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(71) Demandeur/Applicant:
MERCK & CO., INC., US

(72) Inventeur/Inventor:
WANG, JIABING, US

(74) Agent: OGILVY RENAULT

(54) Titre : ANTAGONISTES RECEPTEURS ALPHA V D'INTEGRINE
(54) Title: ALPHA V INTEGRIN RECEPTOR ANTAGONISTS

(57) **Abrégé/Abstract:**

The present invention relates to novel chain-fluorinated alkanolic acid derivatives thereof, their synthesis, and their use as α_v integrin receptor antagonists. More particularly, the compounds of the present invention are antagonists of the integrin receptors $\alpha_v\beta_3$ and/or $\alpha_v\beta_5$ and are useful for inhibiting bone resorption, treating and preventing osteoporosis, and inhibiting vascular restenosis, diabetic retinopathy, macular degeneration, angiogenesis, atherosclerosis, inflammation, inflammatory arthritis, viral disease, cancer, and metastatic tumor growth.



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(71) Applicant (for all designated States except US): **MERCK
& CO., INC.** [US/US]; 126 East Lincoln Avenue, Rahway,
NJ 07065-0907 (US).

(72) Inventor; and

(75) Inventor/Applicant (for US only): **WANG, Jiabing**
[CN/US]; 126 East Lincoln Avenue, Rahway, NJ
07065-0907 (US).

(74) Common Representative: **MERCK & CO., INC.**; 126
East Lincoln Avenue, Rahway, NJ 07065-0907 (US).

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(54) Title: ALPHA V INTEGRIN RECEPTOR ANTAGONISTS

(57) **Abstract:** The present invention relates to novel chain-fluorinated alkanolic acid derivatives thereof, their synthesis, and their use as α_v integrin receptor antagonists. More particularly, the compounds of the present invention are antagonists of the integrin receptors $\alpha_v\beta_3$ and/or $\alpha_v\beta_5$ and are useful for inhibiting bone resorption, treating and preventing osteoporosis, and inhibiting vascular restenosis, diabetic retinopathy, macular degeneration, angiogenesis, atherosclerosis, inflammation, inflammatory arthritis, viral disease, cancer, and metastatic tumor growth.



WO 02/07730 A1

TITLE OF THE INVENTION

ALPHA V INTEGRIN RECEPTOR ANTAGONISTS

FIELD OF THE INVENTION

5 The present invention relates to novel chain-fluorinated alkanolic acid derivatives, their synthesis, and their use as α_v integrin receptor antagonists. More particularly, the compounds of the present invention are antagonists of the integrin receptors $\alpha_v\beta_3$, $\alpha_v\beta_5$, and α_v integrin receptors associated with other β -subunits, and are useful for inhibiting bone resorption, treating and preventing osteoporosis, and
10 inhibiting vascular restenosis, diabetic retinopathy, macular degeneration, angiogenesis, atherosclerosis, inflammation, inflammatory arthritis, viral disease, cancer, and metastatic tumor growth.

BACKGROUND OF THE INVENTION

15 It is believed that a wide variety of disease states and conditions can be mediated by acting on integrin receptors and that integrin receptor antagonists represent a useful class of drugs. Integrin receptors are heterodimeric transmembrane receptors through which cells attach and communicate with extracellular matrices and other cells. (See S.B. Rodan and G.A. Rodan, "Integrin Function In Osteoclasts,"
20 *Journal of Endocrinology*, 154: S47- S56 (1997), which is incorporated by reference herein in its entirety).

 In one aspect of the present invention, the compounds herein are useful for inhibiting bone resorption. Bone resorption is mediated by the action of cells known as osteoclasts. Osteoclasts are large multinucleated cells of up to about 400
25 mm in diameter that resorb mineralized tissue, chiefly calcium carbonate and calcium phosphate, in vertebrates. Osteoclasts are actively motile cells that migrate along the surface of bone, and can bind to bone, secrete necessary acids and proteases, thereby causing the actual resorption of mineralized tissue from the bone. More specifically, osteoclasts are believed to exist in at least two physiological states, namely, the
30 secretory state and the migratory or motile state. In the secretory state, osteoclasts are flat, attach to the bone matrix via a tight attachment zone (sealing zone), become highly polarized, form a ruffled border, and secrete lysosomal enzymes and protons to resorb bone. The adhesion of osteoclasts to bone surfaces is an important initial step in bone resorption. In the migratory or motile state, the osteoclasts migrate across
35 bone matrix and do not take part in resorption until they again attach to bone.

Integrins are involved in osteoclast attachment, activation and migration. The most abundant integrin on osteoclasts, e.g., on rat, chicken, mouse and human osteoclasts, is an integrin receptor known as $\alpha_v\beta_3$, which is thought to interact in bone with matrix proteins that contain the RGD sequence. Antibodies to $\alpha_v\beta_3$ block bone resorption *in vitro* indicating that this integrin plays a key role in the resorptive process. There is increasing evidence to suggest that $\alpha_v\beta_3$ ligands can be used effectively to inhibit osteoclast mediated bone resorption *in vivo* in mammals.

The current major bone diseases of public concern are osteoporosis, hypercalcemia of malignancy, osteopenia due to bone metastases, periodontal disease, hyperparathyroidism, periarticular erosions in rheumatoid arthritis, Paget's disease, immobilization-induced osteopenia, and glucocorticoid-induced osteoporosis. All of these conditions are characterized by bone loss, resulting from an imbalance between bone resorption, i.e. breakdown, and bone formation, which continues throughout life at the rate of about 14% per year on the average. However, the rate of bone turnover differs from site to site; for example, it is higher in the trabecular bone of the vertebrae and the alveolar bone in the jaws than in the cortices of the long bones. The potential for bone loss is directly related to turnover and can amount to over 5% per year in vertebrae immediately following menopause, a condition which leads to increased fracture risk.

In the United States, there are currently about 20 million people with detectable fractures of the vertebrae due to osteoporosis. In addition, there are about 250,000 hip fractures per year attributed to osteoporosis. This clinical situation is associated with a 12% mortality rate within the first two years, while 30% of the patients require nursing home care after the fracture.

Individuals suffering from all the conditions listed above would benefit from treatment with agents which inhibit bone resorption.

Additionally, $\alpha_v\beta_3$ ligands have been found to be useful in treating and/or inhibiting restenosis (i.e. recurrence of stenosis after corrective surgery on the heart valve), atherosclerosis, diabetic retinopathy, macular degeneration, and angiogenesis (i.e. formation of new blood vessels), and inhibiting viral disease. Moreover, it has been postulated that the growth of tumors depends on an adequate blood supply, which in turn is dependent on the growth of new vessels into the tumor; thus, inhibition of angiogenesis can cause tumor regression in animal models (See Harrison's Principles of Internal Medicine, 12th ed., 1991, which is incorporated by reference herein in its entirety). Therefore, $\alpha_v\beta_3$ antagonists which inhibit

angiogenesis can be useful in the treatment of cancer by inhibiting tumor growth (See, e.g., Brooks et al., Cell, 79:1157-1164 (1994), which is incorporated by reference herein in its entirety).

5 Evidence has also been presented suggesting that angiogenesis is a central factor in the initiation and persistence of arthritic disease, and that the vascular integrin $\alpha v \beta 3$ may be a preferred target in inflammatory arthritis. Therefore, $\alpha v \beta 3$ antagonists which inhibit angiogenesis may represent a novel therapeutic approach to the treatment of arthritic disease, such as rheumatoid arthritis (see C.M. Storgard, et al., "Decreased angiogenesis and arthritic disease in rabbits treated with an $\alpha v \beta 3$ antagonist," J. Clin. Invest., 103: 47-54 (1999), which is incorporated by reference
10 herein in its entirety).

Moreover, compounds of this invention can also inhibit neovascularization by acting as antagonists of the integrin receptor, $\alpha v \beta 5$. A monoclonal antibody for $\alpha v \beta 5$ has been shown to inhibit VEGF-induced angiogenesis
15 in rabbit cornea and the chick chorioallantoic membrane model (See M.C. Friedlander, et al., Science 270: 1500-1502 (1995), which is incorporated by reference herein in its entirety). Thus, compounds that antagonize $\alpha v \beta 5$ are useful for treating and preventing macular degeneration, diabetic retinopathy, viral disease, cancer, and metastatic tumor growth.

20 Additionally, compounds of the instant invention can inhibit angiogenesis and inflammation by acting as antagonists of αv integrin receptors associated with other β subunits, such as $\alpha v \beta 6$ and $\alpha v \beta 8$ (See, for example, Melpo Christofidou-Solomidou, et al., "Expression and Function of Endothelial Cell αv Integrin Receptors in Wound-Induced Human Angiogenesis in Human Skin/SCID
25 Mice Chimeras," American Journal of Pathology, 151: 975-83 (1997) and Xiao-Zhu Huang, et al., "Inactivation of the Integrin $\beta 6$ Subunit Gene Reveals a Role of Epithelial Integrins in Regulating Inflammation in the Lungs and Skin," Journal of Cell Biology, 133: 921-28 (1996), which are incorporated by reference herein in their entirety).

30 In addition, certain compounds of this invention antagonize both the $\alpha v \beta 3$ and $\alpha v \beta 5$ receptors. These compounds, referred to as "dual $\alpha v \beta 3 / \alpha v \beta 5$ antagonists," are useful for inhibiting bone resorption, treating and preventing osteoporosis, and inhibiting vascular restenosis, diabetic retinopathy, macular degeneration, angiogenesis, atherosclerosis, inflammation, cancer, and metastatic
35 tumor growth.

Peptidyl as well as peptidomimetic antagonists of the $\alpha v \beta 3$ integrin receptor have been described both in the scientific and patent literature. For example, reference is made to W.J. Hoekstra and B.L. Poulter, Curr. Med. Chem. 5: 195-204 (1998) and references cited therein; WO 95/32710; WO 95/37655; WO 97/01540; 5 WO 97/37655; WO 98/08840; WO 98/18460; WO 98/18461; WO 98/25892; WO 98/31359; WO 98/30542; WO 99/15506; WO 99/15507; WO 00/03973; EP 853084; EP 854140; EP 854145; US Patent Nos. 5,204,350; 5,217,994; 5,639,754; 5,741,796; 5,780,426; 5,929,120; 5,952,341; 6,017,925; and 6,048,861. Evidence of the ability of $\alpha v \beta 3$ integrin receptor antagonists to prevent bone resorption *in vitro* and *in vivo* 10 has been presented (see V.W. Engleman et al., "A Peptidomimetic Antagonist of the $\alpha v \beta 3$ Integrin Inhibits Bone Resorption *In Vitro* and Prevents Osteoporosis *In Vivo*," J. Clin. Invest. 99: 2284-2292 (1997); S.B. Rodan et al., "A High Affinity Non-Peptide $\alpha v \beta 3$ Ligand Inhibits Osteoclast Activity *In Vitro* and *In Vivo*," J. Bone Miner. Res. 11: S289 (1996); J.F. Gourvest et al., "Prevention of OVX-Induced Bone 15 Loss With a Non-peptidic Ligand of the $\alpha v \beta 3$ Vitronectin Receptor," Bone 23: S612 (1998); M.W. Lark et al., "An Orally Active Vitronectin Receptor $\alpha v \beta 3$ Antagonist Prevents Bone Resorption *In Vitro* and *In Vivo* in the Ovariectomized Rat," Bone 23: S219 (1998)).

The $\alpha v \beta 3$ integrin receptor recognizes the Arg-Gly-Asp (RGD) 20 tripeptide sequence in its cognate matrix and cell surface glycoproteins (see J. Samanen, et al., "Vascular Indications for Integrin αv Antagonists," Curr. Pharmaceut. Design 3: 545-584 (1997)). A benzazepine nucleus has been employed among others by Genentech and SmithKline Beecham as a conformationally constrained Gly-Asp mimetic to elaborate nonpeptide $\alpha v \beta 3$ integrin receptor 25 antagonists substituted at the N-terminus with heterocyclic arginine mimetics (see R.M. Keenan et al., "Discovery of Potent Nonpeptide Vitronectin Receptor ($\alpha v \beta 3$) Antagonists," J. Med. Chem. 40: 2289-2292 (1997); R.M. Keenan et al., "Benzimidazole Derivatives As Arginine Mimetics in 1,4-Benzodiazepine Nonpeptide Vitronectin Receptor ($\alpha v \beta 3$) Antagonists," Bioorg. Med. Chem. Lett. 8: 30 3165-3170 (1998); and R.M. Keenan et al., "Discovery of an Imidazopyridine-Containing 1,4-Benzodiazepine Nonpeptide Vitronectin Receptor ($\alpha v \beta 3$) Antagonist With Efficacy in a Restenosis Model," Bioorg. Med. Chem. Lett. 8: 3171-3176 (1998). Patents assigned to SmithKline Beecham that disclose such benzazepine, as well as related benzodiazepine and benzocycloheptene, $\alpha v \beta 3$ integrin receptor

antagonists include WO 96/00574, WO 96/00730, WO 96/06087, WO 96/26190, WO 97/24119, WO 97/24122, WO 97/24124, WO 98/14192, WO 98/15278, WO 99/05107, WO 99/06049, WO 99/15170, WO 99/15178, and WO 99/15506, and to Genentech include WO 97/34865. The dibenzocycloheptene, as well as
5 dibenzoxazepine, nucleus has also been employed as a Gly-Asp mimetic to afford $\alpha_v\beta_3$ antagonists (see WO 97/01540, WO 98/30542, WO 99/11626, WO 99/15508, U.S. Patent Nos. 6,008,213, and 6,069,158, all assigned to SmithKline Beecham).

Other integrin receptor antagonists incorporating backbone conformational ring constraints have been described in the patent literature.

10 Published patent applications or issued patents disclosing antagonists having a phenyl constraint include WO 98/00395, WO 99/32457, WO 99/37621, WO 99/44994, WO 99/45927, WO 99/52872, WO 99/52879, WO 99/52896, WO 00/06169, EP 0 820,988, EP 0 820,991, U.S. Patent Nos. 5,741,796; 5,773,644; 5,773,646; 5,843,906; 5,852,210; 5,929,120; 5,952,381; 6,028,223; and 6,040,311. Published patent
15 applications or issued patents disclosing antagonists having a monocyclic ring constraint include WO 99/26945, WO 99/30709, WO 99/30713, WO 99/31099, WO 99/59992, WO 00/00486, WO 00/09503, EP 0 796,855, EP 0 928,790, EP 0 928,793, U.S. Patent Nos. 5,710,159; 5,723,480; 5,981,546; 6,017,926; and 6,066,648. Published patent applications or issued patents disclosing antagonists having a
20 bicyclic ring constraint include WO 98/23608, WO 98/35949, WO 99/33798, EP 0 853,084, U.S. Patent Nos. 5,760,028; 5,919,792; and 5,925,655.

However, there still remains a need for small-molecule, non-peptidic selective α_v integrin receptor antagonists that display improved potency, pharmacodynamic, and pharmacokinetic properties, such as oral bioavailability and
25 duration of action, over already described compounds. Such compounds would provide an enhancement in the treatment, prevention, or suppression of various pathologies enumerated above that are mediated by α_v integrin receptor binding and cell adhesion and activation.

In US Patent No. 6,048,861, we disclosed a series of 3-substituted
30 straight-chain alkanoic acid derivatives which are potent $\alpha_v\beta_3$ integrin receptor antagonists. In the present invention, we describe novel chain-fluorinated alkanoic acid derivatives, which are substituted at the N-terminus with an optionally substituted heterocycle and at C-3 with an optionally substituted aryl group. The compounds of the present invention exhibit improved *in vivo* pharmacokinetic and/or
35 pharmacodynamic properties over the prior art compounds.

It is therefore an object of the present invention to provide novel chain-fluorinated alkanoic acid derivatives which are useful as α_v integrin receptor antagonists.

5 It is another object of the present invention to provide novel chain-fluorinated alkanoic acid derivatives which are useful as $\alpha_v\beta_3$ receptor antagonists.

It is another object of the present invention to provide novel chain-fluorinated alkanoic acid derivatives which are useful as $\alpha_v\beta_5$ receptor antagonists.

10 It is another object of the present invention to provide novel chain-fluorinated alkanoic acid derivatives which are useful as dual $\alpha_v\beta_3/\alpha_v\beta_5$ receptor antagonists.

It is another object of the present invention to provide pharmaceutical compositions comprising α_v integrin receptor antagonists.

It is another object of the present invention to provide methods for making the pharmaceutical compositions of the present invention.

15 It is another object of the present invention to provide methods for eliciting an α_v integrin receptor antagonizing effect in a mammal in need thereof by administering the compounds and pharmaceutical compositions of the present invention.

20 It is another object of the present invention to provide compounds and pharmaceutical compositions useful for inhibiting bone resorption, restenosis, atherosclerosis, inflammation, inflammatory arthritis, viral disease, diabetic retinopathy, macular degeneration, angiogenesis, cancer, and metastatic tumor growth.

It is another object of the present invention to provide compounds and pharmaceutical compositions useful for treating osteoporosis.

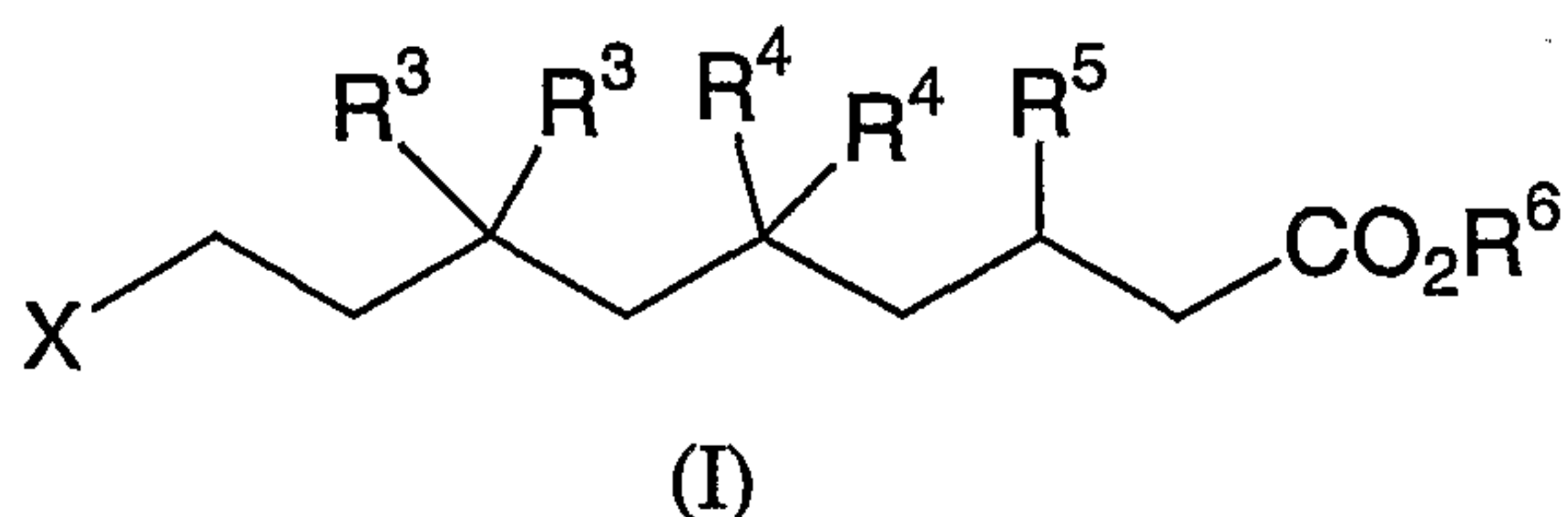
25 It is another object of the present invention to provide methods for inhibiting bone resorption, restenosis, atherosclerosis, inflammation, inflammatory arthritis, viral disease, diabetic retinopathy, macular degeneration, angiogenesis, cancer, and metastatic tumor growth.

30 It is another object of the present invention to provide methods for treating osteoporosis.

These and other objects will become readily apparent from the detailed description which follows.

SUMMARY OF THE INVENTION

The present invention relates to novel chain-fluorinated alkanoic acid derivatives represented by structural formula (I), or a pharmaceutically acceptable salt thereof, which are useful as α_v integrin receptor antagonists.



The present invention also relates to pharmaceutical compositions comprising the compounds of the present invention and a pharmaceutically acceptable carrier.

The present invention also relates to methods for making the pharmaceutical compositions of the present invention.

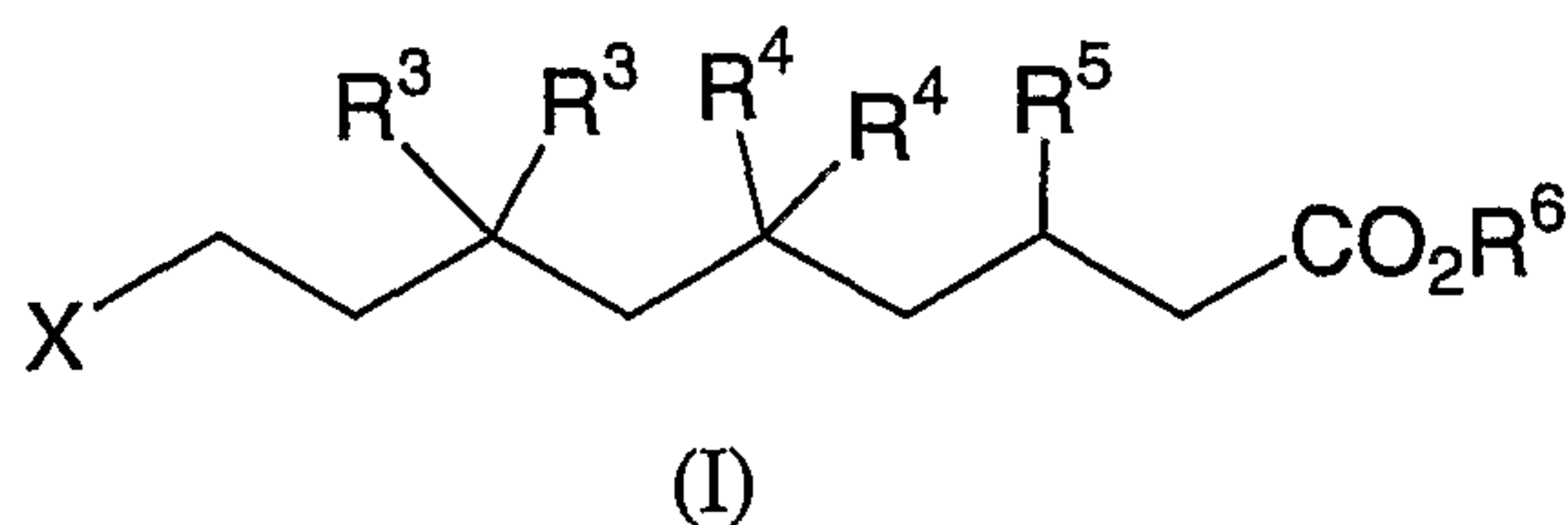
The present invention also relates to methods for eliciting an α_v integrin receptor antagonizing effect in a mammal in need thereof by administering the compounds and pharmaceutical compositions of the present invention.

The present invention also relates to methods for inhibiting bone resorption, restenosis, atherosclerosis, inflammation, inflammatory arthritis, viral disease, diabetic retinopathy, macular degeneration, angiogenesis, cancer, and metastatic tumor growth by administering the compounds and pharmaceutical compositions of the present invention.

The present invention also relates to methods for treating osteoporosis by administering the compounds and pharmaceutical compositions of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

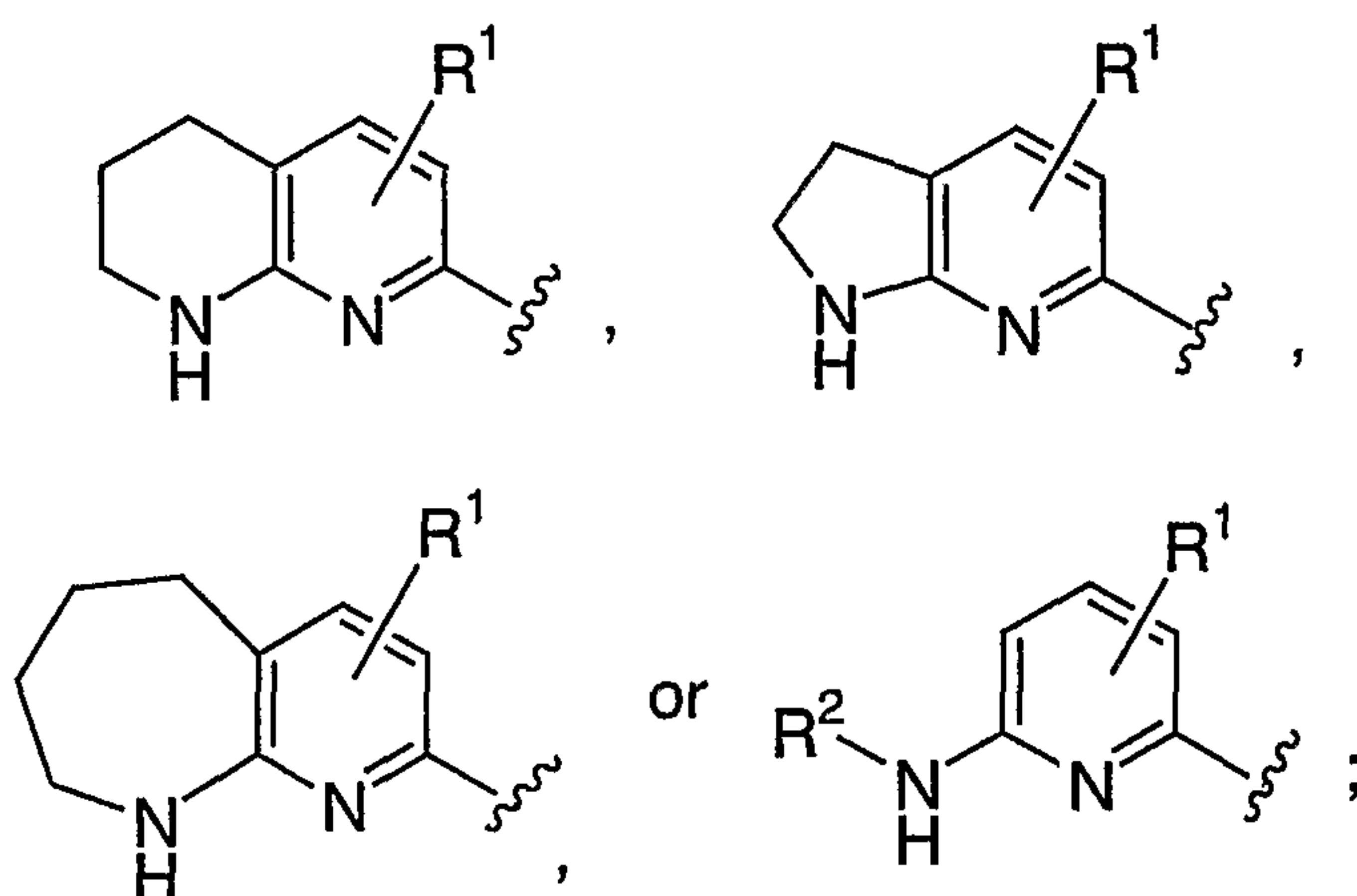
The present invention relates to chain-fluorinated alkanoic acid derivatives useful as α_v integrin receptor antagonists. Compounds of the present invention are described by the following structural formula (I):



or a pharmaceutically acceptable salt thereof, wherein

X is

5



10

wherein each non-aromatic ring carbon atom is unsubstituted or independently substituted with one or two R^1 substituents and each aromatic ring carbon atom is unsubstituted or independently substituted with one R^1 substituent selected from the group consisting of

15

C₁₋₈ alkyl, C₃₋₈ cycloalkyl,
 C₃₋₈ cycloheteroalkyl, C₃₋₈ cycloalkyl-C₁₋₆ alkyl,
 C₃₋₈ cycloheteroalkyl-C₁₋₆ alkyl, aryl, aryl-C₁₋₆ alkyl, amino,
 amino-C₁₋₆ alkyl, C₁₋₃ acylamino, C₁₋₃ acylamino-C₁₋₆ alkyl,
 (C₁₋₆ alkyl)₁₋₂ amino, C₃₋₆ cycloalkyl-C₀₋₂ amino,
 (C₁₋₆ alkyl)₁₋₂ amino-C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₄ alkoxy-C₁₋₆ alkyl,
 hydroxycarbonyl, hydroxycarbonyl-C₁₋₆ alkyl, C₁₋₃ alkoxycarbonyl,
 C₁₋₃ alkoxycarbonyl-C₁₋₆ alkyl, hydroxy, hydroxy-C₁₋₆ alkyl,
 20 nitro, cyano, trifluoromethyl, trifluoromethoxy, trifluoroethoxy,
 C₁₋₈ alkyl-S(O)₀₋₂, (C₁₋₈ alkyl)₀₋₂ aminocarbonyl,

C₁₋₈ alkyloxycarbonylamino, (C₁₋₈ alkyl)₁₋₂ aminocarbonyloxy,
 (aryl C₁₋₃ alkyl)₁₋₂ amino, (aryl)₁₋₂ amino,
 aryl-C₁₋₃ alkylsulfonylamino, and C₁₋₈ alkylsulfonylamino;

or two R¹ substituents, when on the same non-aromatic carbon atom, are taken
 5 together with the carbon atom to which they are attached to form a carbonyl group, or
 two R¹ substituents, together with the non-aromatic carbon atoms to which they are
 attached, join to form a 4- to 6-membered saturated or unsaturated carbocyclic ring;

R² is hydrogen or C₁₋₄ alkyl;

10

R³ is fluoro and R⁴ is hydrogen or R³ is hydrogen and R⁴ is fluoro;

R⁵ is aryl wherein the aryl group is selected from the group consisting of

- | | |
|----|----------------------|
| 15 | (1) phenyl, |
| | (2) naphthyl, |
| | (3) pyridinyl, |
| | (4) furyl, |
| | (5) thienyl, |
| | (6) pyrrolyl, |
| 20 | (7) oxazolyl, |
| | (8) thiazolyl, |
| | (9) imidazolyl, |
| | (10) pyrazolyl, |
| | (11) isoxazolyl, |
| 25 | (12) isothiazolyl, |
| | (13) pyrimidinyl, |
| | (14) pyrazinyl, |
| | (15) pyridazinyl, |
| | (16) quinolyl, |
| 30 | (17) isoquinolyl, |
| | (18) benzimidazolyl, |
| | (19) benzofuryl, |
| | (20) benzothienyl, |
| | (21) indolyl, |

- 5 (22) benzthiazolyl,
 (23) benzoxazolyl,
 (24) dihydrobenzofuryl,
 (25) benzo(1,3)dioxolanyl, and
 (26) benzo(1,4)dioxanyl;

and mono, di, and tri-substituted aryl wherein aryl is as defined above and the substituents are independently hydroxy, hydroxy-C₁₋₆ alkyl, halogen, C₁₋₈ alkyl, C₃₋₈ cycloalkyl, aryl, aryl C₁₋₃ alkyl, amino, amino C₁₋₆ alkyl, C₁₋₃ acylamino, C₁₋₃ acylamino-C₁₋₆ alkyl, C₁₋₆ alkylamino, di(C₁₋₆)alkylamino, C₁₋₆ alkylamino-C₁₋₆ alkyl, di(C₁₋₆)alkylamino-C₁₋₆ alkyl, C₁₋₄ alkoxy, C₁₋₄ alkylthio, C₁₋₄ alkylsulfinyl, C₁₋₄ alkylsulfonyl, C₁₋₄ alkoxy-C₁₋₆ alkyl, hydroxycarbonyl, hydroxycarbonyl-C₁₋₆ alkyl, C₁₋₅ alkoxycarbonyl, C₁₋₃ alkoxycarbonyl-C₁₋₆ alkyl, C₁₋₅ alkylcarbonyloxy, cyano, trifluoromethyl, 1,1,1-trifluoroethyl, trifluoromethoxy, trifluoroethoxy, or nitro; or two adjacent substituents together with the carbon atoms to which they are attached join to form a five- or six-membered saturated or unsaturated ring containing 1 or 2 heteroatoms selected from the group consisting of N, O, and S, whose ring carbon atoms may be substituted with oxo or C₁₋₃ alkyl; and

20 R⁶ is hydrogen or C₁₋₃ alkyl.

In one embodiment of the compounds of the present invention, R⁵ is mono- or di-substituted

25 phenyl,
 pyridinyl,
 quinolyl,
 pyrimidinyl,
 pyrazinyl,
 pyrazolyl, or
 30 dihydrobenzofuryl;

wherein the substituents are independently hydrogen, hydroxy, hydroxy-C₁₋₆ alkyl, halogen, C₁₋₈ alkyl, C₃₋₈ cycloalkyl, aryl, aryl C₁₋₃ alkyl, amino, amino-C₁₋₆ alkyl, C₁₋₃ acylamino, C₁₋₃ acylamino-C₁₋₆ alkyl, C₁₋₆ alkylamino, di(C₁₋₆)alkylamino,

C₁₋₆ alkylamino C₁₋₆ alkyl, di(C₁₋₆)alkylamino-C₁₋₆ alkyl, C₁₋₄ alkoxy, C₁₋₄ alkylthio, C₁₋₄ alkylsulfinyl, C₁₋₄ alkylsulfonyl, C₁₋₄ alkoxy-C₁₋₆ alkyl, hydroxycarbonyl, hydroxycarbonyl-C₁₋₆ alkyl, C₁₋₅ alkoxycarbonyl, C₁₋₃ alkoxycarbonyl C₁₋₆ alkyl, C₁₋₅ alkylcarbonyloxy, cyano, trifluoromethyl, 1,1,1-trifluoroethyl, trifluoromethoxy, trifluoroethoxy, or nitro; or two adjacent substituents together with the carbon atoms to which they are attached join to form a five- or six-membered saturated or unsaturated ring containing 1 or 2 heteroatoms selected from the group consisting of N, O, and S, whose ring carbon atoms may be substituted with oxo or C₁₋₃ alkyl.

10 In a class of this embodiment of the present invention, R⁵ is mono- or di-substituted

quinolyl,
pyridinyl, or
pyrimidinyl;

15 wherein the substituents are independently hydrogen, halogen, phenyl, C₁₋₄ alkyl, C₃₋₆ cycloalkyl, C₁₋₃ alkoxy, amino, C₁₋₃ alkylamino, di(C₁₋₃) alkylamino, hydroxy, cyano, trifluoromethyl, 1,1,1-trifluoroethyl, trifluoromethoxy, or trifluoroethoxy.

20 In a second embodiment of the compounds of the present invention, R¹ is selected from the group consisting of

hydrogen,
amino,
C₁₋₄ alkylamino,
25 C₃₋₆ cycloalkyl-C₀₋₂ alkylamino
cyano,
C₁₋₄ alkyl,
cyclopropyl,
aryl C₁₋₃ alkyl,
30 C₁₋₄ acylamino,
C₁₋₄ alkoxy,
C₁₋₄ alkylthio,
aminocarbonyl,
(C₁₋₆ alkyl)₁₋₂ aminocarbonyl,

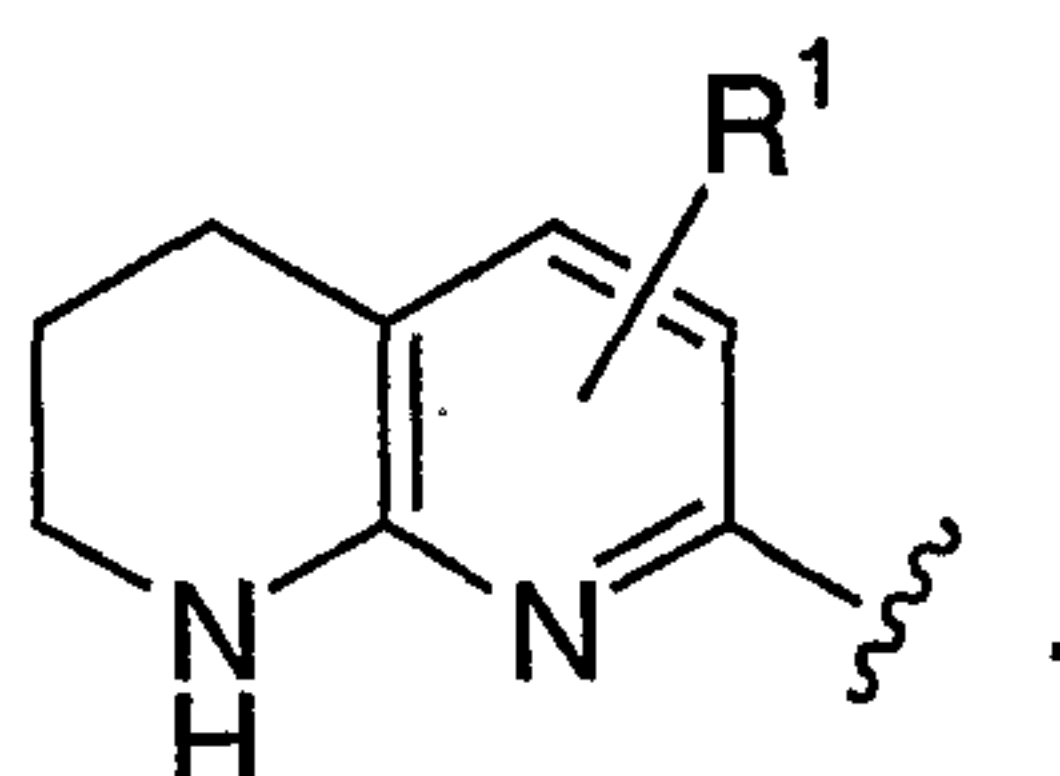
C₁₋₄ alkoxy carbonyl,
trifluoromethyl, and
trifluoromethoxy.

5 In a class of this second embodiment of the present invention, R¹ is
selected from the group consisting of

hydrogen,
amino,
C₁₋₃ alkylamino,
10 C₃₋₆ cycloalkylmethylamino,
C₁₋₄ alkyl,
cyclopropyl,
trifluoromethyl, and
trifluoromethoxy.

15

In a third embodiment of the compounds of the present invention, X is



In a class of this embodiment, R³ is hydrogen and R⁴ is fluoro.

In a subclass of this class of this embodiment, R¹ is C₁₋₄ alkyl or
20 cyclopropyl and R⁵ is mono- or di-substituted
quinolyl,
pyridinyl, or
pyrimidinyl;

wherein the substituents are independently hydrogen, halogen, phenyl, C₁₋₄ alkyl,
25 C₃₋₆ cycloalkyl, C₁₋₃ alkoxy, amino, C₁₋₃ alkylamino, di(C₁₋₃) alkylamino,
hydroxy, cyano, trifluoromethyl, 1,1,1-trifluoroethyl, trifluoromethoxy, or
trifluoroethoxy.

In a fourth embodiment of the compounds of the present invention, R⁶
is hydrogen.

Illustrative but nonlimiting examples of compounds of the present invention that are useful as α_v integrin receptor antagonists are the following:

- 5 5,5-Difluoro-3-(pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-[1,8]-naphthyridin-2-yl)-nonanoic acid;
- 5,5-Difluoro-3(S)-(pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-[1,8]-naphthyridin-2-yl)-nonanoic acid;
- 10 5,5-Difluoro-3(R)-(pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-[1,8]-naphthyridin-2-yl)-nonanoic acid;
- 5,5-Difluoro-3-(2-methoxy-pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-[1,8]-naphthyridin-2-yl)-nonanoic acid;
- 15 5,5-Difluoro-3(R)-(2-methoxy-pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-[1,8]-naphthyridin-2-yl)-nonanoic acid;
- 5,5-Difluoro-3(S)-(2-methoxy-pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-[1,8]-naphthyridin-2-yl)-nonanoic acid;
- 20 5,5-Difluoro-3-(2-methyl-pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-[1,8]-naphthyridin-2-yl)-nonanoic acid;
- 5,5-Difluoro-3(R)-(2-methyl-pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-[1,8]-naphthyridin-2-yl)-nonanoic acid;
- 25 5,5-Difluoro-3(S)-(2-methyl-pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-[1,8]-naphthyridin-2-yl)-nonanoic acid;
- 30 9-(3-Cyclopropyl-5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-5,5-difluoro-3-(2-methyl-pyrimidin-5-yl)-nonanoic acid;
- 9-(3-Cyclopropyl-5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-5,5-difluoro-3(S)-(2-methyl-pyrimidin-5-yl)-nonanoic acid;
- 35

9-(3-Cyclopropyl-5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-5,5-difluoro-3(R)-(2-methyl-pyrimidin-5-yl)-nonanoic acid;

5 5,5-Difluoro-3-(pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-5H-pyrido[2,3-b]azepin-2-yl)-nonanoic acid;

5,5-Difluoro-3(S)-(pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-5H-pyrido[2,3-b]azepin-2-yl)-nonanoic acid;

10

5,5-Difluoro-3(R)-(pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-5H-pyrido[2,3-b]azepin-2-yl)-nonanoic acid;

15 5,5-Difluoro-3-(2-methyl-pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-5H-pyrido[2,3-b]azepin-2-yl)-nonanoic acid;

5,5-Difluoro-3(S)-(2-methyl-pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-5H-pyrido[2,3-b]azepin-2-yl)-nonanoic acid;

20 5,5-Difluoro-3(R)-(2-methyl-pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-5H-pyrido[2,3-b]azepin-2-yl)-nonanoic acid;

5,5-Difluoro-3-(2-methoxy-pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-5H-pyrido[2,3-b]azepin-2-yl)-nonanoic acid;

25

5,5-Difluoro-3(S)-(2-methoxy-pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-5H-pyrido[2,3-b]azepin-2-yl)-nonanoic acid; and

30 5,5-Difluoro-3(R)-(2-methoxy-pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-5H-pyrido[2,3-b]azepin-2-yl)-nonanoic acid;

or a pharmaceutically acceptable salt thereof.

35 Further illustrative of the compounds of the present invention are the following:

- 5,5-Difluoro-3(S)-(pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-[1,8]-naphthyridin-2-yl)-nonanoic acid;
- 5,5-Difluoro-3(R)-(pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-[1,8]-naphthyridin-2-yl)-nonanoic acid;
- 5,5-Difluoro-3(R)-(2-methoxy-pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-[1,8]-naphthyridin-2-yl)-nonanoic acid;
- 10 5,5-Difluoro-3(S)-(2-methoxy-pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-[1,8]-naphthyridin-2-yl)-nonanoic acid;
- 5,5-Difluoro-3(R)-(2-methyl-pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-[1,8]-naphthyridin-2-yl)-nonanoic acid;
- 15 5,5-Difluoro-3(S)-(2-methyl-pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-[1,8]-naphthyridin-2-yl)-nonanoic acid;
- 9-(3-Cyclopropyl-5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-5,5-difluoro-3(S)-(2-methyl-pyrimidin-5-yl)-nonanoic acid;
- 20 9-(3-Cyclopropyl-5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-5,5-difluoro-3(R)-(2-methyl-pyrimidin-5-yl)-nonanoic acid;
- 5,5-Difluoro-3(S)-(pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-5H-pyrido[2,3-b]azepin-2-yl)-nonanoic acid;
- 5,5-Difluoro-3(R)-(pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-5H-pyrido[2,3-b]azepin-2-yl)-nonanoic acid;
- 30 5,5-Difluoro-3(S)-(2-methyl-pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-5H-pyrido[2,3-b]azepin-2-yl)-nonanoic acid;
- 5,5-Difluoro-3(R)-(2-methyl-pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-5H-pyrido[2,3-b]azepin-2-yl)-nonanoic acid;
- 35

5,5-Difluoro-3(S)-(2-methoxy-pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-5H-pyrido[2,3-b]azepin-2-yl)-nonanoic acid; and

- 5 5,5-Difluoro-3(R)-(2-methoxy-pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-5H-pyrido[2,3-b]azepin-2-yl)-nonanoic acid;

or a pharmaceutically acceptable salt thereof.

- 10 For use in medicine, the salts of the compounds of this invention refer to non-toxic "pharmaceutically acceptable salts." Other salts may, however, be useful in the preparation of the compounds according to the invention or of their pharmaceutically acceptable salts. Salts of basic compounds encompassed within the term "pharmaceutically acceptable salts" refer to non-toxic salts of the compounds of
- 15 this invention which are generally prepared by reacting the free base with a suitable organic or inorganic acid. Representative salts of basic compounds of the present invention include, but are not limited to, the following: acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, calcium, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edisylate, estolate,
- 20 esylate, fumarate, gluceptate, gluconate, glutamate, glycolylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, N-methylglucamine ammonium salt, oleate, oxalate, pamoate (embonate), palmitate,
- 25 pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, sulfate, subacetate, succinate, tannate, tartrate, teoclate, tosylate, triethiodide and valerate. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof include, but are not limited to, salts derived from inorganic bases including aluminum, ammonium, calcium, copper, ferric,
- 30 ferrous, lithium, magnesium, manganic, mangamous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, cyclic amines, and basic ion-exchange resins, such as arginine, betaine, caffeine, choline, N,N-
- 35 dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-

dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like.

The compounds of the present invention can have chiral centers and can thus occur as racemates, racemic mixtures, single enantiomers, diastereoisomeric mixtures, and individual diastereoisomers, with all isomeric forms being included in the present invention. Therefore, where a compound is chiral, the separate enantiomers or diastereoisomers, substantially free of the other, are included within the scope of the invention; further included are all mixtures of the two enantiomers.

Some of the compounds described herein contain olefinic double bonds, and unless specified otherwise, are meant to include both E and Z geometric isomers.

Some of the compounds described herein may exist with different points of attachment of hydrogen, referred to as tautomers. Such an example may be a ketone and its enol form, known as keto-enol tautomers. The individual tautomers as well as mixtures thereof are encompassed within the compounds of the present invention.

Compounds of the present invention may be separated into diastereoisomeric pairs of enantiomers by, for example, fractional crystallization from a suitable solvent, for example, methanol or ethyl acetate or a mixture thereof. The pair of enantiomers thus obtained may be separated into individual stereoisomers by conventional means, for example, by the use of an optically active acid as a resolving agent, or by HPLC using a chiral stationary phase. Alternatively, any enantiomer of a compound of the present invention may be obtained by stereospecific synthesis using optically pure starting materials or reagents of known configuration.

Also included within the scope of the invention are polymorphs and hydrates of the compounds of the instant invention.

The present invention includes within its scope prodrugs of the compounds of this invention. In general, such prodrugs will be functional derivatives of the compounds of this invention which are readily convertible *in vivo* into the required compound. Thus, in the methods of treatment of the present invention, the term "administering" shall encompass the treatment of the various conditions described with the compound specifically disclosed or with a compound which may

not be specifically disclosed, but which converts to the specified compound *in vivo* after administration to the patient. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs," ed. H. Bundgaard, Elsevier, 1985, which is incorporated by reference
5 herein in its entirety. Metabolites of these compounds include active species produced upon introduction of compounds of this invention into the biological milieu.

The term "therapeutically effective amount" shall mean that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by a researcher or clinician.

10 The term " α v integrin receptor antagonist," as used herein, refers to a compound which binds to and antagonizes either the α v β 3 receptor or the α v β 5 receptor, or a compound which binds to and antagonizes a combination of these receptors (for example, a dual α v β 3/ α v β 5 receptor antagonist).

15 The term "bone resorption," as used herein, refers to the process by which osteoclasts degrade bone.

The term "alkyl" shall mean straight or branched chain alkanes of one to ten total carbon atoms, or any number within this range (i.e., methyl, ethyl, 1-propyl, 2-propyl, n-butyl, s-butyl, t-butyl, etc.).

20 The term "alkenyl" shall mean straight or branched chain alkenes of two to ten total carbon atoms, or any number within this range.

The term "alkynyl" shall mean straight or branched chain alkynes of two to ten total carbon atoms, or any number within this range.

25 The term "cycloalkyl" shall mean cyclic rings of alkanes of three to eight total carbon atoms, or any number within this range (i.e., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or cyclooctyl).

The term "cycloheteroalkyl," as used herein, shall mean a 3- to 8-membered fully saturated heterocyclic ring containing one or two heteroatoms chosen from N, O, or S. Examples of cycloheteroalkyl groups include, but are not limited to piperidinyl, pyrrolidinyl, azetidiny, morpholinyl, piperazinyl.

30 The term "alkoxy," as used herein, refers to straight or branched chain alkoxides of the number of carbon atoms specified (e.g., C₁₋₅ alkoxy), or any number within this range (i.e., methoxy, ethoxy, etc.).

35 The term "aryl," as used herein, refers to a monocyclic or bicyclic system comprising at least one aromatic ring, wherein the monocyclic or bicyclic system contains 0, 1, 2, 3, or 4 heteroatoms chosen from N, O, or S, and wherein the

monocyclic or bicyclic system is either unsubstituted or substituted with one or more groups independently selected from halogen, C₁₋₈ alkyl, C₃₋₈ cycloalkyl, aryl, aryl C₁₋₃ alkyl, amino, amino C₁₋₆ alkyl, C₁₋₃ acylamino, C₁₋₃ acylamino C₁₋₆ alkyl, C₁₋₆ alkylamino, C₁₋₆ alkylamino C₁₋₆ alkyl, di(C₁₋₆) alkylamino, di(C₁₋₆) alkylamino-C₁₋₆ alkyl, C₁₋₄ alkoxy, C₁₋₄ alkylthio, C₁₋₄ alkylsulfinyl, C₁₋₄ alkylsulfonyl, C₁₋₄ alkoxy C₁₋₆ alkyl, hydroxycarbonyl, hydroxycarbonyl C₁₋₆ alkyl, C₁₋₅ alkoxycarbonyl, C₁₋₃ alkoxycarbonyl C₁₋₆ alkyl, hydroxycarbonyl C₁₋₆ alkyloxy, hydroxy, hydroxy C₁₋₆ alkyl, cyano, trifluoromethyl, trifluoromethoxy, oxo and C₁₋₅ alkylcarbonyloxy. Examples of aryl include, but are not limited to, phenyl, naphthyl, pyridinyl, pyrrolyl, pyrazolyl, pyrazinyl, pyrimidinyl, imidazolyl, benzimidazolyl, benzthiazolyl, benzoxazolyl, indolyl, thienyl, furyl, dihydrobenzofuryl, benzo(1,3)dioxolanyl, benzo(1,4)dioxanyl, oxazolyl, isoxazolyl, thiazolyl, and isothiazolyl, which are either unsubstituted or substituted with one or more groups independently selected from halogen, C₁₋₈ alkyl, C₃₋₈ cycloalkyl, aryl, aryl C₁₋₃ alkyl, amino, amino C₁₋₆ alkyl, C₁₋₃ acylamino, C₁₋₃ acylamino C₁₋₆ alkyl, C₁₋₆ alkylamino, C₁₋₆ alkylamino C₁₋₆ alkyl, di(C₁₋₆) alkylamino, di(C₁₋₆) alkylamino-C₁₋₆ alkyl, C₁₋₄ alkoxy, C₁₋₄ alkylthio, C₁₋₄ alkylsulfinyl, C₁₋₄ alkylsulfonyl, C₁₋₄ alkoxy C₁₋₆ alkyl, hydroxycarbonyl, hydroxycarbonyl C₁₋₆ alkyl, C₁₋₅ alkoxycarbonyl, C₁₋₃ alkoxycarbonyl C₁₋₆ alkyl, hydroxycarbonyl C₁₋₆ alkyloxy, hydroxy, hydroxy C₁₋₆ alkyl, cyano, trifluoromethyl, trifluoromethoxy, oxo, and C₁₋₅ alkylcarbonyloxy. Preferably, the aryl group is unsubstituted, mono-, di-, or tri- substituted with one to three of the above-named substituents; more preferably, the aryl group is unsubstituted, mono- or di-substituted with one to two of the above-named substituents.

Whenever the term "alkyl" or "aryl" or either of their prefix roots appears in a name of a substituent (e.g., aryl C₀₋₈ alkyl), it shall be interpreted as including those limitations given above for "alkyl" and "aryl." Designated numbers of carbon atoms (e.g., C₁₋₈) shall refer independently to the number of carbon atoms in an alkyl or cyclic alkyl moiety or to the alkyl portion of a larger substituent in which alkyl appears as its prefix root.

The terms "arylalkyl" and "alkylaryl" include an alkyl portion where alkyl is as defined above and to include an aryl portion where aryl is as defined above. Examples of arylalkyl include, but are not limited to, benzyl, fluorobenzyl, chlorobenzyl, phenylethyl, phenylpropyl, fluorophenylethyl, chlorophenylethyl, thienylmethyl, thienylethyl, and thienylpropyl. Examples of alkylaryl include, but are

not limited to, toluene, ethylbenzene, propylbenzene, methylpyridine, ethylpyridine, propylpyridine and butylpyridine.

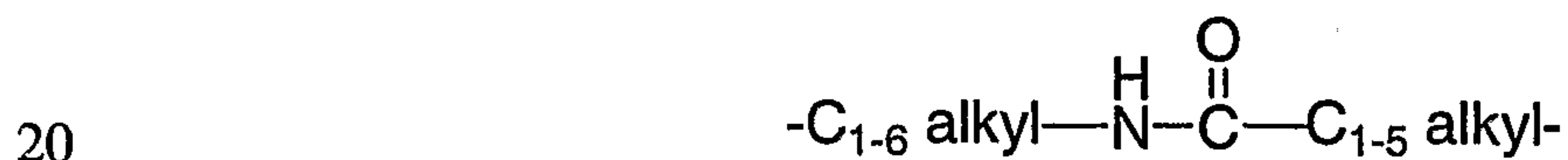
In the compounds of the present invention, two R¹ substituents, when on the same carbon atom, can be taken together with the carbon atom to which they are attached to form a carbonyl group.

The term "halogen" shall include iodine, bromine, chlorine, and fluorine.

The term "oxy" means an oxygen (O) atom. The term "thio" means a sulfur (S) atom. The term "oxo" means "=O". The term "carbonyl" means "C=O."

The term "substituted" shall be deemed to include multiple degrees of substitution by a named substituent. Where multiple substituent moieties are disclosed or claimed, the substituted compound can be independently substituted by one or more of the disclosed or claimed substituent moieties, singly or plurally. By independently substituted, it is meant that the (two or more) substituents can be the same or different.

Under standard nomenclature used throughout this disclosure, the terminal portion of the designated side chain is described first, followed by the adjacent functionality toward the point of attachment. For example, a C₁₋₅ alkylcarbonylamino C₁₋₆ alkyl substituent is equivalent to



In choosing compounds of the present invention, one of ordinary skill in the art will recognize that the various substituents, i.e. X, R¹, R², R³, R⁴, R⁵, and R⁶ are to be chosen in conformity with well-known principles of chemical structure connectivity.

Representative compounds of the present invention typically display submicromolar affinity for the α_v integrin receptors, particularly the $\alpha_v\beta_3$ and $\alpha_v\beta_5$. Compounds of this invention are therefore useful for treating mammals suffering from a bone condition caused or mediated by increased bone resorption, who are in need of such therapy. Pharmacologically effective amounts of the compounds, including pharmaceutically acceptable salts thereof, are administered to the mammal, to inhibit the activity of mammalian osteoclasts.

The compounds of the present invention are administered in dosages effective to antagonize the $\alpha v\beta 3$ receptor where such treatment is needed, as, for example, in the prevention or treatment of osteoporosis.

5 Illustrating the invention is the method wherein the αv integrin receptor antagonizing effect is an $\alpha v\beta 3$ antagonizing effect. More particularly, the $\alpha v\beta 3$ antagonizing effect is selected from inhibition of: bone resorption, restenosis, angiogenesis, diabetic retinopathy, macular degeneration, inflammation, inflammatory arthritis, viral disease, cancer, and metastatic tumor growth. In one embodiment of the method, the $\alpha v\beta 3$ antagonizing effect is the inhibition of bone resorption.

10 Another example of the invention is the method wherein the αv integrin receptor antagonizing effect is an $\alpha v\beta 5$ antagonizing effect. More specifically, the $\alpha v\beta 5$ antagonizing effect is selected from inhibition of restenosis, angiogenesis, diabetic retinopathy, macular degeneration, inflammation, cancer, and metastatic tumor growth.

15 Further illustrating the invention is the method wherein the αv integrin receptor antagonizing effect is a dual $\alpha v\beta 3/\alpha v\beta 5$ antagonizing effect. More particularly, the dual $\alpha v\beta 3/\alpha v\beta 5$ antagonizing effect is selected from inhibition of: bone resorption, restenosis, angiogenesis, diabetic retinopathy, macular degeneration, inflammation, viral disease, cancer, and metastatic tumor growth.

20 More particularly illustrating the invention is a pharmaceutical composition comprising any of the compounds described above and a pharmaceutically acceptable carrier. Another example of the invention is a pharmaceutical composition made by combining any of the compounds described above and a pharmaceutically acceptable carrier. Another illustration of the invention
25 is a process for making a pharmaceutical composition comprising combining any of the compounds described above and a pharmaceutically acceptable carrier.

Further illustrating the invention is a method of treating and/or preventing a condition mediated by antagonism of an αv integrin receptor in a mammal in need thereof, comprising administering to the mammal a therapeutically
30 effective amount of any of the compounds described above. Preferably, the condition is selected from bone resorption, osteoporosis, restenosis, diabetic retinopathy, macular degeneration, angiogenesis, atherosclerosis, inflammation, inflammatory arthritis, viral disease, cancer, tumor growth, and metastasis. More preferably, the condition is selected from osteoporosis and cancer. Most preferably, the condition is
35 osteoporosis.

More specifically exemplifying the invention is a method of eliciting an α_v integrin antagonizing effect in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of any of the compounds or any of the pharmaceutical compositions described above. Preferably, the α_v integrin antagonizing effect is an $\alpha_v\beta_3$ antagonizing effect; more specifically, the $\alpha_v\beta_3$ antagonizing effect is selected from inhibition of bone resorption, inhibition of restenosis, inhibition of atherosclerosis, inhibition of angiogenesis, inhibition of diabetic retinopathy, inhibition of macular degeneration, inhibition of inflammation, inhibition of viral disease, and inhibition of cancer or metastatic tumor growth. Most preferably, the $\alpha_v\beta_3$ antagonizing effect is inhibition of bone resorption.

Alternatively, the α_v integrin antagonizing effect is an $\alpha_v\beta_5$ antagonizing effect or a dual $\alpha_v\beta_3/\alpha_v\beta_5$ antagonizing effect. Examples of $\alpha_v\beta_5$ antagonizing effects are inhibition of restenosis, atherosclerosis, angiogenesis, diabetic retinopathy, macular degeneration, inflammation, viral disease, cancer, and metastatic tumor growth.

Additional examples of the invention are methods of inhibiting bone resorption and of treating and/or preventing osteoporosis in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of any of the compounds or any of the pharmaceutical compositions described above.

Additional illustrations of the invention are methods of treating hypercalcemia of malignancy, osteopenia due to bone metastases, periodontal disease, hyperparathyroidism, periarticular erosions in rheumatoid arthritis, Paget's disease, immobilization-induced osteopenia, and glucocorticoid treatment in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of any of the compounds or any of the pharmaceutical compositions described above.

More particularly exemplifying the invention is the use of any of the compounds described above in the preparation of a medicament for the treatment and/or prevention of osteoporosis in a mammal in need thereof. Still further exemplifying the invention is the use of any of the compounds described above in the preparation of a medicament for the treatment and/or prevention of bone resorption, metastatic tumor growth, cancer, restenosis, atherosclerosis, diabetic retinopathy, macular degeneration, inflammation, inflammatory arthritis, viral disease, and/or angiogenesis.

Also exemplifying the invention are compositions further comprising an active ingredient selected from the group consisting of

- a) an organic bisphosphonate or a pharmaceutically acceptable salt or ester thereof,
 - b) an estrogen receptor modulator,
 - c) an androgen receptor modulator,
 - 5 d) a cytotoxic/antiproliferative agent,
 - e) a matrix metalloproteinase inhibitor,
 - f) an inhibitor of epidermal-derived, fibroblast-derived, or platelet-derived growth factors,
 - g) a VEGF receptor antagonist,
 - 10 h) an antibody to a growth factor or to a growth factor receptor,
 - i) an inhibitor of Flk-1/KDR, Flt-1, Tck/Tie-2, or Tie-1,
 - j) a cathepsin K inhibitor,
 - k) a growth hormone secretagogue,
 - l) an inhibitor of osteoclast proton ATPase,
 - 15 m) an inhibitor of urokinase plasminogen activator (u-PA),
 - n) a tumor-specific antibody-interleukin-2 fusion protein,
 - o) an inhibitor of HMG-CoA reductase, and
 - p) a farnesyl transferase inhibitor or a geranylgeranyl transferase inhibitor or a dual farnesyl/geranylgeranyl transferase inhibitor, and
 - 20 q) a parathyroid hormone (PTH) analog;
- and mixtures thereof.

(See, B. Millauer et al., "Dominant-Negative Inhibition of Flk-1 Suppresses the Growth of Many Tumor Types *In Vivo*", Cancer Research, 56, 1615-1620 (1996), which is incorporated by reference herein in its entirety).

25 Preferably, the active ingredient is selected from the group consisting of:

- a) an organic bisphosphonate or a pharmaceutically acceptable salt or ester thereof,
 - b) an estrogen receptor modulator,
 - 30 c) an androgen receptor modulator,
 - d) an inhibitor of osteoclast proton ATPase,
 - e) a parathyroid hormone (PTH) analog, and
 - f) a cathepsin K inhibitor;
- and mixtures thereof.

35

Nonlimiting examples of such bisphosphonates include alendronate, etidronate, pamidronate, risedronate, ibandronate, and pharmaceutically acceptable salts and esters thereof. A particularly preferred bisphosphonate is alendronate, especially alendronate monosodium trihydrate.

5 Nonlimiting examples of estrogen receptor modulators include estrogen, progesterin, estradiol, droloxifene, raloxifene, and tamoxifene.

Nonlimiting examples of cytotoxic/antiproliferative agents are taxol, vincristine, vinblastine, and doxorubicin.

Cathepsin K, formerly known as cathepsin O2, is a cysteine protease
10 and is described in PCT International Application Publication No. WO 96/13523, published May 9, 1996; U.S. Patent No. 5,501,969, issued March 3, 1996; and U.S. Patent No. 5,736,357, issued April 7, 1998, all of which are incorporated by reference herein in their entirety. Cysteine proteases, specifically cathepsins, are linked to a
15 number of disease conditions, such as tumor metastasis, inflammation, arthritis, and bone remodeling. At acidic pH's, cathepsins can degrade type-I collagen. Cathepsin protease inhibitors can inhibit osteoclastic bone resorption by inhibiting the degradation of collagen fibers and are thus useful in the treatment of bone resorption diseases, such as osteoporosis.

Members of the class of HMG-CoA reductase inhibitors, known as the
20 "statins," have been found to trigger the growth of new bone, replacing bone mass lost as a result of osteoporosis (see The Wall Street Journal, Friday, December 3, 1999, page B1). Therefore, the statins hold promise for the treatment of bone resorption. Nonlimiting examples of statins are lovastatin, simvastatin, atorvastatin, and pravastatin.

25 Evidence for crucial role of the urokinase-urokinase receptor (u-PA-u-PAR) in angiogenesis, tumor invasion, inflammation, and matrix remodeling during wound healing and development has been presented [see Y. Koshelnick et al., "Mechanisms of signaling through Urokinase Receptor and the Cellular Response," Thrombosis and Haemostasis 82: 305-311 (1999) and F. Blasi, "Proteolysis, Cell
30 Adhesion, Chemotaxis, and Invasiveness Are Regulated by the u-PA-u-PAR-PAI-1 System," Thrombosis and Haemostasis 82: 298-304 (1999)]. Thus, specific antagonists of the binding of u-PA to u-PAR inhibit cell-surface plasminogen activation, tumor growth, and angiogenesis in both *in vitro* and *in vivo* models.

H.N. Lode and coworkers in PNAS USA 96: 1591-1596 (1999) have
35 observed synergistic effects between an antiangiogenic α_v integrin antagonist and a

tumor-specific antibody-cytokine (interleukin-2) fusion protein in the eradication of spontaneous tumor metastases. Their results suggested this combination as having potential for the treatment of cancer and metastatic tumor growth.

5 The proton ATPase which is found on the apical membrane of the osteoclast has been reported to play a significant role in the bone resorption process. Therefore, this proton pump represents an attractive target for the design of inhibitors of bone resorption which are potentially useful for the treatment and prevention of osteoporosis and related metabolic diseases (see C. Farina et al., "Selective inhibitors of the osteoclast vacuolar proton ATPase as novel bone antiresorptive agents," DDT,
10 4: 163-172 (1999)).

Evidence has been presented that androgenic steroids play a physiological role in the development of bone mass in men and women and that androgens act directly on bone. Androgen receptors have been demonstrated in human osteoblast-like cell lines and androgens have been shown to directly stimulate
15 bone cell proliferation and differentiation. For a discussion, reference is made to S.R. Davis, "The therapeutic use of androgens in women," J. Steroid Biochem. Mol. Biol., 69: 177-184 (1999) and K.A. Hansen and S.P.T. Tho, "Androgens and Bone Health," Seminars in Reproductive Endocrinology, 16: 129-134 (1998). Thus, androgen receptor modulators may have utility in the treatment and prevention of bone loss in
20 women.

The angiogenic factor VEGF has been shown to stimulate the bone-resorbing activity of isolated mature rabbit osteoclasts via binding to its receptors on osteoclasts (see M. Nakagawa et al., "Vascular endothelial growth factor (VEGF) directly enhances osteoclastic bone resorption and survival of mature osteoclasts,"
25 FEBS Letters, 473: 161-164 (2000)). Therefore, the development of antagonists of VEGF binding to osteoclast receptors, such as KDR/Flk-1 and Flt-1, may provide yet a further approach to the treatment or prevention of bone resorption.

Activators of the peroxisome proliferator-activated receptor- γ (PPAR γ), such as the thiazolidinediones (TZD's), inhibit osteoclast-like cell
30 formation and bone resorption *in vitro*. Results reported by R. Okazaki et al. in Endocrinology, 140, pp 5060-5065, (1999) point to a local mechanism on bone marrow cells as well as a systemic one on glucose metabolism. Nonlimiting examples of PPAR γ activators include troglitazone, pioglitazone, rosiglitazone, and BRL 49653.

The use of parathyroid hormone (PTH) for the treatment of
35 osteoporosis has been suggested in the art. PTH has been found to increase the

activity of osteoblasts, the cells that form bone, thereby promoting the synthesis of new bone (Modern Drug Discovery, Vol. 3, No. 8, 2000). In studies reported at the First World Congress on Osteoporosis held in Chicago in June 2000, women in combined PTH-estrogen therapy exhibited a 12.8% increase in spinal bone mass and a 4.4% increase in total hip mass. Another study presented at the same meeting showed that PTH could increase bone size as well as density. A clinical trial of the effect of the human parathyroid hormone 1-34 fragment [hPTH(1-34)] on postmenopausal osteoporotic women resulted in $\geq 65\%$ reduction in spine fractures and a 54% reduction in nonvertebral fractures, after a median of 22 months of treatment [see J.M. Hock, Bone, 27: 467-469 (2000) and S. Mohan, et al., Bone, 27: 471-478 (2000), and references cited therein]. Thus, PTH and fragments thereof, such as hPTH(1-34), may prove to be efficacious in the treatment of osteoporosis alone or in combination with other agents, such as the $\alpha v \beta 3$ integrin antagonists of the present invention.

The present invention is also directed to combinations of the compounds of the present invention with one or more agents useful in the prevention or treatment of osteoporosis. For example, the compounds of the instant invention may be effectively administered in combination with effective amounts of other agents such as an organic bisphosphonate, an estrogen receptor modulator, an androgen receptor modulator, a cathepsin K inhibitor, an HMG-CoA reductase inhibitor, a PPAR γ activator, a VEGF receptor antagonist, an inhibitor of the osteoclast proton ATPase, or a PTH analog.

Additional illustrations of the invention are methods of treating cancer or metastatic tumor growth in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of a compound described above and one or more agents known to be cytotoxic/antiproliferative. Also, the compounds of the present invention can be administered in combination with radiation therapy for treating cancer and metastatic tumor growth.

In addition, the integrin $\alpha v \beta 3$ antagonist compounds of the present invention may be effectively administered in combination with a growth hormone secretagogue in the therapeutic or prophylactic treatment of disorders in calcium or phosphate metabolism and associated diseases. These diseases include conditions which can benefit from a reduction in bone resorption. A reduction in bone resorption should improve the balance between resorption and formation, reduce bone loss or result in bone augmentation. A reduction in bone resorption can alleviate the pain associated with osteolytic lesions and reduce the incidence and/or growth of those

lesions. These diseases include: osteoporosis (including estrogen deficiency, immobilization, glucocorticoid-induced and senile), osteodystrophy, Paget's disease, myositis ossificans, Bechterew's disease, malignant hypercalcemia, metastatic bone disease, periodontal disease, cholelithiasis, nephrolithiasis, urolithiasis, urinary
5 calculus, hardening of the arteries (sclerosis), arthritis, bursitis, neuritis and tetany. Increased bone resorption can be accompanied by pathologically high calcium and phosphate concentrations in the plasma, which would be alleviated by this treatment. Similarly, the present invention would be useful in increasing bone mass in patients with growth hormone deficiency. Thus, preferred combinations are simultaneous or
10 alternating treatments of an $\alpha v \beta 3$ receptor antagonist of the present invention and a growth hormone secretagogue, optionally including a third component comprising an organic bisphosphonate, preferably alendronate monosodium trihydrate.

In accordance with the method of the present invention, the individual components of the combination can be administered separately at different times
15 during the course of therapy or concurrently in divided or single combination forms. The instant invention is therefore to be understood as embracing all such regimes of simultaneous or alternating treatment, and the term "administering" is to be interpreted accordingly. It will be understood that the scope of combinations of the compounds of this invention with other agents useful for treating integrin-mediated
20 conditions includes in principle any combination with any pharmaceutical composition useful for treating osteoporosis.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified
25 ingredients in the specified amounts.

The compounds of the present invention can be administered in such oral dosage forms as tablets, capsules (each of which includes sustained release or timed release formulations), pills, powders, granules, elixirs, tinctures, suspensions, syrups and emulsions. Likewise, they may also be administered in intravenous (bolus
30 or infusion), intraperitoneal, topical (e.g., ocular eyedrop), subcutaneous, intramuscular or transdermal (e.g., patch) form, all using forms well known to those of ordinary skill in the pharmaceutical arts. An effective but non-toxic amount of the compound desired can be employed as an $\alpha v \beta 3$ antagonist.

The dosage regimen utilizing the compounds of the present invention
35 is selected in accordance with a variety of factors including type, species, age, weight,

sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound or salt thereof employed. An ordinarily skilled physician, veterinarian or clinician can readily determine and prescribe the effective amount of the drug required to prevent, counter or arrest the progress of the condition.

Oral dosages of the present invention, when used for the indicated effects, will range between about 0.01 mg per kg of body weight per day (mg/kg/day) to about 100 mg/kg/day, preferably 0.01 to 10 mg/kg/day, and most preferably 0.1 to 5.0 mg/kg/day. For oral administration, the compositions are preferably provided in the form of tablets containing 0.01, 0.05, 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, 50.0, 100 and 500 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. A medicament typically contains from about 0.01 mg to about 500 mg of the active ingredient, preferably, from about 1 mg to about 100 mg of active ingredient. Intravenously, the most preferred doses will range from about 0.1 to about 10 mg/kg/minute during a constant rate infusion. Advantageously, compounds of the present invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three or four times daily. Furthermore, preferred compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in the art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

In the methods of the present invention, the compounds herein described in detail can form the active ingredient, and are typically administered in admixture with suitable pharmaceutical diluents, excipients or carriers (collectively referred to herein as 'carrier' materials) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, starch, sucrose, glucose, methyl cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and the like; for oral administration in liquid form, the oral drug components can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol,

glycerol, water and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like.

The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

Compounds of the present invention may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxy-ethylaspartamide-phenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and crosslinked or amphipathic block copolymers of hydrogels.

In the Schemes and Examples below, various reagent symbols and abbreviations have the following meanings:

AcOH:	Acetic acid.
Ar:	Argon
BOC(Boc):	t-Butyloxycarbonyl.
CBZ(Cbz):	Carbobenzyloxy or benzyloxycarbonyl.
CH ₂ Cl ₂ :	Methylene chloride.
CH ₃ CN:	Acetonitrile
CHCl ₃ :	Chloroform.

	DAST:	(Diethylamino)sulfur trifluoride.
	DIPEA:	Diisopropylethylamine.
	DMAP:	4-Dimethylaminopyridine.
	DME:	1,2-Dimethoxyethane.
5	DMF:	N,N-Dimethylformamide.
	DMSO:	Dimethylsulfoxide.
	EtOAc:	Ethyl acetate.
	EtOH:	Ethanol.
	HOAc:	Acetic acid.
10	HPLC:	High-performance liquid chromatography
	IBCF:	Isobutylchloroformate
	K ₂ CO ₃ :	Potassium carbonate.
	LDA:	Lithium diisopropylamide.
	MeOH:	Methanol.
15	MgSO ₄ :	Magnesium sulfate.
	MNNG:	1,1-methyl-3-nitro-1-nitrosoguanidine
	NEt ₃ :	Triethylamine.
	NMM:	N-methylmorpholine.
	Pd(PPh ₃) ₂ Cl ₂ :	Dichlorobis(triphenylphosphine)palladium (II)
20	Pd/C:	Palladium on activated carbon catalyst.
	Ph:	Phenyl.
	POCl ₃ :	Phosphorus oxychloride.
	PtO ₂ :	Platinum oxide.
	pTSA	p-Toluenesulfonic acid.
25	TEA:	Triethylamine.
	TFA:	Trifluoroacetic acid.
	THF:	Tetrahydrofuran.
	TLC:	Thin Layer Chromatography.
	TMS:	Trimethylsilyl.

30

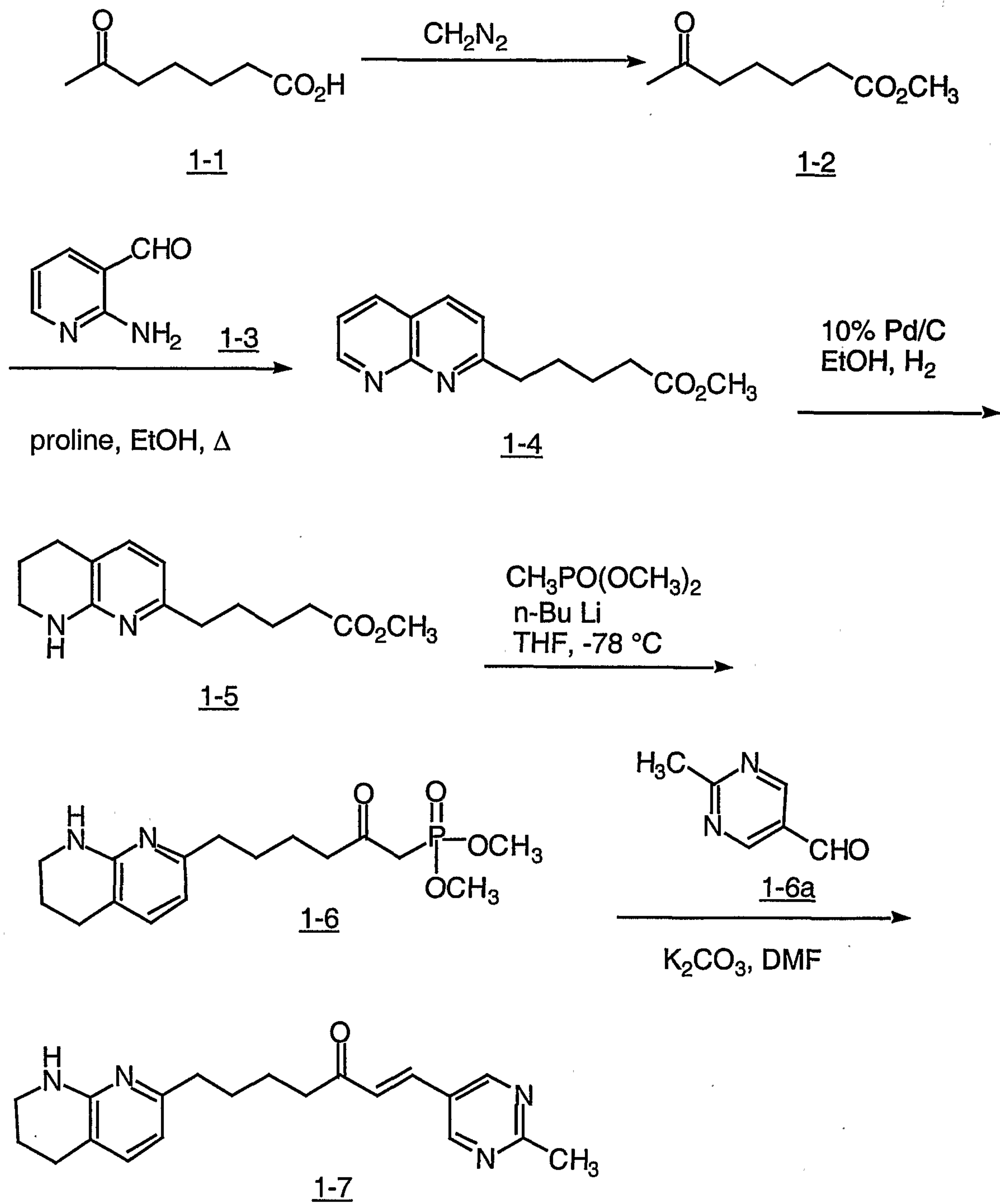
The gem-difluoromethylene compounds of the present invention can be prepared by nucleophilic fluorination of their precursor ketones (for a review, see Tozer, M.J.; Herpin, T.F., *Tetrahedron*, 52 (1996) 8619-8683). Among the fluorinating agents that can be used to accomplish the desired conversion are sulfur

35 tetrafluoride, selenium tetrafluoride, phenylsulfur trifluoride, molybdenum

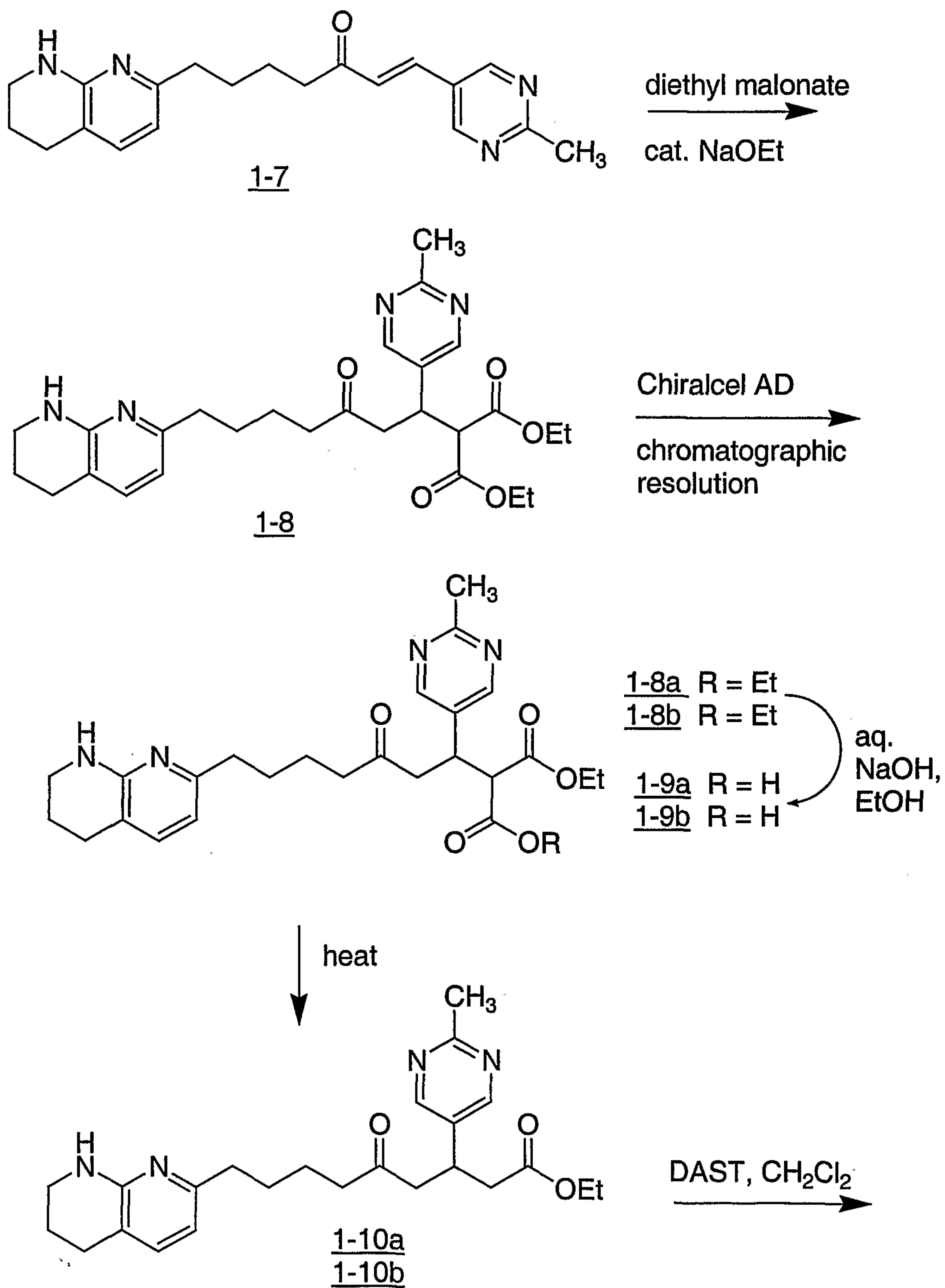
hexafluoride, and (diethylamino)sulfur trifluoride (DAST). The most commonly used of these reagents is DAST (Boulton, K. and Coss, B.E., *J. Chem. Soc., Perkin Trans. 1*, (1979) 1354) where the reaction is carried out in a suitable solvent, such as dichloromethane, chloroform, carbon tetrachloride, diethyl ether, THF, benzene, and toluene. More thermally stable substitutes for DAST include morph-DAST (Messina, P.A.; Mange, K.C.; Middleton, W.J., *J. Fluorine Chem.*, 42 (1989) 137-143) and bis(2-methoxyethyl)aminosulfur trifluoride (Lal, G.S.; et al., *Chem. Commun.* (1999) 215-216. Alternatively, the gem-difluoro compounds can be prepared from the ketone by formation of the corresponding 1,3-dithiolane, followed by reaction with 1,3-dibromo-5,5-dimethylhydantoin and pyridinium poly(hydrogen fluoride) (HF-pyridine) in a solvent, such as dichloromethane (Sondej, S.C. and Katzenellenbogen, J.A., *J. Org. Chem.*, 51 (1986) 3508-3513). An additional method to effect the keto to difluoromethylene transformation involves conversion of the ketone into its ketoxime derivative and subsequent reaction with nitrosonium tetrafluoroborate and HF-pyridine, as described by G. Olah and co-workers in *Synlett.*, 1994, 425-426.

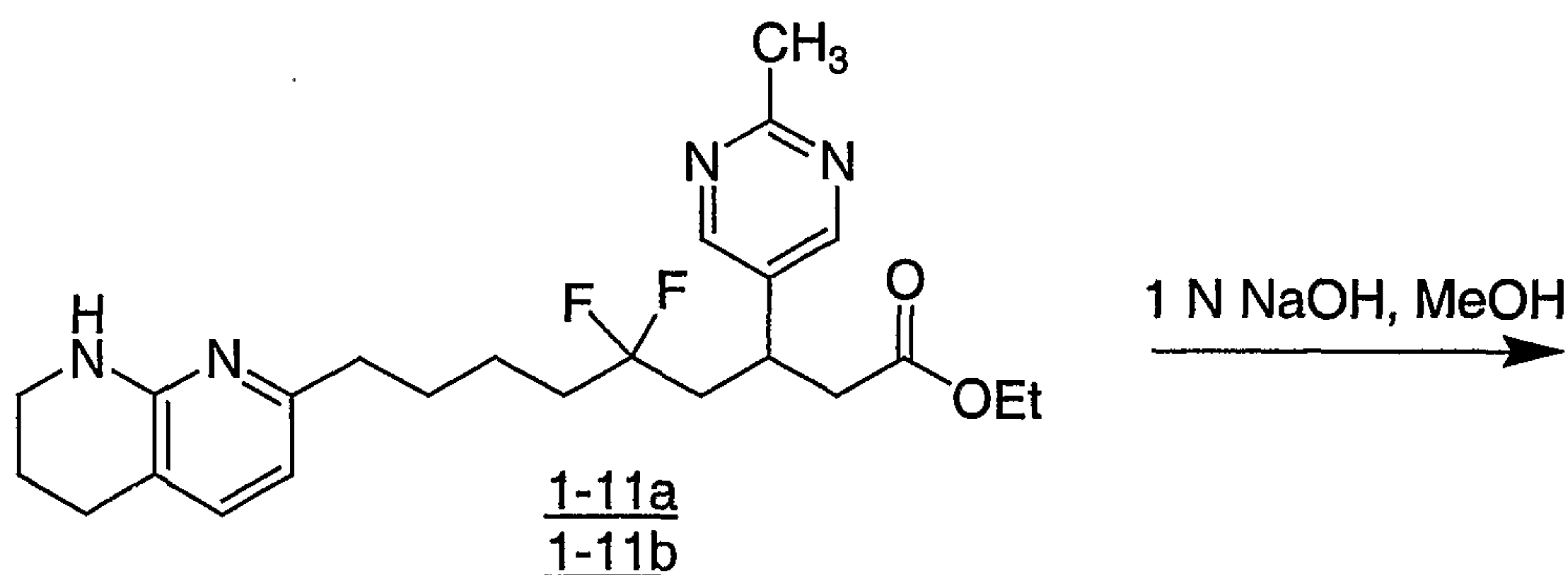
The keto substrates for the fluorination reaction are prepared according to the procedures shown in the Schemes and detailed in the accompanying Examples. The synthetic routes to the ketones have also been described in an international patent publication.

The following Examples are illustrative of the more preferred compounds of the present invention. They are not, however, to be construed as forming the only genus that is considered as the invention. The Examples further illustrate details for preparation of the compounds of the present invention. Those skilled in the art will readily understand that known variations of the conditions and processes of the following preparative procedures can be used to prepare these compounds. Unless stated otherwise, all operations were carried out at room or ambient temperature, and all temperatures are degrees Celsius.

SCHEME 1

SCHEME 1 (Cont.)





EXAMPLE 1

- 5 5,5-Difluoro-3(S or R)-(2-methyl-pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-nonanoic acid (1-12a)

Step A: 6-Oxo-heptanoic acid methyl ester (1-2)

- To a rapidly stirred mixture of diethyl ether (175 ml) and 40% KOH (52 ml) at 0°C was added MNNG (15.4 g, 105 mmol). The mixture was stirred for 10 minutes. The ethereal layer was transferred to a solution of 6-oxo-heptanoic acid 1-1 (5.0 g, 34.68 mmol) and CH₂Cl₂ at 0°C. The solution was purged with argon for 30 minutes and then concentrated. Flash chromatography (silica, 30-50% EtOAc/hexanes) gave ester 1-2 as a clear oil.
- 15 TLC R_f = 0.88 (silica, EtOAc).
¹H NMR (300 MHz, CDCl₃) δ 3.67 (s, 3H), 2.46 (m, 2H), 2.33 (m, 2H), 2.14 (s, 3H), 1.62 (m, 4H).

Step B: 5-[1,8]-Naphthyridin-2-yl-pentanoic acid methyl ester (1-4)

A mixture of 1-2 (1.4 g, 9.04 mmol), 1-3, 2-amino-3-formylpyridine (552 mg, 4.52 mmol) (for preparation, see: *J. Org. Chem.*, 1983, 48, 3401), and proline (260 mg, 2.26 mmol) in absolute ethanol (23 mL) was heated at reflux for 18 h. Following evaporative removal of the solvent, the residue was chromatographed (silica gel, 80% ethyl acetate/hexane, then ethyl acetate) to give ester 1-4 as a white solid.

TLC R_f = 0.38 (silica, EtOAc).

¹H NMR (300 MHz, CDCl₃) δ 9.08 (m, 1H), 8.16 (d, J=8.0 Hz, 1H), 8.10 (d, J=8.3 Hz, 1H), 7.45 (m, 1H), 7.39 (d, J=8.3 Hz, 1H), 3.66 (s, 3H), 3.08 (t, J=7.6 Hz, 2H), 2.39 (t, J=7.6 Hz, 2H), 1.94 (m, 2H), 1.78 (m, 2H).

Step C: 5-(5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-yl)-pentanoic acid methyl ester (1-5)

A mixture of 1-4 (630 mg, 2.58 mmol) and 10% Pd/carbon (95 mg) in EtOH (25 mL) was stirred under a balloon of hydrogen for 72 h. Following filtration and evaporative removal of the solvent, the residue was chromatographed (silica gel, 70% ethyl acetate/hexane) to give 1-5 as a colorless oil.

TLC R_f = 0.58 (silica, ethyl acetate).

¹H NMR (300 MHz, CDCl₃) δ 7.05 (d, J=7.3 Hz, 1H), 6.34 (d, J=7.3 Hz, 1H), 4.72 (s, 1H), 3.66 (s, 3H), 3.40 (m, 2H), 2.69 (t, J=6.3 Hz, 2H), 2.53 (m, 2H), 2.33 (m, 2H), 1.90 (m, 2H), 1.66 (m, 4H).

Step D: 2-Oxo-6-(5,6,7,8-tetrahydro-[1,8]-naphthyridin-2-yl)-hexyl-phosphonic acid dimethyl ester (1-6)

A solution of dimethyl methylphosphonate (13.20 g, 106.5 mmol) in anhydrous THF (165 mL) was cooled to -78° and treated dropwise with 2.5 M n-BuLi (42.3 mL). After stirring at -78° for 45 min, a solution of ester 1-5 (6.6 g, 26.6 mmol) in THF (35 mL) was added dropwise and the resulting solution stirred for 30 min at -78°, quenched with sat. NH₄Cl (100 mL), then extracted with ethyl acetate (3 X 150 mL). The combined organic extracts were dried (MgSO₄), filtered, and concentrated to afford a yellow oil. Chromatography on silica gel (5% MeOH/CH₂Cl₂) afforded 1-6 as a yellow oil.

R_f (silica, 5% MeOH/CH₂Cl₂) = 0.20.

¹H NMR (300 MHz, CDCl₃) δ 7.05 (d, J=7.3 Hz, 1H), 6.34 (d, J=7.32 Hz, 1H), 4.80 (br, s, 1H), 3.81 (s, 3H), 3.75 (s, 3H), 3.4 (m, 2H), 3.08 (d, J=22.7 Hz), 2.7-2.5 (m, 6H), 1.91 (m, 2H), 1.68 (m, 4H).

5 Step E: 1-(2-Methyl-pyrimidin-5-yl)-7-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-hept-1-en-3-one (1-7)

To a solution of 1-6 (5.5 g, 16.2 mmol), 5-formyl-2-methylpyrimidine (1-6a, 1.8 g, 14.7 mmol; for preparation, see *J. Heterocyclic Chem.*, 28, 1281 (1991)) in 40 mL DMF was added K₂CO₃ (4.07 g, 32 mmol). The mixture was stirred at
10 ambient temperature for 15 hr, and concentrated to a paste. The residue was diluted with water, extracted with ethyl acetate, and dried over magnesium sulfate. Following concentration, the residue was chromatographed on silica gel (70 chloroform / 25 ethyl acetate / 5 methanol) to give 1-7 as a white solid.
R_f = 0.20 (silica, 70 chloroform / 20 ethyl acetate / 10 methanol).

15 ¹H NMR (400 MHz, CDCl₃) δ 8.80 (s, 2H), 7.44 (d, 1H, J=16Hz), 7.05 (d, 1H, J=7Hz), 6.81 (d, 1H, J=16Hz), 6.35 (d, 1H, J=7Hz), 4.72 (br s, 1H), 3.39 (m, 2H), 2.69 (s, 3H), 2.64 (m, 4H), 2.58 (m, 2H), 1.91 (m, 2H), 1.74 (m, 4H).

20 Step F: 2-[1(S or R)-(2-Methyl-pyrimidin-5-yl)-3-oxo-7-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-heptyl]-malonic acid diethyl ester (1-8a)

To a solution of 1-7 (1.0 g, 2.97 mmol) and diethyl malonate (0.717 ml, 4.5 mmol) in ethanol (20 mL) and THF (20 mL) was added sodium ethoxide (0.1 mL of a 30% w/w solution in ethanol). After 4 hr, the mixture (1-8) was concentrated, and the residue purified on a 5 x 50 cm Chiralcel AD column (flow = 80
25 mL/min, A:B = 30:70) (A = 0.1% diethylamine/hexane, B = 2-propanol). Product 1-8a eluted at 15 minutes; its enantiomer, 1-8b, eluted at 26 minutes.

¹H NMR (400 MHz, CDCl₃) δ 8.53 (s, 2H), 7.02 (d, 1H, J=7Hz), 6.28 (d, 1H, J=7Hz), 4.07 (br s, 1H), 4.18 (m, 2H), 4.02 (m, 2H), 3.92 (m, 1H), 3.72 (m, 2H), 3.39 (m, 2H), 2.94 (m, 2H), 2.64 (s, 3H), 2.42 (m, 2H), 2.33 (m, 2H), 1.89 (m, 2H), 1.60
30 (m, 4H), 1.26 (m, 4H), 1.19 (t, 3H, J= 3Hz).

Step G: 3(S or R)-(2-Methyl-pyrimidin-5-yl)-5-oxo-9-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-nonanoic acid ethyl ester (1-10a)

To a solution of 1-8a (0.530 g, 1.07 mmol) in ethanol (5 mL) was added NaOH (1.12 mL of 1N solution in water, 1.12 mmol). After stirring at 40°C for 30 minutes, the mixture was treated with HCl (1.12 mL of 1N solution in water, 1.12 mmol) and concentrated. The residue was suspended in toluene (20 mL) and heated at reflux. After 1 h, evaporation of the solvents gave 1-10a as a yellow oil.
R_f = 0.32 (silica, 70 chloroform / 20 ethyl acetate / 10 methanol).

¹H NMR (400 MHz, CDCl₃) δ 8.54 (s, 2H), 7.04 (d, 1H, J=7Hz), 6.31 (d, 1H, J=7Hz), 4.86 (br s, 1H), 4.04 (q, 2H, J=3 Hz), 3.63 (m, 1H), 3.40 (m, 2H), 2.94-2.48 (m, 9H), 2.37 (m, 4H), 1.89 (m, 2H), 1.57 (m, 4H), 1.19 (t, 3H, J= 3Hz).

Step H: 5,5-Difluoro-3(S or R)-(2-methyl-pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-nonanoic acid ethyl ester (1-11a)

To a solution of the ketone 1-10a (0.74g, 1.8 mmol) in anhydrous dichloromethane (5 mL) under N₂ was added ZnF₂ (0.72 g, 7.0 mmol) followed by DAST (1.4g, 8.7 mmol). The yellowish suspension was heated to 50°C overnight. Additional DAST (2.0 g, 12.4mmol) was then added to the brown suspension and heating was continued for 24 hours. The reaction was cooled to 0°C and 30 mL saturated NaHCO₃ solution was slowly added while stirring. The ice bath was removed after five minutes and the mixture stirred vigorously at room temperature for 30 min. This solution was partitioned between CHCl₃ and saturated NaHCO₃ solution. The aqueous phase was reextracted with CHCl₃. The organic phases were combined and dried with MgSO₄ then concentrated to a brown oil. Flash chromatography (silica; 100 % EtOAc to 85% EtOAc/15% MeOH over 20 min.) and concentration yielded 1-11a as a brown oil.
R_f (silica, EtOAc/MeOH 10:1) = 0.3

Step I: 5,5-Difluoro-3(S or R)-(2-methyl-pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-nonanoic acid (1-12a)

To a solution of the ethyl ester 1-11a (0.13 g, 0.29 mmol) in EtOH (1.5 mL) under N₂ was added 1.0 N NaOH solution (0.44 mL). The reaction was stirred overnight. After adding 1.0 N HCl solution (0.44 mL), the reaction mixture was concentrated. Flash chromatography (silica; 100 to 20% EtOAc-0 to 80% 20:1:1 EtOH/ NH₄OH/ H₂O) and concentration yielded 1-12a as a brownish solid.

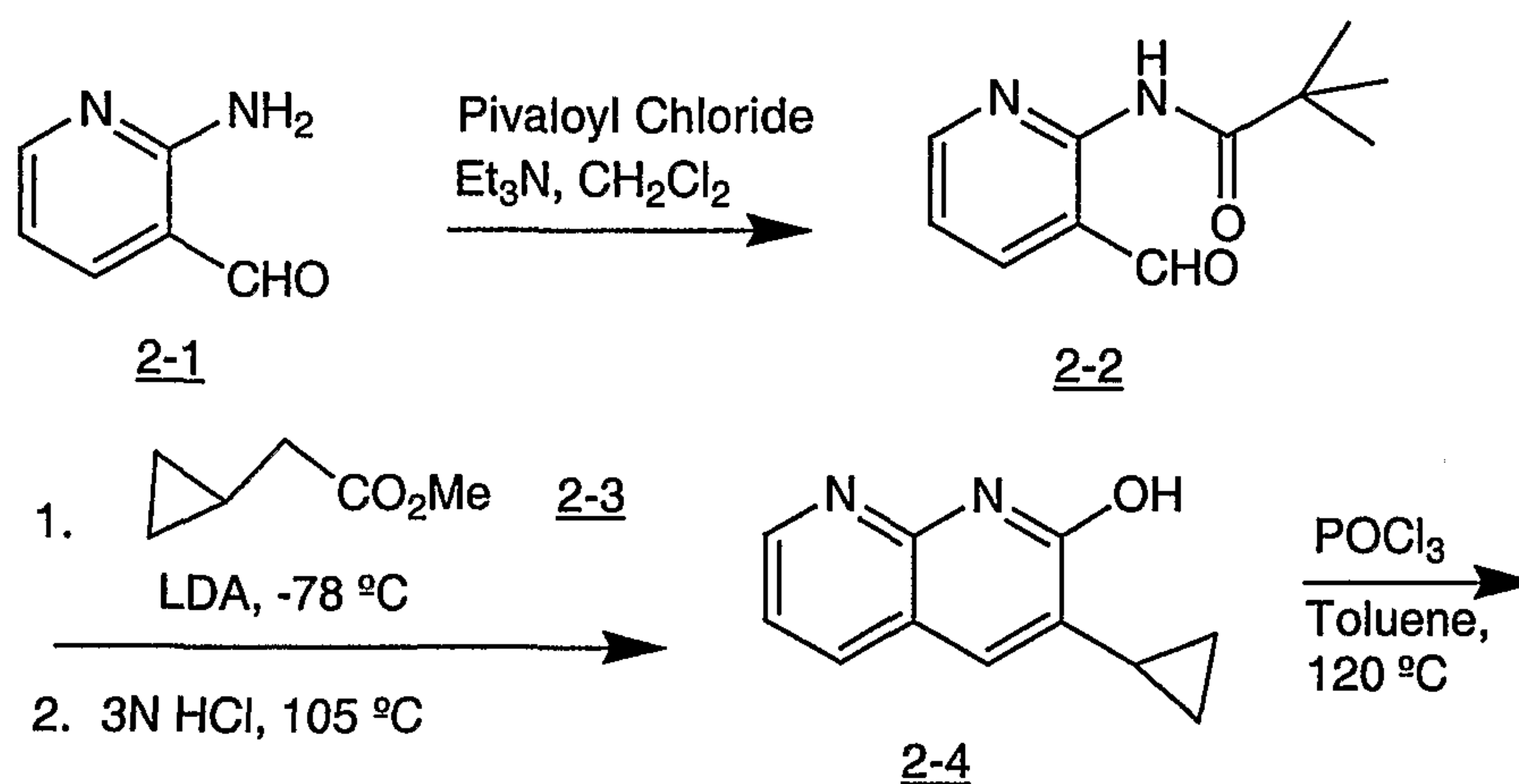
$^1\text{H-NMR}$ ($\text{d}_6\text{-DMSO}$) δ 8.62 (s, 2 H), δ 7.01 (d, $J = 7.3\text{Hz}$, 1 H), δ 6.31 (s, 1 H), δ 6.23 (d, $J = 7.3\text{ Hz}$, 1 H), δ 3.27 (m), δ 3.22 (br t, $J = 5.3\text{ Hz}$, 2 H), δ 2.70-2.49 (m), δ 2.41-2.26 (m, 4 H), δ 1.82-1.71 (m, 4 H), δ 1.54 (m, 2 H), δ 1.33 (m, 2 H).
 MS ($\text{M}^+ + \text{H}$) 419.2224.

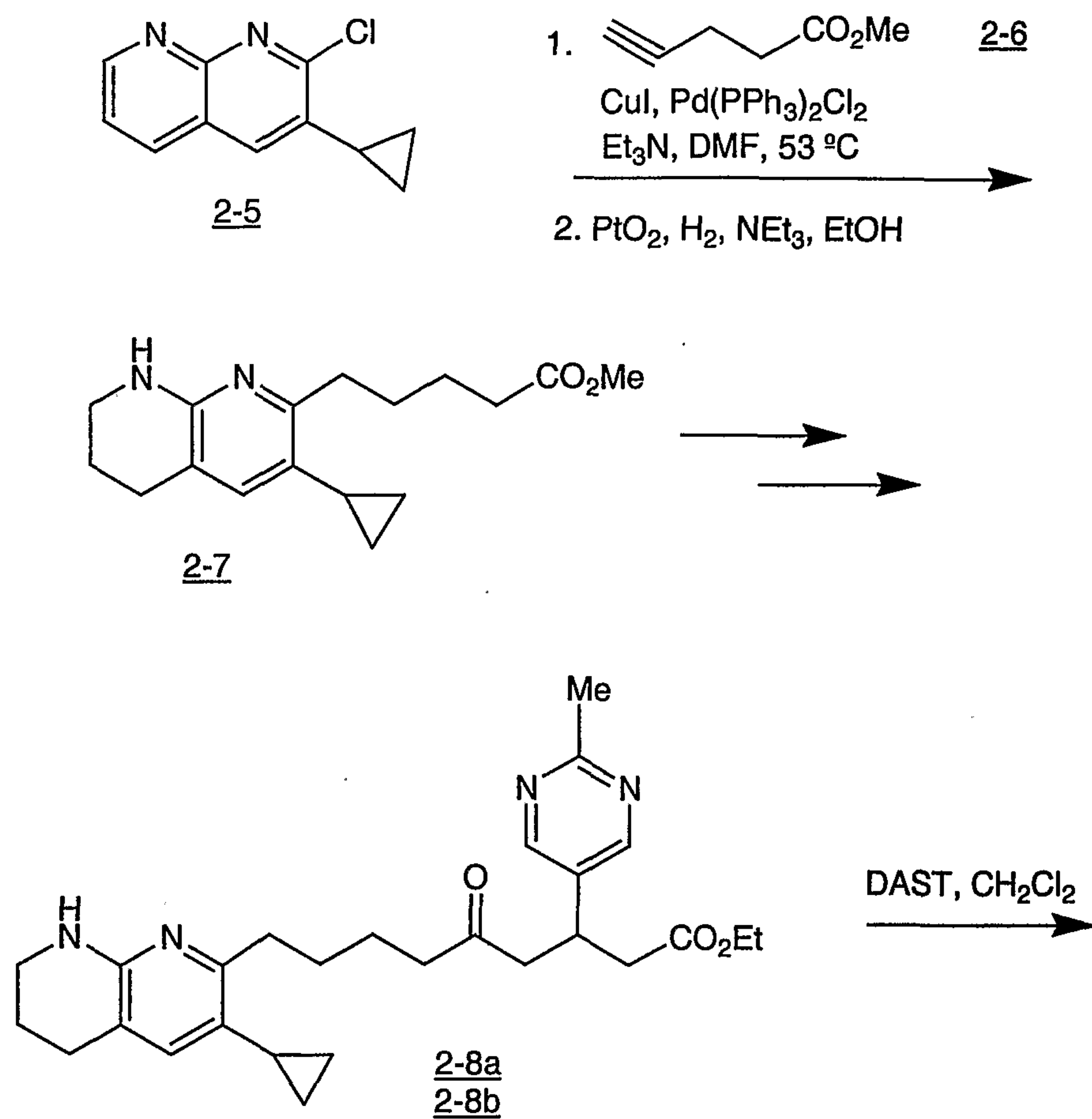
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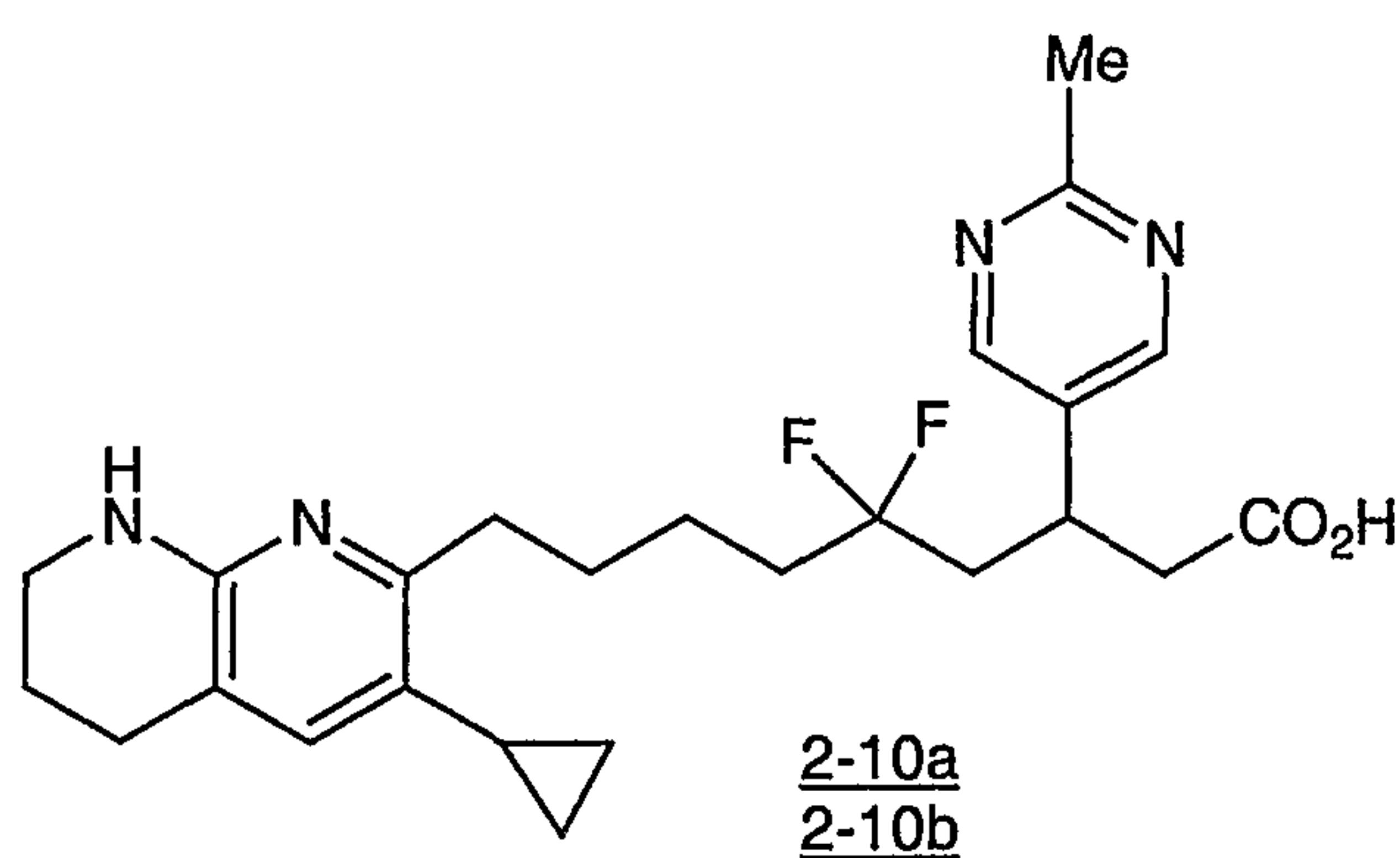
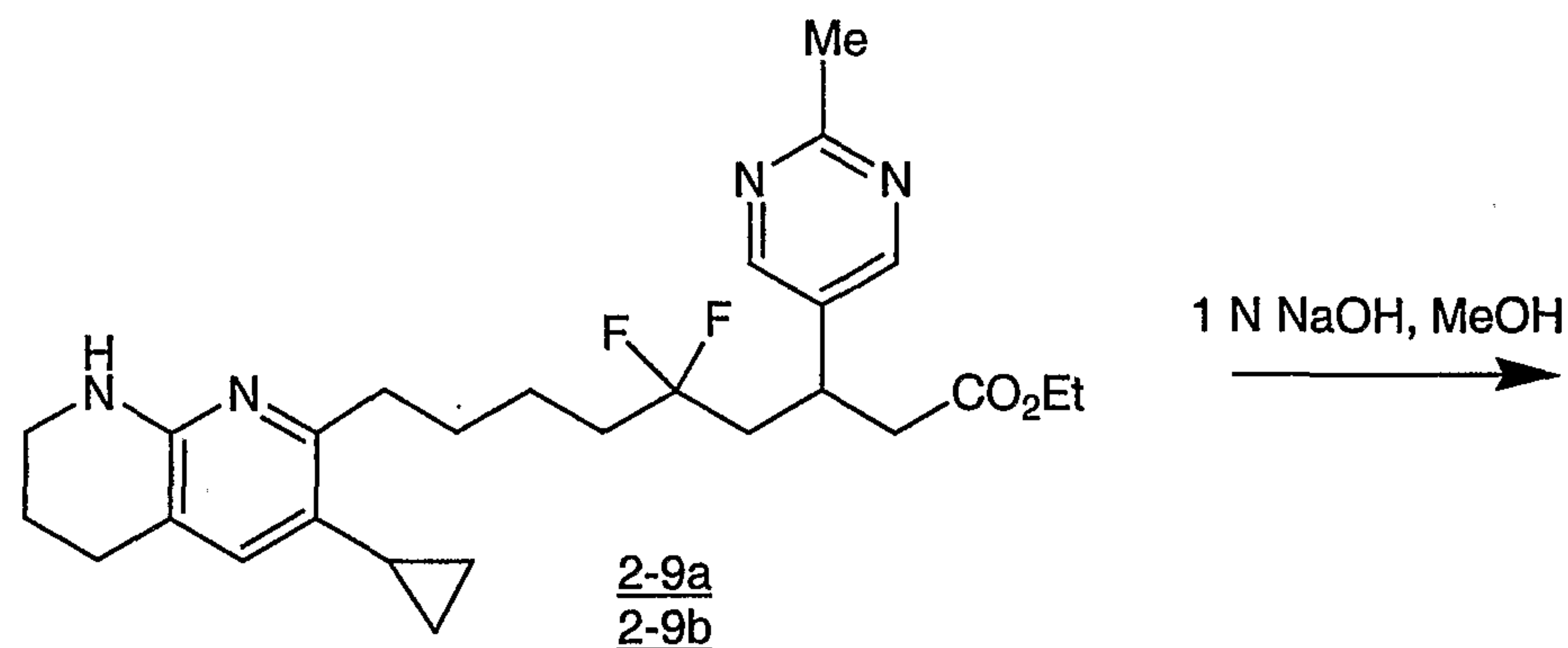
EXAMPLE 2

5,5-Difluoro-3(R or S)-(2-Methyl-pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-nonanoic acid (1-12b)

10 Enantiomer 1-12b is obtained from 1-10b utilizing the same methods described for the preparation of 1-12a in Example 1 above. Its 400 MHz NMR spectrum in $\text{d}_6\text{-DMSO}$ is identical to that of its enantiomer 1-12a.

Scheme 2





EXAMPLE 3

5 9-(3-Cyclopropyl-5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-5,5-difluoro-3(S or R)-
(2-methyl-pyrimidin-5-yl)-nonanoic acid (2-10a)

Step A: N-(3-Formyl-pyridin-2-yl)-2,2-dimethyl-propionamide (2-2)

To a cooled (0°C) solution of 2-amino-3-formylpyridine 2-1 (50g, 409 mmol) in 700 mL of anhydrous CH₂Cl₂ were added Et₃N (80 mL, 532 mmol) in one portion and a solution of trimethylacetyl (pivaloyl) chloride (65 mL, 491 mmol) in 50 mL CH₂Cl₂ gradually over 40 min. The reaction mixture was stirred 30 min and concentrated to a syrup, then 200 mL water was added. The mixture was extracted three times with ethyl acetate. The combined organic layers were washed with water, brine and dried over MgSO₄ and concentrated to afford the desired product 2-2 as a solid.

¹H NMR (400 MHz, CDCl₃): δ 10.85 (s, 1H), 8.70 (s, 1H), 8.0 (s, 1H), 7.20 (q, 1H), 1.30 (s, 9H).

Step B: 3-Cyclopropyl-[1,8] naphthyridin-2-ol (2-4)

To a cooled solution (-78°C) of LDA (2.0 M, 251 mmol) in 600 mL THF was added ester 2-3 (prepared from cyclopropylacetic acid and methanolic HCl solution, 15 g, 131 mmol) gradually over 30 min. The reaction mixture was stirred for 30 min at -78°C . Aldehyde 2-2 (22.5 g, 109 mmol) in 40 mL THF was added. The reaction mixture was stirred at -78°C for 1 hr, then was warmed up to room temperature over 1 hr and quenched with 200 mL NH_4Cl (sat.). The mixture was extracted three times with ethyl acetate. The combined organic layers were washed with water, brine and dried over MgSO_4 and concentrated to give a viscous residue which was subsequently dissolved in 200 mL of 3N HCl. The mixture was refluxed at 105°C for 24 hr. After concentration, the residue was poured into 500 mL ice-water and quenched with K_2CO_3 gradually ($\text{pH}=9$) to yield a solid as the desired product 2-4, which was filtered and dried in vacuum.

^1H NMR (400 MHz, CD_3OD): δ 8.45 (q, 1H), 7.99 (q, 1H), 7.47 (s, 1H), 7.23 (q, 1H), 2.14 (m, 1H), 1.01 (m, 2H), 0.78 (m, 2H).

Step C: 2-Chloro-3-cyclopropyl-[1,8]naphthyridine (2-5)

A mixture of naphthyridine 2-4 (14 g, 77 mmol) and 100 mL POCl_3 and 0.1 mL DMF was refluxed at 120°C for 3 hr and concentrated. The residue was treated with 300 mL ice-water and solid K_2CO_3 until $\text{pH}=9$. The mixture was extracted three times with ethyl acetate, washed with brine and dried over MgSO_4 . After solvent removal, the desired compound 2-5 was obtained as a yellowish solid.

^1H NMR (400 MHz, CDCl_3): δ 9.00 (q, 1H), 8.10 (q, 1H), 7.78 (s, 1H), 7.50 (q, 1H), 2.34 (m, 1H), 1.00 (m, 2H), 0.82 (m, 2H).

Step D: 5-(3-Cyclopropyl-5,6,7,8-tetrahydro[1,8]naphthyridin-2-yl)-pentanoic acid methyl ester (2-7)

A mixture of naphthyridine 2-5 (15.8 g, 77.2 mmol), ester 2-6 (prepared from 4-pentynoic acid and methanolic HCl solution, 11.3 g, 100.4 mmol), CuI (0.7 g, 3.9 mmol), 100 mL Et_3N and 100 mL DMF was gently degassed with argon for 10 min. Then $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ was added in one portion. The reaction mixture was heated at 53°C for 20 hr, cooled to room temperature and quenched with 500 mL water and 100 mL NaHCO_3 (sat.). The aqueous mixture was extracted three times with ethyl acetate. The combined organic layer was washed with brine and dried over

MgSO₄. After solvent removal, the residue was purified by silica gel flash chromatography (EtOAc/Hexane=1/4 to 100% EtOAc over 30 min) to afford an oil, which was subsequently dissolved in 150 mL THF and 50 mL EtOH. Et₃N (15 mL, 104 mmol) and PtO₂ (0.7 g) were added. The mixture was degassed under moderate vacuum and subjected to balloon hydrogenation condition for 6 hrs. It was then filtered and concentrated to provide the desired product 2-7 as an oil.

¹H NMR (400 MHz, CDCl₃): δ 6.80 (s, 1H), 4.75 (s, 1H), 3.62 (s, 3H), 3.36 (m, 2H), 2.76(t, 2H), 2.64 (t, 2H), 2.36 (t, 2H), 1.88 (m, 2H), 1.78 (m, 5H), 0.86 (m, 2H), 0.50 (m, 2H).

Step E: 3(S or R)-(2-Methylpyrimidin-5-yl)-5-oxo-9-(3-cyclopropyl-5,6,7,8-tetrahydro[1,8]naphthyridin-2-yl)-nonanoic acid ethyl ester (2-8a)

Following procedures described in Scheme 1 for the conversion of 1-5 into 1-11a and 1-11b, 2-8a and 2-8b were prepared from 2-7, each as a solid.

Resolution of the enantiomers was carried out by chiral chromatography of the keto diester intermediate corresponding to 1-8.

¹H NMR (300 MHz, CD₃OD): δ 8.65 (s, 2H), 7.22 (s, 1H), 3.74 (m, 1H), 3.40 (t, 2H), 3.10 (m, 1H), 2.90-2.40 (m, 14 H). 1.95-1.60 (m, 5H), 0.94 (m, 2H), 0.60 (m, 2 H).

Step F: 9-(3-Cyclopropyl-5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-5,5-difluoro-3(S or R)-(2-methyl-pyrimidin-5-yl)-nonanoic acid ethyl ester (2-9a)

A solution of the ketone 2-8a (0.20 g, 0.43 mmol) and DAST (1.0 mL) in a sealed tube under Ar was heated to 60°C overnight. The brown solution was cooled to room temperature, diluted with 10 mL CH₂Cl₂, and added slowly to a stirring mixture of 80 mL CH₂Cl₂ and 20 mL saturated NaHCO₃ and then separated. The organic layer was washed with water and brine, then dried with MgSO₄ and concentrated to a dark brown oil. Flash chromatography (silica; 90% EtOAc-10% 20:1:1 EtOH/ NH₄OH/ H₂O) and concentration gave 2-9a as a brown oil.

¹H-NMR (CDCl₃) δ 8.53 (s, 2 H), 6.84 (s, 1 H), δ 5.11 (br s, 1 H), 4.05 (q, J = 7.0 Hz, 2 H), 3.51 (m, 1 H), 3.38 (m, 2 H), 2.99 (m, 1 H), δ 2.72 (m), 2.25 (m, 2 H), 1.63-1.93 (m, 6 H), 1.53 (m, 2 H), 1.16 (t, J = 7.2 Hz, 3 H), 0.85 (m, 2 H), 0.50 (m, 2 H). MS (M⁺ + H) 487.0.

Step G: 9-(3-Cyclopropyl-5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-5,5-difluoro-3(S or R)-(2-methyl-pyrimidin-5-yl)-nonanoic acid (2-10a)

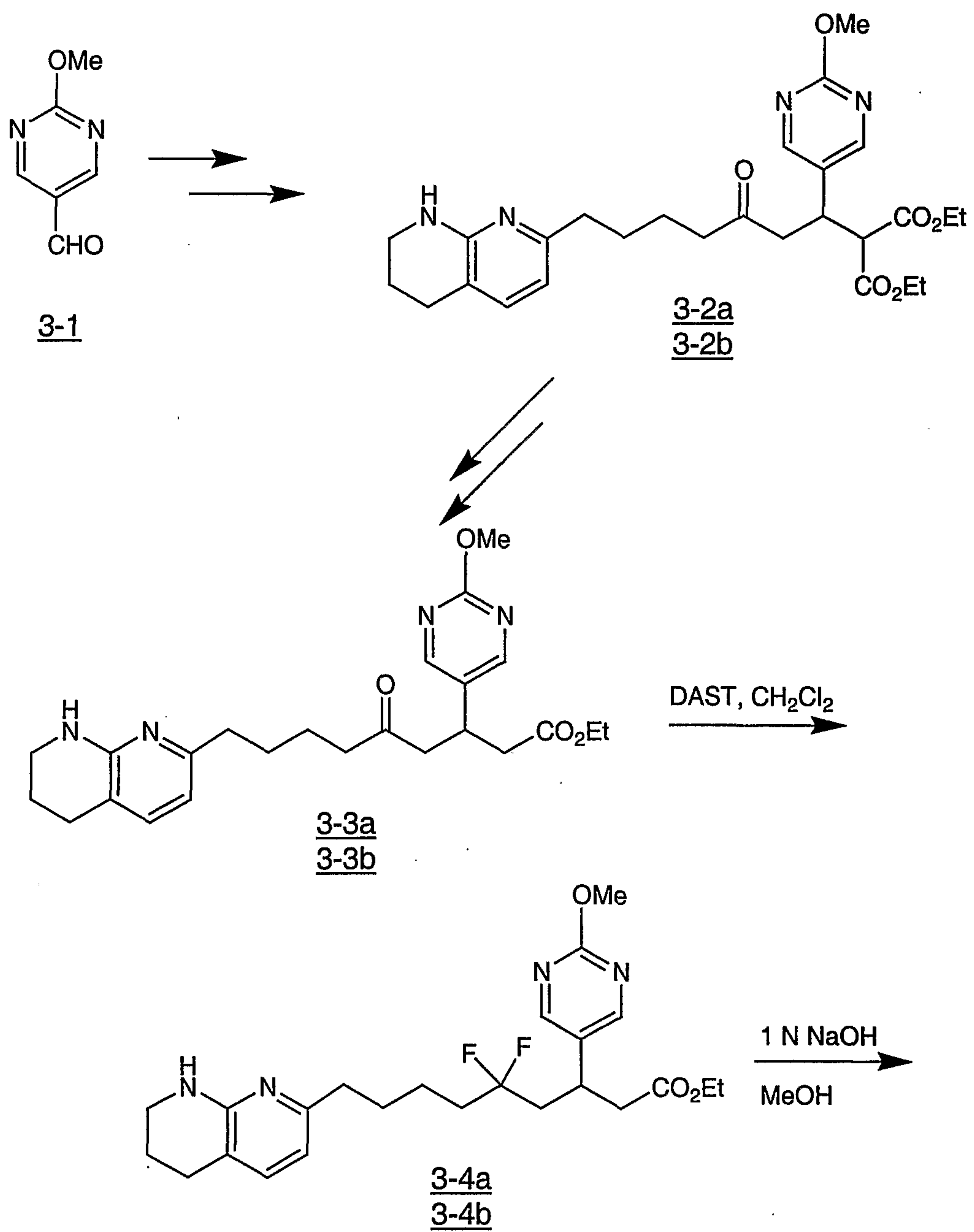
To a solution of the ethyl ester 2-9a (0.047 g, 0.097 mmol) in EtOH
5 (1.0 mL) under argon was added 1.0 N NaOH solution (0.15 mL). The reaction was stirred overnight. After adding 1.0 N HCl solution (0.15 mL), the reaction was concentrated. Flash chromatography (silica; 45% EtOAc-55% 20:1:1 EtOH/ NH₄OH/ H₂O) and concentration afforded 2-10a as a tan solid.
¹H-NMR (d₆-DMSO) δ 8.64 (s, 2 H), 6.82 (s, 1 H), 6.45 (br s, 1 H), 3.48-3.17 (m),
10 2.78-2.56 (m), 2.33 (m, 2 H), 1.91-1.69 (m, 4 H), 1.59 (m, 2 H), δ 1.41 (m, 2 H), 0.79 (m, 2 H), 0.47 (m, 2 H).
MS (M⁺ + H) 459.2590.

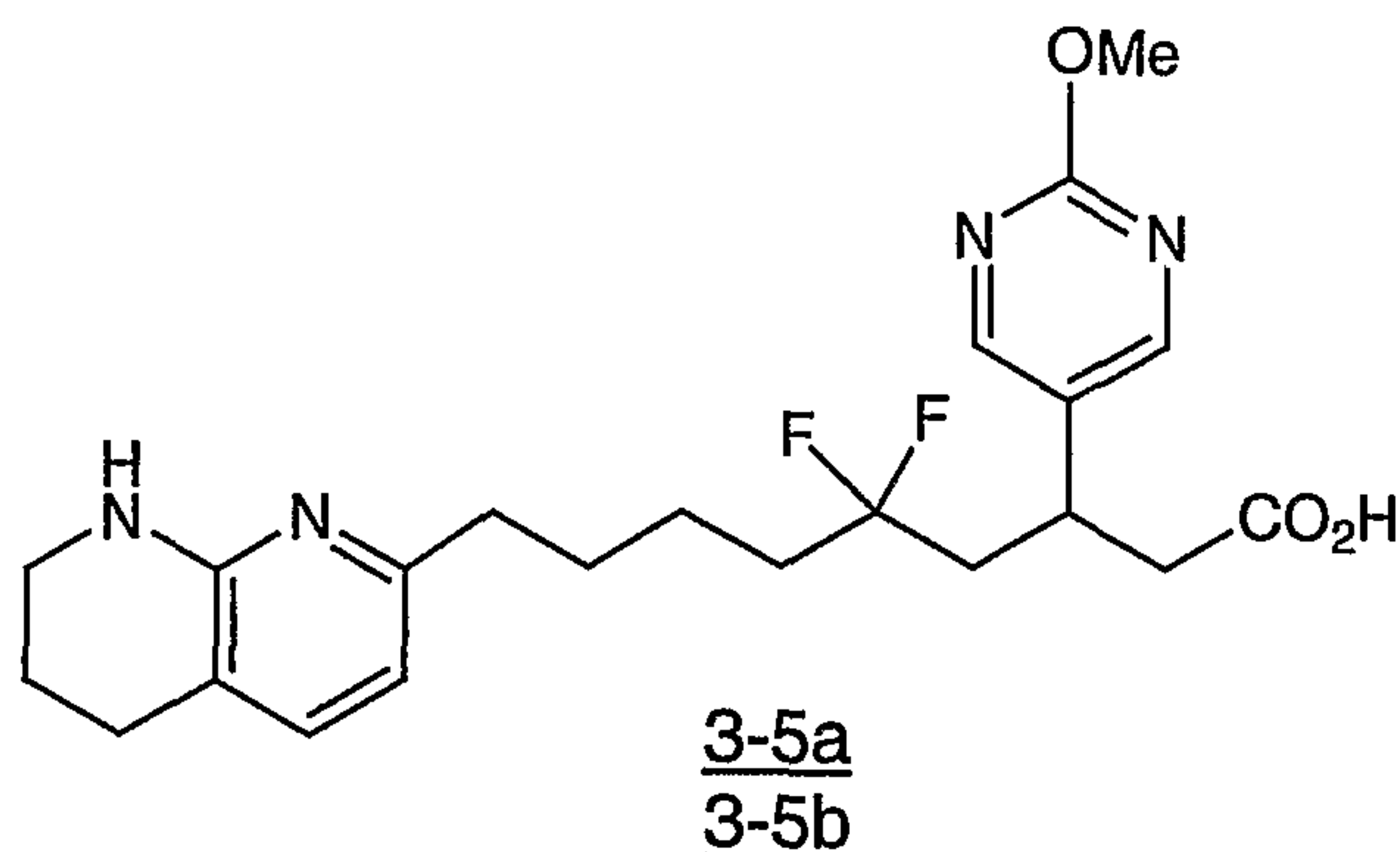
EXAMPLE 4

15

9-(3-Cyclopropyl-5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-5,5-difluoro-3(R or S)-(2-methyl-pyrimidin-5-yl)-nonanoic acid (2-10b)

Enantiomer 2-10b is obtained from 2-8b utilizing the same methods described for the preparation of 2-10a in Example 3 above. Its 400 MHz NMR
20 spectrum in d₆-DMSO is identical to that of its enantiomer 2-10a.

Scheme 3

EXAMPLE 5

5 5,5-Difluoro-3(S or R)-(2-Methoxy-pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-nonanoic acid (3-5a)

Step A: 3(S or R)-(2-Methoxy-pyrimidin-5-yl)-5-oxo-9-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-nonanoic acid ethyl ester (3-3a)

10 2-Methoxy-pyrimidine-5-carboxaldehyde (3-1) (Gupton, J.T.; Gall, J.E.; Riesinger, S.W.; Smith, S.Q.; Bevirt, K.M.; Sikorski, J.A.; Dahl, M.L.; Arnold, Z., *J. Heterocyclic Chem.* 1991, 28, 1281) was converted into keto-diesters 3-2 as per Scheme 1. Separation of the enantiomers of racemic keto-diesters 3-2 was accomplished by HPLC (Chiralcel AD; 50x500 mm column; 70/20 isopropanol/hexanes/0.1% diethylamine over 60 minutes at a flow rate of 80.0 mL/min) to give two enantiomers (R_T = 20-29 min and 32-40 min). Monohydrolysis and decarboxylation of diesters 3-2a and 3-2b as per Scheme 1 provided ethyl esters 3-3a and 3-3b.

TLC R_f = 0.1 (15:15:0.5 EtOAc/EtOH/aq. NH_4OH).

20 ^1H NMR (300 MHz, CD_3OD): δ 8.50 (s, 2H), 7.41 (d, $J=7.2$ Hz, 1H), 6.47 (d, $J=7.2$ Hz, 1H), 3.96 (s, 3H), 3.67 (m, 1H), 3.43 (m, 2H), 3.01 (m, 1H), 2.76 (m, 3H), 2.50 (m, 6H), 1.96 (m, 2H), 1.62 (m, 4H) ppm.

Step B: 5,5-Difluoro-3(S or R)-(2-methoxy-pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-nonanoic acid ethyl ester (3-4a)

To a solution of the ketone 3-3a (50.1 g, 113.7 mmol) in anhydrous dichloromethane (50 mL) under N_2 was added DAST reagent (110.0 g, 682.4 mmol).

The dark solution was heated to 50°C overnight. While stirring, the reaction was slowly added to a 2 L beaker filled with ice. After adding EtOAc (100 mL) the mixture was basified to pH 4-5 with 50% NaOH solution, then to pH 8 with NaHCO₃. The aqueous phase was extracted three times with diethyl ether. The organic phases
5 were combined, dried with MgSO₄, then concentrated to a brown oil. Flash chromatography on silica gel (100 to 95% EtOAc-0 to 5% 20:1:1 EtOH/ NH₄OH/ H₂O over 20 min.) and concentration yielded 3-4a as a yellowish oil.

¹H-NMR (CDCl₃): δ 8.39 (s, 2 H), δ 7.06 (d, J = 7.3 Hz, 1 H), δ 6.32 (d, J = 7.3 Hz, 1 H), δ 4.75 (br s, 1 H), δ 4.06 (m, 2 H). δ 3.99 (s, 3 H), δ 3.47 (m, 1 H), δ 3.39 (m, 2
10 H), δ 2.78 (dd, J = 16.1, 6.0 Hz, 1 H), δ 2.69 (t, J = 6.3 Hz, 2 H), δ 2.59 (dd, J = 15.9, 9.0 Hz, 1 H), δ 2.52 (t, J = 7.6 Hz, 2 H), δ 2.20 (m, 2 H), δ 1.90 (m, 2 H), δ 1.79 (m), δ 1.66(m, 2 H), δ 1.48 (m, 2 H). δ 1.17 (t, J = 7.2 Hz, 3 H).

MS (M⁺ + H) 463.1.

15 Step C: 5,5-Difluoro-3(S or R)-(2-methoxy-pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-nonanoic acid (3-5a)

To a solution of the ester 3-4a (0.11 g, 0.26 mmol) in MeOH (2.0 mL) under N₂ was added 1.0 N NaOH solution (0.385 mL). The reaction was done within 6-7 hrs. After adding 1.0 N HCl solution (0.385 mL), the reaction was concentrated.

20 Flash chromatography on silica gel (100 to 20% EtOAc-0 to 80% 20:1:1 EtOH/ NH₄OH/ H₂O over 15 min.) and concentration afforded 3-5a as a tan solid.

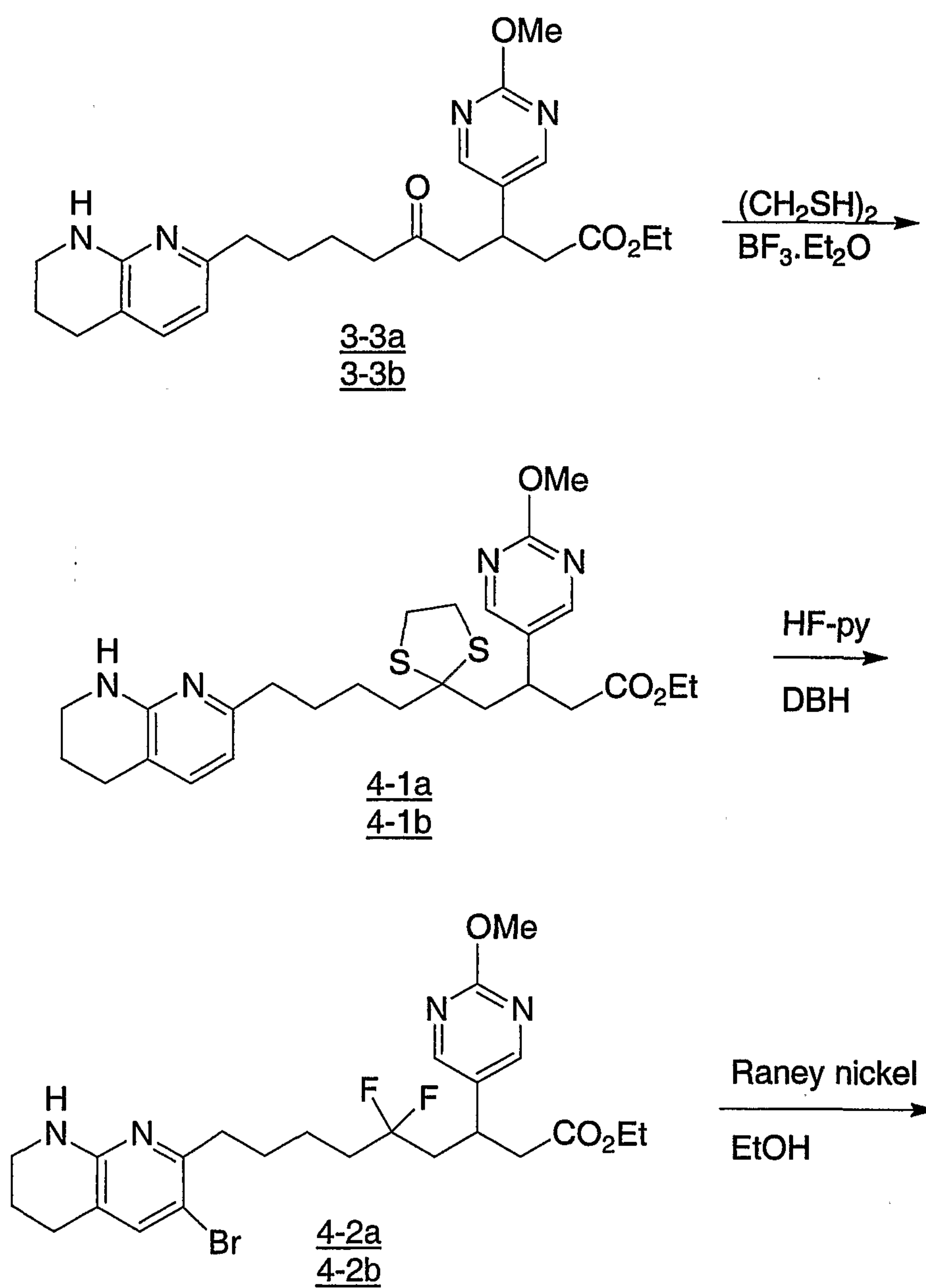
¹H-NMR (d₆-DMSO): δ 8.55 (s, 2 H), 7.02 (d, J = 7.3 Hz, 1 H), 6.31 (br s, 1 H), 6.23 (d, J = 7.1 Hz, 1 H), 3.87 (s, 3 H), 3.31-3.21 (m), 2.73-2.50 (m, 6 H), 2.40 (t, J = 7.5 Hz, 2 H), 2.35-2.25 (m, 2 H), 1.91-1.74 (m, 4 H), 1.55 (m, 2 H), 1.33 (m, 2 H).

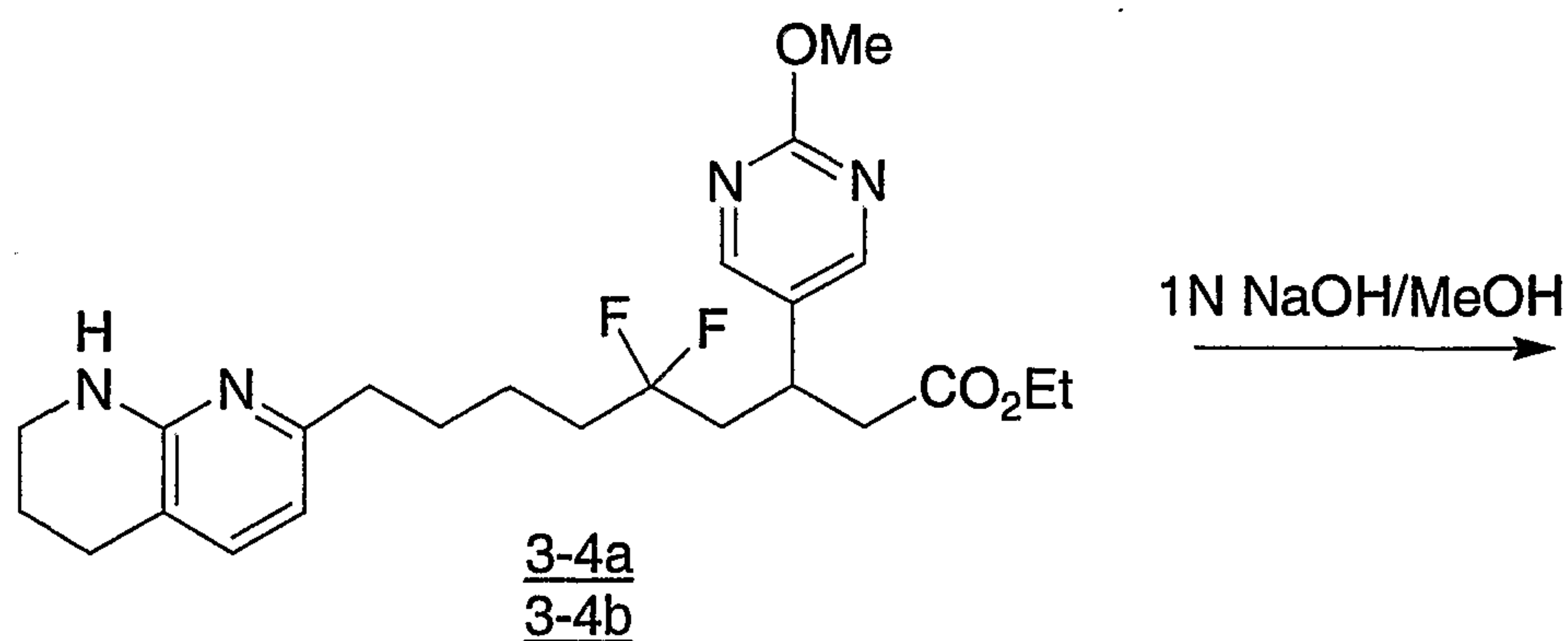
25 MS (M⁺ + H) 435.2186.

EXAMPLE 6

5,5-Difluoro-3(R or S)-(2-Methoxy-pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-nonanoic acid (3-5b)
30

Enantiomer 3-5b is obtained from 3-3b utilizing the same methods described for the preparation of 3-5a in Example 5 above. Its 400 MHz NMR spectrum in d₆-DMSO is identical to that of its enantiomer 3-5a.

Scheme 4

EXAMPLE 7

5

Alternative preparation of 5,5-difluoro-3(S or R)-(2-methoxy-pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-nonanoic acid (3-5a)

10 Step A: 3-(S or R) (2-methoxy-pyrimidin-5-yl)-4-{2-[4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl]-1,3-dithiolan-2-yl}butanoic acid ethyl ester (4-1a)

15 To a mixture of 3-3a (7.6 g, 17.4 mmol) and 1,2-ethanedithiol (17.5 mL, 208.6mmol) in 25 mL AcOH was added BF₃.OEt₂ (17.5 mL, 138.1 mmol) dropwise at 0°C under nitrogen. The reaction mixture was stirred at 0 C for 0.5 hr, then at rt for 3.5 hr. The reaction mixture was slowly poured into ice-cooled 300 mL NaHCO₃ (sat.) and extracted with diethyl ether (2 x 200 mL). The organic layers were combined and washed with brine and dried over Na₂SO₄. After removal of the solvent, the residue was purified by flash chromatography on silica gel (100% EtOAc) to afford the desired product 4-1a as an oil.

LC/MS (M + 1) calculated = 517.71; observed = 517.2.

Step B: 5,5-Difluoro-3(S or R)-(2-methyl-pyrimidin-5-yl)-9-(3-bromo-5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-nonanoic acid ethyl ester (4-2a)

5 To a suspension of 1,3-dibromo-5,5-dimethylhydantoin (DBH) (12.9 g, 45.3 mmol) in 80 mL of anhydrous methylene chloride at -78°C under nitrogen was added HF-pyridine (70%HF, 11.3 mL, 49.8 mmol) and 4-1a (10.5 g, 20.4 mmol) in 15 mL of anhydrous methylene chloride. The reaction mixture was stirred at -78°C for 15 min, then poured into 350 mL ice-cooled saturated aqueous NaHCO_3 . The
10 mixture was stirred at 0°C for 0.5 hr, then extracted with diethyl ether (2 x 200 mL). The combined organic layers were washed with brine and dried over Na_2SO_4 . After removal of the solvent, the residue was purified over flash chromatography on silica gel (5%EtOAc/95%Hexanes to 100% EtOAc) to afford the desired product 4-2a as an oil.

15 LC/MS (M + 1) calculated = 543.4; observed = 543.1.

Step C: 5,5-Difluoro-3(S or R)-(2-methoxy-pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-nonanoic acid ethyl ester (3-4a)

20 A mixture of 4-2a (2.6 g, 4.9 mmol) and Raney Nickel (50% in water, 30 mL) in 50 mL ethanol was stirred at room temperature for 48 hr and filtered. The organic phases were combined and dried with MgSO_4 then concentrated to a brown oil. Flash chromatography on silica gel (100 to 95% EtOAc-0 to 5% 20:1:1 EtOH/ NH_4OH / H_2O over 20 min.) and concentration yielded 3-4a as a yellowish oil.

25 ^1H -NMR (CDCl_3): δ 8.39 (s, 2 H), δ 7.06 (d, $J = 7.3$ Hz, 1 H), δ 6.32 (d, $J = 7.3$ Hz, 1 H), δ 4.75 (br s, 1 H), δ 4.06 (m, 2 H). δ 3.99 (s, 3 H), δ 3.47 (m, 1 H), δ 3.39 (m, 2 H), δ 2.78 (dd, $J = 16.1, 6.0$ Hz, 1 H), δ 2.69 (t, $J = 6.3$ Hz, 2 H), δ 2.59 (dd, $J = 15.9, 9.0$ Hz, 1 H), δ 2.52 (t, $J = 7.6$ Hz, 2 H), δ 2.20 (m, 2 H), δ 1.90 (m, 2 H), δ 1.79 (m), δ 1.66(m, 2 H), δ 1.48 (m, 2 H). δ 1.17 (t, $J = 7.2$ Hz, 3 H).

MS ($\text{M}^+ + \text{H}$) 463.1.

30

Step D: 5,5-Difluoro-3(S or R)-(2-methoxy-pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-nonanoic acid (3-5a)

35 To a solution of the ester 3-4a (0.11 g, 0.26 mmol) in MeOH (2.0 mL) under N_2 was added 1.0 N NaOH solution (0.385 mL). The reaction was done within 6-7 hrs. After adding 1.0 N HCl solution (0.385 mL), the reaction was concentrated.

Flash chromatography on silica gel (100 to 20% EtOAc-0 to 80% 20:1:1 EtOH/
NH₄OH/ H₂O over 15 min.) and concentration afforded 3-5a as a solid.

¹H-NMR (d₆-DMSO): δ 8.55 (s, 2 H), 7.02 (d, J = 7.3 Hz, 1 H), 6.31 (br s, 1 H), 6.23
(d, J = 7.1 Hz, 1 H), 3.87 (s, 3 H), 3.31-3.21 (m), 2.73-2.50 (m, 6 H), 2.40 (t, J = 7.5
5 Hz, 2 H), 2.35-2.25 (m, 2 H), 1.91-1.74 (m, 4 H), 1.55 (m, 2 H), 1.33 (m, 2 H).
MS (M⁺ + H) 435.2186.

EXAMPLE 8

10 Alternative preparation of 5,5-difluoro-3(R or S)-(2-methoxy-pyrimidin-5-yl)-9-
(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-nonanoic acid (3-5b)

Enantiomer 3-5b is obtained from 3-3b by way of the 1,3-dithiolane
intermediate 4-1b utilizing the same methods described for the preparation of 3-5a in
15 Example 7 above. Its 400 MHz NMR spectrum in d₆-DMSO is identical to that of its
enantiomer 3-5a.

The following chain-fluorinated compounds of the present invention
are also prepared according to the Schemes and Examples shown above by
20 nucleophilic fluorination of the corresponding 5- or 7-keto intermediates and
hydrolysis of the resulting esters:

5,5-Difluoro-3(S)-(pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-[1,8]-naphthyridin-2-yl)-
nonanoic acid;

25

5,5-Difluoro-3(R)-(pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-[1,8]-naphthyridin-2-yl)-
nonanoic acid;

30

3(S)-(2-Cyclopropyl-pyrimidin-5-yl)-5,5-difluoro-9-(5,6,7,8-tetrahydro-[1,8]-
naphthyridin-2-yl)-nonanoic acid;

3(R)-(2-Cyclopropyl-pyrimidin-5-yl)-5,5-difluoro-9-(5,6,7,8-tetrahydro-[1,8]-
naphthyridin-2-yl)-nonanoic acid;

- 5,5-Difluoro-3(S)-(2-methyl-pyrimidin-5-yl)-9-(3-methyl-5,6,7,8-tetrahydro-[1,8]-naphthyridin-2-yl)-nonanoic acid;
- 5,5-Difluoro-3(R)-(2-methyl-pyrimidin-5-yl)-9-(3-methyl-5,6,7,8-tetrahydro-[1,8]-naphthyridin-2-yl)-nonanoic acid;
- 5 7,7-Difluoro-3(S)-(2-methyl-pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-[1,8]-naphthyridin-2-yl)-nonanoic acid;
- 10 7,7-Difluoro-3(R)-(2-methyl-pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-[1,8]-naphthyridin-2-yl)-nonanoic acid;
- 5,5-Difluoro-3(S)-(quinolin-3-yl)-9-(5,6,7,8-tetrahydro-[1,8]-naphthyridin-2-yl)-nonanoic acid;
- 15 5,5-Difluoro-3(R)-(quinolin-3-yl)-9-(5,6,7,8-tetrahydro-[1,8]-naphthyridin-2-yl)-nonanoic acid;
- 3(S)-(6-Ethoxy-pyridin-3-yl)-5,5-difluoro-9-(5,6,7,8-tetrahydro-[1,8]-naphthyridin-2-yl)-nonanoic acid;
- 20 3(R)-(6-Ethoxy-pyridin-3-yl)-5,5-difluoro-9-(5,6,7,8-tetrahydro-[1,8]-naphthyridin-2-yl)-nonanoic acid;
- 5,5-Difluoro-3(S)-(6-methoxy-pyridin-3-yl)-9-(3-methyl-5,6,7,8-tetrahydro-[1,8]-naphthyridin-2-yl)-nonanoic acid;
- 5,5-Difluoro-3(R)-(6-methoxy-pyridin-3-yl)-9-(3-methyl-5,6,7,8-tetrahydro-[1,8]-naphthyridin-2-yl)-nonanoic acid;
- 30 5,5-Difluoro-3(S)-(2-methoxy-pyrimidin-5-yl)-9-(3-cyclopropyl-5,6,7,8-tetrahydro-[1,8]-naphthyridin-2-yl)-nonanoic acid;
- 5,5-Difluoro-3(R)-(2-methoxy-pyrimidin-5-yl)-9-(3-cyclopropyl-5,6,7,8-tetrahydro-[1,8]-naphthyridin-2-yl)-nonanoic acid;
- 35

- 5,5-Difluoro-3(S)-(2-isopropyl-pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-[1,8]-naphthyridin-2-yl)-nonanoic acid;
- 5 5,5-Difluoro-3(R)-(2-isopropyl-pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-[1,8]-naphthyridin-2-yl)-nonanoic acid;
- 3(S)-(2-tert-Butyl-pyrimidin-5-yl)-5,5-difluoro-9-(5,6,7,8-tetrahydro-[1,8]-naphthyridin-2-yl)-nonanoic acid;
- 10 3(R)-(2-tert-Butyl-pyrimidin-5-yl)-5,5-difluoro-9-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-nonanoic acid;
- 3(S)-(2-Ethoxy-pyrimidin-5-yl)-5,5-difluoro-9-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-nonanoic acid;
- 15 2-yl)-nonanoic acid;
- 3(R)-(2-Ethoxy-pyrimidin-5-yl)-5,5-difluoro-9-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-nonanoic acid;
- 5,5-Difluoro-3(S)-(quinoxalin-2-yl)-9-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-nonanoic acid;
- 20 nonanoic acid;
- 5,5-Difluoro-3(R)-(quinoxalin-2-yl)-9-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-nonanoic acid;
- 25 5,5-Difluoro-3(S)-(pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-5H-pyrido[2,3-b]azepin-2-yl)-nonanoic acid;
- 5,5-Difluoro-3(R)-(pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-5H-pyrido[2,3-b]azepin-2-yl)-nonanoic acid;
- 30 5,5-Difluoro-3(S)-(2-methyl-pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-5H-pyrido[2,3-b]azepin-2-yl)-nonanoic acid;
- 5,5-Difluoro-3(R)-(2-methyl-pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-5H-pyrido[2,3-b]azepin-2-yl)-nonanoic acid;
- 35 b]azepin-2-yl)-nonanoic acid;

5,5-Difluoro-3(S)-(2-methoxy-pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-5H-pyrido[2,3-b]azepin-2-yl)-nonanoic acid;

5 5,5-Difluoro-3(R)-(2-methoxy-pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-5H-pyrido[2,3-b]azepin-2-yl)-nonanoic acid;

5,5-Difluoro-3(S)-(2,3-dihydro-benzofuran-6-yl)-9-(5,6,7,8-tetrahydro-[1,8]-naphthyridin-2-yl)-nonanoic acid;

10

5,5-Difluoro-3(R)-(2,3-dihydro-benzofuran-6-yl)-9-(5,6,7,8-tetrahydro-[1,8]-naphthyridin-2-yl)-nonanoic acid;

5,5-Difluoro-3(S)-9-(6-methylamino-pyridin-2-yl)-3-(pyrimidin-5-yl)-nonanoic acid;

15

5,5-Difluoro-3(R)-9-(6-methylamino-pyridin-2-yl)-3-(pyrimidin-5-yl)-nonanoic acid;

3(S)-(2-Ethoxy-pyrimidin-5-yl)-5,5-difluoro-9-(6,7,8,9-tetrahydro-5H-pyrido[2,3-b]azepin-2-yl)-nonanoic acid;

20

3(R)-(2-Ethoxy-pyrimidin-5-yl)-5,5-difluoro-9-(6,7,8,9-tetrahydro-5H-pyrido[2,3-b]azepin-2-yl)-nonanoic acid;

5,5-Difluoro-3(S)-(pyrazin-2-yl)-9-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-nonanoic acid;

25

5,5-Difluoro-3(R)-(pyrazin-2-yl)-9-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-nonanoic acid;

5,5-Difluoro-3(S)-(2-methyl-pyrazin-5-yl)-9-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-nonanoic acid;

30

5,5-Difluoro-3(R)-(2-methyl-pyrazin-5-yl)-9-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-nonanoic acid;

35

5,5-Difluoro-3(S)-(6-methoxy-pyridazin-3-yl)-9-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-nonanoic acid;

5 5,5-Difluoro-3(R)-(6-methoxy-pyridazin-3-yl)-9-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-nonanoic acid;

5,5-Difluoro-3(S)-(2-methylamino-pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-nonanoic acid;

10 5,5-Difluoro-3(R)-(2-methylamino-pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-nonanoic acid;

15 5,5-Difluoro-3(S)-(3,4-dihydro-2H-1,4-dioxo-5-aza-naphthalen-7-yl)-9-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-nonanoic acid;

5,5-Difluoro-3(R)-(3,4-dihydro-2H-1,4-dioxo-5-aza-naphthalen-7-yl)-9-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-nonanoic acid;

20 5,5-Difluoro-3(S)-(2-methyl-pyrimidin-5-yl)-9-(6-methyl-5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-nonanoic acid;

5,5-Difluoro-3(R)-(2-methyl-pyrimidin-5-yl)-9-(6-methyl-5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-nonanoic acid;

25 3(S)-(Benzofuran-6-yl)-5,5-difluoro-9-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-nonanoic acid;

3(R)-(Benzofuran-6-yl)-5,5-difluoro-9-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-nonanoic acid;

30 5,5-Difluoro-3(S)-(5-methoxy-pyridin-3-yl)-9-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-nonanoic acid;

35 5,5-Difluoro-3(R)-(5-methoxy-pyridin-3-yl)-9-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-nonanoic acid;

3(S)-(2-Ethoxy-pyrimidin-5-yl)-5,5-difluoro-9-(5,6,7,8-tetrahydro-5H-pyrido[2,3-b]azepin-2-yl)-nonanoic acid;

3(R)-(2-Ethoxy-pyrimidin-5-yl)-5,5-difluoro-9-(5,6,7,8-tetrahydro-5H-pyrido[2,3-b]azepin-2-yl)-nonanoic acid;

5,5-Difluoro-3(S)-(2-methoxy-pyrimidin-5-yl)-9-(3-methyl-5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-nonanoic acid;

5,5-Difluoro-3(R)-(2-methoxy-pyrimidin-5-yl)-9-(3-methyl-5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-nonanoic acid;

5,5-Difluoro-3(S)-(quinolin-3-yl)-9-(3-methyl-5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-nonanoic acid;

5,5-Difluoro-3(R)-(quinolin-3-yl)-9-(3-methyl-5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-nonanoic acid;

3(S)-(2-Ethoxy-pyrimidin-5-yl)-5,5-difluoro-9-(3-cyclopropyl-5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-nonanoic acid;

3(R)-(2-Ethoxy-pyrimidin-5-yl)-5,5-difluoro-9-(3-cyclopropyl-5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-nonanoic acid;

5,5-Difluoro-3(S)-(6-methoxy-pyridin-3-yl)-9-(3-cyclopropyl-5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-nonanoic acid;

5,5-Difluoro-3(R)-(6-methoxy-pyridin-3-yl)-9-(3-cyclopropyl-5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-nonanoic acid;

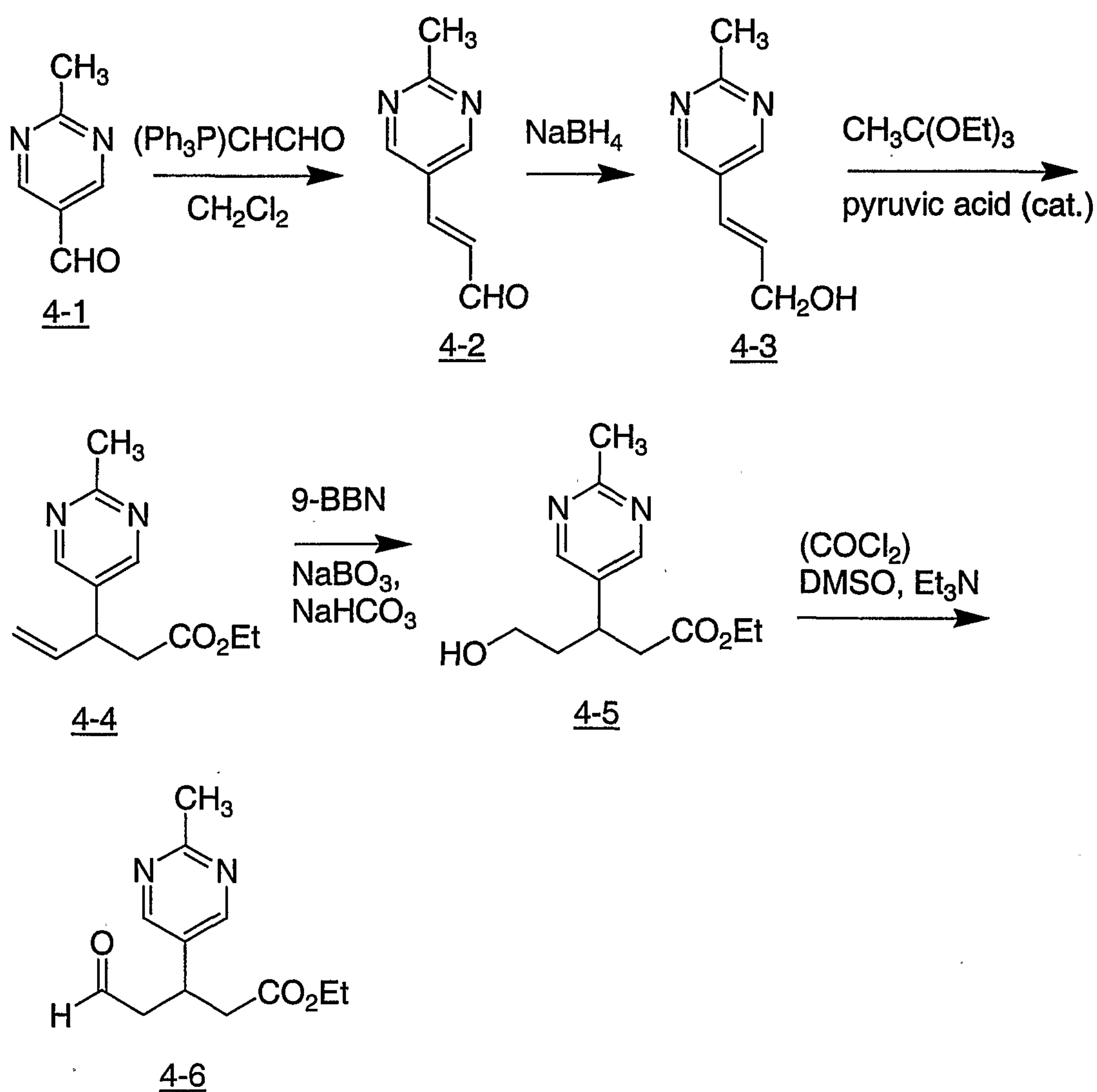
5,5-Difluoro-3(S)-(2-dimethylamino-pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-nonanoic acid; and

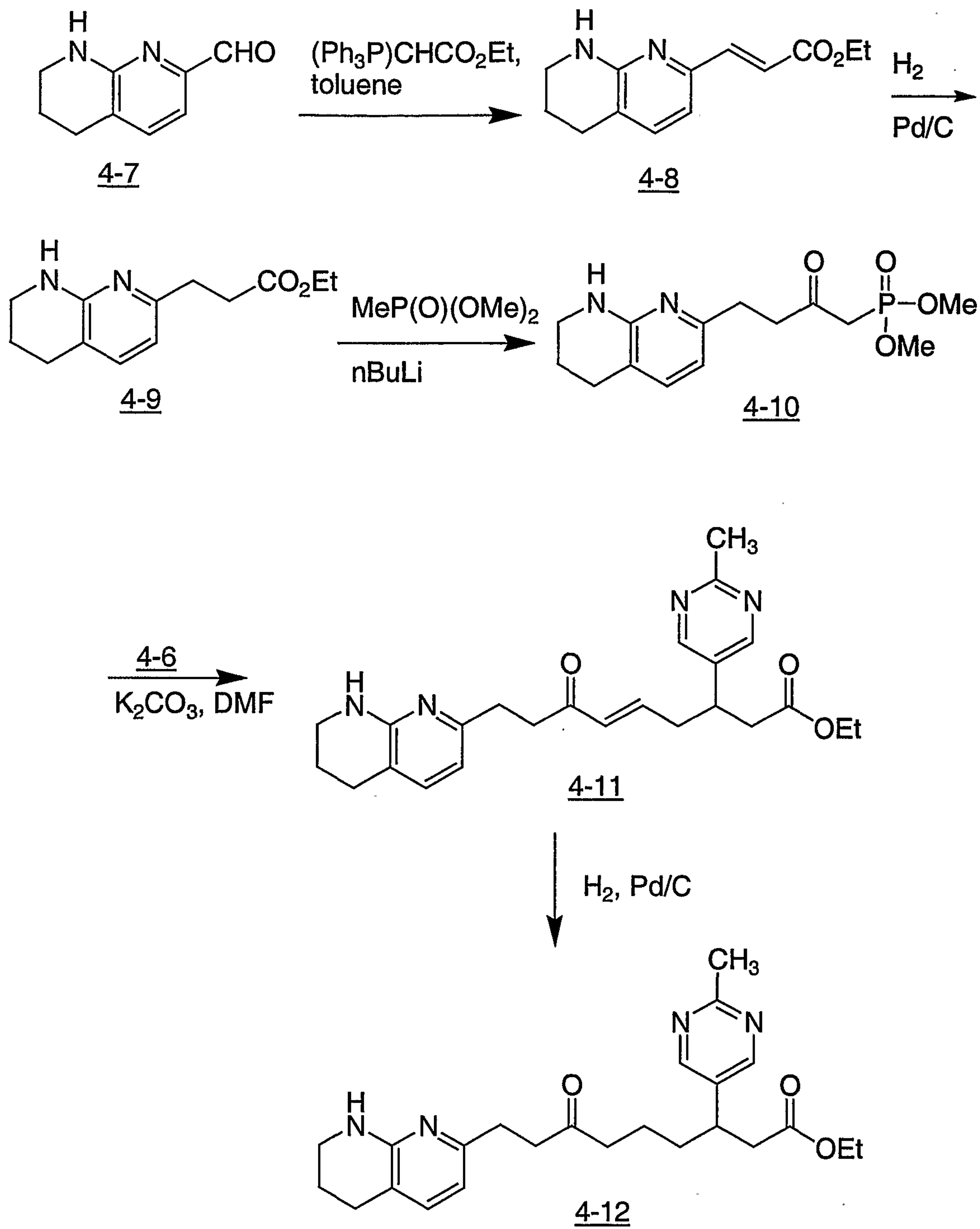
5,5-Difluoro-3(R)-(2-dimethylamino-pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-nonanoic acid.

The 7-keto substrates for the fluorination reaction can be prepared following the procedure shown in Scheme 4 and described below for 3-(2-methylpyrimidin-5-yl)-7-oxo-9-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-nonanoic acid ethyl ester (4-12):

5

SCHEME 4





5 3-(2-Methyl-pyrimidin-5-yl)-7-oxo-9-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-nonanoic acid ethyl ester (4-12)

Step A: 3-(2-Methyl-pyrimidin-5-yl)-propenal (4-2)

To a solution of 4-formyl-2-methylpyrimidine [4-1, 2 g, 16.4 mmol; for preparation, see Smith, S. Q. et al, *J. Heterocyclic Chem.* 28: 1281 (1991)] in methylene chloride (15 mL) was added (formylmethylene)triphenylphosphorane (5.98g, 19.6 mmol). The solution was heated at reflux for 4 h, cooled to room temperature, and solvents evaporated. The residue was chromatographed on silica gel (30% EtOAc/chloroform to 50 EtOAc/50 chloroform/5 methanol) to give the aldehyde 4-2 as a yellow solid.

10 TLC R_f=0.39 (70 chloroform / 25 EtOAc / 5 MeOH).
 ¹H NMR (400 MHz, CDCl₃) δ 9.74 (d, 1H, J=7 Hz), 8.83 (s, 2H), 7.41 (d, 1H, J= 17 Hz), 6.81 (dd, 1H, J= 6 Hz, 15 Hz), 2.77 (s, 3H).

Step B: 3-(2-Methyl-pyrimidin-5-yl)-prop-2-en-1-ol (4-3)

15 To a suspension of 4-2 (0.5 g, 3.7 mmol) in MeOH (5 mL) and THF (15 mL) at -78°C was added sodium borohydride (0.042 g, 1.11 mmol) in one portion. After 5 minutes, the cooling bath was removed, and the mixture allowed to warm and stir for 10 minutes. Concentrated HCl (0.3 mL) was added dropwise, and the volume of the mixture reduced to 2 mL by evaporation. Following the addition of sat.

20 NaHCO₃ (10 mL), the mixture was extracted with chloroform, the organics dried over MgSO₄, and the solvents evaporated to give alcohol 4-3 as a white solid.

 TLC R_f=0.16 (70 chloroform / 25 EtOAc / 5 MeOH).
 ¹H NMR (400 MHz, CDCl₃) δ 8.64 (s, 2H), 6.48 (m, 2H), 4.38 (d, 2H, J= 4 Hz), 2.73 (s, 3H).

25 Step C: 3-(2-Methyl-pyrimidin-5-yl)-pent-4-enoic acid ethyl ester (4-4)

 A solution of 4-3 (0.49 g, 3.6 mmol), propionic acid (10 μL) and trimethylorthoformate (5 mL) was heated to reflux for 18 hours. Evaporative removal of the solvent and one evaporation from toluene gave 4-4 as a brown oil.

30 TLC R_f = 0.725 (silica, 70/25/5 CHCl₃/EtOAc/MeOH)
 ¹H NMR (400 MHz, CDCl₃) δ 8.50 (s, 2H), 5.98 (m, 1H), 5.16 (m, 2H), 4.10 (m, 2H), 3.86 (q, J=7 Hz, 1H), 2.7 (m, 5H), 1.29 (m, 3H).

¹H NMR (400 MHz, CDCl₃) δ 7.46 (d, J=15 Hz, 1H), 7.14 (d, J=8 Hz, 1H), 6.75 (d, J=15 Hz, 1H), 6.62 (d, J=8 Hz, 1H), 4.97 (s, 1H), 4.24 (q, J=7 Hz, 2H), 3.42 (m, 2H), 2.74 (t, J=7 Hz, 2H), 1.91 (m, 2H), 1.30 (m, 3H).

5 Step G: 3-(5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-yl)-propionic acid ethyl ester (4-9)

A mixture of 4-8 (1.4 g, 6.03 mmol) and 10% Pd/carbon (1 g) in EtOH (30 mL) was stirred under a balloon of hydrogen for 18 h. Filtration and evaporative removal of the solvent gave 4-9 as a white solid.

10 TLC R_f = 0.39 (silica, 70% EtOAc/hexanes)

¹H NMR (400 MHz, CDCl₃) δ 7.07 (d, J=7 Hz, 1H), 6.37 (d, J=7 Hz, 1H), 4.12 (m, 2H), 3.40 (m, 2H), 2.87 (m, 2H), 2.67 (m, 4H), 1.91 (t, J=6 Hz, 2H), 1.24 (m, 3H).

15 Step H: [2-Oxo-4-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-butyl]-phosphonic acid dimethyl ester (4-10)

To a stirred solution of dimethyl methylphosphonate (1.9 mL, 17.08 mmol) in THF (20 mL) at -78°C was added nBuLi (10.94 mL, 17.5 mmol). After 30 minutes, 4-9 (1 g, 4.27 mmol) in THF (5 mL) was added. After 1 hour, the reaction was quenched with saturated NH₄Cl (10 mL) and warmed to ambient temperature.

20 The mixture was diluted with ethyl acetate, washed with sat. NaHCO₃, brine, and dried over MgSO₄. Following evaporative removal of the solvent, the residue was chromatographed (silica gel, 70/25/5 CHCl₃/EtOAc/MeOH) to give 4-10 as a yellow oil.

TLC R_f = 0.33 (silica, 70/20/10 CHCl₃/EtOAc/MeOH).

25 ¹H NMR (400 MHz, CDCl₃) δ 7.03 (d, J=7 Hz, 1H), 6.34 (d, J=7 Hz, 1H), 4.93 (s, 1H), 3.77 (d, J=12, 6H), 3.38 (m, 2H), 3.15 (d, J=23, 2H), 2.96 (m, 2H), 2.86 (m, 2H), 2.67 (t, J=6 Hz, 2H), 1.88 (m, 2H).

30 Step I: 3-(2-Methyl-pyrimidin-5-yl)-7-oxo-9-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-non-5-enoic acid ethyl ester (4-11)

To a mixture of 4-10 (100 mg, 0.42 mmol) and 4-6 (160 mg, 0.54 mmol) in DMF (3mL) was added K₂CO₃ (87 mg, 0.63 mmol) followed by heating to 50°C for 18 hours. Following evaporative removal of the solvent, the residue was

chromatographed (silica gel, 70:25:5 CHCl₃/EtOAc/MeOH) to give 4-11 as a clear oil.

TLC R_f = 0.38 (70:20:10 CHCl₃/EtOAc/MeOH).

¹H NMR (400 MHz, CDCl₃) δ 8.49 (s, 1H), 7.03 (d, J=7 Hz, 2H), 6.65 (m, 1H), 6.34
5 (d, J=7 Hz, 1H), 6.07 (d, J=15 Hz, 1H), 4.85 (m, 1H), 4.05 (m, 2H), 3.80 (m, 1H),
3.41 (m, 3H), 2.90-2.54 (m, 13H), 1.88 (m, 4H), 1.18 (m, 3H).

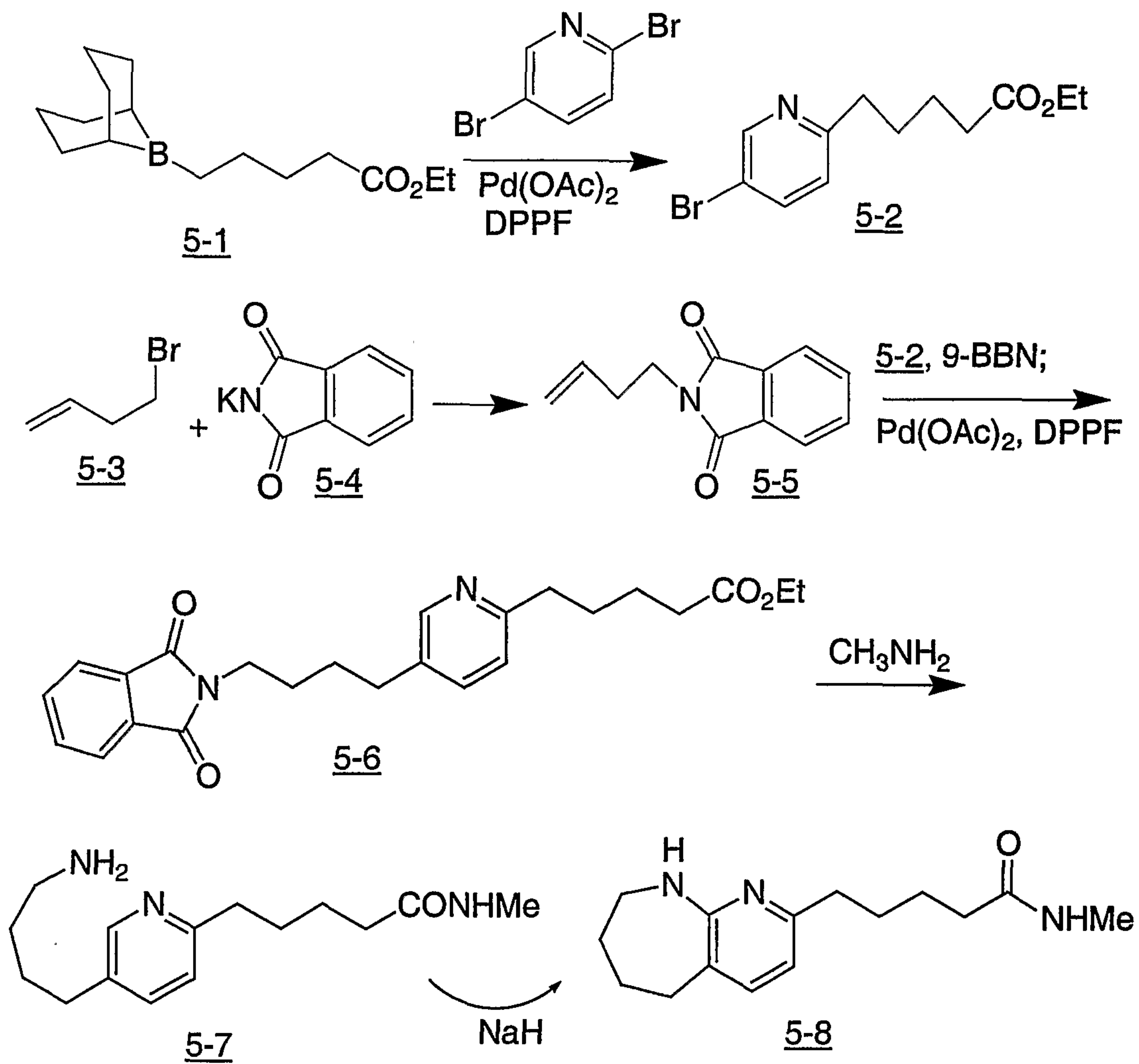
Step J: 3-(2-Methyl-pyrimidin-5-yl)-7-oxo-9-(5,6,7,8-tetrahydro-
 [1,8]naphthyridin-2-yl)-nonanoic acid ethyl ester (4-12)

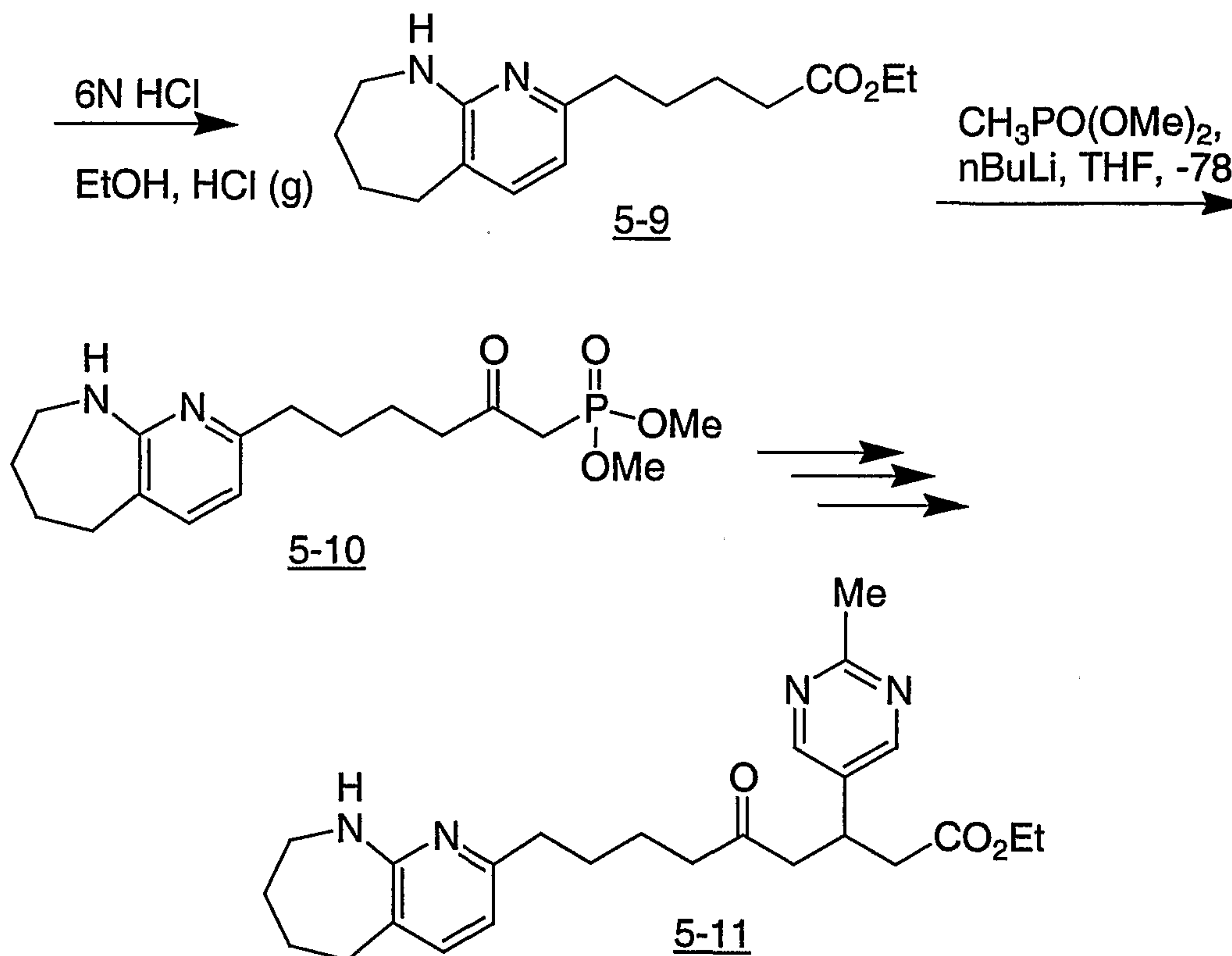
10 A mixture of 4-11 (95 mg, 0.22 mmol) and 10% Pd/carbon (50 mg) in
EtOH (3 mL) was stirred under a balloon of hydrogen for 2 h. Following filtration,
evaporative removal of the solvent gave 4-12 as a clear oil.

TLC R_f = 0.40 (70:20:10 CHCl₃/EtOAc/MeOH).

¹H NMR (400 MHz, CDCl₃) δ 8.47 (s, 2H), 7.04 (d, J=7 Hz, 1H), 6.33 (d, J=7 Hz,
15 1H), 4.03 (m, 2H), 3.78 (m, 1H), 3.38 (m, 2H), 3.01 (m, 1H), 2.74 (m, 10H), 2.54 (m,
1H), 2.40 (t, J=7 Hz, 2H), 1.89 (m, 2H), 1.57 (m, 4H), 1.15 (t, J=7 Hz, 3H).

 The 5-oxo-9-(6,7,8,9-tetrahydro-5H-pyrido[2,3-b]azepin-2-yl)-
nonanoic acid ethyl ester substrates for the fluorination reaction are prepared
20 following the procedure shown in Scheme 5 and exemplified below for 3-(2-methyl-
pyrimidin-5-yl)-5-oxo-9-(5,6,7,8-tetrahydro-5H-pyrido[2,3-b]azepin-2-yl)-nonanoic
acid ethyl ester (5-11).

Scheme 5



3(R) and 3(S)-(2-Methyl-pyrimidin-5-yl)-5-oxo-9-(5,6,7,8-tetrahydro-5H-pyrido[2,3-b]azepin-2-yl)-nonanoic acid ethyl ester (5-11)

5

Step A: 5-(5-Bromo-pyridin-2-yl)-pentanoic acid ethyl ester (5-2)

To a stirred solution of ethyl-1-pentenoic acid (10 g, 78 mmol) in degassed THF (80 mL) at 0°C was added dropwise a solution of 9-BBN (187 mL of 0.5 M in THF, 94 mmol) and the mixture stirred for 18 hours at ambient temperature to produce 5-1. K₂CO₃ (18.4 g, 133 mmol) and 2,5-dibromopyridine (18.5 g, 78 mmol) were added, followed by a premixed and aged (70°C for 30 min) suspension of Pd(OAc)₂ (2.0 g, 8.9 mmol) and DPPF (5.4 g, 9.8 mmol) in degassed DMF (80 mL). The resulting mixture was stirred for 18 hours at 70°C, cooled, diluted with ethyl acetate, washed with water and brine, dried over MgSO₄, and concentrated. To the stirring residue dissolved in THF (400 mL) was added water (150 mL) and NaHCO₃ (33 g) and after 10 minutes, NaBO₃•H₂O (48 g). After vigorous stirring for 30 minutes, the mixture was diluted with ethyl acetate, washed with water and brine,

dried over MgSO_4 , and concentrated to an oil. The residue was chromatographed on silica gel (10-20% EtOAc/hexane) to give 5-2 as a colorless oil.

TLC R_f = 0.75 (silica, 40% EtOAc/hexane).

^1H NMR (400 MHz, CDCl_3): δ 8.57 (s, 1H), 7.70 (m, 1H), 7.05 (d, 1H, J = 8 Hz),
5 4.15 (q, 2H, J = 6 Hz), 2.77 (t, 2H, J = 7 Hz), 2.34 (t, 2H, J = 7 Hz), 1.7 (m, 4H), 1.26 (t,
3H, J = 6 Hz).

Step B: 2-But-3-enyl-isoindole-1,3-dione (5-5)

To a stirred solution of 4-bromo-1-butene (5-3, 20 g, 148 mmol) in
10 DMF (150 mL) was added potassium phthalimide (5-4, 25 g, 133 mmol) and the
mixture stirred for 18 hours at 70°C. After cooling to RT, the mixture was diluted
with ether, washed with water and brine, dried over MgSO_4 , and concentrated to give
5-5 as a white solid.

^1H NMR (400 MHz, CDCl_3): δ 7.85 (m, 2H), 7.72 (m, 2H), 5.82 (m, 1H), 5.08 (m,
15 2H), 3.77 (t, 2H, J = 7 Hz), 2.44 (m, 2H).

Step C: 5-{5-[4-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-butyl]-pyridin-2-yl}-
pentanoic acid ethyl ester (5-6)

To a stirred solution of 5-5 (4.23 g, 21 mmol) in degassed THF (20
20 mL) at 0°C was added dropwise a solution of 9-BBN (50.4 mL of 0.5 M in THF, 25.2
mmol) and the mixture stirred for 18 hours at ambient temperature. K_2CO_3 (5.0 g,
35.8 mmol) and 5-2 (5.0 g, 17.4 mmol) were added, followed by a premixed and aged
(70°C for 30 min) suspension of $\text{Pd}(\text{OAc})_2$ (0.54 g, 2.4 mmol) and DPPF (1.45 g, 2.6
mmol) in degassed DMF (20 mL). The resulting mixture was stirred for 18 hours at
25 70°C, cooled, diluted with ethyl acetate, washed with water and brine, dried over
 MgSO_4 , and concentrated. To the stirring residue dissolved in THF (200 mL) was
added water (75 mL) and NaHCO_3 (16.5 g) and after 10 minutes, $\text{NaBO}_3 \cdot \text{H}_2\text{O}$ (24 g).
After vigorous stirring for 30 minutes, the mixture was diluted with ethyl acetate,
washed with water and brine, dried over MgSO_4 , and concentrated to an oil. The
30 residue was chromatographed on silica gel (20-40% EtOAc/hexane) to give 5-6 as a
yellow solid.

TLC R_f = 0.31 (silica, 50% EtOAc/hexane).

¹H NMR (400 MHz, CDCl₃): δ 8.37 (s, 1H), 7.84 (m, 2H), 7.75 (m, 2H), 7.40 (m, 1H), 7.05 (m, 1H), 4.12 (q, 2H, J=7 Hz), 3.71 (m, 2H), 2.78 (t, 2H, J= 7 Hz), 2.61 (t, 2H, J=7 Hz), 2.33 (t, 2H, J=7 Hz), 1.64 (m, 8H), 1.23 (t, 3H, J=6 Hz).

5 Step D: 5-[5-(4-Amino-butyl)-pyridin-2-yl]-pentanoic acid methylamide (5-7)

A mixture of 5-6 (45 g, 110 mmol) and a saturated solution of methylamine in methanol (300 mL) in a sealed tube was heated at 70°C for 12 hours. The mixture was cooled and concentrated to an oil. The residue was chromatographed on silica gel (10:10:1:1 EtOAc/EtOH/NH₄OH/H₂O) to give 5-7 as a yellow oil.

TLC R_f = 0.16 (silica, 10:10:1:1 EtOAc/EtOH/NH₄OH/H₂O).

¹H NMR (400 MHz, CDCl₃): δ 8.32 (s, 1H), 7.41 (m, 1H), 7.07 (m, 1H), 2.74 (m, 7H), 2.59 (t, 2H, J=6 Hz), 2.21 (t, 2H, J= 6 Hz), 1.69 (m, 6H), 1.48 (m, 2H).

15 Step E: 5-(6,7,8,9-Tetrahydro-5H-pyrido[2,3-b]azepin-2-yl)-pentanoic acid methylamide (5-8)

A mixture of 5-7 (24 g, 91.2 mmol) and NaH (10.9 g of a 60% weight dispersion in mineral oil, 273 mmol) in xylenes (500 mL) was purged with argon for 30 min, and then heated at reflux for 72 hours. The mixture was cooled, quenched with ethanol, diluted with 10% aqueous potassium carbonate and extracted with ethyl acetate. The organics were dried over MgSO₄, and concentrated to an oil. The residue was chromatographed on silica gel (70:25:5 CHCl₃/EtOAc/MeOH/H₂O) to give 5-8 as a white solid.

TLC R_f = 0.15 (silica, 70:25:5 CHCl₃/EtOAc/MeOH).

25 ¹H NMR (400 MHz, CDCl₃): δ 7.24 (d, 1H, J= 7Hz), 6.53 (d, 1H, J=7Hz), 5.43 (br s, 1H), 4.62 (br s, 1H), 3.12 (m, 2H), 2.79 (d, 3H, J=5Hz), 2.63 (m, 4H), 2.18 (m, 2H), 1.81 (m, 2H), 1.68 (m, 6Hz).

30 Step F: 5-(6,7,8,9-Tetrahydro-5H-pyrido[2,3-b]azepin-2-yl)-pentanoic acid ethyl ester (5-9)

A mixture of 5-8 (3 g, 11.5 mmol) and 6 M HCl (100 mL) in a sealed tube was heated at 70°C for 12 hours. The mixture was cooled and concentrated to an oil. The residue was azeotroped from ethanol (50 mL) twice, then dissolved in 4 M HCl in ethanol (100 mL) and heated at 70°C for 1 hour. The mixture was cooled and

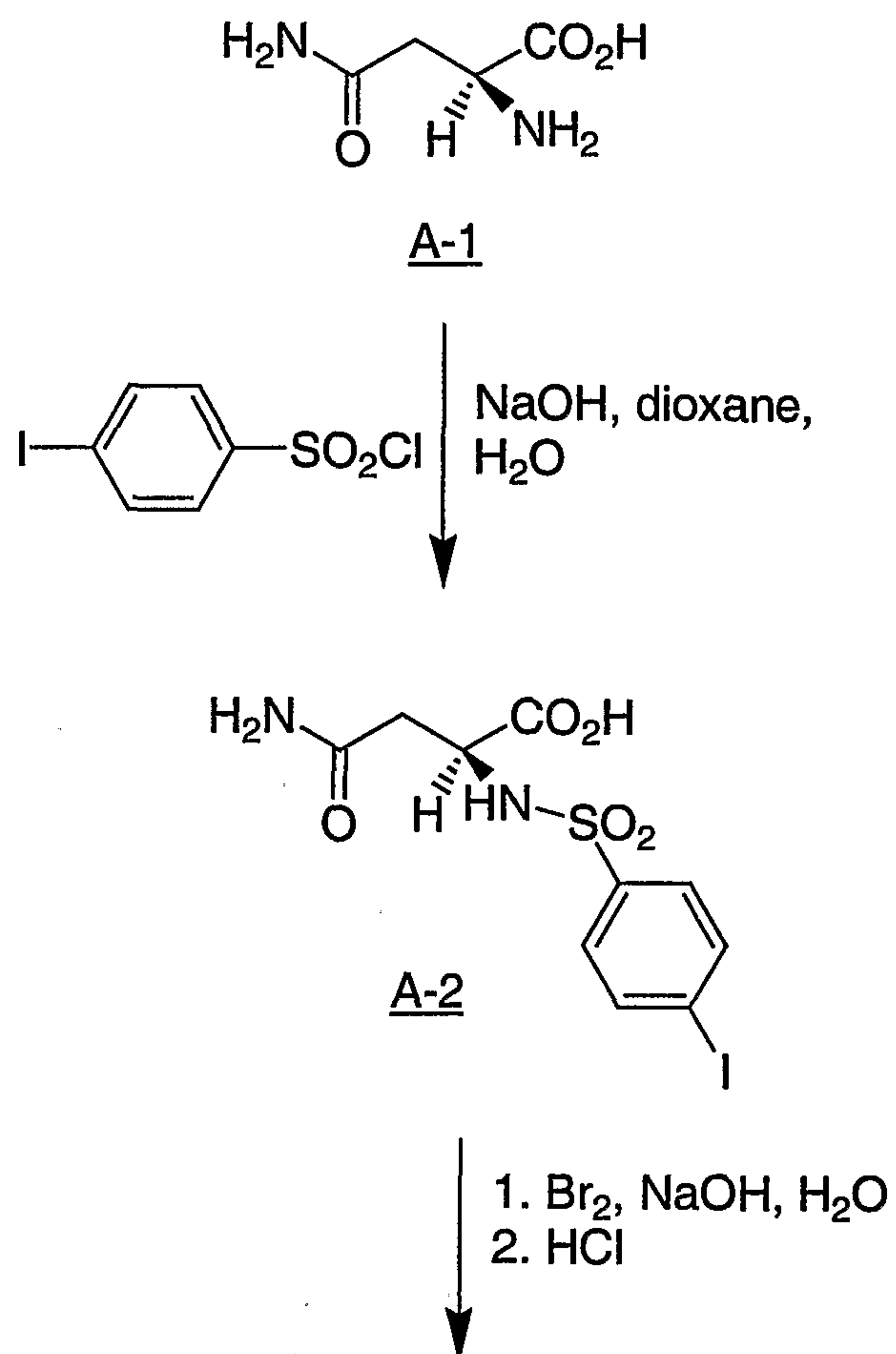
concentrated to an oil. The residue was diluted with ethyl acetate, washed with 10% aqueous potassium carbonate and brine, dried over MgSO_4 , and concentrated to give 5-9 as a brown oil.

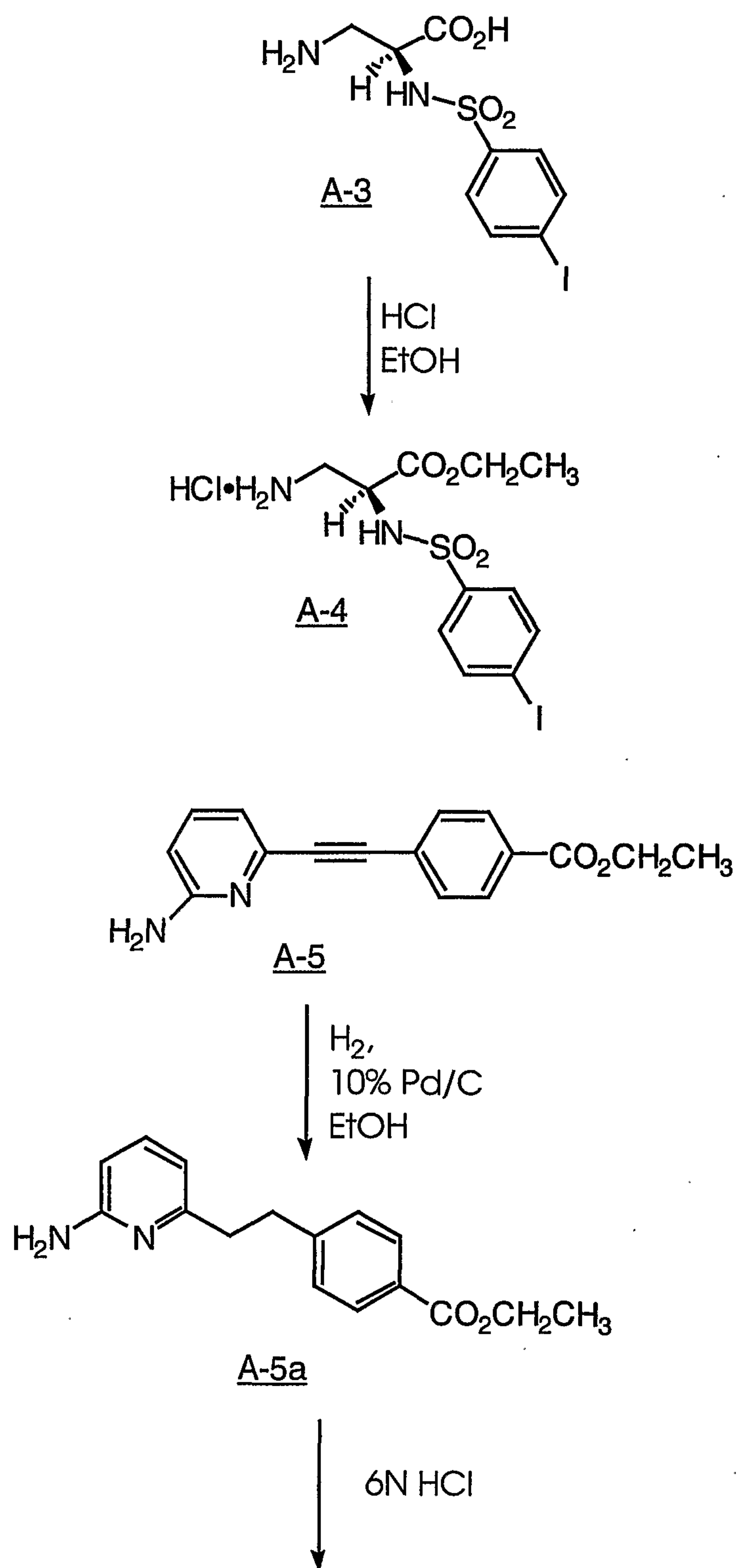
TLC R_f = 0.44 (silica, 70:25:5 $\text{CHCl}_3/\text{EtOAc}/\text{MeOH}$).

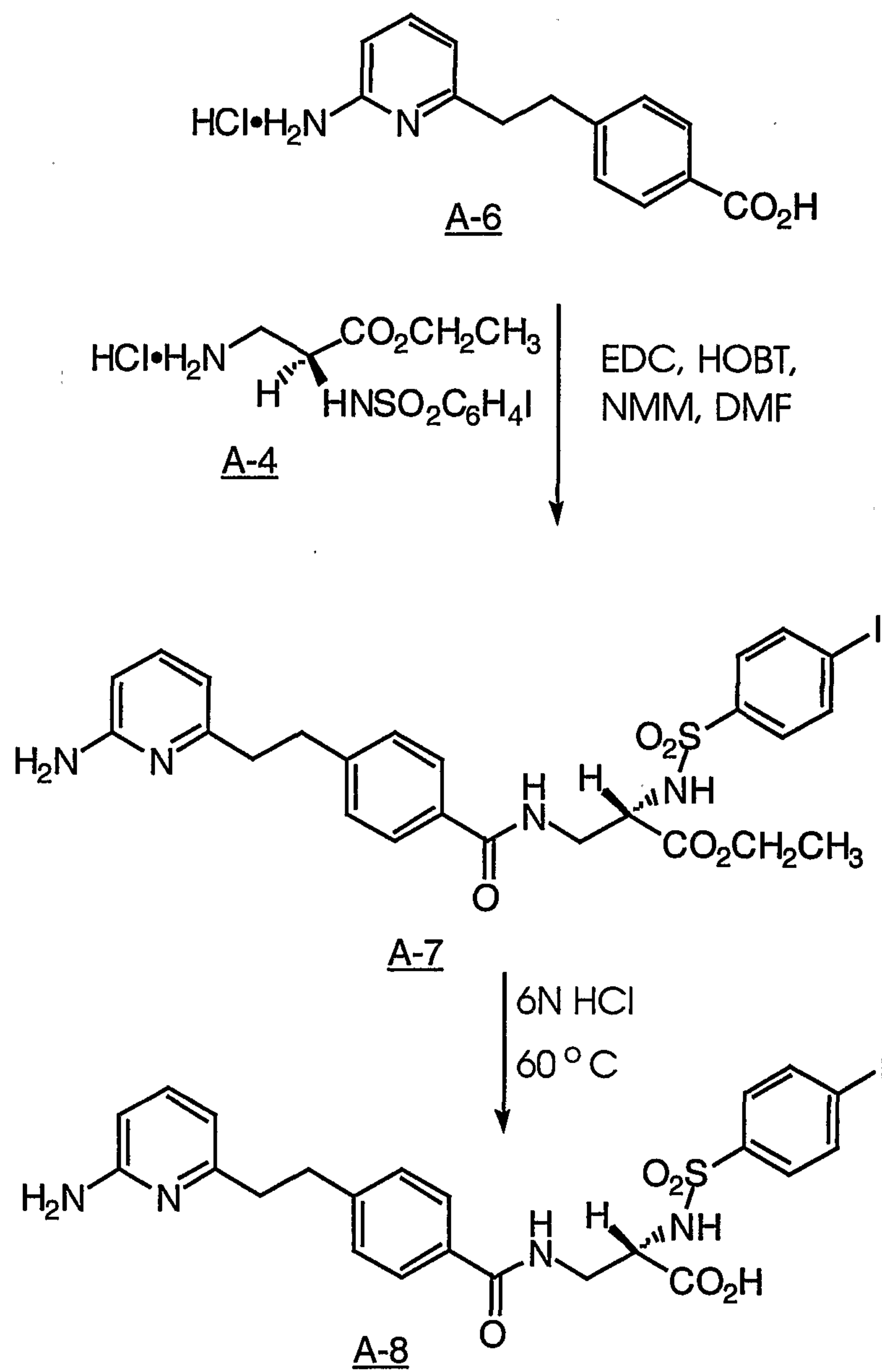
- 5 ^1H NMR (400 MHz, CDCl_3): δ 7.22 (d, 1H, $J=7\text{Hz}$), 6.53 (d, 1H, $J=7\text{ Hz}$), 4.63 (br s, 1H), 4.11 (q, 2H, $J=7\text{Hz}$), 3.12 (m, 2H), 2.66 (m, 2H), 2.62 (t, 2H, $J=6\text{Hz}$), 2.33 (t, 2H, $J=6\text{Hz}$), 1.70 (m, 2H), 1.63 (m, 6H), 1.27 (t, 3H, $J=7\text{Hz}$).

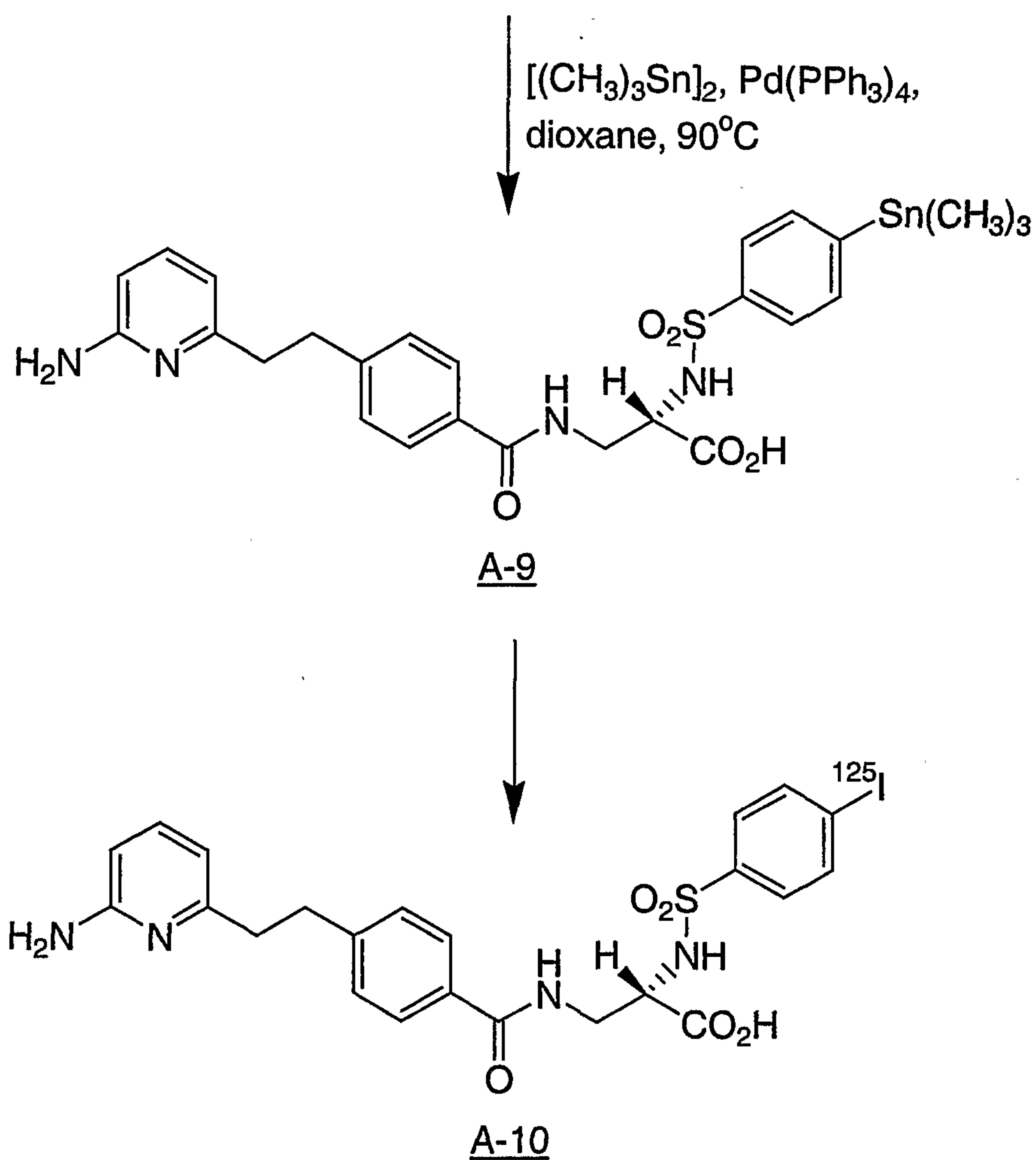
- 10 Step G: 3(R) and 3(S)-(2-Methyl-pyrimidin-5-yl)-5-oxo-9-(6,7,8,9-tetrahydro-5H-pyrido[2,3-b]azepin-2-yl)-nonanoic acid ethyl ester (5-11)

- Utilizing the procedures for the conversion of 1-5 into 1-10, 5-9 was converted into 5-11 by way of 5-10. Resolution of the enantiomers was carried out by chiral chromatography of the keto diester intermediate corresponding to 1-8 on a Chiralcel AD column (10cm x 50cm) using 70% A / 30% B (A = 2-propanol; B =
15 0.1% diethylamine in hexanes) at a flow rate of 250 mL/min.

SCHEME ASynthesis of Radioligand for SPAV3 Assay

SCHEME A, cont'd.

SCHEME A, cont'd



N-(4-Iodo-phenylsulfonylamino)-L-asparagine (A-2)

- 5 To a stirred solution of acid A-1 (4.39 g, 33.2 mmol), NaOH (1.49 g, 37.2 mmol), dioxane (30 ml) and H₂O (30 ml) at 0°C was added pipsyl chloride (10.34 g, 34.2 mmol). After ~5 minutes, NaOH (1.49, 37.2 mmol) dissolved in 15 ml H₂O, was added followed by the removal of the cooling bath. After 2.0 h, the reaction mixture was concentrated. The residue was dissolved in H₂O (300 ml) and
- 10 then washed with EtOAc. The aqueous portion was cooled to 0°C and then acidified with concentrated HCl. The solid was collected and then washed with Et₂O to provide acid A-2 as a white solid.

¹H NMR (300 MHz, D₂O) δ 7.86 (d, 2H, J=8Hz), 7.48 (d, 2H, J=8Hz) 3.70 (m, 1H), 2.39 (m, 2H).

2(S)-(4-Iodo-phenylsulfonylamino)-β-alanine (A-3)

5 To a stirred solution of NaOH (7.14 g, 181.8 mmol) and H₂O (40 ml) at 0°C was added Br₂ (1.30 ml, 24.9 mmol) dropwise over a ten minute period. After ~5 minutes, acid A-2 (9.9 g, 24.9 mmol), NaOH (2.00 g, 49.8 mmol) and H₂O (35 ml) were combined, cooled to 0°C and then added in a single portion to the reaction. After stirring for 20 minutes at 0°C, the reaction was heated to 90°C for 30 minutes
10 and then recooled to 0°C. The pH was adjusted to ~7 by dropwise addition of concentrated HCl. The solid was collected, washed with EtOAc, and then dried *in vacuo* to provide acid A-3 as a white solid.

¹H NMR (300 MHz, D₂O) δ 8.02 (d, 2H, J=8Hz), 7.63 (d, 2H, J=8Hz), 4.36 (m, 1H), 3.51 (dd, 1H, J=5Hz, 13Hz) 3.21 (m, 1H).

15

Ethyl 2(S)-(4-iodo-phenylsulfonylamino)-β-alanine-hydrochloride (A-4)

HCl gas was rapidly bubbled through a suspension of acid A-3 (4.0 g, 10.81 mmol) in EtOH (50 ml) at 0°C for 10 minutes. The cooling bath was removed and the reaction was heated to 60°C. After 18 h, the reaction was concentrated to
20 provide ester A-4 as a white solid.

¹H NMR (300 MHz, CD₃OD) δ 7.98 (d, 2H, J=8Hz), 7.63 (d, 2H, J=8Hz), 4.25 (q, 1H, J=5Hz), 3.92 (m, 2H), 3.33 (m, 1H), 3.06 (m, 1H), 1.01 (t, 3H, J=7Hz).

Ethyl 4-[2-(2-Aminopyridin-6-yl)ethyl]benzoate (A-5a)

25 A mixture of ester A-5 (700 mg, 2.63 mmol), (for preparation, see: Scheme 29 (intermediate 29-3) of U.S. Patent No. 5,741,796 (April 21, 1998)), 10% Pd/C (350 mg) and EtOH were stirred under 1 atm H₂. After 20 h, the reaction was filtered through a celite pad and then concentrated to provide ester A-5a as a brown oil.

30 TLC R_f = 0.23 (silica, 40% EtOAc/hexanes)

¹H NMR (300 MHz, CDCl₃) δ 7.95 (d, 2H, J=8Hz), 7.26 (m, 3H), 6.43 (d, 1H, J=7Hz), 6.35 (d, 1H, J=8Hz), 4.37 (m, 4H), 3.05 (m, 2H), 2.91 (m, 2H), 1.39 (t, 3H, J=7Hz).

4-[2-(2-Aminopyridin-6-yl)ethyl]benzoic acid hydrochloride (A-6)

A suspension of ester A-5a (625 mg, 2.31 mmol) in 6N HCl (12 ml) was heated to 60°C. After ~20 h, the reaction was concentrated to give acid A-6 as a tan solid.

- 5 ¹H NMR (300 MHz, CD₃OD) δ 7.96 (d, 2H, J=8Hz), 7.80 (m, 1H), 7.33 (d, 2H, J=8Hz), 6.84 (d, 1H, J=9Hz), 6.69 (d, 1H, J=7Hz), 3.09 (m, 4H).

Ethyl 4-[2-(2-Aminopyridin-6-yl)ethyl]benzoyl-2(S)-(4-iodo-phenylsulfonylamino)-β-alanine (A-7)

- 10 A solution of acid 15-6 (400 mg, 1.43 mmol), amine A-4 (686 mg, 1.57 mmol), EDC (358 mg, 1.86 mmol), HOBT (252 mg, 1.86 mmol), NMM (632 μl, 5.72 mmol) in DMF (10 ml) was stirred for ~20 h. The reaction was diluted with EtOAc and then washed with sat. NaHCO₃, brine, dried (MgSO₄) and concentrated. Flash chromatography (silica, EtOAc then 5% isopropanol/EtOAc) provided amide
- 15 A-7 as a white solid.

TLC R_f = 0.4 (silica, 10% isopropanol/EtOAc)

- ¹H NMR (300 MHz, CD₃OD) δ 7.79 (d, 2H, J=9Hz) 7.61 (d, 2H, J=8Hz), 7.52 (d, 2H, J=9Hz), 7.29 (m, 1H), 7.27 (d, 2H, J=8Hz), 4.20 (m, 1H), 3.95 (q, 2H, J=7Hz), 3.66 (dd, 1H, J=6Hz, 14Hz), 3.49 (dd, 1H, J=8Hz, 13Hz), 3.01 (m, 2H), 2.86 (m, 2H),
- 20 1.08 (t, 3H, J=7Hz).

4-[2-(2-Aminopyridin-6-yl)ethyl]benzoyl-2(S)-(4-iodophenyl-sulfonylamino)-β-alanine (A-8)

- 25 A solution of ester A-7 (200 mg, 0.3213 mmol) and 6N HCl (30 ml) was heated to 60°C. After ~20 h, the reaction mixture was concentrated. Flash chromatography (silica, 20:20:1:1 EtOAc/EtOH/ NH₄OH/H₂O) provided acid A-8 as a white solid.

TLC R_f = 0.45 (silica, 20:20:1:1 EtOAc/EtOH/NH₄OH/H₂O)

- ¹H NMR (400 MHz, DMSO-d₆) δ 8.40 (m, 1H), 8.14 (Bs, 1H), 7.81 (d, 2H, J=8Hz),
- 30 7.62 (d, 2H, J=8Hz), 7.48 (d, 2H, J=8Hz), 7.27 (m, 3H), 6.34 (d, 1H, J=7Hz), 6.25 (d, 1H, J=8Hz), 5.85 (bs, 2H), 3.89 (bs, 1H), 3.35 (m, 2H), 2.97 (m, 2H), 2.79 (m, 2H).

4-[2-(2-Aminopyridin-6-yl)ethyl]benzoyl-2(S)-(4-trimethylstannyl-phenylsulfonylamino)-β-alanine (A-9)

A solution of iodide A-8 (70 mg, 0.1178 mmol), $[(CH_3)_3Sn]_2$ (49 μ l, 0.2356 mmol), $Pd(PPh_3)_4$ (5 mg) and dioxane (7 ml) was heated to 90°C. After 2 h, the reaction was concentrated and then purified by preparative HPLC (Delta-Pak C₁₈ 15 μ M 100A°, 40 x 100 mm; 95:5 then 5:95 H₂O/CH₃CN) to provide the

trifluoroacetate salt. The salt was suspended in H₂O (10 ml), treated with NH₄OH (5 drops) and then lyophilized to provide amide A-9 as a white solid.

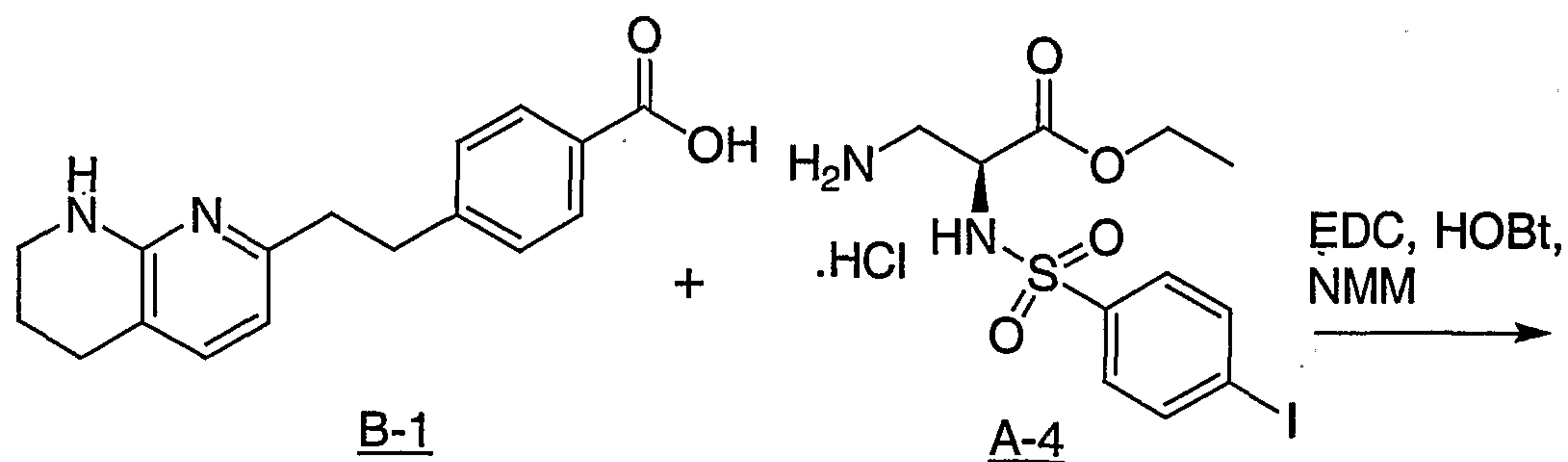
¹H NMR (400 MHz, DMSO-d₆) δ 8.40 (m, 1H), 8.18 (d, 1H, J=8Hz), 7.67 (m, 5H), 7.56 (d, 2H, J=8Hz), 7.29 (d, 2H, J=8Hz), 6.95-7.52 (m, 2H), 6.45 (bs, 2H), 4.00 (m, 1H), 3.50 (m, 1H), 3.33 (m, 1H), 2.97 (m, 2H), 2.86 (m, 2H).

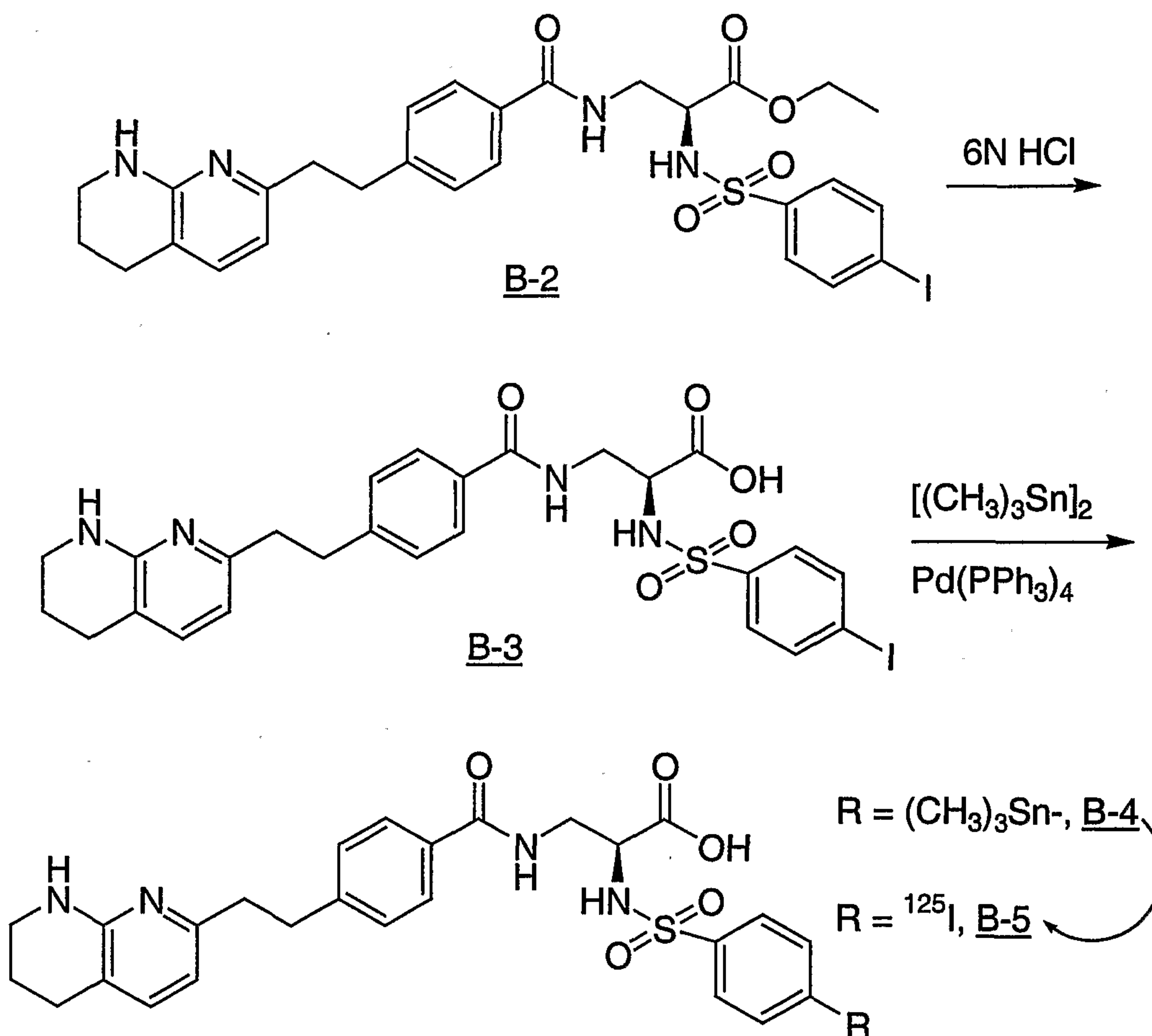
4-[2-(2-Aminopyridin-6-yl)ethyl]benzoyl-2(S)-4-¹²⁵I-iodo-phenylsulfonylamino- β -alanine (A-10)

An iodobead (Pierce) was added to a shipping vial of 5 mCi of Na¹²⁵I (Amersham, IMS30) and stirred for five minutes at room temperature. A solution of 0.1 mg of A-9 in 0.05 mL of 10% H₂SO₄/MeOH was made and immediately added to the Na¹²⁵I/iodobead vial. After stirring for three minutes at room temperature, approximately 0.04-0.05 mL of NH₄OH was added so the reaction mixture was at pH 6-7. The entire reaction mixture was injected onto the HPLC for purification [Vydac peptide-protein C-18 column, 4.6 x 250 mm, linear gradient of 10% acetonitrile (0.1% (TFA):H₂O (0.1% TFA) to 90% acetonitrile (0.1% TFA):H₂O (0.1% TFA) over 30 minutes, 1 mL/min]. The retention time of A-10 is 17 minutes under these conditions. Fractions containing the majority of the radioactivity were pooled, lyophilized and diluted with ethanol to give approximately 1 mCi of A-10, which coeluted on HPLC analysis with an authentic sample of A-8.

SCHEME B

Synthesis of Radioligand for SPAV5 Assay





- 5 2(S)-(4-Iodo-benzenesulfonylamino)-3-{4-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethyl]-benzoylamino}-propionic acid ethyl ester (B-2)

A mixture of B-1 (0.23 g, 0.72 mmol; for preparation see US Patent No. 5,741,796), A-4 (0.343 g, 0.792 mmol), EDC (0.179 g, 0.93 mmol), HOBT (0.126 g, 0.93 mmol), NMM (0.316 mL, 2.86 mmol) in acetonitrile (3 mL) and
 10 DMF (3 mL) was stirred for 2 hours at ambient temperature then diluted with ethyl acetate, washed with water, saturated aqueous $NaHCO_3$, and brine, dried over $MgSO_4$, and concentrated. The residue was chromatographed on silica gel (70:25:5

$CHCl_3/EtOAc/MeOH$) to give B-2 as a white solid.

TLC R_f = 0.22 (silica, 70:25:5 $CHCl_3/EtOAc/MeOH$).

- 15 ^1H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, 2H, $J=8Hz$), 7.63 (d, 2H, $J=8Hz$), 7.54 (d, 2H, $J=8Hz$), 7.27 (d, 2H, $J=8Hz$), 7.04 (d, 1H, $J=7Hz$), 6.60 (m, 1H), 6.29 (d, 1H,

J=7Hz), 4.83 (br s, 1H), 4.09 (m, 3H), 3.84 (m, 1H), 3.68 (m, 1H), 3.42 (m, 2H), 3.01 (m, 4H), 2.86 (m, 4H), 2.69 (t, 2H, J=6Hz), 1.88 (m, 2H).

2(S)-(4-Iodo-benzenesulfonylamino)-3-{4-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethyl]-benzoylamino}-propionic acid (B-3)

A mixture of B-2 (0.38 g, 0.573 mmol) and 6N HCl (50 mL) was stirred for 14 hours at 60°C. After cooling to room temperature, the mixture was concentrated, and the residue chromatographed on silica gel (25:10:1:1 to 15:10:1:1 EtOAc/EtOH/ NH₄OH/H₂O) to give B-3 as a white solid.

TLC R_f = 0.43 (silica, 10:10:1:1 EtOAc/EtOH/ NH₄OH/H₂O).

¹H NMR (300 MHz, DMSO-d₆) δ 8.42 (m, 1H), 7.79 (d, 2H, J=8Hz), 7.63 (d, 2H, J=8Hz), 7.44 (d, 2H, J=8Hz), 7.27 (d, 2H, J=8Hz), 7.10 (d, 1H, J=7Hz), 6.58 (br s, 1H), 6.32 (d, 1H, J=7Hz), 3.96 (m, 1H), 3.51 (m, 1H), 3.30 (m, 5H), 2.96 (m, 2H), 2.78 (m, 2H), 2.62 (m, 2H), 1.77 (m, 2H).

HRMS: For C₂₆H₂₇IN₄O₅S, expected 635.0818, found 635.0831.

3-{4-[2-(5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-yl)-ethyl]-benzoylamino}-2(S)-(4-trimethylstannanyl-benzenesulfonylamino)-propionic acid (B-4)

A mixture of B-3 (0.10 g, 0.16 mmol), hexamethyldistannane (0.065 mL, 0.32 mmol), Pd(PPh₃)₄, and dioxane (10 mL) was stirred for one hour at 90°C. After cooling to room temperature, the mixture was concentrated, and the residue chromatographed on silica gel (50:10:1:1 to 25:10:1:1 EtOAc/EtOH/ NH₄OH/H₂O) to give B-4 as a white solid.

TLC R_f = 0.48 (silica, 15:10:1:1 EtOAc/EtOH/ NH₄OH/H₂O).

¹H NMR (300 MHz, DMSO-d₆) δ 8.38 (m, 1H), 8.14 (m, 1H), 7.63 (m, 4H), 7.28 (d, 2H, J=8Hz), 7.08 (d, 1H, J=7Hz), 6.50 (br s, 1H), 6.28 (d, 1H, J=7Hz), 3.96 (m, 1H), 3.48 (m, 1H), 3.31 (m, 5H), 2.96 (m, 2H), 2.78 (m, 2H), 2.62 (m, 2H), 1.77 (m, 2H), 0.28 (s, 9H).

High resolution mass spectrum: For C₂₉H₃₆N₄O₅SSn, expected 665.1533 (¹¹²Sn) and 673.1507 (¹²⁰Sn), found 665.1510 and 673.1505.

2(S)-(4-¹²⁵Iodo-benzenesulfonylamino)-3-{4-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethyl]-benzoylamino}-propionic acid (B-5)

A stir bar, methanol (0.05 mL) and an iodobead (Pierce) were added to a shipping vial of Na¹²⁵I (10 mCi, Amersham, IMS300) and stirred for five minutes at

room temperature. A solution of B-4 (~0.1 mg) in methanol (0.04 mL) was made and a portion (0.02 mL) was added to a mixture of H₂SO₄ (0.005 mL) in methanol (0.025 mL), and this solution was added immediately to the Na¹²⁵I/iodobead vial. After stirring for two minutes at room temperature, the reaction was quenched with NH₄OH (0.04-0.05 mL) and the entire reaction mixture was injected onto the HPLC for purification [Vydac peptide-protein C-18 column, 4.6 x 250 mm, linear gradient of 10% acetonitrile :H₂O (0.1% TFA) to 90% acetonitrile:H₂O (0.1% TFA) over 20 minutes, 1 mL/min]. The retention time of B-5 is 16 minutes under these conditions. Fractions containing the majority of the radioactivity were pooled, lyophilized and diluted with ethanol to give approximately 1 mCi of B-5, which coeluted on HPLC analysis with an authentic sample of B-3.

Instrumentation: Analytical and preparative HPLC was carried out using a Waters 600E Powerline Multi Solvent Delivery System with 0.1 mL heads with a Rheodyne 7125 injector and a Waters 990 Photodiode Array Detector with a Gilson FC203 Microfraction collector. For analytical and preparative HPLC, a Vydac peptide-protein C-18 column, 4.6 x 250 mm was used with a C-18 Brownlee modular guard column. The acetonitrile used for the HPLC analyses was Fisher Optima grade. The HPLC radiodetector used was a Beckman 170 Radioisotope detector. A Vydac C-18 protein and peptide column, 3.9 x 250 mm was used for analytical and preparative HPLC. Solutions of radioactivity were concentrated using a Speedvac vacuum centrifuge. Calibration curves and chemical concentrations were determined using a Hewlett Packard Model 8452A UV/Vis Diode Array Spectrophotometer. Sample radioactivities were determined in a Packard A5530 gamma counter.

The test procedures employed to measure $\alpha\text{v}\beta 3$ and $\alpha\text{v}\beta 5$ binding and the bone resorption inhibiting activity of the compounds of the present invention are described below.

BONE RESORPTION-PIT ASSAY

When osteoclasts engage in bone resorption, they can cause the formation of pits in the surface of bone that they are acting upon. Therefore, when testing compounds for their ability to inhibit osteoclasts, it is useful to measure the ability of osteoclasts to excavate these resorption pits when the inhibiting compound is present.

Consecutive 200 micron thick cross sections from a 6 mm cylinder of bovine femur diaphysis are cut with a low speed diamond saw (Isomet, Beuler, Ltd., Lake Bluff, IL). Bone slices are pooled, placed in a 10% ethanol solution and refrigerated until further use.

5 Prior to experimentation, bovine bone slices are ultrasonicated twice, 20 minutes each in H₂O. Cleaned slices are placed in 96 well plates such that two control lanes and one lane for each drug dosage are available. Each lane represents either triplicate or quadruplicate cultures. The bone slices in 96 well plates are sterilized by UV irradiation. Prior to incubation with osteoclasts, the bone slices are
10 hydrated by the addition of 0.1 ml α MEM, pH 6.9 containing 5% fetal bovine serum and 1% penicillin/streptomycin.

Long bones from 7-14 day old rabbits (New Zealand White Hare) are dissected, cleaned of soft tissue and placed in α MEM containing 20 mM HEPES. The bones are minced using scissors until the pieces are <1 mm and transferred to a
15 50 ml tube in a volume of 25 ml. The tube is rocked gently by hand for 60 cycles, the tissue is sedimented for 1 min., and the supernatant is removed. Another 25 ml of medium is added to the tissue and rocked again. The second supernatant is combined with the first. The number of cells is counted excluding erythrocytes (typically $\sim 2 \times 10^7$ cells/ml). A cell suspension consisting of 5×10^6 /ml in α MEM containing 5% fetal bovine serum, 10 nM 1,25(OH)₂D₃, and penicillin-streptomycin is prepared. 200
20 ml aliquots are added to bovine bone slices (200 mm x 6 mm) and incubated for 2 hrs. at 37°C in a humidified 5% CO₂ atmosphere. The medium is removed gently with a micropipettor and fresh medium containing test compounds is added. The cultures are incubated for 48 hrs., and assayed for c-telopeptide (fragments of the $\alpha 1$ chain of
25 type I collagen) by Crosslaps for culture media (Herlev, Denmark).

Bovine bone slices are exposed to osteoclasts for 20-24 hrs and are processed for staining. Tissue culture media is removed from each bone slice. Each well is washed with 200 ml of H₂O, and the bone slices are then fixed for 20 minutes in 2.5% glutaraldehyde, 0.1 M cacodylate, pH 7.4. After fixation, any remaining
30 cellular debris is removed by 2 min. ultrasonication in the presence of 0.25 M NH₄OH followed by 2 X 15 min ultrasonication in H₂O. The bone slices are immediately stained for 6-8 min with filtered 1% toluidine blue and 1% borax.

After the bone slices have dried, resorption pits are counted in test and control slices. Resorption pits are viewed in a Microphot Fx (Nikon) fluorescence
35 microscope using a polarizing Nikon IGS filter cube. Test dosage results are

compared with controls and resulting IC₅₀ values are determined for each compound tested.

The appropriateness of extrapolating data from this assay to mammalian (including human) disease states is supported by the teaching found in Sato, M., et al., Journal of Bone and Mineral Research, Vol. 5, No. 1, pp. 31-40, 1990, which is incorporated by reference herein in its entirety. This article teaches that certain bisphosphonates have been used clinically and appear to be effective in the treatment of Paget's disease, hypercalcemia of malignancy, osteolytic lesions produced by bone metastases, and bone loss due to immobilization or sex hormone deficiency. These same bisphosphonates are then tested in the resorption pit assay described above to confirm a correlation between their known utility and positive performance in the assay.

EIB ASSAY

Duong et al., J. Bone Miner. Res., 8: S378 (1993), describes a system for expressing the human integrin $\alpha v \beta 3$. It has been suggested that the integrin stimulates attachment of osteoclasts to bone matrix, since antibodies against the integrin, or RGD-containing molecules, such as echistatin (European Publication 382 451), can effectively block bone resorption.

Reaction Mixture:

1. 175 μ l TBS buffer (50 mM Tris•HCl pH 7.2, 150 mM NaCl, 1% BSA, 1 mM CaCl₂, 1 mM MgCl₂).
2. 25 ml cell extract (dilute with 100 mM octylglucoside buffer to give 2000 cpm/25 μ l).
3. ¹²⁵I-echistatin (25 μ l/50,000 cpm) (see EP 382 451).
4. 25 μ l buffer (total binding) or unlabeled echistatin (non-specific binding).

The reaction mixture was then incubated for 1 h at room temp. The unbound and the bound $\alpha v \beta 3$ were separated by filtration using a Skatron Cell Harvester. The filters (prewet in 1.5% poly-ethyleneimine for 10 mins) were then washed with the wash buffer (50 mM Tris HCl, 1mM CaCl₂/MgCl₂, pH 7.2). The filter was then counted in a gamma counter.

SPAV3 ASSAYMATERIALS:

1. Wheat germ agglutinin Scintillation Proximity Beads (SPA):
5 Amersham
2. Octylglucopyranoside: Calbiochem
3. HEPES: Calbiochem
4. NaCl: Fisher
5. CaCl₂: Fisher
- 10 6. MgCl₂: SIGMA
7. Phenylmethylsulfonylfluoride (PMSF): SIGMA
8. Optiplate: PACKARD
9. Compound A-10 (specific activity 500-1000 Ci/mmol)
10. test compound
- 15 11. Purified integrin receptor: $\alpha v\beta 3$ was purified from 293 cells overexpressing $\alpha v\beta 3$ (Duong et al., J. Bone Min. Res., 8:S378, 1993) according to Pytela (Methods in Enzymology, 144:475, 1987)
12. Binding buffer: 50 mM HEPES, pH 7.8, 100 mM NaCl, 1 mM
20 Ca²⁺/Mg²⁺, 0.5 mM PMSF
13. 50 mM octylglucoside in binding buffer: 50-OG buffer

PROCEDURE:

1. Pretreatment of SPA beads:
25 500 mg of lyophilized SPA beads were first washed four times with 200 ml of 50-OG buffer and once with 100 ml of binding buffer, and then resuspended in 12.5 ml of binding buffer.
2. Preparation of SPA beads and receptor mixture
30 In each assay tube, 2.5 μ l (40 mg/ml) of pretreated beads were suspended in 97.5 μ l of binding buffer and 20 ml of 50-OG buffer. 5 ml (~30 ng/ μ l) of purified receptor was added to the beads in suspension with stirring at room temperature for 30 minutes. The mixture was then centrifuged at 2,500 rpm in a
35 Beckman GPR Benchtop centrifuge for 10 minutes at 4°C. The

pellets were then resuspended in 50 µl of binding buffer and 25 µl of 50-OG buffer.

3. Reaction

5 The following were sequentially added into Optiplate in corresponding wells:

- (i) Receptor/beads mixture (75 µl)
- (ii) 25 µl of each of the following: compound to be tested, binding buffer for total binding or A-8 for non-specific binding (final concentration 1 µM)
- (iii) A-10 in binding buffer (25 µl, final concentration 40 pM)
- (iv) Binding buffer (125 µl)
- (v) Each plate was sealed with plate sealer from PACKARD and incubated overnight with rocking at 4°C

15

4. Plates were counted using PACKARD TOPCOUNT

5. % inhibition was calculated as follows:

A = total counts

20 B = nonspecific counts

C = sample counts

% inhibition = $[(A-B)-(C-B)]/(A-B) \times 100$

OCFORM ASSAY

25 Osteoblast-like cells (1.8 cells), originally derived from mouse calvaria, were plated in CORNING 24 well tissue culture plates in αMEM medium containing ribo- and deoxyribonucleosides, 10% fetal bovine serum and penicillin-streptomycin. Cells were seeded at 40,000/well in the morning. In the afternoon, bone marrow cells were prepared from six week old male Balb/C mice as follows:

30 Mice were sacrificed, tibiae removed and placed in the above medium. The ends were cut off and the marrow was flushed out of the cavity into a tube with a 1 mL syringe with a 27.5 gauge needle. The marrow was suspended by pipetting up and down. The suspension was passed through >100 mm nylon cell strainer. The resulting suspension was centrifuged at 350 x g for seven minutes. The pellet was

resuspended, and a sample was diluted in 2% acetic acid to lyse the red cells. The remaining cells were counted in a hemacytometer. The cells were pelleted and resuspended at 1×10^6 cells/mL. 50 μ L was added to each well of 1.8 cells to yield 50,000 cells/well and 1,25-dihydroxy-vitamin D₃ (D₃) was added to each well to a

5 final concentration of 10 nM. The cultures were incubated at 37°C in a humidified, 5% CO₂ atmosphere. After 48 h, the medium was changed. 72 h after the addition of bone marrow, test compounds were added with fresh medium containing D₃ to quadruplicate wells. Compounds were added again after 48 h with fresh medium containing D₃. After an additional 48 h., the medium was removed, cells were fixed

10 with 10% formaldehyde in phosphate buffered saline for 10 minutes at room temperature, followed by a 1-2 minute treatment with ethanol:acetone (1:1) and air dried. The cells were then stained for tartrate resistant acid phosphatase as follows:

The cells were stained for 10-15 minutes at room temperature with 50 mM acetate buffer, pH 5.0 containing 30 mM sodium tartrate, 0.3 mg/mL Fast Red

15 Violet LB Salt and 0.1 mg/mL Naphthol AS -MX phosphate. After staining, the plates were washed extensively with deionized water and air dried. The number of multinucleated, positive staining cells was counted in each well.

SPAV5 ASSAY

20 MATERIALS:

1. Wheat germ agglutinin Scintillation Proximity Beads (SPA): Amersham
2. Octylglucopyranoside and Phorbo-12-myristate-13-acetate (PMA): Calbiochem
- 25 3. Tris-HCl, NaCl and CaCl₂ : Fisher
4. Minimum Essential Media (MEM): Gibco/BRL
5. Fetal bovine serum (FBS): Hyclone
6. MgCl₂ , MnCl₂ , and Phenylmethylsulfonylfluoride (PMSF): SIGMA
7. Protease inhibitor cocktail tablets: Boehringer Mannheim.
- 30 8. Optiplate-96 wells: PACKARD
9. B-5 was used as radiolabeled ligand (specific activity 500-1000 Ci/mmol) and B-3 (2.5 μ M) was used to achieve 100% inhibition.
10. Test compound.

11. HEK293 cells overexpressing $\alpha_v\beta_5$ integrins (Simon et al., J. Biol. Chem. 272, 29380-29389, 1997) are cultured in 150 mm dishes in 10% FBS/MEM media (Gibco/BRL).
12. Lysis buffer: 100 mM octylglucopyranoside, 50 mM Tris, pH 7.5, 100 mM NaCl, 1 mM CaCl_2 , 1 mM MgCl_2 , 0.5 mM PMSF and protease inhibitors (1 tablet/50 ml buffer).
13. Binding buffer: 50 mM Tris, pH 7.5, 100 mM NaCl, 1 mM CaCl_2 , 1 mM MgCl_2 and 1 mM MnCl_2 .
14. 50 mM octylglucopyranoside in binding buffer: 50-OG buffer

PROCEDURE:

1. $\alpha_v\beta_5$ -cell lysates: HEK 293 cells expressing $\alpha_v\beta_5$ integrins were cultured until confluent. Cells were then starved overnight in media containing 0.5% FBS, followed by treatment with 100nM PMA for 20 min. Cells were washed 2 times with cold phosphate buffer saline (4°C) and solubilized in lysis buffer for 30 min on ice. Lysates were clarified using a Beckman JA-20 at 20,000 xg. Protein concentration of clarified lysates was determined using a micro BCA kit (Pierce) and stored in aliquots at 80 °C.
2. Pretreatment of SPA beads:
500 mg of lyophilized SPA beads were first washed four times with 200 ml of 50-OG buffer and once with 100 ml of binding buffer, and then resuspended in 12.5 ml of binding buffer.
3. Preparation of SPAV5 binding reaction
To each assay well, the following were sequentially added into Optiplate plates:
 - (i) Binding buffer to make up final volume of 125 μl per well.
 - (ii) 3 μl (120 μg /well) of pretreated beads diluted with 22 μl of 50-OG Buffer
 - (iii) 15 μg of $\alpha_v\beta_5$ -cell lysate proteins.
 - (iv) B-5 at 50,000 cpm.
 - (v) 25 μl of graded concentrations of test compound.

(vi) Each plate was sealed with plate sealer from PACKARD and incubated overnight with rocking at 4°C

4. Plates were counted using PACKARD TOPCOUNT microplate scintillation counter.

5. % Inhibition was calculated as follows:
A = total counts (binding of receptor to B-5)
B = nonspecific counts (binding of receptor to B-5 in the presence of 2.5 µM cold ligand)
C = counts from receptor binding to test compound
% inhibition = $[(A-B)-(C-B)]/(A-B)/(A-B) \times 100$

IC₅₀ of test compound was calculated as 50% of inhibition.

Representative compounds of the present invention were tested and found to bind to human αvβ3 integrin. These compounds were generally found to have IC₅₀ values less 10 nM in the SPAV3 assay.

Representative compounds of the present invention were also tested in the SPAV5 assay to determine affinity for the αvβ5 receptor. These compounds were generally found to have IC₅₀ values less than 100 nM.

EXAMPLE OF A PHARMACEUTICAL FORMULATION

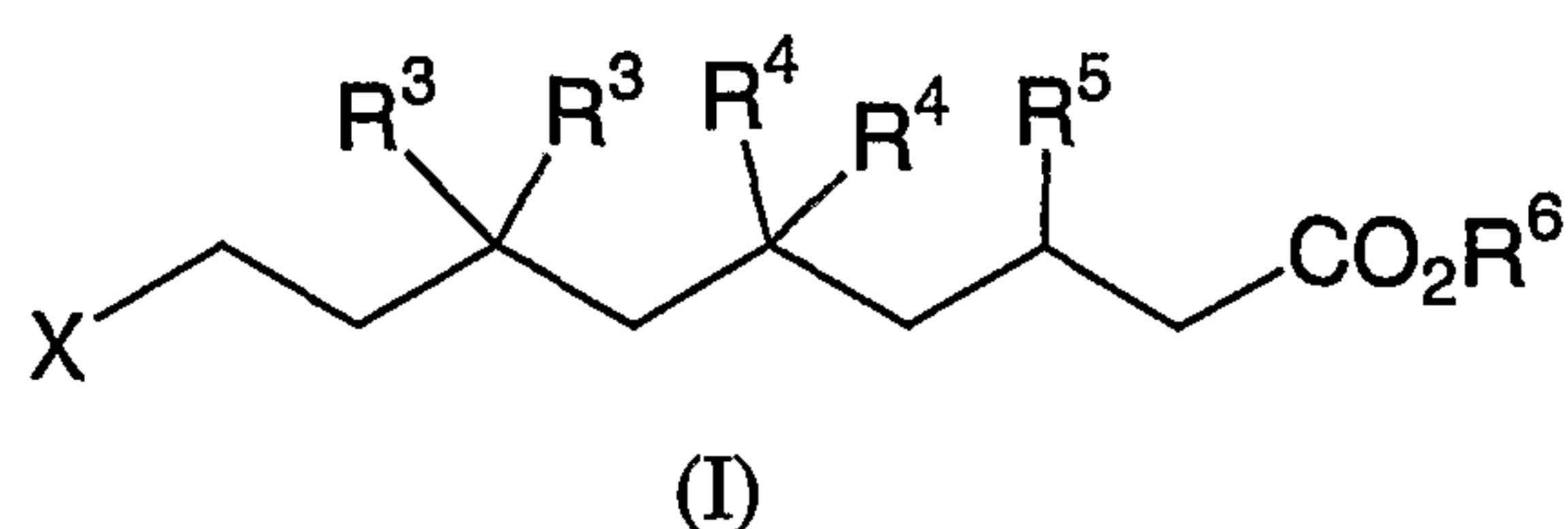
As a specific embodiment of an oral composition, 100 mg of any of the compounds of the present invention are formulated with sufficient finely divided lactose to provide a total amount of 580 to 590 mg to fill a size O hard gel capsule.

While the invention has been described and illustrated in reference to certain preferred embodiments thereof, those skilled in the art will appreciate that various changes, modifications and substitutions can be made therein without departing from the spirit and scope of the invention. For example, effective dosages other than the preferred doses as set forth hereinabove may be applicable as a consequence of variations in the responsiveness of the mammal being treated for severity of bone disorders caused by resorption, or for other indications for the

compounds of the invention indicated above. Likewise, the specific pharmacological responses observed may vary according to and depending upon the particular active compound selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected
5 variations or differences in the results are contemplated in accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be limited only by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.

WHAT IS CLAIMED IS:

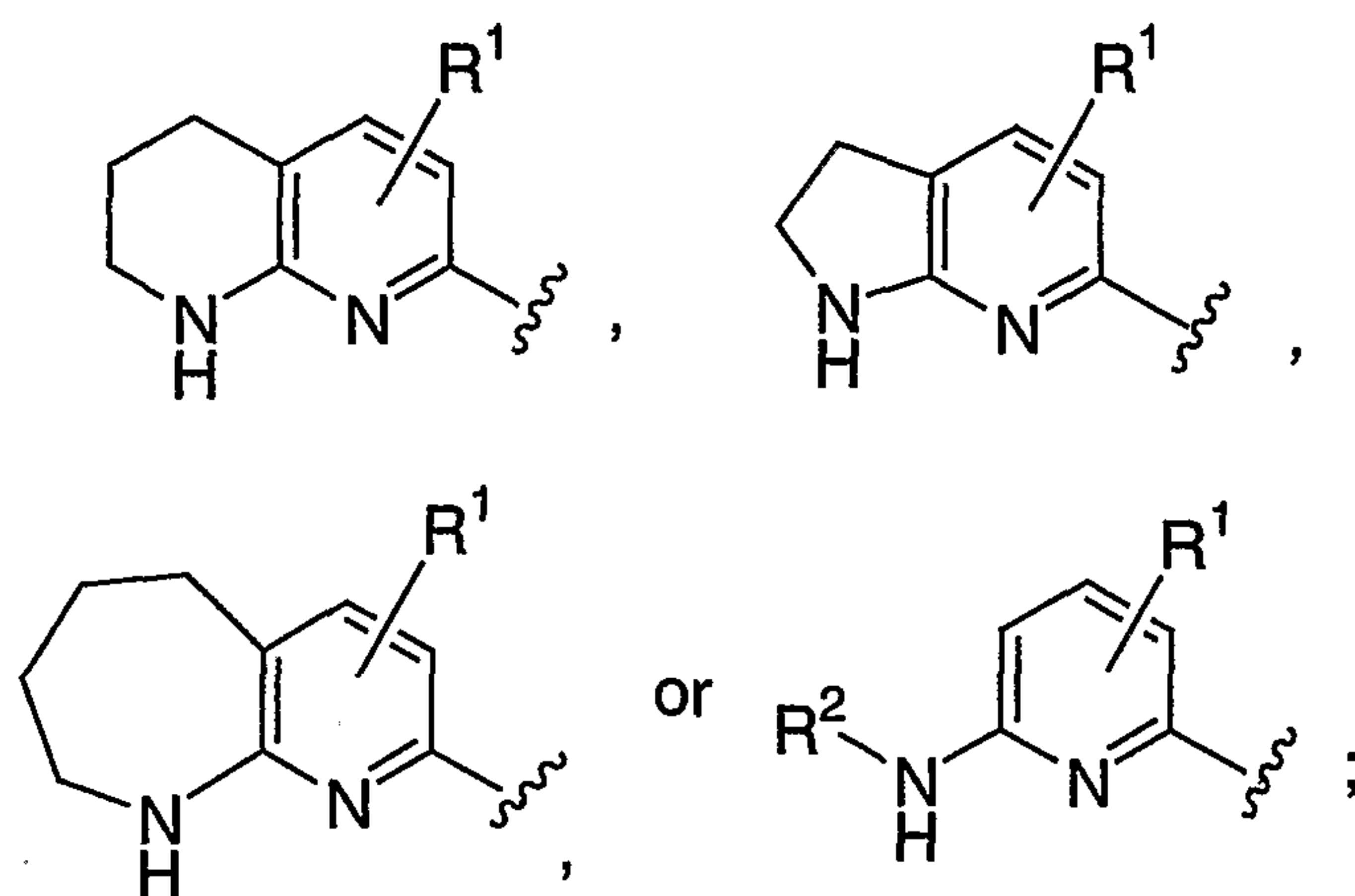
1. A compound of the Formula (I)



5

or a pharmaceutically acceptable salt thereof, wherein:

X is



- 10 wherein each non-aromatic ring carbon atom is unsubstituted or independently substituted with one or two R¹ substituents and each aromatic ring carbon atom is unsubstituted or independently substituted with one R¹ substituent selected from the group consisting of

- 15 C₁-8 alkyl, C₃-8 cycloalkyl,
 C₃-8 cycloheteroalkyl, C₃-8 cycloalkyl-C₁-6 alkyl,
 C₃-8 cycloheteroalkyl-C₁-6 alkyl, aryl, aryl-C₁-6 alkyl, amino,
 amino-C₁-6 alkyl, C₁-3 acylamino, C₁-3 acylamino-C₁-6 alkyl,
 (C₁-6 alkyl)₁₋₂ amino, C₃-6 cycloalkyl-C₀₋₂ amino,
 20 (C₁-6 alkyl)₁₋₂ amino-C₁-6 alkyl, C₁-6 alkoxy, C₁-4 alkoxy-C₁-6 alkyl,
 hydroxycarbonyl, hydroxycarbonyl-C₁-6 alkyl, C₁-3 alkoxycarbonyl,

C₁₋₃ alkoxycarbonyl-C₁₋₆ alkyl, hydroxy, hydroxy-C₁₋₆ alkyl,
 nitro, cyano, trifluoromethyl, trifluoromethoxy, trifluoroethoxy,
 C₁₋₈ alkyl-S(O)₀₋₂, (C₁₋₈ alkyl)₀₋₂ aminocarbonyl,
 C₁₋₈ alkyloxycarbonylamino, (C₁₋₈ alkyl)₁₋₂ aminocarbonyloxy,
 5 (aryl C₁₋₃ alkyl)₁₋₂ amino, (aryl)₁₋₂ amino,
 aryl-C₁₋₃ alkylsulfonylamino, and C₁₋₈ alkylsulfonylamino;
 or two R¹ substituents, when on the same non-aromatic carbon atom, are taken
 together with the carbon atom to which they are attached to form a carbonyl group, or
 two R¹ substituents, together with the non-aromatic carbon atoms to which they are
 10 attached, join to form a 4- to 6-membered saturated or unsaturated carbocyclic ring;

R² is hydrogen or C₁₋₄ alkyl;

R³ is fluoro and R⁴ is hydrogen or R³ is hydrogen and R⁴ is fluoro;
 15

R⁵ is aryl wherein the aryl group is selected from the group consisting of

- (1) phenyl,
- (2) naphthyl,
- (3) pyridinyl,
- 20 (4) furyl,
- (5) thienyl,
- (6) pyrrolyl,
- (7) oxazolyl,
- (8) thiazolyl,
- 25 (9) imidazolyl,
- (10) pyrazolyl,
- (11) isoxazolyl,
- (12) isothiazolyl,
- (13) pyrimidinyl,
- 30 (14) pyrazinyl,
- (15) pyridazinyl,
- (16) quinolyl,
- (17) isoquinolyl,
- (18) benzimidazolyl,

- 5 (19) benzofuryl,
 (20) benzothienyl,
 (21) indolyl,
 (22) benzthiazolyl,
 (23) benzoxazolyl,
 (24) dihydrobenzofuryl,
 (25) benzo(1,3)dioxolanyl, and
 (26) benzo(1,4)dioxanyl;
- 10 and mono, di, and tri-substituted aryl wherein aryl is as defined above and the substituents are independently hydroxy, hydroxy-C₁₋₆ alkyl, halogen, C₁₋₈ alkyl, C₃₋₈ cycloalkyl, aryl, aryl C₁₋₃ alkyl, amino, amino C₁₋₆ alkyl, C₁₋₃ acylamino, C₁₋₃ acylamino-C₁₋₆ alkyl, C₁₋₆ alkylamino, di(C₁₋₆)alkylamino, C₁₋₆ alkylamino-C₁₋₆ alkyl, di(C₁₋₆)alkylamino-C₁₋₆ alkyl, C₁₋₄ alkoxy, C₁₋₄ alkylthio, C₁₋₄ alkylsulfinyl, C₁₋₄ alkylsulfonyl, C₁₋₄ alkoxy-C₁₋₆ alkyl, hydroxycarbonyl, hydroxycarbonyl-C₁₋₆ alkyl, C₁₋₅ alkoxycarbonyl, C₁₋₃ alkoxycarbonyl-C₁₋₆ alkyl, C₁₋₅ alkylcarbonyloxy, cyano, trifluoromethyl, 1,1,1-trifluoroethyl, trifluoromethoxy, trifluoroethoxy, or nitro; or two adjacent substituents together with the carbon atoms to which they are attached join to form a five- or six-membered saturated or
- 15 unsaturated ring containing 1 or 2 heteroatoms selected from the group consisting of N, O, and S, whose ring carbon atoms may be substituted with oxo or C₁₋₃ alkyl; and
- 20

R⁶ is hydrogen or C₁₋₃ alkyl.

- 25 2. The compound of Claim 1 wherein R⁵ is mono- or di-substituted
- phenyl,
 pyridinyl,
 quinolyl,
 30 pyrimidinyl,
 pyrazinyl,
 pyrazolyl, or
 dihydrobenzofuryl;

wherein the substituents are independently hydrogen, hydroxy, hydroxy-C₁₋₆ alkyl, halogen, C₁₋₈ alkyl, C₃₋₈ cycloalkyl, aryl, aryl C₁₋₃ alkyl, amino, amino-C₁₋₆ alkyl, C₁₋₃ acylamino, C₁₋₃ acylamino-C₁₋₆ alkyl, C₁₋₆ alkylamino, di(C₁₋₆)alkylamino, C₁₋₆ alkylamino C₁₋₆ alkyl, di(C₁₋₆)alkylamino-C₁₋₆ alkyl, C₁₋₄ alkoxy, C₁₋₄ alkylthio, C₁₋₄ alkylsulfinyl, C₁₋₄ alkylsulfonyl, C₁₋₄ alkoxy-C₁₋₆ alkyl, hydroxycarbonyl, hydroxycarbonyl-C₁₋₆ alkyl, C₁₋₅ alkoxycarbonyl, C₁₋₃ alkoxycarbonyl C₁₋₆ alkyl, C₁₋₅ alkylcarbonyloxy, cyano, trifluoromethyl, 1,1,1-trifluoroethyl, trifluoromethoxy, trifluoroethoxy, or nitro; or two adjacent substituents together with the carbon atoms to which they are attached join to form a five- or six-membered saturated or unsaturated ring containing 1 or 2 heteroatoms selected from the group consisting of N, O, and S, whose ring carbon atoms may be substituted with oxo or C₁₋₃ alkyl.

3. The compound of Claim 2 wherein R⁵ is mono- or di-substituted

quinolyl,
pyridinyl, or
pyrimidinyl;

wherein the substituents are independently hydrogen, halogen, phenyl, C₁₋₄ alkyl, C₃₋₆ cycloalkyl, C₁₋₃ alkoxy, amino, C₁₋₃ alkylamino, di(C₁₋₃) alkylamino, hydroxy, cyano, trifluoromethyl, 1,1,1-trifluoroethyl, trifluoromethoxy, or trifluoroethoxy.

4. The compound of Claim 1 wherein R¹ is selected from the group consisting of

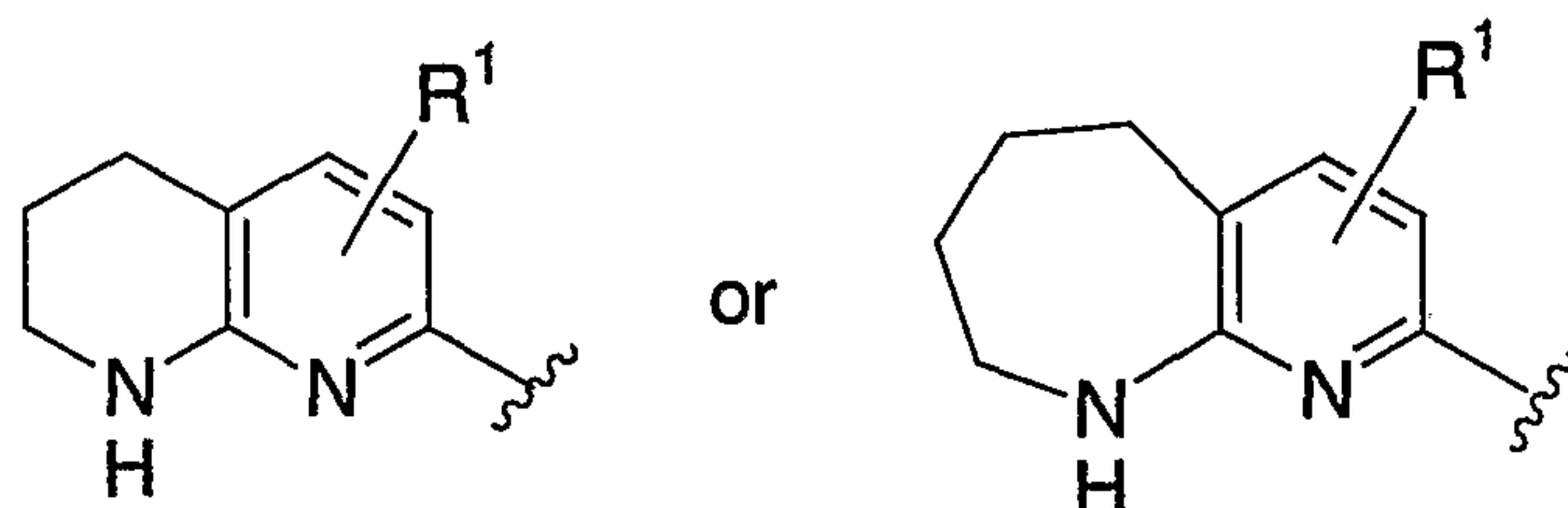
hydrogen,
amino,
C₁₋₄ alkylamino,
C₃₋₆ cycloalkyl-C₀₋₂ alkylamino
cyano,
C₁₋₄ alkyl,
cyclopropyl,
aryl C₁₋₃ alkyl,

C₁₋₄ acylamino,
 C₁₋₄ alkoxy,
 C₁₋₄ alkylthio,
 aminocarbonyl,
 5 (C₁₋₆ alkyl)₁₋₂ aminocarbonyl,
 C₁₋₄ alkoxycarbonyl,
 trifluoromethyl, and
 trifluoromethoxy.

- 10 5. The compound of Claim 4 wherein R¹ is selected from the group consisting of
 hydrogen,
 amino,
 15 C₁₋₃ alkylamino,
 C₃₋₆ cycloalkylmethylamino,
 C₁₋₄ alkyl,
 cyclopropyl,
 trifluoromethyl, and
 trifluoromethoxy.

20

6. The compound of Claim 1 wherein X is



7. The compound of Claim 6 wherein R³ is hydrogen and R⁴ is
 fluoro.

25

8. The compound of Claim 7 wherein R¹ is C₁₋₄ alkyl or
 cyclopropyl and R⁵ is mono- or di-substituted quinolyl, pyridinyl, or pyrimidinyl,
 wherein the substituents are independently hydrogen, halogen, phenyl, C₁₋₄ alkyl,

5 9. The compound of Claim 8 selected from the group consisting
of

10

15

5,5-Difluoro-3-(2-methoxy-pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-[1,8]-naphthyridin-2-yl)-nonanoic acid;

5,5-Difluoro-3(S)-(2-methoxy-pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-[1,8]-naphthyridin-2-yl)-nonanoic acid;

25

5,5-Difluoro-3-(2-methyl-pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-[1,8]-naphthyridin-2-yl)-nonanoic acid;

5,5-Difluoro-3(R)-(2-methyl-pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-[1,8]-naphthyridin-2-yl)-nonanoic acid;

5,5-Difluoro-3(S)-(2-methyl-pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-[1,8]-naphthyridin-2-yl)-nonanoic acid;

- 9-(3-Cyclopropyl-5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-5,5-difluoro-3-(2-methyl-pyrimidin-5-yl)-nonanoic acid;
- 5 9-(3-Cyclopropyl-5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-5,5-difluoro-3(S)-(2-methyl-pyrimidin-5-yl)-nonanoic acid;
- 9-(3-Cyclopropyl-5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-5,5-difluoro-3(R)-(2-methyl-pyrimidin-5-yl)-nonanoic acid;
- 10 5,5-Difluoro-3-(pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-5H-pyrido[2,3-b]azepin-2-yl)-nonanoic acid;
- 5,5-Difluoro-3(S)-(pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-5H-pyrido[2,3-b]azepin-2-yl)-nonanoic acid;
- 15 5,5-Difluoro-3(R)-(pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-5H-pyrido[2,3-b]azepin-2-yl)-nonanoic acid;
- 5,5-Difluoro-3-(2-methyl-pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-5H-pyrido[2,3-b]azepin-2-yl)-nonanoic acid;
- 20 b]azepin-2-yl)-nonanoic acid;
- 5,5-Difluoro-3(S)-(2-methyl-pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-5H-pyrido[2,3-b]azepin-2-yl)-nonanoic acid;
- 25 5,5-Difluoro-3(R)-(2-methyl-pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-5H-pyrido[2,3-b]azepin-2-yl)-nonanoic acid;
- 5,5-Difluoro-3-(2-methoxy-pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-5H-pyrido[2,3-b]azepin-2-yl)-nonanoic acid;
- 30 5,5-Difluoro-3(S)-(2-methoxy-pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-5H-pyrido[2,3-b]azepin-2-yl)-nonanoic acid; and
- 5,5-Difluoro-3(R)-(2-methoxy-pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-5H-pyrido[2,3-b]azepin-2-yl)-nonanoic acid;
- 35 b]azepin-2-yl)-nonanoic acid;

or a pharmaceutically acceptable salt thereof.

10. The compound of Claim 9 selected from the group consisting
- 5 of
- 5,5-Difluoro-3(S)-(pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-[1,8]-naphthyridin-2-yl)-nonanoic acid;
- 10 5,5-Difluoro-3(R)-(pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-[1,8]-naphthyridin-2-yl)-nonanoic acid;
- 5,5-Difluoro-3(R)-(2-methoxy-pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-[1,8]-naphthyridin-2-yl)-nonanoic acid;
- 15 5,5-Difluoro-3(S)-(2-methoxy-pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-[1,8]-naphthyridin-2-yl)-nonanoic acid;
- 5,5-Difluoro-3(R)-(2-methyl-pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-[1,8]-naphthyridin-2-yl)-nonanoic acid;
- 20 2-yl)-nonanoic acid;
- 5,5-Difluoro-3(S)-(2-methyl-pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-[1,8]-naphthyridin-2-yl)-nonanoic acid;
- 25 9-(3-Cyclopropyl-5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-5,5-difluoro-3(S)-(2-methyl-pyrimidin-5-yl)-nonanoic acid;
- 9-(3-Cyclopropyl-5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-5,5-difluoro-3(R)-(2-methyl-pyrimidin-5-yl)-nonanoic acid;
- 30 5,5-Difluoro-3(S)-(pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-5H-pyrido[2,3-b]azepin-2-yl)-nonanoic acid;
- 5,5-Difluoro-3(R)-(pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-5H-pyrido[2,3-b]azepin-2-yl)-nonanoic acid;
- 35

5,5-Difluoro-3(S)-(2-methyl-pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-5H-pyrido[2,3-b]azepin-2-yl)-nonanoic acid;

5 5,5-Difluoro-3(R)-(2-methyl-pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-5H-pyrido[2,3-b]azepin-2-yl)-nonanoic acid;

5,5-Difluoro-3(S)-(2-methoxy-pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-5H-pyrido[2,3-b]azepin-2-yl)-nonanoic acid; and

10

5,5-Difluoro-3(R)-(2-methoxy-pyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-5H-pyrido[2,3-b]azepin-2-yl)-nonanoic acid;

or a pharmaceutically acceptable salt thereof.

15

11. A pharmaceutical composition comprising a compound according to Claim 1 and a pharmaceutically acceptable carrier.

20 12. The composition of Claim 11 which further comprises an active ingredient selected from the group consisting of

- a) an organic bisphosphonate or a pharmaceutically acceptable salt or ester thereof,
- b) an estrogen receptor modulator,
- c) an androgen receptor modulator,
- 25 d) a cytotoxic/antiproliferative agent,
- e) a matrix metalloproteinase inhibitor,
- f) an inhibitor of epidermal-derived, fibroblast-derived, or platelet-derived growth factors,
- g) a VEGF receptor antagonist,
- 30 h) an antibody to a growth factor or a growth factor receptor,
- i) an inhibitor of Flk-1/KDR, Flt-1, Tck/Tie-2, or Tie-1,
- j) a cathepsin K inhibitor,
- k) a growth hormone secretagogue,
- l) an inhibitor of osteoclast proton ATPase,
- 35 m) an inhibitor of urokinase plasminogen activator (u-PA),

- 5 n) a tumor-specific antibody-interleukin-2 fusion protein,
o) an inhibitor of HMG-CoA reductase,
p) a farnesyl transferase inhibitor or a geranylgeranyl transferase inhibitor
or a dual farnesyl/geranylgeranyl transferase inhibitor, and
q) a parathyroid hormone (PTH) analog;
and mixtures thereof.

13. The composition of Claim 12 wherein said active ingredient is
selected from the group consisting of
10 a) an organic bisphosphonate or a pharmaceutically acceptable salt or
ester thereof,
b) an estrogen receptor modulator,
c) an androgen receptor modulator,
d) a cathepsin K inhibitor,
15 e) a parathyroid hormone (PTH) analog, and
f) an inhibitor of osteoclast proton ATPase;
and mixtures thereof.

14. The composition of Claim 13 wherein said organic
20 bisphosphonate or pharmaceutically acceptable salt or ester thereof is alendronate
monosodium trihydrate.

15. A method of eliciting an $\alpha v\beta 3$ integrin receptor antagonizing
effect in a mammal in need thereof, comprising administering to the mammal a
25 therapeutically effective amount of a compound according to Claim 1.

16. The method of Claim 15 wherein the $\alpha v\beta 3$ antagonizing effect
is selected from the group consisting of inhibition of bone resorption, restenosis,
angiogenesis, diabetic retinopathy, macular degeneration, inflammation, inflammatory
30 arthritis, viral disease, cancer, and metastatic tumor growth.

17. The method of Claim 16 wherein the $\alpha v\beta 3$ antagonizing effect
is the inhibition of bone resorption.

18. A method of treating or preventing osteoporosis in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of a compound according to Claim 1.

5 19. A method of eliciting an $\alpha v\beta 3$ integrin receptor antagonizing effect in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of the composition of Claim 11.

10 20. A method of treating or preventing a condition mediated by antagonism of an $\alpha v\beta 3$ integrin receptor in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of the composition of Claim 11.

15 21. A method of treating metastatic tumor growth in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of a compound according to Claim 1 in combination with radiation therapy.