

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

SG 9701137-3



RTMP copy

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 31/47, C07D 221/10	A1	(11) International Publication Number: WO 96/09046 (43) International Publication Date: 28 March 1996 (28.03.96)
(21) International Application Number: PCT/US95/11521 (22) International Filing Date: 14 September 1995 (14.09.95) (30) Priority Data: 08/309,282 20 September 1994 (20.09.94) US (71) Applicant (for all designated States except US): ELI LILLY AND COMPANY [US/US]; Lilly Corporate Center, Indianapolis, IN 46285 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): AUDIA, James, Edmund [US/US]; 6449 Lakeside Woods Circle, Indianapolis, IN 46278 (US). McQUAID, Loretta, Ames [US/US]; 7504 Runningbrook Court, Indianapolis, IN 46254 (US). NEUBAUER, Blake, Lee [US/US]; 6943 Central Avenue, Indianapolis, IN 46220 (US). ROCCO, Vincent, Patrick [US/US]; 3961 Gable Lane Drive, Indianapolis, IN 46208 (US). HAEHL, Kevin, Lee [US/US]; 381 Stoneybrook Grove Drive, Greenwood, IN 46142 (US). KRESS, Thomas, J. [US/US]; 2048 Rigemere Place, Greenwood, IN 46143 (US). WEPSIEC, James, Patrick [US/US]; 6987 Holly Springs Place, Indianapolis, IN 46254 (US).		(74) Agent: LAMMERT, Steven, R.; Barnes & Thornburg, 1313 Merchants Bank Building, 11 South Meridian Street, Indianapolis, IN 46204 (US). (81) Designated States: AM, AU, BB, BG, BR, BY, CN, CZ, EE, FI, GE, HU, IS, KE, KG, KP, KR, KZ, LK, LR, LT, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SG, SI, SK, TJ, TM, TT, UA, UG, US, UZ, VN, OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG). Published <i>With international search report.</i> { ①. PCT Pub + SR ②. IPER + Annexes
(54) Title: 5α-REDUCTASE INHIBITORS (57) Abstract A series of benzoquinolin-3-ones are pharmaceuticals effective in treating conditions consequent on both Type I and Type II 5α-reductase.		

-1-

5 α -REDUCTASE INHIBITORS

5 The present invention belongs to the fields of pharmaceutical chemistry and pharmacology, and provides benzo[f]quinolinones which are pharmaceuticals for the inhibition of 5 α -reductase.

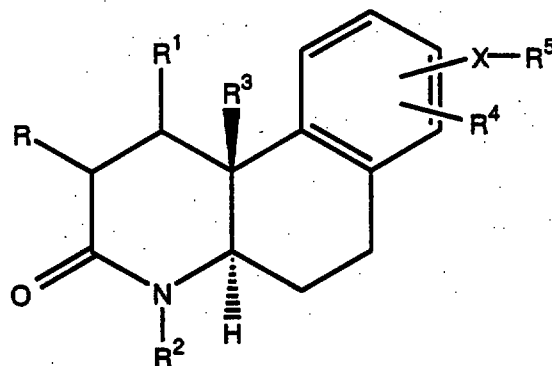
10 It is now widely known that a number of undesirable physiological conditions are androgen-mediated and are dependent on 5 α -dihydrotestosterone (DHT). Such conditions include benign prostatic hyperplasia, male pattern baldness, acne vulgaris, seborrhea, androgenic alopecia, hirsutism and prostate cancer. It has been demonstrated that inhibitors of 5 α -reductase (5AR) block the formation of DHT, because 5AR
15 mediates the conversion of testosterone to the more potent androgen DHT in various target organs. Finasteride, a 5AR inhibitor, is now in the pharmaceutical marketplace and is approved for the treatment of benign prostatic hyperplasia.
20 Mocellini et al., The Prostate, 22, 291-99 (1993).

Recently it has been found that there are at least two 5AR isozymes in the human, Andersson et al., Proc. Natl. Acad. Sci. USA, 87, 3640-44 (1990); Andersson et al., Nature, 354, 159-61 (1991). The two isozymes, usually called Type I
25 and Type II, exhibit differences in their biochemical properties, genetics and pharmacology. Both isozymes are now the subject of considerable research and it has been found that Type I is more prevalent in the scalp and is more involved in conditions such as androgenic alopecia, and that
30 Type II is more prevalent in the prostate. In prostate, Type I is exclusive to the epithelial compartment in normal, benign hyperplastic and cancerous cells, and the Type II isoform predominates in the fibromuscular stroma.

The present invention provides a series of new
35 compounds which are effective inhibitors of 5AR; many of the compounds are effective inhibitors of both of the 5AR isozymes.

-2-

The present invention provides benzo[f]quinolinones of the formula



I

wherein

R and R¹ both represent hydrogen or combine to form a bond;

R² represents hydrogen or C₁-C₃ alkyl;

R³ represents methyl or ethyl;

R⁴ and -X-R⁵ each occupies one of the 7-, 8- and 9-positions;

R⁴ represents hydrogen, halo, methyl or ethyl;

X represents C₁-C₄ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, a bond, -SO-, -SO₂-, -CO-Y-(CH₂)ₙ-, -Y-CO-(CH₂)ₙ-, -CO-, -Z-(CH₂)ₙ-, or -SO₃-; wherein X groups which are not symmetrical may be in either orientation;

Y represents -S-, -O-, or -NH-;

Z represents -O- or -S-;

n represents 0-3;

R⁵ represents phenyl, naphthalenyl, pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, anthracenyl, acenaphthalenyl, thiazolyl, benzimidazolyl, indazolyl, thiophenyl, phenanthrenyl, quinolinyl, fluorenyl, isoquinolinyl, indanyl, benzopyranyl, indolyl, benzoisoquinolinyl, benzindolyl, benzothiazolyl, benzothiophenyl, quinoxalinyl, benzoxazolyl, tetrazolyl, naphthothiazolyl, quinazolinyl, thiazolopyridinyl,

-3-

pyridazinoquinazolinyl, benzisothiazolyl, benzodioxolyl, benzodioxinyl, diphenylmethyl or triphenylmethyl;

the above R⁵ groups are unsubstituted or substituted with 1-3 groups chosen from the group consisting of halo, trifluoromethyl, trifluoroethoxy, C₁-C₄ alkyl, trifluoromethoxy, hydroxy, C₁-C₃ alkoxy, nitro, C₁-C₃ alkylthio, C₁-C₆ alkanoyl, phenyl, oxo, phenoxy, phenylthio, C₁-C₃ alkylsulfinyl, C₁-C₃ alkylsulfonyl, cyano, amino, C₁-C₃ alkylamino, diphenylmethylamino, triphenylmethylamino, benzyloxy, benzylthio, (mono-halo, nitro or CF₃)benzyl(oxy or thio), di(C₁-C₃ alkyl, C₃-C₆ cycloalkyl, or C₄-C₈ cycloalkylalkyl)amino, (mono-C₁-C₃ alkyl, C₁-C₃ alkoxy or halo)-(phenyl, phenoxy, phenylthio, phenylsulfonyl or phenoxysulfonyl), C₂-C₆ alkanoylamino, benzoylamino, diphenylmethylamino(C₁-C₃ alkyl), aminocarbonyl, C₁-C₃ alkylaminocarbonyl, di(C₁-C₃ alkyl)aminocarbonyl, halo-C₁-C₆ alkanoyl, aminosulfonyl, C₁-C₃ alkylaminosulfonyl, di(C₁-C₃ alkyl)aminosulfonyl, phenyl(oxy or thio)(C₁-C₃ alkyl), (halo, C₁-C₃ alkyl or C₁-C₃ alkoxy)phenyl(oxy or thio)(C₁-C₃ alkyl), benzoyl, or (amino, C₁-C₃ alkylamino or di(C₁-C₃ alkyl)amino)(C₁-C₃ alkyl);

or an above R⁵ group is substituted with a morpholino(C₁-C₃ alkyl) group, a phenyl(C₁-C₃ alkyl)piperidinyl group, a phenyl(C₁-C₃ alkyl)-piperidinylaminocarbonyl group, a C₂-C₆ alkanoyl-aminothiophenyl group, or a (amino, C₁-C₃ alkylamino or di(C₁-C₃ alkyl)amino)naphthalenylsulfonylamino group;

or R⁵ is a perhalophenyl group;

or a pharmaceutically acceptable salt thereof.

The invention also provides pharmaceutical compositions comprising a compound of the above formula in combination with a pharmaceutically acceptable carrier, diluent or excipient.

Further, the invention provides a method for inhibiting 5 α -reductase, more preferably, a method for inhibiting both Type I and Type II 5 α -reductase. Further,

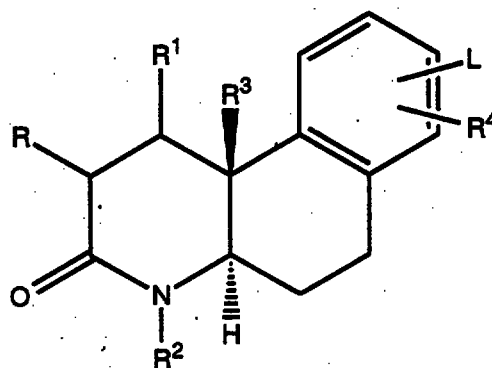
-4-

methods are provided for the treatment of benign prostatic hyperplasia, male pattern baldness, acne vulgaris, seborrhea, androgenic alopecia, hirsutism and prostate cancer, which methods comprise administering an effective amount of a compound of formula I to a patient in need of such treatment. Still further, the invention provides a method for the treatment or prevention of such conditions comprising administering to a patient exhibiting excessive 5AR levels or excessive 5AR activity an effective 5AR-inhibiting amount of a compound of formula I.

Still further, the invention provides the use of the compounds of Formula I for inhibiting 5 α -reductase, particularly for inhibiting both Type I and Type II 5AR. The use of the compounds for treating benign prostatic hyperplasia, male pattern baldness, acne vulgaris, seborrhea, androgenic alopecia, hirsutism and prostate cancer is also provided, as is the use of the compounds for the treatment or prevention of such conditions in a patient exhibiting excessive 5AR levels or excessive 5AR activity.

The invention further provides a process for preparing a compound of Formula I

(a) wherein an intermediate of the formula

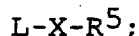


II

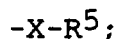
is reacted with a compound of the formula
X-R⁵
in activated form; or

-5-

a compound of Formula II in activated form is reacted with a compound of the formula



5 (b) wherein a compound of Formula I wherein X is $-Z-(CH_2)_n-$ is prepared by reacting a compound of Formula II with a compound of the formula

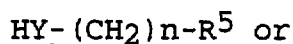


or a compound of Formula II wherein $-L$ has been replaced by $-Z$ is reacted with a compound of the formula

10 $L-X-R^5;$

(c) wherein a compound of Formula I wherein X is $-CO-Y-(CH_2)_n-$ or $-Y-CO-(CH_2)_n-$ is prepared by reacting a compound of Formula II wherein $-L$ has been replaced with one of $-YH$, $-CO-L$, $-(CH_2)_n-YH$, or $-(CH_2)_n-CO-L$, with a compound

15 of one of the formula

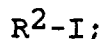


20 provided that one reactant has a $-YH$ group and the other an L group, and no more than one reactant has a $-(CH_2)_n-$ group;

(d) wherein a compound of Formula I wherein X is alkyl is prepared by reacting a compound of Formula II in activated form with an aldehyde or ketone which provides the residue of $-X-R^5$;

25

(e) wherein a compound of Formula I wherein R^2 is C_1-C_3 alkyl is prepared by reacting a compound of Formula I wherein R^2 is hydrogen with an alkyl iodide of the formula



30 (f) or oxidizing the product to prepare a compound of Formula I wherein R and R^1 combine to form a bond;

(g) or oxidizing or reducing an X group;

(h) or removing protecting groups;

(i) or preparing a salt;

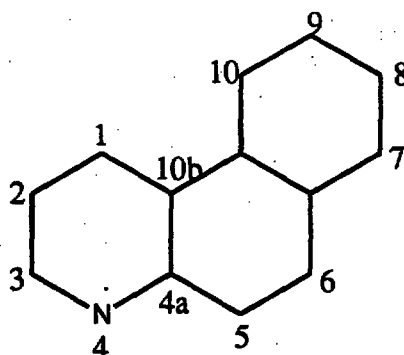
35 (j) or isolating an optical isomer.

-6-

Throughout the present document, all temperatures will be described in degrees Celsius and all expressions of concentration, percentage and proportion will be expressed in weight units, except for mixtures of solvents, which will be described in volume units, unless otherwise stated.

References to compounds of formula I in this document include the pharmaceutically acceptable salts of such compounds, unless otherwise stated.

The various positions on the benzo[f]quinoline ring are indicated below.



The spatial configuration of the group R^3 at 10b and the hydrogen atom at 4a are required, and the synthetic methods for obtaining that configuration will be shown. The reader will understand that most of the compounds can exist in two stereochemical forms, or even more depending on the nature of the R^5 group, and that all stereochemical forms are included in the present invention. In some of the compounds prepared or described below, single enantiomers are prepared in pure form and are identified by (+) or (-) nomenclature. In other cases, the mixture of diastereomers is prepared.

The groups R^4 and $X-R^5$ may occupy either the 7, 8, or 9-position.

The term "halo" includes chloro, bromo and fluoro.

The various alkyl groups, such as C_1 - C_3 alkyl, C_1 - C_4 alkyl and the like include groups such as methyl, ethyl, propyl, isopropyl, *t*-butyl, butyl and isobutyl. When such

-7-

groups link other portions of a molecule, they are bivalent and the location of the linkages will be indicated in the chemical name.

Alkenyl and alkynyl groups constitute linking groups which are bivalent and are bonded to two other groups. For example, C₂-C₄ alkenyl includes 2-propenyl, 3-butenyl and 2-butenyl; and C₂-C₄ alkynyl includes, for example, ethynyl, 2-propynyl, 2-butyne and iso-2-butyne.

The groups C₁-C₆ alkanoyl and C₂-C₆ alkanoyl include such groups as formyl, acetyl, propionyl, isobutyryl, 2-ethylpropionyl and hexanoyl. The group C₃-C₆ cycloalkyl includes cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl, and the group C₄-C₈ cycloalkylalkyl includes, for example, cyclopropylmethyl, cyclohexylethyl, cyclobutylbutyl and cyclohexylmethyl.

Terms such as C₁-C₃ alkoxy, C₁-C₃ alkylsulfonyl, benzylthio, phenoxy, and C₁-C₃ alkylamino refer to the indicated alkyl, benzyl or the like group linked to an oxygen atom, sulfur atom, sulfonyl group or amino group as indicated.

Terms such as halo-C₁-C₆ alkanoyl, halophenyl or C₁-C₃ alkylphenyl refer to the indicated basic group having substituted on it 1, 2, or 3 halo or C₁-C₃ alkyl groups as may be described in the individual case.

The term perhalophenyl refers to a phenyl group which is fully substituted at all available positions with halogen atoms.

The compounds of formula I all have the benzo[f]-quinoline nucleus, on the phenyl ring of which is substituted a cyclic group, frequently an arylcyclic group, which is linked to the benzoquinoline through the X linker, which in many cases is simply a bond. The R⁵ groups may be substituted with additional organic groups, and may bear as many as three of the indicated substituent groups. Multiple substituents may all be the same, as, for example, 2,3,5-trifluorophenyl, or may be different, such as, for example, 3,5-bis(t-butyl)-4-hydroxyphenyl. The specifically named

compounds which appear below in this document will further illustrate the contemplated X, R⁵ and substituent groups.

The X groups which are not symmetrical may be in either orientation on the molecule; for example, the atom Z of the group -Z-(CH₂)_n- may be adjacent either to R⁵ or to the phenyl ring of the nucleus of formula I.

The cyclic R⁵ groups may take any permissible orientation. For example, the following specific R⁵ groups are contemplated.

10	phenyl
	2-quinolinyl
	4-quinolinyl
	7-quinolinyl
	1-isoquinolinyl
15	3-isoquinolinyl
	8-isoquinolinyl
	2-quinoxaliny
	5-quinoxaliny
	7-quinoxaliny
20	2-benzothiazolyl
	4-benzothiazolyl
	6-benzothiazolyl
	7-1H-indazolyl
	3-1H-indazolyl
25	5-2H-indazolyl
	2-2H-indazolyl
	7-2H-indazolyl
	4-3H-indazolyl
	3-3H-indazolyl
30	1-indolyl
	3-indolyl
	3-2H-indolyl
	2-3H-indolyl
	6-2H-indolyl
35	4-3H-indolyl
	2-benzoxazolyl
	5-benzoxazolyl

-9-

3-1,2-benzisothiazolyl
5-1,2-benzisothiazolyl
7-2,1-benzisothiazolyl
4-2,1-benzisothiazolyl
5 2-pyridinyl
4-pyridinyl
3-pyridazinyl
5-pyridazinyl
2-pyrazinyl
10 5-pyrazinyl
2-naphtho[2,3-d]thiazolyl
8-naphtho[2,3-d]thiazolyl
6-naphtho[2,3-d]thiazolyl
1-naphtho[2,1-d]thiazolyl
15 5-naphtho[2,1-d]thiazolyl
2-naphtho[1,2-d]thiazolyl
6-naphtho[1,2-d]thiazolyl
1-naphthalenyl
2-naphthalenyl
20 2-thienyl
3-thienyl
1-anthracenyl
10-anthracenyl
6-anthracenyl
25 1-phenanthrenyl
4-phenanthrenyl
9-phenanthrenyl
1-3H-fluorenyl
3-3H-fluorenyl
30 9-3H-fluorenyl
1-fluorenyl
5-fluorenyl
1-acenaphthalenyl
5-acenaphthalenyl
35 diphenylmethyl
triphenylmethyl
2-thiazolyl

-10-

4-thiazolyl
2-benzimidazolyl
6-benzimidazolyl
1-indanyl
5 4-indanyl
3-2H-1-benzopyranyl
7-2H-1-benzopyranyl
2-chromanyl
5-chromanyl
10 4-4H-1-benzopyranyl
8-4H-1-benzopyranyl
3-5H-1-benzopyranyl
5-5H-1-benzopyranyl
1-benz[g]isoquinoliny1
15 5-benz[g]isoquinoliny1
8-benz[g]isoquinoliny1
4-benz[h]isoquinoliny1
10-benz[h]isoquinoliny1
2-benz[f]isoquinoliny1
20 6-benz[f]isoquinoliny1
3-1H-benz[de]isoquinoliny1
9-1H-benz[de]isoquinoliny1
4-4H-benz[de]isoquinoliny1
6-4H-benz[de]isoquinoliny1
25 1-1H-benz[f]indolyl
4-1H-benz[f]indolyl
2-3H-benz[f]indolyl
7-3H-benz[f]indolyl
2-pyrimidinyl
30 5-pyrimidinyl
1-3H-carbazolyl
5-3H-carbazolyl
3-4aH-carbazolyl
4a-4aH-carbazolyl
35 2-8aH-carbazolyl
7-8aH-carbazolyl
8-carbazolyl

-11-

4-carbazolyl
2-1H-benz[g]indolyl
6-1H-benz[g]indolyl
3-3H-benz[g]indolyl
5 9-3H-benz[g]indolyl
1-1H-benz[e]indolyl
5-1H-benz[e]indolyl
3-3H-benz[e]indolyl
7-3H-benz[e]indolyl
10 2-benz[cd]indolyl
5-benz[cd]indolyl
2-1-benzothiophenyl
5-1-benzothiophenyl
1-2-benzothiophenyl
15 7-2-benzothiophenyl
5-1H-tetrazolyl
1-1H-tetrazolyl
5-2H-tetrazolyl
2-quinazolinyl
20 6-quinazolinyl
2-thiazolo[4,5-b]pyridinyl
6-thiazolo[4,5-b]pyridinyl
7-thiazolo[5,4-b]pyridinyl
4-thiazolo[4,5-c]pyridinyl
25 6-thiazolo[4,5-c]pyridinyl
3-5H-thiazolo[3,2-a]pyridinyl
8-5H-thiazolo[3,2-a]pyridinyl
2-7H-thiazolo[3,2-a]pyridinyl
7-7H-thiazolo[3,2-a]pyridinyl
30 3-3H-thiazolo[3,4-a]pyridinyl
5-3H-thiazolo[3,4-a]pyridinyl
10-10H-pyridazino[3,2-b]quinazolinyl
4-10H-pyridazino[3,2-b]quinazolinyl
8-10H-pyridazino[3,2-b]quinazolinyl
35 3-3H-1,2-benzodioxolyl
5-3H-1,2-benzodioxolyl
2-1,3-benzodioxolyl

-12-

7-1,2-benzodioxolyl
2-1,4-benzodioxinyl
6-1,4-benzodioxinyl

5 Linking X groups, besides the alkyl, alkenyl and alkynyl groups, include the following, for example. The groups are named as they appear in the generic formula, but it will be understood that the groups may, in fact, be oriented in either direction.

10 acetylthio
 sulfinyl
 sulfonyl
 oxycarbonyl
 propoxycarbonyl
15 methylthiocarbonyl
 butyrylamino
 propionyloxy
 ethylaminocarbonyl
 carbonyl
20 oxy
 thio
 methoxy
 propylthio
 a bond
25 oxysulfonyl

The cyclic R⁵ groups may be substituted with a variety of substituent groups, as set out in general in formula I. To assure that the reader fully understands the nature of those substituent groups, a representative group of

30 them will be named as follows:

 chloro
 bromo
 fluoro
35 trifluoromethyl
 methyl
 isopropyl

-13-

s-butyl
trifluoromethoxy
hydroxy
methoxy
5 isopropoxy
nitro
methylthio
ethylthio
formyl
10 acetyl
propionyl
pentanoyl
2,2-dimethylbutyryl
phenyl
15 oxo
phenoxy
phenylthio
methylsulfinyl
propylsulfinyl
20 ethylsulfonyl
isopropylsulfonyl
cyano
amino
methylamino
25 propylamino
diphenylmethylamino
triphenylmethylamino
benzyloxy
benzylthio
30 3-chlorobenzyloxy
4-fluorobenzylthio
2-nitrobenzyloxy
3-trifluoromethylbenzylthio
dimethylamino
35 diethylamino
di(isopropyl)amino
bis(cyclopropyl)amino

-14-

5 bis(cyclohexyl)amino
 methyl(cyclohexyl)amino
 bis(cyclohexylmethyl)amino
 propyl(cyclopentylethyl)amino
 cyclopentyl(cyclopropylpropyl)amino
 3-methylphenyl
 2-propylphenoxy
 4-ethylphenylthio
 3-isopropylphenylsulfonyl
10 4-methoxyphenyl
 2-ethoxyphenoxy sulfonyl
 3-ethoxyphenylthio
 4-chlorophenyl
 4-bromophenylthio
15 3-fluorophenoxy sulfonyl
 acetylamino
 propionylamino
 pentanoylamino
 2-ethylpropionylamino
20 benzoylamino
 diphenylmethylaminomethyl
 3-(diphenylmethylamino)propyl
 aminocarbonyl
 methylaminocarbonyl
25 isopropylaminocarbonyl
 dimethylaminocarbonyl
 ethyl(isopropyl)aminocarbonyl
 chloroacetyl
 3-bromopropionyl
30 4,4,4-trifluorobutyryl
 3-chloro-2-methylbutyryl
 3,4-dichlorohexanoyl
 aminosulfonyl
 methylaminosulfonyl
35 isopropylaminosulfonyl
 diethylaminosulfonyl
 methyl(propyl)aminosulfonyl

-15-

phenoxyethyl
2-phenylthioethyl
2-phenoxypropyl
3-chlorophenylthiomethyl
5 2-(3,4-difluorophenoxy)ethyl
2-(2-methoxy-4-propylphenoxy)ethyl
3-(3,5-diethoxyphenoxy)propyl
3-(4-chloro-3-ethoxyphenylthio)propyl
2,6-dichloro-4-propylphenylthiomethyl
10 benzoyl
aminomethyl
2-aminoisopropyl
methylaminomethyl
2-ethylaminoethyl
15 3-(ethylamino)propyl
dimethylaminomethyl
ethyl(isopropyl)aminomethyl
3-(ethyl(propyl)amino)propyl
morpholinylmethyl
20 2-morpholinylpropyl
3-phenylmethyl-1-piperidinyl
4-(2-phenylpropyl)-1-piperidinyl
2-phenylmethyl-1-piperidinylaminocarbonyl
4-(3-phenylpropyl)-1-piperidinylaminocarbonyl
25 3-acetylamino-5-thiophenyl
2-hexanoylamino-4-thiophenyl
3-butyrylamino-4-thiophenyl
8-amino-2-naphthalenylsulfonylamino
2-methylamino-1-naphthalenylsulfonylamino
30 5-isopropylamino-2-naphthalenylsulfonylamino
4-dimethylamino-2-naphthalenylsulfonylamino
3-methyl(propyl)amino-1-naphthalenylsulfonylamino
perfluorophenyl
perbromophenyl
35

While all of the compounds described by formula I are important in the concept of the present invention,

-16-

certain groups of those compounds constitute preferred aspects of the invention. The following table sets out a number of such preferred groups, each of which constitutes a preferred aspect of the invention, and the formulations, methods of use and the like associated with each such group are also preferred aspects. It will be understood that the reader can combine groups of preferred aspects listed in the following table to produce additional more limited or more comprehensive preferred aspects.

- a) R and R¹ both represent hydrogen;
- b) R³ represents methyl;
- c) R² represents C₁-C₃ alkyl;
- d) R² represents C₁-C₂ alkyl;
- e) R² represents methyl;
- f) R² represents methyl or hydrogen;
- g) R⁴ represents hydrogen;
- h) R⁴ represents hydrogen, halo or methyl;
- i) X represents alkyl, alkenyl or alkynyl;
- j) X represents a bond;
- k) X represents a bond or a sulfur atom;
- l) X represents -SO-, -SO₂-, or -SO₃-;
- m) X represents -CO- or -CO-Y-(CH₂)_n-;
- n) X represents -Z-(CH₂)_n-, alkyl or -CO-;
- o) X represents a bond, -Z-(CH₂)_n-, alkyl or -CO-;
- p) X represents a sulfur atom;
- q) Y represents -O- or -S-;
- r) Y represents -NH-;
- s) n represents 0 or 1;
- t) n represents 2 or 3;
- u) n represents 0;
- v) Z represents -S-;
- w) R⁵ represents phenyl or naphthalenyl;
- x) R⁵ represents pyridinyl, pyrazinyl, pyridazinyl or pyrimidinyl;
- y) R⁵ represents anthracenyl, phenanthrenyl, fluorenyl or acenaphthalenyl;

-17-

- z) R⁵ represents thiazolyl, thiophenyl or tetrazolyl;
aa) R⁵ represents benzimidazolyl, indanyl, indolyl or
indazolyl;
ab) R⁵ represents quinolinyl, isoquinolinyl, quinoxalinyl or
5 quinazolinyl;
ac) R⁵ represents benzopyranyl, benzothiazolyl,
benzothiophenyl or benzisothiazolyl;
ad) R⁵ represents benzothiazolyl;
ae) R⁵ represents benzoxazolyl, benzodioxolyl, or
10 benzodioxinyl;
af) R⁵ represents benzisoquinolyl, benzindolyl,
naphthothiazolyl, thiazolopyridinyl or
pyridazinoquinazolinyl;
ag) R⁵ represents diphenylmethyl or triphenylmethyl.

15

Further preferred classes of compounds are also
important in the practice of the present invention. A
particularly preferred class of compounds includes those
wherein R² represents methyl or hydrogen, particularly
20 methyl; X represents a bond, a sulfur atom or an ethenyl
group, particularly a bond or a sulfur atom; R⁵ represents
phenyl, naphthalenyl, isoquinolinyl, indolyl, benzothiazolyl,
pyridinyl, indazolyl, thiazolonaphthalenyl, quinolinyl or
diphenylmethyl; and the R⁵ group is unsubstituted or
25 substituted with 1-3, particularly 1, groups chosen from the
group consisting of halo, trifluoromethoxy, trifluoroethoxy,
trifluoromethyl, C₁-C₃ alkyl, methoxy, nitro, phenyl,
toluenesulfonyl, and pivaloylamino.

A further preferred class of compounds of the present
30 invention includes those described in the paragraph
immediately above, and, in addition, those wherein X
represents propyl, aminocarbonylmethyl, methoxycarbonyl and
oxycarbonyl; R⁵ represents thiophenyl, fluorenyl, indanyl,
quinoxalinyl, pyridazinyl, thiazolopyridinyl, and
35 benzisoquinolinyl; and the R⁵ group is unsubstituted or
substituted with 1-3, particularly 1, groups chosen from the

-18-

group consisting of hydroxy, C₁-C₄ alkyl, oxo, benzyloxy, phenoxymethyl and benzylpiperidiny1.

As described in formula I, the invention includes pharmaceutically acceptable salts of the compounds defined by the above formula. Although generally neutral, a particular compound of this invention can possess a sufficiently acidic, a sufficiently basic, or both functional groups, and accordingly react with any of a number of nontoxic inorganic bases, and nontoxic inorganic and organic acids, to form a pharmaceutically acceptable salt. Acids commonly employed to form acid addition salts are inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, and the like, and organic acids such as *p*-toluenesulfonic, methanesulfonic acid, oxalic acid, *p*-bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid, acetic acid, and the like. Examples of such pharmaceutically acceptable salts thus are the sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, caproate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, sulfonate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, gamma-hydroxybutyrate, glycollate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, mandelate, and the like. Preferred pharmaceutically acceptable acid addition salts are those formed with mineral acids such as hydrochloric acid and hydrobromic acid, and those formed with organic acids such as maleic acid and methanesulfonic acid.

Base addition salts include those derived from nontoxic inorganic bases, such as ammonium or alkali or alkaline earth metal hydroxides, carbonates, bicarbonates,

-19-

and the like. Such bases useful in preparing the salts of this invention thus include sodium hydroxide, potassium hydroxide, ammonium hydroxide, potassium carbonate. The potassium and sodium salt forms are particularly preferred.

Thus, the groups R^4 and $X-R^5$ include a number of substitutions each of which may be placed at the 7, 8 or 9-position of the nucleus of formula I. All such substituents are easily understandable by the chemist, but a number of the contemplated substituent arrangements will be mentioned for the convenience of the reader.

8-(6-phenoxysulfonyl-4-quinolinyloxy)
7-chloro-8-(3-chloromethyl-7-quinolinylthio)
7-[2-(3-phenoxy-6-isoquinolinylaminocarbonyl)ethyl]

9-fluoro-7-(1-methoxycarbonyl-4-isoquinolinylmethyl)
8-[3-(5-bromo-t-butyl-3-quinoxaliny)propyl]

8-fluoro-7-[3-(8-butylthio-2-quinoxaliny)-3-propynyl]
7-(3-phenyl-1,2-benzisothiazol-5-yloxy carbonyl)

8-bromo-9-(5-hexyloxysulfonylbenzoxazol-2-ylthio)

9-methyl-7-(6-trifluoromethyl-2,1-benzisothiazol-3-yl)

7-(3-isopropoxycarbonylaminopyridinyl-2-ylmethyl)
9-chloro-8-(7-hydroxy-4-benzothiazolylthio)
7-(4-isopentoxycarbonyl-1H-indazol-4-yloxy)

7-ethyl-9-[3-(6-[2-ethyl-5-methylphenoxy sulfonyl]-1H-indazol-3-yl)-2-propynyl]

9-[2-(6-ethoxycarbonyl-2H-indazol-2-yloxy)ethyl]
8-[2-(3-fluoro-2H-indazol-6-yl)ethoxy]

-20-

9-chloro-7-(3-trifluoromethoxy-3H-indazol-4-yl-thiocarbonylmethyl)

7-[2-(5-propoxy-4-[4-fluorophenoxy]-3H-indazol-7-ylthio)ethyl]

8-ethyl-7-[4-(4-[3-chlorophenoxysulfonyl]-2-indolyl)butyl]

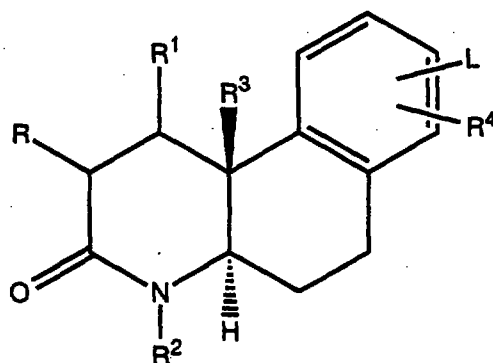
8-[3-(7-methoxy-4-[2,3-dichloropropoxycarbonylamino]2-indolyloxy)propyl]

7-[2-(5-[4-fluoro-3-methylphenoxysulfonyl]-2H-indol-4-yl)ethylcarbonylthio]

8-methyl-7-[3-(6-chloro-2-[3-chloro-5-ethylphenoxyethyl]-2H-indol-3-yl)-2-butynyl]

Synthesis of the compounds of formula I may proceed in various ways, depending in large part on the identity of the group -X-R⁵. It is very often advantageous to form the benzo[f]quinoline nucleus without the -X-R⁵ group, and to add that group in a separate step, thus providing a convergent synthesis. In such a case, the -X-R⁵ group of the compound of formula I is replaced by a leaving group, preferably a chlorine or bromine atom, when the benzo[f]quinoline nucleus is prepared. Since the R⁴ group of the nucleus is small, it may be in place throughout the synthesis. Thus, an important intermediate is the following compound of formula II.

-21-



II

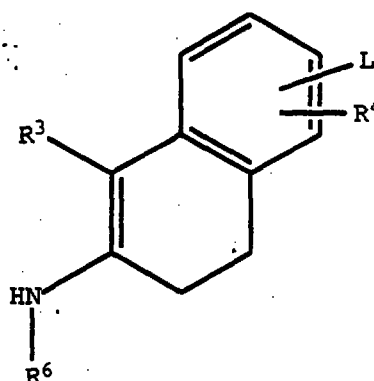
wherein L represents a leaving group, preferably
chloro or bromo.

5

A series of synthetic methods for the preparation
of intermediates of formula II was taught by Audia *et al.* in
U.S. Patent 5,239,075, issued August 24, 1993. That patent
is incorporated by reference herein, and the reader readily
will understand the synthetic methods taught by it.

10

A preferred method for preparing the intermediates
of formula II is the heteroannulation carried out by reacting
an enamine of the formula



III

15

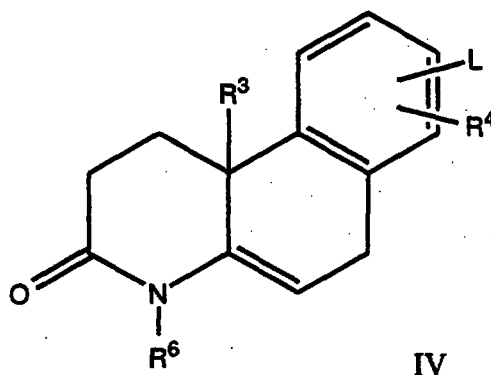
with an acryloyl halide, particularly acryloyl chloride,
acrylic anhydride, or acryloyl toluenesulfonate or
methanesulfonate. The group R6 in the above intermediate is
a chiral directing group, in order to obtain the correct
enantiomer of the intermediate of formula II. The most

20

-22-

preferred R⁶ group is (R)-(+)-1-phenylethyl. This process is taught in general by EPO Publication 0564193.

The product of the heteroannulation just described is of the formula



and the double bond at the 4a,5- position must be reduced in a second step. The reduction is readily carried out under mild conditions with chemical reducing agents such as borohydrides. Cyanoborohydride is preferred; the reduction may be carried out, for example, in formic acid under ambient conditions. More conveniently, the reduction step may be combined with the removal of the R⁶ group, by reaction with trifluoroacetic acid in a reaction medium containing or consisting of triethylsilane at reduced temperature in the range of from about -40° to 0°.

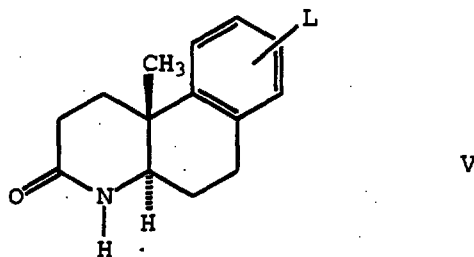
The above heteroannulation is carried out under mild process conditions. In most instances it will be found that excellent yields are obtained in short periods of time at temperatures in the range of ambient. For example, temperatures from about 0° to about 150° are used, and reaction times in the range from a few minutes to a few hours are sufficient. Preferable reaction temperatures are in the range from about -20° to about ambient temperature, and most preferably the reactants are combined at very low temperatures in the range of -20° to -80°, and the reaction mixture is allowed to warm slowly to ambient temperature while the reaction occurs. The reaction mixture may be a biphasic mixture of a convenient organic solvent and an

-23-

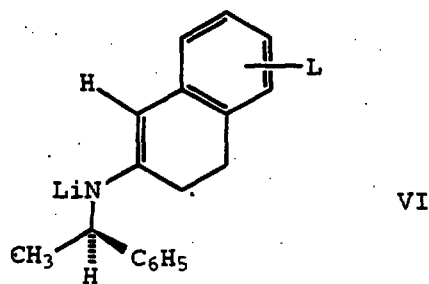
aqueous solution of a mild base. For example, solvents may include haloalkanes, ethers, including tetrahydrofuran, and nitriles including acetonitrile. Preferred mild bases are alkali metal carbonates and bicarbonates; more highly basic reagents, such as alkali and alkaline earth metal hydroxides and the like may be used, but the bicarbonates are usually preferred.

A particularly preferred method of synthesis of a key intermediate of formula II proceeds according to the following scheme.

An intermediate of the formula

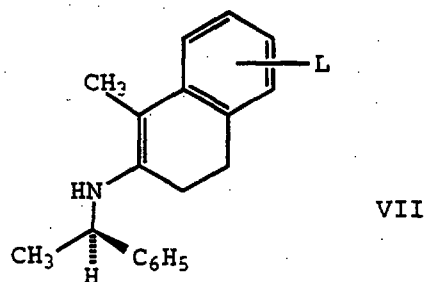


wherein L is chloro or bromo, and is located at the 7-, 8- or 9-position is prepared by reacting a compound of the formula

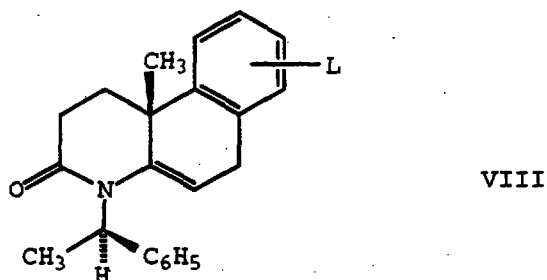


with methyl iodide in an ether solvent to prepare a compound of the formula

-24-

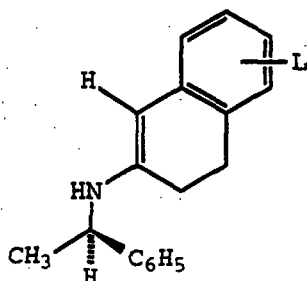


combining acrylic anhydride or acryloyl chloride with the
reaction mixture comprising the compound of formula VII to
prepare a compound of the formula



quenching the reaction with sodium bicarbonate, evaporating
the organic solution comprising the compound of formula VIII;
and combining the residue comprising the compound of formula
VIII with a trialkylsilane and trifluoroacetic acid in the
absence of a solvent to prepare the compound of formula V.

The starting material of formula VI is prepared
most conveniently by a modification of a process shown in
European Patent Publication 0564193. A substituted 2-
tetralone, having the desired L substituent on the
unsaturated ring, is reacted with (R)-(+)-phenethylamine to
prepare the intermediate of the formula



-25-

The reaction is conveniently carried out at elevated temperature, particularly the reflux temperature, in toluene in the presence of a strong acid such as *p*-toluenesulfonic acid. Water must be removed as it is formed in this reaction, and the absence of water being formed is an indication of completion of the reaction. A slight excess of phenethylamine, such as about 1.05-1.10 equivalents, should be used. Alternatively, tetrahydrofuran (THF) may be used as the solvent, and it is particularly convenient in that case to use molecular sieves to dehydrate the reaction mixture, using at least twice the weight of molecular sieves compared to the amount of water which will be released by the process.

The above phenethylamino compound is lithiated to prepare the starting material of formula VI. The reaction may be carried out with, for example, *n*-butyllithium or with lithium diisopropylamide (LDA). When the reaction is carried out, as is preferred, with LDA, the best results are obtained if the LDA is freshly generated from diisopropylamine and *n*-butyllithium immediately before use in the process. A substantial excess, about 15-25%, of LDA should be used for best results.

The LDA reaction is best carried out in THF at a low temperature in the range of about -100° to about 0°, preferably about -78° to about -10°. The phenethylamino compound need not be purified or isolated, but the first reaction mixture should be evaporated under vacuum and the residue taken up in THF. It is preferred to add the phenethylamino material, in solution, to a solution of LDA in cold tetrahydrofuran; the opposite manner of addition is operable but provides lower yields. The reaction may be carried out in quite short periods of time, less than one hour in general.

The lithio compound of formula VI is difficult to isolate and purify, and so it should be introduced into the process as a solution in the lithiation reaction mixture.

In the first step of the present process, the lithio compound of formula VI is reacted with methyl iodide

-26-

to provide the compound of formula VII. It is advisable to use about 15-25% of excess methyl iodide, and to carry out the process in an ether solvent, such as diethyl ether, methyl butyl ether or, preferably, THF. The reaction is very rapid at low temperatures in the range of about -100° to about -50°, most preferably, about -80° to about -60°.

Reaction times in the range of from about a few minutes to about one hour are adequate, and a 20-minute reaction time is often preferred.

If the compound of formula VI is in the form of the reaction mixture from lithiation with LDA, and the reaction mixture therefore contains the residual diisopropylamine, that amine must be neutralized before further reaction of the compound of formula VII. Most conveniently, the methyl iodide mixture is allowed to warm to a temperature close to 0°, and a sufficient amount of methanesulfonic acid is added to neutralize the diisopropylamine. Other strong acids may be used, but methanesulfonic acid is particularly convenient because the resulting methanesulfonate salt of diisopropylamine is only slightly soluble and therefore may be easily removed by simple filtration or centrifugation.

The reaction mixture comprising the compound of formula VII is combined with acrylic anhydride or acryloyl chloride to initiate the aza-annulation reaction which forms the compound of formula VIII. It is best to generate the acrylic anhydride, the preferred reagent, immediately before use by the reaction of acryloyl chloride and acrylic acid, using triethylamine and a stabilizer, such as hydroquinone and butylated hydroxytoluene, in THF.

The aza-annulation is best carried out by adding the acrylic anhydride or acryloyl chloride at a very low temperature, such as from about -100° to about -70°, and allowing the mixture to warm very slowly with stirring to a temperature in the range of about -20° to about 0°, or even up to about 10°-20°. A period of 12-15 hours is not too much for that period of time. When the reaction has gone as far toward completion as is desired, the reaction is quenched by

-27-

addition of sodium bicarbonate. It is preferred to use from about 1.5 to about 4 equivalents of base, most preferably about 2 equivalents. The base may be added as a solution, for example, in water or in an aqueous solvent such as water/dimethylaminopyridine, but it is preferred to add the base in solid form. The reaction mixture is stirred with the quenching base for a brief period, and then the mixture is filtered, the volatiles are removed, and the solvent may be replaced with an ether solvent, preferably diethyl ether, and the organic solution may then be worked up by washing with aqueous base and aqueous acid, and perhaps with additional purification steps such as a wash with a saturated salt solution. If such work up steps are used, the solution is then dehydrated and evaporated under vacuum to obtain the non-volatile portions of the reaction mixture, containing the final intermediate of formula VIII. On the other hand, the residue from the quenched reaction mixture may be carried on without work up if desired.

The residue from the aza-annulation step is cooled, and a chilled mixture of a trialkylsilane and trifluoroacetic acid is added. The addition should take place at a low temperature in the range of from about -40° to about 0° , and no other solvent is used. A large quantity of trifluoroacetic acid, in the range of about 10-50 equivalents, most preferably about 20-30 equivalents is used. The preferred trialkylsilane is triethylsilane, although trimethylsilane, tripropylsilane and the like may also be used. A substantial excess of trialkylsilane, in the range of about 5-20 equivalents, most preferably about 7-15 equivalents is used. The mixture is stirred for about 10-20 hours while it is allowed to warm slowly to about 30° , and then the mixture is slowly heated to an elevated temperature, preferably the reflux temperature, and is stirred at that temperature for a few hours, such as about 2-6 hours to complete the formation of the compound of formula V.

The residue containing the intermediate of formula V is dissolved, preferably in a haloalkane such as

-28-

dichloromethane, washed with base, such as aqueous sodium bicarbonate, and concentrated under vacuum. The residue is thoroughly washed with, for example, an ether solvent which may often preferably be diethyl ether to obtain the purified
5 desired compound of formula V.

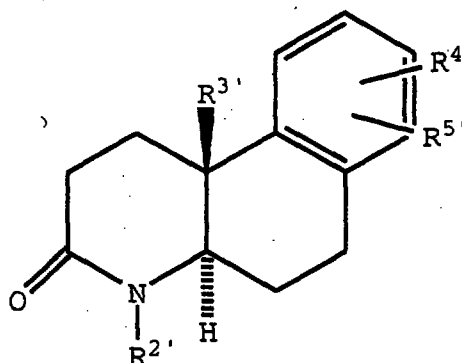
Further details of the process will be shown below as Preparations.

It will be understood that the principles of the above process may be applied to compounds of the present
10 invention other than the specific intermediates shown. So long as the R^4 and $X-R^5$ substituents of the compound to be prepared are stable under the reaction conditions, particularly the exposure to LDA, those substituents may be placed on the starting tetralone and carried through the
15 steps of the process to prepare the complete compound of formula I in a single linked process, although the one-pot aspect of the above process may not be possible with such starting materials.

It is necessary in the synthesis to alkylate the nucleus to add the R^2 substituent, if one is desired. U.S. Patent 5,239,075 shows such alkylation by reaction with an alkyl
20 iodide in the presence of a very strong base such as sodium hydride, a conventional process step. Similar alkylations are shown below in the presence of, preferably, potassium t-
25 butoxide in t-butanol as solvent.

The present invention also provides a superior and preferred process for alkylating certain benzoquinolinone compounds which include many of the compounds of the present
30 invention, and also many of the compounds previously disclosed in U.S. Patent 5,239,075. The process allows particularly economical and ready alkylation of the N-4 position of the molecule without the necessity to use unusually strong bases such as potassium t-butoxide and the
35 like. The compounds which are prepared by the present alkylation process are of the formula

-29-



A

wherein $R^{2'}$ is methyl, ethyl or n-propyl;

$R^{3'}$ is hydrogen or methyl;

R^4 is hydrogen, halo, methyl or ethyl;

5 $R^{5'}$ is halo, nitro, cyano, C₁-C₆ alkyl,

trifluoromethyl or C₁-C₆ alkoxy;

or $R^{5'}$ is a group -A- R^6 wherein A is C₁-C₆ alkyl, C₂-C₆ alkenyl, or C₂-C₆ alkynyl; and R^6 is halo, trifluoromethyl, or C₁-C₆ alkoxy;

10 or $R^{5'}$ is a group -X'- R^7 wherein X' is C₁-C₄ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl or a bond;

and R^7 is phenyl, naphthalenyl, pyridinyl, pyrazinyl,

pyridazinyl, pyrimidinyl, anthracenyl, acenaphthalenyl,

thiazolyl, benzimidazolyl, indazolyl, thiophenyl,

15 phenanthrenyl, quinolinyl, fluorenyl, isoquinolinyl, indanyl,

benzopyranyl, indolyl, benzoquinolinyl, benzindolyl,

benzothiazolyl, benzothiophenyl, quinoxalinyl, benzoxazolyl,

tetrazolyl, naphthothiazolyl, quinazolinyl,

thiazolopyridinyl, pyridazinoquinazolinyl, benzisothiazolyl,

20 benzodioxolyl, benzodioxinyl, diphenylmethyl or

triphenylmethyl;

the above R^7 groups are unsubstituted or substituted

with 1-3 groups chosen from the group consisting of halo,

trifluoromethyl, trifluoroethoxy, C₁-C₄ alkyl,

25 trifluoromethoxy, hydroxy, C₁-C₃ alkoxy, nitro, C₁-C₃

alkylthio, C₁-C₆ alkanoyl, phenyl, oxy, phenoxy, phenylthio,

C₁-C₃ alkylsulfonyl, cyano, benzyloxy, benzylthio, (mono-

halo, nitro or trifluoromethyl)benzyl(oxy or thio), (mono-C₁-

C₃ alkyl, C₁-C₃ alkoxy or halo)-(phenyl, phenoxy, phenylthio,

30 phenylsulfonyl or phenoxysulfonyl), halo-C₁-C₆ alkanoyl,

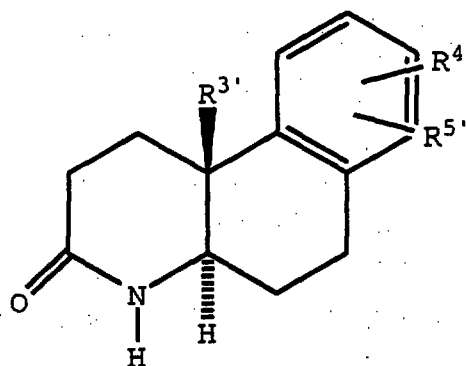
-30-

phenyl(oxy or thio)(C₁-C₃ alkyl), (halo, C₁-C₃ alkyl or C₁-C₃ alkoxy)phenyl(oxy or thio)(C₁-C₃ alkyl), or benzoyl;

or an above R⁷ group is substituted with a morpholino(C₁-C₃ alkyl) group, or a phenyl(C₁-C₃ alkyl)piperidinyl group;

or R⁷ is a perhalophenyl group;

the process comprises reacting a compound of the formula



B

with methyl, ethyl or n-propyl iodide in a reaction mixture comprising an organic solvent chosen from the group consisting of tetrahydrofuran, dimethoxyethane, diethoxyethane and methyl t-butyl ether, and aqueous sodium or potassium hydroxide.

The compounds prepared by the alkylation process are among those which have been described in full above, or have been described in full in the above-mentioned patent. No additional description of the products is necessary.

Similarly, the starting materials of Formula B have also been thoroughly described, and they are prepared by the general methods of preparation described in this document or in U.S. 5,239,075.

The present process itself is readily carried out, and is distinguished by both particularly effective alkylation, under mild and easily controlled conditions, and by particularly easy isolation of the products. Frequently, prior art alkylations of similar types required the use of phase transfer catalysts to isolate the products in satisfactory yield and purity, but it has been found that the

-31-

products of the present alkylations are isolated by simple crystallization.

Certain aspects of the alkylation process are preferred and will be mentioned below specifically. It will be understood that the following aspects are each important individually, and also that preferred aspects may be combined to create further, more limited or more expansive, preferred aspects.

a) $R^{2'}$ is methyl and the compound of formula B is reacted with methyl iodide;

b) $R^{2'}$ is methyl or ethyl and the compound of formula B is reacted with methyl or ethyl iodide;

c) $R^{3'}$ is hydrogen;

d) $R^{3'}$ is methyl;

e) R^4 is hydrogen;

f) $R^{5'}$ is halo;

g) the organic solvent is tetrahydrofuran;

h) the hydroxide is sodium hydroxide;

i) the concentration of the aqueous sodium or potassium hydroxide is near saturation.

The alkylation process is carried out in conventional chemical plant equipment, preferably at ambient pressure and at moderate temperatures. It is preferably begun by slurrying the starting material of formula B in the organic solvent at a temperature near ambient, such as from about 0° to about 50°, more preferably from about 15° to about 25°. The most preferred organic solvent is tetrahydrofuran (THF), and it is preferred to use about 5-15 liters of solvent per kilogram of starting material; more preferable solvent volume is about 10 liters per kilogram. The alkyl iodide is then added as neat liquid. A substantial excess of alkyl iodide is preferably used, such as about 1.2-1.8 equivalents based on the starting material, most preferably about 1.5 equivalents.

The aqueous sodium or potassium hydroxide is then added, still at about ambient temperature, in an amount of about 1-4 liters per kilogram of starting material. The quantity of aqueous base is

-32-

somewhat dependent on the concentration of the base and the choice of sodium or potassium hydroxide; when the most preferred base, 50% sodium hydroxide, is used, the most preferred amount of it is about 2 liters per kilogram of starting material. Then the reaction mixture, consisting of solid material slurried in two liquid phases, is warmed to about 25-65° with vigorous agitation and the reaction is allowed to proceed at about constant temperature with constant agitation. The preferred reaction temperature is about 35-40°. As the reaction proceeds toward completion, the solid starting material and alkyl iodide will dissolve and react, so the disappearance of solids is a crude indication of completion. The reaction may be followed by high pressure liquid chromatography (HPLC) on C-18 silica gel column, eluting with 1:1 acetonitrile:aqueous buffer (5% ammonium acetate) and monitoring at 220 nanometers.

When the reaction has gone as far as is desired toward completion, the mixture is cooled to about ambient and the aqueous layer is separated and discarded.

The preferred purification and isolation procedure proceeds by diluting the organic layer with water, and neutralizing it with aqueous mineral acid. Then the solution is distilled until the vapor temperature rises to about 69-80°, removing most of the THF. Slow cooling to about 5° over a period of about 1-14 hours crystallizes the product, which needs only washing with water and drying to be ready for use as an intermediate or as a pharmaceutical.

The alkylation process provides product in the same stereochemical form as the starting material, in satisfactory purity for the pharmaceutical industry, and in yields of or above 90% when operated according to the preferred manners.

The following Examples further explain the process and provide details which will be of use to the skilled reader.

Example 1

(4aR)-(10bR)-8-chloro-4-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

To a 1-liter flask equipped with a condenser and a stirrer were added 470 mL of THF, 18.7 g of methyl iodide and

-33-

47 g of (4aR)-(10bR)-8-chloro-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one, and stirring was begun at ambient temperature. To the mixture was added 100 ml of 50% aqueous sodium hydroxide in one portion, and gentle heating was begun. The temperature was raised as high as 41° and was then gradually lowered to 29° at the end of 16 hours of stirring. HPLC liquid chromatography, eluting with 1:1 acetonitrile:aqueous buffer (5% ammonium acetate) and monitoring at 220 nanometers, then showed that all the starting material had been consumed and the aqueous layer was removed. The organic layer was concentrated to an oil under vacuum, and the residue was dissolved in ethyl acetate. The solution was washed with brine, and the organic layer was washed with 200 mL of water twice, and was dried over magnesium sulfate and evaporated under vacuum while heptane was added portionwise as the ethyl acetate was removed. A total of 500 mL of heptane was added, and the product began to crystallize when about half of it had been added. The slurry was concentrated to about 300 ml, and filtered, and the solids were washed with heptane and dried in vacuum at 40-50° to obtain 47.03 g of product, m.p. 97-99°, of 98.7% purity.

The following example shows an advantageous manner of isolating the product of the present alkylation.

Example 1A

(4aR)-(10bR)-8-chloro-4-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Two hundred L of THF was added to a reactor, and 24.6 kg of (4aR)-(10bR)-8-chloro-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one was added. Then 35 kg of methyl iodide was added, rinsed in with 10 L of THF. A 79.6 kg portion of 50% aqueous sodium hydroxide was added in 13 minutes at 15-25°, rinsed in with 40 L of THF. The mixture was stirred at 36-39° for 13 hours, and was then cooled to 15-25°. The layers were allowed to separate, and the water/THF phase was neutralized to pH 7 with hydrochloric

-34-

acid and heated to reflux. Distillate was removed until the temperature reached 77°. A total of 154 kg of water was added from time to time. The solution was cooled over 3 hours to 3-10°, and was then stirred vigorously at that temperature until solids began to form. Then the slurry was stirred gently at constant temperature for 3 hours. The slurry was filtered, and the vessel and filter cake were washed with cold water. The cake was air dried at 25-35° for 75 hours to obtain 27.3 kg of the desired product, potency 85.1% by liquid chromatographic analysis.

Example 2

(4aR)-(10bR)-8-chloro-4-ethyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

A 9.4 g portion of (4aR)-(10bR)-8-chloro-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one was combined in a flask with 94 ml of THF, 20 mL of 50% aqueous sodium hydroxide and 9.36 g of ethyl iodide, and was stirred at reflux, about 66°, for about 16 hours. The mixture was cooled to ambient temperature, and the layers were separated. The organic layer was evaporated to an oil, which was dissolved in ethyl acetate and extracted three times with 100 mL portions of water. It was then dried and evaporated to half its volume while heptane was added in portions. The resulting white crystalline product was filtered, washed with heptane and dried under vacuum at 25° to obtain 3.15 g of the desired product, m.p. 108-110°.

Analysis calculated for C₁₅H₁₈ClNO:

C, 68.54; H, 6.83; N, 5.54

Found: C, 68.50; H, 6.88; N, 5.31

Mass spec. (f.d.): M+ 263

Example 3

(4aR)-(10bR)-8-chloro-4-ethyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

A 9.4 g portion of (4aR)-(10bR)-8-chloro-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one was

-35-

combined with 150 mL of THF, 20 mL of 50% aqueous sodium hydroxide and 12.5 g of ethyl iodide in a flask, and was warmed with stirring to about 37°. Stirring at approximately constant temperature was continued for about 72 hours and the reaction was worked up as described above in Example 2 to obtain 3.88 g of the desired product, m.p. 108-110°. The product was found to be 98.6% pure by HPLC, eluting with 1:1 acetonitrile:aqueous buffer (5% ammonium acetate) and monitoring at 220 nanometers.

Example 4

(4aR)-(10bR)-8-chloro-4-propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

A 2.35 g portion of (4aR)-(10bR)-8-chloro-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one was slurried in 40 mL of THF and 5 mL of 50% aqueous sodium hydroxide, and 3.4 g of propyl iodide was added. The mixture was heated to about 60°, and the mixture was stirred at that temperature for about 22 hours. Workup was carried out by separating the organic layer and evaporating it to dryness, and adding water and ethyl acetate. The organic layer was separated, washed twice with water, dried, filtered and evaporated under vacuum to obtain 710 mg of white crystalline product, found to be of about 90% purity. It was then purified by silica gel flash chromatography, eluting with ethyl acetate, to obtain 510 mg of purified product, m.p. 110-110°, of 98.98% purity, by HPLC, eluting with 1:1 acetonitrile:aqueous buffer (5% ammonium acetate) and monitoring at 220 nanometers.

Analysis calculated for C₁₆H₂₀NClo:

C, 69.18; H, 7.26; N, 5.04

Found: C, 68.92; H, 7.09; N, 5.15

If a product of formula I having an isopropyl R² group is desired, alkylation of the intermediate of formula VIII may be accomplished with isopropyl iodide, using sodium hydride as an activating agent and operating the reaction in

-36-

a solvent of the group mentioned just above at an elevated temperature such as the reflux temperature.

Frequently a final stage intermediate such as that of formula VIII is produced in a racemic form as a mixture of the two trans-4a-10b isomers. Such an isomeric mixture may be converted to substantially pure desired enantiomers by a process clearly explained in U.S. Patent 5,239,075, which proceeds by opening the piperidinone ring with a strong acid such as methanesulfonic acid, preparing a chiral salt with (-)- (R,R)-di-p-toluytartaric acid, and separating the desired enantiomeric form of the salt as typically is done in such resolutions. The salt is then sprung with aqueous base and the piperidinone ring is reclosed by simple heating.

Another operation which may be carried out on the nucleus of the compounds of the present invention is oxidation to provide the compounds wherein R and R¹ represent a bond. Such oxidations are conveniently carried out by reaction with an oxidizing agent such as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in the presence of bis(trimethylsilyl)trifluoromethyl acetamide, preferably in dioxane as solvent. The oxidations are carried out at elevated temperature, such as the reflux temperature or from about 50° to about 150°, and preferably the reaction mixtures are stirred at about ambient temperature for a period of time before heating is begun. Further, information about such oxidations can be found below in the Examples.

In the course of preparing compounds having various X-R⁵ groups, it is necessary or convenient to provide nucleus compounds having corresponding leaving groups or reactive groups. For example, compounds having carboxy, thio, hydroxy, amino, formyl and B(OH)₂ groups are needed for various syntheses and are readily prepared, as is demonstrated below, for example, in the Preparations. Such compounds are preferably prepared from compounds having a halogen atom, particularly a bromine atom but also iodine and chlorine atoms on the nucleus.

-37-

Various processes are conveniently used for placing the X-R⁵ groups on the benzoquinolinone nucleus; the choice of processes is primarily dependent on the nature of the X group. Where the X group is merely a bond, a preferred process is dependent on palladium mediated boron chemistry. In one preferred process, a benzoquinolinone nucleus compound having a bromine atom as the L substituent is reacted with an intermediate which constitutes the R⁵ substituent group with a boronic acid (B(OH)₂) at the point of attachment to the benzoquinolinone nucleus. The reaction is conveniently carried out in the presence of a catalytic amount of tetrakis (triphenylphosphine) palladium, in a basic reaction mixture including, for example, aqueous sodium carbonate or triethylamine. The preferred solvent is an ether such as THF or dimethoxyethane (DME), and the reactions go cleanly at elevated temperatures such as the reflux temperature or from about 50° to about 100°. A useful variation on the above process is carried out using an ester of boronic acid as the intermediate, such as a diethylborane. The examples show illustrations of such syntheses.

Similarly, compounds having a bond as the X group may be synthesized by the palladium mediated reaction of a bromine-substituted compound providing the R⁵ group with a boronic acid-substituted benzoquinolinone nucleus.

Still another method for preparing compounds having no X group is to react a halo-substituted nucleus compound of formula IV with a compound comprising the desired R⁵ group, substituted with a tri-n-butylstannyl group at the point of attachment. Such reactions are carried out in the presence of a small amount of bis(triphenylphosphine)palladium halide at high temperatures such as from about 60 to about 120°. A solvent such as acetonitrile may be used, and the reaction should be carried out in inert gas atmosphere.

Another particularly important group of compounds of formula I are those wherein X is a sulfur atom. Such groups are conveniently prepared by at least two main processes. In one process, a halo-substituted

-38-

benzoquinolinone nucleus compound is reacted with a disulfide of the formula $R^5-S-S-R^5$. For example, if a benzylthio substituent is to be provided, the disulfide would be dibenzylidisulfide. The reactions go readily at ambient temperature after combining the reactants at a very low temperature, such as from about -50° to about -100° , in an ether solvent in the presence of a very strong base, particularly a combination of methyllithium and *t*-butyllithium. The reactions are rapid and may be carried out in 1 hour or, at most, a few hours. Another method of synthesis of thiosubstituted compounds, which avoids the use of very low temperatures, is one where either the nucleus or the compound providing the R^5 group is substituted with an SH group and the other is substituted with a bromine, chlorine or iodine atom. Such reactions are carried out at ambient or moderately elevated temperatures, such as from about 50° to about 100° , in a high-boiling solvent such as dimethylformamide and in a basic reaction medium. Such bases as potassium carbonate, sodium bicarbonate, triethylamine and other moderately strong bases are adequate. Numerous examples of such syntheses are shown below.

Similarly, when the group X is an oxygen atom, the compounds are conveniently prepared by reactions where one of the nucleus and the R^5 group - providing compound carries a halogen atom, and the other carries a hydroxy group. As usual with such reactions, basic conditions and moderately elevated temperatures, such as were just described, are adequate to provide reasonably prompt and clean production of the desired compound of formula I.

Compounds wherein X is an oxyalkyl or thioalkyl group are prepared from a nucleus compound having a formyl or formylalkyl L substituent, which material is prepared, as shown below, by reaction of a halo-substituted nucleus compound with dimethylformamide in the presence of a very strong base, to prepare the formyl substituted compound. It is reduced to form a hydroxymethyl group, which is converted

-39-

to a haloalkyl group, and finally reacted with an SH or OH-substituted compound providing the R⁵ group.

The group of compounds of formula I where X is alkyl, alkenyl or alkynyl are made, in general, by processes where a halo-substituted nucleus compound is reacted with a compound providing the X-R⁵ group, in the presence of a 9-borabicyclo[3.3.1]nonane alkyl compound (generated in situ by treatment of the appropriate alkene with 9-borabicyclo[3.3.1]nonane (9-BBN)) or of a bis(tri-substituted-phosphine)palladium compound, at a high temperature in an inert atmosphere. Solvents such as dimethylformamide may be used, and a basic environment provided by triethylamine or the like is appropriate. Temperatures in the range of from about 80° to about 140° may be used for long periods of time up to as much as 24 hours. The resulting compounds may be hydrogenated in conventional manners to reduce them from alkynes to alkenes or from alkenes to alkyls.

Another method of synthesis of alkyl-linked compounds may be carried out by reacting the halo-substituted benzoquinoline nucleus compound with a very strong base, preferably a combination of methyllithium and *t*-butyllithium, and then adding an aldehyde or ketone providing the desired X-R⁵ substituent. For example, an example below shows the preparation of a compound wherein X is a bond and R⁵ is diphenylmethyl by such a reaction of benzophenone. Such reactions should be carried out at low temperature, warming to ambient or slightly elevated temperature, preferably in an ether solvent.

Compounds of formula I wherein X is a carbonyl group, an ester group or a carboxamide are prepared in manners following the general processes for synthesis of such compounds. For example, a compound where X is a carboxamide may conveniently be prepared by reacting a halo-substituted benzoquinolinone nucleus compound with an isocyanate carrying the desired R⁵ group. Such reactions are carried out in

-40-

ether solvents, frequently preferably THF, in the presence of methyllithium/t-butyllithium at low temperatures.

Another method for synthesis of carbonyl-substituted compounds is to react an aldehyde with a halo-substituted nucleus compound, to provide a hydroxymethyl-substituted intermediate. Such a reaction is carried out in the presence of methyllithium/t-butyllithium at low temperatures, again in an ethereal solvent by preference. The hydroxymethyl intermediate is oxidized, as with Jones reagent under the usual conditions for such reactions, to prepare the desired compound where X is a carbonyl group.

The benzoquinolinone intermediate having a carboxy substituent on the phenyl ring, the preparation of which is shown below as a Preparation, is conveniently used to prepare compounds where X incorporates an ester or amide linkage, by conventional esterification reactions with alcohols, or amide preparations with amines. All of the conventional reaction conditions are applicable, such as the use of carbonyldiimidazole as an initiator, or oxalyl chloride/dimethylformamide. When an X group incorporates an alkylene chain together with an ester or amide linkage, appropriate starting materials including the alkylene chain are used as a chemist would anticipate.

On the other hand, when the X group comprises an amide linkage where the nitrogen is linked to the benzoquinolinone, the amino-substituted intermediate prepared below is conveniently reacted with, for example, a carbonyl halide carrying the desired R⁵ group under the conventional reaction conditions. Again, small alkylene groups may be incorporated as desired to make up any of the possible X groups in the contemplation of the present invention.

For example, an unsaturated alkyl-substituted nucleus compound, prepared as discussed above, may be oxidatively cleaved to form the corresponding carboxyalkyl compound. Oxidizing agents such as periodates are commonly used for such transformation and may be used in these instances. The carboxy compound is then esterified or

-41-

amidated in the usual manner to prepare the desired alkyl-ester or alkyl-amide X group.

It will be understood that the above discussions of esters include thioesters where the group Y represents a sulfur atom, as well as the more commonly used esters.

Finally, numerous transformations are or may be carried out on R^5 groups, to transform one compound of the present invention to another compound. For example, a compound where the R^5 group is substituted with a functional group such as alkanoyl, especially formyl, may be reacted with an amine to prepare the corresponding aminoalkyl-substituted compound. Compounds having, for example, nitro groups may be reduced to form the corresponding amino-substituted compounds, and amino-substituted compounds may be reacted with ketones or aldehydes in the presence of reducing agents, or by subsequent reduction, to prepare the corresponding compounds wherein the R^5 group is substituted with alkyl amino.

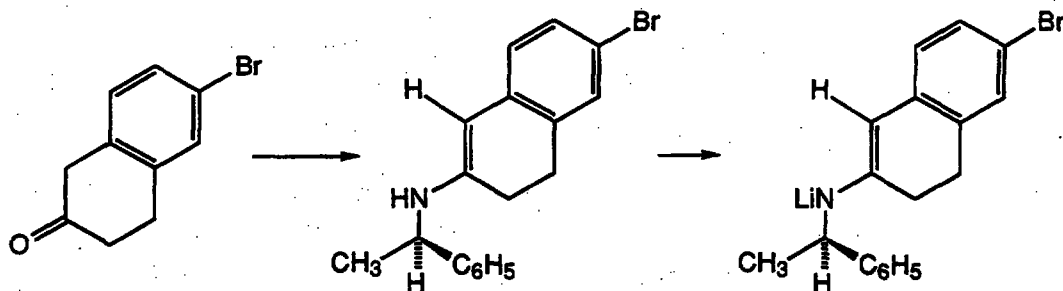
Further information about the preparation of compounds of the present invention is to be found in the following Preparations and Examples, which, while certainly not intended to limit the present invention, are illustrative of the processes by which all of the compounds are prepared.

The first group of Preparations below illustrate the preferred synthesis of the benzoquinolinone nucleus compounds which process was described in detail above.

-42-

Preparation 1

(R)-6-bromo-2-(1-phenylethylamino)-3,4-dihydronaphthalene, lithium salt



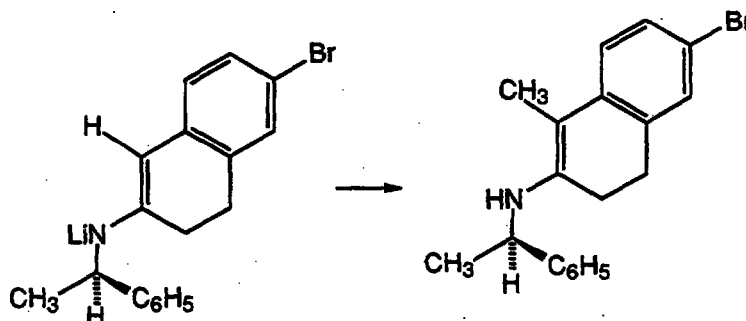
6-Bromo-2-tetralone, (45.0 g, 200 mmol uncorrected, potency of 90%, 0.90 equiv, corrected) was refluxed with (R)-(+)-phenethylamine (26.6 g, 220 mmol, 1.10 equiv, p-toluene-sulfonic acid (160 mg, 0.84 mmol, 0.004 equiv), and toluene (600 mL) in a 2000-mL round bottom flask fitted with a water separator. Reflux was continued until a water-free distillate was observed and then approximately 250 mL of toluene was collected over about 2 to 3 hours. The mixture was cooled to approximately 30-35° and concentrated under house vacuum.

The residue above, containing the enamine intermediate, was dissolved in tetrahydrofuran (THF, 480 g, 540 mL) and cooled below -50°. This solution of the enamine was added via cannula to a solution of lithium diisopropylamide (LDA, 1.15 equiv) at -50 to -60° over 5 minutes. The solution was warmed to -5° over 20 minutes and then recooled to -75° affording a 0.125 M solution of the lithium salt starting material. Proceed immediately to next step - unstable intermediate.

-43-

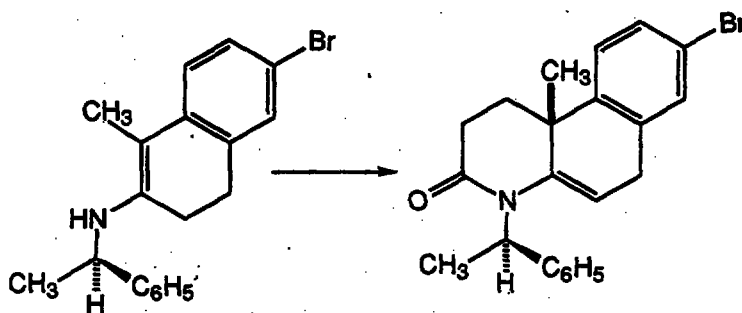
Preparation 2

(4a_R)-10b_R-8-bromo-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

5 Step A - Methyl Iodide

10 Methyl iodide (14.4 mL, 230 mmol, 1.15 equiv.) was added via syringe to the reaction mixture from Preparation 1 at -75 to -70° over 3 minutes. This solution was warmed to -5° in 20 minutes and then treated with methanesulfonic acid (24.8 g, 16.8 mL, 1.3 equiv.) affording a solution of the desired enamine admixed with diisopropylamine methanesulfonate as a slightly soluble, off-white precipitate, which was then removed by filtration.

15

Step B - Aza-Annulation

20

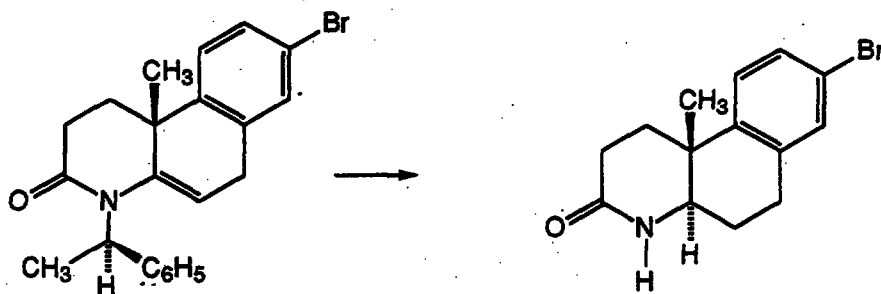
The reaction mixture solution from the above step was treated with acryloyl chloride (1.7 equiv.) at -75° in one portion over about 5 minutes. The mixture was then allowed to warm to -8° over 15 hours. The reaction was

25

-44-

quenched by pouring into sodium bicarbonate (60 g in 240 mL of water at 5 to 7°, 15 minutes addition time, 20 minutes stir, pH should be basic). Dimethylaminopyridine (0.01 equiv, 2 mmol, 244 mg) was added and the mixture stirred
5 another hour. The mixture was concentrated under vacuum (10-25°, initial volume 2000 mL; final volume 400 mL) and methylene chloride (400 mL) was added and the organic phase was washed with aqueous sulfuric acid (1.0 N, two 100 mL portions, pH 1-3) and sodium bicarbonate (1.0 N, 50 mL, pH
10 9). The organic extracts were dried and clarified by filtration over approximately 20 g of 4Å molecular sieves. The mixture was concentrated under vacuum to a total weight of 129.6 g.

15 Step C - Reduction-Cleavage



To about 103 g of the above residue were added 37
20 mL of triethylsilane and 46 mL of trifluoroacetic acid at 25°. After 1.5 hours reduction was approximately 50% complete. After an additional 12 hours the reduction was complete by TLC. The mixture was then refluxed for 2.5 hours. The mixture was allowed to cool and was concentrated
25 in vacuo to approximately 25 g. The residue above was dissolved in 400 mL of methylene chloride, washed with aqueous sodium hydroxide (enough for pH 11), and concentrated under vacuum. This concentrate was then treated with diethyl ether (approximately 5 volumes at 22° then 0° for several
30 hours). The mixture was filtered and rinsed with several small portions of ether affording the desired product after

-45-

drying as a crystalline, white solid (yield = approximately 60% based on purity of bromotetralone).

Analysis by reverse phase high performance liquid chromatography on a Waters NOVA-PAK instrument, C-18 3.9 X 150 mm column, eluting with 2 ml/min. of 25% aqueous acetonitrile containing 1% ammonium acetate, operating the detector at 220 nm.

Potency: 91.2%

Related substances: 6.8%

Anal Calcd for $C_{14}H_{16}NOBr$:

C, 57.16; H, 5.48; N, 4.76; Br, 27.16

Found: C, 55.08; H, 5.43; N, 4.30; Br, 27.78

^{13}C NMR ($CDCl_3$): 21.60, 24.62, 28.24, 29.48, 33.15,

36.90, 57.28, 121.03, 127.42, 130.09, 132.86,

137.51, 143.26, 173.62

1H NMR ($CDCl_3$): 1.18(s, 3H)

α 589 nm - 90°

α 365 nm - 302°

ee% > 98%, determined by chromatography on a Chiracel-OD instrument and 1 mL/min, 40°, eluting with 10% isopropanol in hexane and operating the detector at 220 nm.

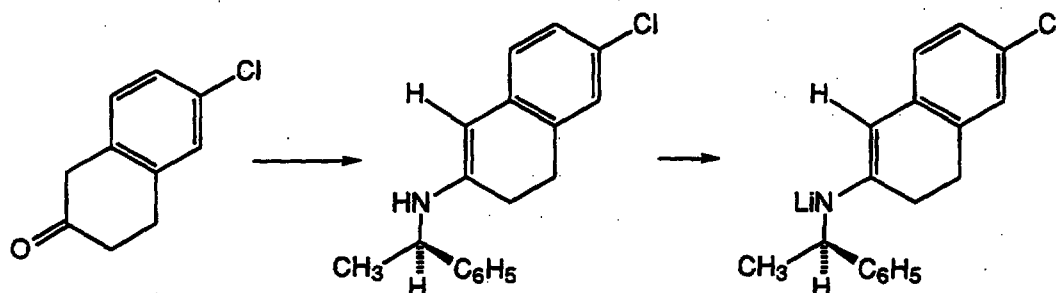
Preparation 3

acrylic anhydride

Two hundred fifty ml of tetrahydrofuran was added to a 1 liter jacketed flask with stir bar and nitrogen purge, and 250 mg of butylated hydroxytoluene, 250 mg of hydroquinone and 25.3 g of triethylamine were added. The solution was cooled to 0°, and to it was added 18.0 g of acrylic acid over a 2 minute period. The solution was cooled again to 0°, and 22.6 g of acryloyl chloride was added over a 10 minute period. It is important to maintain the addition rate constant during the acryloyl chloride addition. Maintaining the jacket temperature at 0° and continuing the nitrogen purge, the solution was stirred for 1 hour, and then it was filtered in a vacuum filter and the cake was washed with 50 ml of additional tetrahydrofuran.

Preparation 4

(R)-6-chloro-2-(1-phenylethylamino)-3,4-dihydronaphthalene, lithium salt

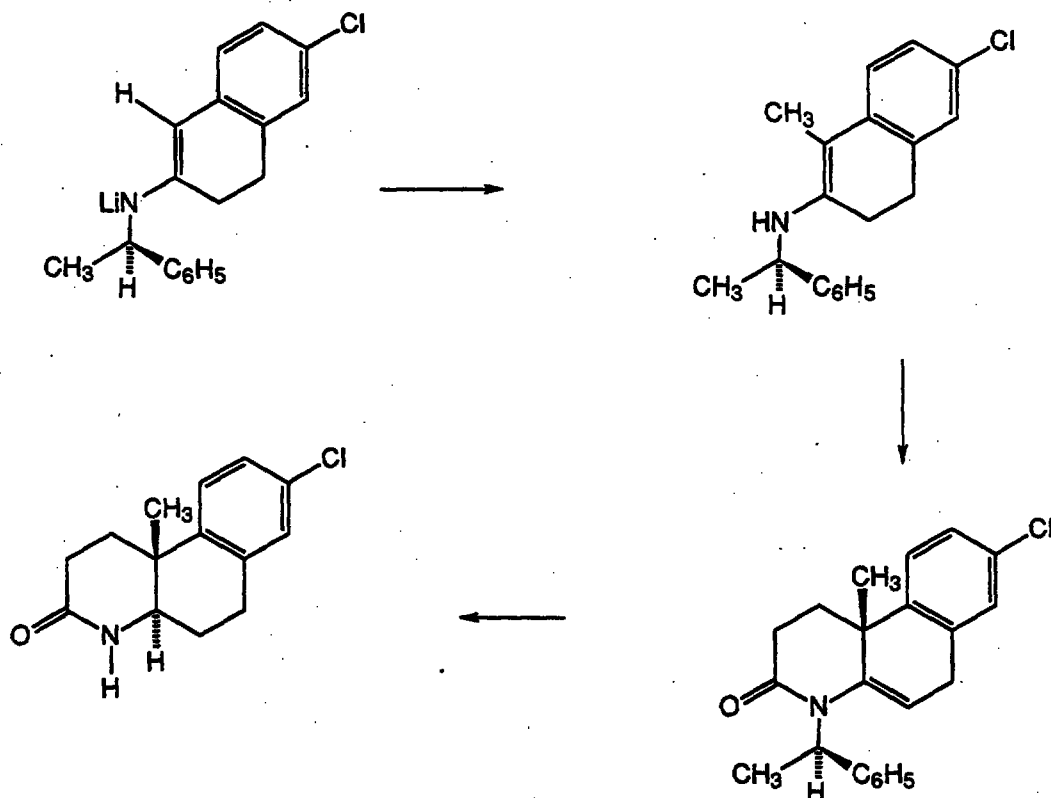


6-Chloro-2-tetralone (4.51 g, 25 mmol) was reacted with 3.32 g of (R)-(+)-phenethylamine and 20 mg of *p*-toluenesulfonic acid. The reaction was carried out as shown in Preparation 1 above in 100 mL of toluene, and when the reaction was complete the mixture was concentrated under vacuum and the residue was dissolved in 70 mL of tetrahydrofuran. The solution was cooled to -50 to -60°, and was added quickly to a solution of 1.15 equivalents of lithium diisopropylamide in 122 mL of tetrahydrofuran at -70 to -65°. The solution was allowed to warm to -20° for 20 minutes, and was then quickly recooled to -75°.

-47-

Preparation 5

(4aR)-(10bR)-8-chloro-10b-methyl-
1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one



To the cold solution from Preparation 4, was added 1.15 equivalents of methyl iodide, and the mixture was allowed to warm to -5° over a 15 minute period with continued good stirring. Then 1.3 equiv. of methanesulfonic acid was added to the mixture over a 5 minute period.

That mixture was vigorously stirred for 10 minutes at -5° , and was then cooled again to -75° . To it was added in one portion, 2.4 equiv. of acrylic anhydride, with continued stirring, and the mixture was allowed to warm from -75° to 15° over a period of 13 hours.

The resulting reaction mixture was poured into a well stirred solution of aqueous sodium bicarbonate (2 g/200 mL at 20°) and 100 mg of dimethylaminopyridine. After two hours of stirring at ambient temperature, most of the volatiles were removed under vacuum, and 130 mL of methylene

-48-

chloride was added. The mixture was washed with 50 mL of 1 N hydrochloric acid, and then with aqueous sodium bicarbonate, and the organic phase was dried and concentrated to a white foam (10.37 g).

5 The foam was placed in a flask in a ice bath and was treated with 40 mL triethylsilane and 60 mL of trifluoroacetic acid for 15 hours at 0° and was then held for four days at 25°. The volatiles were removed under vacuum, and the colorless oil was decanted from the solid product.

10 The residue was dissolved in 200 mL of methylene chloride and washed with saturated aqueous sodium bicarbonate. The extracts were dried with 4A molecular sieves and evaporated. The residue was washed with 76 mL of diethyl ether to obtain 3.87 g of the desired product as a white solid admixed with a
15 small amount of isomeric material.

MS = 249, 251 (M+, M+2)

IR (CHCl₃) = 3396, 1662 cm⁻¹.

Anal Calcd for C₁₄H₁₆NOCl:

C, 67.33; H, 6.46; N, 5.61; Cl, 14.20

20 Found: C, 66.57; H, 6.43; N, 5.40; Cl, 13.91

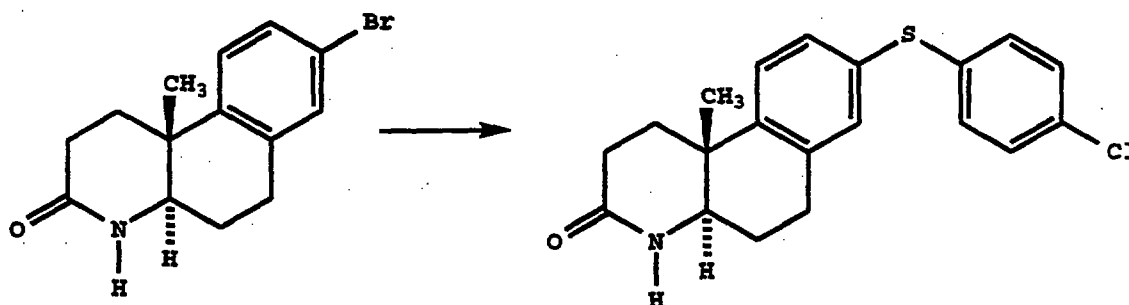
¹H NMR (CDCl₃ 500 MHz): 1.16(s, 3H), 3.54(dxd, 1H),

UV (MeOH): γ205 (21000), 271(600), 280(600)

25 The following group of examples illustrates the preparation of compounds where X is a sulfur atom by reactions with disulfides.

Example 5

(+)-(4aR)-(10bR)-8-(4-chlorophenylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one



To a 3-necked 125 ml flask was added 50 ml of THF and 500 mg of (4aR)-(10bR)-8-bromo-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one at ambient temperature. The solution was cooled to -75° , and to it was added dropwise 1.7 ml of methyllithium in diethyl ether. The mixture was stirred for 15 minutes, and then 2.4 ml of t-butyllithium (1.7 M in pentane) was added and the temperature rose to -70° . The mixture was stirred for 5 minutes and then 1.95 g of bis(4-chlorophenyl)disulfide dissolved in 10 ml of THF was added in portions. The reaction mixture was stirred for 20 minutes at -75° and then was allowed to warm to ambient temperature. It was acidified with 1N hydrochloric acid, and was diluted with 300 ml of ethyl acetate. The organic solution was washed successively with 1N hydrochloric acid, 10% sodium carbonate solution, water and brine, and was then dried and concentrated under vacuum to obtain 2 g of a yellow oil. The oil was purified by chromatography over silica gel, eluting with a solvent beginning with 2% methanol in dichloromethane and going to 3% methanol/dichloromethane. The product-containing fractions were evaporated to obtain 540 mg of foam, which was crystallized from ethyl acetate to obtain 453 mg of purified product. mp 169° - 172° FDMS: m/e=357. $\alpha[D]_{589}=+83.91$, $\alpha[D]_{365}=+293.47$ (methanol).

-50-

<u>Analysis</u>	<u>Calculated</u>	<u>Found</u>
C	67.12	67.33
H	5.63	5.82
N	3.91	3.78

The following examples were carried out according to the process of Example 5.

5

Example 6

(+)-(4aR)-(10bR)-8-(4-methylphenylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

10

Yield: 481 mg of the desired product. mp 209°-212° FDMS: m/e=337. $\alpha[D]_{589} = +85.00$, $\alpha[D]_{365} = +309.00$ (chloroform).

<u>Analysis</u>	<u>Calculated</u>	<u>Found</u>
C	74.74	75.00
H	6.87	6.94
N	4.15	4.10

Example 7

15

(+)-(4aR)-(10bR)-8-(2-chlorophenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 790 mg of the desired product. mp 189°-191° FDMS: m/e=357. $\alpha[D]_{589} = +80.66$, $\alpha[D]_{365} = +281.3$ (chloroform).

20

<u>Analysis</u>	<u>Calculated</u>	<u>Found</u>
C	67.12	67.30
H	5.63	5.52
N	3.91	3.99

-51-

Example 8

(+)-(4aR)-(10bR)-8-(3-chlorophenylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

5 Yield: 810 mg of the desired product. mp 186°-187° FDMS: m/e=357. α [D]₅₈₉ = +80.5, α [D]₃₆₅ = +292.6 (chloroform).

<u>Analysis</u>	<u>Calculated</u>	<u>Found</u>
C	67.12	67.41
H	5.63	5.82
N	3.91	3.88

Example 9

10 (+)-(4aR)-(10bR)-8-(2-methylphenylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 490 mg of the desired product. mp 192°, 196°-199°
FDMS: m/e=337. α [D]₅₈₉ = +87.8, α [D]₃₆₅ = +310.3
15 (chloroform).

<u>Analysis</u>	<u>Calculated</u>	<u>Found</u>
C	74.74	74.46
H	6.87	6.90
N	4.15	3.90

Example 10

20 (+)-(4aR)-(10bR)-8-(3-methylphenylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 480 mg of the desired product. mp 189°-191° FDMS: m/e=337. α [D]₅₈₉ = +87.8, α [D]₃₆₅ = +316.5 (chloroform).

-52-

<u>Analysis</u>	<u>Calculated</u>	<u>Found</u>
C	74.74	75.02
H	6.87	6.90
N	4.15	4.34

Example 11

5 (+)-(4aR)-(10bR)-8-(1-naphthylthio)-10b-methyl-
1,2,3,4,4a, 6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 555 mg of the desired product. mp 199°-201° FDMS:
m/e=373. α [D]₅₈₉ = +76.7, α [D]₃₆₅ = +238.6 (chloroform).

<u>Analysis</u>	<u>Calculated</u>	<u>Found</u>
C	77.18	76.96
H	6.21	6.12
N	3.75	3.64

10

Example 12

(+)-(4aR)-(10bR)-8-(2-methoxyphenylthio)-10b-methyl-
1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

15 Yield: 580 mg of the desired product. mp 176°-179° FDMS:
m/e=353. α [D]₅₈₉ = +80.4, α [D]₃₆₅ = +287.9 (chloroform).

<u>Analysis</u>	<u>Calculated</u>	<u>Found</u>
C	71.36	71.64
H	6.56	6.46
N	3.96	3.72

-53-

Example 13

(+)-(4aR)-(10bR)-8-(4-methoxyphenylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

5 Yield: 630 mg of the desired product. mp 194°-196° FDMS: m/e=353. α [D]₅₈₉ = +86.2, α [D]₃₆₅ = +309.4 (chloroform).

<u>Analysis</u>	<u>Calculated</u>	<u>Found</u>
C	71.36	71.21
H	6.56	6.51
N	3.96	3.71

Example 14

10 (+)-(4aR)-(10bR)-8-(4-fluorophenylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 600 mg of the desired product. mp 179°-181° FDMS: m/e=341. α [D]₅₈₉ = +88.9, α [D]₃₆₅ = +313.2 (chloroform).

15

<u>Analysis</u>	<u>Calculated</u>	<u>Found</u>
C	70.35	70.07
H	5.90	5.85
N	4.10	3.83

Example 15

(4aR)-(10bR)-8-(3-methoxyphenylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

20

Yield: 650 mg of the desired product. mp 154.5°-155.5° FDMS: m/e=353.

<u>Analysis</u>	<u>Calculated</u>	<u>Found</u>
C	71.36	71.29
H	6.56	6.56
N	3.96	3.91

-54-

Example 16

(+)-(4aR)-(10bR)-8-(3-fluorophenylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

5 Yield: 600 mg of the desired product. mp 154°-156° FDMS: m/e=341. α [D]₅₈₉ = +84.8, α [D]₃₆₅ = +300.6 (chloroform).

<u>Analysis</u>	<u>Calculated</u>	<u>Found</u>
C	70.35	70.38
H	5.90	5.96
N	4.10	4.09

Example 17

10 (+)-(4aR)-(10bR)-8-(2-fluorophenylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 640 mg of the desired product. mp 196°-198° FDMS: m/e=341. α [D]₅₈₉ = +84.2, α [D]₃₆₅ = +300.8 (chloroform).

15

<u>Analysis</u>	<u>Calculated</u>	<u>Found</u>
C	70.35	70.24
H	5.90	5.95
N	4.10	3.97

Example 18

(4aR)-(10bR)-8-(3-quinolinylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

20

Yield: 340 mg of the desired product. mp 168°-170° FDMS: m/e=374.

<u>Analysis</u>	<u>Calculated</u>	<u>Found</u>
C	73.76	73.56
H	5.92	5.96
N	7.48	7.36

-55-

Example 19

(4aR)-(10bR)-8-(2-quinolinylthio)-10b-methyl-
1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

5 Yield: 560 mg of the desired product. mp 220°-222° FDMS:
m/e=374.

<u>Analysis</u>	<u>Calculated</u>	<u>Found</u>
C	73.76	73.56
H	5.92	5.92
N	7.48	7.40

Example 20

10 (+)-(4aR)-(10bR)-8-(8-quinolinylthio)-10b-methyl-
1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 375 mg of the desired product. mp >260° FDMS:
m/e=374. $\alpha[D]_{589} = +71.6$, $\alpha[D]_{365}$ = absorbance (chloroform).

15

<u>Analysis</u>	<u>Calculated</u>	<u>Found</u>
C	73.76	73.61
H	5.92	5.99
N	7.48	7.46

Example 21

(4aR)-(10bR)-8-(2-pyridinylthio)-10b-methyl-
1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

20

Yield: 530 mg of the desired product. mp 223°-225° FDMS:
m/e=324.

<u>Analysis</u>	<u>Calculated</u>	<u>Found</u>
C	70.34	70.09
H	6.21	6.24
N	8.63	8.57

-56-

Example 22

(4aR)-(10bR)-8-phenylthio-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

5 Yield: 351 mg of the desired product. mp 183°-185° FDMS:
m/e=323.

<u>Analysis</u>	<u>Calculated</u>	<u>Found</u>
C	74.27	73.99
H	6.54	6.68
N	4.33	4.53

Example 23

10 (4aR)-(10bR)-8-benzylthio-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 329 mg of the desired product. mp 172°-174° FDMS:
m/e=337. $\alpha[D]_{589} = 80.84$ (c=0.57 in chloroform).

15

<u>Analysis</u>	<u>Calculated</u>	<u>Found</u>
C	74.74	74.49
H	6.87	6.85
N	4.15	4.18

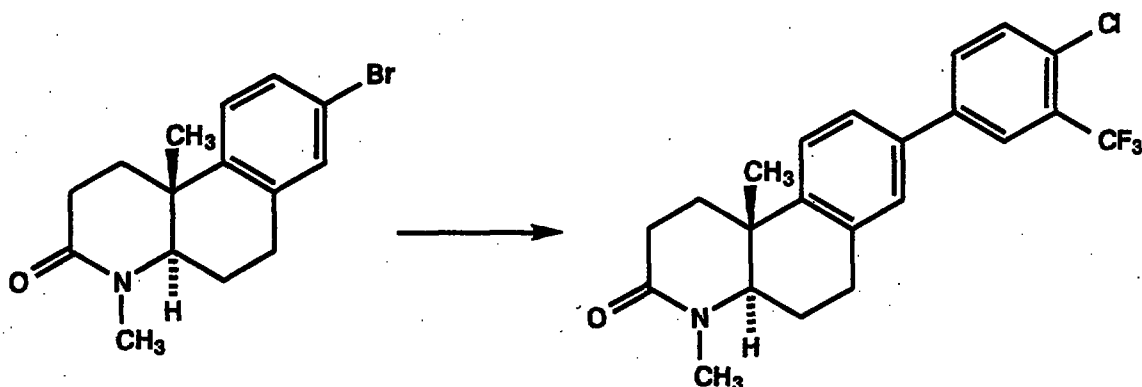
20 The following group of examples demonstrates syntheses in which a bromine-substituted benzoquinolinone nucleus compound is reacted with a compound having a boronic acid leaving group and providing the R⁵ group, where X is a bond.

-57-

Example 24

(+)-(4aR)-(10bR)-4-methyl-8-(4-chloro-3-trifluoromethylphenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]-quinolin-3-one

5



10

15

20

A 15 mL round bottom flask was charged with (+)-(4aR)-(10bR)-4-methyl-8-bromo-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one (200 mg, 0.65 mmol), tetrakis(triphenylphosphine) palladium (0) (23 mg, 0.02 mmol), 4-chloro-3-trifluoromethylphenylboronic acid (175 mg, 0.78 mmol), 0.65 mL of 2 M aq. sodium carbonate solution and 2 mL of THF, fitted with a reflux condenser, and the stirred mixture was heated at 80°, under nitrogen, for 16 h. The mixture was cooled, diluted with chloroform (50 mL) and washed with brine (2 x 25 mL). The combined organic extracts were dried over sodium sulfate, concentrated, and purified by silica gel chromatography (ethyl acetate eluent), to give 188 mg (71%) of the title compound as a white solid. mp 134-137°. FDMS: m/e = 407. α [D]₅₈₉ = +59.74 (c = 1.02, chloroform).

analysis:	calculated	found
C	64.79	64.78
H	5.19	5.23
N	3.43	3.65

-58-

The following examples were carried out according to the process of Example 24.

Example 25

(+)-(4aR)-(10bR)-4-methyl-8-(3-chloro-4-hydroxyphenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 139 mg (61%) of the title compound as a white solid. mp 245°. FDMS: m/e = 355. α [D]₅₈₉ = +17.62 (c = 1.02, chloroform).

analysis:	calculated	found
C	70.88	70.74
H	6.23	6.27
N	3.94	4.10

Example 26

(+)-(4aR)-(10bR)-4-methyl-8-(2,3-difluorophenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 111 mg (50%) of the title compound as a white solid. mp 147-148°. FDMS: m/e = 341 α [D]₅₈₉ = +70.44 (c=1.08, chloroform).

analysis:	calculated	found
C	73.88	73.79
H	6.20	6.27
N	4.10	4.16

Example 27

(+)-(4aR)-(10bR)-4-methyl-8-(3,4-difluorophenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 130 mg (58%) of the title compound as a white solid. mp 143-148°. FDMS: m/e = 341 α [D]₅₈₉ = +65.12 (c=0.97, chloroform).

-59-

analysis:	calculated	found
C	73.88	73.90
H	6.20	6.21
N	4.10	3.86

Example 28

(+)-(4aR)-(10bR)-4-methyl-8-(3-fluoro-4-hydroxyphenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

5

Yield: 111 mg (50%) of the title compound as a white solid.
mp >240°C. FDMS: m/e = 339. $\alpha[D]_{589} = +11.21$ (c = 1.07, chloroform).

analysis:	calculated	found
C	74.31	74.12
H	6.53	6.53
N	4.13	3.88

10

Example 29

(+)-(4aR)-(10bR)-4-methyl-8-(3,4-ethylenedioxyphenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

15

Yield: 189 mg (80%) of the title compound as an amorphous solid. mp 183-189°. FDMS: m/e = 363. $\alpha[D]_{589} = +80.77$ (c = 1.04, chloroform).

analysis:	calculated	found
C	76.01	75.75
H	6.93	6.89
N	3.85	3.62

-60-

Example 30

(+)-(4aR)-(10bR)-4-methyl-8-(3,5-di[t-butyl]-4-hydroxy-phenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]-quinolin-3-one

Yield: 170 mg (58%) of the title compound as a white solid.
mp >265°. FDMS: m/e = 433 α [D]₅₈₉ = +46.45 (c = 1.00, chloroform).

analysis:	calculated	found
C	80.33	78.52
H	9.06	9.01
N	3.23	2.69

Example 31

(+)-(4aR)-(10bR)-4-methyl-8-(2-trifluoromethyl-4-fluorophenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]-quinolin-3-one

Yield: 96 mg (38%) of the title compound as an amorphous foam.
mp 70°. FDMS: m/e = 391. α [D]₅₈₉ = +55.81 (c=0.60, chloroform).

analysis:	calculated	found
C	67.51	66.97
H	5.41	5.31
N	3.58	3.07

Example 32

(+)-(4aR)-(10bR)-4-methyl-8-(1-[4-t-butylcarbonylamino]-naphthyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]-quinolin-3-one

Yield: 239 mg (81%) of the title compound as an amorphous solid. mp >260°. FDMS: m/e = 454. α [D]₅₈₉ = +46.85 (c = 0.51, chloroform).

-61-

analysis:	calculated	found
C	79.26	80.39
H	7.54	7.87
N	6.16	5.82

Example 33

5 (+)-(4aR)-(10bR)-4-methyl-8-(2-chloro-5-trifluoromethyl-phenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]-quinolin-3-one

Yield: 170 mg (64%) of the title compound as an oil. FDMS: m/e = 407. α [D]₅₈₉ = +49.42 (c = 0.58, chloroform).

analysis:	calculated	found
C	64.79	65.65
H	5.19	5.39
N	3.43	3.75

10

Example 34

(+)-(4aR)-(10bR)-4-methyl-8-(3-t-butylcarboxamidophenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

15 Yield: 213 mg (81%) of the title compound as a waxy solid. FDMS: m/e = 404. α [D]₅₈₉ = +54.34 (c = 0.45, chloroform).

analysis:	calculated	found
C	77.19	77.45
H	7.97	7.93
N	6.92	6.64

-62-

Example 35

(+)-(4aR)-(10bR)-4-methyl-8-(2-[1-diethylcarboxamido]-naphthyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]-quinolin-3-one

5

Yield: 240 mg (81%) of the title compound as a white solid.
mp 208-211°. FDMS: m/e = 454. α [D]₅₈₉ = +49.37 (c = 0.51, chloroform).

analysis:	calculated	found
C	79.26	77.29
H	7.54	7.57
N	6.16	6.11

10

Example 36

(+)-(4aR)-(10bR)-4-methyl-8-(4-hydroxy-3-methoxyphenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

15

Yield: 91 mg (40%) of the title compound as a white solid. mp 247-250°. FDMS: m/e = 351. α [D]₅₈₉ = +79.51 (c = 0.75, chloroform).

analysis:	calculated	found
C	75.19	75.13
H	7.17	7.24
N	3.99	3.97

20

Example 37

(+)-(4aR)-(10bR)-4-methyl-8-(4-t-butylcarbonylaminophenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

25

Yield: 104 mg (40%) of the title compound as a brown solid.
mp >265°C. FDMS: m/e = 404. α [D]₅₈₉ = +49.42 (c = 0.56, chloroform).

-63-

analysis:	calculated	found
C	77.19	76.92
H	7.97	8.07
N	6.92	6.73

Example 38

(+)-(4aR)-(10bR)-4-methyl-8-(2-fluorophenyl)-10b-methyl-
1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 172 mg (82%) of the title compound as a foam. mp 142-150°. FDMS: m/e = 323. α [D]₅₈₉ = +77.89 (c=0.69, chloroform).

analysis:	calculated	found
C	77.99	78.09
H	6.86	6.95
N	4.33	4.30

Example 39

(+)-(4aR)-(10bR)-4-methyl-8-(2-methoxyphenyl)-10b-methyl-
1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 160 mg (73%) of the title compound as a white solid. mp 152-156°. FDMS: m/e = 335. α [D]₅₈₉ = +77.45 (c = 0.64, chloroform).

analysis:	calculated	found
C	78.77	78.53
H	7.51	7.25
N	4.18	4.35

-64-

Example 40

(+)-(4aR)-(10bR)-4-methyl-8-(2-methylphenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

5 Yield: 146 mg (70%) of the title compound as an amorphous solid. mp 82-87°. FDMS: m/e =319. α [D]₅₈₉ = +63.96 (c = 0.35, chloroform).

analysis:	calculated	found
C	82.72	82.63
H	7.89	7.95
N	4.38	4.10

10

Example 41

(+)-(4aR)-(10bR)-4-methyl-8-(2-chlorophenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

15 Yield: 186 mg (84 %) of the title compound as an amorphous foam. mp 111-120°. FDMS: m/e =339. α [D]₅₈₉ = +56.86 (c = 0.64, chloroform).

analysis:	calculated	found
C	74.22	74.50
H	6.52	6.46
N	4.12	3.82

Example 42

20 (+)-(4aR)-(10bR)-4-methyl-8-(3,4-dimethoxyphenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

25 Yield: 171 mg (72 %) of the title compound as an amorphous foam. mp 108-112°. FDMS: m/e =365. α [D]₅₈₉ = +73.75 (c = 0.56, chloroform).

-65-

analysis:	calculated	found
C	75.59	75.88
H	7.45	7.57
N	3.83	3.85

Example 43

5 (+)-(4aR)-(10bR)-4-methyl-8-(2-trifluoromethylphenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 201 mg (83 %) of the title compound as an oil. FDMS: m/e =373. α [D]₅₈₉ = +60.00 (c = 0.36, chloroform).

analysis:	calculated	found
C	70.76	70.55
H	5.94	7.97
N	3.75	3.49

10

Example 44

15 (+)-(4aR)-(10bR)-4-methyl-8-(3-fluorophenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 177 mg (84 %) of the title compound as an amorphous foam. mp 116-120°. FDMS: m/e =323. α [D]₅₈₉ = +81.84 (c = 0.47, chloroform).

analysis:	calculated	found
C	77.99	77.69
H	6.86	6.85
N	4.33	4.11

-66-

Example 45

(+)-(4aR)-(10bR)-8-(3-quinolinyl)-10b-methyl-1,2,3,4,4a,-
5,6,10b-octahydrobenzo[f]quinolin-3-one

- 5 Yield: 141 mg (63%) of the title compound as a white solid.
mp 265-266°. FDMS: m/e = 342. α [D]₅₈₉ = +88.70 (c =
0.84, chloroform) .

Example 46

- 10 (+)-(4aR)-(10bR)-4-methyl-8-(4-fluoro-3-trifluoromethyl-
phenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]-
quinolin-3-one

- 15 Yield: 110 mg (43%) of the title compound as an amorphous
foam. FDMS: m/e = 323. α [D]₅₈₉ = +51.47 (c = 0.52,
chloroform).

analysis:	calculated	found
C	67.51	67.80
H	5.41	5.46
N	3.58	3.32

Example 47

- 20 (+)-(4aR)-(10bR)-4-methyl-8-(4-methoxyphenyl)-10b-methyl-
1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

- 25 Yield: 173 mg (79%) of the title compound as a white solid.
mp 150°. FDMS: m/e = 335. α [D]₅₈₉ = +73.82 (c=1.01,
methanol).

analysis:	calculated	found
C	78.77	78.49
H	7.51	7.44
N	4.18	4.43

-67-

Example 48

(+)-(4aR)-(10bR)-4-methyl-8-(3-methoxyphenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

5 Yield: 144 mg (66%) of the title compound as a white solid.
mp 140°. FDMS: m/e = 335. α [D]₅₈₉ = +77.45 (c=1.02, chloroform).

analysis:	calculated	found
C	78.77	78.53
H	7.51	7.50
N	4.18	3.92

10

Example 49

(+)-(4aR)-(10bR)-4-methyl-8-phenyl-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

15 Yield: 139 mg (70%) of the title compound as a white solid.
mp 155°. FDMS: m/e = 305.

analysis:	calculated	found
C	82.59	82.79
H	7.59	7.59
N	4.59	4.39

Example 50

20 (+)-(4aR)-(10bR)-4-methyl-8-(4-chlorophenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 166 mg (75%) of the title compound as a white solid.
mp 192°. FDMS: m/e = 339. α [D]₅₈₉ = +76.14 (c = 1.00, chloroform).

25

analysis:	calculated	found
C	74.22	74.17
H	6.52	6.68
N	4.12	3.97

-68-

Example 51

(+)-(4aR)-(10bR)-4-methyl-8-(4-methylphenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

5

Yield: 150 mg (72%) of the title compound as a white solid.
mp 178°. FDMS: m/e = 319. $\alpha[D]_{589} = +77.14$ (c=1.00, chloroform).

analysis:	calculated	found
C	82.72	82.66
H	7.89	7.95
N	4.38	4.20

10

Example 52

(+)-(4aR)-(10bR)-4-methyl-8-(3,5-dichlorophenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

15

Yield: 145 mg (60%) of the title compound as a white solid.
mp 172°. FDMS: m/e = 374 $\alpha[D]_{589} = +70.91$ (c=0.55, chloroform).

analysis:	calculated	found
C	67.39	67.43
H	5.65	5.67
N	3.74	3.65

20

Example 53

(+)-(4aR)-(10bR)-4-methyl-8-(1-naphthyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

25

Yield: 116 mg (50%) of the title compound as a white solid.
mp 159°. FDMS: m/e = 355. $\alpha[D]_{589} = +60.00$ (c=0.50, chloroform).

-69-

analysis:	calculated	found
C	84.47	84.73
H	7.09	7.08
N	3.94	3.89

Example 54

5 (+)-(4aR)-(10bR)-4-methyl-8-(3-pyridyl)-10b-methyl-
1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 112 mg (56%) of the title compound as a white solid.
mp 135°. FDMS: m/e = 306.

analysis:	calculated	found
C	78.40	78.37
H	7.24	7.37
N	9.14	9.14

10

Example 55

(+)-(4aR)-(10bR)-4-methyl-8-(3-biphenyl)-10b-methyl-
1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

15 Yield: 176 mg (71%) of the title compound as a white solid.
mp 131°. FDMS: m/e = 381. α [D]₅₈₉ = +71.15 (c = 0.52,
CHCl₃).

analysis:	calculated	found
C	85.00	84.77
H	7.13	7.31
N	3.67	3.46

20

Example 56

(+)-(4aR)-(10bR)-4-methyl-8-(4-phenoxyphenyl)-10b-methyl-
1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

-70-

Yield: 206 mg (80%) of the title compound as a white solid.
mp 148-150°. FDMS: m/e = 397. α [D]₅₈₉ = +64.51 (c = 0.62, chloroform).

analysis:	calculated	found
C	81.58	81.47
H	6.85	8.83
N	3.52	3.60

5

Example 57

(+)-(4aR)-(10bR)-4-methyl-8-(3-formylphenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

10 Yield: 141 mg (65%) of the title compound as a white solid.
mp 163°. FDMS: m/e = 333.

analysis:	calculated	found
C	79.25	79.16
H	6.95	6.99
N	4.20	3.92

Example 58

15 (+)-(4aR)-(10bR)-4-methyl-8-(3-formyl-4-hydroxyphenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 85 mg (37%) of the title compound as a white solid. mp 184-187°. FDMS: m/e = 349.

20

analysis:	calculated	found
C	75.62	75.86
H	6.63	6.72
N	4.01	3.87

Example 59

(+)-(4aR)-(10bR)-4-methyl-8-(4-dimethylaminophenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

25

-71-

Yield: 119 mg (53%) of the title compound as an amorphous foam. mp 197-202°. FDMS: m/e = 348. α [D]₅₈₉ = +76.84 (c=0.95, chloroform).

analysis:	calculated	found
C	78.27	77.92
H	8.10	8.12
N	8.04	7.84

5

Example 60

(+)-(4aR)-(10bR)-4-methyl-8-(2-[6-hydroxy]naphthyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

10 Yield: 47 mg (20%) of the title compound as a white solid. mp >260° (decomp.) FDMS: m/e = 371.

analysis:	calculated	found
C	80.83	79.84
H	6.78	6.73
N	3.77	3.25

Example 61

15 (+)-(4aR)-(10bR)-4-methyl-8-(9-anthracenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 112 mg (43%) of the title compound as an amorphous solid. mp 95-110°. FDMS: m/e = 405. α [D]₅₈₉ = +45.73 (c=0.66, chloroform).

20

analysis:	calculated	found
C	85.89	84.93
H	6.71	6.55
N	3.45	3.01

-72-

Example 62

(+)-(4aR)-(10bR)-4-methyl-8-(2-[6-benzyloxy]naphthyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

5 Yield: 73 mg (24%) of the title compound as a white solid. mp 173-176° FDMS: m/e = 361. $\alpha[D]_{589} = +66.07$ (c = 0.56, chloroform).

analysis:	calculated	found
C	83.26	83.50
H	6.77	6.84
N	3.03	3.03

10

Example 63

(+)-(4aR)-(10bR)-4-methyl-8-(3-chlorophenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

15 Yield: 164 mg (74%) of the title compound as an amorphous foam. mp 158-65°. FDMS: m/e = 339. $\alpha[D]_{589} = +74.90$ (c = 1.00, methanol).

analysis:	calculated	found
C	74.22	73.95
H	6.52	6.51
N	4.12	4.89

Example 64

20 (+)-(4aR)-(10bR)-4-methyl-8-(1-[4-fluoro]naphthyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 188 mg (77%) of the title compound as an amorphous foam. mp 115-125°. FDMS: m/e = 373. $\alpha[D]_{589} = +60.78$
25 (c=1.02, chloroform).

-73-

analysis:	calculated	found
C	80.40	78.80
H	6.48	6.35
N	3.75	3.41

Example 65

(+)-(4aR)-(10bR)-4-methyl-8-(1-[4-methyl]naphthyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 36 mg (15%) of the title compound as a white solid. mp 175-178°. FDMS: m/e = 369. α [D]₅₈₉ = +63.81 (c=1.05, chloroform).

analysis:	calculated	found
C	84.51	84.73
H	7.36	7.44
N	3.79	3.54

Example 66

(+)-(4aR)-(10bR)-4-methyl-8-(5-acenaphthenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 170 mg (69%) of the title compound as a white solid. mp > 200° (decomp.) FDMS: m/e = 381 α [D]₅₈₉ = +61.47 (c=0.84, chloroform).

analysis:	calculated	found
C	85.00	85.24
H	7.13	7.17
N	3.67	3.51

-74-

Example 67

(+)-(4aR)-(10bR)-4-methyl-8-(9-phenanthrenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

- 5 Yield: 80 mg (30%) of the title compound as a white solid. mp 218-220°. FDMS: m/e = 405. α [D]₅₈₉ = +63.01 (c=0.98, chloroform).

analysis:	calculated	found
C	85.89	86.06
H	6.71	6.83
N	3.45	3.39

10

Example 68

(+)-(4aR)-(10bR)-4-methyl-8-(4-[N-propyl,N-cyclopropyl-methylamino]-1-naphthyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

- 15 Yield: 193 mg (64%) of the title compound as an oil. FDMS: m/e = 466. α [D]₅₈₉ = +50.52 (c=0.95, chloroform).

Example 69

(+)-(4aR)-(10bR)-4-methyl-8-(2,3-dimethylphenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

20

Yield: 55 mg (25 %) of the title compound as an amorphous solid. mp 133-140°. FDMS: m/e = 333. α [D]₅₈₉ = +61.90 (c = 1.05, methanol).

25

analysis:	calculated	found
C	82.84	82.64
H	8.16	8.07
N	4.20	4.15

-75-

Example 70

(+)-(4aR)-(10bR)-4-methyl-8-(3,4-methylenedioxyphenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

5 Yield: 130 mg (57%) of the title compound as an amorphous solid. mp 146-152°. FDMS: m/e = 349. α [D]₅₈₉ = +67.92 (c = 1.06, chloroform).

analysis:	calculated	found
C	75.62	75.46
H	6.63	6.77
N	4.01	3.80

10

Example 71

(+)-(4aR)-(10bR)-4-methyl-8-(2-naphthyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

15 Yield: 126 mg (55%) of the title compound as a white solid. mp 221-223°. FDMS: m/e = 355. α [D]₅₈₉ = +73.58 (c = 1.06, chloroform).

analysis:	calculated	found
C	84.47	84.63
H	7.09	7.06
N	3.94	3.93

Example 72

20

(+)-(4aR)-(10bR)-4-methyl-8-(1-[2-methyl]naphthyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

25 Yield: 104 mg (44%) of the title compound as a white solid. mp 196-200°. FDMS: m/e = 369. α [D]₅₈₉ = +54.72 (c = 1.06, chloroform).

-76-

analysis:	calculated	found
C	84.51	84.27
H	7.36	7.42
N	3.79	3.93

Example 73

5 (+)-(4aR)-(10bR)-4-methyl-8-(2,3-dichlorophenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 193 mg (79%) of the title compound as an off-white solid. mp 131-134°. FDMS: m/e = 373 α [D]₅₈₉ = +81.02 (c = 1.05, chloroform).

10

analysis:	calculated	found
C	67.39	68.46
H	5.65	5.70
N	3.74	3.75

Example 74

15 (+)-(4aR)-(10bR)-4-methyl-8-(2-[N,N-diethylcarboxamido]-phenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]-quinolin-3-one

Yield: 180 mg (68%) of the title compound as a white solid. mp 147-149°. FDMS: m/e = 404 α [D]₅₈₉ = +56.86 (c = 1.02, chloroform).

20

analysis:	calculated	found
C	77.19	76.99
H	7.97	8.05
N	6.92	6.87

-77-

Example 75

(+)-(4aR)-(10bR)-4-methyl-8-(4-t-butylphenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

5 Yield: 163 mg (69%) of the title compound as an amorphous solid. mp 141-147°. FDMS: m/e = 361 α [D]₅₈₉ = +67.88 (c = 1.05, chloroform).

analysis:	calculated	found
C	83.06	83.34
H	8.64	8.72
N	3.87	3.76

10

Example 76

(+)-(4aR)-(10bR)-4-methyl-8-(4-n-butylphenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

15 Yield: 180 mg (77%) of the title compound as a white solid. mp 102-108°. FDMS: m/e = 361. α [D]₅₈₉ = +68.70 (c = 1.05, chloroform).

analysis:	calculated	found
C	83.06	82.98
H	8.64	8.73
N	3.87	3.64

Example 77

20 (+)-(4aR)-(10bR)-4-methyl-8-(3,4-dichlorophenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

25 Yield: 156mg (64%) of the title compound as a foam. mp 129-135°. FDMS: m/e = 374. α [D]₅₈₉ = +68.66 (c=1.03, chloroform).

-78-

analysis:	calculated	found
C	67.39	68.37
H	5.65	5.81
N	3.74	3.63

Example 78

5 (+)-(4aR)-(10bR)-4-methyl-8-(4-trifluoromethoxyphenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 137 mg (56%) of the title compound as a waxy solid.

FDMS: m/e = 389. $\alpha[D]_{589} = +48.95$ (c = 0.96, chloroform).

10

Example 79

(+)-(4aR)-(10bR)-4-methyl-8-(4-trifluoromethylphenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 137 mg (56%) of the title compound as a white solid.

15 mp 86-89°. FDMS: m/e = 373 $\alpha[D]_{589} = +28.90$ (c = 1.04, chloroform).

analysis:	calculated	found
C	70.76	70.96
H	5.94	6.00
N	3.75	3.09

Example 80

20 (+)-(4aR)-(10bR)-4-methyl-8-(3-trifluoromethylphenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 180 mg (77%) of the title compound as an amorphous foam. mp 4-87°. FDMS: m/e = 373. $\alpha[D]_{589} = +64.42$

25 (c=1.04, chloroform).

-79-

analysis:	calculated	found
C	70.76	71.04
H	5.94	5.98
N	3.75	3.48

Example 81

(+)-(4aR)-(10bR)-4-methyl-8-(2-[6-methoxy]naphthyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 233 mg (93%) of the title compound as a white solid.
mp 216-221°. FDMS: m/e = 385. α [D]₅₈₉ = +59.64 (c=0.97, chloroform).

analysis:	calculated	found
C	81.01	80.72
H	7.06	6.99
N	3.63	3.57

Example 82

(+)-(4aR)-(10bR)-4-methyl-8-(2-benzothienyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 190 mg (81%) of the title compound as a white solid.
mp 247-250°. FDMS: m/e = 361. α [D]₅₈₉ = +93.33 (c=0.36, chloroform).

analysis:	calculated	found
C	76.42	76.29
H	6.41	6.37
N	3.87	3.68

-80-

Example 83

(+)-(4aR)-(10bR)-4-methyl-8-(3,5-dimethylphenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

5 Yield: 186 mg (86 %) of the title compound as a white solid .
mp 129-130°. FDMS: m/e =333. α [D]₅₈₉ = +73.31 (c = 1.00, chloroform).

analysis:	calculated	found
C	82.84	82.59
H	8.16	8.08
N	4.20	4.01

10

Example 84

(+)-(4aR)-(10bR)-4-methyl-8-(4-biphenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

15 Yield: 178 mg (72 %) of the title compound as a white solid.
mp 206-207°. FDMS: m/e =381. α [D]₅₈₉ = +63.93 (c = 1.01, chloroform).

analysis:	calculated	found
C	85.00	84.51
H	7.13	6.85
N	3.67	3.37

Example 85

20 (+)-(4aR)-(10bR)-4-methyl-8-(4-fluorophenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

25 Yield: 140 mg (67 %) of the title compound as a white solid.
mp 121-122°. FDMS: m/e =323. α [D]₅₈₉ = +79.46 (c = 0.99, chloroform).

-81-

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	77.99	77.70
H	6.86	6.85
N	4.33	4.25

Example 86

5 (+)-(4aR)-(10bR)-4-methyl-8-(3-nitrophenyl)-10b-methyl-
1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 159 mg (70 %) of the title compound as a tan solid .
mp 181-183°. FDMS: m/e =350. α [D]₅₈₉ = +80.70 (c = 1.04,
chloroform).

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	71.98	71.85
H	6.33	6.22
N	7.99	7.71

10

Example 87

(+)-(4aR)-(10bR)-4-methyl-8-(3,5-bis[trifluoromethyl]phenyl)-
10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

15 Yield: 194 mg (68 %) of the title compound as a white solid.
mp 110-112°. FDMS: m/e =441 α [D]₅₈₉ = +80.70 (c = 1.05,
methanol).

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	62.58	62.43
H	4.79	4.81
N	3.17	3.40

-82-

Example 88

(+)-(4aR)-(10bR)-4-methyl-8-(3-chloro-4-fluorophenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

5 Yield: 170 mg (73%) of the title compound as a white solid.
mp 114-116°. FDMS: m/e = 357. α [D]₅₈₉ = +86.00 (c = 1.00, methanol).

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	70.48	70.35
H	5.91	6.00
N	3.91	3.95

10

Example 89

(+)-(4aR)-(10bR)-4-methyl-8-(4-[4-ethoxy]biphenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

15 Yield: 166 mg (60%) of the title compound as a white solid.
mp 177-179°. FDMS: m/e = 425. α [D]₅₈₉ = +66.30 (c = 1.03, chloroform).

<u>analysis</u>	<u>calculated</u>	<u>found</u>
C	81.85	81.64
H	7.34	7.12
N	3.29	3.57

Example 90

20 (+)-(4aR)-(10bR)-4-methyl-8-(3-aminophenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 170 mg (82%) of the title compound as a tan solid.
mp 230-231° (decomp.) FDMS: m/e = 320. α [D]₅₈₉ = +80.00 (c = 1.05, methanol).

25

<u>analysis</u>	<u>calculated</u>	<u>found</u>
C	78.71	78.99
H	7.55	7.55
N	8.74	9.12

-83-

Example 91

(+)-(4aR)-(10bR)-4-methyl-8-[3-([5-dimethylamino-1-naphthyl]sulfonylamino)phenyl]-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 94 mg (63%) of the title compound as a yellow solid.
mp 130-140° (decomp.) FDMS: m/e = 553. α [D]₅₈₉ = +3.01 (c = 1.03 methanol).

Example 92

(+)-(4aR)-(10bR)-8-(1-naphthyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 405 mg (70%) of the title compound as a white solid.
mp 247-248°. FDMS: m/e = 341. α [D]₅₈₉ = +1.93 (c = 1.04, methanol).

Example 93

(+)-(4aR)-(10bR)-8-(3-nitrophenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 456 mg (80%) of the title compound as a white solid.
mp 223-225°. FDMS: m/e = 336. α [D]₅₈₉ = +45.63 (c = 1.03, methanol).

Example 94

(+)-(4aR)-(10bR)-4-methyl-8-(2,4-dichlorophenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 157 mg (65%) of the title compound as an amorphous foam. mp 45-48°. FDMS: m/e = 374.

<u>analysis</u>	<u>calculated</u>	<u>found</u>
C	67.39	66.95
H	5.65	5.43
N	3.74	3.82

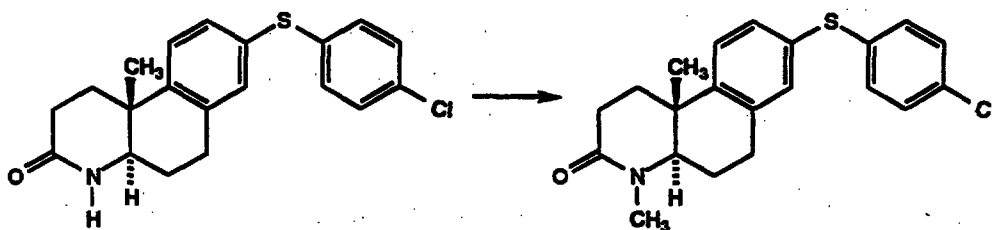
-84-

The following group of examples illustrate alkylations, other than the preferred alkylations of Examples 1-4 above, which provide modifications of the benzoquinolinone nucleus.

5

Example 95

(+)-(4aR)-(10bR)-4,10b-dimethyl-8-(4-chlorophenylthio)-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one



10

A 350 mg portion of (4aR)-(10bR)-10b-methyl-8-(4-chlorophenylthio)-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one was slurried in 14 ml of t-butanol in a nitrogen-blanketed flask, and 0.2 ml of a 25 mg/ml aqueous solution of methyl iodide was added, followed by 330 mg of potassium t-butoxide. The mixture was stirred at ambient temperature for 5 hours, and then the reaction mixture was poured into water, and the mixture was extracted twice with ethyl acetate. The combined organic layers were washed with water and with brine, dried over sodium sulfate and concentrated under vacuum to obtain an oil, which was purified by silica gel chromatography on a Chromatotron (Harrison Research Co.), using dichloromethane containing from 1% to 3% of methanol as the eluent. The product-containing fractions were combined and concentrated under vacuum to obtain 330 mg of solid, which was crystallized from heptane/ethyl acetate to obtain 254 mg of the desired product. mp 122°-124° FDMS: m/e=371. α [D]₅₈₉ = +60.2, α [D]₃₆₅ = +262.55 (chloroform).

30

-85-

<u>Analysis</u>	<u>Calculated</u>	<u>Found</u>
C	67.82	68.05
H	5.96	6.00
N	3.77	3.89

The following examples were carried out according to the process of Example 95.

5

Example 96

(+)-(4aR)-(10bR)-4,10b-dimethyl-8-(4-methylphenylthio)-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

10 Yield: 280 mg of the desired product. mp 154°-156° FDMS: m/e=351. α [D]₅₈₉ = +76.6, α [D]₃₆₅ = +282.53 (chloroform).

<u>Analysis</u>	<u>Calculated</u>	<u>Found</u>
C	75.17	74.95
H	7.17	7.25
N	3.99	4.17

Example 97

15 (+)-(4aR)-(10bR)-4,10b-dimethyl-8-(phenylsulfonyl)-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 144 mg of the desired product. mp 165°-167° FDMS: m/e=369. α [D]₅₈₉ = +76.2, α [D]₃₆₅ = +269.7 (chloroform).

20

<u>Analysis</u>	<u>Calculated</u>	<u>Found</u>
C	68.27	68.44
H	6.27	6.39
N	3.79	3.69

-86-

Example 98

(+)-(4aR)-(10bR)-4,10b-dimethyl-8-(2-naphthylthio)-1,2,3,4,-
4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

5 Yield: 137 mg of the desired product. mp 138°-139.5° FDMS:
m/e=387. α [D]₅₈₉ = +69.6, α [D]₃₆₅ = +261.4 (chloroform).

<u>Analysis</u>	<u>Calculated</u>	<u>Found</u>
C	77.48	77.28
H	6.50	6.63
N	3.61	3.71

Example 99

10 (+)-(4aR)-(10bR)-4,10b-dimethyl-8-(2-chlorophenylthio)-
1,2,3,4,-4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 420 mg of the desired product. mp 123°-125° FDMS:
m/e=371. α [D]₅₈₉ = +76.0, α [D]₃₆₅ = +255.3 (chloroform).

15

<u>Analysis</u>	<u>Calculated</u>	<u>Found</u>
C	67.82	67.87
H	5.96	5.97
N	3.77	3.94

Example 100

(+)-(4aR)-(10bR)-4,10b-dimethyl-8-(3-chlorophenylthio)-
1,2,3,4,-4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

20

Yield: 525 mg. FDMS: m/e=371. α [D]₅₈₉ = +72.9, α [D]₃₆₅ =
+265.2 (chloroform).

<u>Analysis</u>	<u>Calculated</u>	<u>Found</u>
C	67.82	67.60
H	5.96	5.91
N	3.77	3.86

-87-

Example 101

(+)-(4aR)-(10bR)-4,10b-dimethyl-8-(2-methylphenylthio)-
1,2,3,4,-4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

5 Yield: 330 mg of the desired product. mp 105°-106° FDMS:
m/e=351. $\alpha[D]_{589} = +77.0$, $\alpha[D]_{365} = +282.8$ (chloroform).

<u>Analysis</u>	<u>Calculated</u>	<u>Found</u>
C	75.17	75.46
H	7.17	7.34
N	3.98	3.95

Example 102

10 (+)-(4aR)-(10bR)-4,10b-dimethyl-8-(3-methylphenylthio)-
1,2,3,4,-4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 290 mg of the desired product. mp 103°-104° FDMS:
m/e=351. $\alpha[D]_{589} = +80.3$, $\alpha[D]_{365} = +292.2$ (chloroform).

15

<u>Analysis</u>	<u>Calculated</u>	<u>Found</u>
C	75.17	75.40
H	7.17	7.19
N	3.98	3.98

Example 103

(+)-(4aR)-(10bR)-4,10b-dimethyl-8-(1-naphthylthio)-1,2,3,4,-
4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

20

Yield: 300 mg of the desired product. mp 161°-162° FDMS:
m/e=387. $\alpha[D]_{589} = +65.2$, $\alpha[D]_{365} = +248.4$ (chloroform).

<u>Analysis</u>	<u>Calculated</u>	<u>Found</u>
C	77.48	77.64
H	6.50	6.54
N	3.61	3.54

-88-

Example 104

(+)-(4aR)-(10bR)-4,10b-dimethyl-8-(2-methoxyphenylthio)-
1,2,3,4,-4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

5 Yield: 300 mg of the desired product. mp 166°-167.5° FDMS:
m/e=367. α [D]₅₈₉ = +72.7, α [D]₃₆₅ = +265.1 (chloroform).

<u>Analysis</u>	<u>Calculated</u>	<u>Found</u>
C	71.90	71.98
H	6.86	6.64
N	3.81	3.67

Example 105

10 (+)-(4aR)-(10bR)-4,10b-dimethyl-8-(4-methoxyphenylthio)-
1,2,3,4,-4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 400 mg of the desired product. mp 150°-151° FDMS:
m/e=367. α [D]₅₈₉ = +74.1, α [D]₃₆₅ = +276.8 (chloroform).

15

<u>Analysis</u>	<u>Calculated</u>	<u>Found</u>
C	71.90	71.95
H	6.86	6.64
N	3.81	3.85

Example 106

(4aR)-(10bR)-4,10b-dimethyl-8-(3-quinolinylthio)-1,2,3,4,-
4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

20

Yield: 255 mg of the desired product, as an amorphous solid.
FDMS: m/e=388.

<u>Analysis</u>	<u>Calculated</u>	<u>Found</u>
C	74.19	73.94
H	6.23	6.41
N	7.21	7.13

-89-

Example 107

(+)-(4aR)-(10bR)-4,10b-dimethyl-8-(2-quinolinylthio)-
1,2,3,4,-4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

5 Yield: 300 mg of the desired product. mp 175°-177° FDMS:
m/e=388. $\alpha[D]_{589} = +65.9$, $\alpha[D]_{365}$ = absorbance (chloroform).

<u>Analysis</u>	<u>Calculated</u>	<u>Found</u>
C	74.19	74.01
H	6.23	6.10
N	7.21	7.39

Example 108

10 (+)-(4aR)-(10bR)-4,10b-dimethyl-8-(2-fluorophenylthio)-
1,2,3,4,-4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 490 mg of the desired product, which was not
crystalline. mp 100°-103° FDMS: m/e=354. $\alpha[D]_{589} = +76.5$,
15 $\alpha[D]_{365} = +273.6$ (chloroform).

<u>Analysis</u>	<u>Calculated</u>	<u>Found</u>
C	70.96	71.21
H	6.24	6.32
N	3.94	4.16

Example 109

20 (+)-(4aR)-(10bR)-4,10b-dimethyl-8-(3-fluorophenylthio)-
1,2,3,4,-4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 430 mg of the desired product in the form of an oil.
FDMS: m/e=355. $\alpha[D]_{589} = +76.5$, $\alpha[D]_{365} = +275.2$
(chloroform).

25

<u>Analysis</u>	<u>Calculated</u>	<u>Found</u>
C	70.96	71.11
H	6.24	6.32
N	3.94	3.98

-90-

Example 110

(4aR)-(10bR)-4,10b-dimethyl-8-(8-quinolinylthio)-1,2,3,4,-
4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 114 mg of the desired product. mp 241°-242° FDMS:
m/e=388.

<u>Analysis</u>	<u>Calculated</u>	<u>Found</u>
C	74.19	73.98
H	6.23	6.15
N	7.21	7.18

Example 111

(+)-(4aR)-(10bR)-4,10b-dimethyl-8-(2-pyridinylthio)-1,2,3,4,-
4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 330 mg of the desired product. mp 174°-176° FDMS:
m/e=338. $\alpha[D]_{589} = +79.8$, $\alpha[D]_{365} = +288.7$ (chloroform).

<u>Analysis</u>	<u>Calculated</u>	<u>Found</u>
C	70.97	70.70
H	6.55	6.74
N	8.28	8.06

Example 112

(4aR)-(10bR)-4,10b-dimethyl-8-(2-benzothiazolylthio)-
1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 84 mg of the desired product. mp 188°-189° FDMS:
m/e=394.

<u>Analysis</u>	<u>Calculated</u>	<u>Found</u>
C	66.97	66.73
H	5.62	5.65
N	7.10	6.87

-91-

Example 113

(4aR)-(10bR)-4,10b-dimethyl-8-(1-isoquinolinylthio)-1,2,3,4,-
4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

5 Yield: 90 mg of the desired product. mp 196°-199° FDMS:
m/e=388.

<u>Analysis</u>	<u>Calculated</u>	<u>Found</u>
C	74.19	74.08
H	6.23	6.41
N	7.21	7.45

Example 114

10 (4aR)-(10bR)-4,10b-dimethyl-8-(4-isoquinolinylthio)-1,2,3,4,-
4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 140 mg of the desired product. mp 161°-163° FDMS:
m/e=388.

15

<u>Analysis</u>	<u>Calculated</u>	<u>Found</u>
C	74.19	74.05
H	6.23	6.18
N	7.21	7.47

Example 115

(+)-(4aR)-(10bR)-4,10b-dimethyl-8-(4-pyridinylthio)-1,2,3,4,-
4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

20

Yield: 228 mg of the desired product. mp 157°-158° FDMS:
m/e=338. $\alpha[D]_{589} = +77.5$, $\alpha[D]_{365}$ = absorbance (chloroform).

<u>Analysis</u>	<u>Calculated</u>	<u>Found</u>
C	70.97	71.25
H	6.55	6.27
N	8.28	8.27

-92-

Example 116

(4aR)-(10bR)-4,10b-dimethyl-8-phenylthio-1,2,3,4,-4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

- 5 Yield: 0.90 g of white crystals: mp 109-112°; FD MS 337 M+;
Calcd for C₂₁H₂₃N₁O₁S₁.

<u>Analysis</u>	<u>Calculated</u>	<u>Found</u>
C	74.74	74.55
H	6.87	6.79
N	4.15	4.35

Example 117

- 10 (+)-(4aR)-(10bR)-4-methyl-8-(1-naphthyl)-10b-methyl-
3,4,4a,5,6,10b-hexahydrobenzo[f]quinolin-3-one

Yield: 16 mg (70%) of the title compound as a yellow solid,
upon trituration from diethyl ether/hexanes. mp 172-173°.

- 15 FDMS: m/e = 353.

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	84.92	84.70
H	6.56	6.29
N	3.96	3.55

Example 118

- 20 (+)-(4aR)-(10bR)-4-methyl-8-(3-nitrophenyl)-10b-methyl-
3,4,4a,5,6,10b-hexahydrobenzo[f]quinolin-3-one

Yield: 9 mg (75%) of the title compound as a white solid, upon
trituration from diethyl ether/hexanes. mp 175-177°. FDMS:
m/e = 348.

25

-93-

Example 119

(+)-(4aR)-(10bR)-4-methyl-8-(4-nitrophenyl)-10b-methyl-
1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

5 Yield: 10 mg (70%) of the title compound as a white solid.
mp 59-60°. FDMS: m/e = 350.

Example 120

10 (+)-(4aR)-(10bR)-4-methyl-8-(4-methylthiophenyl)-10b-methyl-
1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 15 mg (72%) of the title compound as a white solid.
mp 115-117°. FDMS: m/e = 351.

15

Example 121

(+)-(4aR)-(10bR)-4-methyl-8-(4-cyanophenyl)-10b-methyl-
1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

20 Yield: 20 mg (80%) of the title compound as a white solid.
mp 148-150°. FDMS: m/e = 330.

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	79.97	79.77
H	6.71	6.63
N	8.48	8.69

Example 122

25 (+)-(4aR)-(10bR)-4-methyl-8-(4-[isopropylcarbonyl]phenyl)-
10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 20 mg (54 %) of the title compound as a white solid.
mp 101-103°. FDMS: m/e = 375.

-94-

Example 123

(+)-(4aR)-(10bR)-4-methyl-8-(4-methylsulfonamidophenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

5 Yield: 20 mg (56%) of the title compound as an oil. FDMS:
m/e = 398.

Example 124

10 (+)-(4aR)-(10bR)-4-methyl-8-(2-nitrophenyl)-10b-methyl-
1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 50 mg (80 %) of the title compound as a white solid.
mp 130-131°. FDMS: m/e = 350.

15 Example 125

(+)-(4aR)-(10bR)-4-methyl-8-(2-cyanophenyl)-10b-methyl-
1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

20 Yield: 50 mg (87 %) of the title compound as a white solid.
mp 54-55°. FDMS: m/e = 330. $\alpha[D]_{589} = +74.33$ (c = 0.36,
chloroform).

Example 126

25 (+)-(4aR)-(10bR)-4-methyl-8-(2-[5-(phoxymethyl)thienyl])-
10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 65 mg (90 %) of the title compound as a white solid.
mp 149-151°. FDMS: m/e = 417 $\alpha[D]_{589} = +68.50$ (c = 0.89,
chloroform).

30

Example 127

(+)-(4aR)-(10bR)-4-methyl-8-(2-methylthiophenyl)-10b-methyl-
1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

35 Yield: 15 mg (26 %) of the title compound as an oil. FDMS:
m/e = 351.

-95-

Example 128

(+)-(4aR)-(10bR)-4-methyl-8-(2,4,5-trifluorophenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

5 Yield: 40 mg (89%) of the title compound as a foam. FDMS:
m/e = 359.

Example 129

10 (+)-(4aR)-(10bR)-4-methyl-8-(2-[5-(4-fluorophenoxy-methyl)-
thienyl])-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]-
quinolin-3-one

Yield: 35 mg (71 %) of the title compound as a white solid.
mp 136-138°. FDMS: m/e = 435 α [D]₅₈₉ = +63.40 (c = 0.74,
15 chloroform).

Example 130

20 (+)-(4aR)-(10bR)-4-methyl-8-(2,3,5-trifluorophenyl)-10b-
methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 30 mg (83%) of the title compound as a foam. FDMS:
m/e = 359.

Example 131

25 (+)-(4aR)-(10bR)-4-methyl-8-(2-fluorenyl)-10b-methyl-
1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 26 mg (82%) of the title compound as an off-white
solid. mp 175° (decomp). FDMS: m/e = 393.

30

Example 132

(+)-(4aR)-(10bR)-4-methyl-8-(3-[2,5-dichlororo]thienyl)-10b-
methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

35 Yield: 35 mg (69%) of the title compound as an oil. FDMS:
m/e = 379.

-96-

Example 133

(+)-(4aR)-(10bR)-4-methyl-8-(4-nitro-2-trifluoromethyl-phenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]-quinolin-3-one

5

Yield: 35 mg (70%) of the title compound as a white solid.
mp 128-130°. FDMS: m/e = 418.

Example 134

10 (+)-(4aR)-(10bR)-4-methyl-8-(2-nitro-4-trifluoromethyl-phenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]-quinolin-3-one

15 Yield: 38 mg (76%) of the title compound as an off-white solid. mp 55-57°. FDMS: m/e = 418. α [D]₅₈₉ = +60.50 (c = 0.16, methanol).

Example 135

20 (+)-(4aR)-(10bR)-4-methyl-8-(4-chloro-2,3,5,6-tetrafluorophenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]-quinolin-3-one

25 Yield: 30 mg (66%) of the title compound as an off-white solid. mp 150-151°. FDMS: m/e = 412 α [D]₅₈₉ = +68.57 (c = 0.12, chloroform).

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	61.25	61.04
H	4.41	4.53
N	3.40	3.22

-97-

Example 136

(4aR)-(10bR)-8-benzylthio-4,10b-dimethyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

5 Yield: 150 mg of the desired white solid (52% yield). mp 137-138°. FDMS: m/e = 351. α [D]₅₈₉ = 59.44 (c=0.36 in methanol).

<u>Analysis</u>	<u>Calculated</u>	<u>Found</u>
C	75.17	74.90
H	7.17	7.34
N	3.99	4.03

10

Example 137

(4aR)-(10bR)-8-phenylthiomethyl-4,10b-dimethyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

15 Yield: 134 mg of the desired white solid (82% yield). mp 144-146°. FDMS: m/e = 351. α [D]₅₈₉ = 78.54 (c=0.5 in methanol).

<u>Analysis</u>	<u>Calculated</u>	<u>Found</u>
C	75.17	74.92
H	7.17	7.27
N	3.98	4.19

Example 138

20 (4aR)-(10bR)-8-(2-benzothiazole)thiomethyl-4,10b-dimethyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

25 Yield: 158 mg of the desired white solid (76% yield). mp 182-184°. FDMS: m/e = 408. α [D]₅₈₉ = 67.31 (c=0.5 in methanol).

-98-

<u>Analysis</u>	<u>Calculated</u>	<u>Found</u>
C	67.61	67.74
H	5.92	6.03
N	6.86	6.98

Example 139

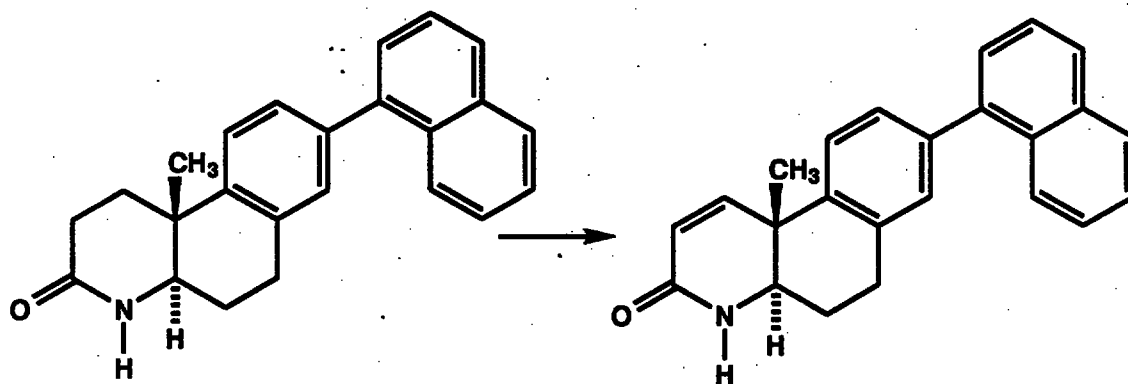
(4aR)-(10bR)-8-diphenylmethyl-4,10b-dimethyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 33 mg of the desired product. mp 145-146°; FDMS: m/e = 396; $\alpha[D]_{589} = 58.93$ (c=0.5 in chloroform).

The following group of examples demonstrate oxidations which provide hexahydroquinolinones in which the groups R and R¹ represent a bond.

Example 140

(+)-(4aR)-(10bR)-8-(1-naphthyl)-10b-methyl-3,4,4a,5,6,10b-hexahydrobenzo[f]quinolin-3-one



To a suspension of (+)-(4aR)-(10bR)-8-(1-naphthyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one (295 mg, 0.865 mmol), in 3.5 mL of 1,4-dioxane was added DDQ (216 mg, 1.1 equiv.) followed by bistrimethylsilyl-trifluoromethyl acetamide (998 mg, 4.5 equiv.), and the solution was stirred at room temperature for 2 h, then heated at 100° for 20h. The mixture was cooled to room temperature,

-99-

diluted with ethyl acetate, and washed with 2 M sodium hydroxide. The organic phase was washed with brine, dried over sodium sulfate, concentrated and chromatographed on silica gel (ethyl acetate eluent) to give, after trituration from ether/hexanes, 60 mg (20%) of the title compound as a white solid. mp 199-201° (decomp.) FDMS m/e = 339. $\alpha[D]_{589} = +35.98$ (c = 0.67, chloroform).

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	84.92	84.72
H	6.24	5.98
N	4.13	3.85

The following examples were carried out according to the process of Example 140.

Example 141

(+)-(4aR)-(10bR)-8-(3-nitrophenyl)-10b-methyl-3,4,4a,5,6,10b-hexahydrobenzo[f]quinolin-3-one
Yield: 55 mg (21%) of the title compound as an orange solid. mp 205-206°. FDMS m/e = 334. $\alpha[D]_{589} = +57.23$ (c = 0.66, chloroform).

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	71.84	71.47
H	5.43	5.49
N	8.38	7.96

Example 142

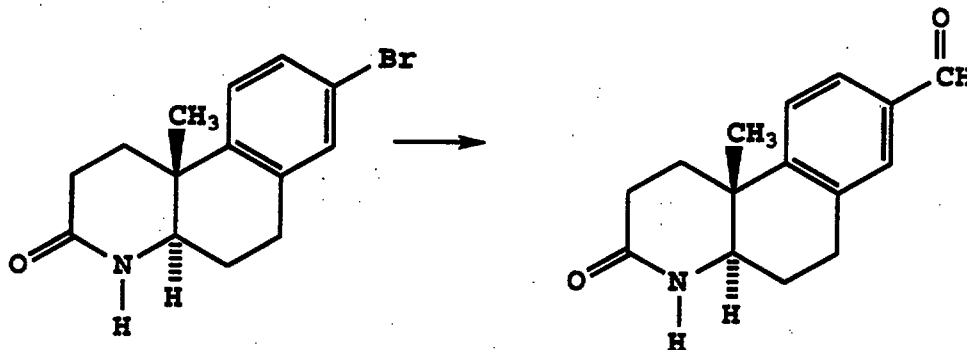
(+)-(4aR)-(10bR)-8-(3-isoquinolinyl)-10b-methyl-3,4,4a,5,6,10b-hexahydrobenzo[f]quinolin-3-one

Yield: 18mg (24%) of the title compound as a white solid. mp 248° (decomp.) FDMS m/e = 340.

-100-

Preparation 6

(4aR)-(10bR)-8-formyl-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

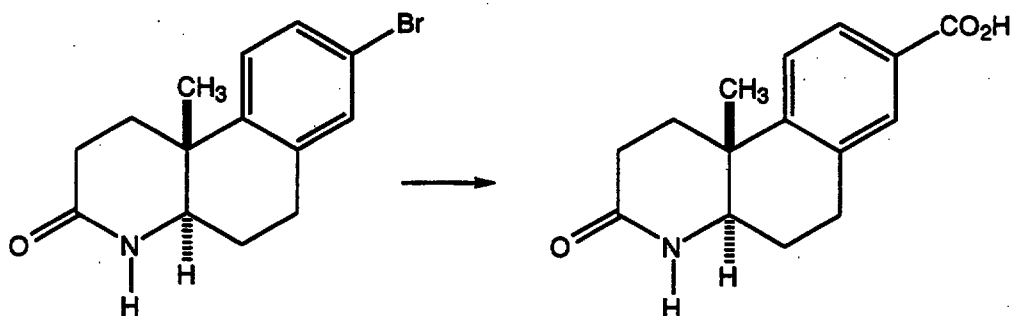


Methylolithium (1.5 mL, 2.1 mmol of a 1.4 M solution in diethyl ether) was added to (4aR)-(10bR)-8-bromo-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one (0.500 g, 1.7 mmol) in 25 mL of anhydrous THF which had been cooled in a dry ice/isopropanol bath under nitrogen, and was stirred for 15 min before addition of *t*-butyllithium (2.0 mL, 3.4 mmol of a 1.7 M solution in pentane.) After 30 min, dimethylformamide (0.4 mL) was added, and the mixture was allowed to warm to 0°, and additional dimethylformamide (0.2 mL) was added. The ice bath was removed and the reaction was quenched with 1 N hydrochloric acid to make pH = 2, and then the mixture was extracted with 10% isopropanol/chloroform. The combined organic extracts were washed well with water, dried over sodium sulfate, and evaporated. The resulting product was slurried in diethyl ether before recrystallizing from 50% ethyl acetate/hexane to give off-white crystals: mp 185-189°. FD MS 243 M⁺; Calcd for C₁₅H₁₇N₁O₂: C, 74.05; H, 7.04; N, 5.76; Found: C, 73.85; H, 7.11; N, 5.91.

-101-

Preparation 7

(4aR)-(10bR)-8-carboxy-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one



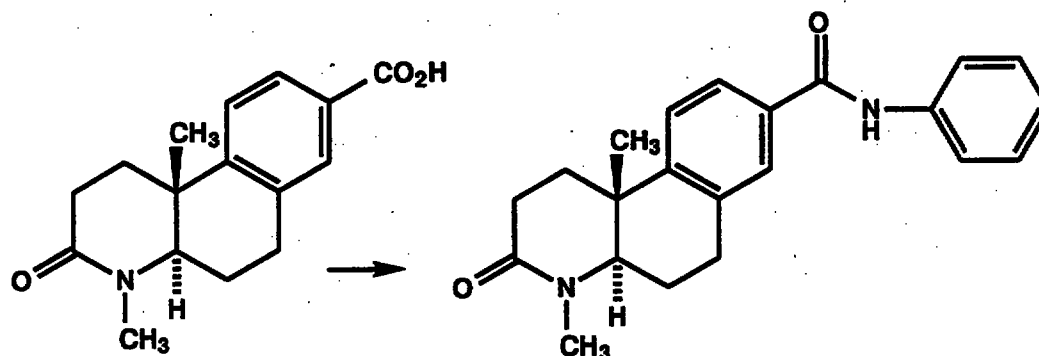
In a flame-dried 3-neck round bottom flask equipped with magnetic stirrer and nitrogen inlet was dissolved (4aR)-(10bR)-8-bromo-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinoline-3-one (500 mg, 1.7 mmol). The solution was cooled to -78° and treated with ethereal methyllithium (1.7 mL, 1.4M, 2.4 mmol) added dropwise over 2 min. After further stirring for 15 min., a solution of *t*-butyllithium (2.9 mL, 1.7 M in pentane, 5.0 mmol) was added dropwise. Following complete addition, the suspension was treated with excess carbon dioxide, (generated from dry ice, dried by passage through calcium sulfate) added subsurface for 2 min. The mixture was allowed to warm to ambient temperature and was acidified with 1N aqueous hydrochloric acid. The mixture was extracted with 10% isopropanol/-chloroform and the organic phase dried over anhydrous magnesium sulfate. Removal of solvent under reduced pressure afforded the crude product (520 mg) contaminated with pivalic acid. Trituration with ethyl acetate afforded product (322 mg) as a white powder (mp $>320^{\circ}$) m/e 259.

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	69.48	69.51
H	6.61	6.63
N	5.40	5.18

-102-

Example 143

(+)-(4aR)-(10bR)-4-methyl-8-(phenylcarboxamido)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one



A 50 mL round bottom flask was charged with (+)-(4aR)-(10bR)-4-methyl-8-carboxy-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one (100 mg, 0.37) and 2 mL of benzene. Oxalyl chloride (1.1 mmol) was added dropwise via syringe to the stirred mixture, followed by a catalytic amount of dimethylformamide (one drop). Allowed to stir at room temperature for 25 min, then removed volatiles in vacuo. Added 1 mL of THF, followed by a solution of aniline and pyridine (4 eq) in 1 mL of THF to the acid chloride solution at 0°. Allowed to warm to room temperature. Diluted with 50 mL of chloroform, and washed with 1 N hydrochloric acid (2 x 25 mL), 10% aq. sodium bicarbonate (2 x 25 mL), water, (2 x 25 mL), and brine (2 x 25 mL). The combined organic extracts were dried over sodium sulfate, concentrated and chromatographed on silica (ethyl acetate eluent), to give 24 mg (19%) of the title compound as an amorphous yellow foam. FDMS: m/e = 348.

The following examples were carried out according to the process of Example 143.

-103-

Example 144

(+)-(4aR)-(10bR)-4-methyl-8-benzyloxycarbonyl-10b-methyl-
1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

5 Yield: 11 mg (8 %) of the title compound as an amorphous
yellow foam. FDMS: m/e = 349.

Example 145

10 (+)-(4aR)-(10bR)-4-methyl-8-phenoxy carbonyl-10b-methyl-
1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 43 mg (11%) of the title compound as a yellow solid.
mp 194-196°. FDMS: m/e = 349. $\alpha[D]_{589} = +78.53$ (c=1.00,
chloroform).

15

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	75.62	75.44
H	6.63	6.74
N	4.01	4.00

Example 146

(+)-(4aR)-(10bR)-4-methyl-8-(benzylcarboxamido)-10b-methyl-
1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

20

Yield: 40 mg (30%) of the title compound as an amorphous
brown foam. FDMS: m/e = 362.

Example 147

25 (4aR)-(10bR)-4,10b-dimethyl-8-diphenylmethoxycarbonyl-
1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

30

Yield: 91 mg (57%) of the desired product. An analytical
sample was recrystallized from ethyl acetate/water. mp 130-
131°. FDMS: m/e = 439.

-104-

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	79.24	79.49
H	6.65	6.57
N	3.19	3.28

Example 148

(4aR)-(10bR)-4,10b-dimethyl-8-diphenylmethylcarboxamido-
1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 94 mg (40%) of the desired product. mp 210-211°.

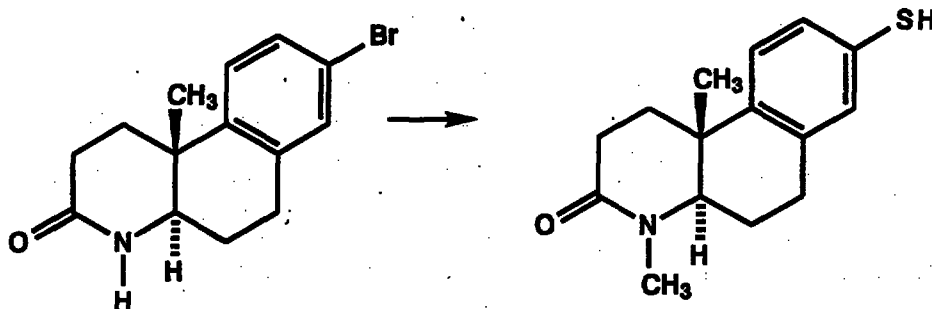
FDMS: m/e = 438.

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	79.42	79.27
H	6.89	6.99
N	6.39	6.42

The following preparation and example illustrates syntheses of compounds making use of an SH-substituted benzoquinolinone nucleus compound.

Preparation 8

(+)-(4aR)-(10bR)-4-methyl-8-mercapto-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one



To a solution of (+)-(4aR)-(10bR)-8-bromo-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one (5.88 g, 20 mmol) in 300 mL of anhydrous THF was added

-105-

methyllithium (158 mL, 1.4 M solution in diethyl ether) at -78°. The mixture was allowed to stir at -78° for 20 min, then t-butyllithium (26 mL, 1.7 M in pentane) was added. The mixture was stirred for an additional 90 min, and N,N-diisopropylthiuram disulfide (14.1 g, 40 mmol) in 80 mL of anhydrous THF was added at -78°. The mixture was stirred for 15 min, the cold bath was removed, and the mixture was allowed to warm to room temperature. To the mixture was added 100 mL of 1N hydrochloric acid, the organic phase was separated and washed with 1 N hydrochloric acid (200 mL), 10% sodium bicarbonate (2 X 200 mL), and brine (2 X 200 mL). The organic layer was dried over sodium sulfate, concentrated, and purified by silica gel chromatography (100% ethyl acetate - 5% methanol/ethyl acetate eluent gradient) to give 6.14 g (79%) of material which was dissolved in 61 mL of t-butanol, and potassium t-butoxide (7.42 g, 62.8 mmol) was added. The mixture was allowed to stir at room temp for 30 min (became homogeneous), cooled to 0°, and methyl iodide (62.8 mmol in 10 mL of t-butanol) was added dropwise via addition funnel. The cold bath was removed and the mixture was allowed to stir at room temperature for 16 h. The mixture was then diluted with 300 mL of ethyl acetate, the organic phase was separated, washed with brine, dried over sodium sulfate and concentrated to give 6.08 g (96%) of (+)-(4aR)-10bR)-4-methyl-8-([N,N-diisopropyl]thiuramyl)-1,2,3,4,4a,5,6,1b-octahydrobenzo[f]-quinolin-3-one as a white solid. mp 181-182°. FDMS m/e = 404. α [D]589 = +72.11 (c = 0.21, chloroform).

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	65.30	65.11
H	7.97	7.96
N	6.92	7.07

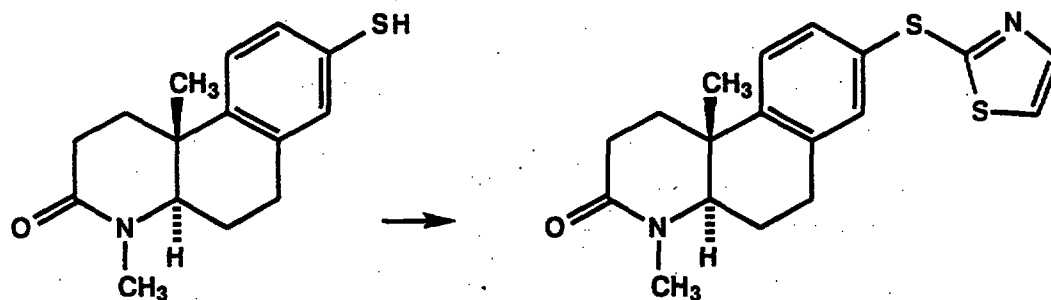
The above thiuram (6.08 g, 15.0 mmol) was dissolved in 250 mL of trifluoroacetic acid and heated at 72° for 16 h. The solution was cooled, the volatiles were removed via

-106-

rotary evaporator, the resulting oil was dissolved in chloroform, and the organic layer was washed with 10% sodium bicarbonate solution (2 X 200 mL) followed by brine (2 X 200 mL). The organic extract was dried over sodium sulfate, and concentrated to give 3.80 g (96%) of the title 8-mercapto compound as oil, used directly without further purification. FDMS m/e = 261.

Example 149

(+)-(4aR)-(10bR)-4-methyl-8-(2-thiazoylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one



A 15 mL round bottom flask was charged with (+)-(4aR)-(10bR)-4-methyl-8-mercapto-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one (100 mg, 0.38 mmol), potassium carbonate (158 mg, 1.14 mmol), 2-bromothiazole (75 mg, 0.46 mmol) and 1 mL of anhydrous dimethylformamide, fitted with a reflux condenser, and the stirred mixture was heated at 60°, under nitrogen, for 18 h. The mixture was cooled, diluted with ethyl acetate (75 mL) and washed with brine (2 x 25 mL). The combined organic extracts were dried over sodium sulfate, concentrated, and purified by silica gel chromatography (ethyl acetate eluent) to give 30 mg (23%) of the title compound as an amorphous solid. mp 140-142°. FDMS: m/e = 344.

-107-

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	62.76	62.52
H	5.85	5.96
N	8.13	7.93

The following examples were carried out according to the process of Example 149.

5

Example 150

(+)-(4aR)-(10bR)-4-methyl-8-(2-benzoxazolylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

10 Yield: 65 mg (45%) of the title compound as an amorphous foam.
FDMS: m/e = 378.

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	69.82	67.82
H	5.86	6.55
N	7.40	7.15

Example 151

15 (+)-(4aR)-(10bR)-4-methyl-8-(2-pyrimidinylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 30 mg (23%) of the title compound as an oil. FDMS:
m/e = 339

20

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	67.23	67.55
H	6.24	5.88
N	12.38	12.25

-108-

Example 152

(+)-(4aR)-(10bR)-4-methyl-8-(2-pyrazinylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

5 Yield: 63 mg (49%) of the title compound as an off white solid. mp 94-95°. FDMS: m/e = 339. α [D]₅₈₉ = +88.14 (c = 0.92, chloroform).

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	67.23	67.26
H	6.24	6.04
N	12.38	11.90

10

Example 153

(+)-(4aR)-(10bR)-4-methyl-8-(2-quinoxalinylylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

15 Yield: 82 mg (55%) of the title compound as an amorphous foam. FDMS: m/e = 389. α [D]₅₈₉ = +68.96 (c = 0.81, chloroform).

Example 154

(+)-(4aR)-(10bR)-4-methyl-8-(2-[3-phenyl]tetrazoylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

20

Yield: 81 mg (53%) of the title compound as a white solid. mp 128-130°. FDMS: m/e = 405. α [D]₅₈₉ = +69.47 (c = 0.57, chloroform).

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	65.16	65.35
H	5.72	5.85
N	17.27	17.08

25

-109-

Example 155

(+)-(4aR)-(10bR)-4-methyl-8-(2-[5-trifluoromethyl]pyridylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]-quinolin-3-one

5

Yield: 90 mg (58%) of the title compound as an amorphous solid.
mp 134-140°. FDMS: m/e = 406. $\alpha[D]_{589} = +76.80$ (c=0.42, chloroform).

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	62.05	61.89
H	5.21	5.31
N	6.89	6.72

10

Example 156

(+)-(4aR)-(10bR)-4-methyl-8-(3-indazolylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

15

Yield: 60 mg (16%) of the title compound as an oil. FDMS:
m/e = 377.

Example 157

(+)-(4aR)-(10bR)-4-methyl-8-(2-[4-isopropyl]benzothiazolylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]-quinolin-3-one

20

Yield: 57mg (34%) of the title compound as an amorphous solid.
mp 166-170°. FDMS: m/e = 436.

25

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	68.77	68.56
H	6.46	6.29
N	6.42	6.36

-110-

Example 158

(+)-(4aR)-(10bR)-4-methyl-8-(6-chloro-2-benzothiazolylthio)-
10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

5 Yield: 86 mg (53%) of the title compound as an amorphous solid
. mp 156-162°. FDMS: m/e = 429. α [D]₅₈₉ = +63.53 (c=0.66,
chloroform).

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	61.60	60.89
H	4.93	5.35
N	6.53	6.10

10

Example 159

(+)-(4aR)-(10bR)-4-methyl-8-(4-methyl-2-benzothiazolylthio)-
10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

15 Yield: 66 mg (43%) of the title compound as an amorphous
solid . mp 134-142°. FDMS: m/e = 408. α [D]₅₈₉ = +62.80
(c=0.74, chloroform).

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	67.61	67.41
H	5.92	6.11
N	6.86	6.63

Example 160

20 (+)-(4aR)-(10bR)-4-methyl-8-(5-nitro-2-benzothiazolylthio)-
10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 97 mg (58%) of the title compound as an amorphous
solid . mp 96-100°. FDMS: m/e = 439. α [D]₅₈₉ = +61.35
25 (c=0.64, chloroform).

-111-

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	60.12	59.85
H	4.82	5.09
N	9.56	9.35

Example 161

5 (+)-(4aR)-(10bR)-4-methyl-8-(6-methoxy-2-benzothiazolylthio)-
10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 76 mg (47%) of the title compound as an amorphous
solid . mp 102-107°. FDMS: m/e = 424. α [D]₅₈₉ = +64.29
(c=0.71, chloroform).

10

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	65.07	64.81
H	5.70	5.98
N	6.60	6.40

Example 162

15 (+)-(4aR)-(10bR)-4-methyl-8-(4-fluoro-2-benzothiazolylthio)-
10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 91 mg (58%) of the title compound as an amorphous solid
. mp 140-145°. FDMS: m/e = 412. α [D]₅₈₉ = +70.06 (c=0.52,
chloroform).

20

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	64.05	64.29
H	5.13	5.21
N	6.79	6.97

-112-

Example 163

(+)-(4aR)-(10bR)-4-methyl-8-(2-naphtho<1,2-d>-thiazolylthio)-
10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]-quinolin-3-
one

5

Yield: 94 mg (56%) of the title compound as an amorphous
solid. mp 179-184°. FDMS: m/e = 444. α [D]₅₈₉ = +60.59
(c=0.67, chloroform).

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	70.24	69.95
H	5.44	5.50
N	6.30	6.16

10

Example 164

(+)-(4aR)-(10bR)-4-methyl-8-(4-chloro-2-benzothiazolylthio)-
10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

15

Yield: 80mg (49%) of the title compound as an amorphous
solid. mp 207-209°. FDMS: m/e = 429 α [D]₅₈₉ = +63.86
(c=0.57, chloroform).

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	61.60	61.80
H	4.93	5.13
N	6.53	6.45

20

Example 165

(+)-(4aR)-(10bR)-4-methyl-8-(5,6-dichloro-2-benzothiazolyl-
thio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]-
quinolin-3-one

25

Yield: 54 mg (31%) of the title compound as an amorphous
foam. FDMS: m/e = 463.

-113-

Example 166

(+)-(4aR)-(10bR)-4-methyl-8-(5-nitro-2-pyridinylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

5 Yield: 106 mg (73%) of the title compound as an amorphous foam. mp 188-191°. FDMS: m/e = 383. α [D]₅₈₉ = +57.07 (c=0.68, chloroform).

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	62.64	62.09
H	5.52	5.76
N	10.96	10.40

10

Example 167

(+)-(4aR)-(10bR)-4-methyl-8-(3-nitro-2-pyridinylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

15 Yield: 95 mg (65%) of the title compound as an amorphous foam . mp 80-84°. FDMS: m/e = 383. α [D]₅₈₉ = +73.78 (c=0.49, chloroform).

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	62.64	62.94
H	5.52	5.68
N	10.96	10.92

Example 168

20 (+)-(4aR)-(10bR)-4-methyl-8-(6-nitro-2-quinolinylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

25 Yield: 88 mg (53%) of the title compound as a tan solid . mp 195-196°. FDMS: m/e = 433. α [D]₅₈₉ = +64.56 (c=0.78, chloroform).

-114-

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	66.49	66.25
H	5.35	5.51
N	9.69	9.41

Example 169

5 (+)-(4aR)-(10bR)-4-methyl-8-(5-nitro-2-quinolinylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 29 mg (56%) of the title compound as an amorphous foam. mp 149-154°. FDMS: m/e = 433. α [D]₅₈₉ = +60.00 (c=0.10, chloroform).

10

Example 170

(+)-(4aR)-(10bR)-4-methyl-8-(8-nitro-2-quinolinylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

15 Yield: 90 mg (55%) of the title compound as a solid. mp 199-200°. FDMS: m/e = 433. α [D]₅₈₉ = +76.80 (c=0.42, chloroform).

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	66.49	66.28
H	5.35	5.52
N	9.69	9.47

20

Example 171

(+)-(4aR)-(10bR)-4-methyl-8-(6-phenyl-3-pyridazinylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

25 Yield: 77 mg (49%) of the title compound as an amorphous solid. mp 199-200°. FDMS: m/e = 415. α [D]₅₈₉ = +67.26 (c=0.63, chloroform).

-115-

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	72.26	72.06
H	6.06	6.21
N	10.11	9.93

Example 172

5 (+)-(4aR)-(10bR)-4-methyl-8-(2-phenyl-4-quinazolinylthio)-
10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one
Yield: 112 mg (63%) of the title compound as an off white
solid. mp 185-193°. FDMS: m/e = 465. α [D]₅₈₉ = +49.59 (c =
0.57, chloroform).

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	74.81	73.56
H	5.84	5.94
N	9.02	8.95

10

Example 173

(+)-(4aR)-(10bR)-4-methyl-8-(6-fluoro-2-quinolinylthio)-10b-
methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one
15 Yield: 96 mg (62%) of the title compound as a solid. mp 152-
155°. FDMS: m/e = 406. α [D]₅₈₉ = +63.16 (c=0.61,
chloroform).

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	70.91	70.76
H	5.70	5.83
N	6.89	6.81

-116-

Example 174

(+)-(4aR)-(10bR)-4-methyl-8-(8-fluoro-2-quinolinylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

5 Yield: 78 mg (50%) of the title compound as an amorphous foam. FDMS: m/e = 406. α [D]₅₈₉ = +63.29 (c = 0.56, chloroform).

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	70.91	71.15
H	5.70	5.82
N	6.89	6.94

10

Example 175

(+)-(4aR)-(10bR)-4-methyl-8-(4-thieno[3,2-c]pyridylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

15 Yield: 37 mg (25%) of the title compound as a white solid. mp 196-197°. FDMS: m/e = 394. α [D]₅₈₉ = +75.17 (c = 0.57, chloroform).

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	66.97	66.70
H	5.62	5.70
N	7.10	6.88

Example 176

20

(+)-(4aR)-(10bR)-4-methyl-8-(10-oxo-10H-2-pyridazino[6,1-b]-quinazolinylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

25 Yield: 103 mg (62%) of the title compound as an amorphous foam. mp 110-114°. FDMS: m/e = 456. α [D]₅₈₉ = +54.77 (c = 0.49, chloroform).

-117-

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	68.40	68.22
H	5.30	5.31
N	12.27	12.01

Example 177

5 (+)-(4aR)-(10bR)-4-methyl-8-(3-phenyl-1-isoquinolinylthio)-
10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 64 mg (42%) of the title compound as an off white
solid. mp 183-189°. FDMS: m/e = 464. α [D]₅₈₉ = +54.61 (c =
0.53, chloroform).

10

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	77.55	77.26
H	6.07	6.16
N	6.03	6.16

Example 178

15 (+)-(4aR)-(10bR)-4-methyl-8-(3-methyl-2-quinolinylthio)-10b-
methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 9 mg (16%) of the title compound as an amorphous foam.
mp 185-193°. FDMS: m/e = 402.

-118-

Example 179

(+)-(4aR)-(10bR)-4-methyl-8-[3-phenyl-4-(4-methoxyphenyl)-2-quinolinylthio]-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

- 5 Yield: 56 mg (43%) of the title compound as an off white solid. mp 239-242°. FDMS: m/e = 570. α [D]₅₈₉ = +45.00 (c = 1.40, chloroform).

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	77.86	77.58
H	6.00	6.12
N	4.91	4.94

10

Example 180

(+)-(4aR)-(10bR)-4-methyl-8-(3-[1,2-benzisothiazolyl]thio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

- 15 Yield: 54 mg (36%) of the title compound as an amorphous foam. FDMS: m/e = 394.

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	66.97	67.05
H	5.62	5.83
N	7.10	7.03

Example 181

20 (+)-(4aR)-(10bR)-4-methyl-8-(2-[4,6-diphenyl]pyridylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 40 mg (27%) of the title compound as an amorphous solid. FDMS: m/e = 490. α [D]₅₈₉ = +37.97 (c = 0.39, chloroform).

25

-119-

Example 182

(+)-(4aR)-(10bR)-4-methyl-8-(4-methoxy-2-benzothiazolylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

5 Yield: 107 mg (66%) of the title compound as an off white solid. mp 200-205°. FDMS: m/e = 424. α [D]₅₈₉ = +60.56 (c = 0.96, chloroform).

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	65.07	64.43
H	5.70	5.55
N	6.60	7.81

10

Example 183

(+)-(4aR)-(10bR)-4-methyl-8-(4-bromo-2-benzothiazolylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

15 Yield: 142 mg (79%) of the title compound as an off white solid. mp 206-210°. FDMS: m/e = 474. α [D]₅₈₉ = +56.25 (c = 0.59, chloroform).

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	55.81	55.63
H	4.47	4.62
N	5.92	6.16

Example 184

20 (+)-(4aR)-(10bR)-4-methyl-8-(4-phenyl-2-benzothiazolylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 110 mg (61%) of the title compound as an amorphous foam. FDMS: m/e = 470. α [D]₅₈₉ = +53.51 (c = 0.66,
25 chloroform).

-120-

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	71.46	71.22
H	5.57	5.69
N	5.95	5.82

Example 185

5 (+)-(4aR)-(10bR)-4-methyl-8-(4,7-dimethyl-2-benzothiazolylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]-quinolin-3-one

10 Yield: 111 mg (69%) of the title compound as an amorphous foam. FDMS: m/e = 422. α [D]₅₈₉ = +63.27 (c=0.95, chloroform).

Example 186

15 (+)-(4aR)-(10bR)-4-methyl-8-(4-propyl-2-benzothiazolylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 116 mg (70%) of the title compound as an amorphous solid. mp 109-111°. FDMS: m/e = 436. α [D]₅₈₉ = +45.00 (c=0.80, chloroform).

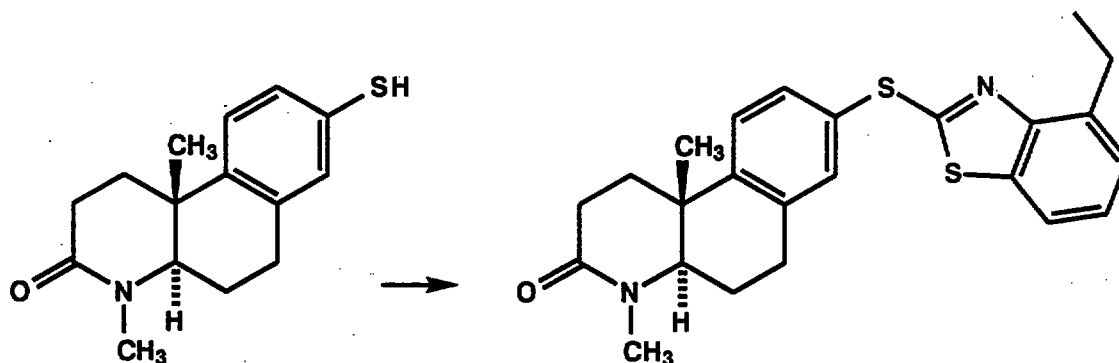
<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	68.77	68.50
H	6.46	6.57
N	6.42	6.44

20

-121-

Example 187

(+)-(4aR)-(10bR)-4-methyl-8-(4-ethyl-2-benzothiazolylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one



5

A 200 mL round bottom flask was charged with (+)-(4aR)-(10bR)-4-methyl-8-mercapto-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one (1.36g, 5.20 mmol), potassium carbonate (2.16 g, 15.6 mmol), 2-chloro-4-ethyl-benzothiazole (1.23g, 6.20 mmol) and 14 mL of anhydrous dimethylformamide, fitted with a reflux condenser, and the stirred mixture was heated at 60°, under nitrogen, for 18h. The mixture was cooled, diluted with ethyl acetate (750 mL) and washed with brine (6 x 250 mL). The combined organic extracts were dried over sodium sulfate, concentrated, and purified by silica gel chromatography (80% ethyl acetate/hexanes eluent) to give 1.51g (69%) of the title compound as an amorphous foam. FDMS: m/e = 422. $\alpha[D]_{589} = +62.74$ (c=0.67, chloroform).

10

15

20

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	68.21	68.40
H	6.20	6.22
N	6.63	6.49

-122-

Example 188

(+)-(4aR)-(10bR)-4-methyl-8-(4-trifluoromethoxy-2-benzothiazolylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]-quinolin-3-one

5

Yield: 141 mg (77%) of the title compound as a white solid.
mp 168-173°. FDMS: m/e = 478. α [D]₅₈₉ = +57.89 (c = 0.59, chloroform).

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	57.73	57.50
H	4.42	4.52
N	5.85	5.78

10

Example 189

(+)-(4aR)-(10bR)-4-methyl-8-[4,7-di(t-butyl)-2-benzothiazolylthio]-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]-quinolin-3-one

15

Yield: 33 mg (17 %) of the title compound as an amorphous foam. FDMS: m/e = 506.

Example 190

(+)-(4aR)-(10bR)-4-methyl-8-(4-methyl-7-trifluoromethyl-2-benzothiazolylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

20

Yield: 94 mg (52%) of the title compound as an amorphous foam. mp 50-54°. FDMS: m/e = 476.

25

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	60.49	60.79
H	4.86	5.14
N	5.88	5.75

-123-

Example 191

(+)-(4aR)-(10bR)-8-(3-isoquinolinylmethylthio)-4,10b-dimethyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinoline-3-one

5 Yield: crystalline solid (91 mg), mp = 129-130°. m/e 402. OR (c=1.0, methanol) @ 589 nM, +64.2°, @ 365 nM, +226.7°.

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	74.59	74.87
H	6.51	6.45
N	6.96	7.09

Example 192

10 (+)-(4aR)-(10bR)-8-(2-benzothiazolylmethylthio)-4,10b-dimethyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinoline-3-one

Yield: a crystalline solid (55 mg), mp = 78-80°. m/e 408. OR (c=0.3, methanol) @589. nM, +66.3°.

15

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	67.61	67.51
H	5.92	6.05
N	6.86	6.63

Example 193

(4aR)-(10bR)-4,10b-dimethyl-8-(7-chloro-2-benzothiazolylthio)-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinoline-3-one

20

Yield: 195 mg of the desired product. mp 90-91°. FDMS: m/e = +428.

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	61.60	61.83
H	4.93	5.09
N	6.53	6.49

25

-124-

Example 194

(4aR)-(10bR)-4,10b-dimethyl-8-(5-chloro-2-benzothiazolylthio)-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinoline-3-one

5 Yield: 56 mg of the desired product. mp 179-180°. FDMS:
m/e = +428.

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	61.60	61.30
H	4.93	4.89
N	6.53	6.51

Example 195

10 (4aR)-(10bR)-8-diphenylmethylthio-4,10b-dimethyl-
1,2,3,4,4a,5,6,10b-octahydrobenzo[f]-quinoline-3-one

Yield: 146 mg of the desired product. mp 102-104°. FDMS:
m/e = +427. $\alpha[D]_{589} = 60,28$.

15

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	78.65	78.65
H	6.84	6.72
N	3.28	3.47

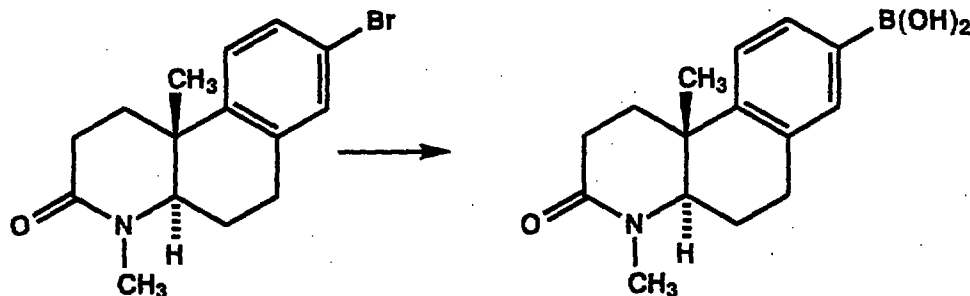
20

The following preparation and examples illustrate the synthesis of compounds of the present invention through an intermediate having a boronic acid substituent on the benzoquinolinone nucleus.

-125-

Preparation 9

(+)-(4aR)-(10bR)-4-methyl-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one-8-boronic acid



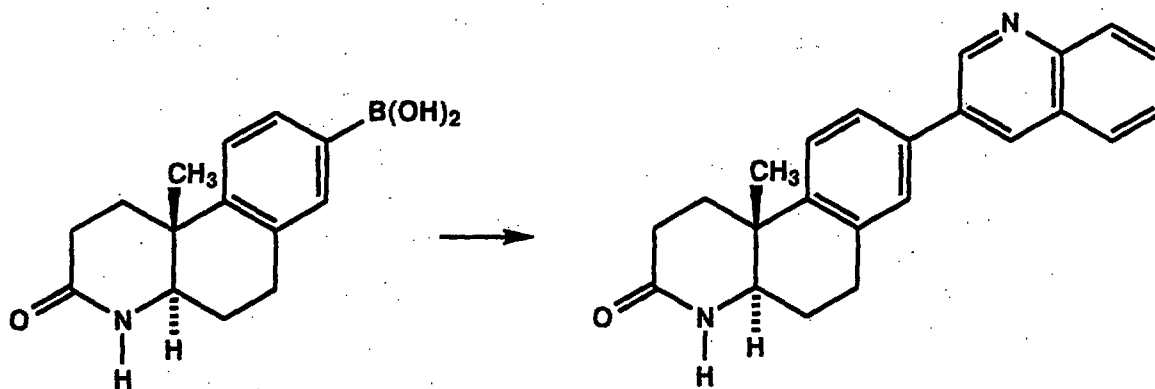
To a solution of (+)-(4aR)-(10bR)-4-methyl-8-bromo-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one (5.0 g, 16.2 mmol) in 500 mL of anhydrous THF was added t-butyllithium (37.5 mL, 1.3 M solution in cyclohexane) at -78° . The mixture was allowed to stir at -78° for 75 min, and a solution of triisopropyl borate (2.0 equiv.) in 12.5 mL of anhydrous THF was added dropwise. The mixture was stirred for an additional 45 min, then the cold bath was removed, and the mixture was allowed to warm to room temperature. The mixture was quenched with 5 N hydrochloric acid (50 mL), and volatiles were removed on rotary evaporator. The mixture was then treated with 35 mL of 5 N sodium hydroxide, and was extracted with THF (300 mL). The organic extract was dried over sodium sulfate, filtered, and concentrated. The resulting solid was heated in boiling ethyl acetate for 15 min, followed by filtration (while still hot), to yield 3.65 g (82%) of the title compound as a white solid. mp 200° (decomp.) $\alpha[D]_{589} = +72.27$ (c = 0.89, methanol).

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	65.96	65.74
H	7.38	7.73
N	5.13	4.94

-126-

Example 196

(+)-(4aR)-(10bR)-8-(3-quinolinyl)-10b-methyl-1,2,3,4,4a,-
5,6,10b-octahydrobenzo[f]quinolin-3-one



A 15 mL round bottom flask was charged with (+)-(4aR)-(10bR)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one-8-boronic acid (168 mg, 0.65 mmol), tetrakis(triphenylphosphine)palladium(0) (23 mg, 0.02 mmol), 3-bromoquinoline (135 mg, 0.65 mmol), 0.65 mL of aqueous 2 M sodium carbonate and 2mL of THF, fitted with a reflux condenser, and the stirred mixture was heated at 80°, under nitrogen, for 24 h. The mixture was cooled, diluted with chloroform (75 mL) and washed with brine (2 x 25 mL). The combined organic extracts were dried over sodium sulfate, concentrated, and purified by silica gel chromatography (5% methanol / ethyl acetate eluent) to give 141 mg (63%) of the title compound as a white solid. mp 265-266°. FDMS: m/e = 342. $\alpha[D]_{589} = +88.70$ (c = 0.84, chloroform).

10

15

20

The following examples were carried out according to the process of Example 196.

-127-

Example 197

(+)-(4aR)-(10bR)-8-(4-[2,8-bistrifluoromethyl]quinolinyl)-
10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

5 Yield: 186 mg (60%) of the title compound as a white solid.
mp 214-215°. FDMS: m/e = 478. α [D]₅₈₉ = +62.00 (c = 1.10,
chloroform) .

Example 198

10 (+)-(4aR)-(10bR)-8-(2-thiazolyl)-10b-methyl-1,2,3,4,4a,-
5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 64 mg (35%) of the title compound as a white solid.
mp 206-207°. FDMS: m/e = 298. α [D]₅₈₉ = +101.7 (c = 0.97,
15 chloroform) .

Example 199

(+)-(4aR)-(10bR)-8-(5-nitro-2-pyridinyl)-10b-methyl-
1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

20 Yield: 71 mg of the title compound as a white solid. mp
123-124°. FDMS: m/e = 337. α [D]₅₈₉ = +85.60 (c = 0.61,
chloroform) .

Example 200

25 (+)-(4aR)-(10bR)-4-methyl-8-(4-isoquinolinyl)-10b-methyl-
1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 110 mg (47%) of the title compound as an amorphous
30 foam. FDMS: m/e = 356. α [D]₅₈₉ = +67.82 (c=0.40, methanol) .

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	80.87	80.57
H	6.79	6.82
N	7.86	7.69

-128-

Example 201

(+)-(4aR)-(10bR)-4-methyl-8-(3-quinolinyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

- 5 Yield: 130 mg (56%) of the title compound as an amorphous solid. mp: 180-185°. FDMS: m/e = 356. α [D]₅₈₉ = +80.22 (c=0.37, chloroform).

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	80.87	80.65
H	6.79	6.52
N	7.86	7.68

10

Example 202

(+)-(4aR)-(10bR)-4-methyl-8-(5-nitro-2-pyridinyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

- 15 Yield: 148 mg (65%) of the title compound as an amorphous foam. mp 70-80°. FDMS: m/e = 351. α [D]₅₈₉ = +85.59 (c = 0.48, chloroform) .

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	68.26	67.81
H	6.02	6.18
N	11.96	11.42

Example 203

- 20 (+)-(4aR)-(10bR)-4-methyl-8-[2,8-bis(trifluoromethyl)-4-quinolinyl]-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]-quinolin-3-one

- 25 Yield: 153 mg (48%) of the title compound as an amorphous foam. mp 100-106°. FDMS: m/e = 492. α [D]₅₈₉ = +51.86 (c = 0.47, chloroform) .

-129-

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	63.41	63.25
H	4.50	4.77
N	5.69	5.40

Example 204

5 (+)-(4aR)-(10bR)-4-methyl-8-(4-methylsulfonylphenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 137 mg (55%) of the title compound as a white solid.
mp 229°. FDMS: m/e = 383.. α [D]₅₈₉ = +28.24 (c = 0.23, chloroform).

10

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	68.90	69.10
H	6.57	6.65
N	3.65.	3.89

Example 205

15 (+)-(4aR)-(10bR)-4-methyl-8-(2,3,4,5,6-pentafluorophenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 97 mg (38%) of the title compound as an amorphous foam. mp 92-100°. FDMS: m/e = 395. α [D]₅₈₉ = +64.15 (c = 0.42, chloroform).

20

Example 206

(+)-(4aR)-(10bR)-4-methyl-8-(3,4,5-trifluorophenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

25 Yield: 117 mg (50%) of the title compound as an amorphous wax. FDMS: m/e = 359 α [D]₅₈₉ = +75.86 (c = 0.47, chloroform).

-130-

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	70.18	70.41
H	5.61	5.81
N	3.90	3.78

Example 207

(+)-(4aR)-(10bR)-4-methyl-8-(1-oxo-5-indanyl)-10b-methyl-
1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 91 mg (39%) of the title compound as a white solid.
mp 175-178°. FDMS: m/e = 359. α [D]₅₈₉ = +74.81 (c = 0.53, chloroform).

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	80.19	79.08
H	7.01	7.01
N	3.90	4.08

Example 208

(+)-(4aR)-(10bR)-4-methyl-8-(2-fluoro-3-trifluoromethyl-
phenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]-
quinolin-3-one

Yield: 130 mg (51%) of the title compound as an oil. FDMS:
m/e = 391. α [D]₅₈₉ = +68.49 (c = 0.38, chloroform).

Example 209

(+)-(4aR)-(10bR)-4-methyl-8-(3-[1-benzyl-4-piperidinyl-
carboxamido]phenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-
octahydrobenzo[f]quinolin-3-one

Yield: 148 mg (44%) of the title compound as an amorphous
foam. FDMS: m/e = 521. α [D]₅₈₉ = +53.50 (c = 0.45, chloroform).

-131-

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	78.28	77.50
H	7.53	7.60
N	8.05	7.65

Example 210

5 (+)-(4aR)-(10bR)-4-methyl-8-(2-fluoro-4-trifluoromethyl-phenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]-quinolin-3-one

Yield: 171 mg (67%) of the title compound as an amorphous solid. mp 72-79°. FDMS: m/e = 391. α [D]₅₈₉ = +62.50
10 (c=0.48, chloroform).

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	67.51	67.72
H	5.41	5.65
N	3.58	3.33

Example 211

15 (+)-(4aR)-(10bR)-4-methyl-8-(2-fluoro-5-trifluoromethyl-phenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]-quinolin-3-one

Yield: 113 mg (44%) of the title compound as an oil. FDMS: m/e = 391. α [D]₅₈₉ = +55.84 (c = 0.34, chloroform).

20

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	67.51	67.73
H	5.41	5.62
N	3.58	3.31

-132-

Example 212

(+)-(4aR)-(10bR)-4-methyl-8-(3-methylthiophenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

- 5 Yield: 110 mg (48%) of the title compound as an oily solid.
FDMS: m/e = 351. $\alpha[D]_{589} = +90.00$ (c=0.17, chloroform).

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	75.17	75.02
H	7.17	7.13
N	3.98	3.77

Example 213

- 10 (+)-(4aR)-(10bR)-4-methyl-8-(4-carboxamidophenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 21 mg (9%) of the title compound as amorphous foam. mp 177-189° (decomp.) FDMS: m/e = 348.

15

Example 214

(+)-(4aR)-(10bR)-4-methyl-8-[2-oxo-3-(N,N-diethyl-carboxamido)-1-2H-benzopyran-6-yl]-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

20

Yield: 138 mg (45%) of the title compound as an amorphous foam. mp 120-125°. FDMS: m/e = 472. $\alpha[D]_{589} = +54.69$ (c = 0.49, chloroform).

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	73.71	73.49
H	6.82	6.85
N	5.93	5.86

25

-133-

Example 215

(+)-(4aR)-(10bR)-4-methyl-8-[2-(t-butylcarbonylamino)-5-pyridinyl]-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]-quinolin-3-one

5

Yield: 84 mg (32%) of the title compound as a brown solid.
mp 248-250°. FDMS: m/e = 405. $\alpha[D]_{589} = +70.74$ (c = 0.45, chloroform).

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	74.04	74.31
H	7.70	7.70
N	10.36	9.85

10

Example 216

(+)-(4aR)-(10bR)-4-methyl-8-(3-fluoro-5-trifluoromethyl-phenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]-quinolin-3-one

15

Yield: 145 mg (57%) of the title compound as an oil. FDMS: m/e = 391. $\alpha[D]_{589} = +67.32$ (c = 0.55, chloroform).

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	67.51	67.90
H	5.41	5.73
N	3.58	3.27

20

Example 217

(+)-(4aR)-(10bR)-4-methyl-8-(5-nitro-2-thienyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

25

Yield: 118 mg (51%) of the title compound as a white solid.
mp 147-149°. FDMS: m/e = 356. $\alpha[D]_{589} = +83.48$ (c = 0.54, chloroform).

-134-

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	64.02	64.30
H	5.66	5.78
N	7.86	7.57

Example 218

5 (+)-(4aR)-(10bR)-4-methyl-8-(5-chloro-2-thienyl)-10b-methyl-
1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 125 mg (56%) of the title compound as an oil. FDMS:
m/e = 345. α [D]₅₈₉ = +74.03 (c = 0.51, chloroform).

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	66.98	67.39
H	5.83	5.90
N	4.05	3.86

10

Example 219

(+)-(4aR)-(10bR)-4-methyl-8-(4-chloro-3-fluorophenyl)-10b-
methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

15 Yield: 125 mg (56%) of the title compound as an amorphous
foam. FDMS: m/e = 357. α [D]₅₈₉ = +74.28 (c = 0.35,
chloroform).

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	70.48	70.54
H	5.91	6.04
N	3.91	3.81

-135-

Example 220

(+)-(4aR)-(10bR)-4-methyl-8-(4-sulfonamidophenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

5 Yield: 34 mg (14%) of the title compound as a white solid.
mp 200° (decomp.) FDMS: m/e = 384. α [D]₅₈₉ = +201.8 (c = 0.43, chloroform).

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	65.60	65.83
H	6.29	6.46
N	7.29	7.52

10

Example 221

(+)-(4aR)-(10bR)-4-methyl-8-[4-(4-chlorobutyryl)phenyl]-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

15 Yield: 113 mg (42%) of the title compound an oil. FDMS: m/e = 409. α [D]₅₈₉ = +60.00 (c = 0.18, chloroform).

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	73.25	72.91
H	6.88	6.80
N	3.42	3.33

Example 222

20 (+)-(4aR)-(10bR)-4-methyl-8-(4-[(2-t-butylcarbonylamino)-5-thienyl]phenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

25 Yield: 88 mg (28%) of the title compound a brown solid. mp 240° (decomp.) FDMS: m/e = 487. α [D]₅₈₉ = +61.73 (c = 0.47, chloroform).

-136-

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	71.43	71.62
H	6.82	7.00
N	8.62	8.05

Example 223

(+)-(4aR)-(10bR)-4-methyl-8-(2,3-dioxo-5-indolinyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 36 mg (15%) of the title compound as a white solid.
mp >250° FDMS: m/e = 374. α [D]₅₈₉ = +75.33 (c = 0.53, chloroform).

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	73.78	73.29
H	5.92	5.98
N	7.48	7.22

Example 224

(+)-(4aR)-(10bR)-4-methyl-8-(2-(2-dimethylaminoethyl)-1H-benzo<de>isoquinolin-6-yl-1,3-(2H)dione)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 141 mg (44%) of the title compound as a white solid.
mp 190-192°. FDMS: m/e = 495. α [D]₅₈₉ = +74.71 (c=0.53, chloroform).

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	75.13	74.94
H	6.71	6.33
N	8.48	8.22

-137-

Example 225

(+)-(4aR)-(10bR)-4-methyl-8-(2aR,4S-1-benzoyl-4-di-propylamino-2,2a,3,4-tetrahydrobenz[cd]-1H-indol-7-yl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 64 mg (17%) of the title compound as an amorphous foam. mp 110-115°. FDMS: m/e = 589. $\alpha[D]_{589} = +80.14$ (c = 0.46, chloroform).

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	79.42	79.58
H	8.03	8.06
N	7.12	6.73

Example 226

(+)-(4aR)-(10bR)-4-methyl-8-(2aR,4S-1-benzoyl-4-amino-2,2a,3,4-tetrahydrobenz[cd]-1H-indol-7-yl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 187 mg (57%) of the title compound as an amorphous foam. mp 134-136°. FDMS: m/e = 505.

Example 227

(+)-(4aR)-(10bR)-4-methyl-8-(3,5-difluorophenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 137 mg (62%) of the title compound as an oil. FDMS: m/e = 341. $\alpha[D]_{589} = +79.29$ (c = 0.28, chloroform).

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	73.88	73.40
H	6.20	6.11
N	4.10	3.99

-138-

Example 228

(+)-(4aR)-(10bR)-4-methyl-8-(2,6-difluorophenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

- 5 Yield: 98 mg (44%) of the title compound as an amorphous solid. mp 125-130°. FDMS: m/e = 341. α [D]₅₈₉ = +71.79 (c = 0.58, chloroform).

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	73.88	74.13
H	6.20	6.32
N	4.10	3.87

10

Example 229

(+)-(4aR)-(10bR)-4-methyl-8-(2,5-difluorophenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

- 15 Yield: 105 mg (47%) of the title compound as an oil. FDMS: m/e = 341. α [D]₅₈₉ = +70.96 (c = 0.38, chloroform).

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	73.88	74.01
H	6.20	6.43
N	4.10	3.76

Example 230

- 20 (+)-(4aR)-(10bR)-4-methyl-8-(2,4,6-trifluorophenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 116 mg (50%) of the title compound as an oil. FDMS: m/e = 359. α [D]₅₈₉ = +68.65 (c = 0.35, chloroform).

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	70.18	70.15
H	5.61	5.86
N	3.90	3.69

25

-139-

Example 231

(+)-(4aR)-(10bR)-4-methyl-8-(2,4-difluorophenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

5 Yield: 106 mg (48%) of the title compound as white solid. mp 108-112°. FDMS: m/e = 341. α [D]₅₈₉ = +82.90 (c = 0.52, chloroform) .

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	73.88	73.94
H	6.20	6.33
N	4.10	4.05

10

Example 232

(+)-(4aR)-(10bR)-4-methyl-8-(2,3,4-trifluorophenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

15 Yield: 100 mg (43%) of the title compound as a white solid. mp 100-102°. FDMS: m/e = 359. α [D]₅₈₉ = +78.37 (c = 0.33, chloroform) .

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	70.18	70.47
H	5.61	5.80
N	3.90	3.78

Example 233

20

(+)-(4aR)-(10bR)-4-methyl-8-(4-[4-nitrobenzyl]thiophenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 166 mg (54%) of the title compound as an oily solid. FDMS: m/e = 472. α [D]₅₈₉ = +65.63 (c=0.41, chloroform) .

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	71.16	71.63
H	5.97	6.21
N	5.93	6.26

-140-

Example 234

(+)-(4aR)-(10bR)-4-methyl-8-(2-(2-[1-morpholino]ethyl)-1H-benzo<de>isoquinolin-6-yl-1,3-(2H)dione)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

5

Yield: 176 mg (50%) of the title compound as an amorphous solid. mp 100-105°. FDMS: m/e = 537. $\alpha[D]_{589} = +45.10$ (c=0.53, chloroform).

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	73.72	73.46
H	6.56	6.73
N	7.82	7.55

10

Example 235

(+)-(4aR)-(10bR)-4-methyl-8-(4-pyridinyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

15

Yield: 85 mg (43%) of the title compound as an oil. FDMS: m/e = 306.

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	78.40	78.56
H	7.24	7.00
N	9.14	8.68

Example 236

(+)-(4aR)-(10bR)-4-methyl-8-(1-p-toluenesulfonylindol-5-yl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

20

Yield: 49 mg (15%) of the title compound as an amorphous foam. FDMS: m/e = 498.

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	72.26	71.04
H	6.06	6.32
N	5.62	4.94

25

-141-

Example 237

(+)-(4aR)-(10bR)-4-methyl-8-(1-acetyl-7-nitroindolin-5-yl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

5 Yield: 63 mg (22%) of the title compound a yellow solid. mp 235-240°. FDMS: m/e = 433. α [D]₅₈₉ = +65.72 (c = 0.99, chloroform).

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	69.27	69.39
H	6.28	6.55
N	9.69	9.54

10

Example 238

(+)-(4aR)-(10bR)-4-methyl-8-(1-acetylindolin-5-yl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

15 Yield: 67 mg (26%) of the title compound as a yellow solid. mp 197-200°. FDMS: m/e = 388. α [D]₅₈₉ = +77.92 (c = 0.36, chloroform).

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	77.29	77.04
H	7.26	7.00
N	7.21	7.12

Example 239

20 (+)-(4aR)-(10bR)-4-methyl-8-(8-quinolinyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

25 Yield: 88 mg (38%) of the title compound as a tan solid. mp 205-207°. FDMS: m/e = 356 α [D]₅₈₉ = +76.28 (c = 0.47, chloroform).

-142-

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	80.87	80.66
H	6.79	6.69
N	7.86	7.76

Example 240

5 (+)-(4aR)-(10bR)-4-methyl-8-(5-quinolinyl)-10b-methyl-
1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 128 mg (55%) of the title compound as an amorphous
foam. mp 100-104°. FDMS: m/e = 356. α [D]₅₈₉ = +61.77 (c
= 0.35, chloroform).

10

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	80.87	79.55
H	6.79	6.92
N	7.86	7.60

Example 241

15 (+)-(4aR)-(10bR)-4-methyl-8-(5-isoquinolinyl)-10b-methyl-
1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 98 mg (42%) of the title compound as an amorphous
solid. mp 182-184°. FDMS: m/e = 356. α [D]₅₈₉ = +57.25 (c
= 0.49, chloroform).

20

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	80.87	80.28
H	6.79	6.86
N	7.86	7.43

-143-

Example 242

(+)-(4aR)-(10bR)-4-methyl-8-(2-pyridinyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

5 Yield: 98 mg (49%) of the title compound as an oil. FDMS: m/e = 306. α [D]₅₈₉ = +83.48 (c = 0.38, chloroform).

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	78.40	77.73
H	7.24	6.96
N	9.14	9.07

Example 243

10 (+)-(4aR)-(10bR)-4-methyl-8-(2,5-difluoro-4-nitrophenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 128 mg (51%) of the title compound as an amorphous solid. mp: 130-140°. FDMS: m/e = 386. α [D]₅₈₉ = +73.44 (c=0.53, chloroform).

15

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	65.28	66.70
H	5.22	5.69
N	7.25	7.64

Example 244

20 (+)-(4aR)-(10bR)-4-methyl-8-(6-quinolinyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 107 mg (46%) of the title compound as an amorphous solid. mp 185-190°. FDMS: m/e = 356. α [D]₅₈₉ = +78.73 (c = 0.56, chloroform).

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	80.87	80.13
H	6.79	6.74
N	7.86	6.99

-144-

Example 245

(+)-(4aR)-(10bR)-4-methyl-8-(1-hydroxy-5-indanyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

- 5 Yield: 79 mg (34%) of the title compound as an amorphous solid. mp: 185-190°. FDMS: m/e = 361. α [D]₅₈₉ = +77.38 (c=0.35, chloroform).

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	79.74	79.01
H	7.53	7.53
N	3.87	3.79

10

Example 246

(+)-(4aR)-(10bR)-4-methyl-8-[2-(4-[N-benzyl]piperidinyl)-1H-benzo<de>isoquinolin-6-yl-1,3-(2H)dione]-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

- 15 Yield: 197 mg (51%) of the title compound as an amorphous foam. FDMS: m/e = 597. α [D]₅₈₉ = +51.09 (c=0.58, chloroform).

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	78.36	76.08
H	6.58	6.80
N	7.03	6.40

20

Example 247

(+)-(4aR)-(10bR)-4-methyl-8-(2-quinolinyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

- 25 Yield: 126 mg (54%) of the title compound as an amorphous foam. mp 140-145°. FDMS: m/e = 356.. α [D]₅₈₉ = +74.01 (c = 0.46, chloroform).

-145-

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	80.87	80.56
H	6.79	6.88
N	7.86	7.45

Example 248

5 (+)-(4aR)-(10bR)-4-methyl-8-(2-oxo-1-benzopyran-6-yl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 108 mg (40%) of the title compound an amorphous solid.
mp 180° (decomp.) FDMS: m/e = 373. α [D]₅₈₉ = +40.48 (c = 0.42, chloroform).

10

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	77.19	76.90
H	6.21	6.48
N	3.75	4.02

Example 249

15 (+)-(4aR)-(10bR)-4-methyl-8-(6-benzothiazolyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 106 mg (47%) of the title compound as an amorphous solid. mp 183-187°. FDMS: m/e = 362. α [D]₅₈₉ = +87.80 (c = 0.55, chloroform).

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	72.90	72.63
H	6.12	6.30
N	7.73	7.49

20

-146-

Example 250

(+)-(4aR)-(10bR)-4-methyl-8-(1-[t-butoxycarbonyl]-5-indolyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

5 Yield: 113 mg (39%) of the title compound as an amorphous foam. FDMS: m/e = 445. α [D]₅₈₉ = +68.17 (c = 0.47, chloroform).

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	75.65	75.82
H	7.25	7.28
N	6.30	5.88

10

Example 251

(+)-(4aR)-(10bR)-4-methyl-8-(2-benzoxazolyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

15

Yield: 45 mg (20%) of the title compound as an amorphous foam. FDMS: m/e = 346.

Example 252

(+)-(4aR)-(10bR)-4-methyl-8-(2-benzothiazolyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

20

Yield: 107 mg (45%) of the title compound as an amorphous solid. mp: 207-212°. FDMS: m/e = 362. α [D]₅₈₉ = +88.83 (c=0.60, chloroform).

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	72.90	72.03
H	6.12	6.06
N	7.73	7.20

25

-147-

Example 253

(+)-(4aR)-(10bR)-4-methyl-8-(2-pyrazinyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

5 Yield: 132 mg (66%) of the title compound as an amorphous foam. FDMS: m/e = 308. α [D]₅₈₉ = +89.71 (c=0.34, chloroform).

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	74.24	73.97
H	6.89	6.55
N	13.67	13.50

10

Example 254

(+)-(4aR)-(10bR)-4-methyl-8-(2-pyrimidinyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

15 Yield: 102 mg (51%) of the title compound as an amorphous foam. mp 160-162°. FDMS: m/e = 307. α [D]₅₈₉ = +95.71 (c=0.28, chloroform).

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	74.24	73.29
H	6.89	6.88
N	13.67	13.52

20

Example 255

(+)-(4aR)-(10bR)-4-methyl-8-(2-quinoxaliny1)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

25 Yield: 156 mg (67%) of the title compound as a foam. mp 129-135°. FDMS: m/e = 357. α [D]₅₈₉ = +72.94 (c=0.63, chloroform).

-148-

Example 256

(+)-(4aR)-(10bR)-4-methyl-8-(2-benzimidazolyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

5 Yield: 57 mg (25%) of the title compound as an amorphous foam. mp 183-186°. FDMS: m/e = 345.

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	76.49	75.99
H	6.71	6.35
N	12.16	11.69

Example 257

10 (+)-(4aR)-(10bR)-4-methyl-8-(3-indazolyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 49 mg (11%) of the title compound as an amorphous foam. FDMS: m/e = 345..

15

Example 258

(+)-(4aR)-(10bR)-4-methyl-8-(2-[3-phenyl]tetrazolyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

20 Yield: 69 mg (28%) of the title compound as an amorphous foam. mp 85-90°. FDMS: m/e = 373. $\alpha[D]_{589} = +84.79$ (c=0.65, chloroform).

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	70.76	70.61
H	6.21	5.97
N	18.75	18.63

-149-

Example 259

(+)-(4aR)-(10bR)-4-methyl-8-(2-[5-trifluoromethyl]pyridinyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

5 Yield: 141 mg (58%) of the title compound as an amorphous foam. mp 65-68°. FDMS: m/e = 374. α [D]₅₈₉ = +81.90 (c = 0.84, chloroform) .

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	67.37	67.12
H	5.65	5.68
N	7.48	7.23

10

Example 260

(+)-(4aR)-(10bR)-4-methyl-8-(2-naphtho<1,2-d>thiazolyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

15 Yield: 192 mg (72%) of the title compound as an amorphous solid. mp 105-107°. FDMS: m/e = 412. α [D]₅₈₉ = +86.44 (c=0.70, chloroform).

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	75.70	75.46
H	5.86	5.58
N	6.79	6.55

Example 261

20 (+)-(4aR)-(10bR)-4-methyl-8-(2-[4-fluoro]benzothiazolyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 181 mg (73%) of the title compound as an amorphous foam. mp 170-190°. FDMS: m/e = 380. α [D]₅₈₉ = +92.40
25 (c=0.50, chloroform).

-150-

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	69.45	69.68
H	5.56	5.80
N	7.36	7.07

Example 262

(+)-(4aR)-(10bR)-4-methyl-8-(2-[4-chloro]benzothiazolyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 177 mg (69%) of the title compound as an amorphous solid. mp 206-209°. m/e = 396. α [D]₅₈₉ = +91.10 (c=0.81, chloroform).

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	66.57	66.77
H	5.33	5.48
N	7.06	6.97

Example 263

(+)-(4aR)-(10bR)-4-methyl-8-(2-[5,6-dichloro]benzothiazolyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 113 mg (40%) of the title compound as an amorphous foam. FDMS: m/e = 431. α [D]₅₈₉ = +79.41 (c=0.79, chloroform).

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	61.26	60.99
H	4.67	4.82
N	6.49	6.31

-151-

Example 264

(+)-(4aR)-(10bR)-4-methyl-8-(2-[4-isopropyl]benzothiazolyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 94 mg (36%) of the title compound as an amorphous solid. mp: 170-180°. FDMS: m/e = 404.

Example 265

(+)-(4aR)-(10bR)-4-methyl-8-(2-[6-chloro]benzothiazolyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

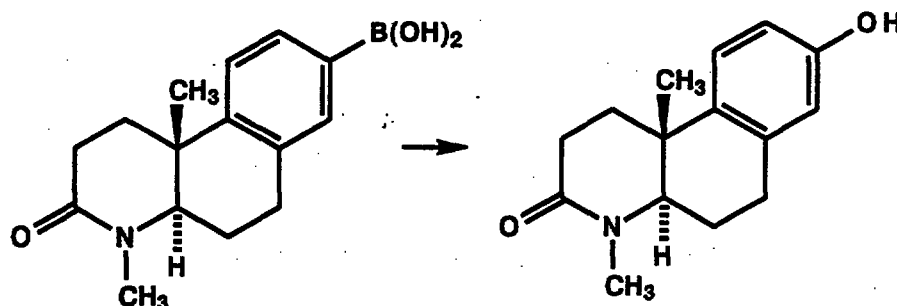
Yield: 100 mg (39%) of the title compound as a white solid. mp: 123-125°. FDMS: m/e = 396. $\alpha[D]_{589} = +73.63$ (c=1.26, methanol).

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	66.57	66.32
H	5.33	5.52
N	7.06	7.01

The following preparation and example illustrate the synthesis of compounds of the present invention wherein the X group is an oxygen atom.

Preparation 10

(+)-(4aR)-(10bR)-4-methyl-8-hydroxy-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

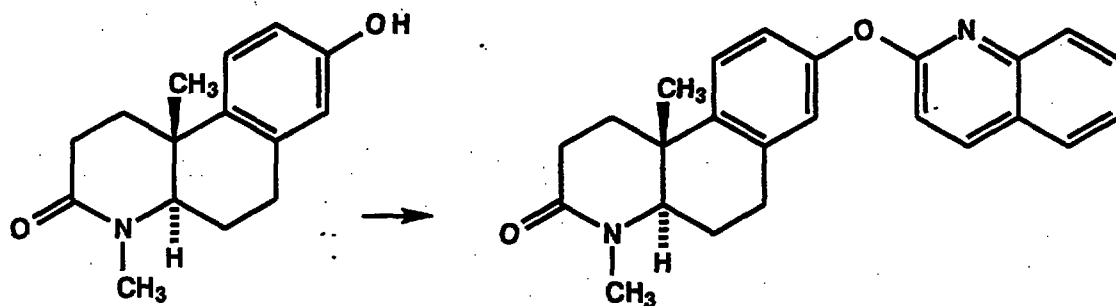


-152-

To a suspension of (+)-(4aR)-(10bR)-4-methyl-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]-quinolin-3-one-8-boronic acid (1.0 g, 3.7 mmol) in 30 mL of THF was added 3 N sodium hydroxide (6 mL) followed by 6.0 mL of 30% hydrogen peroxide at -30°. The cold bath was removed, and the mixture was stirred at room temperature for 2.5 h. Six mL of saturated aqueous sodium sulfite solution was added, followed by 5 N hydrochloric acid until solution was acidic. Volatiles were removed via rotary evaporation, and the crude solid was heated in ethyl acetate and filtered to give 441 mg (53%) of the title compound as an amorphous solid. FDMS m/e = 245.

Example 266

(+)-(4aR)-(10bR)-4-methyl-8-(2-quinolinyloxy)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one



A 50 mL round bottom flask was charged with (+)-(4aR)-(10bR)-4-methyl-8-hydroxy-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one (300 mg, 1.22 mmol), tetrabutylammonium chloride (339 mg, 1.22 mmol), 2-chloroquinoline (200 mg, 1.22 mmol), 4 mL of 50% sodium hydroxide solution, and 4 mL of toluene, fitted with a reflux condenser, and the stirred mixture was heated at 100°, under nitrogen, for 24 h. The mixture was cooled, diluted with water (50 mL) and extracted with chloroform (3 x 100 mL). The combined organic extracts were dried over sodium sulfate, concentrated, and purified by silica gel chromatography (60% ethyl acetate/hexanes eluent; followed by an additional

-153-

chromatography on a short silica column, eluting with 10% ethyl acetate/dichloromethane) to give 52 mg (11%) of the title compound as a white solid. mp 172-174°. FDMS: m/e = 372. $\alpha[D]_{589} = +67.74$ (c=0.43, chloroform).

5

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	77.39	77.32
H	6.49	6.70
N	7.52	7.25

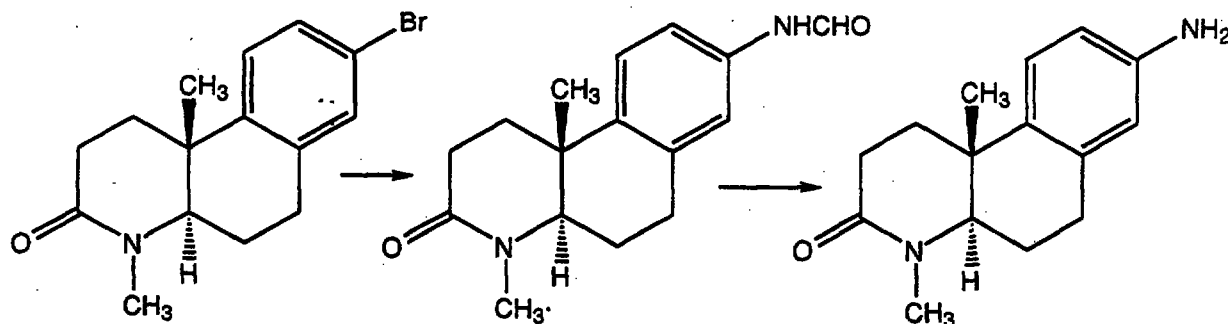
The following preparation and examples illustrate syntheses of compounds of the invention wherein the group X incorporates an amino group, and the synthesis uses a starting material having an amino substituent on the benzoquinolinone nucleus.

10

Preparation 11

(4aR)-(10bR)-8-formamido-4,10b-dimethyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinoline-3-one

15



In a sealable, heavy-walled pyrex tube equipped with teflon stirring bar was placed (4aR)-(10bR)-8-bromo-4,10b-dimethyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinoline-3-one (500 mg, 1.6 mmol), copper(I) iodide (340 mg, 1.8 mmol), powdered potassium carbonate (500 mg, 3.6 mmol) and formamide (40 mL). The mixture was purged with nitrogen for 10 minutes and the tube sealed. The mixture was heated to 125° for 18 h. After cooling to ambient temperature, the tube was opened and the contents partitioned between water

20

25

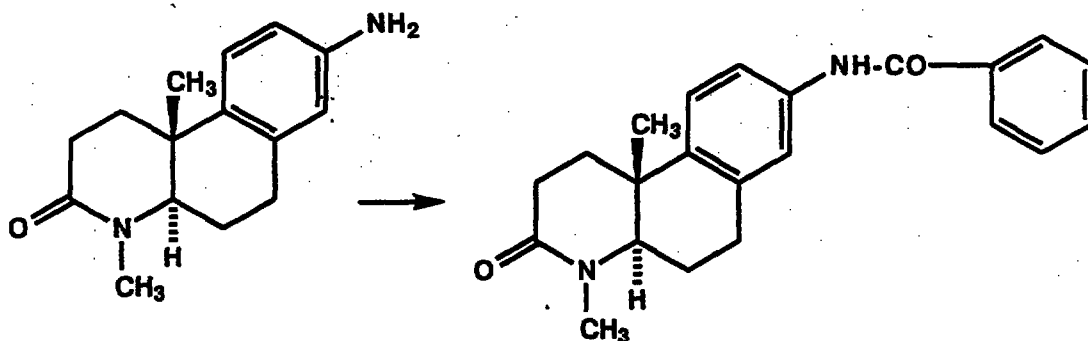
-154-

(250 mL) and ethyl acetate (250 mL). The aqueous phase was extracted with ethyl acetate (2X 100 mL) and the combined organic phase was dried over anhydrous magnesium sulfate and concentrated to afford crude 8-formamido intermediate product (220 mg) which was utilized without further purification.
m/e 272.

The crude intermediate product was dissolved in ethyl acetate (50 mL), 5 N hydrochloric acid solution (10 mL) was added and the solution stirred at ambient temperature for 2.5 h. The mixture was made basic with aqueous ammonium hydroxide solution and extracted with ethyl acetate (2 X 50 mL). The combined organic phase was dried over anhydrous magnesium sulfate and concentrated to afford crude product (90 mg) which was utilized without further purification.
m/e 244.

Example 267

(+)-(4aR)-(10bR)-4,10b-dimethyl-8-benzoylamino-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one



A 200 mg portion of (4aR)-(10bR)-4,10b-dimethyl-8-amino-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]-quinolin-3-one was dissolved in 50 mL of THF and a slight excess of benzoyl chloride was added. The mixture was stirred at ambient temperature for 3 h, and volatiles were then removed under vacuum. The resulting oil was triturated with diethyl ether, and the resulting solids were purified by chromatography on silica gel, eluting with 50% methanol/ethyl acetate. A yield

-155-

of 104 mg of solid product was obtained from the column and found to be the desired product, m.p. 220-222°. FDMS: m/e = 348. $\alpha[D]_{589} = +75.53^\circ$

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	75.83	75.62
H	6.94	6.97
N	8.04	7.98

5

The following examples were carried out according to the process of Example 267.

Example 268

10 (+)-(4aR)-(10bR)-4,10b-dimethyl-8-(3-nitrobenzoylamino)-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 595 mg of the desired product, m.p. 240-242°. FDMS: m/e = 393. $\alpha[D]_{589} = +75.79^\circ$

15

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	67.16	66.92
H	5.89	5.86
N	10.68	10.45

Example 269

(4aR)-(10bR)-4,10b-dimethyl-8-(4-nitrobenzoylamino)-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

20

Yield: 38.2 mg of the desired product, m.p. 269-270°. FDMS: m/e = 393.

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	67.16	66.88
H	5.89	5.82
N	10.68	10.59

-156-

Example 270

(4aR)-(10bR)-4,10b-dimethyl-8-(3-aminobenzoylamino)-
1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

5 Yield: 80.5 mg of purified product, m.p. 154-156°. FDMS:
m/e = 363.

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	72.70	73.00
H	6.93	7.03
N	11.56	11.61

Example 271

10 (4aR)-(10bR)-4,10b-dimethyl-8-(4-aminobenzoylamino)-
1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 30.6 mg of the desired product. FDMS: m/e = 363.

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	66.07	65.84
H	6.55	6.72
N	10.51	10.46

15

Example 272

(+)-(4aR)-(10bR)-4-methyl-8-(3-diphenylmethylaminophenyl)-
10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

20 Yield: 28 mg (83%) of the title compound as a white solid. mp
109-111°. FDMS: m/e = 486. α [D]₅₈₉ = +46.90 (c = 0.49,
methanol).

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	83.91	83.62
H	7.04	7.14
N	5.76	5.51

-157-

Example 273

(+)-(4aR)-(10bR)-4-methyl-8-(3-[benzoylamino]phenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

5 Yield: 50 mg (76%) of the title compound as an amorphous foam.
mp 257-262° (decomp.) FDMS m/e = 424. α [D]₅₈₉ = +62.50 (c = 0.61, chloroform).

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	79.22	79.62
H	6.65	6.50
N	6.60	6.70

10

Example 274

(+)-(4aR)-(10bR)-4-methyl-8-(3-[pivaloylamino]phenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

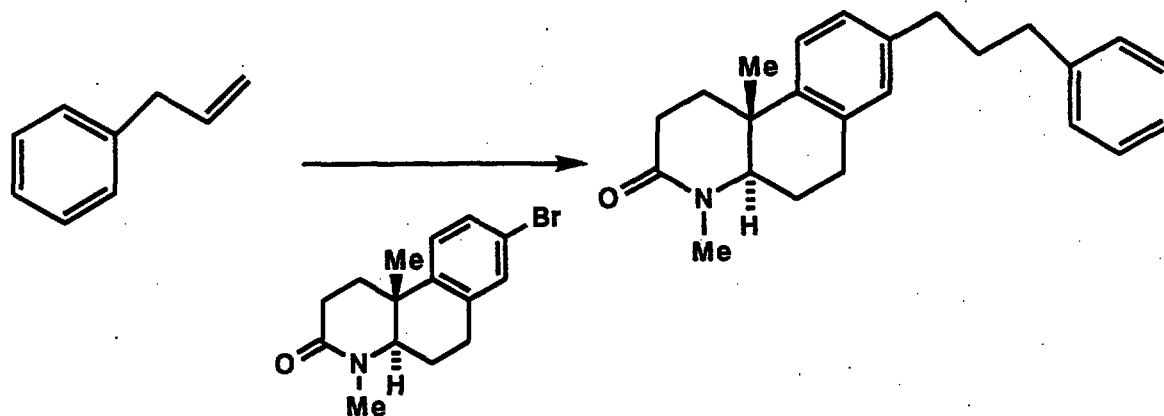
15 Yield: 25 mg (64%) of the title compound as a yellow solid.
mp 95-98°. FDMS m/e = 404. α [D]₅₈₉ = +62.50 (c = 0.16, chloroform).

20 The following group of examples demonstrates
typical synthesis of compounds having X groups which are
alkyl, alkenyl, and alkynyl.

-158-

Example 275

(+)-(4aR)-(10bR)-4-methyl-8-(3-phenylpropyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one



To a solution of allylbenzene (106 mg, 0.89 mmol) in 0.5 mL of THF was added 9-BBN (0.89 mmol, 1 equiv) in THF, at 0°. Let stir for 1 h, warming to 5°. To the mixture was added (+)-(4aR)-(10bR)-8-bromo-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one (250 mg, 0.812 mmol), triphenyl phosphine (42 mg, 0.16 equiv.), tetrakis(triphenylphosphine) palladium(0) (19 mg, 0.02 equiv.), 1 mL of 3 N sodium hydroxide solution and an additional 1 mL of THF. The resulting mixture was heated at 80° for 18 h, cooled, and ethanolamine was added, followed by ethyl acetate. The resulting organic phase was washed with brine, dried over sodium sulfate, concentrated, and purified by silica gel chromatography (50-100% ethyl acetate / hexanes eluent gradient) to give 160 mg (59%) of the title compound as an oil. FDMS m/e = 347.

10

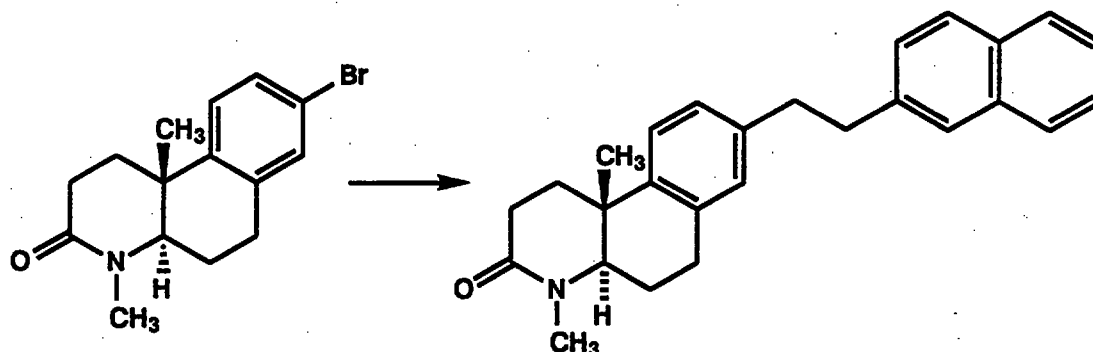
15

20

-159-

Example 276

(+)-(4aR)-(10bR)-4-methyl-8-(2-[2-naphthyl]ethyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one



5

To a solution of 2-vinylnaphthalene (138 mg, 0.89 mmol) in 0.5 mL of THF was added 9-BBN (0.89 mmol, 1 equiv) in THF, at 0°. Let stir for 1 h, warming to 5°. To the mixture was added (+)-(4aR)-(10bR)-4-H-8-bromo-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one (250 mg, 0.812 mmol), triphenyl phosphine, (42 mg, 0.16 equiv.), tetrakis(triphenylphosphine) palladium(0) (19 mg, 0.02 equiv.), 1 mL of 3 N sodium hydroxide solution and an additional 1 mL of THF. The resulting mixture was heated at 80° for 18 h, cooled, and ethanolamine was added, followed by ethyl acetate. The resulting organic phase was washed with brine, dried over sodium sulfate, concentrated, and purified by silica gel chromatography (50-100% ethyl acetate / hexanes eluent gradient) to give 186 mg (60%) of the title compound as a tan solid. mp 109-110°. FDMS m/e = 383. $\alpha_D^{25} = +46.45$ (c = 0.66, chloroform).

10

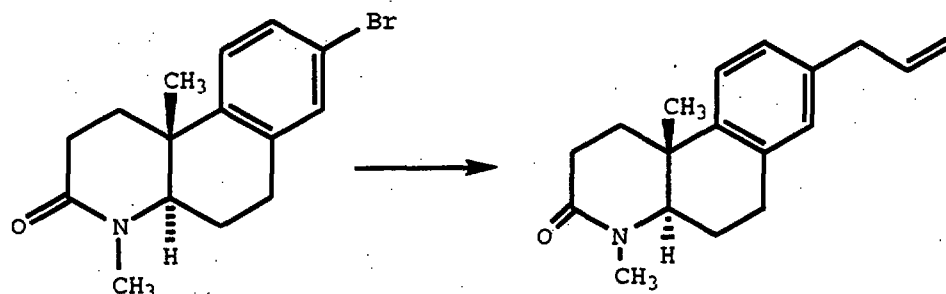
15

20

-160-

Preparation 12

(4aR)-(10bR)-4,10b-dimethyl-8-allyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one



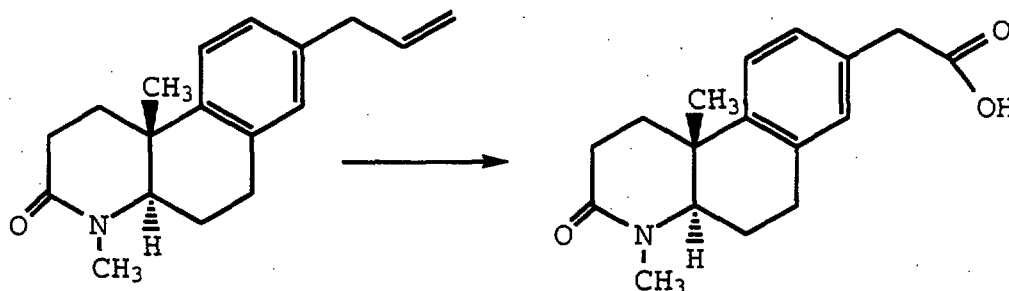
A 9 g portion of (4aR)-(10bR)-4,10b-dimethyl-8-bromo-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one was combined with 11.1 g of tri-n-butyl-2-propenylstannane and 1.69 g of tetrakis(triphenylphosphene) palladium in 40 mL of acetonitrile in a sealable tube. Argon was bubbled through the mixture, the cap replaced, and the reaction heated at 90° for 18 h. Upon cooling, the mixture was filtered and the filtrate was concentrated under vacuum. The residue was triturated with diethyl ether to obtain 4.23 g of crystalline product, and a second crop of 1.31 g of product was also obtained. mp 144.-146°; FDMS 255 M+; Calcd for C₁₇H₂₁N₁O₂:

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	79.96	79.69
H	8.29	8.22
N	5.49	5.73

-161-

Preparation 13

(4aR)-(10bR)-4,10b-dimethyl-8-carboxymethyl-1,2,3,4,4a,-
5,6,10b-octahydrobenzo[f]quinolin-3-one



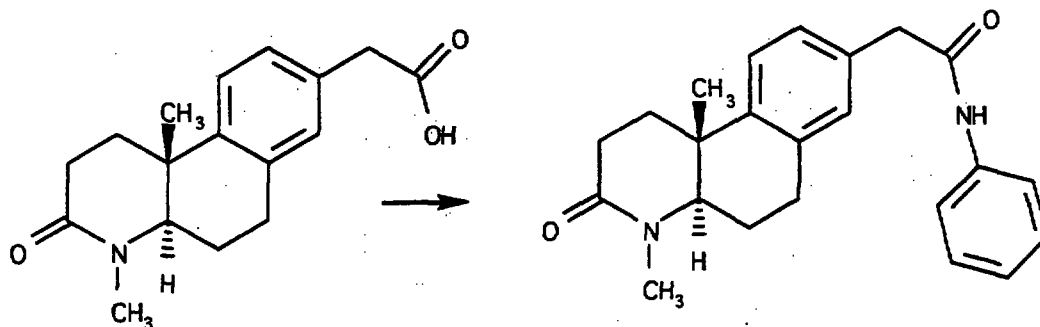
A 158 mg portion of the product of Preparation 12 was dissolved in 4 mL of acetonitrile, and a solution of 378 mg of sodium periodate in 4 mL of water was added, followed by 18 mg of ruthenium trichloride. The mixture was stirred at ambient temperature for 18 h, and diluted with dichloromethane. The organic layer was removed, and the aqueous layer extracted with dichloromethane. The organic layers were combined, washed with water, dried, filtered and evaporated to a brown foam. The residue was dissolved in dichloromethane and extracted with saturated aqueous sodium bicarbonate to which a few milliliters of 10% aqueous sodium carbonate had been added. The basic aqueous extract was made acid with hydrochloric acid, and extracted with dichloromethane. The organic layer was then dried and evaporated under vacuum to obtain 51 mg of a solid, which was recrystallized from ethyl acetate/hexane to obtain the desired product in purified form. mp: 200-202°;

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	71.06	71.22
H	7.37	7.36
N	4.87	5.00

-162-

Example 277

(4aR)-(10bR)-4,10b-dimethyl-8-phenylaminocarbonylmethyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one



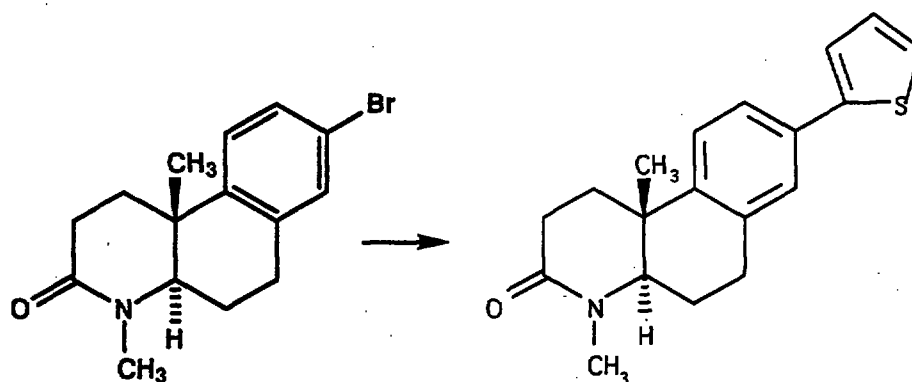
A 200 mg portion of the product of Preparation 13 was dissolved in 5 mL of dimethylformamide, and 135 mg of 1,1'-carbonyldiimidazole was added. The reaction mixture was blanketed with nitrogen, and was stirred at ambient temperature for 4 h, at which time 0.1 mL of aniline was added. The solution was then stirred briefly, and concentrated under vacuum. The residue was dissolved in dichloromethane and washed with 1N hydrochloric acid, 10% sodium sulfate, water and brine. The solution was then dried, filtered and evaporated to obtain 220 mg of crude product. It was purified by chromatography on a silica gel column, eluting with 3% isopropanol in chloroform. The product-containing fractions were combined, evaporated and recrystallized from ethyl acetate to obtain the desired product in pure form. mp 192-195°; FDMS 362 M+;

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	76.21	75.98
H	7.23	7.03
N	7.73	7.81

-163-

Example 278

(4aR)-(10bR)-4,10b-dimethyl-8-(2-thiophenyl)-1,2,3,4,4a,-
5,6,10b-octahydrobenzo[f]quinolin-3-one



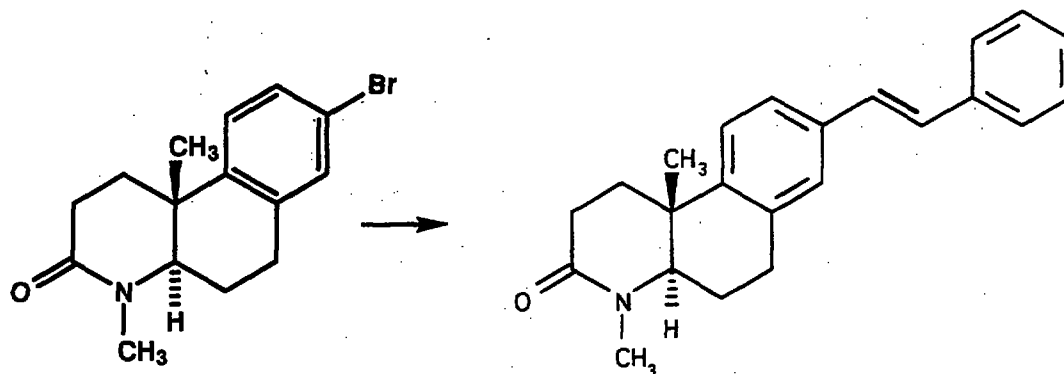
Five hundred mg of (4aR)-(10bR)-4,10b-dimethyl-8-bromo-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one was combined with 730 mg of 2-(tri-n-butylstannyl)thiophene and 100 mg of bis(triphenylphosphine) palladium chloride in 6 mL of acetonitrile in a screw-capped sealable tube. The mixture was flushed with argon for 5 minutes, capped and heated at 90° for 20 h. Upon cooling, the mixture was filtered and the filtrate was concentrated in vacuum. The residue was purified by chromatography on a silica gel column, eluting with ethyl acetate, and the isolated product was recrystallized from ethyl acetate/hexane/chloroform to obtain 167 mg of the desired product. mp: 193-195°; FDMS 311.

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	73.27	73.32
H	6.80	6.94
N	4.50	4.55

-164-

Example 279

(4aR)-(10bR)-4,10b-dimethyl-8-(2-phenylethenyl)-
1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one



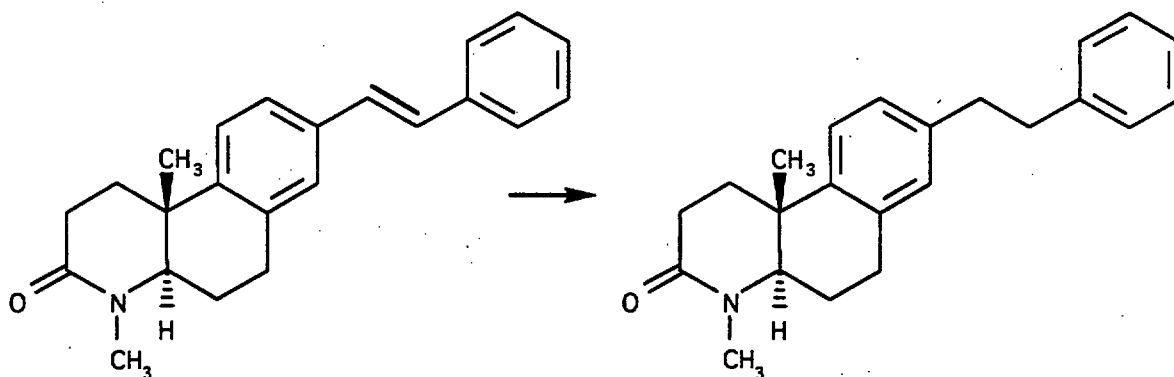
Five hundred mg of (4aR)-(10bR)-4,10b-dimethyl-8-bromo-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one, 4 mg of palladium acetate, 20 mg of tri-o-tolylphosphine, 0.34 mL of triethylamine and 5 mL of dimethylformamide were placed in a screw capped sealable tube with a stir bar. The mixture was warmed to 60° and then 200 mg of styrene was added and the vessel was flushed with argon. The vessel was then capped and heated at 120° for 24 h. The reaction mixture was cooled, diluted with ethyl acetate and filtered and the filtrate was concentrated under vacuum. The residue was dissolved in chloroform and washed twice with water. The organic layer was dried, filtered and evaporated under vacuum to obtain 400 mg of residue, which was recrystallized from ethyl acetate to obtain the desired product. m.p. 173-175°. FDMS m/e = 331.

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	83.34	83.12
H	7.60	7.64
N	4.23	4.14

-165-

Example 280

(4aR)-(10bR)-4,10b-dimethyl-8-(2-phenylethyl)-
1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one



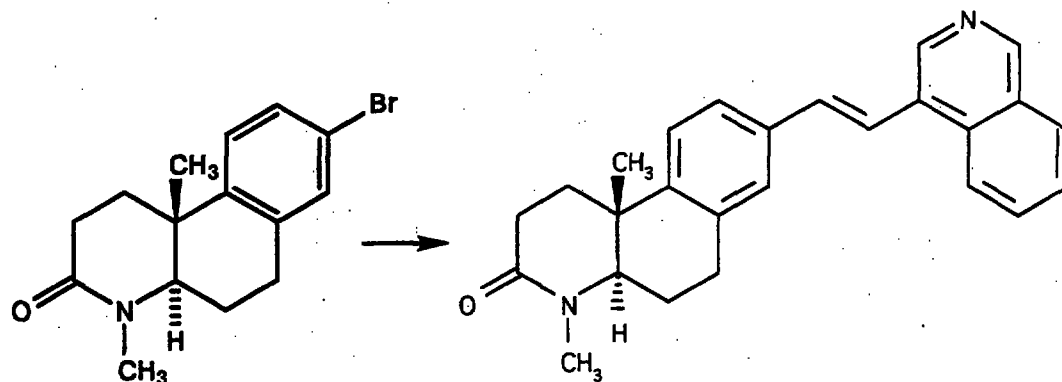
A 150 mg portion of the product of Example 279 was hydrogenated on a Parr apparatus at 40 p.s.i. in 50 mL of ethanol containing 5 mL of dimethylformamide and 20 mg of 10% palladium/carbon catalyst. When the starting material had been consumed, the mixture was filtered and the filtrate was concentrated under vacuum. The residue was purified by chromatography on silica gel, eluting with 90% ethyl acetate/hexane to obtain a product which was recrystallized from ethyl acetate/hexane to produce the desired product. m.p. 109-111°.

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	82.84	83.02
H	8.16	8.10
N	4.20	4.06

-166-

Example 281

(4aR)-(10bR)-4,10b-dimethyl-8-(2-[4-isoquinolinyl]ethenyl)-
1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one



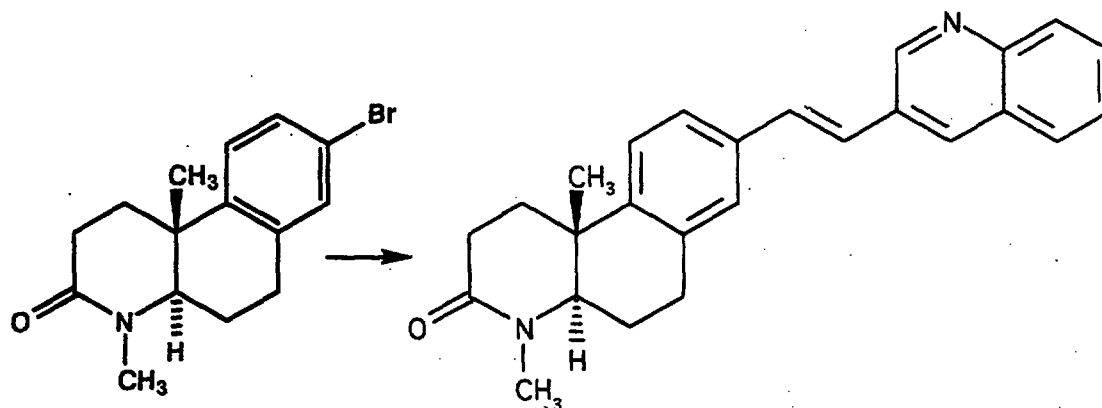
A 508 mg portion of (4aR)-(10bR)-4,10b-dimethyl-8-bromo-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one, 4 mg of palladium acetate, 20 mg of tri-o-tolylphosphine, 0.34 mL of triethylamine and 5 mL of dimethylformamide were combined in a sealable tube with a stir bar, and the mixture was warmed to 50° under argon. An 0.26 g portion of 4-ethenylisoquinoline was added. Then the vessel was blanketed with argon and sealed and the mixture was heated with stirring at 120° for 20 hours. It was then cooled, and concentrated under vacuum and the residue was purified by chromatography on silica gel, eluting with 5% isopropanol in chloroform. An 0.29 g portion of an oil was obtained, which was recrystallized from ethyl acetate/hexane to obtain the desired product in crystalline form. mp 183-185°; FDMS 382 M+.

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	81.64	81.43
H	6.85	6.94
N	7.32	7.22

-167-

Example 282

(4aR) - (10bR) - 4,10b-dimethyl-8-(2-[3-quinolinyl]ethenyl) -
1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one



A 290 mg portion of 3-ethenylquinoline was used in a process otherwise similar to that of Example 281 to obtain the title product. mp 181-183°; FDMS 382.

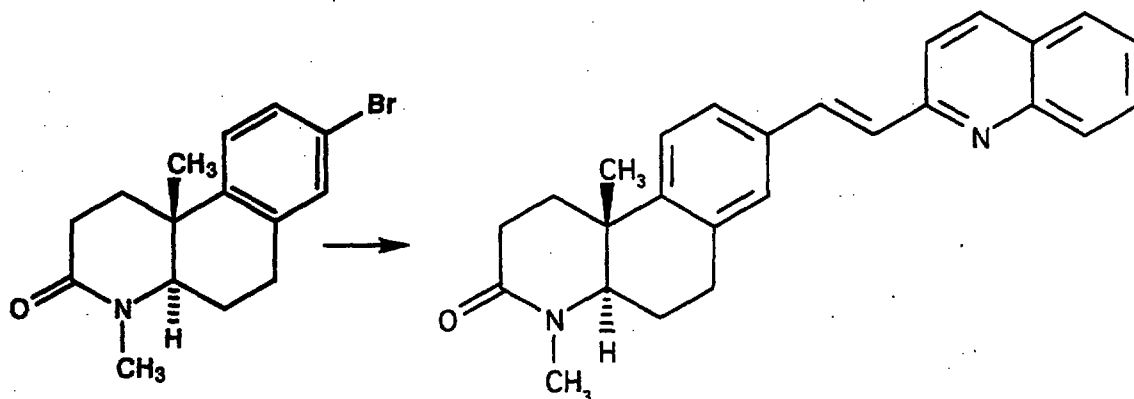
10

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	81.64	81.89
H	6.85	6.71
N	7.32	7.55

-168-

Example 283

(4aR)-(10bR)-4,10b-dimethyl-8-(2-[2-quinolinyl]ethenyl)-
1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one



The process of Example 281 was substantially repeated, using 0.34 g of 2-ethenylquinoline as the starting material to obtain the title product. mp 233-236°; FDMS 382.

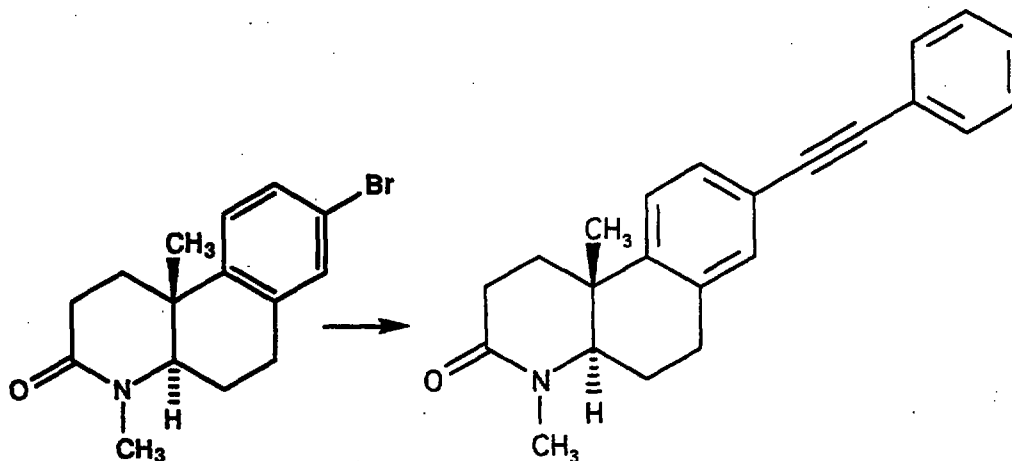
10

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	81.64	81.42
H	6.85	7.00
N	7.32	7.57

-169-

Example 284

(4aR)-(10bR)-4,10b-dimethyl-8-(2-phenylethynyl)-
1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one



5

A 1 g portion of (4aR)-(10bR)-4,10b-dimethyl-8-bromo-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one was reacted with 0.4 mL of phenylacetylene in a process substantially similar to that of Example 281 to obtain the desired title product in pure form. mp 205-208°; FDMS 329.

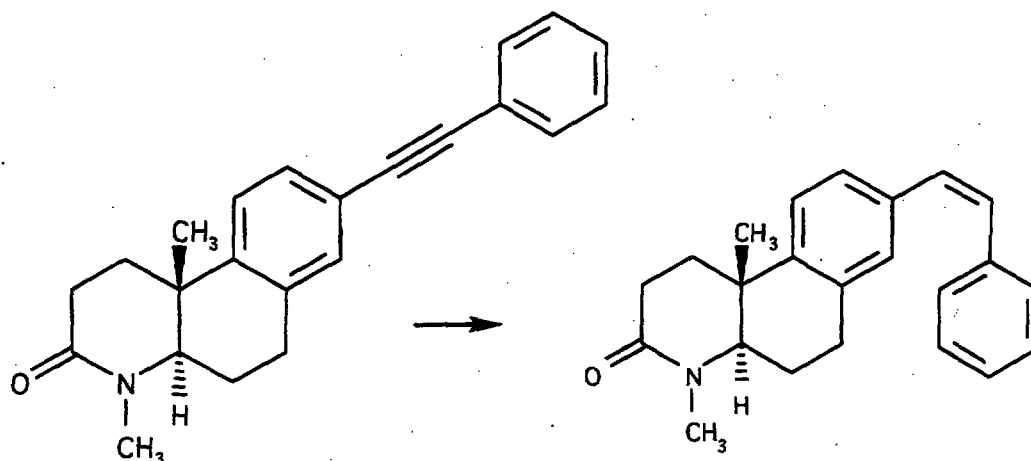
10

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	83.85	84.07
H	7.04	7.05
N	4.25	4.27

-170-

Example 285

(4aR)-(10bR)-4,10b-dimethyl-8-(2-phenylethenyl)-
1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one



A 300 mg portion of the product of Example 284 was hydrogenated over palladium/barium sulfate catalyst in 25 mL of pyridine at 15 psi hydrogen pressure at ambient temperature for 1 h. The mixture was then filtered and concentrated under vacuum, and the residue was purified by chromatography on silica gel, eluting with 75 % ethyl acetate/hexane. The product thereby obtained was further purified on a Chromatatron, eluting with 5% isopropanol in chloroform to obtain the desired product in the form of a yellow oil. High resolution mass spectroscopy showed the correct molecular ion of 332.201440.

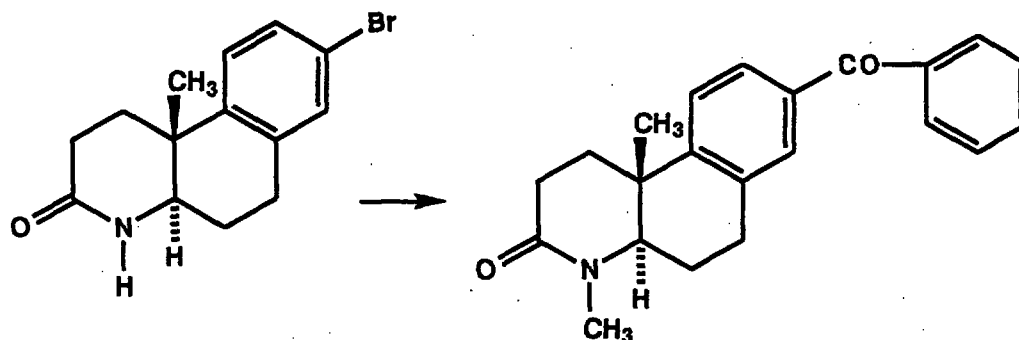
10

15

-171-

Example 286

(4aR)-(10bR)-8-benzoyl-4,10b-dimethyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one



5

A. To a solution of (4aR)-(10bR)-10b-methyl-8-bromo-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one in 25 mL of THF at -78° under an atmosphere of nitrogen was added 330 μ L of a 1.4 M solution of methyllithium in diethyl ether (0.46 mmol). The reaction mixture turned bright yellow, and after 10 min, 470 μ L of a 1.7 M solution of t-butyllithium in pentane (0.80 mmol) was added. The reaction mixture was stirred for 10 min before the addition of benzaldehyde (80 μ L, 0.79 mmol) as a single aliquot. The reaction was warmed to room temperature and stirred for 30 min before partitioning between diethyl ether and 1N hydrochloric acid. The ether layer was dried over sodium sulfate, filtered and evaporated under reduced pressure to afford 0.1818 g crude product. The material was purified on a Chromatotron (2mm plate, dry loaded with chloroform, eluted with 5% methanol/chloroform) to give 106 mg of desired product. A portion of this material was triturated with diethyl ether to yield a white solid. mp 116-118; FDMS: m/e = 321. α [D]₅₈₉ = 100.39

25

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	78.47	78.45
H	7.21	7.26
N	4.36	4.21

-172-

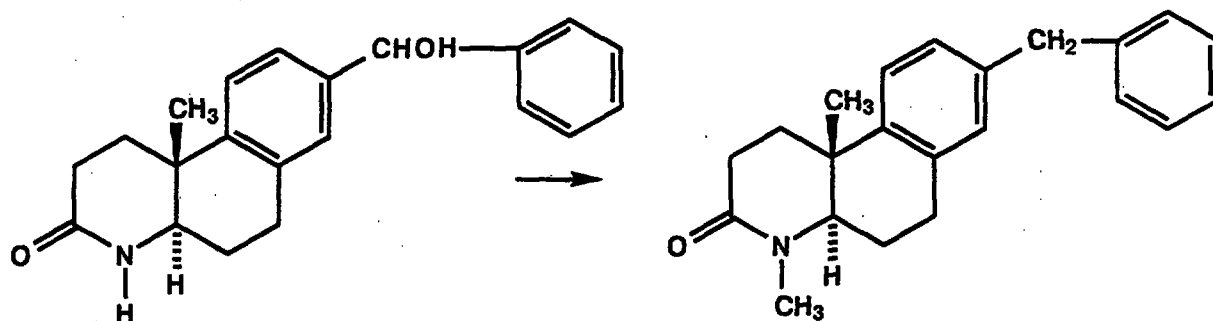
B. To a solution of the alcohol prepared as described above (395 mg, 1.2 mmol) in 40 mL of acetone at 0° was added dropwise 1 mL (2.54 mmol) of a 2.54 M solution of Jones Reagent. The reaction mixture was stirred at 0° for 15 min. before the addition of 2 mL of isopropanol to quench the excess reagent. The mixture was partitioned between ethyl acetate and brine. The aqueous layer was extracted with chloroform. The combined organic layers were washed with water (100 mL), dried (sodium sulfate), filtered and evaporated under reduced pressure to afford crude product. This material was purified on a chromatotron (2mm plate, dry loaded with chloroform, eluted with 5% methanol/chloroform) to give 166 mg of desired product (42% yield). This material was methylated using the standard potassium t-butoxide/methyl iodide in t-butanol method to afford 170 mg crude product. This material was purified on a chromatotron (2mm plate, eluted with ethyl acetate) to give 113 mg of desired white solid (65% yield); mp 173-175°; FDMS: m/e=334; α [D]₅₈₉ = 80.39 (c=0.5 in chloroform).

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	79.25	79.49
H	6.95	7.07
N	4.20	4.30

-173-

Example 287

(4aR)-(10bR)-8-benzyl-4,10b-dimethyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one



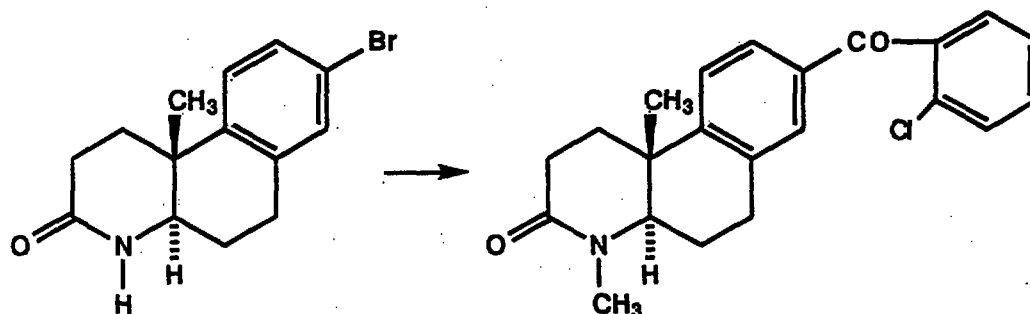
A solution of the hydroxymethyl compound prepared in part A of the example above, in 80 mL of ethanol with 23.5 mg of 10% Pd/C catalyst, was shaken under an atmosphere of 40 psi of hydrogen for 24 h. Reaction was not complete and an additional 29 mg of 10% Pd/C was added. After an additional 48 h, the mixture was filtered through celite and concentrated under reduced pressure to yield 141 mg of crude product which was methylated using the standard potassium t-butoxide/methyl iodide in t-butanol method to afford 120 mg of desired product. This material was purified on a Chromatotron (2mm plate, eluted with 1% isopropanol in ethyl acetate) to give 87 mg of white solid. This material was further purified by recrystallization from a 10:1 mixture of hexane:ethyl acetate to afford 30 mg of product. mp 99-101°C; FDMS: m/e = 319 α [D]₅₈₉ = 77.08

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	82.72	82.68
H	7.89	7.87
N	4.38	4.33

-174-

Example 288

(4aR)-(10bR)-8-(2-chlorobenzoyl)-4,10b-dimethyl-1,2,3,4,4a,-
5,6,10b-octahydrobenzo[f]quinolin-3-one



To a solution of (4aR)-(10bR)-10b-methyl-8-bromo-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one in 50 mL of THF at -78° under an atmosphere of nitrogen was added 2.25 mL of a 1.4 M solution of methyllithium in diethyl ether (3.15 mmol). After 10 min, 3.34 mL of a 1.7 M solution of t-butyllithium in pentane (5.68 mmol) was added. The reaction mixture was stirred for 10 min before the addition of 2-chlorobenzaldehyde (870 mL, 7.72 mmol) as a single aliquot. The reaction was warmed to room temperature and stirred for 2 h before partitioning between ethyl acetate and 1N hydrochloric acid. The organic layer was dried, filtered and evaporated under reduced pressure to afford 1.7 g of crude product. The material was purified on a Chromatotron (4 mm plate, dry loaded with chloroform, eluted with 5% methanol/chloroform) to give 435.5 mg of desired product (47% yield): mp $105-115^{\circ}$; FDMS: $m/e = 355, 357$.

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	70.88	70.87
H	6.23	6.25
N	3.94	3.92

To a solution of the alcohol prepared as described above (211.7 mg, 0.6 mmol) in 25 mL of acetone at 0° was added dropwise 0.5 mL (1.27 mmol) of a 2.54 M solution of Jones Reagent. The reaction mixture was stirred at 0° for 30

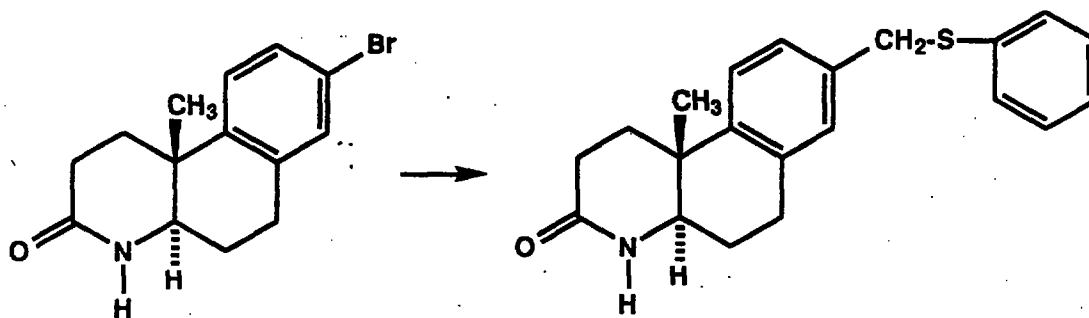
-175-

min before the addition of 2 mL of isopropanol to quench the excess reagent. The mixture was partitioned between chloroform and brine. The organic layer was dried, filtered and evaporated under reduced pressure to afford crude product. This material was purified on a Chromatotron (2mm plate, dry loaded with chloroform, eluted with 5% methanol/chloroform to give 81.0 mg of desired product.

This material was methylated using the standard potassium t-butoxide/methyl iodide in t-butanol method to afford 160 mg crude product. This material was purified on a Chromatotron (2mm plate, eluted with 2% methanol/ethyl acetate) followed by a second Chromatotron run (2mm plate, eluted with 5% methanol/chloroform) to give 61 mg of white foam after concentration from diethyl ether (65%) yield: mp 65-70°

Example 289

(4aR)-(10bR)-8-phenylthiomethyl-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one



A. To a solution of (4aR)-(10bR)-10b-methyl-8-bromo-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one in 60 mL of THF at -78° under an atmosphere of nitrogen was added 2.9 mL of a 1.4 M solution of methyllithium in diethyl ether (4.1 mmol). After 20 min, 4.8 mL of a 1.7 M solution of t-butyllithium in pentane (8.2 mmol) was added. The reaction mixture was stirred for 45 min before the addition of dimethylformamide (0.63 mL, 8.1 mmol). The reaction was warmed to room temperature before partitioning between ethyl acetate and 1 N hydrochloric acid. The organic layer was

-176-

washed with additional 1 N hydrochloric acid, saturated sodium bicarbonate, brine and then dried (sodium sulfate), filtered and evaporated under reduced pressure to afford 665 mg desired product (80% crude yield). This material was taken on without further purification.

B. To a solution of the aldehyde prepared above (665 mg, 2.73 mmol) in 50 mL of absolute ethanol was added 2 equivalents of sodium borohydride (207 mg, 5.4 mmol). The reaction mixture was stirred at room temperature for 18 h before the addition of 50 mL of 1N hydrochloric acid. After stirring for 1.5 h, ethyl acetate was added and the material concentrated to remove ethanol. The residual aqueous layer was extracted with ethyl acetate and the organic layer was washed with brine, dried (sodium sulfate), and concentrated under reduced pressure to afford 436 mg of crude product. This material was purified on a Chromatotron (eluted with 3% methanol/chloroform) to give 310 mg of desired white solid (46 % yield): mp 176-177 °; FDMS: m/e = 245; α [D]₅₈₉ = 120.08 (c = 0.5 in methanol).

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	73.44	73.73
H	7.81	7.96
N	5.71	5.82

C. To a solution of the alcohol prepared as described above (462.3 mg, 1.88 mmol) in 40 mL of anhydrous acetonitrile was added 0.8 mL of neat trimethylsilyl iodide (5.6 mmol). After 30 minutes, the reaction mixture was concentrated and the residue partitioned between ethyl acetate and saturated thiosulfate. The organic layer was washed with brine, dried (sodium sulfate) and concentrated under reduced pressure to yield 664 mg of crude product. This material was purified on a Chromatotron (4 mm plate, eluted with 3% methanol/chloroform) to give 597 mg of desired solid (89 % yield): mp 215-217 °; FDMS: m/e = 355, 228 (m -

-177-

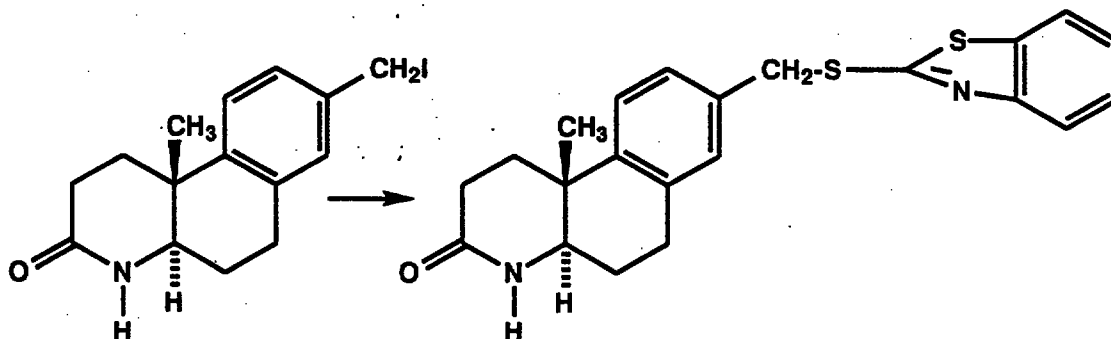
1); α [D]589 = 99.12 (c = 0.5 in methanol). Material was taken on without further purification.

D. To a solution of the iodide prepared as described above (249.4 mg, 0.70 mmol) in 25 mL of THF was added a solution of 145 μ L of phenylmercaptan (1.4 mmol) and 210 μ L of DBU (???) (1.4 mmol) in 5 mL of THF. After stirring at room temperature for 2 days, the reaction mixture was partitioned between 1N hydrochloric acid and ethyl acetate. The organic layer was washed sequentially with 1N hydrochloric acid, 1N sodium hydroxide, and brine before being dried (sodium sulfate) and concentrated under reduced pressure to yield 293 mg of crude product. This material was purified on a Chromatotron (4 mm plate, eluted with 3% methanol/chloroform) followed by recrystallization from ethyl acetate to give 166 mg of desired white solid (70% yield): mp 187-189°; FDMS: m/e = 337; α [D]589 = 82.27 (c = 0.5 in methanol).

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	74.74	74.97
H	6.87	7.11
N	4.15	4.29

Example 290

(4aR)-(10bR)-8-(2-benzothiazolyl)thiomethyl-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one



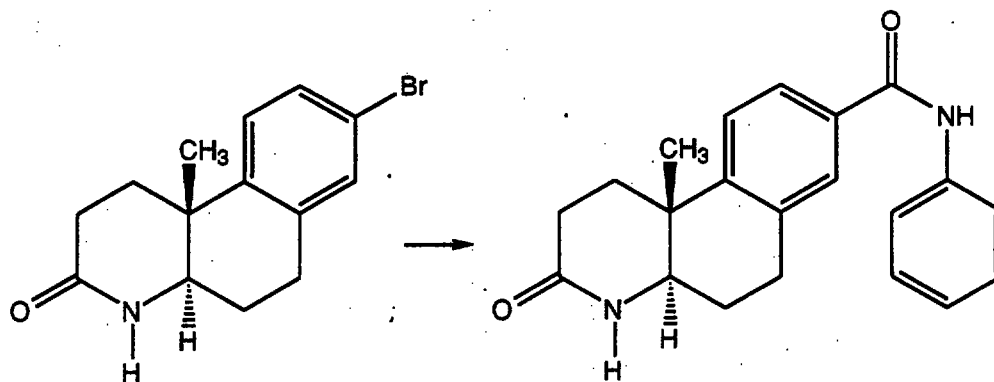
-178-

To a solution of the iodomethyl compound prepared in Step C of Example 289 in 25 mL of THF was added a solution of 252 mg of 2-mercaptobenzothiazole (1.5 mmol) and 226 mL of diazabicycloundecane (DBU) (1.5 mmol) in 5 mL of THF. After stirring at room temperature for 2 days, the reaction mixture was partitioned between 1N hydrochloric acid and ethyl acetate. The organic layer was washed sequentially with 1N hydrochloric acid, 1N sodium hydroxide, and brine before being dried (sodium sulfate) and concentrated under reduced pressure to yield 382 mg of crude product. This material was purified on a Chromatotron (4 mm plate, eluted with 3% methanol/chloroform) followed by recrystallization from ethyl acetate to give 193 mg of desired white solid. mp 201-202°. FDMS: m/e = 394. $\alpha[D]_{589} = 75.70$

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	66.97	67.23
H	5.62	5.82
N	7.10	7.22

Example 291

(+)-(4aR)-(10bR)-8-phenylcarboxamido-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinoline-3-one



In a flame-dried 3-neck round bottom flask equipped with magnetic stirrer and nitrogen inlet was dissolved (+)-(4aR)-(10bR)-8-bromo-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinoline-3-one (500 mg, 1.7 mmol), in anhydrous THF

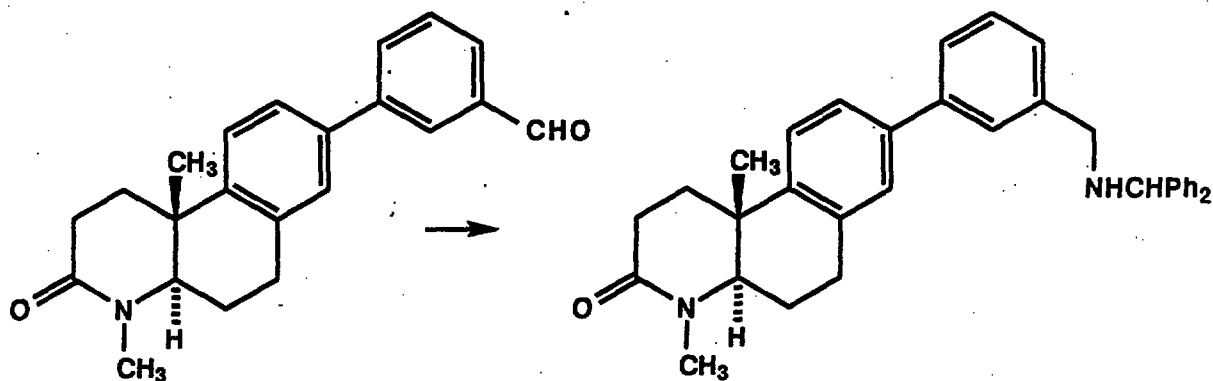
-179-

(50 mL). The solution was cooled to -78° and treated with ethereal methyllithium (1.3 mL, 1.4M, 1.8 mmol) added dropwise over 2 min. After further stirring for 15 min., a solution of *t*-butyllithium (2.1 mL, 1.7 M in pentane, 3.6 mmol) was added dropwise. Following complete addition, the suspension was treated with phenylisocyanate (418 μ L, 3.6 mmol) in a single portion. The mixture was warmed to ambient temperature and acidified with 1 N hydrochloric acid solution. The mixture was extracted with ethyl acetate and the organic phase washed with brine and dried over anhydrous magnesium sulfate. Removal of solvent and chromatography of the crude product on silica gel (0.5% aqueous ammonium hydroxide/ethyl acetate as eluent) and crystallization from ethyl acetate afforded product as tan solid. m/e 334, OR (c=1.0, MeOH) @589 nM, $+100.1^{\circ}$, @365 nM, $+308.4^{\circ}$.

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	75.42	75.22
H	6.63	6.76
N	8.38	8.25

Example 292

(+)-(4aR)-(10bR)-4-methyl-8-(3-diphenylmethylamino-methylphenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydro-benzo[f]quinolin-3-one



-180-

To a suspension of (+)-(4aR)-(10bR)-4-methyl-8-(3-formylphenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one (30 mg, 0.09 mmol), in 0.75 mL of methanol was added benzhydrl amine (0.09 mmol), sodium cyanoborohydride (0.09 mmol) and 2 drops of glacial acetic acid (mixture became homogeneous; pH = 4). The reaction was stirred at room temperature for 60 h. The mixture was diluted with ethyl acetate, saturated aqueous sodium bicarbonate solution was added, and the resulting mixture was extracted repeatedly with ethyl acetate. The combined organic extracts were dried over sodium sulfate, concentrated, and purified by silica gel chromatography (ethyl acetate eluent), followed by trituration of the resulting oil with ether / hexanes, to give 36 mg (80%) of the title compound as a white solid. mp 55-57°. FDMS: m/e = 500. α [D]₅₈₉ = +48.40 (c = 0.64, methanol).

<u>analysis:</u>	<u>calculated</u>	<u>found</u>
C	83.96	83.42
H	7.25	6.92
N	5.60	5.62

-181-

Biological Testing

Representative compounds of the present invention have been tested in standardized biological test methods in order to determine their activity as inhibitors of both Type I and Type II 5AR. The following test methods are adapted to routine use and may be followed conveniently by the skilled reader.

Methodology of Human Type I and Type II Steroid 5 α -Reductase Assays

Preparation of Type I 5 α -Reductase from Human Scalp:

Scalp punch biopsies from graft recipient sites were obtained from human hair transplant procedures immediately after surgery and were frozen on dry ice and stored at -80°C. Approximately 60-75 punches from one surgical procedure were used to generate an enzyme preparation. The subcutaneous tissue was cut away and discarded. The skin was frozen with liquid nitrogen and pulverized to powder. The powder was homogenized in 30 mL of ice-cold buffer (20 mM Tris-HCl, pH 7.5) using a Brinkmann Polytron (Westbury, NY) with a PTA 10-S probe and a setting of 7. The homogenization procedure consisted of four 15 second pulses. Connective tissue was cleared from the probe with forceps between pulses. The homogenate was then filtered through cheese cloth and the filtrate centrifuged at 100,000 x g for one hour in a Beckman L8-60M ultracentrifuge. The pellet was resuspended by homogenization with a Dounce homogenizer using the same buffer solution. An aliquot was taken for protein determination by the Lowry method, Lowry, et al., Protein Measurement with the Folin Phenol Reagent, J. Biol. Chem., 193, 265-75 (1951). Aliquots of the enzyme preparation were stored at -80° until use.

-182-

Preparation of Type II 5 α -Reductase from Human

Prostate: The same procedure as above was used for preparations using tissue from prostate surgery with the following changes: The buffer used was 20 mM sodium phosphate, pH 6.5; and the pellet was resuspended in the sodium phosphate buffer containing 20% glycerol.

Human 5 α -Reductase Assay: This enzyme assay is based on the conversion of [3 H]-testosterone to [3 H]-5 α -dihydrotestosterone (DHT) and other 5 α -reduced metabolites. While about 90% of the 5 α -reduced metabolites formed in these assays was DHT, androstanedione was formed at about 10%. Essentially no androsterone was detected. In a total volume of 1.0 mL, the Type I assay contained 2.6 μ Ci [3 H]-testosterone (50 nM), 500 μ M of reduced nicotine adenine dinucleotide phosphate, 100 mM Tris-HCl, pH 7.5, (in Type II assays, 40 mM sodium acetate at pH 5.5 is used instead of Tris-HCl) and test compounds as indicated. Test compounds were added in 20 μ L of dimethylsulfoxide (20 μ L of dimethylsulfoxide was added to blanks and controls). The reaction was initiated by the addition of 0.5 mg of Type I or Type II 5 α -reductase. The reaction mixture was incubated at 25° for 30 min in Type II assays, or 180 min in Type I assays, and terminated by the addition of 1 mL ice-cold stopping solution. The stopping solution contained 40 μ M each of non-radioactive testosterone, DHT, androstenedione, androstanedione, androsterone, androstan-3 β ,17 β -diol, and androstan-3 α ,17 β -diol.

The samples were prepared for high performance liquid chromatography by solid phase extraction. Disposable solid matrix extraction columns (C-18 reversed phase, 6 mL, 500 mg; Bond ElutTM from Analytichem International; Harbor City, CA) were conditioned by washing with 5 mL of methanol followed by 5 mL of deionized water. The reaction mixtures were then applied to the columns. The columns were subsequently washed

-183-

with 5 mL of acetone:water (1:4), followed by 0.3 mL of methanol. The samples were then eluted with 3 mL of methanol and collected in 20 mL scintillation vials. Three mL of water was then added to each scintillation vial. The solutions were then transferred to tubes and centrifuged for 30 min at 1000 x g to remove any particulate material before chromatography.

The [³H]-testosterone substrate and its metabolites were separated by chromatography using a C-18 reversed phase column (Beckman Ultrasphere 5 μ m spherical 80A pore, part no. 235329, 4.6 mm i.d. x 25 mm length) with an isocratic mobile phase (46 water: 46 methanol: 8 tetrahydrofuran by volume). The column temperature was maintained at 35° and the flow rate was 1.5 mL/min. A 400 μ L aliquot was injected onto the column and radioactivity was determined using a Beckman 171 in-line flow radioisotope detector in conjunction with Rainin Dynamax™ software and a Macintosh computer. The flow rate of the Atomflow™ scintillation fluid was 4.5 mL / min.

While in most instances the compounds listed below have been tested at various concentrations, only the test results at 0.3 μ M concentration are shown here, in order to reduce the bulk of the following table. The data are reported as percent inhibition of Type I and Type II AR produced by each compound at that concentration, compared to control reaction mixtures.

-184-

Table I

Compound of Example No.	Type I	Type II
5	44	0
6	11	23
7	49	42
8	22	59
9	3	31
10	22	40
11	87	40
12	16	22
13	11	22
14	37	25
15	23	39
16	14	28
17	29	19
18	7	15
19	59	56
20	22	48
21	27	42
22	-	19
23	59	31
24	88	28
25	83	31
26	86	46, -2, 33
27	92	58, 1, 50
28	65	36
29	78	26
30	19	21
31	84	22
32	71	18
33	55	40
34	13	5
35	17	27
36	41	52
37	72	58
38	84	56, 38
39	81	34
40	90	35
41	88	18
42	-	32
43	68	18
44	-	27
45	11	45
46	3	31
47	-	16
48	-	12
49	96	4
50	95, 94	32

-185-

51	91	14
52	68	10
53	100, 66	41
54	-	22
55	68	11
56	92	3
57	-	20
58	65	24
59	-	31
60	-	42
61	53	36
62	45	42
63	-	19
64	81	22
65	79	42
66	67	33
67	22	54
68	31	37
69	84	6
70	-	36
71	80	47
72	16	26
73	87	16
74	16	26
75	63	40
76	83	46
77	88	46, 33
78	-	3
79	-	34
80	76	29
81	92	25
82	85	31
83	-	12
84	88	23
85	-	12
86	66	51
87	83	28
88	96	43
89	-	15
90	-	22
91	87	32
92	-	10
93	-	9
94	-	1
95	95	35
96	89	52
97	-	-
98	76	61, 44
99	88	65, 29
100	96	51, 34
101	75	43
102	92	61
103	81	58
104	89	41
105	92	33

-186-

106	73	39
107	80	83
108	100	29
109	97	25
110	97	73
111	44	38
112	64	90, 92
113	70	51
114	55	47
115	31	20
116	-	24
117	46	49
118	25	43
119	84	59, 24
120	93	37
121	-	41
122	-	36
123	10	27
124	23	32
125	64	36
126	85	43
127	-	40
128	82	40
129	91	36
130	83	29
131	57	44
132	87	24
133	77	34
134	97	46
135	92	31
136	100	32
137	90	37
138	88	26
139	30	59
140	-	20
141	-	19
142	22	40
143	63	18
144	90	40
145	85	41
146	13	32
147	35	83, 83
148	2	12
149	58	33
150	67	69
151	31	28
152	47	10
153	49	71
154	56	25
155	58	60
156	71	70
157	88	79
158	78	63
159	87, 87	87, 83
160	61	38

-187-

161	71	51
162	79	87
163	80	86
164	85, 87	86, 85, 79
165	61	74
166	50	49
167	62	31
168	85	41
169	75	61
170		
171	43	63
172	55	36
173	65	78, 77
174	82	80
175	58	40
176	25	15
177	58	15
178		
179	61	28
180	59	30
181	63	31
182	63	100
183	89	88, 87
184	73	81
185	88	90
186	90	79
187	93	94
188	88	78
189	84	19
190	76	26
191	65	19, 28
192	80	33
193	-	-
194	-	-
195	90	71
196	11	45
197	-	37
198	-	7
199	-	30
200	59	72, 64
201	69	60, 57
202	41	48
203	8	34
204	34	39
205	100	37
206	97, 100	32
207	45	16
208	77	10
209	24	11
210	81	38
211	70	29
212	73	31
213	64	28
214	26	29
215	84	42

-188-

216	78	24
217	93	33
218	84	35
219	91	30
220	67	26
221	95	26
222	86	27
223	36	24
224	71	20
225	47	32
226	16	8
227	97	25
228	77	32
229	97	11
230	86	29
231	80	21
232	94	27
233	95	38
234	83	30
235	28	12
236	84	67
237	33	13
238	72	29
239	42	27
240	55	17
241	65	33
242	5	24
243	88	54
244	51	32
245	54	44
246	92	45
247	60	32
248	54	22
249	69	24
250	83	1
251	69	36
252	89	54
253	5	32
254	37	28
255	71	37
256	38	18
257	36	58
258	27	16
259	31	14
260	84	40
261	86	49
262	91	41
263	56	47
264	90	45
265	78	40
266	57	44
267	34	51
268	-	18
269	8	17
270	18	13

-189-

271	-	36
272	86	11
273	-	27
274	34	32
275	75	44
276	92	33
277	42	40
278	-	28
279	85	60
280	97, 100	33
281	75	44
282	75	37
283	87	37
284	86	63
285	93	36
286	53	38
287	82	37
288	19	12
289	23	24
290	25	8
291	-	19
292	86	11

-190-

The Table above clearly shows that the compounds of the present invention are useful for inhibiting the conversion of testosterone to 5α -dihydrotestosterone by 5AR, and, more particularly, that many of the compounds are quite effective in inhibiting that action of both Type I and Type II 5AR. Accordingly, an important embodiment of the present invention is a method for inhibiting 5α -reductase which comprises the administration of a compound of formula I to a patient in need of such treatment. Further, the invention provides a method for treating or preventing conditions consequent upon an excess of 5α -reductase or an excess of 5α -reductase activity, comprising the administration of a compound of formula I to such patient.

Still further, the invention provides for the treatment or prevention of benign prostatic hyperplasia, male pattern baldness, acne vulgaris, seborrhea, androgenic alopecia, hirsutism or prostate cancer, which methods are carried out by the administration of a compound of formula I to a patient suffering from such condition, or to a patient who is predisposed toward such condition by an excess of 5α -reductase or excessive 5α -reductase activity.

As has been noted, Type I 5AR is found particularly in the scalp, and is particularly involved in the pathology of conditions such as alopecia, seborrhea, prostate cancer, acne vulgaris, male pattern baldness and hirsutism. Type II 5AR, on the other hand, is particularly found in the prostate and is a strongly contributing factor to prostatic hyperplasia and perhaps prostate cancer. Accordingly, it is clear that, when a compound is being sought for the treatment of a condition in which Type I 5AR is particularly concerned, one would choose one of the compounds which is particularly active in the inhibition of Type I AR. When the condition to be treated is one which particularly relates to the prostate, then the compound of choice would probably be one which is particularly active against Type II 5AR. It is clear from the above data, however, that the invention provides numerous compounds which are particularly highly active against both

-191-

isozymes, and it is accordingly those doubly highly active compounds which are most preferred and are most preferred for use in the present methods of therapy.

5 The administration of compounds of formula I in order to practice the present methods of therapy is carried out by administering an effective amount of the chosen compound to the patient in need of such treatment or prophylaxis. The effective amount of an individual compound is determined, in the final analysis, by the physician in
10 charge of the case, but depends on factors such as the exact disease to be treated, the severity of the disease and other diseases or conditions from which the patient suffers, the chosen route of administration, other drugs and treatments which the patient may concomitantly require, and no doubt
15 other factors in the physician's judgment. It will be observed that the compounds are active at very low concentrations, and hence at low dosage levels, thereby allowing effective treatment or prophylaxis with slight probability of side effects or cross-reactions with other
20 treatments or drugs. Accordingly, a typical daily dose of a compound of formula I is in the range of from about 0.01 mg/kg to about 1.0 mg/kg of body weight per day. More preferred ranges of daily dosage are from about 0.05 mg/kg to about 0.5 mg/kg, and, more particularly, from about 0.07
25 mg/kg to about 0.3 mg/kg per day. The compounds may be administered in a single daily dose, or the daily dose may be administered in portions at intervals through the day, as is preferred in the judgment of the physician.

30 The compounds can be administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intravenous, intramuscular, intranasal, and topical for male pattern baldness, acne vulgaris, and hirsutism. The compounds of the present invention are preferably formulated
35 prior to administration. Therefore, another embodiment of the present invention is a pharmaceutical formulation comprising an effective amount of a compound of Formula I or

-192-

a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier, diluent or excipient therefor.

When a compound of Formula I is to be administered for treatment of baldness, acne, seborrhea, alopecia or hirsutism, it is often preferred to formulate it in a topical formulation such as a gel, ointment or the like, and apply it to the affected skin.

The active ingredient in such formulations comprises from 1% to 99% by weight of the formulation. By "pharmaceutically acceptable" it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The present pharmaceutical formulations are prepared by known procedures using well known and readily available ingredients. In making the composition of the present invention, the active ingredient will usually be admixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a capsule, sachet, paper, or other container. When the carrier serves as a diluent, it may be a solid, semi-solid or liquid material which acts as a vehicle, excipient or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions solutions, syrups, aerosols, (as a solid or in a liquid medium), soft and hard gelatin capsules, suppositories, sterile injectable solutions, sterile packaged powders, and the like. Typical formulations designed for topical administration are ointments, creams, gels, and lotions containing, for example, up to 10% by weight of the active compound.

Ointments generally are prepared using either (1) an oleaginous base, i.e., one consisting of fixed oils or hydrocarbons, such as white petrolatum or mineral oil, or (2) an absorbant base, i.e., one consisting of an anhydrous substance or substances which can absorb water, for example,

-193-

anhydrous lanolin. Customarily, following formation of the base whether oleaginous or absorbent, the active ingredient is added in an amount affording the desired concentration.

5 Creams are oil/water emulsions. They consist of an oil phase (internal phase), comprising typically fixed oils, hydrocarbons, and the like, such as waxes, petrolatum, mineral oil, and the like, and an aqueous phase (continuous phase), comprising water and any water-soluble substances, such as added salts. The two phases are stabilized by use of
10 an emulsifying agent, for example, a surface active agent, such as sodium lauryl sulfate; hydrophilic colloids, such as acacia colloidal clays, veegum, and the like. Upon formation of the emulsion, the active ingredient customarily is added in an amount to achieve the desired concentration.

15 Gels comprise a base selected from an oleaginous base, water, or an emulsion-suspension base, such as described above. To the base is added a gelling agent which forms a matrix in the base, increasing its viscosity. Examples of gelling agents are hydroxypropyl cellulose,
20 acrylic polymers, and the like. Customarily, the active ingredient is added to the formulation at the desired concentration at a point preceding addition of the gelling agent.

25 The following formulation examples are illustrative only and are not intended to limit the scope of the invention in any way. "Active ingredient," of course, means a compound according to Formula I or a pharmaceutically acceptable salt thereof.

-194-

Formulation 1

Hard gelatin capsules are prepared using the following ingredients.

5		Quantity (mg/capsule)
	Example 186	250
	Starch, dried	200
	Magnesium stearate	<u>10</u>
10	Total	460 mg

Formulation 2

A tablet is prepared using the ingredients below:

15		Quantity (mg/capsule)
	Example 158	250
	Cellulose, microcrystalline	400
	Silicon dioxide, fumed	10
	Stearate acid	<u>5</u>
20	Total	665 mg

The components are blended and compressed to form tablets each weighing 665 mg.

Formulation 3

An aerosol solution is prepared containing the following components:

25		<u>Weight</u>
30	Example 157	0.25
	Ethanol	25.75
	Propellant 22 (Chlorodifluoromethane)	<u>70.00</u>
	Total	100.00

35 The active compound is mixed with ethanol and the mixture added to a portion of the propellant 22, cooled to

-195-

-30°C and transferred to a filling device. The required amount is then fed to a stainless steel container and diluted with the remainder of the propellant. The valve units are then fitted to the container.

5

Formulation 4

	Example 110	60 mg
	Starch	45 mg
10	Microcrystalline cellulose	35 mg
	Polyvinylpyrrolidone	
	(as 10% solution in water)	4 mg
	Sodium carboxymethyl starch	4.5 mg
	Magnesium stearate	0.5 mg
15	Talc	<u>1 mg</u>
	Total	150 mg

The active ingredient, starch and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The aqueous solution containing polyvinyl - pyrrolidone is mixed with the resultant powder, and the mixture then is passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50°C and passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate and talc, previously passed through a No. 60 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 150 mg.

20

25

Formulation 5

Capsules, each containing 80 mg of active ingredient, are made as follows:

30

	Example 107	80 mg
	Starch	59 mg
35	Microcrystalline cellulose	59 mg
	Magnesium stearate	<u>3 mg</u>
	Total	200 mg

-196-

The active ingredient, cellulose, starch, and magnesium stearate are blended, passed through a No. 45 mesh U.S. sieve, and filled into hard gelatin capsules in 200 mg quantities.

Formulation 6

Suppositories, each containing 225 mg of active ingredient per 5 ml dose, are made as follows:

Example 188	225 mg
Saturated fatty acid glycerides	<u>2,000 mg</u>
Total	2,225 mg

The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of nominal 2 g capacity and allowed to cool.

Formulation 7

Suspensions, each containing 50 mg of active ingredient per 5 ml dose, are made as follows:

Example 164	50 mg
Sodium carboxymethyl cellulose	50 mg
Syrup	1.25 ml
Benzoic acid solution	0.10 ml
Flavor	q.v.
Color	q.v.
Purified water to total	5 ml

The active ingredient is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethyl cellulose and syrup to form a smooth paste. The benzoic acid solution, flavor and color are diluted with a portion of the

-197-

water and added, with stirring. Sufficient water is then added to produce the required volume.

Formulation 8

5 An intravenous formulation may be prepared as follows:

Example 159	100 mg
Isotonic saline	1,000 ml

10

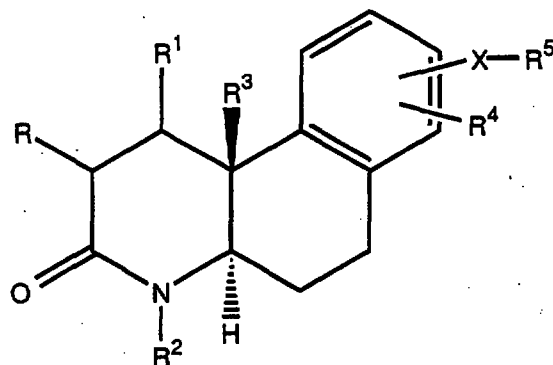
The solution of the above ingredients generally is administered intravenously to a subject at a rate of 1 ml per minute.

15

-198-

Claims

1. A compound of the formula



I

wherein

R and R¹ both represent hydrogen or combine to form a bond;

R² represents hydrogen or C₁-C₃ alkyl;

R³ represents methyl or ethyl;

R⁴ and -X-R⁵ each occupies one of the 7-, 8- and 9-positions;

R⁴ represents hydrogen, halo, methyl or ethyl;

X represents C₁-C₄ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, a bond, -SO-, -SO₂-, -CO-Y-(CH₂)_n-, -Y-CO-(CH₂)_n-, -CO-, -Z-(CH₂)_n-, or -SO₃-; wherein X groups which are not symmetrical may be in either orientation;

Y represents -S-, -O-, or -NH-;

Z represents -O- or -S-;

n represents 0-3;

R⁵ represents phenyl, naphthalenyl, pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, anthracenyl, acenaphthalenyl, thiazolyl, benzimidazolyl, indazolyl, thiophenyl, phenanthrenyl, quinolinyl, fluorenyl, isoquinolinyl, indanyl, benzopyranyl, indolyl, benzisoquinolinyl, benzindolyl, benzothiazolyl, benzothiophenyl, quinoxalinyl, benzoxazolyl, tetrazolyl, naphthothiazolyl, quinazolinyl, thiazolopyridinyl,



-199-

pyridazinoquinazolinyl, benzisothiazolyl, benzodioxolyl, benzodioxinyl, diphenylmethyl or triphenylmethyl;

the above R⁵ groups are unsubstituted or substituted with 1-3 groups chosen from the group consisting of halo, trifluoromethyl, trifluoroethoxy, C₁-C₄ alkyl, trifluoromethoxy, hydroxy, C₁-C₃ alkoxy, nitro, C₁-C₃ alkylthio, C₁-C₆ alkanoyl, phenyl, oxo, phenoxy, phenylthio, C₁-C₃ alkylsulfinyl, C₁-C₃ alkylsulfonyl, cyano, amino, C₁-C₃ alkylamino, diphenylmethylamino, triphenylmethylamino, benzyloxy, benzylthio, (mono-halo, nitro or CF₃)benzyl(oxy or thio), di(C₁-C₃ alkyl, C₃-C₆ cycloalkyl, or C₄-C₈ cycloalkylalkyl)amino, (mono-C₁-C₃ alkyl, C₁-C₃ alkoxy or halo)-(phenyl, phenoxy, phenylthio, phenylsulfonyl or phenoxysulfonyl), C₂-C₆ alkanoylamino, benzoylamino, diphenylmethylamino(C₁-C₃ alkyl), aminocarbonyl, C₁-C₃ alkylaminocarbonyl, di(C₁-C₃ alkyl)aminocarbonyl, halo-C₁-C₆ alkanoyl, aminosulfonyl, C₁-C₃ alkylaminosulfonyl, di(C₁-C₃ alkyl)aminosulfonyl, phenyl(oxy or thio)(C₁-C₃ alkyl), (halo, C₁-C₃ alkyl or C₁-C₃ alkoxy)phenyl(oxy or thio)(C₁-C₃ alkyl), benzoyl, or (amino, C₁-C₃ alkylamino or di(C₁-C₃ alkyl)amino)(C₁-C₃ alkyl);

or an above R⁵ group is substituted with a morpholino(C₁-C₃ alkyl) group, a phenyl(C₁-C₃ alkyl)piperidinyl group, a phenyl(C₁-C₃ alkyl)-piperidinylaminocarbonyl group, a C₂-C₆ alkanoyl-aminothiophenyl group, or a (amino, C₁-C₃ alkylamino or di(C₁-C₃ alkyl)amino)naphthalenylsulfonylamino group;

or R⁵ is a perhalophenyl group;

or a pharmaceutically acceptable salt thereof.

2. A compound of Claim 1 wherein R and R¹ both represent hydrogen.

3. A compound of Claim 2 wherein R³ represents methyl.

4. A compound of Claim 3 wherein R² represents methyl or hydrogen.



-200-

5. A compound of Claim 1 wherein R⁴ represents hydrogen.

6. A compound of Claim 3 wherein X represents -CO-, -CO-Y-(CH₂)_n-, -Z-(CH₂)_n-, alkyl, -CO-, or a bond.

5 7. A compound of Claim 6 wherein X represents a bond or a sulfur atom.

8. A compound of Claim 7 wherein R⁵ represents phenyl, naphthalenyl, pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, anthracenyl, phenanthrenyl, fluorenyl or acenaphthalenyl, wherein the R⁵ group is substituted or
10 unsubstituted.

9. A compound of Claim 7 wherein R⁵ represents benzopyranyl, benzothiazolyl, benzothiophenyl or benzisothiazolyl, wherein the R⁵ group is substituted or
15 unsubstituted.

10. The compound of Claim 1 which is (+)-(4aR)-(10bR)-4-methyl-8-(4-ethyl-2-benzothiazolylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one, or a pharmaceutically acceptable salt thereof.

20 11. A pharmaceutical formulation comprising as an active ingredient, a compound of Formula I, or a pharmaceutically acceptable salt thereof, as claimed in any one of Claims 1 to 10, associated with one or more pharmaceutically acceptable carriers therefor.

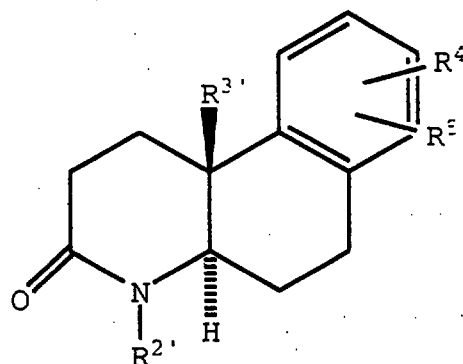
25 12. A compound of Formula I, as claimed in any one of Claims 1 to 10, or a pharmaceutically acceptable salt thereof, for use in treating conditions consequent upon an excess of 5 α -reductase activity.

30 13. A compound of Formula I, as claimed in any one of Claims 1 to 10, or a pharmaceutically acceptable salt thereof, for use in treating benign prostatic hyperplasia.

14. A process for preparing a compound of the formula



-201-



A

wherein $R^{2'}$ is methyl, ethyl or n-propyl;

$R^{3'}$ is hydrogen or methyl;

5 R^4 is hydrogen, halo, methyl or ethyl;

$R^{5'}$ is halo, nitro, cyano, C₁-C₆ alkyl, trifluoromethyl or C₁-C₆ alkoxy;

or $R^{5'}$ is a group -A- R^6 wherein A is C₁-C₆ alkyl, C₂-C₆ alkenyl, or C₂-C₆ alkynyl; and R^6 is halo, trifluoromethyl, or C₁-C₆ alkoxy;

10 or $R^{5'}$ is a group -X'- R^7 wherein X' is C₁-C₄ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl or a bond;

and R^7 is phenyl, naphthalenyl, pyridinyl, pyrazinyl,

pyridazinyl, pyrimidinyl, anthracenyl, acenaphthalenyl,

15 thiazolyl, benzimidazolyl, indazolyl, thiophenyl,

phenanthrenyl, quinolinyl, fluorenyl, isoquinolinyl, indanyl,

benzopyranyl, indolyl, benzisoquinolinyl, benzindolyl,

benzothiazolyl, benzothiophenyl, quinoxalinyl, benzoxazolyl,

tetrazolyl, naphthothiazolyl, quinazolinyl,

20 thiazolopyridinyl, pyridazinoquinazolinyl, benzisothiazolyl,

benzodioxolyl, benzodioxinyl, diphenylmethyl or

triphenylmethyl;

the above R^7 groups are unsubstituted or substituted with 1-3 groups chosen from the group consisting of halo, trifluoromethyl, trifluoroethoxy, C₁-C₄ alkyl, trifluoromethoxy, hydroxy, C₁-C₃ alkoxy, nitro, C₁-C₃

alkylthio, C₁-C₆ alkanoyl, phenyl, oxy, phenoxy, phenylthio,

C₁-C₃ alkylsulfonyl, cyano, benzyloxy, benzylthio, (mono-

halo, nitro or trifluoromethyl)benzyl(oxy or thio), (mono-C₁-

30 C₃ alkyl, C₁-C₃ alkoxy or halo)-(phenyl, phenoxy, phenylthio,

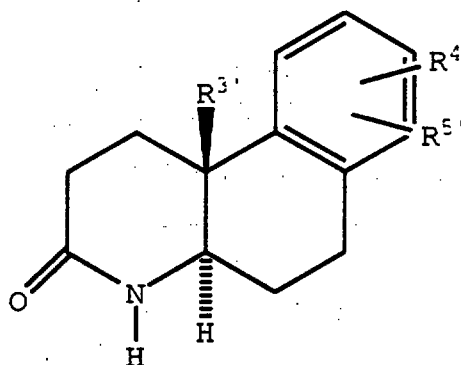


* C L M S *

-202-

phenylsulfonyl or phenoxy sulfonyl), halo-C₁-C₆ alkanoyl, phenyl(oxy or thio)(C₁-C₃ alkyl), (halo, C₁-C₃ alkyl or C₁-C₃ alkoxy)phenyl(oxy or thio)(C₁-C₃ alkyl), or benzoyl; or an above R⁷ group is substituted with a morpholino(C₁-C₃ alkyl) group, or a phenyl(C₁-C₃ alkyl)piperidinyl group; or R⁷ is a perhalophenyl group;

comprising reacting a compound of the formula



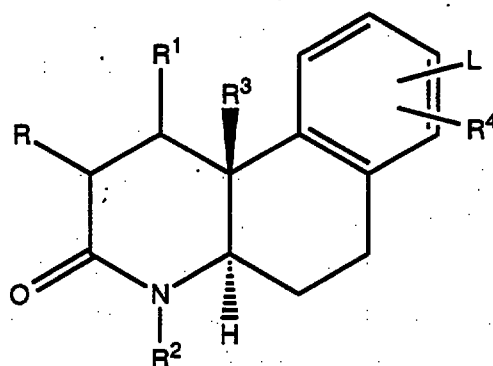
B

with methyl, ethyl or n-propyl iodide in a reaction mixture comprising an organic solvent chosen from the group consisting of tetrahydrofuran, dimethoxyethane, diethoxyethane and methyl t-butyl ether, and aqueous sodium or potassium hydroxide.

15. A process for preparing a compound of Formula

I

(a) wherein an intermediate of the formula



II

is reacted with a compound of the formula

X-R5

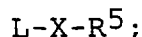
in activated form; or



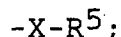


-203-

a compound of Formula II in activated form is reacted with a compound of the formula



5 (b) wherein a compound of Formula I wherein X is $-Z-(CH_2)_n-$ is prepared by reacting a compound of Formula II with a compound of the formula

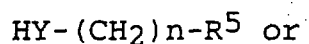
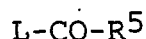
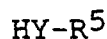


or a compound of Formula II wherein $-L$ has been replaced by $-Z$ is reacted with a compound of the formula

10 $L-X-R^5;$

(c) wherein a compound of Formula I wherein X is $-CO-Y-(CH_2)_n-$ or $-Y-CO-(CH_2)_n-$ is prepared by reacting a compound of Formula II wherein $-L$ has been replaced with one of $-YH$, $-CO-L$, $-(CH_2)_n-YH$, or $-(CH_2)_n-CO-L$, with a compound

15 of one of the formula

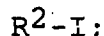


20 provided that one reactant has a $-YH$ group and the other an L group, and no more than one reactant has a $-(CH_2)_n-$ group;

(d) wherein a compound of Formula I wherein X is alkyl is prepared by reacting a compound of Formula II in activated form with an aldehyde or ketone which provides the

25 residue of $-X-R^5;$

(e) wherein a compound of Formula I wherein R^2 is C_1-C_3 alkyl is prepared by reacting a compound of Formula I wherein R^2 is hydrogen with an alkyl iodide of the formula



30 (f) or oxidizing the product to prepare a compound of Formula I wherein R and R^1 combine to form a bond;

(g) or oxidizing or reducing an X group;

(h) or removing protecting groups;

(i) or preparing a salt;

35 (j) or isolating an optical isomer.

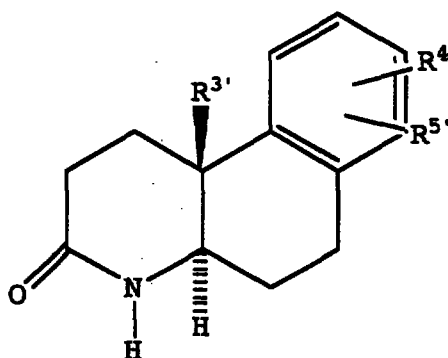


-202-

C₃ alkyl, C₁-C₃ alkoxy or halo)-(phenyl, phenoxy, phenylthio, phenylsulfonyl or phenoxy sulfonyl), halo-C₁-C₆ alkanoyl, phenyl(oxy or thio)(C₁-C₃ alkyl), (halo, C₁-C₃ alkyl or C₁-C₃ alkoxy)phenyl(oxy or thio)(C₁-C₃ alkyl), or benzoyl;

- 5 or an above R⁷ group is substituted with a morpholino(C₁-C₃ alkyl) group, or a phenyl(C₁-C₃ alkyl)piperidinyl group; or R⁷ is a perhalophenyl group;

comprising reacting a compound of the formula



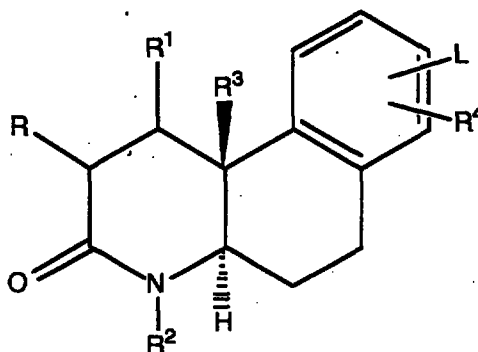
B

with methyl, ethyl or n-propyl iodide in a reaction mixture comprising an organic solvent chosen from the group consisting of tetrahydrofuran, dimethoxyethane, diethoxyethane and methyl t-butyl ether, and aqueous sodium or potassium hydroxide without a phase transfer catalyst.

- 15 15. A process for preparing a compound of Formula

I

(a) wherein an intermediate of the formula



II

is reacted with a compound of the formula

X-R⁵

This is the replacement sheet

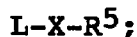
Date:

14 APR 1997

-203-

in activated form; or

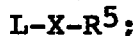
a compound of Formula II in activated form is reacted with a compound of the formula



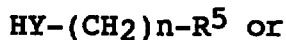
- 5 (b) wherein a compound of Formula I wherein X is -Z-(CH₂)_n- is prepared by reacting a compound of Formula II with a compound of the formula



- 10 or a compound of Formula II wherein -L has been replaced by -Z is reacted with a compound of the formula



- 15 (c) wherein a compound of Formula I wherein X is -CO-Y-(CH₂)_n- or -Y-CO-(CH₂)_n- is prepared by reacting a compound of Formula II wherein -L has been replaced with one of -YH, -CO-L, -(CH₂)_n-YH, or -(CH₂)_n-CO-L, with a compound of one of the formula

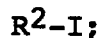


- 20 $L-CO-(CH_2)_n-R^5,$

provided that one reactant has a -YH group and the other an L group, and no more than one reactant has a -(CH₂)_n- group;

- 25 (d) wherein a compound of Formula I wherein X is alkyl is prepared by reacting a compound of Formula II in activated form with an aldehyde or ketone which provides the residue of -X-R⁵;

- 30 (e) wherein a compound of Formula I wherein R² is C₁-C₃ alkyl is prepared by reacting a compound of Formula I wherein R² is hydrogen with an alkyl iodide of the formula



- (f) or oxidizing the product to prepare a compound of Formula I wherein R and R¹ combine to form a bond;

- (g) or oxidizing or reducing an X group;

- (h) or removing protecting groups;

- 35 (i) or preparing a salt;

- (j) or isolating an optical isomer.



This is the replacement sheet

Date: 14 APR 1997