethoxy]-4-(4-fluorophenyl)-piperidine as a light yellow oil; MS: 438 (M)+.

Example 16

The following compounds were obtained in an analogous manner to that described in Example 1(e) by cleavage of the protecting group with tetrabutylammonium fluoride in tetrahydrofuran:

- 1) - 4-(4-Fluorophenyl)-3-[4-[2-(pyridin-2-ylcarbamoyloxy)-ethoxy]-naphthalen-2-ylmethoxy]-piperidine as a colourless solid, MS: 395 [M-(PyNCO)]+, from β -trimethyl-silylethyl 4-(4-fluorophenyl)-3-[4-[2-(pyridin-2-ylcarbamoyloxy)-ethoxy]-naphthalen-2-ylmethoxy]-piperidine-1-carboxylate;
- 2) - (3RS,4RS)-3-[4-(2-benzoyloxy-ethoxy)-naphthalen-2-ylmethoxy]-4-(4-fluorophenyl)-piperidine as a colourless resin, MS: 500 (M+H)+, from β -trimethyl-silylethyl (3RS,4RS)-3-[4-(2-benzoyloxy-ethoxy)-naphthalen-2-ylmethoxy]-4-(4-fluorophenyl)-piperidine-1-carboxylate.

The β -trimethyl-silylethyl carbamates used as the starting materials were obtained as follows:

- (a) A solution of 54 mg (0.10 mmol) of β -trimethyl-silylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-[4-(2-hydroxy-ethoxy)-naphthalen-2-ylmethoxy]-piperidine-1-carboxylate in 5 ml of toluene was treated with 30 mg (0.20 mmol) of 2-pyridylcarbonyl azide [Monatsh. Chem. 33, 397 (1912)] and 5 mg of 4-dimethylaminopyridine. The solution was heated to reflux under argon for 2 hours. The mixture was cooled and the solvent was removed under reduced pressure. The residue was partitioned between methylene chloride and saturated sodium chloride solution, the

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organic phase was dried over magnesium sulphate and finally the solvent was removed under reduced pressure. The crude product (103 mg) was purified by chromatography on silica gel with a 1:2 mixture of ethyl acetate and hexane as the eluent. There were
5 obtained 65 mg (99% of theory) of β -trimethyl-silylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-[4-[2-(pyridin-2-ylcarbamoxyloxy)-ethoxy]-naphthalen-2-ylmethoxy]-piperidine-1-carboxylate as a colourless solid; MS: 660 (M+H)⁺.

10 (b) A solution of 108 mg (0.20 mmol) of β -trimethyl-silylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-[4-(2-hydroxy-ethoxy)-naphthalen-2-ylmethoxy]-piperidine-1-carboxylate in 2 ml of methylene chloride was treated with 56 μ l (41 mg, 0.40 mmol) of triethylamine. 36 μ l (42 mg, 0.30 mmol) of benzoyl chloride
15 were added thereto. The reaction mixture was stirred at room temperature for 6 hours and at 50°C for one hour. Subsequently, the mixture was partitioned between methylene chloride and a 5% sodium hydrogen carbonate solution, the organic phase was dried over magnesium sulphate and finally the solvent was removed
20 under reduced pressure. The crude β -trimethyl-silylethyl (3RS,4RS)-3-[4-(2-benzoyloxy-ethoxy)-naphthalen-2-ylmethoxy]-4-(4-fluorophenyl)-piperidine-1-carboxylate was used directly in the next step.

25

Example 17

The following compound was obtained in an analogous manner to that described in Example 5:

30

The procedure was carried out as follows in analogy to Example 5(a)-(d):

35

(a) From methyl salicylate there was obtained by introduction of the SEM group methyl 2-(2-trimethylsilylethoxymethoxy)-benzoate as a colourless oil; MS 224 [M-(C₂H₄ + CH₂O)]⁺.

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- (b) Reduction of methyl 2-(2-trimethylsilyl-ethoxymethoxy)-benzoate gave [2-(2-trimethylsilylethoxy-methoxy)-phenyl]-methanol as a light yellow oil; MS: 226 [M-(C₂H₄)]⁺.
- 5 (c) Chlorination of [2-(2-trimethylsilylethoxy-methoxy)-phenyl]-methanol yielded 1-chloromethyl-(2-trimethylsilyl-ethoxymethoxy)-benzene as a colourless oil; MS: 214, 216 [M-(C₂H₄ + CH₂O)]⁺.
- 10 (d) Alkylation of β-trimethyl-silylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-(4-hydroxy-naphthalen-2-ylmethoxy)-piperidine-1-carboxylic acid [Example 5 (g)] with 1-chloromethyl-(2-trimethylsilyl-ethoxymethoxy)-benzene yielded β-trimethylsilylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-[4-[2-(2-trimethylsilyl-ethoxymethoxy)-benzyloxy]-naphthalen-2-ylmethoxy]-piperidine-1-carboxylate as a colourless oil; MS: 749 (M+NH₄)⁺;
- 15 (e) From β-trimethylsilylethyl (3RS,4RS)-4-(4-fluorophenyl)-3-[4-[2-(2-trimethylsilyl-ethoxymethoxy)-benzyloxy]-naphthalen-2-ylmethoxy]-piperidine-1-carboxylate by cleaving the β-trimethylsilylethyl carbamate with tetrabutylammonium fluoride in tetrahydrofuran in analogy to the procedure described in Example 5 there was obtained (3RS,4RS)-4-(4-fluorophenyl)-3-[4-[2-(2-trimethylsilyl-ethoxymethoxy)-benzyloxy]-naphthalen-2-ylmethoxy]-piperidine as a rose coloured oil; MS: 588 (M+H)⁺.
- 20 (f) Cleavage of the SEM group from (3RS,4RS)-4-(4-fluorophenyl)-3-[4-[2-(2-trimethylsilyl-ethoxymethoxy)-benzyloxy]-naphthalen-2-ylmethoxy]-piperidine using a 2N solution of hydrogen chloride in methanol analogously to the procedure described in Example 5 (g) yielded (3RS,4RS)-4-(4-fluorophenyl)-3-[4-[2-hydroxy-benzyloxy]-naphthalen-2-ylmethoxy]-piperidine as a colourless resin; MS: 458 (M+H)⁺.
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Example 18

The following compounds were obtained in an analogous manner to that described in Example 12 (d) by cleavage of the
5 2,2,2-trichloroethyl carbamate:

- 1) - (3RS,4RS)-4-(2-Fluorophenyl)-3-(naphthalen-2-yl-methoxy)-piperidine as a light yellow oil, MS: 336 (M+H)⁺, from
2,2,2-trichloroethyl (3RS,4RS)-4-(2-fluorophenyl)-3-(naph-
10 thalen-2-ylmethoxy)-piperidine-1-carboxylate;
- 2) - (3RS,4RS)-4-(3-fluorophenyl)-3-(naphthalen-2-yl-methoxy)-piperidine as a light yellow oil, MS: 336 (M+H)⁺, from
2,2,2-trichloroethyl (3RS,4RS)-4-(3-fluorophenyl)-3-(naph-
15 thalen-2-ylmethoxy)-piperidine-1-carboxylate;
- 3) - (3RS,4RS)-4-(3-hydroxyphenyl)-3-(naphthalen-2-yl-methoxy)-piperidine as a beige solid, MS: 333 (M)⁺, from 2,2,2-trichloroethyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-[3-
20 (2,2,2-trichloro-ethoxycarbonyloxy)-phenyl]-piperidine-1-carboxylate.

The 2,2,2-trichloroethyl carbamates used as the starting materials were prepared as follows:

25

(a) The following procedure was carried out in an analogous manner to that described in Example 1 (a)-(c):

From 2-bromofluorobenzene and 1-benzyl-4-piperidone
30 there was obtained 1-benzyl-4-(2-fluorophenyl)-piperidin-4-ol as a yellow oil; MS: 285 (M)⁺. Subsequent elimination yielded 1-benzyl-4-(2-fluorophenyl)-1,2,3,6-tetrahydro-pyridine as a light yellow oil; MS: 267 (M)⁺. Hydroboration subsequently gave (3RS,4RS)-1-benzyl-4-(2-fluorophenyl)-piperidin-3-ol as a
35 colourless solid; MS: 285 (M)⁺.

(b) In an analogous manner to that described in Example 1 (g), by alkylating (3RS,4RS)-1-benzyl-4-(2-fluorophenyl)-piperidin-

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3-ol with 2-bromomethylnaphthalene there was obtained (3RS,4RS)-1-benzyl-4-(2-fluorophenyl)-3-(naphthalen-2-ylmethoxy)-piperidine as a yellow oil; MS: 284 (M-C₁₁H₉)⁺. By cleavage of the benzyl protecting group with 2,2,2-trichloroethyl chloroformate in an analogous manner to that described in Example 12 (c) there was obtained 2,2,2-trichloroethyl (3RS,4RS)-4-(2-fluorophenyl)-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a yellow oil; MS: 509 (M)⁺.

- 10 (c) The following procedure was carried out in an analogous manner to that described in Example 1 (a)-(c):

From 3-bromofluorobenzene and 1-benzyl-4-piperidone there was obtained 1-benzyl-4-(3-fluorophenyl)-piperidin-4-ol as a colourless solid; MS: 285 (M)⁺. Subsequent elimination yielded 1-benzyl-4-(3-fluorophenyl)-1,2,3,6-tetrahydro-pyridine as a light yellow oil; MS: 267 (M)⁺. Hydroboration subsequently gave (3RS,4RS)-1-benzyl-4-(3-fluorophenyl)-piperidin-3-ol as a colourless oil; MS: 285 (M)⁺.

20

- (d) In an analogous manner to that described in Example 1 (g), by alkylating (3RS,4RS)-1-benzyl-4-(3-fluorophenyl)-piperidin-3-ol with 2-bromomethylnaphthalene there was obtained (3RS,4RS)-1-benzyl-4-(3-fluorophenyl)-3-(naphthalen-2-ylmethoxy)-piperidine as a colourless oil; MS: 426 (M+H)⁺. By cleavage of the benzyl protecting group with 2,2,2-trichloroethyl chloroformate in an analogous manner to that described in Example 12 (c) there was obtained 2,2,2-trichloroethyl (3RS,4RS)-4-(3-fluorophenyl)-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a yellow oil; MS: 510 (M+H)⁺.

30

- (e) The following procedure was carried out in an analogous manner to that described in Example 1 (a)-(c):

35 From 3-benzyloxy-iodobenzene [J. Chem. Soc. 2857 (1932)] and 1-benzyl-4-piperidone there was obtained 1-benzyl-4-(3-benzyloxy-phenyl)-piperidin-4-ol as a light yellow oil; MS: 373 (M)⁺. Subsequent elimination yielded 1-benzyl-4-(3-benzyloxy-

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phenyl)-1,2,3,6-tetrahydro-pyridine as a colourless solid; MS: 355 (M)⁺. Hydroboration subsequently gave (3RS,4RS)-1-benzyl-4-(3-benzyloxy-phenyl)-piperidin-3-ol as a colourless solid; MS: 373 (M)⁺.

5

(f) In an analogous manner to that described in Example 1 (g), by alkylating (3RS,4RS)-1-benzyl-4-(3-benzyloxy-phenyl)-piperidin-3-ol with 2-bromomethylnaphthalene there was obtained (3RS,4RS)-1-benzyl-4-(3-benzyloxy-phenyl)-3-(naphthalen-2-ylmethoxy)-piperidine as a colourless resin; MS: 514 (M+H)⁺.

10

(g) A solution of 250 mg (0.487 mmol) of (3RS,4RS)-1-benzyl-4-(3-benzyloxyphenyl)-3-(naphthalen-2-ylmethoxy)-piperidine in 15 1.1 ml of methylene chloride was treated at room temperature with 247 μ l (236 mg, 1.946 mmol, 4 eq.) of N,N-dimethylaniline and 195 mg (1.46 mmol, 3.0 eq.) of aluminium trichloride and stirred at room temperature for 2.5 hours. Subsequently, the mixture was partitioned between methylene chloride and 5% sodium hydrogen carbonate solution, the organic phase was dried 20 over magnesium sulphate and finally the solvent was removed under reduced pressure. The crude product was purified by chromatography on silica gel with a 4:1 mixture of methylene chloride and hexane as the eluent. There were obtained 65 mg (32% of theory) of (3RS,4RS)-1-benzyl-4-(3-hydroxyphenyl)-3-(naphthalen-2-ylmethoxy)-piperidine as a beige coloured solid; MS: 423 (M)⁺.

25

(h) In an analogous manner to that described in Example 12(c), 30 by cleavage of the benzyl group with 2,2,2-trichloroethyl chloroformate there was obtained 2,2,2-trichloroethyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-[3-(2,2,2-trichloroethoxycarbonyloxy)-phenyl]-piperidine-1-carboxylate, which was used directly as the crude product in the next step.

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Example 19

In analogy to the procedure described in Example 2(e), by catalytically hydrogenating (3RS,4RS)-1-benzyl-4-(3-fluorophenyl)-piperidin-3-ol there was obtained (3RS,4RS)-4-(3-fluorophenyl)-piperidin-3-ol as a colourless solid; MS: 196 (M+H)⁺. Introduction of the BOC group in an analogous manner to that described in Example 1(f) yielded tert-butyl (3RS,4RS)-4-(3-fluorophenyl)-3-hydroxy-piperidine-1-carboxylate as a colourless solid; MS: 296 (M+H)⁺. Subsequent alkylation with 4-benzyloxy-2-chloromethyl-naphthalene in analogy to the procedure described in Example 1(g) gave tert-butyl (3RS,4RS)-3-(4-benzyloxy-naphthalen-2-ylmethoxy)-4-(3-fluorophenyl)-piperidine-1-carboxylate as a colourless solid; MS: 541 (M)⁺. Cleavage of the BOC group using a solution of hydrogen chloride in methanol analogously to the procedure described in Example 1(h) finally led to (3RS,4RS)-3-(4-benzyloxy-naphthalen-2-ylmethoxy)-4-(3-fluorophenyl)-piperidine, which was obtained as a colourless solid; MS: 442 (M+H)⁺.

20

The 4-benzyloxy-2-chloromethyl-naphthalene used as the starting compound was obtained as follows:

(a) By alkylating ethyl 4-hydroxy-naphthalene-2-carboxylate [J. Agric. Chem Soc. Japan 24, 313 (1950)] with benzyl bromide in an analogous manner to that described in Example 14(a) there was obtained ethyl 4-benzyloxy-naphthalene-2-carboxylate as an almost colourless solid; MS: 216 (M)⁺.

(b) Reduction of ethyl 4-benzyloxy-naphthalene-2-carboxylate analogously to Example 5(b) yielded (4-benzyloxy-naphthalen-2-yl)-methanol as a colourless solid; MS: 264 (M)⁺.

(c) Chlorination of (4-benzyloxy-naphthalen-2-yl) [-methanol] using carbon tetrachloride analogously to Example 7(c) yielded 4-benzyloxy-2-chloromethyl-naphthalene as a colourless solid; MS: 282 (M)⁺.

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Example 20

The following compounds were obtained in an analogous manner to that described in Example 1(h) by cleavage of the BOC
5 group using a solution of hydrogen chloride in methanol:

- 1) - (3RS,4RS)-4-(4-Cyano-phenyl)-3-(naphthalen-2-yl-methoxy)-piperidine as a light yellow solid, MS: 342 (M+H)⁺, from
tert-butyl (3RS,4RS)-4-(4-cyano-phenyl)-3-(naphthalen-2-yl-
10 methoxy)-piperidine-1-carboxylate;
- 2) - (3RS,4RS)-4-[4-(phenylsulphonylamino-methyl)-phenyl]-
3-(naphthalen-2-ylmethoxy)-piperidine as a colourless solid,
MS: 485 (M-H)⁻, from tert-butyl 4-[4-(phenylsulphonylamino-
15 methyl)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-
carboxylate;
- 3) - (3RS,4RS)-4-[4-(4-methoxy-benzoylamino)-methyl]-
phenyl-3-(naphthalen-2-ylmethoxy)-piperidine as a colourless
20 resin, MS: 481 (M+H)⁺, from tert-butyl (3RS,4RS)-4-[4-(4-
methoxy-benzoylamino)-methyl]-phenyl-3-(naphthalen-2-
ylmethoxy)-piperidine-1-carboxylate;
- 4) - (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-[4-(phenyl-
25 acetyl-aminomethyl)-phenyl]-piperidine as a colourless resin,
MS: 465 (M+H)⁺, from tert-butyl (3RS,4RS)-3-(naphthalen-2-yl-
methoxy)-4-[4-(phenylacetyl-amino-methyl)-phenyl]-piperidine-
1-carboxylate;
- 30 5) - (3RS,4RS)-4-[4-(benzoylamino-methyl)-phenyl]-3-(4-
hydroxy-naphthalen-2-ylmethoxy)-piperidine as a light orange
coloured solid, MS: 467 (M+H)⁺, from tert-butyl (3RS,4RS)-4-[4-
(benzoylamino-methyl)-phenyl]-3-[4-(2-trimethylsilyl-ethoxy-
methoxy)-naphthalen-2-ylmethoxy]-piperidine-1-carboxylate by
35 simultaneous cleavage of the BOC and SEM groups analogously to
that described in Example 3 and 5 (g).

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The BOC compounds used as the starting materials were prepared as follows:

(a) A suspension of 20 mg (0.30 mmol) of activated zinc powder, 76 mg (1.17 mmol) of potassium cyanide, 52 mg (0.20 mmol) of triphenylphosphine and 74 mg (0.10 mmol) of bis(triphenylphosphine)-nickel(II) dibromide in 2 ml of acetonitrile was heated at 60°C under argon for 5 minutes. 356 mg (1.00 mmol) of tert-butyl (3RS,4RS)-4-(4-bromophenyl)-3-hydroxy-piperidine-1-carboxylate in solid form were added thereto. The green suspension was stirred at 60°C under argon for 20 hours. The resulting dark brown suspension was filtered over Speedex and the insoluble material was washed with methylene chloride. The filtrate was partitioned between methylene chloride and 5% sodium hydrogen carbonate solution, the organic phase was dried over magnesium sulphate and finally the solvent was removed under reduced pressure. The crude product (416 mg) was purified by chromatography on silica gel with a 1:1 mixture of ethyl acetate and hexane as the eluent. There were obtained 168 mg (56% of theory) of tert-butyl (3RS,4RS)-4-(4-cyano-phenyl)-3-hydroxy-piperidine-1-carboxylate as a colourless solid; MS: 302 (M)⁺.

(b) In analogy to the procedure described in Example 1(g), by alkylating tert-butyl (3RS,4RS)-4-(4-cyano-phenyl)-3-hydroxy-piperidine-1-carboxylate with 2-bromomethylnaphthalene there was obtained tert-butyl (3RS,4RS)-4-(4-cyano-phenyl)-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a light yellow resin; MS: 443 (M+H)⁺.

(c) A solution of 133 mg (0.301 mmol) of tert-butyl (3RS,4RS)-4-(4-cyano-phenyl)-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate in 0.5 ml of tetrahydrofuran was treated with 1.5 ml (1.5 mmol) of a 1M borane-tetrahydrofuran complex solution in tetrahydrofuran and the mixture was heated to reflux under argon for 6 hours. The reaction mixture was partitioned between methylene chloride and water, the organic phase was dried over magnesium sulphate and finally the solvent was

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removed under reduced pressure. The crude product (163 mg) was purified by chromatography on silica gel with a 14:1:0.1 mixture of methylene chloride, methanol and a 25% ammonia solution as the eluent. There were obtained 106 mg (79% of theory) of tert-butyl (3RS,4RS)-4-(4-aminomethyl-phenyl)-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a colourless resin; MS: 447 (M+H)+.

(d) A solution of 47 mg (0.105 mmol) of tert-butyl (3RS,4RS)-4-(4-aminomethyl-phenyl)-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate in 2 ml of methylene chloride was treated with 18 μ l (12.7 mg, 0.126 mmol, 1.2 eq.) of triethylamine and cooled to 0°C. 15 μ l (20.4 mg, 0.116 mmol, 1.1 eq.) of benzenesulphonyl chloride were added dropwise, the mixture was warmed to room temperature and stirred for 1 hour. The reaction mixture was partitioned between methylene chloride and 5% sodium hydrogen carbonate solution, the organic phase was dried over magnesium sulphate and finally the solvent was removed under reduced pressure. There were obtained 47 mg of crude tert-butyl (3RS,4RS)-4-[4-(phenylsulphonyl-amino-methyl)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate, which was used in the following step without further purification and characterization.

(e) In an analogous manner to the procedure described under (d), from tert-butyl (3RS,4RS)-4-(4-aminomethyl-phenyl)-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate by acylation with p-anisoyl chloride there was obtained crude tert-butyl (3RS,4RS)-4-[4-(4-methoxy-benzoylamino)-methyl]-phenyl-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate, which was used in the following step without further purification and characterization.

(f) In an analogous manner to the procedure described under (d), from tert-butyl (3RS,4RS)-4-(4-aminomethyl-phenyl)-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate by acylation with phenylacetyl chloride there was obtained crude tert-butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-[4-(phenylacetyl-

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amino-methyl)-phenyl]-piperidine-1-carboxylate, which was used in the following step without further purification and characterization.

5 (g) In an analogous manner to that described in Example 1(g), by alkylating tert-butyl (3RS,4RS)-4-(4-cyano-phenyl)-3-hydroxy-piperidine-1-carboxylate with 2-chloromethyl-4-(β -trimethylsilyl-ethoxymethoxy)-naphthalene there was obtained tert-butyl (3RS,4RS)-4-(4-cyano-phenyl)-3-[4-(2-trimethylsilyl-ethoxymethoxy)-naphthalen-2-ylmethoxy]-piperidine-1-carboxylate as
10 a light yellow oil; MS: 530 [M-(C₂H₄+CH₂O)]⁺.

(h) In analogy to the procedure described under (c), by reducing the nitrile group in tert-butyl (3RS,4RS)-4-(4-cyano-phenyl)-3-
15 [4-(2-trimethylsilyl-ethoxymethoxy)-naphthalen-2-ylmethoxy]-piperidine-1-carboxylate there was obtained tert-butyl (3RS,4RS)-4-(4-aminomethyl-phenyl)-3-[4-(2-trimethylsilyl-ethoxymethoxy)-naphthalen-2-ylmethoxy]-piperidine-1-carboxylate as a light yellow oil; MS: 593 (M+H)⁺.

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(i) In analogy to the procedure described under (d), from tert-butyl (3RS,4RS)-4-(4-aminomethyl-phenyl)-3-[4-(2-trimethylsilyl-ethoxymethoxy)-naphthalen-2-ylmethoxy]-piperidine-1-carboxylate by acylation with benzoyl chloride there was
25 obtained crude tert-butyl (3RS,4RS)-4-[4-(benzoylamino-methyl)-phenyl]-3-[4-(2-trimethylsilyl-ethoxymethoxy)-naphthalen-2-ylmethoxy]-piperidine-1-carboxylate, which was used in the following step without further purification and characterization.

30

Example 21

The following compounds were obtained in an analogous manner to that described in Example 1(h) by cleavage of the BOC
35 group using a solution of hydrogen chloride in methanol:

1) - (3RS,4RS)-4-(4-Chlorophenyl)-4-hydroxy-3-(4-methoxybenzyloxy)-piperidine as a colourless solid, MS: 348 (M+H)⁺, from

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tert-butyl (3RS,4RS)-4-(4-chlorophenyl)-4-hydroxy-3-(4-methoxy-benzyloxy)-piperidine-1-carboxylate;

- 2) - (3RS,4RS)-4-(4-chlorophenyl)-4-hydroxy-3-(naphthalen-2-ylmethoxy)-piperidine as a colourless solid, MS: 226, 228 [M-(C₁₁H₉)]⁺, from tert-butyl (3RS,4RS)-4-(4-chlorophenyl)-4-hydroxy-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate.

The compounds used as the starting materials were prepared as follows:

- (a) A solution of 3.0 g (15.5 mmol) of 4-(4-chlorophenyl)-1,2,3,6-tetrahydro-pyridine in 20 ml of absolute dimethylformamide was treated with 2.37 ml (1.72 g, 17.0 mmol) of triethylamine and cooled to 0°C. A solution of 3.7 g (17.0 mmol) of di-tert-butyl dicarbonate in 8 ml of absolute dimethylformamide was added dropwise at 0°C. The mixture was warmed to room temperature and stirred for 20 hours. The solvent was distilled off at 50-55°C at 0.1 mm Hg. Subsequently, the residue obtained was partitioned between methylene chloride and water, the organic phase was dried over magnesium sulphate and finally the solvent was removed under reduced pressure. The crude product (5.0 g) was purified by chromatography on silica gel with a 95:5 mixture of methylene chloride and ethyl acetate as the eluent. There were obtained 4.5 g (99% of theory) of tert-butyl 4-(4-chlorophenyl)-1,2,3,6-tetrahydro-pyridine-1-carboxylate as a colourless oil; MS: 236, 238 [M-(C₄H₉)]⁺.

- (b) A solution of 2.5 g (8.5 mmol) of tert-butyl 4-(4-chlorophenyl)-1,2,3,6-tetrahydro-pyridine-1-carboxylate in 20 ml of acetone was treated with 0.425 ml (0.0085 mmol, 0.01 eq.) of osmium tetroxide solution (0.02M in tert-butanol) and 8.6 ml of hydrogen peroxide solution (30% in water) and the mixture was stirred at room temperature for 18 hours. The mixture was partitioned between ethyl acetate and water, the organic phase was washed with 10% sodium bisulphite solution and water, dried over magnesium sulphate and finally the solvent was removed under reduced pressure. The crude product (2.2 g) was purified

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by chromatography on silica gel with a 3:1 mixture of methylene chloride and ethyl acetate as the eluent. There were obtained 544 mg (20% of theory) of tert-butyl (3RS,4RS)-4-(4-chlorophenyl)-3,4-dihydroxy-piperidine-1-carboxylate as a colourless resin; MS: 270, 272 [M-(C₄H₉)]⁺.

(c) A solution of 128 mg (0.392 mmol) of tert-butyl (3RS,4RS)-4-(4-chlorophenyl)-3,4-dihydroxy-piperidine-1-carboxylate in 1.5 ml of dimethyl sulfoxide was added dropwise to a suspension of 16 mg (0.4 mmol) of sodium hydride (60% dispersion in refined oil) in 3 ml of dimethyl sulfoxide. After 15 minutes a solution of 61 mg (0.39 mmol) of p-methoxybenzyl chloride in 1 ml of dimethyl sulfoxide was added dropwise at room temperature within 10 minutes and the mixture was stirred for 18 hours. Subsequently, the reaction mixture was partitioned between ethyl acetate and water, the organic phase was dried over magnesium sulphate and finally the solvent was removed under reduced pressure. The crude product (200 mg) was purified by chromatography on silica gel with a 3:1 mixture of hexane and ethyl acetate as the eluent. There were obtained (in addition to starting material and bisalkylated product) 63 mg (38% of theory) of tert-butyl (3RS,4RS)-4-(4-chlorophenyl)-4-hydroxy-3-(4-methoxy-benzyloxy)-piperidine-1-carboxylate as a colourless oil; MS: 448, 450 [M+H]⁺.

25

(d) In an analogous manner to the procedure described under (c), by alkylating tert-butyl (3RS,4RS)-4-(4-chlorophenyl)-3,4-dihydroxy-piperidine-1-carboxylate with 2-bromomethylnaphthalene there was obtained tert-butyl (3RS,4RS)-4-(4-chlorophenyl)-4-hydroxy-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a light yellow oil; MS: 411, 413 [M-(C₄H₈)]⁺.

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Example 22

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(a) 400 ml of a 1.2M solution of n-BuLi in hexane were added dropwise within 45 minutes to a solution, cooled to -70°C, of 112.5 g (0.48 mol) of 1,4-dibromobenzene in 1200 ml of diethyl

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ether in such a manner that the temperature did not rise above -60°C. After completion of the addition the mixture was stirred at -70°C for 2.5 hours. Thereafter, a solution of 90.84 g (0.48 mol) of 1-benzyl-4-piperidone in 300 ml of ether was added dropwise at -70 to -65°C during one hour. After the dropwise addition the mixture was stirred at -70°C for 2 hours. For the working-up, the cold reaction mixture was poured into 1200 ml of a 15% ammonium chloride solution, the mixture was transferred to a separating funnel and the organic phase was separated. The aqueous phase was extracted twice with ether and subsequently the combined organic phases were extracted twice with water and saturated sodium chloride solution. Then, the organic phase was dried over magnesium sulphate evaporated under reduced pressure, with the crude product separating as a yellowish solid. For purification, this was dissolved in hot methylene chloride, the solution was treated with hexane until turbidity began and cooled to room temperature while stirring. The resulting precipitate was filtered off under suction and dried. There were obtained 121.65 g (73% of theory) of 1-benzyl-(4-bromo-phenyl)-piperidin-4-ol as a yellowish solid; m.p.: 106°C, MS: 346, 348 (M+H)⁺.

(b) A mixture of 121.6 g (0.35 mol) of 1-benzyl-4-(4-bromo-phenyl)-piperidin-4-ol and 121.6 g of p-toluenesulphonic acid monohydrate (0.64 mol) in 1200 ml of toluene was heated to reflux on a water separator for 4.5 hours. Subsequently, the reaction mixture was cooled to room temperature and adjusted to pH 10 with 3N sodium hydroxide solution. Thereafter, the mixture was extracted firstly with 200 ml and then with 500 ml of methylene chloride. The combined organic phases were washed twice with 100 ml of water each time, dried over magnesium sulphate and then evaporated under reduced pressure. There were obtained 109.1 g (99% of theory) of 1-benzyl-4-(4-bromo-phenyl)-1,2,3,6-tetrahydro-pyridine as a yellowish solid; MS: 328, 330 (M+H)⁺.

(c) 16.9 g of sodium borohydride were added to a solution of 51.1 g (0.156 mol) of 1-benzyl-4-(4-bromo-phenyl)-1,2,3,6-

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tetrahydro-pyridine in 350 ml of dimethoxyethane and the reaction mixture was stirred at room temperature for 15 minutes. Thereafter, 95.2 ml of boron trifluoride etherate were added dropwise at 25-30°C during 30 minutes, the reaction mixture was subsequently stirred at room temperature for 2 hours. Thereafter, firstly a solution of 98.4 g of potassium hydroxide in 530 ml of water was slowly added dropwise and thereafter within 15 minutes 80.7 ml of a 30% hydrogen peroxide solution were added. Subsequently, the mixture was boiled under reflux for 2 hours. For the working-up, the cooled reaction mixture was filtered over Dicalit and this was rinsed with methylene chloride. The solution obtained was treated with 700 ml of methylene chloride, the organic phase was separated and then the aqueous phase was back-extracted with 300 ml of methylene chloride. The combined organic phases were washed twice with 200 ml of water each time, dried over magnesium sulphate and evaporated under reduced pressure. Crystallization of the crude product from acetone yielded 31 g (57% of theory) of (3RS,4RS)-1-benzyl-4-(4-bromo-phenyl)-piperidin-3-ol as colourless crystals; m.p.: 125-129°C.

(d) A Schlenk tube was charged under argon with 74.9 mg (0.29 mmol) of $\text{PdCl}_2(\text{CH}_3\text{CN})_2$, 168.0 mg (0.303 mmol) of 1,1'-bis(diphenylphosphino)ferrocene and 10 ml of methanol (distilled under argon) and the reaction mixture was stirred at room temperature for 30 minutes. The red-brown suspension was transferred under argon into a 185 ml steel autoclave fitted with a glass insert. Thereafter, 10.0 g (29 mmol) of (3RS,4RS)-1-benzyl-4-(4-bromo-phenyl)-piperidin-3-ol (pre-treated with active charcoal), 60 ml of methanol and 6 ml (43 mmol) of triethylamine (sic) were added. The autoclave was sealed, pressurized to 15 bar with carbon monoxide and the reaction mixture was stirred at 110° for 20 hours under constant pressure. After cooling the autoclave and releasing the gases the orange coloured reaction mixture was evaporated under reduced pressure. The solid, orange coloured residue was dissolved in 20 ml of methylene chloride, the solution was washed twice with 100 ml of 5% sodium carbonate solution each time and,

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respectively, with 100 ml of water and then evaporated under reduced pressure. For purification, the yellow-brown solid residue was chromatographed on silica gel using a 1:1 mixture of ethyl acetate and hexane as the eluent. There were obtained
5 7.74 g (82% of theory) of methyl (3RS,4RS)-4-(1-benzyl-3-hydroxy-piperidin-4-yl)-benzoate as a white solid; m.p.: 103-104°C; MS: 326 (M+H)+.

(e) A solution of 5.0 g (15.3 mmol) of methyl (3RS,4RS)-4-(1-
10 benzyl-3-hydroxy-piperidin-4-yl)-benzoate in 50 ml of tetrahydrofuran was treated at room temperature with 720 mg (32.9 mmol) of lithium borohydride. Subsequently, the reaction mixture was heated to 60°C for 15 hours. For the working-up, the reaction mixture was treated with 20 ml of water while
15 cooling with ice and thereafter extracted twice with 50 ml of ethyl acetate each time. The organic phases were combined, dried over sodium sulphate and evaporated under reduced pressure. The crude (3RS,4RS)-1-benzyl-4-(4-hydroxymethyl-phenyl)-piperidine-3-ol obtained (Rf: 0.23, methylene chloride:methanol:
20 ammonia = 95:5:0.1) was used in the following step without further purification.

(f) A solution of 2.0 g (6.72 mmol) of (3RS,4RS)-1-benzyl-4-(4-hydroxymethyl-phenyl)-piperidin-3-ol in 100 ml of ethanol
25 was hydrogenated at room temperature and 3 bar for 4 hours in the presence of 1.0 g of palladium oxide/charcoal (20%). For the working-up, the catalyst was filtered off under suction over Dicalit and the residue was washed twice with 50 ml of ethanol each time. The ethanol solution was evaporated under reduced
30 pressure and the residue was chromatographed on silica gel using a 65:10:1 mixture of methylene chloride, methanol and ammonia as the eluent. There were obtained 1.1 g (79% of theory) of (3RS,4RS)-4-(4-hydroxymethyl-phenyl)-piperidin-3-ol as a colourless solid; MS: 207 (M)+.

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(g) A solution of 1.10 g (5.31 mmol) of (3RS,4RS)-4-(4-hydroxymethyl-phenyl)-piperidin-3-ol in 20 ml of dimethylformamide was treated at 0°C with 0.59 g (5.82 mmol) of

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triethylamine and 1.22 g (5.57 mmol) of di-tert-butyl dicarbonate and the mixture was stirred at room temperature for 15 hours. Subsequently, the dimethylformamide was distilled off in an oil pump vacuum and, for purification, the residue was
5 chromatographed on silica gel using a 98:2 mixture of methylene chloride and methanol as the eluent. There were obtained 1.51 g (92% of theory) of tert-butyl (3RS,4RS)-3-hydroxy-4-(4-hydroxymethyl-phenyl)-piperidine-1-carboxylate as a colourless foam; MS: 233 (M-C₄H₁₀O)⁺.

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(h) A solution of 1.50 g (5.14 mmol) of tert-butyl (3RS,4RS)-3-hydroxy-4-(4-hydroxymethyl-phenyl)-piperidine-1-carboxylate, 1.73 g (6.16 mmol) of triphenylchloromethane and 674 mg (6.68 mmol) of triethylamine in 20 ml of methylene chloride was
15 stirred at room temperature for 5 hours. For the working-up, the reaction mixture was washed with 10 ml of water and 10 ml of saturated sodium hydrogen carbonate solution, the organic phase was dried over sodium sulphate and evaporated under reduced pressure. The crude product was chromatographed on silica gel
20 using a 95:5 mixture of toluene and ethyl acetate as the eluent. There were obtained 2.08 g (77.5% of theory) of tert-butyl (3RS,4RS)-3-hydroxy-4-(4-trityloxymethyl-phenyl)-piperidine-1-carboxylate as a colourless foam; MS: 567 (M+NH₄)⁺.

25 (i) 290 mg (6.05 mmol) of sodium hydride (50% dispersion in refined oil) were added to a solution of 2.08 g (3.78 mmol) of tert-butyl (3RS,4RS)-3-hydroxy-4-(4-trityloxymethyl-phenyl)-piperidine-1-carboxylate and 1.0 g (4.54 mmol) of 2-bromo-methylnaphthalene in 30 ml of dimethylformamide and the
30 reaction mixture was stirred at room temperature for 2 hours. For the working-up, the reaction mixture was evaporated in an oil pump vacuum, the residue was partitioned between 100 ml of saturated ammonium chloride solution and 100 ml of ethyl acetate and thereafter the separated aqueous phase was
35 extracted twice with 50 ml of ethyl acetate each time. The combined ethyl acetate extracts were dried over sodium sulphate and evaporated under reduced pressure. For purification, the crude product was chromatographed on silica gel using a 4:1

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mixture of methylene chloride and hexane as the eluent. There were obtained 2.27 g (87% of theory) of tert-butyl (3RS,4RS)-3-naphthalen-2-ylmethoxy-4-(4-trityloxymethyl-phenyl)-piperidine-1-carboxylate as a colourless solid; MS: 707 (M+NH₄)⁺.

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(j) A solution of 1.07 g (1.48 mmol) of tert-butyl (3RS,4RS)-3-naphthalen-2-ylmethoxy-4-(4-trityloxymethyl-phenyl)-piperidine-1-carboxylate in 15 ml of methylene chloride was treated at room temperature with 2 ml of 2N hydrogen chloride in methanol and the mixture was stirred at room temperature for 15 minutes. Subsequently, the solution was poured into 30 ml of saturated sodium carbonate solution and this was extracted twice with 50 ml of ethyl acetate each time. The combined organic phases were dried over sodium sulphate and evaporated under reduced pressure. For purification, the crude product was chromatographed on silica gel using a 99:1 mixture of methylene chloride and methanol as the eluent. There were obtained 580 mg (82% of theory) of tert-butyl (3RS,4RS)-4-(4-hydroxymethyl-phenyl)-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a colourless oil; MS: 447 (M)⁺.

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(k) A solution of 45 mg (0.1 mmol) of tert-butyl (3RS,4RS)-4-(4-hydroxymethyl-phenyl)-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate, 12 mg (0.12 mmol) of triethylamine and 12 mg (0.1 mmol) of pivaloyl chloride in 5 ml of methylene chloride was stirred at room temperature for 15 hours. For the working-up, the reaction solution was diluted with 10 ml of methylene chloride, then washed with 5 ml of water, dried over sodium sulphate and evaporated under reduced pressure. The residue was chromatographed on silica gel using a 4:1 mixture of hexane and ethyl acetate as the eluent. There were obtained 39 mg (73% of theory) of tert-butyl (3RS,4RS)-4-[4-(2,2-dimethyl-propionyloxymethyl)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a colourless oil; MS: 549 (M+NH₄)⁺.

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(l) A solution of 35 mg (0.07 mmol) of tert-butyl (3RS,4RS)-4-[4-(2,2-dimethyl-propionyloxymethyl)-phenyl]-3-(naphthalen-2-

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ylmethoxy)-piperidine-1-carboxylate in 2 ml of 2M hydrogen chloride in methanol was stirred at room temperature for 4.5 hours. Subsequently, the reaction solution was evaporated under reduced pressure. The residue was taken up in diethyl ether, with a part (15 mg, 49% of theory) of the (3RS,4RS)-4-(3-naphthalen-2-ylmethoxy-piperidin-4-yl)-benzyl 2,2-dimethyl-propionate hydrochloride being obtained in the form of white crystals; MS: 432 (M+H)⁺.

10 Example 23

A solution of 1.10 g (1.59 mmol) of tert-butyl (3RS,4RS)-3-naphthalen-2-ylmethoxy-4-(4-trityloxymethyl-phenyl)-piperidine-1-carboxylate in 50 ml of methanol was treated at room temperature with 30 ml of a 2M solution of hydrogen chloride in methanol and the mixture was stirred at room temperature for 4 hours. Subsequently, the solution was evaporated under reduced pressure and the residue was partitioned between 30 ml of saturated sodium carbonate solution and 50 ml of ethyl acetate. The aqueous phase was again extracted with 50 ml of ethyl acetate, thereafter the organic phases were combined, dried over sodium sulphate and evaporated under reduced pressure. For purification, the crude product was chromatographed on silica gel using a 90:10 mixture of methylene chloride and methanol as the eluent. There were obtained 462 mg (83% of theory) of (3RS,4RS)-[4-[3-(naphthalen-2-ylmethoxy)-piperidin-4-yl]-phenyl]-methanol as a colourless solid; MS: 348 (M+H)⁺.

30 Example 24

The following compounds were obtained in an analogous manner to that in Example 22 (I) by cleavage of the BOC group using acid

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1) - (3RS,4RS)-4-[3-(Naphthalen-2-ylmethoxy)-piperidin-4-yl]-benzyl benzoate as a colourless foam, MS: 452 (M+H)⁺, from

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tert-butyl (3RS,4RS)-4-(4-benzoyloxymethyl-phenyl)-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate;

2) - (3RS,4RS)-4-(3-naphthalen-2-ylmethoxy-piperidin-4-yl)-benzyl 3-methoxy-benzoate hydrochloride as a colourless solid, MS: 482 (M+H)⁺, from tert-butyl (3RS,4RS)-4-[4-(3-methoxy-benzoyloxymethyl)-phenyl]-3-naphthalen-2-ylmethoxy-piperidine-1-carboxylate;

3) - (3RS,4SR)-4-(3-naphthalen-2-ylmethoxy-piperidin-4-yl)-benzyl 3,5-dimethoxy-benzoate hydrochloride as a colourless solid, MS: 512 (M+H)⁺, from tert-butyl (3RS,4RS)-4-[4-(3,5-dimethoxy-benzoyloxymethyl)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate;

4) - (3RS,4RS)-4-[3-(naphthalen-2-ylmethoxy)-piperidin-4-yl]-benzyl cyclohexanecarboxylate trifluoroacetate as a colourless solid, MS: 458 (M+H)⁺, from tert-butyl (3RS,4RS)-4-(4-cyclohexanecarbonyloxymethyl-phenyl)-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate using trifluoroacetic acid in methylene chloride;

5) - (4RS,3RS)-4-(3-naphthalen-2-ylmethoxy-piperidin-4-yl)-benzyl 2-chloro-benzoate trifluoroacetate as a colourless solid, MS: 486 (M+H)⁺, from tert-butyl (3RS,4RS)-[4-(2-chloro-benzoyloxymethyl)-phenyl]-3-naphthalen-2-ylmethoxy-piperidine-1-carboxylate using trifluoroacetic acid in methylene chloride;

6) - carbonic acid methyl ester (3RS,4RS)-4-(naphthalen-2-ylmethoxy-piperidin-4-yl)-benzyl ester hydrochloride as a colourless oil, MS: 406 (M+H)⁺, from tert-butyl (3RS,4RS)-4-(4-methoxycarbonyloxymethyl-phenyl)-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate;

7) - (3RS,4RS)-4-[3-(naphthalen-2-ylmethoxy)-piperidin-4-yl]-benzyl pyridine-4-carboxylate hydrochloride as a yellow oil, MS: 453 (M+H)⁺, from (3RS,4RS)-4-(1-tert-butoxycarbonyl-3-

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naphthalen-2-ylmethoxy-piperidin-4-yl)-benzyl pyridine-4-carboxylate;

- 8) - (3RS,4RS)-4-(3-naphthalen-2-ylmethoxy-piperidin-4-yl)-benzyl pyrazine-2-carboxylate hydrochloride as a colourless solid, MS: 454 (M+H)⁺, from (3RS,4RS)-4-[1-tert-butoxycarbonyl-3-(naphthalen-2-ylmethoxy)-piperidin-4-yl]-benzyl pyrazine-2-carboxylate;
- 9) - (3RS,4RS)-4-[3-(1-methoxy-naphthalen-2-ylmethoxy)-piperidin-4-yl]-benzyl 2-chloro-benzoate trifluoroacetate as a colourless solid, MS: 516 (M+H)⁺, from tert-butyl (3RS,4RS)-4-[4-(2-chloro-benzoyloxymethyl)-phenyl]-3-(1-methoxy-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate using trifluoroacetic acid in methylene chloride;
- 10) - (3RS,4RS)-4-(3-naphthalen-2-ylmethoxy-piperidin-4-yl)-benzyl 4-hydroxy-benzoate hydrochloride as a yellowish solid, MS: 468 (M+H)⁺, from tert-butyl (3RS,4RS)-4-[4-(4-hydroxy-benzoyloxymethyl)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate using trifluoroacetic acid in methylene chloride and simultaneous cleavage of the acetal group;
- 11) - (3RS,4RS)-4-[3-(naphthalen-2-ylmethoxy)-piperidin-4-yl]-benzyl pyridin-2-yl-carbamate hydrochloride as a colourless foam, R_f : 0.15 (methylene chloride:methanol ammonia = 90:10: 0.1), from tert-butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-[4-(pyridin-2-ylcarbamoxyloxymethyl)-phenyl]-piperidine-1-carboxylate;
- 12) - (3RS,4RS)-4-[4-(3-methoxy-propenyl)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine as a yellow oil, MS: 388 (M+H)⁺, from tert-butyl (3RS,4RS)-4-[4-(3-hydroxy-propenyl)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate;
- 13) - (3RS,4RS)-4-[4-(3-benzoyloxy-propenyl)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine as a yellow oil, MS: 478 (M+H)⁺, from tert-butyl (3RS,4RS)-4-[4-(3-benzoyloxy-

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propenyl)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate;

14) - 3-[4-[3-(naphthalen-2-ylmethoxy)-piperidin-4-yl]-phenyl]-propyl (3RS,4RS)-2-chloro-benzoate as a yellowish oil, MS: 514, 516 (M+H)⁺, from tert-butyl (3RS,4RS)-4-[4-[3-(2-chloro-benzoyloxy)-propyl]-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate.

10 The starting materials were obtained as follows analogously to the procedure described in Example 22(k):

(a) tert-Butyl (3RS,4RS)-4-(4-benzoyloxymethyl-phenyl)-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a colourless oil, MS: 552 (M+H)⁺, from tert-butyl (3RS,4RS)-4-(4-hydroxymethyl-phenyl)-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate and benzoyl chloride.

(b) tert-Butyl (3RS,4RS)-4-[4-(3-methoxy-benzoyloxymethyl)-phenyl]-3-naphthalen-2-ylmethoxy-piperidine-1-carboxylate as a colourless oil, MS: 582 (M+H)⁺, from tert-butyl (3RS,4RS)-4-(4-hydroxymethyl-phenyl)-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate and 3-methoxybenzoyl chloride.

(c) tert-Butyl (3RS,4RS)-4-[4-(3,5-dimethoxy-benzoyloxymethyl)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a colourless oil, MS: 612 (M+H)⁺, from tert-butyl (3RS,4RS)-4-(4-hydroxymethyl-phenyl)-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate and 3,5-dimethoxybenzoyl chloride.

(d) tert-Butyl (3RS,4RS)-4-(4-cyclohexanecarbonyloxymethyl-phenyl)-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a colourless oil, MS: 558 (M+H)⁺, from tert-butyl (3RS,4RS)-4-(4-hydroxymethyl-phenyl)-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate and cyclohexanecarbonyl chloride.

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(e) tert-Butyl (3RS,4RS)-[4-(2-chloro-benzoyloxymethyl)-phenyl]-3-naphthalen-2-ylmethoxy-piperidine-1-carboxylate as a colourless oil, MS: 586 (M+H)⁺, from tert-butyl (3RS,4RS)-4-(4-hydroxymethyl-phenyl)-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate and 2-chlorobenzoyl chloride.

(f) tert-Butyl (3RS,4RS)-4-(4-methoxycarbonyloxymethyl-phenyl)-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a colourless oil from tert-butyl (3RS,4RS)-4-(4-hydroxymethyl-phenyl)-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate and methyl chloroformate.

(g) A solution of 60 mg (0.13 mmol) of tert-butyl (3RS,4RS)-4-(4-hydroxymethyl-phenyl)-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate, 16 mg (0.13 mmol) of isonicotinic acid, 34 mg (0.26 mmol) of ethyldiisopropylamine and 58 mg (0.13 mmol) of benzotriazol-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate (BOP) in 5 ml of acetonitrile was stirred at room temperature for 2 hours. Subsequently, the reaction mixture was evaporated under reduced pressure and the residue, without further working-up, was chromatographed on silica gel using a 3:1 mixture of hexane and ethyl acetate as the eluent. There were obtained 15 mg (21% of theory) of (3RS,4RS)-4-(1-tert-butoxycarbonyl-3-naphthalen-2-ylmethoxy-piperidin-4-yl)-benzyl pyridine-4-carboxylate as a colourless solid; MS: 552 (M)⁺.

(h) In an analogous manner to that described under (g) by condensing tert-butyl (3RS,4RS)-4-(4-hydroxymethyl-phenyl)-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate and pyrazinecarboxylic acid using 1,1-carbonyldiimidazole as the condensation agent there was obtained 4-[1-tert-butoxycarbonyl-3-(naphthalen-2-ylmethoxy)-piperidin-4-yl]-benzyl (3RS,4RS)-pyrazine-2-carboxylate; MS: 554 (M+H)⁺.

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Processing was carried out as follows in an analogous manner to that described in Example 22 (i)-(k):

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- (i) Alkylation of methyl (3RS,4RS)-4-(1-benzyl-3-hydroxy-piperidin-4-yl)-benzoate with 2-bromomethyl-1-methoxy-naphthalene gave tert-butyl (3RS,4RS)-3-(1-methoxy-naphthalen-2-ylmethoxy)-4-(4-trityloxymethyl-phenyl)-piperidine-1-carboxylate as a colourless oil; MS: 720 (M+H)⁺.
- (j) Cleavage of the trityl group from tert-butyl (3RS,4RS)-3-(1-methoxy-naphthalen-2-ylmethoxy)-4-(4-trityloxymethyl-phenyl)-piperidine-1-carboxylate yielded tert-butyl (3RS,4RS)-4-(4-hydroxymethyl-phenyl)-3-(1-methoxy-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a colourless oil; MS: 478 (M+H)⁺.
- (k) Acylation of tert-butyl (3RS,4RS)-4-(4-hydroxymethyl-phenyl)-3-(1-methoxy-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate with 2-chlorobenzoyl chloride gave tert-butyl (3RS,4RS)-4-[4-(2-chloro-benzoyloxymethyl)-phenyl]-3-(1-methoxy-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a colourless oil; MS: 615 (M+H)⁺.
- (l) In an analogous manner to that described under (g) by condensing tert-butyl (3RS,4RS)-4-(4-hydroxymethyl-phenyl)-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate and 4-(2-trimethylsilyl-ethoxymethoxy)-benzoic acid using N-ethyl-N'-(3-dimethylaminopropyl)-carbodiimide hydrochloride (EDC) as the condensation agent there was obtained tert-butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-{4-[4-(2-trimethylsilyl-ethoxymethoxy)-benzoyloxymethyl]-phenyl}-piperidine-1-carboxylate; MS: 715 (M+NH₄)⁺.
- The 4-(2-trimethylsilyl-ethoxymethoxy)-benzoic acid was obtained as a colourless solid in an analogous manner to that described in Example 5 by reaction of methyl 4-hydroxybenzoate with 2-(trimethylsilyl)-ethoxymethyl chloride and subsequent basic saponification of the ester.
- (m) A solution of 57 mg (0.13 mmol) of tert-butyl (3RS,4RS)-4-(4-hydroxymethyl-phenyl)-3-(naphthalen-2-ylmethoxy)-

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piperidine-1-carboxylate, 20 mg (0.14 mmol) of pyridine-2-carbonyl azide [H.Saikachi and T.Kitgawa, Chem.Pharm.Bull. 25 (7), 1651-1657 (1977)] and 3 mg of 4-dimethylaminopyridine in 3 ml of toluene was heated to 90°C for 3 hours. Subsequently, the
5 toluene was evaporated under reduced pressure, the residue was taken up in 15 ml of methylene chloride and the solution was washed with 5 ml of water. The organic phase was thereafter dried over sodium sulphate and evaporated under reduced pressure. The oily residue was taken up with a mixture of ether
10 and hexane and crystallized. There were obtained 64 mg (88% of theory) of tert-butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-[4-(pyridin-2-ylcarbamoxyloxymethyl)-phenyl]-piperidine-1-carboxylate as a colourless solid; MS: 568 (M+H)⁺.

15 (n) A Schlenk tube was charged under argon with 25.6 mg (0.114 mmol) of Pd(OAc)₂, 69.6 mg (0.229 mmol) of tri(o-tolyl)phosphine and 20 ml of DMF (distilled under argon) and the reaction mixture was stirred at room temperature for 15 minutes. A 200 ml sulphonation flask was charged under
20 argon and while stirring with 8.15 g (22.9 mmol) of tert-butyl (3RS,4RS)-4-(4-bromo-phenyl)-3-hydroxy-piperidine-1-carboxylate [Example 25 (c)], 100 ml of DMF, 3.73 ml (34.3 mmol) of ethyl acrylate, 2.25 g (27.5 mmol) of sodium acetate and the yellow catalyst solution. The reaction mixture was stirred at
25 120°C for 6 hours. In order to complete the reaction, a solution of 5.1 mg Pd(OAc)₂ and 14.3 mg of tri(o-tolyl)phosphine in 5 ml of DMF was added after 5 hours. The dark reaction mixture was evaporated on a rotary evaporator. The grey solid residue was taken up in ether and the turbid solution was washed three times
30 with water, dried over sodium sulphate and evaporated under reduced pressure. The yellow solid residue was chromatographed on 250 g of silica gel using a 2:1 mixture of hexane and ethyl acetate as the eluent. After crystallization from ethyl acetate there were obtained 6.66 g (77% of theory) of tert-butyl
35 (3RS,4RS)-4-[4-(2-ethoxycarbonyl-vinyl)-phenyl]-3-hydroxy-piperidine-1-carboxylate as colourless crystals; MS: 376 (M+H)⁺.

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(o) Alkylation of tert-butyl (3RS,4RS)-4-[4-(2-ethoxycarbonyl-vinyl)-phenyl]-3-hydroxy-piperidine-1-carboxylate with 2-bromomethylnaphthalene analogously to the procedure described in Example 22(i) gave tert-butyl (3RS,4RS)-4-[4-(2-ethoxycarbonyl-vinyl)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a light yellow resin; MS: 516 (M+H)⁺.

(p) 5 ml (5 mmol) of a solution of diisobutylaluminium hydride (DIBAH) (1M in hexane) were added dropwise at -50°C to a solution of 698 mg (1.35 mmol) of tert-butyl (3RS,4RS)-4-[4-(2-ethoxycarbonyl-vinyl)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate in 15 ml of toluene and the mixture was stirred at -50°C for 30 minutes. Subsequently, the reaction mixture was treated dropwise at -50°C with 10 ml of ethanol and warmed to room temperature. For the working-up, the reaction mixture was treated with 20 ml of water and 20 ml of saturated potassium sodium tartrate solution while cooling with ice and thereafter extracted three times with 50 ml of ethyl acetate each time. The organic phases were combined, dried over sodium sulphate and evaporated under reduced pressure. The crude product was chromatographed on silica gel using a 6:4 mixture of hexane and ethyl acetate as the eluent. There were obtained 354 mg (55% of theory) of tert-butyl (3RS,4RS)-4-[4-(3-hydroxy-propenyl)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a colourless solid; MS: 474 (M+H)⁺.

(q) Acylation of tert-butyl (3RS,4RS)-4-[4-(3-hydroxy-propenyl)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate with benzoyl chloride analogously to the procedure described in Example 22(k) yielded tert-butyl (3RS,4RS)-4-[4-(3-benzoyloxy-propenyl)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a colourless resin; MS: 578 (M+H)⁺.

(r) A solution of 2.0 g (5.35 mmol) of tert-butyl (3RS,4RS)-4-[4-(2-ethoxycarbonyl-vinyl)-phenyl]-3-hydroxy-piperidine-1-carboxylate in 100 ml of ethanol was treated with 200 mg of palladium/charcoal (Type E101R) and hydrogenated at room temperature for 1 hour. Subsequently, the catalyst was filtered

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off and rinsed with ethanol. The filtrate was evaporated under reduced pressure and the light grey residue (1.97 g) was combined with those from three analogous hydrogenation batches (total 3.08 g). For purification, the crude product was chromatographed on silica gel using a 2:1 mixture of hexane and ethyl acetate as the eluent and thereafter crystallized from ethyl acetate/hexane. There were obtained 2.67 g (87% of theory) of tert-butyl (3RS,4RS)-4-[4-(2-ethoxycarbonyl-ethyl)-phenyl]-3-hydroxy-piperidine-1-carboxylate as colourless crystals;
10 MS: 378 (M+H)⁺.

(s) Analogously to the procedure described in Example 22(i), by alkylating tert-butyl (3RS,4RS)-4-[4-(2-ethoxycarbonyl-ethyl)-phenyl]-3-hydroxy-piperidine-1-carboxylic acid with 2-bromo-
15 methyl-naphthalene there was obtained tert-butyl (3RS,4RS)-4-[4-(2-ethoxycarbonyl-ethyl)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate; MS: 518 (M+H)⁺.

(t) Analogously to the procedure described in Example 22(e), by
20 reducing tert-butyl (3RS,4RS)-4-[4-(2-ethoxycarbonyl-ethyl)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate using lithium borohydride there was obtained tert-butyl (3RS,4RS)-4-[4-(3-hydroxy-propyl)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a colourless solid;
25 MS: 476 (M+H)⁺.

(u) Acylation of tert-butyl (3RS,4RS)-4-[4-(3-hydroxy-propyl)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate with 2-chloro-benzoyl chloride analogously to the procedure
30 described in Example 22(k) gave tert-butyl (3RS,4RS)-4-[4-[3-(2-chloro-benzoyloxy)-propyl]-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a colourless, amorphous solid;
MS: 614.6, 616 (M+H)⁺.

35

Example 25

(a) A mixture of 1.0 g (2.9 mmol) of (3RS,4RS)-1-benzyl-4-(4-bromo-phenyl)-piperidin-3-ol [Example 22(c)], 1.36 ml

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(10.2 mmol) of 2,2,2-trichloroethyl chloroformate and 0.90 g (12.6 mmol) of lithium carbonate in 20 ml of toluene was heated to 105°C for 18 hours. For the working-up, the cooled reaction mixture was poured into 200 ml of ice-water and subsequently
5 extracted three times with 25 ml of ethyl acetate each time. The combined organic phases were dried over sodium sulphate and evaporated under reduced pressure. For purification, the crude material obtained was chromatographed on silica gel using a 2:3 mixture of methylene chloride and hexane as the eluent. There
10 were obtained 1.3 g (76% of theory) of 2,2,2-trichloroethyl (3RS,4RS)-4-(4-bromo-phenyl)-3-(2,2,2-trichloro-ethoxy-carbonyloxy)-piperidine-1-carboxylate as a colourless solid; R_f: 0.17 (methylene chloride:hexane = 1:1), MS: 622, 624, 626 (M+NH₄)⁺.

15 (b) A mixture of 1.3 g (2.1 mmol) of 2,2,2-trichloroethyl (3RS,4RS)-4-(4-bromo-phenyl)-3-(2,2,2-trichloro-ethoxy-carbonyloxy)-piperidine-1-carboxylate 1.54 g of activated zinc in 20 ml of glacial acetic acid was stirred at room temperature
20 for 5 hours. For the working-up, the zinc was filtered off, the residue was rinsed with glacial acetic acid and the solution was subsequently evaporated to dryness under reduced pressure. The residue was partitioned between 20 ml of saturated sodium carbonate solution and 30 ml of ethyl acetate, thereafter the
25 separated aqueous phase was extracted twice with 30 ml of ethyl acetate each time. The combined organic phases were dried over sodium sulphate and evaporated under reduced pressure. Crystallization of the residue using a 1:2 mixture of ethyl acetate and hexane yielded 250 mg (46% of theory) of (3RS,4RS)-4-(4-
30 bromo-phenyl)-piperidin-3-ol as a colourless solid; MS: 255, 257 (M)⁺. The mother liquor was purified by chromatography on silica gel using a 4:1 mixture of methylene chloride and methanol as the eluent. A further 101 mg (18% of theory) were obtained.

35 (c) A solution of 351 mg (1.37 mmol) of (3RS,4RS)-4-(4-bromo-phenyl)-piperidin-3-ol in 12 ml of dimethylformamide was treated with 139 mg (1.37 mmol) of triethylamine and 300 mg (1.37 mg) of di-tert-butyl dicarbonate and the mixture

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was stirred at room temperature for 15 hours. Subsequently, the dimethylformamide was distilled off in an oil pump vacuum and the residue was crystallized from a 1:1 mixture of ether and hexane. There were obtained 318 mg (65% of theory) of tert-butyl (3RS,4RS)-4-(4-bromo-phenyl)-3-hydroxy-piperidine-1-carboxylate as a colourless solid ; MS: 299, 301 (M-C₄H₈)⁺.
Chromatography of the mother liquor on silica gel using a 98:2 mixture of methylene chloride and methanol as the eluent yielded a further 96 mg (19% of theory) of the product.

10

(d) In an analogous manner to that described in Example 22(d), by carbonylating tert-butyl (3RS,4RS)-4-(4-bromo-phenyl)-3-hydroxy-piperidine-1-carboxylate using PdCl₂(CH₃CN)₂ and 1,3-bis(diphenylphosphino)-propane as the catalyst in the presence of triethylamine under 10 bar of carbon monoxide at 100°C for 40 hours there was obtained tert-butyl (3RS,4RS)-3-hydroxy-4-(4-methoxycarbonyl-phenyl)-piperidine-1-carboxylate as white crystals; m.p.: 145.5-146°C, MS: 279 (M-C₄H₈)⁺.

(e) In an analogous manner to that described in Example 22(i), by alkylating tert-butyl (3RS,4RS)-3-hydroxy-4-(4-methoxycarbonyl-phenyl)-piperidine-1-carboxylate with 2-bromomethylnaphthalene there was obtained tert-butyl (3RS,4RS)-4-(4-methoxycarbonyl-phenyl)-3-naphthalen-2-ylmethoxy-piperidine-1-carboxylate as a colourless oil; MS: 476 (M+H)⁺.

(f) In an analogous manner to that described in Example 22(l), after cleavage of the BOC group from tert-butyl (3RS,4RS)-4-(4-methoxycarbonyl-phenyl)-3-naphthalen-2-ylmethoxy-piperidine-1-carboxylate there was obtained methyl (3RS,4RS)-4-(3-naphthalen-2-ylmethoxy-piperidin-4-yl)-benzoate hydrochloride as a colourless solid; MS: 344 (M-OCH₃)⁺.

Example 26

35

The following compounds were obtained in an analogous manner to that described in Example 22(l) by cleavage of the BOC group:

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- 1) - (3RS,4RS)-[3-[3-(4-Benzyloxy-naphthalen-2-ylmethoxy)-piperidin-4-yl]-phenyl}-methanol as a colourless amorphous powder, MS: 454 (M+H)⁺, from tert-butyl (3RS,4RS)-3-(4-benzyl-
5 oxy-naphthalen-2-ylmethoxy)-4-(3-hydroxymethyl-phenyl)-piperidine-1-carboxylate;
- 2) - (3RS,4RS)-3-(3-naphthalen-2-ylmethoxy-piperidin-4-yl)-benzyl benzoate hydrochloride as a colourless solid, MS: 452
10 (M+H)⁺, from tert-butyl (3RS,4RS)-4-(3-benzoyloxymethyl-phenyl)-3-naphthalen-2-ylmethoxy-piperidine-1-carboxylate.

The BOC derivatives used as the starting materials were obtained as follows:

15

- (a) In an analogous manner to that described in Example 22(a)-(d), starting from 3-bromophenyllithium and 1-benzyl-4-piperidone there was obtained methyl (3RS,4RS)-3-(1-benzyl-3-hydroxy-piperidin-4-yl)-benzoate as a light yellow resin; MS: 325
20 (M)⁺.

- (b) The benzyl group was cleaved off from methyl (3RS,4RS)-3-(1-benzyl-3-hydroxy-piperidin-4-yl)-benzoate by catalytic hydrogenation in an analogous manner to that described in
25 Example 2(e). The methyl (3RS,4RS)-3-(3-hydroxy-piperidine-4-yl)-benzoate was converted, without further purification and characterization, with di-tert-butyl dicarbonate analogously to Example 22(g) into tert-butyl (3RS,4RS)-3-hydroxy-4-(3-methoxycarbonyl-phenyl)-piperidine-1-carboxylate, MS: 304 (M-
30 OCH₃)⁺.

- (c) In an analogous manner to that described in Example 22(i), by alkylating tert-butyl (3RS,4RS)-3-hydroxy-4-(3-methoxycarbonyl-phenyl)-piperidine-1-carboxylate with 1-benzyloxy-3-chloromethylnaphthalene there was obtained tert-butyl
35 (3RS,4RS)-3-(4-benzyloxy-naphthalen-2-ylmethoxy)-4-(3-methoxycarbonyl-phenyl)-piperidine-1-carboxylate as a pale yellow amorphous powder; MS: 582 (M+H)⁺.

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- (d) In an analogous manner to that described in Example 22(e), by reducing tert-butyl (3RS,4RS)-3-(4-benzyloxy-naphthalen-2-ylmethoxy)-4-(3-methoxycarbonyl-phenyl)-piperidine-1-carboxylate with lithium borohydride there was obtained tert-butyl (3RS,4RS)-3-(4-benzyloxy-naphthalen-2-ylmethoxy)-4-(3-hydroxymethyl-phenyl)-piperidine-1-carboxylate as a colourless solid; MS: 554 (M+H)⁺.
- (e) In an analogous manner to that described in Example 22(i), by alkylating tert-butyl (3RS,4RS)-3-hydroxy-4-(3-methoxycarbonyl-phenyl)-piperidine-1-carboxylate with 2-bromomethyl-naphthalene there was obtained tert-butyl (3RS,4RS)-4-(3-methoxycarbonyl-phenyl)-3-naphthalen-2-ylmethoxy-piperidine-1-carboxylate as a colourless oil; MS: 493 (M+NH₄)⁺.
- (f) In an analogous manner to that described in Example 22(e), by reducing tert-butyl (3RS,4RS)-4-(3-methoxycarbonyl-phenyl)-3-naphthalen-2-ylmethoxy-piperidine-1-carboxylate with lithium borohydride there was obtained tert-butyl 4-(3-hydroxymethyl-phenyl)-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a colourless oil; MS: 448 (M+H)⁺.
- (g) In an analogous manner to that described in Example 22(k), by acylating tert-butyl (3RS,4RS)-4-(3-hydroxymethyl-phenyl)-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate with benzoyl chloride there was obtained tert-butyl (3RS,4RS)-4-(3-benzoyloxymethyl-phenyl)-3-naphthalen-2-ylmethoxy-piperidine-1-carboxylate as a colourless oil; MS: 569 (M+NH₄)⁺.

Example 27

The following compounds were obtained in an analogous manner to that described in Example 22(l) by cleavage of the BOC group:

- 1) - Methyl (3RS,4RS)-3-[3-(4-benzyloxy-naphthalen-2-ylmethoxy)-piperidin-4-yl]-benzoate as a colourless amorphous

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powder, MS: 482 (M+H)⁺, from tert-butyl (3RS,4RS)-3-(4-benzyloxy-naphthalen-2-ylmethoxy)-4-(3-methoxycarbonyl-phenyl)-piperidine-1-carboxylate;

- 5 2) - methyl (3RS,4RS)-3-[3-(naphthalen-2-ylmethoxy)-piperidin-4-yl]-benzoate as a colourless oil, MS: 376 (M+H)⁺, from tert-butyl (3RS,4RS)-4-(3-methoxycarbonyl-phenyl)-3-naphthalen-2-ylmethoxy-piperidine-1-carboxylate.

10 Example 28

By cleavage of the BOC group from 57 mg of crude tert-butyl (3RS,4RS)-3-(4-benzyloxy-naphthalen-2-ylmethoxy)-4-(3-fluoromethyl-phenyl)-piperidine-1-carboxylate in an analogous
15 manner to that described in Example 22 there was obtained (3RS,4RS)-3-(4-benzyloxy-naphthalen-2-ylmethoxy)-4-(3-fluoromethyl-phenyl)-piperidine as a light yellow resin; MS: 456 (M+H)⁺.

20 The tert-butyl (3RS,4RS)-3-(4-benzyloxy-naphthalen-2-ylmethoxy)-4-(3-fluoromethyl-phenyl)-piperidine-1-carboxylate used as the starting material was prepared as follows:

A solution of 18 mg (0.106 mmol) of diethylamino-sulphur
25 trifluoride (DAST) in 1 ml of methylene chloride was cooled to -65°C and a solution of 56 mg (0.101 mmol) of tert-butyl (3RS,4RS)-3-(4-benzyloxy-naphthalen-2-ylmethoxy)-4-(3-hydroxymethyl-phenyl)-piperidine-1-carboxylate in 1 ml of methylene chloride was added dropwise thereto at -60°C to
30 -65°C within 3 minutes. The resulting yellow solution was warmed to room temperature and stirred for one hour. Subsequently, the mixture was partitioned between methylene chloride and 5% sodium hydrogen carbonate solution, the organic phase was dried over magnesium sulphate and finally the solvent
35 was distilled off under reduced pressure. There were obtained 57 mg of crude tert-butyl (3RS,4RS)-3-(4-benzyloxy-naphthalen-2-ylmethoxy)-4-(3-fluoromethyl-phenyl)-piperidine-

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1-carboxylate, which was used in the next step without further purification and characterization.

Example 29

5

(a) In an analogous manner to that described in Example 22(a), starting from 1-benzyl-4-piperidone and 2-[2-(4-bromo-phenyl)-ethoxy]-tetrahydropyran there was obtained (RS)-1-benzyl-4-[4-[2-(tetrahydro-pyran-2-yloxy)-ethyl]-phenyl]-piperidin-4-ol as a
10 yellow oil; MS: 396 (M+H)⁺.

(b) A solution of 78 g (197 mmol) of (RS)-1-benzyl-4-[4-[2-(tetrahydro-pyran-2-yloxy)-ethyl]-phenyl]-piperidin-4-ol in 400 ml of methanol was treated with 470 ml of 2N hydrochloric
15 acid and stirred at room temperature for 5 hours. For the working-up, the reaction solution was poured into 1500 ml of saturated sodium hydrogen carbonate solution and subsequently extracted three times with 1000 ml of ethyl acetate each time. The combined organic phases were dried over sodium sulphate and
20 evaporated under reduced pressure. For purification of the crude substance, a flash chromatography on silica gel using a 95:5 mixture of methylene chloride and methanol as the eluent was carried out. There were obtained 51.6 g (84% of theory) of 1-benzyl-4-[4-(2-hydroxy-ethyl)-phenyl]-piperidin-4-ol as a
25 yellowish solid; MS: 312 (M+H)⁺.

(c) In an analogous manner to that described in Example 22(b), by an elimination reaction from 1-benzyl-4-[4-(2-hydroxy-ethyl)-phenyl]-piperidin-4-ol using p-toluenesulphonic acid there
30 was obtained 2-[4-(1-benzyl-1,2,3,6-tetrahydro-pyridin-4-yl)-phenyl]-ethanol as a colourless oil; MS: 293 (M)⁺.

(d) In an analogous manner to that described in Example 22(c), from 2-[4-(1-benzyl-1,2,3,6-tetrahydro-pyridin-4-yl)-phenyl]-
35 ethanol by hydroboration there was obtained (3RS,4RS)-1-benzyl-4-[4-(2-hydroxy-ethyl)-phenyl]-piperidin-3-ol as a colourless oil; MS: 311 (M)⁺.

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- (e) In an analogous manner to that described in Example 2(e) and Example 22(g), by catalytically hydrogenating (3RS,4RS)-1-benzyl-4-[4-(2-hydroxy-ethyl)-phenyl]-piperidin-3-ol there was obtained (3RS,4RS)-4-[4-(2-hydroxy-ethyl)-phenyl]-piperidin-3-ol, which, without further purification and characterization, was converted with di-tert-butyl dicarbonate into tert-butyl (3RS,4RS)-3-hydroxy-4-[4-(2-hydroxy-ethyl)-phenyl]-piperidine-1-carboxylate; colourless oil, MS: 322 (M+H)⁺.
- 10 (f) In an analogous manner to that described in Example 22(h), from tert-butyl (3RS,4RS)-3-hydroxy-4-[4-(2-hydroxy-ethyl)-phenyl]-piperidine-1-carboxylate by introduction of the trityl group there was obtained tert-butyl (3RS,4RS)-3-hydroxy-4-[4-(2-trityloxy-ethyl)-phenyl]-piperidine-1-carboxylate as a colourless foam; MS: 581 (M+NH₄)⁺.
- 15 (g) In an analogous manner to that described in Example 22(i), from tert-butyl (3RS,4RS)-3-hydroxy-4-[4-(2-trityloxy-ethyl)-phenyl]-piperidine-1-carboxylate by alkylation with 2-bromo-methylnaphthalene there was obtained tert-butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-[4-(2-trityloxy-ethyl)-phenyl]-piperidine-1-carboxylate as a colourless oil; MS: 721 (M+H)⁺.
- 20 (h) In an analogous manner to that described in Example 22(j), from tert-butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-[4-(2-trityloxy-ethyl)-phenyl]-piperidine-1-carboxylate by cleavage of the trityl group there was obtained tert-butyl (3RS,4RS)-4-[4-(2-hydroxy-ethyl)-phenyl]-3-naphthalen-2-ylmethoxy-piperidine-1-carboxylate as a colourless solid; MS: 462 (M+H)⁺.
- 30 (i) In an analogous manner to that described in Example 22(k), by acylating tert-butyl (3RS,4RS)-4-[4-(2-hydroxy-ethyl)-phenyl]-3-naphthalen-2-ylmethoxy-piperidine-1-carboxylate with cyclopropanecarbonyl chloride there was obtained tert-butyl (3RS,4RS)-4-[4-(2-cyclopropylcarbonyloxy-ethyl)-phenyl]-3-naphthalen-2-ylmethoxy-piperidine-1-carboxylate as a colourless oil; MS: 572 (M+H)⁺.
- 35

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(j) In an analogous manner to that described in Example 22(I), by cleavage of the BOC group from tert-butyl (3RS,4RS)-4-[4-(2-cyclopropylcarbonyloxy-ethyl)-phenyl]-3-naphthalen-2-ylmethoxy-piperidine-1-carboxylate using trifluoroacetic acid in methylene chloride there was obtained (3RS,4RS)-2-[4-(3-naphthalen-2-ylmethoxy-piperidin-4-yl)-phenyl]-ethyl cyclopropanecarboxylate trifluoroacetate as a white solid; MS: 430 (M+H)⁺.

10

Example 30

The following compound was obtained in an analogous manner to that described in Example 23 by simultaneous cleavage of the BOC and trityl groups:

15

- (3RS,4RS)-2-{4-[3-(naphthalen-2-ylmethoxy)-piperidin-4-yl]-phenyl}-ethanol hydrochloride as a white powder, MS: 362 (M+H)⁺, from tert-butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-[4-(2-trityloxy-ethyl)-phenyl]-piperidine-1-carboxylate.

20

Example 31

The following compounds were obtained in an analogous manner to that in Example 22 (I) by cleavage of the BOC group using acid:

25

1) - (3RS,4RS)-2-[4-(3-Naphthalen-2-ylmethoxy-piperidin-4-yl)-phenyl]-ethyl benzoate hydrochloride as a white solid, MS: 466 (M+H)⁺, from tert-butyl (3RS,4RS)-4-[4-(2-benzoyloxy-ethyl)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate;

30

2) - (3RS,4RS)-2-[4-(3-naphthalen-2-ylmethoxy-piperidin-4-yl)-phenyl]-ethyl 3-methoxy-benzoate hydrochloride as a colourless oil, MS: 496 (M+H)⁺, from tert-butyl (3RS,4RS)-4-{4-[2-(3-methoxy-benzoyloxy)-ethyl]-phenyl}-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate;

35

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- 3) - (3RS,4RS)-2-[4-(3-naphthalen-2-ylmethoxy-piperidin-4-yl)-phenyl]-ethyl 2-methoxy-benzoate hydrochloride as a colourless solid, MS: 496 (M+H)⁺, from tert-butyl (3RS,4RS)-4-{4-[2-(2-methoxy-benzoyloxy)-ethyl]-phenyl}-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate;
5
- 4) - (3RS,4RS)-2-[4-(3-naphthalen-2-ylmethoxy-piperidin-4-yl)-phenyl]-ethyl benzyloxy-acetate hydrochloride as a colourless solid, MS: 510 (M+H)⁺, from tert-butyl (3RS,4RS)-4-[4-(2-benzyloxyacetoxy-ethyl)-phenyl]-3-naphthalen-2-ylmethoxy-piperidine-1-carboxylate;
10
- 5) - (3RS,4RS)-2-[4-(3-naphthalen-2-yl-methoxy)-piperidin-4-yl]-phenyl]-ethyl (4-methoxy-phenyl)-acetate trifluoroacetate as a colourless solid, MS: 510 (M+H)⁺, from tert-butyl (3RS,4RS)-4-[4-[2-[(4-methoxy-phenyl)-acetoxy]-ethyl]-phenyl]-3-naphthalen-2-ylmethoxy-piperidine-1-carboxylate using trifluoroacetic acid in methylene chloride;
15
- 6) - (3RS,4RS)-2-[4-(3-naphthalen-2-ylmethoxy-piperidin-4-yl)-phenyl]-ethyl cyclohexanecarboxylate trifluoroacetate as a colourless solid, MS: 472 (M+H)⁺, from tert-butyl (3RS,4RS)-4-[4-(2-cyclohexylcarbonyloxy-ethyl)-phenyl]-3-naphthalen-2-ylmethoxy-piperidine-1-carboxylate using trifluoroacetic acid in methylene chloride;
20
25
- 7) - (3RS,4RS)-2-[4-(3-naphthalen-2-ylmethoxy-piperidin-4-yl)-phenyl]-ethyl 2,6-dichloro-benzoate trifluoroacetate as a colourless solid (sic), MS: 534 (M+H)⁺, from tert-butyl (3RS,4RS)-4-{4-[2-(2,6-dichloro-benzoyloxy)-ethyl]-phenyl}-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate using trifluoroacetic acid in methylene chloride;
30
- 8) - (3RS,4RS)-2-[4-(3-naphthalen-2-ylmethoxy-piperidin-4-yl)-phenyl]-ethyl 2,6-dimethoxy-benzoate trifluoroacetate as a colourless solid, MS: 526 (M+H)⁺, from tert-butyl (3RS,4RS)-4-[4-[2-(2,6-dimethoxy-benzoyloxy)-ethyl]-phenyl]-3-naphthalen-
35

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2-ylmethoxy-piperidine-1-carboxylate using trifluoroacetic acid in methylene chloride;

9) - (3RS,4RS)-2-[4-(3-naphthalen-2-ylmethoxy-piperidin-4-yl)-phenyl]-ethyl 2-acetoxy-benzoate trifluoroacetate as a colourless solid, MS: 524 (M+H)⁺, from tert-butyl (3RS,4RS)-[4-[4-[2-(2-acetoxy-benzoyloxy)-ethyl]-phenyl]-3-naphthalen-2-ylmethoxy-piperidine]-1-carboxylate using trifluoroacetic acid in methylene chloride;

10

10) - (3RS,4RS)-2-[4-(3-naphthalen-2-ylmethoxy-piperidin-4-yl)-phenyl]-ethyl 2-chloro-benzoate trifluoroacetate as a colourless solid, MS: 500 (M+H)⁺, from tert-butyl (3RS,4RS)-[4-[2-(2-chloro-benzoyloxy)-ethyl]-phenyl]-3-naphthalen-2-ylmethoxy-piperidine-1-carboxylate using trifluoroacetic acid in methylene chloride;

11) - (3RS,4RS)-2-[4-(3-naphthalen-2-ylmethoxy-piperidin-4-yl)-phenyl]-ethyl pyridin-2-yl-carbamate hydrochloride as a colourless foam, MS: 482 (M+H)⁺, from tert-butyl (3RS,4RS)-3-naphthalen-2-ylmethoxy-4-[4-(2-pyridin-2-ylcarbamoxyloxy-ethyl)-phenyl]-piperidine-1-carboxylate;

12) - (3RS,4RS)-2-[4-(3-naphthalen-2-ylmethoxy-piperidin-4-yl)-phenyl]-ethyl phenyl-carbamate hydrochloride as a colourless solid, MS: 598 (M+H)⁺, from tert-butyl (3RS,4RS)-3-naphthalen-2-ylmethoxy-4-[4-(2-phenylcarbamoxyloxy-ethyl)-phenyl]-piperidine-1-carboxylate;

13) - (3RS,4SR)-2-[4-(3-naphthalen-2-ylmethoxy-piperidin-4-yl)-phenyl]-ethyl pyridine-3-carboxylate hydrochloride as a colourless solid, MS: 467 (M+H)⁺, from tert-butyl (3RS,4RS)-3-naphthalen-2-ylmethoxy-4-[4-(2-pyridin-3-ylcarbonyloxy-ethyl)-phenyl]-piperidine-1-carboxylate;

35

14) - (3RS,4RS)-2-[4-(3-naphthalen-2-ylmethoxy-piperidin-4-yl)-phenyl]-ethyl pyridine-2-carboxylate as a colourless oil, MS: 467 (M+H)⁺, from 2-{4-[1-tert-butoxycarbonyl-3-

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(naphthalen-2-ylmethoxy)-piperidin-4-yl]-phenyl}-ethyl
(3RS,4RS)-pyridine-2-carboxylate;

15) - (3RS,4RS)-2-[4-(3-naphthalen-2-ylmethoxy-piperidin-4-yl)-phenyl]-ethyl thiophene-3-carboxylate trifluoroacetate as a
5 colourless solid, MS: 472 (M+H)⁺, from tert-butyl (3RS,4RS)-3-naphthalen-2-ylmethoxy-4-[4-(2-thiophen-3-ylcarbonyloxy-ethyl)-phenyl]-piperidine-1-carboxylate using trifluoroacetic acid in methylene chloride;

10

16) - (3RS,4RS)-2-[4-(3-naphthalen-2-ylmethoxy-piperidin-4-yl)-phenyl]-ethyl thiophen-2-ylacetate trifluoroacetate as a
colourless solid, MS: 486 (M+H)⁺, from tert-butyl (3RS,4RS)-3-naphthalen-2-ylmethoxy-4-[4-(2-thiophen-3-ylacetoxo-ethyl)-
15 phenyl]-piperidine-1-carboxylate using trifluoroacetic acid in methylene chloride;

17) - (3RS,4RS)-2-[4-(3-naphthalen-2-ylmethoxy-piperidin-4-yl)-phenyl]-ethyl imidazole-2-carboxylate trifluoroacetate as a
20 colourless solid, MS: 456 (M+H)⁺, from tert-butyl (3RS,4RS)-4-[4-(2-imidazol-2-ylcarbonyloxy-ethyl)-phenyl]-3-naphthalen-2-ylmethoxy]-piperidine-1-carboxylate using trifluoroacetic acid in methylene chloride;

25 18) - (3RS,4RS)-2-[4-[3-(4-benzyloxy-naphthalen-2-yl-methoxy)-piperidin-4-yl]-phenyl]-ethyl benzoate hydrochloride as a yellowish solid, MS: 572 (M+H)⁺, from tert-butyl (3RS,4RS)-4-[4-(2-benzyloxy-ethyl)-phenyl]-3-(4-benzyloxy-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate.

30

The following starting materials were obtained analogously to the procedure described in Example 22 (k):

(a) tert-Butyl (3RS,4RS)-4-[4-(2-benzoyloxy-ethyl)-phenyl]-3-
35 (naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a colourless oil, MS: 583 (M+NH₄)⁺, from tert-butyl (3RS,4RS)-4-[4-(2-hydroxy-ethyl)-phenyl]-3-naphthalen-2-ylmethoxy-piperidine-1-carboxylate and benzoyl chloride;

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- (b) tert-butyl (3RS,4RS)-4-{4-[2-(3-methoxy-benzoyloxy)-ethyl]-phenyl}-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a colourless oil, MS: 593 (M+H)⁺, from tert-butyl (3RS,4RS)-4-[4-(2-hydroxy-ethyl)-phenyl]-3-naphthalen-2-ylmethoxy-piperidine-1-carboxylate and 3-methoxybenzoyl chloride;
- (c) tert-butyl (3RS,4RS)-4-{4-[2-(2-methoxy-benzoyloxy)-ethyl]-phenyl}-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a colourless oil, R_f : 0.35 (SiO₂, hexane:ethyl acetate = 2:1), from tert-butyl (3RS,4RS)-4-[4-(2-hydroxy-ethyl)-phenyl]-3-naphthalen-2-ylmethoxy-piperidine-1-carboxylate and 2-methoxybenzoyl chloride;
- (d) tert-butyl (3RS,4RS)-4-[4-(2-benzyloxyacetoxy-ethyl)-phenyl]-3-naphthalen-2-ylmethoxy-piperidine-1-carboxylate as a colourless oil, MS: 627 (M+NH₄)⁺, from tert-butyl (3RS,4RS)-4-[4-(2-hydroxy-ethyl)-phenyl]-3-naphthalen-2-ylmethoxy-piperidine-1-carboxylate and benzyloxyacetyl chloride;
- (e) tert-butyl (3RS,4RS)-4-[4-[2-[(4-methoxy-phenyl)-acetoxy]-ethyl]-phenyl]-3-naphthalen-2-ylmethoxy-piperidine-1-carboxylate as a colourless oil, MS: 627 (M+NH₄)⁺, from tert-butyl (3RS,4RS)-4-[4-(2-hydroxy-ethyl)-phenyl]-3-naphthalen-2-ylmethoxy-piperidine-1-carboxylate and 4-methoxyphenylacetyl chloride;
- (f) tert-butyl (3RS,4RS)-4-[4-(2-cyclohexylcarbonyloxy-ethyl)-phenyl]-3-naphthalen-2-ylmethoxy-piperidine-1-carboxylate as a colourless oil, MS: 572 (M+H)⁺, from tert-butyl (3RS,4RS)-4-[4-(2-hydroxy-ethyl)-phenyl]-3-naphthalen-2-ylmethoxy-piperidine-1-carboxylate and cyclohexanecarbonyl chloride;
- (g) tert-butyl (3RS,4RS)-4-{4-[2-(2,6-dichloro-benzoyloxy)-ethyl]-phenyl}-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a colourless oil, MS: 651 (M+NH₄)⁺, from tert-

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butyl (3RS,4RS)-4-[4-(2-hydroxy-ethyl)-phenyl]-3-naphthalen-2-ylmethoxy-piperidine-1-carboxylate and 2,6-dichlorobenzoyl chloride;

5 (h) tert-butyl (3RS,4RS)-4-[4-[2-(2,6-dimethoxy-benzoyloxy)-ethyl]-phenyl]-3-naphthalen-2-ylmethoxy-piperidine-1-carboxylate as a colourless amorphous solid, MS: 643 (M+NH₄)⁺, from tert-butyl (3RS,4RS)-4-[4-(2-hydroxy-ethyl)-phenyl]-3-naphthalen-2-ylmethoxy-piperidine-1-carboxylate and 2,6-dimethoxybenzoyl
10 chloride;

(i) tert-butyl (3RS,4RS)-[4-[4-[2-(2-acetoxy-benzoyloxy)-ethyl]-phenyl]-3-naphthalen-2-ylmethoxy-piperidine]-1-carboxylate as a colourless oil, MS: 641 (M+NH₄)⁺, from tert-
15 butyl (3RS,4RS)-4-[4-(2-hydroxy-ethyl)-phenyl]-3-naphthalen-2-ylmethoxy-piperidine-1-carboxylate and O-acetylsalicyloyl chloride;

(j) tert-butyl (3RS,4RS)-[4-[2-(2-chloro-benzoyloxy)-ethyl]-phenyl]-3-naphthalen-2-ylmethoxy-piperidine-1-carboxylate as a
20 colourless oil, MS: 617 (M+NH₄)⁺; from tert-butyl (3RS,4RS)-4-[4-(2-hydroxy-ethyl)-phenyl]-3-naphthalen-2-ylmethoxy-piperidine-1-carboxylate and 2-chlorobenzoyl chloride;

25 (k) In an analogous manner to that described in Example 24(m), by reacting tert-butyl (3RS,4RS)-4-[4-(2-hydroxy-ethyl)-phenyl]-3-naphthalen-2-ylmethoxy-piperidine-1-carboxylate with pyridine-2-carbonyl azide there was obtained tert-butyl (3RS,4RS)-3-naphthalen-2-ylmethoxy-4-[4-(2-pyridin-2-ylcarbamoyloxy-ethyl)-phenyl]-piperidine-1-carboxylate as
30 colourless crystals, MS: 582 (M+H)⁺.

(l) In an analogous manner to that described in Example 24(m), by reacting tert-butyl (3RS,4RS)-4-[4-(2-hydroxy-ethyl)-
35 phenyl]-3-naphthalen-2-ylmethoxy-piperidine-1-carboxylate with phenyl isocyanate there was obtained tert-butyl (3RS,4RS)-3-naphthalen-2-ylmethoxy-4-[4-(2-phenylcarbamoyloxy-ethyl)-

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phenyl]-piperidine-1-carboxylate as a colourless oil, MS: 481 (M+H)⁺.

(m) In an analogous manner to that described in Example 24(g),
5 by condensing tert-butyl (3RS,4RS)-4-[4-(2-hydroxy-ethyl)-phenyl]-3-naphthalen-2-ylmethoxy-piperidine-1-carboxylate and nicotinic acid there was obtained tert-butyl (3RS,4RS)-3-naphthalen-2-ylmethoxy-4-[4-(2-pyridin-3-ylcarbonyloxy-ethyl)-phenyl]-piperidine-1-carboxylate as a colourless oil,
10 MS: 567 (M+H)⁺.

(n) In an analogous manner to that described in Example 24(g),
by condensing tert-butyl (3RS,4RS)-4-[4-(2-hydroxy-ethyl)-phenyl]-3-naphthalen-2-ylmethoxy-piperidine-1-carboxylate and
15 pyridine-2-carboxylic acid using 1,1-carbonyldiimidazole as the condensation agent there was obtained 2-{4-[1-tert-butoxycarbonyl-3-(naphthalen-2-ylmethoxy)-piperidin-4-yl]-phenyl}-ethyl (3RS,4RS)-pyridine-2-carboxylate as a colourless oil,
MS: 467 (M+H)⁺.

20

(o) In an analogous manner to that described in Example 24(g),
by condensing tert-butyl (3RS,4RS)-4-[4-(2-hydroxy-ethyl)-phenyl]-3-naphthalen-2-ylmethoxy-piperidine-1-carboxylate and
thiophene-3-carboxylic acid using 1,1-carbonyldiimidazole as the
25 condensation agent there was obtained tert-butyl (3RS,4RS)-3-naphthalen-2-ylmethoxy-4-[4-(2-thiophen-3-ylcarbonyloxy-ethyl)-phenyl]-piperidine-1-carboxylate as white crystals,
MS: 572 (M+H)⁺.

(p) In an analogous manner to that described in Example 24(g),
by condensing tert-butyl (3RS,4RS)-4-[4-(2-hydroxy-ethyl)-phenyl]-3-naphthalen-2-ylmethoxy-piperidine-1-carboxylate and
3-thiopheneacetic acid using 1,1-carbonyldiimidazole as the
condensation agent there was obtained tert-butyl (3RS,4RS)-3-
35 naphthalen-2-ylmethoxy-4-[4-(2-thiophen-3-ylacetoxymethyl)-phenyl]-piperidine-1-carboxylate as a colourless solid, MS: 603 (M+NH₄)⁺.

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(q) In an analogous manner to that described in Example 24(g), by condensing tert-butyl (3RS,4RS)-4-[4-(2-hydroxy-ethyl)-phenyl]-3-naphthalen-2-ylmethoxy-piperidine-1-carboxylate and imidazole-2-carboxylic acid using 1,1-carbonyldiimidazole as the
5 condensation agent there was obtained tert-butyl (3RS,4RS)-4-[4-(2-imidazol-2-ylcarbonyloxy-ethyl)-phenyl]-3-naphthalen-2-ylmethoxy-piperidine-1-carboxylate as a colourless solid, MS: 556 (M+H)⁺.

10 The following procedure was carried out in an analogous manner to that described in Example 22(i)-(k):

(r) Alkylation of tert-butyl (3RS,4RS)-3-hydroxy-4-[4-(2-trityloxy-ethyl)-phenyl]-piperidine-1-carboxylate with 1-
15 benzyloxy-3-chloromethyl-naphthalene gave tert-butyl (3RS,4RS)-3-(4-benzyloxy-naphthalen-2-ylmethoxy)-4-[4-(2-trityloxy-ethyl)-phenyl]-piperidine-1-carboxylate as a colourless oil, MS: 827 (M+NH₄)⁺.

20 (s) Cleavage of the trityl group from tert-butyl (3RS,4RS)-3-(4-benzyloxy-naphthalen-2-ylmethoxy)-4-[4-(2-trityloxy-ethyl)-phenyl]-piperidine-1-carboxylate yielded tert-butyl (3RS,4RS)-3-(4-benzyloxy-naphthalen-2-ylmethoxy)-4-[4-(2-hydroxy-ethyl)-phenyl]-piperidine-1-carboxylate as a colourless oil, MS: 568
25 (M+H)⁺.

(t) Acylation of tert-butyl (3RS,4RS)-3-(4-benzyloxy-naphthalen-2-ylmethoxy)-4-[4-(2-hydroxy-ethyl)-phenyl]-piperidine-1-carboxylate with benzoyl chloride gave (3RS,4RS)-
30 4-[4-(2-benzyloxy-ethyl)-phenyl]-3-(4-benzyloxy-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a colourless oil, MS: 689 (M+NH₄)⁺.

Example 32

35

The following compounds were obtained in an analogous manner to that described in Example 22(l) by cleavage of the BOC group using acid:

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1) - (3RS,4RS)-3-Naphthalen-2-ylmethoxy-4-(4-naphthalen-2-ylmethoxymethyl-phenyl)-piperidine hydrochloride as a colourless solid, MS: 488 (M+H)⁺, from tert-butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-[4-(naphthalen-2-ylmethoxymethyl)-phenyl]-piperidine-1-carboxylate;

2) - (3RS,4RS)-4-[4-(4-methoxy-phenoxy-methyl)-phenyl]-3-naphthalen-2-ylmethoxy-piperidine as a yellow foam, MS: 454 (M+H)⁺, from tert-butyl (3RS,4RS)-4-[4-(4-methoxy-phenoxy-methyl)-phenyl]-3-naphthalen-2-ylmethoxy-piperidine-1-carboxylate;

3) - (3RS,4RS)-3-(1-methoxy-naphthalen-2-ylmethoxy)-4-[4-(2-phenoxy-ethyl)-phenyl]-piperidine trifluoroacetate as a colourless oil, MS: 468 (M+H)⁺, from tert-butyl (3RS,4RS)-3-(1-methoxy-naphthalen-2-ylmethoxy)-4-[4-(2-phenoxy-ethyl)-phenyl]-piperidine-1-carboxylate using trifluoroacetic acid in methylene chloride;

4) - (3RS,4RS)-4-[4-(2-methoxy-ethyl)-phenyl]-3-naphthalen-2-ylmethoxy]-piperidine as a colourless solid, MS: 376 (M+H)⁺, from tert-butyl (3RS,4RS)-4-[4-(2-methoxy-ethyl)-phenyl]-3-naphthalen-2-ylmethoxy]-piperidine-1-carboxylate.

25

The BOC derivatives use as the starting materials were prepared as follows:

(a) In an analogous manner to that described in Example 22(i), by alkylating tert-butyl (3RS,4RS)-3-hydroxy-4-(4-hydroxymethyl-phenyl)-piperidine-1-carboxylate with 2-bromomethylnaphthalene there was obtained tert-butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-[4-(naphthalen-2-ylmethoxymethyl)-phenyl]-piperidine-1-carboxylate as a colourless oil, R_f: 0.31 (SiO₂, hexane:ethyl acetate = 2:1).

35

b) A solution of 200 mg (0.45 mmol) of tert-butyl (3RS,4RS)-4-(4-hydroxymethyl-phenyl)-3-(naphthalen-2-ylmethoxy)-

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piperidine-1-carboxylate in 10 ml of tetrahydrofuran was treated in sequence with 143 mg (0.58 mmol) of triphenylphosphine, 94 mg (0.58 mmol) of diethylazo dicarboxylate and 166 mg (1.35 mmol) of hydroquinone monomethyl ether and the reaction mixture was stirred at room temperature for 15 hours. For the working-up, the reaction mixture was diluted with 20 ml of methylene chloride and extracted with 20 ml of saturated sodium carbonate solution. The organic phase was dried over sodium sulphate and evaporated under reduced pressure. For purification, the crude product was chromatographed on silica gel using methylene chloride as the eluent. There were obtained 245 mg of colourless oil which contained tert-butyl (3RS,4RS)-4-(4-hydroxymethyl-phenyl)-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate in addition to tert-butyl (3RS,4RS)-4-[4-(4-methoxy-phenoxy-methyl)-phenyl]-3-naphthalen-2-ylmethoxy-piperidine-1-carboxylate, R_f: 0.08 (methylene chloride).

The following procedure was carried out in an analogous manner to that described in Example 22(i)-(j):

20

(c) Alkylation of tert-butyl (3RS,4RS)-3-hydroxy-4-[4-(2-trityloxy-ethyl)-phenyl]-piperidine-1-carboxylate with 2-bromomethyl-1-methoxy-naphthalene gave tert-butyl (3RS,4RS)-3-(1-methoxy-naphthalen-2-ylmethoxy)-4-[4-(2-trityloxy-ethyl)-phenyl]-piperidine-1-carboxylate from which, after cleavage of the trityl group there was obtained tert-butyl (3RS,4RS)-4-[4-(2-hydroxy-ethyl)-phenyl]-3-(1-methoxy-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate and, after reaction with phenol, analogously to the procedure described under (b), tert-butyl (3RS,4RS)-3-(1-methoxy-naphthalen-2-ylmethoxy)-4-[4-(2-phenoxy-ethyl)-phenyl]-piperidine-1-carboxylate as a colourless oil; R_f: 0.34 (SiO₂, hexane:ethyl acetate = 2:1).

35

(d) In an analogous manner to that described in Example 22(i) by alkylating tert-butyl (3RS,4RS)-4-[4-(2-hydroxy-ethyl)-phenyl]-3-naphthalen-2-ylmethoxy-piperidine-1-carboxylate with methyl iodide there was obtained tert-butyl (3RS,4RS)-4-

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[4-(2-methoxy-ethyl)-phenyl]-3-naphthalen-2-ylmethoxy]-piperidine-1-carboxylate as a colourless oil; MS: 493 (M+NH₄)⁺.

Example 33

5

The following compounds were obtained in an analogous manner to that described in Example 22 (I) by cleavage of the BOC group by means of acid:

- 10 1) - (3RS,4RS)-3-naphthalen-2-ylmethoxy-4-[4-(2-phenylsulphanyl-ethyl)-phenyl]-piperidine hydrochloride as white crystals, MS: 454 (M+H)⁺, from tert-butyl (3RS,4RS)-3-naphthalen-2-ylmethoxy-4-[4-(2-phenylsulphanyl-ethyl)-phenyl]-piperidine-1-carboxylate;
- 15 2) - a mixture of (3RS,4RS)-3-naphthalen-2-ylmethoxy-4-[4-[(RS)- and -[(SR)-2-phenylsulphanyl-ethyl]-phenyl]-piperidine as a colourless amorphous solid, MS: 470 (M+H)⁺, from a mixture of tert-butyl (3RS,4RS)-3-naphthalen-2-ylmethoxy-4-[4-[(RS)- and
- 20 -[(SR)-2-phenylsulphanyl-ethyl]-phenyl]-piperidine-1-carboxylate;
- 3) - (3RS,4RS)-3-naphthalen-2-ylmethoxy-4-[4-(2-phenylsulphonyl-ethyl)-phenyl]-piperidine hydrochloride as white
- 25 crystals, MS: 486 (M+H)⁺, from tert-butyl (3RS,4RS)-3-naphthalen-2-ylmethoxy-4-[4-(2-phenylsulphonyl-ethyl)-phenyl]-piperidine-1-carboxylate;
- 4) - (3RS,4RS)-4-[4-(2-benzothiazol-2-ylsulphanyl-ethyl)-phenyl]-3-naphthalen-2-ylmethoxy-piperidine as a colourless
- 30 foam, MS: 511 (M+H)⁺, from tert-butyl (3RS,4RS)-4-[4-(2-benzothiazol-2-ylsulphanyl-ethyl)-phenyl]-3-naphthalen-2-ylmethoxy-piperidine-1-carboxylate;
- 35 5) - (3RS,4RS)-2-[4-(3-naphthalen-2-ylmethoxy-piperidin-4-yl)-benzylsulphanyl]-benzothiazole as a yellow foam, MS: 497 (M+H)⁺, from tert-butyl (3RS,4RS)-4-[4-(benzothiazol-2-yl-

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sulphanylmethyl)-phenyl]-3-naphthalen-2-ylmethoxy-piperidine-1-carboxylate;

6) - (3RS,4RS)-3-naphthalen-2-ylmethoxy-4-[4-(1-phenyl-1H-tetrazol-5-ylsulphanylmethyl)-phenyl]-piperidine hydrochloride as a colourless oil, MS: 508 (M+H)⁺, from tert-butyl (3RS,4RS)-3-naphthalen-2-ylmethoxy-4-[4-(1-phenyl-1H-tetrazol-5-ylsulphanylmethyl)-phenyl]-piperidine-1-carboxylate;

7) - (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-[4-(2-phenoxy-ethyl)-phenyl]-piperidine as a yellowish foam, MS: 438 (M+H)⁺, from tert-butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-[4-(2-phenoxy-ethyl)-phenyl]-piperidine-1-carboxylate.

The BOC derivatives used as the starting materials were prepared as follows:

(a) A mixture of 200 mg (0.43 mmol) of tert-butyl (3RS,4RS)-4-[4-(2-hydroxy-ethyl)-phenyl]-3-naphthalen-2-ylmethoxy-piperidine-1-carboxylate, 263 mg (1.29 mmol) of tributylphosphine and 284 mg (1.29 mmol) of diphenyl sulphide in 1 ml of pyridine was stirred at room temperature for 18 hours. Subsequently, the reaction mixture was evaporated under reduced pressure and the residue, without further working-up, was chromatographed directly on silica gel using methylene chloride as the eluent. The tert-butyl (3RS,4RS)-3-naphthalen-2-ylmethoxy-4-[4-(2-phenylsulphanyl-ethyl)-phenyl]-piperidine-1-carboxylate was obtained as a colourless oil in quantitative yield; MS: 554 (M+H)⁺.

(b) A solution of 216 mg (0.23 mmol) of tetrabutylammonium ozone was added dropwise very slowly at room temperature to a solution of 128 mg (0.23 mmol) of tert-butyl (3RS,4RS)-3-naphthalen-2-ylmethoxy-4-[4-(2-phenylsulphanyl-ethyl)-phenyl]-piperidine-1-carboxylate in 10 ml of methylene chloride. After 6 hours the reaction solution was evaporated under reduced pressure and the crude product was chromatographed on silica gel using a 2:1 mixture of hexane and ethyl acetate as the eluent in

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order to separate the sulphone which had already formed. There were obtained 100 mg (76% of theory) of a mixture of tert-butyl (3RS,4RS)-3-naphthalen-2-ylmethoxy-4-[4-[(RS)- and -[(SR)-2-phenylsulphanyl-ethyl]-phenyl]-piperidine-1-carboxylate as a
5 colourless oil which gradually crystallized out; MS: 570 (M+H)+.

(c) In an analogous manner to that described under (b), starting from tert-butyl (3RS,4RS)-3-naphthalen-2-ylmethoxy-4-[4-(2-phenylsulphanyl-ethyl)-phenyl]-piperidine-1-carboxylate using an
10 excess of tetrabutylammonium oxone there was obtained tert-butyl (3RS,4RS)-3-naphthalen-2-ylmethoxy-4-[4-(2-phenylsulphonyl-ethyl)-phenyl]-piperidine-1-carboxylate as a colourless foam; MS: 603 (M+NH₄)⁺.

15 (d) In an analogous manner to that described under (a), by reacting tert-butyl (3RS,4RS)-4-[4-(2-hydroxy-ethyl)-phenyl]-3-naphthalen-2-ylmethoxy-piperidine-1-carboxylate with bis-(benzothiazol-2-yl) disulphide there was obtained tert-butyl (3RS,4RS)-4-[4-(2-benzothiazol-2-ylsulphanyl-ethyl)-phenyl]-3-
20 naphthalen-2-ylmethoxy-piperidine-1-carboxylate as a yellowish solid; MS: 611 (M+H)+.

(e) In an analogous manner to that described under (a), by reacting tert-butyl (3RS,4RS)-4-(4-hydroxymethyl-phenyl)-3-
25 (naphthalen-2-ylmethoxy)-piperidine-1-carboxylate with (benzothiazol-2-yl) disulphide there was obtained tert-butyl (3RS,4RS)-4-[4-(benzothiazol-2-ylsulphanylmethyl)-phenyl]-3-naphthalen-2-ylmethoxy-piperidine-1-carboxylate as a yellowish foam; MS: 597 (M+H)+.

30

(f) In an analogous manner to that described under (a), by reacting tert-butyl (3RS,4RS)-4-(4-hydroxymethyl-phenyl)-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate with bis-(1-phenyl-1H-tetrazol-5-yl) disulphide there was obtained tert-
35 butyl (3RS,4RS)-3-naphthalen-2-ylmethoxy-4-[4-(1-phenyl-1H-tetrazol-5-ylsulphanylmethyl)-phenyl]-piperidine-1-carboxylate as a colourless foam; MS: 630 (M+Na)+.

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(g) In an analogous manner to that described in Example 32(b), from tert-butyl (3RS,4RS)-4-[4-(2-hydroxy-ethyl)-phenyl]-3-naphthalen-2-ylmethoxy-piperidine-1-carboxylate there was obtained tert-butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-[4-(2-phenoxy-ethyl)-phenyl]-piperidine-1-carboxylate as a
5 colourless oil; MS: 555 (M+NH₄)⁺.

Example 34

10 (a) To a solution of 100 mg (0.22 mmol) of tert-butyl (3RS,4RS)-4-(4-hydroxymethyl-phenyl)-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate in 10 ml of tetrahydrofuran were added 68 mg (0.66 mmol) of triethylamine and thereafter dropwise at 0°C 25 mg (0.26 mmol) of methanesulphonyl chloride.
15 The reaction solution was stirred at room temperature for 90 minutes, thereafter 38 mg (0.33 mmol) of 2-mercaptopyrimidine were added and the mixture was stirred at room temperature for a further 18 hours. For the working-up, the reaction mixture was evaporated under reduced pressure, the
20 residue was taken up in 20 ml of methylene chloride and then extracted with 10 ml of water. The organic phase was dried over sodium sulphate and subsequently evaporated under reduced pressure. For purification, the crude product was chromatographed on silica gel using a 5:1 mixture of hexane and ethyl
25 acetate as the eluent. There were obtained 100 mg (82% of theory) of tert-butyl (3RS,4RS)-3-naphthalen-2-ylmethoxy-4-[4-(pyrimidin-2-ylsulphanylmethyl)-phenyl]-piperidine-1-carboxylate as a yellowish oil; MS: 542 (M+H)⁺.

30 (b) In an analogous manner to that described in Example 22(I), by cleavage of the BOC group there was obtained (3RS,4RS)-2-[4-(3-naphthalen-2-ylmethoxy-piperidin-4-yl)-benzylsulphanyl]-pyrimidine as a yellow foam; MS: 442 (M+H)⁺.

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Example 35

The following compounds were obtained in an analogous manner to that described in Example 22(I) by cleavage of the BOC
5 group using acid:

- 1) - (3RS,4RS)-2-[4-(3-naphthalen-2-ylmethoxy-piperidin-4-yl)-benzylsulphanyl]-6-nitro-benzothiazole hydrochloride as a yellowish foam, MS: 542 (M+H)⁺, from tert-butyl (3RS,4RS)-3-naphthalen-2-ylmethoxy-4-[4-(6-nitro-benzothiazol-2-yl-sulphanylmethyl)-phenyl]-piperidine-1-carboxylate;
10
- 2) - (3RS,4RS)-3-{4-[3-(naphthalen-2-ylmethoxy)-piperidin-4-yl]-phenyl}-propionitrile trifluoroacetate as a white powder,
15 MS: 371 (M+H)⁺, from tert-butyl (3RS,4RS)-4-[4-(2-cyano-ethyl)-phenyl]-3-naphthalen-2-ylmethoxy-piperidine-1-carboxylate using trifluoroacetic acid in methylene chloride.

The BOC derivatives used as the starting materials were
20 obtained as follows:

- (a) In an analogous manner to that described in Example 34(a), by reacting tert-butyl (3RS,4RS)-4-(4-hydroxymethyl-phenyl)-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate with
25 6-nitro-2-mercaptobenzothiazole there was obtained, via the mesylate prepared in situ, tert-butyl (3RS,4RS)-3-naphthalen-2-ylmethoxy-4-[4-(6-nitro-benzothiazol-2-ylsulphanylmethyl)-phenyl]-piperidine-1-carboxylate as a yellow solid, MS: 642 (M+H)⁺.
30
- (b) In an analogous manner to that described in Example 34(a), by reacting tert-butyl (3RS,4RS)-4-[4-(2-hydroxy-ethyl)-phenyl]-3-naphthalen-2-ylmethoxy-piperidine-1-carboxylate with potassium cyanide in dimethylformamide there was
35 obtained, via the corresponding mesylate, tert-butyl (3RS,4RS)-4-[4-(2-cyano-ethyl)-phenyl]-3-naphthalen-2-ylmethoxy-piperidine-1-carboxylate as a white powder, MS: 471 (M+H)⁺.

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Example 36

(a) 6.95 g (44 mmol) of powdered potassium permanganate dissolved in a mixture of 100 ml of water and 100 ml of glacial acetic acid as well as 0.73 g (2 mmol) of tetrabutylammonium iodide were added to a solution of 5.0 g (10.83 mmol) of tert-butyl (3RS,4RS)-4-[4-(2-hydroxy-ethyl)-phenyl]-3-naphthalen-2-ylmethoxy-piperidine-1-carboxylate in 500 ml of benzene. The reaction mixture was stirred intensively for 48 hours. For the working-up, the phases were separated. The organic phase was washed with 100 ml of saturated sodium thiosulphate solution. The aqueous phase was decolorized by the addition of saturated sodium thiosulphate solution and subsequently extracted twice with 100 ml of ethyl acetate and 100 ml of methylene chloride each time. The organic phases were combined, dried over sodium sulphate and evaporated under reduced pressure. For purification, the crude material was chromatographed on silica gel using a 9:1 mixture of methylene chloride and methanol as the eluent after the column had previously been prepared with a 90:10:0.1 mixture of methylene chloride, methanol and ammonia. There were obtained 2.6 g (50% of theory) of (3RS,4RS)-[4-(1-tert-butoxycarbonyl-3-naphthalen-2-ylmethoxy-piperidin-4-yl)-phenyl]-acetic acid as a colourless, amorphous solid; MS: 476 (M+H)⁺.

(b) A solution of 150 mg (0.32 mmol) of (3RS,4RS)-[4-(1-tert-butoxycarbonyl-3-naphthalen-2-ylmethoxy-piperidin-4-yl)-phenyl]-acetic acid and 55 mg (0.32 mmol) of 2-amino-1-phenylethanone in 5 ml of dimethylformamide was treated in sequence with 44.6 µl (0.32 mmol) of triethylamine and 96 mg (0.32 mmol) of O-(1,2-dihydro-2-oxo-1-pyridyl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (TPTU) and the mixture was stirred at room temperature for 18 hours. For the working-up, the reaction was evaporated in an oil pump vacuum, the residue was taken up in 20 ml of methylene chloride and washed with 5 ml of water. The organic phase was dried over sodium sulphate and evaporated under reduced pressure. For purification, the crude material was chromatographed on silica gel using a 95:5 mixture of methylene chloride and methanol as the eluent. There were obtained 120 mg

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(64% of theory) of tert-butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-{4-[(2-oxo-2-phenyl-ethylcarbamoyl)-methyl]-phenyl}-piperidine-1-carboxylate as a colourless oil; MS: 615 (M+Na)+.

5

(c) In an analogous manner to that described in Example 22(I), starting from tert-butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-{4-[(2-oxo-2-phenyl-ethylcarbamoyl)-methyl]-phenyl}-piperidine-1-carboxylate by cleavage of the BOC group using
 10 trifluoroacetic acid in methylene chloride there was obtained (3RS,4RS)-2-{4-[3-(naphthalen-2-ylmethoxy)-piperidin-4-yl]-phenyl}-N-(2-oxo-2-phenyl-ethyl)-acetamide trifluoroacetate as a white powder; MS: 493 (M+H)+.

15

Example 37

The following compounds were obtained in an analogous manner to that described in Example 36(b)-(c):

20 1) - From (3RS,4RS)-[4-(1-tert-butoxycarbonyl-3-naphthalen-2-ylmethoxy-piperidin-4-yl)-phenyl]-acetic acid and 3-amino-1-phenyl-propan-1-one [H.Zinner and G.Brossmann, J. Prakt. Chem. 5, 91 (1958)] there was obtained tert-butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-{4-[(3-oxo-3-phenyl-propylcarbamoyl)-methyl]-phenyl}-piperidine-1-carboxylate, MS: 607 (M+H)+,
 25 15154B66, which, after cleavage of the BOC group, gave (3RS,4RS)-2-[4-[3-(naphthalen-2-ylmethoxy)-piperidin-4-yl]-phenyl]-N-(3-oxo-3-phenyl-propyl)-acetamide trifluoroacetate as a white powder; MS: 507 (M+H)+;

30

2) - from (3RS,4RS)-[4-(1-tert-butoxycarbonyl-3-naphthalen-2-ylmethoxy-piperidin-4-yl)-phenyl]-acetic acid and 2-hydroxy-1-phenyl-ethanone with 1,1-carbonyldiimidazole as the condensation agent there was obtained tert-butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-[4-(2-oxo-2-phenyl-ethoxy-carbonylmethyl)-phenyl]-piperidine-1-carboxylate which, after
 35 cleavage of the BOC group, gave 2-oxo-2-phenyl-ethyl (3RS,4RS)-

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[4-[3-(naphthalen-2-ylmethoxy)-piperidin-4-yl]-phenyl]-acetate trifluoroacetate as a white powder; MS: 494 (M+H)⁺;

3) - from (3RS,4RS)-[4-(1-tert-butoxycarbonyl-3-naphthalen-
5 2-ylmethoxy-piperidin-4-yl)-phenyl]-acetic acid and phenol with
1,1-carbonyldiimidazole as the condensation agent there was
obtained tert-butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-(4-
phenoxycarbonylmethyl-phenyl)-piperidine-1-carboxylate which,
after cleavage of the BOC group, gave phenyl (3RS,4RS)-[4-(3-
10 naphthalen-2-ylmethoxy-piperidin-4-yl)-phenyl]-acetate
trifluoroacetate as white crystals; MS: 452 (M+H)⁺.

Example 38

15 (a) A solution of 100 mg (0.21 mmol) of (3RS,4RS)-[4-(1-tert-
butoxycarbonyl-3-naphthalen-2-ylmethoxy-piperidin-4-yl)-
phenyl]-acetic acid in 5 ml of dimethylformamide was treated
with 50 mg (0.31 mmol) of 1,1-carbonyldiimidazole and the
mixture was stirred at 50°C for one hour. Subsequently, the
20 mixture was cooled to room temperature, a solution of 45 mg
(0.33 mmol) of benzamidoxime in 2 ml of dimethylformamide
was added and the mixture was stirred at 50°C for one hour. For
the working-up, the mixture was cooled to room temperature and
the dimethylformamide was distilled off in an oil pump vacuum.
25 The residue was chromatographed on silica gel using a 98:2:0.1
mixture of methylene chloride, methanol and ammonia as the
eluent. There were obtained 90 mg (72% of theory) of the
benzamidoxime ester as a colourless foam; MS: 594 (M+H)⁺, R_f:
0.68 (SiO₂, methylene chloride:methanol:ammonia = 95:5:0.1)

30

(b) A solution of 90 mg (0.15 mmol) of the benzamidoxime
ester in 10 ml of dimethylformamide was heated to 130°C for
18 hours. For the working-up, the mixture was evaporated under
reduced pressure and the residue was chromatographed on silica
35 gel using a 4:1 mixture of hexane and ethyl acetate as the eluent.
There were obtained 63 mg (72% of theory) of tert-butyl
(3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-[4-(3-phenyl-[1,2,4]-

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oxadiazol-5-ylmethyl)-phenyl]-piperidine-1-carboxylate as a colourless oil; MS: 592 (M+NH₄)⁺.

(c) In an analogous manner to that described in Example 22(I),
 5 starting from tert-butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-[4-(3-phenyl-[1,2,4]oxadiazol-5-ylmethyl)-phenyl]-piperidine-1-carboxylate by cleavage of the BOC group using trifluoroacetic acid in methylene chloride there was obtained (3RS,4RS)-3-(3-naphthalen-2-ylmethoxy)-4-[4-(3-phenyl-[1,2,4]oxadiazol-5-ylmethyl)-phenyl]-piperidine trifluoroacetate as a white powder;
 10 MS: 476 (M+H)⁺.

Example 39

15 (a) A solution of 100 mg (0.21 mmol) of (3RS,4RS)-[4-(1-tert-butoxycarbonyl-3-naphthalen-2-ylmethoxy-piperidin-4-yl)-phenyl]-acetic acid in 5 ml of methylene chloride was treated with 1 ml of ethereal diazomethane solution at room temperature and stirred for a further 2 hours. The reaction solution
 20 was evaporated under reduced pressure and the tert-butyl (3RS,4RS)-4-(4-methoxycarbonylmethyl-phenyl)-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate, R_f: 0.5 (hexane:ethyl acetate = 2:1), obtained in quantitative yield, was used in the following step without further purification and characterization.

25 (b) A solution of 102 mg (0.21 mmol) of tert-butyl (3RS,4RS)-4-(4-methoxycarbonylmethyl-phenyl)-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate in 0.5 ml of hydrazine hydrate was heated to 120°C for 18 hours. For the working-up, the
 30 reaction mixture was cooled to room temperature, treated with 3 ml of ice-water and extracted twice with 5 ml of methylene chloride each time. The combined organic phases were dried over sodium sulphate and evaporated under reduced pressure. There were obtained 63 mg (63% of theory) of tert-butyl (3RS,4RS)-4-(4-hydrazinocarbonylmethyl-phenyl)-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a colourless foam; R_f: 0.22
 35 (SiO₂, methylene chloride:methanol:ammonia = 95:5:0.1).

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(c) A mixture of 60 mg (0.12 mmol) of tert-butyl (3RS,4RS)-4-(4-hydrazinocarbonylmethyl-phenyl)-3-(naphthalen-2-yl-methoxy)-piperidine-1-carboxylate and 27.7 µl (0.12 mmol) of triethyl orthobenzoate in 5 ml of ethanol was boiled under reflux
5 for 18 hours. After cooling the mixture was evaporated under reduced pressure and the residue was chromatographed on silica gel using a 2:1 mixture of hexane and ethyl acetate as the eluent. There were obtained 30 mg (44% of theory) of tert-butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-[4-(5-phenyl-[1,3,4]-
10 oxadiazol-2-ylmethyl)-phenyl]-piperidine-1-carboxylate as a colourless foam; MS: 575 (M+H)+.

(d) In an analogous manner to that described in Example 22(I), starting from tert-butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-
15 4-[4-(5-phenyl-[1,3,4]oxadiazol-2-ylmethyl)-phenyl]-piperidine-1-carboxylate by cleavage of the BOC group using trifluoroacetic acid in methylene chloride there was obtained (3RS,4RS)-3-naphthalen-2-ylmethoxy-4-[4-(5-phenyl-[1,3,4]oxadiazol-2-ylmethyl)-phenyl]-piperidine trifluoroacetate as a white powder;
20 MS: 476 (M+H)+.

Example 40

(a) 70 mg (0.51 mmol) of phenylmagnesium chloride were
25 added using a syringe to a solution of 80 mg (0.17 mmol) of tert-butyl (3RS,4RS)-4-[4-(2-cyano-ethyl)-phenyl]-3-naphthalen-2-ylmethoxy-piperidine-1-carboxylate (Example 35) in 10 ml of toluene. The reaction mixture was boiled under reflux for 3 hours, thereafter cooled to room temperature and hydrolyzed
30 with 4 ml of 1N hydrochloric acid. The mixture was subsequently stirred at 80°C for 1 hour, then cooled to room temperature and extracted twice with ethyl acetate. The combined organic phases were dried over sodium sulphate and evaporated under reduced pressure. The residue was chromatographed on silica gel using a
35 90:10:0.1 mixture of methylene chloride, methanol and ammonia as the eluent. The resulting mixture of (3RS,4RS)-3-[4-(3-naphthalen-2-ylmethoxy-piperidin-4-yl)-phenyl]-1-phenylpropan-1-one and (3RS,4RS)-3-[4-[3-(naphthalen-2-ylmethoxy)-

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piperidin-4-yl]-phenyl}-propionic acid was converted into the corresponding BOC derivative in an analogous manner to that described in Example 1(f) and subsequently chromatographed on silica gel using a 2:1 mixture of hexane and ethyl acetate as the eluent. There were obtained 13 mg (14% of theory) of tert-butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-[4-(3-oxo-3-phenyl-propyl)-phenyl]-piperidine-1-carboxylate as a colourless foam; R_f : 0.38 (hexane: = 2:1).

(b) In an analogous manner to that described in Example 22(l), starting from tert-butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-[4-(3-oxo-3-phenyl-propyl)-phenyl]-piperidine-1-carboxylate by cleavage of the BOC group using trifluoroacetic acid in methylene chloride there was obtained (3RS,4RS)-3-[4-(3-naphthalen-2-ylmethoxy-piperidin-4-yl)-phenyl]-1-phenyl-propan-1-one trifluoroacetate as a white powder; MS: 450 (M+H)⁺.

Example 41

(a) A solution of 60 mg (0.13 mmol) of tert-butyl (3RS,4RS)-4-(3-methoxycarbonyl-phenyl)-3-naphthalen-2-ylmethoxy-piperidine-1-carboxylate [Example 26(e)] and 0.26 ml (0.26 mmol) of 1N sodium hydroxide solution in 2 ml of methanol was stirred at 30°C for 18 hours. For the working-up, the reaction mixture was neutralized with 1N hydrochloric acid and extracted twice with 10 ml of methylene chloride each time. The organic phases were combined, dried over sodium sulphate and evaporated under reduced pressure. The residue was crystallized from a mixture of hexane and diethyl ether. There were obtained 45 mg (75% of theory) of (3RS,4RS)-3-(1-tert-butoxycarbonyl-3-naphthalen-2-ylmethoxy-piperidin-4-yl)-benzoic acid as colourless crystals; MS: 462 (M+H)⁺.

(b) In an analogous manner to that described in Example 36(b), by condensing (3RS,4RS)-3-(1-tert-butoxycarbonyl-3-naphthalen-2-ylmethoxy-piperidin-4-yl)-benzoic acid with benzylamine using 1,1-carbonyldiimidazole as the condensation agent there was obtained tert-butyl (3RS,4RS)-4-(3-benzyl-

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carbamoyl-phenyl)-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a colourless oil; MS: 551 (M+H)⁺.

- (c) In an analogous manner to that described in Example 22(I),
 5 by cleavage of the BOC group from tert-butyl (3RS,4RS)-4-(3-benzylcarbamoyl-phenyl)-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate there was obtained (3RS,4RS)-N-benzyl-3-(3-naphthalen-2-ylmethoxy-piperidin-4-yl)-benzamide hydrochloride as a white powder; MS: 451 (M+H)⁺.

10

Example 42

The following compounds were obtained in an analogous manner to that described in Example 11(I) by cleavage of the BOC
 15 group using trifluoroacetic acid in methylene chloride:

- 1) - (3RS,4RS)-N-benzyl-4-[3-(naphthalen-2-ylmethoxy)-piperidin-4-yl]-benzamide as a white powder, MS: 453 (M+H)⁺, from tert-butyl (3RS,4RS)-4-(4-benzylcarbamoyl-phenyl)-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate;
 20
- 2) - (3RS,4RS)-4-[3-(naphthalen-2-ylmethoxy)-piperidin-4-yl]-N-(3-oxo-3-phenyl-propyl)-benzamide trifluoroacetate as a white powder, MS: 493 (M+H)⁺, from tert-butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-[4-(3-oxo-3-phenyl-propyl-carbamoyl)-phenyl]-piperidine-1-carboxylate;
 25
- 3) - (3RS,4RS)-4-[3-(naphthalen-2-ylmethoxy)-piperidin-4-yl]-N-(2-oxo-2-phenyl-ethyl)-benzamide trifluoroacetate as a white powder, MS: 479 (M+H)⁺, from tert-butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-[4-(2-oxo-2-phenyl-ethyl-carbamoyl)-phenyl]-piperidine-1-carboxamide.
 30

The BOC derivatives used as the starting materials were
 35 obtained as follows:

- (a) In an analogous manner to that described in Example 41(b), by the alkaline saponification of tert-butyl (3RS,4RS)-4-(4-

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methoxycarbonyl-phenyl)-3-naphthalen-2-ylmethoxy-piperidine-1-carboxylate there was obtained (3RS,4RS)-4-(1-tert-butoxycarbonyl-3-naphthalen-2-ylmethoxy-piperidin-4-yl)-benzoic acid as a colourless solid; MS: 461 (M)⁺.

5

(b) In an analogous manner to that described in Example 36(b), by condensing (3RS,4RS)-4-(1-tert-butoxycarbonyl-3-naphthalen-2-ylmethoxy-piperidin-4-yl)-benzoic acid with benzylamine there was obtained tert-butyl (3RS,4RS)-4-(4-benzylcarbamoyl-phenyl)-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a colourless foam; MS: 551 (M+H)⁺.

10

(c) In an analogous manner to that described in Example 36(b), by condensing (3RS,4RS)-4-(1-tert-butoxycarbonyl-3-naphthalen-2-ylmethoxy-piperidin-4-yl)-benzoic acid with 3-amino-1-phenyl-propan-1-one there was obtained tert-butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-[4-(3-oxo-3-phenyl-propylcarbamoyl)-phenyl]-piperidine-1-carboxylate as a colourless foam; MS: 593 (M+H)⁺.

15

(d) In an analogous manner to that described in Example 36(b), by condensing (3RS,4RS)-4-(1-tert-butoxycarbonyl-3-naphthalen-2-ylmethoxy-piperidin-4-yl)-benzoic acid with 2-amino-1-phenyl-ethanone there was obtained tert-butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-[4-(2-oxo-2-phenyl-ethylcarbamoyl)-phenyl]-piperidine-1-carboxylate as a colourless foam; MS: 579 (M+H)⁺.

20

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Example 43

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(a) A solution of 1.0 g (3 mmol) of tert-butyl (3RS,4RS)-3-hydroxy-4-(4-methoxycarbonyl-phenyl)-piperidine-1-carboxylate in 100 ml of methanol was treated with 100 mg of rhodium (5%) on aluminium oxide and hydrogenated for 5 hours at 50°C under 10 bar of hydrogen. Thereafter, the reaction mixture was filtered over 30 g of Dicalit, the filter aid was rinsed with 200 ml of methanol and the solution obtained was evaporated under reduced pressure. There was obtained in quantitative yield

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a 2:1 or 1:2 mixture of tert-butyl (3RS,4RS)-3-hydroxy-4-(trans- and -(cis-4-methoxycarbonyl-cyclohexyl)-piperidine-4-carboxylate as a colourless solid; MS: 342 (M+H)⁺.

5 The following procedure was carried out in an analogous manner to that described in Example 22(e) and (h)-(l):

(b) From a 2:1 or 1:2 mixture of tert-butyl (3RS,4RS)-3-hydroxy-4-(trans- and -(cis-4-methoxycarbonyl-cyclohexyl)-
10 piperidin-4-carboxylate by reduction using lithium borohydride there was obtained a 2:1 or 1:2 mixture of tert-butyl (3RS,4RS)-cis- and -trans-3-hydroxy-4-(4-hydroxymethyl-cyclohexyl)-piperidine-1-carboxylate as a colourless foam; MS: 314 (M+H)⁺.

15 (c) From a 2:1 or 1:2 mixture of tert-butyl (3RS,4RS)-cis- and -trans-3-hydroxy-4-(4-hydroxymethyl-cyclohexyl)-piperidine-1-carboxylate there was obtained by introduction of the trityl group a 2:1 or 1:2 mixture of tert-butyl (3RS,4RS)-cis- and -trans-3-hydroxy-4-(4-trityloxymethyl-cyclohexyl)-piperidine-1-
20 carboxylate as a colourless foam; MS: 573 (M+H)⁺.

(d) Alkylation of a 2:1 or 1:2 mixture of tert-butyl (3RS,4RS)-cis- and -trans-3-hydroxy-4-(4-trityloxymethyl-cyclohexyl)-piperidine-1-carboxylate with 2-bromomethylnaphthalene gave a
25 2:1 or 1:2 mixture of tert-butyl (3RS,4RS)-cis- and -trans-3-naphthalen-2-ylmethoxy-4-(4-trityloxymethyl-cyclohexyl)-piperidine-1-carboxylate as a colourless foam: MS: 713 (M+NH₄)⁺.

(e) From a 2:1 or 1:2 mixture of tert-butyl (3RS,4RS)-cis- and
30 -trans-3-naphthalen-2-ylmethoxy-4-(4-trityloxymethyl-cyclohexyl)-piperidine-1-carboxylate by cleavage of the trityl group using hydrogen chloride in methanol there was obtained a 2:1 or 1:2 mixture of tert-butyl (3RS,4RS)-cis- and -trans-3-naphthalen-2-ylmethoxy-4-(4-hydroxymethyl-cyclohexyl)-
35 piperidine-1-carboxylate as a colourless foam; MS: 453 (M+H)⁺.

(f) Acylation of a 2:1 or 1:2 mixture of tert-butyl (3RS,4RS)-cis- and -trans-3-naphthalen-2-ylmethoxy-4-(4-hydroxymethyl-

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cyclohexyl)-piperidine-1-carboxylate with benzoyl chloride yielded a 2:1 or 1:2 mixture of tert-butyl (3RS,4RS)-cis- and -trans-4-(4-benzoyloxymethyl-cyclohexyl)-3-naphthalen-2-ylmethoxy-piperidine-1-carboxylate as a colourless oil; MS: 558 (M+H)⁺.

(g) From a 2:1 or 1:2 mixture of tert-butyl (3RS,4RS)-cis- and -trans-4-(4-benzoyloxymethyl-cyclohexyl)-3-naphthalen-2-ylmethoxy-piperidine-1-carboxylate by cleavage of the BOC group using hydrogen chloride in methanol there was obtained a 2:1 or 1:2 mixture of (3RS,4RS)-cis- and -trans 4-(3-naphthalen-2-ylmethoxy-piperidin-4-yl)-cyclohexylmethyl benzoate as a colourless foam; MS: 458 (M+H)⁺.

Example 44

The following procedure was carried out in an analogous manner to that described in Example 22(a)-(c):

(a) 1-Benzyl-4-(4-methoxy-phenyl)-piperidin-4-ol was obtained as a colourless solid, MS: 298 (M+H)⁺, from 1-benzyl-4-piperidone and 4-iodoanisole.

(b) 1-Benzyl-4-(4-methoxy-phenyl)-1,2,3,6-tetrahydro-pyridine was obtained as a beige solid, MS: 280 (M+H)⁺, from 1-benzyl-4-(4-methoxy-phenyl)-piperidin-4-ol by elimination.

(c) Hydroboration of 1-benzyl-4-(4-methoxy-phenyl)-1,2,3,6-tetrahydro-pyridine gave (3RS,4RS)-1-benzyl-4-(4-methoxy-phenyl)-piperidin-3-ol as colourless crystals; MS: 297 (M)⁺.

(d) 49.6 ml (49.6 mmol, 2 eq.) of an approximately 1M boron tribromide solution in methylene chloride was added dropwise at 3-7°C within 10 minutes to a solution of 7.38 g (24.82 mmol) of (3RS,4RS)-1-benzyl-4-(4-methoxy-phenyl)-piperidin-3-ol in 248 ml of methylene chloride. This suspension was stirred at room temperature for 3 hours. Subsequently, the reaction mixture was poured into 750 ml of an ice/water mixture, brought

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to pH 8 with 2N sodium hydroxide solution and extracted three times with 500 ml of methylene chloride each time. The organic phases were washed with a small amount of water, dried over magnesium sulphate, evaporated under reduced pressure and dried in a high vacuum. This yielded 6.42 g of (3RS,4RS)-1-benzyl-4-(4-hydroxy-phenyl)-piperidin-3-ol in the form of a white foam; MS: 283 (M)⁺.

(e) A solution of 3.0 g, (10.6 mmol) of (3RS,4RS)-1-benzyl-4-(4-hydroxy-phenyl)-piperidin-3-ol in 75 ml of ethyl methyl ketone was treated in succession with 10.84 g (42.4 mmol, 4.8 eq) of 2-(2-iodo-ethoxy)-tetrahydro-pyran and 5.25 g (53 mmol, 5 eq) of potassium carbonate. This mixture was stirred at 95°C for 25 hours. Subsequently, it was concentrated to a few millilitres, poured into 200 ml of an ice/water mixture and extracted three times with 300 ml of methylene chloride each time. The combined organic phases were washed once with a small amount of water, dried over magnesium sulphate, evaporated under reduced pressure and dried in a high vacuum. The thus-obtained crude product (11.81 g) was separated on silica gel using a 99:1 mixture of methylene chloride and methanol as the eluent and yielded 3.2 g (73% of theory) of a mixture of (3RS,4RS)-1-benzyl-4-[4-[2-[(RS)- and -[(SR)-tetrahydro-pyran-2-yloxy]-ethoxy]-phenyl]-piperidin-3-ol as a colourless oil; R_f: 0.55 (SiO₂, methylene chloride:methanol = 9:1).

(f) In an analogous manner to that described in Example 22(i), by alkylating a mixture of (3RS,4RS)-1-benzyl-4-[4-[2-[(RS)- and -[(SR)-tetrahydro-pyran-2-yloxy]-ethoxy]-phenyl]-piperidin-3-ol with 2-bromomethylnaphthalene there was obtained a mixture of (3RS,4RS)-1-benzyl-3-(naphthalen-2-ylmethoxy)-4-[4-[2-[(RS)- and -[(SR)-tetrahydro-pyran-2-yloxy]-ethoxy]-phenyl]-piperidine as a colourless oil; R_f : 0.46 (SiO₂, methylene chloride: = 1:1).

(g) In an analogous manner to that described Example 25(a), by cleavage of the benzyl group using 2,2,2-trichloroethyl chloroformate and potassium carbonate there was obtained a mixture of 2,2,2-trichloro-ethyl (3RS,4RS)-3-(naphthalen-2-

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ylmethoxy)-4-[4-[2-[(RS)- and -[(SR)-tetrahydro-pyran-2-yloxy]-ethoxy]-phenyl]-piperidine-1-carboxylate as a colourless oil; MS: 653.3, 655 (M+H)⁺.

5 (h) A solution of 500 mg (0.785 mmol) of a mixture of 2,2,2-trichloro-ethyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-[4-[2-[(RS)- and -[(SR)-tetrahydro-pyran-2-yloxy]-ethoxy]-phenyl]-piperidine-1-carboxylate in 10 ml of methanol was treated with
10 1 ml of water and 1.120 g (5.888 mmol) of p-toluenesulphonic acid monohydrate. This suspension was stirred at room temperature for 1.5 hours, then concentrated to half of the volume under reduced pressure and extracted four times with methylene chloride against water. The organic phases were each washed
15 once with saturated sodium hydrogen carbonate solution and saturated sodium chloride solution, dried over magnesium sulphate, evaporated under reduced pressure and dried in a high vacuum. The crude product (465 mg) was separated on silica gel using a 9:1 mixture of methylene chloride and methanol as the eluent. This yielded 344 mg (79% of theory) of 2,2,2-tri-
20 chloroethyl (3RS,4RS)-4-[4-(2-hydroxy-ethoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a colourless, amorphous powder; MS: 569.3, 571 (M+NH₄)⁺.

(i) In an analogous manner to that described in Example 24(m),
25 from 2,2,2-trichloroethyl (3RS,4RS)-4-[4-(2-hydroxy-ethoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate and pyridine-2-carbonyl azide there was obtained 2,2,2-trichloro-ethyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-[4-(2-pyridin-2-ylcarbamoxyloxy-ethoxy)-phenyl]-piperidine-1-carboxy-
30 late as a colourless oil; MS: 672.2, 674 (M+H)⁺.

(j) In an analogous manner to that described in Example 25(b), by treating 2,2,2-trichloroethyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-[4-(2-pyridin-2-ylcarbamoxyloxy-ethoxy)-phenyl]-
35 piperidine-1-carboxylate with zinc in glacial acetic acid there was obtained (3RS,4RS)-2-[4-[3-(naphthalen-2-ylmethoxy)-piperidin-4-yl]-phenoxy]-ethyl pyridine-2-yl-carbamate as a colourless solid; MS: 498 (M+H)⁺.

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Example 45

The following compounds were obtained in an analogous
 5 manner to that described in Example 25(b):

- 1) - (3RS,4RS)-2-[4-[3-(Naphthalen-2-ylmethoxy)-piperidin-4-yl]-phenoxy]-ethyl carbamate as a colourless oil, MS: 421 (M+H)⁺, from 2,2,2-trichloro-ethyl (3RS,4RS)-4-[4-(2-carbamoyloxy-ethoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-
 10 piperidine-1-carboxylate;
- 2) - (3RS,4RS)-2-[4-[3-(naphthalen-2-ylmethoxy)-piperidin-4-yl]-phenoxy]-ethyl morpholine-4-carboxylate as a colourless
 15 oil, MS: 491 (M+H)⁺, from 2,2,2-trichloro-ethyl (3RS,4RS)-4-[4-[2-(morpholin-4-ylcarbonyloxy)-ethoxy]-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate;
- 3) - (3RS,4RS)-4-(4-methoxy-phenyl)-3-(naphthalen-2-ylmethoxy)-piperidine as a colourless oil, MS: 348 (M+H)⁺, from
 20 2,2,2-trichloro-ethyl (3RS,4RS)-4-(4-methoxy-phenyl)-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate;
- 4) - (3RS,4RS)-2-[4-[3-(naphthalen-2-ylmethoxy)-piperidin-4-yl]-phenoxy]-ethanol as a colourless, amorphous solid, MS: 378 (M+H)⁺, from a mixture of 2,2,2-trichloro-ethyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-[4-[2-[(RS)- and -[(SR)-tetrahydropyran-2-yloxy]-ethoxy]-phenyl]-piperidine-1-carboxylate with
 simultaneous cleavage of the THP group.

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The derivatives used as the starting materials were obtained as follows:

- (a) In an analogous manner to that described in Example 24 (m), from 2,2,2-trichloroethyl (3RS,4RS)-4-[4-(2-hydroxy-ethoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate
 35 and sodium isocyanate there was obtained 2,2,2-trichloro-ethyl (3RS,4RS)-4-[4-(2-carbamoyloxy-ethoxy)-phenyl]-3-(naphthalen-

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2-ylmethoxy)-piperidine-1-carboxylate as a colourless oil; R_f : 0.28 (SiO_2 , methylene chloride:acetone = 1:1).

(b) A solution of 250 mg (0.56 mmol) of 2,2,2-trichloroethyl (3RS,4RS)-4-[4-(2-hydroxy-ethoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate in 20 ml of toluene was treated in succession with 250 ml (2.8 mmol, 5.0 eq.) of morpholine-4-carbonyl chloride, 375 mg (3.08 mmol, 5.5 eq.) of 4-dimethylaminopyridine and 20 μl (0.075 mmol, 0.13 eq.) of dibutyltin diacetate. This mixture was boiled under reflux for 64 hours. In the course of the reaction a further 125 ml (1.40 mmol, 5.0 eq.) of morpholine-4-carbonyl chloride and 188 mg (1.56 mmol, 2.3 eq.) of 4-dimethylaminopyridine were added and the mixture was boiled under reflux for a further 24 hours. The reaction mixture, cooled to room temperature, was poured into 100 ml of an ice/water mixture, stirred for 5 minutes and extracted three times with methylene chloride. The organic phases were each washed once with water and saturated sodium chloride solution, dried over magnesium sulphate, evaporated under reduced pressure and dried in a high vacuum. The crude product (546 mg) was separated on silica gel using a 9:1 mixture of hexane and acetone as the eluent. There were obtained 42 mg (14% of theory) of 2,2,2-trichloro-ethyl (3RS,4RS)-4-[4-[2-(morpholin-4-ylcarbonyloxy)-ethoxy]-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a colourless oil; MS: 665.3, 667 ($\text{M}+\text{H}$)⁺.

(c) In an analogous manner to that described in Example 12(b), by alkylating (3RS,4RS)-1-benzyl-4-(4-methoxy-phenyl)-piperidin-3-ol [Example 44 (c)] with 2-bromomethylnaphthalene there was obtained (3RS,4RS)-1-benzyl-4-(4-methoxy-phenyl)-3-(naphthalen-2-ylmethoxy)-piperidine as a beige coloured solid; MS: 437 (M)⁺. Subsequent reaction with 2,2,2-trichloroethyl chloroformate gave 2,2,2-trichloro-ethyl (3RS,4RS)-4-(4-methoxy-phenyl)-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a yellowish oil; MS: 539, 541 ($\text{M}+\text{NH}_4$)⁺.

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Example 46

(a) In an analogous manner to that described in Example 2(e), by hydrogenolytic cleavage of the benzyl group from (3RS,4RS)-1-benzyl-4-(4-hydroxy-phenyl)-piperidin-3-ol [Example 44(d)]
5 there was obtained (3RS,4RS)-4-(4-hydroxy-phenyl)-piperidin-3-ol as a colourless solid; MS: 194 (M+H)⁺.

b) In an analogous manner to that described in Example 22(g),
10 from (3RS,4RS)-4-(4-hydroxy-phenyl)-piperidin-3-ol by introduction of the BOC group there was obtained tert-butyl (3RS,4RS)-3-hydroxy-4-(4-hydroxy-phenyl)-piperidine-1-carboxylate as a colourless foam; MS: 237 (M-C₄H₈)⁺.

15 (c) A mixture of 4.5 g (15.3 mmol) of tert-butyl (3RS,4RS)-3-hydroxy-4-(4-hydroxy-phenyl)-piperidine-1-carboxylate, 20.8 g (91.8 mmol, 6.0 eq.) of 2-(3-chloropropyl)-2-phenyl-[1,3]dioxolane [J. Med. Chem. 34, 12 (1991)], 14.6 g (105.5 mmol, 6.9 eq.) of potassium carbonate and 2.0 g (0.012 mmol, 0.078 eq.)
20 of potassium iodide in 50 ml of methyl ethyl ketone were stirred in a sealed, pressure-tight vessel at a bath temperature of 100°C for 60 hours. The reaction mixture was poured into an ice/water mixture and extracted three times with ethyl acetate. The organic phases were each washed once with water and saturated
25 sodium chloride solution, dried over magnesium sulphate, concentrated under reduced pressure and dried in a high vacuum. The yellow oil (25.72 g) was separated on silica gel using an elution gradient of 4:1 to 1:1 of a mixture of hexane and ethyl acetate as the eluent. This yielded 5.34 g (72% of theory) of
30 white, crystalline tert-butyl (3RS,4RS)-3-hydroxy-4-[4-[3-(2-phenyl-[1,3]dioxolan-2-yl)-propoxy]-phenyl]-piperidine-1-carboxylate; MS: 484 (M+H)⁺.

(d) In an analogous manner to that described in Example 22(i),
35 by alkylating tert-butyl (3RS,4RS)-3-hydroxy-4-[4-[3-(2-phenyl-[1,3]dioxolan-2-yl)-propoxy]-phenyl]-piperidine-1-carboxylate with 2-bromomethylnaphthalene there was obtained tert-butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-[4-[3-(2-phenyl-

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[1,3]dioxolan-2-yl)-propoxy]-phenyl]-piperidine-1-carboxylate as white crystals; MS: 624 (M+H)⁺.

(e) A solution of 193 mg (0.31 mmol) of tert-butyl (3RS,4RS)-
 5 3-(naphthalen-2-ylmethoxy)-4-[4-[3-(2-phenyl-[1,3]dioxolan-2-yl)-propoxy]-phenyl]-piperidine-1-carboxylate in 3 ml of tetrahydrofuran and 3 ml of 2N hydrochloric acid was stirred at room temperature for 12 hours and at 50°C for 24 hours. Subsequently, the reaction mixture was poured into a 1:1 mixture
 10 of water and saturated sodium hydrogen carbonate solution and extracted three times with ethyl acetate. The organic phases were each washed once with water and saturated sodium chloride solution, dried over magnesium sulphate, concentrated under reduced pressure and dried in a high vacuum. The colourless oil
 15 (165 mg) was separated on silica gel using a 9:1 mixture of methylene chloride and methanol (extr. against 5 vol.% conc. NH₄OH). This yielded 127.4 mg of (3RS,4RS)-4-[4-(3-naphthalen-2-ylmethoxy-piperidin-4-yl)-phenoxy]-1-phenyl-butan-1-one in the form of a colourless oil; MS: 502 (M+Na)⁺.

20

Example 47

The following compounds were obtained in an analogous manner to that described in Example 46(d)-(e) and, respectively,
 25 3(c)-(e):

1) - From tert-butyl (3RS,4RS)-3-hydroxy-4-[4-[3-(2-phenyl-[1,3]dioxolan-2-yl)-propoxy]-phenyl]-piperidine-1-carboxylate by alkylation with 5-bromomethyl-benzo[b]thiophene there was
 30 obtained tert-butyl (3RS,4RS)-3-(benzo[b]thiophen-5-yl-methoxy)-4-{4-[3-(2-phenyl-[1,3]dioxolan-2-yl)-propoxy]-phenyl}-piperidine-1-carboxylate, MS: 630 (M+H)⁺, as a light yellow resin. Subsequent cleavage of the BOC and acetal groups yielded (3RS,4RS)-4-[4-[3-(benzo[b]thiophen-5-ylmethoxy)-
 35 piperidin-4-yl]-phenoxy]-1-phenyl-butan-1-one as a colourless resin; MS: 486 (M+H)⁺.

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2) - From tert-butyl (3RS,4RS)-3-hydroxy-4-[4-[3-(2-phenyl-[1,3]dioxolan-2-yl)-propoxy]-phenyl]-piperidine-1-carboxylate by alkylation with 5-(chloromethyl)indane there was obtained tert-butyl (3RS,4RS)-3-(indan-5-ylmethoxy)-4-{4-[3-(2-phenyl-[1,3]dioxolan-2-yl)-propoxy]-phenyl}-piperidine-1-carboxylate, MS: 614 (M+H)⁺, as a light yellow resin. Subsequent cleavage of the BOC and acetyl groups yielded (3RS,4RS)-4-[4-[3-indan-5-ylmethoxy)-piperidin-4-yl]-phenoxy]-1-phenyl-butan-1-one as a colourless resin; MS: 470 (M+H)⁺.

10

3) - From tert-butyl (3RS,4RS)-3-hydroxy-4-[4-[3-(2-phenyl-[1,3]dioxolan-2-yl)-propoxy]-phenyl]-piperidine-1-carboxylate by alkylation with 3-chloromethyl-1-(2-trimethylsilyl-ethoxymethyl)-naphthalene there was obtained tert-butyl (3RS,4RS)-4-[4-[3-(2-phenyl-[1,3]dioxolan-2-yl)-propoxy]-phenyl]-3-[4-(2-trimethylsilyl-ethoxymethoxy)-naphthalen-2-ylmethoxy]-piperidine-1-carboxylate, MS: 770 (M+H)⁺, as a colourless resin. Subsequent cleavage of the BOC group and of the two acetal groups yielded (3RS,4RS)-4-[4-[3-(4-hydroxy-naphthalen-2-ylmethoxy)-piperidin-4-yl]-phenoxy]-1-phenyl-butan-1-one as a colourless resin; R_f: 0.17 (SiO₂, methylene chloride:methanol = 9:1, extracted against 5% ammonia).

4) - From tert-butyl (3RS,4RS)-3-hydroxy-4-(4-hydroxy-phenyl)-piperidine-1-carboxylate by alkylation with 1-bromo-4-(2-bromoethyl)-benzene analogously to Example 46(c) there was obtained tert-butyl (3RS,4RS)-4-[4-[2-(4-bromo-phenoxy)-ethoxy]-phenyl]-3-hydroxy-piperidine-1-carboxylate as a colourless resin. Further alkylation with 2-bromomethyl-naphthalene gave tert-butyl (3RS,4RS)-4-[4-[2-(4-bromo-phenoxy)-ethoxy]-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate, from which by cleavage of the BOC group there was obtained (3RS,4RS)-4-[4-[2-(4-bromo-phenoxy)-ethoxy]-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine as a colourless resin; MS: 532, 534(M+H)⁺.

5) - From tert-butyl (3RS,4RS)-3-hydroxy-4-(4-hydroxy-phenyl)-piperidine-1-carboxylate by alkylation with 2-bromo-

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methyl-5-phenyl-[1,3,4]oxadiazole analogously to Example 44(e) there was obtained tert-butyl (3RS,4RS)-3-hydroxy-4-[4-(5-phenyl-[1,3,4]oxadiazol-2-ylmethoxy)-phenyl]-piperidine-1-carboxylate as a yellowish, amorphous solid. Further alkylation
 5 with 2-bromomethylnaphthalene gave tert-butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-[4-(5-phenyl-[1,3,4]oxadiazol-2-ylmethoxy)-phenyl]-piperidine-1-carboxylate, from which by cleavage of the BOC group there was obtained (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-[4-(5-phenyl-[1,3,4]oxadiazol-2-ylmethoxy)-phenyl]piperidine as a colourless solid; MS: 492
 10 (M+H)⁺.

6) - From (3RS,4RS)-3-hydroxy-4-(4-hydroxy-phenyl)-piperidine-1-carboxylate by alkylation with β -bromophenethol
 15 analogously to Example 46(c) there was obtained tert-butyl (3RS,4RS)-3-hydroxy-4-[4-(2-phenoxy-ethoxy)-phenyl]-piperidine-1-carboxylate; MS: 414 (M+H)⁺. Further alkylation with 2-bromomethylnaphthalene gave tert-butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-[4-(2-phenoxy-ethoxy)-phenyl]-
 20 piperidine-1-carboxylate, MS: 554 (M+H)⁺, from which by cleavage of the BOC group there was obtained (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-[4-(2-phenoxy-ethoxy)-phenyl]-piperidine; MS: 454 (M+H)⁺.

25 7) - From tert-butyl (3RS,4RS)-3-hydroxy-4-[4-(2-phenoxy-ethoxy)-phenyl]-piperidine-1-carboxylate by alkylation with 2-chloromethyl-O-SEM there was obtained tert-butyl (3RS,4RS)-4-[4-(2-phenoxy-ethoxy)-phenyl]-3-[4-(2-trimethylsilanyl-ethoxymethoxy)-naphthalen-2-ylmethoxy]-piperidine-1-carboxylate;
 30 MS: 700 (M+H)⁺. Subsequent cleavage of the BOC and acetal groups yielded (3RS,4RS)-3-{4-[4-(2-phenoxy-ethoxy)-phenyl]-piperidin-3-yloxymethyl}-naphthalen-1-ol; MS: 470 (M+H)⁺.

Example 48

35

A solution of 18.7 mg (0.494 mmol, 6.7 eq.) of sodium borohydride in 0.35 ml of water was added using a syringe to a solution of 44 mg (0.074 mmol) of (3RS,4RS)-4-[4-[3-(4-

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hydroxy-naphthalen-2-ylmethoxy)-piperidin-4-yl]-phenoxy]-1-phenyl-butan-1-one in 1.5 ml of dioxan. The mixture was stirred at room temperature for 1.5 hours. Subsequently, the reaction solution was treated with the same amount by volume of ice-water and the mixture was brought to pH 1 with 2N hydrochloric acid. After stirring at room temperature for 5-10 minutes the mixture was adjusted to pH 9 with concentrated ammonia and the aqueous solution was extracted three times with one equivalent by volume of methylene chloride each time. The combined organic phases were dried over magnesium sulphate, concentrated at 45°C under reduced pressure and dried in a high vacuum. The brownish solid (40.1 mg) was separated on silica gel using a 9:1 mixture of methylene chloride and methanol (extr. against 5 vol.% conc. NH₃ aq.) as the eluent. This yielded 13 mg (35% of theory) of (3RS,4RS)-3-[4-[4-(4-hydroxy-4-phenyl-butoxy)-phenyl]-piperidin-4-yloxymethyl]-naphthalen-1-ol (configuration unknown in the butanol part) as a colourless oil; MS: 498 (M+H)⁺.

Example 49

20

The following alcohols were obtained in an analogous manner to that described in Example 48 by reduction of the ketones:

25 1) - The 2:1 or 1:2 mixture of (RS)- and (SR)-4-[4-[(3RS,4RS)-3-(indan-5-ylmethoxy)-piperidin-4-yl]-phenoxy]-1-phenyl-butan-1-ol as a colourless resin, MS: 472 (M+H)⁺, from (3RS,4RS)-4-[4-[3-indan-5-ylmethoxy)-piperidin-4-yl]-phenoxy]-1-phenyl-butan-1-one;

30

2) - The mixture of (RS)- and (SR)-4-[4-[(3RS,4RS)-3-(benzo[b]thiopen-5-ylmethoxy)-piperidin-4-yl]-phenoxy]-1-phenyl-butan-1-ol as a colourless resin, MS: 488 (M+H)⁺, from (3RS,4RS)-4-[4-[3-(benzo[b]thiophen-5-ylmethoxy)-piperidin-4-yl]-phenoxy]-1-phenyl-butan-1-one;

35

3) - 4-[4-[(3RS,4RS)-3-naphthalen-2-ylmethoxy-piperidin-4-yl]-phenoxy]-1-phenyl-butan-1-ol (configuration unknown in the

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butanol part) as a colourless resin, MS: 482 (M+H)⁺, from (3RS,4RS)-4-[4-(3-naphthalen-2-ylmethoxy-piperidin-4-yl)-phenoxy]-1-phenyl-butan-1-one.

5

Example 50

(a) In an analogous manner to that described in Example 22 (g), from (3RS,4RS)-4-[4-(3-naphthalen-2-ylmethoxy-piperidin-4-yl)-phenoxy]-1-phenyl-butan-1-one by introducing the BOC group
10 there was obtained tert-butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-[4-(4-oxo-4-phenyl-butoxy)-phenyl]-piperidine-1-carboxylate as a colourless solid; MS : 580 (M+H)⁺.

(b) Reduction of tert-butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-[4-(4-oxo-4-phenyl-butoxy)-phenyl]-piperidine-1-carboxylate analogously to Example 48 yielded tert-butyl (3RS,4RS)-4-[4-(4-hydroxy-4-phenyl-butoxy)-phenyl]-3-naphthalen-2-ylmethoxy-piperidine-1-carboxylate (configuration unknown in the butoxy part) as a colourless solid; MS: 582 (M+H)⁺.
20

(c) Alkylation of tert-butyl (3RS,4RS)-4-[4-(4-hydroxy-4-phenyl-butoxy)-phenyl]-3-naphthalen-2-ylmethoxy-piperidine-1-carboxylate with methyl iodide analogously to Example 22(i) gave tert-butyl (3RS,4RS)-4-[4-(4-methoxy-4-phenyl-butoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate (configuration unknown in the butoxy part) as a colourless oil;
25 R_f: 0.61 (SiO₂, hexane:ethyl acetate = 2:1).

(d) In an analogous manner to that described in Example 22(l), from tert-butyl (3RS,4RS)-4-[4-(4-methoxy-4-phenyl-butoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate by cleavage of the BOC group there was obtained (3RS,4RS)-4-[4-(4-methoxy-4-phenyl-butoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine (configuration unknown in the butoxy part) as a colourless resin; MS: 496 (M+H)⁺.
35

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Example 51

A solution of 30 mg (0.052 mmol) of tert-butyl (3RS,4RS)-4-[4-(4-hydroxy-4-phenyl-butoxy)-phenyl]-3-naphthalen-2-ylmethoxy-piperidine-1-carboxylate (configuration unknown in the butoxy part), 25.5 μ l (0.186 mmol, 3.6 eq.) of triethylamine and 1.7 ml of methylene chloride was treated in succession with 21.6 μ l (0.186 mmol, 3.6 eq.) of benzoyl chloride and 2 mg (0.016 mmol) of 4-dimethylaminopyridine. This reaction solution was stirred at room temperature for 10 hours, then poured into 5 ml of water and extracted three times with 10 ml of ethyl acetate each time. The combined organic phases were dried over magnesium sulphate, evaporated under reduced pressure and dried in a high vacuum. The light yellow resin (62 mg) was dissolved in 1 ml of methanol, again concentrated, dried in a high vacuum. Without further purification and characterization the product obtained was reacted with hydrogen chloride in methanol analogously to the procedure described in Example 22(I). The brown-yellow resin (56 mg) was separated on silica gel using a 95:5 mixture of methylene chloride and methanol (extracted against 5 vol.% conc. ammonia) as the eluent. There were obtained 15 mg (50% of theory) of 4-[4-[(3RS,4RS)-3-naphthalen-2-ylmethoxy-piperidin-4-yl]-phenoxy]-1-phenyl-butyl benzoate (configuration unknown in the butoxy part) as a colourless resin; MS: 586 (M+H)+.

Example 52

A mixture of 600 mg (0.962 mmol) of tert-butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-{4-[3-(2-phenyl-[1,3]dioxolan-2-yl)-propoxy]-phenyl}-piperidine-1-carboxylate in 3.0 ml of methylene chloride and 433 mg (1.92 mmol, 2.0 eq.) of zinc bromide was stirred at room temperature for 4 hours. The reaction mixture was poured into water and extracted three times with ethyl acetate. The organic phases were washed in each case once with water and with saturated sodium chloride solution, dried over magnesium sulphate, evaporated under reduced pressure and dried in a high vacuum. The amorphous,

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slightly yellow crude product was separated on silica gel using a 95:5:0.1 mixture of methylene chloride, methanol and ammonia. There were obtained 355 mg (71% of theory) of (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-[4-[3-(2-phenyl-[1,3]dioxolan-2-yl)-propoxy]-phenyl]-piperidine as a colourless resin; MS: 524 (M+H)⁺.

Example 53

(a) In an analogous manner to that described in Example 44(e)-(f), by alkylating tert-butyl (3RS,4RS)-3-hydroxy-4-(4-hydroxy-phenyl)-piperidine-1-carboxylate with 2-(2-iodo-ethoxy)-tetrahydro-pyran there was obtained a mixture of tert-butyl (3RS,4RS)-3-hydroxy-4-[4-[2-[(RS)- and -[(SR)-tetrahydro-pyran-2-yloxy]-ethoxy]-phenyl]-piperidine-1-carboxylate as a yellow oil; R_f : 0.45 (SiO₂, hexane:ethyl acetate = 1:1).

b) In an analogous manner to that described in Example 22(i), by alkylating the mixture of tert-butyl (3RS,4RS)-3-hydroxy-4-[4-[2-[(RS)- and -[(SR)-tetrahydro-pyran-2-yloxy]-ethoxy]-phenyl]-piperidine-1-carboxylate with 2-bromomethyl-naphthalene there was obtained a mixture of tert-butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-[4-[2-[(RS)- and -[(SR)-tetrahydro-pyran-2-yloxy]-ethoxy]-phenyl]-piperidine-1-carboxylate as a colourless solid; MS: 579 (M+H)⁺.

(c) A solution of 1.99 g (3.54 mmol) of a mixture of tert-butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-[4-[2-[(RS)- and -[(SR)-tetrahydro-pyran-2-yloxy]-ethoxy]-phenyl]-piperidine-1-carboxylate in 11.3 ml of methanol was treated with 11.3 ml of 2N hydrogen chloride in methanol and the mixture was stirred at room temperature for 5 minutes. The reaction mixture was poured into 200 ml of a mixture of ice and saturated sodium hydrogen carbonate solution and extracted three times with ethyl acetate. The organic phases were washed with saturated sodium chloride solution, dried over magnesium sulphate, evaporated under reduced pressure and dried in a high vacuum. The yellow resin (1.80 g) was recrystallized from hexane. There were

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obtained 950 mg (56%) of tert-butyl (3RS,4RS)-4-[4-(2-hydroxy-ethoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a colourless solid; MS: 478 (M+H)⁺.

5 d) In an analogous manner to that described in Example 22(k), by acylating tert-butyl (3RS,4RS)-4-[4-(2-hydroxy-ethoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate with 4-chlorobenzoyl chloride there was obtained tert-butyl (3RS,4RS)-4-[4-[2-(4-chloro-benzoyloxy)-ethoxy]-phenyl]-3-
10 (naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a colourless oil; MS : 616 (M+H)⁺.

(e) In an analogous manner to that described in Example 22(l), from tert-butyl (3RS,4RS)-4-[4-[2-(4-chloro-benzoyloxy)-
15 ethoxy]-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate by cleavage of the BOC group there was obtained (3RS,4RS)-2-[4-(3-naphthalen-2-ylmethoxy-piperidin-4-yl)-phenoxy]-ethyl 4-chloro-benzoate hydrochloride as a colourless solid; MS: 516 (M+H)⁺.

20

Example 54

The following compounds were obtained in an analogous manner to that described in Example 22(l) by cleavage of the BOC
25 group using acid:

1) - (3RS,4RS)-2-[4-[3-(Naphthalen-2-ylmethoxy)-piperidin-4-yl]-phenoxy]-ethyl 4-methoxy-benzoate hydrochloride as a colourless solid, MS: 512 (M+H)⁺, from tert-butyl (3RS,4RS)-4-
30 [4-[2-(4-methoxy-benzoyloxy)-ethoxy]-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate;

2) - (3RS,4RS)-2-[4-(3-naphthalen-2-ylmethoxy-piperidin-4-yl)-phenoxy]-ethyl 2-chloro-benzoate hydrochloride as a
35 colourless solid, MS: 516 (M+H)⁺, from tert-butyl (3RS,4RS)-4-[4-[2-(2-chloro-benzoyloxy)-ethoxy]-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate;

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- 3) - (3RS,4RS)-2-[4-[3-(naphthalen-2-yloxy)-piperidin-4-yl]-phenoxy]-ethyl benzoate as a colourless, amorphous solid, MS: 340 (M-naphthylmethyl)+, from tert-butyl (3RS,4RS)-4-[4-(2-benzoyloxy-ethoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-
5 piperidine-1-carboxylate;
- 4) - (3RS,4RS)-2-[4-[3-(naphthalen-2-ylmethoxy)-piperidin-4-yl]-phenoxy]-ethyl 2-benzoyloxymethyl-benzoate hydrochloride as a colourless solid, MS: 616 (M+H)+, from tert-butyl (3RS,4RS)-
10 4-[4-[2-(2-benzoyloxymethyl-benzoyloxy)-ethoxy]-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate;
- 5) - (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-[4-(2-phenylsulphanyl-ethoxy)-phenyl]-piperidine hydrochloride as a colour-
15 less solid, MS: 470 (M+H)+, from tert-butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-[4-(2-phenylsulphanyl-ethoxy)-phenyl]-piperidine-1-carboxylate;
- 6) - (3RS,4RS)-3-naphthalen-2-ylmethoxyxy-4-[4-(2-phenylsulphonyl-ethoxy)-phenyl]-piperidine as a yellowish foam,
20 MS: 502 (M+H)+, from tert-butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-[4-(2-phenylsulphonyl-ethoxy)-phenyl]-piperidine-1-carboxylate;
- 7) - (3RS,4RS)-N-[2-[4-[3-(naphthalen-2-yloxy)-piperidin-4-yl]-phenoxy]-ethyl-benzamide as a colourless, amorphous solid,
25 MS: 481 (M+H)+, from tert-butyl (3RS,4RS)-4-[4-(2-benzoylamino-ethoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate;
- 8) - (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-[4-(2-[1,2,4]-triazol-1-yl-ethoxy)-phenyl]-piperidine hydrochloride as a white
30 powder, MS: 428 (M)+, from tert-butyl (3RS,4RS)-3-naphthalen-2-ylmethoxy-4-[4-(2-[1,2,4]triazol-1-yl-ethoxy)-phenyl]-
35 piperidine-1-carboxylate;
- 9) - (3RS,4RS)-4-[4-(2-benzyloxy-ethoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine, MS: 468 (M+H)+, from

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tert-butyl (3RS,4RS)-4-[4-(2-benzyloxy-ethoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate.

The BOC derivatives used as the starting materials were
5 prepared as follows:

(a) A solution of 150 mg (0.314 mmol) of tert-butyl (3RS,4RS)-4-[4-(2-hydroxy-ethoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate, 3.7 mg (0.031 mmol, 0.1 eq.) of
10 4-dimethylaminopyridine, 65.9 mg (0.375 mmol, 1.2 eq.) of 4-methoxy-benzoyl chloride and 51.7 µl of triethylamine in 10 ml of methylene chloride was stirred at room temperature for 15 hours. This reaction solution was poured into 50 ml of an ice/water mixture and extracted three times with ethyl acetate.
15 The organic phases were washed once with water and once with saturated sodium chloride solution, dried over magnesium sulphate, evaporated under reduced pressure and dried in a high vacuum. The crude product (208 mg) was separated on silica gel using a 95:5 mixture of hexane and acetone as the eluent. There
20 were obtained 104 mg (51% of theory) of tert-butyl (3RS,4RS)-4-[4-[2-(4-methoxy-benzoyloxy)-ethoxy]-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a colourless oil; MS: 612 (M+H)⁺.

25 (b) In an analogous manner to that described in Example 22(k), by acylating (3RS,4RS)-4-[4-(2-hydroxy-ethoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate with 2-chlorobenzoyl chloride there was obtained tert-butyl (3RS,4RS)-4-[4-[2-(2-chloro-benzoyloxy)-ethoxy]-phenyl]-3-
30 (naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a yellow oil; MS: 616 (M+H)⁺.

c) In an analogous manner to that described in Example 22(k), by acylating tert-butyl (3RS,4RS)-4-[4-(2-hydroxy-ethoxy)-
35 phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate with benzoyl chloride there was obtained tert-butyl (3RS,4RS)-4-[4-(2-benzoyloxy-ethoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-

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piperidine-1-carboxylate as a colourless, amorphous solid; R_f : 0.61 (SiO_2 , hexane:acetone = 95:5).

(d) In an analogous manner to that described in Example 22(k),
5 by acylating tert-butyl (3RS,4RS)-4-[4-(2-hydroxy-ethoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate with 2-chlorocarbonyl-benzyl benzoate there was obtained tert-butyl (3RS,4RS)-4-[4-[2-(2-benzoyloxymethyl-benzoyloxy)-ethoxy]-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-
10 carboxylate as a colourless solid; MS: 716 ($M+H$)⁺.

(e) In an analogous manner to that described in Example 33(a),
from tert-butyl (3RS,4RS)-4-[4-(2-hydroxy-ethoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate and diphenyl
15 sulphide there was obtained tert-butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-[4-(2-phenylsulphanyl-ethoxy)-phenyl]-piperidine-1-carboxylate as a colourless solid; MS: 570 ($M+H$)⁺.

(f) In an analogous manner to that described in Example 33(c),
20 by oxidizing tert-butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-[4-(2-phenylsulphanyl-ethoxy)-phenyl]-piperidine-1-carboxylate there was obtained tert-butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-[4-(2-phenylsulphonyl-ethoxy)-phenyl]-piperidine-1-carboxylate as a colourless foam; MS: 619 ($M+NH_4$)⁺.

25
(g) A solution of 478 mg (1.00 mmol) of tert-butyl (3RS,4RS)-4-[4-(2-hydroxy-ethoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate and 93 ml of mesyl chloride in 5 ml of pyridine was stirred at room temperature for 2 hours. Subsequently, the reaction solution was poured into 50 ml of an
30 ice/water mixture and extracted three times with methylene chloride. The organic phases were washed twice with water, dried over magnesium sulphate, evaporated under reduced pressure and dried in a high vacuum. This yielded 569 mg of crude
35 tert-butyl (3RS,4RS)-4-[4-(2-methylsulphonyloxy-ethoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate, which was used in the following step without further purification and characterization.

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(h) A mixture of 569 mg of crude tert-butyl (3RS,4RS)-4-[4-(2-methylsulphonyloxy-ethoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate and 650 mg of sodium azide
5 in 20 ml of dimethyl sulphoxide was stirred at 80°C for 3.5 hours. Subsequently, this reaction solution was poured into 50 ml of an ice/water mixture and extracted three times with ethyl acetate. The organic phases were washed with water, dried over magnesium sulphate, evaporated under reduced pressure and
10 dried in a high vacuum. The yellow oil (670 mg) was separated on silica gel using a 9:1 mixture of hexane and ethyl acetate as the eluent. There were obtained 271 mg (54% of theory over both steps) of tert-butyl (3RS,4RS)-4-[4-(2-azido-ethoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a
15 colourless solid; MS: 503 (M+H)⁺.

(i) A mixture of 115.9 mg (0.231 mmol) of tert-butyl (3RS,4RS)-4-[4-(2-azido-ethoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate, 87.4 mg (0.330 mmol,
20 1.43 eq.) of triphenylphosphine and 6.1 µl (6.1 mg, 0.339 mmol, 1.47 eq.) of deionized water was stirred at room temperature for 4 hours. Subsequently, 3 ml of acetic acid were added and the mixture was stirred at room temperature for 17 hours. This reaction mixture was poured into an ice/water mixture, made
25 basic with saturated sodium hydrogen carbonate solution and extracted three times with ethyl acetate. The organic phases were washed once with water and once with saturated sodium chloride solution, dried over magnesium sulphate, evaporated under reduced pressure and dried in a high vacuum. This yielded
30 192.3 mg of crude tert-butyl (3RS,4RS)-4-[4-(2-amino-ethoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate, which was used in the following reaction without further purification; R_f: 0.10 (SiO₂, methylene chloride:acetone = 95:5 + 0.1% ammonia)

35

j) A solution of 192.4 mg of crude tert-butyl (3RS,4RS)-4-[4-(2-amino-ethoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate in 3 ml of methylene chloride was

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treated at 0°C with 51.7 ml of triethylamine and 64.9 mg (0.462 mmol, 2.0 eq.) of benzoyl chloride and the mixture was stirred at 0°C for 0.75 hr and at room temperature for 3 hours. The reaction mixture was poured into an ice/water mixture, made
5 basic with saturated sodium hydrogen carbonate solution and extracted three times with ethyl acetate. The organic phases were washed once with water and once with saturated sodium chloride solution, dried over magnesium sulphate, evaporated under reduced pressure and dried in a high vacuum. The colourless
10 oil was separated on silica gel using a 95:5 mixture of methylene chloride and acetone as the eluent. There were obtained 44.9 mg (33% of theory) of tert-butyl (3RS,4RS)-4-[4-(2-benzoylamino-ethoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate in the form of a light yellow oil; MS: 581 (M+H)⁺.

15 (k) A solution of 110 mg (0.2 mmol) of crude tert-butyl (3RS,4RS)-4-[4-(2-methylsulphonyloxy-ethoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate in 5 ml of dimethylformamide was treated with 70 mg (1.0 mmol) of 1,2,4-
20 triazole sodium salt and the reaction mixture was heated to 100°C for 6 hours. Subsequently, the mixture was cooled to room temperature and the dimethylformamide was distilled off in an oil pump vacuum. The residue was taken up in 10 ml of methylene chloride, washed with 2 ml of water, the organic phase was
25 dried over sodium sulphate and evaporated under reduced pressure. The residue was chromatographed on silica gel using a 95:5:0.1 mixture of methylene chloride, methanol and ammonia as the eluent. There were obtained 90 mg (85% of theory) of tert-butyl (3RS,4RS)-3-naphthalen-2-ylmethoxy-4-[4-(2-[1,2,4]-
30 triazol-1-yl-ethoxy)-phenyl]-piperidine-1-carboxylate as a colourless oil; MS: 529 (M+H)⁺.

(l) In analogy to the procedure described in Example 3(c), by alkylating tert-butyl (3RS,4RS)-4-[4-(2-hydroxy-ethoxy)-
35 phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate with benzyl bromide there was obtained tert-butyl (3RS,4RS)-4-[4-(2-benzyloxy-ethoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate; MS: 568 (M+H)⁺.

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Example 55

The following compounds were obtained in an analogous
 5 manner to that described in Example 22(I):

- 1) - (3RS,4RS)-2-{4-[3-(4-Hydroxy-naphthalen-2-ylmethoxy)-
 piperidin-4-yl]-phenoxy}-ethyl 2-chloromethyl-benzoate as a
 colourless oil from tert-butyl (3RS,4RS)-4-[4-[2-(2-chloro-
 10 methyl-benzoyloxy)-ethoxy]-phenyl]-3-[4-(2-trimethylsilanyl-
 ethoxymethoxy)-naphthalen-2-ylmethoxy]-piperidine-1-
 carboxylate by simultaneous cleavage of the BOC and acetal
 groups;
- 15 2) - (3RS,4RS)-2-[4-[3-[4-(2-methoxy-benzyloxy)-naphthalen-
 2-ylmethoxy]-piperidin-4-yl]-phenoxy]-ethyl benzoate hydro-
 chloride as a colourless solid, MS: 618 (M+H)⁺, from tert-butyl
 (3RS,4RS)-4-[4-(2-benzoyloxy-ethoxy)-phenyl]-3-[4-(2-
 methoxy-benzyloxy)-naphthalen-2-ylmethoxy]-piperidine-1-
 20 carboxylate;
- 3) - (3RS,4RS)-4-[4-(2-benzyloxy-ethoxy)-phenyl]-3-(4-
 benzyloxy-naphthalen-2-ylmethoxy)-piperidine, MS: 574 (M+H)⁺,
 from tert-butyl (3RS,4RS)-4-[4-(2-benzyloxy-ethoxy)-phenyl]-3-
 25 (4-benzyloxy-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate.

The BOC derivatives used as the starting materials were
 prepared as follows:

- 30 (a) In an analogous manner to that described in Example 44(e),
 by alkylating a mixture of tert-butyl (3RS,4RS)-3-hydroxy-4-[4-
 [2-[(RS)- and -[(SR)-tetrahydro-pyran-2-yloxy]-ethoxy]-phenyl]-
 piperidine-1-carboxylate with 3-chloromethyl-1-(2-trimethyl-
 silanyl-ethoxymethoxy)-naphthalene there was obtained a
 35 mixture of tert-butyl (3RS,4RS)-4-[4-[2-[(RS)- and -[(SR)-
 tetrahydro-pyran-2-yl]-ethoxy]-phenyl]-3-[4-(2-trimethyl-
 silanyl-ethoxymethoxy)-naphthalen-2-ylmethoxy]-piperidine-1-
 carboxylate as a colourless oil; MS: 725 (M+NH₄)⁺.

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- (b) In an analogous manner to that described in Example 53(c), from a mixture of tert-butyl (3RS,4RS)-4-[4-[2-[(RS)- and -[(SR)-tetrahydro-pyran-2-yl]-ethoxy]-phenyl]-3-[4-(2-
5 trimethylsilyl-ethoxymethoxy)-naphthalen-2-ylmethoxy]-piperidine-1-carboxylate there was obtained tert-butyl (3RS,4RS)-4-[4-(2-hydroxy-ethoxy)-phenyl]-3-[4-(2-trimethylsilyl-ethoxymethoxy)-naphthalen-2-ylmethoxy]-piperidine-1-carboxylate as a colourless solid; MS: 624 (M+H)⁺.
- 10 (c) In an analogous manner to that described in Example 22(k), by acylating tert-butyl (3RS,4RS)-4-[4-(2-hydroxy-ethoxy)-phenyl]-3-[4-(2-trimethylsilyl-ethoxymethoxy)-naphthalen-2-ylmethoxy]-piperidine-1-carboxylate with 2-chloromethyl-
15 benzoyl chloride there was obtained tert-butyl (3RS,4RS)-4-[4-[2-(2-chloromethyl-benzoyloxy)-ethoxy]-phenyl]-3-[4-(2-trimethylsilyl-ethoxymethoxy)-naphthalen-2-ylmethoxy]-piperidine-1-carboxylate as a colourless solid; MS: 776 (M+H)⁺.
- 20 (d) 200 mg (0.28 mmol) of a mixture of tert-butyl (3RS,4RS)-4-[4-[2-[(RS)- and -[(SR)-tetrahydro-pyran-2-yl]-ethoxy]-phenyl]-3-[4-(2-trimethylsilyl-ethoxymethoxy)-naphthalen-2-ylmethoxy]-piperidine-1-carboxylate were dissolved in 7.6 ml 0.1M hydrogen chloride in methanol and the mixture was stirred
25 at room temperature for 2 hours. Subsequently, a further 0.36 ml of 2M hydrogen chloride in methanol was added and the mixture was stirred at room temperature for a further 2 hours. This reaction solution was poured into semi-saturated sodium hydrogen carbonate solution and extracted three times with ethyl
30 acetate. The organic phases were washed once with water and once with saturated sodium chloride solution, dried over magnesium sulphate, evaporated under reduced pressure and dried in a high vacuum. The yellowish oil (204 mg) was separated on silica gel using a 1:1 mixture of hexane and ethyl acetate
35 (extracted against concentrated ammonia). This yielded 111 mg (80% of theory) of tert-butyl (3RS,4RS)-4-[4-(2-hydroxy-ethoxy)-phenyl]-3-(4-hydroxy-naphthalen-2-ylmethoxy)-

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piperidine-1-carboxylate in the form of a colourless oil; R_f: 0.26 (SiO₂, hexane:ethyl acetate = 1:1).

(e) In an analogous manner to that described in Example 44(e),
5 by alkylating tert-butyl (3RS,4RS)-4-[4-(2-hydroxy-ethoxy)-phenyl]-3-(4-hydroxy-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate with 2-methoxybenzyl chloride there was obtained tert-butyl (3RS,4RS)-4-[4-(2-hydroxy-ethoxy)-phenyl]-3-[4-(2-methoxy-benzyloxy)-naphthalen-2-ylmethoxy]-piperidine-1-
10 carboxylate as a colourless oil; MS: 652 (M+K)⁺.

(f) In an analogous manner to that described in Example 22(k),
by acylating tert-butyl (3RS,4RS)-4-[4-(2-hydroxy-ethoxy)-phenyl]-3-[4-(2-methoxy-benzyloxy)-naphthalen-2-ylmethoxy]-
15 piperidine-1-carboxylate with benzoyl chloride there was obtained tert-butyl (3RS,4RS)-4-[4-(2-benzoyloxy-ethoxy)-phenyl]-3-[4-(2-methoxy-benzyloxy)-naphthalen-2-ylmethoxy]-piperidine-1-carboxylate as a colourless oil; MS: 736 (M+H)⁺.

20 (g) In an analogous manner to that described in Example 1(g), by two-fold alkylation of tert-butyl (3RS,4RS)-4-[4-(2-hydroxy-ethoxy)-phenyl]-3-(4-hydroxy-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate with benzyl bromide there was obtained tert-butyl (3RS,4RS)-4-[4-(2-benzyloxy-ethoxy)-phenyl]-3-(4-benzyloxy-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate.
25

Example 56

The following compounds were obtained in an analogous
30 manner to that described in Example 22(l) by simultaneous cleavage of the BOC and SEM groups using acid:

1) - (3RS,4RS)-2-[4-(3-Naphthalen-2-ylmethoxy-piperidin-4-yl)-phenoxy]-ethyl 4-hydroxy-benzoate hydrochloride as a
35 colourless solid, MS: 498 (M+H)⁺, from tert-butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-[4-[2-[4-(2-trimethylsilyl-ethoxymethoxy)-benzoyloxy]-ethoxy]-phenyl]-piperidine-1-carboxylate;

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- 2) - (3RS,4RS)-3-[4-[4-(2-benzyloxy-ethoxy)-phenyl]-piperidin-3-yloxymethyl}-naphthalen-1-ol, MS: 484 (M+H)⁺, from tert-butyl (3RS,4RS)-4-[4-(2-benzyloxy-ethoxy)-phenyl]-3-(4-hydroxy-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate.

The BOC derivatives used as the starting materials were prepared as follows:

- (a) In an analogous manner to that described under Example 24(l), from tert-butyl (3RS,4RS)-4-[4-(2-hydroxy-ethoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate and 4-(2-trimethylsilyl-ethoxymethoxy)-benzoic acid using N-ethyl-N'-(3-dimethylaminopropyl)-carbodiimide hydrochloride (EDC) as the condensation agent there was obtained tert-butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-[4-[2-[4-(2-trimethylsilyl-ethoxymethoxy)-benzoyloxy]-ethoxy]-phenyl]-piperidine-1-carboxylate as a colourless, amorphous solid; MS: 728 (M+H)⁺.
- (b) In an analogous manner to that described in Example 1(g), by alkylating tert-butyl (3RS,4RS)-4-[4-(2-hydroxy-ethoxy)-phenyl]-3-[4-(2-trimethylsilyl-ethoxymethoxy)-naphthalen-2-ylmethoxy]-piperidine-1-carboxylate with benzyl bromide there was obtained tert-butyl (3RS,4RS)-4-[4-(2-benzyloxy-ethoxy)-phenyl]-3-(4-hydroxy-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate.

Example 57

- (a) In an analogous manner to that described in Example 44(e), by alkylating tert-butyl (3RS,4RS)-3-hydroxy-4-(4-hydroxy-phenyl)-piperidine-1-carboxylate with 2-(3-bromo-propoxy)-tetrahydro-pyran there was obtained a mixture of tert-butyl (3RS,4RS)-3-hydroxy-4-[4-[3-[(RS)- and -[(SR)-tetrahydro-pyran-2-yloxy]-propoxy]-phenyl]-piperidine-1-carboxylate as a colourless solid; R_f: 0.23 (SiO₂, hexane:ethyl acetate = 4:1).

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- (b) Alkylation of a mixture of tert-butyl (3RS,4RS)-3-hydroxy-4-[4-[3-[(RS)- and -[(SR)-tetrahydro-pyran-2-yloxy]-propoxy]-phenyl]-piperidine-1-carboxylate with 2-bromomethyl-naphthalene analogously to the procedure described in Example 22(i) gave a mixture of tert-butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-[4-[3-[(RS)- and -[(SR)-tetrahydro-pyran-2-yloxy]-propoxy]-phenyl]-piperidine-1-carboxylate as a yellow oil; R_f: 0.35 (SiO₂, hexane:acetone = 4:1).
- 10 (c) A solution of 5.22 g of the crude mixture of tert-butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-[4-[3-[(RS)- and -[(SR)-tetrahydro-pyran-2-yloxy]-propoxy]-phenyl]-piperidine-1-carboxylate in 30 ml of tetrahydrofuran and 30 ml of 2N hydrochloric acid was stirred at room temperature for 14 hours and at
15 40°C for 2 hours. The tetrahydrofuran was subsequently distilled off under reduced pressure and the residual aqueous phase was extracted three times with methylene chloride. The organic phase was dried over magnesium sulphate and thereafter the solvent was distilled off under reduced pressure. The resulting
20 yellow oil (2.9 g) was chromatographed on silica gel using a 9:1 mixture of methylene chloride and ethyl acetate as the eluent. There were obtained 1.08 g (34% of theory over both steps) of tert-butyl (3RS,4RS)-4-[4-(3-hydroxy-propoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate in the form
25 of a white amorphous solid; MS: 491 (M)⁺.
- (d) Reaction of tert-butyl (3RS,4RS)-4-[4-(3-hydroxy-propoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate with mesyl chloride analogously to the procedure
30 described in Example 54(h) gave tert-butyl (3RS,4RS)-4-[4-(3-methylsulphonyloxy-propoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a yellow oil; R_f: 0.50 (SiO₂, hexane:ethyl acetate = 1:1).
- 35 (e) A solution of 850 mg of crude tert-butyl (3RS,4RS)-4-[4-(3-methylsulphonyloxy-propoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate in 6.1 ml (48.98 mmol, 32.4 eq.) of a 33% methylamine solution in ethanol was stirred at room

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temperature for 14 hours. Thereupon, the solution was evaporated under reduced pressure. The yellow solid (932 mg) was chromatographed on silica gel using a 90:10:0.1 mixture of methylene chloride, methanol and ammonia as the eluent. This
 5 yielded 610 mg (80% of theory over both steps) of tert-butyl (3RS,4RS)-4-[4-(3-methylamino-propoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a colourless solid; MS: 505 (M+H)⁺.

10 (f) Acylation of tert-butyl (3RS,4RS)-4-[4-(3-methylamino-propoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate with benzoyl chloride analogously to the procedure described in Example 22(k) gave tert-butyl (3RS,4RS)-4-[4-[3-(benzoyl-methyl-amino)-propoxy]-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a colourless oil; MS: 609
 15 (M+H)⁺.

(g) In an analogous manner to the procedure described in Example 22(l), from tert-butyl (3RS,4RS)-4-[4-[3-(benzoyl-methyl-amino)-propoxy]-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate by cleavage of the BOC group there was
 20 obtained (3RS,4RS)-N-methyl-N-[3-[4-[3-(naphthalen-2-yloxy)-piperidine-4-yl]-phenoxy]-propyl]-benzamide as a colourless solid; MS: 509 (M+H)⁺.

25

Example 58

The following compounds were obtained in analogy to the procedure described in Example 8(g) by cleavage of the BOC group
 30 using hydrochloric acid in methanol:

1) -(3RS,4RS)-2-[4-(3-Naphthalen-2-ylmethoxy-piperidin-4-yl)-phenoxy]-ethyl pyridine-3-carboxylate hydrochloride as a colourless solid, MS: 483 (M+H)⁺, from 2-[4-[1-tert-butoxycarbonyl-3-(naphthalen-2-ylmethoxy)-piperidin-4-yl]-phenoxy]-ethyl (3RS,4RS)-nicotinate;
 35

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- 2) - (3RS,4RS)-2-[4-(3-naphthalen-2-ylmethoxy-piperidin-4-yl)-phenoxy]-ethyl 1,3-benzodioxole-5-carboxylate hydrochloride as a colourless solid, MS: 526 (M+H)⁺, from tert-butyl (3RS,4RS)-4-{4-[2-(benzo[1,3]dioxol-5-carbonyloxy)-ethoxy]-phenyl}-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate;
5
- 3) - (3RS,4RS)-2-[4-(3-naphthalen-2-ylmethoxy-piperidin-4-yl)-phenoxy]-ethyl thiophene-3-carboxylate hydrochloride as a colourless solid, MS: 488 (M+H)⁺, from tert-butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-{4-[2-(thiophene-3-carbonyloxy)-ethoxy]-phenyl}-piperidine-1-carboxylate;
10
- 4) - (3RS,4RS)-2-[4-(3-naphthalen-2-ylmethoxy-piperidin-4-yl)-phenoxy]-ethyl thiophene-2-carboxylate hydrochloride as a colourless solid, MS: 488 (M+H)⁺, from tert-butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-[4-[2-(thiophene-2-carbonyloxy)-ethoxy]-phenyl]-piperidine-1-carboxylate;
15
- 5) - 2-[(3RS,4RS)-4-[3-(naphthalen-2-ylmethoxy)-piperidin-4-yl]-phenoxy]-ethyl furan-3-carboxylate hydrochloride as a colourless solid, MS: 472 (M+H)⁺, from tert-butyl 4-[4-[2-(furan-3-carbonyloxy)-ethoxy]-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidin-1-carboxylate;
20
- 6) - 2-[(3RS,4RS)-4-[3-(naphthalen-2-ylmethoxy)-piperidin-4-yl]-phenoxy]-ethyl furan-2-carboxylate hydrochloride as a colourless solid, MS: 472 (M+H)⁺, from tert-butyl 4-[4-[2-(furan-2-carbonyloxy)-ethoxy]-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate;
25
- 7) - a mixture of (3RS,4RS)-2-[4-(2-naphthalen-2-ylmethoxy-piperidin-4-yl)-phenoxy]-ethyl (RS)- and (SR)-methoxy-phenyl-acetate hydrobromide as a brownish solid, MS: 526 (M+H)⁺, from a mixture of tert-butyl (3RS,4RS)-4-[4-[2-[(RS)- and (SR)-methoxyphenyl-acetoxy]ethoxy]phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate;
30
35

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- 8) - (3RS,4RS)-2-[4-(3-naphthalen-2-yl-methoxy-piperidin-4-yl)-phenoxy]-ethyl 2-methylsulphanyl-benzoate hydrochloride as a beige coloured solid, MS: 528 (M+H)⁺, from tert-butyl (3RS,4RS)-4-[4-[2-(2-methylsulphanyl-benzoyloxy)-ethoxy]-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate;
- 9) - (3RS,4RS)-2-[4-(2-naphthalen-2-ylmethoxy-piperidin-4-yl)-phenoxy]-ethyl (RS)- and (SR)-2-methylsulphanyl-benzoate hydrochloride as a colourless solid, MS: 544 (M+H)⁺, from tert-butyl (3RS,4RS)-4-{4-[2-[(RS)- and (SR)-2-methylsulphanyl-benzoyloxy]-ethoxy]-phenyl}-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate.

The BOC derivatives used as the starting materials were prepared as follows in an analogous manner to that described under Example 24 (I) using N-ethyl-N'-(3-dimethylaminopropyl)-carbodiimide hydrochloride (EDC) as the condensation agent:

- (a) 2-[4-[1-tert-Butoxycarbonyl-3-(naphthalen-2-ylmethoxy)-piperidin-4-yl]-phenoxy]-ethyl (3RS,4RS)-nicotinate as a colourless solid, MS: 481 (M-C₄H₉COO)⁺, from tert-butyl (3RS,4RS)-4-[4-(2-hydroxy-ethoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate and pyridine-3-carboxylic acid.
- (b) tert-Butyl (3RS,4RS)-4-{4-[2-(benzo[1,3]dioxol-5-carbonyloxy)-ethoxy]-phenyl}-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a colourless solid, MS: 626 (M+H)⁺, from tert-butyl (3RS,4RS)-4-[4-(2-hydroxy-ethoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate and piperonylic acid.
- (c) tert-Butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-{4-[2-(thiophen-3-carbonyloxy)-ethoxy]-phenyl}-piperidine-1-carboxylate as a colourless solid, MS: 587 (M)⁺, from tert-butyl (3RS,4RS)-4-[4-(2-hydroxy-ethoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate and thiophene-3-carboxylic acid.

- (d) tert-Butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-[4-[2-(thiophen-2-carbonyloxy)-ethoxy]-phenyl]-piperidine-1-carboxylate as a colourless solid, MS: 588 (M+H)⁺, from tert-butyl (3RS,4RS)-4-[4-(2-hydroxy-ethoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate and thiophene-2-carboxylic acid.
- (e) tert-Butyl 4-[4-[2-(furan-3-carbonyloxy)-ethoxy]-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a colourless solid, MS: 572 (M+H)⁺, from tert-butyl (3RS,4RS)-4-[4-(2-hydroxy-ethoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate and furan-3-carboxylic acid.
- (f) tert-Butyl 4-[4-[2-(furan-2-carbonyloxy)-ethoxy]-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a colourless solid, MS: 572 (M+H)⁺, from tert-butyl (3RS,4RS)-4-[4-(2-hydroxy-ethoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate and furan-2-carboxylic acid.
- (g) tert-Butyl (3RS,4RS)-4-[4-[2-(methoxy-phenyl-acetoxy)-ethoxy]-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a colourless oil, MS: 648 (M+Na)⁺, from tert-butyl (3RS,4RS)-4-[4-(2-hydroxy-ethoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate and (RS)- α -methoxy-phenylacetic acid.
- (h) tert-Butyl (3RS,4RS)-4-[4-[2-(2-methylsulphanyl-benzoyloxy)-ethoxy]-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a colourless solid, MS: 628 (M+H)⁺, from tert-butyl (3RS,4RS)-4-[4-(2-hydroxy-ethoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate and 2-methylsulphanyl-benzoic acid.
- (i) A solution of 170 mg (0.8 mmol) of sodium metaperiodate in 2 ml of water was added to a solution of 250 mg (0.4 mmol) of tert-butyl (3RS,4RS)-4-[4-[2-(2-methylsulphanyl-benzoyloxy)-ethoxy]-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-

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carboxylate in 25 ml of methanol. The resulting reaction mixture was stirred at 50°C for 8 hours. Thereafter, the solvent was distilled off under reduced pressure, the residue was partitioned between ethyl acetate and water, the organic phase was dried
 5 over sodium sulphate and evaporated under reduced pressure. There were obtained 230 mg (90% of theory) of crude tert-butyl (3RS,4RS)-4-{4-[2-[(RS)- and (SR)-2-methylsulphanyl-benzoyloxy]-ethoxy]-phenyl}-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a colourless solid; MS : 644 (M+H)⁺.

10

Example 59

The following compounds were obtained in an analogous manner to that described in Example 22(I) by cleavage of the BOC
 15 group:

- 1) - (3RS,4RS)-4-[4-(3-Morpholin-4-yl-propoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine as a colourless solid, MS: 461 (M+H)⁺, from tert-butyl (3RS,4RS)-4-[4-(3-morpholin-
 20 4-yl-propoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate;
- 2) - (3RS,4RS)-3-[4-(3-naphthalen-2-ylmethoxy-piperidin-4-yl)-phenoxy]-propyl 2,2-dimethyl-propionate as a colourless,
 25 amorphous solid, MS: 476 (M+H)⁺, from tert-butyl (3RS,4RS)-4-[4-[3-(2,2-dimethyl-propionyloxy)-propoxy]-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate;
- 3) - (3RS,4RS)-3-[4-(3-naphthalen-2-ylmethoxy-piperidin-4-
 30 yl)-phenoxy]-propyl benzoate hydrochloride as a colourless solid, MS: 496 (M+H)⁺, from tert-butyl (3RS,4RS)-4-[4-(3-benzoyloxy-propoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate;
- 35 4) - (3RS,4RS)-4-(4-benzyloxy-phenyl)-3-(naphthalen-2-yloxy)-piperidine as a colourless, amorphous solid, MS: 424 (M+H)⁺, from tert-butyl (3RS,4RS)-4-(4-benzyloxy-phenyl)-3-(naphthalen-2-yloxy)-piperidine-1-carboxylate;

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5) - (3RS,4RS)-3-(2-methoxy-benzyloxy)-4-(4-naphthalen-2-ylmethoxy-phenyl)-piperidine hydrochloride as a colourless solid, MS: 454 (M+H)⁺, from tert-butyl (3RS,4RS)-3-(2-methoxy-benzyl-
oxy)-4-[4-(naphthalen-2-ylmethoxy)-phenyl]-piperidine-1-
carboxylate

The BOC derivatives used as the starting materials were prepared as follows:

10

(a) A solution of 200 mg (0.35 mmol) of tert-butyl 3RS,4RS)-4-[4-(3-methylsulphonyloxy-propoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate in 1 ml of ethyl acetate was treated with 60 µl of morpholine and boiled under reflux for
15 3 hours. Subsequently, the reaction solution was diluted with 5 ml of ethyl acetate and extracted twice with 1 ml of saturated sodium hydrogen carbonate solution each time. The organic phases were dried over magnesium sulphate, evaporated under reduced pressure and dried in a high vacuum. The colourless
20 oil (169 mg) was chromatographed on silica gel using ethyl acetate and the eluent. There were obtained 142 mg of tert-butyl (3RS,4RS)-4-[4-(3-morpholin-4-yl-propoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate in the form of white crystals; MS: 561 (M+H)⁺.

25

(b) In an analogous manner to that described in Example 22(k), by acylating tert-butyl (3RS,4RS)-4-[4-(3-hydroxy-propoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate with pivaloyl chloride there was obtained tert-butyl (3RS,4RS)-
30 4-[4-[3-(2,2-dimethyl-propionyloxy)-propoxy]-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a colourless oil; MS: 576 (M+H)⁺.

(c) In an analogous manner to that described in Example 22(k),
35 by acylating (3RS,4RS)-4-[4-(3-hydroxy-propoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate with benzoyl chloride there was obtained tert-butyl (3RS,4RS)-4-[4-(3-benzoyloxy-propoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-

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piperidine-1-carboxylate as a colourless oil; R_f : 0.84 (SiO_2 , hexane:ethyl acetate = 1:1).

(d) A mixture of 1.0 g (3.41 mmol) of tert-butyl (3RS,4RS)-3-hydroxy-4-(4-hydroxy-phenyl)-piperidine-1-carboxylate, 471 mg (34.1 mmol, 10 eq.) of potassium carbonate and 607 ml (5.11 mmol, 1.5 eq.) of benzyl bromide in 30 ml of dimethylformamide was stirred at room temperature for 2 hours and at 80°C for 15 hours. Subsequently, 471 mg (34.1 mmol, 10 eq.) of potassium carbonate and 607 ml (5.11 mmol, 1.5 eq.) of benzyl bromide were again added and the mixture was stirred at 80°C for a further 6 hours. The reaction mixture, cooled to room temperature, was poured into 300 ml of an ice/water mixture and extracted three times with 250 ml of ethyl acetate. The organic phases were washed once with water and once with saturated sodium chloride solution, dried over magnesium sulphate, evaporated under reduced pressure and dried in a high vacuum. The yellow oil (1.82 g) was separated on silica gel using an eluent gradient of 4:1 to 3:2 of a mixture of hexane and ethyl acetate as the eluent. There were obtained 620 mg (72% of theory) of tert-butyl (3RS,4RS)-4-(4-benzyloxy-phenyl)-3-hydroxy-piperidine-1-carboxylate which, after recrystallization from a mixture of methylene chloride and hexane, gave 361 mg (28% of theory) as a white, crystalline product; MS: 383 (M)⁺.

25

(e) In an analogous manner to that described in Example 22(i), by alkylating tert-butyl (3RS,4RS)-4-(4-benzyloxy-phenyl)-3-hydroxy-piperidine-1-carboxylate with 2-bromomethylnaphthalene there was obtained tert-butyl (3RS,4RS)-4-(4-benzyloxy-phenyl)-3-(naphthalen-2-yloxy)-piperidine-1-carboxylate as a colourless, amorphous solid; MS: 523 (M)⁺.

30

(f) In analogy to the procedure described in Example 14, by alkylating tert-butyl (3RS,4RS)-3-hydroxy-4-(4-hydroxy-phenyl)-piperidine-1-carboxylate with 2-bromomethylnaphthalene in the presence of potassium carbonate there was obtained tert-butyl (3RS,4RS)-3-hydroxy-4-[4-(naphthalen-2-

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ylmethoxy)-phenyl]-piperidine-1-carboxylate as a colourless solid; MS: 434 (M+H)⁺.

- (g) In analogy to the procedure described in Example 3(c), by
 5 alkylating tert-butyl (3RS,4RS)-3-hydroxy-4-[4-(naphthalen-2-ylmethoxy)-phenyl]-piperidine-1-carboxylate with 2-methoxybenzyl chloride there was obtained tert-butyl (3RS,4RS)-3-(2-methoxy-benzyloxy)-4-[4-(naphthalen-2-ylmethoxy)-phenyl]-piperidine-1-carboxylate as a colourless solid; MS: 554 (M+H)⁺.

10

Example 60

The following compounds were obtained in an analogous manner to that described in Example 25(b) by cleavage of the
 15 2,2,2-trichloroethyl carbamate by treatment with zinc in glacial acetic acid:

- 1) - 3-{4-[3-(Naphthalen-2-ylmethoxy)-piperidin-4-yl]-phenoxy}-propyl (3RS,4RS)-carbamate as a colourless solid,
 20 MS: 435 (M+H)⁺, from 2,2,2-trichloro-ethyl (3RS,4RS)-4-[4-(3-carbamoyloxy-propoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate;
- 2) - 3-{4-[3-(naphthalen-2-ylmethoxy)-piperidin-4-yl]-phenoxy}-propyl (3RS,4RS)-pyridin-2-yl-carbamate as a
 25 colourless oil, MS: 512 (M+H)⁺, from 2,2,2-trichloro-ethyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-{4-[3-(pyridin-2-ylcarbamoyloxy)-propoxy]-phenyl}-piperidine-1-carboxylate;
- 3) - (3RS,4RS)-2-[3-[3-(naphthalen-2-ylmethoxy)-piperidin-4-yl]-phenoxy]-ethyl pyridin-2-yl-carbamate as a colourless oil,
 30 MS: 498 (M+H)⁺, from 2,2,2-trichloro-ethyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-[3-(2-pyridin-2-ylcarbamoyloxy-ethoxy)-phenyl]-piperidine-1-carboxylate;
- 4) - (3RS,4RS)-2-[3-[3-(naphthalen-2-ylmethoxy)-piperidin-4-yl]-phenoxy]-ethyl carbamate as a colourless, amorphous solid,
 35 MS: 421 (M+H)⁺, from 2,2,2-trichloro-ethyl (3RS,4RS)-4-[3-(2-

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carbamoyloxy-ethoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate;

- 5) - (3RS,4RS)-2-[3-[3-(naphthalen-2-ylmethoxy)-piperidin-4-yl]-phenoxy]-ethanol as a colourless, amorphous solid, MS: 378 (M+H)⁺, from the mixture of 2,2,2-trichloro-ethyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-[3-[2-[(RS)- and -[(SR)-tetrahydropyran-2-yloxy]-ethoxy]-phenyl]-piperidine-1-carboxylate with simultaneous cleavage of the THP group;
- 6) - (3RS,4RS)-2-[4-(3-naphthalen-2-ylmethoxy-piperidin-4-yl)-phenoxy]-ethyl benzoate as a colourless, amorphous solid, MS: 482 (M+H)⁺, from 2,2,2-trichloroethyl (3RS,4RS)-4-[3-(2-benzoyloxy-ethoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate;
- 7) - 3-{3-[3-(naphthalen-2-ylmethoxy)-piperidin-4-yl]-phenoxy}-propyl (3RS,4RS)-pyridin-2-yl-carbamate as a colourless, amorphous solid, MS: 512 (M+H)⁺, from 2,2,2-trichloroethyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-{3-[3-(pyridin-2-ylcarbamoyloxy)-propoxy]-phenyl}-piperidine-1-carboxylate;
- 8) - (3RS,4RS)-4-[3-[3-(naphthalen-2-yloxy)-piperidin-4-yl]-phenoxy]-butyl benzoate as a colourless, amorphous solid, MS: 510 (M+H)⁺, from 2,2,2-trichloro-ethyl (3RS,4RS)-4-[3-(4-benzoyloxy-butoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate.

The 2,2,2-trichloroethyl carbamates used as the starting materials were prepared as follows:

The following procedure was carried out in an analogous manner to that described in Example 22(a)-(c):

- (a) 1-Benzyl-4-(3-methoxy-phenyl)-piperidin-4-ol was obtained as a colourless solid, R_f: 0.18 (SiO₂, methylene chloride: ethyl acetate = 1:1), from 1-benzyl-4-piperidone and 3-iodo-anisole. Subsequent elimination with p-toluenesulphonic acid

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yielded 1-benzyl-4-(3-methoxy-phenyl)-1,2,3,6-tetrahydro-pyridine as a colourless solid, MS: 279 (M)⁺. Hydroboration which followed gave 1-benzyl-4-(3-methoxy-phenyl)-piperidin-3-ol as a colourless powder, MS: 297 (M)⁺.

5

The following procedure was followed in an analogous manner to that described in Example 44 (d)-(i):

(b) From 1-benzyl-4-(3-methoxy-phenyl)-piperidin-3-ol by
 10 cleavage of the methyl ether (RS)- and (SR)-methoxy-phenyl-
 acetate boron tribromide in methylene chloride there was
 obtained (3RS,4RS)-1-benzyl-4-(3-hydroxy-phenyl)-piperidin-3-
 ol as a pale yellow solid; MS: 283 (M)⁺. Alkylation with rac.-2-
 (2-iodo-ethoxy)-tetrahydro-pyran in the presence of potassium
 15 carbonate gave a mixture of (3RS,4RS)-1-benzyl-4-[3-[2-[(RS)-
 and -[(SR)-tetrahydro-pyran-2-yloxy]-ethoxy]-phenyl]-piperidin-
 3-ol as a colourless oil; MS: 410 (M-H)⁺. By subsequent alkylation
 with 2-bromomethylnaphthalene in an analogous manner to that
 described in Example 22(i) there was obtained a mixture of
 20 (3RS,4RS)-1-benzyl-3-(naphthalen-2-ylmethoxy)-4-[3-[2-[(RS)-
 and -[(SR)-tetrahydro-pyran-2-yloxy]-ethoxy]-phenyl]-piperidine
 as a colourless oil; MS: 552 (M)⁺. Then, by cleavage of the benzyl
 group using 2,2,2-trichloroethyl chloroformate and potassium
 carbonate in an analogous manner to that described in Example
 25 25(a) there was obtained a mixture of 2,2,2-trichloroethyl
 (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-[3-[2-[(RS)- and
 -[(SR)-tetrahydro-pyran-2-yloxy]-ethoxy]-phenyl]-piperidine-1-
 carboxylate; R_f: 0.60 (SiO₂, methylene chloride:ethyl acetate =
 2:1). By subsequent cleavage of the THP group using p-toluene-
 30 sulphonic acid there was obtained 2,2,2-trichloro-ethyl
 (3RS,4RS)-4-[3-(2-hydroxy-ethoxy)-phenyl]-3-(naphthalen-2-
 ylmethoxy)-piperidine-1-carboxylate. Finally, by reaction with
 pyridine-2-carbonyl azide in an analogous manner to that
 described in Example 24(m) there was obtained 2,2,2-trichloro-
 35 ethyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-[3-(2-pyridin-2-
 ylcabamoyloxy-ethoxy)-phenyl]-piperidine-1-carboxylate; R_f:
 0.45 (SiO₂, methylene chloride:ethyl acetate = 9:1).

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(c) In an analogous manner to that described in Example 44(e), by alkylating (3RS,4RS)-1-benzyl-4-(4-hydroxy-phenyl)-piperidin-3-ol with rac.-2-(3-bromo-propoxy)-tetrahydro-pyran there was obtained (3RS,4RS)-1-benzyl-4-{4-[3-[(RS)- and (SR)-
 5 tetrahydro-pyran-2-yloxy]-propoxy]-phenyl}-piperidin-3-ol as a colourless solid; MS: 426 (M+H)⁺. Subsequent alkylation with 2-bromomethylnaphthalene according to the procedure described in Example 12(b) gave (3RS,4RS)-1-benzyl-3-(naphthalen-2-ylmethoxy)-4-{4-[3-[(RS)- and (SR)-tetrahydro-pyran-2-yloxy]-
 10 propoxy]-phenyl}-piperidine as a colourless solid; MS: 566 (M+H)⁺. Further reaction with 2,2,2-trichloroethyl chloroformate analogously to Example 12(c) yielded 2,2,2-trichloro-ethyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-{4-[3-[(RS)- and (SR)-tetrahydro-pyran-2-yloxy]-propoxy]-phenyl}-piperidine-1-
 15 carboxylate as a colourless solid; MS: 672 (M+Na)⁺. Cleavage of the THP group using p-toluenesulphonic acid analogously to Example 44(h) gave 2,2,2-trichloro-ethyl (3RS,4RS)-4-[4-(3-hydroxy-propoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a colourless solid; MS: 583 (M+NH₄)⁺.
 20 Finally, by reaction with sodium isocyanate in an analogous manner to that described in Example 24(m) there was obtained 2,2,2-trichloro-ethyl (3RS, 4RS)-4-[4-(3-carbamoyloxy-propoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a colourless solid; MS: 609 (M+H)⁺.

25

(d) In an analogous manner to that described in Example 24(m), by reacting 2,2,2-trichloro-ethyl (3RS,4RS)-4-[4-(3-hydroxy-propoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate with pyridine-2-carbonyl azide there was obtained
 30 2,2,2-trichloro-ethyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-{4-[3-(pyridin-2-ylcarbamoyloxy)-propoxy]-phenyl}-piperidine-1-carboxylate as a colourless solid.

e) In an analogous manner to that described in Example 24(m),
 35 by reacting 2,2,2-trichloro-ethyl (3RS,4RS)-4-[3-(2-hydroxy-ethoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate with sodium isocyanate there was obtained 2,2,2-trichloro-ethyl (3RS,4RS)-4-[3-(2-carbamoyloxy-ethoxy)-

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phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a colourless solid; R_f : 0.40 (SiO_2 , methylene chloride:methanol = 9:1).

5 (f) In an analogous manner to that described in Example 22(k), by acylating 2,2,2-trichloro-ethyl (3RS,4RS)-4-[3-(2-hydroxy-ethoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate with benzoyl chloride there was obtained 2,2,2-trichloroethyl (3RS,4RS)-4-[3-(2-benzoyloxy-ethoxy)-phenyl]-3-
10 (naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a colourless oil.

(g) In an analogous manner to that described in Example 14, by
15 alkylating (3RS,4RS)-1-benzyl-4-(3-hydroxy-phenyl)-piperidin-3-ol with rac.-2-(3-bromo-propoxy)-tetrahydro-pyran in the presence of potassium carbonate there was obtained a mixture of the diastereomeric racemates of (3RS,4RS)-1-benzyl-4-{3-[3-(tetrahydro-pyran-2-yloxy)-propoxy]-phenyl}-piperidin-3-ol as a colourless oil; R_f : 0.38 (hexane:acetone = 1:1). Subsequent alkyl-
20 ation with 2-bromomethylnaphthalene analogously to Example 12(b) gave a mixture of the diastereomeric racemates of 1-benzyl-3-(naphthalen-2-ylmethoxy)-4-{3-[3-(tetrahydro-pyran-2-yloxy)-propoxy]-phenyl}-piperidine as a colourless oil; MS: 566 ($M+H$)⁺. Subsequent reaction with 2,2,2-trichloroethyl
25 (sic) chloroformate analogously to Example 12(c) yielded a mixture of the diastereomeric racemates of 2,2,2-trichloroethyl 3-(naphthalen-2-ylmethoxy)-4-{3-[3-(tetrahydro-pyran-2-yloxy)-propoxy]-phenyl}-piperidine-1-carboxylate which, without further purification and characterization, was reacted with p-
30 toluenesulphonic acid analogously to Example 53(c) to give 2,2,2-trichloroethyl (3RS,4RS)-4-[3-(3-hydroxy-propoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate. Finally, by reaction with pyridine-2-carbonyl azide in an analogous manner to that described in Example 24(m) there was obtained 2,2,2-
35 trichloroethyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-{3-[3-(pyridin-2-ylcarbamoxyloxy)-propoxy]-phenyl}-piperidine-1-carboxylate as a colourless oil; R_f : 0.55 (methylene chloride:ethyl acetate = 1:1).

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(h) In an analogous manner to that described in Example 14, by alkylating (3RS,4RS)-1-benzyl-4-(3-hydroxy-phenyl)-piperidin-3-ol with rac.-2-(4-bromo-butoxy)-tetrahydro-pyran
 5 [S.W.Baldwin et al., J.Org.Chem. 1985, 50, 4432-4439] and further reacting as described under (g) there was obtained 2,2,2-trichloro-ethyl (3RS,4RS)-4-[3-(4-hydroxy-butoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a colourless solid; R_f: 0.50 (methylene chloride:ethyl acetate = 9:1).
 10 Subsequent acylation with benzoyl chloride analogously to Example 22(k) yielded 2,2,2-trichloro-ethyl (3RS,4RS)-4-[3-(4-benzoyloxy-butoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a colourless solid; R_f: 0.85 (SiO₂, methylene chloride:ethyl acetate = 95:5)

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Example 61

The following compounds were obtained in analogy to the procedure described in Example 10(b) by cleavage of the BOC
 20 group using zinc bromide in methylene chloride:

1) - (3RS,4RS)-2-[4-[3-(Naphthalen-2-yloxy)-piperidin-4-yl]-phenoxy]-1-phenyl-ethanone hydrobromide as a colourless solid, MS: 452 (M+H)⁺, from tert-butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-[4-(2-oxo-2-phenyl-ethoxy)-phenyl]-piperidine-1-carboxylate;
 25

2) - (3RS,4RS)-2-[4-[3-(2-methoxy-benzyloxy)-piperidin-4-yl]-phenoxy]-ethyl benzoate hydrobromide as a beige coloured
 30 solid, MS: 462 (M+H)⁺, from tert-butyl (3RS,4RS)-4-[4-(2-benzoyloxy-ethoxy)-phenyl]-3-(2-methoxy-benzyloxy)-piperidine-1-carboxylate;

3) - (3RS,4RS)-4-(4-[1,3]dioxolan-2-ylmethoxy-phenyl)-3-(naphthalen-2-ylmethoxy)-piperidine as a yellowish solid, MS: 420 (M+H)⁺, from tert-butyl (3RS,4RS)-4-[4-([1,3]dioxolan-2-ylmethoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate.
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The BOC derivatives used as the starting materials were obtained as follows:

- 5 (a) In an analogous manner to the procedure described in Example 14, by alkylating tert-butyl (3RS,4RS)-3-hydroxy-4-(4-hydroxy-phenyl)-piperidine-1-carboxylate with allyl bromide in the presence of potassium carbonate there was obtained tert-butyl (3RS,4RS)-4-(4-allyloxy-phenyl)-3-hydroxy-piperidine-1-
10 carboxylate as a colourless solid; m.p.: 113°C (hexane).
- (b) In analogy to the procedure described in Example 3(c) by alkylating tert-butyl (3RS,4RS)-4-(4-allyloxy-phenyl)-3-hydroxy-piperidine-1-carboxylate with 2-bromomethyl-
15 naphthalene there was obtained tert-butyl (3RS,4RS)-4-(4-allyloxy-phenyl)-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a colourless oil; MS: 474 (M+H)+.
- (c) A mixture of 400 mg (0.8 mmol) of tert-butyl (3RS,4RS)-4-(4-allyloxy-phenyl)-3-(naphthalen-2-ylmethoxy)-piperidine-1-
20 carboxylate, 0.2 ml of triethylamine, 0.5 ml of water and 78 mg of tris-(triphenylphosphine)rhodium(I) chloride in 10 ml of ethanol was stirred at reflux for 1 hour. The tert-butyl (3RS,4RS)-4-(4-hydroxy-phenyl)-3-(naphthalen-2-ylmethoxy)-
25 piperidine-1-carboxylate formed in part (30% of theory), MS: 434 (M+H)+, was separated by chromatography and was used in the following step.
- (d) In an analogous manner to the procedure described in
30 Example 14, by alkylating tert-butyl (3RS,4RS)-4-(4-hydroxy-phenyl)-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate with phenacyl bromide in the presence of potassium carbonate there was obtained tert-butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-[4-(2-oxo-2-phenyl-ethoxy)-phenyl]-piperidine-1-
35 carboxylate as a yellowish solid; MS: 551 (M)+.
- (e) In analogy to the procedure described in Example 3(c), by alkylating a mixture of tert-butyl (3RS,4RS)-3-hydroxy-4-[4-[2-

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[(RS)- and -[(SR)-tetrahydro-pyran-2-yloxy]-ethoxy]-phenyl]-
piperidine-1-carboxylate [Example 53(a)] with 2-methoxybenzyl
chloride there was obtained tert-butyl (3RS,4RS)-3-(2-methoxy-
benzyloxy)-4-{4-[2-[(RS)- and [(SR)-tetrahydro-pyran-2-yloxy]-
5 ethoxy]-phenyl}-piperidine-1-carboxylate as a colourless oil.

(f) In analogy to the procedure described in Example 53(c), by
cleaving the THP ether from tert-butyl (3RS,4RS)-3-(2-methoxy-
benzyloxy)-4-{4-[2-[(RS)- and [(SR)-tetrahydro-pyran-2-yloxy]-
10 ethoxy]-phenyl}-piperidine-1-carboxylate there was obtained
tert-butyl (3RS,4RS)-4-[4-(2-hydroxy-ethoxy)-phenyl]-3-(2-
methoxy-benzyloxy)-piperidine-1-carboxylate.

(g) In analogy to the procedure described in Example 22(k), by
15 acylating tert-butyl (3RS,4RS)-4-[4-(2-Hydroxy-ethoxy)-phenyl]-
3-(2-methoxy-benzyloxy)-piperidine-1-carboxylate there was
obtained tert-butyl (3RS,4RS)-4-[4-(2-benzoyloxy-ethoxy)-
phenyl]-3-(2-methoxy-benzyloxy)-piperidine-1-carboxylate as a
colourless, viscous liquid; MS: 562 (M+H)⁺.

20

(h) In an analogous manner to the procedure described in
Example 14, by alkylating tert-butyl (3RS,4RS)-3-hydroxy-4-(4-
hydroxy-phenyl)-piperidine-1-carboxylate with 2-bromomethyl-
1,3-dioxolane in the presence of potassium carbonate there was
25 obtained tert-butyl (3RS,4RS)-4-[4-([1,3]dioxolan-2-ylmethoxy)-
phenyl]-3-hydroxy-piperidine-1-carboxylate as a colourless
solid; m.p.: 136-137°C (hexane).

(i) In analogy to the procedure described in Example 3(c), by
30 alkylating tert-butyl (3RS,4RS)-4-[4-([1,3]dioxolan-2-yl-
methoxy)-phenyl]-3-hydroxy-piperidine-1-carboxylate with
2-bromomethylnaphthalene there was obtained tert-butyl (3RS,
4RS)-4-[4-([1,3]dioxolan-2-ylmethoxy)-phenyl]-3-(naphthalen-2-
ylmethoxy)-piperidine-1-carboxylate as a colourless solid; MS:
35 520 (M+H)⁺.

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Example 62

A solution of 210 mg (0.425 mmol) of tert-butyl (3RS,4RS,5SR)-4-(4-chloro-phenyl)-3-naphthalen-2-ylmethoxy-5-propyl-piperidine-1-carboxylate in 18 ml of methanol was treated with 12 ml of 1N hydrochloric acid and stirred at 50°C overnight. Subsequently, the solution was evaporated under reduced pressure, the residue was taken up in warm toluene and again evaporated, the product beginning to separate out. There were obtained 153 mg (84% of theory) of (3RS,4RS,5SR)-4-(4-chloro-phenyl)-3-naphthalen-2-ylmethoxy-5-propyl-piperidine as a colourless solid. MS: 252 (M-naphthylmethyl)+.

The tert-butyl (3RS,4RS,5SR)-4-(4-chloro-phenyl)-3-naphthalen-2-ylmethoxy-5-propyl-piperidine-1-carboxylate used as the starting material was prepared as follows:

(a) In an analogous manner to the procedure described by A. Ziering et al. in J. Org. Chem. 22, 1521-1528 (1957) for the preparation of piperidin-4-ones from the corresponding acrylic acid esters by reaction with methylamine or benzylamine, reaction with ethyl acrylate or methyl acrylate, cyclization and finally decarboxylation, starting from ethyl 2-propyl-acrylate and methylamine there was obtained (3RS)-1-methyl-3-propyl-piperidin-4-one as a colourless oil; R_f: 0.38 (SiO₂, methylene chloride:methanol = 95:5).

(b) 83.8 ml (134 mmol) of n-BuLi (1.6N in hexane) were added dropwise within 30 minutes to a solution, cooled to -78°C, of 25.68 g (134 mmol) of 1-bromo-4-chloro-benzene in 250 ml of tert-butyl methyl ether. After completion of the addition the mixture was stirred at -78°C for 1 hour. Thereafter, a solution of 10.41 g (67.05 mmol) of (3RS)-1-methyl-3-propyl-piperidin-4-one in 100 ml of tert-butyl methyl ether was added dropwise at -70 to -65°C. After the dropwise addition the mixture was stirred at -78°C for 2 hours. For the working-up, the reaction mixture was poured on to ice, transferred to a separating funnel and the organic phase was separated. The aqueous phase was

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extracted with ethyl acetate and subsequently the combined organic phases were dried over sodium sulphate and evaporated under reduced pressure. For purification, the crude product was chromatographed on silica gel using a 95:5:0.1 mixture of methylene chloride, methanol and ammonia as the eluent. There were
5 obtained 15.9 g (88% of theory) of (3RS,4RS)- and (3RS,4SR)-4-(4-chloro-phenyl)-1-methyl-3-propyl-piperidin-4-ol as a colourless solid; MS: 267 (M)⁺.

10 (c) A solution of 13.68 g (51.06 mmol) of (3RS,4RS)- and (3RS,4SR)-4-(4-chloro-phenyl)-1-methyl-3-propyl-piperidin-4-ol in 67 ml of trifluoroacetic acid was boiled under reflux for 18 hours. Thereafter, the reaction solution was evaporated under reduced pressure. The residue was partitioned between a
15 saturated sodium carbonate solution and ether, the separated aqueous phase was back-extracted with ether and finally the combined organic phases were dried over sodium sulphate and evaporated under reduced pressure. For purification of the crude product and separation of isomeric olefins, [the residue] was
20 chromatographed on silica gel using a 96:4 mixture of methylene chloride and methanol as the eluent. There were obtained 9.71 g (76% of theory) of (RS)-4-(4-chloro-phenyl)-1-methyl-3-propyl-1,2,3,6-tetrahydro-pyridine, MS: 249 (M)⁺, and 1.74 g of 4-(4-chloro-phenyl)-1-methyl-5-propyl-1,2,3,6-tetrahydro-pyridine,
25 MS: 248 (M-H)⁺, each as a yellowish oil.

(d) 2.23 g (60 mmol) of sodium borohydride were added spatula-wise to a suspension of 9.7 g (39 mmol) of (RS)-4-(4-chloro-phenyl)-1-methyl-3-propyl-1,2,3,6-tetrahydro-pyridine
30 in 80 ml of 1,2-dimethoxyethane in such a manner that the temperature did not rise above 35°C. Subsequently, 13.2 ml of boron trifluoride etherate dissolved in 15 ml of 1,2-dimethoxyethane were added dropwise during 45 minutes and thereafter the reaction mixture was stirred at room temperature for
35 2 hours. Subsequently, firstly a solution of 15.65 g (277 mmol) of potassium hydroxide dissolved in 60 ml of water was slowly added dropwise at about 30°C and thereafter within 15 minutes 11.2 ml of a 30% hydrogen peroxide solution was added, with the

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temperature rising to 40°C. Subsequently, the mixture was boiled under reflux for 2.5 hours. For the working-up, the cooled reaction mixture was filtered over Dicalit and this was rinsed with ethyl acetate. The solution obtained was treated with
5 100 ml of ethyl acetate and 100 ml of water, the organic phase was separated and then the aqueous phase was back-extracted with 100 ml of ethyl acetate. The combined organic phases were dried over sodium sulphate and evaporated under reduced pressure. For purification, the crude product was chromatographed on silica gel using a 95:5 mixture of methylene chloride
10 and methanol as the eluent. There were obtained 8.64 g (73% of theory) of (3RS,4SR,5RS)-4-(4-chloro-phenyl)-1-methyl-5-propyl-piperidin-3-ol as a colourless solid; MS: 267 (M)+.

15 (e) A mixture of 7.19 g (26.85 mmol) of (3RS,4SR,5RS)-4-(4-chloro-phenyl)-1-methyl-5-propyl-piperidin-3-ol, 5.96 g (80.7 mmol) of lithium carbonate and 14.22 g (67.1 mmol) of 2,2,2-trichloroethyl chloroformate in 200 ml of toluene was stirred at 105°C for 8 hours. For the working-up, the cooled
20 reaction mixture was treated with aqueous sodium carbonate solution and ethyl acetate. The organic phase was separated, dried over sodium sulphate and evaporated under reduced pressure. For purification, the crude product was chromatographed on silica gel using a 1:1 mixture of methylene chloride
25 and hexane as the eluent. There were obtained 13.05 g (80% of theory) of 2,2,2-trichloro-ethyl (3RS,4SR,5SR)-4-(4-chloro-phenyl)-3-propyl-5-(2,2,2-trichloro-ethoxycarbonyloxy)-piperidine-1-carboxylate as a yellowish oil; MS: 621 (M+NH₄)⁺.

30 (f) A mixture of 13.05 g (21.6 mmol) of 2,2,2-trichloro-ethyl (3RS,4SR,5SR)-4-(4-chloro-phenyl)-3-propyl-5-(2,2,2-trichloro-ethoxycarbonyloxy)-piperidine-1-carboxylate and 14.5 g of zinc in 200 ml of glacial acetic acid was treated in an ultrasound bath for 15 hours. In order to complete the reaction, a further
35 5 g of zinc were subsequently added and the mixture was left in the ultrasound bath for a further 5 hours. For the working-up, the zinc was filtered off under suction, the residue was rinsed with glacial acetic acid and the solution was evaporated to

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dryness under reduced pressure. The residue was partitioned between 1N NaOH and ethyl acetate, the separated aqueous phase was then again extracted with ethyl acetate and finally the combined organic phases were evaporated under reduced pressure.

5 The crude product obtained was crystallized from diethyl ether and gave 3.0 g (55% of theory) of (3RS,4RS, 5SR)-4-(4-chloro-phenyl)-5-propyl-piperidin-3-ol as colourless crystals; MS: 253 (M)⁺. For purification, the mother liquor was chromatographed on silica gel using a 90:10:0.1 mixture of methylene chloride,
10 methanol and ammonia as the eluent. There were obtained a further 1.1 g (20% of theory) of (3RS,4RS,5SR)-4-(4-chloro-phenyl)-5-propyl-piperidin-3-ol.

(g) A solution of 3.05 g (12.0 mmol) of (3RS,4RS,5SR)-4-(4-
15 chloro-phenyl)-5-propyl-piperidin-3-ol in 20 ml of dimethyl-formamide was treated at 0°C with 1.34 g (13.2 mmol) of triethylamine and 3.02 g (13.8 mmol) of di-tert-butyl dicarbonate and the mixture was stirred at room temperature for 15 hours. Subsequently, the dimethylformamide was distilled
20 off in an oil pump vacuum and, for purification, the residue was chromatographed on silica gel using a 99:1 mixture of methylene chloride and methanol as the eluent. There were obtained 3.92 g (92% of theory) of tert-butyl (3RS,4RS,5SR)-4-(4-chloro-phenyl)-3-hydroxy-5-propyl-piperidine-1-carboxylate as a
25 colourless solid; MS: 297 (M-C₄H₈)⁺.

(h) 37 mg (0.85 mmol) of sodium hydride (55% dispersion in refined oil) were added to a solution of 200 mg (0.56 mmol) of tert-butyl (3RS,4RS,5SR)-4-(4-chloro-phenyl)-3-hydroxy-5-
30 propyl-piperidine-1-carboxylate and 188 mg (0.85 mmol) of 2-bromomethylnaphthalene in 10 ml of dimethylformamide and the reaction mixture was stirred at room temperature for 5 hours. For the working-up, the reaction mixture was evaporated in an oil pump vacuum, the residue was partitioned between water and
35 ether and thereafter the separated aqueous phase was extracted five times with 50 ml of ether each time. The combined ether extracts were washed with saturated sodium chloride solution, dried over sodium sulphate and evaporated under reduced

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pressure. For purification, the crude product was chromatographed on silica gel using a 96:4 mixture of toluene and ethyl acetate as the eluent. There were obtained 215 mg (77% of theory) of tert-butyl (3RS,4RS,5SR)-4-(4-chloro-phenyl)-3-naphthalen-2-ylmethoxy-5-propyl-piperidine-1-carboxylate as a colourless oil; MS: 494 (M+H)⁺.

Example 63

10 The following compounds were obtained in an analogous manner to that described in Example 62:

1) - (3RS,4RS,5SR)-4-(4-Chloro-phenyl)-3-(4-methoxy-benzyloxy)-5-propyl-piperidine as a yellowish oil, MS: 252 (M-methoxybenzyl)⁺, from tert-butyl (3RS,4RS,5SR)-4-(4-chloro-phenyl)-3-(4-methoxy-benzyloxy)-5-propyl-piperidine-1-carboxylate;

2) - (3RS,4RS,5SR)-4-(4-chloro-phenyl)-3-(1-ethyl-1H-benzimidazol-2-ylmethoxy)-5-propyl-piperidine hydrochloride as a colourless solid, MS: 412 (M+H)⁺, from tert-butyl (3RS,4RS,5SR)-4-(4-chloro-phenyl)-3-(1-ethyl-1H-benzimidazol-2-ylmethoxy)-5-propyl-piperidine-1-carboxylate.

25 The BOC derivatives used as the starting materials were obtained as follows:

In an analogous manner to that described in Example 62(h), by alkylating tert-butyl (3RS,4RS,5SR)-4-(4-chloro-phenyl)-3-hydroxy-5-propyl-piperidine-1-carboxylate with 4-methoxy-benzyl chloride there was obtained tert-butyl (3RS,4RS,5SR)-4-(4-chloro-phenyl)-3-(4-methoxy-benzyloxy)-5-propyl-piperidine-1-carboxylate as a colourless solid, MS: 416 (M-C₄H₉)⁺.

35

In an analogous manner to that described in Example 62(h), by alkylating tert-butyl (3RS,4RS,5SR)-4-(4-chloro-phenyl)-3-hydroxy-5-propyl-piperidine-1-carboxylate with 2-chloro-

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methy-1-ethyl-1H-benzoimidazole [Acta Pol. Pharm. 1977, 34(4), 359-369] there was obtained tert-butyl (3RS,4RS,5SR)-4-(4-chloro-phenyl)-3-(1-ethyl-1H-benzimidazol-2-ylmethoxy)-5-propyl-piperidine-1-carboxylate as a colourless oil, MS: 495 (M+H)⁺.

Example 64

In an analogous manner to that described in Example 5, by treating 2-trimethylsilanylethyl (3RS,4RS,5SR)-3-(4-benzyloxy-naphthalen-2-ylmethoxy)-4-(4-fluoro-phenyl)-5-propyl-piperidine-1-carboxylate with tetrabutylammonium fluoride solution there was obtained (3RS,4RS,5SR)-3-(4-benzyloxy-naphthalen-2-ylmethoxy)-4-(4-fluoro-phenyl)-5-propyl-piperidine as an almost colourless solid, MS: 484 (M+H)⁺.

The 2-trimethylsilanylethyl (3RS,4RS,5SR)-3-(4-benzyloxy-naphthalen-2-ylmethoxy)-4-(4-fluoro-phenyl)-5-propyl-piperidine-1-carboxylate used as the starting substance was obtained as follows:

(a) In an analogous manner to that described in Example 62(a)-(d), starting from (RS)-1-benzyl-3-propyl-piperidin-4-one, MS: 231 (M)⁺, and 1-bromo-4-fluorobenzene there was obtained (3RS,4RS,5SR)-1-benzyl-4-(4-fluoro-phenyl)-5-propyl-piperidin-3-ol as a colourless solid, MS: 327 (M)⁺.

(b) In an analogous manner to that described in Example 62(h), by alkylating (3RS,4RS,5SR)-1-benzyl-4-(4-fluoro-phenyl)-5-propyl-piperidin-3-ol with 1-benzyloxy-3-chloromethyl-naphthalene there was obtained (3RS,4RS,5SR)-1-benzyl-3-(4-benzyloxy-naphthalen-2-ylmethoxy)-4-(4-fluoro-phenyl)-5-propyl-piperidine as a yellow resin, MS (ISP): 574 (M+H)⁺.

(c) In an analogous manner to that described in Example 1(d), by reacting (3RS,4RS,5SR)-1-benzyl-3-(4-benzyloxy-naphthalen-2-ylmethoxy)-4-(4-fluoro-phenyl)-5-propyl-piperidine with β -trimethylsilylethyl chloroformate [Synthesis 346 (1987)] there

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was obtained 2-trimethylsilanylethyl (3RS,4RS,5SR)-3-(4-benzyloxy-naphthalen-2-ylmethoxy)-4-(4-fluoro-phenyl)-5-propyl-piperidine-1-carboxylate as a pale yellow syrup, MS: 628 (M+H)⁺.

5

The 1-benzyloxy-3-chloromethyl-naphthalene used as the starting material was obtained as follows:

(a) In an analogous manner to that described in Example 14(a),
10 by alkylating ethyl 4-hydroxy-naphthalene-2-carboxylate [J. Agric. Chem Soc. Japan 24, 313 (1950)] with benzyl bromide there was obtained ethyl 4-benzyloxy-naphthalene-2-carboxylate as an almost colourless solid, R_f: 0.53 (SiO₂, hexane:ethyl acetate = 4:1).

15

(b) Reduction of ethyl 4-benzyloxy-naphthalene-2-carboxylate analogously to Example 7 (b) yielded (4-benzyloxy-naphthalen-2-yl)-methanol as a colourless solid, R_f: 0.42 (SiO₂, hexane:ethyl acetate = 2:1).

20

(c) Chlorination of (4-benzyloxy-naphthalen-2-yl)-methanol analogously to Example 7(c) yielded 1-benzyloxy-3-chloromethyl-naphthalene as a colourless solid, MS: 282 (M)⁺.

25

Example 65

The following compounds were prepared in an analogous manner to that described in Example 62:

30

1) - (3RS,4RS,5SR)-4-(4-Chloro-phenyl)-5-isopropyl-3-(naphthalen-2-ylmethoxy)-piperidine hydrochloride as a colourless solid, MS: 394 (M+H)⁺, from tert-butyl (3RS,4RS,5SR)-4-(4-chloro-phenyl)-5-isopropyl-3-naphthalen-2-ylmethoxy-
35 piperidine-1-carboxylate;

2) - (3RS,4RS,5SR)-4-(4-bromo-phenyl)-5-isobutyl-3-naphthalen-2-ylmethoxy-piperidine hydrochloride as a colourless

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solid, MS: 310 (M-naphthylmethyl)⁺, from tert-butyl (3RS,4RS,5SR)-4-(4-bromo-phenyl)-5-isobutyl-3-naphthalen-2-yl-methoxy-piperidine-1-carboxylate;

- 5 3) - (3RS,4RS,5SR)-4-(4-fluoro-phenyl)-5-methyl-3-naphthalen-2-ylmethoxy-piperidine hydrochloride as a colourless solid, R_f: 0.37 (SiO₂, methylene chloride:methanol:ammonia = 95:5:0.1), from tert-butyl (3RS,4RS,5SR)-4-(4-fluoro-phenyl)-5-methyl-3-naphthalen-2-ylmethoxy-piperidine-1-carboxylate;

10

- 4) - (3RS,4RS,5SR)-5-benzyl-4-(4-fluoro-phenyl)-3-naphthalen-2-ylmethoxy-piperidine hydrochloride as a colourless solid, MS: 426 (M+H)⁺, from tert-butyl (3RS,4RS,5SR)-5-benzyl-4-(4-fluoro-phenyl)-3-(naphthalen-2-ylmethoxy)-piperidine-1-

15 carboxylate.

The BOC derivatives used as the starting materials were obtained as follows:

- 20 The following procedure was carried out in an analogous manner to that described in Example 62(a)-(h):

- (a) Starting from ethyl 2-isopropyl-acrylate and methylamine there was obtained (3RS)-1-methyl-3-isopropyl-piperidin-4-one as a colourless oil; MS: 155 (M)⁺. By reaction with 1-bromo-4-chlorobenzene there was obtained (3RS,4RS)- and (3RS,4SR)-4-(4-chloro-phenyl)-3-isopropyl-1-methyl-piperidin-4-ol as a colourless solid; MS: 267 (M)⁺. Following elimination using trifluoroacetic acid and subsequent chromatographic separation gave the two isomeric olefins, (RS)-4-(4-chloro-phenyl)-3-isopropyl-1-methyl-1,2,3,6-tetrahydro-pyridine, MS: 249 (M)⁺, and 4-(4-chloro-phenyl)-5-isopropyl-1-methyl-1,2,3,6-tetrahydro-pyridine, each as a colourless oil. Hydroboration of (RS)-4-(4-chloro-phenyl)-3-isopropyl-1-methyl-1,2,3,6-tetrahydro-pyridine gave (3RS,4RS,5SR)-4-(4-chloro-phenyl)-5-isopropyl-1-methyl-piperidin-3-ol as a colourless solid; MS: 267 (M)⁺. Further reaction with 2,2,2-trichloroethyl chloroformate yielded 2,2,2-trichloroethyl (3SR,4RS,5RS)-4-(4-chloro-phenyl)-3-isopropyl-

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5-(2,2,2-trichloro-ethoxycarbonyloxy)-piperidine-1-carboxylate as a yellowish oil; MS: 619, 621, 623, 625 (M+NH₄)⁺. Cleavage of the TROC group with zinc in glacial acetic acid gave (3RS,4RS,5SR)-4-(4-chloro-phenyl)-5-isopropyl-piperidin-3-ol as a colourless solid; MS: 253 (M)⁺. By introduction of the BOC group there was obtained therefrom tert-butyl (3RS,4RS,5SR)-4-(4-chloro-phenyl)-3-hydroxy-5-isopropyl-piperidine-1-carboxylate as a colourless solid; MS: 297 (M-C₄H₈)⁺. Finally, alkylation with 2-bromomethylnaphthalene yielded tert-butyl (3RS,4RS,5SR)-4-(4-chloro-phenyl)-5-isopropyl-3-naphthalen-2-ylmethoxy-piperidine-1-carboxylate as a colourless solid; MS: 437 (M-C₄H₈)⁺.

The following procedure was carried out in an analogous manner to that described in Example 62(a)-(h):

(b) Starting from methyl 2-isobutyl-acrylate and benzylamine there was obtained (3RS)-1-benzyl-3-isobutyl-piperidin-4-one as a yellowish oil; MS: 245 (M)⁺. By reaction with 1,4-dibromobenzene and subsequent elimination using trifluoroacetic acid as well as chromatographic separation there were obtained the two isomeric olefins, (RS)-1-benzyl-4-(4-bromo-phenyl)-3-isobutyl-1,2,3,6-tetrahydro-pyridine, MS: 383 (M)⁺, and 1-benzyl-4-(4-bromo-phenyl)-5-isobutyl-1,2,3,6-tetrahydro-pyridine, each as a brownish oil. Subsequent hydroboration of (RS)-1-benzyl-4-(4-bromo-phenyl)-3-isobutyl-1,2,3,6-tetrahydro-pyridine gave (3RS,4RS,5SR)-1-benzyl-4-(4-bromo-phenyl)-5-isobutyl-piperidin-3-ol as a colourless solid; MS: 401 (M)⁺. Further reaction with 2,2,2-trichloroethyl chloroformate yielded 2,2,2-trichloro-ethyl (3RS,4R,5SR)-4-(4-bromo-phenyl)-5-isobutyl-3-(2,2,2-trichloro-ethoxycarbonyloxy)-piperidine-1-carboxylate as a colourless solid; R_f: 0.25 (SiO₂, methylene chloride:hexane = 1:1). Cleavage of the TROC group with zinc in glacial acetic acid gave (3RS,4RS,5SR)-4-(4-bromo-phenyl)-5-isobutyl-piperidine-3-ol as a colourless solid; MS: 311 (M)⁺. By introduction of the BOC group there was obtained therefrom tert-butyl (3RS,4RS,5SR)-4-(4-bromo-phenyl)-3-hydroxy-5-isobutyl-piperidine-1-carboxylate as a colourless solid; MS: 412 (M+H)⁺. Finally,

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alkylation with 2-bromomethylnaphthalene yielded tert-butyl (3RS,4RS,5SR)-4-(4-bromo-phenyl)-5-isobutyl-3-naphthalen-2-ylmethoxy-piperidine-1-carboxylate as a colourless foam; MS: 552 (M+H)+.

5

The following procedure was carried out in an analogous manner to that described in Example 62(b)-(d):

(c) From (RS)-1-benzyl-3-methyl-piperidin-4-one and
10 1-bromo-4-fluorobenzene there was obtained (3RS,4RS)- and (3RS, 4SR)-1-benzyl-4-(4-fluoro-phenyl)-3-methyl-piperidine-4-ol as a colourless solid; MS: 299 (M)+. By elimination using trifluoroacetic acid and subsequent chromatographic separation there were obtained the two isomeric olefins, (RS)-1-benzyl-4-
15 (4-fluoro-phenyl)-3-methyl-1,2,3,6-tetrahydro-pyridine, MS: 281 (M)+, and 1-benzyl-4-(4-fluoro-phenyl)-5-methyl-1,2,3,6-tetrahydro-pyridine, MS: 281 (M)+, each as a brownish oil. Subsequent hydroboration of the (RS)-1-benzyl-4-(4-fluoro-phenyl)-3-methyl-1,2,3,6-tetrahydro-pyridine gave (3RS,4RS,
20 5SR)-1-benzyl-4-(4-fluoro-phenyl)-5-methyl-piperidine-3-ol as a colourless solid; MS: 299 (M)+.

(d) A solution of 600 mg (2 mmol) of (3RS,4RS,5SR)-1-benzyl-4-(4-fluoro-phenyl)-5-methyl-piperidin-3-ol in 20 ml of
25 methanol was hydrogenated with 60 mg of palladium/charcoal (10%) at room temperature under normal pressure. For the working-up, the catalyst was filtered off, stirred in warm methanol and again filtered off. The combined methanol solutions were evaporated under reduced pressure. The resulting crude
30 product (410 mg) was used without further purification in the following step. For analytical purposes, a sample was recrystallized from ether/hexane. The (3RS,4RS,5SR)-4-(4-fluoro-phenyl)-5-methyl-piperidin-3-ol hydrochloride was obtained in the form of colourless crystals; MS: 209 (M)+.

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(e) From (3RS,4RS,5SR)-4-(4-fluoro-phenyl)-5-methyl-piperidin-3-ol hydrochloride by introduction of the BOC protecting group there was obtained tert-butyl (3RS,4RS,5SR)-4-(4-

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fluoro-phenyl)-3-hydroxy-5-methyl-piperidine-1-carboxylate as a colourless oil; MS: 253 (M-C₄H₈)⁺. Finally, alkylation with 2-bromomethylnaphthalene yielded tert-butyl (3RS,4RS,5SR)-4-(4-fluoro-phenyl)-5-methyl-3-naphthalen-2-ylmethoxy-piperidine-1-carboxylate as a colourless solid; MS: 393 (M-C₄H₈)⁺.

The following procedure was carried out in an analogous manner to that described in Example 62(a)-(d) and (g)-(h):

(a) Starting from ethyl 2-benzyl-acrylate and benzylamine there was obtained (3RS)-1,3-dibenzyl-piperidin-4-one as a yellowish oil; MS: 279 (M)⁺. By reaction with 1-bromo-4-fluorobenzene there was obtained (3RS,4RS)- and (3RS,4SR)-1,3-dibenzyl-4-(4-fluoro-phenyl)-piperidin-4-ol as a colourless solid; MS: 375 (M)⁺. By elimination using trifluoroacetic acid and subsequent chromatographic separation there were obtained the two isomeric olefins, (RS)-1,3-dibenzyl-4-(4-fluoro-phenyl)-1,2,3,6-tetrahydro-pyridine as a yellow solid, MS: 357 (M)⁺, and 1,5-dibenzyl-4-(4-fluoro-phenyl)-1,2,3,6-tetrahydro-pyridine. Subsequent hydroboration of the (RS)-1,3-dibenzyl-4-(4-fluoro-phenyl)-1,2,3,6-tetrahydro-pyridine gave (3RS,4RS,5SR)-1,5-dibenzyl-4-(4-fluoro-phenyl)-piperidin-3-ol as a colourless solid; MS: 375 (M)⁺. Cleavage of the benzyl group was effected using catalytic hydrogenation in an analogous manner to that described in the above Example and yielded (3RS,4RS,5SR)-5-benzyl-4-(4-fluoro-phenyl)-piperidin-3-ol as a colourless solid; MS: 285 (M)⁺. By introduction of the BOC group there was obtained therefrom tert-butyl (3RS,4SR,5SR)-3-benzyl-4-(4-fluoro-phenyl)-5-hydroxy-piperidine-1-carboxylate as a colourless solid; MS: 329 (M-C₄H₈)⁺. Finally, alkylation with 2-bromomethylnaphthalene yielded tert-butyl (3RS,4RS,5SR)-5-benzyl-4-(4-fluoro-phenyl)-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a colourless foam; R_f: 0.32 (SiO₂, toluene:ethyl acetate = 95:5).

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Example 66

40 mg (0.08 mmol) of tert-butyl (3SR,4RS,5RS)-4-(4-chloro-phenyl)-3-(1-ethyl-propyl)-5-(naphthalen-2-ylmethoxy)-piperidine-carboxylate were dissolved in 5 ml of dry methylene chloride and treated with 35 mg (0.16 mmol) of anhydrous zinc bromide in an analogous manner to the procedure described by A. Mann et al. in Synth. Comm. 19(18), 3139-3142 (1989). The reaction mixture was stirred at room temperature for 5 hours. For the working-up, the reaction mixture was evaporated under reduced pressure and the crude product obtained was purified by chromatography on silica gel using a 90:10:0.1 mixture of methylene chloride, methanol and ammonia as the eluent. There were obtained 28 mg (86% of theory) of (3SR,4RS,5RS)-4-(4-chloro-phenyl)-3-(1-ethyl-propyl)-5-(naphthalen-2-ylmethoxy)-piperidine as a colourless oil; MS: 422 (M+H)+.

The tert-butyl (3SR,4RS,5RS)-4-(4-chloro-phenyl)-3-(1-ethyl-propyl)-5-(naphthalen-2-ylmethoxy)-piperidine-carboxylate used as the starting material was obtained as follows in an analogous manner to that described in Example 62(a)-(h):

Starting from methyl 2-(1-ethyl-propyl)-acrylate and methylamine there was obtained (3RS)-3-(1-ethyl-propyl)-1-methyl-piperidin-4-one as a colourless oil; MS: 183 (M)+. By reaction with 1-bromo-4-chlorobenzene there was obtained therefrom (3RS,4RS)- and (3RS,4SR)-4-(4-chloro-phenyl)-3-(1-ethyl-propyl)-1-methyl-piperidin-4-ol as a colourless solid; MS: 295 (M)+. Subsequent elimination using trifluoroacetic acid and chromatographic separation gave the two isomeric olefins, (RS)-4-(4-chloro-phenyl)-3-(1-ethyl-propyl)-1-methyl-1,2,3,6-tetrahydro-pyridine, MS: 277 (M)+, and 4-(4-chloro-phenyl)-5-(1-ethyl-propyl)-1-methyl-1,2,3,6-tetrahydro-pyridine, each as a colourless oil. Subsequent hydroboration of the (RS)-4-(4-chloro-phenyl)-3-(1-ethyl-propyl)-1-methyl 1,2,3,6-tetrahydro-pyridine gave (3RS,4RS,5SR)-4-(4-chloro-phenyl)-5-(1-ethyl-propyl)-1-methyl-piperidin-3-ol as a colourless solid; MS: 296

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(M+H)⁺. Further reaction with 2,2,2-trichloroethyl chloroformate yielded 2,2,2-trichloro-ethyl (3SR,4RS,5RS)-4-(4-chloro-phenyl)-3-(1-ethyl-propyl)-5-(2,2,2-trichloro-ethoxycarbonyloxy)-piperidine-1-carboxylate as a colourless oil; MS: 653

5 (M+Na)⁺. Cleavage of the TROC group with zinc in glacial acetic acid gave (3RS,4RS,5SR)-4-(4-chloro-phenyl)-5-(1-ethyl-propyl)-piperidin-3-ol as a colourless solid: MS: 281 (M)⁺. By introduction of the BOC protecting group there was obtained therefrom tert-butyl (3SR,4RS,5RS)-4-(4-chloro-phenyl)-3-(1-

10 ethyl-propyl)-5-hydroxy-piperidine-1-carboxylate as a colourless oil; MS: 325 (M-C₄H₈)⁺. Finally, alkylation with 2-bromomethylnaphthalene yielded tert-butyl (3SR,4RS,5RS)-4-(4-chloro-phenyl)-3-(1-ethyl-propyl)-5-(naphthalen-2-ylmethoxy)-piperidine-carboxylate; R_f: 0.41 (SiO₂, toluene:ethyl acetate =

15 95:5).

Example 67

In an analogous manner to that described in Example 66,

20 from tert-butyl (3SR,4RS,5RS)-4-(4-chloro-phenyl)-3-isopropyl-5-(4-methoxy-benzyloxy)-piperidine-carboxylate there was obtained (3SR,4RS,5RS)-4-(4-chloro-phenyl)-3-isopropyl-5-(4-methoxy-benzyloxy)-piperidine as a colourless oil; R_f: 0.21 (SiO₂, methylene chloride:methanol:ammonia = 95:5:0.1).

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The tert-butyl (3SR,4RS,5RS)-4-(4-chloro-phenyl)-3-isopropyl-5-(4-methoxy-benzyloxy)-piperidine-carboxylate used as the starting material was obtained in an analogous manner to that described in Example 62(h) by alkylating tert-butyl

30 (3RS,4RS,5SR)-4-(4-chloro-phenyl)-3-hydroxy-5-isopropyl-piperidine-1-carboxylate (Example 65) with 4-methoxy-benzyl chloride; R_f: 0.39 (SiO₂, toluene:ethyl acetate = 9:1).

Example 68

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A solution of 60 mg (0.11 mg) of tert-butyl (3RS,4RS,5SR)-4-(4-bromo-phenyl)-5-methoxymethyl-3-naphthalen-2-ylmethoxy-piperidine-1-carboxylate in 5 ml of methylene chloride

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was treated with 2 ml of 2N hydrogen chloride in methanol and stirred at room temperature for 2 hours. For the working-up, the reaction solution was evaporated under reduced pressure. The residue was recrystallized from diethyl ether and gave 53 mg
5 (98% of theory) of (3RS,4RS,5SR)-4-(4-bromo-phenyl)-5-methoxymethyl-3-naphthalen-2-yl-methoxy-piperidine hydrochloride as a colourless solid; MS: 442 (M+H)+.

The tert-butyl (3RS,4RS,5SR)-4-(4-bromo-phenyl)-5-
10 methoxymethyl-3-naphthalen-2-ylmethoxy-piperidine-1-carboxylate used as the starting substance was obtained as follows:

(a) A solution of 7.45 g (33.7 mmol) of (3RS,4RS)-1-benzyl-3-
15 hydroxymethyl-piperidin-4-ol and (3SR,4RS)-1-benzyl-3-hydroxymethyl-piperidin-4-ol [E. Jaeger and J.H. Biel, J. Org. Chem. 30(3), 740-744 (1965)], 10.89 g (39.6 mmol) of tert-butyldiphenylchlorosilane, 3.44 g (50.5 mmol) of imidazole and 0.2 g (1.6 mmol) of 4-dimethylaminopyridine in 80 ml of
20 dimethylformamide was stirred at room temperature for 4 days in the presence of molecular sieve (4 Å). For the working-up, the molecular sieve was filtered off under suction and the solution was evaporated in an oil pump vacuum. The residue was digested four times in a mixture of ether and methylene chloride, the
25 solutions obtained were combined, dried over sodium sulphate and evaporated under reduced pressure. For purification, the crude product was chromatographed on silica gel using a 98:2 mixture of methylene chloride and methanol as the eluent. There were obtained 8.23 g (53% of theory) of a mixture of (3RS,4RS)- and
30 (3RS,4SR)-1-benzyl-3-(tert-butyl-diphenyl-silanyloxymethyl)-piperidin-4-ol as a colourless oil; MS: 459 (M)+.

(b) A solution of 2.45 g (19.33 mmol) of oxalyl chloride in
60 ml of methylene chloride was cooled to -70°C, then treated
35 dropwise with 3.02 g (38.66 mmol) of dimethyl sulphoxide and stirred at -70° for 5 minutes. A solution of 8.08 g (17.6 mmol) of a mixture of (3RS,4RS)- and (3RS,4SR)-1-benzyl-3-(tert-butyl-diphenyl-silanyloxymethyl)-piperidin-4-ol in 15 ml of

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methylen chloride was added dropwise thereto, the mixture was then stirred for 15 minutes. Subsequently, 8.86 g (87.6 mmol) of triethylamine were added dropwise at -70°C. After warming the reaction mixture to room temperature (about 15 minutes) it was
5 hydrolyzed in ice-water and thereafter extracted three times with 200 ml of methylen chloride each time. The combined organic phases were dried over sodium sulphate and evaporated under reduced pressure. For purification, the crude product was chromatographed on silica gel using methylen chloride as the
10 eluent. There were obtained 6.5 g (81% of theory) of (3RS)-1-benzyl-3-(tert-butyl-diphenyl-silanyloxymethyl)-piperidin-4-one as a colourless oil; MS: 458 (M+H)⁺.

(c) In an analogous manner to that described in Example 62(b),
15 from (3RS)-1-benzyl-3-(tert-butyl-diphenyl-silanyloxymethyl)-piperidin-4-one and 1,4-dibromobenzene there was obtained (3RS,4RS)- and/or (3RS,4SR)-1-benzyl-4-(4-bromo-phenyl)-3-(tert-butyl-diphenyl-silanyloxymethyl)-piperidin-4-ol as a colourless foam; MS: 616 (M+H)⁺.

20

(d) In an analogous manner to that described in Example 62(c), from (3RS,4RS)- and/or (3RS,4SR)-1-benzyl-4-(4-bromo-phenyl)-3-(tert-butyl-diphenyl-silanyloxymethyl)-piperidin-4-ol by eliminating the tert. alcohol and simultaneous cleavage of the
25 silyl group using trifluoroacetic acid there was obtained (3RS)-[1-benzyl-4-(4-bromo-phenyl)-1,2,3,6-tetrahydro-pyridin-3-yl]-methanol as a colourless solid; MS: 360 (M+H)⁺.

(e) In an analogous manner to that described in Example 62(d),
30 by hydroborating (3RS)-[1-benzyl-4-(4-bromo-phenyl)-1,2,3,6-tetrahydro-pyridin-3-yl]-methanol there was obtained a mixture of (3RS,4RS,5SR)-1-benzyl-4-(4-bromo-phenyl)-5-hydroxymethyl-piperidin-3-ol and (3RS,4RS)- and/or (3RS,4SR)-1-benzyl-4-(4-bromo-phenyl)-3-hydroxymethyl-piperidin-4-ol as a
35 colourless foam.

(f) In an analogous manner to that described in (e), by treating the above mixture with 2,2,2-trichloroethyl chloroformate there

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was obtained a mixture of 2,2,2-trichloro-ethyl (3RS,4RS,5SR)-4-(4-bromo-phenyl)-3-(2,2,2-trichloro-ethoxycarbonyloxy)-5-(2,2,2-trichloro-ethoxycarbonyloxymethyl)-piperidine-1-carboxylate and 2,2,2-trichloro-ethyl (3RS,4RS)- and/or
5 (3RS,4SR)-4-(4-bromo-phenyl)-4-(2,2,2-trichloro-ethoxycarbonyloxy)-3-(2,2,2-trichloro-ethoxycarbonyloxymethyl)-piperidine-1-carboxylate as a colourless foam.

(g) In an analogous manner to that described in Example 62(f),
10 by reacting the above mixture with zinc in glacial acetic acid there was obtained a 4:1 mixture of (3RS,4RS,5RS)-4-(4-bromo-phenyl)-5-hydroxymethyl-piperidin-3-ol and (3RS,4RS)- and/or (3RS,4SR)-4-(4-bromo-phenyl)-3-hydroxymethyl-piperidin-4-ol as a colourless foam.

15

(h) In an analogous manner to that described in Example 62(g), by introducing the BOC group and subsequent chromatographic separation there was obtained the mixture of tert-butyl (3RS,4RS,5SR)-4-(4-bromo-phenyl)-3-hydroxy-5-hydroxymethyl-piperidine-1-carboxylate as a colourless foam, MS: 386 (M+H)⁺,
20 and tert-butyl (3RS,4RS)- and/or (3RS,4SR)-4-(4-bromo-phenyl)-4-hydroxy-3-hydroxymethyl-piperidine-1-carboxylate as a colourless solid, MS: 386 (M+H)⁺.

(i) A solution of 735 mg (1.91 mmol) of tert-butyl (3RS,4RS,5SR)-4-(4-bromo-phenyl)-3-hydroxy-5-hydroxymethyl-piperidine-1-carboxylate, 766 mg (2.75 mmol) of triphenylchloromethane and 324 mg (3.20 mmol) of triethylamine in 8 ml of methylene chloride was stirred at room temperature for
30 15 hours. For the working-up, the reaction mixture was evaporated under reduced pressure and the crude product was chromatographed directly on silica gel using methylene chloride as the eluent. There were obtained 1.01 g (84.5% of theory) of tert-butyl (3RS,4RS,5SR)-4-(4-bromo-phenyl)-3-hydroxy-5-trityloxymethyl-piperidine-1-carboxylate as a colourless foam;
35 MS: 646 (M+NH₄)⁺.

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(j) In an analogous manner to that described in Example 62(h), by alkylating tert-butyl (3RS,4RS,5SR)-4-(4-bromo-phenyl)-3-hydroxy-5-trityloxymethyl-piperidine-1-carboxylate with 2-bromomethylnaphthalene there was obtained tert-butyl
5 (3RS,4RS, 5SR)-4-(4-bromo-phenyl)-3-naphthalen-2-ylmethoxy-5-trityloxymethyl-piperidine-1-carboxylate as a colourless foam; MS: 785 (M+NH₄)⁺.

(k) A solution of 990 mg (1.29 mmol) of tert-butyl (3RS,4RS,
10 5SR)-4-(4-bromo-phenyl)-3-naphthalen-2-ylmethoxy-5-trityloxymethyl-piperidine-1-carboxylate and 4 ml of 2N hydrogen chloride/methanol in 5 ml of methylene chloride was stirred at room temperature for 45 minutes. For the working-up, the reaction solution was poured into 40 ml of saturated sodium
15 carbonate solution and this was extracted twice with 40 ml of methylene chloride each time. The combined organic phases were dried over sodium sulphate and evaporated under reduced pressure. For purification and separation, the product obtained was chromatographed on silica gel: firstly with a 98:2 mixture of
20 methylene chloride and methanol as the eluent. There were thus obtained 360 mg (54% of theory) of tert-butyl (3RS,4RS,5SR)-4-(4-bromo-phenyl)-5-hydroxymethyl-3-naphthalen-2-ylmethoxy-piperidine-1-carboxylate as a colourless solid; MS: 528 (M+H)⁺. Then with a 90:10:1 mixture of methylene chloride, methanol and
25 ammonia, with (3SR,4RS,5RS)-4-(4-bromo-phenyl)-5-naphthalen-2-ylmethoxy-piperidin-3-yl]-methanol being obtained as a colourless solid; MS: 426 (M+H)⁺.

(l) In an analogous manner to that described in Example 62(h),
30 by alkylating (3SR,4RS,5RS)-4-(4-bromo-phenyl)-5-naphthalen-2-ylmethoxy-piperidin-3-yl]-methanol with methyl iodide there was obtained tert-butyl (3RS,4RS,5SR)-4-(4-bromo-phenyl)-5-methoxymethyl-3-naphthalen-2-yl-methoxy-piperidine-1-carboxylate as a colourless solid; MS: 540 (M+H)⁺.

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Example 69

- a) A solution of 32.5 g (163 mmol) of tert-butyl 4-oxo-piperidine-1-carboxylate in 200 ml of chloroform was treated
5 with 24.0 g (168 mmol) of disodium hydrogen phosphate and cooled to 5°C. A solution of 27.9 g (175 mmol) of bromine in 75 ml of chloroform was added dropwise during 1 hour, thereafter the reaction mixture was warmed to room temperature and stirred for 18 hours. The reaction mixture was worked-up by
10 extraction with ice-water and methylene chloride, the organic phase was dried over magnesium sulphate, filtered and the solvent was distilled off in a water-jet vacuum. The crude product (38 g) was chromatographed on silica gel with methylene chloride and ethyl acetate as the eluent. The thus-obtained
15 product was recrystallized from ethyl acetate and n-hexane. There were obtained 19.1 g (42% of theory) of tert-butyl 3-bromo-4-oxo-piperidine-1-carboxylate as a pale yellow solid; MS: 277, 279 (M)⁺.
- 20 b) A solution of 2.78 g (10 mmol) of tert-butyl 3-bromo-4-oxo-piperidine-1-carboxylate and 2.09 g (12 mmol) of 2-mercaptomethylnaphthalene in 100 ml of absolute acetonitrile was treated with 13.8 g (100 mmol) of anhydrous potassium carbonate and thereafter the mixture was stirred at room
25 temperature for 18 hours. The reaction mixture was filtered, the filtrate was poured on to ice-water and adjusted to pH 2-3 with concentrated hydrochloric acid; the aqueous phase was extracted three times with 200 ml of ethyl acetate each time, the organic phase was washed once with 200 ml of water, dried over
30 magnesium sulphate, filtered and concentrated in a water-jet vacuum. The crude product (5.5 g) was chromatographed on silica gel with hexane and ethyl acetate as the eluent. The product was recrystallized from ethyl acetate and hexane. There were obtained 2.27 g (61% of theory) of tert-butyl (3RS)-3-
35 (naphthalen-2-ylmethylthio)-4-oxo-piperidine-1-carboxylate as a colourless solid; MS: 371 (M)⁺.

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c) 0.31 g (12.8 mg atoms) of magnesium shavings were suspended in 5 ml of absolute tetrahydrofuran under argon, then reacted at reflux with a solution of 1.75 g (10 mmol) of 4-bromofluorobenzene in 10 ml of tetrahydrofuran. After the reaction had died down a solution of 1.86 g (5 mmol) of tert-butyl (3RS)-3-(naphthalen-2-ylmethylthio)-4-oxo-piperidine-1-carboxylate in 10 ml of tetrahydrofuran was added dropwise at room temperature and the mixture was then stirred for a further 4 hours. After hydrolysis with 10 ml of water the reaction mixture was worked-up by extraction with ethyl acetate. The organic phase was dried over magnesium sulphate, filtered and the solvent was distilled off in a water-jet vacuum. The crude product (2.6 g) was chromatographed on silica gel with hexane and ethyl acetate as the eluent. There were obtained 1.45 g (62% of theory) of tert-butyl (3RS,4SR or 3RS,4RS)-4-(4-fluorophenyl)-4-hydroxy-3-(naphthalen-2-ylmethylthio)-piperidine-1-carboxylate as a colourless solid, MS: 468 (M+H)⁺, and 0.37 g (16% of theory) of tert-butyl (3RS,4RS or 3RS,4SR)-4-(4-fluorophenyl)-4-hydroxy-3-(naphthalen-2-ylmethylthio)-piperidine-1-carboxylate as a colourless solid; MS: 468 (M+H)⁺.

d) A solution of 0.23 g (0.5 mmol) of tert-butyl (3RS,4SR or 3RS,4RS)-4-(4-fluorophenyl)-4-hydroxy-3-(naphthalen-2-ylmethylthio)-piperidine-1-carboxylate in 5 ml of absolute methanol was treated with 1 ml of hydrochloric acid in methanol (1.4 molar) and thereafter stirred at 50°C for 3 hours. After distillation of the solvent in a water-jet vacuum the product was recrystallized from methanol. There was thus obtained 0.18 g (89% of theory) of (3RS,4SR or 3RS,4RS)-4-(4-fluorophenyl)-4-hydroxy-3-(naphthalen-2-ylmethylthio)-piperidine hydrochloride as a pale yellow solid; MS: 368 (M+H)⁺.

Example 70

A solution of 0.23 g (0.5 mmol) of tert-butyl (3RS,4RS or 3RS,4SR)-4-(4-fluorophenyl)-4-hydroxy-3-(naphthalen-2-ylmethylthio)-piperidine-1-carboxylate [Example 70(c)] in 5 ml of absolute methanol was treated with 1 ml of hydrochloric acid in

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methanol (1.4 molar) and thereafter stirred at 50°C for 3 hours. After distillation of the solvent in a water-jet vacuum the residue was partitioned between methylene chloride and water, neutralized with saturated sodium bicarbonate solution and
5 extracted; the organic phase was dried over magnesium sulphate, filtered and concentrated. The crude product (0.15 g) was chromatographed on silica gel with methylene chloride and methanol as the eluent. There was thus obtained 0.041 g (22% of theory) of (3RS,4RS or 3RS,4SR)-4-(4-fluorophenyl)-4-methoxy-
10 3-(naphthalen-2-ylmethylthio)-piperidine as a yellow oil, MS: 381 (M)⁺, and 0.067 g (37% of theory) of (3RS,4RS or 3RS,4SR)-4-(4-fluorophenyl)-4-hydroxy-3-(naphthalen-2-ylmethylthio)-piperidine as a pale yellow solid; MS: 367 (M)⁺.

15 Example 71

(a) 2.33 g (10.0 mmol) of benzyl rac-3-aza-7-oxa-bicyclo-[4.1.0]heptane-3-carboxylate [S. V. D'Andrea et al., J. Org. Chem. (1991), 56(9), 3133-3137] and 1.88 g (20.0 mmol, 2 eq.) of phenol
20 were dissolved in 30 ml of acetonitrile and treated at room temperature with 10.0 ml of 2N sodium hydroxide solution. This solution was stirred at 95°C for 5 hours. Subsequently, the solution, cooled to room temperature, was treated with 60 ml of water and extracted three times with methylene chloride. The
25 organic phases were washed with 100 ml of 2N sodium hydroxide solution and twice with water, dried over magnesium sulphate, evaporated under reduced pressure and dried in a high vacuum. The crude product (3.05 g) was separated on silica gel using a 7:3 mixture of hexane and ethyl acetate as the eluent. This yielded
30 2.06 g (63% of theory) of benzyl (3RS,4RS)-3-hydroxy-4-phenoxy-piperidine-1-carboxylate as a colourless oil; MS: 327 (M)⁺.

(b) A dispersion of 262 mg (6.0 mmol, 2 eq.) of sodium hydride (60% dispersion in refined oil) in 40 ml of dimethyl sulphoxide
35 was treated with a solution of 982 mg (3.0 mmol, 1 eq.) of benzyl (3RS,4RS)-3-hydroxy-4-phenoxy-piperidine-1-carboxylate in 67 ml of dimethyl sulphoxide. This mixture was stirred at 40°C for 2 hours, then cooled to room temperature and treated drop-

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wise with a solution of 1326 mg (6.0 mmol, 2 eq.) of 2-bromo-methylnaphthalene in 40 ml of dimethyl sulphoxide and stirred at room temperature for 4 hours. The mixture was poured into 1 l of an ice/water mixture, stirred for 10 minutes and extracted
5 three times with diethyl ether. The organic phases were washed once with water and once with saturated sodium chloride solution, dried over magnesium sulphate, evaporated under reduced pressure and dried in a high vacuum. The pale yellow oil (1.75 g) was separated on silica gel using a 4:1 mixture of hexane
10 and ethyl acetate as the eluent. This yielded 647 mg (46% of theory) of benzyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-phenoxy-piperidine-1-carboxylate as an amorphous solid; MS: 476 (M-benzyl)+.

15 (c) 30 mg, 0.065 mmol) of benzyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-phenoxy-piperidine-1-carboxylate were dissolved in 1.6 ml of tetrahydrofuran, cooled to 0°C and treated in succession within 25 minutes with a solution of 95 ml (0.32 mmol, approximately 5 eq.) of a 70% sodium dihydrido-bis-(2-
20 methoxyethoxy)-aluminate solution (SDMA) in toluene and 1.6 ml of tetrahydrofuran. This reaction solution was stirred at 0°C for 2.5 hours. Subsequently, it was poured into a mixture of saturated potassium sodium tartrate solution and ice and extracted four times with 50 ml of methylene chloride each
25 time. The organic phases were washed twice with water, evaporated under reduced pressure and dried in a high vacuum. The orange coloured resin was separated on silica gel using a 95:5 mixture of methylene chloride and methanol as the eluent. There were obtained 10 mg (47% of theory) of (3RS,4RS)-3-(naphthalen-
30 2-ylmethoxy)-4-phenoxy-piperidine as a colourless, amorphous solid; R_f: 0.38 (SiO₂, methylene chloride:methanol = 9:1).

Example 72

35 The following compounds were obtained in an analogous manner to that described in Example 71 by cleavage of the benzyloxycarbonyl group:

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1) - (3RS,4RS)-4-(4-Bromophenoxy)-3-(naphthalen-2-yl-methoxy)-piperidine as a colourless, amorphous solid, MS: 412.4, 414 (M+H)⁺, from benzyl (3RS,4RS)-4-(4-bromo-phenyl)-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate;

5

2) - (3RS,4RS)-4-(4-chlorophenylsulphanyl)-3-(naphthalen-2-ylmethoxy)-piperidine as a colourless, amorphous solid, MS: 384 (M+H)⁺, from benzyl (3RS,4RS)-4-(4-chloro-phenylsulphanyl)-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate.

10

The derivatives used as the starting materials were obtained as follows:

(a) In an analogous manner to that described in Example 71(a)-
15 (b), from benzyl rac-3-aza-7-oxa-bicyclo[4.1.0]heptane-3-carboxylate by reaction with 4-bromophenol there was obtained (3RS,4RS)-1-[4-(4-bromo-phenoxy)-3-hydroxy-piperidin-1-yl]-2-phenyl-ethanone as a colourless solid [R_f: 0.40 (SiO₂, methylene chloride:ethyl acetate = 2:1)], alkylation of which with 2-bromo-
20 methylnaphthalene gave benzyl (3RS,4RS)-4-(4-bromo-phenyl)-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a colourless solid; MS: 454, 456 (M-benzyl)⁺.

(b) A mixture of 2.33 g (10.0 mmol) of benzyl rac-3-aza-7-
25 oxa-bicyclo[4.1.0]heptane-3-carboxylate, 2.89 g (20.0 mmol, 2 eq.) of p-chlorothiophenol and 10.0 ml of 2N sodium hydroxide solution in 20.5 ml of acetonitrile was boiled under reflux for 4 hours. Subsequently, the solution, cooled to room temperature, was treated with 25 ml of water and extracted three times with
30 methylene chloride. The organic phases were washed once with 1N sodium hydroxide solution and twice with water, dried over magnesium sulphate, evaporated under reduced pressure and dried in a high vacuum. The crude product (3.55 g) was separated on silica gel using a 9:1 mixture of methylene chloride and ethyl
35 acetate as the eluent. This yielded 1.89 g (46% of theory) of benzyl (3RS,4RS)-4-(4-chloro-phenylsulphanyl)-3-hydroxy-piperidine-1-carboxylate as a colourless solid, MS: 377 (M)⁺, and

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169 mg (4%) of benzyl (3RS,4SR)-4-(4-chloro-phenylsulphanyl)-3-hydroxy-piperidine-1-carboxylate.

- (c) In an analogous manner to that described in Example 71(b),
5 from benzyl (3RS,4RS)-4-(4-chloro-phenylsulphanyl)-3-hydroxy-piperidine-1-carboxylate by alkylation with 2-bromomethyl-naphthalene there was obtained benzyl (3RS,4RS)-4-(4-chloro-phenylsulphanyl)-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a colourless solid; MS: 518 (M+H)+.

10

Example 73

- a) A solution of 5.0 g (16.9 mmol) of tert-butyl (3RS,4RS)-4-(4-fluoro-phenyl)-3-hydroxy-piperidine-1-carboxylate in 50 ml
15 of methylene chloride was treated with 240 mg (1.96 mmol) of 4-dimethylamino-pyridine and 4.2 ml (29 mmol) of triethylamine and cooled to 0°C. Subsequently, 4.65 g (24.4 mmol) of 2-naphthoyl chloride were added portionwise and the reaction mixture was stirred at room temperature for 18 hours. There-
20 upon, the reaction mixture was treated with ice-water and extracted with methylene chloride. The combined methylene chloride phases were dried over magnesium sulphate, filtered and the solvent was distilled off in a water-jet vacuum. The crude product was chromatographed on silica gel with methylene
25 chloride as the eluent. The thus-obtained product fractions were recrystallized from ether and n-hexane. There were obtained 7.4 g (97% of theory) of tert-butyl (3RS,4RS)-4-(4-fluoro-phenyl)-3-(naphthalen-2-ylcarbonyloxy)-piperidine-1-carboxylate as a colourless solid; MS: 450 (M+H)+.

30

- b) A solution of 2.7 ml (24.6 mmol) of titanium tetrachloride in 18 ml of methylene chloride was added dropwise at 0°C under argon and with the exclusion of moisture to 30 ml of tetrahydrofuran, a yellow suspension resulting. After warming to room
35 temperature 15 ml (95 mmol) of tetramethylethylenediamine were added and the reaction mixture was stirred for 10 minutes. After the addition of 3.6 g (55 mmol) of zinc dust the mixture was stirred at room temperature for a further 30 minutes.

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Thereupon, a solution of 2.1 ml (30 mmol) of dibromomethane and 2.7 g (6.0 mmol) of tert-butyl (3RS,4RS)-4-(4-fluoro-phenyl)-3-(naphthalen-2-ylcarbonyloxy)-piperidine-1-carboxylate dissolved in 30 ml of tetrahydrofuran was added dropwise in such a manner
5 that the temperature did not rise above 36°C. Subsequently, the reaction mixture was stirred at room temperature for 60 hours, then poured into saturated ammonium chloride solution and extracted with ether. The combined ether phases were dried over magnesium sulphate, concentrated and the residue was chromatographed on silica gel using a 99:1 mixture of methylene chloride
10 and triethylamine as the eluent. Therefrom there were obtained 1.23 g (46% of theory) of tert-butyl (3RS,4RS)-4-(4-fluoro-phenyl)-3-(1-naphthalen-2-yl-vinyloxy)-piperidine-1-carboxylate as an amorphous colourless solid; MS: 448 (M+H)⁺.

15

c) A solution of 70 mg (0.156 mmol) of tert-butyl (3RS,4RS)-4-(4-fluoro-phenyl)-3-(1-naphthalen-2-yl-vinyloxy)-piperidine-1-carboxylate in 10 ml of tetrahydrofuran was treated with 0.2 ml of triethylamine and 100 mg of palladium on charcoal and
20 hydrogenated in a hydrogen atmosphere at room temperature and normal pressure. Subsequently, the reaction mixture was suction filtered over a 0.8 µ cellulose filter and the solvent was evaporated in a water-jet vacuum. There were obtained 68.4 mg (97% of theory) of a mixture of tert-butyl (3RS,4RS)-4-(4-fluoro-phenyl)-3-[(RS)- and -[(SR)-1-naphthalen-2-yl-ethoxy]-
25 piperidine-1-carboxylate as an amorphous colourless solid; MS: 450 (M+H)⁺.

d) 69 mg (0.153 mmol) of a mixture of tert-butyl (3RS,4RS)-4-(4-fluoro-phenyl)-3-[(RS)- and -[(SR)-1-naphthalen-2-yl-ethoxy]-piperidine-1-carboxylate were dissolved in 2 ml of methylene chloride, treated with 104 mg (0.46 mmol) of anhydrous zinc bromide and stirred at room temperature for 2.5 hours. Thereupon, the reaction mixture was poured into
35 aqueous sodium carbonate solution and this was extracted with methylene chloride. The combined methylene chloride phases were dried over magnesium sulphate, concentrated and the thus-obtained residue was chromatographed on silica gel with a 9:1

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mixture of methylene chloride and methanol as the eluent. There were thus obtained 22.1 mg (41% of theory) of (3RS,4RS)-4-(4-fluoro-phenyl)-3-[(RS)- or -[(SR)-1-naphthalen-2-yl-ethoxy]-piperidine as an amorphous yellowish solid; MS: 350 (M+H)⁺, and
5 13.6 mg (25% of theory) of (3RS,4RS)-4-(4-fluoro-phenyl)-3-[(SR)- or -[(RS)-1-naphthalen-2-yl-ethoxy]-piperidine as an amorphous colourless solid; MS: 350 (M+H)⁺.

Example 74

10

a) 13.8 g (100 mmol) of potassium carbonate were added to a solution of 10.0 g (46.8 mmol) of 4-(4-fluoro-phenyl)-1,2,3,6-tetrahydro-pyridine hydrochloride in 400 ml of ethanol and the reaction mixture was subsequently heated to reflux temperature.
15 A solution of 5.8 ml (49 mmol) of benzyl bromide in 100 ml of ethanol was added dropwise within one hour and thereafter the mixture was stirred at this temperature for a further 1 hour. The reaction mixture was cooled to room temperature and filtered, the filtrate was extracted with water and ethyl acetate
20 and finally the organic phase was dried over magnesium sulphate. After evaporation in a water-jet vacuum the crude product obtained was chromatographed on silica gel with hexane and ethyl acetate as the eluent. There were obtained 8.90 g (71% of theory) of 1-benzyl-4-(4-fluoro-phenyl)-1,2,3,6-tetrahydro-
25 pyridine; MS: 267 (M)⁺.

b) 4.5 g (16.8 mmol) of 1-benzyl-4-(4-fluoro-phenyl)-1,2,3,6-tetrahydro-pyridine were suspended in 55 ml of water, then partially dissolved by the addition of 70 ml of concentrated
30 hydrochloric acid, 1.36 g (45.3 mmol) of paraformaldehyde were added and the mixture was stirred at 100°C for 5 hours. After cooling to room temperature the mixture was adjusted to pH 5-6 with sodium hydroxide solution and the product was extracted twice with 100 ml of ethyl acetate. The organic phases were
35 washed once with 100 ml of water, dried over magnesium sulphate, filtered and concentrated in a water-jet vacuum. The thus-obtained crude product was chromatographed on silica gel with hexane and ethyl acetate as the eluent (sic). There were

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obtained 3.91 g (78% of theory) of (RS)-[1-benzyl-4-(4-fluoro-phenyl)-1,2,3,6-tetrahydro-pyridin-3-yl]-methanol; MS: 297 (M)+.

c) 58 ml (203 mmol) of sodium dihydrido-bis-(2-methoxy-ethoxy)aluminate (70% in toluene) were added dropwise under argon at room temperature while stirring to a solution of 17.4 g (58.5 mmol) of (RS)-[1-benzyl-4-(4-fluoro-phenyl)-1,2,3,6-tetrahydro-pyridin-3-yl]-methanol in 580 ml of absolute toluene. Subsequently, the mixture was stirred at 80°C for 4 hours.

10 100 ml of water were added dropwise to the reaction mixture at room temperature, with working-up thereafter being carried out by extraction with water and ethyl acetate. The crude product was chromatographed on silica gel with hexane and ethyl acetate as the eluent. There were obtained 3.90 g (44% of theory) of (3RS,4SR)-[1-benzyl-4-(4-fluoro-phenyl)-piperidin-3-yl]-methanol; MS: 300 (M+H)+.

d) 6.86 g (22.9 mmol) of (3RS,4SR)-[1-benzyl-4-(4-fluoro-phenyl)-piperidin-3-yl]-methanol were hydrogenated at room temperature in 70 ml of methanol with the addition of 1.5 g of Pd-charcoal (10%). After filtration of the catalyst the solvent was distilled off in a water-jet vacuum. There were thus obtained 4.79 g (100% of theory) of (3RS,4SR)-[4-(4-fluoro-phenyl)-piperidin-3-yl]-methanol; MS: 210 (M+H)+.

25 e) 4.20 g (50 mmol) of sodium hydrogen carbonate and 20 ml of water were added to a solution of 4.89 g (23.4 mmol) of (3RS,4SR)-[4-(4-fluoro-phenyl)-piperidin-3-yl]-methanol in 60 ml of dioxan, then 6.10 g (28 mmol) of di-tert-butyl dicarbonate were introduced portionwise and the mixture was stirred at room temperature for 4 hours. The reaction mixture was poured on to ice-water and the product was extracted twice with 200 ml of ethyl acetate each time; the organic phases were washed once with 300 ml of water, dried over magnesium sulphate, filtered and concentrated in a water-jet vacuum. The thus-obtained crude product was chromatographed on silica gel with methylene chloride and methanol as the eluent. There were obtained 7.03 g

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(97% of theory) of tert-butyl (3RS,4SR)-4-(4-fluoro-phenyl)-3-hydroxymethyl-piperidine-1-carboxylate; MS: 309 (M)⁺.

f) 3.28 ml (46.2 mmol) of dimethyl sulphoxide were added
5 dropwise at -70°C under argon to a solution of 2.34 ml
(27.3 mmol) of oxalyl chloride in 250 ml of methylene chloride.
After 30 minutes 6.50 g (21 mmol) of tert-butyl (3RS,4SR)-4-(4-fluoro-phenyl)-3-hydroxymethyl-piperidine-1-carboxylate
dissolved in 75 ml of methylene chloride were added dropwise
10 and the mixture was stirred at -70°C for 2 hours. Subsequently,
7.25 ml (52.5 mmol) of triethylamine were added dropwise. The
reaction mixture was warmed to room temperature during
3 hours and subsequently extracted with water and methylene
chloride. After drying over magnesium sulphate and evaporation
15 in a water-jet vacuum the product was purified by recrystal-
lization from n-hexane. There were thus obtained 5.51 g (85% of
theory) of tert-butyl (3RS,4SR)-4-(4-fluoro-phenyl)-3-formyl-
piperidine-1-carboxylate; MS: 279 (M-CO)⁺.

20 g) 28.0 ml (54 mmol) of hexabutyldistannate were placed in
150 ml of tetrahydrofuran at 0°C under argon. Thereto there were
added dropwise 31.3 ml (50 mmol) of n-butyllithium solution
(1.6M in n-hexane). After 30 minutes a solution of 11.1 g
(50 mmol) of 2-bromomethyl-naphthalene in 50 ml of tetra-
25 hydrofuran were added dropwise and thereafter the mixture was
stirred at room temperature. After 2 hours the solvent was
distilled off in a water-jet vacuum and the residue was
chromatographed on silica gel using hexane and ethyl acetate as
the eluent. There were obtained 16.8 g (78% of theory) of
30 tributyl-naphthalen-2-ylmethyl-stannate; MS: 432 (M+H)⁺.

h) 16.8 g (38.9 mmol) of tributyl-naphthalen-2-ylmethyl-
stannate were dissolved in 150 ml of tetrahydrofuran under
argon. Thereafter, 12.5 ml (20 mmol) of n-butyllithium solution
35 (1.6M in n-hexane) were added dropwise at -78°C. After
30 minutes a solution of 4.80 g (15.6 mmol) of tert-butyl (3RS,
4SR)-4-(4-fluoro-phenyl)-3-formyl-piperidine-1-carboxylate in
70 ml of tetrahydrofuran was added dropwise at -78°C and the

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reaction mixture was stirred for a further 2 hours. Subsequently, the mixture was warmed to room temperature for 3 hours and stirred for a further 18 hours. After distillation of the solvent in a water-jet vacuum the reaction mixture was
5 partitioned between water and methylene chloride, the organic phase was dried over magnesium sulphate and concentrated. The crude product was chromatographed on silica gel with hexane and ethyl acetate as the eluent. There were obtained 5.50 g (78% of theory) of a mixture of tert-butyl (3RS,4SR)-4-(4-fluoro-phenyl-
10 3-[(RS)- and -[(SR)-1-hydroxy-2-naphthalen-2-yl-ethyl]-piperidine-1-carboxylate; MS: 450 (M+H)⁺.

i) 0.45 g (1 mmol) of the mixture of tert-butyl (3RS,4SR)-4-(4-fluoro-phenyl-3-[(RS)- and -[(SR)-1-hydroxy-2-naphthalen-2-
15 yl-ethyl]-piperidine-1-carboxylate was dissolved in 10 ml of methanol. 2.0 ml (2.8 mmol) of HCl in methanol were added to the solution and the reaction mixture was stirred at 50°C for 1 hour. After distillation of the solvent in a water-jet vacuum the residue was recrystallized from methanol and ether. There
20 was obtained 0.16 g (42% of theory) of a mixture of (RS)- and (SR)-1-[(3RS,4SR)-4-(4-fluoro-phenyl)-piperidin-3-yl]-2-naphthalen-2-yl-ethanol hydrochloride (1:1) in the form of colourless crystals; MS: 350 (M+H)⁺.

25

Example 75

a) 0.45 g (1 mmol) of a mixture of tert-butyl (3RS,4SR)-4-(4-fluoro-phenyl-3-[(RS)- and -[(SR)-1-hydroxy-2-naphthalen-2-yl-ethyl]-piperidine-1-carboxylate was dissolved in 5 ml of
30 dimethylformamide under argon, then treated in succession with 0.16 g (1.2 mmol) of 4-dimethylamino-pyridine and 0.14 ml (1.2 mmol) of benzoyl chloride and stirred at room temperature for 16 hours. The reaction mixture was subsequently worked-up by extraction with ice-water and methylene chloride. The thus-
35 obtained crude product was chromatographed on silica gel with hexane and ethyl acetate as the eluent. There were obtained 0.27 g (49% of theory) of tert-butyl (3RS,4SR)-3-[(RS)- or -[(SR)-1-benzoyloxy-2-naphthalen-2-yl-ethyl]-4-(4-fluoro-

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phenyl)-piperidine-1-carboxylate, MS: 554 (M+H)⁺, and 0.19 g (34% of theory) of tert-butyl (3RS,4SR)-3-[(SR)- or -[(RS)-1-benzoyloxy-2-naphthalen-2-yl-ethyl]-4-(4-fluoro-phenyl)-piperidine-1-carboxylate, MS: 554 (M+H)⁺, .

- 5 b) 0.15 g (0.27 mmol) of tert-butyl (3RS,4SR)-3-[(SR)- or -[(RS)-1-benzoyloxy-2-naphthalen-2-yl-ethyl]-4-(4-fluoro-phenyl)-piperidine-1-carboxylate was stirred at 50°C for 1 hour in 10 ml of methanol with the addition of 1.0 ml (1.4 mmol) of HCl in methanol. After distillation of the solvent in a water-jet vacuum and subsequent drying in a high vacuum there was obtained 0.12 g (91% of theory) of (SR)- or (RS)-1-[(3RS,4SR)-4-(4-fluoro-phenyl)-piperidin-3-yl]-2-naphthalen-2-yl-ethyl benzoate hydrochloride (1:1) as a colourless foam; MS: 454 (M+H)⁺.

Example 76

- a) 0.25 g (0.45 mmol) of tert-butyl (3RS,4SR)-3-[(RS)- or -[(SR)-1-benzoyloxy-2-naphthalen-2-yl-ethyl]-4-(4-fluoro-phenyl)-piperidine-1-carboxylate was reacted with 1.2 ml (1.68 mmol) of HCl in methanol in analogy to Example 75(b). There was thus obtained 0.21 g (95% of theory) of (RS)- or (SR)-1-[(3RS,4SR)-4-(4-fluoro-phenyl)-piperidin-3-yl]-2-naphthalen-2-yl-ethyl benzoate hydrochloride (1:1) as a colourless foam; MS: 454 (M+H)⁺.

Example 77

- a) 0.45 g (1 mmol) of a mixture of tert-butyl (3RS,4SR)-4-(4-fluoro-phenyl)-3-[(RS)- and -[(SR)-1-hydroxy-2-naphthalen-2-yl-ethyl]-piperidin-1-carboxylate was reacted with 0.09 ml (1.26 mmol) of acetyl chloride and 0.16 g (1.3 mmol) of 4-dimethylamino-pyridine in analogy to Example 75(a). There was thus obtained 0.38 g (77% of theory) of a mixture of tert-butyl (3RS,4SR)-3-[(RS)- and -[(SR)-1-acetyloxy-2-naphthalen-2-yl-ethyl]-4-(4-fluoro-phenyl)-piperidine-1-carboxylate, which was used directly in the next step.

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b) 0.15 g (0.31 mmol) of the mixture of tert-butyl (3RS,4SR)-3[(RS)- and -[(SR)-1-of acetyloxy-2-naphthalen-2-yl-ethyl]-4-(4-fluoro-phenyl)-piperidine-1-carboxylate was treated in 10 ml
 5 of methylene chloride which 0.5 ml (6.5 mmol) of trifluoroacetic acid and the mixture was stirred at room temperature for 16 hours. After distillation of the solvent in a water-jet vacuum and subsequent drying in a high vacuum there was obtained 0.15 g (96% of theory) of a mixture of (RS)- and (SR)-1-[(3RS,4SR)-4-(4-fluoro-phenyl)-piperidin-3-yl]-2-naphthalen-2-yl-ethyl
 10 acetate trifluoroacetate (1:1) as a colourless foam; MS: 392 (M+H)⁺.

Example 78

15

a) 0.45 g (1 mmol) of a mixture of tert-butyl (3RS,4SR)-4-(4-fluoro-phenyl)-3-[(RS)- and -[(SR)-1-hydroxy-2-naphthalen-2-yl-ethyl]-piperidine-1-carboxylate was dissolved in 10 ml of dimethylformamide under argon and 0.07 g (1.6 mmol) of sodium
 20 hydride dispersion (55% in mineral oil) was added thereto at room temperature while stirring. After 1 hour 0.14 ml (1.2 mmol) of benzyl bromide was added dropwise and the reaction mixture was stirred at room temperature for 18 hours. Subsequently, the mixture was worked-up by extraction with ice-water and
 25 methylene chloride. The thus-obtained crude product was chromatographed on silica gel with hexane and ethyl acetate as the eluent. There were obtained 0.21 g (39% of theory) of tert-butyl (3RS,4SR)-3-[(RS)- or -[(SR)-1-benzyloxy-2-naphthalen-2-yl-ethyl]-4-(4-fluoro-phenyl)-piperidine-1-carboxylate, MS: 540
 30 (M+H)⁺, and 0.17 g (31% of theory) of tert-butyl (3RS,4SR)-3-[(SR)- or -[(RS)-1-benzyloxy-2-naphthalen-2-yl-ethyl]-4-(4-fluoro-phenyl)-piperidine-1-carboxylate, MS: 540 (M+H)⁺.

b) 0.12 g (0.22 mmol) of tert-butyl 3RS,4SR)-3-[(RS)- or
 35 -[(SR)-1-benzyloxy-2-naphthalen-2-yl-ethyl]-4-(4-fluoro-phenyl)-piperidine-1-carboxylate was reacted with 1.0 ml (1.40 mmol) of HCl in methanol in analogy to Example 75(b). There was thus obtained 0.10 g (95% or theory) of (3RS,4SR)-3-

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[(RS)- or -[(SR)-1-benzyloxy-2-naphthalen-2-yl-ethyl]-4-(4-fluoro-phenyl)-piperidine hydrochloride (1:1) as a colourless foam; MS: 440 (M+H)⁺.

5

Example 79

a) 0.16 g (0.3 mmol) of tert-butyl (3RS,4SR)-3-[(SR)- or -[(RS)-1-benzyloxy-2-naphthalen-2-yl-ethyl]-4-(4-fluoro-phenyl)-piperidine-1-carboxylate was reacted with 1.0 ml
10 (1.40 mmol) of HCl in methanol in analogy to Example 75(b). After distillation of the solvent in a water-jet vacuum the residue was recrystallized from methanol and diethyl ether. There was thus obtained 0.085 g (60% of theory) of (3RS,4SR)-3-[(SR)- or -[(RS)-1-benzyloxy-2-naphthalen-2-yl-ethyl]-4-(4-
15 fluoro-phenyl)-piperidine hydrochloride (1:1) as a white solid; MS: 440 (M+H)⁺.

Example 80

20 a) 0.45 g (1 mmol) of a mixture of tert-butyl (3RS,4SR)-4-(4-fluoro-phenyl)-3-[(RS)- and -[(SR)-1-hydroxy-2-naphthalen-2-yl-ethyl]-piperidine-1-carboxylate was dissolved in 10 ml of dimethylformamide under argon, then 0.07 g (1.6 mmol) of sodium hydride dispersion (55% in mineral oil) was added at room
25 temperature while stirring. After 1 hour 0.27 g (1.2 mmol) of 2-(bromomethyl)-naphthalene was added and the mixture was stirred at room temperature for 72 hours. Subsequently, the mixture was extracted with ice-water and ethyl acetate, the organic phase was dried over magnesium sulphate and subse-
30 quently evaporated in a water-jet vacuum. The thus-obtained crude product was chromatographed on silica gel with hexane and ethyl acetate as the eluent. There was obtained 0.19 g (32% of theory) of tert-butyl (3RS,4SR)-4-(4-fluoro-phenyl)-3-[(SR)- or (RS)-2-naphthalen-2-yl-1-(naphthalen-2-ylmethoxy)-ethyl]-
35 piperidine-1-carboxylate, which was used directly in the next step, and 0.09 g (15% of theory) of tert-butyl (3RS,4SR)-4-(4-fluoro-phenyl)-3-[(RS)- or (SR)-2-naphthalen-2-yl-1-

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(naphthalen-2-ylmethoxy)-ethyl]-piperidine-1-carboxylate, which was likewise used directly in the next step.

b) 0.19 g (0.32 mmol) of tert-butyl (3RS,4SR)-4-(4-fluoro-phenyl)-3-[(SR)- or (RS)-2-naphthalen-2-yl-1-(naphthalen-2-ylmethoxy)-ethyl]-piperidine-1-carboxylate was reacted with 1.0 ml (1.40 mmol) of HCl in methanol in analogy to Example 75(b). The reaction solution was poured on to ice-water, neutralized with saturated sodium hydrogen carbonate solution, the product was then extracted twice with 50 ml of methylene chloride. The organic phases were dried over magnesium sulphate, filtered and the solvent was distilled off in a water-jet vacuum. The thus-obtained crude product was chromatographed on silica gel with methylene chloride and methanol as the eluent. There was thus obtained 0.28 g (18% of theory) of (3RS,4SR)-4-(4-fluoro-phenyl)-3-[(SR)- or (RS)-2-naphthalen-2-yl-1-(naphthalen-2-ylmethoxy)-ethyl]-piperidine as an amorphous, colourless solid; MS: 490 (M+H)⁺.

20

Example 81

a) 0.09 g (0.15 mmol) of tert-butyl (3RS,4SR)-4-(4-fluoro-phenyl)-3-[(RS)- or (SR)-2-naphthalen-2-yl-1-(naphthalen-2-ylmethoxy)-ethyl]-piperidine-1-carboxylate was reacted with 1.0 ml (1.40 mmol) of HCl in methanol in analogy to Example 75(b). The reaction solution was poured on to ice-water (sic), neutralized with saturated sodium hydrogen carbonate solution, then the product was extracted twice with 50 ml of methylene chloride. The organic phases were dried over magnesium sulphate, filtered and the solvent was distilled off in a water-jet vacuum. The thus-obtained crude product was chromatographed on silica gel with methylene chloride and methanol as the eluent. There was thus obtained 0.036 g (49% of theory) of (3RS,4SR)-4-(4-fluoro-phenyl)-3-[(RS)- or (SR)-2-naphthalen-2-yl-1-(naphthalen-2-ylmethoxy)-ethyl]-piperidine as an amorphous, colourless solid; MS: 490 (M+H)⁺.

Example 82

a) A solution of 1.08 g (4.3 mmol) of (1RS,2RS,3RS,5SR)-3-(4-chloro-phenyl)-8-methyl-8-aza-bicyclo[3.2.1]octan-2-ol [J. Org. Chem. 35, 802, 1970)] in 5 ml of tetrahydrofuran was added dropwise to a suspension of 0.206 g (4.3 mmol) of sodium hydride (50% dispersion in refined oil) in 6 ml of tetrahydrofuran and the mixture was stirred at 50°C for 60 minutes. Subsequently, the mixture was cooled to room temperature and treated with 0.95 g (4.3 mmol) of 2-bromomethylnaphthalene in 5 ml of tetrahydrofuran. After 2 hours at 50°C the reaction solution was poured into 60 ml of ice-water and extracted three times with 25 ml of ethyl acetate. The organic phases were washed with saturated sodium chloride solution, dried over magnesium sulphate, filtered and evaporated. The residue was chromatographed on silica gel using a 95:5 mixture of methylene chloride and methanol as the eluent and yielded 1.04 g (62% of theory) of (1RS,2RS,3RS,5SR)-3-(4-chloro-phenyl)-8-methyl-2-(naphthalen-2-ylmethoxy)-8-aza-bicyclo[3.2.1]octane as a light yellow oil, R_f : 0.43 (silica gel, methylene chloride:methanol = 95:5), MS: 392 (M)⁺.

20

(b) A solution of 1.02 g (2.6 mmol) of (1RS,2RS,3RS,5SR)-3-(4-chloro-phenyl)-8-methyl-2-(naphthalen-2-ylmethoxy)-8-aza-bicyclo[3.2.1]octane in 40 ml of toluene was treated with 150 mg of potassium carbonate and heated to 100°C. Subsequently, 0.635 g (0.400 ml) (3 mmol) of 2,2,2-trichloroethyl chloroformate was added thereto and the mixture was stirred at 100°C for 12 hours. The reaction solution was evaporated under reduced pressure, the residue was taken up in 70 ml of ethyl acetate and washed with 30 ml of water and 30 ml of saturated sodium hydrogen carbonate solution. Drying over magnesium sulphate, filtration and evaporation yielded a colourless oil which was chromatographed on silica gel using a 3:2 mixture of hexane and ethyl acetate. There were obtained 1.14 g (79 % of theory) of 2,2,2-trichloroethyl (1RS,2RS,3RS,5SR)-3-(4-chloro-phenyl)-2-(naphthalen-2-ylmethoxy)-8-aza-bicyclo[3.2.1]octane-8-carboxylate as a colourless oil, R_f : 0.38 (silica gel, hexane:ethyl acetate = 3:2).

35

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(c) A suspension of 1.14 g (2.06 mmol) of 2,2,2-trichloroethyl (1RS,2RS,3RS,5SR)-3-(4-chloro-phenyl)-2-(naphthalen-2-ylmethoxy)-8-aza-bicyclo[3.2.1]octane-8-carboxylate and 400 mg of zinc in 10 ml of acetic acid was stirred at room temperature for 12 hours. The reaction solution was diluted with 50 ml of water and extracted four times with 40 ml of methylene chloride. The organic phase was washed twice with 50 ml of 1N sodium hydroxide solution, dried over sodium sulphate, filtered and evaporated. The residue was chromatographed on silica gel using a 9:1 mixture of methylene chloride and methanol as the eluent. There was obtained 0.480 g (61% of theory) of (1RS,2RS,3RS,5SR)-3-(4-chloro-phenyl)-2-(naphthalen-2-ylmethoxy)-8-aza-bicyclo[3.2.1]octane of m.p. 184-185°; MS: 379 (M+H)⁺.

Example 83

The following compounds were prepared in an analogous manner to that described in Example 82(a)-(c):

- 1) -From (1RS,2RS,3RS,5SR)-3-(4-chloro-phenyl)-8-methyl-8-aza-bicyclo[3.2.1]octan-2-ol and 4-chloromethyl-biphenyl, (1RS,2RS,3RS,5SR)-2-(biphenyl-4-ylmethoxy)-3-(4-chloro-phenyl)-8-aza-bicyclo[3.2.1]octane, MS: 236 (M-C₁₃H₁₁)⁺, which was converted with hydrogen chloride in ethanol into the hydrochloride of m.p. 175-177°(dec.);
- 2) - from (1RS,2RS,3RS,5SR)-3-(4-chloro-phenyl)-8-methyl-8-aza-bicyclo[3.2.1]octane-2-ol and 3,4-dichloro-1-chloromethylbenzene, 3-(4-chloro-phenyl)-2-(3,4-dichloro-benzyloxy)-8-aza-bicyclo[3.2.1]octane, MS: 236 (M-C₇H₅Cl₂)⁺, which was converted with hydrogen chloride in ethanol into the hydrochloride of m.p. 211-213°;
- 3) - from (1RS,2RS,3RS,5SR)-3-(4-chloro-phenyl)-8-methyl-8-aza-bicyclo[3.2.1]octane-2-ol and 1-chloro-methyl-4-methoxy-benzene, (1RS,2RS,3RS,5SR)-3-(4-chloro-phenyl)-2-(4-methoxy-benzyloxy)-8-aza-bicyclo[3.2.1]octane, MS: 358 (M+H)⁺, which was converted with methanesulphonic acid in dioxan/water

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and subsequent lyophilization into the corresponding methanesulphonate, R_f: 0.26 (silica gel, methylene chloride: methanol:ammonia = 200:10:1);

5 4) - from (1RS,2RS,3RS,5SR)-3-(4-chloro-phenyl)-8-methyl-8-aza-bicyclo[3.2.1]octane-2-ol and 3-chloromethyl-benzo-[b]thiophene (J. Am. Chem. Soc. 71, 2856 (1949), 2-(benzo-[b]thiophen-2-ylmethoxy)-3-(4-chloro-phenyl)-8-aza-bicyclo[3.2.1]octane, MS: 236 (M-C₈H₇S)⁺, which was converted with
10 hydrogen chloride in ethanol into the hydrochloride of m.p. 196-198°C (dec.);

5) - from (1RS,2RS,3RS,5SR)-3-(4-chloro-phenyl)-8-methyl-8-aza-bicyclo[3.2.1]octane-2-ol and methyl 4'-bromomethyl-
15 biphenyl-2-carboxylate [J. Med. Chem. 34, 2525 (1991), methyl (1RS,2RS,3RS,5SR)-4'-[3-(4-chloro-phenyl)-8-aza-bicyclo[3.2.1]oct-2-yloxymethyl]-biphenyl-2-carboxylate, MS: 236 (M-C₁₅H₁₃O₂)⁺, which was converted with hydrogen chloride in ethanol into the hydrochloride of m.p. 101-103°C (dec.);

20

6) - from (1RS,2RS,3RS,5SR)-3-(4-chloro-phenyl)-8-methyl-8-aza-bicyclo[3.2.1]octane-2-ol and 6-chloromethyl-1,1,4,4,-tetramethyl-1,2,3,4-tetrahydronaphthalene, (1RS,2RS,3RS,5SR)-3-(4-chloro-phenyl)-2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-
25 naphthalen-2-ylmethoxy)-8-aza-bicyclo[3.2.1]octane, MS: 437 (M)⁺, which was converted with hydrogen chloride in ethanol into the hydrochloride of m.p. 87-90°C (dec.).

Example 84

30

(a) Cleavage of the N-methyl group by reacting 2,2,2-trichloroethyl chloroformate with (1RS,2RS,3RS,5SR)-3-(4-fluoro-phenyl)-8-methyl-8-aza-bicyclo[3.2.1]octane-2-ol, obtained analogously to the 4-chloro-phenyl derivative [J. Org.
35 Chem. 35, 802, 1970)], was effected in an analogous manner to the procedure described in Example 12(c). There was thus obtained 2,2,2-trichloro-ethyl (1RS,2RS,3RS,5RS)-3-(4-fluoro-phenyl)-2-(2,2,2-trichloro-ethoxycarbonyloxy)-8-aza-bicyclo-

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[3.2.1]octane-8-carboxylate as a yellowish solid; MS: 587, 589, 591, 593 (M+NH₄)⁺.

(b) By cleavage of the 2,2,2-trichloroethyl carbamate and
 5 2,2,2-trichloroethyl carbonate from 2,2,2-trichloro-ethyl
 (1RS,2RS,3RS,5RS)-3-(4-fluoro-phenyl)-2-(2,2,2-trichloro-
 ethoxycarbonyloxy)-8-aza-bicyclo[3.2.1]octane-8-carboxylate in
 an analogous manner to that described in Example 12(d) there was
 obtained (1RS,2RS,3RS,5RS)-3-(4-fluoro-phenyl)-8-aza-
 10 bicyclo[3.2.1]octan-2-ol as a colourless solid; MS: 221 (M)⁺.

(c) In analogy to the procedure described in Example 1(f), from
 (1RS,2RS,3RS,5RS)-3-(4-fluoro-phenyl)-8-aza-bicyclo[3.2.1]-
 octane-2-ol by introduction of the BOC group there was obtained
 15 tert-butyl (1RS,2RS,3RS,5RS)-3-(4-fluoro-phenyl)-2-hydroxy-8-
 aza-bicyclo[3.2.1]octane-8-carboxylate as a colourless foam;
 MS: 265 (M-C₄H₈)⁺.

(d) Alkylation of tert-butyl (1RS,2RS,3RS,5RS)-3-(4-fluoro-
 20 phenyl)-2-hydroxy-8-aza-bicyclo[3.2.1]octane-8-carboxylate
 with 1-benzyloxy-3-chloromethyl-naphthalene (Example 19)
 analogously to the procedure described in Example 1(g) yielded
 tert-butyl (1RS,2RS,3RS,5SR)-2-(4-benzyloxy-naphthalen-2-yl-
 methoxy)-3-(4-fluoro-phenyl)-8-aza-bicyclo[3.2.1]octane-8-
 25 carboxylate as a colourless solid; MS: 568 (M+H)⁺.

(e) Cleavage of the BOC group using hydrogen chloride in
 ethanol analogously to the procedure described in Example 22(l)
 gave (1RS,2RS,3RS,5SR)-2-(4-benzyloxy-naphthalen-2-yl-
 30 methoxy)-3-(4-fluoro-phenyl)-8-aza-bicyclo[3.2.1]octane as a
 beige coloured solid; MS: 468 (M+H)⁺.

Example 85

35 A solution of 0.330 g (0.71 mmol) of methyl (1RS,2RS,3RS,
 5SR)-4'-[3-(4-chloro-phenyl)-8-aza-bicyclo[3.2.1]oct-2-yloxy-
 methyl]-biphenyl-2-carboxylate in 10 ml of ether was slowly
 added dropwise to a suspension of 33 mg of lithium aluminium

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hydride in 5 ml of ether and the mixture was stirred at room temperature for 4 hours. After the addition of aqueous ether and subsequently water the phases were separated, the organic phase was washed with saturated sodium chloride solution, dried over sodium sulphate, filtered and evaporated. The residue was chromatographed on silica gel using a 140:10:1 mixture of methylene chloride, methanol and ammonia as the eluent. There was obtained 0.210 g (68% of theory) of [4'-[3-(4-chloro-phenyl)-8-aza-bicyclo[3.2.1]oct-2-yloxymethyl]-biphenyl-2-yl]-ethanol as a colourless foam, R_f: 0.18 (methylene chloride:methanol: ammonia = 140:10:1), MS: 434 (M+H)⁺.

Example 86

The following compounds were prepared by cleavage of the BOC group:

- 1) From tert-butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-(4-prop-2-ynyloxy-phenyl)-piperidine-1-carboxylate with tri-fluoroacetic acid, (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-[4-(prop-2-ynyloxy)-phenyl]-piperidine trifluoroacetate as a colourless solid; m.p.: 186°C (dec.);
- 2) from tert-butyl (3RS,4RS)-4-(4-allyloxy-phenyl)-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate with hydrochloric acid in methanol, (3RS,4RS)-4-(4-allyloxy-phenyl)-3-naphthalen-2-ylmethoxy-piperidine as a light oil; MS: 374 (M+H)⁺;
- 3) from a mixture of tert-butyl (3RS,4RS)- and (3SR,4SR)-4-[4-[(RS)-2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy]-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate with hydrochloric acid in methanol with simultaneous cleavage of the isopropylidene group, a mixture of (RS)- and (SR)-3-[(3RS,4RS)-4-[3-(naphthalen-2-ylmethoxy)-piperidin-4-yl]-phenoxy]-propane-1,2-diol as a yellowish solid; MS: 408 (M+H)⁺;

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4) from a mixture of tert-butyl (3RS,4RS)- and (3SR,4SR)-4-[4-[(RS)-2-hydroxy-3-phenoxy-propoxy]-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate with trifluoroacetic acid, a mixture of (RS)- and (SR)-1-[4-[(3RS,4RS)-3-(naphthalen-2-ylmethoxy)-piperidin-4-yl]-phenoxy]-3-phenoxy-propan-2-ol trifluoroacetate as a white solid; MS: 484 (M+H)⁺;

5) from a mixture of tert-butyl (3RS,4RS)- and (3SR,4SR)-4-[4-[(RS)-2-benzyloxy-3-methoxy-propoxy]-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate with trifluoroacetic acid, a mixture of (RS)- and (SR)-4-[(3RS,4RS)-4-(2-benzyloxy-3-methoxy-propoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine trifluoroacetate as a white solid; m.p.: 138-139°C.

6) from a mixture of tert-butyl (3RS,4RS)- and (3SR,4SR)-4-[4-[(RS)-2-hydroxy-3-phenylsulphanyl-propoxy]-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate with trifluoroacetic acid, a mixture of (RS)- and (SR)-1-[(3RS,4RS)-4-[3-(naphthalen-2-ylloxymethyl)-piperidine-4-yl]-phenoxy]-3-phenylsulphanyl-propan-2-ol trifluoroacetate as a white solid; MS: 500 (M+H)⁺;

7) from a mixture of tert-butyl (3RS,4RS)- and (3SR,4SR)-4-[4-[(RS)-2-methoxy-3-phenoxy-propoxy]-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate with trifluoroacetic acid, a mixture of (3RS,4RS)-4-[4-[(RS) and [(SR)-2-methoxy-3-phenoxy-propoxy]-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine trifluoroacetate as a white solid; MS: 498 (M+H)⁺;

8) from a mixture of tert-butyl (3RS,4RS)- and (3SR,4SR)-4-[4-[(RS)-2-benzoyloxy-3-methoxy-propoxy]-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate with trifluoroacetic acid, a mixture of (RS)- and (SR)-1-methoxymethyl-2-[4-[(3RS,4RS)-3-(naphthalen-2-ylmethoxy)-piperidin-4-yl]-phenoxy]-ethyl benzoate trifluoroacetate as a white solid; MS: 526 (M+H)⁺;

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9) from a mixture of tert-butyl (3RS,4RS)-4-[4-[(RS)- and
 [(SR)-(3-benzyloxy-2-methoxy-propoxy)-phenyl]-3-(naphthalen-
 2-ylmethoxy)-piperidine-1-carboxylate, a mixture of (3RS,4RS)-
 4-[4-[(RS)- and -[(SR)-3-benzyloxy-2-methoxypropoxy]-phenyl]-
 5 3-(naphthalen-2-ylmethoxy)-piperidine trifluoroacetate as a
 white solid; MS: 512 (M+H)+;

10) from tert-butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-
 {4-[2-(pyridin-3-ylmethoxy)-ethoxy]-phenyl}-piperidine-1-
 10 carboxylate with hydrogen chloride in methanol, (3RS,4RS)-3-(2-
 [4-[3-(naphthalen-2-ylmethoxy)-piperidine-4-yl]-phenoxy]-
 ethoxymethyl)-pyridine as a colourless resin; MS: 469 (M+H)+;

11) from tert-butyl (3RS,4RS)-4-{4-[2-(pyridin-3-ylmethoxy)-
 15 ethoxy]-phenyl}-3-[4-(2-trimethylsilanyl-ethoxymethoxy)-
 naphthalen-2-ylmethoxy]-piperidine-1-carboxylate with hydrogen
 chloride in methanol with simultaneous cleavage of the SEM
 group, (3RS,4RS)-3-(4-[4-[2-(pyridin-3-ylmethoxy)-ethoxy]-
 phenyl]-piperidin-3-yloxymethyl)-naphthalen-1-ol as a
 20 colourless resin; MS: 485(M+H)+;

12) from tert-butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-
 {4-[2-(pyridin-4-ylmethoxy)-ethoxy]-phenyl}-piperidine-1-
 carboxylate with hydrogen chloride in methanol, (3RS,4RS)-4-(2-
 25 {4-[3-(naphthalen-2-ylmethoxy)-piperidin-4-yl]-phenoxy}-
 ethoxymethyl)-pyridine as a colourless resin; MS: 469 (M+H)+;

13) from tert-butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-
 {4-[2-(pyridin-2-ylmethoxy)-ethoxy]-phenyl}-piperidine-1-
 30 carboxylate with hydrogen chloride in methanol, (3RS,4RS)-2-(2-
 {4-[3-(naphthalen-2-ylmethoxy)-piperidin-4-yl]-phenoxy}-
 ethoxymethyl)-pyridine as a colourless resin; MS: 469 (M+H)+;

14) from tert-butyl (3RS,4RS)-4-[4-(3-benzyloxy-propoxy)-
 35 phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate
 with hydrogen chloride in methanol, (3RS,4RS)-4-[4-(3-
 benzyloxy-propoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-
 piperidine as a colourless resin; MS: 482 (M+H)+;

- 15) from tert-butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-[4-[3-(pyridin-2-ylmethoxy)-propoxy]-phenyl]-piperidine-1-carboxylate with hydrogen chloride in methanol, (3RS,4RS)-2-(3-
5 {4-[3-(naphthalen-2-ylmethoxy)-piperidin-4-yl]-phenoxy}-propoxymethyl)-pyridine as a colourless solid; MS: 483 (M+H)⁺;
- 16) from tert-butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-[4-[3-(pyridin-2-ylmethoxy)-propyl]-phenyl]-piperidine-1-
10 carboxylate with hydrogen chloride in methanol, (3RS,4RS)-2-[3-[4-[3-(naphthalen-2-ylmethoxy)-piperidin-4-yl]-phenyl]-propoxymethyl]-pyridine as a colourless amorphous solid; MS: 467 (M+H)⁺;
- 15 17) from tert-butyl (3RS,4RS)-4-[4-[3-(benzyl-methyl-amino)-propoxy]-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate with hydrogen chloride in methanol, (3RS,4RS)-benzyl-methyl-(3-{4-[3-(naphthalen-2-ylmethoxy)-piperidin-4-yl]-phenoxy}-propyl)-amine as a colourless solid; MS: 495 (M+H)⁺;
- 20 18) from tert-butyl (3RS,4RS)-4-[4-[3-(benzothiazol-2-ylsulphonyl)-propoxy]-phenyl]-3-(1-methoxy-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate with hydrogen chloride in methanol, (3RS,4RS)-2-[3-[4-[3-(1-methoxy-naphthalen-2-
25 ylmethoxy)-piperidin-4-yl]-phenoxy]-propylsulphonyl]-benzothiazole as a colourless foam; MS: 571 (M+H)⁺;
- 19) from tert-butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-[4-(3-phenylsulphanyl-propyl)-phenyl]-piperidine-1-carboxylate
30 with hydrogen chloride in methanol, (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-[4-(3-phenylsulphanyl-propyl)-phenyl]-piperidine as a white solid; MS: 468 (M+H)⁺;
- 20) from tert-butyl (3RS,4RS)-4-{4-[3-(benzothiazol-2-
35 ylsulphanyl)-propyl]-phenyl}-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate with hydrogen chloride in methanol, (3RS,4RS)-2-(3-{4-[3-(naphthalen-2-ylmethoxy)-piperidin-4-yl]-

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phenyl}-propylsulphanyl)-benzothiazole as a white solid; MS: 525 (M+H)⁺;

21) from tert-butyl (3RS,4RS)-4-{4-[2-(pyrimidin-2-yl-
5 sulphanyl)-ethyl]-phenyl}-3-[4-(2-trimethylsilanyl-ethoxy-
methoxy)-naphthalen-2-ylmethoxy]-piperidine-1-carboxylate
with hydrogen chloride in methanol with simultaneous cleavage
of the SEM group, (3RS,4RS)-3-[4-[4-[2-(pyrimidin-2-
ylsulphanyl)-ethyl]-phenyl]-piperidin-3-yloxymethyl]-
10 naphthalen-1-ol as colourless foam; MS: 472 (M+H)⁺;

22) from tert-butyl (3RS,4RS)-4-{4-[2-(pyridin-2-yl-
sulphanyl)-ethyl]-phenyl}-3-[4-(2-trimethylsilanyl-ethoxy-
methoxy)-naphthalen-2-ylmethoxy]-piperidine-1-carboxylate
15 with hydrogen chloride in methanol with simultaneous cleavage
of the SEM group, (3RS,4RS)-3-(4-{4-[2-(pyridin-2-ylsulphanyl)-
ethyl]-phenyl}-piperidin-3-yloxymethyl)-naphthalen-1-ol; MS:
471 (M+H)⁺;

23) from tert-butyl (3RS,4RS)-4-[4-[2-(benzothiazol-2-
20 ylsulphanyl)-ethyl]-phenyl]-3-[4-(2-trimethylsilanyl-ethoxy-
methoxy)-naphthalen-2-ylmethoxy]-piperidine-1-carboxylate
with hydrogen chloride in methanol with simultaneous cleavage
of the SEM group, (3RS,4RS)-3-[4-[4-[2-(benzothiazol-2-
25 ylsulphanyl)-ethyl]-phenyl]-piperidin-3-yloxymethyl]-
naphthalen-1-ol as a colourless solid MS: 527 (M+H)⁺;

24) from tert-butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-
[4-(pyridin-3-ylmethoxymethyl)-phenyl]-piperidine-1-
30 carboxylate with hydrogen chloride in methanol, (3RS,4RS)-3-[4-
[3-(naphthalen-2-ylmethoxy)-piperidin-4-yl]-benzyloxymethyl]-
pyridine as a colourless foam; MS: 438 (M)⁺;

25) from a mixture of tert-butyl (3RS,4RS)-4-(4-{2-[(RS)-2-
35 and (SR)-2-(4-fluoro-phenyl)-3-methyl-butyryloxy]-ethoxy}-
phenyl)-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate
with zinc bromide in methylene chloride, a mixture of (3RS,4RS)-
2-[4-(3-naphthalen-2-ylmethoxy-piperidin-4-yl)-phenoxy]-ethyl

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(RS)- and (SR)-2-(4-fluoro-phenyl)-3-methyl-butyrate hydrobromide as a white solid; MS: 556 (M+H)⁺;

26) from tert-butyl (3RS,4RS)-4-[4-[2-(1-methyl-1H-pyrrol-2-carbonyloxy)-ethoxy]-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate with zinc bromide in methylene chloride, (3RS,4RS)-[4-[3-(naphthalen-2-ylmethoxy)-piperidin-4-yl]-phenoxy]-ethyl 1-methyl-1H-pyrrole-2-carboxylate hydrobromide as a beige solid; MS: 485 (M+H)⁺;

10

27) from tert-butyl (3RS,4RS)-4-[4-(3-benzoyloxy-propyl)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate with hydrogen chloride in methanol, (3RS,4RS)-3-{4-[3-(naphthalen-2-ylmethoxy)-piperidin-4-yl]-phenyl}-propyl benzoate as a yellow syrup; MS: 480 (M+H)⁺;

15

28) from tert-butyl (3RS,4RS)-4-{4-[3-(3-methoxy-benzoyloxy)-propyl]-phenyl}-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate with hydrogen chloride in methanol, (3RS,4RS)-3-{4-[3-(naphthalen-2-ylmethoxy)-piperidin-4-yl]-phenyl}-propyl 3-methoxy-benzoate as a yellow solid; MS: 510 (M+H)⁺;

20

29) from tert-butyl (3RS,4RS)-4-[4-(3-methoxy-benzoyloxy-methyl)-phenyl]-3-[1-(2-trimethylsilanyl-ethoxymethoxy)-naphthalen-2-ylmethoxy]-piperidine-1-carboxylate with hydrogen chloride in methanol with simultaneous cleavage of the SEM group, (3RS,4RS)-4-[3-(1-hydroxy-naphthalen-2-ylmethoxy)-piperidin-4-yl]-benzyl 3-methoxy-benzoate as a colourless foam; MS: 498 (M+H)⁺;

30

30) from tert-butyl (3RS,4RS)-4-(4-ethoxycarbonylmethoxy-phenyl)-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate with trifluoroacetic acid, ethyl (3RS,4RS)-[4-[3-(naphthalen-2-ylmethoxy)-piperidin-4-yl]-phenoxy]-acetate trifluoroacetate as a white solid; MS: 420 (M+H)⁺;

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31) from tert-butyl (3RS,4RS)-4-[4-(benzylcarbamoyl-methoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate with trifluoroacetic acid, (3RS,4RS)-N-benzyl-2-[4-[3-(naphthalen-2-ylmethoxy)-piperidin-4-yl]-phenoxy]-acetamide
5 trifluoroacetate as a white solid; m.p.: 185°C;

32) from tert-butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-[4-(pyridin-2-ylcarbamoxyloxy)-phenyl]-piperidine-1-carboxylate with trifluoroacetic acid, (3RS,4RS)-4-[3-(naphthalen-2-ylmethoxy)-piperidin-4-yl]-3-phenyl pyridin-2-yl-carbamate
10 trifluoroacetate as a white solid; m.p.: 158°C;

33) from tert-butyl (3RS,4RS)-4-(4-carboxymethoxy-phenyl)-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate [Example
15 86 (ee)] with trifluoroacetic acid, (3RS,4RS)-[4-[3-(naphthalen-2-ylmethoxy)-piperidin-4-yl]-phenoxy]-acetic acid trifluoroacetate as a white colourless solid; m.p.: 183-184°C;

34) from tert-butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-[4-(2-oxo-3-phenoxypropoxy)-phenyl]-piperidine-1-carboxylate
20 with trifluoroacetic acid, (3RS,4RS)-1-[4-[3-(naphthalen-2-ylmethoxy)-piperidin-4-yl]-phenoxy]-3-phenoxy-propan-2-one trifluoroacetate as a white solid; m.p.: 145-146°C;

25 35) from tert-butyl (3RS,4RS)-4-[4-(2-ethoxycarbonyl-ethyl)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate [Example 24 (s)] with zinc bromide in methylene chloride, ethyl (3RS,4RS)-3-{4-[3-(naphthalen-2-ylmethoxy)-piperidin-4-yl]-phenyl}-propionate as a yellow syrup; MS: 418 (M+H)+;

30 36) from a mixture of tert-butyl (3RS,4RS)-4-[4-[(RS)-2- and [(SR)-2-hydroxy-2-phenyl-ethyl]-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate with hydrogen chloride in methanol, a mixture of (RS)- and (SR)-2-[4-[(3RS,4RS)-3-naphthalen-2-ylmethoxy-piperidin-4-yl]-phenyl]-1-phenyl-ethanol hydrochloride; MS: 438 (M+H)+;
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37) from tert-butyl (3RS,4RS)-4-(4-fluoro-phenyl)-3-(2-
{[(pyridin-2-carbonyl)-amino]-methyl}-benzyloxy)-piperidine-1-
carboxylate with hydrogen chloride in methanol, pyridine-2-
carboxylic acid (3RS,4RS)-2-[4-(4-fluoro-phenyl)-piperidin-3-
yloxymethyl]-benzylamide dihydrochloride as a white solid; MS:
5 420 (M+H)⁺;

38) from tert-butyl (3RS,4RS)-3-(3-benzoyl-benzyloxy)-4-(4-
fluoro-phenyl)-piperidine-1-carboxylate with hydrogen chloride
10 in methanol, (3RS,4RS)-[3-[4-(4-fluoro-phenyl)-piperidin-3-
yloxymethyl]-phenyl]-phenyl-methanone hydrochloride as a white,
amorphous solid; MS: 390 (M+H)⁺;

39) from tert-butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-
15 [4-[2-(5-phenyl-[1,2,4]oxadiazol-3-yl)-ethyl]-phenyl]-piperidine-
1-carboxylate with hydrogen chloride in methanol, (3RS,4RS)-3-
(naphthalen-2-ylmethoxy)-4-[4-[2-(5-phenyl-[1,2,4]oxadiazol-3-
yl)-ethyl]-phenyl]-piperidine as a white solid; MS: 490 (M+H)⁺;

20 40) from tert-butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-
[4-[2-(3-phenyl-[1,2,4]oxadiazol-5-yl)-ethyl]-phenyl]-piperidine-
1-carboxylate with hydrogen chloride in methanol, (3RS,4RS)-3-
(naphthalen-2-ylmethoxy)-4-[4-[2-(3-phenyl-[1,2,4]oxadiazol-5-
yl)-ethyl]-phenyl]-piperidine as a white solid; MS: 490 (M+H)⁺;

25 41) from tert-butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-
[4-(3-phenyl-[1,2,4]oxadiazol-5-ylmethoxy)-phenyl]-piperidine-
1-carboxylate with trifluoroacetic acid, (3RS,4RS)-3-
(naphthalen-2-ylmethoxy)-4-[4-(3-phenyl-[1,2,4]oxadiazol-5-
ylmethoxy)-phenyl]-piperidine trifluoroacetate as a white solid;
30 m.p.: 195-196°C;

42) from tert-butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-
[4-(3-pyridin-3-yl-[1,2,4]oxadiazol-5-ylmethoxy)-phenyl]-
35 piperidine-1-carboxylate with trifluoroacetic acid, (3RS,4RS)-3-
(5-[4-[3-(naphthalen-2-ylmethoxy)-piperidin-4-yl]-
phenoxymethyl]-[1,2,4]oxadiazol-3-yl)-pyridine trifluoroacetate
as a white solid; MS: 493 (M+H)⁺;

43) from tert-butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-[4-(3-phenyl-isoxazol-5-ylmethoxy)-phenyl]-piperidine-1-carboxylate with trifluoroacetic acid, (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-[4-(3-phenyl-isoxazol-5-ylmethoxy)-phenyl]-piperidine trifluoroacetate as a white solid; MS: 491 (M+H)⁺;

44) from tert-butyl (3RS,4RS)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-(3-methoxy-benzyloxy)-piperidine-1-carboxylate by means of hydrogen chloride in methanol, (3RS,4RS)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-(3-methoxy-benzyloxy)-piperidine hydrochloride as a colourless oil; MS: 462 (M+H)⁺;

45) from tert-butyl (3RS,4RS)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-[3-(2-trimethylsilanyl-ethoxymethoxy)-benzyloxy]-piperidine-1-carboxylate with hydrogen chloride in methanol with simultaneous cleavage of the SEM group, (3RS,4RS)-3-{4-[4-(3-benzyloxy-propoxy)-phenyl]-piperidin-3-ylloxymethyl}-phenol as a colourless oil; MS: 448 (M+H)⁺;

46) from tert-butyl (3RS,4RS)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-(3-chloro-4-methoxy-benzyloxy)-piperidine-1-carboxylate with zinc bromide in methylene chloride, (3RS,4RS)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-(3-chloro-4-methoxy-benzyloxy)-piperidine hydrobromide as a colourless oil; MS: 497 (M+H)⁺;

47) from tert-butyl (3RS,4RS)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-(3,4-dichloro-benzyloxy)-piperidine-1-carboxylate by means of hydrogen chloride in methanol, (3RS,4RS)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-(3,4-dichloro-benzyloxy)-piperidine hydrochloride as a colourless oil; MS: 500 (M)⁺;

48) from tert-butyl (3RS,4RS)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-(2,5-dichloro-benzyloxy)-piperidine-1-carboxylate by means of hydrogen chloride in methanol, (3RS,4RS)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-(2,5-dichloro-benzyloxy)-piperidine hydrochloride as a colourless oil; MS: 500 (M)⁺;

- 49) from tert-butyl (3RS,4RS)-3-benzyloxy-4-[4-(3-benzyloxy-propoxy)-phenyl]-piperidine-1-carboxylate with zinc bromide in methylene chloride, (3RS,4RS)-3-benzyloxy-4-[4-(3-benzyloxy-propoxy)-phenyl]-piperidine hydrobromide as a colourless solid;
5 MS: 432 (M+H)+;
- 50) from tert-butyl (3RS,4RS)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-(2,5-dimethyl-benzyloxy)-piperidine-1-carboxylate
10 with zinc bromide in methylene chloride, (3RS,4RS)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-(2,5-dimethyl-benzyloxy)-piperidine hydrobromide as a colourless oil; MS: 460 (M+H)+;
- 51) from tert-butyl (3RS,4RS)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-(4-ethyl-benzyloxy)-piperidine-1-carboxylate with
15 zinc bromide in methylene chloride, (3RS,4RS)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-(4-ethyl-benzyloxy)-piperidine as a colourless oil; MS: 460 (M+H)+;
- 20 52) from a mixture of tert-butyl (3RS,4RS)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-(3- and 4-vinyl-benzyloxy)-piperidine-1-carboxylate with zinc bromide in methylene chloride, a mixture of (3RS,4RS)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-(3 and 4-vinyl-benzyloxy)-piperidine hydrobromide as a colourless solid; MS: 458
25 (M+H)+;
- 53) from tert-butyl (3RS,4RS)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-(2,3-dihydro-benzo[1,4]dioxin-6-ylmethoxy)-piperidine-1-carboxylate with zinc bromide in methylene
30 chloride, (3RS,4RS)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-(2,3-dihydro-benzo[1,4]dioxin-6-ylmethoxy)-piperidine as a colourless resin; MS: 490 (M+H)+;
- 54) from tert-butyl (3RS,4RS)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-(5,6,7,8-tetrahydro-naphthalen-2-ylmethoxy)-
35 piperidine-1-carboxylate with zinc bromide in methylene chloride, (3RS,4RS)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-

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(5,6,7,8-tetrahydro-naphthalen-2-ylmethoxy)-piperidine as a colourless resin; MS: 486 (M+H)⁺;

55) from tert-butyl (3RS,4RS)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-[4-(2-trimethylsilanyl-ethoxymethoxy)-naphthalen-2-ylmethoxy]-piperidine-1-carboxylate with hydrogen chloride in methanol with simultaneous cleavage of the SEM group, (3RS,4RS)-3-{4-[4-(3-benzyloxy-propoxy)-phenyl]-piperidin-3-yloxymethyl}-naphthalen-1-ol as a colourless resin; MS: 498 (M+H)⁺;

56) from tert-butyl (3RS,4RS)-4-[4-(4-benzyloxy-butoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate with hydrogen chloride in methanol, (3RS,4RS)-4-[4-(4-benzyloxy-butoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine as a colourless oil; MS: 496 (M+H)⁺;

57) from tert-butyl (3SR,4RS,5RS)-4-[4-(2-chloro-benzoyloxymethyl)-phenyl]-3-methoxymethyl-5-(naphthalen-2-ylmethoxy)-piperazine-1-carboxylate with hydrogen chloride in methanol, (3SR,4RS,5RS)-4-[3-methoxymethyl-5-(naphthalen-2-ylmethoxy)-piperidin-4-yl]-benzyl 2-chloro-benzoate as a colourless foam; MS: 530 (M+H)⁺;

58) from tert-butyl (3SR,4RS,5RS)-4-(4-methoxycarbonyl-phenyl)-3-methoxymethyl-5-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate with hydrogen chloride in methanol, methyl (3SR,4RS,5RS)-4-[3-methoxymethyl-5-naphthalen-2-ylmethoxy-piperidin-4-yl]-benzoate as a colourless solid; MS: 420 (M+H)⁺;

59) from tert-butyl (3SR,4RS,5RS)-4-(4-benzyloxymethyl-phenyl)-3-methoxymethyl-5-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate with hydrogen chloride in methanol, (3SR,4RS,5RS)-4-(4-benzyloxymethyl-phenyl)-3-methoxymethyl-5-(naphthalen-2-ylmethoxy)-piperidine as a colourless foam; MS: 482 (M+H)⁺;

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60) from tert-butyl (1RS,2RS,3RS,5SR)-3-[4-(2-benzyloxy-propoxymethyl)-phenyl]-2-(naphthalen-2-ylmethoxy)-8-aza-bicyclo[3.2.1]octane-8-carboxylate with hydrogen chloride in methanol, (1RS,2RS,3RS, 5SR)-2-(naphthalen-2-ylmethoxy)-3-[4-
5 (3-phenoxy-propoxymethyl)phenyl]-8-azabicyclo[3.2.1]octane as a colourless oil; MS: 508 (M+H)⁺.

The BOC derivatives used as starting materials were prepared as follows:

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(a) In an analogous manner to that described in Example 44 (e), by alkylating tert-butyl (3RS,4RS)-3-hydroxy-4-(4-hydroxy-phenyl)-piperidine-1-carboxylate [Example 46 (b)] with propargyl bromide in the presence of potassium carbonate in acetone there
15 was obtained tert-butyl (3RS,4RS)-3-hydroxy-4-(4-prop-2-ynyloxy-phenyl)-piperidine-1-carboxylate, alkylation of which with 2-bromomethylnaphthalene in analogy to Example 1 (g) gave tert-butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-(4-prop-2-ynyloxy-phenyl)-piperidine-1-carboxylate as a pale yellow solid;
20 MS: 472 (M+H)⁺.

(b) In an analogous manner to that described in Example 44 (e), by alkylating tert-butyl (3RS,4RS)-3-hydroxy-4-(4-hydroxy-phenyl)-piperidine-1-carboxylate [Example 46 (b)] with allyl
25 bromide in the presence of potassium carbonate in acetone there was obtained tert-butyl (3RS,4RS)-4-(4-allyloxy-phenyl)-3-hydroxy-piperidine-1-carboxylate, alkylation of which with 2-bromomethylnaphthalene in analogy to Example 1 (g) gave tert-butyl (3RS,4RS)-4-(4-allyloxy-phenyl)-3-(naphthalen-2-yl-
30 methoxy)-piperidine-1-carboxylate as a colourless resin; MS: 474 (M+H)⁺.

(c) In an analogous manner to that described in Example 1 (g), by alkylating tert-butyl (3RS,4RS)-3-hydroxy-4-(4-hydroxy-phenyl)-piperidine-1-carboxylate [Example 46 (b)] with (RS)-2,2-
35 dimethyl-[1,3]dioxolan-4-ylmethyl methanesulphonate in the presence of sodium hydride there was obtained a mixture of tert-butyl (3RS,4RS)- and (3SR,4SR)-4-[4-[(RS)-2,2-dimethyl-

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[1,3]dioxolan-4-ylmethoxy]-phenyl]-3-hydroxy-piperidine-1-carboxylate, alkylation of which with 2-bromomethylnaphthalene in analogy to Example 1 (g) gave a mixture of tert-butyl (3RS,4RS)- and (3SR,4SR)-4-[4-[(RS)-2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy]-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a white solid; MS: 547 (M)⁺.

(d) In an analogous manner to that described in Example 1 (g), by alkylating tert-butyl (3RS,4RS)-3-hydroxy-4-(4-hydroxy-phenyl)-piperidine-1-carboxylate [Example 46 (b)] with (RS)-2,3-epoxypropyl p-toluenesulphonate in the presence of sodium hydride there was obtained a mixture of tert-butyl (3RS,4RS)- and (3SR,4SR)-3-hydroxy-4-[(RS)-4-oxiranylmethoxy-phenyl]-piperidine-1-carboxylate, alkylation of which with 2-bromomethylnaphthalene in analogy to Example 1 (g) gave a mixture of tert-butyl (3RS,4RS)- and (3SR,4SR)-3-(naphthalen-2-ylmethoxy)-4-[(RS)-4-oxiranylmethoxy-phenyl]-piperidine-1-carboxylate. Subsequent epoxide opening with potassium phenolate in analogy to Example 71 (a) yielded a mixture of tert-butyl (3RS,4RS)- and (3SR,4SR)-4-[4-[(RS)-2-hydroxy-3-phenoxy-propoxy]-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a white solid; MS: 584 (M+H)⁺.

(e) Epoxide opening of a mixture of tert-butyl (3RS,4RS)- and (3SR,4SR)-3-(naphthalen-2-ylmethoxy)-4-[(RS)-4-oxiranylmethoxy-phenyl]-piperidine-1-carboxylate [Example 86 (d)] with sodium methylate in N,N-dimethylformamide yielded a mixture of tert-butyl (3RS,4RS)- and (3SR,4SR)-4-[4-[(RS)-2-hydroxy-3-methoxy-propoxy]-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate, alkylation of which with benzyl bromide analogously to Example 1 (g) gave a mixture of tert-butyl (3RS,4RS)- and (3SR,4SR)-4-[4-[(RS)-2-benzyloxy-3-methoxy-propoxy]-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a colourless resin; MS: 612 (M+H)⁺.

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(f) Epoxide opening of a mixture of tert-butyl (3RS,4RS)- and (3SR,4SR)-3-(naphthalen-2-ylmethoxy)-4-[(RS)-4-oxiranylmethoxy-phenyl]-piperidine-1-carboxylate [Example 86 (d)] with

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sodium thiophenolate in analogy to Example 71 (a) gave a mixture of tert-butyl (3RS,4RS)- and (3SR,4SR)-4-[4-[(RS)-2-hydroxy-3-phenylsulphanyl-propoxy]-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a white solid; MS: 600 (M+H)⁺.

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(g) Alkylation of a mixture of tert-butyl (3RS,4RS)- and (3SR,4SR)-4-[4-[(RS)-2-hydroxy-3-phenoxy-propoxy]-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate [Example 86 (d)] with methyl iodide in analogy to Example 1 (g) yielded a
 10 mixture of tert-butyl (3RS,4RS)- and (3SR,4SR)-4-[4-[(RS)-2-methoxy-3-phenoxy-propoxy]-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a colourless resin; MS: 598 (M+H)⁺.

15 (h) In analogy to Example 22 (k), by benzoylating a mixture of tert-butyl (3RS,4RS)- and (3SR,4SR)-4-[4-[(RS)-2-hydroxy-3-methoxy-propoxy]-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate [Example 86 (e)] there was obtained a mixture of tert-butyl (3RS,4RS)- and (3SR,4SR)-4-[4-[(RS)-2-
 20 benzoyloxy-3-methoxy-propoxy]-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a colourless resin; MS: 626 (M+H)⁺.

(i) Epoxide opening of a mixture of tert-butyl (3RS,4RS)- and
 25 (3SR,4SR)-3-(naphthalen-2-ylmethoxy)-4-[(RS)-4-oxiranyl-methoxy-phenyl]-piperidine-1-carboxylate [Example 86 (d)] with sodium benzylate in N,N-dimethylformamide gave a mixture of tert-butyl (3RS,4RS)- and (3SR,4SR)-4-[4-[(RS)-3-Benzoyloxy-2-hydroxy-propoxy]-phenyl]-3-(naphthalen-2-ylmethoxy)-
 30 piperidine-1-carboxylate, alkylation of which with methyl iodide analogously to Example 1 (g) yielded a mixture of tert-butyl (3RS,4RS)- and (3SR,4SR)-4-[4-[(RS)-3-benzyloxy-2-methoxy-propoxy]-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a colourless resin; MS: 612 (M+H)⁺.

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(j) In an analogous manner to that described in Example 1 (g) by alkylating tert-butyl (3RS,4RS)-4-[4-(2-hydroxy-ethoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate

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[Example 53 (c)] with 3-chloromethyl-pyridine there was obtained tert-butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-{4-[2-(pyridin-3-ylmethoxy)-ethoxy]-phenyl}-piperidine-1-carboxylate; MS: 569 (M+H)+.

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(k) In an analogous manner to that described in Example 1 (g), by alkylating tert-butyl (3RS,4RS)-4-[4-(2-hydroxy-ethoxy)-phenyl]-3-[4-(2-trimethylsilanyl-ethoxymethoxy)-naphthalen-2-ylmethoxy]-piperidine-1-carboxylate [Example 55 (b)] with 3-chloromethyl-pyridine there was obtained tert-butyl (3RS,4RS)-4-{4-[2-(pyridin-3-ylmethoxy)-ethoxy]-phenyl}-3-[4-(2-trimethylsilanyl-ethoxymethoxy)-naphthalen-2-ylmethoxy]-piperidine-1-carboxylate.

15 (l) In an analogous manner to that described in Example 1 (g), by alkylating tert-butyl (3RS,4RS)-4-[4-(2-hydroxy-ethoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate [Example 53 (c)] with 4-chloromethyl-pyridine there was obtained tert-butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-{4-[2-(pyridin-4-ylmethoxy)-ethoxy]-phenyl}-piperidine-1-carboxylate as a colourless oil.

(m) In an analogous manner to that described in Example 1 (g), by alkylating tert-butyl (3RS,4RS)-4-[4-(2-hydroxy-ethoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate [Example 53 (c)] with 2-chloromethyl-pyridine there was obtained tert-butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-{4-[2-(pyridin-2-ylmethoxy)-ethoxy]-phenyl}-piperidine-1-carboxylate as a colourless oil.

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(n) In an analogous manner to that described in Example 44 (e), by alkylating tert-butyl (3RS,4RS)-3-hydroxy-4-(4-hydroxy-phenyl)-piperidine-1-carboxylate [Example 46 (b)] with benzyl 3-bromopropyl ether in the presence of potassium carbonate in butan-2-one there was obtained tert-butyl (3RS,4RS)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-hydroxy-piperidine-1-carboxylate, alkylation of which with 2-bromomethyl-naphthalene analogously to Example 1 (g) gave tert-butyl (3RS,4RS)-4-[4-(3-benzyloxy-

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propoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a colourless oil; MS: 582 (M+H)⁺.

(o) In an analogous manner to that described in Example 1 (g), by
 5 alkylating tert-butyl (3RS,4RS)-4-[4-(3-hydroxy-propoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate [Example 57 (c)] with 2-chloromethyl-pyridine there was obtained tert-butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-[4-[3-(pyridin-2-ylmethoxy)-propoxy]-phenyl]-piperidine-1-
 10 carboxylate as a colourless resin; MS: 583 (M+H)⁺.

(p) In an analogous manner to that described in Example 1 (g), by
 alkylating tert-butyl (3RS,4RS)-4-[4-(3-hydroxy-propyl)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate
 15 [Example 24 (t)] with 2-chloromethyl-pyridine there was obtained tert-butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-[4-[3-(pyridin-2-ylmethoxy)-propyl]-phenyl]-piperidine-1-carboxylate as a colourless, amorphous solid, which was used in the following step without further purification and characterization.

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(q) In an analogous manner to that described in Example 44 (e), by
 alkylating tert-butyl (3RS,4RS)-4-[4-(3-methylamino-propoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate [Example 57 (e)] with benzyl bromide there was obtained tert-
 25 butyl (3RS,4RS)-4-[4-[3-(benzyl-methyl-amino)-propoxy]-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a colourless solid; MS: 595 (M+H)⁺.

(r) In an analogous manner to that described in Example 1 (g), by
 30 alkylating a mixture of tert-butyl (3RS,4RS)- and (3SR,4SR)-3-hydroxy-4-[4-[3-[(RS)-tetrahydro-pyran-2-yloxy]-propoxy]-phenyl]-piperidine-1-carboxylate [Example 57 (a)] with 1-methoxy-2-bromomethyl-naphthalene [Example 7 (f)] there was obtained a mixture of tert-butyl (3RS,4RS)- and (3SR,4SR)-3-(1-methoxy-naphthalen-2-ylmethoxy)-4-[4-[3-[(RS)-tetrahydro-pyran-2-yloxy]-propoxy]-phenyl]-piperidine-1-carboxylate.
 35 Cleavage of the THP group by means of pyridinium (toluene-4-sulphonate) in ethanol analogously to Example 53 (c) gave tert-

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butyl (3RS,4RS)-4-[4-(3-hydroxy-propoxy)-phenyl]-3-(1-methoxy-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate, reaction of which with bis-(benzothiazol-2-yl) disulphide analogously to Example 33 (a) gave tert-butyl (3RS,4RS)-4-[4-[3-(benzothiazol-2-ylsulphonyl)-propoxy]-phenyl]-3-(1-methoxy-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a colourless liquid; MS: 671 (M+H)⁺.

(s) In an analogous manner to that described in Example 33 (a), by reacting tert-butyl (3RS,4RS)-4-[4-(3-hydroxy-propyl)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate [Example 24 (t)] with diphenyl disulphide there was obtained tert-butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-[4-(3-phenylsulphanyl-propyl)-phenyl]-piperidine-1-carboxylate as a colourless, amorphous solid; MS: 568 (M+H)⁺.

(t) In an analogous manner to that described in Example 33 (a), by reacting tert-butyl (3RS,4RS)-4-[4-(3-hydroxy-propyl)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate [Example 24 (t)] with bis-(benzothiazol-2-yl) disulphide there was obtained tert-butyl (3RS,4RS)-4-{4-[3-(benzothiazol-2-yl-sulphanyl)-propyl]-phenyl}-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate, which was used in the following step without further purification and characterization.

(u) (α) In an analogous manner to that described in Example 1 (g), by alkylating tert-butyl (3RS,4RS)-3-hydroxy-4-[4-(2-trityloxy-ethyl)-phenyl]-piperidine-1-carboxylate [Example 29 (t)] with 3-chloromethyl-1-(2-trimethylsilyl-ethoxymethoxy)-naphthalene [Example 5 (c)] there was obtained tert-butyl (3RS,4RS)-3-[4-(2-trimethylsilyl-ethoxymethoxy)-naphthalen-2-ylmethoxy]-4-[4-(2-trityloxy-ethyl)-phenyl]-piperidine-1-carboxylate.

(β) Selective cleavage of the trityl group was effected analogously to the procedure published by E. Krainer et al. in Tetrahedron Letters 1993, 1713-1716 by treating a solution of 780 mg (0.92 mmol) of tert-butyl (3RS,4RS)-3-[4-(2-trimethylsilyl-ethoxymethoxy)-naphthalen-2-ylmethoxy]-4-[4-(2-

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trityloxy-ethyl)-phenyl]-piperidine-1-carboxylate in 15 ml of methylene chloride with a solution of 436 mg (3.68 mmol) of trifluoroacetic acid and 803 mg (3.68 mmol) of trifluoroacetic anhydride in 2 ml of methylene chloride. After 30 seconds the
5 reaction mixture was cooled to 0°C and treated with 4 ml of triethylamine. After 5 minutes 10 ml of methanol were added and the mixture was stirred for 10 minutes. Subsequently, the mixture was washed with saturated sodium hydrogen carbonate solution and the aqueous phase was thereafter back-extracted
10 with 10 ml of methylene chloride. The combined organic phases were dried over sodium sulphate and then evaporated under reduced pressure. The crude product was chromatographed on silica gel using a 4:1 mixture of hexane and ethyl acetate as the eluent. There were obtained 553 mg of tert-butyl (3RS,4RS)-4-
15 [4-(2-hydroxy-ethyl)-phenyl]-3-[4-(2-trimethylsilyl-ethoxymethoxy)-naphthalen-2-ylmethoxy]-piperidine-1-carboxylate as a colourless oil.

(γ) In an analogous manner to that described in Example 34, from
20 tert-butyl (3RS,4RS)-4-[4-(2-hydroxy-ethyl)-phenyl]-3-[4-(2-trimethylsilyl-ethoxymethoxy)-naphthalen-2-ylmethoxy]-piperidine-1-carboxylate via the corresponding mesylate by reaction with 2-mercaptopyrimidine there was obtained tert-butyl (3RS,4RS)-4-{4-[2-(pyrimidin-2-ylsulphanyl)-ethyl]-
25 phenyl}-3-[4-(2-trimethylsilyl-ethoxymethoxy)-naphthalen-2-ylmethoxy]-piperidine-1-carboxylate as a colourless oil, which was used in the following step without further purification and characterization.

(v) In an analogous manner to that described in Example 33 (a),
30 from tert-butyl (3RS,4RS)-4-[4-(2-hydroxy-ethyl)-phenyl]-3-[4-(2-trimethylsilyl-ethoxymethoxy)-naphthalen-2-ylmethoxy]-piperidine-1-carboxylate by reaction with 2,2'-dithiopyridine there was obtained tert-butyl (3RS,4RS)-4-{4-[2-(pyridin-2-
35 ylsulphanyl)-ethyl]-phenyl}-3-[4-(2-trimethylsilyl-ethoxymethoxy)-naphthalen-2-ylmethoxy]-piperidine-1-carboxylate as a colourless oil, which was used in the following step without further purification and characterization.

(w) In an analogous manner to that described in Example 33 (a), from tert-butyl (3RS,4RS)-4-[4-(2-hydroxy-ethyl)-phenyl]-3-[4-(2-trimethylsilyl-ethoxymethoxy)-naphthalen-2-ylmethoxy]-piperidine-1-carboxylate by reaction with bis-(benzothiazol-2-yl) disulphide there was obtained tert-butyl (3RS,4RS)-4-[4-[2-(benzothiazol-2-ylsulphonyl)-ethyl]-phenyl]-3-[4-(2-trimethylsilyl-ethoxymethoxy)-naphthalen-2-ylmethoxy]-piperidine-1-carboxylate as a colourless foam; MS: 757 (M+H)⁺.

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(x) In an analogous manner to that described in Example 1 (g), by alkylating tert-butyl (3RS,4RS)-4-(4-hydroxymethyl-phenyl)-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate [Example 22 (j)] with 3-chloromethyl-pyridine there was obtained tert-butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-[4-(pyridin-3-yl-methoxymethyl)-phenyl]-piperidine-1-carboxylate as a colourless oil; MS: 539 (M+H)⁺.

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(y) In an analogous manner to that described in Example 9 (c), by esterifying tert-butyl (3RS,4RS)-4-[4-(2-hydroxy-ethoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate [Example 53 (c)] with (RS)-2-(4-fluoro-phenyl)-3-methyl-butyric acid (DE 2365555) in the presence of EDC there was obtained a mixture of tert-butyl (3RS,4RS)- and (3SR,4SR)-4-(4-2-[(RS)-2-(4-fluoro-phenyl)-3-methyl-butyryloxy]-ethoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a colourless solid; MS: 656 (M+H)⁺.

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(z) In an analogous manner to that described in Example 9 (c), by esterifying tert-butyl (3RS,4RS)-4-[4-(2-hydroxy-ethoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate [Example 53 (c)] with 1-methyl-pyrrole-2-carboxylic acid in the presence of EDC there was obtained tert-butyl (3RS,4RS)-4-[4-[2-(1-methyl-1H-pyrrol-2-carbonyloxy)-ethoxy]-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a colourless oil; MS: 585 (M+H)⁺.

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(aa) In an analogous manner to that described in Example 22 (k), by acylating tert-butyl (3RS,4RS)-4-[4-(3-hydroxy-propyl)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate [Example 24 (t)] with benzoyl chloride there was obtained tert-butyl (3RS,4RS)-4-[4-(3-benzoyloxy-propyl)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as an almost colourless solid; MS: 580 (M+H)⁺.

(bb) In an analogous manner to that described in Example 22 (k), by acylating tert-butyl (3RS,4RS)-4-[4-(3-hydroxy-propyl)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate [Example 24 (t)] with 3-methoxy-benzoyl chloride there was obtained tert-butyl (3RS,4RS)-4-{4-[3-(3-Methoxy-benzoyloxy)-propyl]-phenyl}-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a colourless, amorphous solid; MS: 610 (M+H)⁺.

(cc) In an analogous manner to that described in Example 1 (g), by alkylating tert-butyl (3RS,4RS)-3-hydroxy-4-(4-trityloxy-methyl-phenyl)-piperidine-1-carboxylate [Example 22 (h)] with 2-chloromethyl-1-(2-trimethylsilanyl-ethoxymethoxy)-naphthalene [Example 6 (c)] there was obtained tert-butyl (3RS,4RS)-3-[1-(2-trimethylsilanyl-ethoxymethoxy)-naphthalen-2-ylmethoxy]-4-(4-trityloxymethyl-phenyl)-piperidine-1-carboxylate. Selective cleavage of the trityl group analogously to Example 86 (u) (β) gave tert-butyl (3RS,4RS)-4-(4-hydroxy-methyl-phenyl)-3-[1-(2-trimethylsilanyl-ethoxymethoxy)-naphthalen-2-ylmethoxy]-piperidine-1-carboxylate, acylation of which with 3-methoxy-benzoyl chloride analogously to Example 22 (k) gave tert-butyl (3RS,4RS)-4-[4-(3-methoxy-benzoyloxy-methyl)-phenyl]-3-[1-(2-trimethylsilanyl-ethoxymethoxy)-naphthalen-2-ylmethoxy]-piperidine-1-carboxylate as a colourless oil, MS: 745 (M+NH₄)⁺.

(dd) In an analogous manner to that described in Example 44 (e), by alkylating tert-butyl (3RS,4RS)-4-(4-hydroxy-phenyl)-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate [Example 61 (c)] with ethyl bromoacetate there was obtained tert-butyl (3RS,4RS)-4-(4-ethoxycarbonylmethoxy-phenyl)-3-(naphthalen-

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2-ylmethoxy)-piperidine-1-carboxylate as a colourless solid; MS: 520 (M+H)⁺.

(ee) Saponification of tert-butyl (3RS,4RS)-4-(4-ethoxycarbonylmethoxy-phenyl)-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate [Example 86 (dd)] with 1N sodium hydroxide in methanol yielded tert-butyl (3RS,4RS)-4-(4-carboxymethoxy-phenyl)-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate, condensation of which with benzylamine in the presence of HBTU analogously to Example 36 (b) gave tert-butyl (3RS,4RS)-4-[4-(benzylcarbamoyl-methoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a yellowish solid; MS: 598 (M+NH₄)⁺.

(ff) In an analogous manner to that described in Example 24 (m), by reacting tert-butyl (3RS,4RS)-4-(4-hydroxy-phenyl)-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate with 2-pyridyl isocyanate there was obtained tert-butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-[4-(pyridin-2-ylcarbamoyloxy)-phenyl]-piperidine-1-carboxylate as a white solid; MS: 554 (M+H)⁺.

(gg) In an analogous manner to that described in Example 68 (b), by Swern oxidation of a mixture of tert-butyl (3RS,4RS)- and (3SR,4SR)-4-[4-[(RS)-2-hydroxy-3-phenoxy-propoxy]-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate there was obtained tert-butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-[4-(2-oxo-3-phenoxypropoxy)-phenyl]-piperidine-1-carboxylate as a white solid; MS: 582 (M+H)⁺.

(hh) (α) A solution of 5 mg (0.04 mmol) of potassium bromide and 20 mg (0.24 mmol) of sodium hydrogen carbonate in 10 ml of water was added at room temperature and while stirring to a solution of 0.270 g (0.58 mmol) of tert-butyl (3RS,4RS)-4-[4-(2-hydroxy-ethyl)-phenyl]-3-naphthalen-2-ylmethoxy-piperidine-1-carboxylate [Example 29(h)] in 10 ml of methylene chloride under argon. The reaction mixture was cooled to 0°C and treated with 2 mg (0.01 mmol) of 2,2,6,6-tetramethyl-1-

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piperidinyloxy (TEMPO). Then, 1 ml (0.658 mmol) of Javelle water was sprayed into the reaction mixture while stirring continuously. After the addition the reaction mixture was stirred at 0°C for about 30 minutes. For the working-up, 20 ml of a 1:1 mixture of methylene chloride and water were added, the reaction mixture was washed with 10 ml of saturated sodium chloride solution and the aqueous phase was back-extracted with 10 ml of methylene chloride. The combined organic phases were dried over sodium sulphate and evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel with a 2:1 mixture of hexane and ethyl acetate as the eluent. There were obtained 200 mg (75% of theory) of tert-butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-[4-(2-oxo-ethyl)-phenyl]-piperidine-1-carboxylate as a foam; MS: 460 (M+H)⁺.

(β) In an analogous manner to that described in Example 40 (a), by a Grignard reaction of tert-butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-[4-(2-oxo-ethyl)-phenyl]-piperidine-1-carboxylate with phenylmagnesium chloride there was obtained a mixture of tert-butyl (3RS,4RS)-4-[4-[(RS)-2- and [(SR)-2-hydroxy-2-phenyl-ethyl]-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a colourless oil.

(ii) In an analogous manner to that described in Example 9 (a) - (c), by alkylating tert-butyl (3RS,4RS)-4-(4-fluoro-phenyl)-3-hydroxy-piperidine-1-carboxylate [Example 3 (b)] with 2-bromomethylbenzonitrile there was obtained tert-butyl (3RS,4RS)-3-(2-cyano-benzyloxy)-4-(4-fluoro-phenyl)-piperidine-1-carboxylate, reduction of which using borane-dimethyl sulphide complex gave tert-butyl (3RS,4RS)-3-(2-aminomethyl-benzyloxy)-4-(4-fluoro-phenyl)-piperidine-1-carboxylate. Subsequent acylation with pyridine-2-carboxylic acid in the presence of EDC yielded tert-butyl (3RS,4RS)-4-(4-fluoro-phenyl)-3-(2-[(pyridine-2-carbonyl)-amino]-methyl)-benzyloxy)-piperidine-1-carboxylate as a white solid.

(jj) In an analogous manner to that described in Example 1 (g), by alkylating tert-butyl (3RS,4RS)-4-(4-fluoro-phenyl)-3-hydroxy-

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piperidine-1-carboxylate [Example 3 (b)] with (3-bromomethyl-phenyl)-phenyl-methanone [J.Med.Chem. 1984, 27 (12), 1682-1690] there was obtained tert-butyl (3RS,4RS)-3-(3-benzoyl-benzyloxy)-4-(4-fluoro-phenyl)-piperidine-1-carboxylate as a
5 yellowish liquid; MS: 490 (M+H)+.

(kk) (α) A solution of 470 mg (1.0 mmol) of tert-butyl (3RS,4RS)-4-[4-(2-cyano-ethyl)-phenyl]-3-naphthalen-2-ylmethoxy-piperidine-1-carboxylate [Example 35 (b)] and 348 mg
10 (5.0 mmol) of hydroxylamine hydrochloride in 6 ml of a 1M sodium methylate solution in methanol was stirred at 65°C for 5 hours. For working-up, the mixture was partitioned between 40 ml of ethyl acetate and 40 ml of water and thereafter the organic phase was separated. The aqueous phase was extracted
15 twice with 40 ml of ethyl acetate each time. The combined organic phases were dried over magnesium sulphate and finally the solvent was distilled off under reduced pressure. The crude product (550 mg) was purified by chromatography on silica gel with a 20:1:0.1 mixture of methylene chloride, methanol and 28%
20 ammonia solution. There were obtained 501 mg (99% of theory) of tert-butyl (3RS,4RS)-4-{4-[2-(N-hydroxycarbamimidoyl)-ethyl]-phenyl}-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a yellow oil, which was used directly in the next step.

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(b) In an analogous manner to that described in Example 38, by condensing tert-butyl (3RS,4RS)-4-{4-[2-(N-hydroxycarbamimidoyl)-ethyl]-phenyl}-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate with benzoic acid in the presence of
30 EDC and subsequent cyclization there was obtained tert-butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-[4-[2-(5-phenyl-[1,2,4]oxadiazol-3-yl)-ethyl]-phenyl]-piperidine-1-carboxylate; MS: 590 (M+H)+.

35 (ll) By alkaline saponification of tert-butyl (3RS,4RS)-4-[4-(2-ethoxycarbonyl-ethyl)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate [Example 24 (s)] with aqueous sodium hydroxide in tetrahydrofuran there was obtained tert-butyl

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(3RS,4RS)-4-[4-(2-carboxy-ethyl)-phenyl]-3-(naphthalen-2-ylmethoxy)piperidine-1-carboxylate, condensation of which with N-hydroxy-benzamidine in the presence of EDC in an analogous manner to that described in Example 38 gave the corresponding N-hydroxy-benzamidine ester and cyclization of the latter yielded
5 tert-butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-[4-[2-(3-phenyl-[1,2,4]oxadiazol-5-yl)-ethyl]-phenyl]-piperidine-1-carboxylate as a yellowish, amorphous solid; MS: 590 (M+H)+.

10 (mm) Saponification of tert-butyl (3RS,4RS)-4-(4-ethoxycarbonylmethoxy-phenyl)-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate [Example 86 (dd)] with 1N sodium hydroxide in methanol yielded tert-butyl (3RS,4RS)-4-(4-carboxymethoxy-phenyl)-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate, condensation of which with N-hydroxy-benzamidine in the presence of HBTU in an analogous manner to that described in Example 38 gave the corresponding N-hydroxy-benzamidine ester and cyclization of the latter gave tert-butyl
15 (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-[4-(3-phenyl-[1,2,4]oxadiazol-5-ylmethoxy)-phenyl]-piperidine-1-carboxylate as a colourless oil; MS: 592 (M+H)+.

(nn) In an analogous manner to that described in Example 38, by condensing tert-butyl (3RS,4RS)-4-(4-carboxymethoxy-phenyl)-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate [Example
25 86 (mm)] with 3-pyridinamidoxime in the presence of HBTU and subsequent cyclization there was obtained tert-butyl (3RS,4RS)-3-(naphthalen-2-ylmethoxy)-4-[4-(3-pyridin-3-yl-[1,2,4]oxadiazol-5-ylmethoxy)-phenyl]-piperidine-1-carboxylate as a
30 yellowish solid; MS: 593 (M+H)+.

(oo) In an analogous manner to that described in Example 44 (e), by alkylating tert-butyl (3RS,4RS)-4-(4-hydroxy-phenyl)-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate [Example 61
35 (c)] with 5-hydroxymethyl-3-phenyl-4,5-dihydro-isoxazole mesylate, prepared according to a generally known procedure, there was obtained tert-butyl (3RS,4RS)-3-(naphthalen-2-

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ylmethoxy)-4-[4-(3-phenyl-isoxazol-5-ylmethoxy)-phenyl]-piperidine-1-carboxylate as a colourless solid; MS: 591 (M+H)⁺.

The following BOC derivatives were obtained in an analogous manner to that described in Example 1 (g) by alkylating tert-butyl (3RS,4RS)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-hydroxy-piperidine-1-carboxylate [Example 86 (n)] as follows:

(pp) with 3-methoxybenzyl chloride to give tert-butyl (3RS,4RS)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-(3-methoxy-benzyloxy)-piperidine-1-carboxylate, which was obtained as a colourless oil; MS: 579 (M+NH₄)⁺.

(qq) with 1-chloromethyl-3-(2-trimethylsilanyl-ethoxy-methoxy)-benzene to give tert-butyl (3RS,4RS)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-[3-(2-trimethylsilanyl-ethoxy-methoxy)-benzyloxy]-piperidine-1-carboxylate, which was obtained as a colourless oil; MS: 695 (M+NH₄)⁺.

The 1-chloromethyl-3-(2-trimethylsilanyl-ethoxy-methoxy)-benzene used as the alkylating agent was prepared in analogy to Example 5 (a) - (d) by converting methyl 3-hydroxy-benzoate into methyl 3-(2-trimethylsilanyl-ethoxymethoxy)-benzoate by introduction of the SEM group. Subsequent reduction with lithium aluminium hydride gave [3-(2-trimethylsilanyl-ethoxy-methoxy)-phenyl]-methanol and chlorination of the latter gave 1-chloromethyl-3-(2-trimethylsilanyl-ethoxymethoxy)-benzene as a colourless oil; MS: 272 (M)⁺.

(rr) with 3-chloro-4-methoxy-benzyl chloride to give tert-butyl (3RS,4RS)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-(3-chloro-4-methoxy-benzyloxy)-piperidine-1-carboxylate, which was used in the following step without further purification and characterization;

(ss) with 3,4-dichloro-benzyl chloride to give tert-butyl (3RS,4RS)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-(3,4-dichloro-

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benzyloxy)-piperidine-1-carboxylate, which was used in the following step without further purification and characterization;

(tt) with 2,5-dichloro-benzyl chloride to give tert-butyl
5 (3RS,4RS)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-(2,5-dichloro-benzyloxy)-piperidine-1-carboxylate, which was used in the following step without further purification and characterization;

(uu) with benzyl chloride to give tert-butyl (3RS,4RS)-3-
10 benzyloxy-4-[4-(3-benzyloxy-propoxy)-phenyl]-piperidine-1-carboxylate, which was used in the following step without further purification and characterization;

(vv) with 2,5-dimethyl-benzyl chloride to give tert-butyl
15 (3RS,4RS)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-(2,5-dimethyl-benzyloxy)-piperidine-1-carboxylate, which was used in the following step without further purification and characterization;

(ww) with 4-ethyl-benzyl chloride to give tert-butyl (3RS,4RS)-
20 4-[4-(3-benzyloxy-propoxy)-phenyl]-3-(4-ethyl-benzyloxy)-piperidine-1-carboxylate, which was used in the following step without further purification and characterization;

(xx) with a mixture of 3- and 4-vinyl-benzyl chloride to give a
25 mixture of tert-butyl (3RS,4RS)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-(3- and 4-vinyl-benzyloxy)-piperidine-1-carboxylate, which was used in the following step without further purification and characterization;

30 (yy) with 6-chloromethyl-2,3-dihydro-benzo[1,4]dioxin to give tert-butyl (3RS,4RS)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-(2,3-dihydro-benzo[1,4]dioxin-6-ylmethoxy)-piperidine-1-carboxylate, which was obtained as a colourless resin; MS: 607 (M+NH₄)⁺;

35 (zz) with 6-chloromethyl-1,2,3,4-tetrahydro-naphthalene to give tert-butyl (3RS,4RS)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-(5,6,7,8-tetrahydro-naphthalen-2-ylmethoxy)-piperidine-1-

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carboxylate, which was obtained as a colourless resin; MS: 603 (M+NH₄)⁺;

(aaa) with 3-chloromethyl-1-(2-trimethylsilyl-ethoxy-methoxy)-naphthalene [Example 5 (c)] to give tert-butyl (3RS,4RS)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-[4-(2-trimethylsilyl-ethoxymethoxy)-naphthalen-2-ylmethoxy]-piperidine-1-carboxylate, which was obtained as a colourless resin; MS: 745 (M+NH₄)⁺.

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(bbb) In an analogous manner to that described in Example 44 (e), by alkylating tert-butyl (3RS,4RS)-3-hydroxy-4-(4-hydroxy-phenyl)-piperidine-1-carboxylate [Example 46 (b)] with 2-(4-chloro-butoxy)-tetrahydro-2H-pyran there was obtained a mixture of tert-butyl (3RS,4RS)- and (3SR,4SR)-3-hydroxy-4-[4-[4-[(RS)-tetrahydropyran-2-yloxy]-butoxy]-phenyl]-piperidine-1-carboxylate, alkylation of which with 2-bromomethyl-naphthalene analogously to Example 1 (g) gave a mixture of (3RS,4RS)- and (3SR,4SR)-3-(naphthalen-2-ylmethoxy)-4-[4-[4-[(RS)-tetrahydro-pyran-2-yloxy]-butoxy]-phenyl]-piperidine-1-carboxylate. Cleavage of the THP group with hydrogen chloride in methanol analogously to Example 53 (c) yielded tert-butyl (3RS,4RS)-4-[4-(4-hydroxy-butoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate, alkylation of which with benzyl bromide analogously to Example 1 (g) gave tert-butyl (3RS,4RS)-4-[4-(4-benzyloxy-butoxy)-phenyl]-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a colourless oil; MS: 613 (M+NH₄)⁺.

(ccc) In an analogous manner to that described in Example 22 (d), from tert-butyl (3RS,4RS,5SR)-4-(4-bromo-phenyl)-5-methoxymethyl-3-naphthalen-2-yl-methoxy-piperidine-1-carboxylate [Example 68 (I)] by a palladium-catalyzed carbonylation with carbon monoxide in methanol there was obtained tert-butyl (3SR,4RS,5RS)-4-(4-methoxycarbonyl-phenyl)-3-methoxymethyl-5-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate, reduction of which with lithium borohydride analogously to Example 22 (e) yielded tert-butyl (3SR,4RS,5RS)-4-(4-hydroxymethyl-phenyl)-3-

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methoxymethyl-5-(naphthalen-2-yl-methoxy)-piperidine-1-carboxylate. Subsequent acylation with 2-chlorobenzoyl chloride analogously to Example 22 (k) gave tert-butyl (3SR,4RS,5RS)-4-[4-(2-chloro-benzoyloxymethyl)-phenyl]-3-methoxymethyl-5-
5 (naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a colourless foam; MS: 630 (M+H)+.

(ddd) In an analogous manner to that described in Example 1 (g), by alkylating tert-butyl (3SR,4RS,5RS)-4-(4-hydroxymethyl-
10 phenyl)-3-methoxymethyl-5-(naphthalen-2-yl-methoxy)-piperidine-1-carboxylate with benzyl bromide there was obtained tert-butyl (3SR,4RS,5RS)-4-(4-benzyloxymethyl-phenyl)-3-methoxymethyl-5-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate as a colourless oil; MS: 582 (M+H)+.

15 (eee) In an analogous manner to that described in Example 12 (c) - (d), cleavage of the N-methyl group from (1RS,2RS,3RS,5SR)-3-(4-bromo-phenyl)-8-methyl-8-aza-bicyclo[3.2.1]octan-2-ol, obtained analogously to the 4-chlorophenyl derivative
20 [J.Org.Chem. 35, 802 (1970)], was effected by firstly synthesizing (1RS,2RS,3RS,5SR)-3-(4-bromo-phenyl)-2-(2,2,2-trichloroethoxycarbonyloxy)-8-aza-bicyclo[3.2.1]octane-8-carboxylate by reaction with 2,2,2-trichloroethyl chloroformate and subsequently reacting with zinc in glacial acetic acid to give
25 (1RS,2RS,3RS,5SR)-3-(4-bromo-phenyl)-8-aza-bicyclo[3.2.1]-octan-2-ol. Subsequent introduction of the BOC group analogously to Example 1 (f) gave tert-butyl (1RS,2RS,3RS,5SR)-3-(4-bromo-phenyl)-2-hydroxy-8-aza-bicyclo[3.2.1]octane-8-carboxylate, palladium-catalyzed carbonylation of which with carbon
30 monoxide in methanol analogously to Example 22 (d) yielded tert-butyl (1RS,2RS,3RS,5SR)-2-hydroxy-3-(4-methoxycarbonyl-phenyl)-8-aza-bicyclo[3.2.1]octane-8-carboxylate. Subsequent reduction with lithium borohydride analogously to Example 22 (e) gave tert-butyl (1RS,2RS,3RS,5SR)-2-hydroxymethyl-phenyl)-8-
35 aza-bicyclo[3.2.1]octane-8-carboxylate, reaction of which with trityl chloride analogously to Example 22 (h) gave tert-butyl (1RS,2RS,3RS,5SR)-2-hydroxy-3-(4-trityloxymethyl)-phenyl)-8-aza-bicyclo[3.2.1]octane-8-carboxylate. Further reaction with 2-

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bromomethyl-naphthalene analogously to Example 1 (g) gave tert-butyl (1RS,2RS,3RS,5SR)-2-(naphthalen-2-ylmethoxy)-3-(4-trityloxymethyl-phenyl)-8-aza-bicyclo[3.2.1]octane-8-carboxylate. In an analogous manner to that described in Example 86 (u) (b), by cleavage of the trityl group with a mixture of trifluoroacetic acid and trifluoroacetic anhydride there was obtained tert-butyl (1RS,2RS,3RS,5SR)-3-(4-hydroxymethyl-phenyl)-2-(naphthalen-2-ylmethoxy)-8-aza-bicyclo[3.2.1]octane-8-carboxylate, alkylation of which with benzyl 3-bromopropyl ether analogously to Example 44 (e) gave tert-butyl (1RS,2RS,3RS,5SR)-3-[4-(2-benzyloxy-propoxymethyl)-phenyl]-2-(naphthalen-2-ylmethoxy)-8-aza-bicyclo[3.2.1]octane-8-carboxylate as a colourless oil.

Example 87

The following compounds were obtained in an analogous manner to that described in Example 73 (d) by cleavage of the BOC group using anhydrous zinc bromide:

- 1) - From tert-butyl (3RS,4RS)-3-(naphthalen-2-carbonyloxy)-4-[4-(2-phenoxy-ethoxy)-phenyl]-piperidine-1-carboxylate, (3RS,4RS)-4-[4-(2-phenoxy-ethoxy)-phenyl]-piperidin-3-yl naphthalene-2-carboxylate as a colourless solid; MS: 468 (M+H)⁺;
- 2) - from a mixture of tert-butyl (3RS,4RS)-4-(4-fluoro-phenyl)-3-[(RS)- and (SR)-2-hydroxy-1-naphthalen-2-yl-ethoxy]-piperidine-1-carboxylate, a mixture of (RS)- and (SR)-2-[(3RS,4RS)-4-(4-fluoro-phenyl)-piperidine-3-yloxy]-2-naphthalen-2-yl-ethanol as a colourless, amorphous solid; MS: 366 (M+H)⁺.

The BOC derivatives used as the starting materials were prepared as follows:

- (a) 250 mg of 4-dimethylamino-pyridine and 2.5 ml of triethylamine were added to a solution of 5.50 g (13.3 mmol) of tert-butyl (3RS,4RS)-3-hydroxy-4-[4-(2-phenoxy-ethoxy)-

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phenyl]-piperidine-1-carboxylate (Example 47.6) in 50 ml of methylene chloride and 2.77 g (14.5 mmol) of solid 2-naphthoyl chloride were subsequently added while cooling with ice. Thereupon, the reaction mixture was stirred at room temperature for 20 hours, partitioned between water and methylene chloride, the combined methylene chloride phases were dried over magnesium sulphate and concentrated, and the thus-obtained residue was chromatographed on silica gel with methylene chloride/ether (95:5). There were thus obtained 7.3 g (97% of theory) of tert-butyl (3RS,4RS)-3-(naphthalen-2-carbonyloxy)-4-[4-(2-phenoxy-ethoxy)-phenyl]-piperidine-1-carboxylate in the form of an amorphous, colourless solid; MS: 568 (M+H)⁺.

(b) Under argon and with the exclusion of moisture, 255 mg (0.57 mmol) of tert-butyl (3RS,4RS)-4-(4-fluoro-phenyl)-3-(1-naphthalen-2-yl-vinyloxy)-piperidine-1-carboxylate [Example 73 (b)] were dissolved in 3 ml of tetrahydrofuran, treated at 0°C with 50 mg of triethylamine followed by 0.11 ml (about 1.1 mmol) of borane-dimethyl sulphide complex and stirred at room temperature for 30 minutes. Thereupon, again while cooling with ice, 1.5 ml of 50% KOH solution in water followed by 1.5 ml of 30% hydrogen peroxide solution in water were added and the reaction mixture was heated under reflux for 1.5 hours. Now, the reaction solution was partitioned between water and methylene chloride, the combined methylene chloride phases were dried over magnesium sulphate, concentrated and the thus-obtained residue was chromatographed on silica gel with hexane/ethyl acetate (1:1). There were thus obtained 30 mg (11% of theory) of a mixture of tert-butyl (3RS,4RS)-4-(4-fluoro-phenyl)-3-[(RS)- and (SR)-2-hydroxy-1-naphthalen-2-yl-ethoxy]-piperidine-1-carboxylate in the form of an amorphous, colourless solid; MS: 466 (M+H)⁺.

Example 88

(a) 25.23 g (91 mmol) of tert-butyl 4-(4-fluoro-phenyl)-1,2,3,6-tetrahydro-pyridine-1-carboxylate [prepared from 4-(4-fluorophenyl)-1,2,3,6-tetrahydro-pyridine and di-tert-butyl

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dicarbonate in analogy to Example 1 (f)] were suspended in 200 ml of 1,2-dimethoxyethane, 5.1 g (135 mmol) of sodium borohydride were added thereto at 20°C and subsequently a solution of 22.85 ml (182 mmol) of boron trifluoride ethyl etherate in 35 ml of 1,2-dimethoxyethane was added dropwise during 45 minutes while cooling occasionally at 20°C. After stirring at room temperature for 2 1/2 hours a solution of 82 g (1.26 mmol) of potassium hydroxide (86%) in 430 ml of distilled water was added dropwise at room temperature during 1 hour while stirring intensively. Thereupon, 69.3 ml (0.68 mmol) of hydrogen peroxide (30%) were added dropwise at room temperature within 30 minutes and then the mixture was stirred at reflux for 3 hours. After cooling to room temperature the mixture was poured on to ice-water, the product was extracted 3 times with 200 ml of ethyl acetate each time, the organic phases were washed twice with 300 ml of distilled water each time, then dried over magnesium sulphate, filtered and concentrated in a water-jet vacuum. After drying in a high vacuum at room temperature for 90 minutes there were thus obtained 24.4 g (91% of theory) of tert-butyl (3RS,4RS)-4-(4-fluoro-phenyl)-3-hydroxy-piperidine-1-carboxylate in the form of colourless crystals; MS: 296 (M+H)+.

(b) 39.2 g (0.2 mol) of 3-methylbenzophenone and 38.4 g (0.24 mol) of bromine were stirred at reflux in 1 l of carbon tetrachloride for 8 hours. After distillation of the solvent in a water-jet vacuum the crude product obtained was chromatographed on 500 g of silica gel with hexane and methylene chloride. The thus-purified product was recrystallized from n-hexane. There were thus obtained 21.76 g (40% of theory) of (3-bromomethyl-phenyl)-phenyl-methanone in the form of colourless crystals; MS: 274, 276 (M)+.

(c) 0.29 g (1 mmol) of tert-butyl (3RS,4RS)-4-(4-fluoro-phenyl)-3-hydroxy-piperidine-1-carboxylate and 0.30 g (1.1 mmol) of (3-bromomethyl-phenyl)-phenyl-methanone were dissolved in 10 ml of dimethylformamide under argon at room temperature, then treated with 0.056 g (1.3 mmol) of sodium

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hydride dispersion (55% in mineral oil) with the addition of 0.25 g (1.5 mmol) of potassium iodide and stirred at room temperature for 18 hours. The reaction mixture was poured on to ice-water, the product was extracted 3 times with methylene chloride, the organic phases were washed twice with distilled water, then dried over magnesium sulphate, filtered and concentrated in a water-jet vacuum. The thus-obtained crude product was chromatographed on silica gel with methylene chloride and methanol. There was thus obtained 0.42 g (86% of theory) of tert-butyl (3RS,4RS)-3-(3-benzoyl-benzyloxy)-4-(4-fluoro-phenyl)-piperidine-1-carboxylate as a colourless oil; MS: 490 (M+H)⁺.

(d) In an analogous manner to that described in Example 22 (l), from tert-butyl (3RS,4RS)-3-(3-benzoyl-benzyloxy)-4-(4-fluoro-phenyl)-piperidine-1-carboxylate by cleavage of the BOC group with hydrogen chloride in methanol there was obtained [3-[(3RS,4RS)-4-(4-fluoro-phenyl)-piperidin-3-yloxymethyl]-phenyl]-phenyl-methanone hydrochloride (1:1) in the form of colourless crystals; MS: 390 (M+H)⁺.

Example 89

The following compounds were obtained in an analogous manner to that described in Example 73 (d) by cleavage of the BOC group using anhydrous zinc bromide:

1) - From tert-butyl (E)-(3RS,4RS)-4-(4-fluoro-phenyl)-3-(3-phenyl-allyloxy)-piperidine-1-carboxylate, (E)-(3RS,4RS)-4-(4-fluoro-phenyl)-3-(3-phenyl-allyloxy)-piperidine as a pale yellow oil; MS: 312 (M+H)⁺;

2) - from tert-butyl (3R,4s,5S)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3,5-bis-(4,5-dimethoxy-pyrimidin-2-yloxymethyl)-piperidine-1-carboxylate, 2-[(3R,4s,5S)-4-[4-(3-benzyloxy-propoxy)-phenyl]-5-(4,5-dimethoxy-pyrimidin-2-yloxymethyl)-piperidine-3-ylmethoxy]-4,5-dimethoxy-pyrimidine as a pale yellow resin; MS: 662 (M+H)⁺;

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- 3) - from tert-butyl (3R,4s,5S)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3,5-bis-(4-methoxy-phenoxy-methyl)-piperidine-1-carboxylate, (3R,4S,5S)-4-[4-(3-benzyloxy-propoxy)-phenyl]-
 5 3,5-bis-(4-methoxy-phenoxy-methyl)-piperidine as a pale yellow oil; MS: 598 (M+H)⁺;
- 4) - from tert-butyl (3R,4s,5S)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3,5-bis-p-tolylsulphanylmethyl-piperidine-1-carboxylate, (3R,4s,5S)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3,5-bis-p-tolylsulphanylmethyl-piperidine as a pale yellow oil; MS: 598 (M+H)⁺.
- 5) - from (3RS,4RS)-4-[4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl]-3-[7-[2-(4-methyl-piperazin-1-yl)-ethoxy]-naphthalen-2-ylmethoxy]-piperidin-1-carboxylic acid tert-butylester, 1-[2-[7-[(3RS,4RS)-4-[4-[3-(2-methoxy-benzyloxy)-propoxy]-piperidin-3-yloxymethyl]-naphthalin-2-yloxy]-ethyl]-4-methyl-piperazin as a amorphous, colourless solid; MS: 654 (M+H)⁺.
- 20 The BOC derivatives used as the starting materials were prepared as follows:
- (a) 1.48 g (5 mmol) of tert-butyl (3RS,4RS)-4-(4-fluorophenyl)-3-hydroxy-piperidine-1-carboxylate [Example 88 (a)] and 1.08 g (5.5 mmol) of 3-bromo-1-phenyl-propene were dissolved in 10 ml of dimethylformamide under argon at room temperature, then treated with 0.284 g (6.5 mmol) of sodium hydride dispersion (55% in mineral oil) with the addition of 1.25 g
 30 (7.5 mmol) of potassium iodide and stirred at room temperature for 18 hours. The reaction mixture was poured on to ice-water, the product was extracted 3 times with methylene chloride, the organic phases were washed twice with distilled water, dried over magnesium sulphate, filtered and concentrated in a water-jet vacuum. The thus-obtained crude product was chromatographed on silica gel with methylene chloride and methanol. There were thus obtained 1.01 g (49% of theory) of tert-butyl (E)-

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(3RS,4RS)-4-(4-fluoro-phenyl)-3-(3-phenyl-allyloxy)-piperidine-1-carboxylate as a colourless oil; MS: 412 (M+H)+.

(b) 0.49 g (1 mmol) of tert-butyl (3R,4s,5S)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3,5-bis-hydroxymethyl-piperidine-1-carboxylate [Example 101 (f)] and 0.45 g (2 mmol) of 4,5-dimethoxy-2-methylsulphonyl-pyrimidine [prepared from 4,5-dimethoxy-2-methylsulphanyl-pyrimidine by oxidation with m-chloroperbenzoic acid in an analogous manner to that described in Example 129 (c)] were placed in 5 ml of dimethylformamide under argon at 5°C, treated while stirring with 0.10 g (2.2 mmol) of sodium hydride dispersion (55% in mineral oil) and stirred at room temperature for 2 hours. The reaction mixture was thereupon poured on to ice-water, the product was extracted 3 times with methylene chloride, the organic phases were washed twice with distilled water, dried over magnesium sulphate, filtered and concentrated in a water-jet vacuum. The thus-obtained crude product was chromatographed on silica gel with methylene chloride and methanol. There was thus obtained 0.47 g (61% of theory) of tert-butyl (3R,4s,5S)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3,5-bis-(4,5-dimethoxy-pyrimidin-2-yloxymethyl)-piperidine-1-carboxylate as a colourless oil; MS: 762 (M+H)+.

(c) (α) 2.91 g (6 mmol) of tert-butyl (3R,4s,5S)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3,5-bis-hydroxymethyl-piperidine-1-carboxylate [Example 101 (f)] and 1.93 ml (24 mmol) of pyridine were placed in 30 ml of acetonitrile under argon at 5°C, 8.00 g (18 mmol) of triphenylphosphine dibromide were introduced portionwise while stirring and the mixture was thereafter stirred at room temperature. After 90 minutes the reaction mixture was poured on to ice-water, the product was then extracted 3 times with ethyl acetate, the organic phases were washed twice with distilled water, dried over magnesium sulphate, filtered and concentrated in a water-jet vacuum. The thus-obtained crude product was chromatographed on silica gel with n-hexane and ethyl acetate. There were thus-obtained 2.81 g (77% of theory) of tert-butyl (3R,4s,5S)-4-[4-(3-

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benzyloxy-propoxy)-phenyl]-3,5-bis-bromomethyl-piperidine-1-carboxylate as a colourless oil; MS: 610 (M+H)⁺.

(c) (β) 0.30 g (0.5 mmol) of tert-butyl (3R,4s,5S)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3,5-bis-bromomethyl-piperidine-1-carboxylate and 0.19 g (1.5 mmol) of hydroquinone monomethyl ether were stirred at reflux under argon for 18 hours with the addition of 0.69 g (5 mmol) of anhydrous potassium carbonate in 15 ml of acetonitrile. After cooling to room temperature the reaction mixture was poured on to ice-water, the product was extracted 3 times with methylene chloride, the organic phases were washed twice with distilled water, then dried over magnesium sulphate, filtered and concentrated in a water-jet vacuum. The thus-obtained crude product was chromatographed on silica gel with methylene chloride and methanol. There was thus obtained 0.15 g (43% of theory) of tert-butyl (3R,4s,5S)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3,5-bis-(4-methoxy-phenoxy-methyl)-piperidine-1-carboxylate as pale yellow crystals; MS: 698 (M+H)⁺.

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(d) In an analogous manner to that described in Example 89 (c) (β), from tert-butyl (3R,4s,5S)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3,5-bis-bromomethyl-piperidine-1-carboxylate and 4-methyl-thiophenol there was obtained tert-butyl (3R,4s,5S)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3,5-bis-p-tolylsulphanyl-methyl-piperidine-1-carboxylate in the form of a colourless oil; MS: 698 (M+H)⁺.

(e) in an analogous manner as described in Example 95 (a) there was obtained from (3RS,4RS)-3-hydroxy-4-[4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl]-piperidin-1-carboxylic acid tert-butylester [Example 120 (g) (α)] and 2-chloromethyl-7-(2-trimethylsilyl-ethoxymethoxy)-naphthalene [Example 6 (u)] (3RS,4RS)-4-[4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl]-3-[7-(2-trimethylsilyl-ethoxymethoxy)-naphthalen-2-ylmethoxy]-piperidin-1-carboxylic acid tert-butylester as a pale yellow oil; MS: 758 (M+H)⁺. Then, (3RS,4RS)-4-[4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl]-3-[7-(2-trimethylsilyl-

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ethoxymethoxy)-naphthalen-2-ylmethoxy]-piperidin-1-carboxylic acid tert-butylester was reacted in analogy to Example 95 (b) by cleaving of the SEM protecting group to afford (3RS,4RS)-4-[4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl]-3-(7-hydroxy-naphthalin-2-ylmethoxy)-piperidin-1-carboxylic acid tert-butylester [yellow oil; MS: 628 (M+H)⁺] which, on alkylation with 1-(2-chloro-ethyl)-4-methyl-piperazine hydrochloride (1:2) [Chim. Ther. 4, 283 (1969)] in analogy to Example 90 (n) gave (3RS,4RS)-4-[4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl]-3-[7-[2-(4-methyl-piperazin-1-yl)-ethoxy]-naphthalen-2-ylmethoxy]-piperidin-1-carboxylic acid tert-butylester as a light brown oil; MS: 754 (M+H)⁺.

Example 90

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The following compounds were obtained in an analogous manner to that described in Example 22 (l) by cleavage of the BOC group using hydrogen chloride in methanol:

- 20 1) - From a mixture of tert-butyl (3RS,4SR)-4-(4-fluoro-phenyl)-3-[(RS)- and -[(SR)-1-[4-(2-morpholin-4-yl-ethoxy)-benzoyloxy]-2-naphthalen-2-yl-ethyl]-piperidine-1-carboxylate, a mixture of (RS)- and (SR)-1-[(3RS,4SR)-4-(4-fluoro-phenyl)-piperidin-3-yl]-2-naphthalen-2-yl-ethyl 4-(2-morpholin-4-ylethoxy)-benzoate as a colourless oil; MS: 583 (M+H)⁺;
- 2) - from tert-butyl (3RS,4SR)-4-(4-fluoro-phenyl)-3-(naphthalen-2-yl-acetyl)-piperidine-1-carboxylate, 1-[(3RS,4SR)-4-(4-fluoro-phenyl)-piperidin-3-yl]-2-naphthalen-2-yl-ethanone hydrochloride (1:1) in the form of colourless crystals; MS: 348 (M+H)⁺;
- 3) - from a mixture of tert-butyl (E)- and (Z)-(3RS,4SR)-3-(1-carboxymethoxyimino-2-naphthalen-2-yl-ethyl)-4-(4-fluoro-phenyl)-piperidine-1-carboxylate, a 3:1 mixture of methyl (E)- and (Z)-[1-[(3RS,4SR)-4-(4-fluoro-phenyl)-piperidine-3-yl]-2-naphthalen-2-yl-ethylidene-aminoxy]-acetate as a yellow oil; MS: 435 (M+H)⁺;

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- 4) - from tert-butyl (3RS,4RS)-3-[2-(3H-benzoimidazol-5-yloxy)-ethoxy]-4-[4-(3-benzyloxy-propoxy)-phenyl]-piperidine-1-carboxylate, 6-[2-[(3RS,4RS)-4-[4-(3-benzyloxy-propoxy)-phenyl]-piperidin-3-yloxy]-ethoxy]-1H-benzoimidazole as a yellow oil; MS: 502 (M+H)⁺;
- 5) - from tert-butyl 3RS,4RS)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-[2-(2-oxo-2,3-dihydro-1H-benzoimidazol-5-yloxy)-ethoxy]-piperidine-1-carboxylate, 5-[2-[(3RS,4RS)-4-[4-(3-benzyloxy-propoxy)-phenyl]-piperidin-3-yloxy]-ethoxy]-1,3-dihydro-benzoimidazol-2-one in the form of yellow crystals; MS: 518 (M+H)⁺;
- 6) - from tert-butyl (3RS,4RS)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-[2-(3,4-dinitro-phenoxy)-ethoxy]-piperidine-1-carboxylate [Example 94 (d)], (3RS,4RS)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-[2-(3,4-dinitro-phenoxy)-ethoxy]-piperidine as an amorphous, yellow foam; MS: 552 (M+H)⁺;
- 7) - from tert-butyl (3RS,4RS)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-[7-(2-morpholin-4-yl-ethoxy)-naphthalen-2-ylmethoxy]-piperidine-1-carboxylate, 4-[2-[7-[(3RS,4RS)-4-[4-(3-benzyloxy-propoxy)-phenyl]-piperidin-3-yloxymethyl]-naphthalen-2-yloxy]-ethyl]-morpholine hydrochloride (1:2) in the form of beige crystals; MS: 611 (M+H)⁺;
- 8) - from a mixture of tert-butyl (3RS,4RS)- and (3SR,4SR)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-[7-[(RS)-2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy]-naphthalen-2-ylmethoxy]-piperidine-1-carboxylate, a mixture of (RS)- and (SR)-3-[7-[(3RS,4RS)-4-[4-(3-benzyloxy-propoxy)-phenyl]-piperidin-3-yloxymethyl]-naphthalen-2-yloxy]-propane-1,2-diol as a colourless oil; MS: 572 (M+H)⁺;
- 9) - from tert-butyl (3RS,4RS)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-[6-(2-trimethylsilanyl-ethoxymethoxy)-naphthalen-2-ylmethoxy]-piperidine-1-carboxylate [Example 97 (a)], 6-

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[(3RS,4RS)-4-[4-(3-benzyloxy-propoxy)-phenyl]-piperidin-3-yloxymethyl]-naphthalen-2-ol hydrochloride (1:1) in the form of colourless crystals; MS: 498 (M+H)⁺;

5 10) - from a mixture of tert-butyl [3RS,4RS]- and [3SR,4SR]-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-[6-[(RS)-2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-naphthalen-2-ylmethoxy]-piperidine-1-carboxylate with simultaneous cleavage of the dioxolane protecting group, a mixture of (RS)- and (SR)-3-[6-[(3RS,4RS)-4-
10 [4-(3-benzyloxy-propoxy)-phenyl]-piperidin-3-yloxymethyl]-naphthalen-2-yloxy]-propane-1,2-diol hydrochloride (1:1) in the form of pale brown crystals; MS: 572 (M+H)⁺;

11) - from a mixture of tert-butyl (3RS,4RS)- and (3SR,4SR)-4-
15 [4-(3-benzyloxy-propoxy)-phenyl]-3-[6-[2-[(RS)-2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy]-ethoxy]-naphthalen-2-ylmethoxy]-piperidine-1-carboxylate with simultaneous cleavage of the dioxolane protecting group, a mixture of [RS]- and [SR]-3-[2-[6-[(3RS,4RS)-4-[4-(3-benzyloxy-propoxy)-phenyl]-piperidin-3-
20 yloxymethyl]-naphthalen-2-yloxy]-ethoxy]-propane-1,2-diol hydrochloride (1:1) in the form of colourless crystals; MS: 616 (M+H)⁺;

12) - from a mixture of tert-butyl (3RS,4SR)-4-[4-(3-
25 benzyloxy-propoxy)-phenyl]-3-[(RS)- and -[(SR)-1-hydroxy-2-naphthalen-2-yl-ethyl]-piperidine-1-carboxylate [Example 100 (b)], a mixture of (RS)- and (SR)-1-[(3RS,4SR)-4-[4-(3-benzyl-oxy-propoxy)-phenyl]-piperidin-3-yl]-2-naphthalen-2-yl-ethanol hydrochloride (1:1) in the form of beige crystals; MS: 496 (M+H)⁺;

30 13) from tert-butyl (3RS,4RS)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-[7-[2-(4-methyl-piperazin-1-yl)-ethoxy]-naphthalen-2-ylmethoxy]-piperidine-1-carboxylate, 1-[2-[7-[(3RS,4RS)-4-[4-(3-benzyloxy-propoxy)-phenyl]-piperidin-3-yloxymethyl]-
35 naphthalen-2-yloxy]-ethyl]-4-methyl-piperazine hydrochloride (1:3) in the form of colourless crystals; MS: 624 (M+H)⁺;

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14) from a mixture of tert-butyl (E)- and (Z)-(3RS,4SR)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-(1-methoxycarbonyl-methoxy-imino-2-naphthalen-2-yl-ethyl)-piperidine-1-carboxylate, a mixture of methyl (E)- and (Z)-(1-[(3RS,4SR)-4-[4-(3-benzyloxy-propoxy)-phenyl]-piperidin-3-yl]-2-naphthalen-2-yl-ethylidene-aminoxy)-acetate as a pale yellow oil; MS: 581 (M+H)⁺;

15) from tert-butyl (3R,4s,5S)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3,5-bis-(2-morpholin-4-yl-ethoxymethyl)-piperidine-1-carboxylate [Example 101 (g)], (3R,4s,5S)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3,5-bis-(2-morpholin-4-yl-ethoxymethyl)-piperidine as a yellow oil; MS: 612 (M+H)⁺.

The BOC derivatives used as the starting materials were prepared as follows:

(a) 0.45 g (1 mmol) of a mixture of tert-butyl (3RS,4SR)-4-(4-fluoro-phenyl)-3-[(RS)- and -[(SR)-1-hydroxy-2-naphthalen-2-yl-ethyl]-piperidine-1-carboxylate [Example 74 (h)] and 0.28 g (1.1 mmol) of 4-(2-morpholin-4-yl-ethoxy)-benzoic acid (prepared by alkylating methyl 4-hydroxybenzoate with 4-(2-chloroethyl)-morpholine in dimethylformamide in the presence of potassium carbonate at 100°C and subsequently saponifying with base were dissolved in 15 ml of methylene chloride under argon, 0.23 g (1.2 mmol) of N-ethyl-N'-(3-dimethylaminopropyl)-carbodiimide hydrochloride and 0.04 g (0.33 mmol) of 4-dimethylamino-pyridine were then added and the mixture was stirred at room temperature for 70 hours. After distillation of the solvent in a water-jet vacuum the crude product was chromatographed on silica gel with n-hexane, methylene chloride and methanol. There was thus obtained 0.54 g (79% of theory) of a mixture of tert-butyl (3RS,4SR)-4-(4-fluoro-phenyl)-3-[(RS)- and -[(SR)-1-[4-(2-morpholin-4-yl-ethoxy)-benzoyloxy]-2-naphthalen-2-yl-ethyl]-piperidine-1-carboxylate as a pale yellow oil; MS: 683 (M+H)⁺.

(b) In an analogous manner to that described in Example 74 (f), from a mixture of tert-butyl (3RS,4SR)-4-(4-fluoro-phenyl)-3-

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[(RS)- and -[(SR)-1-hydroxy-2-naphthalen-2-yl-ethyl]-
piperidine-1-carboxylate [Example 74 (h)] by oxidation with
dimethyl sulphoxide/oxalyl chloride in methylene chloride there
was obtained tert-butyl (3RS,4SR)-4-(4-fluoro-phenyl)-3-
5 (naphthalen-2-yl-acetyl)-piperidine-1-carboxylate as a yellow
oil; MS: 447 (M)⁺.

(c) 0.22 g (0.5 mmol) of tert-butyl (3RS,4SR)-4-(4-fluoro-
phenyl)-3-(naphthalen-2-yl-acetyl)-piperidine-1-carboxylate and
10 0.11 g (1 mmol) of aminooxy-acetic acid hydrochloride (1:0.5)
[Organic Synthesis Collect. Vol. III, 172 (1955)] were stirred at
60°C in 2 ml of pyridine for 18 hours under argon. The reaction
mixture was thereupon poured on to ice-water, the product was
extracted 3 times with ethyl acetate, the organic phases were
15 washed twice with distilled water, dried over magnesium
sulphate, filtered and concentrated in a water-jet vacuum. The
thus-obtained crude product was chromatographed on silica gel
with methylene chloride and methanol. There was thus obtained
0.24 g (92% of theory) of a mixture of tert-butyl (E)- and (Z)-
20 (3RS,4SR)-3-(1-carboxymethoxyimino-2-naphthalen-2-yl-ethyl)-
4-(4-fluoro-phenyl)-piperidine-1-carboxylate as a pale yellow
oil; MS: 521 (M+H)⁺.

(d) 0.55 g (0.93 mmol) of tert-butyl (3RS,4RS)-4-[4-(3-
25 benzyloxy-propoxy)-phenyl]-3-[2-(3,4-diamino-phenoxy)-ethoxy]-
piperidine-1-carboxylate [Example 94 (e)] was stirred at 50°C in
5 ml of triethyl orthoformate for 1 hour under argon. The
reaction mixture was poured on to ice-water, the product was
extracted 3 times with methylene chloride, the organic phases
30 were washed twice with distilled water, then dried over
potassium carbonate, filtered and concentrated in a water-jet
vacuum. The thus-obtained crude product was chromatographed on
silica gel with methylene chloride and methanol. There was thus
obtained 0.38 g (68% of theory) of tert-butyl 3-[2-(3H-
35 benzoimidazol-5-yloxy)-ethoxy]-4-[(3RS,4RS)-4-(3-benzyloxy-
propoxy)-phenyl]-piperidine-1-carboxylate as a pale brown oil;
MS: 602 (M+H)⁺.

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(e) 0.60 g (1.0 mmol) of tert-butyl (3RS,4RS)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-[2-(3,4-diamino-phenoxy)-ethoxy]-piperidine-1-carboxylate [Example 94 (e)] was dissolved in 5 ml of dimethylformamide under argon at room temperature and then
5 0.18 g (1.1 mmol) of 1,1'-carbonyldiimidazole was added. After 1 hour the reaction mixture was poured on to ice to ice-water, the product was extracted 3 times with methylene chloride, the organic phases were washed twice with distilled water, then dried over magnesium sulphate, filtered and concentrated in a
10 water-jet vacuum. The thus-obtained crude product was chromatographed on silica gel with methylene chloride and methanol. There was thus obtained 0.46 g (74% of theory) of tert-butyl (3RS,4RS)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-[2-(2-oxo-2,3-dihydro-1H-benzo-imidazol-5-yloxy)-ethoxy]-
15 piperidine-1-carboxylate as a yellow oil; MS: 618 (M+H)⁺.

(g) 0.30 g (0.5 mmol) of tert-butyl (3RS,4RS)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-(7-hydroxy-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate [Example 95 (b)] and 0.13 g
20 (0.7 mmol) of 4-(2-chloroethyl)-morpholine hydrochloride were stirred at 60°C under argon for 18 hours in 15 ml of dimethylformamide with the addition of 0.69 g (5 mmol) of potassium carbonate (anhydrous). The reaction mixture was poured on to ice-water, the product was extracted 3 times with methylene
25 chloride, the organic phases were washed twice with distilled water, then dried over magnesium sulphate, filtered and concentrated in a water-jet vacuum. The thus-obtained crude product was chromatographed on silica gel with methylene chloride and methanol. There was thus obtained 0.32 g (90% of
30 theory) of tert-butyl (3RS,4RS)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-[7-(2-morpholin-4-yl-ethoxy)-naphthalen-2-ylmethoxy]-piperidine-1-carboxylate as a colourless oil; MS: 711 (M+H)⁺.

35 (h) 0.33 g (0.54 mmol) of tert-butyl (3RS,4RS)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-(7-hydroxy-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate [Example 95 (b)] and 0.20 g (0.70 mmol) of D,L- α,β -isopropylidene-glycerol γ -tosylate were

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stirred at reflux for 3 hours under argon in 15 ml of dimethyl-formamide with the addition of 0.69 g (5 mmol) of potassium carbonate (anhydrous). The reaction mixture was thereupon poured on to ice-water, the product was extracted 3 times with
 5 methylene chloride, the organic phases were washed twice with distilled water, then dried over magnesium sulphate, filtered and concentrated in a water-jet vacuum. The thus-obtained crude product was chromatographed on silica gel with methylene chloride and methanol. There was thus obtained 0.32 g (83% of
 10 theory) of a mixture of tert-butyl (3RS,4RS)- and (3SR,4SR)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-[7-[(RS)-2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy]-naphthalen-2-ylmethoxy]-piperidine-1-carboxylate as a colourless oil; MS: 712 (M+H)+.

15 (k) In an analogous manner to that described in Example 90 (h), from tert-butyl (3RS,4RS)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-(6-hydroxy-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate [Example 97 (b)] there was obtained a mixture of tert-butyl
 [3RS,4RS]- and [3SR,4SR]-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-
 20 [6-[(RS)-2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy]-naphthalen-2-ylmethoxy]-piperidine-1-carboxylate in the form of colourless crystals; MS: 712 (M+H)+.

(l) In an analogous manner to that described in Example 90 (g),
 25 from tert-butyl (3RS,4RS)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-(6-hydroxy-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate [Example 97 (b)] and (RS)-2-(2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-ethyl toluene 4-sulphonate [Example 98 (a)] there was obtained a mixture of tert-butyl (3RS,4RS)- and (3SR,4SR)-
 30 4-[4-(3-benzyloxy-propoxy)-phenyl]-3-[6-[2-[(RS)-2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy]-ethoxy]-naphthalen-2-ylmethoxy]-piperidine-1-carboxylate in the form of colourless crystals; MS: 773 (M+NH₄)⁺.

35 (n) 0.30 g (0.5 mmol) of tert-butyl (3RS,4RS)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-(7-hydroxy-naphthalen-2-ylmethoxy)-piperidine-1-carboxylate [Example 95 (b)] and 0.47 g (2 mmol) of 1-(2-chloro-ethyl)-4-methyl-piperazine hydro-

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chloride (1:2) [Chim. Ther. 4, 283 (1969)] were dissolved in 5 ml of dimethylformamide under argon at room temperature and then stirred at 100°C for 3 hours with the addition of 0.05 g (0.3 mmol) of potassium iodide and 0.22 g (5 mmol) of sodium hydride dispersion (55% in mineral oil). The reaction mixture was poured on to ice-water, the product was extracted 3 times with methylene chloride, the organic phases were washed twice with distilled water, then dried over magnesium sulphate, filtered and concentrated in a water-jet vacuum. The thus-obtained crude product was chromatographed on silica gel with methylene chloride and methanol. There was thus obtained 0.20 g (55% of theory) of tert-butyl (3RS,4RS)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-[7-[2-(4-methyl-piperazin-1-yl)-ethoxy]-naphthalen-2-ylmethoxy]-piperidine-1-carboxylate as a pale yellow oil; MS: 724 (M+H)⁺.

(o) In an analogous manner to that described in Example 102 (a), from tert-butyl (3RS,4SR)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-(naphthalen-2-yl-acetyl)-piperidine-1-carboxylate [Example 100 (c)] and methyl aminooxy-acetate hydrochloride [J. Med. Chem. 28, 1447 (1985)] there was obtained a mixture of tert-butyl (E)- und (Z)-(3RS,4SR)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-(1-methoxycarbonylmethoxyimino-2-naphthalen-2-yl-ethyl)-piperidine-1-carboxylate as a colourless oil; MS: 698 (M+NH₄)⁺.

Example 91

(a) 0.90 g (2 mmol) of a mixture of tert-butyl (3RS,4SR)-4-(4-fluoro-phenyl)-3-[(RS)- and -(SR)-1-hydroxy-2-naphthalen-2-yl-ethyl]-piperidine-1-carboxylate [Example 74 (h)] and 0.55 g (2.2 mmol) of 4-(2-morpholin-4-yl-ethoxy)-benzoic acid (prepared by alkylating methyl 4-hydroxybenzoate with 4-(2-chloroethyl)morpholine in dimethylformamide in the presence of potassium carbonate at 100°C and subsequently saponifying with base) were dissolved in 30 ml of tetrahydrofuran under argon, then 0.44 ml (2.8 mmol) of diethyl azodicarboxylate was added dropwise after the addition of 0.66 g (2.5 mmol) of triphenyl-

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phosphine and the mixture was subsequently stirred at room temperature for 18 hours. After distillation of the solvent in a water-jet vacuum the crude product was purified on silica gel with n-hexane and ethyl acetate. There was thus obtained 0.31 g
5 (23% of theory) of tert-butyl (E)-(3RS,4SR)-4-(4-fluoro-phenyl)-3-(2-naphthalen-2-yl-vinyl)-piperidine-1-carboxylate as a pale yellow resin; MS: 432 (M+H)+.

(b) In an analogous manner to that described in Example 22 (I),
10 by cleaving off the BOC group using hydrogen chloride in methanol from tert-butyl (E)-(3RS,4SR)-4-(4-fluoro-phenyl)-3-(2-naphthalen-2-yl-vinyl)-piperidine-1-carboxylate there was obtained (E)-(3RS,4SR)-4-(4-fluoro-phenyl)-3-(2-naphthalen-2-yl-vinyl)-piperidine as a pale yellow oil; MS: 331 (M)+.

15 (c) 0.060 g (0.18 mmol) of (E)-(3RS,4SR)-4-(4-fluoro-phenyl)-3-(2-naphthalen-2-yl-vinyl)-piperidine was hydrogenated under normal conditions in 3 ml of methanol with the addition of 30 mg of Pd-C (10%). After filtering off the
20 catalyst the solvent was distilled off in a water-jet vacuum. There was thus obtained 0.055 g (92% of theory) of (3RS,4SR)-4-(4-fluoro-phenyl)-3-(2-naphthalen-2-yl-ethyl)-piperidine as a pale yellow oil; MS: 334 (M+H)+.

25 Example 92

(a) 2.95 g (10 mmol) of tert-butyl (3RS,4RS)-4-(4-fluoro-phenyl)-3-hydroxy-piperidine-1-carboxylate [Example 88 (a)] and 3.82 g (11 mmol) of tert-butyl 4'-bromomethyl-biphenyl-2-
30 carboxylate [J. Med. Chem. 34, 2525 (1991)] were dissolved in 100 ml of dimethylformamide under argon at room temperature, then firstly 2.49 g (15 mmol) of potassium iodide and thereafter 0.57 g (13 mmol) of sodium hydride dispersion (55% in mineral oil) were added. After stirring at room temperature for 4 hours
35 the reaction mixture was poured on to ice-water, the product was extracted 3 times with methylene chloride, the organic phases were washed twice with distilled water, then dried over magnesium sulphate, filtered and concentrated in a water-jet

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vacuum. The thus-obtained crude product was chromatographed on silica gel with n-hexane and ethyl acetate. There were thus obtained 5.08 g (90% of theory) of tert-butyl (3RS,4RS)-3-(2'-tert-butoxycarbonyl-biphenyl-4-ylmethoxy)-4-(4-fluoro-phenyl)-piperidine-1-carboxylate as an amorphous, colourless foam.

(b) 2.25 g (4 mmol) of tert-butyl (3RS,4RS)-3-(2'-tert-butoxycarbonyl-biphenyl-4-ylmethoxy)-4-(4-fluoro-phenyl)-piperidine-1-carboxylate were stirred at reflux for 18 hours in 50 ml of ethylene glycol monomethyl ether with the addition of 8 ml (36 mmol) of sodium hydroxide solution (14%). After distillation of the solvent in a water-jet vacuum the residue was dissolved in ice-water, then adjusted to pH 3 with 2N hydrochloric acid and the product was extracted 3 times with methylene chloride, the organic phases were washed twice with distilled water, then dried over magnesium sulphate, filtered and concentrated in a water-jet vacuum. The thus-obtained product was chromatographed on silica gel with methylene chloride and methanol. There were thus obtained 1.66 g (82% of theory) of tert-butyl (3RS,4RS)-3-(2'-carboxy-biphenyl-4-ylmethoxy)-4-(4-fluoro-phenyl)-piperidine-1-carboxylate as an amorphous, colourless foam; MS: 504 (M-H)+.

(c) 0.51 g (1 mmol) of tert-butyl (3RS,4RS)-3-(2'-carboxy-biphenyl-4-ylmethoxy)-4-(4-fluoro-phenyl)-piperidine-1-carboxylate and 0.18 g (1 mmol) of 2-chloro-4,6-dimethoxy-1,3,5-triazine were dissolved in a mixture of 3.5 ml of dimethylformamide and 5 ml of acetonitrile under argon, 0.22 ml (2 mmol) of N-methylmorpholine was added dropwise thereto at 0°C and the mixture was stirred at 0°C for 2 hours. Now, a solution of 0.08 ml (1 mmol) of (RS)-3-amino-1,2-propanediol in 6 ml of acetonitrile was added dropwise and thereafter the mixture was stirred at room temperature for 18 hours. The reaction mixture was poured on to ice-water, the product was extracted 3 times with methylene chloride, the organic phases were washed twice with distilled water, then dried over magnesium sulphate, filtered and concentrated in water-jet

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vacuum. The thus-obtained crude product was chromatographed on silica gel with methylene chloride and methanol. There was thus obtained 0.29 g (50% of theory) of a mixture of tert-butyl (3RS,4RS)- and (3SR,4SR)-3-[2'[(RS)-(2,3-dihydroxy-propyl-carbamoyl)]-biphenyl-4-ylmethoxy]-4-(4-fluoro-phenyl)-piperidine-1-carboxylate as an amorphous, colourless foam; MS: 579 (M+H)+.

(d) In an analogous manner to that described in Example 22 (l), from a mixture of tert-butyl (3RS,4RS)- and (3SR,4SR)-3-[2'[(RS)-(2,3-dihydroxy-propylcarbamoyl)]-biphenyl-4-ylmethoxy]-4-(4-fluoro-phenyl)-piperidine-1-carboxylate by cleavage of the BOC protecting group with hydrogen chloride in methanol there was obtained a mixture of 4'-[(3RS,4RS)-4-(4-fluoro-phenyl)-piperidin-3-yloxymethyl]-biphenyl-2-carboxylic acid (RS)- and (SR)-(2,3-dihydroxy-propyl)-amide hydrochloride (1:1) as an amorphous, colourless foam: MS: 479 (M+H)+.

Example 93

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(a) 0.050 g (0.12 mmol) of a 3:1 mixture of methyl (E)- and (Z)-[1-[(3RS,4SR)-4-(4-fluoro-phenyl)-piperidin-3-yl]-2-naphthalen-2-yl-ethylideneaminoxy]-acetate {Example 90.03} was stirred at 50°C for 18 hours in 3 ml of methanol with the addition of 1.0 ml of 1N sodium hydroxide solution. After cooling to room temperature 1.0 ml of 1N hydrochloric acid was added dropwise and thereafter the mixture was concentrated in a water-jet vacuum. The residue was suspended in ethanol, then filtered, 0.025 ml (0.3 mmol) of hydrochloric acid (37%) was added to the filtrate and the mixture was again concentrated in a water-jet vacuum. This residue was now dried at room temperature in a high vacuum for 2 hours. There was thus obtained 0.040 g (73% of theory) of a mixture of (E)- and (Z)-(3RS,4SR)-[1-[4-(4-fluoro-phenyl)-piperidin-3-yl]-2-naphthalen-2-yl-ethylideneaminoxy]-acetic acid hydrochloride (1:1) as an amorphous, pale yellow foam; MS: 421 (M+H)+.

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Example 94

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- (a) 4.30 g (9.7 mmol) of tert-butyl (3RS,4RS)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-hydroxy-piperidine-1-carboxylate [Example 86 (n)] were placed in 215 ml of tetrahydrofuran at 0°C under argon and 1.23 g (28.1 mmol) of sodium hydride dispersion (55% in mineral oil) were added while stirring. After 30 minutes a solution of 1.86 ml (12.7 mmol) of tert-butyl bromoacetate in 10 ml of tetrahydrofuran were added dropwise and the mixture was warmed to room temperature. The reaction mixture was poured on to ice-water, the product was extracted 3 times with ethyl acetate, the organic phases were washed twice with distilled water, then dried over magnesium sulphate, filtered and concentrated in a water-jet vacuum. The thus-obtained crude product was chromatographed on silica gel with methylene chloride and methanol. There were thus obtained 4.77 g (88% of theory) of tert-butyl (3RS,4RS)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-tert-butoxycarbonylmethoxy-piperidine-1-carboxylate as a yellow oil; MS: 556 (M+H)⁺.
- (b) 0.36 g (16.5 mmol) of lithium borohydride was placed in 55 ml of tetrahydrofuran at room temperature under argon and a solution of 4.58 g (8.24 mmol) of tert-butyl (3RS,4RS)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-tert-butoxycarbonylmethoxy-piperidine-1-carboxylate in 55 ml of tetrahydrofuran was added dropwise while stirring and the mixture was subsequently heated under reflux. After 4 hours the reaction mixture was poured on to ice-water, adjusted to pH 3 with hydrochloric acid (2N) and then the product was extracted 3 times with ethyl acetate. The organic phases were thereupon washed twice with distilled water, dried over magnesium sulphate, filtered and concentrated in a water-jet vacuum. There were thus obtained 3.95 g (99% of theory) of tert-butyl (3RS,4RS)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-(2-hydroxy-ethoxy)-piperidine-1-carboxylate as a yellow oil; MS: 486 (M+H)⁺.
- (c) 5.56 g (13.2 mmol) of triphenylphosphine dibromide were dissolved in 20 ml of acetonitrile under argon, then 1.06 ml (13.2 mmol) of pyridine were added dropwise at 0°C; this

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solution was added dropwise to a solution of 3.95 g (8.1 mmol) of tert-butyl (3RS,4RS)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-(2-hydroxy-ethoxy)-piperidine-1-carboxylate in 20 ml of acetonitrile at 0°C and subsequently the mixture was stirred at room temperature for 18 hours. The reaction mixture was poured on to ice-water, the product was then extracted 3 times with ethyl acetate, the organic phases were washed twice with distilled water, then dried over magnesium sulphate, filtered and concentrated in a water-jet vacuum. The thus-obtained crude product was chromatographed on silica gel with n-hexane and ethyl acetate. There were thus obtained 3.14 g (71% of theory) of tert-butyl (3RS,4RS)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-(2-bromo-ethoxy)-piperidine-1-carboxylate as a yellow oil; MS: 548,550 (M+H)⁺.

(d) 3.14 g (5.72 mmol) of tert-butyl (3RS,4RS)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-(2-bromo-ethoxy)-piperidine-1-carboxylate and 2.53 g (13.76 mmol) of 3,4-dinitrophenol in 230 ml of acetonitrile were stirred at reflux under argon for 22 hours with the addition of 7.9 g (57.2 mmol) of potassium carbonate (anhydrous). After distillation of the solvent in a water-jet vacuum the residue was poured on to ice-water and the product was extracted 3 times with methylene chloride, the organic phases were washed twice with distilled water, then dried over magnesium sulphate, filtered and concentrated in a water-jet vacuum. The thus-obtained crude product was chromatographed on silica gel with n-hexane and ethyl acetate. There were thus obtained 2.57 g (69% of theory) of tert-butyl (3RS,4RS)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-[2-(3,4-dinitro-phenoxy)-ethoxy]-piperidine-1-carboxylate as a brown oil; MS: 652 (M+H)⁺.

(e) 1.63 g (2.5 mmol) of tert-butyl (3RS,4RS)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-[2-(3,4-dinitro-phenoxy)-ethoxy]-piperidine-1-carboxylate were hydrogenated under normal conditions for 2 hours in 80 ml of ethyl acetate with the addition of 0.50 g of platinum oxide. The catalyst was filtered off over a Dicalite pad and the solvent was distilled off in a

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CECI EST LE TOME 1 DE 2

NOTE: Pour les tomes additionels, veuillez contacter le Bureau canadien des brevets

JUMBO APPLICATIONS/PATENTS

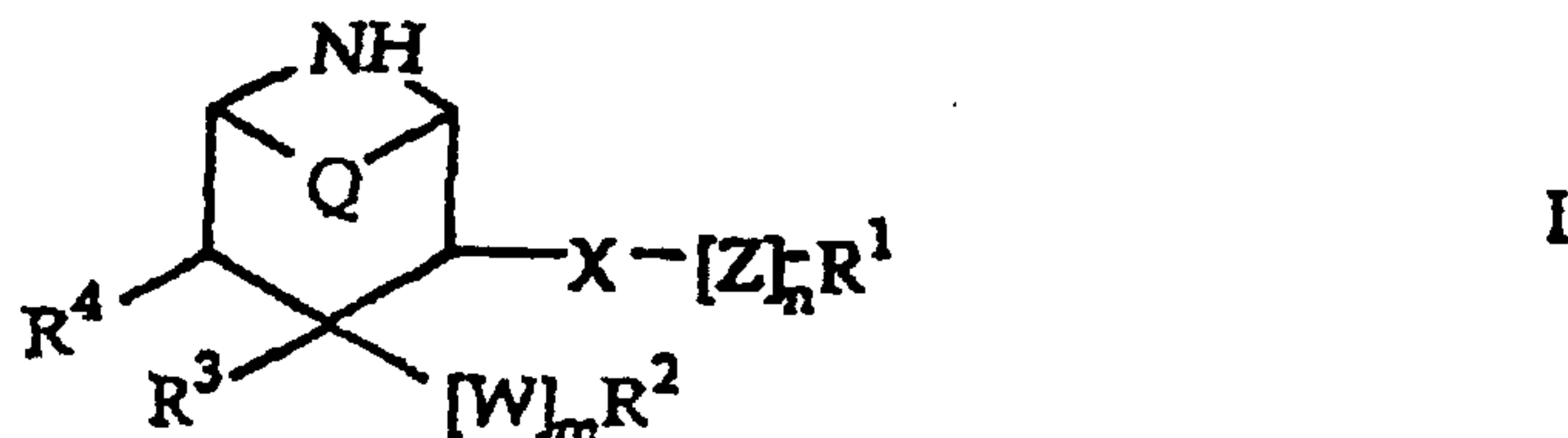
THIS SECTION OF THE APPLICATION/PATENT CONTAINS MORE
THAN ONE VOLUME

THIS IS VOLUME 1 OF 2

NOTE: For additional volumes please contact the Canadian Patent Office

WE CLAIM:

1. Piperidine derivatives having the general formula I



wherein

R¹ denotes phenyl or phenyl substituted by C₁₋₆-alkyl, C₁₋₆-alkenyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, halogen, hydroxy, hydroxy-C₁₋₆-alkoxy, C₁₋₆-alkoxy-C₁₋₆-alkoxy, C₁₋₆-alkylsulfinyl, C₁₋₆-alkylsulfonyl, cyano, trifluoromethyl, trifluoromethoxy, carboxy, cyclobutylmethoxy-C₁₋₆-alkyl, C₁₋₆-alkylenedioxy, phenyl, phenoxy, C₁₋₆-alkoxycarbonylphenyl, hydroxy-C₁₋₆-alkylphenyl, 2,3-dihydroxypropylaminocarbonylphenyl, benzyloxy, benzoyl, pyridyl-C₁₋₆-alkoxy-C₁₋₆-alkyl or nicotinoylamino-C₁₋₆-alkyl; or naphthyl or naphthyl substituted by hydroxy, oxo, C₁₋₆-alkoxyl C₁₋₆-alkenyloxy, C₁₋₆-alkoxy-C₁₋₆-alkoxy, di-C₁₋₆-alkylamino, 2, 3-dihydroxypropoxy, 2,3-dihydroxypropoxy-C₁₋₆-alkoxy, 2,3-dimethoxypropoxy, C₁₋₆-alkoxycarbonyl-C₁₋₆-alkoxy, carbamoyl-C₁₋₆-alkoxy, methoxybenzyloxy, hydroxybenzyloxy, phenethyloxy, methylenedioxybenzyloxy, dioxolanyl-C₁₋₆-alkoxy, cyclopropyl-C₁₋₆-alkoxy, hydroxy-C₁₋₆-alkoxy, carbamoyloxy-C₁₋₆-alkoxy, pyridyl-carbamoyloxy-C₁₋₆-alkoxy, morpholino-C₁₋₆-alkoxy, 3-morpholino-2-hydroxypropoxy, N-methylpiperazino-N-C₁₋₆-alkoxy, benzoyloxy-C₁₋₆-alkoxy or picolyloxy; or tetrahydronaphthyl or indanyl substituted by methyl; or pyridyl, benzimidazolyl, Di-C₁₋₆-alkoxypyrimidinyl or 2- or 5-benzo[b]thienyl, 6- or 7-quinolyl, 6- or 7-isoquinolyl, 6- or 7-tetrahydroquinolyl, 6- or 7-tetrahydroisoquinolyl, 6-quinoxaliny, 6- or 7-quinazoliny or 6- or 7-quinoliny, 6- or 7-isoquinoliny, 6- or 7-tetrahydroquinoliny, 6- or 7-tetrahydroisoquinoliny, 6-quinoxaliny or 6- or 7-quinazoliny substituted by hydroxy, oxo, C₁₋₆-alkoxy, C₁₋₆-alkenyloxy, C₁₋₆-alkoxy-C₁₋₆-alkoxy, di-C₁₋₆-alkylamino, 2, 3-dihydroxypropoxy, 2,3-dihydroxypropoxy-C₁₋₆-alkoxy, 2,3-dimethoxypropoxy, C₁₋₆-alkoxycarbonyl-C₁₋₆-alkoxy, carbamoyl-C₁₋₆-alkoxy, methoxybenzyloxy, hydroxybenzyloxy, phenethyloxy, methylenedioxybenzyloxy, dioxolanyl-C₁₋₆-alkoxy, cyclopropyl-C₁₋₆-alkoxy, hydroxy-C₁₋₆-alkoxy, carbamoyloxy-C₁₋₆-alkoxy, pyridyl-carbamoyloxy-C₁₋₆-alkoxy, morpholino-C₁₋₆-alkoxy, 3-morpholino-2-hydroxypropoxy, N-methylpiperazino-N-C₁₋₆-alkoxy, benzoyloxy-C₁₋₆-alkoxy or picolyloxy;

R² denotes phenyl, naphthyl, acenaphthyl, cyclohexyl, pyridyl, pyrimidinyl, pyrazinyl, oxo-pyridinyl, diazinyl, triazolyl, thienyl, oxazolyl, oxadiazolyl, thiazolyl, pyrrolyl or furyl, the said radicals optionally being substituted by 1-3 halogen, hydroxy, cyano, trifluoromethyl, C₁₋₆-alkyl, halo-C₁₋₆-alkyl, hydroxy-C₁₋₆-alkyl, C₁₋₆-alkoxy-C₁₋₆-alkyl, cyano-C₁₋₆-alkyl, carboxy-C₁₋₆-alkyl, C₁₋₆-alkanoyloxy-C₁₋₆-alkyl, C₁₋₆-alkoxycarbonyloxy-C₁₋₆-alkyl, C₁₋₆-alkoxycarbonyl or C₁₋₆-alkoxy groups, or a C₁₋₆-alkylenedioxy group and/or by a radical L¹-T¹-L²-T²-L³-T³-L⁴-T⁴-L⁵-U;

L¹, L², L³, L⁴ and L⁵ independently of one another denote a bond, C₁₋₈-alkylene, C₂₋₈-alkenylene or C₂₋₈ alkynylene, or are absent;

T¹, T², T³ and T⁴ independently of one another denote (a) a bond, or are absent, or denote one of the groups (b) -CH(OH)-; (c) -CR(OR⁶)-; (d) -CH(NR⁵R⁶)-; (e) -CO-; (f) -CR⁷R⁸-; (g) -O- or -NR⁶-, (h) -S(O)₀₋₂-; (i) -SO₂NR⁶-; (j) -NR⁶SO₂-; (k) -CONR⁶-; (l) -NR⁶CO-; (m) -O-CO-; (n) -CO-O-; (o) -O-CO-O-; (p) -O-CO-NR⁶-; (q) -N(R⁶)-CO-N(R⁶)- or (r) -N(R⁶)-CO-O-, wherein the bonds starting from (b), (d), (e) and (g) - (r) lead to a C atom in the neighbouring group and the said C atom is saturated if the bond starts from a heteroatom, and wherein not more than two groups (b)-(f), three groups (g)-(h) and one group (i)-(p) are present;

R³ denotes hydrogen, hydroxy, C₁₋₆-alkoxy or C₁₋₆-alkenyloxy;

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R^4 denotes hydrogen, C_{1-6} -alkyl, C_{1-6} -alkenyl, C_{1-6} -alkoxy, hydroxy- C_{1-6} -alkyl, C_{1-6} -alkoxy- C_{1-6} -alkyl, benzyl, oxo or a group $R^{4a} - Z^1 - X^1$, wherein

R^{4a} denotes a group (a) H-; (b) C_{1-6} -alkyl-; (c) C_{1-6} -alkenyl-; (d) hydroxy- C_{1-6} -alkyl-; (e) polyhydroxy- C_{1-6} -alkyl-; (f) C_{1-6} -alkyl-O- C_{1-6} -alkyl-; (g) aryl-; (h) heterocyclyl-; (i) aryl- C_{1-6} -alkyl-; (j) heterocyclyl- C_{1-6} -alkyl-; (k) aryloxy- C_{1-6} -alkyl-; (l) heterocycliloxy- C_{1-6} -alkyl-; (m) $(R^5, R^6) - N - (CH_2)_{1-3}$ -; (n) $(R^5, R^6) - N$ -; (o) C_{1-6} -alkyl-S(O)₀₋₂-; (p) aryl-S(O)₀₋₂-; (q) heterocyclyl-S(O)₀₋₂-; (r) HO-SO₃- or salts thereof; (s) H₂N-C(NR)-NH-; or (t) NC- and the bonds starting from (n) - (t) lead to a C atom in the neighbouring group and the said C atom is saturated if the bond starts from a heteroatom;

Z^1 denotes (a) a bond, is absent, or denotes one of the groups (b) C_{1-6} -alkylene-; (c) C_{1-6} -alkenylene-; (d)-O-, -N(R¹¹)-, -S(O)₀₋₂-; (e) -CO-; (f) -O-CO-; (g) -O-CO-O-; (h) -O-CO-N(R¹¹)-; (i) -N(R¹¹)-CO-O-; (j) -CO-N(R¹¹)-; (k) -N(R¹¹)-CO-; (l) -N(R¹¹)-CO-N(R¹¹)- or (m) -CH(OR⁹)- and the bonds starting from (d) and (f) - (m) lead to a C atom in the neighbouring group and the said C atom is saturated if the bond starts from a heteroatom;

X^1 (a) denotes a bond or is absent or denotes one of the groups (b) -O-; (c) -N(R¹¹)-; (d) -S(O)₀₋₂-; or (e) -CH₂)₁₋₃; or

R^3 and R^4 together denote a bond;

R^5 and R^6 denote hydrogen, C_{1-6} -alkyl, C_{1-6} -alkenyl, aryl- C_{1-6} -alkyl or acyl, or together with the N atom to which they are bonded denote a 5- or 6-member heterocyclic ring which can contain an additional N-, O- or S- atom or an -SO- or -SO₂- group, wherein the additional N atom can if required be substituted by C_{1-6} -alkyl radicals;

R^7 and R^8 together with the C atom to which they are bonded denote a 3-7 member ring which can contain one or more -O- or -S- atoms or -SO- or -SO₂- groups;

R^9 denotes hydrogen, C_{1-6} -alkyl, acyl or aryl- C_{1-6} -alkyl;

R^{10} denotes carboxy- C_{1-6} -alkyl, C_{1-6} -alkoxycarbonyl- C_{1-6} -alkyl, C_{1-6} -alkyl or hydrogen;

R^{11} denotes hydrogen or C_{1-6} -alkyl;

U denotes hydrogen, C_{1-6} -alkyl, C_{3-6} -cycloalkyl, cyano, optionally substituted C_{3-6} -cycloalkyl, aryl or heterocyclyl;

Q denotes ethylene or is absent;

X denotes a bond, oxygen, sulphur or a group -CHOR⁹-, -O-CO-, -CO- or C=NOR¹⁰-, wherein the bond starting from an oxygen or sulphur atom leads to a saturated C atom in the group Z or to R¹;

W denotes oxygen or sulphur;

Z denotes C_{1-6} -alkylene, C_{1-6} -alkenylene, hydroxy- C_{1-6} -alkylidene, -alk-O- or -alk-S-, wherein alk denotes C_{1-6} -alkylene; and wherein if X is a bond, Z denotes C_{1-6} -alkenylene;

n is 1 or if X denotes -O-CO-, is 0 or 1;

m is 0 or 1;

and pharmaceutically usable salts thereof

except for the compounds 4-(4-fluorophenyl)-3-(3,4-methylenedioxybenzyloxy)piperidine, the hydrochloride thereof and trans-3-(3-chlorophenoxy)-4-(3,4-dimethyl-phenoxy)piperidine or pharmaceutically compatible salts thereof and

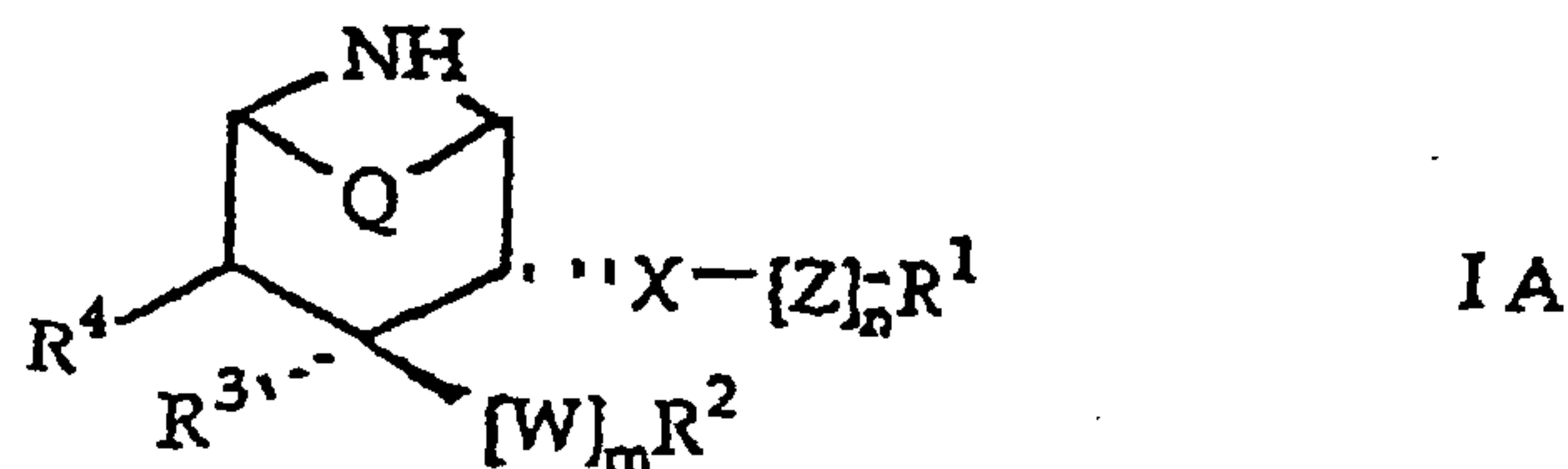
"acyl" denotes C₁₋₆-alkanoyl radicals or benzoyl;

"aryl" alone or in compounds denotes phenyl, naphthyl or tetrahydronaphthyl, these groups being substitutable if required one or more times by C₁₋₆-alkyl, trifluoromethyl, nitro, amino, C₁₋₆-alkenyl, C₁₋₆-alkoxy, C₁₋₆-alkylcarbonyloxy, hydroxy, halogen, cyano, carbamoyl, C₁₋₆-alkylenedioxy, phenyl substituted if required by halogen, C₁₋₆-alkyl, C₁₋₆-alkoxy or dihydroxy-C₁₋₆-alkylaminocarbonyl, or by similarly substituted phenoxy, phenylthio, phenyl-C₁₋₆-alkyl, phenyl-C₁₋₆-alkoxy, C₁₋₆-alkoxycarbonylphenyl, hydroxy-C₁₋₆-alkylphenyl, benzyloxy, pyridylcarbonylamino-C₁₋₆-alkyl, C₁₋₆-alkenyloxy, C₁₋₆-alkoxy-C₁₋₆-alkoxy, methoxybenzyloxy, hydroxybenzyloxy, phenylethyloxy, methylenedioxybenzyloxy, dioxolanyl-C₁₋₆-alkoxy, cyclopropyl-C₁₋₆-alkoxy, hydroxy-C₁₋₆-alkoxy, carbamoyloxy-C₁₋₆-alkoxy, pyridyl-carbamoyloxy-C₁₋₆-alkoxy, benzoyloxy-C₁₋₆-alkoxy; or by pyridyl, pyridyloxy, pyridylthio, pyridylamino, pyridyl-C₁₋₆-alkyl, pyridyl-C₁₋₆-alkoxy, pyrimidinyl, pyrimidinylthio, pyrimidinylamino, pyrimidinyl-C₁₋₆-alkyl, pyrimidinyl-C₁₋₆-alkoxy, thienyl, thienyl-C₁₋₆-alkyl, thienyl-C₁₋₆-alkoxy, furyl, furyl-C₁₋₆-alkyl and/or furyl-C₁₋₆-alkoxy, substituted if required by halogen, C₁₋₆-alkyl, C₁₋₆-alkoxy or dihydroxy-C₁₋₆-alkylaminocarbonyl; and

"heterocyclic ring" or "heterocyclyl" alone or in compounds denotes monocyclic or bicyclic, saturated or unsaturated heterocyclic radicals with 1 to 4 carbon and/or 1 or 2 sulphur or oxygen atoms substituted one or more times.

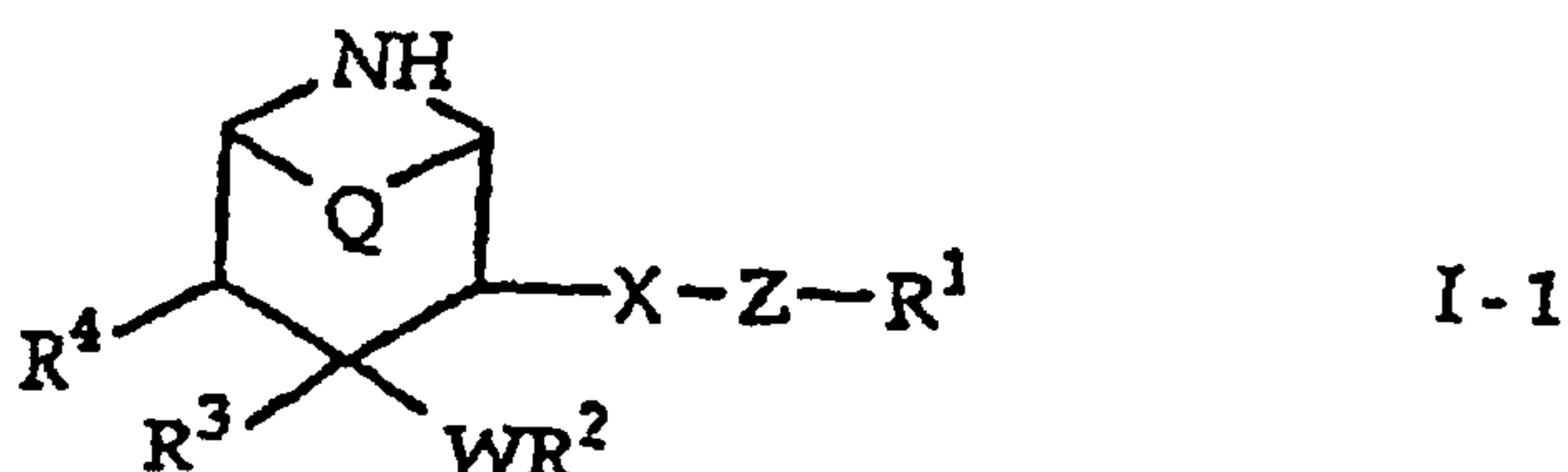
2. The derivatives according to claim 1, wherein the substituents in the heterocyclic ring or heterocyclyl in the case of unsaturated heterocyclyl radicals are C₁₋₆-alkyl, hydroxy, C₁₋₆-alkoxy, nitro or halogen or substituents as defined hereinbefore for "aryl" or in the case of saturated heterocyclyl radicals the substituents are selected from C₁₋₆-alkyl and C₁₋₆-alkoxy.

3. The derivatives according to claim 1 or 2 having the general formula:



wherein R¹ - R⁴, Q, W, X and Z, n and m have the meanings given in claim 1 except for the compounds 4-(4-fluorophenyl)-3-(3,4-methylenedioxy-benzyloxy) piperidine, the hydrochloride thereof and trans-3-(3-chlorophenoxy)-4-(3,4-dimethyl-phenoxy)piperidine or pharmaceutically acceptable salts thereof.

4. The derivatives according to claim 1 or 2 having the general formula I:



wherein

R¹ has the meanings given in claim 1;

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R² denotes phenyl, cyclohexyl, phenyl or cyclohexyl substituted by halogen, hydroxy, cyano, trifluoromethyl, C₁₋₆-alkyl, halo-C₁₋₆-alkyl, hydroxy-C₁₋₆-alkyl, C₁₋₆-alkoxy-C₁₋₆-alkyl, cyano-C₁₋₆-alkyl, carboxy-C₁₋₆-alkyl, C₁₋₆-alkanoyloxy-C₁₋₆-alkyl, C₁₋₆-alkoxycarbonyloxy-C₁₋₆-alkyl, C₁₋₆-alkoxycarbonyl, C₁₋₆-alkoxy, C₁₋₆-alkylenedioxy or by a radical L¹-T¹-L²-T²-L³-T³-L⁴-T⁴-L⁵-U or naphthyl or acenaphthyl;

L¹, L², L³, L⁴ and L⁵ independently of one another denote a bond, C₁₋₈-alkylene, C₂₋₈-alkenylene or C₂₋₈-alkynylene, or are absent;

T¹, T², T³ and T⁴ independently of one another denote (a) a bond, or are absent, or denote one of the groups (b) -CH(OH)-; (c) -CH(OR⁶)-; (d) -CH(NR⁵R⁶)-; (e) -CO-; (f) -CR⁷R⁸-; (g) -O- or -NR⁶-, (h) -S(O)₀₋₂-; (i) -SO₂NR⁶-; (j) -NR⁶SO₂-; (k) -CONR⁶-; (l) -NR⁶CO-; (m) -O-CO-; (n) -CO-O-; (o) -O-CO-O-; or (p) -O-CO-NR⁶-; wherein the bonds starting from (b), (d), (e) and (g) - (p) lead to a C atom in the neighbouring group and the said C atom is saturated if the bond starts from a heteroatom and wherein not more than two groups (b) - (f), three groups (g) - (h) and one group (i) - (p) are present;

R³ denotes hydrogen, hydroxy, C₁₋₆-alkoxy or C₁₋₆-alkenyloxy;

R⁴ denotes hydrogen, C₁₋₆-alkyl, C₁₋₆-alkenyl, C₁₋₆-alkoxy, hydroxy-C₁₋₆-alkyl, C₁₋₆-alkoxy-C₁₋₆-alkyl or benzyl;

R⁵ and **R⁶** denote hydrogen, C₁₋₆-alkyl or acyl or together with the N atom to which they are bonded denote a 5- or 6-member heterocyclic ring which can contain an additional N-, O- or S-atom;

R⁷ and **R⁸** together with the C atom to which they are bonded denote a 3-7-member ring which can contain one or more oxygen or sulphur atoms;

U denotes hydrogen, C₁₋₆-alkyl, C₃₋₆-cycloalkyl, cyano, aryl or heterocyclyl;

Q denotes ethylene or is absent;

X denotes oxygen, sulphur, -CO- or a group -CHOR⁹-, or -OCO- and **R⁹** denotes hydrogen, C₁₋₆-alkyl, acyl or aryl-C₁₋₆-alkyl;

W is absent or can denote oxygen or sulphur if **R³** is hydrogen;

Z denotes C₁₋₆-alkylene or is absent.

5. The derivatives according to claims 1-4 in which **W** is absent.
6. The derivatives according to claims 1-5 in which **Q** is absent.
7. The derivatives according to claims 1-6 in which **X** is oxygen, sulphur or -CO-.
8. The derivatives according to claims 1-7 in which **Z** is methylene.
9. The derivatives according to claims 1-8 in which **R²** denotes phenyl, or phenyl substituted by halogen, hydroxy,

cyano, trifluoromethyl, C₁₋₆-alkyl, halo-C₁₋₆-alkyl, hydroxy-C₁₋₆-alkyl, C₁₋₆-alkoxy-C₁₋₆-alkyl, cyano-C₁₋₆-alkyl, carboxy-C₁₋₆-alkyl, C₁₋₆-alkanoyloxy-C₁₋₆-alkyl, C₁₋₆-alkoxycarbonyloxy-C₁₋₆-alkyl, C₁₋₆-alkoxycarbonyl, C₁₋₆-alkoxy or C₁₋₆-alkylenedioxy.

10. The derivatives according to claims 1-8, in which R² denotes phenyl substituted by a radical L¹-T¹-L²-T²-L³-T³-L⁴-T⁴-L⁵-U wherein L¹ and L² are absent or denote C₁₋₈-alkylene and L³ is absent and U denotes hydrogen, C₁₋₆-alkyl, C₃₋₆-cycloalkyl, phenyl, phenyl substituted by C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkylthio, C₁₋₆-alkylsulfinyl, C₁₋₆-alkylenedioxy, halogen, benzoyl-C₁₋₆-alkyl, halogen-C₁₋₆-alkyl, C₁₋₆-alkanoyloxy or hydroxy; or naphthyl; or pyridyl, thienyl, pyrazinyl, triazolyl, imidazolyl, phenyl-oxadiazolyl, thienyl-oxadiazolyl, furyl-oxadiazolyl, phenyl-oxazolyl, benzothiazolyl, furyl, pyrimidinyl, nitrobenzothiazolyl, phenyltetrazolyl or morpholinyl.
11. The derivatives according to claims 1-8 in which R² denotes phenyl or phenyl substituted by 2-benzothiazolylthio-C₁₋₆-alkyl, 2-benzyloxy-3-methoxypropoxy, 2-benzoyloxy-3-methoxypropoxy, 2,3-dihydroxypropoxy, 2-hydroxy-3-benzylamino-propoxy, 2-hydroxy-3-phenoxypropoxy, 2-hydroxy-3-phenylthiopropoxy, 2-methoxy-3-phenoxypropoxy, 2-methoxy-3-benzyloxypropoxy, 2-methyl-3-fluoro-phenylbutyryloxy-C₁₋₆-alkoxy, 2-C₂₋₆-alkenyloxy-4-phenylbutyl, 3,4,5-trimethoxyphenyl-oxadiazolyl-C₁₋₆-alkoxy, 6-nitro-2-benzothiazolylthio-C₁₋₆-alkyl, benzamido-C₁₋₆-alkoxy, benzamido-C₁₋₆-alkyl, benzoyl-C₁₋₆-alkoxy or ketyls thereof, benzoyl-C₁₋₆-alkyl or ketyls thereof, benzoyl-C₁₋₆-alkyl-aminocarbonyl-C₁₋₆-alkyl, benzoyl-C₁₋₆-alkoxycarbonyl-C₁₋₆-alkyl, benzoyl-C₁₋₆-alkylaminocarbonyl, benzoyloxy, benzoyloxy-C₁₋₆-alkyl benzoyloxy-C₁₋₆-alkoxy, benzoyloxy-C₁₋₆-alkoxy, benzoyloxy-C₁₋₆-alkyl, benzthiazolylthio-C₁₋₆-alkoxy, benzthiazolylthio-C₁₋₆-alkyl, benzylcarbamoyl-C₁₋₆-alkoxy, benzyloxy-C₁₋₆-alkylcarbonyloxy-C₁₋₆-alkyl, benzyloxy-C₁₋₆-alkoxy, benzylthio-C₁₋₆-alkoxy, carbamoyloxy-C₁₋₆-alkoxy, carbamoyloxy-C₁₋₆-alkyl, carboxy-C₁₋₆-alkoxy, carboxy-C₁₋₆-alkyl, cyano, cyano-C₁₋₆-alkoxy, cyano-C₁₋₆-alkyl, cyanophenyl-C₁₋₆-alkoxy, cyclohexylcarbonyloxy-C₁₋₆-alkyl, cyclopropylcarbonyloxy-C₁₋₆-alkyl, cyclopropyloxy-benzyloxy-C₁₋₆-alkoxy, dioxolanyl-C₁₋₆-alkoxy, furyl-oxadiazolyl-C₁₋₆-alkoxy, furyloxy-C₁₋₆-alkoxy, halo-phenoxy-C₁₋₆-alkyl, halobenzoyl-C₁₋₆-alkoxy, halobenzoyloxy-C₁₋₆-alkyl, halobenzyloxy-C₁₋₆-alkoxy, halobenzyloxy-C₁₋₆-alkoxy, halogen, halogen-C₁₋₆-alkyl, halophenoxy, halophenyl-oxadiazolyl-C₁₋₆-alkoxy, hydroxy, hydroxy-benzoyloxy-C₁₋₆-alkyl, hydroxy-benzyloxy-C₁₋₆-alkoxy, hydroxy-C₁₋₆-alkoxy, hydroxy-C₁₋₆-alkyl, imidazolylcarbonyloxy-C₁₋₆-alkyl, methoxybenzoyl-C₁₋₆-alkyl, methoxybenzyl-oxy-C₁₋₆-alkoxy, methylenedioxybenzoyl-C₁₋₆-alkoxy, morpholino-C₁₋₆-alkoxy, morpholinocarbonyloxy-C₁₋₆-alkoxy, morpholinocarbonyloxy-C₁₋₆-alkyl, N-methylaminophenyl-carbonyloxy-C₁₋₆-alkyl, N-methyl-benzylamino-C₁₋₆-alkoxy, N-methylpyrrollylcarbonyloxy-C₁₋₆-alkoxy, N-C₁₋₆-alkylbenzamido-C₁₋₆-alkyl, naphthyl-C₁₋₆-alkoxy, nicotinoyloxy-C₁₋₆-alkoxy, nicotinoyloxy-C₁₋₆-alkyl, C₁₋₆-alkanoylbenzoyloxy-C₁₋₆-alkyl, C₁₋₆-alkanoyloxy-C₁₋₆-alkoxy, C₁₋₆-alkanoyloxy-C₁₋₆-alkyl, C₁₋₆-alkenyl-benzyloxy-C₁₋₆-alkoxy, C₁₋₆-alkenyloxy, C₁₋₆-alkenyloxy-benzyloxy-C₁₋₆-alkoxy, C₁₋₆-alkoxy, C₁₋₆-alkoxy-benzoyloxy-C₁₋₆-alkyl, C₁₋₆-alkoxy-carbonyl, C₁₋₆-alkoxy-C₁₋₆-alkyl, C₁₋₆-alkoxybenzoylamino-C₁₋₆-alkyl, C₁₋₆-alkoxybenzylcarbonyloxy-C₁₋₆-alkoxy, C₁₋₆-alkoxy-benzyloxy-C₁₋₆-alkoxy, C₁₋₆-alkoxy-benzylthio-C₁₋₆-alkoxy, C₁₋₆-alkoxycarbonyl, C₁₋₆-alkoxycarbonyl-C₁₋₆-alkoxy, C₁₋₆-alkoxycarbonyl-C₁₋₆-alkyl, C₁₋₆-alkoxyphenyl-oxadiazolyl-C₁₋₆-alkoxy, C₁₋₆-alkyl, C₁₋₆-alkylbenzyloxy-C₁₋₆-alkoxy, C₁₋₆-alkylenedioxy, C₁₋₆-alkylenedioxybenzyloxy-C₁₋₆-alkoxy, C₁₋₆-alkylsulfonylbenzoyl-C₁₋₆-alkoxy, C₁₋₆-alkylthiobenzoyloxy-C₁₋₆-alkoxy, C₁₋₆-alkylthiobenzyloxy-C₁₋₆-alkoxy, benzoylpxybenzyl-C₁₋₆-alkoxy, hydroxybenzyl-C₁₋₆-alkoxy, C₁₋₆-alkoxybenzyl-C₁₋₆-alkoxy, C₁₋₆-alkoxybenzylcarbonyloxy-alkoxy, phenoxy-benzyloxy-C₁₋₆-alkoxy, phenoxybenzoyl-C₁₋₆-alkyl, phenoxy-C₁₋₆-alkenyloxy, phenoxy-C₁₋₆-alkinyloxy, phenyl-C₁₋₆-alkanoylamino-C₁₋₆-alkyl, phenyl-C₁₋₆-alkenyloxy, phenyl-C₁₋₆-alkoxy, phenoxy-C₁₋₆-alkyl, phenyl-C₁₋₆-alkylaminocarbonyl, phenoxy-C₁₋₆-alkylcarbonyl-C₁₋₆-alkoxy, phenyl-C₁₋₆-alkylaminocarbonyl-C₁₋₆-alkyl, phenylaminocarbonyloxy-C₁₋₆-alkoxy, phenylaminocarbonyloxy-C₁₋₆-alkyl, phenyl-hydroxy-C₁₋₆-alkyl, phenyl-oxadiazolyl-C₁₋₆-alkoxy, phenyl-oxadiazolyl-C₁₋₆-alkoxy, phenyl-oxadiazolyl-C₁₋₆-alkyl, phenyl-oxazolyl-C₁₋₆-alkoxy, phenyloxy-C₁₋₆-alkoxy, 1 phenylsulfamoyl-C₁₋₆-alkyl, phenylsulfinyl-C₁₋₆-alkyl, phenylsulfonyl-C₁₋₆-alkoxy, phenylsulfonyl-C₁₋₆-alkyl, phenyltetrazolylthio-C₁₋₆-alkyl, phenylthio-C₁₋₆-alkoxy, phenylthio-C₁₋₆-alkyl, pyrazinylcarbonyloxy-C₁₋₆-alkyl, pyridylaminocarbonyloxy-C₁₋₆-alkoxy, pyridylaminocarbonyloxy-C₁₋₆-alkyl, pyridylcarbamoyloxy, pyridyl-C₁₋₆-alkoxy-C₁₋₆-alkoxy, pyridyl-C₁₋₆-alkoxy-C₁₋₆-alkyl, pyridyl-oxadiazolyl-C₁₋₆-alkoxy, pyridylthio-C₁₋₆-alkyl, pyrimidinoyloxy-C₁₋₆-alkoxy, pyrimidinylthio-C₁₋₆-alkyl, thenoyloxy-C₁₋₆-alkoxy, thenoyloxy-C₁₋₆-alkyl, thienyl-oxadiazolyl-C₁₋₆-alkoxy, triazolyl-C₁₋₆-alkoxy, trifluoromethylbenzyloxy-C₁₋₆-alkoxy or trifluoromethyl.

12. The derivatives according to claims 1-8 in which R² denotes cyclohexyl or benzoyloxycyclohexyl.
13. The derivatives according to claims 1-8, in which R² denotes naphthyl, tetrahydronaphthyl or acenaphthyl.
14. The derivatives according to claims 1-3 in which R² denotes pyridyl or oxopyridyl, or pyridyl or oxopyridyl substituted by 3-H-2 thioxo-benzthiazolyl, C₁₋₆-alkoxyphenyl-C₁₋₆-alkoxy-C₁₋₆-alkoxy, phenyl-C₁₋₆-alkoxy-C₁₋₆-alkoxy, phenyl-C₁₋₆-alkyl, cyclohexyl-C₁₋₆-alkoxy, phenoxy-C₁₋₆-alkyl or phenyl-C₁₋₆-alkoxy-C₁₋₆-alkyl.
15. The derivatives according to claims 1-3, in which R² denotes pyrimidinyl or pyrimidinyl substituted by benzodioxanyl-C₁₋₆-alkoxy, biphenyloxy, biphenyl-C₁₋₆-alkoxy, cyclohexyl-C₁₋₆-alkoxy, cyclohexyloxy-C₁₋₆-alkoxy, halophenyl-C₁₋₆-alkoxy, halophenyl-oxadiazolyl-C₁₋₆-alkoxy, indanyl-C₁₋₆-alkoxy, naphthyl-C₁₋₆-alkoxy, phenyl-C₁₋₆-alkyl, N-C₁₋₆-alkylphenyl-C₁₋₆-alkoxy-C₁₋₆-alkylamino, N-C₁₋₆-alkylphenyl-C₁₋₆-alkylamino, C₁₋₆-alkylthio, C₁₋₆-alkoxy, C₁₋₆-alkoxyphenyl-C₁₋₆-alkoxy-C₁₋₆-alkoxy, C₁₋₆-alkoxyphenyl-C₁₋₆-alkylamino, C₁₋₆-alkylphenyl-C₁₋₆-alkylamino, halophenyl-C₁₋₆-alkylamino, halophenoxy-C₁₋₆-alkoxy, C₁₋₆-alkylpyridyl-C₁₋₆-alkoxy, phenylalkoxy-C₁₋₆-alkoxy, phenyl-C₁₋₆-alkoxy-C₁₋₆-alkylthio, phenyl-C₁₋₆-alkoxy-C₁₋₆-alkylamino, phenoxy-phenyl-C₁₋₆-alkoxy, phenoxy-phenoxy, phenyl-C₁₋₆-alkylthio, phenyl-C₁₋₆-alkoxy-C₁₋₆-alkoxy, phenylthio-C₁₋₆-alkoxy, phenyl-oxazolyl-C₁₋₆-alkoxy, phenyl-C₁₋₆-alkylthio, phenyl-C₁₋₆-alkenylthio, phenyl-C₁₋₆-alkylamino, phenyl-pyridyl-C₁₋₆-alkoxy or phenylpyridyl-C₁₋₆-alkylamino.
16. The derivatives according to claims 1-3 in which R² is halobenzoyl-C₁₋₆-alkyl-triazolyl, phenyl-C₁₋₆-alkoxy-C₁₋₆-alkyl-triazolyl or phenyl-C₁₋₆-alkoxy-C₁₋₆-alkoxy-C₁₋₆-alkyl-triazolyl.
17. The derivatives according to claims 1-3 in which R⁴ denotes 2-oxo-imidazolidin-1-yl-C₁₋₆-alkyl, 4-hydroxy-piperidin-1-yl-C₁₋₆-alkoxy, 4-hydroxy-piperidin-1-yl-C₁₋₆-alkoxy-C₁₋₆-alkyl, 4-methyl-piperazin-1-yl-C₁₋₆-alkoxy, 4-methyl-piperazin-1-yl-C₁₋₆-alkoxy-C₁₋₆-alkyl, 4-methyl-piperazin-1-yl-C₁₋₆-alkyl-carbamoyloxy-C₁₋₆-alkyl, 1, 2, 4-triazolyl-C₁₋₆-alkyl, amino, amino-C₁₋₆-alkyl, amino-C₁₋₆-alkyl-amino, amino-C₁₋₆-alkyl-amino-C₁₋₆-alkyl, amino-C₁₋₆-alkoxyl, amino-C₁₋₆-alkoxyl-C₁₋₆-alkyl, aminocarbonyloxy-C₁₋₆-alkyl, benzyloxy, benzyloxy substituted by C₁₋₆-alkyl, C₁₋₆-alkenyl, C₁₋₆-alkoxy, trifluoromethoxy, C₁₋₆-alkylthio, hydroxy or halogen, benzyloxy, benzyloxy-C₁₋₆-alkyl or by C₁₋₆-alkyl C₁₋₆-alkenyl, C₁₋₆-alkoxy or halogen, carbamoyloxy-C₁₋₆-alkyl, cyano-C₁₋₆-alkyl, di-C₁₋₆-alkyl-amino, di-C₁₋₆-alkyl-amino-C₁₋₆-alkyl, di-C₁₋₆-alkyl-amino-C₁₋₆-alkyl-(N-C₁₋₆-alkyl) -amino-C₁₋₆-alkyl, di-C₁₋₆-alkyl-amino-C₁₋₆-alkyl-amino di-C₁₋₆-alkyl-amino-C₁₋₆-alkyl-amino-C₁₋₆-alkyl, di-C₁₋₆-alkyl-amino-C₁₋₆-alkoxyl di-C₁₋₆-alkyl-amino-C₁₋₆-alkoxyl-C₁₋₆-alkyl, dihydroxy-C₁₋₆-alkoxy, dihydroxy-C₁₋₆-alkoxy-C₁₋₆-alkyl, dihydroxy-C₁₋₆-alkyl-amino, dihydroxy-C₁₋₆-alkyl-amino-C₁₋₆-alkyl, guanidinyl-C₁₋₆-alkoxy-C₁₋₆-alkyl, guanidinyl-C₁₋₆-alkyl, hydroxy, hydroxy-C₁₋₆-alkyl, sulfooxy-C₁₋₆-alkyl, hydroxy-C₁₋₆-alkoxyl, hydroxy-C₁₋₆-alkoxyl-C₁₋₆-alkyl, morpholin-4-yl-C₁₋₆-alkoxy, morpholin-4-yl-C₁₋₆-alkoxy-C₁₋₆-alkyl, morpholin-4-yl-C₁₋₆-alkyl-carbamoyloxy-C₁₋₆-alkyl, naphthyl-alkoxy or naphthyl-alkoxy, C₁₋₆-alkoxy, C₁₋₆-alkoxy-C₁₋₆-alkoxy-C₁₋₆-alkoxy-C₁₋₆-alkoxy-C₁₋₆-alkyl, C₁₋₆-alkoxy-C₁₋₆-alkyl, C₁₋₆-alkyl, C₁₋₆-alkylsulfonylamino-C₁₋₆-alkyl, phenoxy-C₁₋₆-alkyl substituted by C₁₋₆-alkoxy or by phenoxy-C₁₋₆-alkyl, phenyl-thio-C₁₋₆-alkyl substituted by C₁₋₆-alkyl, C₁₋₆-alkoxy or by phenyl-thio-C₁₋₆-alkyl, piperazin-4-yl-C₁₋₆-alkoxy, piperazin-4-yl-C₁₋₆-alkoxy-C₁₋₆-alkyl, piperidin-1-yl-C₁₋₆-alkyl-carbamoyloxy-C₁₋₆-alkyl, piperidin-4-yl-C₁₋₆-alkoxy, piperidin-4-yl-C₁₋₆-alkoxy-C₁₋₆-alkyl, pyridyl-C₁₋₆-alkoxyl, pyridyl-C₁₋₆-alkoxy-C₁₋₆-alkyl, pyridylthio-C₁₋₆-alkyl, pyrimidinyl-C₁₋₆-alkyl substituted by C₁₋₆-alkoxy or by pyrimidinyl-C₁₋₆-alkyl, tetrazolyl-C₁₋₆-alkyl, trifluoromethylsulfonylamino-C₁₋₆-alkyl substituted by C₁₋₆-alkoxy or hydrogen.
18. The derivatives according to claims 1-17,
4-[2-[7-[(3R,4R)-4-[4-(3-benzyloxy-propoxy)-phenyl]-piperidin-3-yloxymethyl]-naphthalin-2-yloxy]-ethyl]-morpholine,
(R)-3[7-[(3R,4R)-4-[4-(3-benzyloxy-propoxy)-phenyl]-piperidin-3-yloxymethyl]-naphthalin-2-yloxy]-propane-1,2-diol,

(S)-3-[7-[(3R,4R)-4-[4-(3-benzyloxy-propoxy)-phenyl]-piperidin-3-yloxymethyl]-naphthalin-2-yloxy]-propane-1,2-diol,

(R)-3-[2-[7-[(3R,4R)-4-[4-(3-benzyloxy-propoxy)-phenyl]-piperidin-3-yloxymethyl]-naphthalin-2-yloxy]-ethoxy]-propane-1,2-diol,

(S)-3-[2-[7-[(3R,4R)-4-[4-(3-benzyloxy-propoxy)-phenyl]-piperidin-3-yloxymethyl]-naphthalin-2-yloxy]-ethoxy]-propane-1,2-diol,

1-[2-[7-[(3R,4R)-4-[4-(3-benzyloxy-propoxy)-phenyl]-piperidin-3-yloxymethyl]-naphthalin-2-yloxy]-ethyl]-4-methyl-piperazine,

1-[3R,4S-4-[4-(3-benzyloxy-propoxy)-phenyl]-piperidin-3-yl]-2-naphthalin-2-yl-ethanone,

(3R,4S,5S)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-(1,4-dimethoxy-naphthalin-2-ylmethoxy)-piperidin-5-ol,

3R,4R)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-[7-[(R)-2,3-dihydroxy-propoxymethyl]-naphthalin-2-ylmethoxy]-piperidine,

3R,4R)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-[7-[(S)-2,3-dihydroxy-propoxymethyl]-naphthalin-2-ylmethoxy]-piperidine,

3R,4R)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-[6-[(R)-2,3-dihydroxy-propoxymethyl]-naphthalin-2-ylmethoxy]-piperidine,

3R,4R)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-[6-[(S)-2,3-dihydroxy-propoxymethyl]-naphthalin-2-ylmethoxy]-piperidine,

4-[(3R,4S,5S))-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-naphthalin-2-ylmethoxy]-piperidine-5-yloxy]-butan-1-ol,

3-[(3R,4S,5S))-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-naphthalin-2-ylmethoxy]-piperidine-5-yloxy]-propan-1-ol,

1-[2-[(3R,4R,5S)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-naphthalin-2-ylmethoxy]-piperidine-5-yloxy]-ethyl]-4-methyl-piperazine,

(3R,4R,5R)-4-[2-[4-[4-(3-benzyloxy-propoxy)-phenyl]-5-(naphthalin-2-ylmethoxy)-piperidin-3-ylmethoxy]-ethyl]-morpholine,

(3R,4S,5S)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-(4-methoxy-benzyloxy)-piperidine-5-ol,

(3R,4S,5S)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3,5-bis-(4-methoxy-benzyloxy) -piperidine,

(3S,4R,5R)-4-[2-[4-[4-(3-benzyloxy-propoxy)-phenyl]-5-(naphthalin-2-ylmethoxy)-piperidin-3-ylmethoxy]-ethyl]-morpholine,

(3S,4R,5R)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-methoxymethyl-5-(naphthalin-2-ylmethoxy)-piperidine,

[3-(4-methyl-piperazin-1-yl)-propyl]-carbamic acid (3S,4R,5R)-4-[4-(3-benzyloxy-propoxy)-phenyl]-5-(naphthalin-2-ylmethoxy)-piperidine-3-ylmethylester,

(3S,4R,SR)-4-[4-[4-(3-benzyloxy-propoxy)-phenyl]-5-(naphthalin-2-ylmethoxy)-piperidine-3-ylmethylsulfa-
nyl]-pyridine,

2-(4-cyclohexyl-butoxy)-5-[(3R,4R)-3-(1,4-dimethoxy-naphthalin-2-ylmethoxy)-piperidin-4-yl]-pyrimidine,

(3'R,4'R)-6-(3-cyclohexyl-propoxy)-3'-(1,4-dimethoxy-naphthalin-2-ylmethoxy)-1',2',3',4',5',6'-hexahy-
dro-[3,4']bipyridine,

(3S,4R,5R)-[4-[4-(3-benzyloxy-propoxy)-phenyl]-5-(naphthalin-2-ylmethoxy)-piperidin-3-yl]-methanol,

(3S,4R,5R)-N-[4-[4-(3-benzyloxy-propoxy)-phenyl]-5-(naphthalin-2-ylmethoxy)-piperidin-3-ylmethyl]-N,N,N'-
trimethyl-ethane-1,2-diamine,

(3S,4R,5R)-[4-[4-(3-benzyloxy-propoxy)-phenyl]-5-(naphthalin-2-ylmethoxy)-piperidin-3-ylmethyl]-diethyl-
amine,

1-[(3R,4S,5S)-4-[4-(3-benzyloxy-propoxy)-phenyl]-5-(2-morpholin-4-yl-ethoxymethyl)-piperidin-3-yl]-2-naph-
thalin-2-yl-ethanone,

(3R,4R)-3-(1,4-dimethoxy-naphthalin-2-ylmethoxy)-4-[4-[3-(2-methoxy-phenoxy)-propoxy]-phenyl]-piperid-
ine,

(3R,4S,5S)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3,5-bis-(3,4,5-trimethoxy-benzyloxy)-piperidine,

(3R,4R,5S)-4-[4-(3-benzyloxy-propoxy)-phenyl]-3-(naphthalin-2-ylmethoxy)-5-[1,2,4]triazol-1-ylmethyl-pipe-
ridine,

(3R,4R)-4-[4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl]-3-(quinolin-7-ylmethoxy)-piperidine,

2-(7-[(3R,4R)-4-[4-(3-benzyloxy-propoxy)-phenyl]-piperidin-3-yloxymethyl]-naphthalin-2-ylmethoxy)-ethanol,

7-[(3R,4R)-4-[4-(3-benzyloxy-propoxy)-phenyl]-piperidin-3-yloxymethyl]-naphthalin-2-ylmethyl)-dimethyl-
amine,

(3R,4R)-3-(4-benzyloxy-naphthalin-2-ylmethoxy)-4-(4-fluoro-phenyl)-piperidine(3'R,4'R)-3'-(1,4-dimethoxy-
naphthalin-2-ylmethoxy)-6-[3-(2-methoxybenzyloxy)-propoxy]-1',2',3',4',5',6'-hexahydro-[3,4']bipyridine,

(3R,4R)-3-(1,4-dimethoxy-naphthalin-2-ylmethoxy)-4-[4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl]-piperid-
ine,

(3S,4R,5R)-1-[4-[4-(3-benzyloxy-propoxy)-phenyl]-5-(naphthalin-2-ylmethoxy)-piperidin-3-ylmethyl]-imida-
zolidin-2-one,

(3R,4R)-4-[4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl]-3-(2-oxo-1,2-dihydro-quinoline-7-ylmethoxy)-pipe-
ridine,

(3R,4R)-3-(isoquinoline-7-ylmethoxy)-4-[4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl]-piperidine,

(3R,4R)-4-[4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl]-3-(1,2,3,4-tetrahydroquinolin-7-ylmethoxy)-piperid-
ine,

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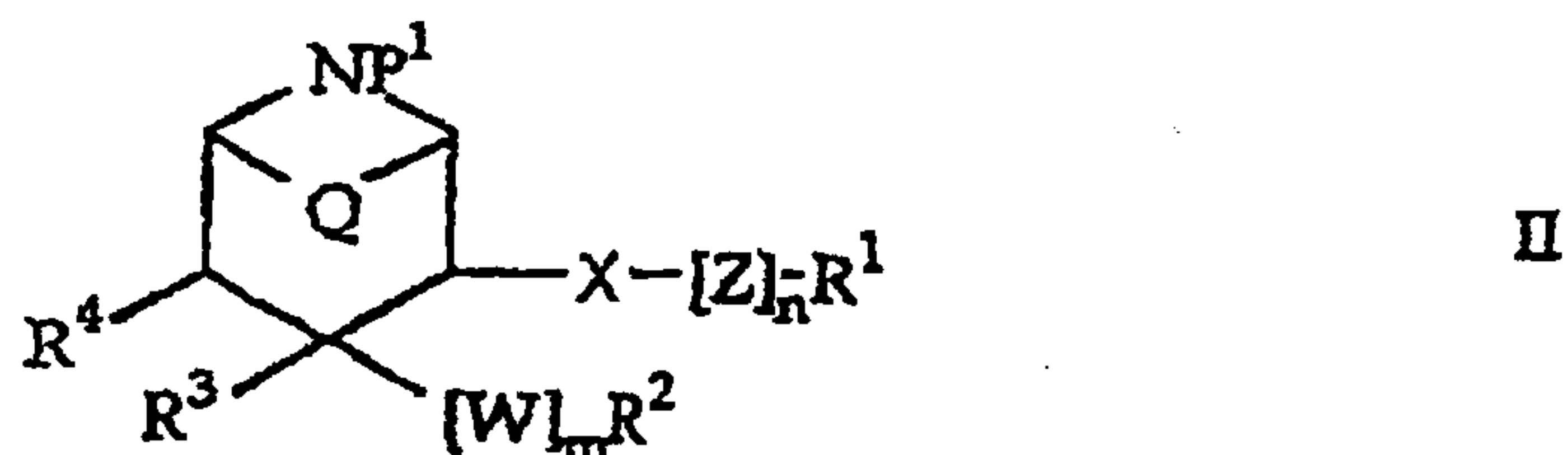
1-[2-[7-[(3R,4R)-4-[4-[3-(2-methoxy-benzyloxy)-propoxy]-piperidin-3-yloxymethyl]-naphthalin-2-yloxy]-ethyl]-4-methyl-piperazine,

1-[2-[7-[(3R,4S,5S)-5-hydroxy-4-[4-[3-(2-methoxy-benzyloxy)-propoxy]-piperidine-3-yloxymethyl]-naphthalin-2-yloxy]-ethyl]-4-methyl-piperazine,

(3R,4S,5S)-3-(1,4-dimethoxy-naphthalin-2-ylmethoxy)-4-[4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl]-piperidine-5-ol and

(3R,4R,5S)-3-(1,4-dimethoxy-naphthalin-2-ylmethoxy)-4-[4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl]-5-(1H-tetrazol-5-ylmethyl)-piperidine.

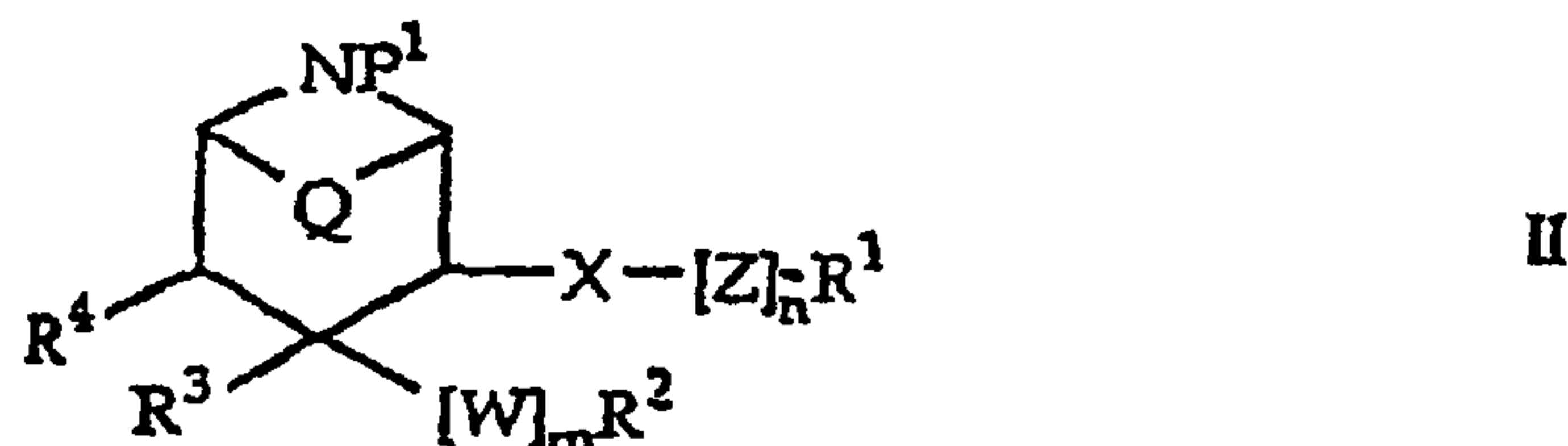
19. Compounds having the formula II



in which P¹ denotes a protective group selected from the group consisting of tert-butoxycarbonyl, benzyloxy-carbonyl, vinyloxycarbonyl and alkylsilylalkyloxycarbonyl, and the other symbols having the meanings given in claim 1 and any hydroxy groups in R¹, R² and R⁴ can be in protected form.

20. A pharmaceutical composition for treatment or prevention of high blood pressure and heart or kidney insufficiency, containing a formula I derivative as defined in claim 1 and a therapeutically inert excipient.

21. A method of producing a derivative as defined in any one of claims 1-18, wherein the protective group or groups are split off from a formula II compound

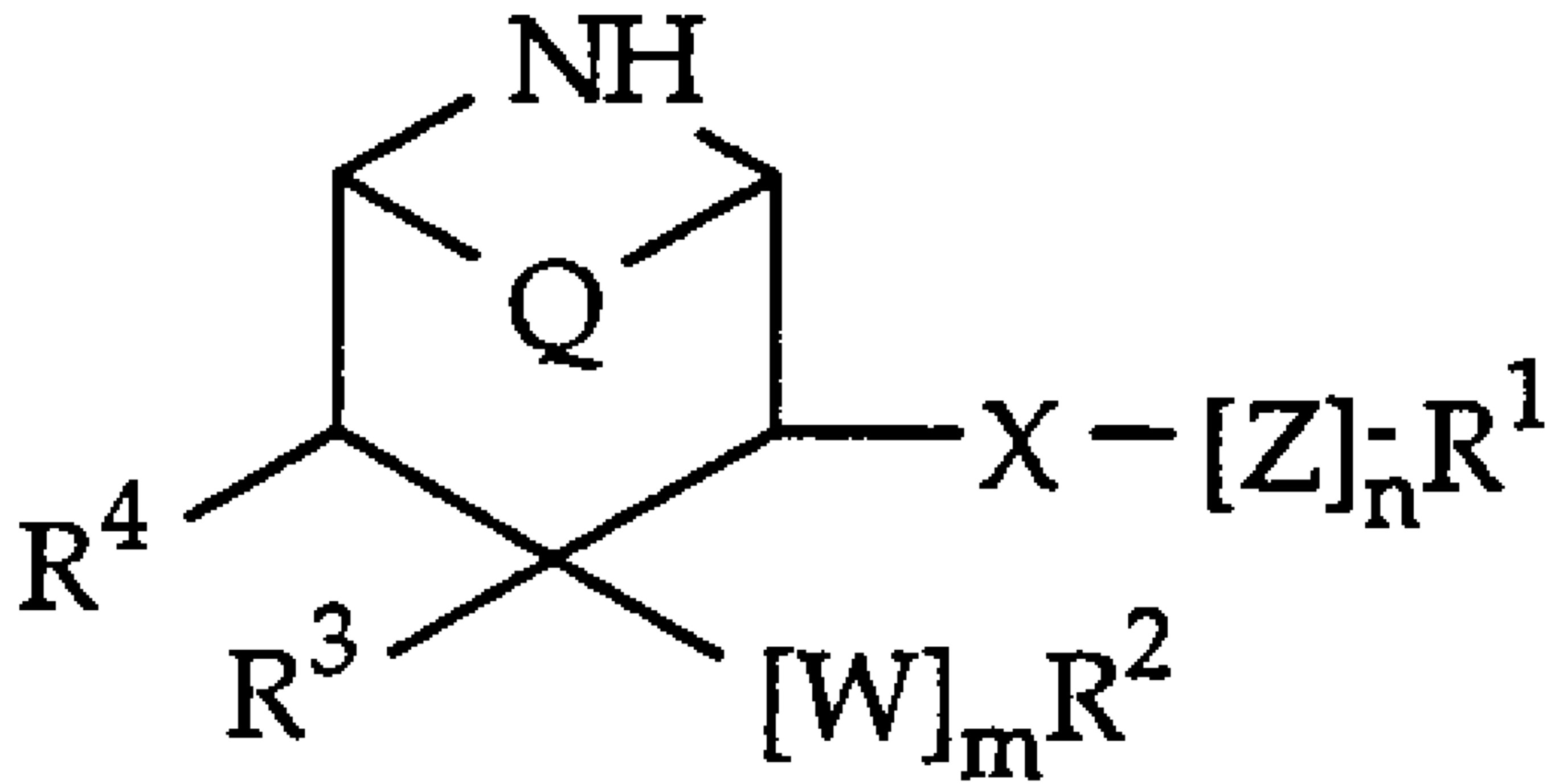


in which P¹ denotes a protective group and the other symbols have the meaning given in claim 1 and any hydroxy groups in R¹, R² and R⁴ can be in protected form, the protective group or groups are split off, any reactive groups in the thus-obtained formula I compound are functionally modified if required, and/or the formula I compound is converted into a pharmaceutically acceptable salt.

22. Derivatives according to claims 1 to 18 for use as therapeutic active substances for the treatment of high blood pressure and heart or kidney insufficiency.

23. Use of the formula I derivatives as defined in claim 1 in the production of pharmaceutical compositions for treatment of high blood pressure and heart or kidney insufficiency.

24. Use of the formula I derivatives as defined in claim 1 for treatment of high blood pressure and heart or kidney insufficiency.



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