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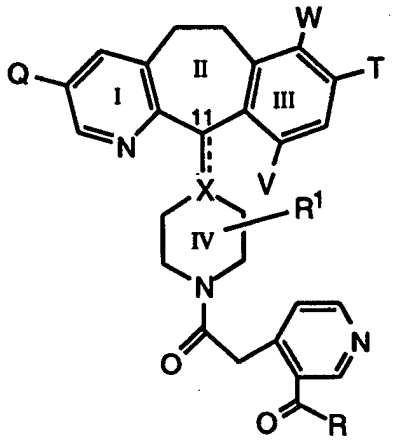
(57) Abstract

Compounds of formula (I) useful for inhibiting Ras function and therefore inhibiting or treating the abnormal growth of cells (farnesyl protein transferase inhibitors) are disclosed or an N–oxide thereof, or a pharmaceutically acceptable salt or solvate thereof, wherein: Q and T are independently selected from halo; W and V are independently selected from H and halo, provided that at least one of W and V is H; R^1 is H or alkyl; X represents N, CH, or C when the double bond is present at the C–11 position; R is $-OR^3$, $-NR^3R^4$ or $-SR^3$; and R^3 and R^4 are independently selected from the group consisting of H, alkyl, arylalkyl, substituted arylalkyl, heteroarylalkyl and substituted heteroarylalkyl.



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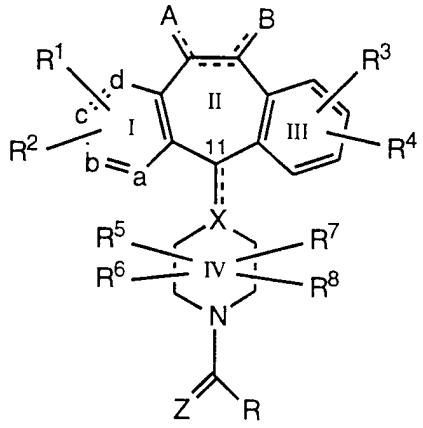
CARBOXY PIPERIDYLACETAMIDE TRICYCLIC COMPOUNDS USEFUL FOR INHIBITION OF G-PROTEIN FUNCTION AND FOR TREATMENT OF PROLIFERATIVE DISEASES (FARNESYL PROTEIN TRANSFERASE INHIBITORS)

BACKGROUND

International Publications Numbers WO95/10516, published April 20, 1995, and WO96/30363, published October 3, 1996, disclose compounds of the formula:



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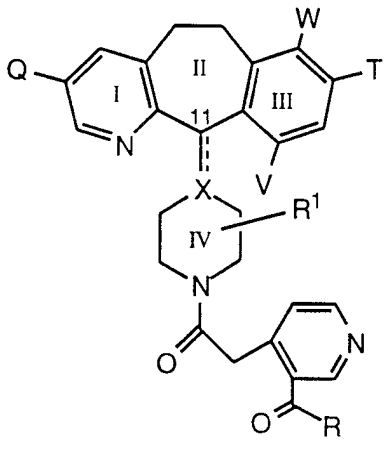
wherein R can be pyridylmethyl or an N-oxide thereof; optional substitution on the pyridyl ring is disclosed. The compounds are said to be useful for inhibiting farnesyl protein transferase.

SUMMARY OF THE INVENTION

Compounds of the present invention are represented by Formula I:



I

or an N-oxide thereof, or a pharmaceutically acceptable salt or solvate thereof, wherein:

Q and T are independently selected from halo;

W and V are independently selected from H and halo, provided that at least one of W and V is H;

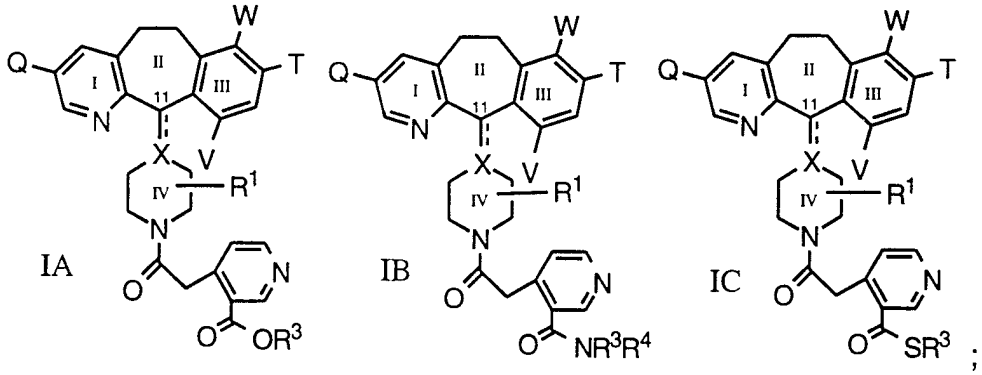
R^1 is H or alkyl;

X represents N, CH, or C when the double bond is present at the C-11 position;

R is $-OR^3$, $-NR^3R^4$ or $-SR^3$; and

R^3 and R^4 are independently selected form the group consisting of H, alkyl, arylalkyl, substituted arylalkyl, heteroarylalkyl and substituted heteroarylalkyl.

Representative compounds of the invention are shown in the following formulas:



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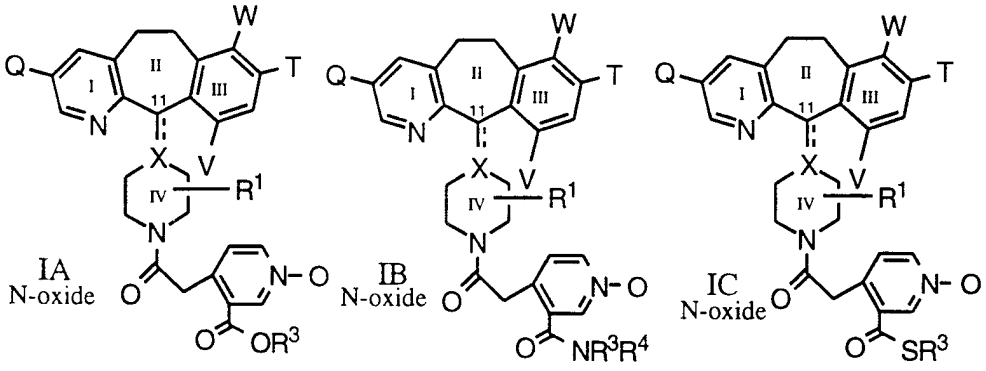
N-Oxides of formulas IA, IB and IC are represented by the following structures:



Compounds of formula I can also form an N-oxide at the pyridinyl ring designated ring I in the tricyclic portion of the structure, and can also form di-oxides, wherein the pyridinyl ring in the tricyclic portion and the pendant pyridyl ring are both N-oxides.

For each of the structures IA, IB, IC and the corresponding N-oxides, preferably Q is Br, T is halo and W is halo; or Q is Br, T is halo and V is halo; or Q is Br, T is halo and W and V are each H. T is preferably Br or Cl. When W or V is halo, it is preferably Br or Cl. X is preferably N or CH. R^1 is preferably H.

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. This invention further provides a method of inhibiting 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, breast cancer, prostate cancer, 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 and epidermal carcinoma.

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;

Bu represents butyl; Et represents ethyl; Me represents methyl; Ph represents phenyl;

alkyl (including the alkyl portions of alkoxy, alkylamino and dialkylamino) represents straight and branched carbon chains and contains from one to twenty carbon atoms, preferably one to six carbon atoms;

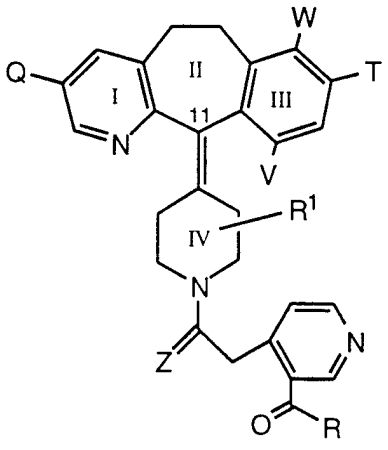
aryl (including the aryl portion of aryloxy and aralkyl) represents a carbocyclic group containing from 6 to 15 carbon atoms and having at least one aromatic ring (e.g., aryl is a phenyl ring), with all available substitutable carbon atoms of the carbocyclic group being intended as possible points of attachment, said carbocyclic group being optionally substituted (e.g., 1 to 3) with one or more of halo, alkyl, hydroxy, alkoxy, phenoxy, CF_3, amino, alkylamino, dialkylamino, -$COOR^{10}$, wherein R^{10} is H, alkyl, aryl or aralkyl (e.g., benzyl), or -NO_2;

halo represents fluoro, chloro, bromo and iodo; and

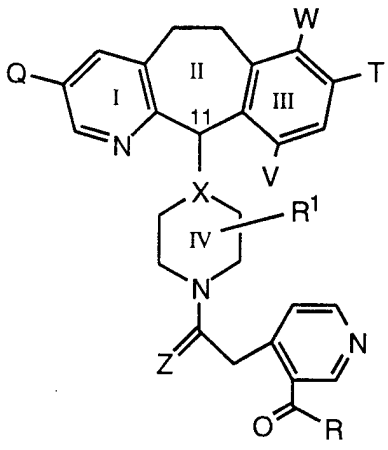
heteroaryl represents cyclic groups, optionally substituted as defined above for aryl, having at least one heteroatom selected from O, S or N, said heteroatom interrupting a carbocyclic ring structure and having a sufficient number of delocalized pi electrons to provide aromatic character, with the aromatic heterocyclic groups preferably containing from 2 to 14 carbon atoms, e.g., triazolyl, 2-, 3- or 4-pyridyl or pyridyl N-oxide.

The following solvents and reagents may be referred to herein by the abbreviations indicated: tetrahydrofuran (THF); ethanol (EtOH); methanol (MeOH); acetic acid (HOAc or AcOH); ethyl acetate (EtOAc); N,N-dimethylformamide (DMF); trifluoroacetic acid (TFA); trifluoroacetic anhydride (TFAA); 1-hydroxybenzotriazole (HOBT); m-chloroperbenzoic acid (MCPBA); triethylamine (Et_3N); diethyl ether (Et_2O); ethyl chloroformate ($ClCO_2Et$); and 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (DEC).

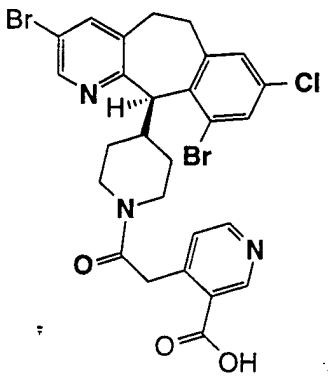
Representative structures of Formula I with respect to X and the optional double bond are as follows:



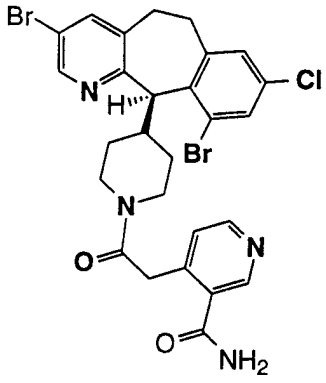
and



Representative compounds of the invention include:



and



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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 and diastereoisomers) forms. The invention contemplates all such isomers both in pure form and in admixture, including racemic mixtures. Enol forms are also included.

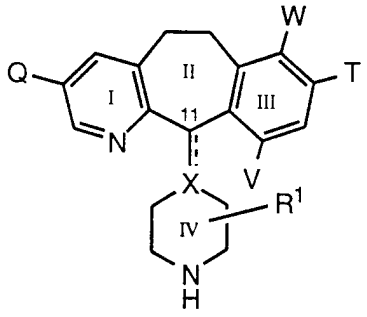
Certain tricyclic compounds will be acidic in nature, e.g. those compounds which possess a carboxyl or phenolic hydroxyl group. These compounds may form pharmaceutically acceptable salts. Examples of such salts may include sodium, potassium, calcium, aluminum, gold and silver salts. Also contemplated 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 purpopses of the invention.

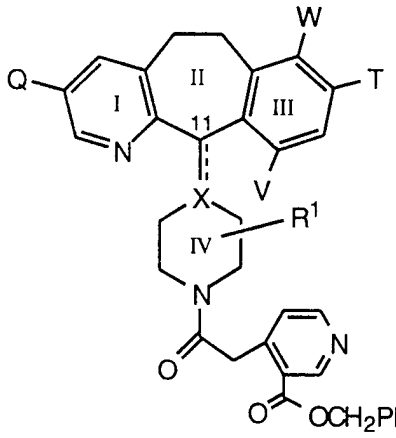
Compounds of the invention may be made by the methods described in the examples below, and by the methods described in WO 95/10516 -- see, for example, the methods for preparing compounds of Formula 400.00 -- and in WO 96/30363.

Compounds of the invention can be prepared by reacting a compound of the formula:



II

wherein all substituents are as defined for Formula I, with lithium 3-(benzyloxycarbonyl)-pyridylacetate under standard coupling conditions e.g., at room temperature in a solvent such as DMF and in the presence of coupling agents such as DEC, HOBT and N-methylmorpholine, to produce a compound of the formula:



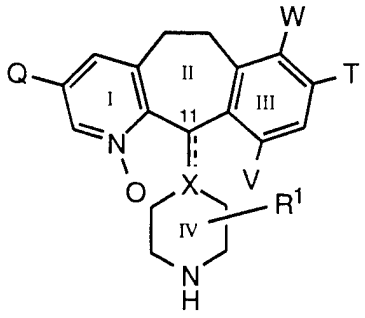
Ia

Compounds of formula Ia can be converted to other compounds of formula I by methods well known in the art. For example, the benzyl group can be removed by treatment with trimethylsilyl iodide to obtain the corresponding carboxy-substituted compound (i.e., compounds of formula IA wherein R^3 is H). A carboxy-substituted compound can be reacted with an amine under standard coupling conditions to obtain an amide (i.e., compounds of formula IB), or can be esterified under standard conditions

to obtain corresponding compounds of formula IA wherein R^3 is alkyl. Similarly, a carboxy-substituted compound can be reacted with a suitable base (e.g., K_2CO_3) and either an aralkyl halide or a heteroaralkyl halide in a solvent such as DMF to obtain the corresponding aralkyl or heteroaraklyl esters. Aryl esters can be prepared by condensing the appropriate phenol or phenoxide with the carboxy compound and a suitable coupling agent. Thioesters can be prepared, for example, by reacting the carboxy-substituted compound with diethylcyanophosphonate, Et_3N and the appropriate thiol as described in J. Org. Chem., 39, 22 (1974), p. 3302-3303.

N-oxide compounds of formulas IA to IC can be prepared by coupling compounds of formula II with lithium 3-(benzyloxycarbonyl)-pyridyl N-oxide acetate (prepared by MCPBA oxidation of lithium 3-(benzyloxycarbonyl)-pyridylacetate using a procedure similar to that decribed below).

Compounds of formula I comprising a pyridyl N-oxide in ring I of the tricyclic portion can be prepared by procedures well known in the art. For example, the compound of formula II protected at the piperidyl nitrogen with a BOC group can be reacted with MCPBA in a suitable organic solvent, e.g., CH_2Cl_2, at a suitable temperature, followed by acid hydrolysis of the BOC protecting group, to obtain an N-oxide of formula IIa



IIa

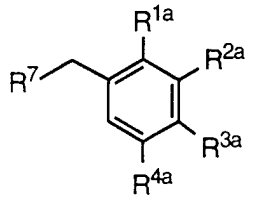
Generally, the organic solvent solution of formula II is cooled to about 0°C before the MCPBA is added. The reaction is then allowed to warm to room temperature during the reaction period. The desired product can be recovered by standard separation means, for example, the reaction mixture can be washed with an aqueous solution of a suitable base, e.g., saturated $NaHCO_3$ or NaOH (e.g., i N NaOH), and then dried over anhydrous $MgSO_4$. The solution containing the product can be concentrated in vacuo, and the product can be purified by standard means, e.g., by chromatography using silica gel (e.g., flash column chromatography).

If a compound of formula I comprising pyridyl groups in ring I and in the pendant ring is treated with MCPBA as described above, di-N-oxides will be prepared.

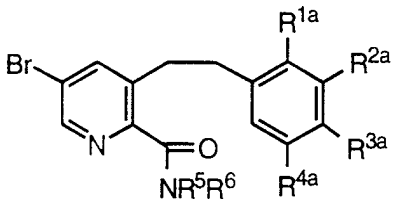
Compounds of formula II are prepared by methods known in the art, for example by methods disclosed in WO 95/10516, in U.S. 5,151,423 and those described below. Compounds of formula II wherein the C-3 postion of the pyridine ring in the tricyclic structure is substituted by bromo can also be prepared by a procedure comprising the following steps:

(a) reacting an amide of the formula

wherein R^{11} is Br, R^5 is hydrogen and R^6 is C_1-C_6 alkyl, aryl or heteroaryl; R^5 is C_1-C_6 alkyl, aryl or heteroaryl and R^6 is hydrogen; R^5 and R^6 are independently selected from the group consisting of C_1-C_6 alkyl and aryl; or R^5 and R^6, together with the nitrogen to which they are attached, form a ring comprising 4 to 6 carbon atoms or comprising 3 to 5 carbon atoms and one hetero moiety selected from the group consisting of -O- and -NR^9-, wherein R^9 is H, C_1-C_6 alkyl or phenyl;
with a compound of the formula

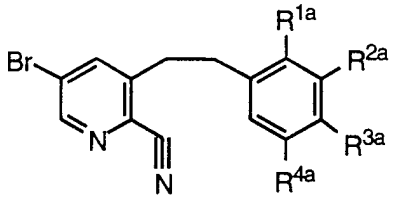


wherein R^{1a}, R^{2a}, R^{3a} and R^{4a} are are independently selected from the group consisting of hydrogen and halo and R^7 is Cl or Br, in the presence of a strong base to obtain a compound of the formula



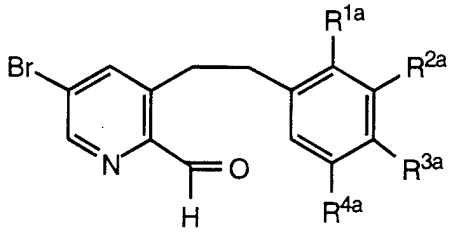
(b) reacting a compound of step (a) with

(i) $POCl_3$ to obtain a cyano compound of the formula

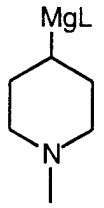


; or

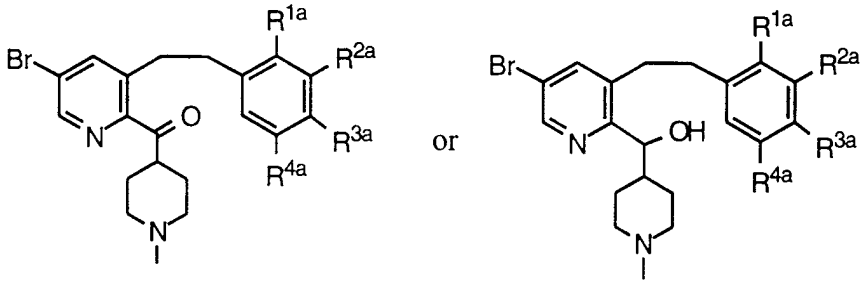
(ii) DIBALH to obtain an adlehyde of the formula



(c) reacting the cyano compound or the aldehyde with a piperidine derivative of the formula



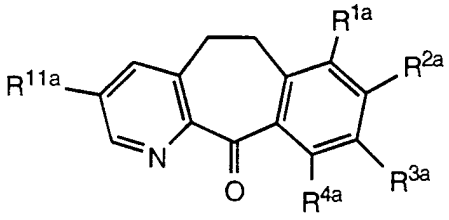
wherein L is a leaving group selected from the group consisting of Cl and Br, to obtain an aldehyde or an alcohol of the formula below, respectively:



(d)(i) cyclizing the aldehyde with CF_3SO_3H to obtain a compound of formula II wherein the dotted line represents a double bond; or

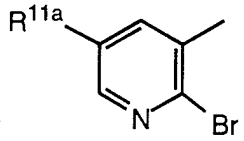
(d)(ii) cyclizing the alcohol with polyphosphoric acid to obtain a compound of formula II wherein the dotted line represents a single bond.

Methods for preparing compounds of formula II disclosed in WO 95/10516, U.S. 5,151,423 and described below employ a tricyclic ketone intermediate. Such intermediates of formula IV

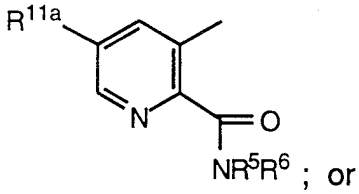


wherein R^{11a}, R^{1a}, R^{2a}, R^{3a} and R^{4a} are independently selected from the group consisting of hydrogen and halo, can be prepared by the following process comprising :

(a) reacting a compound of the formula

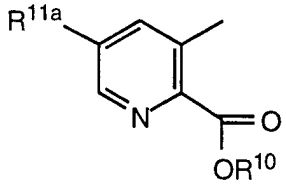


(i) with an amine of the formula NHR^5R^6, wherein R^5 and R^6 are as defined in the process above; in the presence of a palladium catalyst and carbon monoxide to obtain an amide of the formula:



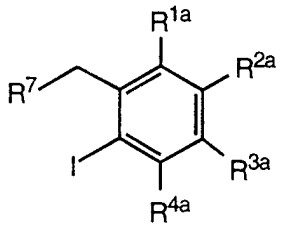
; or

(ii) with an alcohol of the formula $R^{10}OH$, wherein R^{10} is C_1-C_6 lower alkyl or C_3-C_6 cycloalkyl, in the presence of a palladium catalyst and carbon monoxide to obtain the ester of the formula

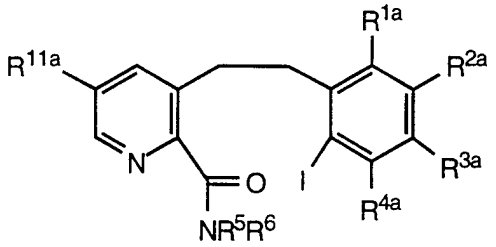


followed by reacting the ester with an amine of formula NHR^5R^6 to obtain the amide;

(b) reacting the amide with an iodo-substituted benzyl compound of the formula



wherein R^{1a}, R^{2a}, R^{3a}, R^{4a} and R^7 are as defined above, in the presence of a strong base to obtain a compound of the formula



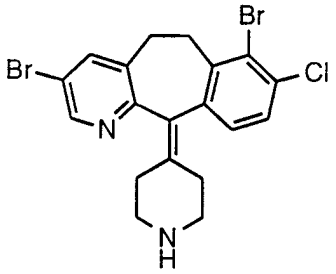
;

(c) cyclizing a compound of step (b) with a reagent of the formula R^8MgL, wherein R^8 is C_1-C_8 alkyl, aryl or heteroaryl and L is Br or Cl, provided that prior to cyclization, compounds wherein R^5 or R^6 is hydrogen are reacted with a suitable N-protecting group.

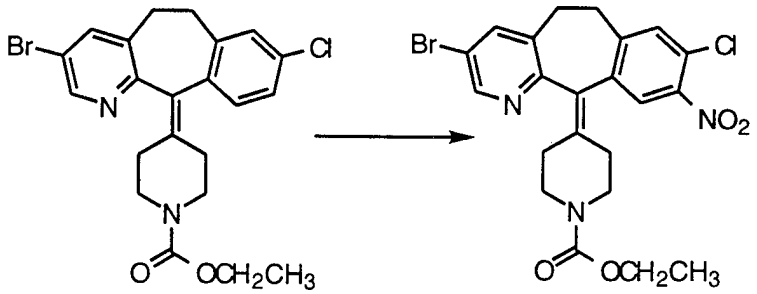
(+)-Isomers of compounds of formula II wherein X is CH can be prepared with high enantioselectivity by using a process comprising enzyme catalyzed transesterification. Preferably, a racemic compound of formula II, wherein X is C, the double bond is present and V is not H, is reacted with an enzyme such as Toyobo LIP-300 and an acylating agent such as trifluoroethly isobutyrate; the resultant (+)-amide is then hydrolyzed, for example by refluxing with an acid such as H_2SO_4, to obtain the corresponding optically enriched (+)-isomer wherein X is CH and V is not H. Alternatively, a racemic compound of formula II, wherein X is C, the double bond is present and V is not H, is first reduced to the corresponding racemic compound of formula II wherein X is CH and then treated with the enzyme (Toyobo LIP-300) and acylating agent as described above to obtain the (+)-amide, which is hydrolyzed to obtain the optically enriched (+)-isomer.

Compounds useful in this invention are exemplified by the following preparative examples, which should not be construed to limit the scope of the disclosure. Alternative mechanistic pathways and analogous structures within the scope of the invention may be apparent to those skilled in the art.

PREPARATIVE EXAMPLE 1



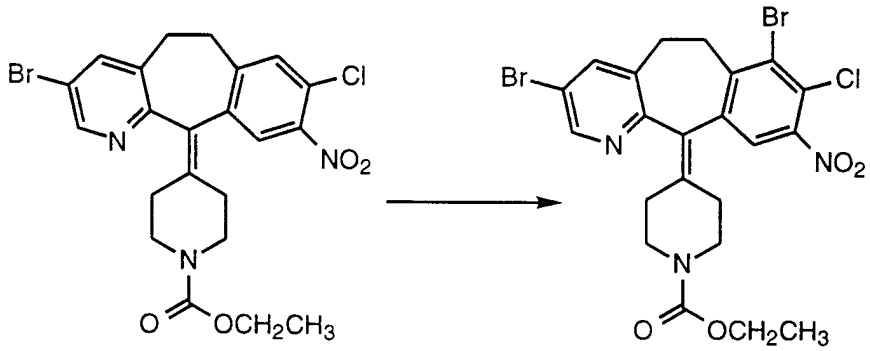
Step A:



Combine 25.86 g (55.9 mmol) of 4-(8-chloro-3-bromo-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)-1-piperidine-1-carboxylic acid ethyl ester and 250 mL of concentrated H_2SO_4 at -5°C, then add 4.8 g (56.4 mmol) of $NaNO_3$ and stir for 2 hours. Pour the mixture into 600 g of ice and basify with concentrated NH_4OH (aqueous). Filter the mixture, wash with 300 mL of water, then extract with 500 mL of CH_2Cl_2. Wash the extract with 200 mL of water, dry over $MgSO_4$, then filter and concentrate *in vacuo* to a residue. Chromatograph the residue (silica gel, 10% EtOAc/ CH_2Cl_2) to give 24.4 g (86% yield) of the product. m.p. = 165-167°C, Mass Spec.: MH^+ = 506, 508 (Cl).

elemental analysis: calculated - C, 52.13; H, 4.17; N, 8.29
found - C, 52.18; H, 4.51; N, 8.16

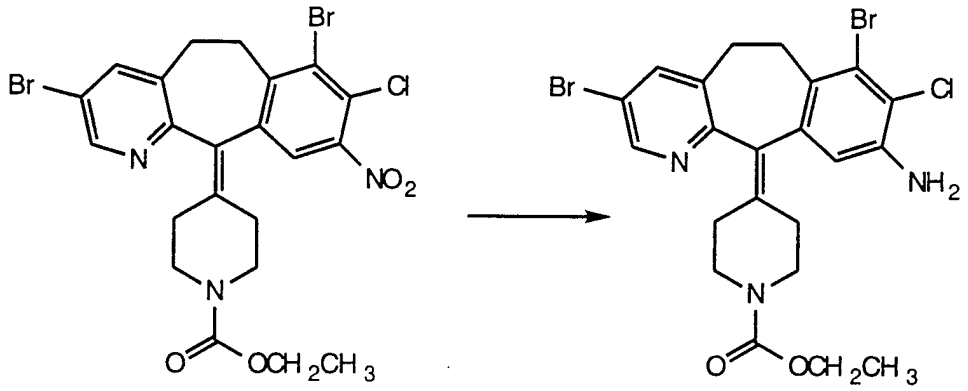
Step B:



Combine 20 g (40.5 mmol) of the product of Step A and 200 mL of concentrated H_2SO_4 at 20°C, then cool the mixture to 0°C. Add 7.12 g (24.89 mmol) of 1,3-dibromo-5,5-dimethyl-hydantoin to the mixture and stir for 3 hours at 20°C. Cool to 0°C, add an additional 1.0 g (3.5 mmol) of the dibromohydantoin and stir at 20°C for 2 hours. Pour the mixture into 400 g of ice, basify with concentrated NH_4OH (aqueous) at 0°C, and collect the resulting solid by filtration. Wash the solid with 300 mL of water, slurry in 200 mL of acetone and filter to provide 19.79 g (85.6% yield) of the product. m.p. = 236-237°C, Mass Spec.: MH^+ = 586 (Cl).

elemental analysis: calculated - C, 45.11; H, 3.44; N, 7.17
found - C, 44.95; H, 3.57; N, 7.16

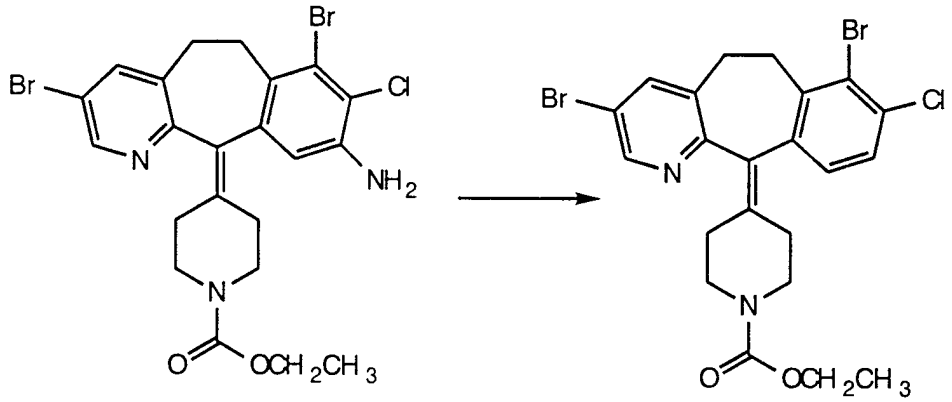
Step C:



Combine 25 g (447 mmol) of Fe filings, 10 g (90 mmol) of $CaCl_2$ and a suspension of 20 g (34.19 mmol) of the product of Step B in 700 mL of 90:10 EtOH/water at 50°C. Heat the mixture at reflux overnight, filter through Celite® and wash the filter cake with 2 X 200 mL of hot EtOH. Combine the filtrate and washes, and concentrate *in vacuo* to a residue. Extract the residue with 600 mL of CH_2Cl_2, wash with 300 mL of water and dry over $MgSO_4$. Filter and concentrate *in vacuo* to a residue, then chromatograph (silica gel, 30% EtOAc/CH_2Cl_2) to give 11.4 g (60% yield) of the product. m.p. = 211-212°C, Mass Spec.: MH^+ = 556 (Cl).

elemental analysis: calculated - C, 47.55; H, 3.99; N, 7.56
found - C, 47.45; H, 4.31; N, 7.49

Step D:

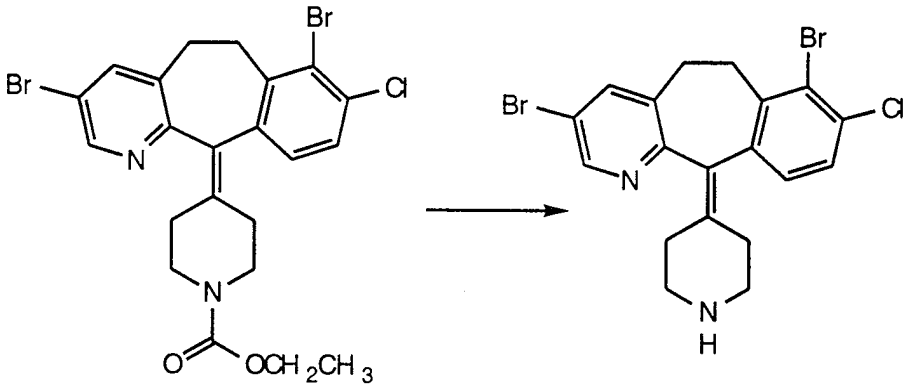


Slowly add (in portions) 20 g (35.9 mmol) of the product of Step C to a solution of 8 g (116 mmol) of $NaNO_2$ in 120 mL of concentrated HCl (aqueous) at -10°C. Stir the resulting mixture at 0°C for 2 hours, then slowly add (dropwise) 150 mL (1.44 mole) of 50% H_3PO_2 at 0°C over a 1 hour period. Stir at 0°C for 3 hours, then pour into 600 g of ice and basify with concentrated NH_4OH (aqueous). Extract with 2 X 300 mL of CH_2Cl_2, dry the extracts over $MgSO_4$, then filter and concentrate *in vacuo* to a residue. Chromatograph the residue (silica gel, 25% EtOAc/ hexanes) to

give 13.67 g (70% yield) of the product. m.p. = 163-165°C, Mass Spec.: MH^+ = 541 (CI).

elemental analysis: calculated - C, 48.97; H, 4.05; N, 5.22
found - C, 48.86; H, 3.91; N, 5.18

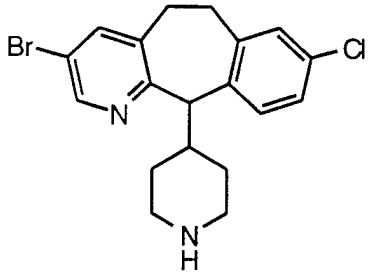
Step E:



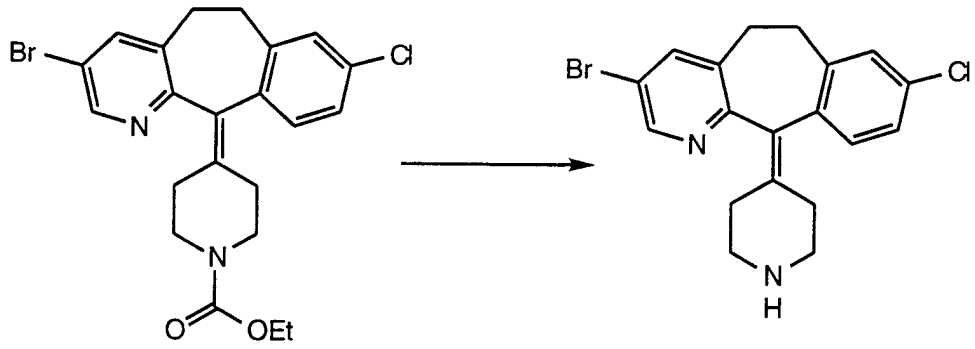
Combine 6.8 g (12.59 mmol) of the product of Step D and 100 mL of concentrated HCl (aqueous) and stir at 85°C overnight. Cool the mixture, pour it into 300 g of ice and basify with concentrated NH_4OH (aqueous). Extract with 2 x 300 mL of CH_2Cl_2, then dry the extracts over $MgSO_4$. Filter, concentrate *in vacuo* to a residue, then chromatograph (silica gel, 10% MeOH/EtOAc + 2% NH_4OH (aq.)) to give 5.4 g (92% yield) of the title compound. m.p. = 172-174°C, Mass Spec.: MH^+ = 469 (FAB).

elemental analysis: calculated - C, 48.69; H, 3.65; N, 5.97
found - C, 48.83; H, 3.80; N, 5.97

PREPARATIVE EXAMPLE 2

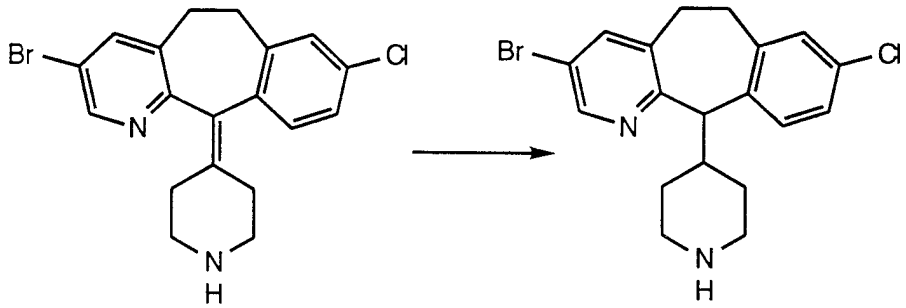


Step A:



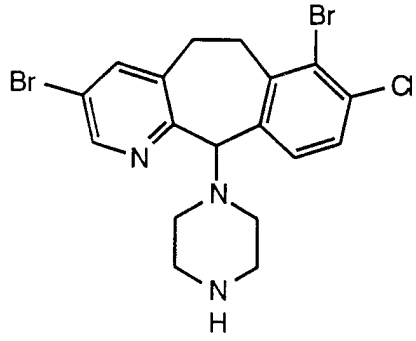
Hydrolyze 2.42 g of 4-(8-chloro-3-bromo-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)-1-piperidine-1-carboxylic acid ethyl ester by dissolving in concentrated HCl and heating to about 100°C for @ 16 hours. Cool the mixture, the neutralize with 1 M NaOH (aqueous). Extract with CH_2Cl_2, dry the extracts over $MgSO_4$, filter and concentrate *in vacuo* to give 1.39 g (69% yield) of the product.

Step B:



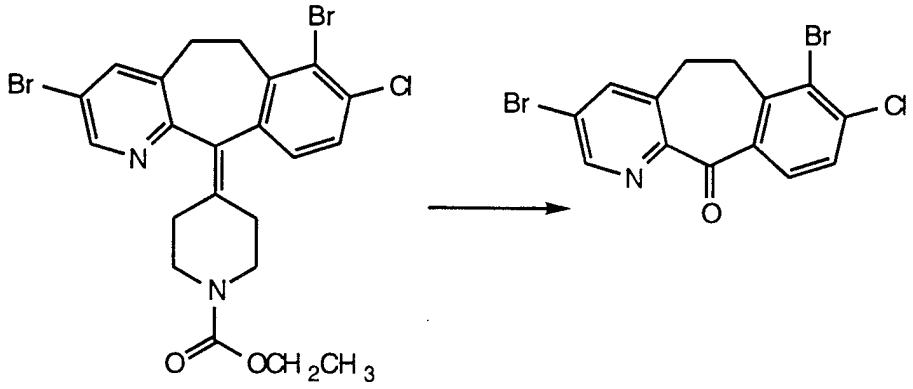
Combine 1 g (2.48 mmol) of the product of Step A and 25 mL of dry toluene, add 2.5 mL of 1 M DIBAL in toluene and heat the mixture at reflux. After 0.5 hours, add another 2.5 mL of 1 M DIBAL in toluene and heat at reflux for 1 hour. (The reaction is monitored by TLC using 50% MeOH/ CH_2Cl_2 +NH_4OH (aqueous).) Cool the mixture to room temperature, add 50 mL of 1 N HCl (aqueous) and stir for 5 min. Add 100 mL of 1 N NaOH (aqueous), then extract with EtOAc (3 X 150 mL). Dry the extracts over $MgSO_4$, filter and concentrate *in vacuo* to give 1.1 g of the title compound.

PREPARATIVE EXAMPLE 3



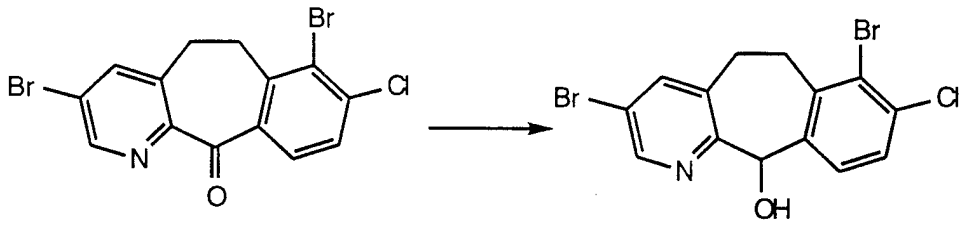
[racemic as well as (+)- and (-)-isomers]

Step A:



Combine 16.6 g (0.03 mole) of the product of Preparative Example 1, Step D, with a 3:1 solution of CH_3CN and water (212.65 mL CH_3CN and 70.8 mL of water) and stir the resulting slurry overnight at room temperature. Add 32.833 g (0.153 mole) of $NaIO_4$ and then 0.31 g (2.30 mmol) of RuO_2 and stir at room temperature give 1.39 g (69% yield) of the product. (The addition of RuO is accompanied by an exothermic reaction and the temperature climbs from 20° to 30°C.) Stir the mixture for 1.3 hrs. (temperature returned to 25°C after about 30 min.), then filter to remove the solids and wash the solids with CH_2Cl_2. Concentrate the filtrate *in vacuo* to a residue and dissolve the residue in CH_2Cl_2. Filter to remove insoluble solids and wash the solids with CH_2Cl_2. Wash the filtrate with water, concentrate to a volume of about 200 mL and wash with bleach, then with water. Extract with 6 N HCl (aqueous). Cool the aqueous extract to 0°C and slowly add 50% NaOH (aqueous) to adjust to pH = 4 while keeping the temperature <30°C. Extract twice with CH_2Cl_2, dry over $MgSO_4$ and concentrate *in vacuo* to a residue. Slurry the residue in 20 mL of EtOH and cool to 0°C. Collect the resulting solids by filtration and dry the solids *in vacuo* to give 7.95 g of the product. ^1H NMR ($CDCl_3$, 200 MHz): 8.7 (s, 1H); 7.85 (m, 6H); 7.5 (d, 2H); 3.45 (m, 2H); 3.15 (m, 2H).

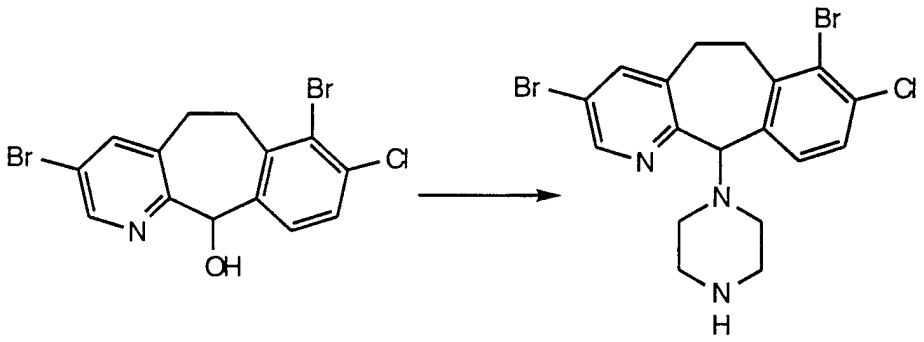
Step B:



Combine 21.58 g (53.75 mmol) of the product of Step A and 500 mL of an anhydrous 1:1 mixture of EtOH and toluene, add 1.43 g (37.8 mmol) of $NaBH_4$ and heat the mixture at reflux for 10 min. Cool the

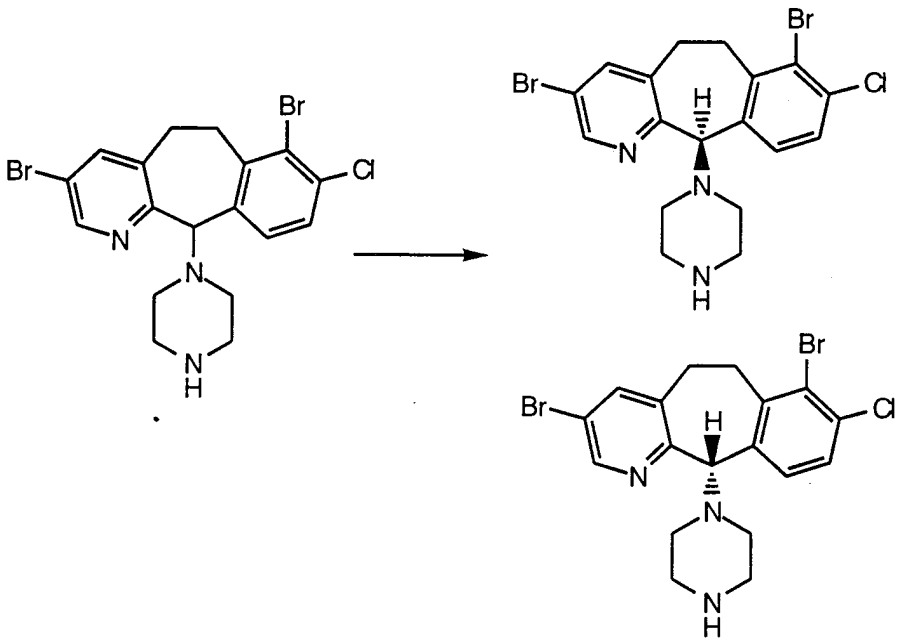
mixture to 0°C, add 100 mL of water, then adjust to pH≈ 4-5 with 1 M HCl (aqueous) while keeping the temperature <10°C. Add 250 mL of EtOAc and separate the layers. Wash the organic layer with brine (3 X 50 mL) then dry over Na_2SO_4. Concentrate *in vacuo* to a residue (24.01 g) and chromatograph the residue (silica gel, 30 % hexane/CH_2Cl_2) to give the product. Impure fractions were purified by rechromatography. A total of 18.57 g of the product was obtained. ^1H NMR (DMSO-d_6, 400 MHz): 8.5 (s, 1H); 7.9 (s, 1H); 7.5 (d of d, 2H); 6.2 (s, 1H); 6.1 (s, 1H); 3.5 (m, 1H); 3.4 (m, 1H); 3.2 (m, 2H).

Step C:



Combine 18.57 g (46.02 mmol) of the product of Step B and 500 mL of $CHCl_3$, then add 6.70 mL (91.2 mmol) of $SOCl_2$, and stir the mixture at room temperature for 4 hrs. Add a solution of 35.6 g (0.413 mole) of piperazine in 800 mL of THF over a period of 5 min. and stir the mixture for 1 hr. at room temperature. Heat the mixture at reflux overnight, then cool to room temperature and dilute the mixture with 1 L of CH_2Cl_2. Wash with water (5 X 200 mL), and extract the aqueous wash with $CHCl_3$ (3 X 100 mL). Combine all of the organic solutions, wash with brine (3 X 200 mL) and dry over $MgSO_4$. Concentrate *in vacuo* to a residue and chromatograph (silica gel, gradient of 5%, 7.5%, 10% MeOH/CH_2Cl_2 + NH_4OH) to give 18.49 g of the title compound as a racemic mixture.

Step D - Separation of Enantiomers:

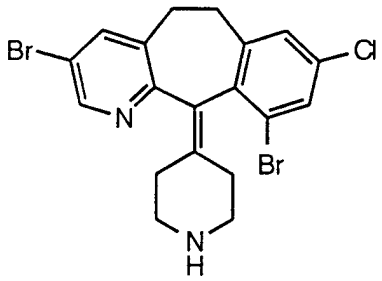


The racemic title compound of Step C is separated by preparative chiral chromatography (Chiralpack AD, 5 cm X 50 cm column, flow rate 100 mL/min., 20% iPrOH/hexane + 0.2% diethylamine), to give 9.14 g of the (+)-isomer and 9.30 g of the (-)-isomer.

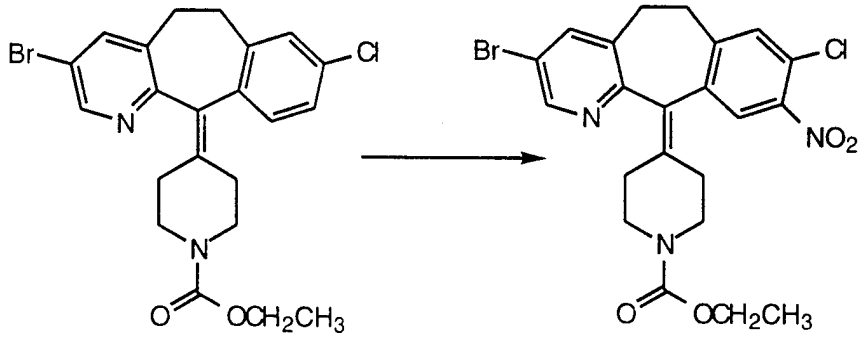
Physical chemical data for (+)-isomer: m.p. = 74.5°-77.5°C; Mass Spec. MH^+ = 471.9; $[a]_D^{25}$ = +97.4° (8.48 mg/ 2mL MeOH).

Physical chemical data for (-)-isomer: m.p. = 82.9°-84.5°C; Mass Spec. MH^+ = 471.8; $[a]_D^{25}$ = -97.4° (8.32 mg/ 2mL MeOH).

PREPARATIVE EXAMPLE 4

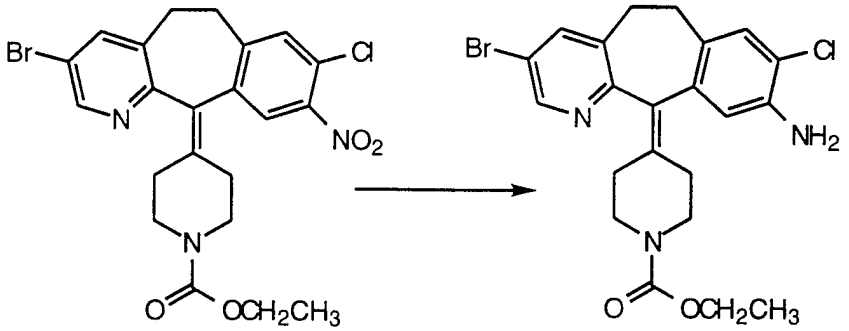


Step A:



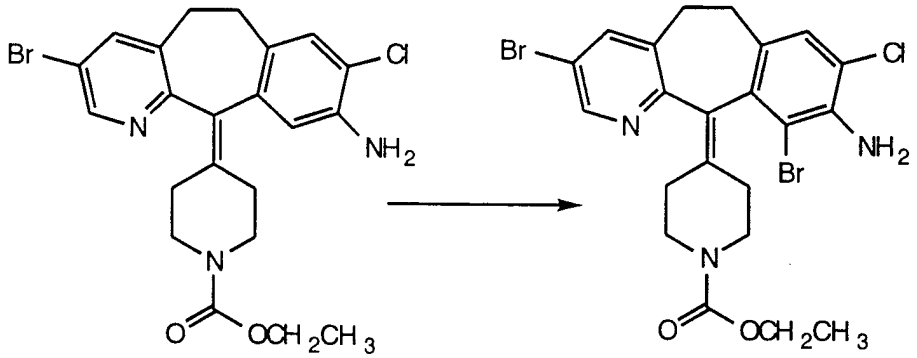
Combine 15 g (38.5 mmol) of 4-(8-chloro-3-bromo-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)-1-piperidine-1-carboxylic acid ethyl ester and 150 mL of conc. H_2SO_4 at -5°C, then add 3.89 g (38.5 mmol) of KNO_3 and stir for 4 h. Pour the mixture into 3 L of ice and basify with 50% NaOH (aqueous). Extract with CH_2Cl_2, dry over $MgSO_4$, then filter and concentrate *in vacuo* to a residue. Recrystallize the residue from acetone to give 6.69 g of the product. ^1H NMR ($CDCl_3$, 200 MHz): 8.5 (s, 1H); 7.75 (s, 1H); 7.6 (s, 1H); 7.35 (s, 1H); 4.15 (q, 2H); 3.8 (m, 2H); 3.5-3.1 (m, 4H); 3.0-2.8 (m, 2H); 2.6-2.2 (m, 4H); 1.25 (t, 3H).

Step B:



Combine 6.69 g (13.1 mmol) of the product of Step A and 100 mL of 85% EtOH/water, add 0.66 g (5.9 mmol) of $CaCl_2$ and 6.56 g (117.9 mmol) of Fe and heat the mixture at reflux overnight. Filter the hot reaction mixture through celite® and rinse the filter cake with hot EtOH. Concentrate the filtrate *in vacuo* to give 7.72 g of the product. Mass Spec.: MH^+ = 478.0

Step C:



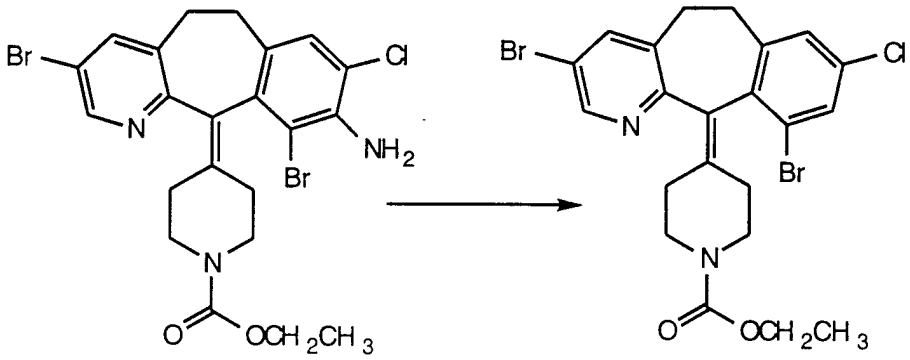
Combine 7.70 g of the product of Step B and 35 mL of HOAc, then add 45 mL of a solution of Br_2 in HOAc and stir the mixture at room temperature overnight. Add 300 mL of 1 N NaOH (aqueous) , then 75 mL of 50% NaOH (aqueous) and extract with EtOAc. Dry the extract over $MgSO_4$ and concentrate *in vacuo* to a residue. Chromatograph the residue (silica gel, 20%-30% EtOAc/hexane) to give 3.47 g of the product

(along with another 1.28 g of partially purified product).

Mass Spec.: MH^+ = 555.9.

^1H NMR ($CDCl_3$, 300 MHz): 8.5 (s, 1H); 7.5 (s, 1H); 7.15 (s, 1H); 4.5 (s, 2H); 4.15 (m, 3H); 3.8 (br s, 2H); 3.4-3.1 (m, 4H); 9-2.75 (m, 1H); 2.7-2.5 (m, 2H); 2.4-2.2 (m, 2H); 1.25 (m, 3H).

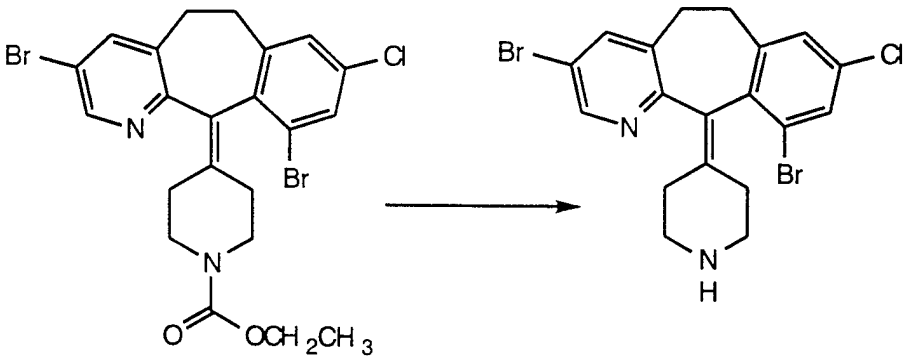
Step D:



Combine 0.557 g (5.4 mmol) of t-butylnitrite and 3 mL of DMF, and heat the mixture at to 60°-70°C. Slowly add (dropwise) a mixture of 2.00 g (3.6 mmol) of the product of Step C and 4 mL of DMF, then cool the mixture to room temperature. Add another 0.64 mL of t-butylnitrite at 40°C and reheat the mixture to 60°-70°C for 0.5 hrs. Cool to room temperature and pour the mixture into 150 mL of water. Extract with CH_2Cl_2, dry over $MgSO_4$ and concentrate *in vacuo* to a residue. Chromatograph the residue (silica gel, 10%-20% EtOAc/hexane) to give 0.74 g of the product.

Mass Spec.: MH^+ = 541.0. ^1H NMR (CDCl3, 200 MHz): 8.52 (s, 1H); 7.5 (d, 2H); 7.2 (s, 1H); 4.15 (q, 2H); 3.9-3.7 (m, 2H); 3.5-3.1 (m, 4H); 3.0-2.5 (m, 2H); 2.4-2.2 (m, 2H); 2.1-1.9 (m, 2H); 1.26 (t, 3H).

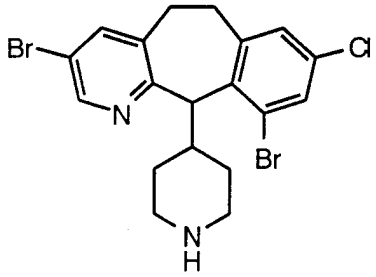
Step E:



Combine 0.70 g (1.4 mmol) of the product of Step D and 8 mL of concentrated HCl (aqueous) and heat the mixture at reflux overnight. Add 30 mL of 1 N NaOH (aqueous), then 5 mL of 50% NaOH (aqueous) and extract with CH_2Cl_2. Dry the extract over $MgSO_4$ and concentrate *in*

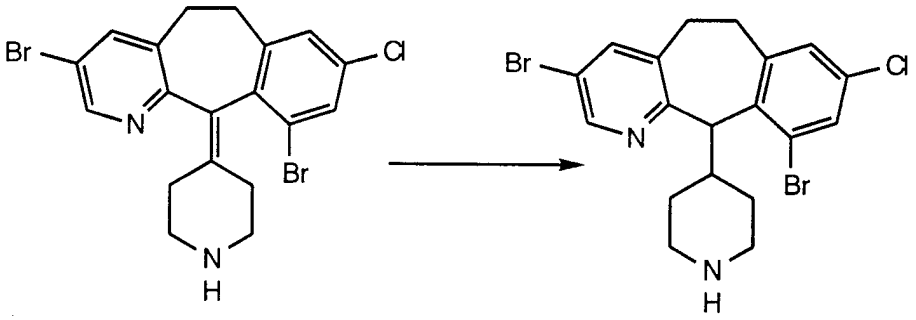
vacuo to give 0.59 g of the title compound. Mass Spec.: M^+ = 468.7. m.p. = 123.9°-124.2°C.

PREPARATIVE EXAMPLE 5



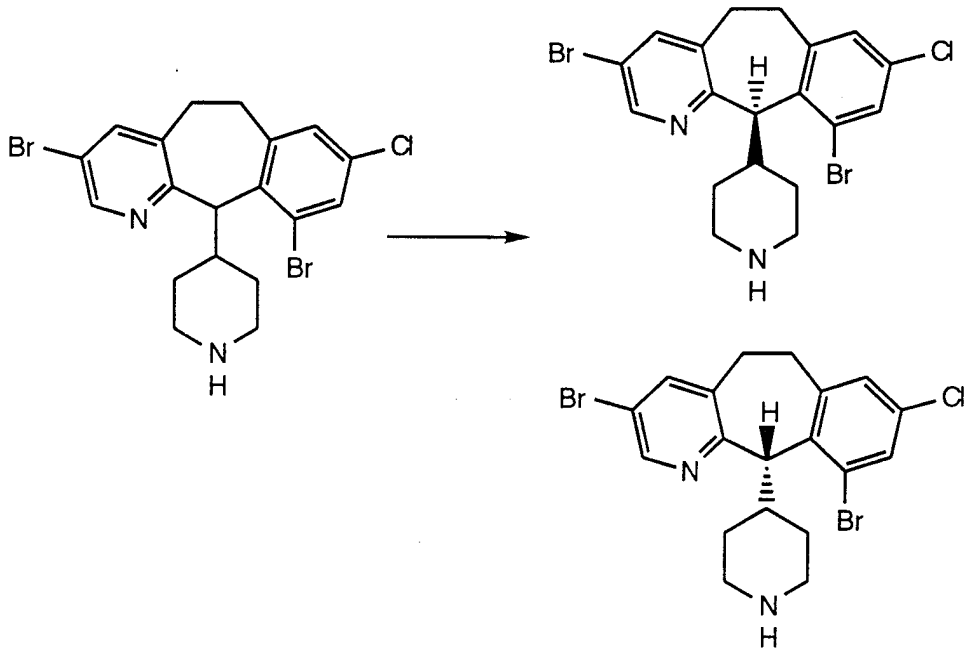
[racemic as well as (+)- and (-)-isomers]

Step A:



Prepare a solution of 8.1 g of the title compound from Preparative Example 4 in toluene and add 17.3 mL of a 1M solution of DIBAL in toluene. Heat the mixture at reflux and slowly add (dropwise) another 21 mL of 1 M DIBAL/toluene solution over a period of 40 min. Cool the reaction mixture to about 0°C and add 700 mL of 1 M HCl (aqueous). Separate and discard the organic phase. Wash the aqueous phase with CH_2Cl_2, discard the extract, then basify the aqueous phase by adding 50% NaOH (aqueous). Extract with CH_2Cl_2, dry the extract over $MgSO_4$ and concentrate *in vacuo* to give 7.30 g of the title compound, which is a racemic mixture of enantiomers.

Step B - Separation of Enantiomers:

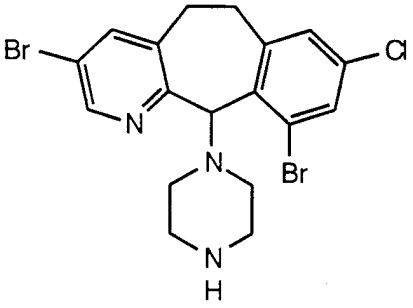


The racemic title compound of Step A is separated by preparative chiral chromatography (Chiralpack AD, 5 cm X 50 cm column, using 20% iPrOH/hexane + 0.2% diethylamine), to give the (+)-isomer and the (-)-isomer of the title compound.

Physical chemical data for (+)-isomer: m.p. = 148.8°C; Mass Spec. MH^+ = 469; $[a]_D^{25}$ = +65.6° (mg/ 2mL MeOH).

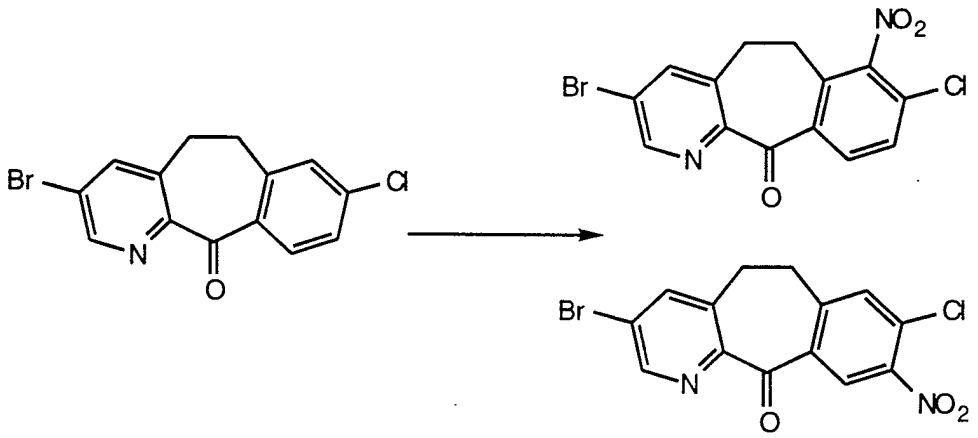
Physical chemical data for (-)-isomer: m.p. = 112°C; Mass Spec. MH^+ = 469; $[a]_D^{25}$ = -65.2° (mg/ 2mL MeOH).

PREPARATIVE EXAMPLE 6



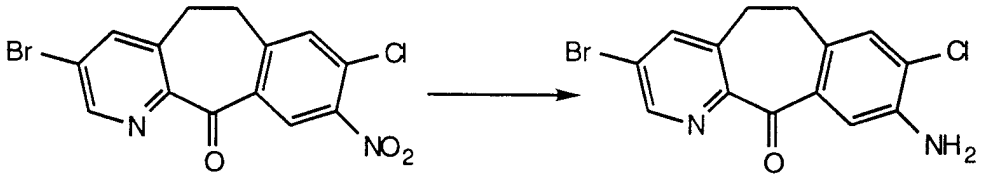
[racemic as well as (+)- and (-)-isomers]

Step A:



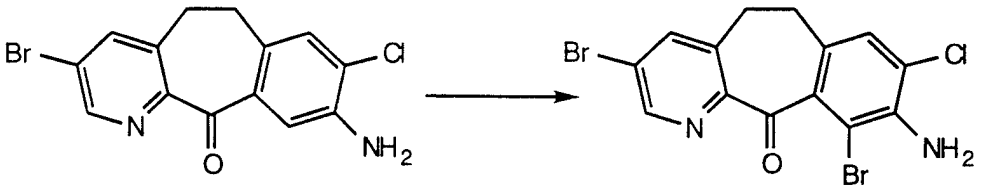
Combine 40.0 g (0.124 mole) of the starting ketone and 200 mL of H_2SO_4 and cool to 0°C. Slowly add 13.78 g (0.136 mole) of KNO_3 over a period of 1.5 hrs., then warm to room temperature and stir overnight. Work up the reaction using substantially the same procedure as described for Preparative Example 1, Step A. Chromatograph (silica gel, 20%, 30%, 40%, 50% EtOAc/hexane, then 100% EtOAc) to give 28 g of the 9-nitro product, along with a smaller quantity of the 7-nitro product and 19 g of a mixture of the 7-nitro and 9-nitro compounds.

Step B:



React 28 g (76.2 mmol) of the 9-nitro product of Step A, 400 mL of 85% EtOH/water, 3.8 g (34.3 mmol) of $CaCl_2$ and 38.28 g (0.685 mole) of Fe using substantially the same procedure as described for Preparative Example 1, Step C, to give 24 g of the product

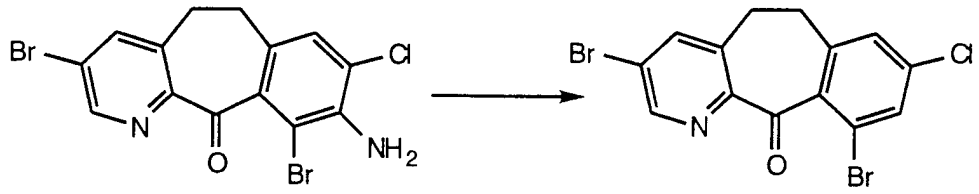
Step C:



Combine 13 g (38.5 mmol) of the product of Step B, 140 mL of HOAc and slowly add a solution of 2.95 mL (57.8 mmol) of Br_2 in 10 mL of HOAc over a period of 20 min. Stir the reaction mixture at room temperature, then concentrate *in vacuo* to a residue. Add CH_2Cl_2 and

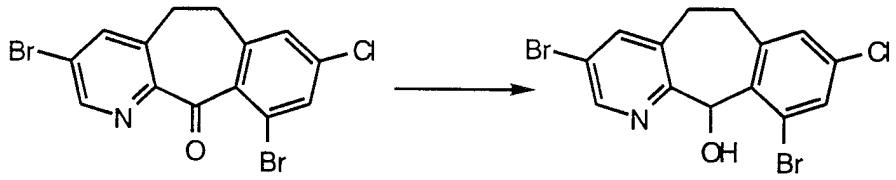
water, then adjust to pH = 8-9 with 50% NaOH (aqueous). Wash the organic phase with water, then brine and dry over Na_2SO_4. Concentrate *in vacuo* to give 11.3 g of the product.

Step D:



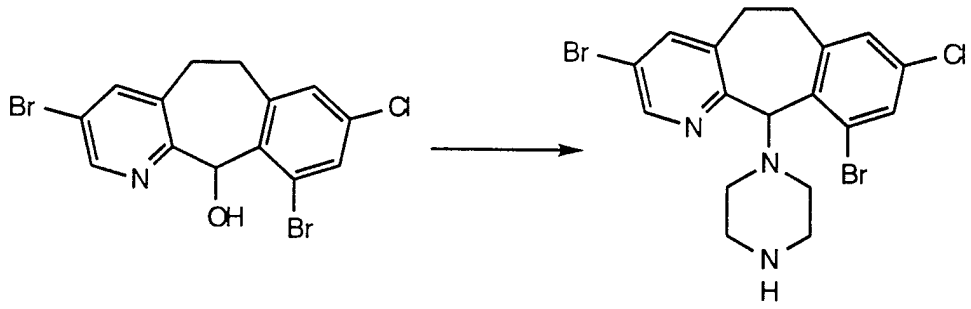
Cool 100 mL of concentrated HCl (aqueous) to 0°C, then add 5.61 g (81.4 mmol) of $NaNO_2$ and stir for 10 min. Slowly add (in portions) 11.3 g (27.1 mmol) of the product of Step C and stir the mixture at 0°-3°C for 2.25 hrs. Slowly add (dropwise) 180 mL of 50% H_3PO_2 (aqueous) and allow the mixture to stand at 0°C overnight. Slowly add (dropwise) 150 mL of 50% NaOH over 30 min., to adjust to pH = 9, then extract with CH_2Cl_2. Wash the extract with water, then brine and dry over Na_2SO_4. Concentrate *in vacuo* to a residue and chromatograph (silica gel, 2% EtOAc/ CH_2Cl_2) to give 8.6 g of the product.

Step E:



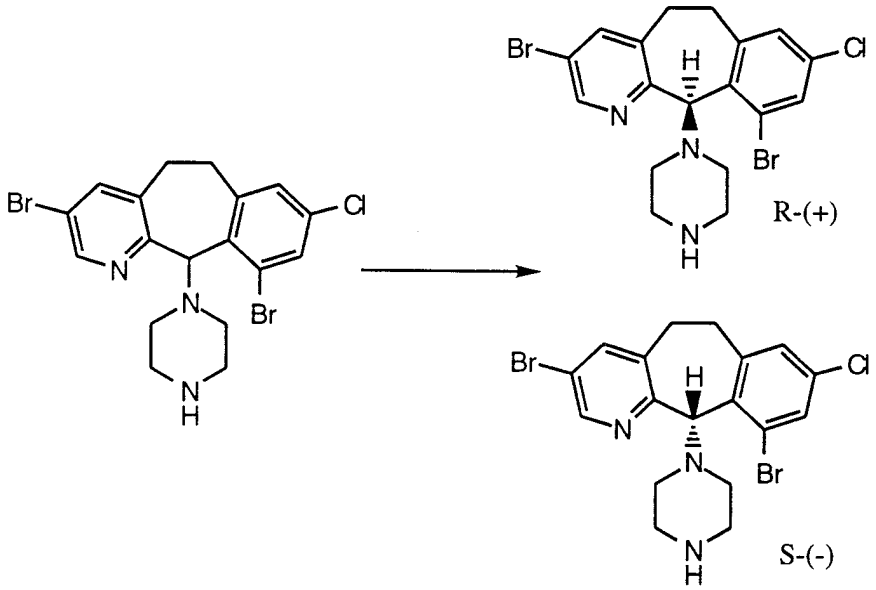
Combine 8.6 g (21.4 mmol) of the product of Step D and 300 mL of MeOH and cool to 0°-2°C. Add 1.21 g (32.1 mmol) of $NaBH_4$ and stir at ~0°C for 1 hr. Add another 0.121 g (3.21 mmol) of $NaBH_4$, stir for 2 hr. at 0°C, then let stand overnight at 0°C. Concentrate *in vacuo* to a residue then partition the residue between CH_2Cl_2 and water. Separate the organic phase and concentrate *in vacuo* (50°C) to give 8.2 g of the product.

Step F:



Combine 8.2 g (20.3 mmol) of the product of Step E and 160 mL of CH_2Cl_2, cool to 0°C, then slowly add (dropwise) 14.8 mL (203 mmol) of $SOCl_2$ over a 30 min. period. Warm the mixture to room temperature and stir for 4.5 hrs., then concentrate *in vacuo* to a residue, add CH_2Cl_2 and wash with 1 N NaOH (aqueous) then brine and dry over Na_2SO_4. Concentrate *in vacuo* to a residue, then add dry THF and 8.7 g (101 mmol) of piperazine and stir at room temperature overnight. Concentrate *in vacuo* to a residue, add CH_2Cl_2, and wash with 0.25 N NaOH (aqueous), water, then brine. Dry over Na_2SO_4 and concentrate *in vacuo* to give 9.46 g of the crude product. Chromatograph (silica gel, 5% MeOH/CH_2Cl_2 + NH_3) to give 3.59 g of the title compound, as a racemate. ^1H NMR ($CDCl_3$, 200 MHz): 8.43 (d, 1H); 7.55 (d, 1H); 7.45 (d, 1H); 7.11 (d, 1H); 5.31 (s, 1H); 4.86-4.65 (m, 1H); 3.57-3.40 (m, 1H); 2.98-2.55 (m, 6H); 2.45-2.20 (m, 5H).

Step G - Separation of Enantiomers:

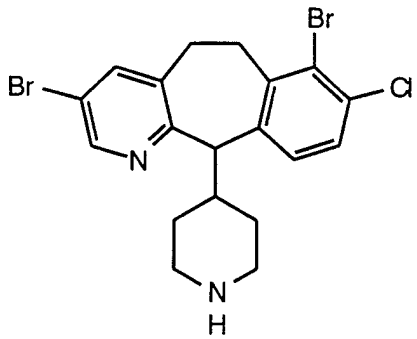


The racemic title compound from Step F (5.7 g) is chromatographed as described for Preparative Example 3, Step D, using 30% iPrOH/hexane + 0.2% diethylamine, to give 2.88 g of the R-(+)-isomer and 2.77 g of the S-(-)-isomer of the title compound.

Physical chemical data for the R-(+)-isomer: Mass Spec. MH^+ = 470; $[a]_D^{25}$ = +12.1° (10.9 mg/ 2mL MeOH).

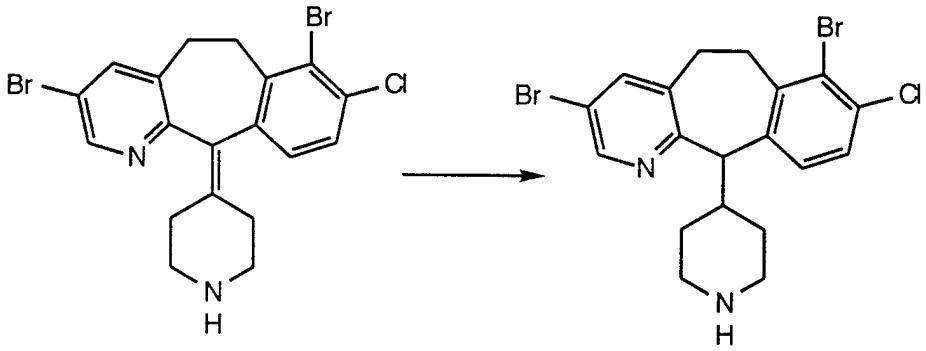
Physical chemical data for the S-(-)-isomer: Mass Spec. MH^+ = 470; $[a]_D^{25}$ = -13.2° (11.51 mg/ 2mL MeOH).

PREPARATIVE EXAMPLE 7



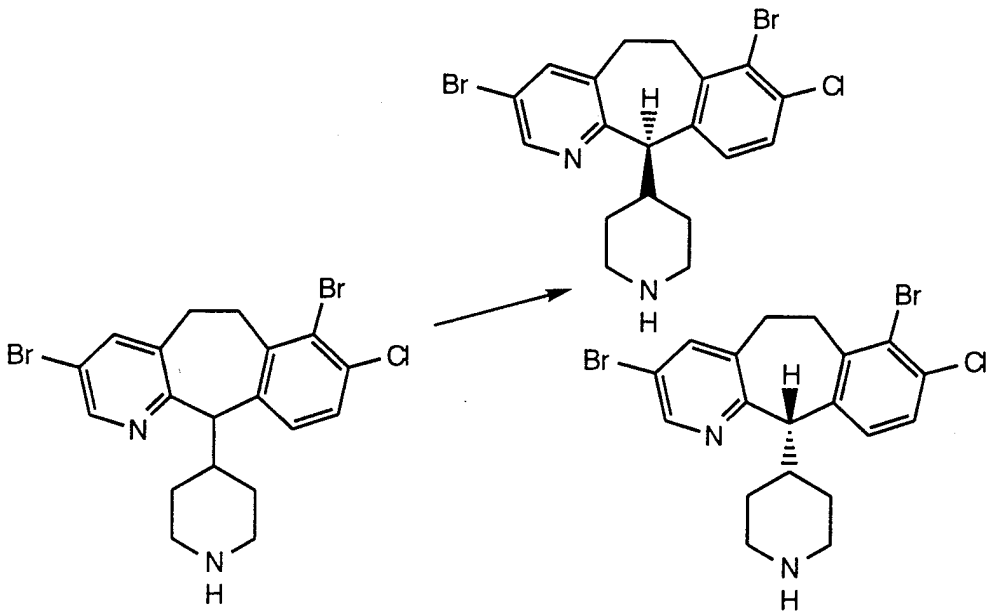
[racemic as well as (+)- and (-)-isomers]

Step A:



Combine 13 g (33.3 mmol) of the title compound from Preparative Example 1, Step D, and 300 mL of toluene at 20°C, then add 32.5 mL (32.5 mmol) of a 1 M solution of DIBAL in toluene. Heat the mixture at reflux for 1 hr., cool to 20°C, add another 32.5 mL of 1 M DIBAL solution and heat at reflux for 1 hr. Cool the mixture to 20°C and pour it into a mixture of 400 g of ice, 500 mL of EtOAc and 300 mL of 10% NaOH (aqueous). Extract the aqueous layer with CH_2Cl_2 (3 x 200 mL), dry the organic layers over $MgSO_4$, then concentrate *in vacuo* to a residue. Chromatograph (silica gel, 12% MeOH/CH_2Cl_2 + 4% NH_4OH) to give 10.4 g of the title compound as a racemate. Mass Spec.: MH^+ = 469 (FAB). partial ^1H NMR ($CDCl_3$, 400 MHz): 8.38 (s, 1H); 7.57 (s, 1H); 7.27 (d, 1H); 7.06 (d, 1H); 3.95 (d, 1H).

Step B - Separation of Enantiomers:

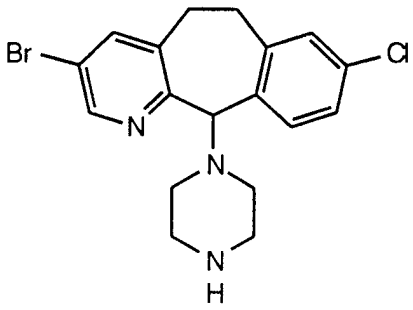


The racemic title compound of Step A is separated by preparative chiral chromatography (Chiralpack AD, 5 cm X 50 cm column, using 5% iPrOH/hexane + 0.2% diethylamine), to give the (+)-isomer and the (-)-isomer of the title compound.

Physical chemical data for (+)-isomer: Mass Spec. MH^+ = 470.9 (FAB); $[a]_D^{25}$ = +43.5° (c=0.402, EtOH); partial ^1H NMR ($CDCl_3$, 400 MHz): 8.38 (s, 1H); 7.57 (s, 1H); 7.27 (d, 1H); 7.05 (d, 1H); 3.95 (d, 1H).

Physical chemical data for (-)-isomer: Mass Spec. MH^+ = 470.9 (FAB); $[a]_D^{25}$ = -41.8° (c=0.328 EtOH); partial ^1H NMR ($CDCl_3$, 400 MHz): 8.38 (s, 1H); 7.57 (s, 1H); 7.27 (d, 1H); 7.05 (d, 1H); 3.95 (d, 1H).

PREPARATIVE EXAMPLE 8



[racemic as well as R-(+)- and S-(-)-isomers]

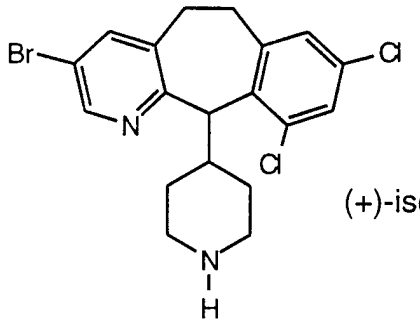
Treat 4-(8-chloro-3-bromo-5,6-dihydro-11H-benzo[5,6]cyclohepta-[1,2-b]pyridin-11-ylidene)-1-piperidine-1-carboxylic acid ethyl ester via substantially the same procedure as described in Preparative Example 3, Steps A-D, to give as the product of Step C, the racemic title compound,

and as the products of Step D the R-(+)-isomer and S-(-)-isomer of the title compound.

Physical chemical data for the R-(+)-isomer: ^{13}C NMR ($CDCl_3$): 155.8 (C); 146.4 (CH); 140.5 (CH); 140.2 (C); 136.2 (C); 135.3 (C); 133.4 (C); 132.0 (CH); 129.9 (CH); 125.6 (CH); 119.3 (C); 79.1 (CH); 52.3 (CH_2); 52.3 (CH); 45.6 (CH_2); 45.6 (CH_2); 30.0 (CH_2); 29.8 (CH_2). $[a]_D^{25}$ = +25.8° (8.46 mg/2 mL MeOH).

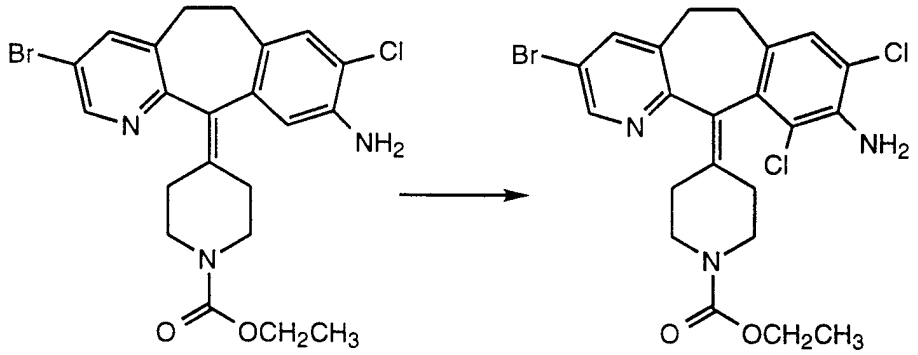
Physical chemical data for the S-(-)-isomer: ^{13}C NMR ($CDCl_3$): 155.9 (C); 146.4 (CH); 140.5 (CH); 140.2 (C); 136.2 (C); 135.3 (C); 133.3 (C); 132.0 (CH); 129.9 (CH); 125.5 (CH); 119.2 (C); 79.1 (CH); 52.5 (CH_2); 52.5 (CH); 45.7 (CH_2); 45.7 (CH_2); 30.0 (CH_2); 29.8 (CH_2). $[a]_D^{25}$ = -27.9° (8.90 mg/2 mL MeOH).

PREPARATIVE EXAMPLE 9



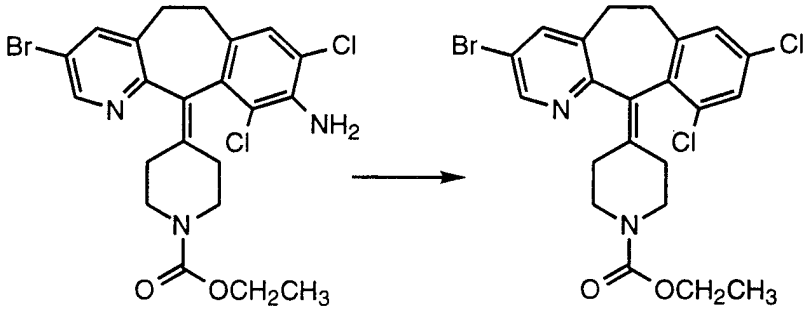
(+)-isomer

Step A:



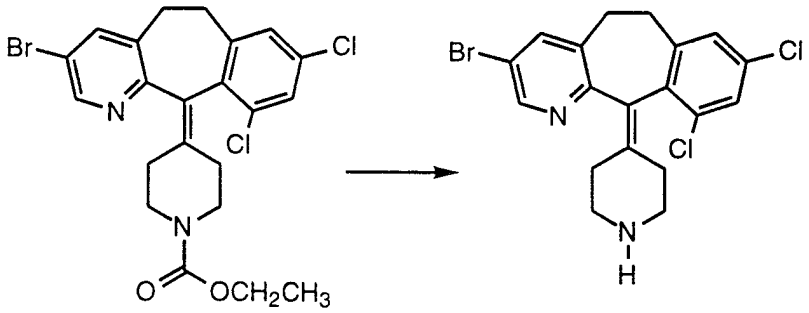
Dissolve 9.90 g (18.9 mmol) of the product of Preparative Example 4, Step B, in 150 mL CH_2Cl_2 and 200 mL of CH_3CN and heat to 60°C. Add 2.77 g (20.8 mmol) N-chlorosuccinimide and heat to reflux for 3 h., monitoring the reaction by TCL (30%EtOAc/H_2O). Add an additional 2.35 g (10.4 mmol) of N-chlorosuccinimide and reflux an additional 45 min. Cool the reaction mixture to room temperature and extract with 1N NaOH and CH_2Cl_2. Dry the CH_2Cl_2 layer over $MgSO_4$, filter and purify by flash chromatography (1200 mL normal phase silica gel, eluting with 30% EtOAc/H_2O) to obtain 6.24 g of the desired product. M.p. 193-195.4°C.

Step B:



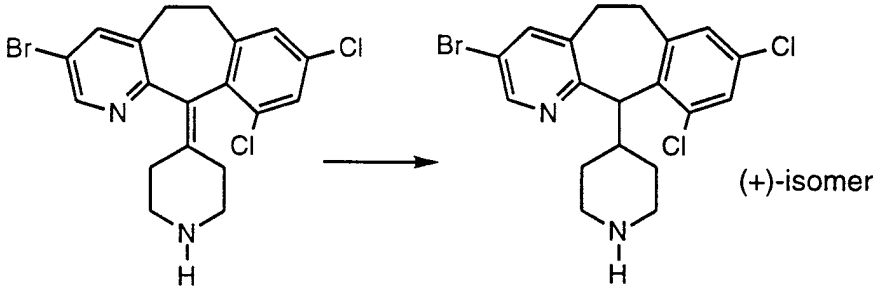
To 160 mL of conc. HCl at -10°C add 2.07 g (30.1 mmol) $NaNO_2$ and stir for 10 min. Add 5.18 g (10.1 mmol) of the product of Step A and warm the reaction mixture from -10°C to 0°C for 2 h. Cool the reaction to -10°C, add 100 mL H_3PO_2 and let stand overnight. To extract the reaction mixture, pour over crushed ice and basifiy with 50% NaOH/ CH_2Cl_2. Dry the organic layer over $MgSO_4$, filter and concentrate to dryness. Purify by flash chromatography (600 mL normal phase silica gel, eluting with 20% EtOAc/hexane) to obtain 3.98 g of product. Mass spec.: MH^+=497.2.

Step C:



Dissolve 3.9 g of the product of Step B in 100 mL conc. HCl and reflux overnight. Cool the mixture, basify with 50 % w/w NaOH and extract the resultant mixture with CH_2Cl_2. Dry the CH_2Cl_2 layer over $MgSO_4$, evaporate the solvent and dry under vacuum to obtain 3.09 g of the desired product. Mass spec.: MH^+=424.9.

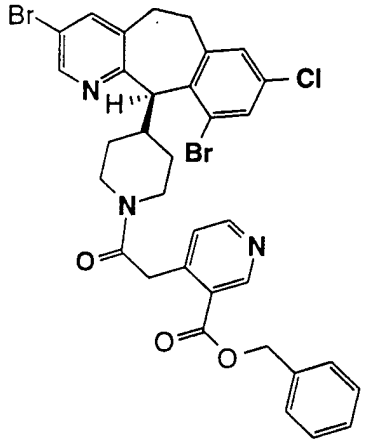
Step D:



Using a procedure similar to that described in Preparative Example 5, obtain 1.73 g of the desired product, m.p. 169.6-170.1°C; $[a]_D^{25}$ = +48.2° (c=1, MeOH).

EXAMPLE 1

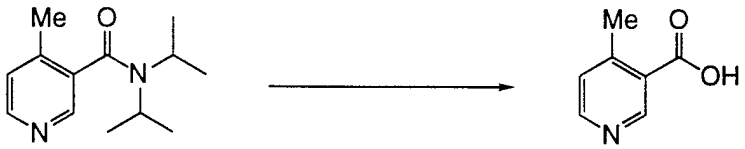
(+) -4-(3,10-Dibromo-8-Chloro-6,11-Dihydro-5H-Benzo[5,6]-Cyclohepta[1,2-B]Pyridin-11(R)-yl)-1-[[3-(Phenylmethoxycarbonyl)-4-Pyridinyl]Acetyl]Piperidine



Step 1: 4-Methyl-3-(Diisopropylcarboxamido)Pyridine

To 3-(diisopropylcarboxamido)pyridine (1 mmol) [*Tet. Lett.* **21**, 4739 (1980)] dissolved in anhydrous THF (50 mL) and cooled to -78°C add lithium diisopropylamide (1.1 mmol) diluted with anhydrous THF (10 mL). After stirring the reaction mixture at -78°C for 2 hours, add the mixture slowly to a -78 °C solution of CH_3I (10 mmol) in anhydrous THF (20 mL) and allow to warm to room temperature overnight. Concentrate the mixture *in vacuo*, dilute with water and extract with CH_2Cl_2. Dry the organic phase over anhydrous $MgSO_4$, filter and concentrate *in vacuo* to provide the title compound.

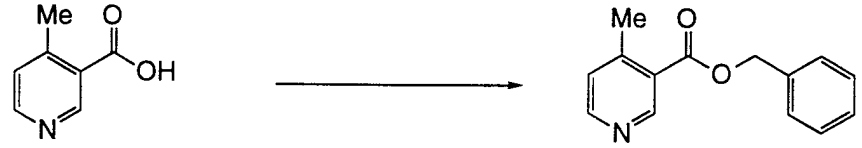
Step 2: 4-Methylnicotinic Acid



Reflux the product of Step 1 (1 mmol) for 24 hours in concentrated HCl (50 mL) containing 2 mL of absolute EtOH. Adjust the pH of the reaction mixture with 10% aqueous NaOH to a pH of 4 and extract the

resulting mixture with CH_2Cl_2. Dry the organic phase over anhydrous $MgSO_4$, filter and concentrate *in vacuo* to afford the title compound.

Step 3: Benzyl 4-Methylnicotinate

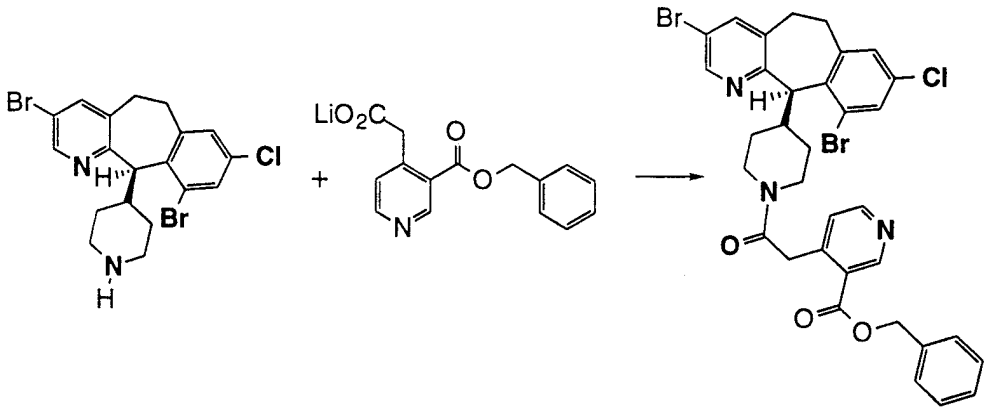


To the product of Step 2 (1.0 mmol) dissolved in anhydrous DMF add solid K_2CO_3 (1.2 mmol, anhydrous) and benzyl bromide (1.0 mmol). After stirring the reaction mixture at room temperature for 24 hours, concentrate the mixture *in vacuo*, dilute with CH_2Cl_2 and wash with water. Dry the organic phase over anhydrous $MgSO_4$, filter and concentrate *in vacuo* to afford the title compound.

Step 4: Lithium 3-(Benzyloxycarbonyl)-4-Pyridylacetate

Dissolve the product of Step 3 in anhydrous THF (50 mL), cool to -78°C and add dropwise to a solution of lithium diisopropylamide (1.1 mmol) in anhydrous THF (10 mL). After stirring the reaction mixture at -78°C for 1 hour, pour the solution over a slurry of dry ice in anhydrous Et_2O and allow the reaction mixture to warm to room temperature over night. Filter the resulting precipitate, wash with Et_2O and dry under vacuum to afford the title compound.

Step 5:

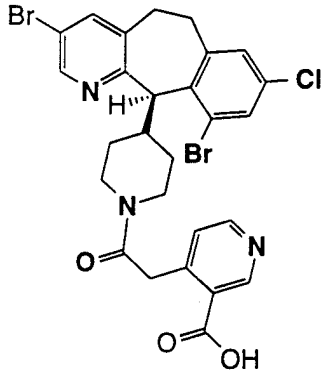


Combine the tricyclic amine of Preparation 5 (1 mmol) with HOBT hydrate (1 mmol), DEC (1 mmol), the product of Step 4 (1 mmol) and anhydrous DMF (10 mL) and stir the resulting mixture at room temperature under N_2 overnight. Concentrate *in vacuo* and dilute the resultant oil with

CH_2Cl_2, wash with 1*M* HCl and 1 *M* aqueous NaOH, then dry over anhydrous $MgSO_4$. Filter and concentrate *in vacuo* to afford the title compound.

EXAMPLE 2

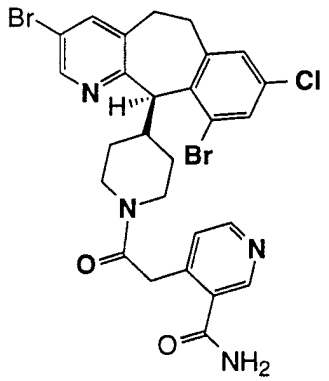
(+) -4-(3,10-Dibromo-8-Chloro-6,11-Dihydro-5H-Benzo[5,6]-Cyclohepta[1,2-B]Pyridin-11(R)-YL)-1-[[3-(Carboxy)-4-Pyridinyl]Acetyl]Piperidine



To the product of Example 1 (1 mmol) dissolved in anhydrous $CHCl_3$ (10 mL) add trimethylsilyl iodide (1.5 mmol) and stir the resulting mixture at reflux for 2 hours. Cool the reaction mixture to room temperature, dilute with CH_2Cl_2 and wash with 1 *M* HCl. Dry the organic phase over anhydrous $MgSO_4$, filter and concentrate *in vacuo* to afford the title compound.

EXAMPLE 3

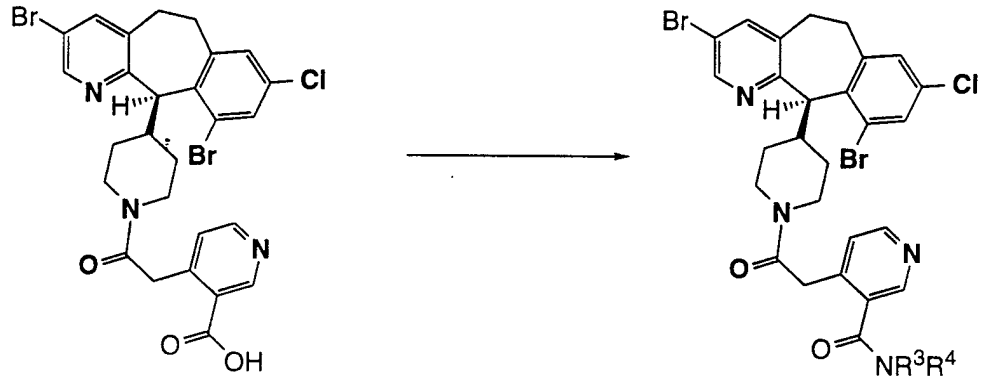
(+) -4-(3,10-Dibromo-8-Chloro-6,11-Dihydro-5H-Benzo[5,6]-Cyclohepta[1,2-B]Pyridin-11(R)-yl)-1-[[3-(Carboxamido)-4-Pyridinyl]Acetyl]Piperidine

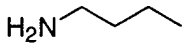
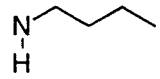
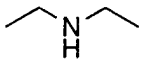
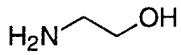
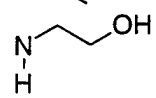
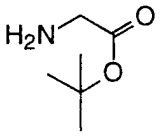
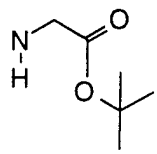
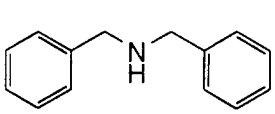
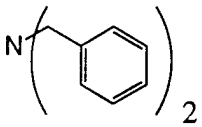
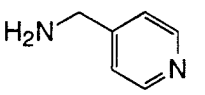
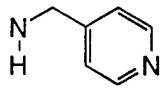
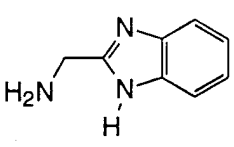
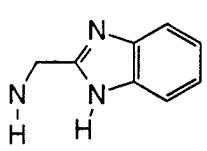


To the product of Example 2 (1 mmol) dissolved in anhydrous DMF (10 mL) add HOBT hydrate (2 mmol), DEC (2 mmol), NH_4Cl (2 mmol) and N-methylmorpholine (2.2 mmol), and stir the resulting mixture at room temperature under N_2 overnight. Concentrate *in vacuo* to provide an oil. Dilute the resultant oil with CH_2Cl_2, wash with 1*M* HCl and 1 *M* aqueous

NaOH, then dry over anhydrous $MgSO_4$. Filter and concentrate *in vacuo* to afford the title compound.

Using the product of Example 2 and and the substituted amines listed in the table below in the procedure of Example 3, the following amides can be prepared:



AMINE	AMIDE (-NR^3R^4)
	
	
	
	
	
	
	

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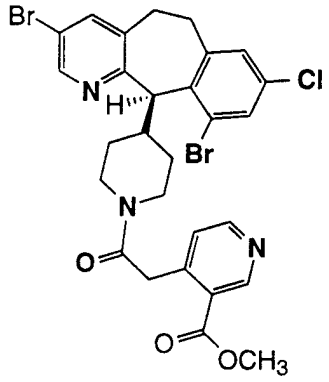
EXAMPLE 4

(+) -4-(3,10-Dibromo-8-Chloro-6,11-Dihydro-5H-Benzo[5,6]-Cyclohepta[1,2-B]Pyridin-11(R)-yl)-1-[[3-(Methoxycarbonyl)-4-Pyridinyl]Acetyl]Piperidine



To the product of Example 2 (1.0 mmol) dissolved in anhydrous DMF add solid K_2CO_3 (1.2 mmol, anhydrous) and CH_3I (1.2 mmol). After stirring the reaction mixture at room temperature for 24 hours, concentrate the mixture *in vacuo*, dilute with CH_2Cl_2 and wash with water. Dry the organic phase over anhydrous $MgSO_4$, filter and concentrate *in vacuo* to afford the title compound.

FPT IC_{50} (inhibition of farnesyl protein transferase, in vitro enzyme assay), COS Cell IC_{50} (Cell-Based Assay), GGPT IC_{50} (inhibition of geranylgeranyl protein transferase, in vitro enzyme assay), Cell Mat Assay, and anti-tumor activity (in vivo anti-tumor studies) are determined by the assay procedures described in WO 95/10516.

For preparing pharmaceutical compositions from the compounds described by this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. The powders and tablets may be comprised of from about 5 to about 70 percent active ingredient. Suitable solid carriers are known in the art, e.g. magnesium carbonate, magnesium stearate, talc, sugar, lactose. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration.

For preparing suppositories, a low melting wax such as a mixture of fatty acid glycerides or cocoa butter is first melted, and the active ingredient is dispersed homogeneously therein as by stirring. The molten

homogeneous mixture is then poured into convenient sized molds, allowed to cool and thereby solidify.

Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection.

Liquid form preparations may also include solutions for intranasal administration.

Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier, such as an inert compressed gas.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

The compounds of the invention may also be deliverable transdermally. The transdermal compositions can take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

Preferably the compound is administered orally.

Preferably, the pharmaceutical preparation is in unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component, e.g., an effective amount to achieve the desired purpose.

The quantity of active compound in a unit dose of preparation may be varied or adjusted from about 0.1 mg to 1000 mg, more preferably from about 1 mg. to 300 mg, according to the particular application.

The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day if desired.

The amount and frequency of administration of the compounds of the invention and the pharmaceutically acceptable salts thereof will be regulated according to the judgment of the attending clinician considering

such factors as age, condition and size of the patient as well as severity of the symptoms being treated. A typical recommended dosage regimen is oral administration of from 10 mg to 2000 mg/day preferably 10 to 1000 mg/day, in two to four divided doses to block tumor growth. The compounds are non-toxic when administered within this dosage range.

The following are examples of pharmaceutical dosage forms which contain a compound of the invention. The scope of the invention in its pharmaceutical composition aspect is not to be limited by the examples provided.

Pharmaceutical Dosage Form Examples

EXAMPLE A

Tablets

No.	Ingredients	mg/tablet	mg/tablet
1.	Active compound	100	500
2.	Lactose USP	122	113
3.	Corn Starch, Food Grade, as a 10% paste in Purified Water	30	40
4.	Corn Starch, Food Grade	45	40
5.	Magnesium Stearate	3	7
	Total	300	700

Method of Manufacture

Mix Item Nos. 1 and 2 in a suitable mixer for 10–15 minutes. Granulate the mixture with Item No. 3. Mill the damp granules through a coarse screen (e.g., 1/4", 0.63 cm) if necessary. Dry the damp granules. Screen the dried granules if necessary and mix with Item No. 4 and mix for 10–15 minutes. Add Item No. 5 and mix for 1–3 minutes. Compress the mixture to appropriate size and weigh on a suitable tablet machine.

EXAMPLE B

Capsules

No.	Ingredient	mg/capsule	mg/capsule
1.	Active compound	100	500
2.	Lactose USP	106	123
3.	Corn Starch, Food Grade	40	70
4.	Magnesium Stearate NF	7	7
	Total	253	700

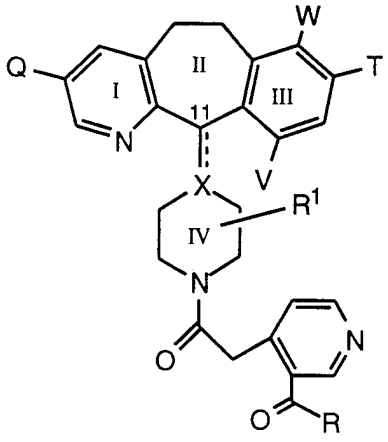
Method of Manufacture

Mix Item Nos. 1, 2 and 3 in a suitable blender for 10-15 minutes. Add Item No. 4 and mix for 1-3 minutes. Fill the mixture into suitable two-piece hard gelatin capsules on a suitable encapsulating machine.

While the present invention has been described in conjunction with the specific embodiments set forth above, many alternatives, modifications and variations thereof will be apparent to those of ordinary skill in the art. All such alternatives, modifications and variations are intended to fall within the spirit and scope of the present invention.

WHAT IS CLAIMED IS:

1. A compound represented by the structural formula



I

or an N-oxide thereof, or a pharmaceutically acceptable salt or solvate thereof, wherein:

Q and T are independently selected from halo;

W and V are independently selected from H and halo, provided that at least one of W and V is H;

R^1 is H or alkyl;

X represents N, CH, or C when the double bond is present at the C-11 position;

R is $-OR^3$, $-NR^3R^4$ or $-SR^3$; and

R^3 and R^4 are independently selected form the group consisting of H, alkyl, arylalkyl, substituted arylalkyl, heteroarylalkyl and substituted heteroarylalkyl.

2. A compound of claim 1 wherein Q is bromo and T is chloro or bromo.

3. A compound of claim 1 wherein Q is bromo, T is chloro or bromo, W is H, and V is chloro or bromo.

4. A compound of claim 1 wherein Q is bromo, T is chloro or bromo, V is H, and W is chloro or bromo.

5. A compound of any of claims 1, 2, 3 or 4 wherein R is $-OR^3$ and R^3 is H, CH_3 or benzyl.

6. A pharmaceutical composition for inhibiting the abnormal growth of cells comprising an effective amount of compound of any of claims 1, 2, 3, 4 or 5 in combination with a pharmaceutically acceptable carrier.

7. The use of a compound of any of claims 1, 2, 3, 4 or 5 for the preparation of a medicament for treating tumor cells expressing an activated ras oncogene.

8. The use of claim 7 wherein the cells treated are pancreatic tumor cells, breast cancer cells, prostatic cancer cells, lung cancer cells, myeloid leukemia tumor cells, thyroid follicular tumor cells, myelodysplastic tumor cells, epidermal carcinoma tumor cells, bladder carcinoma tumor cells or colon tumors cells.

9. The method of claim 7 wherein the inhibition is of tumor cells wherein the Ras protein is activated as a result of oncogenic mutation in genes other than the Ras gene.

10. The use of a compound of any of claims 1, 2, 3, 4 or 5 for the preparation of a medicament for inhibiting farnesyl protein transferase.

INTERNATIONAL SEARCH REPORT

Inter ›nal Application No
PCT/US 98/11503

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D401/04 A61K31/55 A61K31/445 //(C07D401/04,221:00, 211:00)

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 95 10516 A (SCHERING CORP) 20 April 1995 cited in the application * see page 208, ex. 134, page 216, ex. 321 * see the whole document ---	1-10
Y	WO 96 30363 A (SCHERING CORP) 3 October 1996 cited in the application see the whole document ---	1-10
Y	WO 96 30362 A (SCHERING CORP) 3 October 1996 see the whole document ---	1-10

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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

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

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

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

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

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 October 1998	13/10/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Stellmach, J

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INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/US 98/11503

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication.where appropriate, of the relevant passages	Relevant to claim No.
Y	NJOROGE F G ET AL: "NOVEL TRICYCLIC AMINOACETYL AND SULFONAMIDE INHIBITORS OF RAS FARNESYL PROTEIN TRANSFERASE" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 6, no. 24, 1996, pages 2977-2982, XP002056550 see the whole document	1-10
Y	BISHOP W R ET AL: "NOVEL TRICYCLIC INHIBITORS OF FARNESYL PROTEIN TRANSFERASE BIOCHEMICAL CHARACTERIZATION AND INHIBITION OF RAS MODIFICATION IN TRANSFECTED COS CELLS" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 270, no. 51, 22 December 1995, pages 30611-30618, XP002050604 see the whole document	1-10
Y	NJOROGE F G ET AL: "DISCOVERY OF NOVEL NONPEPTIDE TRICYCLIC INHIBITORS OF RAS FARNESYL PROTEIN TRANSFERASE" BIOORGANIC & MEDICINAL CHEMISTRY, vol. 5, no. 1, 1997, pages 101-113, XP002056551 see the whole document	1-10
P,X	WO 97 23478 A (SCHERING CORP) 3 July 1997 * see page 49, ex. 7, page 56, ex. 11 * see the whole document	1-10

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte. onal Application No
PCT/US 98/11503

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