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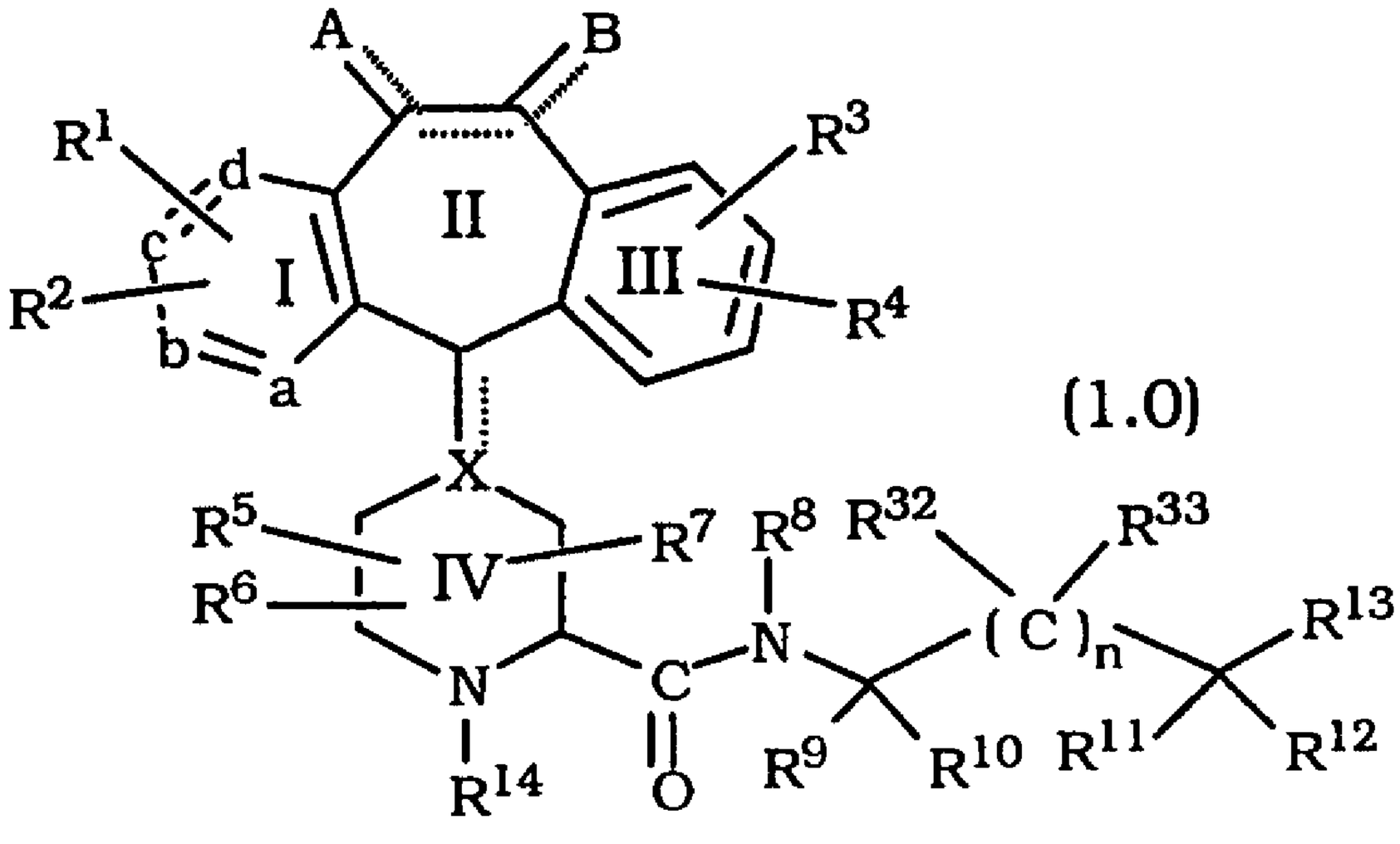
(54) Titre : INHIBITEURS DE LA FARNESYL PROTEINE TRANSFERASE TRYCICLIQUE
(54) Title: TRICYCLIC FARNESYL PROTEIN TRANSFERASE INHIBITORS



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(57) Abrégé/Abstract:
Disclosed are compounds of formula (1.0) wherein R^{13} represents an imidazole ring; R^{14} represents a carbamate, urea, amide or sulfonamide group; R^{8} represents H when the alkyl chain between the amide group and the R^{13} imidazole group is substituted, or R^{8} represents a substituent such aa arylalkyl, heteroarylalkyl or cycloalkyl; and the remaining substituents are as defined herein. Also disclosed are compounds wherein R^{8} is H, and the alkyl chain between the amide group and the R^{13} imidazole group is unsubstituted. Also disclosed is a method of treating cancer and a method of inhibiting farnesyl protein transferase using the disclosed compounds.

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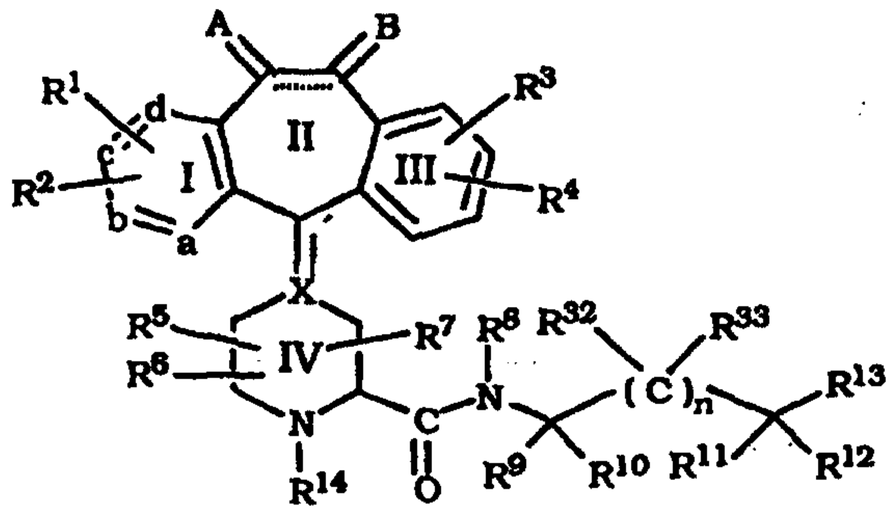
(54) Title: TRICYCLIC FARNESYL PROTEIN TRANSFERASE INHIBITORS



(1.0)

(57) Abstract

Disclosed are compounds of formula (1.0) wherein R^{13} represents an imidazole ring; R^{14} represents a carbamate, urea, amide or sulfonamide group; R^8 represents H when the alkyl chain between the amide group and the R^{13} imidazole group is substituted, or R^8 represents a substituent such aa arylalkyl, heteroarylalkyl or cycloalkyl; and the remaining substituents are as defined herein. Also disclosed are compounds wherein R^8 is H, and the alkyl chain between the amide group and the R^{13} imidazole group is unsubstituted. Also disclosed is a method of treating cancer and a method of inhibiting farnesyl protein transferase using the disclosed compounds.

DEMANDES OU BREVETS VOLUMINEUX

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TRICYCLIC FARNESYL PROTEIN TRANSFERASE INHIBITORS

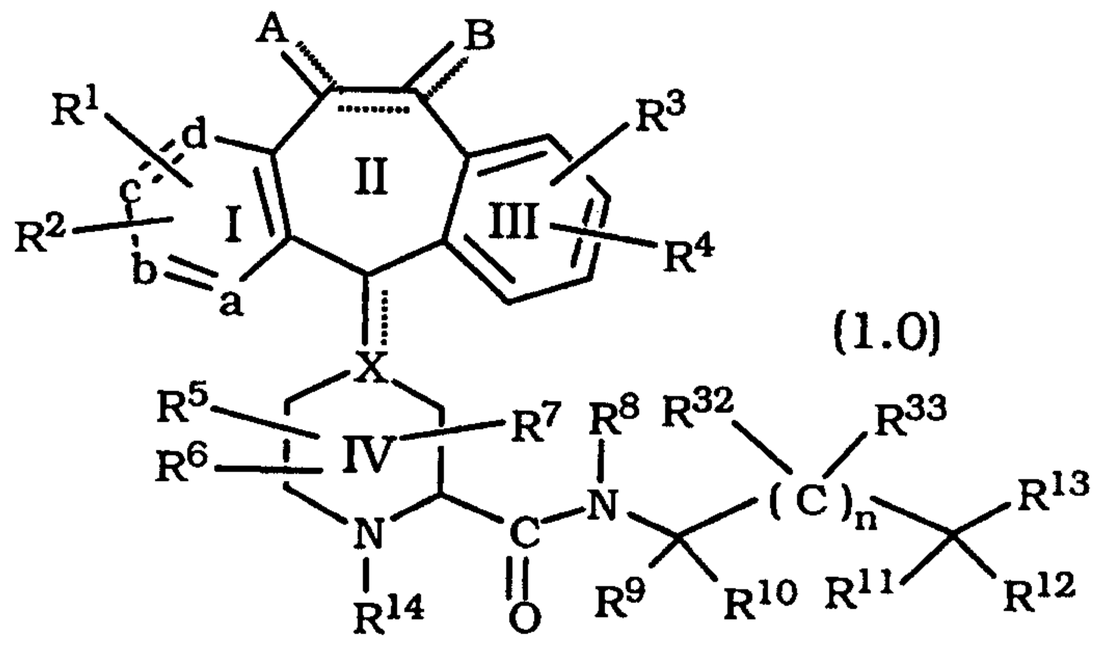
BACKGROUND

WO 95/10516, published April 20, 1995, WO96/31478, published October 10, 1996, and copending Application Serial No. 09/094687 filed June 15, 1998 discloses tricyclic compounds useful for inhibiting farnesyl protein transferase.

In view of the current interest in inhibitors of farnesyl protein transferase, a welcome contribution to the art would be compounds useful for the inhibition of farnesyl protein transferase. Such a contribution is provided by this invention.

SUMMARY OF THE INVENTION

This invention provides compounds useful for the inhibition of farnesyl protein transferase (FPT). The compounds of this invention are represented by the formula:



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or a pharmaceutically acceptable salt or solvate thereof, wherein:

one of a, b, c and d represents N or N^+O^-, and the remaining a, b, c and d groups represent CR^1 or CR^2; or

each of a, b, c, and d are independently selected from CR^1 or CR^2;

X represents N or CH when the optional bond (represented by the dotted line) is absent, and represents C when the optional bond is present;

the dotted line between carbon atoms 5 and 6 represents an optional bond, such that when a double bond is present, A and B independently represent $-R^{15}$, halo, $-OR^{16}$, $-OCO_2R^{16}$ or $-OC(O)R^{15}$, and when no double bond is present between carbon atoms 5 and 6, A and B each independently represent H_2, $-(OR^{16})_2$, H and halo, dihalo, alkyl and H, $(alkyl)_2$, -H and $-OC(O)R^{15}$, H and $-OR^{15}$, =O, aryl and H, $=NOR^{15}$ or $-O-(CH_2)_p-O-$ wherein p is 2, 3 or 4;

each R^1 and each R^2 is independently selected from H, halo, $-CF_3$, $-OR^{15}$ (e.g., $-OCH_3$), $-COR^{15}$, $-SR^{15}$ (e.g., $-SCH_3$ and $-SCH_2C_6H_5$), $-S(O)_tR^{16}$ (wherein t is 0, 1 or 2, e.g., $-SOCH_3$ and $-SO_2CH_3$), $-N(R^{15})_2$, $-NO_2$, $-OC(O)R^{15}$, $-CO_2R^{15}$, $-OCO_2R^{16}$, -CN, $-NR^{15}COOR^{16}$, $-SR^{16}C(O)OR^{16}$ (e.g., $-SCH_2CO_2CH_3$), $-SR^{16}N(R^{17})_2$ (provided that R^{16} in $-SR^{16}N(R^{17})_2$ is not $-CH_2-$) wherein each R^{17} is independently selected from H or $-C(O)OR^{16}$ (e.g., $-S(CH_2)_2NHC(O)O$-t-butyl and $-S(CH_2)_2NH_2$), benzotriazol-1-yloxy, tetrazol-5-ylthio, or substituted tetrazol-5-ylthio (e.g., alkyl substituted tetrazol-5-ylthio such as 1-methyl-tetrazol-5-ylthio), alkynyl, alkenyl or alkyl, said alkyl or alkenyl group optionally being substituted with halo, $-OR^{15}$ or $-CO_2R^{15}$;

R^3 and R^4 are the same or different and each independently represents H, any of the substituents of R^1 and R^2, or R^3 and R^4 taken together represent a saturated or unsaturated C_5-C_7 fused ring to the benzene ring (Ring III);

R^5, R^6, and R^7 each independently represents H, $-CF_3$,

-COR^{15}, alkyl or aryl, said alkyl or aryl optionally being substituted with -OR^{15}, -SR^{15}, -$S(O)_tR^{16}$, -$NR^{15}COOR^{16}$, -$N(R^{15})_2$, -NO_2, -COR^{15}, -$OCOR^{15}$, -OCO_2R^{16}, -CO_2R^{15}, OPO_3R^{15}, or R^5 is combined with R^6 to represent =O or =S;

R^8 is selected from: H, C_3 to C_4 alkyl (preferably branched chain alkyl, and most preferably C_4 to C_7 branched chain alkyl), aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, substituted alkyl, substituted aryl, substituted arylalkyl, substituted heteroaryl, substituted heteroarylalkyl, substituted cycloalkyl, substituted cycloalkylalkyl;

the substutuents for the R^8 substituted groups being selected from: alkyl, aryl, arylalkyl, cycloalkyl, -$N(R^{18})_2$, -OR^{18}, cycloalkyalkyl, halo, CN, -$C(O)N(R^{18})_2$, -$SO_2N(R^{18})_2$ or -CO_2R^{18}; provided that the -OR^{18} and -$N(R^{18})_2$ substituents are not bound to the carbon that is bound to the N of the -$C(O)NR^8$- moiety;

each R^{18} is independently selected from: H, alkyl, aryl, arylalkyl, heteroaryl or cycloalkyl;

R^9 and R^{10} are independently selected from: H, alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl or -$CON(R^{18})_2$ (wherein R^{18} is as defined above); and the substitutable R^9 and R^{10} groups are optionally substituted with one or more (e.g., 1-3) substituents selected from: alkyl (e.g., methyl, ethyl, isopropyl, and the like), cycloalkyl, arylalkyl, or heterarylalkyl (i.e., the R^9 and/or R^{10} groups can be unsubtituted or can be substituted with 1-3 of the substitutents described above, except when R^9 and/or R^{10} is H); or

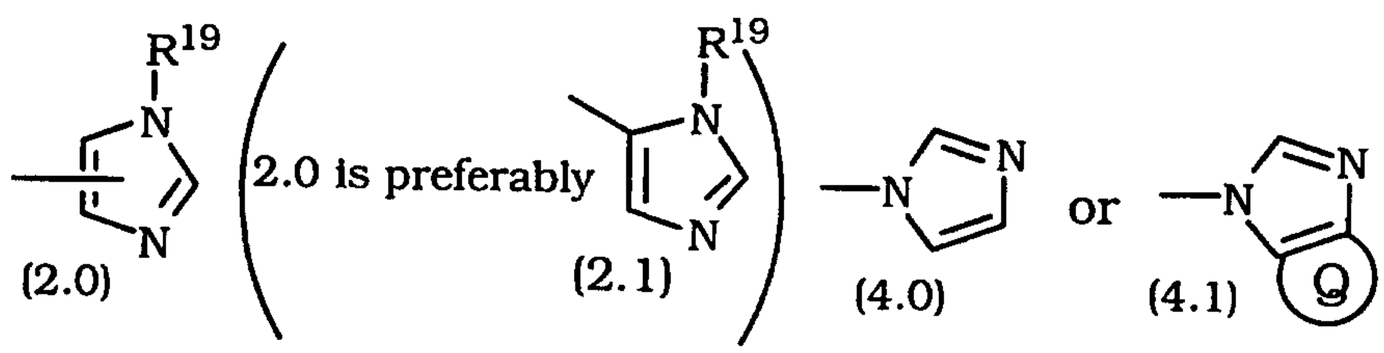
R^9 and R^{10} together with the carbon atom to which they are bound, form a C_3 to C_6 cycloalkyl ring;

R^{11} and R^{12} are independently selected from: H, alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl, -$CON(R^{18})_2$ -OR^{18} or -$N(R^{18})_2$; wherein R^{18} is as defined above; provided that the

$-OR^{18}$ and $-N(R^{18})_2$ groups are not bound to a carbon atom that is adjacent to a nitrogen atom; and wherein said substitutable R^{11} and R^{12} groups are optionally substituted with one or more (e.g., 1-3) substituents selected from: alkyl (e.g., methyl, ethyl, isopropyl, and the like), cycloalkyl, arylalkyl, or heterarylalkyl; or

R^{11} and R^{12} together with the carbon atom to which they are bound, form a C_3 to C_6 cycloalkyl ring;

R^{13} is an imidazolyl ring selected from:



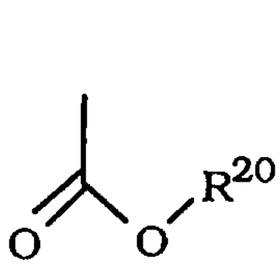
wherein R^{19} is selected from: (1) H, (2) alkyl, (3) alkyl, (4) aryl, (5) arylalkyl, (6) substituted arylalkyl wherein the substituents are selected from halo (e.g., F and Cl) or CN, (7) $-C(aryl)_3$ (e.g., $-C(phenyl)_3$, i.e., trityl) or (8) cycloalkyl;

said imidazolyl ring 2.0 or 2.1 optionally being substituted with one or two substituents and said imidazole ring 4.0 optionally being substituted with 1-3 substituents and said imidazole ring 4.1 being optionally substituted with one substituent wherein said optional substituents for rings 2.0, 2.1, 4.0 and 4.1 are bound to the carbon atoms of said imidazole rings and said optional substituents are independently selected from: $-NHC(O)R^{18}$, $-C(R^{34})_2OR^{35}$, $-OR^{18}$, $-SR^{18}$, F, Cl, Br, alkyl, aryl, arylalkyl, cycloalkyl, or $-N(R^{18})_2$ (wherein each R^{18} is independently selected); R^{18} is as defined above; each R^{34} is independently selected from H or alkyl (preferably $-CH_3$), preferably H; R^{35} is selected from H, $-C(O)OR^{20}$, or $-C(O)NHR^{20}$, and R^{20} is as defined below (preferably R^{20} is alkyl or cycloalkyl, most preferably cyclopentyl or cyclohexyl); Q represents an aryl ring (e.g., phenyl), a cycloalkyl ring (e.g., cyclopentyl or cyclohexyl) or a heteroaryl ring (e.g., furanyl, pyrrolyl, thienyl, oxazolyl or thiazolyl), said Q is optionally substituted with 1

to 4 substituents inedependently selected from halo (e.g., F or Cl), alkyl, aryl, $-OR^{18}$, $-N(R^{18})_2$ (wherein each R^{18} is independently selected), $-OC(O)R^{18}$, or $-C(O)N(R^{18})_2$ (wherein each R^{18} is independently selected), and wherein R^{18} is as defined above;

(examples of the $-C(R^{34})_2OR^{35}$ group include $-CH_2OH$, $-CH_2OC(O)OR^{20}$ and $-CH_2OC(O)NHR^{20}$);

R^{14} is selected from: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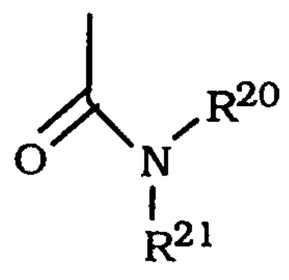
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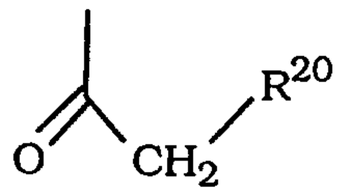
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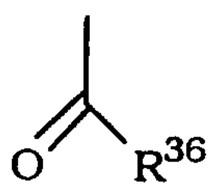
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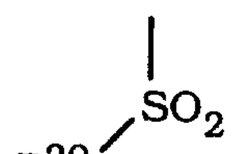
or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R^{15} is selected from: H, alkyl, aryl or arylalkyl;

R^{16} is selected from: alkyl or aryl;

R^{20} is selected from: H, alkyl, alkoxy, aryl, arylalkyl, cycloalkyl, heteroaryl, heteroarylalkyl or heterocycloalkyl, provided that R^{20} is not H when R^{14} is group 5.0 or 8.0;

when R^{20} is other than H, then said R^{20} group is optionally substituted with one or more (e.g., 1-3) substituents selected from: halo, alkyl, aryl, $-OC(O)R^{18}$ (e.g., $-OC(O)CH_3$), $-OR^{18}$ or $-N(R^{18})_2$, wherein each R^{18} group is the same or different, and wherein R^{18} is as defined above, provided that said optional substituent is not bound to a carbon atom that is adjacent to an oxygen or nitrogen atom;

R^{21} is selected from: H, alkyl, aryl, arylalkyl, cycloalkyl, heteroaryl, heteroarylalkyl or heterocycloalkyl;

when R^{21} is other than H, then said R^{21} group is optionally substituted with one or more (e.g., 1-3) substituents selected from: halo, alkyl, aryl, $-OR^{18}$ or $-N(R^{18})_2$, wherein each R^{18} group is the same or different, and wherein R^{18} is as defined above, provided that said optional substituent is not bound to a carbon atom that is adjacent to an oxygen or nitrogen atom;

n is 0-5;

each R^{32} and R^{33} for each n (i.e., for each -C(R^{32})(R^{33})- group), are independently selected from: H, alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl, -CON(R^{18})$_2$, -OR^{18} or -N(R^{18})$_2$; wherein R^{18} is as defined above; and wherein said substitutable R^{32} and R^{33} groups are optionally substituted with one or more (e.g., 1-3) substituents selected from: alkyl (e.g., methyl, ethyl, isopropyl, and the like), cycloalkyl, arylalkyl, or heterarylalkyl; or

R^{32} and R^{33} together with the carbon atom to which they are bound, form a C_3 to C_6 cycloalkyl ring; and

R^{36} is selected from branched alkyl, unbranched alkyl cycloalkyl, heterocycloalkyl, or aryl (e.g., phenyl); and

provided that:

(1) when R^{14} is selected from: group 6.0, 7.0, 7.1 or 8.0, and X is N, then R^8 is selected from: C_3 to C_{10} alkyl, substituted C_3 to C_{10} alkyl, arylalkyl, substituted arylalkyl, heteroarylalkyl, substituted heteroarylalkyl, cycloalkylalkyl, or substituted cycloalkylalkyl; and

(2) when R^{14} is selected from: group 6.0, 7.0, 7.1 or 8.0, and X is N, and R^8 is H, then the alkyl chain between R^{13} (i.e., imidazole ring 2.0, 4.0 or 4.1) and the amide moiety (i.e., the -C(O)NR^{18} group) is substituted, i.e.,: (a) at least one of R^9, R^{10}, R^{11}, R^{12}, R^{32}, or R^{33} is other than H, and/or (b) R^9 and R^{10}, and/or R^{11} and R^{12}, are taken together to form a cycloalkyl ring.

This invention also provides compounds of formula 1.0, as described above, wherein when R^{14} is group 5.0, and X is N, and R^8 is H, then the alkyl chain between R^{13} (i.e., imidazole ring 2.0, 4.0 or 4.1) and the amide moiety (i.e., the -C(O)NR^{18} group) is substituted, i.e.,: (a) at least one of R^9, R^{10}, R^{11}, R^{12}, R^{32}, or R^{33} is other than H, and/or (b) R^9 and R^{10}, and/or R^{11} and R^{12}, are taken together to form a cyloalkyl ring.

The compounds of this invention: (i) potently inhibit farnesyl protein transferase, but not geranylgeranyl protein transferase I, in

vitro; (ii) block the phenotypic change induced by a form of transforming Ras which is a farnesyl acceptor but not by a form of transforming Ras engineered to be a geranylgeranyl acceptor; (iii) block intracellular processing of Ras which is a farnesyl acceptor but not of Ras engineered to be a geranylgeranyl acceptor; and (iv) block abnormal cell growth in culture induced by transforming Ras.

The compounds of this invention inhibit farnesyl protein transferase and the farnesylation of the oncogene protein Ras. Thus, this invention further provides a method of inhibiting farnesyl protein transferase, (e.g., ras farnesyl protein transferase) in mammals, especially humans, by the administration of an effective amount of the tricyclic compounds described above. The administration of the compounds of this invention to patients, to inhibit farnesyl protein transferase, is useful in the treatment of the cancers described below.

This invention provides a method for inhibiting or treating the abnormal growth of cells, including transformed cells, by administering an effective amount of a compound of this invention. Abnormal growth of cells refers to cell growth independent of normal regulatory mechanisms (e.g., loss of contact inhibition). This includes the abnormal growth of: (1) tumor cells (tumors) expressing an activated Ras oncogene; (2) tumor cells in which the Ras protein is activated as a result of oncogenic mutation in another gene; and (3) benign and malignant cells of other proliferative diseases in which aberrant Ras activation occurs.

This invention also provides a method for inhibiting or treating tumor growth by administering an effective amount of the tricyclic compounds, described herein, to a mammal (e.g., a human) in need of such treatment. In particular, this invention provides a method for inhibiting or treating the growth of tumors expressing an activated Ras oncogene by the administration of an effective amount of the above described compounds. Examples of tumors which may be inhibited or treated include, but are not limited to, lung cancer

(e.g., lung adenocarcinoma), pancreatic cancers (e.g., pancreatic carcinoma such as, for example, exocrine pancreatic carcinoma), colon cancers (e.g., colorectal carcinomas, such as, for example, colon adenocarcinoma and colon adenoma), myeloid leukemias (for example, acute myelogenous leukemia (AML)), thyroid follicular cancer, myelodysplastic syndrome (MDS), bladder carcinoma, epidermal carcinoma, melanoma, breast cancer and prostate cancer.

It is believed that this invention also provides a method for inhibiting or treating proliferative diseases, both benign and malignant, wherein Ras proteins are aberrantly activated as a result of oncogenic mutation in other genes--i.e., the Ras gene itself is not activated by mutation to an oncogenic form--with said inhibition or treatment being accomplished by the administration of an effective amount of the tricyclic compounds described herein, to a mammal (e.g., a human) in need of such treatment. For example, the benign proliferative disorder neurofibromatosis, or tumors in which Ras is activated due to mutation or overexpression of tyrosine kinase oncogenes (e.g., neu, src, abl, lck, and fyn), may be inhibited or treated by the tricyclic compounds described herein.

The tricyclic compounds useful in the methods of this invention inhibit or treat the abnormal growth of cells. Without wishing to be bound by theory, it is believed that these compounds may function through the inhibition of G-protein function, such as ras p21, by blocking G-protein isoprenylation, thus making them useful in the treatment of proliferative diseases such as tumor growth and cancer. Without wishing to be bound by theory, it is believed that these compounds inhibit ras farnesyl protein transferase, and thus show antiproliferative activity against ras transformed cells.

DETAILED DESCRIPTION OF THE INVENTION

As used herein, the following terms are used as defined below unless otherwise indicated:

MH^+-represents the molecular ion plus hydrogen of the molecule in the mass spectrum;

BOC-represents tert-butyloxycarbonyl;

CBZ-represents $-C(O)OCH_2C_6H_5$ (i.e., benzyloxycarbonyl);

CH_2Cl_2-represents dichloromethane;

CIMS-represents chemical ionization mass spectrum;

DEAD-represents diethylazodicarboxylate;

DEC-represents EDCI which represents 1-(3-dimethyl-aminopropyl)-3-ethylcarbodiimide hydrochloride;

DMF-represents N,N-dimethylformamide;

Et-represents ethyl;

EtOAc-represents ethyl acetate;

EtOH-represents ethanol;

HOBT-represents 1-hydroxybenzotriazole hydrate;

IPA-represents isopropanol;

iPrOH-represents isopropanol;

Me-represents methyl;

MeOH-represents methanol;

MS-represents mass spectroscopy;

NMM-represents N-methylmorpholine;

Ph-represents phenyl;

Pr-represents propyl;

TBDMS-represents tert-butyldimethylsilyl;

TEA-represents triethylamine;

TFA-represents trifluoroacetic acid;

THF-represents tetrahydrofuran;

Tr-represents trityl;

alkyl-represents straight and branched carbon chains and contains from one to twenty carbon atoms, preferably one to six carbon atoms;

acyl-represents a G-C(O)- group wherein G represents alkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, -O-alkyl, -O-aryl, or $NR^{25}R^{26}$ wherein R^{25} and R^{26} are independently selected from alkyl or aryl;

arylalkyl-represents an alkyl group, as defined above, substituted with an aryl group, as defined below, such that the bond from another substituent is to the alkyl moiety;

aryl-(including the aryl portion of arylalkyl)-represents a carbocyclic group containing from 6 to 15 carbon atoms and having at least one aromatic ring (e.g., aryl is a phenyl ring), with all available substitutable carbon atoms of the carbocyclic group being intended as possible points of attachment, said carbocyclic group being optionally substituted (e.g., 1 to 3) with one or more of halo, alkyl, hydroxy, alkoxy, phenoxy, CF_3, $-C(O)N(R^{18})_2$, $-SO_2R^{18}$, $-SO_2N(R^{18})_2$, amino, alkylamino, dialkylamino, $-COOR^{23}$ or $-NO_2$, wherein R^{23} represents alkyl or aryl; and

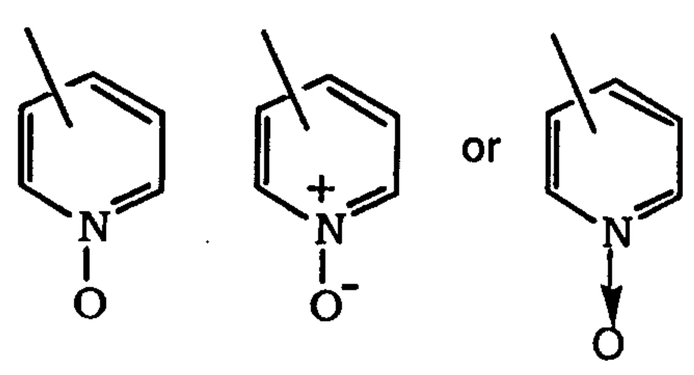
cycloalkyl-represents saturated carbocyclic rings of from 3 to 20 carbon atoms, preferably 3 to 7 carbon atoms, said cycloalkyl ring being optionally substituted with one or more (e.g., 1, 2 or 3) alkyl groups (e.g., methyl or ethyl) and when there is more than one alkyl group each alkyl group is independently selected;

cycloalkylalkyl-represents a cycloalkyl group, as defined above, substituted with an alkyl group, as defined above, such that the bond from another substituent is to the alkyl moiety;

halo-represents fluoro, chloro, bromo and iodo;

heteroaralkyl-represents an alkyl group, as defined above, substituted with a heteroaryl group, as defined below, such that the bond from another substituent is to the alkyl moiety;

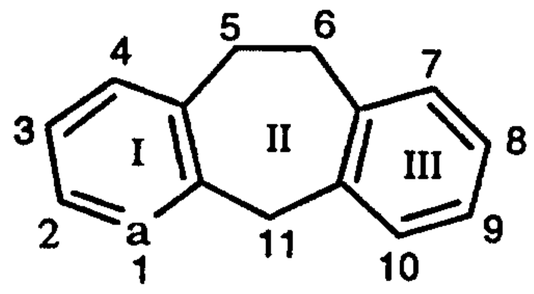
heteroaryl-represents cyclic groups, optionally substituted with R^3 and R^4, having at least one heteroatom selected from O, S or N, said heteroatom interrupting a carbocyclic ring structure and having a sufficient number of delocalized pi electrons to provide aromatic character, with the aromatic heterocyclic groups preferably containing from 2 to 14 carbon atoms, e.g., 2- or 3-furyl, 2- or 3-thienyl, 2-, 4- or 5-thiazolyl, 2-, 4- or 5-imidazolyl, 2-, 4- or 5-pyrimidinyl, 2-pyrazinyl, 3- or 4-pyridazinyl, 3-, 5- or 6-[1,2,4-triazinyl], 3- or 5-[1,2,4-thiadizolyl], 2-, 3-, 4-, 5-, 6- or 7-benzofuranyl, 2-, 3-, 4-, 5-, 6- or 7-indolyl, 3-, 4- or 5-pyrazolyl, 2-, 4- or 5-oxazolyl, triazolyl,2-, 3- or 4-pyridyl or pyridyl N-oxide (optionally substituted with R^3 and R^4), wherein pyridyl N-oxide can be represented as:



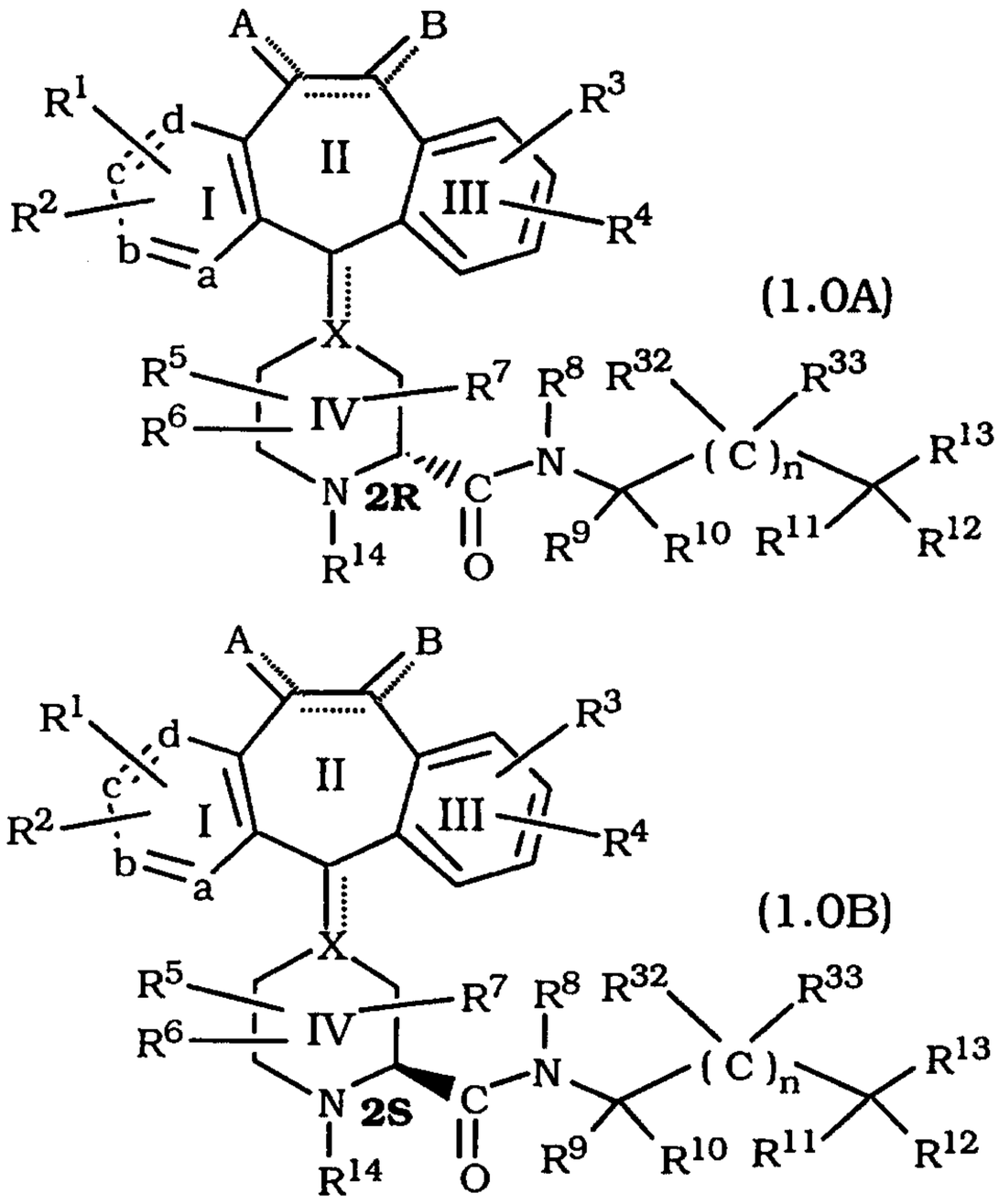
; and

heterocycloalkyl-represents a saturated, branched or unbranched carbocylic ring containing from 3 to 15 carbon atoms, preferably from 4 to 6 carbon atoms, which carbocyclic ring is interrupted by 1 to 3 hetero groups selected from -O-, -S- or - NR^{24}, wherein R^{24} represents alkyl, aryl, $-C(O)N(R^{18})_2$ wherein R^{18} is as above defined (e.g., $-C(O)NH_2$) or acyl-(suitable heterocycloalkyl groups include 2- or 3-tetrahydrofuranyl, 2- or 3- tetrahydrothienyl, 2-, 3- or 4-piperidinyl, 2- or 3-pyrrolidinyl, 2- or 3-piperizinyl, 2- or 4-dioxanyl, morpholinyl, etc.).

The positions in the tricyclic ring system are:



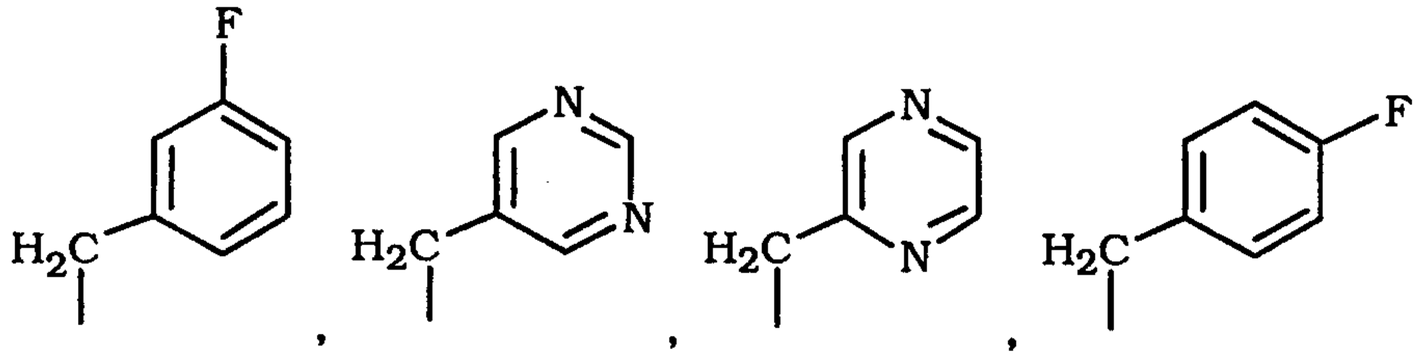
The compounds of formula 1.0 include the 2R and 2S isomers shown below (2R is preferred):



(1.0A)

(1.0B)

Examples of R^8 substituents include: benzyl, $-CH_2C(CH_3)_2$, $-CH_2$-cyclohexyl, $-CH_2$-cyclopropyl, $-(CH_2)_2CH_3$,



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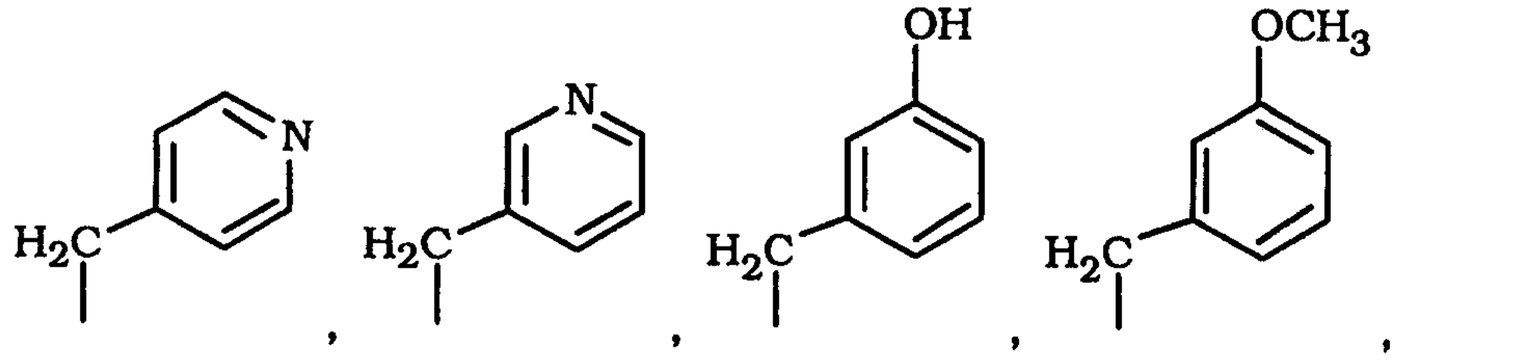

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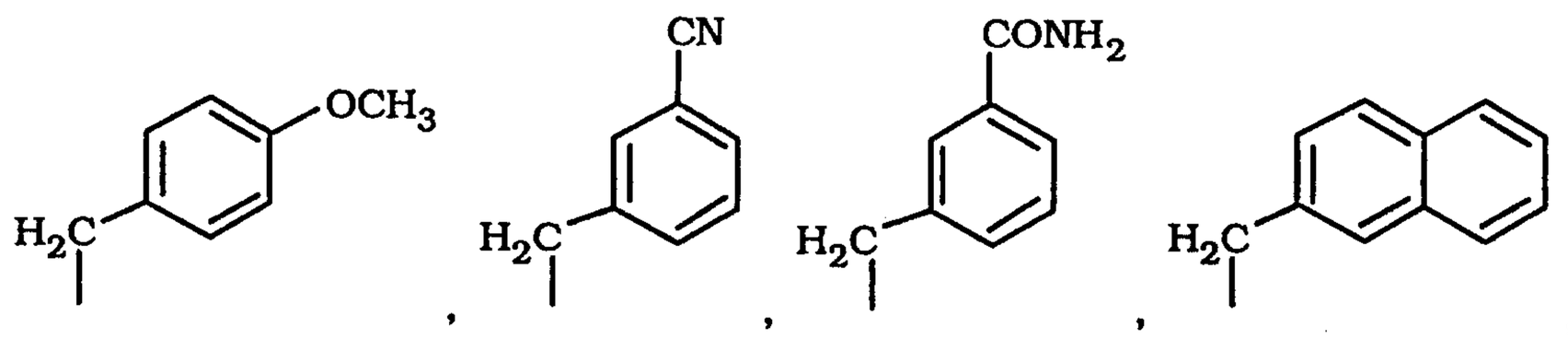

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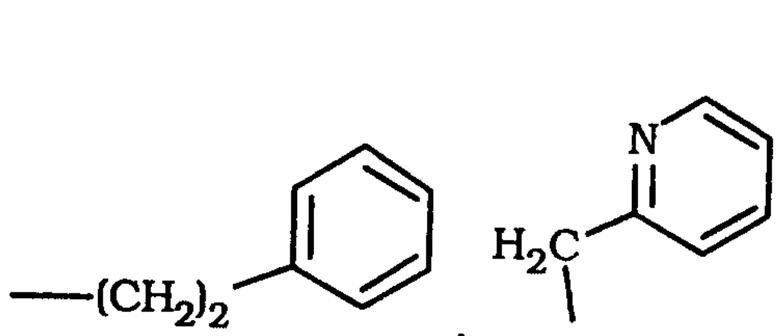
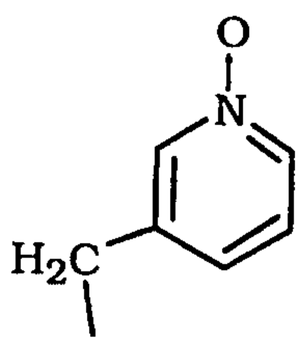




Examples of R^9 and R^{10} groups include H and benzyl

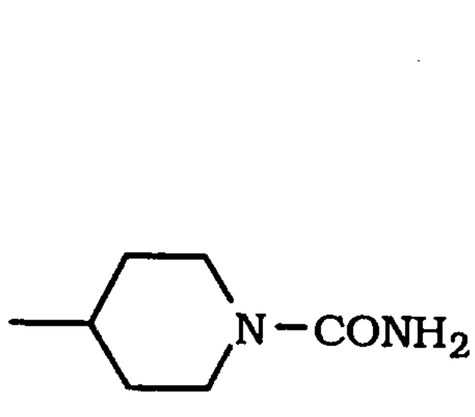
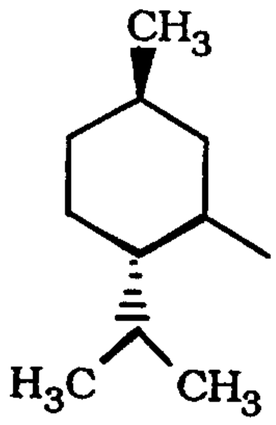
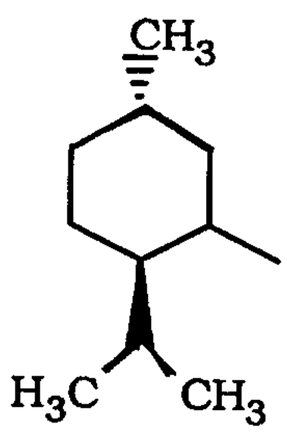
Examples of R^{11} and R^{12} groups include: H, $-CH_3$, $-CH_2CH(CH_3)_2$, $-(CH_2)_3CH_3$, benzyl, ethyl, p-chlorophenyl, and -OH.

Cyclopropyl is an Example of the R^{11} and R^{12} group being taken together with the carbon atom to which they are bound to form a cycloalkyl ring.

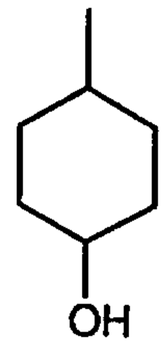
Examples of the optional substituents for the R^{13} moiety include: $-CH_3$, $-CH_2OH$, $-CH_2OC(O)O$-cyclohexyl, $-CH_2OC(O)O$-cyclopentyl, ethyl, isopropyl, NH_2, and $-NHC(O)CF_3$.

Examples of R^{19} include: -C(O)NH-cyclohexyl, $-C(phenyl)_3$, H, methyl or ethyl.

Examples of R^{20} for group 5.0 include: t-butyl, ethyl, benzyl, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$, $-(CH_2)_2CH_3$, n-butyl, n-hexyl, n-octyl, p-chlorophenyl, cyclohexyl, cyclopentyl,

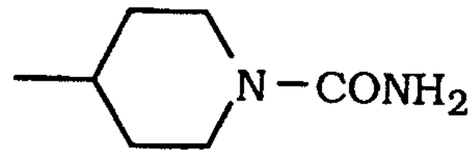
Another example of R^{20} for group 5.0 is



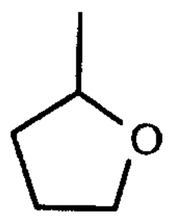
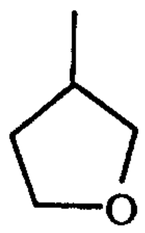
Examples of R^{20} and R^{21} for 6.0 include: cyclohexyl, t-butyl, H, $-CH(CH_3)_2$, ethyl, $-(CH_2)_2CH_3$, phenyl, benzyl, $-(CH_2)_2$phenyl, and $-CH_3$.

Examples of R^{20} for 7.0 include: 4-pyridylNO, $-OCH_3$,

-$CH(CH_3)_2$, -t-butyl, H, propyl, cyclohexyl and



Examples for R^{36} for 7.1 include: cyclohexyl, cyclopentyl, cyclobutyl, cyclopropyl,

 and  .

Examples for R^{20} for 8.0 include: methyl, i-propyl and cyclohexylmethyl.

Examples of R^{32} and R^{33} include: H, phenyl, -OH and benzyl.

Compounds of this invention include compounds of formula 1.0 wherein when R^{14} is selected from: group 6.0, 7.0, 7.1 or 8.0, and X is C or CH (preferably CH), then R^8 is selected from: C_3 to C_{10} alkyl, substituted C_3 to C_{10} alkyl, arylalkyl, substituted arylalkyl, heteroarylalkyl, substituted heteroarylalkyl, cycloalkylalkyl, or substituted cycloalkylalkyl.

Compounds of this invention include compounds of formula 1.0 wherein when R^{14} is selected from: group 6.0, 7.0, 7.1 or 8.0, and X is C or CH (preferably CH), and R^8 is H, then the alkyl chain between R^{13} (i.e., imidazole ring 2.0, 4.0 or 4.1) and the amide moiety (i.e., the -C(O)NR^{18} group) is substituted, i.e.,: (a) at least one of R^9, R^{10}, R^{11}, R^{12}, R^{32}, or R^{33} is other than H, and/or (b) R^9 and R^{10}, and/or R^{11} and R^{12}, are taken together to form a cyloalkyl ring.

Compounds of this invention include compounds of formula 1.0 wherein when R^{14} is group 5.0, and X is C or CH (preferably CH), and R^8 is H, then the alkyl chain between R^{13} (i.e., imidazole ring 2.0, 4.0 or 4.1) and the amide moiety (i.e., the -C(O)NR^{18} group) is substituted, i.e.,: (a) at least one of R^9, R^{10}, R^{11}, R^{12}, R^{32}, or R^{33} is other than H; and/or (b) R^9 and R^{10}, and/or R^{11} and R^{12}, are taken together to form a cyloalkyl ring.

Compounds of this invention include compounds of formula 1.0 wherein when R^{14} is selected from: group 6.0, 7.0, 7.1 or 8.0, and X is C or CH (preferably CH), then R^8 is selected from: arylalkyl, substituted arylalkyl, heteroarylalkyl, substituted heteroarylalkyl, cycloalkylalkyl, or substituted cycloalkylalkyl.

Compounds of this invention include compounds of formula 1.0 wherein when R^{14} is 5.0 and X is C or CH (preferably CH), then R^8 is selected from: arylalkyl, substituted arylalkyl, heteroarylalkyl, substituted heteroarylalkyl, cycloalkylalkyl, or substituted cycloalkylalkyl.

Compounds of this invention include compounds of formula 1.0 wherein when R^{14} is selected from: group 6.0, 7.0, 7.1 or 8.0, and X is N, then R^8 is selected from: arylalkyl, substituted arylalkyl, heteroarylalkyl, substituted heteroarylalkyl, cycloalkylalkyl, or substituted cycloalkylalkyl.

Compounds of this invention include compounds of formula 1.0 wherein when R^{14} is 5.0 and X is N, then R^8 is selected from: arylalkyl, substituted arylalkyl, heteroarylalkyl, substituted heteroarylalkyl, cycloalkylalkyl, or substituted cycloalkylalkyl.

Thus, one embodiment of this invention is directed to compounds wherein R^{14} is the carbamate group 5.0 and the other substituents are as defined for formula 1.0.

Another embodiment of this invention is directed to compounds wherein R^{14} is the carbamate group 5.0, X is N and the other substituents are as defined for formula 1.0.

Another embodiment of this invention is directed to compounds wherein R^{14} is the carbamate group 5.0, X is C or CH (preferably CH) and the other substituents are as defined for formula 1.0.

Another embodiment of this invention is directed to compounds wherein R^{14} is the carbamate group 5.0, X is N, R^8 is arylalkyl or substituted arylalkyl (preferably arylalkyl), and the other substituents are as defined for formula 1.0.

Another embodiment of this invention is directed to compounds wherein R^{14} is the carbamate group 5.0, X is N, R^8 is heteroarylalkyl or substituted heteroarylalkyl (preferably heteroarylalkyl), and the other substituents are as defined for formula 1.0.

Another embodiment of this invention is directed to compounds wherein R^{14} is the carbamate group 5.0, X is N, R^8 is cycloalkylalkyl or substituted cycloalkylalkyl (preferably cycloalkylalkyl), and the other substituents are as defined for formula 1.0.

Another embodiment of this invention is directed to compounds wherein R^{14} is the carbamate group 5.0, X is C or CH (preferably CH), R^8 is arylalkyl or substituted arylalkyl (preferably arylalkyl), and the other substituents are as defined for formula 1.0.

Another embodiment of this invention is directed to compounds wherein R^{14} is the carbamate group 5.0, X is C or CH (preferably CH), R^8 is heteroarylalkyl or substituted heteroarylalkyl (preferably heteroarylalkyl), and the other substituents are as defined for formula 1.0.

Another embodiment of this invention is directed to compounds wherein R^{14} is the carbamate group 5.0, X is C or CH (preferably CH), R^8 is cycloalkylalkyl or substituted cycloalkylalkyl (preferably cycloalkylalkyl), and the other substituents are as defined for formula 1.0.

Another embodiment of this invention is directed to compounds wherein when R^{14} is group 5.0, and X is C or CH (preferably CH), and R^8 is H, then the alkyl chain between R^{13} (i.e., imidazole ring 2.0, 4.0 or 4.1) and the amide moiety (i.e., the -C(O)NR^{18} group) is substituted, i.e.,: (a) at least one of R^9, R^{10}, R^{11}, R^{12}, R^{32}, or R^{33} is other than H, and/or (b) R^9 and R^{10}, and/or R^{11} and R^{12}, are taken together to form a cyloalkyl ring, and the other substituents are as defined for formula 1.0.

Another embodiment of this invention is directed to compounds wherein when R^{14} is group 5.0, and X is N, and R^8 is H, then the alkyl chain between R^{13} (i.e., imidazole ring 2.0, 4.0 or 4.1) and the amide moiety (i.e., the -C(O)NR^{18} group) is substituted, i.e.,: (a) at least one of R^9, R^{10}, R^{11}, R^{12}, R^{32}, or R^{33} is other than H, and/or (b) R^9 and R^{10}, and/or R^{11} and R^{12}, are taken together to form a cyloalkyl ring, and the other substituents are as defined for formula 1.0.

Another embodiment of this invention is directed to compounds wherein R^{14} is a group selected from: 6.0, 7.0, 7.1 or 8.0, X is N, R^8 is arylalkyl or substituted arylalkyl (preferably arylalkyl) and the other substituents are as defined for formula 1.0.

Another embodiment of this invention is directed to compounds wherein R^{14} is a group selected from: 6.0, 7.0, 7.1 or 8.0, X is N, R^8 is heteroarylalkyl or substituted heteroarylalkyl (preferably heteroarylalkyl) and the other substituents are as defined for formula 1.0.

Another embodiment of this invention is directed to compounds wherein R^{14} is a group selected from: 6.0, 7.0, 7.1 or 8.0, X is N, R^8 is cycloalkylalkyl or substituted cycloalkylalkyl (preferably, cycloalkylalkyl) and the other substituents are as defined for formula 1.0.

Another embodiment of this invention is directed to compounds wherein R^{14} is a group selected from:6.0, 7.0, 7.1 or 8.0, X is C or CH (preferably, CH), R^8 is arylalkyl or substituted arylalkyl (preferably arylalkyl) and the other substituents are as defined for formula 1.0.

Another embodiment of this invention is directed to compounds wherein R^{14} is a group selected from: 6.0, 7.0, 7.1 or 8.0, X is C or CH (preferably, CH), R^8 is heteroarylalkyl or substituted heteroarylalkyl (preferably, heteroarylalkyl) and the other substituents are as defined for formula 1.0.

Another embodiment of this invention is directed to compounds wherein R^{14} is a group selected from: 6.0, 7.0, 7.1 or 8.0, X is C or CH (preferably, CH), R^8 is cycloalkylalkyl or substituted cycloalkylalkyl (preferably, cycloalkylalkyl) and the other substituents are as defined for formula 1.0.

R^1, R^2, R^3, and R^4 are preferably selected from H or halo, and are more preferably selected from H, Br, F, or Cl, and are most preferably selected from H, Br or Cl. Representative compounds of formula 1.0 include trihalo, dihalo and monohalo substituted compounds, such as, for example: (1) 3,8,10-trihalo; (2) 3,7,8-trihalo; (3) 3,8-dihalo; (4) 8-halo; and (5) 10-halo substituted compounds; wherein each halo is independently selected. Preferred compounds of formula 1.0 include: (1) 3-Br,8-Cl,10-Br-substituted compounds; (2) 3-Br,7-Br,8-Cl-substituted compounds; (3) 3-Br,8-Cl-substituted compounds; (4) 8-Cl-substituted compounds; and (5) 10-Cl-substituted compounds. The 3,8-dihalo compounds are more preferred and the 8-halo compounds are most preferred. Thus, for example, 3-Br,8-Cl substituted compounds are more preferred and 8-Cl substituted compounds are most preferred.

Substituent a is preferably N or N^+O^- with N being preferred.

A and B are preferably H_2, i.e., the optional bond is absent and the C5-C6 bridge is unsubstituted.

R^5, R^6, and R^7 are preferably H.

X is preferably N or CH (i.e., the optional bond is absent), and more preferably X is N.

R^8 is preferably selected from: arylalkyl, substituted aryl alkyl, heteroarylalkyl, substituted heteroarylalkyl, cycloalkylalkyl or substituted cycloalkylalkyl. Most preferably, R^8 is selected from: aryl-(C_1-C_4)alkyl, substituted aryl-(C_1-C_4)alkyl, heteroaryl-(C_1-C_4)alkyl, substituted heteroaryl-(C_1-C_4)alkyl, cycloalkyl-(C_1-C_4)alkyl, or substituted cycloalkyl-(C_1-C_4)alkyl. More preferably, R^8 is selected from: aryl-CH_2-, substituted aryl-CH_2-, heteroaryl-CH_2-, substituted heteroaryl-CH_2, cycloalkyl-CH_2- or substituted

cycloalkyl-CH_2-. Even more preferably, R^8 is selected from: benzyl, 3-pyridylmethyl, 4-fluoro-benzyl or cyclopropylmethyl, and still more preferably R^8 is benzyl.

R^{13} is preferably ring 2.0 or 4.0. When substituted on the substitutable carbon atoms of the imidazole ring, the substituents are generally selected from: $-N(R^{18})_2$, $-NHC(O)R^{18}$, $-C(R^{34})_2OR^{35}$, or alkyl, e.g., $-CH_3$, $-CH_2OH$, $-CH_2OC(O)O$-cyclohexyl, $-CH_2OC(O)O$-cyclopentyl, ethyl, isopropyl, NH_2, or $-NHC(O)CF_3$.

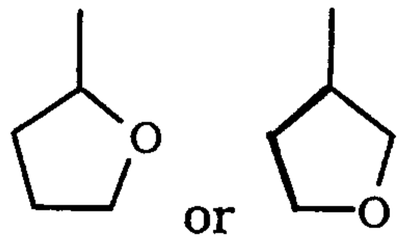
R^{19} is preferably H or alkyl, most preferably H, methyl or ethyl, and more preferably methyl.

R^{14} is preferably a carbamate group represented by substituent 5.0 described above. Preferably, R^{20} for substituent 5.0 is selected from: alkyl, substituted alkyl, aryl, cycloalkyl, or cycloalkyl substituted with -OH provided that said -OH substituent is not bound to a carbon that is adjacent to an oxygen atom. More preferably R^{20} for substituent 5.0 is selected from: C_1 to C_4 alkyl and C_5 to C_7 cycloalkyl. Most preferably R^{20} for substituent 5.0 is selected from: t-butyl, i-propyl and cyclohexyl, with i-propyl and cyclohexyl being more preferred, and with cyclohexyl being even more preferred.

R^{20} in substituent 6.0 is preferably selected from: alkyl or cycloalkyl; most preferably t-butyl, isopropyl or cyclohexyl; and more preferably cyclohexyl. R^{21} is preferably selected from: H or alkyl; most preferably H, methyl or isopropyl; and more preferably H.

R^{20} in substituent 7.0 is preferably selected from: cycloalkyl or alkyl; most preferably cyclohexyl, cyclopentyl, isopropyl; and more preferably cyclohexyl.

R^{36} in substituent 7.1 is preferably selected from: phenyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl,



and most preferably selected from: cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

R^{20} in substituent 8.0 is preferably selected from: alkyl or cycloalkylalkyl; most preferably methyl, isopropyl or cyclohexylmethyl; more preferably methyl or isopropyl; and even more preferably methyl.

R^9, R^{10}, R^{11}, and R^{12} are preferably selected from: H, C_1 to C_4 alkyl (e.g., methyl or isopropyl), $-CON(R^{18})_2$ (e.g., $-CONH_2$), or when R^9 and R^{10}, and/or R^{11} and R^{12} are taken together to form a cycloalkyl ring, said ring is preferably cyclopropyl cyclopentyl or cyclohexyl.

R^9, R^{10}, R^{11}, and R^{12} are preferably H when R^{14} is the carbamate substituent 5.0 and R^8 is not H.

When R^{14} is selected from substituents 6.0, 7.0, 7.1 and 8.0, and at least one of R^9, R^{10}, R^{11}, and R^{12} is other than H, then at least one of R^9, R^{10}, R^{11}, and R^{12} is:

(I) preferably selected from: (1) C_1 to C_4 alkyl, (2) $-CON(R^{18})_2$ or (3) the cycloalkyl ring formed when R^9 and R^{10}, and/or R^{11} and R^{12}, are taken together along with the carbon atom to which they are bound;

(II) most preferably selected from: (1) methyl, (2) isopropyl, (3) $-CONH_2$ or (4) cyclopropyl; and

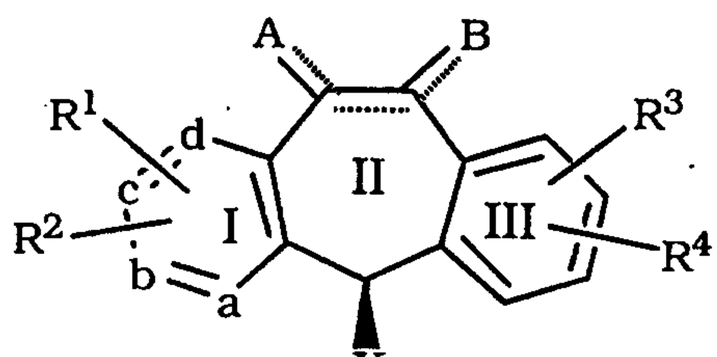
(III) more preferably selected from: (1) R^9 and R^{10} being H, and one of R^{11} and R^{12} being selected from: alkyl (preferably, methyl or isopropyl), and the other being selected from H or alkyl (preferably, methyl); (2) R^9 and R^{10} being H, and R^{11} and R^{12} being taken together to form a cycloalkyl ring (preferably, cyclopropyl); or (3) R^{11} and R^{12} being H, and one of R^9 and R^{10} being $-CONH_2$, and the other being H.

Preferred compounds, when at least one of R^9, R^{10}, R^{11}, and R^{12} is other than H, also include compounds wherein: R^9 and R^{10} are H, and R^{11} and R^{12} are the same or different alkyl, preferably the same, wherein said alkyl is more preferably methyl.

For compounds of the invention, n is preferably 0-4, more preferably 0-2, and most preferably 0 or 1.

Preferably, each R^{32} and R^{33} are independently selected from: H, $-OR^{18}$, aryl or arylalkyl (e.g., benzyl); most preferably H, -OH or phenyl; and more preferably H.

Compounds of formula 1.0, wherein X is N or CH, include, with reference to the C-11 bond, the R- and S- isomers:



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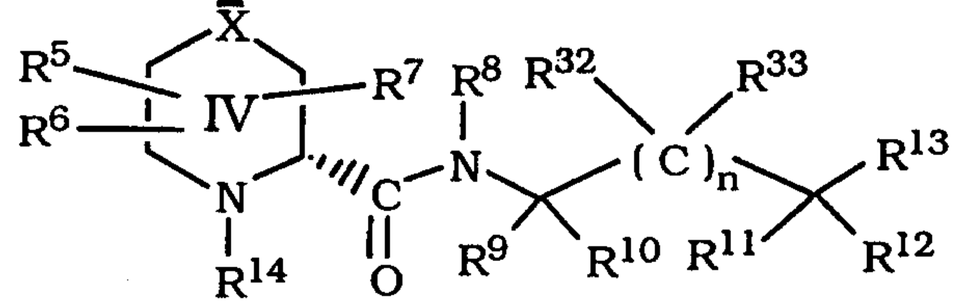
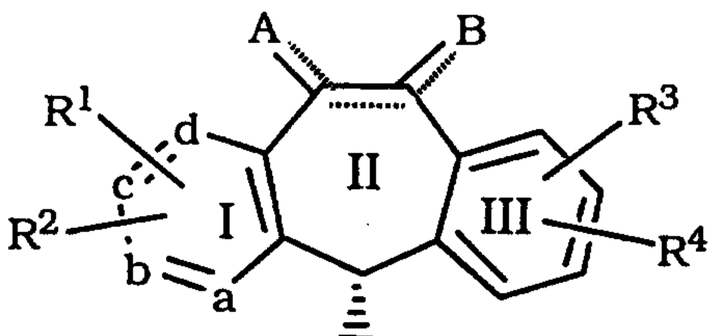
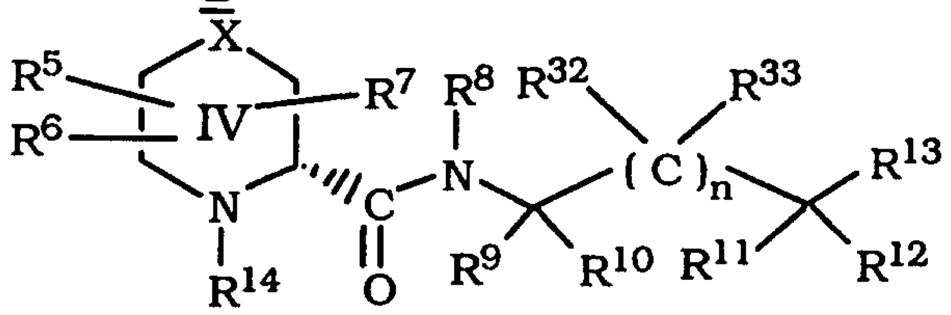




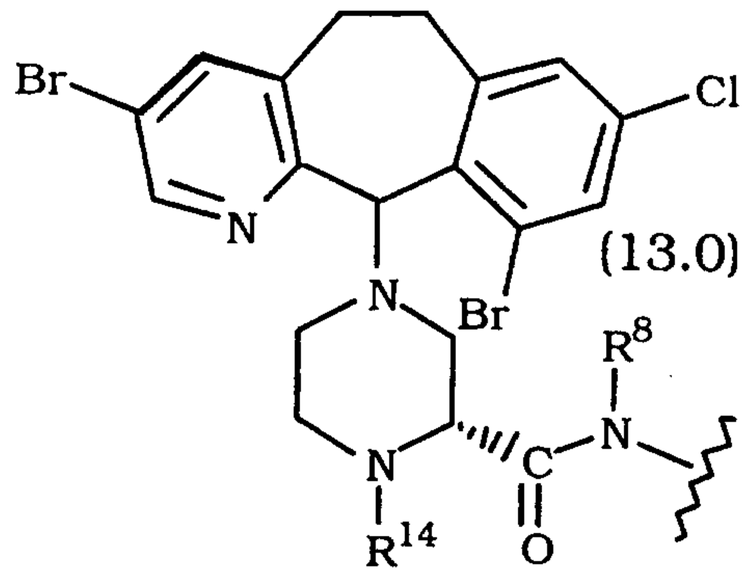
(10.0)

(S)

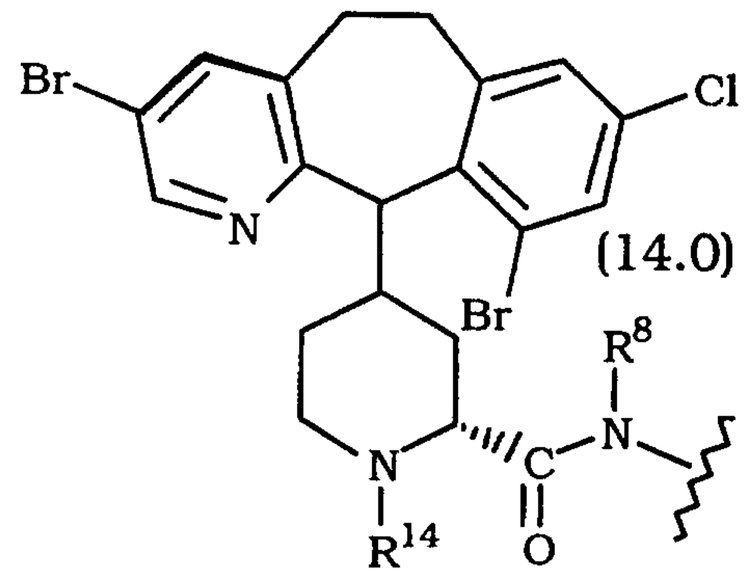


Compounds of formula 1.0 also include compounds having the 2S stereochemistry and the C-11 R- or C-11 S- stereochemistry.

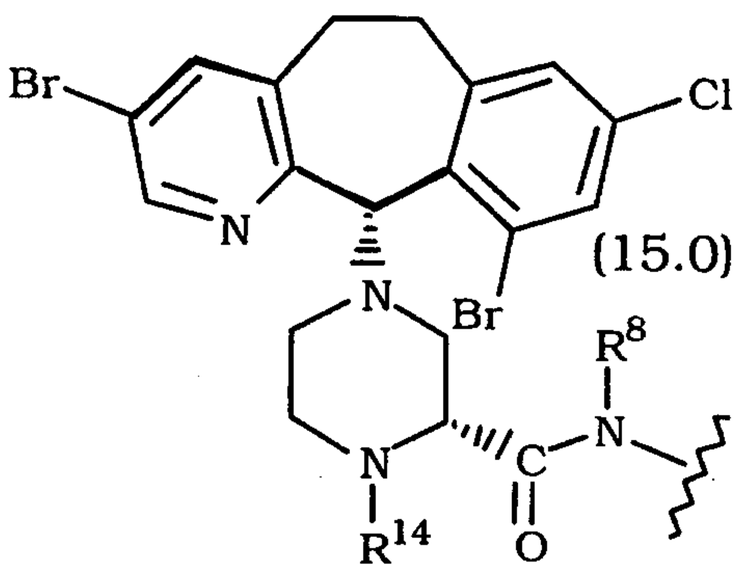
Compounds of this invention include:



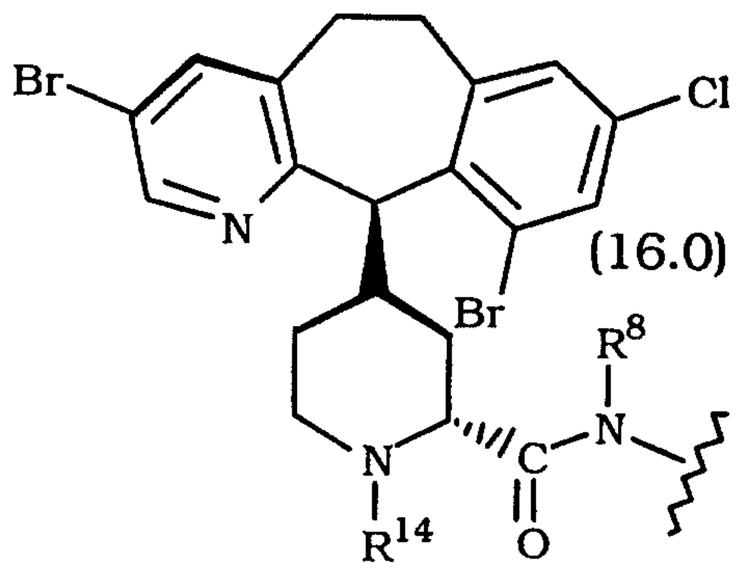
(13.0)



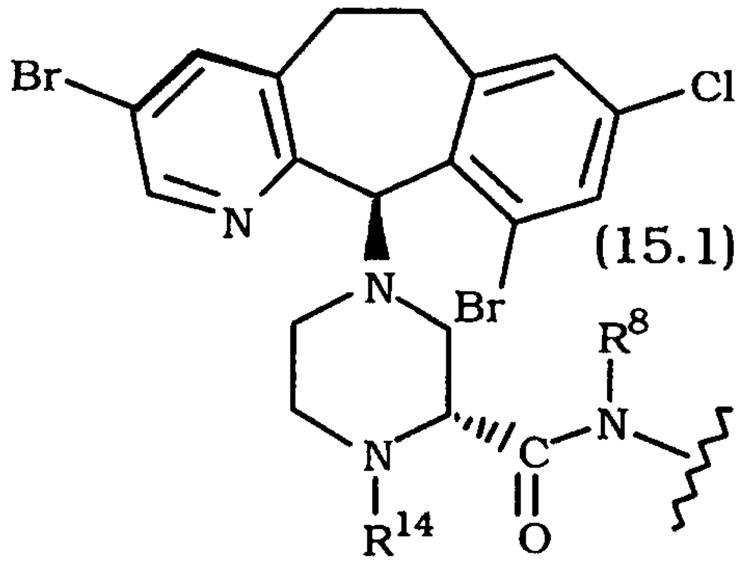
(14.0)



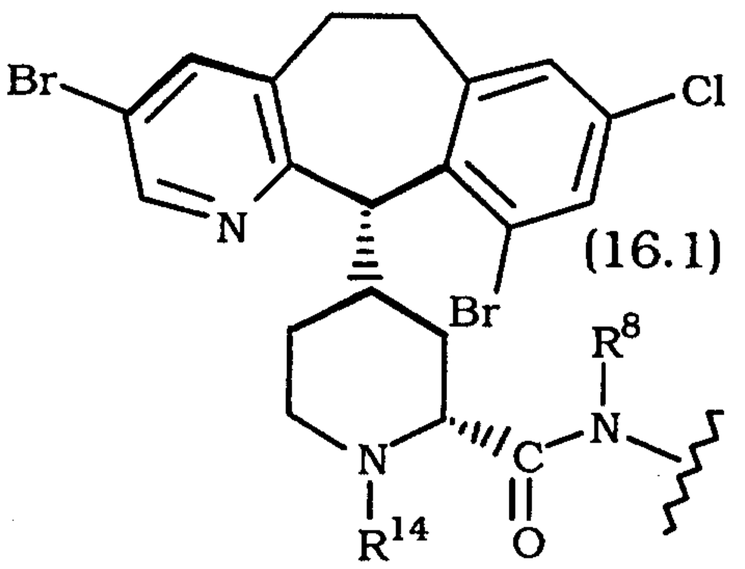
(15.0)



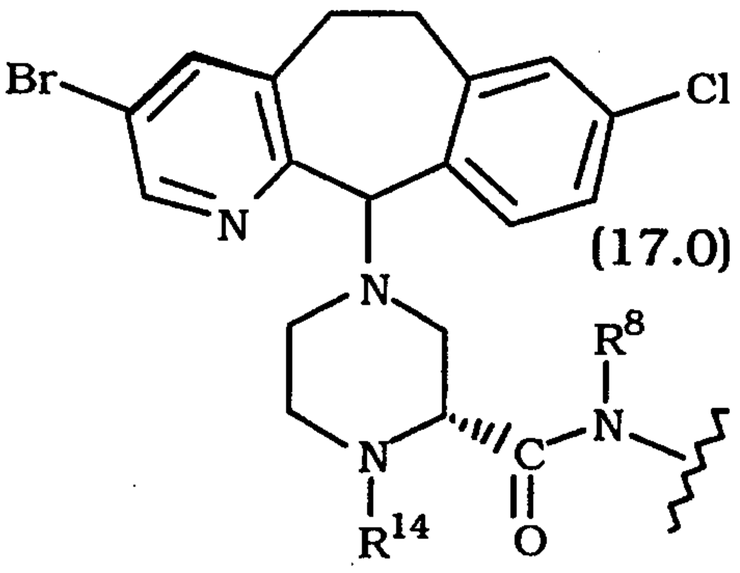
(16.0)



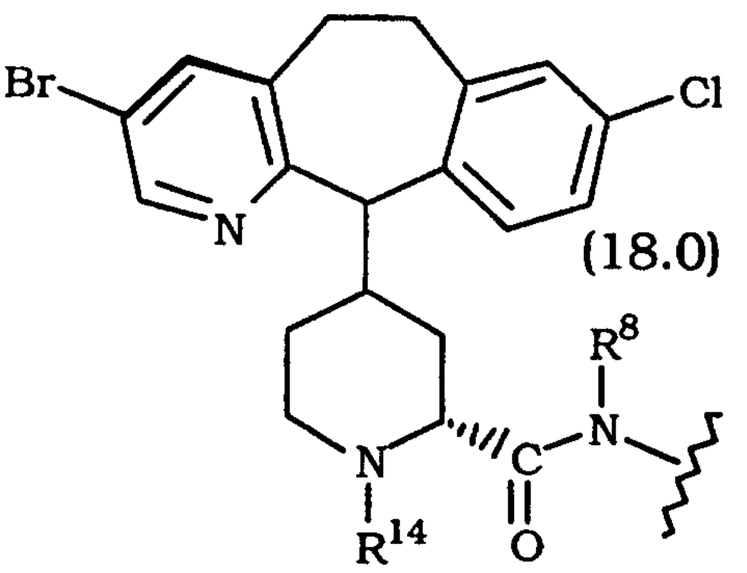
(15.1)



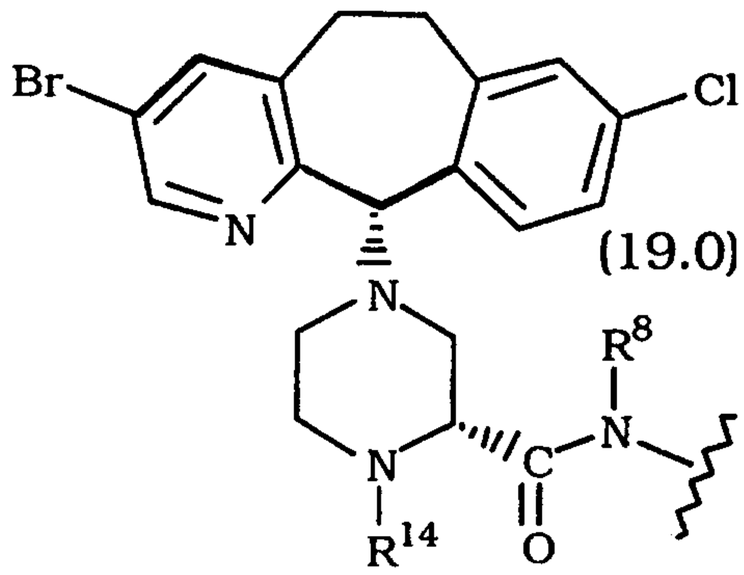
(16.1)



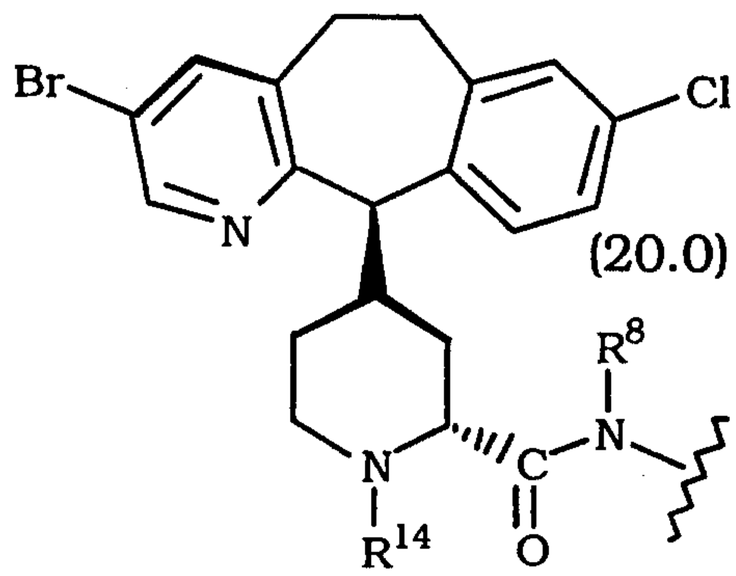
(17.0)



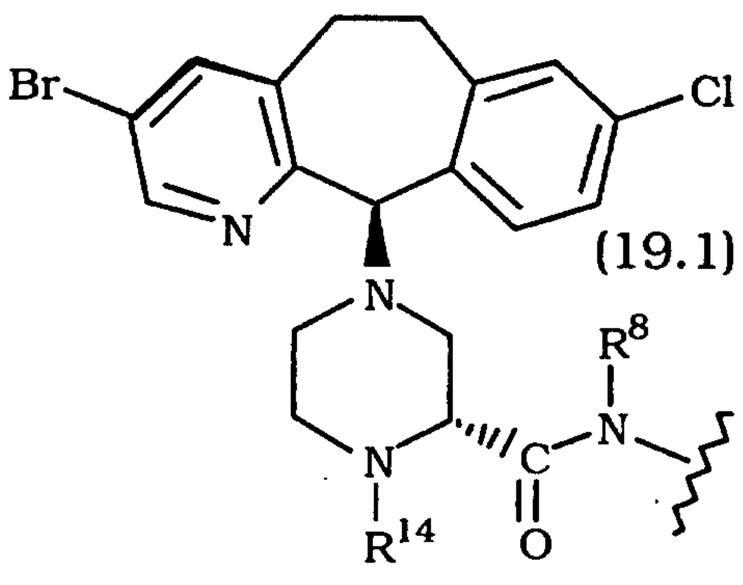
(18.0)



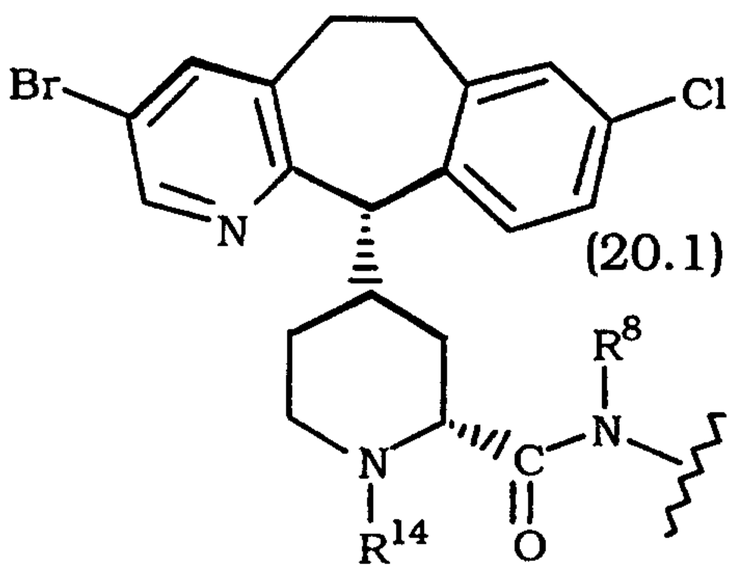
(19.0)



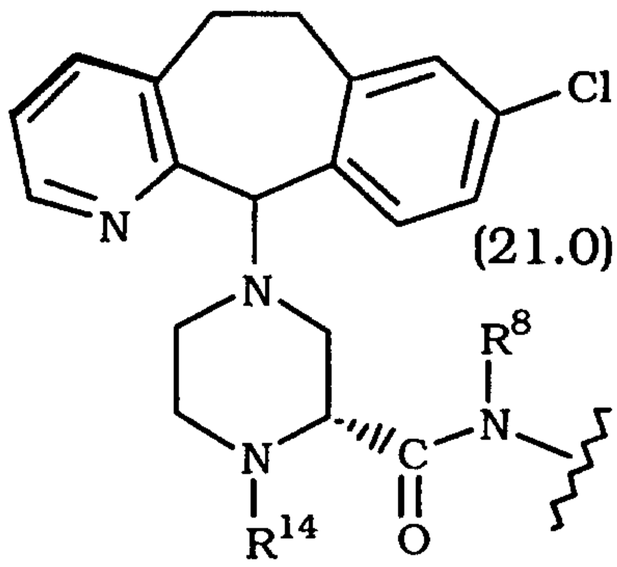
(20.0)



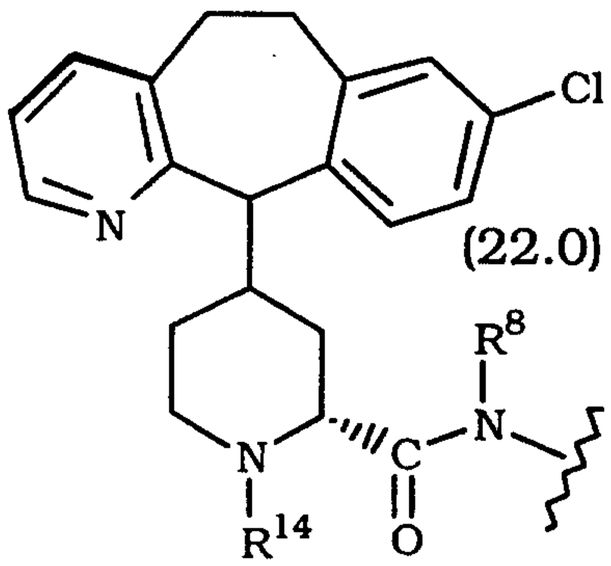
(19.1)



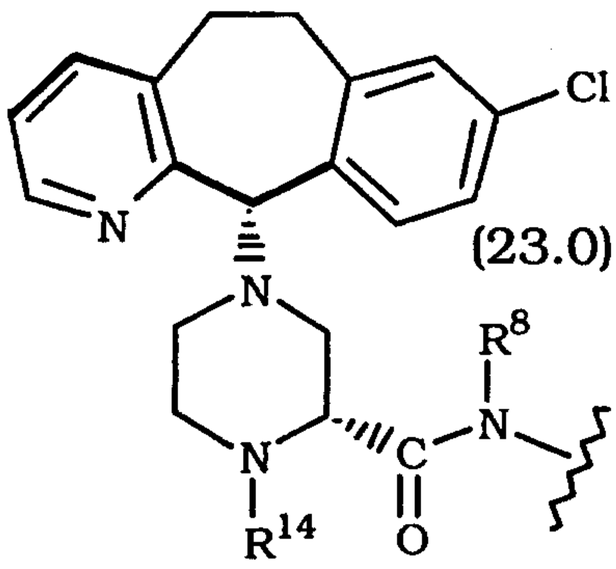
(20.1)



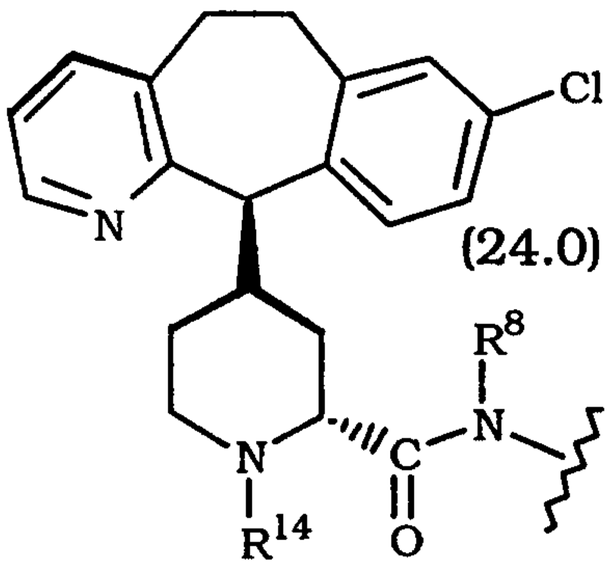
(21.0)



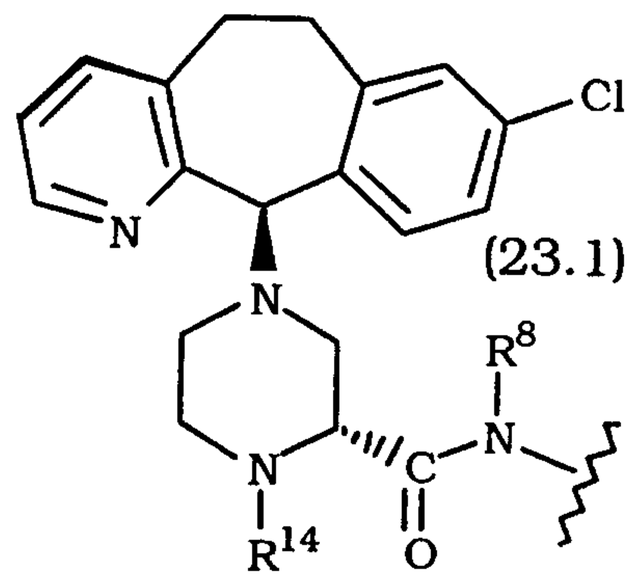
(22.0)

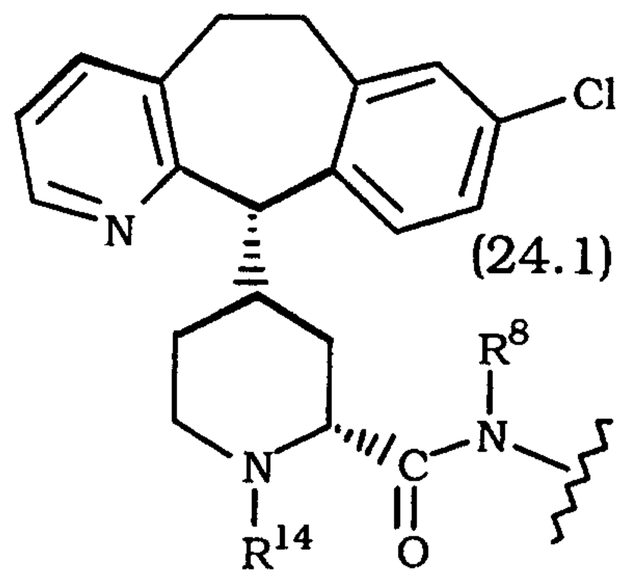


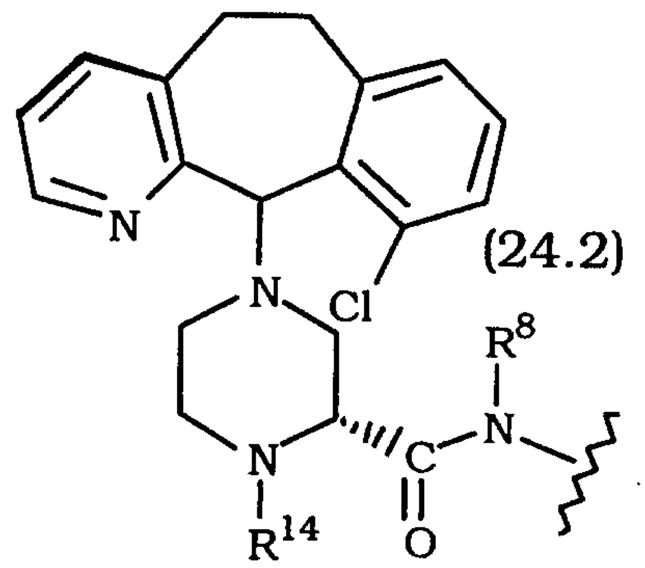
(23.0)

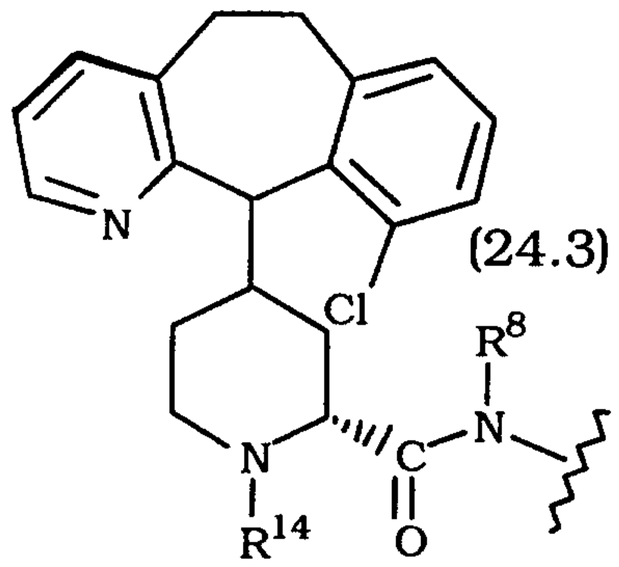


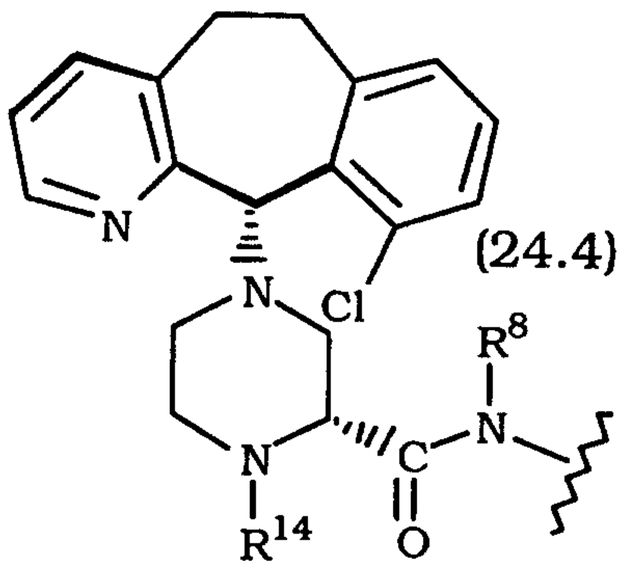
(24.0)

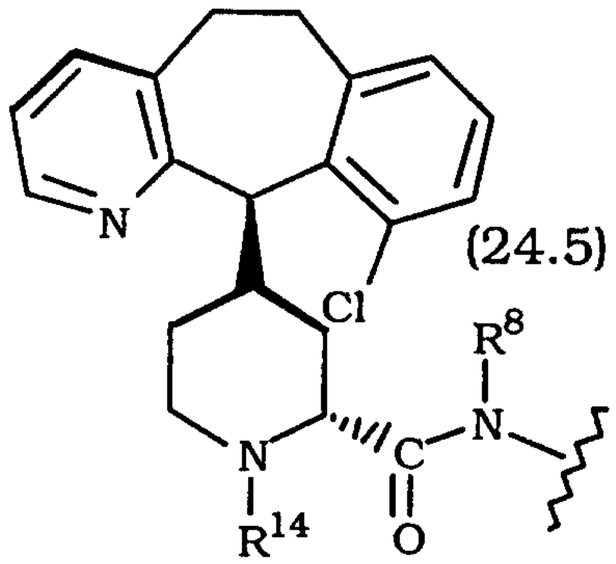

(23.1)

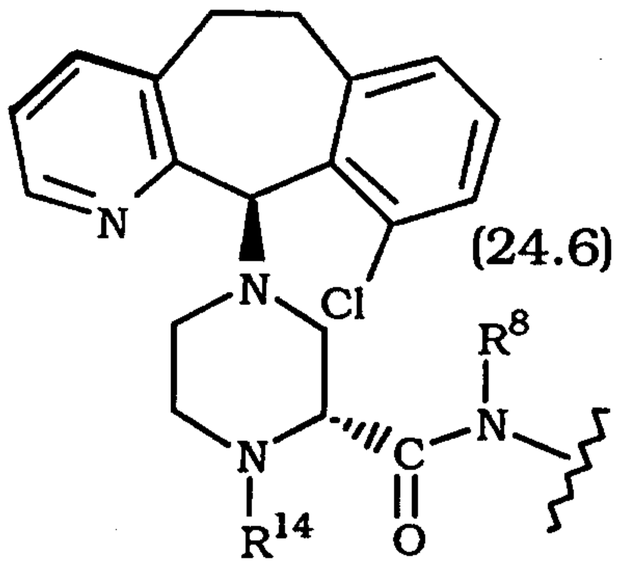

(24.1)

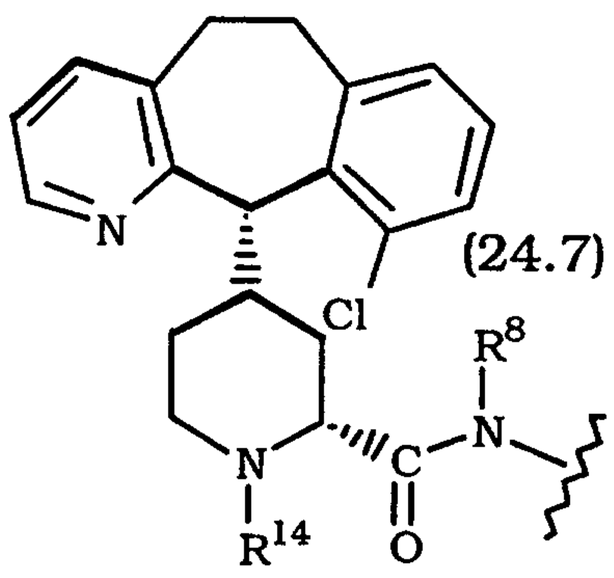

(24.2)


(24.3)


(24.4)


(24.5)


(24.6)

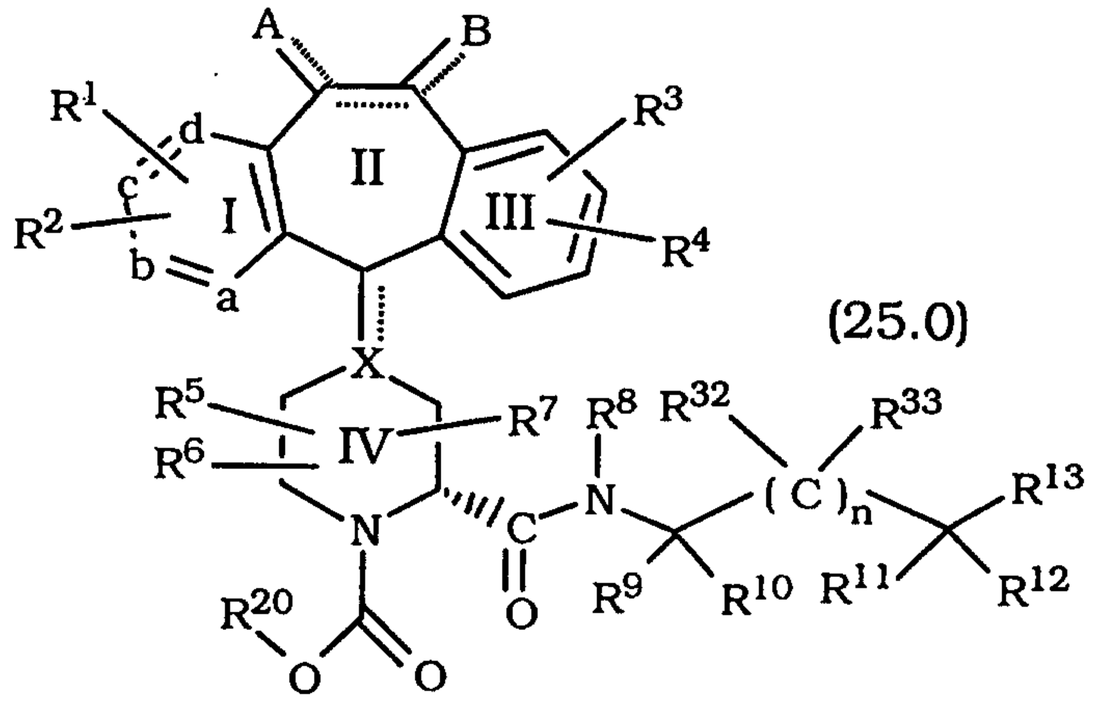

(24.7)

Compounds of the invention also include compounds corresponding to 13.0-15.0, 15.1, 16.0, 16.1, 17.0-19.0, 19.1, 20.0, 20.1, 21.0-23.0, 23.1, 24.0, and 24.1-24.7, except that the compounds have the 2S stereochemistry.

Compounds of the invention also include compounds corresponding to 13.0-15.0, 15.1, 16.0, 16.1, 17.0-19.0, 19.1, 20.0, 20.1, 21.0-23.0, 23.1, 24.0, and 24.1-24.7, except that Ring I is phenyl instead of pyridyl.

Compounds of the invention also include compounds corresponding to 13.0-15.0, 15.1, 16.0, 16.1, 17.0-19.0, 19.1, 20.0, 20.1, 21.0-23.0, 23.1, 24.0, and 24.1-24.7, except that Ring I is phenyl instead of pyridyl and the compounds have the 2S stereochemistry.

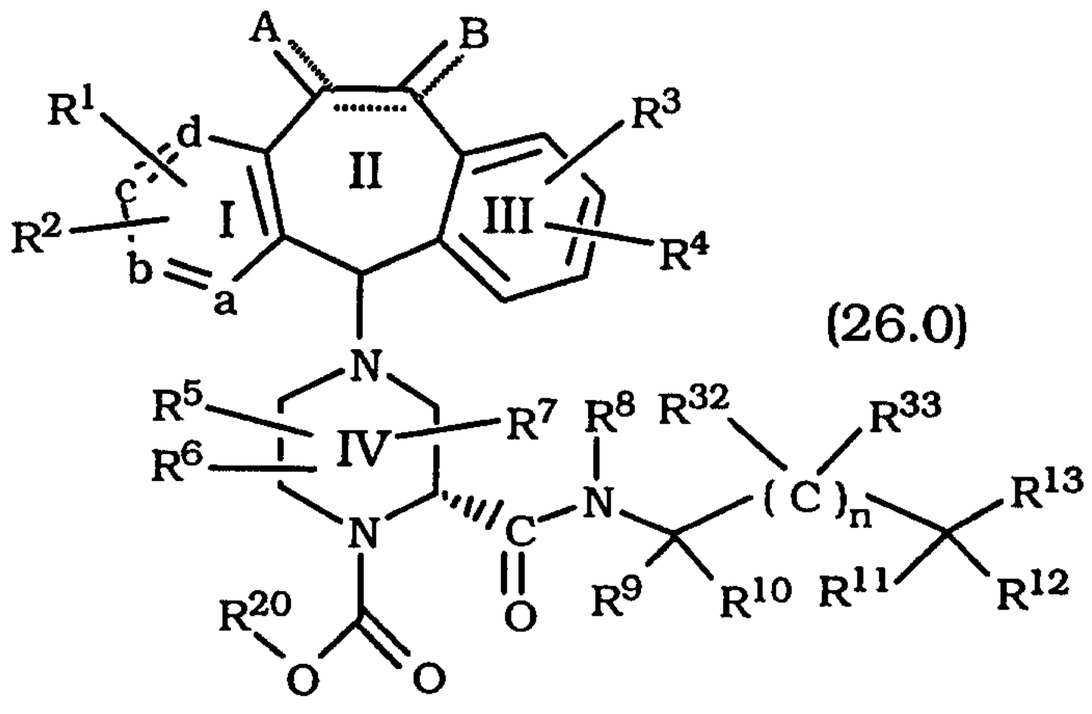
Preferred compounds of formula 1.0 include compounds of the formula:



(25.0)

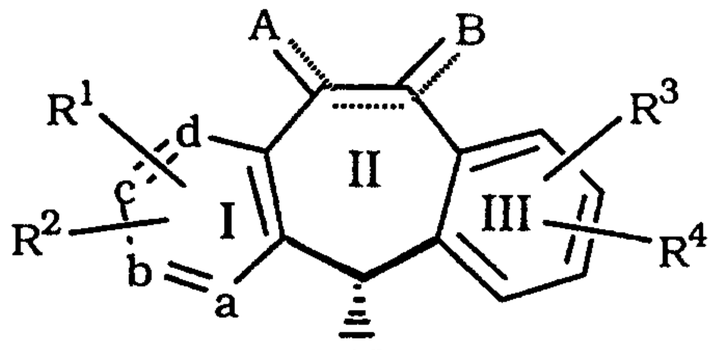
(i.e., wherein R^{14} is the carbamate group 5.0) wherein all substituents are as above defined.

A preferred compound of formula 25.0 is:

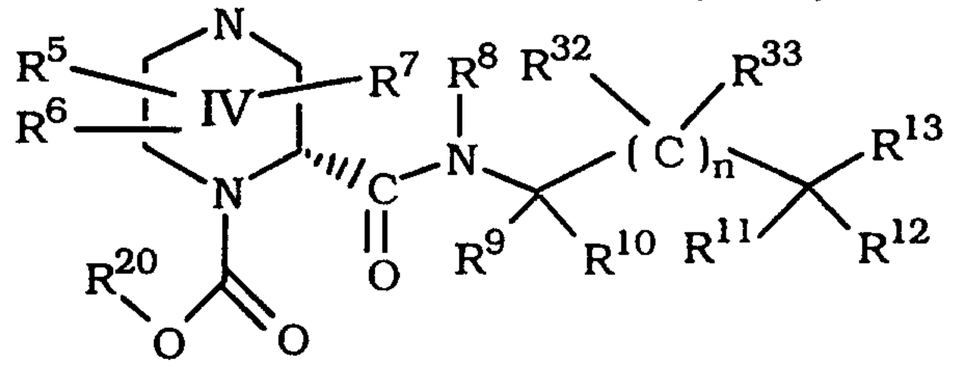


(26.0)

with formula 27.0:

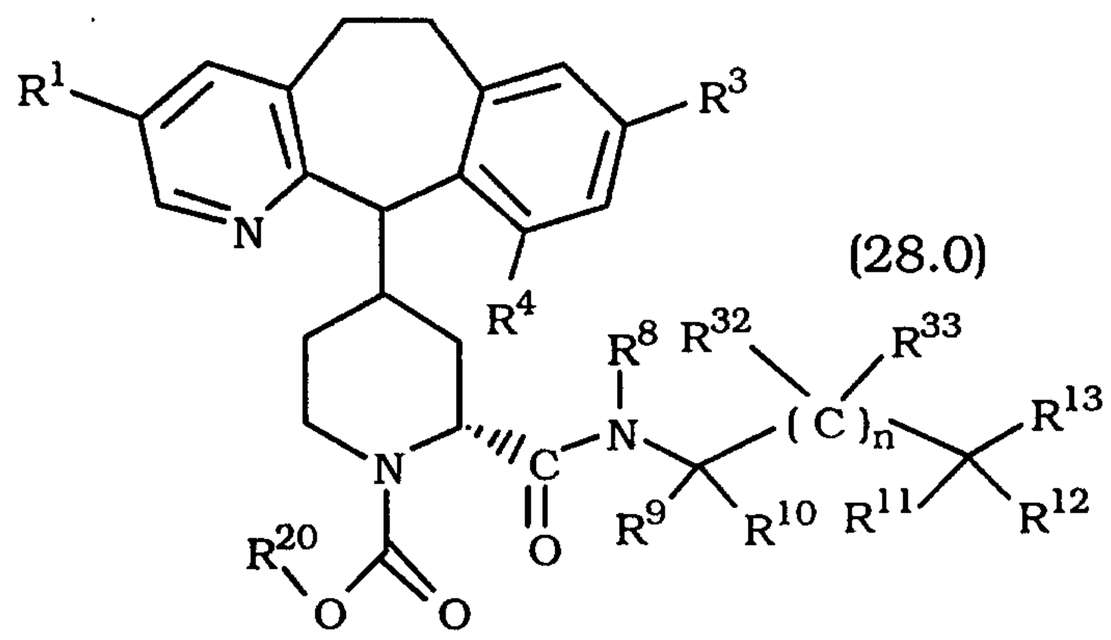


(27.0)



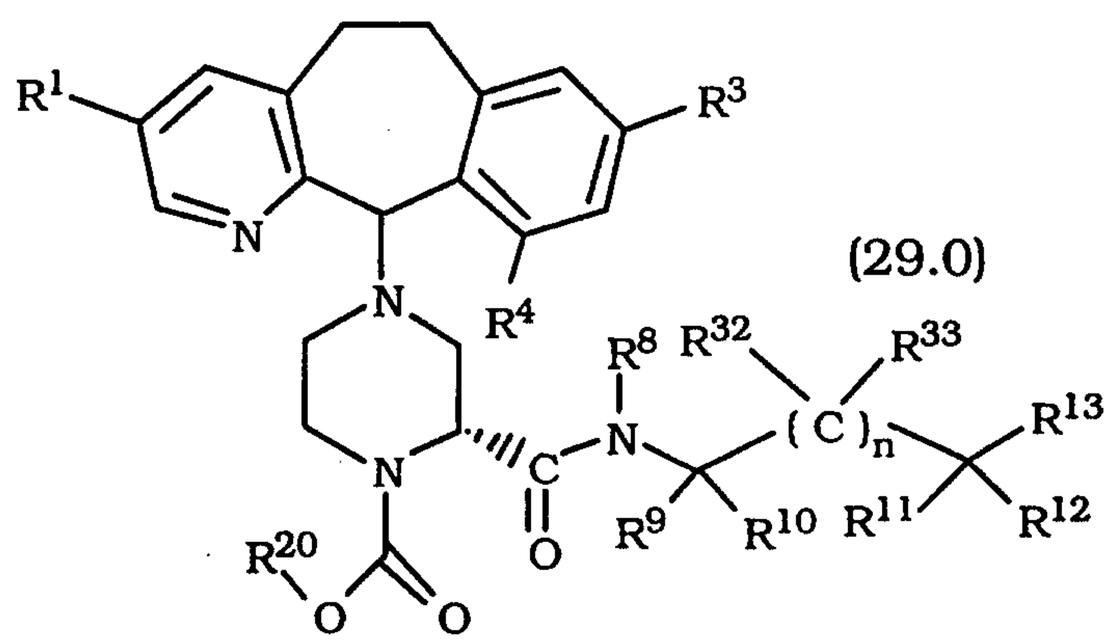
being most preferred (wherein all substituents are as defined above).

Compounds of formula 25.0 include:



(28.0)

and



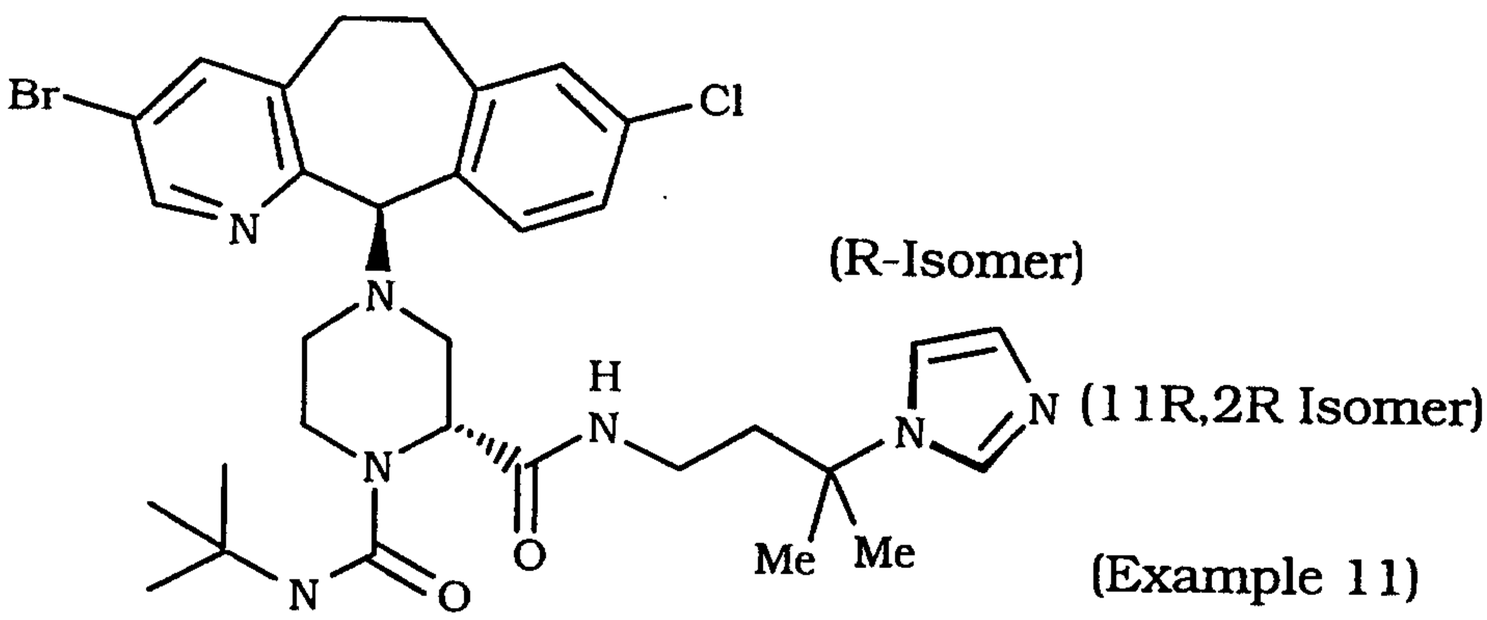
(29.0)

wherein all substituents are as defined above.

Preferred compounds of formulas 28.0 and 29.0 are those wherein the R^1 to R^4 substituents are selected to produce trihalo, dihalo and monohalo substituted compounds, as described above.

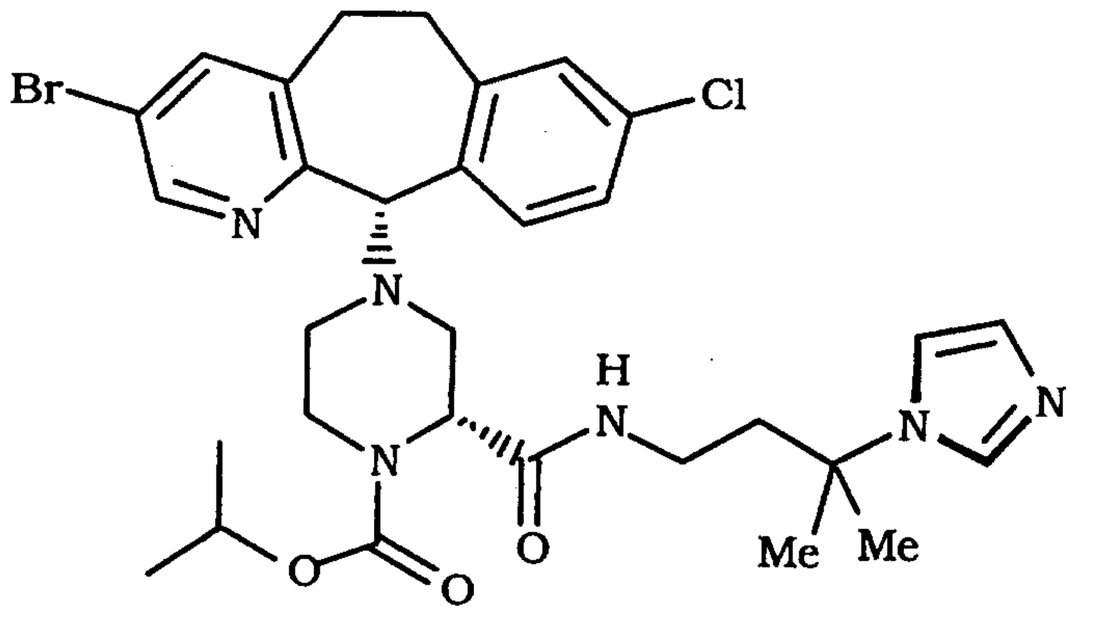
Compounds of formula 29.0 are preferred. Most preferred are compounds of formula 29.0 wherein R^8 is selected from: benzyl, 4-fluorobenzyl, 3-pyridylmethyl or cyclopropylmethyl; R^{20} is cyclohexyl, i-propyl or t-butyl (more preferred is cyclohexyl), R^1 is Br or H, R^3 is Cl, and R^4 is H. More preferred are compounds of formula 29.0 wherein R^8 is benzyl, R^{20} is cyclohexyl, i-propyl or t-butyl (even more preferred cyclohexyl), R^1 is H, R^3 is Cl, and R^4 is H or Cl.

Preferred compounds of this invention include:

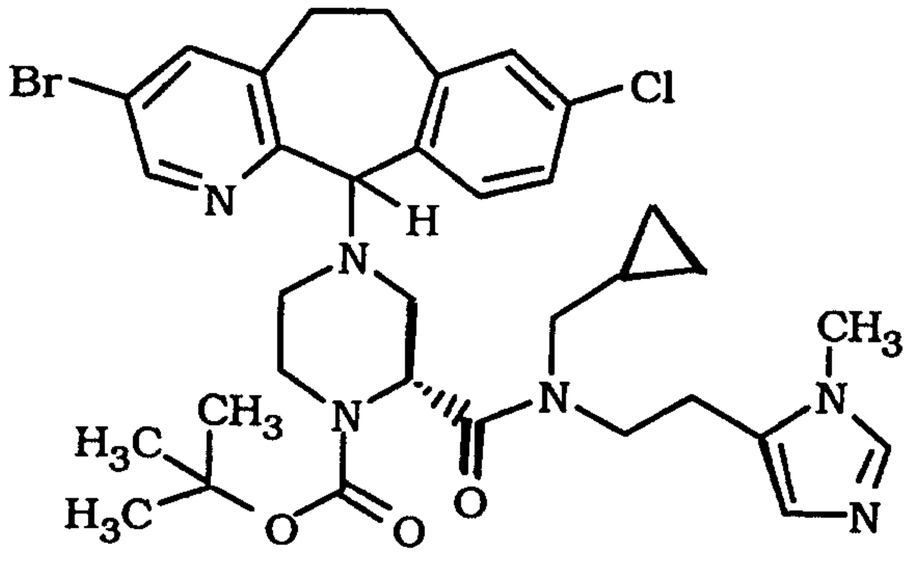


H

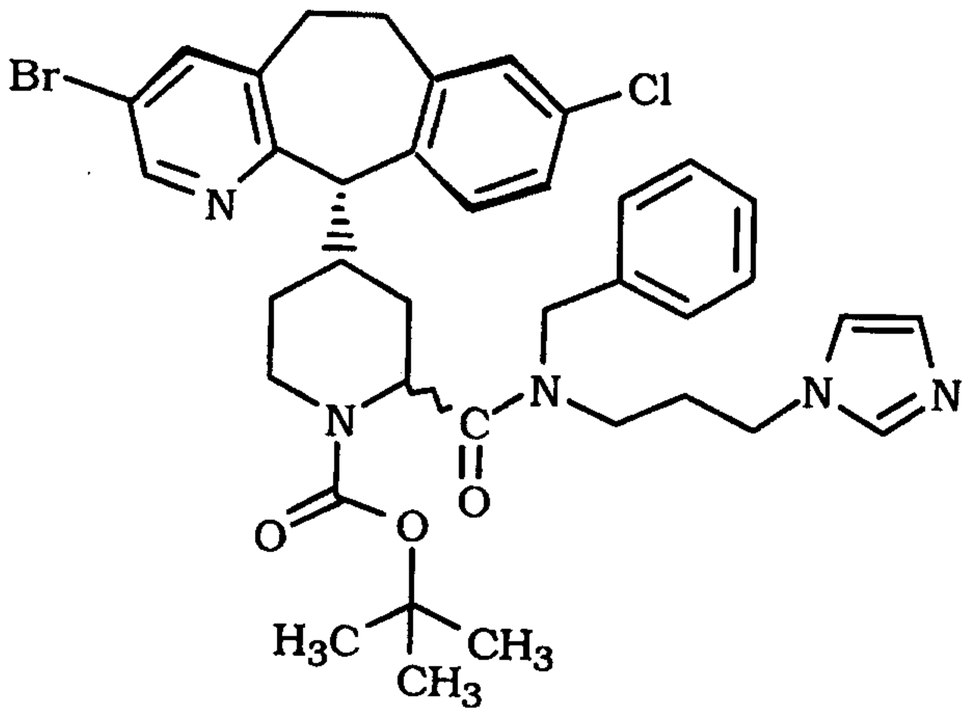
;



;

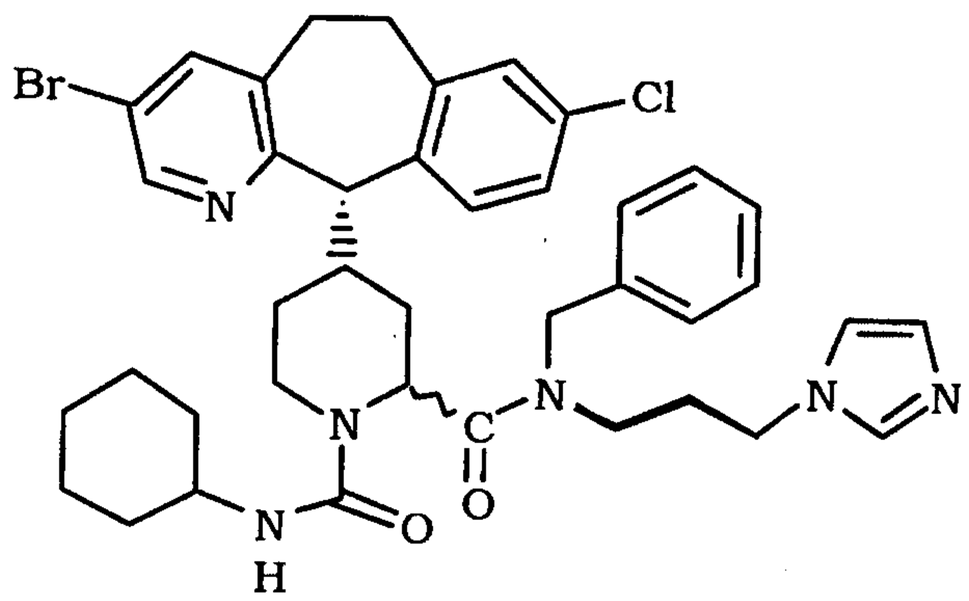


;



(Example 78 Step B)

;



(Example 79 Step B Isomer A)

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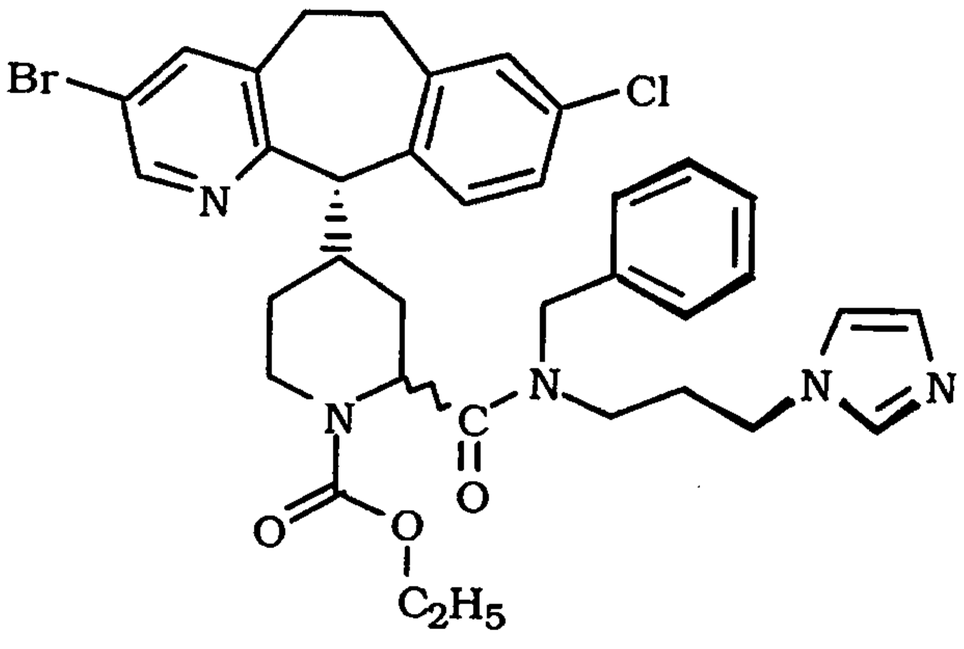
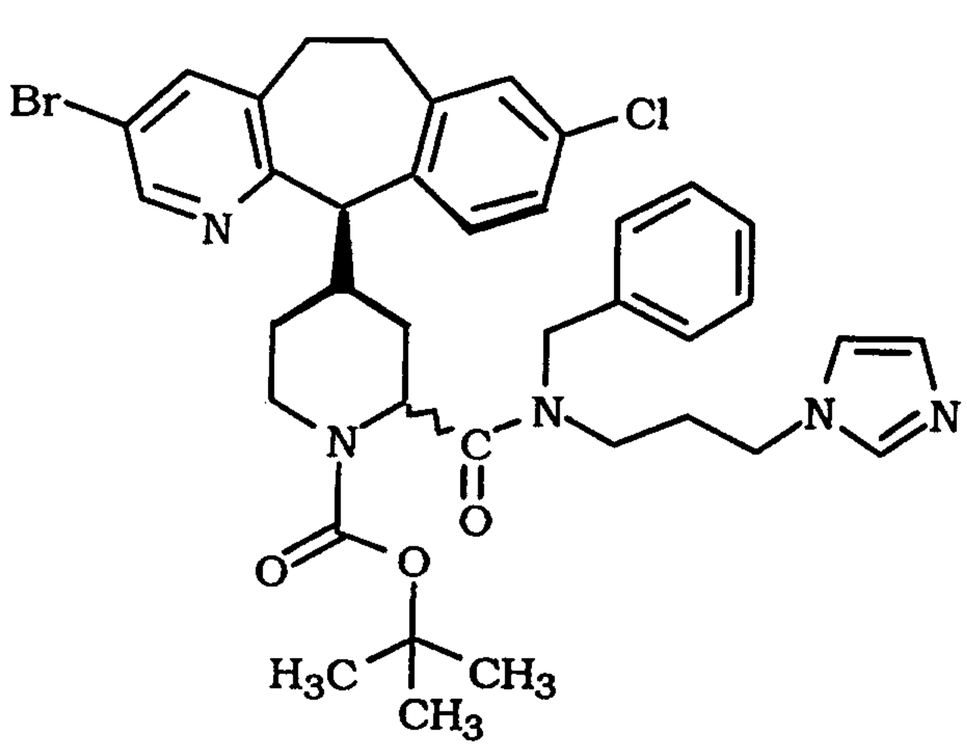


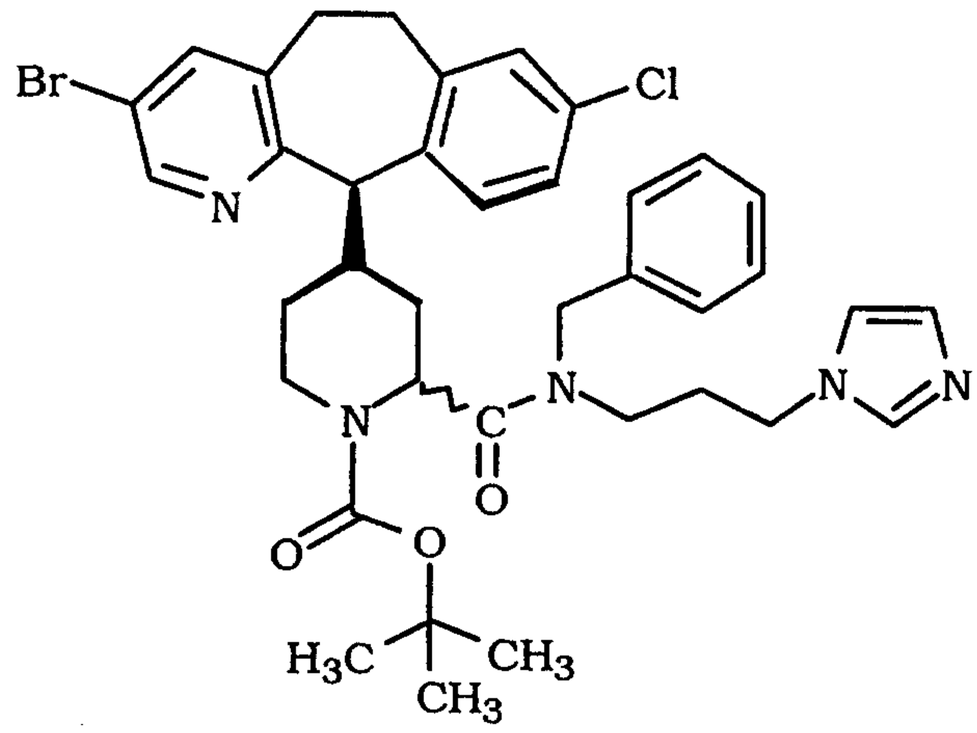
(Example 80 Isomer A)

;



(Example 88 Isomer A)

;



(Example 93 Isomer D)

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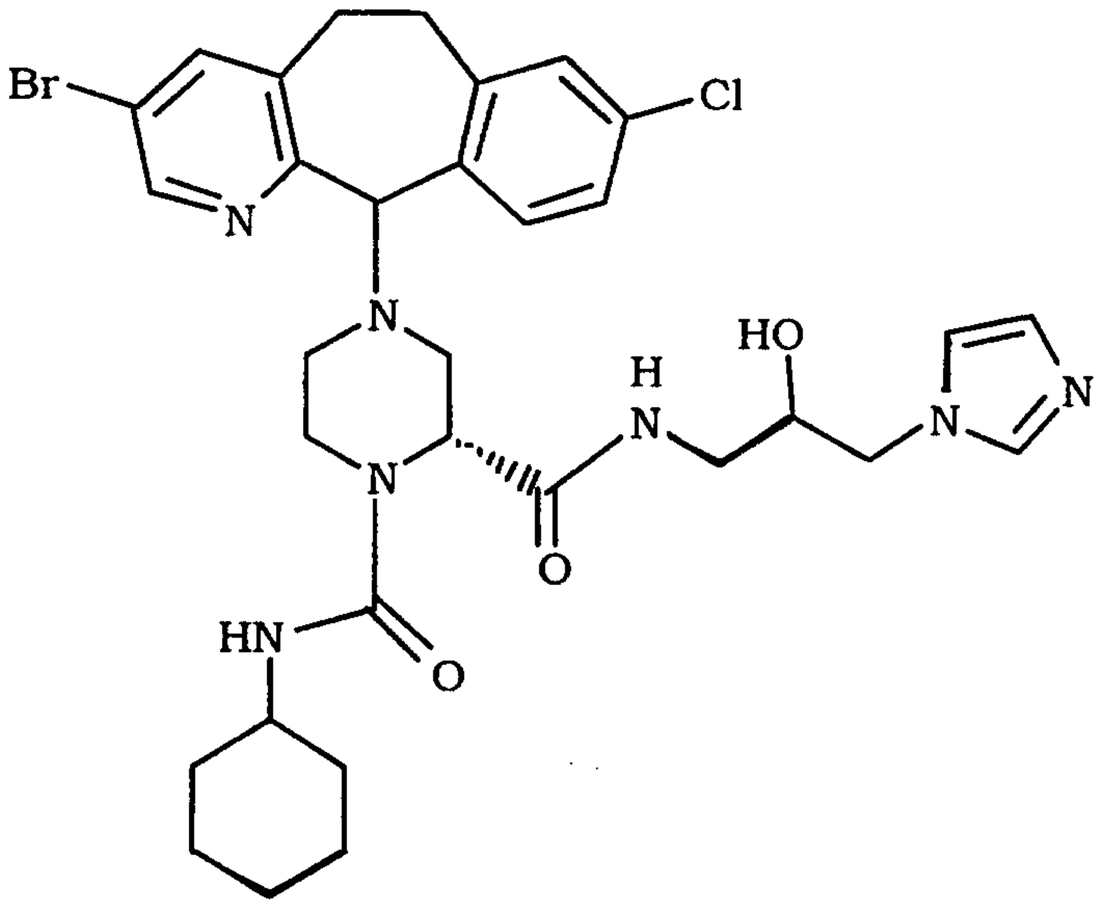

(Example 99)

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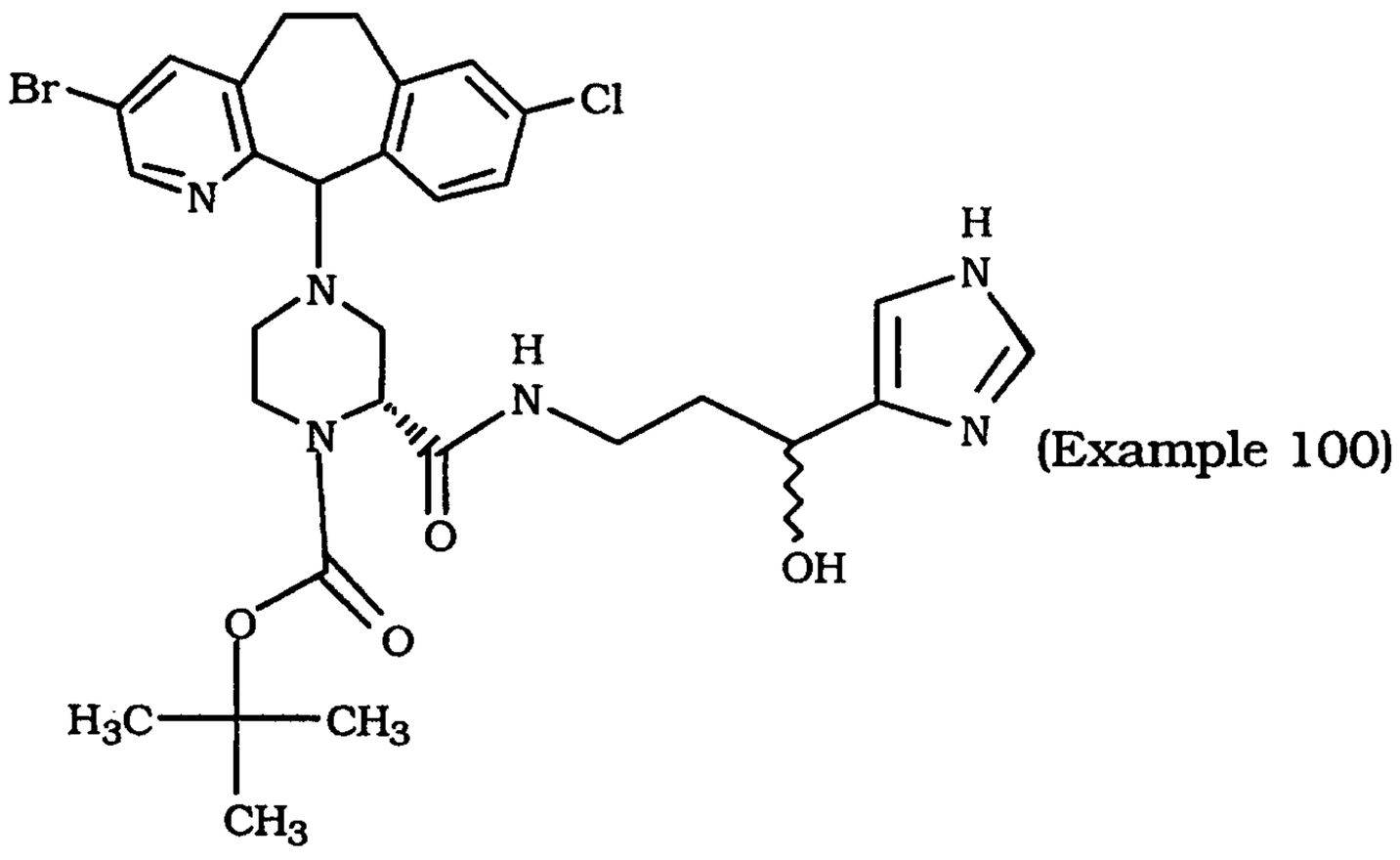
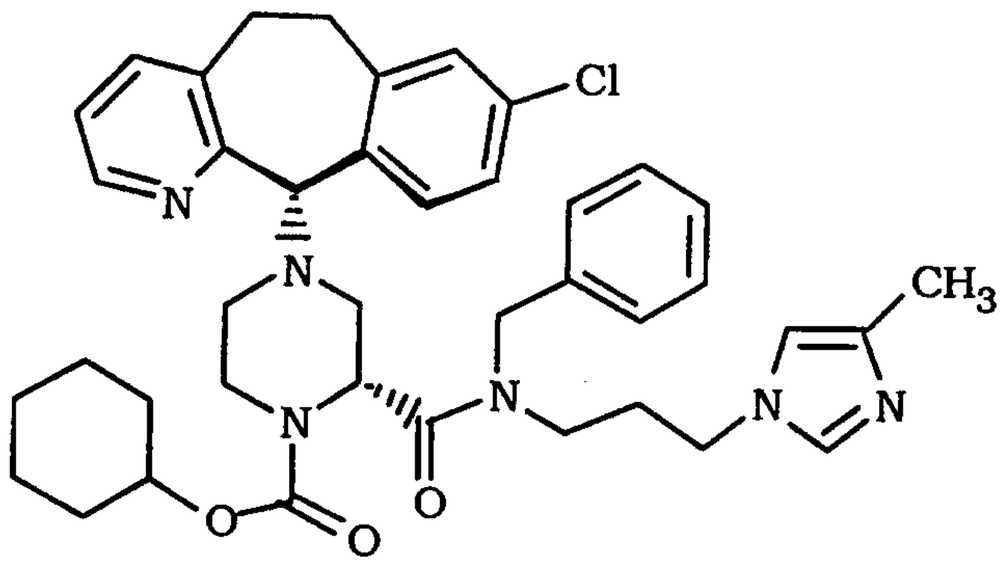
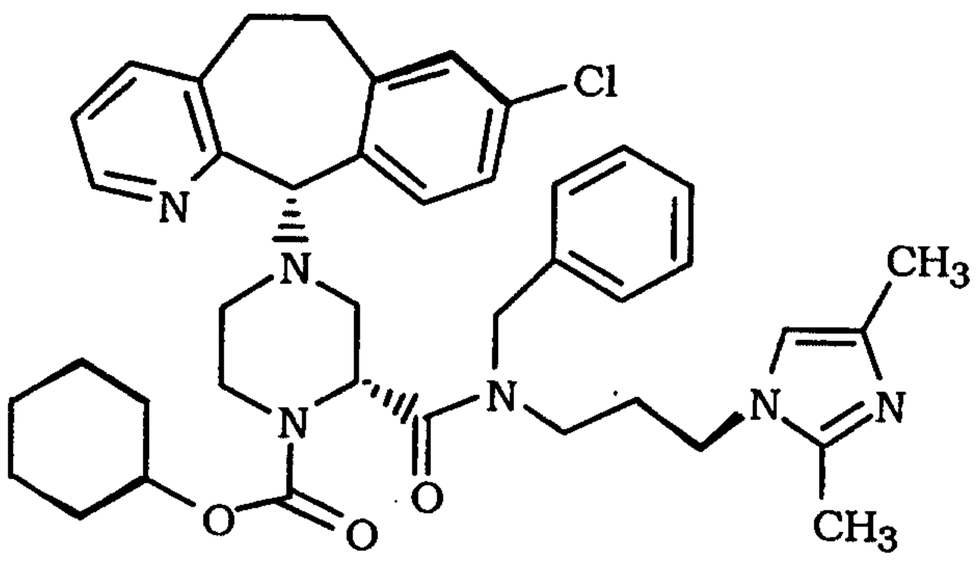


(Example 100)

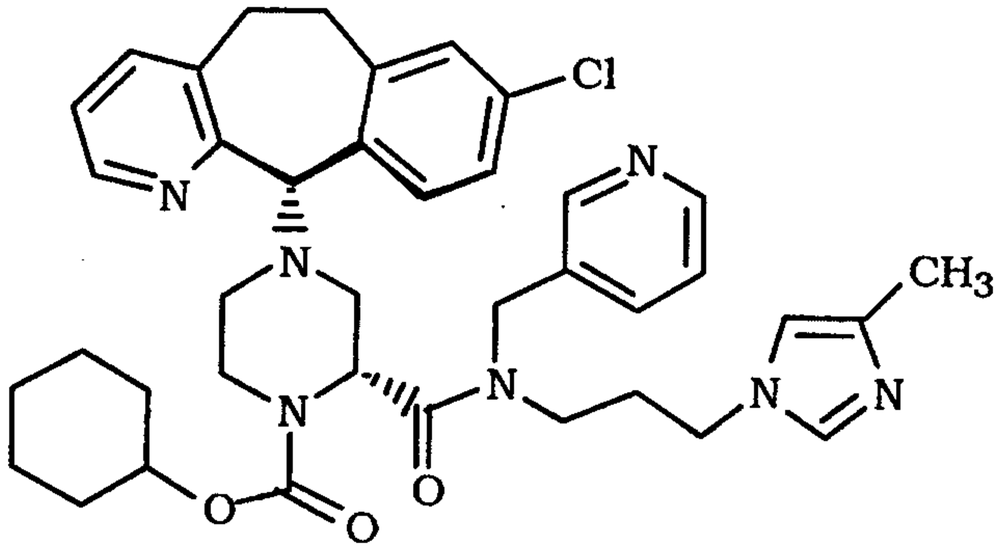
;



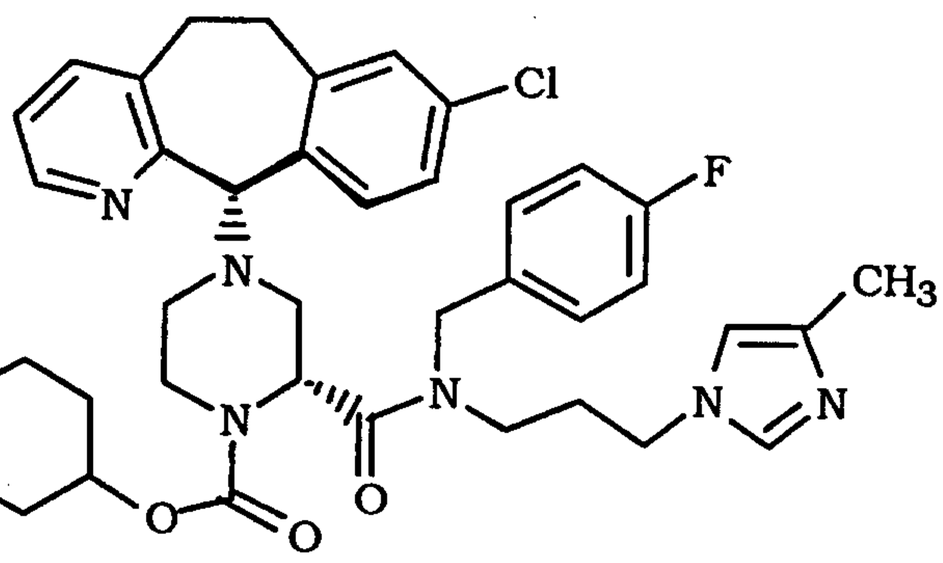
(Example 225)



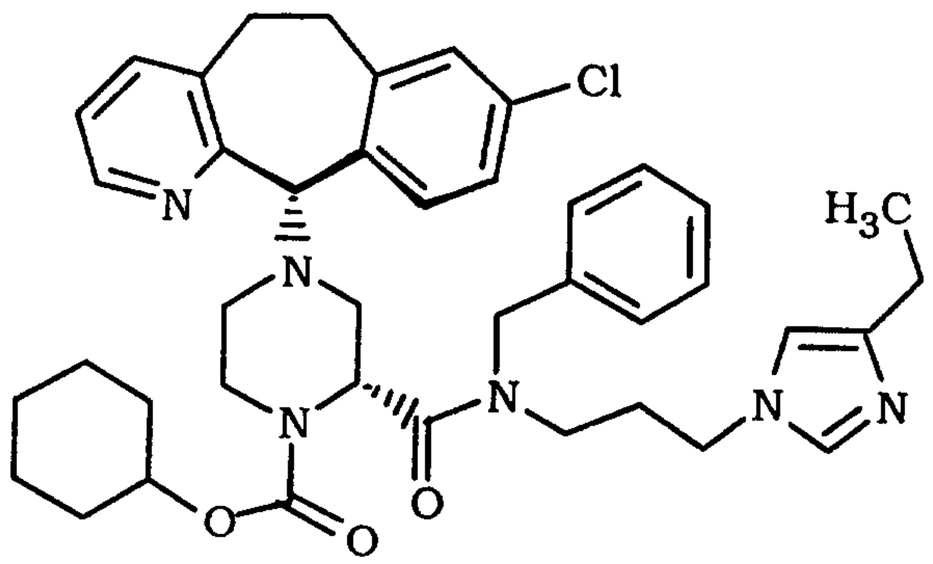
(Example 226)



(Example 227)



(Example 228)



(Example 229)

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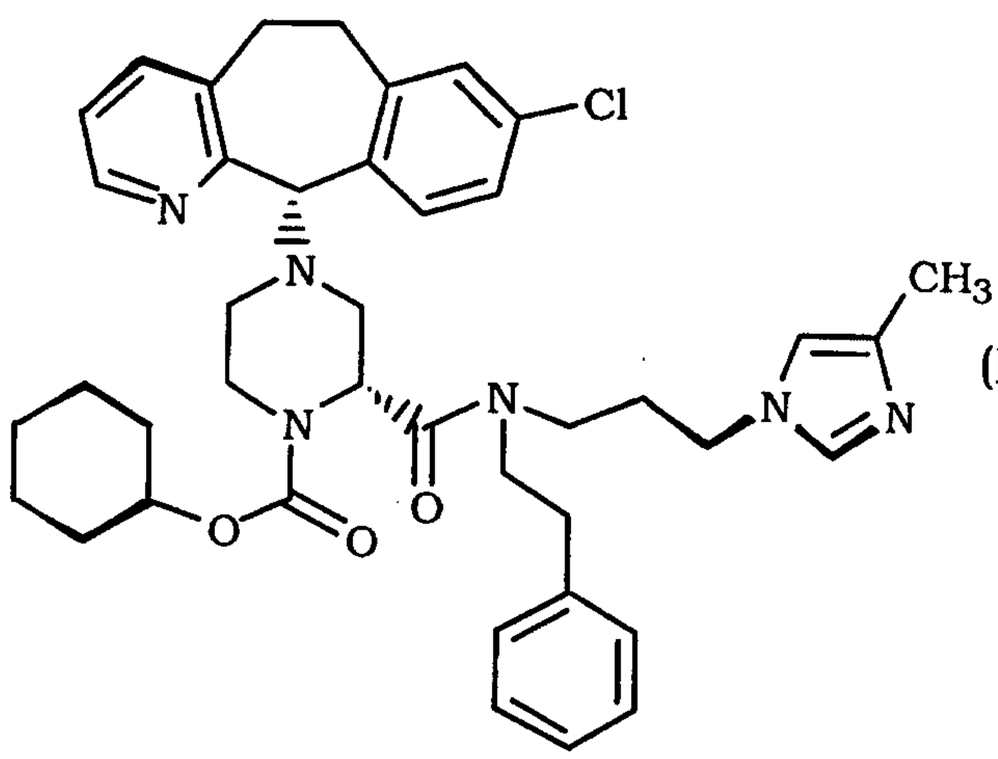
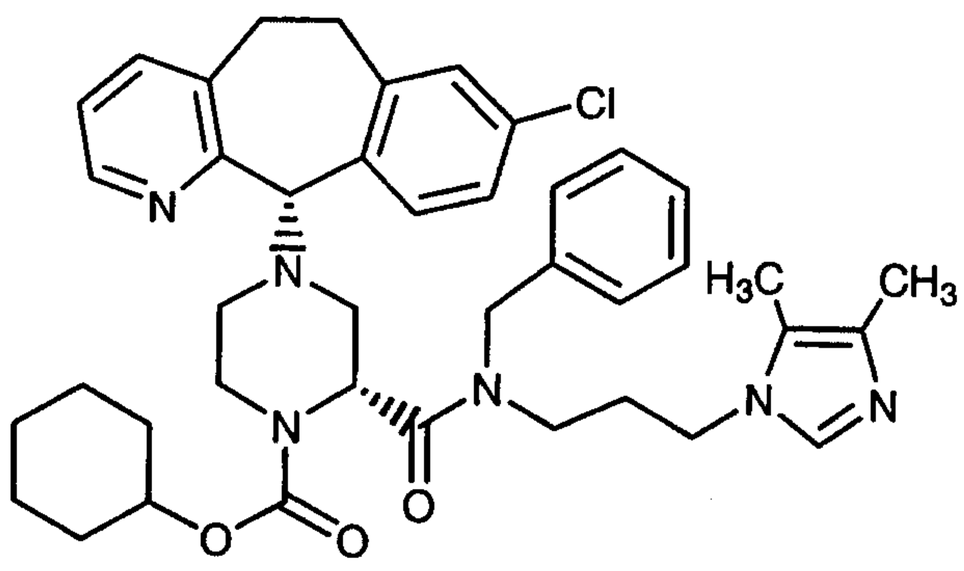


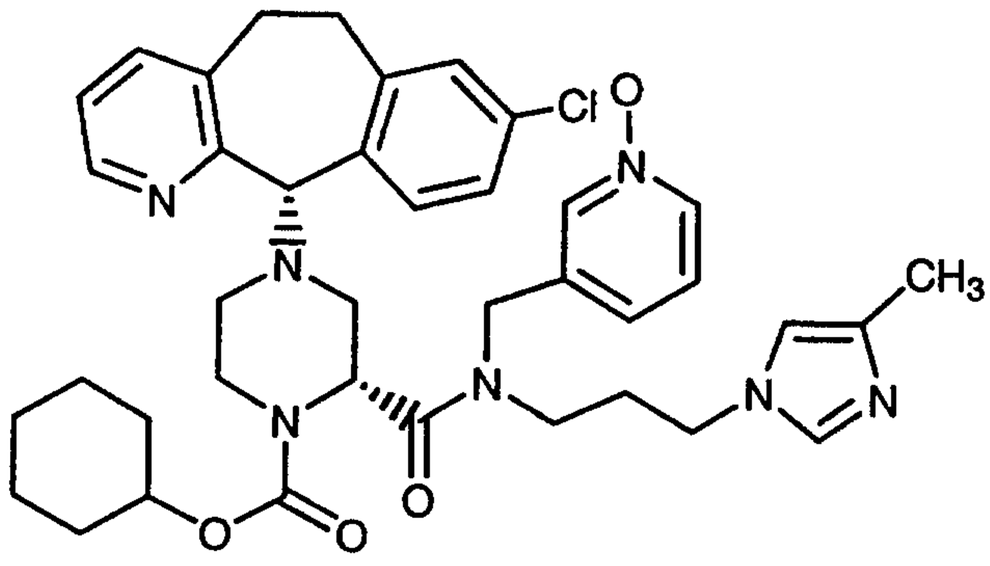
(Example 232)

;



(Example 326)

;



(Example 330)

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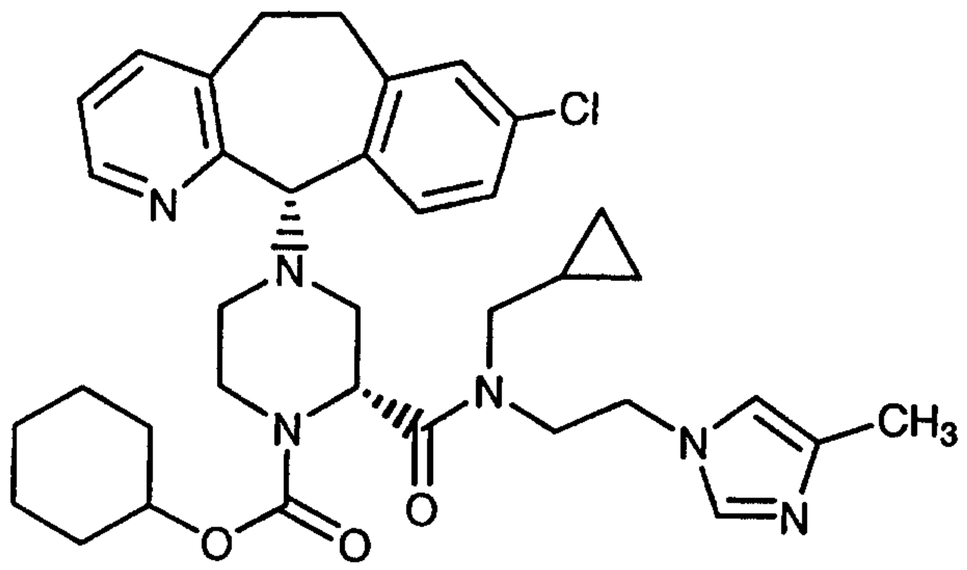

(Example 327)

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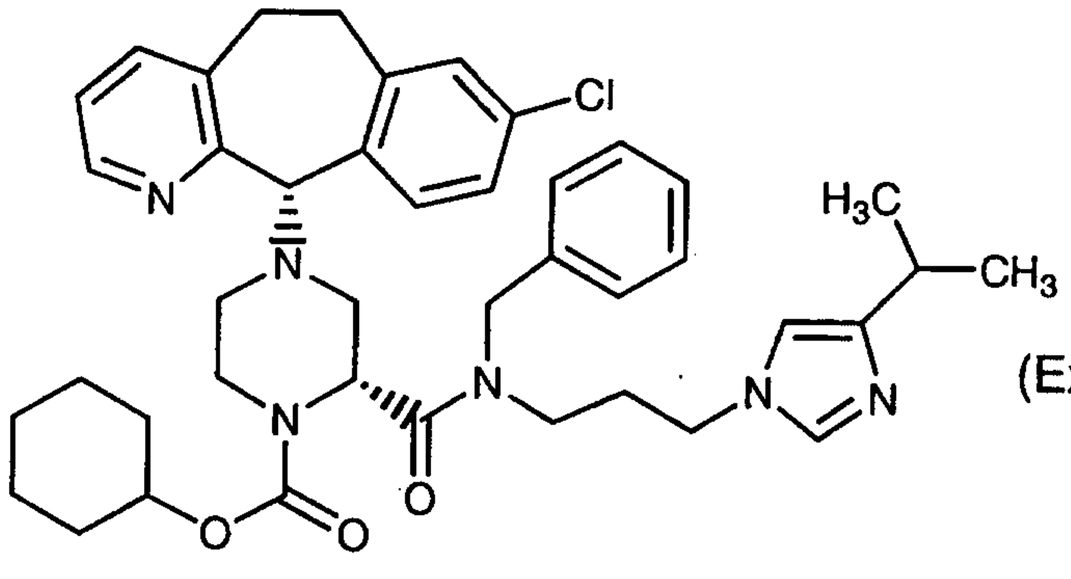

(Example 328)

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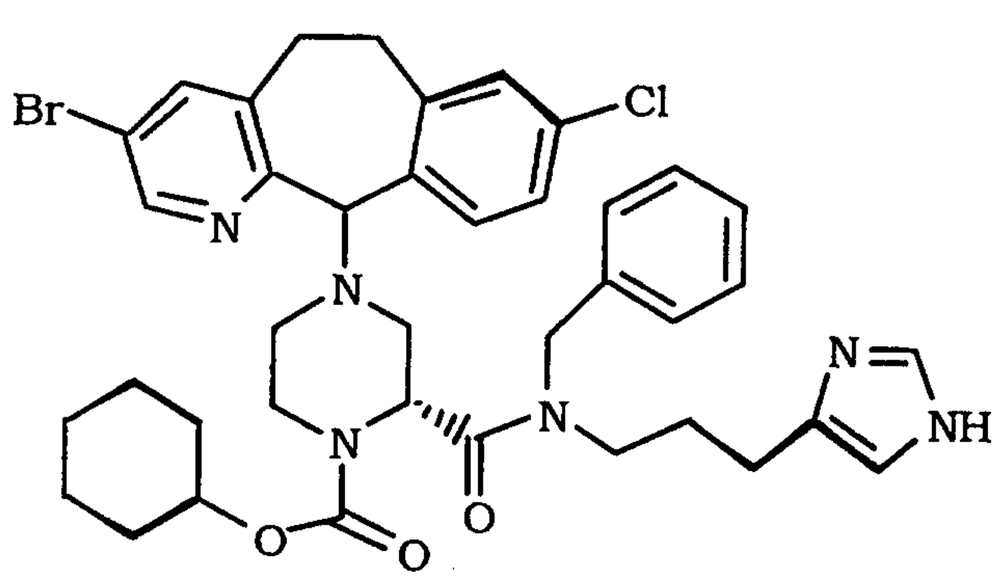

(Example 243)

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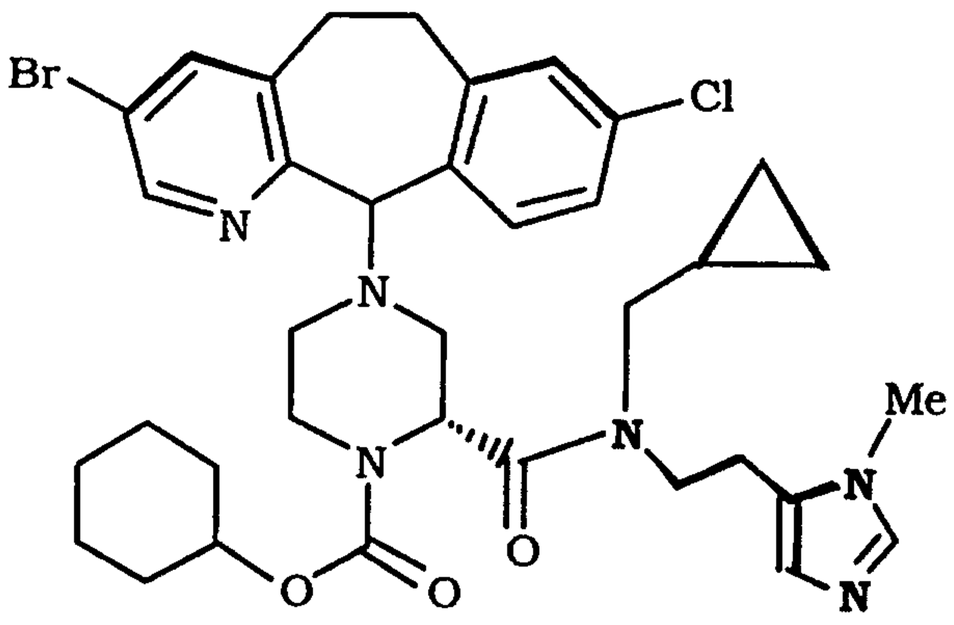

(Example 286A)

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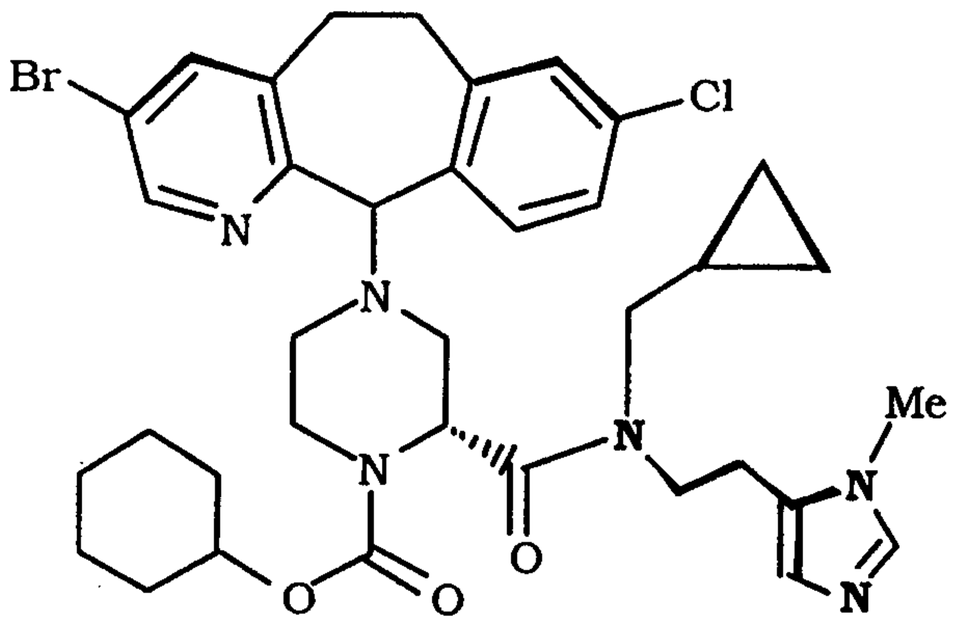
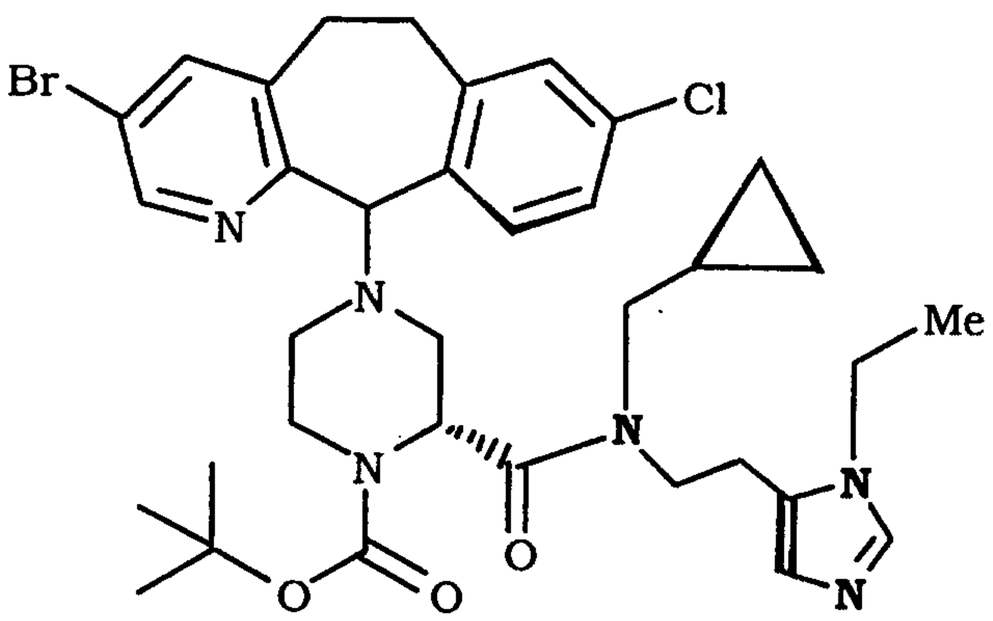


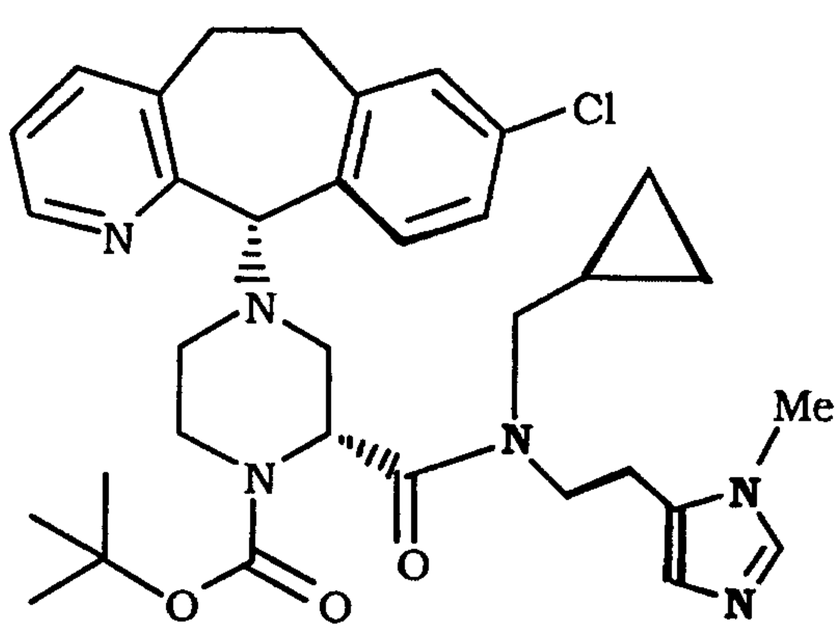
(Example 286B)

;



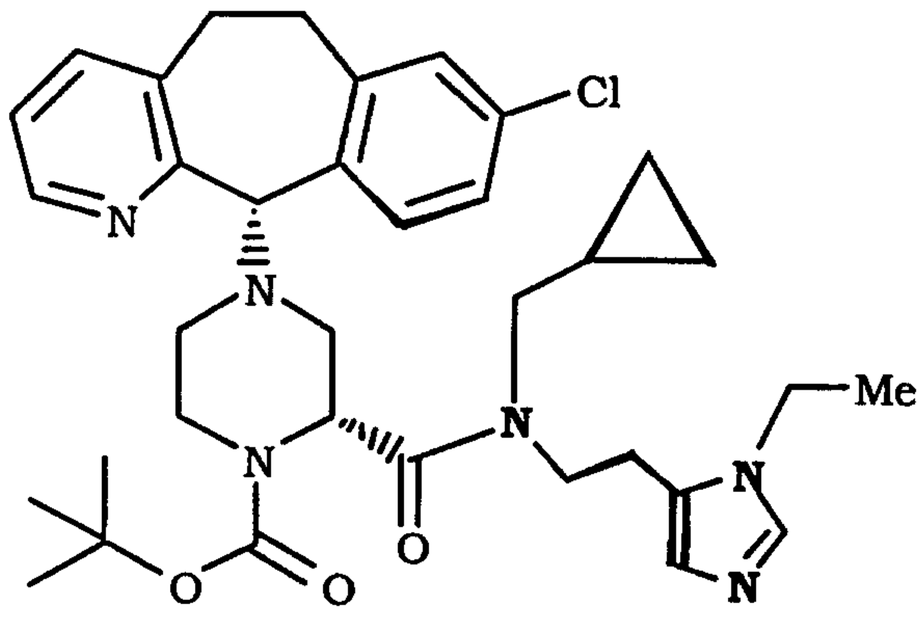
(Example 304)

;



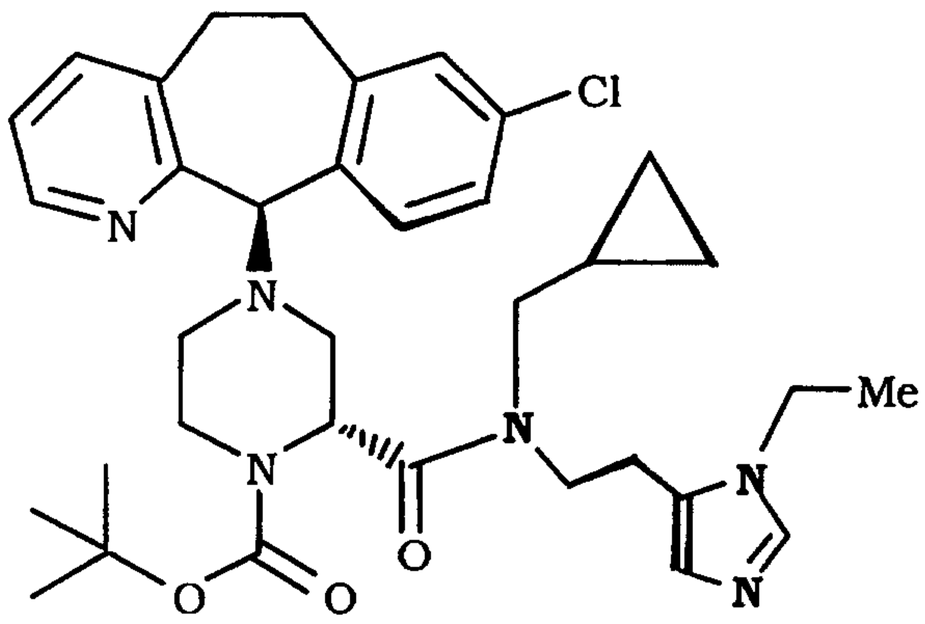
(Example 306)

;



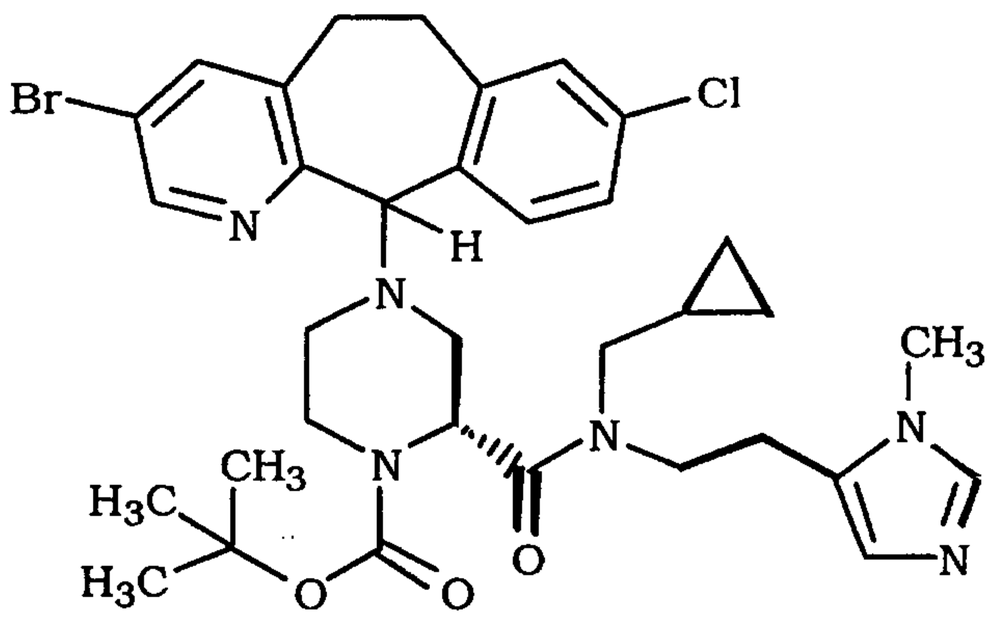
(Example 307)

; or



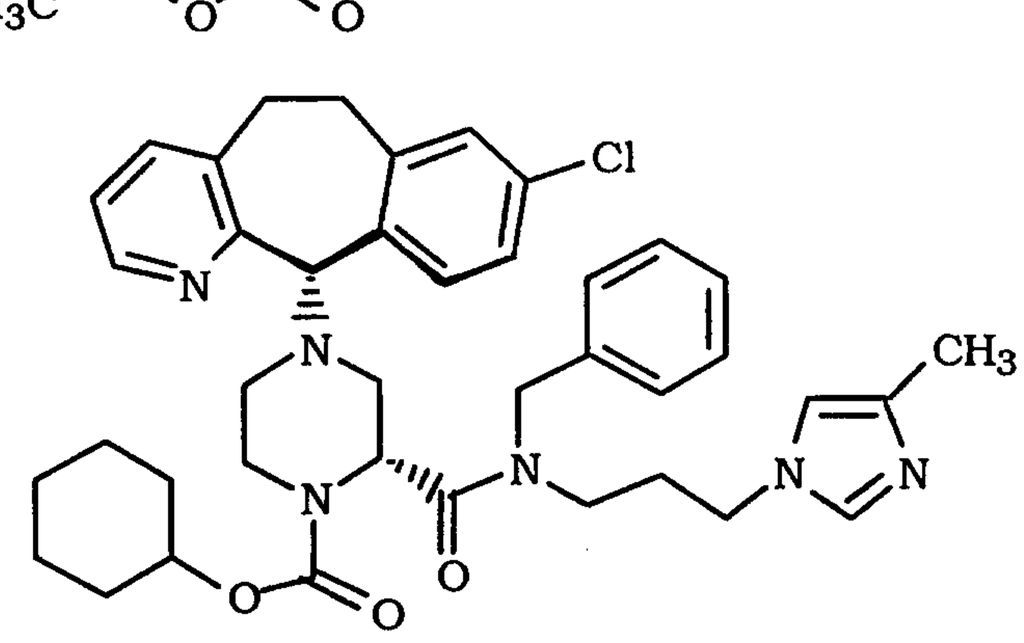
(Example 308)

Most preferred compounds include the compounds



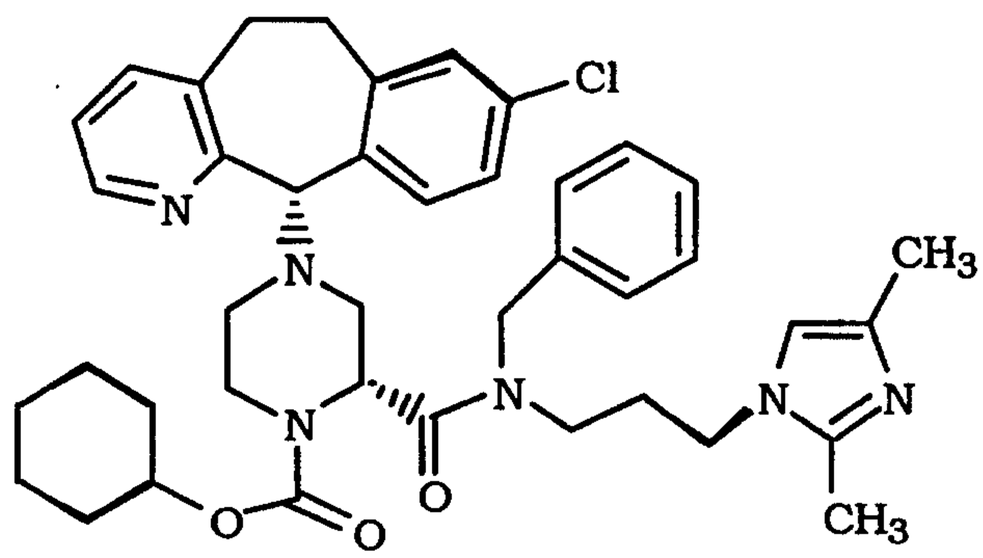
Example 58

;



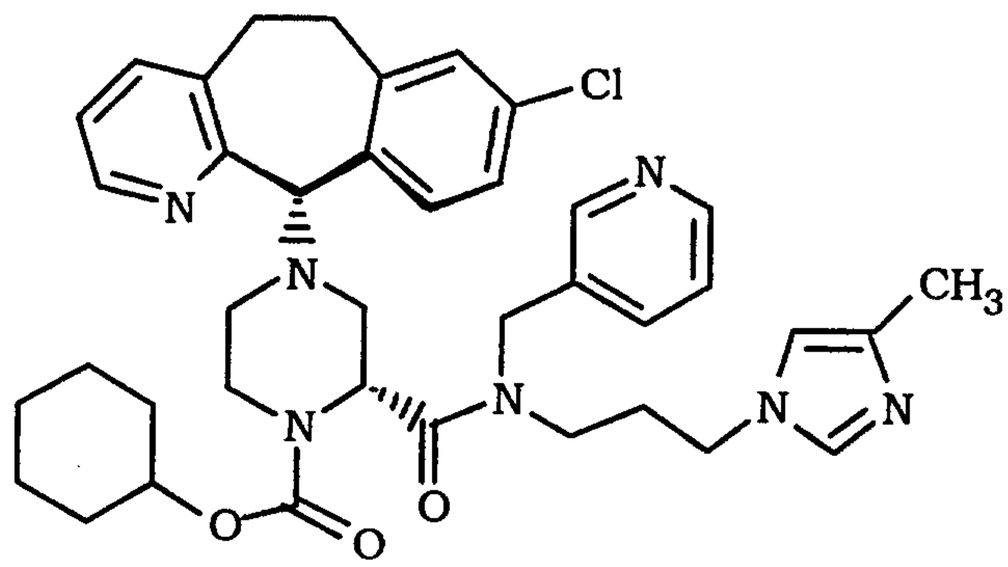
(Example 225)

;

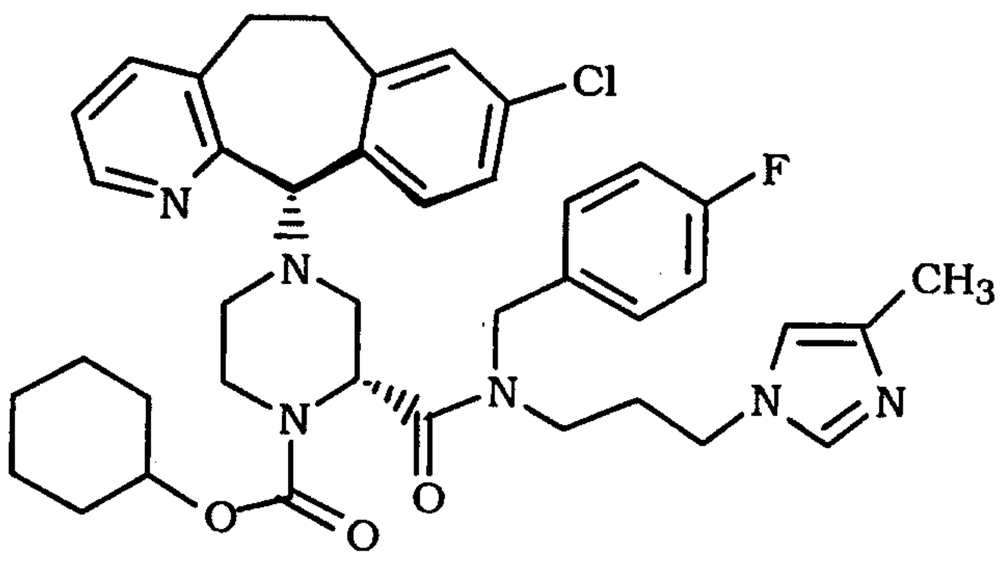


(Example 226)

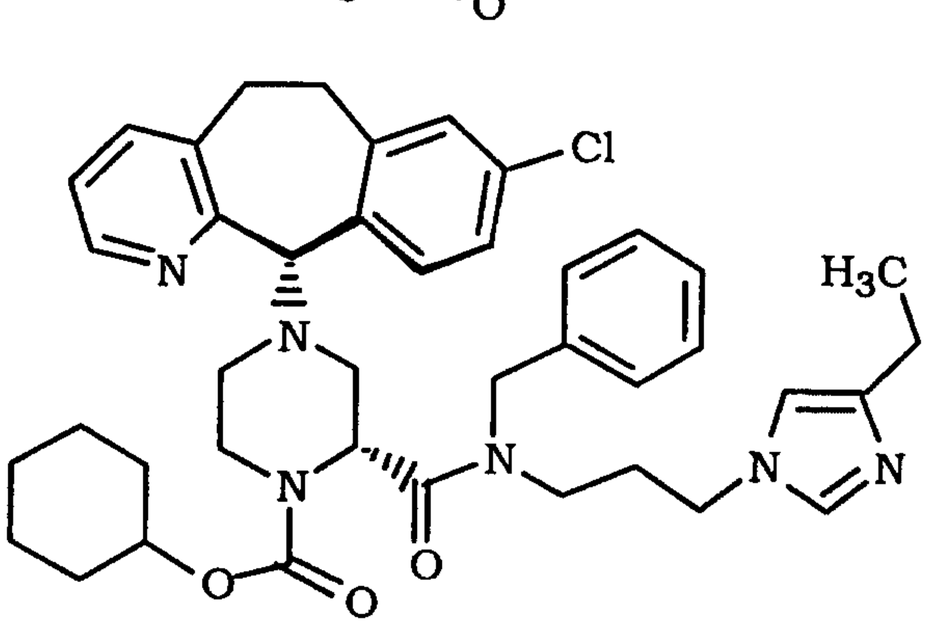
;



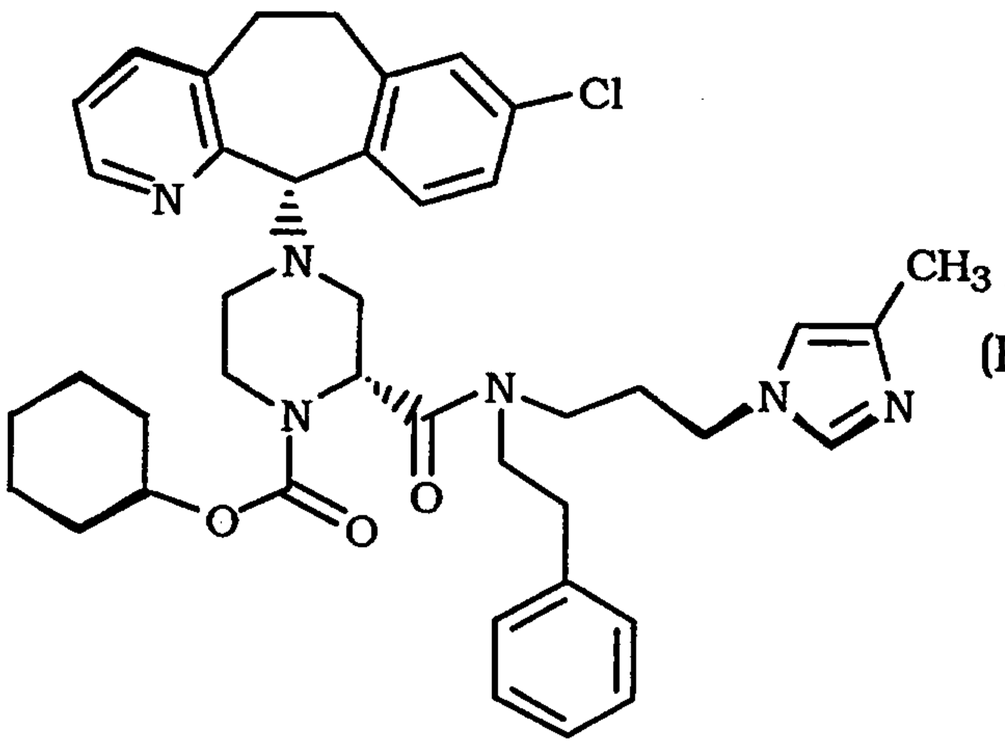
(Example 227)



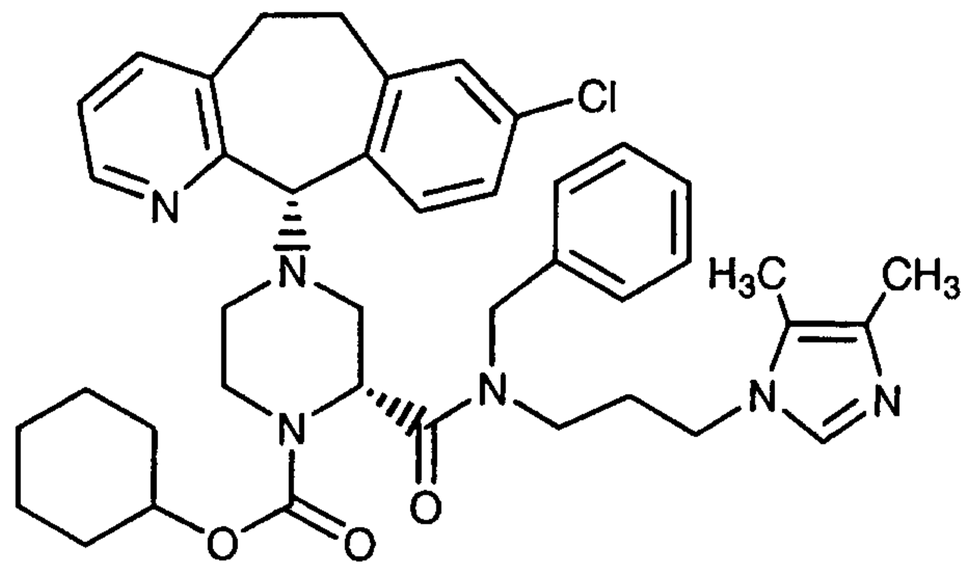
(Example 228)



(Example 229)

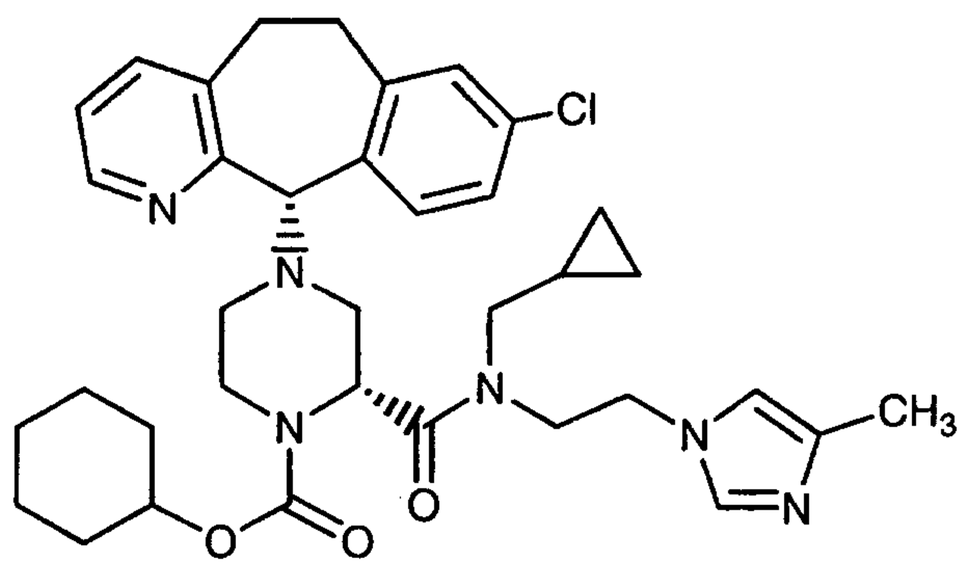


(Example 232)



(Example 326)

; and



(Example 327)

More preferred compounds include the compounds of Examples 58, 199, 225, 226, 229, 232 and 326. Compounds of Examples 58, 199, 225, 229 and 326 are even more preferred. The compound of Example 225 is even still more preferred. Preferably the compound of Examples 225, 229 and 326 are administered orally.

This invention is also directed to the compounds of Examples 26, 30, 32, 41, 42, 43, 44, 81, 105, 106, 293, and 309. The compound of Example 309 is preferred.

This invention is also directed to the compounds of Examples 31, 34, 35, 36, 37, 38, 39, 40, 67, 68, 69, 70, 73, 75, 263, 282, 283, 284, 287, and 289. The compounds of Examples 67, 68, 69, and 70 are preferred.

This invention is also directed to the compounds of Examples 27, 28, 29, 71, 72, 74, 76, 98, 101, 103, 104, 107, 108, 110, 111, 255, 256, 257, 258, 259, 260, 261, 262, 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 285, 286, 286A, 290, 291, 292, 294, 295, 296, 297, 299, 300, 301, 302, and 303.

Compounds of Examples 101, 103, 71, 72 Step B, 72 Step C and 259 are preferred

This invention is also directed to compounds of Examples 33, 279, 280, and 281.

Lines drawn into the ring systems indicate that the indicated bond may be attached to any of the substitutable ring carbon atoms.

Certain compounds of the invention may exist in different isomeric (e.g., enantiomers, diastereoisomers, atropisomers) forms. The invention contemplates all such isomers both in pure form and in admixture, including racemic mixtures. Enol forms are also included.

Certain tricyclic compounds will be acidic in nature, e.g. those compounds which possess a carboxyl or phenolic hydroxyl group. These compounds may form pharmaceutically acceptable salts. Examples of such salts may include sodium, potassium, calcium, aluminum, gold and silver salts. Also contemplated are salts formed with pharmaceutically acceptable amines such as ammonia, alkyl amines, hydroxyalkylamines, N-methylglucamine and the like.

Certain basic tricyclic compounds also form pharmaceutically acceptable salts, e.g., acid addition salts. For example, the pyrido-nitrogen atoms may form salts with strong acid, while compounds having basic substituents such as amino groups also form salts with weaker acids. Examples of suitable acids for salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic and other mineral and carboxylic acids well known to those in the art. The salts are prepared by contacting the free base form with a sufficient amount of the desired acid to produce a salt in the conventional manner. The free base forms may be regenerated by treating the salt with a suitable dilute aqueous base solution such as dilute aqueous NaOH, potassium carbonate,

ammonia and sodium bicarbonate. The free base forms differ from their respective salt forms somewhat in certain physical properties, such as solubility in polar solvents, but the acid and base salts are otherwise equivalent to their respective free base forms for purposes of the invention.

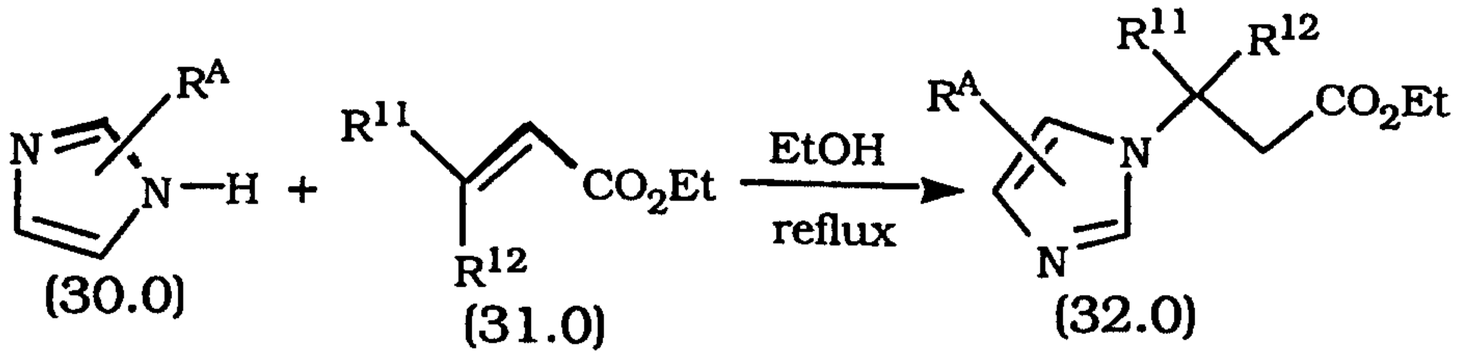
All such acid and base salts are intended to be pharmaceutically acceptable salts within the scope of the invention and all acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of the invention.

The compounds of formula 1.0 can exist in unsolvated as well as solvated forms, including hydrated forms, e.g., hemi-hydrate. In general, the solvated forms, with pharmaceutically acceptable solvents such as water, ethanol and the like are equivalent to the unsolvated forms for purposes of the invention.

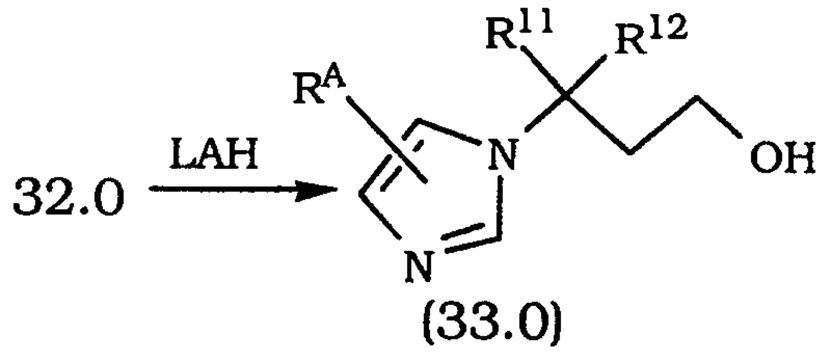
Compounds of the invention may be prepared according to the procedures described in WO 95/10516 published April 20, 1995, WO96/31478 published October 10, 1996, WO 97/23478 published July 3, 1997, U.S. 5,719,148 issued February 17, 1998, and copending Application Serial No. 09/094687 filed June 15, 1998 (see also WO98/57960 published December 23, 1998); the disclosures of each being incorporated herein by reference thereto; and according to the procedures described below.

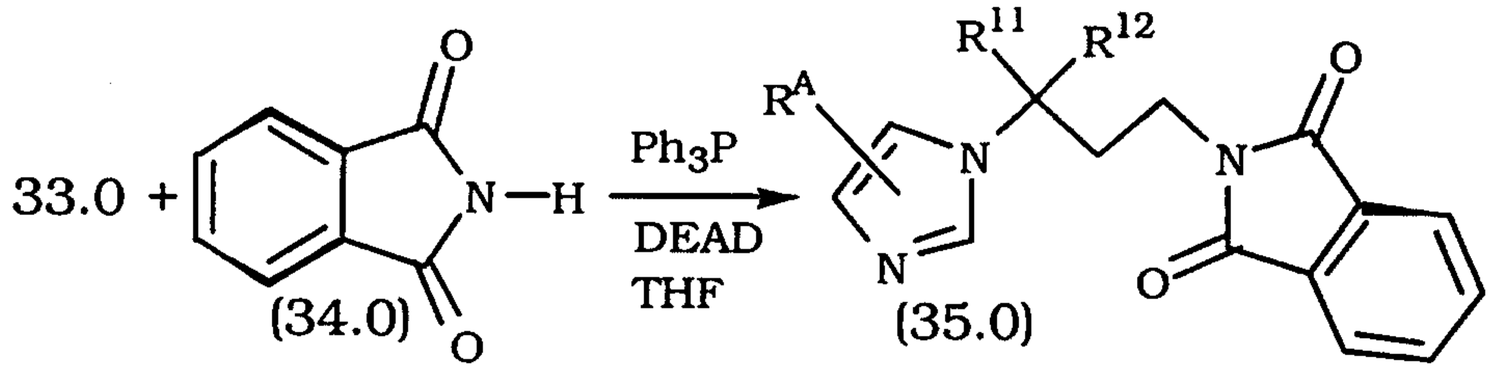
Compounds of the invention can be prepared according to the reaction schemes described below.

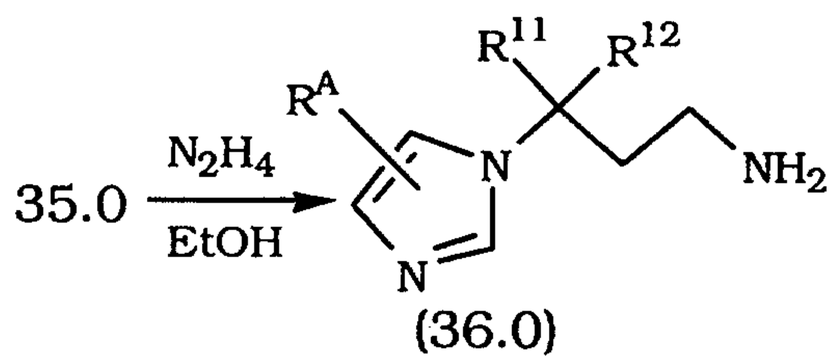
Reaction Scheme 1 (n is 1)

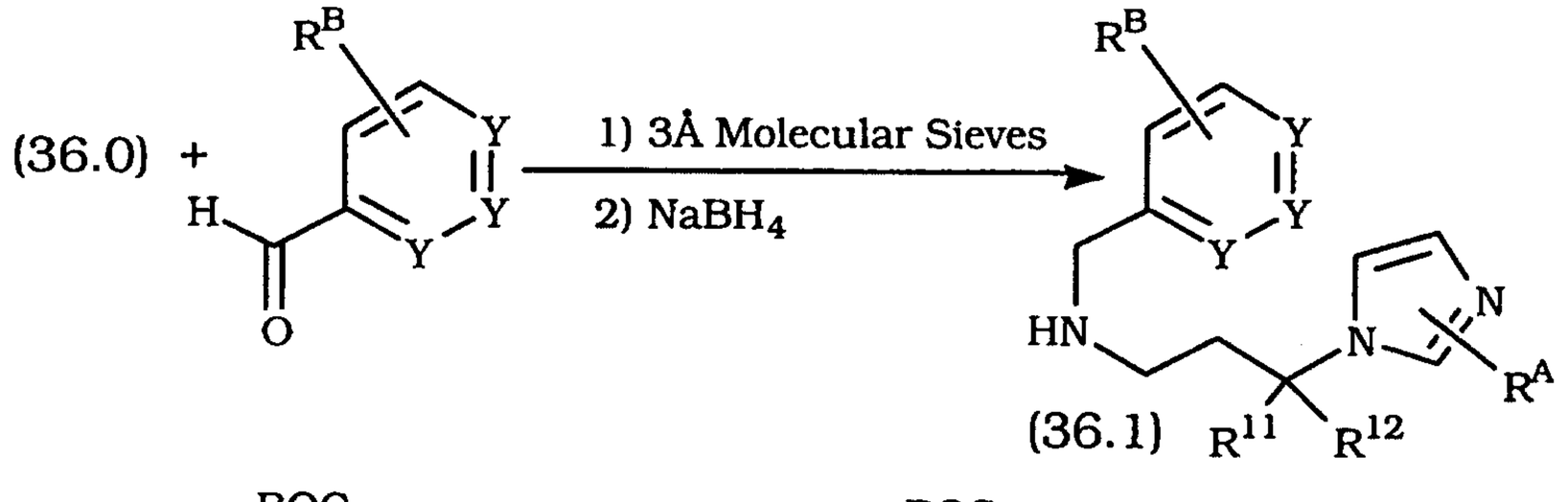


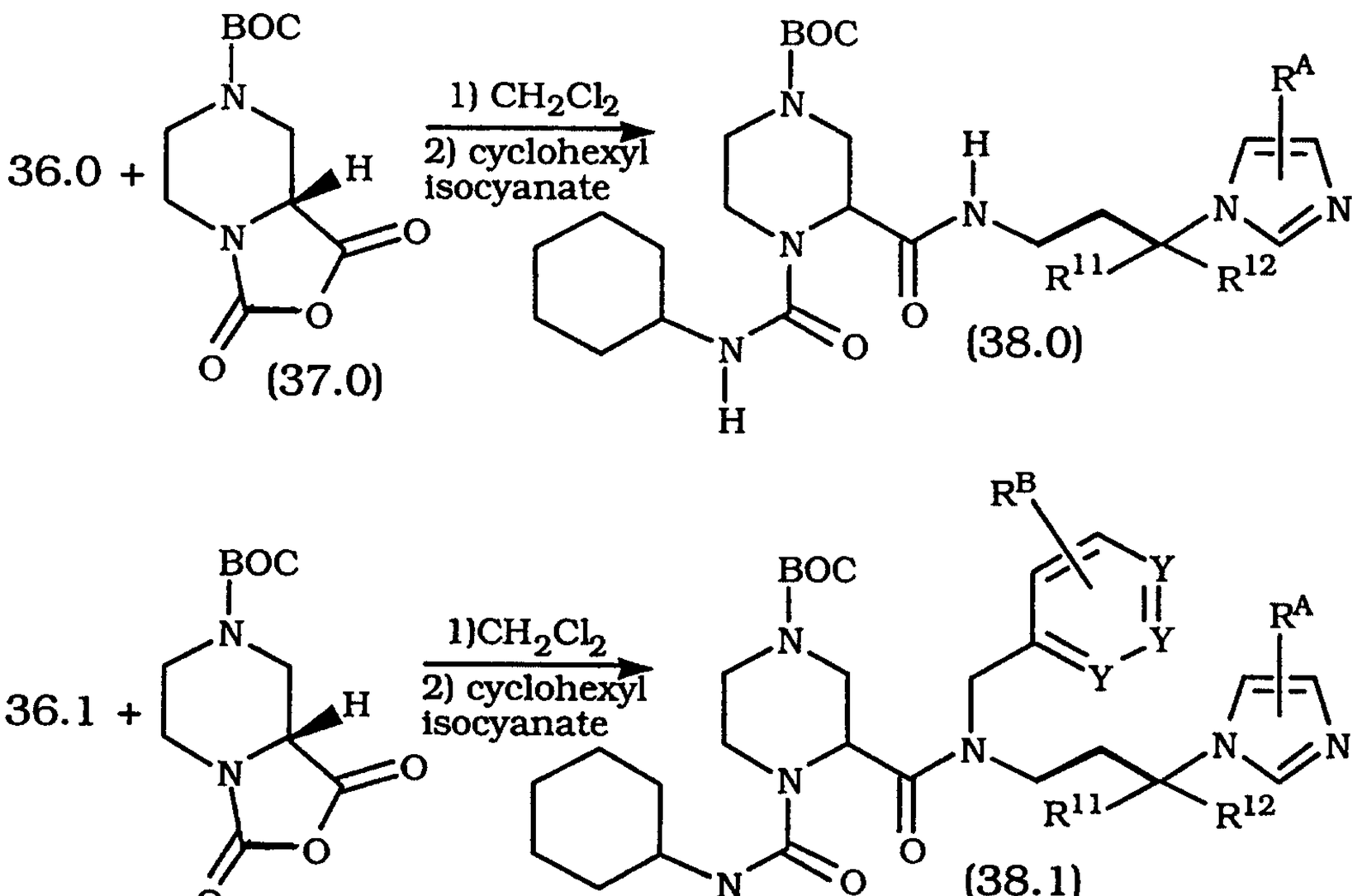
(30.0) (31.0) (32.0)

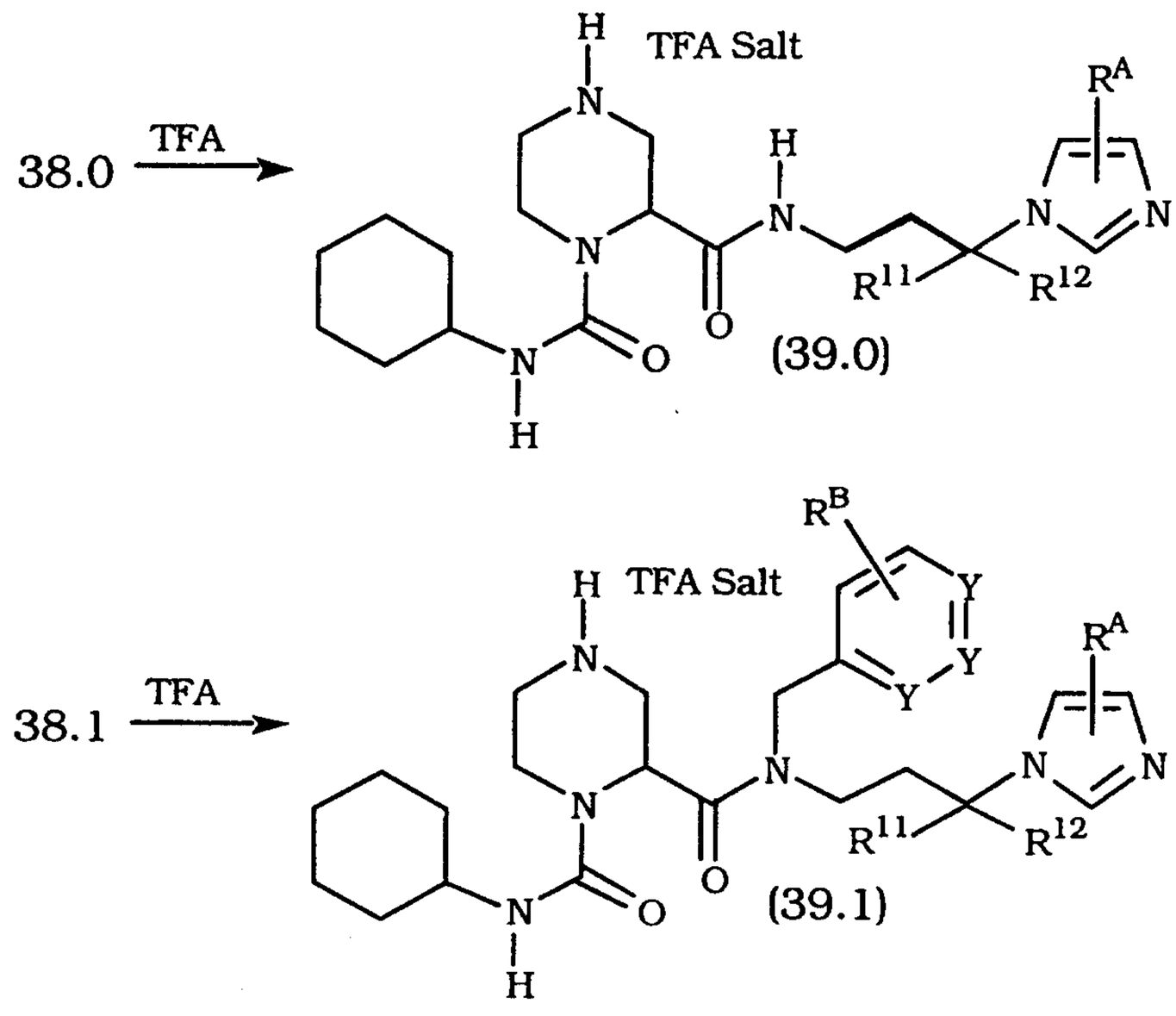


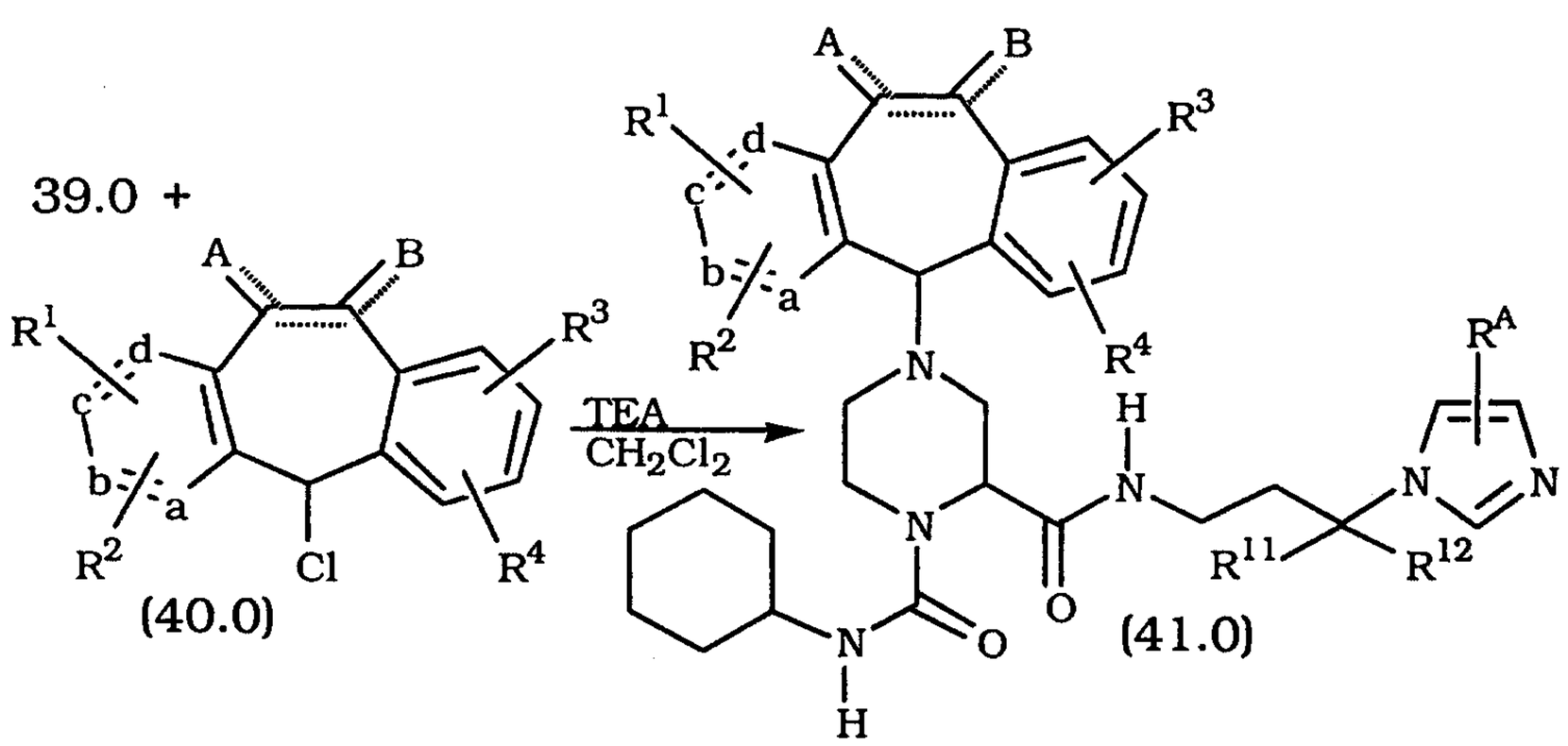


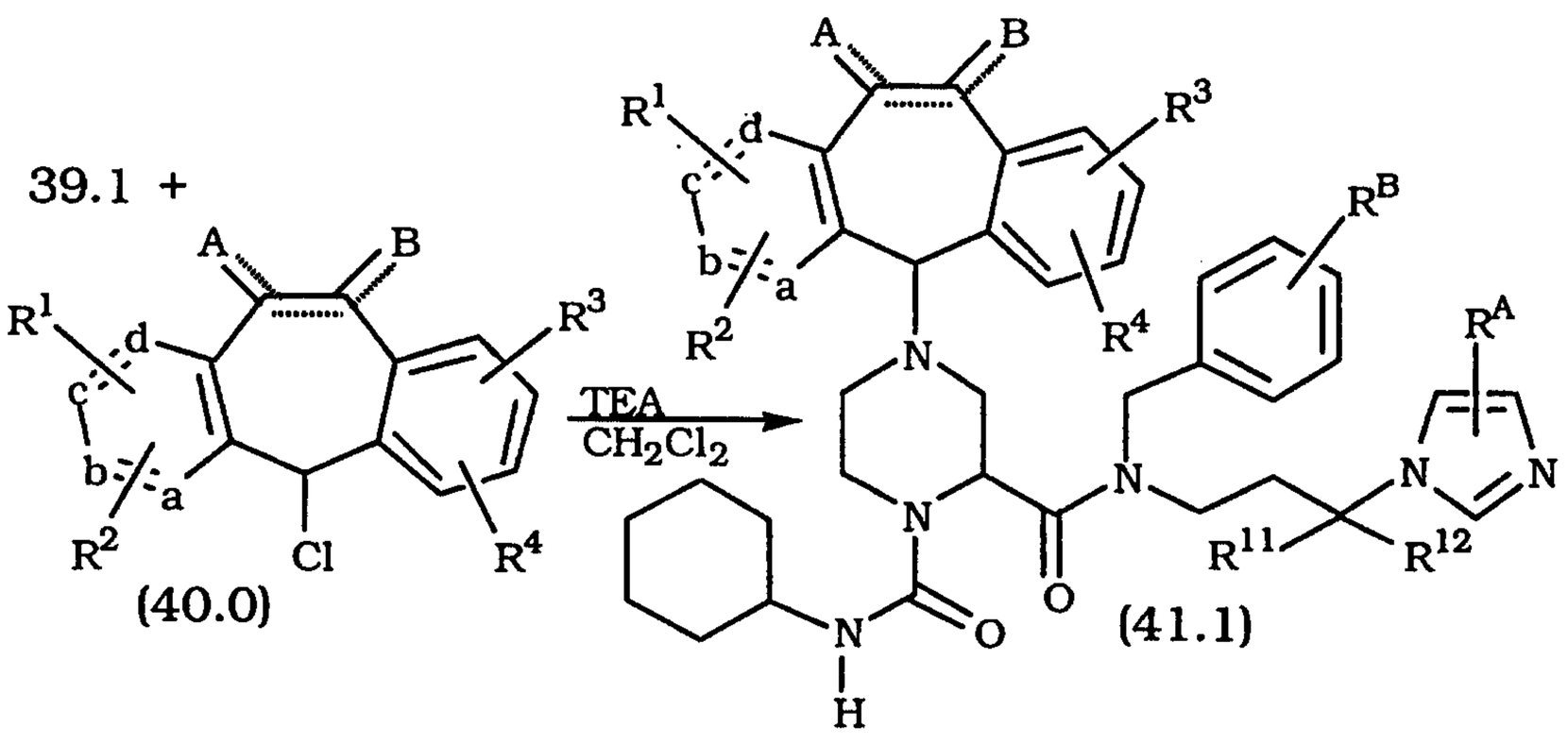







38.0
TFA
TFA Salt
(39.0)
38.1
TFA
TFA Salt
(39.1)


39.0 +
(40.0)
TEA
CH_2Cl_2
(41.0)

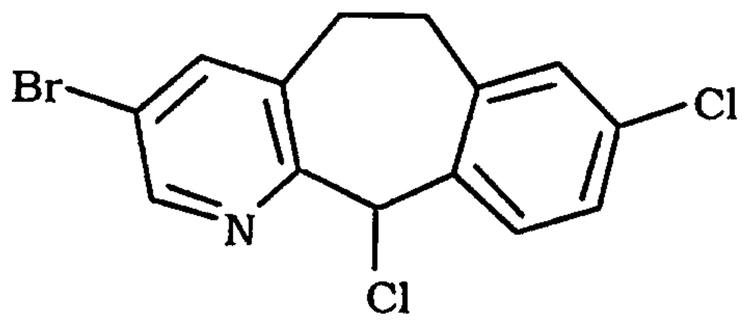

39.1 +
(40.0)
TEA
CH_2Cl_2
(41.1)

In Scheme 1, R^{11} and R^{12} are preferably methyl when H is bound to the amide nitrogen (i.e., when R^8 in formula 1.0 is H), e.g., 41.0, and are preferably H when the amide nitrogen is substituted (i.e., R^8 in formula 1.0 is other than H), e.g., 41.1. Those skilled in the art will appreciate that other acylating agents can be used in place of cyclohexyl isocyanate to obtain compounds having different groups bound to the carbonyl group that is bound to the piperazine nitrogen. Those skilled in the art will also appreciate that other esters can be used in place of compound 31.0 to obtain compounds having different carbon chains between the imidazole ring and the -C(O)NH-group.

Compounds of 41.0 can be prepared beginning with the conjugate addition of imidazole (2-, 4-, and/or 5-substituted) to an appropriately substituted acrylate 31.0 in EtOH at reflux or neat at 90°C. Standard LAH reduction of the ester 32.0 gives the alcohol 33.0 which can be converted to the phthalimide 35.0 via the Mitsunobu reaction. Removal of the phthalimido group with hydrazine in EtOH at reflux gives amine 36.0. This amine readily opens the piperazine anhydride 37.0 with the evolution of CO_2 and subsequent reaction with isocyanates gives the one pot conversion to urea 38.0. Removal of the BOC-group with 50% TFA at room temperature gives the salt 39.0, which can be readily coupled to the tricyclic chloride 40.0 to give the desired product 41.0.

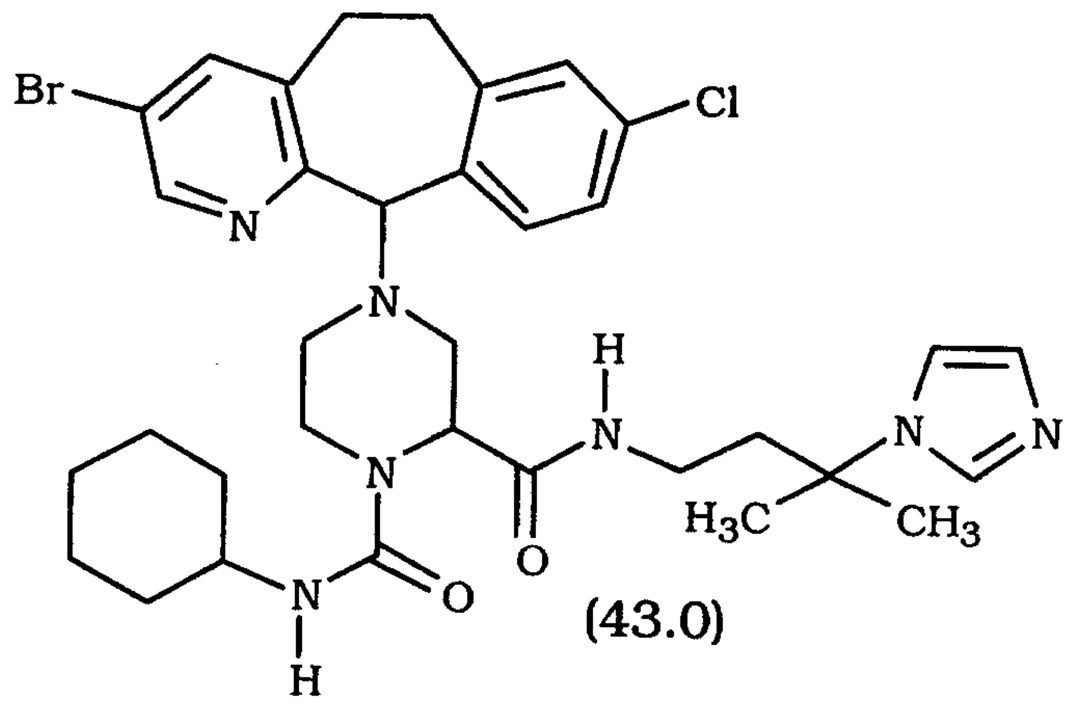
In Scheme 1, and the Schemes that follow, Y represents C, N or N^+O^- such that there can only be 0-2 Y substituents that are independently selected from N or N^+O^-. R^A represents the optional substituents in the imidazole ring that are defined for imidazole ring 4.0 above. R^B represents the optional substituents defined above for the aryl or heteroaryl groups for R^8.

For example, following Reaction Scheme 1, wherein R^{11} and R^{12} are methyl, and using compound 42.0 (see Preparative Example 40 in WO 95/10516 published April 20, 1995)



(42.0)

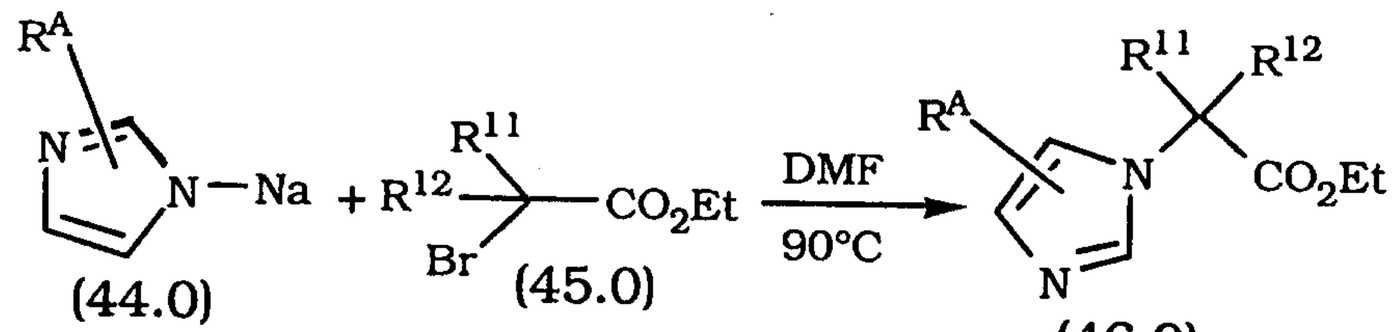
compound 43.0



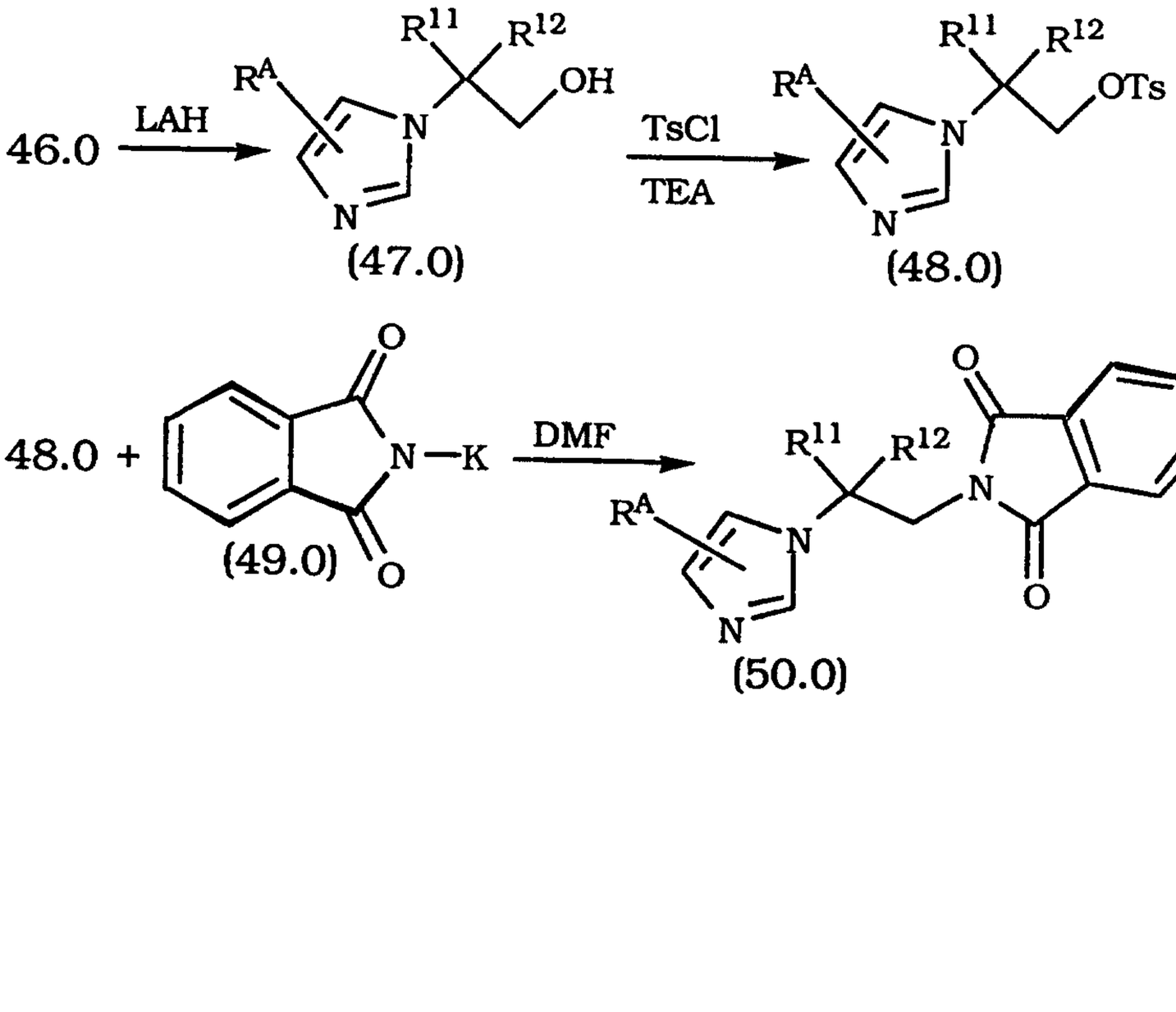
(43.0)

can be obtained.

Reaction Scheme 2 (n is 0)

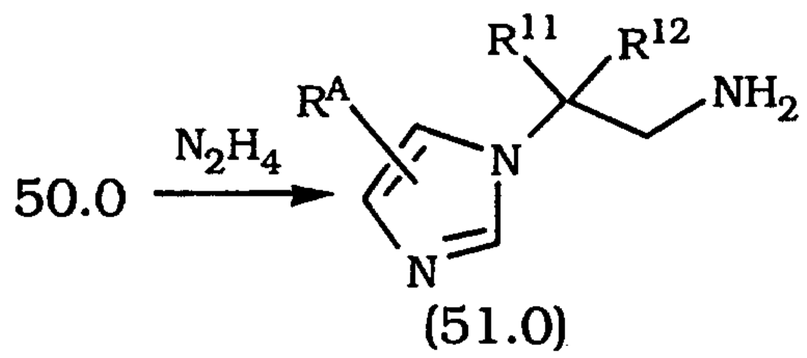


(44.0) (45.0) (46.0)

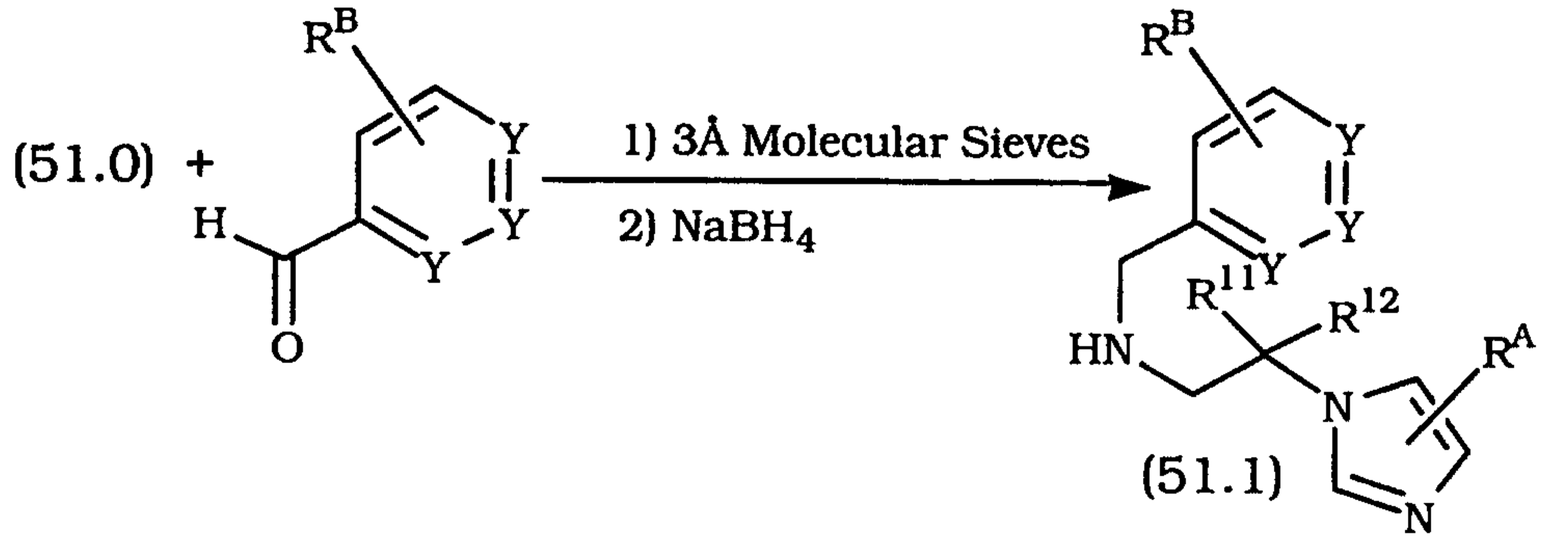


(47.0) (48.0)

(49.0) (50.0)



(51.0)

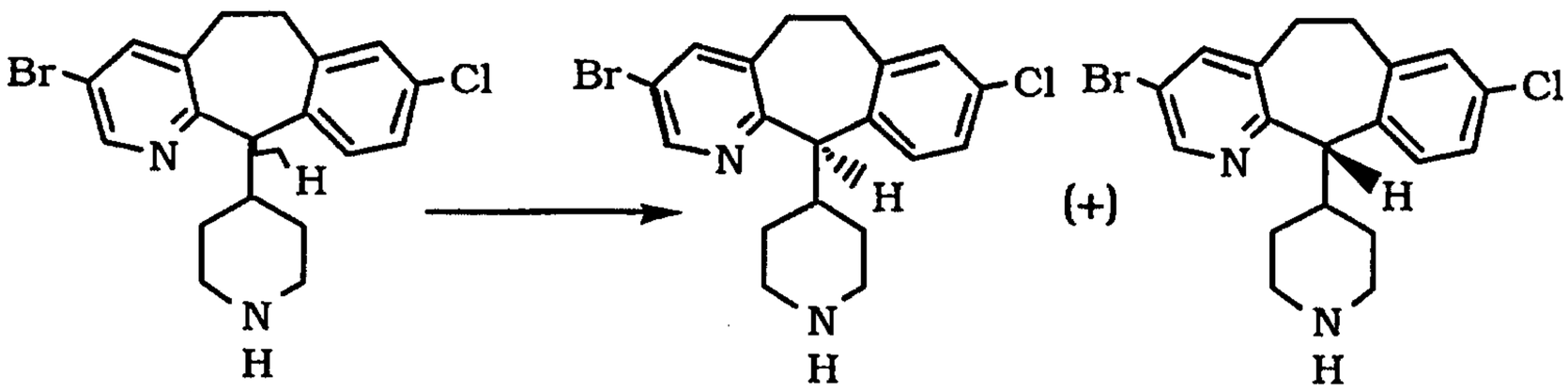


(51.1)

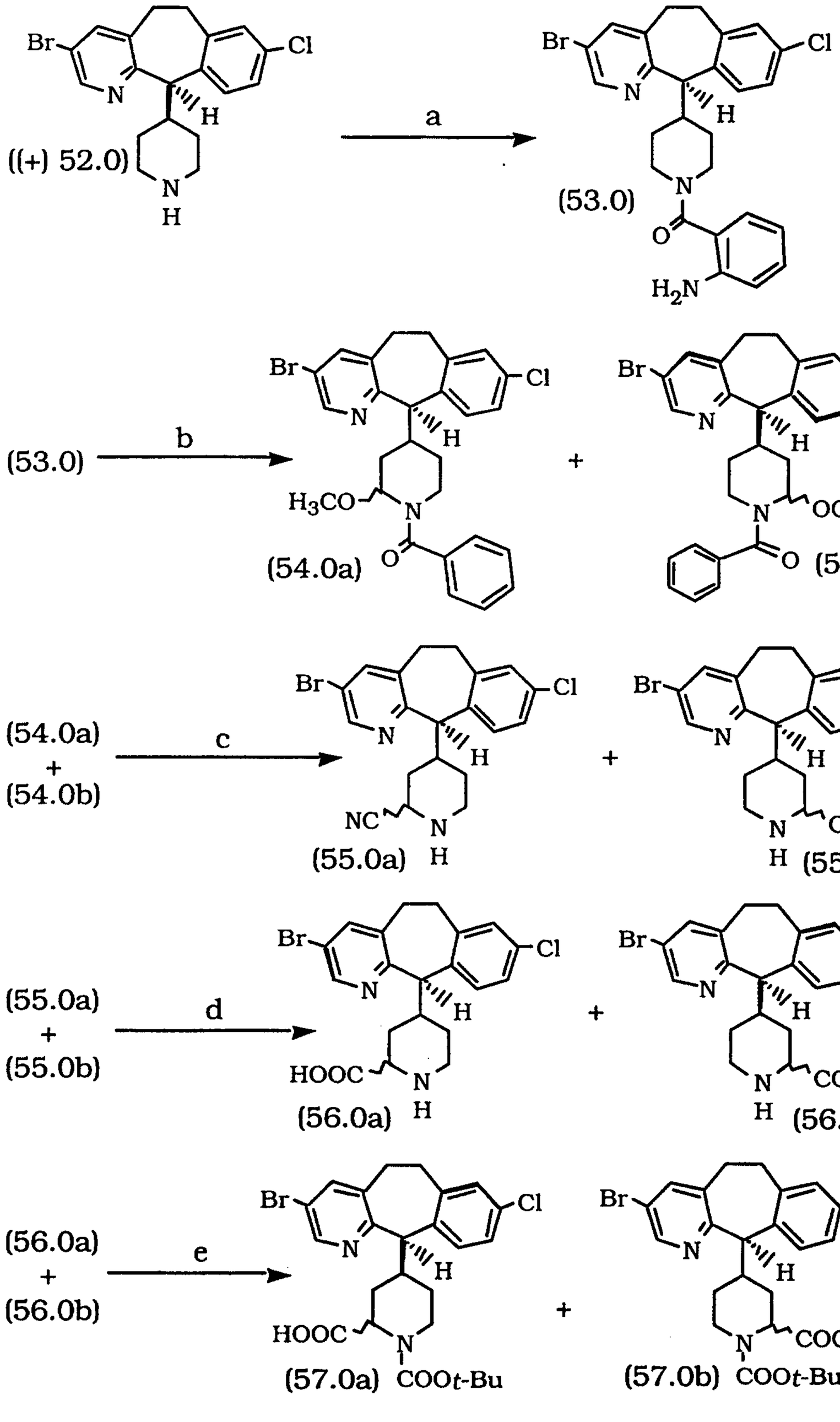
The synthesis of the intermediate amine 51.0 begins with the alkylation of the sodium salt of imidazole (or substituted imidazole) 44.0 with 45.0 at 90°C. Standard LAH reduction of the ester 46.0 gives the alcohol 47.0. Tosylation of 47.0 and displacement of tosylate with potassium phthalimide 49.0 in DMF at 90°C gives the phthalimido derivative 50.0 which can be readily converted to the amine 51.0 with hydrazine in refluxing EtOH. Compounds wherein $R^8 \neq H$ can be prepared as described in Scheme 1.

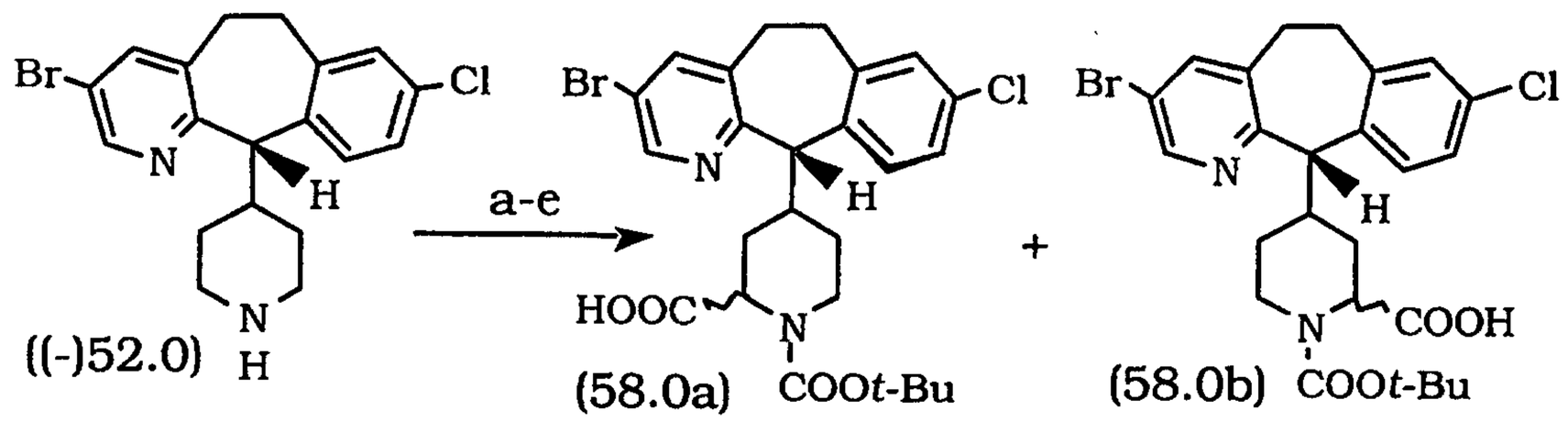
Similar to the procedure set forth in Scheme 1 for 36.0 and 36.1, 51.0 and 51.1 in Scheme 2 are reacted to form compounds of formula 1.0. In Scheme 2, R^{11} and R^{12} are preferably methyl when H is bound to the amide nitrogen (i.e., when R^8 in formula 1.0 is H), and are preferably H when the amide nitrogen is substituted (i.e., R^8 in formula 1.0 is other than H).

Reaction Scheme 3 Ring IV = piperidine)



((±) 52.0) ((+) 52.0) ((-) 52.0)

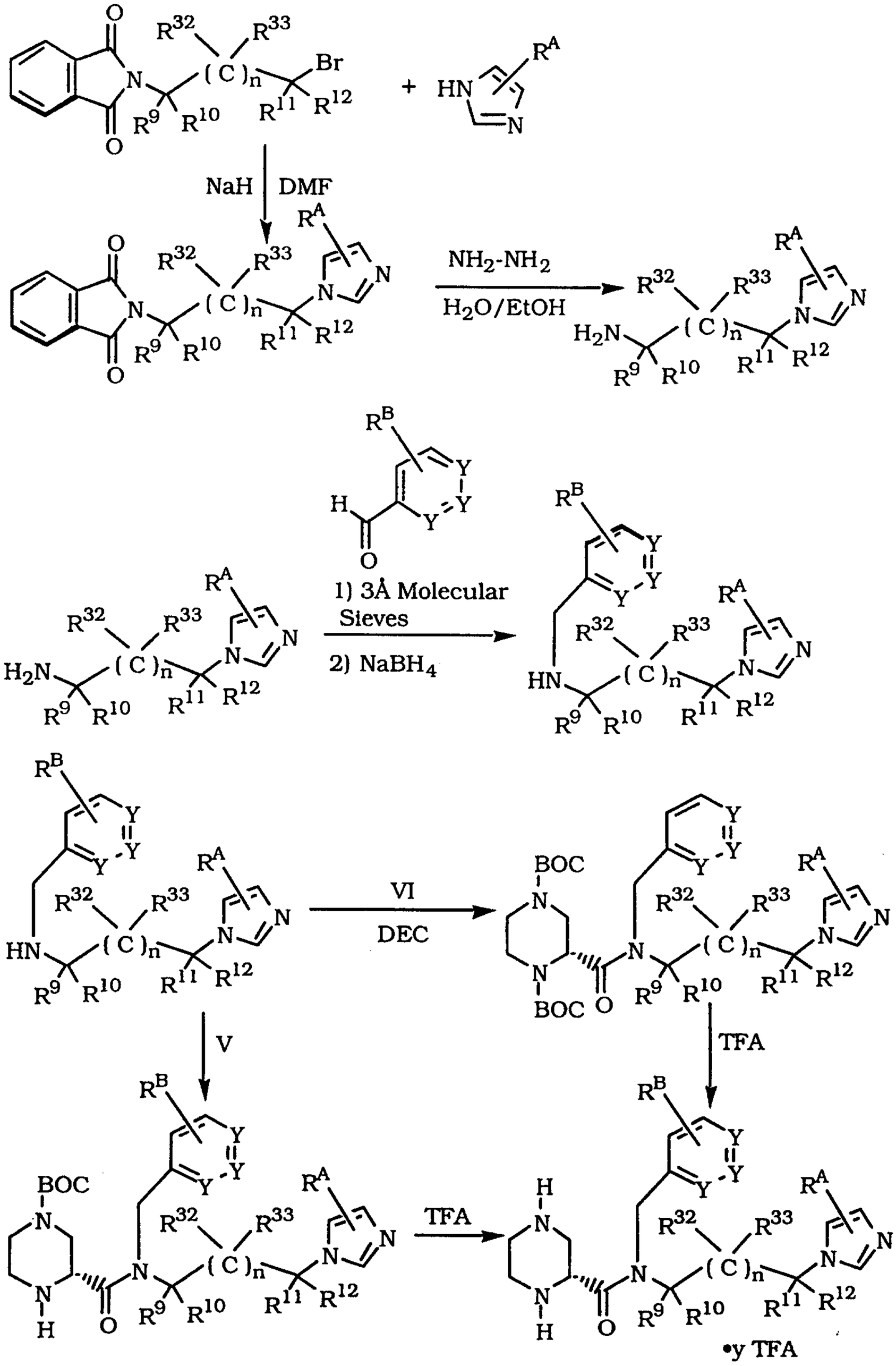

Br
Cl
N
H
((+) 52.0)
N
H
a
(53.0)
O
H_2N
b
H_3CO
OCH_3
(54.0a)
(54.0b)
c
NC
CN
(55.0a)
(55.0b)
d
HOOC
COOH
(56.0a)
(56.0b)
e
COO*t*-Bu
(57.0a)
(57.0b)

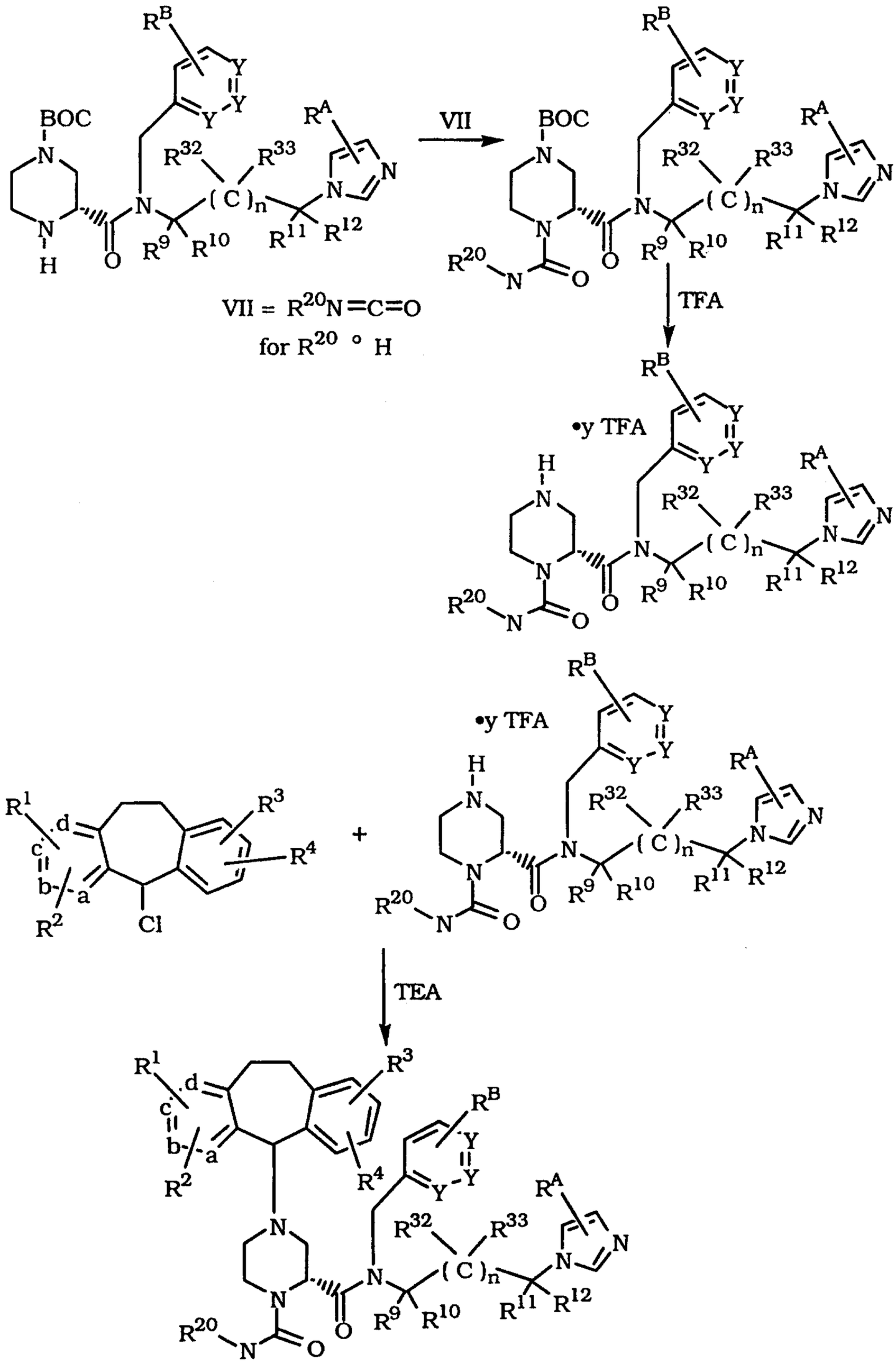


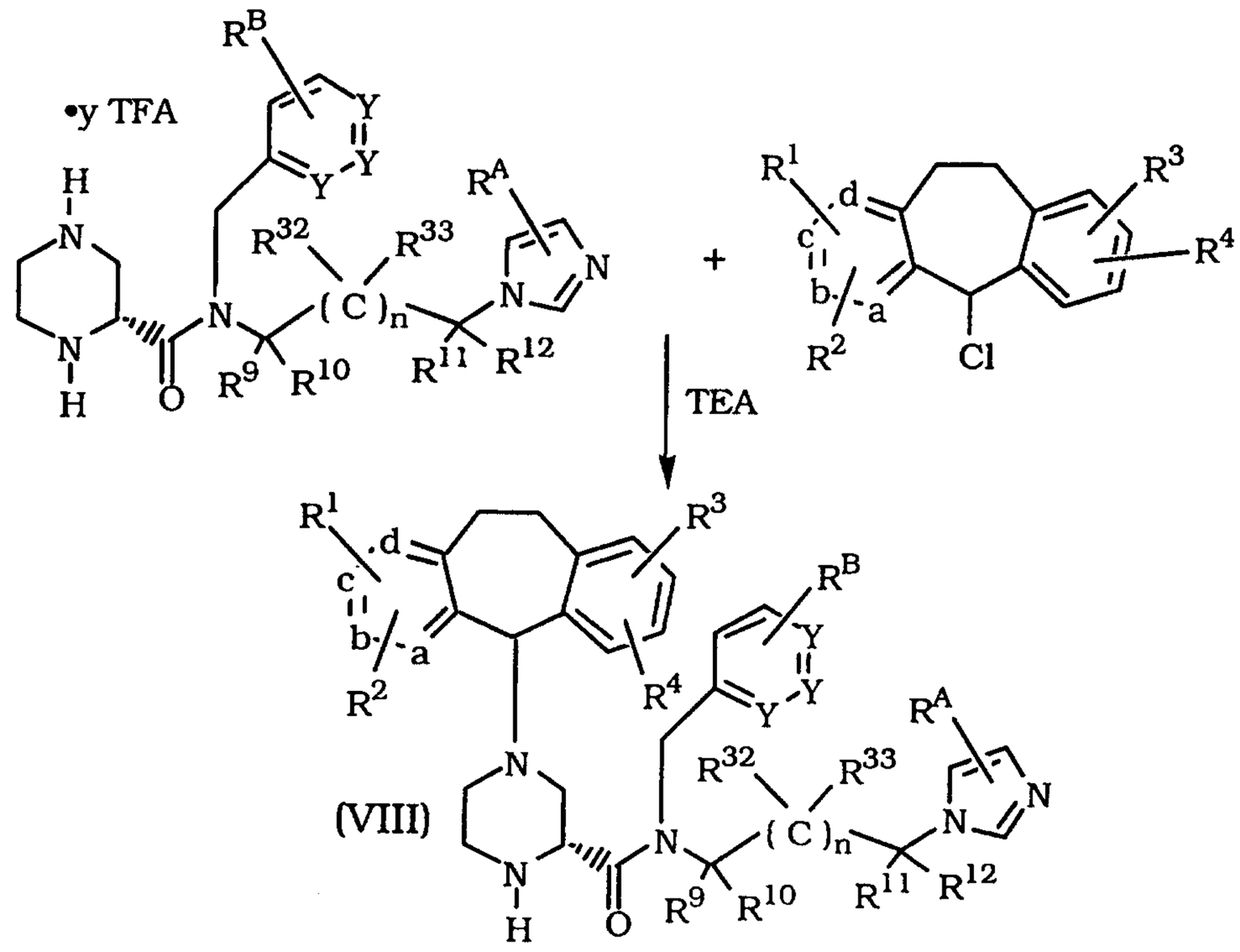
Compound (±) 52.0 is resolved following procedures similar to those disclosed in WO97/23478 (published July 3, 1997).

The reagents used in Reaction Scheme 3 are: Reaction Step a: Isatoic anhydride/methylene chloride; Reaction Step b: sodium nitrite/hydrochloric acid/methanol/cuprous chloride; Reaction Step c: (i) aq. hydrochloric acid/methanol/reflux (ii) sodium hydroxide/sodium cyanide; Reaction Step d: conc. hydrochloric acid/reflux.; and Reaction Step e: di-*tert*.butyldicarbonate/-sodium hydroxide/tetrahydrofuran.

Reaction Scheme 4 (n is 1-5)

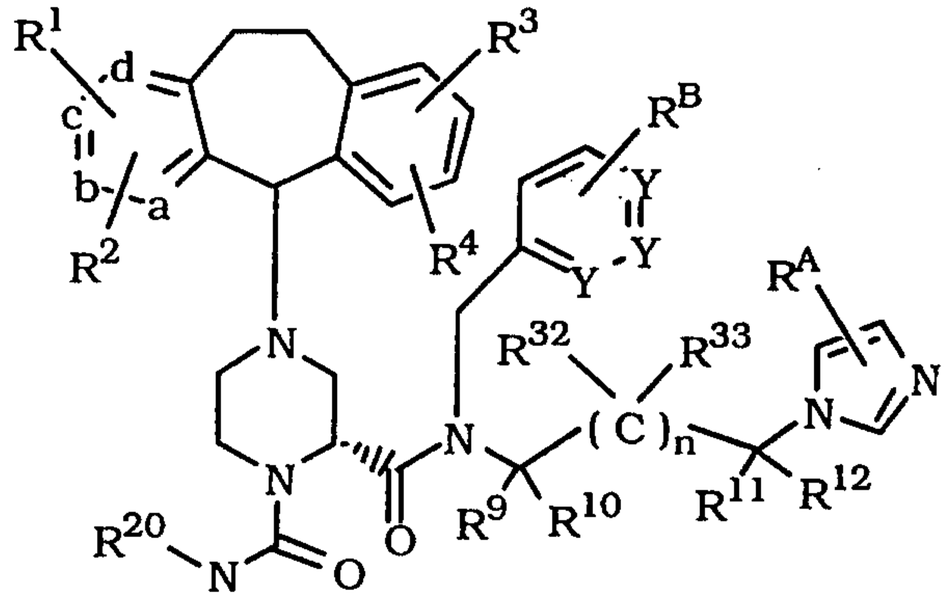


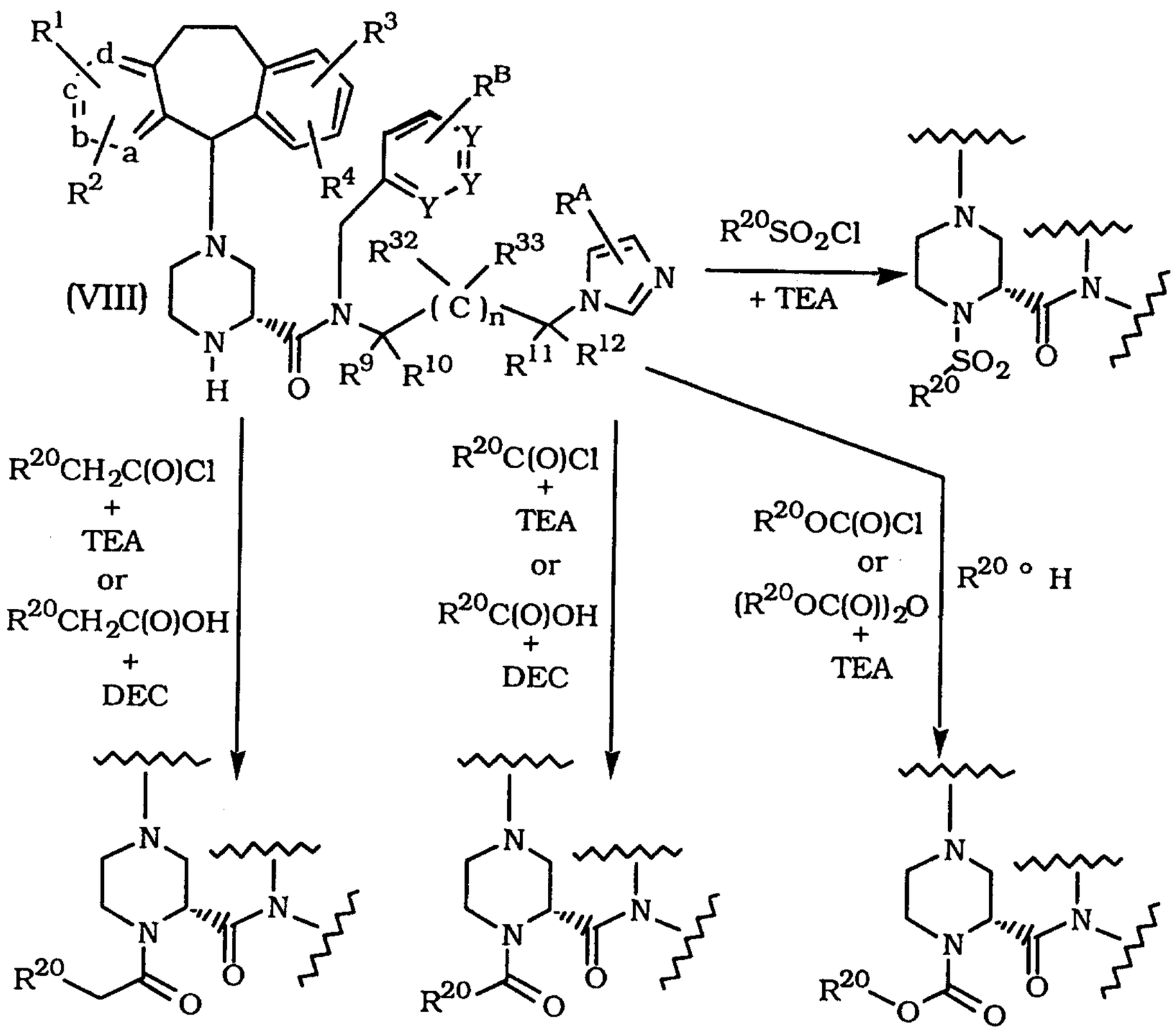

VII
VII = R20N=C=O
for R20 ° H
TFA
•y TFA
TEA



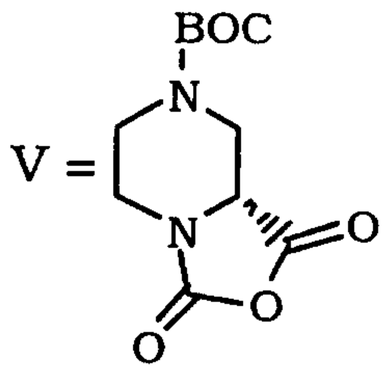
(VIII) + $R^{20}N=C=O$ ⟶

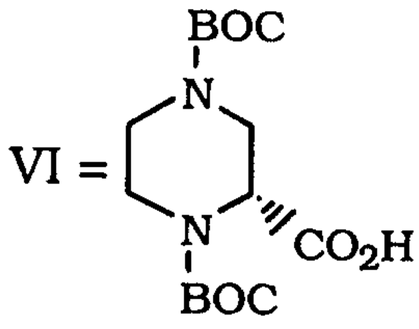
for R^{20} ° H



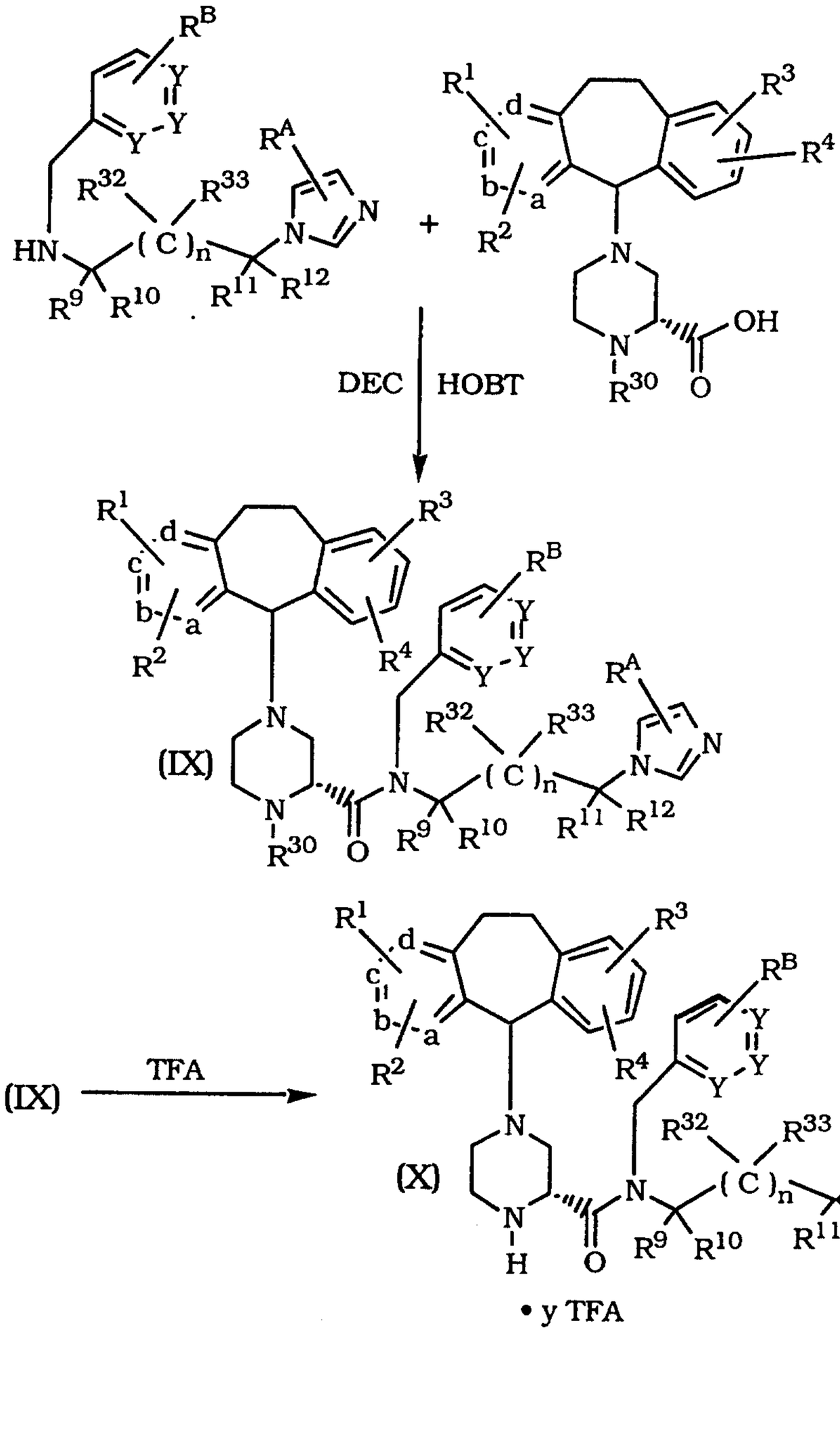


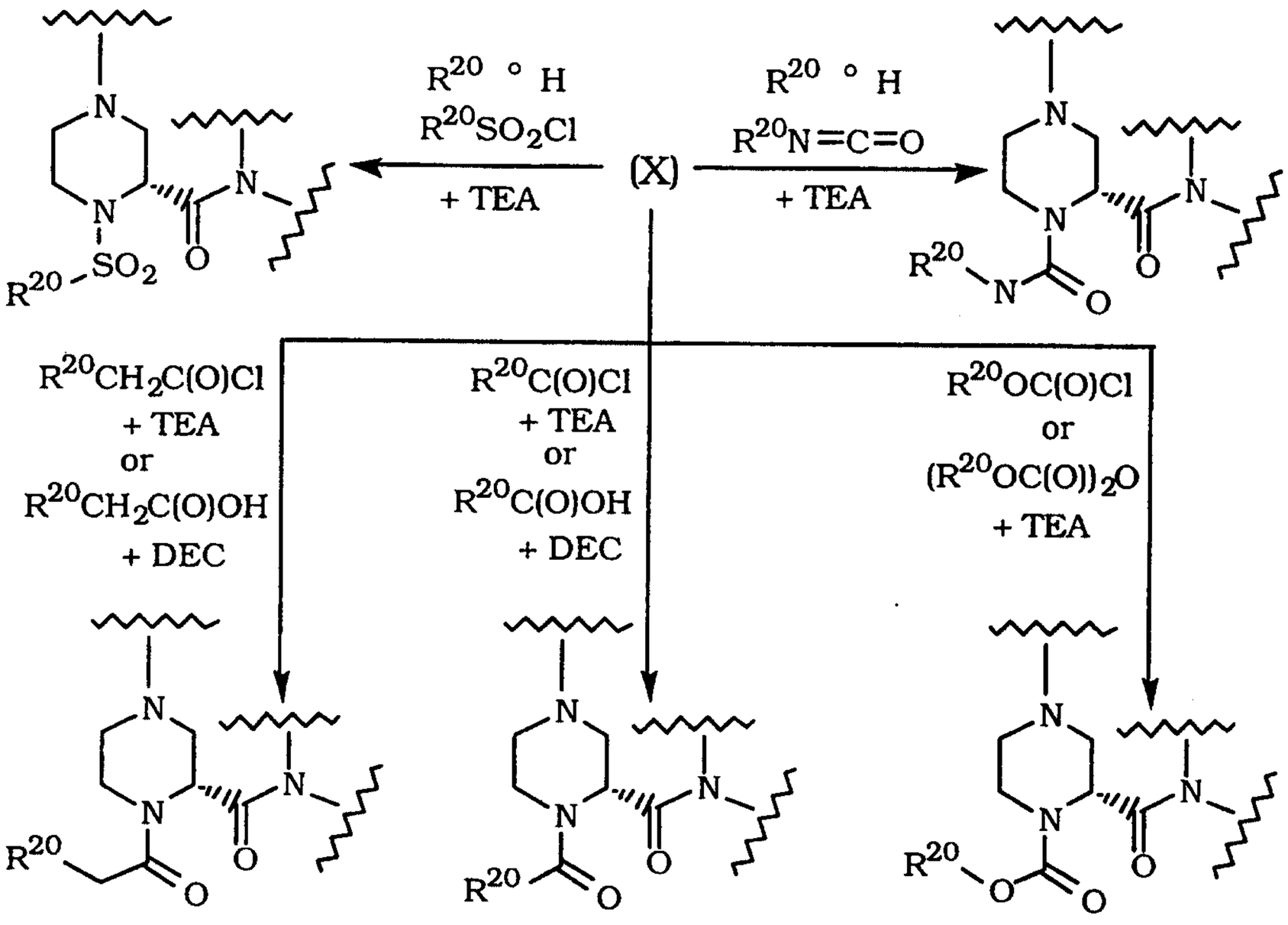
Reactants V and VI are:



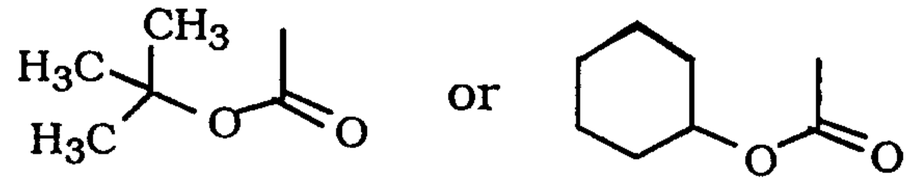


Reaction Scheme 5



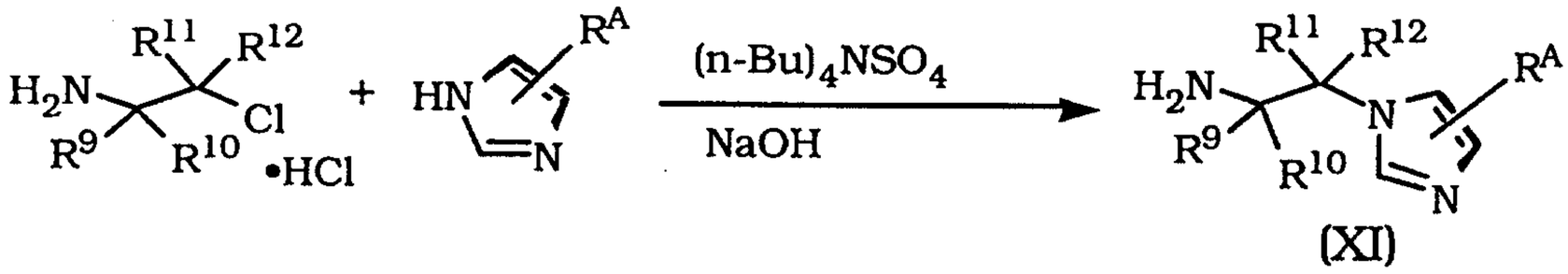


In Scheme 5, R^{30} represents:



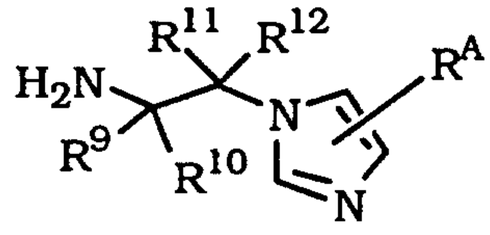
or

5 Reaction Scheme 6 - n is 0



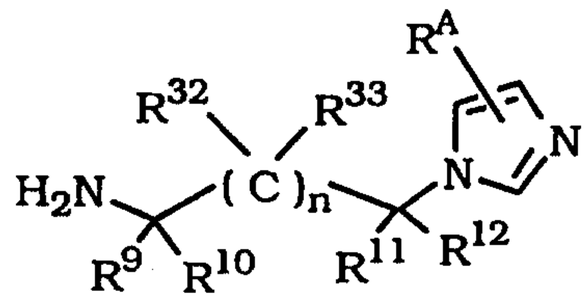
(XI)

In Scheme 6, the procedure set forth in Scheme 4 is followed, but using

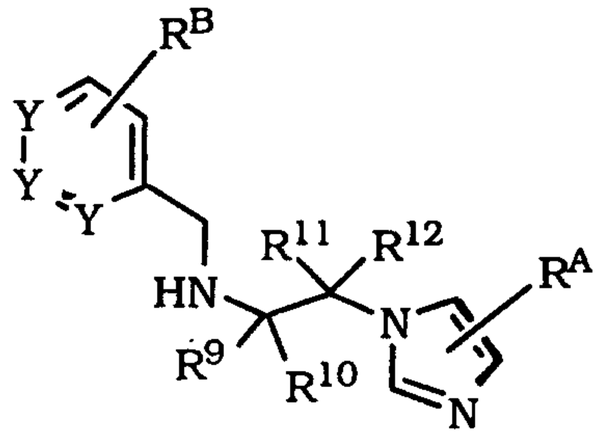


(XI)

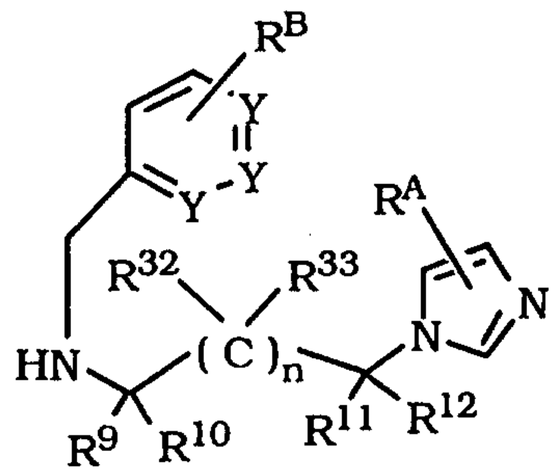
10 instead of



to obtain the corresponding urea (-C(O)NHR^{20}), amide (-C(O)CH$_2$R^{20} or -C(O)R^{20}), sulfonamide (-SO$_2$R^{20}) or carbamate (-C(O)OR^{20}) products, wherein n is 0, can be prepared. Similarly, using

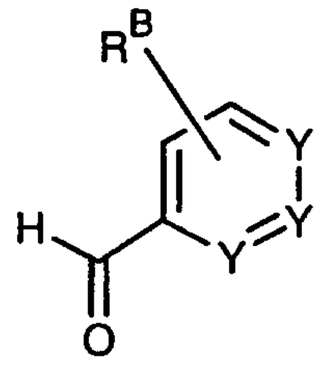


(obtained from XI following the procedures in Scheme 4), instead of



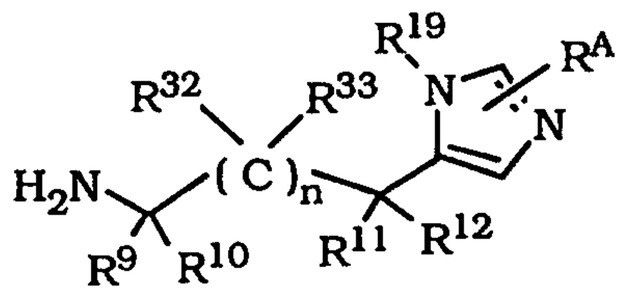
in Scheme 4 and 5 produces the corresponding ureas, amides, sulfonamides and carbamates wherein n is 0.

Those skilled in the art will appreciate that in Schemes 1, 2 and 4-6, other aldehydes can be used in place of

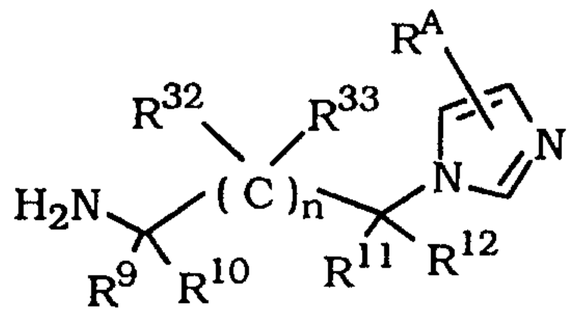


to obtain the other substituents for R^8 in formula 1.0.

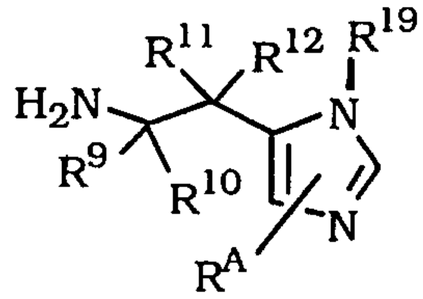
Those skilled in the art will also appreciate that using



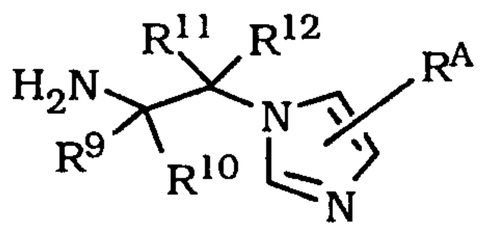
instead of



in Schemes 4 and 5, and using

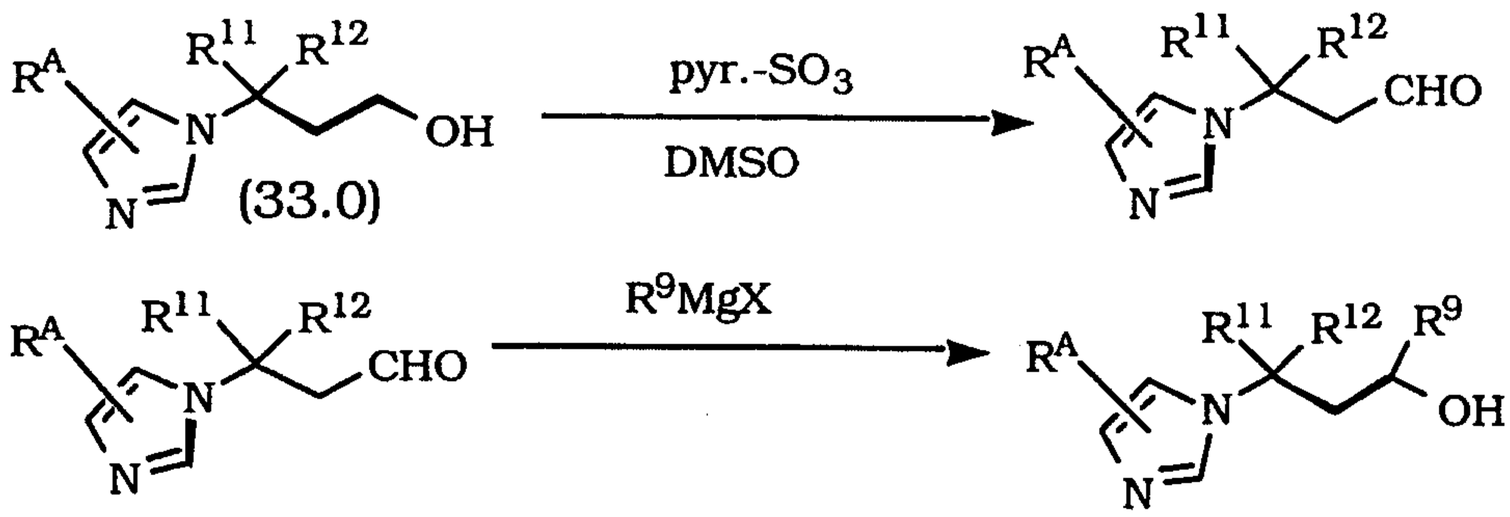


instead of



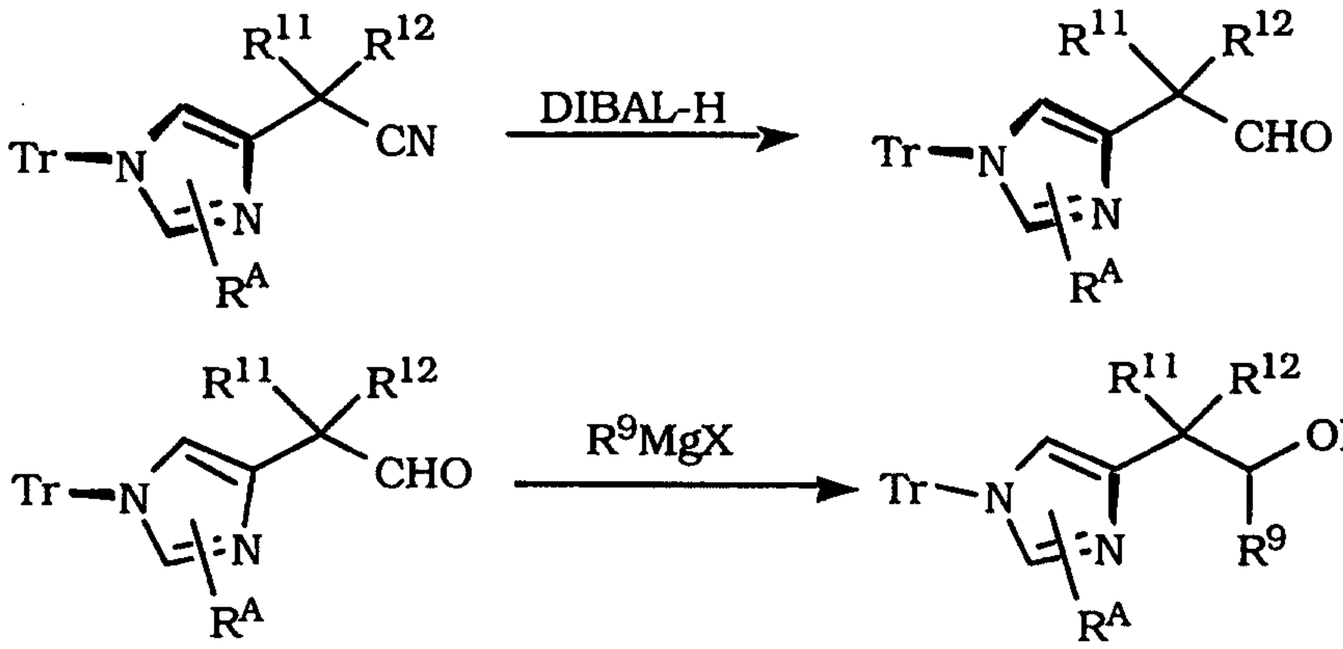
in Scheme 6 will provide the corresponding compounds wherein the imidazole is bound to the alkyl chain by a ring carbon.

Reaction Scheme 7 (R^9 and R^{10} Are Other Than H)



In Scheme 7, the alcohol 33.0 can be oxidized under standard conditions to give the aldehyde. Addition of the corresponding Grignard of R^9 gives the alcohol which can be carried on to amine as in Scheme 1 or subject to reoxidation to the ketone followed by Grignard addition of R^{10}. In the case where R^9=R^{10}, the ester 32.0 (Scheme 1) can be used as the electrophile with 2 equivalents of the appropriate Grignard reagent being added.

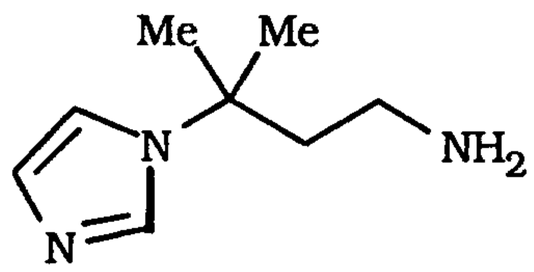
Reaction Scheme 8 (R^9 and R^{10} Are Other Than H, C-Linked Imidazole)



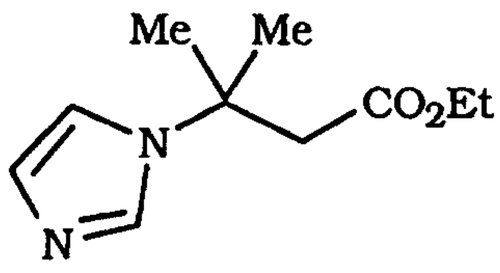
In Scheme 8, the nitrile may be reduced with DIBAL-H to the aldehyde. Similar to the procedure in Scheme 7, the aldehyde can then be treated with the appropriate Grignard reagent to give the alcohol. There can be an additional round of oxidation and Grignard addition to give the R^9, R^{10} disubstituted derivatives with either $R^9 = R^{10}$ or $R^9 \bullet R^{10}$. The resulting alcohol may be converted to the amine by the methodology shown in either Schemes 1 or 2.

Compounds useful in this invention are exemplified by the following examples, which examples should not be construed as limiting the scope of the disclosure.

PREPARATIVE EXAMPLE 1



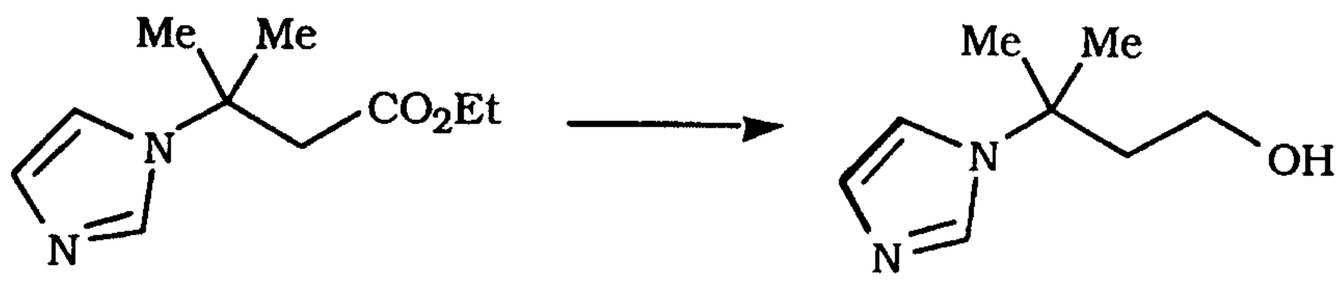
Step A



Ethyl 2,2-dimethyl acrylate (50.0g, 2.0 eq.) was stirred with imidazole (13.28g, 200 mmol) at 90° C for 48 hours. The resulting

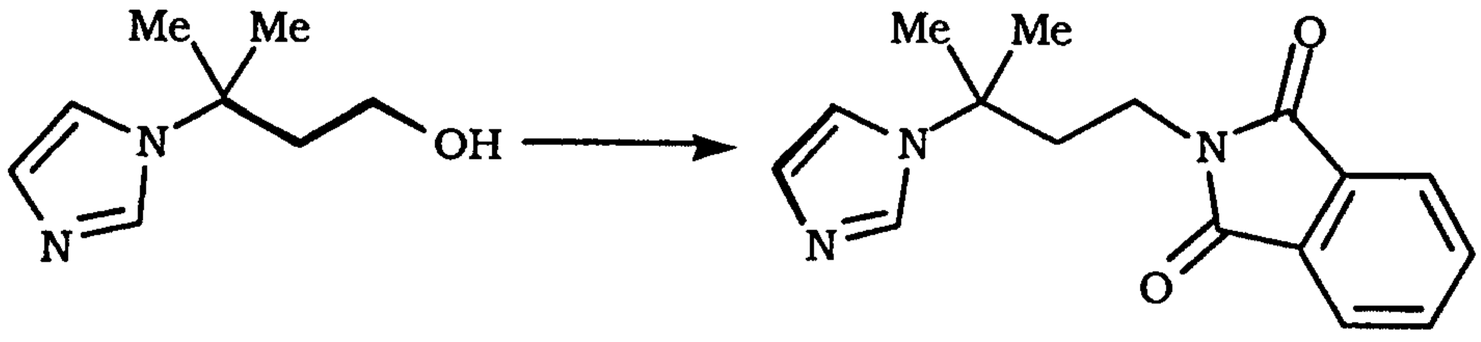
solution was cooled, diluted with water (150 mL) and CH_2Cl_2 (150 mL) and separated. The aqueous layer was washed with CH_2Cl_2 (2 x 75 mL) and the combined organics were dried over Na_2SO_4 and concentrated *in vacuo*. The crude mixture was purified by flash chromatography using a 10% MeOH in CH_2Cl_2 solution as eluent to give the pure product as a clear oil (11.27g, 29% yield). CIMS: MH^+= 197.

Step B



A solution of the title compound from Step A (10.0g, 50.96 mmol) was treated with $LiAlH_4$ (51 mL, 1M solution in ether, 1.0 eq.). The reaction mixture was stirred one hour at room temperature before quenching by the dropwise addition of saturated Na_2SO_4 (~3.0 mL). The resulting slurry was dried with Na_2SO_4 (solid), diluted with EtOAc (100 mL) and filtered through a plug of Celite. The filtrate was concentrated to give a yellow oil (6.87, 87% yield) which was used without further purification. CIMS: MH^+= 155.

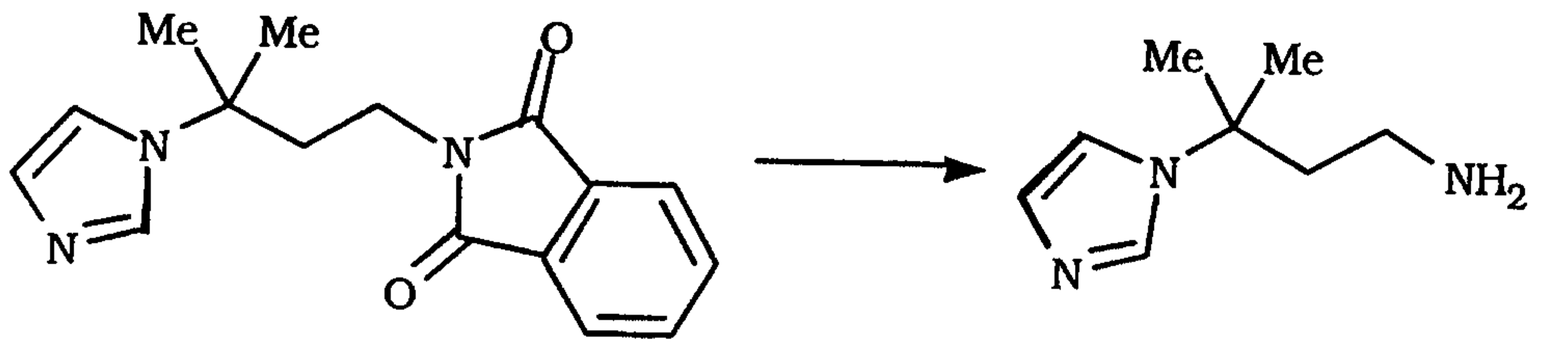
Step C



To a solution of the title compound Step B (6.85g, 44.42 mmol), phthalimide (7.19g, 1.1 eq.), and Ph_3P (12.82g, 1.1 eq.) in THF (200 mL) at 0°C was added DEAD (7.69 mL, 1.1 eq.) over 10 minutes. The resulting solution was warmed to room temperature and stirred 48 hours. The reaction mixture was concentrated under

reduced pressure and the product isolated by crystallization from CH_2Cl_2/Et_2O to give a white solid (10.03 g, 79% yield). CIMS: MH^+= 284

Step D

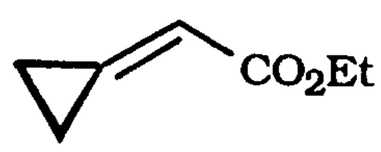
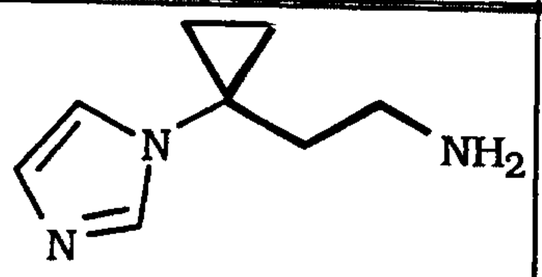


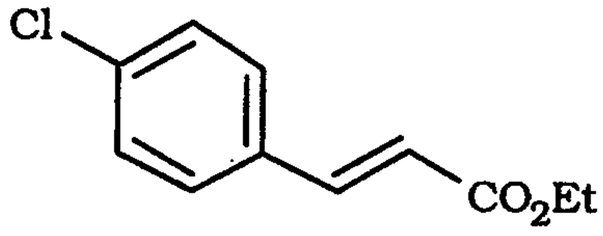
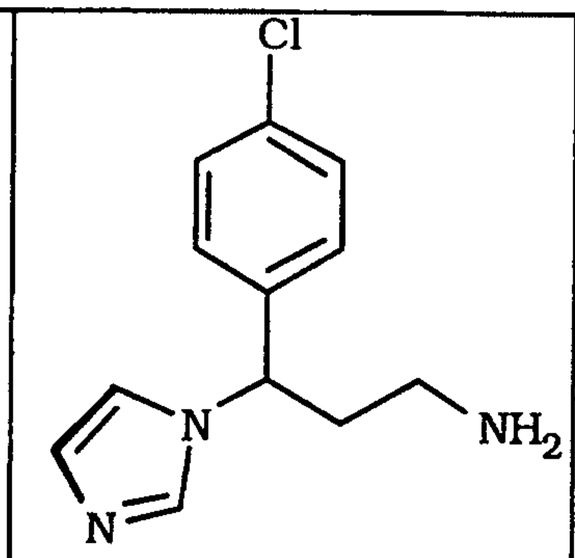
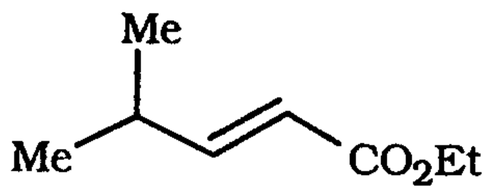
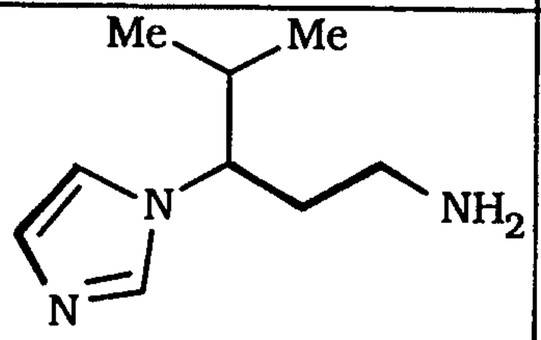
A solution of the title compound from Step C (9.50g, 33.53 mmol) and N_2H_4 (1.25 mL, 1.2 eq.) in EtOH (100 mL) was heated at reflux 4 hours. The resulting slurry was cooled, filtered, and the filtrate concentrated under reduced pressure. The crude product was purified by flash chromatography using a 15% (10% NH_4OH in MeOH) solution in CH_2Cl_2 as eluent to give a pale yellow oil (2.80g, 53% yield). LCMS: MH^+= 154

PREPARATIVE EXAMPLES 2-4

By essentially the same procedure as that set forth in Example 1, the amines in Column 3 of Table 1 were synthesized from the esters in Column 2. "No." represents "Preparative Example Number".

TABLE 1

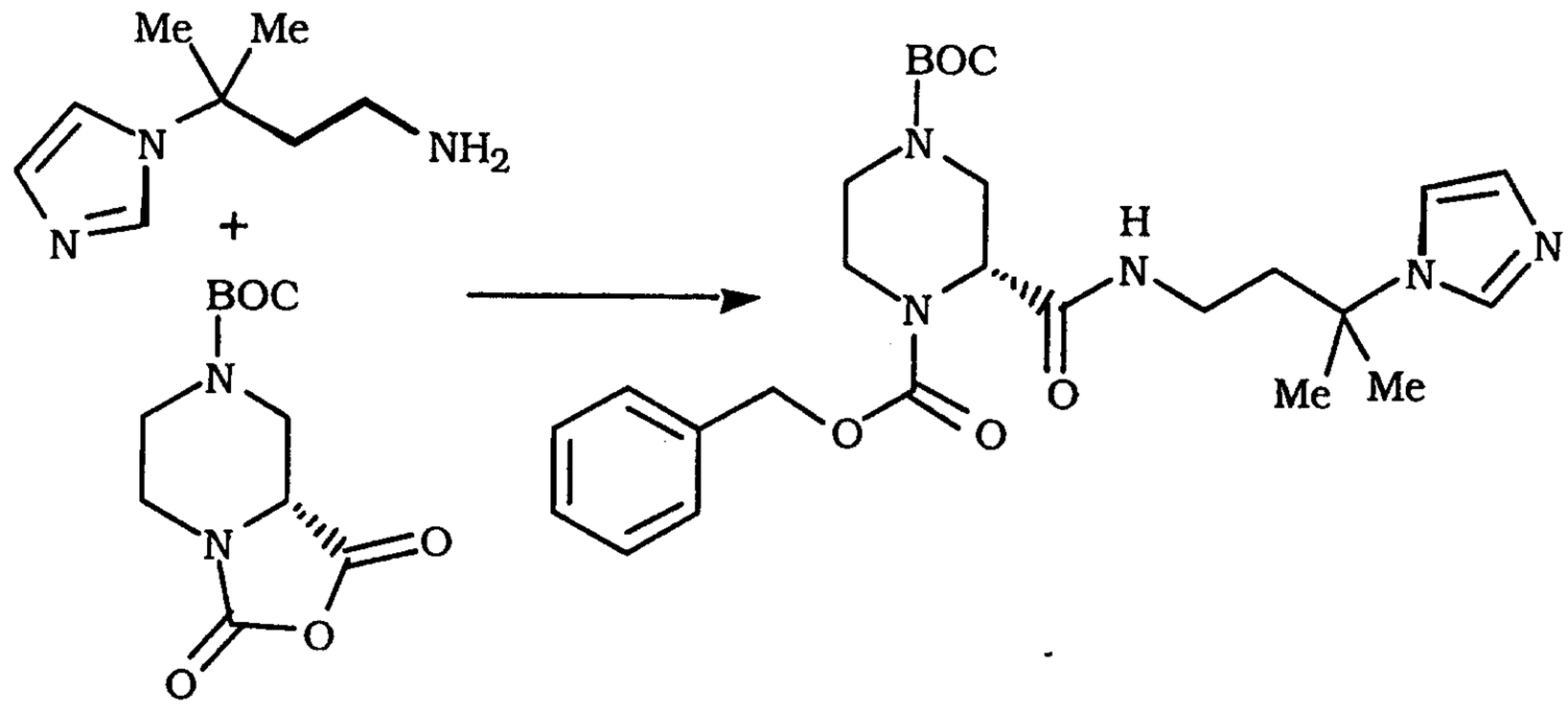
No.	ESTER	AMINE	Mass Spec
2			CIMS: MH^+= 152

3			CIMS: MH^+= 236
4			MH^+= 168

PREPARATIVE EXAMPLE 5

Piperazine anhydride (Preparative Example 44) (0.28g, 1.0 eq.) was added portionwise to a solution of the title compound from Example 1 (0.17g, 1.2 mmol) in CH_2Cl_2 (5.0 mL) and the resulting solution stirred 10 minutes at room temperature before adding cyclohexyl isocyanate (0.21 mL, 1.5 eq.). After stirring at room temperature 15 minutes, the reaction mixture was quenched by the addition of MeOH (1 mL), concentrated in vacuo, and purified by flash chromatography using a 10% MeOH in CH_2Cl_2 solution as eluent to yield a white solid (0.46g, 85% yield). FABMS: MH^+= 491.

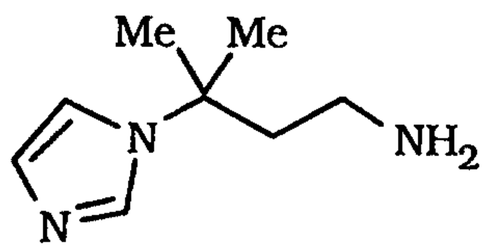
PREPARATIVE EXAMPLE 6



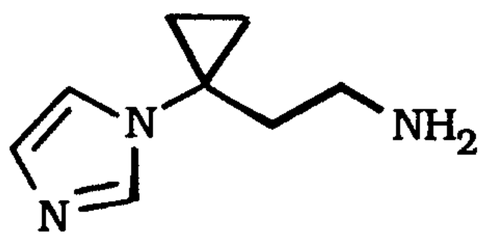
By the essentially the same procedure as that set forth in Preparative Example 5, except using = N-(benzyloxycarbonyloxy)-succinimide (CBZ-OSuc) instead of cyclohexyl isocyanate, the title compound was prepared (0.16g, 84% yield).

PREPARATIVE EXAMPLE 6.1

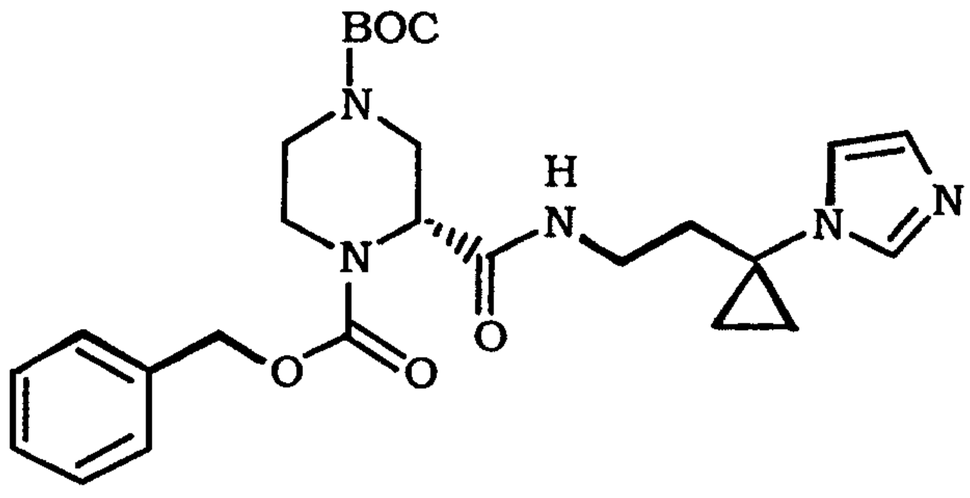
By essentially the same procedure as set forth in Preparative Example 6, except instead of the amine



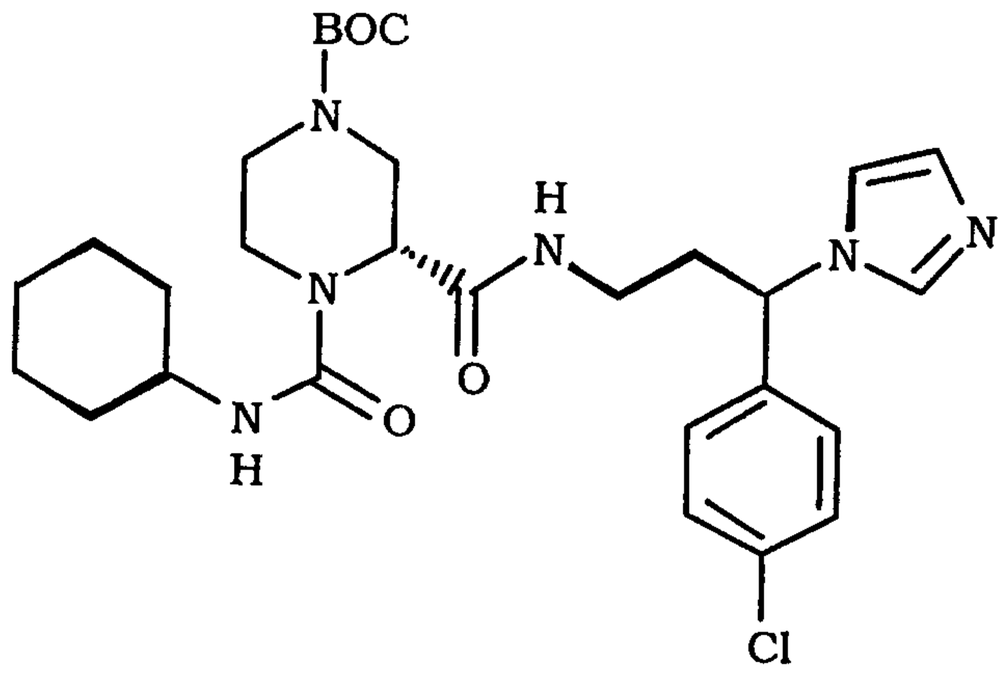
use the amine from Preparative Example 2



to obtain

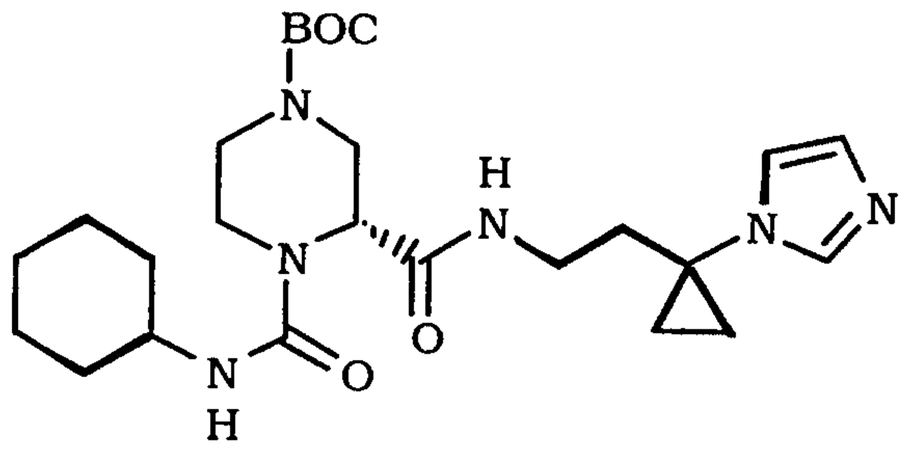


PREPARATIVE EXAMPLE 7



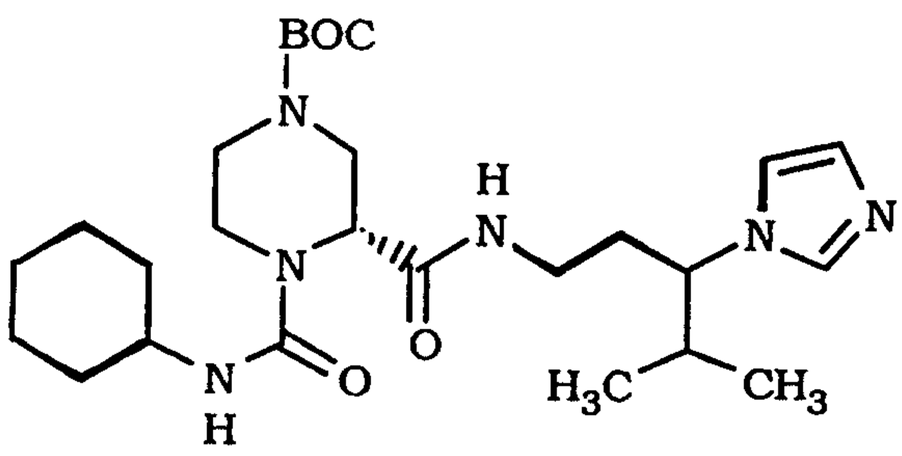
By essentially the same procedure as that set forth in Preparative Example 5, except using the title compound from Preparative Example 3 (Table 1), the title compound was prepared. LCMS: MH^+= 573.

PREPARATIVE EXAMPLE 7.1



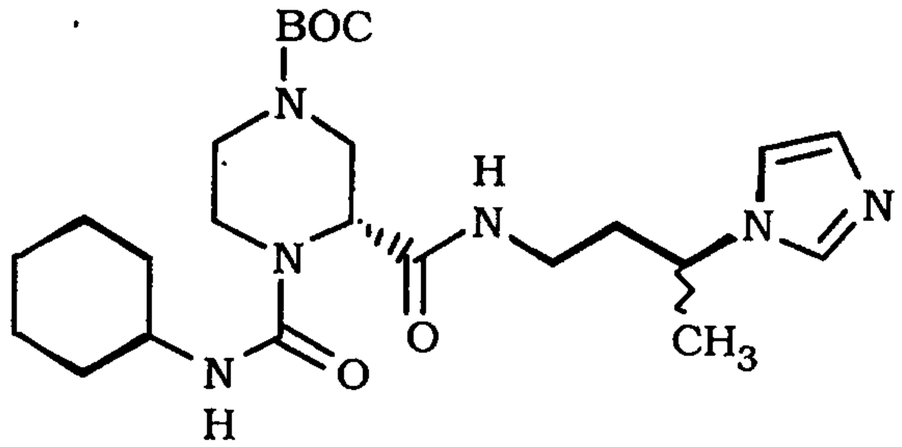
Follow the same procedure as that set forth in Preparative Example 5, except use the amine from Preparative Example 2 to obtain the title compound.

PREPARATIVE EXAMPLE 7.2



Follow the same procedure as that set forth in Preparative Example 5, except use the amine from Preparative Example 4 to obtain the title compound.

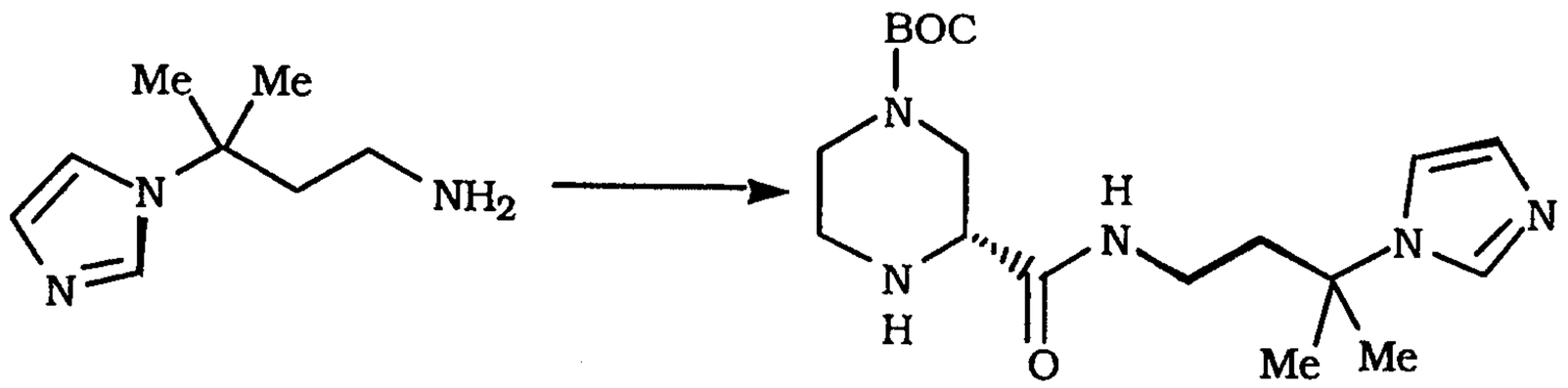
PREPARATIVE EXAMPLE 7.3



Follow the same procedure as that set forth in Preparative Example 5, except use the amine from Preparative Example 10 to obtain the title compound.

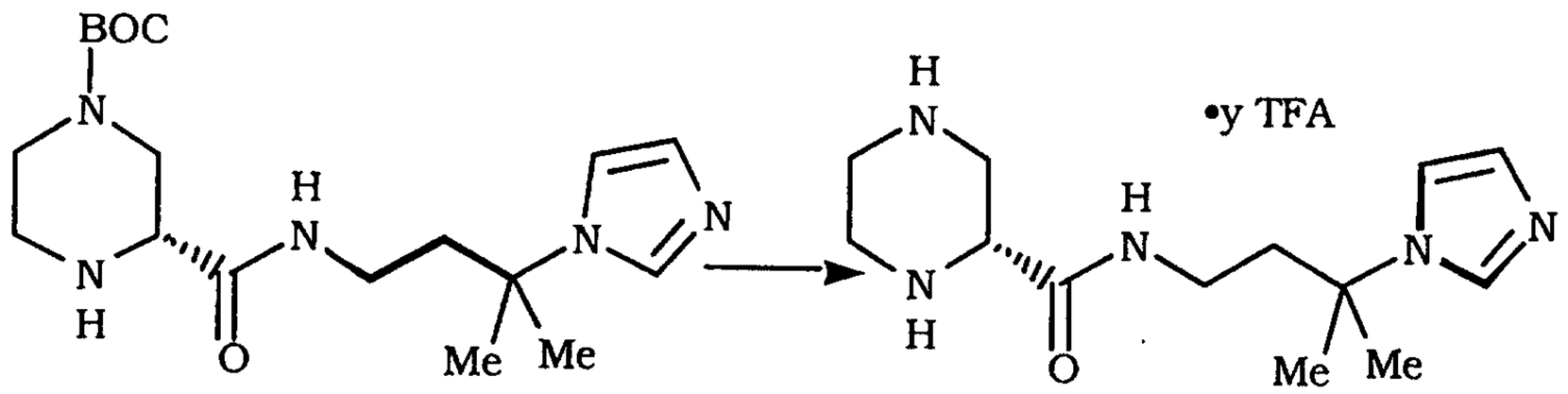
PREPARATIVE EXAMPLE 8

Step A



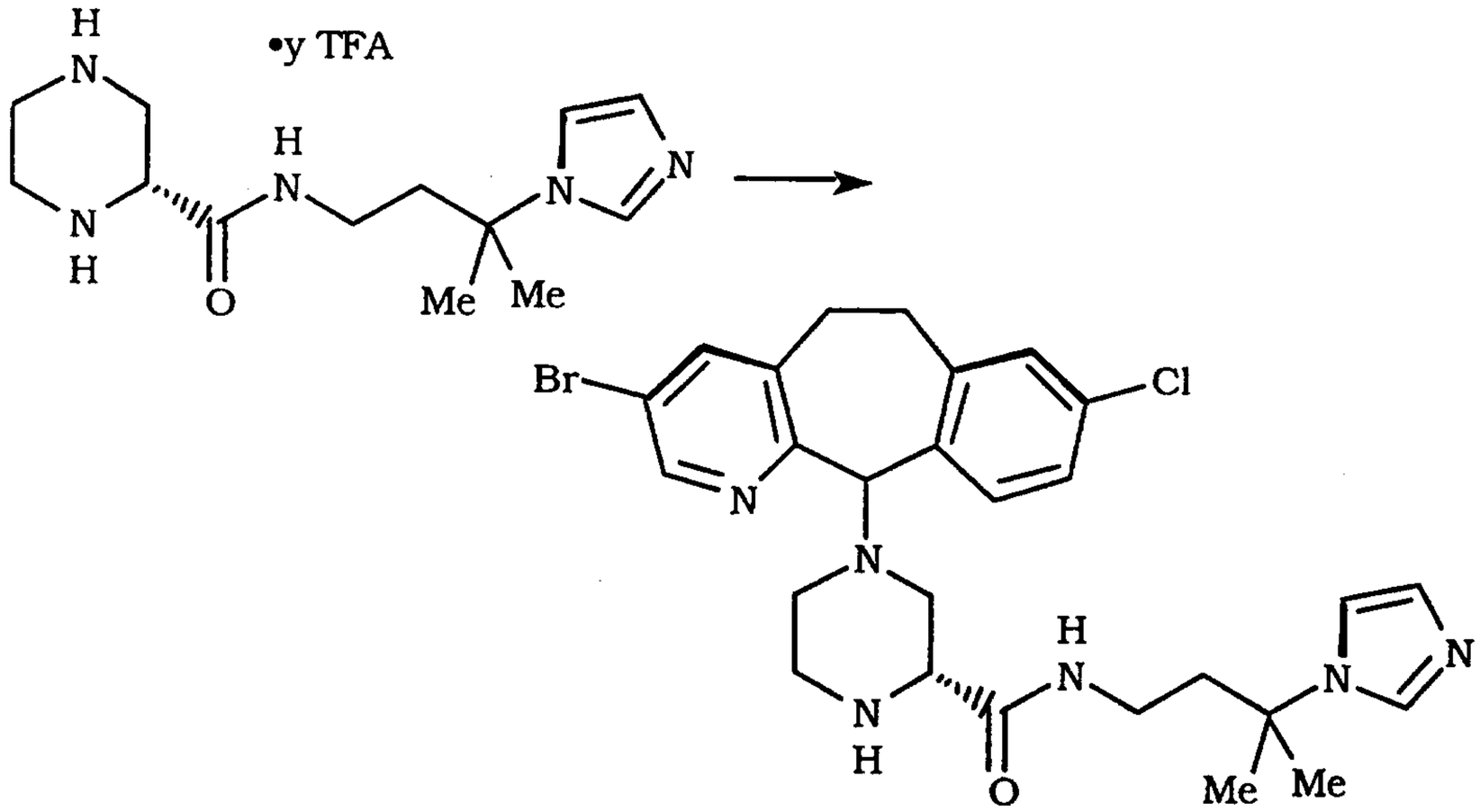
To the title compound from Preparative Example 1, Step D, (0.82g, 5.35 mmol) in CH_2Cl_2 (10 mL) and TEA (0.75 mL, 1.0 eq) was added piperazine anhydride (1.65g, 1.2 eq.) (prepared as described in Preparative Example 44) portionwise and the resulting solution was stirred at room temperature. When the reaction was complete (TLC), the solution was concentrated *in vacuo* and the crude product was purified by flash chromatography using a 10% (10% NH_4OH in MeOH) in CH_2Cl_2 then 20% (10% NH_4OH in MeOH) in CH_2Cl_2 as eluent. CIMS: MH^+= 366.

Step B

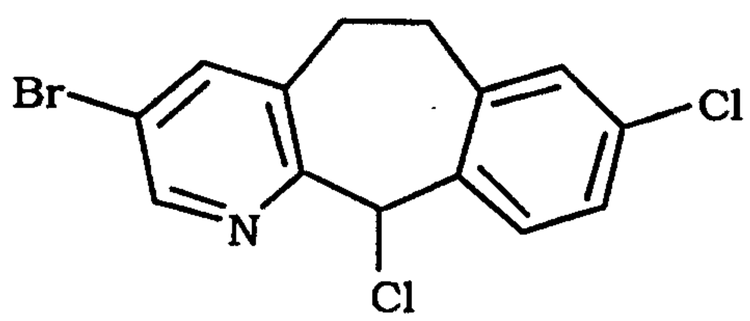


The title compound from Step A was stirred at room temperature in a 50% solution of TFA in CH_2Cl_2 (25 mL) for 2 hours. The resulting solution was concentrated under reduced pressure. Any residual TFA was removed by azeotroping with toluene to give the crude product which was used without further purification. CIMS: MH^+= 266.

Step C



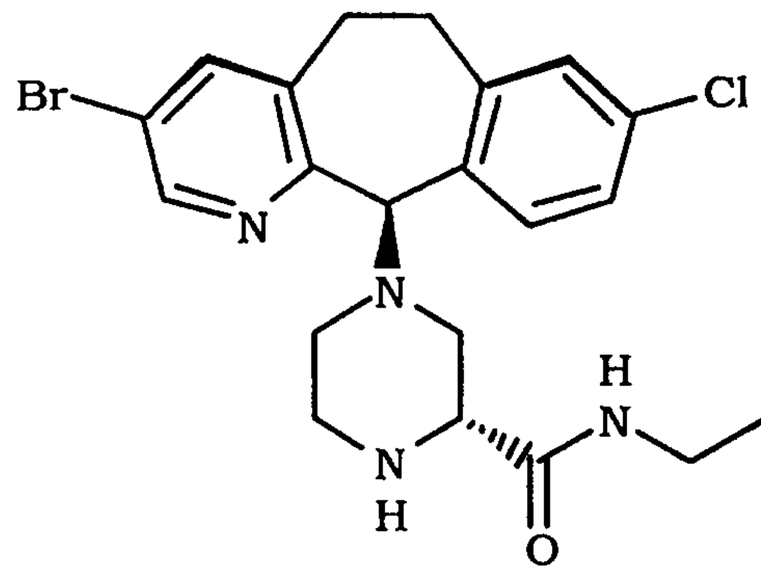
The title compound from Step B was dissolved in CH_2Cl_2 (30 mL) and TEA (7.62 mL, 10 eq.) was added. The reaction mixture was stirred 5 minutes before adding chloride



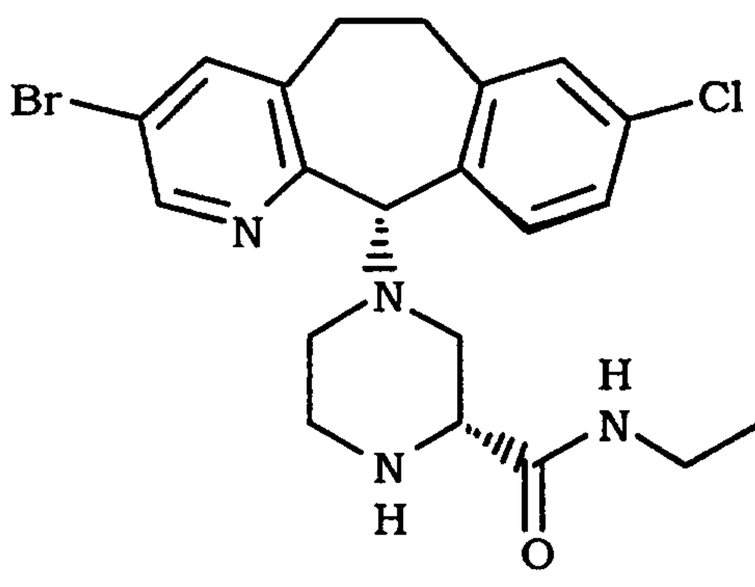
(42.0)

(0.908g, 0.5 eq.). The resulting solution was stirred at room temperature for 96 hours. The reaction mixture was diluted with water (50 mL), separated and the aqueous layer extracted with CH_2Cl_2 (2 x 200 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography using a 5%, 7.5%, and then 10% (10% NH_4OH in MeOH) in CH_2Cl_2 solution as eluent (0.926 g, 30% yield). CIMS: MH^+= 571.

Step D



(11R,2R(-)-Isomer)



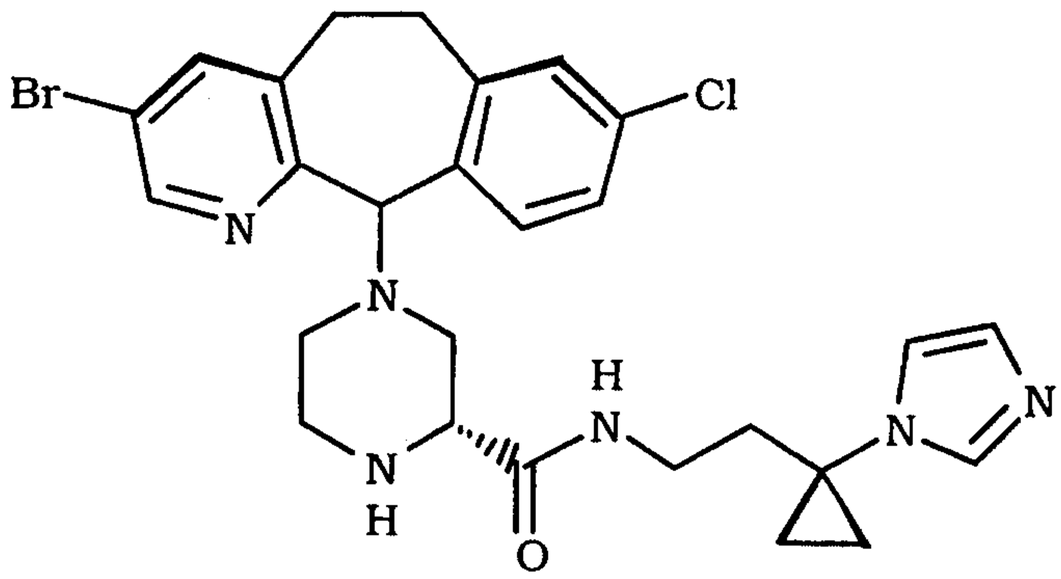
(11S,2R(-)-Isomer)

The title compound from Step C was separated into individual diasteromers by Preparative HPLC using a ChiralPak AD column using a 20% IPA in hexanes with 0.2% diethylamine solution as eluent:

Isomer A (11S,2R(-)-Isomer): retention time= 18.2 minutes; $[\alpha]^{20}_D$= -31.7 (3.0 mg in 2.0 mL MeOH).

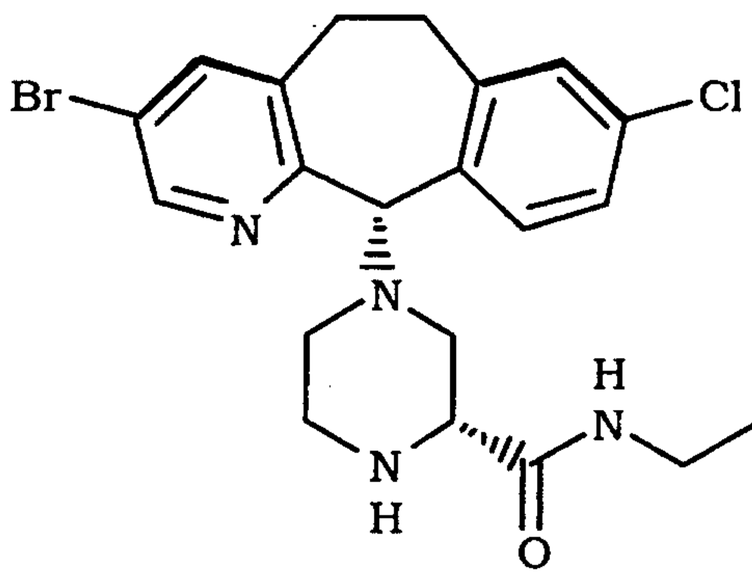
Isomer B (11R,2R(-)-Isomer): retention time= 30.3 minutes; $[\alpha]^{20}_D$= -6.2 (2.4 mg in 2.0 mL MeOH).

PREPARATIVE EXAMPLE 9

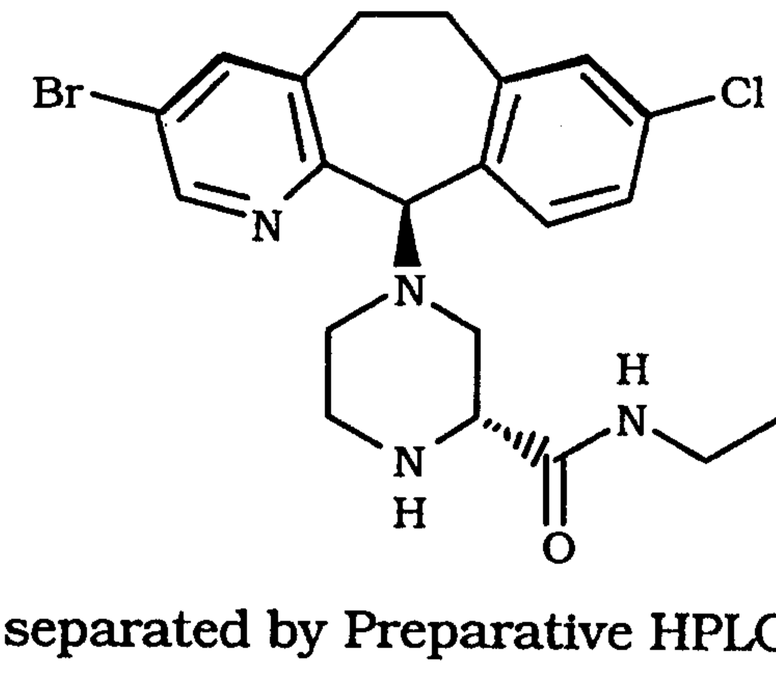


By essentially the same procedure as described in Preparative Example 8, except using the title compound from Preparative Example 2 (Table 1), the title compound was prepared.

The 11(S)- and 11(R)-isomers



(11S,2R(-)-Isomer)



(11R,2R(-)-Isomer)

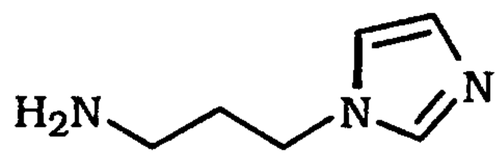
were separated by Preparative HPLC using a CHIRALPAK AD column using a 30% IPA in hexanes containing 0.2% diethylamine solution as eluent.

11S,2R(-)-isomer : retention time= 10.2 minutes; MH^+= 569; $[\alpha]^{20}_D$= -32.7 (4.04 mg in 2.0mL MeOH).

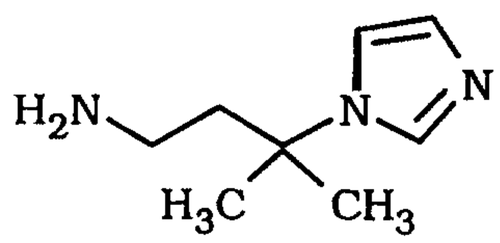
11R,2R(-)-isomer: retention time= 22.8 minutes; MH^+=569; $[\alpha]^{20}_D$= -1.2 (3.40 mg in 2.0 mL MeOH).

PREPARATIVE EXAMPLE 9.1

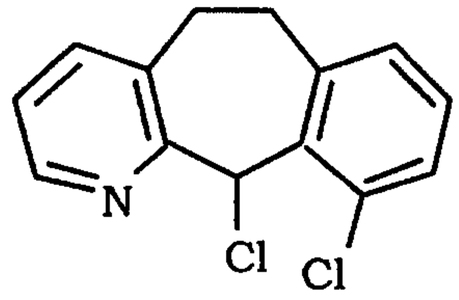
Follow the procedure set forth in Preparative Example 8, except use the amine



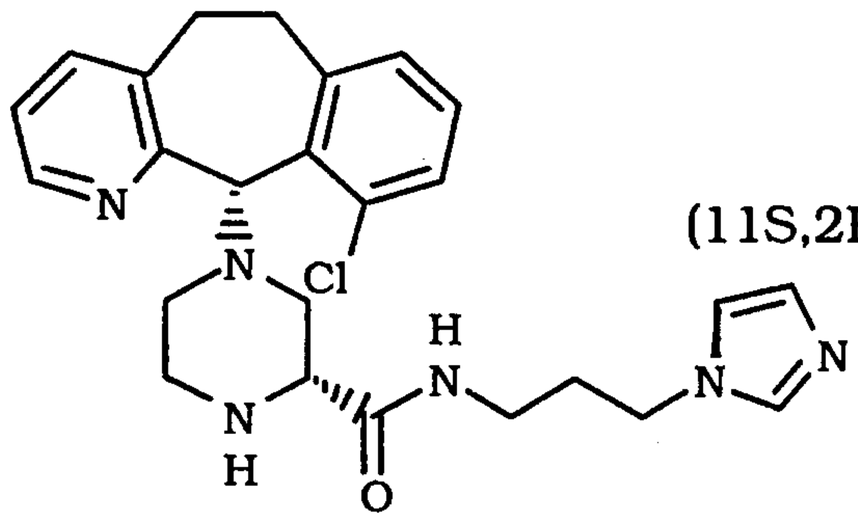
in Step A instead of



and use the 10-Cl tricycle chloride

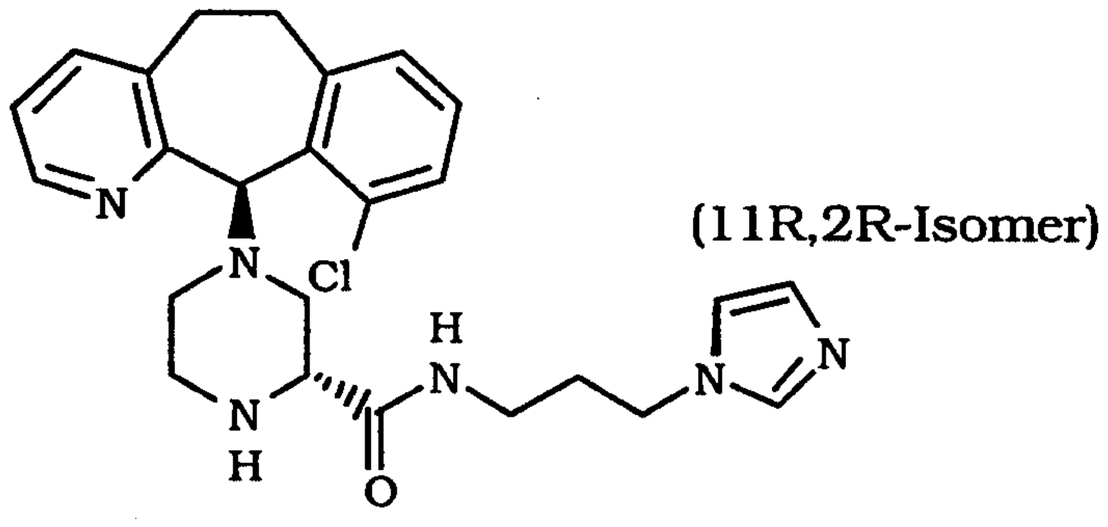


in Step C instead of the 3-Br-8-Cl-tricycle chloride (Compound 42.0) to obtain the compounds



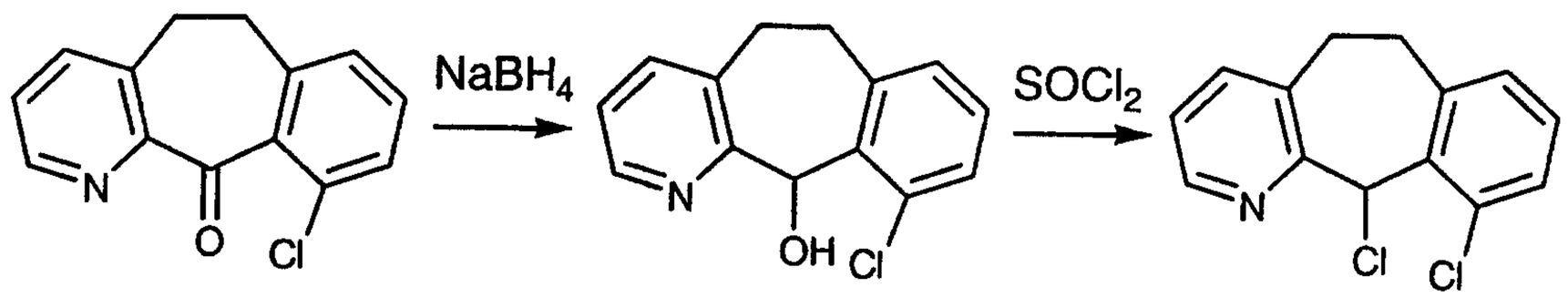
(11S,2R-Isomer)

and



(11R,2R-Isomer)

Obtain the 10-Cl tricycle chloride (10,11- diChloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-B]pyridine) as follows:

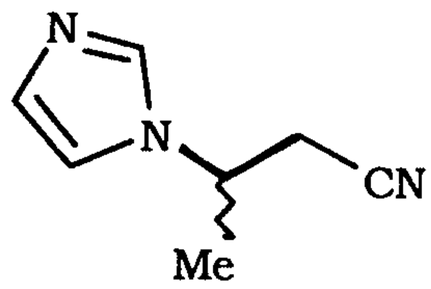


The ketone (starting material) 5,6-dihydro-10-Chloro-11H-benzo[5,6]cyclohepta[1,2-c]pyridine-11-one, can be prepared following the procedure described by Villani et al., J. Het. Chem. 8, 73-81 (1971). The product was prepared substituting the 10-Chloro for the 10H tricycle and following the procedure described in Preparative Example 169.

1H NMR ($CDCl_3$ δ) 2.97 (m, 2H), 3.55 (m, 1H), 4.03 (m, 1H), 7.11 (s,1H), 7.13 (d, 1H), 7.22 (m, 2H), 7.31 (d, 1H), 7.53 (d, 1H), 8.49 (d, 1H).

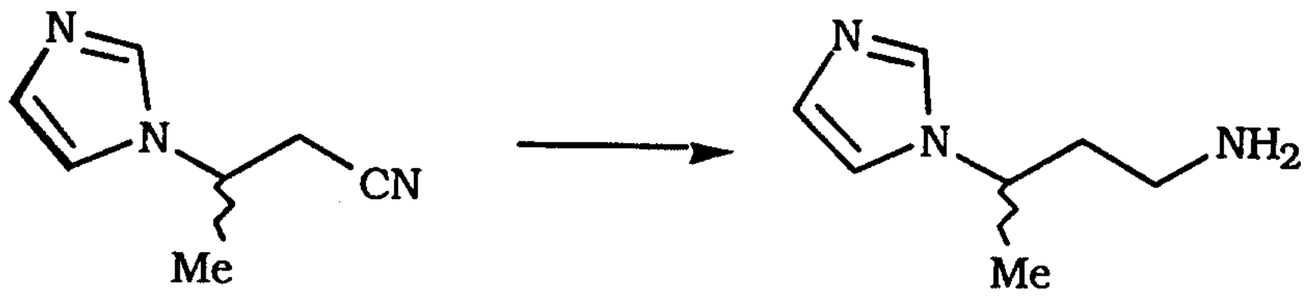
PREPARATIVE EXAMPLE 10

Step A



Imidazole (2.73g, 40.1 mmol) in crotonitrile (10 mL) was heated to reflux overnight. The resulting solution was concentrated *in vacuo*, the residue diluted with Et_2O (50 mL) and washed with water (2 X 100 mL) and brine (1 X 25 mL). The combined organics were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography using a 15% MeOH in CH_2Cl_2 solution as eluent (2.13g, 39% yield). FABMS: MH^+= 136.

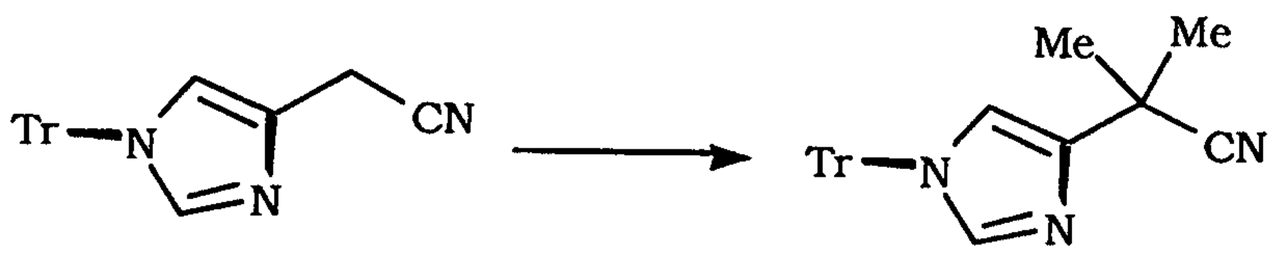
Step B



A solution of the title compound from Step A (0.50 g, 0.0037 mmol) in THF (10 mL) was treated with LAH (5.5 mL, 1.0 M in Et_2O, 1.1 eq.). The reaction mixture was stirred at room temperature 3 hours and quenched by the dropwise addition of saturated Na_2SO_4. The resulting slurry was dried by the addition of solid Na_2SO_4 and filtered through a plug of Celite. The filtrate was concentrated under reduced pressure and the crude residue purified by flash chromatography using a 20% (10% NH_4OH in MeOH) solution as eluent (0.03g, 6% yield).

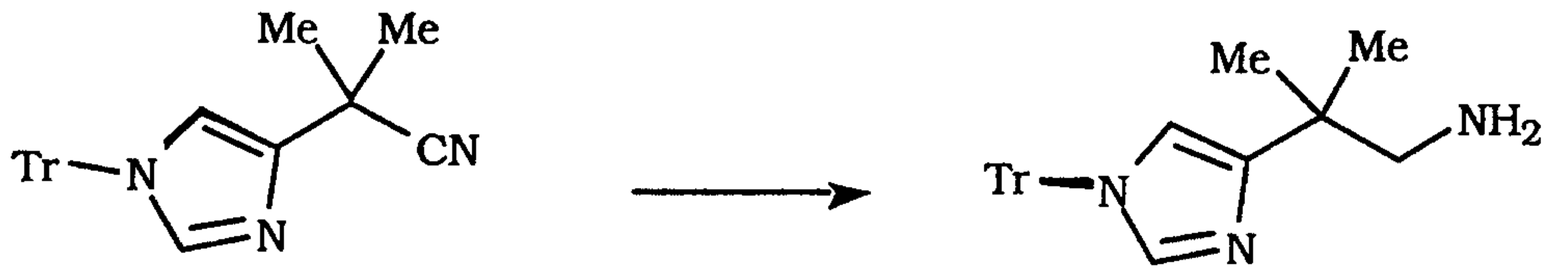
PREPARATIVE EXAMPLE 11

Step A



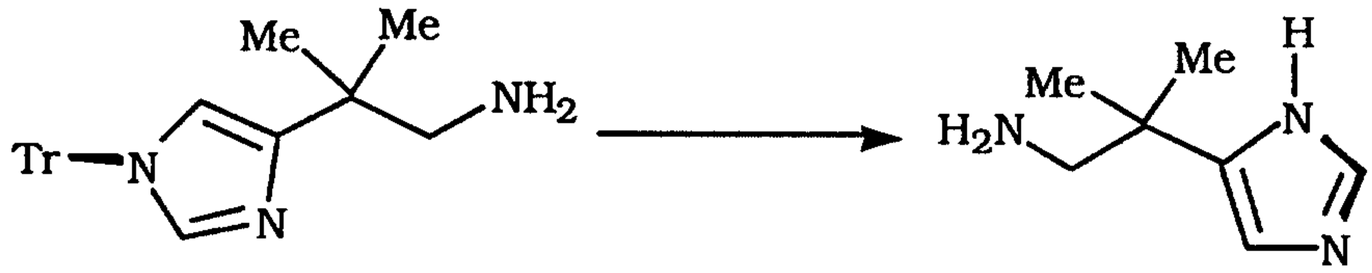
nBuLi (2.5 mL; 2.5M in hexanes; 2.1 eq.) was added to iPr_2NH (0.87 mL, 2.1 eq.) in THF (8.0 mL) at 0°C. The resulting solution was stirred 45 minutes before adding the nitrile (1.0g, 2.97 mmol) in THF (7.0 mL). The reaction mixture was stirred at 0°C for 30 minutes before adding MeI (0.37 mL, 2.0 eq.). The resulting solution was warmed to room temperature and stirred one hour. The reaction was quenched by the addition of 1N HCl until acidic, diluted with water (40 mL) and extracted with EtOAc (2 X 200 mL). The combined organics were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography using a 40% EtOAc solution in hexanes as eluent (0.37 g, 33% yield). MH^+= 378.

Step B



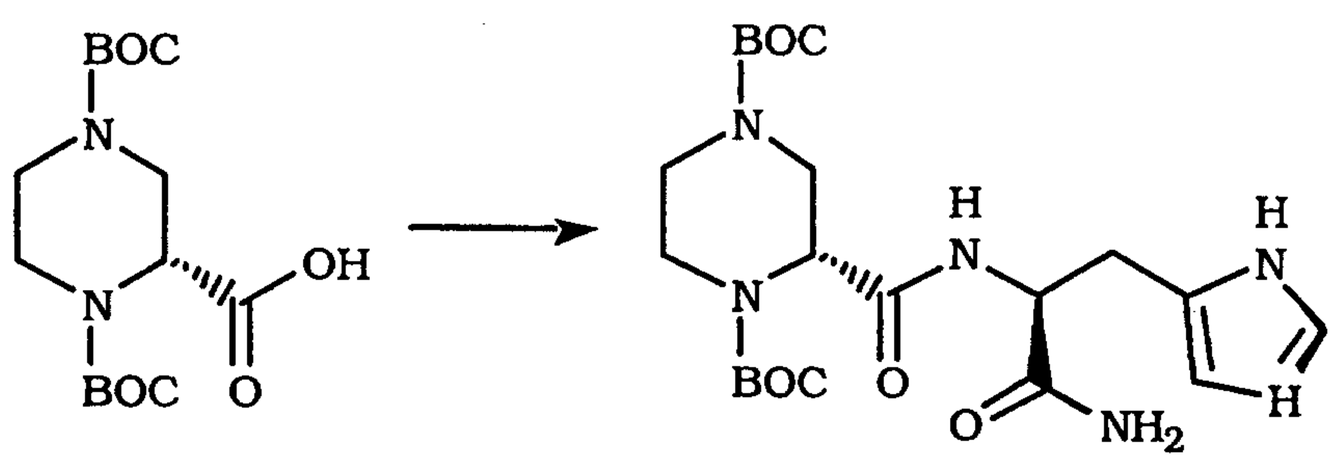
$LiAlH_4$ (2.7 mL; 1.0 M solution in THF; 1.5 eq.) was added to the title compound from Step A (0.68g, 1.80 mmol) in THF (5.0 mL). The resulting solution was stirred at room temperature 1.5 hours and quenched by the dropwise addition of saturated Na_2SO_4 (10 mL). The solution was extracted with Et_2O (2 X 200 mL), the combined organics dried over $MgSO_4$ and concentrated under reduced pressure (0.6 g, 88% yield).

Step C



following the same procedure as set forth in Preparative Example 27 Step C, the title compound was prepared.

PREPARATIVE EXAMPLE 12

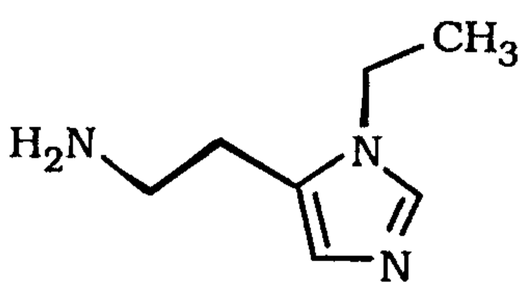


A solution of the piperazine carboxylic acid (0.29 g, 0.881 mmol) prepared as described in Preparative Example 43, L-histidinamide dihydrochloride (0.20 g, 1.0 eq.), DEC (0.25 g, 1.5 eq.), HOBT (0.18 g, 1.5 eq.), and NMM (0.48 mL, 1.5 eq.) in DMF (5 mL) was stirred at room temperature overnight. The reaction mixture was diluted with water (25 mL) and CH_2Cl_2 (50 mL),

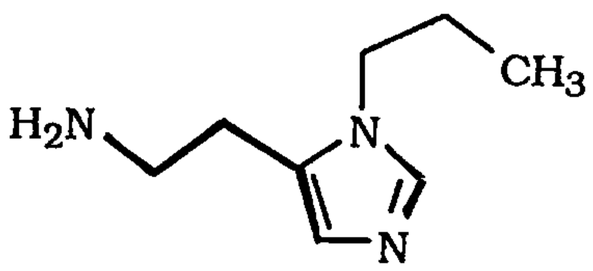
separated, and the aqueous layer extracted with CH_2Cl_2 (2 X 50 mL). The combined organics were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography using a 15% MeOH in CH_2Cl_2 solution as eluent (0.24g, 59% yield). FABMS: MH^+= 467.

PREPARATIVE EXAMPLES 13-17

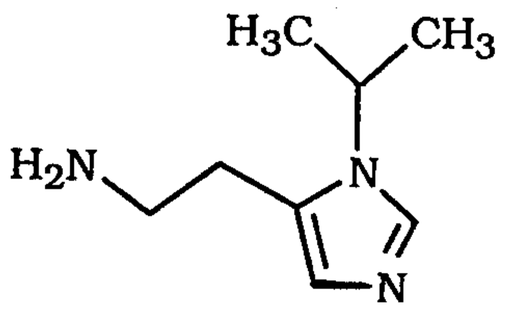
Following the procedures found in J. Chem. Soc. Perkin I (1979), 1341-1344, the following N-substituted histamines were prepared:



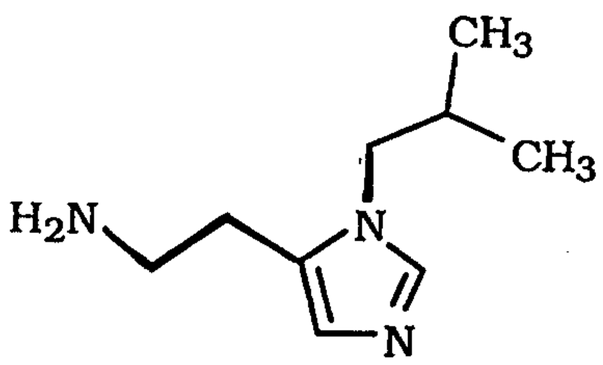
Preparative Example 13,



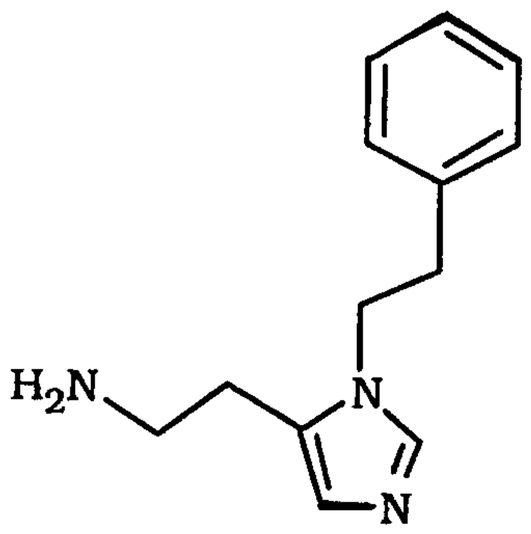
Preparative Example 14,



Preparative Example 15,



Preparative Example 16, and

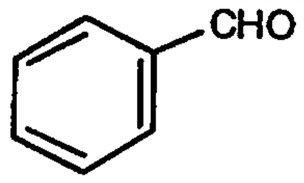
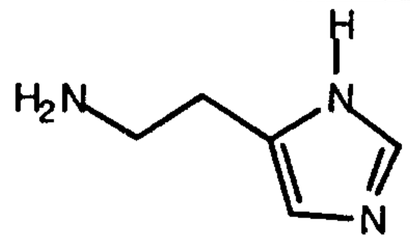
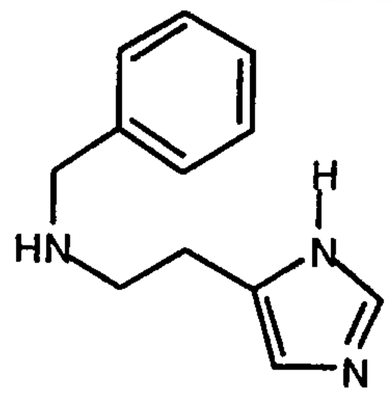
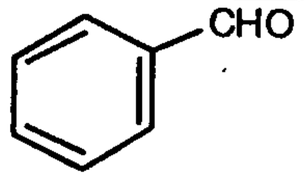
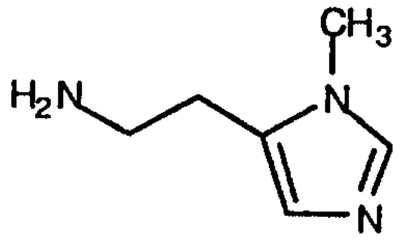
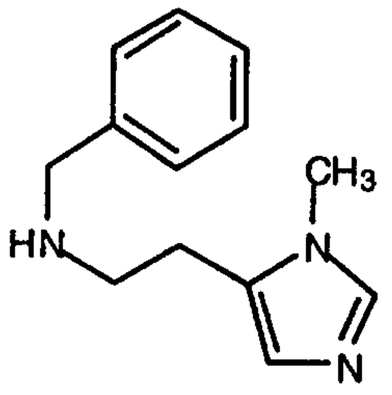
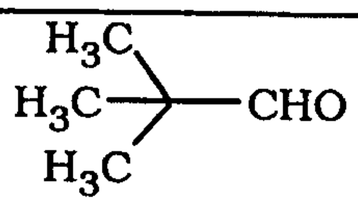
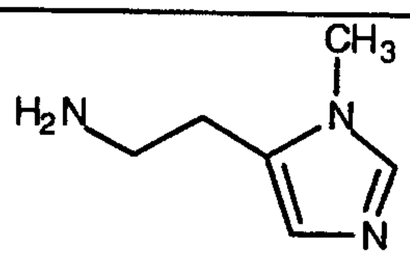
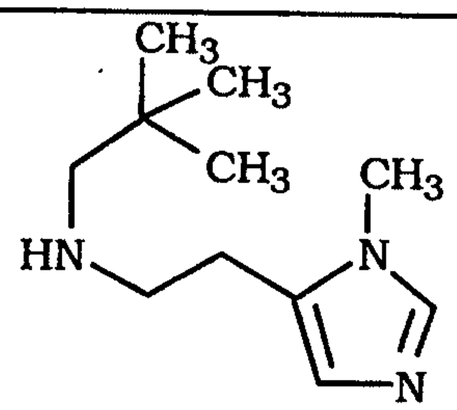
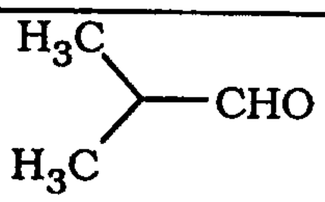
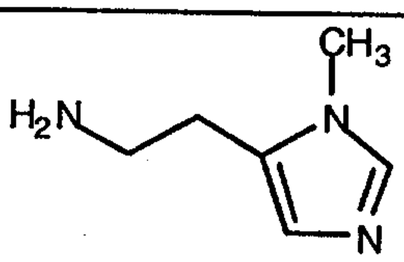
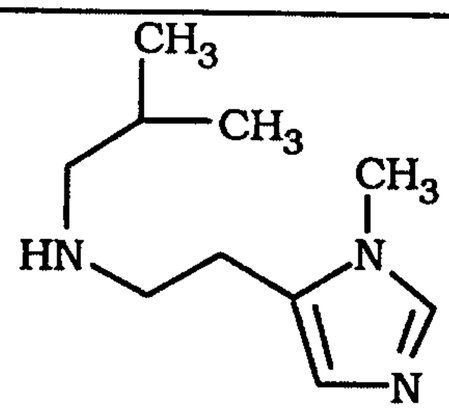
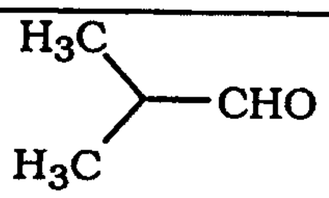
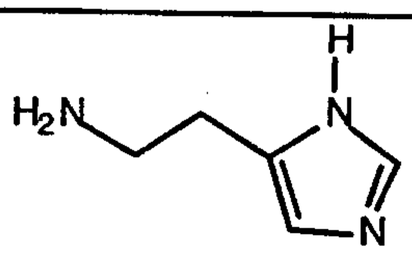
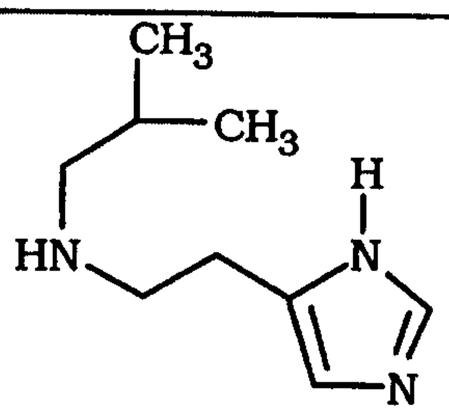


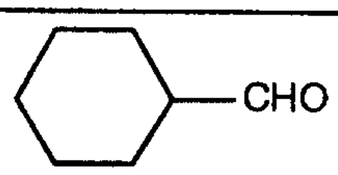
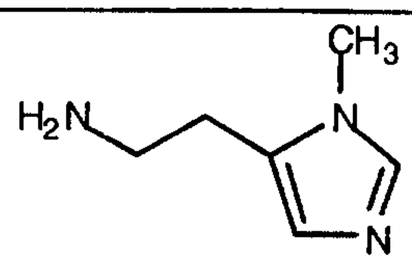
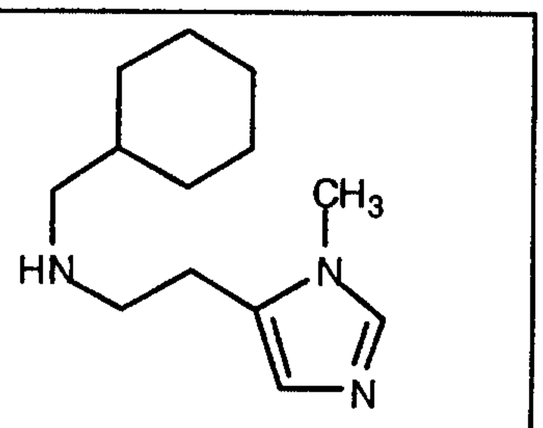
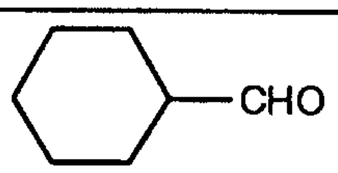
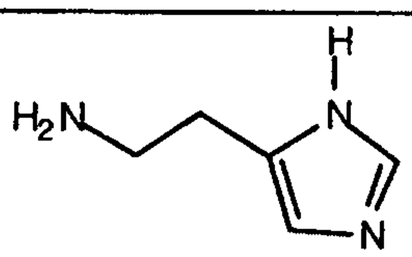
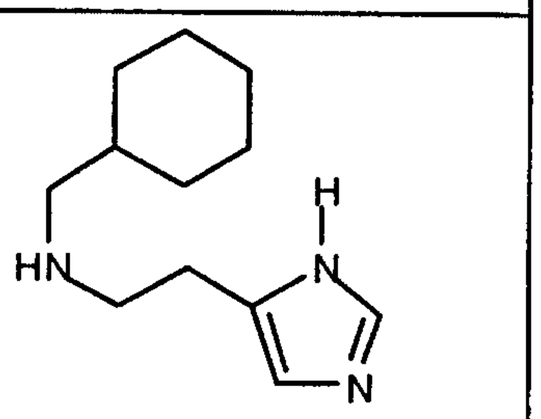
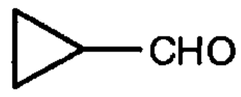
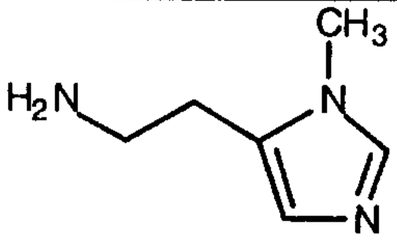
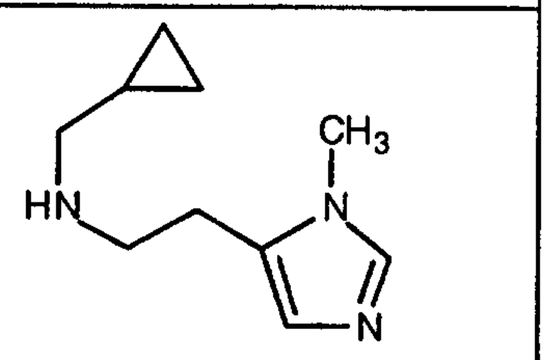
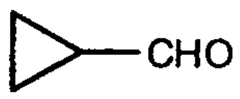
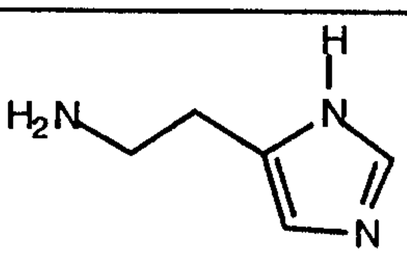
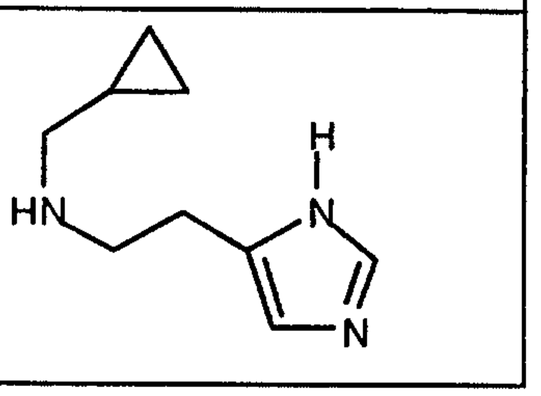
Preparative Example 17.

PREPARATIVE EXAMPLES 18-26

By essentially the same procedure as that set forth in Preparative Example 74, and using the aldehydes and amines set forth in Table 2, one can obtain the intermediate products shown in Table 2.

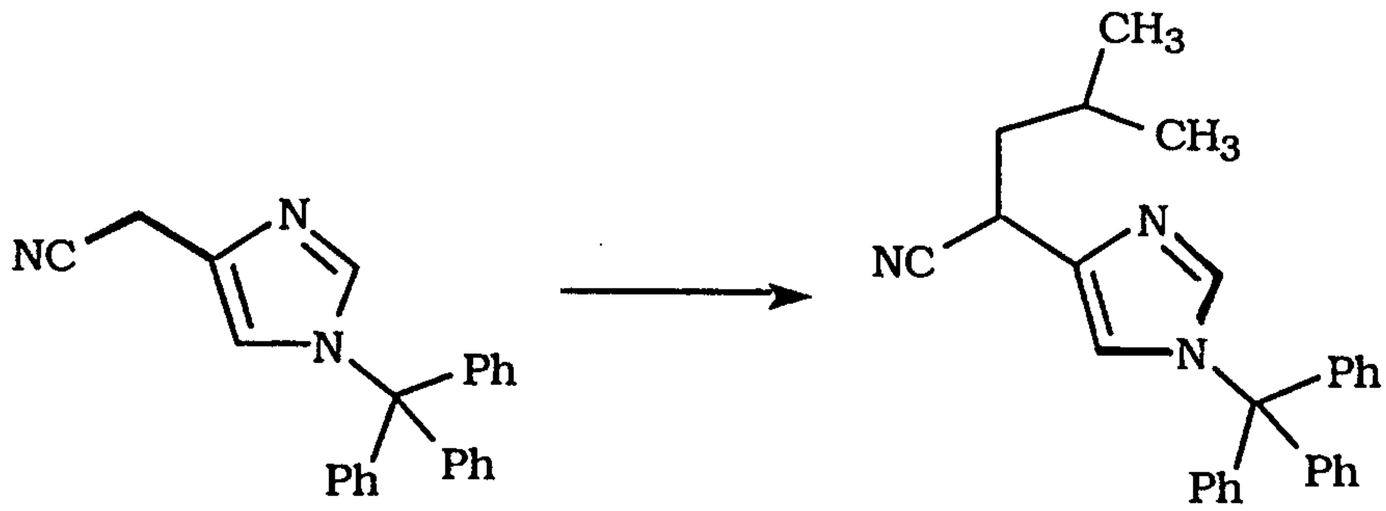
TABLE 2

Prep Ex.	Aldehyde	Amine	Product
18			
19			
20			
21			
22			

23			
24			
25			
26			

PREPARATIVE EXAMPLE 27

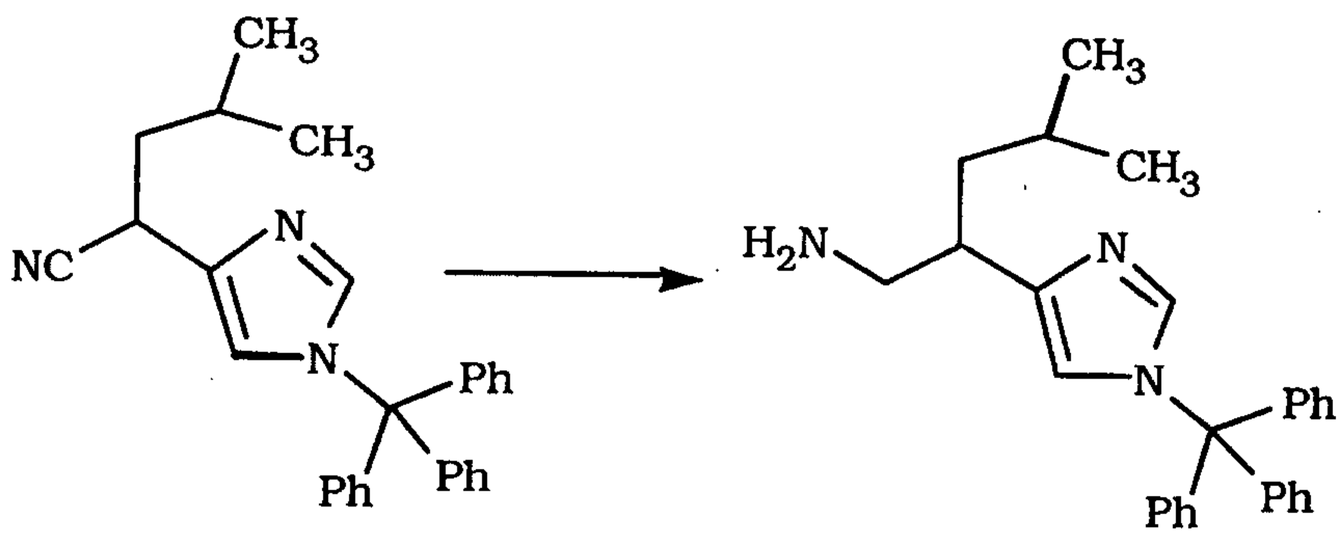
Step A



Dissolve the nitrile (1.5 g, 4.29 mmol) in 10 mL of THF and cool to -78°C under nitrogen. Add 20 mL of a 1.5 M LDA solution (in cyclohexane). Then add dropwise over 2 hr, a solution of 790 mg (4.293 mmol) of 2-methylpropyliodide in 10 mL of THF. Allow to warm to room temperature and stir overnight. Add 10 mL of water

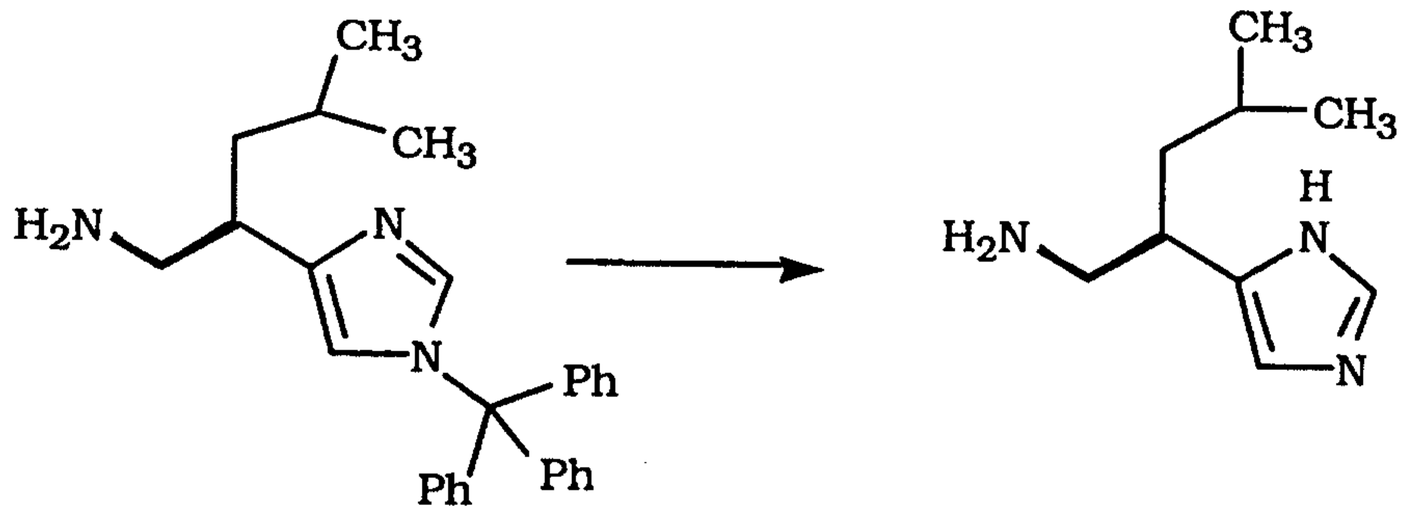
followed by 1N HCl until pH of 10-11. Dilute with 100 mL of methylene chloride followed by 20 mL of sat. aqueous Na_2SO_4. Add $MgSO_4$ until solution is clear. Separate the organic layer and dry over $MgSO_4$. Concentrate under vacuum and flash chromatograph on silica gel using ethyl acetate-hexane (1-3) to give the product as a tan semi-solid.

Step B



Dissolve the product of Step A (0.5 g, 1.23 mmol) in 10 mL of ethanol saturated with ammonia. Add 8.8 mg (0.017 mmol) of $H_2PtCl_6.6H_2O$, 1 g of Raney Ni in water and hydrogenate at 54 psi on a Parr shaker over night. Filter through Celite and concentrate under vacuum.

Step C

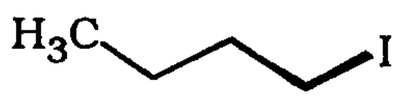


Dissolve the product of Step B (0.165 g, 0.403 mmol) in 4 mL of 2M HCl and 2 mL of methanol. Reflux for 100 min. then concentrate under vacuum. Triturate the residue with ether to give the product hydrochloride as a white solid.

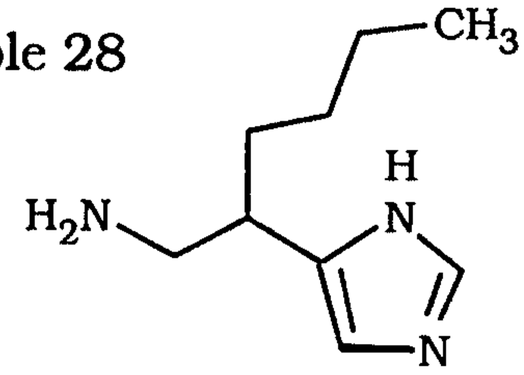
PREPARATIVE EXAMPLES 28-29, 29.1 and 30

Following the procedure set forth in Preparative Example 27, but using the indicated alkyl or benzyl halide in place of 2-methyl propyl iodide, the substituted histamines shown were prepared.

Preparative Example 28

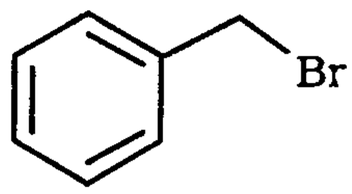


Halide

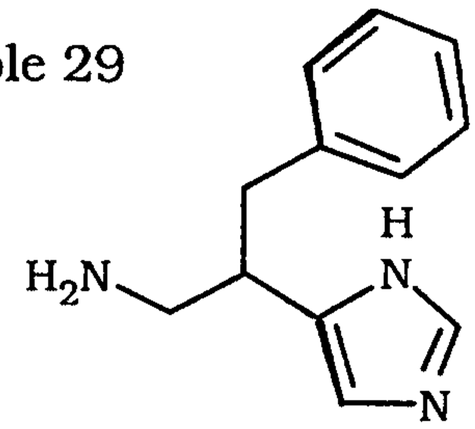


Substituted Histamine

Preparative Example 29

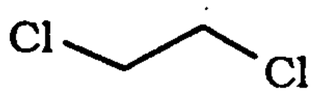


Halide

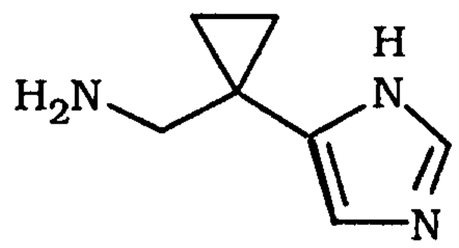


Substituted Histamine

Preparative Example 29.1



Halide



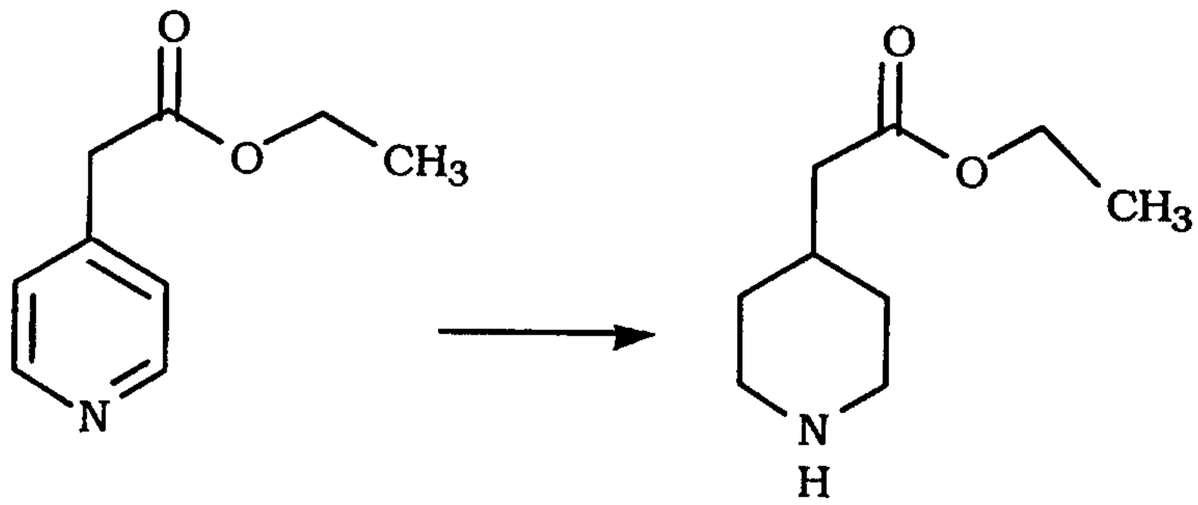
Substituted Histamine

Preparative Example 30

Halide

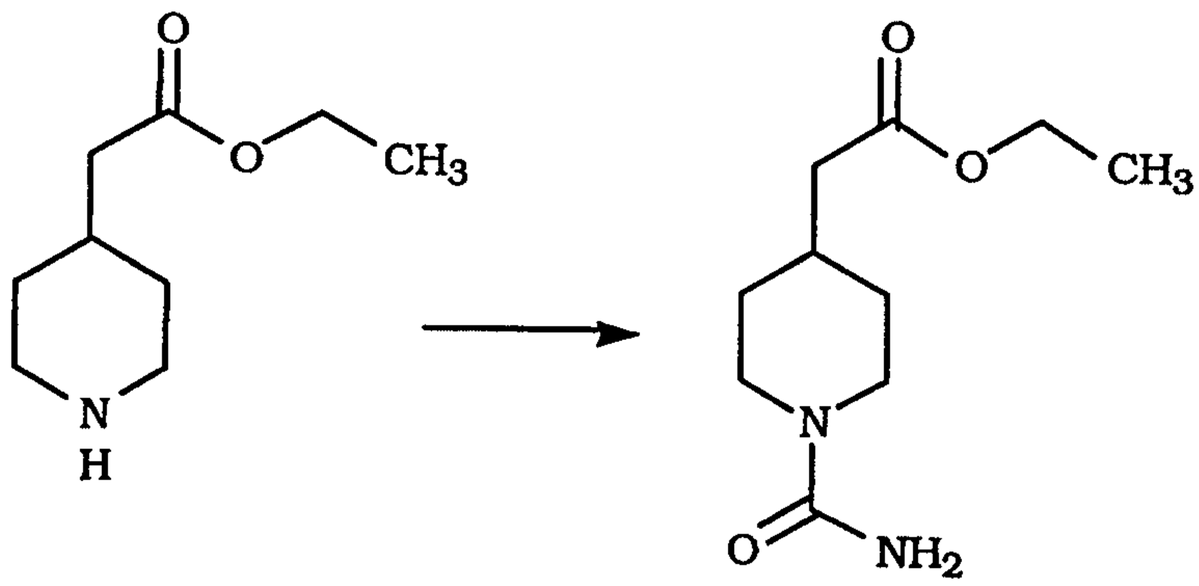
Substituted Histamine

PREPARATIVE EXAMPLE 31



Ethyl 4-pyridyl acetate (4.5g, 27.24mmoles) was placed in a 500mL Parr bottle and dissolved in anhydrous EtOH (70mL). To the bottle was added 10% Palladium on charcoal (1.0g). The bottle was put on a hydrogenator and the contents shaken under 55 psi hydrogen pressure at 25°C for 94h. The mixture was filtered through Celite® and washed with 4x40mL anhydrous EtOH. The filtrate was rotovapped down and the residue chromatographed on silica gel using 3% (10% conc. NH_4OH in methanol)dichloromethane as the eluant to give the title compound (Yield: 2.944g, 63%): FABMS: m/z 172.2(MH^+); δ_C ($CDCl_3$) CH_3: 14.3; CH_2: 33.2, 33.2, 41.9, 46.5, 46.5 60.2; CH: 33.4; C: 172.7 ; δ_H ($CDCl_3$) 1.18 (m,1H,H_4), 1.26 (t,3H,CH_3), 1.71(2H) , 1.90(1H), 1.96(1H), 2.22(d,2H), 2.63(2H), 3.07(2H), 4.13(q,2H,$CH_3\underline{CH_2}$-).

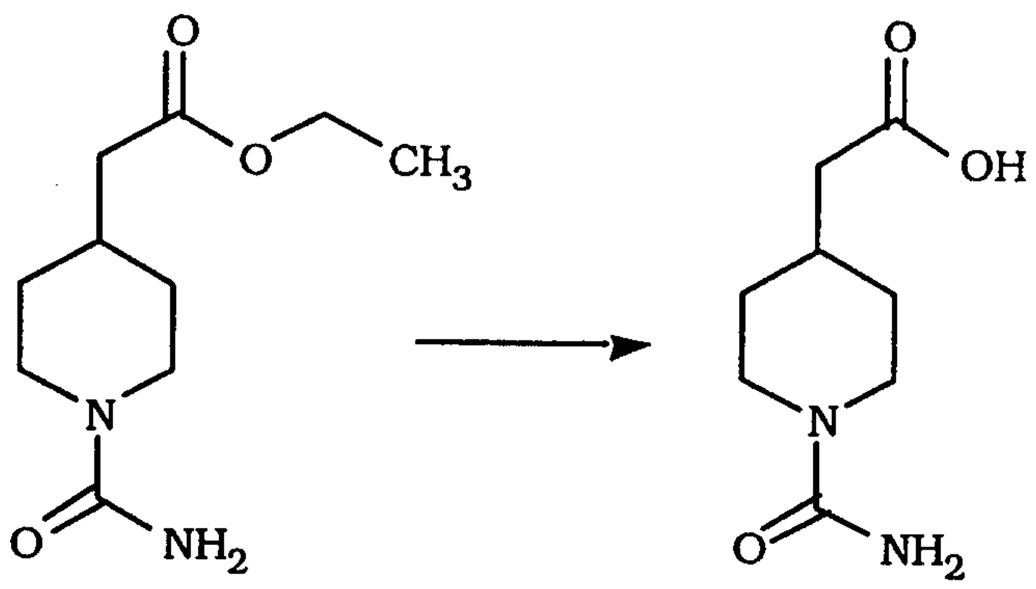
PREPARATIVE EXAMPLE 32



Ethyl 4-piperidinyl acetate from Preparative Example 31 (500mg; 2.92mmoles) was dissolved in anhydrous CH_2Cl_2 (25mL). To the stirring solution was added trimethylsilyl isocyanate (5.9mL; 43.8mmoles) and the solution was stirred at 25°C for 17h. The

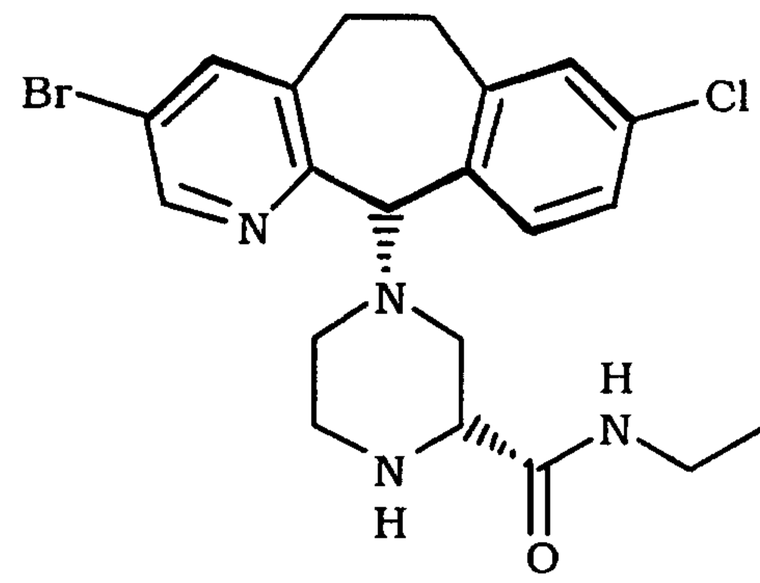
solution was worked up in CH_2Cl_2-saturated $NaHCO_3$ and the product chromatographed on silica gel using 2→3%(conc. NH_4OH in methanol)dichloro-methane as the eluant to give the title compound (Yield: 622mg, 99%): CIMS: m/z 215.3 (MH^+); δ_C ($CDCl_3$): CH_3: 14.2; CH_2: 31.6, 31.6, 41.0, 44.2, 44.2, 60.4; CH: 32.9; C: 158.2, 172.4; δ_H ($CDCl_3$): 1.23 (m,1H,H_4), 1.27 (t,3H,CH_3), 1.75 (d,2H), 1.98 (m,1H), 2.26 (d,2H), 2.85 (t,2H), 3.94 (d, 2H), 4.15 (q,2H,$CH_3\underline{CH_2}$-), 4.56 (bs,2H).

PREPARATIVE EXAMPLE 33

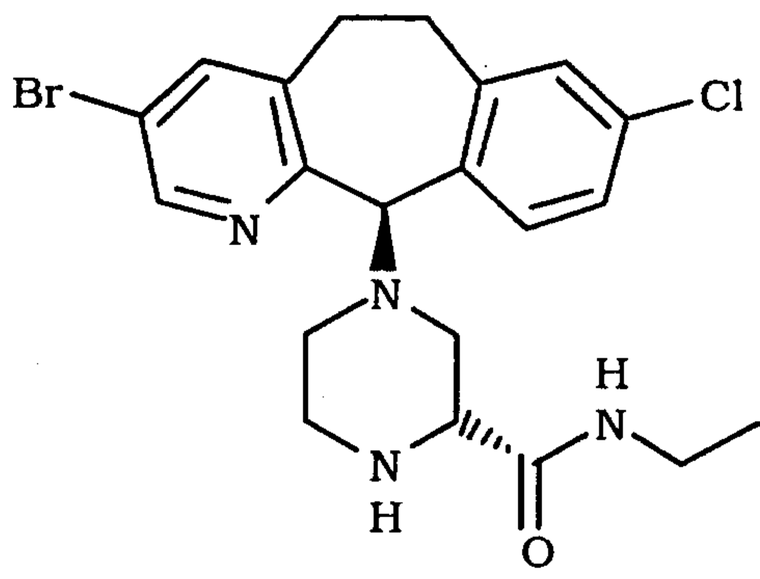


Ethyl 1-aminocarbonyl-4-piperidinyl acetate from Preparative Example 32 (153.6mg, 0.717mmoles) was dissolved in anhydrous CH_2Cl_2 (3.58mL) and EtOH (3.58mL). To the solution was added 1.0M LiOH (1.73mL, 1.73mmoles) and the mixture was stirred at 50°C for 5.5h. The mixture was cooled quickly to 25°C and 1.0N HCl (2.02mL, 2.02mmoles) was added and the mixture stirred for 5 minutes and then rotovapped to dryness to give the title compound which was used without further purification.

PREPARATIVE EXAMPLE 34



(11S,2R(-)-Isomer)



(11R,2R(-)-Isomer)

The C_{11}-racemate of the above isomers (Preparative Example 141) (62% pure) was subjected to preparative HPLC on a Chiralpak AD® column (50X5cm) using 75% hexane- 25% isopropyl alcohol-0.2% diethylamine as the eluant to give, in the order of elution, the 11-S(-)-isomer and the 11-R(-)-isomer.

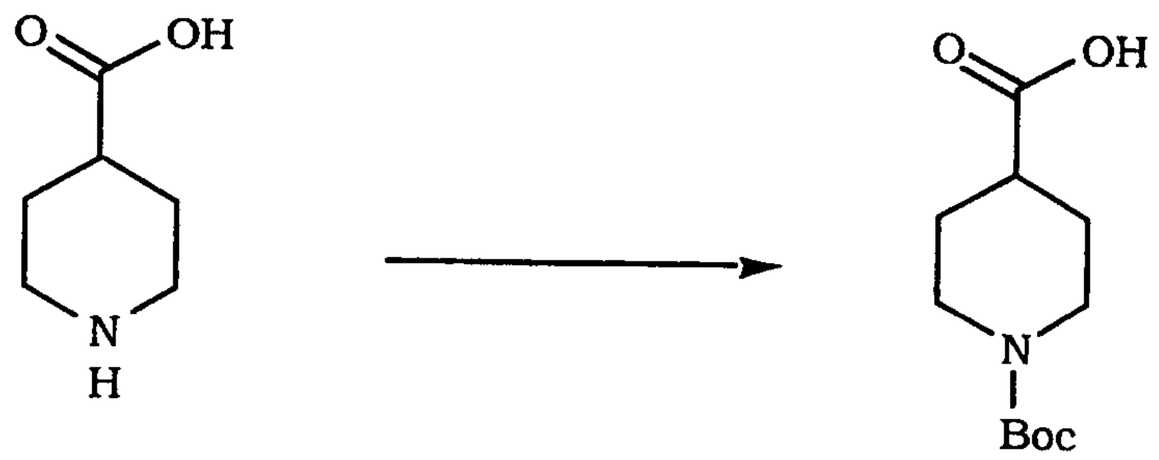
11S,2R(-)-isomer: (Yield: 0.8756g, 55%): LCMS: m/z 543.1 (MH^+); δ_C ($CDCl_3$) CH_2: 30.3, 30.4, 31.0, 36.3, 44.3, 44.7, 52.0, 54.5; CH: 58.7, 79.4, 118.8, 126.0, 129.6, 130.4, 132.3, 137.1, 141.3, 147.0; C: 120.0, 134.0, 135.4, 136.7, 140.9, 155.4, 172.2; δ_H ($CDCl_3$) 2.02 (2H, m, 2"-CH_2), 3.32 (2H, m, 3"-CH_2), 3.98 (2H, dd, 1"-CH_2), 4.30 (1H, s, H_{11}), 6.93 (1H, s, Im-H_5), 6.97 (1H, t, CON<u>H</u>CH_2), 7.06 (1H, s, Im-H_4), 7.11 (1H, s, Ar-H), 7.13 (2H, s, Ar-H), 7.16 (1H, s, Ar-H), 7.49 (1H, s, Ar-H_{10}), 7.57 (1H, d, Im-H_2) and 8.33 ppm (1H, s, Ar-H_2); $[a]_D^{20°C}$ -45.0° (MeOH, c=9.32mg/2mL).

11R,2R(-)-isomer: (Yield: 0.5979g, 38%): LCMS: m/z 543.1 (MH^+); δ_C ($CDCl_3$) CH_2: 30.2, 30.3, 31.1, 36.4, 44.1, 44.7, 52.2, 54.0; CH: 58.2, 79.4, 118.8, 126.1, 129.6, 130.7, 132.3, 137.0, 141.2, 146.8; C: 119.9, 134.0, 135.2, 136.9, 140.7, 155.7, 172.1; δ_H

($CDCl_3$) 3.34 (2H, m, 3"-CH_2), 3.97 (2H, dd, 1"-CH_2), 4.30 (1H, s, H_{11}), 6.93 (1H, s, Im-H_5), 7.06 (1H, s, Im-H_4), 7.08 (1H, s, Ar-H), 7.11 (2H, s, Ar-H), 7.14 (1H, s, Ar-H), 7.15 (1H, t, CON<u>H</u>CH_2), 7.50 (1H, s, Ar-H_{10}), 7.58 (1H, d, Im-H_2) and 8.35 ppm (1H, s, Ar-H_2); $[a]_D^{23.5°C}$ - 12.0° (MeOH, c=10.19mg/2mL).

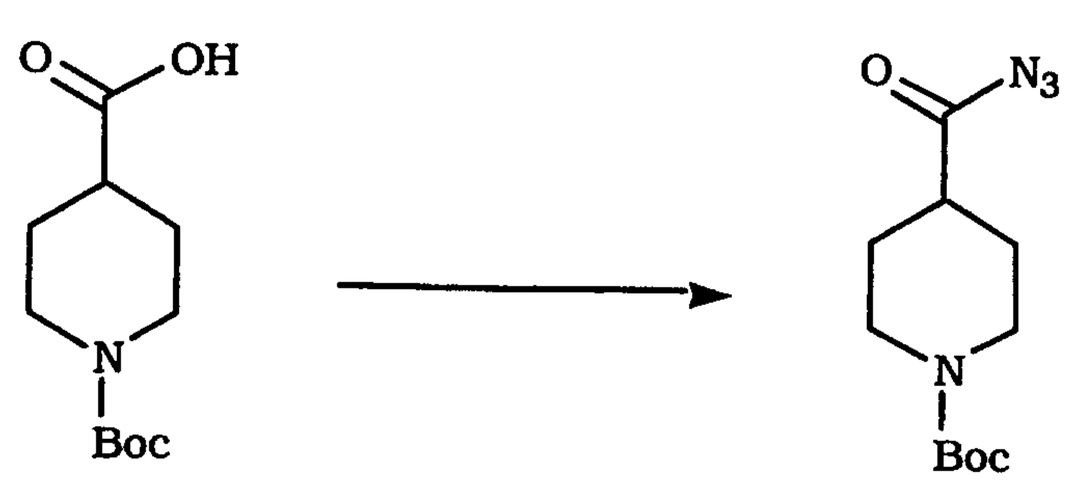
PREPARATIVE EXAMPLE 35

Step A



Isonipecotic acid (10g, 77.42mmoles) and sodium hydroxide (3.097g, 77.42mmoles) were dissolved in THF-water (1:1) (230mL) and di-t-butyldicarbonate (18.59mL, 85.17mmoles) was added. The solution was stirred at 25°C for 90h. The mixture was treated with BioRad® 50W-X4(H^+) ion exchange resin (86.6mL) and the resin was filtered off and washed with THF and then water. The combined filtrates were evaporated to dryness to give the title compound which was used without further purification in the next step: FABMS: m/z 229.9 (MH^+); δ_C (d_6-DMSO) CH_3: 28.0, 28.0, 28.0; CH_2: 42.0-43.1(broad signal); CH: obscured; C: 78.5, 153.8, 175.6.

Step B

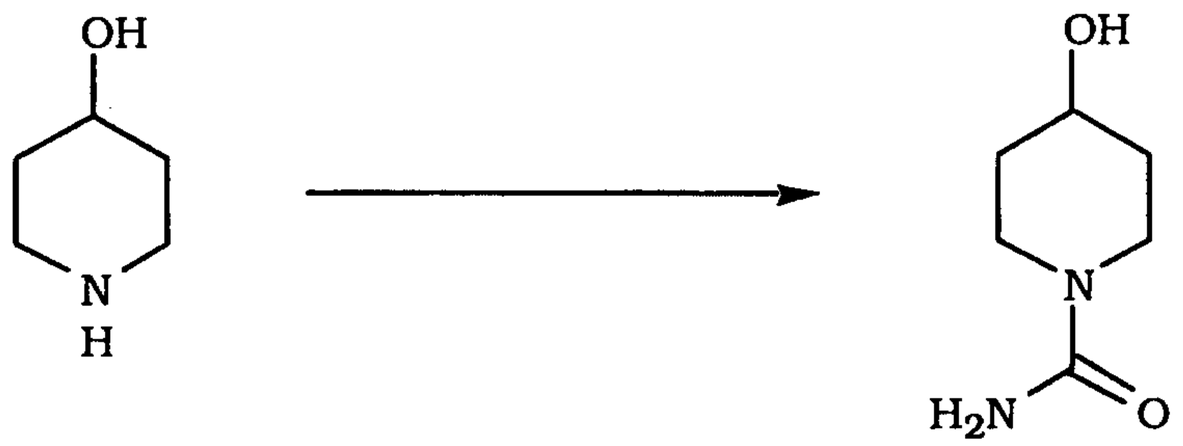


The title compound from Step A above (2g, 8.72mmoles) was dissolved in dry DMF (40mL) and the solution was stirred at 0°C

under an argon atmosphere. Diphenylphosphoryl azide (2.07mL, 9.59mmoles) was added over 10min followed by triethylamine (2.68mL, 9.59mmoles) and the mixture was stirred at 0°C for 1h and then at 25°C for 19h. Evaporation to dryness followed by chromatography on a silica gel column using 5% increasing to 7% methanol in dichloromethane afforded the title compound: (Yield: 1.57g, 72%): δ_C ($CDCl_3$) CH_3: 28.5, 28.5, 28.5; CH_2: 32.9 (broad), 42.8 (broad); CH: 47.3; C: 79.7, 154.8, 156.5.

PREPARATIVE EXAMPLE 36

Step A



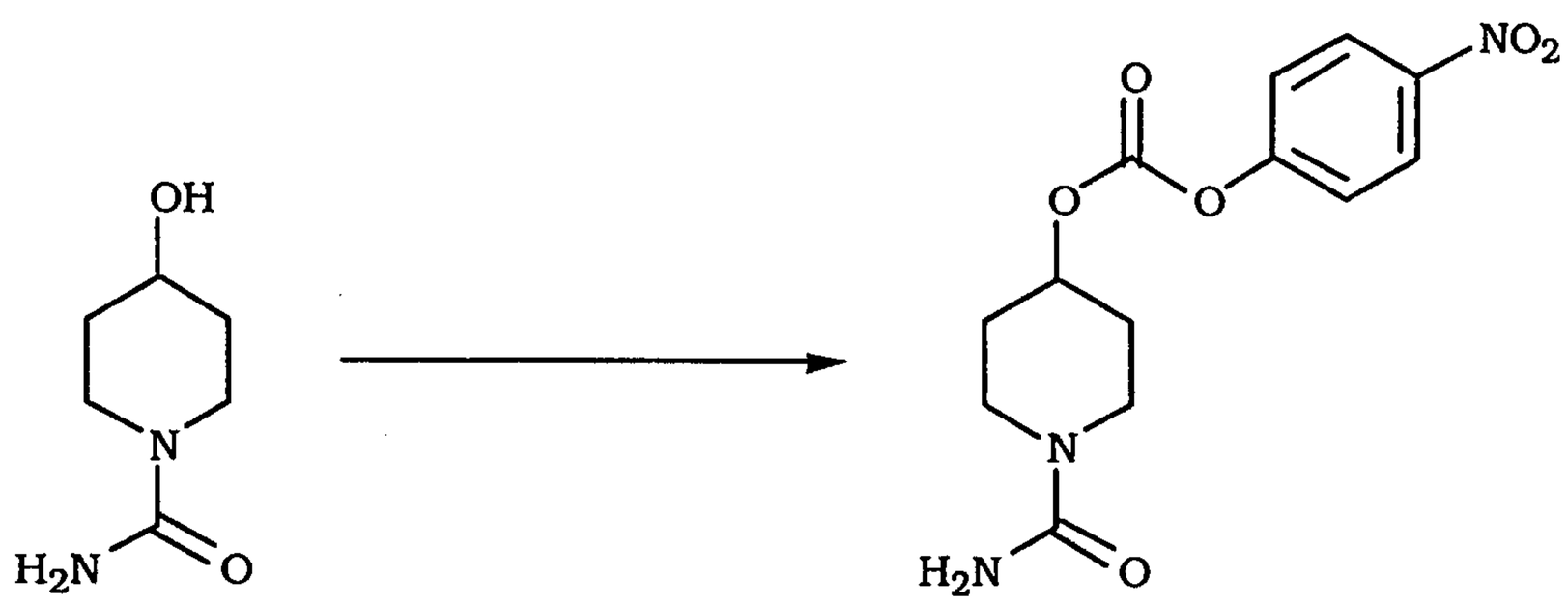
Method 1:

4-Hydroxypiperidine (5g, 49.43mmoles) was dissolved in anhydrous dichloromethane (50mL) and trimethylsilyl isocyanate (6.27g, 7.36mL, 54.38mmoles) was added. The mixture was stirred at 25°C under an argon atmosphere for 24h. Water (10mL) was added and the mixture was evaporated to dryness. The residue was chromatographed on a silica gel column using 10%(10% conc. NH_4OH in methanol)-dichloromethane as the eluent to give the title compound: (Yield: 6.895g, 97%): CIMS: m/z 145.1 (MH^+); δ_C (d_6-DMSO) CH_2: 34.2, 34.2, 41.3, 41.3; CH: 66.1; C: 158.0; δ_H (d_6-DMSO) 1.22 (2H, m, 3/5-CH_2), 1.68 (2H, m, 3/5-CH_2), 2.84 (2H, m, 2/6-CH_2), 3.60 (1H, m, 4-CH), 3.68 (2H, m, 2/6-CH_2), 4.67 (1H, d, OH) and 5.87ppm (2H, s, NH_2).

Method 2:

4-Hydroxypiperidine (10g, 98.86mmoles) and urea (59.4g, 988.6mmoles) were dissolved in distilled water (100mL) and the solution was heated at 100°C for 67h. The solution was evaporated to dryness and the product was chromatographed on a silica gel column using 10%(10% conc. NH_4OH in methanol)-dichloromethane as the eluent to give the title compound: (Yield: 8.3g, 58%).

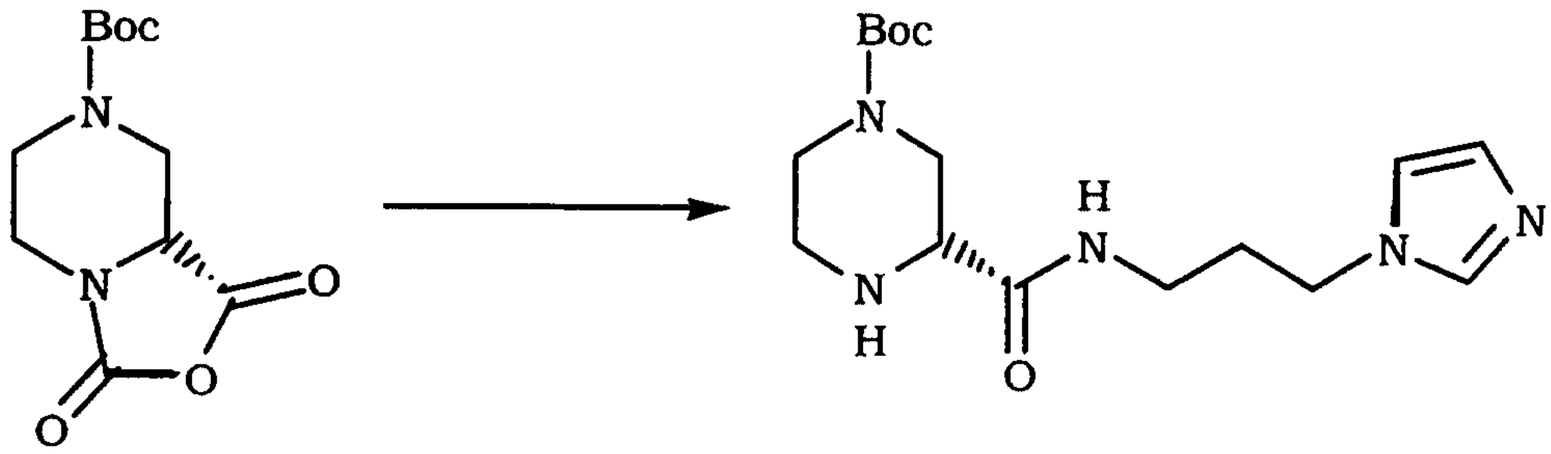
Step B



The title compound from Step A above (1g, 6.94mmoles) and 4-nitrophenyl chloroformate (1.54g, 7.63mmoles) were dissolved in anhydrous pyridine (10mL) and the mixture was stirred at 25°C for 24h. The mixture was evaporated to dryness and the residue was azeotroped with toluene. The resulting product was chromatographed on a silica gel column using 3% methanol in dichloromethane as the eluant to give the title compound: (1.35g, 63%): CIMS: m/z 310.05 (MH^+); δ_C ($CDCl_3$) CH_2: 29.9, 29.9, 40.7, 40.7; CH: 74.9, 121.7, 121.7, 125.2, 125.2; C: 145.2, 151.7, 155.3, 158.7; δ_H ($CDCl_3$) 1.82 (2H, m, 3/5-CH_2), 2.01 (2H, m, 3/5-CH_2), 3.06 (2H, s, NH_2), 3.31 (2H, m, 2/6-CH_2), 3.68 (2H, m, 2/6-CH_2), 4.98 (1H, m, 4-CH), 7.39 (2H, d, Ar-H1/6) and 8.28ppm (2H, d, Ar-H3/5).

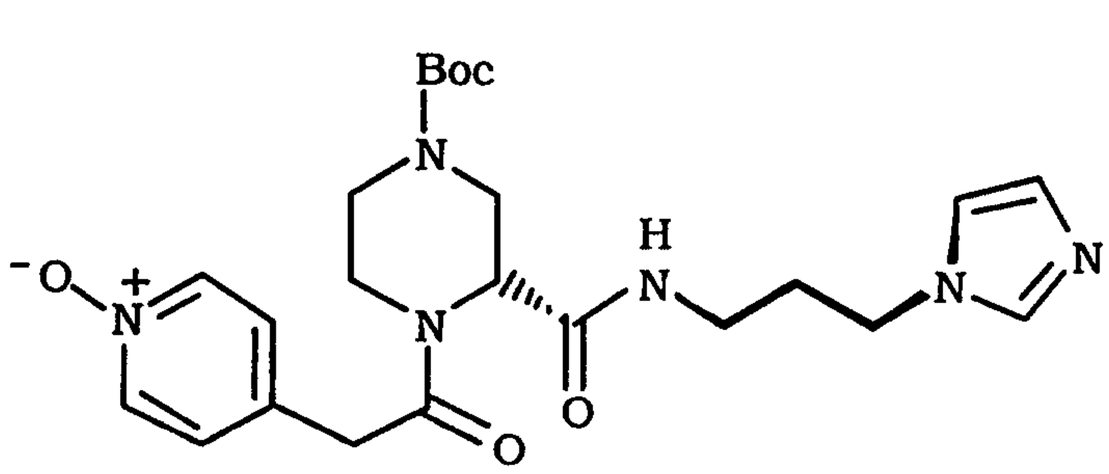
PREPARATIVE EXAMPLE 37

Step A



The anhydride (0.5088g, 1.99mmoles) (prepared as described in Preparative Example 44) and 1-(3-aminopropyl)-imidazole (0.260mL, 2.18mmoles) were dissolved in anhydrous dichloromethane (10mL) and the mixture was stirred under argon at 25°C for 5min. The mixture was diluted with dichloromethane and extracted with saturated aqueous sodium bicarbonate. The dichloromethane layer was dried ($MgSO_4$), filtered and evaporated to dryness. The resulting product was chromatographed on a silica gel column using 10% (conc, NH_4OH in methanol)-dichloromethane as the eluent to give the title compound: (Yield: 0.4955g, 74%); LCMS: m/z 338.1 (MH^+); δ_C ($CDCl_3$) CH_3: 28.4, 28.4, 28.4; CH_2: 31.1, 36.5, ~43.5(broad), 44.8, ~46.5(broad),; CH: 58.2, ~119.0(broad), ~129.7(broad), ~137.3(broad); C: 80.2, 154.7, 171.5; δ_H ($CDCl_3$) 1.47 (9H, s, CH_3), 6.96 (1H, s, Im-H_5), 7.08 (1H, s, Im-H_4) and 7.52ppm (1H, s, Im-H_2).

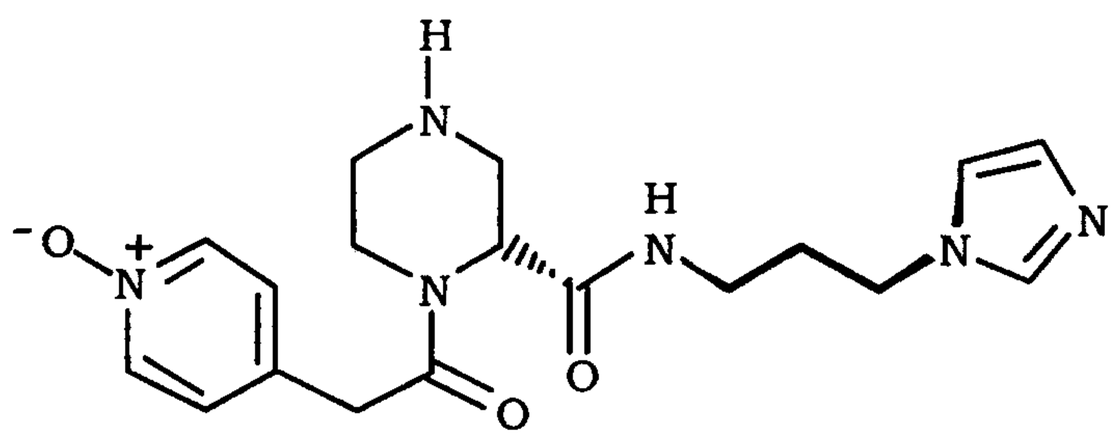
Step B



The title compound from Step A above (0.3248g, 0.96mmoles), 4-pyridylacetic acid N1-oxide (0.1916g, 1.25mmoles), 1[3-(dimethylamino)propyl]-3-ethylcarbodimide hydrochloride (0.24g,

1.25mmoles), 1-hydroxybenzotriazole (0.169g, 1.25mmoles) and 4-methylmorpholine (0.1376mL, 1.25mmoles) were dissolved in anhydrous DMF (11mL) and the mixture was stirred under argon at 25°C for 18h. The mixture was evaporated to dryness and the residue was dissolved in dichloromethane and washed with saturated aqueous sodium bicarbonate. The organic layer was dried ($MgSO_4$), filtered and evaporated to dryness. The product was chromatographed on a silica gel column using 5% (10% conc. NH_4OH in methanol)-dichloromethane as the eluant to give the title compound: (Yield: 0.4333g, 95%); LCMS: m/z 473.1 (MH^+); δ_C ($CDCl_3$) CH_3: 28.3, 28.3, 28.3; CH_2: 30.8, 36.5, 38.7, 43.2, ~43.5 (broad), ~44.5 (broad); CH: 53.8, ~119.2 (broad), 127.4, 127.6, ~129.3 (broad), ~137.5 (broad), 138.7, 138.9; C: 80.7, 134.5, 154.4, 169.6, 169.6; δ_H ($CDCl_3$) 1.44 (9H, s, CH_3), 6.97 (1H, broad s, Im-H_5), 7.09 (1H, broad s, Im-H_4), 7.20 (2H, m, Ar-H), 7.53 (1H, broad s, Im-H_2) and 8.14ppm (2H, d, Ar-H).

Step C

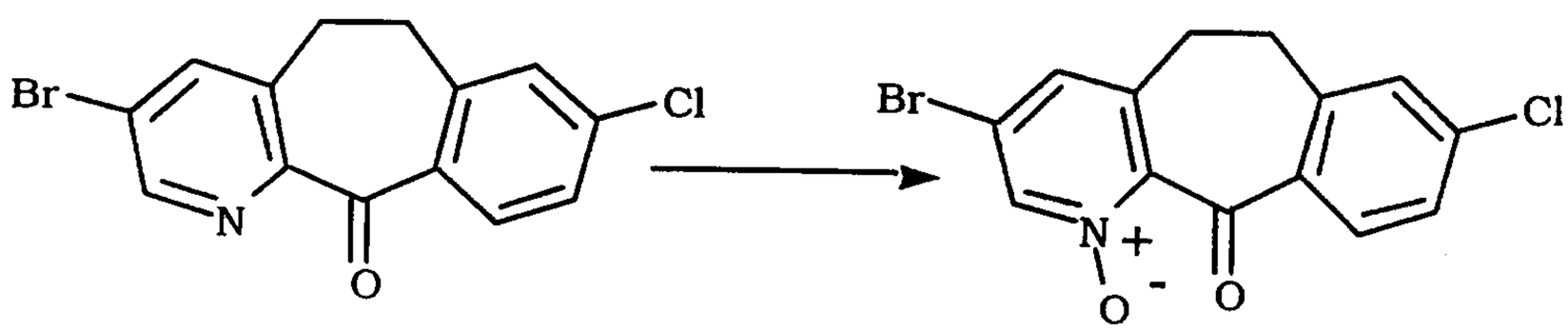


The title compound from Step B above (0.289g, 0.612mmoles) was dissolved in anhydrous dichloromethane (7.8mL) and trifluoroacetic acid (2.026mL, 26.3mmoles) was added. The mixture was stirred at 25°C for 1.25h under argon and then evaporated to dryness. The product was chromatographed on a silica gel column using 5% increasing to 10% (10% conc. NH_4OH in methanol)-dichloromethane as the eluant to give the title compound: (Yield: 0.208g, 91%); LCMS: m/z 373.1 (MH^+); δ_C ($CDCl_3$-CD_3OD) CH_2: 30.4, 36.2, 38.2, 43.9, 44.5, 46.2, 46.7; CH: 52.3, ~119.2 (broad), 127.7,

127.7, ~128.3 (broad), 137.4 (broad), 138.4, 138.5, 138.5; C: 137.3, 169.8, 170.6; δ_H ($CDCl_3$-CD_3OD) 6.90 (1H, broad s, Im-H_5), 6.94 (1H, broad s, Im-H_4), 7.22 (2H, m, Ar-H), 7.47 (1H, broad s, Im-H_2) and 8.12ppm (2H, d, Ar-H); $[\alpha]_D^{26.3°}$ +81.1° (c=10.43mg/2mL, methanol).

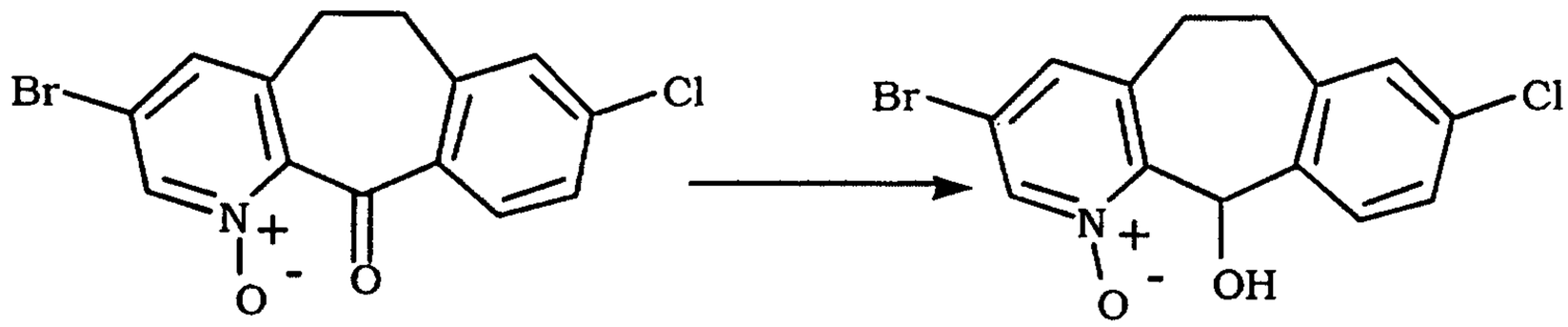
PREPARATIVE EXAMPLE 38

Step A



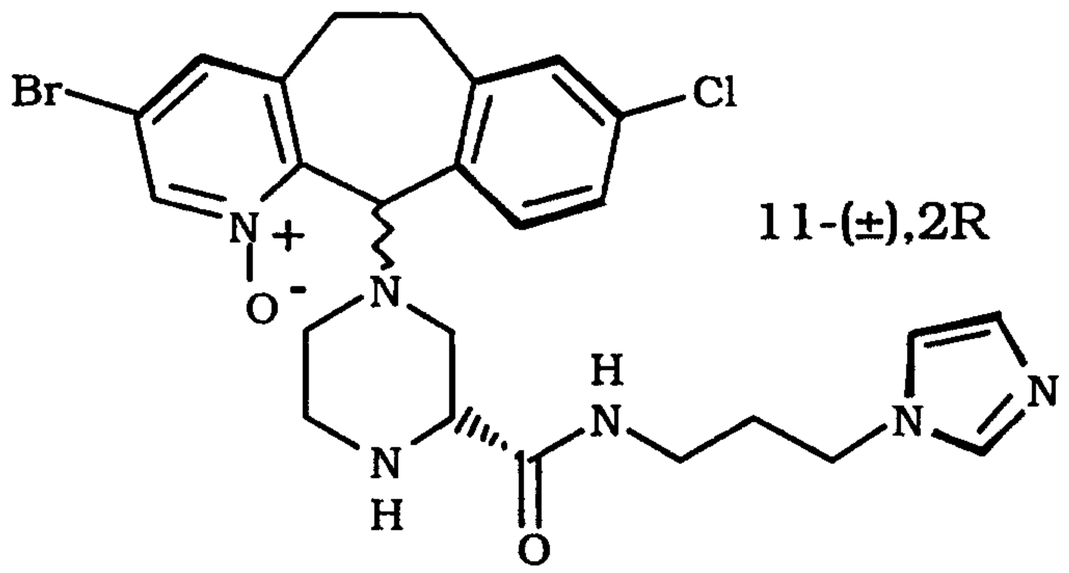
To a solution of 3-bromo-8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-one (2g) (6.2mmoles) in anhydrous dichloromethane (14ml) at 0°C and under an argon atmosphere, was added a solution of 3-chloroperbenzoic acid (1.76g) (10.4mmoles) in anhydrous dichloromethane (35ml) dropwise over a period of 30 minutes. The mixture was allowed to warm to room temperature and after 18h additional 3-chloro-perbenzoic acid (0.88g) (5.2mmoles) in anhydrous dichloro-methane (25ml) was added and the mixture was stirred for a total of 42h. The mixture was diluted with dichloromethane and washed with 1N NaOH (200ml). The aqueous layer was extracted with additional dichloromethane (2X200ml) and the combined organic layers were dried over magnesium sulfate, filtered and evaporated to dryness. The product was chromatographed on silica gel using 0.25%-0.5%-1% (10% conc. NH_4OH in methanol)dichloromethane as the eluant to give the title compound (Yield:1.386g, 66%): ESIMS; m/z 338.1 (MH^+); δ_C ($CDCl_3$) CH_2: 30.5, 34.0; CH: 126.9, 127.6, 130.3, 132.5, 140.4; C: 121.0, 135.1, 138.3, 139.7, 141.6, 145.3, 188.0ppm.

Step B



The title compound of Step A (1.3422g) (3.96mmoles) was dissolved in methanol (18ml) and dichloromethane (20ml) and sodium borohydride (0.219g) (5.79mmoles) was added. The mixture was stirred under argon at 0°C for 1h and then allowed to warm up to 25°C over a period of 1h. The mixture was diluted with dichloromethane (800ml) and washed with 1N NaOH (150ml). The aqueous layer was extracted with dichloromethane (2X100ml) and the combined organic layers were dried over magnesium sulfate, filtered and evaporated to dryness. The product was chromatographed on silica gel using 1% (10% conc. NH_4OH in methanol)dichloro-methane as the eluant to give the title compound (Yield: 1.24g, 92%): ESIMS: m/z 340.1 (MH^+); δ_C ($CDCl_3$) CH_2: 31.2, 32.0; CH: 69.1, 126.8, 129.5, 131.7, 131.7, 136.7; C: 118.3, 134.7, 135.2, 139.7, 141.0, 148.9ppm.

Step C

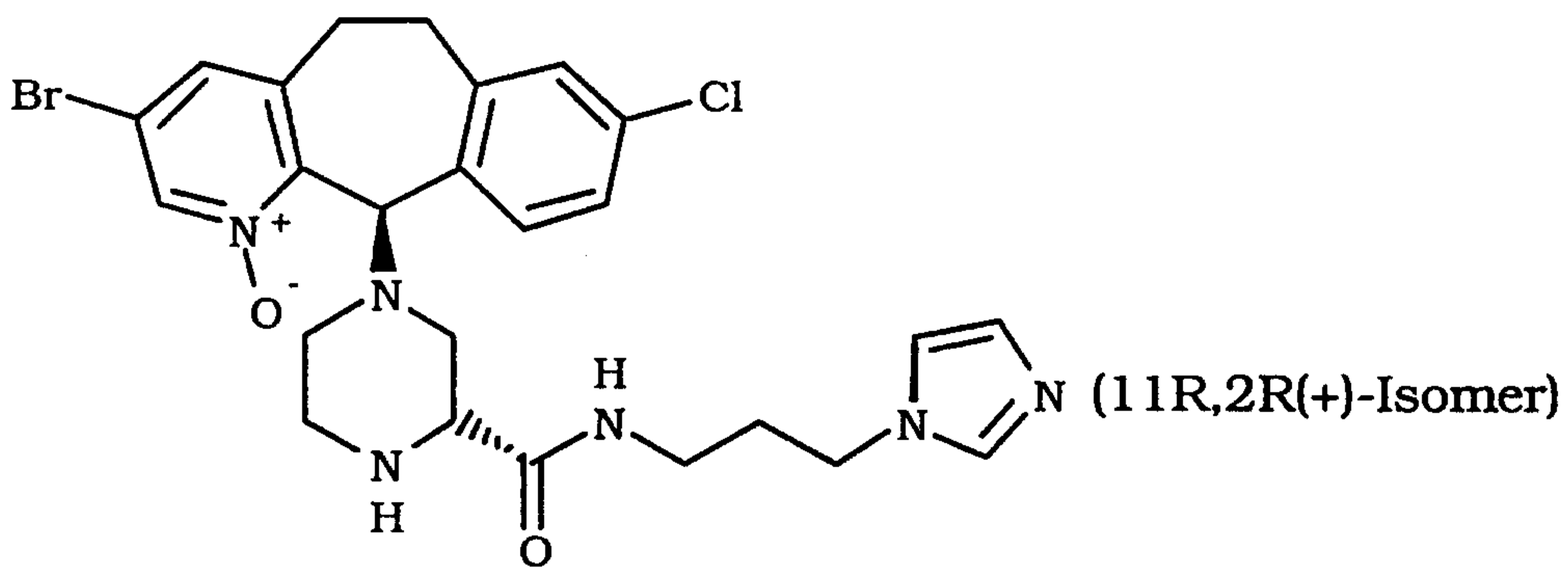


11-(±),2R

The title compound from Step B (0.552g, 1.62mmoles) and triethylamine (1.19mL, 8.52mmoles) were dissolved in anhydrous dichloromethane (8.5mL) and the solution was cooled to 0°C. Methanesulfonyl chloride (0.4mL, 5.16mmoles) was added over

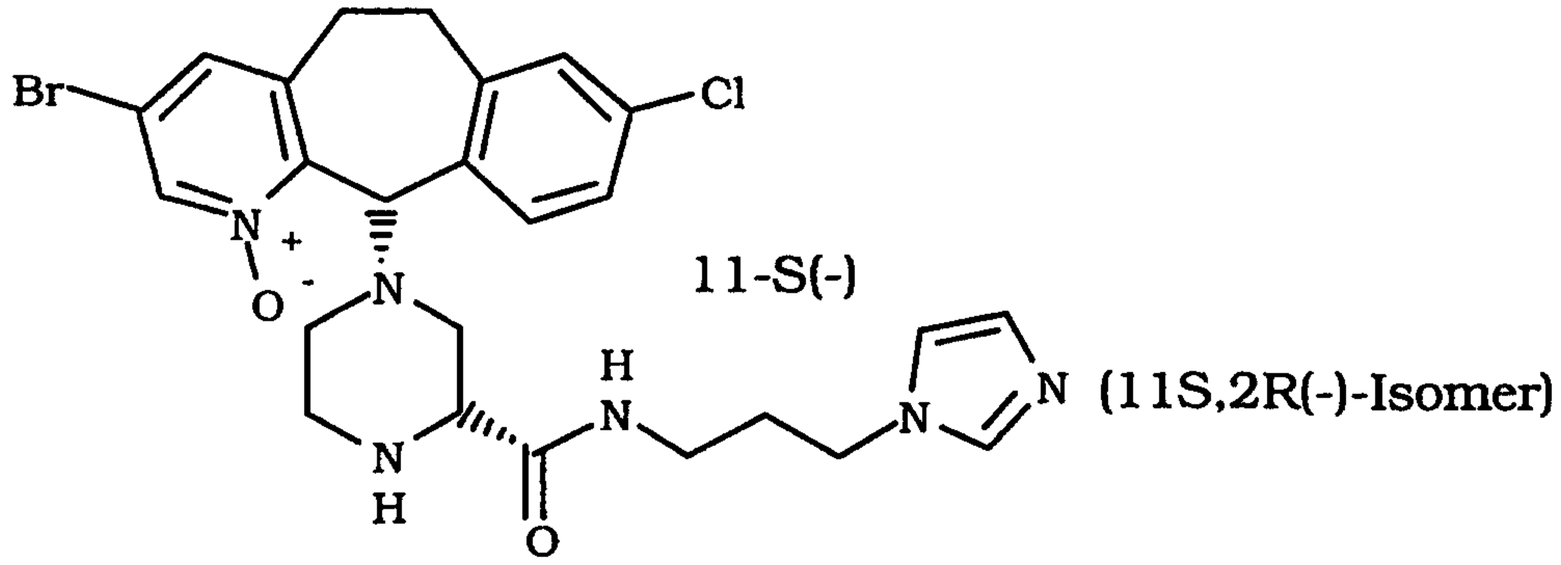
30min and the mixture was stirred at 0°C for a total of 1.25h. The solution was evaporated to dryness to give the 11-mesyl derivative which was used without further purification. The latter was dissolved in anhydrous dichloromethane (40mL) and the solution was stirred at 0°C. N-[3-(1H-Imidazol-1-yl)propyl]-2(R)-piperazinecarboxamide (Preparative Example 136) (0.5g, 2.11mmoles) dissolved in anhydrous dichloromethane (20mL) and anhydrous DMF (20mL) was added at 0°C and the solution was stirred and allowed to warm up to 25°C over 2h. The reaction was allowed to proceed at 25°C for 18h and was then diluted with dichloromethane and washed with saturated aqueous sodium bicarbonate, dried ($MgSO_4$), filtered and evaporated to dryness. The product was chromatographed on a silica gel column using 4% (10% conc. NH_4OH in methanol)-dichloro-methane as the eluant to give the title racemic compound: Yield: 0.399g, 44%); FABMS: m/z 559.3 (MH^+).

Step D



(11R,2R(+)-Isomer)

11-S(-)



(11S,2R(-)-Isomer)

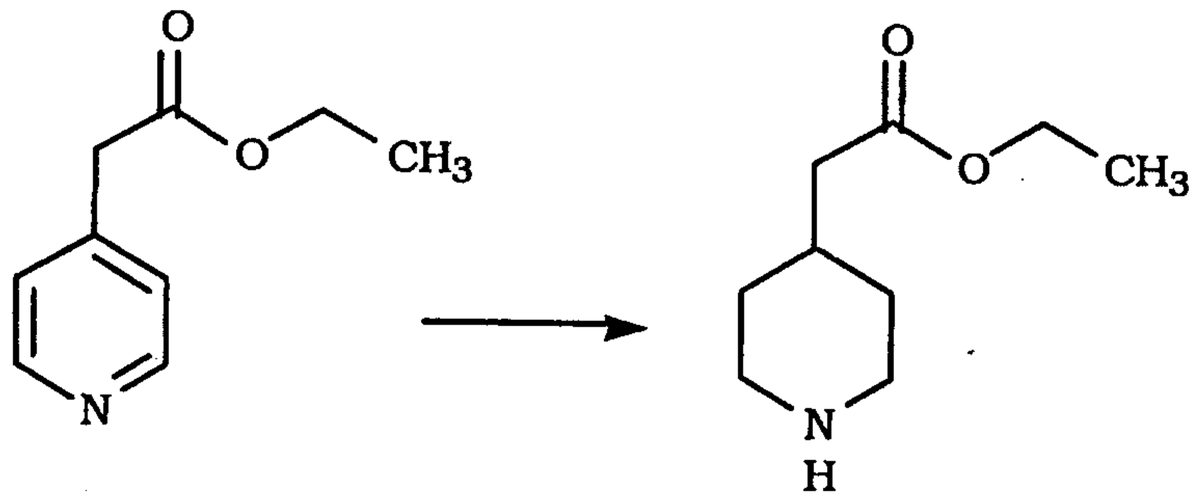
The title racemic compound from Step C above (0.395g) was subjected to preparative HPLC on a Chiralpak AD® column (50X5cm) using 65% hexane- 35% isopropyl alcohol- 0.2% diethylamine as the eluant to give in the order of elution the 11-R(+)-diastereoisomer of the title compound followed by the 11-S(-)-diastereoisomer of the title compound.

11R,2R(+)-diastereoisomer: (Yield: 0.1854g); FABMS: m/z 559.2 (MH^+); δ_C ($CDCl_3$) CH_2: 30.1, 30.3, 31.2, 36.4, 43.9, 44.7, 51.6, 52.8; CH: 57.8, 64.3, 118.9, 126.3, 129.6, 130.6, 130.7, 133.4, 137.3, 138.4; C: 118.2, 133.6, 134.6, 140.1, 141.0, 148.1, 172.0; δ_H ($CDCl_3$) 5.70 (1H, s, H_{11}), 6.95 (1H, broad s, Im-H_5), 7.04 (1H, broad s, Im-H_4), 7.51 (1H, broad s, Im-H_2) and 8.22ppm (1H, s, Ar-H_2); $[a]_D^{20°}$ +41.2° (c=11.08mg/2mL, methanol).

11S,2R(-)-diastereoisomer: (Yield: 0.18g); FABMS: m/z 559.2 (MH^+); δ_C ($CDCl_3$) CH_2: 30.1, 30.3, 31.1, 36.5, 44.4, 44.8, 51.6, 53.4; CH: 58.9, 64.4, ~119.2, 126.3, 129.5, 130.6, 130.7, 133.4, ~137.3, 138.5; C: 118.3, 133.7, 134.6, 139.9, 141.0, 148.1, 172.1; δ_H ($CDCl_3$) 5.69 (1H, s, H_{11}), 6.94 (1H, broad s, Im-H_5), 7.07 (1H, broad s, Im-H_4), 7.51 (1H, broad s, Im-H_2) and 8.26ppm (1H, s, Ar-H_2); $[a]_D^{19.9°}$ -71.0° (c=10.32mg/2mL, methanol).

PREPARATIVE EXAMPLE 39

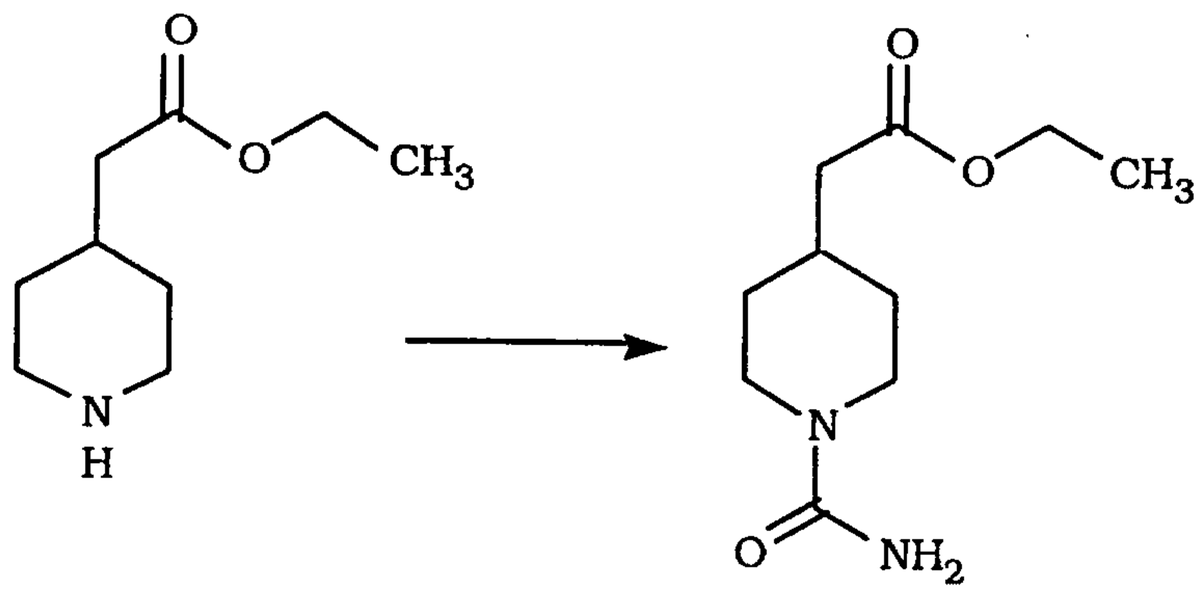
Step A



Ethyl 4-pyridyl acetate (4.5g, 27.24mmoles) was placed in a 500mL Parr bottle and dissolved in anhydrous EtOH (70mL). 10% Palladium on charcoal (1.0g) was added and the contents shaken under 55 psi hydrogen pressure at 25°C for 94h. The mixture was

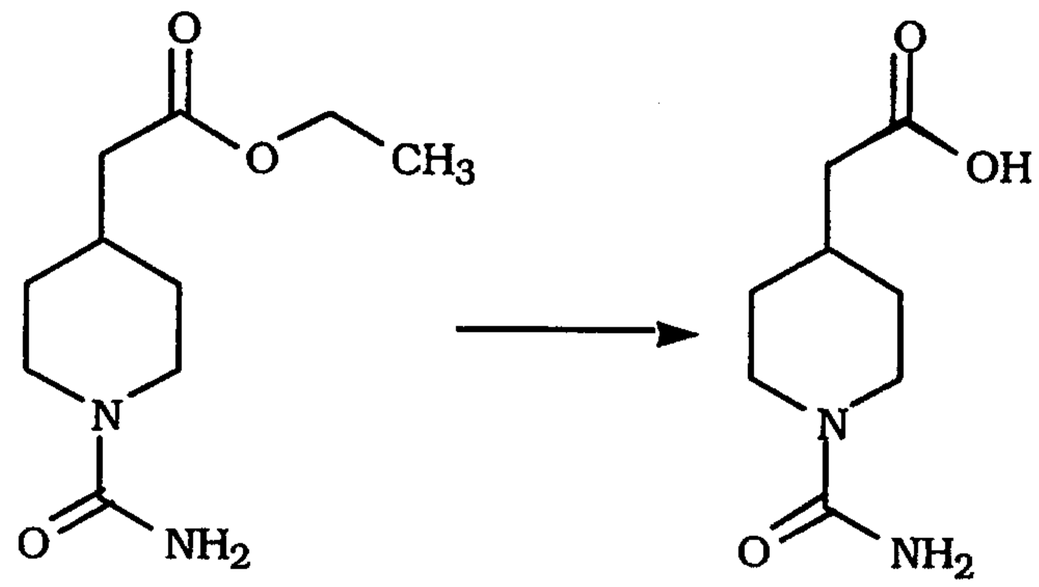
filtered through Celite® and washed with 4x40mL anhydrous EtOH. The filtrate was evaporated to dryness and the residue was chromatographed on silica gel using 3% (10% conc. NH_4OH in methanol)-dichloromethane as the eluant to give the title compound: (Yield: 2.944g, 63%): FABMS: m/z 172.2 (MH^+); δC ($CDCl_3$) CH_3: 14.3; CH_2: 33.2, 33.2, 41.9, 46.5, 46.5 60.2; CH: 33.4; C: 172.7 ; δH ($CDCl_3$) 1.18 (1H, m, H_4), 1.26 (3H, t,CH_3), 1.71(2H), 1.90(1H), 1.96(1H), 2.22(2H, d), 2.63(2H), 3.07(2H), 4.13ppm (2H, q, $CH_3\underline{CH_2}$-).

Step B



Ethyl 4-piperidinyl acetate (500mg; 2.92mmoles) from Step A above was dissolved in anhydrous dichloromethane (25mL). To the stirred solution was added trimethylsilyl isocyanate (5.9mL; 43.8mmoles) and the solution was stirred at 25°C for 17h. The solution was diluted with dichloromethane and washed with saturated aqueous sodium bicarbonate. The dichloromethane layer was dried ($MgSO_4$), filtered and evaporated to dryness. The product was chromatographed on silica gel using 2% increasing to 3%(10% conc. NH_4OH in methanol)-dichloromethane as the eluant to give the title compound: (Yield: 622mg, 99%): CIMS: m/z 215.3 (MH^+); δ_c ($CDCl_3$): CH_3: 14.2; CH_2: 31.6, 31.6, 41.0, 44.2, 44.2, 60.4; CH: 32.9; C: 158.2, 172.4; δ_H ($CDCl_3$): 1.23 (1H, m, H_4), 1.27 (3H, t, CH_3), 1.75 (2H, d), 1.98 (1H, m), 2.26 (2H, d), 2.85 (2H, t), 3.94 (2H, d), 4.15 (2H, q, $CH_3\underline{CH_2}$-), 4.56 (2H, bs).

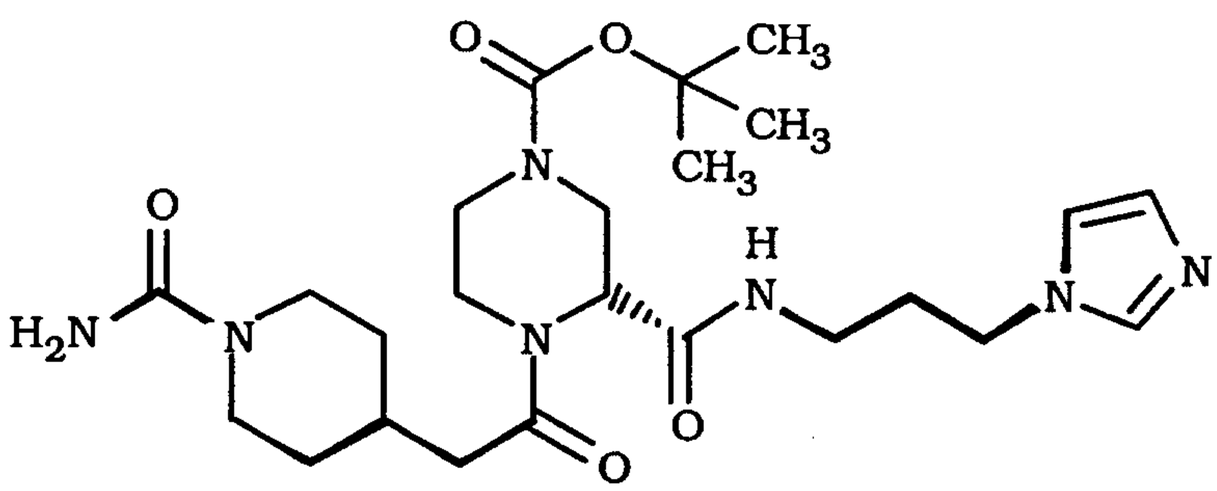
Step C



Ethyl 1-aminocarbonyl-4-piperidinyl acetate (153.6mg, 0.717mmoles) from Step B above was dissolved in anhydrous dichloromethane (3.58mL) and ethanol (3.58mL). To the solution was added 1.0M LiOH (1.73mL, 1.73mmoles) and the mixture was stirred at 50°C for 5.5h. The mixture was cooled quickly to 25°C and 1.0N HCl (2.02mL, 2.02mmoles) was added and the mixture stirred for 5 minutes and then evaporated to dryness to give the title compound, which was used without further purification.

PREPARATIVE EXAMPLE 40

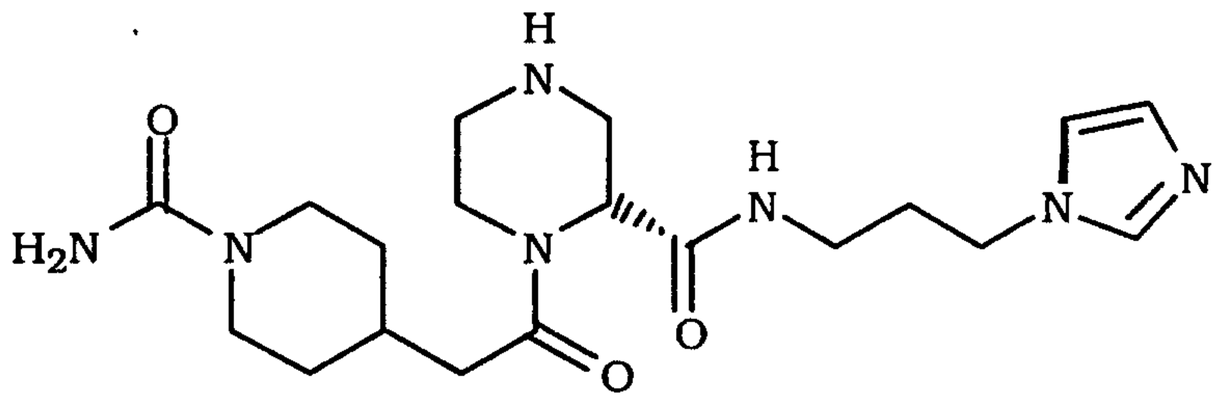
Step A



The title compound from Preparative Example 37, Step A above (0.45g, 1.33mmoles), 1[3-(dimethylamino)propyl]-3-ethylcarbodimide hydrochloride (0.332g, 1.73mmoles), 1-hydroxybenzotriazole (0.234g, 1.73mmoles) and 4-methyl-morpholine (0.382mL, 3.46mmoles) were dissolved in anhydrous DMF (7mL). The title compound from Preparative Example 33, Step C above (0.3228g, 1.73mmoles) dissolved in anhydrous DMF (8mL)

was added and the mixture was stirred at 25°C for 22h. The solution was evaporated to dryness and the residue was taken up in dichloromethane and washed with saturated aqueous sodium bicarbonate, dried ($MgSO_4$), filtered and evaporated to dryness. The residue was chromatographed on a silica gel column using 5% (10% conc. NH_4OH in methanol)-dichloromethane as the eluant to give the title compound: (Yield: 0.3553g, 53%).

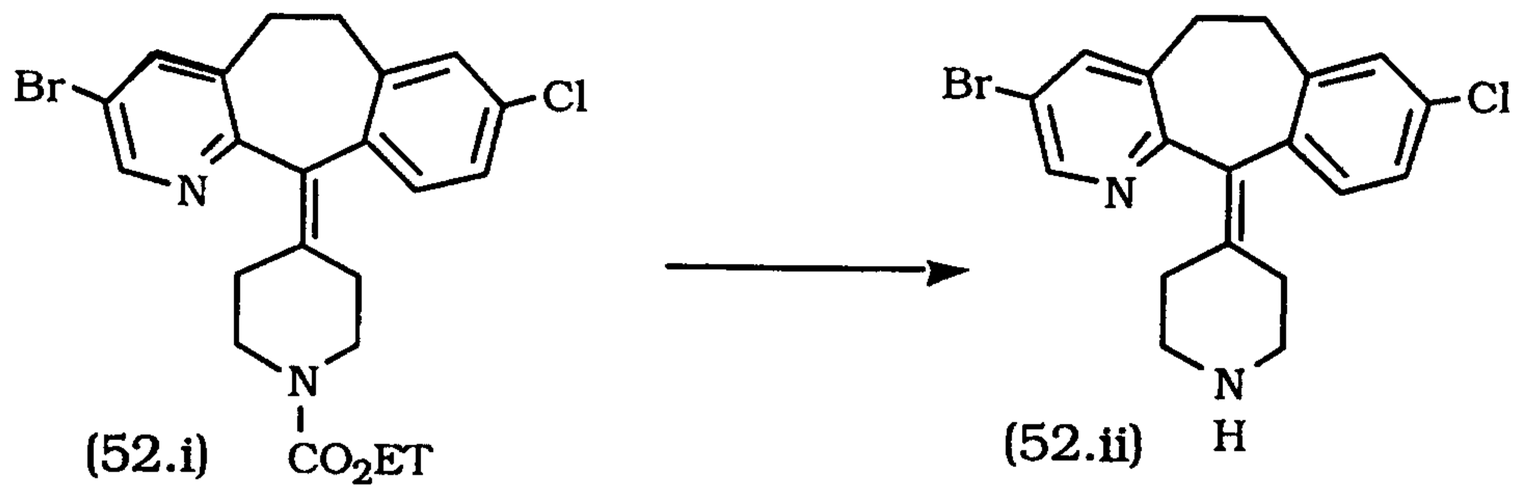
Step B



The title compound from Step A above (0.45g, 0.9mmoles) was dissolved in methanol (5.625mL). A 10% (v/v) solution of conc. H_2SO_4 in dioxane (13.5mL) was added and the mixture was stirred at 25°C for 2h. Anhydrous methanol (200mL) was added followed by BioRad® AG1-X8 (OH^-) resin until the solution was neutral to pH paper. The resin was filtered off and washed with methanol and the combined filtrates were evaporated to dryness. The residue was chromatographed on a silica gel column using 5% increasing to 6.5% (10% conc. NH_4OH in methanol)dichloro-methane as the eluant to give the title compound: (Yield: 0.317g, 96%); FABMS: m/z 406.2 (MH^+); δ_C ($CDCl_3$-~5% CD_3OD) CH_2: 30.8, 31.9, 31.9, 36.2/36.3/36.6, 39.1/39.3/39.5, 44.1/44.2, 44.4, 44.4, 44.8, 44.8; CH: 51.2/56.3, 119.0, 128.8, 137.0; C: 158.7, 171.0/171.1, 171.9/172.6; δ_H ($CDCl_3$- 2.86% CD_3OD) 4.84 (1H, d, H_2), 6.96 (1H, broad s, Im-H_5), 7.04 (1H, broad s, Im-H_4) and 7.53ppm (1H, broad s, Im-H_2).

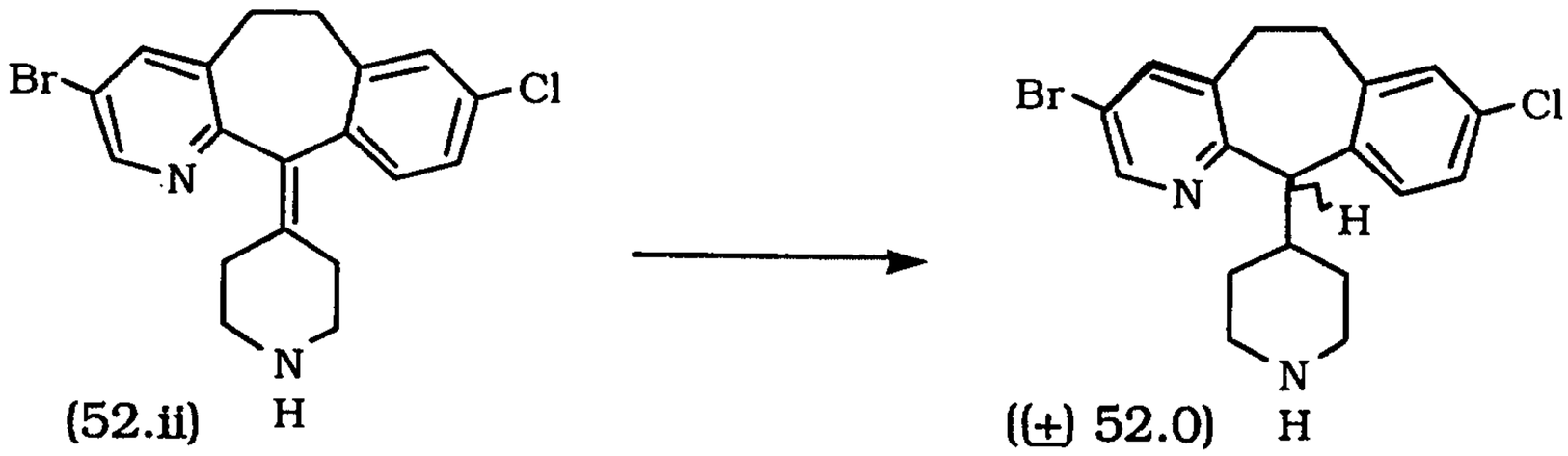
PREPARATIVE EXAMPLE 40A

Step A



A solution of 52.i (J. Med. Chem. 4890-4902 (1988))(205 g) in conc. HCl (1 L) and water (100 mL) is refluxed for 18h, then poured into ice (3 Kg). Aq. 50% NaOH is added to pH 12 followed by extraction with EtOAc (3x4 L), the extracts are washed with brine, dried and evaporated to afford 52.ii (166 g).

Step B



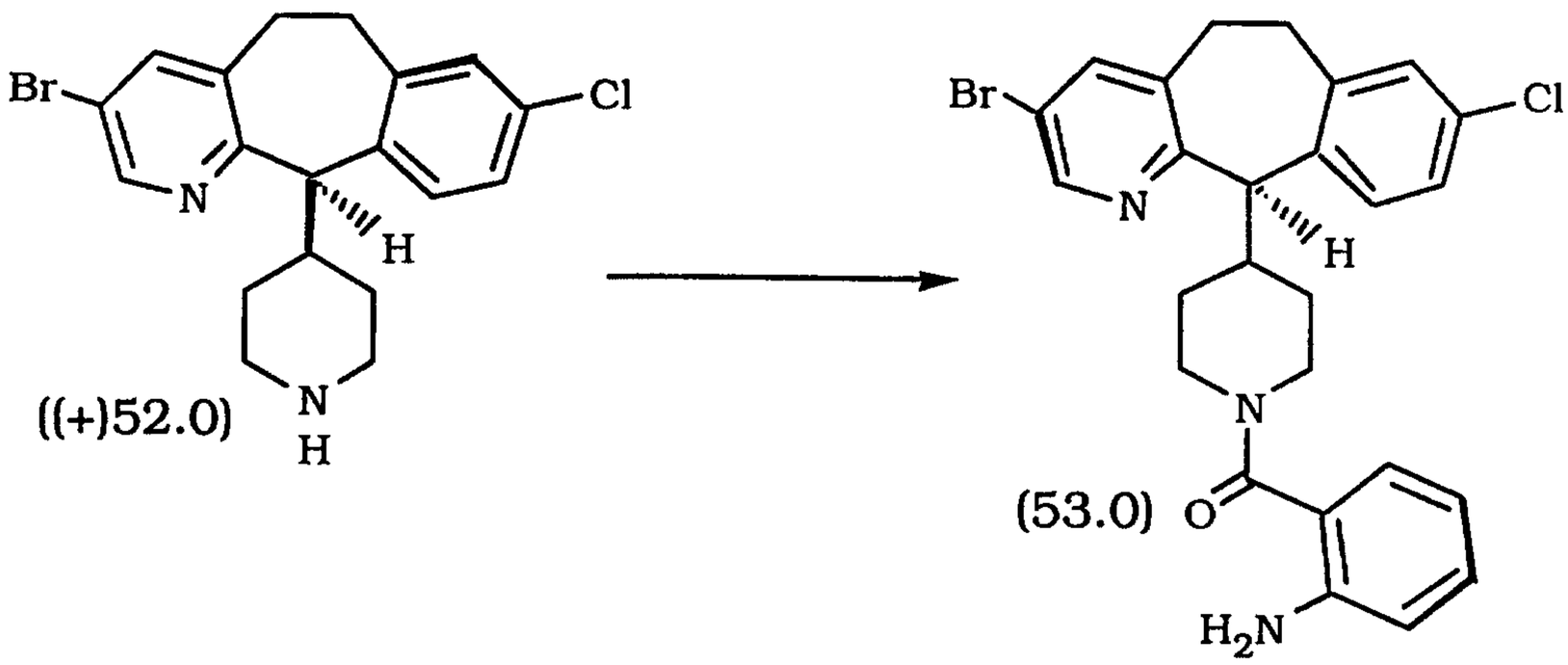
A 1M solution of DIBAL in toluene (908 mL) is added dropwise during 2h to a solution of 52.ii (166 g) in toluene (4 L) at rt. followed by stirring for 18 h. The mixture is cooled to 0–5°C and stirred for 1h and extracted with 1N HCl (2 L). The aqueous extract is basified to pH 10 with 50% NaOH and extracted with EtOAc (3x2 L). The extracts are evaporated and chromatographed on silica-gel (1 Kg). Elution with 10% MeOH/CH_2Cl_2 affords the title compound (+) 52.0 (104 g): HRMS (FAB) calcd for $C_{19}H_{21}N_2{}^{79}BrCl$ 393.0556, found 393.0554.

Step C

The racemate (±) 52.0 (96 g) is resolved by HPLC on a 8x30 cm CHIRALPAK AD column at 25°C with the UVdetector set at 290 nm. Elution with 0.05% diethylamine-methanol affords: Peak 1 (-) 52.0 (40 g): $[\alpha]_D^{20}$ -28.4° (*c* 0.3, MeOH); Further elution with the same solvent affords: Peak 2 (+) 52.0 (42 g): $[\alpha]_D^{20}$ +27.5° (*c* 0.3, MeOH).

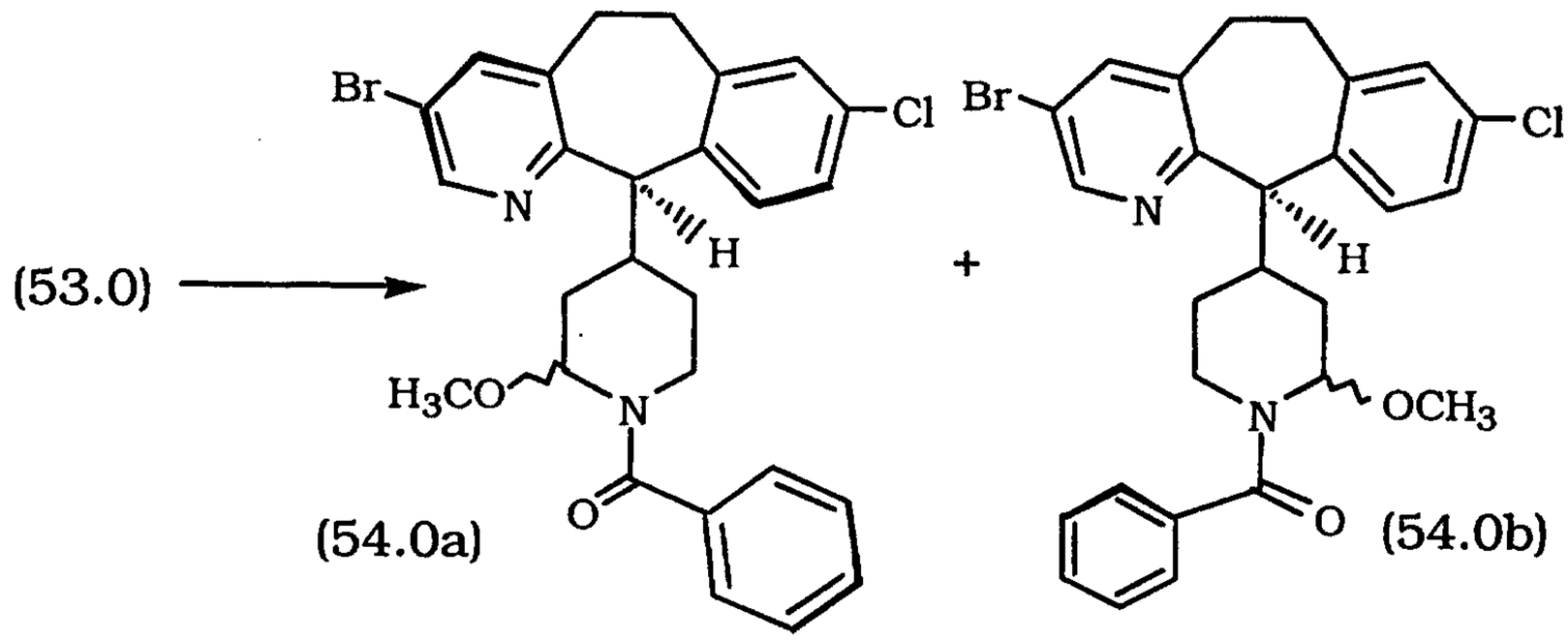
PREPARATIVE EXAMPLE 41

Step A



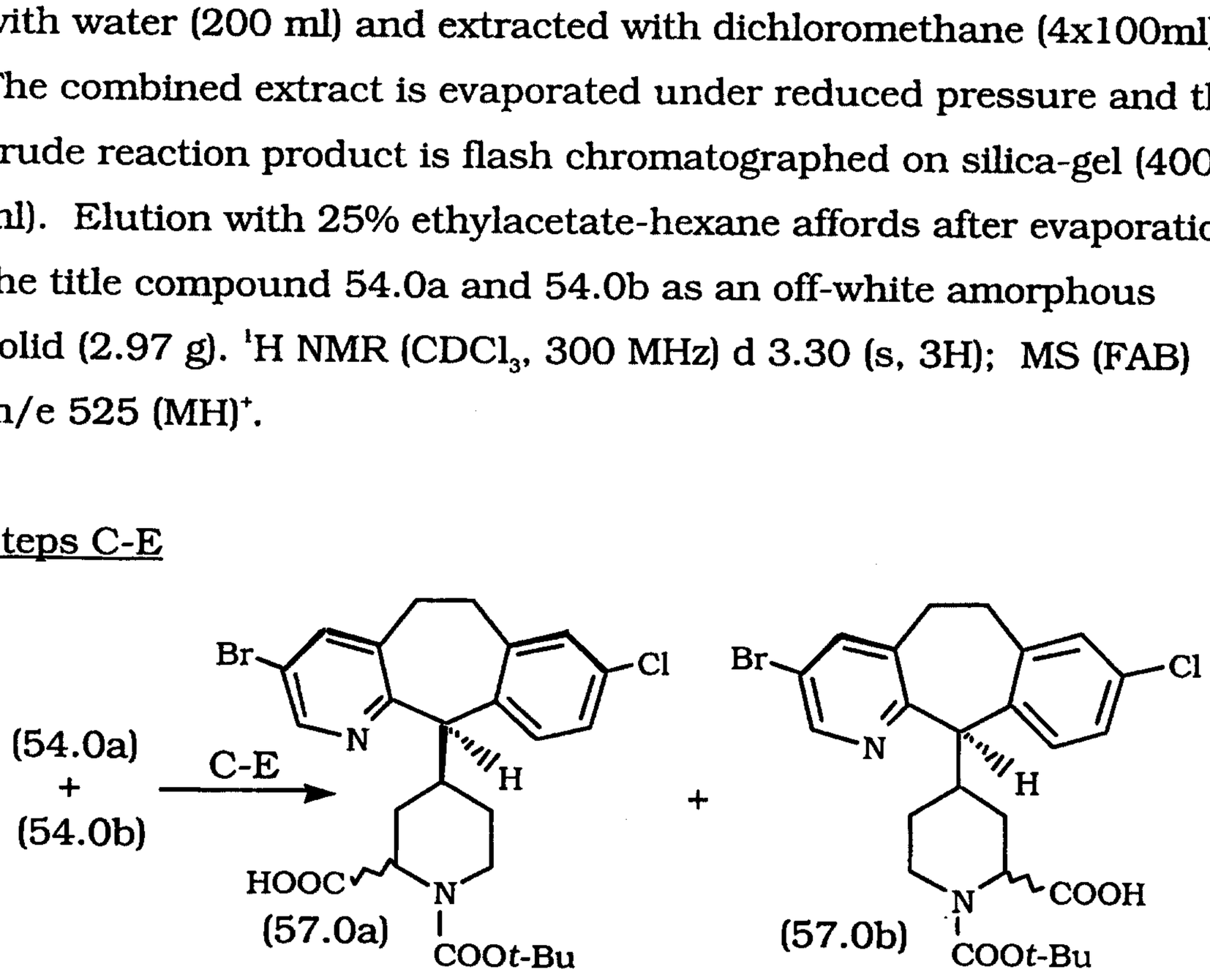
A solution of (+)-52.0 (2.3 g) in dimethylformamide (30 ml) is reacted with isatoic anhydride (1.25 g) in the presence of DMAP (0.1 g) at r.t. for 3hrs and is then evaporated under reduced pressure and residual dimethylformamide is azeotroped with toluene. The residue is dissolved in ethylacetate (50 ml) and the solution is extracted with 10% sodium carbonate (3x100 ml). The organic layer is filtered through silica-gel (100ml) followed by elution with ethylacetate. The filtrate is evaporated under reduced pressure to afford the title compound 53.0 as an amorphous solid (3.68 g). MS(FAB): m/z 510 $(MH)^+$.

Step B



A solution of 53.0 (3.1 g) and sodium nitrite (0.8 g) in methanol (500 ml) is stirred at r.t. under nitrogen with cuprous chloride (0.15 g) while adding dropwise over 10 minutes a 4M hydrochloric acid/dioxane solution (3.9 ml). The reaction mixture is stirred for 24hrs followed by the addition of 10% sodium carbonate to pH 8, concentrated under reduced pressure, diluted with water (200 ml) and extracted with dichloromethane (4x100ml). The combined extract is evaporated under reduced pressure and the crude reaction product is flash chromatographed on silica-gel (400 ml). Elution with 25% ethylacetate-hexane affords after evaporation the title compound 54.0a and 54.0b as an off-white amorphous solid (2.97 g). ^{1}H NMR ($CDCl_3$, 300 MHz) d 3.30 (s, 3H); MS (FAB) m/e 525 $(MH)^+$.

Steps C-E



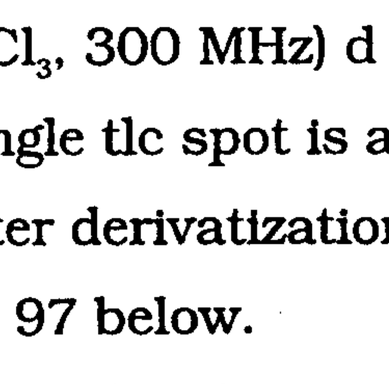
A solution of 54.0a and 54.0b (17 g) in methanol (150 ml) and 2N hydrochloric acid (170 ml) and conc. HCl (60 ml) is heated under

reflux for 17 hrs, followed by evaporation under reduced pressure. The resulting amorphous solid is dissolved in methanol (160 ml) and sodium cyanide (15 g) is added with stirring until the reaction is basic (pH 8). The reaction is stirred for 2 h, diluted with dichloromethane (300 ml) and filtered. The filtrate is evaporated and the residue is dissolved in conc HCl (150 ml) and the mixture is heated in an oil bath (120°C) for 4h and is then evaporated under reduced pressure. The residue is dissolved in THF (100 ml) and 10% NaOH (30 ml) is added to pH>8 followed by the dropwise addition of a solution of $(BOC)_2O$ (9 g) in THF (50 ml) with vigorous stirring for 24 h. The solution is concentrated to a low volume, stirred with hexane (2x120 ml) and ice-water followed by acidification of the aqueous layer with citric acid and extraction with EtOAc. The crude product obtained by evaporating the extract is purified by flash chromatography to afford the mixture of 57.0a and 57.0b as light tan solid that appears as a single tlc spot (16 g). ^1H NMR ($CDCl_3$, 300 MHz) d 1.40 (s, 9H); MS (FAB) m/z 535 $(MH)^+$.

The single tlc spot is a mixture of four isomers which are separated after derivatization into the compounds of Examples 77 to 79 and 87 to 97 below.

Following the above procedure (Steps A-E), except using Compound (-)-52.0 (17 g), a mixture of 58.0a and 58.0b is obtained as a light solid that appears as a single tlc spot (17 g). MS(ES) m/z 535 (MH^+).

PREPARATIVE EXAMPLE 42

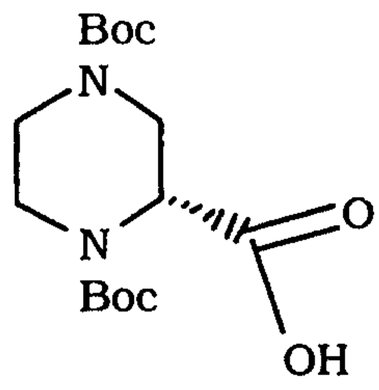


•2Camphorsulfonic acid

To 2.5 kg of (R)-(-)-camphorsulfonic acid stirring at 60°C in 1250 ml of distilled water was added a soution of the potassium salt

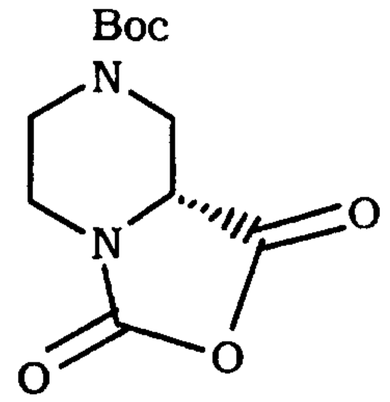
of 2-carboxyl-piperazine (565 gm, 3.35 mol). The mixture was allowed to stir at 95°C until completely dissolved. The solution was allowed to stand at ambient temperature for 48 hrs. The resulting precipitate was filtered to obtain 1444 gm of damp solid. The solids were then dissolved in 1200 ml of distilled water and heated on a steam bath until all solids dissolved. The hot solution was then set aside to cool slowly for 72 hrs. The crystalline solids were filtered to give 362 gm of the pure 2-R-enantiomeric product as a white crystalline solid. $[\alpha]_D$=-14.9°.

PREPARATIVE EXAMPLE 43



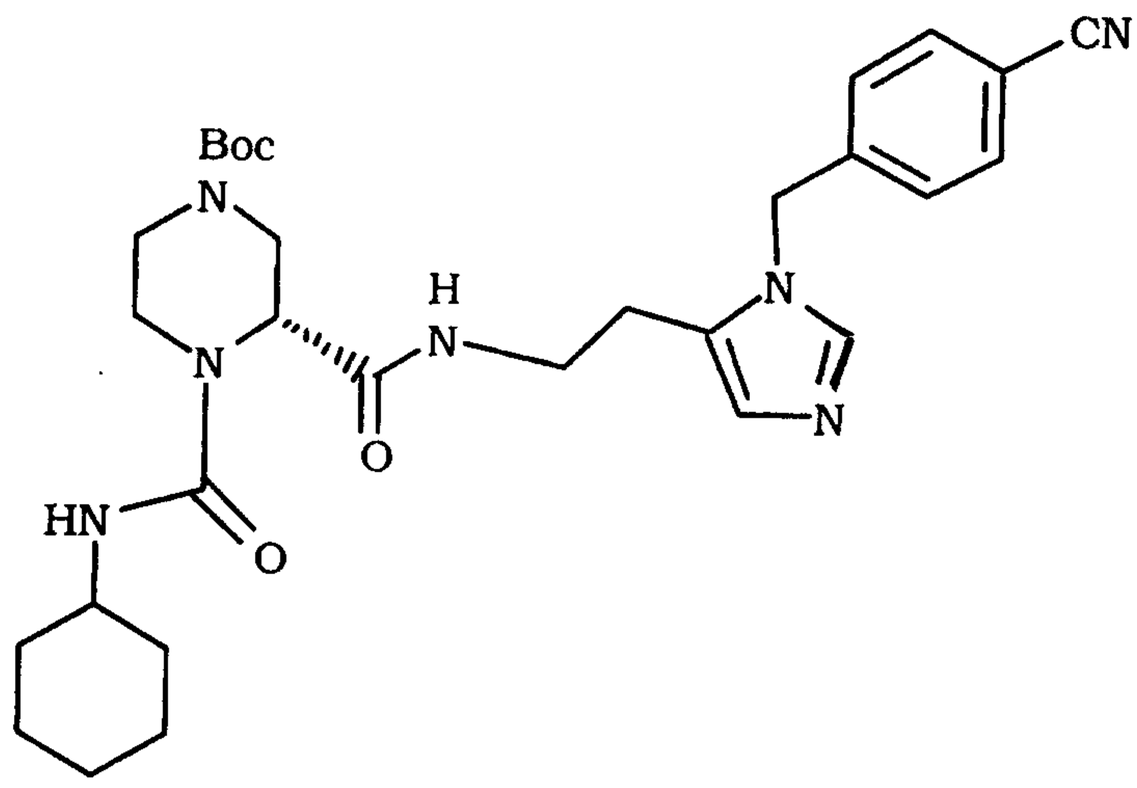
2-R-carboxyl-piperazine-di-(R)-(-)-camphorsulfonic acid (Preparative Example 42) (362 gm, 0.608 mol) was dissolved in 1.4 L of distilled water and 1.4 L of methanol. 75 ml of 50% NaOH was dripped in to the stirred reaction mixture to obtain a ~pH 9.5 solution. To this solution was added di-tert-butyl-dicarbonate (336 gm, 1.54 mol) as a solid. The pH dropped to ~7.0. The pH of the reaction mixture was maintained at 9.5 with 50% NaOH (total of 175 ml), and the reaction mixture stirred for 2.5 hours to obtain a white precipitate. The reaction mixture was diluted to 9 L with ice/water followed by washing with 2 L of ether. The ether was discarded and the pH of the aqueous layer adjusted to pH 3.0 by the portionwise addition of solid citric acid. The acidified aqueous layer was then extracted with dichloro-methane 3X with 2L. The organic layers were combined, dried over sodium sulfate, filtered and evaporated to obtain 201.6 gm of title compound as a white glassy solid. FABMS (M+1)=331.

PREPARATIVE EXAMPLE 44



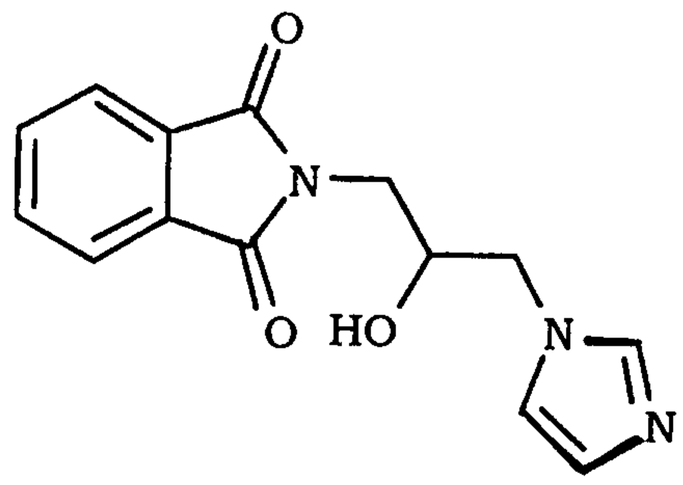
To an ice cold solution N,N-dimethylformamide (49.6 ml) was added, dropwise, thionylchloride (46.7 ml) over a period of 5 minutes in a 5 L round bottom flask under a nitrogen atmosphere. The reaction mixture was allowed to stir for 5 min. and the ice bath removed and the reaction mixture allowed to stir at ambient temperature for 30 min. The reaction mixture was cooled again in an ice bath and a solution of of N,N-di-tert-butoxycarbonyl-2-R-carboxyl-piperazine (Preparative Example 43) (201.6 gm, 0.61 mmol) in 51.7 ml of pyridine and 1.9 L of acetonitrile was cannulated into the reaction mixture. The reaction mixture was allowed to warm to ambient temperature to obtain a yellowish turbid solution. After stirring at ambient temperature for 18 hours, the reaction mixture was filtered and the filtrate poured into ice water (7L) and then extracted with 4X 2 L of ethyl acetate, dried over sodium sulfate, filtered and evaporated to dryness under vacuo to obtain 115.6 gm (73%) of the title product as a white solid.

PREPARATIVE EXAMPLE 45



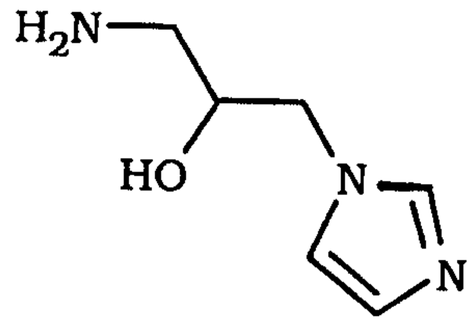
1N-p-Cyanobenzyl histamine (0.34, 1.5 mmol) (prepared as described in Preparative Example 163) was added to a solution of the Boc-anhydride (Preparative Example 44) (0.38 gm, 1.5 mmol) in 10 ml of dichloromethane and stirred under a nitrogen. After 1 hr, 0.15 gm more of the Boc-anhydride was added and the reaction monitored for completion by normal phase tlc using 10% methanol/dichloromethane as the eluent. After the reaction went to completion (~1 hour), 0.25 ml (2 mmol) of cyclohexyl isocyanate was added to the reaction mixture and stirred for 1 hour. The reaction mixture was poured into brine and extracted with dichloromethane (3X). The dichloromethane layers were combined, dried over $MgSO_4$, filtered and evaporated to dryness. The residue was chromatographed on a flash column of silica gel using 5% methanol/dichloromethane to obtain 0.714 gm of pure title compound as a solid. FABMS (M+1)=564.

PREPARATIVE EXAMPLE 46



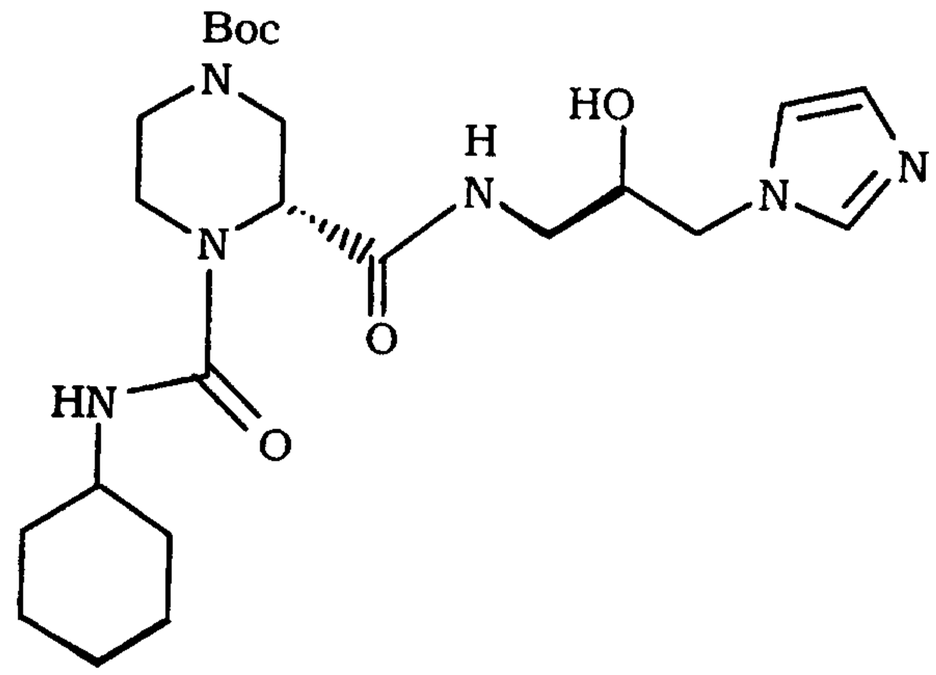
N-(2,3-Epoxypropyl)phthalimide (2.3 gm, 11.3 mmol) was dissolved in N,N-dimethylformamide and imidazole (1.53 gm, 1.5 eq.) was added and the reaction mixture stirred at 90 °C for 5 hours. Brine was added and the product extracted with ethylacetate to obtain the title product (0.67 gm).

PREPARATIVE EXAMPLE 47



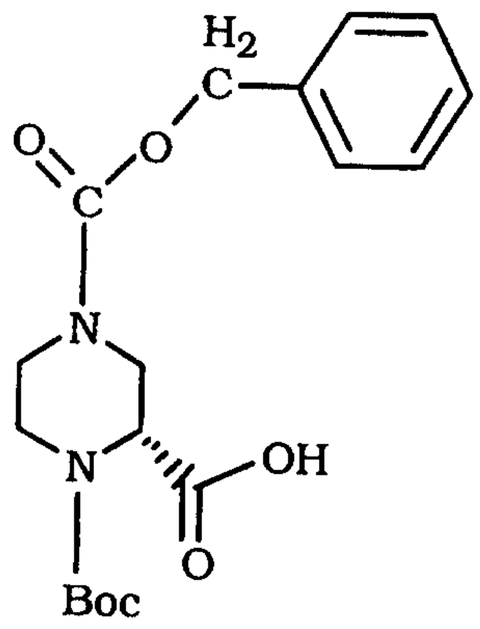
1-Phthalamido-2-hydroxy-3-1-H-imidazole-propane (from Preparative Example 46) (0.6 gm) was dissolved in ethanol and 5 ml of hydrazine hydrate added. The reaction mixture was refluxed for 3 hours. The reaction mixture was cooled to ambient temperature and the resulting precipitate filtered. The filtrate was evaporated to dryness to obtain the title product which was used without further purification.

PREPARATIVE EXAMPLE 48



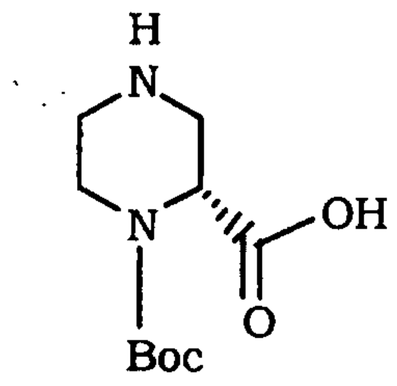
1-Amino-2-hydroxy-3-1-H-imidazole-propane (from Preparative Example 47) (2.2 mmol) was added to a solution of the Boc-anhydride (Preparative Example 44) (0.57gm, 2.2 mmol) in 10 ml of dichloromethane and stirred under nitrogen. After 1 hr, 0.15 gm more of the Boc-anhydride was added and the reaction monitored for completion by normal phase tlc using 10% methanol/dichloromethane as the eluent. After the reaction went to completion (~1 hour), 0.85 ml (6.6 mmol) of cyclohexyl-isocyanate was added to the reaction mixture and stirred for 1 hour. The reaction mixture was poured into brine and extracted with dichloromethane (3X). The dichloromethane layers were combined, dried over $MgSO_4$, filtered and evaporated to dryness. The residue was chromatographed on a flash column of silica gel using 5% methanol/dichloromethane to obtain 0.487 gm of pure title compound as a solid.

PREPARATIVE EXAMPLE 49



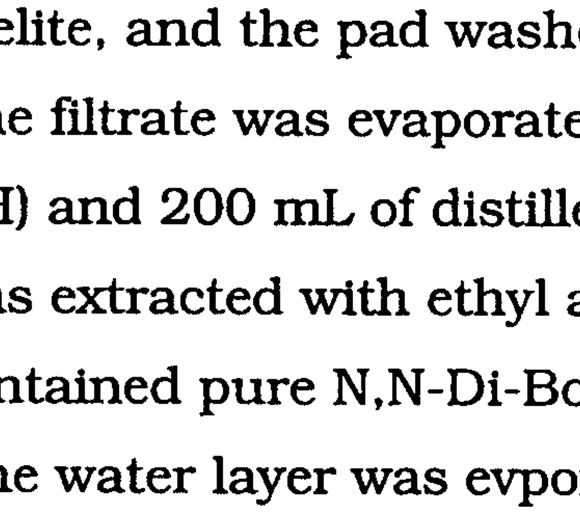
2-Carboxy-piperazine-dicamphorsulfonic acid salt (Preparative Example 42) (17.85 gm, 30 mmole) was dissolved in 180 ml of distilled water. Dioxane (180 mL) was added and the pH adjusted to 11.0 with 50% NaOH. The reaction mixture was cooled to 0-5°C in an ice-MeOH bath and a solution of benzyl-chloroformate (4.28 mL, 30 mmol) in 80 mL of dioxane was added over a period of 30-45 minutes while stirring at 0-5°C and keeping the pH at 10.5 to 11.0 with 50% NaOH. After the addition was complete, stirring was continued for 1 hr. The reaction mixture was then evaporated to dryness (to get rid of the dioxane for extraction). The residue was dissolved in 180 mL of dist. water and the pH adjusted slowly to 4.0 with 1N HCl. The aqueous solution was washed with 3X180 mL of ethyl acetate (The ethyl acetate was dried over $MgSO_4$, filtered, and evaporated to obtain N,N-di-CBZ-2-carboxy-piperazine and saved). The pH of the aqueous layer, which contains the desired product, was adjusted to 10.5 to 11.0 with 50% NaOH and solid di-tert-butyl-dicarbonate (7.86 gm, 36 mmol) was added and the mixture was stirred while keeping the pH at 10.5 to 11.0 with 50% NaOH. After 1 hr. the pH stabilized. When reaction was complete, the reaction mixture was washed with 2X180 mL of Et_2O. The aqueous layer was cooled in an ice bath and adjusted pH to 2.0 with 1N HCl (slowly). Extract the product with 3X200 mL of ethyl acetate. Dry over $MgSO_4$, filter and evaporate to obtain 9.68 gm (88%) of pure product as a white solid.

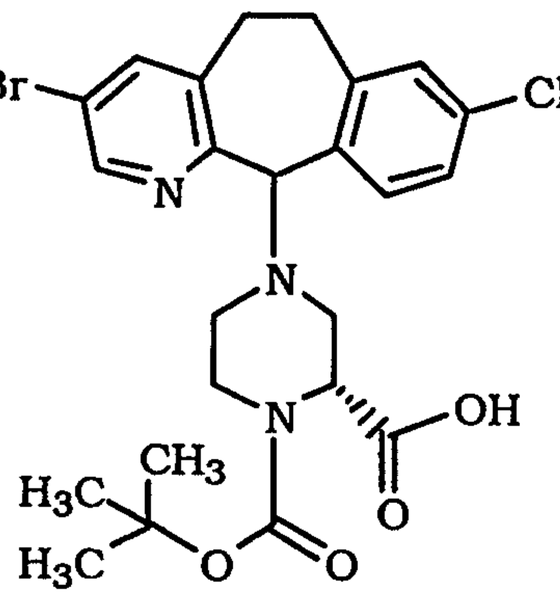
PREPARATIVE EXAMPLE 50



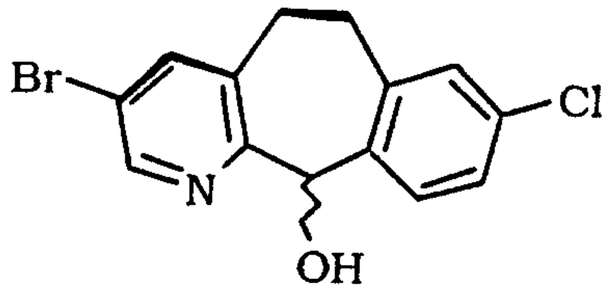
4-N-CBZ-1N-Boc-2-carboxy-piperazine (Preparative Example 49) (9.6 gm, 26.3 mmol) was dissolved in 100 mL of absolute ethanol in a hydrogenation vessel. The vessel was flushed with nitrogen and 3 gm of 10% Pd/C (50% by weight with water) was added. The mixture was hydrogenated at 55 psi of H_2 for 18 hours. After 18 hrs, the reaction mixture had a precipitate. The tlc was checked (30% MeOH/NH_3/CH_2Cl_2). The reaction mixture was filtered on a pad of Celite, and the pad washed with EtOH followed by distilled water. The filtrate was evaporated to ~1/3 the volume (to get rid of the EtOH) and 200 mL of distilled water was added. The aqueous layer was extracted with ethyl acetate three times (the ethyl acetate layer contained pure N,N-Di-Boc-2-carboxy-piperazine which was saved). The water layer was evporated to dryness and evaporated from methanol two times to obtain 3.98 (17.37gm, mmol) of pure product.

PREPARATIVE EXAMPLE 51



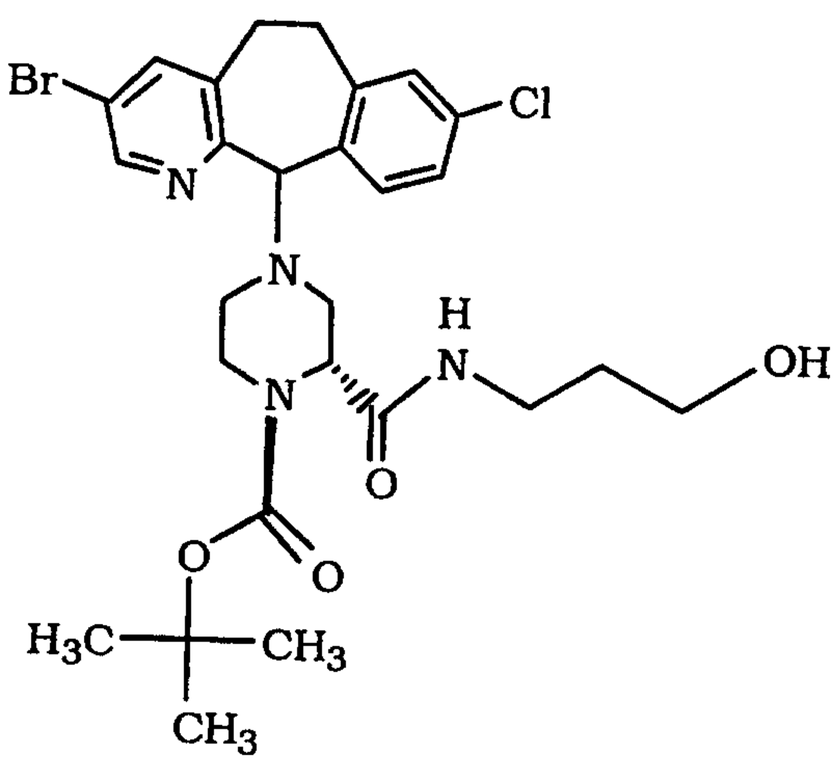


The tricyclic alcohol (Preparative Example 40 in WO 95/10516)



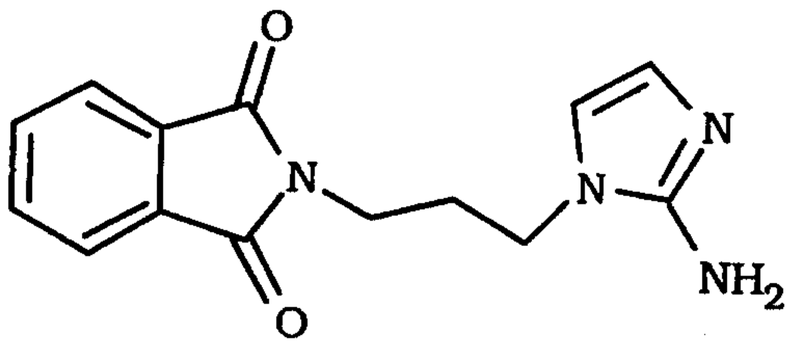
(5.6 gm, 17.33 mmol) was dissolved in 56 ml of dichloromethane and 2.46 ml of thionyl chloride was added while stirring under a dry nitrogen atmosphere. After 5 hrs. the tlc was checked (by adding an aliquot of the reaction mixture to 1N NaOH and shaking with dichloromethane and checking the dichloromethane layer by tlc using 50% EtOAc/Hexanes as the eluent). The mixture was evaporated to give a gum which was evaporated from dry toluene twice and once from dichloro-methane to give the 11-chloro derivative as a foamy solid which was used without further purification. The resulting 11-chloro-tricyclic compound was dissolved in 100 ml of dry DMF, 1N-Boc-2-carboxy-piperazine (Preparative Example 50) (3.98 gm) was added followed by 12.11 ml of triethylamine and the mixture stirred at ambient temperature under a nitrogen atmosphere. After 24 hours the DMF was evaporated and the residue dissolved in 200 ml of ethyl acetate and washed with brine. The brine layer was washed with ethyl acetate two more times and the ethyl acetate layers combined, dried over magnesium sulfate, filtered, and evaporated to give a foamy solid. The solid was chromatographed on a 1 1/2" X 14" column of silica gel eluting with 2L of 0.4% 7N MeOH/NH_3:CH_2Cl_2, 6L of 0.5% 7N MeOH/-NH_3:CH_2Cl_2, 2L of 0.65% 7N MeOH/NH_3:CH_2Cl_2, 2L of 0.8% 7N MeOH/NH_3:CH_2Cl_2, 4L of 1% 7N MeOH/NH_3:CH_2Cl_2, 2L of 3% 2N MeOH/NH_3:CH_2Cl_2, 2L of 5% 2N MeOH/NH_3:CH_2Cl_2, 2L of 10% 2N MeOH/NH_3:CH_2Cl_2, 2L of 15% 2N MeOH/NH_3:CH_2Cl_2, 4L of 20% 2N MeOH/NH_3:CH_2Cl_2 to obtain 4.63 gm of final product.

PREPARATIVE EXAMPLE 52



The title compound from Preparative Example 51 (1 gm, 1.86 mmol) was dissolved in 50 ml of DMF and 1-amino-3-propanol (0.214ml, 1.5 eq.), DEC (0.71 gm, 2 eq.), HOBT (0.5 gm, 2 eq.), and N-methyl-morpholine (1.02 ml, 5 eq.) was added and the reaction mixture stirred for 18 hours. The reaction mixture was added to brine and the product extracted with ethyl acetate 3 times to obtain a crude oil, after the solvent was evaporated under reduced pressure, which was purified by chromatography on a silica gel column 20%-50% ethyl acetate/hexanes as the eluent. The product containing fractions were pooled to obtain 0.67 gm (60%) of pure title compound.

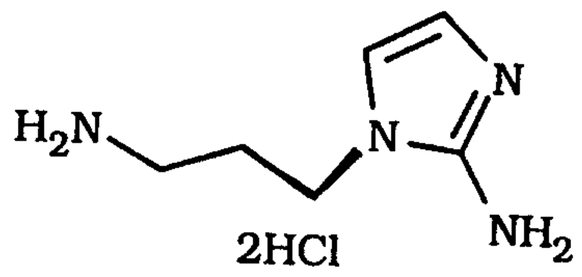
PREPARATIVE EXAMPLE 53



2-Aminoimidazole (8 g, 60 mmol) was dissolved in 200 ml of DMF and cooled in an ice bath. Sodium hydride 60% oil dispersion (2.4 g, 60 mmol) was added portionwise and the reaction mixture stirred for 1 hour. N-(3-Bromopropyl)-phthalimide (16g, 74 mmol) was added and the reaction mixture stirred for 1/2 hour at 0°C, 1 hour at ambient temperature, and then 1 hour at 85°C. The

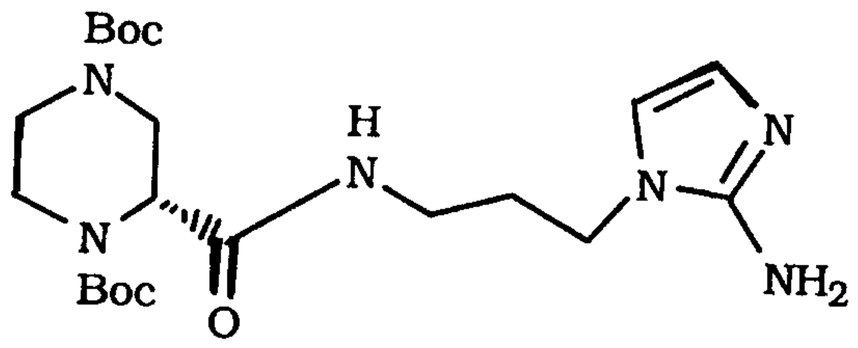
reaction mixture was then cooled to ambient temperature and added to brine and extracted with ethyl acetate to obtain the crude product which was purified by column chromatography using 2% methanol/methylene chloride to obtain 4.88 gm of title compound.

PREPARATIVE EXAMPLE 54



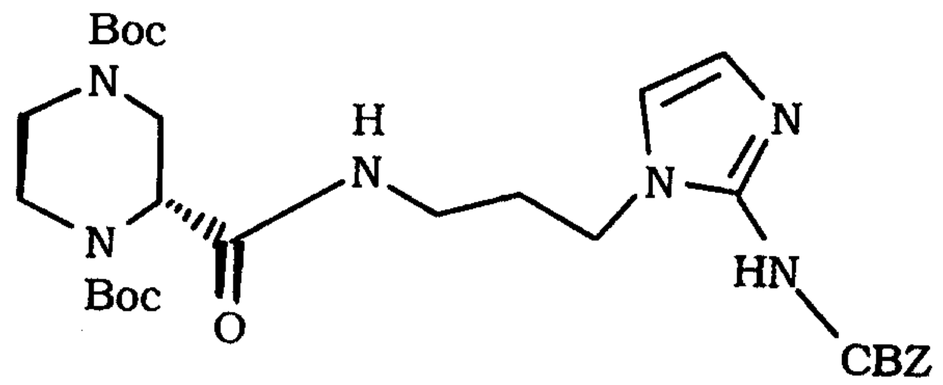
0.5 gm of 1-phthalimidopropyl-2-aminoimidazole (from Preparative Example 53) was refluxed in 20 ml of 6N HCl for 6 hours. The mixture was washed with ethyl acetate and the aqueous layer evaporated to dryness to obtain 0.45 g of the title product.

PREPARATIVE EXAMPLE 55



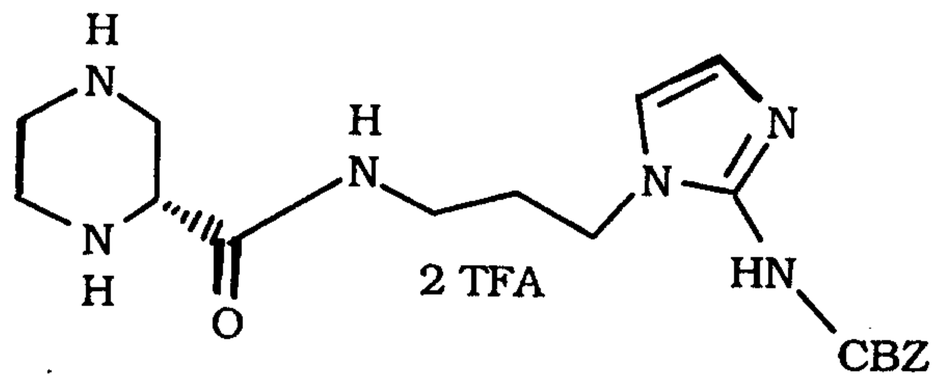
1-Aminopropyl-2-aminoimidazole (Preparative Example 54) (0.25 gm) and N,N-di-butoxycarbonyl-2-R-carboxyl-piperazine (from Preparative Example 43) (0.32 gm) was dissolved in 10 ml of DMF. DEC (0.2 gm.), 1-hydroxybenzotriazole (0.135 gm), and N-methyl-morpholine (0.54 ml) was added and the reaction mixture stirred for 5 hours. The reaction was poured into brine and extracted with dichloromethane to obtain 0.43 gm of the title product after chromatography on silica gel using 2% methanol/-dichloromethane up to 10 %. FABMS M+1= 453.3.

PREPARATIVE EXAMPLE 56



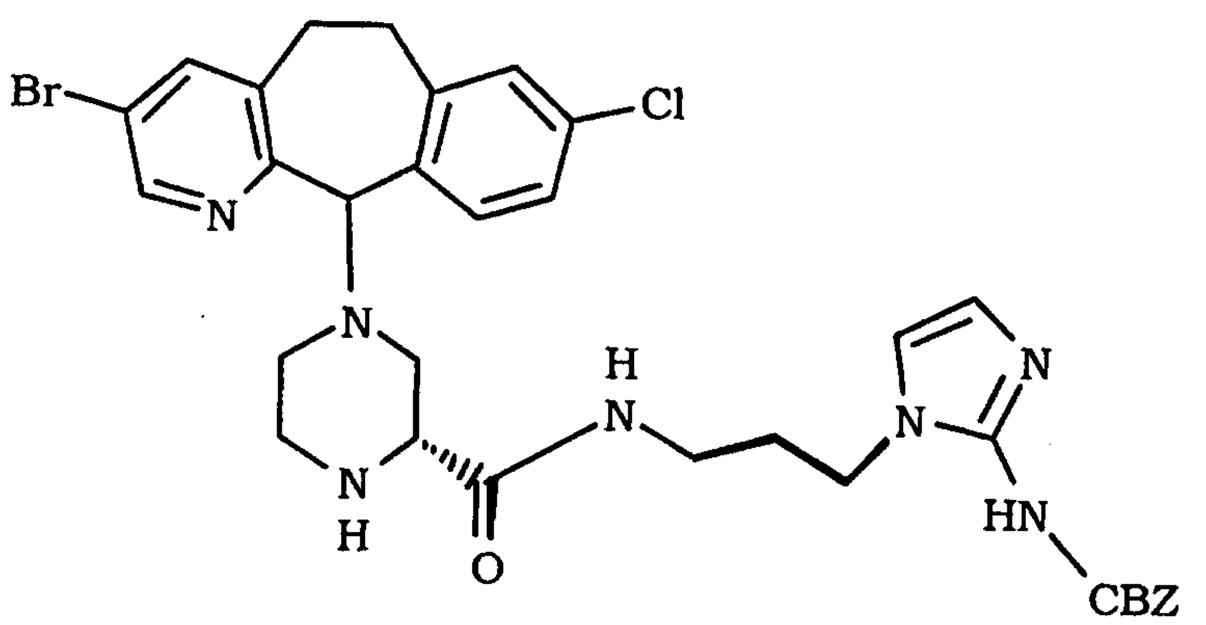
1-Aminopropyl-2-aminoimidazolyl-N1,N4-di-tert.butyl-1,2(R)-piperazinedicarboxamide (Preparative Example 55) (0.38gm) was dissolved in 20 mL of dichloromethane and 0.24 ml of triethylamine. Benzyloxycarbonyl-N-hydroxysuccinimide (0.22 gm) was added and the reaction mixture stirred for 18 hours at ambient temperature. The reaction mixture was washed with brine and chromatographed on a silica gel column using ethyl acetate as the eluent to obtain 0.39 gm of title product. FABMS M+1=587.3.

PREPARATIVE EXAMPLE 57



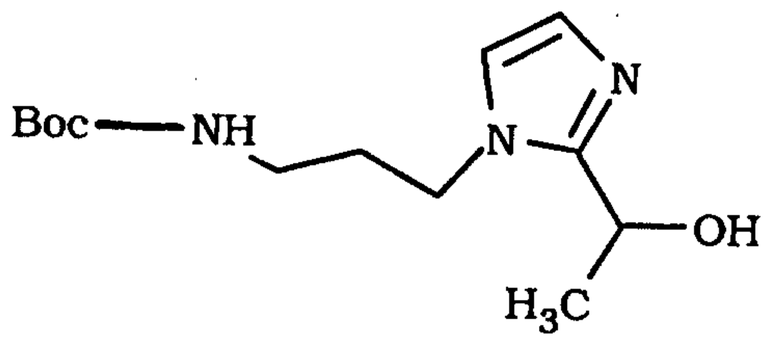
1-benzyloxycarbonylaminopropyl-2-aminoimidazolyl-N1,N4-di-tert.butyl-1,2(R)-piperazinedicarboxamide (Preparative Example 56) (0.4 gm) was dissolved in 3 ml of dichloromethane and 1 ml of trifluoroacetic acid was added and the reaction mixture stirred for 3 hours at ambient temperature. The reaction mixture was then evaporated to dryness to obtain the pure title product.

PREPARATIVE EXAMPLE 58



1-benzyloxycarbonylaminopropyl-2-aminoimidazolyl- 1,2(R)-piperazinedicarboxamide (Preparative Example 57) was dissolved in 50 ml of DMF and 0.46 ml of triethylamine. 3-Bromo-8,11-dichloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine (171 mg) was added and the reaction mixture stirred for 24 hours. The reaction mixture was added to brine and extracted with dichloromethane to obtain 82 mg of pure title product after silica gel chromatography using methanol/dichloro-methane as the eluent. FABMS (M+1) = 694.

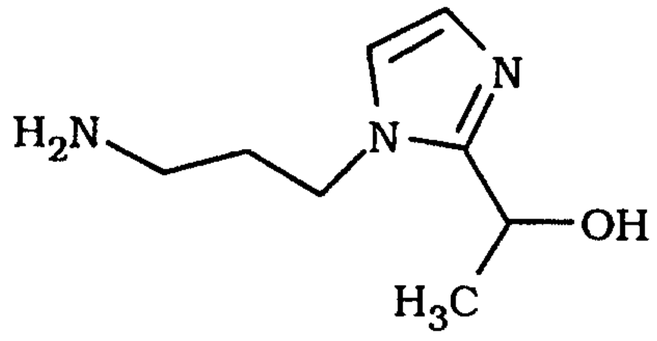
PREPARATIVE EXAMPLE 59



1-tert-Butoxycarbonylaminopropyl-imidazole (0.991 gm, 4.4 mmol) was dissolved in 25 mol of dry THF and cooled to -78°C. A 2.5M solution of n-butyllithium (3.88 ml, 9.68 mmol) in cyclohexanes was added dropwise and the reaaction stirred for 1/2 hour. Acetaldehyde (0.49 ml, 8.8 mmol) was added and the reaction stirred for 1/2 hour. The reaction mixture was allowed to warm to ambient temperature. The reaction was diluted with ethyl acetate and washed with brine. The ethyl acetate layer was

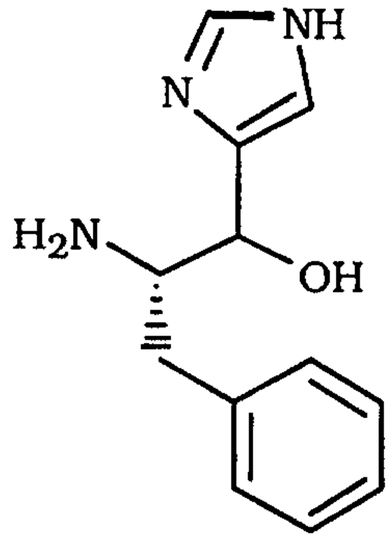
evaporated to obtain a gum which was chromatographed on silica gel to obtain 0.54 gm of title product. (MH^+ = 170).

PREPARATIVE EXAMPLE 60



1-tert-Butoxycarbonylaminopropyl-2-hydroxyethyl-imidazole (Preparative Example 59) (0.51gm) was dissolved in trifluoroacetic acid and stirred for 3-4 hours. The mixture was evaporated to dryness to obtain the pure TFA salt of the title compound.

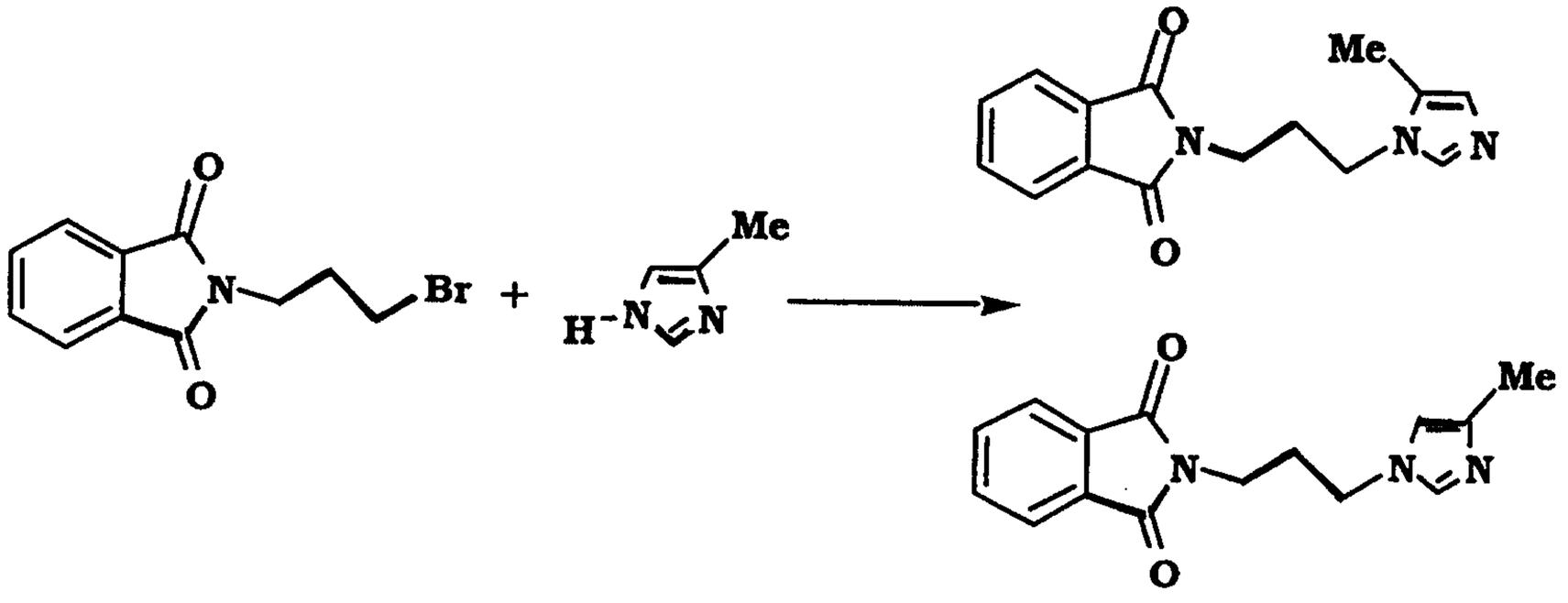
PREPARATIVE EXAMPLE 61



1-N-Trityl-4-iodoimidazole (1.91 gm) was dissolved in 20 ml of dichloromethane and 1.46 ml of ethyl magnesiumbromide was added while stirring. After 15 min. N-Boc-phenylalanine aldehyde (0.5 gm) was added and the reaction mixture was stirred for 18 hours. The reaction mixture was washed with saturated ammonium chloride, dried over magnesium sulfate, and chromatographed on silica gel to obtain 0.8 gm of the intermediate blocked product. FABMS (M+1)= 561. This was then treated with 4M HCl/dioxane for 18 hours. The mixture was evaporated to dryness and dissolved in distilled water and washed with ethyl acetate. The aqueous layer was evaporated to obtain pure title product. (MH^+ = 218).

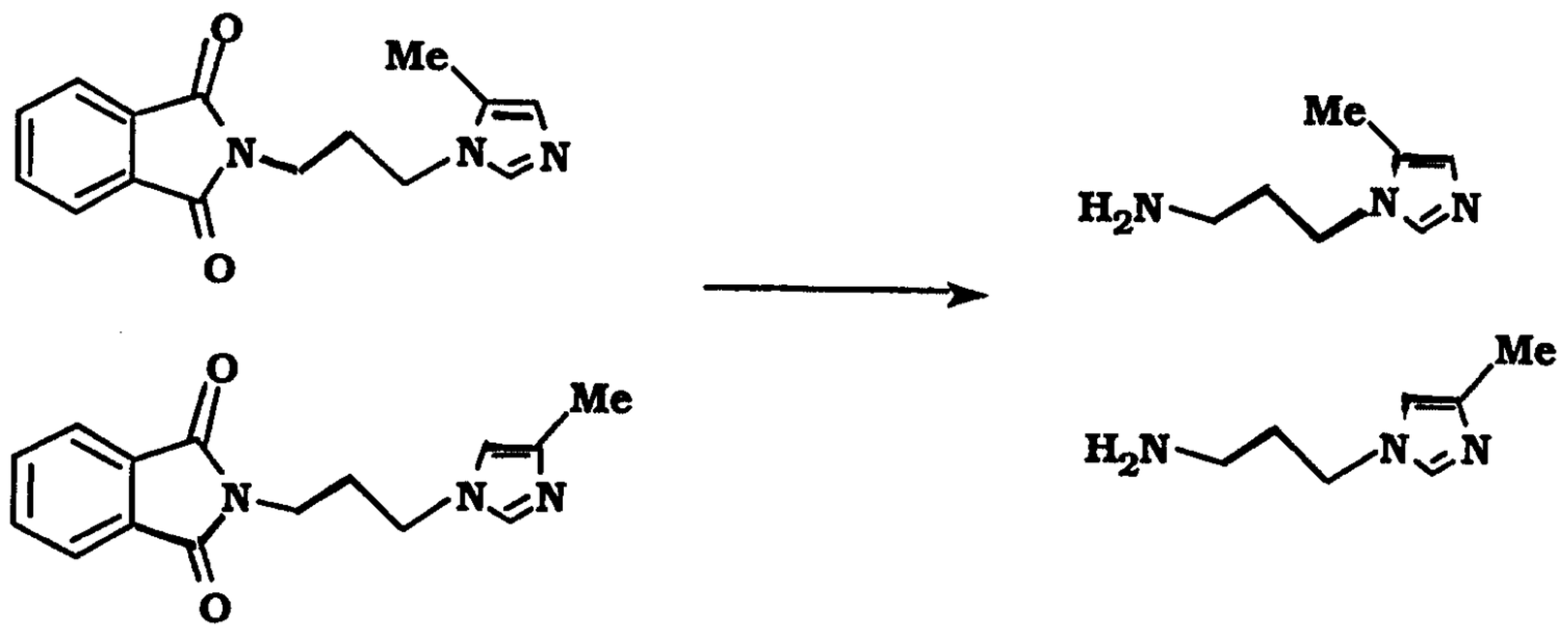
PREPARATIVE EXAMPLE 62

Step A



A mixture of N-(3-bromopropyl)phthalimide (12.3 g, 46 mmol), 4-methylimidazole (3.78 g, 46 mmol), sodium hydride (60% in mineral oil, 1.84 g, 46 mmol) and anhydrous DMF (50 mL) was stirred at 25-70°C under N_2 overnight. The mixture was concentrated *in vacuo* to give a residue which was diluted with dichloromethane, filtered, concentrated *in vacuo* and purified by flash column chromatography (silica gel) using 1% MeOH-CH_2Cl_2 saturated with aqueous ammonium hydroxide to give the title compound as an oil (8.04 g, 65%, MH^+ = 270).

Step B



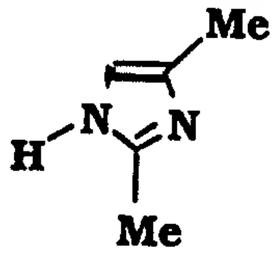
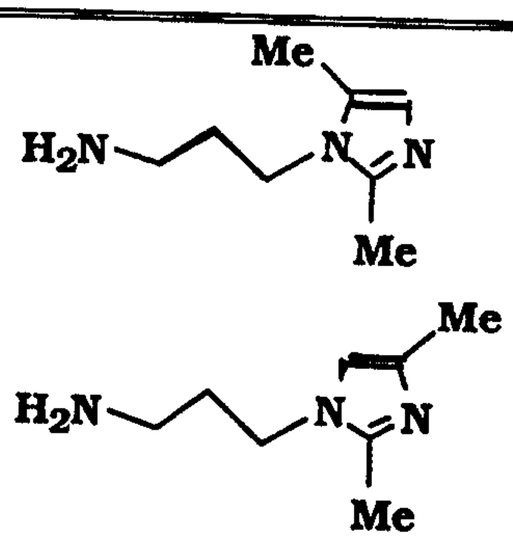
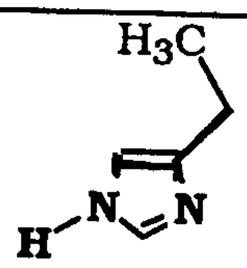
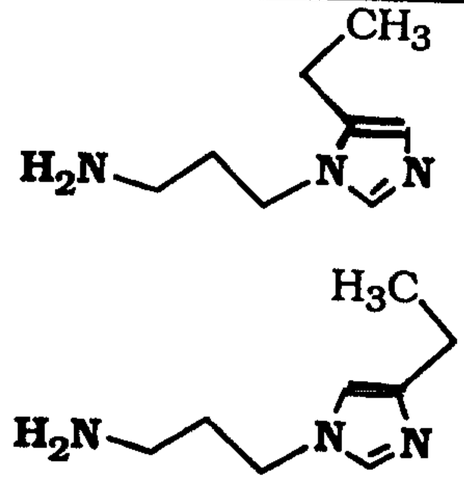
To a solution of the title compound from Step A (8.02 g, 29.8 mmol) dissolved in absolute EtOH (150 mL) was added hydrazine-mono hydrate (15 mL) and the mixture was stirred at reflux for 12 h

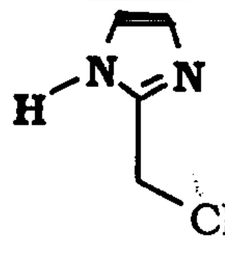
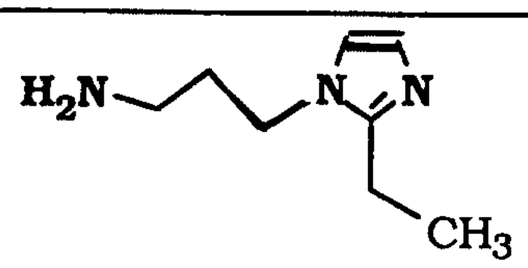
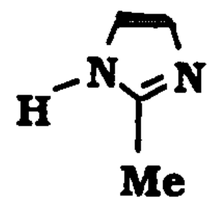
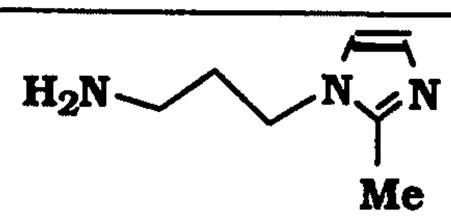
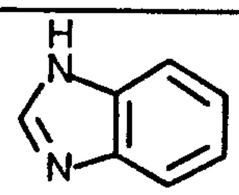
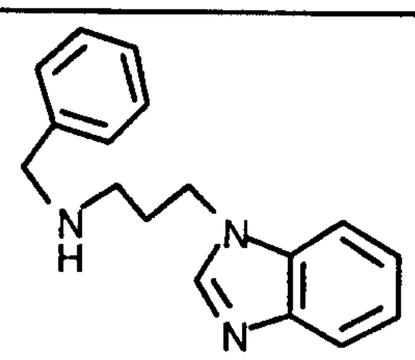
under N_2. The mixture was diluted with dichloromethane, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel) using 5% MeOH-CH_2Cl_2 saturated with aqueous ammonium hydroxide to give the title compound as an oil (2.95 g, 71%, MH^+ = 140).

PREPARATIVE EXAMPLES 63-67

Following the procedure set forth in Preparative Example 62, but using the substituted imidazole in Table 3 below instead of 4-methylimidazole in Step A, the amines (Product) listed in Table 3 were prepared.

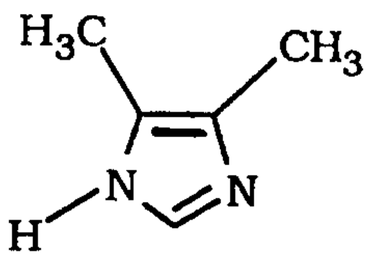
TABLE 3

Prep. Ex.	Imidazole	Product	MH^+	Yield (%)
63			154	70
64			154	60

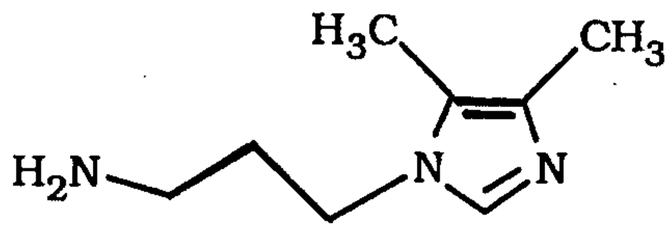
65			154	68
66			140	46
66.1		 MH$^+$ 266.1657	----	88

PREPARATIVE EXAMPLE 67

If the procedure set forth in Preparative Example 62 were followed, except the imidazole



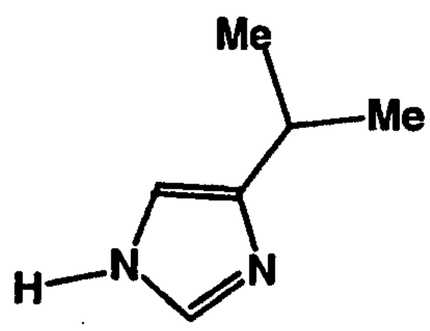
would be used instead of 4-methylimidazole in Step A, the amine



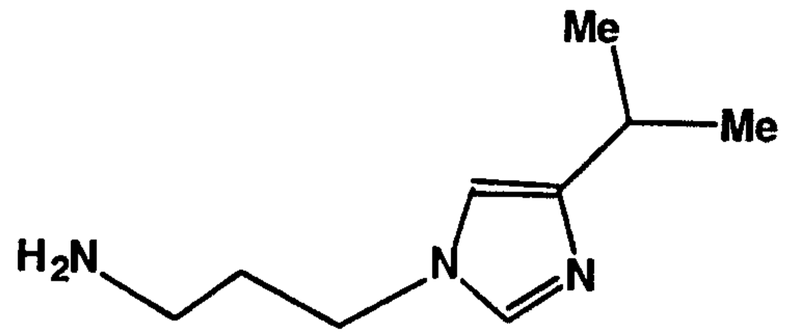
would be obtained.

PREPARATIVE EXAMPLE 67.1

If the procedure set forth in Preparative Example 62 were followed, except the imidazole

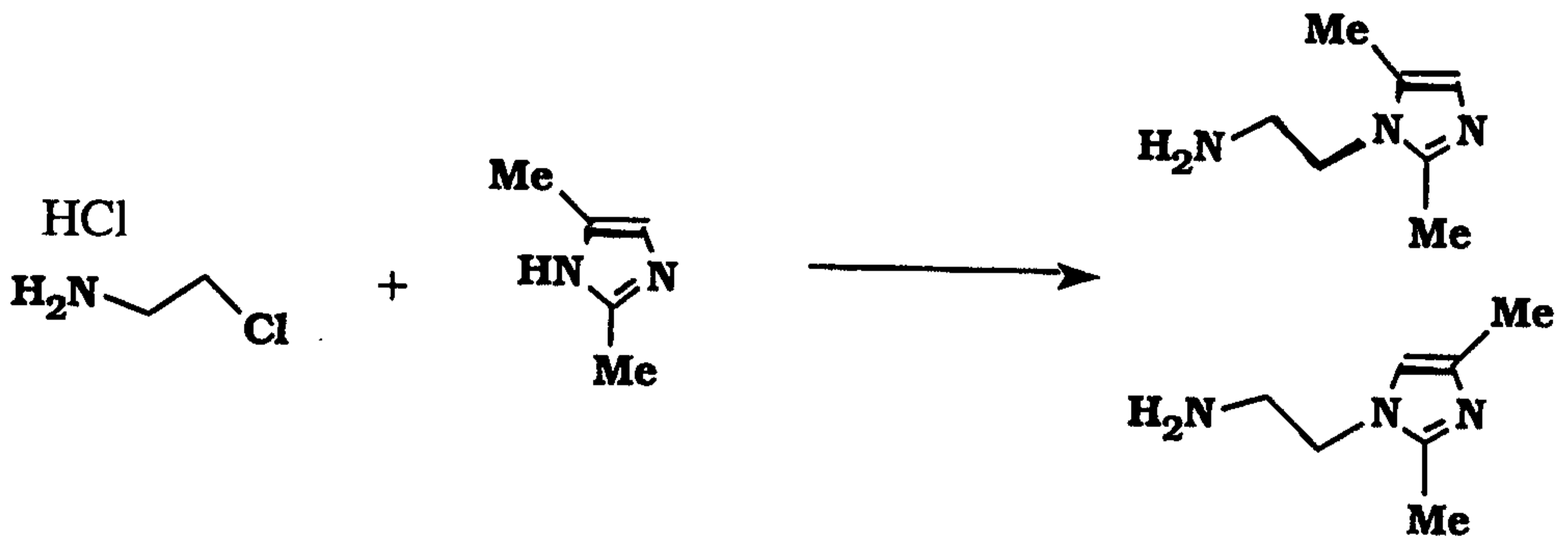


would be used instead of 4-methylimidazole in Step A, the amine



would be obtained.

PREPARATIVE EXAMPLE 68

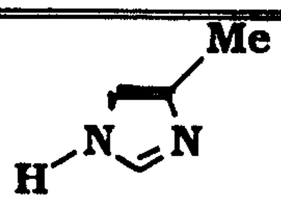
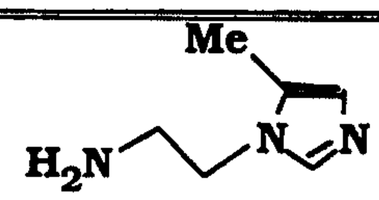
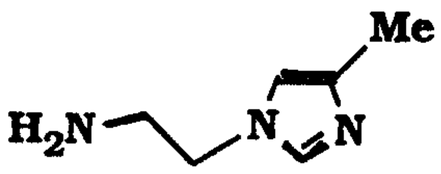
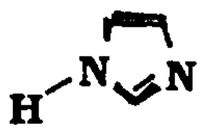
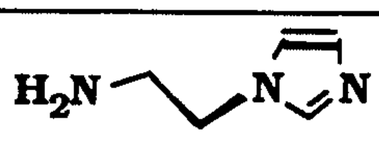
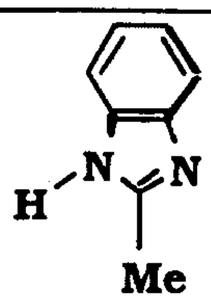
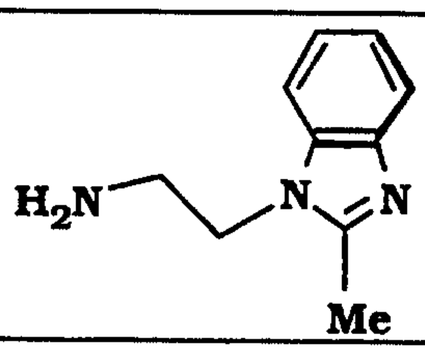
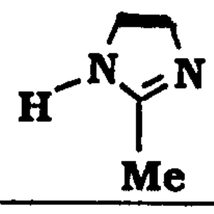
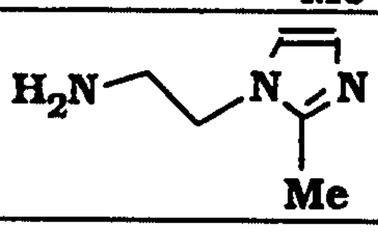
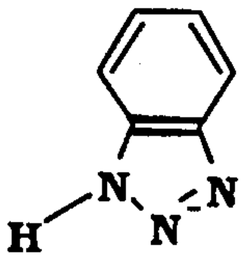
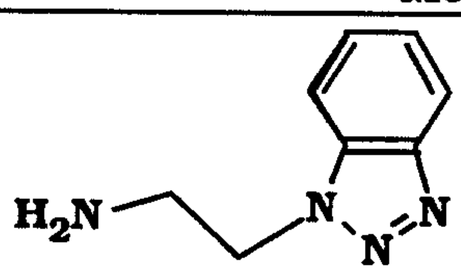
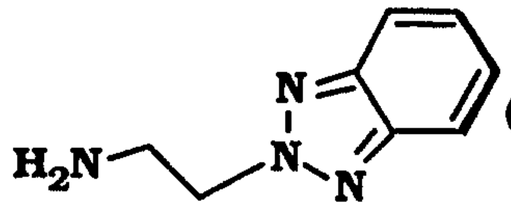


A mixture of 2-chloroethylamine hydrochloride (7.66 g, 66 mmol), 2,4-dimethylimidazole (5.88 g, 61 mmol), tetrabutyl ammonium sulfate (0.83 g, 2.5 mmol), solid NaOH (8.81 g, 220 mmol) and anhydrous acetonitrile (80 mL) was stirred at reflux for 48 h under N_2. The mixture was filtered, concentrated *in vacuo* and purified by flash column chromatography (silica gel) using 2% MeOH-CH_2Cl_2 saturated with aqueous ammonium hydroxide to give the title compound as an oil (10.7 g, 100%, MH^+ = 140).

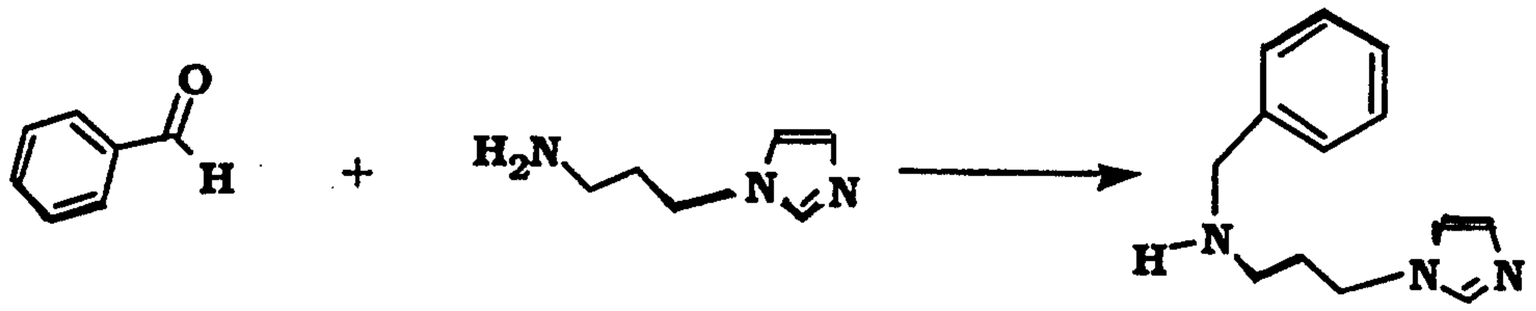
PREPARATIVE EXAMPLES 69-73

Following the procedure set forth in Preparative Example 68, but using the substituted imidazole or triazole in Table 4 below instead of 2,4-dimethylimidazole, the amines (Product) listed in Table 4 were prepared.

TABLE 4

Prep. Ex.	Imidazole	Product	MH^+	Yield (%)
69		 	126	75
70			112	65
71			176	55
72			126	53
73		 (A)  (B)	(A): 163 (B) : 163	(A): 60 (B): 40

PREPARATIVE EXAMPLE 74



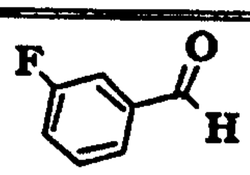
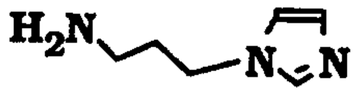
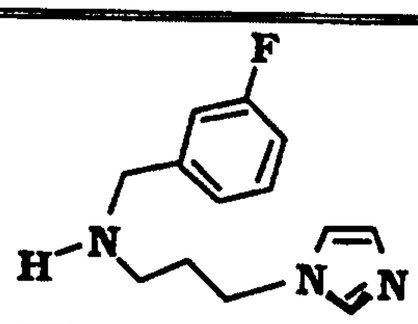
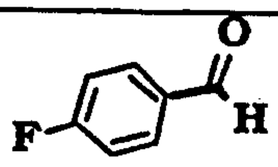
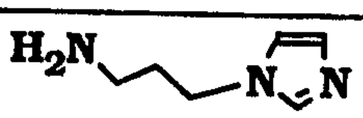
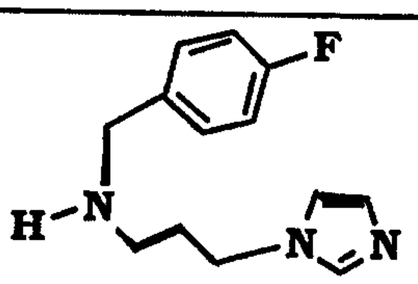
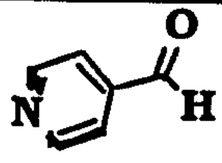
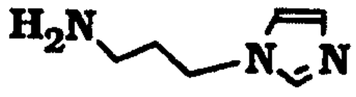
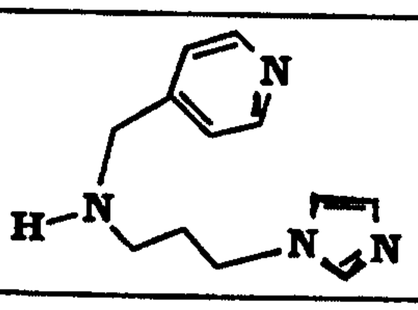
A mixture of 1-(3-aminopropyl)imidazole (37.1 g, 297 mmol), benzaldehyde (30 g, 283 mmol), 3Å molecular sieves (50 g), sodium acetate (24.1 g, 283 mmol) and anhydrous methanol (700 mL) was stirred at room temperature under N_2 overnight. The mixture was

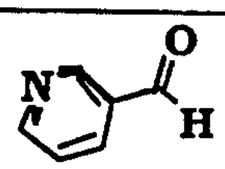
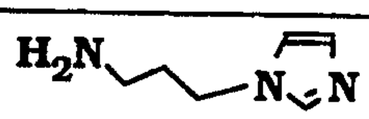
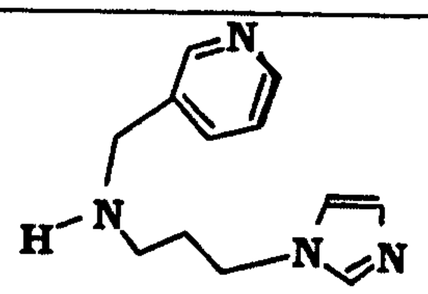
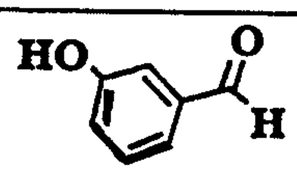
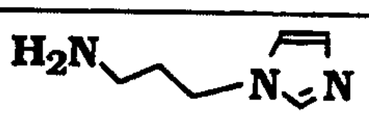
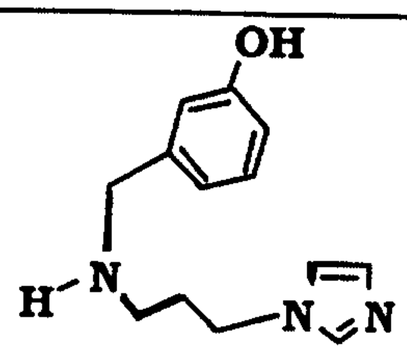
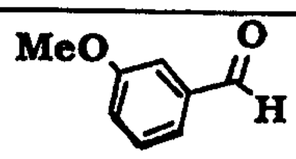
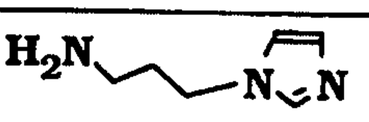
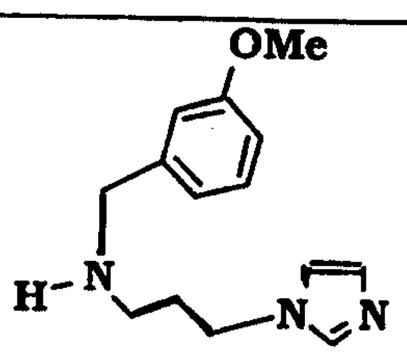
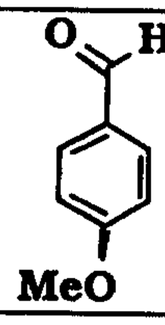
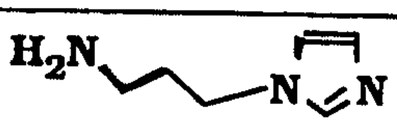
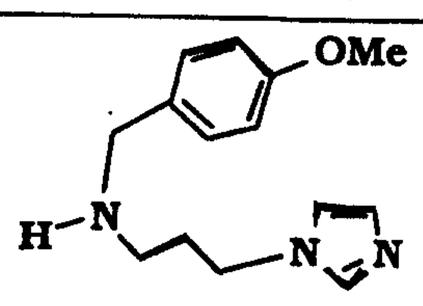
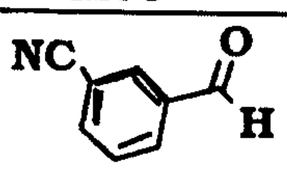
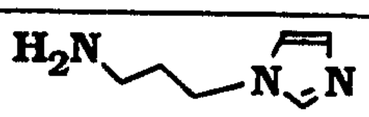
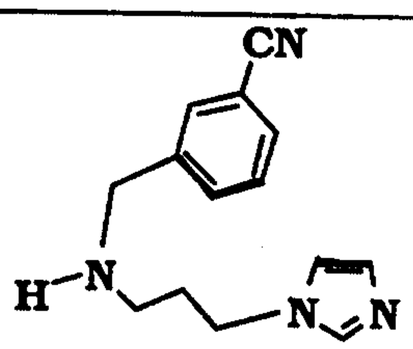
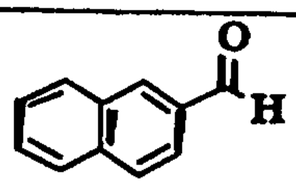
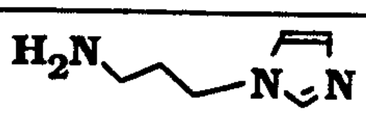
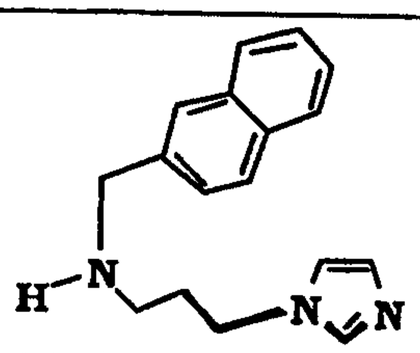
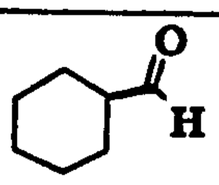
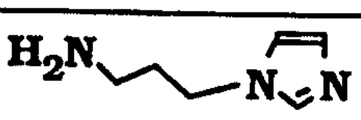
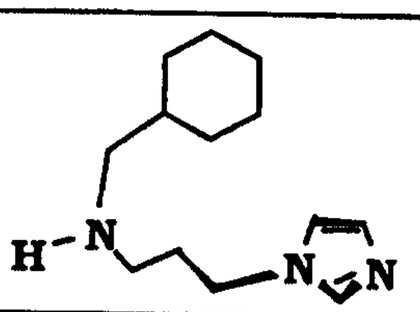
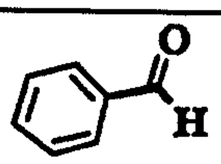
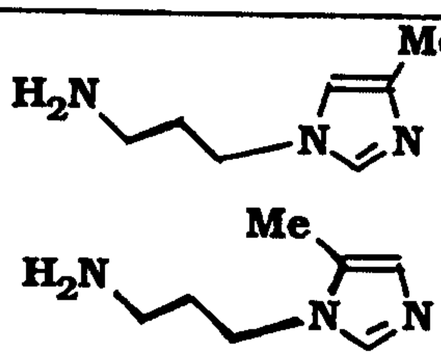
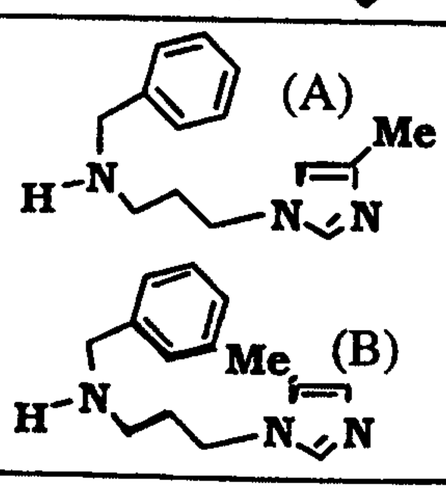
cooled to 0°C and sodium borohydride (10.9 g, 288 mmol) was added portionwise over 1 hour. The mixture was stirred at room temperature for 3 hours. The mixture was filtered through celite, washed with methanol, and concentrated *in vacuo* to give a residue which was diluted with dichloro-methane and washed with 10% aqueous sodium hydroxide. The organic phases were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo to give the title compound as a pale yellow oil (56.3 g, 92%, MH^+ = 216).

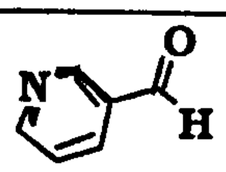
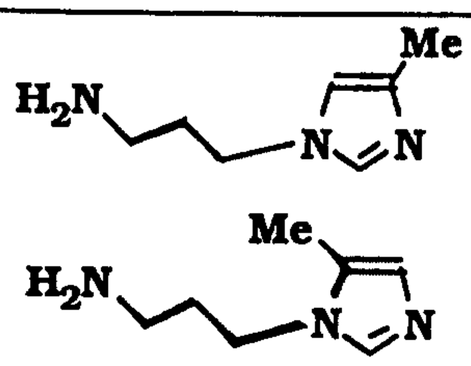
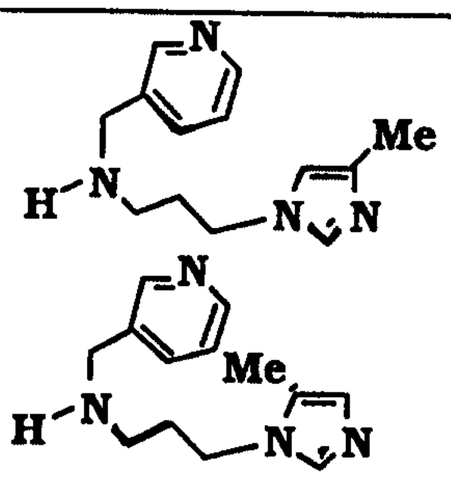
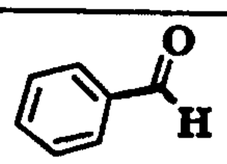
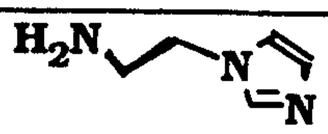
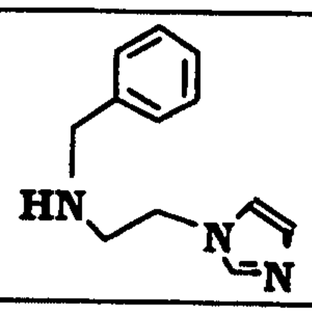
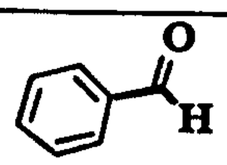
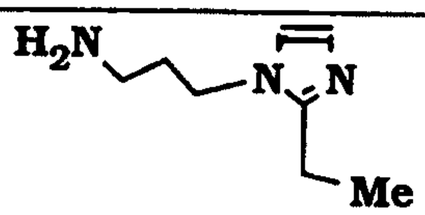
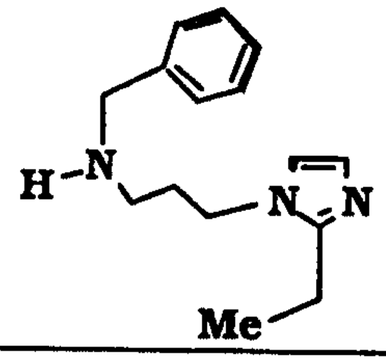
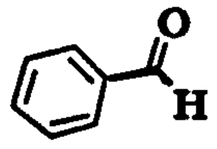
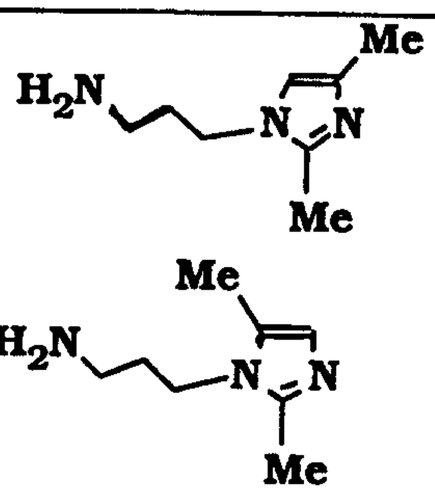
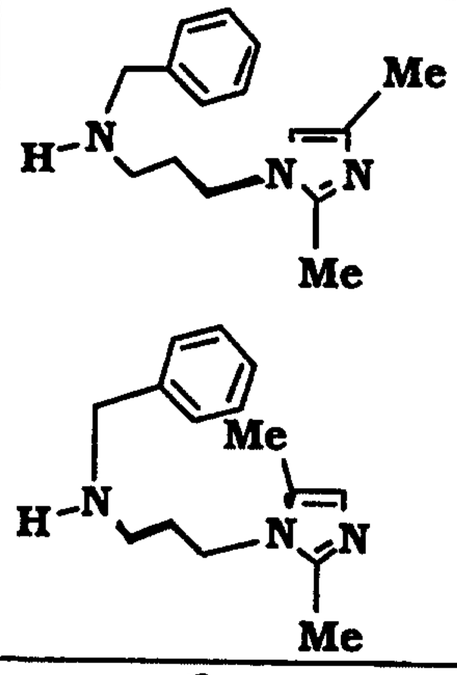
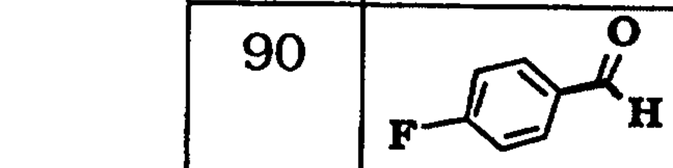
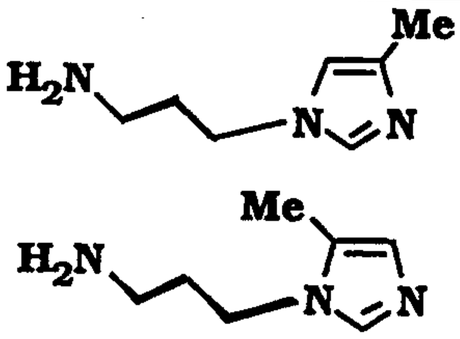
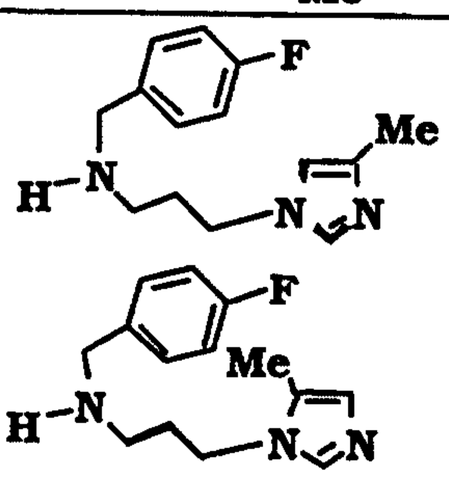
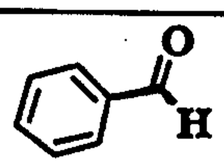
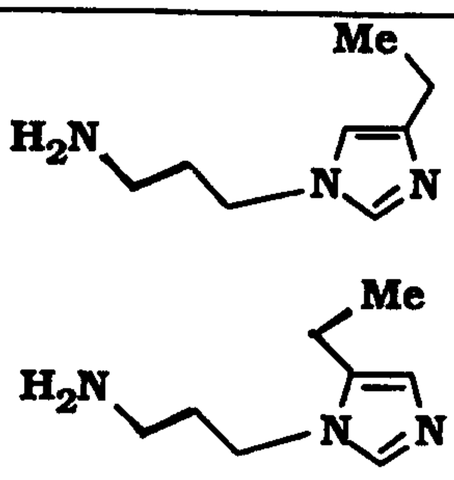
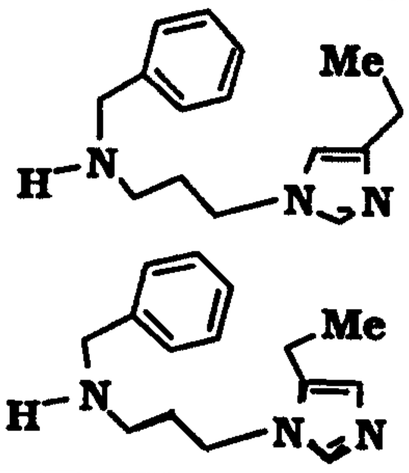
PREPARATIVE EXAMPLES 75-95

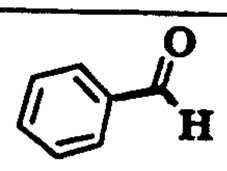
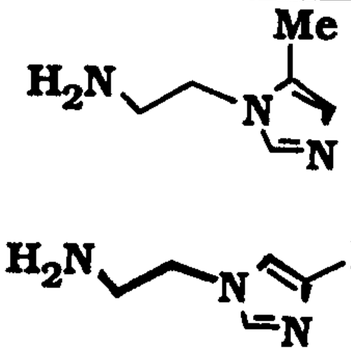
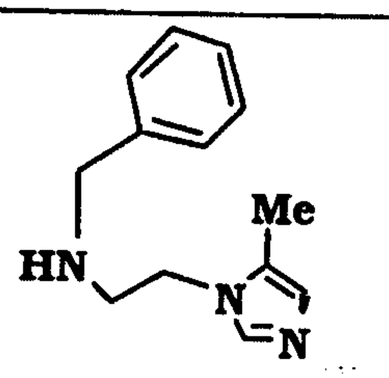
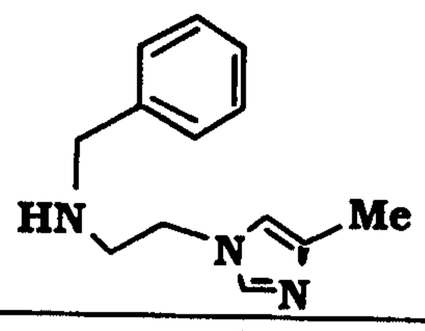
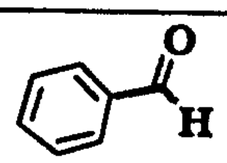
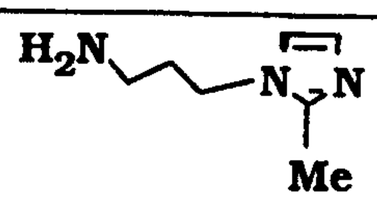
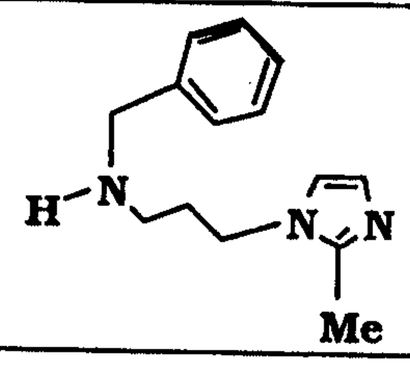
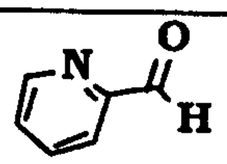
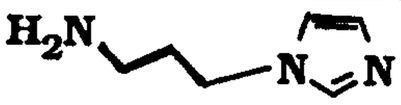
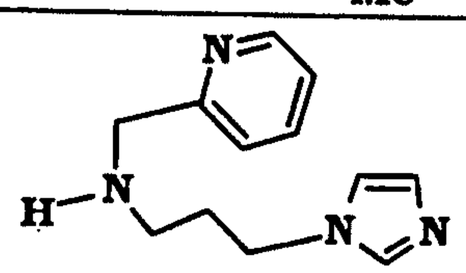
Following the procedure set forth in Preparative Example 74, but using the aldehyde and imidazolylalkyl amine (Imidazole) in Table 5, the amines (Product) in Table 5 were obtained.

TABLE 5

Prep Ex.	Aldehyde	Imidazole	Product	% Yield (MH^+)
75				46 (234)
76				91 (234)
77				74 (217)

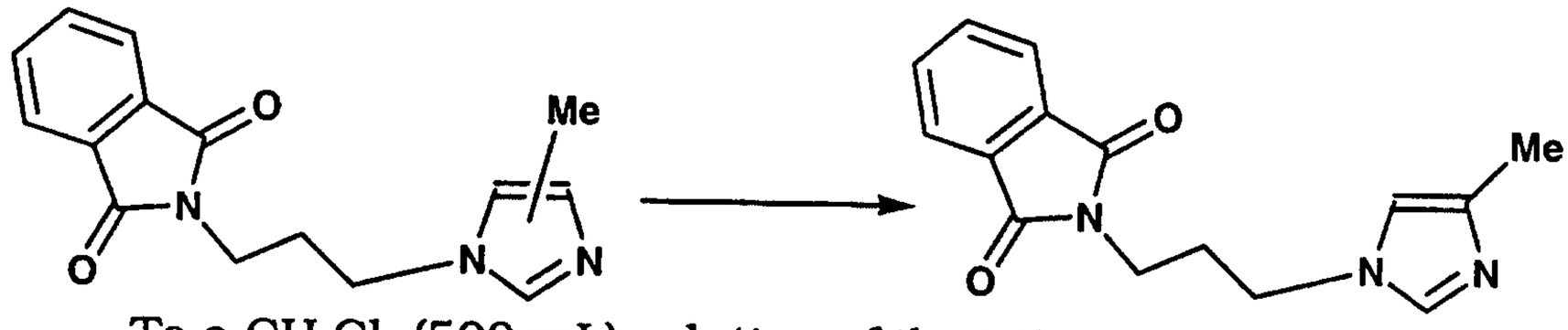
78				92 (217)
79				98 (232)
80				97 (246)
81				81 (246)
82				68 (241)
83				87 (266)
84				84 (222)
85				(A): 45 (230) (B): 21 (230)

86				62 (239)
87				80 (202)
88				63 (244)
89				86 (244)
90				83 (248)
91				20 (244)

93			 	44 (216)
94				95 (230)
95				68 (217)

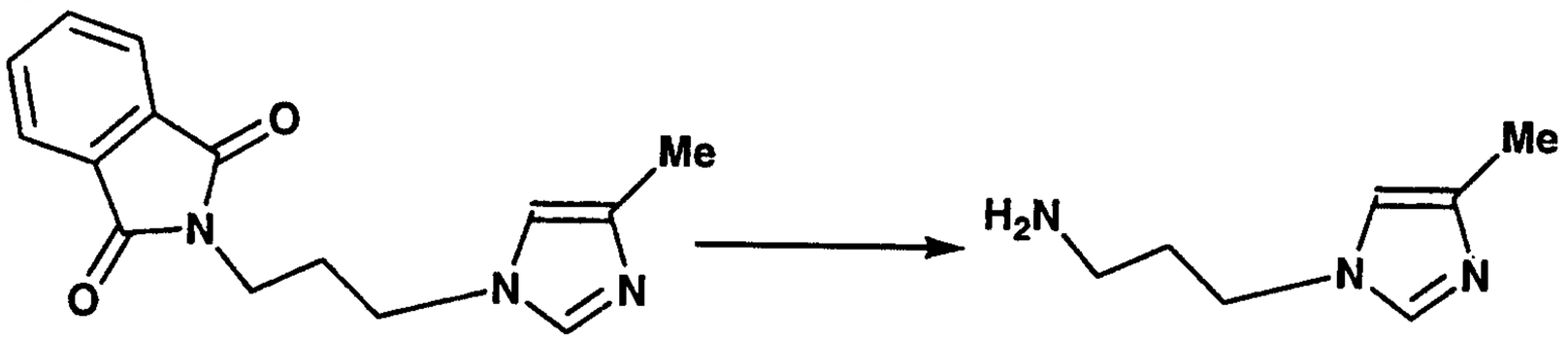
PREPARATIVE EXAMPLE 95.1

Step A



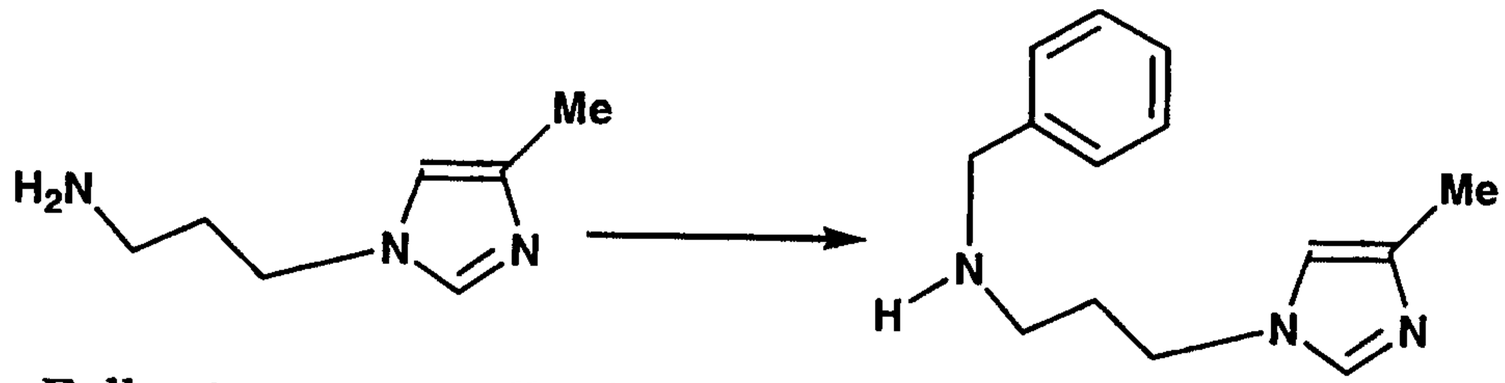
To a CH_2Cl_2 (500 mL) solution of the title compound from Preparative Example 62 Step A (65.7 g) cooled to 0°C was added trityl chloride (27.2 g). The resulting mixture was warmed to and stirred at room temperature for 1.5 hr, then concentrated in vacuo without heating. Purification by flash column chromatography (silica, 1:1 Acetone-EtOAc) afforded the pure 4-methyl isomer (35.02 g, MH^+ = 270).

Step B



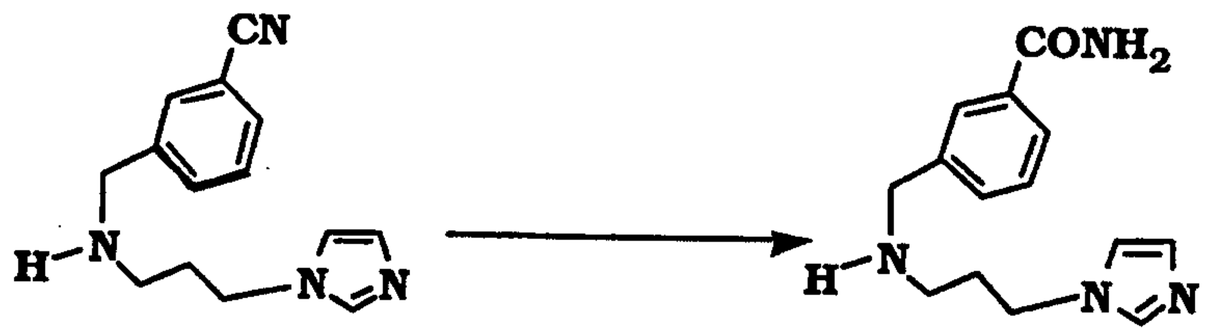
Following essentially the same procedure as that described in Preparative Example 62 Step B except using the pure 4-methylimidazole product from Preparative Example 95.1 Step A (35.02 g), the title compound was afforded (16.12 g, MH^+ = 140).

Step C



Following essentially the same procedure as that described in Preparative Example 74 except using the pure 4-methylimidazolepropylamine product from Preparative Example 95.1 Step B above (16.12 g) instead of 1-(3-aminopropyl)imidazole, the title compound was afforded (18.03 g, MH^+ = 230).

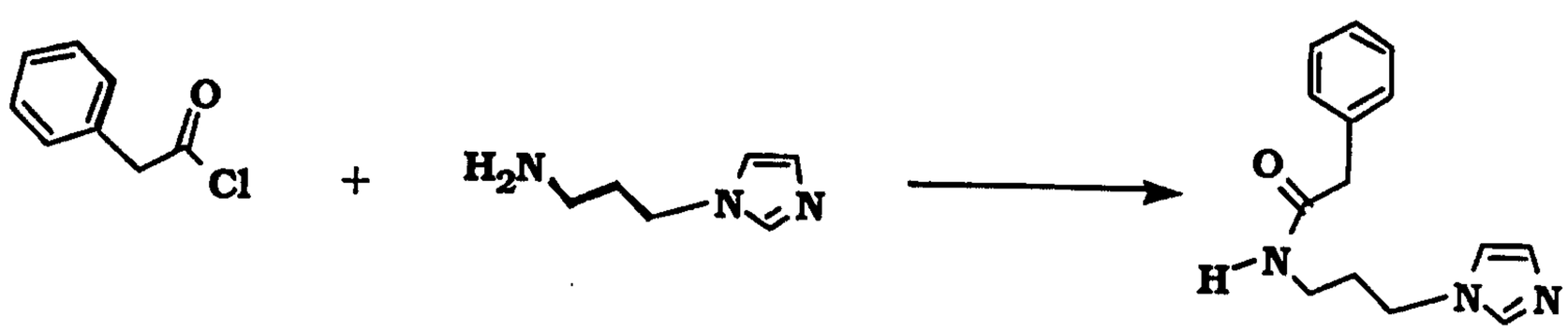
PREPARATIVE EXAMPLE 97



A mixture of the title compound from Preparative Example 82 (0.50 g, 2.1 mmol), absolute EtOH (50 mL), 30% hydrogen peroxide (aq) (0.45 mL, 4.4 mmol) and 1M NaOH (aq) (4.4 mL, 4.4 mmol) was stirred at 50°C for 12 h. The mixture was concentrated *in vacuo* and purified by flash column chromatography (silica gel) using 10%

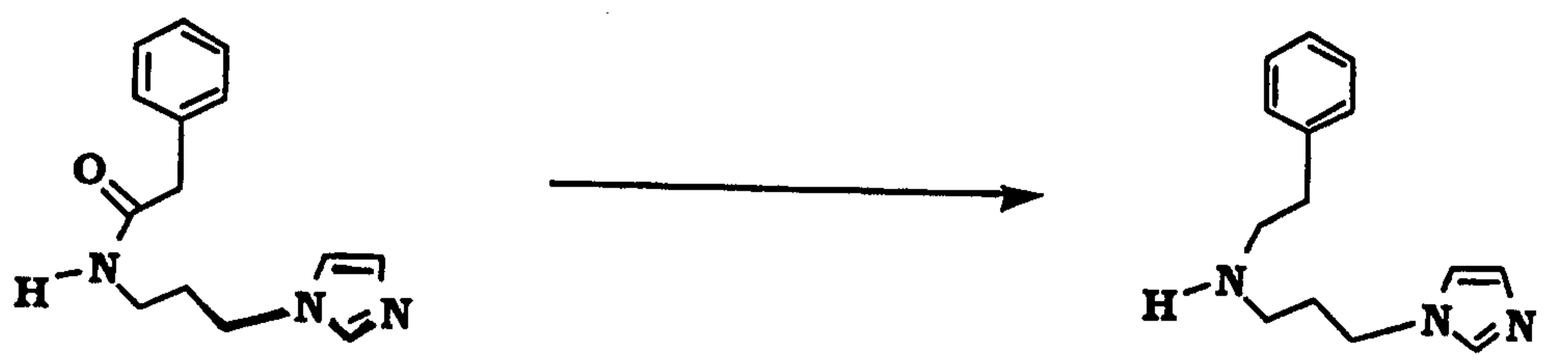
$MeOH-CH_2Cl_2$ saturated with aqueous ammonium hydroxide to give the title compound as an oil (0.33 g, 61%, MH^+ = 259).

PREPARATIVE EXAMPLE 98



To a cooled (0°C) solution of 1-(3-aminopropyl)imidazole (Aldrich, 1.9 mL, 16 mmol) and triethylamine (5.6 mL, 40 mmol) dissolved in anhydrous CH_2Cl_2 (20 mL) was added phenylacetyl chloride (2.12 mL, 16 mmol). The mixture was warmed to and stirred at room temperature overnight. The mixture was washed with 1N aqueous NaOH, dried over anhydrous $MgSO_4$ and filtered. The solution was concentrated *in vacuo* and purified by flash column chromatography (silica gel) using 2% MeOH-98% CH_2Cl_2 saturated with aqueous ammonium hydroxide to give the title compound as an oil (1.8 g, 45%, MH^+ = 244).

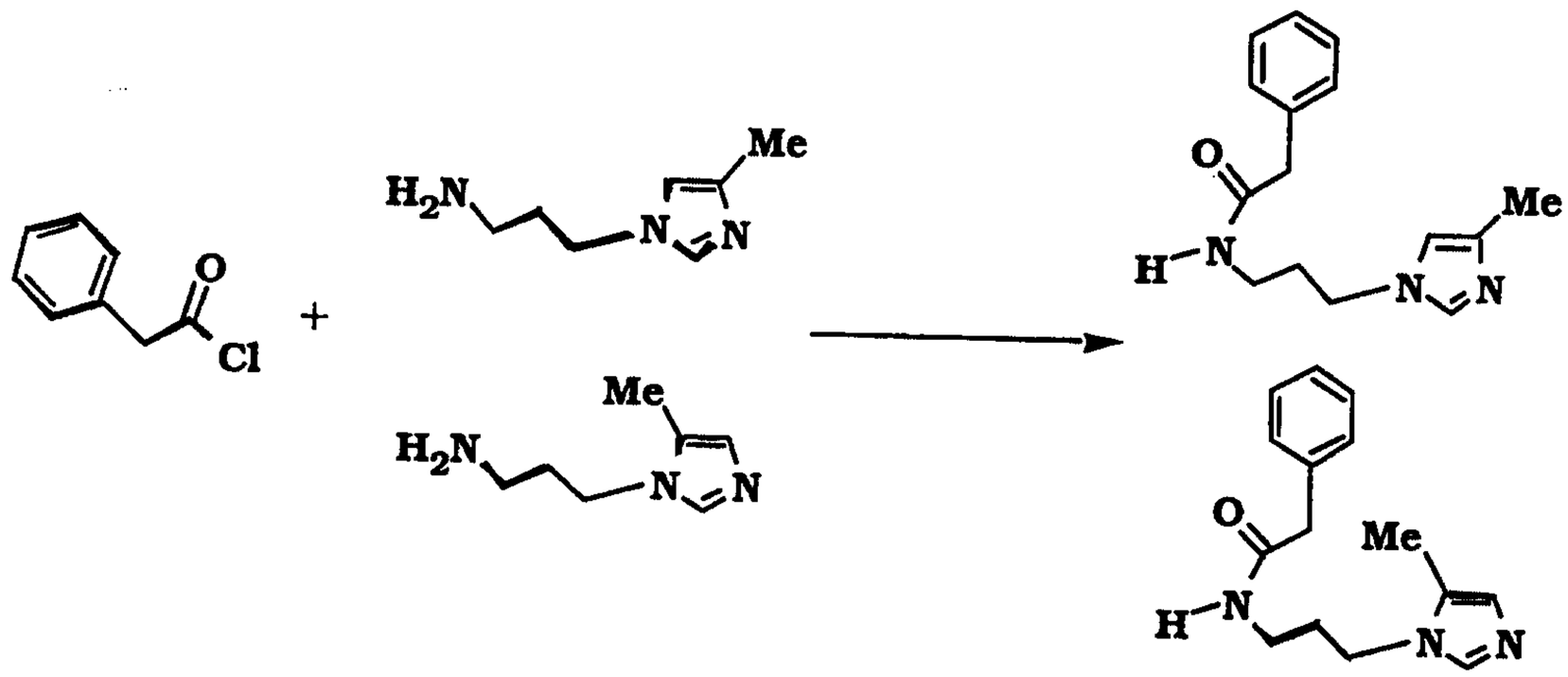
PREPARATIVE EXAMPLE 99



To a refluxing solution of the title compound from Preparative Example 98 (0.51 g, 2.1 mmol) dissolved in anhydrous THF (5 mL) was added borane dimethylsulfide complex (6.3 mL, 2M in THF, 13 mmol). After 1 hr, the mixture was cooled to room temperature and stirred overnight. Hydrochloric acid (1N) was added dropwise until the reaction mixture was determined to be acidic (pH paper). The mixture was basified with 1N aqueous NaOH, extracted with

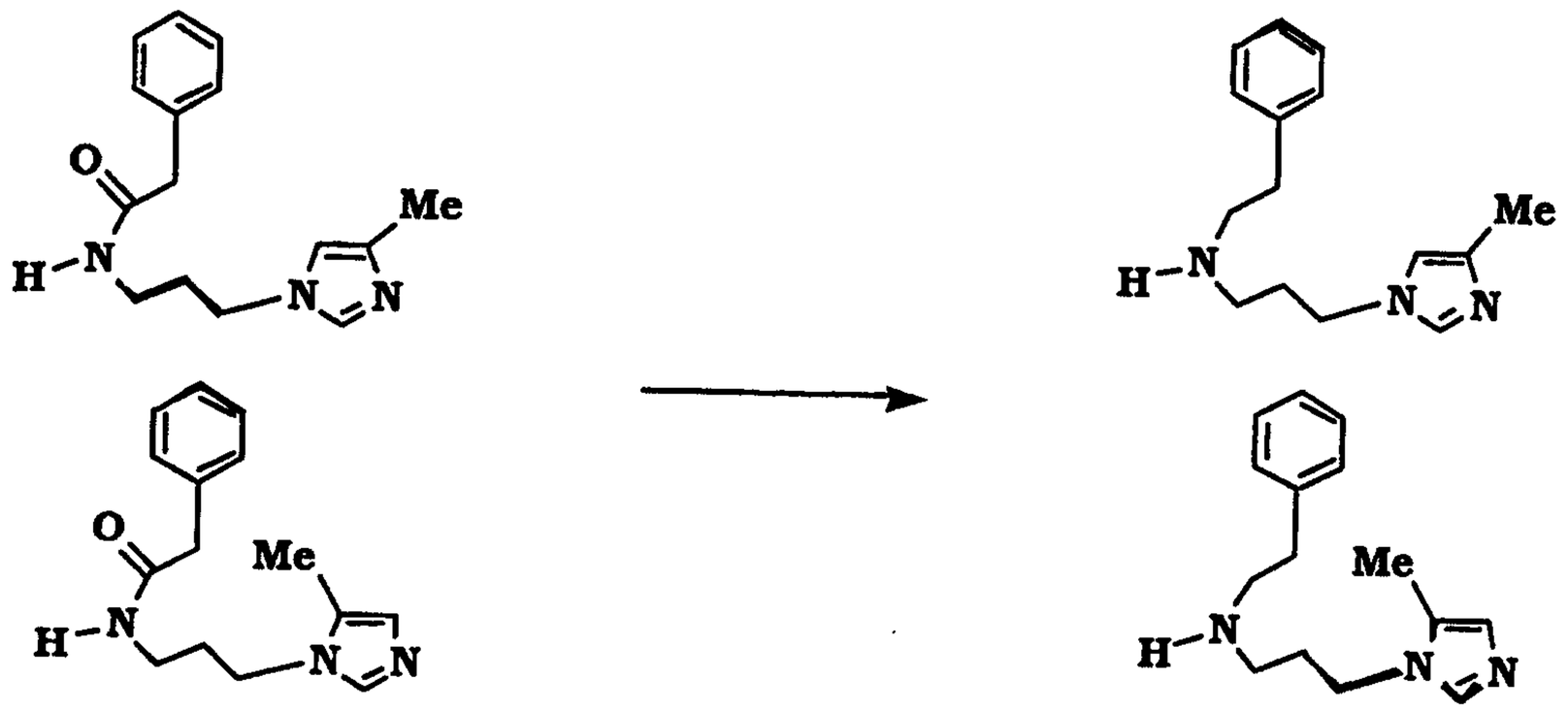
CH_2Cl_2, dried over anhydrous $MgSO_4$ and filtered. The solution was concentrated *in vacuo* and purified by flash column chromatography (silica gel) using 2% MeOH-98% CH_2Cl_2 saturated with aqueous ammonium hydroxide to give the title compound as an oil (0.25 g, 52%, MH^+ = 230).

PREPARATIVE EXAMPLE 100



To a cooled (0°C) solution of the title compound from Preparative Example 62 Step B (0.7 g, 5 mmol) and triethylamine (1.7 mL, 12.5 mmol) dissolved in anhydrous CH_2Cl_2 (10 mL) was added phenylacetyl chloride (0.67 mL, 5 mmol). The mixture was warmed to and stirred at room temperature overnight. The mixture was washed with 1M HCl (aq) and the aqueous phase was basified with 1N aqueous NaOH. This phase was extracted with CH_2Cl_2 and dried over anhydrous $MgSO_4$ and filtered. The solution was concentrated *in vacuo* to give the title compound as an oil (0.72 g, 56%, MH^+ = 258).

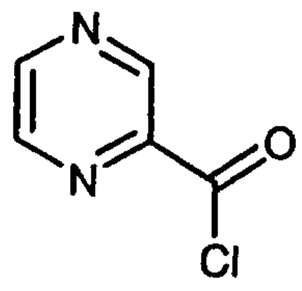
PREPARATIVE EXAMPLE 101



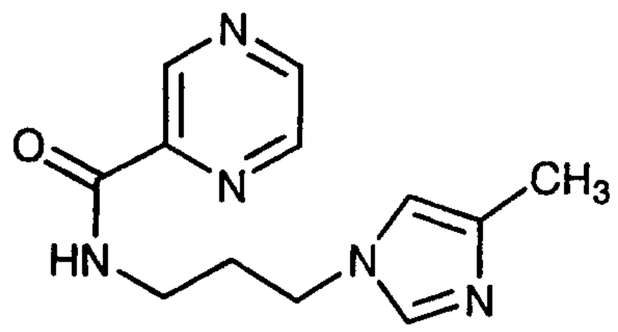
To a refluxing solution of the title compound from Preparative Example 100 (0.66 g, 2.5 mmol) dissolved in anhydrous THF (15 mL) was added borane-THF complex (5 mL, 1M in THF, 5 mmol). The mixture was refluxed for 12 h, then cooled to room temperature and concentrated *in vacuo*. The residue was diluted with 1M HCl and washed with CH_2Cl_2 then the aqueous phase was basified with 50% aqueous NaOH and extracted with CH_2Cl_2 and dried over anhydrous $MgSO_4$ and filtered. The solution was concentrated *in vacuo* and purified by preparative plate chromatography (silica gel) using 3% MeOH-CH_2Cl_2 saturated with aqueous ammonium hydroxide to give the title compound as an oil (0.21 g, 35%, MH^+ = 244) which was purified by preparative chiral chromatography (Chiralpack AD, 5 cm X 50 cm column, flow rate 80 mL/min, 5-8% IPA-Hexane +0.2% diethylamine).

PREPARATIVE EXAMPLE 101.1

If the procedure of Preparative Example 100 were followed, but the compound



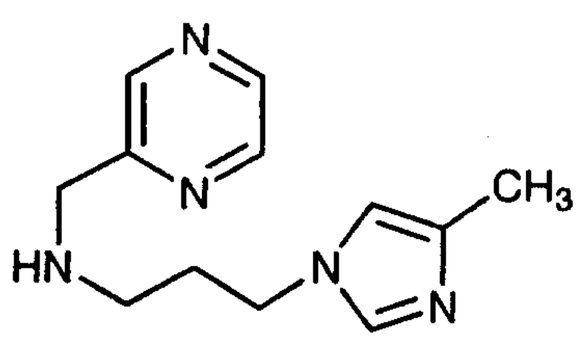
was to be reacted with the title compound from Preparative Example 62 Step B, then the Product



would be obtained.

PREPARATIVE EXAMPLE 101.2

If the procedure of Preparative Example 101 were followed, but the Product from Preparative Example 101.1 was to be used, then the Product



would be obtained=.

PREPARATIVE EXAMPLE 102

Step A

To a cooled (0°C) solution of 1-(3-aminopropyl)imidazole (10 g, 80 mmol) and triethylamine (17.1 mL, 120 mmol) dissolved in anhydrous CH_2Cl_2 (50 mL) was added trifluoroacetic anhydride (12.4 mL, 88 mmol). The mixture was warmed to and stirred at room temperature overnight. The mixture was washed with water, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give the title compound as an oil (15.7 g, 88%, MH^+ = 222).

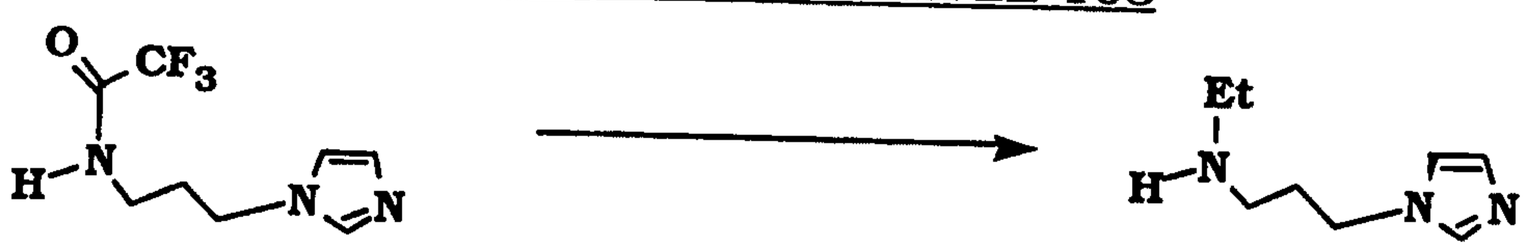
Step B

To the title compound from Step A (0.24 g, 1.1 mmol) dissolved in anhydrous DMF (10 mL) was added solid sodium hydride (85 mg, 2.1 mmol, 60% dispersion in mineral oil). When gas evolution ceased, methyl iodide (0.1 mL, 1.1 mmol) was added and the mixture was stirred at 70°C for 40 min. The resulting mixture was cooled to room temperature, concentrated in vacuo, diluted with CH_2Cl_2 and washed with water. The solution was dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to give an oil (0.28 g). Purification by preparative plate chromatography (silica gel) using 2% MeOH-98% CH_2Cl_2 saturated with aqueous ammonium hydroxide gave the title compound as a yellow oil (78 mg, 30%, MH^+ = 236).

Step C

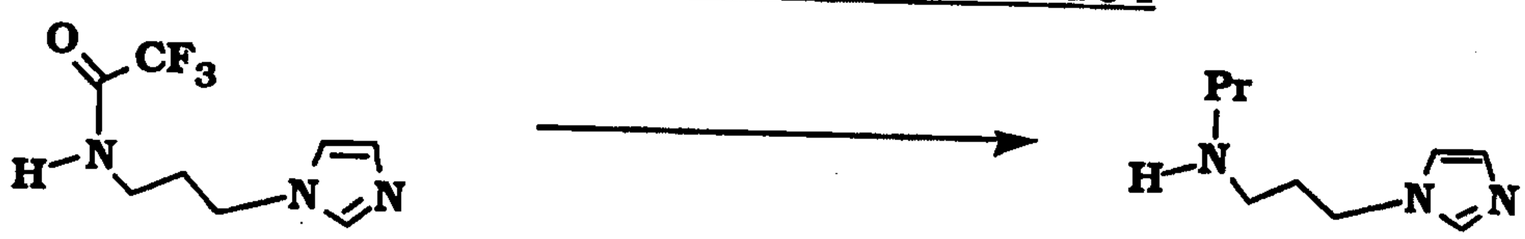
A mixture of the title compound from Step B (74 mg, 0.3 mmol) and 20% KOH in H_2O (0.6 mL) was stirred at room temperature for 15 min. The resulting mixture was concentrated in vacuo and purified by flash column chromatography (silica gel) using 10% MeOH-90% CH_2Cl_2 saturated with aqueous ammonium hydroxide to gave the title compound as an oil (65 mg, 100%, MH^+ = 140).

PREPARATIVE EXAMPLE 103



Following a similar procedure as that used for the preparation of the title compounds from Preparative Example 102 Steps B-C, but using ethyl iodide instead of methyl iodide, the ethyl amine was obtained as an oil (893 mg, 43%, MH^+ = 154).

PREPARATIVE EXAMPLE 104

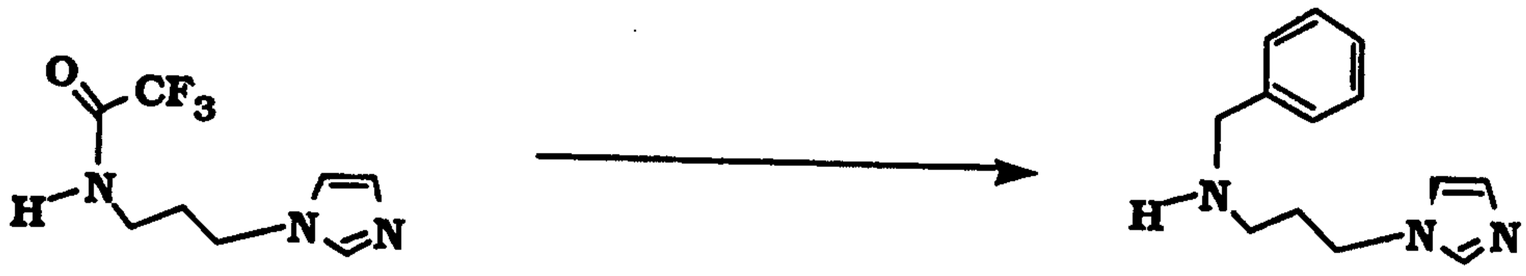


Pr=propyl

Following a similar procedure as that used for the preparation of the title compounds from Preparative Example 102 Steps B-C, but using propyl iodide instead of methyl iodide, the propyl amine was obtained as an oil (649 mg, 29%, MH^+ = 168).

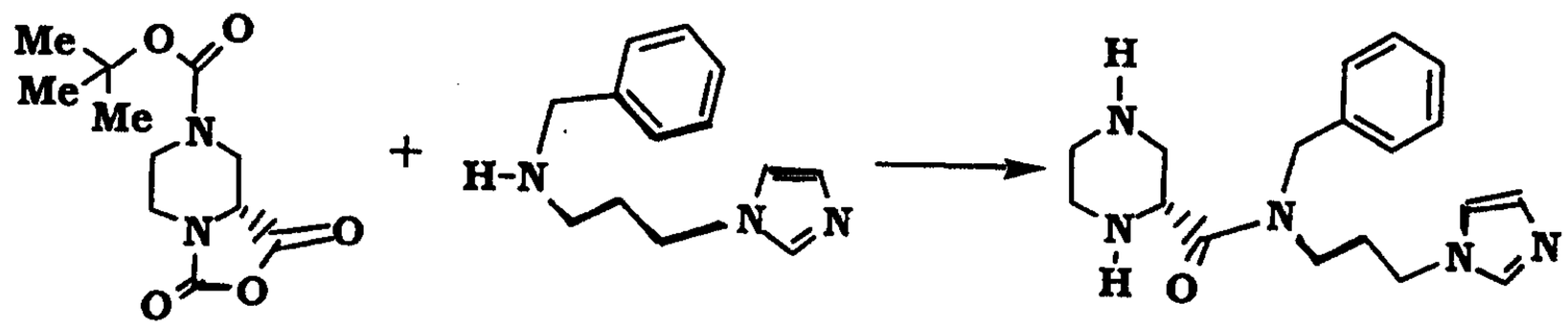
PREPARATIVE EXAMPLE 105

(Alternative Procedure to Preparative Example 74



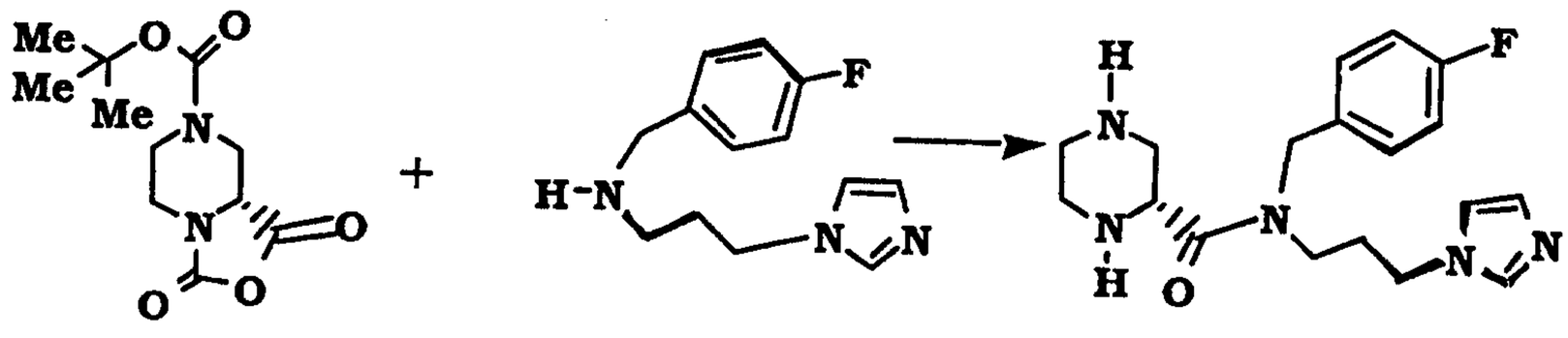
Following a similar procedure as that used for the preparation of the title compounds from Preparative Example 102 Steps B-C, but using benzyl bromide instead of methyl iodide), the benzyl amine was obtained as an oil (1.64 g, 56%, MH^+ = 216).

PREPARATIVE EXAMPLE 106



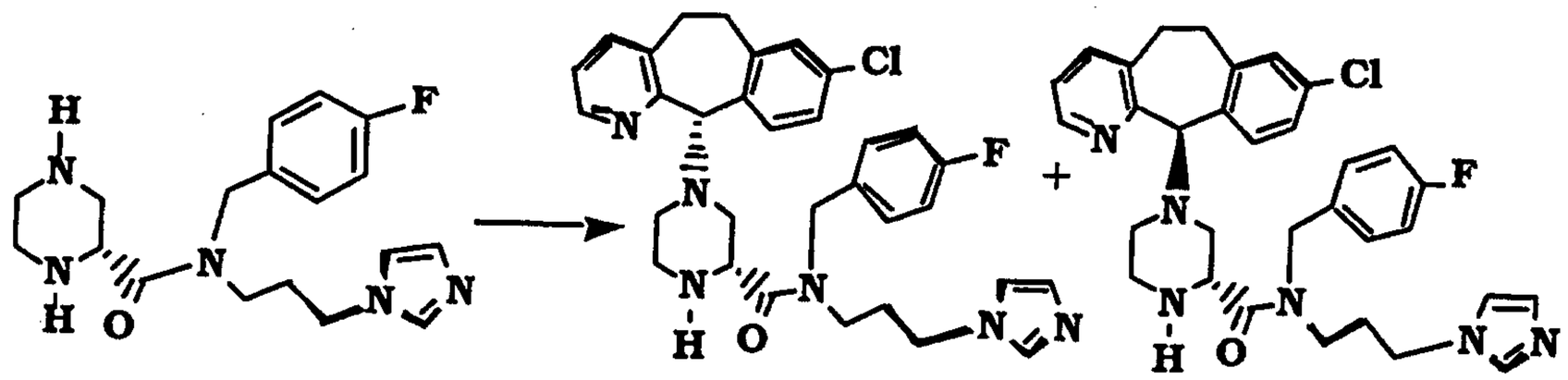
A mixture of the title compound from Preparative Example 74 (1.34 g, 6.2 mmol), the title compound from Preparative Example 44 (1.6 g, 6.2 mmol), triethyl amine (1.3 mL, 9.3 mmol) and anhydrous CH_2Cl_2 (10 mL) was stirred at room temperature for 48 hrs. Trifluoroacetic acid (10 mL) was added and the resulting mixture was stirred for an additional 1.5 hrs. Aqueous NaOH (1N) was added dropwise to neutralize the reaction mixture and the resulting mixture was extracted with CH_2Cl_2. The organic phase was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give a residue which was purified by flash column chromatography (silica gel) using 1% MeOH-99% CH_2Cl_2 saturated with aqueous ammonium hydroxide to give the title compound as an oil (520 mg, 26%, MH^+ = 328).

PREPARATIVE EXAMPLE 107

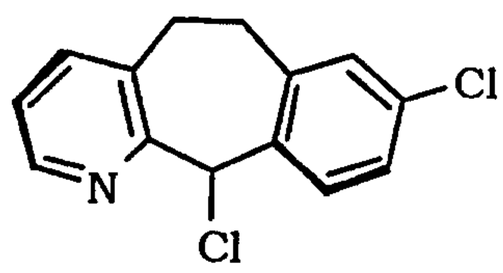


Using the procedure described for Preparative Example 106, but using the title compound from Preparative Example 76, the title compound was prepared: 0.16 g, 10%, MH^+ = 346).

PREPARATIVE EXAMPLE 108

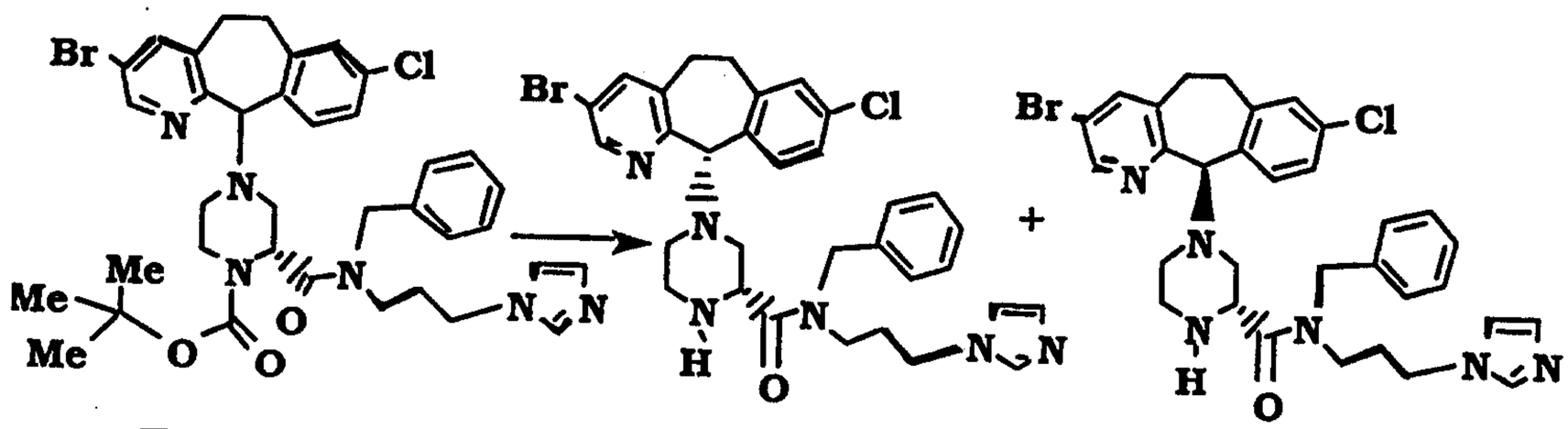


Using the procedure described for Preparative Example 110 (below), but using the title compound from Preparative Example 107 (146 mg, 0.55 mmol), and the 8-Cl-tricyclic chloride (see Preparative Example 7 in WO 95/10516)



(159 mg, 0.46 mmol), the title compounds were prepared and separated by preparative plate chromatography (silica gel) using 2% MeOH-CH_2Cl_2 saturated with aqueous ammonium hydroxide: diastereomer A (45, 17.1%, MH^+ = 573); diastereomer B (43 mg, 16.3%, MH^+ = 573).

PREPARATIVE EXAMPLE 109



To a solution of the title compound from Example 113 (below) (4.90, 6.7 mmol) dissolved in anhydrous CH_2Cl_2 (25 mL) was added TFA (15 mL). The solution was stirred at room temperature under N_2 for 2 hrs, then concentrated *in vacuo*, diluted with CH_2Cl_2, washed with a saturated aqueous solution of $NaHCO_3$ and dried over anhydrous $MgSO_4$. The mixture was filtered, concentrated *in vacuo* and purified by flash column chromatography (silica gel)

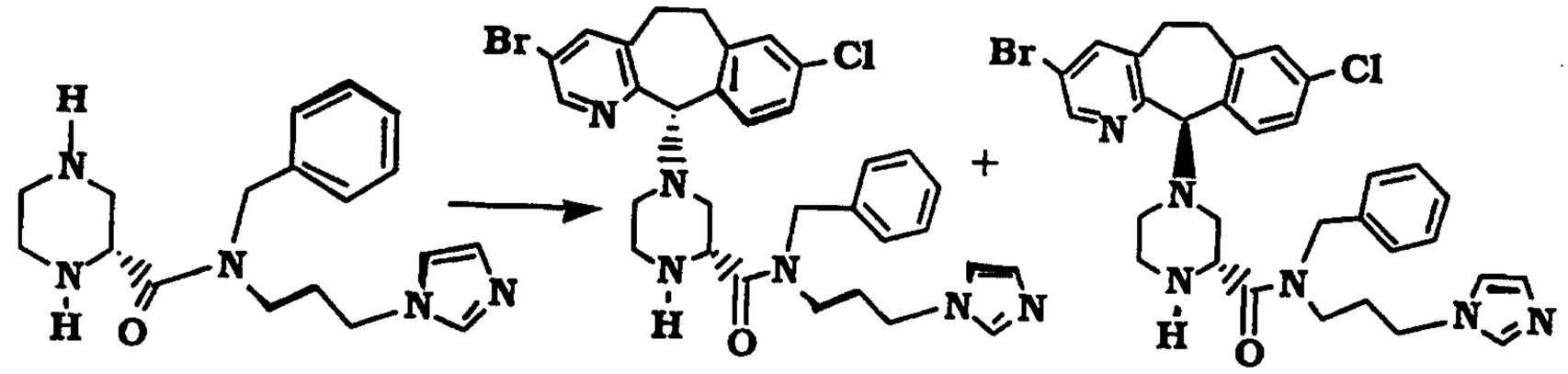
using 2% MeOH-98% CH_2Cl_2 saturated with aqueous ammonium hydroxide to give the title compound as a mixture of diastereomers (3.66 g, quantitative). The diastereomers were separated by preparative chiral chromatography (Chiralpack AD, 5 cm X 50 cm column, flow rate 80 mL/min., 99.8% MeOH +0.2% diethylamine) to give 1.62g of the 11S,2R diastereomer A and 1.97 g of the 11R,2R diastereomer B.

Physical chemical data 11S,2R diastereomer A: mp = 109.3°C; MH^+ = 633; $[\alpha]^{20}_D$= -66.2° (3.93 mg/2 mL MeOH).

Physical chemical data 11R,2R diastereomer B: mp = 64.5°C; MH^+ = 633; $[\alpha]^{20}_D$= -41.8° (4.69 mg/2 mL MeOH).

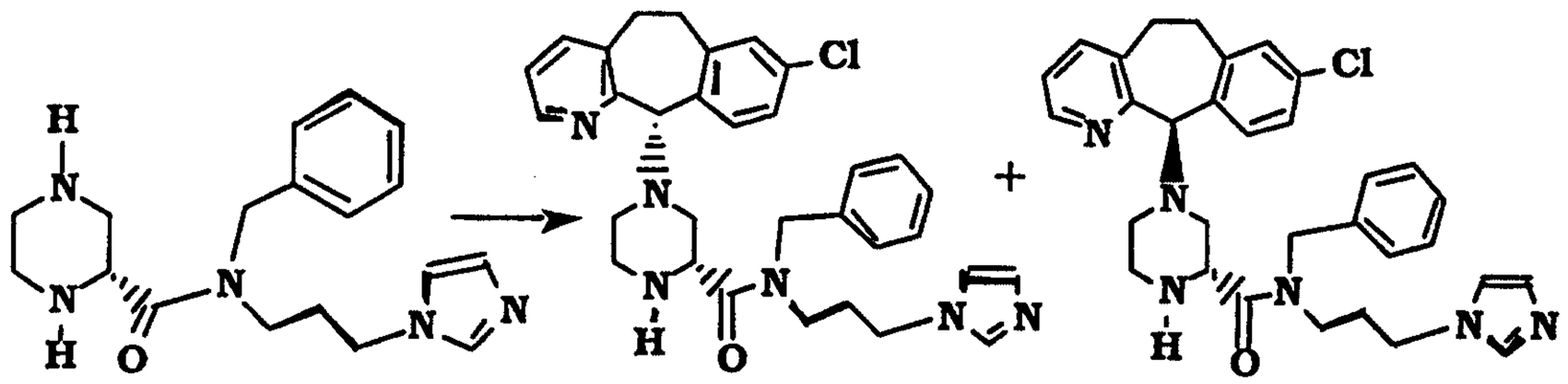
PREPARATIVE EXAMPLE 110

(Alternative procedure to Preparative Example 109)



A mixture of the title compound from Preparative Example 106 (510 mg, 1.6 mmol), the tricyclic chloride (Compound No. 42.0) (534 mg, 1.6 mmol), triethylamine (1.1 mL, 7.8 mmol) and CH_2Cl_2 (10 mL) was stirred at room temperature overnight. The reaction mixture was concentrated *in vacuo* and purified by flash column chromatography (silica gel) using 2% MeOH-98% CH_2Cl_2 saturated with aqueous ammonium hydroxide to give the title compound as a light yellow solid (420 mg, 42%, MH^+ = 633). The diastereomers were separated by preparative chiral chromatography (Chiralpack AD, 5 cm X 50 cm column, flow rate 80 mL/min., 99.8% MeOH +0.2% diethylamine) to give 182 mg of diastereomer A and 126 mg of diastereomer B.

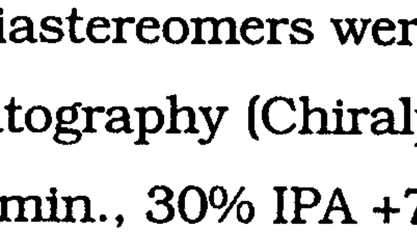
PREPARATIVE EXAMPLE 111



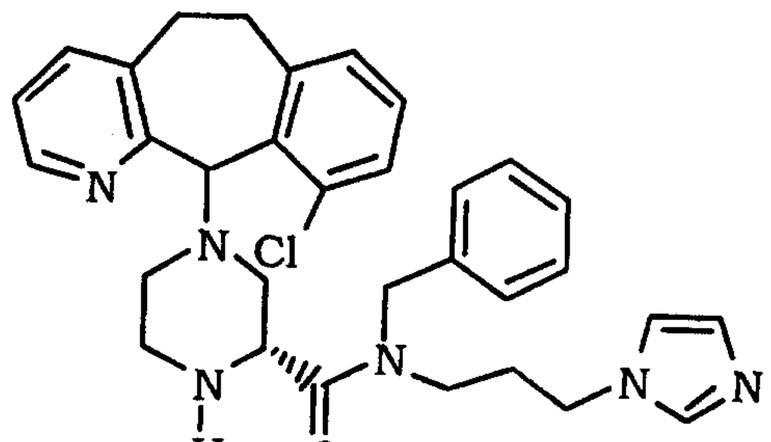
A mixture of the title compound from Preparative Example 106 (1.93 g, 5.9 mmol), the 8-Cl-tricyclic chloride (see Preparative Example 7 in WO95/10516) (1.56 g, 5.9 mmol), triethylamine (4.1 mL, 29.5 mmol) and CH_2Cl_2 (10 mL) was stirred at room temperature for 48 h. The reaction mixture was concentrated *in vacuo* and purified by flash column chromatography (silica gel) using 2% MeOH-98% CH_2Cl_2 saturated with aqueous ammonium hydroxide to give the title compound as a light yellow solid (1.56 g, 49%, MH^+ = 555). The diastereomers were separated by preparative chiral chromatography (Chiralpack AD, 5 cm X 50 cm column, flow rate 80 mL/min., 30% IPA +70% Hexane +0.2% diethylamine) to give 0.72 g of the 11S,2R diastereomer A and 0.57 g of the 11R,2R diastereomer B.

PREPARATIVE EXAMPLE 111.1

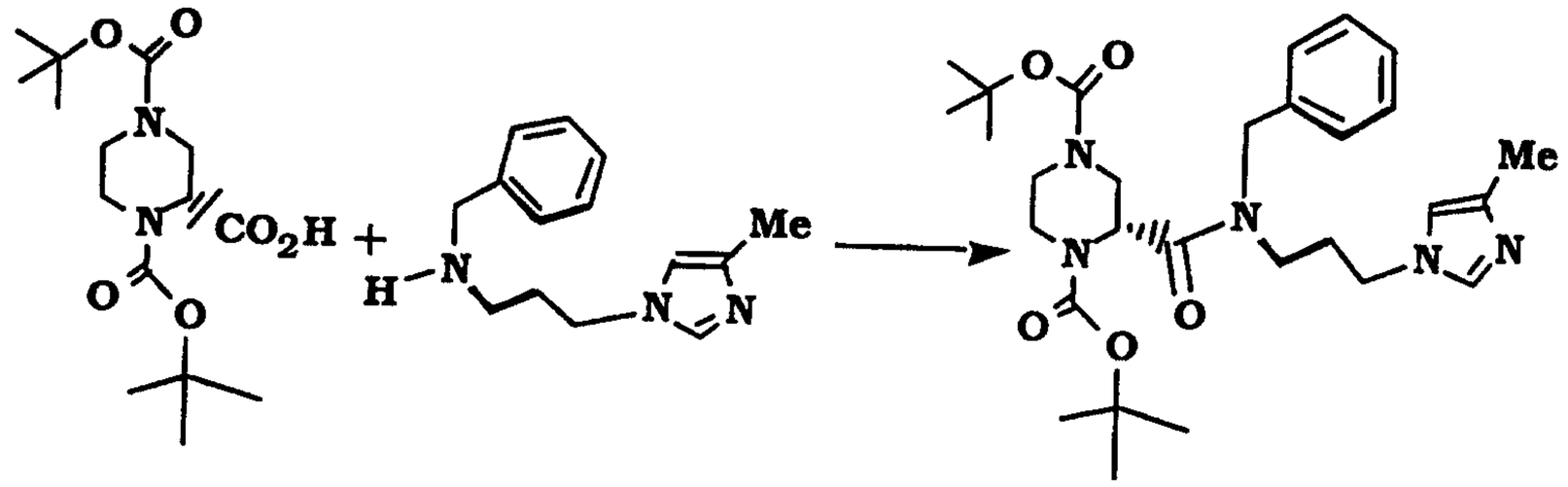
Follow the procedure of Preparative Example 111, but use the 10-Cl-tricycle chloride



to obtain

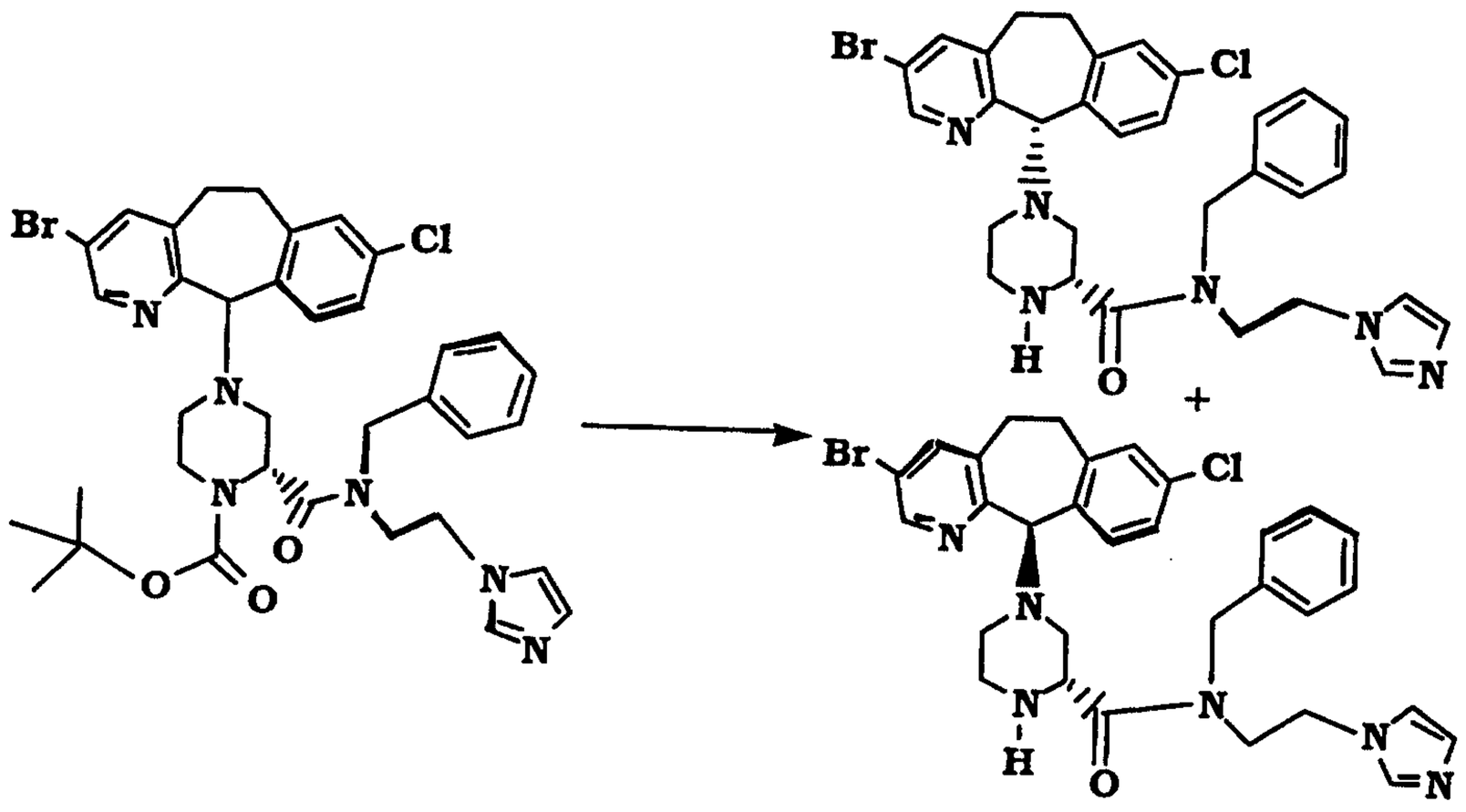


PREPARATIVE EXAMPLE 112



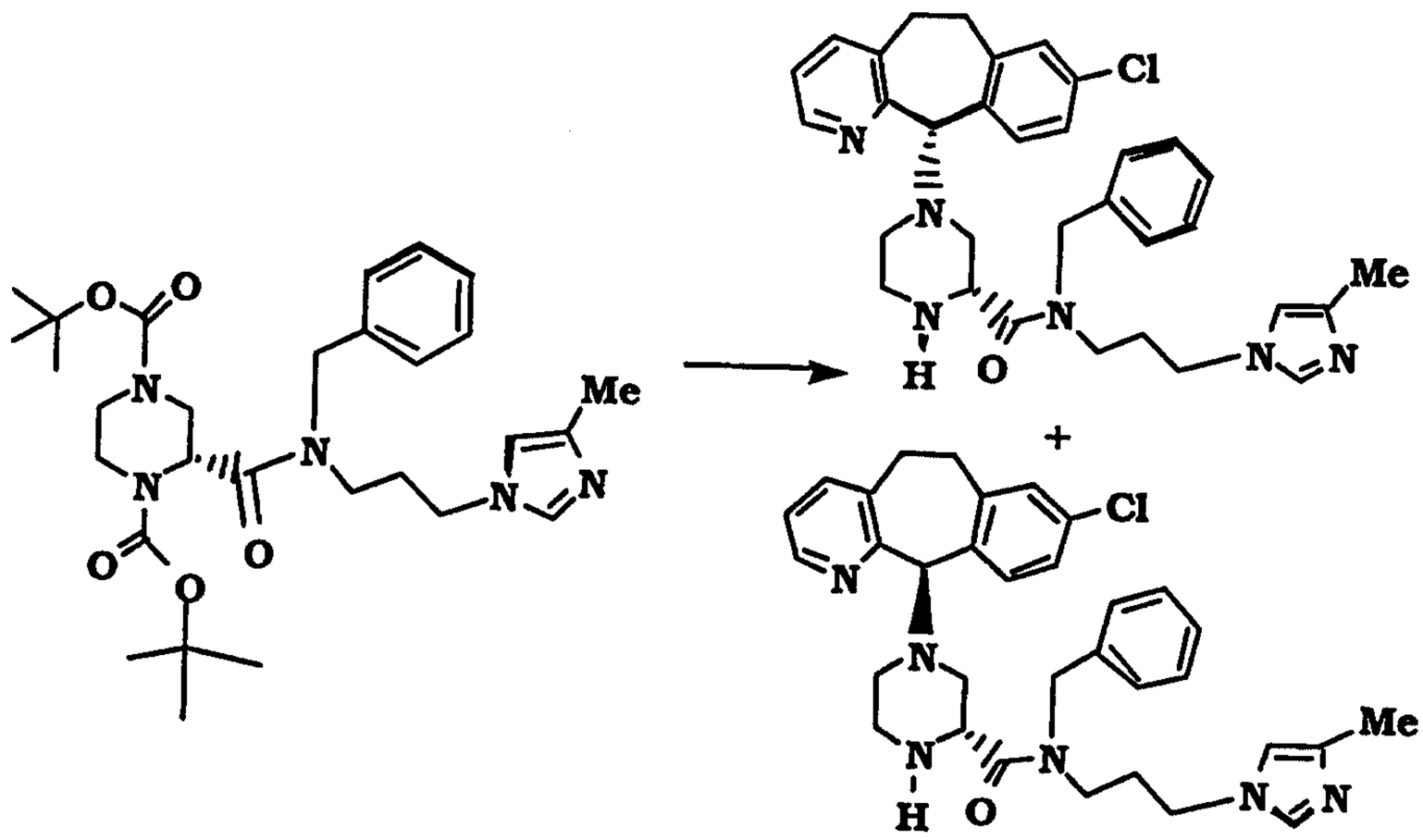
To the carboxylic acid from Preparative Example 43 (2 g, 6 mmol) were added HOBT (0.82 g, 6.1 mmol), DEC (1.2 g, 6.0 mmol), the title compound from Preparative Example 85 (1.39 g, 6.1 mmol, isolated by preparative chiral chromatography (Chiralpack AD, 5 cm X 50 cm column, flow rate 80 mL/min., 8% IPA +92% Hexane +0.2% diethylamine), NMM (1.7 mL, 15.5 mmol) and anhydrous DMF (60 mL). The mixture was stirred at room temperature under N_2 overnight. The mixture was concentrated *in vacuo*, diluted with CH_2Cl_2 and washed with NaOH (aq). The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel) using 2-15% MeOH-CH_2Cl_2 saturated with aqueous ammonium hydroxide to give the title compound (1.8 g, 55%, MH^+ = 542).

PREPARATIVE EXAMPLE 113



Using the procedure described for Preparative Example 109, but using the title compound from Example 126 below, the title compounds were prepared and separated: 11S,2R(-)- diastereomer A: 25.4% yield,MH^+ = 619; $[\alpha]^{20}_D$= -46.7° (1.86 mg/2 mL MeOH); 11R,2R(-)- diastereomer B: 21.1% yield, MH^+ = 619; $[\alpha]^{20}_D$= -23.0° (2.6 mg/2 mL MeOH).

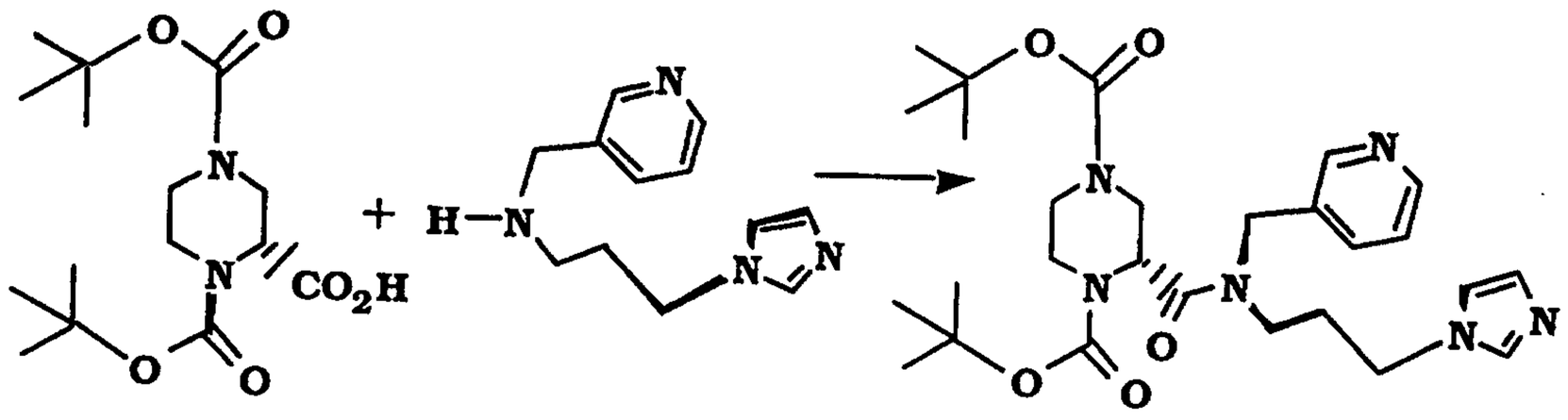
PREPARATIVE EXAMPLE 114



To a solution of the title compound from Preparative Example 112 (1.8, 3.33 mmol) dissolved in anhydrous CH_2Cl_2 (5 mL) was added TFA (5 mL). The solution was stirred at room temperature

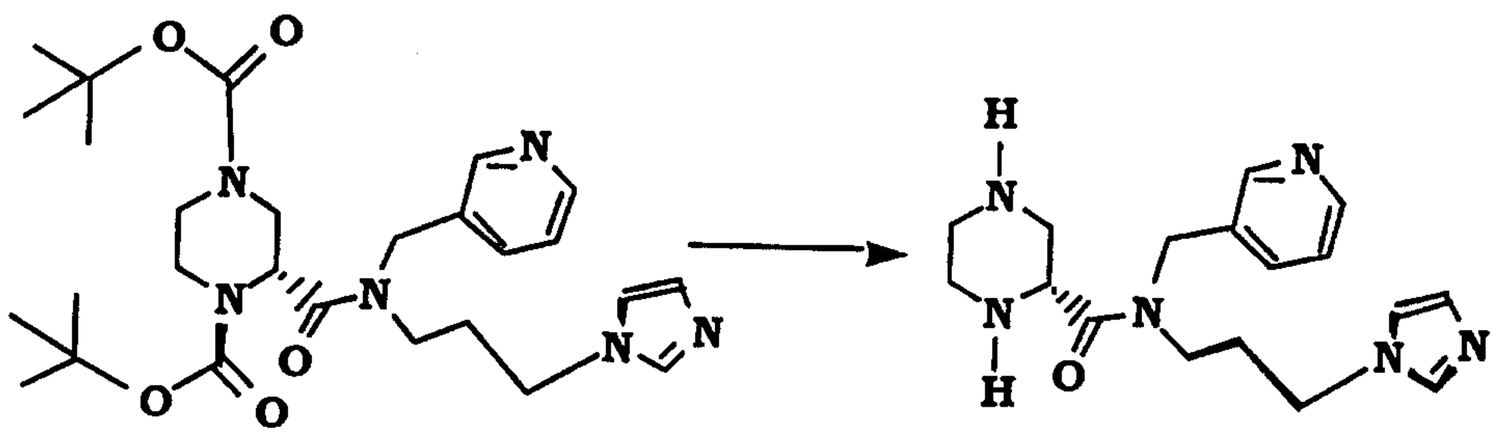
under N_2 overnight, concentrated *in vacuo* and diluted with DMF (10 mL). To this was added the 8-Cl-tricyclic chloride (562 mg, 1.1 mmol) and triethylamine (10 mL) and allowed to stir at room temperature for 48 h. The reaction mixture was concentrated *in vacuo*, diluted with CH_2Cl_2, washed with a saturated aqueous solution of $NaHCO_3$ and dried over anhydrous $MgSO_4$. After filtration and concentration *in vacuo*, the residue was purified by flash column chromatography (silica gel) using 3-10% MeOH-98% CH_2Cl_2 saturated with aqueous ammonium hydroxide to give the title compounds (11S,2R diastereomer A, 152 mg, 27%, MH^+ = 569; and 11R,2R diastereomer B, 316 mg, 56%, MH^+ = 569).

PREPARATIVE EXAMPLE 115



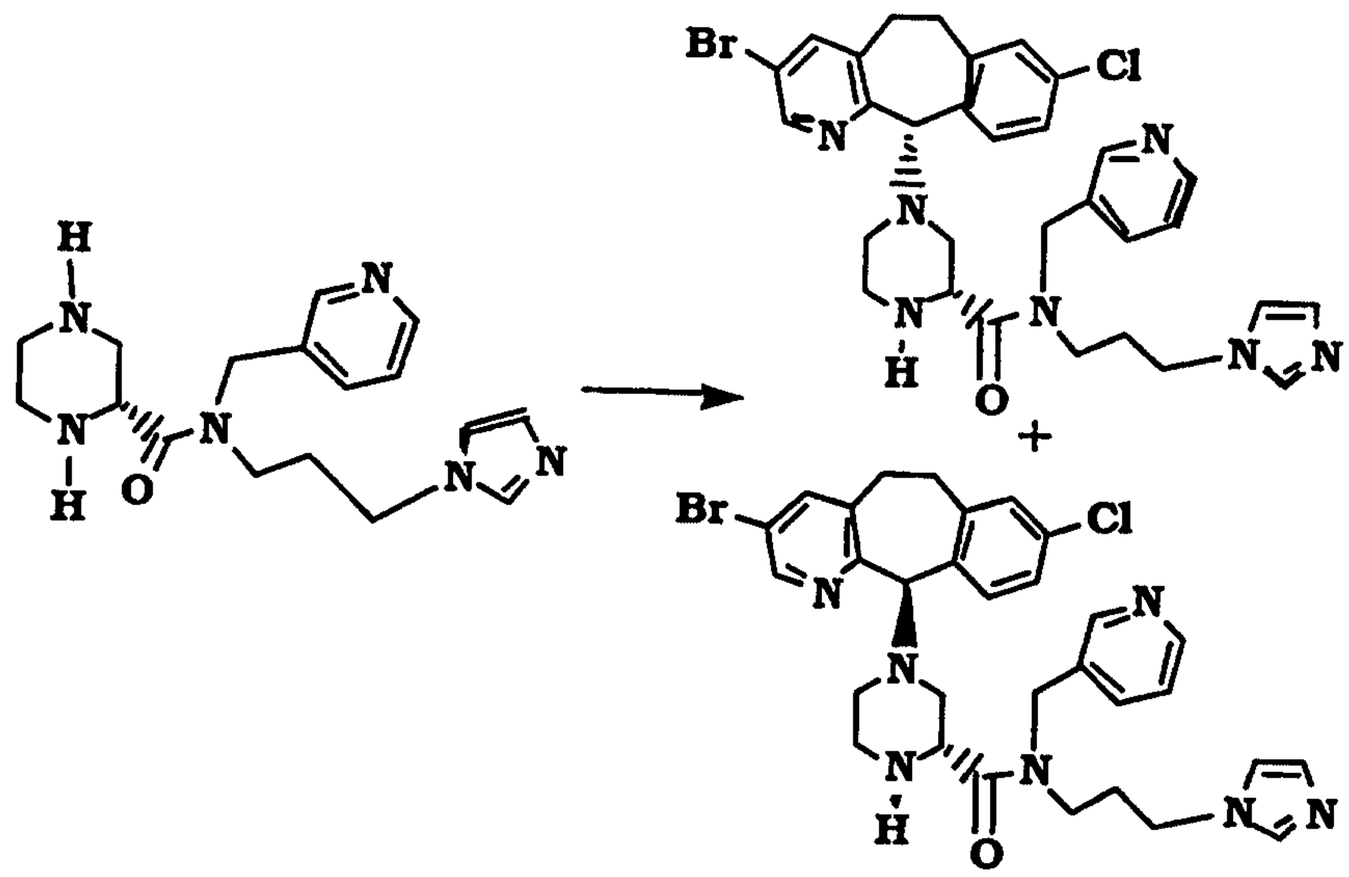
To the title compound from Preparative Example 43 (2.64 g, 8.0 mmol) were added HOBT (1.26 g, 9.3 mmol), DEC (1.79 g, 9.3 mmol), the title compound from Preparative Example 78 (1.44 g, 6.7 mmol), NMM (1.5 mL, 13.6 mmol) and anhydrous DMF (10 mL). The mixture was stirred at room temperature under N_2 overnight. The mixture was concentrated *in vacuo*, diluted with CH_2Cl_2 and washed with NaOH (aq). The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel) using 1% MeOH-CH_2Cl_2 saturated with aqueous ammonium hydroxide to give the title compound (0.94 g, 27%, MH^+ = 529).

PREPARATIVE EXAMPLE 116



The title compound from Preparative Example 115 (0.73 g, 1.38 mmol) and anhydrous CH_2Cl_2 (5 mL) was stirred at room temperature for 48 hrs. Trifluoroacetic acid (2 mL) was added and the resulting mixture was stirred for an additional 1.5 hrs. Aqueous NaOH (1N) was added dropwise to neutralize the reaction mixture and the resulting mixture was extracted with CH_2Cl_2. The organic phase was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give a residue which was purified by flash column chromatography (silica gel) using 5-15% MeOH-CH_2Cl_2 saturated with aqueous ammonium hydroxide to give the title compound as an oil (346 mg, 76%, MH^+ = 329).

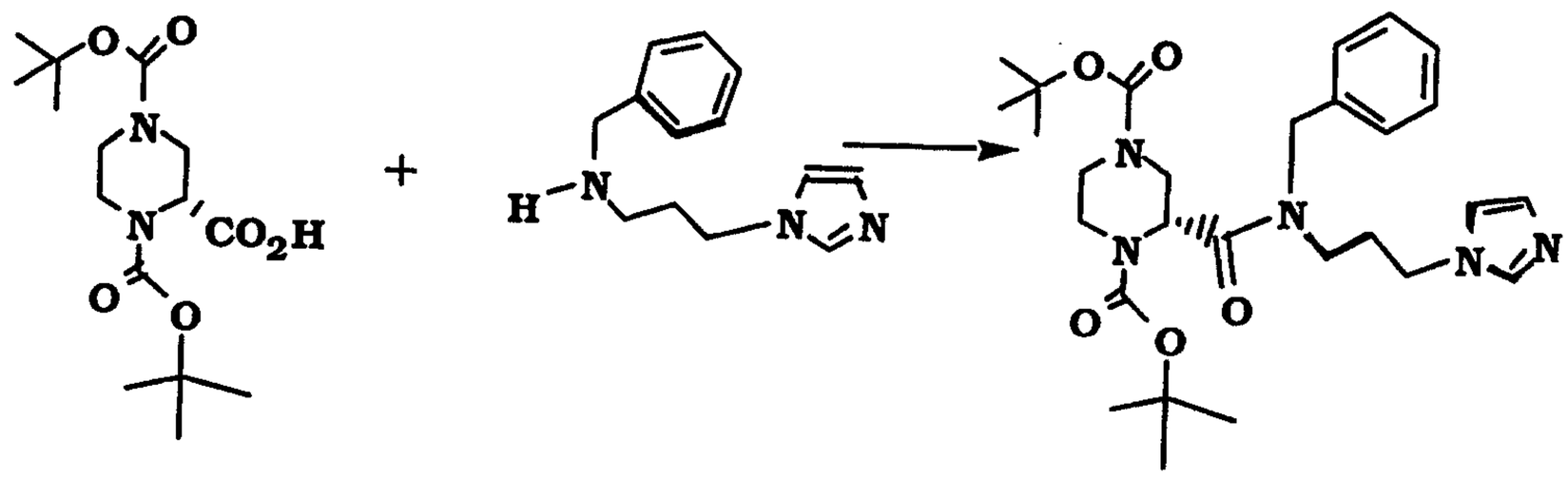
PREPARATIVE EXAMPLE 117



Using the procedure described for Preparative Example 110, but using the title compound from Preparative Example 116 (343 mg, 1 mmol) and the tricyclic chloride (Compound No. 42.0) (718

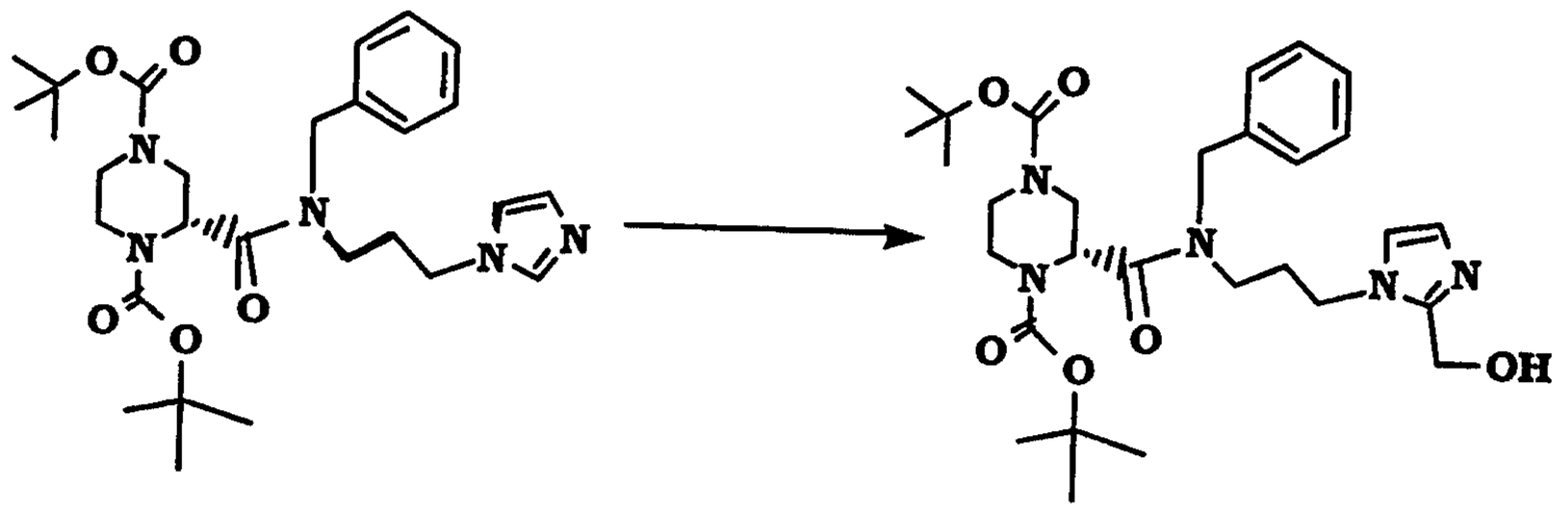
mg, 2 mmol), the title compounds were prepared and separated: 11S,2R diastereomer A: 135 mg, 29%, MH^+ = 634; 11R,2R diastereomer B: 126 mg, 27%, MH^+ = 634.

PREPARATIVE EXAMPLE 118



To the carboxylic acid from Preparative Example 43 (7.26 g, 22 mmol) were added HOBt (3.92 g, 29 mmol), DEC (5.49 g, 29 mmol), the title compound from Preparative Example 74 (4.73 g, 22 mmol), NMM (4.84 mL, 44 mmol) and anhydrous DMF (35 mL). The mixture was stirred at room temperature under N_2 overnight. The mixture was concentrated *in vacuo*, diluted with CH_2Cl_2 and washed with NaOH (aq). The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel) using 1% MeOH-CH_2Cl_2 saturated with aqueous ammonium hydroxide to give the title compound (1.71 g, 15%, MH^+ = 528).

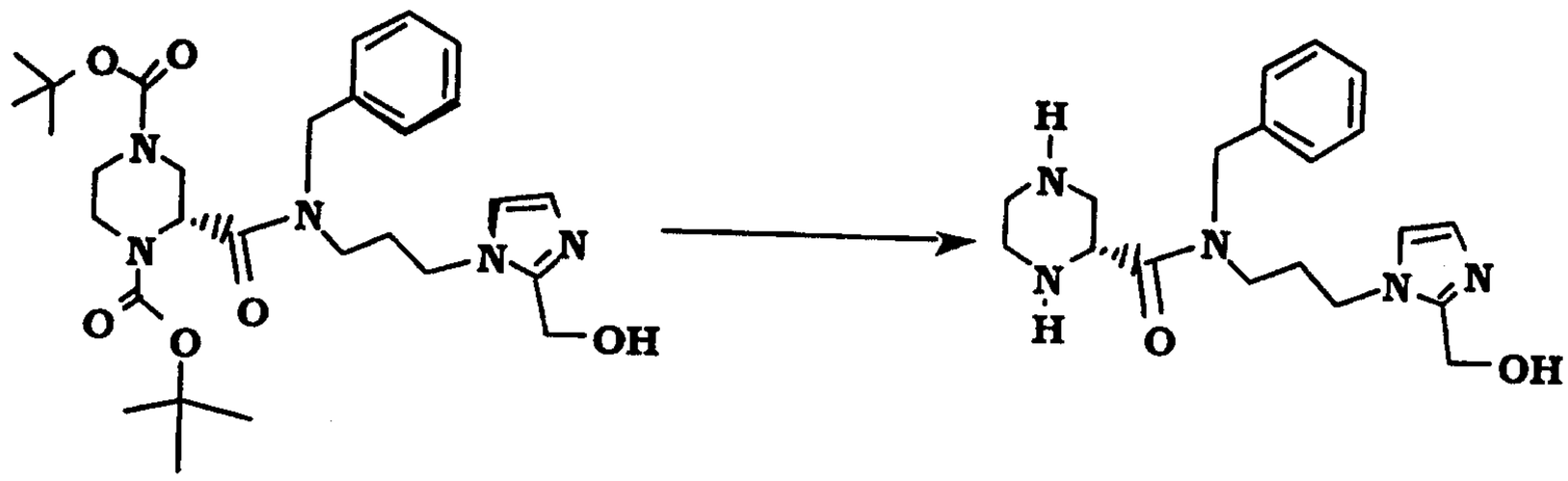
PREPARATIVE EXAMPLE 119



The title compound from Preparative Example 118 (1.4 g, 2.7 mmol) and paraformaldehyde (solid, 2.8 g) were heated at 130°C in

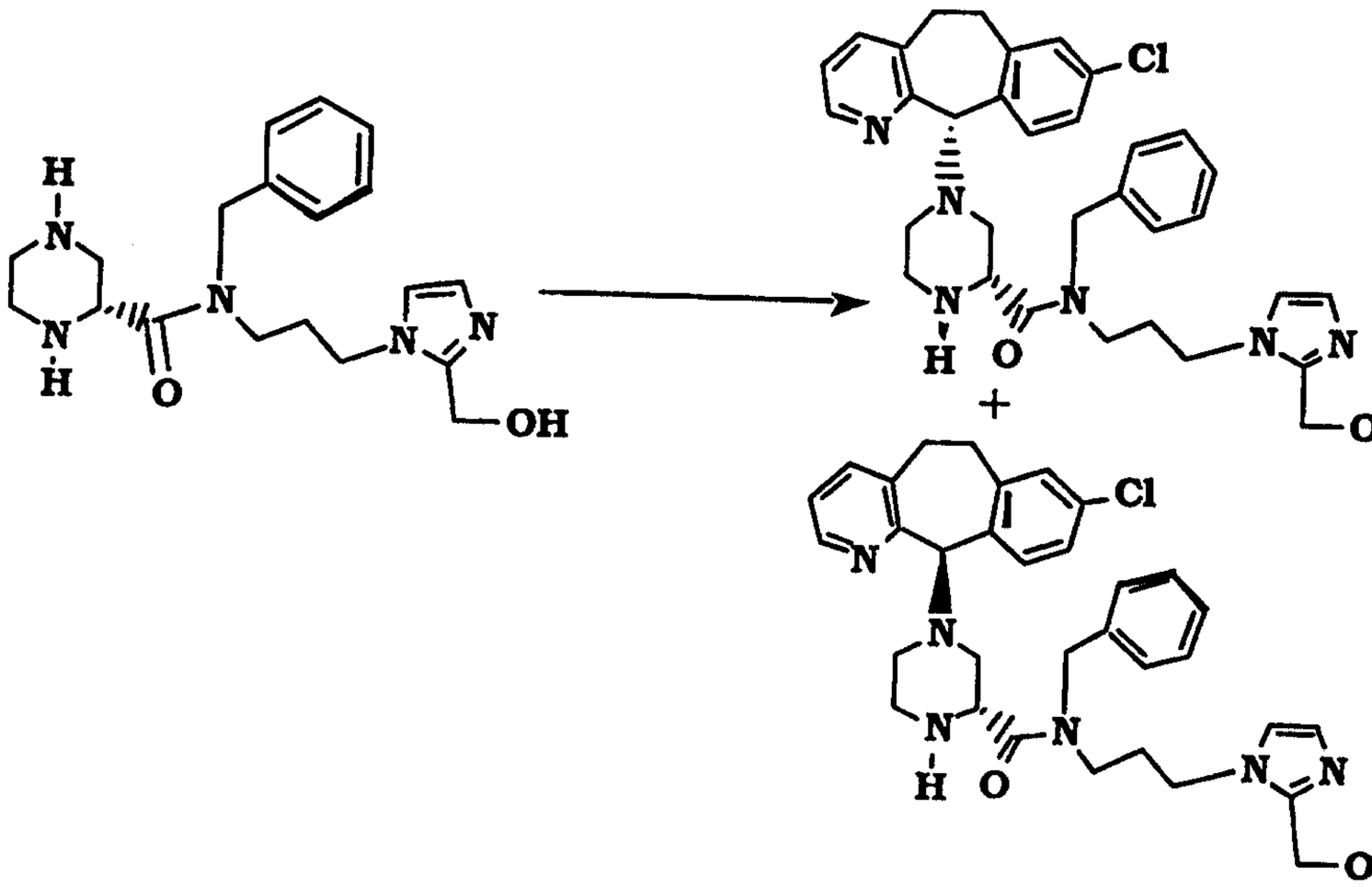
a sealed tube for 12 h. The mixture was diluted with CH_2Cl_2 and filtered. The organic phase was concentrated *in vacuo* and purified by flash column chromatography (silica gel) using 1% MeOH-CH_2Cl_2 saturated with aqueous ammonium hydroxide to give the title compound (0.89 g, 59%, MH^+ = 558).

PREPARATIVE EXAMPLE 120



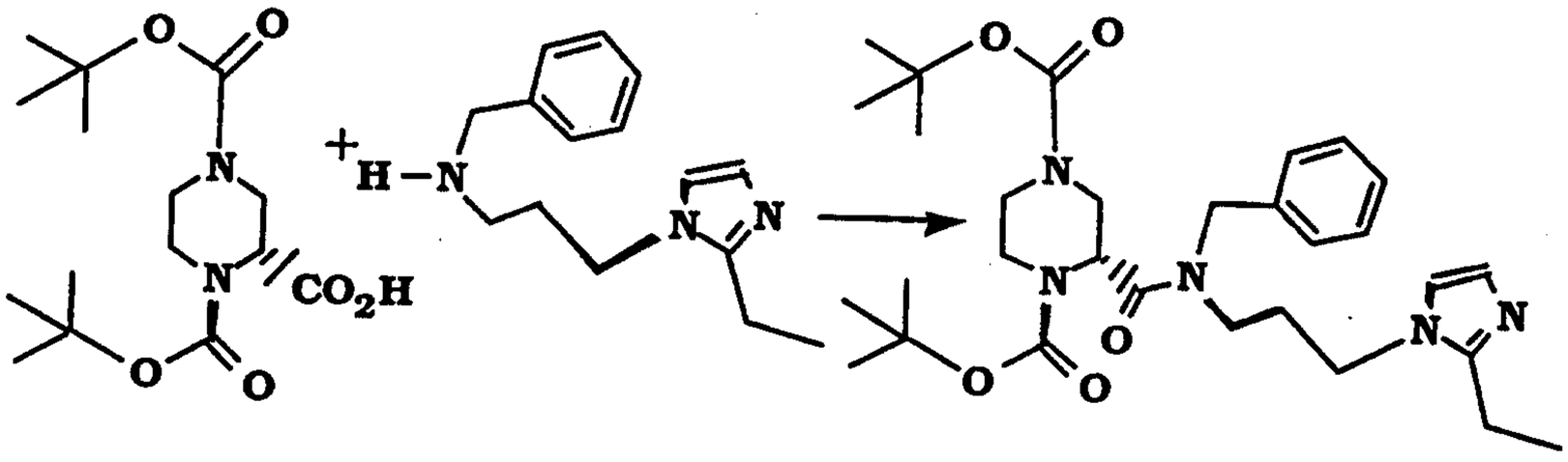
The title compound from Preparative Example 119 (0.88 g, 1.6 mmol), anhydrous CH_2Cl_2 (10 mL) and trifluoroacetic acid (10 mL) were stirred at room temperature for 1.5 hrs. Aqueous NaOH (1N) was added dropwise to neutralize the reaction mixture followed by concentration *in vacuo* and purification by flash column chromatography (silica gel) using 5-12% MeOH-CH_2Cl_2 saturated with aqueous ammonium hydroxide to give the title compound as an oil (503 mg, 88%, MH^+ = 358).

PREPARATIVE EXAMPLE 121



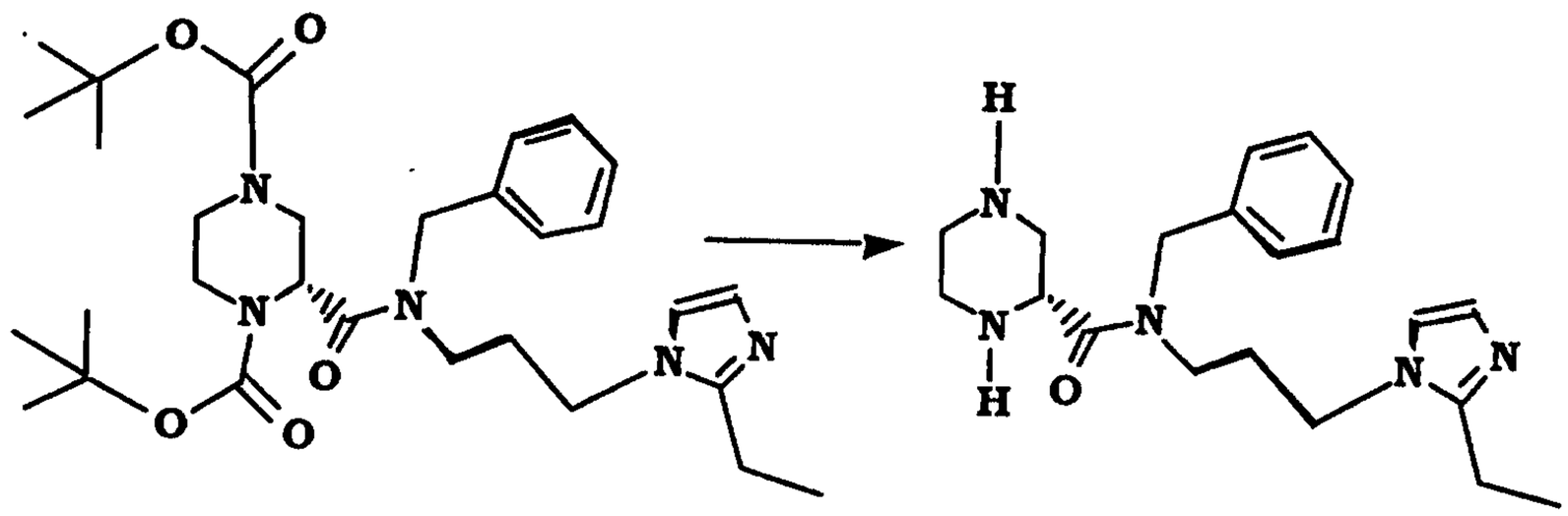
The title compound from Preparative Example 120 (498 mg, 1.4 mmol) was dissolved in anhydrous CH_2Cl_2 (10 mL). To this was added the 8-Cl-tricyclic chloride (370 mg, 1.4 mmol) and triethylamine (0.6 mL) and allowed to stir at room temperature for 24 h. The reaction mixture was concentrated *in vacuo* and diluted with CH_2Cl_2, purified by flash column chromatography (silica gel) using 3% MeOH-CH_2Cl_2 saturated with aqueous ammonium hydroxide to give the title compounds as a mixture of diastereomers (38% yield) which were separated by preparative chiral chromatography (Chiralpack AD, 5 cm X 50 cm column, flow rate 80 mL/min, 30% IPA-Hexane +0.2% diethylamine). (diastereomer A: 178 mg, MH^+ = 585; and diastereomer B: 130 mg, MH^+ = 585).

PREPARATIVE EXAMPLE 122



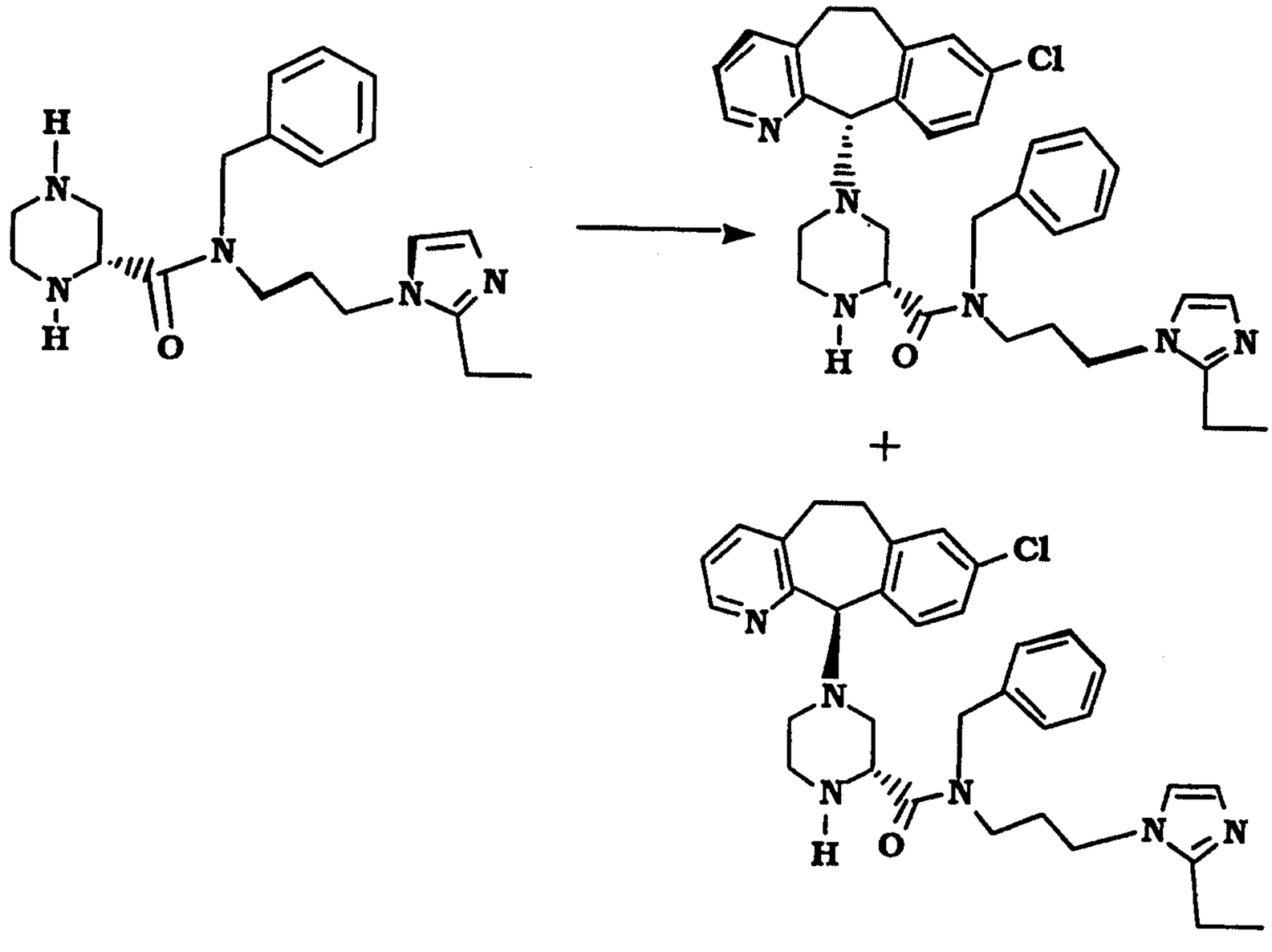
To the carboxylic acid from Preparative Example 43 (8.11 g, 25 mmol) were added HOBT (4.39 g, 33 mmol), DEC (6.33 g, 33 mmol), the title compound from Preparative Example 88 (5.97 g, 25 mmol), NMM (5.5 mL, 50 mmol) and anhydrous DMF (40 mL). The mixture was stirred at room temperature under N_2 for 48 h. The mixture was concentrated *in vacuo*, diluted with CH_2Cl_2 and washed with NaOH (aq). The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel) using 1% MeOH-CH_2Cl_2 saturated with aqueous ammonium hydroxide to give the title compound (5.24 g, 38%, MH^+ = 556).

PREPARATIVE EXAMPLE 123



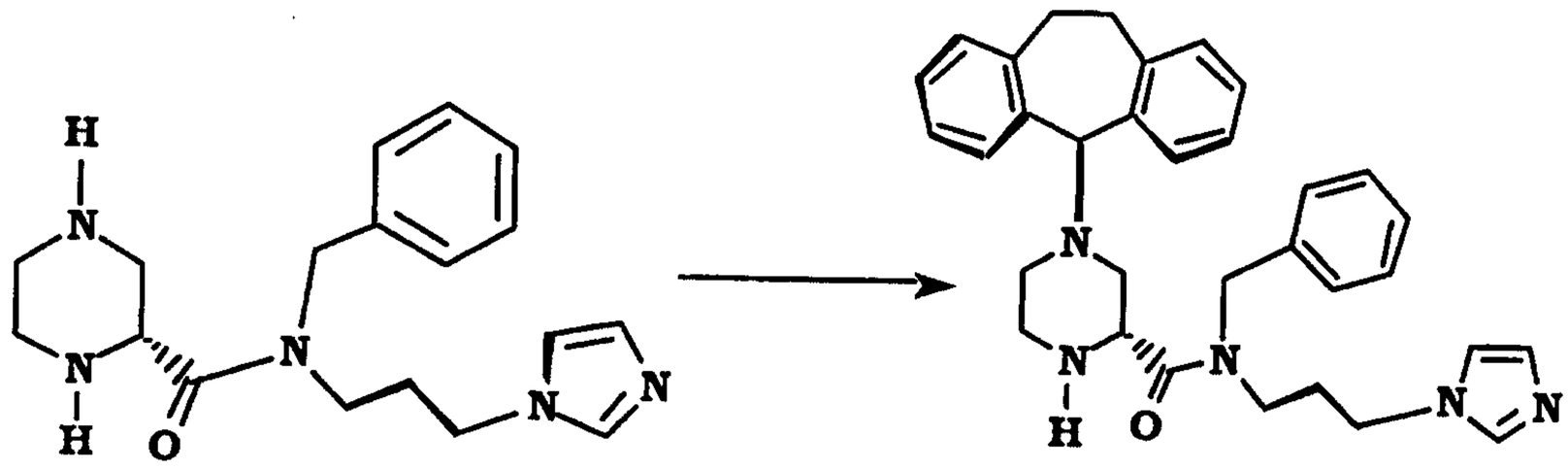
The title compound from Preparative Example 122 (5.23 g, 9.4 mmol), anhydrous CH_2Cl_2 (10 mL) and trifluoroacetic acid (10 mL) were stirred overnight. Aqueous NaOH (1N) was added dropwise to neutralize the reaction mixture, concentrated *in vacuo*, and purified by flash column chromatography (silica gel) using 5-9% MeOH-CH_2Cl_2 saturated with aqueous ammonium hydroxide to give the title compound as an oil (2.69 mg, 81%, MH^+ = 356).

PREPARATIVE EXAMPLE 124



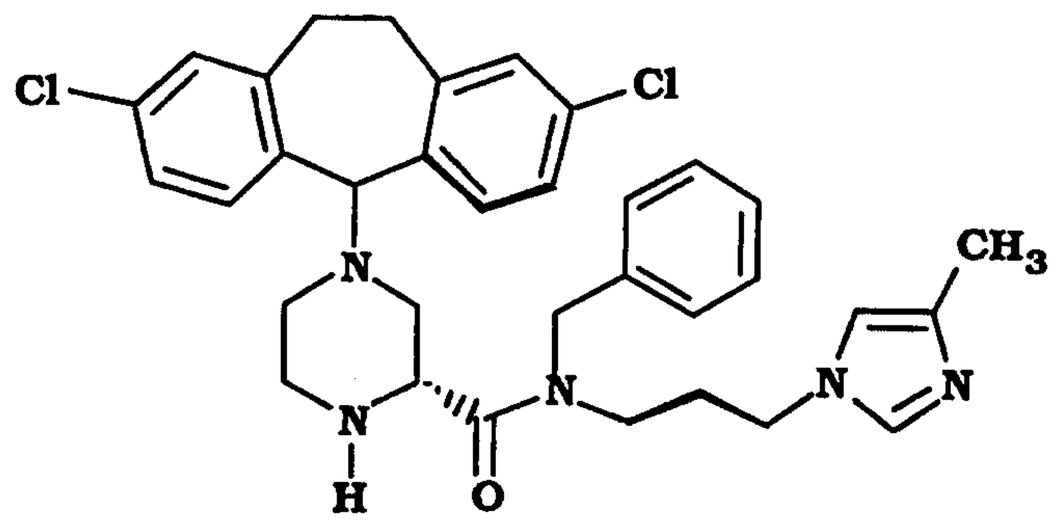
The title compound from Preparative Example 123 (2.67, 7.5 mmol) was dissolved in anhydrous CH_2Cl_2 (40 mL). To this was added the 8-Cl-tricyclic chloride (1.98 g, 7.5 mmol) and triethylamine (3.14 mL) and allowed to stir at room temperature for 12 h. The reaction mixture was concentrated *in vacuo*, diluted with CH_2Cl_2, washed with a saturated aqueous solution of $NaHCO_3$ and dried over anhydrous $MgSO_4$. After filtration and concentration *in vacuo*, the residue was purified by flash column chromatography (silica gel) using 1-2% MeOH-CH_2Cl_2 saturated with aqueous ammonium hydroxide to give the title compounds in 43% yield (diastereomer A, 1.2 g, MH^+ = 583; and diastereomer B, 681 mg, MH^+ = 583).

PREPARATIVE EXAMPLE 125

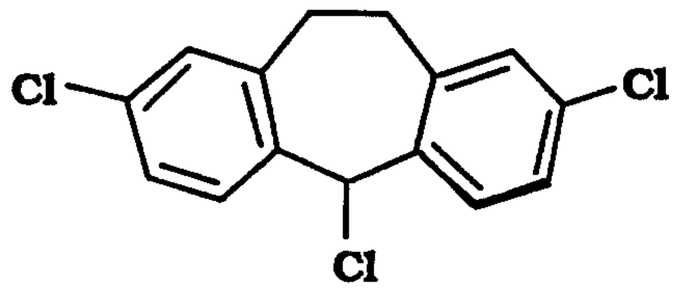


A mixture of the title compound from Preparative Example 106 (200 mg, 0.61 mmol), chlorobenzosuberane (140 mg, 0.61 mmol), triethylamine (0.43 mL, 3.1 mmol) and CH_2Cl_2 (10 mL) was stirred at room temperature overnight. The reaction mixture was concentrated *in vacuo* and purified by preparative plate chromatography (silica gel) using 2% MeOH-CH_2Cl_2 saturated with aqueous ammonium hydroxide to give the title compound as a light yellow solid (63 mg, 20%, MH^+ = 520).

PREPARATIVE EXAMPLE 126



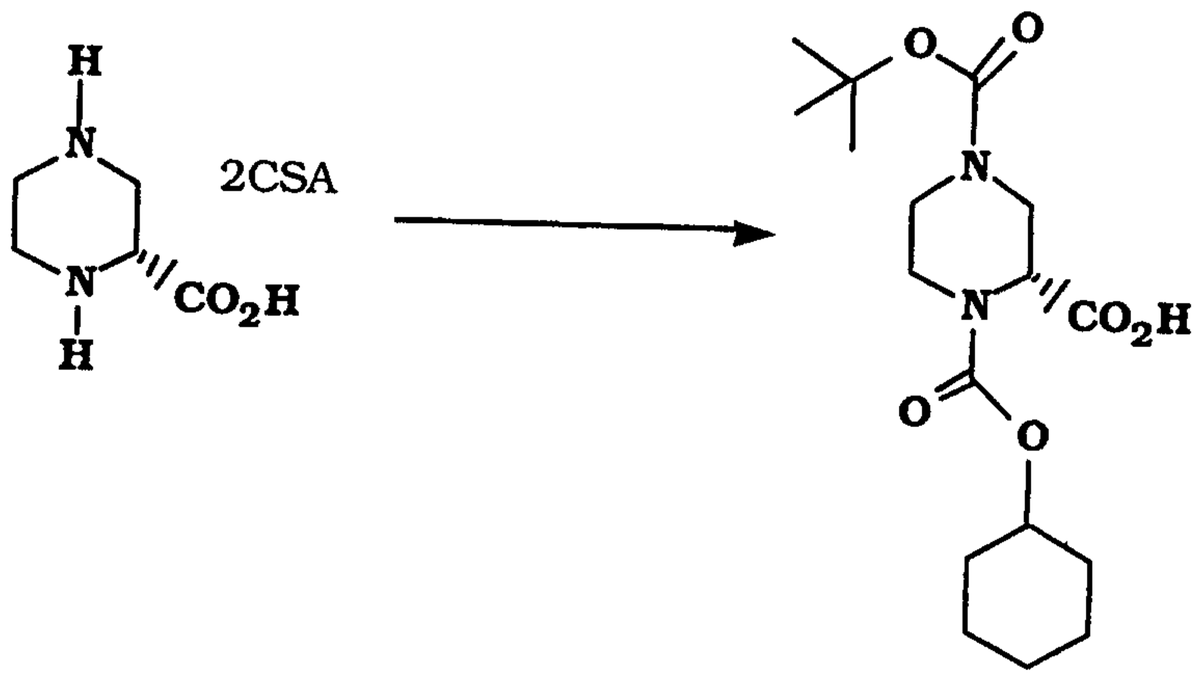
If the procedure of Preparative Example 114 is followed, except the 3,8-dichloro tricyclic compound



is used instead of the 8-Cl-tricycle chloride, the title compound would be obtained.

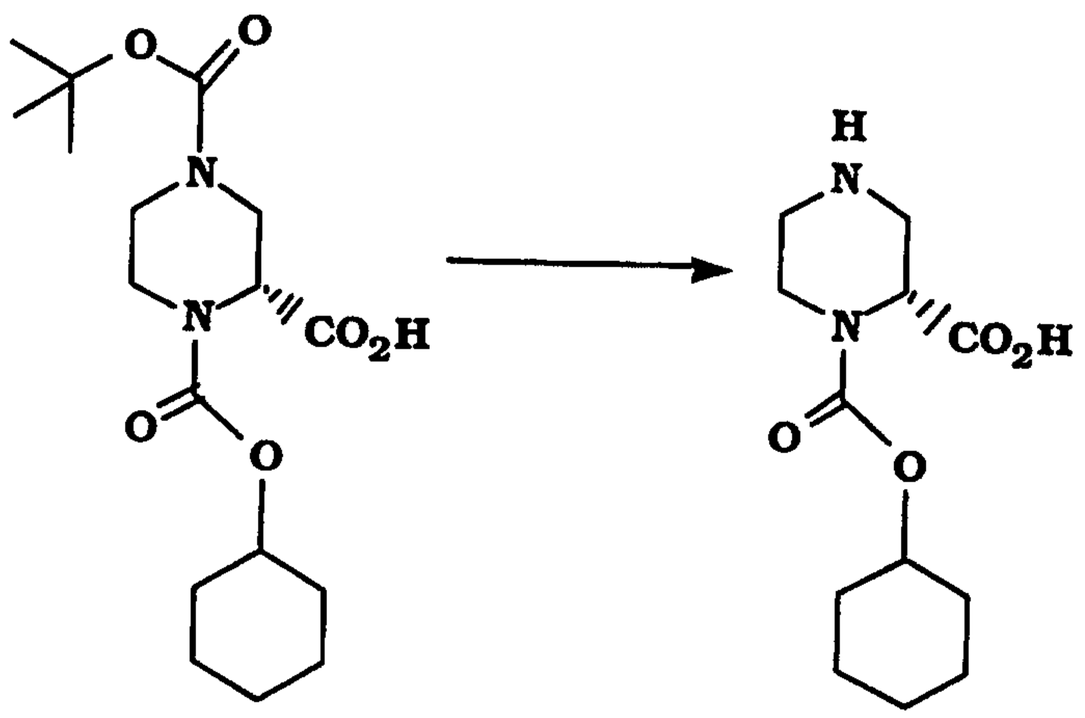
PREPARATIVE EXAMPLE 127

Step A



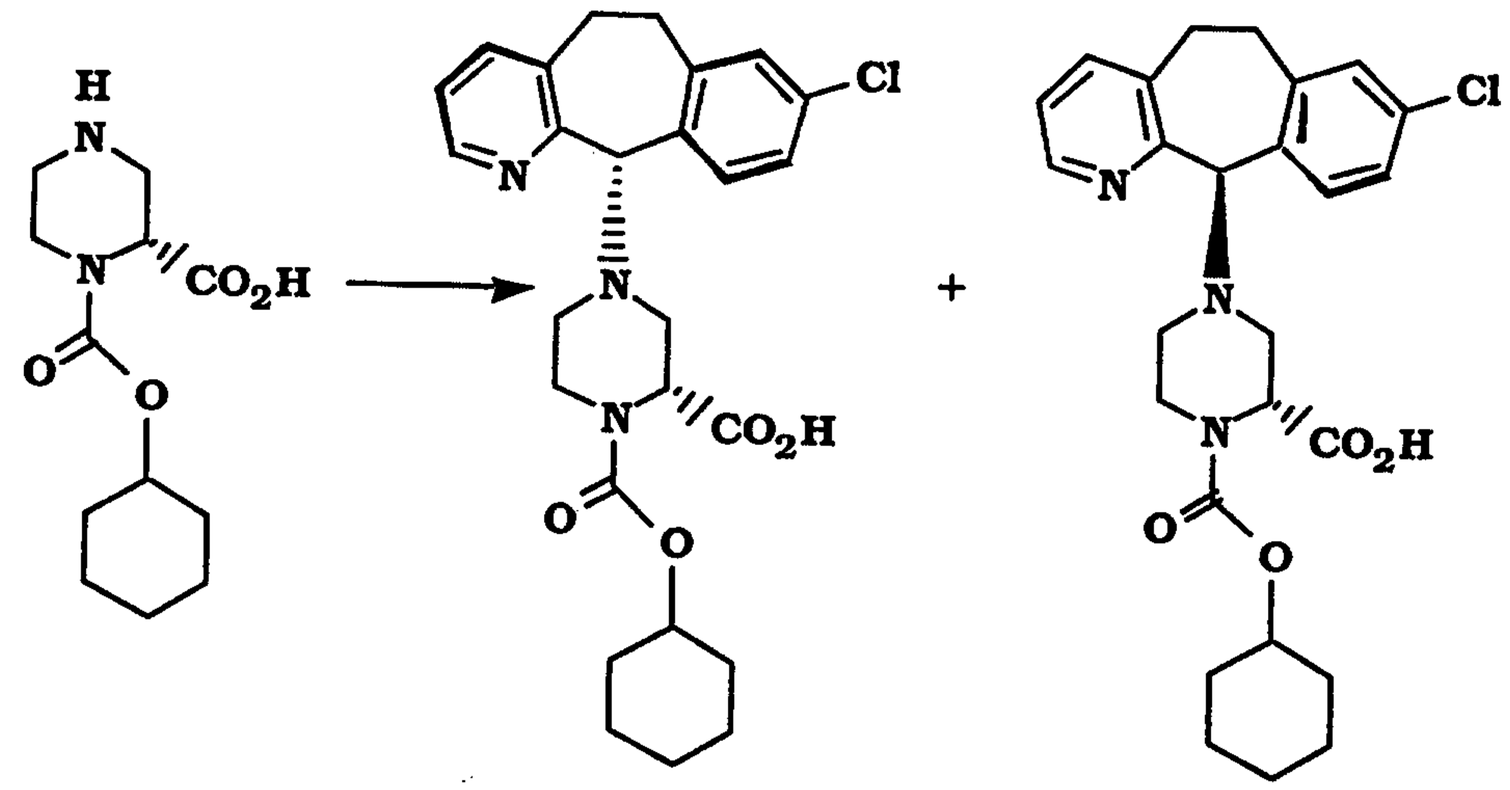
To the piperazine carboxylic acid dicamphorsulfonic acid salt (Preparative Example 42) (14.63 g, 24.6 mmol) dissolved in water (80 mL) and dioxane (80 mL) was added 50% NaOH (aq) until pH 11. BOC-ON (6.65 g, 27.04 mmol) was added while stirring at room temperature for 6.5 hrs and while maintaining the pH at 11 with 50% NaOH. The pH was lowered to 9.5 using 10% HCl (aq) and cyclohexyl chloroformate (4.0 g, 24.6 mmol) was added dropwise while maintaining the pH at 9.5 with a slow addition of 50% NaOH (aq) with stirring at 25°C for an additional 12 h. The mixture was extracted with Et_2O and the aqueous phase was acidified to pH 3 with 6M HCl (aq). This aqueous phase was extracted with EtOAc and the organic phase was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*, and purified by flash chromatography (silica gel) using 25-50% EtOAc-hexane to give the title compound (6.65 g, 76%, MH^+ = 357).

Step B



The title compound from Step A (6.65 g, 18.7 mmol) and trifluoroacetic acid (20 mL) dissolved in anhydrous CH_2Cl_2 (50 mL) were stirred at room temperature for 1 hr. The organic phase was concentrated *in vacuo* to give a residue.

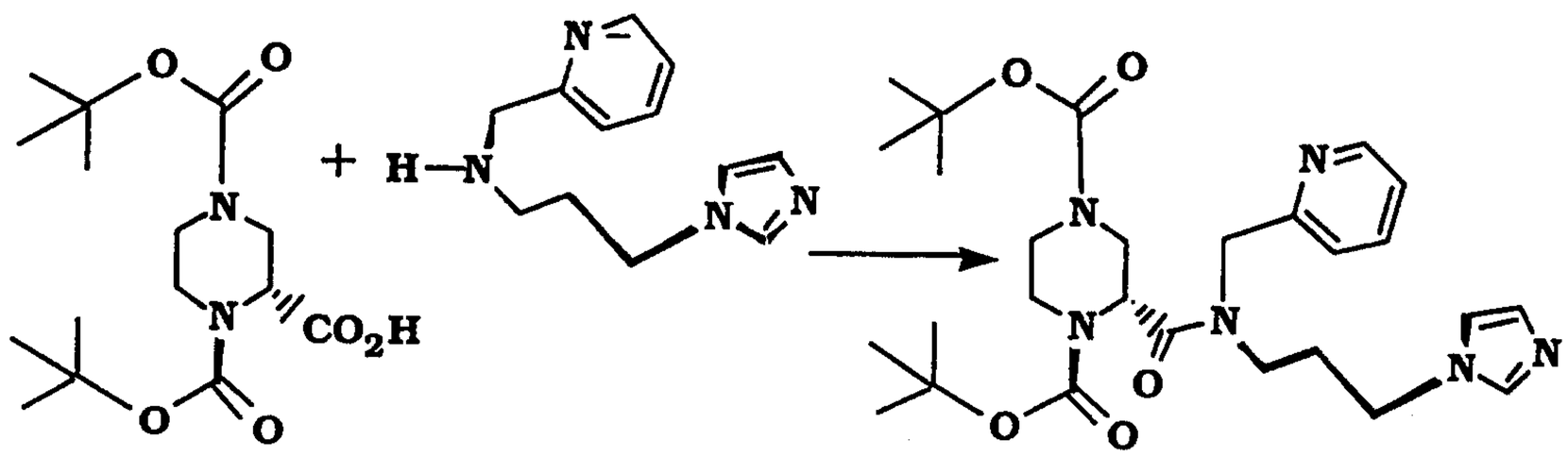
Step C



The title compound from Step B was dissolved in anhydrous CH_2Cl_2 (50 mL) and DMF (50 mL). To this was added the 8-Cl-tricyclic chloride (8.42 g, 31.8 mmol) and triethylamine (3 mL) and allowed to stir at room temperature for 48 h. The reaction mixture was concentrated *in vacuo*, diluted with EtOAc, washed with 3N NaOH and the organic phase was neutralized with 50% citric acid and dried over anhydrous Na_2SO_4. After filtration and concentration *in vacuo*, the residue was purified by flash column

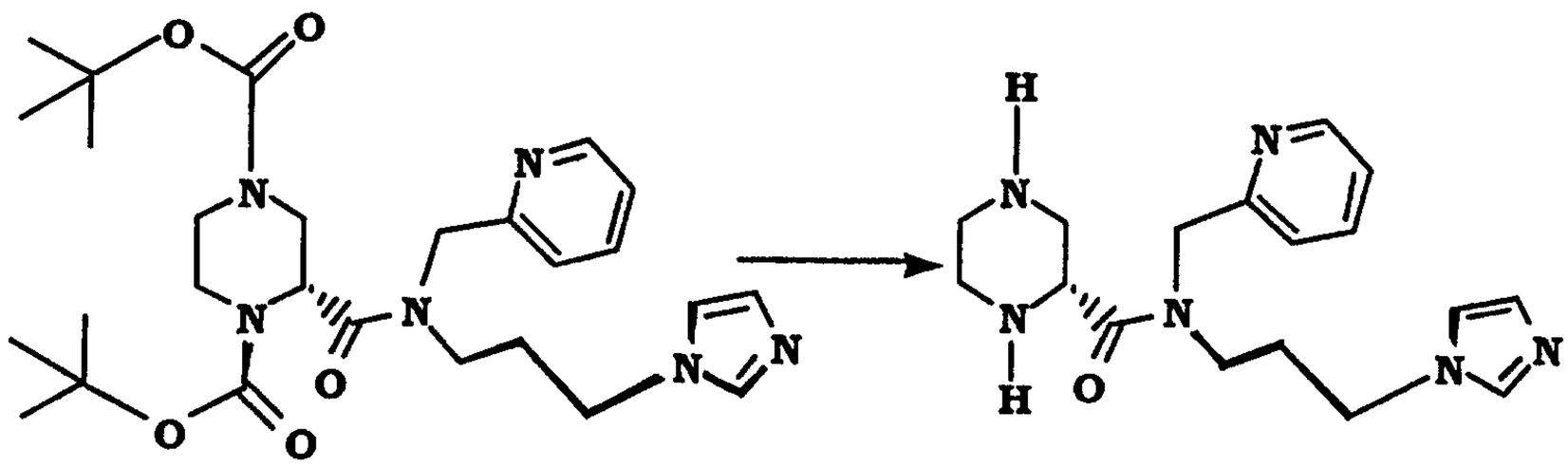
chromatography (silica gel) using 2-5% MeOH-CH_2Cl_2 to give the title compounds (11S,2R diastereomer A, 2.43 g, 27%, MH^+ = 485; and 11R,2R diastereomer B, 2.5 g, 30%, MH^+ = 484).

PREPARATIVE EXAMPLE 128



To the title compound from Preparative Example 43 (1.83 g, 5.6 mmol) were added HOBT (0.88 g, 6.5 mmol), DEC (1.24 g, 6.5 mmol), the title compound from Preparative Example 95 (1 g, 4.6 mmol), NMM (1.0 mL, 9.25 mmol) and anhydrous DMF (10 mL). The mixture was stirred at room temperature under N_2 overnight. The mixture was concentrated *in vacuo*, diluted with CH_2Cl_2 and washed with NaOH (aq). The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel) using 10% MeOH-CH_2Cl_2 saturated with aqueous ammonium hydroxide to give the title compound (0.70 g, 24%, MH^+ = 529).

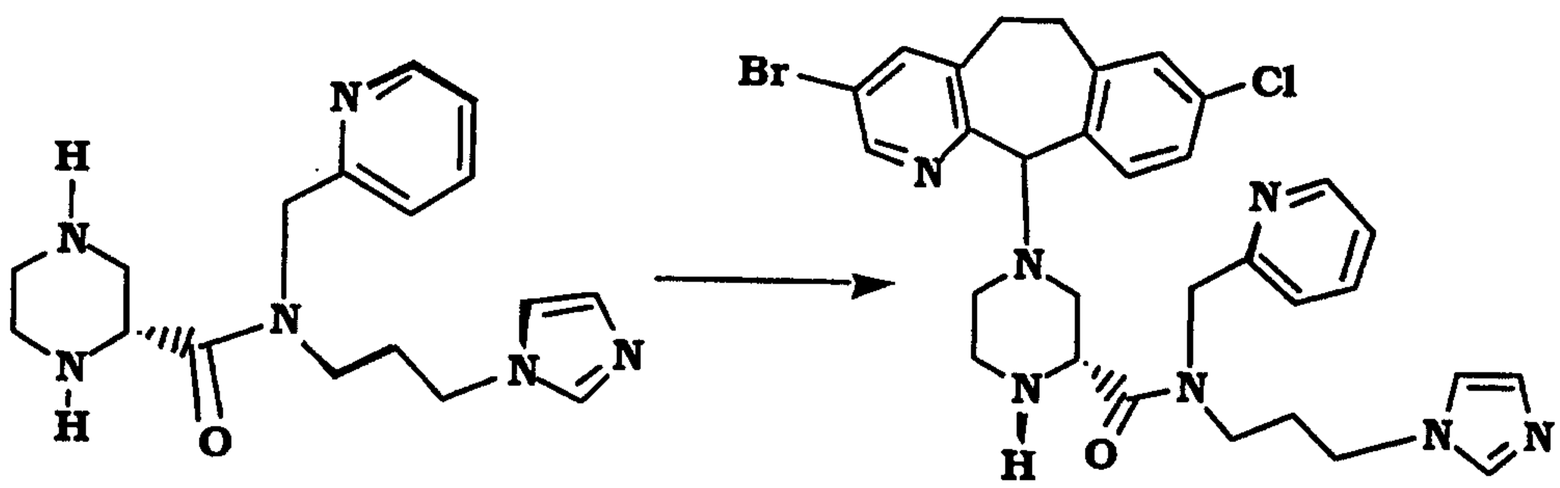
PREPARATIVE EXAMPLE 129



The title compound from Preparative Example 128 (0.70 g, 1.3 mmol), anhydrous CH_2Cl_2 (10 mL) and trifluoroacetic acid (10

mL) were stirred at room temperature for 12 h, then concentrated *in vacuo*. Aqueous NaOH (1N) was added dropwise to neutralize the reaction mixture and the resulting mixture was extracted with CH_2Cl_2. The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give a residue which was purified by flash column chromatography (silica gel) using 10% MeOH-CH_2Cl_2 saturated with aqueous ammonium hydroxide to give the title compound as a brown oil (232 mg, 53%, MH^+ = 329).

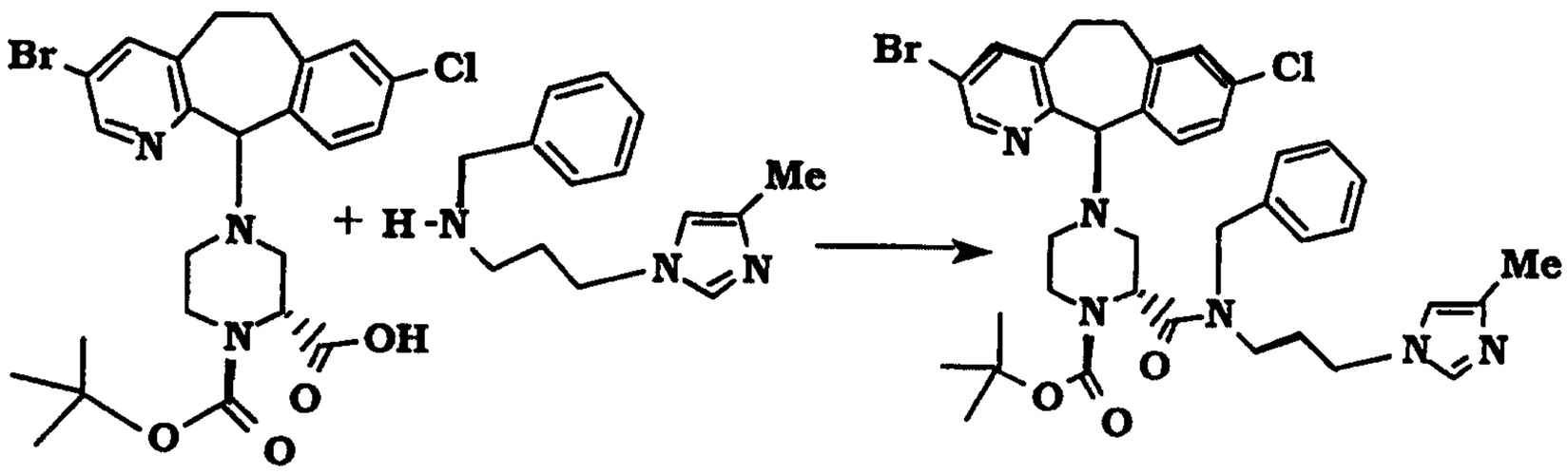
PREPARATIVE EXAMPLE 130



The title compound from Preparative Example 129 (0.20 g, 0.61 mmol) was dissolved in anhydrous DMF (5 mL). To this was added the tricyclic chloride (Compound No. 42.0) (0.2 g, 0.58 mmol) and triethylamine (0.43 mL, 3.0 mmol) and allowed to stir at room temperature for 12 h. The reaction mixture was poured into brine and extracted with EtOAc. The organic extract was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash column chromatography (silica gel) using 10% MeOH-CH_2Cl_2 saturated with aqueous ammonium hydroxide afforded the title compound (100 mg, 27%, MH^+ = 634).

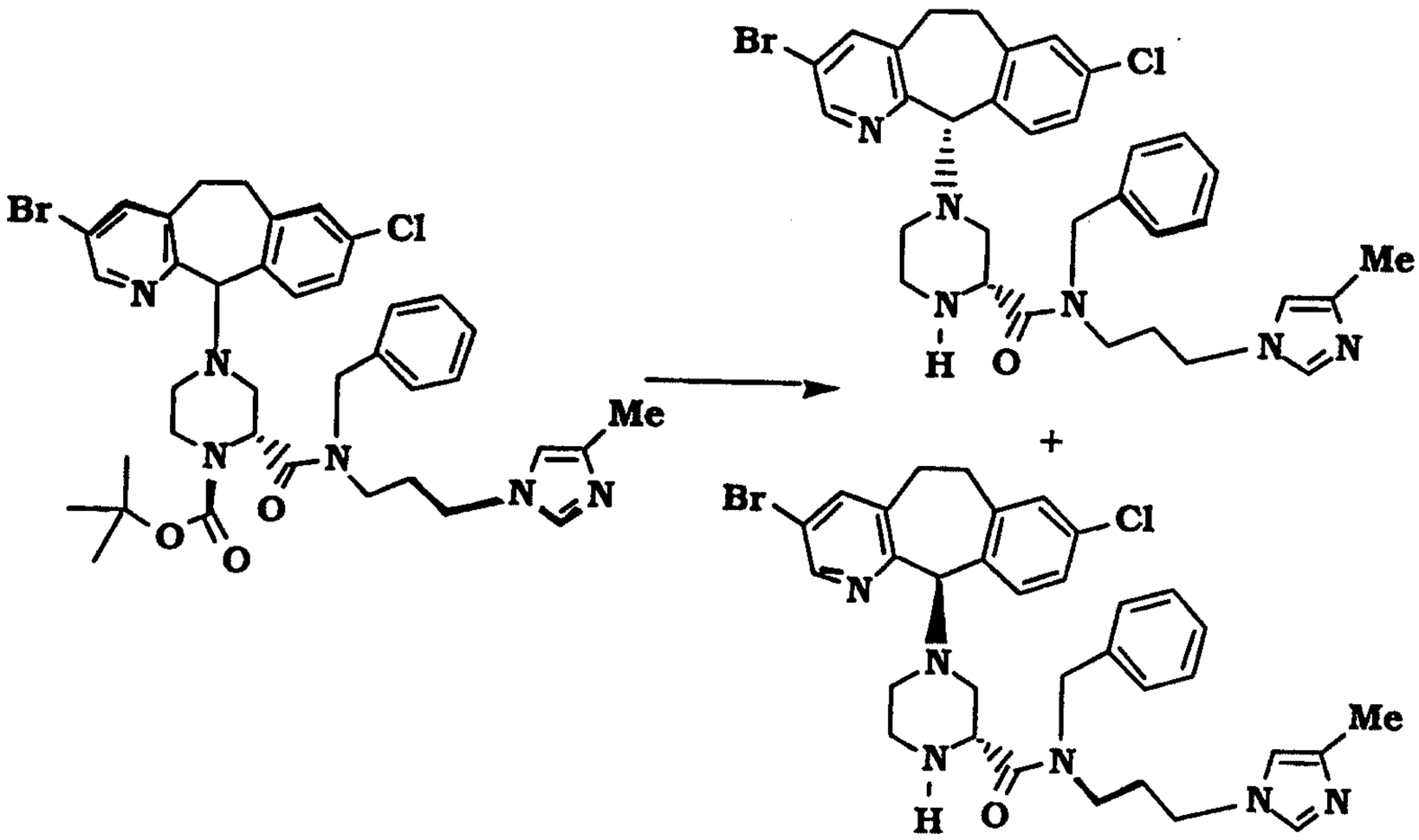
PREPARATIVE EXAMPLE 131

Step A



To the title compound from Preparative Example 51 (1.4 g, 70% purity, 1.8 mmol) and CH_2Cl_2 (10 mL) cooled to °C were added triethylamine (0.5 mL, 3.6 mmol) and isobutyl chloro-formate (0.25 mL, 1.9 mmol). After stirring the mixture at 0°C for 3 h, the title compound from Preparative Example 95.1 (0.4 g, 1.7 mmol, isolated by preparative chiral chromatography (Chiralpack AD, 5 cm X 50 cm column, flow rate 80 mL/min, 8% IPA +92% Hexane +0.2% diethylamine) was added and the mixture was stirred at room temperature under N_2 overnight. The mixture was washed with 1*M* NaOH(aq) and the organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel) using 2-5% MeOH-CH_2Cl_2 saturated with aqueous ammonium hydroxide to give the title compound as a mixture of diastereomers (0.45 g, 34%, MH^+ = 747).

Step B

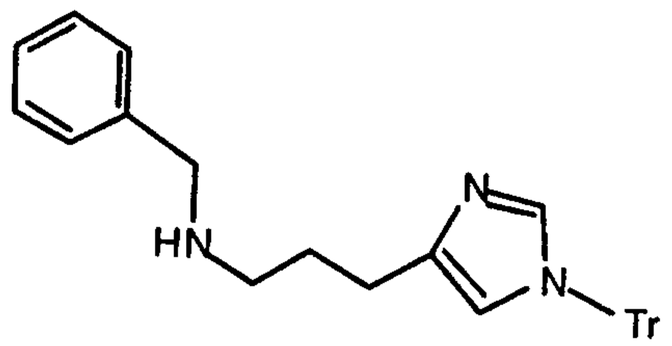


To a solution of the title compound from Step A (0.45, 0.60 mmol) dissolved in anhydrous CH_2Cl_2 (5 mL) was added TFA (5 mL). The solution was stirred at room temperature under N_2 overnight, then concentrated *in vacuo*, diluted with CH_2Cl_2, washed with 1N NaOH (aq) and dried over anhydrous Na_2SO_4. The mixture was filtered, concentrated *in vacuo* and purified by flash column chromatography (silica gel) using 2-5% MeOH-CH_2Cl_2 saturated with aqueous ammonium hydroxide to give the title compound as a mixture of diastereomers. The diastereomers were separated by preparative chiral chromatography (Chiralpack AD, 5 cm X 50 cm column, flow rate 80 mL/min., 60% IPA + 40% hexane +0.2% diethylamine) to give 0.11 g of diastereomer A and 0.23 g of diastereomer B.

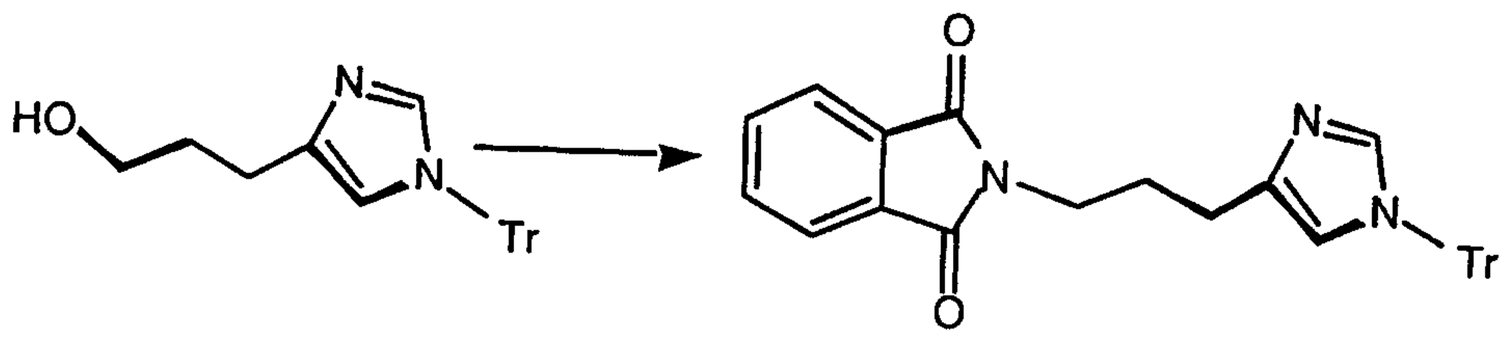
Physical chemical data for the 11S,2R(-)-diastereomer A: MH^+ = 647; $[\alpha]^{20}_D$= -45.4° (2.91 mg/2 mL MeOH).

Physical chemical data for the 11R,2R(-)-diastereomer B: MH^+ = 647; $[\alpha]^{20}_D$= -23.5° (2.21 mg/2 mL MeOH).

PREPARATIVE EXAMPLE 132

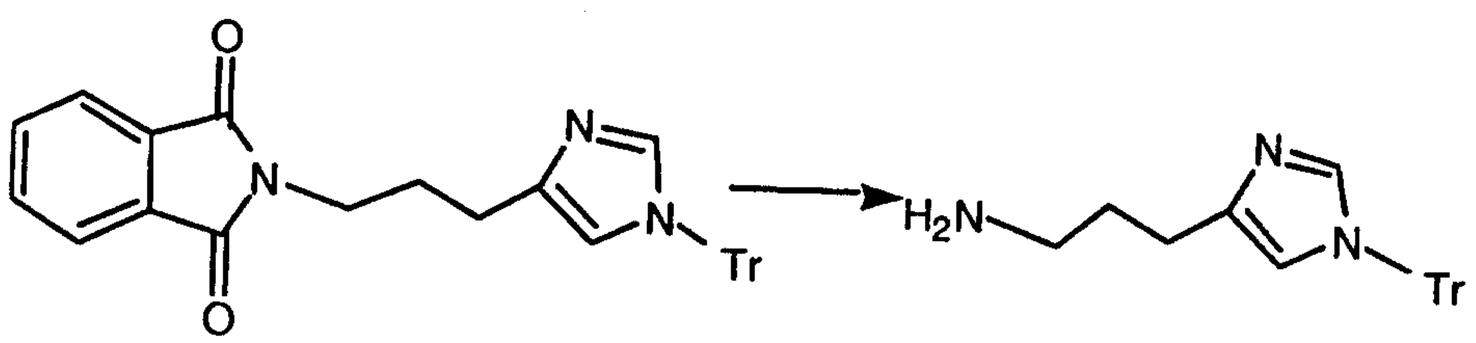


Step A



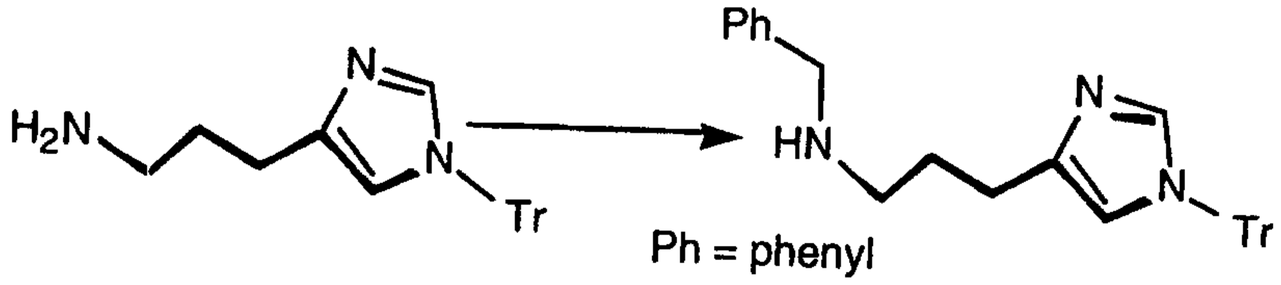
To a stirred solution of 1-(triphenylmethyl-1H-imidazol-4-yl)-3-hydroxypropane (WO 9629315) (5.04g, 13.68 mmoles), phthalimide (2g, 13.6 mmoles) and triphenyl phosphine (3.57g, 13.6 mmoles) in THF (100 mL) at 0°C was added diethyl azodicarboxylate (2.14 mL, 13.6 mmoles) dropwise. The reaction mixture stirred for 1h at 0°C and then at room temperature for 16h. Filtered to give the title compound (4.6g, 100%), CIMS: m/z (MH^+) = 498 ; δ_H ($CDCl_3$) 1.72 (bs, 1H), 1.9 (m, 1H), 2.05 (m, 1H), 2.6 (m, 1H), 3.75 (m, 2H), 6.6- 7.8 (m, 21H).

Step B



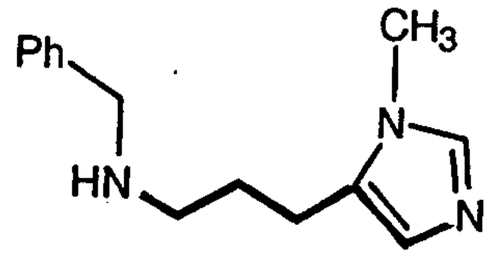
The title compound from Step A (2g, 4.02 mmoles) and hydrazinehydrate (3.89 mL, 80.39 mmoles) were heated under reflux in ethanol (80 mL) for 16h. The solids were filtered off and the filtrate was evaporated to give the title compound (1.35g, 91%), CIMS: m/z (MH^+) 368; δ_H ($CDCl_3$) 1.8-1.85 (m, 2H), 2.6-2.62 (m, 2H), 2.8-2.83 (m, 2H), 7.1(s, 1H), 7.3 (s, 1H).

Step C

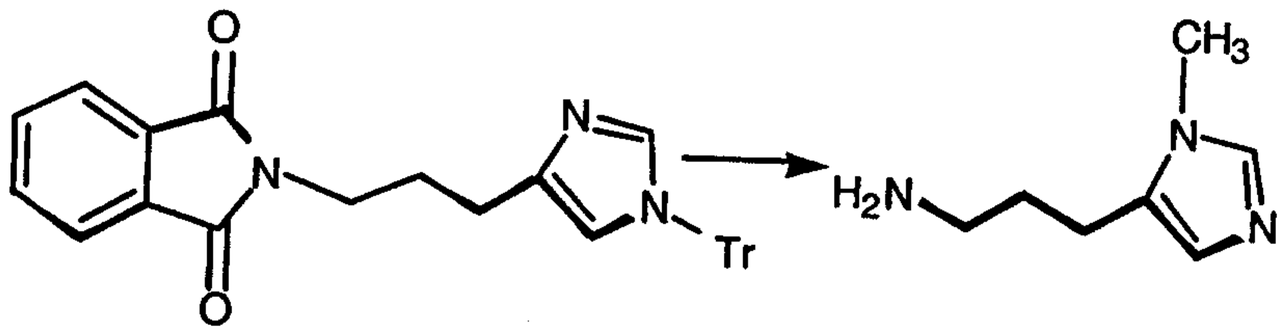


To a stirred solution of the title compound from Step B (1.5g, 4.08 mmoles) and benzaldehyde (0.433g, 4.08 mmoles) was added sodium cyanoborohydride (0.256g, 4.08 mmoles). The pH of the solution was adjusted to ~4.25 with acetic acid. The reaction mixture was then stirred for 2h. The pH was then adjusted to 11.5 with 50% NaOH and extracted with ethyl acetate. The ethyl acetate extract was washed with water and brine and dried ($MgSO_4$) Evaporated to give a crude residue which was chromatographed on silica gel using 4% (10% conc NH_4OH in methanol)-CH_2Cl_2 as the eluant to give the title compound (1.04 g, 78%), CIMS: m/z (MH^+) = 458; δ_H ($CDCl_3$) 1.8-1.82 (m, 2H), 2.58-2.64 (m, 4H), 3.6 (s, 2H), 6.5 (s, 1H), 7.15-7.4 (m, 6H).

PREPARATIVE EXAMPLE 133



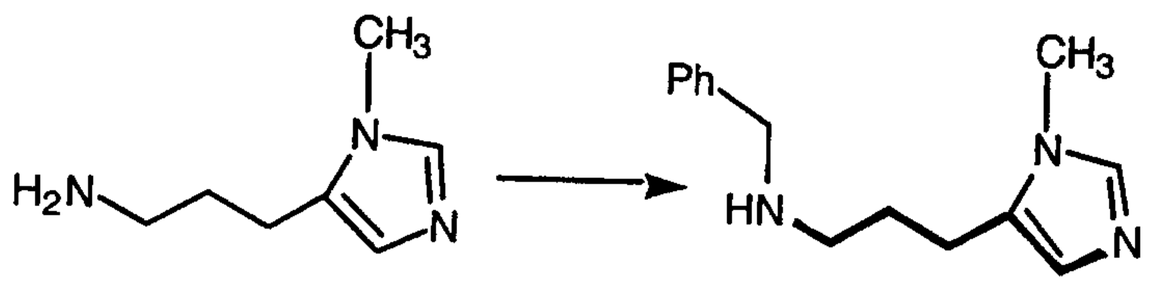
Step A



The title compound from Preparative Example 132 Step A (2g, 4.1 mmoles) in CH_2Cl_2 (20 mL) was treated with methyl iodide (0.75 mL 12.05 mmoles) and stirred for 16h. Evaporated to dryness to a gummy residue which was then refluxed with 6N HCl (25 mL) for 16h. Evaporation to dryness gave a semisolid which was

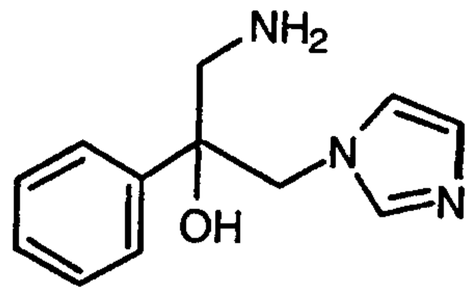
neutralized with aqueous $NaHCO_3$ and evaporation to dryness again gave semi-white solids. Stirred with CH_2Cl_2 (100 mL)and MeOH (50 mL) and filtered off the solids. The filtrate was evaporated to give the title compound (0.3g), CIMS: m/z (MH^+) 140; δ_H ($CDCl_3$) 1.8 (m, 2H), 2.6-2.8 (m, 4H), 3.6 (s, 3H), 6.68 (s, 1H), 7.4 (s, 1H).

Step B

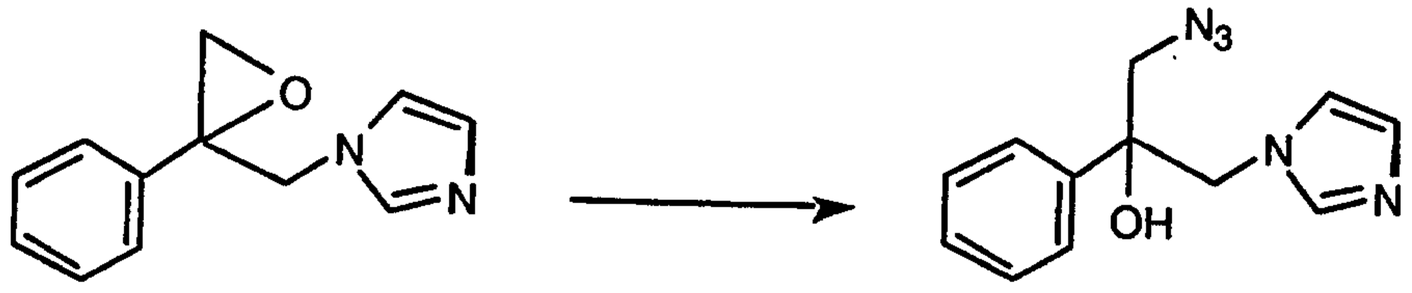


The title compound from Step A (1.97g 14.14 mmoles), benzaldehyde (1.65g 15.55mmoles), sodium acetate (1.1g, 13.42 mmoles) and 3Å molecular sieves (2g) in methanol were stirred for 18h. To this sodium borohydride (0.519g 13.72 mmoles) was added and stirred for 4h. The solids were filtered off and the filtrate was evaporated to a residue which was chromatographed to give the title compound (0.59g 18.5%) CIMS: m/z (MH^+) 230; δ_H ($CDCl_3$)1.8 (q, 2H), 2.6 (t, 2H), 2.65 (t, 2H), 3.25 (s, 3H), 3.8 (s, 2H), 7.2-7.4 (m, 7H).

PREPARATIVE EXAMPLE 134



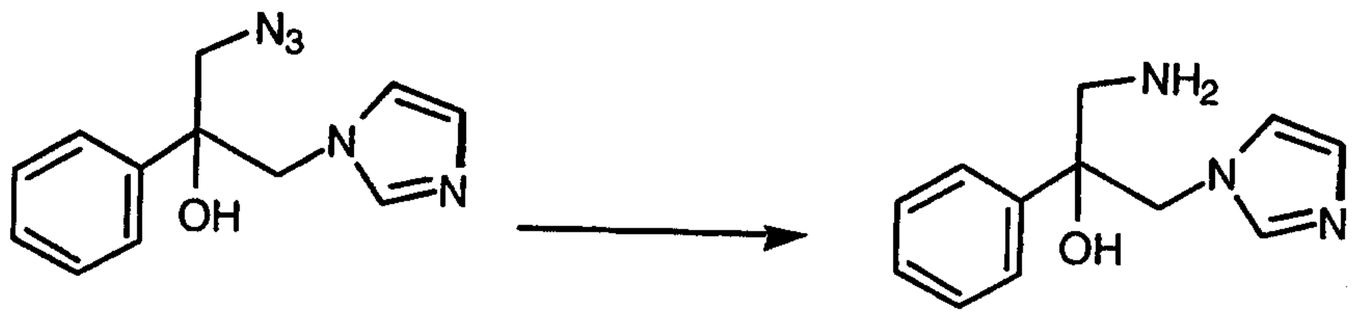
Step A



1-(2-Phenyl-2,3-epoxypropyl)-1H-imidazole (GB 2 099818 A) (2.15g, 10.85 mmoles) and sodium azide (1.41g, 21.71 mmoles)

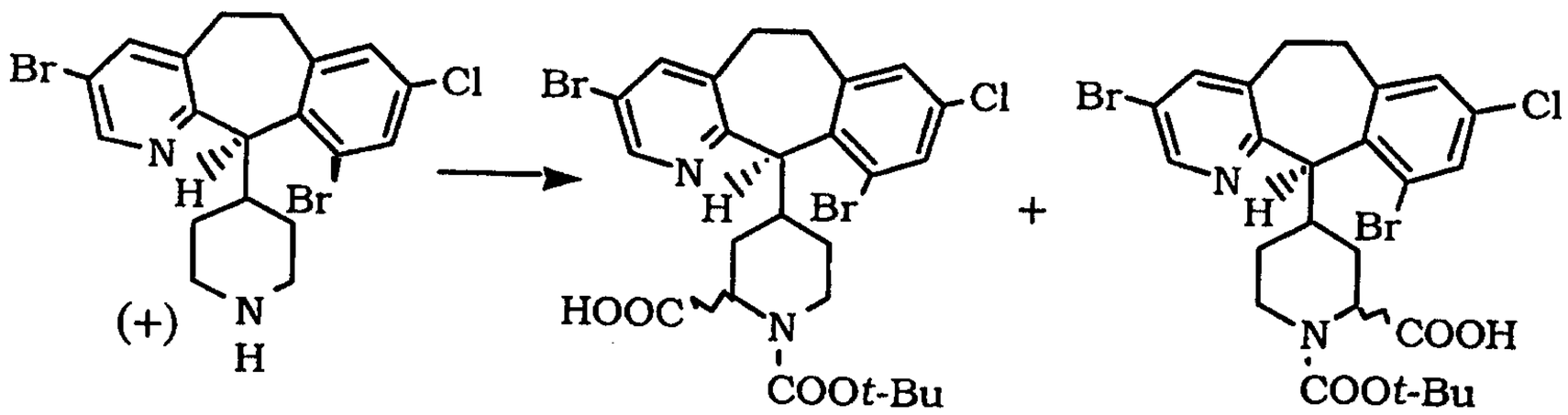
were heated in DMF (20 mL) at 60°C for 16h. Evaporated to dryness and extracted with CH_2Cl_2, washed with brine and dried ($MgSO_4$). Evaporated to give the title compound (0.932g, 36%), CIMS: m/z (MH^+) = 244; δ_H ($CDCl_3$) 3.7 (q, 2H0, 4.5 (dd, 2H), 6.6 (s, 1H), 6.95 (s, 1H), 7.3-7.45 (m, 5H), 8.2 (s, 1H).

Step B



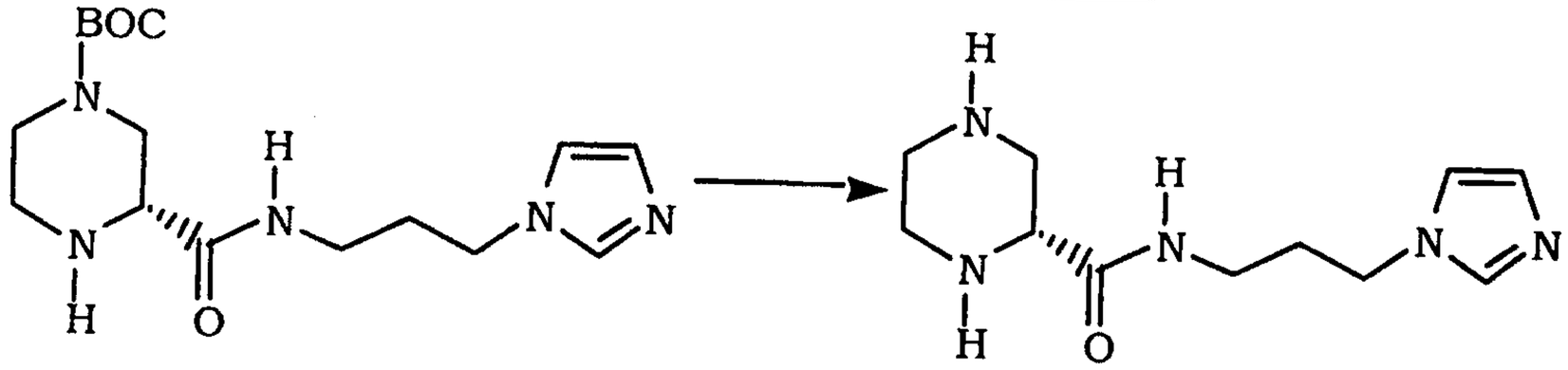
The title compound from Step A (0.8g, 3.31 mmoles) in ethanol (15 mL) was hydrogenated over 10% Pd on carbon (0.2g) at 50 psi overnight. The catalyst was filtered off and evaporated to give the title compound (0.71g 98%). CIMS: m/z (MH^+) = 218.

PREPARATIVE EXAMPLE 135



By following Steps a to e of Preparative Example 41 starting with the (+) isomer, a mixture of the title compounds A and B is obtained as a light tan solid that appears as a single tlc spot: ^{1}NMR ($CDCl_3$, 300 MHz) δ 1.42 (s, 9H), 4.85 (m, 2H), 7.12 (s, 1H), 7.50 (s, 1H), 7.55 (s, 1H), 8.48 (m, 1H); HRMS (FAB) calcd for $C_{25}H_{28}N_2O_4BrCl^{81}Br$ 615.0084, found 615.0092.

PREPARATIVE EXAMPLE 136

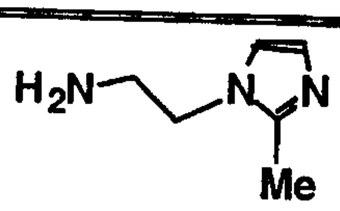
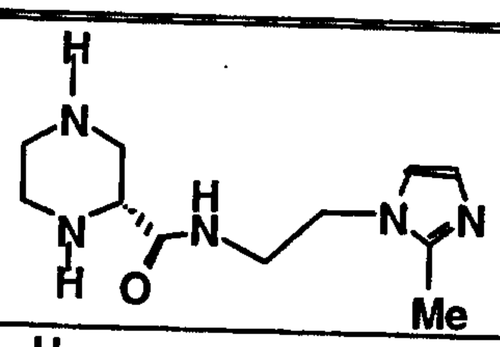
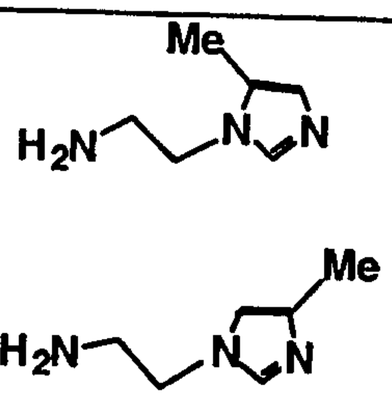
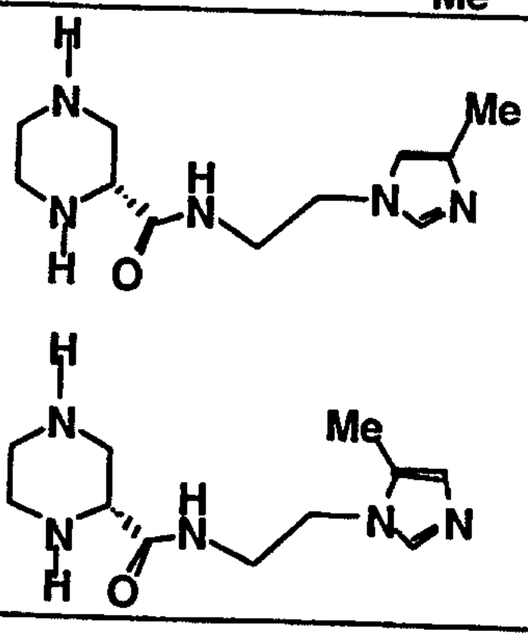


Following the procedure set forth in Preparative Example 123, but using the title compound from Preparative Example 37 Step A. the title compound was obtained (quantitative yield; $MH^+ = 338$).

PREPARATIVE EXAMPLES 137-138

Following the procedure described for Preparative Example 106, the piperazines listed in Table 5A below were prepared using the corresponding amines.

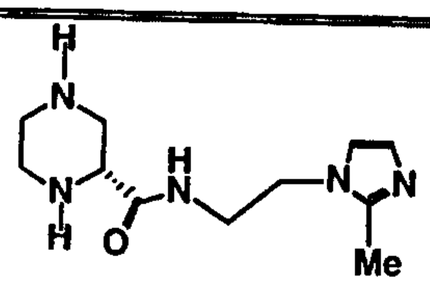
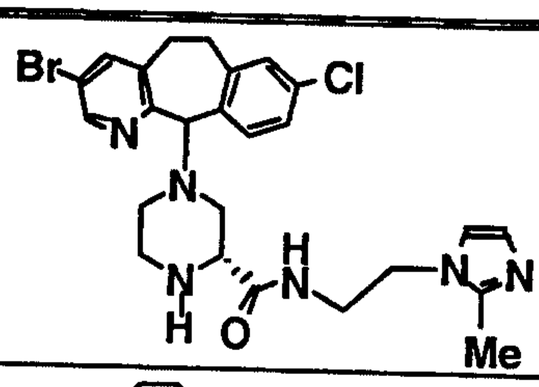
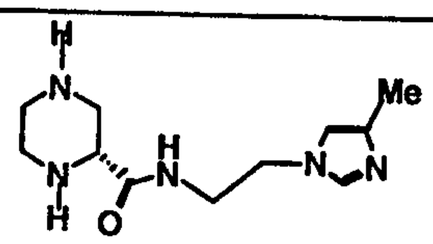
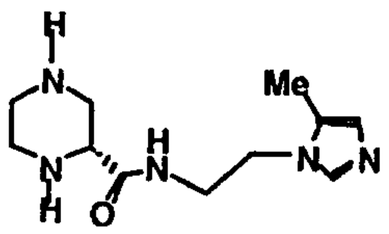
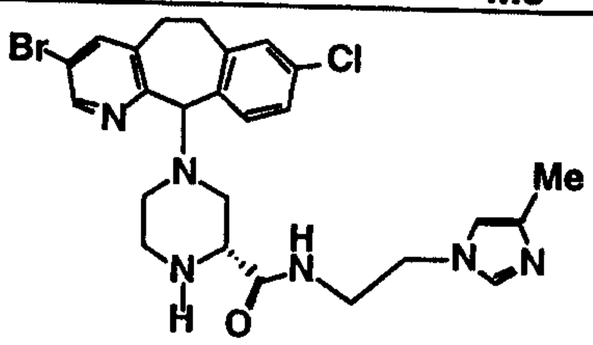
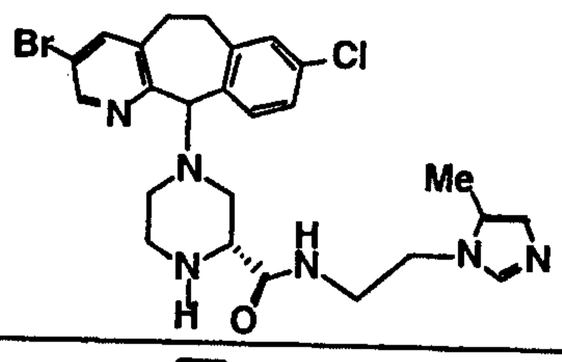
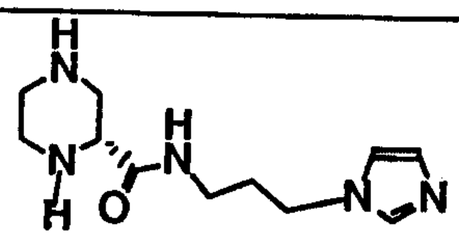
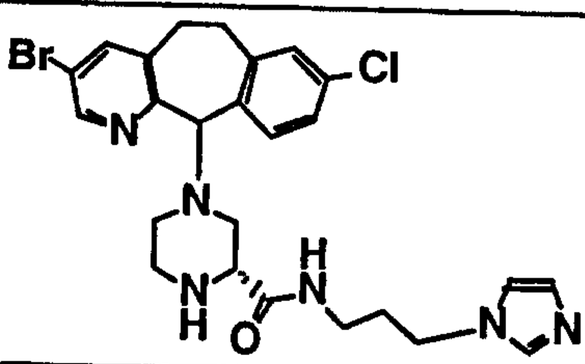
TABLE 5A

Prep. Ex.	Amine	Product	yield (%)	MH^+
137			47	238
138			100	238

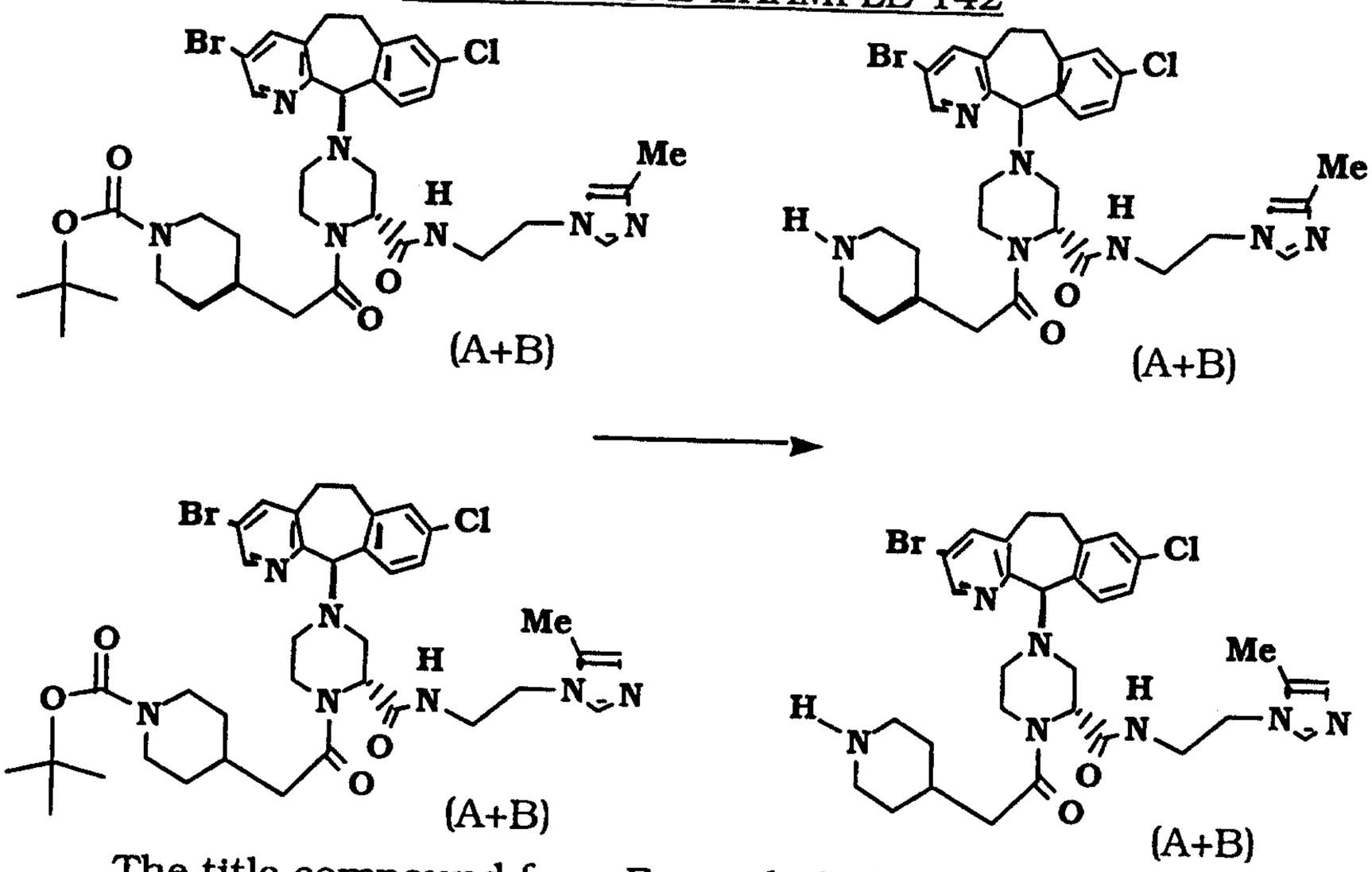
PREPARATIVE EXAMPLES 139-141

Similarly, using the procedure described for Preparative Example 110 and the piperazines listed in the Table 5B below, the corresponding tricyclic amines were prepared.

TABLE 5B

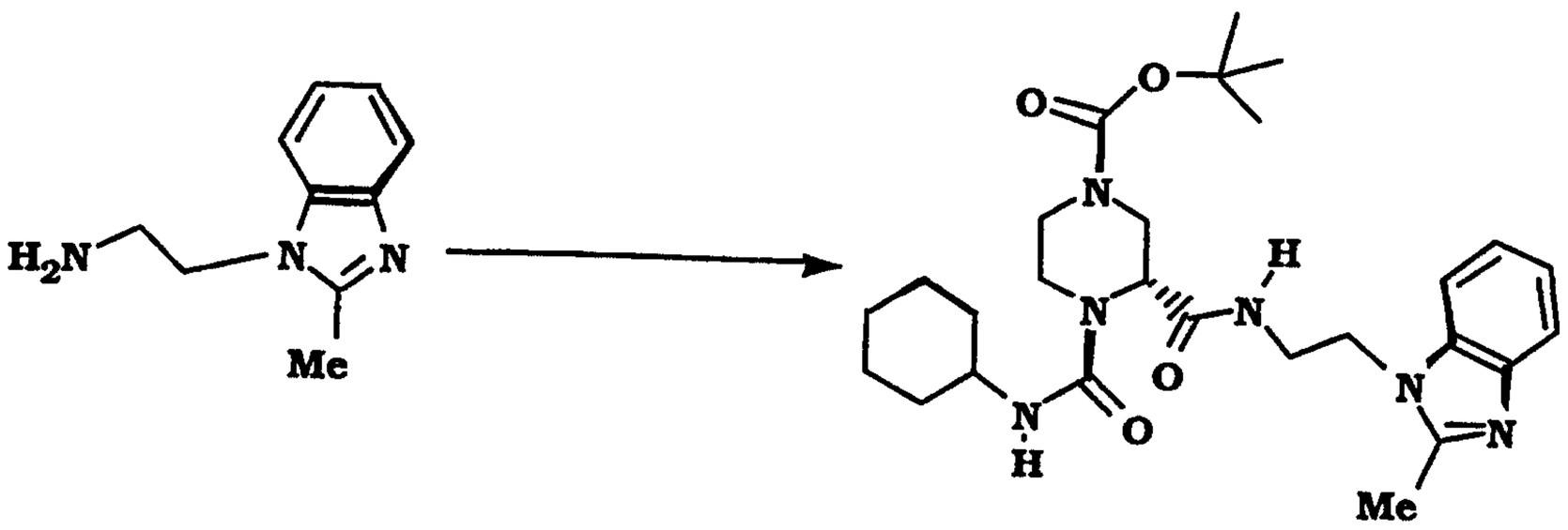
Prep. Ex.	Piperazine	Product	yield (%)	MH^+
139			73	543
140	 	 	34	543
141			31	543

PREPARATIVE EXAMPLE 142



The title compound from Example 289 (0.39 g, 0.51 mmol), anhydrous CH_2Cl_2 (3 mL) and trifluoroacetic acid (3 mL) were stirred at room temperature for 2 h, then concentrated *in vacuo*. Aqueous NaOH (1N) was added dropwise to neutralize the reaction mixture and the resulting mixture was extracted with CH_2Cl_2. The organic phase was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give a residue which was purified by flash column chromatography (silica gel) using 5% MeOH-CH_2Cl_2 saturated with aqueous ammonium hydroxide to give the title compound as an off-white solid (52 mg, 15%, mp = 150°C, MH^+ = 768).

PREPARATIVE EXAMPLE 143

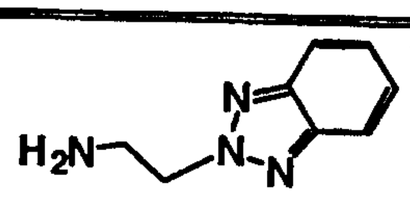
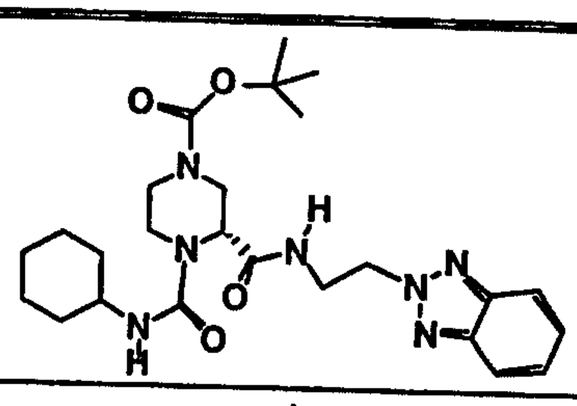
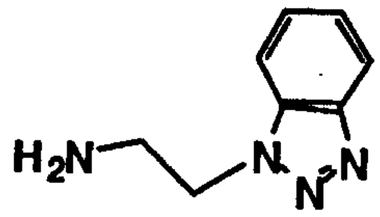
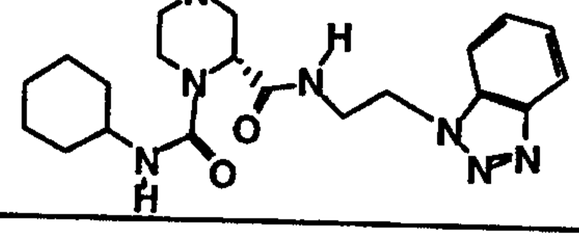


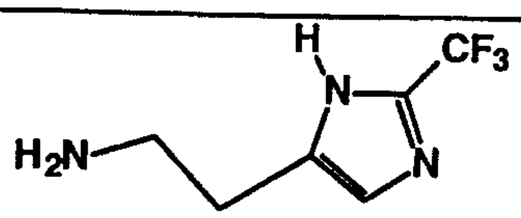
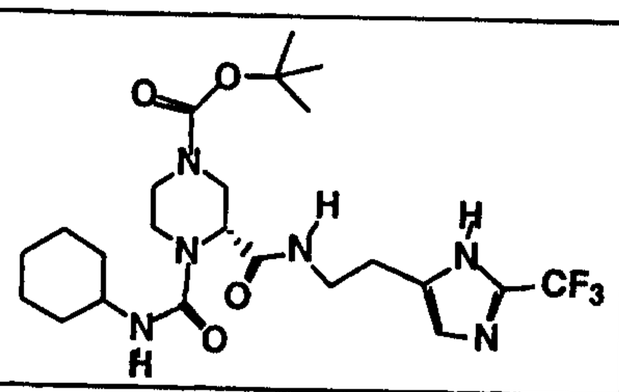
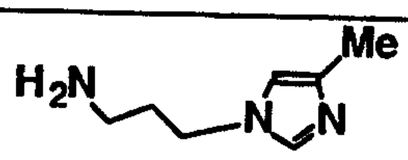
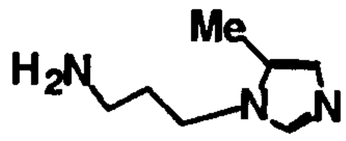
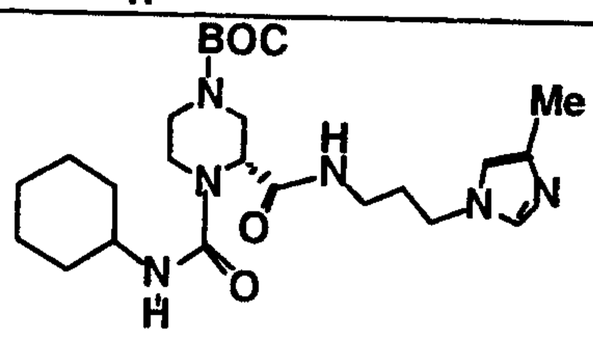
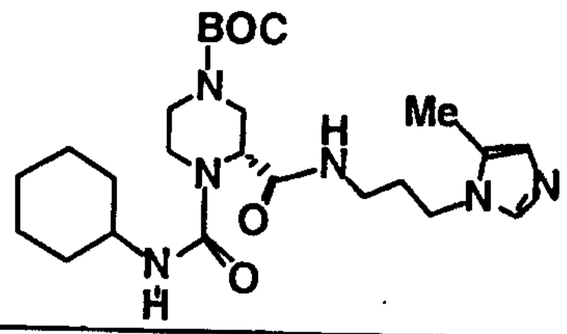
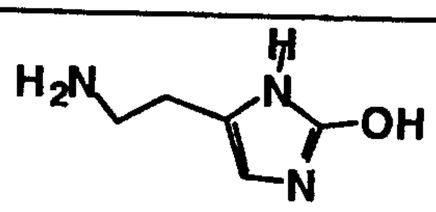
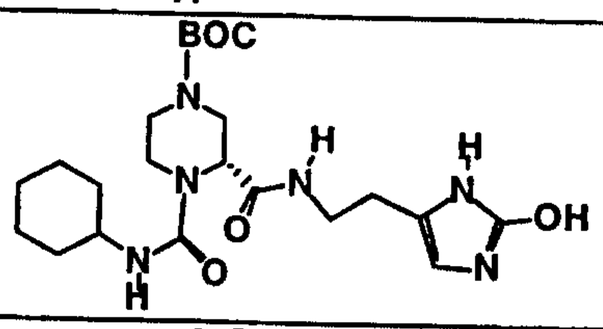
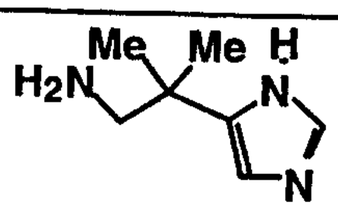
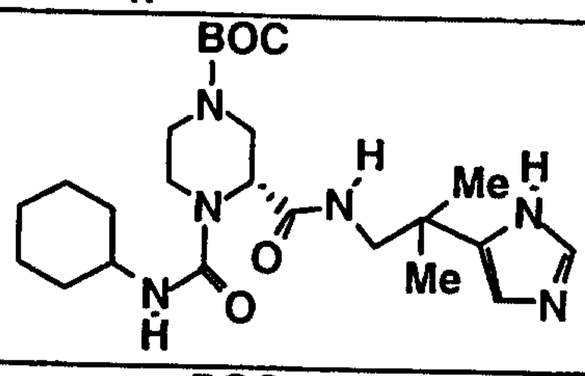
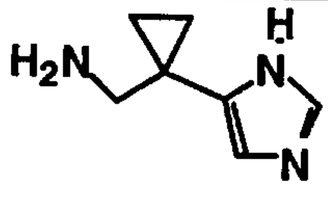
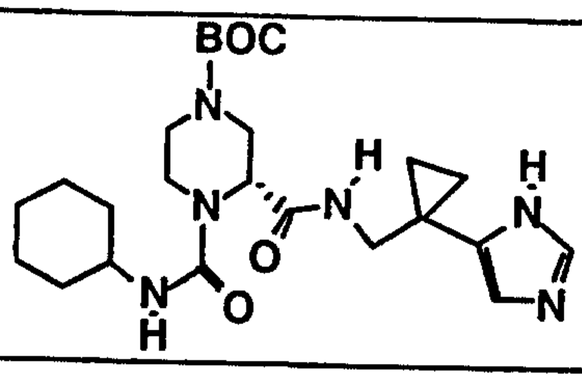
A solution of the title compound from Preparative Example 71 (0.9 g, 5.14 mmol) and the anhydride from Preparative Example 44 (1.38 g, 1.05 eq) dissolved in anhydrous dichloromethane (10 ml) was stirred at room temperature overnight. Additional anhydride (0.105 g) was added and after 1 hr cyclohexyl isocyanate (0.98 mL, 7.71 mmol) was added to the reaction mixture which was stirred for an additional 1.5 hrs. Concentration *in vacuo* and purification by flash column chromatography (silica gel) using 1-3% MeOH-CH_2Cl_2 saturated with ammonium hydroxide as eluent afforded the title compound as a white solid (1.82 g, 69%, mp = 126.9-128.9 °C, MH^+ = 513).

PREPARATIVE EXAMPLES 144-149

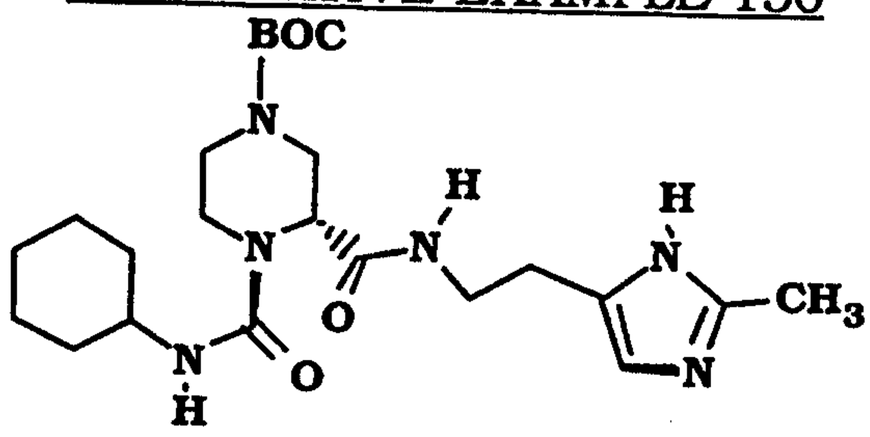
Following essentially the same procedure as that described for Preparative Example 143, the BOC-protected piperazines listed in Table 5C below were prepared using the corresponding amines.

TABLE 5C

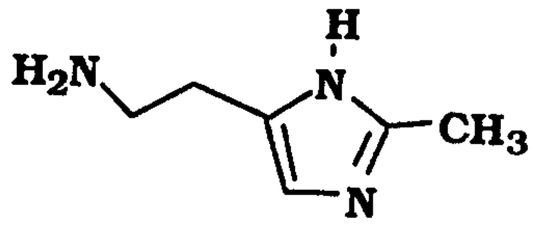
Prep. Ex.	Amine	Product	yield (%)	MH^+
144			100	500
145			100	500

146			57	517
147	 	 	100	477
149			58	465
149A			----	----
149B			----	----

PREPARATIVE EXAMPLE 150

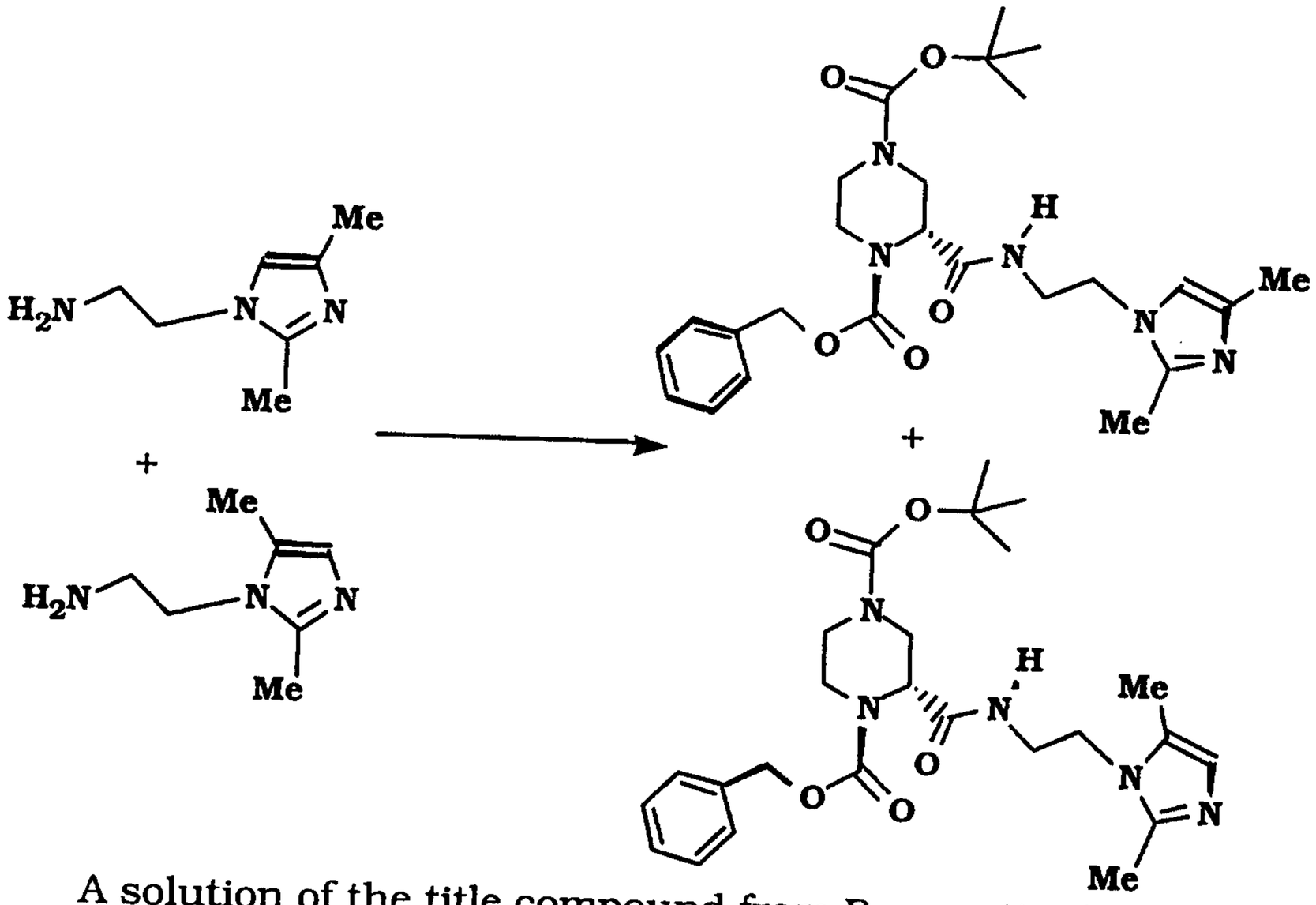


If one were to follow essentially the same procedure as that described for Preparative Example 143, but using the amine



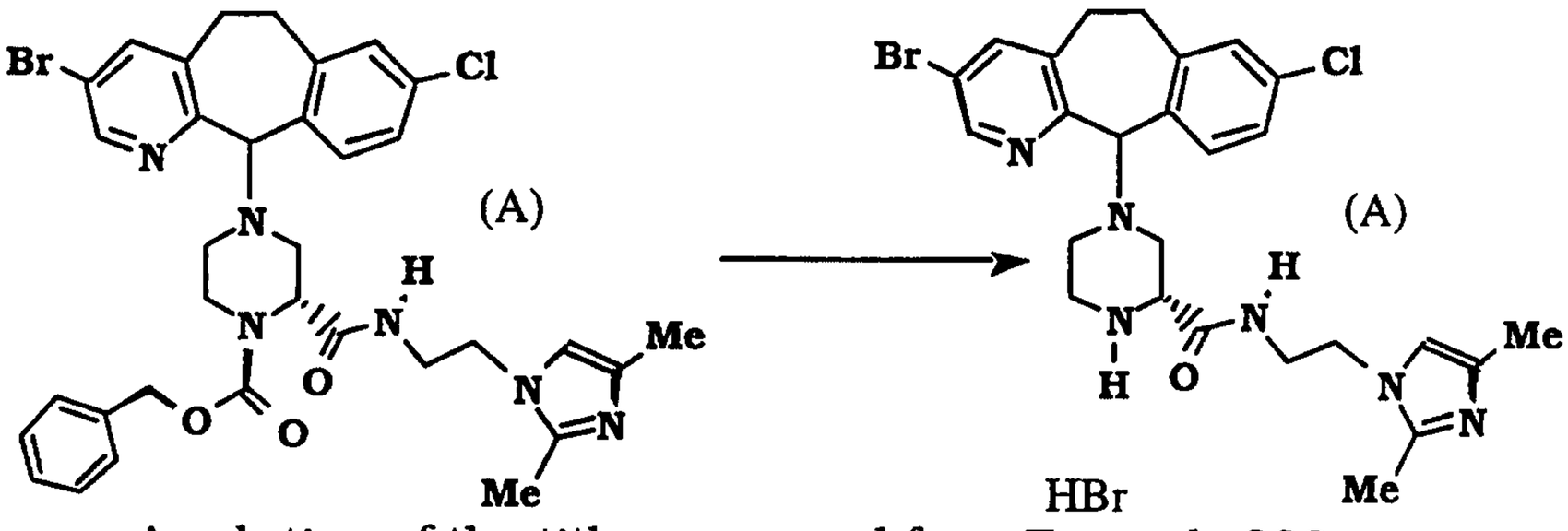
instead of the amine from Preparative Example 71, the title compound would be obtained.

PREPARATIVE EXAMPLE 151



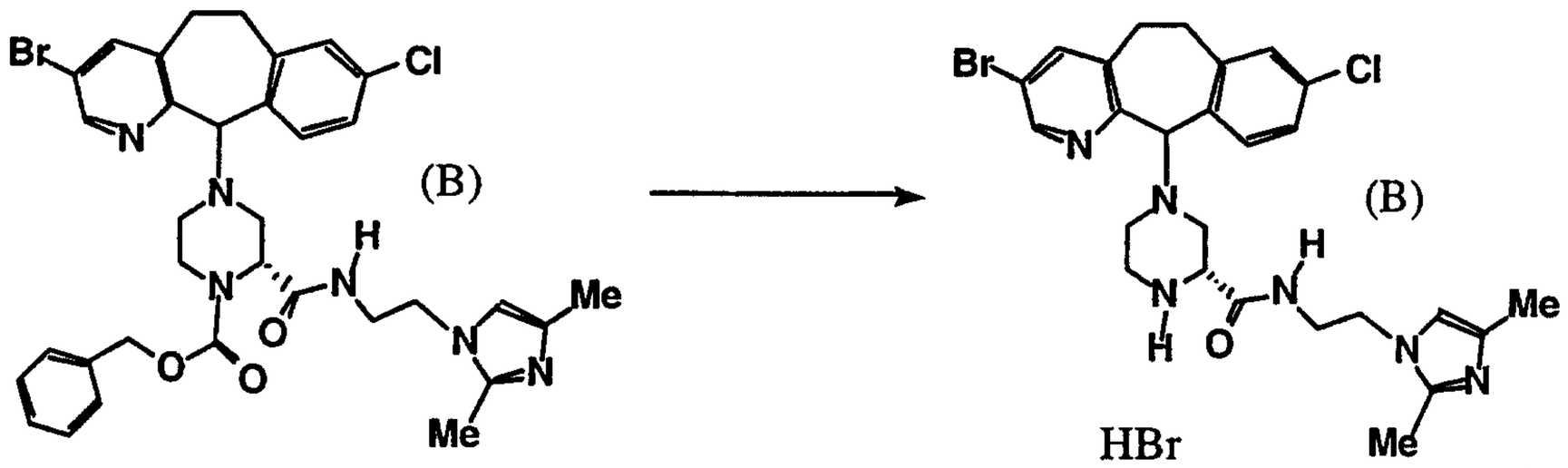
A solution of the title compound from Preparative Example 68 (2.12 g, 15.2 mmol), triethylamine (30.4 mmol) and the anhydride from Preparative Example 44 (3.89 g, 15.2 mmol) dissolved in anhydrous dichloromethane (30 ml) was stirred at room temperature for 30 min. Benzyloxycarbonylsuccinimide (4.17 g, 16.7 mmol) was added and the resulting mixture was stirred at room temperature overnight. Concentration *in vacuo* and purification by flash column chromatography (silica gel) using 2% MeOH-CH_2Cl_2 saturated with ammonium hydroxide as eluent afforded the title compounds (2.57 g, 35%). The regioisomers were separated by HPLC (Chiracel AD column) using 5% isopropanol-95% hexane-0.2% diethylamine to give the 2,4-dimethyl isomer (mp = 64.2°C, MH^+ = 486) and the 2,5-dimethyl isomer (mp = 71.5 °C, MH^+ = 486).

PREPARATIVE EXAMPLE 152



A solution of the title compound from Example 293 diastereomer A (0.386 g, 0.56 mmol), glacial acetic acid (3 mL) and 33% HBr in acetic acid (1 mL) was stirred at room for 2 hr. Diethyl ether was added and the precipitate filtered and dried under *vacuo* to afford the title compound (0.48 g, 100%, MH^+ = 557.

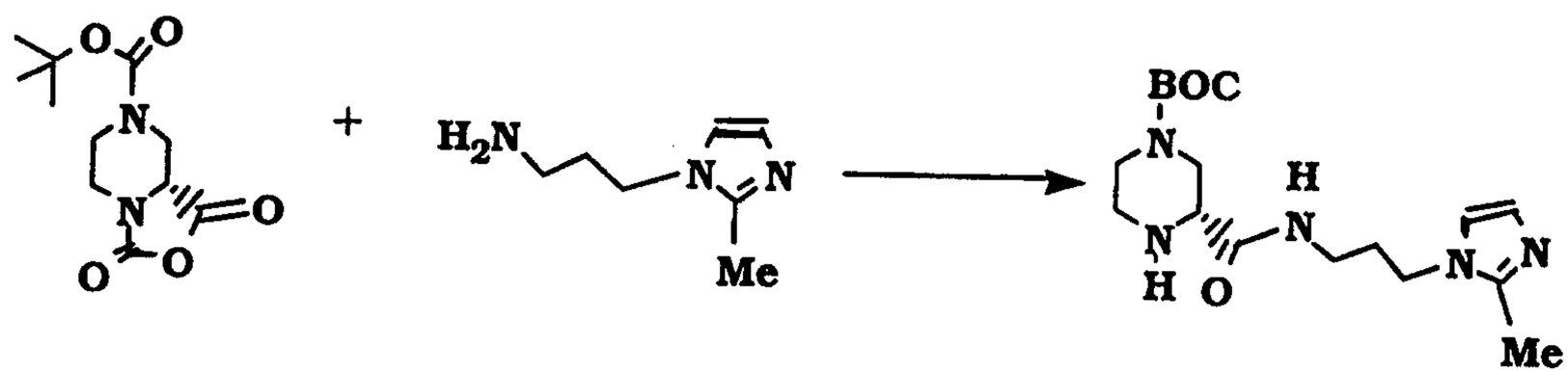
PREPARATIVE EXAMPLE 153



A solution of the title compound from Example 293 diastereomer B (0.372 g), glacial acetic acid (3 mL) and 33% HBr in acetic acid (1 mL) was stirred at room for 2 hr. Diethyl ether was added and the precipitate filtered and dried *in vacuo* to afford the title compound (0.433 g, 100%, MH^+ = 557.

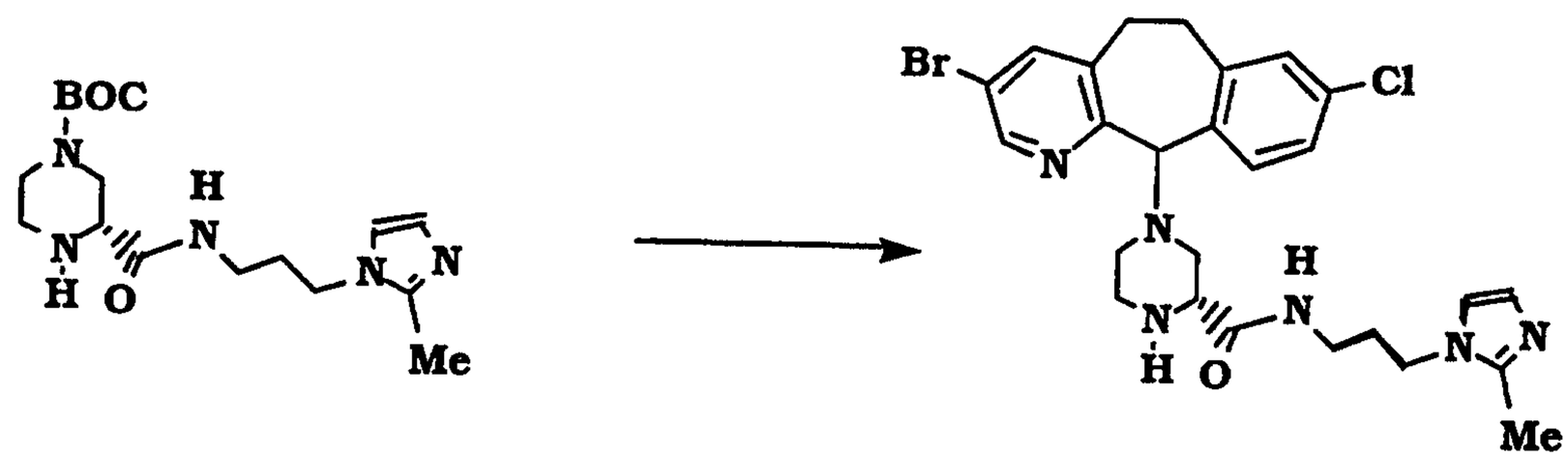
PREPARATIVE EXAMPLE 154

Step A



A mixture of the title compound from Preparative Example 66 (1.0 g, 7.2 mmol), the anhydride from Preparative Example 44 (2.2 g, 8.6 mmol), triethyl amine (1.5 mL, 10.8 mmol) and anhydrous CH_2Cl_2 (10 mL) was stirred at room temperature for 12 hrs. The mixture was concentrated *in vacuo*, diluted with CH_2Cl_2 and washed with a saturated aqueous solution of $NaHCO_3$. The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*.

Step B

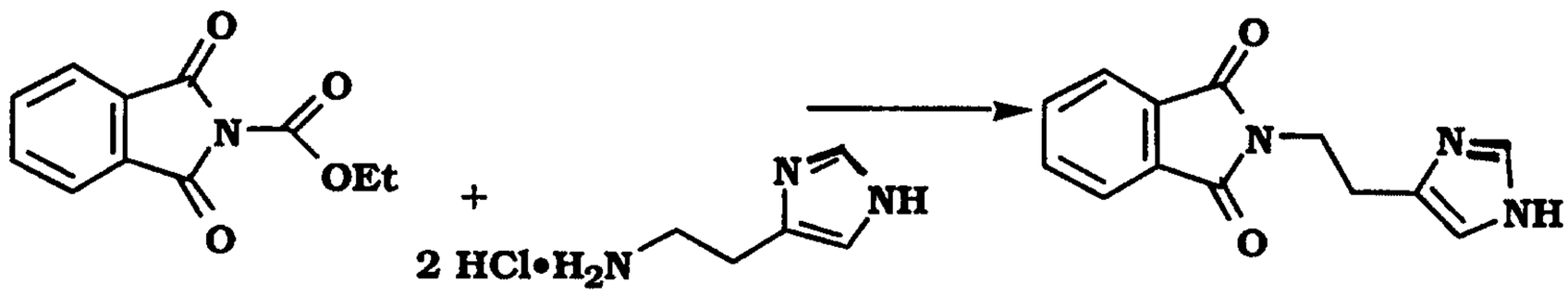


Trifluoroacetic acid (10 mL) was added to the title compound from Step A above (1.0 g, 7.2 mmol) dissolved in CH_2Cl_2 (10 mL) and the resulting mixture was stirred for 5 hrs at 25°C. The mixture was concentrated *in vacuo*, diluted with CH_2Cl_2 (50 mL) and combined with the tricyclic chloride (compound # 42.0) (2.7 g, 7.9 mmol) and triethylamine (5-10 mL) and stirred at room temperature overnight. The mixture was concentrated *in vacuo*, diluted with CH_2Cl_2 and washed with a saturated aqueous solution of $NaHCO_3$. The organic phase was dried over anhydrous Na_2SO_4, filtered, concentrated *in vacuo* and purified by flash column chromatography

(silica gel) using 5% MeOH-CH_2Cl_2 saturated with aqueous ammonium hydroxide to give the title compound as a mixture of diastereomers (1.9 g, 47%, MH^+ = 557).

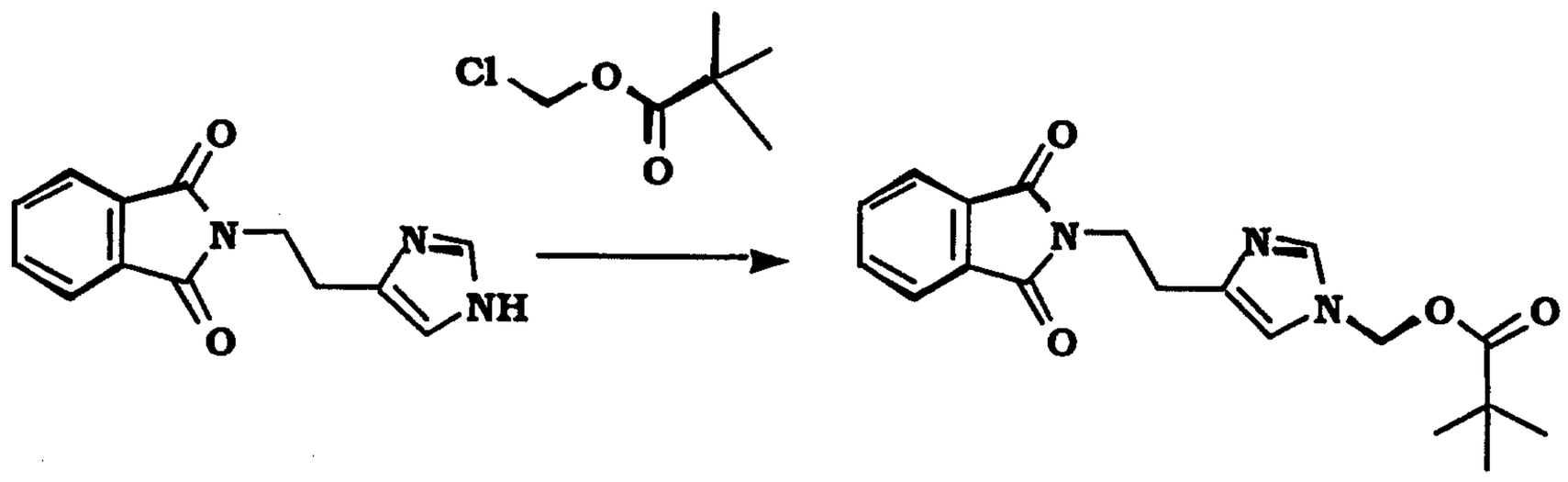
PREPARATIVE EXAMPLE 155

Step A



N-Carbethoxyphthalimide (62.8 g, 0.275 mol, 1.1 eq.) was added portionwise over a period of 30 minutes to a stirred solution of histamine dihydrochloride (46.7 g, 0.250 mol, 1.0 eq.) and sodium carbonate (54.3 g, 0.513 mol, 2.05 eq.) in distilled water (1250 ml) at room temperature. The resulting snow-white suspension was stirred vigorously at room temperature for 90 minutes. The solid was filtered off and thoroughly washed with ice-cold distilled water (4 x 50 ml). The solid was collected and dried under vacuum over P_2O_5 at 60°C for 12h to give the title compound (59.2 g, 0.245 mol, 98%, MH^+ = 242).

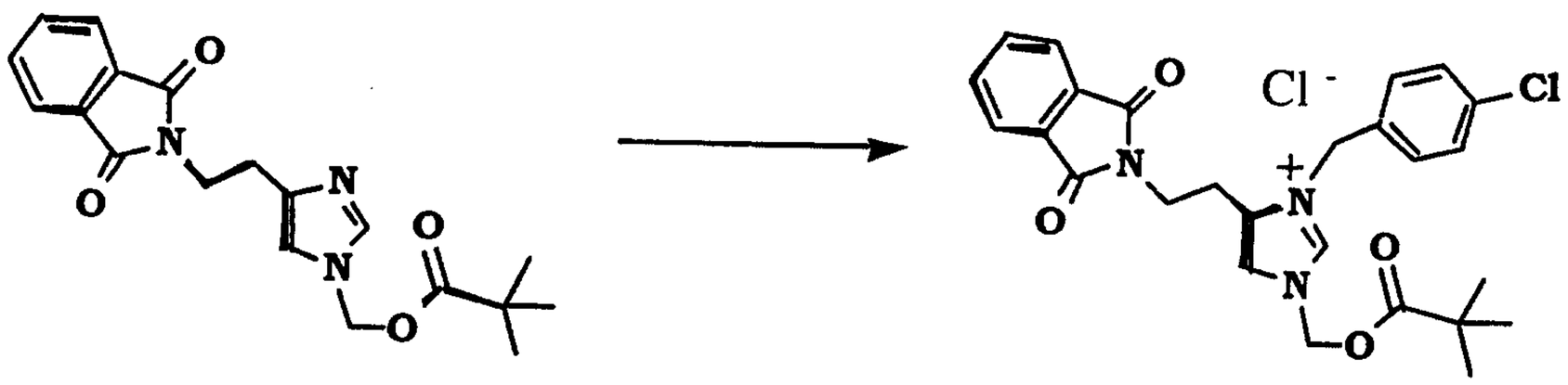
Step B



A solution of chloromethyl pivalate (18.5 ml, 0.125 mol, 1.2 eq.) in anhydrous *N*,*N*-dimethylformamide (DMF, 100 ml) was added dropwise over a period of one hour to a stirred mixture of Step A above (25.0 g, 0.104 mol, 1.0 eq.) and potassium carbonate (17.2 g,

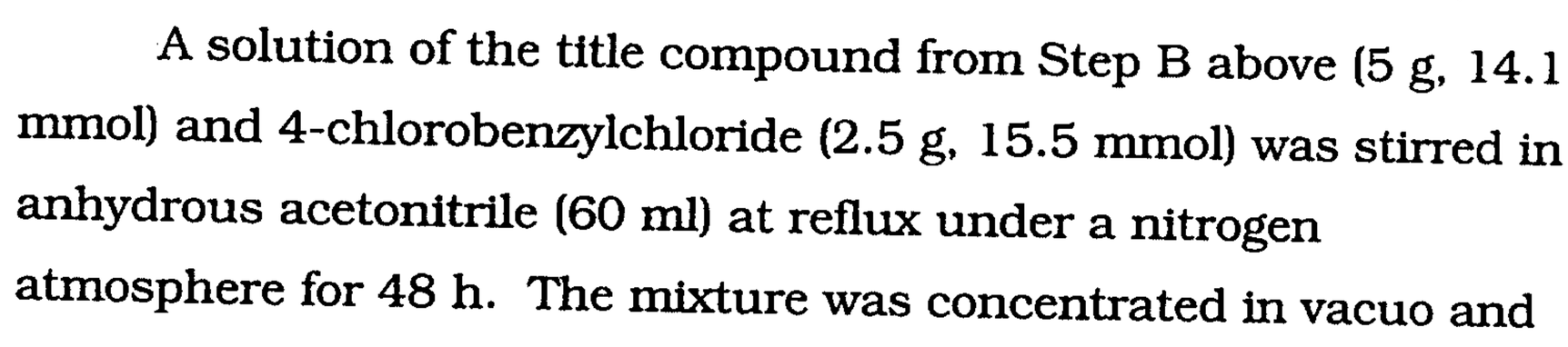
0.125 mol, 1.2 eq.) in anhydrous DMF (500 ml) at 90°C under a nitrogen atmosphere. The mixture was stirred at 90°C for 12h. The volatiles were removed under vacuum at 50°C. The residue was taken up in brine (100 ml) and extracted with ethyl acetate (4 x 25 ml). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under vacuum at 30°C. The residual off-white solid was flash-chromatographed (hexanes : acetone = 6 : 4 v/v) over silica gel to give the title compound (20 g, 0.056 mol, 54%, MH^+ = 356).

Step C



A solution of the title compound from Step B above (5 g, 14.1 mmol) and 4-chlorobenzylchloride (2.5 g, 15.5 mmol) was stirred in anhydrous acetonitrile (60 ml) at reflux under a nitrogen atmosphere for 48 h. The mixture was concentrated in vacuo and recrystallized from ethyl acetate-hexane to give the title compound as a solid (3.2 g, 47%, MH+ = 480), and the filtrate which was concentrated to give additional product (3.6 g, 53%).

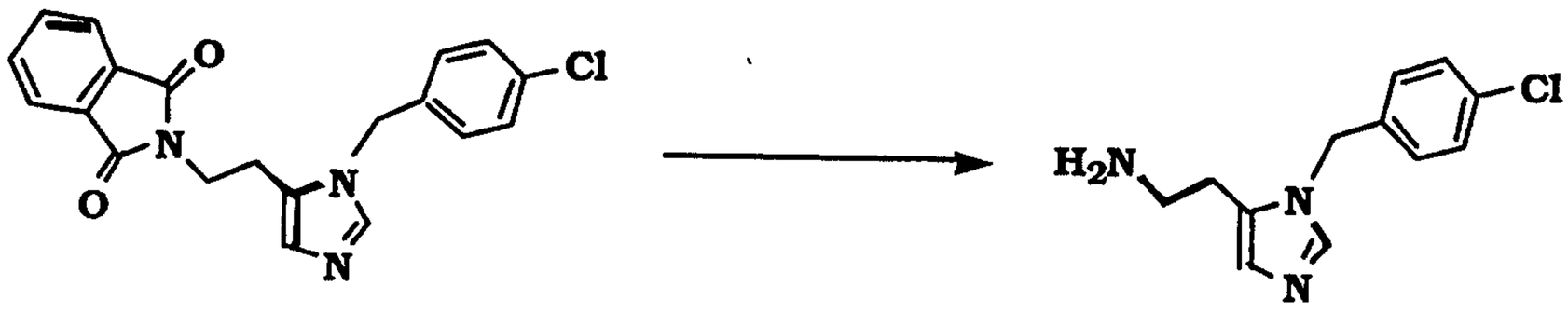
Step D



A 7 N solution of ammonia in methanol (10 ml, 0.07 mol) was added slowly to a stirred solution of the title compound from Step C above (3.2 g, 6.6 mmol) diluted with MeOH (10 mL) at

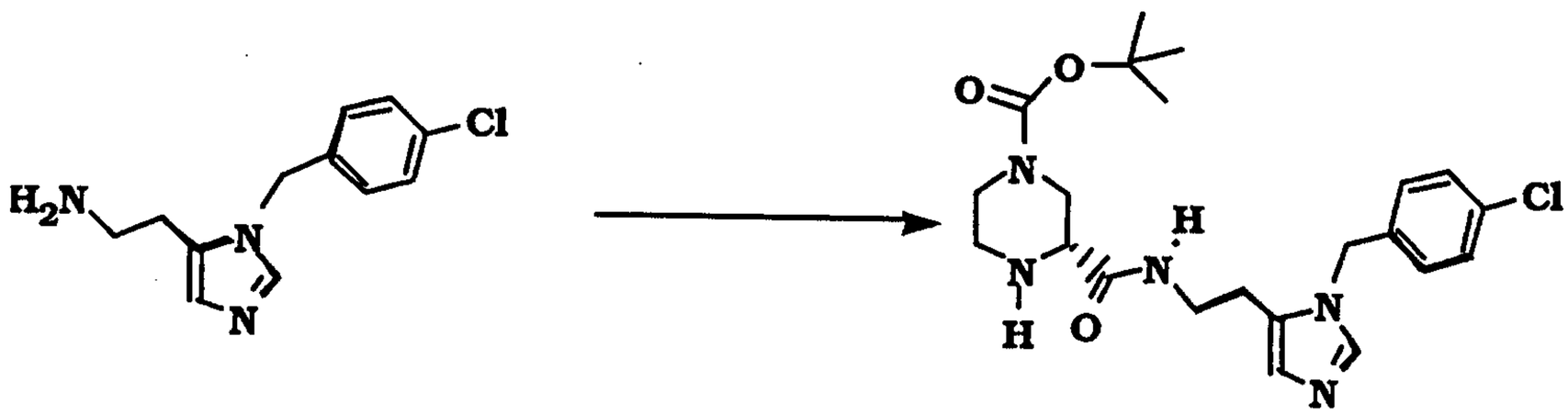
-20°C. The resulting mixture was warmed to room temperature and stirred for another 12 h, then concentrated in vacuo and purified by flash column chromatography (silica gel) using 3% MeOH-CH_2Cl_2 saturated with ammonium hydroxide as eluent to afford the title compound as a sticky solid (1.2 g, 51%, MH^+ = 366).

Step E



A solution of the title compound from Step D above (1.21 g, 3.3 mmol) and hydrazine monohydrate (1.7 ml, 0.033 mol, 10 eq.) in absolute ethanol (20 ml) was stirred at 50 °C under a nitrogen atmosphere for 20 min. The resulting suspension was diluted with ethanol and dichloromethane and filtered. The filtrate was concentrated *in vacuo* to afford the title compound as a yellow oily solid (0.7 g, 91%, MH^+ = 236).

Step F



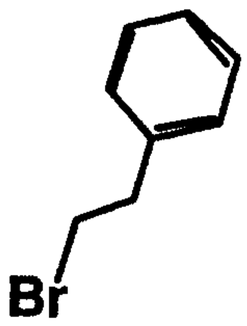
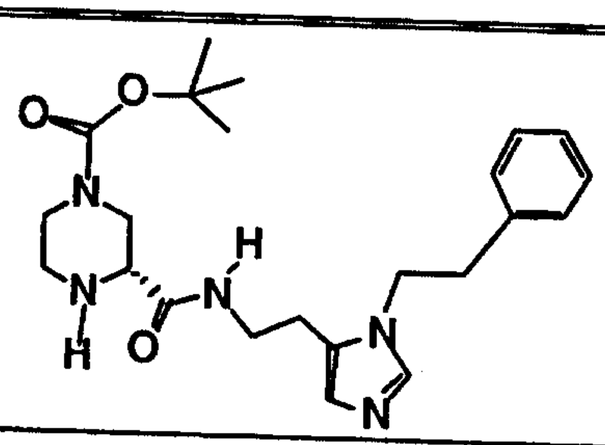
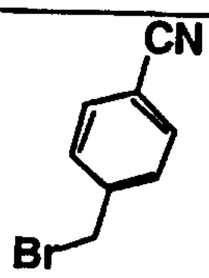
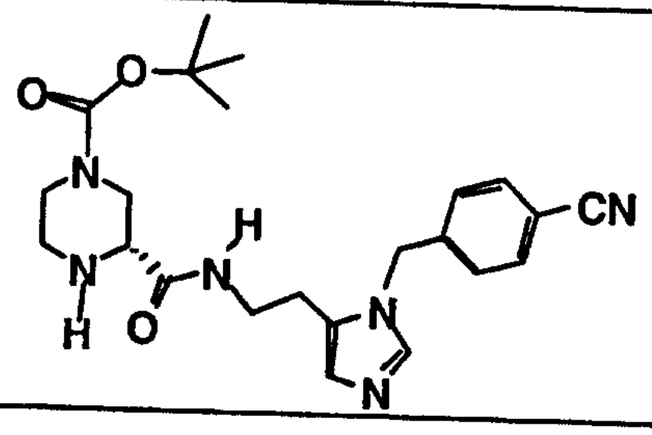
A solution of the title compound from Step E above (0.695 g, 2.94 mmol) and the anhydride from Preparative Example 44 (0.75 g, 2.94 mmol) dissolved in anhydrous dichloromethane (10 ml) was stirred at room temperature overnight. Additional anhydride (0.1 g) was added and after 1 hr the reaction mixture was diluted with CH_2Cl_2 and extracted with 1*M* HCl (aq). The aqueous phase was basified with 1*N* NaOH (aq), extracted with CH_2Cl_2 and the organic

phase dried over anhydrous $MgSO_4$. After filtration, the organic phase was concentrated *in vacuo* to afford a white foam (0.744 g, 57%, MH^+ = 448).

PREPARATIVE EXAMPLES 156-157

Following the procedure described for Preparative Example 155 Steps C-F, the piperazines listed in Table 5D below were prepared using the corresponding arylalkyl halides.

TABLE 5D

Prep. Ex.	Halide	Product	MH^+
156			428
157			441

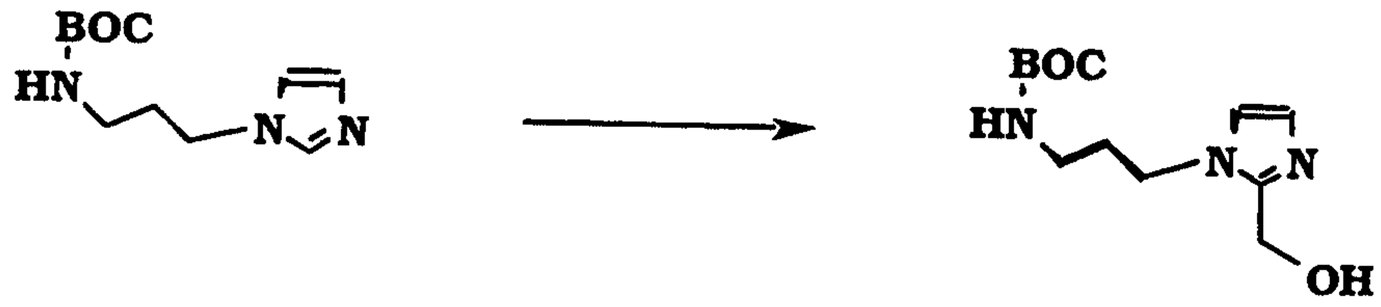
PREPARATIVE EXAMPLE 158

STEP A

To 3-(1H-imidazol-1-yl)propylamine (20 mL, 167.6 mmol) dissolved in water (200 mL) and MeOH (200 mL) was added 50% NaOH (aq) until pH 9.5. Di-*tert*-butyldicarbonate (41 g, 187.9 mmol) was added while stirring at room temperature for 4 hrs and while maintaining the pH at 9.5 with 50% NaOH. The mixture was

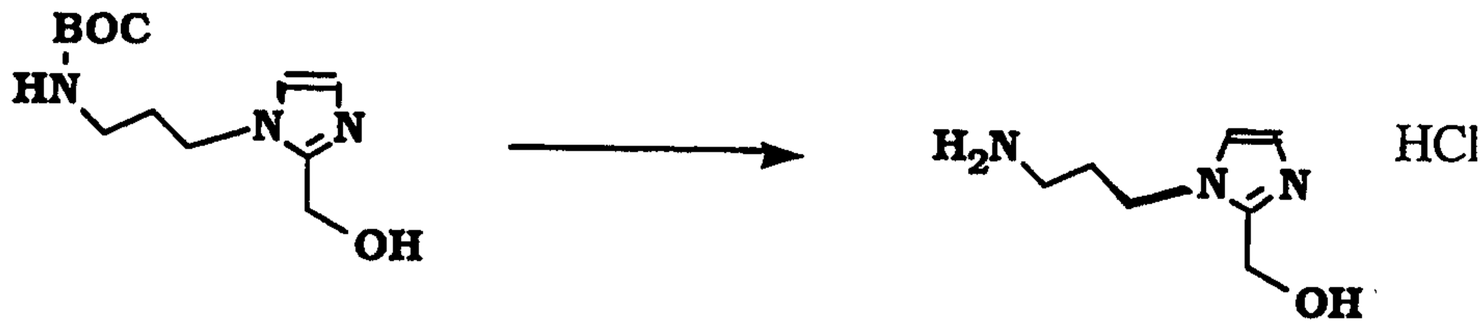
concentrated *in vacuo* to remove most MeOH, then extracted with CH_2Cl_2. The organic phase was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give the title compound (23.7 g, 63%, MH^+ =226).

Step B



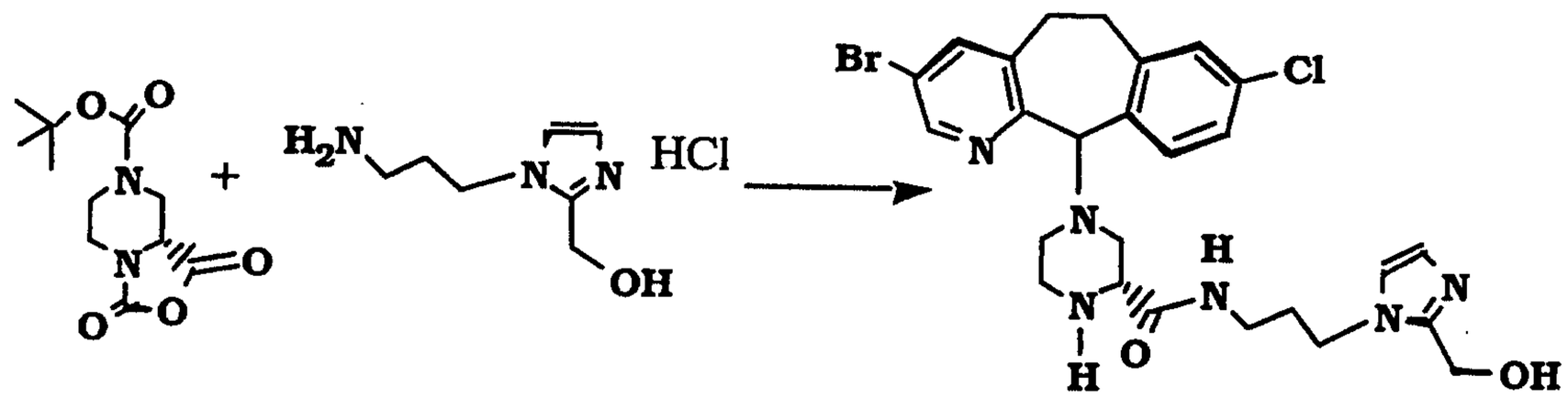
To a solution of the title compound from Step A above (0.50 g, 2.22 mmol) dissolved in anhydrous THF (15 ml) and stirred at -78°C was added n-butyllithium (2.8 mL, 1.75M in hexane) and the resulting mixture was warmed to and stirred at -20°C for 1.5 h. The reaction mixture was recooled to -78°C and anhydrous DMF (0.35 mL, 4.52 mmol) was added. After warming to and stirring at 25°C for 2 h, MeOH (2 mL) and $NaBH_4$ (171 mg, 4.5 mmol) were added and the resulting mixture was stirred for 1 h at 25°C. The mixture was concentrated *in vacuo*, diluted with dichloromethane, washed with water, and the organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (silica gel) using 5-10% MeOH-CH_2Cl_2 saturated with ammonium hydroxide as eluent afforded the title compound (0.32 g, 56%, MH^+ = 256).

Step C



To the title compound from Step B above (0.31 g, 1.2 mmol) was added 4M HCl in dioxane (5 mL) and the mixture was stirred at 25°C for 12 h. Concentration *in vacuo* afforded a residue which was used directly in Step D.

Step D



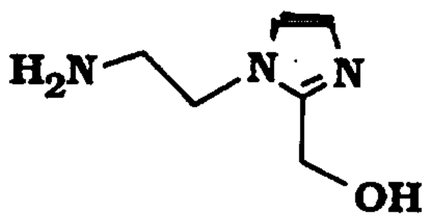
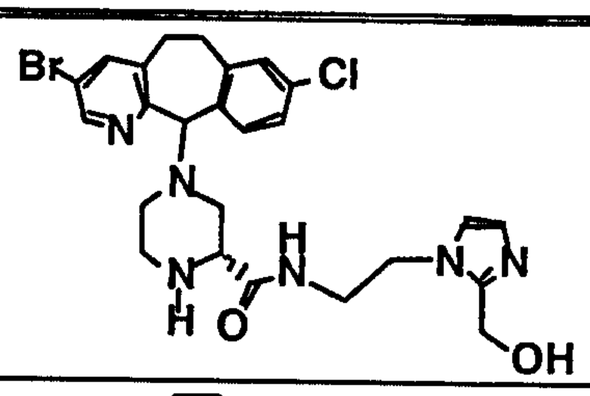
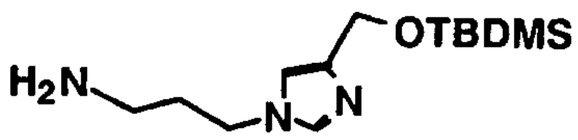
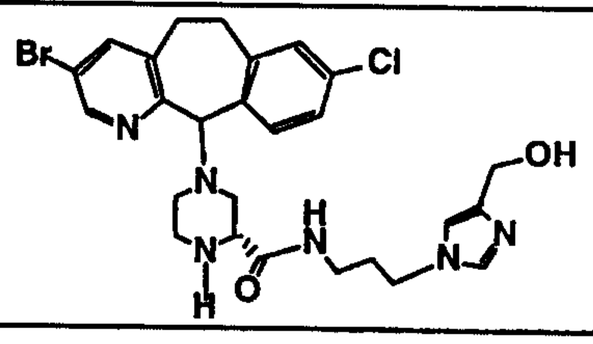
A mixture of the title compound from Step C above, triethylamine (4 mL) and the anhydride from Preparative Example 44 (0.55 g, 2.15 mmol) dissolved in anhydrous DMF (10 ml) was stirred at room temperature overnight. The mixture was concentrated *in vacuo* and diluted with anhydrous CH_2Cl_2 (5 mL), DMF (5 mL) and trifluoroacetic acid (10 mL). The resulting mixture was stirred for 12 hrs at room temperature, then concentrated *in vacuo* and diluted with anhydrous CH_2Cl_2 (5 mL) and DMF (5 mL). The tricyclic chloride (compound # 42.0) (0.75 g, 2.17 mmol) and triethylamine (3 mL) were added and the mixture was stirred at 25°C for 48 h. The mixture was concentrated *in vacuo*, diluted with CH_2Cl_2 and washed with a saturated aqueous solution of $NaHCO_3$. The organic phase was dried over anhydrous Na_2SO_4, filtered, concentrated *in vacuo* and purified by flash column chromatography (silica gel) using 5-10% MeOH-CH_2Cl_2 saturated with aqueous

ammonium hydroxide to give the title compound as a mixture of diastereomers (0.376 g, 33%, MH^+ = 573).

PREPARATIVE EXAMPLES 159-160

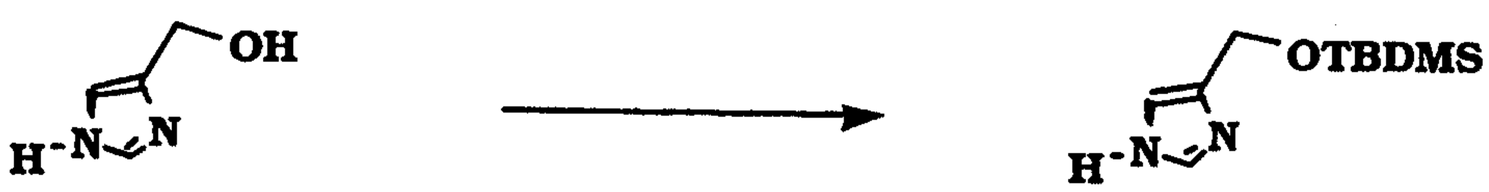
Following the procedure described for Preparative Example 158 Step D, the piperazines listed in Table 5E below were prepared using the corresponding amines or amine hydrochlorides.

TABLE 5E

Prep. Ex.	Amine	Product	1. yield (%) 2. MH^+
159	HCl 		1. 37 2. 559
160			1. 25 2. 573

PREPARATIVE EXAMPLE 161

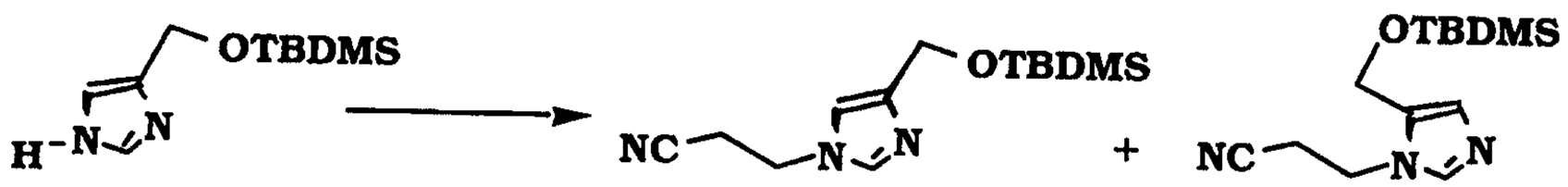
Step A



A mixture of 4-hydroxymethylimidazole (2 g, 14.9 mmol), triethylamine (5 mL) and TBDMS-Cl (2.5 g, 16.6 mmol) dissolved in anhydrous CH_2Cl_2 (20 ml) was stirred at room temperature overnight. The mixture was filtered, diluted with anhydrous Et_2O and refiltered. The filtrate was concentrated *in vacuo*, diluted with CH_2Cl_2 and washed with a saturated aqueous solution of $NaHCO_3$.

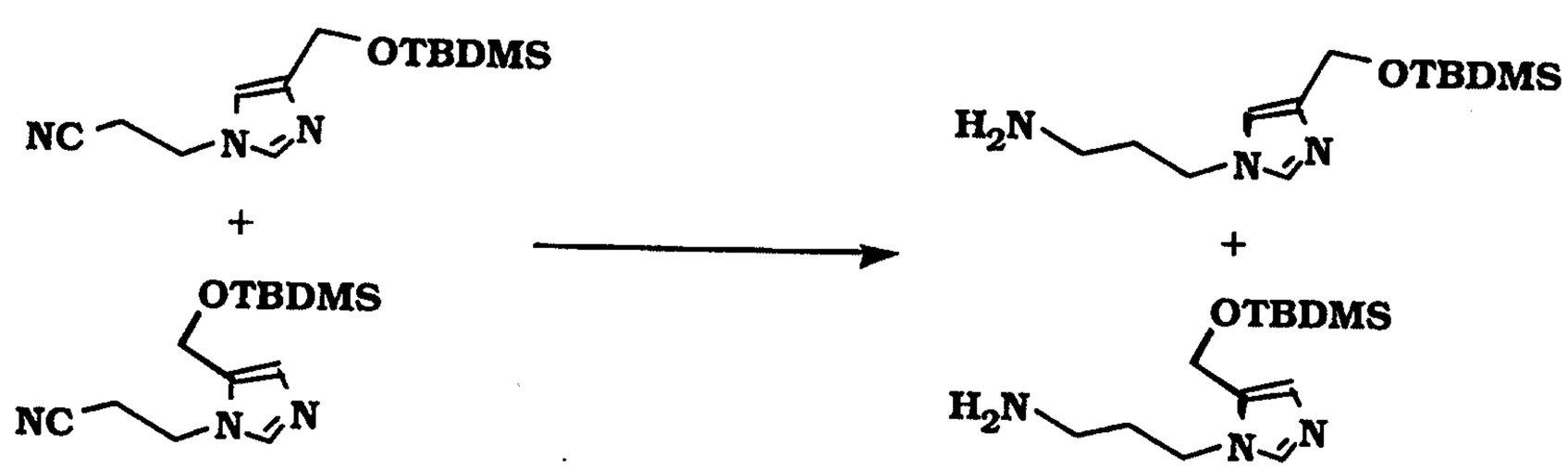
The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound (2.22 g, 71%, MH^+ = 213).

Step B



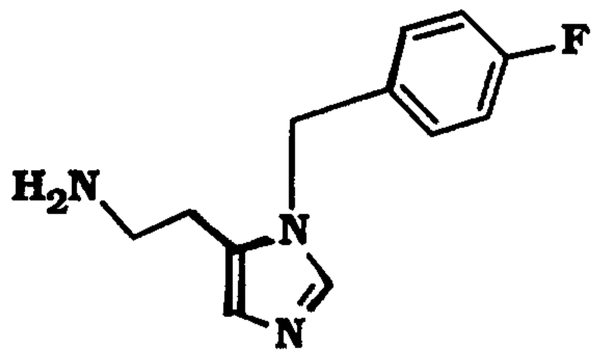
A solution of the title compound from Step A above (2.22 g, 10.5 mmol) dissolved in acrylonitrile (10 ml) was stirred at reflux for 48 h. Concentration *in vacuo* afforded the title compound (2.09 g, 75%, MH^+ = 266).

Step C



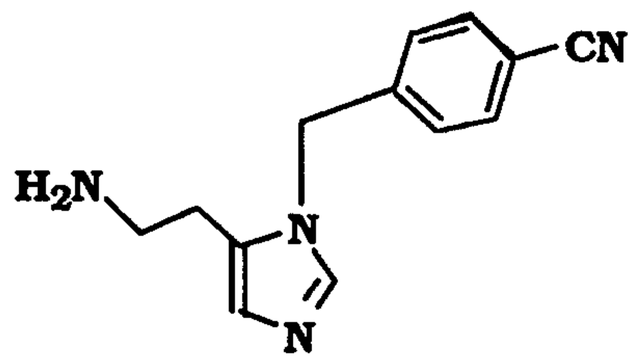
A mixture of the title compound from Step B above (2.08 g, 7.85 mmol), Raney nickel (230 mg), MeOH (20 mL) and NH_4OH (7.5 mL) was stirred in a Parr hydrogenator at room temperature for 48 h. The mixture was filtered through celite, concentrated *in vacuo*, diluted with CH_2Cl_2 and washed with a saturated aqueous solution of $NaHCO_3$. The organic phase was dried over anhydrous Na_2SO_4, filtered, concentrated *in vacuo* and purified by flash column chromatography (silica gel) using 5% MeOH-CH_2Cl_2 saturated with aqueous ammonium hydroxide to give the title compounds [(4-substituted isomer, 465 mg, 22%, MH^+ = 270) and (5-substituted isomer, 220 mg, 10%, MH^+ = 270)].

PREPARATIVE EXAMPLE 162



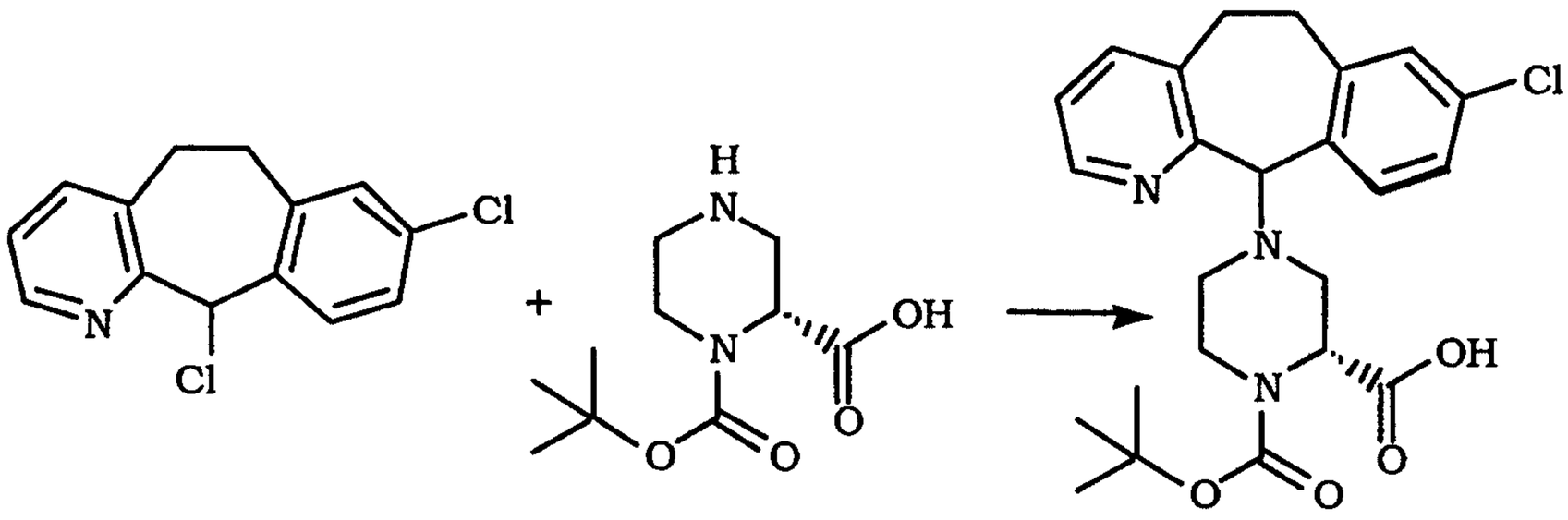
Following the procedure described for Preparative Example 155 Steps C-E, except using 4-fluorobenzyl bromide instead of 4-chlorobenzyl chloride in Preparative Example 155 Step C, the title compound was prepared (52%, $MH^+ = 220$).

PREPARATIVE EXAMPLE 163



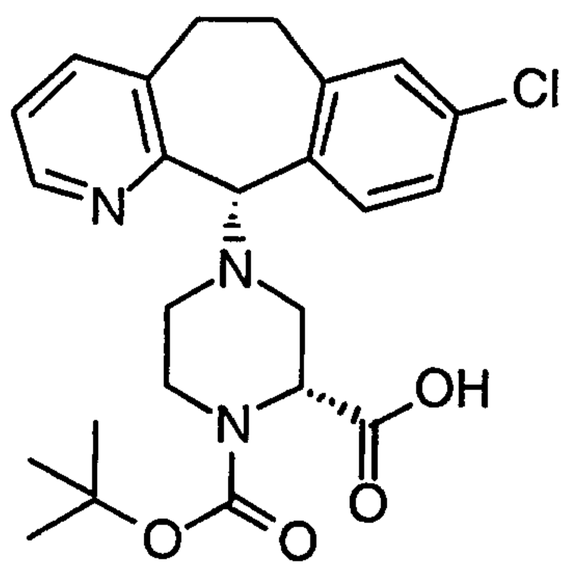
Following the procedure described for Preparative Example 155 Steps C-E, except using 4-cyanobenzyl bromide instead of 4-chlorobenzyl chloride in Preparative Example 155 Step C, the title compound was prepared (63%, $MH^+ = 227$).

PREPARATIVE EXAMPLE 164



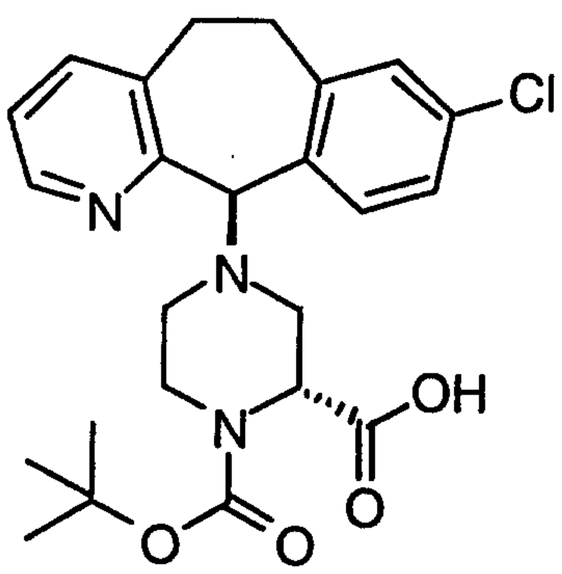
Tricyclic chloride (5.04g, 1.1 eq.) was added to a solution of the title compound from Preparative Example 50 (4.0g, 17.3 mmol) and TEA (12.05 mL, 5 eq.) in DMF (60 mL). The resulting solution was stirred at room temperature 72 hours at which time the

reaction mixture was concentrated under reduced pressure. The residue was diluted with 3M NaOH and extracted with EtOAc. The aqueous layer was neutralized with 50% citric acid and extracted with EtOAc. The combine organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography using a 12% (10% NH_4OH in MeOH) solution in CH_2Cl_2 as eluent to give the C-11 (S)-isomer (2.13g, 54%) as the first eluting isomer and the C-11 (R)-isomer (2.4g, 61%) as the second eluting isomer.



11S,2R(+)-Isomer

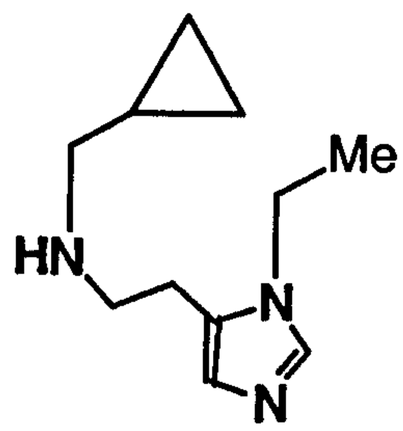
11(S),2(R)(+)-isomer (first eluting isomer): $[\alpha]^{20}_D$= +84.9 (5.18mg in 5.0 mL MeOH); LCMS: MH^+= 458.



11R,2R Isomer

11(R),2(R)-isomer (second eluting isomer): FABMS: MH^+= 458.

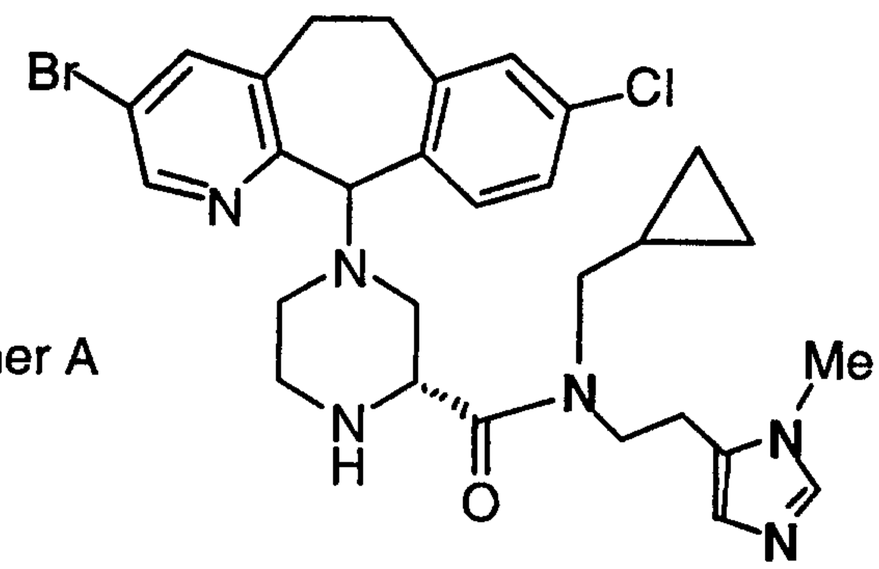
PREPARATIVE EXAMPLE 165



Following the procedure described for Preparative Example 25, except using the title compound from Preparative Example 13 instead of N-1-methyl histamine, the title compound was prepared (33%, MH^+ = 195).

PREPARATIVE EXAMPLE 166

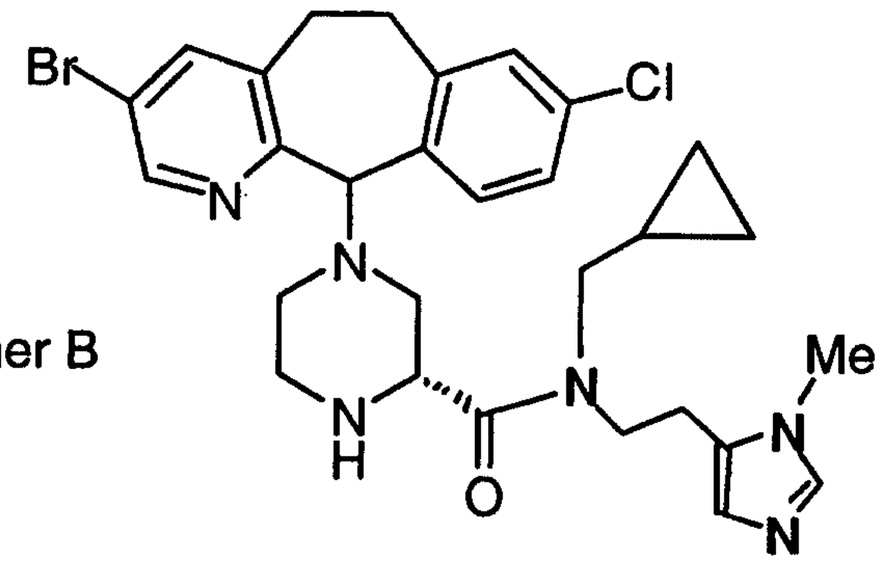
Diastereomer A



Similarly, using the procedure described for Preparative Example 142, except using the title compound from Example 305 diastereomer A instead of the title compound from Example 289, the title compound was prepared (80%, MH^+ = 599).

PREPARATIVE EXAMPLE 167

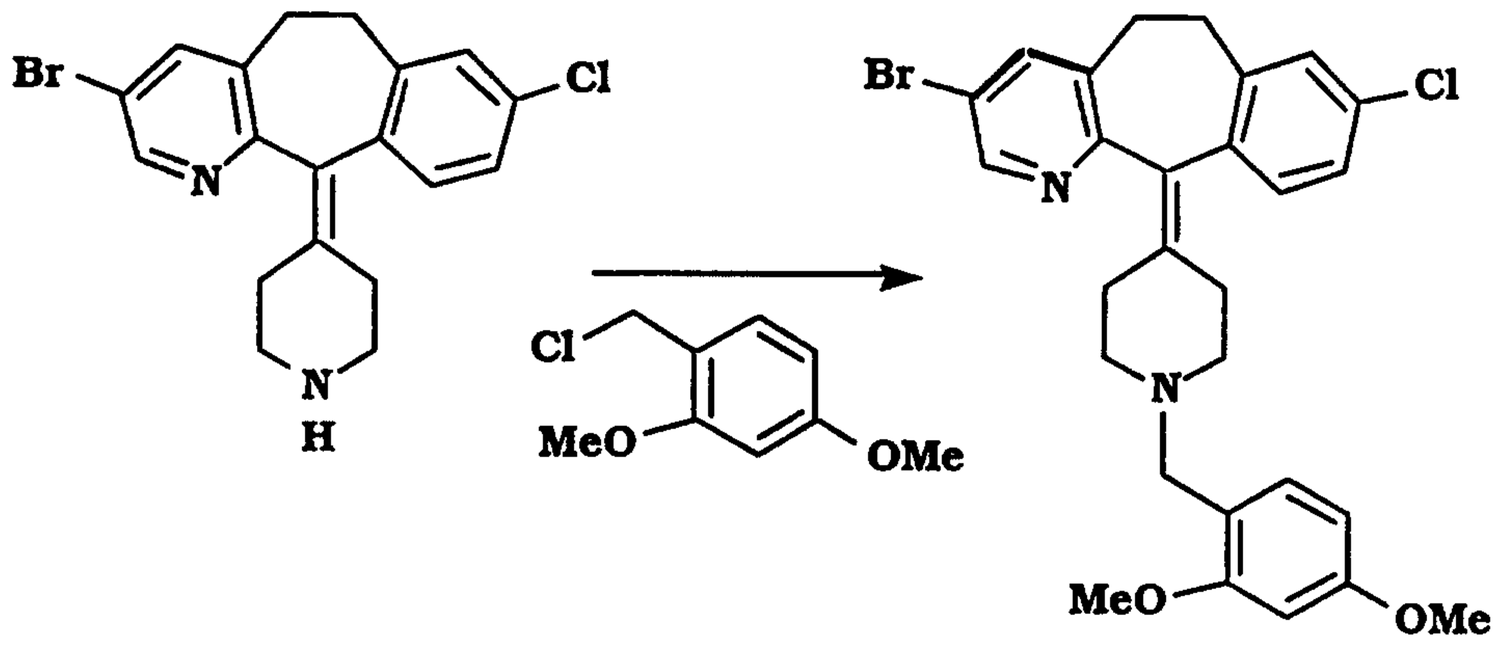
Diastereomer B



Following the procedure described for Preparative Example 142, except using the title compound from Example 305 diastereomer B instead of the title compound from Example 289, the title compound was prepared (100%, MH^+ = 599).

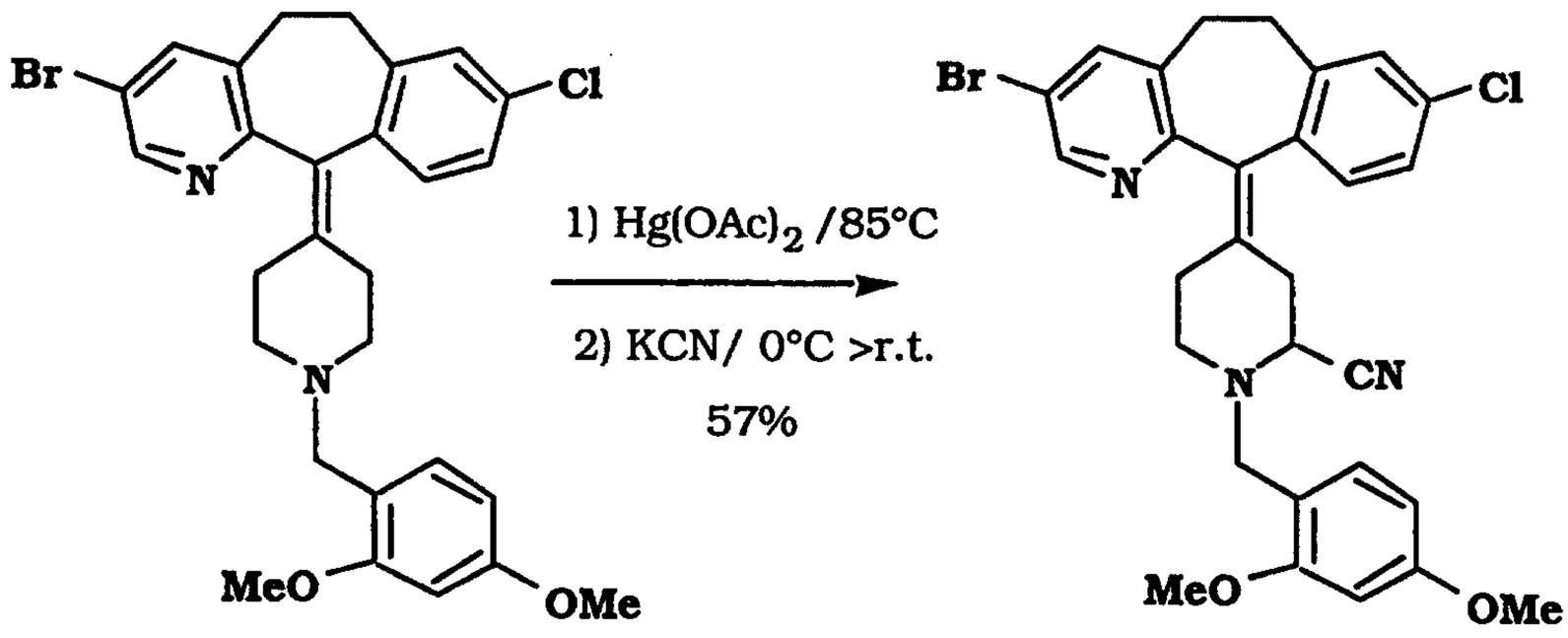
PREPARATIVE EXAMPLE 168

Step A



The title compound from Preparative Example 40A Step A (compound 52.ii) (5 g, 12.8 mmol) was dissolved in 2.7 ml of 2,4-dimethoxybenzaldehyde by heating to 120°C. Formic acid (1.3mL) was dripped into the reaction mixture while the reaction mixture stirred at 120 °C for 45 min. The resulting solid mixture was dissolved in dichloromethane and dried over magnesium sulfate, filtered and evaporated to dryness to obtain a solid which was chromatographed on silica gel to obtain 5.17 g of title product. FABMS (M+1)= 463.4

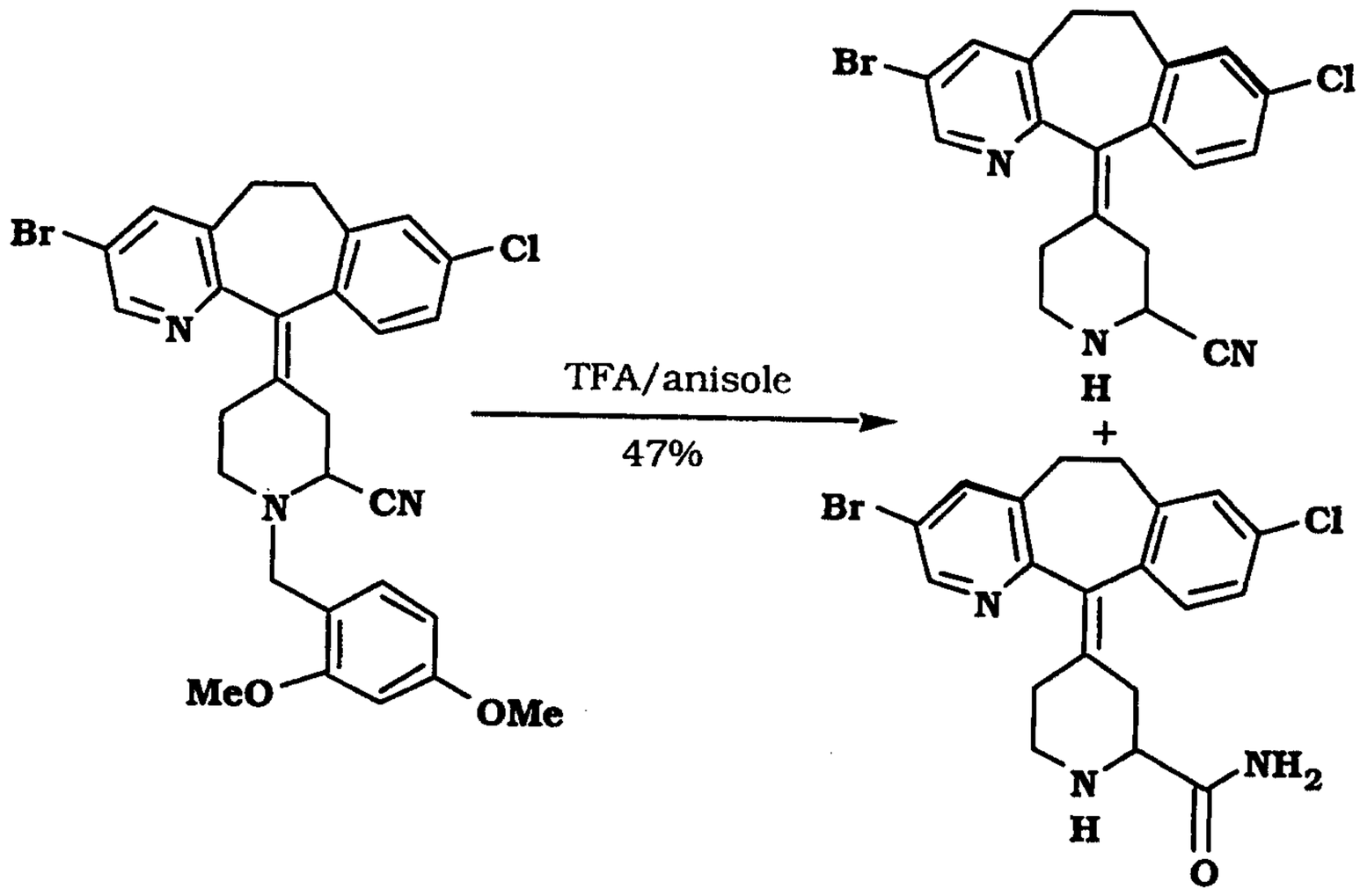
Step B



The title compound from Step A (1 gm, 1.8 mmol) was dissolved in 45 ml of 5% acetic acid/water and stirred at 85°C. Mercuric acetate (2.3 gm) was added and the reaction mixture stirred for 5 hours. After cooling in an ice bath, potassium cyanide (1.25 gm) was added and the reaction mixture stirred vigorously for

18 hours. 1N Sodium hydroxide (excess) was added and the product extracted with ethyl acetate three times. After chromatography on silica gel using ethylacetate as the eluent,0.747 gm of title product was obtained.

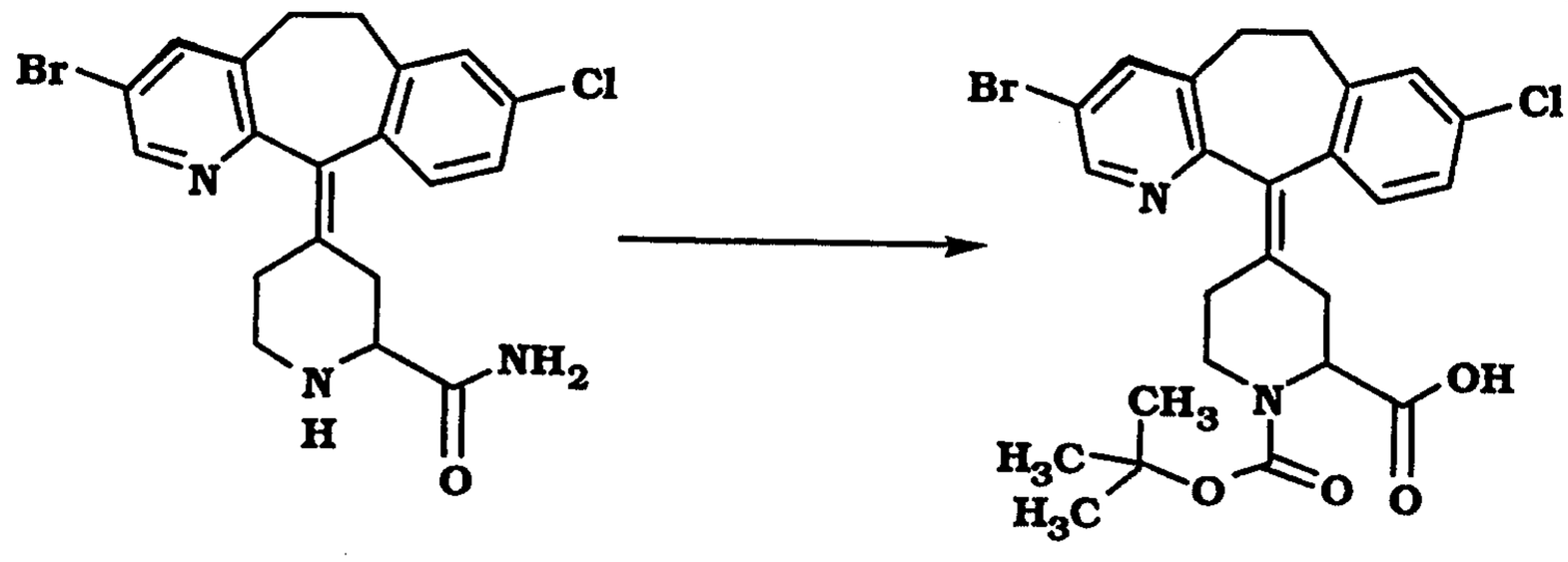
Step C



major

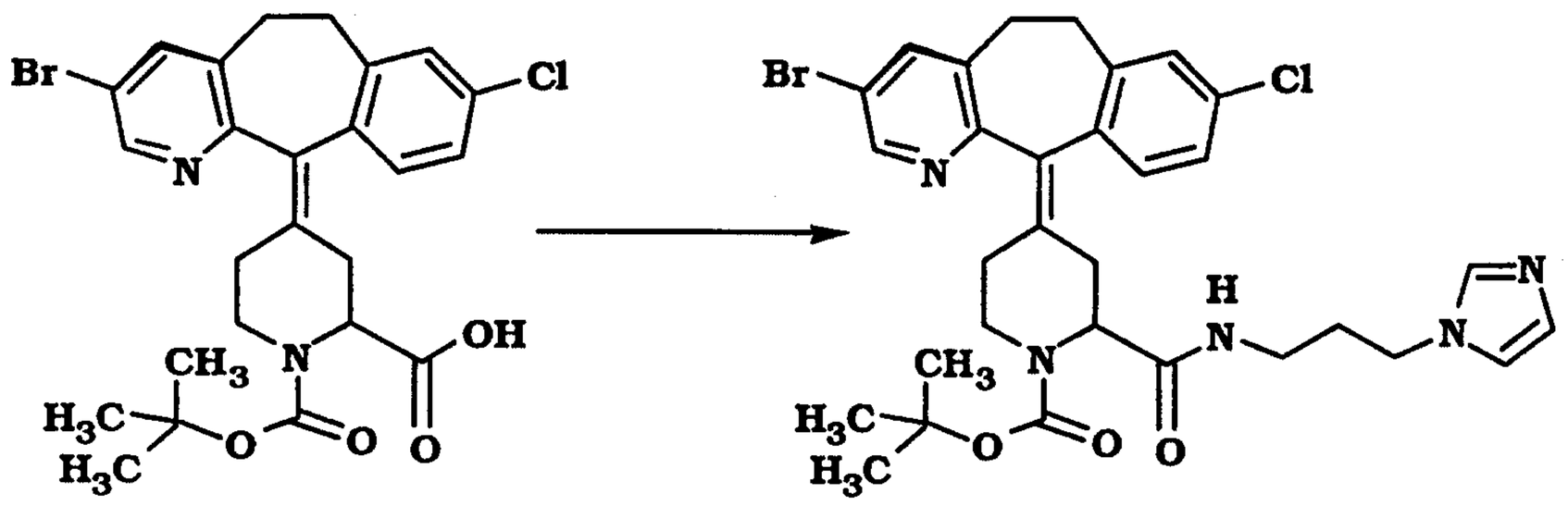
The title product from Step B (0.2 gm) was dissolved in 6 ml of trifluoroacetic acid and 0.5 ml of anisole and stirred for 1 hour at 60°C to obtain the title carboxamide product (72 mg) after silica gel chromatography using 2% methanol/dichloro-methane as the eluent. FABMS (M+1)= 432.

Step D



The major product (carboxamide) from Step C (0.19 gm) was dissolved in 10 ml of 6N hydrochloric acid and refluxed for 24 hours. The 6 N HCl was removed under vacuum and the residue dissolved in water (5 ml). Di-tert-butyldicarbonate (0.13 gm) was added and the pH of the reaction mixture brought to 9.0 with 1 N sodium hydroxide. After stirring 2 hours at ambient temperature, the reaction mixture was added to citric acid and extracted with dichloromethane to obtain the crude product which was chromatographed on silica gel to obtain 93 mg of title product. FABMS (M+1)= 533.

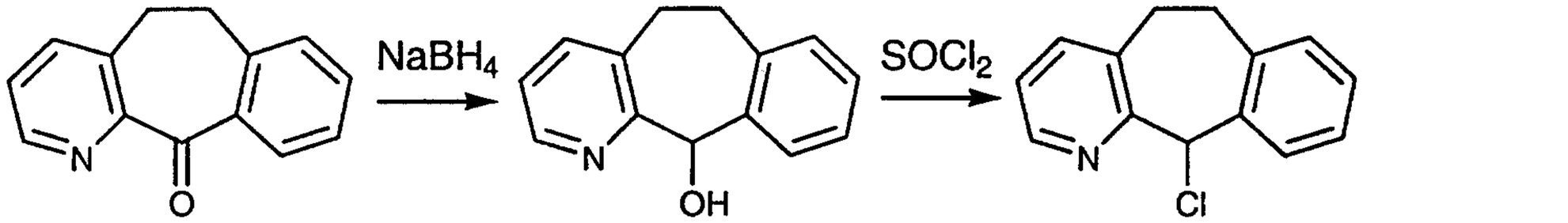
Step E



The title compound from Step D (70 mg, 0.13 mmol) was dissolved in 2 ml of DMF and DEC (37 mg, 0.19 mmol.), HOBT (26 mg, 0.19 mmol), and N-methyl-morpholine (42 uL, 0.4 mmol) were added and the reaction mixture stirred at ambient temperature for 7 hours. After addition to water and extraction with dichloromethane, the crude product was chromatographed on a silica gel column to obtain 86 mg of title product. FABMS (M+1) = 640.

PREPARATIVE EXAMPLE 169

11-Chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-B]pyridine.



The ketone (starting material) 5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-c]pyridine-11-one, may be prepared by following the methods described in U.S. 3,419,565.

Sodium borohydride (2g, 53.3mmol) was added to a solution of the ketone (3g,14.35mmol) in methanol (50ml) at 0°C, then stirred for 2 hours at room temperature. The reaction was quenched by addition of ice (10g) and 2N HCl (10ml, basified with 2N NaOH (13ml)and extracted with $MeCl_2$ (2x50ml). The organic layer was separated,dried over $MgSO_4$, filtered and solvent evaporated yielding the alcohol (3g, 100%).

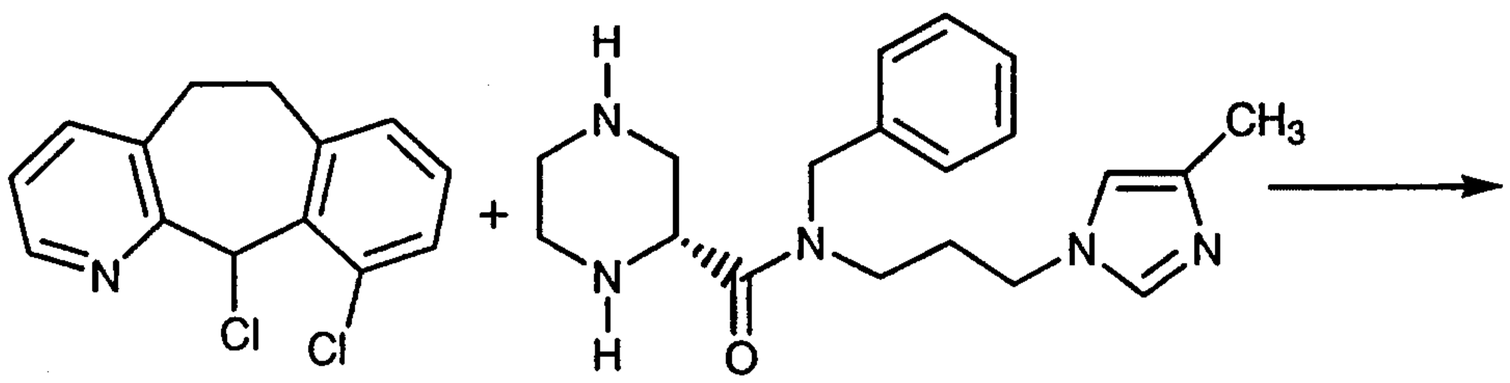
1H NMR (DMSO, δ) 3.0-3.4(m,4H) 6.101(brs,2H) 7.0-7.3(m,4H) 7.5(m,2H) 8.314(d,1H).

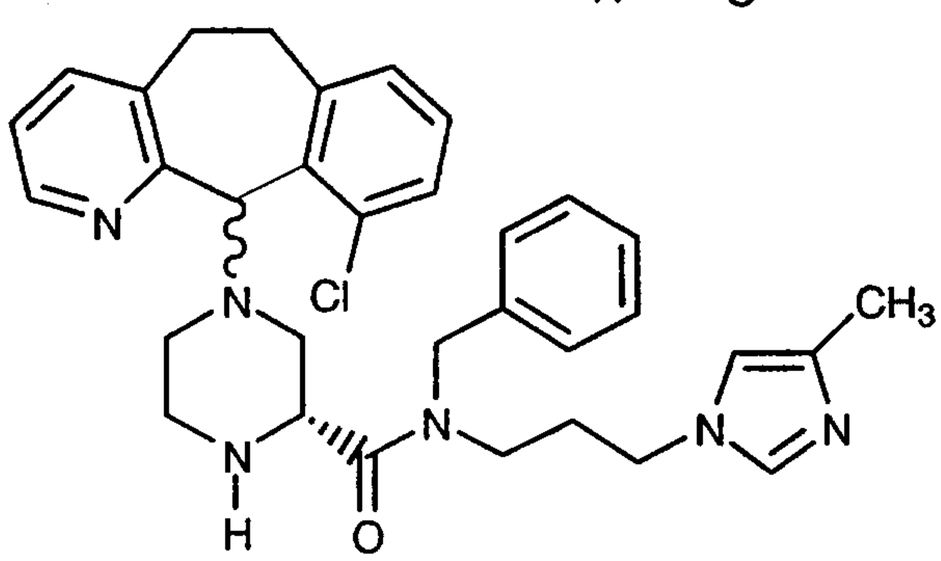
Thionyl chloride (3ml, 41.12mmol) was added to a solution of the alcohol (2.5g, 11.84 mmol) in $MeCl_2$(50ml) at room temperature,then stirred for 1 hour. The solvent was evaporated, water 50 (ml) and 5% NaOH (10ml) were added. The mixture was extracted with $MeCl_2$ (100ml), organic layer was dried over $MgSO_4$, filtered, and solvent evaporated yielding a tan solid, which was triturated with ether, and filtrate concentrated yielding a white solid. (1.5g).

1H NMR ($CDCl_3$, δ) 2.9-3.0 (m, 2H), 3.6 (m, 1H), 3.9 (m, 1H), 6.3 (s, 1H), 7.2 (m,3H). 7.3 (d, 1H), 7.4 (d, 1H), 7.5(d, 1H), 8.42 (d, 1H).

The filtered solid was dried yielding (0.9g) of additional material. Total yield (2.4g, 87%).

PREPARATIVE EXAMPLE 170



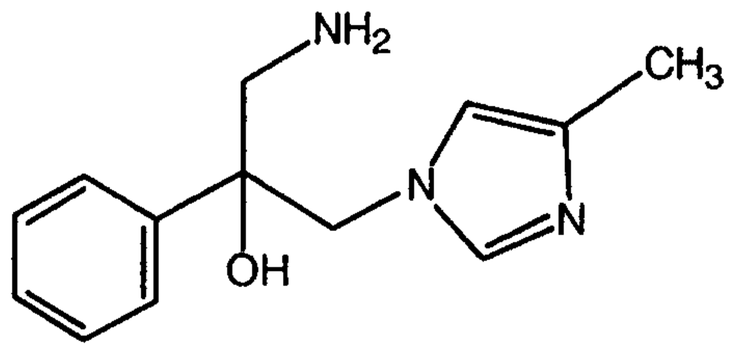


Acetonitrile (5ml) was added to a mixture of the 10-Chloro tricycle (0.5g, 1.90mmol) (Preparative Example 9.1) and the substituted piperazine (0.78g, 1.90mmol).Triethylamine (1ml, 7.18mmol) was added,and the mixture stirred overnight at room temperature.Water (50ml) and 5% NaOH were added and the mixture was extracted with $MeCl_2$ (2x100ml). The organic layer was separated,dried over $MgSO_4$ and solvent was evaporated yielding desired product (0.7g, 57%) as a mixture of 2 diastereomers, which were separated by column chromatography on silica gel, eluting with 5% v/vMeOH/$MeCl_2$ containing 2% NH_4OH. Isomer A (the less polar isomer) eluted first.

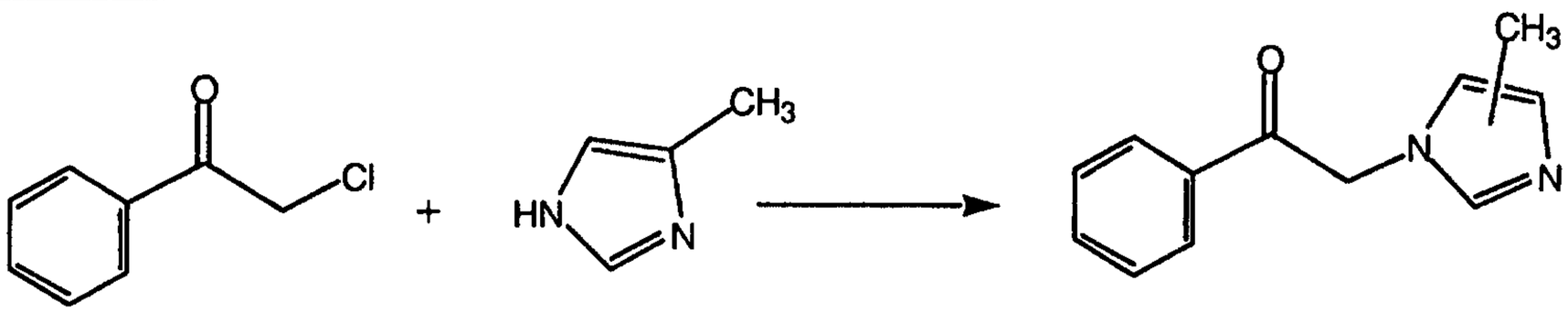
TABLE 5F

Isomer	Mass (Fabs, MH)	$[\alpha]_D^{20}$
A, B	569.1	------
A	569.2786	-55.9° ^{c}= 0.1085
B	569.2816	-27.4^{oc}= 0.1085

PREPARATIVE EXAMPLE 171

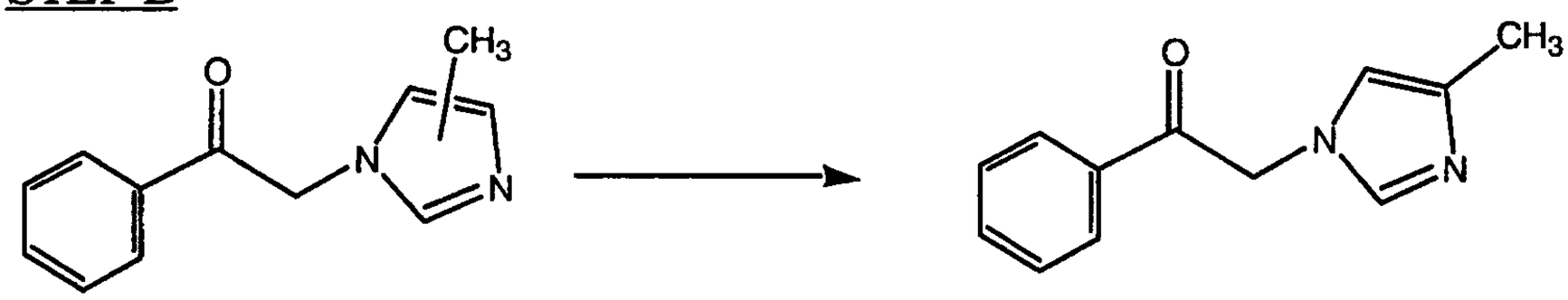


STEP A



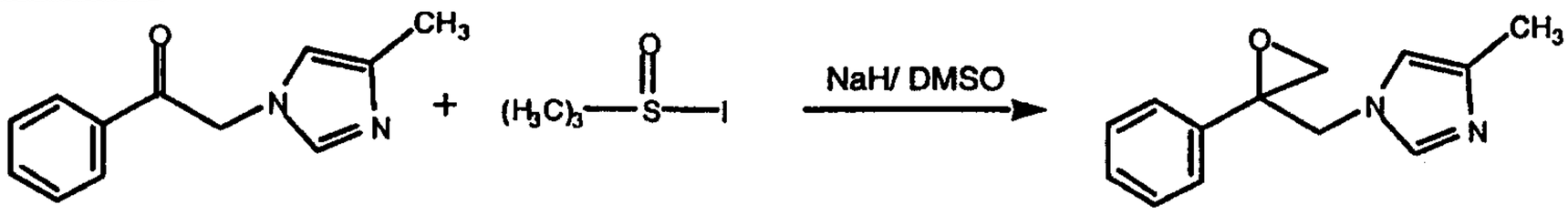
A mixture of 2-chloroacetophenone (25g, 0.16 moles) and 4-methyl imidazole (66.1g, 0.8 moles) was heated at 100 °C for 2h. Cooled and the crude product chromatographed on a silica gel column eluting with CH_2Cl_2/ 3% CH3OH saturated with aqueous ammonium hydroxide to give mixture of 4- and 5- methyl 1H-imidazolyl acetophenone (23g, 73%), MS, MH^+ = 201).

STEP B



Trityl chloride (7.28g, 0.26 moles) was added to the product from Step A in CH_2Cl_2 (200 mL) and stirred overnight at room temperature. The mixture was chromatographed on a silica gel column eluting with ethyl acetate / acetone (3:1) to give 4-methyl–1H-imidazolyl acetophenone (15.5 g), FabMS: MH^+= 201.

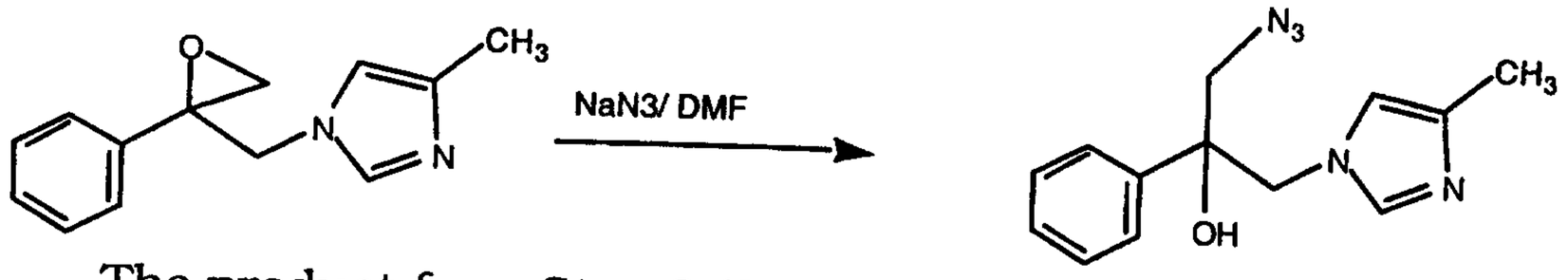
STEP C



To a mixture of NaH (0.998 g, 24.97 mmoles, and trimethyl sulfoxonium iodide (5.49g, 24.97 mmoles) in DMSO (50 mL) the

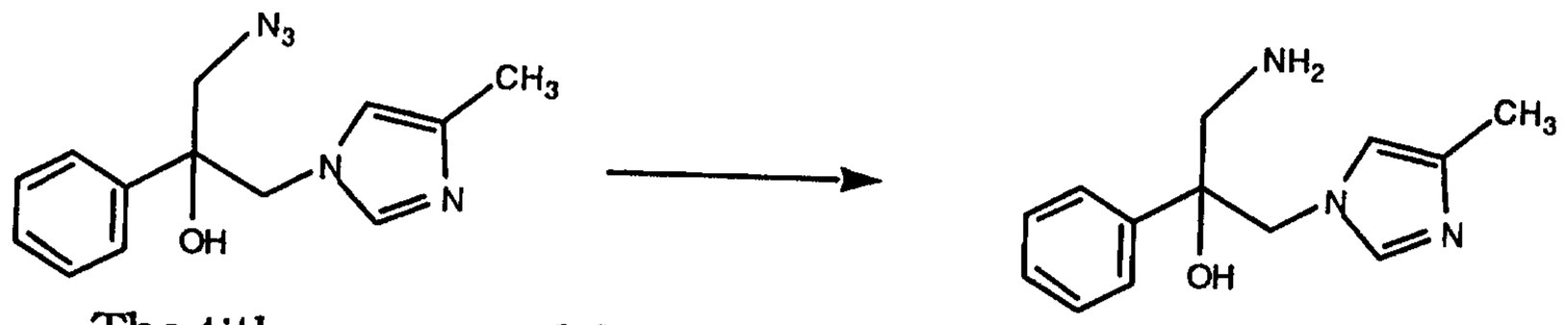
product (5g) from Step B was added and stirred for 1.5h. Extracted the product with ethyl acetate and washed with brine, dried and solvent evaporated to give 1 –(2-phenyl-2,3-epoxypropyl)-1H-4-methyl imidazole (3.44 g, 64 %) , FABMS : MH^+ = 215)

STEP D



The product from Step C (3.45g, 16.11 mmoles) and sodium azide (2.093g, 32.21 mmoles) were heated in DMF (100 mL) at 60 0 C for 12h. Evaporated to dryness and extracted with CH_2Cl_2, washed with brine and dried ($MgSO_4$). Evaporated to give the title compound (3.83g, 93%). FABMS: MH^+ = 258

STEP E

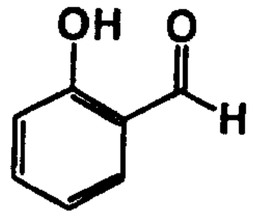
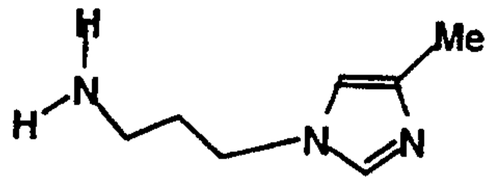
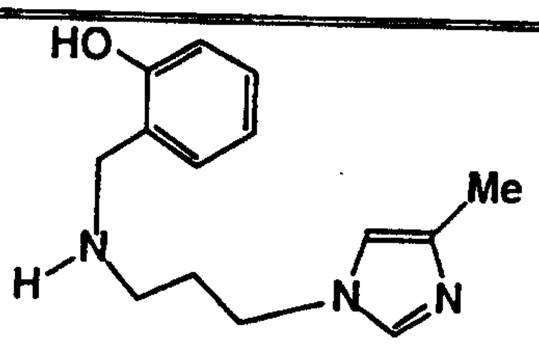
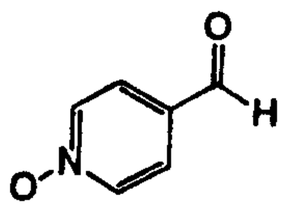
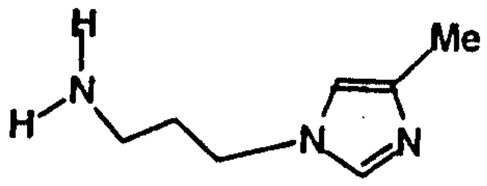
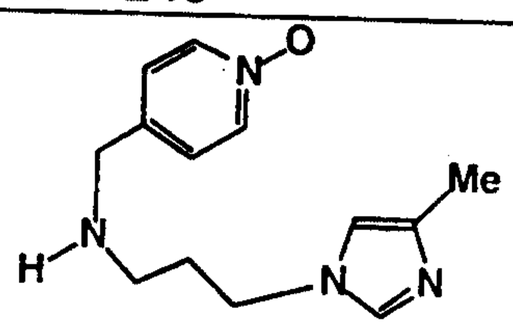
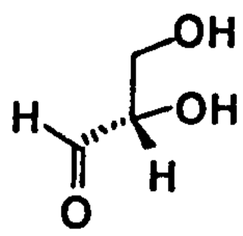
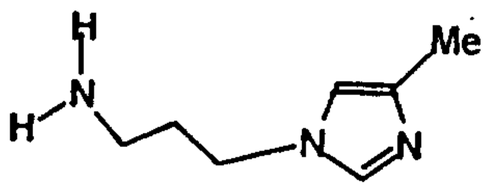
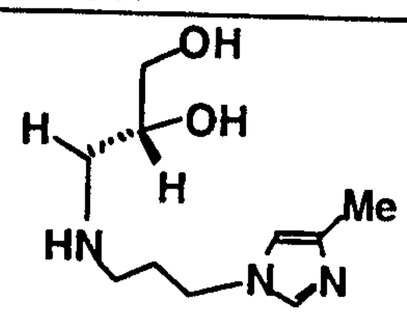
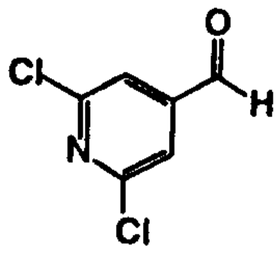
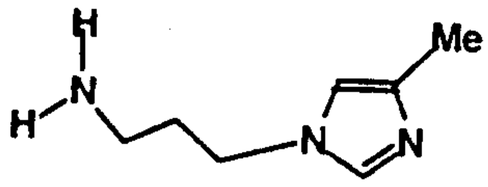
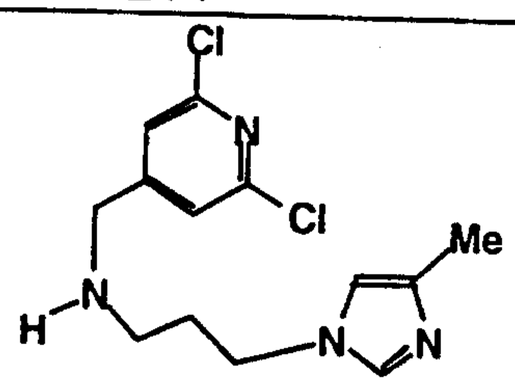
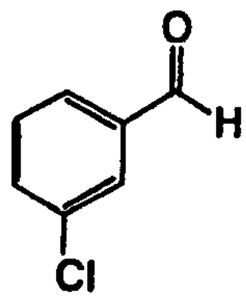
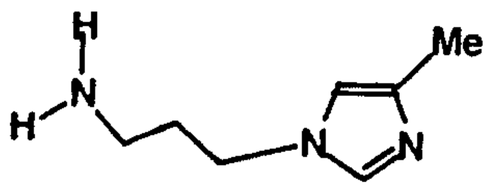


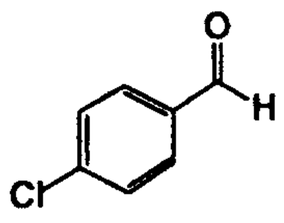
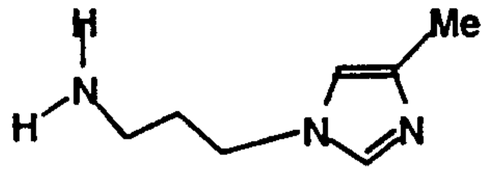
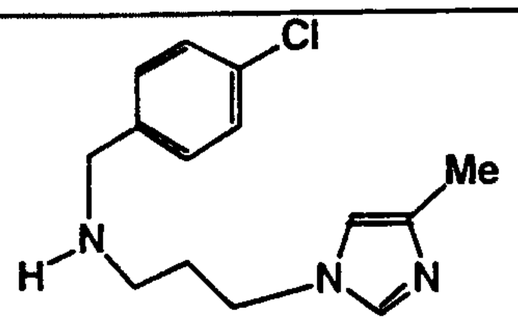
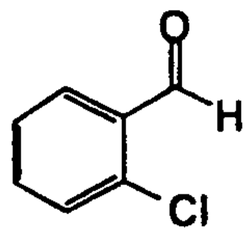
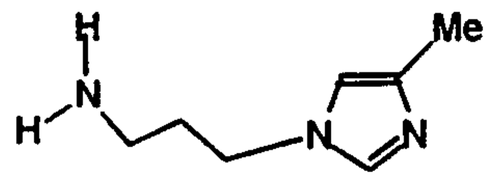
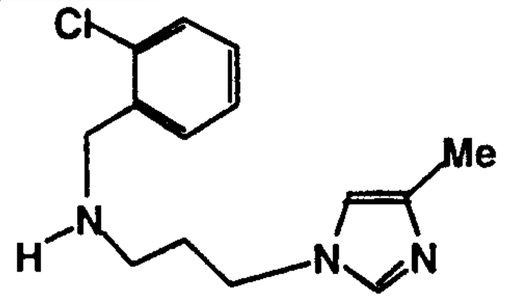
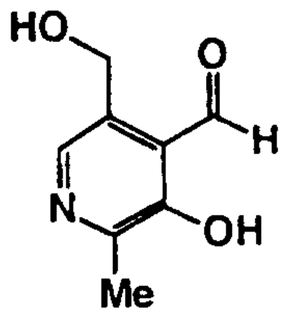
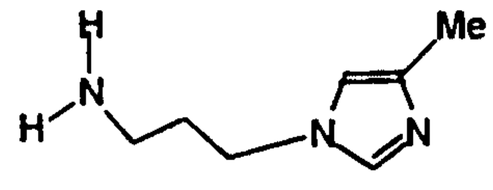
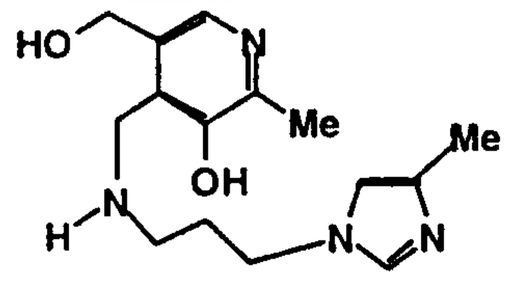
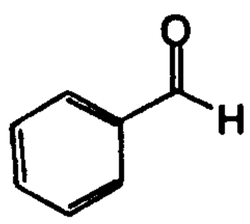
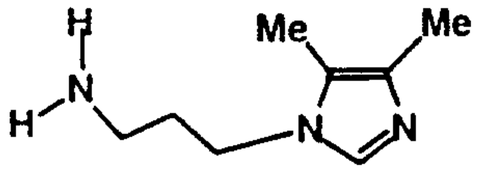
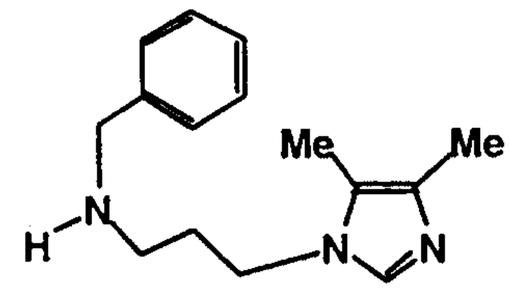
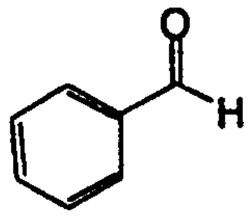
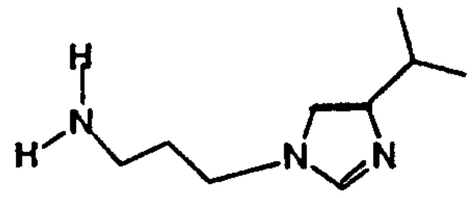
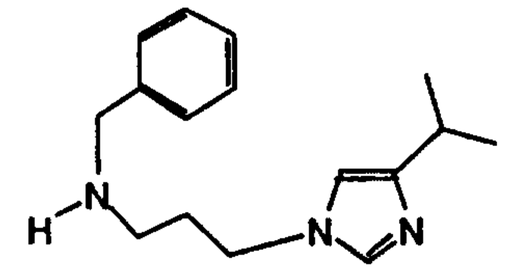
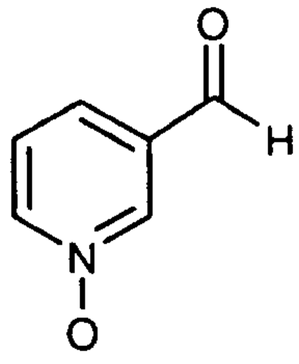
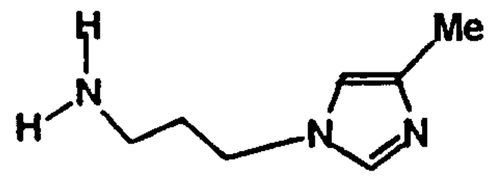
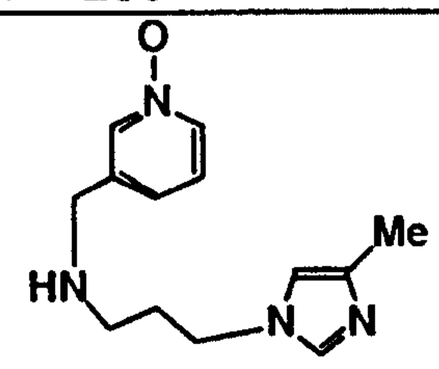
The title compound from Step D in ethanol (80 mL) was hydrogenated over 10% Pd on carbon (1.2 g) at 50 psi overnight. The catalyst was filtered off and evaporated to give the title compound (2.83g, as yellow viscous oil).

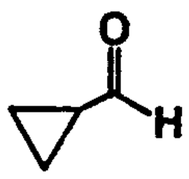
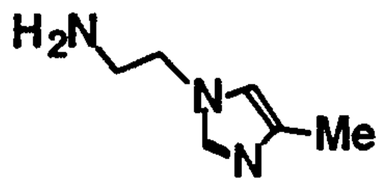
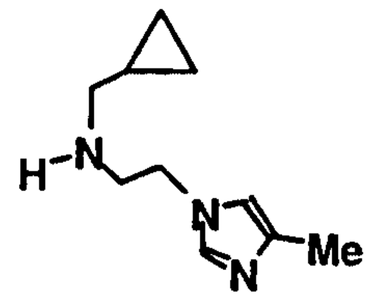
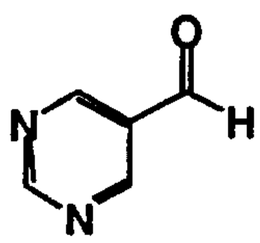
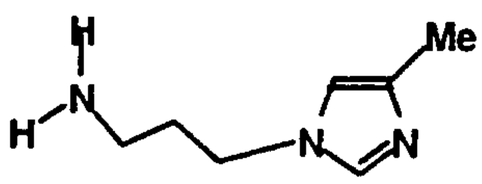
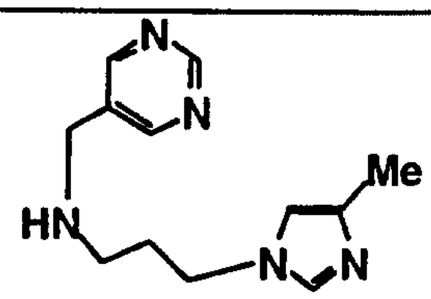
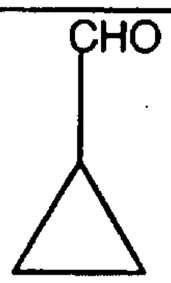
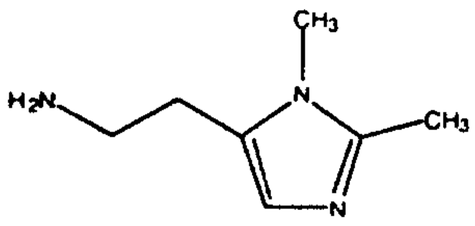
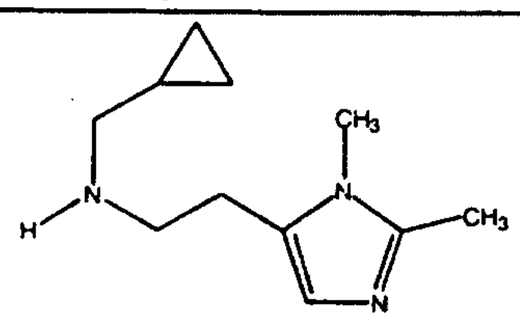
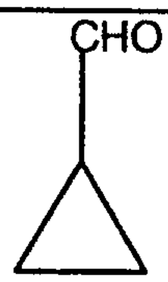
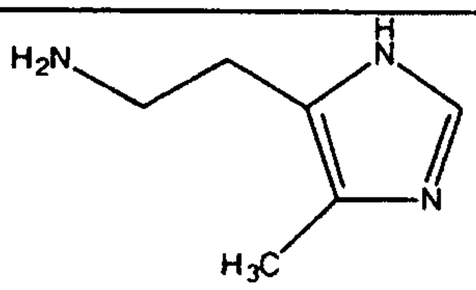
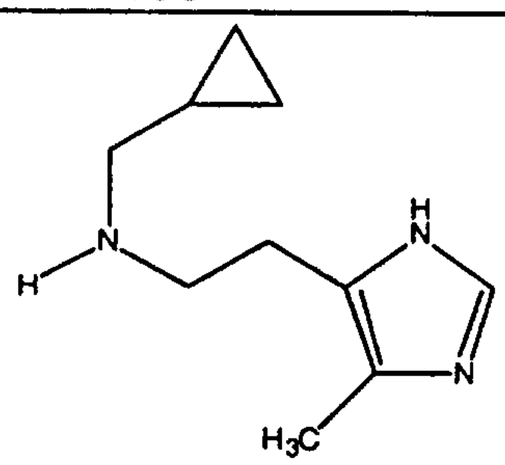
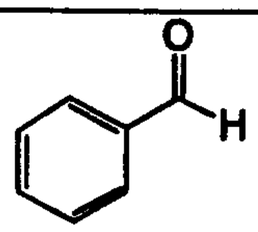
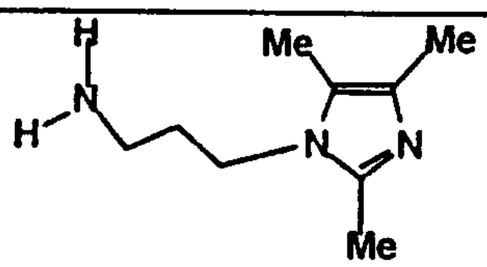
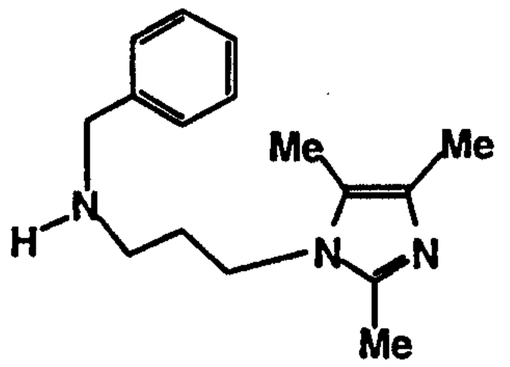
PREPARATIVE EXAMPLES 172-188

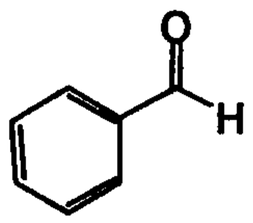
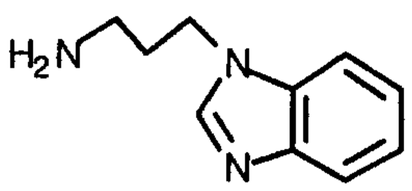
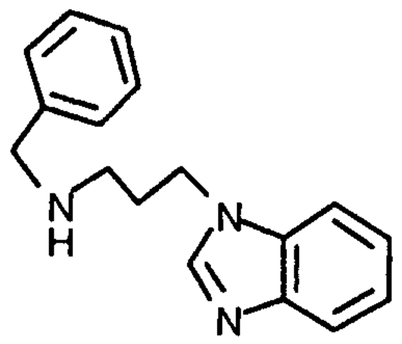
Following the procedure set forth in Preparative Example 74 but using the aldehyde and imidazoalkyl amine (Imidazole) in Table 5G, the amines (Product) in Table 5G were obtained.

TABLE 5G

Prep Ex.	Aldehyde	Imidazole	Product
172			 %Yield = 60 MH^+ = 246
173			 %Yield = 22 MH^+ = 247
174			 %Yield = 27 MH^+ = 214
175			 %Yield = 59 MH^+ = 299
176			%Yield = 76 MH^+ = 264

177			 %Yield = 77 MH⁺ = 264
178			 %Yield = 79 MH⁺ = 264
179			 %Yield = 45 MH⁺ = 291
180			 %Yield = 71 MH⁺ = 244
181			 %Yield = 25 MH⁺ = 258
182			 %Yield = 89 MH⁺ = 247

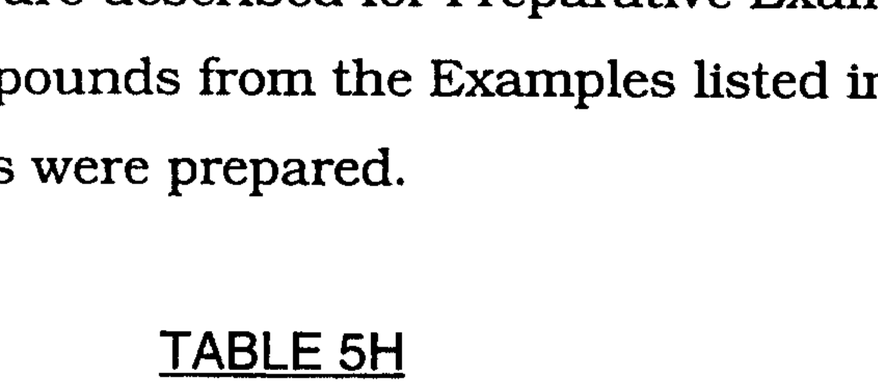
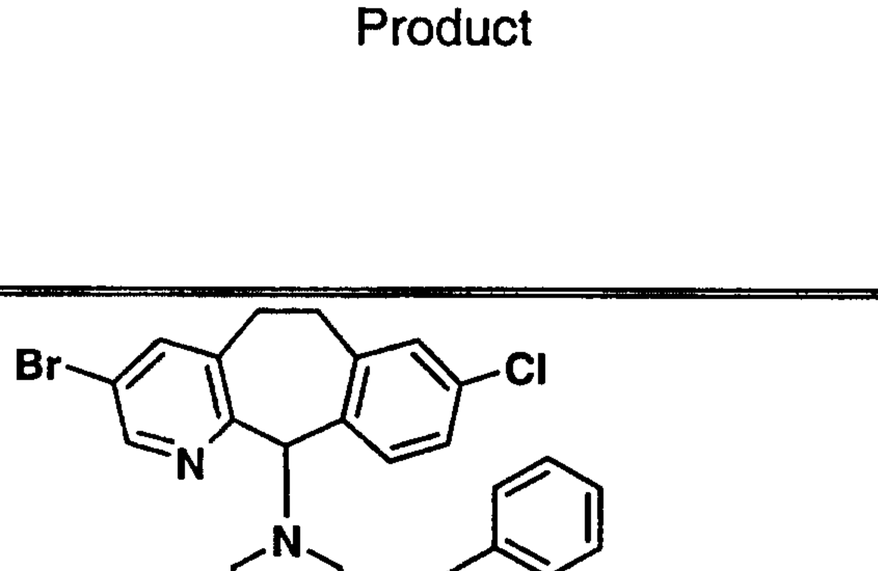
183			 %Yield = 13 MH^+ = 180
184			 %Yield = 27 MH^+ = 232
185			 %Yield = 50 MH^+ = 195
186			 %Yield = 12 MH^+ = 180
187			 %Yield = 84 MH^+ = 258

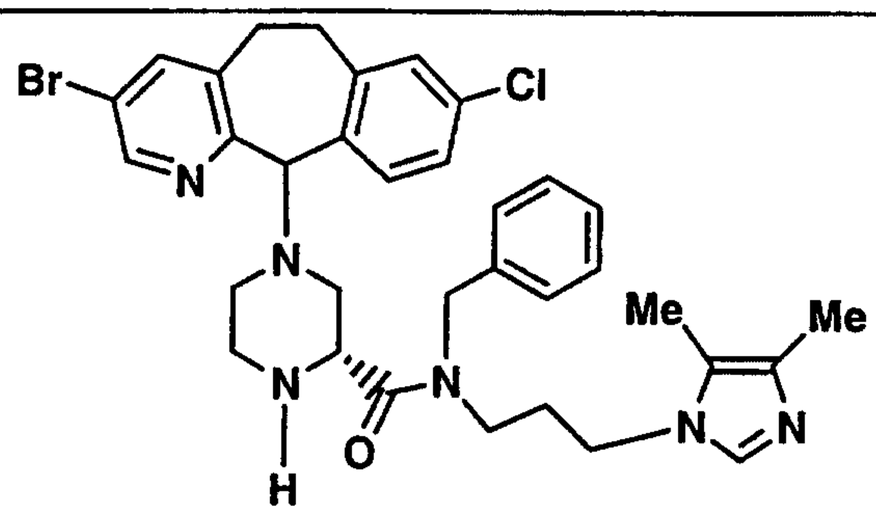
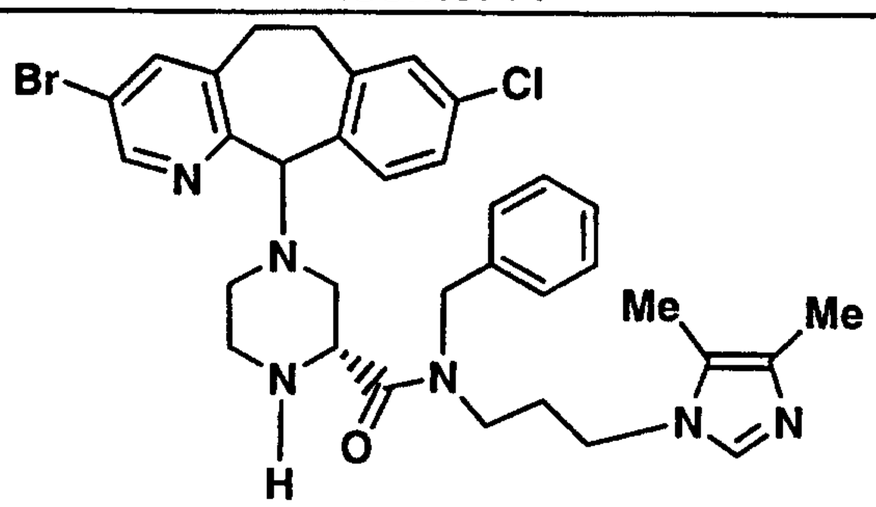
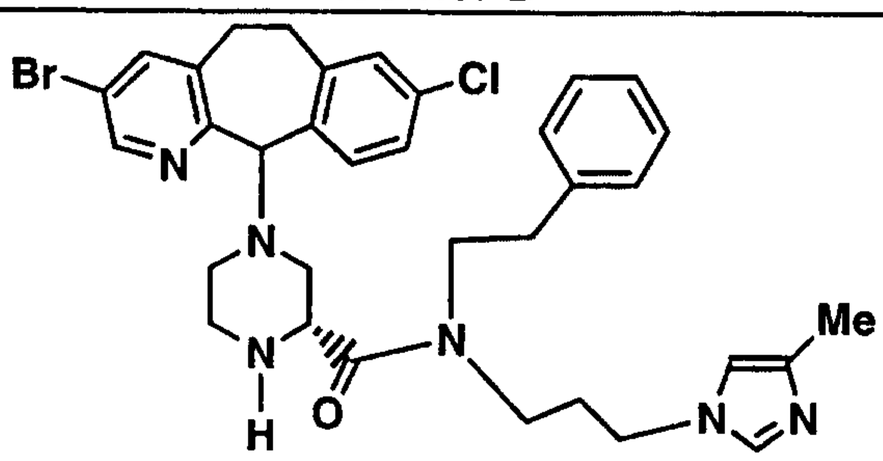
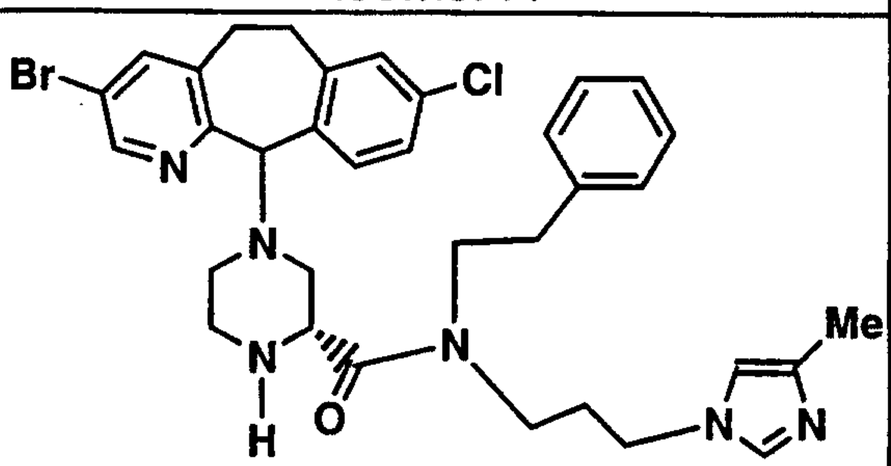
188			 %Yield = 88 MH^+ = 266

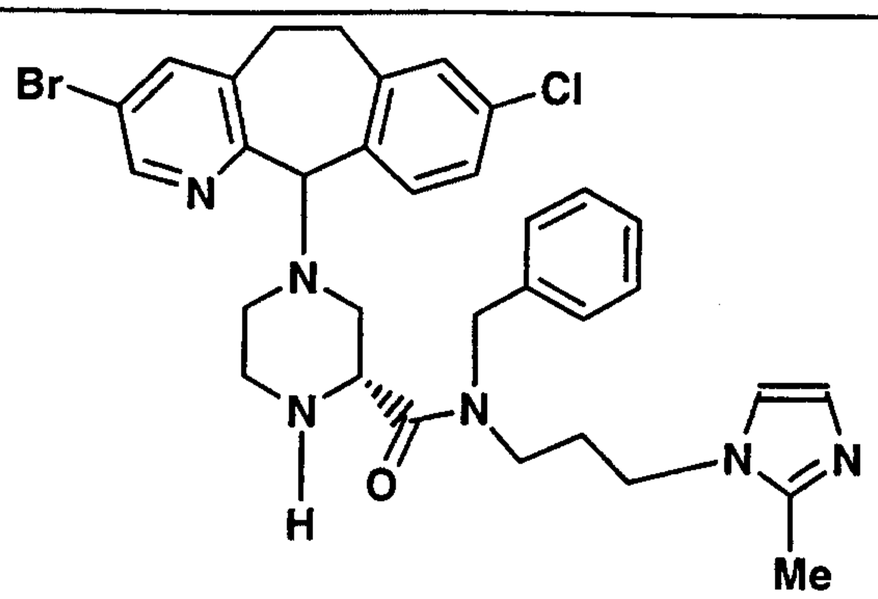
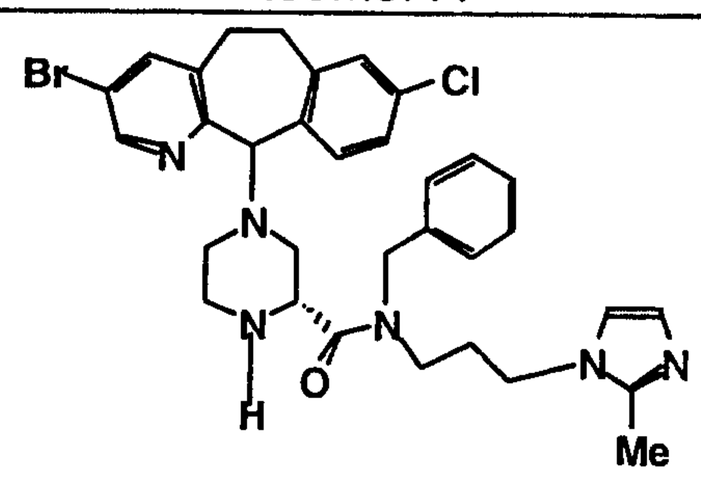
PREPARATIVE EXAMPLES 190-197

Using the procedure described for Preparative Example 109, but using the title compounds from the Examples listed in the Table 5H, the Product amines were prepared.

TABLE 5H

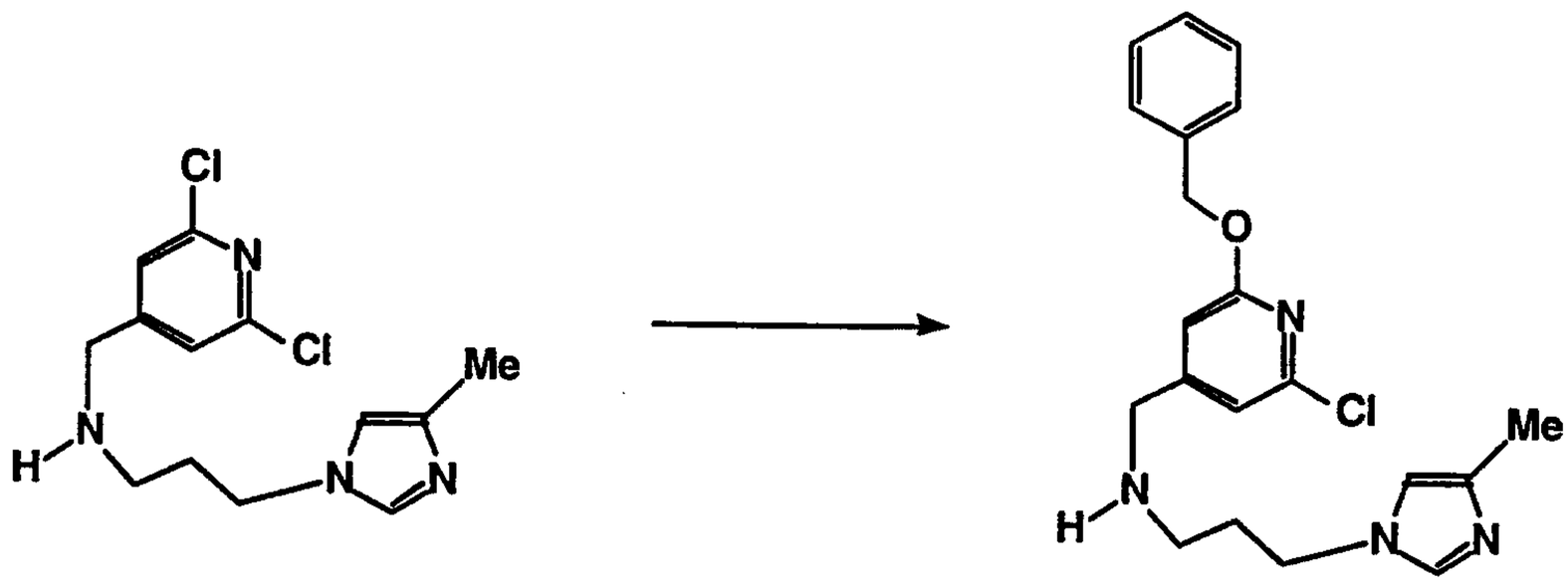
Prep. Ex.	BOC compound from Ex. No.	Product	1.Yield (%) 2. MH^+
190	343	 Isomer A	1. 661 2. 87
191	344	 Isomer B	1. 661 2. 80

192	345	 Isomer A	1. 72 2. 661
193	346	 Isomer B	1. 71 2. 661
194	347	 Isomer A	1. 93 2. 661
195	348	 Isomer B	1. 92 2. 661

196	349	 Isomer A	1. 85 2. 647
197	350	 Isomer B	1. 87 2. 647

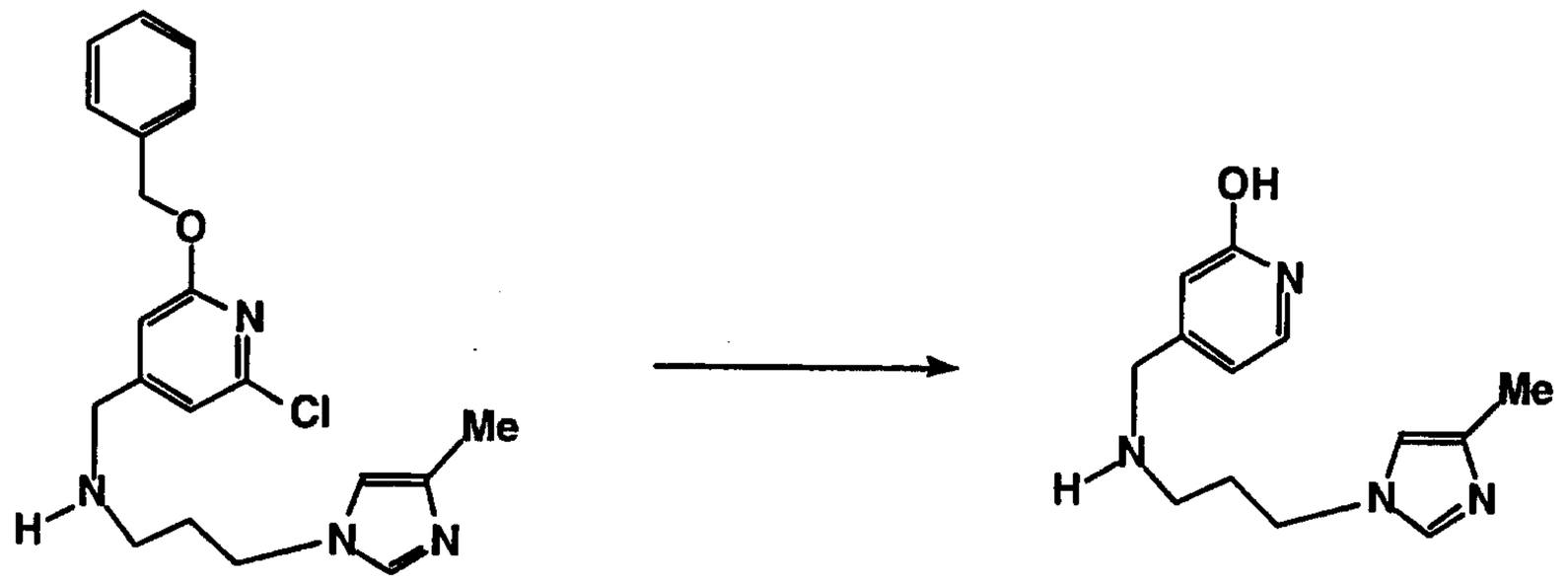
PREPARATIVE EXAMPLE 199

Step A



The title compound from Preparative Example 175 (0.9 g), benzyl alcohol (0.68 mL), solid potassium hydroxide (0.66 g), 18-crown-6-ether (80 mg) and anhydrous toluene (20 mL) were stirred at reflux. Purification by preparative plate chromatography (silica, 4% MeOH-CH_2Cl_2, NH_4OH saturated) afforded the benzyl ether (0.73 g, 68%, MH^+ = 371).

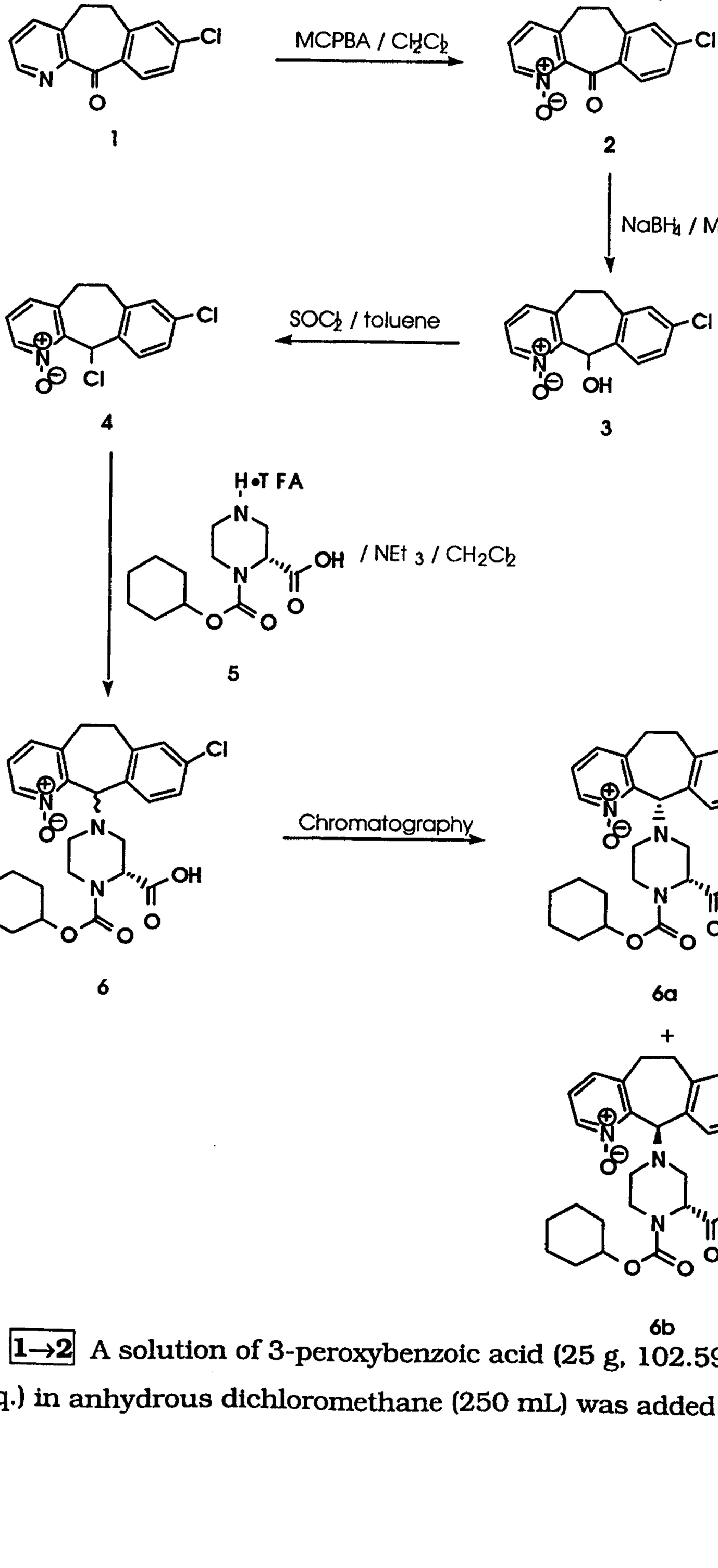
Step B



The title compound from Step A above (0.72 g), methanol (60 mL) and 10%palladium on carbon (300 mg) were stirred under 50 psi hydrogen atmosphere for 3 days. Filtration through celite afforded a solution which was treated with TEA (3 equiv) and CH_2Cl_2. Filtration and purification by preparative plate chromatography (silica, 5% MeOH-CH_2Cl_2, NH_4OH saturated) afforded the title compound (0.20 g, 42%, MH^+ = 247).

PREPARATIVE EXAMPLE 200

Preparation of the tricyclic N-oxide moiety



1→2 A solution of 3-peroxybenzoic acid (25 g, 102.59 mmol, 2.5 eq.) in anhydrous dichloromethane (250 mL) was added

dropwise over a period of one hour to a stirred solution of 8-chloro-4-aza-10,11-dihydro-5*H*-dibenzo[a,d]cyclohepten-5-one **1** (10 g, 41.04 mmol, 1.0 eq.) in anhydrous dichloromethane (100 mL) at 0 °C under a nitrogen atmosphere. The solution was slowly (3h) warmed to room temperature and stirred for another 12h. The solution was extracted with 1 *M* aqueous sodium hydroxide solution (5 x 100 mL), washed with brine (2 x 100 mL), dried over Na_2SO_4, filtered, and concentrated under house vacuum at 30 °C to give **2** as a canary-yellow solid. The title compound **2** was used directly without further attempts at purification.

Yield: 10 g ≡ 38.51 mmol ≡ 94%

$[M + H]^+$: 260

HRMS (FAB+):

Calculated for $C_{14}H_{11}ClNO_2$ ($[M + H]^+$): 260.0475

Observed: 260.0478

2→3 Sodium borohydride (2.21 g, 57.76 mmol, 1.5 eq.) was added portionwise over a period of 15 minutes to a solution of **2** (10 g, 38.51 mmol, 1.0 eq.) in anhydrous methanol (500 mL) at 0 °C under a nitrogen atmosphere. The resulting suspension was stirred at 0 °C for one hour and at room temperature for another hour. The volatiles were removed under house vacuum at 30 °C and the residue was taken up in 1 *M* aqueous NaOH solution (250 mL). The aqueous solution was extracted with dichloromethane (5 x 100 mL). The combined organic extracts were washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated under house vacuum at 30 °C to give **3** as a lime-green solid. Compound **3** was used directly without any attempts at purification.

Yield: 9 g ≡ 34.39 mmol ≡ 89%

$[M + H]^+$: 262

HRMS (FAB+):

Calculated for $C_{14}H_{13}ClNO_2$ ($[M + H]^+$): 262.0635

Observed: 262.0636

3→4 Thionyl chloride (5 mL, 68.78 mmol, 2.0 eq.) was added dropwise over a period of 10 minutes to a stirred suspension of **3** (9 g, 34.39 mmol, 1.0 eq.) and anhydrous toluene (150 mL) at 0 °C under a nitrogen atmosphere. The cream-colored suspension was slowly (3h) warmed to room temperature and stirred for another 12h. The volatiles were removed under house vacuum at 30 °C. The residue was taken up in dichloromethane (250 mL) and washed with ice-cold, saturated aqueous $NaHCO_3$ solution (5 x 100 mL) until the aqueous washings were moderately basic at pH 9. The organic layer was washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated under house vacuum at 30 °C to give **4** as a cream-colored solid in essentially quantitative yield. Due to its high reactivity, compound **4** was used directly without any attempts at purification or characterization (other than ^1H NMR).

Yield: 9.55 g ≡ 34.09 mmol ≡ 99%

4→6 Triethylamine (18 mL, 126.65 mmol, 5.0 eq.) was added dropwise to a stirred solution of **5** (previously described in the art; 9.38 g, 25.33 mmol, 1.0 eq.) in anhydrous dichloromethane (50 mL) at room temperature under a nitrogen atmosphere. The solution was stirred at room temperature for 30 minutes and was cooled to 0 °C. A solution of **4** (8.52 g, 30.39 mmol, 1.2 eq.) in anhydrous dichloromethane (50 mL) was added dropwise over a period of 25 minutes. The mixture was slowly (3h) warmed to room temperature and stirred for another 12h. The volatiles were removed under house vacuum at 30 °C. The residue was taken up in 50% m/v aqueous citric acid solution (100 mL) and extracted with ethyl acetate (5 x 100 mL). The organic extracts were combined and dried over Na_2SO_4, filtered, and concentrated under house vacuum at 30 °C. The residual cream-colored solid was flash-chromatographed

(CH_2Cl_2:MeOH = 19:1 v/v) to give the diastereomerically pure isomers **6a** and **6b** at C-11 of the tricycle.

For 6a:

Yield: 5.75 g ≡ 11.50 mmol ≡ 45%

Off-white foam; M.p.: 78-83 °C

$[M + H]^+$: 500

HRMS (FAB+):

Calculated for $C_{26}H_{31}ClN_3O_5$ ($[M + H]^+$): 500.1953

Observed: 500.1952

For 6b:

Yield: 3.00 g ≡ 6.00 mmol ≡ 24%

Off-white solid; M.p.: 94-99 °C

$[M + H]^+$: 500

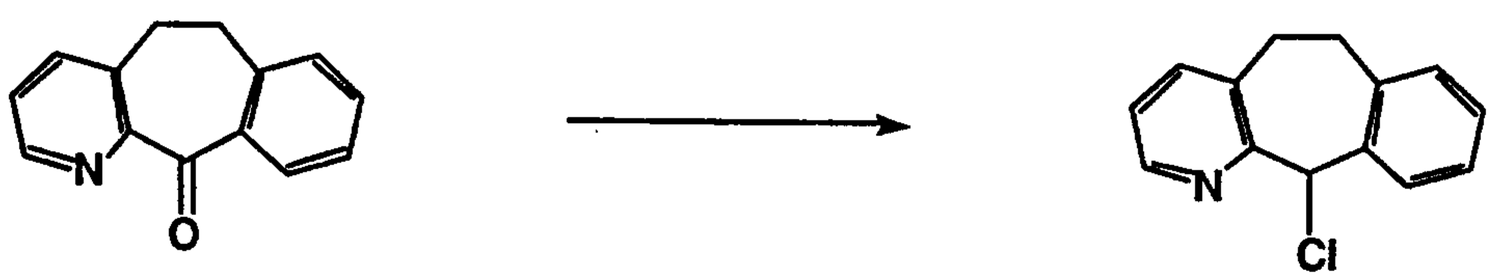
HRMS (FAB+):

Calculated for $C_{26}H_{31}ClN_3O_5$ ($[M + H]^+$): 500.1953

Observed: 500.1952

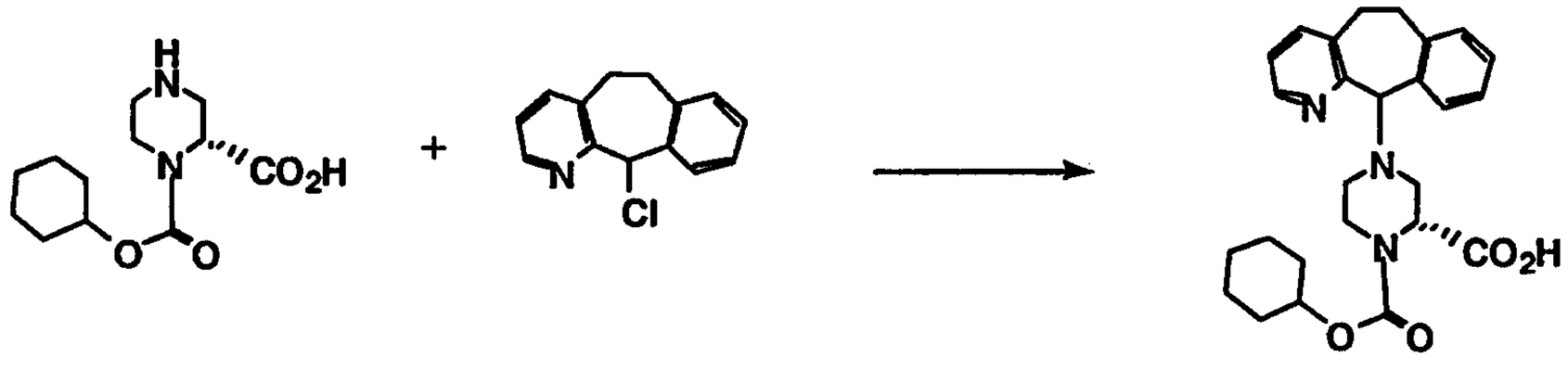
PREPARATIVE EXAMPLE 201

Step A



Following the procedure outlined in US 5,151,423, except substituting the 8-chloro tricycle with the 8-H analog described in US 3,419,565, the 8-hydrido tricyclic chloride is obtained.

Step B



Following the procedure described for Preparative Example 127 Step C, except using the 8-hydrido tricyclic chloride from Preparative Example 201 Step A instead of the 8-chloro tricyclic chloride, the title compounds were isolated.

The isomers were separated by column chromatography (silica) using 3% MeOH/CH_2Cl_2.

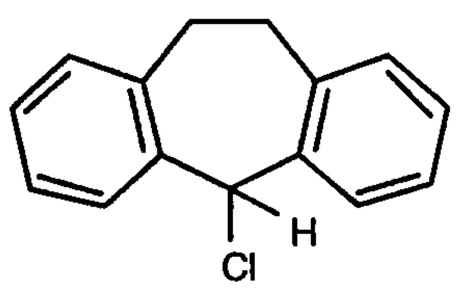
Isomer A: C(11)-(S): 38%, MH^+=450.

Isomer B: C(11)-(R): 31%, MH^+=450.

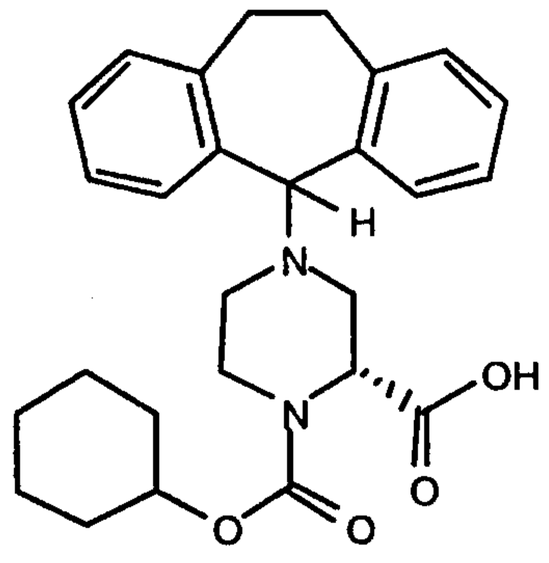
PREPARATIVE EXAMPLE 202

Step A

Following the procedure set forth in Preparative Example 127 Step C, but substituting the tricyclic chloride

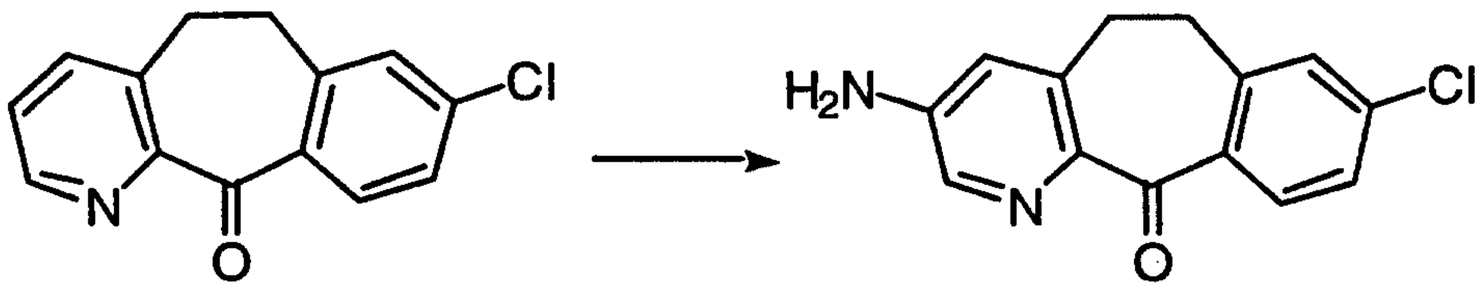


for the 8-Cl tricyclic chloride, one obtains the following acid:



Solid, 51% yield, mp=120.5-125.1°C.

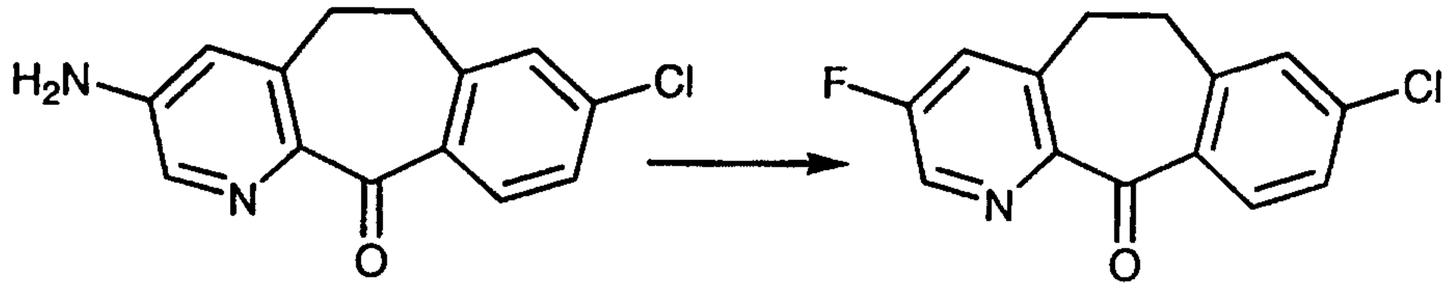
PREPARATIVE EXAMPLE 202A



By essentially the same procedure set forth in Njoroge et. al. (J. Med. Chem. (1997),**40**, 4290) for the preparation of 3-

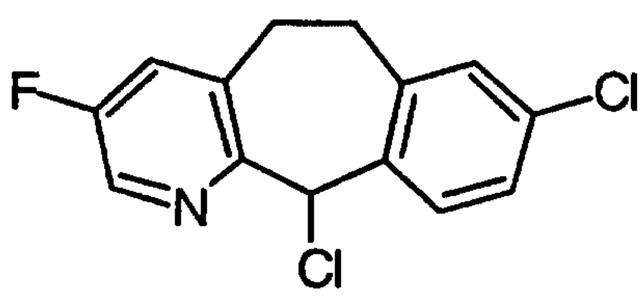
aminoloratadine only substituting the 3-H ketone (J. Het. Chem (1971) **8**, 73) for loratadine, the title compound was prepared.

PREPARATIVE EXAMPLE 203



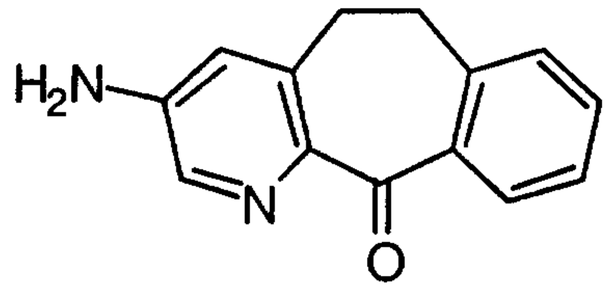
The title compound from Preparative Example 202A (1.62g, 6.26 mmol) was added portionwise to NO^+BF4^- (0.81g, 1.1 eq.) in toluene (10 mL) at 0 °C. The resulting slurry was stirred at 0 °C for 2.5 hours before warming to room temperature. The reaction mixture was heated at reflux for 2 hours, cooled, neutralized with 1N NaOH and extracted with EtOAc (3 X 50 mL). The combined organics were washed with 1N HCl (2 X 25 ml), saturated $NaHCO_3$ (1 X 25 mL), and water (1 X 15 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography using a 70 : 30 hexanes : EtOAc mix as eluent to yield a yellow solid (0.68g, 42% yield). LCMS: MH^+=262.

PREPARATIVE EXAMPLE 204



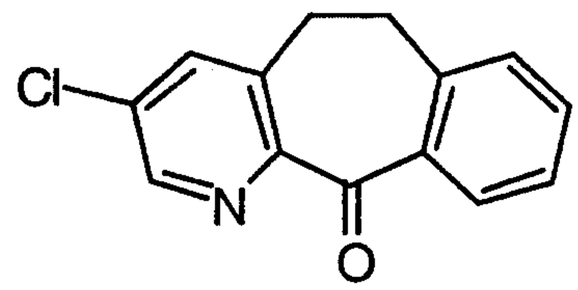
By essentially the same procedure set forth in Preparative Example 201 Step A, the title compound was prepared from the ketone of Preparative Example 203 and used without further purification (0.66g, 100% crude yield).

PREPARATIVE EXAMPLE 205



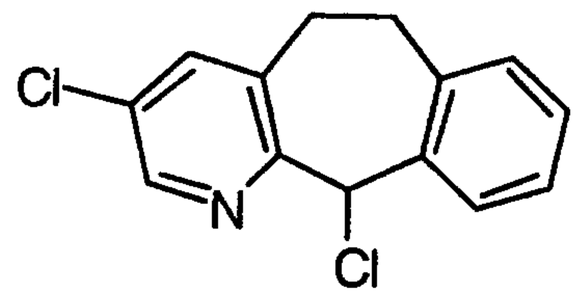
$^{+}NH_4HCO_2^{-}$ (2.44g, 10eq.) was added to a solution of the title compound from Preparative Example 202A (2.00g, 7.74 mmol) and 5% Pd/C (0.50g) in EtOH (100 mL) and the resulting solution was heated to reflux 2 hours. The reaction mixture was cooled, filtered through a plug of Celite and concentrated under reduced pressure. The residue was diluted with H_2O (100 mL) and extracted with CH_2Cl_2 (3 x 75 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated in vacuo to give a yellow solid (1.22g, 70% yield) which was used without further purification: FABMS: MH^{+}= 225.

PREPARATIVE EXAMPLE 206



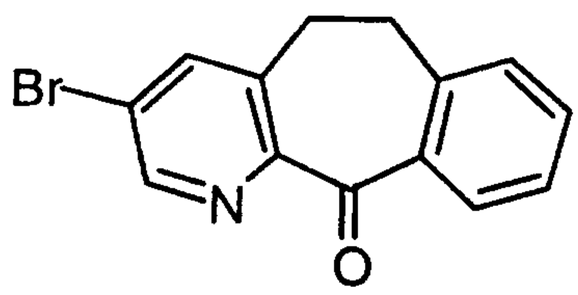
The title compound from Preparative Example 205 (1.22g, 5.44mmol) was added portionwise to $CuCl_2$ (0.88g, 1.2eq) and tBuONO (0.98mL, 1.5eq) in CH_3CN (25mL) at 0 °C. The resulting solution was warmed to RT and stirred for 72 hours. The reaction mixture was quenched by the addition of 1M HCl (10mL), neutralized with 15% NH_4OH and extracted with EtOAc (3 x 100mL). The combined organics were washed with 15% NH_4OH (1 x 50mL), 1M HCl (1 x 50mL) and saturated $NaHCO_3$, dried over Na_2SO_4, filtered and concentrated. The crude product was purified by flash chromatography using a 50:50 EtOAc:hexanes mixture as eluent to give a pale yellow solid (0.81g, 61% yield): CIMS: MH^{+}=244.

PREPARATIVE EXAMPLE 207



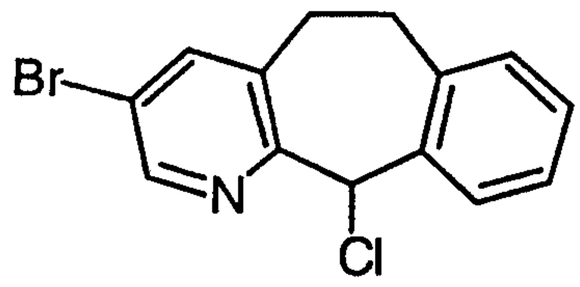
By essentially the same procedure set forth in Preparative Example 201 Step A, the title compound was prepared from the ketone of Preparative Example 206 and used without further purification.

PREPARATIVE EXAMPLE 208



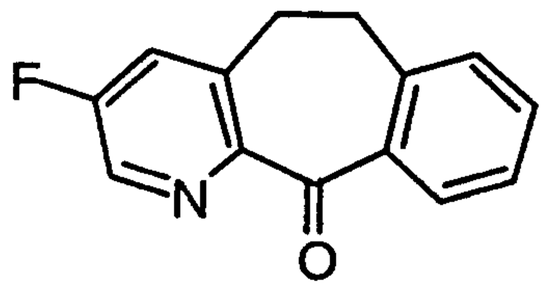
By essentially the same procedure set forth in Preparative Example 206, only substituting $CuBr_2$ for $CuCl_2$ the title compound was prepared (1.33g, 60% yield):FABMS: MH^+= 244.

PREPARATIVE EXAMPLE 209



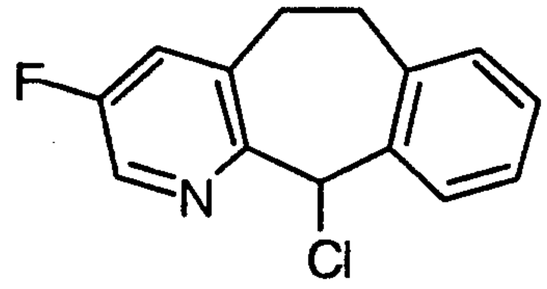
By essentially the same procedure set forth in Preparative Example 201 Step A, the title compound was prepared from the ketone of Preparative Example 208 and used without further purification.

PREPARATIVE EXAMPLE 210



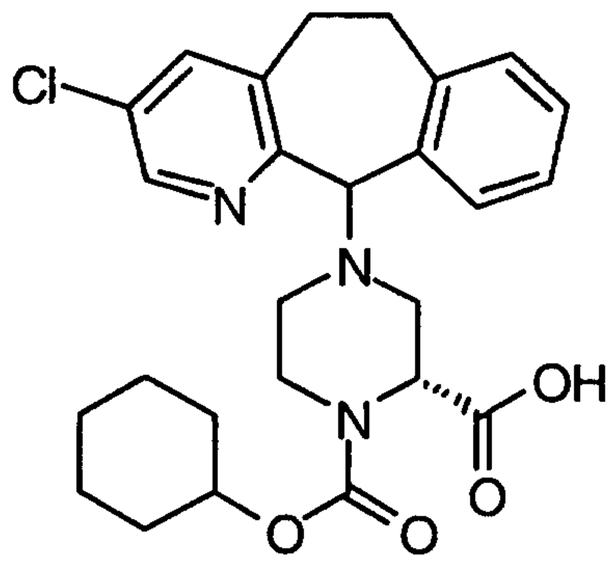
By essentially the same procedure set forth in Preparative Example 203 only substituting the title compound from Preparative Example 205, the title compound can be prepared.

PREPARATIVE EXAMPLE 211



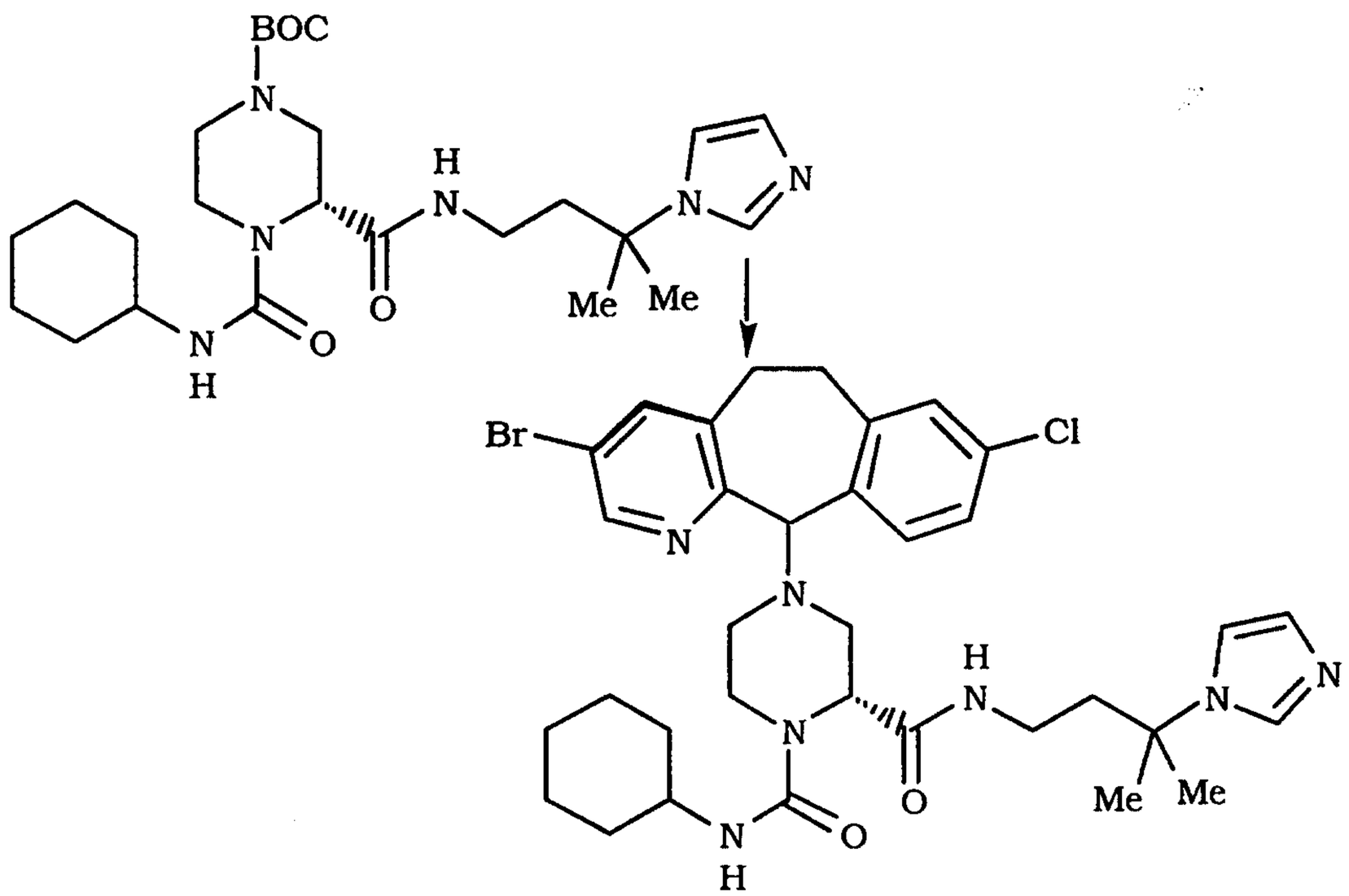
By essentially the same procedure set forth in Preparative Example 201 Step A, except starting with the ketone of Preparative Example 210, the title compound can be prepared.

PREPARATIVE EXAMPLE 212

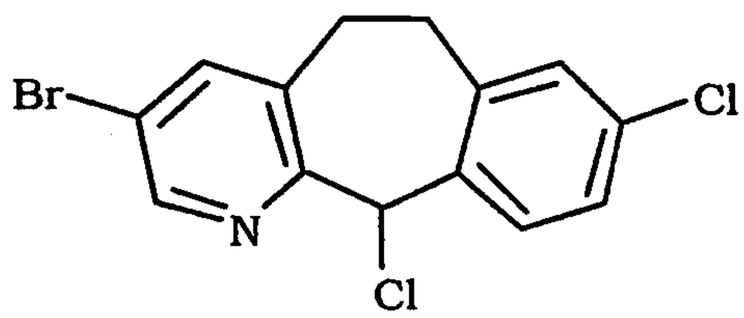


By essentially the same procedure set forth in Preparative Example 127 Step C, only substituting the 3-Cl, 8-H tricyclic chloride prepared in Preparative Example 207 for the 3-H, 8-Cl tricyclic chloride the title compound (C-11(S)- and (R)-isomers) was prepared. FABMS: MH^+= 484.

EXAMPLE 1



A solution of the title compound from Preparative Example 5 (0.44g, 0.897 mmol) was stirred at room temperature in CH_2Cl_2 (10 mL) and TFA (4 mL) until starting material was consumed (TLC). The reaction mixture was concentrated under reduced pressure to remove any excess TFA and the compound was redissolved in CH_2Cl_2 (5 mL), treated with chloride (42.0)

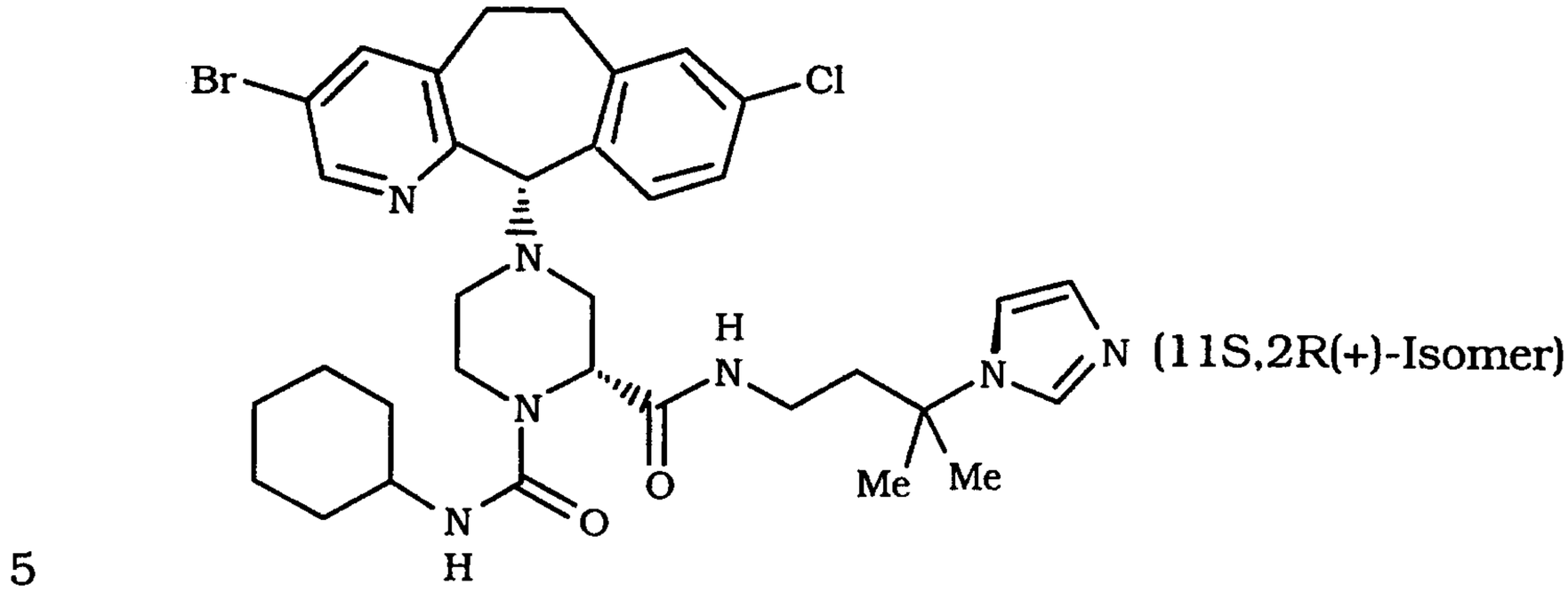


(42.0)

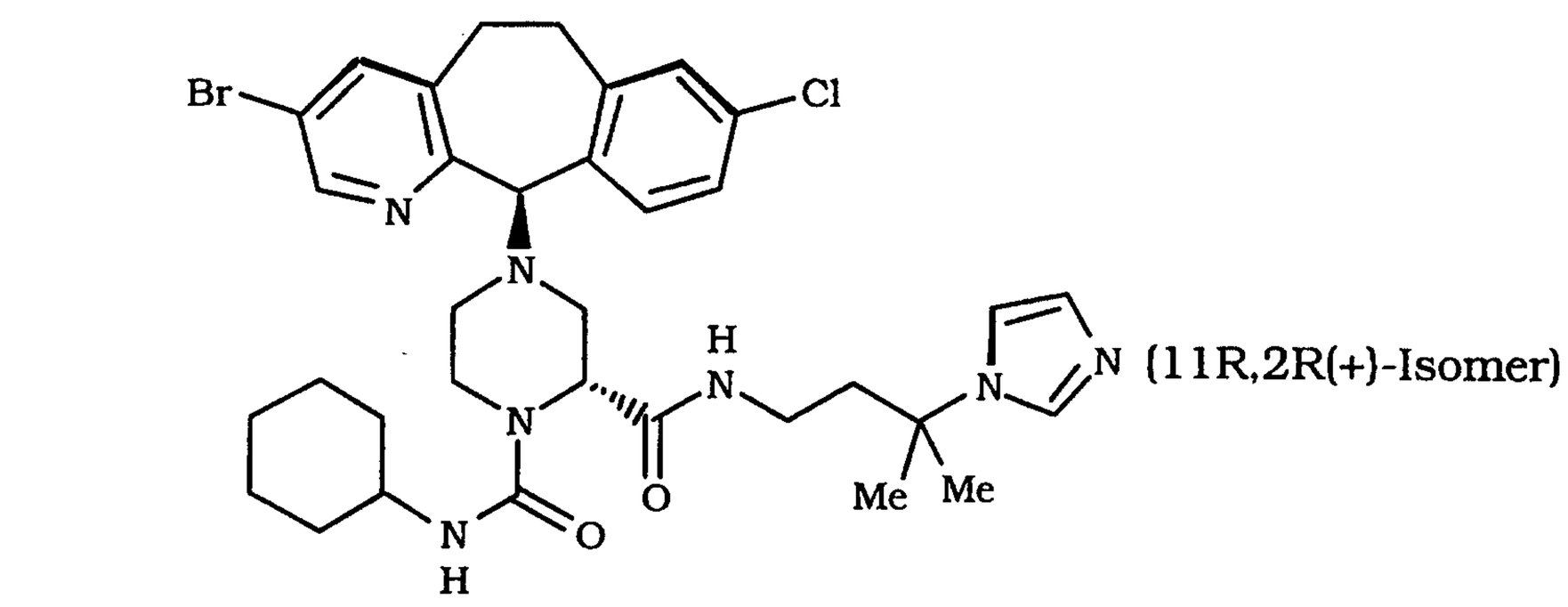
(0.37g, 1.2 eq.) and TEA (2.5 mL, 10 eq.) and stirred at room temperature for 84 hours. The reaction mixture was diluted with saturated $NaHCO_3$ (25 mL), water (25 mL), and CH_2Cl_2 (25 mL) and separated. The aqueous layer was extracted with CH_2Cl_2 and the combined organics dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography using a 5% (10% NH_4OH in MeOH) solution in

CH_2Cl_2 as eluent to yield a tan solid (0.45g, 71% yield). mp 142-144°C; FABMS: MH^+= 696.

EXAMPLE 2



(11S,2R(+)-Isomer)



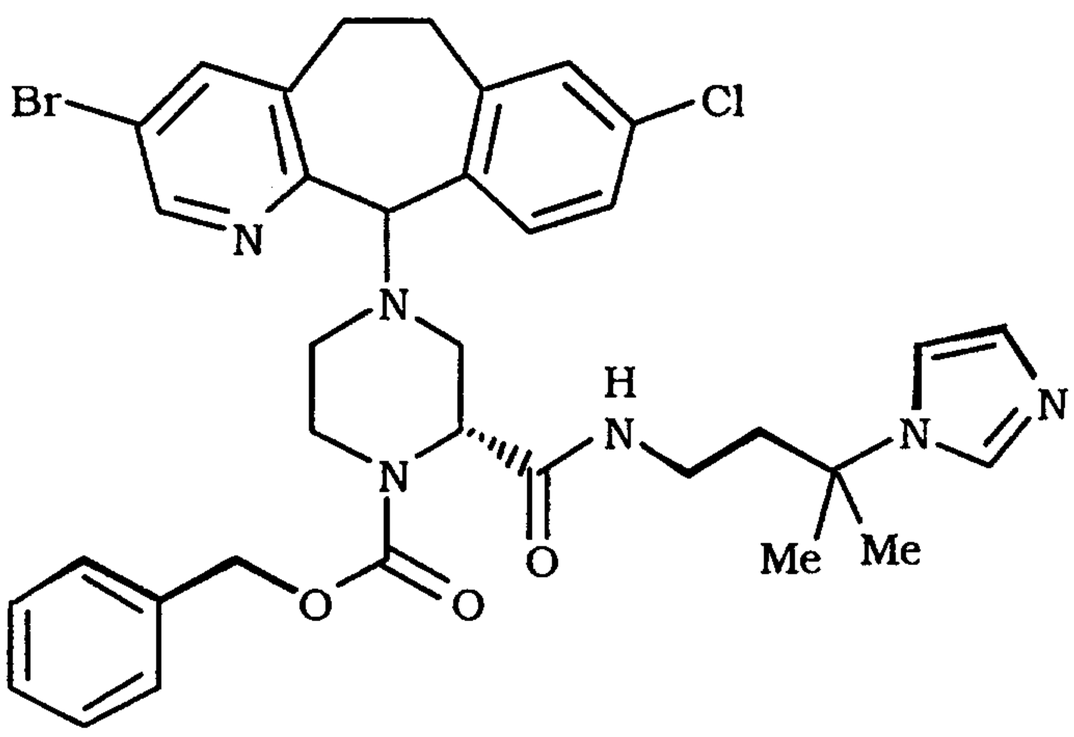
(11R,2R(+)-Isomer)

The title compound from Example 1 was separated into the 11(S)(+)- and 11(R)(+)- diastereomers by preparative HPLC using a CHIRALPAK AD column using a 12% i-PrOH in hexanes solution with 0.2% diethylamine as eluent:

11S,2R(+)-Isomer: retention time= 29.21 minutes; $[\alpha]^{23.5}_D$= +19.1 (3.35 mg in 2.0 mL $CHCl_3$); mp= 147-149°C; LCMS: MH^+= 696.

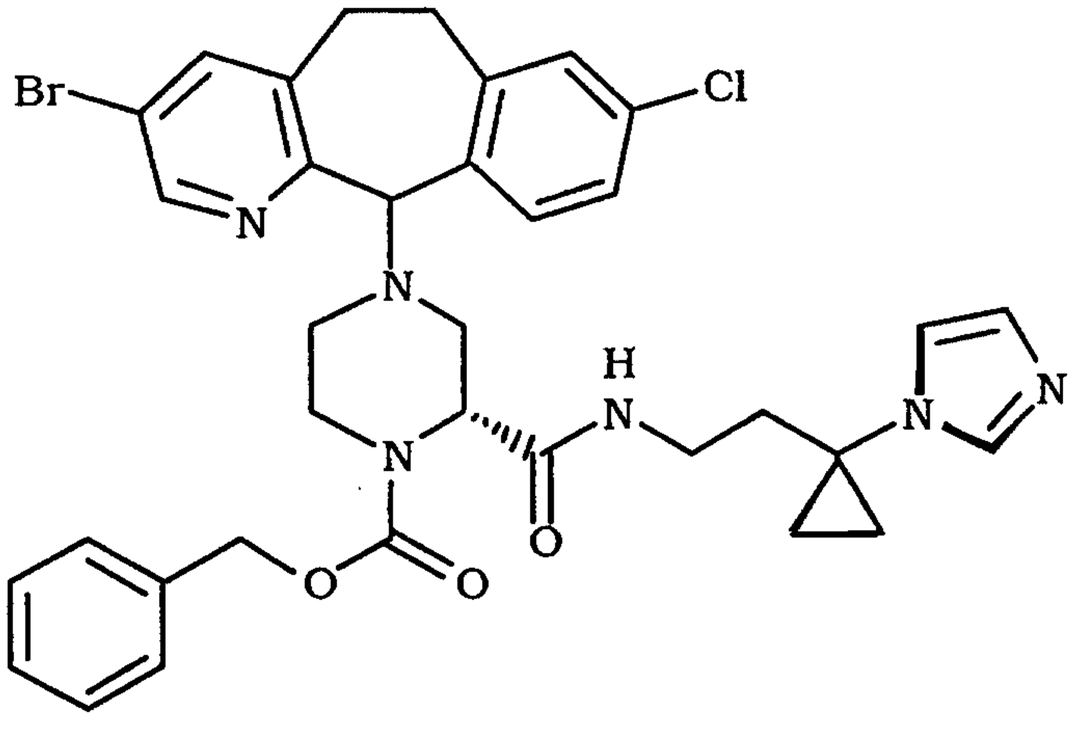
11R,2R(+)-Isomer: retention time= 39.8 minutes; $[\alpha]^{24.1}_D$= +73.0 (3.07 mg in 2.0 mL $CHCl_3$; mp= 128-131°C; LCMS: MH^+= 696.

EXAMPLE 3



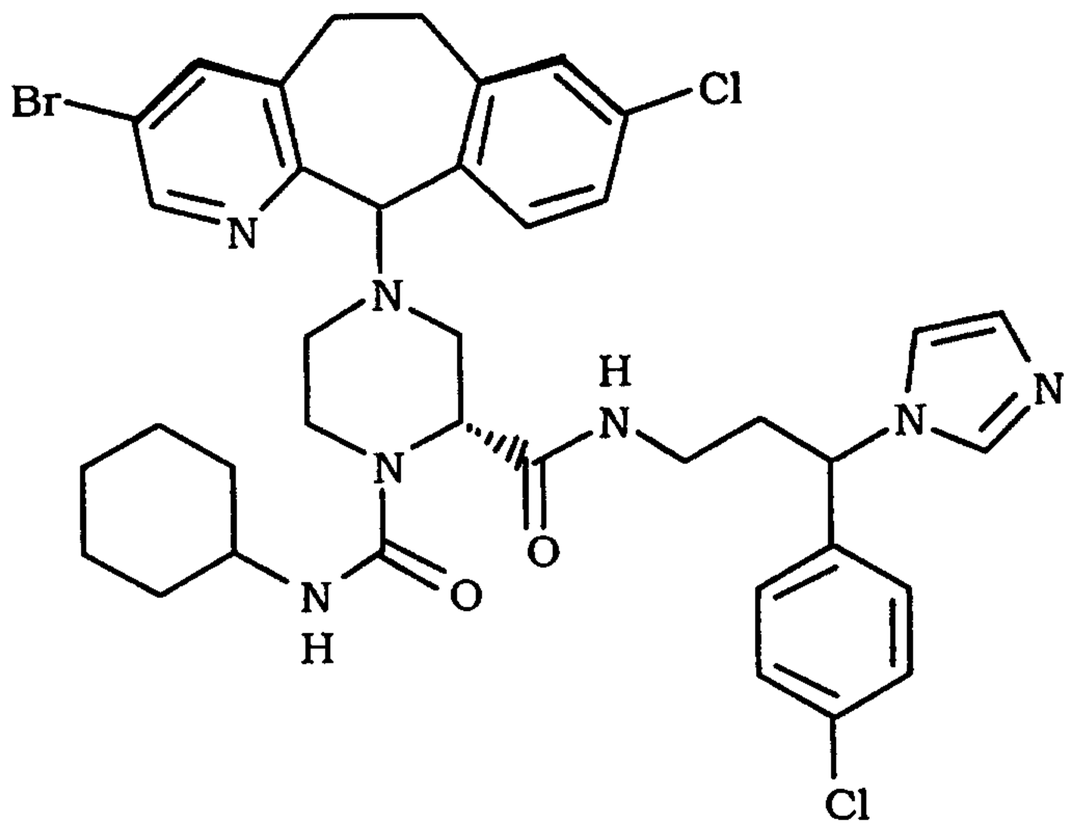
By essentially the same procedure as that set forth in Example 1, except using the title compound from Preparative Example 6, the title compound was prepared (0.085g, 45% yield). mp 103-106°C; LCMS: MH^+= 705.

EXAMPLE 4



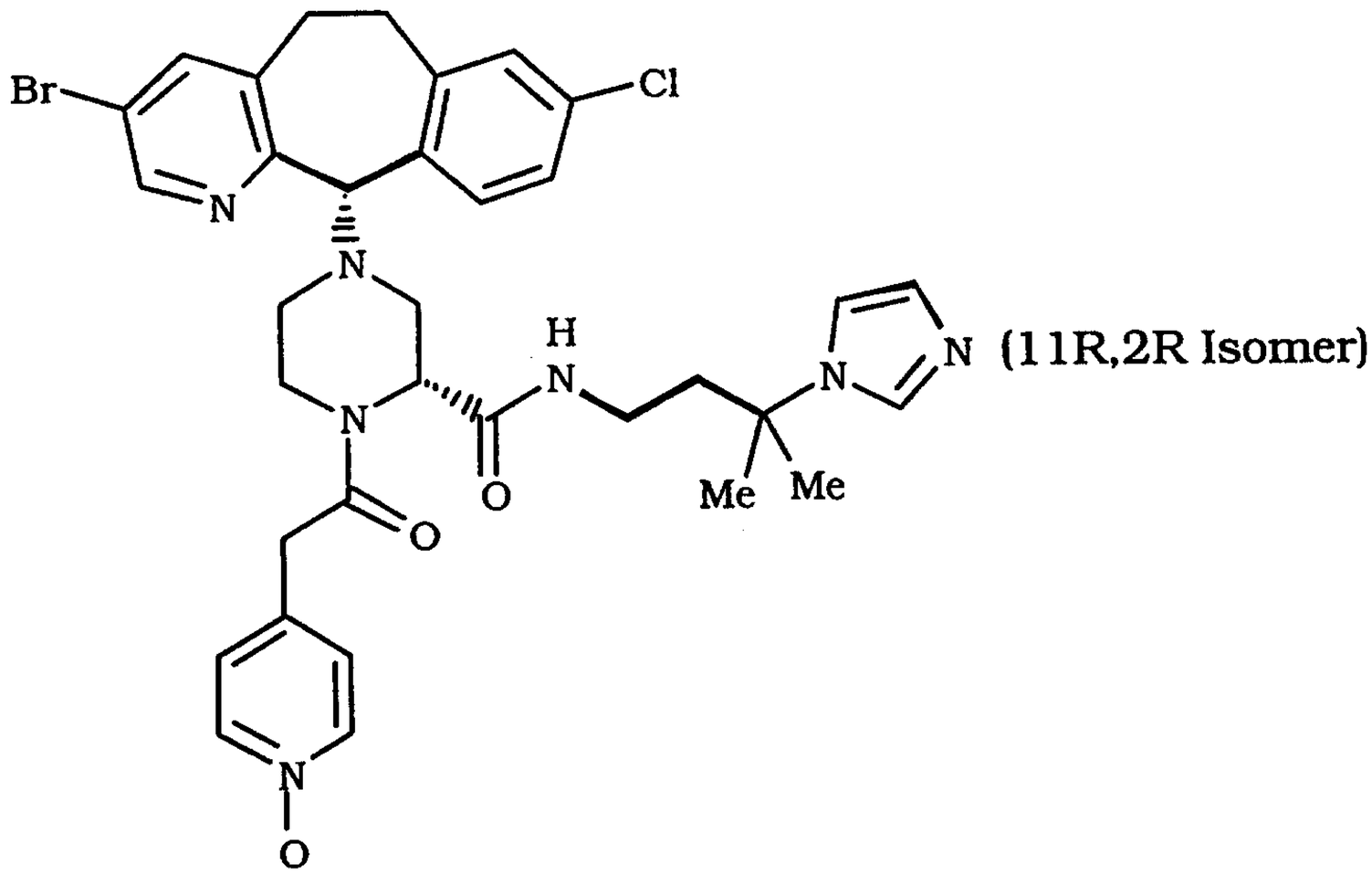
By essentially the same procedure as that set forth in Example 3, except using the title compound from Preparative Example 6.1, the title compound was prepared. mp = 111-115°C; MH^+ = 703

EXAMPLE 5



By essentially the same procedure as that set forth in Example 1, except using the title compound from Preparative Example 7, the title compound was prepared. mp 138-140°C; LCMS: MH^+= 778.

EXAMPLE 6



(11R,2R Isomer)

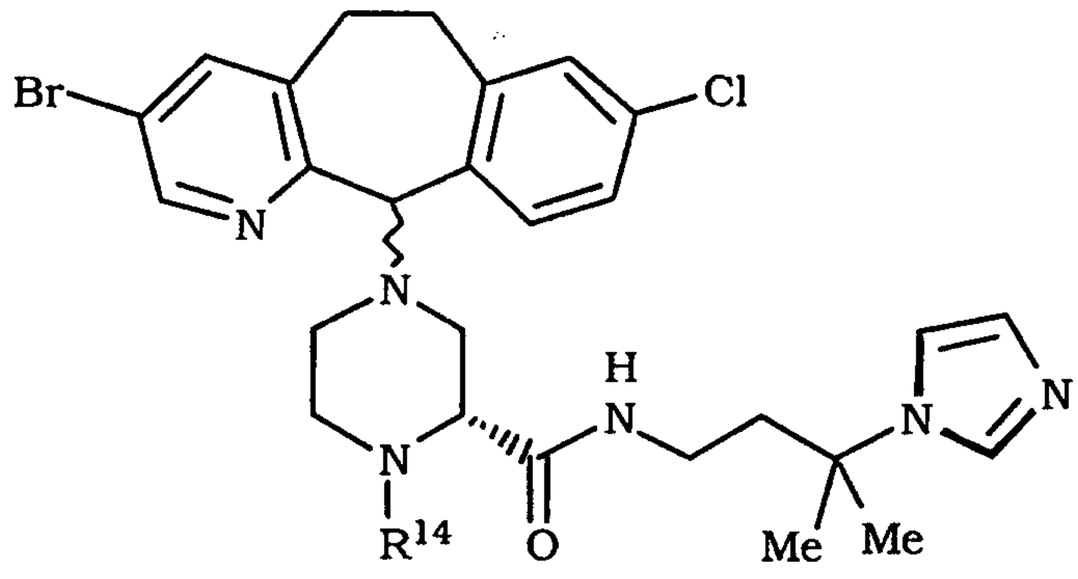
A solution of the title compound from Preparative Example 8 (0.10 g, 0.17 mmol) (11S,2R(-)-isomer) in DMF (1.0 mL) was treated with 4-pyridylacetic acid N-oxide (0.039 g, 1.5 eq.), NMM (0.03 mL, 1.5 eq), DEC (0.049 g, 1.5 eq.), and HOBT (0.034 g, 1.5 eq.) and the resulting solution stirred at room temperature overnight. The

reaction mixture was quenched by the addition of saturated $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (4 X 50 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by Preparative TLC using a 15% (10% NH_4OH in MeOH) solution in CH_2Cl_2 as eluent to yield the 11S,2R isomer(0.044g, 39% yield). mp= 115-117°C; LCMS: MH^+= 706.

By essentially the same procedure, except using the racemate or 11R,2R isomer from Preparative Example 8, one can obtain the corresponding racemate or 11R,2R isomer product.

EXAMPLES 7-9

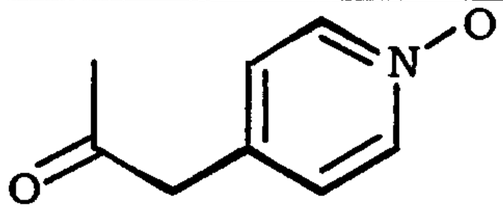
By essentially the same procedure as that set forth in Example 6, the compounds of the formula

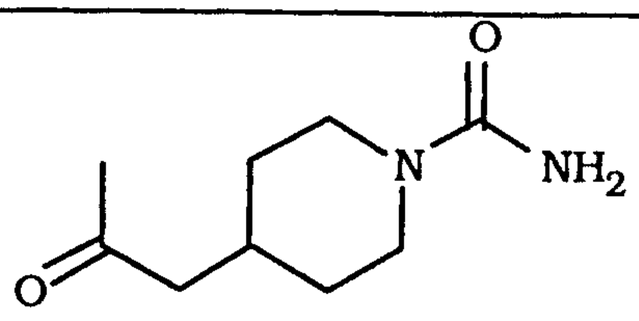
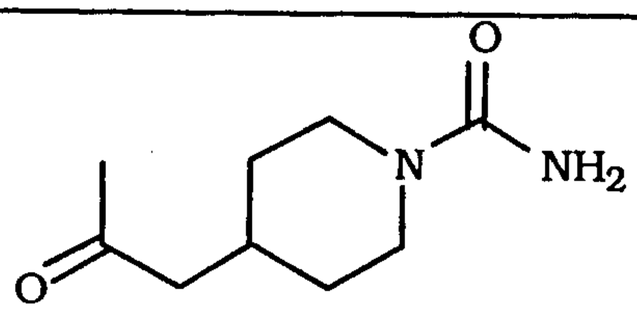


,

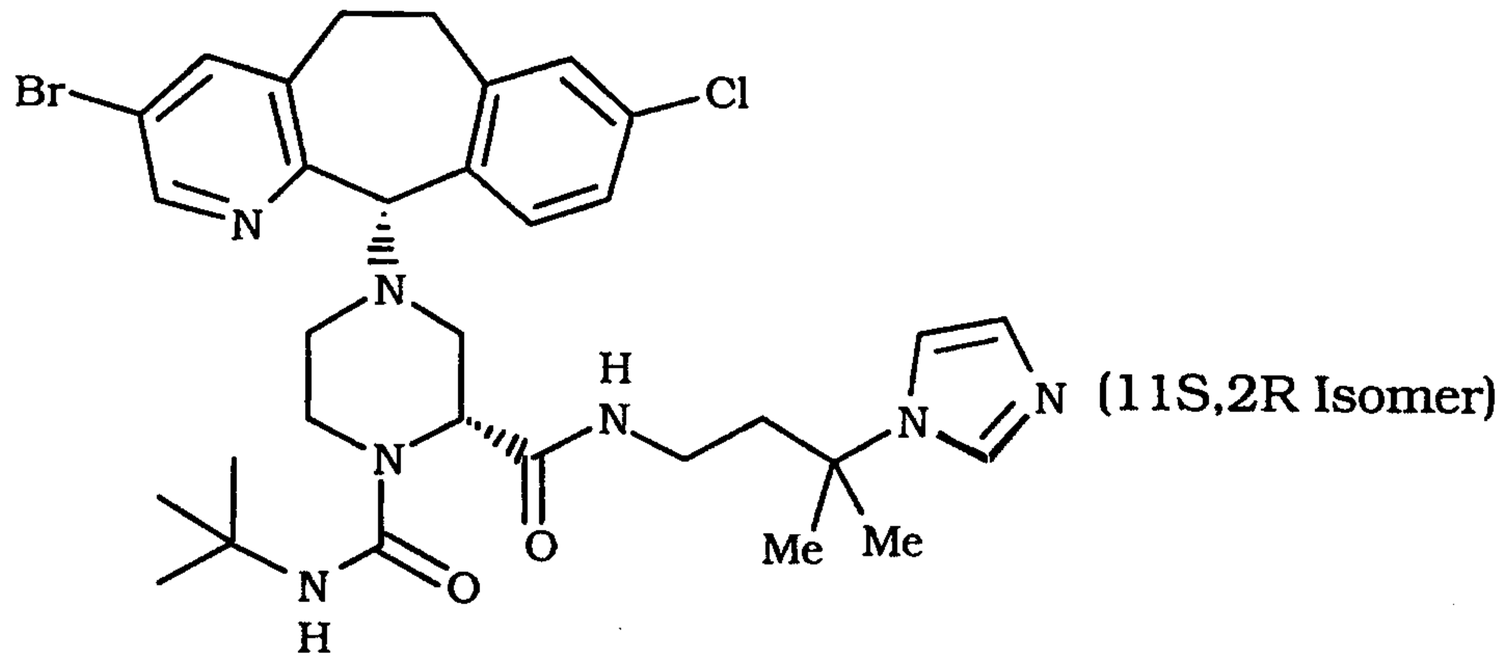
wherein R^{14} is as defined in Table 6 below, were obtained.

TABLE 6

EX.	R^{14}=	MP (°C)	Mass Spec
7	 11R,2R isomer	148-150	LCMS: MH^+=706

8	 11S,2R isomer	123-127	LCMS: MH^+=739
9	 11R,2R isomer	150-153	LCMS: MH^+=739

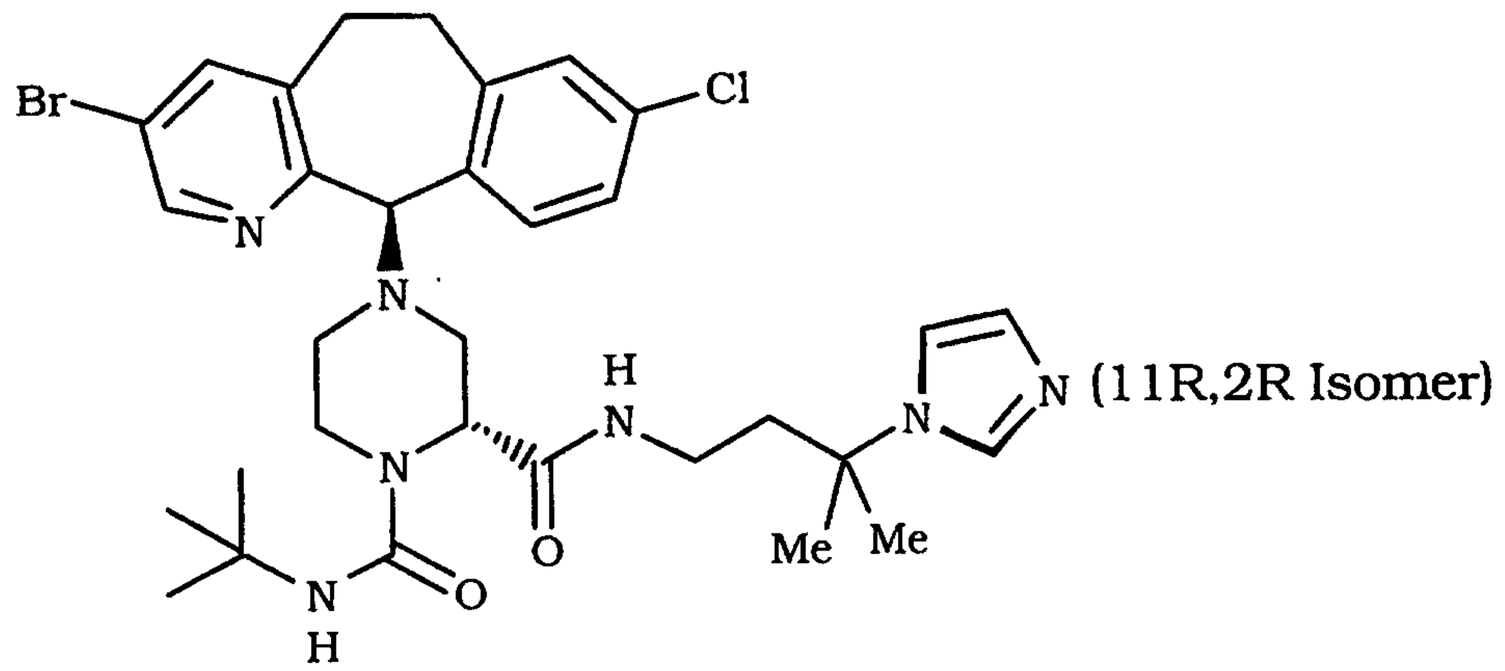
EXAMPLE 10



(11S,2R Isomer)

A solution of the title compound from Preparative Example 8 (11S,2R-isomer) (0.080 g, 0.14 mmol) in CH_2Cl_2 (2.0 mL) was treated with t-BuNCO (0.080 mL, 5.0 eq). The resulting solution was stirred at room temperature overnight and concentrated under reduced pressure. The crude product was purified by preparative TLC using a 10% (10% NH_4OH in MeOH) solution in CH_2Cl_2 as eluent to give the title compound (0.045g, 48% yield). mp=139-142°C; LCMS: MH^+= 670.

EXAMPLE 11

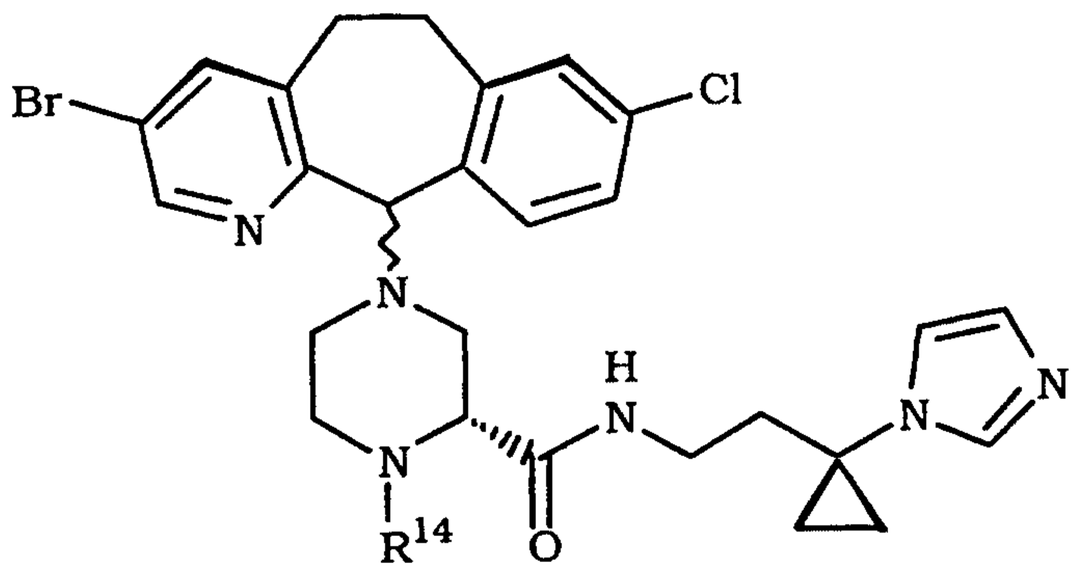


(11R,2R Isomer)

The title compound was prepared by essentially the same procedure as that set forth in Example 10, but substituting the 11R,2R-isomer from Preparative Example 8. mp= 157-159°C; LCMS: MH^+= 670.

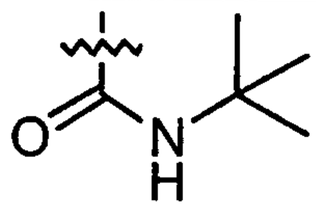
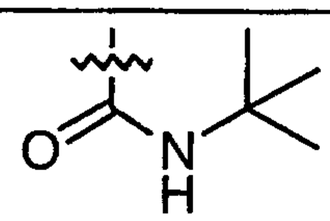
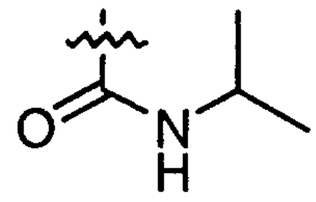
EXAMPLES 12-14

By essentially the same procedure as that set forth in Example 10, except the title compounds from Preparative Example 9 are used, the compounds of the formula

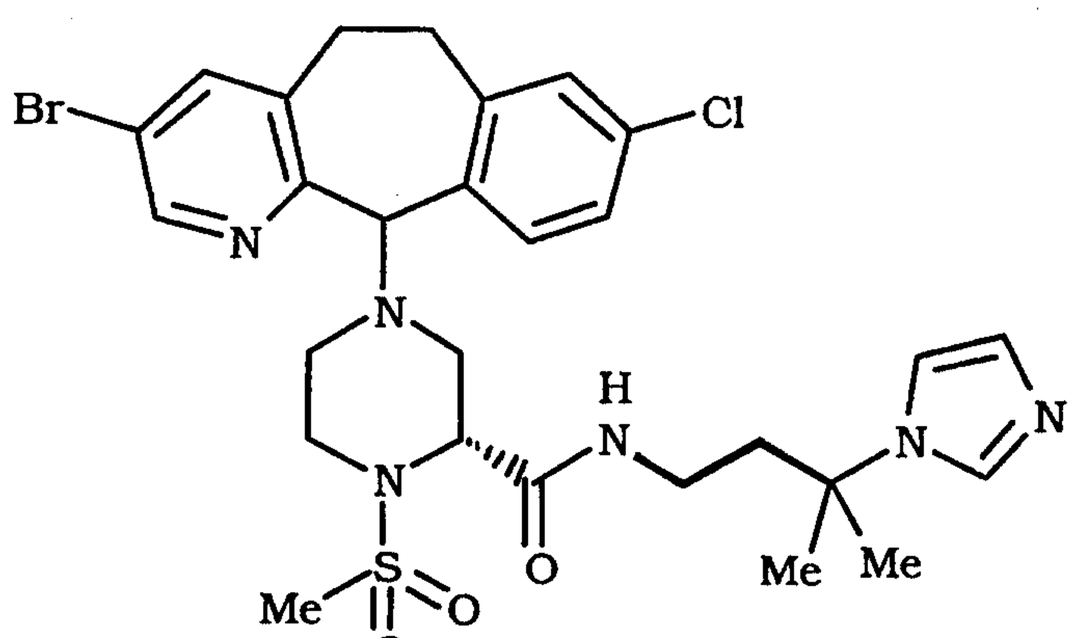


wherein R^{14} is as defined in Table 7 below, were obtained.

TABLE 7

EX.	R=	MP (°C)	Mass Spec
12	 ; 11S,2R isomer	136-139	LCMS: MH^+= 668
13	 11R,2R isomer	106-110	LCMS: MH^+= 668
14	 11R/S,2R isomers	133-139	LCMS: MH^+= 654

EXAMPLE 15



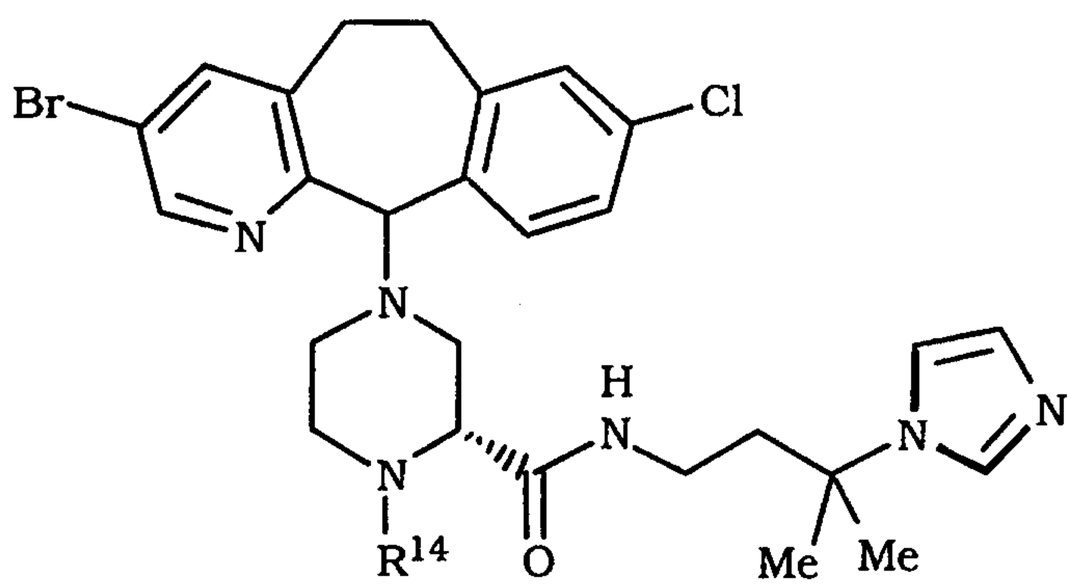
To a solution of the title compound (11-racemate) from Preparative Example 8 (0.072g, 0.12 mmol) and TEA (0.010 mL, 1.1 eq.) in CH_2Cl_2 (4 mL) was added $MeSO_2Cl$ (0.01 mL, 1.1 eq.) and the resulting solution was stirred at room temperature overnight. The reaction mixture was quenched by the addition of saturated $NaHCO_3$ (5 mL), separated and extracted with CH_2Cl_2 (2 X 50 mL).

The combined organics were dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by preparative TLC using a 10% (10% NH_4OH in MeOH) solution in CH_2Cl_2 as eluent (44 mg, 63% yield). mp= 107-110°C; LCMS: MH^+= 649.

By essentially the same procedure, the 11R,2R or 11S,2R isomers can be obtained by using the 11R,2R or 11S,2R isomer, respectively, title compounds from Preparative Example 8.

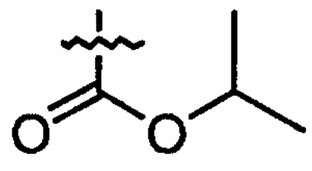
EXAMPLES 16-18

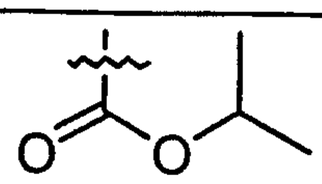
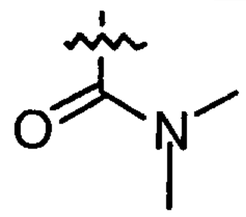
By essentially the same procedure as that set forth in Example 15, compounds of the formula:



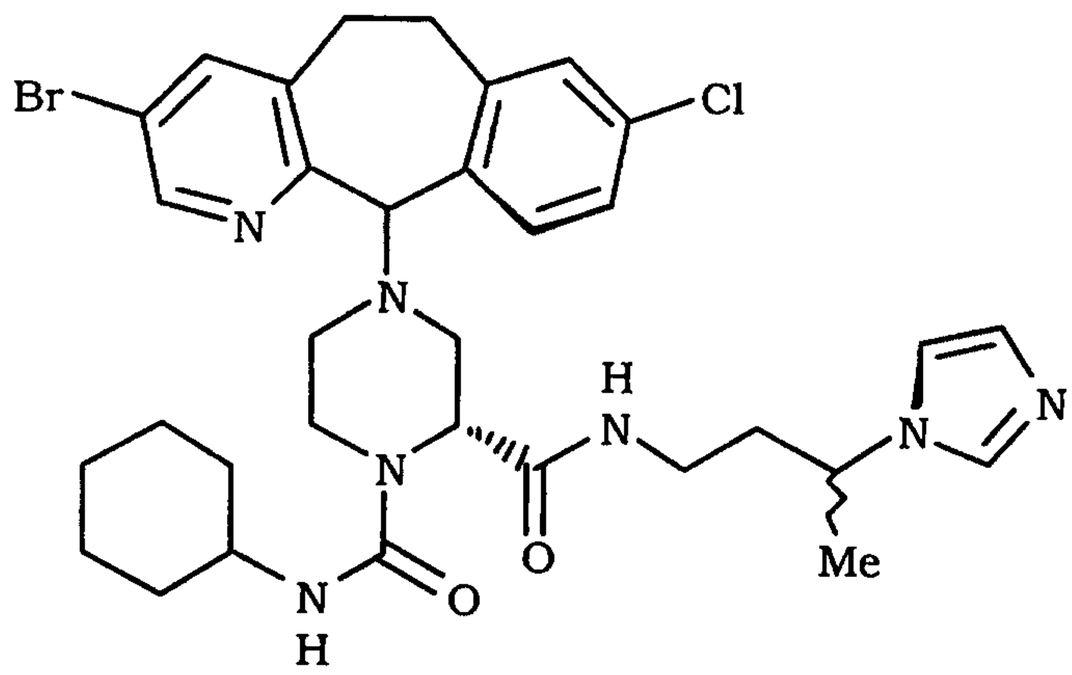
wherein R^{14} is as defined in Table 8, were obtained.

TABLE 8

EX.	R=	MP (°C)	Mass Spec
16	 11S,2R isomer	109-111	LCMS: MH^+=657

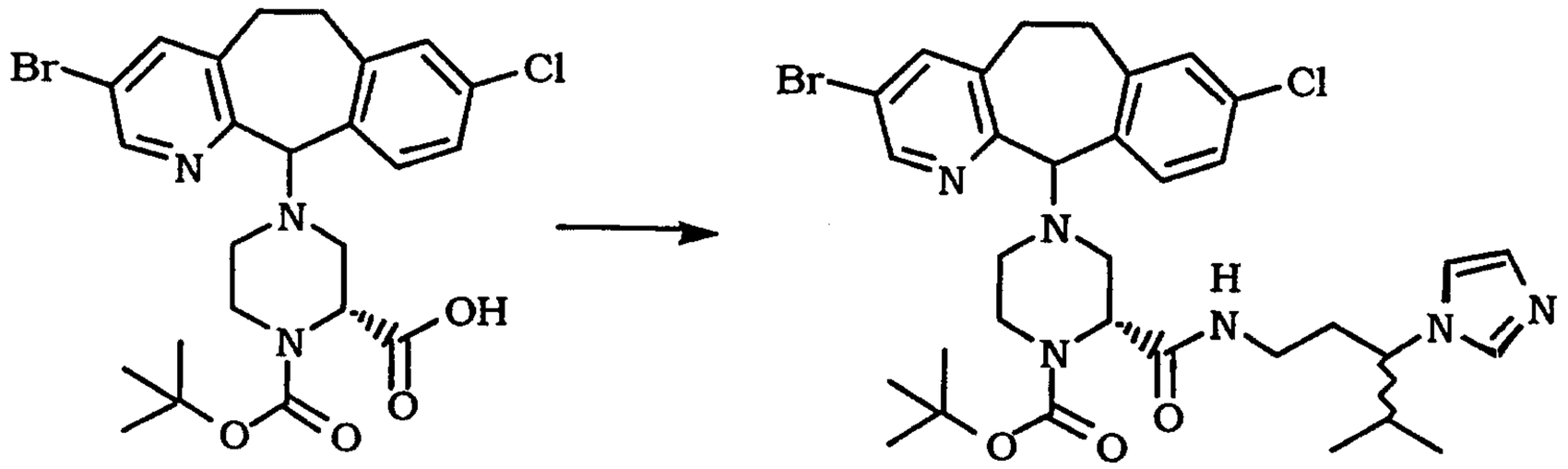
17	 11R,2R isomer	107-108	LCMS: MH^+=657
18	 11R/S,2R isomers	139-142	LCMS: MH^+=642

EXAMPLE 19



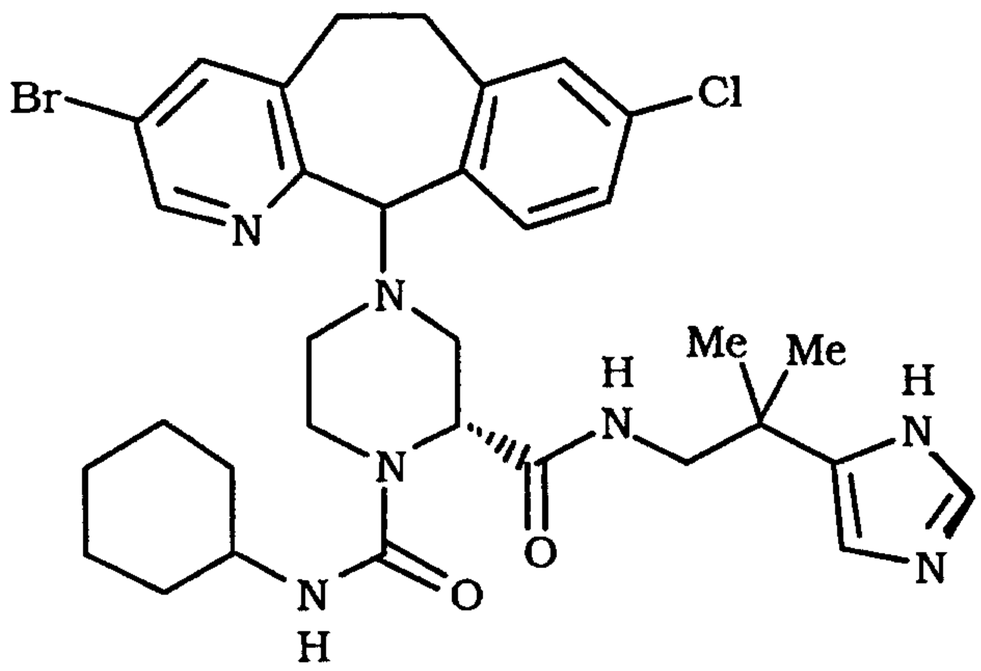
By essentially the same procedure as that set forth in Example 1, except using the title compound from Preparative Example 7.3, the title compound was obtained. mp= 133-138°C; LCMS: MH^+= 682.

EXAMPLE 20



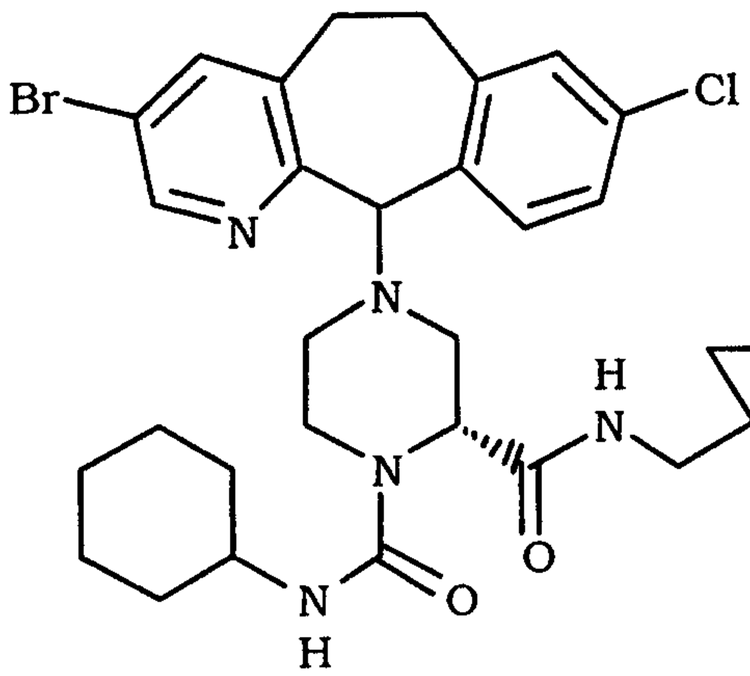
The title compound from Preparative Example 4 (0.211 g, 1.4 eq.) found in Table 1 was added to a solution of acid from Preparative Example 51 (0.487 g, 0.90 mmol), DEC (0.201 g, 1.2 eq.), HOBT (0.73 g, 6.0 eq.), and NMM (0.60 mL, 6.0 eq.) in DMF (6.0 mL). The resulting solution was stirred at room temperature 3 days. The crude product was precipitated from the reaction mixture by the addition of water and filtered. The residue was purified by flash chromatography using a gradient of 0.5% to 3% by 0.5% increments (10% NH_4OH in MeOH) solution in CH_2Cl_2 as eluent to give the title compound (0.411 g, 67% yield). mp= 178-179°C; MH^+= 685.

EXAMPLE 21



The title compound was prepared by essentially the same procedure as that set forth in Example 110, but substituting the title compound from Preparative Example 11 Step C. mp= 150-154°C; MH^+= 682.

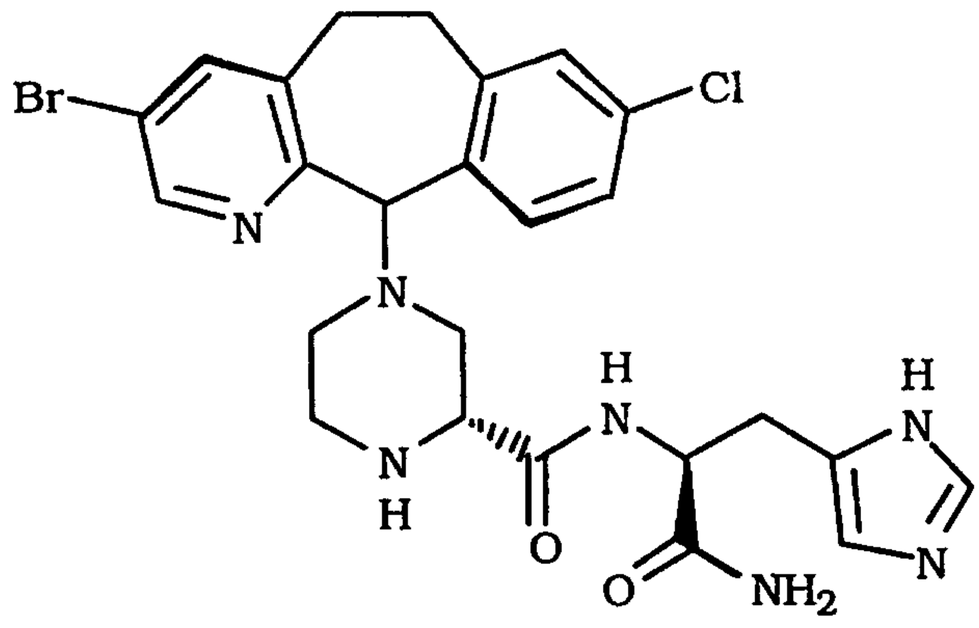
EXAMPLE 22



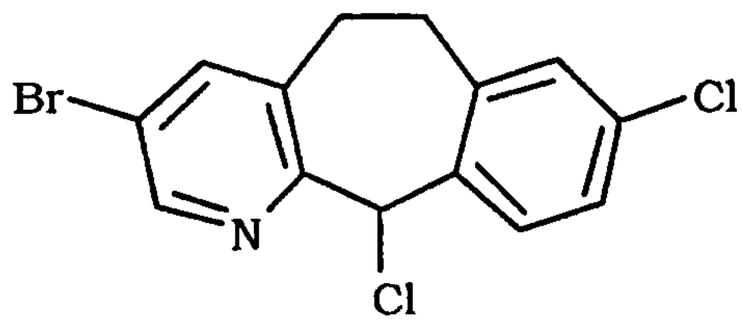
The title compound was prepared by essentially the same procedure as that set forth in Example 110, but substituting for the title compound from Preparative Example 102 Step C the amine prepared by the method described in Preparative Example 11 Steps A-C only substituting dichloroethane for methyl iodide in Preparative Example 11 Step A. mp= 156-158°C; MH^+= 680.

EXAMPLE 24

Step A



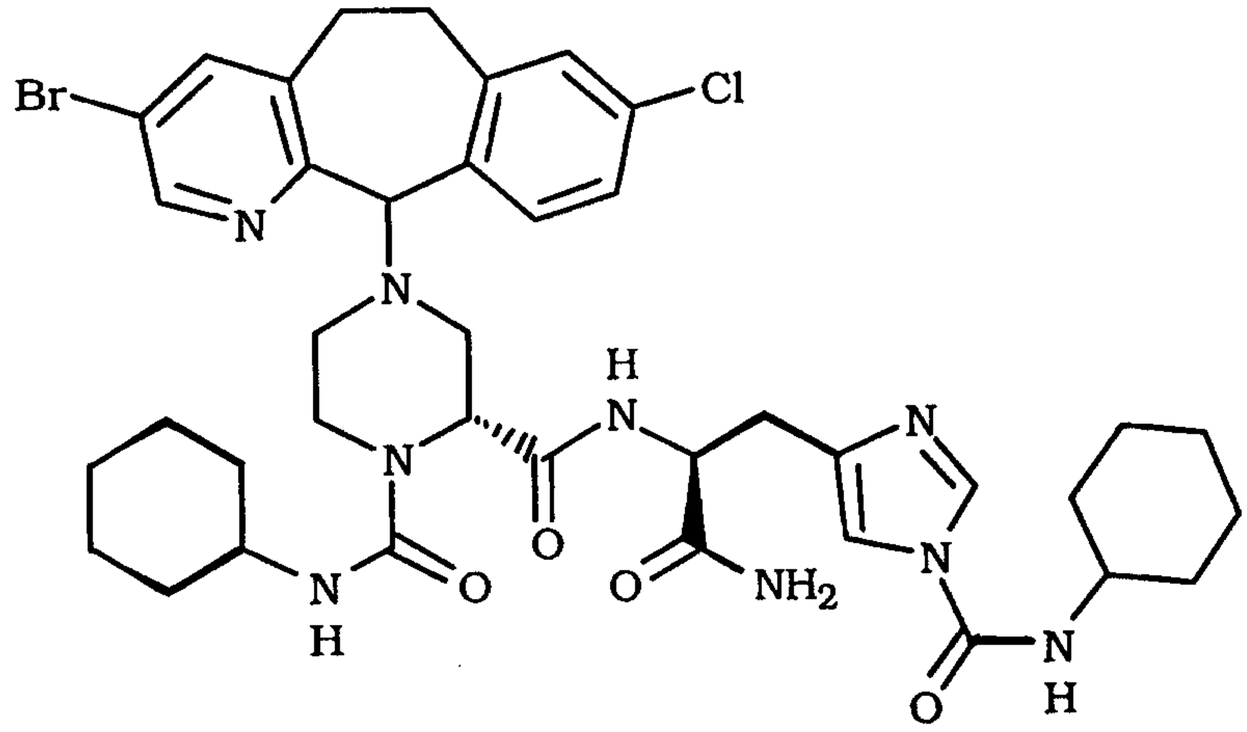
The title compound from Preparative Example 12 (0.23 g, 0.49 mmol) in CH_2Cl_2 (5.0 mL) and TFA (3.0 mL) was stirred at room temperature 2 hours and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (5.0 mL) and treated with TEA (0.45 mL, 20 eq.) and chloride



(42.0)

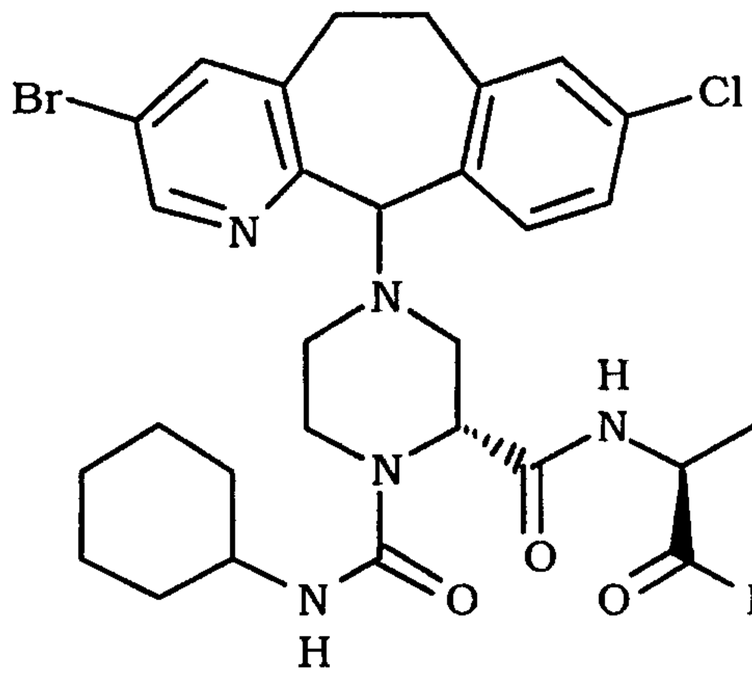
(0.056 g, 0.33 eq.) and stirred at room temperature 48 hours. The reaction mixture was diluted with saturated $NaHCO_3$ (5.0 mL), water (15 mL), and extracted with CH_2Cl_2 (2 X 50 mL). The combined organics were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography using a 15% (10% NH_4OH in MeOH) solution in CH_2Cl_2 as eluent (0.063g, 67% yield). mp= 157°C(dec.); FABMS: MH^+= 572.

Step B



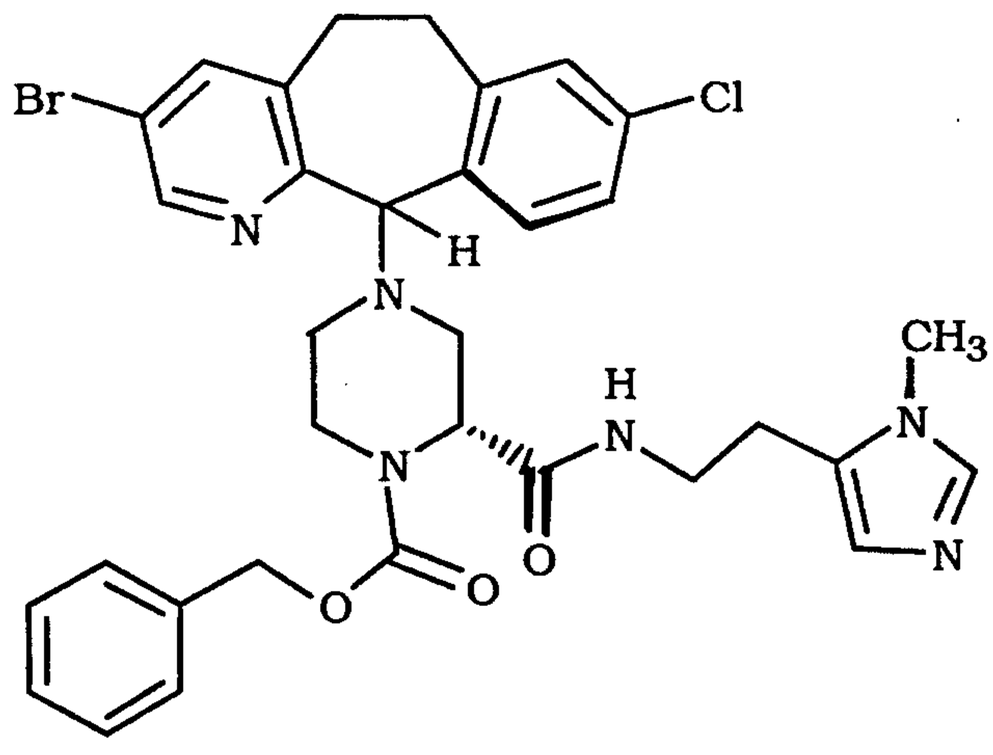
The title compound from Step A (0.058 g, 0.101 mmol) in CH_2Cl_2 (3 mL) was treated with excess cyclohexyl isocyanate and stirred at room temperature for one hour. The reaction mixture was concentrated *in vacuo* and purified by flash chromatography using an 8% MeOH in CH_2Cl_2 solution as eluent to give the title compound (0.062g, 75% yield). mp= 164-167°C;FABMS: MH^+= 822.

EXAMPLE 25

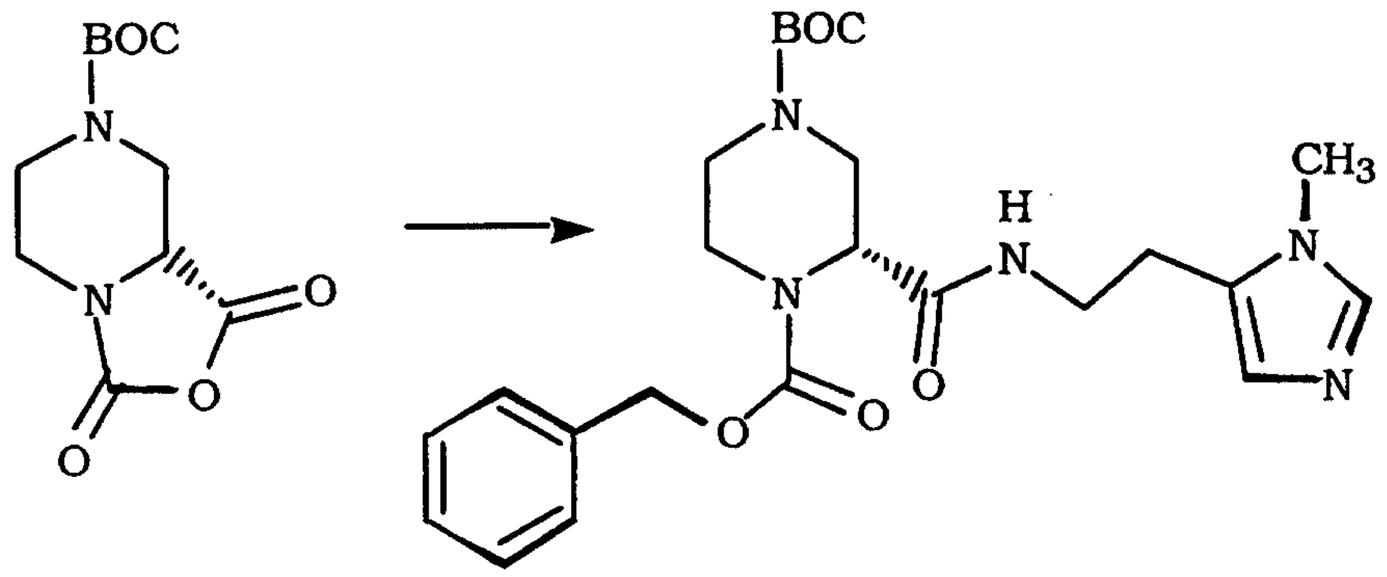


The title compound from Example 24 (0.045 g, 0.0547 mmol) was stirred in concentrated NH_4OH (3.0 mL) and MeOH (3.0 mL) overnight. The resulting solution was concentrated *in vacuo* and the residue purified by flash chromatography using a 15% MeOH in CH_2Cl_2 solution as eluent to give the title compound (0.022 g, 58% yield). mp= 164-169°C; FABMS: MH^+= 697.

EXAMPLE 26

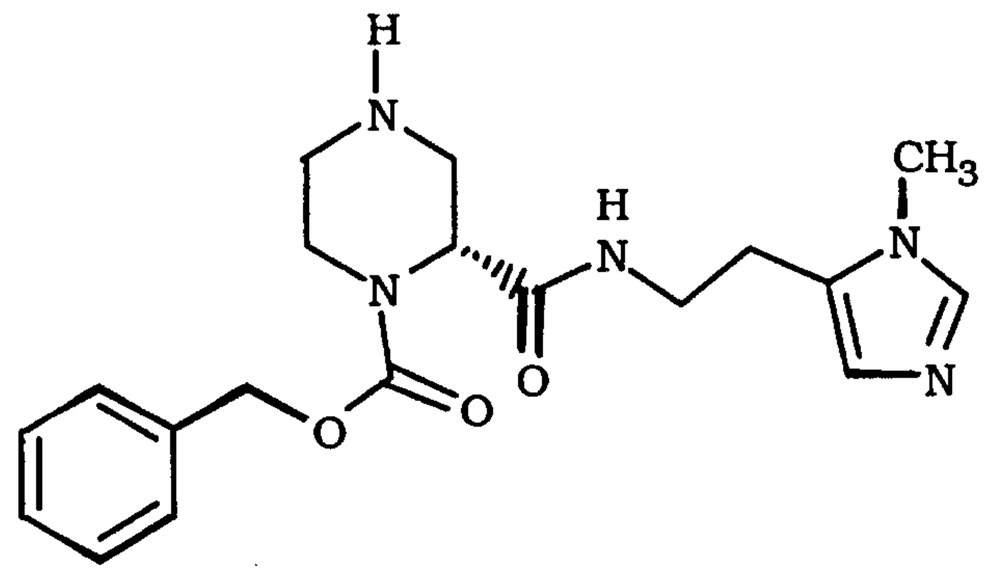


Step A



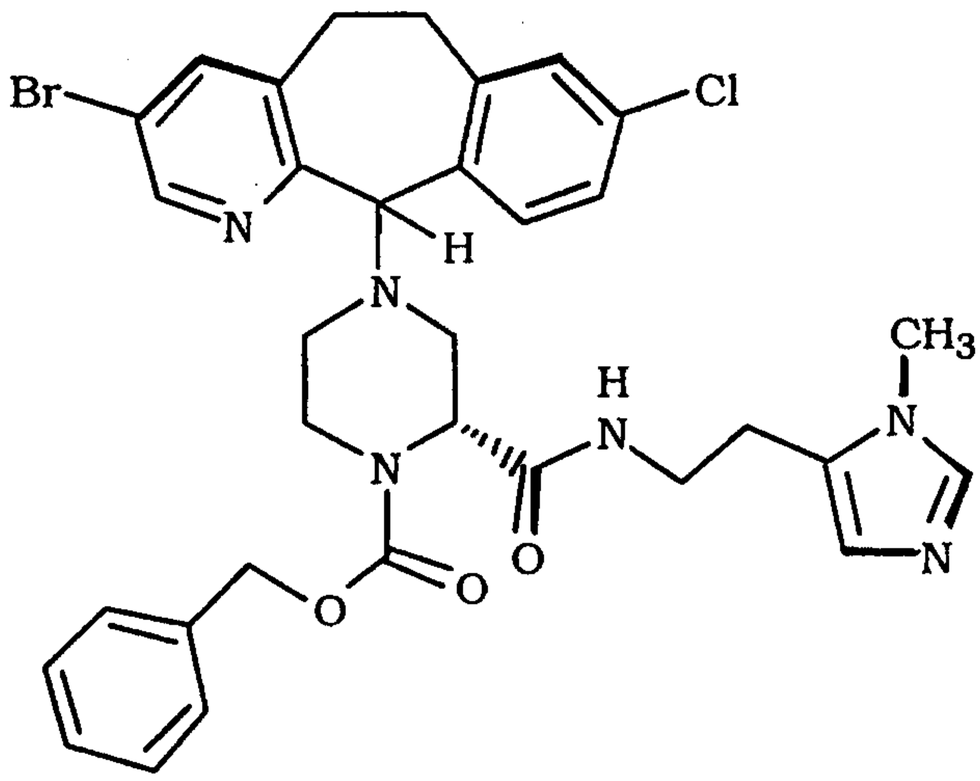
Dissolve 2.99 g (15.09 mmol) of the 3-methylhistamine hydrochloride in 100 mL of methylene chloride followed by 3.21 g (31.70 mmole) of triethylamine. Stir under nitrogen for 30 min then add, in small portions, 4.83 g (18.87 mmol) of anhydride from Preparative Example 44 and stir under nitrogen for 30 min. Add 4.14 g (16.60 mmol) of benzyl chloroformate and stir over night. Dilute with 100 mL of methylene chloride and wash with aqueous $NaHCO_3$ solution. Dry the organic layer over $MgSO_4$ and concentrate *in vacuo*. Flash chromatograph on 650 g of silica gel using 97% CH_2Cl_2 (NH_4OH) - 3% methanol to give the product as a white solid, mp = 51.8-63.2°C.

Step B

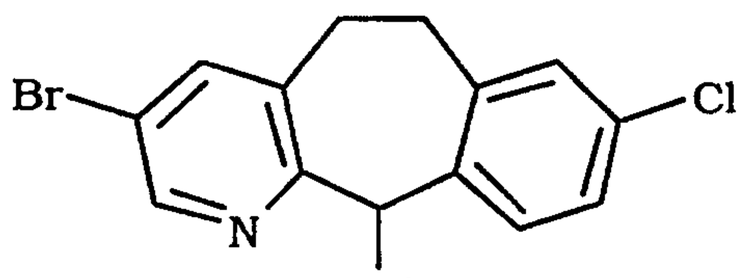


Dissolve 4.9 g of the product from Step A in 30 mL of methylene chloride and add 13 mL of trifluoroacetic acid. Stir overnight under nitrogen then concentrate *in vacuo*. The residue was triturated with ether then dried *in vacuo* giving the product as a clear oil.

Step C



Dissolve 10.01 g (11.04 mmol) of the product of Step B in 50 mL of DMF containing 5.6 g (55.19 mmol) of triethylamine. Add dropwise a solution of the chloride

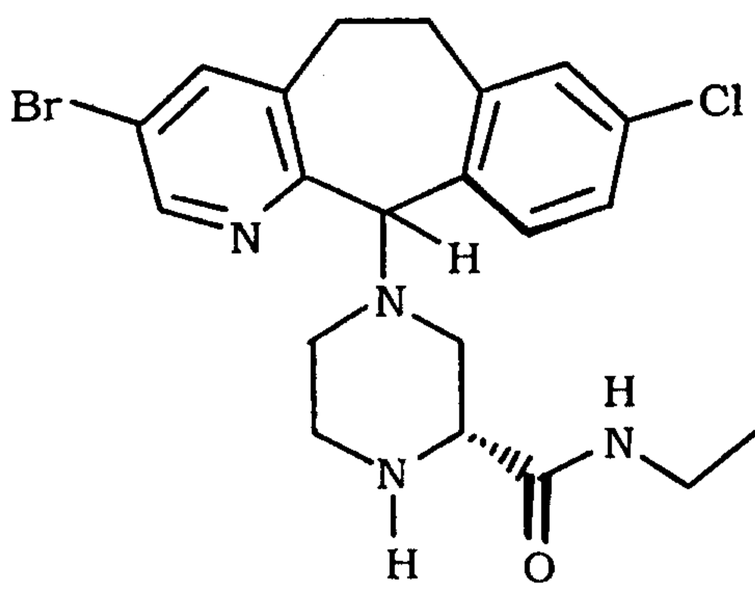


(42.0)

in 70 mL of DMF and stir under nitrogen overnight. Concentrate under vacuo and dissolve the residue in 50 mL of methylene chloride. Wash with aqueous $NaHCO_3$ solution, dry the organic layer over $MgSO_4$ and concentrate *in vacuo*. Flash chromatograph the residue on 640 g of silica gel using 97% CH_2Cl_2 (NH_4OH) - 3% methanol to give the product as a tan solid, mp = 111.8-114.5°C, MH^+ = 677 (FAB).

EXAMPLE 27

Step A

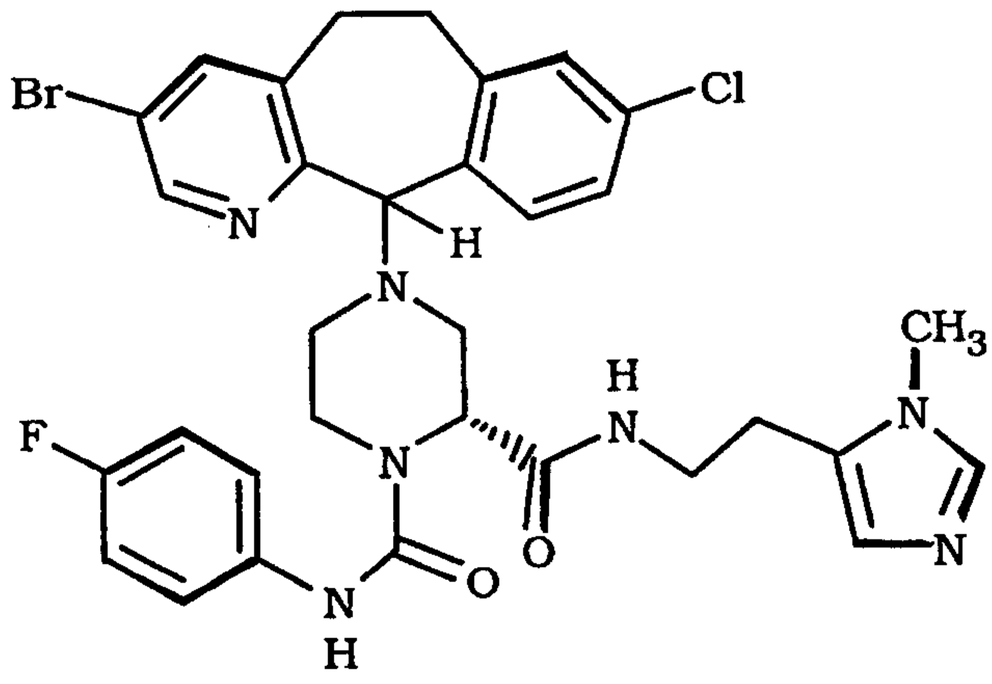


Dissolve 4.61 g (6.8 mmol) of the product of Example 26, Step C, in 6 mL of acetic acid 9 mL of a 5.7 M (33%) solution of HBr in acetic. After 3 hr the reaction was complete by silica gel tlc (95% CH_2Cl_2 (NH_4OH) - 5% methanol). Add 25 mL of diethyl ether and filter the resulting precipitate under nitrogen giving 5.8 g of a tan solid. Chromatograph on a Chiralpack AD, 5 cm x 50 cm column (Chiral Technologies) using 25% 2-propanol/-hexane + 0.2% diethylamine, and a flow rate of 80 mL/min to give the two diastereomers.

Diastereomer A: Mp = 122.2-130.2°C, MH^+ = 543 (FAB).

Diastereomer B: Mp = 122.1-130.2°C, MH^+ = 543 (FAB).

Step B

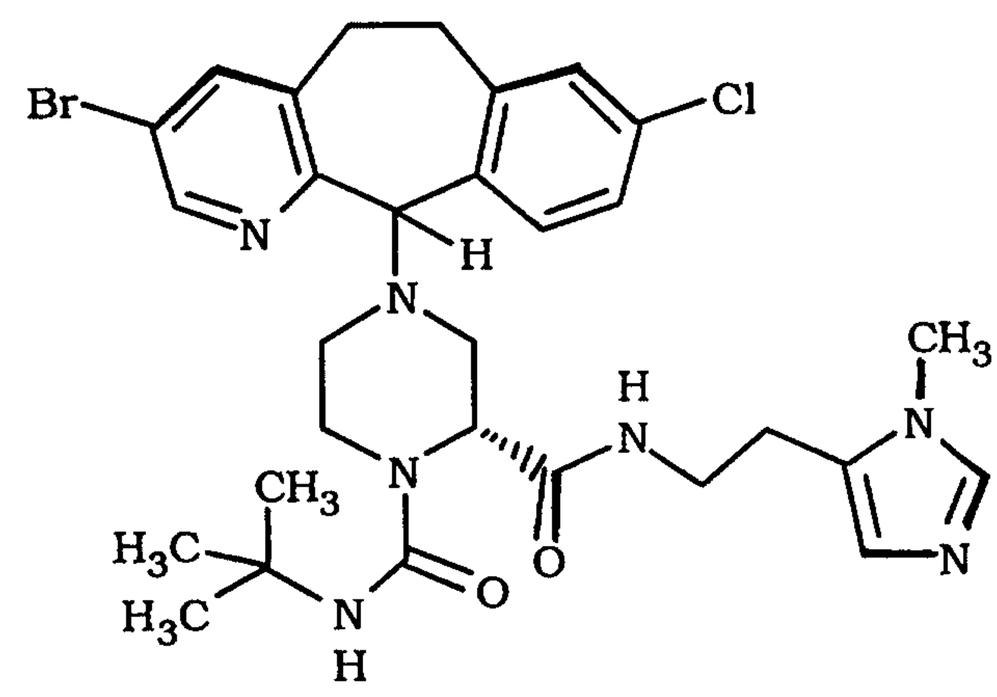


Dissolve 0.07 g (0.129 mmol) of Diastereomer A of Step A in 2 mL of methylene chloride followed by 0.021 g (0.155 mmol) of 4-fluorophenylisocyanate and stir over night under nitrogen. Dilute

with 20 mL of methylene chloride and wash with aqueous $NaHCO_3$ solution, dry the organic layer over $MgSO_4$ and concentrate under vacuo. Chromatograph the residue by preparative silica gel TLC using 95% CH_2Cl_2 (NH_4OH) - 5% methanol to give 0.0179 g of the product as a white solid. Diastereomer A: Mp = 143.1-145.2°C, MH^+ = 680 (FAB).

In a similar manner react 0.07 g (0.129 mmol) of Diastereomer B from Step A with 4-fluorophenylisocyanate to obtain 0.018 g of the Diastereomer B product as a white solid. Diastereomer B: Mp = 140.1-149.4°C, MH^+ = 680 (FAB).

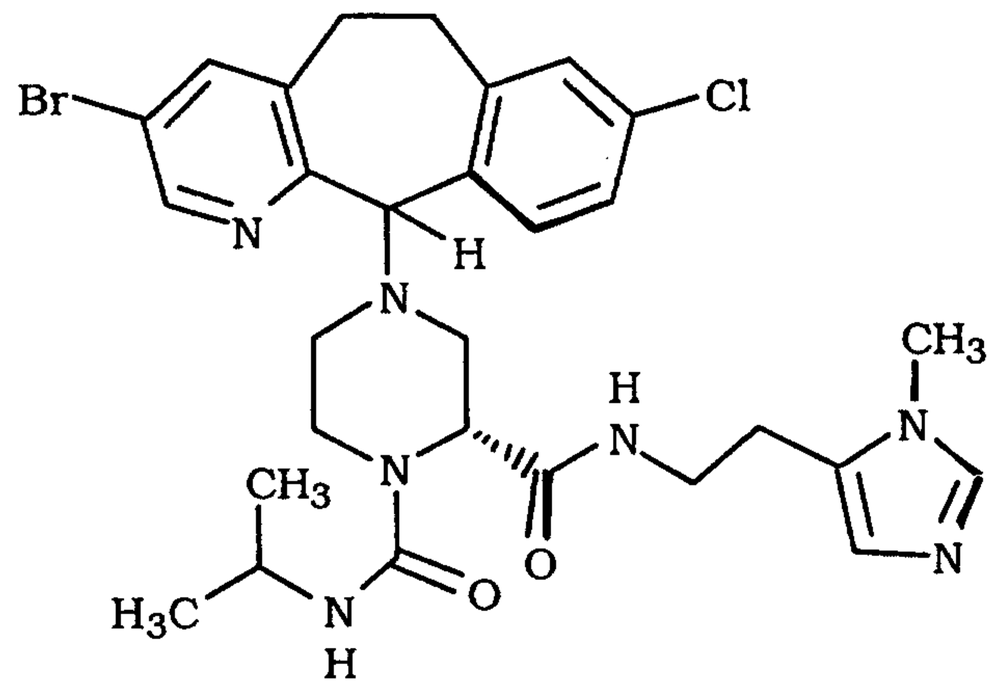
EXAMPLE 28



Following the procedure of Example 27, react 0.07 g (0.129 mmol) of Diastereomer A from Example 27, Step A, with tert-butylisocyanate to obtain 0.065 g of the Diastereomer A product as a white solid. Mp = 125.1-133.5°C, MH^+ = 642 (FAB).

Following the above procedure, but using Diastereomer B from Example 27, Step A, obtain 0.052 g of the Diastereomer B product as a white solid. Mp = 128.1-135.2°C, MH^+ = 642 (FAB).

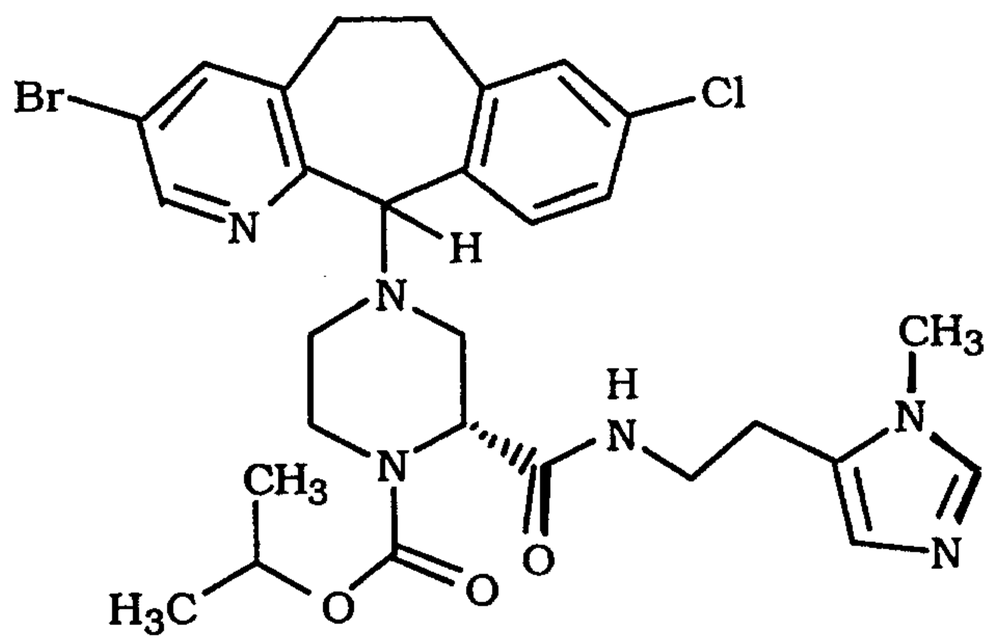
EXAMPLE 29



Following the procedure of Example 27, react 0.10 g (0.184 mmol) of Diastereomer A from Example 27, Step A, with iso-propylisocyanate to obtain 0.041 g of the Diastereomer A product as a white solid. Mp = 128.1-133.3°C, MH^+ = 628 (FAB).

Following the above procedure, but using Diastereomer B from Example 27, Step A, obtain 0.040 g of the Diastereomer B product as a white solid. Mp = 128.1-133.4°C, MH^+ = 628 (FAB).

EXAMPLE 30



Dissolve 0.116 g (0.202 mmol) of Diastereomer A of Example 27, Step A, in 2 mL of methylene chloride followed by 0.02 g (0.202 mmol) of triethyl amine and 0.24 mL (0.24 mmol) of a 1.0M solution of isopropyl chloroformate in toluene and stir overnight under nitrogen. Dilute with 20 mL of methylene chloride and wash with aqueous $NaHCO_3$ solution, dry the organic layer over $MgSO_4$ and concentrate under vacuo. Chromatograph the residue by

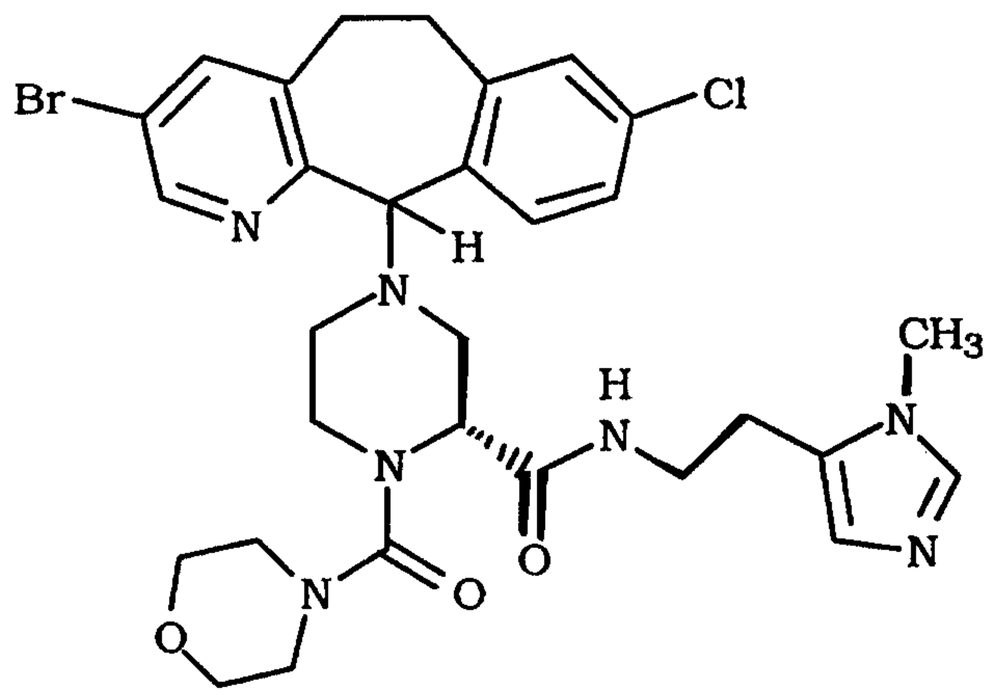
preparative silica gel TLC using 95% CH_2Cl_2 (NH_4OH) - 5% methanol to give 0.044 g of the Diastereomer A product as a white solid.

Following the above procedure, but using Diastereomer B from Example 27, Step A, obtain 0.038 g of the Diastereomer B product as a white solid.

Diastereomer A: Mp = 120.5-125.5°C, MH^+ = 629 (FAB).

Diastereomer B: Mp = 120.3-126.1°C, MH^+ = 629 (FAB).

EXAMPLE 31



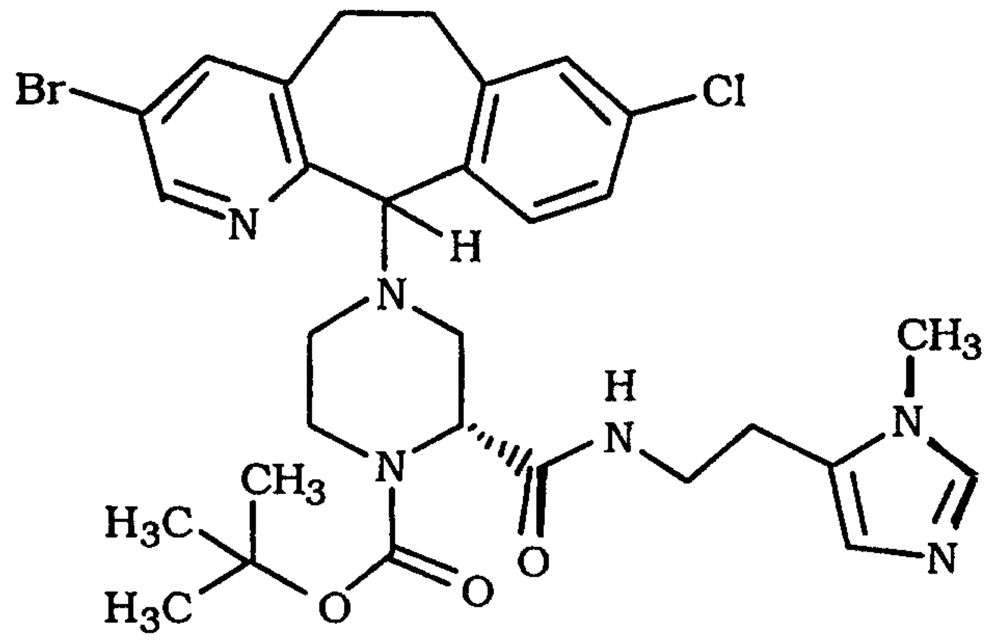
Following the procedure of Example 30, react 0.07 g (0.128 mmol) of Diastereomer A from Example 27, Step A, with 0.021 g (0.142 mmol) of 4-morpholinecarbonyl chloride and 0.035 g (0.256 mmol) triethylamine to obtain 0.024 g of the Diastereomer A product as a white solid.

Following the above procedure, but using Diastereomer B from Example 27, Step A, obtain 0.019 g of the Diastereomer B product as a white solid.

Diastereomer A: Mp = 137.9-138.9°C, MH^+ = 656 (FAB).

Diastereomer B: Mp = 136.4-138.6°C, MH^+ = 656 (FAB).

EXAMPLE 32



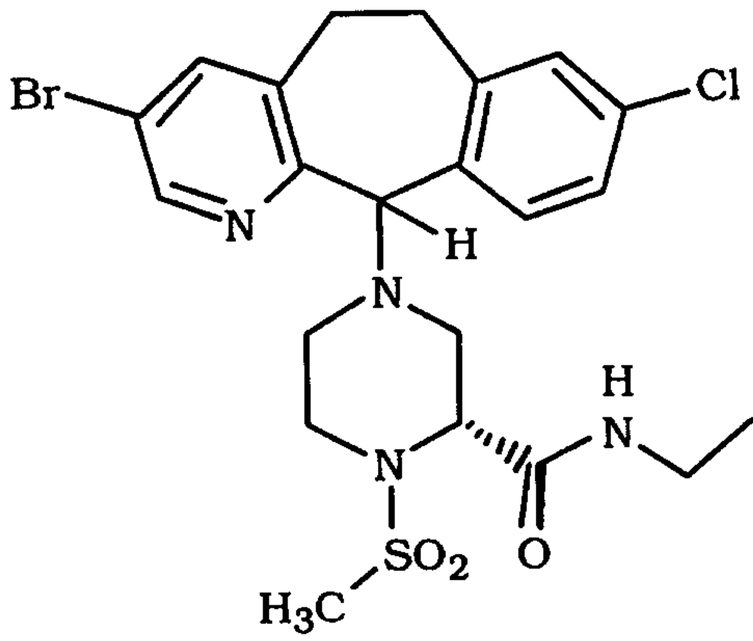
Dissolve 0.07 g (0.129 mmol) of Diastereomer A of Example 27, Step A, in 0.5 mL of methylene chloride followed by 0.033 g (0.152 mmol) di-tert-butyldicarbonate and stir overnight under nitrogen. Dilute with 20 mL of methylene chloride and wash with aqueous $NaHCO_3$ solution, dry the organic layer over $MgSO_4$ and concentrate under vacuo. Chromatograph the residue by preparative silica gel TLC using 95% CH_2Cl_2 (NH_4OH) - 5% methanol to give 0.024 g of the Diastereomer A product as a white solid.

Following the above procedure, but using Diastereomer B from Example 27, Step A, obtain 0.026 g of the Diastereomer B product as a white solid.

Diastereomer A: Mp = 127.1-128.4°C, MH^+ = 643 (FAB).

Diastereomer B: Mp = 134.9-137.5°C, MH^+ = 643 (FAB).

EXAMPLE 33



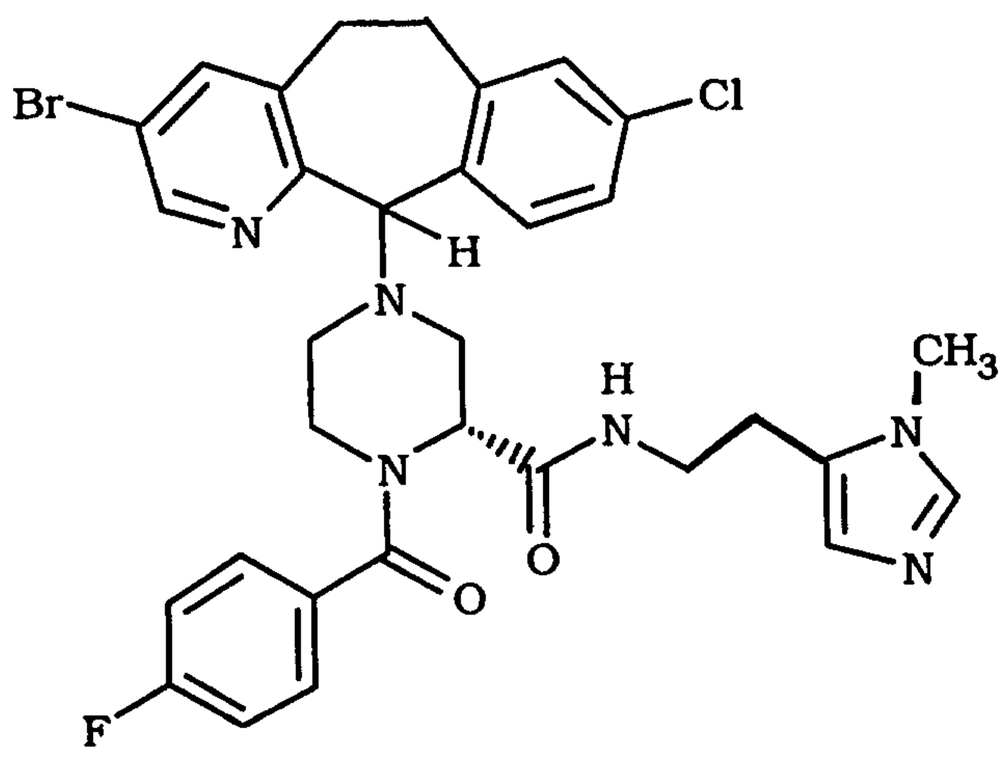
Following the procedure of Example 30, react 0.05 g (0.092 mmol) of Diastereomer A from Example 27, Step A, with 1.1g (0.10 mmol) of methanesulfonyl chloride and 0.019 g (0.183 mmol) triethylamine in 1.5 mL of methylene chloride to obtain 0.011 g of the Diastereomer A product as a white solid.

Following the above procedure, but using Diastereomer B from Example 27, Step A, obtain 0.032 g of the Diastereomer B product as a white solid.

Diastereomer A: Mp = 138.1-144.6°C, MH^+ = 621 (FAB).

Diastereomer B: Mp = 139-145.1°C, MH^+ = 621 (FAB).

EXAMPLE 34



Dissolve 0.07 g (0.129 mmol) of Diastereomer A of Example 27, Step A, in 1.0 mL of DMF followed by 0.023 g (0.167 mmol) 4-fluorobenzoic acid, 0.032 g (0.167 mmol) DEC, 0.0225 g (0.167

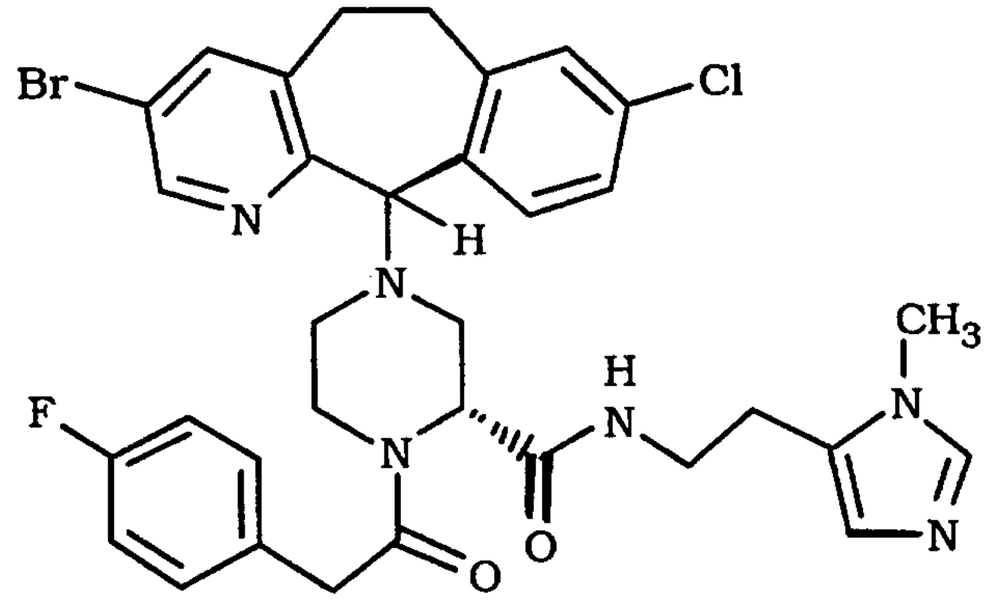
mmol) HOBT and 0.018 mL (0.167 mmol) N-methylmorpholine and stir overnight under nitrogen. Concentrate *in vacuo* and dissolve the residue in 20 mL of methylene chloride. Wash with aqueous 1N NaOH, dry the organic layer over $MgSO_4$ and concentrate in vacuo. Flash chromatograph on silica gel using 93% CH_2Cl_2 (NH_4OH) - 7% methanol to give 0.060 g of the Diastereomer A product as a white solid.

Following the above procedure, but using Diastereomer B from Example 27, Step A, obtain the Diastereomer B product as a white solid.

Diastereomer A: Mp = 141.5-145.8°C, MH^+ = 665 (FAB).

Diastereomer B: Mp = 144.9-148.7°C, MH^+ = 665 (FAB).

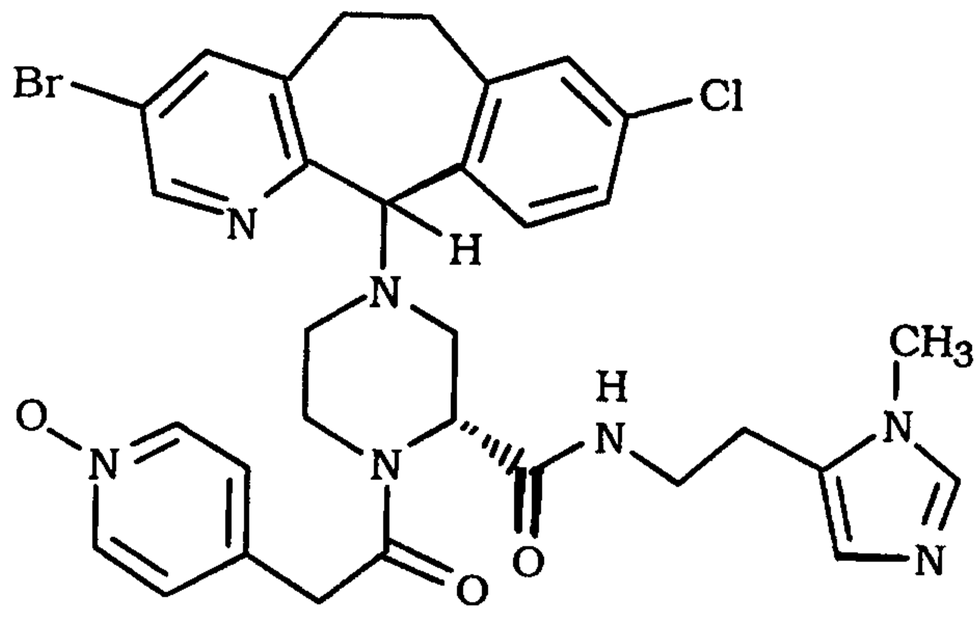
EXAMPLE 35



Following the procedure of Example 34, use 4-fluorophenylacetic acid instead of 4-fluorobenzoic acid to obtain the Diastereomer A product as a white solid. Mp = 132.8-140.1°C, MH^+ = 679 (FAB).

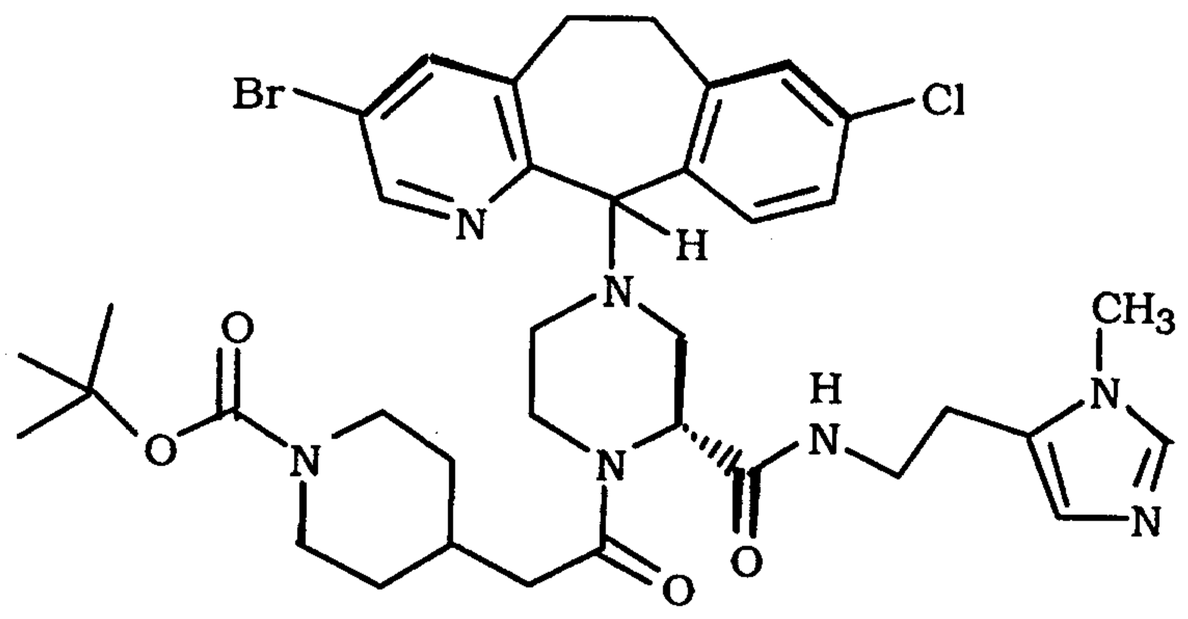
Following the above procedure obtain the Diastereomer B product as a white solid. Mp = 132.5-139.7°C, MH^+ = 679 (FAB).

EXAMPLE 36



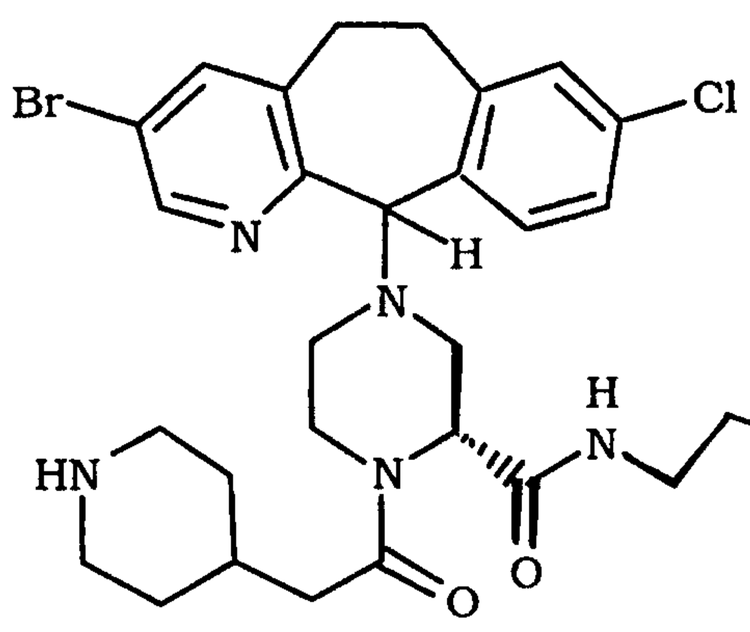
Following the procedure of Example 34, use 4-pyridylacetic acid N-oxide instead of 4-fluorobenzoic acid to obtain the Diastereomer A product as a white solid, and the Diastereomer B product as a white solid. Diastereomer A: Mp = 168.5-172.4°C, MH^+ = 678 (FAB). . Diastereomer B: Mp = 168.9-172.3°C, MH^+ = 678 (FAB).

EXAMPLE 37



Following the procedure of Example 34, use N-t-butoxy-carbony-4-piperidinacetic acid instead of 4-fluorobenzoic acid to obtain the Diastereomer A product as a white solid, and the Diastereomer B product as a white solid. Diastereomer A: Mp = 135.1-142.1°C, MH^+ = 768 (FAB). . Diastereomer B: Mp = 141.7-143.2°C, MH^+ = 768 (FAB).

EXAMPLE 38



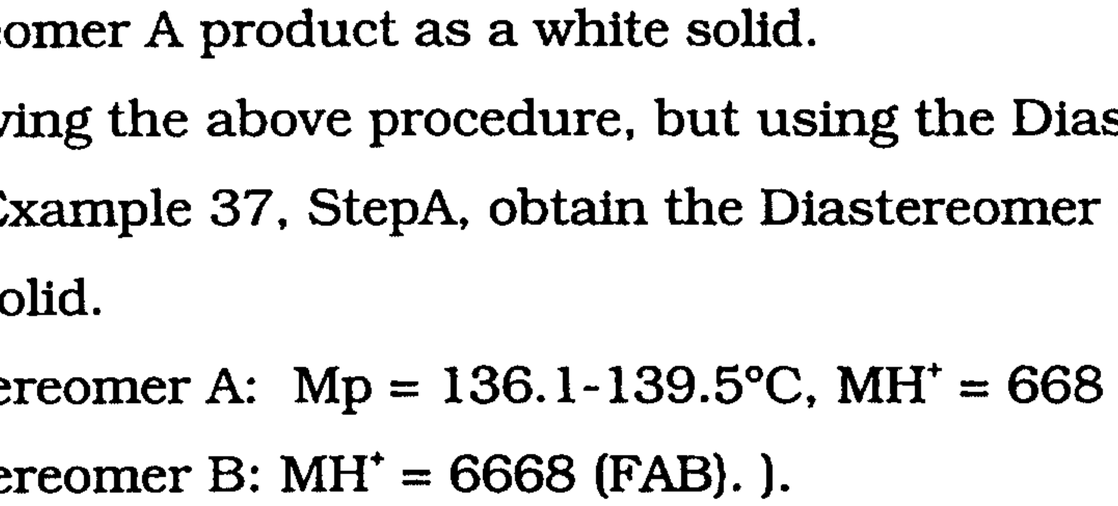
Dissolve 0.23 g (0.31 mmol) of the Diastereomer A product of Example 37 in 3 mL of methylene chloride and 3 mL of trifluoroacetic acid and stir under nitrogen for 3.5 hr. Concentrate under vacuo and dissolve the residue in 20 mL methylene chloride and wash with 1.0 N aqueous NaOH. Concentrate the organic layer *in vacuo* and chromatograph the residue by preparative silica gel TLC using 80% CH_2Cl_2 (NH_4OH) - 20% methanol to give 0.113 g of the Diastereomer A product as a white solid.

Following the above procedure, but using the Diastereomer B product of Example 37, StepA, obtain the Diastereomer B product as a white solid.

Diastereomer A: Mp = 136.1-139.5°C, MH^+ = 668 (FAB).

Diastereomer B: MH^+ = 6668 (FAB).).

EXAMPLE 39



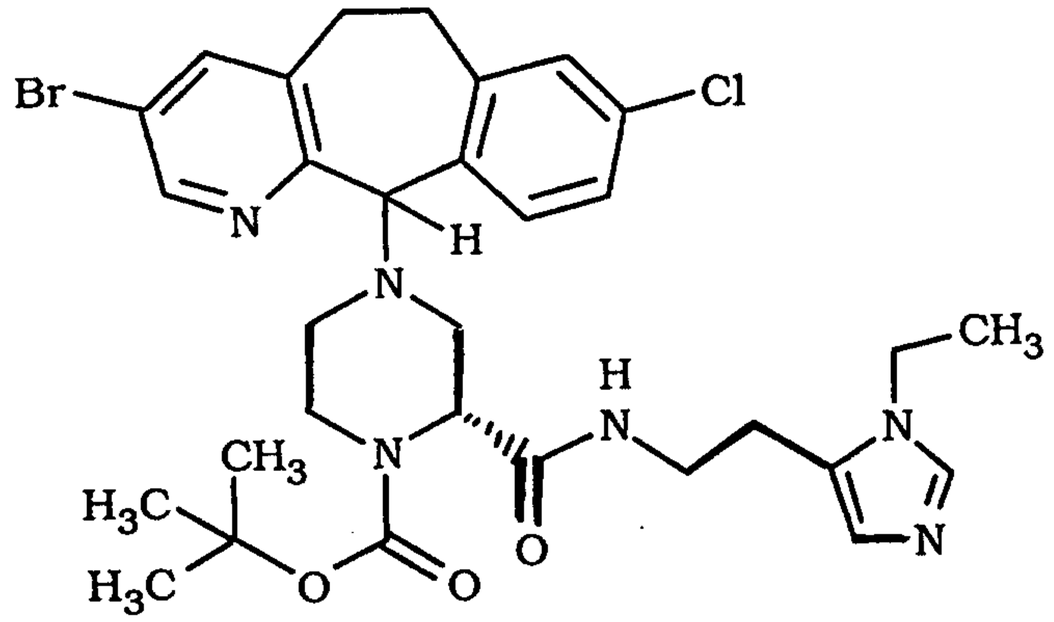
Dissolve 0.073 g (0.11 mmol) of the Diastereomer A product from Example 38 in 3 mL methylene chloride containing 0.013 g (0.121 mmol) of trimethylsilyl isocyanate and stir under nitrogen overnight. Dilute with 5 mL methylene chloride and wash with 10 mL sat aqueous $NaHCO_3$. Dry the organic layer over $MgSO_4$ and concentrate *in vacuo*. Chromatograph the residue by preparative silica gel TLC using 90% CH_2Cl_2 (NH_4OH) - 10% methanol to give 0.032 g of the Diastereomer A product as a white solid.

Following the above procedure, but using the Diastereomer B product of Example 38, obtain the Diastereomer B product as a white solid.

Diastereomer A: Mp = 148.2-151.3°C, MH^+ = 711 (FAB).

Diastereomer B: Mp = 148.1-150.4°C, MH^+ = 711 (FAB).).

EXAMPLE 40



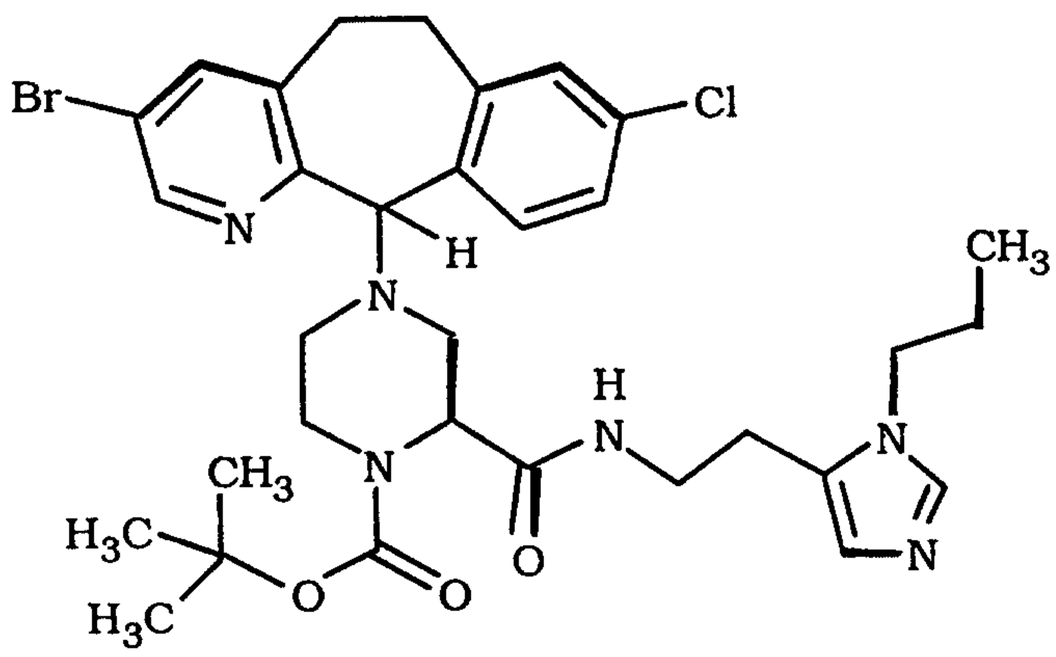
Dissolve the carboxylic acid from Preparative Example 51 (0.32 g, 0.596 mmol), the product from Preparative Example 13 (0.108 g, 0.775 mmol), DEC (0.149 g, 0.775 mmol), HOBT (0.105 g, 0.775 mmol) and 0.13 mL of N-methylmorpholine in 5 mL of DMF and stir overnight. Concentrate *in vacuo* and dissolve the residue in 20 mL of methylene chloride. Wash with satd. $NaHCO_3$ solution, dry over $MgSO_4$ and flash chromatograph on silica gel using 97% CH_2Cl_2 (NH_4OH) - 3% methanol to give 0.2 g of the product as a white solid. Separate the diastereomers by preparative chiral

chromatography (Chiralpack AD, 5 cm x 50 cm column, flow rate 100 mL/min., 15% 2-propanol/hexane + 0.2% diethylamine).

Diastereomer A: Mp = 54-58°C, MH^+ = 657 (FAB).

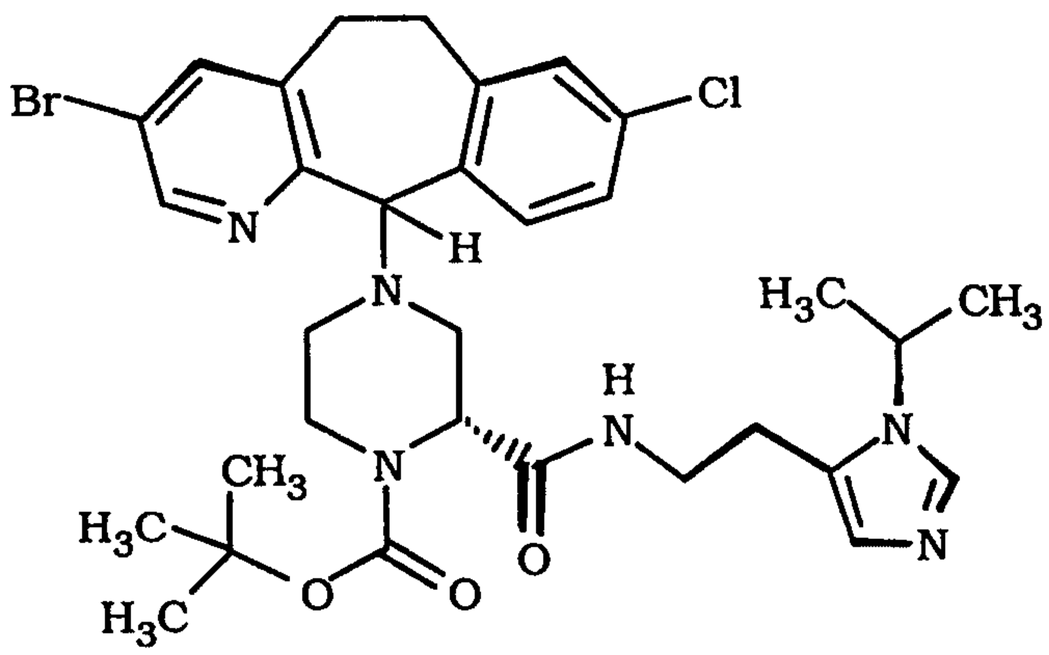
Diastereomer A: Mp = 64-58°C, MH^+ = 657 (FAB).

EXAMPLE 41



Following the procedure of Example 40, use the product from Preparative Example 14 instead of Preparative Example 13 to obtain the product as a white solid. Mp = 116-123°C, MH^+ = 671 (FAB).

EXAMPLE 42

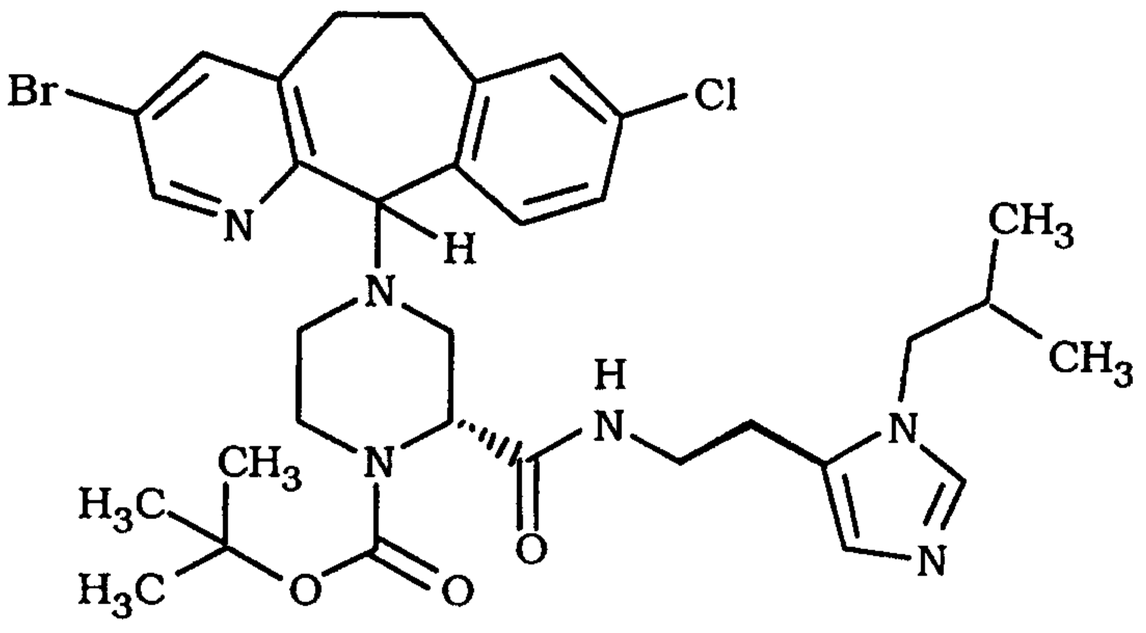


Following the procedure of Example 40, use the product from Preparative Example 15 instead of Preparative Example 13 to obtain the product as a white solid.

Diastereomer A: Mp = 115-120°C, MH^+ = 671 (FAB).

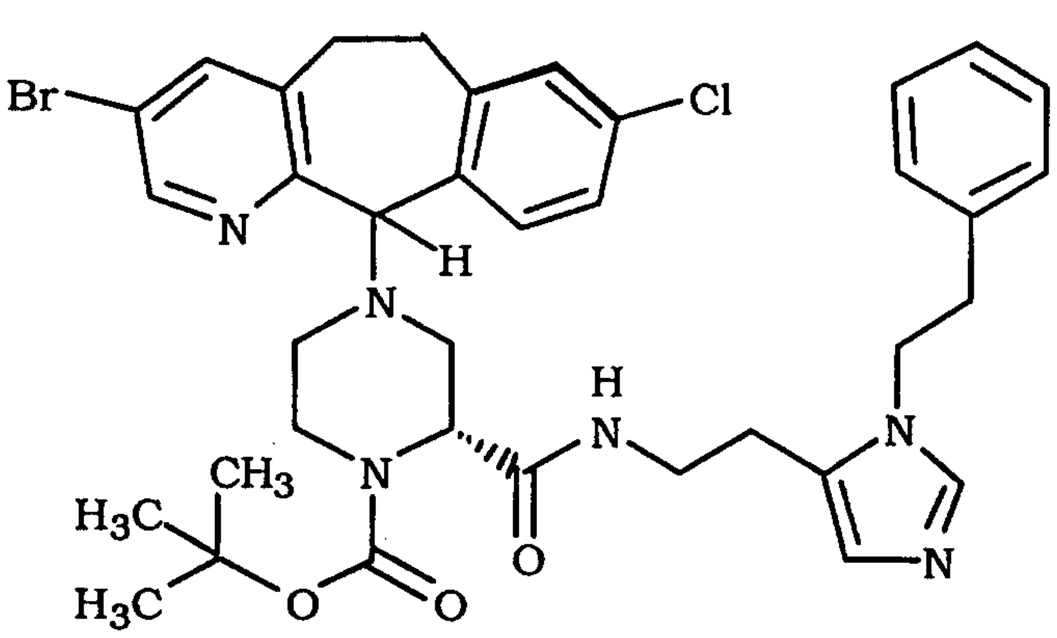
Diastereomer A: Mp = 98-101°C, MH^+ = 671 (FAB).

EXAMPLE 43



Following the procedure of Example 40, use the product from Preparative Example 16 instead of Preparative Example 13 to obtain the product as a white solid. Mp = 120-122°C, MH^+ = 685 (FAB).

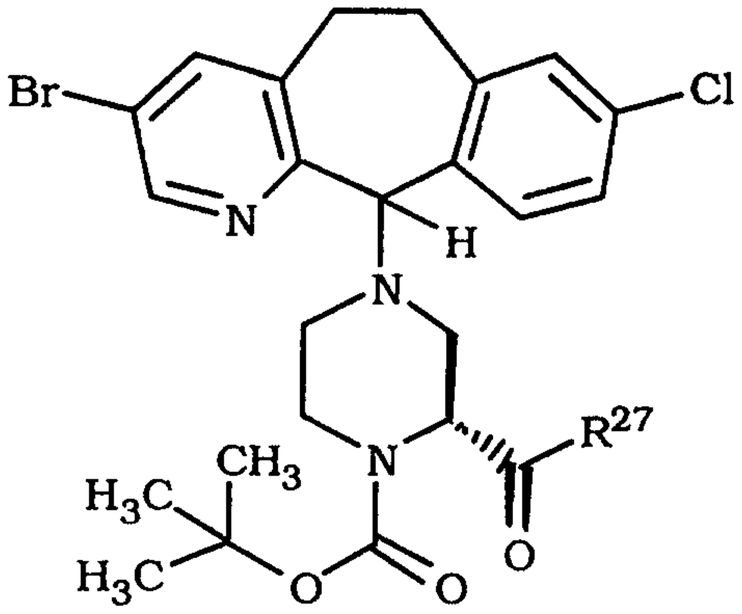
EXAMPLE 44



Following the procedure of Example 40, use the product from Preparative Example 17 instead of Preparative Example 13 to obtain the product as a white solid. Mp = 101-103°C, MH^+ = 733 (FAB).

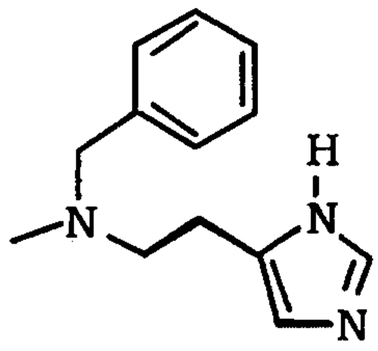
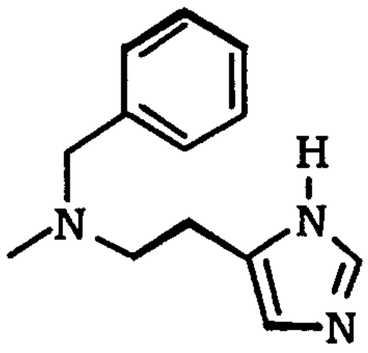
EXAMPLES 45-59

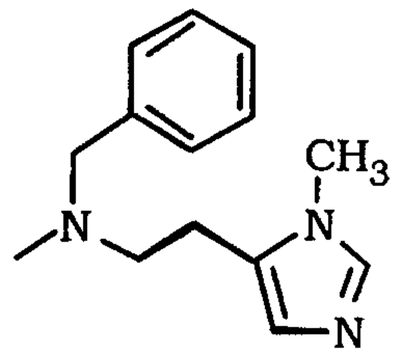
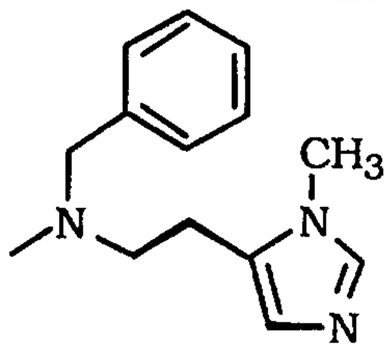
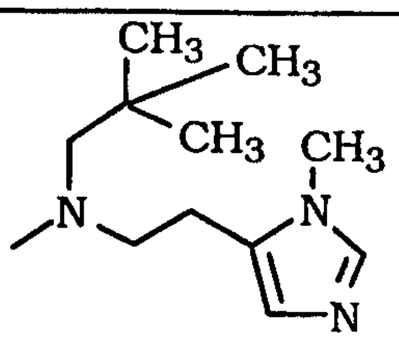
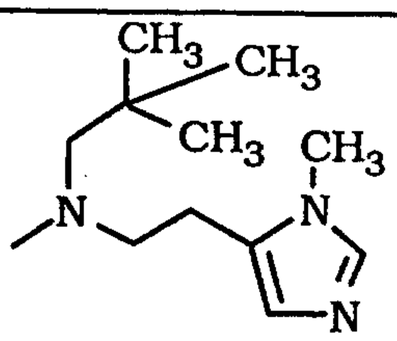
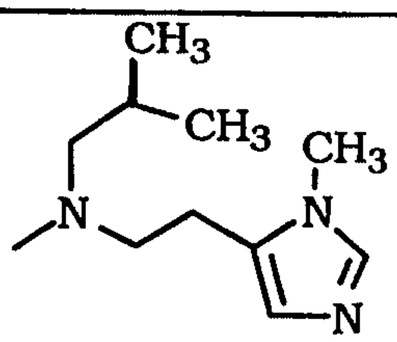
Following the procedure of Example 40, use the amines from Preparative Examples 18-26 instead of Preparative Example 13 to obtain the compounds

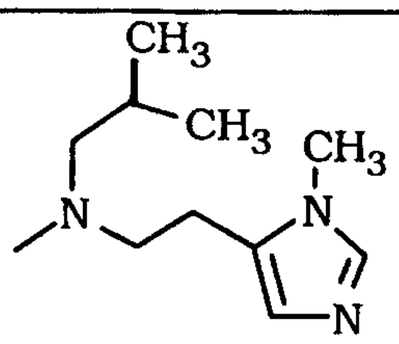
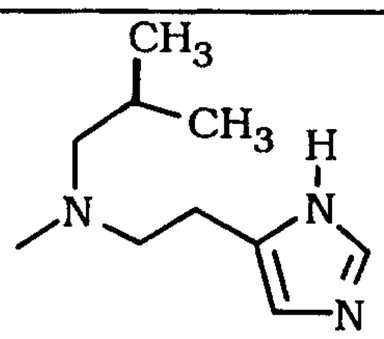
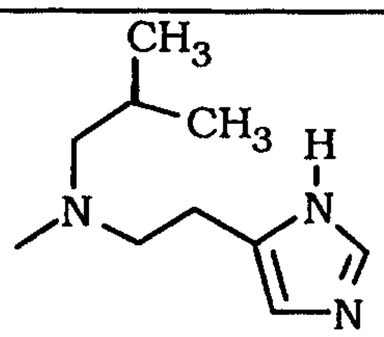
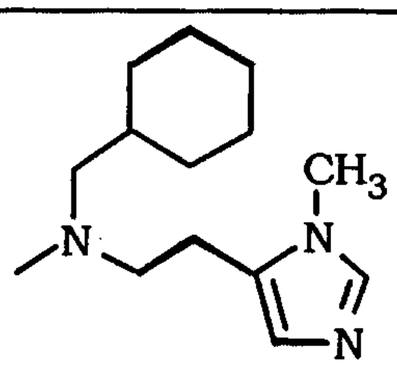
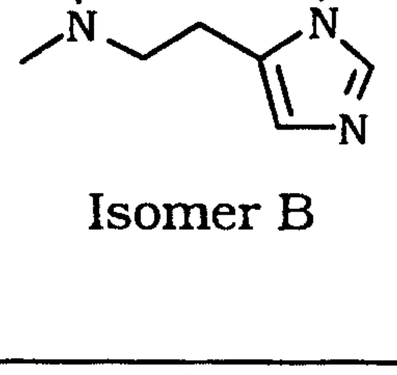


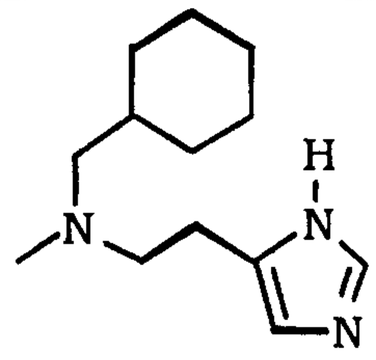
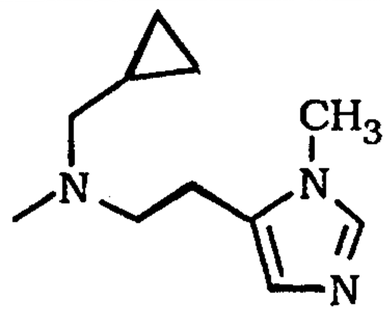
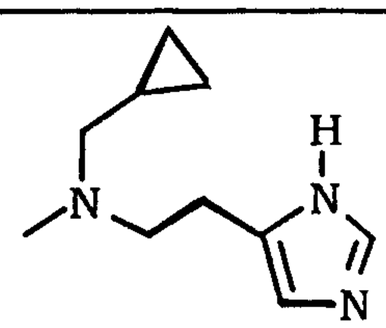
wherein R^{27} is defined in Table 9.

TABLE 9

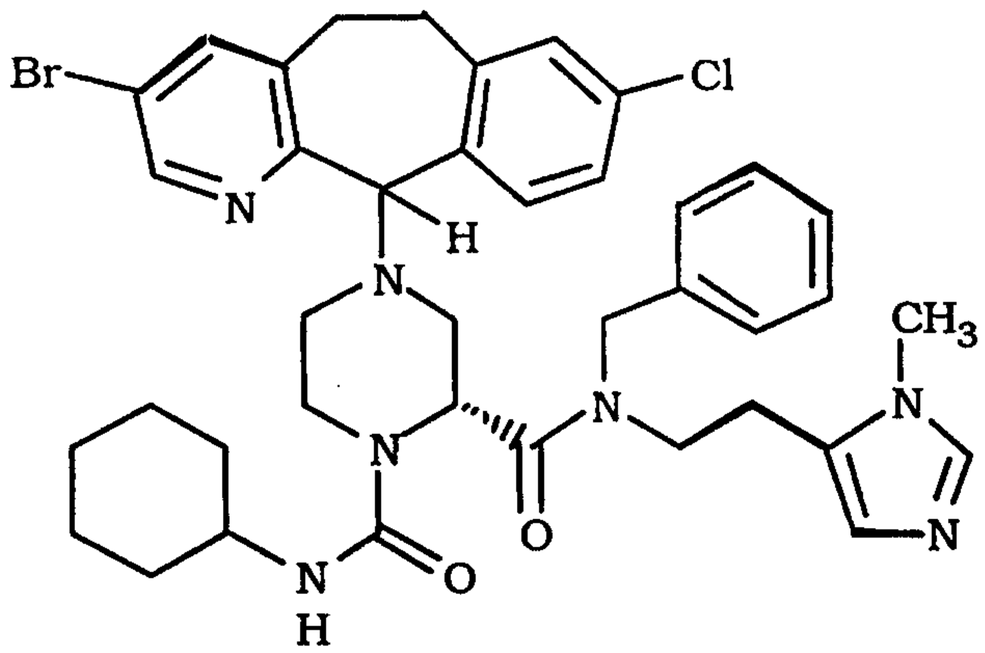
Ex.	Prep. Ex. (amine)	Product R^{27}=	Melting Point (°C)	Mass Spec MH+
45	18	 Isomer A	128-133	719
46	18	 Isomer B	129-132	719

47	19	 Isomer A	106-112	733
48	19	 Isomer B	105-111	733
49	20	 Isomer A	115-117	713
50	20	 Isomer B	108-110	713
51	21	 Isomer A	86-89	699

52	21	 Isomer B	58-86	699
53	22	 Isomer A	106-111	685
54	22	 Isomer B	110-114	685
55	23	 Isomer A	98-111	739
56	23	 Isomer B	99-111	739

57	24		136-144	725
58	25		101-103	697
59	26		128-133	683

EXAMPLE 60



Step A

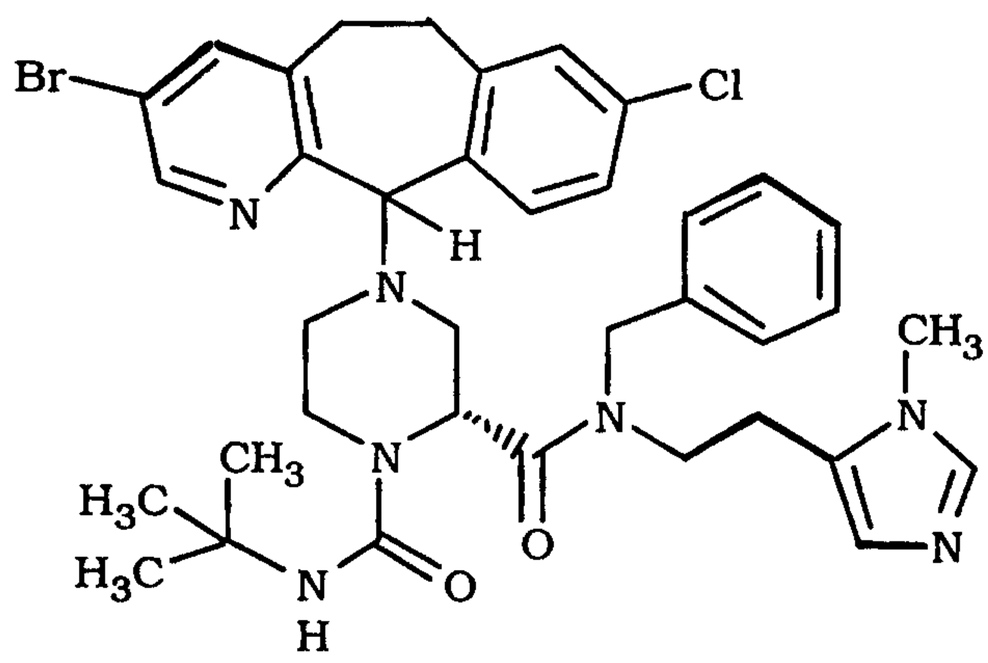
Dissolve the product of Example 47 (0.148 g, 0.202 mmol) in 0.78 mL of methylene chloride and add 0.45 mL of trifluoroacetic acid and stir under nitrogen for 2 hr. Concentrate under vacuum. Dissolve the residue in 20 mL of methylene chloride and wash with aqueous $NaHCO_3$, dry the organic layer over $MgSO_4$, and concentrate under vacuum to give the amine as a white solid.

Step B

Dissolve the product of Step A (0.05 g, 0.078 mmol) in 2 mL of methylene chloride and add 0.015 g, 0.118 mmol of cyclohexyl isocyanate. Stir overnight then concentrate under vacuum. Flash chromatograph the residue on silica gel using 99% CH_2Cl_2 (NH_4OH) - 1% methanol giving the Isomer A product as a white solid. Mp = 138-142°C, MH^+ = 758 (FAB).

Follow the above procedure, but use the product of Example 48 instead of Example 47 in Step A, to obtain the Isomer B product as a white solid. Mp = 130-139°C, MH^+ = 758 (FAB).

EXAMPLE 61



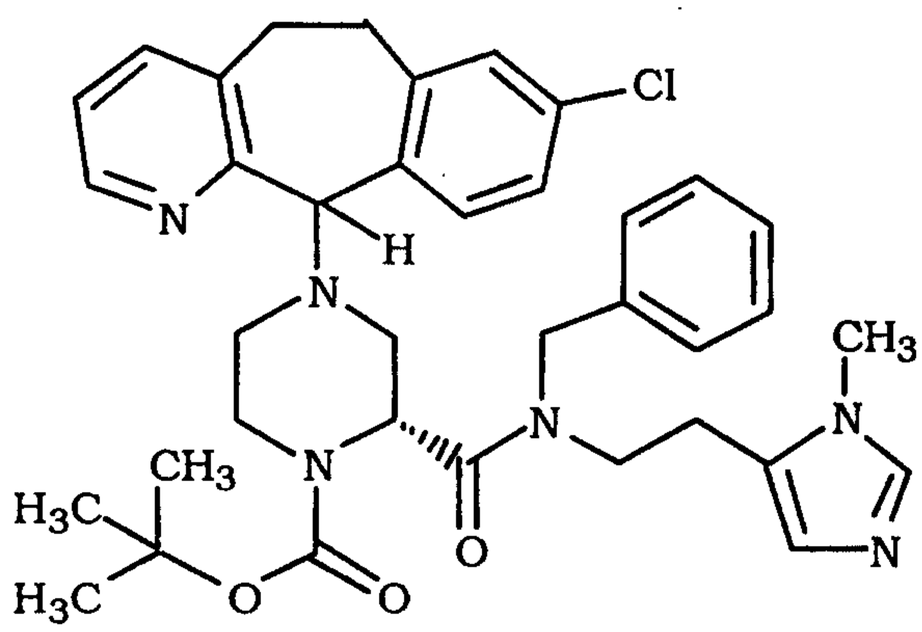
Step A

Using the product of Example 47, follow the procedure of Example 60, but use t-butyl isocyanate instead of cyclohexyl isocyanate in Step B, to obtain the Isomer A product as a white solid. Mp = 127-132°C, MH^+ = 732 (FAB).

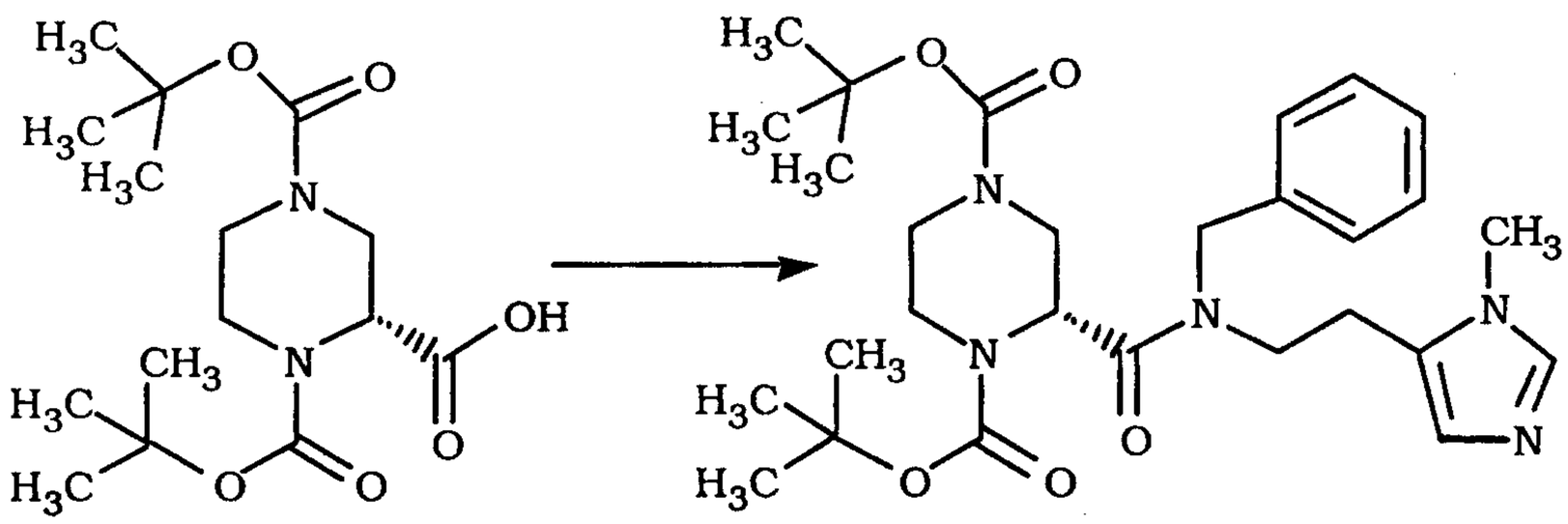
Step B

Follow the procedure of Example 60, but use the product of Example 48 instead of Example 47 in Step A and t-butyl isocyanate instead of cyclohexyl isocyanate in Step B to obtain the Isomer B product as a white solid. Mp = 127-130°C, MH^+ = 732 (FAB).

EXAMPLE 62

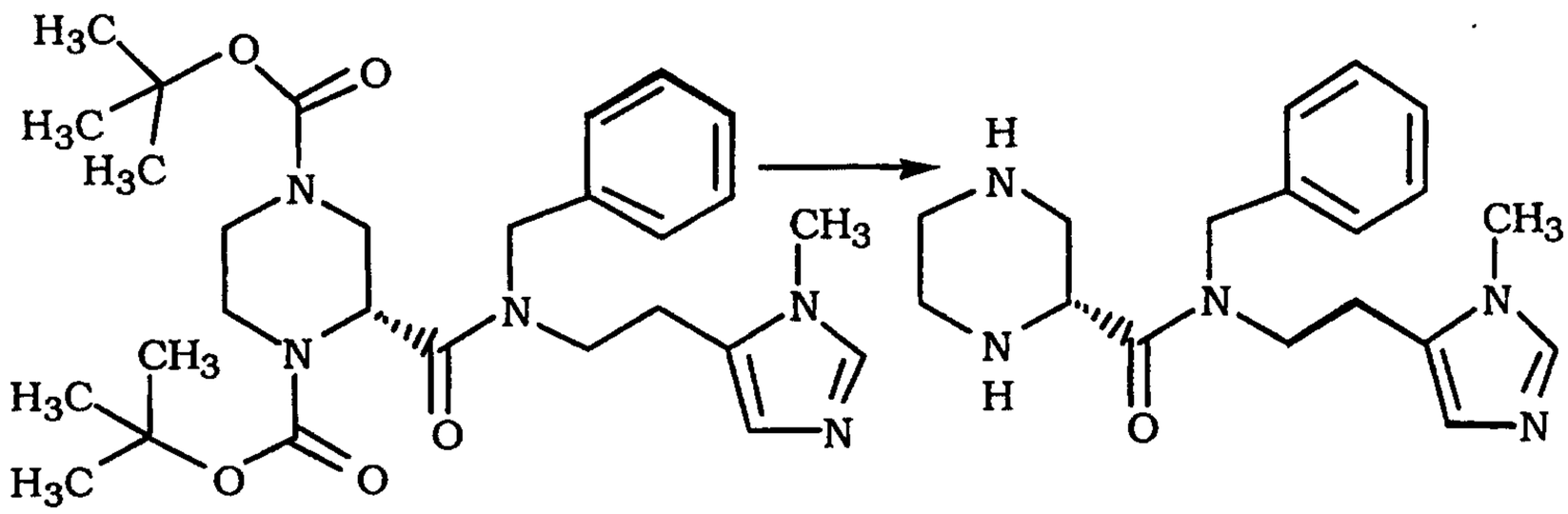


Step A



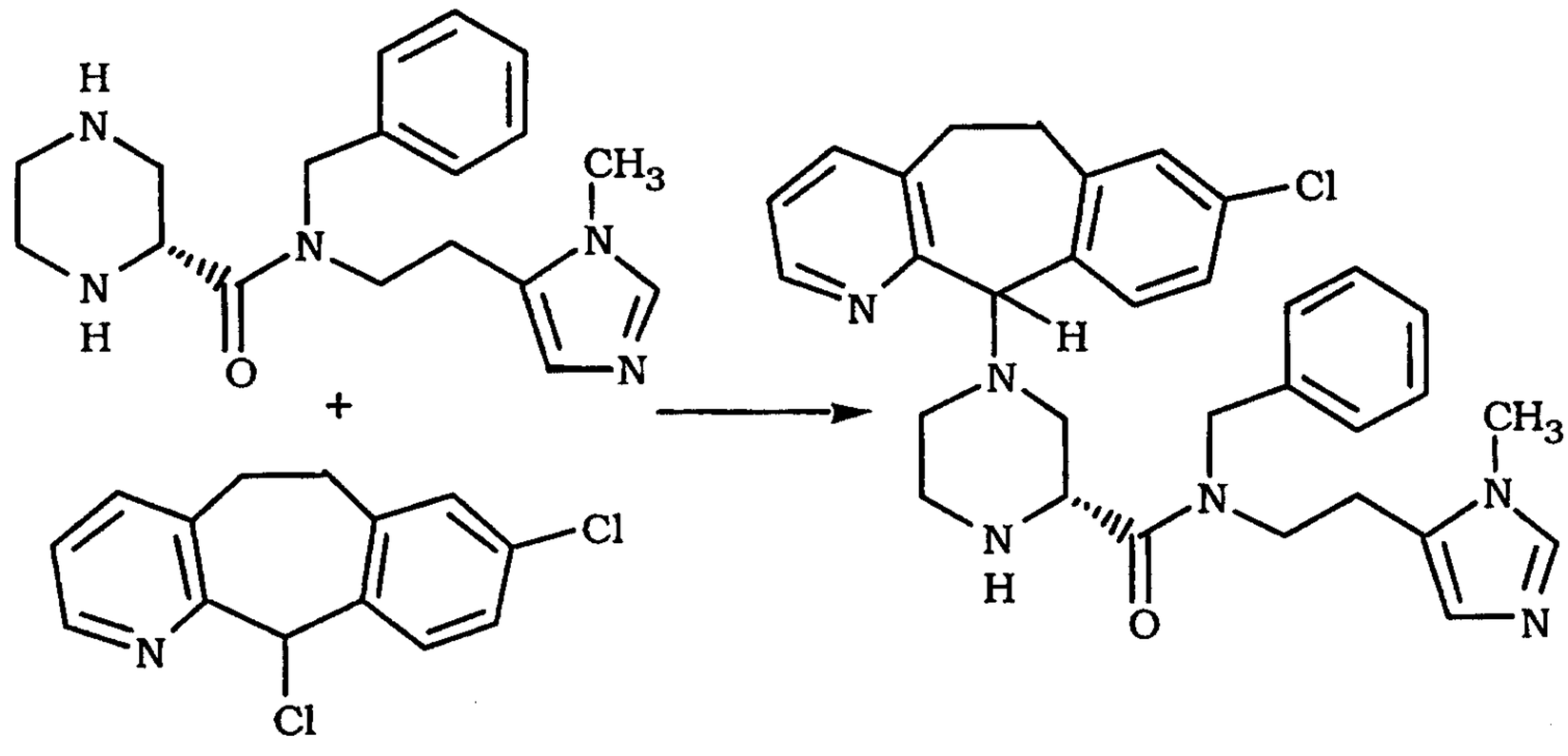
Dissolve the acid from Preparative Example 43 (0.37 g, 1.12 mmol), the product from Preparative Example 19 (0.29 g, 1.35 mmol), DEC (0.289 g, 1.46 mmol), HOBT (0.197 g, 1.46 mmol), N-methylmorpholine (0.25 mL, 2.24 mmol) in 20 mL of DMF and stir under nitrogen over night. Concentrate under vacuum. Dissolve the residue in 50 mL of methylene chloride, wash with sat. $NaHCO_3$ soln., dry the organic layer over $MgSO_4$ and concentrate under vacuum. Flash chromatograph the residue on silica gel using 100% CH_2Cl_2 (NH_4OH) giving a white solid.

Step B



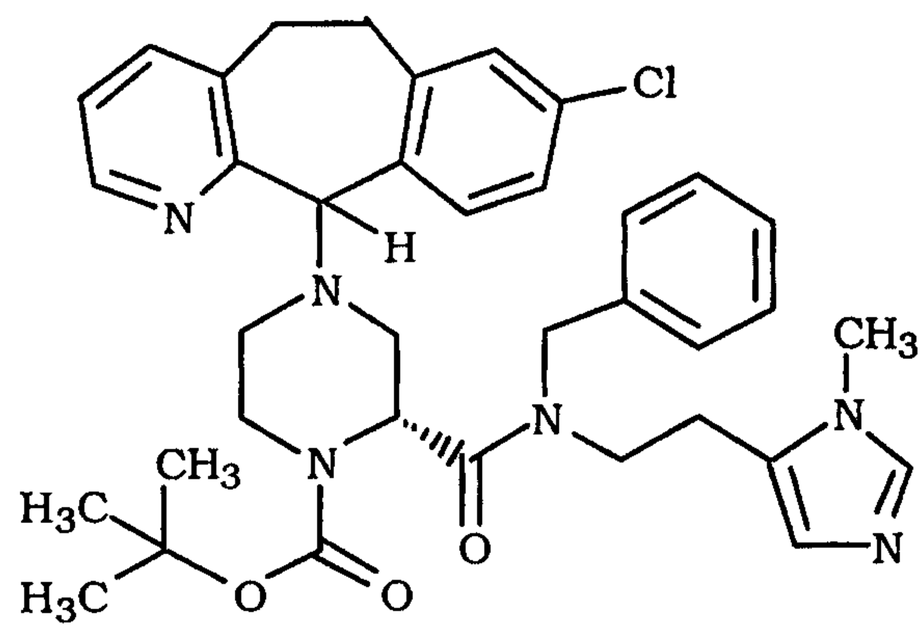
Dissolve the product of Step A (0.59 g, 1.048 mmol) in 3 mL of methylene chloride and add 2.5 mL of trifluoroacetic acid. Stir overnight and concentrate under vacuum.

Step C



Dissolve the product of Step B (0.5 g, 1.048 mmol), the 8-Cl-tricyclic chloride (0.359 g, 1.048 mmol) and triethyl amine (2.19 mL, 15.72 mmol) in 5 mL of methylene chloride and stir overnight. Concentrate under vacuum and flash chromatograph the residue on silica gel using 95% CH_2Cl_2 (NH_4OH) - 5% methanol giving the product as a white solid.

Step D

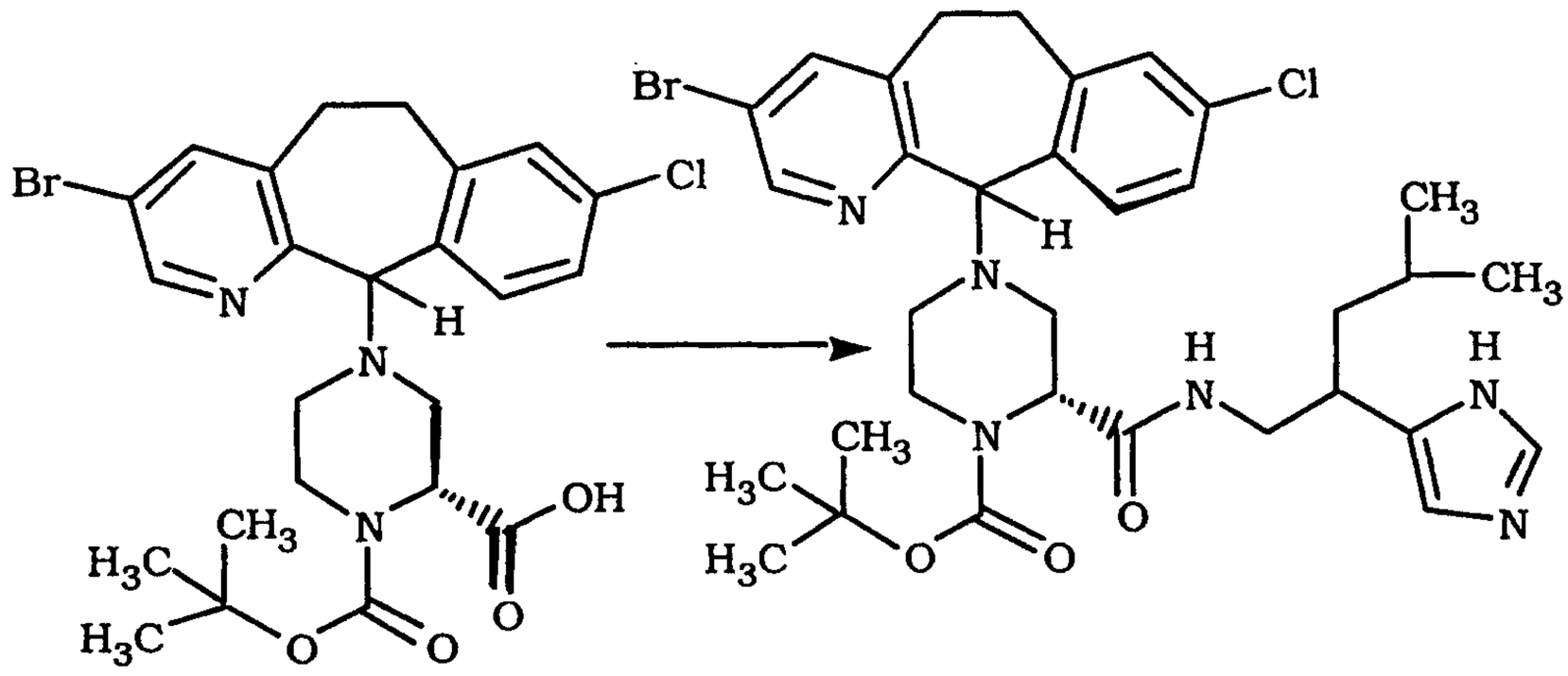


Dissolve the product of Step C (0.27 g, 0.486 mmol) in 2 mL of methylene and add di-tert-butyldicarbonate (0.125 g, 0.57 mmol) and stir for 2 hr. Concentrate under vacuum and separate the diastereomers by preparative chiral chromatography (Chiralpack AD, 5 cm x 50 cm column, flow rate 100 mL/min., 5% 2-propanol/hexane + 0.2% diethylamine) giving the products as white solids.

Diastereomer A: Mp = 93.1-99.8°C, MH^+ = 655 (FAB).

Diastereomer B: Mp = 93.1-99.8°C, MH^+ = 655 (FAB).

EXAMPLE 63

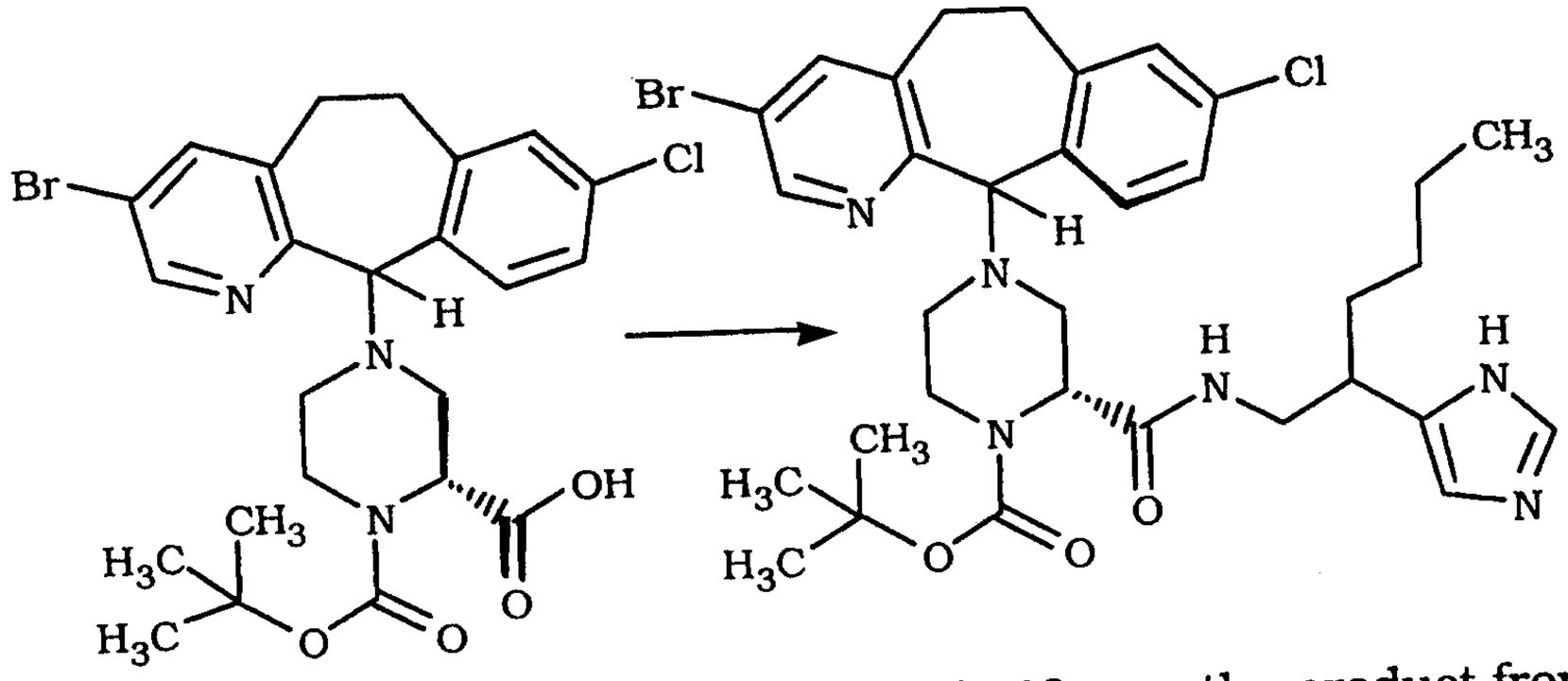


Following the procedure of Example 40, use the product from Preparative Example 27 instead of Preparative Example 13 to obtain the products as white solids.

Isomer mix 1: Mp = 148-151°C, MH^+ = 687 (FAB).

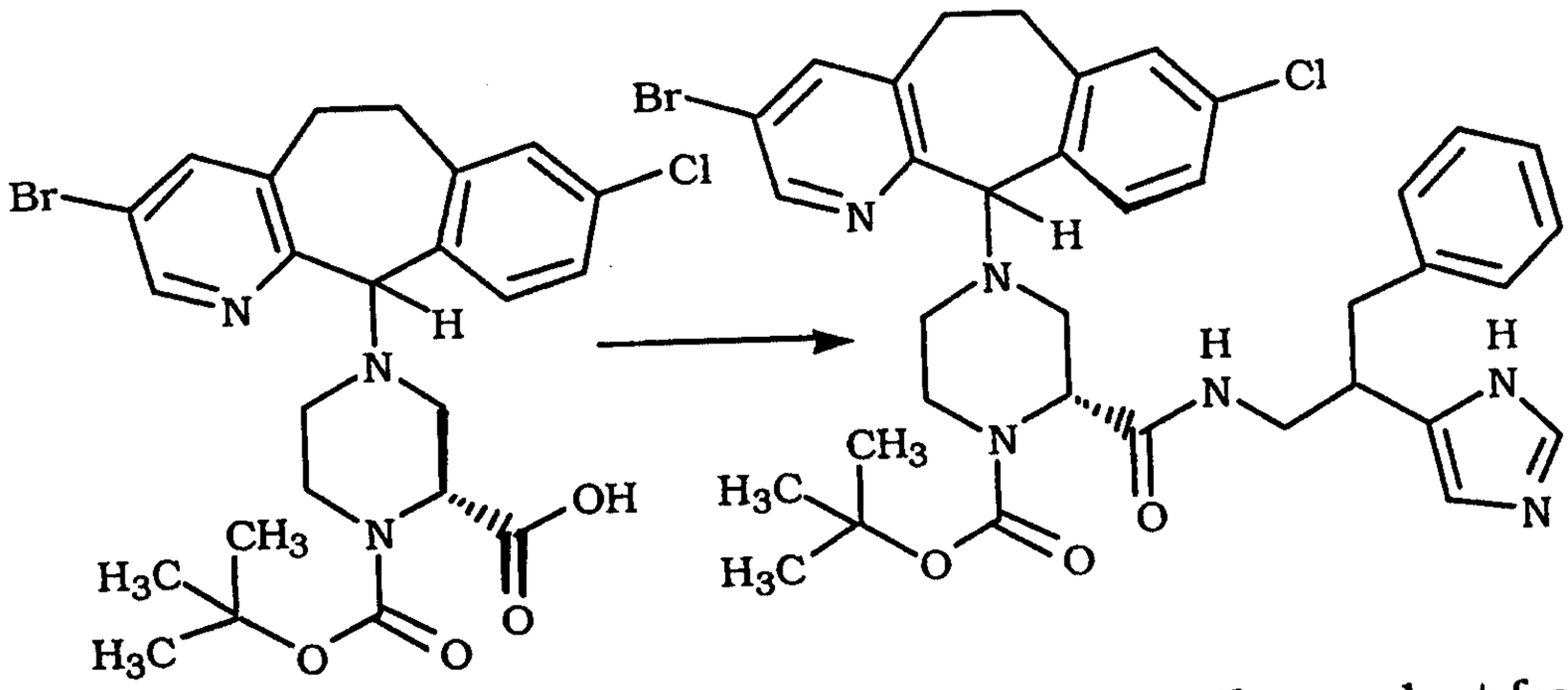
Isomer mix 2: Mp = 110-114°C, MH^+ = 687 (FAB).

EXAMPLE 64



Following the procedure of Example 40, use the product from Preparative Example 28 instead of Preparative Example 13 to obtain the product as a white solid: Mp = 131-138°C decomp., MH^+ = 687 (FAB).

EXAMPLE 65

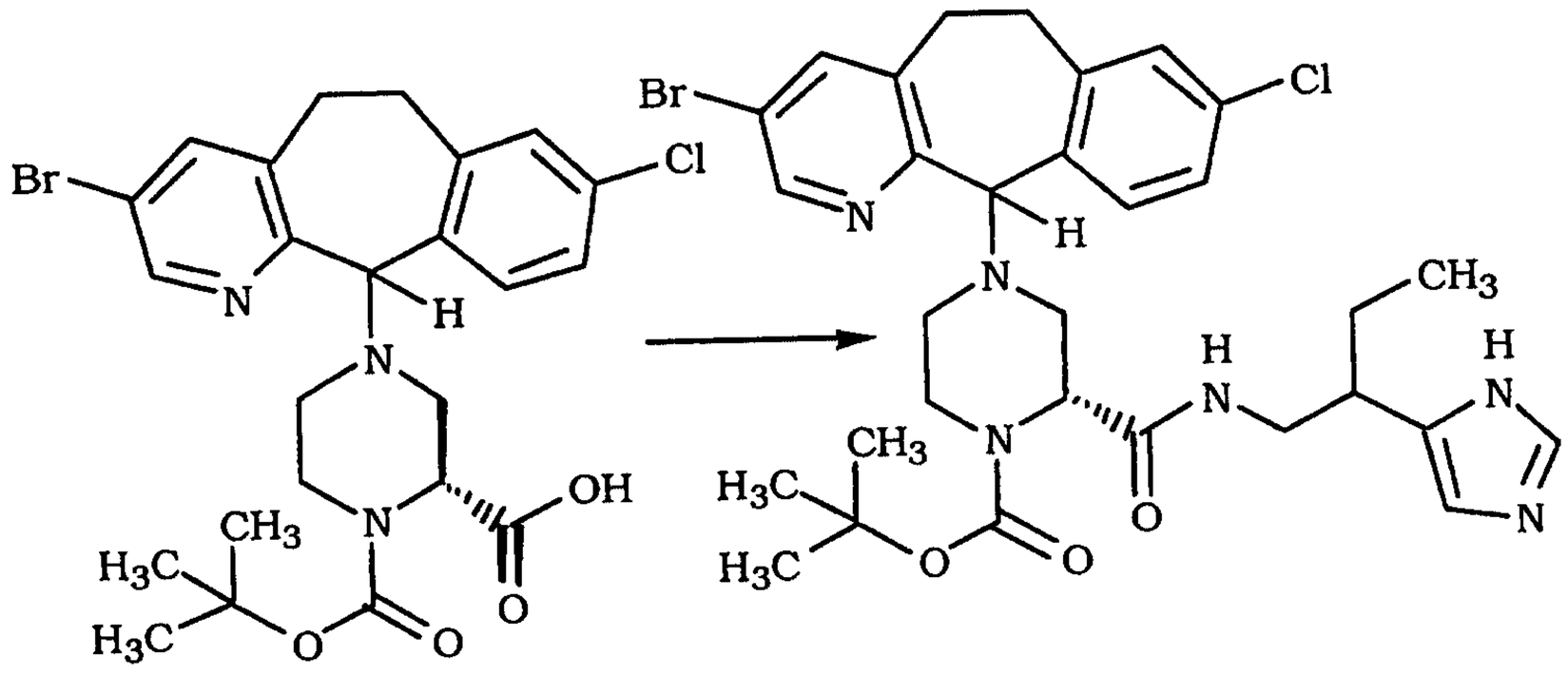


Following the procedure of Example 40, use the product from Preparative Example 29 instead of Preparative Example 13 to obtain the products as white solids.

Isomer mix 1: Mp = 148-157°C, MH^+ = 721 (FAB).

Isomer mix 2: Mp = 120-126°C, MH^+ = 721 (FAB).

EXAMPLE 66

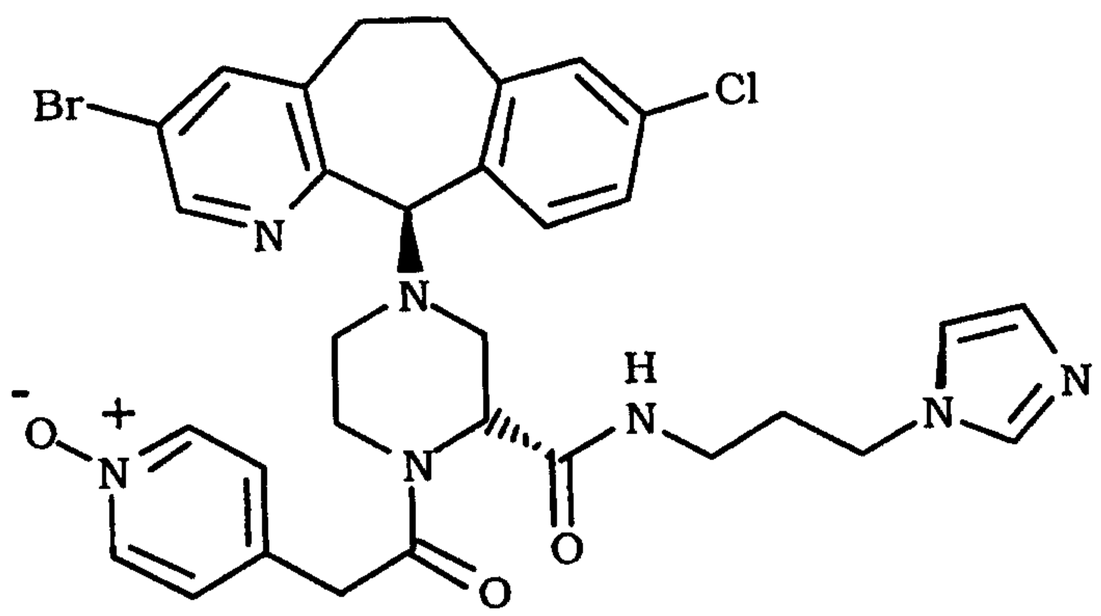


Following the procedure of Example 40, use the product from Preparative Example 30 instead of Preparative Example 13 to obtain the products as white solids.

Isomer mix 1: Mp = 146-154°C, MH^+ = 657 (FAB).

Isomer mix 2: Mp = 122-127°C, MH^+ = 657 (FAB).

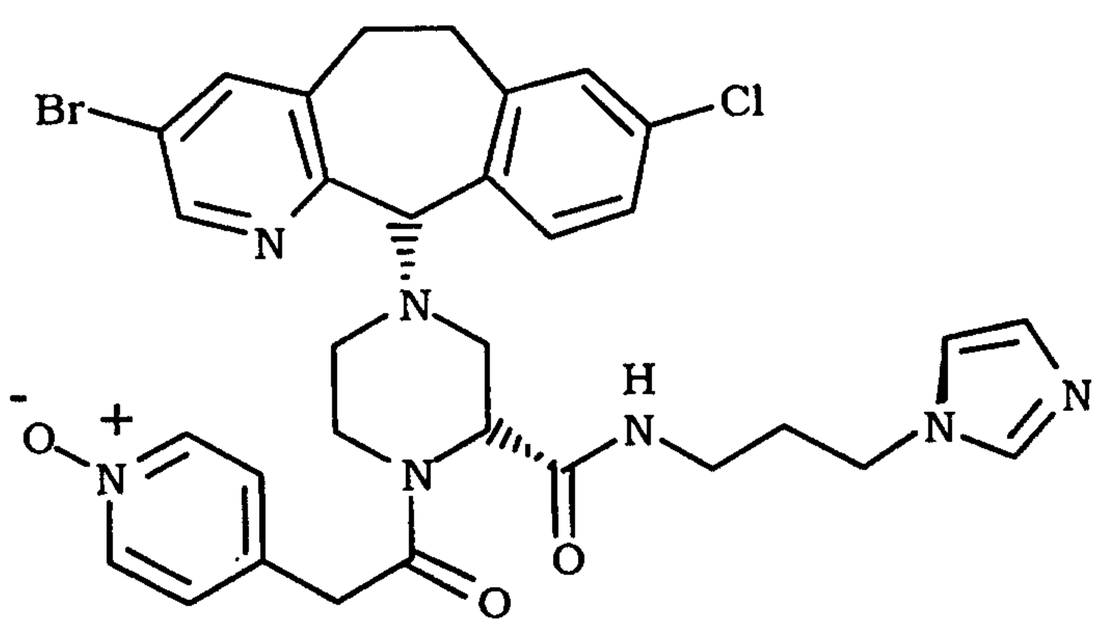
EXAMPLE 67



The 11R,2R(-)-diastereoisomer from Preparative Example 34 (0.25g, 0.46mmoles), 4-pyridylacetic acid N1-oxide (0.0915g, 0.598mmoles) (see Preparative Example 61 of US 5,719,148 issued February 17, 1998), DEC (0.1146g, 0.598mmoles), HOBt (0.0807g, 0.598mmoles) and 4-methyl-morpholine (0.0657mL, 0.598mmoles) were dissolved in anhydrous DMF (9mL) and the mixture was stirred under argon at 25°C for 96h. The reaction was worked up as described in Preparative Example 40, Step A above, and

chromatographed on a silica gel column using 5% (10% conc. NH_4OH in methanol)-dichloromethane as the eluant to give the title compound: (Yield: 0.2434g, 78%); FABMS: m/z 678.0 (MH^+); δ_C ($CDCl_3$) 30.1, 30.3, 30.9, 36.5, 38.5, 44.1, 44.3, 50.7, 52.5; CH: 53.4, 78.3, ~119.1, 126.2, 127.3, 127.3, ~129.1, 130.6, 132.3, ~137.1, 138.6, 138.6, 141.1, 146.9; C: 120.1, 134.2, 134.6, 134.8, 137.1, 140.8, 155.1, 169.2, 169.8; δ_H ($CDCl_3$) 4.31 (1H, s, H_{11}), 4.97 (1H, broad s, C<u>H</u>CO), 6.74 (1H, broad s, Im-H_5), 6.91 (1H, broad s, Im-H_4), 7.02 (1H, broad s, Ar-H), 7.07-7.17 (5H, m, CON<u>H</u>CH_2 and Ar-H), 7.38 (1H, broad s, Im-H_2), 7.56 (1H, s, Ar-H), 8.08, (1H, d, Ar-H), 8.10 (1H, d, Ar-H) and 8.35ppm (1H, s, Ar-H_2); $[a]_D^{23.2°}$ +44.4° (c=10.64mg/2mL, methanol).

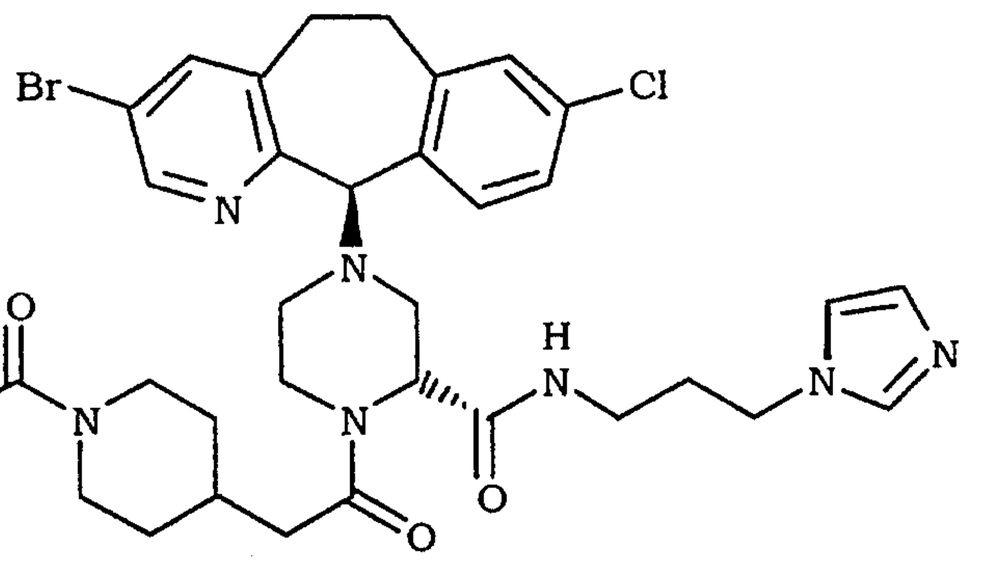
<u>EXAMPLE 68</u>



The 11S,2R(-)-diastereoisomer from Preparative Example 34 (0.3g, 0.552mmoles), 4-pyridylacetic acid N1-oxide (0.110g, 0.718mmoles) (US 5,719,148 , Feb. 17, 1998), DEC (0.1375g, 0.718mmoles), HOBt (0.0969g, 0.718mmoles) and 4-methylmorpholine (0.0788mL, 0.718mmoles) were dissolved in anhydrous DMF (9mL) and the mixture was stirred under argon at 25°C for 19h. The reaction was worked up as described in Preparative Example 40, Step A above, and chromatographed on a silica gel column using 6% (10% conc. NH_4OH in methanol)-dichloromethane as the eluant to give the title compound: (Yield:

0.2847g, 80%); FABMS: m/z 678.0 (MH^+); δ_c ($CDCl_3$) 30.1, 30.6, 30.8, 36.5, 38.5, 44.0, 44.4, 51.1, 52.7; CH: 53.4, 78.5, ~119.0, 126.2/126.3, 127.2/127.3, 127.2/127.3, ~129.2, 130.3, 132.4/132.6, ~137.1, 138.7, 138.7, 141.2/141.5, 147.0/147.2; C: 120.1, 134.2/134.4, 134.3, 134.9, 136.9, 141.5, 154.4/154.7, 168.8/169.2, 169.0/169.9; δ_H ($CDCl_3$) 4.30 (1H, s, H_{11}), 4.96 (1H, broad s, C<u>H</u>CO), 6.64 (1H, broad s, CON<u>H</u>CH_2), 6.89-7.02 (3H, broad overlap, Im-H_5, Im-H_4 and Ar-H), 7.10-7.18 (4H, m, Ar-H), 7.33 (1H, broad s, Im-H_2), 7.59 (1H, s, Ar-H), 8.08, (1H, d, Ar-H), 8.10 (1H, d, Ar-H) and 8.37ppm (1H, s, Ar-H_2); $[a]_D^{23.4°}$ +6.9° (c=10.48mg/2mL, methanol).

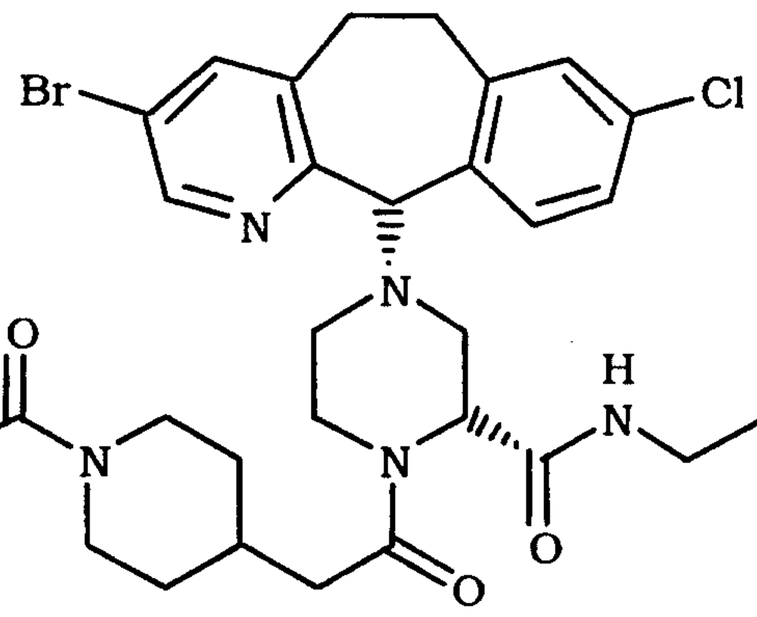
<u>EXAMPLE 69</u>



The 11R,2R(-)-diastereoisomer from Preparative Example 34 (0.3g, 0.552mmoles), 1-aminocarbonyl-4-piperidinylacetic acid (0.1335g, 0.718mmoles) (Preparative Example 33), DEC (0.1375g, 0.718mmoles), HOBt (0.0969g, 0.718mmoles) and 4-methylmorpholine (0.157mL, 1.436mmoles) were dissolved in anhydrous DMF (7mL) and the mixture was stirred under argon at 25°C for 68h. The reaction was worked up as described in Preparative Example 40, Step A above, and chromatographed on a silica gel column using 6% (10% conc. NH_4OH in methanol)-dichloromethane as the eluant to give the title compound: (Yield: 0.3547g, 90%); LCMS: m/z 711.2 (MH^+); δ_c ($CDCl_3$): 30.3, 30,4, 31.2,

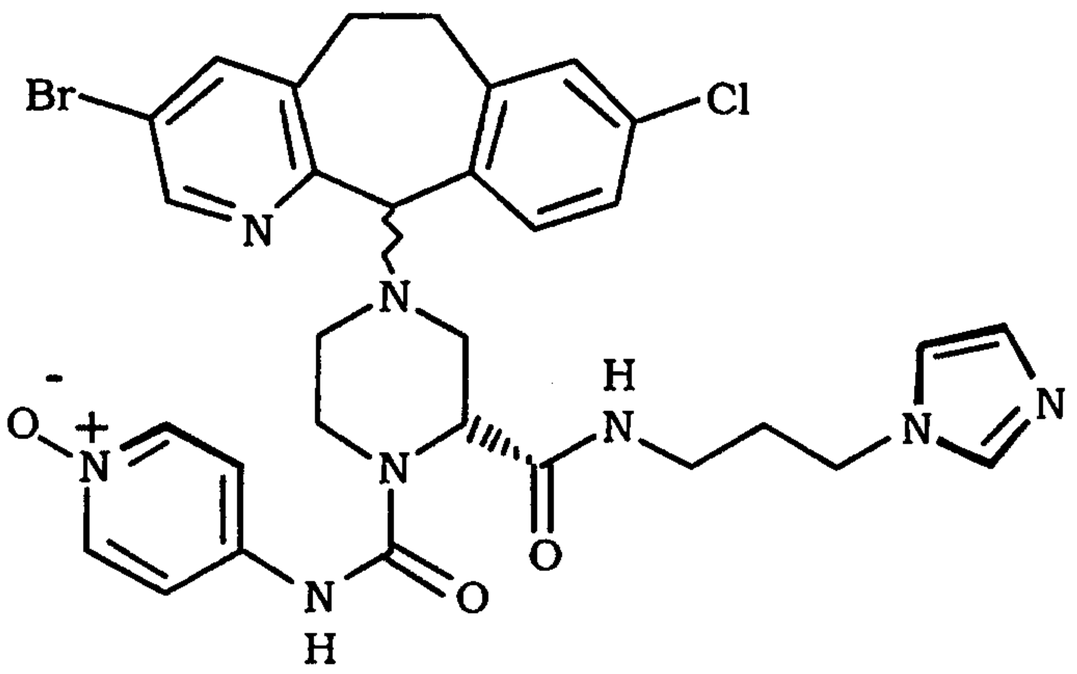
32.0, 32.0, 36.6/37.2, 39.3/39.6, 43.9, 44.4, 44.4, 44.4, 51.0, 51.8; CH: 32.9, 53.0, 78.7, 118.9, 126.2, 129.7, 130.5/130.7, 132.3, 137.3, 141.3, 147.0; C: 120.3, 134.3, 135.1, 137.3, 141.1, 155.1, 157.9, 170.0, 171.9; δ_H ($CDCl_3$) 4.30 (1H, s, H_{11}), 4.89 (2H, s, NCON$\underline{H}_2$), 4.98 (1H, s, C$\underline{H}$CO), 6.92 (1H, broad s, Im-H_5), 6.99 (1H, broad s, Im-H_4), 7.07-7.14 (3H, m, Ar-H), 7.41 (1H, broad s, Im-H_2), 7.57 (1H, s, Ar-H), 7.59 (1H, broad s, CON$\underline{H}$CH$_2$) and 8.35ppm (1H, s, Ar-H_2); $[a]_D^{20.0°}$ +35.5° (c=9.40mg/2mL, methanol).

EXAMPLE 70



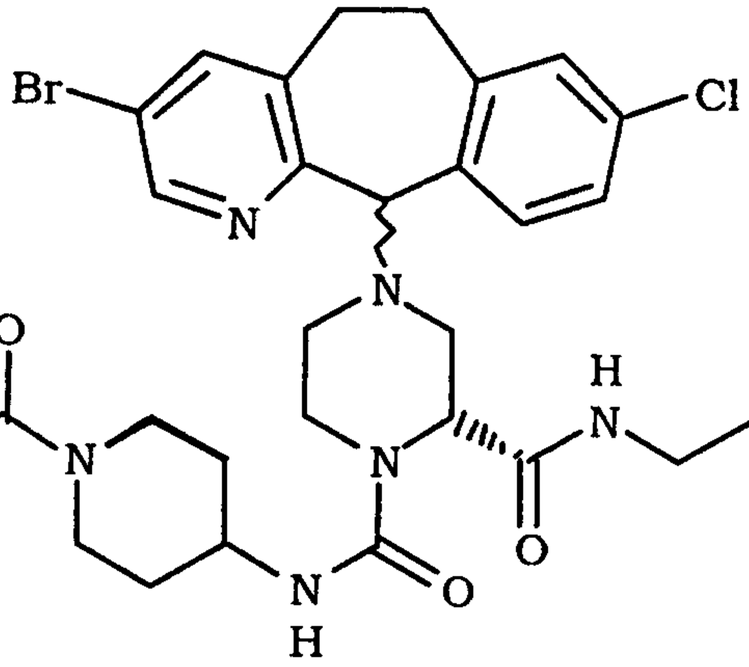
Following the procedure of Example 69, except using the 11S,2R(-)-diastereoisomer from Preparative Example 34 instead of the 11R,2R(-)-diastereoisomer, and stirring under argon for 96h instead of 68h, the title compound was obtained: (Yield: 0.3241g, 83%); LCMS: m/z 711.2 (MH^+); δ_c ($CDCl_3$): 30.2, 30,6, 31.1, 32.0, 32.0, 36.5/36.8, 39.6/39.7, 43.8, 44.4, 44.4, 44.4, 51.3, 51.6; CH: 32.9, 53.0, 78.8, 119.0, 126.3/126.4, 129.4, 130.4/130.6, 132.5/132.6, 137.1, 141.5, 147.1; C: 120.2, 134.3, 135.0, 137.1, 141.5, 155.1, 158.1, 170.3, 172.4; δ_H ($CDCl_3$) 4.29 (1H, s, H_{11}), 4.55 (2H, s, NCON$\underline{H}_2$), 4.98 (1H, s, C$\underline{H}$CO), 6.23 (1H, t, CON$\underline{H}$CH$_2$), 6.92 (1H, broad s, Im-H_5), 7.03 (1H, broad s, Im-H_4), 7.10-7.17 (3H, m, Ar-H), 7.43 (1H, broad s, Im-H_2), 7.59 (1H, s, Ar-H) and 8.37ppm (1H, s, Ar-H_2); $[a]_D^{23.1°}$ +1.0° (c=10.00mg/2mL, methanol).

EXAMPLE 71

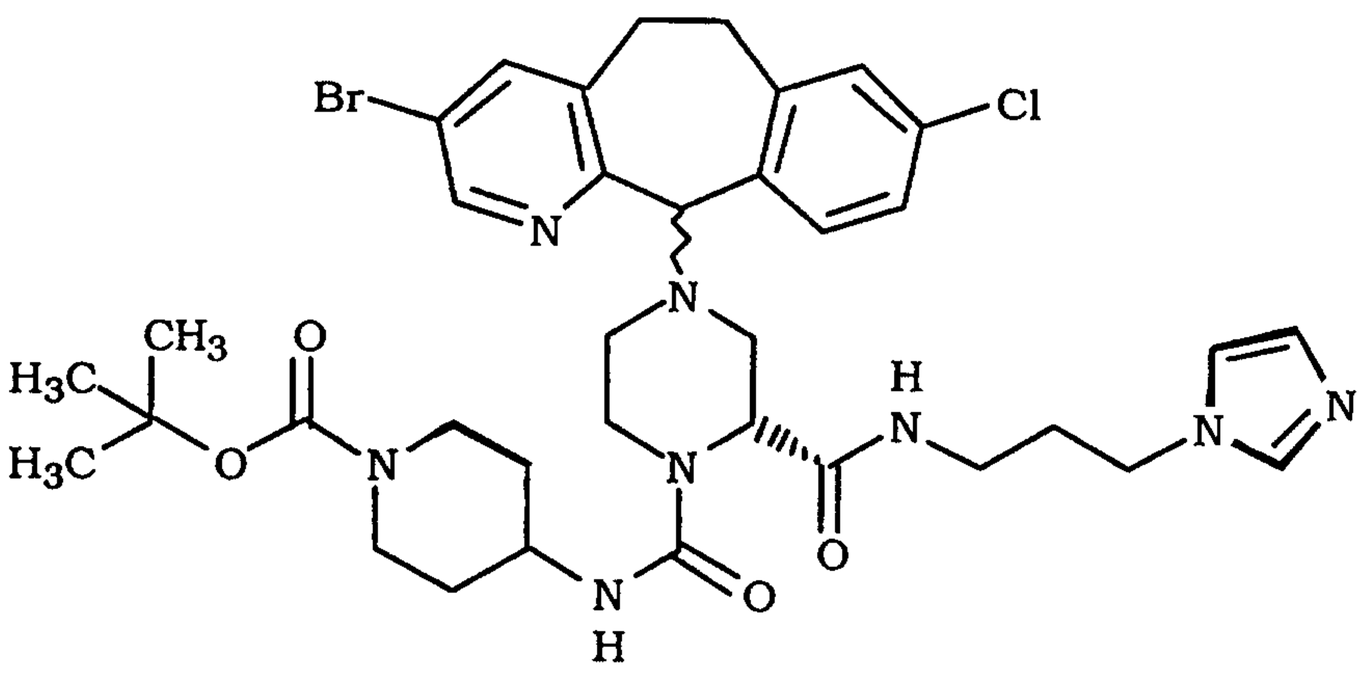


Pyridine-4-acylazide N1-oxide (*J. Med. Chem., 1998*, **41**, 877-893) (0.346g, 2.30mmoles) was dissolved in dry toluene (30mL) and the solution was heated under reflux in an argon atmosphere at 110°C for 1h. The solution was cooled to room temperature and the C_{11}-Racemic title compound from Preparative Example 141 (0.250g, 0.46mmoles) was added. The mixture was stirred at 25°C for 22h. The solution was evaporated to dryness and the residue was chromatographed on a silica gel column using 4% (10% conc. NH_4OH in methanol)-dichloro-methane as the eluant to give the title compound: (Yield: 0.1265g, 32%); LCMS: m/z 679.2 (MH^+); δ_C ($CDCl_3$) CH_2: 30.3, 30.6, 31.0/31.1, 36.7/36.8, 42.6, 44.6, 51.0/51.3, 52.4/52.6; CH: 55.1/55.2, 78.8, 115.8, 115.8, 119.2, 126.3, 129.1, 130.5/130.6, 132.7, 137.2, 138.6, 138.6, 141.4, 147.0/147.2; C: 120.2, 134.2, 134.3, 134.9, 136.9, 141.3, 155.0, 155.2, 170.4; δ_H ($CDCl_3$) 4.34 (1H, s, H_{11}), 4.67 (1H, s, C<u>H</u>CO), 6.89 (1H, d, Im-H_5), 6.99 (1H, d, Im-H_4), 7.10-7.15 (3H, m, Ar-H), 7.46 (2H, d, Ar-H), 7.59 (1H, s, Im-H_2), 7.90 (2H, d, Ar-H), 8.39 (1H, s, Ar-H_2) and 9.77ppm (1H, broad s, NCON<u>H</u>).

EXAMPLE 72



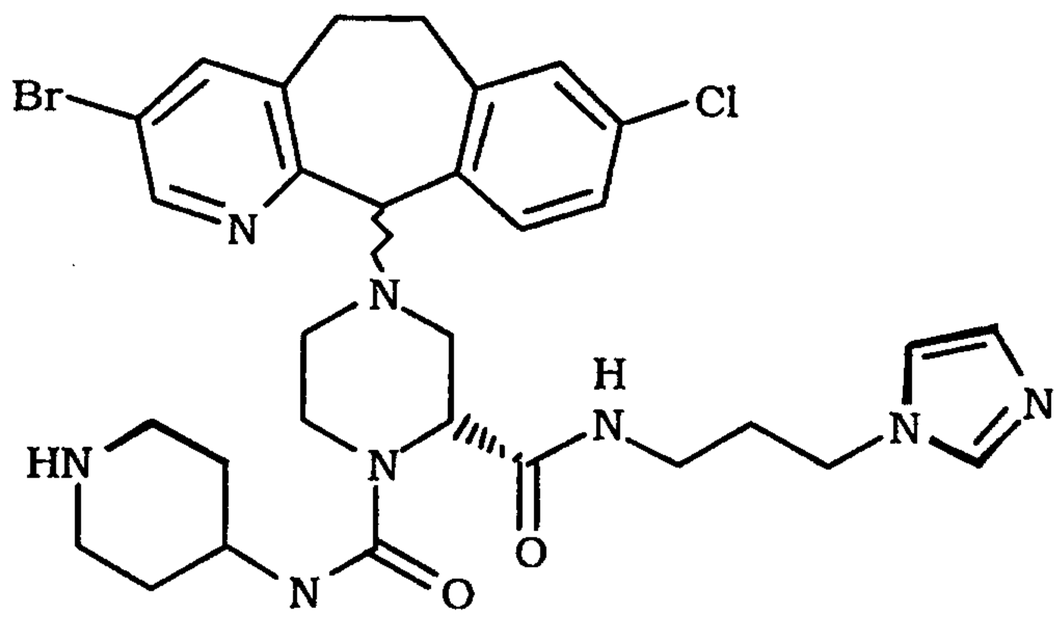
Step A



1-N-t-Butoxycarbonylpiperidine-3-acylazide (Preparative Example 35, Step B above) (1.177g, 4.63mmoles), was dissolved in dry toluene (150mL) and the solution was heated under reflux in an argon atmosphere at 110°C for 1h. The solution was cooled to room temperature and added in three portions (1.47mmoles at 0h; 2.21mmoles at 69h and 0.95mmoles at 93h) to a solution of the C_{11}-Racemic title compound from Preparative Example 141 (0.4g, 0.735mmoles) in anhydrous dichloromethane (26mL). The mixture was stirred at 25°C for 117h. The solution was evaporated to dryness and the residue was chromatographed on a silica gel column using 4% (10% conc. NH_4OH in methanol)-dichloromethane as the eluant to give the title compound: (Yield: 0.1265g, 32%); LCMS: m/z 679.2 (MH^+); δ_C ($CDCl_3$) CH_3: 28.5, 28.5, 28.5; CH_2: 30.5, 30.6, 31.2/31.3, 32.5, 32.5, 36.6, 41.8, 42.7, 42.7, 44.6, 50.9/51.1, 51.9/52.2; CH: 48.2, 54.9/55.0, 78.9/79.0, ~119.0, 126.4/126.5,

~129.6, 130.5/130.6, 132.8, ~137.1, 141.3/141.4, 147.1/147.3; C: 79.6, 120.3, 134.5, 134.7, 136.9, 141.1, 154.7, 154.8, 157.6, 171.0; δ_H($CDCl_3$) 1.46 (9H, s, CH_3), 4.33 (1H, s, H_{11}), 4.41 (1H, broad s, C<u>H</u>CO), 5.18 (1H, d, NCON<u>H</u>), 6.55 (1H, broad m, CON<u>H</u>CH_2), 6.92 (1H, broad s, Im-H_5), 7.08 (1H, broad s, Im-H_4), 7.10-7.15 (3H, m, Ar-H), 7.50 (1H, broad s, Im-H_2), 7.59 (1H, d, Ar-H) and 8.40ppm (1H, s, Ar-H_2).

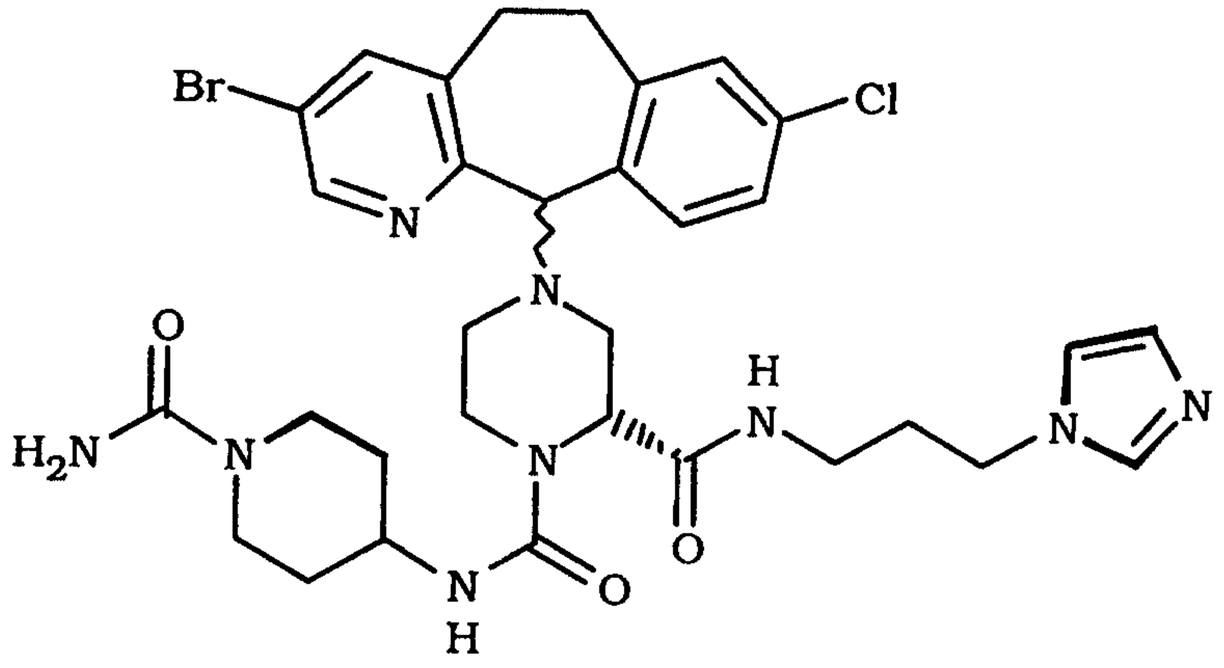
<u>Step B</u>



The title compound from Step A above (0.2361g, 0.307mmoles) was dissolved in methanol (1.61mL) and a 10% (v/v) solution of conc. H_2SO_4 in dioxane (4.18mL) was added. The mixture was stirred under argon at 25°C for 1h. The mixture was passed over a bed of BioRad® AG1-X8 (OH^-) resin and the resin was washed with methanol. The combined eluates were evaporated to dryness and the residue was chromatographed on a silica gel column using 20% (10% conc. NH_4OH in methanol)-dichloromethane as the eluant to give the title compound: (Yield: 0.1984g, 97%); LCMS: m/z 669.2 (MH^+); δ_C ($CDCl_3$) CH_2: 30.3, 30.5, 30.9, 31.6, 31.6, 36.3/36.4, 42.3, 42.3, 42.3, 44.3, 50.8/51.2, 52.1/52.4; CH: 47.2/47.3, 54.8, 78.9, 119.1, 126.3, 129.0, 130.5/130.6, 132.7, 137.5, 141.3, 147.0/147.1; C: 120.1, 134.2/134.3, 134.9, 136.9, 141.2, 155.2, 157.7/157.8, 171.2; δ_H ($CDCl_3$) 4.29 (1H, s, H_{11}), 4.61 (1H, broad s, C<u>H</u>CO), 5.72 (1H, broad m, NCON<u>H</u>), 6.85 (1H, m, CON<u>H</u>CH_2), 6.92 (1H, broad s, Im-H_5),

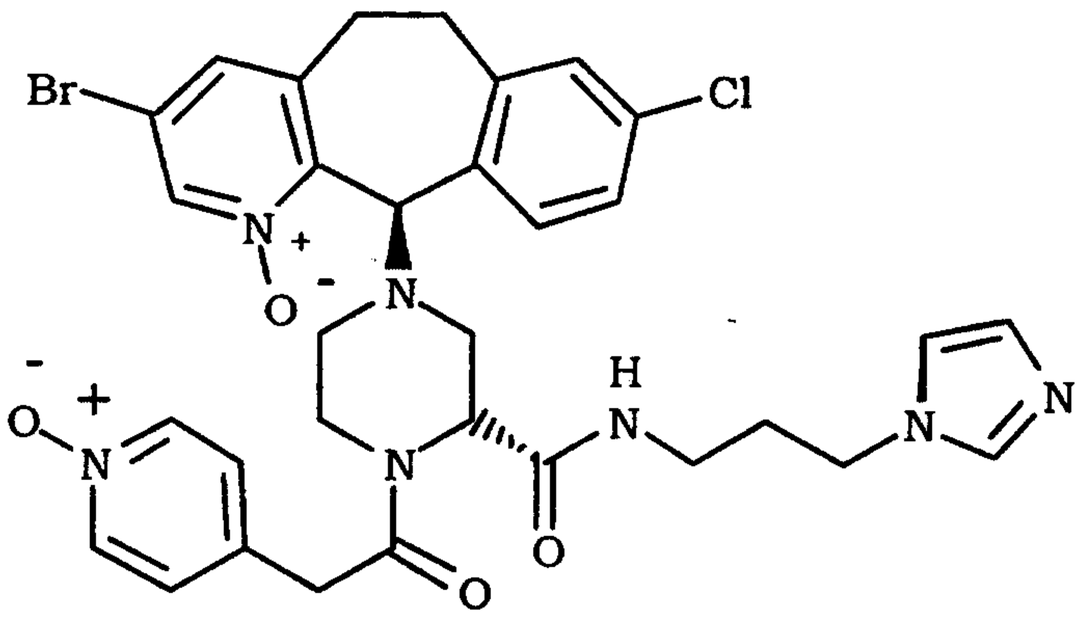
6.99 (1H, broad s, Im-H_4), 7.10-7.15 (3H, m, Ar-H), 7.57 (1H, s, Ar-H), 7.66 (1H, broad s, Im-H_2) and 8.37ppm (1H, s, Ar-H_2).

Step C



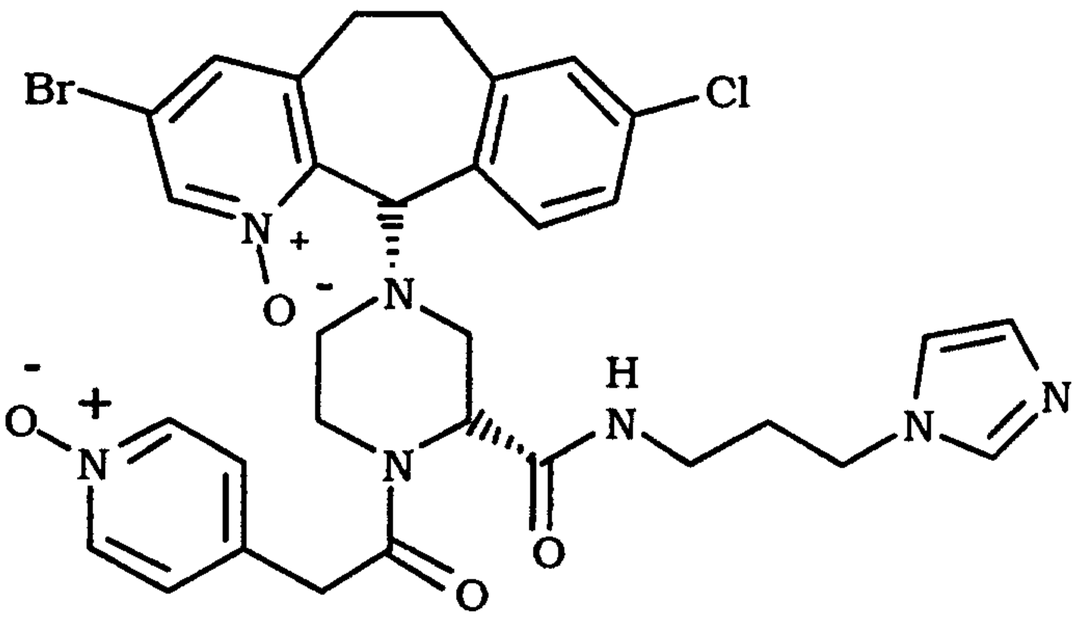
The title compound from Step B above (0.195g, 0.291mmoles) was dissolved in anhydrous dichloromethane (10mL) and trimethylsilyl isocyanate (0.394mL, 2.91mmoles) was added. The mixture was stirred under argon at 25°C for 20h. Additional trimethylsilyl isocyanate (0.188mL, 0.873mmoles) was added and the mixture was stirred for a total of 23h. The mixture was diluted with dichloromethane (900mL) and washed with saturated aqueous sodium bicarbonate, dried ($MgSO_4$), filtered and evaporated to dryness. The product was chromatographed on a silica gel column using 4% (10% conc. NH_4OH in methanol)-dichloromethane as the eluant to give the title compound: (Yield: 0.1325g, 64%); LCMS: m/z 712.2 (MH^+), δ_C ($CDCl_3$) CH_2: 30.3/30.4, 30.6, 31.0/31.1, 32.4, 32.4, 36.5, 42.0, 43.4, 43.4, 44.4, 50.9/51.2, 52.4/52.6; CH: 48.1, 54.9/55.0, 78.9, 119.0, 126.3/126.4, 129.4, 130.5/130.6, 132.7, 137.3, 141.3/141.4, 147.1/147.2; C: 120.2, 134.2/134.3, 135.1, 136.9, 141.2, 155.1, 157.8/157.9, 158.1, 171.4/171.5; δ_H: ($CDCl_3$) 4.31 (1H, s, H_{11}), 4.53 (1H, broad s, C<u>H</u>CO), 4.75 (2H, broad s, NCON<u>H</u>$_2$), 5.73 (1H, d, NCON<u>H</u>), 6.65 (1H, t, CON<u>H</u>CH_2), 6.92 (1H, broad s, Im-H_5), 7.04 (1H, broad s, Im-H_4), 7.10-7.15 (3H, m, Ar-H), 7.46 (1H, s, Ar-H), 7.58 (1H, broad s, Im-H_2) and 8.38ppm (1H, s, Ar-H_2).

EXAMPLE 73



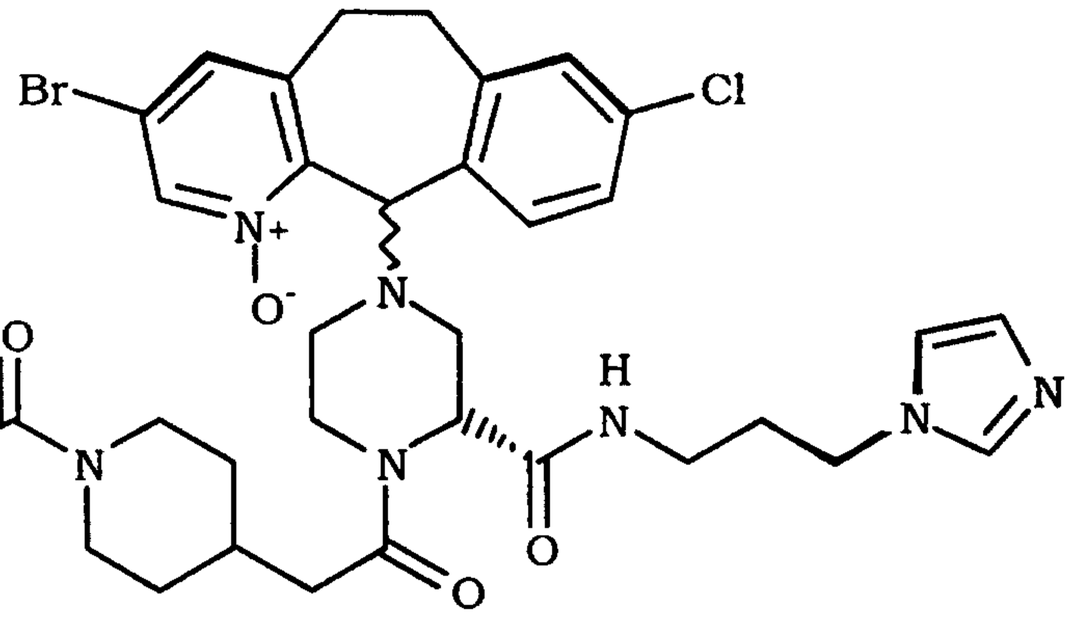
The 11R,2R(+)-diastereoisomer from Preparative Example 38, Step D above (0.1647g, 0.294mmoles), 4-pyridylacetic acid N1-oxide (0.0586g, 0.382mmoles), DEC (0.0733g, 0.382mmoles), HOBt (0.0517g, 0.382mmoles) and 4-methyl-morpholine (0.042mL, 0.382mmoles) were dissolved in anhydrous DMF (5mL) and the mixture was stirred under argon at 25°C for 25h. The reaction was worked up as described in Preparative Example 40, Step A above, and chromatographed on a silica gel column using 2% increasing to 6% (10% conc. NH_4OH in methanol)-dichloromethane as the eluant to give the title compound: (Yield: 0.1048g, 51%); SIMS: m/z 694.5 (MH^+); δ_C ($CDCl_3$) 30.0, 30.4, 31.0, 36.7, 38.5, 44.1, 44.5, 50.5, 51.3; CH: 53.6, 63.6, 119.1, 126.4, 127.4, 127.4, ~129.1, 130.7, 130.8, 133.4, ~137.2, 138.4/138.6, 138.7, 138.7; C: 118.5, 133.3, 134.6, 134.9, 140.4, 141.4, 147.4, 169.2, 169.9; δ_H($CDCl_3$) 4.98 (1H, broad s, C<u>H</u>CO), 5.70 (1H, s, H_{11}), 6.92/6.97 (1H, broad s, Im-H_5), 7.01 (1H, broad s, Im-H_4), 7.08-7.18 (5H, m, Ar-H), 7.43/7.51 (1H, broad s, Im-H_2), 7.79 (1H, t, CON<u>H</u>CH_2), 8.05 (1H, d, Ar-H), 8.09 (2H, d, Ar-H), 8.26/8.31ppm (1H, s, Ar-H_2); $[a]_D^{20.0°}$ +82.8° (c=9.11mg/2mL, methanol).

EXAMPLE 74



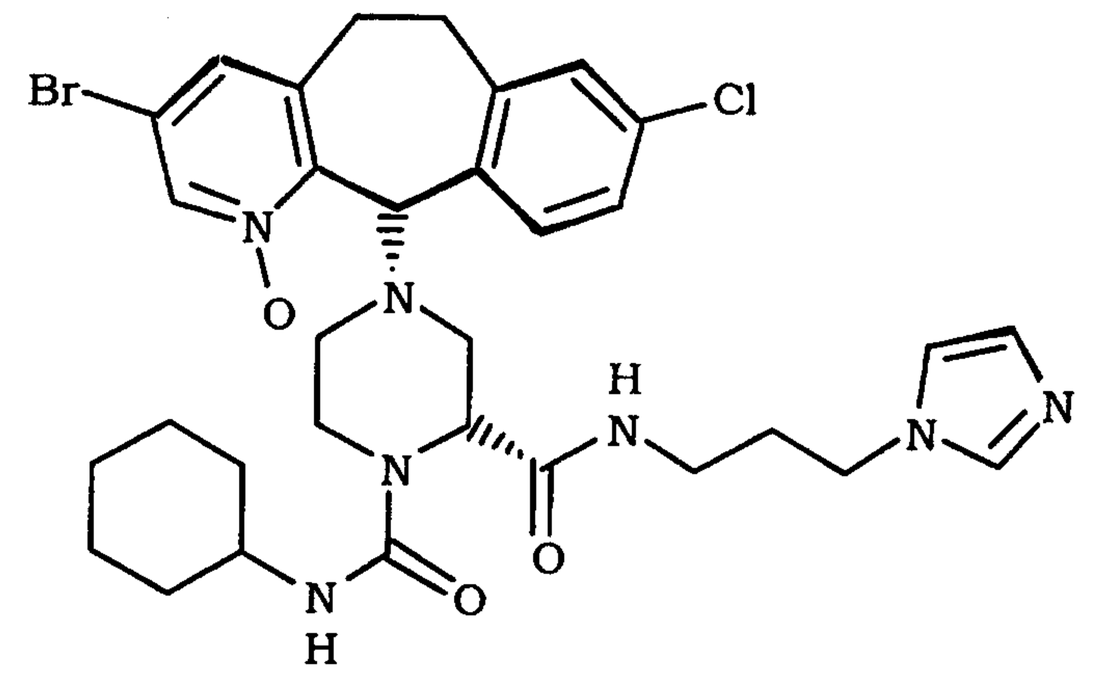
The 11S,2R(-)-diastereoisomer from Preparative Example 38, Step D above (0.1576g, 0.281mmoles), 4-pyridylacetic acid N1-oxide (0.0560g, 0.366mmoles), DEC (0.0702g, 0.366mmoles), HOBt (0.0495g, 0.366mmoles) and 4-methyl-morpholine (0.040mL, 0.366mmoles) were dissolved in anhydrous DMF (5mL) and the mixture was stirred under argon at 25°C for 26h. The reaction was worked up as described in Preparative Example 40, Step A above, and chromatographed on a silica gel column using 2% increasing to 6% (10% conc. NH_4OH in methanol)-dichloromethane as the eluant to give the title compound: (Yield: 0.1017g, 50%); SIMS: m/z 694.5 (MH^+); δ_C ($CDCl_3$) 29.7, 30.5, 30.8, 36.5, 38.4, 44.2, 44.3, 50.1, 52.3; CH: 53.4, 63.6, ~119.0, 126.4, 127.4, 127.4, ~129.1, 130.3, 130.9, 133.3, ~137.3, 138.3/138.7, 138.7, 138.7; C: 118.4, 133.3, 134.6, 134.8, 140.1, 141.6, 147.4, 169.2, 169.9; δ_H($CDCl_3$) 4.97 (1H, broad s, C<u>H</u>CO), 5.71 (1H, s, H_{11}), 6,58 (1H, t, CON<u>H</u>CH_2), 6.88 (1H, broad s, Im-H_5), 6.98/7.03 (1H, broad s, Im-H_4), 7.09-7.21 (5H, m, Ar-H), 7.34/7.41 (1H, broad s, Im-H2), 8.09 (1H, d, Ar-H), 8.10 (2H, d, Ar-H), 8.27/8.28ppm (1H, s, Ar-H_2); $[a]_D^{20.0°}$ -12.7° (c=10.08mg/2mL, methanol).

EXAMPLE 75

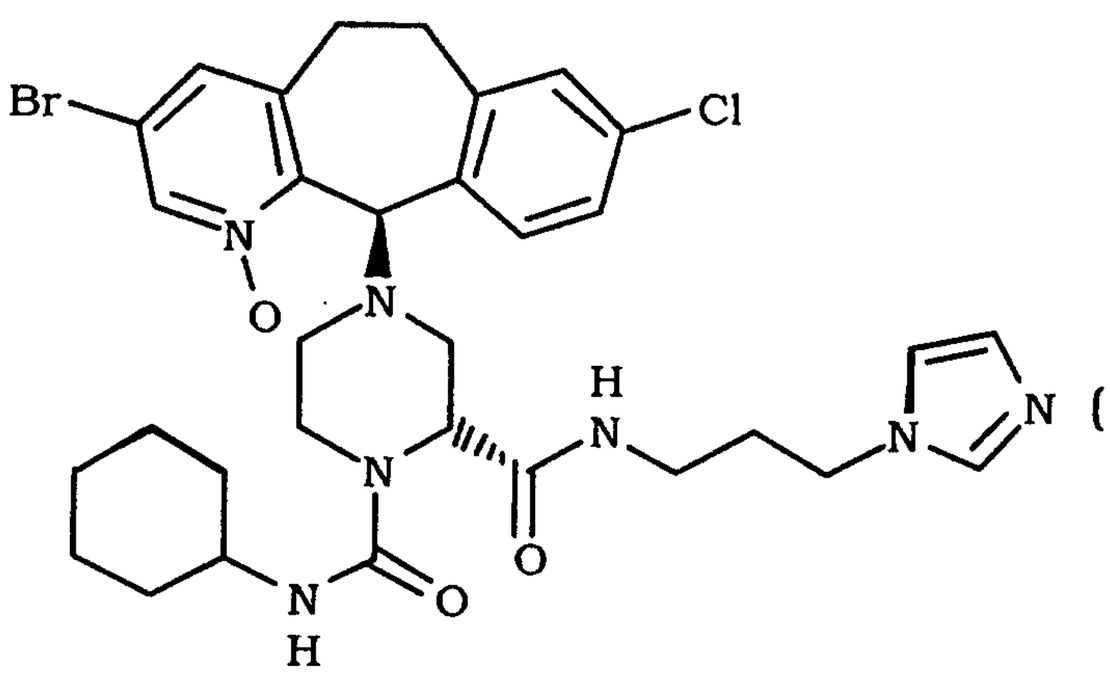


3-Bromo-8,11-dichloro-6,11-dihydro-5H-benzo[5,5]cyclohepta[1,2-b]pyridine N1-oxide (Preparative Example, 38 Step C) (0.2656g, 0.74mmoles) in anhydrous dichloromethane (3.8mL) was added to 1-[2-[N-[3-(1H-imidazol-1-yl)propyl]-2(R)-piperazinecarboxamide]-2-oxoethyl-1-piperidinecarboxamide (Preparative Example 40, Step B above) (0.3g, 0.74mmoles) and triethylamine (1.0316mL, 7.40mmoles) in anhydrous dichloromethane (6mL) and the mixture was stirred at 25°C under argon for 19h. The solution was directly chromatographed on a silica gel column using 3.5% (10% conc. NH_4OH in methanol)-dichloromethane as the eluant to give the title compound: (Yield: 0.3727g, 69%); LCMS: m/z 727.2 (MH^+); δ_C ($CDCl_3$) CH_2: 29.9/30.1, 30.4/30.5, 31.1/31.2, 32.0, 32.0, 36.5/36.6, 39.6, 44.0/44.4, 44.0/44.4, 44.4, 44.4, 50.5/50.7/51.1, 52.1; CH: 32.9, 53.0/53.1, 63.8, ~119.2, 126.4/126.5, ~129.4, 130.5/130.7, 130.9, 133.4, ~137.2, 138.4; C: 118.5, 133.3/133.4, 134.8/134.9, 140.2/140.5, 141.4/141.6, 147.6/147.8, 158.1, 169.3/170.2, 171.4/172.0; δ_H ($CDCl_3$) 4.60 (1H, s, $NCONH_2$), 4.98 (1H, broad s, C<u>H</u>CO), 5.69 (1H, s, H_{11}), 6.29/6.53 (1H, t, CON<u>H</u>CH_2, S(-) and R(+) isomers at C_{11} respectively), 6.92 (1H, broad s, Im-H_5), 7.05 (1H, broad s, Im-H_4), 7.14 (2H, m, Ar-H), 7.18 (1H, m Ar-H), 7.20 (1H, m, Ar-H), 7.56 (1H, broad s, Im-H_2) and 8.27ppm (1H, s, Ar-H_2).

EXAMPLE 76



(11S,2R(-)-Isomer)



(11R,2R(+)-Isomer)

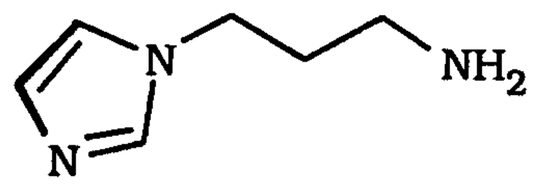
Method 1:

3-Bromo-8,11-dichloro-6,11-dihydro-5H-benzo[5,5]cyclohepta[1,2-b]pyridine N1-oxide (Preparative Example 38, Step C) (0.2818g, 0.785mmoles) in anhydrous dichloromethane (4mL) was added to N1-cyclohexyl-N2-[3-(1H-imidazol-1-yl)propyl]-1,2(R)-piperazinedicarboxamide (below) (0.2844g, 0.785mmoles) and triethylamine (1.094mL, 7.85mmoles) in anhydrous dichloromethane (4.5mL) and the mixture was stirred at 25°C under argon for 67h. The solution was directly chromatographed on a silica gel column using 3% (10% conc. NH_4OH in methanol)-dichloromethane as the eluant to give the racemic mixture of the title compounds: (Yield: 0.4664g, 87%). The mixture was subjected to preparative HPLC on a Chiralpak AD® column (50X5cm) using 65% hexane- 35% isopropyl alcohol- 0.2% diethylamine as the eluant to give in the order of elution the 11S,2R(-)-diastereoisomer and the 11R,2R(+)-diastereoisomer.

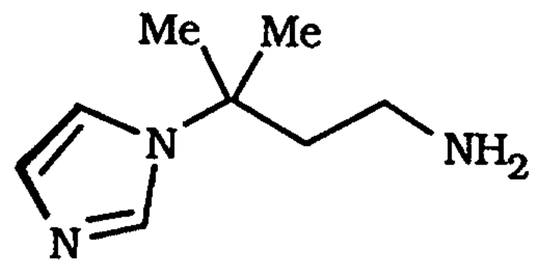
11S,2R(-)-diastereoisomer: (Yield: 0155.5g); LCMS: m/z 684.2 (MH^+); δ_C ($CDCl_3$) 25.0, 25.1, 25.6, 30.1, 30.5, 31.1, 33.7, 33.7, 36.4, 42.4, 44.5, 50.2, 51.5; CH: 49.9, 54.8, 64.1, 119.1, 126.5, 129.3, 130.5, 130.8, 133.5, 137.2, 138.4; C: 118.4, 133.1, 134.9, 140.2, 141.4, 147.8, 157.6, 171.2; δ_H ($CDCl_3$) 4.53 (1H, broad s, CHCO), 4.91 (1H, d, NCONH), 5.68 (1H, s, H_{11}), 6.62 (1H, t, CONHCH$_2$), 6.94 (1H, broad s, Im-H_5), 7.08 (1H, broad s, Im-H_4), 7.15 (1H, m, Ar-H), 7.17 (1H, s, Ar-H), 7.21 (1H, s, Ar-H), 7.23 (1H, m, Ar-H), 7.55 (1H, broad s, Im-H_2) and 8.27ppm (1H, s, Ar-H_2); $[a]_D^{20.0°}$ -33.1° (c=8.76mg/2mL, methanol).

11R,2R(+)-diastereoisomer: (Yield: 0.1890g); LCMS: m/z 684.2 (MH^+); δ_C ($CDCl_3$) 25.1, 25.1, 25.6, 30.3, 30.7, 31.1, 33.7, 33.7, 36.5, 42.3, 44.7, 50.2, 50.7; CH: 50.0, 55.0, 64.2, 119.1, 126.3, 128.8, 130.6, 130.9, 133.5, 137.2, 138.5; C: 118.5, 133.1, 134.7, 140.4, 141.4, 147.5, 157.5, 171.1; δ_H ($CDCl_3$) 4.52 (1H, broad s, CHCO), 4.95 (1H, d, NCONH), 5.69 (1H, s, H_{11}), 6.97 (1H, t, CONHCH$_2$), 6.97 (1H, broad s, Im-H_5), 7.10 (1H, broad s, Im-H_4), 7.13 (1H, m, Ar-H), 7.18 (2H, s, Ar-H), 7.21 (1H, m, Ar-H), 7.69 (1H, broad s, Im-H_2) and 8.27ppm (1H, s, Ar-H_2); $[a]_D^{20.0°}$ +49.9° (c=10.23mg/2mL, methanol).

The starting reactant N1-cyclohexyl-N2-[3-(1H-imidazol-1-yl)propyl]-1,2(R)-piperazinedicarboxamide is obtained following the procedure of Preparative Example 5, except that



is used instead of

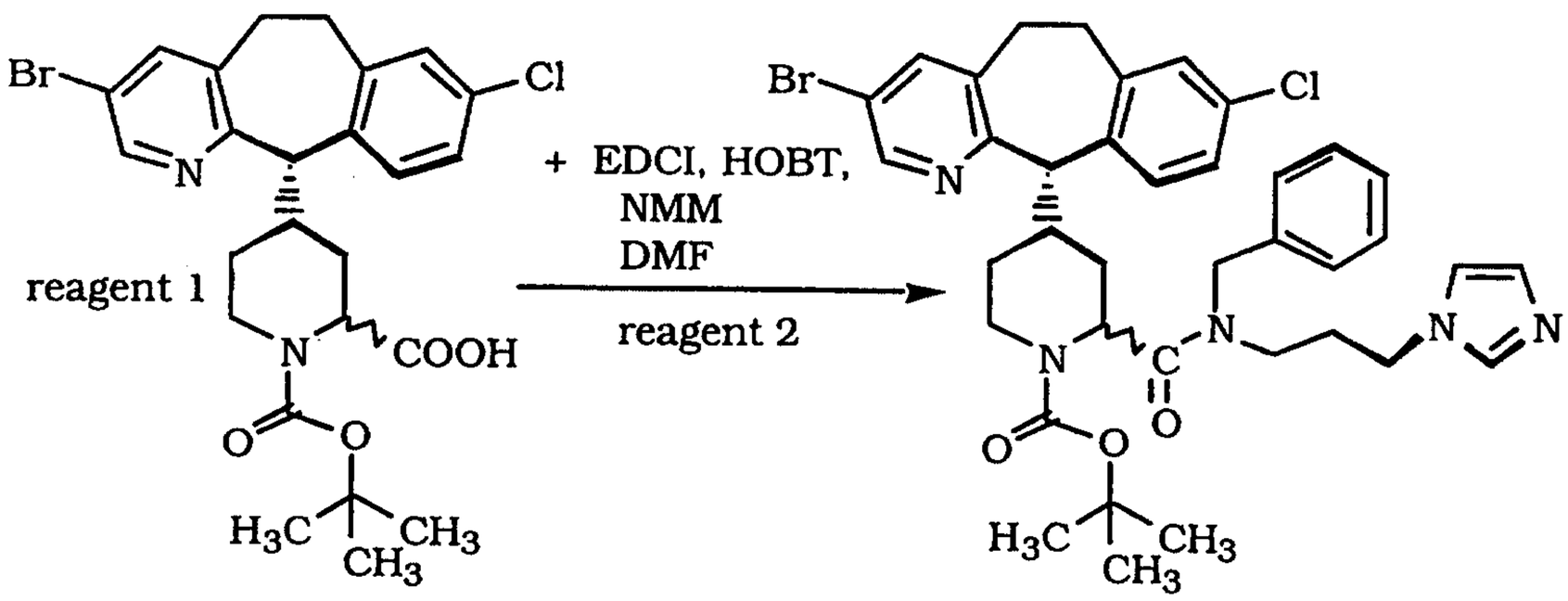


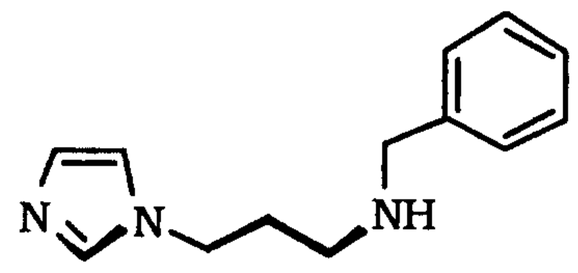
The resulting BOC protected compound is deprotected with TFA following the procedure in Preparative Example 8, Step B.

Method 2:

The 11S,2R(-)-diastereoisomer (Preparative Example 38, Step D above) (1mg, 0.00179mmoles) was dissolved in anhydrous dichloromethane (0.05mL) and cyclohexylisocyanate (0.0023mL, 0.0179mmoles) was added. The mixture was stirred at 25°C for 0.5h under argon. The solution was evaporated to dryness to give the title compound which was identical on chiral HPLC to the 11S,2R(-)-diastereoisomer prepared in Method 1 above.

EXAMPLE 77



Reagent 2 = 

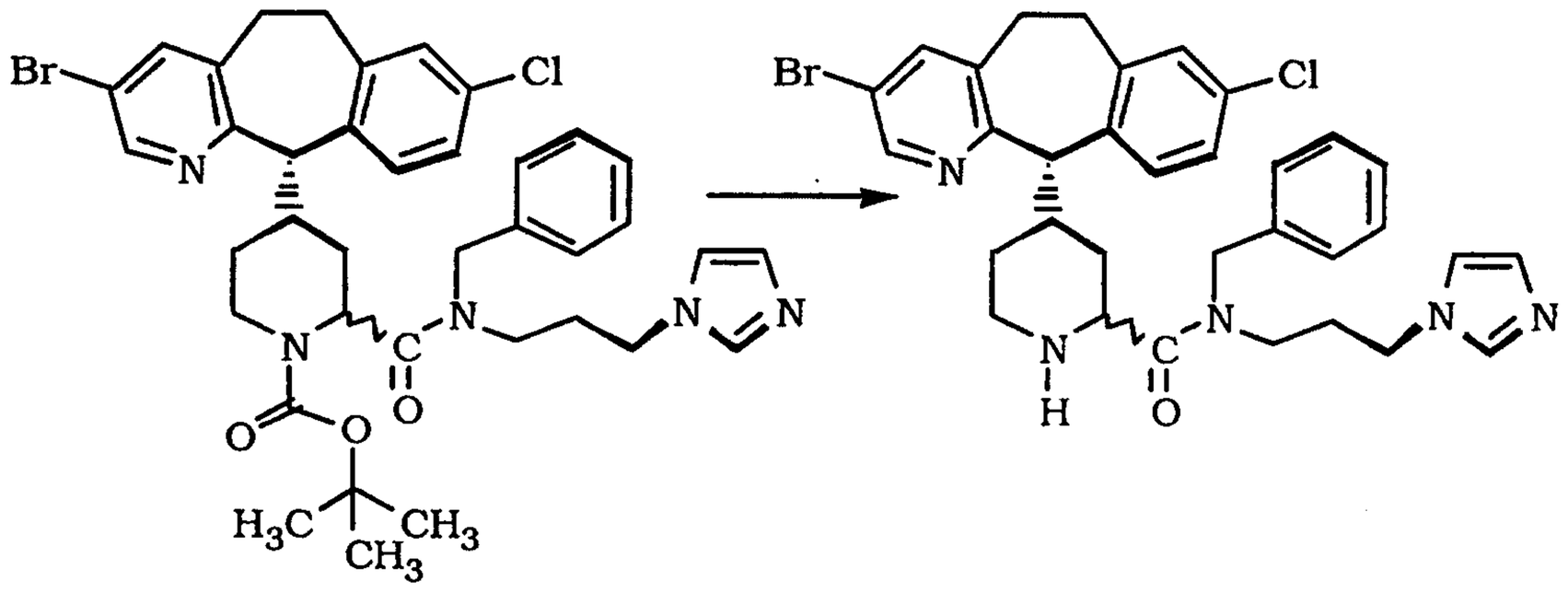
The imidazole from Preparative Example 74 (Reagent 2), (250mg,1.16mmol), was added to a solution of the BOC-acid (Reagent 1, see Preparative Example 41), (0.45g,0.842mmol) , EDCI (200mg,1.043mmol), HOBT (130mg, 0.962mmol),and N-methyl morpholine (0.2ml,1.81mmol) in DMF (anhydrous, 2ml) at room temperature (20°C). The resultant solution was stirred overnight at 20°C. The solvent was evaporated, water (70ml) and EtOAC (120 ml) were added. The organic layer was separated, and washed with 10% Na_2CO_3 solution (50ml), then dried over $MgSO_4$, filtered and evaporated solvent yielding an oil, which chromatographed on silica gel eluting with 100% EtOAC yielding the product as a white solid (300mg). Mixture of 4 isomers A,B,C,D.

Mass Spec: High Resolution(ES) Estimated(MH^+) 732.2316

Observed 732.2332

EXAMPLE 78

Step A



A solution of the title compound from Example 77, (Isomers A, B, C and D), (150mg,0.205mmol) in 50% trifluoro-acetic acid-CH_2Cl_2 was stirred at 20°C for 3 hours. The solvent was evaporated, water (25ml) and 10% NaOH (4ml) were added, then extracted with CH_2Cl_2 (2x100ml). The organic layer was separated, dried over $MgSO_4$, and solvent evaporated yielding a solid which was purified by chromatography on silica gel eluting with 3% MeOH- CH_2Cl_2 containing 2% NH_4OH yielding the product as a white solid (70mg, 54% yield).

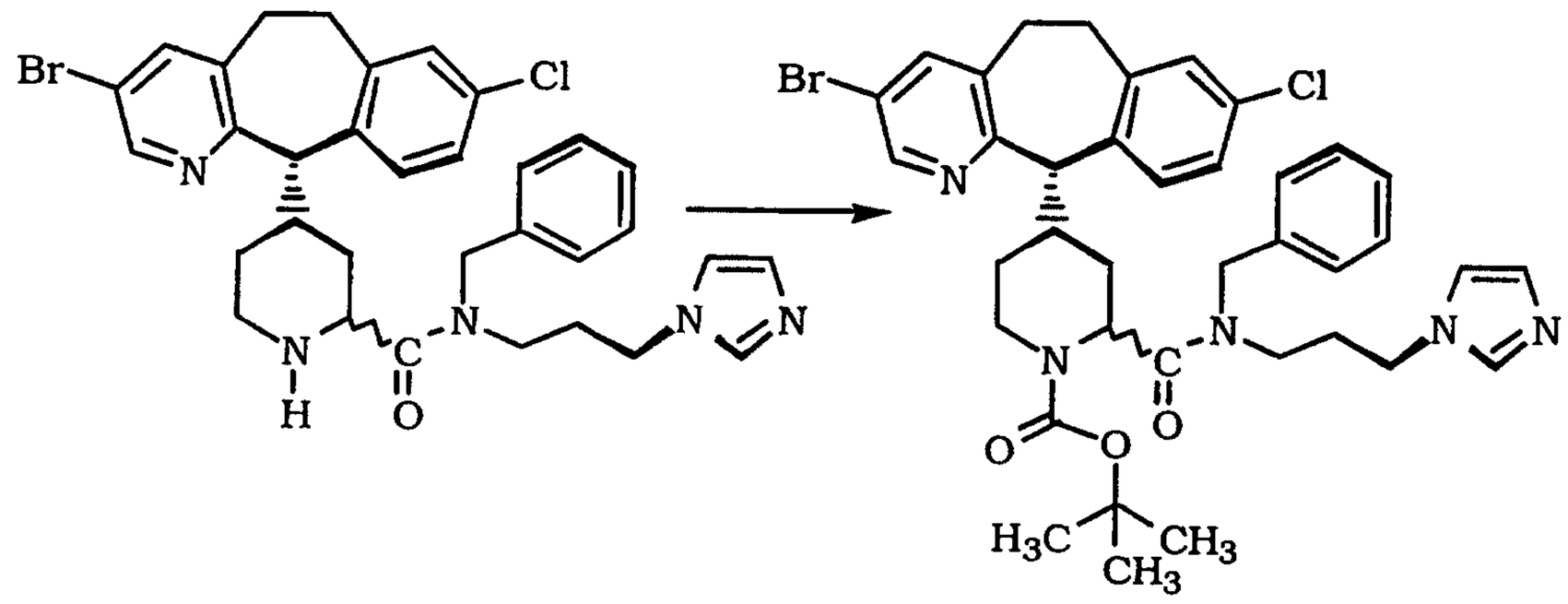
The product was obtained as a mixture of 2 Isomers (C and D). (Product 1) Mass Spec FABS (MH) 632.

Further elution yielded a white solid (25mg,20% yield). This product was a mixture of 2 Isomers (A and B) (Product 2) Mass Spec FABS (MH^+) 632.

Product 2 was separated into single isomers on a Chiralcell AD column eluting with 40% IPA-Hexanes yielding Isomer A as a white solid FABS (MH^+) 632. Further elution yielded Isomer B as a white solid, FABS (MH^+) 632.

Product 1 was derivatised and separated into constituent Isomers C and D as shown in Step B below.

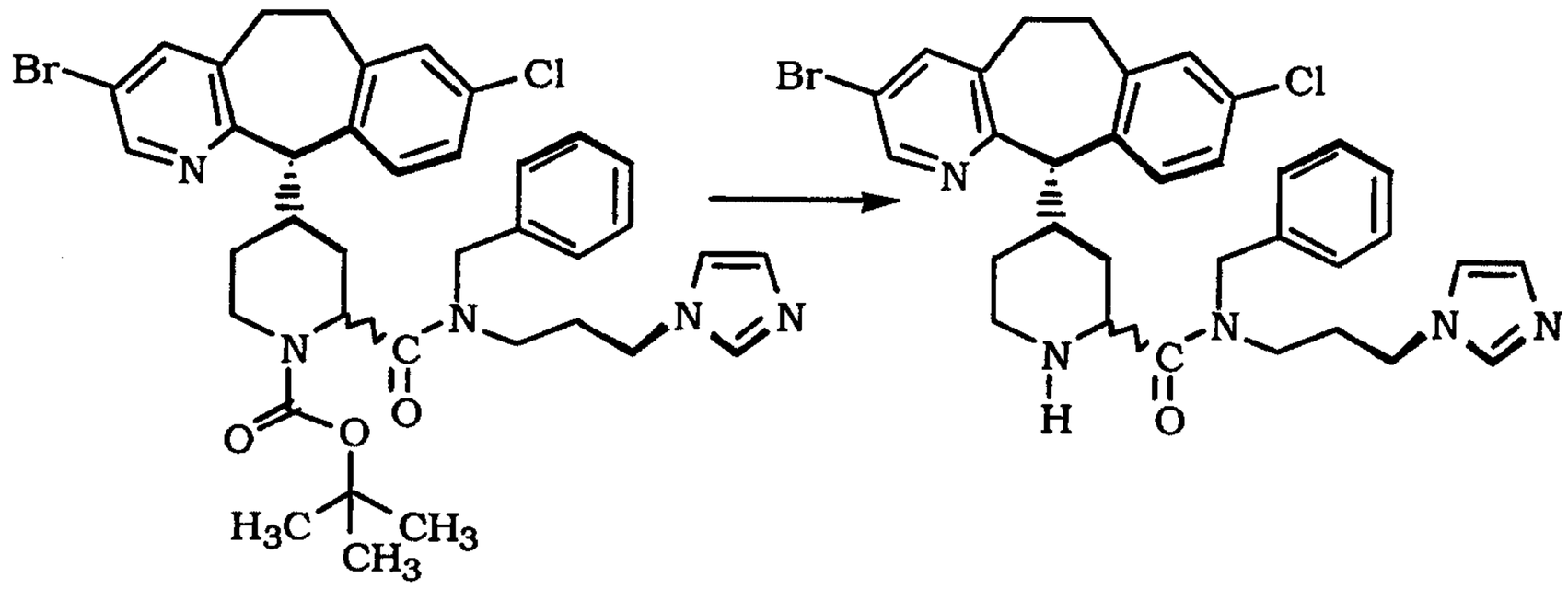
Step B



A solution of di-tert-butyldicarbonate (65mg,0.29mmol) in CH_2Cl_2 (2ml) was added to a solution of Product 1 (Step A, Isomers C and D) (150mg, 0.237mmol) in CH_2Cl_2 (10ml), at 0°C, then stirred at 20°C for 10 minutes. The reaction was cooled to 0°C, water (5ml), 10% NaOH (2ml) and CH_2Cl_2 (10ml) were added. The organic layer was separated, dried over $MgSO_4$, filtered and solvent evaporated yielding an oil, which was chromatographed on silica gel, eluting with 3% v/v MeOH: CH_2Cl_2 yielding the product as a white solid (150mg) as a mixture of 2 isomers, which were separated on Chiralcell AD column, eluting with 30% IPA-Hexanes/ 0.2% Diethylamine yielding Isomer C 60mg. Mass Spec (FABS, MH^+) Calculated ($C_{38}H_{44}N_5O_3BrCl$:734.2296) Measured: 734.2304. Further elution yielded Isomer D 70mg. Mass Spec (FABS, MH^+) CALC MH (734.2296) Measured: (734.2305).

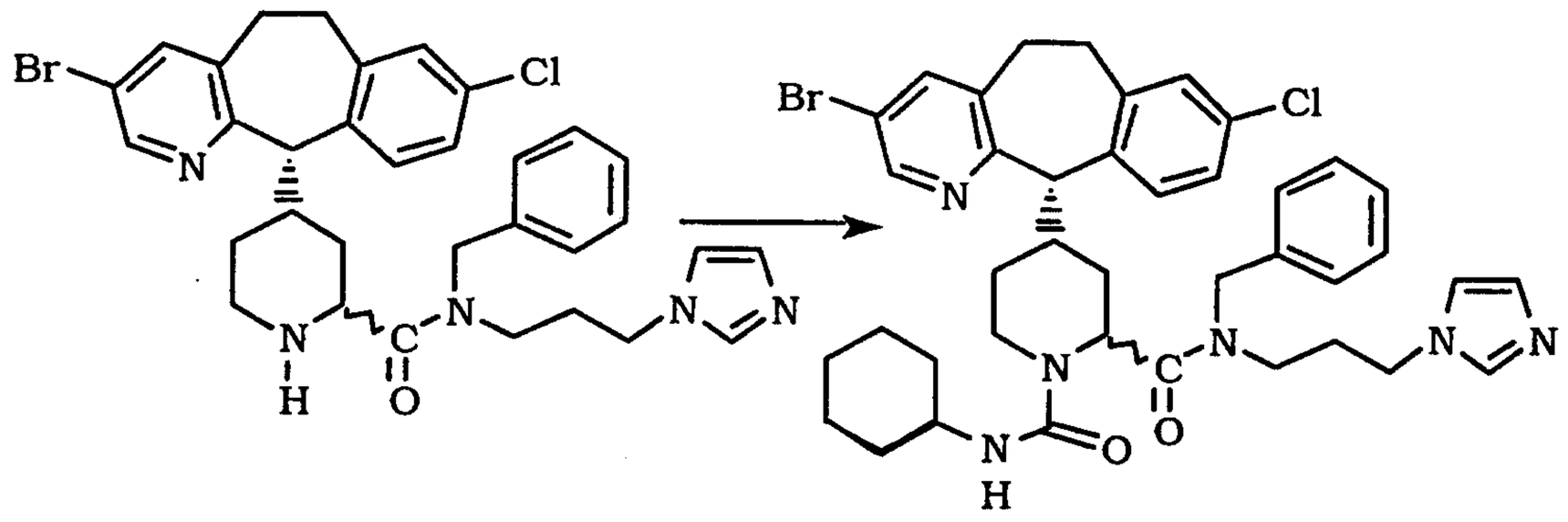
EXAMPLE 79

Step A



Following the procedure of Example 78 Step A, the BOC group of the Isomer C product of Step B was removed to produce the Isomer C title product as a white solid (Mass Spec, MH^+) FABS (632).

Step B



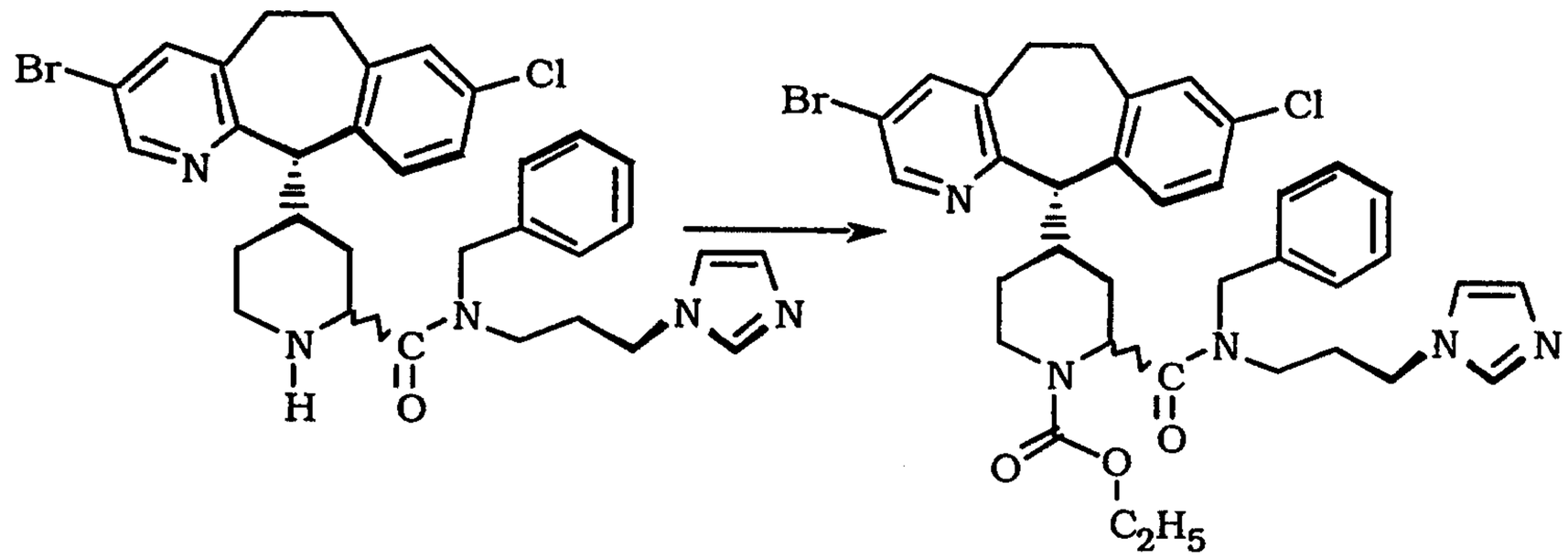
Cyclohexyl isocyanate (0.025ml,0.19mmol) was added to a solution of Isomer A (Example 78, Step A) (25mg, 0.039mmol), in CH_2Cl_2 (3ml) at 0°C, then stirred at 20°C for 30 minutes. Methylene chloride (20ml) and water (20ml) were added. The organic layer was separated, dried over $MgSO_4$, filtered and solvent was evaporated yielding a residue, which chromatographed on silica gel, eluting with 2% v/v MeOH: CH_2Cl_2, yielding the product (Isomer A) as a white solid (25mg). High resolution Mass Spec (ES) Calculated: $C_{40}H_{47}O_2N_6ClBr$ (757.2632)(Br=79) Measured: 757.2643.

Following the above procedure, but substituting an equivalent quantity of Isomer B (Example 78, Step A) for Isomer A, the title product (Isomer B) was obtained. Mass Spec (FABS, HRMS) Calculated 759.2612 (Br=81) Measured 759.2626

Following the above procedure, but substituting an equivalent quantity of Isomer C (Example 79, Step A) for Isomer A, the title product Isomer C was obtained. Mass Spec (ES, MH^+) 757 (Br =79)

Following the above procedure, except using the mixture of Isomers C and D (Product 1 from Example 78 Step A), yields the C and D isomer mixture of the title compound Mass Spec (ES,MH^+) 757

EXAMPLE 80

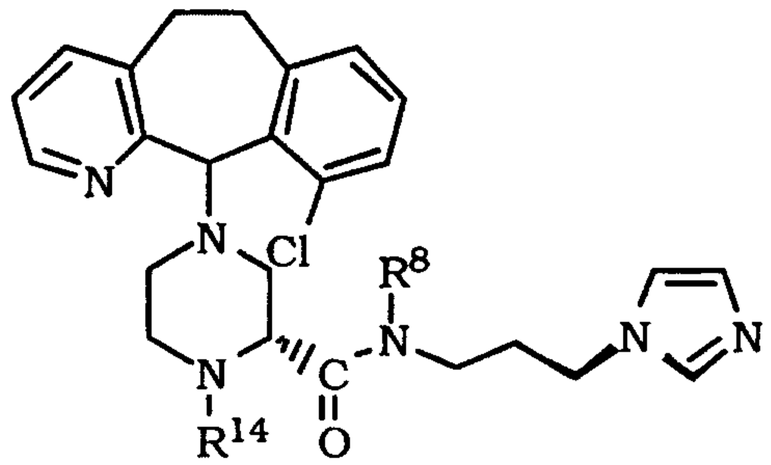


Ethyl chloroformate (0.1ml, 1.04mmol) was added to a solution of the Isomer A (Example 78, Step A) (20mg, 0.03mmol) in CH_2Cl_2 (2ml) at 20°C. Triethylamine (0.1ml, 0.7mmol) was added, and the solution was stirred for 30 minutes at 20°C. The solvent was evaporated, and the residue chromatographed on silica gel, eluting with 3% v/v MeOH: CH_2Cl_2 containing 2% NH_4OH, yielding the Isomer A product as a white solid (20mg). Mass Spec (ES, MH^+) 704.

Following the above procedure, but substituting an equivalent quantity of the Isomer B (Example 78, Step A) for Isomer A, the Isomer B product was obtained. Mass Spec (ES, MH^+) 704: HRMS (ES) Calculated (704.2003) (Br= 79) Measured (704.2012).

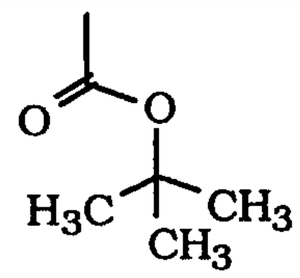
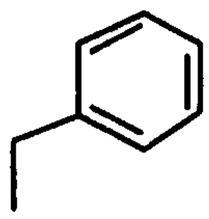
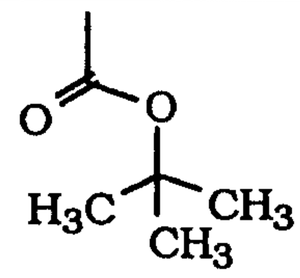
EXAMPLES 81-85

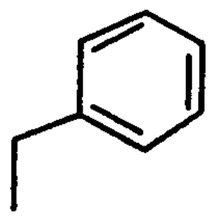
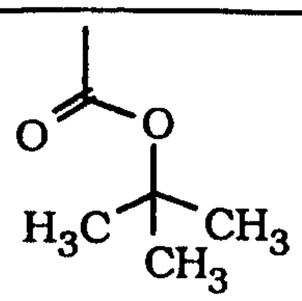
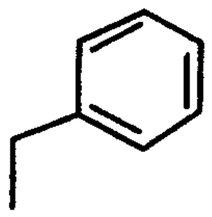
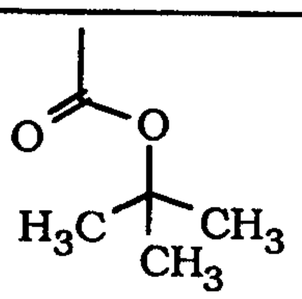
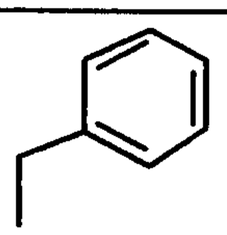
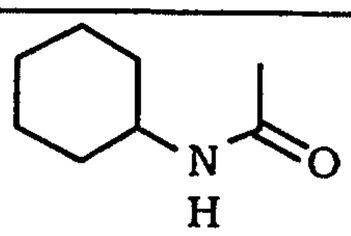
Follow the procedure of Examples 127 and 80, but use the title compounds from Preparative Examples 9.1 or 111.1 with the appropriate isocyanate or chloroformate to obtain compounds of the formula:



wherein R^8 and R^{14} are defined in Table 10 below are obtained.

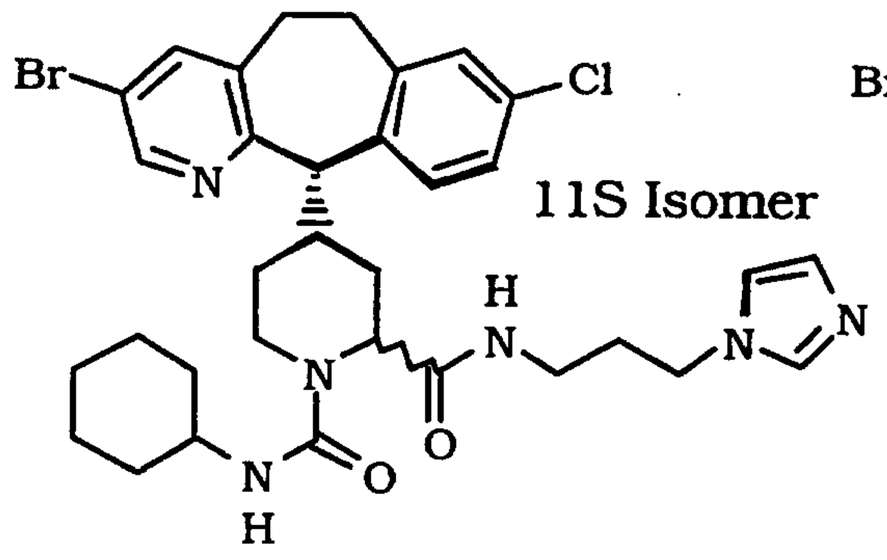
TABLE 10

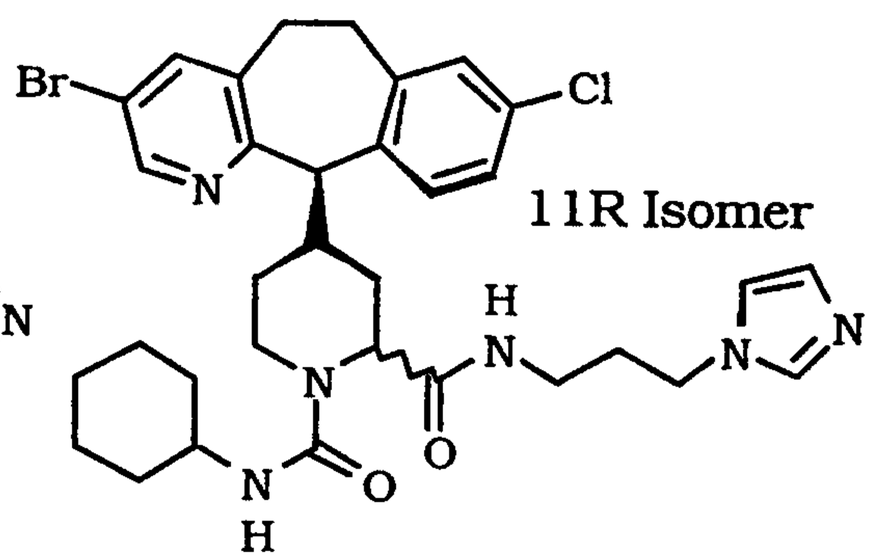
Ex.	R^8	R^{14}	Isomer	MS
81 (Product of Prep. Ex. 9.1 and di-t-butyldicarbonate)	H		A and B (R,S)	Fabs (MH) 565
82 (Product of Prep. Ex. 111.1 and di-t-butyldicarbonate)			A and B (R,S)	ES (MH) 655

83 (Product of Prep. Ex. 111.1 and di-t-butyldicarbonate)		 $[\alpha]_D^{20}$=+2.5°	A (R(+))	ES (MH) 655
84 (Product of Prep. Ex. 111.1 and di-t-butyldicarbonate)		 $[\alpha]_D^{20}$=-34.9°	B (S(-))	ES (MH) 655
85 (Product of Prep. Ex. 111.1 and cyclohexyl isocyanate)			A and B (R,S)	ES (MH) 680

The compounds of Examples 83 and 84 were separated on Chiralcell AD column.

EXAMPLE 86



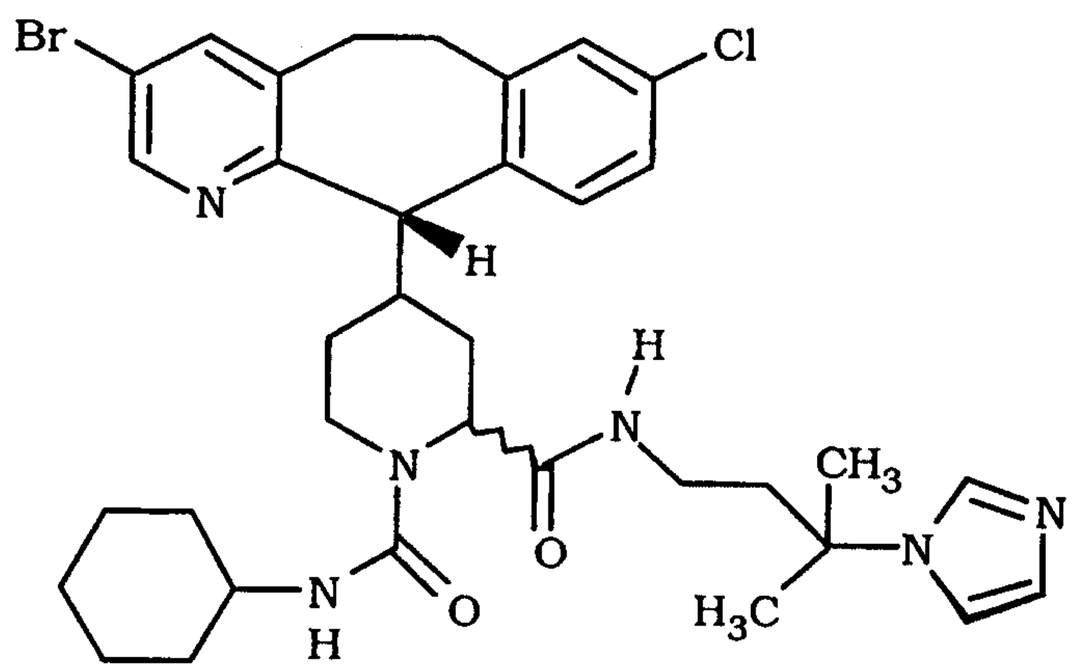


Following the procedures of Examples 77-79, but substituting an equivalent quantity of 1-(3-aminopropyl)imidazole for the N-benzyl substituted imidazole from Preparative Example 74 in Example 77, the title compounds are obtained.

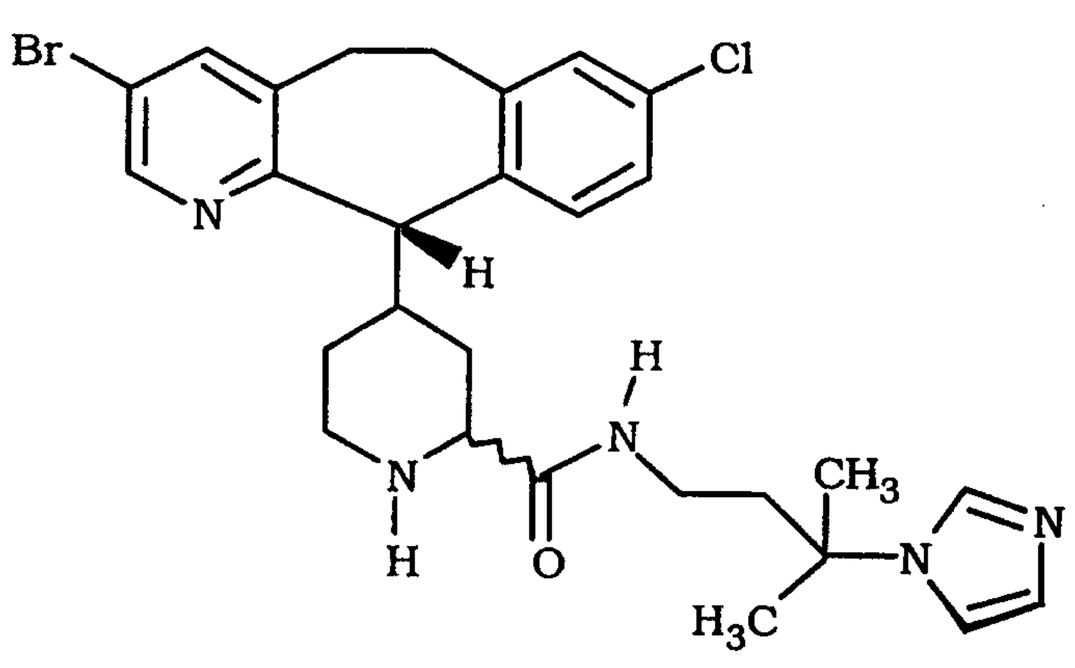
11S-Isomer: Mass Spec: Fabs (MH^+) 667(Br=79) HRMS Calc (MH) $C_{33}H_{41}N_6O_2Cl(81)Br$ 669.2142 Measured 669.2151

11R-Isomer: FABS (MH^+) 667.

EXAMPLE 86A



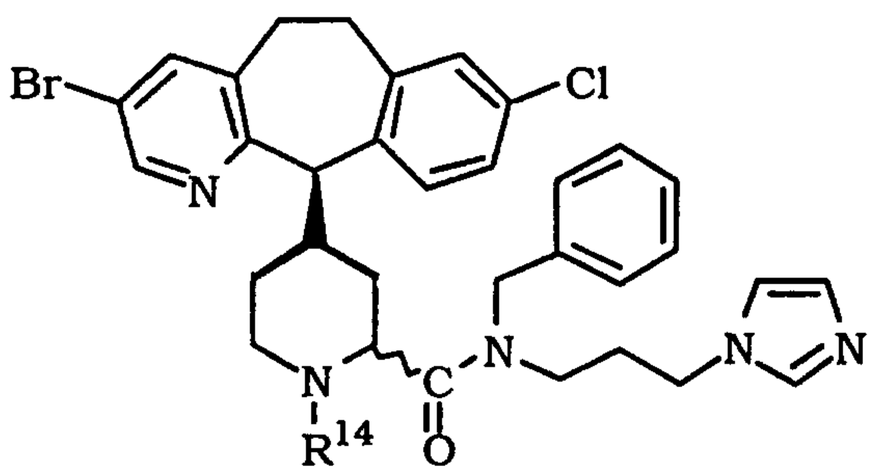
Use the imidazole from Preparative Example 1 Step D and follow the procedure of Example 77 and Example 79 Step A to obtain the compound



which is then reacted with cyclohexyl isocyanate according to the procedure set forth in Example 79 Step B. Mass Spec: Fabs (MH) 695 (Br=79) 669.2142.

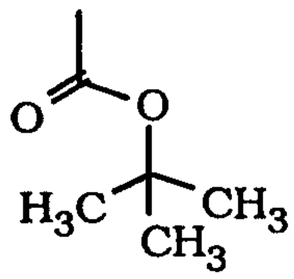
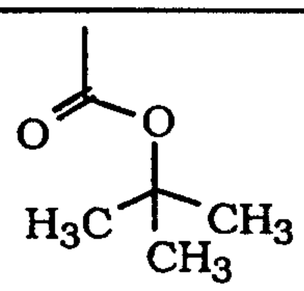
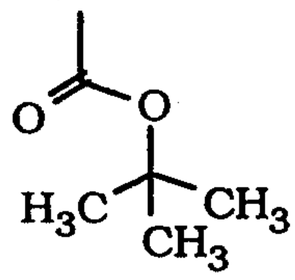
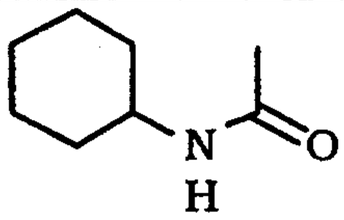
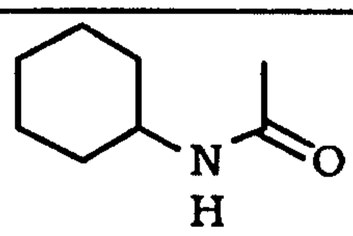
EXAMPLES 87-97

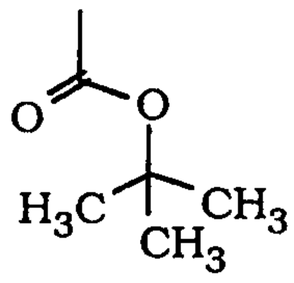
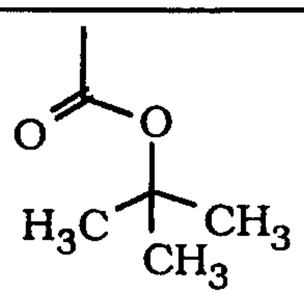
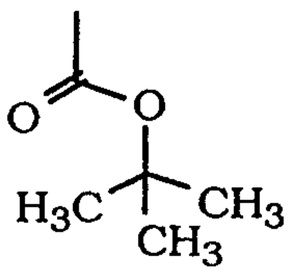
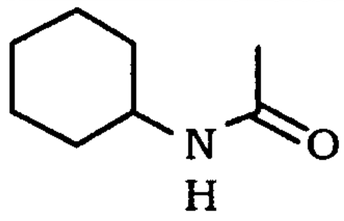
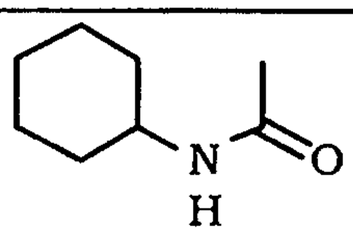
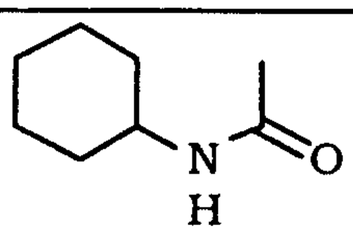
Following the procedures set forth in Examples 77-80, but using the 11(R)-isomer, compounds of the formula:



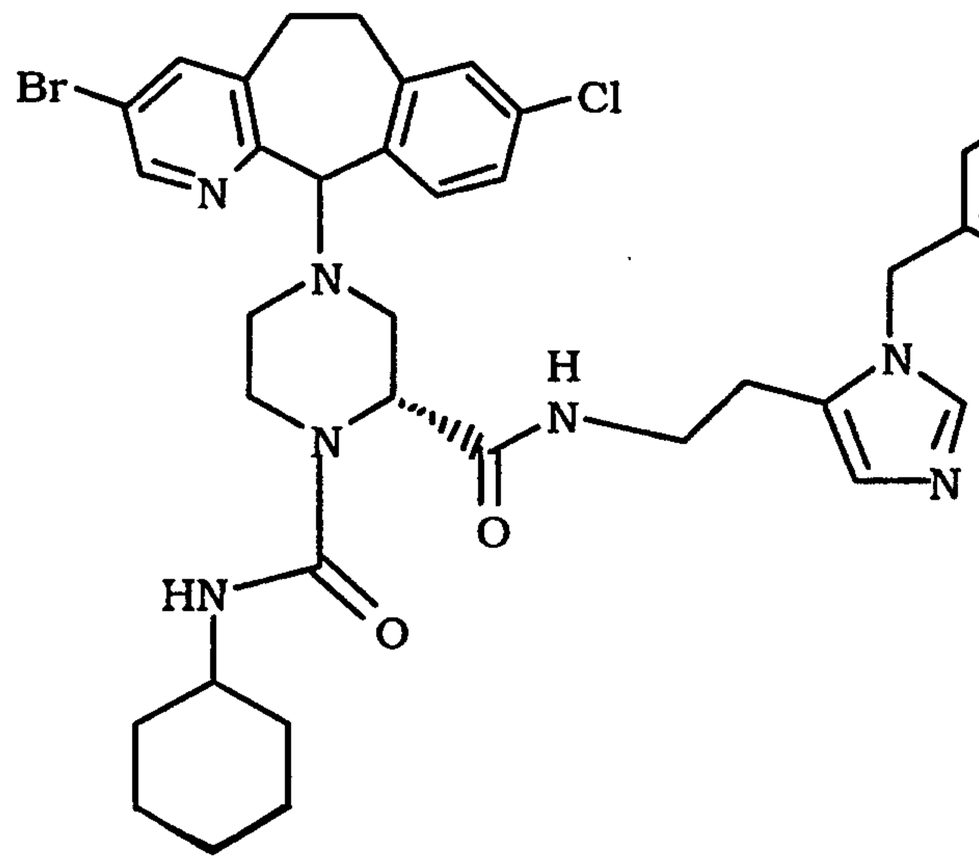
are obtained. R^{14} is defined in Table 11.

TABLE 11

Ex.	R^{14}	Isomer	Mass Spec Observed (Estimated)
87		A, B, C, D	732.2343 (732.2316)
88		A	732.2332 (732.2316)
89		B	734.2305 (743.2296)
90		A	757.2641 (757.2632)
91		B	759.2618 (759.2612)

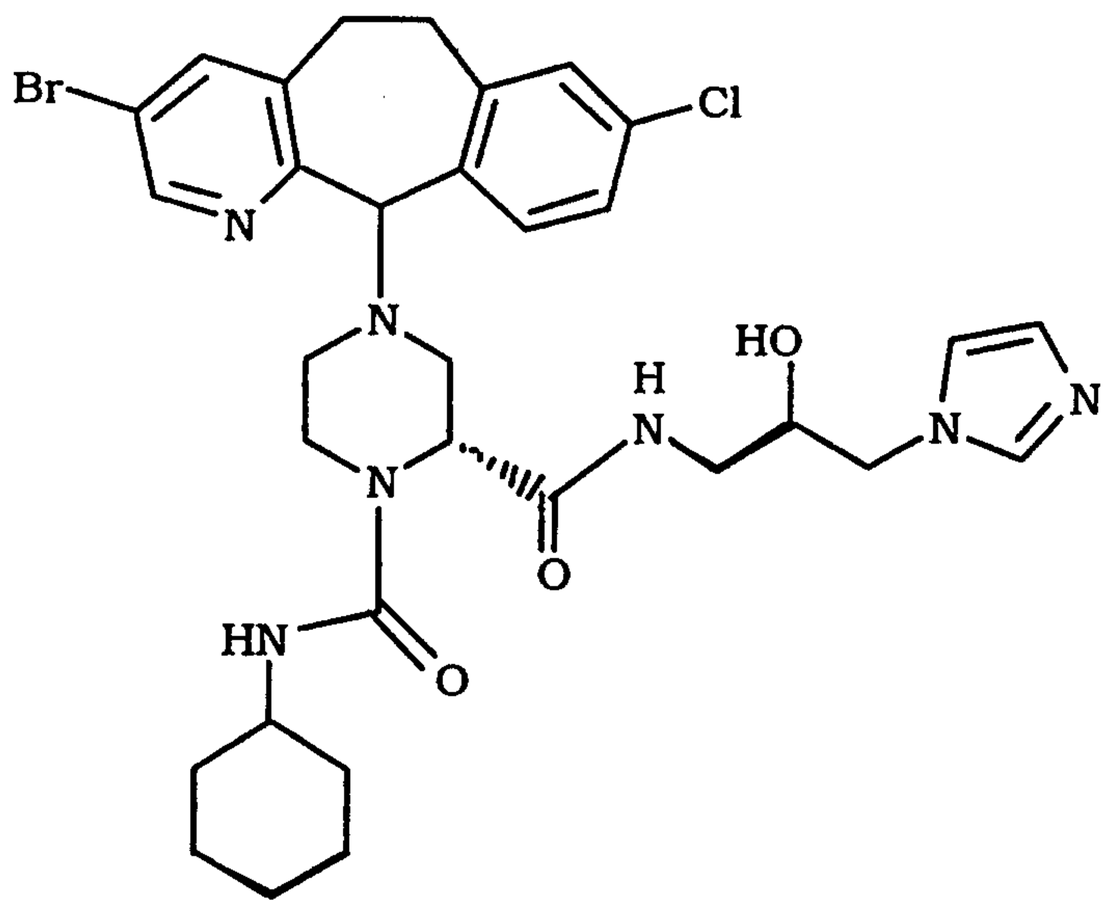
92		C	734.2296 (732.2296)
93		D	734.2297 (734.2296)
94		C, D	734.2318 (734.2296)
95		C	759.2611 (759.2612)
96		D	759.2618 (759.2612)
97		C, D	759.2626 (759.2612)

EXAMPLE 98



The product of Preparative Example 45 (0.6 gm) was dissolved in 6 ml of dichloromethane and 6 ml of trifluoroacetic acid was added and the reaction mixture stirred for 2 hours. After 2 hours the reaction mixture was evaporated to an oil. The oil was dissolved in N,N,-dimethylformamide and triethyl amine (0.445 mL, 3 eq.) was added and 3-bromo-8,11-dichloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine (0.39 gm, 113 mmol.) was added and the reaction mixture stirred for 24 hours. The reaction mixture was added to brine and the product extracted with ethylacetate 3 times to obtain a crude oil after the solvent was evaporated under reduced pressure, which was purified by chromatography on a silica gel column using 2% up to 4% methanol/dichloromethane as the eluent. The product containing fractions were pooled to obtain 0.34 gm of pure title compound. The compound was separated into its pure enantiomeric forms by HPLC on a Chiral Technologies AD column using 20% isopropanol/hexanes. Isomer 1: mp= 148.3-157.5°C; Isomer 2: mp= 148.3-157.5°C

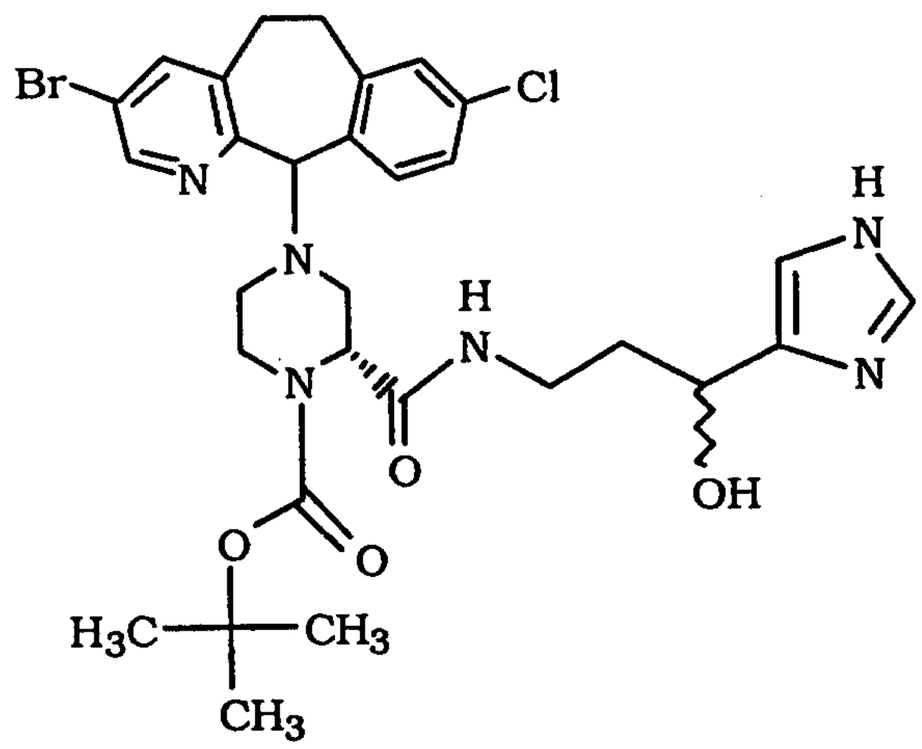
EXAMPLE 99



The title compound from Preparative Example 48 (0.487 gm) was dissolved in dichloromethane (3 ml) and trifluoroacetic acid (3

ml) and the reaction mixture stirred for 2 hours. The reaction mixture was evaporated to dryness and dissolved in 10 mL of N,N-dimethyl-formamide. Triethylamine (1.42 mL, 10 eq.) was added and 3-bromo-8,11-dichloro-6,11-dihydro-5H-benzo-[5,6]cyclohepta[1,2-b]pyridine (Compound No. 42.0) (0.45 gm, 1.2 eq.) was added and the reaction mixture stirred for 24 hours. The reaction mixture was added to brine and the product extracted with ethylacetate 3 times to obtain a crude oil after the solvent was evaporated under reduced pressure, which was purified by chromatography on a silica gel column using 2% up to 4% methanol/dichloromethane as the eluent. The product containing fractions were pooled to obtain 0.26 gm of pure title compound as a mixture of isomers. Isomers were separated by HPLC on a Chiral Technologies AD column using 20-30% isopropanol/hexanes. Isomer 1: mp= 192.7-194.3 °C; Isomer 2: mp= 189.2-190.7°C

EXAMPLE 100



The title compound from Preparative Example 52 (0.3 gm, 0.5 mmol) was stirred in a mixture of 10 ml of dichloromethane and 15 μL of water and Dess-Martin Periodinane (0.32 gm, 1.5 eq.) was added and the reaction mixture stirred at ambient temperature. After 24 hours the reaction mixture was washed with 20% $Na_2S_2O_3$ solution followed by sodium bicarbonate solution and evaporated to dryness under vacuum. This compound was dissolved in

DEMANDES OU BREVETS VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

CECI EST LE TOME 1 DE 2

NOTE: Pour les tomes additionels, veuillez contacter le Bureau canadien des brevets

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JUMBO APPLICATIONS/PATENTS

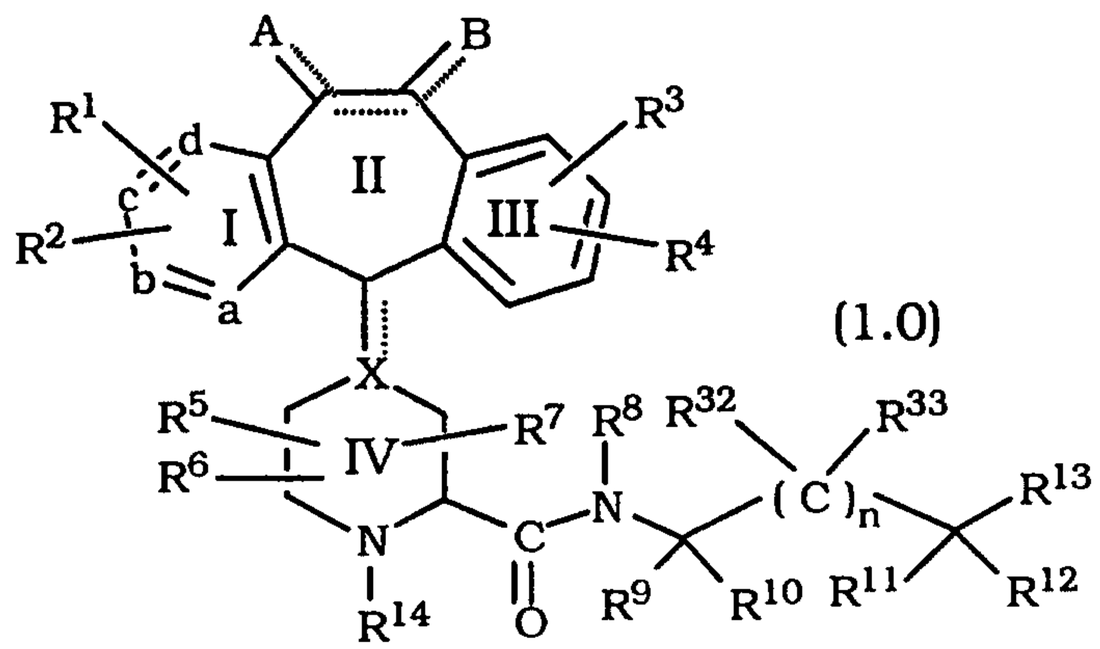
THIS SECTION OF THE APPLICATION/PATENT CONTAINS MORE THAN ONE VOLUME

THIS IS VOLUME 1 OF 2

NOTE: For additional volumes please contact the Canadian Patent Office

WHAT IS CLAIMED IS:

1. A compound of the formula:



(1.0)

or a pharmaceutically acceptable salt or solvate thereof, wherein:

one of a, b, c and d represents N or N^+O^-, and the remaining a, b, c and d groups represent CR^1 or CR^2; or

each of a, b, c, and d are independently selected from CR^1 or CR^2;

X represents N or CH when the optional bond (represented by the dotted line) is absent, and represents C when the optional bond is present;

the dotted line between carbon atoms 5 and 6 represents an optional bond, such that when a double bond is present, A and B independently represent $-R^{15}$, halo, $-OR^{16}$, $-OCO_2R^{16}$ or $-OC(O)R^{15}$, and when no double bond is present between carbon atoms 5 and 6, A and B each independently represent H_2, $-(OR^{16})_2$, H and halo, dihalo, alkyl and H, $(alkyl)_2$, -H and $-OC(O)R^{15}$, H and $-OR^{15}$, =O, aryl and H, $=NOR^{15}$ or $-O-(CH_2)_p-O-$ wherein p is 2, 3 or 4;

each R^1 and each R^2 is independently selected from H, halo, $-CF_3$, $-OR^{15}$, $-COR^{15}$, $-SR^{15}$, $-S(O)_tR^{16}$ (wherein t is 0, 1 or 2, $-N(R^{15})_2$, $-NO_2$, $-OC(O)R^{15}$, $-CO_2R^{15}$, $-OCO_2R^{16}$, -CN, $-NR^{15}COOR^{16}$, $-SR^{16}C(O)OR^{16}$, $-SR^{16}N(R^{17})_2$ (provided that R^{16} in $-SR^{16}N(R^{17})_2$ is not $-CH_2-$) wherein each R^{17} is independently

selected from H or -C(O)OR^{16}, benzotriazol-1-yloxy, tetrazol-5-ylthio, or substituted tetrazol-5-ylthio, alkynyl, alkenyl or alkyl, said alkyl or alkenyl group optionally being substituted with halo, -OR^{15} or -CO_2R^{15};

R^3 and R^4 are the same or different and each independently represents H, any of the substituents of R^1 and R^2, or R^3 and R^4 taken together represent a saturated or unsaturated C_5-C_7 fused ring to the benzene ring (Ring III);

R^5, R^6, and R^7 each independently represents H, -CF_3, -COR^{15}, alkyl or aryl, said alkyl or aryl optionally being substituted with -OR^{15}, -SR^{15}, -S(O)$_t$R^{16}, -NR^{15}COOR^{16}, -N(R^{15})$_2$, -NO_2, -COR^{15}, -OCOR^{15}, -OCO_2R^{16}, -CO_2R^{15}, OPO_3R^{15}, or R^5 is combined with R^6 to represent =O or =S;

R^8 is selected from: H, C_3 to C_4 alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, substituted alkyl, substituted aryl, substituted arylalkyl, substituted heteroaryl, substituted heteroarylalkyl, substituted cycloalkyl, substituted cycloalkylalkyl;

the substutuents for the R^8 substituted groups being selected from: alkyl, aryl, arylalkyl, cycloalkyl, -N(R^{18})$_2$, -OR^{18}, cycloalkyalkyl, halo, CN, -C(O)N(R^{18})$_2$, -SO_2N(R^{18})$_2$ or -CO_2R^{18}; provided that the -OR^{18} and -N(R^{18})$_2$ substituents are not bound to the carbon that is bound to the N of the -C(O)NR^8- moiety;

each R^{18} is independently selected from: H, alkyl, aryl, arylalkyl, heteroaryl or cycloalkyl;

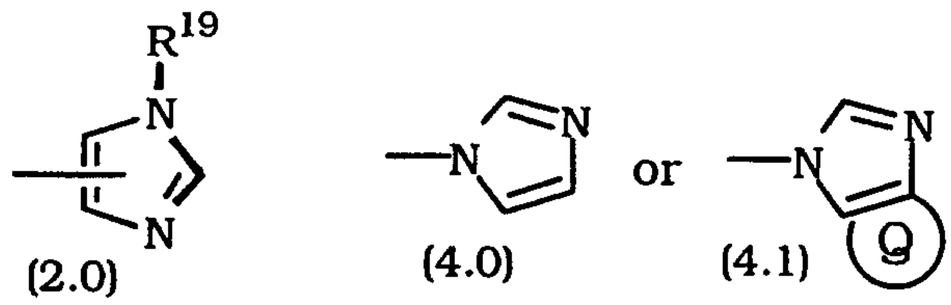
R^9 and R^{10} are independently selected from: H, alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl or -CON(R^{18})$_2$ (wherein R^{18} is as defined above); and the substitutable R^9 and R^{10} groups are optionally substituted with one or more substituents selected from: alkyl, cycloalkyl, arylalkyl, or heterarylalkyl; or

R^9 and R^{10} together with the carbon atom to which they are bound, form a C_3 to C_6 cycloalkyl ring;

R^{11} and R^{12} are independently selected from: H, alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl, $-CON(R^{18})_2$ $-OR^{18}$ or $-N(R^{18})_2$; wherein R^{18} is as defined above; provided that the $-OR^{18}$ and $-N(R^{18})_2$ groups are not bound to a carbon atom that is adjacent to a nitrogen atom; and wherein said substitutable R^{11} and R^{12} groups are optionally substituted with one or more substituents selected from: alkyl, cycloalkyl, arylalkyl, or heterarylalkyl; or

R^{11} and R^{12} together with the carbon atom to which they are bound, form a C_3 to C_6 cycloalkyl ring;

R^{13} is an imidazolyl ring selected from:

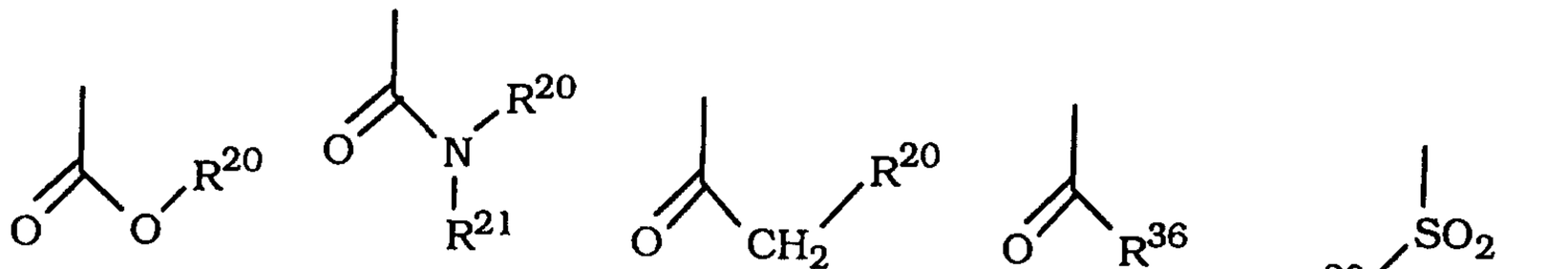


(2.0) (4.0) or (4.1)

wherein R^{19} is selected from: (1) H, (2) alkyl, (3) alkyl, (4) aryl, (5) arylalkyl, (6) substituted arylalkyl wherein the substituents are selected from halo or CN, (7) $-C(aryl)_3$ or (8) cycloalkyl;

said imidazolyl ring 2.0 optionally being substituted with one or two substituents, and said imidazole ring 4.0 optionally being substituted with 1-3 substituents, and said imidazole ring 4.1 being optionally substituted with one substituent wherein said optional substituents for rings 2.0, 4.0 and 4.1 are independently selected from : $-NHC(O)R^{18}$, $-C(R^{34})_2OR^{35}$, $-OR^{18}$, $-SR^{18}$, F, Cl, Br, alkyl, aryl, arylalkyl, cycloalkyl, or $-N(R^{18})_2$ (wherein each R^{18} is independently selected); wherein R^{18} is as defined above; wherein each R^{34} is independently selected from H or alkyl; wherein R^{35} is selected from H, $-C(O)OR^{20}$, or $-C(O)NHR^{20}$, and R^{20} is as defined below; Q represents an aryl ring, a cycloalkyl ring or a heteroaryl ring, said Q is optionally substituted with 1 to 4 substituents inedependently selected from halo, alkyl, aryl, $-OR^{18}$, $-N(R^{18})_2$ (wherein each R^{18} is independently selected), $-OC(O)R^{18}$, or $-C(O)N(R^{18})_2$ (wherein each R^{18} is independently selected), and wherein R^{18} is as defined above;

R^{14} is selected from:



(5.0), (6.0), (7.0), (7.1) or (8.0)

R^{15} is selected from: H, alkyl, aryl or arylalkyl;

R^{16} is selected from: alkyl or aryl;

R^{20} is selected from: H, alkyl, alkoxy, aryl, arylalkyl, cycloalkyl, heteroaryl, heteroarylalkyl or heterocycloalkyl, provided that R^{20} is not H when R^{14} is group 5.0 or 8.0;

when R^{20} is other than H, then said R^{20} group is optionally substituted with one or more substituents selected from: halo, alkyl, aryl, $-OC(O)R^{18}$, $-OR^{18}$ or $-N(R^{18})_2$, wherein each R^{18} group is the same or different, and wherein R^{18} is as defined above, provided that said optional substituent is not bound to a carbon atom that is adjacent to an oxygen or nitrogen atom;

R^{21} is selected from: H, alkyl, aryl, arylalkyl, cycloalkyl, heteroaryl, heteroarylalkyl or heterocycloalkyl;

when R^{21} is other than H, then said R^{21} group is optionally substituted with one or more substituents selected from: halo, alkyl, aryl, $-OR^{18}$ or $-N(R^{18})_2$, wherein each R^{18} group is the same or different, and wherein R^{18} is as defined above, provided that said optional substituent is not bound to a carbon atom that is adjacent to an oxygen or nitrogen atom;

n is 0-5;

each R^{32} and R^{33} for each n are independently selected from: H, alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl, $-CON(R^{18})_2$ $-OR^{18}$ or $=-N(R^{18})_2$; wherein R^{18} is as defined above; and wherein said substitutable R^{32} and R^{33} groups are optionally substituted with one or more substituents selected from: alkyl, cycloalkyl, arylalkyl, or heterarylalkyl; or

R^{32} and R^{33} together with the carbon atom to which they are bound, form a C_3 to C_6 cycloalkyl ring; and

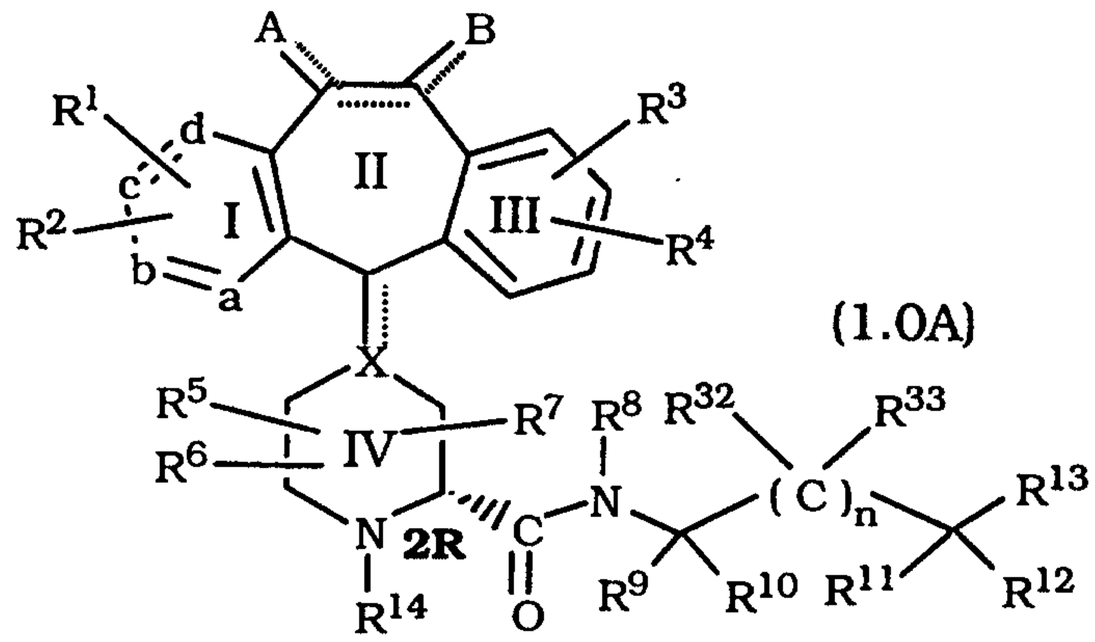
R^{36} is selected from branched alkyl, unbranched alkyl, cycloalkyl, heterocycloalkyl, or aryl; and

provided that:

(1) when R^{14} is selected from: group 6.0, 7.0, 7.1 or 8.0, and X is N, then R^8 is selected from: C_3 to C_{10} alkyl, substituted C_3 to C_{10} alkyl, arylalkyl, substituted arylalkyl, heteroarylalkyl, substituted heteroarylalkyl, cycloalkylalkyl, or substituted cycloalkylalkyl; and

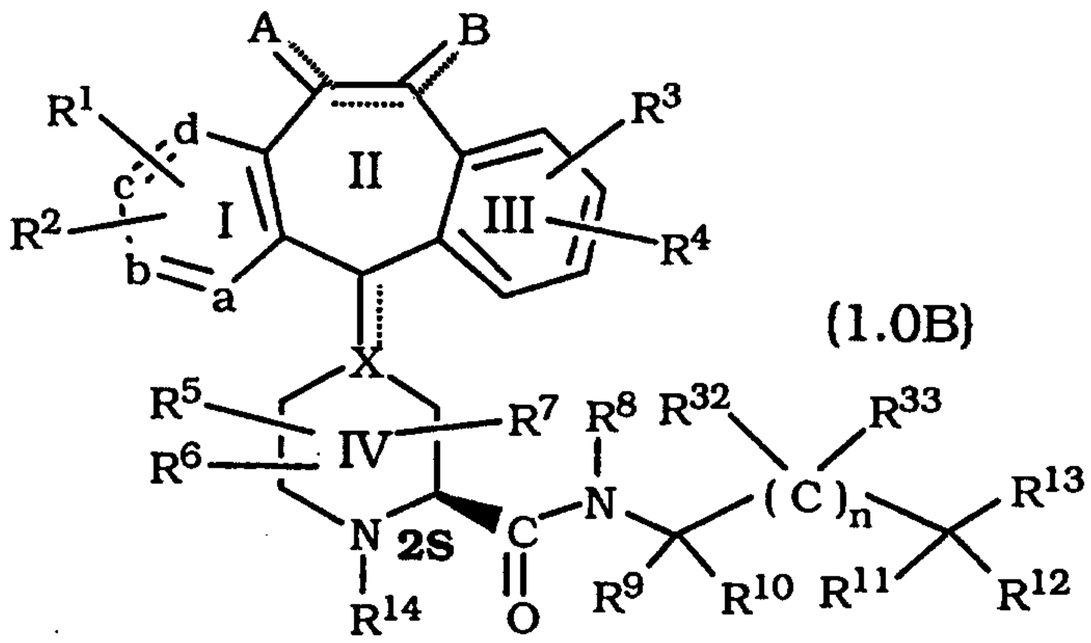
(2) when R^{14} is selected from: group 6.0, 7.0, 7.1 or 8.0, and X is N, and R^8 is H, then the alkyl chain between R^{13} and the amide moiety is substituted.

2. The compound of Claim 1 having the structure:



(1.0A)

or



(1.0B)

3. The compound of Claim 1 wherein: R^1 to R^4 is independently selected from H, Br or Cl; R^5 to R^7 is H; a is N and the

remaining b, c and d substituents are carbon, or a, b, c, and d are carbon; A and B are H_2; n is 0 or 1; and R^{13} is group 2.0 or 4.0.

4. The compound of claim 1 wherein:

(a) R^8 is selected from: arylalkyl, substituted arylalkyl, cycloalkylalkyl, substituted cycloalkylalkyl, heteroarylalkyl or substituted heteroarylalkyl

(b) R^9 and R^{10} are independently selected from: H, alkyl, $-C(O)N(R^{18})_2$, or arylalkyl;

(c) R^{11} and R^{12} are independently selected from: H, alkyl, substituted aryl, $-OR^{18}$, or R^{11} and R^{12} taken together with the carbon atom to which they are bound form a cycloalkyl ring;

(d) R^{32} and R^{33} are independently selected from: H, $-OR^{18}$, arylalkyl or aryl;

(e) R^{19} is selected from: $-C(O)N(R^{18})_2$, alkyl, arylalkyl, or $-C(aryl)_3$; and

(f) said optional R^{13} substitutents are selected from: $-N(R^{18})_2$, $-NHC(O)R^{18}$, $-C(R^{34})_2OR^{35}$, alkyl, or cycloalkyl substituted with -OH provided that the -OH substitutent is not bound to a carbon that is adjacent to an oxygen atom.

5. The compound of claim 1 wherein R^{14} is:

(a) 5.0 and R^{20} is selected from: alkyl, arylalkyl, heterocycloalkyl, aryl, aryl substituted with halo, cycloalkyl, or cycloalkyl substituted with alkyl;

(b) 6.0 wherein R^{20} and R^{21} are independently selected from: H, cycloalkyl, alkyl, aryl, or arylalkyl;

(c) 7.0 wherein R^{20} is selected from: heteroaryl, cycloalkyl, heterocycloalkyl, alkoxy, heterocycloalkyl substituted with $-C(O)N(R^{18})_2$;

(d) 7.1 wherein R^{36} is selected from: cycloalkyl or heterocycloalkyl; or

(e) 8.0 wherein R^{20} is selected from: alkyl or cycloalkyl.

6. The compound of Claim 1 wherein:

(a) R^1 to R^4 is independently selected from H, Br or Cl;

(b) R^5 to R^7 is H;

(c) a is N and the remaining b, c and d substituents are carbon;

(d) A and B are H_2;

(e) n is 0 or 1;

(f) R^{13} is group 2.0 or 4.0, and said optional R^{13} substitutents are selected from: $-N(R^{18})_2$, $-NHC(O)R^{18}$, $-C(R^{34})_2OR^{35}$, or alkyl;

(g) R^8 is selected from: arylalkyl, substituted arylalkyl, cycloalkylalkyl, substituted cycloalkylalkyl, heteroarylalkyl, or substituted heteroarylalkyl;

(a) R^9 and R^{10} are independently selected from: H, alkyl, $-C(O)N(R^{18})_2$, or arylalkyl;

(h) R^{11} and R^{12} are independently selected from: H, alkyl, substituted aryl, $-OR^{18}$, or R^{11} and R^{12} taken together with the carbon atom to which they are bound form a cycloalkyl ring;

(i) R^{11} and R^{12} are independently selected from: H, alkyl, substituted aryl, $-OR^{18}$, or R^{11} and R^{12} taken together with the carbon atom to which they are bound form a cycloalkyl ring;

(j) X is CH or N;

(k) R^{19} is selected from: $-C(O)N(R^{18})_2$, alkyl, arylalkyl, or $-C(aryl)_3$;

(l) R^{20} for 5.0 is selected from: (1) alkyl, (2) arylalkyl, (3) heterocycloalkyl, (4) aryl, (5) aryl substituted with halo, (6) cycloalkyl, (7) cycloalkyl substituted with alkyl, or (8) cycloalkyl substituted with $-OC(O)R^{18}$ or -OH provided said -OH substitutent is not bound to a carbon atom that is adjacent to an oxygen atom;

(m) R^{20} and R^{21} for 6.0 are independently selected from: H, cycloalkyl, alkyl, aryl, or arylalkyl;

(n) R^{20} for 7.0 is selected from: heteroaryl, cycloalkyl, alkoxy, heterocycloalkyl substituted with $-C(O)N(R^{18})_2$;

(o) R^{36} for 7.1 is selected from heterocycloalkyl or cycloalkyl;

(p) R^{20} for 8.0 is selected from: alkyl or cycloalkyl; and

(q) R^{32} and R^{33} are independently selected from: H, $-OR^{18}$, arylalkyl or aryl.

7. The compound of Claim 6 wherein:

(a) R^8 is selected from arylalkyl, cycloalkylalkyl, or heteroarylalkyl;

(b) R^9 and R^{10} are independently selected from: H or benzyl;

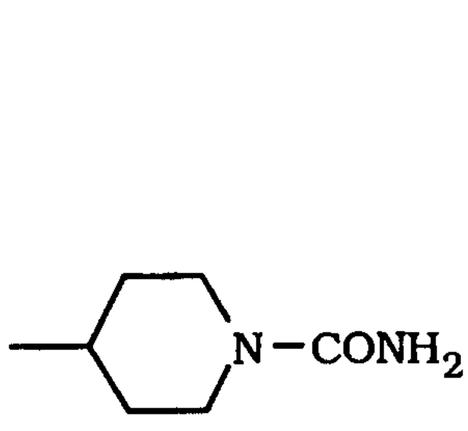
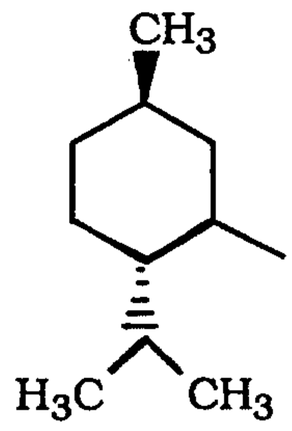
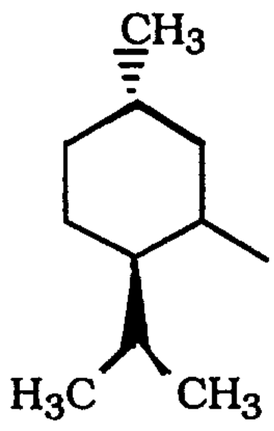
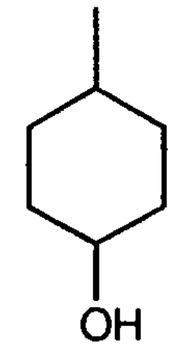
(c) R^{11} and R^{12} are independently selected from: H, $-CH_3$, $-CH_2CH(CH_3)_2$, $-(CH_2)_3CH_3$, benzyl, ethyl, p-chlorophenyl, -OH, or R^{11} and R^{12} taken together with the carbon atom to which they are bound form a cyclopropyl ring;

(d) R^{32} and R^{33} are independently selected from: H, phenyl, -OH or benzyl;

(e) R^{19} is selected from: -C(O)NH-cyclohexyl, $-C(phenyl)_3$, H, methyl or ethyl;

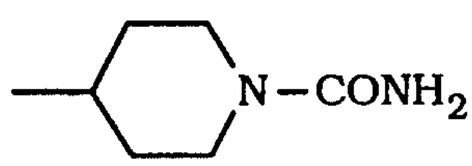
(f) said optional R^{13} substitutents are selected from: $-CH_3$, $-CH_2OH$, $-CH_2OC(O)O$-cyclohexyl, $-CH_2OC(O)O$-cyclopentyl, ethyl, isopropyl, NH_2, or $-NHC(O)CF_3$;

(g) R^{20} for group 5.0 is selected from: t-butyl, ethyl, benzyl, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$, $-(CH_2)_2CH_3$, n-butyl, n-hexyl, n-octyl, p-chlorophenyl, cyclohexyl, cyclopentyl,

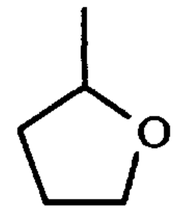
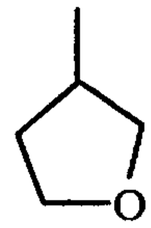

, 
, 
or 
;

(h) R^{20} and R^{21} for 6.0 are independently selected from: cyclohexyl, t-butyl, H, -$CH(CH_3)_2$, ethyl, -$(CH_2)_2CH_3$, phenyl, benzyl, -$(CH_2)_2$phenyl, or -CH_3;

(i) R^{20} for 7.0 is selected from: 4-pyridylNO, -OCH_3, -$CH(CH_3)_2$, -t-butyl, H, propyl, cyclohexyl or

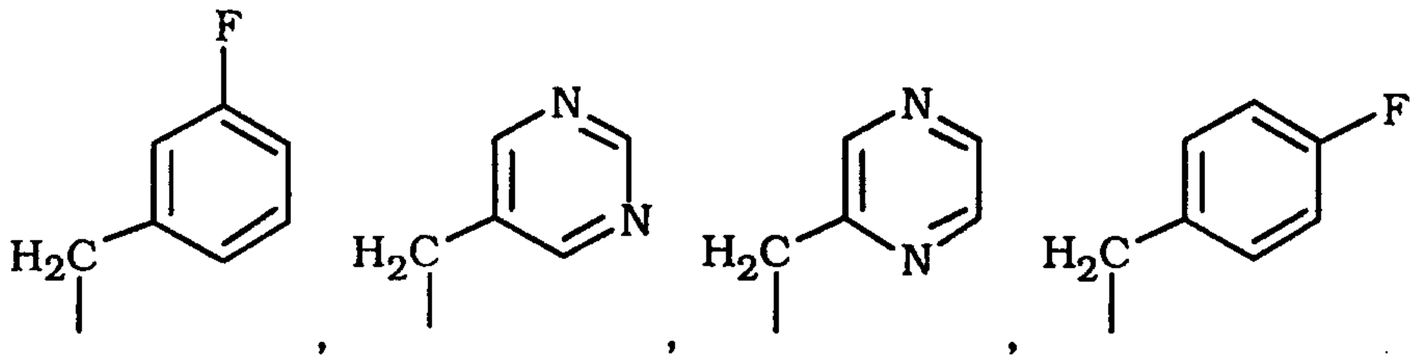
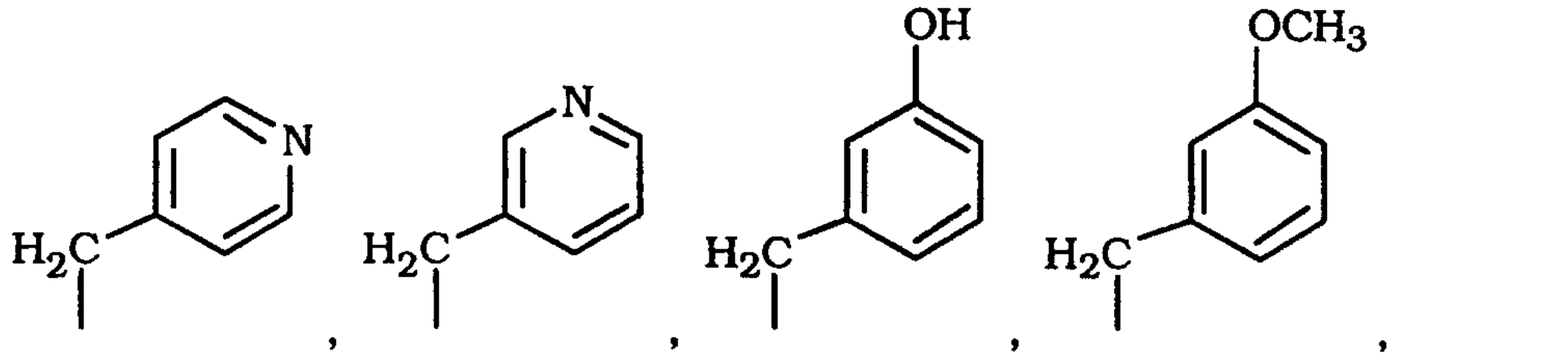
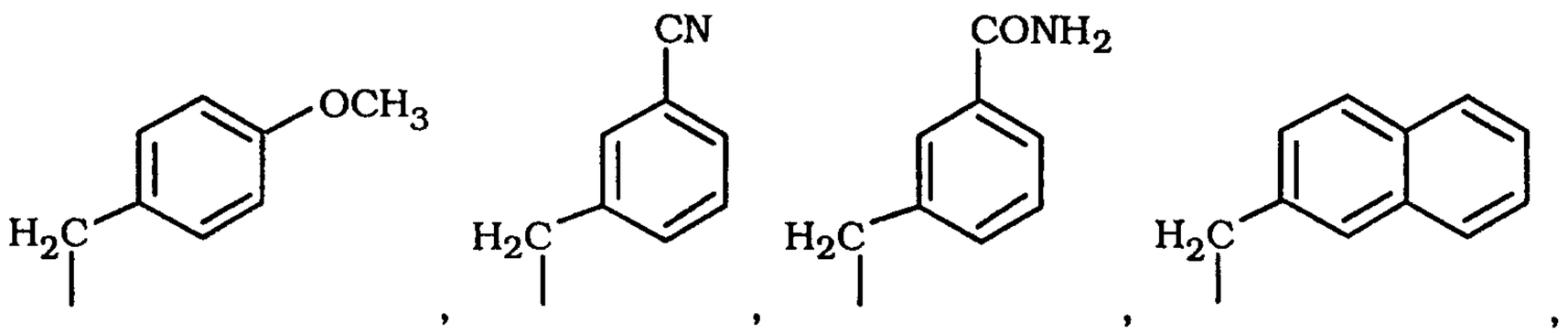
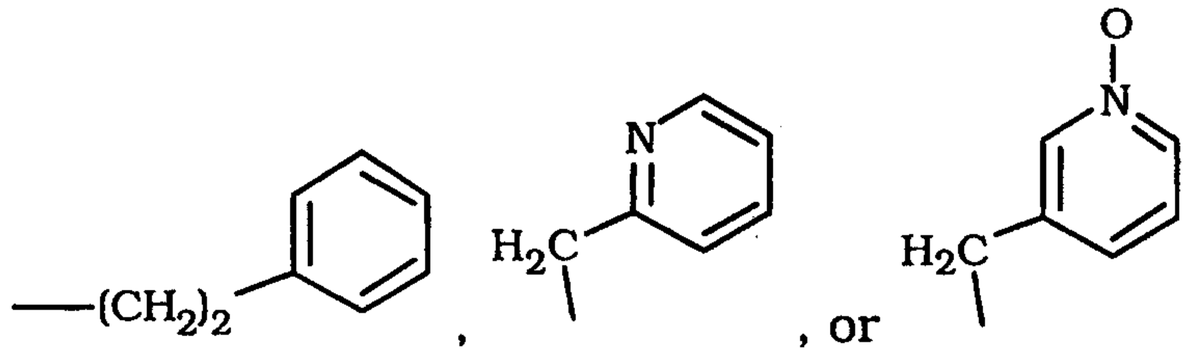

;

(j) R^{36} for 7.1 is selected from: cyclohexyl, cyclopentyl, cyclobutyl, cyclopropyl,


or 
; and

(k) R^{20} for 8.0 is selected from: methyl, i-propyl or cyclohexylmethyl.

8. The compound of Claim 7 wherein R^8 is selected from: benzyl, -$CH_2C(CH_3)_2$, -CH_2-cyclohexyl, -CH_2-cyclopropyl, -$(CH_2)_2CH_3$,

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9. The compound of Claim 8 wherein:

(a) R^8 is selected from: benzyl or -CH_2-cyclopropyl;

(b) R^{20} for 5.0 is cyclohexyl;

(c) R^{20} for 6.0 is selected from: t-butyl, i-propyl, or cyclohexyl; and R^{21} is selected from: H, -CH_3 or i-propyl;

(d) R^{20} for 7.0 is selected from: cyclohexyl, cyclopentyl, or i-propyl;

(e) R^{36} for 7.1 is selected from: cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl; and

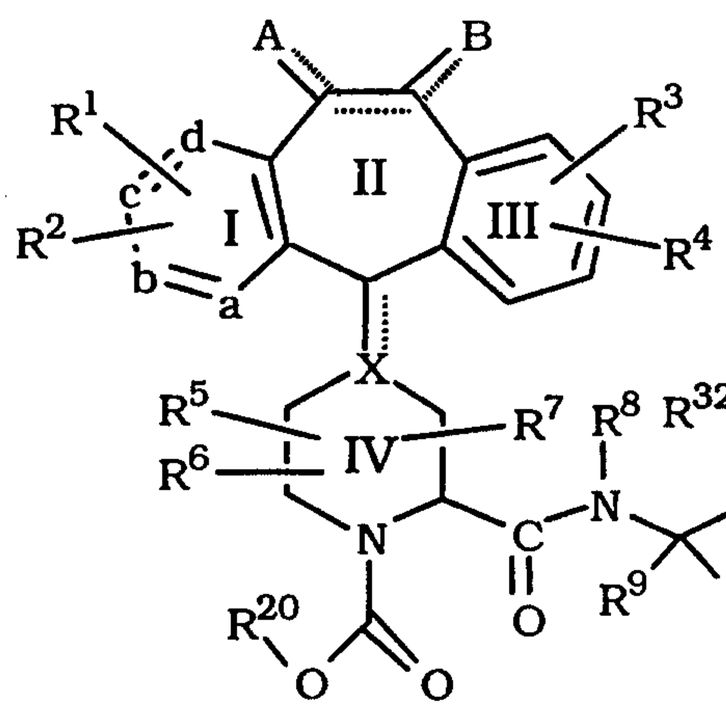
(d) R^{20} for 8.0 is methyl.

10. The compound of Claim 9 wherein said compound is the 2R isomer.

11. The compound of Claim 1 wherein R^8 is H and the alkyl chain between the amide substituent -C(O)NR^8 and R^{13} is substituted.

12. The compound of Claim 1 wherein when R^{14} is group 5.0, and X is N, and R^8 is H, then (a) the alkyl chain between R^{13} and the amide moiety is substituted and/or (b) R^9 and R^{10}, and/or R^{11} and R^{12}, are taken together to form a cyloalkyl ring.

13. A compound of the formula:



(25.0A)

or a pharmaceutically acceptable salt or solvate thereof, wherein:

one of a, b, c and d represents N or N^+O^-, and the remaining a, b, c and d groups represent CR^1 or CR^2; or

each of a, b, c, and d are independently selected from CR^1 or CR^2;

X represents N or CH when the optional bond (represented by the dotted line) is absent, and represents C when the optional bond is present;

the dotted line between carbon atoms 5 and 6 represents an optional bond, such that when a double bond is present, A and B independently represent -R^{15}, halo, -OR^{16}, -OCO_2R^{16} or -OC(O)R^{15}, and when no double bond is present between carbon atoms 5 and 6, A and B each independently represent H_2, -$(OR^{16})_2$, H and halo, dihalo, alkyl and H, $(alkyl)_2$, -H and

$-OC(O)R^{15}$, H and $-OR^{15}$, =O, aryl and H, $=NOR^{15}$ or $-O-(CH_2)_p-O-$ wherein p is 2, 3 or 4;

each R^1 and each R^2 is independently selected from H, halo, $-CF_3$, $-OR^{15}$, $-COR^{15}$, $-SR^{15}$, $-S(O)_tR^{16}$ (wherein t is 0, 1 or 2, $-N(R^{15})_2$, $-NO_2$, $-OC(O)R^{15}$, $-CO_2R^{15}$, $-OCO_2R^{16}$, -CN, $-NR^{15}COOR^{16}$, $-SR^{16}C(O)OR^{16}$, $-SR^{16}N(R^{17})_2$ (provided that R^{16} in $-SR^{16}N(R^{17})_2$ is not $-CH_2-$) wherein each R^{17} is independently selected from H or $-C(O)OR^{16}$, benzotriazol-1-yloxy, tetrazol-5-ylthio, or substituted tetrazol-5-ylthio, alkynyl, alkenyl or alkyl, said alkyl or alkenyl group optionally being substituted with halo, $-OR^{15}$ or $-CO_2R^{15}$;

R^3 and R^4 are the same or different and each independently represents H, any of the substituents of R^1 and R^2, or R^3 and R^4 taken together represent a saturated or unsaturated C_5-C_7 fused ring to the benzene ring (Ring III);

R^5, R^6, and R^7 each independently represents H, $-CF_3$, $-COR^{15}$, alkyl or aryl, said alkyl or aryl optionally being substituted with $-OR^{15}$, $-SR^{15}$, $-S(O)_tR^{16}$, $-NR^{15}COOR^{16}$, $-N(R^{15})_2$, $-NO_2$, $-COR^{15}$, $-OCOR^{15}$, $-OCO_2R^{16}$, $-CO_2R^{15}$, OPO_3R^{15}, or R^5 is combined with R^6 to represent =O or =S;

R^8 is selected from: H, C_3 to C_4 alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, substituted alkyl, substituted aryl, substituted arylalkyl, substituted heteroaryl, substituted heteroarylalkyl, substituted cycloalkyl, substituted cycloalkylalkyl;

the substutuents for the R^8 substituted groups being selected from: alkyl, aryl, arylalkyl, cycloalkyl, $-N(R^{18})_2$, $-OR^{18}$, cycloalkyalkyl, halo, CN, $-C(O)N(R^{18})_2$, $-SO_2N(R^{18})_2$ or $-CO_2R^{18}$; provided that the $-OR^{18}$ and $-N(R^{18})_2$ substituents are not bound to the carbon that is bound to the N of the $-C(O)NR^8-$ moiety;

each R^{18} is independently selected from: H, alkyl, aryl, arylalkyl, heteroaryl or cycloalkyl;

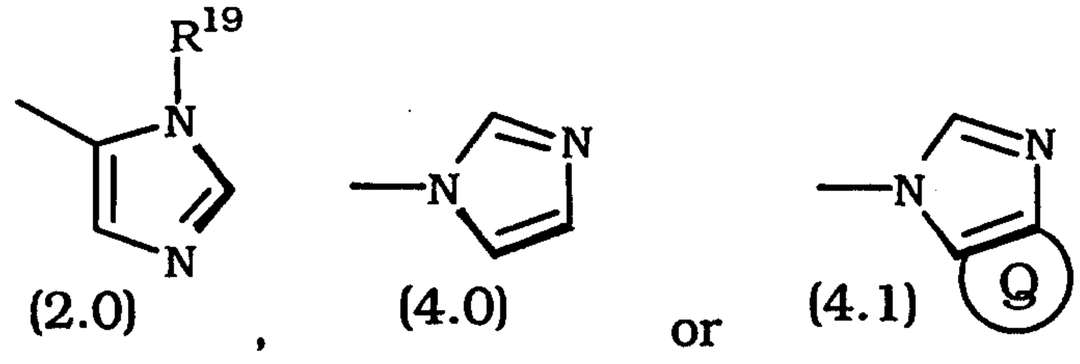
R^9 and R^{10} are independently selected from: H, alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl or $-CON(R^{18})_2$ (wherein R^{18} is as defined above); and wherein said substitutable R^9 and R^{10} groups are optionally substituted with one or more substituents selected from: alkyl, cycloalkyl, arylalkyl, or heterarylalkyl; or

R^9 and R^{10} together with the carbon atom to which they are bound, form a C_3 to C_6 cycloalkyl ring;

R^{11} and R^{12} are independently selected from: H, alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl, $-CON(R^{18})_2$ $-OR^{18}$ or $-N(R^{18})_2$; wherein R^{18} is as defined above; provided that the $-OR^{18}$ and $-N(R^{18})_2$ groups are not bound to a carbon atom that is adjacent to a nitrogen atom; and wherein said substitutable R^{11} and R^{12} groups are optionally substituted with one or more substituents selected from: alkyl, cycloalkyl, arylalkyl, or heterarylalkyl; or

R^{11} and R^{12} together with the carbon atom to which they are bound, form a C_3 to C_6 cycloalkyl ring;

R^{13} is an imidazolyl ring selected from:



(2.0) , (4.0) or (4.1) ,

wherein R^{19} is selected from: (1) H, (2) alkyl, (3) alkyl, (4) aryl, (5) arylalkyl, (6) substituted arylalkyl wherein the substituents are selected from halo or CN, (7) $-C(aryl)_3$ or (8) cycloalkyl;

said imidazolyl ring 2.0 optionally being substituted with one or two substituents and said imidazole ring 4.0 optionally being substituted with 1-3 substituents and said imidazole ring 4.1 being optionally substituted with one substituent wherein said optional substituents for rings 2.0, 4.0 and 4.1 are independently selected

from selected from: -NHC(O)R^{18}, -C(R^{34})$_2$OR^{35}, -OR^{18}, -SR^{18}, F, Cl, Br, alkyl, aryl, arylalkyl, cycloalkyl, or -N(R^{18})$_2$; wherein R^{18} is as defined above; wherein each R^{34} is independently selected from H or alkyl; wherein R^{35} is selected from H, -C(O)OR^{20}, or -C(O)NHR^{20}, and R^{20} is as defined below; Q represents an aryl ring, a cycloalkyl ring or a heteroaryl ring, said Q is optionally substituted with 1 to 4 substituents independently selected from halo, alkyl, aryl, -OR^{18}, -N(R^{18})$_2$ (wherein each R^{18} is independently selected), -OC(O)R^{18}, or –C(O)N(R^{18})$_2$ (wherein each R^{18} is independently selected), and wherein R^{18} is as defined above;

R^{15} is selected from: H, alkyl, aryl or arylalkyl;

R^{16} is selected from: alkyl or aryl;

R^{20} is selected from: alkyl, alkoxy, aryl, arylalkyl, cycloalkyl, heteroaryl, heteroarylalkyl or heterocycloalkyl;

said R^{20} group is optionally substituted with one or more substituents selected from: halo, alkyl, aryl, -OC(O)R^{18}, -OR^{18} or -N(R^{18})$_2$, wherein each R^{18} group is the same or different, and wherein R^{18} is as defined above, provided that said optional substituent is not bound to a carbon atom that is adjacent to an oxygen or nitrogen atom;

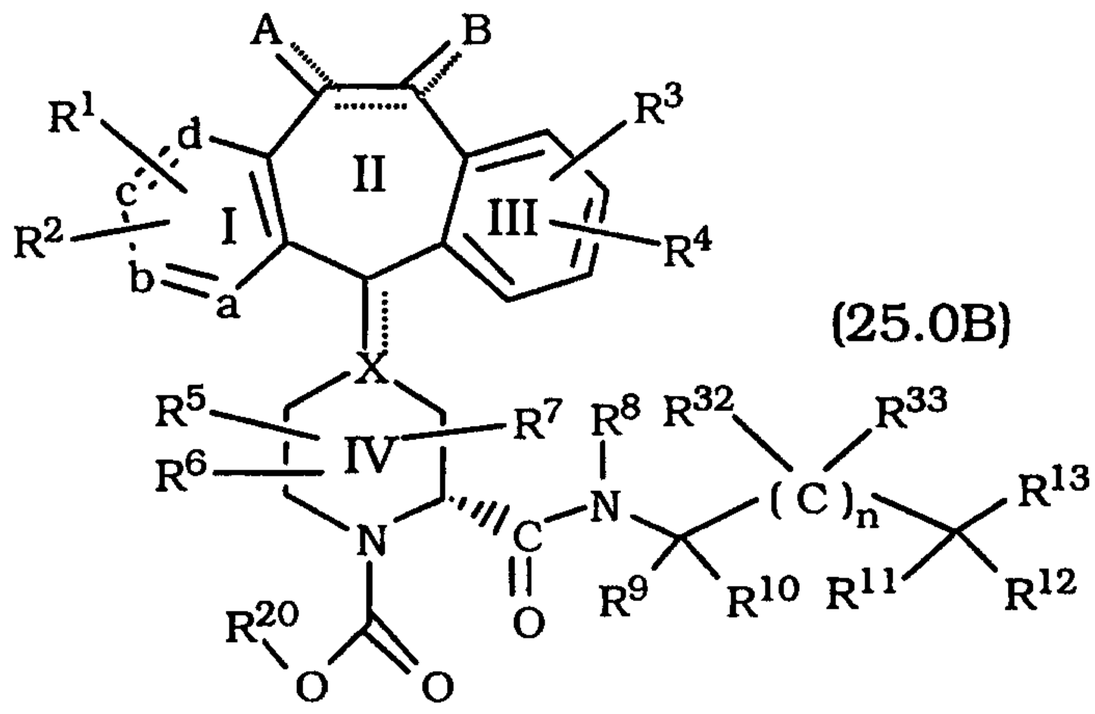
n is 0-5;

each R^{32} and R^{33} for each n are independently selected from: H, alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl, -CON(R^{18})$_2$ -OR^{18} or =-N(R^{18})$_2$; wherein R^{18} is as defined above; and wherein said substitutable R^{32} and R^{33} groups are optionally substituted with one or more substituents selected from: alkyl, cycloalkyl, arylalkyl, or heterarylalkyl; or

R^{32} and R^{33} together with the carbon atom to which they are bound, form a C_3 to C_6 cycloalkyl ring; and

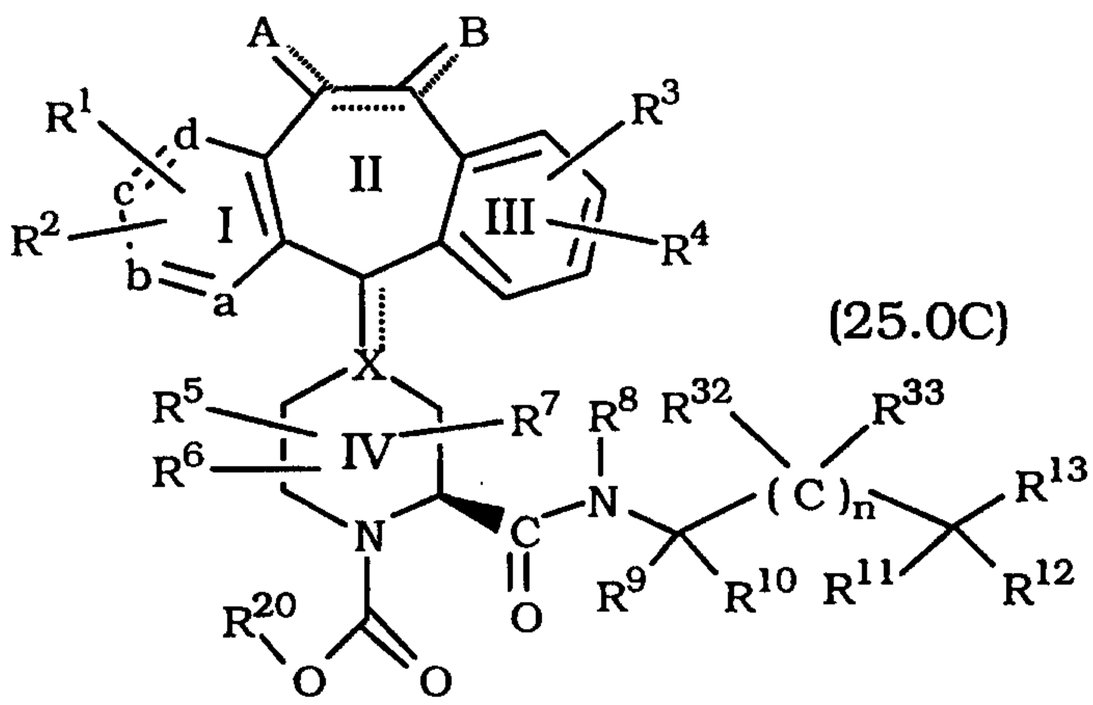
provided that when X is N, and R^8 is H, then the alkyl chain between R^{13} and the amide moiety is substituted.

14. The compound of Claim 13 having the structure:



(25.0B)

or



(25.0C)

15. The compound 25.0B of Claim 14 wherein R^8 is H and the alkyl chain between the amide substituent -C(O)NR^8 and R^{13} is substituted.

16. The compound 25.0B of Claim 14 wherein:

(a) R^1 to R^4 is independently selected from H, Br or Cl;

(b) R^5 to R^7 is H;

(c)

(1) a, b, c, and d are carbon, and R^{20} is selected from: alkyl, alkoxy, aryl, arylalkyl, cycloalkyl, heteroaryl, heteroarylalkyl or heterocycloalkyl; said R^{20} group is optionally substituted with one or more substituents selected from: halo, alkyl, aryl, -OC(O)R^{18}, -OR^{18} or -N$(R^{18})_2$, wherein each R^{18} group is the

same or different, and wherein R^{18} is as defined above, provided that said optional substituent is not bound to a carbon atom that is adjacent to an oxygen or nitrogen atom; or

(2) a is N and the remaining b, c and d substituents are carbon, and R^{20} is selected from: alkyl, arylalkyl, heterocycloalkyl, aryl, aryl substituted with halo, cycloalkyl, cycloalkyl substituted with alkyl, or cycloalkyl substituted with -OH provided that said -OH substituent is not bound to a carbon adjacent to an oxygen atom;

(d) A and B are H_2;

(e) n is 0 or 1;

(f) R^{13} is group 2.0 or 4.0;

(g) R^8 is selected from: arylalkyl, substituted arylalkyl, cycloalkylalkyl, substituted cycloalkylalkyl, heteroarylalkyl or substituted heteroarylalkyl; and

(h) X is CH or N;

(i) R^9 and R^{10} are independently selected from: H, alkyl, $-C(O)N(R^{18})_2$, or arylalkyl;

(j) R^{11} and R^{12} are independently selected from: H, alkyl, substituted aryl, $-OR^{18}$, or R^{11} and R^{12} taken together with the carbon atom to which they are bound form a cycloalkyl ring;

(k) R^{32} and R^{33} are independently selected from: H, $-OR^{18}$, arylalkyl or aryl;

(l) R^{19} is selected from: $-C(O)N(R^{18})_2$, alkyl, arylalkyl, or $-C(aryl)_3$; and

(m) said optional R^{13} substitutents are selected from: $-N(R^{18})_2$, $-NHC(O)R^{18}$, $-C(R^{34})_2OR^{35}$, or alkyl.

17. The compound of Claim 16 wherein a is N and the remaining b, c, and d substituents are carbon and:

(a) R^8 is selected from arylalkyl, cycloalkylalkyl, or heteroarylalkyl;

(b) R^9 and R^{10} are independently selected from: H or benzyl;

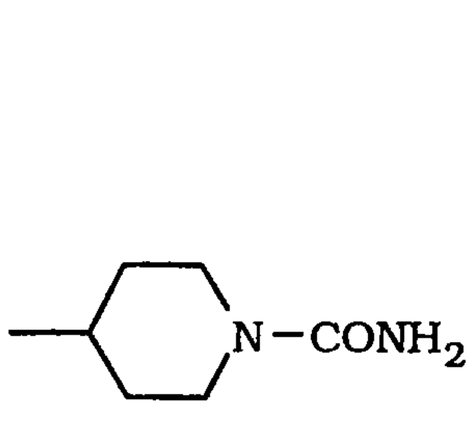
(c) R^{11} and R^{12} are independently selected from: H, $-CH_3$, $-CH_2CH(CH_3)_2$, $-(CH_2)_3CH_3$, benzyl, ethyl, p-chlorophenyl, -OH, or R^{11} and R^{12} taken together with the carbon atom to which they are bound form a cyclopropyl ring;

(d) R^{32} and R^{33} are independently selected from: H, phenyl, -OH or benzyl;

(e) R^{19} is selected from: -C(O)NH-cyclohexyl, $-C(phenyl)_3$, H, methyl or ethyl;

(f) said optional R^{13} substitutents are selected from: $-CH_3$, $-CH_2OH$, $-CH_2OC(O)O$-cyclohexyl, $-CH_2OC(O)O$-cyclopentyl, ethyl, isopropyl, NH_2, or $-NHC(O)CF_3$; and

(g) R^{20} is selected from: t-butyl, ethyl, benzyl, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$, $-(CH_2)_2CH_3$, n-butyl, n-hexyl, n-octyl, p-chlorophenyl, cyclohexyl, cyclopentyl,



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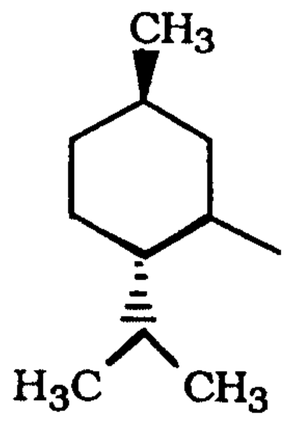

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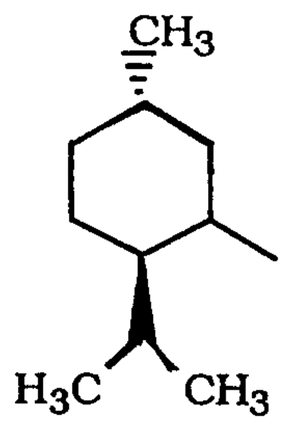

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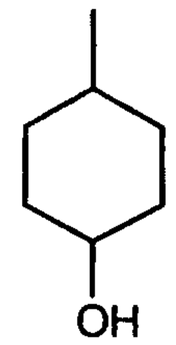

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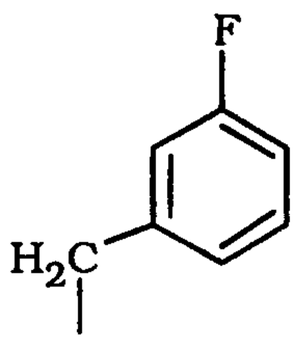
18. The compound of Claim 17 wherein R^9, R^{10}, R^{11}, R^{12}, R^{32}, and R^{33} are H.

19. The compound of Claim 17 wherein R^8 is selected from: benzyl, $-CH_2C(CH_3)_2$, $-CH_2$-cyclohexyl, $-CH_2$-cyclopropyl, $-(CH_2)_2CH_3$,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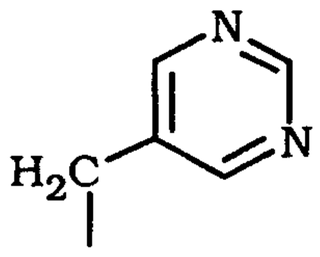
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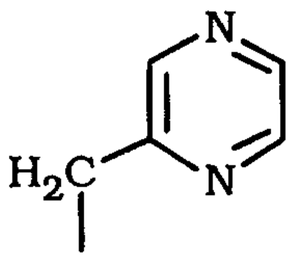
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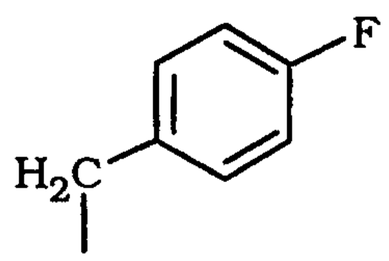
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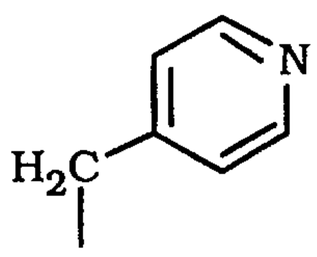
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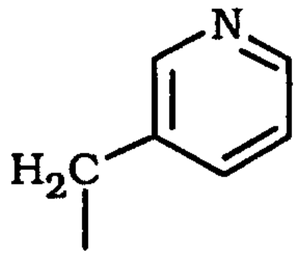
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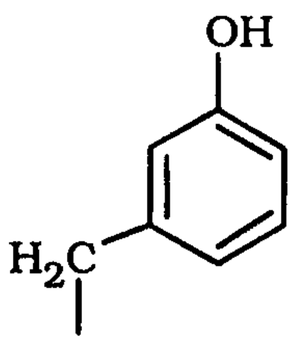
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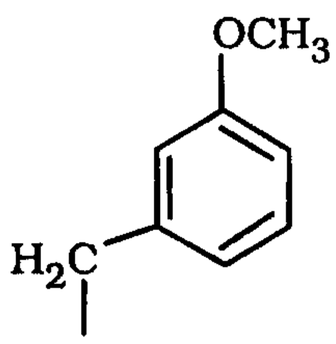
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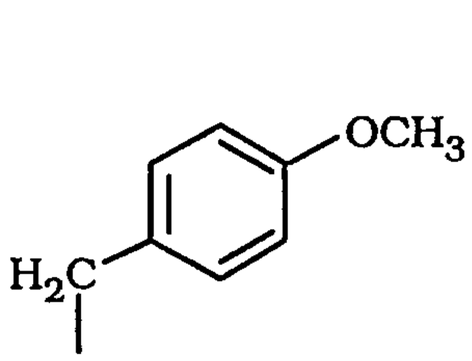
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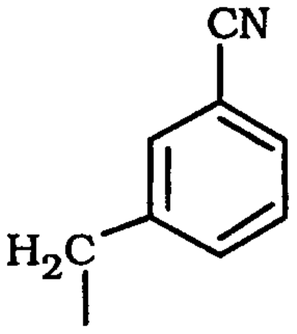
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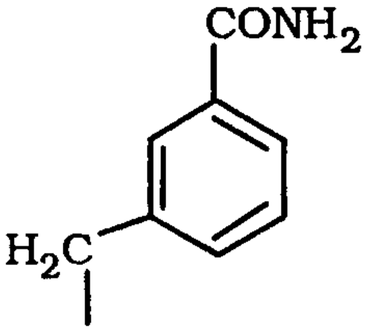
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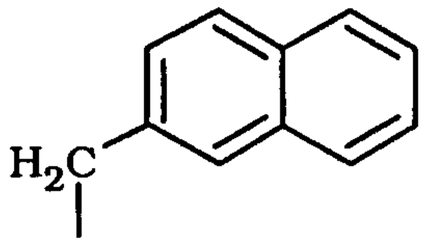
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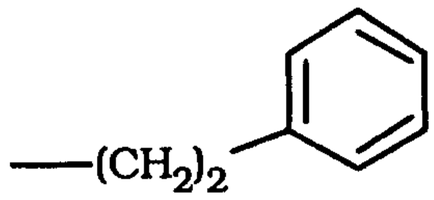
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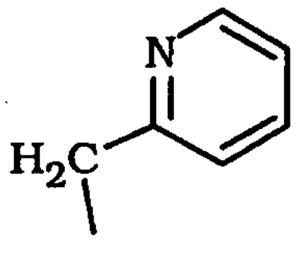
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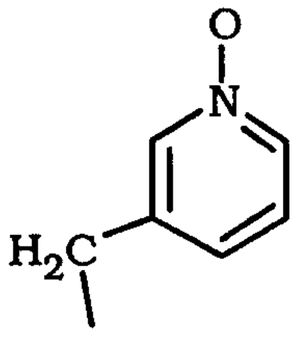
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20. The compound of Claim 19 wherein:

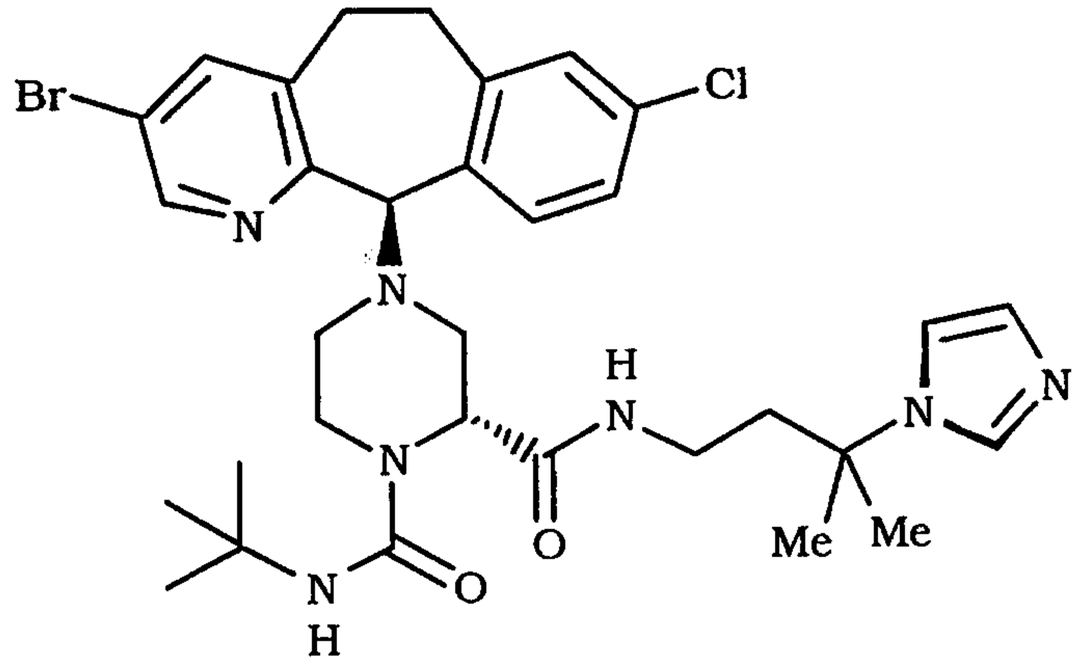
(a) R^8 is selected from: benzyl or $-CH_2$-cyclopropyl; and

15 (b) R^{20} is cyclohexyl.

21. The compound of Claim 20 which is (1) a 3-Br-8-Cl-compound, an 8-Cl-compound, or a 10-Cl-compound; or (2) a 3-Br-

8-Cl-compound, an 8-Cl-compound, or a 10-Cl-compound wherein R^9, R^{10}, R^{11}, R^{12}, R^{32}, and R^{33} are H.

22. The compound of Claim 1 selected from:



(11R,2R Isomer)

(Example 11)

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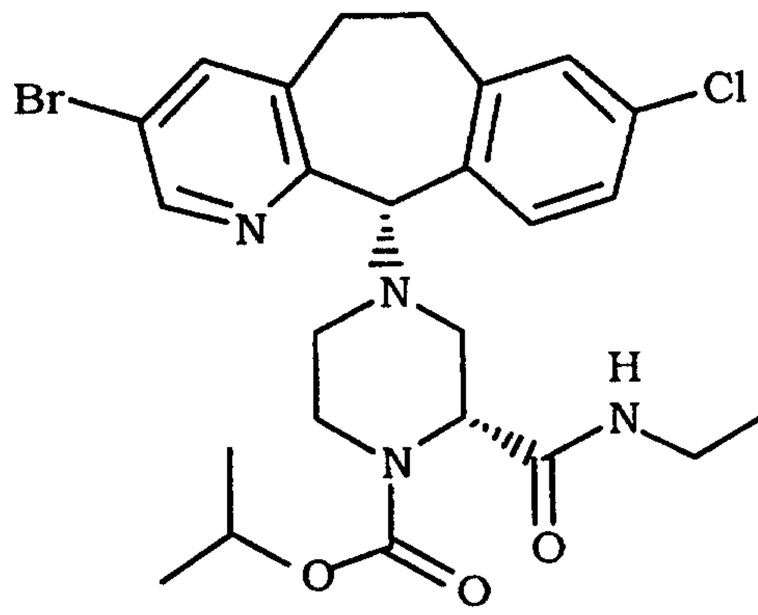

(11S,2R Isomer)

(Example 16)

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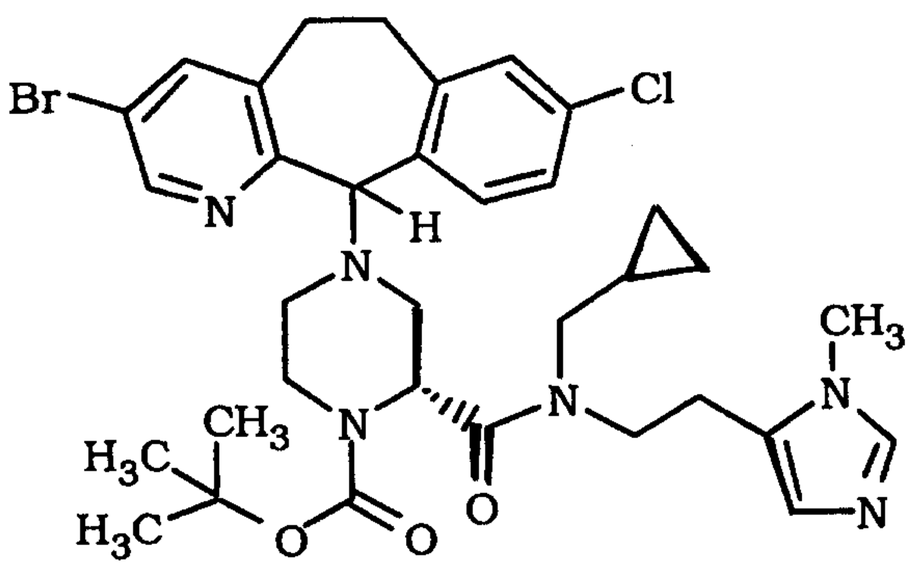
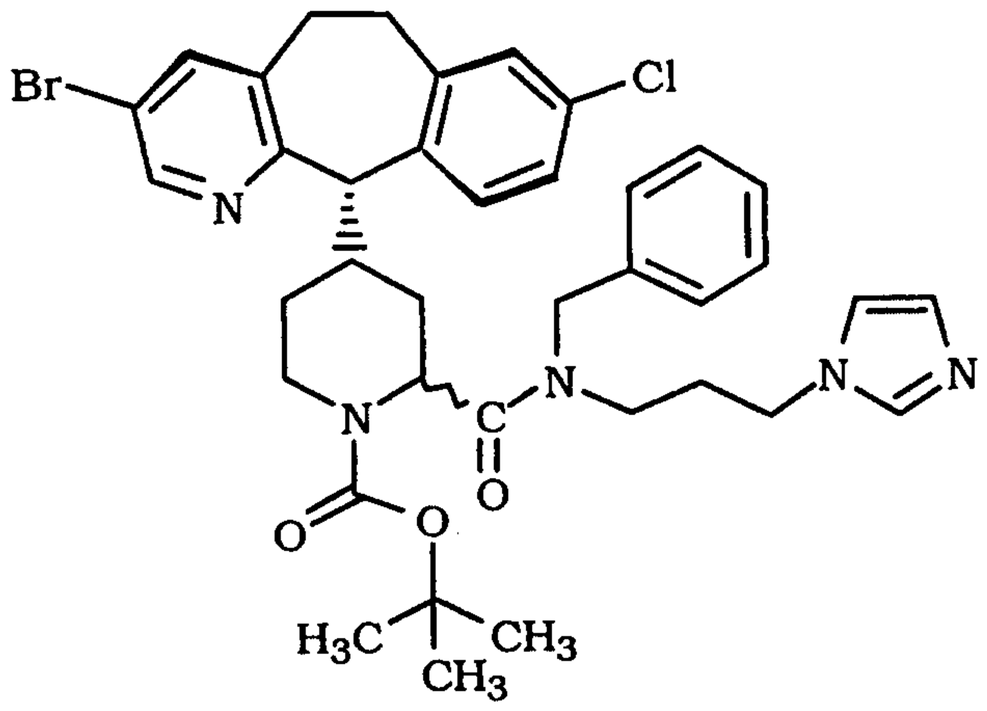


(Example 58);



(Example 78 Step B)

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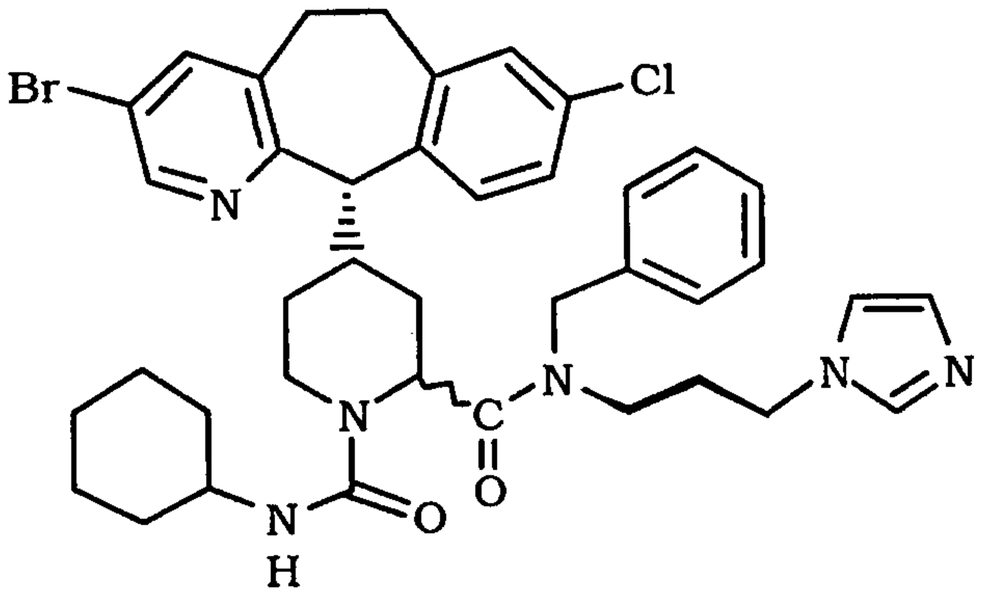

(Example 79 Isomer A)

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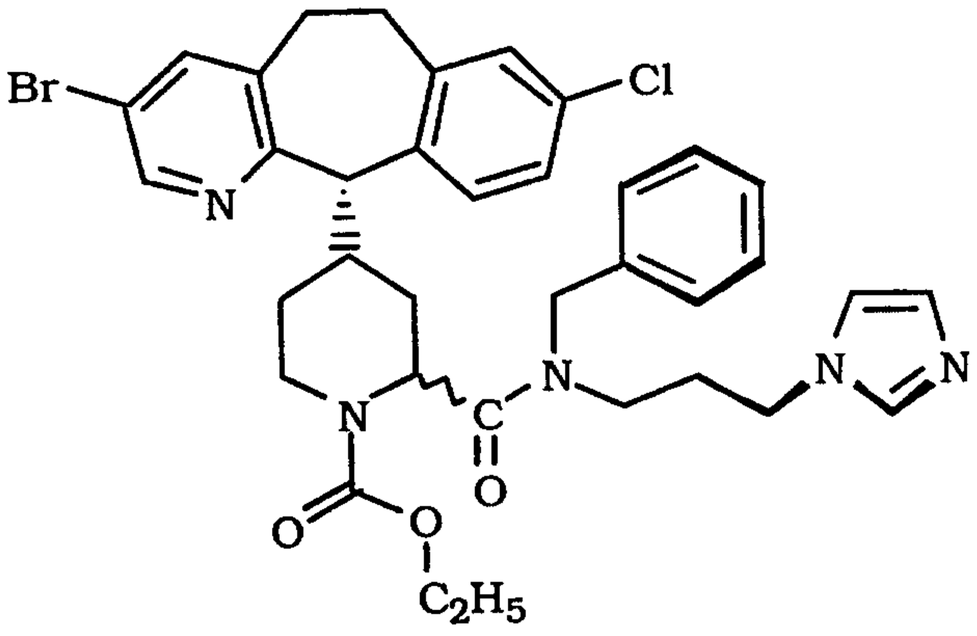

(Example 80 Isomer A)

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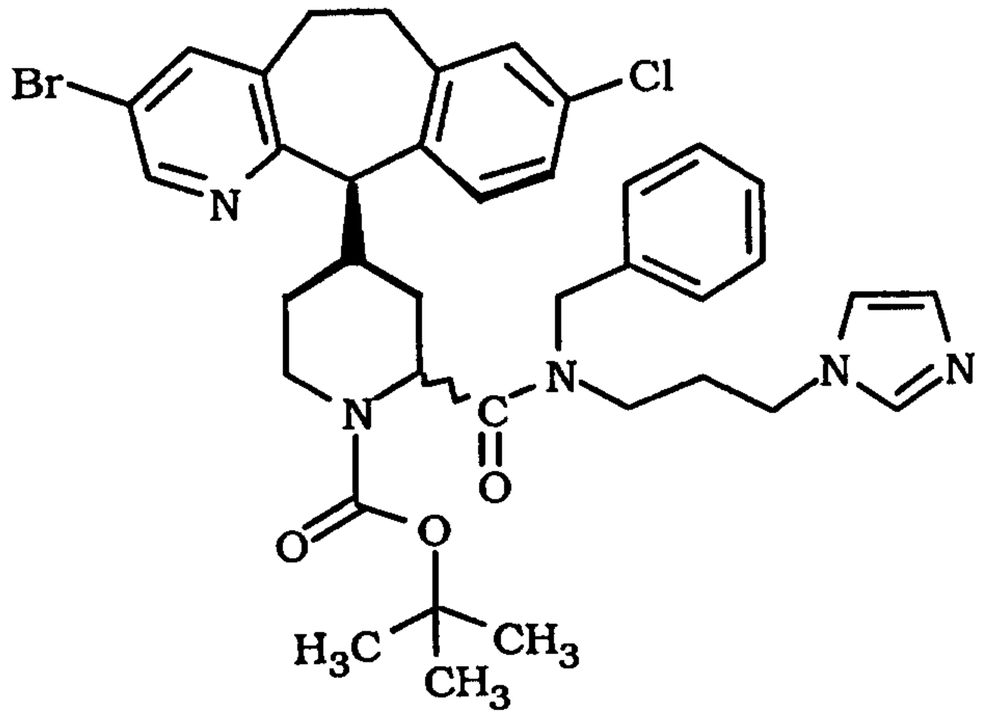
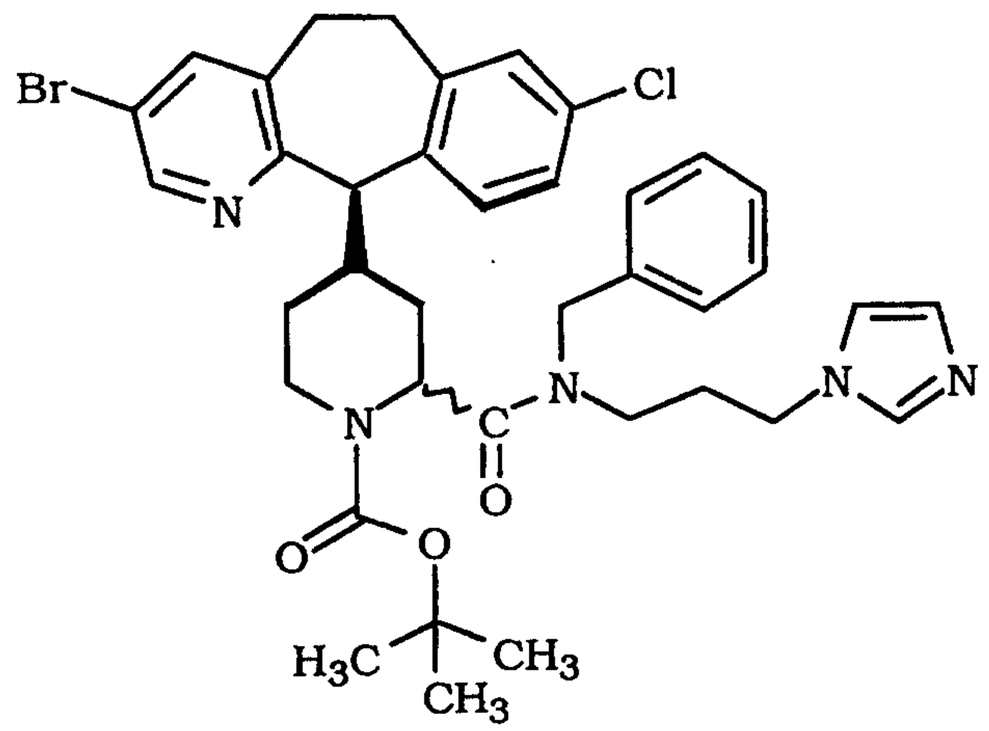


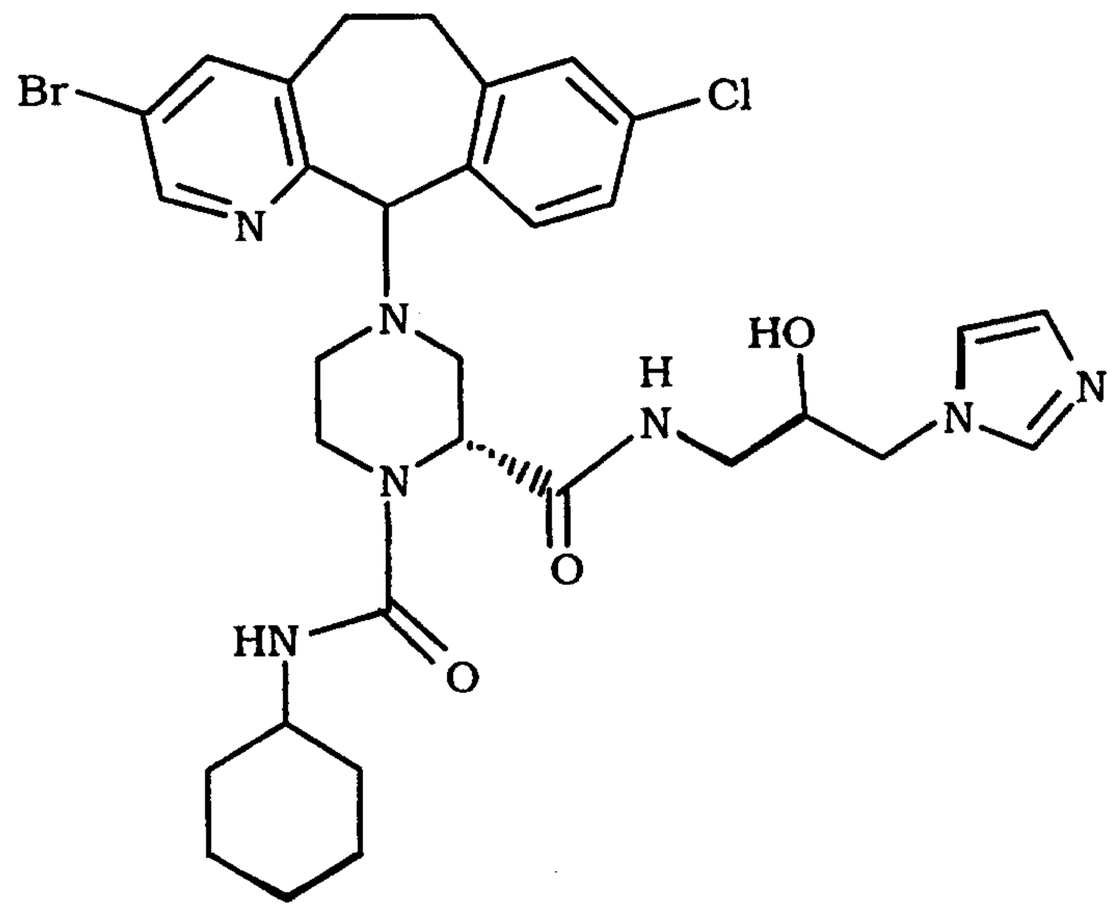
(Example 88 Isomer A)

;



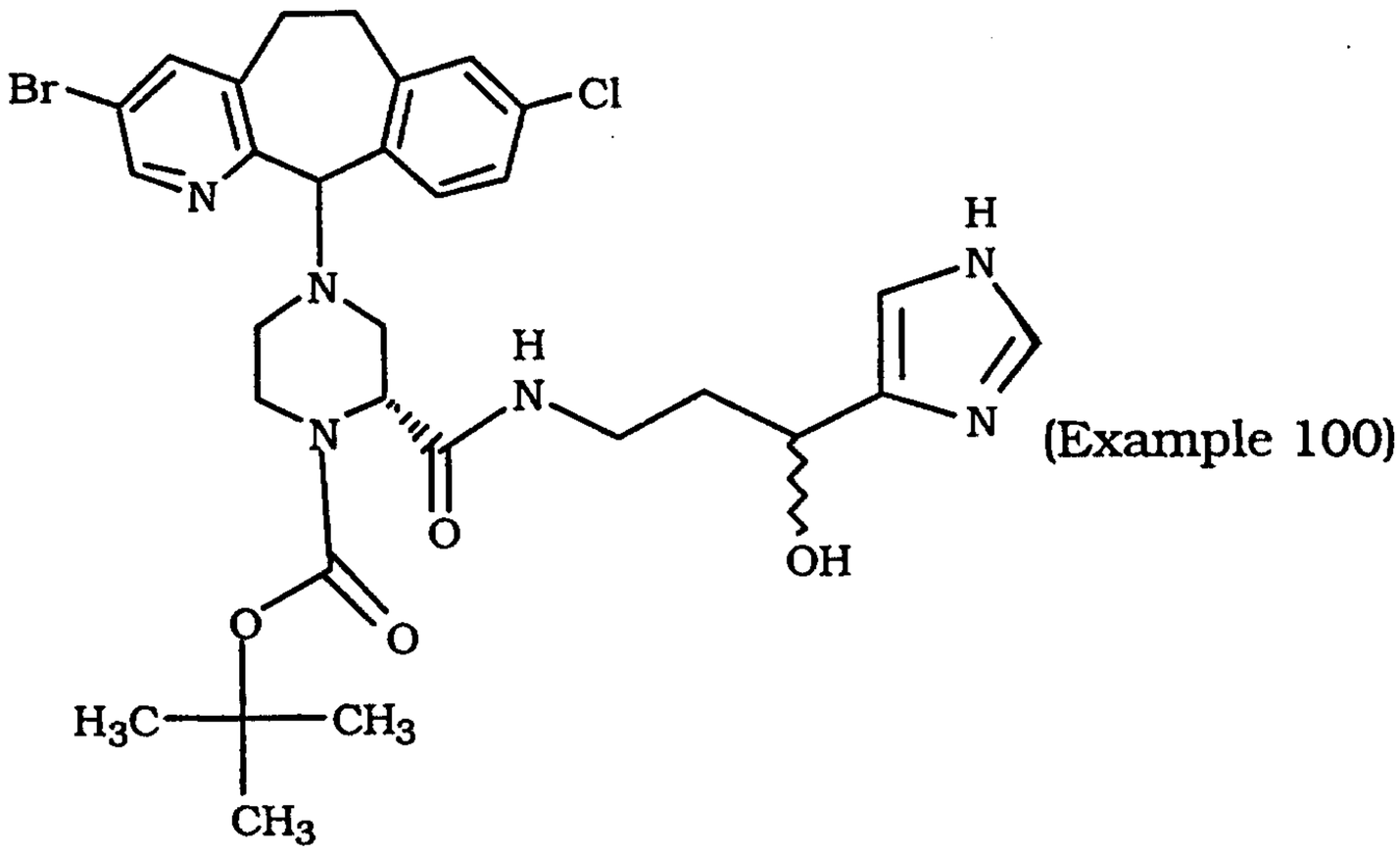
(Example 93 Isomer D)

;



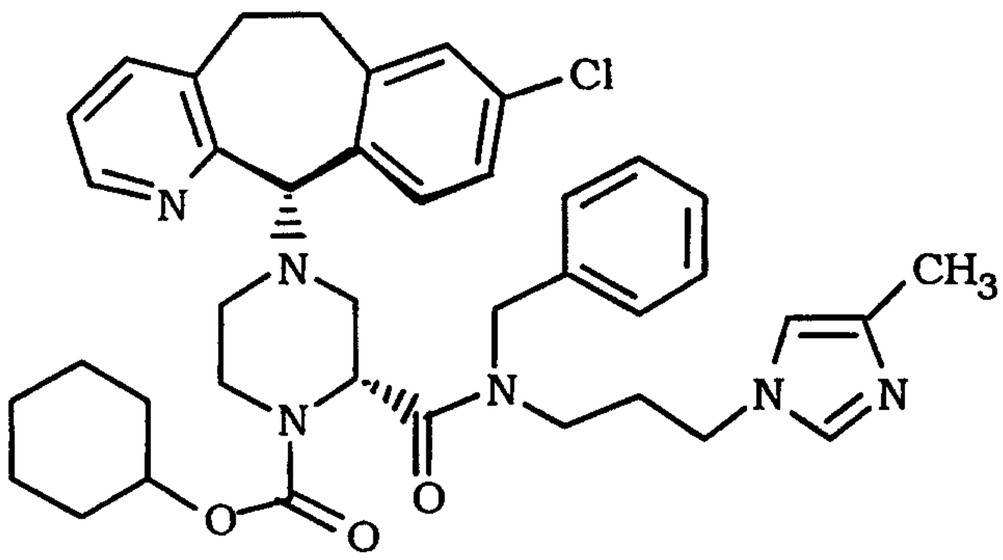
(Example 99)

;

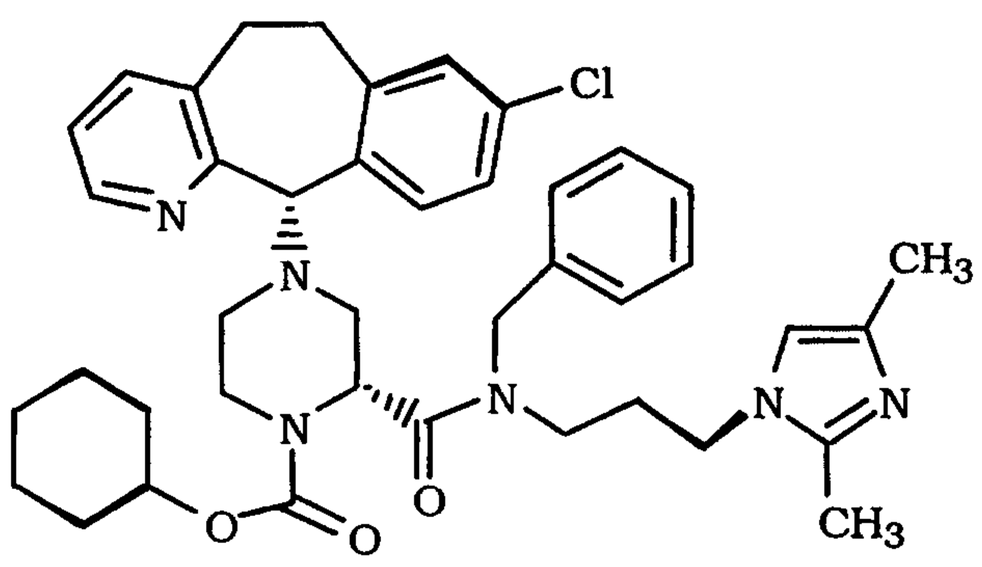


(Example 100)

;

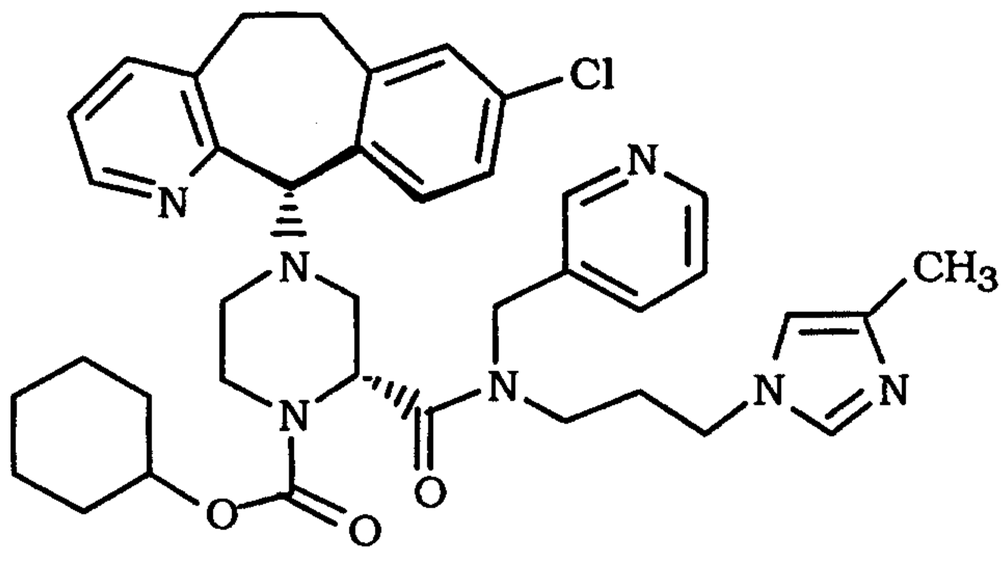


(Example 225)



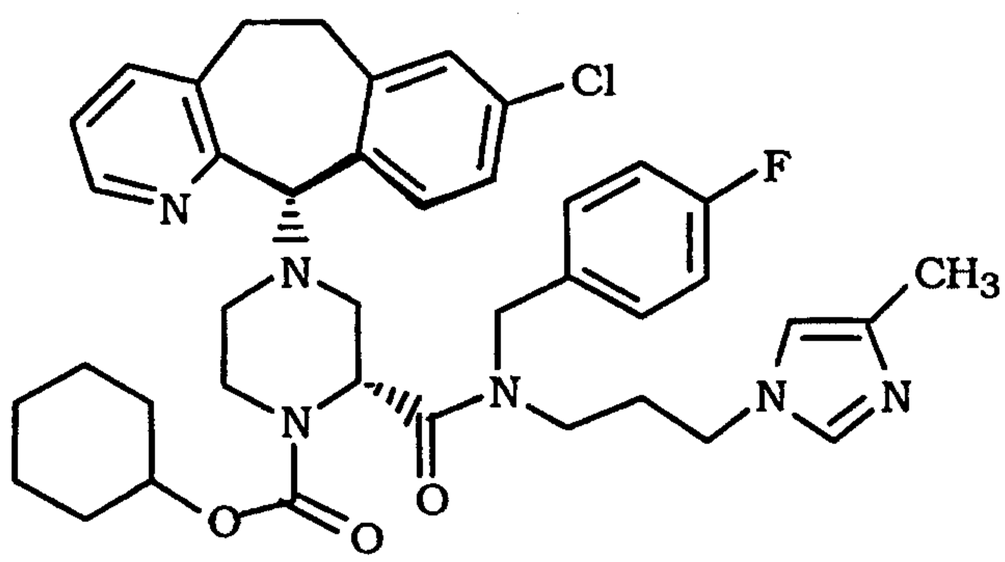
(Example 226)

;



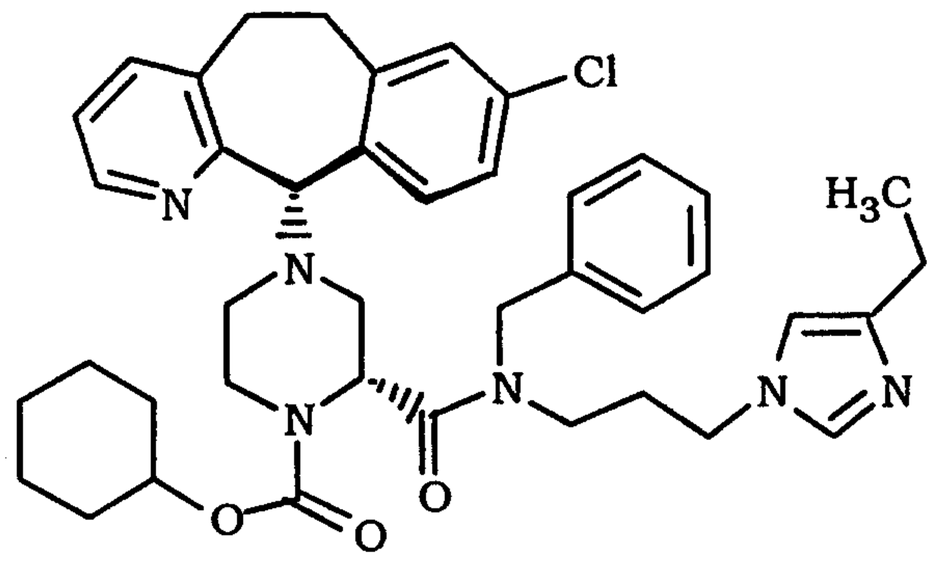
(Example 227)

;



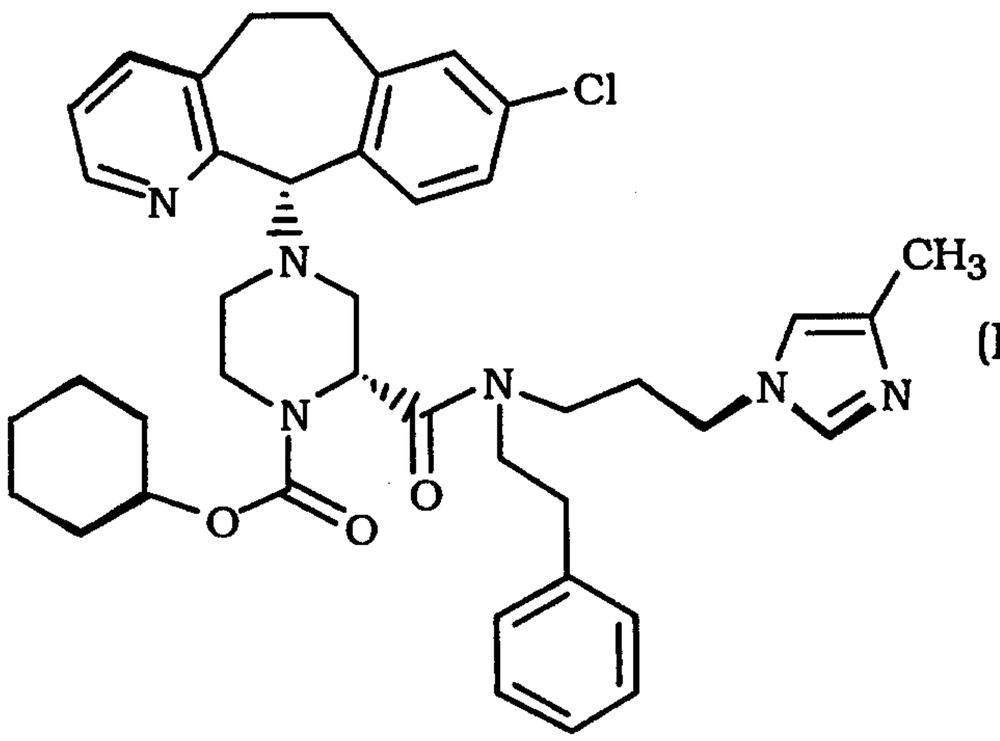
(Example 228)

;



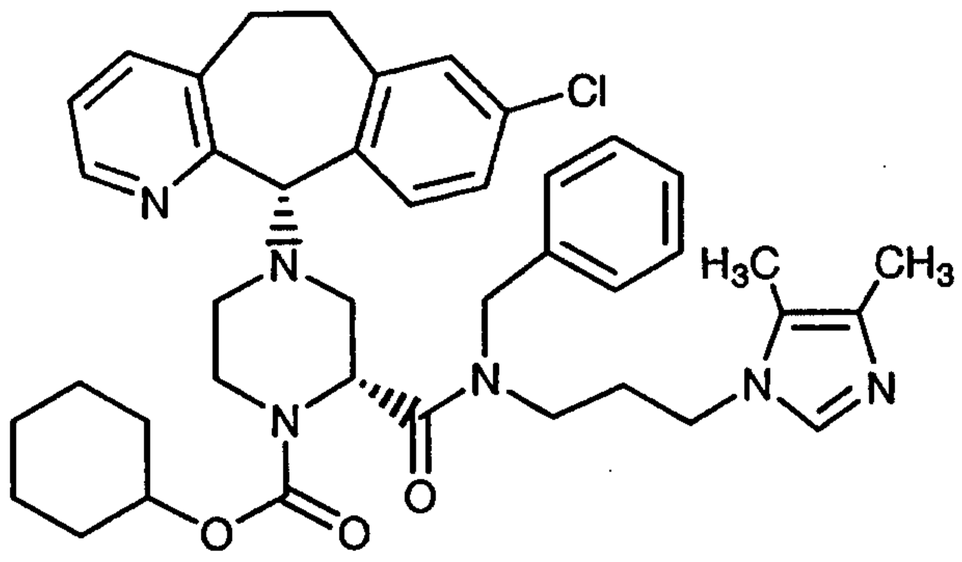
(Example 229)

;



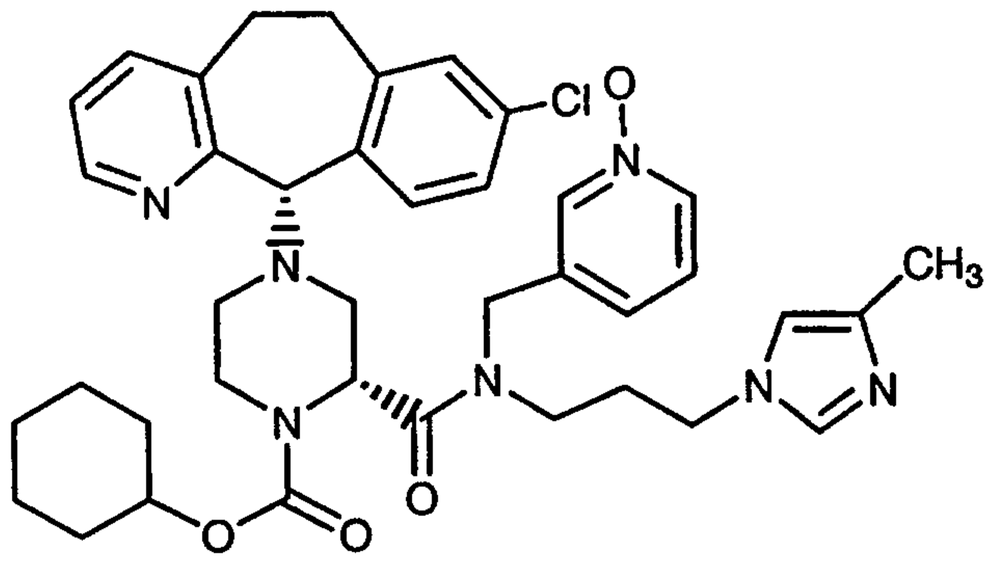
(Example 232)

;



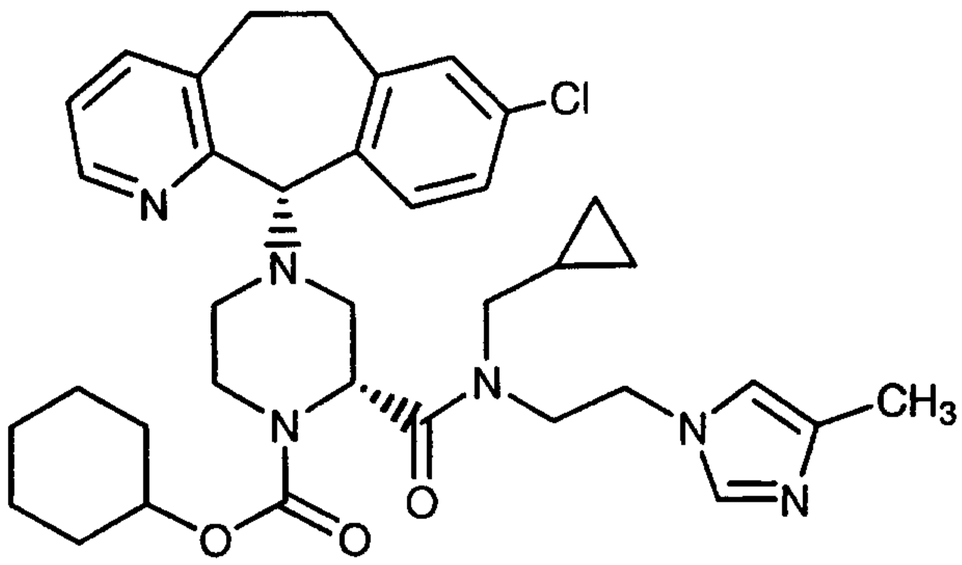
(Example 326)

;



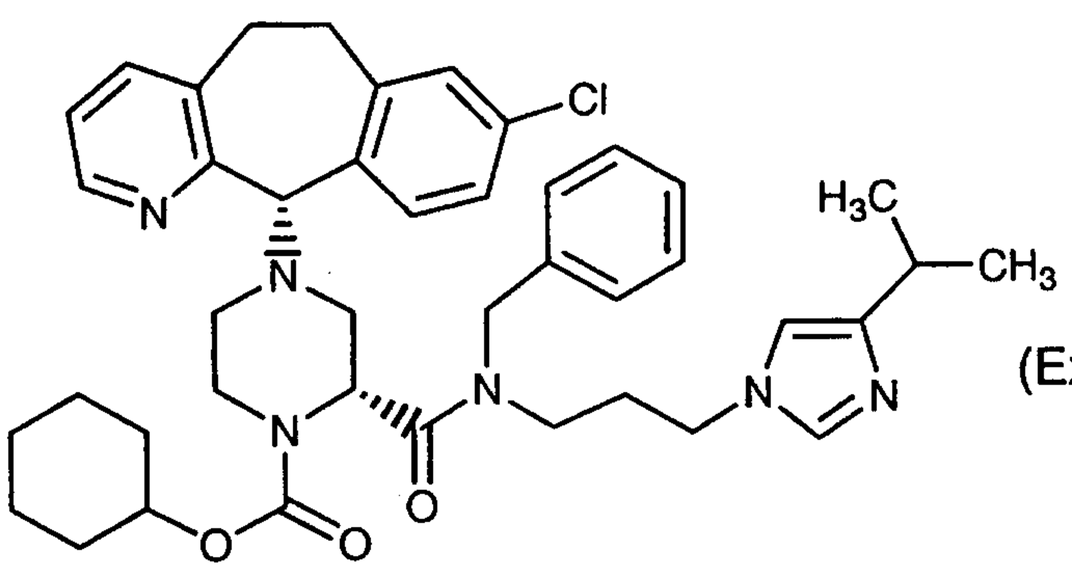
(Example 330)

;



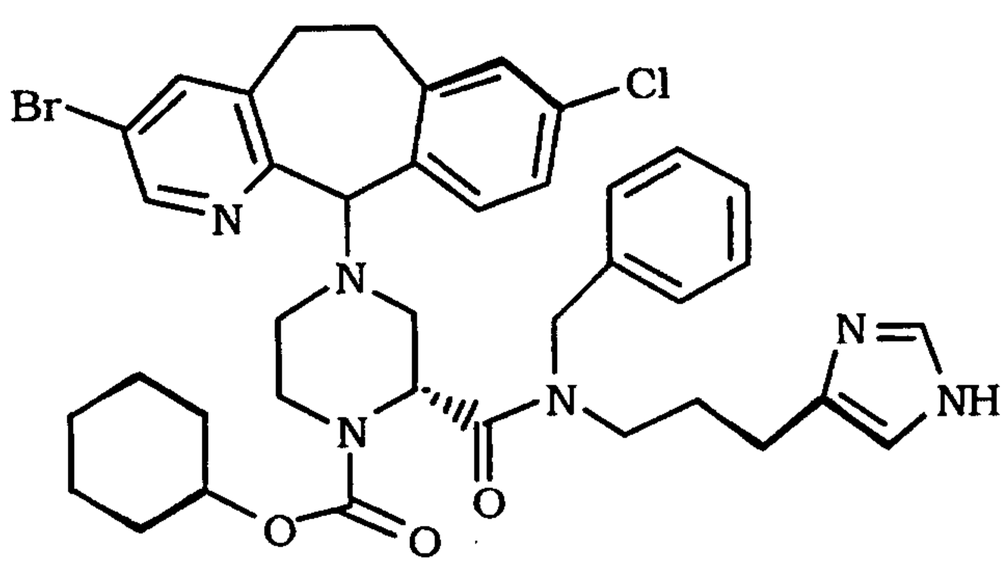
(Example 327)

;



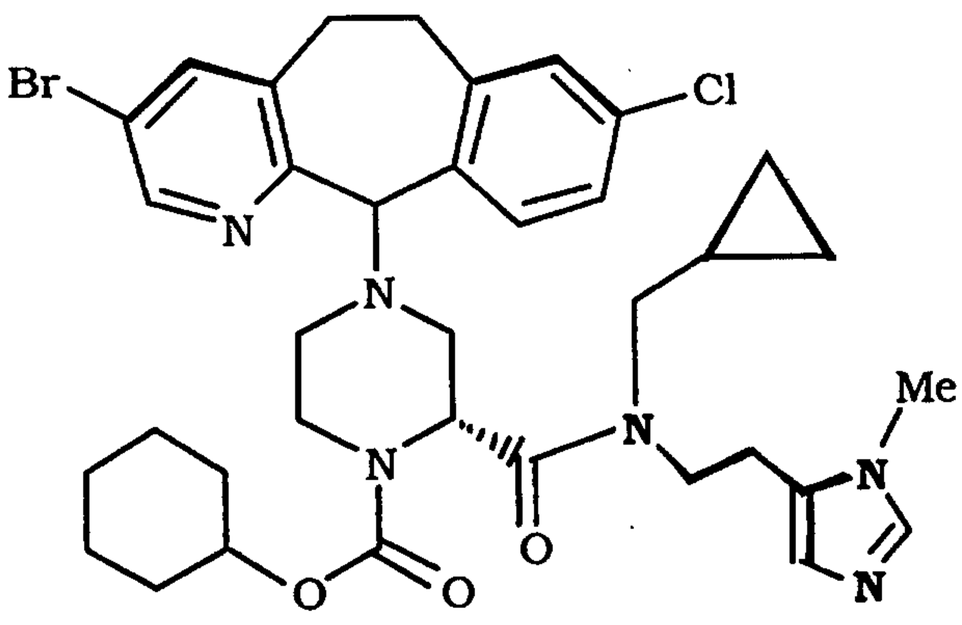
(Example 328)

;



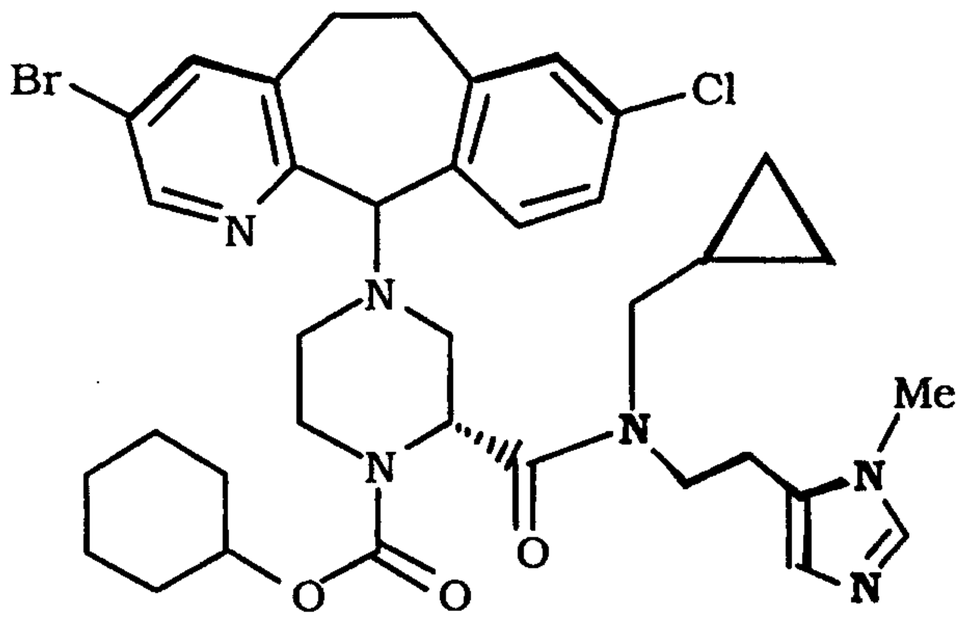
(Example 243)

;



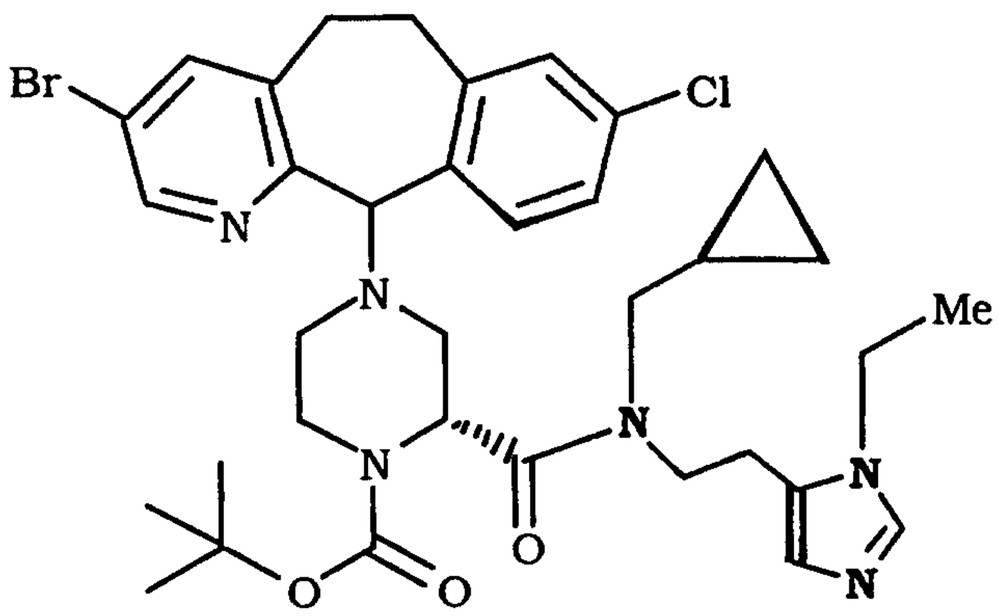
(Example 286A)

;



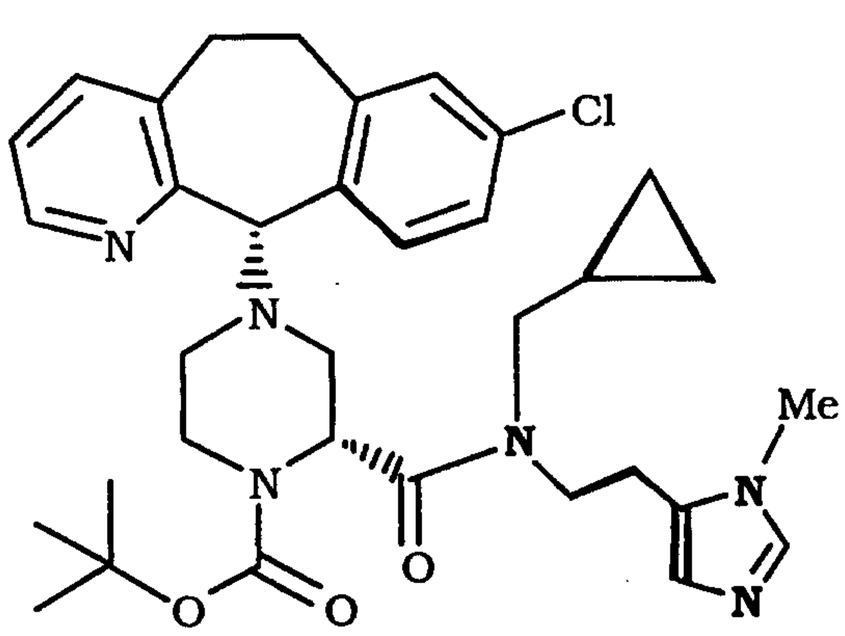
(Example 286B)

;



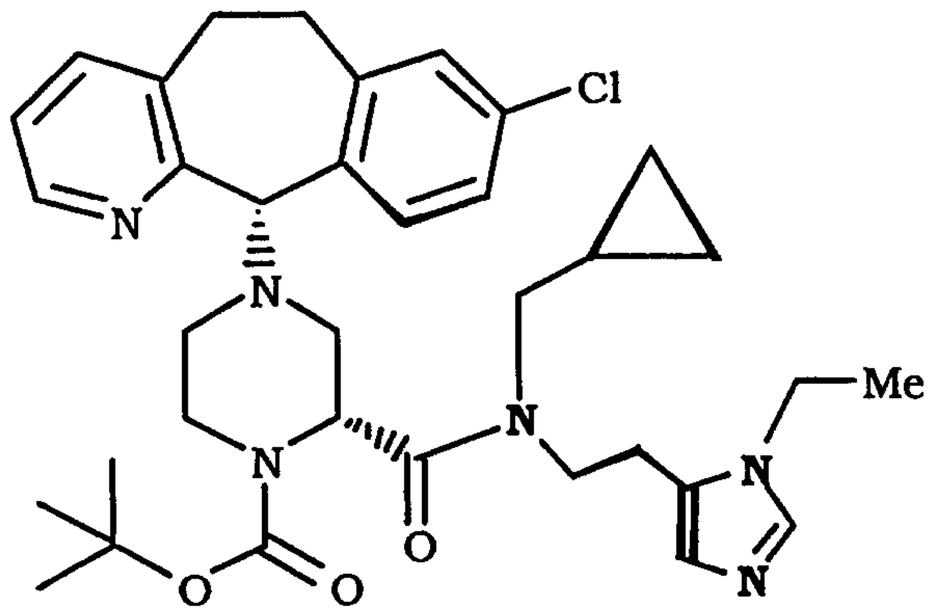
(Example 304)

;



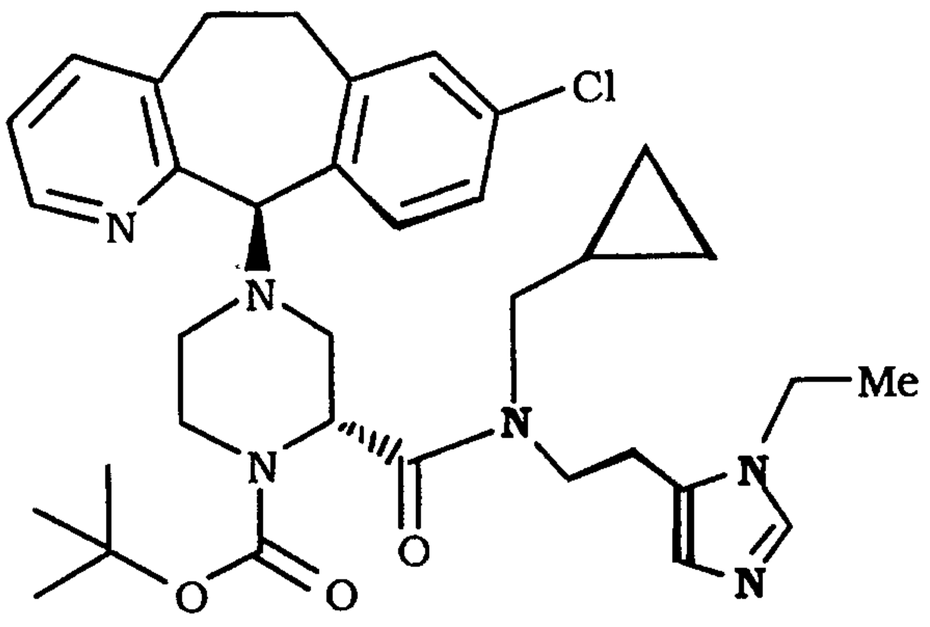
(Example 306)

;



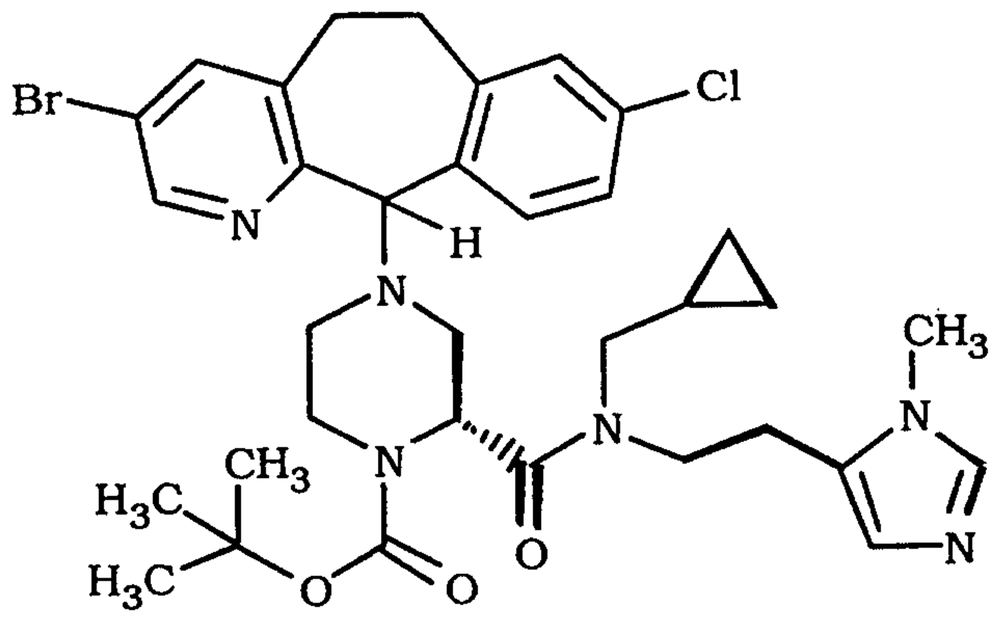
(Example 307)

; or

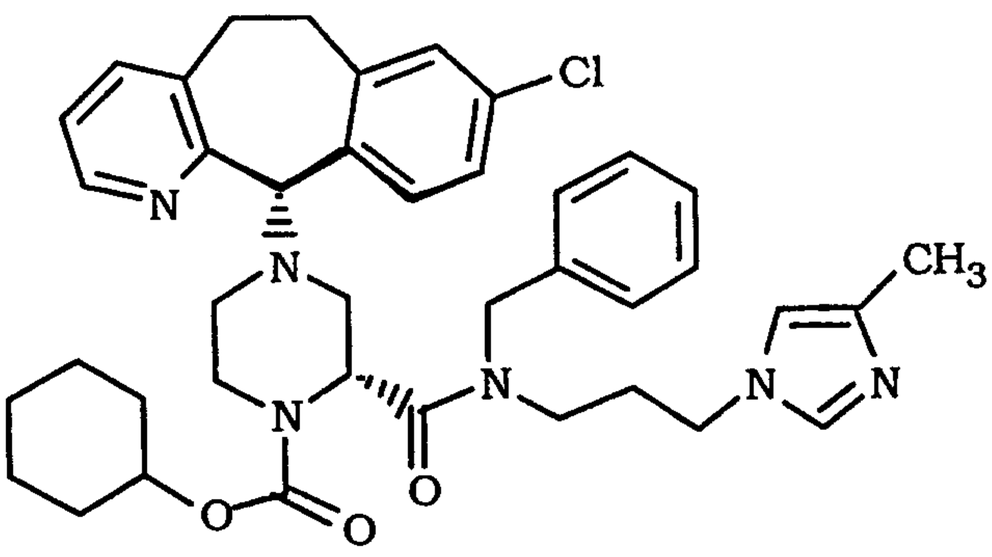


(Example 308)

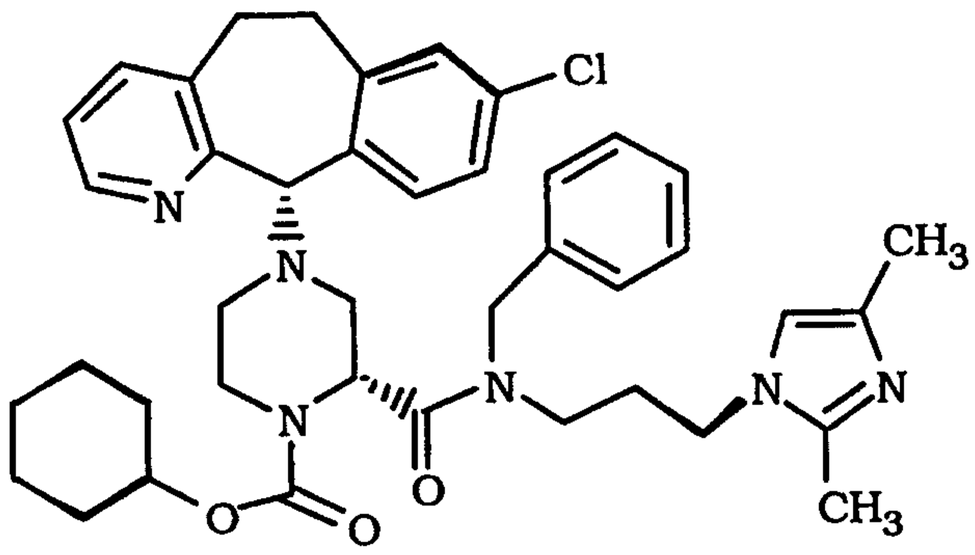
23 The compound of Claim 1 selected from:



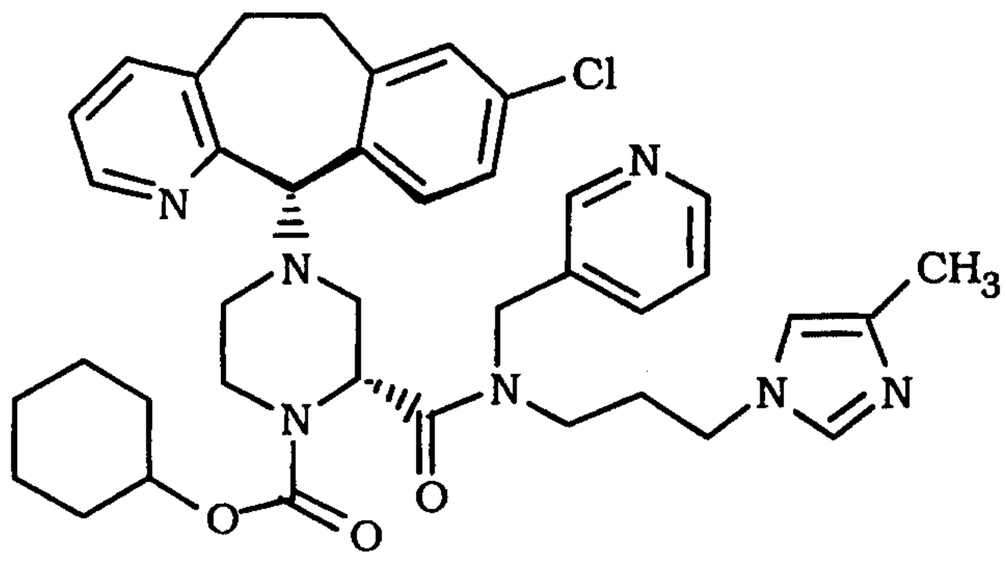
Example 58 ;



(Example 225) ;

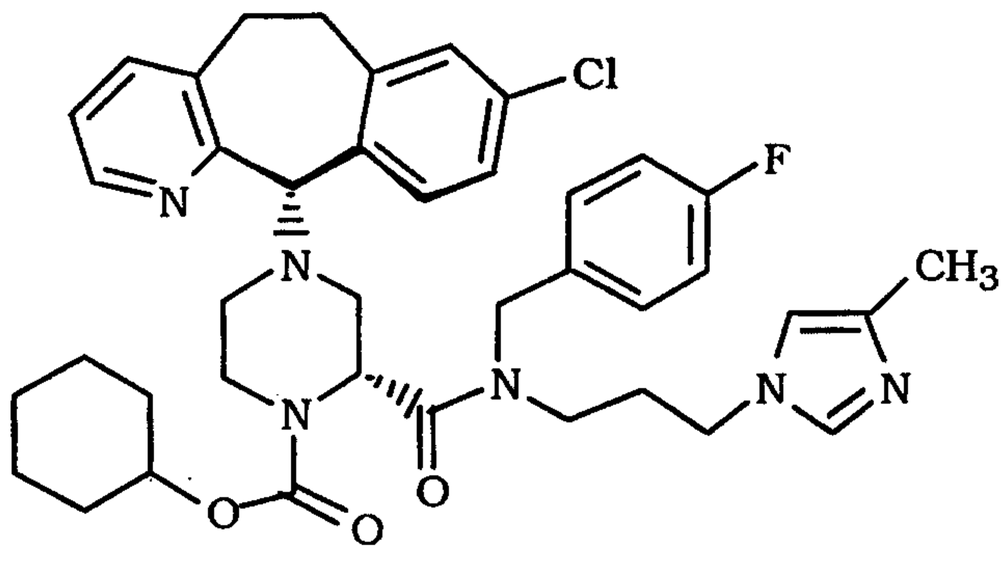


(Example 226) ;



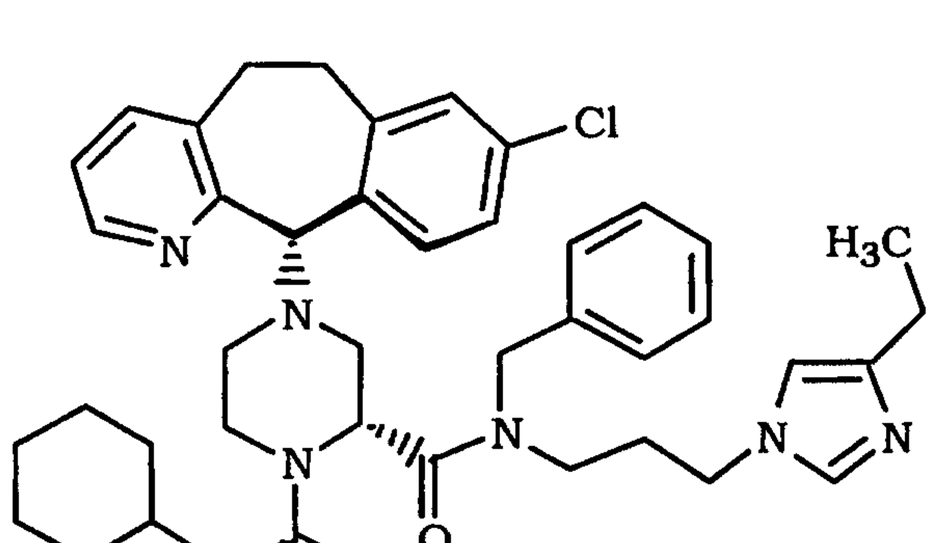
(Example 227)

;



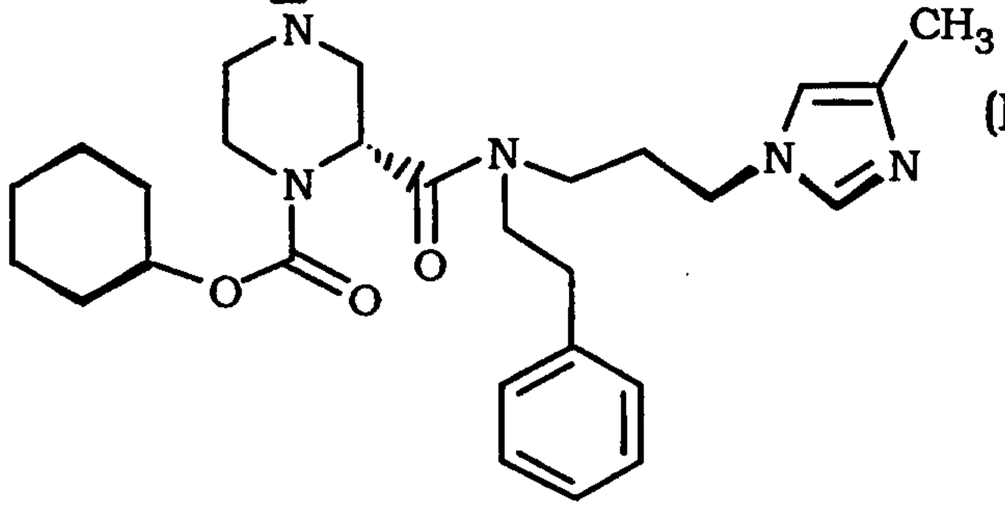
(Example 228)

;



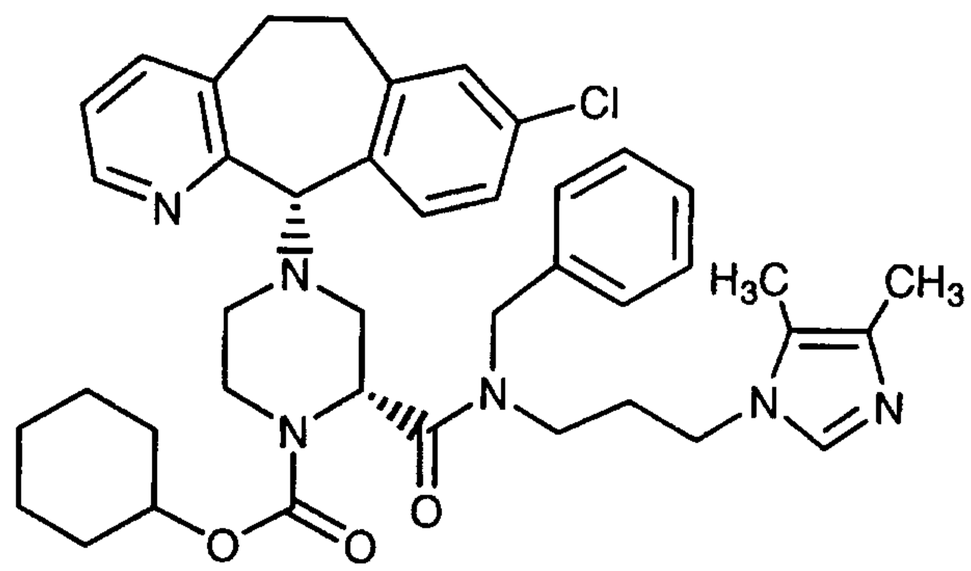
(Example 229)

;

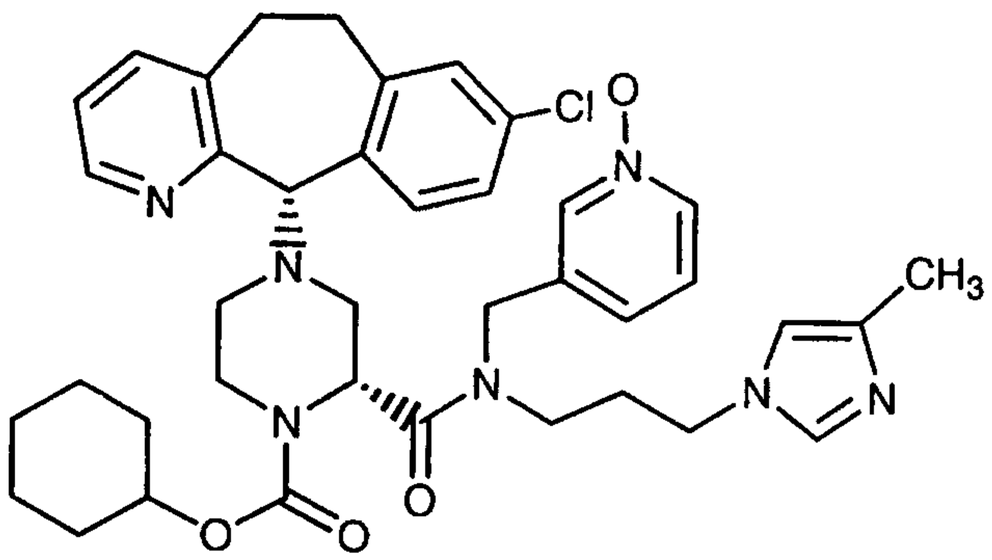


(Example 232)

;

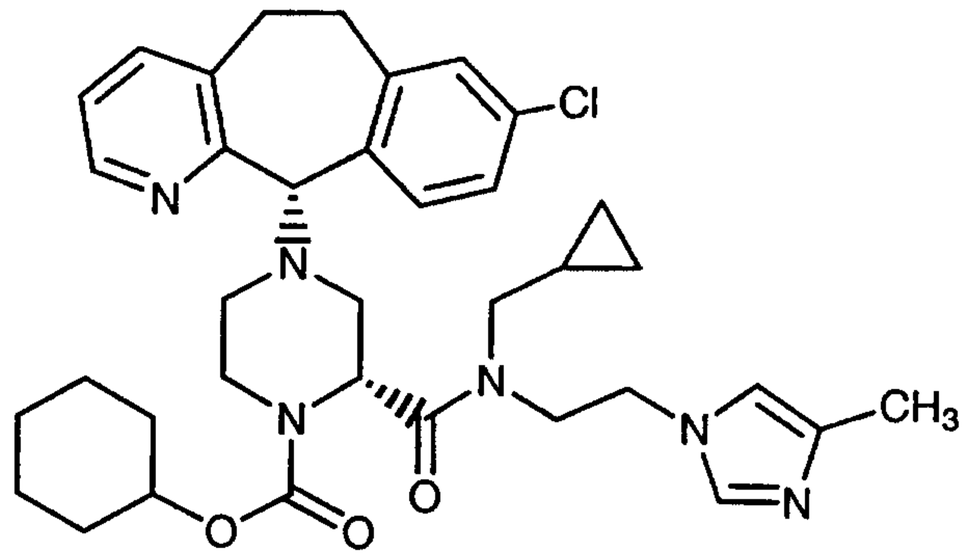


(Example 326)



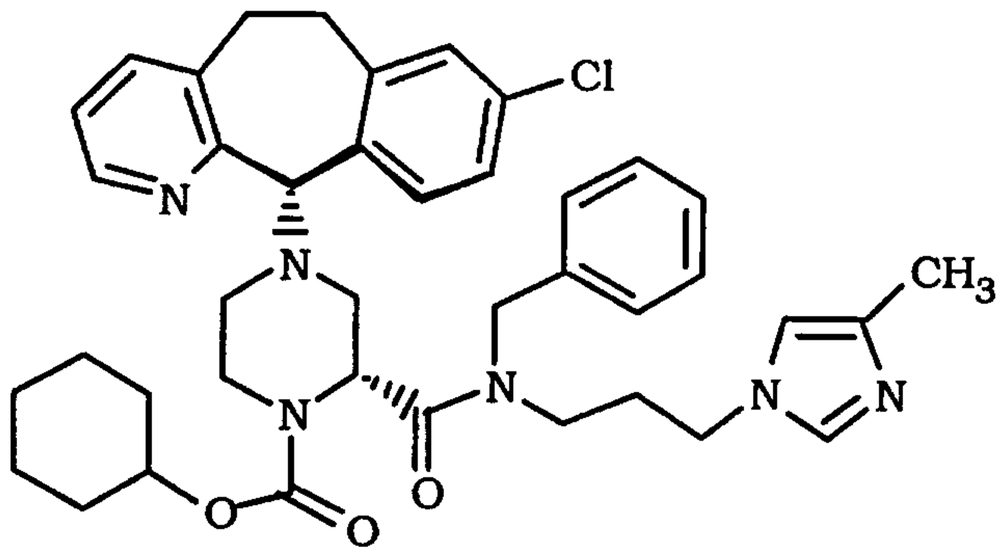
(Example 330)

; or



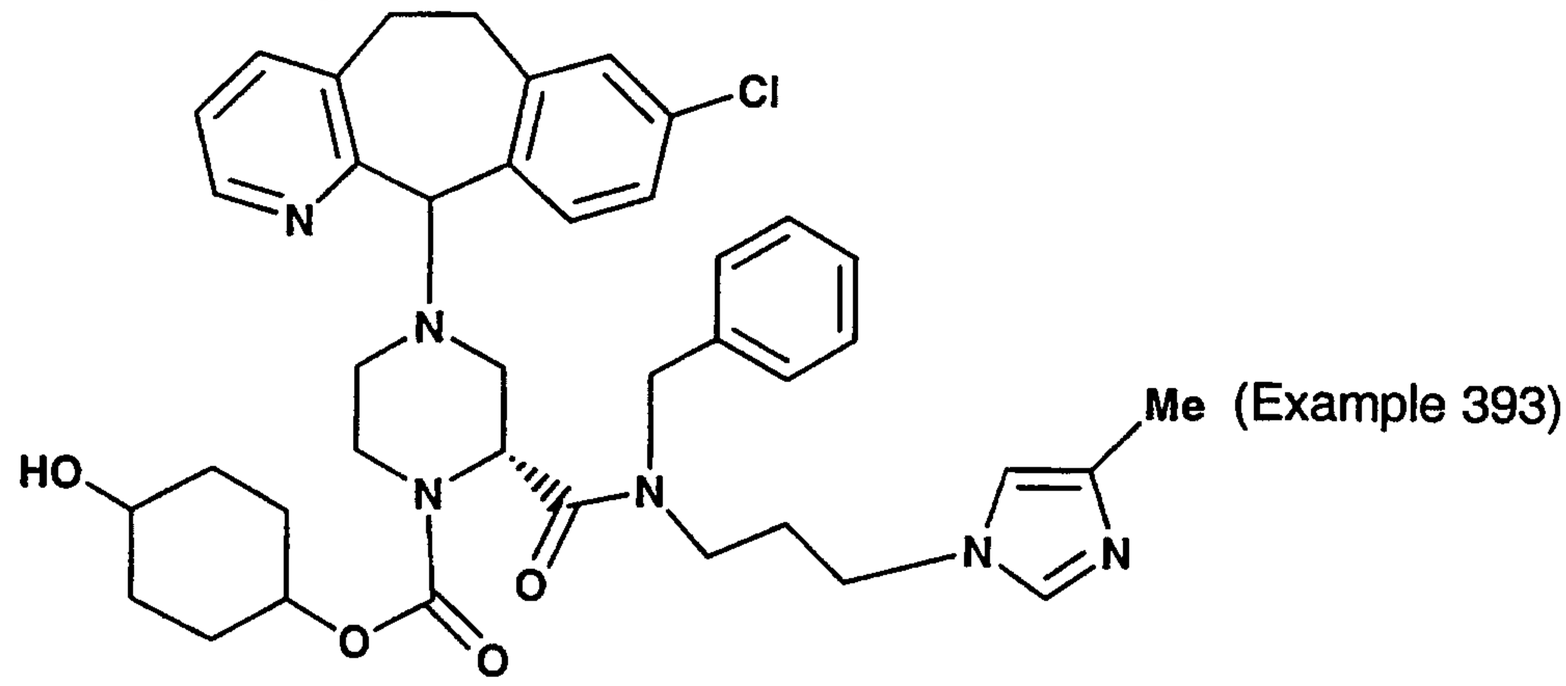
(Example 327)

24. A compound of the formula:



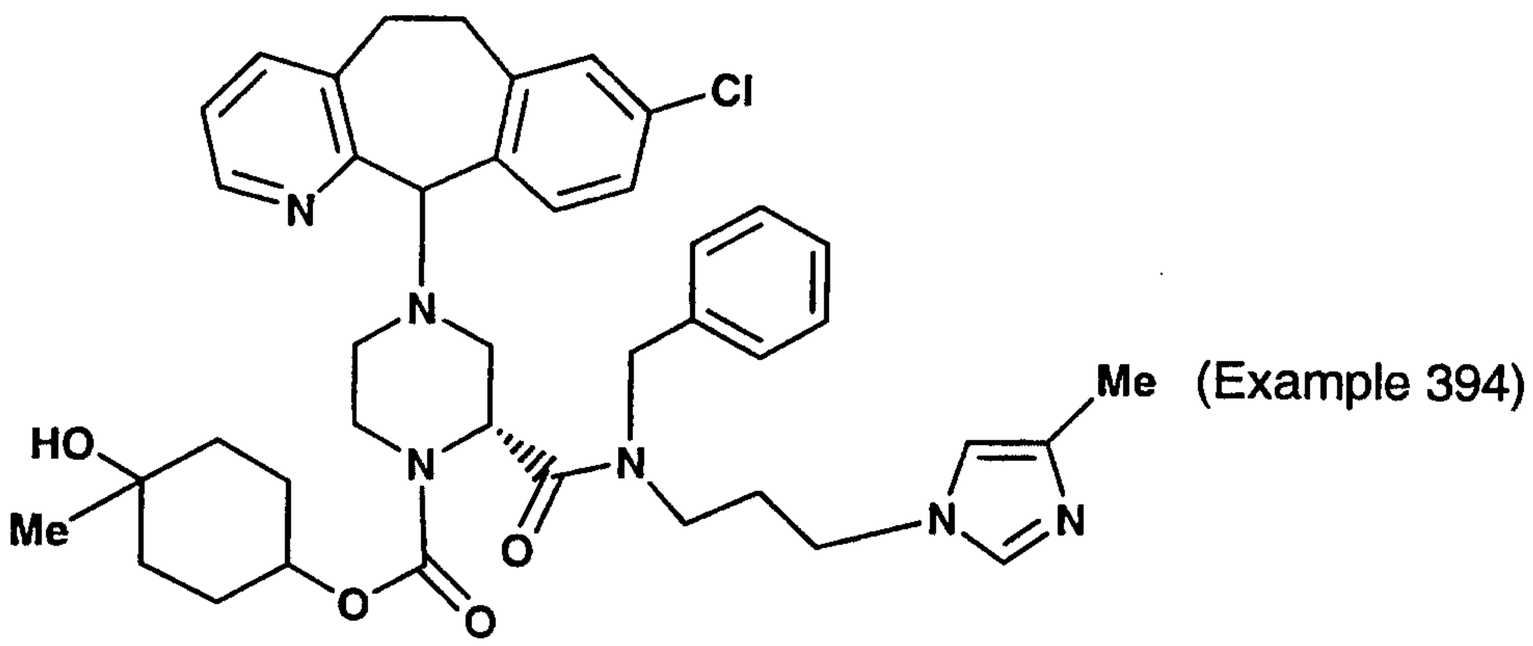
(Example 225)

25. A compound of the formula:



(Example 393)

or



(Example 394)

26. The compound of Claim 1 selected from a compound of Example 1-22, 25, 45-66, 77, 78 Step B, 79, 80, 82-85, 86, 86A, 87-97, 99, 100, 102, 112-208, 208A, 209, 209A, 210, 210A, 210B, 211-220, 220A, 221-232, 234B, 234C, 234E, 235-254, 286A, 286B, 304-308, 310-342, 343-366, 367-373 or 375-382.

27. A compound selected from a compound of Example 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 81, 98, 101, 103, 104, 105, 106, 107, 108, 110, 111, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 285, 286, 287, 289, 290, 291, 292, 293, 294, 295, 296, 297 299, 300, 301, 302, 303 or 309.

28. A method of treating tumor cells comprising administering an effective amount of a compound of any of Claims 1-27.

29. The method of Claim 28 wherein the tumor cells treated are pancreatic tumor cells, lung cancer cells, myeloid leukemia tumor cells, thyroid follicular tumor cells, myelodysplastic tumor cells, epidermal carcinoma tumor cells, bladder carcinoma tumor cells, colon tumors cells, melanoma, breast tumor cells and prostate tumor cells.

30. A method of treating tumor cells wherein the Ras protein is activated as a result of oncogenic mutation in genes other than the Ras gene, comprising administering an effective amount of a compound of any of Claims 1-27.

31. A method of inhibiting farnesyl protein transferase comprising the administration of an effective amount of a compound of any of Claims 1-27.

32. A pharmaceutical composition for inhibiting farnesyl protein transferase comprising an effective amount of a compound of any of Claims 1-27 in combination with a pharmaceutically acceptable carrier.

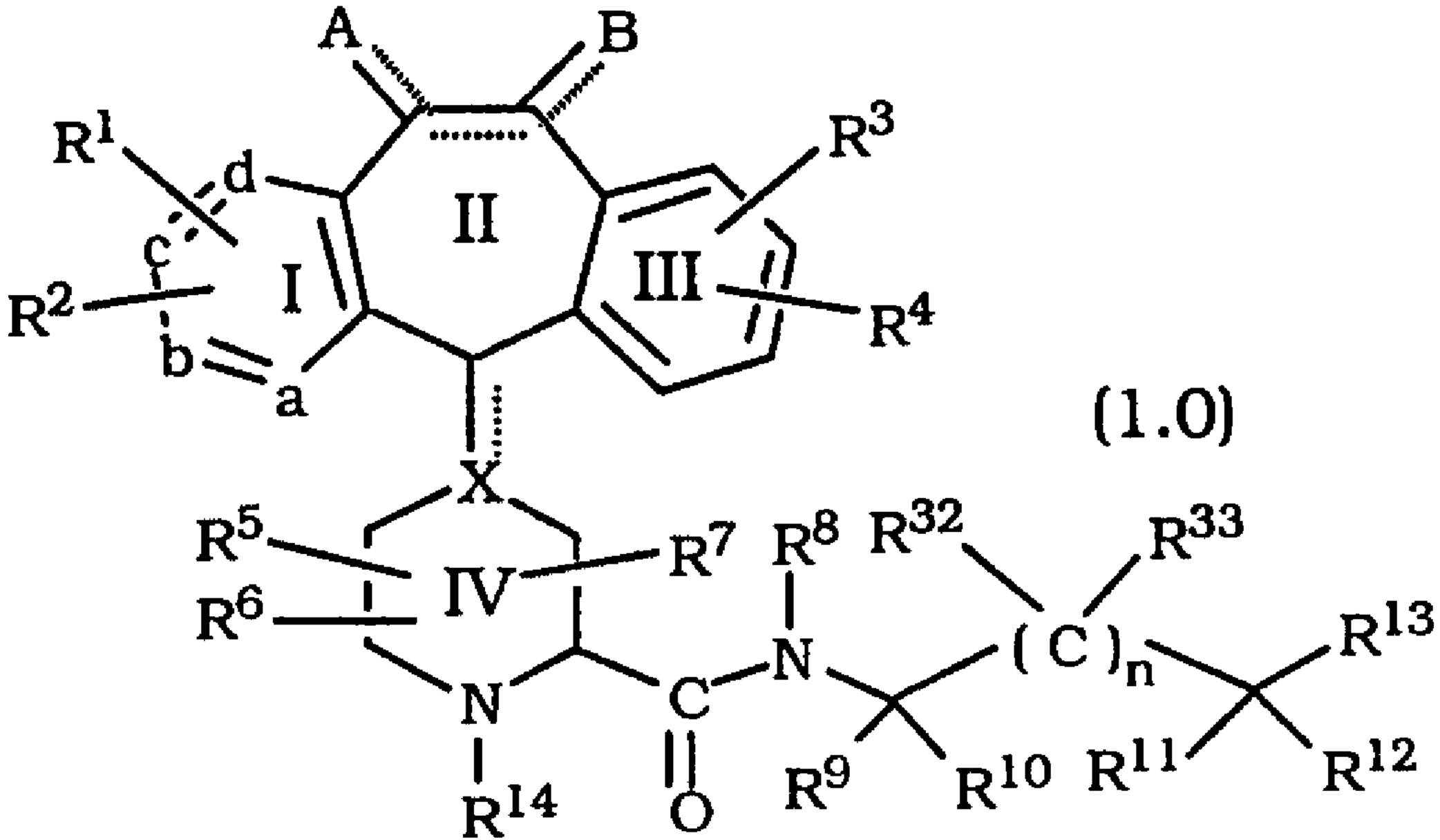
33. A use of a compound of any of Claims 1-27 for the manufacture of a medicament for inhibiting farnesyl protein transferase.

34. A use of a compound of any of Claims 1-27 for the manufacture a medicament for treating pancreatic tumor cells, lung cancer cells, myeloid leukemia tumor cells, thyroid follicular tumor cells, myelodysplastic tumor cells, epidermal carcinoma tumor cells,

bladder carcinoma tumor cells, colon tumors cells, melanoma, breast tumor cells and prostate tumor cells.

35. A use of a compound of any of Claims 1-27 for inhibiting farnesyl protein transferase.

36. A use of a compound of any of Claims 1-27 for treating pancreatic tumor cells, lung cancer cells, myeloid leukemia tumor cells, thyroid follicular tumor cells, myelodysplastic tumor cells, epidermal carcinoma tumor cells, bladder carcinoma tumor cells, colon tumors cells, melanoma, breast tumor cells and prostate tumor cells.


A
B
R1
d
R3
c
II
I
III
R2
R4
b
a
X
R5
R7
R8
R32
R33
R6
IV
N
C
N
(C)n
R13
N
C
R9
R10
R11
R12
R14
O

(1.0)