



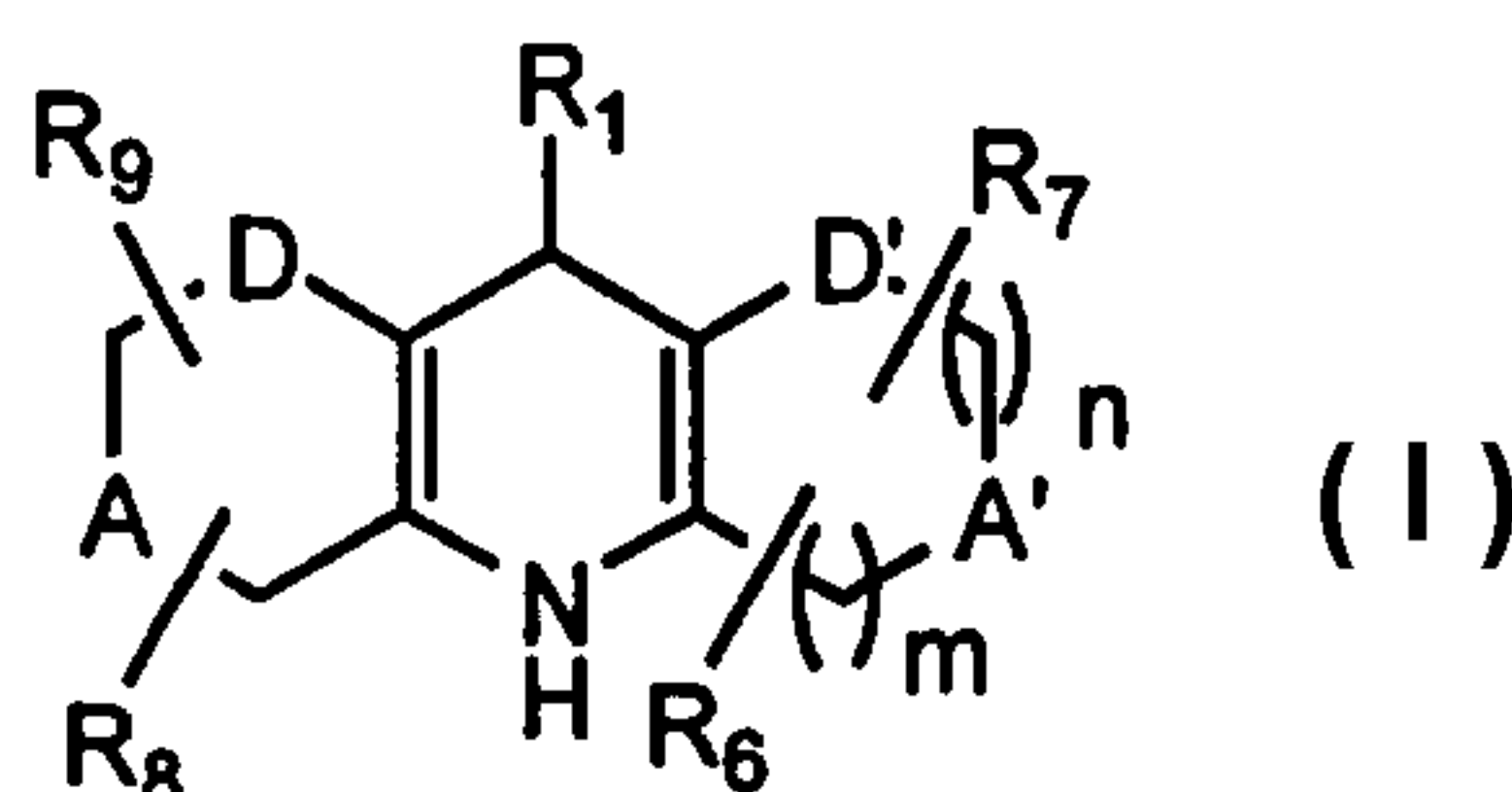
(86) Date de dépôt PCT/PCT Filing Date: 2001/05/03
(87) Date publication PCT/PCT Publication Date: 2001/11/08
(45) Date de délivrance/Issue Date: 2010/01/12
(85) Entrée phase nationale/National Entry: 2002/10/31
(86) N° demande PCT/PCT Application No.: US 2001/014457
(87) N° publication PCT/PCT Publication No.: 2001/083484
(30) Priorité/Priority: 2000/05/03 (US09/563,287)

(51) Cl.Int./Int.Cl. *C07D 471/14* (2006.01),
A61K 31/4745 (2006.01), *A61P 13/10* (2006.01),
A61P 15/00 (2006.01), *C07C 205/44* (2006.01),
C07C 45/00 (2006.01), *C07C 45/29* (2006.01),
C07C 45/41 (2006.01), *C07C 45/63* (2006.01),
C07D 471/04 (2006.01), *C07D 491/14* (2006.01),
C07D 495/14 (2006.01)

(72) Inventeurs/Inventors:
CARROLL, WILLIAM A., US;
AGRIOS, KONSTANTINOS A., US;
ALTENBACH, ROBERT J., US;
DRIZIN, IRENE, US;
KORT, MICHAEL J., US

(73) Propriétaire/Owner:

(54) Titre : COMPOSES PYRANO, PIPERIDINO ET THIOPYRANO ET TECHNIQUES D'UTILISATION
(54) Title: PYRANO, PIPERIDINO, AND THIOPYRANO COMPOUNDS AND METHODS OF USE



(57) Abrégé/Abstract:

The present invention provides novel compounds of formula (I), which may be useful in hyperpolarizing cell membranes, opening potassium channels, relaxing smooth muscle cells, and inhibiting bladder contractions.

(73) Propriétaires(suite)/Owners(continued):ABBOTT LABORATORIES, US

(74) Agent: TORYS LLP

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
8 November 2001 (08.11.2001)

PCT

(10) International Publication Number
WO 01/83484 A1(51) International Patent Classification⁷: **C07D 471/14**,
491/14, 495/14, 471/04, A61K 31/4745, A61P 13/10,
15/00IL 60031 (US). **DRIZIN, Irene**; 16764 W. Cherrywood
Lan, Wadsworth, Il Illinois 60083 (US). **KORT, Michael,**
J.; 507 N. Green Avenue, Lake Bluff, IL 60044-1529 (US).

(21) International Application Number: PCT/US01/14457

(74) Agents: **WARD, Michael, J.** et al.; Abbott Laboratories,
D377 AP6D/2, 100 Abbott Park Road, Abbott Park, IL
60064-6050 (US).

(22) International Filing Date: 3 May 2001 (03.05.2001)

(25) Filing Language:

English

(81) Designated States (*national*): CA, JP, MX.

(26) Publication Language:

English

(84) Designated States (*regional*): European patent (AT, BE,
CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC,
NL, PT, SE, TR).

(30) Priority Data:

09/563,287

3 May 2000 (03.05.2000)

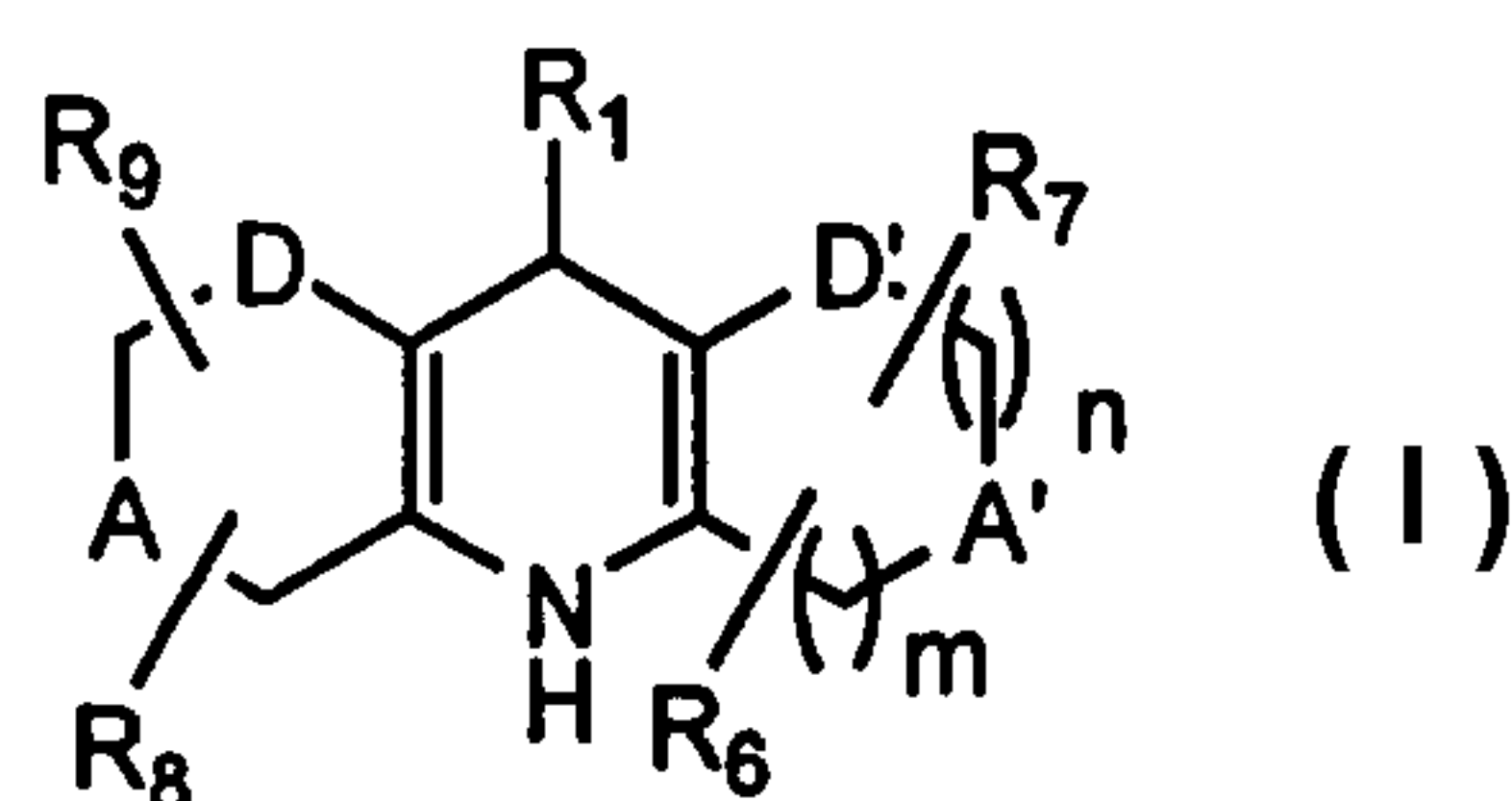
US

(71) Applicant: **ABBOTT LABORATORIES** [US/US];
D377 AP6D, 100 Abbott Park Road, Abbott Park, IL
60064-6050 (US).**Published:**

— with international search report

— before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
amendments(72) Inventors: **CARROLL, William, A.**; 2325 Ridgeway Av-
enue, Evanston, IL 60201 (US). **AGRIOS, Konstantinos,**
A.; Apartment 501, 702 Ash Street, San Diego, CA 92101
(US). **ALTENBACH, Robert, J.**; 7405 N. Oketo, Chicago,For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: PYRANO, PIPERIDINO, AND THIOPYRANO COMPOUNDS AND METHODS OF USE

(57) Abstract: The present invention provides novel compounds of formula (I),
which may be useful in hyperpolarizing cell membranes, opening potassium chan-
nels, relaxing smooth muscle cells, and inhibiting bladder contractions.

PYRANO, PIPERIDINO, AND THIOPYRANO COMPOUNDS
AND METHODS OF USE

TECHNICAL FIELD

Novel dihydropyridine compounds and their derivatives can open potassium channels and are useful for treating a variety of medical conditions.

BACKGROUND OF INVENTION

Potassium channels play an important role in regulating cell membrane excitability. When the potassium channels open, changes in the electrical potential across the cell membrane occur and result in a more polarized state. A number of diseases or conditions can be treated with therapeutic agents that open potassium channels; see (K. Lawson, *Pharmacol. Ther.*, v. 70, pp. 39-63 (1996)); (D.R. Gehlert et al., *Prog. Neuro-Psychopharmacol & Biol. Psychiat.*, v. 18, pp. 1093-1102 (1994)); (M. Gopalakrishnan et al., *Drug Development Research*, v. 28, pp. 95-127 (1993)); (J.E. Freedman et al., *The Neuroscientist*, v. 2, pp. 145-152 (1996)); (D. E. Nurse et al., *Br. J. Urol.*, v. 68 pp. 27-31 (1991)); (B. B. Howe et al., *J. Pharmacol. Exp. Ther.*, v. 274 pp. 884-890 (1995)); and (D. Spanswick et al., *Nature*, v. 390 pp. 521-25 (December 4, 1997)). Such diseases or conditions include asthma, epilepsy, male sexual dysfunction, female sexual dysfunction, migraine, pain, urinary incontinence, stroke, Raynaud's Syndrome, eating disorders, functional bowel disorders, and neurodegeneration.

Potassium channel openers also act as smooth muscle relaxants. Because urinary incontinence can result from the spontaneous, uncontrolled contractions of the smooth muscle of the bladder, the ability of potassium channel openers to hyperpolarize bladder

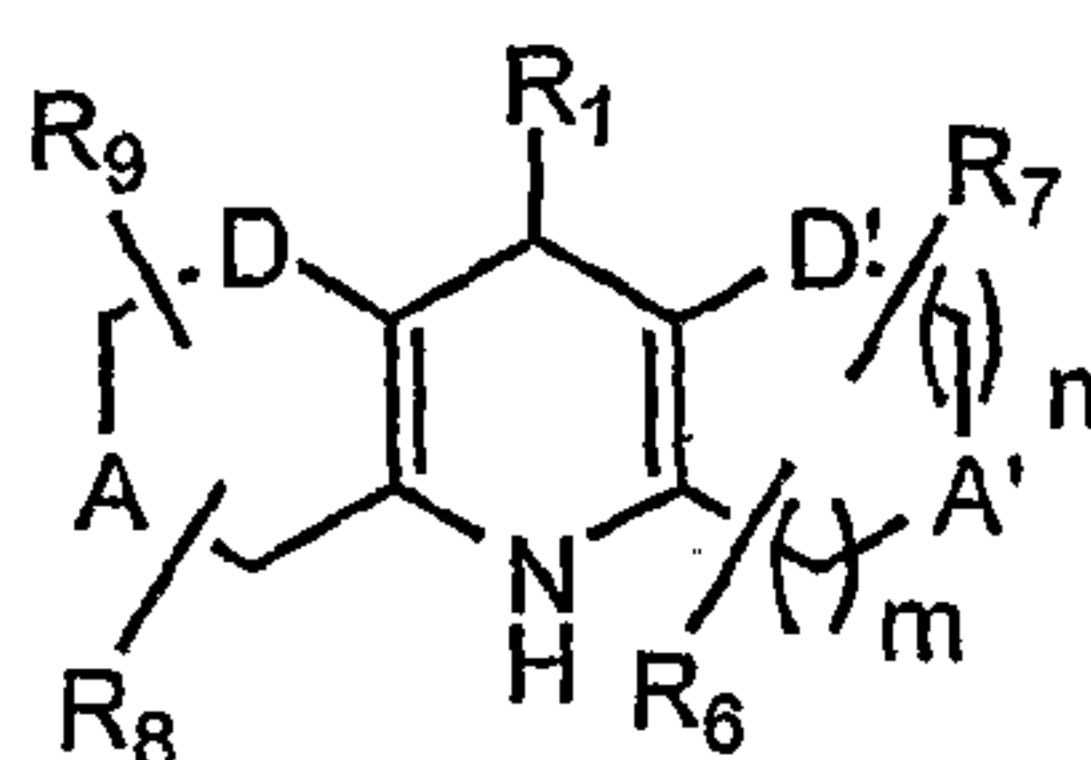
cells and relax bladder smooth muscle provides a method to ameliorate or prevent urinary incontinence.

Journal of Cardiovascular Pharmacology 8:1168-1175, (1986) Raven Press, New York, EP 0 059 291, EP 87051738, US 4,321,384, US 4,551,534, US 4,596,873, and US 4,618,678 all disclose 4-(aryl)-4,5,6,7,8,-hexahydro-2-alkyl-5-oxo-1,7-naphthyridine-3-carboxylic esters as calcium entry blockers that may be useful as antihypertensive agents.

Compounds of the present Invention are novel, hyperpolarize cell membranes, open potassium channels, relax smooth muscle cells, inhibit bladder contractions and are useful for treating diseases that can be ameliorated by opening potassium channels.

SUMMARY OF THE INVENTION

In its principle embodiment of the present invention, compounds of the present invention have formula I



I,

or a pharmaceutically acceptable salt, amide, ester, or prodrug thereof, wherein

n is 0-1;

m is 1-2;

A is selected from the group consisting of NR₂, O, and S;

A' is selected from the group consisting of NR₃, O, S, and CR₄R₅;

D is selected from the group consisting of CH₂ and C(O);

D' is selected from the group consisting of CH₂, C(O), S(O), and S(O)₂;

R₁ is selected from the group consisting of aryl and heterocycle;

R₂ and R₃ are independently selected from the group consisting of hydrogen, alkoxyalkyl, alkyl, arylalkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, heterocyclealkyl, hydroxy, hydroxyalkyl, -NZ₁Z₂, and (NZ₁Z₂)alkyl wherein Z₁ and Z₂ are independently

selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, aryl, arylalkyl, and formyl;

R_4 and R_5 are independently selected from the group consisting of hydrogen and alkyl;

5 or

R_4 and R_5 together with the carbon atom to which they are attached form a 3-6 membered carbocyclic ring;

R_6 and R_7 are independently selected from the group consisting of hydrogen and alkyl;

10 or

R_6 and R_7 together with the carbon atom to which they are attached form a 3-6 membered carbocyclic ring; and

R_8 and R_9 are independently selected from the group consisting of hydrogen and alkyl;

15 or

R_8 and R_9 together with the carbon atom to which they are attached form a 3-6 membered carbocyclic ring;

with the proviso that when D is CH_2 then D' is other than CH_2 ; and

with the proviso that when D' is $\text{S}(\text{O})$ or $\text{S}(\text{O})_2$ then A' is CR_4R_5 .

20

DETAILED DESCRIPTION OF THE INVENTION

All patents, patent applications, and literature references cited in the specification are herein incorporated by reference in their entirety. In the case of inconsistencies, the present disclosure, including definitions, will prevail.

25

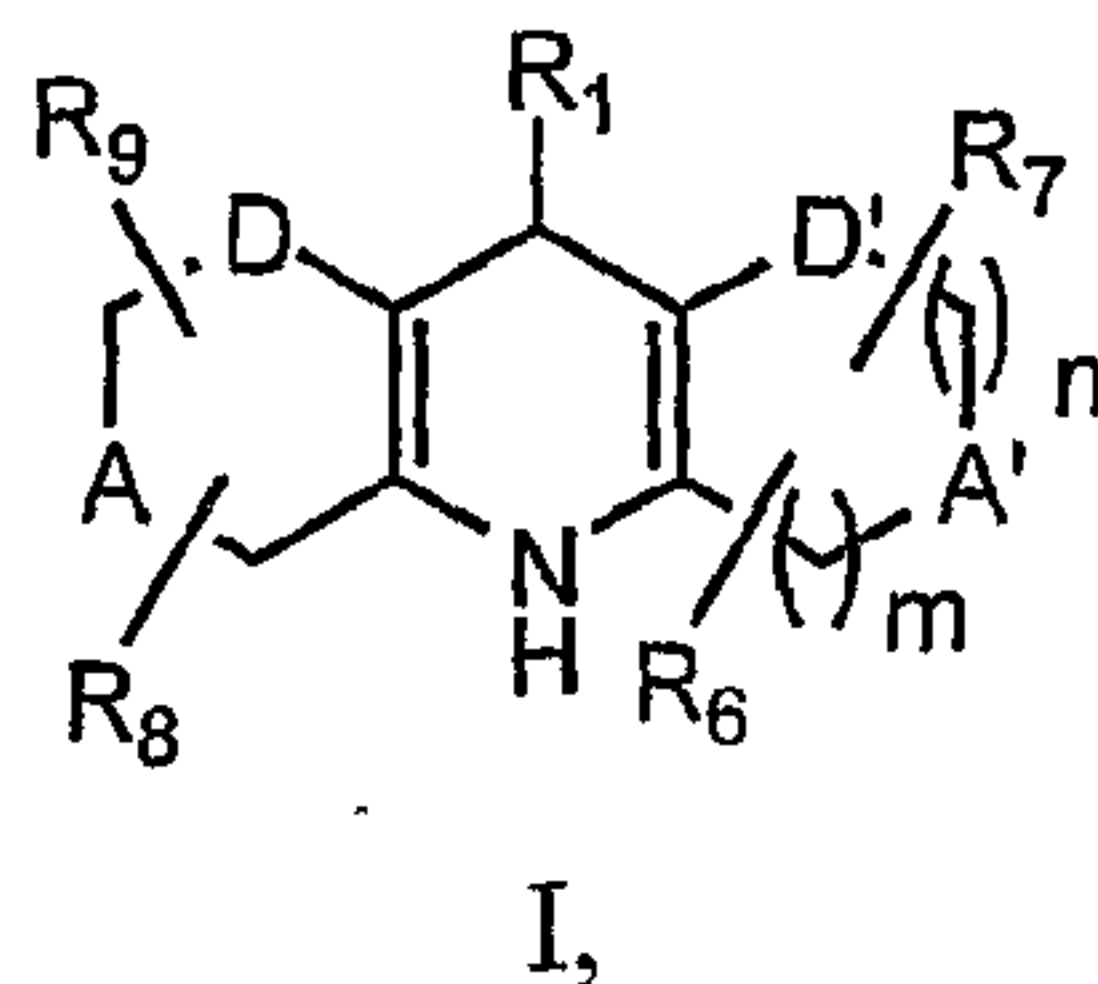
It is understood that the foregoing detailed description and accompanying examples are merely illustrative and are not to be taken as limitations upon the scope of the invention, which is defined solely by the appended claims and their equivalents. Various changes and modifications to the disclosed embodiments will be apparent to those skilled in the art. Such changes and modifications, including without limitation those relating to the chemical structures, substituents, derivatives, intermediates, syntheses,

30

4

formulations and/or methods of use of the invention, may be made without departing from the spirit and scope thereof.

In its principle embodiment of the present invention, compounds of the present invention have formula I



or a pharmaceutically acceptable salt, amide, ester, or prodrug thereof, wherein

n is 0-1;

m is 1-2;

A is selected from the group consisting of NR₂, O, and S;

A' is selected from the group consisting of NR₃, O, S and CR₄R₅;

D is selected from the group consisting of CH₂ and C(O);

D' is selected from the group consisting of CH₂, C(O), S(O), and S(O)₂;

R₁ is selected from the group consisting of aryl and heterocycle;

R₂ and R₃ are independently selected from the group consisting of hydrogen, alkoxyalkyl, alkyl, arylalkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, heterocyclealkyl, hydroxy, hydroxyalkyl, -NZ₁Z₂, and (NZ₁Z₂)alkyl wherein Z₁ and Z₂ are independently selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, aryl, arylalkyl, and formyl;

R₄ and R₅ are independently selected from the group consisting of hydrogen and alkyl;

or

R₄ and R₅ together with the carbon atom to which they are attached form a 3-6 membered carbocyclic ring;

R₆ and R₇ are independently selected from the group consisting of hydrogen and alkyl;

or

5

R_6 and R_7 together with the carbon atom to which they are attached form a 3-6 membered carbocyclic ring; and

R_8 and R_9 are independently selected from the group consisting of hydrogen and alkyl;

5 or

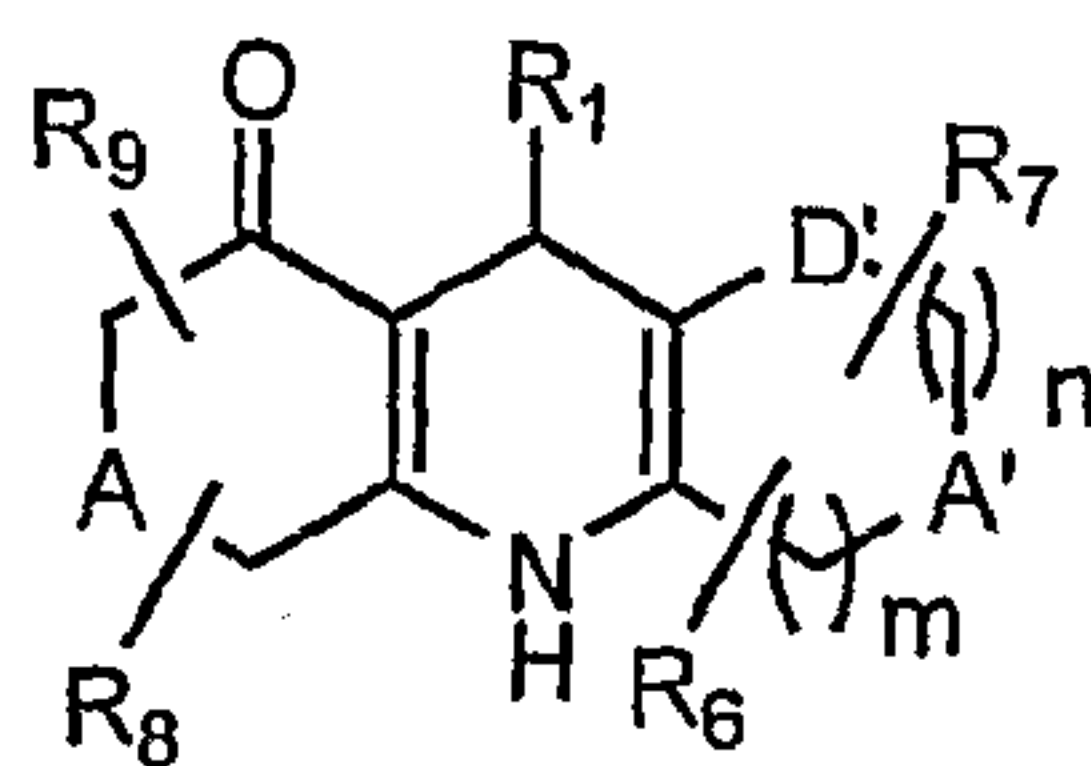
R_8 and R_9 together with the carbon atom to which they are attached form a 3-6 membered carbocyclic ring;

with the proviso that when D is CH_2 then D' is other than CH_2 ; and

with the proviso that when D' is $S(O)$ or $S(O)_2$ then A' is CR_4R_5 .

10

In another embodiment, the present invention discloses compounds having formula II:



II,

15 or a pharmaceutically acceptable salt, ester, amide, or prodrug thereof wherein, A, A', D', R_1 , R_6 , R_7 , R_8 , R_9 , m, and n are as defined in formula I.

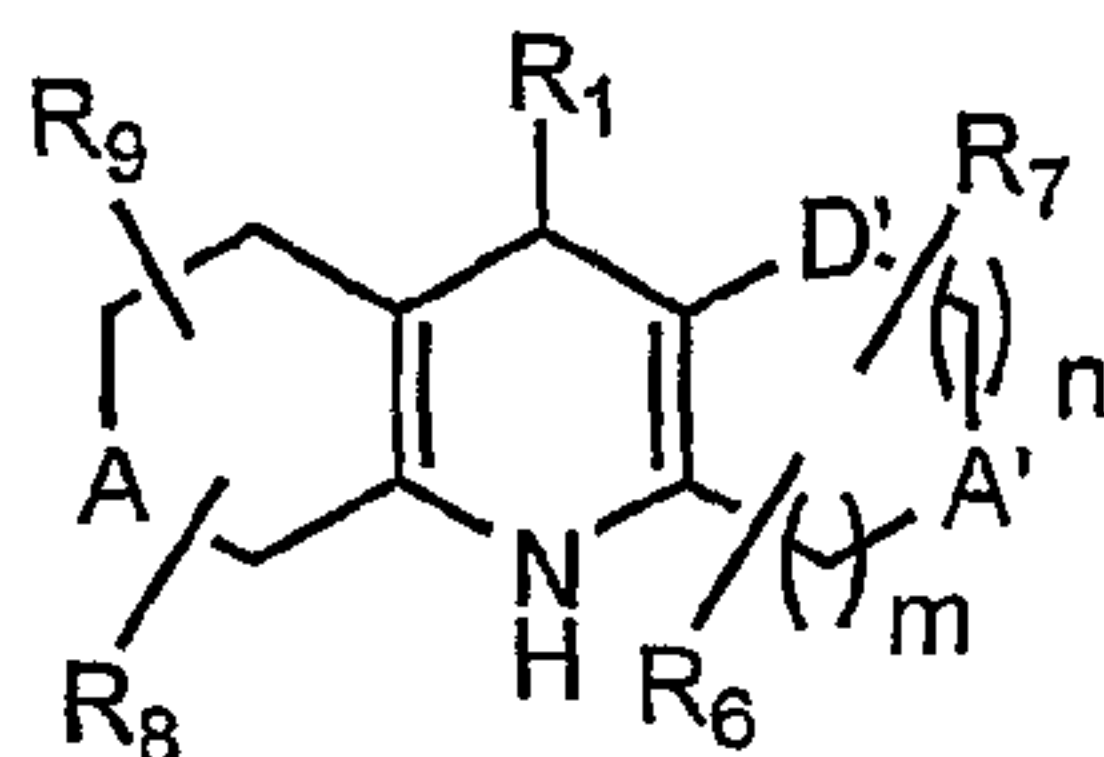
In another embodiment of the present invention, compounds have formula II wherein, A is NR_2 ; and A', D', R_1 , R_2 , R_6 , R_7 , R_8 , R_9 , m, and n are as defined in formula I.

20 In another embodiment of the present invention, compounds have formula II wherein, A is O; and A', D', R_1 , R_6 , R_7 , R_8 , R_9 , m, and n are as defined in formula I.

In another embodiment of the present invention, compounds have formula II wherein, A is S; and A', D', R_1 , R_6 , R_7 , R_8 , R_9 , m, and n are as defined in formula I.

6

In another embodiment, the present invention discloses compounds having formula III:



III,

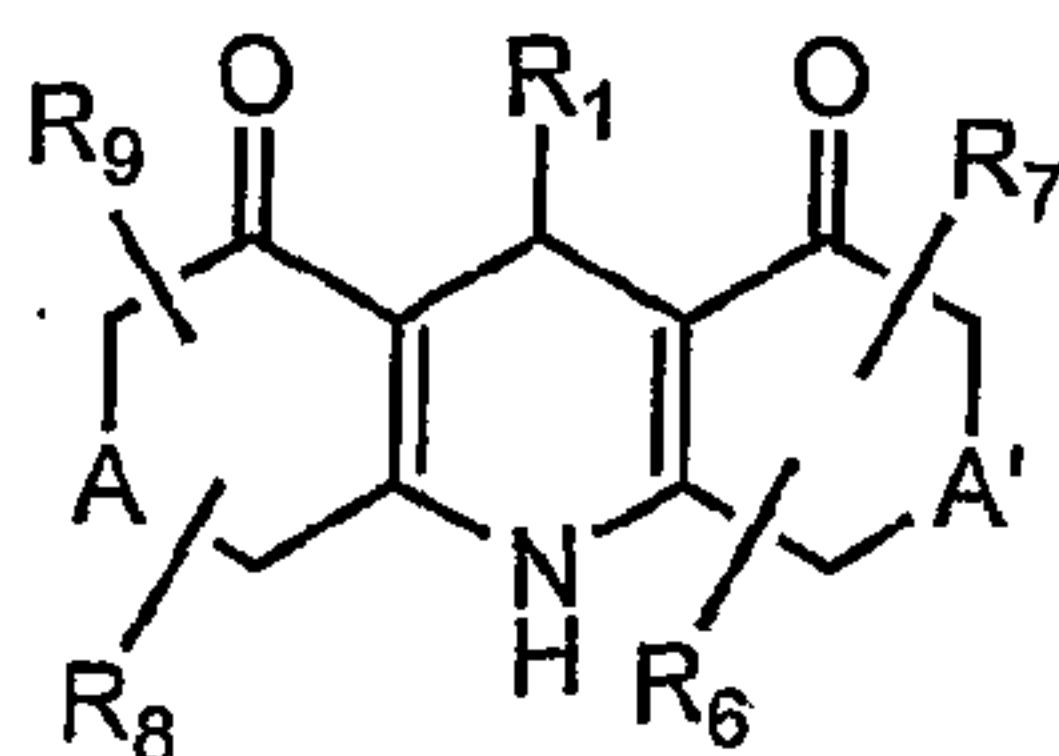
or a pharmaceutically acceptable salt, ester, amide, or prodrug thereof wherein, A, A', D', R₁, R₆, R₇, R₈, R₉, m, and n are as defined in formula I with the proviso that D' is not CH₂.

In another embodiment of the present invention, compounds have formula III wherein, A is NR₂; and A', D', R₁, R₂, R₆, R₇, R₈, R₉, m, and n are as defined in formula I.

In another embodiment of the present invention, compounds have formula III wherein, A is O; and A', D', R₁, R₆, R₇, R₈, R₉, m, and n are as defined in formula I.

In another embodiment of the present invention, compounds have formula III wherein, A is S; and A', D', R₁, R₆, R₇, R₈, R₉, m, and n are as defined in formula I.

In another embodiment, the present invention discloses compounds having formula IV:



IV,

or a pharmaceutically acceptable salt, ester, amide, or prodrug thereof wherein, A, A', R₁, R₆, R₇, R₈, and R₉, are as defined in formula I.

In another embodiment of the present invention, compounds have formula IV wherein, A is NR₂; A' is NR₃; and R₁, R₂, R₃, R₆, R₇, R₈, and R₉ are as defined in formula I.

In another embodiment of the present invention, compounds have formula IV wherein, A is NR₂; A' is NR₃; R₆ is hydrogen; R₇ is hydrogen; R₈ is hydrogen; R₉ is hydrogen; and R₁, R₂, and R₃ are as defined in formula I.

In another embodiment of the present invention, compounds have formula IV wherein, A is NR_2 ; A' is O; and R_1 , R_2 , R_6 , R_7 , R_8 , and R_9 are as defined in formula I.

In another embodiment of the present invention, compounds have formula IV wherein, A is NR_2 ; A' is S; and R_1 , R_2 , R_6 , R_7 , R_8 , and R_9 are as defined in formula I.

5 In another embodiment of the present invention, compounds have formula IV wherein, A is O; A' is NR_3 ; and R_1 , R_3 , R_6 , R_7 , R_8 , and R_9 are as defined in formula I.

In another embodiment of the present invention, compounds have formula IV wherein, A is O; A' is NR_3 ; R_6 is hydrogen; R_7 is hydrogen; R_8 is hydrogen; R_9 is hydrogen; and R_1 and R_3 are as defined in formula I.

10 In another embodiment of the present invention, compounds have formula IV wherein, A is O; A' is O; and R_1 , R_6 , R_7 , R_8 , and R_9 are as defined in formula I.

In another embodiment of the present invention, compounds have formula IV wherein, A is O; A' is O; R_6 is hydrogen; R_7 is hydrogen; R_8 is hydrogen; R_9 is hydrogen; and R_1 is as defined in formula I.

15 In another embodiment of the present invention, compounds have formula IV wherein, A is O; A' is O; R_6 is hydrogen; R_7 is hydrogen; R_8 is alkyl; R_9 is selected from hydrogen and alkyl; and R_1 is as defined in formula I.

In another embodiment of the present invention, compounds have formula IV wherein, A is O; A' is O; R_6 is alkyl; R_7 is selected from hydrogen and alkyl; R_8 is alkyl;
20 R_9 is selected from hydrogen and alkyl; and R_1 is as defined in formula I.

In another embodiment of the present invention, compounds have formula IV wherein, A is O; A' is S; and R_1 , R_6 , R_7 , R_8 , and R_9 are as defined in formula I.

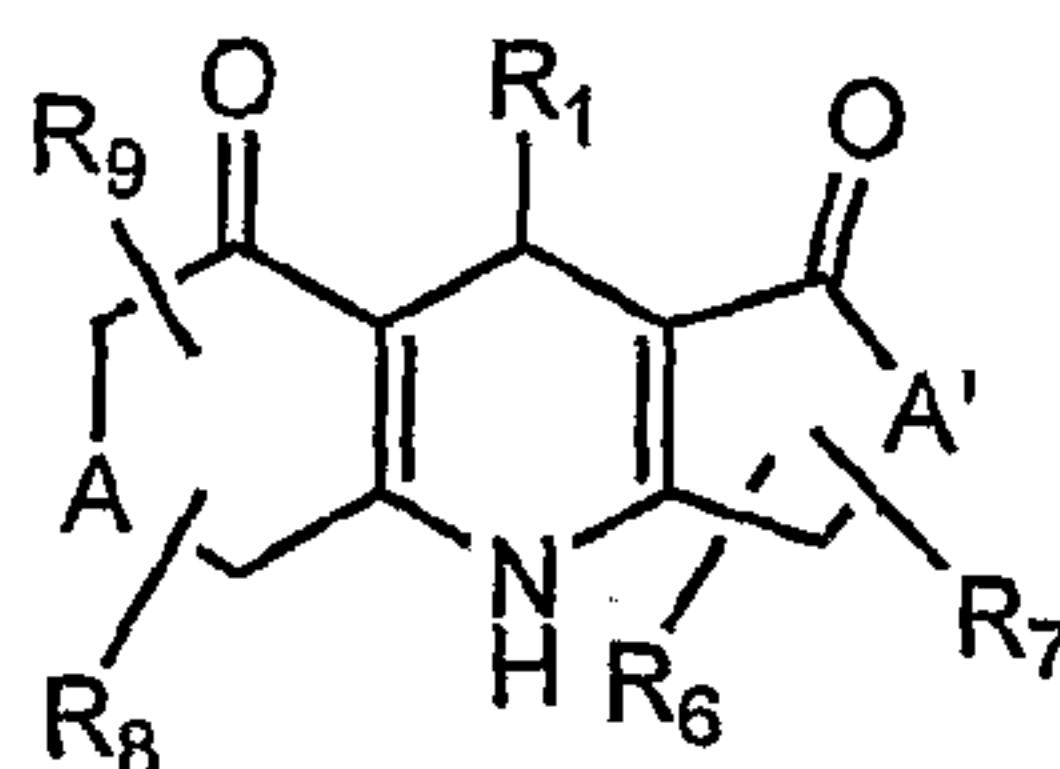
In another embodiment of the present invention, compounds have formula IV wherein, A is O; A' is S; R_6 is hydrogen; R_7 is hydrogen; R_8 is hydrogen; R_9 is hydrogen;
25 and R_1 is as defined in formula I.

In another embodiment of the present invention, compounds have formula IV wherein, A is S; A' is NR_3 ; and R_1 , R_3 , R_6 , R_7 , R_8 , and R_9 are as defined in formula I.

In another embodiment of the present invention, compounds have formula IV wherein, A is S; A' is O; and R_1 , R_6 , R_7 , R_8 , and R_9 are as defined in formula I.

In another embodiment of the present invention, compounds have formula IV wherein, A is S; A' is S; and R₁, R₆, R₇, R₈, and R₉ are as defined in formula I.

In another embodiment, the present invention discloses compounds having
5 formula V:



V,

or a pharmaceutically acceptable salt, ester, amide, or prodrug thereof wherein, A, A', R₁, R₆, R₇, R₈, and R₉, are as defined in formula I.

10 In another embodiment of the present invention, compounds have formula V wherein, A is NR₂; A' is NR₃; and R₁, R₂, R₃, R₆, R₇, R₈, and R₉ are as defined in formula I.

In another embodiment of the present invention, compounds have formula V wherein, A is NR₂; A' is O; and R₁, R₂, R₆, R₇, R₈, and R₉ are as defined in formula I.

15 In another embodiment of the present invention, compounds have formula V wherein, A is NR₂; A' is O; R₆ is hydrogen; R₇ is hydrogen; R₈ is hydrogen; R₉ is hydrogen; and R₁ and R₂ are as defined in formula I.

In another embodiment of the present invention, compounds have formula V wherein, A is NR₂; A' is S; and R₁, R₂, R₆, R₇, R₈, and R₉ are as defined in formula I.

20 In another embodiment of the present invention, compounds have formula V wherein, A is NR₂; A' is CR₄R₅; and R₁, R₂, R₄, R₅, R₆, R₇, R₈, and R₉ are as defined in formula I.

In another embodiment of the present invention, compounds have formula V wherein, A is NR₂; A' is CR₄R₅; R₄ is hydrogen; R₅ is hydrogen; R₆ is hydrogen; R₇ is hydrogen; R₈ is hydrogen; R₉ is hydrogen; and R₁ and R₂ are as defined in formula I.

25 In another embodiment of the present invention, compounds have formula V wherein, A is O; A' is NR₃; and R₁, R₃, R₆, R₇, R₈, and R₉ are as defined in formula I.

In another embodiment of the present invention, compounds have formula V

wherein, A is O; A' is NR₃; R₆ is hydrogen; R₇ is hydrogen; R₈ is hydrogen; R₉ is hydrogen; and R₁ and R₃ are as defined in formula I.

In another embodiment of the present invention, compounds have formula V wherein, A is O; A' is O; and R₁, R₆, R₇, R₈, and R₉ are as defined in formula I.

5 In another embodiment of the present invention, compounds have formula V wherein, A is O; A' is O; R₆ is hydrogen; R₇ is hydrogen; R₈ is hydrogen; R₉ is hydrogen; and R₁ is as defined in formula I.

In another embodiment of the present invention, compounds have formula V wherein, A is O; A' is O; R₆ is hydrogen; R₇ is hydrogen; R₈ is alkyl; R₉ is selected from
10 hydrogen and alkyl; and R₁ is as defined in formula I.

In another embodiment of the present invention, compounds have formula V wherein, A is O; A' is O; R₆ is alkyl; R₇ is selected from hydrogen and alkyl; R₈ is hydrogen; R₉ is hydrogen; and R₁ is as defined in formula I.

In another embodiment of the present invention, compounds have formula V
15 wherein, A is O; A' is S; and R₁, R₆, R₇, R₈, and R₉ are as defined in formula I.

In another embodiment of the present invention, compounds have formula V wherein, A is O; A' is CR₄R₅; and R₁, R₄, R₅, R₆, R₇, R₈, and R₉ are as defined in formula I.

In another embodiment of the present invention, compounds have formula V wherein, A is O; A' is CR₄R₅; R₄ is hydrogen; R₅ is hydrogen; R₆ is hydrogen; R₇ is
20 hydrogen; R₈ is hydrogen; R₉ is hydrogen; and R₁ is as defined in formula I.

In another embodiment of the present invention, compounds have formula V wherein, A is O; A' is CR₄R₅; R₄ is hydrogen; R₅ is hydrogen; R₆ is hydrogen; R₇ is hydrogen; R₈ is alkyl; R₉ is selected from hydrogen and alkyl; and R₁ is as defined in
formula I.

25 In another embodiment of the present invention, compounds have formula V wherein, A is S; A' is NR₃; and R₁, R₃, R₆, R₇, R₈, and R₉ are as defined in formula I.

In another embodiment of the present invention, compounds have formula V wherein, A is S; A' is O; and R₁, R₆, R₇, R₈, and R₉ are as defined in formula I.

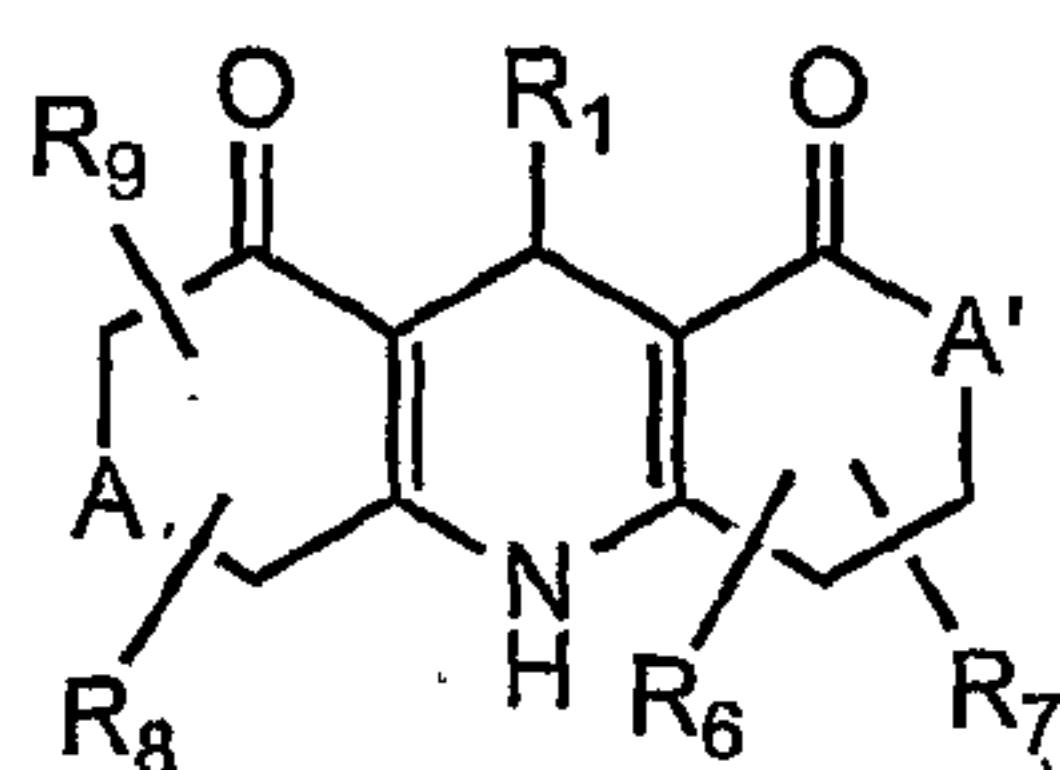
In another embodiment of the present invention, compounds have formula V
30 wherein, A is S; A' is S; and R₁, R₆, R₇, R₈, and R₉ are as defined in formula I.

10

In another embodiment of the present invention, compounds have formula V wherein, A is S; A' is CR₄R₅; and R₁, R₄, R₅, R₆, R₇, R₈, and R₉ are as defined in formula I.

In another embodiment of the present invention, compounds have formula V wherein, A is S; A' is CR₄R₅; R₄ is hydrogen; R₅ is hydrogen; R₆ is hydrogen; R₇ is hydrogen; R₈ is hydrogen; R₉ is hydrogen; and R₁ is as defined in formula I.

In another embodiment, the present invention discloses compounds having formula VI:



VI,

or a pharmaceutically acceptable salt, ester, amide, or prodrug thereof wherein, A, A', R₁, R₆, R₇, R₈, and R₉, are as defined in formula I.

In another embodiment of the present invention, compounds have formula VI wherein, A is NR₂; A' is NR₃; and R₁, R₂, R₃, R₆, R₇, R₈, and R₉ are as defined in formula I.

In another embodiment of the present invention, compounds have formula VI wherein, A is NR₂; A' is O; and R₁, R₂, R₆, R₇, R₈, and R₉ are as defined in formula I.

In another embodiment of the present invention, compounds have formula VI wherein, A is NR₂; A' is S; and R₁, R₂, R₆, R₇, R₈, and R₉ are as defined in formula I.

In another embodiment of the present invention, compounds have formula VI wherein, A is NR₂; A' is CR₄R₅; and R₁, R₂, R₄, R₅, R₆, R₇, R₈, and R₉ are as defined in formula I.

In another embodiment of the present invention, compounds have formula VI wherein, A is NR₂; A' is CR₄R₅; R₄ is hydrogen; R₅ is hydrogen; R₆ is hydrogen; R₇ is hydrogen; R₈ is hydrogen; R₉ is hydrogen; and R₁ and R₂ are as defined in formula I.

In another embodiment of the present invention, compounds have formula VI wherein, A is O; A' is NR₃; and R₁, R₃, R₆, R₇, R₈, and R₉ are as defined in formula I.

In another embodiment of the present invention, compounds have formula VI

wherein, A is O; A' is NR₃; R₆ is hydrogen; R₇ is hydrogen; R₈ is hydrogen; R₉ is hydrogen; and R₁ and R₃ are as defined in formula I.

In another embodiment of the present invention, compounds have formula VI wherein, A is O; A' is O; and R₁, R₆, R₇, R₈, and R₉ are as defined in formula I.

5 In another embodiment of the present invention, compounds have formula VI wherein, A is O; A' is S; and R₁, R₆, R₇, R₈, and R₉ are as defined in formula I.

In another embodiment of the present invention, compounds have formula VI wherein, A is O; A' is CR₄R₅; and R₁, R₄, R₅, R₆, R₇, R₈, and R₉ are as defined in formula I.

10 In another embodiment of the present invention, compounds have formula VI wherein, A is O; A' is CR₄R₅; R₆ is hydrogen; R₇ is hydrogen; R₈ is hydrogen; R₉ is hydrogen; and R₁, R₄, and R₅ are as defined in formula I.

In another embodiment of the present invention, compounds have formula VI wherein, A is O; A' is CR₄R₅; R₄ is hydrogen; R₅ is hydrogen; R₆ is hydrogen; R₇ is hydrogen; R₈ is hydrogen; R₉ is hydrogen; and R₁ is as defined in formula I.

15 In another embodiment of the present invention, compounds have formula VI wherein, A is O; A' is CR₄R₅; R₄ is methyl; R₅ is methyl; R₆ is hydrogen; R₇ is hydrogen; R₈ is hydrogen; R₉ is hydrogen; and R₁ is as defined in formula I.

In another embodiment of the present invention, compounds have formula VI wherein, A is S; A' is NR₃; and R₁, R₃, R₆, R₇, R₈, and R₉ are as defined in formula I.

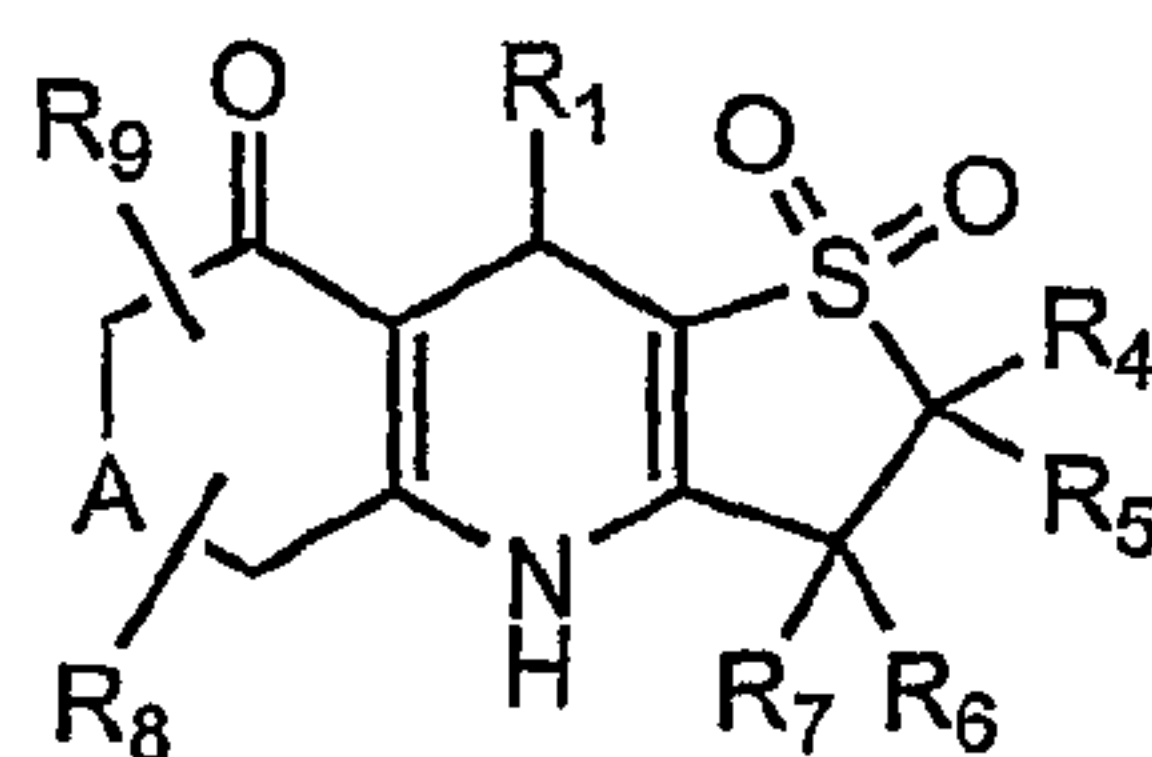
20 In another embodiment of the present invention, compounds have formula VI wherein, A is S; A' is O; and R₁, R₆, R₇, R₈, and R₉ are as defined in formula I.

In another embodiment of the present invention, compounds have formula VI wherein, A is S; A' is S; and R₁, R₆, R₇, R₈, and R₉ are as defined in formula I.

25 In another embodiment of the present invention, compounds have formula VI wherein, A is S; A' is CR₄R₅; and R₁, R₄, R₅, R₆, R₇, R₈, and R₉ are as defined in formula I.

In another embodiment of the present invention, compounds have formula VI wherein, A is S; A' is CR₄R₅; R₄ is hydrogen; R₅ is hydrogen; R₆ is hydrogen; R₇ is hydrogen; R₈ is hydrogen; R₉ is hydrogen; and R₁ is as defined in formula I.

In another embodiment, the present invention discloses compounds having formula VII:



VII,

5 or a pharmaceutically acceptable salt, ester, amide, or prodrug thereof wherein, A, R₁, R₄, R₅, R₆, R₇, R₈, and R₉, are as defined in formula I.

In another embodiment of the present invention, compounds have formula VII wherein, A is NR₂; and R₁, R₂, R₄, R₅, R₆, R₇, R₈, and R₉ are as defined in formula I.

10 In another embodiment of the present invention, compounds have formula VII wherein, A is NR₂; R₄ is hydrogen; R₅ is hydrogen; R₆ is hydrogen; R₇ is hydrogen; R₈ is hydrogen; R₉ is hydrogen; and R₁ and R₂ are as defined in formula I.

In another embodiment of the present invention, compounds have formula VII wherein, A is O; and R₁, R₄, R₅, R₆, R₇, R₈, and R₉ are as defined in formula I.

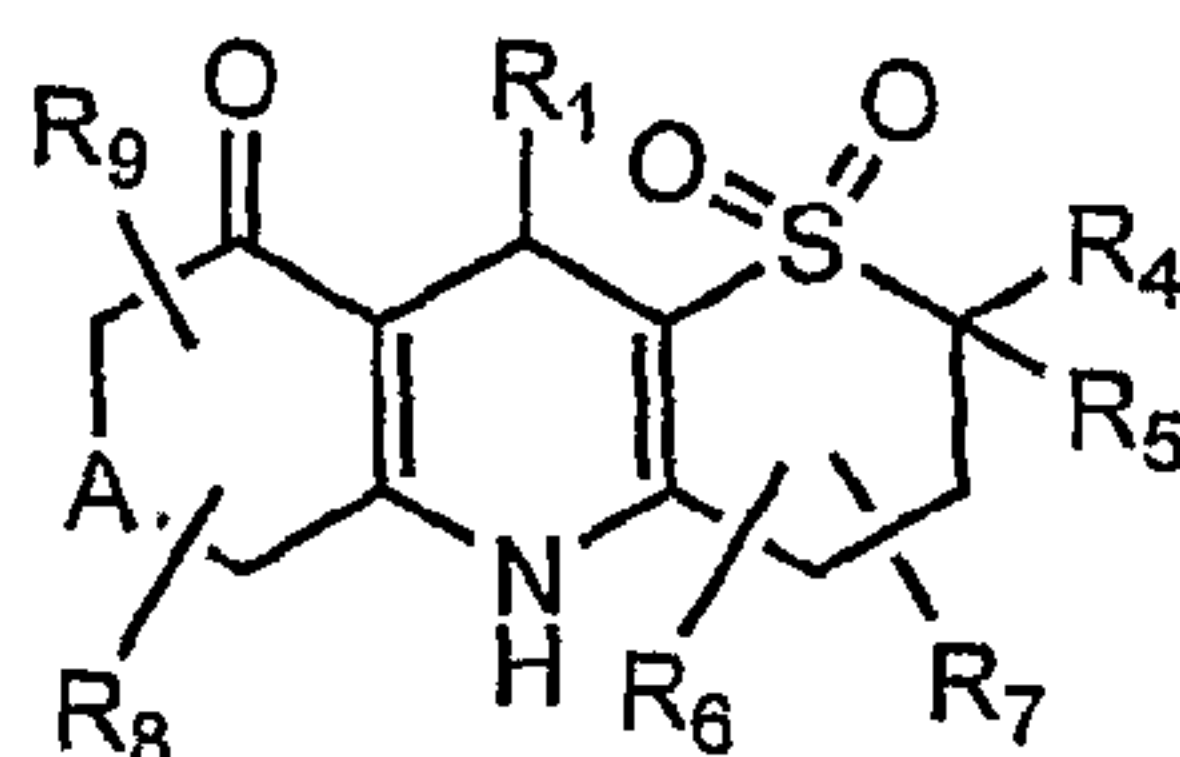
15 In another embodiment of the present invention, compounds have formula VII wherein, A is O; R₄ is hydrogen; R₅ is hydrogen; R₆ is hydrogen; R₇ is hydrogen; R₈ is hydrogen; R₉ is hydrogen; and R₁ is as defined in formula I.

In another embodiment of the present invention, compounds have formula VII wherein, A is O; R₄ is hydrogen; R₅ is hydrogen; R₆ is hydrogen; R₇ is hydrogen; R₈ is alkyl; R₉ is selected from hydrogen and alkyl; and R₁ is as defined in formula I.

20 In another embodiment of the present invention, compounds have formula VII wherein, A is S; and R₁, R₄, R₅, R₆, R₇, R₈, and R₉ are as defined in formula I.

13

In another embodiment, the present invention discloses compounds having formula VIII:



VIII,

5 or a pharmaceutically acceptable salt, ester, amide, or prodrug thereof wherein, A, R₁, R₄, R₅, R₆, R₇, R₈, and R₉, are as defined in formula I.

In another embodiment of the present invention, compounds have formula VIII wherein, A is NR₂; and R₁, R₂, R₄, R₅, R₆, R₇, R₈, and R₉ are as defined in formula I.

10 In another embodiment of the present invention, compounds have formula VIII wherein, A is NR₂; R₄ is hydrogen; R₅ is hydrogen; R₆ is hydrogen; R₇ is hydrogen; R₈ is hydrogen; R₉ is hydrogen; and R₁ and R₂ are as defined in formula I.

In another embodiment of the present invention, compounds have formula VIII wherein, A is O; and R₁, R₄, R₅, R₆, R₇, R₈, and R₉ are as defined in formula I.

15 In another embodiment of the present invention, compounds have formula VIII wherein, A is O; R₄ is hydrogen; R₅ is hydrogen; R₆ is hydrogen; R₇ is hydrogen; R₈ is hydrogen; R₉ is hydrogen; and R₁ is as defined in formula I.

In another embodiment of the present invention, compounds have formula VIII wherein, A is S; and R₁, R₄, R₅, R₆, R₇, R₈, and R₉ are as defined in formula I.

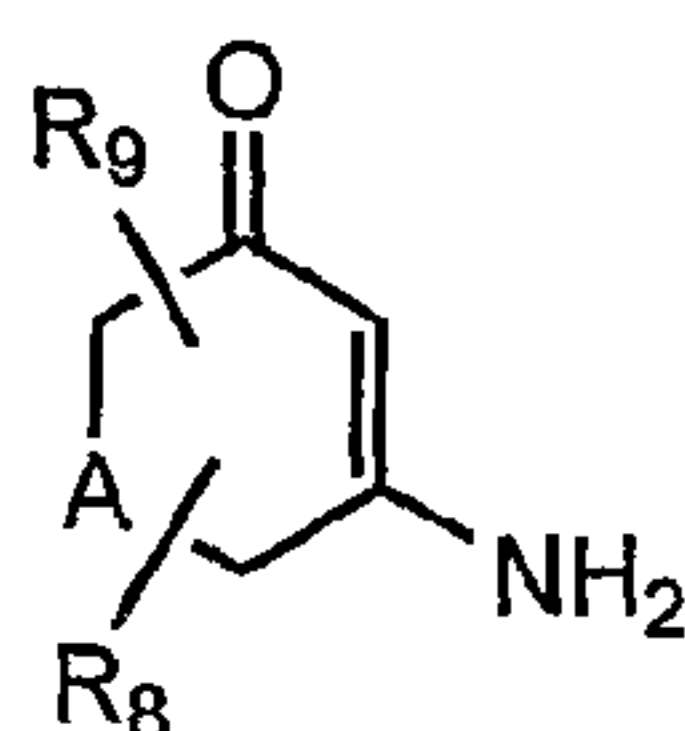
20 Another embodiment of the present invention relates to pharmaceutical compositions comprising a therapeutically effective amount of a compound of formula I-VIII or a pharmaceutically acceptable salt, ester, amide, or prodrug thereof in combination with a pharmaceutically acceptable carrier.

25 Another embodiment of the invention relates to a method of treating male sexual dysfunction including, but not limited, to male erectile dysfunction and premature ejaculation comprising administering a therapeutically effective amount of a compound of formula I-VIII or a pharmaceutically acceptable salt, ester, amide, or prodrug thereof.

Another embodiment of the invention relates to a method of treating female sexual dysfunction including, but not limited to, female anorgasmia, clitoral erectile insufficiency, vaginal engorgement, dyspareunia, and vaginismus comprising administering a therapeutically effective amount of a compound of formula I-VIII or a pharmaceutically acceptable salt, ester, amide, or prodrug thereof.

Yet another embodiment of the invention relates to a method of treating asthma, epilepsy, Raynaud's syndrome, migraine, pain, eating disorders, urinary incontinence, functional bowel disorders, neurodegeneration and stroke comprising administering a therapeutically effective amount of a compound of formula I-VIII or a pharmaceutically acceptable salt, ester, amide, or prodrug thereof.

The present invention utilizes novel intermediates for making compounds of formula I. In particular, an intermediate of formula IX may be used in the process of synthesizing compounds of formula I,



IX,

wherein A is selected from the group consisting of O, S, and NR₂, wherein R₂ is selected from the group consisting of hydrogen, alkoxyalkyl, alkyl, arylalkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, heterocyclealkyl, hydroxy, hydroxyalkyl, -NZ₁Z₂, and (NZ₁Z₂)alkyl wherein Z₁ and Z₂ are independently selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, aryl, arylalkyl, and formyl;

with the proviso that R₂ is other than benzyl; and

R₈ and R₉ are independently selected from the group consisting of hydrogen and alkyl or R₈ and R₉ together with the carbon atom to which they are attached form a 3-6 membered carbocyclic ring.

Definition of Terms

The term "alkenyl," as used herein, refers to a straight or branched chain hydrocarbon containing from 2 to 10 carbons and containing at least one carbon-carbon double bond formed by the removal of two hydrogens. Representative examples of alkenyl include, but are not limited to, ethenyl, 2-propenyl, 2-methyl-2-propenyl, 3-butenyl, 4-pentenyl, 5-hexenyl, 2-heptenyl, 2-methyl-1-heptenyl, 3-decenyl and the like.

The term "alkoxy," as used herein, refers to an alkyl group, as defined herein, appended to the parent molecular moiety through an oxy moiety, as defined herein. Representative examples of alkoxy include, but are not limited to, methoxy, ethoxy, propoxy, 2-propoxy, butoxy, tert-butoxy, pentyloxy, hexyloxy and the like.

The term "alkoxyalkoxy," as used herein, refers to an alkoxy group, as defined herein, appended to the parent molecular moiety through another alkoxy group, as defined herein. Representative examples of alkoxyalkoxy include, but are not limited to, tert-butoxymethoxy, 2-ethoxyethoxy, 2-methoxyethoxy, methoxymethoxy, and the like.

The term "alkoxyalkoxyalkyl," as used herein, refers to an alkoxyalkoxy group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of alkoxyalkoxyalkyl include, but are not limited to, tert-butoxymethoxymethyl, ethoxymethoxymethyl, (2-methoxyethoxy)methyl, 2-(2-methoxyethoxy)ethyl, and the like.

The term "alkoxyalkyl," as used herein, refers to an alkoxy group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of alkoxyalkyl include, but are not limited to, tert-butoxymethyl, 2-ethoxyethyl, 2-methoxyethyl, methoxymethyl, and the like.

The term "alkoxycarbonyl," as used herein, refers to an alkoxy group, as defined herein, appended to the parent molecular moiety through a carbonyl group, as defined herein. Representative examples of alkoxycarbonyl include, but are not limited to, methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl, and the like.

The term "alkoxycarbonylalkyl," as used herein, refers to an alkoxycarbonyl group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of alkoxycarbonylalkyl include, but are not

limited to, 3-methoxycarbonylpropyl, 4-ethoxycarbonylbutyl, 2-tert-butoxycarbonylethyl, and the like.

The term "alkyl," as used herein, refers to a straight or branched chain hydrocarbon containing from 1 to 10 carbon atoms. Representative examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, 3-methylhexyl, 2,2-dimethylpentyl, 2,3-dimethylpentyl, n-heptyl, n-octyl, n-nonyl, n-decyl, and the like.

The term "alkylcarbonyl," as used herein, refers to an alkyl group, as defined herein, appended to the parent molecular moiety through a carbonyl group, as defined herein. Representative examples of alkylcarbonyl include, but are not limited to, acetyl, 1-oxopropyl, 2,2-dimethyl-1-oxopropyl, 1-oxobutyl, 1-oxopentyl, and the like.

The term "alkylcarbonylalkyl," as used herein, refers to an alkylcarbonyl group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of alkylcarbonylalkyl include, but are not limited to, 2-oxopropyl, 3,3-dimethyl-2-oxopropyl, 3-oxobutyl, 3-oxopentyl, and the like.

The term "alkylcarbonyloxy," as used herein, refers to an alkylcarbonyl group, as defined herein, appended to the parent molecular moiety through an oxy moiety, as defined herein. Representative examples of alkylcarbonyloxy include, but are not limited to, acetyloxy, ethylcarbonyloxy, tert-butylcarbonyloxy, and the like.

The term "alkylsulfinyl," as used herein, refers to an alkyl group, as defined herein, appended to the parent molecular moiety through a sulfinyl group, as defined herein. Representative examples of alkylsulfinyl include, but are not limited, methylsulfinyl, ethylsulfinyl, and the like.

The term "alkylsulfonyl," as used herein, refers to an alkyl group, as defined herein, appended to the parent molecular moiety through a sulfonyl group, as defined herein. Representative examples of alkylsulfonyl include, but are not limited, methylsulfonyl, ethylsulfonyl, and the like.

The term "alkylthio," as used herein, refers to an alkyl group, as defined herein, appended to the parent molecular moiety through a thio moiety, as defined herein.

Representative examples of alkylthio include, but are not limited, methylsulfanyl, ethylsulfanyl, tert-butylsulfanyl, hexylsulfanyl, and the like.

The term "alkynyl," as used herein, refers to a straight or branched chain hydrocarbon group containing from 2 to 10 carbon atoms and containing at least one carbon-carbon triple bond. Representative examples of alkynyl include, but are not limited, to acetylenyl, 1-propynyl, 2-propynyl, 3-butynyl, 2-pentynyl, 1-butynyl and the like.

The term "aryl," as used herein, refers to a monocyclic carbocyclic ring system or a bicyclic carbocyclic fused ring system having one or more aromatic rings. Representative examples of aryl include, azulenyl, indanyl, indenyl, naphthyl, phenyl, tetrahydronaphthyl, and the like.

The aryl groups of this invention can be substituted with 1, 2, 3, 4, or 5 substituents independently selected from alkenyl, alkoxy, alkoxyalkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, alkylcarbonyloxy, alkylsulfinyl, alkylsulfonyl, alkylthio, alkynyl, aryl, azido, arylalkoxy, arylalkyl, aryloxy, carboxy, cyano, formyl, halogen, haloalkyl, haloalkoxy, hydroxy, hydroxyalkyl, mercapto, nitro, sulfo, sulfonate, $-NR_{80}R_{81}$ (wherein, R_{80} and R_{81} are independently selected from hydrogen, alkyl, alkylcarbonyl, aryl, arylalkyl and formyl), and $-C(O)NR_{82}R_{83}$ (wherein, R_{82} and R_{83} are independently selected from hydrogen, alkyl, aryl, and arylalkyl).

The term "arylalkoxy," as used herein, refers to an aryl group, as defined herein, appended to the parent molecular moiety through an alkoxy group, as defined herein. Representative examples of arylalkoxy include, but are not limited to, 2-phenylethoxy, 3-naphth-2-ylpropoxy, 5-phenylpentyloxy, and the like.

The term "arylalkoxycarbonyl," as used herein, refers to an arylalkoxy group, as defined herein, appended to the parent molecular moiety through a carbonyl group, as defined herein. Representative examples of arylalkoxycarbonyl include, but are not limited to, benzyloxycarbonyl, naphth-2-ylmethoxycarbonyl, and the like.

The term "arylalkyl," as used herein, refers to an aryl group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein.

Representative examples of arylalkyl include, but are not limited to, benzyl, 2-phenylethyl, 3-phenylpropyl, 2-naphth-2-ylethyl, and the like.

The term "arylcarbonyl," as used herein, refers to an aryl group, as defined herein, appended to the parent molecular moiety through a carbonyl group, as defined herein.

5 Representative examples of arylcarbonyl include, but are not limited to, benzoyl, naphthoyl, and the like.

The term "aryloxy," as used herein, refers to an aryl group, as defined herein, appended to the parent molecular moiety through an oxy moiety, as defined herein. Representative examples of aryloxy include, but are not limited to, phenoxy, naphthyloxy, 10 3-bromophenoxy, 4-chlorophenoxy, 4-methylphenoxy, 3,5-dimethoxyphenoxy, and the like.

The term "aryloxyalkyl," as used herein, refers to an aryloxy group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of aryloxyalkyl include, but are not limited to, 2-phenoxyethyl, 15 3-naphth-2-yloxypropyl, 3-bromophenoxyethyl, and the like.

The term "azido," as used herein, refers to a $-N_3$ group.

The term "carbonyl," as used herein, refers to a $-C(O)-$ group.

The term "carboxy," as used herein, refers to a $-CO_2H$ group.

The term "carboxyalkyl," as used herein, refers to a carboxy group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. 20 Representative examples of carboxyalkyl include, but are not limited to, carboxymethyl, 2-carboxyethyl, 3-carboxypropyl, and the like.

The term "cyano," as used herein, refers to a $-CN$ group.

The term "cyanoalkyl," as used herein, refers to a cyano group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. 25 Representative examples of cyanoalkyl include, but are not limited to, cyanomethyl, 2-cyanoethyl, 3-cyanopropyl, and the like.

The term "cycloalkyl," as used herein, refers to a saturated cyclic hydrocarbon group containing from 3 to 8 carbons. Representative examples of cycloalkyl include, but

are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl and the like.

The term "cycloalkylalkyl," as used herein, refers to cycloalkyl group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein.

5 Representative examples of cycloalkylalkyl include, but are not limited to, cyclopropylmethyl, 2-cyclobutylethyl, cyclopentylmethyl, cyclohexylmethyl, 4-cycloheptylbutyl, and the like.

The term "formyl," as used herein, refers to a -C(O)H group.

The term "halo" or "halogen," as used herein, refers to -Cl, -Br, -I or -F.

10 The term "haloalkoxy," as used herein, refers to at least one halogen, as defined herein, appended to the parent molecular moiety through an alkoxy group, as defined herein. Representative examples of haloalkoxy include, but are not limited to, chloromethoxy, 2,2,2-trifluoroethoxy, trifluoromethoxy, pentafluoroethoxy, and the like.

The term "haloalkyl," as used herein, refers to at least one halogen, as defined
15 herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of haloalkyl include, but are not limited to, chloromethyl, 2-fluoroethyl, trifluoromethyl, pentafluoroethyl, 2-chloro-3-fluoropentyl, and the like.

The term "heterocycle," as used herein, refers to a monocyclic- or a bicyclic-ring system. Monocyclic ring systems are exemplified by any 5- or 6-membered ring
20 containing 1, 2, 3, or 4 heteroatoms independently selected from oxygen, nitrogen and sulfur. The 5-membered ring has from 0-2 double bonds and the 6-membered ring has from 0-3 double bonds. Representative examples of monocyclic ring systems include, but are not limited to, azetidine, azepine, aziridine, diazepine, 1,3-dioxolane, dioxane, dithiane, furan, imidazole, imidazoline, imidazolidine, isothiazole, isothiazoline,
25 isothiazolidine, isoxazole, isoxazoline, isoxazolidine, morpholine, oxadiazole, oxadiazoline, oxadiazolidine, oxazole, oxazoline, oxazolidine, piperazine, piperidine, pyran, pyrazine, pyrazole, pyrazoline, pyrazolidine, pyridine, pyrimidine, pyridazine, pyrrole, pyrroline, pyrrolidine, tetrahydrofuran, tetrahydrothiophene, tetrazine, tetrazole, thiadiazole, thiadiazoline, thiadiazolidine, thiazole, thiazoline, thiazolidine, thiophene,
30 thiomorpholine, thiomorpholine sulfone, thiopyran, triazine, triazole, trithiane, and the

like. Bicyclic ring systems are exemplified by any of the above monocyclic ring systems fused to an aryl group as defined herein, a cycloalkyl group as defined herein, or another monocyclic ring system as defined herein. Representative examples of bicyclic ring systems include but are not limited to, for example, benzimidazole, benzothiazole, benzothiadiaazole, benzothiophene, benzoxadiazole, benzoxazole, benzofuran, benzopyran, benzothiopyran, benzodioxine, 1,3-benzodioxole, cinnoline, indazole, indole, indoline, indolizine, naphthyridine, isobenzofuran, isobenzothiophene, isoindole, isoindoline, isoquinoline, phthalazine, pyranopyridine, quinoline, quinolizine, quinoxaline, quinazoline, tetrahydroisoquinoline, tetrahydroquinoline, thiopyranopyridine, and the like.

The heterocycle groups of this invention can be substituted with 1, 2, or 3 substituents independently selected from alkenyl, alkoxy, alkoxyalkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, alkylcarbonyloxy, alkylsulfinyl, alkylsulfonyl, alkylthio, alkynyl, aryl, azido, arylalkoxy, arylalkoxycarbonyl, arylalkyl, aryloxy, carboxy, cyano, formyl, halogen, haloalkyl, haloalkoxy, hydroxy, hydroxyalkyl, mercapto, nitro, sulfo, sulfonate, $-NR_{80}R_{81}$ (wherein, R_{80} and R_{81} are independently selected from hydrogen, alkyl, alkylcarbonyl, aryl, arylalkyl and formyl), and $-C(O)NR_{82}R_{83}$ (wherein, R_{82} and R_{83} are independently selected from hydrogen, alkyl, aryl, and arylalkyl).

The term "heterocyclealkyl," as used herein, refers to a heterocycle, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of heterocyclealkyl include, but are not limited to, pyrid-3-ylmethyl, 2-pyrimidin-2-ylpropyl, and the like.

The term "hydroxy," as used herein, refers to an -OH group.

The term "hydroxyalkyl," as used herein, refers to a hydroxy group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of hydroxyalkyl include, but are not limited to, hydroxymethyl, 2-hydroxyethyl, 3-hydroxypropyl, 2-ethyl-4-hydroxyheptyl, and the like.

The term "lower alkyl," as used herein is a subset of alkyl and refers to a straight or branched chain hydrocarbon group containing from 1-to-4 carbon atoms. Representative examples of lower alkyl include, but are not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl,

iso-butyl, tert-butyl, and the like.

The term "mercapto" as used herein, refers to a -SH group.

The term "nitro", as used herein, refers to a -NO₂ group.

The term "N-protecting group" or "nitrogen protecting group," as used herein, refers
 5 to those groups intended to protect an amino group against undesirable reactions during
 synthetic procedures. N-protecting groups comprise carbamates, amides including those
 containing hetero arylgroups, N-alkyl derivatives, amino acetal derivatives, N-benzyl
 derivatives, imine derivatives, enamine derivatives and N-heteroatom derivatives. Preferred
 N-protecting groups are formyl, acetyl, benzoyl, pivaloyl, phenylsulfonyl, benzyl,
 10 triphenylmethyl (trityl), t-butyloxycarbonyl (Boc), benzyloxycarbonyl (Cbz), and the like.
 Commonly used N-protecting groups are disclosed in T.H. Green and P.G.M. Wuts,
 Protective Groups in Organic Synthesis, 2nd edition, John Wiley & Sons, New York (1991).

The term "-NZ₁N₂," as used herein, refers to two groups, Z₁ and Z₂, which are
 appended to the parent molecular moiety through a nitrogen atom. Z₁ and Z₂ are
 15 independently selected from hydrogen, alkyl, alkylcarbonyl, aryl, arylalkyl, and formyl.
 Representative examples of -NZ₁Z₂ include, but are not limited to, amino, benzylamino,
 methylamino, acetylamino, acetylmethylamino, and the like.

The term "(NZ₁Z₂)alkyl," as used herein, refers to a -NZ₁Z₂ group, as defined herein,
 appended to the parent molecular moiety through an alkyl group, as defined herein.
 20 Representative examples of (NZ₁Z₂)alkyl include, but are not limited to, aminomethyl,
 dimethylaminomethyl, 2(amino)ethyl, 2-(dimethylamino)ethyl, and the like.

The term "oxo," as used herein, refers to a =O moiety.

The term "oxy," as used herein, refers to a -O- moiety.

The term "sulfinyl," as used herein, refers to a -S(O)- group.

25 The term "sulfo," as used herein, refers to a -SO₃H group.

The term "sulfonate," as used herein, refers to -S(O)₂OR₉₆ group, wherein R₉₆ is
 selected from alkyl, aryl, and arylalkyl, as defined herein.

The term "sulfonyl," as used herein, refers to -SO₂- group.

The term "thio," as used herein, refers to a -S- moiety.

The term "pharmaceutically acceptable prodrugs" as used herein represents those prodrugs of the compounds of the present invention which are, within the scope of sound medical judgement, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the invention. Prodrugs of the present invention may be rapidly transformed in vivo to the parent compound of the above formula, for example, by hydrolysis in blood. A thorough discussion is provided in (T. Higuchi and V. Stella, Pro-drugs as Novel Delivery Systems, V. 14 of the A.C.S. Symposium Series, and in Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press (1987)).

The present invention contemplates pharmaceutically active metabolites formed by in vivo biotransformation of compounds of formula I-VIII. The term pharmaceutically active metabolite, as used herein, refers to a compound formed by the in vivo biotransformation of compounds of formula I-VIII. A thorough discussion of biotransformation is provided in Goodman and Gilman's, The Pharmacological Basis of Therapeutics, seventh edition.

Compounds of the present invention may exist as stereoisomers wherein asymmetric or chiral centers are present. These stereoisomers are "R" or "S" depending on the configuration of substituents around the chiral carbon atom. The present invention contemplates various stereoisomers and mixtures thereof. Stereoisomers include enantiomers and diastereomers, and mixtures of enantiomers or diastereomers. Individual stereoisomers of compounds of the present invention may be prepared synthetically from commercially available starting materials which contain asymmetric or chiral centers or by preparation of racemic mixtures followed by resolution well-known to those of ordinary skill in the art. These methods of resolution are exemplified by (1) attachment of a mixture of enantiomers to a chiral auxiliary, separation of the resulting mixture of diastereomers by recrystallization or chromatography and liberation of the optically pure product from the auxiliary or (2) direct separation of the mixture of optical enantiomers on chiral chromatographic columns.

Preferred compounds of formula I include, but are not limited to:

5-[3-(2-furyl)-4-methylphenyl]-5,10-dihydro-1H,3H-dipyrano[3,4-b:4,3-e]pyridine-4,6(7H,9H)-dione,

5-[3-chloro-4-(trifluoromethyl)phenyl]-5,10-dihydro-1H,3H-dipyrano[3,4-b:4,3-e]pyridine-4,6(7H,9H)-dione,

9-(3-bromo-4-fluorophenyl)-2,3,5,6,7,9-hexahydro-1H-pyrrolo[3,4-b][1,7]naphthyridine-1,8(4H)-dione,

5-(3-bromo-4-fluorophenyl)-5,8,9,10-tetrahydro-1H-thiopyrano[3,4-b][1,7]naphthyridine-4,6(3H,7H)-dione,

5-(3-bromo-4-fluorophenyl)-5,10-dihydro-1H,3H-dithiopyrano[3,4-b:4,3-e]pyridine-4,6(7H,9H)-dione,

9-(3-bromo-4-fluorophenyl)-5,9-dihydro-3H-furo[3,4-b]thiopyrano[4,3-e]pyridine-1,8(4H,7H)-dione,

9-(3-bromo-4-fluorophenyl)-2,3,5,9-tetrahydropyrrolo[3,4-b]thiopyrano[4,3-e]pyridine-1,8(4H,7H)-dione,

10-(3-bromo-4-fluorophenyl)-3,4,6,7,8,10-hexahydropyrido[3,4-b][1,6]naphthyridine-1,9(2H,5H)-dione,

10-(3-bromo-4-fluorophenyl)-3,4,6,7,8,10-hexahydro-1H-pyrano[4,3-b][1,7]naphthyridine-1,9(5H)-dione,

10-(3-bromo-4-fluorophenyl)-3,4,6,10-tetrahydrodipyrano[3,4-b:3,4-e]pyridine-1,9(5H,8H)-dione,

10-(3-bromo-4-fluorophenyl)-3,4,6,10-tetrahydro-2H-thiopyrano[3,4-b][1,6]naphthyridine-1,9(5H,8H)-dione,

10-(3-bromo-4-fluorophenyl)-3,4,6,10-tetrahydropyrano[4,3-b]thiopyrano[4,3-e]pyridine-1,9(5H,8H)-dione,

5-(3-bromo-4-fluorophenyl)-7,7-dimethyl-2,3,5,8,9,10-hexahydrobenzo[b][1,7]naphthyridine-4,6(1H,7H)-dione,

9-(3-bromo-4-fluorophenyl)-2,3,5,9-tetrahydro-4H-thieno[3,2-b]thiopyrano[4,3-e]pyridin-8(7H)-one 1,1-dioxide,

10-(3-bromo-4-fluorophenyl)-3,4,6,10-tetrahydro-2H,5H-dithiopyrano[3,2-b:4,3-e]pyridin-9(8H)-one 1,1-dioxide, and

5-(3-bromo-4-fluorophenyl)-7,7-dimethyl-5,8,9,10-tetrahydro-1H-thiopyrano[3,4-b]quinoline-4,6(3H,7H)-dione or a pharmaceutically acceptable salt, ester, amide, or
5 prodrug thereof.

More preferred compounds of formula I include, but are not limited to:

5-(3-bromo-4-fluorophenyl)-5,10-dihydro-1H,3H-dipyran[3,4-b:4,3-e]pyridine-4,6(7H,9H)-dione;

5-(3-bromo-4-fluorophenyl)-2,3,5,8,9,10-hexahydrobenzo[b][1,7]naphthyridine-4,6(1H,7H)-dione;

5-(3-bromo-4-fluorophenyl)-2-methyl-2,3,5,8,9,10-hexahydrobenzo[b][1,7]naphthyridine-4,6(1H,7H)-dione;

5-(3-bromo-4-fluorophenyl)-2,3,5,8,9,10-hexahydropyrido[3,4-b][1,7]naphthyridine-4,6(1H,7H)-dione;

15 (-)-5-(3-bromo-4-fluorophenyl)-2,3,5,7,8,9-hexahydro-1H-cyclopenta[b][1,7]naphthyridine-4,6-dione;

(+)-5-(3-bromo-4-fluorophenyl)-2,3,5,7,8,9-hexahydro-1H-cyclopenta[b][1,7]naphthyridine-4,6-dione;

20 (-)-5-(3-bromo-4-fluorophenyl)-2,3,5,8,9,10-hexahydrobenzo[b][1,7]naphthyridine-4,6(1H,7H)-dione;

(+)-5-(3-bromo-4-fluorophenyl)-2,3,5,8,9,10-hexahydrobenzo[b][1,7]naphthyridine-4,6(1H,7H)-dione;

10-(3-bromo-4-fluorophenyl)-3,4,6,7,8,10-hexahydro-2H-thiopyrano[3,2-b][1,7]naphthyridin-9(5H)-one 1,1-dioxide;

25 9-(3-bromo-4-fluorophenyl)-2,3,5,6,7,9-hexahydrothieno[3,2-b][1,7]naphthyridin-8(4H)-one 1,1-dioxide;

9-(3-bromo-4-fluorophenyl)-2,3,5,9-tetrahydro-4H-pyrano[3,4-b]thieno[2,3-e]pyridin-8(7H)-one 1,1-dioxide;

30 (+)-9-(3-bromo-4-fluorophenyl)-2,3,5,9-tetrahydro-4H-pyrano[3,4-b]thieno[2,3-e]pyridin-8(7H)-one 1,1-dioxide;

(-)-9-(3-bromo-4-fluorophenyl)-2,3,5,9-tetrahydro-4H-pyrano[3,4-b]thieno[2,3-e]pyridin-8(7H)-one 1,1-dioxide;

9-(3-cyanophenyl)-2,3,5,9-tetrahydro-4H-pyrano[3,4-b]thieno[2,3-e]pyridin-8(7H)-one 1,1-dioxide;

5 (+) 9-(3-cyanophenyl)-2,3,5,9-tetrahydro-4H-pyrano[3,4-b]thieno[2,3-e]pyridin-8(7H)-one 1,1-dioxide;

(-) 9-(3-cyanophenyl)-2,3,5,9-tetrahydro-4H-pyrano[3,4-b]thieno[2,3-e]pyridin-8(7H)-one 1,1-dioxide;

10 9-(4-chloro-3-nitrophenyl)-2,3,5,9-tetrahydro-4H-pyrano[3,4-b]thieno[2,3-e]pyridin-8(7H)-one 1,1-dioxide;

(+)-9-(4-chloro-3-nitrophenyl)-2,3,5,9-tetrahydro-4H-pyrano[3,4-b]thieno[2,3-e]pyridin-8(7H)-one 1,1-dioxide;

(-)-9-(4-chloro-3-nitrophenyl)-2,3,5,9-tetrahydro-4H-pyrano[3,4-b]thieno[2,3-e]pyridin-8(7H)-one 1,1-dioxide;

15 5-(3-bromo-4-fluorophenyl)-5,8,9,10-tetrahydro-1H-pyrano[3,4-b]quinoline-4,6(3H,7H)-dione;

10-(3-bromo-4-fluorophenyl)-3,4,6,10-tetrahydro-2H,5H-pyrano[3,4-b]thiopyrano[2,3-e]pyridin-9(8H)-one 1,1-dioxide;

20 5-(3-bromo-4-fluorophenyl)-5,10-dihydro-1H,3H-pyrano[3,4-b]thiopyrano[4,3-e]pyridine-4,6(7H,9H)-dione;

5-(3-bromo-4-fluorophenyl)-5,7,8,9-tetrahydrocyclopenta[b]pyrano[4,3-e]pyridine-4,6(1H,3H)-dione;

5-(3-bromo-4-fluorophenyl)-5,8,9,10-tetrahydro-1H-pyrano[3,4-b][1,7]naphthyridine-4,6(3H,7H)-dione;

25 9-(3-bromo-4-fluorophenyl)-5,9-dihydro-3H-furo[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione;

9-(3-bromo-4-fluorophenyl)-2-methyl-2,3,5,9-tetrahydropyrano[3,4-b]pyrrolo[3,4-e]pyridine-1,8(4H,7H)-dione;

30 9-(3-bromo-4-fluorophenyl)-2,3,5,9-tetrahydropyrano[3,4-b]pyrrolo[3,4-e]pyridine-1,8(4H,7H)-dione;

5-(4-chloro-3-nitrophenyl)-5,10-dihydro-1H,3H-dipyrano[3,4-b:4,3-e]pyridine-4,6(7H,9H)-dione;

5-(3-cyanophenyl)-5,10-dihydro-1H,3H-dipyrano[3,4-b:4,3-e]pyridine-4,6(7H,9H)-dione;

5 5-(4-fluoro-3-iodophenyl)-5,10-dihydro-1H,3H-dipyrano[3,4-b:4,3-e]pyridine-4,6(7H,9H)-dione;

5-(5-bromo-2-hydroxyphenyl)-5,10-dihydro-1H,3H-dipyrano[3,4-b:4,3-e]pyridine-4,6(7H,9H)-dione;

10 5-[4-fluoro-3-(trifluoromethyl)phenyl]-5,10-dihydro-1H,3H-dipyrano[3,4-b:4,3-e]pyridine-4,6(7H,9H)-dione;

5-(3,4-dichlorophenyl)-5,10-dihydro-1H,3H-dipyrano[3,4-b:4,3-e]pyridine-4,6(7H,9H)-dione;

5-(2,1,3-benzoxadiazol-5-yl)-5,10-dihydro-1H,3H-dipyrano[3,4-b:4,3-e]pyridine-4,6(7H,9H)-dione;

15 5-(5-nitro-2-thienyl)-5,10-dihydro-1H,3H-dipyrano[3,4-b:4,3-e]pyridine-4,6(7H,9H)-dione;

5-(5-nitro-3-thienyl)-5,10-dihydro-1H,3H-dipyrano[3,4-b:4,3-e]pyridine-4,6(7H,9H)-dione;

20 (+) 9-(4-fluoro-3-iodophenyl)-2,3,5,9-tetrahydro-4H-pyrano[3,4-b]thieno[2,3-e]pyridin-8(7H)-one 1,1-dioxide;

(-) 9-(4-fluoro-3-iodophenyl)-2,3,5,9-tetrahydro-4H-pyrano[3,4-b]thieno[2,3-e]pyridin-8(7H)-one 1,1-dioxide;

(+) 5-(3-chloro-4-fluorophenyl)-2,3,5,7,8,9-hexahydro-1H-cyclopenta[b][1,7]naphthyridine-4,6-dione;

25 (-) 5-(3-chloro-4-fluorophenyl)-2,3,5,7,8,9-hexahydro-1H-cyclopenta[b][1,7]naphthyridine-4,6-dione;

9-(3-bromo-4-fluorophenyl)-5,6,7,9-tetrahydrofuro[3,4-b][1,7]naphthyridine-1,8(3H,4H)-dione;

30 (+) 9-(3-bromo-4-fluorophenyl)-5,6,7,9-tetrahydrofuro[3,4-b][1,7]naphthyridine-1,8(3H,4H)-dione;

(-) 9-(3-bromo-4-fluorophenyl)-5,6,7,9-tetrahydrofuro[3,4-b][1,7]naphthyridine-1,8(3H,4H)-dione;

5-(3-bromo-4-fluorophenyl)-7,7-dimethyl-5,8,9,10-tetrahydro-1H-pyrano[3,4-b]quinoline-4,6(3H,7H)-dione;

5 (9R)-9-(3-bromo-4-fluorophenyl)-5,9-dihydro-3H-furo[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione;

(9S)-9-(3-bromo-4-fluorophenyl)-5,9-dihydro-3H-furo[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione;

10 10-(3-chloro-4-fluorophenyl)-3,4,6,10-tetrahydro-2H-pyrano[3,4-b][1,6]naphthyridine-1,9(5H,8H)-dione;

10-(3,4-dichlorophenyl)-3,4,6,10-tetrahydro-2H-pyrano[3,4-b][1,6]naphthyridine-1,9(5H,8H)-dione;

10-[4-chloro-3-(trifluoromethyl)phenyl]-3,4,6,10-tetrahydro-2H-pyrano[3,4-b][1,6]naphthyridine-1,9(5H,8H)-dione;

15 10-(4-chloro-3-nitrophenyl)-3,4,6,10-tetrahydro-2H-pyrano[3,4-b][1,6]naphthyridine-1,9(5H,8H)-dione;

10-(3,4-dibromophenyl)-3,4,6,10-tetrahydro-2H-pyrano[3,4-b][1,6]naphthyridine-1,9(5H,8H)-dione;

20 10-(5-nitro-3-thienyl)-3,4,6,10-tetrahydro-2H-pyrano[3,4-b][1,6]naphthyridine-1,9(5H,8H)-dione;

5-(3-bromo-4-fluorophenyl)-5,8,9,10-tetrahydro-1H-thiopyrano[3,4-b]quinoline-4,6(3H,7H)-dione;

5-(3-bromo-4-fluorophenyl)-5,7,8,9-tetrahydrocyclopenta[b]thiopyrano[4,3-e]pyridine-4,6(1H,3H)-dione;

25 10-(3-bromo-4-fluorophenyl)-3,4,6,10-tetrahydro-2H-pyrano[3,4-b][1,6]naphthyridine-1,9(5H,8H)-dione;

5-(3-bromo-4-methylphenyl)-5,10-dihydro-1H,3H-dipyran[3,4-b:4,3-e]pyridine-4,6(7H,9H)-dione;

30 5-(3-iodo-4-methylphenyl)-5,10-dihydro-1H,3H-dipyran[3,4-b:4,3-e]pyridine-4,6(7H,9H)-dione;

5-(3,4-dibromophenyl)-5,10-dihydro-1H,3H-dipyrano[3,4-b:4,3-e]pyridine-4,6(7H,9H)-dione;

5-[4-chloro-3-(trifluoromethyl)phenyl]-5,10-dihydro-1H,3H-dipyrano[3,4-b:4,3-e]pyridine-4,6(7H,9H)-dione;

5 5-[4-fluoro-3-(2-furyl)phenyl]-5,10-dihydro-1H,3H-dipyrano[3,4-b:4,3-e]pyridine-4,6(7H,9H)-dione;

5-(5-bromo-4-fluoro-2-hydroxyphenyl)-5,10-dihydro-1H,3H-dipyrano[3,4-b:4,3-e]pyridine-4,6(7H,9H)-dione;

10 5-(4-methyl-3-nitrophenyl)-5,10-dihydro-1H,3H-dipyrano[3,4-b:4,3-e]pyridine-4,6(7H,9H)-dione;

5-(4-bromo-3-chlorophenyl)-5,10-dihydro-1H,3H-dipyrano[3,4-b:4,3-e]pyridine-4,6(7H,9H)-dione;

5-(3-bromo-4-chlorophenyl)-5,10-dihydro-1H,3H-dipyrano[3,4-b:4,3-e]pyridine-4,6(7H,9H)-dione;

15 5-[3-iodo-4-(trifluoromethyl)phenyl]-5,10-dihydro-1H,3H-dipyrano[3,4-b:4,3-e]pyridine-4,6(7H,9H)-dione;

5-[3-bromo-4-(trifluoromethyl)phenyl]-5,10-dihydro-1H,3H-dipyrano[3,4-b:4,3-e]pyridine-4,6(7H,9H)-dione;

20 5-(4-fluoro-3-isopropenylphenyl)-5,10-dihydro-1H,3H-dipyrano[3,4-b:4,3-e]pyridine-4,6(7H,9H)-dione;

5-(4-fluorophenyl)-5,10-dihydro-1H,3H-dipyrano[3,4-b:4,3-e]pyridine-4,6(7H,9H)-dione;

5-(3-bromo-4-fluorophenyl)-3,3,7,7-tetramethyl-5,10-dihydro-1H,3H-dipyrano[3,4-b:4,3-e]pyridine-4,6(7H,9H)-dione;

25 5-(3-bromo-4-fluorophenyl)-3,3-dimethyl-5,10-dihydro-1H,3H-dipyrano[3,4-b:4,3-e]pyridine-4,6(7H,9H)-dione;

9-(3-bromo-4-methylphenyl)-5,9-dihydro-3H-furo[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione;

30 9-(3-iodo-4-methylphenyl)-5,9-dihydro-3H-furo[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione;

9-(4-fluoro-3-iodophenyl)-5,9-dihydro-3H-furo[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione;

9-(3,4-dibromophenyl)-5,9-dihydro-3H-furo[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione;

5 9-(3,4-dichlorophenyl)-5,9-dihydro-3H-furo[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione;

9-[4-chloro-3-(trifluoromethyl)phenyl]-5,9-dihydro-3H-furo[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione;

10 9-(3-bromo-4-chlorophenyl)-5,9-dihydro-3H-furo[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione;

9-(4-methyl-3-nitrophenyl)-5,9-dihydro-3H-furo[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione;

9-[3-(2-furyl)-4-methylphenyl]-5,9-dihydro-3H-furo[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione;

15 9-[4-fluoro-3-(2-furyl)phenyl]-5,9-dihydro-3H-furo[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione;

(9S)-9-(4-fluoro-3-iodophenyl)-5,9-dihydro-3H-furo[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione;

20 (9R)-9-(4-fluoro-3-iodophenyl)-5,9-dihydro-3H-furo[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione;

(9R)-9-(3-bromo-4-methylphenyl)-5,9-dihydro-3H-furo[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione;

(9S)-9-(3-bromo-4-methylphenyl)-5,9-dihydro-3H-furo[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione;

25 (+) 9-(3-iodo-4-methylphenyl)-5,9-dihydro-3H-furo[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione;

(-) 9-(3-iodo-4-methylphenyl)-5,9-dihydro-3H-furo[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione;

30 (trans)-9-(3-bromo-4-fluorophenyl)-7-methyl-5,9-dihydro-3H-furo[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione;

(cis)-9-(3-bromo-4-fluorophenyl)-7-methyl-5,9-dihydro-3H-furo[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione;

9-(3-bromo-4-fluorophenyl)-7,7-dimethyl-2,3,5,9-tetrahydro-4H-pyrano[3,4-b]thieno[2,3-e]pyridin-8(7H)-one 1,1-dioxide;

5 5-(3-bromo-4-fluorophenyl)-3,3-dimethyl-5,7,8,9-tetrahydrocyclopenta[b]pyrano[4,3-e]pyridine-4,6(1H,3H)-dione;

(trans)-9-(3-bromo-4-fluorophenyl)-5-methyl-5,9-dihydro-3H-furo[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione;

10 (cis)-9-(3-bromo-4-fluorophenyl)-5-methyl-5,9-dihydro-3H-furo[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione;

(trans)-9-(3-bromo-4-fluorophenyl)-3-methyl-5,9-dihydro-3H-furo[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione;

(cis)-9-(3-bromo-4-fluorophenyl)-3-methyl-5,9-dihydro-3H-furo[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione;

15 9-(3-bromo-4-fluorophenyl)-7,7-dimethyl-5,9-dihydro-3H-furo[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione;

spiro[5-(3-bromo-4-fluorophenyl)-5,10-dihydro-1H,3H-dipyrano[3,4-b:4,3-e]pyridine-4,6(7H,9H)-dione-3,1'-cyclopentane];

20 5-(3-bromo-4-fluorophenyl)-3,3-diethyl-5,10-dihydro-1H,3H-dipyrano[3,4-b:4,3-e]pyridine-4,6(7H,9H)-dione;

(cis)-9-(3-bromo-4-fluorophenyl)-3-ethyl-5,9-dihydro-3H-furo[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione;

(trans)-9-(3-bromo-4-fluorophenyl)-3-ethyl-5,9-dihydro-3H-furo[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione;

25 (cis)-9-(3-bromo-4-fluorophenyl)-3-propyl-5,9-dihydro-3H-furo[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione;

(trans)-9-(3-bromo-4-fluorophenyl)-3-propyl-5,9-dihydro-3H-furo[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione;

30 9-(3-bromo-4-fluorophenyl)-3,3-dimethyl-5,9-dihydro-3H-furo[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione;

(+) (cis)-9-(3-bromo-4-fluorophenyl)-3-methyl-5,9-dihydro-3H-furo[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione; and

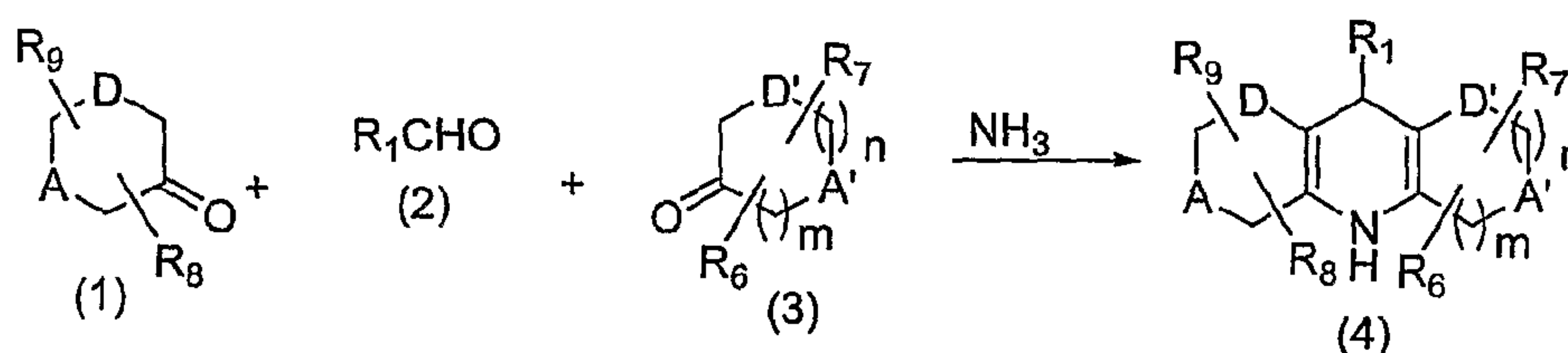
(-) (cis)-9-(3-bromo-4-fluorophenyl)-3-methyl-5,9-dihydro-3H-furo[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione or a pharmaceutically acceptable salt, ester, amide, or prodrug thereof.

Preparation of Compounds of The Invention

The following Schemes and Examples are intended as an illustration of and not a limitation upon the scope of the invention as defined in the appended claims.

The compounds of this invention can be prepared by a variety of synthetic routes. Representative procedures are shown in Schemes 1-58. Further, all citations herein are incorporated by reference.

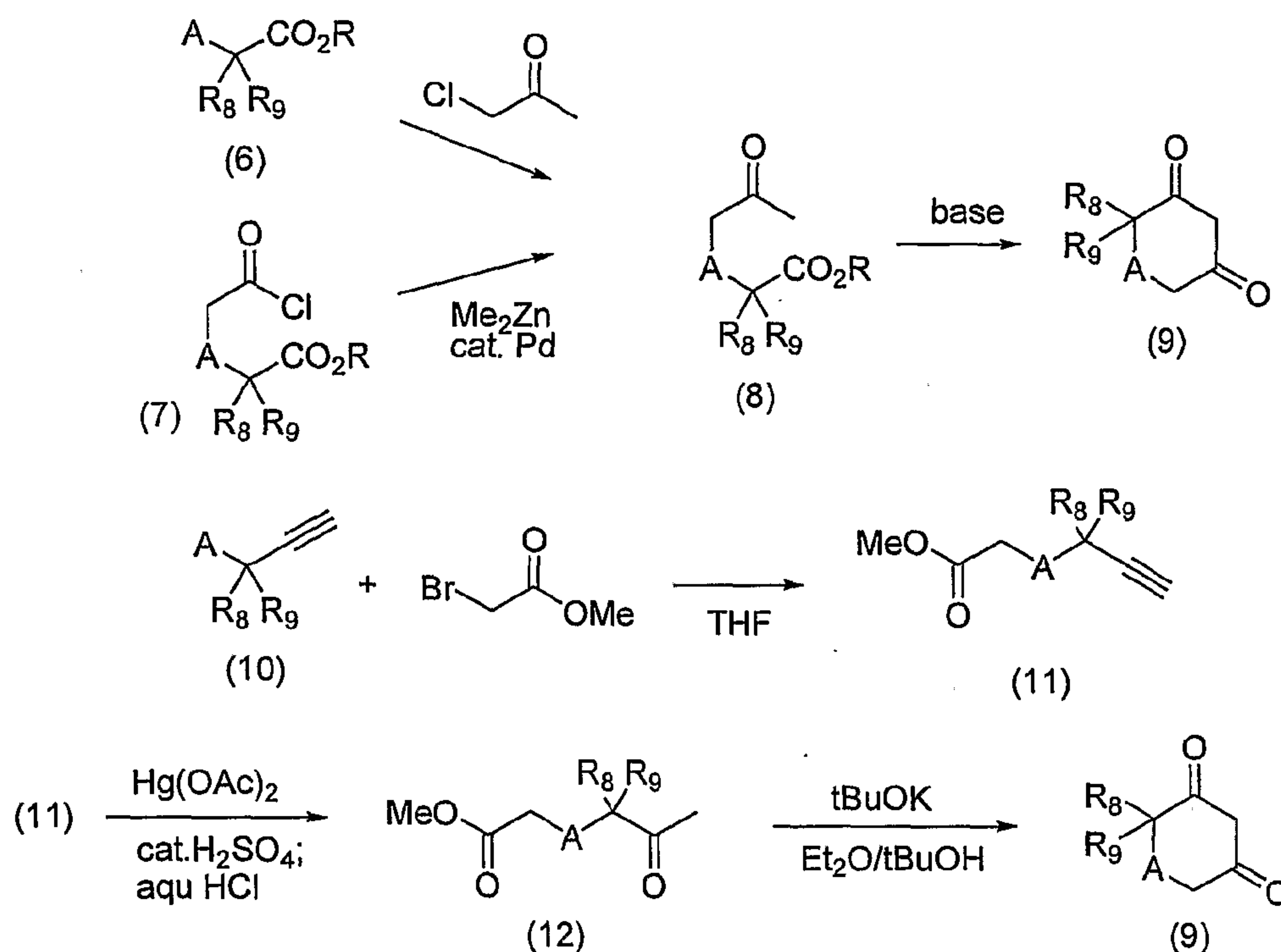
Scheme 1



Dihydropyridines of general formula (4), wherein A, A', D, D', R₁, R₆, R₇, R₈, R₉, m and n are as defined in formula I, can be prepared as described in Scheme 1. Carbonyl compounds of general formula (1), aldehydes of general formula (2), and carbonyl compounds of general formula (3) can be combined in the presence of ammonia with heating in a solvent such as ethanol to provide dihydropyridines of general formula (4).

32

Scheme 2



Dicarbonyl compounds of general formula (9), wherein R_8 , R_9 , and A are as defined in formula I, can be prepared as described in Scheme 2. Esters of general formula (6), wherein A is selected from S or NR_2 and wherein R_2 is as defined in formula I, can be alkylated with chloroacetone to provide ketoesters of general formula (8). Ketoesters of general formula (8) can be cyclized in the presence of a base such as potassium tert-butoxide to provide dicarbonyl compounds of general formula (9). An alternative method of preparing ketoesters of general formula (8) can also be used. Acid chlorides of general formula (7), wherein A is O , prepared as described in (Terasawa, J. Org. Chem. (1977), 42, 1163-1169), can be treated with dimethyl zinc in the presence of a palladium catalyst to provide ketoesters of general formula (8).

An alternative method of preparing dicarbonyl compounds of general formula (9) can be used as described in Scheme 2. Alkynes of general formula (10) can be treated with methyl bromoacetate to provide ethers of general formula (11). A base such as sodium hydride may be necessary when A is O or S . Alkynes of general formula (11) can be treated with a catalyst such as mercuric acetate in the presence of a catalytic amount of sulfuric acid with heating in a solvent such as methanol followed by treatment with

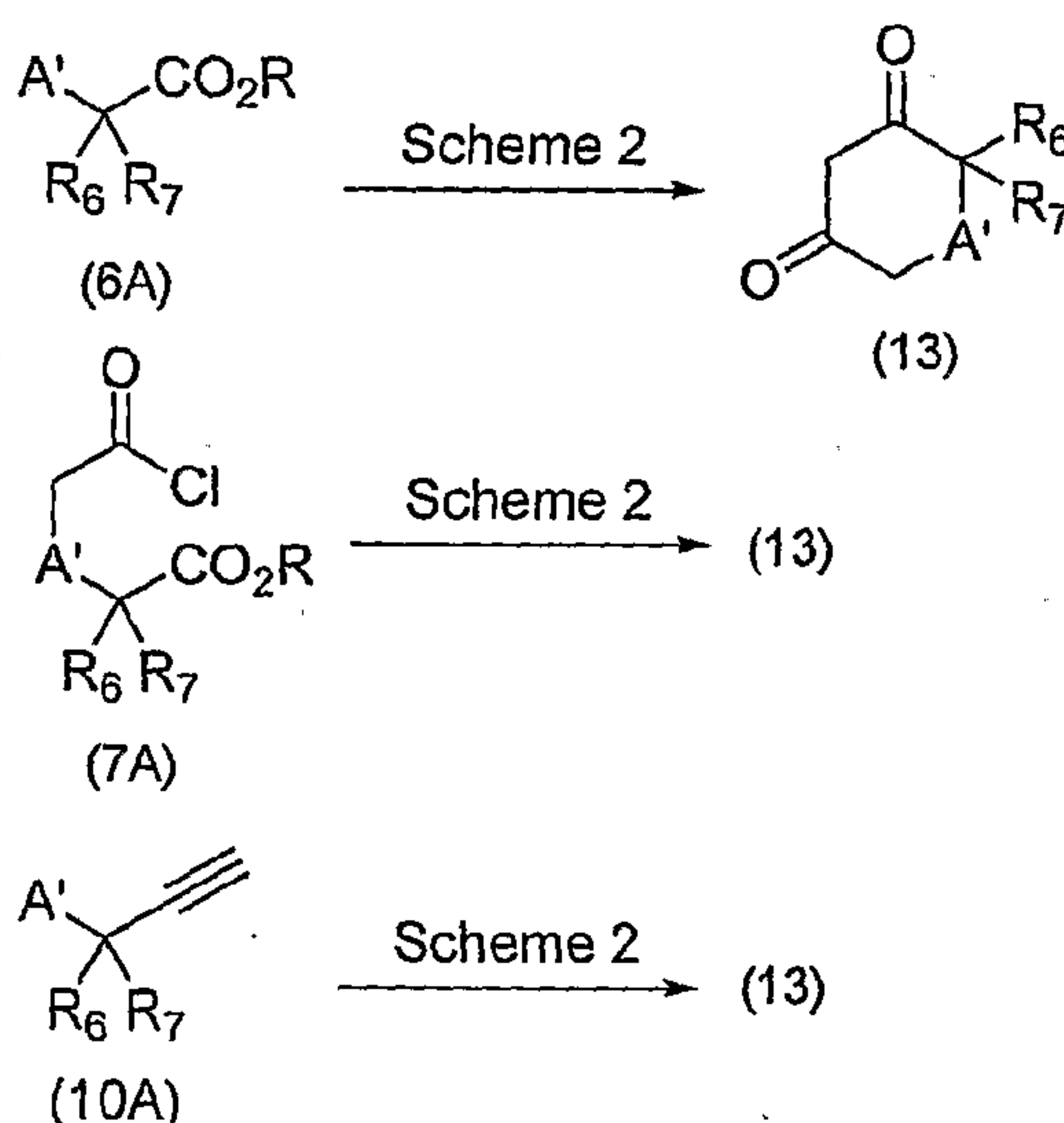
aqueous acid to provide methyl ketones of general formula (12). Methyl ketones of general formula (12) can be treated with a base such as potassium tert-butoxide to provide dicarbonyl compounds of general formula (9).

Alkynes of general formula (10), wherein A = O, can be purchased or prepared by reaction of a nucleophilic source of acetylene such as ethynylmagnesium bromide or lithium acetylide with an appropriate ketone or aldehyde.

Chiral alkynes of general formula (10), wherein A = O, can also be purchased or generated by known methods (Midland, M. Tetrahedron (1984), 40, 1371-1380; Smith, R. J. Med. Chem. (1988), 31, 1558-1566) and then processed to provide chiral dicarbonyl compounds of general formula (9).

Dicarbonyl compounds of general formula (9) may also be prepared using the procedures described in (Ziegler, J. Amer. Chem. Soc. (1973), 95, 7458-7464; Terasawa, T., Journal of Organic Chemistry 42 (1977) 1163; Fehnel, J. Amer. Chem. Soc., (1955), 77, 4241-4242; Morgan, J. Amer. Chem. Soc. (1957), 79, 422; and Er, Helv. Chim. Acta, (1992), 75, 2265-2269).

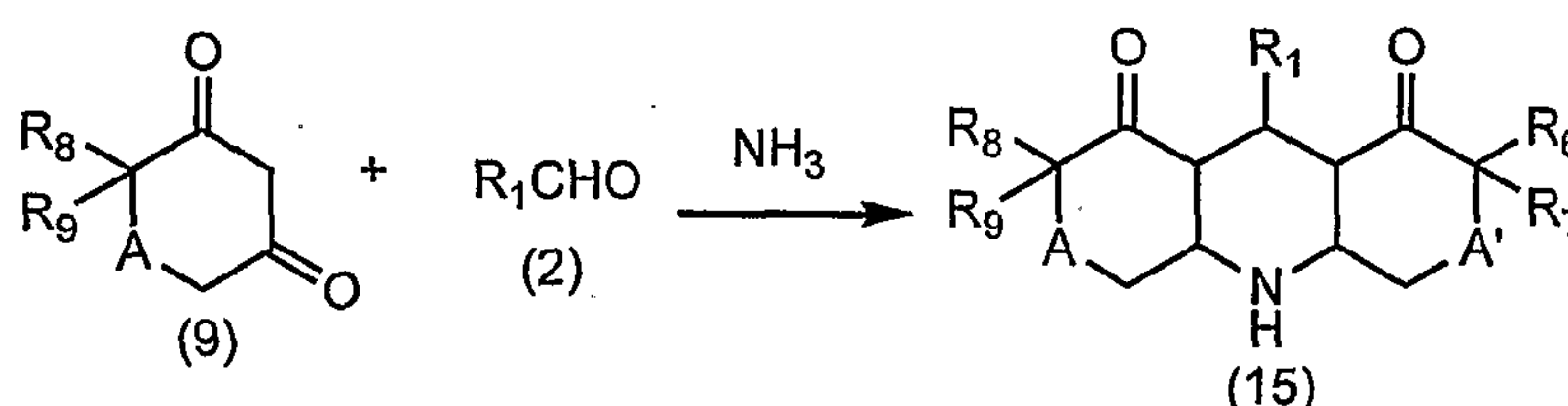
Scheme 3



Dicarbonyl compounds of general formula (13), wherein R₆ and R₇ are defined as in formula I and A' is selected from O, S, and NR₃ wherein R₃ is selected from alkoxyalkyl, alkyl, arylalkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, heterocyclealkyl,

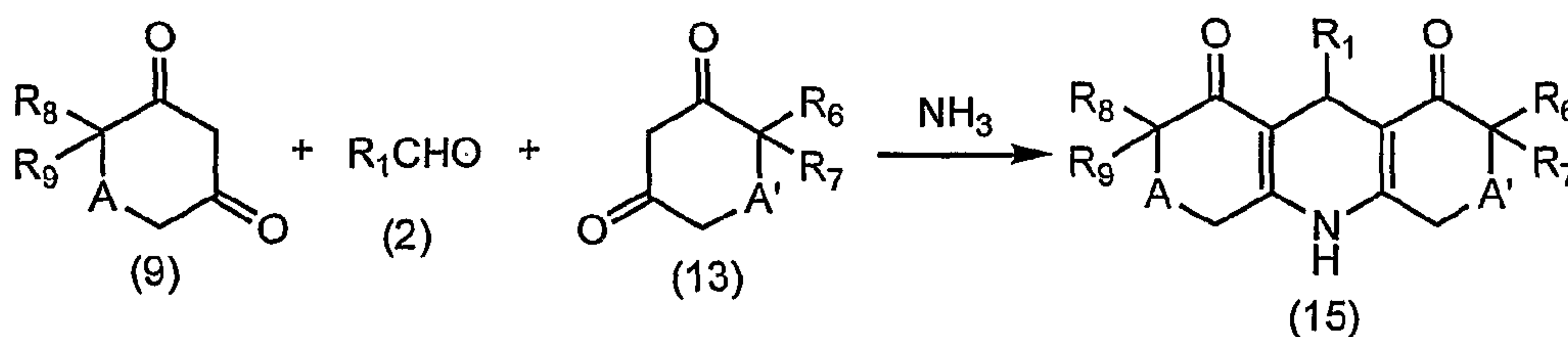
hydroxyalkyl, $-NZ_1Z_2$, and (NZ_1Z_2) alkyl wherein Z_1 and Z_2 are independently selected from the group consisting of alkyl, alkylcarbonyl, aryl, arylalkyl, and formyl, can be prepared as described in Scheme 3. Compounds of general formulas (6A), (7A) and (10A) can be processed as described in Scheme 2 to provide dicarbonyl compounds of general formula (13).

Scheme 4



Symmetrical dihydropyridines of formula (15), wherein $A=A'$, $R_6=R_8$, and $R_7=R_9$, and A , R_1 , R_6 , and R_7 are as defined in formula I, can be prepared as described in Scheme 4. Two equivalents of dicarbonyl compounds of general formula (9) can be treated with aldehydes of general formula (2) and one equivalent of ammonia with heating in a solvent such as ethanol to provide symmetrical dihydropyridines of general formula (15).

Scheme 5

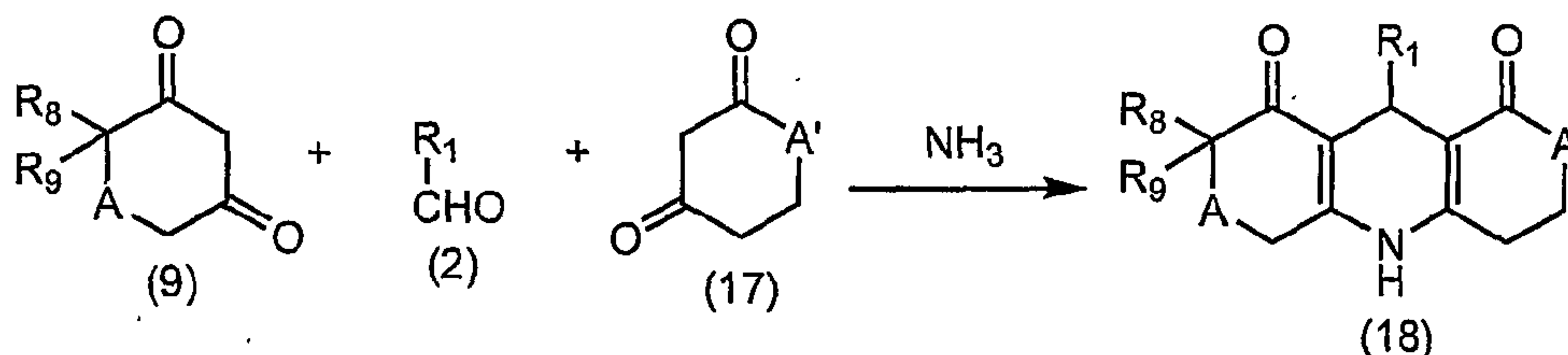


Dihydropyridines of general formula (15), wherein A , A' , R_1 , R_6 , R_7 , R_8 , and R_9 are as defined in formula I, can be prepared as described in Scheme 5. One of the dicarbonyl components (9) or (13) can be treated with ammonia followed by addition of aldehydes of general formula (2) and the other dicarbonyl compound (9) or (13) with heating to provide dihydropyridines of general formula (15).

When R_6 and R_7 are not equivalent or R_8 and R_9 are not equivalent, a mixture of diastereomers results. These diastereomers, as well as diastereomers described in Schemes to follow, can be separated by methods known to those skilled in the art.

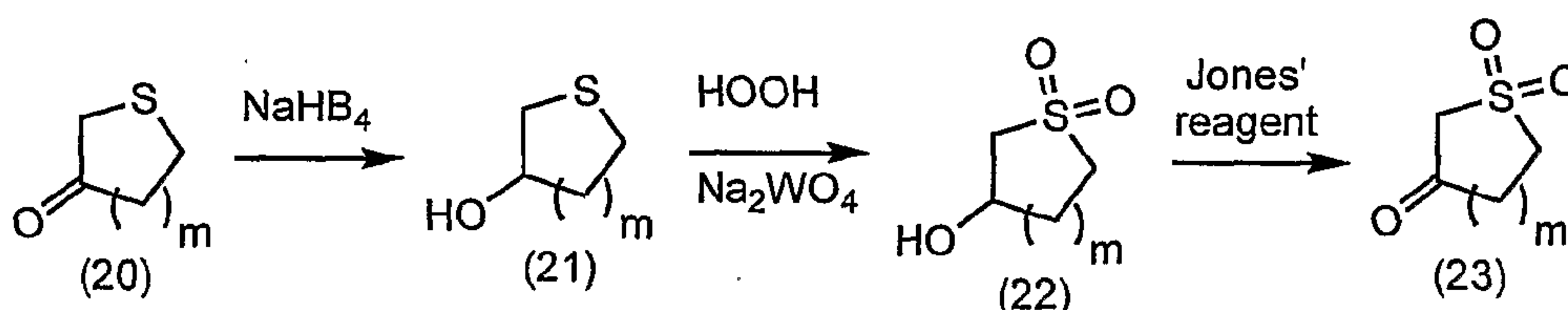
35

Scheme 6



Dihydropyridines of general formula (18), wherein A , A' , R_1 , R_8 , and R_9 are as defined in formula I, can be prepared as described in Scheme 6. One of the dicarbonyl components (9) or (17) can be treated with ammonia followed by addition of aldehydes of general formula (2) and the other dicarbonyl compound (9) or (17) with heating to provide dihydropyridines of general formula (18). Dicarbonyl compounds of general formula (17) can be prepared as described in (d'Angelo, Tett. Lett. (1991), 32, 3063-3066; Nakagawa, Heterocycles (1979), 13, 477-495).

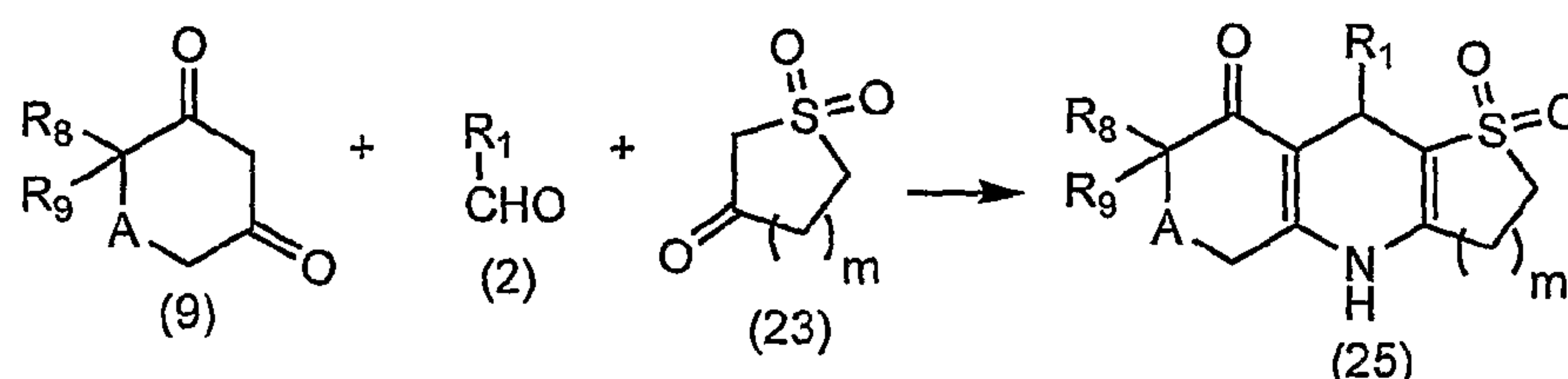
Scheme 7



Ketosulfones of general formula (23), wherein m is 1 or 2, can be prepared as described in Scheme 7. Reduction of ketone (20) with sodium borohydride (or the like) in a solvent such as ethanol provides alcohol (21) which can be oxidized to the corresponding sulfone (22) using an oxidizing agent such as hydrogen peroxide catalyzed by sodium tungstate. Oxidation of (22) using Jones' reagent or the like provides the desired keto sulfone (23).

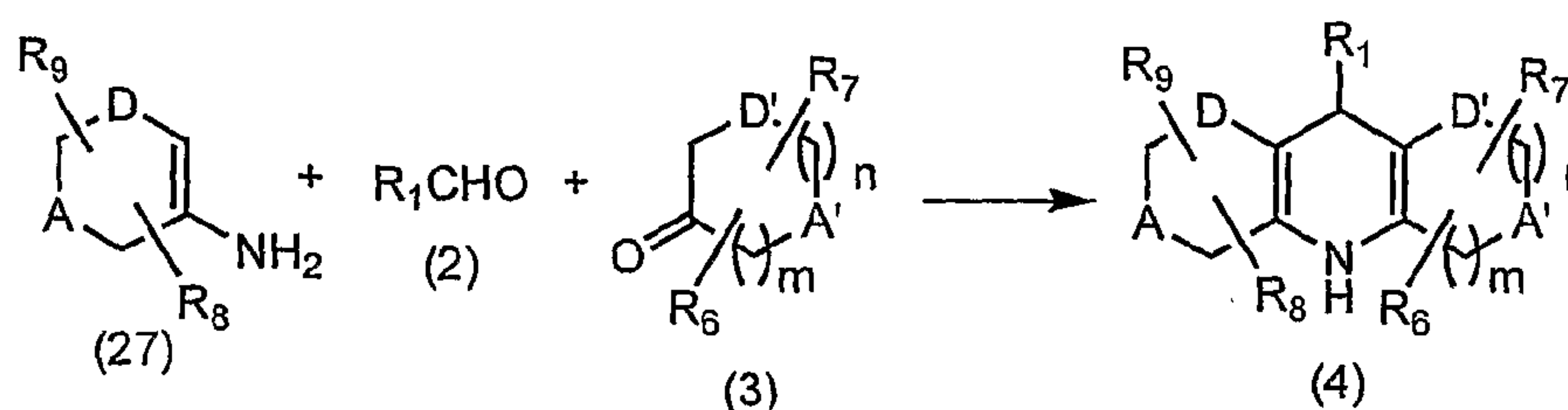
36

Scheme 8



Dihydropyridines of general formula (25), wherein A, m, R₁, R₈, and R₉ are as defined in formula I, can be prepared as described in Scheme 8. Dicarbonyl compounds of general formula (9) can be treated with ammonia, followed by addition of (2) and ketosulfone (23) with heating in a solvent such as ethanol to provide dihydropyridines of general formula (25). An additional heating step, with an acid such as HCl, may be required to drive the reaction to completion.

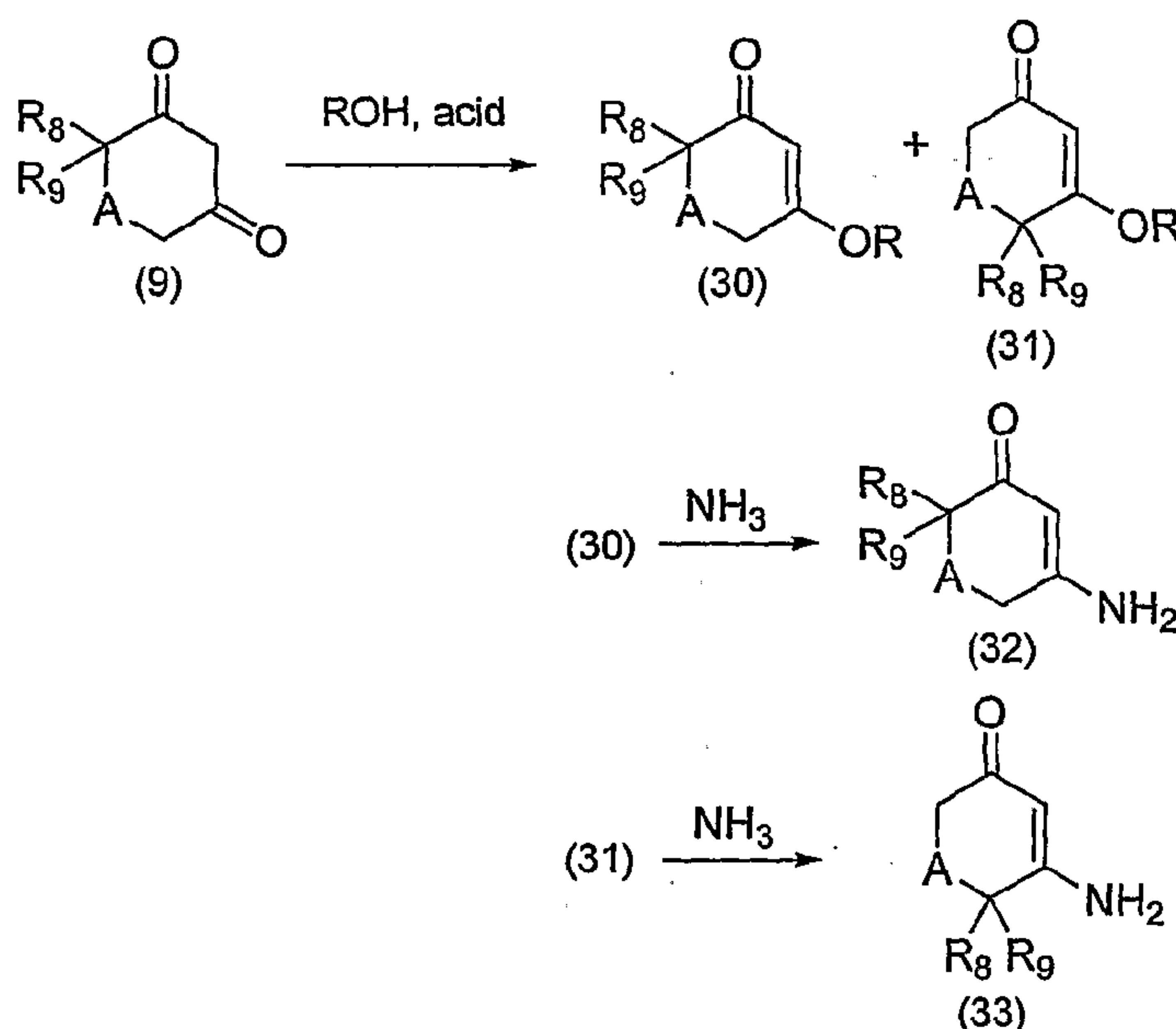
Scheme 9



An alternate method of preparing dihydropyridines of general formula (4), wherein A, A', D, D', R₁, R₆, R₇, R₈, R₉, m and n are as defined in formula I, can be used as described in Scheme 9. Enamines of general formula (27) can be treated with aldehydes (2) and carbonyl compounds (3) with heating in a solvent such as ethanol to provide dihydropyridines of general formula (4).

37

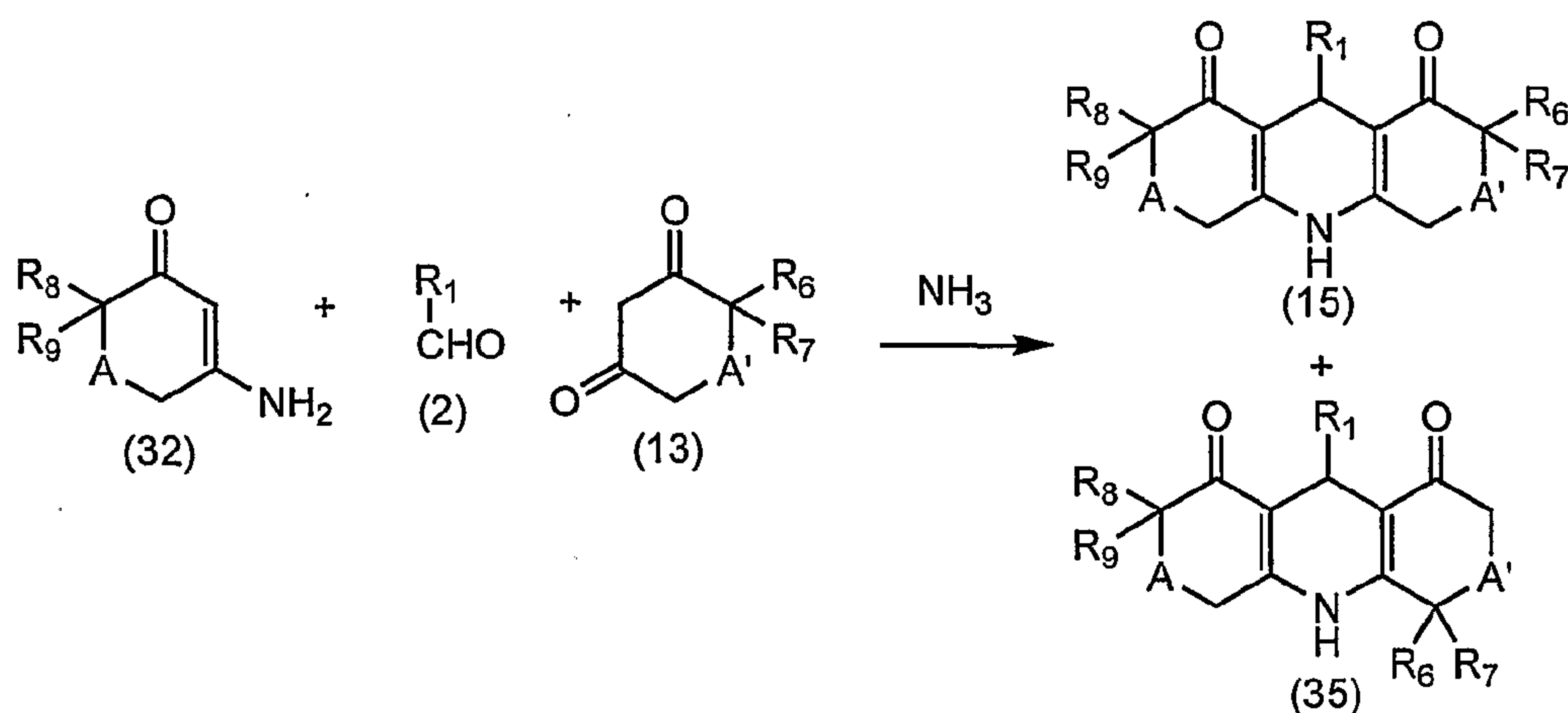
Scheme 10



Enaminones of general formula (32) and (33), wherein A , R_8 , and R_9 are as defined in formula I, can be prepared as described in Scheme 10. Dicarbonyl compounds (9) can be treated with an alcohol such as ethyl alcohol in the presence of an acid catalyst such as para-toluenesulfonic acid to provide vinyl ethers of general formula (30) and (31), wherein R is lower alkyl. Vinyl ethers of general formula (30) and (31) can be separated by a separatory method such as chromatography. Vinyl ethers of general formula (30) can be treated with ammonia in a solvent such as methanol to provide enaminones of general formula (32). Vinyl ethers of general formula (31) can be treated with ammonia in a solvent such as methanol to provide enaminones of general formula (33).

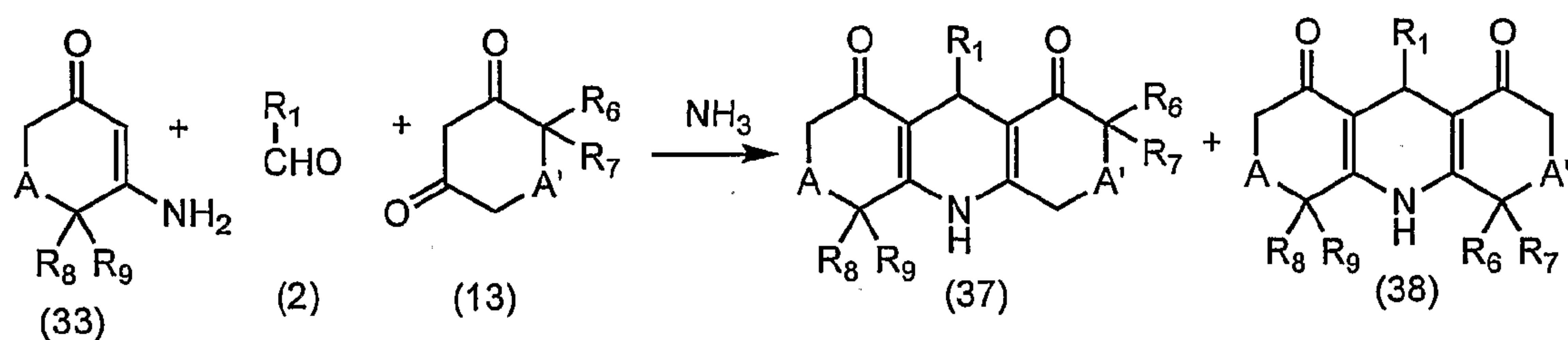
38

Scheme 11



A method of preparing dihydropyridines of general formula (15) and (35), wherein A, A', R₁, R₆, R₇, R₈ and R₉ are as defined in formula I, can be used as described in Scheme 11. Enaminones of general formula (32) can be treated with aldehydes of general formula (2) and dicarbonyls of general formula (13) with heating in a solvent such as ethanol to provide dihydropyridines of general formula (15) and (35).

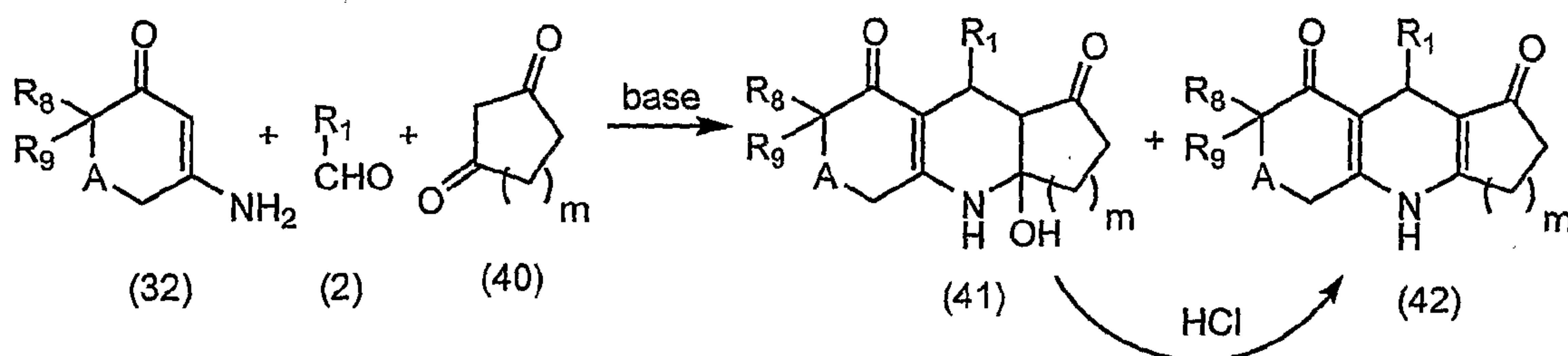
Scheme 12



A method of preparing dihydropyridines of general formula (37) and (38), wherein A, A', R₁, R₆, R₇, R₈ and R₉ are as defined in formula I, can be used as described in Scheme 12. Enaminones of general formula (33) can be treated with aldehydes (2) and dicarbonyls (13) with heating in a solvent such as ethanol to provide dihydropyridines of general formula (37) and (38).

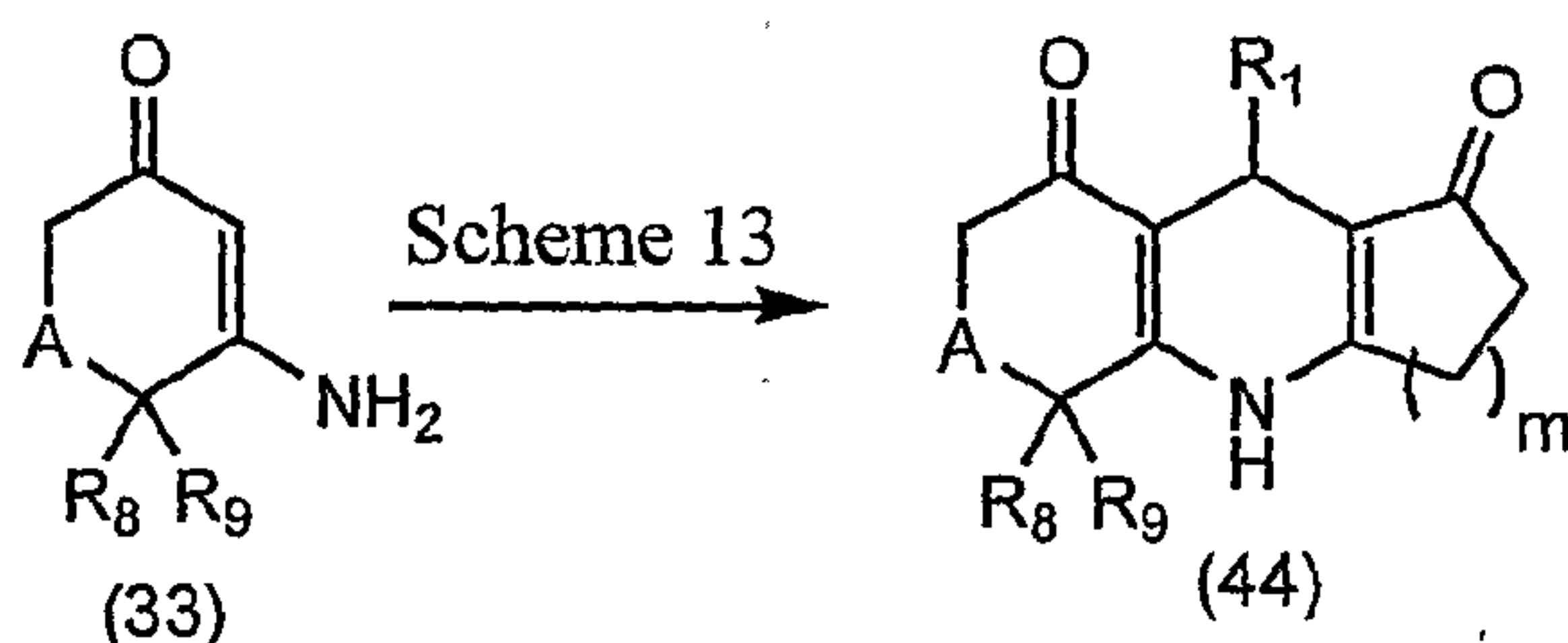
39

Scheme 13



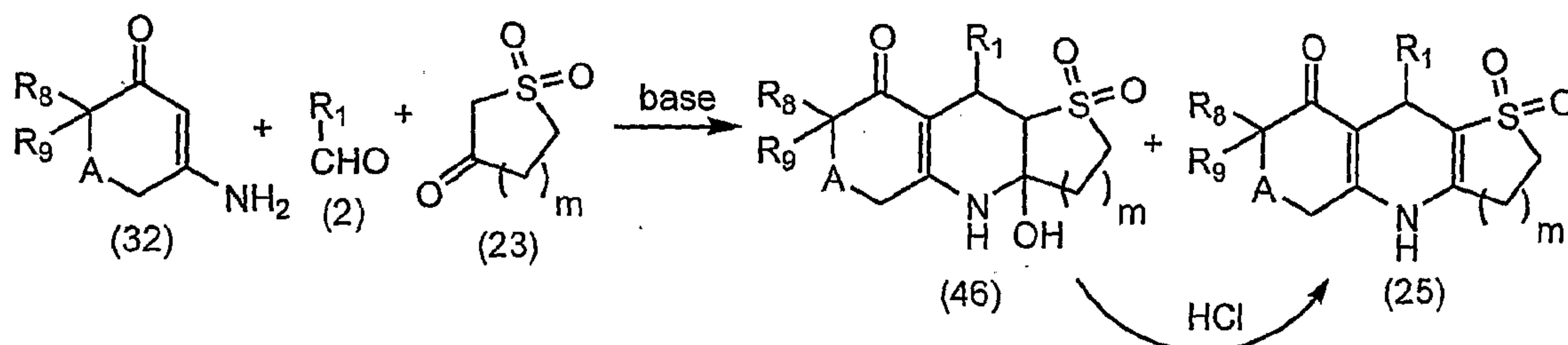
Dihydropyridines of general formula (42), wherein A, R₁, R₈ and R₉ and m are as defined in formula I, can be prepared as described in Scheme 13. Enaminones of general formula (32) can be treated with aldehydes (2) and dicarbonyl compounds of general formula (40) with heating in a solvent such as ethanol in the presence of a base such as triethylamine to provide a mixture of hemiaminals of general formula (41) and dihydropyridines of general formula (42). Hemiaminals (41) can be treated with heat in the presence of an acid such as HCl in a solvent such as ethanol to provide dihydropyridines of general formula (42).

Scheme 14



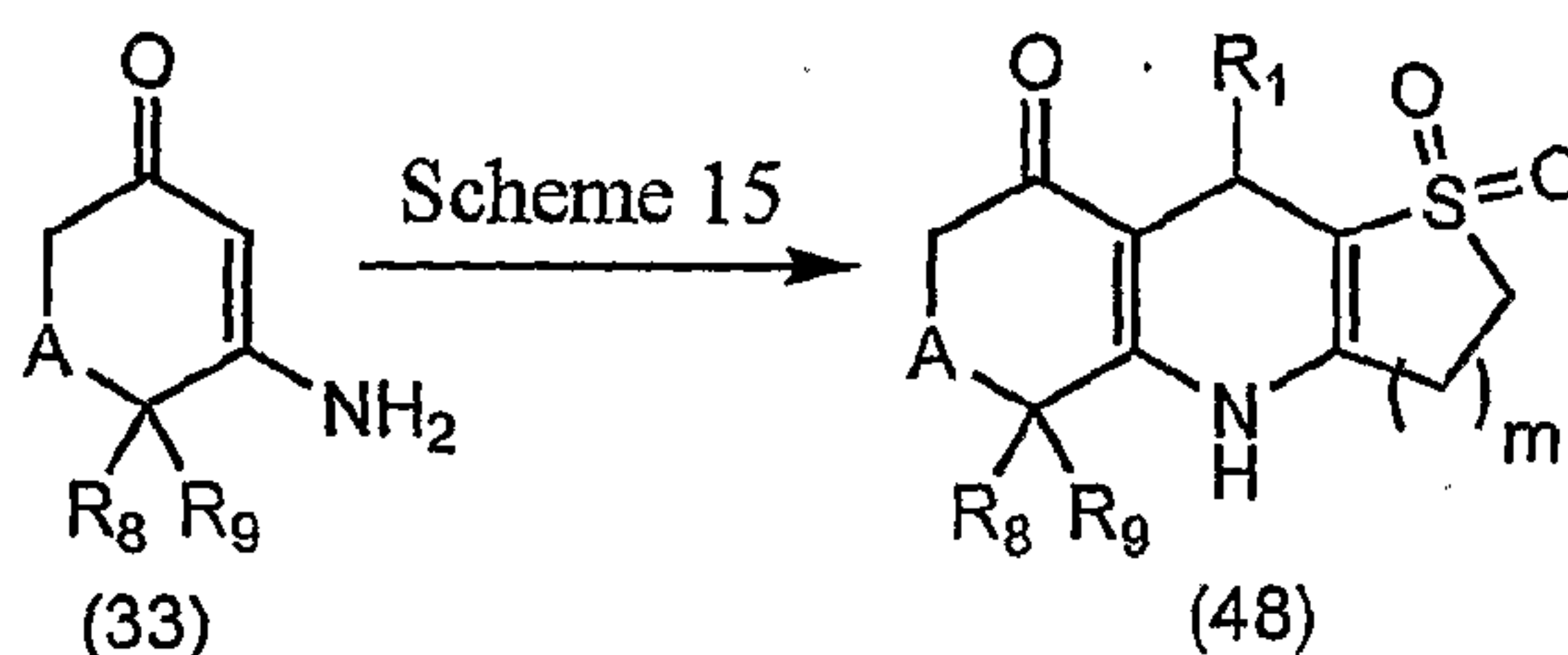
Dihydropyridines of general formula (44), wherein A, R₁, R₈ and R₉ and m are as defined in formula I, can be prepared as described in Scheme 14. Enaminones of general formula (33) can be processed as described in Scheme 13 to provide dihydropyridines of general formula (44).

Scheme 15



An alternate method of preparing dihydropyridines of general formula (25), wherein A, R₁, R₈ and R₉ and m are as defined in formula I, can be used as described in Scheme 15. Enaminones of general formula (32) can be treated with aldehydes (2) and ketosulfones (23) with heating in a solvent such as ethanol in the presence of a base such as triethylamine to provide hemiaminals of general formula (46) and dihydropyridines of general formula (25). Hemiaminals (46) can be treated with heat in the presence of an acid such as HCl in a solvent such as ethanol to provide dihydropyridines of general formula (25).

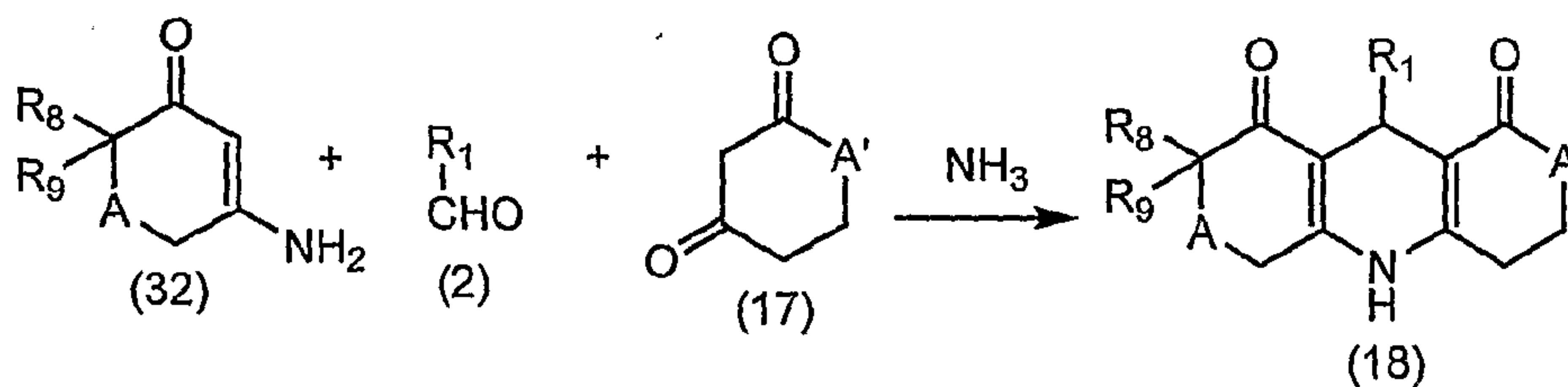
Scheme 16



A method of preparing dihydropyridines of general formula (48), wherein A, R₁, R₈ and R₉ and m are as defined in formula I, can be used as described in Scheme 16.

Enaminones of general formula (33) can be processed as described in Scheme 15 to provide dihydropyridines of general formula (48).

Scheme 17



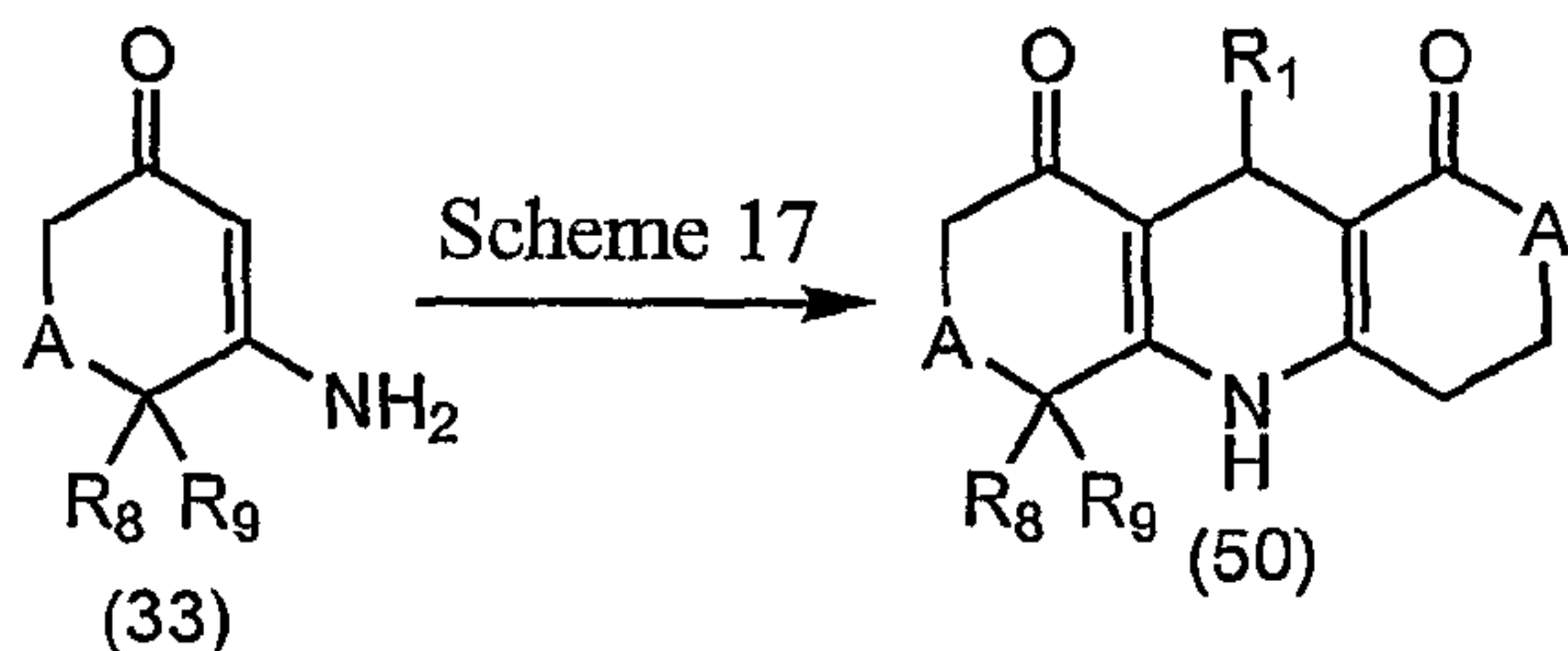
An alternate method of preparing dihydropyridines of general formula (18), wherein A, A', and R₁, R₈ and R₉ are as defined in formula I, can be used as described in Scheme 17. Enaminones of general formula (32) can be treated with aldehydes (2) and dicarbonyls of general formula (17) with heating in a solvent such as ethanol in the

41

presence of a base such as triethylamine to provide dihydropyridines of general formula (18). An additional heating step, with an acid such as HCl, may be required to drive the reaction to completion.

5

Scheme 18

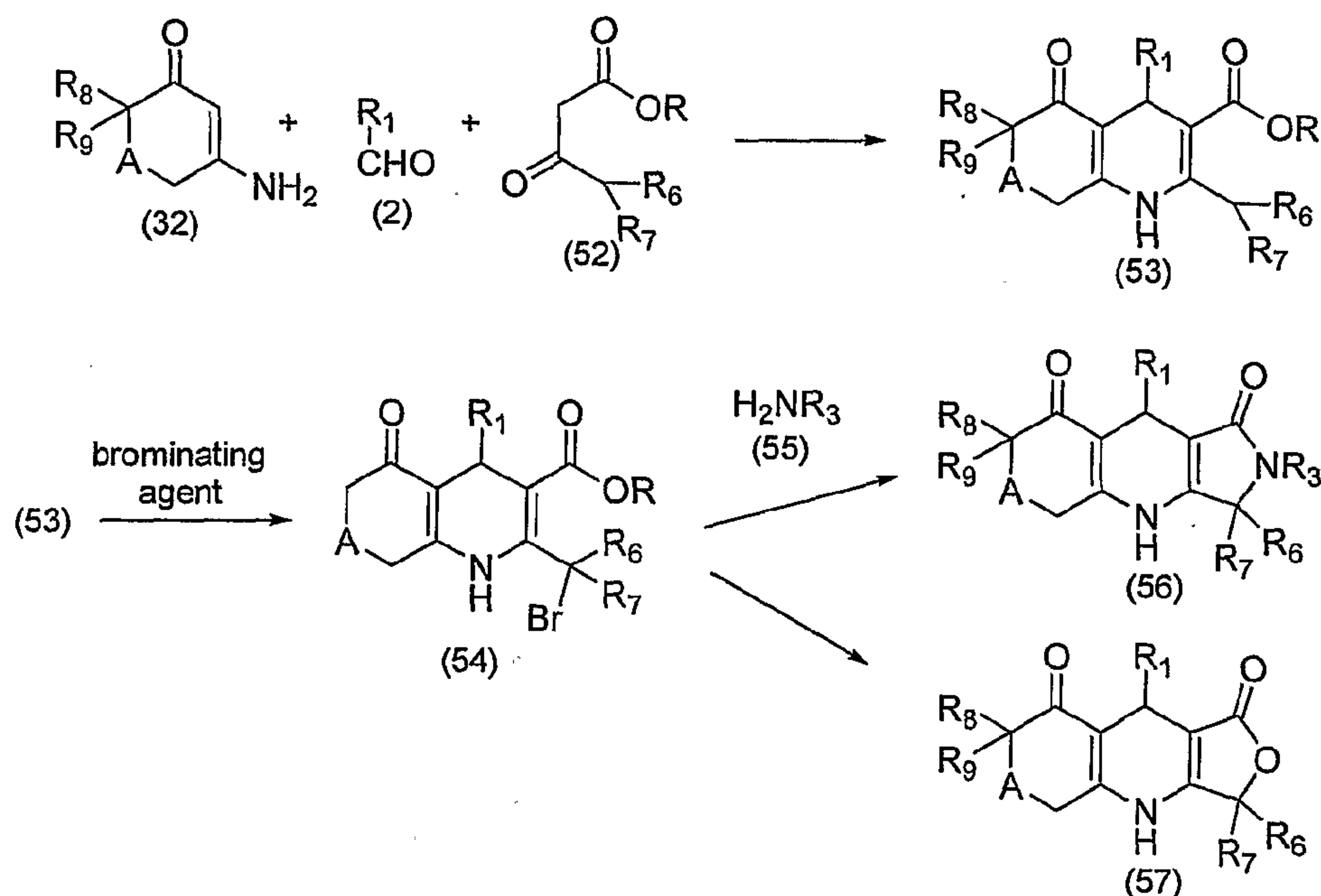


A method of preparing dihydropyridines of general formula (50), wherein A, A', and R₁, R₈ and R₉ are as defined in formula I, can be used as described in Scheme 18.

Enaminones of general formula (33) can be processed as described in Scheme 17 to provide dihydropyridines of general formula (50).

10

Scheme 19



Dihydropyridines of general formula (56) and (57), wherein A, R₁, R₃, R₆, R₇, R₈, and R₉ are as defined in formula I, can be prepared as described in Scheme 19.

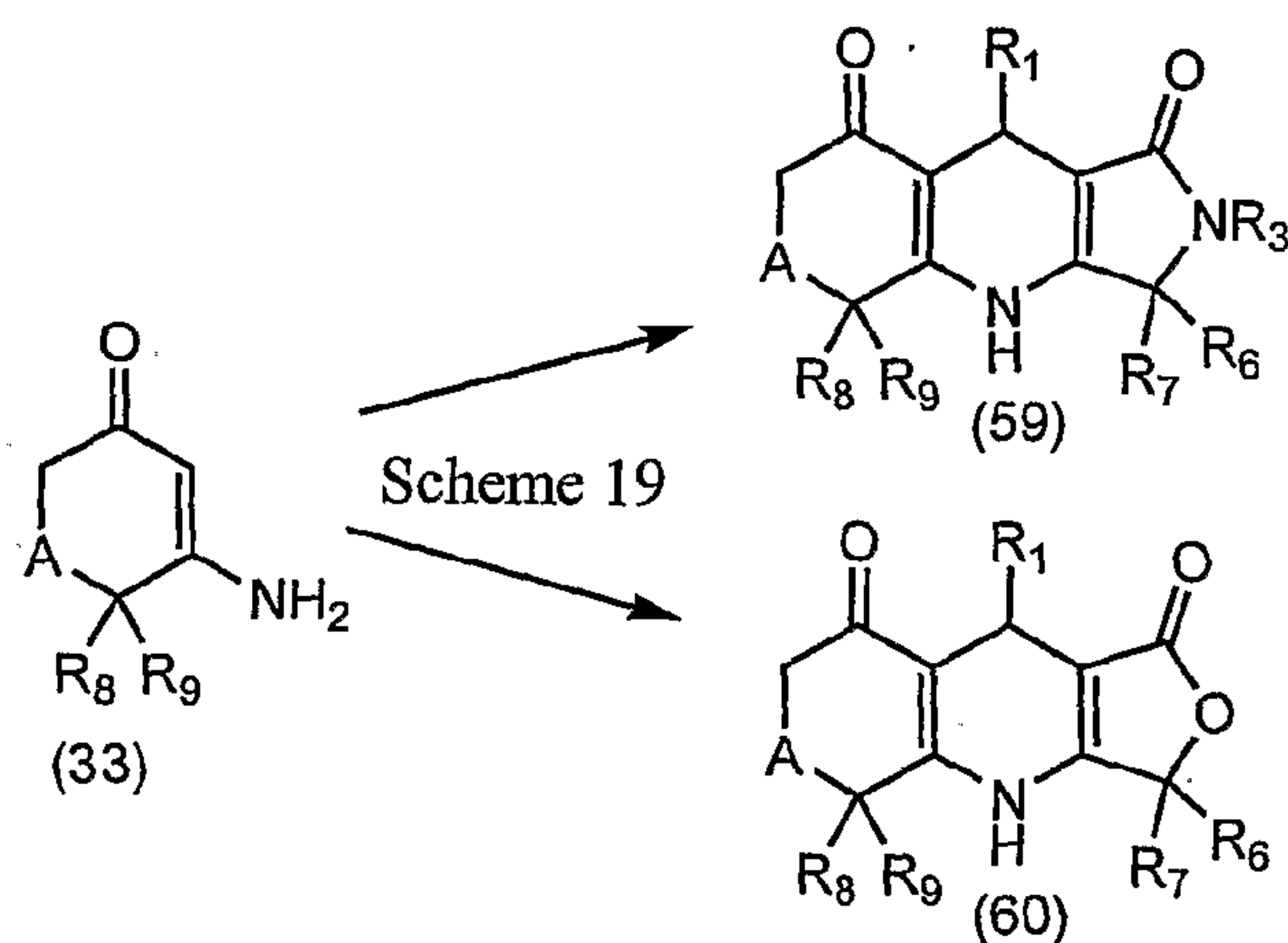
15

Enaminones of general formula (32) can be treated with aldehydes (2) and acetoacetates of

general formula (52), wherein R is lower alkyl, to provide dihydropyridines of general formula (53). Dihydropyridines of general formula (53) can be treated with brominating agents such as N-bromosuccinimide or pyridinium tribromide in a solvent such as methanol, ethanol, isopropanol, or chloroform to provide dihydropyridines of general formula (54). Dihydropyridines of general formula (54) can be treated with primary amines of general formula (55) or ammonia with heat in a solvent such as ethanol to provide dihydropyridines of general formula (56). Dihydropyridines of general formula (54) can be heated neat or in a solvent such as chloroform to provide dihydropyridines of general formula (57).

10

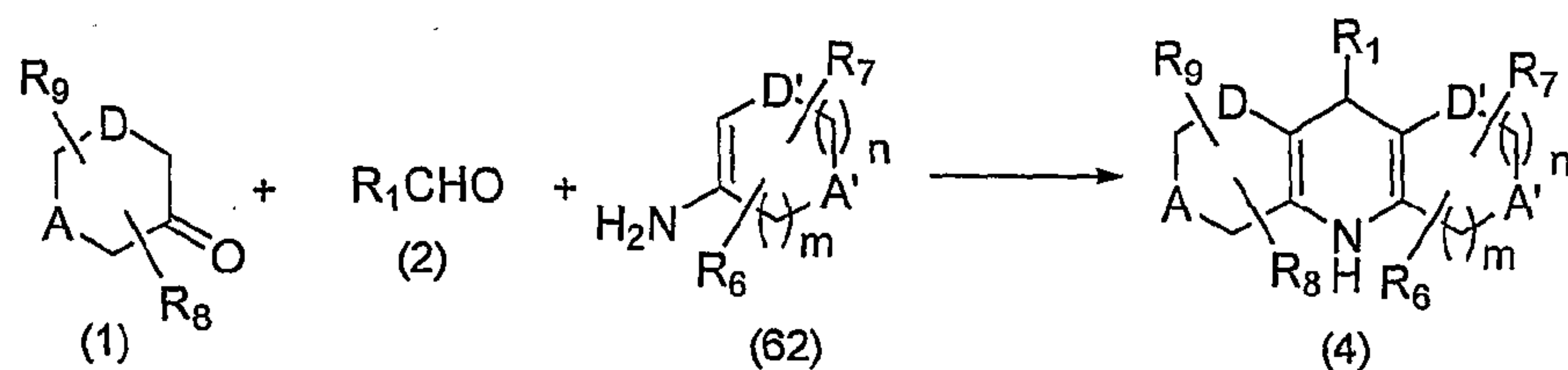
Scheme 20



Dihydropyridines of general formula (59) and (60), wherein A, R₁, R₃, R₆, R₇, R₈, R₉ are as defined in formula I, can be prepared as described in Scheme 20. Enaminones of general formula (33) can be processed as described in Scheme 19 to provide dihydropyridines of general formula (59) and (60).

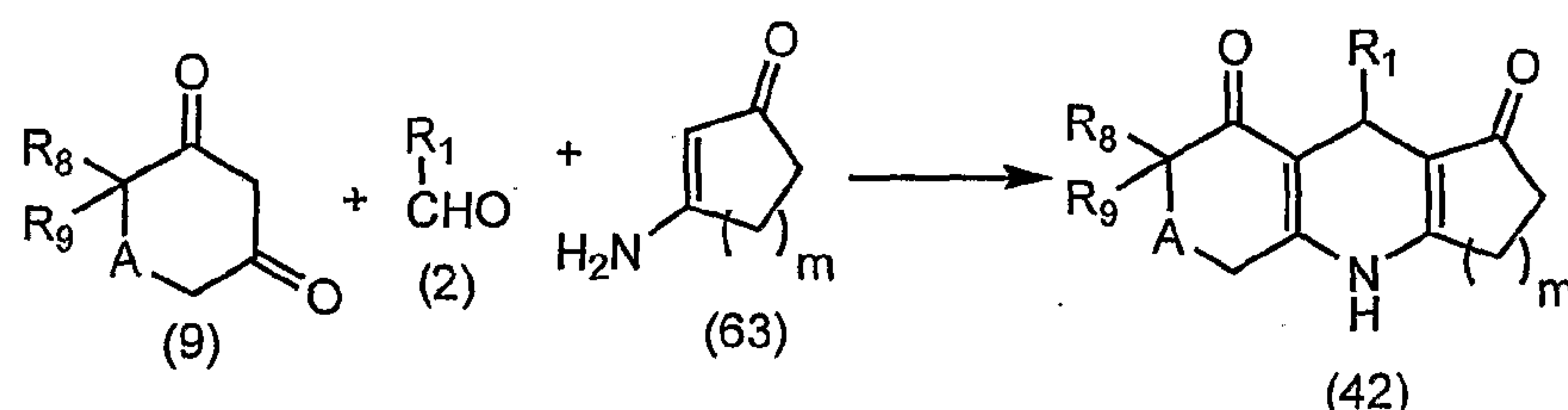
15

Scheme 21



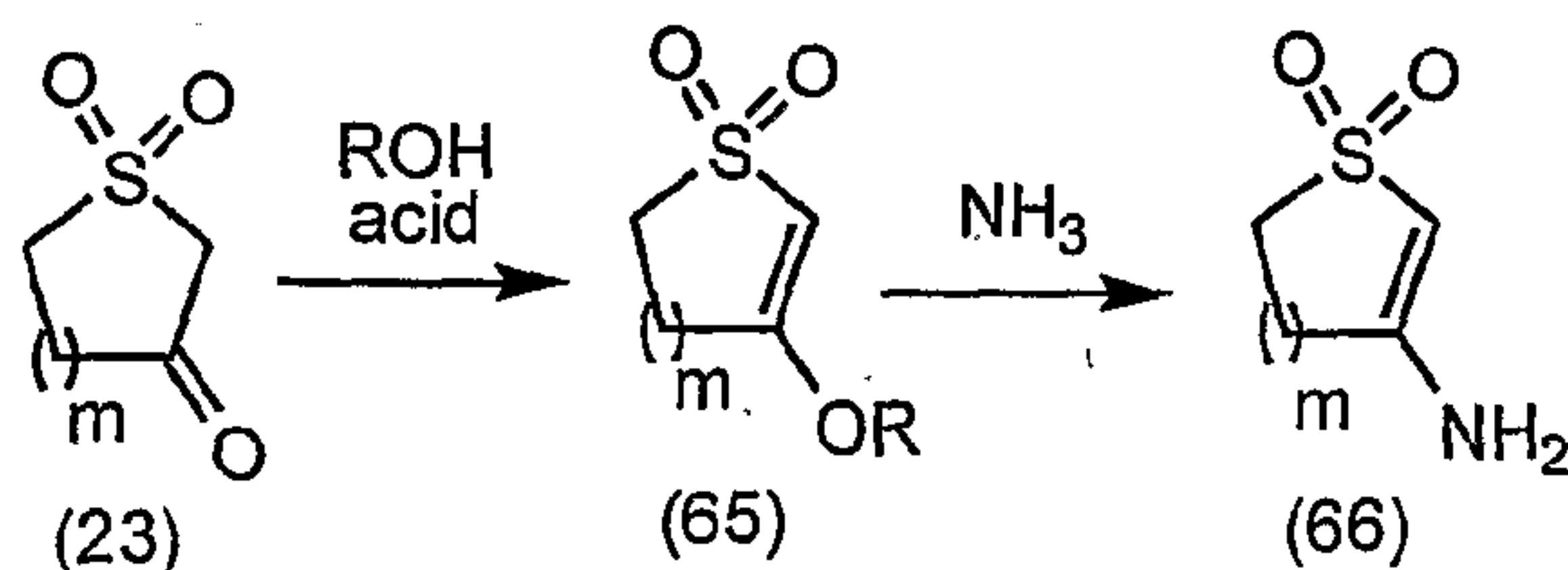
An alternate method of preparing dihydropyridines of general formula (4), wherein A, A', D, D', R₁, R₆, R₇, R₈, R₉ m and n are as defined in formula I, can be used as described in Scheme 21. Carbonyl compounds of general formula (1) can be treated with aldehydes of general formula (2) and enamines of general formula (62) with heating in a solvent such as ethanol to provide dihydropyridines of general formula (4).

Scheme 22



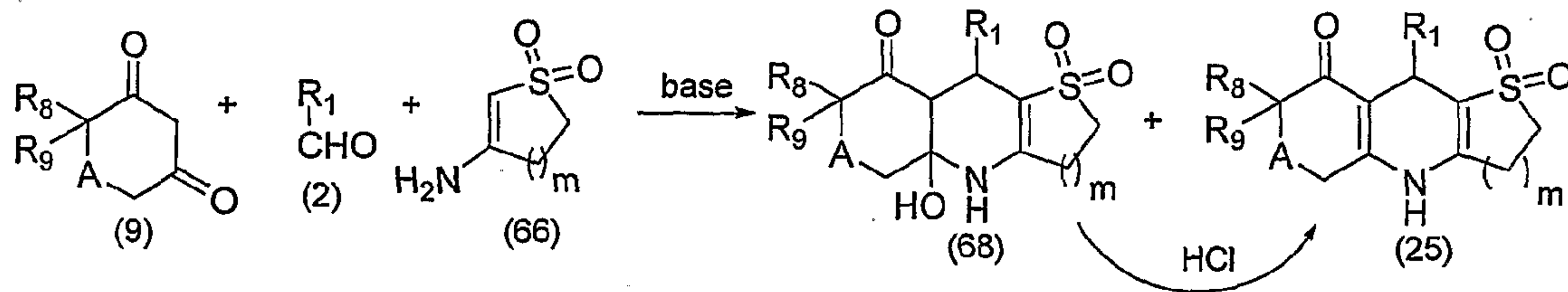
An alternate method of preparing dihydropyridines of general formula (42), wherein A, R₁, R₈, R₉, and m are as defined in formula I, can be used as described in Scheme 22. Dicarbonyl compounds of general formula (9) can be treated with aldehydes (2) and aminocycloalkenones of general formula (63) with heating in a solvent such as ethanol to provide dihydropyridines of general formula (42). An additional heating step, with an acid such as HCl, may be required to drive the reaction to completion. Aminocycloalkenones of general formula (63) can be purchased commercially such as 3-amino-2-cyclohexene-1-one (Fluka) or prepared as described in (Kikani, B. Synthesis, (1991), 2, 176).

Scheme 23



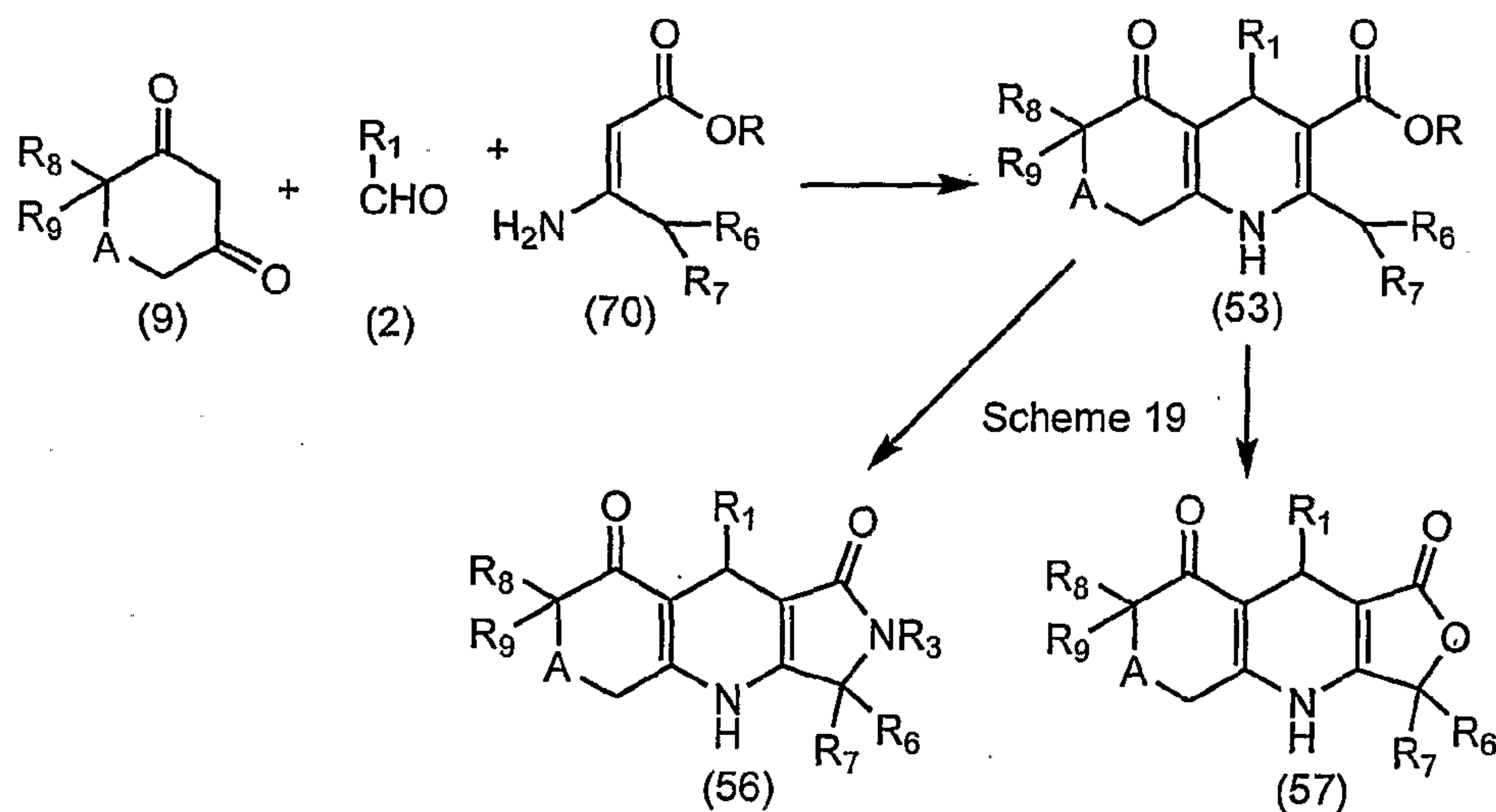
As shown in Scheme 23, enamines of general formula (66), wherein m is an integer from 1-2, can be prepared. Carbonyl compounds (23), from Scheme 7, can be converted to an intermediate enol ether of general formula (65) and thence to enamines of general formula (66).

Scheme 24



An alternate method of preparing dihydropyridines of general formula (25), wherein A, R₁, R₈, R₉ and m are as defined in formula I, can be used as described in Scheme 24. Diones of general formula (9) can be treated with aldehydes of general formula (2) and aminosulfones of general formula (66) with heating in a solvent such as ethanol in the presence of a base such as triethylamine to provide hemiaminals of general formula (68) and dihydropyridines of general formula (25). The resulting mixture of hemiaminals (68) and dihydropyridines (25) can be heated with HCl in a solvent such as ethanol to provide dihydropyridines of general formula (25).

Scheme 25



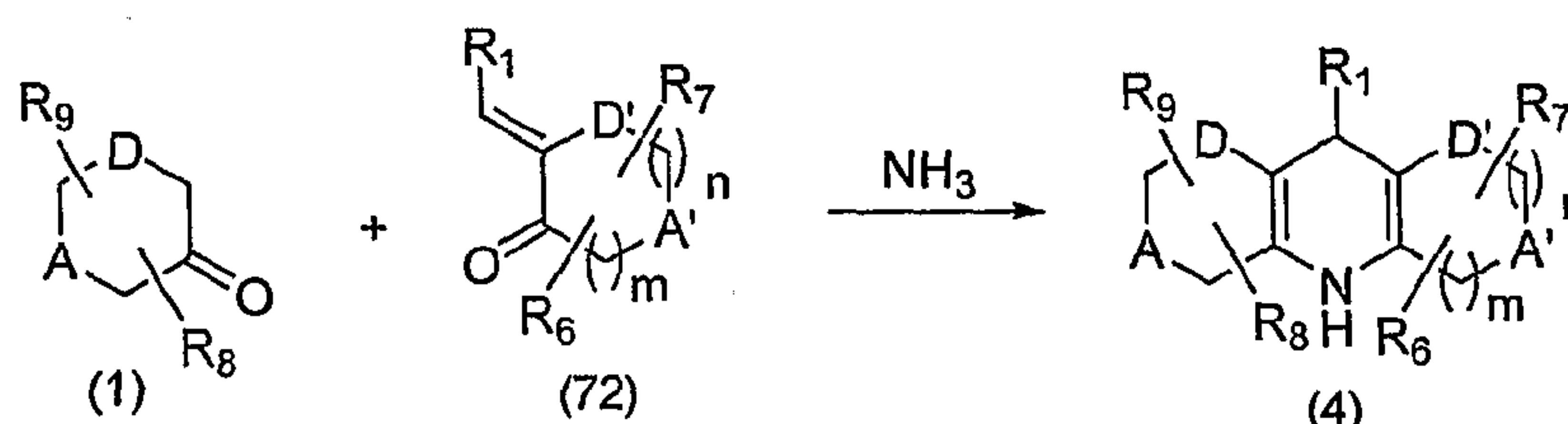
An alternate method of preparing dihydropyridines of general formula (56) and (57), wherein A, R₁, R₃, R₆, R₇, R₈, and R₉ are as defined in formula I, can be used as described in Scheme 25. Diones of general formula (9) can be treated with aldehydes of general formula (2) and aminocrotonates of general formula (70), wherein R is lower

45

alkyl, to provide dihydropyridines of general formula (53) which can be processed as described in Scheme 19 to provide dihydropyridines of general formula (56) and (57). Aminocrotonates of general formula (70) can be generated from reaction of acetoacetates of general formula (52) with ammonia.

5

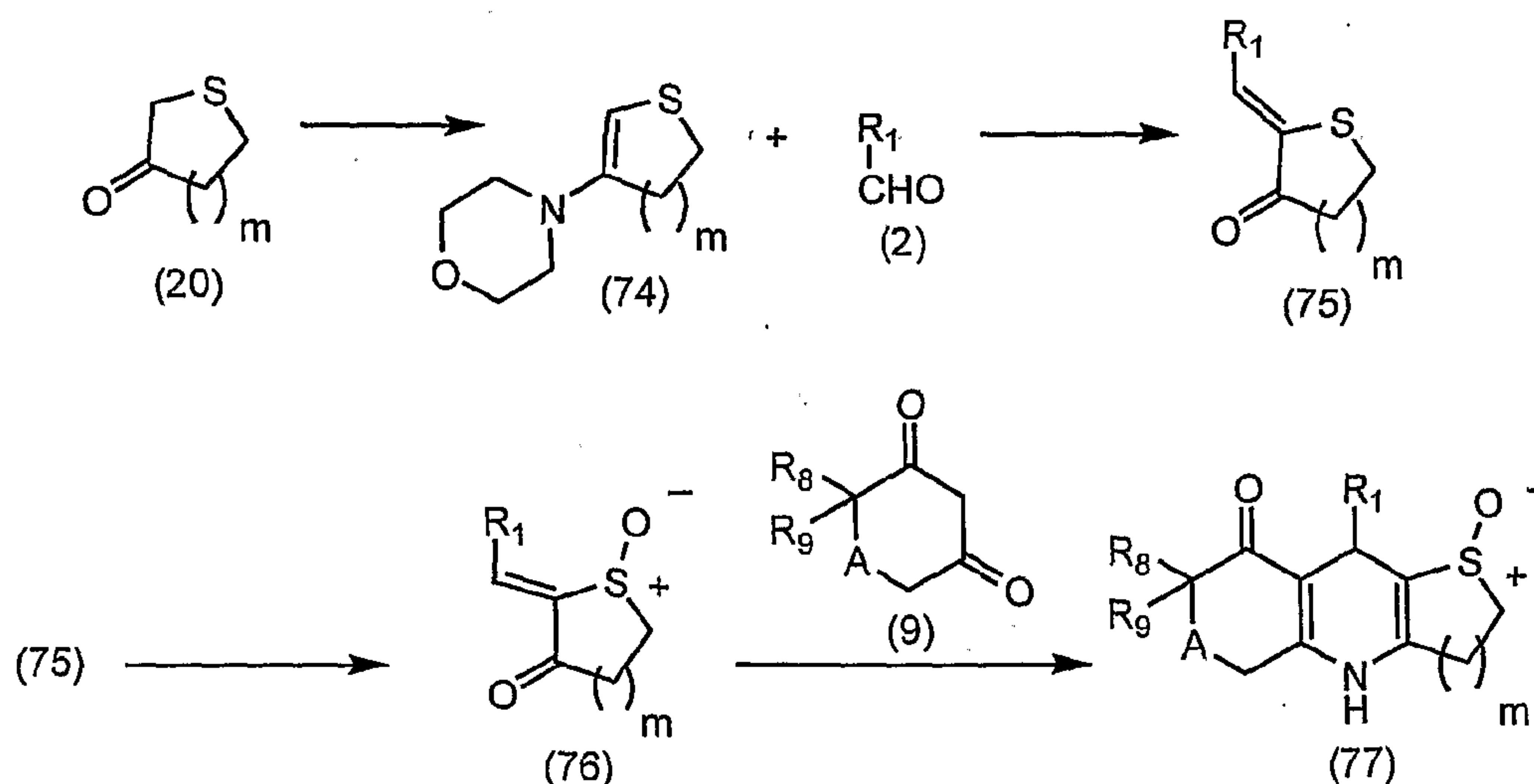
Scheme 26



10

An alternate method of preparing dihydropyridines of general formula (4), wherein A , A' , D , D' , R_1 , R_6 , R_7 , R_8 , R_9 , m and n are as defined in formula I, can be used as described in Scheme 26. Carbonyls of general formula (1) can be treated with α,β -unsaturated ketones of general formula (72) in the presence of ammonia with heating in a solvent such as ethanol to provide dihydropyridines of general formula (4).

Scheme 27

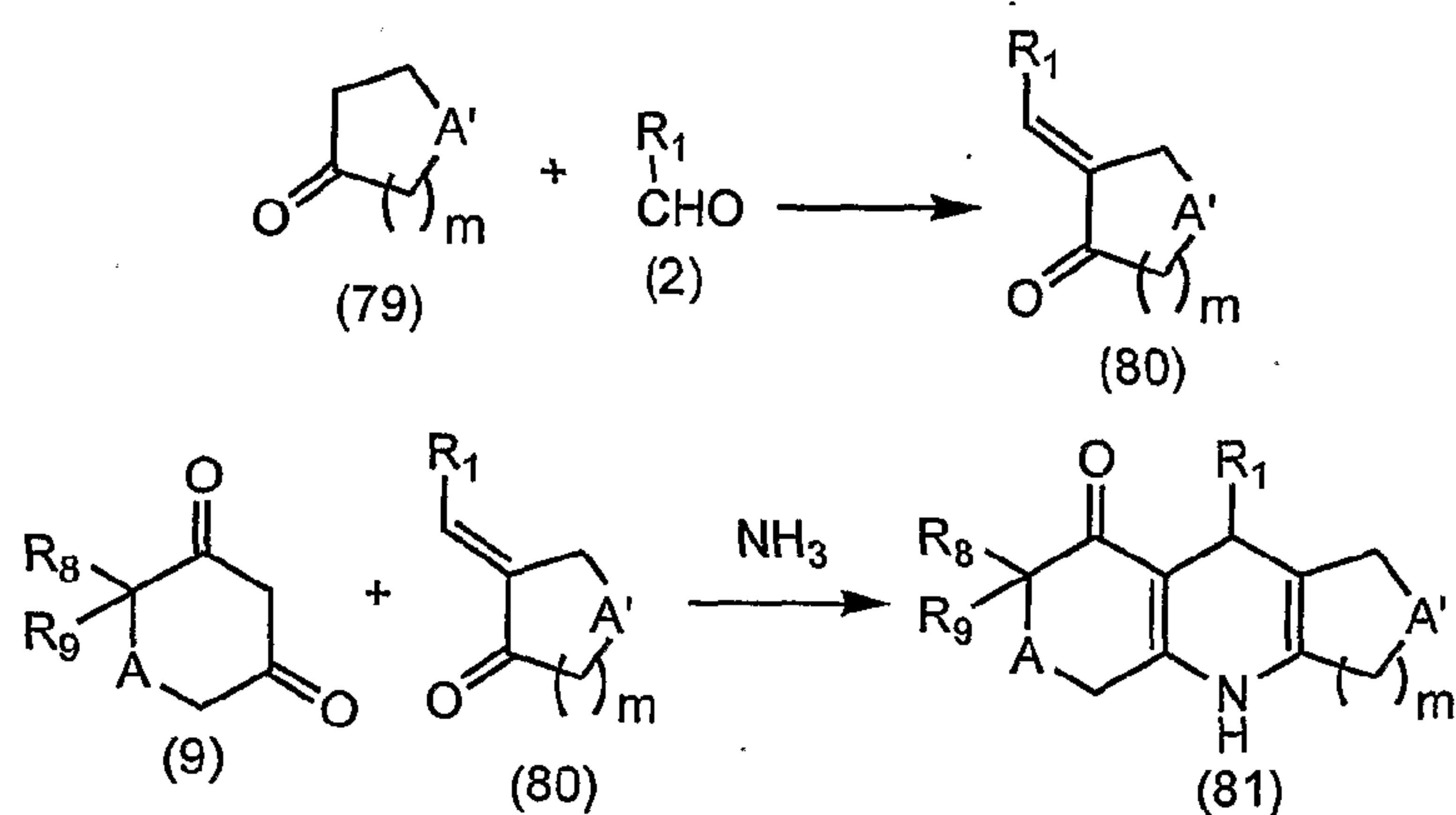


15

Dihydropyridines of general formula (77), wherein A , R_1 , R_8 , R_9 and m are as defined in formula I, can be prepared as described in Scheme 27. β -Keto sulfides (20) can be treated with secondary amines such as morpholine, pyrrolidine or piperidine to provide

enamines (74) which can be condensed with aldehydes of general formula (2) in an appropriate organic solvent to provide sulfides of general formula (75). Sulfides of general formula (75) can be oxidized with an oxidant such as meta-chloroperoxybenzoic acid to sulfoxides of general formula (76). Sulfoxides of general formula (76) can be treated with dicarbonyls of general formula (9) and a source of ammonia such as ammonia, ammonium acetate or ammonium hydroxide with heating in a solvent such as ethyl alcohol or similar alcoholic solvent, acetonitrile or dimethylformamide to provide dihydropyridines of general formula (77).

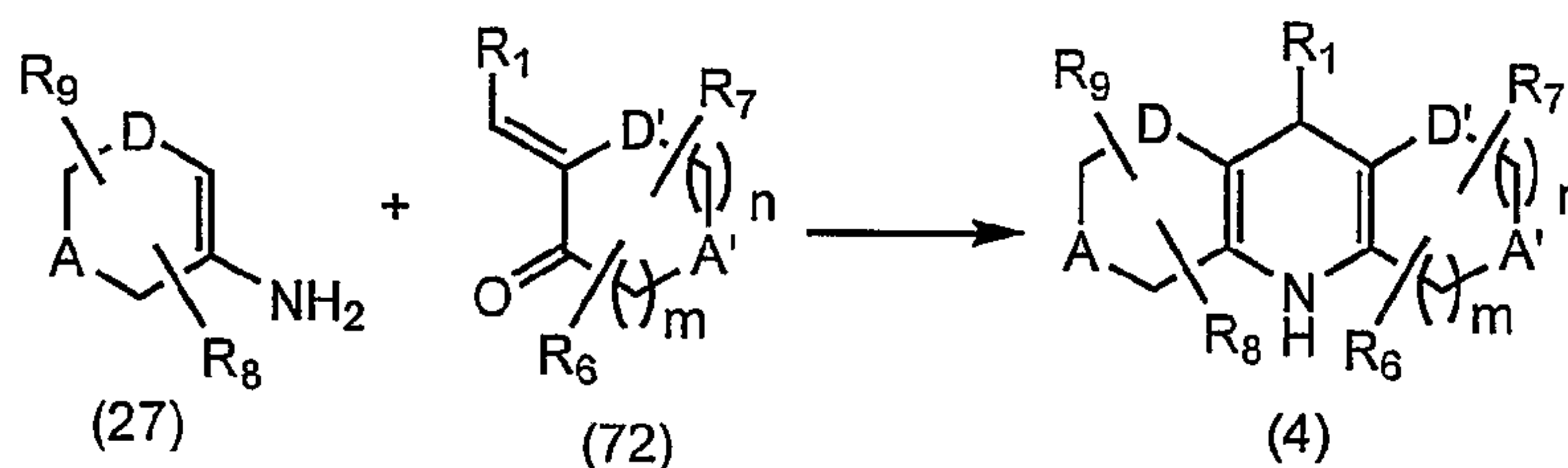
Scheme 28



Dihydropyridines of general formula (81), wherein A , A' , R_1 , R_8 , R_9 and m are as defined in formula I, can be prepared as described in Scheme 28. Carbonyl compounds of general formula (79) can be treated with aldehydes of general formula (2) using the Aldol reaction to provide ketones of general formula (80). The Aldol reaction and the conditions for this transformation are well known to those skilled in the art. Preferably, ketones of general formula (80) can be prepared by conversion of (79) to an enamine of morpholine, pyrrolidine or piperidine followed by direct reaction with aldehydes (2). Ketones of general formula (80) can be treated with diones of general formula (9) and ammonia to provide dihydropyridines of general formula (81).

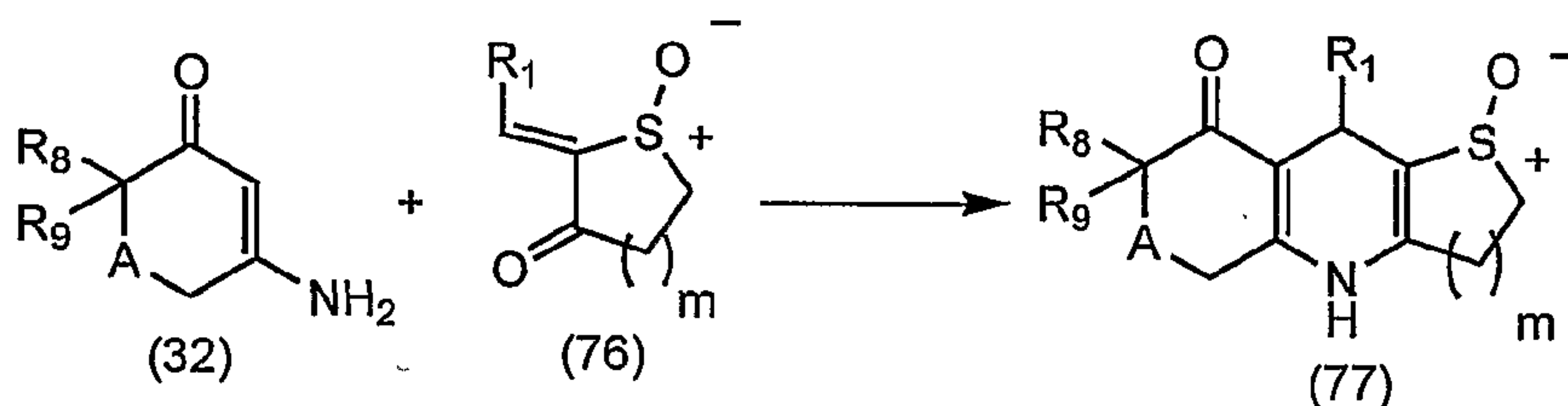
47

Scheme 29



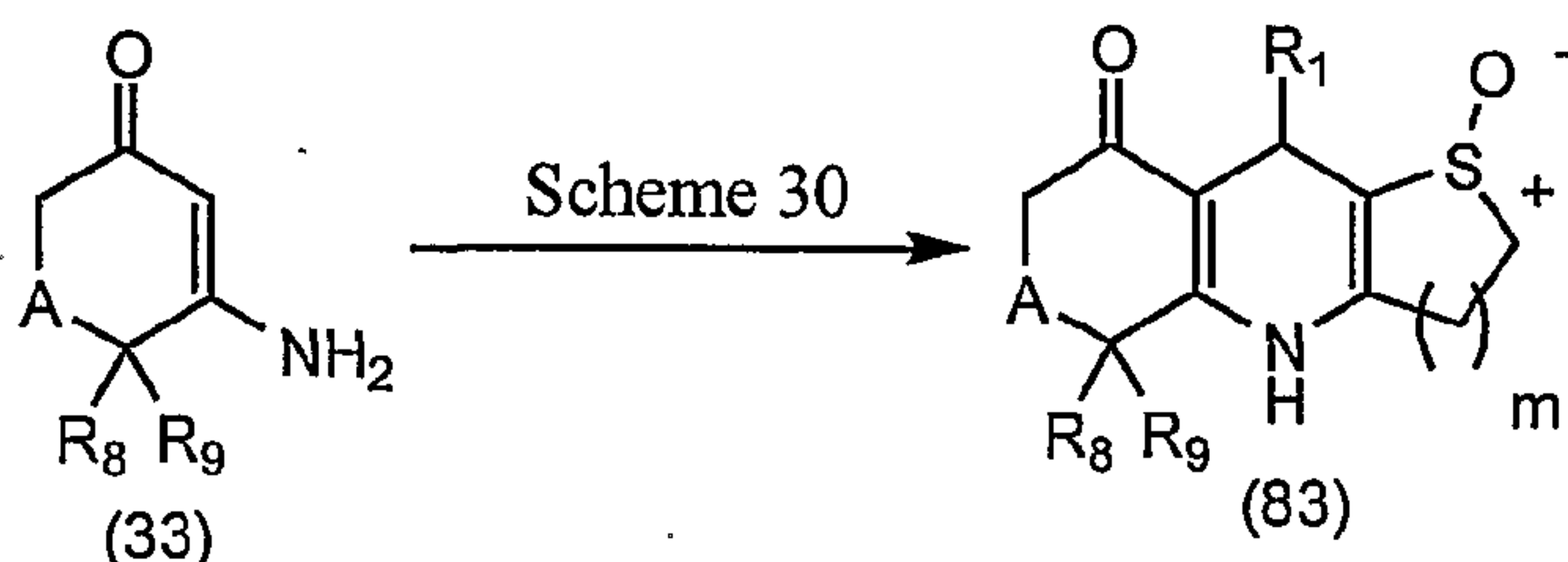
An alternate method of preparing dihydropyridines of general formula (4), wherein A , A' , D , D' , R_1 , R_6 , R_7 , R_8 , R_9 , m , and n are as defined in formula I, can be used as described in Scheme 29. Enamines of general formula (27) can be treated with α,β -unsaturated ketones of general formula (72) with heating in a solvent such as ethanol to provide dihydropyridines of general formula (4).

Scheme 30



An alternate method for preparing dihydropyridines of general formula (77), wherein A , R_1 , R_8 , R_9 and m are as defined in formula I, can be used as described in Scheme 30. Enaminones of general formula (32) can be treated with α,β -unsaturated sulfoxides (76) with heating in a solvent such as ethyl alcohol or similar alcoholic solvent, acetonitrile or dimethylformamide to provide dihydropyridines of general formula (77).

Scheme 31

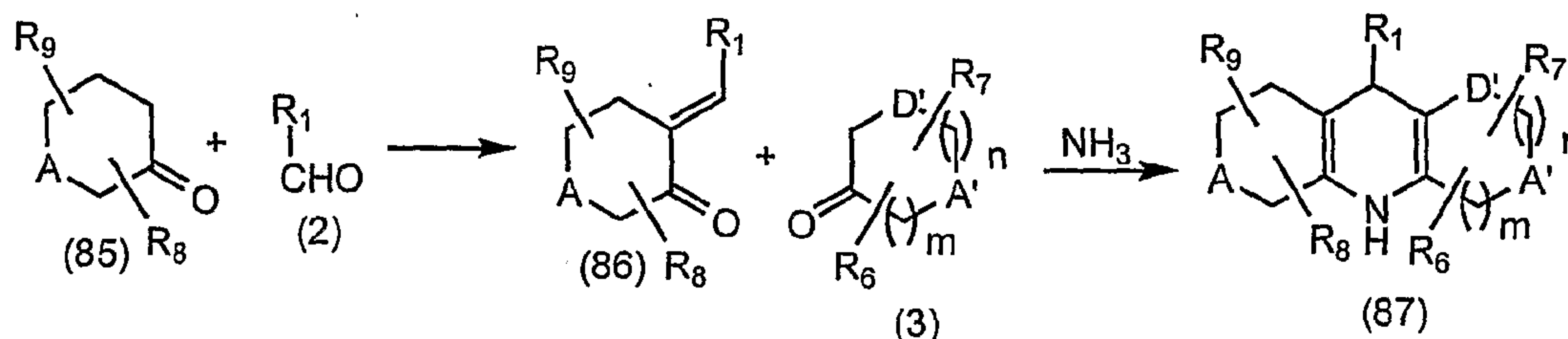


A method for preparing dihydropyridines of general formula (83), wherein A , R_1 , R_8 , R_9 and m are as defined in formula I, can be used as described in Scheme 31.

48

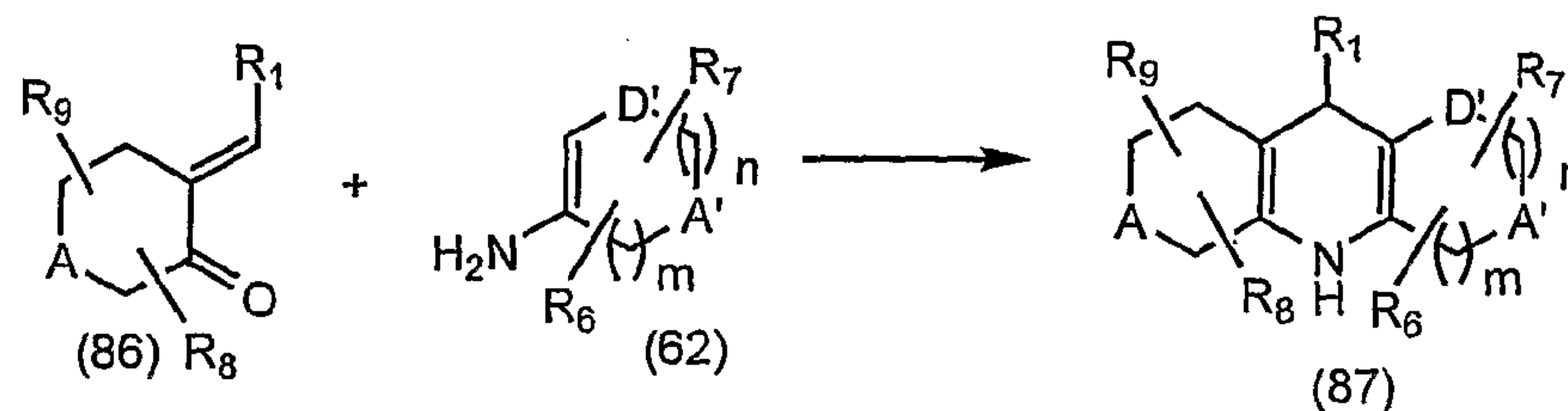
Enaminones of general formula (33) can be processed as described in Scheme 30 to provide dihydropyridines of general formula (83).

Scheme 32



Dihydropyridines of general formula (87), wherein A, A', R₁, D', R₆, R₇, R₈, R₉, m, and n are as defined in formula I, can be prepared as described in Scheme 32. Carbonyls of general formula (85) can be treated with aldehydes of general formula (2) to provide α,β -unsaturated ketones of general formula (86) as described in (Eiden, F., Liebigs Ann.Chem., (1984), 11, 1759-1777). α,β -Unsaturated ketones of general formula (86) can be treated with carbonyls of general formula (3) in the presence of ammonia with heating in a solvent such as ethanol to provide dihydropyridines of general formula (87).

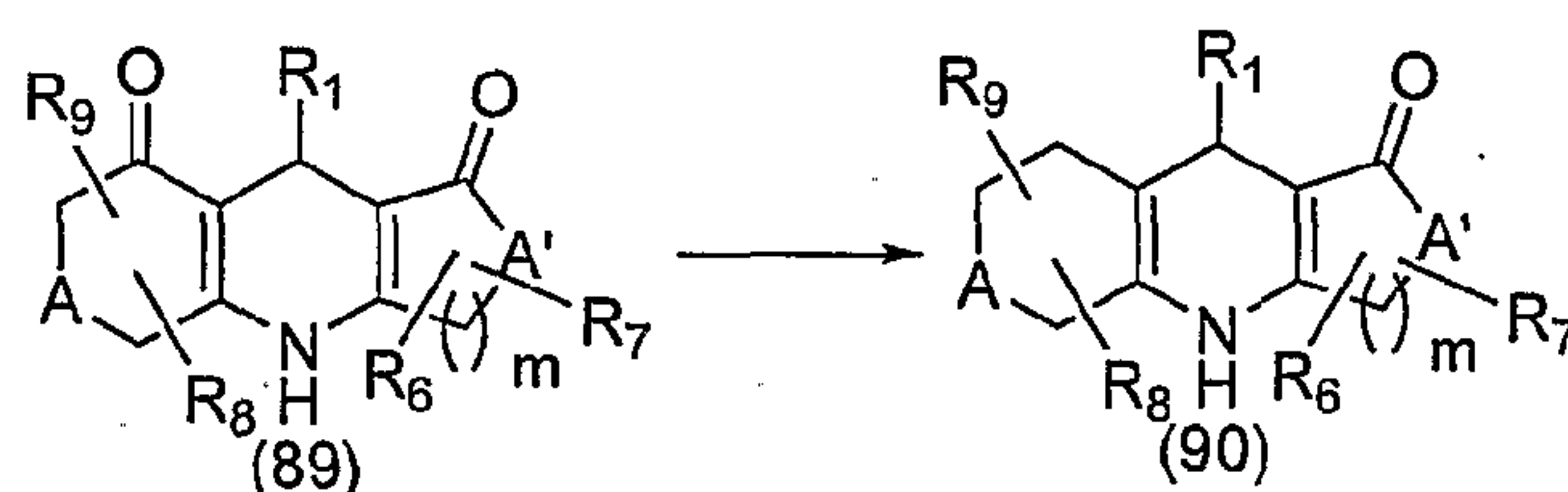
Scheme 33



An alternate method of preparing dihydropyridines of general formula (87), wherein A, A', D', R₁, R₆, R₇, R₈, R₉, m, and n are as defined in formula I, can be used as described in Scheme 33. α,β -Unsaturated ketones of general formula (86) can be treated with enamines of general formula (62) with heating in a solvent such as ethanol to provide dihydropyridines of general formula (87).

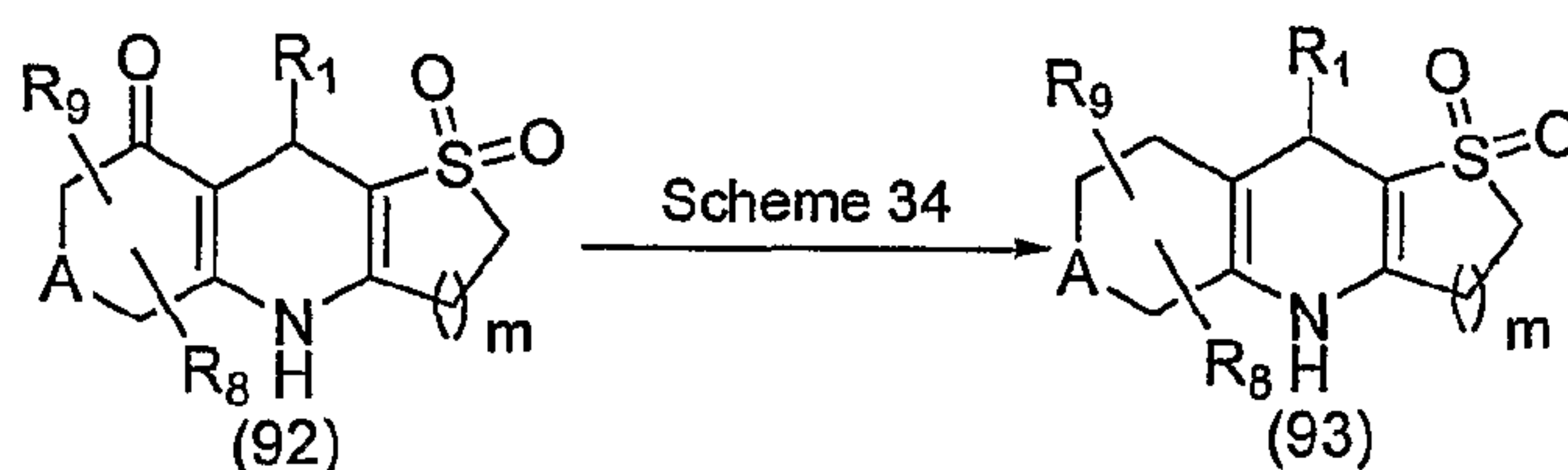
49

Scheme 34



An alternate method of preparing dihydropyridines of general formula (90), wherein A, A', R₁, R₆, R₇, R₈, R₉ and m are as defined in formula I, can be accomplished as described in Scheme 34. Dihydropyridines of general formula (89), from previous Schemes, can be reduced to provide dihydropyridines of general formula (90). Preferably, this transformation can be accomplished by conversion of (89) to the iminoether with trimethyl or triethyloxonium tetrafluoroborate and reduction with sodium borohydride. Alternatively, the carbonyl can be converted to the thiocarbonyl using Lawesson's reagent. Desulfurization of the thiocarbonyl can be accomplished with Raney nickel under a hydrogen atmosphere. Desulfurization can also be accomplished by conversion to the sulfonium species via addition of an alkyl halide such as iodomethane and then reduction with sodium borohydride. The carbonyl may also be reduced to the methylene under conditions described in (Lakhvich, F.A., et. al., J. Org. Chem. USSR (Eng. Transl.) 25 (1989) 1493-1498).

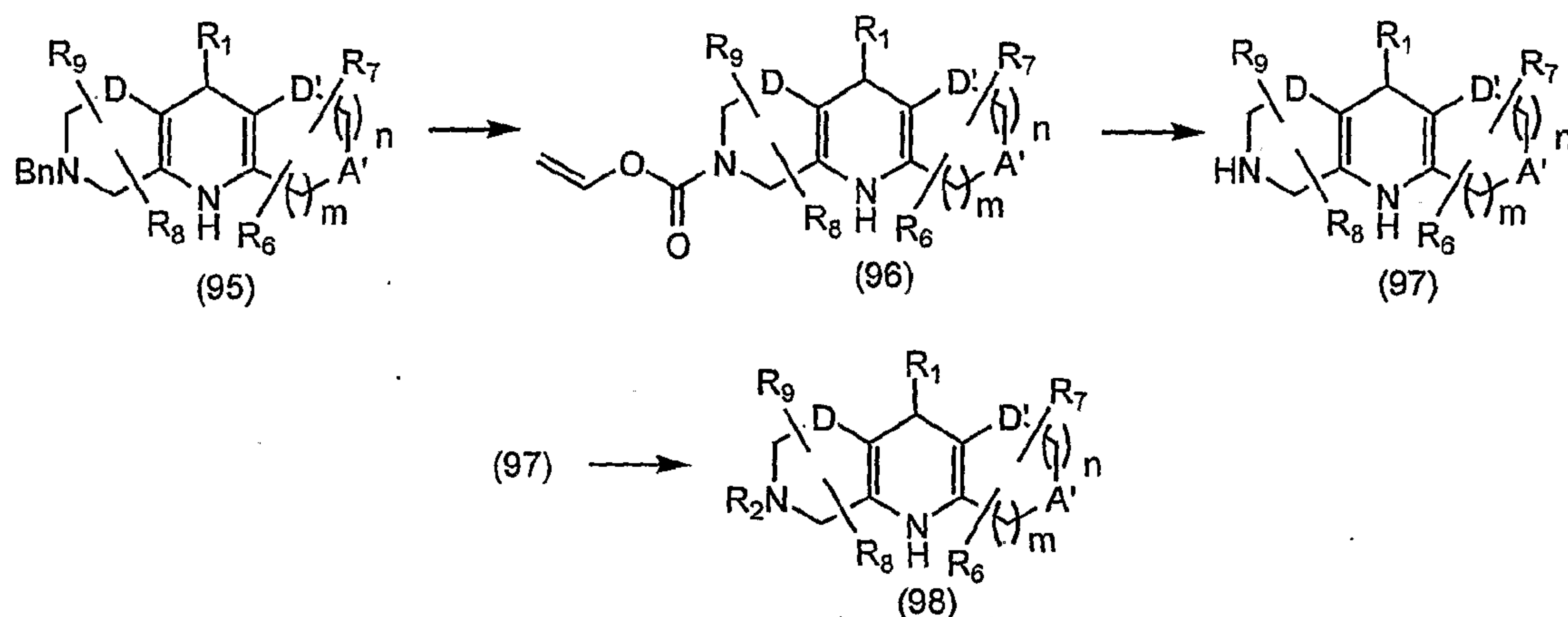
Scheme 35



A method of preparing dihydropyridines of general formula (93), wherein A, R₁, R₈, R₉ and m are as described in formula I, can be used as described in Scheme 35. Dihydropyridines of general formula (92), prepared as described in previous Schemes can be processed as described in Scheme 34 to provide dihydropyridines of general formula (93).

50

Scheme 36

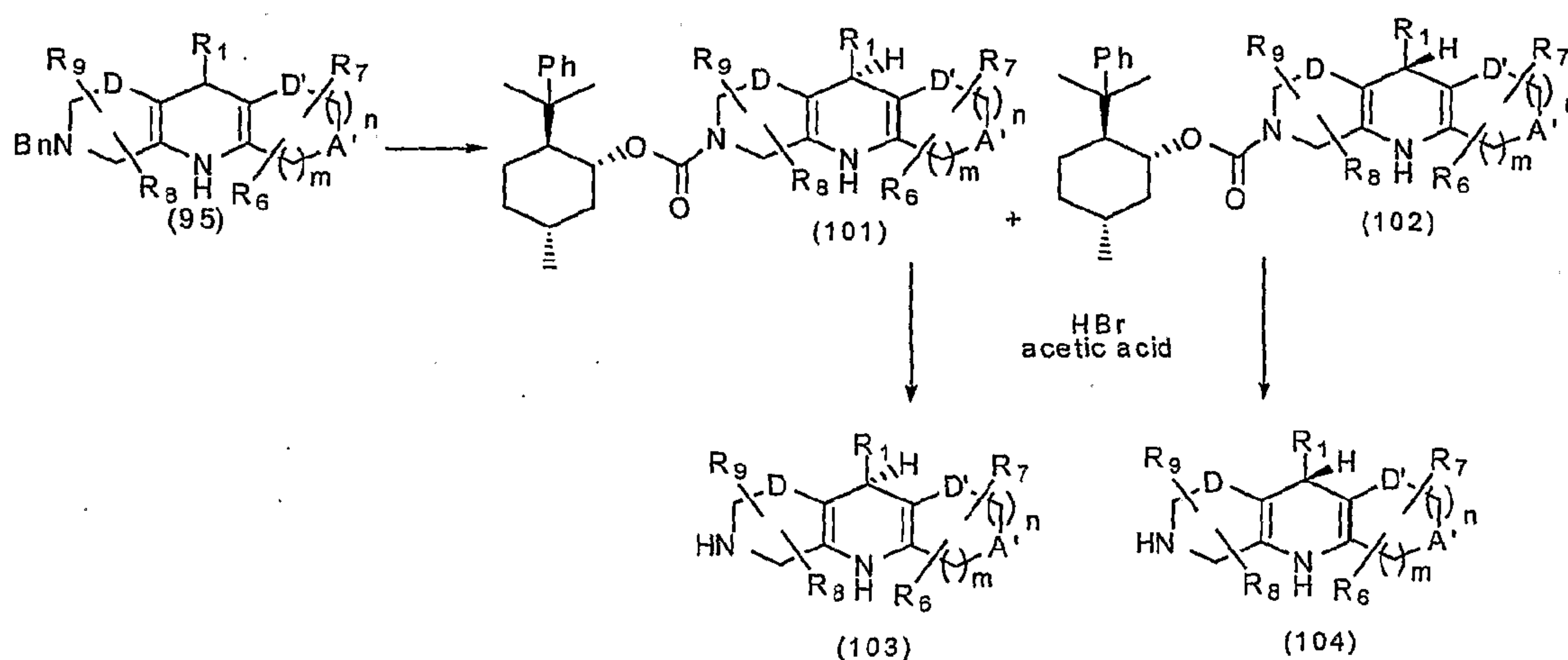


Dihydropyridines of general formula (98), wherein D, D', A', R₁, R₂, R₆, R₇, R₈, R₉,
 5 m, and n are as defined in formula I, can be prepared as described in Scheme 36.

Dihydropyridines of general formula (95) prepared as described in previous Schemes can
 be treated with vinyl chloroformate to provide dihydropyridines of general formula (96).

Dihydropyridines of general formula (96) can be treated with an acid such as hydrochloric
 acid in a protic solvent such as water or methanol with heating to provide dihydropyridines
 10 of general formula (97). Dihydropyridines of general formula (97) can be alkylated using
 standard chemistry known to those skilled in the art to provide dihydropyridines of general
 formula (98).

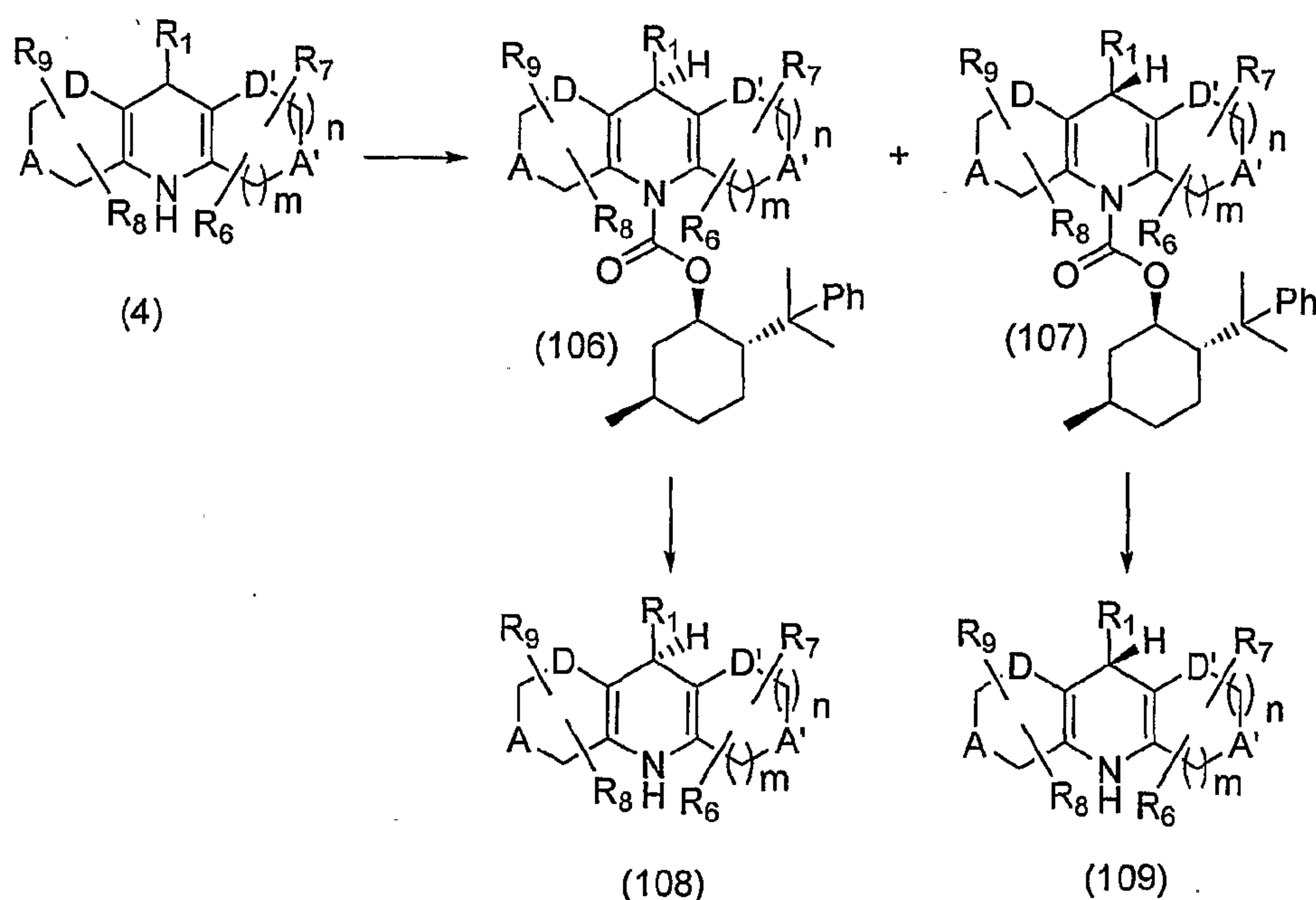
Scheme 37



15

Dihydropyridines of general formula (103) and (104), wherein A', D, D', R₁, R₆, R₇, R₈, R₉, m, and n are as defined in formula I, can be prepared as described in Scheme 37. Dihydropyridines of general formula (95), prepared as described in previous Schemes in particular Schemes 13 and 22, can be debenzylated as described in Scheme 36 and then treated with (8)-phenylmenthol chloroformate prepared from (-) 8-phenylmenthol in a solvent such as tetrahydrofuran, methylene chloride, or chloroform or treated with (-) 8-phenylmenthol chloroformate directly to produce a mixture of diastereomeric carbamates of general formula (101) and (102). The diastereomers (101) and (102) can be separated by column chromatography over silica gel and then treated with HBr in acetic acid to produce the enantiomeric dihydropyridines of general formula (103) and (104).

Scheme 38

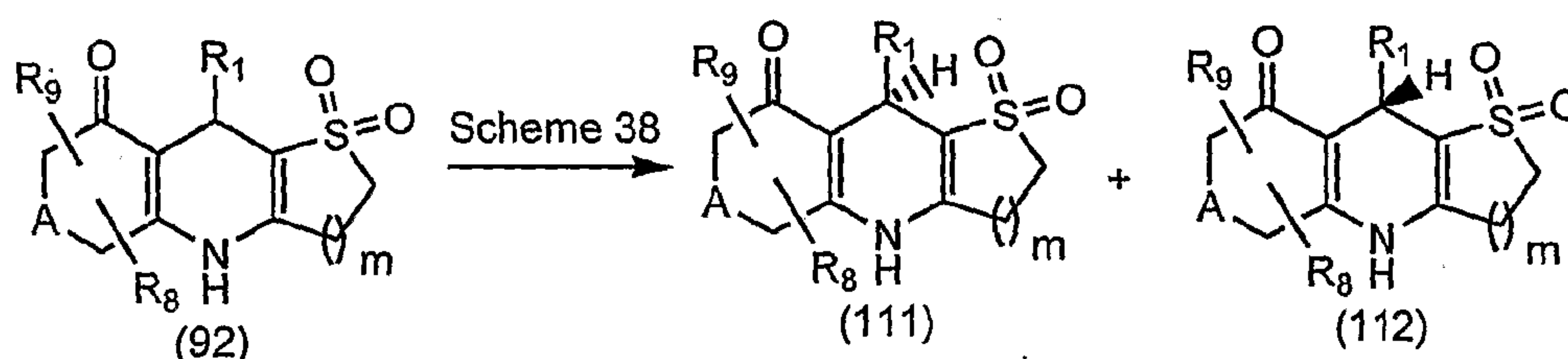


Enantiomers of general formula (108) and (109), wherein A, A', D, D', R₁, R₆, R₇, R₈, R₉, m, and n are as defined in formula I, may be prepared as single enantiomers by the method illustrated in Scheme 38. Dihydropyridines of general formula (4) can be treated with a base such as potassium tert-butoxide in a solvent such as THF and the resulting anion can be reacted with the (-)-8-phenylmenthol chloroformate to produce a mixture of

diastereomeric carbamates (106) and (107). These diastereomers can be separated by separatory methods known to those skilled in the art such as column chromatography over silica gel. The individual carbamates (106) and (107) can be treated with sodium methoxide in methanol to produce the single enantiomers (108) and (109) respectively.

5

Scheme 39



Enantiomers of general formula (111) and (112), wherein A, R₁, R₈, R₉, and m are as defined in formula I, may be prepared as single enantiomers by the method illustrated in Scheme 39. Dihydropyridines of general formula (92) can be processed as described in Scheme 38 to provide the single enantiomers (111) and (112).

Many of the starting aryl and heteroaryl aldehydes necessary to carry out the methods described in the preceeding and following Schemes may be purchased from commercial sources or may be synthesized by known procedures found in the chemical literature. Appropriate literature references for the preparation of aryl and heteroaryl aldehydes may be found in the following section or in the Examples. For starting materials not previously described in the literature the following Schemes are intended to illustrate their preparation through a general method.

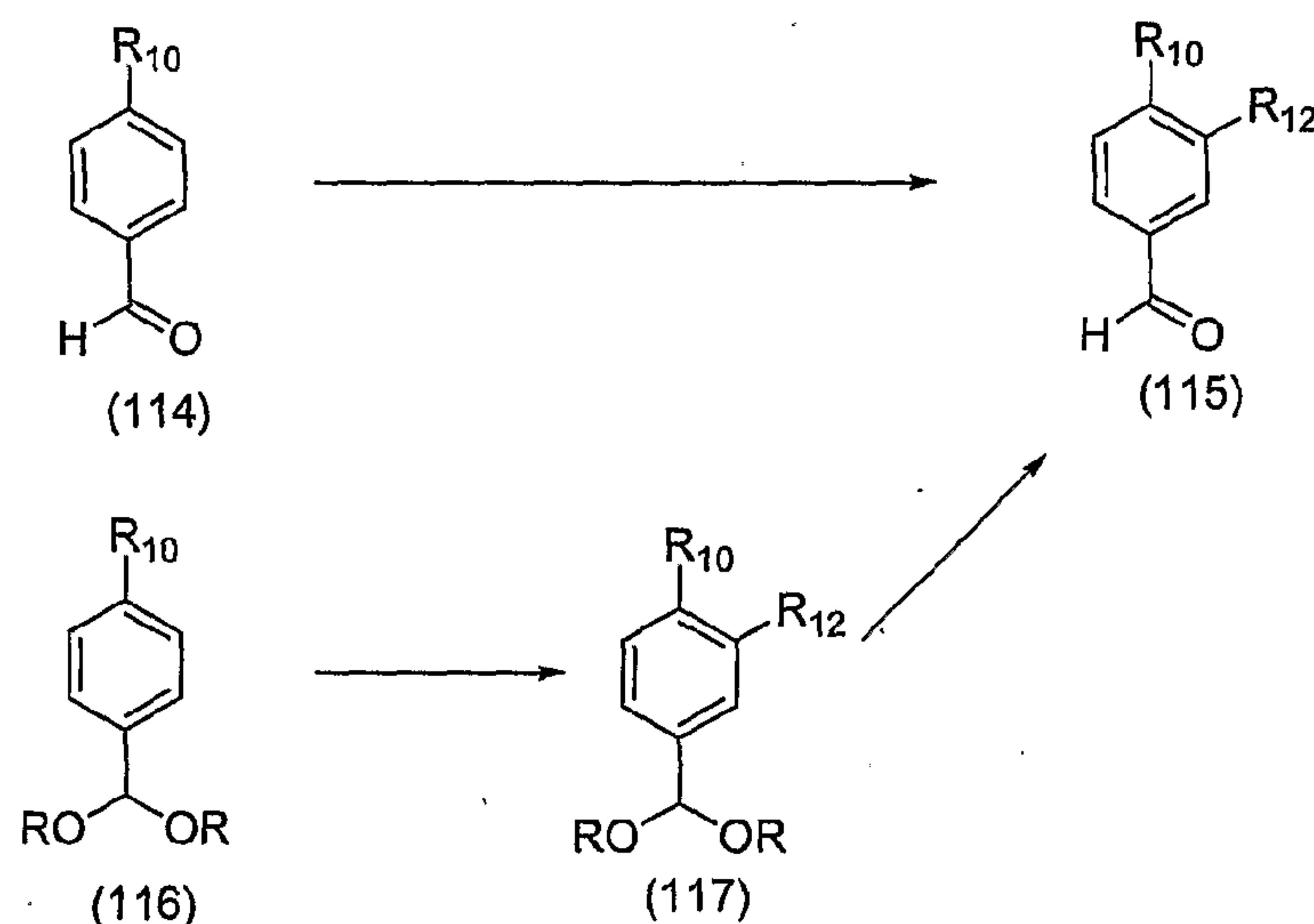
The preparation of aldehydes used to synthesize many preferred compounds of the invention may be found in the following literature references: Pearson, Org. Synth. Coll. Vol V (1973), 117; Nwaukwa, Tetrahedron Lett. (1982), 23, 3131; Badder, J. Indian Chem. Soc. (1976), 53, 1053; Khanna, J. Med. Chem. (1997), 40, 1634; Rinkes, Recl. Trav. Chim. Pays-Bas (1945), 64, 205; van der Lee, Recl. Trav. Chim. Pays-Bas (1926), 45, 687; Widman, Chem. Ber. (1882), 15, 167; Hodgson, J. Chem. Soc. (1927), 2425; Clark, J. Fluorine Chem. (1990), 50, 411; Hodgson, J. Chem. Soc. (1929), 1635; Duff, J.

25

Chem. Soc. (1951), 1512; Crawford, J. Chem. Soc. (1956), 2155; Tanouchi, J. Med. Chem. (1981), 24, 1149; Bergmann, J. Am. Chem. Soc. (1959), 81, 5641; Other: Eistert, Chem. Ber. (1964), 97, 1470; Sekikawa, Bull. Chem. Soc. Jpn. (1959), 32, 551.

5

Scheme 40



10

15

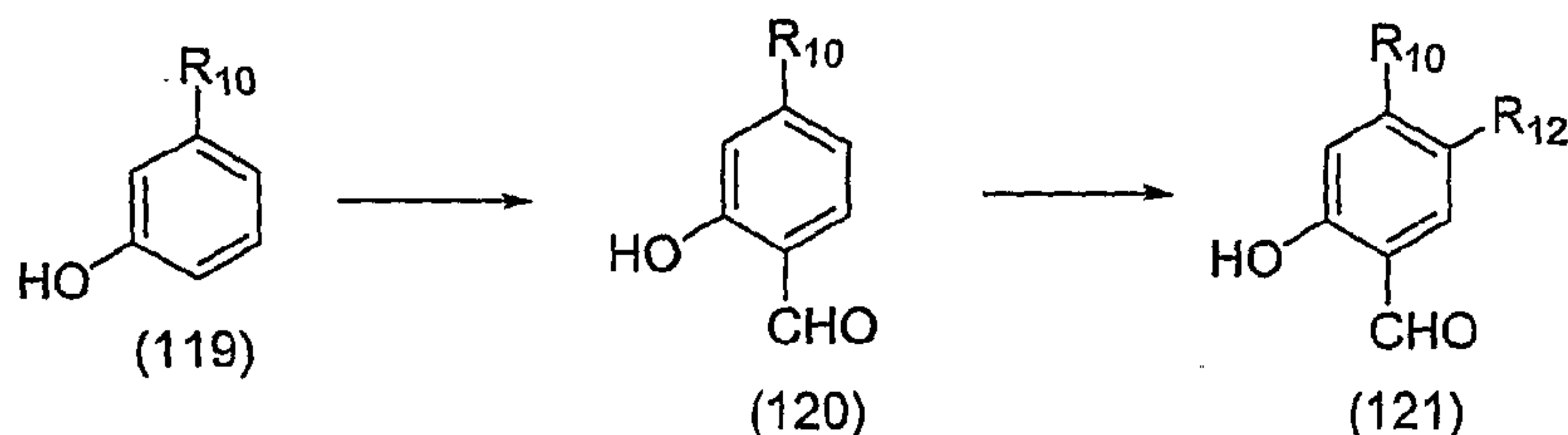
Meta, para-disubstituted aldehydes of general formula (115), wherein R_{10} is selected from alkyl, haloalkyl, halo, haloalkoxy, alkoxy, alkylthio, $-NZ_1Z_2$, and $-C(O)NZ_1Z_2$, wherein Z_1 and Z_2 are independently selected from hydrogen, alkyl, alkylcarbonyl, aryl, arylalkyl, and formyl and R_{12} is selected from nitro, halo, and alkylcarbonyl, can be prepared according to the method described in Scheme 40. A para substituted aldehyde of general formula (114) or the corresponding acetal protected aldehyde of general formula (116), wherein R is selected from alkyl or together with the oxygen atoms to which they are attached form a 5 or 6 membered ring wherein 1,3-dioxolanes are preferred, may be subjected to conditions of an electrophilic aromatic substitution reaction to provide aldehydes of general formula (115) or protected aldehydes of general formula (117). Preferred protecting groups for compounds of general formula (116) and (117) include dimethyl or diethyl acetals or the 1,3-dioxolanes. These protecting groups can be introduced and removed using methods well known to those

54

skilled in the art of organic chemistry. Removal of the protecting group of the compounds of general structure (117) provides substituted aldehydes of general formula (115).

5

Scheme 41

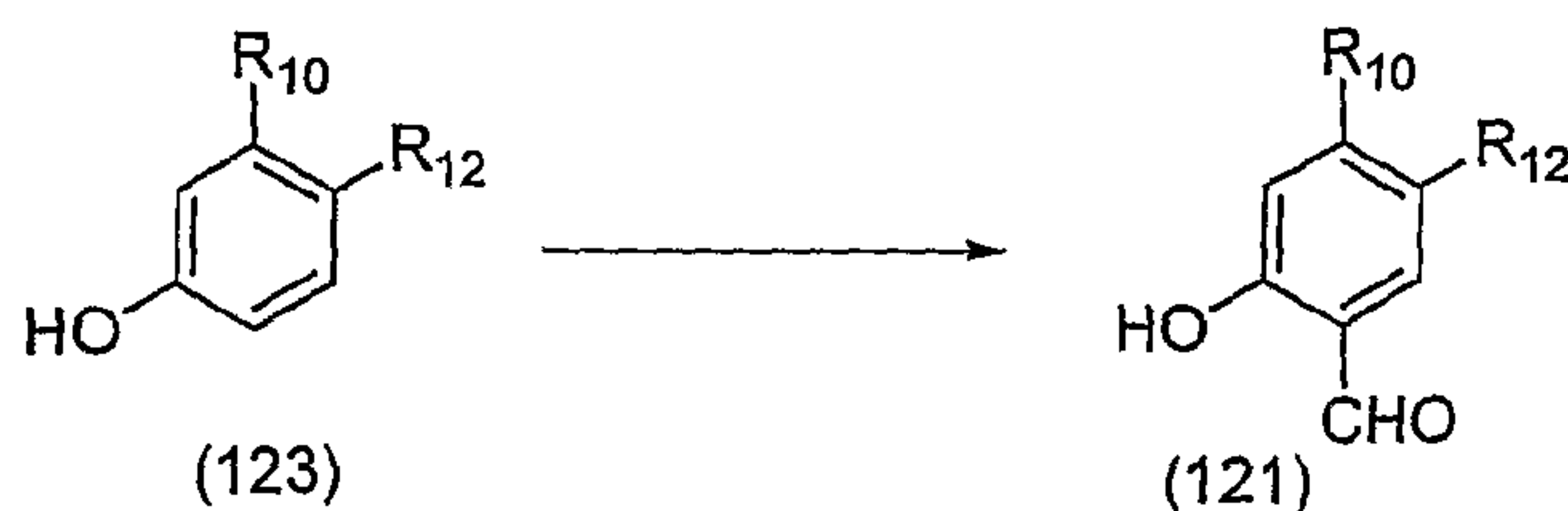


10

Aldehydes of general formula (121), wherein R_{10} is selected from alkyl, haloalkyl, halo, haloalkoxy, alkoxy, alkylthio, $-NZ_1Z_2$, and $-C(O)NZ_1Z_2$, wherein Z_1 and Z_2 are independently selected from hydrogen, alkyl, alkylcarbonyl, aryl, arylalkyl, and formyl and R_{12} is selected from nitro, halo, and alkylcarbonyl, can be prepared by the method described in Scheme 41. A meta substituted phenol (119) is converted to the para substituted salicylaldehyde (120) by reaction with a base such as sodium hydroxide and a reagent such as trichloromethane or tribromomethane, known as the Reimer-Tiemann reaction. An alternate set of reaction conditions involves reaction with magnesium methoxide and paraformaldehyde (Aldred, J. Chem. Soc. Perkin Trans. 1 (1994), 1823). The aldehyde (120) may be subjected to conditions of an electrophilic aromatic substitution reaction to provide meta, para disubstituted salicylaldehydes of general formula (121).

20

Scheme 42

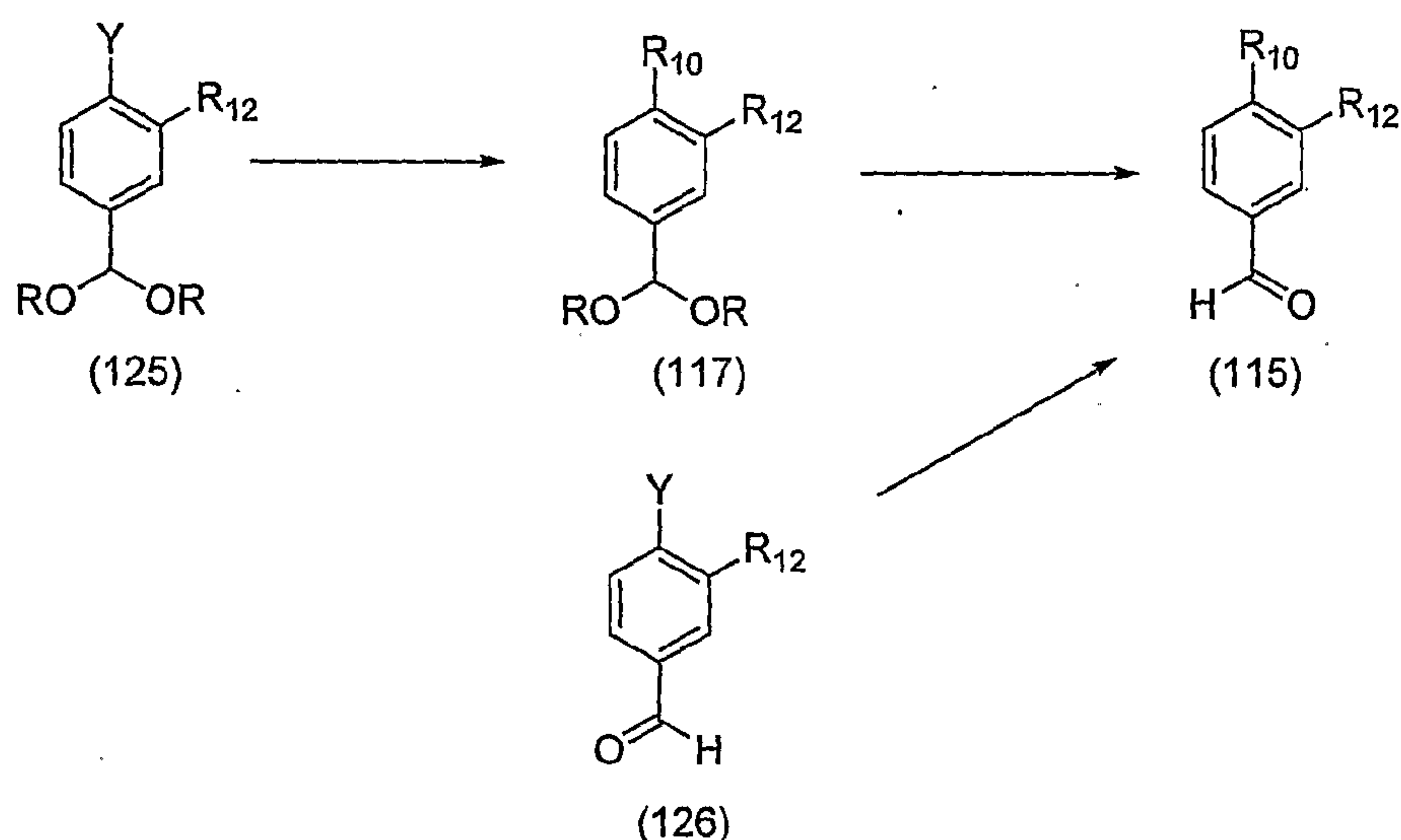


An alternative method of preparing meta, para disubstituted salicylaldehydes of general formula (121), wherein R_{10} is selected from alkyl, haloalkyl, halo, haloalkoxy, alkoxy, alkylthio, $-NZ_1Z_2$, and $-C(O)NZ_1Z_2$, wherein Z_1 and Z_2 are independently selected

55

from hydrogen, alkyl, alkylcarbonyl, aryl, arylalkyl, and formyl and R_{12} is selected from nitro, halo, and alkylcarbonyl, can be used as described in Scheme 42. A meta, para disubstituted phenol of general formula (123) can be reacted with a base such as sodium hydroxide and a reagent such as trichloromethane or tribromomethane, known as the Reimer-Tiemann reaction, to provide disubstituted salicylaldehydes of general formula (121). An alternate set of reaction conditions involves reaction with magnesium methoxide and paraformaldehyde (Aldred, J. Chem. Soc. Perkin Trans. 1 (1994), 1823).

Scheme 43



An alternative method of preparing benzaldehydes of general formula (115), wherein R_{12} is selected from alkyl, haloalkyl, chlorine, fluorine, haloalkoxy, alkoxy, alkylthio, nitro, alkylcarbonyl, arylcarbonyl, $-NZ_1Z_2$, and $-C(O)NZ_1Z_2$, wherein Z_1 and Z_2 are independently selected from hydrogen, alkyl, alkylcarbonyl, aryl, arylalkyl, and formyl, and R_{10} is selected from alkyl, hydroxyalkyl, alkylthio, alkylcarbonyl, and formyl, is described in Scheme 43. Protected benzaldehydes of general formula (125), wherein Y is selected from bromine and iodine, and wherein R is selected from alkyl or together with the oxygen atoms to which they are attached form a 5 or 6 membered ring wherein 1,3-dioxolanes are preferred, can be converted to the 3,4-disubstituted protected benzaldehyde of general formula (117) via conversion to an intermediate lithio or magnesio derivative, followed by reaction with an appropriate electrophile such as an aldehyde,

dialkyldisulfide, a Weinreb amide, dimethylformamide, an alkyl halide or the like.

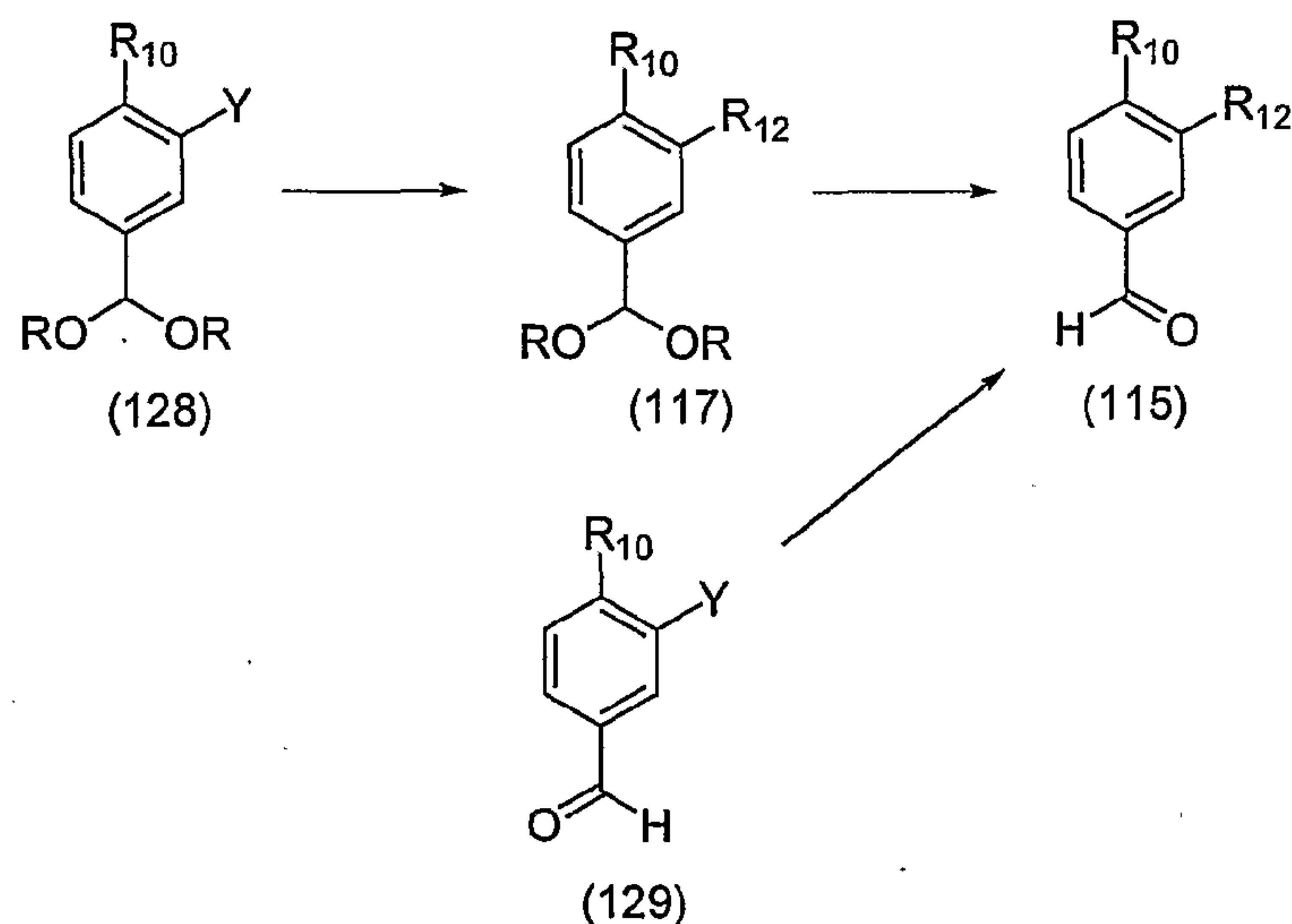
Deprotection of protected benzaldehydes of general structure (117) provide benzaldehydes of general formula (115).

An alternative method of preparing benzaldehydes of general formula (115),
5 wherein R_{12} is selected from alkyl, alkylcarbonyl, alkylsulfonyl, aryl, heteroaryl, cyano, haloalkyl, chlorine, fluorine, haloalkoxy, nitro, alkoxy, and alkylthio, and $-C(O)NZ_1Z_2$, wherein Z_1 and Z_2 are independently selected from hydrogen, alkyl, alkylcarbonyl, aryl, arylalkyl, and formyl, and R_{10} is selected from alkyl, alkynyl, vinyl, aryl, heteroaryl, cyano and the like, is also described in Scheme 43. Protected benzaldehydes of general
10 formula (125), wherein Y is selected from bromine, iodine, and triflate, and wherein R is selected from alkyl or together with the oxygen atoms to which they are attached form a 5 or 6 membered ring wherein 1,3-dioxolanes are preferred, can be treated with an suitable tin, boronic acid, alkyne, or unsaturated halide reagent in the presence of a catalyst such as a palladium catalyst with heating in a solvent such as dimethylformamide to effect a
15 coupling reaction that provides protected benzaldehydes of general formula (117). Deprotection of the acetal of general formula (117) provides benzaldehydes of general formula (115).

An alternative method of preparing benzaldehydes of general formula (115), wherein R_{12} is selected from alkyl, alkylcarbonyl, alkylsulfonyl, aryl, heteroaryl, cyano,
20 haloalkyl, chlorine, fluorine, haloalkoxy, nitro, alkoxy, and alkylthio, and $-C(O)NZ_1Z_2$, wherein Z_1 and Z_2 are independently selected from hydrogen, alkyl, alkylcarbonyl, aryl, arylalkyl, and formyl, and R_{10} is selected from alkyl, alkynyl, vinyl, aryl, heteroaryl, cyano and the like, is also described in Scheme 43. Benzaldehydes of general formula (126) can be treated with a suitable tin, boronic acid, alkyne, or unsaturated halide reagent
25 in the presence of a catalyst such as a palladium catalyst with heating in a solvent such as dimethylformamide to effect a coupling reaction that provides aldehydes of general formula (115).

57

Scheme 44



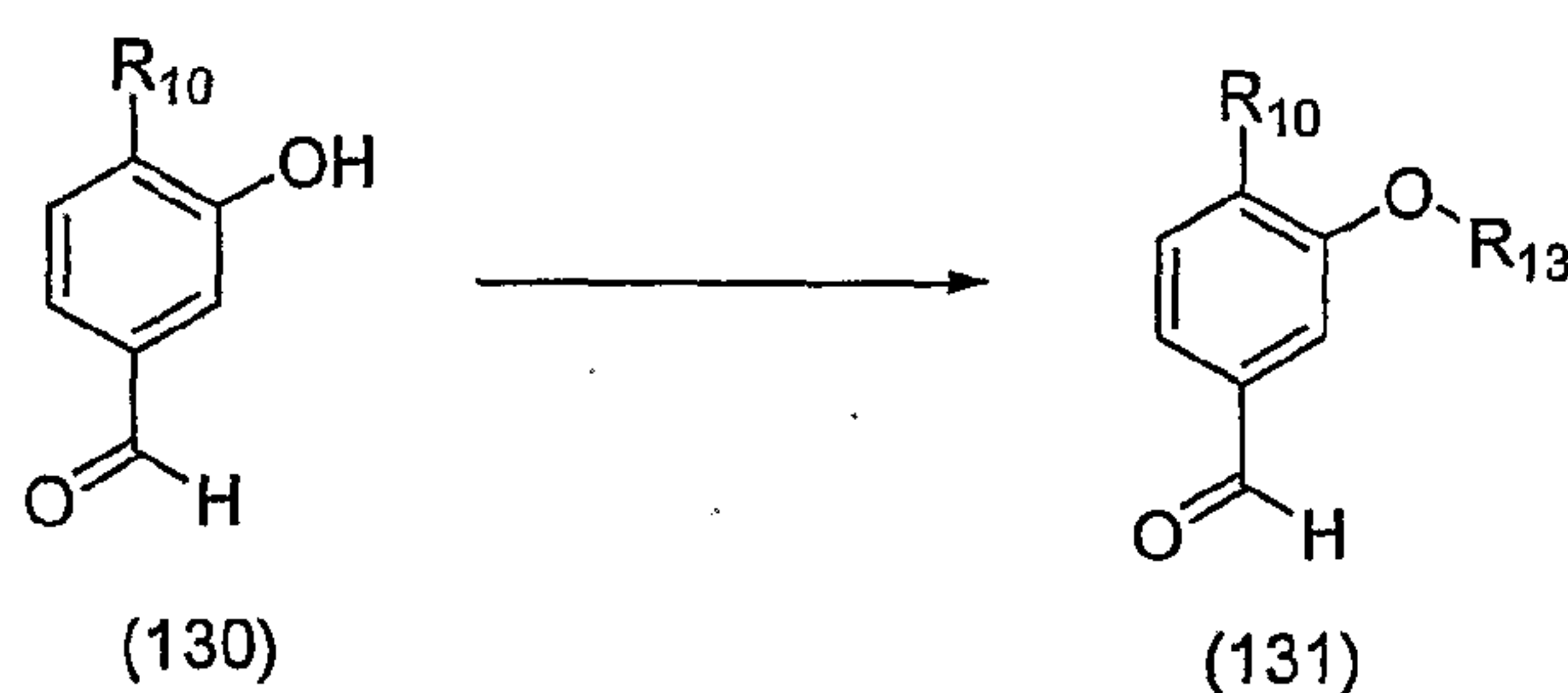
An alternative method of preparing benzaldehydes of general formula (115), wherein R_{10} is selected from alkyl, haloalkyl, chlorine, fluorine, haloalkoxy, alkoxy, alkylthio, $-NZ_1Z_2$, and $-C(O)NZ_1Z_2$, wherein Z_1 and Z_2 are independently selected from hydrogen, alkyl, alkylcarbonyl, aryl, arylalkyl, and formyl, R_{12} is selected from alkyl, hydroxyalkyl, alkylthio, alkylcarbonyl, arylcarbonyl, and formyl, can be used as described in Scheme 44. Protected benzaldehydes of general formula (128), wherein Y is selected from bromine and iodine, and wherein R is selected from alkyl or together with the oxygen atoms to which they are attached form a 5 or 6 membered ring wherein 1,3-dioxolanes are preferred can be converted to the 3,4-disubstituted protected benzaldehyde of general formula (117) via conversion to an intermediate lithio or magnesio derivative, followed by reaction with an appropriate electrophile such as an aldehyde, dialkyldisulfide, a Weinreb amide, dimethylformamide, an alkyl halide or the like. Deprotection of protected benzaldehydes of general structure (117) provide benzaldehydes of general formula (115).

An alternative method of preparing benzaldehydes of general formula (115), wherein R_{10} is selected from alkyl, alkylcarbonyl, alkylsulfonyl, aryl, heteroaryl, cyano, haloalkyl, chlorine, fluorine, haloalkoxy, nitro, alkoxy, and alkylthio, and $-C(O)NZ_1Z_2$, wherein Z_1 and Z_2 are independently selected from hydrogen, alkyl, alkylcarbonyl, aryl, arylalkyl, and formyl, and R_{12} is selected from alkyl, alkynyl, vinyl, aryl, heteroaryl, cyano and the like, is also described in Scheme 44. Protected benzaldehydes of general

formula (128), wherein Y is selected from bromine, iodine, and triflate, and wherein R is selected from alkyl or together with the oxygen atoms to which they are attached form a 5 or 6 membered ring wherein 1,3-dioxolanes are preferred, can be treated with an suitable tin, boronic acid, alkyne, or unsaturated halide reagent in the presence of a catalyst such as a palladium catalyst with heating in a solvent such as dimethylformamide to effect a coupling reaction that provides protected benzaldehydes of general formula (117). Deprotection of the acetal of general formula (117) provides benzaldehydes of general formula (115).

An alternative method of preparing benzaldehydes of general formula (115), wherein R_{10} is selected from alkyl, alkylcarbonyl, alkylsulfonyl, aryl, heteroaryl, cyano, haloalkyl, chlorine, fluorine, haloalkoxy, nitro, alkoxy, and alkylthio, and $-C(O)NZ_1Z_2$, wherein Z_1 and Z_2 are independently selected from hydrogen, alkyl, alkylcarbonyl, aryl, arylalkyl, and formyl, and R_{12} is selected from alkyl, alkynyl, vinyl, aryl, heteroaryl, cyano and the like, is also described in Scheme 44. Benzaldehydes of general formula (129) can be treated with a suitable tin, boronic acid, alkyne, or unsaturated halide reagent in the presence of a catalyst such as a palladium catalyst with heating in a solvent such as dimethylformamide to effect a coupling reaction that provides aldehydes of general formula (115).

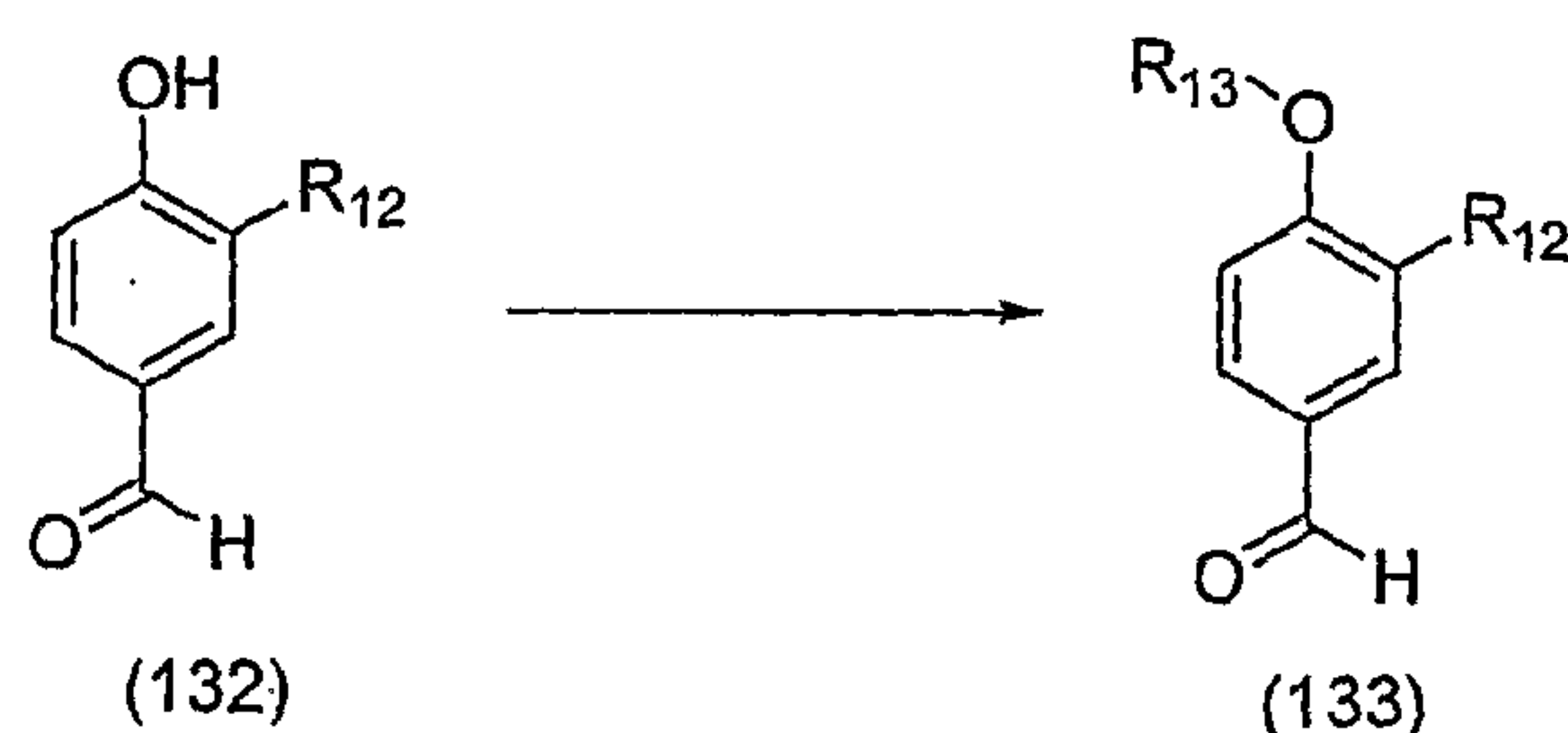
Scheme 45



Benzaldehydes of general formula (131), wherein R_{10} is selected from hydrogen, alkyl, alkylsulfonyl, aryl, heteroaryl, cyano, haloalkyl, halo, haloalkoxy, nitro, alkoxy, alkylthio, $-NZ_1Z_2$, and $-C(O)NZ_1Z_2$, wherein Z_1 and Z_2 are independently selected from hydrogen, alkyl, alkylcarbonyl, aryl, arylalkyl, and formyl, and R_{13} is selected from alkyl, arylalkyl, and haloalkyl wherein preferred haloalkyl groups are selected from

difluoromethyl, 2,2,2-trifluoroethyl and bromodifluoromethyl, can be prepared as
 described in Scheme 45. 3-Hydroxybenzaldehyde of general formula (130) can be treated
 with suitable alkylating reagents such as benzylbromide, iodomethane, 2-iodo-1,1,1-
 trifluoroethane, chlorodifluoromethane, or dibromodifluoromethane in the presence of
 5 base such as potassium carbonate, potassium tert-butoxide or sodium tert-butoxide, to
 provide benzaldehydes of general formula (131). The synthesis of useful 3-
 hydroxybenzaldehydes of general formula (130) may be found in the following literature
 references: J. Chem. Soc. (1923), 2820; J. Med Chem. (1986), 29, 1982; Monatsh.
 Chem. (1963), 94, 1262; Justus Liebigs Ann. Chem. (1897), 294, 381; J. Chem. Soc.
 10 Perkin Trans. 1 (1990), 315; Tetrahedron Lett. (1990), 5495; J. Chem. Soc. Perkin Trans.
 1 (1981), 2677.

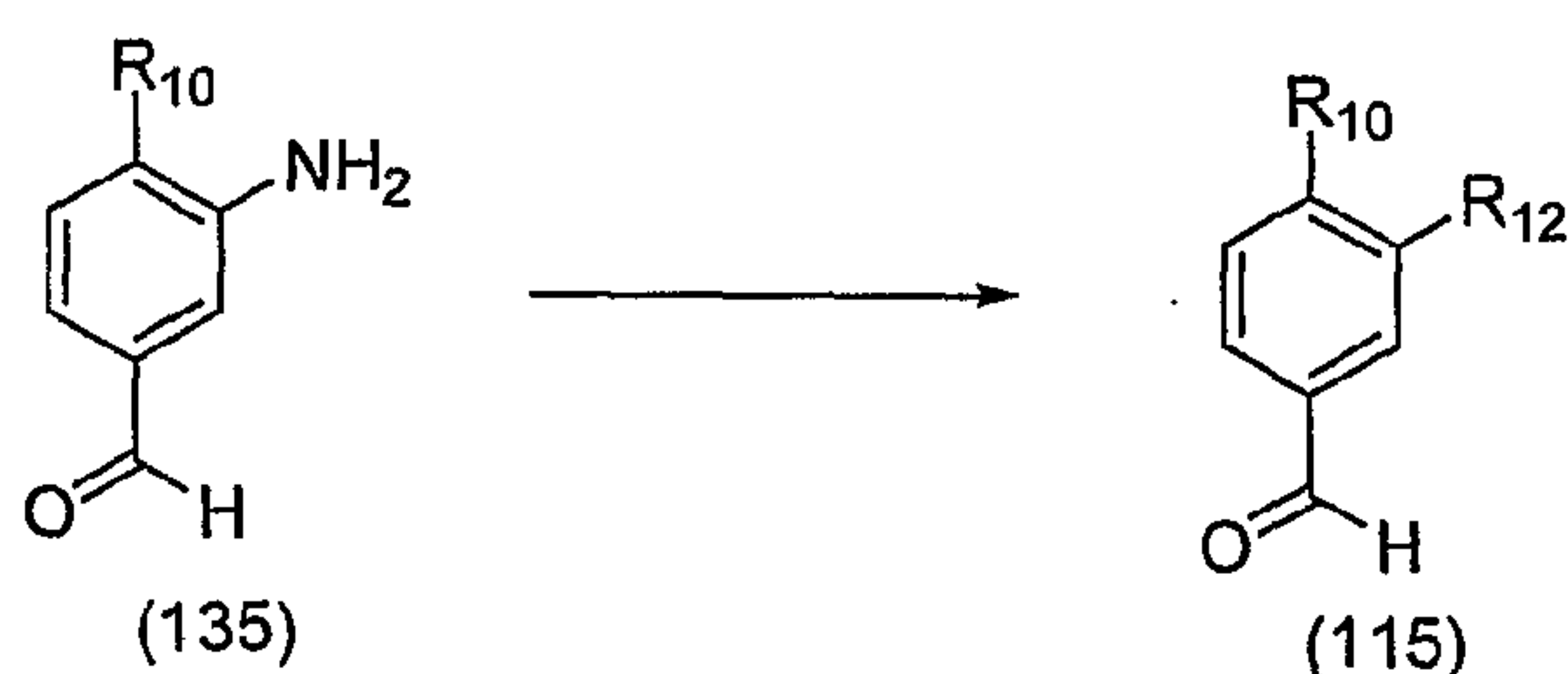
Scheme 46



15 Benzaldehydes of general formula (133), wherein R_{12} is selected from hydrogen,
 alkyl, alkylsulfonyl, aryl, heteroaryl, cyano, haloalkyl, halo, haloalkoxy, nitro, alkoxy,
 alkylthio, $-NZ_1Z_2$, and $-C(O)NZ_1Z_2$, wherein Z_1 and Z_2 are independently selected from
 hydrogen, alkyl, alkylcarbonyl, aryl, arylalkyl, and formyl, and R_{13} is selected from alkyl,
 arylalkyl, and haloalkyl wherein preferred haloalkyl groups are selected from
 20 difluoromethyl, 2,2,2-trifluoroethyl, and bromodifluoromethyl, can be prepared as
 described in Scheme 46. 4-Hydroxybenzaldehydes of general formula (132) can be treated
 with suitable alkylating reagents such as benzylbromide, iodomethane, 2-iodo-1,1,1-
 trifluoroethane, chlorodifluoromethane, or dibromodifluoromethane, in the presence of
 base such as potassium carbonate, potassium tert-butoxide or sodium tert-butoxide to
 25 provide benzaldehydes of general formula (133). The synthesis of useful 4-
 hydroxybenzaldehydes of general formula (132) may be found in the following literature

references: Angyal, J. Chem. Soc. (1950), 2141; Ginsburg, J. Am. Chem. Soc. (1951), 73, 702; Claisen, Justus Liebigs Ann. Chem. (1913), 401, 107; Nagao, Tetrahedron Lett. (1980), 21, 4931; Ferguson, J. Am. Chem. Soc. (1950), 72, 4324; Barnes, J. Chem. Soc. (1950), 2824; Villagomez-Ibarra, Tetrahedron (1995), 51, 9285; Komiyama, J. Am. Chem. Soc. (1983), 105, 2018; DE 87255; Hodgson, J. Chem. Soc. (1929), 469; Hodgson, J. Chem. Soc. (1929), 1641.

Scheme 47



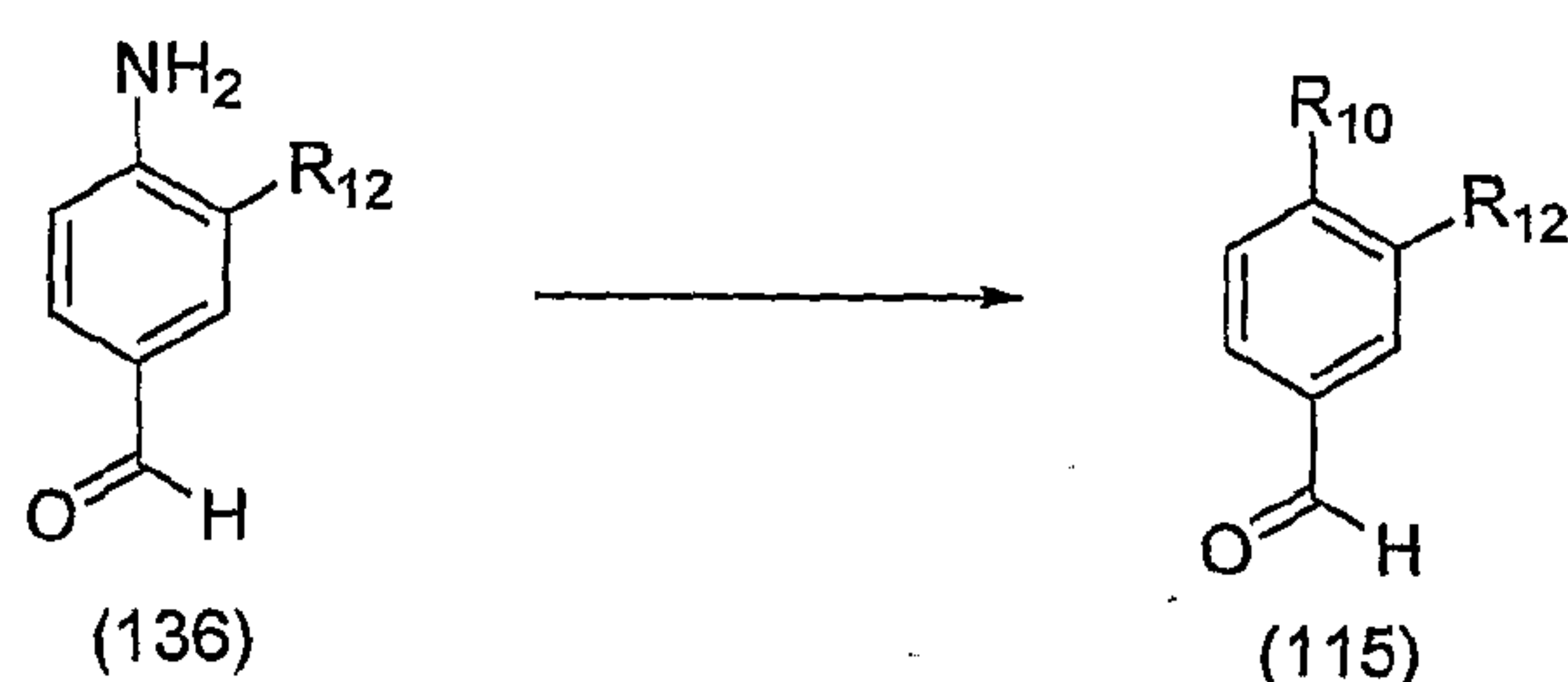
An alternate method for introduction of substituents at the 3-position of benzaldehydes of general formula (115), wherein R_{10} is selected from hydrogen, alkyl, alkylsulfonyl, aryl, heteroaryl, cyano, haloalkyl, halo, haloalkoxy, nitro, alkoxy, alkylthio, and $-C(O)NZ_1Z_2$, wherein Z_1 and Z_2 are independently selected from hydrogen, alkyl, alkylcarbonyl, aryl, arylalkyl, and formyl can be used as described in Scheme 47. This method, also known as the Sandmeyer reaction, involves converting 3-amino benzaldehydes of general formula (135) to an intermediate diazonium salt with sodium nitrite. The diazonium salts can be treated with a bromine or iodine source to provide the bromide or iodide. The Sandmeyer reaction and conditions for effecting the transformation are well known to those skilled in the art of organic chemistry. In order to successfully carry out this transformation it may in certain circumstances be advantageous to perform the Sandmeyer reaction on a protected aldehyde. The types of R_{12} substituents that may be introduced in this fashion include cyano, hydroxy, or halo. In order to successfully carry out this transformation it may in certain circumstances be advantageous to perform the Sandmeyer reaction on a protected aldehyde. The resulting iodide or bromide can then be treated with unsaturated halides, boronic acids or tin reagents in the presence of a palladium catalyst such as tetrakis(triphenylphosphine)palladium (0) to

61

provide benzaldehydes of general formula (115). The diazonium salts can also be treated directly with unsaturated halides, boronic acids or tin reagents in the presence of a palladium catalyst such as tetrakis(triphenylphosphine)palladium (0) to provide benzaldehydes of general formula (115).

5

Scheme 48

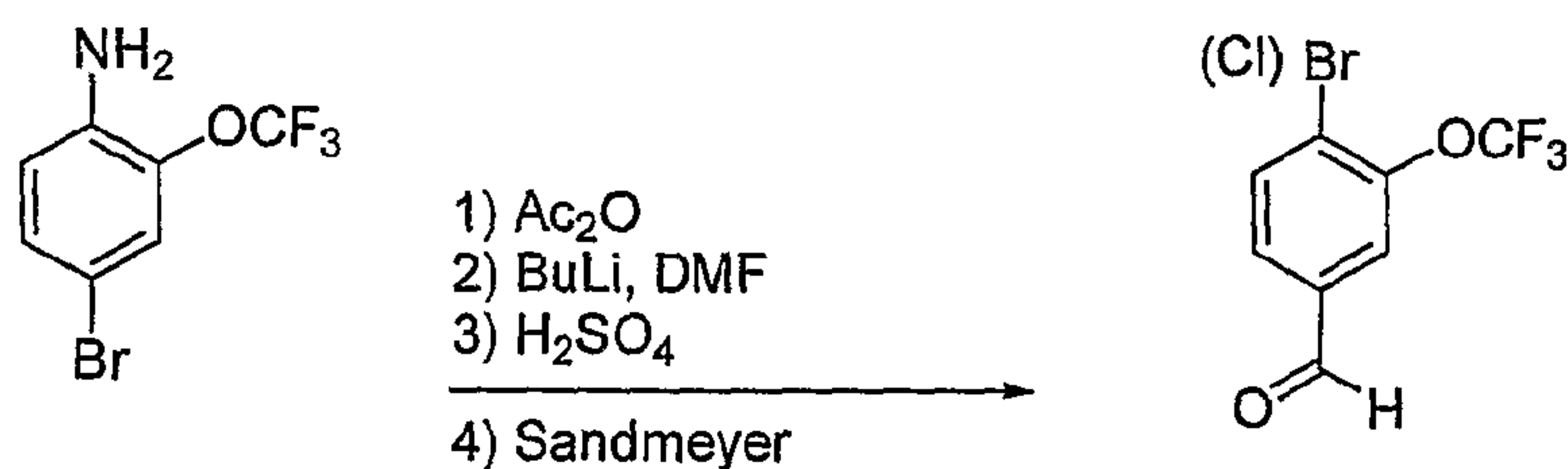


An alternate method for introduction of substituents at the 4-position of benzaldehydes of general formula (115), wherein R₁₂ is selected from hydrogen, alkyl, alkylsulfonyl, aryl, heteroaryl, cyano, haloalkyl, halo, haloalkoxy, nitro, alkoxy, alkylthio, and -C(O)NZ₁Z₂, wherein Z₁ and Z₂ are independently selected from hydrogen, alkyl, alkylcarbonyl, aryl, arylalkyl, and formyl, can be used as described in Scheme 48. This method, also known as the Sandmeyer reaction, involves converting 4-amino benzaldehydes of general formula (136) to an intermediate diazonium salt with sodium nitrite and then treating the diazonium salts in a similar manner as that described in Scheme 47. The types of R₁₀ substituents that may be introduced in this fashion include cyano, hydroxy, or halo. The Sandmeyer reaction and conditions for effecting the transformation are well known to those skilled in the art of organic chemistry. In order to successfully carry out this transformation it may in certain circumstances be advantageous to perform the Sandmeyer reaction on a protected aldehyde.

20

62

Scheme 49



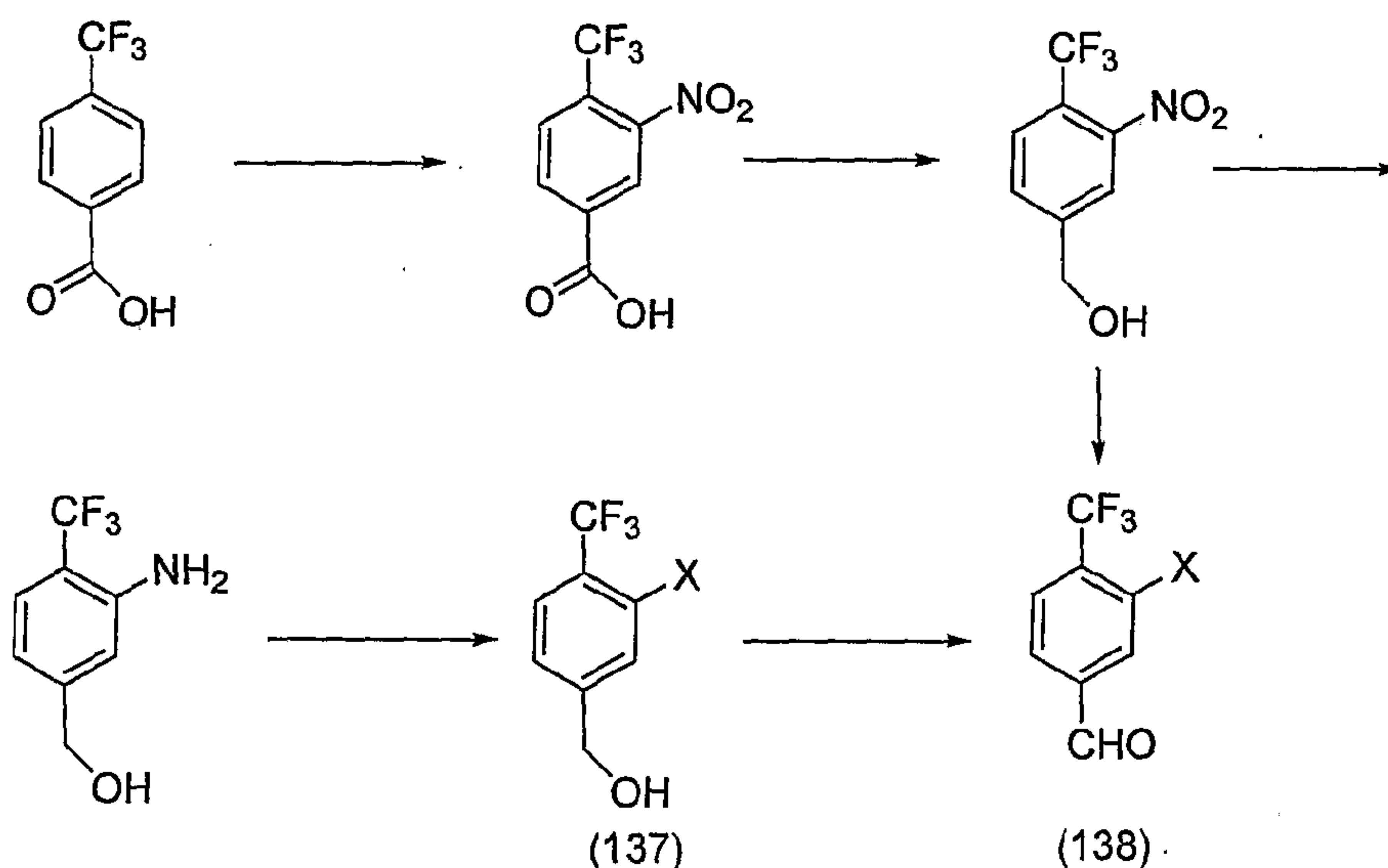
4-Bromo-3-(trifluoromethoxy)benzaldehyde or 4-chloro-3-

(trifluoromethoxy)benzaldehyde can be prepared as described in Scheme 49. The

commercially available 4-bromo-2-(trifluoromethoxy)aniline can be protected on the amino group with a suitable N-protecting group well known to those skilled in the art of organic chemistry such as acetyl or tert-butoxycarbonyl. The bromine can then be converted to the lithio or magnesio derivative and reacted directly with dimethylformamide to provide the 4-aminoprotected-3-(trifluoromethoxy)benzaldehyde derivative. Removal of the N-protecting group followed by conversion of the amine to a bromide or chloride via the Sandmeyer method of Scheme 47 followed by hydrolysis of the dioxolane provides 4-bromo-3-(trifluoromethoxy)benzaldehyde or 4-chloro-3-(trifluoromethoxy)benzaldehyde.

15

Scheme 50

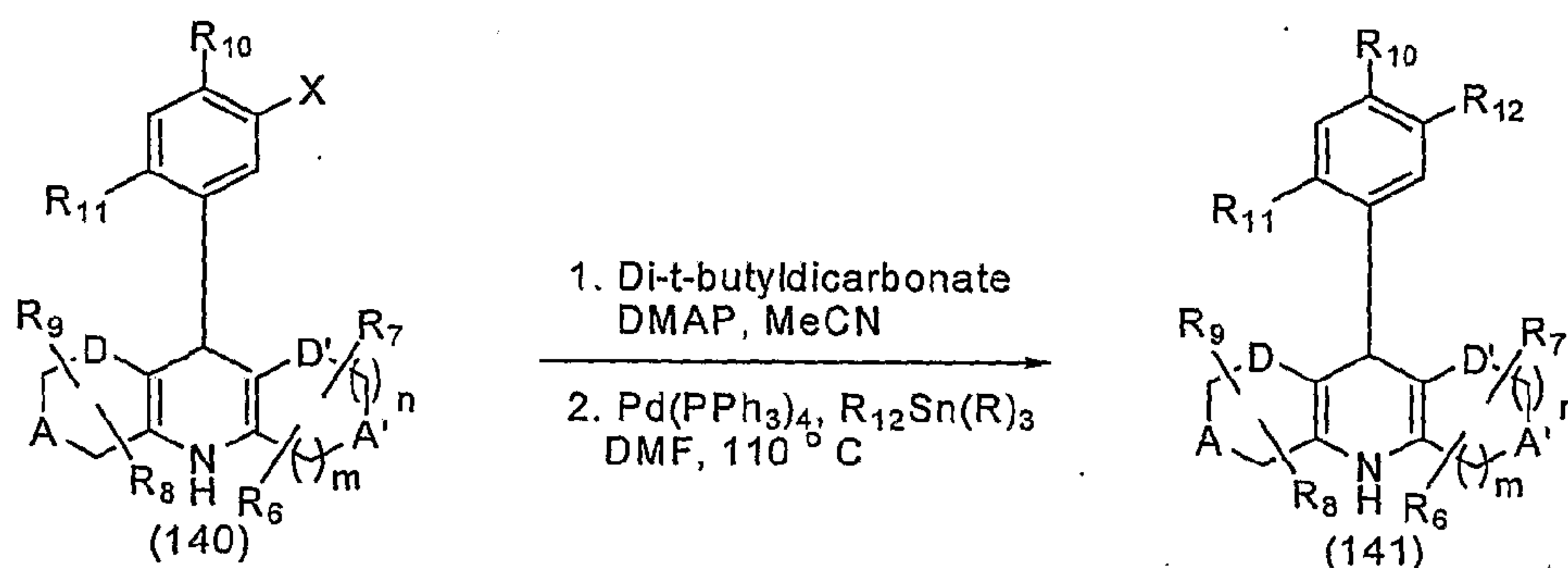


4-Trifluoromethylbenzaldehydes of general formula (138), wherein X is selected from cyano, nitro, and halo may be prepared according to the method of Scheme 50. 4-

Trifluoromethylbenzoic acid is first nitrated, using suitable conditions well known in the literature such as nitric acid with sulfuric acid, and the carboxylic acid group reduced with borane to provide 3-nitro-4-trifluoromethylbenzyl alcohol. 3-Nitro-4-trifluoromethylbenzyl alcohol may be oxidized directly to 3-nitro-4-trifluoromethylbenzaldehyde by oxidation with typical reagents such as manganese dioxide. Alternatively, 3-nitro-4-trifluoromethylbenzyl alcohol can be reduced to the corresponding aniline using any of a number of different conditions for effecting this transformation among which a preferred method is hydrogenation over a palladium catalyst. The aniline can be converted to either a halo or cyano substituent using the Sandmeyer reaction described in Scheme 47 providing benzyl alcohols of general structure (137). Benzyl alcohols of general formula (137) can be oxidized using conditions well known to those skilled in the art such as manganese dioxide or Swern conditions to provide benzaldehydes of general formula (138).

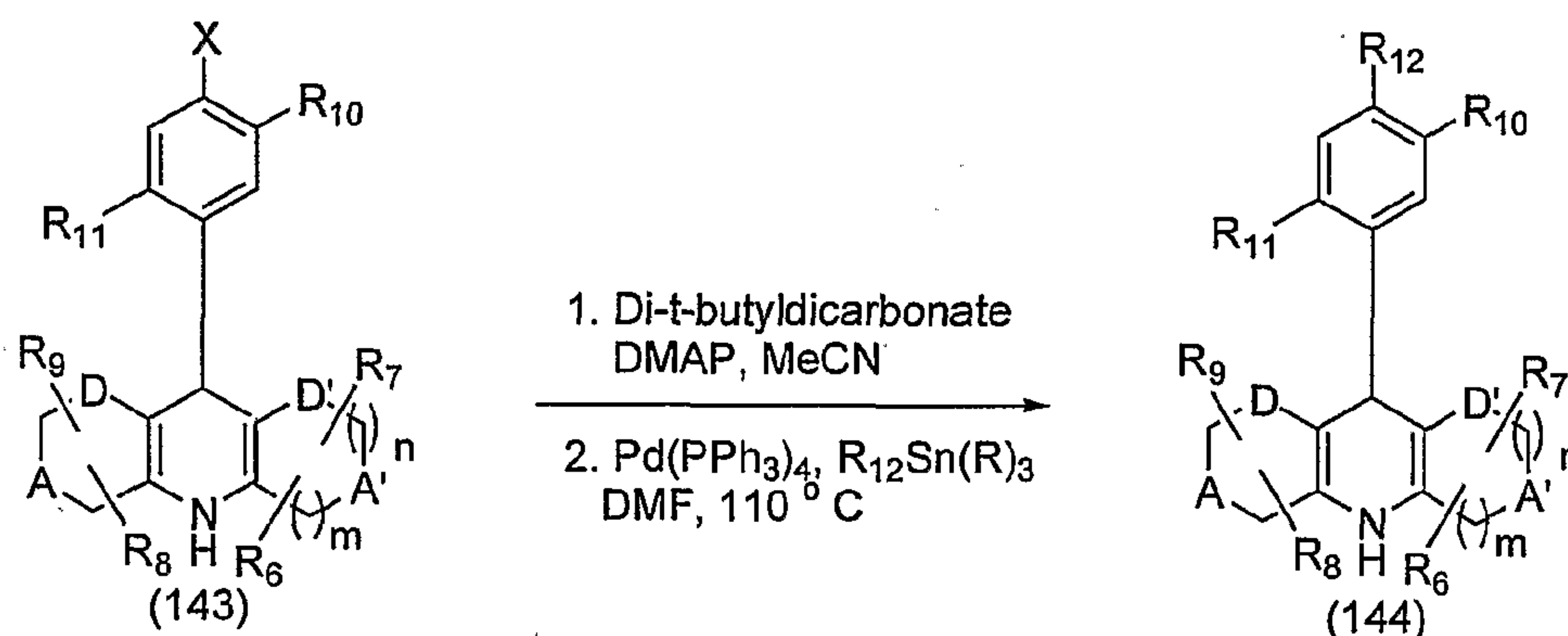
For certain aromatic ring substitutions of R_1 for compounds of the present invention it is preferable to effect transformations of the aromatic ring substitutions after the aldehyde has been incorporated into the core structure of the present invention. As such, compounds of the present invention may be further transformed to other distinct compounds of the present invention. These transformations involve Stille, Suzuki and Heck coupling reactions all of which are well known to those skilled in the art of organic chemistry. Shown below are some representative methods of such transformations of compounds of the present invention to other compounds of the present invention.

Scheme 51



Dihydropyridines of general formula (141), wherein A, A', D, D', R₆, R₇, R₈, R₉, n and m are as defined in formula I, R₁₀ is selected from hydrogen, alkyl, alkylcarbonyl, alkylsulfonyl, aryl, heteroaryl, cyano, haloalkyl, chlorine, fluorine, haloalkoxy, nitro, alkoxy, and alkylthio, and -C(O)NZ₁Z₂, wherein Z₁ and Z₂ are independently selected from hydrogen, alkyl, alkylcarbonyl, aryl, arylalkyl, and formyl, R₁₁ is selected from hydrogen, hydroxy, alkoxy, haloalkoxy, and arylalkoxy, R₁₂ is selected from alkyl, vinyl, aryl, heteroaryl, cyano and the like, can be prepared as described in Scheme 51. Compounds of general formula (140), wherein X is selected from bromine, iodine, and triflate, are protected with a tert-butoxycarbonyl (Boc) group using standard procedures. The aromatic bromide, iodide, or triflate can be treated with a suitable tin, boronic acid, or unsaturated halide reagent in the presence of a palladium catalyst with heating in a solvent such as dimethylformamide to effect a coupling reaction that provides dihydropyridines of general formula (141). The conditions for this transformation also effect the removal of the Boc protecting group.

Scheme 52

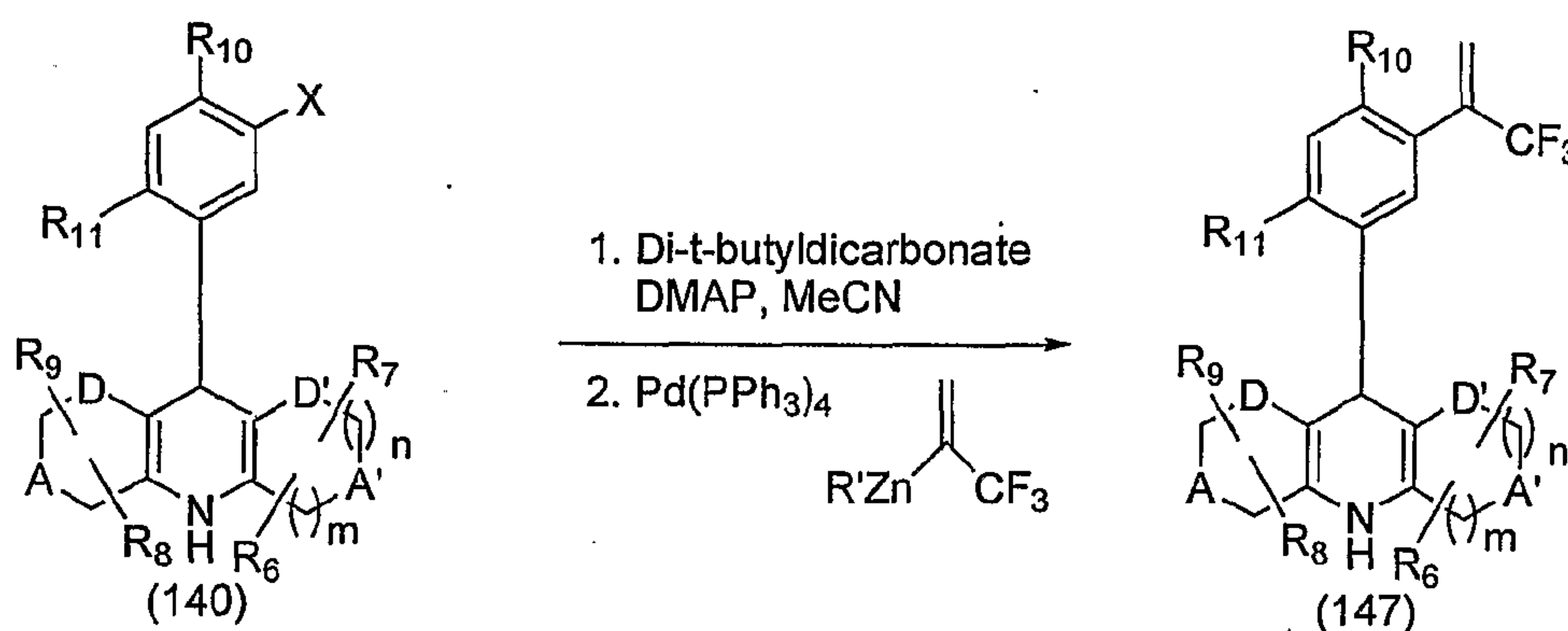


Dihydropyridines of general formula (144), wherein A, A', D, D', R₆, R₇, R₈, R₉, m, and n are as defined in formula I, R₁₀ is selected from hydrogen, alkyl, alkylcarbonyl, alkylsulfonyl, aryl, heteroaryl, cyano, haloalkyl, chlorine, fluorine, haloalkoxy, nitro, alkoxy, alkylthio, and -C(O)NZ₁Z₂, wherein Z₁ and Z₂ are independently selected from hydrogen, alkyl, alkylcarbonyl, aryl, arylalkyl, and formyl, R₁₁ is selected from hydrogen, hydroxy, alkoxy, haloalkoxy, and arylalkoxy, R₁₂ is selected from alkyl, vinyl, aryl, heteroaryl, cyano and the like, can be prepared as described in Scheme 52.

65

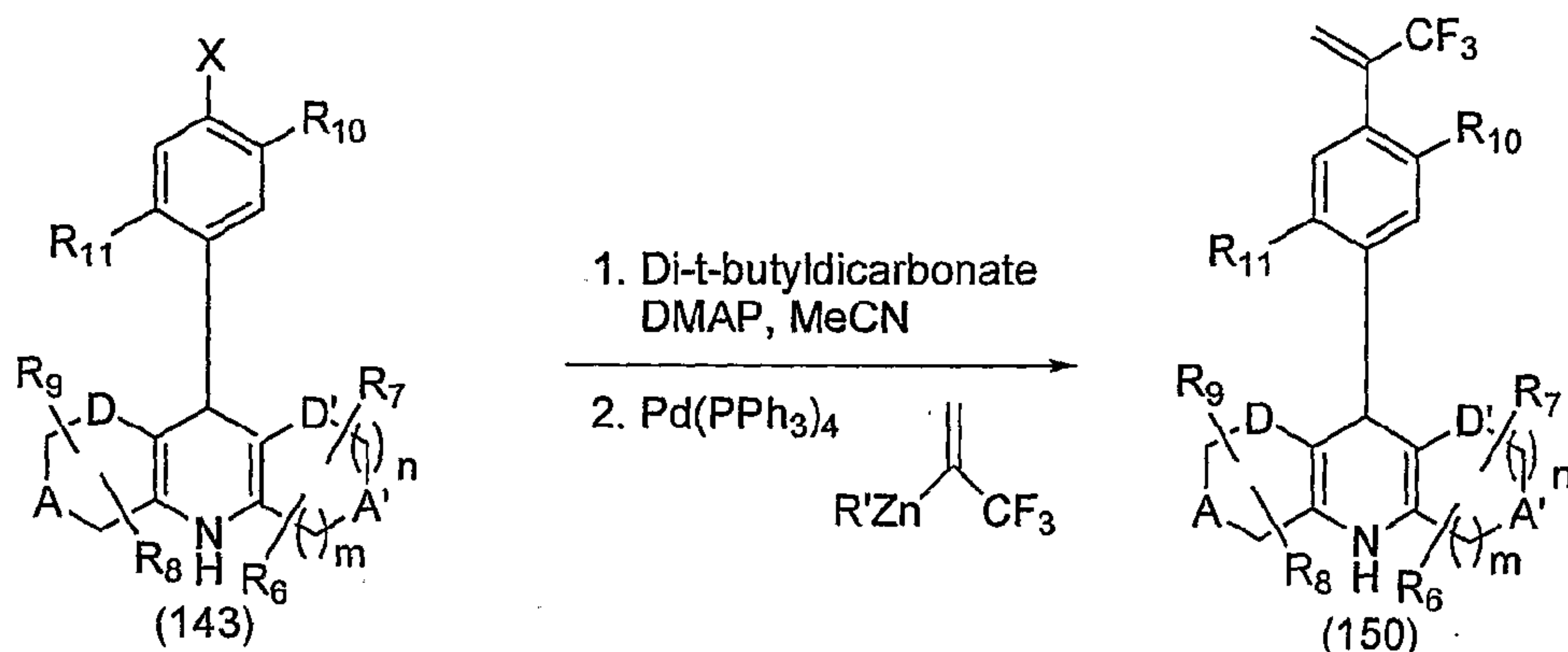
Dihydropyridines of general formula (143), wherein X is selected from bromine, iodine, and triflate, can be protected with a tert-butoxycarbonyl (Boc) group using standard procedures. The aromatic bromide, iodide, or triflate can be reacted with a suitable tin, boronic acid, or unsaturated halide reagent in the presence of a palladium catalyst with heating in a solvent such as dimethylformamide to effect a coupling reaction that provides dihydropyridines of general formula (144). The conditions for this transformation also effect the removal of the Boc protecting group.

Scheme 53



Dihydropyridines of general formula (147), wherein A, A', D, D', R_6 , R_7 , R_8 , R_9 , m, and n are as defined in formula I, R_{10} is selected from hydrogen, alkyl, alkylcarbonyl, alkylsulfonyl, aryl, heteroaryl, cyano, haloalkyl, chlorine, fluorine, haloalkoxy, nitro, alkoxy, alkylthio, and $-\text{C}(\text{O})\text{NZ}_1\text{Z}_2$, wherein Z_1 and Z_2 are independently selected from hydrogen, alkyl, alkylcarbonyl, aryl, arylalkyl, and formyl, and R_{11} is selected from hydrogen, hydroxy, alkoxy, haloalkoxy, and arylalkoxy, can be prepared as described in Scheme 53. Dihydropyridines of general formula (140), wherein X is selected from bromine, iodine, and triflate can be protected with a tert-butoxycarbonyl (Boc) group using standard procedures. The aromatic bromide, iodide, or triflate can be treated with a suitable halozinc reagent in the presence of a palladium catalyst with heating in a solvent such as dimethylformamide to effect a coupling reaction that provides dihydropyridines of general formula (147). The conditions for this transformation also effect the removal of the Boc protecting group. The types of meta substituents that may be introduced in this fashion include trihalopropenyl and more specifically the trifluoropropenyl group.

Scheme 54

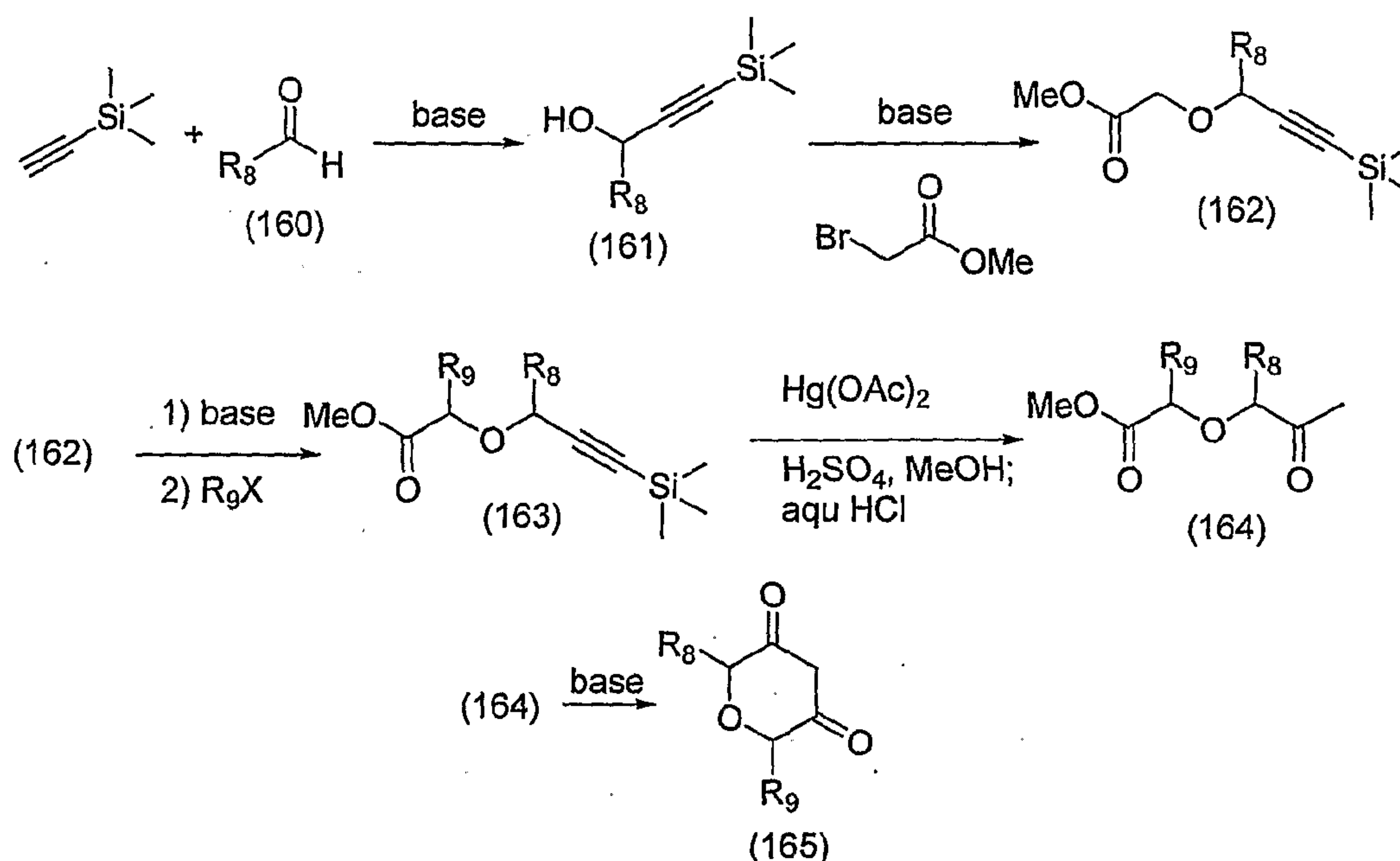


Dihydropyridines of general formula (150), wherein A, A', D, D', R₆, R₇, R₈, R₉, m and n are as defined in formula I, R₁₀ is selected from hydrogen, alkyl, alkylcarbonyl, alkylsulfonyl, aryl, heteroaryl, cyano, haloalkyl, chlorine, fluorine, haloalkoxy, nitro, alkoxy, alkylthio, -C(O)NZ₁Z₂, wherein Z₁ and Z₂ are independently selected from hydrogen, alkyl, alkylcarbonyl, aryl, arylalkyl, and formyl, R₁₁ is selected from hydrogen, hydroxy, alkoxy, haloalkoxy, and arylalkoxy, can be prepared as described in Scheme 54.

Dihydropyridines of general formula (143), wherein X is selected from bromine, iodine, and triflate can be protected with a tert-butoxycarbonyl (Boc) group using standard procedures. The aromatic bromide, iodide, or triflate can be treated with a suitable halozinc reagent in the presence of a palladium catalyst with heating in a solvent such as dimethylformamide to effect a coupling reaction that provides dihydropyridines of general formula (150). The conditions for this transformation also effect the removal of the Boc protecting group. The types of para substituents that may be introduced in this fashion include trihalopropenyl and more specifically the trifluoropropenyl group.

67

Scheme 55



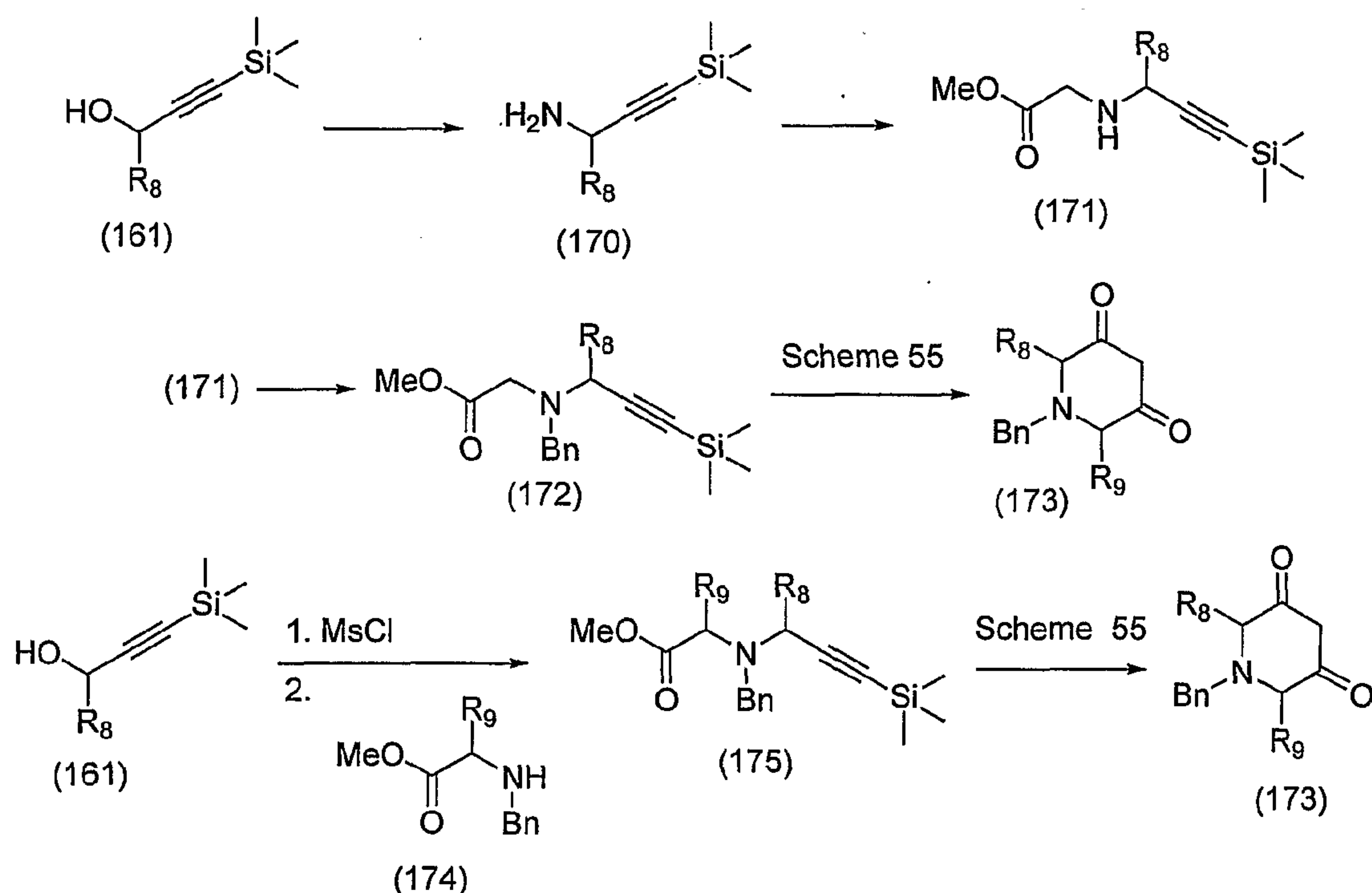
Dicarbonyl pyrans of general formula (165), wherein R_8 and R_9 are as defined in formula I, can be prepared as described in Scheme 55. (Trimethylsilyl)acetylene can be deprotonated with a base such as n-butyllithium, methyllithium or ethyl magnesium bromide in a solvent such as diethyl ether or tetrahydrofuran and then treated with an aldehyde of general formula (160) to provide propargyl alcohols of general formula (161). Propargyl alcohols of general formula (161) can be treated with a base such as sodium hydride and then treated with methyl bromoacetate in a solvent such as tetrahydrofuran to provide alkynes of general formula (162). Alkynes of general formula (162) can be treated with a base such as lithium diisopropylamide or lithium bis(trimethylsilyl)amide and then treated with an alkylating agent such as an alkyl halide, alkyl triflate or the like in a solvent such as tetrahydrofuran to provide alkynes of general formula (163). Alkynes of general formula (163) can be treated with a source of mercury(II) such as mercury(II) acetate in the presence of acid in a solvent such as methanol followed by treatment with aqueous acid to provide methyl ketones of general formula (164). Methyl ketones of general formula (164) can be treated with a base such as potassium tert-butoxide to provide dicarbonyl pyrans of general formula (165). Dicarbonyl pyrans of general formula

(165) can be processed as described in previous schemes to provide compounds of the present invention.

Propargyl alcohols of general formula (161) can be separated into single enantiomers as described in (Burgess, J. Amer. Chem. Soc. (1990), 112, 7434-7435; Burgess, J. Amer. Chem. Soc. (1991), 113, 6129-6139; Takano, Synthesis (1993), 12, 1253-1256; and Allevi, Tetrahedron Assymetry (1997), 8, 93-100). Single enantiomers of general formula (161) can be processed as described in Scheme 55 to provide enantiomerically pure dicarbonyl pyrans of general formula (165).

10

Scheme 56



15

Dicarbonyl piperidines of general structure (173), wherein R_8 and R_9 are as defined in formula I, can be prepared as described in Scheme 56. Propargyl alcohols of general formula (161) from Scheme 55 can be converted to amines of general formula (170) under Mitsunobu conditions directly using ammonia or indirectly through an azide or a phthalimide intermediate as described in (Holmes, J. Chem. Soc. Perkin Trans. 1, (1991), 12, 3301-3306; Tabor, J. Chem. Soc., Chem. Comm. (1989), 15, 1025-1027; Cossy, Bioorg. Med. Chem. Lett. (1997), 7, 1699-1700; Mukai, Tett. Lett. (1991), 32, 7553-7556;

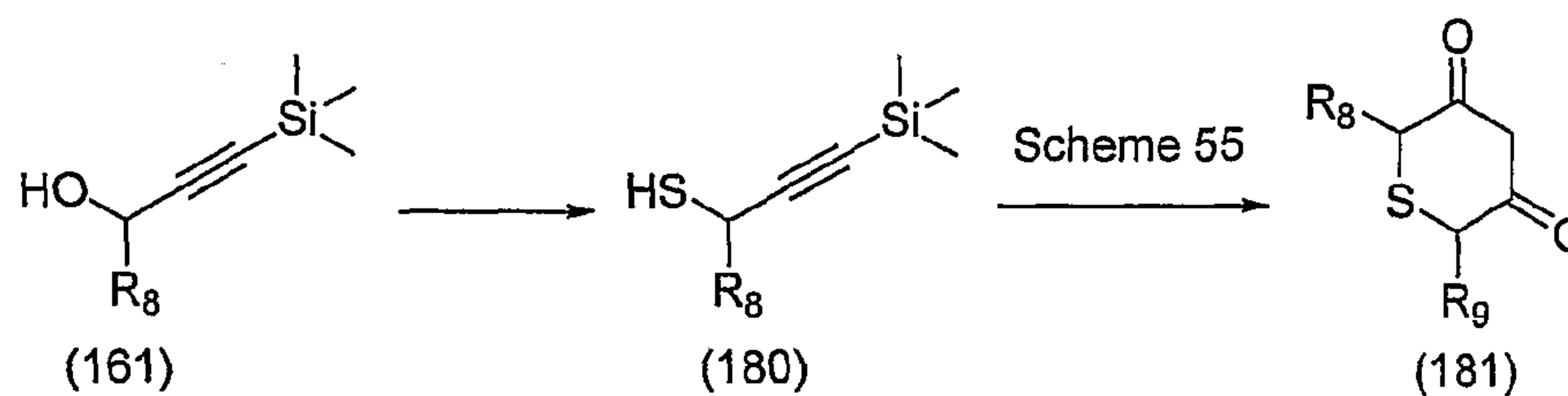
and Mukai, J. Chem. Soc., Perkin Trans. 1, (1993), 5, 563-572). Amines of general formula (170) can be treated with methyl bromoacetate to provide aminoesters of general formula (171). Aminoesters of general formula (171) can be benzylated using a benzylating agent such as benzyl bromide in the presence of a base such as triethylamine to provide esters of general formula (172). Esters of general formula (172) can be processed as described in Scheme 55 to provide dicarbonyl compounds of general formula (173). Dicarbonyl piperidines of general structure (173) can be used as described in previous Schemes to provide compounds of the present invention.

An alternate method of preparing dicarbonyl compounds of general structure (173) can be used as described in Scheme 56. Propargyl alcohols of general formula (161) from Scheme 55 can be treated with methanesulfonyl chloride or the like to provide an intermediate sulfonate which can be further treated with a N-benzyl protected amino acid ester of general formula (174) to provide esters of general formula (175) as described in (Olsson, Acta Chem. Scand. Ser. B (1979), 33, 679-684; Geri, Gazz. Chim. Ital. (1994), 124, 241-248; Imada, J. Org. Chem, (1983), 26, 1036-1042; Sahlberg, J. Med. Chem. (1983), 26, 1036-1042; Bates, Tetrahedron (1995), 51, 12939-12954). Many N-benzyl protected amino acid ester of general formula (174) are known in the literature and can be synthesized enantiomerically pure. Esters of general formula (175) can be processed as described in Scheme 55 to provide dicarbonyl compounds of general structure (173).

Chiral dicarbonyl piperidines of general structure (173) can be prepared as described in Scheme 56. Enantiomerically pure propargyl alcohols of general formula (161) can be processed to provide enantiomerically pure dicarbonyl piperidines of general structure (173). Enantiomerically pure N-benzyl protected amino acid ester of general formula (174) can be processed to provide enantiomerically pure dicarbonyl piperidines of general structure (173).

70

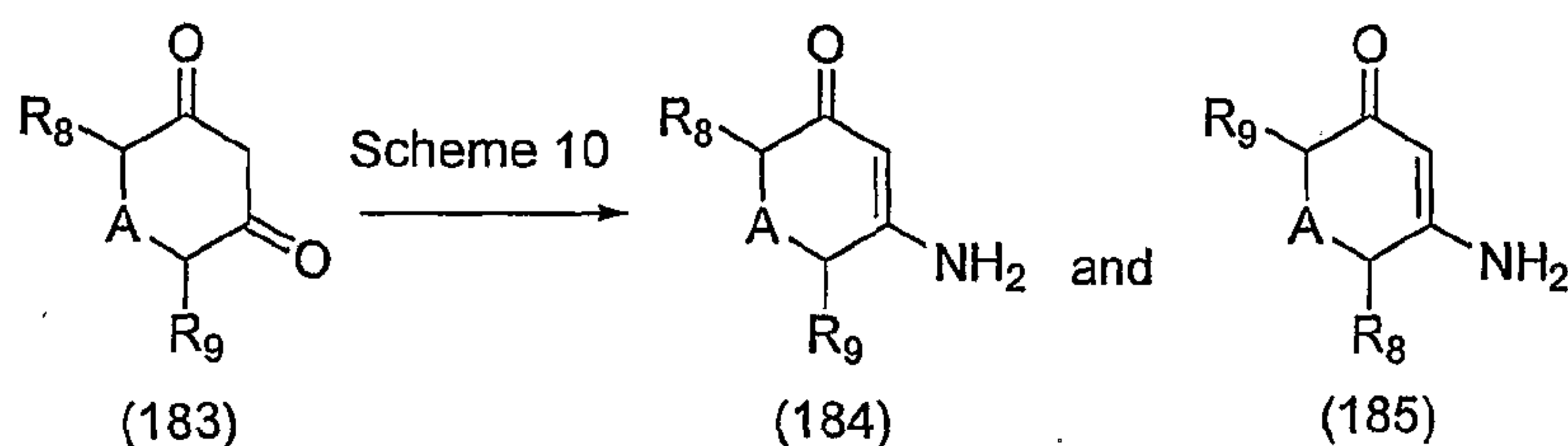
Scheme 57



Dicarbonyl thiopyrans of general structure (181), wherein R₈ and R₉ are as defined in formula I, can be prepared as described in Scheme 57. Propargyl alcohols of general formula (161) from Scheme 55 can be converted to the corresponding chlorides using chlorinating agents well known to those of skill in the art such as phosphorous oxychloride and then treated with a source of sulfur such as sodium hydrogen sulfide to provide thiols of general formula (180) as described in (Komasov, Bull. Acad. Sci. USSR Div. Chem. Sci. (Engl. Trans.) (1963), 81-85). Thiols of general structure (180) can be processed as described in Scheme 55 to provide dicarbonyl thiopyrans of general structure (181). Dicarbonyl thiopyrans of general structure (181) can be processed as described in previous Schemes to provide compounds of the present invention.

Alternatively, dicarbonyl compounds of general formula (181) may be prepared using procedures as described in (Bergel, Nature(London) (1945), 155, 481).

Scheme 58



Enaminones of general formula (184) and (185) can be prepared as described in Scheme 58. Dicarbonyl compounds of general structure (183) can be processed as described in Scheme 10 to provide enaminones of general formula (184) and (185). Enaminones of general formula (184) and (185) can be processed as described in the previous Schemes to provide compounds of the present invention.

In addition to the use of the methods illustrated in Schemes 37 and 38, individual enantiomers of compounds of the present invention may also be separated by chiral chromatography.

5

Example 15-(3-bromo-4-fluorophenyl)-5,10-dihydro-1H,3H-dipyran[3,4-b:4,3-e]pyridine-4,6(7H,9H)-dione

A solution of tetrahydropyran-3,5-dione (Terasawa, J. Org. Chem. (1977), 42, 1163-1169) (1.2 g, 10.5 mmol), 3-bromo-4-fluorobenzaldehyde (1.1 g, 5.4 mmol) and
10 2.0M ammonia in ethyl alcohol (8 mL, 16 mmol) was heated in a sealed tube to 80°C for 36 hours and then allowed to cool to ambient temperature. The insolubles were filtered off and the filtrate evaporated to dryness. The residue was purified by flash chromatography over silica gel (5% methanol/methylene chloride) to provide an orange foam that was
15 triturated with ether and ethyl acetate to provide the title compound (111 mg) as an orange solid.

mp >250°C;

MS (APCI(+)) m/z 392 (M-H)⁺;¹H NMR (DMSO-d₆) δ 4.06 (s, 4H), 4.41-4.60 (AB qu, 4H), 4.94 (s, 1H), 7.19-7.32 (m, 2H), 7.42 (dd, 1H), 10.12 (br s, 1H);

20 Anal. Calcd for C₁₇H₁₃BrFNO₄·0.5 H₂O: C, 50.64; H, 3.49; N, 3.47. Found: C, 50.66; H, 3.56; N, 3.90.

Example 25-(3-bromo-4-fluorophenyl)-2,3,5,8,9,10-hexahydrobenzo
25 [b][1,7]naphthyridine-4,6(1H,7H)-dione hydrochloride

72

Example 2A2-benzyl-5-(3-bromo-4-fluorophenyl)-2,3,5,8,9,10-hexahydrobenzo[b][1,7]naphthyridine-4,6(1H,7H)-dione hydrochloride

A solution of 3-amino-2-cyclohexen-1-one (0.55 g, 5.0 mmol), 3-bromo-4-fluorobenzaldehyde (1.01 g, 5.0 mmol) and N-benzylpiperidine-3,5-dione (Ziegler, J. Amer. Chem. Soc. (1973), 95, 7458-7464) (1.01 g, 5.0 mmol) was heated for 3 days in ethyl alcohol (10 mL) in a sealed tube and then allowed to cool to ambient temperature. The solvent was evaporated and the residue was purified by flash chromatography over silica gel (5% ethanol/methylene chloride) to provide the title compound (0.84 g) which was converted to the HCl salt.

mp 240-241°C;

MS (DCI/NH₃) m/z 481 (M+H)⁺;

¹H NMR (CDCl₃)(free base) δ 2.0 (m, 2H), 2.67 (m, 2H), 2.48 (m, 2H), 3.05-3.48 (m, 4H), 3.7 (m, 2H), 5.1 (s, 1H), 6.05 (bs, 1H), 6.99 (t, 1H), 7.32 (m, 6H), 7.41 (dd, 1H);

Anal. Calcd for C₂₅H₂₂BrFN₂O₂·HCl: C, 57.99; H, 4.48; N, 5.41. Found: C, 57.87; H, 4.46; N, 5.35.

Example 2Bvinyl 5-(3-bromo-4-fluorophenyl)-4,6-dioxo-3,4,5,6,7,8,9,10-octahydrobenzo[b][1,7]naphthyridine-2(1H)-carboxylate

A solution of the free base of the product from Example 2A (0.40 g, 0.83 mmol) in methylene chloride (50 mL) was treated with vinyl chloroformate (0.085 mL) and allowed to stir at ambient temperature overnight. The solvent was evaporated and the residue was purified by flash chromatography over silica gel (5:95:1 ethanol/methylene chloride/saturated ammonium hydroxide) to provide the title compound (0.25 g).

MS (ESI(+)) m/z 461 (M+H)⁺;

¹H NMR(CDCl₃) δ 2.08 (m, 2H), 2.4 (m, 2H), 2.55 (m, 2H), 3.9 (d, 1H), 4.15 (d, 1H), 4.43 (d, 1H), 4.57 (d, 1H), 4.75 (d, 1H), 4.85 (d, 1H), 5.12 (s, 1H), 6.9 (t, 1H), 7.14 (m, 1H), 7.3 (m, 1H), 7.48 (m, 1H).

73

Example 2C5-(3-bromo-4-fluorophenyl)-2,3,5,8,9,10-hexahydrobenzo[b][1,7]naphthyridine-4,6(1H,7H)-dione hydrochloride

A solution of the product from Example 2B (0.25 g) in ethyl alcohol (20 mL) was
5 treated with 6M HCl (20 mL) and heated to reflux for 1.5 hours. The ethyl alcohol was
evaporated and the aqueous portion basified with 1N sodium hydroxide. The basified
solution was extracted with methylene chloride (3x). The combined methylene chloride
extractions were concentrated and the residue was purified by flash chromatography over
silica gel (10:90:1 ethanol/methylene chloride/saturated ammonium hydroxide) to provide
10 the title compound (0.10g) which was converted to the hydrochloride salt.

mp 220-222°C;

MS (ESI(+)) m/z 391 (M+H)⁺;

MS (ESI(-)) m/z 389 (M-H)⁻;

¹H NMR (DMSO-d₆) (free base) δ 1.72-2.0 (m, 2H), 2.21 (t, 2H), 2.51 (m, 2H), 3.17 (s,
15 2H), 3.58 (m, 2H), 4.89 (s, 1H), 7.19 (m, 2H), 7.4 (m, 1H), 9.6 (s, 1H);-

Anal. Calcd for C₁₈H₁₅N₂FBrO₂·HCl: C, 50.67; H, 3.78; N, 6.51. Found: C, 50.73; H, 4.34;
N, 6.18.

Example 35-(3-bromo-4-fluorophenyl)-2-methyl-2,3,5,8,9,10-hexahydrobenzo[b][1,7]naphthyridine-4,6(1H,7H)-dione hydrochloride

A solution of the product from Example 2C (0.10 g) in methyl alcohol (4 mL) was
treated with 37% aqueous formaldehyde (0.4 mL), sodium cyanoborohydride (23 mg) and
glacial acetic acid (added dropwise to bring the pH to 5) and allowed to stir overnight at
25 ambient temperature. The reaction mixture was concentrated and the residue partitioned
between aqueous sodium bicarbonate and methylene chloride. The methylene chloride
layer was dried with sodium sulfate, filtered, and the solvent evaporated to provide the free
base of the title compound (70 mg). The free base was converted to the hydrochloride salt
and crystallized from ethanol/ether.

30 mp 248-250°C;

74

MS (APCI(+)) m/z 405 (M+H)⁺;

¹H NMR (DMSO-d₆) (free base) δ 1.78-2.0 (m, 2H), 2.22 (m, 2H), 2.29 (s, 3H), 3.1 (m, 2H), 3.5 (m, 2H), 4.83 (s, 1H), 7.15 (m, 1H), 7.2 (t, 1H), 7.37 (dd, 1H), 9.72 (s, 1H);

Anal. Calcd for C₁₉H₁₇N₂FBrO₂·HCl: C, 51.78; H, 4.11; N, 6.35. Found: C, 51.73; H, 4.40;

N, 6.21.

Example 4

5-(3-bromo-4-fluorophenyl)-2,3,5,8,9,10-hexahydropyrido
[3,4-b][1,7]naphthyridine-4,6(1H,7H)-dione dihydrochloride

Example 4A

2,8-dibenzyl-5-(3-bromo-4-fluorophenyl)-2,3,5,8,9,10-hexahydropyrido[3,4-
b][1,7]naphthyridine-4,6(1H,7H)-dione

A solution of N-benzylpiperidine-3,5-dione (Ziegler, J. Amer. Chem. Soc. (1973),
95, 7458-7464) (2.2 g, 10 mmol), 3-bromo-4-fluorobenzaldehyde (1.02 g, 5.0 mmol) and
2.0 M ammonia in ethyl alcohol (2.5 mL) was heated in ethyl alcohol (10 mL) at 70 °C for
3 days. The reaction mixture was allowed to cool to ambient temperature and was
concentrated. The residue was purified by chromatography over silica gel (5%
ethanol/methylene chloride) to provide the title compound (0.62g).

MS (ESI(-)) m/z 570 (M-H)⁻;

¹H NMR (DMSO-d₆) δ 2.97 (d, 2H), 3.16 (m, 2H), 3.42 (m, 3H), 3.61 (q, 4H), 4.82 (s,
1H), 7.13-7.42 (m, 13H), 9.32 (s, 1H).

Example 4B

divinyl 5-(3-bromo-4-fluorophenyl)-4,6-dioxo-4,5,6,7,9,10-hexahydropyrido[3,4-
b][1,7]naphthyridine-2,8(1H,3H)-dicarboxylate

A solution of the product from Example 4A (0.5 g, 0.87 mmol) in methylene
chloride (5 mL) was treated with vinyl chloroformate, (0.16 mL, 1.9 mmol) and allowed to
stir at ambient temperature overnight. The solvent was evaporated and the residue purified
by flash chromatography over silica gel (8:2 ethyl acetate/hexane) to provide the title

75

compound (0.30 g).

MS (ESI(+)) m/z 532 (M+H)⁺;

¹H NMR (DMSO-d₆) δ 3.95 (d, 2H), 4.2 (d, 2H), 4.46 (d, 2H), 4.65 (d, 2H), 4.77-4.94 (m, 4H), 5.15 (s, 1H), 7.0 (t, 1H), 7.1 (d, 1H), 7.14 (d, 1H), 7.32 (m, 1H), 7.4 (m, 1H).

5

Example 4C

5-(3-bromo-4-fluorophenyl)-2,3,5,8,9,10-hexahydropyrido

[3,4-b][1,7]naphthyridine-4,6(1H,7H)-dione dihydrochloride

A solution of the product from Example 4B (0.22 g, 0.41 mmol) in ethyl alcohol (5 mL) was treated with concentrated hydrochloric acid (0.10 mL), refluxed for 3 hours, allowed to cool to ambient temperature and treated with ether. The resulting solid precipitate was collected and dried to provide the title compound (0.12 g).

MS (ESI(-)) m/z 391 (M-H)⁻;

¹H NMR (DMSO-d₆) δ 3.78 (q, 4H), 4.22 (q, 4H), 4.95 (s, 1H), 7.22 (t, 1H), 7.32 (m, 1H), 7.48 (dd, 1H), 11.48 (s, 1H);

Anal. Calcd for C₁₇H₁₅N₃O₂FBr₂HCl: C, 43.90; H, 3.68; N, 9.03. Found: C, 44.45; H, 3.86; N, 8.75.

Example 5

(-)-5-(3-bromo-4-fluorophenyl)-2,3,5,7,8,9-hexahydro-1H-cyclopenta[b][1,7]naphthyridine-4,6-dione hydrochloride

Example 5A

2-benzyl-5-(3-bromo-4-fluorophenyl)-2,3,5,7,8,9-hexahydro-1H-

cyclopenta[b][1,7]naphthyridine-4,6-dione

A solution of 3-amino-2-cyclopenten-1-one (Kikani, B.B., Synthesis, (1991), 2, 176) (0.97 g, 10 mmol), 3-bromo-4-fluorobenzaldehyde (2.0 g, 10 mmol) and N-benzylpiperidine-3,5-dione (Ziegler, J. Amer. Chem. Soc. (1973), 95, 7458-7464) (2.2 g, 10 mmol) in ethyl alcohol (10 mL) was heated to reflux for 72 hours and then allowed to cool to ambient temperature. The solvent was evaporated and the residue was purified by

30

76

flash chromatography over silica gel (5% ethanol/methylene chloride) to provide the title compound (3.0 g).

MS (ESI(-)) m/z 465 (M-H)⁻;

¹H NMR (DMSO-d₆) δ 2.28 (m, 2H), 2.5-2.7 (m, 2H), 3.07 (AB qu, 2H), 3.4 (m, 2H), 3.65 (s, 2H), 4.65 (s, 1H), 7.15-7.45 (m, 8H), 10.25, (s, 1H).

Example 5B

(1R,2S,5R)-5-methyl-2-(1-methyl-1-phenylethyl)cyclohexyl 5-(3-bromo-4-fluorophenyl)-4,6-dioxo-1,3,4,5,6,7,8,9-octahydro-2H-cyclopenta[b][1,7]naphthyridine-2-carboxylate

10 A solution of the product from Example 5A (1.9 g, 4.0 mmol) in THF (30 mL) was treated with 8-phenylmenthol chloroformate prepared from (-)-8-phenylmenthol as described in (Yamamoto, Y., J.Amer.Chem.Soc. (1992), 114, 121-125) (1.45 g, 4.92 mmol) in THF (10 mL), stirred for 3 days at ambient temperature and partitioned between aqueous sodium bicarbonate and methylene chloride. The organic layer was separated, 15 dried with sodium sulfate, filtered and concentrated to provide a mixture of diastereomeric carbamates. The diastereomeric mixture was subjected to column chromatography over silica gel (20% hexanes/ethyl acetate) to provide the title compound (0.32g) as the less polar diastereomer and mixed fractions containing both diastereomers (0.9 g).

MS (ESI(-)) m/z 635 (M-H)⁻;

20 ¹H NMR (DMSO-d₆) δ 0.8 (m, 4H), 1.1 (s, 3H), 1.18 (m, 2H), 1.22 (s, 3H), 1.6 (m, 2H), 1.8 (m, 1H), 2.02 (m, 2H), 2.3 (m, 2H), 2.6 (m, 1H), 2.75 (m, 1H), 3.02 (d, 1H), 3.62 (d, 1H), 3.9 (d, 1H), 4.58 (d, 2H), 4.68 (s, 1H), 7.02-7.38 (m, 8H).

Example 5C

25 (1R,2S,5R)-5-methyl-2-(1-methyl-1-phenylethyl)cyclohexyl 5-(3-bromo-4-fluorophenyl)-4,6-dioxo-1,3,4,5,6,7,8,9-octahydro-2H-cyclopenta[b][1,7]naphthyridine-2-carboxylate

The diastereomeric mixture from Example 5B was crystallized from ethyl alcohol to provide the title compound (0.45 g) as the more polar diastereomer.

MS (ESI(-)) m/z 635 (M-H)⁻;

30 ¹H NMR (DMSO-d₆) δ 0.82 (d, 3H), 1.02 (s, 3H), 1.18 (s, 3H), 1.18 (m, 2H), 1.58 (m,

77

2H), 1.68 (s, 1H), 1.98 (m, 2H), 2.3 (m, 2H), 2.61 (m, 1H), 2.75 (m, 1H), 3.2 (m, 1H), 3.6 (m, 2H), 4.0 (m, 1H), 4.52 (m, 2H), 4.55 (s, 1H), 6.45 (m, 1H), 6.82 (m, 2H), 7.1 (m, 2H), 7.25 (m, 2H), 7.41 (m, 1H).

5

Example 5D

(-)-5-(3-bromo-4-fluorophenyl)-2,3,5,7,8,9-hexahydro-1H-
cyclopenta[b][1,7]naphthyridine-4,6-dione hydrochloride

A solution of the product from Example 5B (0.32 g, 0.52 mmol) was treated with 48% hydrogen bromide in acetic acid (4 mL), heated to 50°C for 48, allowed to cool to ambient temperature, neutralized with concentrated ammonium hydroxide, and extracted with methylene chloride (3 x). The combined organic layers were dried with sodium sulfate, filtered, and concentrated. The residue was purified by flash chromatography over silica gel (10% ethanol/ammonia saturated methylene chloride) to provide the title compound (0.10 g) as the free base which was converted to the hydrochloride salt.

10

15

$[\alpha]_D^{20}$ -125.88° (DMSO);

MS (ESI(-)) m/z 375 (M-H)⁻;

¹H NMR (DMSO-d₆) (free base) δ 2.28 (t, 2H), 2.53-2.76 (m, 2H), 3.18 (s, 2H), 3.62 (d, 2H), 4.67 (s, 1H), 7.22 (d, 2H), 7.45 (d, 1H) 10.1 (s, 1H);

Anal. Calcd for C₁₇H₁₃N₂FBrO₂HCl·0.5 H₂O: C, 48.43; H, 4.08; N, 6.28. Found: C, 48.42; H, 3.59; N, 6.64.

20

Example 6

(+)-5-(3-bromo-4-fluorophenyl)-2,3,5,7,8,9-hexahydro-1H-
cyclopenta[b][1,7]naphthyridine-4,6-dione hydrochloride

25

A solution of the product from Example 5C (0.25 g, 0.41 mmol) in acetic acid (3 mL) was treated with 48% hydrogen bromide and was heated for 3 days at 50°C. The reaction mixture was allowed to cool to ambient temperature, neutralized with concentrated ammonium hydroxide, and extracted with methylene chloride. The combined organic phases were dried with sodium sulfate, filtered concentrated. The residue was purified by flash chromatography over silica gel (10% ethanol/ammonia saturated

30

78

methylene chloride) to provide the title compound (0.070 g) as a free base which was converted to the hydrochloride salt.

$[\alpha]_D^{20} +117.64^\circ$ (DMSO);

MS (ESI(-)) m/z 375 (M-H)⁻;

5 ^1H NMR (DMSO- d_6) (free base) δ 2.28 (t, 2H), 2.52-2.65 (m, 2H), 3.18 (s, 2H), 3.52 (d, 2H), 4.68 (s, 1H), 7.2 (m, 2H), 7.43 (d, 1H) 10.1 (s, 1H);

Anal. Calcd for $\text{C}_{17}\text{H}_{13}\text{N}_2\text{FBrO}_2\cdot\text{HCl}\cdot 0.5\text{H}_2\text{O}$: C, 48.43; H, 4.08; N, 6.28. Found: C, 48.83; H, 3.97; N, 6.32.

10

Example 7

(-)-5-(3-bromo-4-fluorophenyl)-2,3,5,8,9,10-hexahydrobenzo[b][1,7]naphthyridine-4,6(1H,7H)-dione hydrochloride

Example 7A

15 (1R,2S,5R)-5-methyl-2-(1-methyl-1-phenylethyl)cyclohexyl 5-(3-bromo-4-fluorophenyl)-4,6-dioxo-3,4,5,6,7,8,9,10-octahydrobenzo[b][1,7]naphthyridine-2(1H)-carboxylate

The product from Example 2A (1.23 g, 2.5 mmol) was treated according to the method described for Example 5B. The diastereomeric mixture was subjected to column chromatography over silica gel (4:1 ethyl acetate/hexanes) to provide both the title
20 compound as the less polar diastereomer (0.32 g) and the more polar diastereomer (0.30 g).

MS (ESI(-)) 649 (M-H)⁻;

^1H NMR(CDCl_3) δ 0.88(d, 3H), 0.9 (m, 1H), 1.13 (m, 1H), 1.19 (s, 3H), 1.28 (m, 2H), 1.32 (s, 3H), 1.72 (m, 2H), 1.88 (m, 1H), 2.05 (m, 3H), 2.38 (m, 2H), 2.51 (m, 2H), 2.72
25 (d, 1H), 3.56 (d, 1H), 3.82 (d, 1H), 4.71 (m, 2H), 5.07 (s, 1H), 6.92 (t, 1H), 7.12 (m, 1H), 7.28 (m, 6H).

79

Example 7B

(1R,2S,5R)-5-methyl-2-(1-methyl-1-phenylethyl)cyclohexyl 5-(3-bromo-4-fluorophenyl)-4,6-dioxo-3,4,5,6,7,8,9,10-octahydrobenzo[b][1,7]naphthyridine-2(1H)-carboxylate

The more polar diastereomer from Example 7A (0.30 g) was crystallized from methylene chloride/ether to provide the title compound (0.24 g).

MS (ESI(-)) m/z 649 (M-H)⁻;

¹H NMR (CDCl₃) δ 0.88 (d, 3H), 0.92 (m, 1H), 1.13 (s, 3H), 1.18-1.32 (m, 6H), 1.73 (m, 2H), 1.92 (m, 1H), 2.05 (m, 3H), 2.38 (m, 2H), 2.53 (m, 2H), 2.81 (d, 1H), 3.2 (d, 1H), 3.9 (d, 1H), 4.56 (d, 1H), 4.75 (m, 1H), 5.1 (s, 1H), 6.41 (t, 1H), 6.8 (m, 2H), 7.05 (m, 1H), 7.12 (d, 1H), 7.31 (m, 1H), 7.4 (m, 1H), 7.5 (d, 1H).

Example 7C

(-)-5-(3-bromo-4-fluorophenyl)-2,3,5,8,9,10-hexahydrobenzo[b][1,7]naphthyridine-4,6(1H,7H)-dione hydrochloride

The product from Example 7A (0.32 g) was treated according to the method described for Example 5D to provide the title compound (0.125g) as the free base which was then converted to the hydrochloride salt.

[α]_D²⁰ -10° (CH₃CN);

MS (ESI(-)) m/z 389 (M-H)⁻;

¹H NMR (DMSO-d₆) (free base) δ 1.72-1.99 (m, 2H), 2.22 (t, 2H), 2.98 (m, 1H), 3.15 (s, 2H), 3.4 (m, 2H), 3.57 (s, 2H), 4.88 (s, 1H), 7.18 (m, 2H), 7.4 (d, 1H);

Anal. Calcd for C₁₈H₁₅BrFN₂O₂·HCl: C, 50.67; H, 3.78; N, 6.57. Found: C, 50.18; H, 4.22; N, 6.16.

Example 8

(+)-5-(3-bromo-4-fluorophenyl)-2,3,5,8,9,10-hexahydrobenzo[b][1,7]naphthyridine-4,6(1H,7H)-dione hydrochloride

The product from Example 7B (0.24 g) was treated according to the method described for Example 5D to provide the title compound (0.070 g) as the free base which was converted to the hydrochloride salt.

$[\alpha]_D^{20} +9.52^\circ$ (CH₃CN);

MS (ESI(-)) m/z 389 (M-H)⁻;

¹H NMR (DMSO-d₆) δ 1.75-1.98 (m, 2H), 2.25 (t, 2H), 2.95 (s, 1H), 3.15 (s, 2H), 3.45 (m, 2H), 3.57 (s, 2H), 4.89 (s, 1H), 7.17 (m, 2H), 7.39 (d, 1H), 9.6 (s, 1H);

5 Anal. Calcd for C₁₈H₁₆BrFN₂O₂·HCl: C, 50.67; H, 3.78; N, 6.57. Found: C, 50.54; H, 4.05; N, 6.32.

Example 9

10 10-(3-bromo-4-fluorophenyl)-3,4,6,7,8,10-hexahydro-2H-thiopyrano[3,2-b][1,7]naphthyridin-9(5H)-one 1,1-dioxide hydrochloride

Example 9A

7-benzyl-10-(3-bromo-4-fluorophenyl)-3,4,6,7,8,10-hexahydro-2H-thiopyrano[3,2-b][1,7]naphthyridin-9(5H)-one 1,1-dioxide

15 A solution of N-benzylpiperidine-3,5-dione (Ziegler, J. Amer. Chem. Soc. (1973), 95, 7458-7464) (0.55 g, 2.5 mmol) in ethyl alcohol (5 mL) was treated with 2.0M ammonia in ethyl alcohol (1.25 mL, 2.5 mmol), stirred for 30 minutes in a sealed tube, treated with tetrahydrothiopyran-3-one-1,1-dioxide (0.36 g, 2.5 mmol), treated with 3-bromo-4-fluorobenzaldehyde (0.51 g, 2.5 mmol), stirred at 75°C for 48 hours, cooled and
20 concentrated. The residue was purified by flash chromatography over silica gel (5% ethanol/methylene chloride) to provide the title compound (0.50 g).

MS (ESI(-)) m/z 517 (M-H)⁻;

¹H NMR (DMSO-d₆) δ 2.18 (m, 2H), 2.42 (m, 2H), 2.95 (m, 2H), 3.15 (m, 4H), 3.42 (m, 2H), 3.6 (q, 2H), 5.0 (s, 1H), 7.18-7.5 (m, 8H), 9.5 (s, 1H).

25

Example 9B

vinyl 10-(3-bromo-4-fluorophenyl)-9-oxo-3,4,6,8,9,10-hexahydro-2H-thiopyrano[3,2-b][1,7]naphthyridine-7(5H)-carboxylate 1,1-dioxide

A solution of the product from Example 9A (0.48 g, 0.92 mmol) in THF (5 mL)
30 was treated with vinyl chloroformate (0.10 mL, 0.94 mmol) and stirred at ambient

temperature overnight. The solvent was evaporated and the residue was purified by flash chromatography over silica gel (ethyl acetate and then 10% ethanol/methylene chloride) to provide the title compound (0.25 g).

MS (ESI(-)) m/z 497 (M-H)⁻;

5 ¹H NMR (DMSO-d₆) δ 2.21 (m, 2H), 2.68 (m, 2H), 3.18 (m, 2H), 3.28 (m, 2H), 3.5 (m, 1H), 3.75 (q, 2H), 4.11 (s, 2H), 5.08 (s, 1H), 7.28 (m, 2H), 7.41 (d, 1H), 9.5 (br s, 1H).

Example 9C

10-(3-bromo-4-fluorophenyl)-3,4,6,7,8,10-hexahydro-2H-thiopyrano[3,2-
10 b][1,7]naphthyridin-9(5H)-one 1,1-dioxide hydrochloride

A solution of the product from Example 9B (0.25 g) in ethyl alcohol was treated with 6N HCl (1 mL), refluxed for 2 hours, cooled to ambient temperature and concentrated. The residue was purified by flash chromatography over silica gel (15% ethanol/ammonia saturated methylene chloride) to provide the title compound (0.09 g) as
15 the free base which was converted to the hydrochloride salt.

MS (ESI(-)) m/z 425 (M-H)⁻;

¹H NMR (DMSO-d₆) (free base) δ 2.2 (m, 2H), 2.6 (m, 2H), 3.15 (s, 2H), 3.22 (m, 2H), 3.52 (d, 2H), 5.02 (s, 1H), 7.22 (m, 2H), 7.4 (m, 1H), 9.5 (br s, 1H);

Anal. Calcd for C₁₇H₁₆N₂BrSO₃·HCl·0.5 C₂H₅OH: C, 44.41; H, 4.14; N, 5.75; Cl, 7.28.

20 Found: C, 44.80; H, 4.16; N, 5.68; Cl, 7.40.

Example 10

9-(3-Bromo-4-fluorophenyl)-2,3,5,6,7,9-hexahydrothieno
25 [3,2-b][1,7]naphthyridin-8(4H)-one, 1,1-dioxide hydrochloride

Example 10A

Tetrahydrothiophene-3-ol

A solution of tetrahydrothiophene-3-one (10.2 g, 100 mmol) in ethanol (100 mL) was treated slowly with sodium borohydride (4.3 g, 114 mmol), stirred for 1 hour at
30 ambient temperature, concentrated to a volume of approximately 50 mL, treated with

water (400 mL) and extracted with methylene chloride (3x). The combined methylene chloride layers were washed with 1N HCl, dried (MgSO₄), filtered, and concentrated to provide 9.0 g of the title compound as a clear oil which was carried onto the next step without purification.

5

Example 10B

Tetrahydrothiophene-3-ol-1,1-dioxide

A mixture of Example 10A (10.0 g, 96.0 mmol), sodium tungstate dihydrate (0.315 g, 0.96 mmol) and acetic acid (7.5 mL, 130 mmol) in water (42 mL) at 0°C was treated with 30 % hydrogen peroxide (31.6 g, 280 mmol) dropwise over 1 hour stirred for 30 minutes at 0°C, stirred at ambient temperature for 45 minutes, transferred to a 100 mm x 190 mm crystallizing dish and concentrated by heating on a steam bath to provide the title compound as an oil which was carried on to the next step without purification.

15

Example 10C

Tetrahydrothiophene-3-one-1,1-dioxide

A mechanically stirred solution of the crude product from Example 10B in acetone (300 mL) was treated with Jones reagent (2.7M, 30 mL total) in portions over 2 hours until the brown color persisted, stirred for 1 hour, treated slowly with isopropyl alcohol (7.5 mL), stirred for 15 minutes, diluted with acetone (400 mL) and filtered through celite to remove the chromium salts. The filtrate was concentrated and purified by chromatography on silica gel (1:1 hexane:ethyl acetate) to provide 5.88 g of the title compound. ¹H NMR (CDCl₃) δ 3.08 (t, 2H), 3.58 (t, 2H), 3.70 (s, 2H).

25

Example 10D

6-benzyl-9-(3-bromo-4-fluorophenyl)-2,3,5,6,7,9-hexahydrothieno[3,2-b][1,7]naphthyridin-8(4H)-one 1,1-dioxide

A solution of N-benzylpiperidine-3,5-dione (Ziegler, J. Amer. Chem. Soc. (1973), 95, 7458-7464) (0.55 g, 2.5 mmol) in ethyl alcohol (5 mL) was treated with 2.0M ammonia in ethyl alcohol (1.25 mL, 2.5 mmol), stirred 4 hours in a sealed tube, treated

30

83

with the product from Example 10C (0.33 g, 2.5 mmol), treated with 3-bromo-4-fluorobenzaldehyde (0.51 g, 2.5 mmol), stirred at 75°C for 48 hours, cooled and concentrated. The residue was purified by flash chromatography over silica gel (5-10% ethanol/methylene chloride) to provide the title compound (0.28 g).]

5 MS (ESI(-)) m/z 501 (M - H)⁻;

¹H NMR (DMSO-d₆) δ 2.8 (m, 1H), 3.0 (m, 2H), 3.08 -3.3 (m, 2H), 3.42 (m, 3H), 3.62 (m, 2H), 4.85 (s, 1H), 7.2 - 7.48 (m, 8H), 9.98 (s, 1H).

Example 10E

10 vinyl 9-(3-bromo-4-fluorophenyl)-8-oxo-2,3,5,7,8,9-hexahydrothieno[3,2-b][1,7]naphthyridine-6(4H)-carboxylate 1,1-dioxide

A solution of the product from Example 10D (0.22 g, 0.43 mmol) in methylene chloride (5 mL) was treated with vinyl chloroformate (0.10 mL, 0.94 mmol), stirred at ambient temperature overnight, diluted with methylene chloride and washed with aqueous
15 sodium bicarbonate. The methylene chloride layer was separated, dried with sodium sulfate, filtered, and concentrated to provide the title compound (0.28 g).

MS (ESI(-)) m/z 497 (M - H)⁻;

¹H NMR (DMSO-d₆) δ 2.88 (m, 2H), 3.1 (m, 3H), 3.5 (m, 1H), 3.75 (q, 2H), 4.12 (s, 2H), 4.9 (s, 1H), 7.29 (m, 2H), 7.48 (d, 1H), 10.1 (s, 1H).

20

Example 10F

9-(3-Bromo-4-fluorophenyl)-2,3,5,6,7,9-hexahydrothieno[3,2-b][1,7]naphthyridin-8(4H)-one, 1,1-dioxide hydrochloride

The product from Example 10E in ethyl alcohol (5 mL) was treated with 6N HCl
25 (1 mL), refluxed for 3 hours, cooled to ambient temperature and concentrated. The residue was purified by flash chromatography over silica gel (10% ethanol/ammonia saturated methylene chloride) to provide the title compound (0.070 g) which was converted to the hydrochloride salt.

MS (ESI(-)) m/z 411 (M - H)⁻;

30 ¹H NMR (DMSO-d₆) δ 2.75 (m, 2H), 3.02 (m, 1H), 3.15 (s, 2H), 3.58 (m, 3H), 4.87 (s,

1H), 7.25 (d, 2H), 7.43 (d, 1H), 9.9 (s, 1H);

Anal. Calcd for $C_{16}H_{14}BrFN_2SO_3 \cdot HCl \cdot 0.5C_2H_5OH$: C, 43.19; H, 3.84; N, 5.93; Cl, 7.50.

Found: C, 43.69; H, 3.85; N, 5.83; Cl, 7.66.

5

Example 11

9-(3-bromo-4-fluorophenyl)-2,3,5,9-tetrahydro-4H-pyrano[3,4-b]thieno[2,3-e]pyridin-8(7H)-one 1,1-dioxide

Example 11A

10

methyl (2-oxopropoxy)acetate

15

A solution of 2M dimethyl zinc in toluene (21 mL, 42 mmol) was cooled to 0°C under nitrogen, treated with trans-benzyl(chloro)bis(triphenylphosphine)palladium(II) (0.57 g, 76 mmol), treated with methyl 2-(chloroformylmethoxy)acetate (12.6 g, 76 mmol) dropwise over 0.5 hours, stirred for 0.5 hours at 0°C, stirred for 16 hours at ambient temperature, treated with 1M HCl (40 mL) and then brine (20 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated. The residue was purified by flash chromatography over silica gel (1:2 ethyl acetate/hexanes) to provide the title compound (5.2 g).

20

Example 11B

2H-pyran-3,5(4H,6H)-dione

25

A solution of the product from Example 11A (5.0 g, 34 mmol) in diethyl ether (40 mL) was added dropwise over 2.5 hours to a 0°C solution of 1M potassium tert-butoxide (in tert-butanol, 34 mL) in diethyl ether (270 mL). The mixture was treated with 1M HCl (120 mL) followed by ethyl acetate (250 mL) and brine (50 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (twice, 250 mL). The combined organic layers were washed with brine (2x, 60 mL), dried ($MgSO_4$), filtered and concentrated (keeping the temperature below 40 °C) to provide the title compound (Terasawa, J. Org. Chem. (1977), 42, 1163-1169) in approximately 30 % purity which can

85

be further purified by chromatography on silica gel using 200:1:1:100 ethyl acetate:formic acid:water:hexane to provide the title compound.

Example 11C

5

5-amino-2H-pyran-3(6H)-one

The 30% pure product of Example 11B was treated with benzene (60 mL), then ethanol (20 mL), then para-toluenesulfonic acid (100 mg), and then heated to reflux for 6 hours and concentrated. The obtained product, 5-ethoxy-2H-pyran-3(6H)-one, was treated with 2M ammonia in methanol (100 mL), stirred for 16 hours and concentrated. The
10 residue was purified by flash chromatography over silica gel (5% and then 10 % methanol/methylene chloride) to provide the title compound (1.3 g).

MS (DCI/NH₃) m/z 114 (M+H)⁺, 131 (M+NH₄)⁺;

¹H NMR (DMSO-d₆) δ 3.80 (s, 2H), 4.19 (s, 2H), 5.01 (s, 1H), 7.01 (bs, 2H).

15

Example 11D

9-(3-bromo-4-fluorophenyl)-2,3,5,9-tetrahydro-4H-pyrano[3,4-b]thieno[2,3-e]pyridin-8(7H)-one 1,1-dioxide

A mixture of the product from Example 11C (1.5 g, 13 mmol), 3-bromo-4-fluorobenzaldehyde (3.2 g, 16 mmol), tetrahydrothiophene-3-oxo-1,1-dioxide prepared as
20 described in (J. Heterocycl. Chem., v. 27 pp. 1453 (1990)) (1.8 g, 13 mmol) and triethylamine (0.93 mL, 6.6 mmol) in ethanol (20 mL) was stirred in a sealed tube at 80°C for 60 hours, cooled and concentrated to dryness. The residue was treated with ethanol (50 mL), then 1 M HCl (in diethyl ether, 5 mL), and heated to reflux for 5 minutes and kept at ambient temperature for 3 hours. The resulting solid was collected by filtration, washed
25 with ethanol and dried under vacuum for 16 hours to provide the title compound (3.2 g) mp > 260°C;

MS (ESI(+)) m/z 414 (M+H)⁺, 431 (M+NH₄)⁺;

MS (ESI(-)) m/z 412 (M-H)⁻;

¹H NMR (DMSO-d₆) δ 2.85 (m, 1H), 3.08 (m, 1H), 3.33-3.42 (m, 2H), 4.03 (s, 2H), 4.49
30 (AB q, 2H), 4.90 (s, 1H), 7.27 (m, 2H), 7.45 (dd, 1H), 10.14 (s, 1H);

86

Anal. Calcd for $C_{16}H_{13}NO_4SBr$: C, 46.39; H, 3.16; N, 3.38. Found: C, 46.25; H, 3.24; N, 3.26.

Example 12

5 (+)-9-(3-bromo-4-fluorophenyl)-2,3,5,9-tetrahydro-
 4H-pyrano[3,4-b]thieno[2,3-e]pyridin-8(7H)-one 1,1-dioxide

Example 12A

(1R,2S,5R)-5-methyl-2-(1-methyl-1-phenylethyl)cyclohexyl 9-
10 (3-bromo-4-fluorophenyl)-8-oxo-2,3,5,7,8,9-hexahydro-
 4H-pyrano[3,4-b]thieno[2,3-e]pyridine-4-carboxylate 1,1-dioxide

To a suspension of the product from Example 11D (1.58 g, 3.7 mmol) in THF (40 mL) at 0°C under a nitrogen atmosphere was added a 1M solution of potassium tert-butoxide in THF (4.1 mL) dropwise over 5 minutes. The mixture was stirred at ambient
15 temperature for 30 minutes, cooled to 0°C, treated with a solution of 8-phenylmenthol chloroformate prepared from (-)-8-phenylmenthol as described in (Yamamoto, Y., J.Amer.Chem.Soc. (1992), 114, 121-125) (1.31 g, 4.4 mmol) in THF (20 mL) over 5 minutes, stirred at ambient temperature for 16 hours, diluted with methylene chloride (150 mL) and washed with aqueous sodium bicarbonate (30 mL). The layers were separated
20 and the aqueous layer was extracted with methylene chloride (50 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated. The residue was purified by flash chromatography over silica gel (3:2:1 chloroform/hexanes/diethyl ether) to provide 0.98 g of the less polar diastereomer.

MS (ESI(+)) m/z 672 ($M+H$)⁺, 689 ($M+NH_4$)⁺;

25 MS (ESI(-)) m/z 670 ($M-H$)⁻.

87

Example 12B

(1R,2S,5R)-5-methyl-2-(1-methyl-1-phenylethyl)cyclohexyl
9-(3-bromo-4-fluorophenyl)-8-oxo-2,3,5,7,8,9-hexahydro-
4H-pyrano[3,4-b]thieno[2,3-e]pyridine-4-carboxylate 1,1-dioxide

5 The impure more polar diastereomer from Example 12A was rechromatographed on silica gel gel (3:2:1 chloroform/hexanes/diethyl ether) to provide 1.0 g of pure more polar diastereomer.

MS (ESI(+)) m/z 672 (M+H)⁺, 689 (M+NH₄)⁺;

MS (ESI(-)) m/z 670 (M-H)⁻.

10

Example 12C

(+)-9-(3-bromo-4-fluorophenyl)-2,3,5,9-tetrahydro-
4H-pyrano[3,4-b]thieno[2,3-e]pyridin-8(7H)-one 1,1-dioxide

A solution of Example 12A (0.98 g, 1.4 mmol) in methanol/methylene chloride (40
15 mL/10mL) was degassed with nitrogen, treated with of 25% sodium methoxide in methanol (30 drops), stirred for 16 hours, filtered, and concentrated to a volume of 5 mL of methanol. The solid which had precipitated was collected by filtration, washed with methanol and dried under vacuum for 16 hours to provide the title compound (0.36 g).

$[\alpha]_D^{23} +117^\circ$ (DMSO, c 0.925);

20 MS (ESI(+)) m/z 414 (M+H)⁺, 431 (M+NH₄)⁺;

MS (ESI(-)) m/z 412 (M-H)⁻;

¹H NMR (DMSO-d₆) δ 2.85 (m, 1H), 3.08 (m, 1H), 3.33-3.42 (m, 2H), 4.03 (s, 2H), 4.49 (AB q, 2H), 4.90 (s, 1H), 7.27 (m, 2H), 7.45 (dd, 1H), 10.14 (s, 1H);

Anal. Calcd for C₁₆H₁₃NO₄SFBr: C, 46.39; H, 3.16; N, 3.38. Found: C, 46.07; H, 3.02; N,

25

3.19.

88

Example 13(-)-9-(3-bromo-4-fluorophenyl)-2,3,5,9-tetrahydro-4H-pyrano[3,4-b]thieno[2,3-e]pyridin-8(7H)-one 1,1-dioxide

A solution of Example 12B (1.0 g, 15 mmol) was processed as described in

Example 12C to provide the title compound (0.40 g).

$[\alpha]_D^{23}$ -117° (DMSO, c 1.01);

MS (ESI(+)) m/z 414 (M+H)⁺, 431 (M+NH₄)⁺;

MS (ESI(-)) m/z 412 (M-H)⁻;

¹H NMR (DMSO-d₆) δ 2.85 (m, 1H), 3.08 (m, 1H), 3.33-3.42 (m, 2H), 4.03 (s, 2H), 4.49

(AB q, 2H), 4.90 (s, 1H), 7.27 (m, 2H), 7.45 (dd, 1H), 10.14 (s, 1H);

Anal. Calcd for C₁₆H₁₃NO₄SFBr: C, 46.39; H, 3.16; N, 3.38. Found: C, 46.12; H, 3.23; N, 3.34.

Example 149-(3-cyanophenyl)-2,3,5,9-tetrahydro-4H-pyrano[3,4-b]thieno[2,3-e]pyridin-8(7H)-one 1,1-dioxide

A mixture of the product from Example 11C (0.74 g, 6.5 mmol), 3-cyanobenzaldehyde (1.0 g, 7.8 mmol), tetrahydrothiophene-3-oxo-1,1-dioxide (0.87 g, 6.5 mmol) and triethylamine (0.45 mL, 3.2 mmol) in ethanol (20 mL) was stirred in a sealed tube at 80°C for 60 hours, cooled and the solid collected by filtration and washed with ethanol. The solid was treated with ethanol (30 mL) and 1M HCl (in diethyl ether, 4 mL), heated to reflux for 15 minutes and kept at ambient temperature for 16 hours. The title compound (1.4 g) was collected by filtration, washed with ethanol and dried under vacuum for 16 hours.

MS (ESI(+)) m/z 360 (M+NH₄)⁺;

MS (ESI(-)) m/z 341 (M-H)⁻;

¹H NMR (DMSO-d₆) δ 2.86 (m, 1H), 3.09 (m, 1H), 3.38 (m, 2H), 4.02 (s, 2H), 4.49 (AB q, 2H), 4.97 (s, 1H), 7.49 (t, 1H), 7.56-7.68 (m, 3H), 10.14 (s, 1H);

Anal. Calcd for C₁₇H₁₄N₂O₄S·0.25 EtOH: C, 59.4; H, 4.41; N, 7.92. Found: C, 59.19; H, 4.40; N, 7.88.

Example 15

(+) 9-(3-cyanophenyl)-2,3,5,9-tetrahydro-4H-pyrano
[3,4-b]thieno[2,3-e]pyridin-8(7H)-one 1,1-dioxide

5

Example 15A

(1S,2R,5S)-5-methyl-2-(1-methyl-1-phenylethyl)cyclohexyl 9-(3-cyanophenyl)-8-oxo-
2,3,5,7,8,9-hexahydro-4H-pyrano[3,4-b]thieno[2,3-e]pyridine-4-carboxylate 1,1-dioxide

The product from Example 14 (1.3 g, 3.8 mmol) was processed as in Example 12A
10 and 12B to provide 0.50 g of the less polar diastereomer and 0.50 g of the more polar
diastereomer.

(less polar diastereomer)

MS (ESI(+)) m/z 618 (M+NH₄)⁺;

MS (ESI(-)) m/z 599 (M-H)⁻;

15 (more polar diastereomer)

MS (ESI(+)) m/z 618 (M+NH₄)⁺;

MS (ESI(-)) m/z 599 (M-H)⁻.

Example 15B

20

(+) 9-(3-cyanophenyl)-2,3,5,9-tetrahydro-4H-pyrano
[3,4-b]thieno[2,3-e]pyridin-8(7H)-one 1,1-dioxide

A suspension of the less polar diastereomer from Example 15A (0.50 g, 0.83 mmol)
in methanol (10 mL) was treated with 25% sodium methoxide in methanol (30 drops),
stirred for 16 hours, filtered, concentrated to dryness, treated with ethanol (20 mL), heated
25 on a steam bath until crystallization began and allowed to stand at ambient temperature for
5 hours. The solid was collected by filtration, washed with ethanol and dried under
vacuum for 16 hours to provide the title compound (0.15 g).

[α]_D²³ +105° (DMSO, c 1.0);

MS (ESI(+)) m/z 360 (M+NH₄)⁺;

30 MS (ESI(-)) m/z 341 (M-H)⁻;

90

¹H NMR (DMSO-d₆) δ 2.86 (m, 1H), 3.09 (m, 1H), 3.38 (m, 2H), 4.02 (s, 2H), 4.49 (AB q, 2H), 4.97 (s, 1H), 7.49 (t, 1H), 7.56-7.68 (m, 3H), 10.14 (s, 1H);

Anal. Calcd for C₁₇H₁₄N₂O₄S: C, 59.64; H, 4.12; N, 8.18. Found: C, 59.39; H, 4.25; N, 7.80.

5

Example 16

(-) 9-(3-cyanophenyl)-2,3,5,9-tetrahydro-4H-pyrano [3,4-b]thieno[2,3-e]pyridin-8(7H)-one 1,1-dioxide

A suspension of the more polar diastereomer from Example 15A (0.50 g, 0.83 mmol) in methanol (30 mL) and methylene chloride (5 mL) was treated with 25% sodium methoxide in methanol (10 drops), stirred for 16 hours, filtered, treated dropwise with acetic acid until the yellow color disappeared, concentrated to dryness, treated with ethanol (30 mL), heated on a steam bath until crystallization began and allowed to stand at ambient temperature for 5 hours. The solid was collected by filtration, washed with ethanol and dried under vacuum for 16 hours to provide the title compound (0.18 g).

15

$[\alpha]_D^{23}$ -103° (DMSO, c 1.0);

MS (ESI(+)) m/z 360 (M+NH₄)⁺;

MS (ESI(-)) m/z 341 (M-H)⁻;

¹H NMR (DMSO-d₆) δ 2.86 (m, 1H), 3.09 (m, 1H), 3.38 (m, 2H), 4.02 (s, 2H), 4.49 (AB q, 2H), 4.97 (s, 1H), 7.49 (t, 1H), 7.56-7.68 (m, 3H), 10.14 (s, 1H);

20

Anal. Calcd for C₁₇H₁₄N₂O₄S·0.5 H₂O: C, 58.86; H, 4.21; N, 8.08. Found: C, 58.90; H, 4.48; N, 7.80.

Example 17

25

9-(4-chloro-3-nitrophenyl)-2,3,5,9-tetrahydro-4H- pyrano[3,4-b]thieno[2,3-e]pyridin-8(7H)-one 1,1-dioxide

A mixture of the product from Example 11C (0.74 g, 6.5 mmol), 4-chloro-3-nitrobenzaldehyde (1.5 g, 7.8 mmol), tetrahydrothiophene-3-oxo-1,1-dioxide (0.87 g, 6.5 mmol) and triethylamine (0.45 mL, 3.2 mmol) in ethanol (20 mL) was processed as in Example 11D yielding a residue which was purified by flash chromatography over silica

30

gel (5% methanol/methylene chloride) and crystallized from ethanol to provide the title compound (1.46 g).

MS (ESI(+)) m/z 414 (M+NH₄)⁺;

MS (ESI(-)) m/z 395 (M-H)⁻;

5 ¹H NMR (DMSO-d₆) δ 2.80-2.93 (m, 1H), 3.01-3.13 (m, 1H), 3.39 (t, 2H), 4.04 (s, 2H), 4.49 (AB q, 2H), 5.02 (s, 1H), 7.58 (dd, 1H), 7.69 (d, 1H), 7.86 (d, 1H), 10.22 (s, 1H);
Anal. Calcd for C₁₆H₁₃N₂O₆SCl: C, 48.43; H, 3.30; N, 7.06. Found: C, 48.13; H, 3.38; N, 6.79.

10

Example 18

(+)-9-(4-chloro-3-nitrophenyl)-2,3,5,9-tetrahydro-4H-pyrano[3,4-b]thieno[2,3-e]pyridin-8(7H)-one 1,1-dioxide

Example 18A

15

(1R,2S,5R)-5-methyl-2-(1-methyl-1-phenylethyl)cyclohexyl
9-(4-chloro-3-nitrophenyl)-8-oxo-2,3,5,7,8,9-hexahydro-4H-pyrano[3,4-b]thieno[2,3-e]pyridine-4-carboxylate 1,1-dioxide

20

The product from Example 17 (1.3 g, 3.3 mmol) was processed as in Example 12A and 12B to provide 0.71 g of the less polar diastereomer and 0.81 g of the more polar diastereomer.

(less polar diastereomer)

MS (ESI(+)) m/z 672 (M+NH₄)⁺;

MS (ESI(-)) m/z 653 (M-H)⁻;

(more polar diastereomer)

25

MS (ESI(+)) m/z 672 (M+NH₄)⁺;

MS (ESI(-)) m/z 653 (M-H)⁻.

92

Example 18B

(+)-9-(4-chloro-3-nitrophenyl)-2,3,5,9-tetrahydro-4H-pyrano[3,4-b]thieno[2,3-e]pyridin-8(7H)-one 1,1-dioxide

The less polar diastereomer from Example 18A (0.71 g, 1.1 mmol) was processed
5 as in Example 16 to provide the title compound (0.23 g).

$[\alpha]_D^{23} +75^\circ$ (c = 1.0, DMSO);

MS (ESI(-)) m/z 395 (M-H)⁻;

¹H NMR (DMSO-d₆) δ 2.80-2.93 (m, 1H), 3.01-3.13 (m, 1H), 3.39 (t, 2H), 4.04 (s, 2H),
4.49 (AB q, 2H), 5.02 (s, 1H), 7.58 (dd, 1H), 7.69 (d, 1H), 7.86 (d, 1H), 10.22 (s, 1H);

10 Anal. Calcd for C₁₆H₁₃N₂O₆SCl: C, 48.43; H, 3.30; N, 7.06. Found: C, 48.26; H, 3.48; N,
6.98.

Example 19

(-)-9-(4-chloro-3-nitrophenyl)-2,3,5,9-tetrahydro-4H-pyrano[3,4-b]thieno[2,3-e]pyridin-8(7H)-one 1,1-dioxide

15

The more polar diastereomer from Example 18A (0.81 g, 1.2 mmol) was processed
as in Example 16 to provide the title compound (0.29 g).

$[\alpha]_D^{23} -74^\circ$ (DMSO, c 0.97);

MS (ESI(+)) m/z 414 (M+NH₄)⁺;

20 MS (ESI(-)) m/z 395 (M-H)⁻;

¹H NMR (DMSO-d₆) δ 2.80-2.93 (m, 1H), 3.01-3.13 (m, 1H), 3.39 (t, 2H), 4.04 (s, 2H),
4.49 (AB q, 2H), 5.02 (s, 1H), 7.58 (dd, 1H), 7.69 (d, 1H), 7.86 (d, 1H), 10.22 (s, 1H);

Anal. Calcd for C₁₆H₁₃N₂O₆SCl: C, 48.43; H, 3.30; N, 7.06. Found: C, 48.42; H, 3.31; N,
6.91.

25

Example 20

5-(3-bromo-4-fluorophenyl)-5,8,9,10-tetrahydro-1H-pyrano[3,4-b]quinoline-4,6(3H,7H)-dione

A mixture of the product from Example 11C (0.23 g, 2.0 mmol), 3-bromo-4-
30 fluorobenzaldehyde (0.49 g, 2.4 mmol), 1,3-cyclohexanedione (0.23 g, 2.0 mmol) and

93

triethylamine (0.14 mL, 1.0 mmol) in ethanol (4 mL) was stirred at 80°C in a sealed tube for 60 hours and cooled to ambient temperature. The resulting solid was collected by filtration, washed with ethanol, dissolved in a mixture of methylene chloride/methanol (4:1), heated on a steam bath to remove the methylene chloride and allowing to crystallize for 4 hours. The crystals were collected by filtration, washed with methanol and dried under vacuum for 16 hours to provide the title compound (0.37 g).

MS (ESI(+)) m/z 392 (M+H)⁺;

MS (ESI(-)) m/z 390 (M-H)⁻;

¹H NMR (DMSO-d₆) δ 1.76-2.01 (m, 2H), 2.25 (t, 2H), 2.43-2.64 (m, 2H), 4.01 (s, 2H), 4.48 (AB q, 2H), 4.90 (s, 1H), 7.20 (m, 2H), 7.39 (dd, 1H), 9.82 (bs, 1H);

Anal. Calcd for C₁₈H₁₅HO₃FBr: C, 55.12; H, 3.85; N, 3.57. Found: C, 54.99; H, 4.04; N, 3.49.

Example 21

10-(3-bromo-4-fluorophenyl)-3,4,6,10-tetrahydro-2H,5H-pyrano[3,4-b]thiopyrano[2,3-e]pyridin-9(8H)-one 1,1-dioxide

A mixture of the product from Example 11C (0.23 g, 2.0 mmol), 3-bromo-4-fluorobenzaldehyde (0.49 g, 2.4 mmol), 1,1-dioxotetrahydro-1-thiopyran-3-one (Dodd, J.H., J. Heterocyclic Chem., (1990), 27, 1453-1456) (0.30 g, 2.0 mmol) and triethylamine (0.14 mL, 1.0 mmol) in ethanol (4 mL) was processed as described in Example 14 to provide the title compound (0.25 g).

MS (ESI(+)) m/z 428 (M+H)⁺, 445 (M+NH₄)⁺;

MS (ESI(-)) m/z 426 (M-H)⁻;

¹H NMR (DMSO-d₆) δ 2.22 (m, 2H), 2.41-2.56 (m, 1H), 2.64 (dt, 1H), 3.09-3.35 (m, 2H), 4.02 (s, 2H), 4.43 (AB q, 2H), 5.06 (s, 1H), 7.25 (m, 2H), 7.41 (dd, 1H), 9.67 (bs, 1H);

Anal. Calcd for C₁₇H₁₅NO₄SFBr: C, 47.68; H, 3.53; N, 3.27. Found: C, 47.36; H, 3.65; N, 3.06.

Example 225-(3-bromo-4-fluorophenyl)-5,10-dihydro-1H,3H-pyrano[3,4-b]thiopyrano[4,3-e]pyridine-4,6(7H,9H)-dione

A mixture of the product from Example 11C (0.23 g, 2.0 mmol), 3-bromo-4-fluorobenzaldehyde (0.49 g, 2.4 mmol), thiopyran-3,5-dione (Fehnel, E.A., J. Amer. Chem. Soc., (1955), 77, 4241-4244) (0.26 g, 2.0 mmol) and triethylamine (0.14 mL, 1.0 mmol) in ethanol (4 mL) was processed as in Example 20 to provide the title compound (0.37 g).

MS (ESI(+)) m/z 410 (M+H)⁺, 427 (M+NH₄)⁺;

MS (ESI(-)) m/z 408 (M-H)⁻;

¹H NMR (DMSO-d₆) δ 3.12 (d, 1H), 3.50 (d, 2H), 3.81 (dd, 1H), 4.03 (s, 2H), 4.48 (AB q, 2H), 4.97 (s, 1H), 7.20 (ddd, 1H), 7.26 (t, 1H), 7.40 (dd, 1H), 9.98 (bs, 1H);

Anal. Calcd for C₁₇H₁₃NO₃SFBr: C, 49.77; H, 3.19; N, 3.41. Found: C, 49.43; H, 3.28; N, 3.21.

Example 235-(3-bromo-4-fluorophenyl)-5,7,8,9-tetrahydrocyclopenta[b]pyrano[4,3-e]pyridine-4,6(1H,3H)-dione

A mixture of the product from Example 11C (0.23 g, 2.0 mmol), 3-bromo-4-fluorobenzaldehyde (0.49 g, 2.4 mmol), 1,3-cyclopentanedione (0.20 g, 2.0 mmol) and triethylamine (0.14 mL, 1.0 mmol) in ethanol (4 mL) was processed as described in Example 14. The solid was dissolved in a mixture of methylene chloride/methanol (4:1), heated on a steam bath to remove the methylene chloride and allowing to crystallize for 4 hours. The crystals were collected by filtration, washed with methanol and dried under vacuum for 16 hours to provide the title compound (0.14 g).

MS (ESI(+)) m/z 378 (M+H)⁺, 395 (M+NH₄)⁺;

MS (ESI(-)) m/z 376 (M-H)⁻;

¹H NMR (DMSO-d₆) δ 2.31 (t, 2H), 2.59 (dt, 1H), 2.73 (dt, 1H), 4.04 (s, 2H), 4.53 (AB q, 2H), 4.71 (s, 1H), 7.22 (m, 2H), 7.43 (dd, 1H), 10.36 (bs, 1H);

95

Anal. Calcd for $C_{17}H_{13}NO_3FBr$: C, 53.99; H, 3.46; N, 3.70. Found: C, 53.68; H, 3.63; N, 3.63.

Example 24

5 5-(3-bromo-4-fluorophenyl)-5,8,9,10-tetrahydro-1H-
pyrano[3,4-b][1,7]naphthyridine-4,6(3H,7H)-dione hydrochloride

Example 24A

10 8-benzyl-5-(3-bromo-4-fluorophenyl)-5,8,9,10-
tetrahydro-1H-pyrano[3,4-b][1,7]naphthyridine-4,6(3H,7H)-dione

A mixture of the product from Example 11C (0.13 g, 1.1 mmol), 3-bromo-4-fluorobenzaldehyde (0.28 g, 1.4 mmol), N-benzylpiperidine-3,5-dione (Ziegler, J. Amer. Chem. Soc. (1973), 95, 7458-7464) (0.23 g, 1.1 mmol) and triethylamine (0.14 mL, 1.0 mmol) in ethanol (3 mL) was processed as in Example 2A to provide the title compound
15 (0.35 g).

MS (ESI(+)) m/z 483 (M+H)⁺, 505 (M+NH₄)⁺;

MS (ESI(-)) m/z 481 (M-H)⁻.

Example 24B

20 vinyl 5-(3-bromo-4-fluorophenyl)-4,6-dioxo-4,5,6,7,9,10-
hexahydro-1H-pyrano[3,4-b][1,7]naphthyridine-8(3H)-carboxylate

A solution of the product from Example 24A (0.29 g, 0.69 mmol) in methylene chloride (4 mL) was treated with vinyl chloroformate (0.10 mL, 1.2 mmol) and processed as in Example 2B. Purification by flash chromatography over silica gel (ethyl acetate)
25 provided the title compound (0.13 g).

MS (ESI(+)) m/z 463 (M+H)⁺, 480 (M+NH₄)⁺;

MS (ESI(-)) m/z 461 (M-H)⁻.

96

Example 24C5-(3-bromo-4-fluorophenyl)-5,8,9,10-tetrahydro-1H-pyrano[3,4-b][1,7]naphthyridine-4,6(3H,7H)-dione hydrochloride

A solution of Example 24B in ethanol (10 mL) was treated with 6N HCl (5 mL),
5 refluxed for 3 hours and concentrated. Purification by flash chromatography over silica gel
(10% methanol/ammonia saturated methylene chloride) provided the title compound
(0.080 g) which was converted to the hydrochloride salt.

mp 232-235°C;

MS (ESI(+)) m/z 393 (M+H)⁺, 410 (M+NH₄)⁺;

10 MS (ESI(-)) m/z 391 (M-H)⁻;

¹H NMR (DMSO-d₆) δ 3.78 (AB q, 2H), 4.07 (s, 2H), 4.19 (s, 2H), 4.54 (AB q, 2H), 4.95
(s, 1H), 7.27 (m, 2H), 7.46 (dd, 1H), 9.86 (bs, 2H), 10.71 (s, 1H);

Anal. Calcd for C₁₇H₁₄N₂O₃BrH₂O·0.25 EtOH : C, 45.77; H, 4.06; N, 6.10. Found: C,
45.89; H, 4.23; N, 5.91.

Example 259-(3-bromo-4-fluorophenyl)-5,9-dihydro-3H-furo
[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dioneExample 25Amethyl 4-(3-bromo-4-fluorophenyl)-2-methyl-5-oxo-4,5,6,8-
tetrahydro-1H-pyrano[3,4-b]pyridine-3-carboxylate

A mixture of tetrahydropyran-3,5-dione (Terasawa, J. Org. Chem. (1977), 42,
1163-1169) (1.4 g, 12 mmol), 3-bromo-4-fluorobenzaldehyde (3.0 g, 15 mmol), methyl 3-
25 aminocrotonate (1.4 g, 12 mmol) and ethyl alcohol (10 mL) was processed as described in
Example 2A. Purification by flash chromatography over silica gel (1% then 2% and then
5% methyl alcohol/methylene chloride) provided the title compound (2.4 g) as a solid.
mp 206-208.

97

Example 25B

methyl 4-(3-bromo-4-fluorophenyl)-2-(bromomethyl)-5-oxo-
4,5,6,8-tetrahydro-1H-pyrano[3,4-b]pyridine-3-carboxylate

A solution of the product from Example 25A (0.87 g, 2.2 mmol) in chloroform (10
5 mL) was cooled to -10 °C, treated with pyridine (0.21 mL, 2.6 mmol), then treated with
pyridinium tribromide (0.84 g, 2.6 mmol), stirred for 1 hour, diluted with methylene
chloride (150 mL) and washed with 1N HCl (25 mL). The organic layer was dried
(MgSO₄), filtered and concentrated. The residue was purified by flash chromatography
over silica gel (1% and then 2% methanol/methylene chloride) to provide the title
10 compound (0.68 g) as an oil.

Example 25C

9-(3-bromo-4-fluorophenyl)-5,9-dihydro-3H-furo
[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione

15 The product from Example 25B (0.30 g, 0.63 mmol) was heated neat under a
nitrogen atmosphere to 130°C for 15 minutes and cooled to ambient temperature. The
residue was treated with methylene chloride and the resulting solid was collected by
filtration, washed with methylene chloride and dried to provide the title compound (0.074
g) as a white solid.

20 mp 166-168°C;

MS (ESI(+)) m/z 380 (M+H)⁺, 397 (M+NH₄)⁺;

MS (ESI(-)) m/z 378 (M-H)⁻;

¹H NMR (DMSO-d₆) δ 4.06 (s, 2H), 4.54 (AB q, 2H), 4.75 (s, 1H), 4.88 (d, 1H), 5.03 (d,
1H), 7.28 (d, 2H), 7.48 (d, 1H), 10.50 (s, 1H);

25 Anal. Calcd for C₁₆H₁₁NO₄FBr: C, 50.55; H, 2.92; N, 3.68. Found: C, 50.28; H, 3.03; N,
3.61.

Example 269-(3-bromo-4-fluorophenyl)-2-methyl-2,3,5,9-tetrahydropyrano[3,4-b]pyrrolo[3,4-e]pyridine-1,8(4H,7H)-dione

A solution of the product from Example 25B (0.16 g, 0.34 mmol) and 2M methyl amine in methanol (3.5 mL, 7.0 mmol) was stirred at ambient temperature for 16 hours and concentrated. Purification of the residue on silica gel (5% and then 10% methanol in methylene chloride) provided an oil which was crystallized from ethanol, collected by filtration and dried to yield the title compound (0.016 g) as a white solid.

MS (ESI(+)) m/z 393 (M+H)⁺;

MS (ESI(-)) m/z 391 (M-H)⁻;

¹H NMR (DMSO-d₆) δ 2.81 (s, 3H), 3.98 (d, 1H), 4.03 (s, 2H), 4.15 (d, 1H), 4.50 (AB q, 2H), 4.75 (s, 1H), 7.23 (m, 2H), 7.46 (dd, 1H), 10.11 (s, 1H);

Anal. Calcd for C₁₇H₁₄N₂O₃FBr0.5 H₂O: C, 50.76; H, 3.76; N, 6.96. Found: C, 50.64; H, 3.66; N, 6.59.

Example 279-(3-bromo-4-fluorophenyl)-2,3,5,9-tetrahydropyrano[3,4-b]pyrrolo[3,4-e]pyridine-1,8(4H,7H)-dione

The product from Example 25B (0.22 g, 0.46 mmol) was treated with a 1:1 ammonia/methanol mixture (60 mL) in a metal Parr stirred reactor for 2.5 days at ambient temperature. The solvent was allowed to evaporate and the residue was purified by chromatography on silica gel (5 % and then 10% methanol in methylene chloride) to provide the title compound (0.026 g) as a solid.

mp > 260°C;

MS (ESI(+)) m/z 379 (M+H)⁺, 396 (M+NH₄)⁺;

MS (ESI(-)) m/z 377 (M-H)⁻;

¹H NMR (DMSO-d₆) δ 3.90 (d, 1H), 4.03 (s, 2H), 4.07 (d, 1H), 4.50 (AB q, 2H), 4.75 (s, 1H), 7.19-7.29 (m, 2H), 7.44 (dd, 1H), 7.59 (s, 1H), 10.09 (s, 1H);

Anal. Calcd for C₁₆H₁₂N₂O₃FBr0.5 H₂O: C, 49.50; H, 3.38; N, 7.22. Found: C, 49.34; H, 3.26; N, 7.21.

Example 285-(4-chloro-3-nitrophenyl)-5,10-dihydro-1H,3H-dipyran[3,4-b:4,3-e]pyridine-4,6(7H,9H)-dione

5 A mixture of tetrahydropyran-3,5-dione (Terasawa, J. Org. Chem. (1977), 42, 1163-1169) (0.27 g, 2.4 mmol), 4-chloro-3-nitrobenzaldehyde (0.54 g, 2.9 mmol) and the product from Example 11C (0.27 g, 2.4 mmol) in ethanol (3 mL) was heated to 80°C for 60 hours and then allowed to stand at ambient temperature for 5 hours. The solid was collected by filtration, washed with ethanol, dissolved in 1:1 methanol/methylene chloride, 10 filtered, heated on steam bath (replacing the methylene chloride with methanol and concentrating the mixture to approximately 5 mL) and allowed to stand at ambient temperature for 2 hours. The resulting solid was collected by filtration, washed with methanol and dried to provide the title compound (0.061 g).

mp > 260;

15 MS (ESI(+)) m/z 377 (M+H)⁺;

MS (ESI(-)) m/z 375 (M-H)⁻;

¹H NMR (DMSO-d₆) δ 4.06 (s, 4H), 4.51 (AB q, 4H), 5.02 (s, 1H), 7.54 (dd, 1H), 7.68 (d, 1H), 7.79 (d, 1H), 10.18 (bs, 1H);

Anal. Calcd for C₁₇H₁₃N₂O₆Cl: C, 54.20; H, 3.48; N, 7.44. Found: C, 53.84; H, 3.81; N,

20 7.14.

Example 295-(3-cyanophenyl)-5,10-dihydro-1H,3H-dipyran[3,4-b:4,3-e]pyridine-4,6(7H,9H)-dione

A mixture of tetrahydropyran-3,5-dione (Terasawa, J. Org. Chem. (1977), 42, 1163-1169) (0.27 g, 2.4 mmol), 3-cyanobenzaldehyde (0.54 g, 2.9 mmol) and the product from Example 11C (0.27 g, 2.4 mmol) in ethanol (3 mL) was heated to 80°C for 60 hours, cooled and concentrated. The residue was purified by chromatography on silica gel (5 % methanol in methylene chloride) to provide a product which was dissolved in 1:5 methanol/methylene chloride, filtered, concentrated on a steam bath to remove the 30 methylene chloride and allowed to stand at ambient temperature for 16 hours. The

100

resulting solid was collected by filtration, washed with methanol and dried to provide the title compound (0.062 g).

mp > 260;

MS (ESI(+)) m/z 323 (M+H)⁺;

5 MS (ESI(-)) m/z 321 (M-H)⁻;

¹H NMR (DMSO-d₆) δ 4.05 (s, 4H), 4.51 (AB q, 4H), 4.99 (s, 1H), 7.48 (m, 1H), 7.54-7.64 (m, 2H), 10.12 (bs, 1H);

Anal. Calcd for C₁₈H₁₄N₂O₄: C, 67.08; H, 4.38; N, 8.69. Found: C, 66.76; H, 4.67; N, 8.56.

10

Example 30

5-(4-fluoro-3-iodophenyl)-5,10-dihydro-1H,3H-dipyran[3,4-b:4,3-e]pyridine-4,6(7H,9H)-dione

15

Example 30A

3-Amino-4-fluorobenzyl alcohol

3-Amino-4-fluorobenzoic acid (15 g, 97 mmol) in tetrahydrofuran at 0°C was treated with 1.0M borane-tetrahydrofuran complex (50 mL), stirred overnight at room temperature, treated with an additional 130 mL of 1.0M borane-tetrahydrofuran complex, stirred 10 hours, quenched by the addition of methanol, stirred 3 hours at room temperature, concentrated and partitioned between aqueous sodium bicarbonate/methylene chloride. The methylene chloride layer was separated, dried (sodium sulfate), filtered, and concentrated. The residue was purified by flash chromatography over silica gel (ethyl acetate/hexane 1:1) to provide 7.0 g of the title compound.

20

25 ¹H NMR (CDCl₃) δ 4.58 (s, 2H), 6.67 (br m, 1H), 6.81 (d, 1H), 6.95 (t, 1H).

Example 30B

4-Fluoro-3-iodobenzylalcohol

The product from Example 30A (7.0 g, 50 mmol) in water (100 mL) at 0°C was treated slowly with concentrated sulfuric acid (30 mL) at a rate to maintain the temperature

30

101

below 10°C and then treated dropwise with an aqueous solution of sodium nitrite (3.45 g, 50 mmol). This solution was then added to a solution of potassium iodide (8.13 g, 50 mmol) in water (15 mL), heated to 60°C for 2 hours, cooled and extracted with methylene chloride. The methylene chloride layer was washed with 10% sodium hydroxide, washed
5 with 1M sodium thiosulfate, washed with 10% hydrochloric acid, washed with aqueous sodium bicarbonate, dried (sodium sulfate), filtered, and concentrated. The residue was purified by flash chromatography over silica gel (ethyl acetate/hexane 7:3) to provide 6.4 g of the title compound.

¹H NMR (CDCl₃) δ 1.69 (t, 1H), 4.66 (d, 2H), 7.05 (t, 1H), 7.60 (d, 1H), 7.78 (dd, 1H).

10

Example 30C

4-Fluoro-3-iodobenzaldehyde

The product from Example 30B (6.4 g, 26 mmol) in chloroform (300 mL) was treated with manganese dioxide (4.5 g, 50 mmol), stirred overnight, treated with an
15 additional portion of manganese dioxide (2.25 g), stirred overnight, filtered and concentrated. The residue was purified by flash chromatography over silica gel (ethyl acetate/hexane 1:4) to provide 1.9 g of the title compound.

¹H NMR (CDCl₃) δ 7.23 (t, 1H), 7.89 (m, 1H), 8.32 (dd, 1H), 9.91 (s, 1H).

20

Example 30D

5-(4-fluoro-3-iodophenyl)-5,10-dihydro-1H,3H-

dipyranol[3,4-b:4,3-e]pyridine-4,6(7H,9H)-dione

A mixture of the 30 % pure product from Example 11B (tetrahydropyran-3,5-dione) (Terasawa, J. Org. Chem. (1977), 42, 1163-1169) (0.365 g, 2.4 mmol), the product
25 from Example 30C (0.20 g, 0.80 mmol) and the product from Example 11C (0.090 g, 0.80 mmol) in ethanol (2 mL) were processed as described in Example 29 to provide the title compound (0.087 g) as a white solid.

mp > 260°C;

¹H NMR (DMSO-d₆) δ 4.05 (s, 4H), 4.50 (AB q, 4H), 4.90 (s, 1H), 7.15 (t, 1H), 7.20 (m,
30 1H), 7.57 (dd, 1H), 10.10 (bs, 1H);

MS (ESI+) m/z 442 (M+H)⁺;

MS (ESI-) m/z 440 (M-H)⁻;

Anal. Calcd for C₁₇H₁₃NO₄FI: C, 46.28; H, 2.97; N, 3.17. Found: C, 45.38; H, 3.68; N, 2.91.

5

Example 31

5-(5-bromo-2-hydroxyphenyl)-5,10-dihydro-1H,3H-dipyran[3,4-b:4,3-e]pyridine-4,6(7H,9H)-dione

A mixture of 30% pure product from Example 11B (tetrahydropyran-3,5-dione) (Terasawa, J. Org. Chem. (1977), 42, 1163-1169) (0.81 g, 1.7 mmol), 5-bromosalicylaldehyde (0.43 g, 2.2 mmol) and the product from Example 11C (0.20 g, 1.7 mmol) in ethanol (4 mL) was heated to 80°C for 60 hours and then allowed to stand at ambient temperature for 4 hours. The resulting solid was collected by filtration, washed with ethanol and dried to provide the title compound (0.12 g).

15 mp > 260°C;

MS (ESI(+)) m/z 392 (M+H)⁺;

MS (ESI(-)) m/z 390 (M-H)⁻;

¹H NMR (DMSO-d₆) δ 4.03 (s, 4H), 4.48 (AB q, 4H), 4.93 (s, 1H), 6.66 (d, 1H), 7.07-7.15 (m, 2H), 9.50 (s, 1H), 10.09 (bs, 1H);

20 Anal. Calcd for C₁₇H₁₄NO₅Br: C, 52.06; H, 3.60; N, 3.57. Found: C, 51.81; H, 3.45; N, 3.48.

Example 32

5-[4-fluoro-3-(trifluoromethyl)phenyl]-5,10-dihydro-1H,3H-dipyran[3,4-b:4,3-e]pyridine-4,6(7H,9H)-dione

25

A mixture of 30% pure product from Example 11B (tetrahydropyran-3,5-dione) (Terasawa, J. Org. Chem. (1977), 42, 1163-1169) (0.81 g, 1.7 mmol), 4-fluoro-3-(trifluoromethyl)benzaldehyde (0.42 g, 2.2 mmol) and the product from Example 11C (0.20 g, 1.7 mmol) in ethanol (4 mL) was processed as described in Example 31 to provide the title compound (0.12 g) as a white solid.

30

103

mp > 260°C;

MS (ESI(+)) m/z 384 (M+H)⁺, 401 (M+NH₄)⁺;

MS (ESI(-)) m/z 382 (M-H)⁻;

¹H NMR (DMSO-d₆) δ 4.06 (s, 4H), 4.51 (AB q, 4H), 5.01 (s, 1H), 7.40 (t, 1H), 7.52 (d, 2H), 10.11 (bs, 1H);

Anal. Calcd for C₁₈H₁₃NO₄F₄: C, 56.40; H, 3.42; N, 3.65. Found: C, 56.13; H, 3.62; N, 3.45.

Example 33

5-(3,4-dichlorophenyl)-5,10-dihydro-1H,3H-dipyran[3,4-b:4,3-e]pyridine-4,6(7H,9H)-dione

A mixture of 30% pure product from Example 11B (tetrahydropyran-3,5-dione) (Terasawa J. Org. Chem. (1977), 42, 1163-1169) (0.81 g, 1.7 mmol), 3,4-dichlorobenzaldehyde (0.39 g, 2.2 mmol) and the product from Example 11C (0.20 g, 1.7 mmol) in ethanol (4 mL) was processed as described in Example 31 to provide the title compound (0.15 g) as a white solid.

mp > 260°C;

MS (ESI(+)) m/z 366 (M+H)⁺, 383 (M+NH₄)⁺;

MS (ESI(-)) m/z 364 (M-H)⁻;

¹H NMR (DMSO-d₆) δ 4.05 (s, 4H), 4.50 (AB q, 4H), 4.94 (s, 1H), 7.19 (dd, 1H), 7.36 (d, 1H), 7.53 (d, 1H), 10.12 (bs, 1H);

Anal. Calcd for C₁₇H₁₃NO₄Cl₂·0.375 C₂H₆O: C, 55.60; H, 4.01; N, 3.65. Found: C, 55.21; H, 3.64; N, 3.36.

Example 34

5-(2,1,3-benzoxadiazol-5-yl)-5,10-dihydro-1H,3H-dipyran[3,4-b:4,3-e]pyridine-4,6(7H,9H)-dione

A mixture of tetrahydropyran-3,5-dione (Terasawa, J. Org. Chem. (1977), 42, 1163-1169) (0.27 g, 2.4 mmol), 2,1,3-benzoxadiazole-5-carboxaldehyde (Gasco, A. M. Eur.J.Med.Chem.Chim.Ther. (1996), 31,3-10) (0.54 g, 2.9 mmol) and the product from

104

Example 11C (0.27 g, 2.4 mmol) in ethanol (3 mL) was processed as described in Example 29 to provide the title compound (0.088) as a solid.

mp > 260°C;

MS (ESI(-)) m/z 338 (M-H)⁻;

5 ¹H NMR (DMSO-d₆) δ 4.08 (s, 4H), 4.54 (AB q, 4H), 5.06 (s, 1H), 7.61 (m, 2H), 7.97 (d, 1H), 10.23 (bs, 1H);

Anal. Calcd for C₁₇H₁₃N₃O₅·0.5 C₂H₆O: C, 59.15; H, 4.26; N, 11.83. Found: C, 59.09; H, 4.32; N, 11.99.

10

Example 35

5-(5-nitro-2-thienyl)-5,10-dihydro-1H,3H-dipyrano[3,4-b:4,3-e]pyridine-4,6(7H,9H)-dione

A mixture of 30% pure Example 11B (tetrahydropyran-3,5-dione) (Terasawa, J. Org. Chem. (1977), 42, 1163-1169) (0.60 g, 1.3 mmol), 5-nitro-2-thiophene carboxaldehyde (0.25 g, 1.6 mmol) and the product from Example 11C (0.15 g, 1.3 mmol) in ethanol (3 mL) was processed as described in Example 29 to provide the title compound (0.087 g) as a solid.

MS (ESI(+)) m/z 366 (M+NH₄)⁺;

MS (ESI(-)) m/z 347 (M-H)⁻;

20 ¹H NMR (DMSO-d₆) δ 4.10 (dd, 2H), 4.17 (d, 2H), 4.52 (AB q, 4H), 5.22 (s, 1H), 6.86 (dd, 1H), 7.93 (d, 1H), 10.35 (s, 1H);

Anal. Calcd for C₁₅H₁₂N₂O₆S·0.25 H₂O·0.25 C₂H₆O: C, 51.10; H, 3.87; N, 7.69. Found: C, 51.04; H, 3.92; N, 7.41.

Example 36

25 5-(5-nitro-3-thienyl)-5,10-dihydro-1H,3H-dipyrano[3,4-b:4,3-e]pyridine-4,6(7H,9H)-dione

A mixture of 30% pure product from Example 11B (tetrahydropyran-3,5-dione) (Terasawa, J. Org. Chem. (1977), 42, 1163-1169) (0.60 g, 1.3 mmol), 2-nitrothiophene 4-carboxaldehyde (0.25 g, 1.6 mmol) and the product from Example 11C (0.15 g, 1.3 mmol) in ethanol (3 mL) was processed as described in Example 29 to provide the title compound (0.084 g) as a solid.

30

105

mp > 260°C;

MS (ESI(+)) m/z 366 (M+NH₄)⁺;

MS (ESI(-)) m/z 347 (M-H)⁻;

¹H NMR (DMSO-d₆) δ 4.09 (AB q, 4H), 4.50 (AB q, 4H), 5.01 (s, 1H), 7.58 (d, 1H), 7.76 (d, 1H), 10.15 (bs, 1H);

Anal. Calcd for C₁₅H₁₂N₂O₆S·0.25 H₂O: C, 51.06; H, 3.57; N, 7.94. Found: C, 51.33; H, 3.78; N, 7.57.

Example 37

9-(4-fluoro-3-iodophenyl)-2,3,5,9-tetrahydro-4H-pyrano[3,4-b]thieno[2,3-e]pyridin-8(7H)-one 1,1-dioxide

Example 37A

tert-butyl 9-(3-bromo-4-fluorophenyl)-8-oxo-2,3,5,7,8,9-hexahydro-4H-pyrano[3,4-b]thieno[2,3-e]pyridine-4-carboxylate 1,1-dioxide

A mixture of the product from Example 12C (0.040 g, 0.096 mmol), di-tert-butyl dicarbonate (0.12 g, 0.55 mmol) and 4-dimethylaminopyridine (0.0020 g, 0.016 mmol) in acetonitrile (3 mL) was stirred for 2 hours at ambient temperature and concentrated. The residue was purified by chromatography on silica gel (2:1 and then 1:1 hexanes/ethyl acetate) to provide the title compound (0.035 g) which crystallized on standing.

MS (ESI(+)) m/z 531 (M+NH₄)⁺.

Example 37B

tert-butyl 9-[4-fluoro-3-(trimethylstannyl)phenyl]-8-oxo-2,3,5,7,8,9-hexahydro-4H-pyrano[3,4-b]thieno[2,3-e]pyridine-4-carboxylate 1,1-dioxide

A mixture of the product from Example 37A (0.035 g, 0.068 mmol) in anhydrous 1,4-dioxane (1 mL) under an atmosphere of nitrogen was treated with hexamethylditin (0.14 mL, 0.5 mmol), treated with tetrakis(triphenylphosphine)palladium(0) (0.050g, 0.043 mmol), stirred at 100°C for 1 hour, cooled to ambient temperature and concentrated.

The residue was purified by chromatography on silica gel (3:2 hexanes:ethyl acetate) to

106

provide the title compound (0.031 g) which crystallized on standing.

MS (ESI(+)) m/z 598 (M+H)⁺.

Example 37C

5 9-(4-fluoro-3-iodophenyl)-2,3,5,9-tetrahydro-4H-pyrano
 [3,4-b]thieno[2,3-e]pyridin-8(7H)-one 1,1-dioxide

A mixture of the product from Example 37B (0.023 g, 0.038 mmol) in 1% acetic acid in methanol (25 mL) was treated with N-chlorosuccinimide (0.010 g, 0.077 mmol), then treated with sodium iodide (0.011 g, 0.077 mmol), stirred for 10 minutes, treated with
10 pulverized sodium thiosulfate pentahydrate (0.020 g, 0.080 mmol), stirred for 10 minutes and concentrated to dryness. The residue was treated with trifluoroacetic acid (3 mL), stirred at ambient temperature for 15 minutes and concentrated to dryness. The residue was treated with trifluoroacetic acid (3 mL), heated gently on a steam bath for 1 minute, cooled to ambient temperature and concentrated to dryness. The residue was purified by
15 chromatography on silica gel (2% methanol and then 5% methanol in methylene chloride) to provide the title compound (0.0156 g).

mp > 260°C;

MS (ESI(-)) m/z 460 (M-H)⁻;

¹H NMR (DMSO-d₆) δ 2.77-2.90 (m, 1H), 3.01-3.14 (m, 1H), 3.32-3.43 (m, 2H), 4.02 (s, 2H), 4.49 (AB q, 2H), 4.87 (s, 1H), 7.16 (t, 1H), 7.24 (m, 1H), 7.59 (dd, 1H), 10.13 (bs, 1H);

Anal. Calcd for C₁₆H₁₃NO₄SFI: C, 41.66; H, 2.84; N, 3.04. Found: C, 41.28; H, 2.79; N, 2.87.

25 Example 38

5-(3-chloro-4-fluorophenyl)-2,3,5,7,8,9-hexahydro-1H-
cyclopenta[b][1,7]naphthyridine-4,6-dione hydrochloride

107

Example 38A2-benzyl-5-(3-chloro-4-fluorophenyl)-2,3,5,7,8,9-hexahydro-1H-cyclopenta[b][1,7]naphthyridine-4,6-dione

A mixture of 3-amino-2-cyclopenten-1-one (Kikani, B.B., Synthesis, (1991), 2, 176) (0.78 g, 8 mmol), 3-chloro-4-fluorobenzaldehyde (1.12 g, 8 mmol), and N-benzylpiperidine-3,5-dione (Ziegler, J. Amer. Chem. Soc. (1973), 95, 7458-7464) (1.78 g, 8 mmol) in ethanol (8 mL) was processed as in Example 5A to provide 1.8 g of the title compound.

MS (ESI(-)) m/z 421 (M-H)⁻;

¹H NMR (DMSO-d₆) δ 2.3 (m, 2H), 2.5-2.72 (m, 2H), 3.07 (Abqu, 2H), 3.5 (m, 2H), 3.67 (s, 2H), 4.65 (s, 1H), 7.15 (s, 1H), 7.42 (m, 7H), 10.28 (s, 1H).

Example 38B(1R,2S,5R)-5-methyl-2-(1-methyl-1-phenylethyl)cyclohexyl 5-(3-chloro-4-fluorophenyl)-4,6-dioxo-1,3,4,5,6,7,8,9-octahydro-2H-cyclopenta[b][1,7]naphthyridine-2-carboxylate

The product from Example 38A (1.8 g, 4.3 mmol) was processed as in Example 5B to provide 0.2 g of the title compound as the less polar isomer.

MS (ESI(-)) m/z 589 (M-H)⁻.

20

Example 38C5-(3-chloro-4-fluorophenyl)-2,3,5,7,8,9-hexahydro-1H-cyclopenta[b][1,7]naphthyridine-4,6-dione hydrochloride

The product from Example 38B (0.2 g, 0.33 mmol) was treated with 48% hydrogen bromide in acetic acid (4 mL), stirred for 72 hours, neutralized with concentrated ammonium hydroxide, and extracted with methylene chloride (3x). The combined organic layers were dried (Na₂SO₄), filtered, and concentrated. Purification of the residue on silica gel (10% ethanol/ammonia saturated methylene chloride) to provide the title compound (0.03 g) which was converted to the HCl salt.

MS (ESI(-)) m/z 331 (M-H)⁻;

¹H NMR (DMSO-d₆) δ 2.28 (t, 2H), 2.52-2.7 (m, 2H), 3.18 (s, 2H), 3.6 (m, 2H), 4.68 (s,

108

1H), 7.2 (m, 1H), 7.23 (t, 1H), 7.32 (dd, 1H), 10.18 (s, 1H);

Anal. Calcd for C₁₇H₁₄N₂FCIO₂·HCl·2H₂O: C, 50.49; H, 4.51; N, 6.73. Found: C, 49.52; H, 4.26; N, 6.09.

5

Example 39

9-(3-bromo-4-fluorophenyl)-5,6,7,9-tetrahydrofuro
[3,4-b][1,7]naphthyridine-1,8(3H,4H)-dione hydrochloride

Example 39A

10

methyl 7-benzyl-4-(3-bromo-4-fluorophenyl)-2-
methyl-5-oxo-1,4,5,6,7,8-hexahydro[1,7]naphthyridine-3-carboxylate

15

A solution of methyl 3-aminocrotonate (0.58 g, 5 mmol), 3-bromo-4-fluorobenzaldehyde (1.0 g, 5 mmol) and N-benzylpiperidine-3,5-dione (Ziegler, J. Amer. Chem. Soc. (1973), 95, 7458-7464) (1.1 g, 5 mmol) in ethanol (5 mL) was heated at reflux in a sealed tube for 24 hours and concentrated. Purification of the residue on silica gel eluting with 5% ethanol/methylene chloride provided the title compound (1.3 g) as a yellow foam.

MS (ESI(-)) m/z 485 (M-H)⁻.

20

Example 39B

6-benzyl-9-(3-bromo-4-fluorophenyl)-5,6,7,9-
tetrahydrofuro[3,4-b][1,7]naphthyridine-1,8(3H,4H)-dione

25

A solution of the product from Example 39A (3.1 g, 6.3 mmol) in chloroform (50 mL) was cooled to 0°C, treated with 90% pyridinium tribromide (2.45 g, 6.9 mmol), warmed to ambient temperature, stirred for 16 hours and washed with water. The chloroform layer was isolated, dried (MgSO₄), filtered, refluxed for 16 hours and cooled in an ice bath. The resulting precipitate was collected by filtration and dried to provide the title compound (2.1 g) as tan crystals.

MS (ESI(-))m/z 467 (M-H)⁻;

109

¹H NMR (DMSO-d₆) δ 3.08 (AB q, 2H), 3.5 (d, 2H), 3.65 (d, 2H), 4.7 (s, 1H), 4.9 (AB q, 2H), 7.3 (m, 7H), 7.47 (m, 1H), 10.1 (1H).

Example 39C

5 9-(3-bromo-4-fluorophenyl)-5,6,7,9-tetrahydrofuro
 [3,4-b][1,7]naphthyridine-1,8(3H,4H)-dione hydrochloride

A solution of product from Example 39B (0.35 g, 0.75 mmol) in methylene chloride (10 ml) was treated with vinyl chloroformate (0.1 mL, 1.2 mmol), stirred at ambient temperature for 16 hours, concentrated to dryness, treated with ethanol (10 mL),
10 treated with 6N HCl (3 mL), refluxed for 5 hours and concentrated to dryness. Purification of the residue on silica gel (10:90:1 ethanol/methylene chloride/saturated ammonium hydroxide) provided the title compound (0.08 g) which was converted the HCl salt.

mp 255-257°C;

15 MS (ESI(-)) m/z 377 (M-H);

¹H NMR (DMSO-d₆) δ 3.2 (s, 2H), 3.62 (s, 2H), 4.7 (s, 1H), 4.83 (d, 1H), 4.99 (d, 1H), 7.27 (m, 2H), 7.49 (dd, 1H), 10.25 (s, 1H);

Anal. Calcd for C₁₆H₁₁N₂FBrO₃·HCl·0.5 C₂H₅OH: C, 46.65; H, 3.45; N, 6.40. Found: C, 46.99; H, 3.69; N, 6.42.

20

Example 40

9-(3-bromo-4-fluorophenyl)-5,6,7,9-tetrahydrofuro
 [3,4-b][1,7]naphthyridine-1,8(3H,4H)-dione hydrochloride

25

Example 40A

(1R,2S,5R)-5-methyl-2-(1-methyl-1-phenylethyl)cyclohexyl 9-(3-bromo-4-fluorophenyl)-
1,8-dioxo-1,4,5,7,8,9-hexahydrofuro[3,4-b][1,7]naphthyridine-6(3H)-carboxylate

A solution of the product from Example 39C (1.46 g, 2.13 mmol) in tetrahydrofuran (70 ml) was treated with 8-phenylmenthol chloroformate prepared from
30 (-)-8-phenylmenthol as described in (Yamamoto, Y., J.Amer.Chem.Soc. (1992), 114, 121-

110

125) (1.1 g, 3.74 mmol), refluxed for 36 hours, filtered to remove the unreacted starting material and concentrated. Purification of the residue on silica gel (9:9:2 methylene chloride/ ethyl acetate/hexane) provided the title compound (0.46 g) as the less polar diastereomer.

5 MS (ESI(-)) m/z 635 (M-H)⁻.

Example 40B

9-(3-bromo-4-fluorophenyl)-5,6,7,9-tetrahydrofuro

[3,4-b][1,7]naphthyridine-1,8(3H,4H)-dione hydrochloride

10 A solution of the product from Example 40A (0.4 g, 0.63 mmol) in acetic acid (2 mL) was treated with 48% hydrobromic acid (0.5 mL), heated to 60°C for 5 hours, cooled to ambient temperature, neutralized with saturated ammonium hydroxide and extracted with chloroform (10 mL). The organic layer was dried (MgSO₄), filtered concentrated. The residue was purified on silica gel (20:80:1 ethanol/methylene chloride/saturated
15 ammonium hydroxide) to provide the unreacted starting material (0.21 g) and the title compound (0.05 g) which was converted to the HCl salt.

MS (ESI(-)) m/z 379 (M-H)⁻;

¹H NMR (DMSO-d₆) (free base) δ 3.25 (s, 2H), 3.68 (s, 2H), 4.7 (s, 1H), 4.85 (d, 1H), 4.98 (d, 1H), 7.28 (m, 2H), 7.5 (dd, 1H), 10.23 (s, 1H);

20 Anal. Calcd for C₁₆H₁₁N₂BrFO₃·HCl·H₂O: C, 44.42; H, 3.26; N, 6.47. Found: C, 44.74; H, 3.93; N, 6.51.

Example 41

5-(3-bromo-4-fluorophenyl)-7,7-dimethyl-5,8,9,10-

tetrahydro-1H-pyrano[3,4-b]quinoline-4,6(3H,7H)-dione

25 A mixture of the product from Example 11C (0.16 g, 1.4 mmol), 3-bromo-4-fluorobenzaldehyde (0.29 g, 1.4 mmol), 4,4-dimethyl-1,3-cyclohexanedione (2.0 g, 1.4 mmol) and ethanol (18 mL) was heated at 80°C for 60 hours, cooled, concentrated to an oil and triturated with 3:1 ethanol/diethyl ether (3x). The resulting solid was dried to
30 provide the title compound (0.11 g) as a yellow solid.

111

mp >260°C;

MS (DCI/NH₃) m/z 420 (M+H)⁺;

¹H NMR (DMSO-d₆) δ 9.76 (br s, 1H), 7.38 (dd, 1H, J=6.8, 2.0 Hz), 7.24-7.13 (m, 2H), 4.88 (s, 1H), 4.46 (AB q, 2H, JAB=11.2, dvAB=15.9 Hz), 4.01 (s, 2H), 2.68-2.48 (m, 2H), 1.78 (t, 2H), 0.98 (s, 3H), 0.93 (s, 3H);

¹³C NMR (DMSO-d₆) δ 199.7, 191.2, 155.9, 149.9, 144.5, 131.9, 128.5, 116.2, 110.1, 108.6, 107.2, 107.0, 71.2, 63.2, 39.6, 34.0, 31.4, 24.7, 24.0, 23.1;

Anal. Calcd for C₂₀H₁₉BrFNO₃: C, 57.16; H, 4.56; N, 3.33. Found: C, 57.10; H, 4.70; N, 3.19.

Example 42

(9R)-9-(3-bromo-4-fluorophenyl)-5,9-dihydro-3H-furo [3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione

The enantiomers of Example 25C were separated by chiral chromatography on a Chiralpak AS column (5.0 cm inner diameter, 50 cm length, 20 micron packing) using 80:20 hexane:ethanol at a flow rate of 117 mL/minute as the mobile phase. A total of 227 mg in 100 mL hot ethanol (three injections of 20 mL, 40 mL and 40 mL) was used to provide the faster moving isomer which was repurified by chromatography on silica gel using a gradient of 1%-2% and 5% methanol in methylene chloride to provide the title compound (0.080 g) which was determined to have an absolute configuration of (R) via X-ray analysis.

X-ray data: MW=380.17, C₁₆H₁₁NO₄FBr, crystal dimensions 0.60X0.20X0.10 mm, orthorhombic, P2₁2₁2₁ (#19), a=7.7839(2) Å, b=13.5605(7) Å, c=14.0248(7) Å, V=1480.4(1) Å³, Z=4, D_{calc}=1.706 g/cm³, Crystallographic data were collected using Mo Kα radiation (λ=0.71069 Å³). Refinement of the structure using full matrix least squares refinement of 208 parameters on 1986 reflections with I>3.00σ(I) gave R=0.039, R_w=0.046;

MS (ESI(+)) m/z 380 (M+H)⁺, 397 (M+NH₄)⁺;

MS (ESI(-)) m/z 378 (M-H)⁻;

¹H NMR (DMSO-d₆) δ 4.06 (s, 2H), 4.54 (AB q, 2H), 4.75 (s, 1H), 4.88 (d, 1H), 5.03 (d,

112

1H), 7.28 (d, 2H), 7.48 (d, 1H), 10.50 (s, 1H);

Anal. Calcd for C₁₆H₁₁NO₄FBr0.1875 CH₂Cl₂: C, 49.09; H, 2.89; N, 3.54. Found: C, 49.11; H, 2.93; N, 3.17.

5

Example 43(9S)-9-(3-bromo-4-fluorophenyl)-5,9-dihydro-3H-furo[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione

The title compound (0.080 g) was provided as the slower moving enantiomer from the procedure described in Example 42.

10 MS (ESI(+)) m/z 380 (M+H)⁺, 397 (M+NH₄)⁺;

MS (ESI(-)) m/z 378 (M-H)⁻;

¹H NMR (DMSO-d₆) δ 4.06 (s, 2H), 4.54 (AB q, 2H), 4.75 (s, 1H), 4.88 (d, 1H), 5.03 (d, 1H), 7.28 (d, 2H), 7.48 (d, 1H), 10.50 (s, 1H);

Anal. Calcd for C₁₆H₁₁NO₄FBr0.125 CH₂Cl₂: C, 49.56; H, 2.90; N, 3.58. Found: C, 49.54; H, 3.07; N, 3.27.

15

Example 4410-(3-chloro-4-fluorophenyl)-3,4,6,10-tetrahydro-2H-pyrano[3,4-b][1,6]naphthyridine-1,9(5H,8H)-dione

20

A mixture of the product from Example 11C (0.023 g, 0.2 mmol), piperidine-2,4-dione (Nakagawa, S., Heterocycles (1979), 13, 477-495) (0.23 g, 0.2 mmol), 3-chloro-4-fluorobenzaldehyde (0.032 g, 0.2 mmol) and ethanol (2 mL) was heated to 80°C for 60 hours and cooled to ambient temperature. The resulting solid was collected by filtration, washed with ethanol and dried under vacuum to provide the title compound.

25

MS (APCI(+)) m/z 349 (M+H)⁺;

MS (APCI(-)) m/z 347 (M-H)⁻;

¹H NMR (DMSO-d₆) δ 2.34-2.57 (m, 2H), 3.13-3.28 (m, 2H), 4.00 (s, 2H), 4.45 (AB q, 2H), 4.96 (s, 1H), 7.08 (d, 1H), 7.17 (ddd, 1H), 7.26 (t, 1H), 7.28 (dd, 1H), 9.55 (s, 1H).

30

113

Example 4510-(3,4-dichlorophenyl)-3,4,6,10-tetrahydro-2H-pyrano
[3,4-b][1,6]naphthyridine-1,9(5H,8H)-dione

Example 11C was processed as in Example 44 but substituting 3,4-
5 dichlorobenzaldehyde for 3-chloro-4-fluorobenzaldehyde to provide the title compound.

MS (APCI(+)) m/z 365 (M+H)⁺;

MS (APCI(-)) m/z 363 (M-H)⁻;

¹H NMR (DMSO-d₆) δ 2.36-2.58 (m, 2H), 3.14-3.26 (m, 2H), 4.00 (AB q, 2H), 4.45 (AB
q, 2H), 4.96 (s, 1H), 7.09 (d, 1H), 7.17 (dd, 1H), 7.34 (d, 1H), 7.49 (d, 1H), 9.57 (s, 1H).

10

Example 4610-[4-chloro-3-(trifluoromethyl)phenyl]-3,4,6,10-
tetrahydro-2H-pyrano[3,4-b][1,6]naphthyridine-1,9(5H,8H)-dione

Example 11C was processed as in Example 44 but substituting 4-chloro-3-
15 (trifluoromethyl)benzaldehyde for 3-chloro-4-fluorobenzaldehyde to provide the title
compound.

MS (APCI(+)) m/z 399 (M+H)⁺;

MS (APCI(-)) m/z 397 (M-H)⁻;

¹H NMR (DMSO-d₆) δ 2.36-2.58 (m, 2H), 3.15-3.26 (m, 2H), 4.00 (AB q, 2H), 4.45 (AB
20 q, 2H), 5.02 (s, 1H), 7.11 (s, 1H), 7.46 (dd, 1H), 7.59 (d, 1H), 7.63 (d, 1H), 9.60 (s, 1H).

20

Example 4710-(4-chloro-3-nitrophenyl)-3,4,6,10-tetrahydro-2H-
pyrano[3,4-b][1,6]naphthyridine-1,9(5H,8H)-dione

Example 11C was processed as in Example 44 but substituting 4-chloro-3-
25 nitrobenzaldehyde for 3-chloro-4-fluorobenzaldehyde to provide the title compound.

MS (APCI(-)) m/z 374 (M-H)⁻;

¹H NMR (DMSO-d₆) δ 2.42-2.57 (m, 2H), 3.16-3.30 (m, 2H), 4.01 (AB q, 2H), 4.46 (AB
q, 2H), 5.03 (s, 1H), 7.12 (d, 1H), 7.52 (dd, 1H), 7.64 (d, 1H), 7.76 (d, 1H), 9.62 (s, 1H).

30

114

Example 48

10-(3,4-dibromophenyl)-3,4,6,10-tetrahydro-2H-
pyrano[3,4-b][1,6]naphthyridine-1,9(5H,8H)-dione

Example 11C was processed as in Example 44 but substituting 3,4-
5 dibromobenzaldehyde for 3-chloro-4-fluorobenzaldehyde to provide the title compound.

MS (APCI(+)) m/z 453 (M+H)⁺;

MS (APCI(-)) m/z 451 (M-H)⁻;

¹H NMR (DMSO-d₆) δ 2.41-2.57 (m, 2H), 3.18-3.26 (m, 2H), 4.00 (AB q, 2H), 4.45 (AB
q, 2H), 4.93 (s, 1H), 7.09 (bs, 1H), 7.12 (dd, 1H), 7.49 (d, 1H), 7.61 (d, 1H), 9.56 (s, 1H).

10

Example 49

10-(5-nitro-3-thienyl)-3,4,6,10-tetrahydro-2H-pyrano
[3,4-b][1,6]naphthyridine-1,9(5H,8H)-dione

Example 11C was processed as in Example 44 but substituting 5-nitrothiophene-3-
15 carboxaldehyde for 3-chloro-4-fluorobenzaldehyde to provide the title compound.

MS (APCI(+)) m/z 348 (M+H)⁺;

MS (APCI(-)) m/z 346 (M-H)⁻;

¹H NMR (DMSO-d₆) δ 2.39-2.54 (m, 2H), 3.19-3.30 (m, 2H), 4.02 (s, 2H), 4.42 (AB q,
2H), 5.00 (s, 1H), 7.09 (d, 1H), 7.48 (d, 1H), 7.75 (d, 1H), 9.69 (bs, 1H).

20

Example 50

5-(3-bromo-4-fluorophenyl)-5,8,9,10-tetrahydro-1H-
thiopyrano[3,4-b]quinoline-4,6(3H,7H)-dione

A mixture of thiopyran-3,5-dione (Fehnel, E.A., J. Amer. Chem. Soc., (1955), 77,
25 4241-4244) (0.12 g, 1.0 mmol), 3-bromo-4-fluorobenzaldehyde (0.20 g, 1.0 mmol), 3-
amino-2-cyclohexene-1-one (0.11 g, 1.0 mmol) and ethanol (5 mL) was heated to 80°C in
a sealed tube for 60 hours and cooled to ambient temperature. The resulting solid was
collected by filtration, washed with ethanol and dried for 16 hours under high vacuum to
provide the title compound (0.13 g).

30

MS (APCI(+)) m/z 408 (M+H)⁺;

115

MS (APCI(-)) m/z 406 (M-H)⁻;

¹H NMR (DMSO-d₆) δ 1.77-1.88 (m, 1H), 1.89-1.98 (m, 1H), 2.25 (dd, 2H), 2.46-2.62 (m, 2H), 3.10 (dd, 1H), 3.48 (ddd, 2H), 3.82 (d, 1H), 4.96 (s, 1H), 7.15-7.24 (m, 2H), 7.41 (dd, 1H), 9.71 (s, 1H);

5 Anal. Calcd for C₁₈H₁₅BrFNO₂S: C, 52.95; H, 3.70; N, 3.43. Found: C, 52.81; H, 3.79; N, 3.17.

Example 51

5-(3-bromo-4-fluorophenyl)-5,7,8,9-tetrahydrocyclopenta

[b]thiopyrano[4,3-e]pyridine-4,6(1H,3H)-dione

10 Thiopyran-3,5-dione (Fehnel, E.A., J. Amer. Chem. Soc., (1955), 77, 4241-4244) (0.12 g, 1.0 mmol) was processed as described in Example 50 but substituting 3-amino-2-cyclopentene-1-one for 3-amino-2-cyclohexene-1-one to provide a solid. The solid was purified by chromatography on silica gel eluting with 1:1 acetone:methylene chloride to
15 provide the title compound (0.13 g).

MS (APCI(+)) m/z 394 (M+H)⁺;

MS (APCI(-)) m/z 392 (M-H)⁻;

¹H NMR (DMSO-d₆) δ 2.28 (t, 2H), 2.48-2.73 (m, 2H), 3.14 (dd, 1H), 3.47 (dd, 1H), 3.54 (dd, 1H), 3.82 (dd, 1H), 4.72 (s, 1H), 7.18-7.25 (m, 2H), 7.42 (dd, 1H), 10.27 (s, 1H);

20 Anal. Calcd for C₁₇H₁₃NO₂SFBr: C, 51.79; H, 3.32; N, 3.55. Found: C, 51.46; H, 3.49; N, 3.39.

Example 52

10-(3-bromo-4-fluorophenyl)-3,4,6,10-tetrahydro-

2H-pyrano[3,4-b][1,6]naphthyridine-1,9(5H,8H)-dione

25 Example 11C was processed as in Example 44 but substituting 3-bromo-4-fluorobenzaldehyde for 3-chloro-4-fluorobenzaldehyde to provide the title compound (0.79 g).

MS (APCI(+)) m/z 393 (M+H)⁺;

30 MS (APCI(-)) m/z 391 (M-H)⁻;

116

¹H NMR (DMSO-d₆) δ 2.38-2.60 (m, 2H), 3.18-3.26 (m, 2H), 4.00 (s, 2H), 4.45 (AB q, 2H), 4.95 (s, 1H), 7.14 (s, 1H), 7.16-7.28 (m, 2H), 7.41 (dd, 1H), 9.59 (s, 1H);

Anal. Calcd for C₁₇H₁₄N₂O₃FBr: C, 51.93; H, 3.59; N, 7.12. Found: C, 51.68; H, 3.83; N, 7.10.

5

Example 53

5-(3-bromo-4-methylphenyl)-5,10-dihydro-1H,3H-dipyrano[3,4-b:4,3-e]pyridine-4,6(7H,9H)-dione

The product from Example 11C (0.11 g, 0.96 mmol), the 30% pure product from Example 11B (0.49 g) and 3-bromo-4-methylbenzaldehyde (Pearson.; Org. Synth. Coll. Vol. V, 1973, 117) (0.21 g, 0.86 mmol) were processed as described in Example 31 to provide the title compound (0.050 g).

¹H NMR (DMSO-d₆) δ 2.25 (s, 3H), 4.04 (s, 4H), 4.48 (q, 4H, J=16.27 Hz), 4.90 (s, 1H), 7.10 (m, 1H), 7.22 (d, 1H, J=8.12 Hz), 7.33 (d, 1H, J=2.17 Hz);

MS (ESI+) 391m/z (M+H)⁺;

Anal. Calcd for C₁₈H₁₆BrNO₄: C, 55.40; H, 4.13; N, 3.59. Found: C, 54.78; H, 4.30; N, 3.29.

Example 54

5-(3-iodo-4-methylphenyl)-5,10-dihydro-1H,3H-dipyrano[3,4-b:4,3-e]pyridine-4,6(7H,9H)-dione

Example 54A

3-iodo-4-methylbenzaldehyde

3-Iodo-4-methylbenzoic acid (1.0g, 3.96 mmol) in dry CH₂Cl₂:THF 1:1 (200mL) was treated with oxalyl chloride (1 mL, 11.9 mmol) and several drops of DMF. The mixture was heated at 65°C for 30 minutes, cooled to ambient temperature, and concentrated under reduced pressure to provide a light yellow solid. The obtained solid was dissolved in THF (200 mL) and treated with a 1M solution of lithium tri-tert-butoxyaluminumhydride in THF (4.1 mL, 4.1 mmol) via syringe at -78°C. After 30 minutes

117

at -78°C, a saturated solution of Rochelle's salt was added and the mixture was allowed to warm to ambient temperature. The organic layer was washed in succession with 1N HCl, saturated NaHCO₃ and brine, dried over Na₂SO₄, and concentrated. The resulting residue was purified by flash chromatography using hexanes:ethyl acetate (4:1) as the eluent to provide the title compound as a white solid (300 mg, 18%).

Example 54B

5-(3-iodo-4-methylphenyl)-5,10-dihydro-1H,3H-dipyrano[3,4-b:4,3-e]pyridine-4,6(7H,9H)-dione

The product from Example 11C (0.097 g, 0.86 mmol), the 30 % pure product from Example 11B (0.49 g) and the product from Example 54A (0.21 g, 0.86 mmol) were processed as described in Example 31 to provide the title compound (0.050 g).

¹H NMR (DMSO-d₆) δ 2.27 (s, 3H), 4.04 (s, 4H), 4.51 (m, 4H), 4.87 (s, 1H), 7.09 (m, 1H), 7.21 (d, 1H, J=8.01 Hz), 7.60 (d, 1H, J=1.84 Hz);

MS (ESI-) m/z 436 (M-H)⁻;

Anal. Calcd for C₁₈H₁₆INO₄: C, 49.45; H, 3.69; N, 3.20. Found: C, 49.31; H, 3.92; N, 2.89.

Example 55

5-(3,4-dibromophenyl)-5,10-dihydro-1H,3H-dipyrano[3,4-b:4,3-e]pyridine-4,6(7H,9H)-dione

The product from Example 11C (0.080 g, 0.71 mmol), the 30% pure product from Example 11B (0.35 g) and 3,4-dibromobenzaldehyde (0.23 g, 0.85 mmol) were processed as described in Example 31 to provide the title compound (0.060 g).

¹H NMR (DMSO-d₆) δ 4.04 (s, 4H), 4.50 (AB q, 4H), 4.91 (s, 1H), 7.13 (m, 1H), 7.49 (d, 1H), 7.65 (d, 1H), 10.12 (bs, 1H);

MS (ESI+) m/z 454 (M+H)⁺;

MS (ESI-) m/z 452 (M-SH)⁻;

Anal. Calcd for C₁₇H₁₃NO₄Br₂: C, 44.87; H, 2.88; N, 3.08. Found: C, 44.79; H, 2.78; N, 2.78.

Example 565-[4-chloro-3-(trifluoromethyl)phenyl]-5,10-dihydro-1H,3H-dipyrano[3,4-b:4,3-e]pyridine-4,6(7H,9H)-dione

5 The product from Example 11C (0.23 g, 2.0 mmol), the 30% pure product from Example 11B (0.46 g) 4-chloro-3-(trifluoromethyl)benzaldehyde (0.473 g, 2.4 mmol) were processed as described in Example 29 to provide the title compound (0.24 g).

¹H NMR (DMSO-d₆) δ 4.05 (s, 4H), 4.50 (AB q, 4H), 5.00 (s, 1H), 7.47 (dd, 1H), 7.60-7.66 (m, 2H), 10.14 (bs, 1H); MS (ESI+) m/z 400 (M+H)⁺;

10 MS (ESI-) m/z 398 (M-SH)⁻;

Anal. Calcd for C₁₈H₁₃NO₄ClF₃ 0.25 H₂O: C, 53.48; H, 3.37; N, 3.46. Found: C, 53.12; H, 3.64; N, 3.17.

Example 575-[4-fluoro-3-(2-furyl)phenyl]-5,10-dihydro-1H,3H-dipyrano[3,4-b:4,3-e]pyridine-4,6(7H,9H)-dioneExample 57A4-fluoro-3-(2-furyl)-benzaldehyde

20 3-Bromo-4-fluorobenzaldehyde (1 g, 4.93 mmol) in DMF (25 ml) was treated with 2-(tributylstannyl)furan (2.4 ml, 1.05 mmol), di-tert-butyl dicarbonate (1.75 g, 4.94 mmol), and tetrakis(triphenylphosphine)palladium (0) (570 mg, 0.4 mmol). The mixture was heated at 110°C in a sealed high pressure tube over night, allowed to cool to ambient temperature, diluted with ethyl acetate, and washed with brine. The organic layer was
25 further washed with 1N HCl, saturated NaHCO₃, brine, dried (Na₂SO₄), and concentrated under reduced pressure. The residue was purified by flash chromatography using hexanes:diethyl ether (20:1) as eluent to provide the title compound as a pale yellow oil (0.96g, 98%).

Example 57B5-[4-fluoro-3-(2-furyl)phenyl]-5,10-dihydro-1H,3H-dipyrano[3,4-b:4,3-e]pyridine-4,6(7H,9H)-dione

The product from Example 11C (0.065 g, 0.58 mmol), the product from Example 11B (0.14 g, 1.2 mmol) and the product from Example 57A (0.15 g, 0.79 mmol) were processed as described in Example 31 to provide the title compound (0.13 g).

¹H NMR (DMSO-d₆) δ 4.05 (s, 4H), 4.49 (m, 4H), 5.00 (s, 1H), 6.66 (m, 1H), 6.81 (t, 1H, J=3.72 Hz), 7.01-7.29 (m, 2H), 7.62 (dd, 1H, J=8.01, 7.32 Hz), 7.86 (d, 1H, J=1.47 Hz); MS (ESI-) m/z 380 (M-H)⁻;

Anal. Calcd for C₂₁H₁₆FNO₅: C, 66.14; H, 4.23; N, 3.67. Found: C, 65.81; H, 4.36; N, 3.35.

Example 585-(5-bromo-4-fluoro-2-hydroxyphenyl)-5,10-dihydro-1H,3H-dipyrano[3,4-b:4,3-e]pyridine-4,6(7H,9H)-dioneExample 58A4-fluoro-2-hydroxybenzaldehyde

Magnesium methoxide (13 g, 150 mmol, 6% in methanol) in methanol (50 mL) was treated with 3-fluorophenol (22.4 g, 200 mmol). The solution was heated to reflux and approximately half the methanol distilled off. Toluene (300 mL) was added and the reaction mixture was heated with azeotropic removal of solvent until the temperature of the distillate reached 95°C. A slurry of paraformaldehyde powder (22 g, 720 mmol) in toluene (20 mL) was added in small portions over 1 hour to the reaction with concurrent removal of volatile materials by distillation. The mixture was stirred was at 95°C for 1 hour, cooled to 25°C, quenched by slow addition to 10% sulfuric acid and stirred at 30-40°C for 2 hours. The layers were separated and the aqueous portion extracted with toluene (2x50 mL). The organic layers were combined, washed with 10% sulfuric acid, washed with water, dried with sodium sulfate, filtered and the solvent was evaporated.

The resulting yellow oil was purified by flash chromatography over silica gel eluting with

120

hexane:ethyl acetate (5:1) to provide 9.7 g of the title compound as a white solid.

^1H NMR (CDCl_3) δ 6.70 (m, 2H), 7.58 (m, 1H), 9.85 (s, 1H), 11.35 (s, 1H);

MS (APCI-) m/z 139 (M-H) $^-$.

5

Example 58B

4-fluoro-5-bromo-2-hydroxybenzaldehyde

The product from Example 58A (2.00 g, 14.3 mmol) in chloroform (10 mL) was treated slowly with a solution of bromine (0.70 mL, 13 mmol) in chloroform (6 mL) at room temperature. After the free bromine had disappeared, the mixture was treated with 20% sodium hydroxide (20 mL), refluxed for 4 hours, cooled and concentrated. The resulting solid was dissolved in ethyl acetate, acidified with 1N hydrochloric acid to pH=5, and the solvents were evaporated. The crude product was purified by flash chromatography over silica gel eluting with hexane:ethyl acetate (6:1) to provide 1.95 g of the title compound.

15 MS (ESI+) m/z : 219 (M+H) $^+$;

^1H NMR (CDCl_3) δ 6.78 (d, 1H, J=9 Hz), 7.75 (d, 1H, J=9 Hz), 9.80 (s, 1H), 11.25 (s, 1H).

Example 58C

5-(5-bromo-4-fluoro-2-hydroxyphenyl)-5,10-dihydro-

20

1H,3H-dipyran[3,4-b:4,3-e]pyridine-4,6(7H,9H)-dione

The product from Example 11C (0.12 g, 1.1 mmol), the product from Example 11B (0.12 g, 1.1 mmol) and the product from Example 58B (0.22 g, 1.0 mmol) were processed as described in Example 31 to provide the title compound (0.23 g).

^1H NMR ($\text{DMSO}-d_6$) δ 4.02 (s, 4H), 4.53 (m, 4H), 4.96 (s, 1H), 6.65 (d, 1H, J=10.86 Hz), 7.19 (d, 1H, J=10.86 Hz), 10.01 (s, 1H), 10.10 (s, 1H);

25

MS (ESI-) m/z 409 (M-H) $^-$;

Anal. Calcd for $\text{C}_{17}\text{H}_{13}\text{BrFNO}_5$: C, 49.78; H, 3.19; N, 3.41. Found: C, 49.40; H, 3.22; N, 3.32.

30

121

Example 595-(4-methyl-3-nitrophenyl)-5,10-dihydro-1H,3H-dipyrano[3,4-b:4,3-e]pyridine-4,6(7H,9H)-dione

The product from Example 11C (0.10 g, 0.09 mmol), the product from Example 11B (0.13 g, 1.2 mmol) and 4-methyl-3-nitrobenzaldehyde (0.25 g, 1.1 mmol) were processed as described in Example 31 to provide the title compound (0.22 g).

¹H NMR (DMSO-d₆) δ 2.43 (s, 3H), 4.04 (s, 4H), 4.50 (m, 4H), 5.00 (s, 1H), 7.30-7.49 (m, 2H), 7.74 (d, 1H, J=1.7 Hz), 10.11 (s, 1H);

MS (ESI-) m/z 355 (M-H)⁻;

Anal. Calcd for C₁₈H₁₆N₂O₆: C, 60.67; H, 4.53; N, 7.86. Found: C, 60.44; H, 4.55; N, 7.62.

Example 605-(4-bromo-3-chlorophenyl)-5,10-dihydro-1H,3H-dipyrano[3,4-b:4,3-e]pyridine-4,6(7H,9H)-dioneExample 60A4-Bromo-3-nitrobenzaldehyde

A suspension of sodium nitrate (1.37 g, 16.2 mmol) in concentrated sulfuric acid (15 mL) was stirred at 10°C until a homogeneous solution was obtained. The solution was treated with 4-bromobenzaldehyde (2.50 g, 13.5 mmol) in portionwise fashion over a 20 minute period. The solution was poured onto ice (50 g) and the resulting pale yellow precipitate was collected by filtration. The precipitate was washed with copious amounts of water then dried at 30°C under reduced pressure to provide the title compound as a pale yellow solid (2.95 g, 12.8 mmol, 95%).

Example 60B3-Amino-4-bromobenzaldehyde

(Reference: Park, K. K.; Oh, C. H.; Joung, W. K. Tetrahedron Lett. 1993, 34, 7445-7446)

The product from Example 60A (992 mg, 4.31 mmol) in CH₂Cl₂ at 23°C (6 mL) was

122

treated with water (1.5 mL) and N,N'-diheptyl-4,4'-bipyridinium dibromide (43 mg, 10 mg/mmol of substrate). The biphasic mixture was cooled to 5°C and treated with a solution of sodium dithionite (3.00 g, 17.2 mmol) and K₂CO₃ (2.68 g, 19.4 mmol) in water (3.5 mL). The cooling bath was removed and the biphasic mixture stirred vigorously at 23°C for 4 hours. The mixture was partitioned between additional CH₂Cl₂ (15 mL) and water (10 mL) and the aqueous layer was extracted with CH₂Cl₂ (10 mL). The combined organic portions were washed with brine (10 mL) and dried (Na₂SO₄). Ethyl acetate (5 mL) was added along with silica gel (5 g) and the suspension was filtered through a small pad of Celite, rinsing with 10% ethyl acetate/CH₂Cl₂ (15 mL). The filtrate was concentrated to provide the title compound (716 mg, 3.58 mmol, 82%) as an off-yellow powder.

MS (DCI/NH₃) m/e 218 (M+NH₄)⁺.

Example 60C

4-Bromo-3-chlorobenzaldehyde

The product from Example 60B (1.97 g, 9.85 mmol) in concentrated HCl (20 mL) at 0°C was treated with NaNO₂ (714 mg, 10.3 mmol). The reaction mixture was stirred for 30 minutes and then was transferred cold in portionwise fashion by dropping pipet to a stirred solution of CuCl (1.37 g, 13.8 mmol) in concentrated HCl (15 mL) at 23°C (significant frothing!). The lime green solution was heated at 60°C for 45 minutes, cooled, diluted with ethyl acetate (200 mL) and water (50 mL) and the layers partitioned. The organic portion was washed in succession with water (4 x 50 mL), aqueous NaHCO₃ (2 x 60 mL), brine (100 mL), dried (Na₂SO₄) and concentrated. The residue was purified by flash chromatography (elution with 10% ethyl acetate/hexanes) to provide the title compound as a waxy, off-white solid (1.45 g, 6.59 mmol, 68%).

MS (DCI/NH₃) m/e 234 (M+NH₄)⁺.

123

Example 60D5-(4-bromo-3-chlorophenyl)-5,10-dihydro-1H,3H-dipyrano[3,4-b:4,3-e]pyridine-4,6(7H,9H)-dione

The product from Example 60C (291 mg, 1.33 mmol), the product from Example 11B (127 mg, 1.11 mmol), and the product from Example 11C (125 mg, 1.11 mmol) in ethanol (20 mL) were heated at reflux for 48 hours. The reaction mixture was cooled and concentrated to provide a pale yellow residue. The residue was triturated with 25% ethanol/diethyl ether, then 15% CH₂Cl₂/diethyl ether, then diethyl ether to provide the title compound as a pale tan solid (287 mg, 0.699 mmol, 63%).

mp >270°C;

¹H NMR (DMSO-d₆) δ 4.15 (s, 4H), 4.51 (ABq, 4H, J_{AB}=10.8 Hz, Dn_{AB}=18.0 Hz), 4.92 (s, 1H), 7.10 (dd, 1H, J=7.4, 1.3 Hz), 7.36 (d, 1H, J=1.2 Hz), 7.66 (d, 1H, J=7.5 Hz), 10.13 (s, 1H);

MS (DCI/NH₃) m/z 429 (M+NH₄)⁺;

Anal. Calcd for C₁₇H₁₃BrClNO₄: C, 49.72; H, 3.19; N, 3.41. Found: C, 46.69; H, 3.23; N, 3.26.

Example 615-(3-bromo-4-chlorophenyl)-5,10-dihydro-1H,3H-dipyrano[3,4-b:4,3-e]pyridine-4,6(7H,9H)-dioneExample 61A3-Amino-4-chlorobenzaldehyde

4-Chloro-3-nitrobenzaldehyde (4.00 mg, 21.6 mmol) in CH₂Cl₂ (150 mL) at 23°C was treated with water (50 mL) and N,N'-diheptyl-4,4'-bipyridinium dibromide (220 mg, 10 mg/mmol of substrate). The biphasic mixture was cooled to 5°C and treated with a solution of sodium dithionite (15.0 g, 86.0 mmol) and K₂CO₃ (13.4 g, 87.0 mmol) in water (45 mL). The cooling bath was removed and the biphasic mixture stirred vigorously at 23°C for 4 hours. The mixture was partitioned between additional CH₂Cl₂ (75 mL) and water (50 mL) and the aqueous layer was extracted with CH₂Cl₂ (75 mL). The organic

124

portions were washed with brine (75 mL) and dried (Na₂SO₄). The residue was treated with ethyl acetate (25 mL) and silica gel (75 g) and the suspension was filtered through a small pad of Celite™, rinsing with 10% ethyl acetate/CH₂Cl₂ (15 mL). The filtrate was concentrated to provide the title compound as an off-yellow powder (3.44 g, 22%). MS (DCI/NH₃) m/e 218 (M+NH₄)⁺.

Example 61B

3-Bromo-4-chlorobenzaldehyde

The product from Example 61A (3.4 g, 22 mmol) in concentrated 48% aqueous HBr (20 mL) at 0°C was treated with a 0°C solution of NaNO₂ (1.5 g, 22 mmol) in water (30 mL). The reaction mixture was stirred for 30 minutes and then transferred cold to a stirred solution of CuBr (4.44 g, 31 mmol) in 48% aqueous HBr (20 mL) at 23°C (significant frothing!). Water (40 mL) was added and the solution was heated at 60°C for 45 minutes, cooled, diluted with ethyl acetate (200 mL) and water (50 mL) and the layers were partitioned. The aqueous layer was extracted with ethyl acetate (2 x, 50 mL). The organic layers were combined, washed with 1M HCl (2x, 100 mL), washed with brine (50 mL), dried (Na₂SO₄), filtered and concentrated to provide the title compound as a pale yellow powder (3.9 g, 82%).

Example 61C

5-(3-bromo-4-chlorophenyl)-5,10-dihydro-1H,3H-dipyrido[3,4-b:4,3-e]pyridine-4,6(7H,9H)-dione

The product from Example 61B, the product from Example 11B, and the product from Example 11C were processed as in Example 60D to afford the title compound.

mp>270°C;

¹H NMR (DMSO-d₆) δ 4.04 (s, 4H), 4.51 (ABq, 4H, J_{AB}=13.3 Hz, Dn_{AB}=20.6 Hz), 4.94 (s, 1H), 7.21 (dd, 1H, J=7.5, 1.1 Hz), 7.50 (d, 1H, J=1.2 Hz), 7.3 (d, 1H, J=7.6 Hz), 10.12 (s, 1H);

MS (DCI/NH₃) m/z 429 (M+NH₄)⁺;

125

Anal. Calcd for $C_{17}H_{13}BrClNO_4$: C, 49.72; H, 3.19; N, 3.41. Found: C, 46.94; H, 3.24; N, 3.26.

Example 62

5 5-[3-iodo-4-(trifluoromethyl)phenyl]-5,10-dihydro-
1H,3H-dipyrano[3,4-b:4,3-e]pyridine-4,6(7H,9H)-dione

Example 62A

[3-nitro-4-(trifluoromethyl)phenyl]methanol

10 α,α,α -trifluoromethyl-p-toluic acid (15 g, 78.9 mmol) in 90 mL of concentrated
sulfuric acid was treated dropwise with a mixture of fuming nitric acid (2 mL) and sulfuric
acid (24 mL). The reaction mixture was stirred at ambient temperature for 48 hours and
quenched into ice-water. The resulting precipitate (12 g), comprising a mixture of
nitration products and unreacted starting material was collected by filtration, washed with
15 water and dried under reduced pressure. The resulting dry solid (12 g) was dissolved in
THF (300 mL), cooled to 0°C, treated with 1M borane-tetrahydrofuran complex (80 mL)
and stirred at room temperature overnight. The mixture was treated carefully with
methanol (5 mL), treated carefully with concentrated HCl (5 mL), refluxed for 1 hour and
evaporated to dryness and partitioned between water and diethyl ether. The organic layer
20 was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was
chromatographed on silica gel eluting with 30% ethyl acetate /hexanes to provide the title
compound (3.6 g, 20%yield).

^1H NMR ($CDCl_3$) δ 4.9 (s, 2H), 7.7 (d, 1H), 7.8 (d, 1H), 7.9 (s, 1H).

25

Example 62B

[3-amino-4-(trifluoromethyl)phenyl]methanol

The product from Example 62A (3.6 g, 16.28 mmol) in methanol (100 mL) was
hydrogenated in the presence of a catalytic amount of Pd /C for 4 hours. The catalyst was
filtered off and the volatiles were evaporated to yield 2.7 g of the title compound.

30

^1H NMR ($CDCl_3$) δ 4.62 (s, 2H), 6.75 (m, 2H), 7.5 (d, 1H).

Example 62C[3-iodo-4-(trifluoromethyl)phenyl]methanol

5 The product from Example 62B (0.76 g, 4 mmol) in water (8 mL) at 0°C was treated with concentrated H₂SO₄ (3 mL) and then treated dropwise with an aqueous solution of sodium nitrite (0.41 g, 6 mmol) keeping the temperature below 10°C. After stirring for 1 hour, this solution was then added dropwise to a solution of KI (0.83 g, 5 mmol) in water (10 mL). The resulting mixture was heated to 60°C for 2 hours, cooled to room temperature and extracted with ethyl acetate. The organic layer was washed in succession with 10% sodium bicarbonate, 1M sodium thiosulfate, 10% hydrochloric acid, aqueous sodium bicarbonate, dried over MgSO₄ and concentrated to provide the title compound.

¹H NMR (CDCl₃) δ 4.7 (s, 2H), 7.4 (d, 1H), 7.63 (d, 1H), 8.01 (s, 1H).

Example 62D3-iodo-4-(trifluoromethyl)benzaldehyde

20 The product from Example 62C in chloroform (60 mL) was treated with manganese dioxide (1.45 g, 16 mmol). After refluxing for 12 hours, the mixture was allowed to cool to ambient temperature, filtered and the filtrate concentrated under reduced pressure. The residue was chromatographed on silica gel eluting with 15% ethyl acetate:hexanes to provide the title compound (0.5 g, 42% yield).

¹H NMR (CDCl₃) δ 7.81 (d, 1H), 7.95 (d, 1H), 8.5 (s, 1H), 10.01 (s, 1H).

Example 62E5-[3-iodo-4-(trifluoromethyl)phenyl]-5,10-dihydro-1H,3H-dipyrano[3,4-b:4,3-e]pyridine-4,6(7H,9H)-dione

30 The product from Example 11C (0.09 g, 0.8 mmol), the product from Example 62D (0.24 g, 0.8 mmol) and the product from Example 11B (0.09g, 0.8 mmol) in ethanol

127

(2 mL) were stirred in a sealed tube at 80°C for 48 hours. The reaction mixture was concentrated and the residue was chromatographed on silica gel eluting with 5% ethanol/methylene chloride to provide the title compound as the off-white solid (0.25 g).
¹H NMR (DMSO-d₆) δ 4.06 (s, 4H), 4.51 (q, 4H), 4.96 (s, 1H), 7.39 (d, 1H), 7.68 (d, 1H),
5 7.9 (s, 1H), 10.15 (s, 1H);
MS (ESI-) m/z 490 (M-H)⁻;
Anal. Calcd for C₁₈H₁₃NB₃IO₄: C, 44.01; H, 2.67; N, 2.85. Found: C, 43.64; H, 2.99; N, 2.66.

Example 63

10 5-[3-bromo-4-(trifluoromethyl)phenyl]-5,10-
dihydro-1H,3H-dipyrido[3,4-b:4,3-e]pyridine-4,6(7H,9H)-dione

Example 63A

[3-bromo-4-(trifluoromethyl)phenyl]methanol

15 The product from Example 62B (0.76 g, 4 mmol) in water (8 mL) at 0°C was treated with concentrated H₂SO₄ (3 mL) and then treated dropwise with an aqueous solution of sodium nitrite (0.41 g, 6 mmol) keeping the temperature below 10°C. After stirring for 1 hour, this solution was added to a solution of copper(I) bromide (0.85 g, 5 mmol) in 48% hydrobromic acid (50 mL). The reaction mixture was heated at 60°C for 3
20 hours, cooled to ambient temperature and partitioned between water and ethyl acetate. The organic layer was washed with aqueous sodium carbonate, dried over MgSO₄ and concentrated to provide the title compound contaminated with approximately 30% of 2-bromo-4-(bromomethyl)-1-(trifluoromethyl)benzene.

25 Example 63B

3-bromo-4-(trifluoromethyl)benzaldehyde

The product from Example 63A in chloroform (100 mL) was treated with manganese dioxide (1.1 g, 12.6 mmol) and stirred overnight. The mixture was filtered and the filtrate was concentrated. The residue was chromatographed on silica gel eluting with

128

15% ethyl acetate/hexanes to provide the title compound (0.28 g).

^1H NMR (CDCl_3) δ 7.9 (m, 2H), 8.2 (s, 1H), 10.02 (s, 1H).

Example 63C

5 5-[3-bromo-4-(trifluoromethyl)phenyl]-5,10-dihydro-
 1H,3H-dipyrano[3,4-b:4,3-e]pyridine-4,6(7H,9H)-dione

The product from Example 11C (0.085 g, 0.75 mmol), the product from 63B (0.18 g, 0.75 mmol) and the product from 11B (0.085g, 0.75 mmol) in ethanol (2 mL) were processed as described in Example 62E to provide the title compound as the off-white
10 solid (0.1 g).

^1H NMR (DMSO) δ 4.05 (s, 4H), 4.51 (q, 4H), 5.0 (s, 1H), 7.4 (d, 1H), 7.62 (s, 1H), 7.74 (d, 1H), 10.13 (s, 1H);

MS (ESI-) m/z 442 (M-H) $^-$;

Anal. Calcd for $\text{C}_{18}\text{H}_{13}\text{NBrF}_3\text{O}_4 \cdot 0.5 \text{H}_2\text{O}$: C, 47.70; H, 3.11; N, 3.09. Found: C, 47.74; H,
15 3.13; N, 2.86.

Example 64

5-(4-fluoro-3-isopropenylphenyl)-5,10-dihydro-
 1H,3H-dipyrano[3,4-b:4,3-e]pyridine-4,6(7H,9H)-dione

20 The product from Example 1 (0.046 g, 0.12 mmol), tributyl(isopropenyl)stannane (Ratier, M. Synth. Commun. 1989, 19, 285) (0.27 g, 0.82 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.027 g, 0.023 mmol) in DMF (1.5 mL) under a nitrogen atmosphere were heated at 120°C for 16 hours. After cooling to ambient temperature, the mixture was treated with dichloromethane (15 mL). The organic phase
25 was washed with water (3 x, 10 mL), brine, filtered through celite and the filtrate concentrated to dryness. The residue was triturated with ethyl acetate to provide the title compound as a solid.

^1H NMR ($\text{DMSO}-d_6$) δ 4.02 (s, 4H), 4.48 (q, 4H), 4.96 (s, 1H), 5.17 (s, 1H), 5.23 (s, 1H), 7.08 (m, 2H), 7.17 (d, 1H), 10.01 (s, 1H);

30 MS (APCI-) m/z 354 (M-H) $^-$;

129

Anal. Calcd for $C_{20}H_{18}FNO_4$: C, 67.60; H, 5.11; N, 3.94. Found: C, 67.24; H, 4.99; N, 3.62.

Example 65

5 5-(4-fluorophenyl)-5,10-dihydro-1H,3H-dipyrano[3,4-b:4,3-e]pyridine-4,6(7H,9H)-dione

The product from Example 11C (0.048 g, 0.42 mmol), the product from Example 11B (0.061 g, 0.54 mmol) and 4-fluorobenzaldehyde (0.062 g, 0.50 mmol) were processed as described in Example 31 to provide the title compound (0.080 g).

^1H NMR (DMSO- d_6) δ 4.03 (s, 2H), 4.49 (AB q, 2H), 4.95 (s, 1H), 7.05 (m, 1H), 7.19 (m,
10 2H), 10.02 (s, 1H).;

MS (ESI+) m/z 316 (M+H) $^+$;

MS (ESI-) m/z 318 (M-H) $^-$;

Anal. Calcd for $C_{17}H_{14}FNO_4$: C, 64.76; H, 4.48; N, 4.44. Found: C, 64.56; H, 4.40; N, 4.47.

Example 66

5-(3-bromo-4-fluorophenyl)-3,3,7,7-tetramethyl-5,10-dihydro-1H,3H-dipyrano[3,4-b:4,3-e]pyridine-4,6(7H,9H)-dione

Example 66A

methyl [(1,1-dimethyl-2-propynyl)oxy]acetate

20 A mechanically stirred suspension of sodium hydride (10.0 g, 0.25 mol) in THF (170 mL) at 0°C under N_2 gas was treated dropwise with a solution of 2-methyl-3-butyne-2-ol (29.1 mL, 0.30 mol) in THF (70 mL). After stirring at 0°C for 1 hour, the reaction
25 mixture was treated at 0°C with a solution of methyl bromoacetate (35.5 mL, 0.38 mol) in THF (100 mL). After stirring at ambient temperature overnight, the reaction mixture was quenched into 1M HCl (300 mL) and extracted with ethyl acetate (3 x 300 mL). The organic layers were combined, dried over Na_2SO_4 , and concentrated to half the volume.

130

The residue was distilled by vacuum distillation (bp. 118-120°C/20 mmHg) to provide the title compound (10.0 g).

¹H NMR (CDCl₃) δ 1.52 (s, 6H), 2.47 (s, 1H), 3.77 (s, 3H), 4.25 (s, 2H).

5

Example 66B

methyl (1,1-dimethyl-2-oxopropoxy)acetate

The product from Example 66A (10.0 g, 64 mmol) in methanol (320 mL) was treated with mercury(II) acetate (2.0 g, 6.4 mmol) and sulfuric acid (0.5 mL). After refluxing for 1.5 hours, the mixture was allowed to cool to ambient temperature, concentrated to a volume of 100 mL, poured into 1N HCl (300 mL) and extracted with dichloromethane (3 x 300 mL). The organic layers were combined, washed with aqueous NaHCO₃, washed with brine, dried over Na₂SO₄ and concentrated to provide the title compound (10.3 g).

15

¹H NMR (CDCl₃) δ 1.34 (s, 6H), 2.25 (s, 3H), 3.76 (s, 3H), 4.01 (s, 2H).

Example 66C

2,2-dimethyl-2H-pyran-3,5(4H,6H)-dione

A solution of potassium tert-butoxide (1M in tert-butanol, 12.1 mL, 12.1 mmol) in diethyl ether (7.5 mL) at 0°C under N₂ gas was treated with a solution of the product from Example 66B in diethyl ether (3 mL). After 10 minutes, the reaction mixture was quenched into 2N HCl (25 mL) and extracted with diethyl ether (3 x 25 mL). The organic layers were combined, washed with brine, dried over Na₂SO₄, concentrated to an oil, treated with 10% dichloromethane in hexane (5 mL), and placed in the freezer for 1 hour. The resulting crystals were collected by filtration, washed with a cold solution of 10% dichloromethane in hexane, and dried to provide the title compound (431 mg).

25

¹H NMR (CDCl₃) δ 1.25 (s, 6H), 4.16 (s, 2H), 5.20 (s, 1H), 11.70 (s, 1H).

131

Example 66D5-amino-2,2-dimethyl-2H-pyran-3(6H)-one

The product from Example 66C (1.5 g, 11 mmol) in ethanol (40 mL) was treated with concentrated sulfuric acid (0.4 mL), refluxed for 4 hours, cooled to ambient temperature, treated with 2M ammonia in ethanol (50 mL), stirred at ambient temperature for 16 hours and concentrated. The residue was purified by chromatography on silica gel eluting with 10 % methanol in dichloromethane to provide the title compound (1.0 g).

Example 66E

5-(3-bromo-4-fluorophenyl)-3,3,7,7-tetramethyl-5,10-dihydro-1H,3H-dipyrano[3,4-b:4,3-e]pyridine-4,6(7H,9H)-dione

The product from Example 66C (0.20 g, 1.4 mmol), the product from Example 66D (0.20 g, 1.4 mmol) and 3-bromo-4-fluorobenzaldehyde (0.30 g, 1.4 mmol) were processed as described in Example 29 to provide the title compound (0.20 g).

¹H NMR (DMSO-d₆) δ 1.15 (s, 6H), 1.25 (s, 6H), 4.49 (s, 4H), 4.81 (s, 1H), 7.24 (m, 2H), 7.39 (m, 1H), 9.94 (s, 1H);

MS (APCI+) m/z 450 (M+H)⁺;

Anal. Calcd for C₂₁H₂₁BrFNO₄: C, 56.01; H, 4.70; N, 3.11. Found: C, 55.67; H, 4.59; N, 2.99.

Example 67

5-(3-bromo-4-fluorophenyl)-3,3-dimethyl-5,10-dihydro-1H,3H-dipyrano[3,4-b:4,3-e]pyridine-4,6(7H,9H)-dione

The product from Example 66C (0.15 g, 1.1 mmol), the product from Example 11C (0.13 g, 1.1 mmol) and 3-bromo-4-fluorobenzaldehyde (0.23 g, 1.1 mmol) were processed as described in Example 29 to provide the title compound (0.22 g).

¹H NMR (DMSO-d₆) δ 1.17 (s, 3H), 1.25 (s, 3H), 4.04 (s, 2H), 4.50 (m, 4H), 4.89 (s, 1H), 7.24 (m, 2H), 7.40 (dd, 1H), 10.02 (s, 1H);

MS (APCI+) m/z 422 (M+H)⁺;

132

Anal. Calcd for $C_{19}H_{17}NO_4BrF \cdot 0.25 H_2O$: C, 53.48; H, 4.13; N, 3.28. Found: C, 53.21; H, 3.83; N, 3.16.

Example 68

5 9-(3-bromo-4-methylphenyl)-5,9-dihydro-3H-furo
 [3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione

Example 68A

methyl 4-(3-bromo-4-methylphenyl)-2-methyl-5-oxo-
10 4,5,6,8-tetrahydro-1H-pyrano[3,4-b]pyridine-3-carboxylate

The product from Example 11B (0.34 g, 3.0 mmol), 3-bromo-4-methylbenzaldehyde (Pearson.; Org. Synth. Coll. Vol. V, 1973, 117) (0.60 g, 3.0 mmol) and methyl 3-aminocrotonate (0.35 g, 3.0 mmol) in methanol (8 mL) were heated at 80°C in a sealed tube for 60 hours. After cooling to ambient temperature, the mixture was
15 filtered and the filter cake washed with methanol and dried to provide the title compound (0.63 g).

Example 68B

9-(3-bromo-4-methylphenyl)-5,9-dihydro-3H-furo
20 [3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione

The product from Example 68A (0.63 g, 1.6 mmol) in chloroform (10 mL) under a nitrogen atmosphere was treated with pyridine (0.16 mL, 1.9 mmol) and pyridinium tribromide (0.57 g, 1.8 mmol) at -10°C. After stirring at -10°C for 2 hours, the mixture was allowed to warm to ambient temperature and then was treated with 1M HCl and
25 extracted with chloroform. The chloroform layer was dried ($MgSO_4$), filtered, concentrated, heated to 130°C under nitrogen for 1 hour and cooled to ambient temperature. Purification of the residue by chromatography on silica gel eluting with 10% methanol in dichloromethane provided the title compound (0.30 g).

133

¹H NMR (DMSO) δ 2.27 (s, 3H), 4.04 (s, 2H), 4.53 (q, 2H), 4.69 (s, 1H), 4.94 (q, 2H), 7.13 (d, 1H), 7.24 (d, 1H), 7.37 (s, 1H), 10.43 (s, 1H);
MS (ESI-) m/z 374 (M-H)⁻.

5

Example 69

9-(3-iodo-4-methylphenyl)-5,9-dihydro-3H-furo
[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione

Example 69A

10

methyl 4-(3-iodo-4-methylphenyl)-2-methyl-5-oxo-
4,5,6,8-tetrahydro-1H-pyrano[3,4-b]pyridine-3-carboxylate

The product from Example 11B (0.34 g, 3.0 mmol), the product from Example 54A (0.74 g, 3.0 mmol) and methyl 3-aminocrotonate (0.35 g, 3.0 mmol) in methanol (8 mL) were processed as described in Example 68A to provide the title compound (0.60 g).

15

Example 69B

9-(3-iodo-4-methylphenyl)-5,9-dihydro-3H-furo
[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione

The product from Example 69A (0.60 g, 1.4 mmol) was processed as described in Example 68B to provide the title compound (0.28 g).

20

¹H NMR (DMSO-d₆) δ 2.29 (s, 3H), 4.04 (s, 2H), 4.52 (q, 2H), 4.67 (s, 1H), 4.93 (q, 2H), 7.13 (d, 1H), 7.22 (d, 1H), 7.62 (s, 1H), 10.42 (s, 1H);
MS (ESI+) m/z 424 (M+H)⁺.

25

Example 70

9-(4-fluoro-3-iodophenyl)-5,9-dihydro-3H-furo
[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione

134

Example 70A

methyl 4-(4-fluoro-3-iodophenyl)-2-methyl-5-oxo-
4,5,6,8-tetrahydro-1H-pyrano[3,4-b]pyridine-3-carboxylate

5 The product from Example 11B (0.34 g, 3.0 mmol), the product from Example 30C (0.74 g, 3.0 mmol) and methyl 3-aminocrotonate (0.35 g, 3.0 mmol) in methanol (8 mL) were processed as described in Example 68A to provide the title compound (0.60 g).

Example 70B

10 9-(4-fluoro-3-iodophenyl)-5,9-dihydro-3H-furo
[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione

The product from Example 70A (0.59 g, 1.3 mmol) was processed as described in Example 68B to provided the title compound (0.27 g).

¹H NMR (DMSO-d₆) δ 4.05 (s, 2H), 4.52 (q, 2H), 4.72 (s, 1H), 4.95 (q, 2H), 7.17 (t, 1H), 7.25 (m, 1H), 7.62 (d, 1H), 10.46 (s, 1H);

15 MS (ESI-) m/z 426 (M-H)⁻.

Example 71

9-(3,4-dibromophenyl)-5,9-dihydro-3H-furo
[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione

20

Example 71A

methyl 4-(3,4-dibromophenyl)-2-methyl-5-oxo-
4,5,6,8-tetrahydro-1H-pyrano[3,4-b]pyridine-3-carboxylate

25 The product from Example 11B (0.17 g, 1.5 mmol), the product from 3,4-dibromobenzaldehyde (0.53 g, 2.0 mmol) and methyl 3-aminocrotonate (0.15 g, 1.3 mmol) in ethanol (8 mL) were heated at 80°C in a sealed tube for 60 hours and then cooled to ambient temperature. The mixture was filtered and the filter cake was washed with ethanol and dried to provide the title compound (0.39 g).

135

Example 71B9-(3,4-dibromophenyl)-5,9-dihydro-3H-furo
[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione

The product from Example 71A (0.095 g, 0.21 mmol) in chloroform (5 mL) was
5 treated with N-bromosuccinimide (0.037 g, 0.21 mmol) and heated to 110°C for 16 hours.
The mixture was cooled to ambient temperature and purified by chromatography on silica
gel eluting with 5% methanol in dichloromethane to provide the title compound (0.043 g).
¹H NMR (DMSO-d₆) δ 2.43 (s, 3H), 4.04 (s, 4H), 4.50 (m, 4H), 5.00 (s, 1H), 7.30-7.49 (m,
2H), 7.74 (d, 1H, J=1.7 Hz), 10.11 (s, 1H);
10 MS (ESI-) m/z 355 (M-H)⁻;
Anal. Calcd for C₁₈H₁₆N₂O₆: C, 60.67; H, 4.53; N, 7.86. Found: C, 60.44; H, 4.55; N,
7.62.

Example 729-(3,4-dichlorophenyl)-5,9-dihydro-3H-furo
[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione

3,4-Dichlorobenzaldehyde was processed as described in Example 71A and 71B to
provide the title compound.

¹H NMR (DMSO-d₆) δ 4.05 (s, 2H), 4.53 (AB q, 2H), 4.75 (s, 1H), 4.78 (d, 1H), 5.03 (d,
20 1H), 7.24 (dd, 1H), 7.43 (d, 1H), 7.56 (d, 1H), 10.52 (s, 1H);
MS (ESI+) m/z 352 (M+H)⁺;
MS (ESI-) m/z 350 (M-H)⁻;
Anal. Calcd for C₁₆H₁₁Cl₂NO₄: C, 54.57; H, 3.15; N, 3.98. Found: C, 54.25; H, 3.01; N,
3.66.

Example 739-[4-chloro-3-(trifluoromethyl)phenyl]-5,9-dihydro-
3H-furo[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione

4-Chloro-3-(trifluoromethyl)benzaldehyde processed as described in Example 71A
30 and 71B to provide the title compound.

136

¹H NMR (DMSO-d₆) δ 4.06 (s, 2H), 4.55 (AB q, 2H), 4.61 (s, 1H), 4.81 (d, 1H), 5.01 (d, 1H), 7.6 (d, 1H), 7.65 (d, 1H), 7.66 (d, 1H), 10.55 (s, 1H);

MS (ESI+) m/z 386 (M+H)⁺;

MS (ESI-) m/z 384 (M-H)⁻;

5 Anal. Calcd for C₁₇H₁₁ClF₃NO₄: C, 52.94; H, 2.87; N, 3.63. Found: C, 52.58; H, 2.71; N, 3.50.

Example 74

9-(3-bromo-4-chlorophenyl)-5,9-dihydro-3H-furo[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione

10 The product from Example 61B was processed as described in Example 71A and 71B to provide the title compound.

¹H NMR (DMSO-d₆) δ 4.05 (s, 2H), 4.53 (AB q, 2H), 4.60 (s, 1H), 4.87 (d, 1H), 5.02 (d, 1H), 7.26 (d, 1H), 7.65 (m, 2H), 10.52 (s, 1H);

MS (ESI+) m/z 397 (M+H)⁺;

15 MS (ESI-) m/z 395 (M-H)⁻;

Anal. Calcd for C₁₆H₁₁BrClNO₄: C, 48.45; H, 2.80; N, 3.53. Found: C, 48.45; H, 2.78; N, 3.17.

Example 75

9-(4-methyl-3-nitrophenyl)-5,9-dihydro-3H-furo[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione

20 4-Methyl-3-nitrobenzaldehyde was processed as described in Example 71A and 71B to provide the title compound.

25 ¹H NMR (DMSO-d₆) δ 2.49 (s, 3H), 4.05 (s, 2H), 4.53 (AB q, 2H), 4.60 (s, 1H), 4.87 (d, 1H), 5.02 (d, 1H), 7.40 (d, 1H), 7.50 (d, 1H), 7.78 (d, 1H), 10.52 (s, 1H);

MS (ESI+) m/z 343 (M+H)⁺;

MS (ESI-) m/z 341 (M-H)⁻.

137

Example 769-[3-(2-furyl)-4-methylphenyl]-5,9-dihydro-3H-furo
[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione

The product from Example 68B (0.081 g, 0.21 mmol) in DMF (2 mL) was treated
5 with 2-(tributylstannyl)furan (0.082 ml, 0.26 mmol), di-tert-butyl dicarbonate (0.057 g,
0.26 mmol), and tetrakis(triphenylphosphine)palladium (0) (0.020 g, 0.02 mmol). The
mixture was heated at 110°C in a sealed high pressure tube overnight, allowed to cool to
ambient temperature, filtered through a plug of cotton and concentrated to dryness. The
residue was purified by chromatography on silica gel eluting with 1% and then 3%
10 methanol in dichloromethane. The purified product was then crystallized from a mixture
of diethyl ether/dichloromethane/methanol to provide the title compound (0.65 g).

¹H NMR (DMSO-d₆) δ 2.49 (s, 3H), 4.03 (s, 2H), 4.53 (AB q, 2H), 4.60 (s, 1H), 4.87 (d,
1H), 5.02 (d, 1H), 6.60 (m, 1H), 6.67 (d, 1H), 7.05 (d, 1H), 7.19 (d, 1H), 7.51 (d, 1H), 7.80
(d, 1H), 10.48 (s, 1H);

15 MS (ESI+) m/z 364 (M+H)⁺;

MS (ESI-) m/z 362 (M-H)⁻;

Anal. Calcd for C₂₁H₁₇NO₅ · 0.5H₂O: C, 67.74; H, 4.87; N, 3.76. Found: C, 67.90; H, 4.62;
N, 3.68.

Example 779-[4-fluoro-3-(2-furyl)phenyl]-5,9-dihydro-3H-furo
[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione

The product from Example 25C (0.30 g, 0.79 mmol) was processed as described in
Example 76 to provide the title compound (0.092 g).

25 ¹H NMR (DMSO-d₆) δ 4.03 (s, 2H), 4.53 (AB q, 2H), 4.60 (s, 1H), 4.87 (d, 1H), 5.02 (d,
1H), 6.67 (m, 1H), 6.81 (t, 1H), 7.10 -7.31 (m, 3H), 7.65 (dd, 1H), 7.86 (d, 1H), 10.48 (s,
1H);

MS (ESI+) m/z 368 (M+H)⁺;

MS (ESI-) m/z 366 (M-H)⁻.

138

Example 78(9S)-9-(4-fluoro-3-iodophenyl)-5,9-dihydro-3H-furo
[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione

The enantiomers of the product from Example 70B were separated on a (R, R)
5 Whelk-O chiral HPLC column eluting with 15:2:1 hexane:methanol:dichloromethane to
provide the title compound as the faster moving enantiomer which was determined to have
an absolute configuration of (S) via X-ray analysis.

X-ray data: MW=427.17, C₁₆H₁₁NO₄FI, crystal dimensions 0.80X0.20X0.20 mm,
orthorhombic, P2₁2₁2₁ (#19), a=7.8950(1) Å, b=13.6229(2) Å, c=14.0899(2) Å,
10 V=1515.41(3) Å³, Z=4, D_{calc}=1.872 g/cm³, Crystallographic data were collected using Mo
Kα radiation (λ=0.71069 Å³). Refinement of the structure using full matrix least squares
refinement of 208 parameters on 2907 reflections with I>3.00σ(I) gave R=0.059,
R_w=0.080.

¹H NMR (DMSO-d₆) δ 4.05 (s, 2H), 4.52 (q, 2H), 4.72 (s, 1H), 4.95 (q, 2H), 7.17 (t, 1H),
15 7.25 (m, 1H), 7.62 (d, 1H), 10.46 (s, 1H);

MS (ESI-) m/z 426 (M-H)⁺;

Anal. Calcd for C₁₆H₁₁FINO₄: C, 44.99; H, 2.60; N, 3.28. Found: C, 45.02; H, 2.63; N,
3.24.

20

Example 79(9R)-9-(4-fluoro-3-iodophenyl)-5,9-dihydro-3H-furo
[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione

The enantiomers of the product from Example 70B were separated on a (R, R)
Whelk-O chiral HPLC column eluting with 15:2:1 hexane:methnaol:dichloromethane to
25 provide the title compound as the slower moving enantiomer.

¹H NMR (DMSO-d₆) δ 4.05 (s, 2H), 4.52 (q, 2H), 4.72 (s, 1H), 4.95 (q, 2H), 7.17 (t, 1H),
7.25 (m, 1H), 7.62 (d, 1H), 10.46 (s, 1H);

MS (ESI-) m/z 426 (M-H)⁺;

Anal. Calcd for C₁₆H₁₁FINO₄: C, 44.99; H, 2.60; N, 3.28. Found: C, 44.95; H, 2.72; N,
30 2.98.

Example 80(9R)-9-(3-bromo-4-methylphenyl)-5,9-dihydro-3H-furo
[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione

5 The enantiomers of the product from Example 68B were separated on a Chiralpak AS chiral HPLC column eluting with 60:40 hexanes:ethanol to provide the title compound as the faster moving enantiomer.

¹H NMR (DMSO-d₆) δ 2.27 (s, 3H), 4.04 (s, 2H), 4.53 (q, 2H), 4.69 (s, 1H), 4.94 (q, 2H), 7.13 (d, 1H), 7.24 (d, 1H), 7.37 (s, 1H), 10.43 (s, 1H);

10 MS (ESI-) m/z 374 (M-H)⁻;

Anal. Calcd for C₁₇H₁₄BrNO₄: C, 54.28; H, 3.75; N, 3.72. Found: C, 54.11; H, 3.85; N, 3.64.

Example 81(9S)-9-(3-bromo-4-methylphenyl)-5,9-dihydro-3H-furo
[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione

15 The enantiomers of the product from Example 68B were separated on a Chiralpak AS chiral HPLC column eluting with 60:40 hexane:ethanol to provide the title compound as the slower moving enantiomer which was determined to have an absolute configuration of (S) via X-ray analysis.

20 X-ray data: MW=376.21, C₁₇H₁₄NO₄Br, crystal dimensions 0.00X0.00X0.00 mm, orthorhombic, P2₁2₁2₁ (#19), a=6.5426(5) Å, b=11.8558(9) Å, c=20.912(2) Å, V=1622.1(2) Å³, Z=4, D_{calc}=1.540 g/cm³, Crystallographic data were collected using Mo Kα radiation (λ=0.71069 Å³). Refinement of the structure using full matrix least squares refinement of 208 parameters on 2512 reflections with I>3.00σ(I) gave R=0.065, R_w=0.066.

¹H NMR (DMSO-d₆) δ 2.27 (s, 3H), 4.04 (s, 2H), 4.53 (q, 2H), 4.69 (s, 1H), 4.94 (q, 2H), 7.13 (d, 1H), 7.24 (d, 1H), 7.37 (s, 1H), 10.43 (s, 1H);

MS (ESI-) m/z 374 (M-H)⁻;

30 Anal. Calcd for C₁₇H₁₄BrNO₄: C, 54.28; H, 3.75; N, 3.72. Found: C, 54.52; H, 3.78; N,

140

3.39.

Example 82

9-(3-iodo-4-methylphenyl)-5,9-dihydro-3H-furo
5 [3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione

The enantiomers of the product from Example 69B were separated on a Chiralpak AS chiral HPLC column eluting with 60:40 hexane:ethanol to provide the title compound as the faster moving enantiomer.

¹H NMR (DMSO-d₆) δ 2.29 (s, 3H), 4.04 (s, 2H), 4.52 (q, 2H), 4.67 (s, 1H), 4.93 (q, 2H),
10 7.13 (d, 1H), 7.22 (d, 1H), 7.62 (s, 1H), 10.42 (s, 1H);

MS (ESI+) m/z 424 (M+H)⁺;

Anal. Calcd for C₁₇H₁₄INO₄: C, 48.25; H, 3.33; N, 3.31. Found: C, 48.47; H, 3.32; N, 3.28.

Example 83

9-(3-iodo-4-methylphenyl)-5,9-dihydro-3H-furo
15 [3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione

The enantiomers of the product from Example 69B were separated on a Chiralpak AS chiral HPLC column eluting with 60:40 hexane:ethanol to provide the title compound
20 as the slower moving enantiomer.

¹H NMR (DMSO-d₆) δ 2.29 (s, 3H), 4.04 (s, 2H), 4.52 (q, 2H), 4.67 (s, 1H), 4.93 (q, 2H),
7.13 (d, 1H), 7.22 (d, 1H), 7.62 (s, 1H), 10.42 (s, 1H);

MS (ESI+) m/z 424 (M+H)⁺;

Anal. Calcd for C₁₇H₁₄INO₄: C, 48.25; H, 3.33; N, 3.31. Found: C, 48.60; H, 3.30; N,
25 3.31.

Example 84

(trans)-9-(3-bromo-4-fluorophenyl)-7-methyl-5,9-dihydro-
3H-furo[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione

30

141

Example 84Amethyl [(1-methyl-2-propynyl)oxy]acetate

A mechanically stirred suspension of sodium hydride (60% dispersion in mineral oil, 10 g, 0.25 mol) in tetrahydrofuran (160 mL) at 0°C under nitrogen was treated with a solution of (±)-3-butyn-2-ol (21 g, 0.30 mol) in tetrahydrofuran (35 mL) over 30 minutes, stirred for 35 minutes, treated with a solution of methyl bromoacetate in tetrahydrofuran (50 mL) over 10 minutes, stirred for 30 minutes at 0°C, stirred at ambient temperature for 16 hours and treated with 2M HCl (150 mL). The organic layer was isolated and the aqueous layer was extracted with ethyl acetate (2X, 100 mL). The combined organic layers were washed with brine, dried (MgSO₄), filtered, concentrated and distilled under vacuum to provide the title compound (20 g).

¹H NMR (CDCl₃) δ 1.51 (d, 3H), 2.46 (d, 1H), 3.76 (s, 3H), 4.25 (AB q, 2H), 4.39 (dq, 1H).

15

Example 84Bmethyl (1-methyl-2-oxopropoxy)acetate

The product from Example 84A (20 g, 0.14 mol) in methanol (700 mL) was treated with mercury(II) acetate (4.6 g, 0.014 mol), heated to reflux for 1 hour, concentrated to approximately 100 mL total volume, treated with 1 M HCl (100 mL) and extracted with dichloromethane (3X, 100 mL). The extractions were combined, dried (MgSO₄), filtered and concentrated to provide the title compound.

¹H NMR (CDCl₃) δ 1.37 (d, 3H), 2.31 (s, 3H), 3.76 (s, 3H), 3.96 (q, 1H), 4.15 (AB q, 2H).

Example 84C

25

2-methyl-2H-pyran-3,5(4H,6H)-dione

A mechanically stirred solution of potassium tert-butoxide in tert-butanol (1 M, 203 mL) under a nitrogen atmosphere was treated with anhydrous ether (125 mL), cooled to 0°C, treated with the product from Example 84B (15.5 g, 97 mmol) in ether (55 mL) over 2 minutes, stirred for 10 minutes and then treated with 2M HCl (240 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (2X, 200 mL). The

142

combined organic layers were washed with brine, dried (MgSO₄), filtered and concentrated. The residue was purified on silica gel eluting with ethyl acetate:formic acid:water:hexane (200:1:1:200) to provide the title compound.

¹H NMR (CDCl₃) δ 1.48 (d, 3H), 3.43 (d, 1H), 3.92 (d, 1H), 3.97 (q, 1H), 4.04 (d, 1H),
5 4.44 (d, 1H).

Example 84D

methyl 4-(3-bromo-4-fluorophenyl)-2,6-dimethyl-5-oxo- 4,5,6,8-tetrahydro-1H-pyrano[3,4-b]pyridine-3-carboxylate

10 The product from Example 84C (1.3 g, 10 mmol), 3-bromo-4-fluorobenzaldehyde (2.4 g, 12 mmol) and methyl 3-aminocrotonate (1.2 g, 10 mmol) in ethanol (10 mL) were heated at 80°C in a sealed tube for 60 hours. After cooling to ambient temperature, the mixture was filtered and the filtercake washed with ethanol and dried to provide the title compound. The filtrate was concentrated and chromatographed on silica gel eluting with
15 1% and then 2% and then 5% methanol in dichloromethane to provide additional quantities of the title compound.

MS (ESI+) m/z 410 (M+H)⁺;

MS (ESI-) m/z 408 (M-H)⁻.

20

Example 84E

(trans)-9-(3-bromo-4-fluorophenyl)-7-methyl-5,9-dihydro- 3H-furo[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione

The product from Example 84D (1.0 g, 2.5 mmol) was dissolved in chloroform (15 mL) under a nitrogen atmosphere, cooled to -10°C, treated with pyridine (0.24 mL, 3.0
25 mmol) and pyridinium tribromide (0.97 g, 3.0 mmol), stirred at -10°C for 20 minutes, diluted with dichloromethane (100 mL) and treated with 1M HCl (10 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (50 mL). The combined organic layers were dried (MgSO₄), filtered, concentrated, heated to 130°C under nitrogen for 15 minutes and cooled to ambient temperature. The residue was
30 purified by chromatography on silica gel eluting with 38:1:1:40 ethyl acetate:formic

143

acid:water:hexane to provide the title compound as the faster moving diastereomer which was crystallized from dichloromethane.

^1H NMR (DMSO- d_6) δ 1.22 (d, 3H), 4.12 (q, 1H), 4.48 (d, 1H), 4.65 (d, 1H), 4.68 (s, 1H), 4.86 (dd, 1H), 4.99 (d, 1H), 7.24-7.28 (m, 2H), 7.48 (dd, 1H), 10.42 (bs, 1H);

5 MS (ESI+) m/z 394 ($M + H$) $^+$, 411 ($M + \text{NH}_4$) $^+$;

MS (ESI-) m/z 392 ($M - H$) $^-$;

Anal. Calcd for $\text{C}_{17}\text{H}_{13}\text{NO}_4\text{FBr}$ 0.1875 CH_2Cl_2 : C, 50.34; H, 3.29; N, 3.42. Found: C, 50.40; H, 3.11; N, 3.23.

10

Example 85

(cis)-9-(3-bromo-4-fluorophenyl)-7-methyl-5,9-dihydro-3H-furo[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione

The title compound was obtained from the residue from Example 84E following chromatography on silica gel eluting with 38:1:1:40 ethyl acetate:formic acid:water:hexane as the slower moving diastereomer which was crystallized from acetone/hexane and determined to have the cis configuration via X-ray analysis.

15

X-ray data: MW=394.20, $\text{C}_{17}\text{H}_{13}\text{NO}_4\text{FBr}$, crystal dimensions 0.30X0.30X0.20 mm, monoclinic, $P2_1/c$ (#14), $a=12.3346(4)$ Å, $b=9.4925(4)$ Å, $c=13.6854(5)$ Å, $\beta=93.620(1)^\circ$, $V=1599.17(9)$ Å ^{3} , $Z=4$, $D_{\text{calc}}=1.637$ g/cm ^{3} , Crystallographic data were collected using Mo K α radiation ($\lambda=0.71069$ Å ^{3}). Refinement of the structure using full matrix least squares refinement of 217 parameters on 1996 reflections with $I>3.00\sigma(I)$ gave $R=0.052$, $R_w=0.061$.

20

mp 234-239°C;

^1H NMR (DMSO- d_6) δ 1.16 (d, 3H), 4.11 (q, 1H), 4.55 (s, 2H), 4.72 (s, 1H), 4.86 (dd, 1H), 5.01 (d, 1H), 7.22-7.32 (m, 2H), 7.46 (dd, 1H), 10.45 (bs, 1H);

25

MS (ESI+) m/z 394 ($M + H$) $^+$, 411 ($M + \text{NH}_4$) $^+$;

MS (ESI-) m/z 392 ($M - H$) $^-$;

Anal. Calcd for $\text{C}_{17}\text{H}_{13}\text{NO}_4\text{FBr}$: C, 51.80; H, 3.32; N, 3.55. Found: C, 52.07; H, 3.26; N, 3.37.

30

144

Example 86

9-(3-bromo-4-fluorophenyl)-7,7-dimethyl-2,3,5,9-tetrahydro-4H-pyrano[3,4-b]thieno[2,3-e]pyridin-8(7H)-one 1,1-dioxide

The product from Example 66D (0.20 g, 1.4 mmol) was processed as described in Example 11D to provide the title compound (0.12 g).

¹H NMR (DMSO-d₆) δ 1.12 (s, 3H), 1.24 (s, 3H), 2.82 (m, 1H), 3.05 (m, 1H), 3.35 (m, 2H), 4.49 (s, 2H), 4.83 (s, 1H), 7.25 (m, 2H), 7.42 (dd, 1H), 10.04 (s, 1H);

MS (APCI+) m/z 442 (M+H)⁺;

Anal. Calcd for C₁₈H₁₇NO₄FBrS 0.75H₂O: C, 47.43; H, 4.09; N, 3.07. Found: C, 47.79; H, 3.96; N, 2.68.

Example 87

5-(3-bromo-4-fluorophenyl)-3,3-dimethyl-5,7,8,9-tetrahydrocyclopenta[b]pyrano[4,3-e]pyridine-4,6(1H,3H)-dione

3-Amino-2-cyclopenten-1-one (Kikani, B.B., Synthesis, (1991), 2, 176) (0.099 g, 1.0 mmol), 3-bromo-4-fluorobenzaldehyde (0.21 g, 1.0 mmol) and the product from Example 66C (0.15 g, 1.0 mmol) were processed as described in Example 31 to provide the title compound (0.22 g).

¹H NMR (DMSO-d₆) δ 1.15 (s, 3H), 1.24 (s, 3H), 2.29 (t, 2H), 2.50-2.75 (m, 2H), 4.53 (s, 2H), 4.64 (s, 1H), 7.21 (m, 2H), 7.41 (dd, 1H), 10.29 (s, 1H);

MS (APCI+) m/z 406 (M+H)⁺;

Anal. Calcd for C₁₉H₁₇BrFNO₃: C, 56.17; H, 4.22; N, 3.45. Found: C, 56.36; H, 4.31; N, 3.36.

Example 88

(cis or trans)-9-(3-bromo-4-fluorophenyl)-5-methyl-5,9-dihydro-3H-furo[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione

145

Example 88A5-ethoxy-2-methyl-2H-pyran-3(6H)-one

The product from Example 84C (3.0 g, 23 mmol) was dissolved in ethanol (50 mL), treated with concentrated sulfuric acid (5 drops), heated to reflux for 3 hours and concentrated. The residue was purified by chromatography eluting with 10:1 and then 5:1 and then 2:1 hexane:ethyl acetate to provide the title compound as the faster moving isomer.

¹H NMR (DMSO-d₆) δ 1.38 (t, 3H), 1.40 (d, 3H), 3.89-4.06 (m, 3H), 4.29 (s, 2H), 5.41 (s, 1H).

Example 88B5-ethoxy-6-methyl-2H-pyran-3(6H)-one

The residue from Example 88A was purified by chromatography eluting with 10:1 and then 5:1 and then 2:1 hexane:ethyl acetate to provide the title compound as the slower moving isomer.

¹H NMR (DMSO-d₆) δ 1.39 (t, 3H), 1.44 (d, 3H), 3.91-4.01 (m, 2H), 4.03 (dd, 1H), 4.21 (d, 1H), 4.37 (q, 1H), 5.41 (s, 1H).

Example 88C5-amino-2-methyl-2H-pyran-3(6H)-one

The product from Example 88A was treated with ammonia saturated ethanol (60 mL), stirred at ambient temperature for 16 hours and concentrated to provide the title compound (0.98 g).

¹H NMR (DMSO-d₆) δ 1.18 (d, 3H), 3.86 (q, 1H), 4.21 (s, 2H), 4.95 (s, 1H), 6.89 (bs, 2H).

Example 88D5-amino-6-methyl-2H-pyran-3(6H)-one

The product from Example 88B was treated with ammonia saturated ethanol (60 mL), stirred at ambient temperature for 16 hours and concentrated to provide the title compound (0.52 g).

146

¹H NMR (DMSO-d₆) δ 1.38 (d, 3H), 3.77 (d, 1H), 3.91 (d, 1H), 4.32 (q, 1H), 4.96 (s, 1H), 6.84 (bs, 1H), 7.07 (bs, 1H).

Example 88E

5 methyl 4-(3-bromo-4-fluorophenyl)-2,8-dimethyl-5-oxo-
 4,5,6,8-tetrahydro-1H-pyrano[3,4-b]pyridine-3-carboxylate

The product from Example 88D (0.50 g, 3.9 mmol), 3-bromo-4-fluorobenzaldehyde 0.96 g, 4.7 mmol) and methyl acetoacetate (0.46 g, 3.9 mmol) in ethanol (4 mL) was heated to 80°C in a sealed tube for 60 hours, cooled to ambient
10 temperature and concentrated. The residue was chromatographed on silica gel eluting with 1% and then 2% methanol in dichloromethane to provide the title compound (0.97 g).
MS (ESI+) m/z 410 (M+H)⁺;
MS (ESI-) m/z 408 (M-H)⁻.

15 Example 88F

(trans)-9-(3-bromo-4-fluorophenyl)-5-methyl-5,9-dihydro-
 3H-furo[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione

The product from Example 88E (0.97 g, 2.4 mmol) was processed as described in Example 84E to provide a residue which was chromatographed on silica gel eluting with
20 38:1:1:40 and then 38:1:1:30 and then 38:1:1:20 ethyl acetate:formic acid:water:hexanes to provide the title compound (0.049 g) as the faster moving diastereomer which was crystallized from ethyl acetate/hexanes.

mp 240-243°C;

25 ¹H NMR (DMSO-d₆) δ 1.50 (d, 3H), 3.96 (d, 1H), 4.24 (d, 1H), 4.72-4.80 (m, 2H), 4.88 (d, 1H), 5.01 (d, 1H), 7.25-7.29 (m, 2H), 7.48 (dd, 1H), 10.32 (bs, 1H);

MS (ESI+) m/z 394 (M+H)⁺, 411 (M+NH₄)⁺;

MS (ESI-) m/z 392 (M-H)⁻;

Anal. Calcd for C₁₇H₁₃NO₄FBr 0.25 H₂O: C, 51.21; H, 3.41; N, 3.51. Found: C, 51.27; H, 3.57; N, 3.26.

30

147

Example 89(cis)-9-(3-bromo-4-fluorophenyl)-5-methyl-5,9-dihydro-3H-furo[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione

The product from Example 88E (0.97 g, 2.4 mmol) was processed as described in Example 84E to provide a residue which was chromatographed on silica gel eluting with 38:1:1:40 and then 38:1:1:30 and then 38:1:1:20 ethyl acetate:formic acid:water:hexane to provide the title compound as the slower moving diastereomer which was crystallized from ethyl acetate/hexane (0.18 g) and determined to have the cis configuration via X-ray analysis.

X-ray data: MW=394.20, C₁₇H₁₃NO₄FBr, crystal dimensions 0.30X0.30X0.30 mm, monoclinic, P2₁/n (#14), a=15.9903(2) Å, b=13.1888(2) Å, c=16.0097(5) Å, β=109.102(1)°, V=3190.42(7) Å³, Z=8, D_{calc}=1.641 g/cm³, Crystallographic data were collected using Mo Kα radiation (λ=0.71069 Å³). Refinement of the structure using full matrix least squares refinement of 442 parameters on 3412 reflections with I>3.00σ(I) gave R=0.074, R_w=0.091.

mp 260-263°C;

¹H NMR (DMSO-d₆) δ 1.52 (d, 3H), 4.07 (s, 2H), 4.66 (q, 1H), 4.77 (s, 1H), 4.86 (dd, 1H), 5.02 (d, 1H), 7.20-7.26 (m, 1H), 7.29 (t, 1H), 7.46 (dd, 1H), 10.12 (bs, 1H);

MS (ESI+) m/z 394 (M + H)⁺, 411 (M+NH₄)⁺;

MS (ESI-) m/z 392 (M-H)⁻;

Anal. Calcd for C₁₇H₁₃NO₄FBr: C, 51.80; H, 3.32; N, 3.55. Found: C, 51.71; H, 3.35; N, 3.30.

Example 90(trans)-9-(3-bromo-4-fluorophenyl)-3-methyl-5,9-dihydro-3H-furo[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione

148

Example 90Amethyl 4-(3-bromo-4-fluorophenyl)-2-ethyl-5-oxo-4,5,6,8-tetrahydro-1H-pyran[3,4-b]pyridine-3-carboxylate

The product from Example 11C (0.82 g, 7.3 mmol), 3-bromo-4-fluorobenzaldehyde (1.8 g, 8.7 mmol) and methyl 3-oxo-pentanoate (1.0 g, 7.3 mmol) in ethanol (8 mL) were heated at 80°C in a sealed tube for 60 hours, cooled to ambient temperature and concentrated. The residue was chromatographed on silica gel eluting with 1% and then 2% methanol in dichloromethane to provide the title compound (0.53 g).
MS (ESI+) m/z 410 (M+H)⁺;
MS (ESI-) m/z 408 (M-H)⁻.

Example 90B(trans)-9-(3-bromo-4-fluorophenyl)-3-methyl-5,9-dihydro-3H-furo[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione

The product from Example 90A (0.53 g, 1.3 mmol) was processed as described in Example 84E to provide a residue which was chromatographed on silica gel eluting with 38:1:1:40 and then 38:1:1:30 and then 38:1:1:20 ethyl acetate:formic acid:water:hexanes to provide the title compound as the faster moving diastereomer which was crystallized from ethyl acetate/hexane (0.070 g).
¹H NMR (DMSO-d₆) δ 1.43 (d, 3H), 4.05 (s, 2H), 4.55 (AB q, 2H), 4.74 (s, 1H), 5.26 (q, 1H), 7.26-7.30 (m, 2H), 7.49 (d, 1H), 10.44 (bs, 1H);
MS (ESI+) m/z 394 (M+H)⁺, 411 (M+NH₄)⁺;
MS (ESI-) m/z 392 (M-H)⁻;
Anal. Calcd for C₁₇H₁₃NO₄FBr: C, 51.80; H, 3.32; N, 3.55. Found: C, 51.66; H, 3.29; N, 3.37.

149

Example 91(cis)-9-(3-bromo-4-fluorophenyl)-3-methyl-5,9-dihydro-3H-furo[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione

The product from Example 90A (0.53 g, 1.3 mmol) was processed as described in Example 84E to provide a residue which was chromatographed on silica gel eluting with 38:1:1:40 and then 38:1:1:30 and then 38:1:1:20 ethyl acetate:formic acid:water:hexane to provide the title compound as the slower moving diastereomer which was crystallized from ethyl acetate/hexane (0.077 g) and determined to have the cis configuration via X-ray analysis.

X-ray data: MW=394.20, C₁₇H₁₃NO₄FBr, crystal dimensions 0.80X0.30X0.10 mm, monoclinic, P2₁/n (#14), a=13.2761(2) Å, b=13.2707(2) Å, c=20.2652(5) Å, β=98.841(1)°, V=3527.97(8) Å³, Z=8, D_{calc}=1.484 g/cm³, Crystallographic data were collected using Mo Kα radiation (λ=0.71069 Å³). Refinement of the structure using full matrix least squares refinement of 433 parameters on 4009 reflections with I>3.00σ(I) gave R=0.117,

R_w=0.147.

mp 213-216°C;

¹H NMR (DMSO-d₆) δ 1.45 (d, 3H), 4.05 (s, 2H), 4.55 (AB q, 2H), 4.75 (s, 1H), 5.15 (q, 1H), 7.19-7.25 (m, 1H), 7.29 (t, 1H), 7.47 (dd, 1H), 10.48 (bs, 1H);

MS (ESI+) m/z 394 (M+H)⁺, 411 (M+NH₄)⁺;

MS (ESI-) m/z 392 (M-H)⁻;

Anal. Calcd for C₁₇H₁₃NO₄FBr: C, 51.80; H, 3.32; N, 3.55. Found: C, 51.94; H, 3.38; N, 3.26.

Example 929-(3-bromo-4-fluorophenyl)-7,7-dimethyl-5,9-dihydro-3H-furo[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione

The product from Example 66C (0.50 g, 3.5 mmol), 3-bromo-4-fluorobenzaldehyde (0.88 g, 4.2 mmol) and methyl 3-aminocrotonate (0.40 g, 3.5 mmol) in ethanol (5 mL) were processed as described in Example 71 to provide the title compound (0.31 g).

150

¹H NMR (DMSO-d₆) δ 1.15 (s, 3H), 1.26 (s, 3H), 4.55 (s, 2H), 4.68 (s, 1H), 4.83 (dd, 1H), 4.98 (d, 1H), 7.26 (m, 2H), 7.46 (dd, 1H), 10.40 (s, 1H);

MS (APCI+) m/z 408 (M+H)⁺;

Anal. Calcd for C₁₈H₁₅BrFNO₄ 0.1CHCl₃: C, 51.74; H, 3.62; N, 3.33. Found: C, 51.71; H, 3.35; N, 3.21.

Example 93

spiro[5-(3-bromo-4-fluorophenyl)-5,10-dihydro-1H,3H-dipyran[3,4-b:4,3-e]pyridine-4,6(7H,9H)-dione-3,1'-cyclopentane]

Example 93A

methyl [(1-ethynylcyclopentyl)oxy]acetate

A mechanically stirred suspension of sodium hydride (60% dispersion in mineral oil, 1.5 g, 38 mmol) in tetrahydrofuran (10 mL) at 0 °C under nitrogen was treated with a solution of 1-ethynylcyclopentanol (5.0 g, 45 mmol) in tetrahydrofuran (20 mL) over 15 minutes. After stirring at 0 °C for 1 hour, the mixture was treated with methyl bromoacetate (5.4 mL, 56 mmol). After stirring at ambient temperature for 16 hours, the mixture was treated with 2M HCl (25 mL) and then treated with ethyl acetate (25 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (50 mL). The organic layers were combined, washed with brine, dried (MgSO₄), filtered, concentrated and used without purification in the next step.

Example 93B

methyl [(1-acetylcyclopentyl)oxy]acetate

The crude product from Example 93A was processed as described in Example 84B. The resultant crude product was purified by chromatography on silica gel eluting with (hexanes:ethyl acetate, 20:1 to 10:1 to 5:1) to provide the title compound (3.1 g).

¹H NMR (CDCl₃) δ 1.60-2.02 (m, 8H), 2.25 (s, 3H), 3.76 (s, 3H), 3.94 (s, 2H).

151

Example 93C6-oxaspiro[4.5]decane-8,10-dione

The product from Example 93B (3.1 g, 15 mmol) was processed as described in Example 84C to provide the title compound which was used in the next step without further purification.

¹H NMR (DMSO-d₆) δ 1.60-1.72 (m, 4H), 1.72-1.91 (m, 4H), 4.14 (s, 2H), 5.27 (s, 1H), 11.5 (bs, 1H).

Example 93Dspiro[5-(3-bromo-4-fluorophenyl)-5,10-dihydro-1H,3H-dipyrano[3,4-b:4,3-e]pyridine-4,6(7H,9H)-dione-3,1'-cyclopentane]

The product from Example 93C, the product from Example 11C, and 3-bromo-4-fluorobenzaldehyde were processed as described in Example 29. The residue was purified by chromatography eluting with 2% methanol in dichloromethane. The purified product was crystallized from dichloromethane to provide the title compound (0.16 g).

mp > 260 °C;

¹H NMR (DMSO) δ 1.40-1.53 (m, 1H), 1.53-1.71 (m, 5H), 1.87-1.98 (m, 1H), 2.04-2.14 (m, 1H), 4.04 (s, 2H), 4.48 (AB q, 2H), 4.51 (s, 2H), 4.90 (s, 1H), 7.18-7.24 (m, 1H), 7.27 (t, 1H), 7.41 (dd, 1H), 10.06 (bs, 1H);

MS (ESI+) m/z 448 (M+H)⁺, 465 (M + NH₄)⁺;

MS (ESI-) m/z 446 (M-H)⁻;

Anal. Calcd for C₂₁H₁₉NO₄Br 0.125 CH₂Cl₂: C, 55.29; H, 4.23; N, 3.04. Found: C, 55.42; H, 4.19; N, 2.81.

Example 945-(3-bromo-4-fluorophenyl)-3,3-diethyl-5,10-dihydro-1H,3H-dipyrano[3,4-b:4,3-e]pyridine-4,6(7H,9H)-dione

3-Ethyl-1-pentyn-3-ol was processed as described in Example 93 to provide the title compound.

mp 260-262 °C;

152

¹H NMR (DMSO) δ 0.54 (t, 3H), 0.81 (t, 3H), 1.39-1.54 (m, 2H), 1.60-1.84 (m, 2H), 4.04 (s, 2H), 4.44-4.56 (m, 4H), 4.94 (s, 1H), 7.18-7.24 (m, 1H), 7.25 (t, 1H), 7.41 (dd, 1H), 10.01 (bs, 1H);

MS (ESI+) m/z 450 (M + H)⁺, 467 (M+NH₄)⁺;

5 MS (ESI-) m/z 448 (M-H)⁻;

Anal. Calcd for C₂₁H₂₁NO₄FBr 0.5 CH₂Cl₂: C, 52.40; H, 4.50; N, 2.84. Found: C, 52.46; H, 4.40; N, 2.62.

Example 95

10 9-(3-bromo-4-fluorophenyl)-3-ethyl-5,9-dihydro-3H-furo[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione

Example 95A

ethyl (2E)-3-amino-2-hexenoate

15 Ethyl butyrylacetate (2.7 g, 17 mmol) in ethanol (7 mL) was treated with ammonium acetate (2.0, 26 mmol) and heated to reflux in a sealed tube for 16 hours, cooled to ambient temperature and concentrated. The residue was purified by chromatography eluting with 2% methanol in ammonia saturated dichloromethane to provide the title compound.

20 ¹H NMR (CDCl₃) δ 0.96 (t, 3H), 1.26 (t, 3H), 1.51-1.68 (m, 2H), 2.10 (t, 2H), 4.11 (q, 2H), 4.54 (s, 1H).

Example 95B

25 ethyl 4-(3-bromo-4-fluorophenyl)-5-oxo-2-propyl-4,5,6,8-tetrahydro-1H-pyrano[3,4-b]pyridine-3-carboxylate

The product from Example 95A (0.083 g, 0.52 mmol), the product from Example 11B (0.050 g, 0.44 mmol) and 3-bromo-4-fluorobenzaldehyde (0.116 g, 0.57 mmol) in ethanol (1 mL) were heated to 80 C for 16 hours in a sealed tube, cooled to ambient temperature and concentrated to dryness. The residue was purified on silica gel eluting
30 with 2 % methanol in dichloromethane to provide the title compound (0.17 g).

153

MS (ESI+) m/z 438 (M+H)⁺;MS (ESI-) m/z 436 (M-H)⁻.Example 95C5 9-(3-bromo-4-fluorophenyl)-3-ethyl-5,9-dihydro-
 3H-furo[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione

The product from Example 95B (0.69 g, 1.6 mmol) in chloroform (30 mL) under nitrogen was treated with N-bromosuccinimide (0.34 g, 1.9 mmol), stirred at ambient temperature for 30 minutes, refluxed for 16 hours, concentrated to dryness, heated neat to
10 130 °C under nitrogen for 15 minutes and allowed to cool to ambient temperature. The resulting two isomers were separated by chromatography on silica gel eluting with (ethyl acetate:formic acid:water:hexane, 38:1:1:40 to 38:1:1:30 to 38:1:1:20). The faster moving isomer was crystallized from dichloromethane. The crystals of this faster moving isomer were collected by filtration, washed with dichloromethane and dried under reduced
15 pressure at 50 °C for 30 minutes to provide the title compound (0.055 g).

mp 161-162 °C;

¹H NMR (DMSO-d₆) δ 0.84 (t, 3H), 1.54-1.70 (m, 1H), 1.92-2.06 (m, 1H), 4.05 (s, 2H), 4.55 (AB q, 2H), 4.74 (s, 1H), 5.21 (dd, 1H), 7.27-7.31 (m, 2H), 7.49 (m, 1H), 10.42 (bs, 1H);

20 MS (ESI+) m/z 408 (M+H)⁺, 425 (M+NH₄)⁺;MS (ESI-) m/z 406 (M-H)⁻;

Anal. Calcd for C₁₈H₁₅NO₄FBr: C, 52.96; H, 3.70; N, 3.43. Found: C, 52.92; H, 3.67; N, 3.45.

25 Example 96 9-(3-bromo-4-fluorophenyl)-3-ethyl-5,9-dihydro-
 3H-furo[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione

The slower moving isomer from Example 95C was crystallized from ethyl acetate/hexanes. The crystals were collected by filtration, washed with ethyl acetate and
30 dried under reduced pressure to provide the title compound (0.037 g).

154

mp 246-248 °C;

¹H NMR (DMSO-d₆) δ 0.81 (t, 3H), 1.63-1.79 (m, 1H), 1.95-2.09 (m, 1H), 4.05 (s, 2H), 4.55 (AB q, 2H), 4.74 (s, 1H), 5.12 (m, 1H), 7.23 (ddd, 1H), 7.29 (t, 1H), 7.45 (dd, 1H), 10.43 (bs, 1H);

5 MS (ESI+) m/z 408 (M+H)⁺, 425 (M+NH₄)⁺;

MS (ESI-) m/z 406 (M-H)⁻;

Anal. Calcd for C₁₈H₁₅NO₄FBr: C, 52.96; H, 3.70; N, 3.43. Found: C, 52.75; H, 3.83; N, 3.29.

10

Example 97

9-(3-bromo-4-fluorophenyl)-3-propyl-5,9-dihydro-3H-furo[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione

Example 97A

15

ethyl (2E)-3-amino-2-heptenoate

Ethyl 3-oxoheptanoate was processed as described in Example 95A to provide the title compound.

¹H NMR (CDCl₃) δ 0.92 (t, 3H), 1.26 (t, 3H), 1.30-1.42 (m, 2H), 1.48-1.59 (m, 2H), 2.12 (t, 2H), 4.11 (q, 2H), 4.54 (s, 1H).

20

Example 97B

ethyl 4-(3-bromo-4-fluorophenyl)-2-butyl-5-oxo-4,5,6,8-tetrahydro-1H-pyrano[3,4-b]pyridine-3-carboxylate

25

The product from Example 97A was processed as described in Example 95B to provide the title compound.

MS (ESI+) m/z 452 (M+H)⁺;

MS (ESI-) m/z 450 (M-H)⁻.

155

Example 97C9-(3-bromo-4-fluorophenyl)-3-propyl-5,9-dihydro-
3H-furo[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione

The product from Example 97B (0.77 g, 1.7 mmol) in chloroform (30 mL) under
5 nitrogen was treated with N-bromosuccinimide (0.36 g, 2.0 mmol), stirred at ambient
temperature for 30 minutes, refluxed for 16 hours and concentrated to dryness. The
resulting two isomers were separated by chromatography on silica gel eluting with (ethyl
acetate:formic acid:water:hexane, 38:1:1:40 to 38:1:1:30 to 38:1:1:20). The faster moving
isomer was rechromatographed on silica gel eluting with 2% methanol in ammonia
10 saturated dichloromethane and then rechromatographed again on silica gel eluting with
(hexanes:acetone, 3:1). The faster moving isomer was then crystallized from
acetone/hexanes and the resulting crystals were collected by filtration, washed with
acetone/hexanes and dried under reduced pressure to provide the title compound (0.058 g).
mp 206-208 °C;

15 ¹H NMR (DMSO-d₆) δ 0.92 (t, 3H), 1.28-1.42 (m, 2H), 1.47-1.61 (m, 1H), 1.86-1.98 (m,
1H), 4.05 (s, 2H), 4.54 (AB q, 2H), 4.73 (s, 1H), 5.23 (dd, 1H), 7.29 (m, 2H), 7.48 (dd,
1H), 10.42 (bs, 1H);

MS (ESI+) m/z 422 (M+H)⁺, 439 (M+NH₄)⁺;

MS (ESI-) m/z 420 (M-H)⁻;

20 Anal. Calcd for C₁₉H₁₇NO₄FBr: C, 54.05; H, 4.06; N, 3.32. Found: C, 54.36; H, 3.95; N,
3.37.

Example 989-(3-bromo-4-fluorophenyl)-3-propyl-5,9-dihydro-
25 3H-furo[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione

The slower moving isomer from Example 97C was crystallized from ethyl
acetate/hexanes. The crystals were collected by filtration, washed with ethyl acetate and
dried under reduced pressure to provide the title compound (0.046 g).
mp 219-220 °C;

30 ¹H NMR (DMSO-d₆) δ 0.91 (t, 3H), 1.22-1.42 (m, 2H), 1.53-1.69 (m, 1H), 1.88-2.02 (m,

156

1H), 4.05 (s, 2H), 4.55 (AB q, 2H), 4.74 (s, 1H), 5.13 (dd, 1H), 7.22 (ddd, 1H), 7.29 (t, 1H), 7.44 (dd, 1H), 10.44 (bs, 1H);

MS (ESI+) m/z 422 (M+H)⁺, 439 (M+NH₄)⁺;

MS (ESI-) m/z 420 (M-H)⁻;

5 Anal. Calcd for C₁₉H₁₇NO₄FBr 0.25 C₆H₁₄: C, 55.48; H, 4.66; N, 3.16. Found: C, 55.59; H, 4.95; N, 2.80.

Example 99

10 9-(3-bromo-4-fluorophenyl)-3,3-dimethyl-5,9-dihydro-3H-furo[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione

Example 99A

ethyl (2E)-3-amino-4-methyl-2-pentenoate

15 Ethyl 4-methyl-3-oxopentanoate (2.0 g, 13 mmol) was treated with 2M ammonia in ethanol (20 mL), heated to 80 C in a sealed tube for 16 hours and concentrated to dryness to provide the title compound.

¹H NMR (CDCl₃) δ 1.16 (d, 6H), 1.26 (t, 3H), 2.32 (m, 1H), 4.11 (q, 2H), 4.57 (s, 1H).

Example 99B

20 ethyl 4-(3-bromo-4-fluorophenyl)-2-isopropyl-5-oxo-4,5,6,8-tetrahydro-1H-pyrano[3,4-b]pyridine-3-carboxylate

The product from Example 99A was processed as described in Example 95B to provide the title compound.

MS (ESI+) m/z 438 (M+H)⁺;

25 MS (ESI-) m/z 436 (M-H)⁻.

157

Example 99C9-(3-bromo-4-fluorophenyl)-3,3-dimethyl-5,9-dihydro-3H-furo[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione

The product from Example 99B (0.58 g, 1.3 mmol) was processed as described in Example 95C. The crude product was purified by chromatography on silica gel eluting with 2% methanol in dichloromethane and crystallized from the ethyl acetate/hexanes. The crystals were collected by filtration, washed with ethyl acetate/hexanes and dried under reduced pressure at 60 °C for 1 hour to provide the title compound (0.127 g). mp > 260 °C;

¹H NMR (DMSO-d₆) δ 1.49 (s, 3H), 1.50 (s, 3H), 4.06 (s, 2H), 4.57 (AB q, 2H), 4.73 (s, 1H), 7.22 (m, 1H), 7.29 (t, 1H), 7.47 (dd, 1H), 10.44 (bs, 1H);

MS (ESI+) m/z 408 (M+H)⁺, 425 (M+NH₄)⁺;

MS (ESI-) m/z 406 (M-H)⁻;

Anal. Calcd for C₁₈H₁₅NO₄FBr: C, 52.96; H, 3.70; N, 3.43. Found: C, 52.85; H, 3.80; N, 3.24.

Example 100(cis)-9-(3-bromo-4-fluorophenyl)-3-methyl-5,9-dihydro-3H-furo[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione

The enantiomers of the product from Example 91 were separated on a Chiralpak AS chiral HPLC column eluting with (hexanes:ethanol, 50:50) to provide the title compound as the faster moving enantiomer. The faster moving enantiomer was rechromatographed on silica gel eluting with 2% methanol in dichloromethane. mp 230-233 °C;

¹H NMR (DMSO) δ 1.45 (d, 3H), 4.05 (s, 2H), 4.55 (AB q, 2H), 4.75 (s, 1H), 5.15 (q, 1H), 7.19-7.25 (m, 1H), 7.29 (t, 1H), 7.47 (dd, 1H), 10.48 (bs, 1H);

MS (ESI+) m/z 394 (M+H)⁺, 411 (M+NH₄)⁺;

MS (ESI-) m/z 392 (M-H)⁻;

Anal. Calcd for C₁₇H₁₃NO₄FBr: C, 51.80; H, 3.32; N, 3.55. Found: C, 51.55; H, 3.53; N, 3.41.

Example 101(cis)-9-(3-bromo-4-fluorophenyl)-3-methyl-5,9-dihydro-3H-furo[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione

5 The enantiomers of the product from Example 91 were separated on a Chiralpak AS chiral HPLC column eluting with (hexanes:ethanol, 50:50) to provide the title compound as the slower moving enantiomer.

mp 230-233 °C;

¹H NMR (DMSO-d₆) δ 1.45 (d, 3H), 4.05 (s, 2H), 4.55 (AB q, 2H), 4.75 (s, 1H), 5.15 (q, 10 1H), 7.19-7.25 (m, 1H), 7.29 (t, 1H), 7.47 (dd, 1H), 10.48 (bs, 1H);

MS (ESI+) m/z 394 (M+H)⁺, 411 (M+NH₄)⁺;

MS (ESI-) m/z 392 (M-H)⁻;

Anal. Calcd for C₁₇H₁₃NO₄FBr: C, 51.80; H, 3.32; N, 3.55. Found: C, 51.66; H, 3.43; N, 3.44.

15 Isolation and purification of the compounds and intermediates described herein can be effected, if desired, by any suitable separation or purification procedure such as, for example, filtration, extraction, crystallization, column chromatography, thin-layer chromatography, thick-layer chromatography, preparative low or high-pressure liquid chromatography, or a combination of these procedures. Specific illustrations of suitable separation and isolation procedures can be had by reference to the Schemes and Examples 20 herein. However, other equivalent separation or isolation procedures could, of course, be used.

Determination of Potassium Channel Opening ActivityMembrane Hyperpolarization Assays

25 Compounds were evaluated for potassium channel opening activity using primary cultured guinea-pig urinary bladder (GPB) cells.

For the preparation of urinary bladder smooth muscle cells, urinary bladders were removed from male guinea-pigs (Hartley, Charles River, Wilmington, MA) weighing 300-30 400 grams (g) and placed in ice-cold Ca²⁺-free Krebs solution (Composition, millimolar

(mM): KCl, 2.7; KH_2PO_4 , 1.5; NaCl, 75; Na_2HPO_4 , 9.6; $\text{Na}_2\text{HPO}_4 \cdot 7\text{H}_2\text{O}$, 8; MgSO_4 , 2; glucose, 5; HEPES, 10; pH 7.4). Cells were isolated by enzymatic dissociation (Klockner, U. and Isenberg, G., *Pflugers Arch.* (1985), 405, 329-339). The bladder was cut into small sections and incubated in 5 milliliters (mL) of the Kreb's solution containing 1 milligram per milliliter (mg/mL) of collagenase (Sigma, St. Louis, MO) and 0.2 mg/mL of pronase (Calbiochem, La Jolla, CA) with continuous stirring in a cell incubator for 30 minutes. The mixture was then centrifuged at 1300 x g for 5 minutes, and the pellet resuspended in Dulbecco's phosphate buffered saline (PBS) (GIBCO, Gaithersburg, MD) and recentrifuged to remove residual enzyme. The cell pellet was resuspended in 5 mL growth media (composition: Dulbecco's modified Eagle's medium supplemented with 10% fetal bovine serum, 100 units/mL penicillin, 100 units/mL streptomycin and 0.25 mg/mL amphotericin B) and further dissociated by pipetting the suspension through a flame-polished Pasteur pipette and passing it through a polypropylene mesh membrane (Spectrum, Houston, TX). The cell density was adjusted to 100,000 cells/mL by resuspension in growth media. Cells were plated in clear-bottomed black 96-well plates (Packard) for membrane potential studies at a density of 20,000 cells/well and maintained in a cell incubator with 90% air:10% CO_2 until confluent. Cells were confirmed to be of smooth muscle type by cytoskeletal staining using a monoclonal mouse anti human- α -smooth muscle actin (Biomed, Foster City, CA).

Functional activity at potassium channels was measured by evaluating changes in membrane potential using the bis-oxonol dye DiBAC(4)₃ (Molecular Probes) in a 96-well cell-based kinetic assay system using a Fluorescent Imaging Plate Reader (FLIPR) (K.S. Schroeder et al., *J. Biomed. Screen.*, v. 1 pp. 75-81 (1996)). DiBAC(4)₃ is an anionic potentiometric probe which partitions between cells and extracellular solution in a membrane potential-dependent manner. With increasing membrane potential (for example, K^+ depolarization), the probe further partitions into the cell; this is measured as an increase in fluorescence due to dye interaction with intracellular lipids and proteins. Conversely, decreasing membrane potential (hyperpolarization by potassium channel openers) evokes a decrease in fluorescence.

Confluent guinea-pig urinary bladder cells cultured in black clear-bottomed 96-well plates were rinsed twice with 200 mL assay buffer (composition, mM: HEPES, 20; NaCl, 120; KCl, 2; CaCl₂, 2; MgCl₂, 1; glucose, 5; pH 7.4 at 25 °C) containing 5 µM DiBAC(4)₃ and incubated with 180 mL of the buffer in a cell incubator for 30 minutes at 37 °C to ensure dye distribution across the membrane. After recording the baseline fluorescence for 5 minutes, the reference or test compounds, prepared at 10 times the concentration in the assay buffer, were added directly to the wells. Changes in fluorescence were monitored for an additional 25 minutes. Hyperpolarization responses were corrected for any background noise and were normalized to the response observed with 10 µM of the reference compound P1075 (assigned as 100%), a potent opener of smooth muscle K_{ATP} channels (Quast et al., Mol. Pharmacol., v. 43 pp. 474-481 (1993)).

Routinely, five concentrations of P1075 or test compounds (log or half-log dilutions) were evaluated and the maximal steady-state hyperpolarization values (expressed as % relative to P1075) plotted as a function of concentration. The EC₅₀ (concentration that elicits 50% of the maximal response for the test sample) values were calculated by non-linear regression analysis using a four parameter sigmoidal equation. The maximal micromolar EC₅₀ response of each compound (expressed as % relative to P1075) is reported. Stock solutions of compounds were prepared in 100% DMSO and further dilutions were carried out in the assay buffer and added to a 96-well plate.

161

Table 1Membrane Hyperpolarization (MHP) in Guinea-Pig Bladder (GPB) Cells

Example Number	Maximal Response (% P1075)	EC ₅₀ (μ M)
1	96	0.027
2	88	0.65
3	41	27
4	21	
5	97	0.19
6	83	1.0
7	75	0.57
8	33	5.0
9	89	2.6
10	87	1.4
11	104	0.023
12	101	0.014
13	101	0.24
14	99	0.40
15	90	0.64
16	57	8.8
17	93	0.0042
18	95	0.058
19	94	1.8
20	93	0.035
21	79	0.066
22	85	0.046
23	82	0.040
24	74	0.73

162

25	106	0.0098
26	90	0.013
27	87	0.97
28	98	0.064
29	87	1.1
30	81	0.0050
31	83	1.3
32	102	0.015
33	92	0.0034
34	88	0.091
35	98	0.025
36	98	0.082
37	105	0.00064
38	82	0.39
39	80	0.68
40	111	0.32
41	66	0.071
42	102	0.026
43	98	0.011
44	96	
45	85	0.20
46	83	0.34
47	91	0.49
48	91	0.084
49	85	2.3
50	108	0.084
51	88	0.12
52	105	0.38
53	98	0.019

163

54	101	0.0095
55	108	0.0039
56	96	0.015
57	69	4.0
58	94	0.046
59	94	0.099
60	88	0.023
61	97	0.0063
62	77	0.058
64	84	0.25
78	97	0.0049
79	90	0.014

In vitro Functional models

Compounds were evaluated for functional potassium channel opening activity using tissue strips obtained from Landrace pig bladders.

Landrace pig bladders were obtained from female Landrace pigs of 9-30 kg. Landrace pigs were euthanized with an intraperitoneal injection of pentobarbital solution, Somlethal®, J.A. Webster Inc., Sterling MA. The entire bladder was removed and immediately placed into Krebs Ringer bicarbonate solution (composition, mM: NaCl, 120; NaHCO₃, 20; dextrose, 11; KCl, 4.7; CaCl₂, 2.5; MgSO₄, 1.5; KH₂PO₄, 1.2; K₂EDTA, 0.01, equilibrated with 5% CO₂/95% O₂ pH 7.4 at 37 °C). Propranolol (0.004 mM) was included in all of the assays to block β-adrenoceptors. The trigonal and dome portions were discarded. Strips 3-5 millimeters (mm) wide and 20 mm long were prepared from the remaining tissue cut in a circular fashion. The mucosal layer was removed. One end was fixed to a stationary glass rod and the other to a Grass FT03 transducer at a basal preload of 1.0 g. Two parallel platinum electrodes were included in the stationary glass rod to provide field stimulation of 0.05 Hz, 0.5 milli-seconds at 20 volts. This low frequency stimulation produced a stable twitch response of 100-500 centigrams. Tissues were allowed to equilibrate for at least 60 minutes and primed with 80 mM KCl. A

control concentration response curve (cumulative) was generated for each tissue using the potassium channel opener P1075 as the control agonist. P1075 completely eliminated the stimulated twitch in a dose dependent fashion over a concentration range of 10^{-9} to 10^{-5} M using 1/2 log increments. After a 60 minute rinsing period, a concentration response curve (cumulative) was generated for the test agonist in the same fashion as that used for the control agonist P1075. The maximal efficacy of each compounds (expressed as % relative to P1075) is reported. The amount of agent necessary to cause 50% of the agent's maximal response (ED_{50}) was calculated using "ALLFIT" (DeLean et al., Am. J. Physiol., 235, E97 (1980)), and agonist potencies were expressed as pD_2 (the negative logarithm). Agonist potencies were also expressed as an index relative to P1075. The index was calculated by dividing the ED_{50} for P1075 by the ED_{50} for the test agonist in a given tissue. Each tissue was used for only one test agonist, and the indices obtained from each tissue were averaged to provide an average index of potency. These data are shown in Table 2.

Table 2

Functional Potassium Channel Opening Activity in Isolated Bladder Strips

Example Number	Landrace Pig Bladder		
	Efficacy (%P1075)	pD_2	Index
1	97	6.9	0.36
2	99	5.8	0.041
5	100	6.4	0.16
6	100	5.4	0.022
7	97	5.4	0.040
8	90	5.2	0.023
9	82	3.9	0.0015
10	96	4.3	0.0028
11	91	6.8	1.2
12	85	7.2	3.3
13	98	5.9	0.13

165

15	100	5.7	0.027
18	100	7.3	1.6
19	100	6.0	0.70
20	93	5.6	0.43
22	100	5.6	0.027
24	100	6.0	0.055
28	94	6.7	0.42
29	89	5.8	0.075
30	100	7.6	1.1
31	85	5.1	0.065
32	100	6.3	0.41
33	93	5.9	0.27
34	93	7.0	0.96
35	100	7.4	1.8
36	100	6.5	0.24
37	95	7.3	2.1
38	80	5.3	0.024
39	96	5.6	0.036
40	91	6.0	0.13
42	95	6.2	0.17
43	88	6.7	0.68
50	96	6.2	0.28
52	99	5.3	0.069
53	100	7.0	0.44
54	100	6.9	0.48
55	80	6.2	0.35
57	45	5.6	0.090
58	84	6.2	0.19
59	73	5.9	0.17

166

64	95	5.5	0.031
78	96	7.1	0.79
79	95	6.8	0.40
81	93	6.4	0.23
82	98	7.5	1.4

As shown by the data in Tables 1 and 2, the compounds of this invention reduce stimulated contractions of the bladder by opening potassium channels and therefore may have utility in the treatment of symptoms and/or diseases prevented by or ameliorated with potassium channel openers.

The term "pharmaceutically acceptable carrier," as used herein, means a non-toxic, inert solid, semi-solid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. Some examples of materials which can serve as pharmaceutically acceptable carriers are sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols; such a propylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator.

The present invention provides pharmaceutical compositions which comprise compounds of the present invention formulated together with one or more non-toxic pharmaceutically acceptable carriers. The pharmaceutical compositions can be formulated for oral administration in solid or liquid form, for parenteral injection or for rectal administration.

Further included within the scope of the present invention are pharmaceutical compositions comprising one or more of the compounds of formula I-VIII prepared and formulated in combination with one or more non-toxic pharmaceutically acceptable compositions. The pharmaceutical compositions can be formulated for oral administration
5 in solid or liquid form, for parenteral injection or for rectal administration.

The pharmaceutical compositions of this invention can be administered to humans and other mammals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments or drops), buccally or as an oral or nasal spray. The term "parenterally," as used herein, refers to modes of administration
10 which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous, intraarticular injection and infusion.

Pharmaceutical compositions of this invention for parenteral injection comprise pharmaceutically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions and sterile powders for reconstitution into sterile injectable
15 solutions or dispersions. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (propylene glycol, polyethylene glycol, glycerol, and the like), suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Proper fluidity may be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required
20 particle size in the case of dispersions, and by the use of surfactants.

These compositions may also contain adjuvants such as preservative agents, wetting agents, emulsifying agents, and dispersing agents. Prevention of the action of microorganisms may be ensured by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be
25 desirable to include isotonic agents, for example, sugars, sodium chloride and the like. Prolonged absorption of the injectable pharmaceutical form may be brought about by the use of agents delaying absorption, for example, aluminum monostearate and gelatin.

In some cases, in order to prolong the effect of a drug, it is often desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be
30 accomplished by the use of a liquid suspension of crystalline or amorphous material with

poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form.

Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

5 Suspensions, in addition to the active compounds, may contain suspending agents, as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar, tragacanth, and mixtures thereof.

10 If desired, and for more effective distribution, the compounds of the present invention can be incorporated into slow-release or targeted-delivery systems such as polymer matrices, liposomes, and microspheres. They may be sterilized, for example, by filtration through a bacteria-retaining filter or by incorporation of sterilizing agents in the form of sterile solid compositions, which may be dissolved in sterile water or some other sterile injectable medium immediately before use.

15 The active compounds can also be in micro-encapsulated form, if appropriate, with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active compound can be admixed with at
20 least one inert diluent such as sucrose, lactose, or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such as magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. They may optionally contain opacifying agents and can
25 also be of such composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes.

30 Injectable depot forms are made by forming microencapsulated matrices of the drug in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of

drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides) Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissues.

5 The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium just prior to use.

10 Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic, parenterally acceptable diluent or solvent such as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium
15 chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

20 Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid; b) binders such as carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia; c) humectants such as glycerol; d)
25 disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; e) solution retarding agents such as paraffin); f) absorption accelerators such as quaternary ammonium compounds; g) wetting agents such as cetyl alcohol and glycerol monostearate;) absorbents such as kaolin and bentonite clay; and i) lubricants such as talc, calcium stearate, magnesium stearate, solid

polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high
5 molecular weight polyethylene glycols and the like.

The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or
10 preferentially, in a certain part of the intestinal tract in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes.

Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository
15 wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in
20 the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and
25 mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

Dosage forms for topical or transdermal administration of a compound of this invention include ointments, pastes, creams, lotions, gels, powders, solutions, sprays,
30 inhalants or patches. The active component is admixed under sterile conditions with a

pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, ear drops, eye ointments, powders and solutions are also contemplated as being within the scope of this invention.

The ointments, pastes, creams and gels may contain, in addition to an active
5 compound of this invention, excipients such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

Powders and sprays can contain, in addition to the compounds of this invention, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and
10 polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants such as chlorofluorohydrocarbons.

Transdermal patches have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispensing the compound in the proper medium. Absorption enhancers can also be used to increase the
15 flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

Compounds of the present invention may also be administered in the form of liposomes. As is known in the art, liposomes are generally derived from phospholipids or other lipid substances. Liposomes are formed by mono- or multi-lamellar hydrated liquid
20 crystals that are dispersed in an aqueous medium. Any non-toxic, physiologically acceptable and metabolizable lipid capable of forming liposomes may be used. The present compositions in liposome form may contain, in addition to the compounds of the present invention, stabilizers, preservatives, excipients, and the like. The preferred lipids are the natural and synthetic phospholipids and phosphatidylcholines (lecithins) used
25 separately or together.

Methods to form liposomes are known in the art. See, for example, Prescott, Ed., Methods in Cell Biology, Volume XIV, Academic Press, New York, N. Y., (1976), p 33 et seq.

The term "pharmaceutically acceptable cation," as used herein, refers to a
30 positively-charged inorganic or organic ion that is generally considered suitable for human

consumption. Examples of pharmaceutically acceptable cations are hydrogen, alkali metal (lithium, sodium and potassium), magnesium, calcium, ferrous, ferric, ammonium, alkylammonium, dialkylammonium, trialkylammonium, tetraalkylammonium, diethanolammmonium, and choline. Cations may be interchanged by methods known in the art, such as ion exchange.

The terms "pharmaceutically acceptable salts, esters and amides," as used herein, refer to carboxylate salts, amino acid addition salts, zwitterions, esters and amides of compounds of formula I-VIII which are, within the scope of sound medical judgement, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, and the like, are commensurate with a reasonable benefit/risk ratio, and are effective for their intended use.

The term "pharmaceutically acceptable salt," as used herein, refers to salts that are well known in the art. For example, S. M Berge et al. describe pharmaceutically acceptable salts in detail in (J. Pharmaceutical Sciences, 66:1-19 (1977)). Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid, or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include nitrate, bisulfate, borate, formate, butyrate, valerate, 3-phenylpropionate, camphorate, adipate, benzoate, oleate, palmitate, stearate, laurate, lactate, fumarate, ascorbate, aspartate, nicotinate, p-toluenesulfonate, camphorsulfonate, methanesulfonate, 2-hydroxyethanesulfonate, gluconate, glucoheptonate, lactobionate, glycerophosphate, pectinate, lauryl sulfate, and the like, metal salts such as sodium, potassium, magnesium or calcium salts or amino salts such as ammonium, triethylamine salts, and the like, all of which may be prepared according to conventional methods.

The term "pharmaceutically acceptable ester," as used herein, refers to esters of compounds of the present invention which hydrolyze in vivo and include those that break down readily in the human body to leave the parent compound or a salt thereof. Examples of pharmaceutically acceptable, non-toxic esters of the present invention include C₁-to-C₆

alkyl esters and C₅-to-C₇ cycloalkyl esters, although C₁-to-C₄ alkyl esters are preferred. Esters of the compounds of formula I-VIII may be prepared according to conventional methods.

The term "pharmaceutically acceptable amide," as used herein, refers to non-toxic amides of the present invention derived from ammonia, primary C₁-to-C₆ alkyl amines and secondary C₁-to-C₆ dialkyl amines. In the case of secondary amines, the amine may also be in the form of a 5- or 6-membered heterocycle containing one nitrogen atom. Amides derived from ammonia, C₁-to-C₃ alkyl primary amides and C₁-to-C₂ dialkyl secondary amides are preferred. Amides of the compounds of formula I-VIII may be prepared according to conventional methods. It is intended that amides of the present invention include amino acid and peptide derivatives of the compounds of formula I-VIII, as well.

The term "pharmaceutically acceptable prodrug" or "prodrug," as used herein, represents those prodrugs of the compounds of the present invention which are, within the scope of sound medical judgement, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use. Prodrugs of the present invention may be rapidly transformed in vivo to the parent compound of the above formula I-VIII, for example, by hydrolysis in blood. A thorough discussion is provided in (T. Higuchi and V. Stella, Pro-drugs as Novel Delivery Systems, V. 14 of the A.C.S. Symposium Series, and in Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press (1987)).

The term "prodrug ester group," as used herein refers, to any of several ester-forming groups that are hydrolyzed under physiological conditions. Examples of prodrug ester groups include pivoyloxymethyl, acetoxymethyl, phthalidyl, indanyl and methoxymethyl, as well as other such groups known in the art. Other examples of prodrug ester groups can be found in the book ("Pro-drugs as Novel Delivery Systems," by Higuchi and Stella) cited above.

Dosage forms for topical administration of a compound of this invention include powders, sprays, ointments and inhalants. The active compound is mixed under sterile

conditions with a pharmaceutically acceptable carrier and any needed preservatives, buffers or propellants which can be required. Ophthalmic formulations, eye ointments, powders and solutions are also contemplated as being within the scope of this invention.

Actual dosage levels of active ingredients in the pharmaceutical compositions of this invention can be varied so as to obtain an amount of the active compound(s) which is effective to achieve the desired therapeutic response for a particular patient, compositions and mode of administration. The selected dosage level will depend upon the activity of the particular compound, the route of administration, the severity of the condition being treated and the condition and prior medical history of the patient being treated. However, it is within the skill of the art to start doses of the compound at levels lower than required for to achieve the desired therapeutic effect and to gradually increase the dosage until the desired effect is achieved.

The present invention contemplates pharmaceutically active metabolites formed by *in vivo* biotransformation of compounds of formula I-VIII. The term pharmaceutically active metabolite, as used herein, refers to a compound formed by the *in vivo* biotransformation of compounds of formula I-VIII. The present invention contemplates compounds of formula I-VIII and metabolites thereof. A thorough discussion of biotransformation is provided in Goodman and Gilman's, The Pharmacological Basis of Therapeutics, seventh edition.

The compounds of the invention, including but not limited to those specified in the examples, possess potassium channel opening activity in mammals (especially humans). As potassium channel openers, the compounds of the present invention are useful for the treatment and prevention of diseases such as asthma, epilepsy, Raynaud's syndrome, impotence, migraine, pain, eating disorders, urinary incontinence, functional bowel disorders, neurodegeneration and stroke.

The ability of the compounds of the invention to treat asthma, epilepsy, Raynaud's syndrome, male sexual dysfunction, female sexual dysfunction, migraine, pain, eating disorders, urinary incontinence, functional bowel disorders, neurodegeneration and stroke can be demonstrated according to the methods described (D. E. Nurse et al., Br. J. Urol., v. 68 pp. 27-31 (1991); B. B. Howe et al., J. Pharmacol. Exp. Ther., v. 274 pp. 884-890

(1995); K. Lawson, Pharmacol. Ther., v. 70 pp. 39-63 (1996); D. R. Gehlert, et al., Neuro-Psychopharmacol & Biol. Psychiat., v. 18 pp. 1093-1102 (1994); M. Gopalakrishnan et al., Drug Development Research, v. 28 pp. 95-127 (1993); J.E. Freedman et al., The Neuroscientist, v. 2 pp. 145-152 (1996); D. Spanswick et al., Nature, v. 390 pp. 521-25
5 (December 4, 1997)).

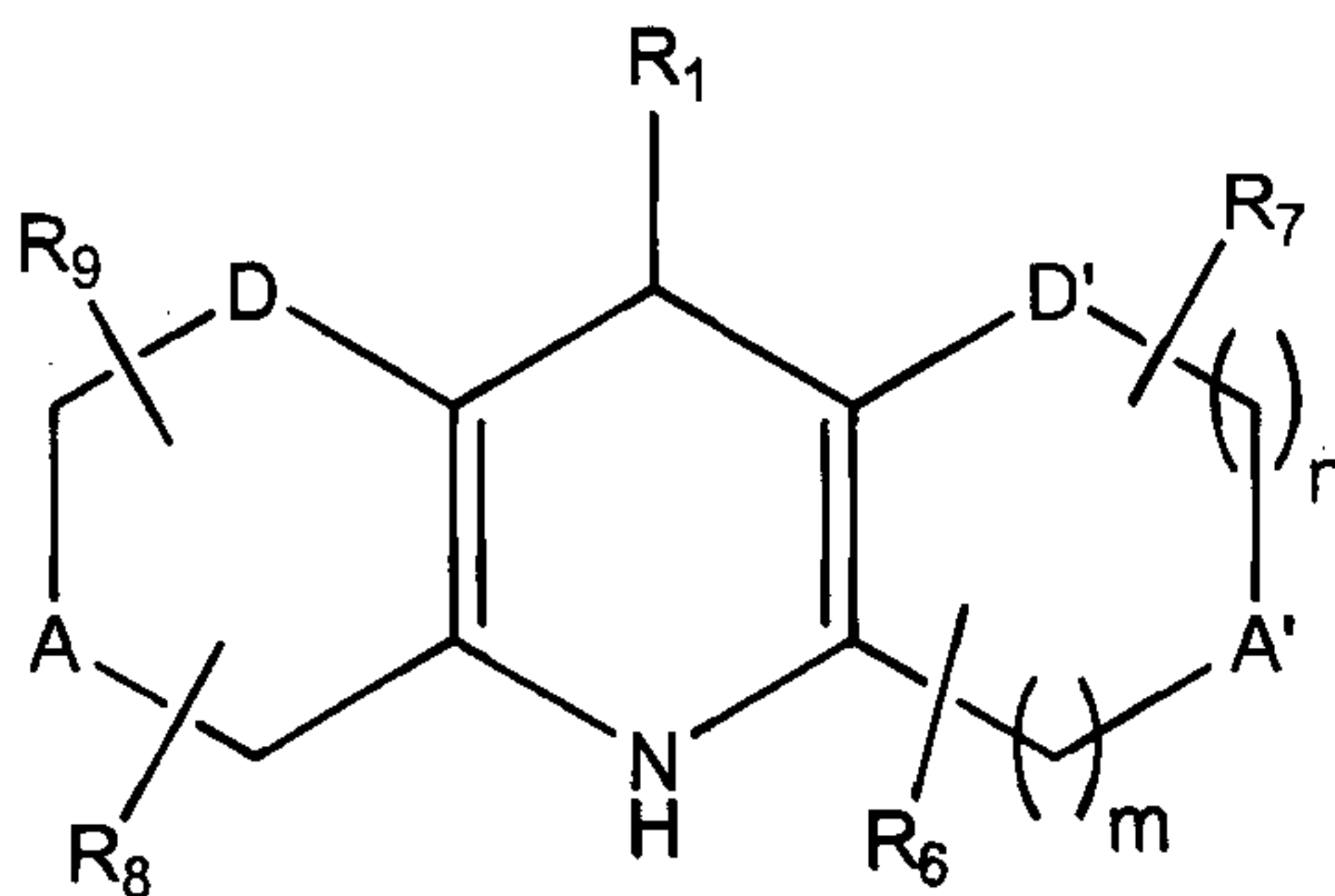
Aqueous liquid compositions of the present invention are particularly useful for the treatment and prevention of asthma, epilepsy, Raynaud's syndrome, male sexual dysfunction, female sexual dysfunction, migraine, pain, eating disorders, urinary incontinence, functional bowel disorders, neurodegeneration and stroke.

10 When used in the above or other treatments, a therapeutically effective amount of one of the compounds of the present invention can be employed in pure form or, where such forms exist, in pharmaceutically acceptable salt, ester, amide or prodrug form. Alternatively, the compound can be administered as a pharmaceutical composition containing the compound of interest in combination with one or more pharmaceutically
15 acceptable excipients. The phrase "therapeutically effective amount" of the compound of the invention means a sufficient amount of the compound to treat disorders, at a reasonable benefit/risk ratio applicable to any medical treatment. It will be understood, however, that the total daily usage of the compounds and compositions of the present invention will be decided by the attending physician within the scope of sound medical judgement. The
20 specific therapeutically effective dose level for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of
25 the treatment; drugs used in combination or coincidental with the specific compound employed; and like factors well known in the medical arts. For example, it is well within the skill of the art to start doses of the compound at levels lower than required to achieve the desired therapeutic effect and to gradually increase the dosage until the desired effect is achieved.

The total daily dose of the compounds of this invention administered to a human or lower animal may range from about 0.003 to about 10 mg/kg/day. For purposes of oral administration, more preferable doses can be in the range of from about 0.01 to about 5 mg/kg/day. If desired, the effective daily dose can be divided into multiple doses for purposes of administration; consequently, single dose compositions may contain such amounts or submultiples thereof to make up the daily dose.

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. A compound having formula I



I,

or a pharmaceutically acceptable salt thereof, wherein

n is 0-1;

m is 1-2;

A is NR₂, O, or S;

A' is NR₃, O, S, or CR₄R₅;

D is CH₂ or C(O);

D' is CH₂, C(O), S(O), or S(O)₂;

R₁ is aryl or heterocycle;

R₂ and R₃ are independently hydrogen, alkoxyalkyl, alkyl, arylalkyl, cycloalkyl,

cycloalkylalkyl, haloalkyl, heterocycloalkyl, hydroxy, hydroxyalkyl, -NZ₁Z₂, or (NZ₁Z₂)alkyl wherein Z₁ and Z₂ are independently hydrogen, alkyl, alkylcarbonyl, aryl, arylalkyl, or formyl;

R₄ and R₅ are independently hydrogen or alkyl;

or

R₄ and R₅ together with the carbon atom to which they are attached form a 3-6 membered carbocyclic ring;

R₆ and R₇ are independently hydrogen or alkyl;

or

R₆ and R₇ together with the carbon atom to which they are attached form a 3-6 membered carbocyclic ring; and

R₈ and R₉ are independently hydrogen or alkyl with the proviso that R₈ and R₉ are not both hydrogen, and when one of R₈ and R₉ occupies the same position as R₂, and R₂ and the one of R₈ and R₉ are alkyl, then the other of R₈ and R₉ is not hydrogen;

178

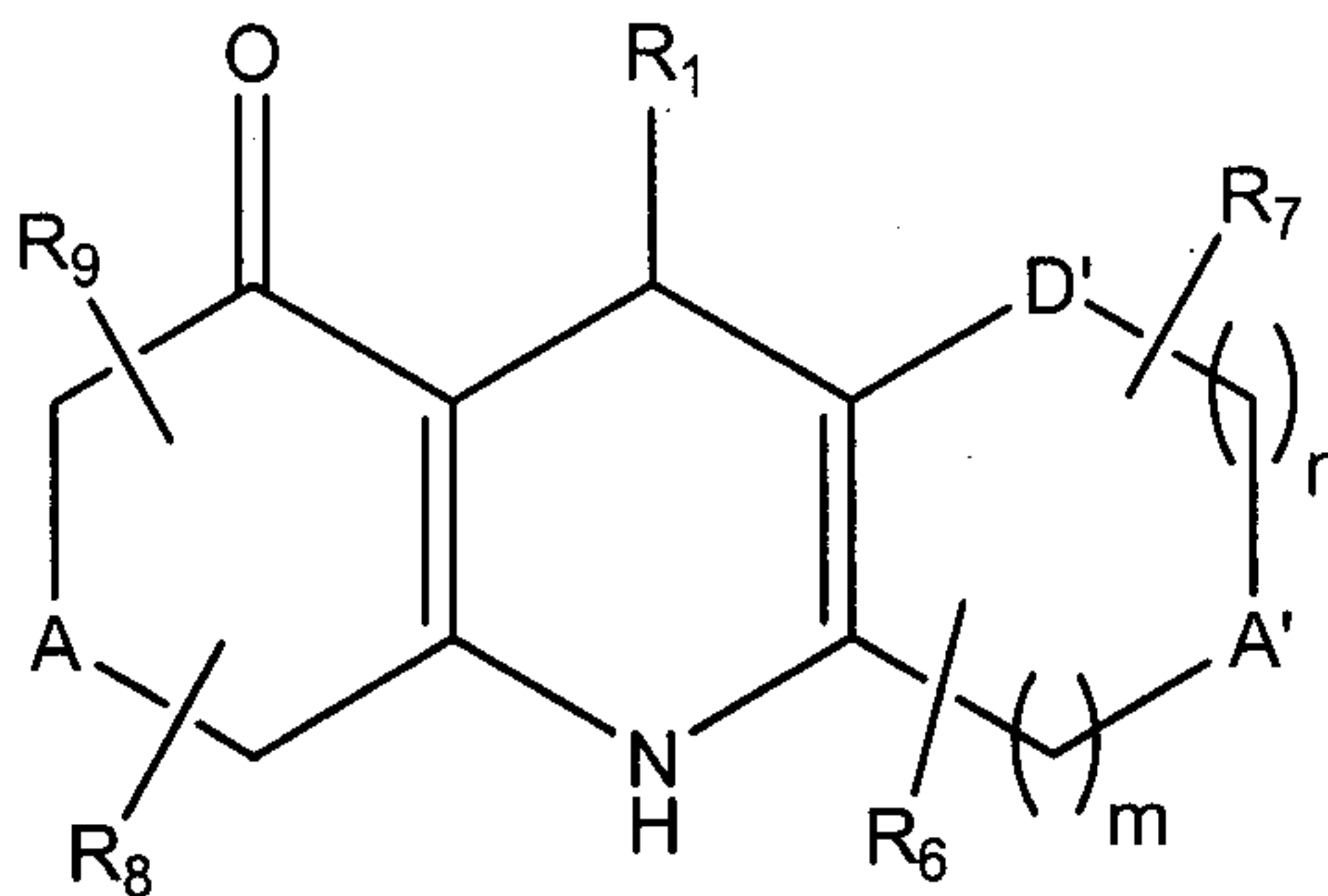
or

R_8 and R_9 together with the carbon atom to which they are attached form a 3-6 membered carbocyclic ring;

with the proviso that when D is CH_2 then D' is other than CH_2 ; and

5 with the proviso that when D' is S(O) or S(O)_2 then A' is CR_4R_5 .

2. A compound according to claim 1 of formula II:



II,

or a pharmaceutically acceptable salt thereof wherein,

10 n is 0-1;

m is 1-2;

A is NR_2 , O, or S;

A' is NR_3 , O, S or CR_4R_5 ;

D' is CH_2 , C(O) , S(O) , or S(O)_2 ;

15 R_1 is aryl or heterocycle;

R_2 and R_3 are independently hydrogen, alkoxyalkyl, alkyl, arylalkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, heterocycloalkyl, hydroxy, hydroxyalkyl, $-\text{NZ}_1\text{Z}_2$, or $(\text{NZ}_1\text{Z}_2)\text{alkyl}$ wherein Z_1 and Z_2 are independently hydrogen, alkyl, alkylcarbonyl, aryl, arylalkyl, or formyl;

20 R_4 and R_5 are independently hydrogen or alkyl;

or

R_4 and R_5 together with the carbon atom to which they are attached form a 3-6 membered carbocyclic ring;

R_6 and R_7 are independently hydrogen or alkyl;

25 or

R_6 and R_7 together with the carbon atom to which they are attached form a 3-6 membered carbocyclic ring; and

R_8 and R_9 are independently hydrogen or alkyl with the proviso that R_8 and R_9 are not both hydrogen, and when one of R_8 and R_9 occupies the same position as R_2 , and R_2 and the one of R_8 and R_9 are alkyl, then the other of R_8 and R_9 is not hydrogen;

or

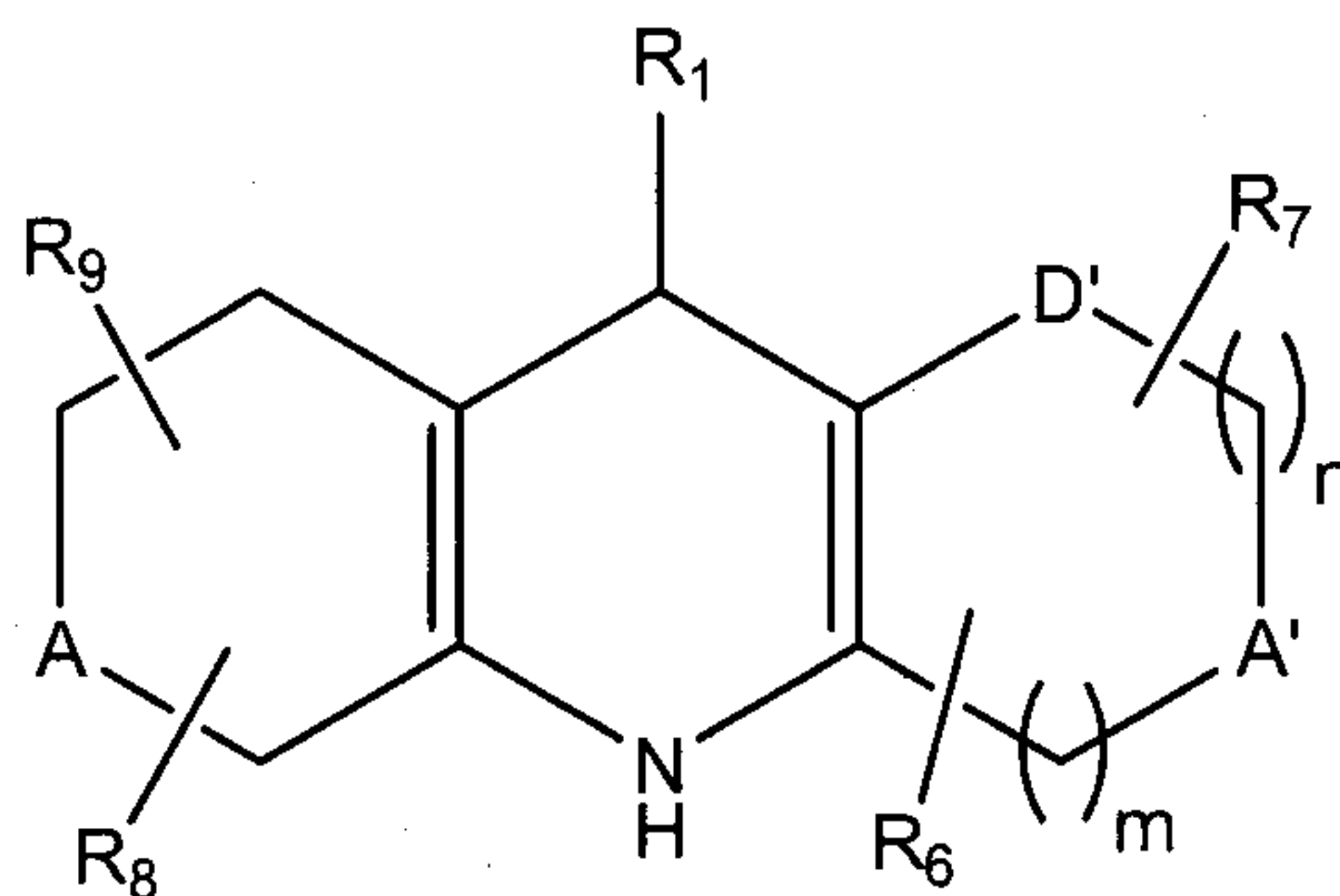
5 R_8 and R_9 together with the carbon atom to which they are attached form a 3-6 membered carbocyclic ring.

3. A compound according to claim 2 wherein A is NR_2 .

4. A compound according to claim 2 wherein A is O.

5. A compound according to claim 2 wherein A is S.

10 6. A compound according to claim 1 of formula III:



III,

or a pharmaceutically acceptable salt thereof wherein,

n is 0-1;

15 m is 1-2;

A is NR_2 , O, or S;

A' is NR_3 , O, S or CR_4R_5 ;

D' is CH_2 , C(O), S(O), or S(O)₂;

R_1 is aryl or heterocycle;

20 R_2 and R_3 are independently hydrogen, alkoxyalkyl, alkyl, arylalkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, heterocycloalkyl, hydroxy, hydroxyalkyl, $-NZ_1Z_2$, or (NZ_1Z_2) alkyl wherein Z_1 and Z_2 are independently hydrogen, alkyl, alkylcarbonyl, aryl, arylalkyl, or formyl;

R_4 and R_5 are independently hydrogen or alkyl;

25 or

R_4 and R_5 together with the carbon atom to which they are attached form a 3-6 membered carbocyclic ring;

R_6 and R_7 are independently hydrogen or alkyl;

or

- 5 R_6 and R_7 together with the carbon atom to which they are attached form a 3-6 membered carbocyclic ring; and

R_8 and R_9 are independently hydrogen or alkyl with the proviso that R_8 and R_9 are not both hydrogen, and when one of R_8 and R_9 occupies the same position as R_2 , and R_2 and the one of R_8 and R_9 are alkyl, then the other of R_8 and R_9 is not hydrogen;

- 10 or

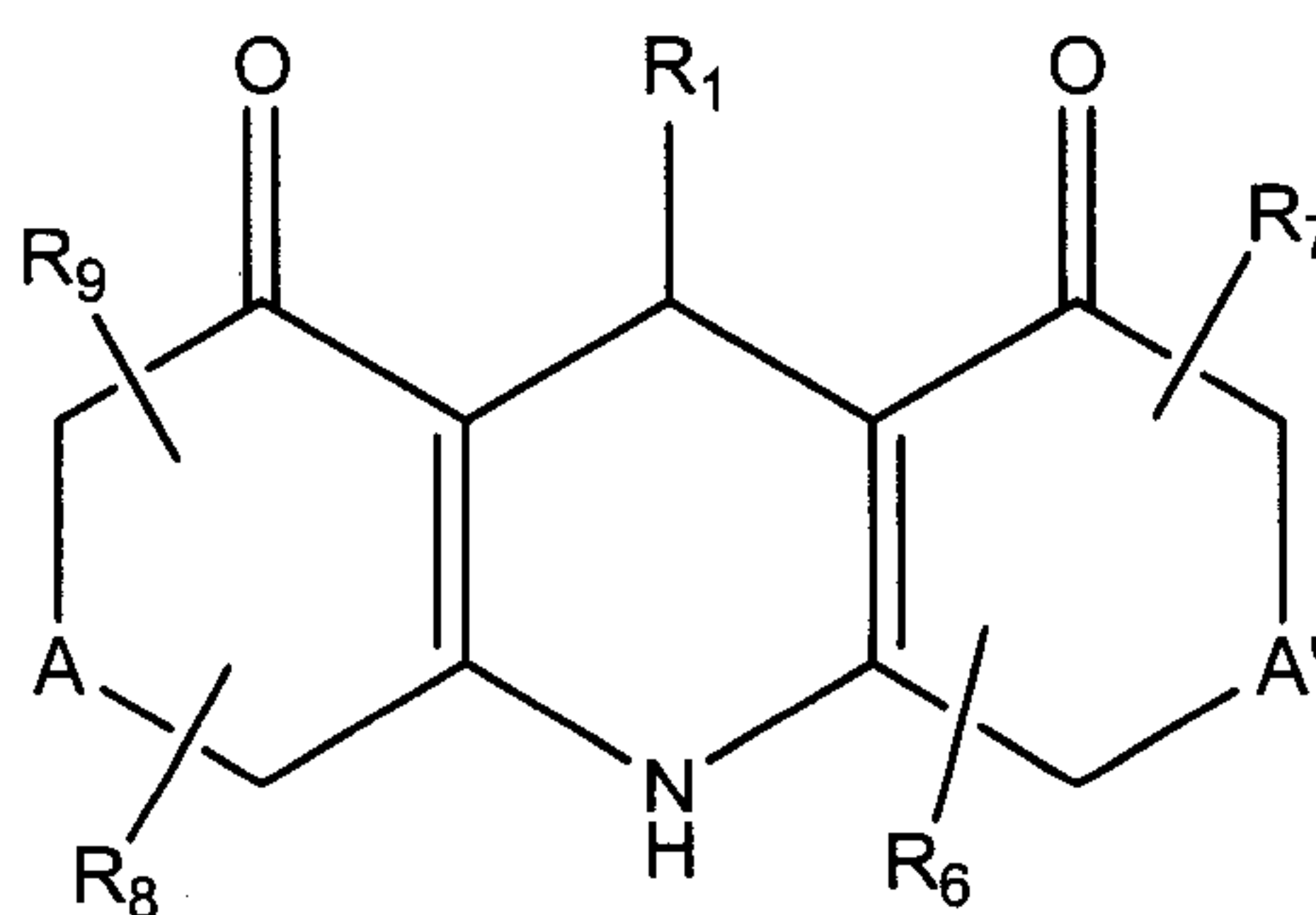
R_8 and R_9 together with the carbon atom to which they are attached form a 3-6 membered carbocyclic ring.

7. A compound according to claim 6 wherein A is NR_2 .

8. A compound according to claim 6 wherein A is O.

- 15 9. A compound according to claim 6 wherein A is S.

10. A compound according to claim 1 of formula IV:



IV,

or a pharmaceutically acceptable salt thereof wherein,

- 20 A is NR_2 , O, or S;

A' is NR_3 , O, S or CR_4R_5 ;

R_1 is aryl or heterocycle;

R_2 and R_3 are independently hydrogen, alkoxyalkyl, alkyl, arylalkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, heterocycloalkyl, hydroxy, hydroxyalkyl, $-NZ_1Z_2$, or

(NZ₁Z₂)alkyl wherein Z₁ and Z₂ are independently hydrogen, alkyl, alkylcarbonyl, aryl, arylalkyl, or formyl;

R₄ and R₅ are independently hydrogen or alkyl;

or

5 R₄ and R₅ together with the carbon atom to which they are attached form a 3-6 membered carbocyclic ring;

R₆ and R₇ are independently hydrogen or alkyl;

or

10 R₆ and R₇ together with the carbon atom to which they are attached form a 3-6 membered carbocyclic ring; and

R₈ and R₉ are independently hydrogen or alkyl with the proviso that R₈ and R₉ are not both hydrogen, and when one of R₈ and R₉ occupies the same position as R₂, and R₂ and the one of R₈ and R₉ are alkyl, then the other of R₈ and R₉ is not hydrogen;

or

15 R₈ and R₉ together with the carbon atom to which they are attached form a 3-6 membered carbocyclic ring.

11. A compound according to claim 10 wherein

A is NR₂; and

A' is NR₃.

20 12. A compound according to claim 10 wherein

A is NR₂;

A' is NR₃;

R₆ is hydrogen;

R₇ is hydrogen; and

25 R₈ is hydrogen.

13. A compound according to claim 10 wherein

A is NR₂; and

A' is O.

14. A compound according to claim 10 wherein
A is NR_2 ; and
A' is S.
- 5 15. A compound according to claim 10 wherein
A is O; and
A' is NR_3 .
- 10 16. A compound according to claim 10 wherein
A is O;
A' is NR_3 ;
 R_6 is hydrogen;
 R_7 is hydrogen; and
 R_8 is hydrogen.
- 15 17. A compound according to claim 10 wherein
A is O;
A' is O.
- 20 18. A compound according to claim 10 wherein
A is O;
A' is O;
 R_6 is hydrogen;
 R_7 is hydrogen; and
 R_8 is hydrogen.
- 25 19. A compound according to claim 18 that is:
5-(3-bromo-4-methylphenyl)-5,10-dihydro-1H,3H-dipyrano[3,4-b:4,3-e]pyridine-4,6(7H,9H)-dione;
5-(3-iodo-4-methylphenyl)-5,10-dihydro-1H,3H-dipyrano[3,4-b:4,3-e]pyridine-4,6(7H,9H)-dione;
5-(3,4-dibromophenyl)-5,10-dihydro-1H,3H-dipyrano[3,4-b:4,3-e]pyridine-4,6(7H,9H)-dione;
5-[4-chloro-3-(trifluoromethyl)phenyl]-5,10-dihydro-1H,3H-dipyrano[3,4-b:4,3-e]pyridine-4,6(7H,9H)-dione;
- 30

- 5-[4-fluoro-3-(2-furyl)phenyl]-5,10-dihydro-1H,3H-dipyrano[3,4-b:4,3-e]pyridine-4,6(7H,9H)-dione;
- 5-(5-bromo-4-fluoro-2-hydroxyphenyl)-5,10-dihydro-1H,3H-dipyrano[3,4-b:4,3-e]pyridine-4,6(7H,9H)-dione;
- 5 5-(4-methyl-3-nitrophenyl)-5,10-dihydro-1H,3H-dipyrano[3,4-b:4,3-e]pyridine-4,6(7H,9H)-dione;
- 5-(4-bromo-3-chlorophenyl)-5,10-dihydro-1H,3H-dipyrano[3,4-b:4,3-e]pyridine-4,6(7H,9H)-dione;
- 10 5-(3-bromo-4-chlorophenyl)-5,10-dihydro-1H,3H-dipyrano[3,4-b:4,3-e]pyridine-4,6(7H,9H)-dione;
- 5-[3-iodo-4-(trifluoromethyl)phenyl]-5,10-dihydro-1H,3H-dipyrano[3,4-b:4,3-e]pyridine-4,6(7H,9H)-dione;
- 5-[3-bromo-4-(trifluoromethyl)phenyl]-5,10-dihydro-1H,3H-dipyrano[3,4-b:4,3-e]pyridine-4,6(7H,9H)-dione;
- 15 5-(4-fluoro-3-isopropenylphenyl)-5,10-dihydro-1H,3H-dipyrano[3,4-b:4,3-e]pyridine-4,6(7H,9H)-dione; or
- 5-(4-fluorophenyl)-5,10-dihydro-1H,3H-dipyrano[3,4-b:4,3-e]pyridine-4,6(7H,9H)-dione.
20. A compound according to claim 10 wherein
- A is O;
- 20 A' is O;
- R₆ is hydrogen;
- R₇ is hydrogen;
- R₈ is alkyl; and
- R₉ is hydrogen or alkyl.
- 25 21. A compound according to claim 20 that is 5-(3-bromo-4-fluorophenyl)-3,3-dimethyl-5,10-dihydro-1H,3H-dipyrano[3,4-b:4,3-e]pyridine-4,6(7H,9H)-dione.
22. A compound according to claim 10 wherein
- A is O;
- A' is O;
- 30 R₆ is alkyl;
- R₇ is hydrogen or alkyl;

R₈ is alkyl; and

R₉ is hydrogen or alkyl.

23. A compound according to claim 22 that is 5-(3-bromo-4-fluorophenyl)-3,3,7,7-tetramethyl-5,10-dihydro-1H,3H-dipyrano[3,4-b:4,3-e]pyridine-4,6(7H,9H)-dione.

5 24. A compound according to claim 10 wherein
A is O; and
A' is S.

10 25. A compound according to claim 10 wherein
A is O;
A' is S;
R₆ is hydrogen;
R₇ is hydrogen; and
R₈ is hydrogen.

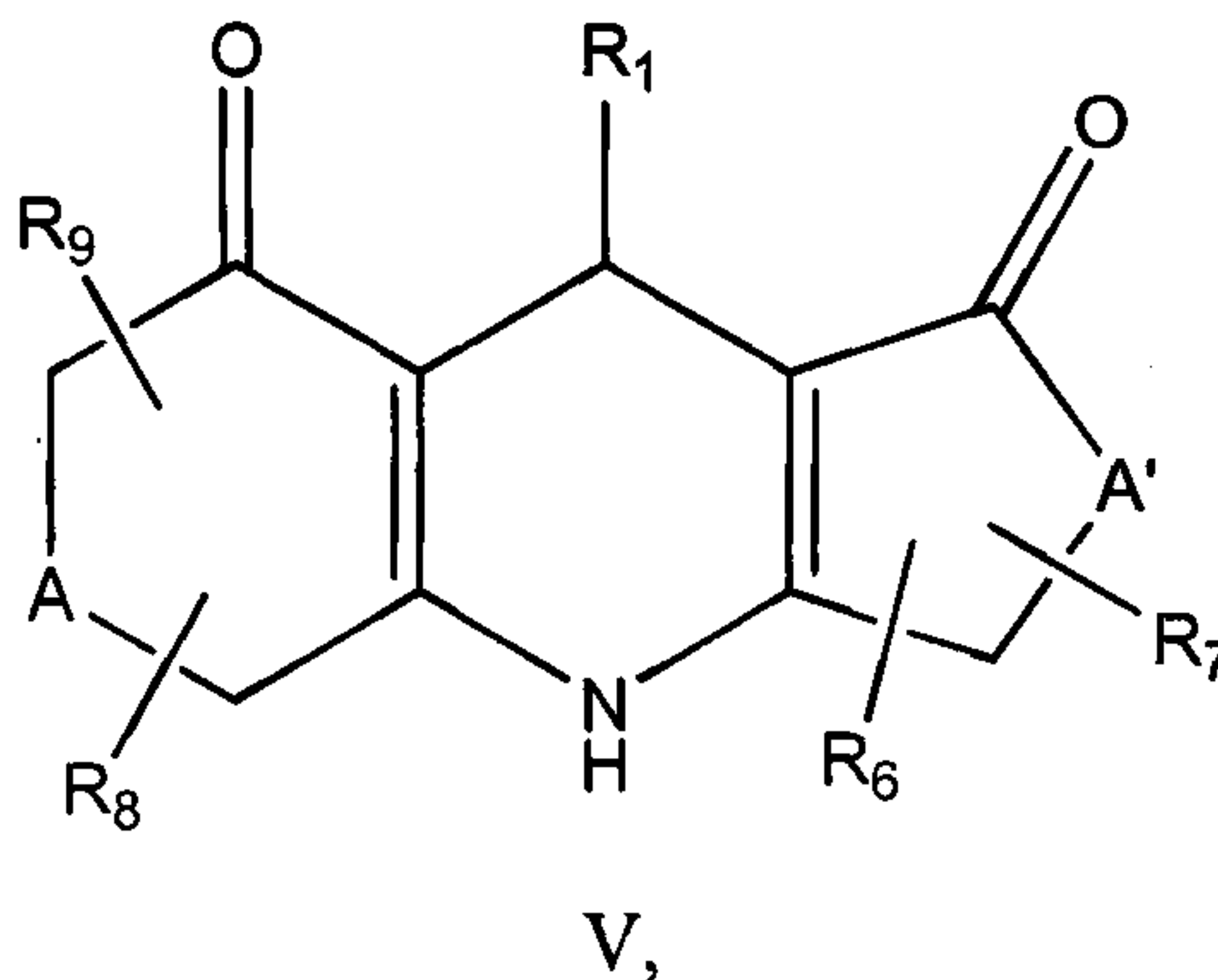
15 26. A compound according to claim 10 wherein
A is S; and
A' is NR₃.

27. A compound according to claim 10 wherein
A is S; and
A' is O.

20 28. A compound according to claim 10 wherein
A is S; and
A' is S.

185

29. A compound according to claim 1 of formula V:



or a pharmaceutically acceptable salt thereof wherein,

5 A is NR_2 , O, or S;

A' is NR_3 , O, S or CR_4R_5 ;

R_1 is aryl or heterocycle;

10 R_2 and R_3 are independently hydrogen, alkoxyalkyl, alkyl, arylalkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, heterocycloalkyl, hydroxy, hydroxyalkyl, $-\text{NZ}_1\text{Z}_2$, or $(\text{NZ}_1\text{Z}_2)\text{alkyl}$ wherein Z_1 and Z_2 are independently hydrogen, alkyl, alkylcarbonyl, aryl, arylalkyl, or formyl;

R_4 and R_5 are independently hydrogen or alkyl;

or

15 R_4 and R_5 together with the carbon atom to which they are attached form a 3-6 membered carbocyclic ring;

R_6 and R_7 are independently hydrogen or alkyl;

or

20 R_6 and R_7 together with the carbon atom to which they are attached form a 3-6 membered carbocyclic ring; and

R_8 and R_9 are independently hydrogen or alkyl with the proviso that R_8 and R_9 are not both hydrogen, and when one of R_8 and R_9 occupies the same position as R_2 , and R_2 and the one of R_8 and R_9 are alkyl, then the other of R_8 and R_9 is not hydrogen;

or

25 R_8 and R_9 together with the carbon atom to which they are attached form a 3-6 membered carbocyclic ring.

30. A compound according to claim 29 wherein
A is NR_2 ; and
A' is NR_3 .

5 31. A compound according to claim 29 wherein
A is NR_2 ; and
A' is O.

10 32. A compound according to claim 29 wherein
A is NR_2 ;
A' is O;
 R_6 is hydrogen;
 R_7 is hydrogen; and
 R_8 is hydrogen.

15 33. A compound according to claim 29 wherein
A is NR_2 ; and
A' is S.

34. A compound according to claim 29 wherein
A is NR_2 ; and
A' is CR_4R_5 .

20 35. A compound according to claim 29 wherein
A is NR_2 ;
A' is CR_4R_5 ;
 R_4 is hydrogen;
 R_5 is hydrogen;
 R_6 is hydrogen;
25 R_7 is hydrogen; and
 R_8 is hydrogen.

36. A compound according to claim 29 wherein
A is O; and
A' is NR_3 .

37. A compound according to claim 29 wherein

A is O;

A' is NR₃;

R₆ is hydrogen;

5 R₇ is hydrogen; and

R₈ is hydrogen.

38. A compound according to claim 29 wherein

A is O; and

A' is O.

10 39. A compound according to claim 29 wherein

A is O;

A' is O;

R₆ is hydrogen;

R₇ is hydrogen; and

15 R₈ is hydrogen.

40. A compound according to claim 39 that is:

9-(3-bromo-4-methylphenyl)-5,9-dihydro-3H-furo[3,4-b]pyrano[4,3-e]pyridine-
1,8(4H,7H)-dione;

20 9-(3-iodo-4-methylphenyl)-5,9-dihydro-3H-furo[3,4-b]pyrano[4,3-e]pyridine-
1,8(4H,7H)-dione;

9-(4-fluoro-3-iodophenyl)-5,9-dihydro-3H-furo[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-
dione;

9-(3,4-dibromophenyl)-5,9-dihydro-3H-furo[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-
dione;

25 9-(3,4-dichlorophenyl)-5,9-dihydro-3H-furo[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-
dione;

9-[4-chloro-3-(trifluoromethyl)phenyl]-5,9-dihydro-3H-furo[3,4-b]pyrano[4,3-e]pyridine-
1,8(4H,7H)-dione;

30 9-(3-bromo-4-chlorophenyl)-5,9-dihydro-3H-furo[3,4-b]pyrano[4,3-e]pyridine-
1,8(4H,7H)-dione;

- 9-(4-methyl-3-nitrophenyl)-5,9-dihydro-3H-furo[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione;
- 9-[3-(2-furyl)-4-methylphenyl]-5,9-dihydro-3H-furo[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione;
- 5 9-[4-fluoro-3-(2-furyl)phenyl]-5,9-dihydro-3H-furo[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione;
- (9S)-9-(4-fluoro-3-iodophenyl)-5,9-dihydro-3H-furo[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione;
- (9R)-9-(4-fluoro-3-iodophenyl)-5,9-dihydro-3H-furo[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione;
- 10 (9R)-9-(3-bromo-4-methylphenyl)-5,9-dihydro-3H-furo[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione;
- (9S)-9-(3-bromo-4-methylphenyl)-5,9-dihydro-3H-furo[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione;
- 15 (+) 9-(3-iodo-4-methylphenyl)-5,9-dihydro-3H-furo[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione; or
- (-) 9-(3-iodo-4-methylphenyl)-5,9-dihydro-3H-furo[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione.
41. A compound according to claim 29 wherein
- 20 A is O;
- A' is O;
- R₆ is hydrogen;
- R₇ is hydrogen;
- R₈ is alkyl; and
- 25 R₉ is hydrogen or alkyl.
42. A compound according to claim 41 that is:
- (trans)-9-(3-bromo-4-fluorophenyl)-7-methyl-5,9-dihydro-3H-furo[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione;
- (cis)-9-(3-bromo-4-fluorophenyl)-7-methyl-5,9-dihydro-3H-furo[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione;
- 30 (trans)-9-(3-bromo-4-fluorophenyl)-5-methyl-5,9-dihydro-3H-furo[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione;

(cis)-9-(3-bromo-4-fluorophenyl)-5-methyl-5,9-dihydro-3H-furo[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione; or
9-(3-bromo-4-fluorophenyl)-7,7-dimethyl-5,9-dihydro-3H-furo[3,4-b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione.

- 5 43. A compound according to claim 29 wherein
 A is O;
 A' is O;
 R₆ is alkyl;
 R₇ is hydrogen or alkyl; and
10 R₈ is hydrogen.
44. A compound according to claim 43 that is:
 (trans)-9-(3-bromo-4-fluorophenyl)-3-methyl-5,9-dihydro-3H-furo[3,4-b]pyrano[4,3-
 e]pyridine-1,8(4H,7H)-dione;
 (cis)-9-(3-bromo-4-fluorophenyl)-3-methyl-5,9-dihydro-3H-furo[3,4-b]pyrano[4,3-
15 e]pyridine-1,8(4H,7H)-dione;
 (cis)-9-(3-bromo-4-fluorophenyl)-3-ethyl-5,9-dihydro-3H-furo[3,4-b]pyrano[4,3-
 e]pyridine-1,8(4H,7H)-dione;
 (trans)-9-(3-bromo-4-fluorophenyl)-3-ethyl-5,9-dihydro-3H-furo[3,4-b]pyrano[4,3-
 e]pyridine-1,8(4H,7H)-dione;
20 (cis)-9-(3-bromo-4-fluorophenyl)-3-propyl-5,9-dihydro-3H-furo[3,4-b]pyrano[4,3-
 e]pyridine-1,8(4H,7H)-dione;
 (trans)-9-(3-bromo-4-fluorophenyl)-3-propyl-5,9-dihydro-3H-furo[3,4-b]pyrano[4,3-
 e]pyridine-1,8(4H,7H)-dione;
 9-(3-bromo-4-fluorophenyl)-3,3-dimethyl-5,9-dihydro-3H-furo[3,4-b]pyrano[4,3-
25 e]pyridine-1,8(4H,7H)-dione;
 (+) (cis)-9-(3-bromo-4-fluorophenyl)-3-methyl-5,9-dihydro-3H-furo[3,4-
 b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione; or
 (-) (cis)-9-(3-bromo-4-fluorophenyl)-3-methyl-5,9-dihydro-3H-furo[3,4-
 b]pyrano[4,3-e]pyridine-1,8(4H,7H)-dione.

45. A compound according to claim 29 wherein
A is O; and
A' is S.
- 5 46. A compound according to claim 29 wherein
A is O; and
A' is CR₄R₅.
- 10 47. A compound according to claim 32 wherein
A is O;
A' is CR₄R₅;
R₄ is hydrogen;
R₅ is hydrogen;
R₆ is hydrogen;
R₇ is hydrogen; and
R₈ is hydrogen.
- 15 48. A compound according to claim 29 wherein
A is O;
A' is CR₄R₅;
R₄ is hydrogen;
R₅ is hydrogen;
20 R₆ is hydrogen;
R₇ is hydrogen;
R₈ is alkyl; and
R₉ is hydrogen or alkyl.
- 25 49. A compound according to claim 48 that is 5-(3-bromo-4-fluorophenyl)-3,3-dimethyl-
5,7,8,9-tetrahydrocyclopenta[b]pyrano[4,3-e]pyridine-4,6(1H,3H)-dione.
50. A compound according to claim 29 wherein
A is S; and
A' is NR₃.

51. A compound according to claim 29 wherein

A is S; and

A' is O.

52. A compound according to claim 29 wherein

A is S; and

A' is S.

53. A compound according to claim 29 wherein

A is S; and

A' is CR₄R₅.

54. A compound according to claim 29 wherein

A is S;

A' is CR₄R₅;

R₄ is hydrogen;

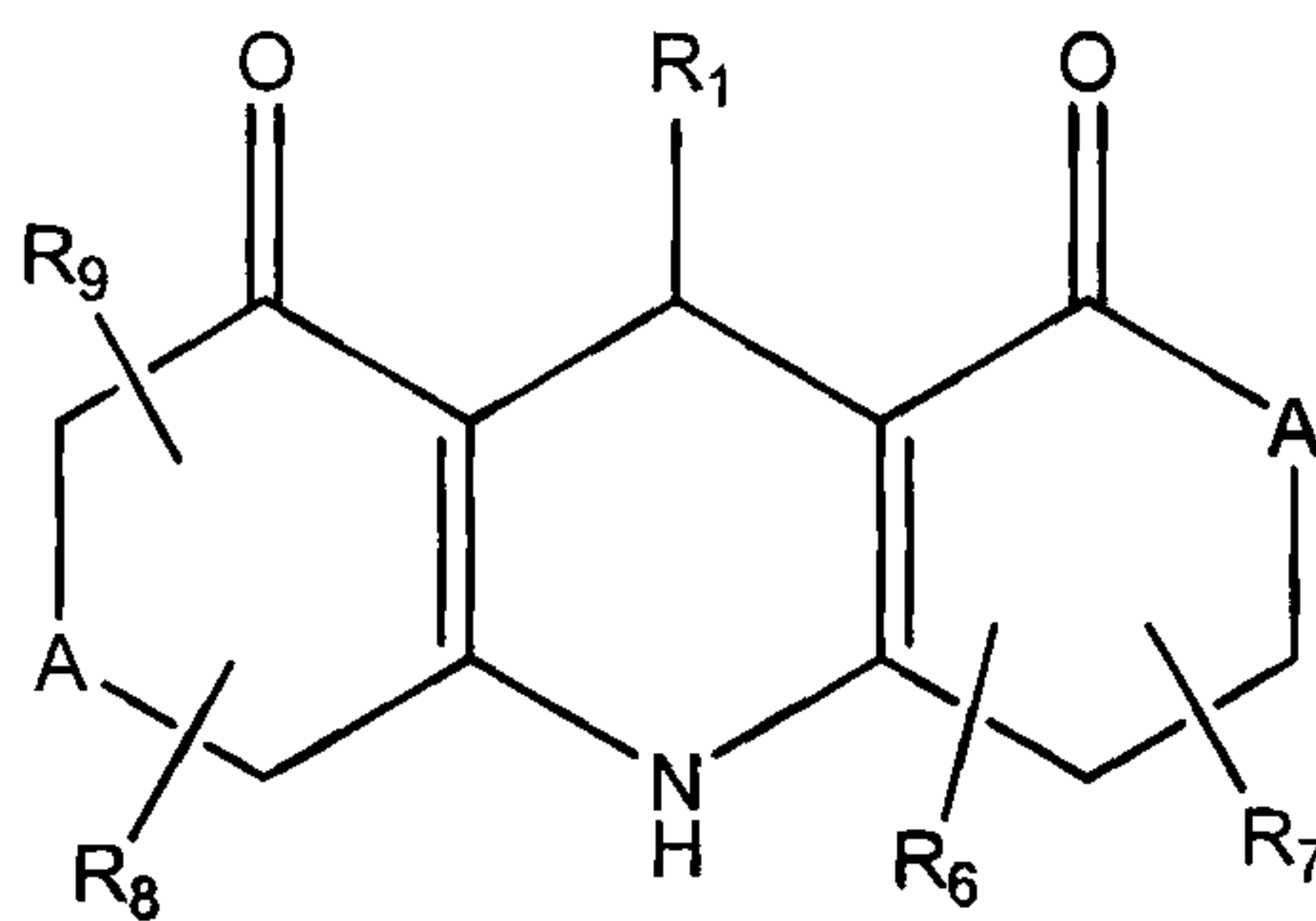
R₅ is hydrogen;

R₆ is hydrogen;

R₇ is hydrogen; and

R₈ is hydrogen.

55. A compound according to claim 1 of formula VI:



VI,

or a pharmaceutically acceptable salt thereof wherein,

A is NR₂, O, or S;

A' is NR₃, O, S or CR₄R₅;

R₁ is aryl or heterocycle;

R_2 and R_3 are independently hydrogen, alkoxyalkyl, alkyl, arylalkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, heterocycloalkyl, hydroxy, hydroxyalkyl, $-NZ_1Z_2$, or (NZ_1Z_2) alkyl wherein Z_1 and Z_2 are independently hydrogen, alkyl, alkylcarbonyl, aryl, arylalkyl, or formyl;

5 R_4 and R_5 are independently hydrogen or alkyl;

or

R_4 and R_5 together with the carbon atom to which they are attached form a 3-6 membered carbocyclic ring;

R_6 and R_7 are independently hydrogen or alkyl;

10 or

R_6 and R_7 together with the carbon atom to which they are attached form a 3-6 membered carbocyclic ring; and

15 R_8 and R_9 are independently hydrogen or alkyl with the proviso that R_8 and R_9 are not both hydrogen, and when one of R_8 and R_9 occupies the same position as R_2 , and R_2 and the one of R_8 and R_9 are alkyl, then the other of R_8 and R_9 is not hydrogen;

or

R_8 and R_9 together with the carbon atom to which they are attached form a 3-6 membered carbocyclic ring.

56. A compound according to claim 55 wherein

20 A is NR_2 ; and

A' is NR_3 .

57. A compound according to claim 55 wherein

A is NR_2 ; and

A' is O.

25 58. A compound according to claim 55 wherein

A is NR_2 ; and

A' is S.

59. A compound according to claim 55 wherein

A is NR_2 ; and

30 A' is CR_4R_5 .

60. A compound according to claim 55 wherein
A is NR_2 ;
A' is CR_4R_5 ;
R₄ is hydrogen;
5 R₅ is hydrogen;
R₆ is hydrogen;
R₇ is hydrogen; and
R₈ is hydrogen.
61. A compound according to claim 55 wherein
10 A is O; and
A' is NR_3 .
62. A compound according to claim 55 wherein
A is O;
A' is NR_3 ;
15 R₆ is hydrogen;
R₇ is hydrogen; and
R₈ is hydrogen.
63. A compound according to claim 55 wherein
A is O; and
20 A' is O.
64. A compound according to claim 55 wherein
A is O; and
A' is S.
65. A compound according to claim 55 wherein
25 A is O; and
A' is CR_4R_5 .

66. A compound according to claim 55 wherein
A is O;
A' is CR₄R₅;
R₆ is hydrogen;
5 R₇ is hydrogen; and
R₈ is hydrogen.
67. A compound according to claim 55 wherein
A is O;
A' is CR₄R₅;
10 R₄ is hydrogen;
R₅ is hydrogen;
R₆ is hydrogen;
R₇ is hydrogen; and
R₈ is hydrogen.
- 15 68. A compound according to claim 55 wherein
A is O;
A' is CR₄R₅;
R₄ is methyl;
R₅ is methyl;
20 R₆ is hydrogen;
R₇ is hydrogen; and
R₈ is hydrogen.
69. A compound according to claim 55 wherein
A is S; and
25 A' is NR₃.
70. A compound according to claim 55 wherein
A is S; and
A' is O.

71. A compound according to claim 55 wherein

A is S; and

A' is S.

72. A compound according to claim 55 wherein

A is S; and

A' is CR₄R₅.

73. A compound according to claim 5563 wherein

A is S;

A' is CR₄R₅;

R₄ is hydrogen;

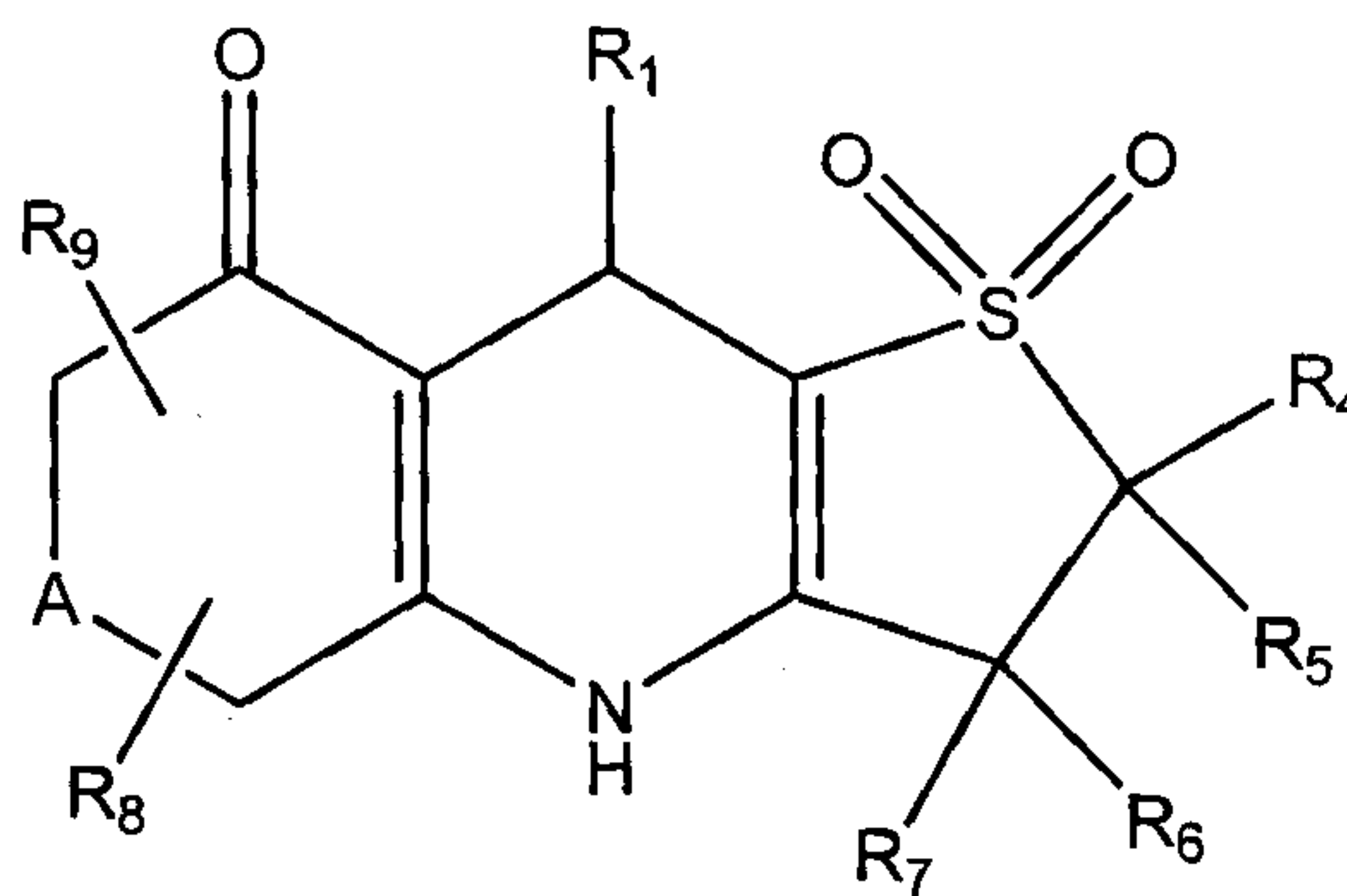
R₅ is hydrogen;

R₆ is hydrogen;

R₇ is hydrogen; and

R₈ is hydrogen.

74. A compound according to claim 1 of formula VII:



VII,

or a pharmaceutically acceptable salt thereof wherein,

A is NR₂, O, or S;

R₁ is aryl or heterocycle;

R₂ is hydrogen, alkoxyalkyl, alkyl, arylalkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, heterocycloalkyl, hydroxy, hydroxyalkyl, -NZ₁Z₂, or (NZ₁Z₂)alkyl wherein Z₁ and Z₂ are independently hydrogen, alkyl, alkylcarbonyl, aryl, arylalkyl, and formyl;

R₄ and R₅ are independently hydrogen or alkyl;

or

R₄ and R₅ together with the carbon atom to which they are attached form a 3-6 membered carbocyclic ring;

R₆ and R₇ are independently hydrogen or alkyl;

or

5 R₆ and R₇ together with the carbon atom to which they are attached form a 3-6 membered carbocyclic ring.

R₈ and R₉ are independently hydrogen or alkyl with the proviso that R₈ and R₉ are not both hydrogen, and when one of R₈ and R₉ occupies the same position as R₂, and R₂ and the one of R₈ and R₉ are alkyl, then the other of R₈ and R₉ is not hydrogen;

10 or

R₈ and R₉ together with the carbon atom to which they are attached form a 3-6 membered carbocyclic ring.

75. A compound according to claim 74 wherein A is NR₂.

76. A compound according to claim 74 wherein

15 A is NR₂;

R₄ is hydrogen;

R₅ is hydrogen;

R₆ is hydrogen;

R₇ is hydrogen; and

20 R₈ is hydrogen.

77. A compound according to claim 74 wherein A is O.

78. A compound according to claim 74 wherein

A is O;

R₄ is hydrogen;

25 R₅ is hydrogen;

R₆ is hydrogen;

R₇ is hydrogen; and

R₈ is hydrogen.

79. A compound according to claim 78 that is:

of 9-(3-bromo-4-fluorophenyl)-2,3,5,9-tetrahydro-4H-pyrano[3,4-b]thieno[2,3-e]pyridin-8(7H)-one 1,1-dioxide;

(+)-9-(3-bromo-4-fluorophenyl)-2,3,5,9-tetrahydro-4H-pyrano[3,4-b]thieno[2,3-e]pyridin-8(7H)-one 1,1-dioxide;

(-)-9-(3-bromo-4-fluorophenyl)-2,3,5,9-tetrahydro-4H-pyrano[3,4-b]thieno[2,3-e]pyridin-8(7H)-one 1,1-dioxide;

9-(3-cyanophenyl)-2,3,5,9-tetrahydro-4H-pyrano[3,4-b]thieno[2,3-e]pyridin-8(7H)-one 1,1-dioxide;

(+) 9-(3-cyanophenyl)-2,3,5,9-tetrahydro-4H-pyrano[3,4-b]thieno[2,3-e]pyridin-8(7H)-one 1,1-dioxide;

(-) 9-(3-cyanophenyl)-2,3,5,9-tetrahydro-4H-pyrano[3,4-b]thieno[2,3-e]pyridin-8(7H)-one 1,1-dioxide;

9-(4-chloro-3-nitrophenyl)-2,3,5,9-tetrahydro-4H-pyrano[3,4-b]thieno[2,3-e]pyridin-8(7H)-one 1,1-dioxide;

(+)-9-(4-chloro-3-nitrophenyl)-2,3,5,9-tetrahydro-4H-pyrano[3,4-b]thieno[2,3-e]pyridin-8(7H)-one 1,1-dioxide; or

(-)-9-(4-chloro-3-nitrophenyl)-2,3,5,9-tetrahydro-4H-pyrano[3,4-b]thieno[2,3-e]pyridin-8(7H)-one 1,1-dioxide. .

80. A compound according to claim 74 wherein

A is O;

R₄ is hydrogen;

R₅ is hydrogen;

R₆ is hydrogen;

R₇ is hydrogen;

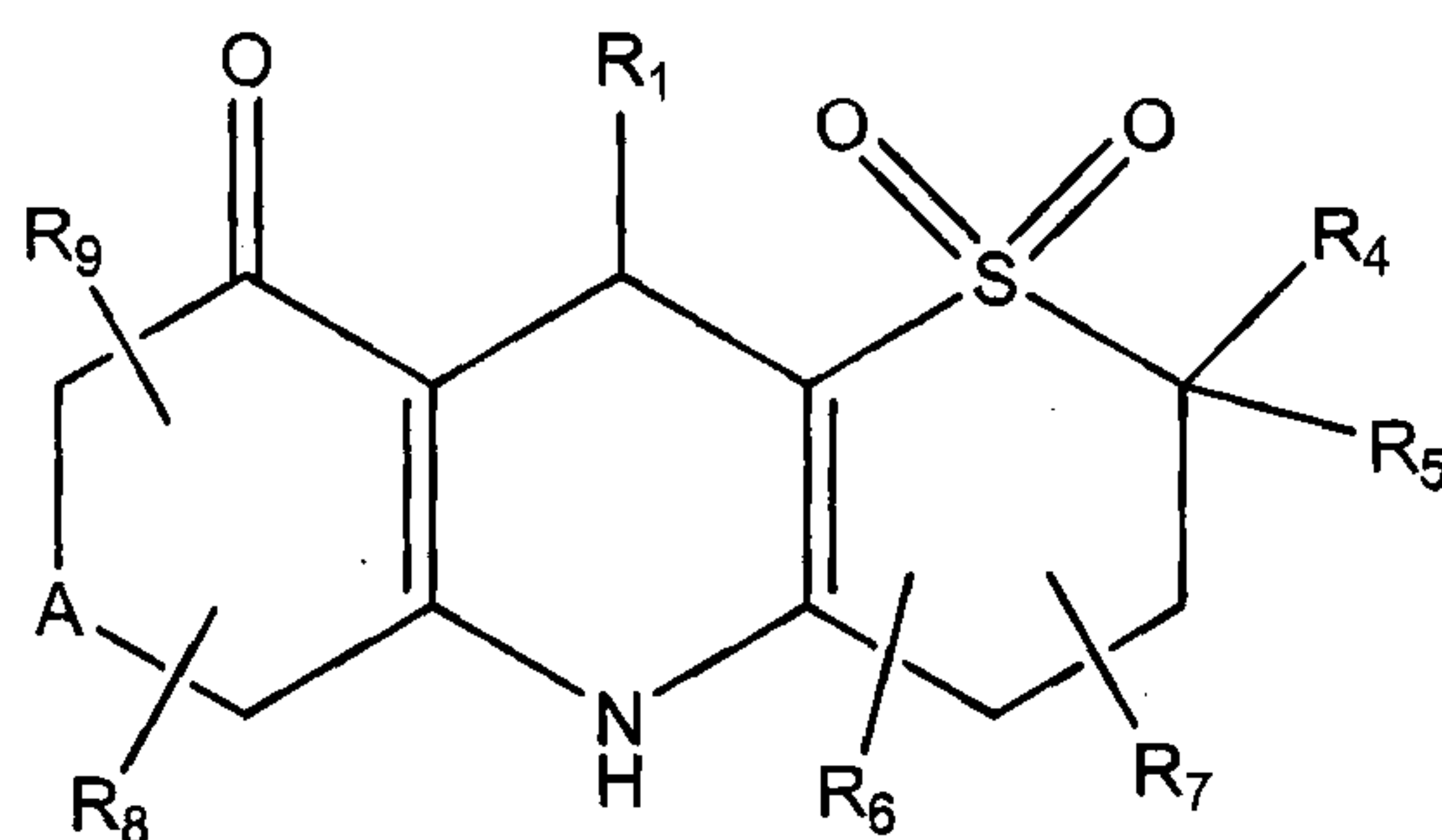
R₈ is alkyl; and

R₉ is hydrogen or alkyl.

81. A compound according to claim 80 that is 9-(3-bromo-4-fluorophenyl)-7,7-dimethyl-2,3,5,9-tetrahydro-4H-pyrano[3,4-b]thieno[2,3-e]pyridin-8(7H)-one 1,1-dioxide.

82. A compound according to claim 74 wherein A is S.

83. A compound according to claim 1 of formula VIII:



VIII,

or a pharmaceutically acceptable salt thereof wherein,

A is NR_2 , O, or S;

R_1 is aryl or heterocycle;

R_2 is hydrogen, alkoxyalkyl, alkyl, arylalkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, heterocycloalkyl, hydroxy, hydroxyalkyl, $-\text{NZ}_1\text{Z}_2$, or $(\text{NZ}_1\text{Z}_2)\text{alkyl}$ wherein Z_1 and Z_2 are independently hydrogen, alkyl, alkylcarbonyl, aryl, arylalkyl, or formyl;

R_4 and R_5 are independently hydrogen and alkyl;

or

R_4 and R_5 together with the carbon atom to which they are attached form a 3-6 membered carbocyclic ring;

R_6 and R_7 are independently hydrogen or alkyl;

or

R_6 and R_7 together with the carbon atom to which they are attached form a 3-6 membered carbocyclic ring; and

R_8 and R_9 are independently hydrogen or alkyl with the proviso that R_8 and R_9 are not both hydrogen, and when one of R_8 and R_9 occupies the same position as R_2 , and R_2 and the one of R_8 and R_9 are alkyl, then the other of R_8 and R_9 is not hydrogen;

or

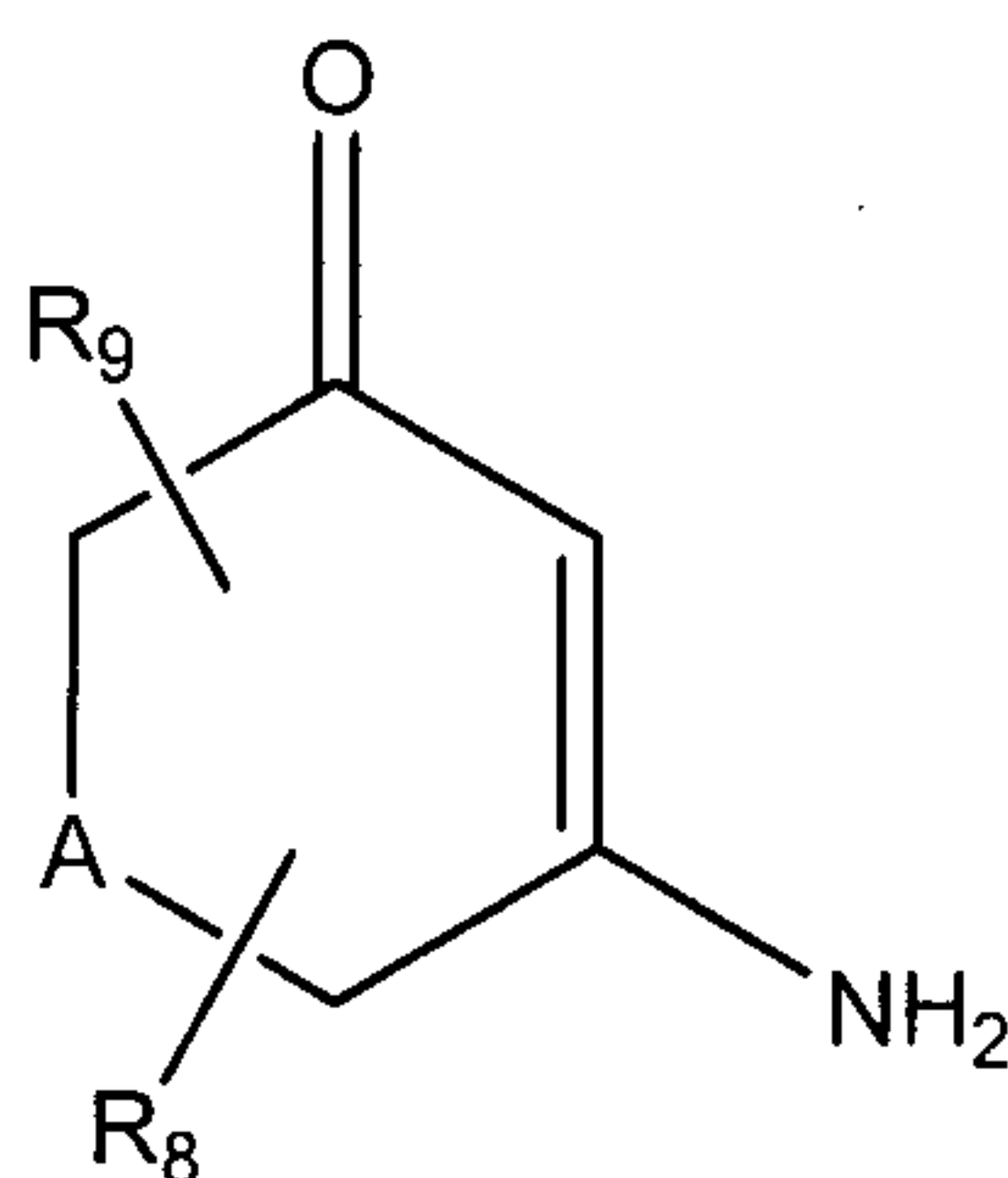
R_8 and R_9 together with the carbon atom to which they are attached form a 3-6 membered carbocyclic ring;

84. A compound according to claim 83 wherein A is NR_2 .

85. A compound according to claim 83 wherein
A is NR_2 ;
 R_4 is hydrogen;
 R_5 is hydrogen;
5 R_6 is hydrogen;
 R_7 is hydrogen; and
 R_8 is hydrogen.
86. A compound according to claim 85 that is 10-(3-bromo-4-fluorophenyl)-3,4,6,7,8,10-
heahydro-2H-thiopyrano[3,2-b][1,7]naphthyridin-9(5H)-one 1,1-dioxide.
- 10 87. A compound according to claim 83 wherein A is O.
88. A compound according to claim 83 wherein
A is O;
 R_4 is hydrogen;
 R_5 is hydrogen;
15 R_6 is hydrogen;
 R_7 is hydrogen;
 R_8 is hydrogen; and
 R_9 is hydrogen.
89. A compound according to claim 83 wherein A is S.
- 20 90. A pharmaceutical composition comprising a therapeutically effective amount of a
compound of claim 1 in combination with a pharmaceutically acceptable carrier.
91. Use of a compound of claim 1 in the treatment of asthma, epilepsy, Raynaud's syndrome,
migraine, pain, eating disorders, functional bowel disorders, neurodegeneration or stroke.
92. Use of a compound of claim 1 in the treatment of urinary incontinence.
- 25 93. Use of a compound of claim 1 in the treatment of male erectile dysfunction.
94. Use of a compound of claim 1 in the treatment of female anorgasmia, clitoral erectile
insufficiency, vaginal engorgement, dyspareunia, or vaginismus.

95. Use of a compound of claim 1 in the manufacture of a medicament for use in the treatment of asthma, epilepsy, Raynaud's syndrome, migraine, pain, eating disorders, functional bowel disorders, neurodegeneration or stroke.
96. Use of a compound of claim 1 in the manufacture of a medicament for use in the treatment of urinary incontinence.
97. Use of a compound of claim 1 in the manufacture of a medicament for use in the treatment of male erectile dysfunction.
98. Use of a compound of claim 1 in the manufacture of a medicament for use in the treatment of female anorgasmia, clitoral erectile insufficiency, vaginal engorgement, dyspareunia, or vaginismus.

99. A compound of formula IX:



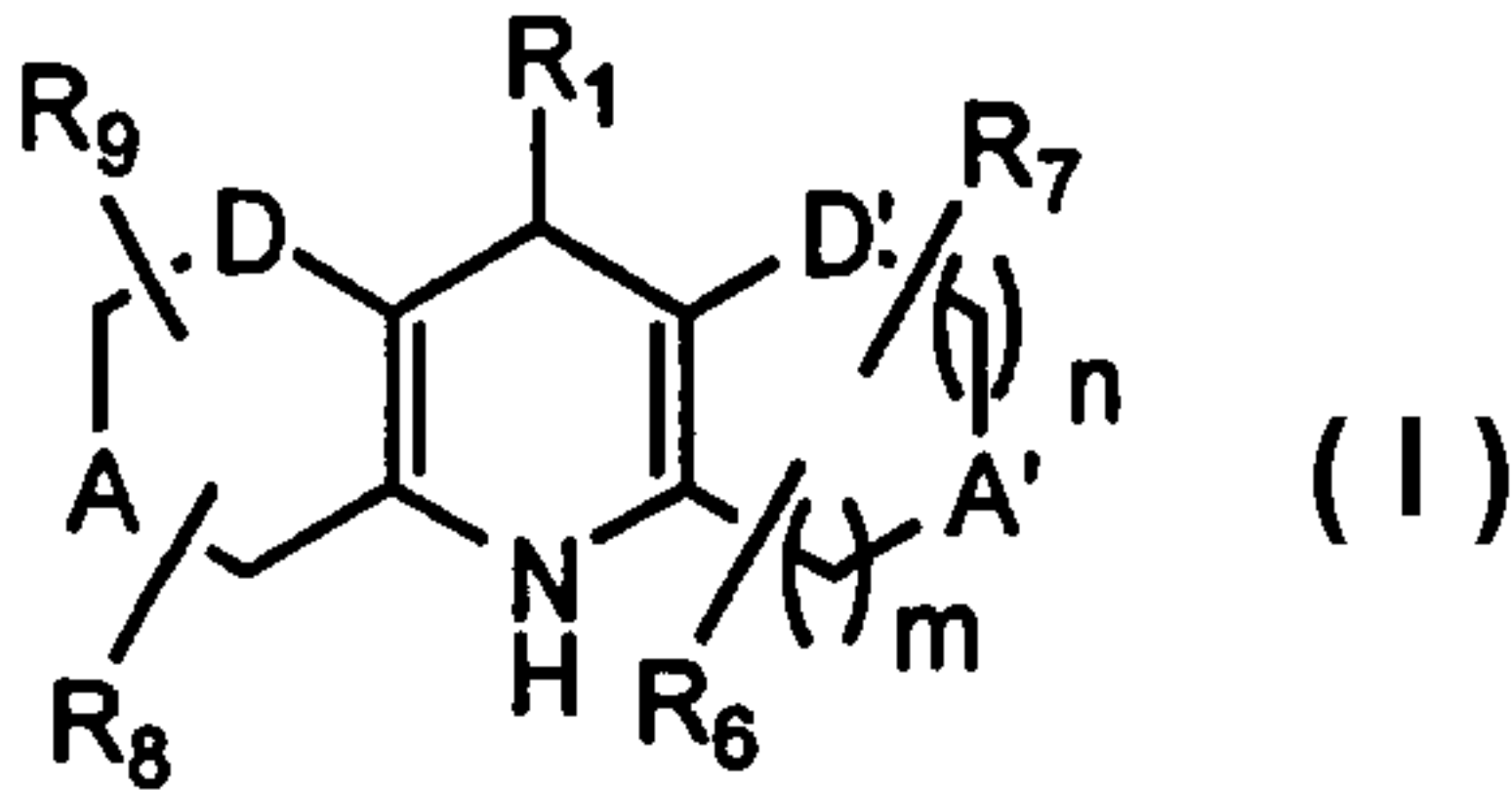
IX,

wherein,

A is O, S, or NR₂ wherein R₂ is hydrogen, alkoxyalkyl, alkyl, arylalkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, heterocycloalkyl, hydroxy, hydroxyalkyl, -NZ₁Z₂, or (NZ₁Z₂)alkyl wherein Z₁ and Z₂ are independently hydrogen, alkyl, alkylcarbonyl, aryl, arylalkyl, or formyl;

with the proviso that R₂ is other than benzyl; and

R₈ and R₉ are hydrogen or alkyl with the proviso that R₈ and R₉ are not both hydrogen, and when one of R₈ and R₉ occupies the same position as R₂, and R₂ and the one of R₈ and R₉ are alkyl, then the other of R₈ and R₉ is not hydrogen, or R₈ and R₉ together with the carbon atom to which they are attached form a 3-6 membered carbocyclic ring.



(73) Propriétaires(suite)/Owners(continued):ABBOTT LABORATORIES, US

(74) Agent: TORYS LLP