



(12) **DEMANDE DE BREVET CANADIEN
CANADIAN PATENT APPLICATION**

(13) **A1**

(86) Date de dépôt PCT/PCT Filing Date: 2004/08/19
(87) Date publication PCT/PCT Publication Date: 2005/03/03
(85) Entrée phase nationale/National Entry: 2006/02/09
(86) N° demande PCT/PCT Application No.: CA 2004/001524
(87) N° publication PCT/PCT Publication No.: 2005/019161
(30) Priorité/Priority: 2003/08/21 (US60/496,825)

(51) Cl.Int./Int.Cl. *C07C 255/46* (2006.01),
C07D 277/30 (2006.01), *C07D 277/20* (2006.01),
C07D 277/02 (2006.01), *A61P 19/00* (2006.01),
A61K 31/426 (2006.01), *C07C 255/45* (2006.01),
C07C 255/44 (2006.01), *A61P 19/10* (2006.01),
A61P 19/08 (2006.01)

(71) Demandeur/Applicant:
MERCK FROSST CANADA LTD., CA

(72) Inventeurs/Inventors:
GAUTHIER, JACQUES YVES, CA;
TRUONG, VOUY LINH, CA

(74) Agent: OGILVY RENAULT LLP/S.E.N.C.R.L.,S.R.L.

(54) Titre : INHIBITEURS DE CATHEPSINE ET DE CYSTEINE PROTEASE
(54) Title: CATHEPSIN CYSTEINE PROTEASE INHIBITORS

(57) **Abrégé/Abstract:**

This invention relates to a novel class of compounds, represented by the formula below, wherein the meanings of G, E, E, n, R₁, R₂, R₃ et R₄ are indicated therein, which are cysteine protease inhibitors, including but not limited to, inhibitors of cathepsins K, L, S and B. These compounds are useful for treating diseases in which inhibition of bone resorption is indicated, such as osteoporosis.



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

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
3 March 2005 (03.03.2005)

PCT

(10) International Publication Number
WO 2005/019161 A1

(51) International Patent Classification⁷: **C07C 255/46**,
255/44, 255/45, C07D 277/02, 277/20, 277/30, A61K
31/426, A61P 19/00, 19/00, 19/08, 19/10

(21) International Application Number:
PCT/CA2004/001524

(22) International Filing Date: 19 August 2004 (19.08.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/496,825 21 August 2003 (21.08.2003) US

(71) Applicant (*for all designated States except US*):
MERCK FROSST CANADA & CO. [CA/CA]; 16711
Trans-Canada Highway, Kirkland, Quebec H9H 3L1 (CA).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **GAUTHIER,**
Jacques, Yves [CA/CA]; 16711 Trans-Canada Highway,
Kirkland, Quebec H9H 3L1 (CA). **TRUONG, Vouy,**
Linh [CA/CA]; 16711 Trans-Canada Highway, Kirkland,
Quebec H9H 3L1 (CA).

(74) Agent: **OGILVY RENAULT**; Suite 1600, 1981 McGill
College Avenue, Montreal, Quebec H3A 2Y3 (CA).

(81) Designated States (*unless otherwise indicated, for every
kind of national protection available*): AE, AG, AL, AM,
AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN,
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI,
GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE,
KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD,
MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG,
PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM,
TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM,
ZW.

(84) Designated States (*unless otherwise indicated, for every
kind of regional protection available*): ARIPO (BW, GH,
GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM,
ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI,
FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI,
SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report
- before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
amendments

*For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.*

(54) Title: CATHEPSIN CYSTEINE PROTEASE INHIBITORS

(57) Abstract: This invention relates to a novel class of compounds, represented by the formula below, wherein the meanings of G, E, E, n, R₁, R₂, R₃ et R₄ are indicated therein, which are cysteine protease inhibitors, including but not limited to, inhibitors of cathepsins K, L, S and B. These compounds are useful for treating diseases in which inhibition of bone resorption is indicated, such as osteoporosis.

WO 2005/019161 A1

TITLE OF THE INVENTION

CATHEPSIN CYSTEINE PROTEASE INHIBITORS

BACKGROUND OF THE INVENTION

5 A variety of disorders in humans and other mammals involve or are associated with abnormal bone resorption. Such disorders include, but are not limited to, osteoporosis, glucocorticoid induced osteoporosis, Paget's disease, abnormally increased bone turnover, periodontal disease, tooth loss, bone fractures, rheumatoid arthritis, osteoarthritis, periprosthetic osteolysis, osteogenesis imperfecta, atherosclerosis, obesity, chronic obstructive pulmonary disease, metastatic bone disease, hypercalcemia of malignancy or multiple myeloma. One of the most common of these disorders is osteoporosis, which in its most frequent manifestation occurs in postmenopausal women. Osteoporosis is a systemic skeletal disease characterized by a low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture. Osteoporotic fractures are a major cause of morbidity and mortality in the elderly population. As many as 50% of women and a third of men will experience an osteoporotic fracture. A large segment of the older population already has low bone density and a high risk of fractures. There is a significant need to both prevent and treat osteoporosis and other conditions associated with bone resorption. Because osteoporosis, as well as other disorders associated with bone loss, are generally chronic conditions, it is believed that appropriate therapy will typically require chronic treatment.

20 Osteoporosis is characterized by progressive loss of bone architecture and mineralization leading to the loss in bone strength and an increased fracture rate. The skeleton is constantly being remodeled by a balance between osteoblasts that lay down new bone and osteoclasts that breakdown, or resorb, bone. In some disease conditions and advancing age the balance between bone formation and resorption is disrupted; bone is removed at a faster rate. Such a prolonged imbalance of resorption over formation leads to weaker bone structure and a higher risk of fractures.

25 Bone resorption is primarily performed by osteoclasts, which are multinuclear giant cells. Osteoclasts resorb bone by forming an initial cellular attachment to bone tissue, followed by the formation of an extracellular compartment or lacunae. The lacunae are maintained at a low pH by a proton-ATP pump. The acidified environment in the lacunae allows for initial demineralization of bone followed by the degradation of bone proteins or collagen by proteases such as cysteine proteases. See Delaisse, J. M. *et al.*, 1980, *Biochem J* 192:365-368; Delaisse, J. *et al.*, 1984, *Biochem Biophys Res Commun*:441-447; Delaisse, J. M. *et al.*, 1987, *Bone* 8:305-313, which are hereby incorporated by reference in their entirety. Collagen constitutes 95 % of the organic matrix of bone. Therefore, proteases involved in collagen degradation are an essential component of bone turnover, and as a consequence, the development and progression of osteoporosis.

35

Cathepsins belong to the papain superfamily of cysteine proteases. These proteases function in the normal physiological as well as pathological degradation of connective tissue. Cathepsins play a major role in intracellular protein degradation and turnover and remodeling. To date, a number of cathepsins have been identified and sequenced from a number of sources. These cathepsins are naturally found in a wide variety of tissues. For example, cathepsin B, C, F, H, L, K, O, S, V, W, and Z have been cloned. Cathepsin K (which is also known by the abbreviation cat K) is also known as cathepsin O and cathepsin O2. See PCT Application WO 96/13523, Khepri Pharmaceuticals, Inc., published May 9, 1996, which is hereby incorporated by reference in its entirety. Cathepsin L is implicated in normal lysosomal proteolysis as well as several disease states, including, but not limited to, metastasis of melanomas. Cathepsin S is implicated in Alzheimer's disease, asthma, atherosclerosis, chronic obstructive pulmonary disease and certain autoimmune disorders, including, but not limited to juvenile onset diabetes, multiple sclerosis, pemphigus vulgaris, Graves' disease, myasthenia gravis, systemic lupus erythematosus, rheumatoid arthritis and Hashimoto's thyroiditis; allergic disorders, including, but not limited to asthma; and allogenic immune responses, including, but not limited to, rejection of organ transplants or tissue grafts. Increased Cathepsin B levels and redistribution of the enzyme are found in tumors, suggesting a role in tumor invasion and metastasis. In addition, aberrant Cathepsin B activity is implicated in such disease states as rheumatoid arthritis, osteoarthritis, pneumocystis carinii, acute pancreatitis, inflammatory airway disease and bone and joint disorders.

Mammalian cathepsins are related to the papain-like cysteine proteases expressed by disease-causing parasites including those from the families protozoa, platyhelminthes, nematodes and arthropodes. These cysteine proteases play an essential role in the life cycle of these organisms.

Cysteine protease inhibitors such as E-64 (*trans*-epoxysuccinyl-L-leucylamide-(4-guanidino) butane) are known to be effective in inhibiting bone resorption. See Delaisse, J. M. *et al.*, 1987, *Bone* 8:305-313, which is hereby incorporated by reference in its entirety. Recently, cathepsin K was cloned and found specifically expressed in osteoclasts See Tezuka, K. *et al.*, 1994, *J Biol Chem* 269:1106-1109; Shi, G. P. *et al.*, 1995, *FEBS Lett* 357:129-134; Bromme, D. and Okamoto, K., 1995, *Biol Chem Hoppe Seyler* 376:379-384; Bromme, D. *et al.*, 1996, *J Biol Chem* 271:2126-2132; Drake, F. H. *et al.*, 1996, *J Biol Chem* 271:12511-12516, which are hereby incorporated by reference in their entirety. Concurrent to the cloning, the autosomal recessive disorder, pycnodysostosis, characterized by an osteopetrotic phenotype with a decrease in bone resorption, was mapped to mutations present in the cathepsin K gene. To date, all mutations identified in the cathepsin K gene are known to eliminate collagenase activity. See Gelb, B. D. *et al.*, 1996, *Science* 273:1236-1238; Johnson, M. R. *et al.*, 1996, *Genome Res* 6:1050-1055; Hou, W.-S. *et al.*, 1999 *J. Clin. Invest.* 103, 731-738 which are hereby incorporated by reference in their entirety. Therefore, it appears that cathepsin K is involved in osteoclast mediated bone resorption.

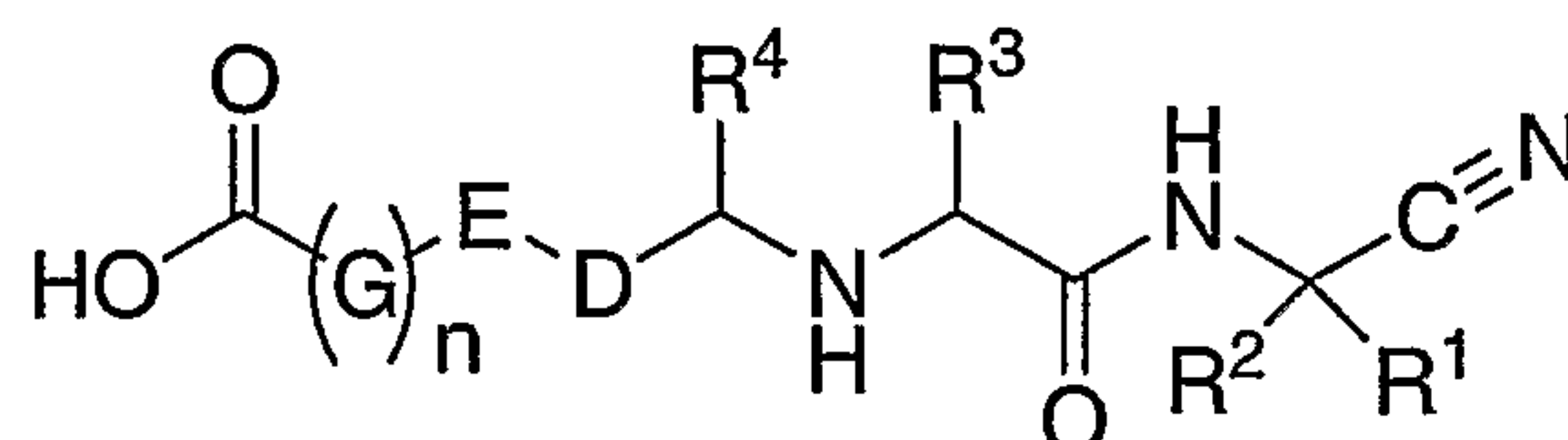
Cathepsin K is synthesized as a 37 kDa pre-pro enzyme, which is localized to the lysosomal compartment and where it is presumably autoactivated to the mature 27 kDa enzyme at low pH. See McQueney, M. S. *et al.*, 1997, *J Biol Chem* 272:13955-13960; Littlewood-Evans, A. *et al.*, 1997, *Bone* 20:81-86, which are hereby incorporated by reference in their entirety. Cathepsin K is most closely related to cathepsin S having 56 % sequence identity at the amino acid level. The S₂P₂ substrate specificity of cathepsin K is similar to that of cathepsin S with a preference in the P1 and P2 positions for a positively charged residue such as arginine, and a hydrophobic residue such as phenylalanine or leucine, respectively. See Bromme, D. *et al.*, 1996, *J Biol Chem* 271: 2126-2132; Bossard, M. J. *et al.*, 1996, *J Biol Chem* 271:12517-12524, which are hereby incorporated by reference in their entirety.

Cathepsin K is active at a broad pH range with significant activity between pH 4-8, thus allowing for good catalytic activity in the resorption lacunae of osteoclasts where the pH is about 4-5.

Human type I collagen, the major collagen in bone is a good substrate for cathepsin K. See Kafienah, W., *et al.*, 1998, *Biochem J* 331:727-732, which is hereby incorporated by reference in its entirety. *In vitro* experiments using antisense oligonucleotides to cathepsin K, have shown diminished bone resorption *in vitro*, which is probably due to a reduction in translation of cathepsin K mRNA. See Inui, T., *et al.*, 1997, *J Biol Chem* 272:8109-8112, which is hereby incorporated by reference in its entirety. The crystal structure of cathepsin K has been resolved. See McGrath, M. E., *et al.*, 1997, *Nat Struct Biol* 4:105-109; Zhao, B., *et al.*, 1997, *Nat Struct Biol* 4: 109-11, which are hereby incorporated by reference in their entirety. Also, selective peptide based inhibitors of cathepsin K have been developed. See Bromme, D., *et al.*, 1996, *Biochem J* 315:85-89; Thompson, S. K., *et al.*, 1997, *Proc Natl Acad Sci U S A* 94:14249-14254, which are hereby incorporated by reference in their entirety. Accordingly, inhibitors of Cathepsin K can reduce bone resorption. Such inhibitors would be useful in treating disorders involving bone resorption, such as osteoporosis.

SUMMARY OF THE INVENTION

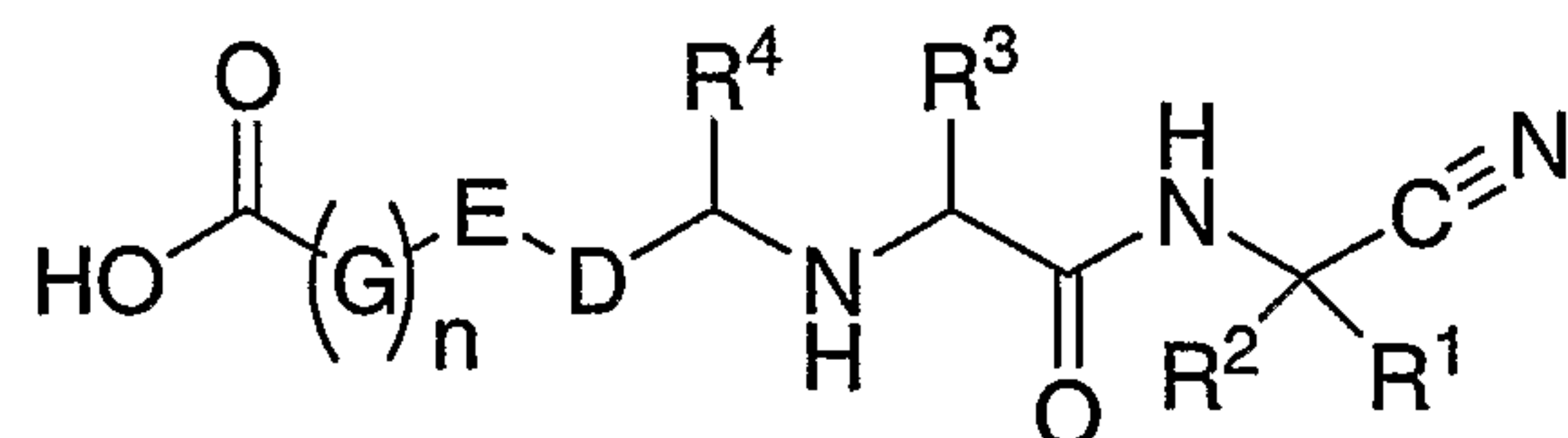
The present invention relates to compounds that are capable of treating and/or preventing cathepsin dependent conditions or disease states in a mammal in need thereof. One embodiment of the present invention is illustrated by a compound of Formula I, and the pharmaceutically acceptable salts, esters, stereoisomers and N-oxide derivatives thereof:



I.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to compounds of the following chemical formula:



- wherein R¹ is hydrogen, C₁-6 alkyl or C₂-6 alkenyl wherein said alkyl and alkenyl groups are optionally substituted with one to six halo, C₃-6 cycloalkyl, -SR⁵, -SOR⁵, -SO₂R⁵, -SO₂CH(R^a)(R^b), -OR⁵, -N(R⁵)₂, aryl, heteroaryl or heterocyclyl wherein said aryl, heteroaryl and heterocyclyl groups are optionally substituted with one or two substituents independently selected from the group consisting of C₁-6 alkyl, halo, hydroxyalkyl, hydroxy, alkoxy and keto;
- R² is hydrogen, C₁-6 alkyl or C₂-6 alkenyl wherein said alkyl and alkenyl groups are optionally substituted with one to six halo, C₃-6 cycloalkyl, -SR⁵, -SOR⁵, -SO₂R⁵, -SO₂CH(R^a)(R^b), -OR⁵, -N(R⁵)₂, aryl, heteroaryl or heterocyclyl wherein said aryl, heteroaryl and heterocyclyl groups are optionally substituted with one or two substituents independently selected from the group consisting of C₁-6 alkyl, halo, hydroxyalkyl, hydroxy, alkoxy and keto;
- or R¹ and R² can be taken together with the carbon atom to which they are attached to form a C₃-8 cycloalkyl or heterocyclyl ring wherein said ring system is optionally substituted with one or two substituents independently selected from the group consisting of C₁-6 alkyl, hydroxyalkyl, haloalkyl, or halo;
- R³ is hydrogen, C₁-6 alkyl or C₂-6 alkenyl wherein said alkyl and alkenyl groups are optionally substituted with C₃-6 cycloalkyl or one to six halo;
- R⁴ is hydrogen or C₁-6 alkyl substituted with 1-6 halo;
- D is aryl or heteroaryl, wherein said aryl or heteroaryl group, which may be monocyclic or bicyclic, is optionally substituted on either the carbon or the heteroatom with one to five substituents independently selected from the group consisting of C₁-6 alkyl, haloalkyl, halo, keto, alkoxy, -SR⁵, -OR⁵, N(R⁵)₂, -SO₂R⁵, and -SO₂R^a;
- E is aryl or heteroaryl, wherein said aryl or heteroaryl group, which may be monocyclic or bicyclic, is optionally substituted on either the carbon or the heteroatom with one to five substituents independently selected from the group consisting of C₁-6 alkyl, haloalkyl, halo, keto, alkoxy, -SR⁵, -OR⁵, N(R⁵)₂, -SO₂R⁵, and -SO₂R^a;
- Each G is independently C₁-6 alkyl, C₁-6 alkyloxy, aryl, heteroaryl, C₃-8 cycloalkyl, heterocyclyl, -O-, NR⁵, S(O)_m, or carbonyl wherein said groups are optionally substituted on either the carbon or the heteroatom with one to five substituents independently selected from the group consisting of C₁-6 alkyl,

halo, keto, haloalkyl, hydroxyalkyl, $-OR^5$, $-NHS(O)_2R^5$, $-SO_mR^5$, $-SO_mN(R^a)(R^b)$, $-C(R^a)(R^b)OH$, ,
heterocycyl, aryl or heteroaryl;

R^5 is hydrogen, C_{1-6} alkyl, aryl, aryl(C_{1-4})alkyl, heteroaryl, heteroaryl(C_{1-4})alkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl(C_{1-4})alkyl, or heterocyclyl(C_{1-4})alkyl wherein said groups can be optionally substituted

5 with one, two, or three substituents independently selected from the group consisting of halo, alkoxy, cyano, $-NR^a$ or $-SR^a$ or $-SO_mR^5$;

R^a is hydrogen or C_{1-6} alkyl which is optionally substituted with one, two, or three substituents independently selected from the group consisting of halo and $-OR^5$;

R^b is hydrogen or C_{1-6} alkyl which is optionally substituted with one, two, or three substituents
10 independently selected from the group consisting of halo and $-OR^5$;
or R^a and R^b can be taken together with the nitrogen atom to which they are attached or are between them to form a C_{3-8} heterocyclyl ring which is optionally substituted with one or two substituents independently selected from the group consisting of C_{1-6} alkyl, halo hydroxyalkyl, hydroxy, alkoxy and keto;

15 m is an integer from zero to two;

n is an integer from one to three;

or a pharmaceutically acceptable salt, stereoisomer or N-oxide derivative thereof.

In one class of the invention, R^1 and R^2 can be taken together with the carbon atom to which they are attached to form a C_{3-8} cycloalkyl ring wherein said ring system is optionally substituted
20 with one or two substituents selected from C_{1-6} alkyl or halo.

In another class of the invention, R^3 is C_{1-6} alkyl which is optionally substituted with one to six halo.

In another class of the invention, R^3 is n-propyl, isobutyl, 2-fluoro-2-methylpropyl, 2-trifluoromethylpropyl, 3-fluoro-2-(2-fluoromethyl)propyl, 2,2-difluoroethyl, 2,2-difluoropropyl, 3,3,3-trifluoropropyl, or 2,2-dichloroethyl.
25

In another class of the invention, R^4 is difluoromethyl, 2,2-difluoroethyl, trifluoromethyl or 3,3,3,2,2-pentafluoroethyl.

In another class of the invention, D is phenyl.

In another class of the invention, E is phenyl or heteroaryl, wherein said phenyl or
30 heteroaryl group, is optionally substituted on either the carbon or the heteroatom with one to five halo.

In another class of the invention, each G is independently C_{1-6} alkyl, C_{3-8} cycloalkyl or $SO_mCH(R^a)(R^b)$.

Reference to the preferred embodiments set forth above is meant to include all combinations of particular and preferred groups unless stated otherwise.

35

Specific embodiments of the present invention include, but are not limited to:

- 1-[4'-[(1*S*)-1-[[[(1*S*)-1-[(1-cyanocyclopropyl)amino]carbonyl]-3-fluoro-3-methylbutyl]amino]-2,2,2-trifluoroethyl][1,1'-biphenyl]-4-yl]-cyclopropanecarboxylic acid;
- N*¹-(1-cyanocyclopropyl)-*N*²-{(1*S*)-2,2-difluoro-1-{4'-[1-(carboxy)cyclopropyl]biphenyl-4-yl}-ethyl}-L-leucinamide;
- N*¹-(1-cyanocyclopropyl)-*N*²-{(1*S*)-2,2-difluoro-1-{4'-[1-(carboxy)cyclopropyl]biphenyl-4-yl}-ethyl}-4-fluoro-L-leucinamide;
- 1-[2-[4-[(1*S*)-1-[[[(1*S*)-1-[(1-cyanocyclopropyl)amino]carbonyl]-3-fluoro-3-methylbutyl]amino]-2,2,2-trifluoroethyl]phenyl]-4-thiazolyl]-cyclopropanecarboxylic acid;
- 1-[[4'-[(1*S*)-1-[[[(1*S*)-1-[(1-cyanocyclopropyl)amino]carbonyl]-3-methylbutyl]amino]-2,2-difluoroethyl][1,1'-biphenyl]-3-yl]methyl]-cyclobutanecarboxylic acid;
- 4'-[(1*S*)-1-[[[(1*S*)-1-[(1-cyanocyclopropyl)amino]carbonyl]-3-fluoro-3-methylbutyl]amino]-2,2,2-trifluoroethyl]- α,α -dimethyl-[1,1'-biphenyl]-4-propanoic acid;
- 1-[4'-[(1*S*)-1-[[[(1*S*)-1-[(1-cyanocyclopropyl)amino]carbonyl]-3-methylbutyl]amino]-2,2,2-trifluoroethyl][1,1'-biphenyl]-4-yl]-cyclopropanecarboxylic acid;
- 1-[4'-[(1*S*)-1-[[[(1*S*)-1-[(1-cyanocyclopropyl)amino]carbonyl]-3-fluoro-3-methylbutyl]amino]-2,2,2-trifluoroethyl][1,1'-biphenyl]-3-yl]-cyclopropanecarboxylic acid;
- 4'-[(1*S*)-1-[[[(1*S*)-1-[(1-cyanocyclopropyl)amino]carbonyl]-3-fluoro-3-methylbutyl]amino]-2,2,2-trifluoroethyl]- α -methyl-[1,1'-biphenyl]-4-acetic acid;
- 4'-[(1*S*)-1-[[[(1*S*)-1-[(1-cyanocyclopropyl)amino]carbonyl]-3-fluoro-3-methylbutyl]amino]-2,2,2-trifluoroethyl]- α,α -dimethyl-[1,1'-biphenyl]-4-acetic acid;
- 1-[4'-[(1*S*)-1-[[[(1*S*)-1-[(1-cyanocyclopropyl)amino]carbonyl]-3-fluoro-3-methylbutyl]amino]-2,2,2-trifluoroethyl][1,1'-biphenyl]-4-yl]-cyclopropaneacetic acid;
- 1-[4'-[(1*S*)-1-[[[(1*S*)-1-[(1-cyanocyclopropyl)amino]carbonyl]-3-methylbutyl]amino]-2,2,2-trifluoroethyl][1,1'-biphenyl]-4-yl]-cyclopropanecarboxylic acid;
- 1-[4'-[(1*S*)-1-[[[(1*S*)-1-[(1-cyanocyclopropyl)amino]carbonyl]butyl]amino]-2,2,2-trifluoroethyl][1,1'-biphenyl]-4-yl]-cyclopropanecarboxylic acid;
- 4'-[(1*S*)-1-[[[(1*S*)-1-[(1-cyanocyclopropyl)amino]carbonyl]-3-fluoro-3-methylbutyl]amino]-2,2,2-trifluoroethyl]-[1,1'-biphenyl]-4-acetic acid;
- N*¹-(1-cyanocyclopropyl)-4-fluoro-*N*²-[(1*S*)-2,2,2-trifluoro-1-{4'-[(1*S*)-1-carboxyethyl]biphenyl-4-yl}-ethyl)-L-leucinamide;

and the pharmaceutically acceptable salts, esters, stereoisomers and N-oxide derivatives thereof.

Also included within the scope of the present invention is a pharmaceutical composition which is comprised of a compound of Formula I as described above and a pharmaceutically acceptable carrier. The invention is also contemplated to encompass a pharmaceutical composition which is

comprised of a pharmaceutically acceptable carrier and any of the compounds specifically disclosed in the present application, alone or in combination with any other disclosed compound. These and other aspects of the invention will be apparent from the teachings contained herein.

5 Utilities

The compounds of the present invention are inhibitors of cathepsins and are therefore useful to treat or prevent cathepsin dependent diseases or conditions in mammals, preferably humans. Specifically, the compounds of the present invention are inhibitors of Cathepsin K and are therefore useful to treat or prevent Cathepsin K dependent diseases or conditions in mammals, preferably humans.

10 “Cathepsin dependent diseases or conditions” refers to pathologic conditions that depend on the activity of one or more cathepsins. “Cathepsin K dependent diseases or conditions” refers to pathologic conditions that depend on the activity of Cathepsin K. Diseases associated with Cathepsin K activities include osteoporosis, glucocorticoid induced osteoporosis, Paget’s disease, abnormally increased bone turnover, periodontal disease, tooth loss, bone fractures, rheumatoid arthritis,
15 osteoarthritis, periprosthetic osteolysis, osteogenesis imperfecta, atherosclerosis and cancer including metastatic bone disease, hypercalcemia of malignancy, and multiple myeloma. In treating such conditions with the instantly claimed compounds, the required therapeutic amount will vary according to the specific disease and is readily ascertainable by those skilled in the art. Although both treatment and prevention are contemplated by the scope of the invention, the treatment of these conditions is the
20 preferred use.

An embodiment of the invention is a method of inhibiting cathepsin activity 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.

25 A class of the embodiment is the method wherein the cathepsin activity is cathepsin K activity.

Another embodiment of the invention is a method of treating or preventing cathepsin dependent conditions 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.

30 A class of the embodiment is the method wherein the cathepsin activity is cathepsin K activity.

Another embodiment of the invention is a method of inhibiting bone loss 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. Another embodiment of the
35 invention is a method of reducing bone loss 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. The utility of cathepsin K inhibitors in the inhibition of bone resorption is known in the literature, see Stroup, G.B., Lark, M.W., Veber, DF., Bhattacharrya, A., Blake, S., Dare, L.C., Erhard, K.F., Hoffman, S.J., James, I.E., Marquis, R.w., Ru, Y., Vasko-Moser, J.A., Smith, B.R.,
5 Tomaszek, T. and Gowen, M. Potent and selective inhibition of human cathepsin K leads to inhibition of bone resorption in vivo in a nonhuman primate. *J. Bone Miner. Res.*, 16:1739-1746;2001; and Votta, B.J., Levy, M.A., Badger, A., Dodds, R.A., James, I.E., Thompson, S., Bossard, M.J., Carr, T., Connor, J.R., Tomaszek, T.A., Szewczuk, L., Drake, F.H., Veber, D., and Gowen, M. Peptide aldehyde inhibitors of cathepsin K inhibit bone resorption both in vivo and in vitro. *J. Bone Miner. Res.* 12:1396-
10 1406; 1997.

Another embodiment of the invention is a method of treating 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 above pharmaceutical compositions described above. The utility of cathepsin K inhibitors in the treatment or prevention of osteoporosis is known in the literature, see
15 Saftig, P., Hunziker, E., Wehmeyer, O., Jones, S., Boyde, A., Rommerskirch, W., Moritz, J.D., Schu, P., and Vonfigura, K. Impaired osteoclast bone resorption leads to osteopetrosis in cathepsin K-deficient mice. *Proc. Natl. Acad. Sci. USA* 95:13453-13458; 1998.

Another embodiment of the invention is a method of treating or preventing rheumatoid arthritic condition in a mammal in need thereof, comprising administering to the mammal a
20 therapeutically effective amount of any of the compounds or any of the pharmaceutical compositions described above. It is known in the literature that progressive destruction of the periarticular bone is a major cause of joint dysfunction and disability in patients with rheumatoid arthritis (RA), see Goldring SR, "Pathogenesis of bone erosions in rheumatoid arthritis". *Curr. Opin. Rheumatol.* 2002; 14: 406-10. Analysis of joint tissues from patients with RA have provided evidence that cathepsin K positive
25 osteoclasts are the cell types that mediate the focal bone resorption associated with rheumatoid synovial lesion, see Hou, W-S, Li, W, Keyszer, G, Weber, E, Levy, R, Klein, MJ, Gravallesse, EM, Goldring, SR, Bromme, D, "Comparision of Cathepsin K and S expression within the Rheumatoid and Osteoarthritic Synovium", *Arthritis Rheumatism* 2002; 46: 663-74. In addition, generalized bone loss is a major cause of morbidity associated with severe RA. The frequency of hip and spinal fractures is substantially
30 increased in patients with chronic RA, see Gould A, Sambrook, P, Devlin J et al, "Osteoclastic activation is the principal mechanism leading to secondary osteoporosis in rheumatoid arthritis". *J. Rheumatol.* 1998; 25: 1282-9. The utility of cathepsin K inhibitors in the treatment or prevention of resorption in subarticular bone and of generalized bone loss represent a rational approach for pharmacological intervention on the progression of rheumatoid arthritis.

Another embodiment of the invention is a method of treating or preventing the progression of osteoarthritis 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. It is known in the literature that osteoarthritis (OA) is accompanied with a well-defined changes in the joints, including erosion of the articular cartilage surface, peri-articular endochondral ossification/osteophytosis, and subchondral bony sclerosis and cyst formation, see Oettmeier R, Abendroth, K, "Osteoarthritis and bone: osteologic types of osteoarthritis of the hip", *Skeletal Radiol.* 1989; 18: 165-74. Recently, the potential contribution of subchondral bone sclerosis to the initiation and progression of OA have been suggested. Stiffened subchondral bone as the joint responding to repetitive impulsive loading, is less able to attenuate and distribute forces through the joint, subjecting it to greater mechanical stress across the articular cartilage surface. This in turn accelerates cartilage wear and fibrillate, see Radin, EL and Rose RM, "Role of subchondral bone in the initiation and progression of cartilage damage", *Clin. Orthop.* 1986; 213: 34-40. Inhibition of excessive subarticular bone resorption by an anti-resorptive agent such as a cathepsin K inhibitor, will lead to inhibition of subchondral bone turnover, thus may have a favorable impact on OA progression. In addition to the above hypothesis, cathepsin K protein expression was recently identified in synovial fibroblasts, macrophage-like cells, and chondrocytes from synovium and articular cartilage specimens derived from OA patients, see Hou, W-S, Li, W, Keyszer, G, Weber, E, Levy, R, Klein, MJ, Gravallese, EM, Goldring, SR, Bromme, D, "Comparison of Cathepsin K and S expression within the Rheumatoid and Osteoarthritic Synovium", *Arthritis Rheumatism* 2002; 46: 663-74; and Dodd, RA, Connor, JR, Drake, FH, Gowen, M, "Expression of Cathepsin K messenger RNA in giant cells and their precursors in human osteoarthritic synovial tissues". *Arthritis Rheumatism* 1999; 42: 1588-93; and Konttinen, YT, Mandelin, J, Li, T-F, Salo, J, Lassus, J et al. "Acidic cysteine endoproteinase cathepsin K in the degeneration of the superficial articular hyaline cartilage in osteoarthritis", *Arthritis Rheumatism* 2002; 46: 953-60. These recent studies thus implicated the role of cathepsin K in the destruction of collagen type II in the articular cartilage associated with the progression of osteoarthritis. The utility of cathepsin K inhibitors in the treatment or prevention of osteoarthritis as described in this invention thus comprise of two different mechanisms, one is on the inhibition of osteoclast-driven subchondral bone turnover, and two is on the direct inhibition of collagen type II degeneration in the synovium and cartilage of patients with OA.

Another embodiment of the invention is a method of treating cancer 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. It is known in the literature that cathepsin K is expressed in human breast carcinoma, prostate cancer and chordoma and has matrix degrading capabilities, see Littlewood-Evans AJ, Bilbe G, Bowler WB, Farley D, Wlodarski B, Kokubo T, Inaoka T, Sloane J, Evans DB, Gallagher JA, "The osteoclast-associated protease cathepsin K is

expressed in human breast carcinoma.” *Cancer Res* 1997 Dec 1;57(23):5386-90, Brubaker KD, Vessella RL, True LD, Thomas R., Corey E. “Cathepsin K mRNA and protein expression in prostate cancer progression.” *J Bone Miner Res* 2003 18, 222-30, Haeckel C, Krueger S, Kuester D, Ostertag H, Samii M, Buehling F, Broemme D, Czerniak B, Roessner A. “Expression of cathepsin K in chordoma.” *Hum Pathol* 2000 Jul;31(7):834-40.

Another embodiment of the invention is a method treating atherosclerosis 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. It is known in the literature that cathepsin K is expressed in human atheroma and has significant elastase activity, see Sukhova GK, Shi GP, Simon DI, Chapman HA, Libby P. “Expression of the elastolytic cathepsins S and K in human atheroma and regulation of their production in smooth muscle cells.” *J Clin Invest* 1998 Aug 102, 576-83.

Another embodiment of the invention is a method treating obesity 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. It is known in the literature that cathepsin K mRNA is increased in adipose tissue in several mouse models of obesity and also in adipose tissue of obese human males, see Chiellini C, Costa M, Novelli SE, Amri EZ, Benzi L, Bertacca A, Cohen P, Del Prato S, Friedman JM, Maffei M. “Identification of cathepsin K as a novel marker of adiposity in white adipose tissue.” *J Cell Physiol* 2003, 195, 309-21.

Another embodiment of the invention is a method of treating chronic obstructive pulmonary disease 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. It is known in the literature that cathepsin K plays a role in lung fibrosis, see Buehling, F., *et al.*, “Pivotal role of cathepsin K in lung fibrosis,” *Am J Pathol.* 2004 Jun;164(6):2203-16.

Another embodiment of the invention is a method of treating parasitic infections 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. It is known in the literature that mammalian cathepsins are related to the papain-like cysteine proteases which play an important role in the life cycle of these parasites. Such parasites are involved in the diseases of malaria, american trypanosomiasis, african trypanosomiasis, leishmaniasis, giardiasis, trichomoniasis, amoebiasis, schistosomiasis, fascioliasis, paragonimiasis and intestinal roundworms, see Lecaille F, Kaleta J, Bromme D., Human and parasitic papain-like cysteine proteases: their role in physiology and pathology and recent developments in inhibitor design. *Chem Rev* 2002 102, 4459-88.

Another embodiment of the invention is a method of treating mammalian diseases associated with cathepsin S including Alzheimer’s disease, atherosclerosis, chronic obstructive

pulmonary disease, cancer and certain autoimmune disorders, including, but not limited to juvenile onset diabetes, multiple sclerosis, pemphigus vulgaris, Graves' disease, myasthenia gravis, systemic lupus erythematosus, rheumatoid arthritis and Hashimoto's thyroiditis; allergic disorders, including, but not limited to asthma; and allogenic immune responses, including, but not limited to, rejection of organ transplants or tissue grafts. It is known in the literature that cathepsin S activity is associated with the above disease states, see Munger JS, Haass C, Lemere CA, Shi GP, Wong WS, Teplow DB, Selkoe DJ, Chapman HA. Lysosomal processing of amyloid precursor protein to A beta peptides: a distinct role for cathepsin S. *Biochem J* 1995 311, 299-305, Sukhova GK, Zhang Y, Pan JH, Wada Y, Yamamoto T, Naito M, Kodama T, Tsimikas S, Witztum JL, Lu ML, Sakara Y, Chin MT, Libby P, Shi GP. Deficiency of cathepsin S reduces atherosclerosis in LDL receptor-deficient mice. *J Clin Invest* 2003 111, 897-906, Zheng T, Zhu Z, Wang Z, Homer RJ, Ma B, Riese RJ Jr, Chapman HA Jr, Shapiro SD, Elias JA. Inducible targeting of IL-13 to the adult lung causes matrix metalloproteinase- and cathepsin-dependent emphysema. *J Clin Invest* 2000 106, 1081-93, Shi GP, Sukhova GK, Kuzuya M, Ye Q, Du J, Zhang Y, Pan JH, Lu ML, Cheng XW, Iguchi A, Perrey S, Lee AM, Chapman HA, Libby P. Deficiency of the cysteine protease cathepsin S impairs microvessel growth. *Circ Res* 2003 92, 493-500, Nakagawa TY, Brissette WH, Lira PD, Griffiths RJ, Petrushova N, Stock J, McNeish JD, Eastman SE, Howard ED, Clarke SR, Rosloniec EF, Elliott EA, Rudensky AY. Impaired invariant chain degradation and antigen presentation and diminished collagen-induced arthritis in cathepsin S null mice. *Immunity* 1999 10, 207-17.

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 loss, bone resorption, bone fractures, metastatic bone disease and/or disorders related to cathepsin functioning.

The compounds of this invention may be administered to mammals, preferably humans, either alone or, preferably, in combination with pharmaceutically acceptable carriers or diluents, optionally with known adjuvants, such as alum, in a pharmaceutical composition, according to standard pharmaceutical practice. The compounds can be administered orally or parenterally, including the intravenous, intramuscular, intraperitoneal, subcutaneous, rectal and topical routes of administration.

In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch, and lubricating agents, such as magnesium stearate, are commonly added. For oral administration in capsule form, useful diluents include lactose and dried corn starch. For oral use of a therapeutic compound according to this invention, the selected compound may be administered, for example, in the form of tablets or capsules, or as an aqueous solution or suspension. 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.

5 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
10 cellulose, agar, bentonite, xanthan gum and the like. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring agents may be added. For intramuscular, intraperitoneal, subcutaneous and intravenous use, sterile solutions of the active ingredient are usually prepared, and the pH of the solutions
15 should be suitably adjusted and buffered. For intravenous use, the total concentration of solutes should be controlled in order to render the preparation isotonic.

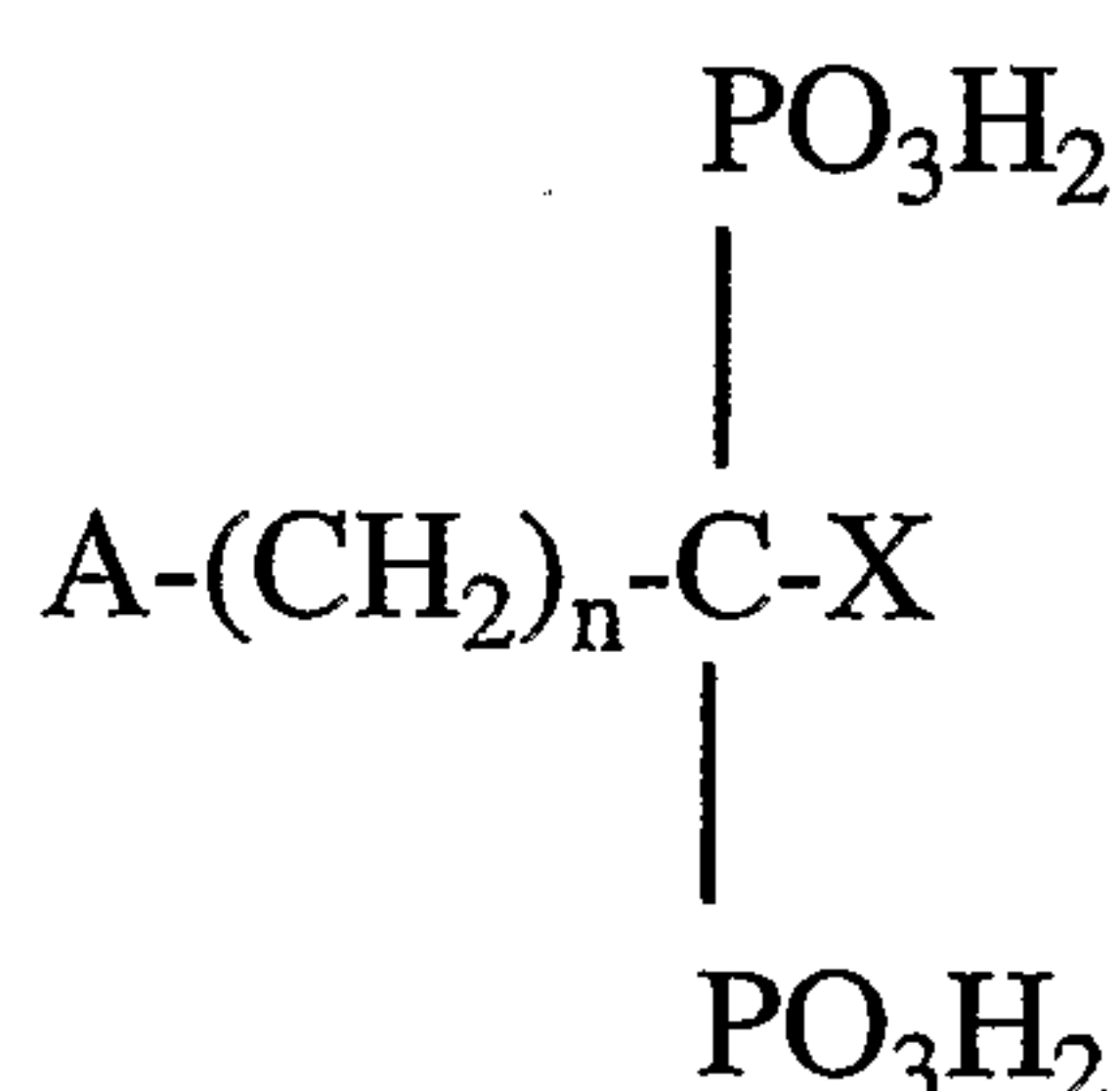
The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol,
20 stearylamine or phosphatidylcholines.

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,
25 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 polyactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and crosslinked or
30 amphipathic block copolymers of hydrogels.

The instant compounds are also useful in combination with known agents useful for treating or preventing osteoporosis, glucocorticoid induced osteoporosis, Paget's disease, abnormally increased bone turnover, periodontal disease, tooth loss, bone fractures, rheumatoid arthritis, osteoarthritis, periprosthetic osteolysis, osteogenesis imperfecta, metastatic bone disease, hypercalcemia
35 of malignancy, and multiple myeloma. Combinations of the presently disclosed compounds with other

agents useful in treating or preventing osteoporosis or other bone disorders are within the scope of the invention. A person of ordinary skill in the art would be able to discern which combinations of agents would be useful based on the particular characteristics of the drugs and the disease involved. Such agents include the following: an organic bisphosphonate; an estrogen receptor modulator; an androgen receptor modulator; an inhibitor of osteoclast proton ATPase; an inhibitor of HMG-CoA reductase; an integrin receptor antagonist; an osteoblast anabolic agent, such as PTH; and the pharmaceutically acceptable salts and mixtures thereof. A preferred combination is a compound of the present invention and an organic bisphosphonate. Another preferred combination is a compound of the present invention and an estrogen receptor modulator. Another preferred combination is a compound of the present invention and an androgen receptor modulator. Another preferred combination is a compound of the present invention and an osteoblast anabolic agent.

“Organic bisphosphonate” includes, but is not limited to, compounds of the chemical formula



wherein n is an integer from 0 to 7 and wherein A and X are independently selected from the group consisting of H, OH, halogen, NH₂, SH, phenyl, C1-C30 alkyl, C3-C30 branched or cycloalkyl, bicyclic ring structure containing two or three N, C1-C30 substituted alkyl, C1-C10 alkyl substituted NH₂, C3-C10 branched or cycloalkyl substituted NH₂, C1-C10 dialkyl substituted NH₂, C1-C10 alkoxy, C1-C10 alkyl substituted thio, thiophenyl, halophenylthio, C1-C10 alkyl substituted phenyl, pyridyl, furanyl, pyrrolidinyl, imidazolyl, imidazopyridinyl, and benzyl, such that both A and X are not selected from H or OH when n is 0; or A and X are taken together with the carbon atom or atoms to which they are attached to form a C3-C10 ring.

In the foregoing chemical formula, the alkyl groups can be straight, branched, or cyclic, provided sufficient atoms are selected for the chemical formula. The C1-C30 substituted alkyl can include a wide variety of substituents, nonlimiting examples which include those selected from the group consisting of phenyl, pyridyl, furanyl, pyrrolidinyl, imidazolyl, NH₂, C1-C10 alkyl or dialkyl substituted NH₂, OH, SH, and C1-C10 alkoxy.

The foregoing chemical formula is also intended to encompass complex carbocyclic, aromatic and hetero atom structures for the A and/or X substituents, nonlimiting examples of which include naphthyl, quinolyl, isoquinolyl, adamantyl, and chlorophenylthio.

Pharmaceutically acceptable salts and derivatives of the bisphosphonates are also useful
5 herein. Non-limiting examples of salts include those selected from the group consisting alkali metal, alkaline metal, ammonium, and mono-, di-, tri-, or tetra-C1-C30-alkyl-substituted ammonium. Preferred salts are those selected from the group consisting of sodium, potassium, calcium, magnesium, and ammonium salts. More preferred are sodium salts. Non-limiting examples of derivatives include those selected from the group consisting of esters, hydrates, and amides.

10 It should be noted that the terms "bisphosphonate" and "bisphosphonates", as used herein in referring to the therapeutic agents of the present invention are meant to also encompass diphosphonates, biphosphonic acids, and diposphonic acids, as well as salts and derivatives of these materials. The use of a specific nomenclature in referring to the bisphosphonate or bisphosphonates is not meant to limit the scope of the present invention, unless specifically indicated. Because of the mixed
15 nomenclature currently in use by those of ordinary skill in the art, reference to a specific weight or percentage of a bisphosphonate compound in the present invention is on an acid active weight basis, unless indicated otherwise herein. For example, the phrase "about 5 mg of a bone resorption inhibiting bisphosphonate selected from the group consisting of alendronate, pharmaceutically acceptable salts thereof, and mixtures thereof, on an alendronic acid active weight basis" means that the amount of the
20 bisphosphonate compound selected is calculated based on 5 mg of alendronic acid.

Non-limiting examples of bisphosphonates useful herein include the following:

Alendronic acid, 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid.

Alendronate (also known as alendronate sodium or alendronate monosodium trihydrate),
4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium trihydrate.

25 Alendronic acid and alendronate are described in U.S. Patents 4,922,007, to Kieczkowski et al., issued May 1, 1990; 5,019,651, to Kieczkowski et al., issued May 28, 1991; 5,510,517, to Dauer et al., issued April 23, 1996; 5,648,491, to Dauer et al., issued July 15, 1997, all of which are incorporated by reference herein in their entirety.

Cycloheptylaminomethylene-1,1-bisphosphonic acid, YM 175, Yamanouchi
30 (incadronate, formerly known as cimadronate), as described in U.S. Patent 4,970,335, to Isomura et al., issued November 13, 1990, which is incorporated by reference herein in its entirety.

1,1-dichloromethylene-1,1-diphosphonic acid (clodronic acid), and the disodium salt (clodronate, Procter and Gamble), are described in Belgium Patent 672,205 (1966) and *J. Org. Chem* 32, 4111 (1967), both of which are incorporated by reference herein in their entirety.

35 1-hydroxy-3-(1-pyrrolidiny)-propylidene-1,1-bisphosphonic acid (EB-1053).

1-hydroxyethane-1,1-diphosphonic acid (etidronic acid).

1-hydroxy-3-(N-methyl-N-pentylamino)propylidene-1,1-bisphosphonic acid, also known as BM-210955, Boehringer-Mannheim (ibandronate), is described in U.S. Patent No. 4,927,814, issued May 22, 1990, which is incorporated by reference herein in its entirety.

5 1-hydroxy-2-imidazo-(1,2-a)pyridin-3-ylethylidene (minodronate).

6-amino-1-hydroxyhexylidene-1,1-bisphosphonic acid (neridronate).

3-(dimethylamino)-1-hydroxypropylidene-1,1-bisphosphonic acid (olpadronate).

3-amino-1-hydroxypropylidene-1,1-bisphosphonic acid (pamidronate).

10 [2-(2-pyridinyl)ethylidene]-1,1-bisphosphonic acid (piridronate) is described in U.S. Patent No. 4,761,406, which is incorporated by reference in its entirety.

1-hydroxy-2-(3-pyridinyl)-ethylidene-1,1-bisphosphonic acid (risedronate).

(4-chlorophenyl)thiomethane-1,1-disphosphonic acid (tiludronate) as described in U.S. Patent 4,876,248, to Breliere et al., October 24, 1989, which is incorporated by reference herein in its entirety.

15 1-hydroxy-2-(1H-imidazol-1-yl)ethylidene-1,1-bisphosphonic acid (zoledronate).

Nonlimiting examples of bisphosphonates include alendronate, cimadronate, clodronate, etidronate, ibandronate, incadronate, minodronate, neridronate, olpadronate, pamidronate, piridronate, risedronate, tiludronate, and zolendronate, and pharmaceutically acceptable salts and esters thereof. A particularly preferred bisphosphonate is alendronate, especially a sodium, potassium, calcium, magnesium or ammonium salt of alendronic acid. Exemplifying the preferred bisphosphonate is a sodium salt of alendronic acid, especially a hydrated sodium salt of alendronic acid. The salt can be hydrated with a whole number of moles of water or non whole numbers of moles of water. Further exemplifying the preferred bisphosphonate is a hydrated sodium salt of alendronic acid, especially when the hydrated salt is alendronate monosodium trihydrate.

25 It is recognized that mixtures of two or more of the bisphosphonate actives can be utilized.

The precise dosage of the organic bisphosphonate will vary with the dosing schedule, the particular bisphosphonate chosen, the age, size, sex and condition of the mammal or human, the nature and severity of the disorder to be treated, and other relevant medical and physical factors. Thus, a precise pharmaceutically effective amount cannot be specified in advance and can be readily determined by the caregiver or clinician. Appropriate amounts can be determined by routine experimentation from animal models and human clinical studies. Generally, an appropriate amount of bisphosphonate is chosen to obtain a bone resorption inhibiting effect, i.e. a bone resorption inhibiting amount of the bisphosphonate is administered. For humans, an effective oral dose of bisphosphonate is typically from about 1.5 to about 6000 $\mu\text{g/kg}$ body weight and preferably about 10 to about 2000 $\mu\text{g/kg}$ of body weight.

For alendronate monosodium trihydrate, common human doses which are administered are generally in the range of about 2 mg/day to about 40 mg/day, preferably about 5 mg/day to about 40 mg/day. In the U.S. presently approved dosages for alendronate monosodium trihydrate are 5 mg/day for preventing osteoporosis, 10 mg/day for treating osteoporosis, and 40 mg/day for treating Paget's disease.

5 In alternative dosing regimens, the bisphosphonate can be administered at intervals other than daily, for example once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing. In a once weekly dosing regimen, alendronate monosodium trihydrate would be administered at dosages of 35 mg/week or 70 mg/week.

10 "Selective estrogen receptor modulators" refers to compounds which interfere or inhibit the binding of estrogen to the receptor, regardless of mechanism. Examples of estrogen receptor modulators include, but are not limited to, estrogen, progestogen, estradiol, droloxifene, raloxifene, lasofoxifene, TSE-424, tamoxifen, idoxifene, LY353381, LY117081, toremifene, fulvestrant, 4-[7-(2,2-dimethyl-1-oxopropoxy-4-methyl-2-[4-[2-(1-piperidinyl)ethoxy]phenyl]-2H-1-benzopyran-3-yl)-phenyl-2,2-dimethylpropanoate, 4,4'-dihydroxybenzophenone-2,4-dinitrophenyl-hydrazone, and SH646.

15 An "estrogen receptor beta modulator" is a compound that selectively agonizes or antagonizes estrogen receptor beta (ER β). Agonizing ER β increases transcription of the tryptophan hydroxylase gene (TPH, the key enzyme in serotonin synthesis) via an ER β mediated event. Examples of estrogen receptor beta agonists can be found in PCT International publication WO 01/82923, which published on November 08, 2001, and WO 02/41835, which published on May 20, 2002, both of which
20 are hereby incorporated by reference in their entirety.

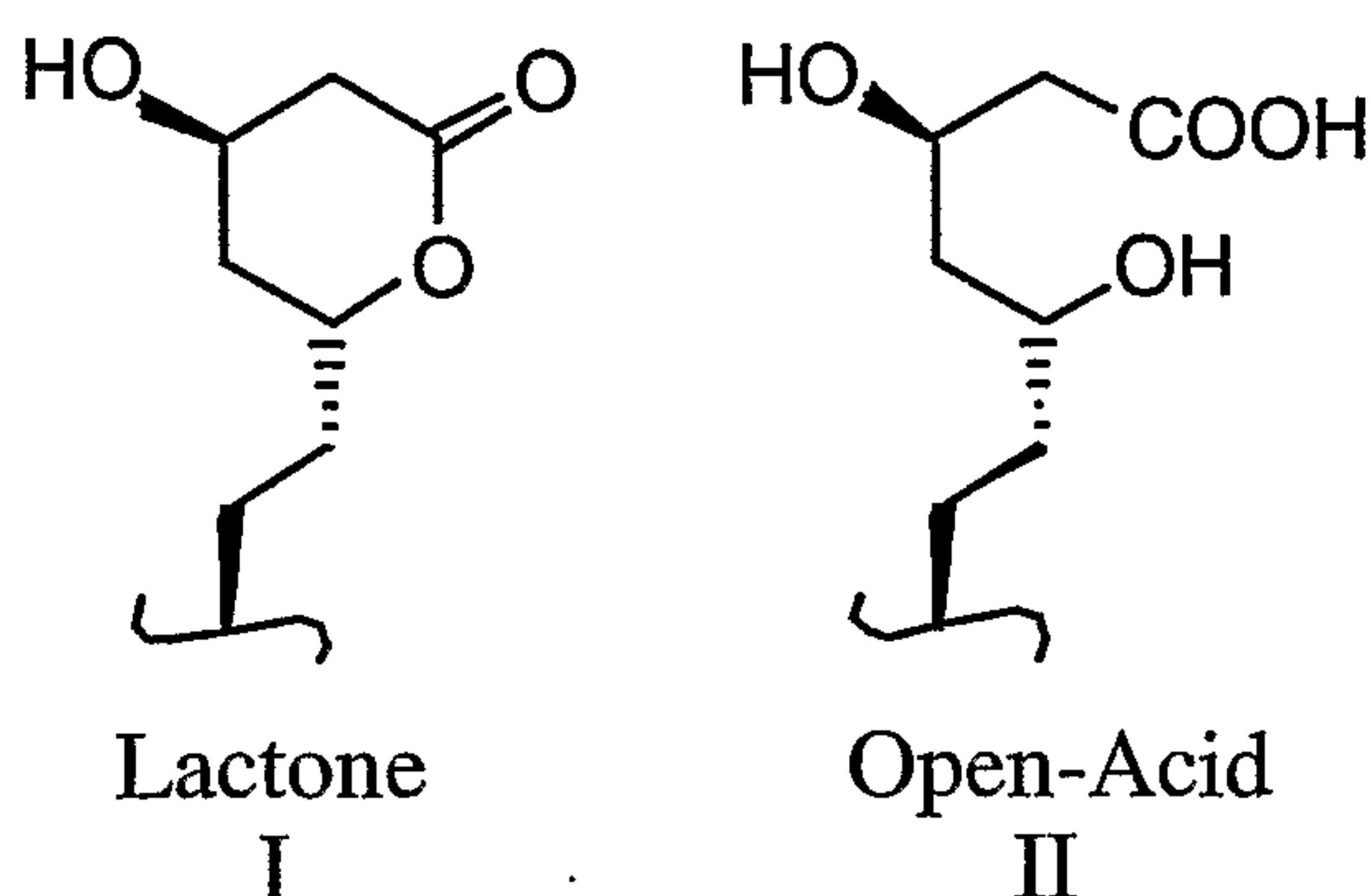
"Androgen receptor modulators" refers to compounds which interfere or inhibit the binding of androgens to the receptor, regardless of mechanism. Examples of androgen receptor modulators include finasteride and other 5 α -reductase inhibitors, nilutamide, flutamide, bicalutamide, liarozole, and abiraterone acetate.

25 "An inhibitor of osteoclast proton ATPase" refers to an inhibitor of the proton ATPase, which is found on the apical membrane of the osteoclast, and has been reported to play a significant role in the bone resorption process. 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
30 vacuolar proton ATPase as novel bone antiresorptive agents," DDT, 4: 163-172 (1999)), which is hereby incorporated by reference in its entirety.

"HMG-CoA reductase inhibitors" refers to inhibitors of 3-hydroxy-3-methylglutaryl-CoA reductase. Compounds which have inhibitory activity for HMG-CoA reductase can be readily identified by using assays well-known in the art. For example, see the assays described or cited in U.S.

Patent 4,231,938 at col. 6, and WO 84/02131 at pp. 30-33. The terms "HMG-CoA reductase inhibitor" and "inhibitor of HMG-CoA reductase" have the same meaning when used herein.

Examples of HMG-CoA reductase inhibitors that may be used include but are not limited to lovastatin (MEVACOR[®]; see U.S. Patent Nos. 4,231,938, 4,294,926 and 4,319,039), simvastatin (ZOCOR[®]; see U.S. Patent Nos. 4,444,784, 4,820,850 and 4,916,239), pravastatin (PRAVACHOL[®]; see U.S. Patent Nos. 4,346,227, 4,537,859, 4,410,629, 5,030,447 and 5,180,589), fluvastatin (LESCOL[®]; see U.S. Patent Nos. 5,354,772, 4,911,165, 4,929,437, 5,189,164, 5,118,853, 5,290,946 and 5,356,896), atorvastatin (LIPITOR[®]; see U.S. Patent Nos. 5,273,995, 4,681,893, 5,489,691 and 5,342,952) and cerivastatin (also known as rivastatin and BAYCHOL[®]; see US Patent No. 5,177,080). The structural formulas of these and additional HMG-CoA reductase inhibitors that may be used in the instant methods are described at page 87 of M. Yalpani, "Cholesterol Lowering Drugs", *Chemistry & Industry*, pp. 85-89 (5 February 1996) and US Patent Nos. 4,782,084 and 4,885,314. The term HMG-CoA reductase inhibitor as used herein includes all pharmaceutically acceptable lactone and open-acid forms (i.e., where the lactone ring is opened to form the free acid) as well as salt and ester forms of compounds which have HMG-CoA reductase inhibitory activity, and therefor the use of such salts, esters, open-acid and lactone forms is included within the scope of this invention. An illustration of the lactone portion and its corresponding open-acid form is shown below as structures I and II.



In HMG-CoA reductase inhibitors where an open-acid form can exist, salt and ester forms may preferably be formed from the open-acid, and all such forms are included within the meaning of the term "HMG-CoA reductase inhibitor" as used herein. Preferably, the HMG-CoA reductase inhibitor is selected from lovastatin and simvastatin, and most preferably simvastatin. Herein, the term "pharmaceutically acceptable salts" with respect to the HMG-CoA reductase inhibitor shall mean non-toxic salts of the compounds employed in this invention which are generally prepared by reacting the free acid with a suitable organic or inorganic base, particularly those formed from cations such as sodium, potassium, aluminum, calcium, lithium, magnesium, zinc and tetramethylammonium, as well as those salts formed from amines such as ammonia, ethylenediamine, N-methylglucamine, lysine, arginine, ornithine, choline, N,N'-dibenzylethylenediamine, chloroprocaine, diethanolamine, procaine, N-

benzylphenethylamine, 1-p-chlorobenzyl-2-pyrrolidine-1'-yl-methylbenz-imidazole, diethylamine, piperazine, and tris(hydroxymethyl) aminomethane. Further examples of salt forms of HMG-CoA reductase inhibitors may include, but are not limited to, acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, calcium edetate, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycolylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynapthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylsulfate, mucate, napsylate, nitrate, oleate, oxalate, pamaote, palmitate, panthothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, tannate, tartrate, teoclate, tosylate, triethiodide, and valerate.

Ester derivatives of the described HMG-CoA reductase inhibitor compounds may act as prodrugs which, when absorbed into the bloodstream of a warm-blooded animal, may cleave in such a manner as to release the drug form and permit the drug to afford improved therapeutic efficacy.

As used above, "integrin receptor antagonists" refers to compounds which selectively antagonize, inhibit or counteract binding of a physiological ligand to the $\alpha_v\beta_3$ integrin, to compounds which selectively antagonize, inhibit or counteract binding of a physiological ligand to the $\alpha_v\beta_5$ integrin, to compounds which antagonize, inhibit or counteract binding of a physiological ligand to both the $\alpha_v\beta_3$ integrin and the $\alpha_v\beta_5$ integrin, and to compounds which antagonize, inhibit or counteract the activity of the particular integrin(s) expressed on capillary endothelial cells. The term also refers to antagonists of the $\alpha_v\beta_6$, $\alpha_v\beta_8$, $\alpha_1\beta_1$, $\alpha_2\beta_1$, $\alpha_5\beta_1$, $\alpha_6\beta_1$ and $\alpha_6\beta_4$ integrins. The term also refers to antagonists of any combination of $\alpha_v\beta_3$, $\alpha_v\beta_5$, $\alpha_v\beta_6$, $\alpha_v\beta_8$, $\alpha_1\beta_1$, $\alpha_2\beta_1$, $\alpha_5\beta_1$, $\alpha_6\beta_1$ and $\alpha_6\beta_4$ integrins. H.N. Lode and coworkers in PNAS USA 96: 1591-1596 (1999) have 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. $\alpha_v\beta_3$ integrin receptor antagonists inhibit bone resorption through a new mechanism distinct from that of all currently available drugs. Integrins are heterodimeric transmembrane adhesion receptors that mediate cell-cell and cell-matrix interactions. The α and β integrin subunits interact non-covalently and bind extracellular matrix ligands in a divalent cation-dependent manner. The most abundant integrin on osteoclasts is $\alpha_v\beta_3$ ($>10^7$ /osteoclast), which appears to play a rate-limiting role in cytoskeletal organization important for cell migration and polarization. The $\alpha_v\beta_3$ antagonizing effect is selected from inhibition of bone resorption, inhibition of restenosis, inhibition of macular degeneration, inhibition of arthritis, and inhibition of cancer and metastatic growth.

"An osteoblast anabolic agent" refers to agents that build bone, such as PTH. The intermittent administration of parathyroid hormone (PTH) or its amino-terminal fragments and analogues

have been shown to prevent, arrest, partially reverse bone loss and stimulate bone formation in animals and humans. For a discussion refer to D.W. Dempster et al., "Anabolic actions of parathyroid hormone on bone," *Endocr Rev* 14: 690-709 (1993). Studies have demonstrated the clinical benefits of parathyroid hormone in stimulating bone formation and thereby increasing bone mass and strength.

5 Results were reported by RM Neer et al., in *New Eng J Med* 344 1434-1441 (2001).

In addition, parathyroid hormone-related protein fragments or analogues, such as PTHrP-(1-36) have demonstrated potent anticalciuric effects [see M.A. Syed et al., "Parathyroid hormone-related protein-(1-36) stimulates renal tubular calcium reabsorption in normal human volunteers: implications for the pathogenesis of humoral hypercalcemia of malignancy," *JCEM* 86: 1525-1531 (2001)] and may
10 also have potential as anabolic agents for treating osteoporosis.

"Nonsteroidal anti-inflammatory drugs" or NSAIDs, inhibit the metabolism of arachidonic acid to proinflammatory prostaglandins via cyclooxygenase (COX)-1 and COX-2. Nonlimiting examples of NSAIDs include: aspirin, ibuprofen, naproxen, diclofenac, etodolac, fenopofen, flubiprofen, indomethacin, ketoprofen, ketorolac, meloxicam, nabumetone, oxaprozin,
15 piroxicam, sulindac, tolmetin, diflunisal, meclofenamate and phenylbutazone.

A "selective cyclooxygenase-2 inhibitor," or COX-2 inhibitor, refers to a type of nonsteroidal anti-inflammatory drug (NSAID), that inhibit the COX-2 coenzyme, which contributes to pain and inflammation in the body. Nonlimiting examples of COX-2 inhibitors include: celecoxib, etoricoxib, parecoxib, rofecoxib, valdecoxib and lumiracoxib.

20 An "inhibitor of interleukin-1 beta" or IL-1 β refers to inhibitors of IL-1, which is a soluble factor produced by monocytes, macrophages, and other cells which activates T-lymphocytes and potentiates their response to mitogens or antigens. Nonlimiting examples of IL-1B inhibitors include diacerein and rhein.

A "LOX/COX inhibitor" refers to an inhibitor of all three of the major enzymes involved
25 in arachidonic acid pathway - namely, 5-LOX, COX-1 and COX-2. A nonlimiting example of a LOX/COX inhibitor is licofelone.

If formulated as a fixed dose, such combination products employ the compounds of this invention within the dosage range described below and the other pharmaceutically active agent(s) within its approved dosage range. Compounds of the instant invention may alternatively be used sequentially
30 with known pharmaceutically acceptable agent(s) when a combination formulation is inappropriate.

The term "administration" and variants thereof (e.g., "administering" a compound) in reference to a compound of the invention means introducing the compound or a prodrug of the compound into the system of the animal in need of treatment. When a compound of the invention or prodrug thereof is provided in combination with one or more other active agents (e.g., a cytotoxic agent, etc.),
35 "administration" and its variants are each understood to include concurrent and sequential introduction of

the compound or prodrug thereof and other agents. 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 herein in its entirety. Metabolites of these compounds include active species produced upon introduction of compounds of this invention into the biological milieu.

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 ingredients in the specified amounts.

The term "therapeutically effective amount" as used herein means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician.

The terms "treating" or "treatment" of a disease as used herein includes: preventing the disease, i.e. causing the clinical symptoms of the disease not to develop in a mammal that may be exposed to or predisposed to the disease but does not yet experience or display symptoms of the disease; inhibiting the disease, i.e., arresting or reducing the development of the disease or its clinical symptoms; or relieving the disease, i.e., causing regression of the disease or its clinical symptoms.

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

The present invention also encompasses a pharmaceutical composition useful in the treatment of osteoporosis or other bone disorders, comprising the administration of a therapeutically effective amount of the compounds of this invention, with or without pharmaceutically acceptable carriers or diluents. Suitable compositions of this invention include aqueous solutions comprising compounds of this invention and pharmacologically acceptable carriers, e.g., saline, at a pH level, e.g., 7.4. The solutions may be introduced into a patient's bloodstream by local bolus injection.

When a compound according to this invention is administered into a human subject, the daily dosage will normally be determined by the prescribing physician with the dosage generally varying according to the age, weight, and response of the individual patient, as well as the severity of the patient's symptoms.

In one exemplary application, a suitable amount of compound is administered to a mammal undergoing treatment for a cathepsin dependent 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.

The compounds of the present invention can be used in combination with other agents useful for treating cathepsin-mediated conditions. The individual components of such combinations can be administered separately at different times 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 cathepsin-mediated conditions includes in principle any combination with any pharmaceutical composition useful for treating disorders related to estrogen functioning.

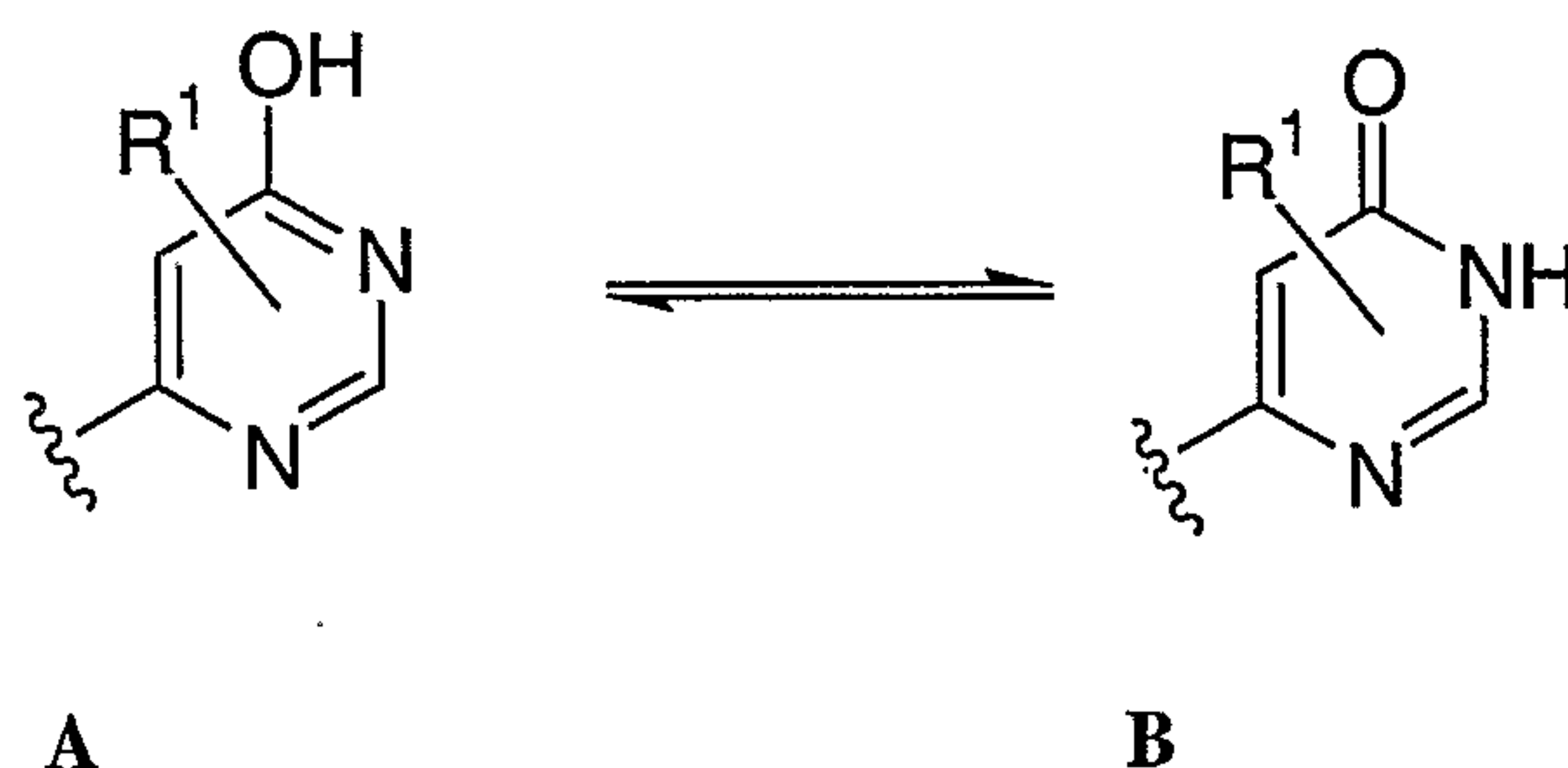
The scope of the invention therefore encompasses the use of the instantly claimed compounds in combination with a second agent selected from: an organic bisphosphonate; an estrogen receptor modulator; an androgen receptor modulator; an inhibitor of osteoclast proton ATPase; an inhibitor of HMG-CoA reductase; an integrin receptor antagonist; an osteoblast anabolic agent, such as PTH; and the pharmaceutically acceptable salts and mixtures thereof.

These and other aspects of the invention will be apparent from the teachings contained herein.

Definitions

The compounds of the present invention may have asymmetric centers, chiral axes, and chiral planes (as described in: E.L. Eliel and S.H. Wilen, *Stereochemistry of Carbon Compounds*, John Wiley & Sons, New York, 1994, pages 1119-1190), and occur as racemates, racemic mixtures, and as individual diastereomers, with all possible isomers and mixtures thereof, including optical isomers, being

included in the present invention. In addition, the compounds disclosed herein may exist as tautomers and both tautomeric forms are intended to be encompassed by the scope of the invention, even though only one tautomeric structure is depicted. For example, any claim to compound A below is understood to include tautomeric structure B, and vice versa, as well as mixtures thereof.



When any variable (e.g. R1, R2, Ra etc.) occurs more than one time in any constituent, its definition on each occurrence is independent at every other occurrence. Also, combinations of substituents and variables are permissible only if such combinations result in stable compounds. Lines drawn into the ring systems from substituents indicate that the indicated bond may be attached to any of the substitutable ring carbon atoms. If the ring system is polycyclic, it is intended that the bond be attached to any of the suitable carbon atoms on the proximal ring only.

It is understood that substituents and substitution patterns on the compounds of the instant invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art, as well as those methods set forth below, from readily available starting materials. If a substituent is itself substituted with more than one group, it is understood that these multiple groups may be on the same carbon or on different carbons, so long as a stable structure results. The phrase "optionally substituted with one or more substituents" should be taken to be equivalent to the phrase "optionally substituted with at least one substituent" and in such cases the preferred embodiment will have from zero to three substituents.

As used herein, "alkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having one to ten carbon atoms unless otherwise specified. For example, C₁-C₁₀, as in "C₁-C₁₀ alkyl" is defined to include groups having 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbons in a linear, branched, or cyclic arrangement. For example, "C₁-C₁₀ alkyl" specifically includes methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, and so on.

"Alkoxy" or "alkyloxy" represents an alkyl group as defined above, unless otherwise indicated, wherein said alkyl group is attached through an oxygen bridge.

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

If no number of carbon atoms is specified, the term "alkenyl" refers to a non-aromatic hydrocarbon radical, straight or branched, containing from 2 to 10 carbon atoms and at least 1 carbon to carbon double bond. Preferably 1 carbon to carbon double bond is present, and up to 4 non-aromatic carbon-carbon double bonds may be present. Thus, "C₂-C₆ alkenyl" means an alkenyl radical having from 2 to 6 carbon atoms. Alkenyl groups include ethenyl, propenyl, butenyl and cyclohexenyl. As described above with respect to alkyl, the straight, branched or cyclic portion of the alkenyl group may contain double bonds and may be substituted if a substituted alkenyl group is indicated.

The term "cycloalkenyl" shall mean cyclic rings of 3 to 10 carbon atoms, unless otherwise specified, containing at least 1 carbon to carbon double bond (i.e., cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl or cyclooctenyl).

The term "alkynyl" refers to a hydrocarbon radical straight or branched, containing from 2 to 10 carbon atoms, unless otherwise specified, containing at least 1 carbon to carbon triple bond. Up to 3 carbon-carbon triple bonds may be present. Thus, "C₂-C₆ alkynyl" means an alkynyl radical having from 2 to 6 carbon atoms. Alkynyl groups include ethynyl, propynyl and butynyl. As described above with respect to alkyl, the straight, branched or cyclic portion of the alkynyl group may contain triple bonds and may be substituted if a substituted alkynyl group is indicated.

In certain instances, substituents may be defined with a range of carbons that includes zero, such as (C₀-C₆)alkylene-aryl. If aryl is taken to be phenyl, this definition would include phenyl itself as well as -CH₂Ph, -CH₂CH₂Ph, CH(CH₃)CH₂CH(CH₃)Ph, and so on.

As used herein, "aryl" is intended to mean any stable monocyclic or bicyclic carbon ring of up to 12 atoms in each ring, wherein at least one ring is aromatic. Examples of such aryl elements include phenyl, naphthyl, tetrahydronaphthyl, indanyl, biphenyl, phenanthryl, anthryl or acenaphthyl. In cases where the aryl substituent is bicyclic and one ring is non-aromatic, it is understood that attachment is via the aromatic ring.

The term "heteroaryl", as used herein, represents a stable monocyclic, bicyclic or tricyclic ring of up to 10 atoms in each ring, wherein at least one ring is aromatic and contains from 1 to 4 heteroatoms selected from the group consisting of O, N and S. Heteroaryl groups within the scope of this definition include but are not limited to: benzoimidazolyl, benzofuranyl, benzofurazanyl, benzopyrazolyl, benzotriazolyl, benzothiophenyl, benzoxazolyl, carbazolyl, carbolinyl, cinnolinyl, furanyl, indolinyl, indolyl, indolazinyll, indazolyl, isobenzofuranyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthpyridinyl, oxadiazolyl, oxazolyl, oxazoline, isoxazoline, pyranyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridopyridinyl, pyridyl, pyrimidinyl, pyrrolyl, quinazolinyl, quinolyl, quinoxalinyl,

tetrazolyl, tetrazolopyridyl, thiadiazolyl, thiazolyl, thienyl, triazolyl, dihydrobenzoimidazolyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, dihydrobenzoxazolyl, dihydroindolyl, dihydroquinolyl, methylenedioxybenzene, benzothiazolyl, benzothienyl, quinolyl, isoquinolyl, oxazolyl, and tetrahydroquinoline. In cases where the heteroaryl substituent is bicyclic and one ring is non-aromatic or contains no heteroatoms, it is understood that attachment is via the aromatic ring or via the heteroatom containing ring, respectively. If the heteroaryl contains nitrogen atoms, it is understood that the corresponding N-oxides thereof are also encompassed by this definition.

As appreciated by those of skill in the art, "halo" or "halogen" as used herein is intended to include chloro, fluoro, bromo and iodo. The term "keto" means carbonyl (C=O). The term "alkoxy" as used herein means an alkyl portion, where alkyl is as defined above, connected to the remainder of the molecule via an oxygen atom. Examples of alkoxy include methoxy, ethoxy and the like.

The term "haloalkyl" means an alkyl radical as defined above, unless otherwise specified, that is substituted with one to five, preferably one to three halogen. Representative examples include, but are not limited to trifluoromethyl, dichloroethyl, and the like.

The term "haloalkoxy" represents a radical -OR where R is alkyl as defined above that is substituted with one to five, preferably one to three halogen. Representative examples include, but are not limited to trifluoromethyloxy, dichloroethyloxy, and the like.

The term "arylalkyl" includes 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, and chlorophenylethyl. Examples of alkylaryl include, but are not limited to, toluyl, ethylphenyl, and propylphenyl.

The term "heteroarylalkyl" as used herein, shall refer to a system that includes a heteroaryl portion, where heteroaryl is as defined above, and contains an alkyl portion. Examples of heteroarylalkyl include, but are not limited to, thienylmethyl, thienylethyl, thienylpropyl, pyridylmethyl, pyridylethyl and imidazolylmethyl.

The term "cycloalkylalkyl" includes an alkyl portion where alkyl is as defined above and also includes an cycloalkyl portion where cycloalkyl is as defined above. Examples of cycloalkylalkyl include, but are not limited to, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, cyclopropylethyl, and the like.

The term "hydroxyalkyl" means a linear monovalent hydrocarbon radical of one to six carbon atoms or a branched monovalent hydrocarbon radical of three to six carbons substituted with one or two hydroxy groups, provided that if two hydroxy groups are present they are not both on the same carbon atom. Representative examples include, but are not limited to, hydroxymethyl, 2-hydroxyethyl, 2-hydroxypropyl, 3-hydroxypropyl, and the like.

The term "heterocycle" or "heterocyclyl" as used herein is intended to mean a 5- to 10-membered nonaromatic ring, unless otherwise specified, containing from 1 to 4 heteroatoms selected from the group consisting of O, N, S, SO, or SO₂ and includes bicyclic groups. "Heterocyclyl" therefore includes, but is not limited to the following: piperazinyl, piperidinyl, pyrrolidinyl, morpholinyl, 5 thiomorpholinyl, tetrahydropyranyl, dihydropiperidinyl, tetrahydrothiophenyl and the like. If the heterocycle contains a nitrogen, it is understood that the corresponding N-oxides thereof are also encompassed by this definition.

The present invention also includes N-oxide derivatives and protected derivatives of compounds of Formula I. For example, when compounds of Formula I contain an oxidizable nitrogen 10 atom, the nitrogen atom can be converted to an N-oxide by methods well known in the art. Also when compounds of Formula I contain groups such as hydroxy, carboxy, thiol or any group containing a nitrogen atom(s), these groups can be protected with a suitable protecting groups. A comprehensive list of suitable protective groups can be found in T.W. Greene, *Protective Groups in Organic Synthesis*, John Wiley & Sons, Inc. 1981, the disclosure of which is incorporated herein by reference in its entirety. The 15 protected derivatives of compounds of Formula I can be prepared by methods well known in the art.

Whenever the term "alkyl" or "aryl" or either of their prefix roots appear 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., C₁₋₁₀) 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 20 which alkyl appears as its prefix root.

The pharmaceutically acceptable salts of the compounds of this invention include the conventional non-toxic salts of the compounds of this invention as formed inorganic or organic acids. For example, conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like, as well as salts prepared 25 from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pantoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxy-benzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, trifluoroacetic and the like. The preparation of the pharmaceutically acceptable salts described above and other typical pharmaceutically acceptable salts is more fully described by Berg *et al.*, 30 "Pharmaceutical Salts," *J. Pharm. Sci.*, 1977:66:1-19, hereby incorporated by reference. The pharmaceutically acceptable salts of the compounds of this invention can be synthesized from the compounds of this invention which contain a basic or acidic moiety by conventional chemical methods. Generally, the salts of the basic compounds are prepared either by ion exchange chromatography or by reacting the free base with stoichiometric amounts or with an excess of the desired salt-forming inorganic

or organic acid in a suitable solvent or various combinations of solvents. Similarly, the salts of the acidic compounds are formed by reactions with the appropriate inorganic or organic base.

For purposes of this specification, the following abbreviations have the indicated meanings:

5			
	AcOH	=	acetic acid
	BF ₃	=	boron trifluoride
	Boc	=	t-butyloxycarbonyl
	Boc ₂ O	=	di-tert-butyl dicarbonate
10	BuLi	=	butyl lithium
	CCl ₄	=	carbon tetrachloride
	CH ₂ Cl ₂	=	methylene chloride
	CH ₃ CN	=	acetonitrile
	CHCl ₃	=	chloroform
15	Cs ₂ CO ₃	=	cesium carbonate
	CuI	=	copper iodide
	DAST	=	diethylaminosulfur trifluoride
	DIPEA	=	diisopropylethylamine
	DMA	=	<i>N,N</i> -dimethyl acetamide
20	DMAP	=	4-(dimethylamino)pyridine
	DMF	=	<i>N,N</i> -dimethylformamide
	DMSO	=	dimethylsulfoxide
	DPPA	=	diphenylphosphoryl azide
	EDCI	=	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
25	Et ₂ O	=	diethyl ether
	Et ₃ N	=	triethylamine
	EtOAc	=	ethyl acetate
	EtOH	=	ethanol
	HATU	=	<i>o</i> -(7-azabenzotriazol-1-yl)- <i>N,N,N',N'</i> -tetramethyluronium
30			hexafluorophosphate
	HOAc	=	acetic acid
	K ₂ CO ₃	=	potassium carbonate
	KHMDS	=	potassium hexamethyldisilazane
	KOBu ^t	=	potassium <i>tert</i> -butoxide
35	LDA	=	lithium diisopropylamide

	LiOH	=	lithium hydroxide
	mCPBA	=	metachloroperbenzoic acid
	MeOH	=	methanol
	MeSO ₃ H	=	methane sulfonic acid
5	MgSO ₄	=	magnesium sulfate
	Ms	=	methanesulfonyl = mesyl
	MsCl	=	methanesulfonyl chloride
	NaBH ₄	=	sodium borohydride
	NaH	=	sodium hydride
10	NaI	=	sodium iodide
	NaCNBH ₃	=	sodium cyanoborohydride
	Na ₂ CO ₃	=	sodium carbonate
	NaHCO ₃	=	sodium hydrogencarbonate
	NaOH	=	sodium hydroxide
15	Na ₂ SO ₄	=	sodium sulfate
	NBS	=	N-bromosuccinimide
	NH ₃	=	ammonia
	NH ₄ Cl	=	ammonium chloride
	Pd/C	=	palladium on carbon
20	PdCl ₂	=	dichloropalladium(II)
	PdCl ₂ (dppf)	=	[1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)
	Pd ₂ (dba) ₃	=	tris(dibenzylideneacetone)dipalladium(0)
	PG	=	protecting group
	PPh ₃	=	triphenylphosphine
25	(PhO) ₃ PMeI	=	methyltriphenoxyposphonium iodide
	PPTS	=	pyridinium p-toluenesulfonate
	<i>i</i> Pr ₂ NLi	=	lithium diisopropyl amide
	PyBOP	=	benzotriazol-1-yloxytris(pyrrolidino)phosphonium-hexafluorophosphate
	rt	=	room temperature
30	sat. aq.	=	saturated aqueous
	TFA	=	trifluoroacetic acid
	THF	=	tetrahydrofuran
	TiCl ₄	=	titanium(IV) chloride
	tlc	=	thin layer chromatography
35	TMSCl	=	chlorotrimethylsilane

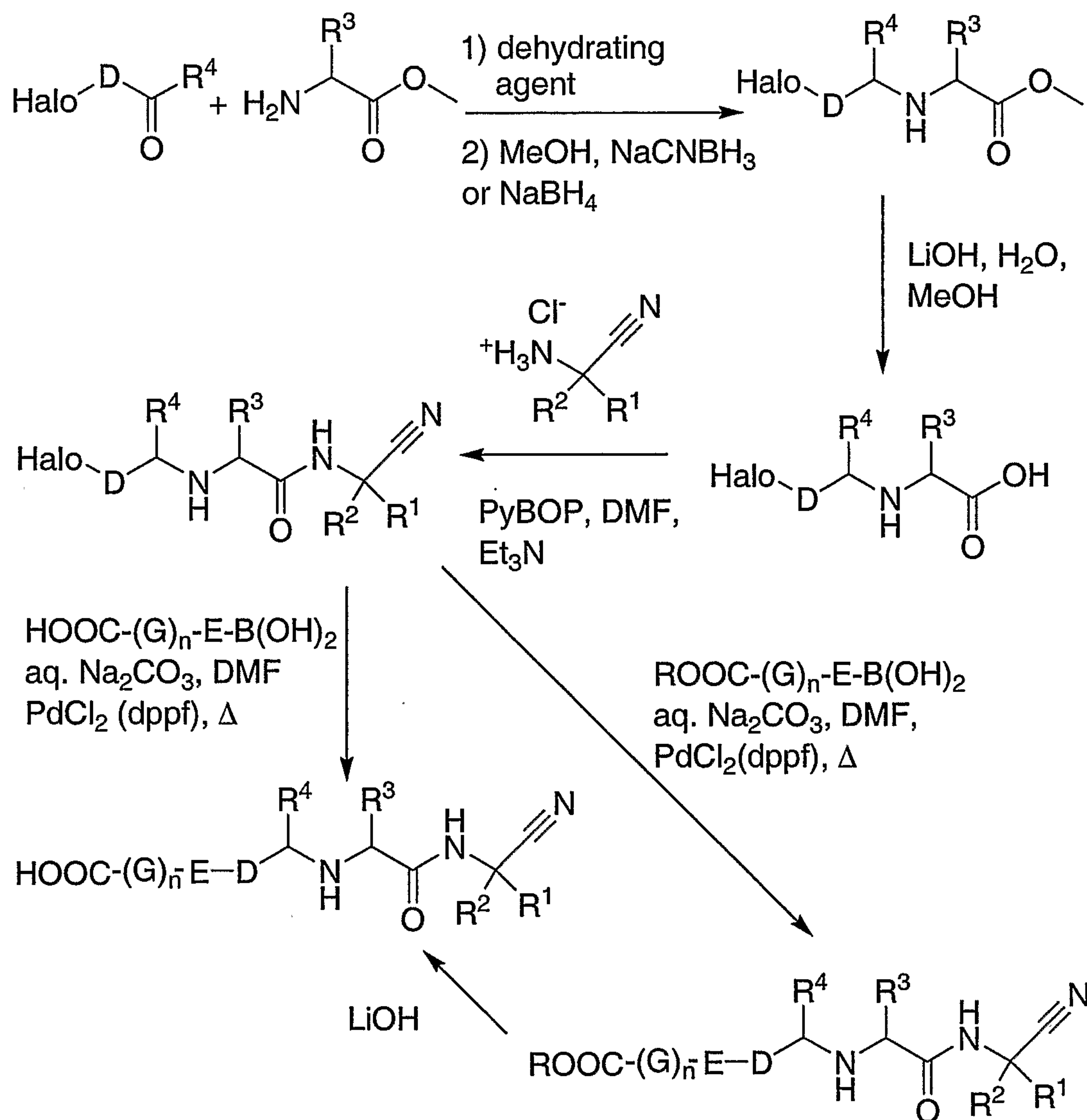
	Me	=	methyl
	Et	=	ethyl
	n-Pr	=	normal propyl
	i-Pr	=	isopropyl
5	n-Bu	=	normal butyl
	i-Bu	=	isobutyl
	s-Bu	=	secondary butyl
	t-Bu	=	tertiary butyl

10 The novel compounds of the present invention can be prepared according to the following general procedures using appropriate materials and are further exemplified by the following specific examples. The compounds illustrated in the examples are not, however, to be construed as forming the only genus that is considered as the invention. The following examples further illustrate details for the preparation of the compounds of the present invention. Those skilled in the art will readily
15 understand that known variations of the conditions and processes of the following preparative procedures can be used to prepare these compounds. All temperatures are degrees Celsius unless otherwise noted.

SCHEMES

20 Compounds of the present invention can be prepared according to Scheme 1, as indicated below. Thus an α -amino ester may be added to a haloalkyl ketone to form an aminal which may be dehydrated to an imine in the presence of a dehydrating agent such as TiCl_4 , MgSO_4 or isopropyl trifluoroacetate. Reduction of the imine with a reducing agent such as sodium cyanoborohydride or
25 sodium borohydride provides the amine. Ester hydrolysis and amide formation with an appropriately substituted aminoacetonitrile provides compounds of the current invention. If the substituent on D system is a halogen, a palladium-catalyzed Suzuki coupling with an appropriate boronic acid provides additional compounds of the current invention. The boronic acid moiety in this reaction could be replaced by a boron pinacolate species or an appropriate aryl stannane. The carboxylic acid group in the
30 boronic acid may optionally be protected as an alkyl ester, which may then be hydrolyzed to provide compounds of the current invention.

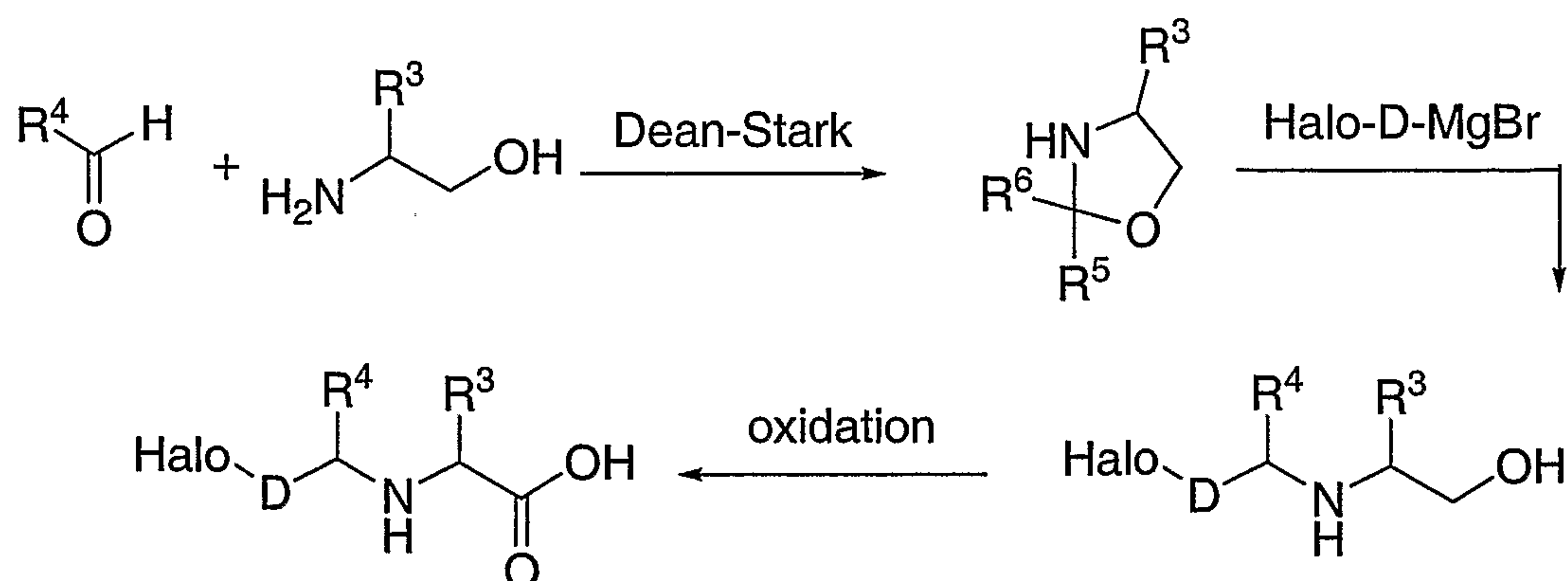
SCHEME 1



Compounds of the present invention may also be prepared according to Scheme 2, as indicated below.

- 5 An aldehyde may be condensed with an amino alcohol to give a cyclic aminal. Treatment with 3 equivalents of a Grignard reagent or organolithium reagent will provide the appropriate alkylated amino alcohol. Oxidation of the alcohol with a chromium system such as a Jones oxidation or H₅IO₆/CrO₃, or alternatively by a two-step oxidation (eg oxalyl chloride/ DMSO/Et₃N followed by NaClO) will provide the corresponding carboxylic acid. Peptide coupling and Suzuki reaction as described in Scheme 1 will
- 10 provide compounds of the current invention

SCHEME 2

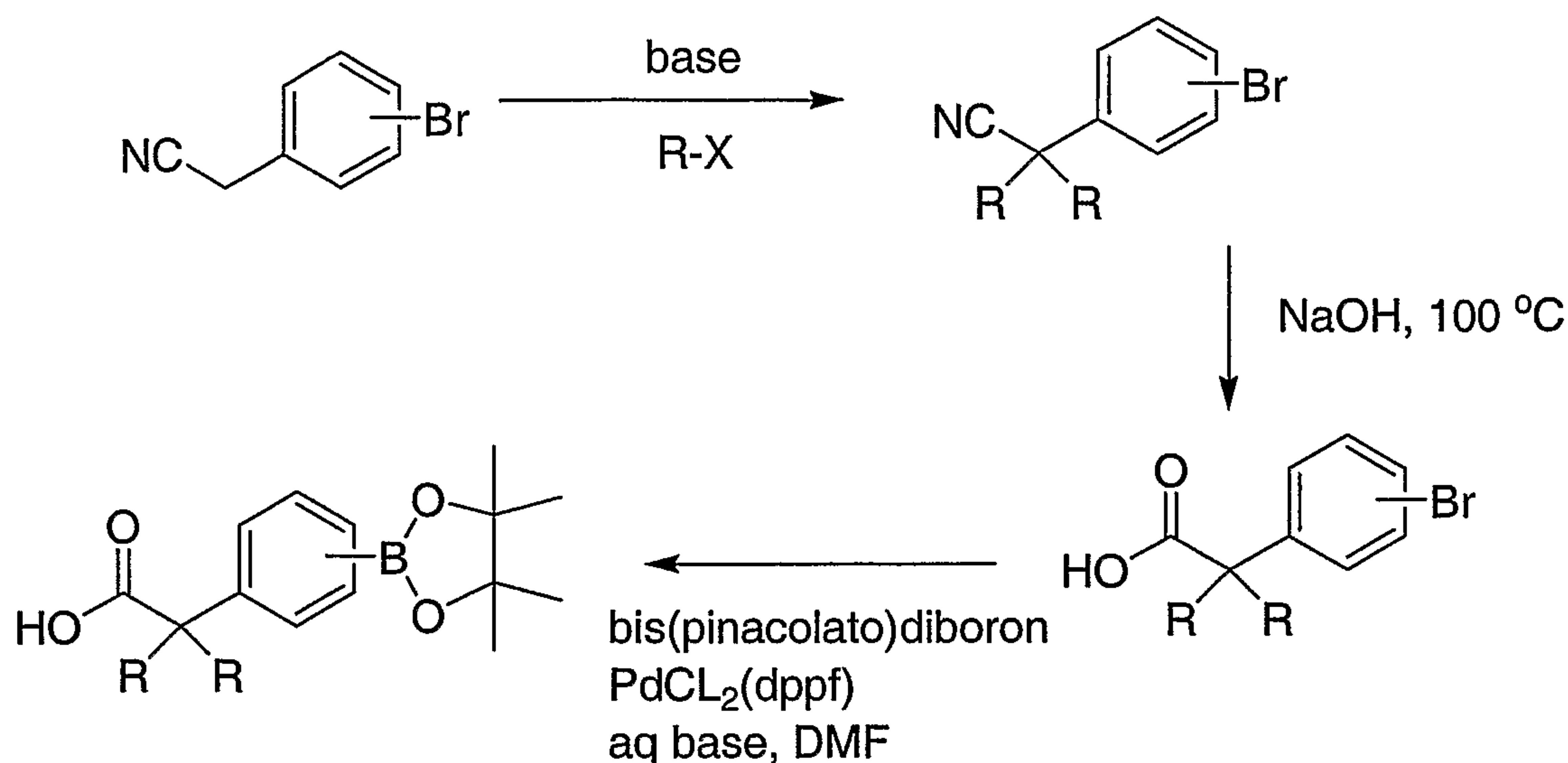


Carboxylic acid-aryl bromides used to make compounds of the current invention may be prepared as shown in Scheme 3. Treatment of a bromophenylacetonitrile with a base such as LDA or KHMDS

5 followed by treatment with an alkyl halide such as methyl iodide or 1-bromo-2-chloroethane gives alpha-substituted benzonitriles. Alternatively, this alkylation may be carried out under phase transfer conditions using sodium hydroxide, the alkyl halide and a suitable phase transfer catalyst such as benzyltriethylammonium chloride. Hydrolysis of the nitrile under basic conditions provides the

10 corresponding carboxylic acid. This substituted aryl bromide may be coupled with an arylboron pinacolate as described in Scheme 14 to give compounds of the current invention. Alternatively, the aryl bromide may itself be converted into an arylboron pinacolate by a palladium-catalyzed reaction with bis(pinacolato)diboron. This resulting arylboron pinacolate may be used in place of a boronic acid in the Suzuki coupling reactions shown in Schemes 1, 2, 5, 6, or 13 to provide compounds of the current invention.

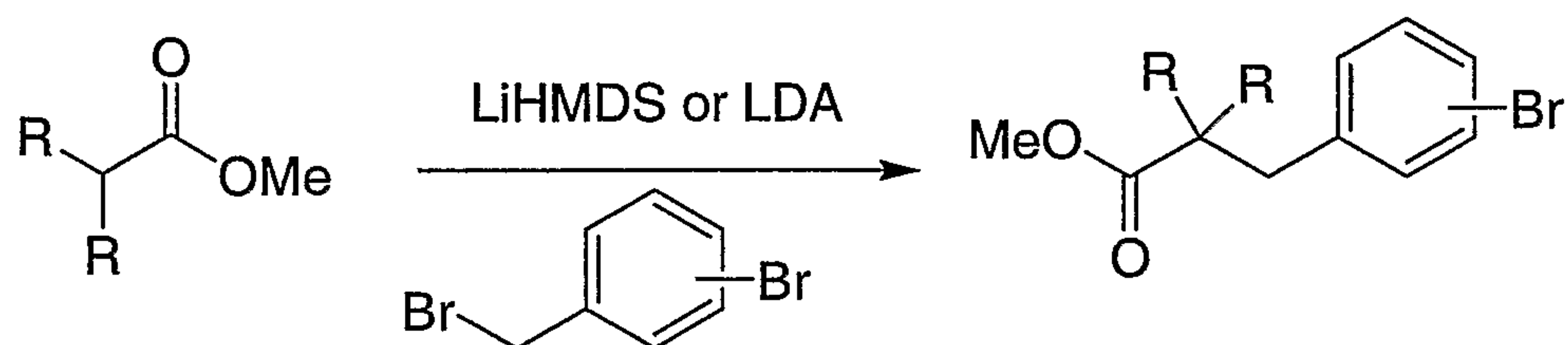
SCHEME 3



- 5 Carboxylic acid-aryl bromides used to make compounds of the current invention may also be prepared as shown in Scheme 4. Treatment of a bromophenylbenzyl bromide with the enolate of a suitably substituted ester provides the bromoaryl-alkyl carboxylic ester. This intermediate may be coupled with a suitably substituted arylboronic acid, as described in Scheme 14, followed by basic hydrolysis of the ester, to give compounds of the current invention.

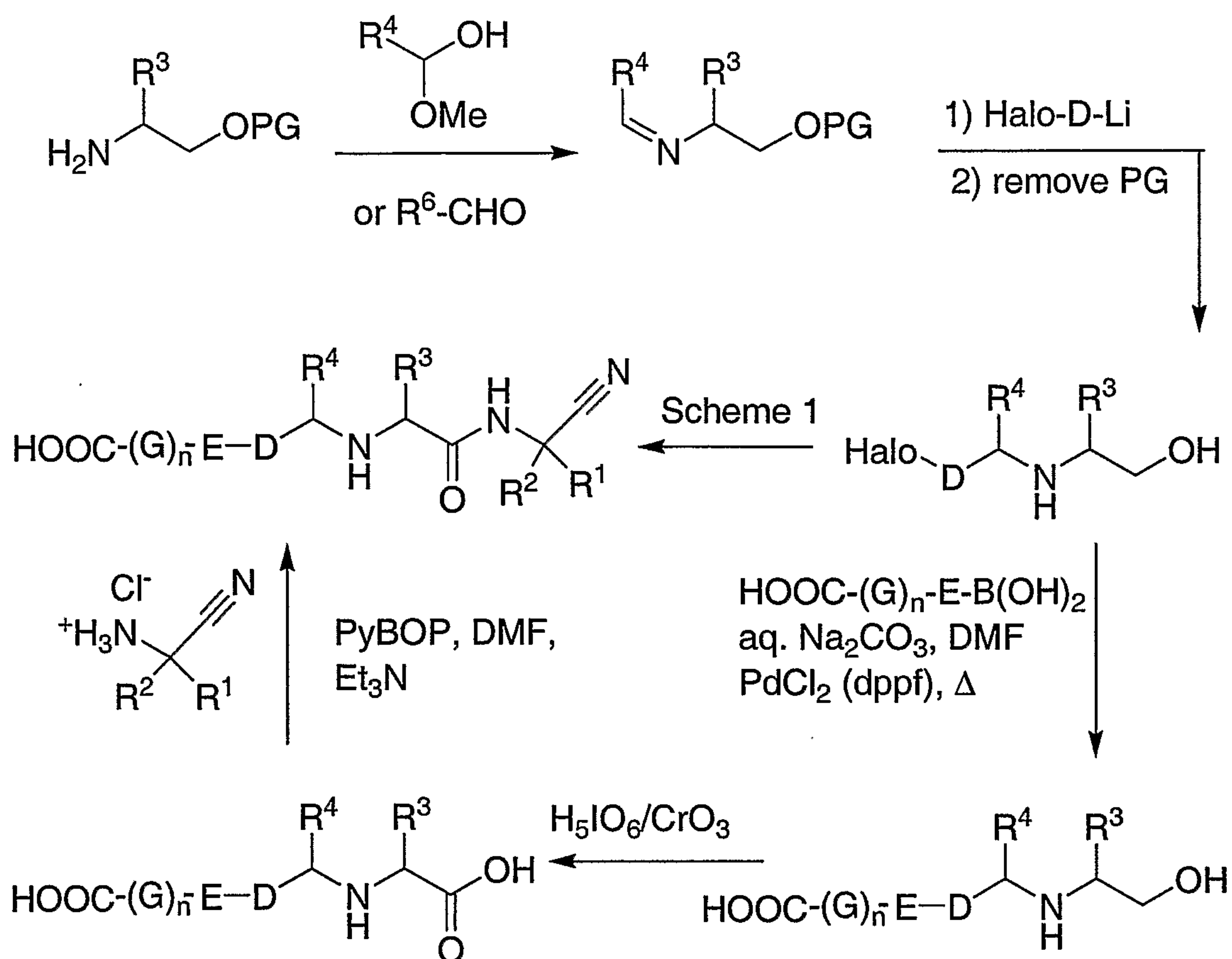
10

SCHEME 4



- 15 Compounds of the current invention may also be prepared according to Scheme 5, as shown below. An aldehyde or a hemiacetal may be condensed with an amino alcohol in which the alcohol moiety is protected with a suitable protecting group with azeotropic removal of water. Treatment of the resulting imine with a Grignard reagent or organolithium reagent will provide the appropriate alkylated amino alcohol. The alcohol protecting group can then be removed and the alcohol can be converted into compounds of the current invention either by the method described in Scheme 1 or by first conducting the Suzuki reaction, followed by oxidizing the alcohol with $\text{H}_5\text{IO}_6/\text{CrO}_3$ and then peptide coupling.
- 20

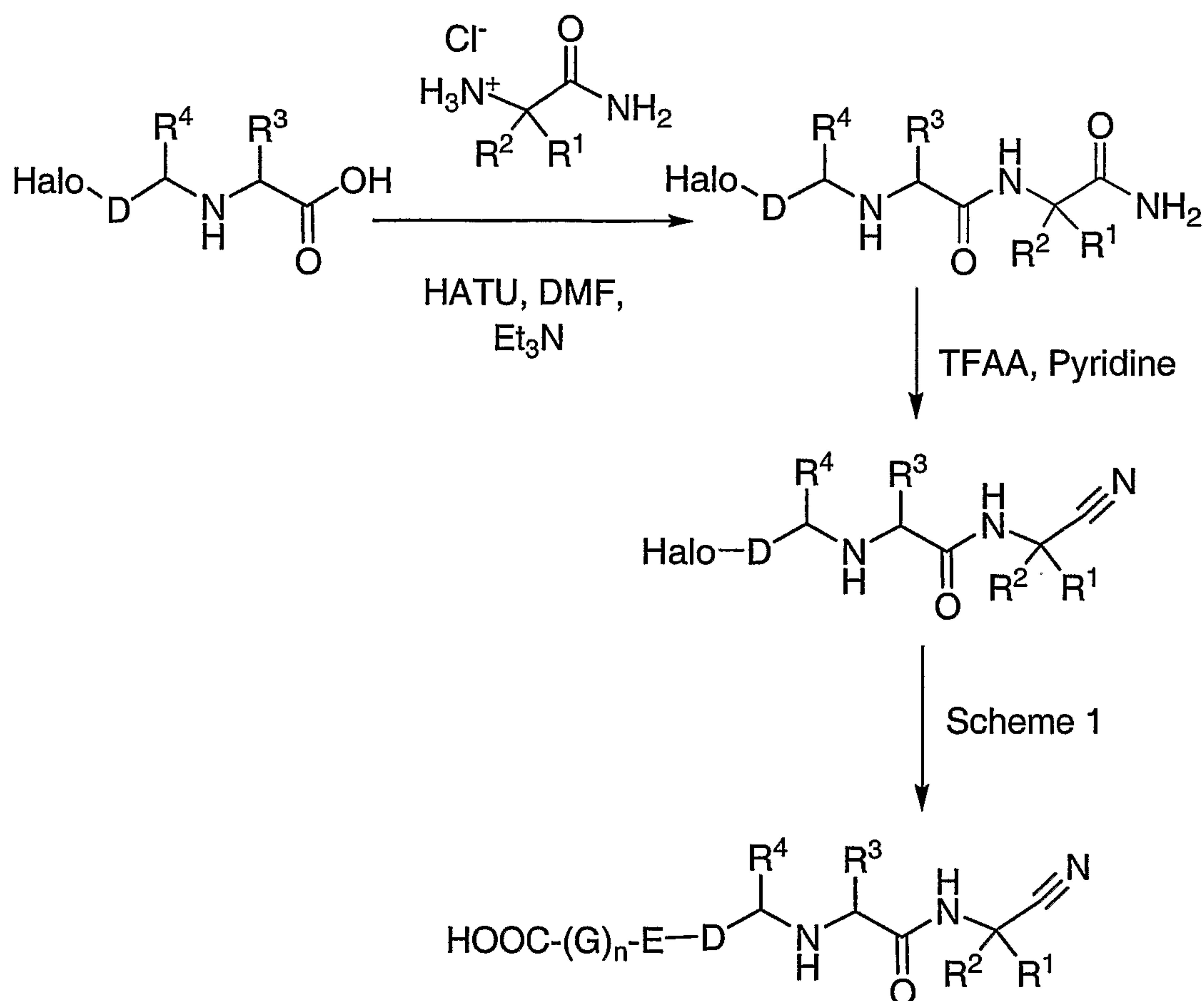
SCHEME 5



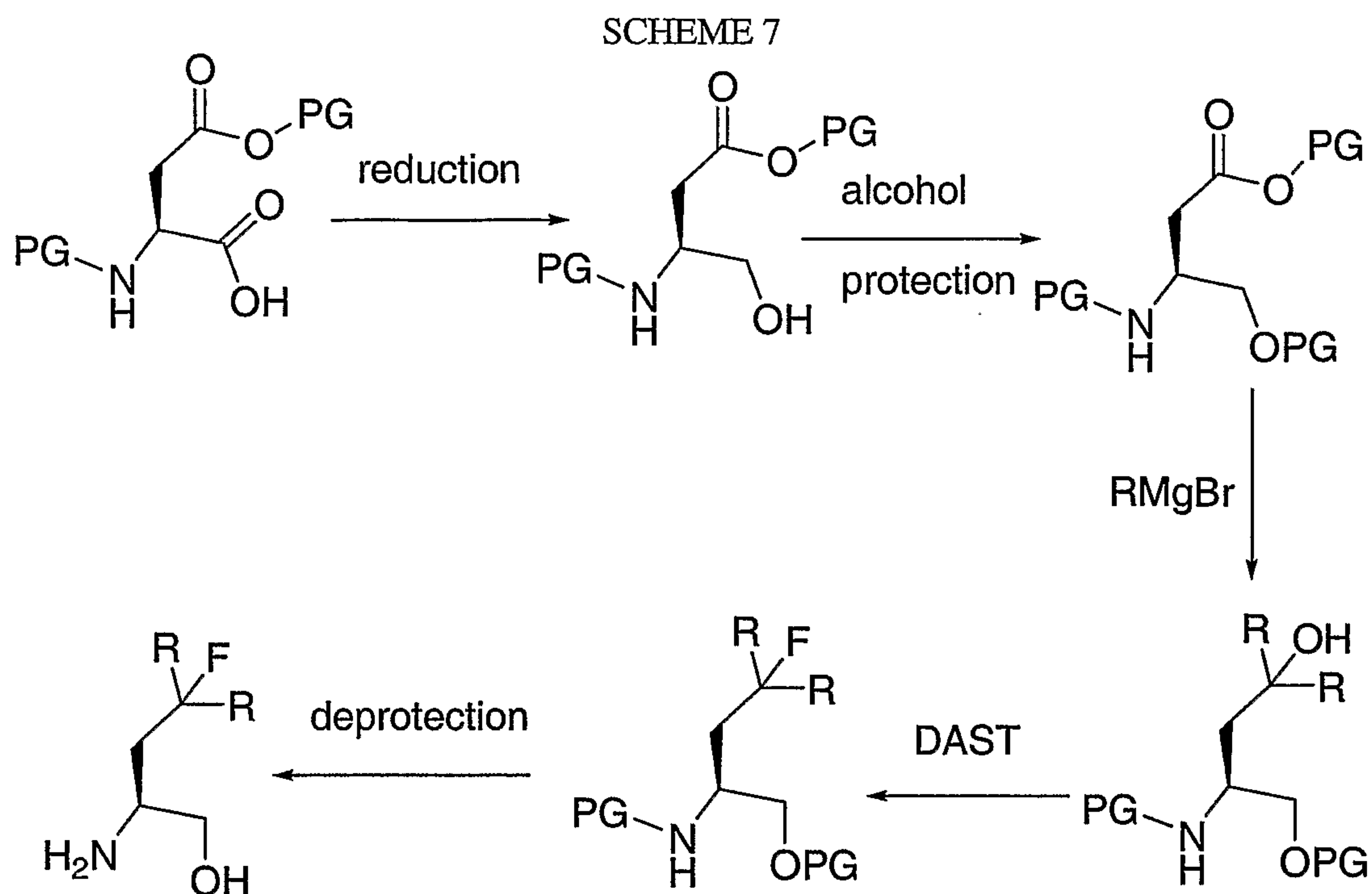
Compounds of the current invention may also be prepared according to Scheme 6, as indicated below.

The peptide coupling of an alpha-amino acid described in Schemes 1, 2, or 5, with an alpha-amino amide followed by dehydration of the resulting primary amide (Voegel, J. J.; Benner, S. A. *Helv. Chem. Acta* **1996**, 79, 1863) will provide compounds of the current invention.

SCHEME 6

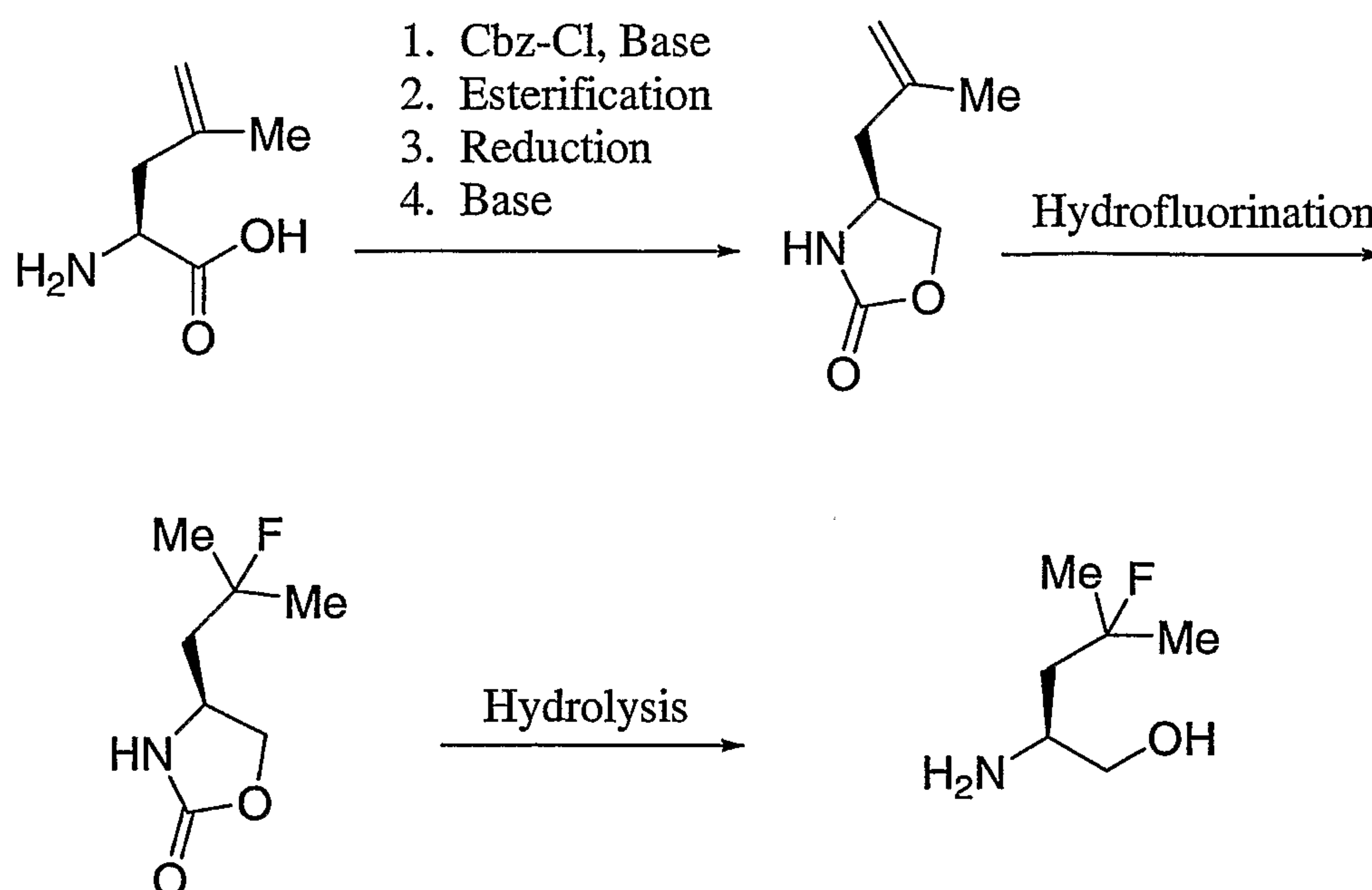


The synthesis of some of the amino alcohols used at the beginning of Schemes 2 and 5 are described in
 5 Schemes 7-11. For example, the synthesis of (2*S*)-2-amino-4-fluoro-4-methylpentan-1-ol where R=Me is
 described in Scheme 7 below. Starting with a suitable diprotected aspartic acid, the carboxy group can
 be reduced to an alcohol using standard literature procedures (i.e. mixed anhydride formation followed
 by NaBH₄ reduction). A protected version of 2-amino-4-methylpentane-1,4-diol (R=Me) can then be
 generated by an appropriate Grignard or organolithiation reaction. Finally, the hydroxy moiety can be
 10 converted to the desired fluoro using a fluorinating agent such as DAST. The protected or unprotected
 version of this amino alcohol can then be converted to compounds of the current invention according to
 Schemes 1, 2, and 5.



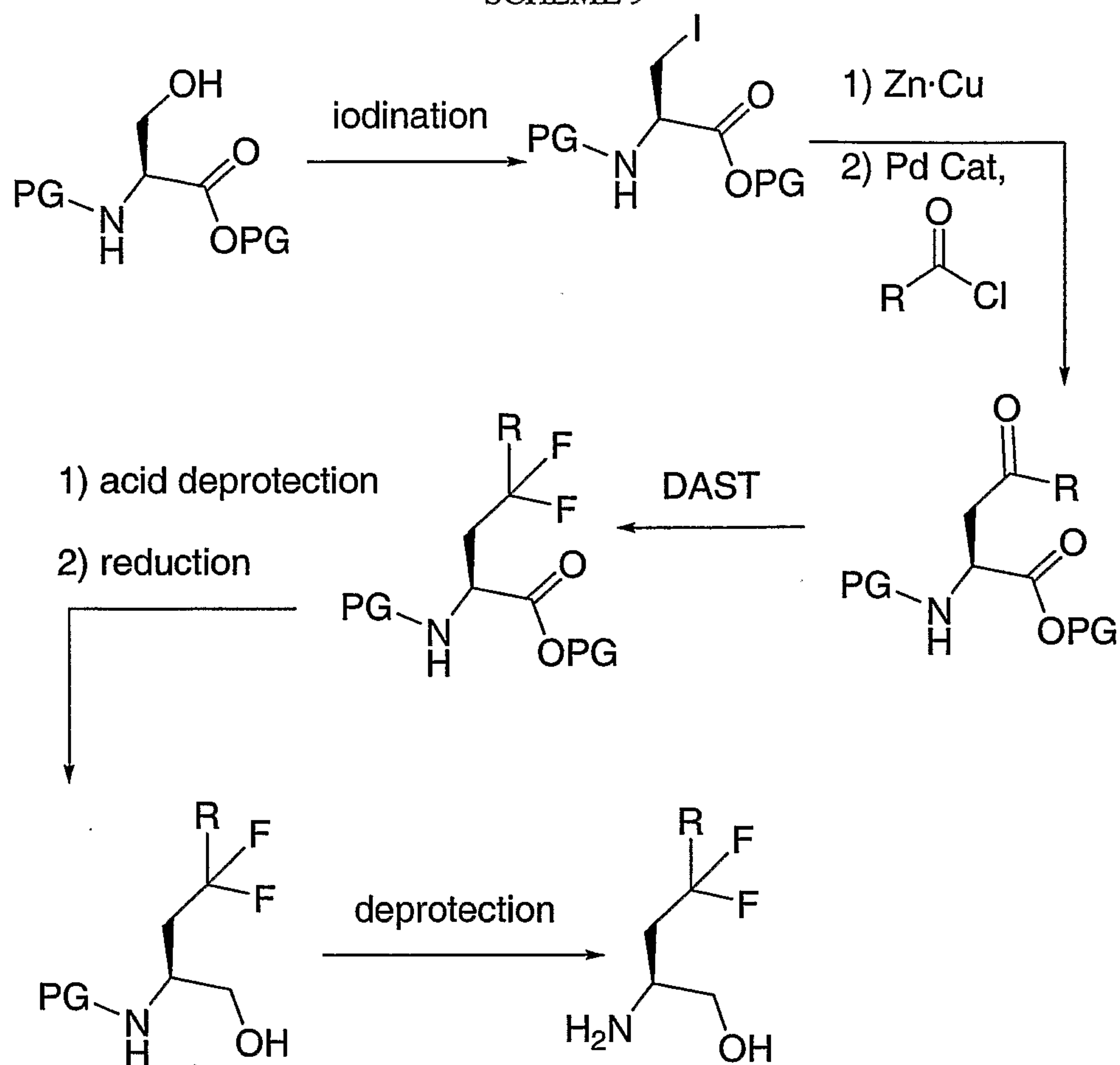
- 5 The 4-fluoroleucinol can also be synthesized according to Scheme 8. 4,5-Dehydroleucine is converted to (4*S*)-4-(2-methylprop-2-enyl)-1,3-oxazolidin-2-one as described in the scheme below. This intermediate is then treated with a hydrofluorination reagent such as HF-pyridine to give (4*S*)-4-(2-fluoro-2-methylpropyl)-1,3-oxazolidin-2-one. Basic hydrolysis (i.e. Ba(OH)₂ or NaOH) then affords (2*S*)-2-amino-4-fluoro-4-methylpentan-1-ol.

SCHEME 8



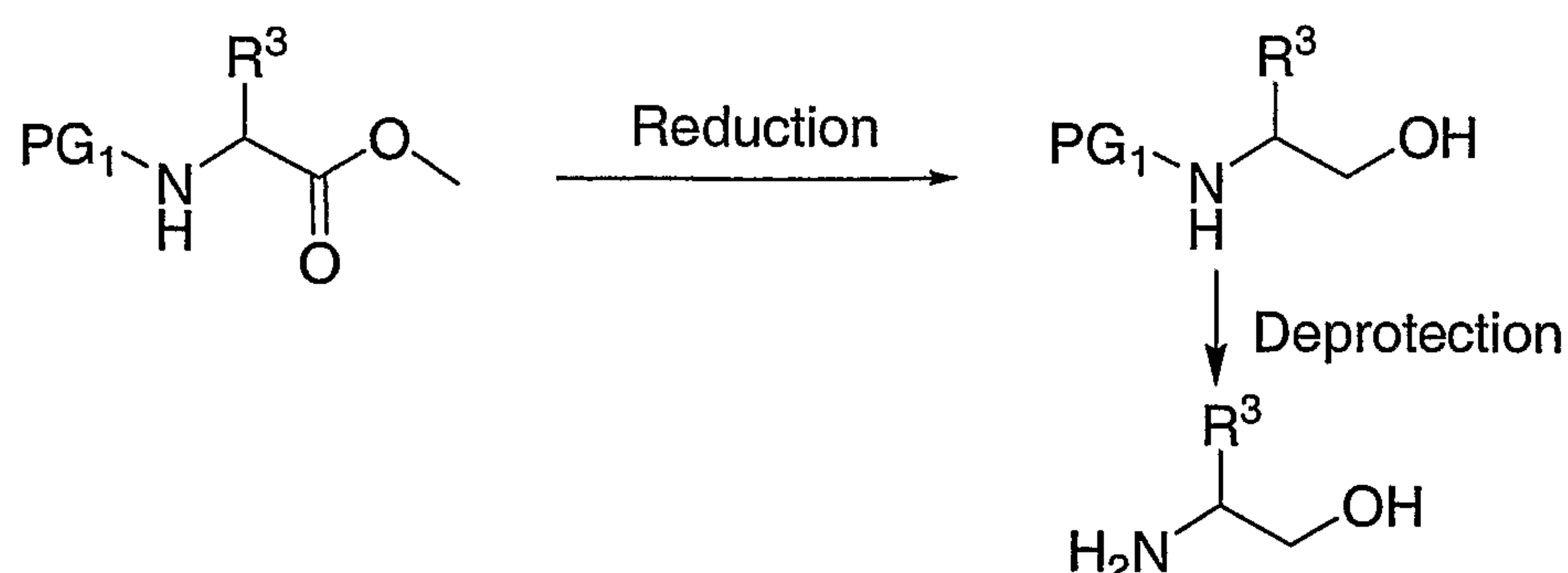
- 5 The synthesis of 4,4-difluoro-L-norvaline where R=Me is described in Scheme 9 below. Starting with a suitable diprotected serine, iodination can be carried out using a reagent such as $(\text{PhO})_3\text{P}^+\text{MeI}^-$. Zincation of the resultant iodide may proceed using Zn-Cu couple and TMSCl . The resultant zincate can then undergo a palladium catalyzed coupling reaction with alkanoyl chloride to generate the ketone. Finally, the ketone moiety can be converted to the desired difluoro derivative using a fluorinating agent
- 10 such as DAST. The protected or unprotected version of this amino acid or amino alcohol can then be converted to compounds of the current invention according to Schemes 1, 2, 3 and 5.

SCHEME 9



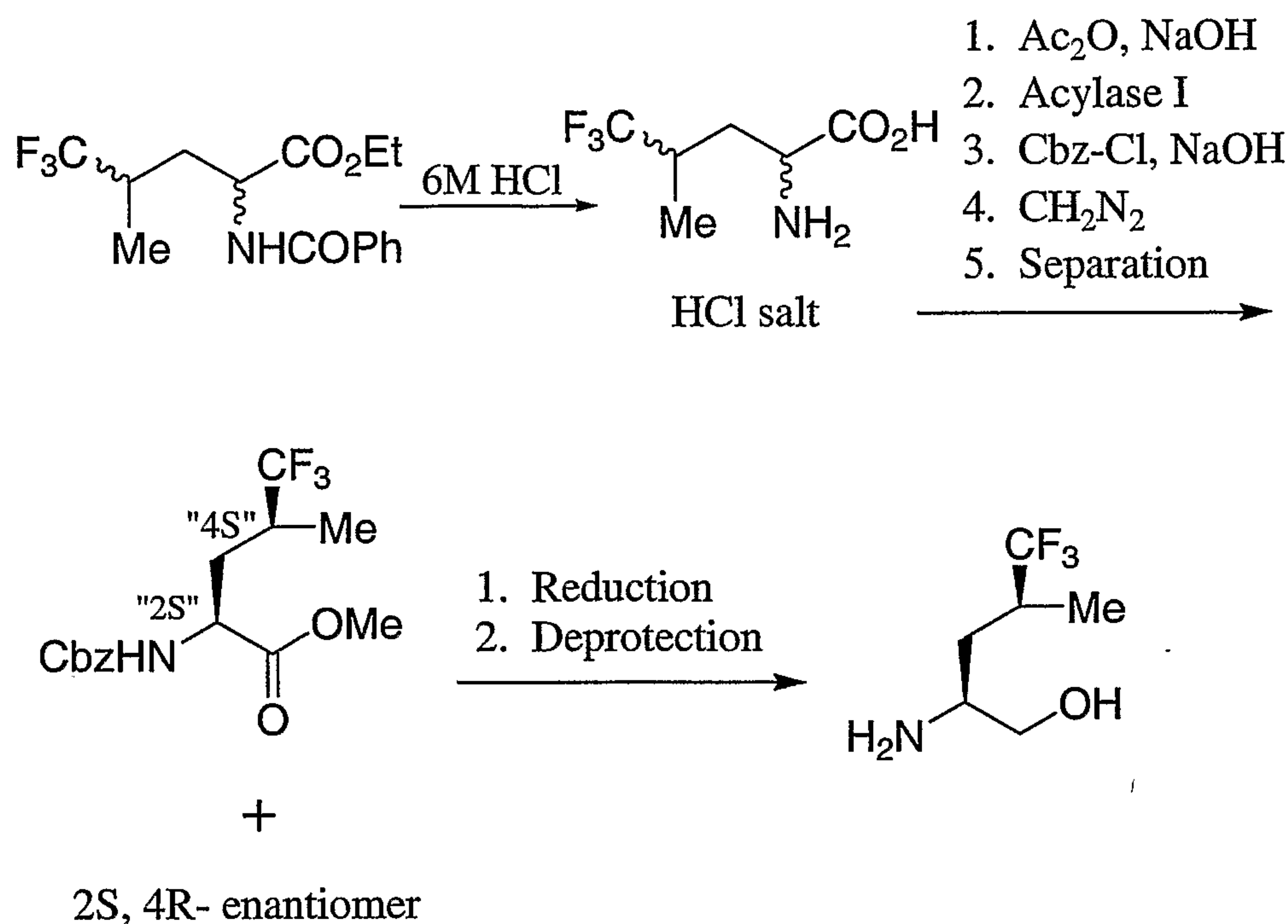
The amino alcohols used for the present invention may also be synthesized according to Scheme 10. A
 5 protected amino acid is reduced with a reducing agent such as NaBH_4 with or without an additive such as LiCl , in a solvent such as EtOH or a mixed solvent system such as EtOH/THF . The amino protecting group is then removed with the appropriate method according to the nature of the protecting group.

SCHEME 10



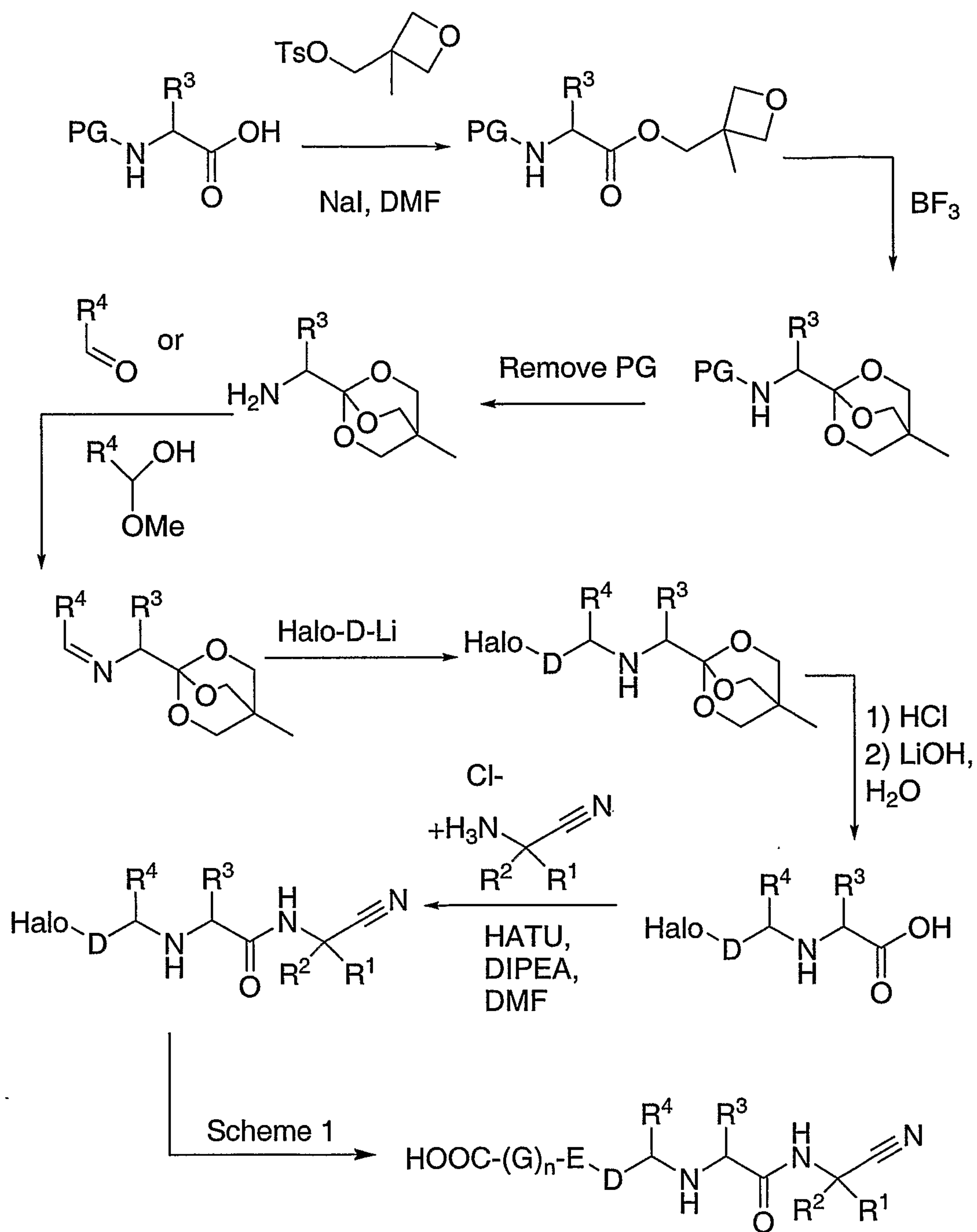
- 5 Synthesis of (2S,4S)-2-amino-5,5,5-trifluoro-4-methylpentan-1-ol used in the present invention is described in Scheme 11. N-benzoyl-5,5,5-trifluoroleucine (Ojiima, et. al. J. Org. Chem., **1989**, 54, 4511 – 4522) can be hydrolysed with an aqueous acid such as 6M HCl under refluxing conditions. The amino acid HCl salt intermediate is then converted to the N-acetyl-5,5,5-trifluoroleucine and the amino group chiral centre is resolved by an enzymatic method (Synthetic Communications, **1996**, 26, 1109 – 1115.).
- 10 The isolated 5,5,5-trifluoro-L-leucine is then protected with a protecting group such as benzyl carbamate and the carboxylic acid group is esterified. The two diastereomers at the 4-position are then separated by flash column chromatography. One of the enantiomers, the (2S,4S) protected amino acid is then converted to the amino alcohol as described in scheme 10.

SCHEME 11



- 5 Compounds of the current invention may also be prepared according to Scheme 13, as shown below. Reaction of a suitably N-protected amino acid derivative with oxetane tosylate in the presence of sodium iodide in a suitable organic solvent such as dimethylformamide provides the corresponding oxetane ester which upon treatment with diborane provides the ortho ester. Removal of the amino protecting group affords an amine which upon condensation with an aldehyde of formula R^4CHO or a hemiacetal of
- 10 formula $\text{R}^4\text{C}(\text{OH})(\text{OR})$ (where R is an alkyl group) under the reaction conditions described above provides an imine. Treatment of the imine with a Grignard or organolithium reagent under the reaction conditions described above provides an N-alkylated derivative. Removal of the ortho ester provides the corresponding carboxylic acid which is then converted into compounds of the current invention by condensation with an aminoacetonitrile under peptide coupling conditions, followed by Suzuki reaction
- 15 as described above.

SCHEME 13



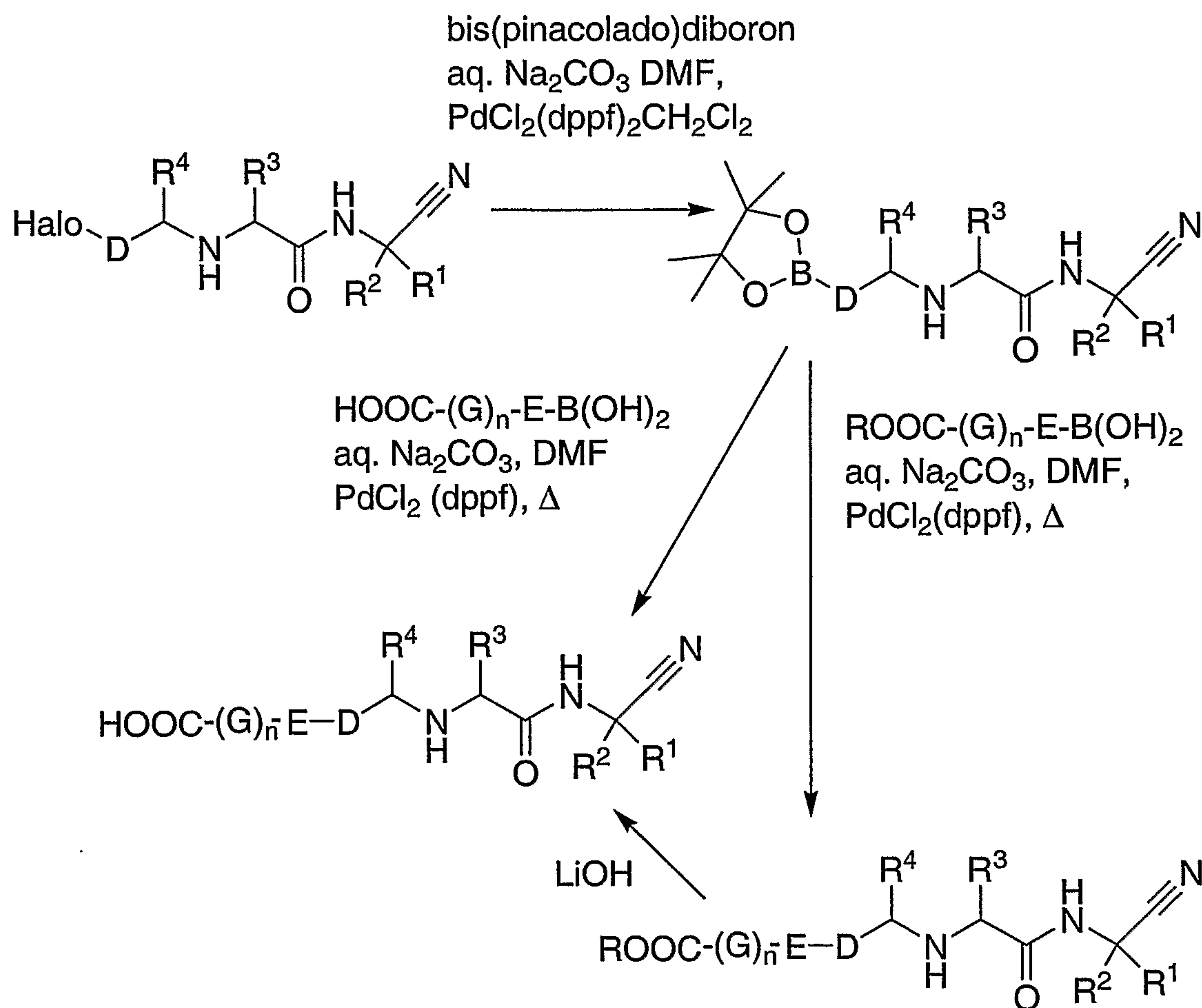
5

Compounds of the current invention may also be prepared as shown in Scheme 14. A aryl halide containing appropriate R¹, R², R³ and R⁴ groups may be coupled with bis(pinacolato)diboron to give the aryl pinacolate. This may be coupled with carboxylic acid-containing arylbromides under Suzuki

conditions to provide compounds of the current invention. Alternatively, this aryl pinacolate may be coupled with carboxylic ester-containing arylbromides under Suzuki conditions to provide an alkyl ester which may then be hydrolyzed to provide compounds of the current invention.

5

SCHEME 14

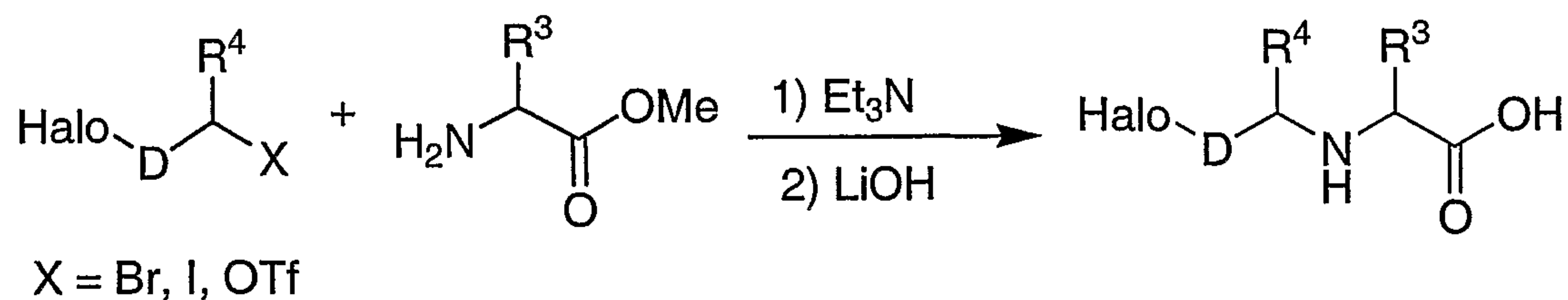


10

Carboxylic acids of the form $\text{Halo-D-CH(R}^4\text{)NHCH(R}^3\text{)COOH}$ shown in Schemes 1, 2, and 6 may also be prepared as shown in Scheme 15. An appropriately substituted benzyl bromide, iodide or triflate (which may be chiral or racemic) may be coupled with an alpha amino ester under basic conditions. Hydrolysis with aqueous base then provides the acid which can be converted into examples of the current invention.

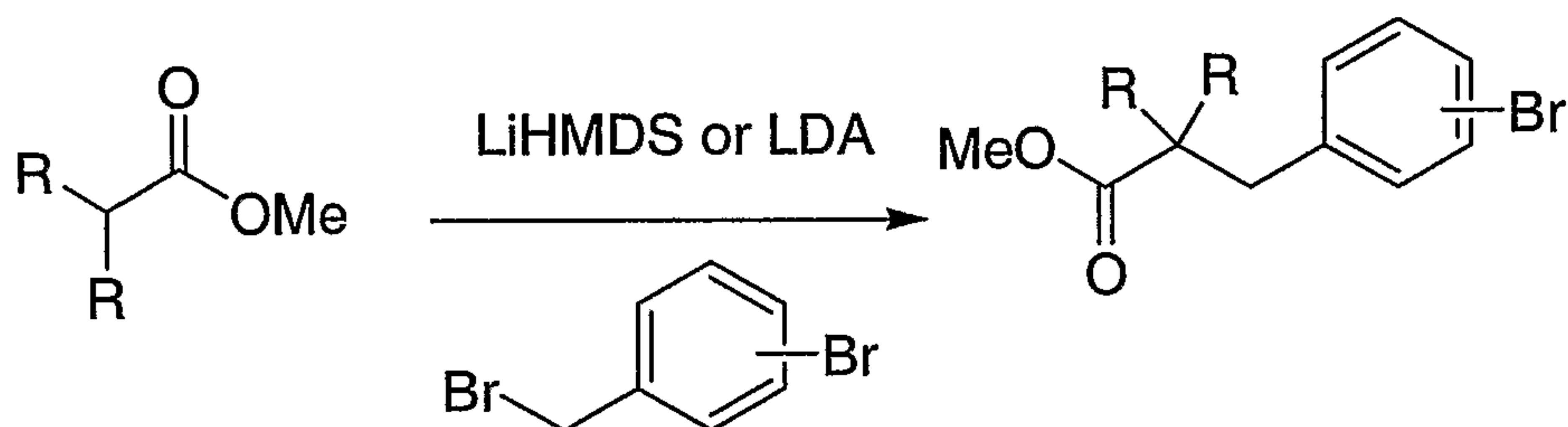
15

SCHEME 15

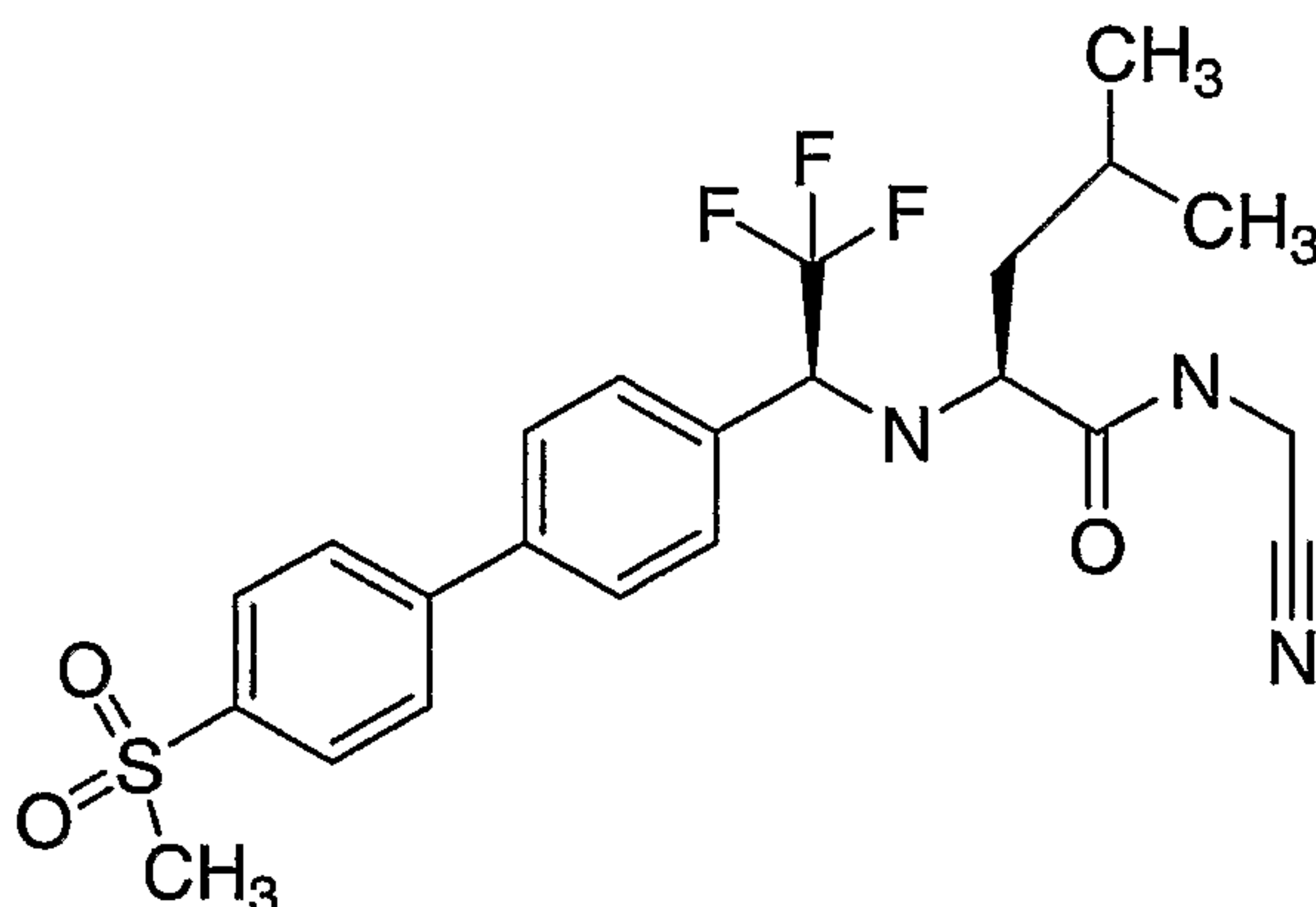


Carboxylic acid bromides of the form HOOC-G-E-Br used to make compounds of the current invention may be prepared as shown in Scheme 16. Treatment of a bromophenylbenzyl bromide with the enolate of a suitably substituted ester provides the bromoaryl-alkyl carboxylic ester. This intermediate may be coupled with a suitably substituted arylboronic acid, as described in Scheme 14, followed by basic hydrolysis of the ester, to give compounds of the current invention. Alternatively, the ester may be hydrolyzed prior to the Suzuki coupling described in Scheme 14.

SCHEME 16



The following examples describe the synthesis of selected compounds of the present invention.

EXAMPLE 1Synthesis of N¹(cyanomethyl)-N²{(1S)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)-1,1'-biphenyl-4-yl]ethyl}-L-leucinamideStep 1: (2S)-1-{[*tert*-butyl(dimethyl)silyl]oxy}-4-methylpentan-2-amine

To a room temperature dichloromethane (100 mL) solution of L-leucinol (6.0 g) was added triethylamine (11 mL), DMAP (0.1 g) and t-butyldimethylsilyl chloride (8.5 g). The mixture was stirred at room temperature for 2 hours and then water was added. The organic layer was separated and the aqueous further extracted with dichloromethane. The combined organic layers were washed with brine, dried with magnesium sulfate and the solvent was removed in vacuo to yield the title compound, a residue which was used as such in the next reaction.

¹H NMR (CD₃COCD₃) δ 3.48(m, 2H), 3.32(m, 1H), 2.76(m, 1H), 1.78(m, 1H), 1.22-1.02(m, 2H), 0.88(m, 15H), 0.06(s, 6H).

Step 2: (2S)-1-{[*tert*-butyl(dimethyl)silyl]oxy}-4-methyl-N-[(1E)-2,2,2-trifluoroethylidene]pentan-2-amine

A toluene (300 mL) solution of (2S)-1-{[*tert*-butyl(dimethyl)silyl]oxy}-4-methylpentan-2-amine from Step 1 (50 g) and trifluoroacetaldehyde methyl hemiacetal (35 mL) was heated to reflux for 16 hours during which time water was collected in a Dean-Stark trap. The solvent was evaporated in vacuum and the residue was purified on SiO₂ using hexanes and ethyl acetate (9:1) as eluant to yield the title compound.

¹H NMR (CD₃COCD₃) δ 7.88(m, 1H), 3.76-3.45(m, 3H), 1.60-1.25(m, 3H), 0.88(m, 15H), 0.06(s, 3H), 0.04(s, 3H).

Step 3: (2S)-2-{[(1S)-1-(4-bromophenyl)-2,2,2-trifluoroethyl]amino}-4-methylpentan-1-ol

n-BuLi (2.5 M in hexanes, 42 mL) was added to a -70°C THF (400 mL) solution of 1,4-dibromobenzene (25.8 g) and the mixture was stirred for 25 minutes. A THF (30 mL) solution of (2S)-1-{[*tert*-butyl(dimethyl)silyl]oxy}-4-methyl-*N*-[(1*E*)-2,2,2-trifluoroethylidene]pentan-2-amine (31 g) was then added dropwise and the mixture was stirred for 1.5 hour. It was then poured slowly into a mixture of ethyl acetate (500 mL), water (2 L), ice (300 g) and ammonium chloride (100 g) under vigorous stirring. The organic layer was separated and the aqueous further extracted with ethyl acetate (2 X 500 mL). The combined organic layers were washed with brine, dried with magnesium sulfate and the solvent was removed in vacuo to yield a residue, which was used as such. The residue from above was dissolved in THF (250 mL) and the solution was cooled to 0°C . A 1 M THF solution of *t*-butylammonium fluoride (110 mL) was added dropwise and the mixture was reacted for 4 hours. It was poured into ethyl acetate (300 mL), water (2 L) and ammonium chloride (100 g) under vigorous stirring. The organic layer was separated and the aqueous further extracted with ethyl acetate (2 X 100 mL). The combined organic layers were washed with brine, dried with magnesium sulfate and the solvent was removed in vacuo to yield a residue which was purified on SiO_2 using a gradient of ethyl acetate and hexanes (1:5 to 1:4) as eluant to yield the title compound.

^1H NMR (CD_3COCD_3) δ 7.6(2H, d), 7.45(2H, d), 4.55(1H, m), 3.65-3.7(1H, m), 3.5-3.55(1H, m), 3.25-3.35(1H, m), 2.6-2.7(1H, m), 2.25-2.35(1H, m), 1.65-1.75(1H, m), 1.3-1.4(1H, m), 1.2-1.3(1H, m), 0.75-0.9(6H, dd).

Step 4: (2S)-4-methyl-2-({(1S)-2,2,2-trifluoro-1-[4'-(methylthio)-1,1'-biphenyl-4-yl]ethyl}amino)pentan-1-ol

A stream of nitrogen was passed through a suspension made of the bromide from Step 3 (27.7 g), 4-(methylthio)phenylboronic acid (15.7 g), 2 M Na_2CO_3 (100 mL) and *n*-propanol (500 mL) for 15 minutes. A 1:3 mixture (3.5 g) of $\text{Pd}(\text{OAc})_2$ and PPh_3 was then added and the reaction was warmed to 70°C and stirred under nitrogen for 8 hours. The mixture was cooled to room temperature, diluted with ethylacetate (500 mL) and poured over water (2 L) and ice (500 g). The ethyl acetate layer was separated and the aqueous further extracted with ethyl acetate (200 mL). The combined ethyl acetate extracts were washed with 0.5 N NaOH (2 X 200 mL), with aqueous NH_4Cl , brine and dried with magnesium sulfate. Removal of the solvent left a residue that was purified by chromatography on SiO_2 using a gradient of ethyl acetate and hexanes (1:4 to 1:3) and again with acetone and toluene (1:10). The residue was dissolve in hot hexanes (200 mL) and the solution was allowed to cool to 0°C under stirring. The obtained solid was filtered and dried to yield the title compound.

¹H NMR (CD₃COCD₃) δ 7.7(2H, d), 7.65(2H, d), 7.6(2H, d), 7.35(2H, d), 4.5-4.6(1H, m), 3.7(1H(OH), m), 3.5-3.6(1H, m), 3.3-3.4(1H, m), 2.7(1H, m), 2.5(3H, s), 2.3-2.4(1H(NH), m), 1.65-1.75(1H, m), 1.2-1.4(3H, m), 0.8-0.9(6H, dd).

5 Step 5: (2S)-4-methyl-2-((1S)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)-1,1'-biphenyl-4-yl]ethyl)amino)pentan-1-ol

To a 0 °C solution of the sulfide (19 g) from Step 4 in toluene (400 mL) was added Na₂WO₄•2H₂O (0.16 g) and Bu₄NHSO₄ (0.81 g). Then 30 % hydrogen peroxide (12.2 mL) was slowly added and the mixture was stirred at room temperature for 4.5 hours. The mixture was poured slowly on
10 a mixture of ice, dilute aqueous sodium thiosulfate and ethyl acetate. The organic layer was separated and the aqueous further extracted with ethyl acetate (2 X 100 mL). The combined organic layers were washed with brine, dried with magnesium sulfate and the solvent were removed in vacuo to yield a residue which was purified on SiO₂ using ethyl acetate and hexanes (1:1) as eluant to yield the product.

15 ¹H NMR (CD₃COCD₃) δ 8.05(2H, d), 8.0(2H, d), 7.85(2H, d), 7.7(2H, d), 4.6-4.7(1H, m), 3.75(1H, m), 3.6(1H, m), 3.35-3.45(1H, m), 3.2(3H, s), 2.7-2.8(1H, m), 2.35-2.45(1H, m), 1.7-1.8(1H, m), 1.2-1.5(2H, m), 0.8-0.95(6H, dd).

20 Step 6: Preparation of N-((1S)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)-1,1'-biphenyl-4-yl]ethyl)-L-leucine

A suspension of H₅IO₆/CrO₃ (529 mL of 0.44 M in CH₃CN; see Note below) was cooled to 0 °C and a solution of the alcohol from Step 5 (20 g) in CH₃CN (230 mL) was added dropwise. The mixture was stirred at 0-5 °C for 3.5 hours. It was poured into pH 4 Na₂HPO₄ (1.5 L) under vigorous
25 stirring and the mixture was extracted with diethyl ether (3 X 250 mL). The combined ether extracts were washed with water and brine (1:1), with dilute aqueous NaHSO₃ and brine. The organic extract was dried with sodium sulfate, filtered and the solvents were evaporated to dryness to yield a residue that was split into two batches for the following purification.

The crude acid from above (10 g) was dissolved in isopropyl acetate (250 mL) and
30 extracted into cold 0.1 N NaOH (3 X 250 mL). The combined extracts were washed with diethyl ether (250 mL) and then slowly acidified with 6 N HCl to pH 4. The carboxylic acid was extracted with isopropyl acetate (2 X 250 mL) and the isopropyl acetate layer dried and concentrated to yield the product essentially pure and used as such in the next step.

Note: The oxidizing reagent ($\text{H}_5\text{IO}_6/\text{CrO}_3$) was prepared as described in Tetrahedron Letters 39 (1998) 5323-5326 but using HPLC grade CH_3CN (contains 0.5% water); no water was added.

^1H NMR (CD_3COCD_3) δ 8.05(2H, d), 7.95(2H, d), 7.8(2H, d), 7.65(2H, d), 4.45-4.55(1H, m), 3.55-3.6(1H, m), 3.2(3H, s), 2.8-3.0(broad m, NH/OH) 1.95-2.05(1H, m), 1.55-1.6(2H, m), 0.9-1.0(6H, m).

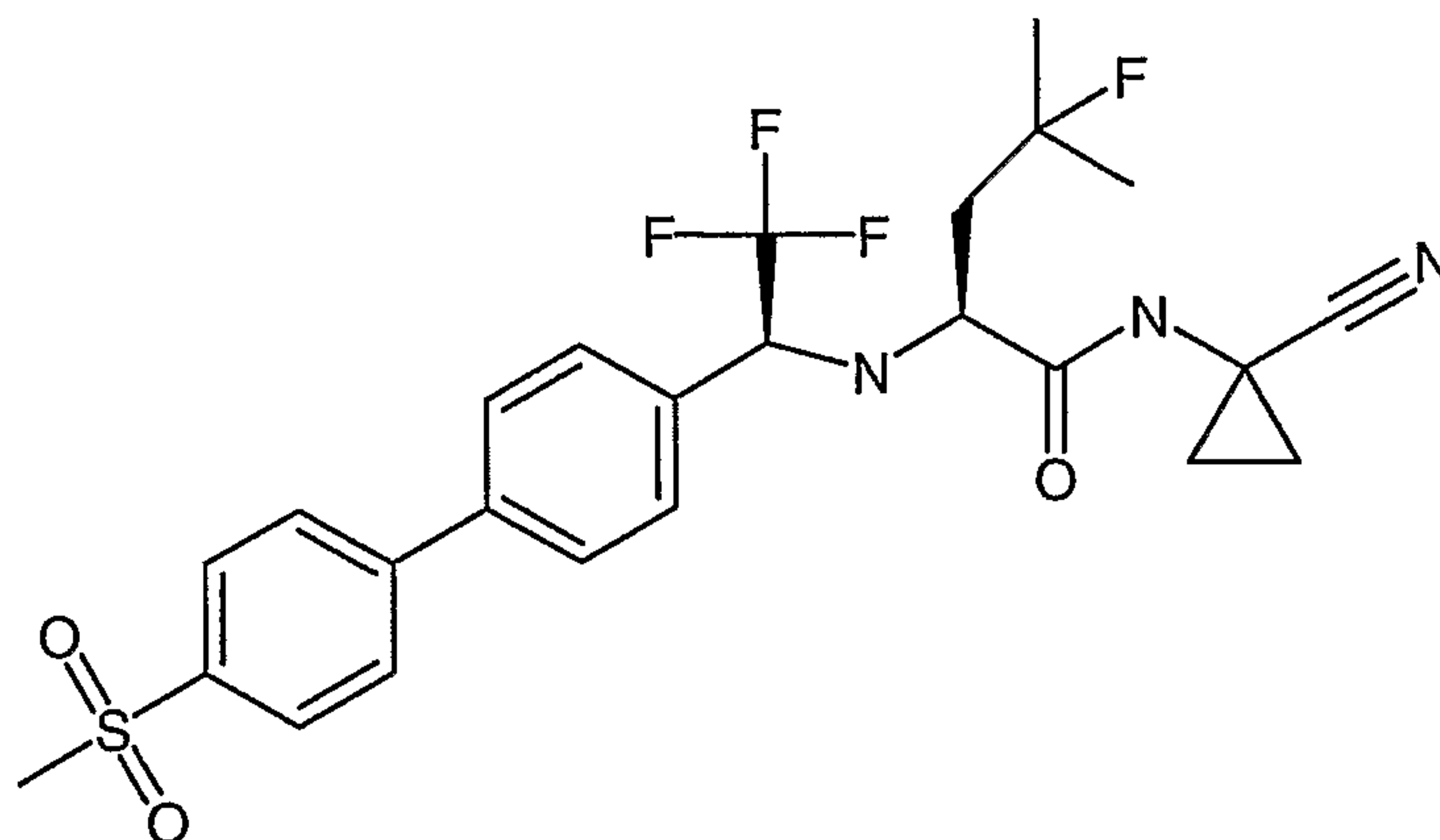
Step 7: Preparation of N^1 (cyanomethyl)- N^2 {(1S)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)-1,1'-biphenyl-4-yl]ethyl}-L-leucinamide

To a DMF (200 mL) solution of the acid from Step 7 (9 g) was added benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (11.6 g), aminoacetonitrile hydrochloride (3.94 g) and the mixture was cooled to 0°C . Triethylamine (9.9 mL) was added dropwise and the mixture warmed to room temperature and stirred for 16 hours. It was poured into ice and saturated aqueous sodium bicarbonate and extracted with diethyl ether (3 X 100 mL). The combined extracts were washed with brine, dried with magnesium sulfate and the solvent removed in vacuo. The residue was purified by chromatography on SiO_2 using ethyl acetate and hexanes (1:1). The title compound was then stirred in diethyl ether for 16 hours, filtered and dried (mp 140.5°C).

^1H NMR (CD_3COCD_3) δ 8.0(2H, d), 7.95(2H, d), 7.8(2H, d), 7.65(2H, d), 4.35-4.45(1H, m), 4.1-4.2(2H, m), 3.45-3.55(1H, m), 3.15(3H, s), 2.65-2.7(1H, m), 1.85-1.95(1H, m), 1.4-1.6(2H, m), 0.85-0.95(6H, m).

EXAMPLE 2

Preparation of N^1 -(1-cyanocyclopropyl)-4-fluoro- N^2 -(1S)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)-1,1'-biphenyl-4-yl]ethyl}-L-leucinamide



Step 1: Benzyl (3S)-3-[(tert-butoxycarbonyl)amino]-4-hydroxybutanoate

N-(tert-Butoxycarbonyl)-L-aspartic acid 4-benzyl ester (30 g) was dissolved in dimethoxyethane (90 mL) and the solution was cooled to -5°C . N-Methylmorpholine (10.32 mL) was added followed by isobutyl chloroformate (12.7 mL) in such a way to keep the temperature below -10°C . The mixture was aged for 0.5 hour. The solids were quickly filtered and washed with dimethoxyethane (90 mL). To the filtrate cooled to -50°C was carefully added sodium borohydride (4.4 g) as a solution in water (45 mL) in such a way to keep the temperature between -30°C and -15°C . After all the hydride had been added, water (500 mL) was added in such a way to maintain the temperature below -15°C . The suspension was filtered, the solid washed with water (400 mL) and dried to yield benzyl (3S)-3-[(tert-butoxycarbonyl)amino]-4-hydroxybutanoate.

^1H NMR (CD_3COCD_3) δ 7.3-7.45(5H, m), 5.85-5.95(1H, NH), 5.15(2H, s), 3.95-4.1(2H, m), 3.5-3.7(2H, m), 2.55-2.75(2H, m), 1.4(9H, s).

15 Step 2: Benzyl [(4S)-2-oxo-1,3-oxazolidin-4-yl]acetate

To the alcohol (95.7 g) from Step 1 dissolved in dichloroethane (925 mL) was added pyridine (625 mL) and the mixture was cooled to $0-5^{\circ}\text{C}$. Anhydrous p-toluenesulfonic anhydride (105.7 g.) was added and the mixture was warmed to room temperature and stirred for 1 hour. It was then heated to 90°C for 2 hours. The mixture was cooled, diluted with dichloromethane (1000 mL) and washed with 1N HCl (3 X 600 mL). The organic layer was washed with brine, dried with sodium sulfate and the solvents were removed *in vacuo*. The residue was purified by chromatography on SiO_2 using ethyl acetate and hexanes in a 1:1 ratio followed by ethyl acetate to yield benzyl [(4S)-2-oxo-1,3-oxazolidin-4-yl]acetate.

25 ^1H NMR (CD_3SOCD_3) δ 7.8(1H, NH), 7.3-7.45(5H, m), 5.05-5.15(2H, m), 4.4-4.5(1H, m), 4.1-4.2(1H, m), 4.0-4.05(1H, m), 3.6-3.8(2H, m).

Step 3: (4S)-4-(2-Hydroxy-2-methylpropyl)-1,3-oxazolidin-2-one.

30 Methylmagnesium bromide (227 mL of 3M solution in diethyl ether) was added to a mixture of toluene (340 mL) and THF (340 mL) at -20°C . The ester from Step 2 (40 g) as a warm THF solution (170 mL) was then added dropwise maintaining the temperature below -10°C and the mixture was aged for 2 hours. The mixture was then slowly added to a mixture of water (1000 mL) and acetic acid (200 mL) and the mixture was stirred for 2 hours at room temperature. The aqueous layer was separated and the organic extracted with water (2 X 200 mL). The product was extracted from the combined aqueous layers using dichloromethane and a continuous extractor. The dichloromethane

extract was evaporated to dryness with the help of heptane. The residue was purified by chromatography on SiO₂ using ethanol and dichloromethane (1:30) to yield (4*S*)-4-(2-hydroxy-2-methylpropyl)-1,3-oxazolidin-2-one.

5 ¹H NMR (CD₃COCD₃) δ 6.1-6.4(1H, NH), 4.45-4.55(1H, m), 4.1-4.2(1H, m), 3.95-4.05(1H, m), 3.7(1H, s), 1.65-1.85(2H, m), 1.25(6H, m).

Step 4: (4*S*)-4-(2-Fluoro-2-methylpropyl)-1,3-oxazolidin-2-one.

10 The alcohol (47.8 g.) from Step 3 as a dichloromethane (100 mL) solution was added to a -70 °C solution of (diethylamino)sulfur trifluoride (48.5 g.) in dichloromethane (500 mL). The mixture was warmed to room temperature and stirred for 1 hour. It was then carefully added to a 0 °C mixture of saturated aqueous NaHCO₃ (800 mL). The organic layer was separated and washed with saturated aqueous NaHCO₃. The aqueous was further extracted with dichloromethane (100 mL) and the combined dichloromethane layers were dried and concentrated. The residue was purified by chromatography on
15 SiO₂ using ethyl acetate and hexanes (1:5) followed by ethyl acetate to yield (4*S*)-4-(2-fluoro-2-methylpropyl)-1,3-oxazolidin-2-one.

¹H NMR (CD₃SOCD₃) δ 7.6(1H, NH), 4.4-4.5(1H, m), 3.95-4.05(1H, m), 3.9-3.95(1H, m), 1.8-1.95(2H, m), 1.25-1.4(6H, 2s).

20 Step 5: (2*S*)-2-Amino-4-fluoro-4-methylpentan-1-ol.
To the fluoro derivative (21.0 g) from Step 4 dissolved in 90% aqueous ethyl alcohol (216 mL) was added potassium hydroxide (21.9 g). The mixture was heated at reflux for 4 hours and cooled to room temperature. The mixture was then concentrated and co-evaporated with toluene (3 X 300
25 mL). The residue was dissolved in dichloromethane (500 mL) and stirred for 0.5 hour. The suspension was filtered through celite and the celite was washed with dichloromethane (3 X 100 mL). The filtrate was concentrated to dryness to yield (2*S*)-2-amino-4-fluoro-4-methylpentan-1-ol.

¹H NMR (CD₃OD) δ 3.4-3.5(1H, m), 3.2-3.3(1H, m), 3.0-3.1(1H, m), 1.5-1.7(2H, m), 1.35(3H, s),
30 1.3(3H, s).

Step 6: (2*S*)-1-{[*tert*-butyl(dimethyl)silyl]oxy}-4-fluoro-4-methylpentan-2-amine

The amino alcohol (21.0 g) from Step 5 was dissolved in dichloromethane (300 mL) and the solution was cooled to 0 °C. 4-(Dimethylamino)pyridine (0.051 g.) and *tert*-butyldimethylsilyl
35 chloride (21 g.) were added followed by triethylamine (25 mL). The mixture was stirred at room

temperature overnight. The reaction mixture was slowly poured into 0 °C saturated aqueous ammonium chloride and extracted with dichloromethane (3 X 300 mL). The organic layer was washed with brine, dried with sodium sulfate and the solvents were removed *in vacuo* to yield (2S)-1- $\{[tert\text{-butyl(dimethyl)silyl]oxy}\}$ -4-fluoro-4-methylpentan-2-amine.

5 ^1H NMR (CD_3OD) δ 3.6-3.65(1H, m), 3.4-3.5(1H, m), 3.1-3.2(1H, m), 1.6-1.8(2H, m), 1.35-1.45(6H, m), 0.93(9H, s), 0.1(6H, s).

Step 7: (2S)-1- $\{[tert\text{-butyl(dimethyl)silyl]oxy}\}$ -4-fluoro-4-methyl-N-[(1E)-2,2,2-trifluoroethylidene]pentan-2-amine.

10 To the amine (31.5 g) from Step 6 dissolved in benzene (126 mL) was added trifluoroacetaldehyde methyl hemiacetal (21.6 mL). The solution was heated at reflux overnight using a Dean-Stark trap to collect water. The reaction mixture was cooled to room temperature and concentrated to dryness. The residue was purified on SiO_2 using 4% of ethyl acetate in hexanes to yield (2S)-1- $\{[tert\text{-butyl(dimethyl)silyl]oxy}\}$ -4-fluoro-4-methylpentan-2-amine.

15 ^1H NMR (CD_3COCD_3) δ 7.9-7.95(1H, m), 3.75-3.85(1H, m), 3.7-3.75(1H, m), 3.53-3.6(1H, m), 1.9-2.0(2H, m), 1.3-1.4(6H, m), 0.9(9H, s), 0.1(3H, s), 0.05(3H, s).

Step 8: (2S)-2- $\{[(1S)\text{-1-(4-Bromophenyl)-2,2,2-trifluoroethyl}]\text{amino}\}$ -4-fluoro-4-methylpentan-1-ol.

20 To a -75 °C solution of 1,4-dibromobenzene (0.26 g) in THF (4 mL) was added n-BuLi (0.42 mL of a 2.5M hexanes solution) and the mixture was aged for 20 minutes. The imine (0.329 g.) from Step 7 in THF (2 mL) was added and the mixture was aged 2 hours. The mixture was then added to a mixture of water (50 mL), NH_4Cl (1 g.) and crushed ice. It was extracted with ethyl acetate (2 X 25 mL) and the combined ethyl acetate layers were dried and evaporated to dryness.

25 The same procedure was repeated but using dibromobenzene (1.2 g.), n-BuLi (1.84 mL) and the imine (1.38 g.) and the reaction mixture was treated as above. The combined residues from both preparations were dissolved in THF (10 mL) and cooled to 0 °C. n-Tetrabutylammonium fluoride (6 mL from a 1M THF solution) was added and the mixture was stirred at + 5 °C for 16 hrs. It was poured into a mixture of water (50 mL), ammonium chloride (1 g.) and crushed ice and the organic layer was separated. The aqueous was further extracted with ethyl acetate (2X 15 mL) and the combined organic layers were dried and concentrated. The residue was purified on SiO_2 using ethyl acetate and hexanes (1:5) to yield (2S)-2- $\{[(1S)\text{-1-(4-bromophenyl)-2,2,2-trifluoroethyl}]\text{amino}\}$ -4-fluoro-4-methylpentan-1-ol.

30

¹H NMR (CD₃COCD₃) δ 7.65(2H, m), 7.5(2H, m), 4.5-4.6(1H, m), 3.8(1H, m), 3.6(1H, m), 3.3-3.4(1H, m), 2.85-2.0(1H, m), 2.55(1H, m), 1.7-1.9(2H, s), 1.3-1.4(6H, m).

Step 9: N-[(1S)-1-(4-bromophenyl)-2,2,2-trifluoroethyl]-4-fluoro-L-leucine.

5 A suspension of H₅IO₆/CrO₃ (66 mL of 0.44 M in CH₃CN; *Note*) was cooled to 0 °C and a solution of the alcohol from Step 8 (1.55 g) in CH₃CN (5 mL) was added dropwise. The mixture was stirred at 0-5 °C for 3.5 hours. It was poured into pH 4 Na₂HPO₄ (200 mL) under vigorous stirring and the mixture was extracted with diethyl ether (3 X 50 mL). The combined ether extracts were washed with water and brine (1:1) followed by dilute aqueous NaHSO₃ and brine. It was dried with sodium sulfate,
10 filtered and the solvents were evaporated to dryness to yield of N-[(1S)-1-(4-bromophenyl)-2,2,2-trifluoroethyl]-4-fluoro-L-leucine used as such in the next step.

Note. The oxidizing reagent (H₅IO₆/CrO₃) was prepared as described in Tetrahedron Letters 39 (1998) 5323-5326 but using HPLC grade CH₃CN (contains 0.5% water); no water was added.

15

Step 10: N²-[(1S)-1-(4-bromophenyl)-2,2,2-trifluoroethyl]-N¹-(1-cyanocyclopropyl)-4-fluoro-L-leucinamide.

Diisopropylethylamine (4.2 mL) was added to a 0 °C suspension of the acid (1.5 g) from Step 9, 1-amino-1-cyclopropanecarbonitrile hydrochloride (1.18 g), O-(7-azabenzotriazol-1-yl)-N, N, N',
20 N'-tetramethyluronium hexafluorophosphate (1.94 g) and dimethylformamide (5 mL) and the mixture was reacted at room temperature for 48 hrs. It was then poured on ice and dilute aqueous ammonium chloride. The mixture was extracted with ethyl acetate and ether (1:1) and the combined organic layers were washed with pH 3 dilute Na₂HPO₄ and brine. The solvents were evaporated to dryness and the residue was purified by chromatography on SiO₂ using ethyl acetate and hexanes (1:2) to yield N²-[(1S)-
25 1-(4-bromophenyl)-2,2,2-trifluoroethyl]-N¹-(1-cyanocyclopropyl)-4-fluoro-L-leucinamide in a sufficient purity state for the next step.

¹H NMR (CD₃COCD₃) δ 8.15(1H, NH), 7.6(2H, m), 7.45(2H, m), 4.35-4.45(1H, m), 3.45-3.55(1H, m), 1.9-2.1(2H, m), 1.75-1.85(1H, NH), 1.35-1.55(8H, m), 1.1-1.15(1H, m), 0.95-1.05(1H, m).

30

Step 11: N¹-(1-cyanocyclopropyl)-4-fluoro-N²-[(1S)-2,2,2-trifluoro-1-[4'-(methylthio)-1,1'-biphenyl-4-yl]ethyl]-L-leucinamide.

A stream of nitrogen was passed through a suspension made of the bromide from Step 10 (0.338 g.), 4-(methylthio)phenylboronic acid (0.252 g), 2M Na₂CO₃ (0.8 mL) and DMF (4 mL) for 15
35 minutes. PdCl₂·dppf (0.1 g) was then added and the reaction was warmed to 85 °C and stirred under

nitrogen for 5 hours. The mixture was cooled to room temperature, diluted with ethyl acetate (10 mL) and poured into water (50 mL) and ice. The ethyl acetate layer was separated and the aqueous further extracted with ethyl acetate. The combined ethyl acetate extracts were dried and the solvents removed *in vacuo*. The residue was purified by chromatography on SiO₂ using ethyl acetate and hexanes (1:2) to yield *N*¹-(1-cyanocyclopropyl)-4-fluoro-*N*²-{(1*S*)-2,2,2-trifluoro-1-[4'-(methylthio)-1,1'-biphenyl-4-yl]ethyl}-L-leucinamide.

¹H NMR (CD₃COCD₃) δ 8.15(1H, NH), 7.1-7.2(4H, m), 7.5-7.55(2H, m), 7.35-7.4(2H, m), 4.3-4.4(1H, m), 3.45-3.55(1H, m), 2.75-2.8(1H, NH), 2.5(3H, s), 1.9-2.05(2H, m), 1.3-1.5(8H, m), 1.0-1.1(1H, m), 0.85-0.95(1H, m).

Step 12: Preparation of *N*¹-(1-cyanocyclopropyl)-4-fluoro-*N*²-{(1*S*)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)-1,1'-biphenyl-4-yl]ethyl}-L-leucinamide

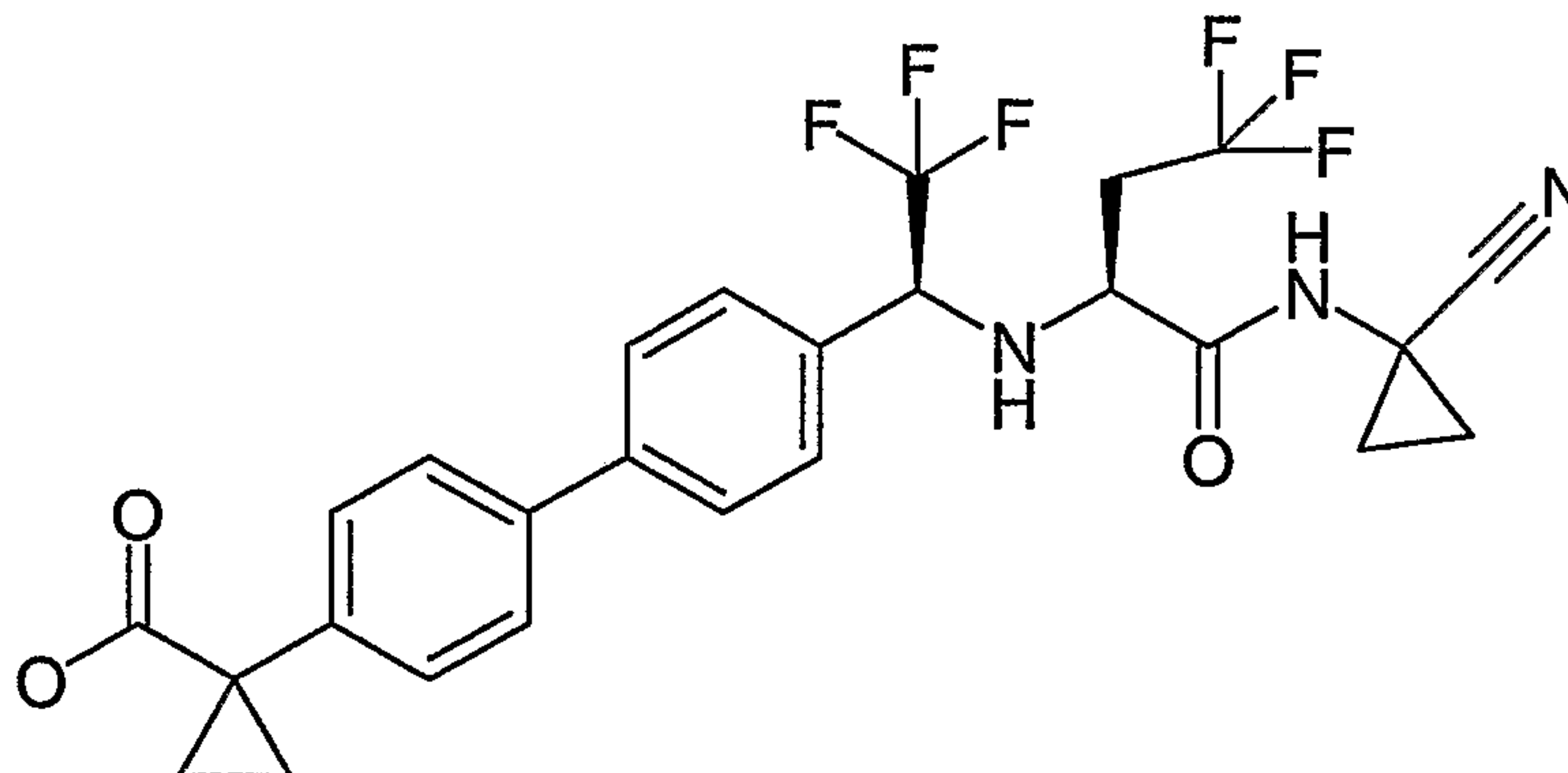
To a 0 ° solution of the sulfide (0.265 g) from Step 11 in toluene (5 mL) and dichloromethane (5 mL) was added Na₂WO₄•2H₂O (0.002 g) and n-Bu₄NHSO₄ (0.01 g). Then 30 % hydrogen peroxide (0.137 mL) was slowly added and the mixture was stirred at room temperature for 3 hours. The mixture was poured slowly on a mixture of ice, dilute aqueous sodium thiosulfate and ethyl acetate. The organic layer was separated and the aqueous further extracted with ethyl acetate. The combined organic layers were washed with brine, dried with magnesium sulfate and the solvent were removed *in vacuo* to yield a residue which was purified on SiO₂ using ethyl acetate, hexanes and dichloromethane (1:1:0.1) as eluant. The residue was triturated in diethyl ether to yield *N*¹-(1-cyanocyclopropyl)-4-fluoro-*N*²-{(1*S*)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)-1,1'-biphenyl-4-yl]ethyl}-L-leucinamide.

¹H NMR (CD₃COCD₃) δ 8.2(1H, NH), 8.05-8.1(2H, m), 7.95-8.0(2H, m), 7.8(2H, m), 7.65(2H, m), 4.35-4.45(1H, m), 3.5-3.6(1H, m), 3.2(3H, s), 2.8-2.9(1H, NH), 1.9-2.1(2H, m), 1.3-1.5(8H, m), 1.05-1.15(1H, m), 0.9-1.0(1H, m).

EXAMPLE 3

Preparation of 1-[4'-[(1S)-1-[[[(1S)-1-[[[(1-cyanocyclopropyl)amino]carbonyl]-3-fluoro-3-methylbutyl]amino]-2,2,2-trifluoroethyl][1,1'-biphenyl]-4-yl]- cyclopropanecarboxylic acid

5



Step 1 : 1-(4-bromophenyl)cyclopropanecarbonitrile

To a room temperature solution of 4-bromophenylacetonitrile (18.0 g) in 22 mL of sodium hydroxide (50% in water W/W) were added 1-bromo-2-chloroethane and (12.0 mL) and benzyltriethylammonium chloride (627 mg). The mixture was heated at 60 °C overnight. The reaction mixture was cooled to room temperature and diethyl ether was added (300 mL. The ether layer was washed with water (100 mL), hydrogen chloride (100 mL, 10% HCl in water) and brine. The organic layer was dried with magnesium sulfate and the solvent removed in vacuo. The residue was purified by trituration using diethyl ether and hexanes to yield the title compound.

¹H NMR (CD₃COCD₃) δ 7.60(2H, d), 7.35(2H, d), 1.74-1.80(2H, m), 1.52-1.57(2H, m).

Step 2 : 1-(4-bromophenyl)cyclopropanecarboxylic acid

To a room temperature solution of 1-(4-bromophenyl)cyclopropanecarbonitrile from Step 1 (13 g) in ethyl alcohol (110 mL) was added a solution of 56 mL of sodium hydroxide (25% NaOH in water w/w). The mixture was heated at 100 °C overnight. It was cooled to room temperature, poured into ice and hydrogen chloride (1 N) and extracted with dichloromethane (2 x 100 mL). The combined extracts were washed with brine, dried with magnesium sulfate and the solvent removed in vacuo to yield the title compound.

¹H NMR (CD₃COCD₃) δ 7.50(2H, d), 7.35(2H, d), 1.53-1.60(2H, m), 1.18-1.22(2H, m).

Step 3: *N*¹-(1-cyanocyclopropyl)-4-fluoro-*N*²-{[(1*S*)-2,2,2-trifluoro-1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)]phenyl]ethyl}-L-leucinamide

A stream of nitrogen was passed through a DMF (40 mL) suspension of *N*²-[(1*S*)-1-(4-bromophenyl)-2,2,2-trifluoroethyl]-*N*¹-(1-cyanocyclopropyl)-4-fluoro-L-leucinamide from Example 2, Step 10 (2.0 g), bis(pinacolato)diboron (1.24 g) and potassium acetate (1.53 g) for 15 minutes. The catalyst [1, 1'-bis(diphenylphosphino)-ferrocene]dichloropalladium(II), complex (1:1) with dichloromethane (181 mg) was then added and the mixture warmed to 65 °C overnight under nitrogen. The mixture was cooled to room temperature, diluted with ethyl acetate and hexanes (1:1, 100 mL) and poured over water (50 mL) and ice (50 g). The organic layer was separated and the aqueous layer further extracted with ethyl acetate and hexanes (1:1, 3 X 50 mL). The combined extracts were washed with brine and dried with magnesium sulfate. Removal of the solvent left a residue which was purified by chromatography on SiO₂ using ethyl acetate and hexanes (1:3 to 1:2) to yield the title compound.

¹H NMR (CD₃COCD₃) δ 8.15(1H, bs), 7.78(2H, d), 7.50(2H, d), 4.31-4.40 (1H, m), 3.47-3.54 (1H, m), 2.72-2.80 (2H, m), 1.32-1.48(9H, m), 1.05-1.11(1H, m), 0.87-0.95(1H, m).

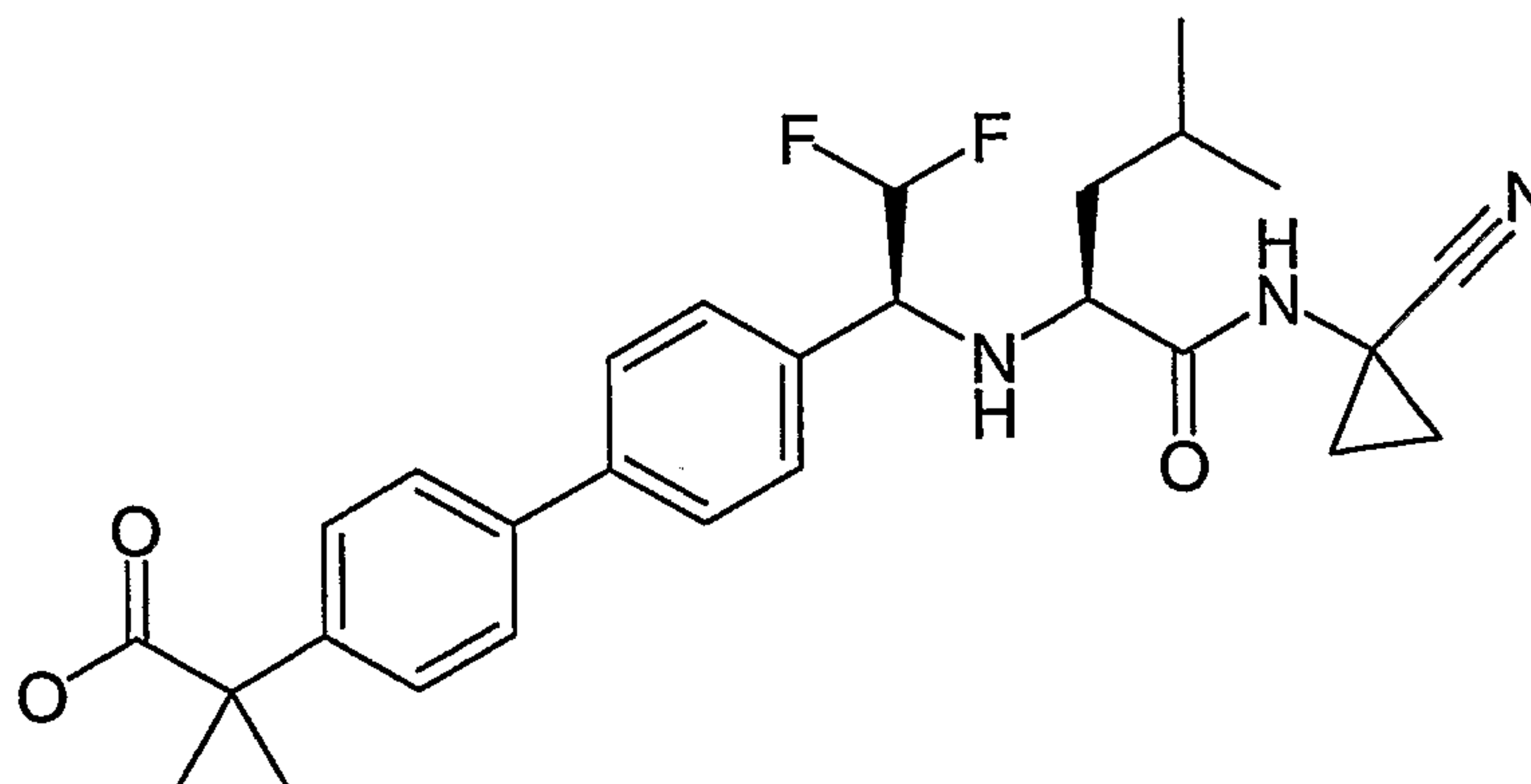
Step 4: 1-[4'-[(1*S*)-1-[[[(1*S*)-1-[(1-cyanocyclopropyl)amino]carbonyl]-3-fluoro-3-methylbutyl]amino]-2,2,2-trifluoroethyl][1,1'-biphenyl]-4-yl]-cyclopropanecarboxylic acid

A stream of nitrogen was passed through a solution of DMF (4 mL) of the boronate from Step 3 (150 mg), 1-(4-bromophenyl)cyclopropanecarboxylic acid (65 mg) and 2 M Na₂CO₃ (400 µL) for 15 minutes followed by the addition of [1, 1'-bis(diphenylphosphino)-ferrocene]dichloropalladium(II), complex (1:1) with dichloromethane (12 mg). The mixture was warmed to 80 °C for 3 hours under nitrogen. The mixture was cooled to room temperature, poured into ice (10 g) and 1.0 N hydrogen chloride (15 mL) and extracted with 50 % ethyl acetate in diethyl ether (3 X 30 mL). The combined extracts were washed with brine and dried with magnesium sulfate. Removal of the solvent left a residue that was purified by chromatography on SiO₂ using ethyl acetate, hexanes and acetic acid (1:1:1%) as eluants, followed by a swish using diethyl ether to yield the title compound.

¹H NMR (CD₃COCD₃) δ 8.16(1H, bs), 7.69(2H, d), 7.61(2H, d), 7.53(2H, d), 7.48(2H, d), 4.33-4.38 (1H, m), 3.50-3.55 (1H, m), 1.92-2.05 (2H, m), 1.57-1.61(2H, m), 1.40-1.50(6H, m), 1.38-1.48(2H, m), 1.20-1.27(2H, m), 1.02-1.09(1H, m), 0.87-0.95(1H, m);
MS (+APCI): 532.4 (M+1)⁺.

EXAMPLE 4

*N*¹-(1-cyanocyclopropyl)-*N*²-{(1*S*)-2,2-difluoro-1-{4'-[1-(carboxy)cyclopropyl]biphenyl-4-yl}-ethyl}-L-leucinamide.



Step 1: Preparation of (2*S*)-1-{[*tert*-butyl(dimethyl)silyl]oxy}-*N*-[(1*Z*)-2,2-difluoroethylidene]-4-methylpentan-2-amine

A mixture of (2*S*)-1-{[*tert*-butyl(dimethyl)silyl]oxy}-4-methylpentan-2-amine (Example 4, Step 1, 8.5 g, 36.8 mmol) and difluoroacetaldehyde ethyl hemiacetal (5.0g, 39.7 mmol) in benzene was refluxed with a Dean-stark trap overnight. Solvent was removed in vacuo. The residue was passed through a short silica column and eluted with hexanes: EtOAc (10:1) to give the title compound as a pale yellow oil.

¹H NMR (CD₃COCD₃) δ 7.72(m, 1H), 6.12(dt, 1H), 3.70(dd, 1H), 3.54(dd, 1H), 3.36(m, 1H), 1.48(m, 2H), 1.32(m, 1H), 0.95 – 0.78(m, 15H), 0.06(s, 3H), 0.02(s, 3H).

Step 2: Preparation of (2*S*)-2-{[(1*S*)-1-(4-bromophenyl)-2,2-difluoroethyl]amino}-4-methylpentan-1-ol

n-BuLi (2.5 M in hexanes, 1.43 mL) was added to a -70 °C THF (8.5 mL) solution of 1,4-dibromobenzene (884 mg) and the mixture was stirred for 15 minutes. A THF (8.5 mL) solution of (2*S*)-1-{[*tert*-butyl(dimethyl)silyl]oxy}-4-methyl-*N*-[(1*E*)-2,2-difluoroethylidene]pentan-2-amine (1.0 g) was then added dropwise and the mixture was stirred for 1.5 hours. It was then poured slowly into an icy saturated solution of ammonium chloride under vigorous stirring. It was extracted with 3 portions of ethyl acetate. The combined organic layers were washed with brine, dried with magnesium sulfate and the solvent was removed in vacuo to yield a residue, which was purified on SiO₂ using a gradient of hexanes and ethyl acetate (90:10 to 75:25) as eluent to yield the title compound. The compound (200 mg) from above was dissolved in CH₃CN (4 mL) and the solution was cooled to 0 °C. HF-pyridine (40

μM) was added dropwise and the mixture was reacted for 16 hours. It was poured into a saturated solution of sodium bicarbonate, ethyl acetate was added and it was vigorously shaken. The organic layer was separated and the aqueous further extracted with ethyl acetate (2 X 50 mL). The combined organic layers were washed with brine, dried with magnesium sulfate and the solvent was removed in vacuo to yield a residue which was purified on SiO₂ using a gradient of hexanes and ethyl acetate (80:20 to 60:40) as eluent to yield the title compound.

¹H NMR (CD₃COCD₃) δ 7.6(2H, d), 7.45(2H, d), 6.0 (1H, dt), 4.25(1H, m), 3.65 (1H, t), 3.5-3.55(1H, m), 3.3-3.35(1H, m), 2.55-2.65(1H, m), 2.15-2.25(1H, m), 1.6-1.7(1H, m), 1.3-1.4(1H, m), 1.2-1.3(1H, m), 0.9(3H, d), 0.8(3H, d).

Step 3: Preparation of N-[(1S)-1-(4-bromophenyl)-2,2-difluoroethyl]-L-leucine

A suspension of H₅IO₆/CrO₃ (5.5 mL of 0.40 M in CH₃CN; see Note below) was cooled to 0 °C and a solution of the alcohol from Step 2 (250 mg) in CH₃CN (3.7 mL) was added dropwise. The mixture was stirred at 0-5 °C for 3.5 hours. After this period, 2.0 mL of the oxidant were added. After 1.5 hours it was poured into Na₂HPO₄ buffer (0.4g in 10 mL) under vigorous stirring and the mixture was extracted with diethyl ether (3 X 20 mL). The combined ether extracts were washed with water and brine (1:1), with dilute aqueous NaHSO₃ and brine. The organic extract was dried with magnesium sulfate, filtered and the solvent was evaporated to dryness to yield a residue that was used without further purification.

Note: The oxidizing reagent (H₅IO₆/CrO₃) was prepared as described in *Tetrahedron Letters* 39 (1998) 5323-5326 but using HPLC grade CH₃CN (contains 0.5% water); no water was added.

¹H NMR (CD₃COCD₃) δ 7.55(2H, d), 7.4(2H, d), 6.05(1H, dt), 3.95-4.05(1H, m), 3.45(1H, t), 2.7-3.0(broad m, NH/OH), 1.85-1.95(1H, m), 1.5(2H, t), 0.95 (3H, d), 0.9(3H, d).

Step 4: Preparation of N²-[(1S)-1-(4-bromophenyl)-2,2-difluoroethyl]-N¹-(1-cyanocyclopropyl)-L-leucinamide

To a DMF (2 mL) solution of the acid from Step 3 (258 mg) were added O-(7-azabenzotriazol-1-yl)-N, N, N', N'-tetramethyluronium hexafluorophosphate (337 mg), 1-aminocyclopropanecarbonitrile hydrochloride (175 mg). After 1 minute of stirring, diisopropylethylamine (0.45 mL) was added dropwise and the mixture was stirred for 16 hours. It was poured into saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 X 15 mL). The combined extracts were washed with brine, dried with magnesium sulfate and the solvent removed in

vacuo. The residue was purified by chromatography on SiO₂ using hexanes and ethyl acetate (80:20 to 50:50).

¹H NMR (CD₃COCD₃) δ 8.05(1H, m), 7.55(2H, d), 7.4(2H, d), 6.05(1H, dt), 3.95-4.05(1H, m), 3.25-3.3(1H, m), 2.4-2.45(1H, m), 1.8-1.9 (1H, m), 1.4-1.55(2H, m), 0.95-1.1 (2H, m), 0.95(6H, t).

Step 5: Preparation of N¹-(1-cyanocyclopropyl)-N²-{(1S)-2,2-difluoro-1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]ethyl}-L-leucinamide.

To a DMF (60 mL) solution of the arylbromide from Step 4 (5.23 g) and of bis(pinacolato)diboron (3.8 g) were added potassium acetate (3.7 g) and PdCl₂dppf (309 mg). A stream of nitrogen was passed through the suspension for 1 minute. The reaction mixture was heated at 80°C for 16h. It was allowed to cool to room temperature and transferred to a sep. funnel. A saturated solution of NaHCO₃ (~120 mL) and EtOAc (100 mL) were added. Organic layer was separated and the aqueous layer was further extracted with 2 portions of EtOAc (2X100mL). Combined organic layers were washed with brine, dried over MgSO₄ and concentrated. Crude material was purified on silica gel (80:20 to 50:50 hex/EtOAc) to yield the desired boronate.

¹H NMR (CD₃COCD₃) δ 8.15(bs, NH), 7.72(2H, d), 7.40(2H, d), 6.02(1H, dt), 3.95(1H, m), 3.25(1H, q), 2.38(1H, m), 1.72(1H, m), 1.27-1.50(16H, m), 0.85-1.05(8H, m).

Step 6: Preparation of N¹-(1-cyanocyclopropyl)-N²-{(1S)-2,2-difluoro-1-[4'-[1-(carboxy)cyclopropyl]biphenyl-4-yl]-ethyl}-L-leucinamide

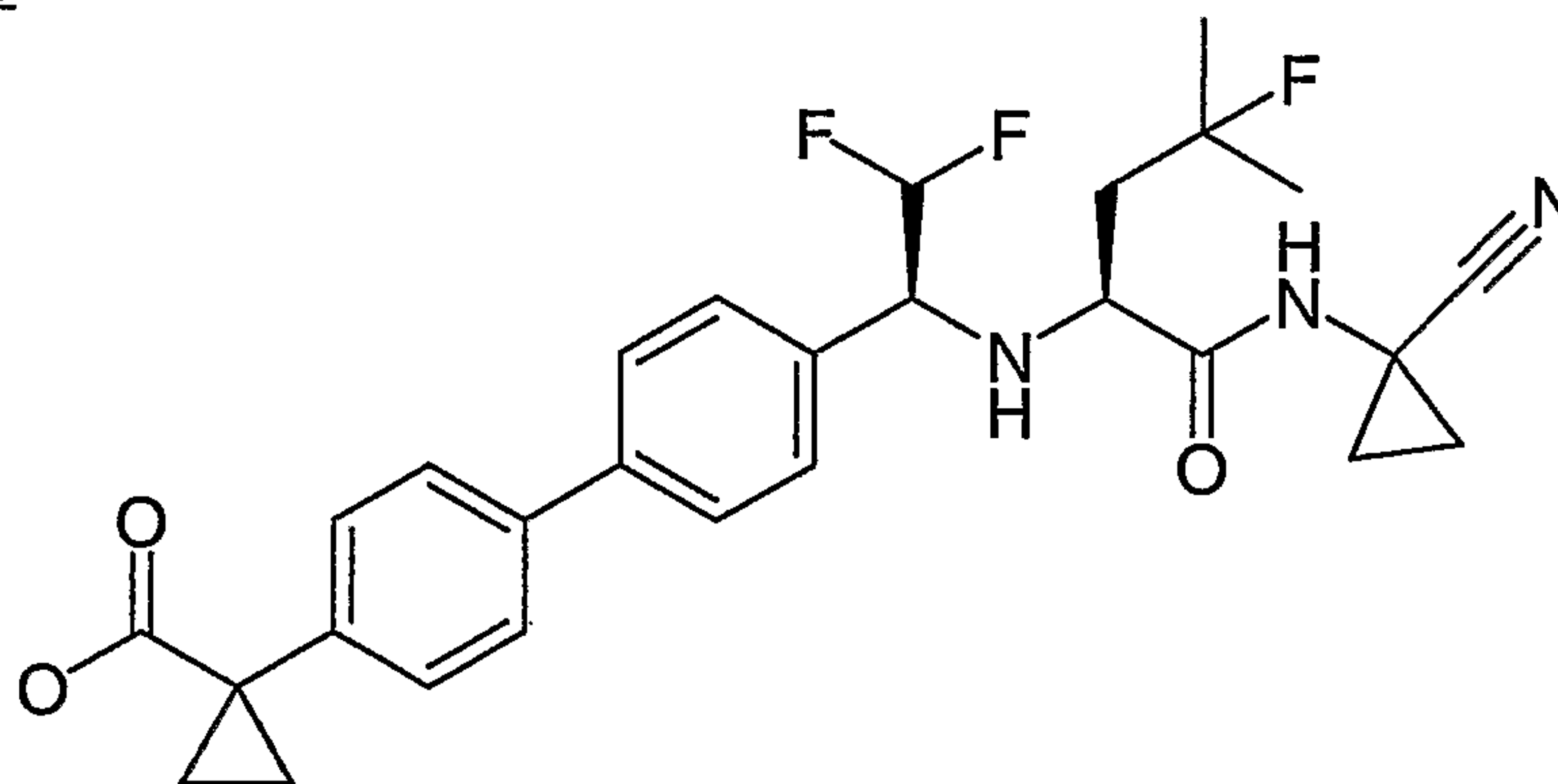
In a sealable tube for microwave, a stream of nitrogen was passed through a suspension made of the aryl boronate from Step 5 (220 mg), 1-(4-bromophenyl)cyclopropanecarboxylic acid (Example 3, Step 2, 70 mg), 2 M Na₂CO₃ (0.65 mL), DMF (4.5 mL) and PdCl₂dppf (11 mg) for 1 minute. The mixture was then heated in microwave (SmithCreator) for 500 seconds (fixed hold time: OFF) at 120°C (absorption level: high). It was cooled to room temperature, diluted with ethyl acetate (20 mL) and poured into a saturated solution of ammonium chloride. The ethyl acetate layer was separated and the aqueous further extracted with ethyl acetate (2 x 15 mL). The combined ethyl acetate extracts were washed with brine and dried with magnesium sulfate. Removal of the solvent left a residue that was purified by chromatography on SiO₂ using a gradient of hexanes and ethyl acetate (90:10 to 30:70 hex/EtOAc).

^1H NMR (CD_3COCD_3) δ 8.13(bs, NH), 7.70 (2H, d), 7.62 (2H, d), 7.51(4H, m), 6.09(1H, td), 4.00(1H, m), 3.33(1H, m), 1.88(1H, m), 1.60 (2H, m), 1.45-1.55(2H, m), 1.38 (2H, m), 1.26 (2H, m), 1.00 (2H, m), 0.94 (6H, m).

EXAMPLE 5

5

N^1 -(1-cyanocyclopropyl)- N^2 -{(1*S*)-2,2-difluoro-1-{4'-[1-(carboxy)cyclopropyl]biphenyl-4-yl}-ethyl}-4-fluoro-L-leucinamide



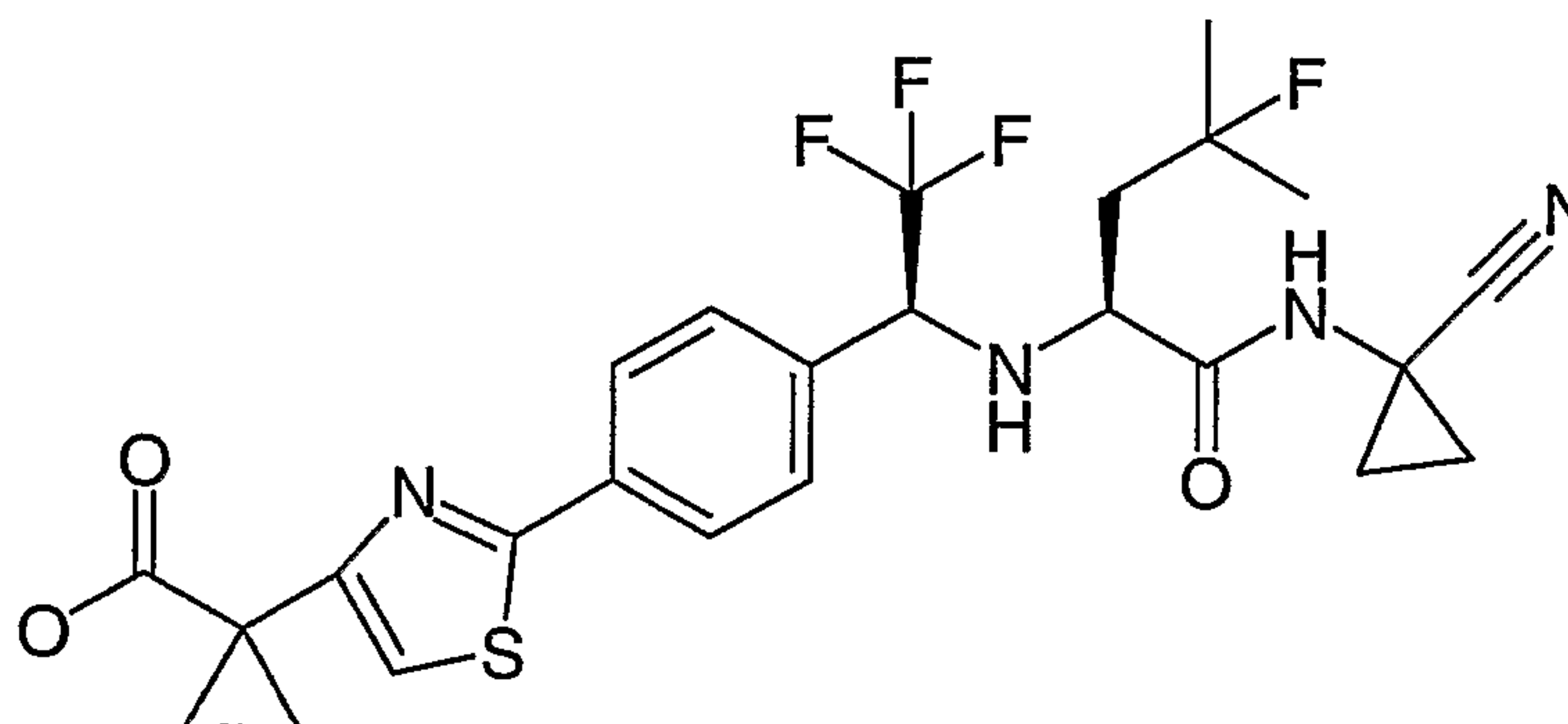
- 10 The title compound was prepared from N^1 -(1-cyanocyclopropyl)- N^2 -{(1*S*)-2,2-difluoro-1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]ethyl}-4-fluoro-L-leucinamide and 1-(4-bromophenyl)cyclopropanecarboxamide as described in Example 4.

- 15 ^1H NMR (500 MHz, acetone d_6): δ 8.2 (s, 1H), 7.7 (d, 2H), 7.62 (d, 2H), 7.55 (d, 2H), 7.5 (d, 2H), 6.25-6.0 (m, 1H), 4.1--4.02(m, 1H), 3.5-3.42(m, 1H), 2.05-1.94 (m, 2H), 1.62-1.56 (m, 2H), 1.5-1.34 (m, 8H), 1.28-1.2 (m, 2H), 1.05-0.92 (m, 2H)

ESI (M+1): 514

EXAMPLE 6

- 20 1-[2-[4-[(1*S*)-1-[[[(1*S*)-1-[(1-cyanocyclopropyl)amino]carbonyl]-3-fluoro-3-methylbutyl]amino]-2,2,2-trifluoroethyl]phenyl]-4-thiazolyl]-cyclopropanecarboxylic acid



Step 1: Ethyl (2-bromo-1,3-thiazol-4-yl)acetate

To a 0 °C mixture of ethyl (2-amino-1,3-thiazol-4-yl)acetate (10 g, 53.7 mmol) and CuBr₂ (14.4 g, 64 mmol) in acetonitrile (56 mL) was slowly added isoamyl nitrite (10.8 mL, 80 mmol).

5 The mixture was warmed to room temperature and stirred overnight, then concentrated, suspended in 1:2 ethyl acetate:hexanes and filtered. Purification by SiO₂ chromatography (5% ethyl acetate/hexanes) provided the title compound.

Step 2: Ethyl 1-(2-bromo-1,3-thiazol-4-yl)cyclopropanecarboxylate

10 To a solution of ethyl (2-bromo-1,3-thiazol-4-yl)acetate (1.0 g, 4 mmol) in DMF (20 mL) was added 60% NaH dispersion (176 mg, 4.4 mmol) followed by dibromoethane (0.38 mL, 4.4 mmol). The mixture was stirred 3h at 50 °C, then overnight at room temperature. An additional equivalent each of NaH and dibromoethane were added, and the mixture was stirred at 55 °C for 2h and cooled. The reaction mixture was partitioned between water and ethyl acetate, washed with brine and dried over
15 MgSO₄. Purification by SiO₂ chromatography (5% ethyl acetate/hexanes) provided the title compound.

Step 3: Ethyl 1-[2-[4-[(1S)-1-[[[(1S)-1-[(1-cyanocyclopropyl)amino]carbonyl]-3-fluoro-3-methylbutyl]amino]-2,2,2-trifluoroethyl]phenyl]-4-thiazolyl]-cyclopropanecarboxylate

20 A solution of ethyl 1-(2-bromo-1,3-thiazol-4-yl)cyclopropanecarboxylate (166 mg, 1.2 mmol) and *N*¹-(1-cyanocyclopropyl)-4-fluoro-*N*²-{(1S)-2,2,2-trifluoro-1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]ethyl}-L-leucinamide (Example 3, Step 3, 250 mg, 0.5 mmol) in DMF (5 mL) and 2M Na₂CO₃ (0.63 mL) was degassed with a stream of nitrogen for 10 min, then PdCl₂(dppf) (41 mg, 0.05 mmol) was added and the mixture heated to 80 °C for 8h. The mixture was cooled and partitioned between ethyl acetate and saturated aqueous ammonium chloride. The organic phase was washed with
25 brine, dried over MgSO₄ and evaporated. Purification by SiO₂ chromatography (30% ethyl acetate/hexanes) provided the title compound.

Step 4: 1-[2-[4-[(1S)-1-[[[(1S)-1-[(1-cyanocyclopropyl)amino]carbonyl]-3-fluoro-3-methylbutyl]amino]-2,2,2-trifluoroethyl]phenyl]-4-thiazolyl]-cyclopropanecarboxylic acid

30 To a solution of ethyl 1-[2-[4-[(1S)-1-[[[(1S)-1-[(1-cyanocyclopropyl)amino]carbonyl]-3-fluoro-3-methylbutyl]amino]-2,2,2-trifluoroethyl]phenyl]-4-thiazolyl]-cyclopropanecarboxylate (100 mg, 0.18 mmol) in 1:1 MeOH/THF (2.5 mL) was added 1M LiOH (1.2 mL) and the mixture was stirred 3h at room temperature. The mixture was acidified with 10% acetic acid, extracted with ethyl acetate, washed

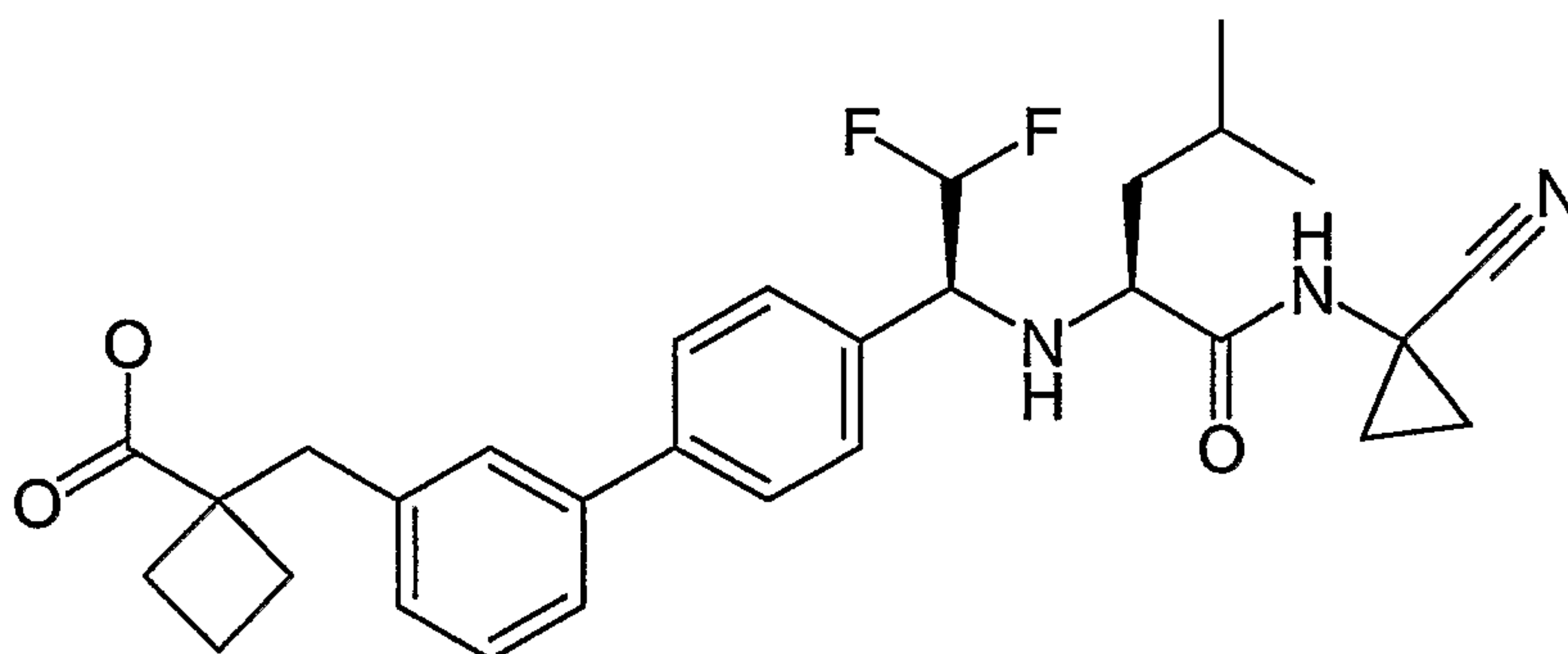
with brine and dried over MgSO_4 . Purification by SiO_2 chromatography (40% ethyl acetate/hexanes + 1% acetic acid) provided the title compound.

^1H NMR (500 MHz, acetone d_6): δ 8.17 (s, 1H), 7.98 (m, 2H), 7.80 (s, 1H), 7.585 (d, 2H), 4.4 (br s, 1H), 3.53 (m, 1H), 2.0 (m, 2H), 1.7 (m, 2H), 1.6 (m, 2H), 1.4 (m, 8H), 1.1 (m, 1H), 0.95 (m, 1H)

MS (+ESI): 538.9 $[\text{M}+1]^+$

EXAMPLE 7

1-[[4'-[(1S)-1-[[[(1S)-1-[(1-cyanocyclopropyl)amino]carbonyl]-3-methylbutyl]amino]-2,2-difluoroethyl][1,1'-biphenyl]-3-yl]methyl]-cyclobutanecarboxylic acid



Step 1: Methyl 1-(3-bromobenzyl)cyclobutanecarboxylate

To a -78°C solution of LiHMDS (1M in THF, 50 mL, 50 mmol) is added a solution of methyl cyclobutanecarboxylate (6.7 g, 52 mmol) in THF (200 mL). After 30 min, a solution of 3-bromobenzyl bromide (13.1 g, 52 mmol) in THF (100 mL) is added and the mixture is warmed to room temperature. The mixture is partitioned between ether and 1M HCl, washed with aq NaHCO_3 , brine and dried over MgSO_4 . Purification by SiO_2 chromatography (10% ethyl acetate/hexanes) provided the title compound.

Step 2: Methyl 1-[[4'-[(1S)-1-[[[(1S)-1-[(1-cyanocyclopropyl)amino]carbonyl]-3-methylbutyl]amino]-2,2-difluoroethyl][1,1'-biphenyl]-3-yl]methyl]-cyclobutanecarboxylate

Using the bromide from Step 1, the title compound was prepared as described in Example 4, Step 6.

Step 3: 4'-[(1S)-1-[[[(1S)-1-[(1-cyanocyclopropyl)amino]carbonyl]-3-methylbutyl]amino]-2,2-difluoroethyl][1,1'-biphenyl]-3-yl]methyl]-cyclobutanecarboxylic acid

The methyl ester from Step 2 was hydrolyzed as described in Example 6, Step 4 to provide the title compound.

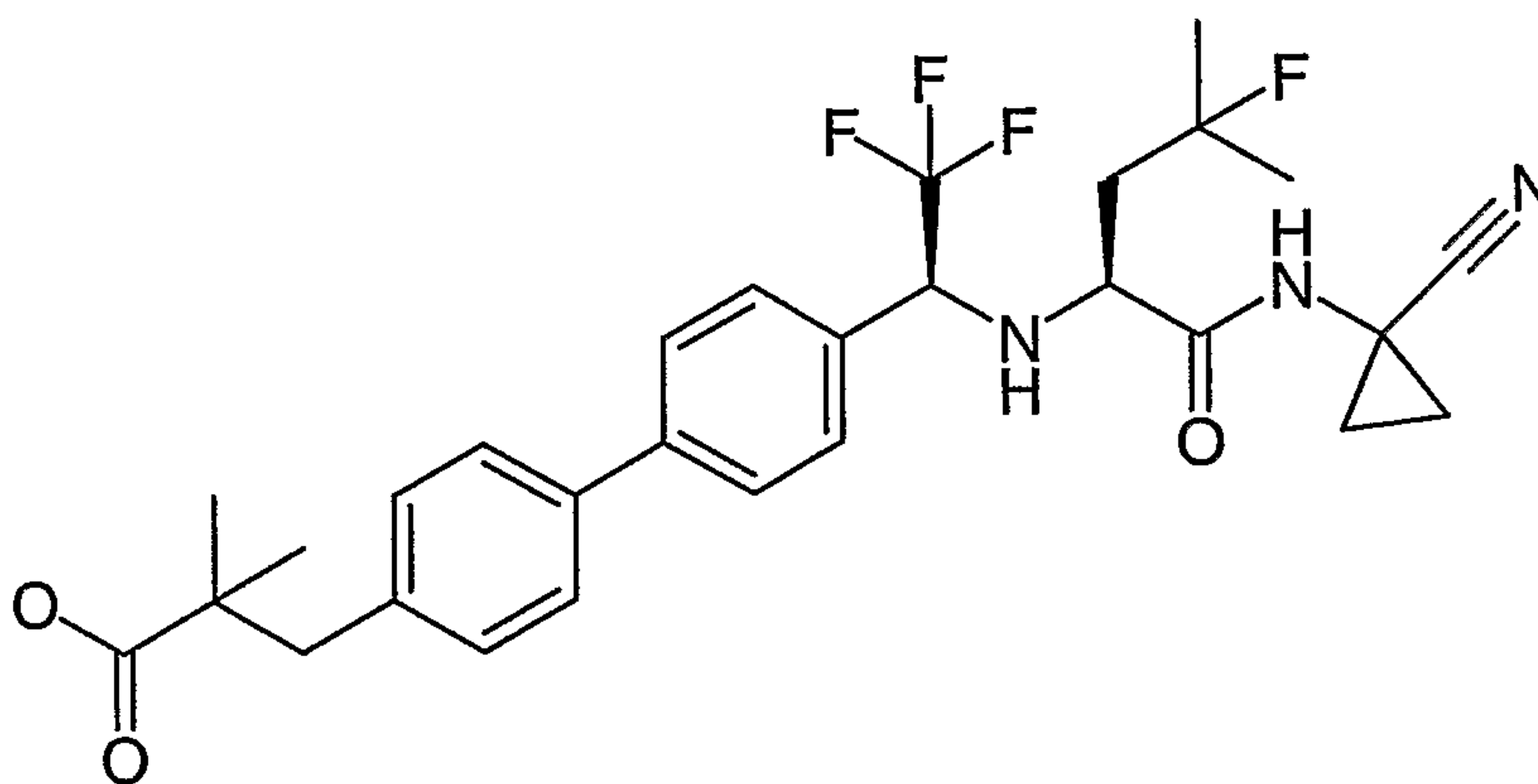
5

¹H NMR (500 MHz, acetone d₆): δ 8.17 (s, 1H), 7.65 (m, 2H), 7.52 (m, 4H), 7.38 (m, 1H), 7.27 (m, 1H), 6.09 (dt, 1H), 4.0 (m, 1H), 3.33 (m, 1H), 3.25 (s, 2H), 2.43 (m, 2H), 2.15 (m, 2H), 1.9 (m, 3H), 1.5 (m, 2H), 1.3 (m, 2H), 1.4 (m, 8H), 1.0 (m, 2H), 0.9 (m, 6H)

10

EXAMPLE 8

4'-[(1S)-1-[[[(1S)-1-[(1-cyanocyclopropyl)amino]carbonyl]-3-fluoro-3-methylbutyl]amino]-2,2,2-trifluoroethyl]-α,α-dimethyl-[1,1'-biphenyl]-4-propanoic acid



15

Step 1: 3-(4-bromophenyl)-2,2-dimethylpropanoic acid

A THF (10 mL) solution of ethyl isobutyrate (2.32 g) was added to -78 °C LiHMDS (20 mL of 1M THF solution) in THF (60 mL). The mixture was reacted for 60 minutes and 4-bromobenzyl bromide (6.25 g) as a THF (10 mL) solution was added. The mixture was reacted 1 hour at -78 °C and then 2 hours at 0 °C. The mixture was poured in ice and 1N HCl (100 mL). The mixture was filtered. The ethyl acetate layer was separated and the aqueous further extracted with ethyl acetate. The combined ethyl acetate layers were washed with brine, dried with magnesium sulphate, filtered and the solvent removed *in vacuo*. The residue was suspended in diethyl ether (50 mL), filtered and concentrated to dryness. The residue was dissolved in ethanol (70 mL) and 2M LiOH (15 mL) added. The reaction mixture was heated at 70 °C for 2 hours then cooled to room temperature. 1N NaOH (20 mL) was added and the mixture was washed with i-PrOAc (2x25 mL). The aqueous was cooled in ice, acidified with 1N HCl and extracted with ethyl acetate (2x25 mL). The combined extracts were washed with brine and

25

dried with magnesium sulfate. Removal of the solvent left a residue which was triturated in hexanes to yield the title compound.

¹H NMR (CD₃COCD₃) δ 10.65-10.75(1H, COOH), 7.35-7.45(2H, d), 7.1-7.2(2H, d), 3.85(2H, s), 1.15-1.2(6H, s).

Step 2: 4'-[(1S)-1-[[[(1S)-1-[(1-cyanocyclopropyl)amino]carbonyl]-3-fluoro-3-methylbutyl]amino]-2,2,2-trifluoroethyl]-α,α-dimethyl-[1,1'-biphenyl]-4-propanoic acid

A stream of nitrogen was passed through a DMF (4 mL) solution of the boronate from Step 3, Example 3 (249 mg), 3-(4-bromophenyl)-2,2-dimethylpropanoic acid (153 mg) and 2 M Na₂CO₃ (800 μL) for 15 minutes. The catalyst [1, 1'-bis(diphenylphosphino)-ferrocene]dichloropalladium(II), complex (1:1) with dichloromethane (50 mg) was then added and the mixture was warmed to 80 °C for 3 hours under nitrogen. The mixture was cooled to room temperature, poured into ice (10 g), water (20 mL), dilute hydrochloric acid (5 mL) and ethyl acetate (10 mL). It was then extracted with ethyl acetate (2 x 10 mL). The combined extracts were washed with brine and dried with magnesium sulfate. Removal of the solvent left a residue which was purified by chromatography on SiO₂ using ethyl acetate, hexanes and acetic acid (1:2:0.01) as eluant to yield the title compound.

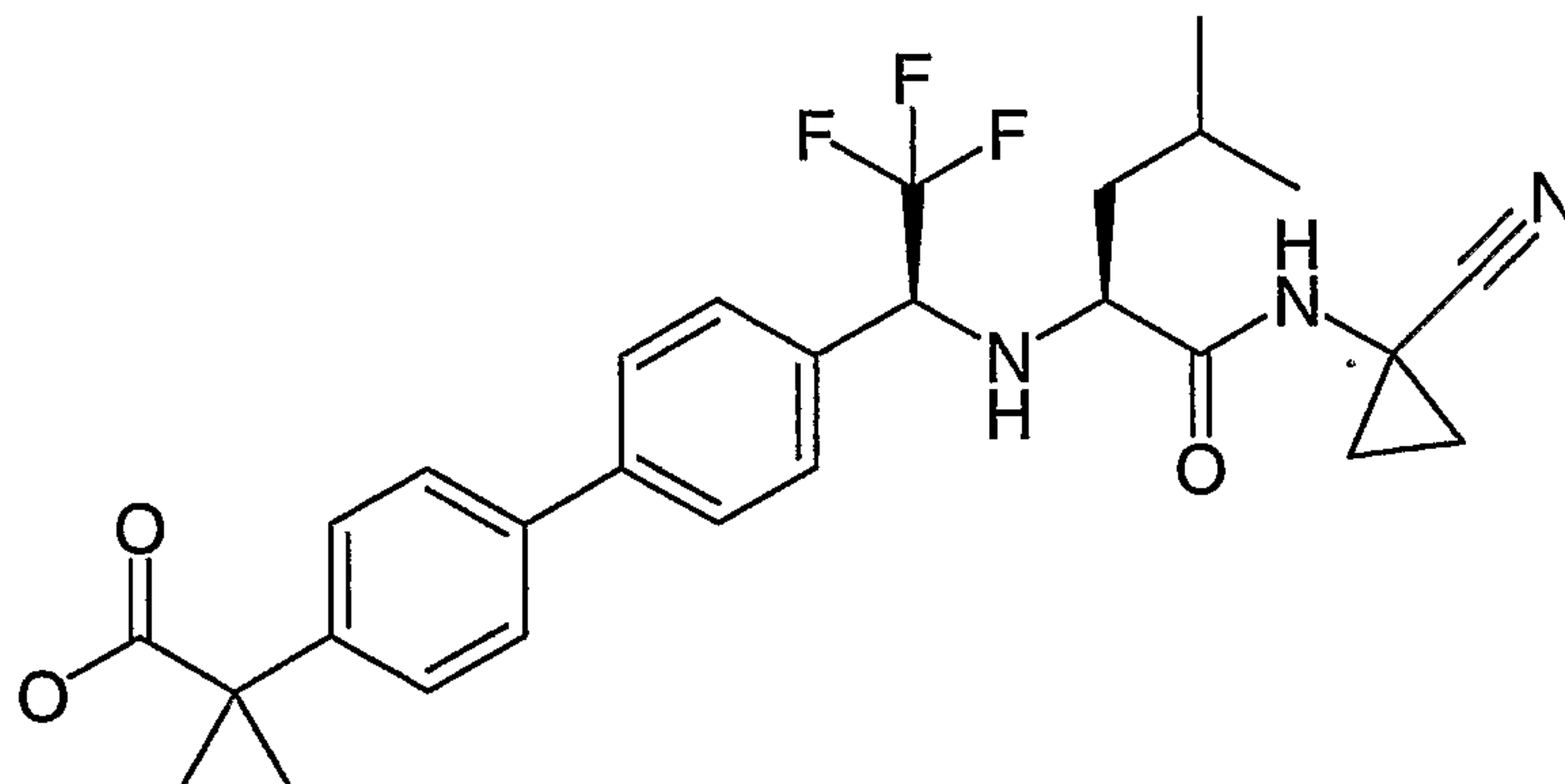
¹H NMR (CD₃COCD₃) δ 8.2(1H, bs), 7.7(2H, d), 7.5-7 (4H, m), 7.55-7.6(2H, d), 7.35(2H, d), 4.35-4.45(1H, m), 3.5-3.6(1H, m), 2.95(2H, bs), 2.75-2.85(1H, m), 1.9-2.1(2H, m), 1.4-1.5(6H, m), 1.3-1.4(1H, m), 1.2(6H, s), 0.9-1.15(2H, m).

MS (+APCI) : 548.2(M+1)⁺

EXAMPLE 9

1-[4'-[(1S)-1-[[[(1S)-1-[(1-cyanocyclopropyl)amino]carbonyl]-3-methylbutyl]amino]-2,2,2-
trifluoroethyl][1,1'-biphenyl]-4-yl]-cyclopropanecarboxylic acid

5



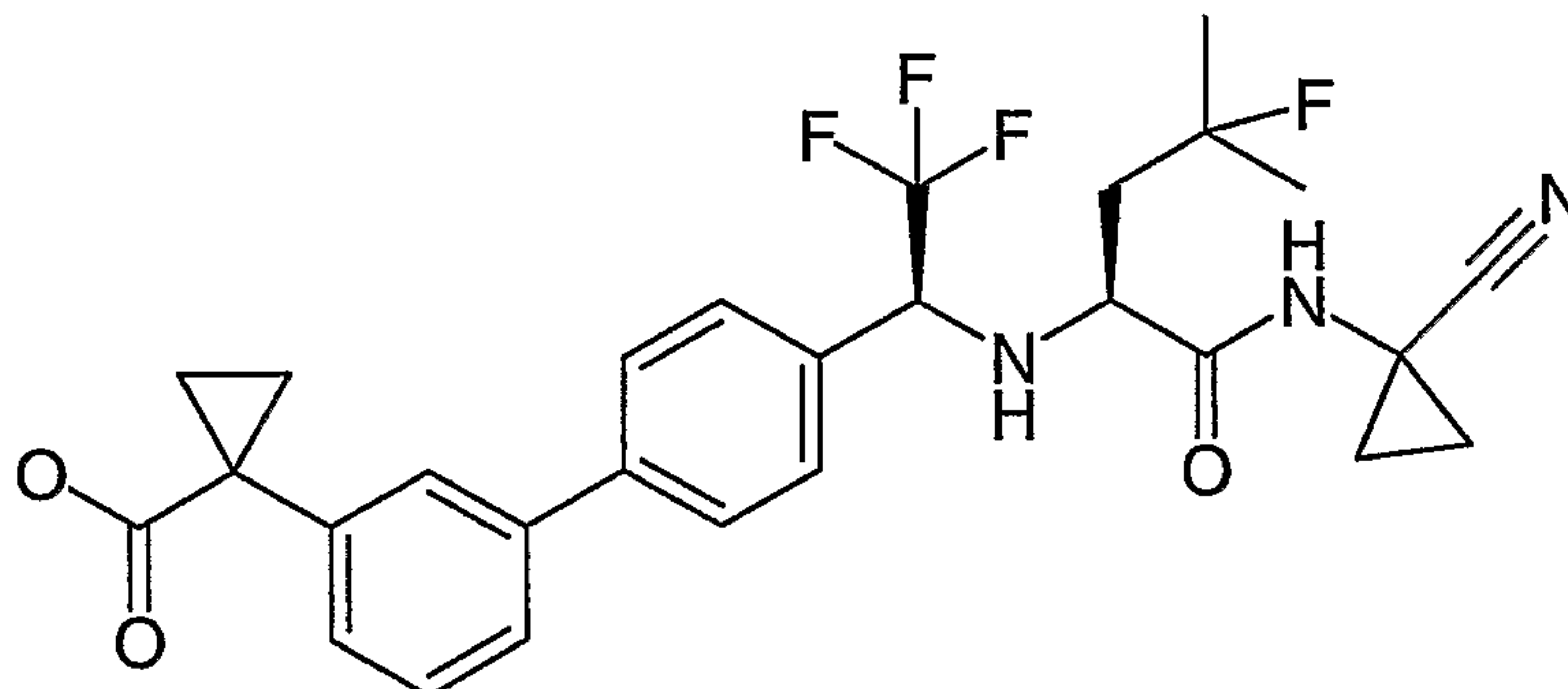
The title compound was prepared as described in Example 3.

10 MS data:

EXAMPLE 10

1-[4'-[(1S)-1-[[[(1S)-1-[(1-cyanocyclopropyl)amino]carbonyl]-3-fluoro-3-methylbutyl]amino]-2,2,2-
trifluoroethyl][1,1'-biphenyl]-3-yl]-cyclopropanecarboxylic acid

15



20 Step 1: 1-(3-bromophenyl)cyclopropanecarbonitrile

To a room temperature solution of 3-bromophenylacetonitrile (15.0 g) in a solution of 18.4 mL of sodium hydroxide (50% in water w/w) were added 1-bromo-2-chloroethane and (9.5 mL) and benzyltriethylammonium chloride (522 mg). The mixture was heated at 60 °C overnight. The reaction mixture was cooled to room temperature and diethyl ether was added (300 mL) and partitioned. The ether layer was washed with water (100 mL), 10% aq. HCl (100 mL) and brine, then dried over magnesium

25

sulfate and the solvent removed in vacuo. The residue was purified by swish using diethyl ether and hexanes to yield the title compound.

¹H NMR (CD₃COCD₃) δ 7.56(1H, s), 7.53(1H, d), 7.36-7.43(2H, m), 1.79-1.83(2H, m), 1.58-1.64(2H, m).

Step 2: 1-(3-bromophenyl)cyclopropanecarboxylic acid

To a room temperature solution of 1-(3-bromophenyl)cyclopropanecarbonitrile from Step 1 (12 g) in ethyl alcohol (100 mL) was added a solution of 50 mL of sodium hydroxide (25% NaOH in water w/w). The mixture was heated at 100 °C overnight. It was cooled to room temperature and poured into ice and 1N HCl, and extracted with dichloromethane (2 x 100 mL). The combined extracts were washed with brine, dried over magnesium sulfate and the solvent removed in vacuo to yield the title compound.

¹H NMR (CD₃COCD₃) δ 10.80 (1H, bs), 7.60(1H, s), 7.43(1H, d), 7.41(1H, d), 7.29(1H, t), 1.58-1.61(2H, m), 1.23-1.28(2H, m).

Step 3: 1-[4'-[(1S)-1-[[[(1S)-1-[(1-cyanocyclopropyl)amino]carbonyl]-3-fluoro-3-methylbutyl]amino]-2,2,2-trifluoroethyl]][1,1'-biphenyl]-3-yl]-cyclopropanecarboxylic acid

A stream of nitrogen was passed through a solution of DMF (4 mL) of the boronate from Example 3, Step 3 (150 mg), 1-(4-bromophenyl)cyclopropanecarboxylic acid (65 mg) and 2 M Na₂CO₃ (400 µL) for 15 minutes followed by the addition of [1, 1'-bis(diphenylphosphino)-ferrocene]dichloropalladium(II), complex (1:1) with dichloromethane (12 mg). The mixture was warmed to 80 °C for 3 hours under nitrogen. The mixture was cooled to room temperature, poured into ice (10 g) and 1.0 N HCl (15 mL) and extracted with 50 % ethyl acetate in diethyl ether (3 x 30 mL). The combined extracts were washed with brine and dried with magnesium sulfate. Removal of the solvent left a residue that was purified by chromatography on SiO₂ using ethyl acetate, hexanes and acetic acid (1:3:1% to 1:2:1%) as eluants, followed by a swish using diethyl ether to yield the title compound.

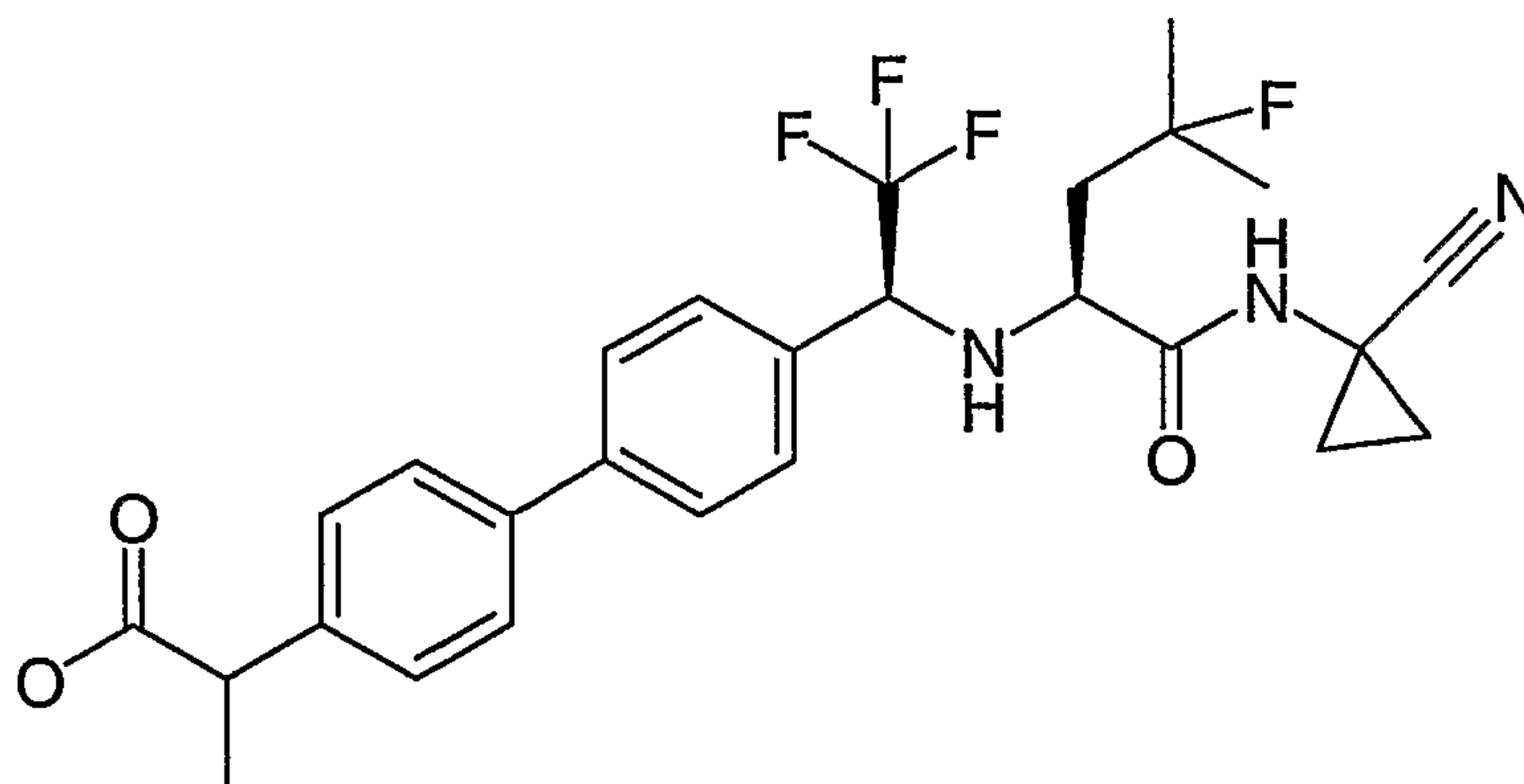
¹H NMR (CD₃COCD₃) δ 10.70(1H, bs), 8.17(1H, bs), 7.70-7.77(3H, m), 7.53-7.62(3H, m), 7.41-7.47(2H, m), 4.37-4.43 (1H, m), 3.52-3.59 (1H, m), 1.95-2.05 (2H, m), 1.59-1.65(2H, m), 1.40-1.50(6H, m), 1.35-1.40(2H, m), 1.28-1.33(2H, m), 1.07-1.11(1H, m), 0.93-0.99(1H, m).

MS (+APCI): 532.4 (M+1)⁺.

EXAMPLE 11

4'-[(1*S*)-1-[(1*S*)-1-[(1-cyanocyclopropyl)amino]carbonyl]-3-fluoro-3-methylbutyl]amino]-2,2,2-trifluoroethyl]- α -methyl-[1,1'-biphenyl]-4-acetic acid

5

Step 1: Methyl (4-bromophenyl)acetate

Acetyl chloride (10 mL) was added to methanol (100 mL) at -78 °C and stirred for 30 minutes followed by the addition of 4-bromophenylacetic acid. The mixture was then warmed up to room temperature and stirred overnight. Removal of the solvent left a residue that was dissolved in diethyl ether. The mixture was dried with magnesium sulfate and the solvent removed in vacuo to yield the title compound.

¹H NMR (CD₃COCD₃) δ 7.52(2H, d), 7.29(2H, d), 3.68(2H, s), 3.50(3H, s).

Step 2: Methyl 2-(4-bromophenyl) propanoate

To a 0 °C solution of diisopropylamine (3.9 mL) in THF (100 mL) was slowly added butyl lithium (11.1 mL). The reaction mixture was stirred at 0 °C for 15 minutes. It was cooled to -78 °C and the solution of ester from Step 1 (5.8 g) in THF (50 mL) was slowly added. The mixture was stirred at -78 °C for 30 minutes. Then a solution of iodomethane (6.3 mL) in THF (50 mL) was added dropwise and the mixture was stirred at -78 °C for 30 minutes then warmed up slowly to room temperature and stirred for 1 hour. The reaction mixture was poured into ice (50 g) and saturated aqueous ammonium chloride (200 mL), extracted with ethyl acetate (3 x 100 mL). The combined extracts were washed with brine, dried with magnesium sulfate and the solvent removed in vacuo. The residue was purified by chromatography on SiO₂ (Combiflash) using ethyl acetate in hexanes (2 to 15 % for 20 minutes) as eluants to yield the title compound.

¹H NMR (CD₃COCD₃) δ 7.55(2H, d), 7.30(2H, d), 3.81(1H, q), 3.64(3H, s), 1.45(3H, d).

Step 3: 2-(4-Bromophenyl) propanoic acid

To a 0 °C solution of methyl 2-(4-bromophenyl) propanoate from Step 2 (2.0 g) in THF (24 mL) and methyl alcohol (12 mL) was added a solution of 16.5 mL of lithium hydroxide (1.0 N). The mixture was stirred at room temperature for 2 hours. Then the reaction mixture was poured into ice and 1N HCl, and extracted with dichloromethane (2 x 50 mL). The combined extracts were washed with brine, dried with magnesium sulfate and the solvent removed in vacuo to yield the title compound.

¹H NMR (CD₃COCD₃) δ 7.52(2H, d), 7.35(2H, d), 3.80(1H, q), 1.45(3H, d).

Step 4: 4'-[(1*S*)-1-[[[(1*S*)-1-[(1-cyanocyclopropyl)amino]carbonyl]-3-fluoro-3-methylbutyl]amino]-2,2,2-trifluoroethyl]-α-methyl-[1,1'-biphenyl]-4-acetic acid

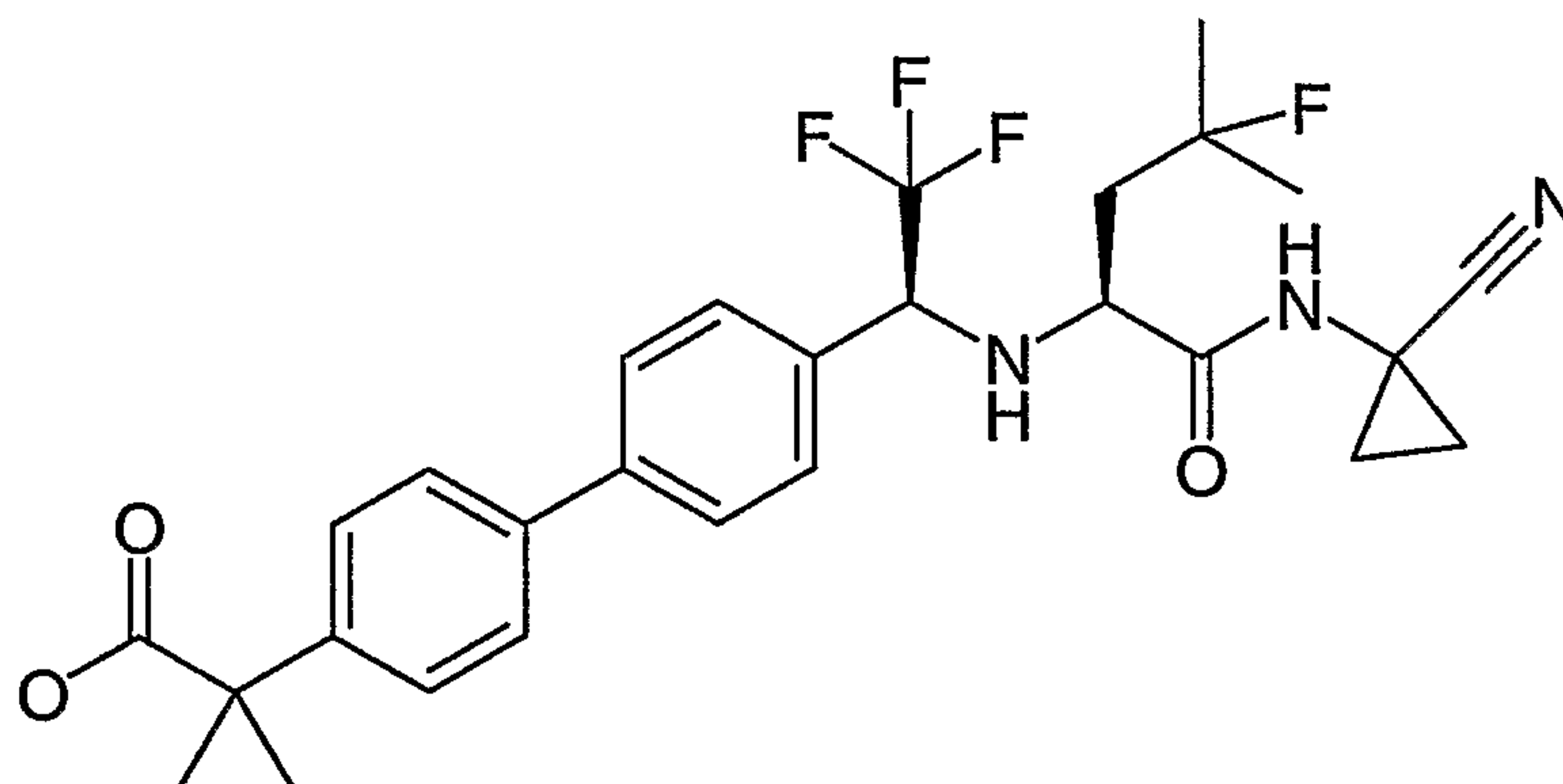
A stream of nitrogen was passed through a solution of DMF (4 mL) of the boronate from Example 3, Step 3 (137 mg), 2-(4-bromophenyl) propanoic acid from Step 3 (62 mg) and 2 M Na₂CO₃ (350 μL) for 15 minutes followed by the addition of [1, 1'-bis(diphenylphosphino)-ferrocene]dichloropalladium(II), complex (1:1) with dichloromethane (11 mg). The mixture was warmed to 80 °C for 3 hours under nitrogen. The mixture was cooled to room temperature, poured into ice (10 g) and 1.0 N hydrogen chloride (15 mL) and extracted with 50 % ethyl acetate in diethyl ether (3 X 30 mL). The combined extracts were washed with brine and dried with magnesium sulfate. Removal of the solvent left a residue that was purified by chromatography on SiO₂ using ethyl acetate, hexanes and acetic acid (1:3:1% to 1:1:1%) as eluants, followed by a swish using diethyl ether to yield the title compound.

¹H NMR (CD₃COCD₃) δ 10.80(1H, bs), 8.16(1H, bs), 7.70(2H, d), 7.68(2H, d), 7.58(2H, d), 7.48(2H, d), 4.36-4.45 (1H, m), 3.85(1H, q), 3.50-3.60 (1H, m), 1.93-2.05 (2H, m), 1.52 (3H, d), 1.42-1.50(6H, m), 1.32-1.42(2H, m), 1.06-1.11(1H, m), 0.89-0.97(1H, m).

MS (-ESI): 518.4 (M-1)⁺.

EXAMPLE 12

4'-[(1*S*)-1-[[[(1*S*)-1-[(1-cyanocyclopropyl)amino]carbonyl]-3-fluoro-3-methylbutyl]amino]-2,2,2-trifluoroethyl]- α,α -dimethyl-[1,1'-biphenyl]-4-acetic acid



Step 1: 2-(4-Bromophenyl)-2-methylpropanoic acid

To a 0 °C solution of diisopropylamine (1.52 mL) in THF (50 mL) was slowly added butyllithium (4.3 mL). The reaction mixture was stirred at 0 °C for 15 minutes. It was cooled to -78 °C and a solution of methyl 2-(4-bromophenyl) propanoate from Example 11 Step 2 (2.4 g) in THF (25 mL) was slowly added. The mixture was stirred at -78 °C for 30 minutes. Then a solution of iodomethane (2.5 mL) in THF (25 mL) was added dropwise and the mixture was stirred at -78 °C for 30 minutes then warmed up slowly to room temperature and stirred for 1 hour. ¹H NMR showed 50% conversion. The reaction mixture was cooled to 0 °C and 20 mL of potassium *t*-butoxide (1.0 M in THF) was added dropwise. The mixture was stirred at 0 °C for 30 minutes, warmed up to room temperature and stirred for 1 hour. The reaction mixture was poured into ice (50 g) and saturated aqueous ammonium chloride (100 mL), extracted with ethyl acetate (3 x 100 mL). The combined extracts were washed with brine, dried with magnesium sulfate and the solvent removed in vacuo to yield a residue which was diluted with THF (30 mL) and methyl alcohol (15 mL). The solution was cooled to 0 °C and 20 mL of lithium hydroxide (1.0 N) was added. The mixture was stirred at room temperature for 3 hours. Then the reaction mixture was poured into ice and 1N HCl and extracted with dichloromethane (2 x 100 mL). The combined extracts were washed with brine, dried with magnesium sulfate and the solvent removed in vacuo. The residue was purified by swish using diethyl ether and hexanes to yield the title compound.

¹H NMR (CD₃COCD₃) δ 10.85(1H, bs), 7.53(2H, d), 7.48(2H, d), 1.50(6H, s).

Step 2: 4'-[(1S)-1-[[[(1S)-1-[[[(1-cyanocyclopropyl)amino]carbonyl]-3-fluoro-3-methylbutyl]amino]-2,2,2-trifluoroethyl]- α,α -dimethyl-[1,1'-biphenyl]-4-acetic acid

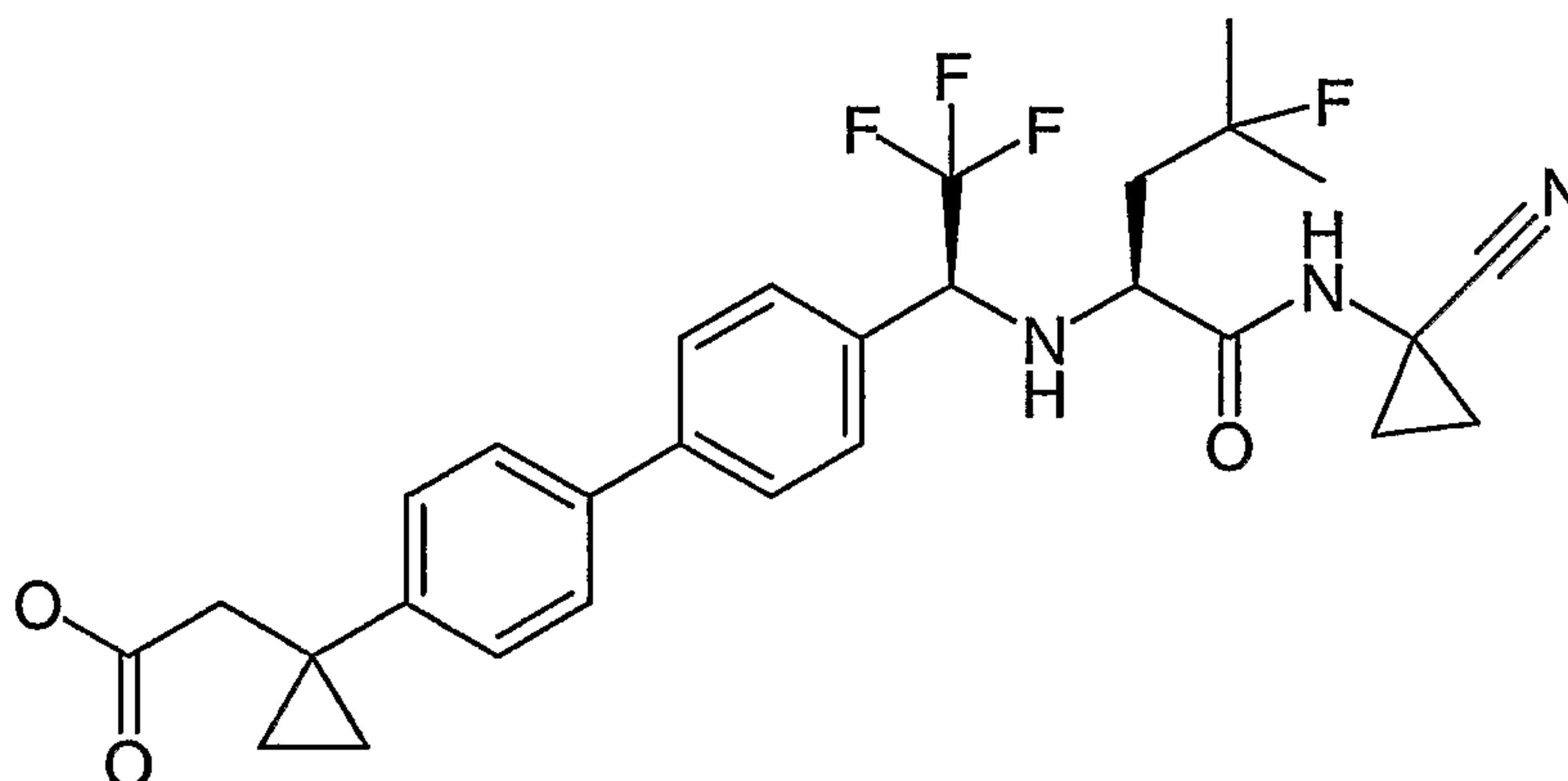
A stream of nitrogen was passed through a solution of DMF (4 mL) of the boronate from Example 3, Step 3 (160 mg), 2-(4-bromophenyl)-2-methylpropanoic acid from Step 1 (77 mg) and 2 M Na₂CO₃ (400 μ L) for 15 minutes followed by the addition of [1, 1'-bis(diphenylphosphino)-ferrocene]dichloropalladium(II), complex (1:1) with dichloromethane (13 mg). The mixture was warmed to 80 °C for 3 hours under nitrogen. The mixture was cooled to room temperature, poured into ice (10 g) and 1.0 N HCl (15 mL) and extracted with 50 % ethyl acetate in diethyl ether (3 x 30 mL). The combined extracts were washed with brine and dried with magnesium sulfate. Removal of the solvent left a residue that was purified by chromatography on SiO₂ using ethyl acetate, hexanes and acetic acid (1:3:1% to 1:1:1%) as eluants, followed by a swish using diethyl ether to yield the title compound.

¹H NMR (CD₃COCD₃) δ 10.80(1H, bs), 8.17(1H, bs), 7.73(2H, d), 7.69(2H, d), 7.57(2H, d), 7.55(2H, d), 4.36-4.43 (1H, m), 3.54-3.60 (1H, m), 1.93-2.05 (2H, m), 1.63 (6H, s), 1.42-1.50(6H, m), 1.30-1.40(2H, m), 1.06-1.11(1H, m), 0.90-0.97(1H, m); leucine NH not observed.

MS (+APCI): 534.2 (M+1)⁺.

EXAMPLE 13

Synthesis of 1-[4'-[(1S)-1-[[[(1S)-1-[[[(1-cyanocyclopropyl)amino]carbonyl]-3-fluoro-3-methylbutyl]amino]-2,2,2-trifluoroethyl][1,1'-biphenyl]-4-yl]-cyclopropaneacetic acid



Step 1: 1-(4-bromophenyl)-cyclopropanemethanol

To a -10 °C solution of 1-(4-bromophenyl)-cyclopropanecarboxylic acid (1.2 g) in 1,2-dimethoxyethane (25 mL) was added successively N, N-diisopropylethylamine (1.2 mL) and isobutyl chloroformate (0.778 mL). After 0.5 hour the mixture was filtered and the filtrate cooled to -30 °C.

Sodium borohydride (0.185 g) in water (5 mL) was added and the mixture reacted 1 hour. It was then warmed to room temperature and poured in water (100 mL) and 10 % NaHCO₃ (20 mL). It was extracted with ethyl acetate (2 X 30 mL) and the combined layers were washed with brine, dried with magnesium sulphate and the solvent were removed *in vacuo*. The residue was triturated in hexanes to yield a residue
 5 pure enough to be used in the next step.

¹H NMR (CD₃COCD₃) δ 7.45(2H, d), 7.35(2H, d), 4.7-4.8(1H, OH), 3.65(2H, bs), 0.75-0.95(4H, m).

Step 2: 1-(4-bromophenyl)cyclopropanecarbonitrile

To a -78 °C solution of 1-(4-bromophenyl)-cyclopropanemethanol (0.225 g) in dichloromethane (5 mL) was added triethylamine (0.163 mL) followed by methanesulfonyl chloride (0.085 mL). The mixture was reacted 1 hour at -78 °C and 1 hour at 0 °C. It was poured on ice and 1N HCl (20 mL) and extracted in dichloromethane (2 X 25 mL). The combined organic layers were washed with NaHCO₃, brine and dried with magnesium sulphate. After removal of the solvent, the residue was
 15 dissolved in DMF (4 mL) and sodium cyanide (0.147 g) was added. The mixture was heated at 70 °C for 2 hours and then cooled to room temperature. It was poured in water and extracted with ethyl acetate (2 x 25 mL). The combined extracts were washed with brine, dried with magnesium sulphate and the solvent removed *in vacuo*. The residue was passed on a short bed of silica gel eluting with ethyl acetate and hexanes (1:5) to yield the title compound.

¹H NMR (CD₃COCD₃) δ 7.5-7.55(2H, d), 7.35-7.4(2H, d), 2.85(2H, s), 0.95-1.05(4H, m).

Step 3: [1-(4-bromophenyl)cyclopropyl]acetic acid

An ethanol (4 mL) solution of 1-(4-bromophenyl)cyclopropanecarbonitrile (0.59 g) containing water (0.5 mL) and KOH (0.566 g) was heated at 110 °C for 16 hours. Most ethanol was removed *in vacuo* and to the residue was added water (50 mL). The mixture was acidified to pH 4-5 and then extracted twice with ethyl acetate. The combined extracts were washed with brine, dried with magnesium sulphate and the solvent removed *in vacuo*. The residue used as such in the next step.

¹H NMR (CD₃COCD₃) δ 7.4(2H, d), 7.25-7.3(2H, d), 2.6(2H, s), 0.85-0.95(4H, m).

Step 4: 1-[4'-[(1S)-1-[[[(1S)-1-[(1-cyanocyclopropyl)amino]carbonyl]-3-fluoro-3-methylbutyl]amino]-2,2,2-trifluoroethyl][1,1'-biphenyl]-4-yl]-cyclopropaneacetic acid

A stream of nitrogen was passed through a DMF (4 mL) solution of the boronate from
 35 Step 3, Example 3 (.249 g), [1-(4-bromophenyl)cyclopropyl]acetic acid (0.153 g) and 2 M Na₂CO₃ (800

μL) for 15 minutes. The catalyst [1, 1'-bis(diphenylphosphino)-ferrocene]dichloropalladium(II), complex (1:1) with dichloromethane (50 m g) was then added and the mixture was warmed to 80 °C for 3 hours under nitrogen. The mixture was cooled to room temperature, poured into ice (10 g), water (20 mL), dilute hydrochloric acid (5 mL) and ethyl acetate (10 mL). It was then extracted with ethyl acetate (2 X 10 mL). The combined extracts were washed with brine and dried with magnesium sulfate. Removal of the solvent left a residue which was purified by chromatography on SiO₂ using ethyl acetate, hexanes and acetic acid (2:3:0.01) as eluant followed by triturating in diethyl ether and hexanes to yield the title compound.

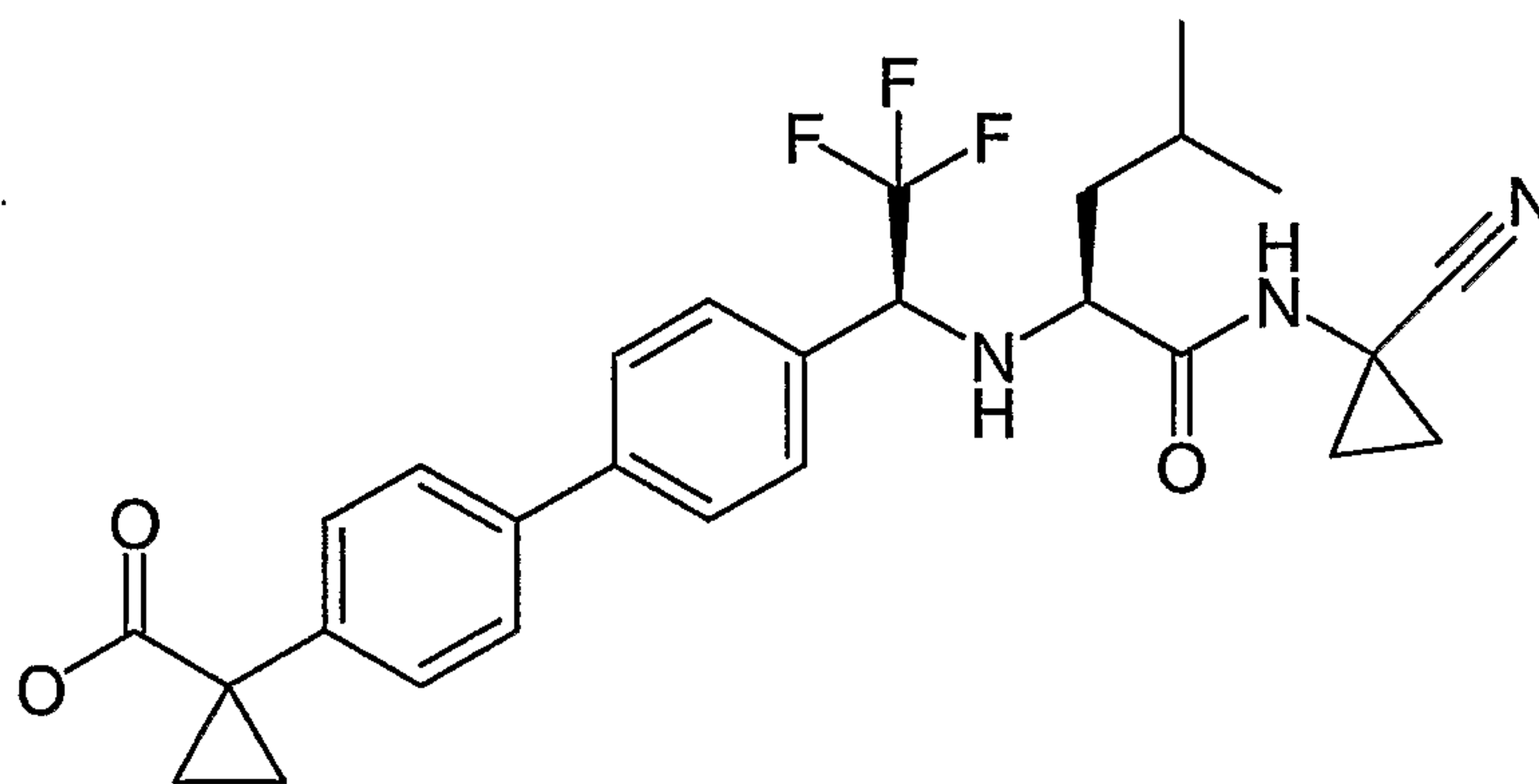
¹H NMR (CD₃COCD₃) δ 8.15(1H, NH), 7.65(2H, d), 7.6(2H, d), 7.5(2H, d), 7.4(2H, d), 4.3-4.4(1H, m), 3.5(1H, m), 3.8-3.9(1H, NH), 2.55(2H, s), 1.35-1.5(6H, m), 0.8-1.35(8H, m).

MS (+ESI) : 546.0 (M+1)⁺

15

EXAMPLE 14

1-[4'-[(1S)-1-[[[(1S)-1-[(1-cyanocyclopropyl)amino]carbonyl]-3-methylbutyl]amino]-2,2,2-trifluoroethyl][1,1'-biphenyl]-4-yl]-cyclopropanecarboxylic acid



20

The title compound was prepared as described in Example 3

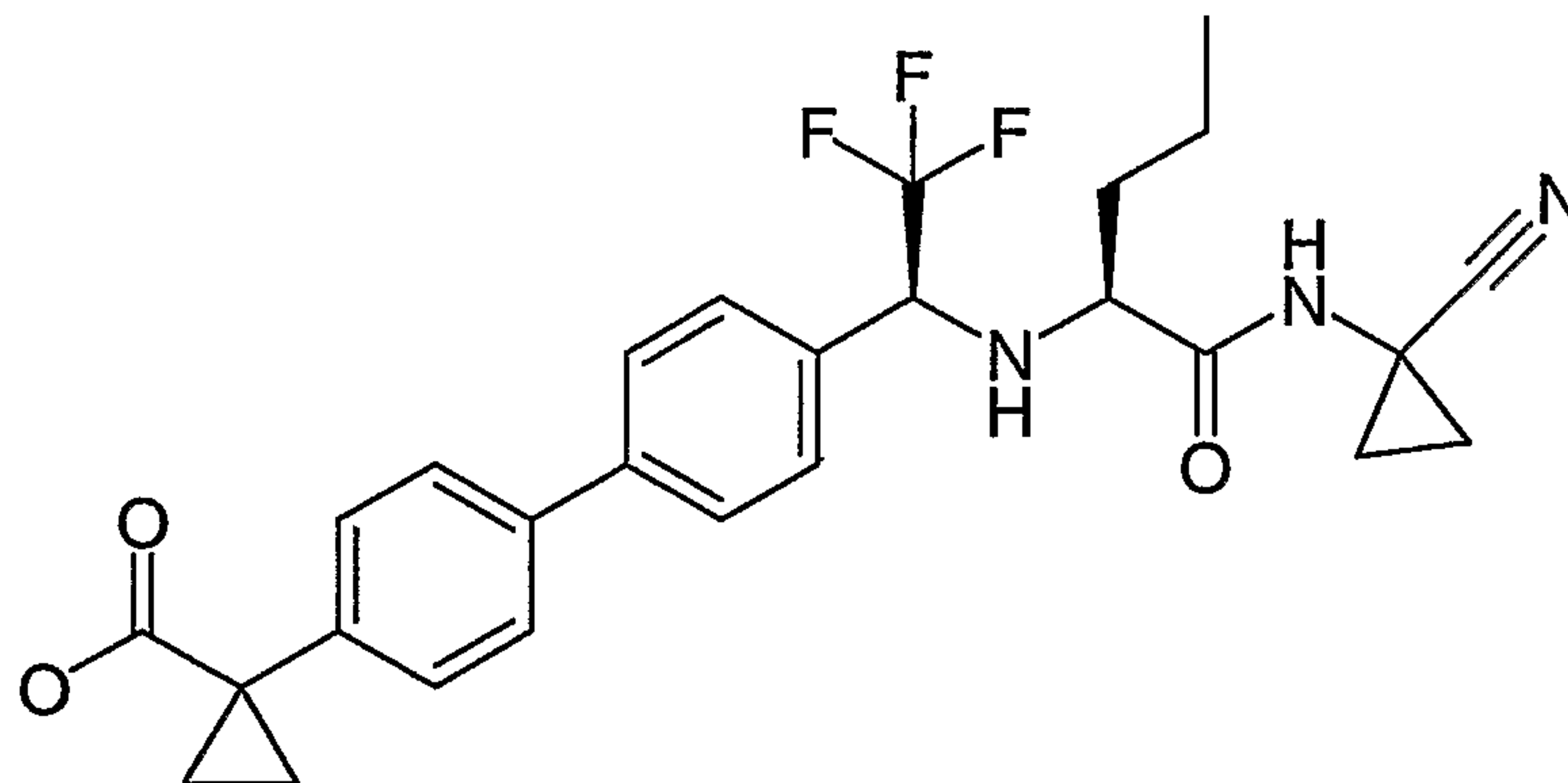
MS (+APCI): 514.2 (M+1)⁺.

25

EXAMPLE 15

1-[4'-[(1S)-1-[[[(1S)-1-[(1-cyanocyclopropyl)amino]carbonyl]butyl]amino]-2,2,2-trifluoroethyl]][1,1'-biphenyl]-4-yl]-cyclopropanecarboxylic acid

5



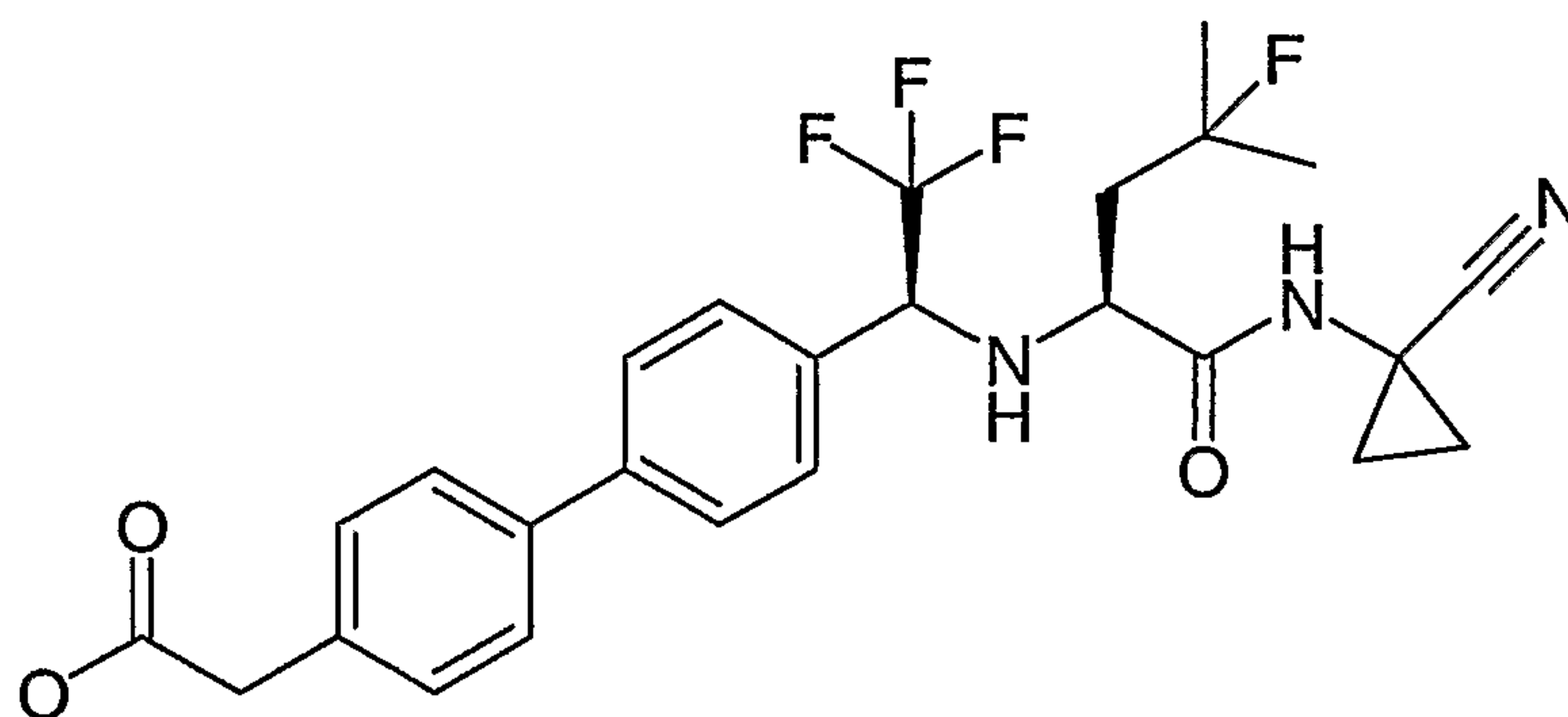
The title compound was prepared as described in Example 3

10 MS (+APCI): 500.2 (M+1)⁺.

EXAMPLE 16

Synthesis of 4'-[(1S)-1-[[[(1S)-1-[(1-cyanocyclopropyl)amino]carbonyl]-3-fluoro-3-methylbutyl]amino]-2,2,2-trifluoroethyl]-[1,1'-biphenyl]-4-acetic acid

15



A stream of nitrogen was passed through a DMF (4 mL) solution of the boronate from Step 3, Example 3 (0.249 g), 4-bromophenylacetic acid (0.151 g) and 2 M Na₂CO₃ (800 μL) for 15 minutes. The catalyst [1, 1'-bis(diphenylphosphino)-ferrocene]dichloropalladium(II), complex (1:1) with dichloromethane (50 mg) was then added and the mixture was warmed to 80 °C for 3 hours under nitrogen. The mixture was cooled to room temperature, poured into ice (10 g), water (20 mL), dilute hydrochloric acid (5 mL) and ethyl acetate (10 mL). It was then extracted with ethyl acetate (2 x 10 mL). The combined extracts were

washed with brine and dried with magnesium sulfate. Removal of the solvent left a residue which was purified by chromatography on SiO₂ using ethyl acetate, hexanes and acetic acid (1:1:0.01) as eluants, followed by a swish using diethyl ether to yield the title compound.

¹H NMR (CD₃COCD₃) δ 10.5-11(1H, COOH), 8.2(1H, bs), 7.7-7.75(2H, d), 7.65-7.0(2H, d), 7.55-7.6(2H, d), 7.4-7.45(2H, d), 4.35-4.45(1H, m), 3.7-3.75(2H, s), 3.5-3.6(1H, m), 1.9-2.05(2H, m), 1.4-1.55(6H, m), 1.3-1.4(2H, m), 1.05-1.1(1H, m), 0.85-1.0(1H, m).

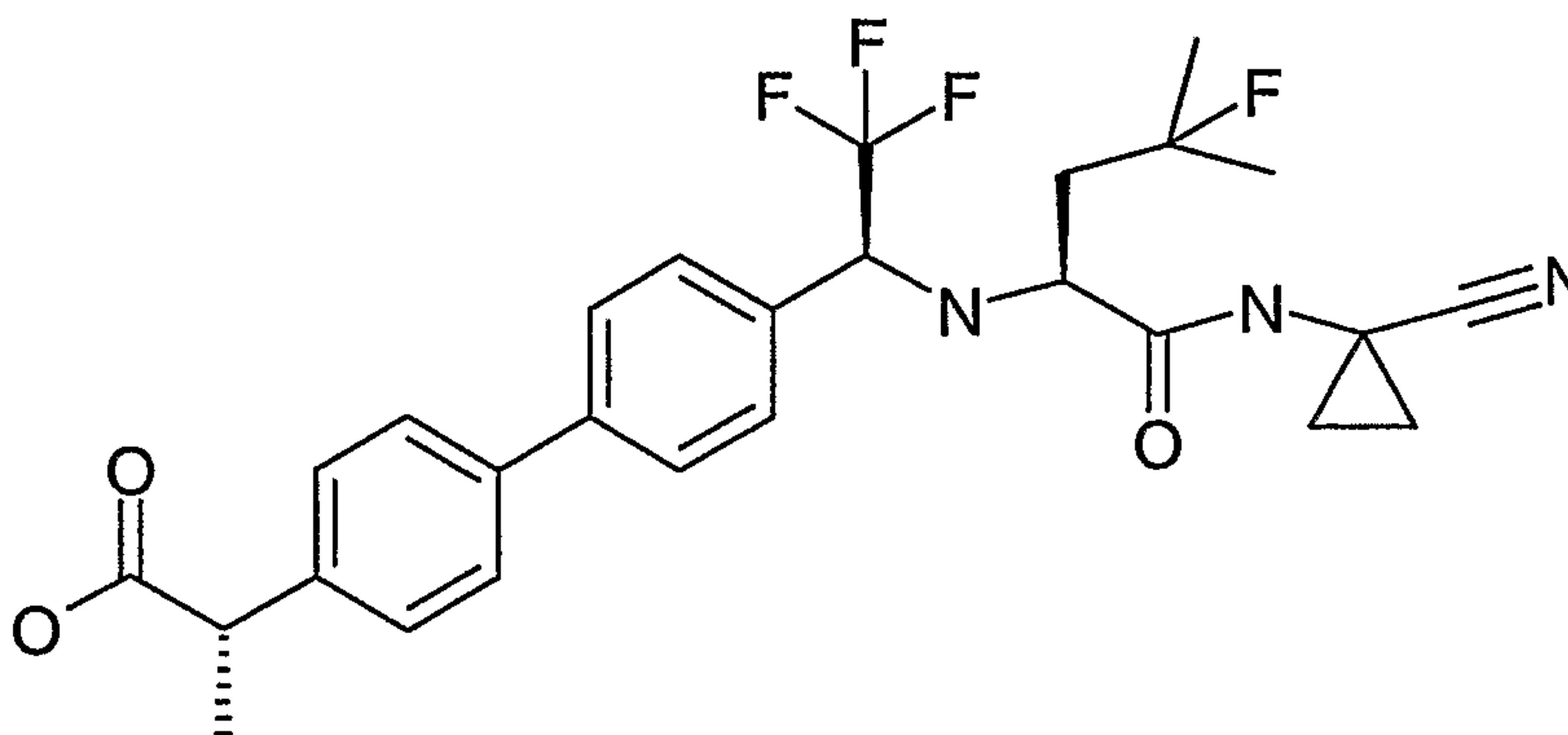
MS (+APCI) : 506.2(M+1)⁺

10

EXAMPLE 17

Synthesis of *N*¹-(1-cyanocyclopropyl)-4-fluoro-*N*²-((1*S*)-2,2,2-trifluoro-1-{4'-[(1*S*)-1-carboxyethyl]biphenyl-4-yl}ethyl)-L-leucinamide

15



Step 1: Preparation of 2-(4-bromophenyl)propanoic acid

To a solution of 4-bromophenylacetic acid (60 g), 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (60.5 mL) and iodomethane (18 mL) in THF (900 mL) at -20°C was added dropwise lithium bis(trimethylsilyl)amide 1M THF (586 mL) over 30 minutes. The reaction mixture was stirred at -20°C for 2 h and warmed up to room temperature over 2 h and finally stirred at room temperature for 2 h. NMR of an aliquot showed 50% of conversion. It was cooled to -20°C and lithium bis(trimethylsilyl)amide 1M THF (140 mL) was added. The mixture was warmed up to room temperature over 2 h and aged overnight at room temperature. NMR of aliquot showed 75% of conversion. The reaction mixture was poured into ice and 6N HCl (190 mL), partitioned and extracted with ether (2 X 400 mL). The combined organic layers were washed with a saturated NaCl solution, dried (MgSO₄) and concentrated under vacuum to yield the title compound. NMR showed about 20% of 4-bromophenylacetic acid. It was used as such in Step 2.

¹H NMR of title compound (CD₃COCD₃) δ 7.52(2H, d), 7.32(2H, d), 3.79(1H, q), 1.46(3H, d). Peaks of starting material not listed.

5 Step 2: Preparation of (1S)-2-ethoxy-1-methyl-2-oxoethyl (2S)-2-(4-bromophenyl)propanoate

To a solution of 2-(4-bromophenyl)propanoic acid from Step 1 (60.8 g) in toluene (925 mL) at 21°C was added oxalyl chloride (28 mL) followed by slow addition of N,N-Dimethylformamide (530 uL). The reaction mixture was stirred at room temperature for 2 h. It was cooled to 5°C and N,N-Dimethylethylamine (86 mL) was added dropwise over 20 minutes. The temperature rose to 15°C during addition and the batch was aged at room temperature for 2 h. It was cooled to -78°C and a solution of (S)-(-)-ethyl lactate (37 mL) in toluene (400 mL) was added dropwise. The mixture was stirred at -78°C for 2 h, then warmed up to 0°C and stirred overnight. The reaction mixture was poured into ice and water (700 mL) with vigorous stirring. It was then partitioned and extracted with toluene (700 mL). The combined organic layers were washed with 10% HCl (700 mL), (1:1) water/brine (700 mL), 50% Na₂CO₃ solution (700 mL) and a saturated NaCl solution, dried (MgSO₄) and concentrated under vacuum. The residue was purified by chromatography on silica gel using ethyl acetate and hexanes (1:99 to 10:90) to yield the title compound.

¹H NMR of title compound (CD₃COCD₃) δ 7.54(2H, d), 7.34(2H, d), 5.04(1H, q), 4.12-4.0 (2H, m), 3.90-3.86(1H, m), 1.48(3H, d), 1.41 (3H, d), 1.16(3H, t).

25 Step 3: Preparation of (2S)-2-(4-bromophenyl)propanoic acid

To a solution of (1S)-2-ethoxy-1-methyl-2-oxoethyl (2S)-2-(4-bromophenyl)propanoate from Step 2 (43.8 g) in MeOH (440 mL) at 0°C was added dropwise hydrogen peroxide 30% (37 mL) followed by slow addition of lithium hydroxide 4N (37 mL) while maintaining the internal temperature below 5°C. The reaction mixture was stirred at 0°C for 3 h. The reaction mixture was poured into ice and 6N HCl (40 mL) to adjust to a pH of about 1. Aqueous sodium sulfite (2M, 170 mL) was added dropwise while maintaining the internal temperature below 20°C with vigorous stirring. Then 6N HCl was added to adjust the pH to about 4. It was extracted with toluene (2 X 600 mL). The combined organic layers were washed with water (3 X 700 mL), dried (MgSO₄) and concentrated under vacuum. The residue was purified by swish using hexanes to yield the title compound.

¹H NMR of title compound (CD₃COCD₃) δ 10.81(1H, s), 7.53(2H, d), 7.33(2H, d), 3.79(1H, q), 1.46 (3H, d).

Step 4: Preparation of (1*R*)-1-phenylethanaminium (2*S*)-2-(4-bromophenyl)propanoate

To a solution of (2*S*)-2-(4-bromophenyl)propanoic acid from Step 3 (20 g) in 2-propanol (350 mL) and water (18 mL) at 21°C was added in one portion a solution of (R)-(+)-alpha-Methylbenzylamine (11.23 mL) in 14 mL of 2-propanol. The mixture was stirred at room temperature for 5 30 minutes then heated to 77 °C to dissolve all the precipitate. The mixture was slowly cooled to room temperature and allowed to stand overnight to precipitate the salt. It was filtered, washed with 2-propanol (2 X 35 mL) and put under vacuum to yield the title compound. The mother liquors were concentrated to 170 mL of solvent and heated to 77°C to dissolve all the precipitate. The mixture was slowly cooled to room temperature and allowed to stand overnight to have the salt precipitated. It was filtered, washed 10 with 2-propanol (2 X 30 mL) and dried under vacuum to yield more of the title compound.

¹H NMR of title compound (CD₃SOCD₃) δ 6.65-6.60(5H, m), 6.59(2H, d), 6.48(2H, d), 3.60 (1H, q), 2.76 (1H, q), 0.80 (3H, d), 0.61 (3H, d).

15 Step 5: Preparation of (2*S*)-2-(4-bromophenyl)propanoic acid

To a suspension of (1*R*)-1-phenylethanaminium (2*S*)-2-(4-bromophenyl)propanoate from Step 4 (11 g) in water (1 L) at 0°C was added dropwise sodium hydroxide (1N, 47 mL) while maintaining the internal temperature below 5°C. The aqueous layer was washed with isopropyl acetate (2 X 900 mL). The aqueous layer was cooled to 0°C again and treated with 1N HCl (about 52 mL) to adjust 20 the pH to 4. It was extracted with isopropyl acetate (2 X 900 mL) and the organic layers were washed with water (2 X 900 mL) and brine (1 L). It was dried (MgSO₄) and concentrated under vacuum to yield the title compound.

¹H NMR of title compound (CD₃COCD₃) δ 10.84 (1H, bs), 7.53 (2H, d), 7.33(2H, d), 3.79(1H, q), 1.46 25 (3H, d).

Optical rotation = +53.4 (C=1, MeOH)

Step 6: Preparation of *N*¹-(1-cyanocyclopropyl)-4-fluoro-*N*²-((1*S*)-2,2,2-trifluoro-1-{4'-[(1*S*)-1-carboxyethyl]biphenyl-4-yl}ethyl)-L-leucinamide

30 To a solution of *N*¹-(1-cyanocyclopropyl)-4-fluoro-*N*²-{(1*S*)-2,2,2-trifluoro-1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]ethyl}-L-leucinamide (400 mg) and (2*S*)-2-(4-bromophenyl)propanoic acid from Step 5 (180 mg) in DMF (8 mL) was added 2M sodium carbonate (2.8 mL). The mixture was bubbled with nitrogen for 10 minutes and [1, 1'-bis(diphenylphosphino)-ferrocene]dichloropalladium(II), complex (1:1) with dichloromethane (33 mg) was added. The mixture 35 was bubbled again with nitrogen for 10 minutes. Then the reaction mixture was stirred at 80°C for 2.5

hrs, cooled to 0°C and 1N HCl (~4 mL) was added to adjust the pH to 4. It was extracted with EtOAc (1 X 80 mL). The organic layer was washed with water (2 X 80 mL) followed by a saturated NaCl solution, dried (MgSO₄) and concentrated under vacuum. The residue was purified by chromatography on silica gel using ethyl acetate and hexanes (1:3 (500 mL) then 1% ethanol in ethyl acetate) to yield the title
5 compound.

¹H NMR of title compound (CD₃COCD₃) δ 10.75(1H, bs) 8.17 (s, 1 H), 7.72(2H, d), 7.69 (2H, d), 7.57 (2H, d), 7.48(2H, d), 4.40-4.37(1H, m), 3.85(1H, q), 3.54(1H, m), 2.00-1.90(2H, m), 1.52-1.34 (10H, m), 1.21-1.18(1H, m), 1.08-1.06 (1H, m), 0.99-0.9 (1H, m), proton of trifluoroethylamine was not observed.

10 Optical rotation = +72.5 (C= 1, MeOH)

Pharmaceutical Composition

As a specific embodiment of this invention, 100 mg of *N*¹-(1-cyanocyclopropyl)-*N*²-{(1*S*)-2,2-difluoro-1-{4'-[1-(carboxy)cyclopropyl]biphenyl-4-yl}-ethyl}-L-leucinamide is formulated
15 with sufficient finely divided lactose to provide a total amount of 580 to 590 mg to fill a size 0, hard-gelatin capsule.

The compounds disclosed in the present application exhibited activity in the following assays. In addition, the compounds disclosed in the present application have an enhanced pharmacological profile relative to previously disclosed compounds.

Cathepsin K Assay

Serial dilutions (1/3) from 500 μM down to 0.0085 μM of test compounds were prepared in dimethyl sulfoxide (DMSO). Then 2 μL of DMSO from each dilution were added to 50 μL of assay buffer (MES, 50 mM (pH 5.5); EDTA, 2.5 mM; DTT, 2.5 mM and 10% DMSO) and 25 μL of human
25 cathepsin K (0.4 nM) in assay buffer solution. The assay solutions were mixed for 5-10 seconds on a shaker plate and incubated for 15 minutes at room temperature. Z-Leu-Arg-AMC (8 μM) in 25 μL of assay buffer was added to the assay solutions. Hydrolysis of the coumarin leaving group (AMC) was followed by spectrofluorometry (Exλ = 355 nm; Emλ = 460 nm) for 10 minutes. Percent of inhibition were calculated by fitting experimental values to standard mathematical model for dose response curve.

Cathepsin L Assay

Serial dilutions (1/3) from 500 μM down to 0.0085 μM of test compounds were prepared in dimethyl sulfoxide (DMSO). Then 2 μL of DMSO from each dilution were added to 50 μL of assay buffer (MES, 50 mM (pH 5.5); EDTA, 2.5 mM; DTT, 2.5 mM and 10% DMSO) and 25 μL of human
35 cathepsin L (0.5 nM) in assay buffer solution. The assay solutions were mixed for 5-10 seconds on a

shaker plate and incubated for 15 minutes at room temperature. Z-Leu-Arg-AMC (8 μ M) in 25 μ L of assay buffer was added to the assay solutions. Hydrolysis of the coumarin leaving group (AMC) was followed by spectrofluorometry ($Ex\lambda$ = 355 nm; $Em\lambda$ = 460 nm) for 10 minutes. Percent of inhibition were calculated by fitting experimental values to standard mathematical model for dose response curve.

5

Cathepsin B Assay

Serial dilutions (1/3) from 500 μ M down to 0.0085 μ M of test compounds were prepared in dimethyl sulfoxide (DMSO). Then 2 μ L of DMSO from each dilution were added to 50 μ L of assay buffer (MES, 50 mM (pH 5.5); EDTA, 2.5 mM; DTT, 2.5 mM and 10% DMSO) and 25 μ L of human cathepsin B (4.0 nM) in assay buffer solution. The assay solutions were mixed for 5-10 seconds on a shaker plate and incubated for 15 minutes at room temperature. Z-Leu-Arg-AMC (8 μ M) in 25 μ L of assay buffer was added to the assay solutions. Hydrolysis of the coumarin leaving group (AMC) was followed by spectrofluorometry ($Ex\lambda$ = 355 nm; $Em\lambda$ = 460 nm) for 10 minutes. Percent of inhibition were calculated by fitting experimental values to standard mathematical model for dose response curve.

10

15

Cathepsin S Assay

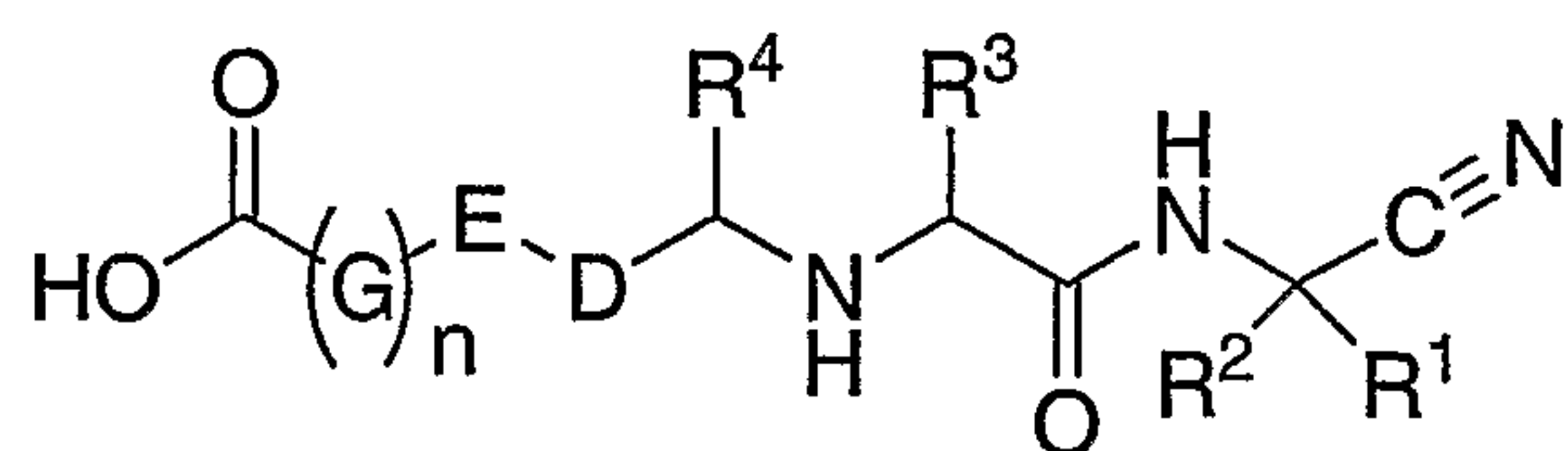
Serial dilutions (1/3) from 500 μ M down to 0.0085 μ M of test compounds were prepared in dimethyl sulfoxide (DMSO). Then 2 μ L of DMSO from each dilution were added to 50 μ L of assay buffer (MES, 50 mM (pH 5.5); EDTA, 2.5 mM; DTT, 2.5 mM and 10% DMSO) and 25 μ L of human cathepsin S (20 nM) in assay buffer solution. The assay solutions were mixed for 5-10 seconds on a shaker plate and incubated for 15 minutes at room temperature. Z-Leu-Arg-AMC (8 μ M) in 25 μ L of assay buffer was added to the assay solutions. Hydrolysis of the coumarin leaving group (AMC) was followed by spectrofluorometry ($Ex\lambda$ = 355 nm; $Em\lambda$ = 460 nm) for 10 minutes. Percent of inhibition were calculated by fitting experimental values to standard mathematical model for dose response curve.

20

25

WHAT IS CLAIMED IS:

1. The present invention relates to compounds of the following chemical formula:



- 5 wherein R¹ is hydrogen, C₁₋₆ alkyl or C₂₋₆ alkenyl wherein said alkyl and alkenyl groups are optionally substituted with one to six halo, C₃₋₆ cycloalkyl, -SR⁵, -SOR⁵, -SO₂R⁵, -SO₂CH(R^a)(R^b), -OR⁵, -N(R⁵)₂, aryl, heteroaryl or heterocyclyl wherein said aryl, heteroaryl and heterocyclyl groups are optionally substituted with one or two substituents independently selected from the group consisting of C₁₋₆ alkyl, halo, hydroxyalkyl, hydroxy, alkoxy and keto;
- 10 R² is hydrogen, C₁₋₆ alkyl or C₂₋₆ alkenyl wherein said alkyl and alkenyl groups are optionally substituted with one to six halo, C₃₋₆ cycloalkyl, -SR⁵, -SOR⁵, -SO₂R⁵, -SO₂CH(R^a)(R^b), -OR⁵, -N(R⁵)₂, aryl, heteroaryl or heterocyclyl wherein said aryl, heteroaryl and heterocyclyl groups are optionally substituted with one or two substituents independently selected from the group consisting of C₁₋₆ alkyl, halo, hydroxyalkyl, hydroxy, alkoxy and keto;
- 15 or R¹ and R² can be taken together with the carbon atom to which they are attached to form a C₃₋₈ cycloalkyl or heterocyclyl ring wherein said ring system is optionally substituted with one or two substituents independently selected from the group consisting of C₁₋₆ alkyl, hydroxyalkyl, haloalkyl, or halo;
- 20 R³ is hydrogen, C₁₋₆ alkyl or C₂₋₆ alkenyl wherein said alkyl and alkenyl groups are optionally substituted with C₃₋₆ cycloalkyl or one to six halo;
- R⁴ is hydrogen or C₁₋₆ alkyl substituted with 1-6 halo;
- 25 D is aryl or heteroaryl, wherein said aryl or heteroaryl group, which may be monocyclic or bicyclic, is optionally substituted on either the carbon or the heteroatom with one to five substituents independently selected from the group consisting of C₁₋₆ alkyl, haloalkyl, halo, keto, alkoxy, -SR⁵, -OR⁵, N(R⁵)₂, -SO₂R⁵, and -SO₂R^a;

E is aryl or heteroaryl, wherein said aryl or heteroaryl group, which may be monocyclic or bicyclic, is optionally substituted on either the carbon or the heteroatom with one to five substituents independently selected from the group consisting of C₁₋₆ alkyl, haloalkyl, halo, keto, alkoxy, -SR⁵, -OR⁵, N(R⁵)₂, -SO₂R⁵, and -SO₂R^a;

5

Each G is independently C₁₋₆ alkyl, C₁₋₆ alkyloxy, aryl, heteroaryl, C₃₋₈ cycloalkyl, heterocyclyl, -O-, NR⁵, S(O)_m, or carbonyl wherein said groups are optionally substituted on either the carbon or the heteroatom with one to five substituents independently selected from the group consisting of C₁₋₆ alkyl, halo, keto, haloalkyl, hydroxyalkyl, -OR⁵, -NHS(O)₂R⁵, -SO_mR⁵, -SO_mN(R^a)(R^b), -C(R^a)(R^b)OH, , heterocycl, aryl or heteroaryl;

10

R⁵ is hydrogen, C₁₋₆ alkyl, aryl, aryl(C₁₋₄)alkyl, heteroaryl, heteroaryl(C₁₋₄)alkyl, C₃₋₈cycloalkyl, C₃₋₈cycloalkyl(C₁₋₄)alkyl, or heterocyclyl(C₁₋₄)alkyl wherein said groups can be optionally substituted with one, two, or three substituents independently selected from the group consisting of halo, alkoxy, cyano, -NR^a or -SR^a or -SO_mR⁵;

15

R^a is hydrogen or C₁₋₆ alkyl which is optionally substituted with one, two, or three substituents independently selected from the group consisting of halo and -OR⁵;

R^b is hydrogen or C₁₋₆ alkyl which is optionally substituted with one, two, or three substituents

20 independently selected from the group consisting of halo and -OR⁵;

or R^a and R^b can be taken together with the nitrogen atom to which they are attached or are between them to form a C₃₋₈ heterocycl ring which is optionally substituted with one or two substituents independently selected from the group consisting of C₁₋₆ alkyl, halo hydroxyalkyl, hydroxy, alkoxy and keto;

25

m is an integer from zero to two;

n is an integer from one to three;

or a pharmaceutically acceptable salt, stereoisomer or N-oxide derivative thereof.

30

2. The compound of Claim 1 wherein R¹ and R² can be taken together with the carbon atom to which they are attached to form a C₃₋₈ cycloalkyl ring wherein said ring system is optionally substituted with one or two substituents selected from the group consisting of C₁₋₆ alkyl and halo.

35

3. The compound of Claim 2 wherein R³ is C₁₋₆ alkyl which is optionally substituted with one to six halo.

4. The compound of Claim 3 wherein R³ is n-propyl, isobutyl, 2-fluoro-2-methylpropyl, 2-trifluoromethylpropyl, 3-fluoro-2-(2-fluoromethyl)propyl, 2,2-difluoroethyl, 2,2-difluoropropyl, 3,3,3-trifluoropropyl, or 2,2-dichloroethyl.

5. The compound of Claim 2 wherein R⁴ is difluoromethyl, 2,2-difluoroethyl, trifluoromethyl or 3,3,3,2,2-pentafluoroethyl.

6. The compound of Claim 5 wherein D is phenyl.

7. The compound of Claim 6 wherein E is phenyl or heteroaryl.

8. The compound of Claim 7 wherein each G is independently C₁₋₆ alkyl, C₃₋₈ cycloalkyl or SO_mCH(R^a)(R^b).

9. The compound of Claim 1 which is:

1-[4'-[(1S)-1-[[[(1S)-1-[(1-cyanocyclopropyl)amino]carbonyl]-3-fluoro-3-methylbutyl]amino]-2,2,2-trifluoroethyl][1,1'-biphenyl]-4-yl]-cyclopropanecarboxylic acid;

N¹-(1-cyanocyclopropyl)-N²-{(1S)-2,2-difluoro-1-{4'-[1-(carboxy)cyclopropyl]biphenyl-4-yl}-ethyl}-L-leucinamide;

N¹-(1-cyanocyclopropyl)-N²-{(1S)-2,2-difluoro-1-{4'-[1-(carboxy)cyclopropyl]biphenyl-4-yl}-ethyl}-4-fluoro-L-leucinamide;

1-[2-[4-[(1S)-1-[[[(1S)-1-[(1-cyanocyclopropyl)amino]carbonyl]-3-fluoro-3-methylbutyl]amino]-2,2,2-trifluoroethyl]phenyl]-4-thiazolyl]-cyclopropanecarboxylic acid;

1-[[4'-[(1S)-1-[[[(1S)-1-[(1-cyanocyclopropyl)amino]carbonyl]-3-methylbutyl]amino]-2,2-difluoroethyl][1,1'-biphenyl]-3-yl]methyl]-cyclobutanecarboxylic acid;

4'-[(1S)-1-[[[(1S)-1-[(1-cyanocyclopropyl)amino]carbonyl]-3-fluoro-3-methylbutyl]amino]-2,2,2-trifluoroethyl]-α,α-dimethyl-[1,1'-biphenyl]-4-propanoic acid;

1-[4'-[(1*S*)-1-[[[(1*S*)-1-[(1-cyanocyclopropyl)amino]carbonyl]-3-methylbutyl]amino]-2,2,2-trifluoroethyl][1,1'-biphenyl]-4-yl]-cyclopropanecarboxylic acid;

5 1-[4'-[(1*S*)-1-[[[(1*S*)-1-[(1-cyanocyclopropyl)amino]carbonyl]-3-fluoro-3-methylbutyl]amino]-2,2,2-trifluoroethyl][1,1'-biphenyl]-3-yl]-cyclopropanecarboxylic acid;

4'-[(1*S*)-1-[[[(1*S*)-1-[(1-cyanocyclopropyl)amino]carbonyl]-3-fluoro-3-methylbutyl]amino]-2,2,2-trifluoroethyl]- α -methyl-[1,1'-biphenyl]-4-acetic acid;

10 4'-[(1*S*)-1-[[[(1*S*)-1-[(1-cyanocyclopropyl)amino]carbonyl]-3-fluoro-3-methylbutyl]amino]-2,2,2-trifluoroethyl]- α,α -dimethyl-[1,1'-biphenyl]-4-acetic acid;

15 1-[4'-[(1*S*)-1-[[[(1*S*)-1-[(1-cyanocyclopropyl)amino]carbonyl]-3-fluoro-3-methylbutyl]amino]-2,2,2-trifluoroethyl][1,1'-biphenyl]-4-yl]-cyclopropaneacetic acid;

1-[4'-[(1*S*)-1-[[[(1*S*)-1-[(1-cyanocyclopropyl)amino]carbonyl]-3-methylbutyl]amino]-2,2,2-trifluoroethyl][1,1'-biphenyl]-4-yl]-cyclopropanecarboxylic acid;

20 1-[4'-[(1*S*)-1-[[[(1*S*)-1-[(1-cyanocyclopropyl)amino]carbonyl]butyl]amino]-2,2,2-trifluoroethyl][1,1'-biphenyl]-4-yl]-cyclopropanecarboxylic acid;

4'-[(1*S*)-1-[[[(1*S*)-1-[(1-cyanocyclopropyl)amino]carbonyl]-3-fluoro-3-methylbutyl]amino]-2,2,2-trifluoroethyl]-[1,1'-biphenyl]-4-acetic acid;

25 *N*¹-(1-cyanocyclopropyl)-4-fluoro-*N*²-((1*S*)-2,2,2-trifluoro-1-{4'-[(1*S*)-1-carboxyethyl]biphenyl-4-yl}-ethyl)-L-leucinamide;

or a pharmaceutically acceptable salt, stereoisomer or N-oxide derivatives thereof.

30

10. A pharmaceutical composition comprising a compound according to any one of claims 1 to 9, or a pharmaceutically acceptable salt, stereoisomer or N-oxide derivatives thereof, and a pharmaceutically carrier.

11. The use of a compound of any one of claims 1 to 9, or a pharmaceutically acceptable salt, stereoisomer or N-oxide derivatives thereof, in the preparation of a medicament useful for the treatment of: osteoporosis, glucocorticoid induced osteoporosis, Paget's disease, abnormally increased bone turnover, periodontal disease, tooth loss, bone fractures, rheumatoid arthritis, osteoarthritis, periprosthetic osteolysis, osteogenesis imperfecta, atherosclerosis, obesity, chronic obstructive pulmonary disease, metastatic bone disease, hypercalcemia of malignancy or multiple myeloma in a mammal in need thereof a therapeutically effective amount of a compound according to Claim 1.

12. A pharmaceutical composition comprising a compound of any one of claims 1 to 9, or a pharmaceutically acceptable salt, stereoisomer or N-oxide derivatives thereof, and another agent selected from the group consisting of: an organic bisphosphonate, an estrogen receptor modulator, an estrogen receptor beta modulator, an androgen receptor modulator, an inhibitor of osteoclast proton ATPase, an inhibitor of HMG-CoA reductase, an integrin receptor antagonist, or an osteoblast anabolic agent, a Nonsteroidal anti-inflammatory drug, a selective cyclooxygenase-2 inhibitor, an inhibitor of interleukin-1 beta, a LOX/COX inhibitor and the pharmaceutically acceptable salts and mixtures thereof.

13. The use of a compound of any one of claims 1 to 9, or a pharmaceutically acceptable salt, stereoisomer or N-oxide derivatives thereof, and another agent selected from the group consisting of: an organic bisphosphonate, an estrogen receptor modulator, an androgen receptor modulator, an inhibitor of osteoclast proton ATPase, an inhibitor of HMG-CoA reductase, an integrin receptor antagonist, an osteoblast anabolic agent, a Nonsteroidal anti-inflammatory drug, a selective cyclooxygenase-2 inhibitor, an inhibitor of interleukin-1 beta, a LOX/COX inhibitor and the pharmaceutically acceptable salts and mixtures thereof, in the preparation of a medicament useful for the treatment of: osteoporosis, glucocorticoid induced osteoporosis, Paget's disease, abnormally increased bone turnover, periodontal disease, tooth loss, bone fractures, rheumatoid arthritis, osteoarthritis, periprosthetic osteolysis, osteogenesis imperfecta, atherosclerosis, obesity, chronic obstructive pulmonary disease, metastatic bone disease, hypercalcemia of malignancy or multiple myeloma in a mammal in need thereof.