

TITLE OF THE INVENTION
CETP INHIBITORS

FIELD OF THE INVENTION

This invention relates to a class of chemical compounds that inhibit cholesterol ester transfer protein (CETP) and therefore may have utility in the treatment and prevention of atherosclerosis.

BACKGROUND OF THE INVENTION

Atherosclerosis and its clinical consequences, coronary heart disease (CHD), stroke and peripheral vascular disease, represent a truly enormous burden to the health care systems of the industrialized world. In the United States alone, approximately 13 million patients have been diagnosed with CHD, and greater than one half million deaths are attributed to CHD each year. Further, this toll is expected to grow over the next quarter century as an epidemic in obesity and diabetes continues to grow.

It has long been recognized that in mammals, variations in circulating lipoprotein profiles correlate with the risk of atherosclerosis and CHD. The clinical success of HMG-CoA Reductase inhibitors, especially the statins, in reducing coronary events is based on the reduction of circulating Low Density Lipoprotein cholesterol (LDL-C), levels of which correlate directly with increased risk for atherosclerosis. More recently, epidemiologic studies have demonstrated an inverse relationship between High Density Lipoprotein cholesterol (HDL-C) levels and atherosclerosis, leading to the conclusion that low serum HDL-C levels are associated with an increased risk for CHD.

Metabolic control of lipoprotein levels is a complex and dynamic process involving many factors. One important metabolic control in man is the cholesteryl ester transfer protein (CETP), a plasma glycoprotein that catalyzes the movement of cholesteryl esters from HDL to the apoB containing lipoproteins, especially VLDL (see Hesler, C.B., et. al. (1987) *Purification and characterization of human plasma cholesteryl ester transfer protein. J. Biol. Chem.* 262(5), 2275-2282)). Under physiological conditions, the net reaction is a heteroexchange in which CETP carries triglyceride to HDL from the apoB lipoproteins and transports cholesterol ester from HDL to the apoB lipoprotein.

In humans, CETP plays a role in reverse cholesterol transport, the process whereby cholesterol is returned to the liver from peripheral tissues. Intriguingly, many animals do not possess CETP, including animals that have high HDL levels and are known to be resistant to coronary heart disease, such as rodents (see Guyard-Dangremont, V., et. al., (1998) *Phospholipid and cholesteryl ester transfer activities in plasma from 14 vertebrate species. Relation to atherogenesis susceptibility, Comp.*

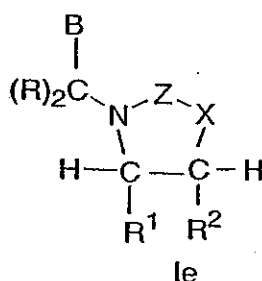
Biochem. Physiol. B Biochem. Mol. Biol. **120**(3), 517-525). Numerous epidemiologic studies correlating the effects of natural variation in CETP activity with respect to coronary heart disease risk have been performed, including studies on a small number of known human null mutations (see Hirano, K.-I., Yamashita, S. and Matsuzawa, Y. (2000) *Pros and cons of inhibiting cholesteryl ester transfer protein*, *Curr. Opin. Lipidol.* **11**(6), 589-596). These studies have clearly demonstrated an inverse correlation between plasma HDL-C concentration and CETP activity (see Inazu, A., et. al. (2000) *Cholesteryl ester transfer protein and atherosclerosis*, *Curr. Opin. Lipidol.* **11**(4), 389-396), leading to the hypothesis that pharmacologic inhibition of CETP lipid transfer activity may be beneficial to humans by increasing levels of HDL-C while lowering those of LDL.

Despite the significant therapeutic advance that statins such as simvastatin (ZOCOR®) represent, statins only achieve a risk reduction of approximately one-third in the treatment and prevention of atherosclerosis and ensuing atherosclerotic disease events. Currently, few pharmacologic therapies are available that favorably raise circulating levels of HDL-C. Certain statins and some fibrates offer modest HDL-C gains. Niacin, which provides the most effective therapy for raising HDL-C that has been clinically documented, suffers from patient compliance issues, due in part to side effects such as flushing. An agent that safely and effectively raises HDL cholesterol levels can answer a significant, but as yet unmet medical need by offering a means of pharmacologic therapy that can significantly improve circulating lipid profiles through a mechanism that is complementary to existing therapies.

New classes of chemical compounds that inhibit CETP are being investigated at several pharmaceutical companies or are in clinical trials. No CETP inhibitors are currently being marketed. New compounds are needed so that one or more pharmaceutical compounds can be found that are safe and effective. The compounds described herein are very potent CETP inhibitors.

SUMMARY OF THE INVENTION

In a first aspect, there is provided a compound having Formula Ie, or a pharmaceutically acceptable salt thereof, wherein

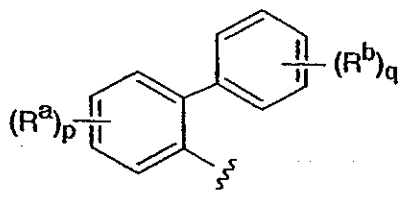


X is selected from the group consisting of -O-, -NH-, -N(C₁-C₅alkyl)- and -(CH₂)-;

Z is selected from the group consisting of -C(=O)-, -S(O)₂-, and -C(=N-R⁹)-, wherein R⁹ is selected from the group consisting of H, -CN, and C₁-C₅alkyl optionally substituted with 1-11 halogens;

Each R is independently selected from the group consisting of H and -CH₃;

B is selected from the group consisting of A¹ and A², wherein A¹ has the structure:



R¹ is selected from the group consisting of H, -C₁-C₅ alkyl, and -(C(R)₂)_nA², wherein -C₁-C₅ alkyl is optionally substituted with 1-11 halogens;

R² is selected from the group consisting of H, -C₁-C₅ alkyl, A¹, and -(C(R)₂)_nA², wherein -C₁-C₅alkyl is optionally substituted with 1-11 halogens;

Wherein one of B and R² is A¹; and one of B, R¹, and R² is A² or -(C(R)₂)_nA²; so that the compound of Formula Ie comprises one group A¹ and one group A²;

A² is selected from the group consisting of phenyl, cyclohexyl, and pyridyl, wherein A² is optionally substituted with 1-2 substituent groups independently selected from halogen, -C₁-C₄ alkyl, and -CN, wherein -C₁-C₄ alkyl is optionally substituted with 1-3 halogens;

5 Each R^a is independently selected from the group consisting of -C₁-C₃ alkyl and halogen, wherein -C₁-C₃ alkyl is optionally substituted with 1-3 halogens;

Each R^b is independently selected from the group consisting of Cl, F, -C₁-C₄ alkyl, and -OC₁-C₄ alkyl, wherein -C₁-C₄ alkyl and -OC₁-C₄ alkyl are optionally substituted with 1-5 F;

10 n is 0 or 1;

p is an integer from 0-2; and

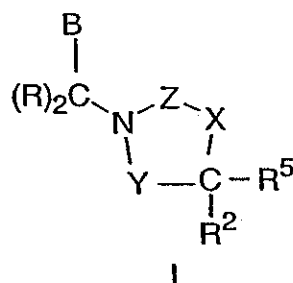
q is an integer from 0-3.

In a second aspect, there is provided the use of the compound as defined above or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for raising HDL-C in a patient in need of such treatment.

In a third aspect, there is provided the use of the compound as defined above or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of atherosclerosis.

In a fourth aspect, there is provided a pharmaceutical composition comprising the compound as defined above or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

Compounds having Formula I, including pharmaceutically acceptable salts of the compounds, may be CETP inhibitors, having the utilities described below:



In the compounds of Formula I,

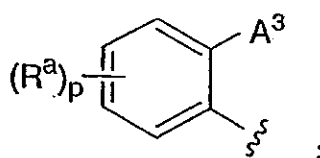
Y is selected from -C(=O)- and -(CRR¹)-;

X is selected from -O-, -NH-, -N(C₁-C₅alkyl)-, and -(CRR⁶)-;

Z is selected from -C(=O)-, -S(O)₂-, and -C(=N-R⁹)-, wherein R⁹ is selected from the group consisting of H, -CN, and -C₁-C₅alkyl optionally substituted with 1-11 halogens;

Each R is independently selected from the group consisting of H, -C₁-C₅ alkyl, and halogen, wherein -C₁-C₅ alkyl is optionally substituted with 1-11 halogens;

B is selected from the group consisting of A¹ and A², wherein A¹ has the structure:



R¹ and R⁶ are each independently selected from H, -C₁-C₅ alkyl, halogen, and -(C(R)₂)_nA², wherein -C₁-C₅ alkyl is optionally substituted with 1-11 halogens;

R² is selected from the group consisting of H, -C₁-C₅ alkyl, halogen, A¹, and -(C(R)₂)_nA², wherein -C₁-C₅ alkyl is optionally substituted with 1-11 halogens;

Wherein one of B and R² is A¹; and one of B, R¹, R², and R⁶ is A² or -(C(R)₂)_nA²; so that the compound of Formula I comprises one group A¹ and one group A²;

A³ is selected from the group consisting of:

- (a) an aromatic ring selected from phenyl and naphthyl;
- (b) a phenyl ring fused to a 5-7 membered non-aromatic cycloalkyl ring, which optionally comprises 1-2 double bonds;
- (c) a 5-6-membered heterocyclic ring having 1-4 heteroatoms independently selected from N, S, O, and -N(O)-, and optionally also comprising 1-3 double bonds and a carbonyl group, wherein the point of attachment of A³ to the phenyl ring to which A³ is attached is a carbon atom; and
- (d) a benzoheterocyclic ring comprising a phenyl ring fused to a 5-6-membered heterocyclic ring having 1-2 heteroatoms independently selected from O, N, and S, and optionally also having 1-2 double bonds (in addition to the double bond of the fused phenyl ring) wherein the point of attachment of A³ to the phenyl ring to which A³ is attached is a carbon atom;

A² is selected from the group consisting of:

- (a) an aromatic ring selected from phenyl and naphthyl;
- (b) a phenyl ring fused to a 5-7 membered non-aromatic cycloalkyl ring, which optionally comprises 1-2 double bonds;
- (c) a 5-6-membered heterocyclic ring having 1-4 heteroatoms independently selected from N, S, O, and -N(O)-, and optionally also comprising 1-3 double bonds and a carbonyl group;
- (d) a benzoheterocyclic ring comprising a phenyl ring fused to a 5-6-membered heterocyclic ring having 1-2 heteroatoms independently selected from O, N, and S, and optionally also having 1-2 double bonds (in addition to the double bond of the fused phenyl ring); and
- (e) a -C₃-C₈ cycloalkyl ring optionally having 1-3 double bonds;

wherein A³ and A² are each optionally substituted with 1-5 substituent groups independently selected from R^a;

Each R^a is independently selected from the group consisting of -C₁-C₆ alkyl, -C₂-C₆ alkenyl, -C₂-C₆ alkynyl, -C₃-C₈ cycloalkyl optionally having 1-3 double bonds, -OC₁-C₆alkyl, -OC₂-C₆ alkenyl, -OC₂-C₆ alkynyl, -OC₃-C₈ cycloalkyl optionally having 1-3 double bonds, -C(=O)C₁-C₆alkyl, -C(=O)C₃-C₈ cycloalkyl, -C(=O)H, -CO₂H, -CO₂C₁-C₆alkyl, -C(=O)SC₁-C₆alkyl, -NR³R⁴, -C(=O)NR³R⁴, -NR³C(=O)OC₁-C₆ alkyl, -NR³C(=O)NR³R⁴, -S(O)_xC₁-C₆ alkyl, -S(O)_yNR³R⁴,

-NR³S(O)_yNR³R⁴, halogen, -CN, -NO₂, and a 5-6-membered heterocyclic ring having 1-4 heteroatoms independently selected from N, S, and O, said heterocyclic ring optionally also comprising a carbonyl group and optionally also comprising 1-3 double bonds, wherein the point of attachment of said heterocyclic ring to the attached ring is a carbon atom, wherein said heterocyclic ring is optionally substituted with 1-5 substituent groups independently selected from halogen, -C₁-C₃ alkyl, and -OC₁-C₃ alkyl, wherein -C₁-C₃ alkyl and -OC₁-C₃ alkyl are optionally substituted with 1-7 halogens;

wherein for compounds in which R^a is selected from the group consisting of -C₁-C₆ alkyl, -C₂-C₆ alkenyl, -C₂-C₆ alkynyl, -C₃-C₈ cycloalkyl optionally having 1-3 double bonds, -OC₁-C₆alkyl, -OC₂-C₆ alkenyl, -OC₂-C₆ alkynyl, -OC₃-C₈ cycloalkyl optionally having 1-3 double bonds, -C(=O)C₁-C₆alkyl, -C(=O)C₃-C₈ cycloalkyl, -CO₂C₁-C₆alkyl, -C(=O)SC₁-C₆alkyl, -NR³C(=O)OC₁-C₆ alkyl, and -S(O)_xC₁-C₆ alkyl, R^a is optionally substituted with 1-15 halogens and is optionally also substituted with 1-3 substituent groups independently selected from (a) -OH, (b) -CN, (c) -NR³R⁴, (d) -C₃-C₈ cycloalkyl optionally having 1-3 double bonds and optionally substituted with 1-15 halogens, (e) -OC₁-C₄alkyl optionally substituted with 1-9 halogens and optionally also substituted with 1-2 substituent groups independently selected from -OC₁-C₂ alkyl, (f) -OC₃-C₈ cycloalkyl optionally having 1-3 double bonds and optionally substituted with 1-15 halogens, (g) -CO₂H, (h) -C(=O)CH₃, and (i) -CO₂C₁-C₄alkyl which is optionally substituted with 1-9 halogens;

with the proviso that when B is A¹, X and Y are -CH₂-, Z is -C(=O)-, R² is A², and A² is phenyl which has a substituent R^a in the 4-position, wherein R^a is -OC₁-C₆alkyl which is optionally substituted with 1-11 halogens, then there are no other R^a substituents on A² in which R^a is selected from -OC₁-C₆alkyl, -OC₂-C₆ alkenyl, -OC₂-C₆ alkynyl, and -OC₃-C₈ cycloalkyl optionally having 1-3 double bonds;

n is 0 or 1;

p is an integer from 0-4;

x is 0, 1, or 2;

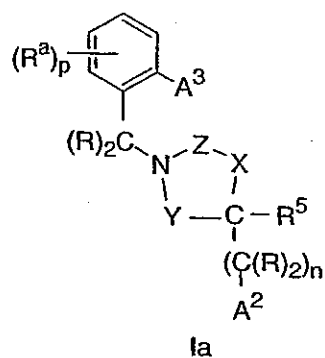
y is 1 or 2;

R³ and R⁴ are each independently selected from H, -C₁-C₅ alkyl, -C(=O)C₁-C₅ alkyl and -S(O)_yC₁-C₅ alkyl, wherein -C₁-C₅ alkyl in all instances is optionally substituted with 1-11 halogens; and

R⁵ is selected from the group consisting of H, -OH, -C₁-C₅ alkyl, and halogen, wherein -C₁-C₅ alkyl is optionally substituted with 1-11 halogens.

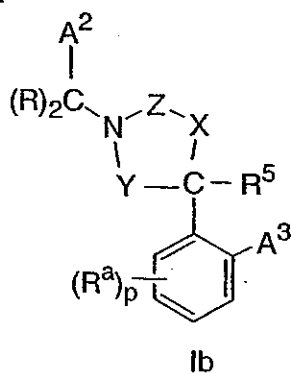
5 DETAILED DESCRIPTION OF THE INVENTION

Many of compounds of this invention have a structure in accordance with Formula Ia, written below, or a pharmaceutically acceptable salt thereof:



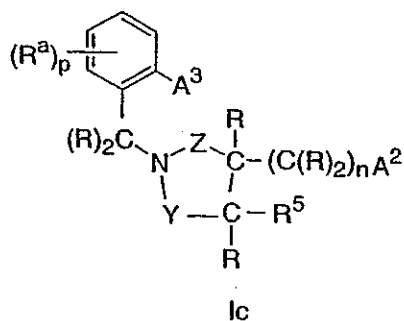
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Many compounds of the invention have the structure of Formula Ib, or a pharmaceutically acceptable salt thereof:



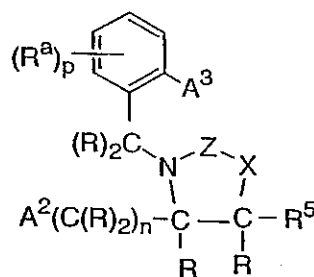
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Many other compounds have the structure of Formula Ic or a pharmaceutically acceptable salt thereof:



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Still other compounds of the invention have a structure in accordance with Formula Id, or a pharmaceutically acceptable salt thereof:



Id

In many of the compounds of Formula I, Ia, Ib, Ic and Id, and pharmaceutically acceptable salts thereof,

A³ is phenyl, which is optionally substituted with 1-4 substituent groups R^a, wherein R^a is independently selected from -C₁-C₅ alkyl, -OC₁-C₃alkyl, -CO₂C₁-C₃alkyl, -CO₂H, halogen, -NR³R⁴, -C(=O)C₁-C₃alkyl, -C(=O)H, -C(=O)NR³R⁴, -SC₁-C₃ alkyl, -C₂-C₃ alkenyl, -CN, -NO₂, and 1,2,4-oxadiazolyl, wherein -C₁-C₃ alkyl and -C₁-C₅ alkyl in all occurrences is optionally substituted with 1-6 substituents independently selected from 1-5 halogens and one -OH group; and -C₂-C₃ alkenyl is optionally substituted with 1-3 halogens.

In many of the compounds of Formula I, Ia, Ib, Ic, and Id, and pharmaceutically acceptable salts thereof,

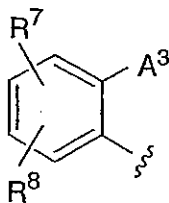
A² is selected from the group consisting of phenyl, cyclohexyl, and a heterocyclic 5-6 membered ring comprising 1-2 heteroatoms independently selected from O, N, S, and -N(O)- and optionally also comprising 1-3 double bonds, wherein A² is optionally substituted with 1-2 substituent groups independently selected from -C₁-C₄ alkyl, -OC₁-C₃ alkyl, -NO₂, -CN, -S(O)_xC₁-C₃ alkyl, -NHS(O)₂C₁-C₃ alkyl, -NR³R⁴, -NR³C(=O)R⁴, -C₂-C₃ alkenyl, -C(=O)NR³R⁴, halogen, and pyridyl, wherein C₁-C₃ alkyl, C₁-C₄ alkyl, and C₂-C₃alkenyl in all instances is optionally substituted with 1-3 halogens, with the proviso that for compounds of formula Ia, when X and Y are CH₂, Z is -(C=O)-, n is 0, and A² is phenyl, then the number of R_a groups on A² that are selected from -OC₁-C₃alkyl is 0 or 1.

In many of the compounds of Formula I, Ia, Ib, Ic, and Id, and pharmaceutically acceptable salts thereof,

R³ and R⁴ are each independently selected from H and -C₁-C₃ alkyl.

In many of the compounds of Formula I, Ia, Ib, Ic, and Id, and pharmaceutically acceptable salts thereof, p is 0-2.

In subgroups of compounds of Formula I, including pharmaceutically acceptable salts thereof, A¹ is



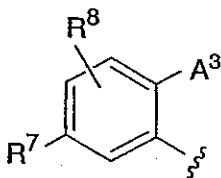
Wherein R⁷ and R⁸ are each independently selected from the group consisting of H, halogen, -NR³R⁴, -C₁-C₃ alkyl, -OC₁-C₃ alkyl, -CN, -NO₂, and pyridyl, wherein C₁-C₃ alkyl in all instances is optionally substituted with 1-3 halogens.

In sub-groups of the compounds of formula I, A² is selected from the group consisting of phenyl, pyridyl, and cyclohexyl, wherein A² is optionally substituted with 1-2 substituents independently selected from -C₁-C₄ alkyl, -OC₁-C₄ alkyl, -NO₂, -CN, and halogen, wherein C₁-C₄ alkyl in all uses is optionally substituted with 1-3 halogens, with the proviso that for compounds of formula Ia, when X and Y are CH₂, Z is -(C=O)-, and A² is phenyl, then the number of R_a groups on A² that are selected from -OC₁-C₄alkyl optionally substituted with 1-3 halogens is 0 or 1.

In other subgroups, A² is optionally substituted with 1-2 substituent groups independently selected from halogen, -C₁-C₄ alkyl, and -CN, wherein -C₁-C₄ alkyl is optionally substituted with 1-3 halogens.

In many embodiments of the invention, as described above, including pharmaceutically acceptable salts,

A¹ is



Wherein R⁷ is selected from H, halogen, -NR³R⁴, -C₁-C₃ alkyl, -OC₁-C₃ alkyl, -CN, -NO₂, and pyridyl, wherein C₁-C₃ alkyl in all instances is optionally substituted with 1-3 halogens; and

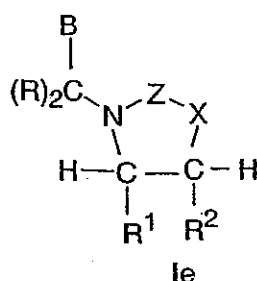
R⁸ is selected from the group consisting of H, halogen, -CH₃, -CF₃, -OCH₃, and -OCF₃.

In many preferred embodiments of this invention, A³ is phenyl, which is substituted with 1-3 substituents independently selected from C₁-C₄alkyl, OC₁-C₄alkyl, -CN, Cl, F, -C(=O) CH₃, -

CH=CH₂, -CO₂H, -CO₂CH₃, -S-CH₃, -S(O)CH₃, -S(O)₂CH₃, and -C(=O)NR³R⁴, wherein C₁-C₄alkyl and -OC₁-C₄alkyl are optionally substituted with 1-5 F substituents and optionally also substituted with one group -OH.

In other embodiments, A₃ is phenyl which is optionally substituted with 1-3 substituents independently selected from the group consisting of Cl, F, -C₁-C₄ alkyl, and -OC₁-C₄ alkyl, wherein -C₁-C₄ alkyl and -OC₁-C₄ alkyl are optionally substituted with 1-5 F.

A preferred subgroup of compounds has Formula Ie, including pharmaceutically acceptable salts thereof

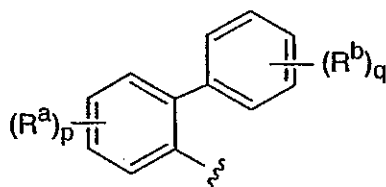


In compounds of formula Ie, X is selected from the group consisting of -O-, -NH-, -N(C₁-C₅alkyl)- and -(CH₂)-;

Z is selected from the group consisting of -C(=O)-, -S(O)₂-, and -C(=N-R⁹)-, wherein R⁹ is selected from the group consisting of H, -CN, and C₁-C₅alkyl optionally substituted with 1-11 halogens;

Each R is independently selected from the group consisting of H and -CH₃;

B is selected from the group consisting of A¹ and A², wherein A¹ has the structure:



R¹ is selected from the group consisting of H, -C₁-C₅ alkyl, and -(C(R)₂)_nA², wherein -C₁-C₅ alkyl is optionally substituted with 1-11 halogens;

R² is selected from the group consisting of H, -C₁-C₅ alkyl, A¹, and -(C(R)₂)_nA², wherein -C₁-C₅alkyl is optionally substituted with 1-11 halogens;

Wherein one of B and R² is A¹; and one of B, R¹, and R² is A² or -(C(R)₂)_nA²; so
5 that the compound of Formula Ie comprises one group A¹ and one group A²;

A² is selected from the group consisting of phenyl, cyclohexyl, and pyridyl, wherein A² is optionally substituted with 1-2 substituent groups independently selected from halogen, -C₁-C₄ alkyl, and -CN, wherein -C₁-C₄ alkyl is optionally substituted with 1-3 halogens;
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Each R^a is independently selected from the group consisting of -C₁-C₃ alkyl and halogen, wherein -C₁-C₃ alkyl is optionally substituted with 1-3 halogens;

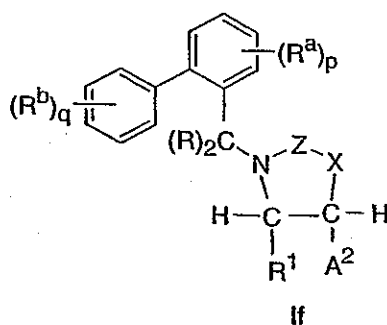
Each R^b is independently selected from the group consisting of Cl, F, -C₁-C₄ alkyl, and
15 -OC₁-C₄ alkyl, wherein -C₁-C₄ alkyl and -OC₁-C₄ alkyl are optionally substituted with 1-5 F;

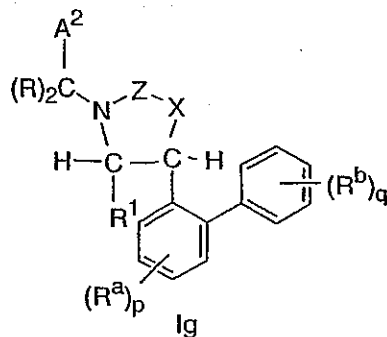
n is 0 or 1;

p is an integer from 0-2; and

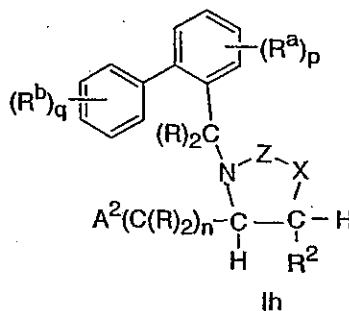
q is an integer from 0-3.

20 Subsets of compounds having formula Ie include compounds of formula If, Ig, and Ih, and pharmaceutically acceptable salts thereof:





, and



In the compounds of formula If, Ig, and Ih, R^1 and R^2 are each independently selected from H and -C₁-C₅ alkyl, wherein -C₁-C₅ alkyl is optionally substituted with 1-11 halogens.

In subsets of the compounds described above, A^2 may be selected from the group consisting of phenyl, cyclohexyl, and pyridyl, wherein A^2 is optionally substituted with 1-2 substituent groups independently selected from halogen, -CH₃, -CF₃, and -CN.

In subsets of the compounds described above, each R^a independently is selected from the group consisting of -CF₃ and Cl.

In subsets of the compounds described above, each R^b is independently selected from the group consisting of -C₁-C₃ alkyl, -OCH₃, and F.

In subsets of the compounds described above, R^1 and R^2 are each independently selected from the group consisting of H and -C₁-C₂ alkyl.

In subsets of the compounds described above, X is selected from -O-, -NH-, -N(CH₃)-, and -CH₂-.

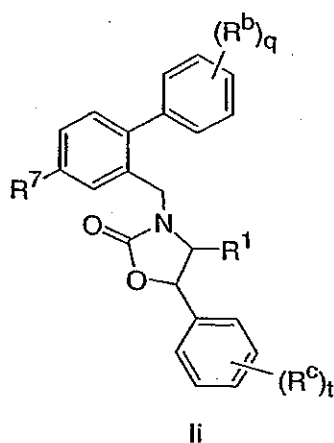
In subsets of the compounds described above, Z is selected from the group consisting of -C(=O)-, -S(O)₂-, and -C(=N-CN)-.

In subsets of the compounds described above, n is 0 or 1.

In subsets of the compounds described above, p is 1.

In subsets of the compounds described above, q is 2 or 3.

5 A subset of compounds defined previously comprises compounds having formula Ii, and pharmaceutically acceptable salts thereof:

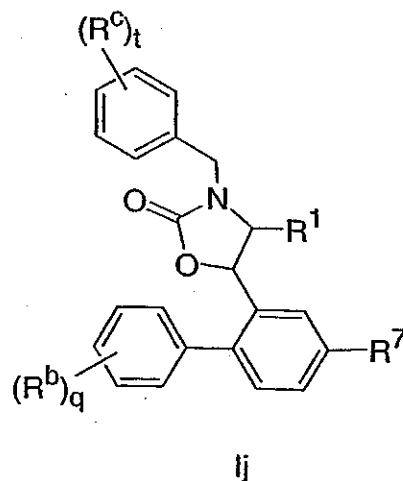


In formula Ii, R^7 is selected from the group consisting of Cl and $-CF_3$;

R^c is selected from the group consisting of halogen, $-CH_3$, $-CF_3$, and $-CN$; and

10 t is an integer from 0-2. Other groups are as defined previously.

A subset of compounds defined previously comprises compounds having formula Ij, or a pharmaceutically acceptable acceptable salt thereof, wherein:



15 In formula Ii, R^7 is selected from the group consisting of Cl and $-CF_3$;

R^c is selected from the group consisting of halogen, $-CH_3$, $-CF_3$, and $-CN$; and

t is an integer from 0-2. Other groups are as defined previously.

Definitions

"Ac" is acetyl, which is $\text{CH}_3\text{C}(=\text{O})-$.

5 "Alkyl" means saturated carbon chains which may be linear or branched or combinations thereof, unless the carbon chain is defined otherwise. Other groups having the prefix "alk", such as alkoxy and alkanoyl, also may be linear or branched or combinations thereof, unless the carbon chain is defined otherwise. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, sec- and tert-butyl, pentyl, hexyl, heptyl, octyl, nonyl, and the like.

3 "Alkylene" groups are alkyl groups that are difunctional rather than monofunctional. For example, methyl is an alkyl group and methylene ($-\text{CH}_2-$) is the corresponding alkylene group.

1 "Alkenyl" means carbon chains which contain at least one carbon-carbon double bond, and which may be linear or branched or combinations thereof. Examples of alkenyl include vinyl, allyl, isopropenyl, pentenyl, hexenyl, heptenyl, 1-propenyl, 2-butenyl, 2-methyl-2-butenyl, and the like.

5 "Alkynyl" means carbon chains which contain at least one carbon-carbon triple bond, and which may be linear or branched or combinations thereof. Examples of alkynyl include ethynyl, propargyl, 3-methyl-1-pentynyl, 2-heptynyl and the like.

0 "Cycloalkyl" means a saturated carbocyclic ring having from 3 to 8 carbon atoms, unless otherwise stated (e.g., cycloalkyl may be defined as having one or more double bonds). The term also includes a cycloalkyl ring fused to an aryl group. Examples of cycloalkyl include cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl, and the like. "Cycloalkenyl" means a non-aromatic carbocyclic ring having one or more double binds.

5 "Aryl" (and "arylene") when used to describe a substituent or group in a structure means a monocyclic or bicyclic compound in which the rings are aromatic and which contains only carbon ring atoms. The term "aryl" can also refer to an aryl group that is fused to a cycloalkyl or heterocycle. Preferred "aryls" are phenyl and naphthyl. Phenyl is generally the most preferred aryl group.

"EDC" is 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide.

"Heterocyclyl," "heterocycle," and "heterocyclic" means a fully or partially saturated or aromatic 5-6 membered ring containing 1-4 heteroatoms independently selected from N, S and O, unless otherwise stated.

0 "Benzoheterocycle" represents a phenyl ring fused to a 5-6-membered heterocyclic ring having 1-2 heteroatoms, each of which is O, N, or S, where the heterocyclic ring may be saturated or unsaturated. Examples include indole, benzofuran, 2,3-dihydrobenzofuran and quinoline.

"DIPEA" is diisopropylethylamine.

"Halogen" includes fluorine, chlorine, bromine and iodine.

5 "HOBT" is 1-Hydroxybenzotriazole.

"IPAC" is isopropyl acetate.

"Me" represents methyl.

"Weinreb amine" is N,O-dimethylhydroxylamine.

5 The term "composition," as in pharmaceutical composition, is intended to encompass a product comprising the active ingredient(s), and the inert ingredient(s) that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the pharmaceutical compositions of the present invention encompass any composition made by admixing a compound of the
10 present invention and a pharmaceutically acceptable carrier.

The substituent "tetrazole" means a 2*H*-tetrazol-5-yl substituent group and tautomers thereof.

Optical Isomers - Diastereomers - Geometric Isomers - Tautomers

15 Compounds of Formula I may contain one or more asymmetric centers and can thus occur as racemates, racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. The present invention is meant to comprehend all such isomeric forms of the compounds of Formula I. When structures are shown with a stereochemical representation, other stereochemical structures are also included, such as enantiomers, other diastereoisomers (where diastereomers are
20 possible), and mixtures of the enantiomers and/or diastereomers, including racemic mixtures.

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

Some of the compounds described herein may exist as tautomers. An example is a ketone and its enol form, known as keto-enol tautomers. The individual tautomers as well as mixtures
25 thereof are encompassed with compounds of Formula I.

Compounds of Formula I having one or more asymmetric centers may be separated into diastereoisomers, enantiomers, and the like by methods well known in the art.

Alternatively, enantiomers and other compounds with chiral centers may be synthesized by stereospecific synthesis using optically pure starting materials and/or reagents of known
30 configuration.

Some of the biphenyl and biaryl compounds herein are observed as mixtures of atropisomers (rotamers) in the NMR spectra. The individual atropisomers as well as mixtures thereof are encompassed with the compounds of this invention.

35 Salts

The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic or organic bases and inorganic or organic acids. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like.

Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts in the solid form may exist in more than one crystal structure, and may also be in the form of hydrates. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethyl-morpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like.

When the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pantoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid, and the like.

Particularly preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, and tartaric acids.

It will be understood that, as used herein, references to the compounds of Formula I are meant to also include the pharmaceutically acceptable salts.

Metabolites – Prodrugs

Therapeutically active metabolites, where the metabolites themselves fall within the scope of the claimed invention, are also compounds of the current invention. Prodrugs, which are compounds that are converted to the claimed compounds as they are being administered to a patient or after they have been administered to a patient, are also compounds of this invention.

Utilities

Compounds of the current invention are potent inhibitors of CETP. They are therefore useful in treating diseases and conditions that are treated by inhibitors of CETP.

One aspect of the present invention provides a method for treating or reducing the risk of developing a disease or condition that may be treated or prevented by inhibition of CETP by

administering a therapeutically effective amount of a compound of this invention to a patient in need of treatment. A patient is a human or mammal, and is most often a human. A "therapeutically effective amount" is the amount of compound that is effective in obtaining a desired clinical outcome in the treatment of a specific disease.

5 Diseases or conditions that may be treated with compounds of this invention, or which the patient may have a reduced risk of developing as a result of being treated with the compounds of this invention, include: atherosclerosis, peripheral vascular disease, dyslipidemia, hyperbetalipoproteinemia, hypoalphalipoproteinemia, hypercholesterolemia, hypertriglyceridemia, familial-hypercholesterolemia, cardiovascular disorders, angina, ischemia, cardiac ischemia, stroke, myocardial infarction, reperfusion
10 injury, angioplastic restenosis, hypertension, vascular complications of diabetes, obesity and endotoxemia.

The compounds of this invention are expected to be particularly effective in raising HDL-C and/or increasing the ratio of HDL-C to LDL-C. These changes in HDL-C and LDL-C may be beneficial in treating atherosclerosis, reducing or reversing the development of atherosclerosis, reducing
15 the risk of developing atherosclerosis, or preventing atherosclerosis.

Administration and Dose Ranges

Any suitable route of administration may be employed for providing a mammal, especially a human, with an effective dose of a compound of the present invention. For example, oral,
20 rectal, topical, parenteral, ocular, pulmonary, nasal, and the like may be employed. Dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules, creams, ointments, aerosols, and the like. Preferably compounds of Formula I are administered orally.

The effective dosage of active ingredient employed may vary depending on the particular compound employed, the mode of administration, the condition being treated and the severity of the
25 condition being treated. Such dosage may be ascertained readily by a person skilled in the art.

When treating the diseases for which compounds of Formula I are indicated, generally satisfactory results are obtained when the compounds of the present invention are administered at a daily dosage of from about 0.01 milligram to about 100 milligram per kilogram of animal or human body weight, preferably given as a single daily dose or in divided doses two to six times a day, or in sustained
30 release form. In the case of a 70 kg adult human, the total daily dose will generally be from about 0.5 milligram to about 500 milligrams. For a particularly potent compound, the dosage for an adult human may be as low as 0.1 mg. The dosage regimen may be adjusted within this range or even outside of this range to provide the optimal therapeutic response.

Oral administration will usually be carried out using tablets. Examples of doses in tablets are 0.5 mg, 1 mg, 2 mg, 5 mg, 10 mg, 25 mg, 50 mg, 100 mg, 250 mg, and 500 mg. Other oral forms can also have the same dosages (e.g. capsules).

Pharmaceutical Compositions

Another aspect of the present invention provides pharmaceutical compositions which comprise a compound of Formula I and a pharmaceutically acceptable carrier. The pharmaceutical compositions of the present invention comprise a compound of Formula I or a pharmaceutically acceptable salt as an active ingredient, as well as a pharmaceutically acceptable carrier and optionally other therapeutic ingredients. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic bases or acids and organic bases or acids. A pharmaceutical composition may also comprise a prodrug, or a pharmaceutically acceptable salt thereof, if a prodrug is administered. Pharmaceutical compositions may also consist essentially of a compound of Formula I and a pharmaceutically acceptable carrier without other therapeutic ingredients.

The compositions include compositions suitable for oral, rectal, topical, parenteral (including subcutaneous, intramuscular, and intravenous), ocular (ophthalmic), pulmonary (nasal or buccal inhalation), or nasal administration, although the most suitable route in any given case will depend on the nature and severity of the conditions being treated and on the nature of the active ingredient. They may be conveniently presented in unit dosage form and prepared by any of the methods well-known in the art of pharmacy.

In practical use, the compounds of Formula I can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral (including intravenous). In preparing the compositions for oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like in the case of oral liquid preparations, such as, for example, suspensions, elixirs and solutions; or carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents and the like in the case of oral solid preparations such as, for example, powders, hard and soft capsules and tablets, with the solid oral preparations being preferred over the liquid preparations.

Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be coated by standard aqueous or nonaqueous techniques. Such compositions and preparations should contain at least 0.1 percent of active compound. The percentage of active compound

in these compositions may, of course, be varied and may conveniently be between about 2 percent to about 60 percent of the weight of the unit. The amount of active compound in such therapeutically useful compositions is such that an effective dosage will be obtained. The active compounds can also be administered intranasally as, for example, liquid drops or spray.

5 The tablets, pills, capsules, and the like may also contain a binder such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, lactose or saccharin. When a dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as a fatty oil.

10 Various other materials may be present as coatings or to modify the physical form of the dosage unit. For instance, tablets may be coated with shellac, sugar or both. A syrup or elixir may contain, in addition to the active ingredient, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and a flavoring such as cherry or orange flavor.

15 Compounds of formula I may also be administered parenterally. Solutions or suspensions of these active compounds can be prepared in water suitably mixed with a surfactant such as hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

20 The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g. glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils.

Combination Therapy

30 Compounds of the invention (e.g. Formula I and Ia - Ij) may be used in combination with other drugs that may also be useful in the treatment or amelioration of the diseases or conditions for which compounds of Formula I are useful. Such other drugs may be administered, by a route and in an amount commonly used therefor, contemporaneously or sequentially with a compound of Formula I.

35 Therapeutic compounds that can be administered with the compounds of this invention include compounds that are useful in improving a patient's lipid profile (i.e. raising HDL-C and lowering LDL-C). Preferred compound are statins, including simvastatin, lovastatin, rosuvastatin, pravastatin, fluvastatin, atorvastatin, rivastatin, itavastatin, and ZD-4522.

CETP ASSAY

An in vitro continuous assay for determining IC_{50} 's to identify compounds that are CETP inhibitors was performed based on a modification of the method described by Epps et al. employing BODIPY®-CE as the cholesteryl ester lipid donor. See Epps et al.(1995) *Method for measuring the activities of cholesteryl ester transfer protein (lipid transfer protein)*, *Chem. Phys. Lipids*. 77, 51-63.

Particles used in the assay were created from the following sources: Synthetic donor HDL particles containing DOPC (Dioleoyl Phosphatidyl Choline), BODIPY®-CE (Molecular Probes C-3927), triolein (a triglyceride), and apoHDL were essentially created by probe sonication as described by Epps et al, but with the addition of a non-diffusible quencher molecule, dabcyI dicetylamine, in order to reduce background fluorescence. DabcyI dicetylamine was made by heating dabcyI n-succinimide with dicetylamine in DMF at 95°C overnight in the presence of diisopropylamine catalyst. Native lipoproteins from human blood were used as acceptor particles. Particles having a density less than 1.063 g/ml were collected by ultracentrifugation. These particles include VLDL, IDL, and LDL. Particle concentrations were expressed in terms of protein concentration as determined by BCA assay (Pierce, USA). Particles were stored at 4°C until use.

Assays were performed in Dynex Microfluor 2 U-bottom black 96-well plates (Cat #7205). An assay cocktail containing CETP, 1X CETP buffer (50 mM Tris, pH 7.4, 100 mM NaCl, 1 mM EDTA), and half the final concentration of acceptor particles was prepared, and 100 μ L of the assay cocktail was added to each well of the plate. Test compounds in DMSO were added in a volume of 3 μ L. The plate was mixed on a plate shaker and then incubated at 25 °C for 1 hour. A second assay cocktail containing donor particles, the remaining acceptor particles and 1X CETP buffer was prepared. 47 μ L of the second assay cocktail was added to the reaction wells to start the assay. Assays were performed at 25°C in a final volume of 150 μ L. Final concentrations of materials were: 5 ng/ μ L donor particles, 30 ng/ μ L acceptor particles (each expressed by protein content), 1X CETP buffer, 0.8 nM recombinant human CETP (expressed in CHO cells and partially purified), and up to 2% DMSO when testing compounds. The assay was followed in a fluorescence plate reader (Molecular Devices Spectramax GeminiXS) set for a 45 minute kinetic run at 25°C which read the samples every 45 sec at Ex = 480 nm, Em = 511 nm, with a cutoff filter at 495 nm, photomultiplier tube setting of medium, calibration on, and 6 reads/well.

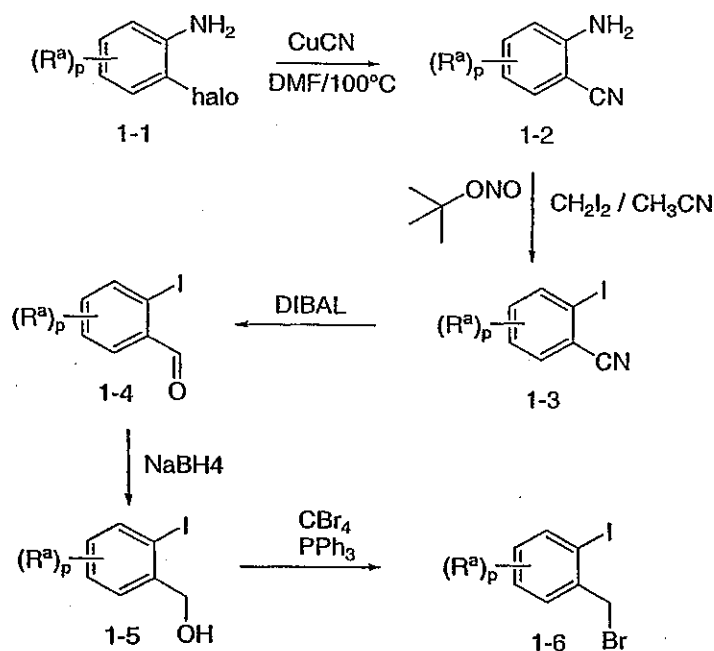
Data was evaluated by obtaining an initial rate, expressed in relative fluorescence units per second, for the pseudolinear portion of the curve, often 0-500 or 1000 sec. Comparison of the rates of samples with inhibitors to an uninhibited (DMSO only) positive control yielded a percent inhibition. A plot of percent inhibition vs. log of inhibitor concentration, fit to a Sigmoidal 4 parameter equation was used to calculate IC_{50} .

EXAMPLES

5 The following schemes and examples are provided so that the invention will be more fully appreciated and understood. Starting materials are made using known procedures or as shown below.

The examples should not be construed as limiting the invention in any way. The scope of the invention is defined by the appended claims. Compounds of this invention have an IC₅₀ value as measured using the assay described above of less than or equal to 50 μ M.

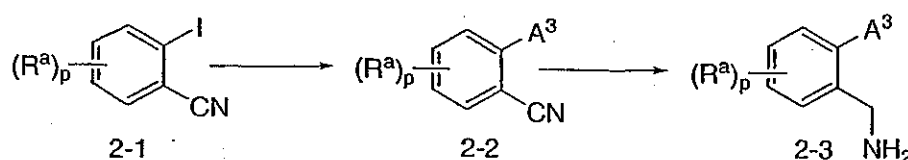
SCHEME 1



5

Intermediates 1-2, 1-3, 1-4, 1-5 and 1-6 utilized in the present invention can be purchased or prepared as shown in Scheme 1. An appropriately substituted 2-haloaniline 1-1 wherein R^a and p are as defined in the claims and where the halogen is preferably iodo or bromo is treated with CuCN in DMF at elevated temperature to afford the corresponding 2-cyanoaniline. Alternatively, the nitrile can be prepared by treatment of 1-1 with KCN and CuI in the presence of a palladium (II) salt or in the presence of certain copper or nickel complexes (See: Smith, M. B. and March, J. "March's Advanced Organic Chemistry", 5th Ed., John Wiley and Sons, New York, pp. 867 (2001) and references therein). Iodides 1-3 are prepared by treatment of 1-2 with isoamyl nitrite, n-pentyl nitrite, t-butyl nitrite or the like in the presence of diiodomethane (see for example: Smith et al., *J. Org. Chem.* 55, 2543, (1990) and references cited therein) either neat or in a solvent such as THF or acetonitrile. Alternatively, the iodide can be prepared first by diazonium formation using isoamyl nitrite, n-pentyl nitrite, t-butyl nitrite, sodium nitrite, nitrous acid or the like followed by heating in the presence of iodine or an iodide salt such as copper iodide, sodium iodide, potassium iodide, tetrabutylammonium iodide or the like. Reduction of 1-3 with DIBAL in dichloromethane affords aldehyde 1-4. Reduction of aldehyde 1-4 with sodium borohydride or the like in methanol or ethanol or the like gives alcohol 1-5. Treatment of 1-5 with carbon tetrabromide and triphenylphosphine in solvents such as dichloromethane, dichloroethane or the like gives benzyl bromide 1-6 (See: Smith, M. B. and March, J. "March's Advanced Organic Chemistry", 5th Ed., John Wiley and Sons, New York, pp. 518-519 (2001) and references therein).

SCHEME 2

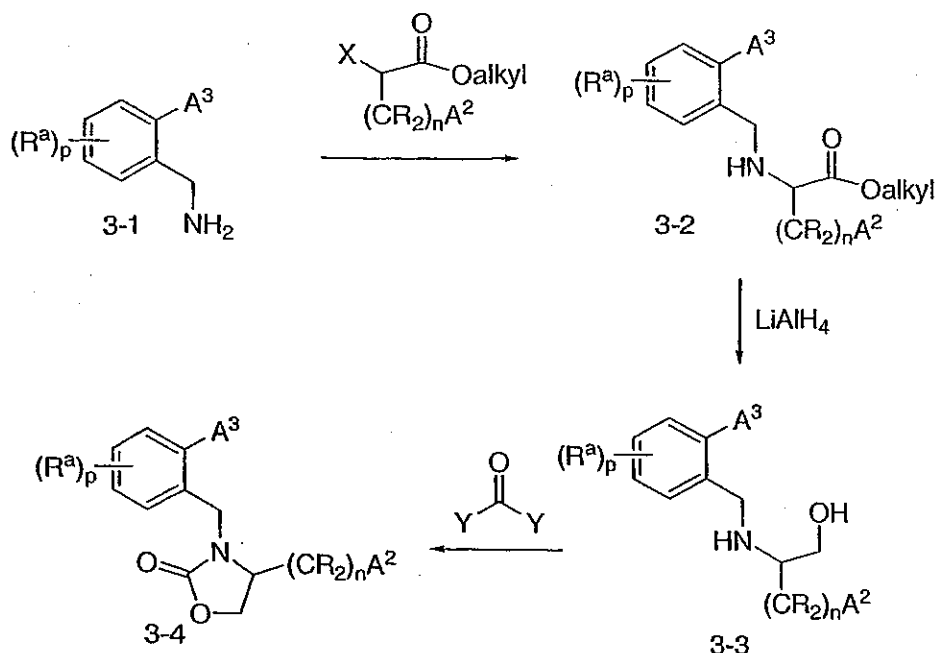


5

Intermediates 2-2 and 2-3 of the present invention wherein R^a , p , and A^3 are as defined in the claims can be prepared as shown in Scheme 2. 2-Cyano iodobenzenes 2-1 can be purchased or prepared according to the procedures outlined in Scheme 1. Compounds 2-2 are prepared via a Suzuki or Stille reaction or variation thereof employing palladium catalyzed cross coupling of iodide 2-1 with an appropriately substituted aryl- or heteroaryl-boronic acid, -boronate ester or -trialkyl tin as described in Miyaura et al., *Chem. Rev.* 95, 2457 (1995) and references cited within and as described in Smith, M. B. and March, J. "March's Advanced Organic Chemistry", 5th Ed., John Wiley and Sons, New York, pp. 868-869 (2001) and references cited therein. Reduction of nitrile 2-2 is accomplished with lithium aluminum hydride in diethyl ether to afford 2-aminomethyl aniline 2-3. Alternatively, the nitrile can be reduced with

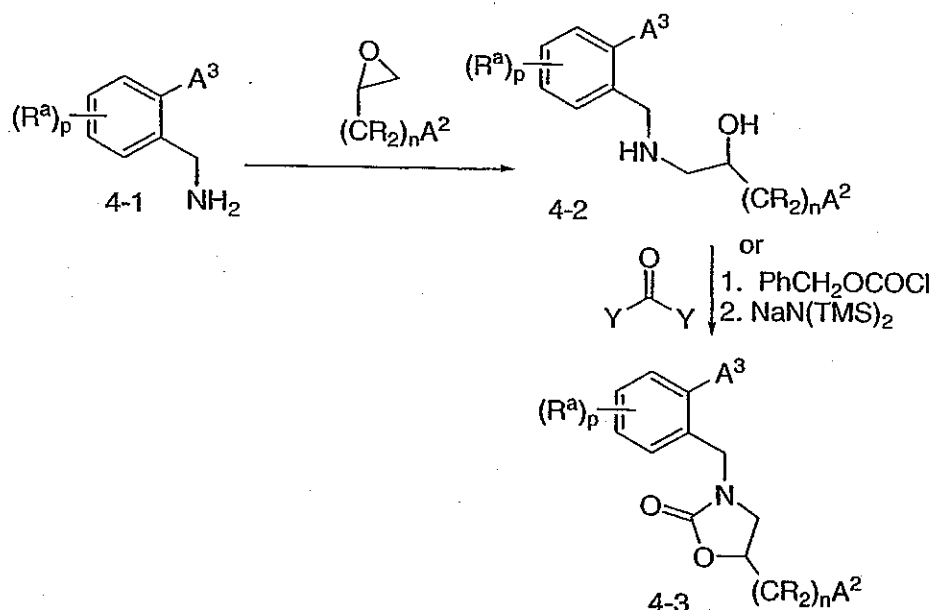
15 palladium on carbon or Raney nickel under hydrogen atmosphere in methanol, ethanol or the like. Other methods for reduction of a nitrile to an aminomethyl group can be found in Smith, M. B. and March, J. "March's Advanced Organic Chemistry", 5th Ed., John Wiley and Sons, New York, pp. 1204 (2001) and references therein.

SCHEME 3



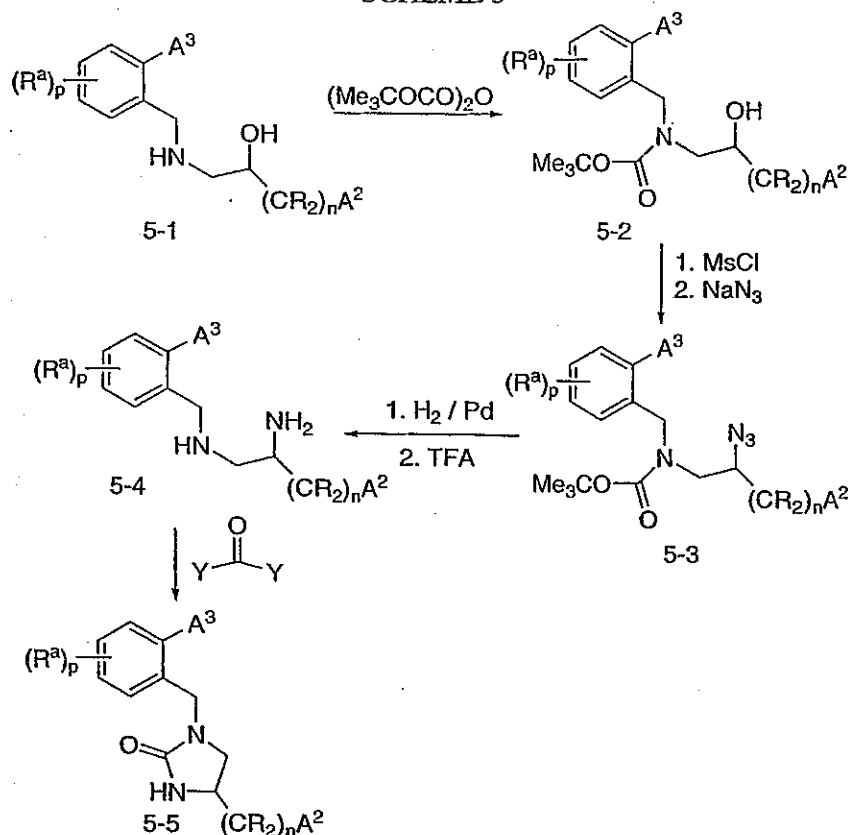
- 5 Compounds 3-4 of the present invention wherein R, R^a, p, A², A³ and n are as defined in the claims can be prepared according to the procedure outlined in Scheme 3. Benzyl amines 3-1 can be purchased or prepared according to the procedure outlined in Scheme 2. Reaction of 3-1 with an appropriately substituted alkyl acetate bearing a leaving group at the 2-position affords secondary amine 3-2. Alkyl acetates can be purchased or prepared using known methods. The preferred leaving group is bromide or iodide, but may also be mesylate, tosylate or the like and the solvent may be dichloromethane, dichloroethane, tetrahydrofuran, dimethoxyethane, or the like. The reaction may be run with or without a base such as triethylamine, diisopropylethylamine, N-methylmorpholine, or the like. Reduction of the ester functionality of 3-2 affords amino alcohol 3-3. The preferred reducing reagent is LiAlH₄, in a solvent such as ether, tetrahydrofuran, dimethoxyethane, dioxane, or the like. Other methods for reduction of an ester can be found in "March's Advanced Organic Chemistry" 5th Ed., John Wiley and Sons, New York, pp 1551. Amino alcohol 3-3 can be cyclised to oxazolidinone 3-4 using phosgene (Y=Cl) or a phosgene equivalent such as triphosgene (Y=OCCl₃) or carbonyl-diimidazole (Y=imidazole) or the like in a solvent such as dichloromethane, dichloroethane, tetrahydrofuran, dimethoxyethane, or the like and a base such as triethylamine, diisopropylethylamine, N-methylmorpholine, or the like.
- 0 Enantiopure products may be obtained via chiral chromatography.

SCHEME 4



Compounds of the present invention 4-3 wherein R , R^a , p , A^2 , A^3 and n are as defined in the claims can be prepared as shown in Scheme 4. An appropriately substituted benzylamine 4-1 can be reacted with an appropriately substituted oxirane to give amino alcohol 4-2. The oxiranes may be purchased or prepared from the corresponding aldehyde and a sulfur ylide as described in "March's Advanced Organic Chemistry" 5th Ed., John Wiley and Sons, New York, pp 1247. Alternatively the epoxide may be made from epoxidation of an olefin, cyclization of a halohydrin or 1, 2-diol, or other methods described in "March's Advanced Organic Chemistry" 5th Ed., John Wiley and Sons, New York, pp 1051. The preferred solvent for this reaction is isopropanol. Alternatively, the epoxide opening may be carried out in a solvent such as acetonitrile or the like with the aid of a Lewis Acid catalyst such as $Yb(OTf)_3$ or the like. Amino alcohol 4-2 can be cyclised to oxazolidinone 4-3 using phosgene ($Y=Cl$) or a phosgene equivalent such as triphosgene ($Y=OCCl_3$) or carbonyl-diimidazole ($Y=imidazole$) or the like in a solvent such as dichloromethane, dichloroethane, tetrahydrofuran, dimethoxyethane, or the like and a base such as triethylamine, diisopropylethylamine, N-methylmorpholine, or the like. Alternatively, aminoalcohol 4-2 can be converted to an appropriate carbamate by treatment with reagents such as dibenzyl dicarbonate or benzyl chloroformate in the presence of bases such as triethylamine, diisopropylethylamine or the like in solvents such as dichloromethane, dichloroethane, tetrahydrofuran, dimethoxyethane or the like. The carbamates can then be converted into oxazolidinones 4-3 by treating with bases like lithium-, sodium- or potassium hexamethyldisilazide in solvents like tetrahydrofuran, dimethoxyethane or the like. Enantiopure products may be obtained via chiral chromatography.

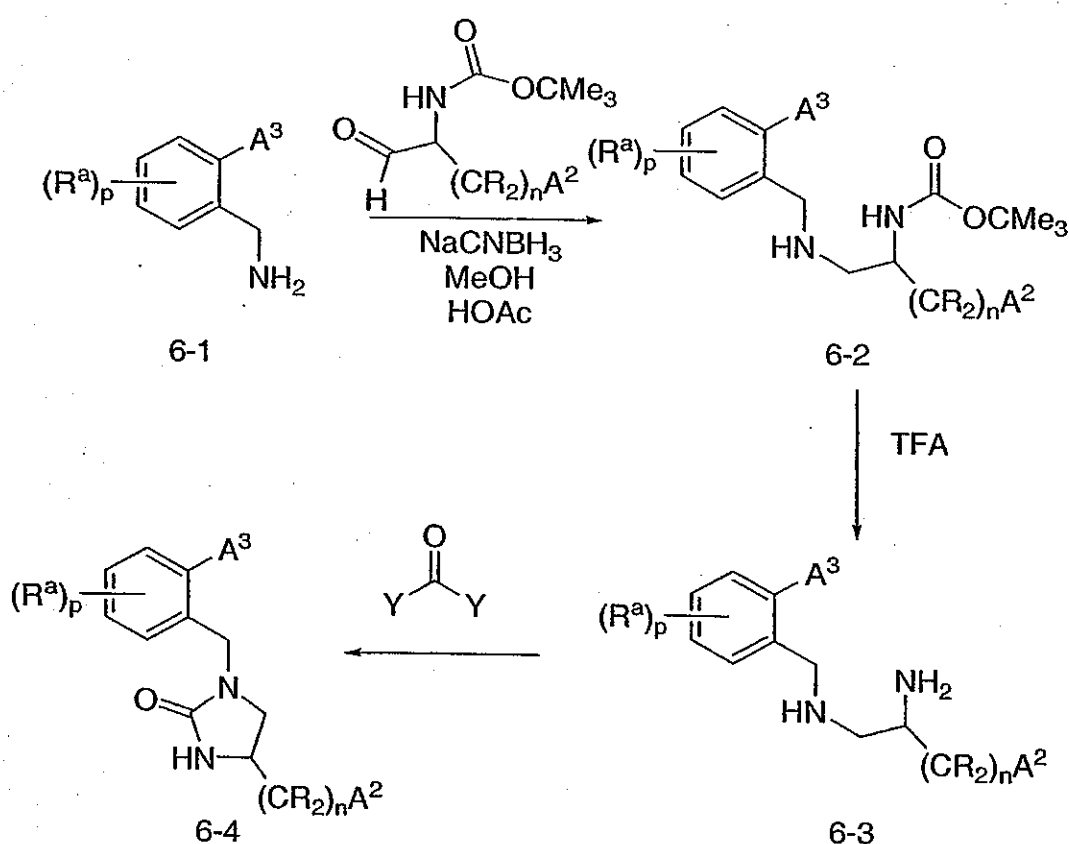
SCHEME 5



- 5 Compounds of the present invention 5-5 wherein R, R^a , p, A^2 , A^3 and n are as defined in the claims can be prepared as shown in Scheme 5. Appropriately substituted aminoalcohol 5-1 can be prepared as shown in Scheme 4 and preferentially protected as a carbamate such as *t*-butyl carbamate (BOC) or benzyl carbamate (Cbz). Other carbamate and alternative protecting groups for nitrogen can be found in "Protective Groups in Organic Synthesis", 3rd Ed. John Wiley and Sons, New York, pp 494. Protection of the nitrogen with a BOC or Cbz group can be carried out by reaction of 5-1 with di-*t*-butyldicarbonate or dibenzoyldicarbonate in an appropriate solvent such as dichloromethane, dichloroethane, tetrahydrofuran, dimethoxyethane, or the like. Alcohol 5-2 can be converted to azide 5-3 by reaction with methanesulfonyl chloride in dichloromethane, dichloroethane, tetrahydrofuran, dimethoxyethane, or the like in the presence of an appropriate base such as triethylamine, diisopropylethylamine, N-methylmorpholine, or the like. Alternatively, the alcohol may be converted to an alternative leaving group, such as tosylate, iodide, bromide, or the like. The mesylate is then displaced by an azide source, such as NaN_3 , LiN_3 , Bu_4NN_3 or the like in an appropriate solvent, such as DMF, DMPU, or the like. Azide 5-3 can also be prepared by treatment of alcohol 5-2 with diphenylphosphoryl azide, diethylazodicarboxylate and triphenylphosphine in THF. Azide 5-3 can be reduced by hydrogenation

over a metal catalyst such as PtO_2 or Pd/C or the like in an appropriate solvent, such as EtOAc , THF, EtOH, or the like. Following reduction and removal of the protecting group diamine 5-4 is obtained. For the BOC protecting group, TFA/ CH_2Cl_2 is the preferred method of removal; for the CBZ protecting group, hydrogenation over a metal catalyst, such as PtO_2 or Pd/C or the like in an appropriate solvent, such as EtOAc , THF, EtOH, or the like is the preferred method of removal. Diamines 5-4 are cyclized to imidazolidinones 5-5 using phosgene ($\text{Y}=\text{Cl}$) or a phosgene equivalent such as triphosgene ($\text{Y}=\text{OCCl}_3$) or carbonyldiimidazole ($\text{Y}=\text{imidazole}$) or the like in a solvent such as dichloromethane, dichloroethane, tetrahydrofuran, dimethoxyethane, or the like and a base such as triethylamine, diisopropylethylamine, N-methylmorpholine, or the like. Enantiopure products may be obtained via chiral chromatography.

SCHEME 6

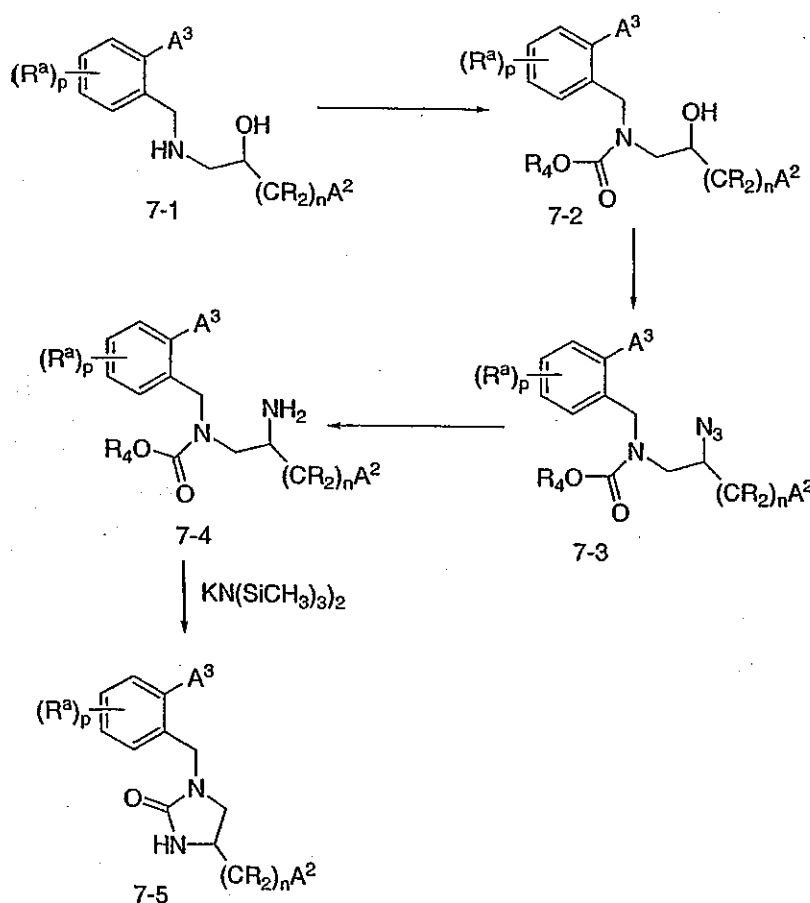


Compounds of the present invention 6-4 wherein R , R^a , p , A^2 , A^3 and n are as defined in the claims can be prepared as shown in Scheme 6. Treatment of 6-1 with an appropriately substituted protected aminoaldehyde which can be purchased or prepared by known methods in the presence of a reducing agent such as sodium borohydride, sodium cyanoborohydride, sodium triacetoxyborohydride or the like

in methanol, ethanol, dichloroethane, tetrahydrofuran or the like or according to methods described in Smith, M. B. and March, J. "March's Advanced Organic Chemistry", 5th Ed., John Wiley and Sons, New York, pp. 1187-1189 (2001) and references cited therein affords 6-2. Preferred conditions for this transformation are sodium cyanoborohydride in methanol with catalytic acetic acid. Deprotection of 6-2 affords 6-3. For the BOC protecting group, TFA/CH₂Cl₂ is the preferred method of deprotection.

Diamines 6-3 are then cyclized to imidazolidinones 6-4 using phosgene (Y=Cl) or a phosgene equivalent such as triphosgene (Y=OCCl₃) or carbonyl-diimidazole (Y=imidazole) or the like in a solvent such as dichloromethane, dichloroethane, tetrahydrofuran, dimethoxyethane, or the like and a base such as triethylamine, diisopropylethylamine, N-methylmorpholine, or the like. Enantiopure products may be obtained using chiral chromatography.

SCHEME 7

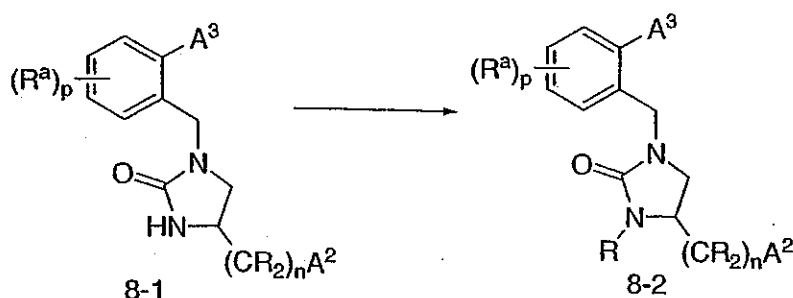


Compounds of the present invention 7-5 wherein R, R^a, p, A², A³ and n are as defined in the claims can be prepared as shown in Scheme 7. Treatment of amine 7-1, prepared as described in Scheme 4 with an appropriate dicarbonate or chloroformate affords 7-2. 7-2 can be converted to azide 7-3 by reaction with methanesulfonyl chloride in dichloromethane, dichloroethane, tetrahydrofuran, dimethoxyethane, or the

like in the presence of an appropriate base such as triethylamine, diisopropylethylamine, N-methylmorpholine, or the like. Alternatively, the alcohol may be converted to an alternative leaving group, such as tosylate, iodide, bromide, or the like. The mesylate is then displaced by an azide source, such as NaN₃, LiN₃, Bu₄NN₃ or the like in an appropriate solvent, such as DMF, DMPU, or the like.

- 5 Azide 7-3 can also be prepared by treatment of alcohol 5-2 with diphenylphosphoryl azide, diethylazodicarboxylate and triphenylphosphine in THF. Azide 7-3 can be reduced to amine 7-4 with H₂ over PtO₂ with THF as a solvent when R₄ is benzyl. Cyclization of 7-4 to imidazolidinones 7-5 is accomplished through the use of an appropriate base, such as lithium diisopropylamide or lithium-, sodium-, or potassium bis(trimethylsilyl)amide or the like in an appropriate solvent, such as THF, dimethoxyethane, DMF, DMA, or the like. Enantiopure products may be obtained via chiral chromatography.

SCHEME 8



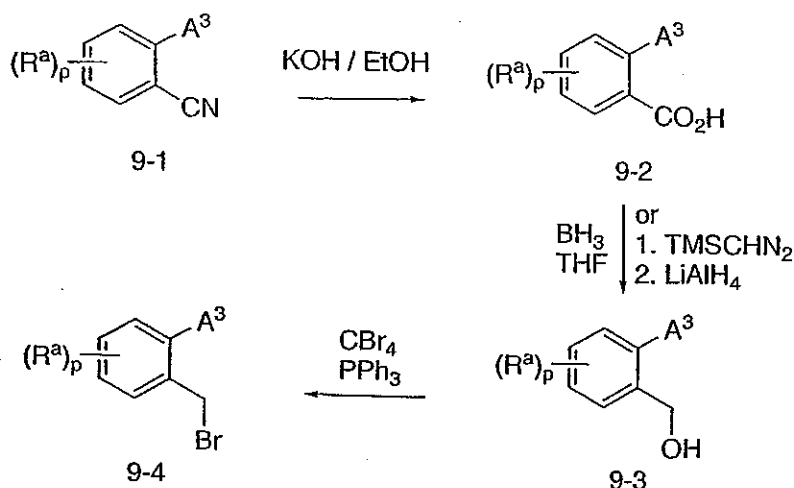
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- Compound 8-1 (prepared as described in Schemes 5, 6, and 7) wherein R, R_a, A², A³, p, and n are as defined in the claims can be converted to 8-2 by treatment with an appropriate alkylating agent such as an alkyl halide, alkyl tosylate, alkyl mesylate, or the like (for example methyl iodide) in an appropriate solvent such as THF, dimethoxyethane, DMF, DMA, or the like, in the presence of an appropriate base, such as lithium diisopropylamide or lithium-, sodium-, or potassium bis(trimethylsilyl)amide or the like.

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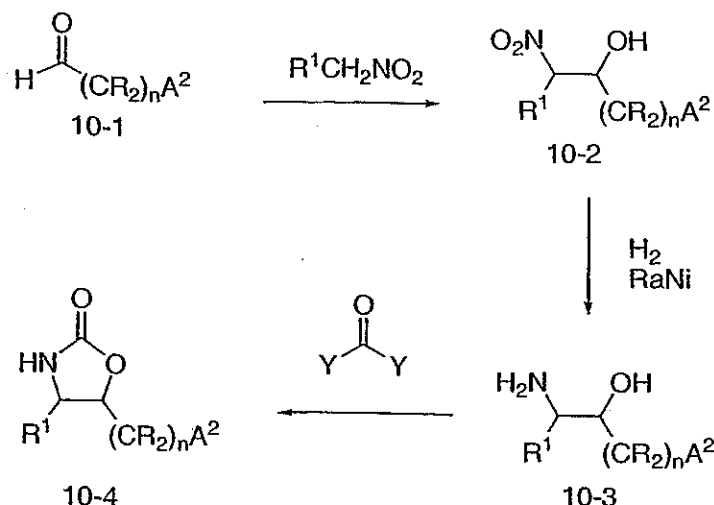
SCHEME 9

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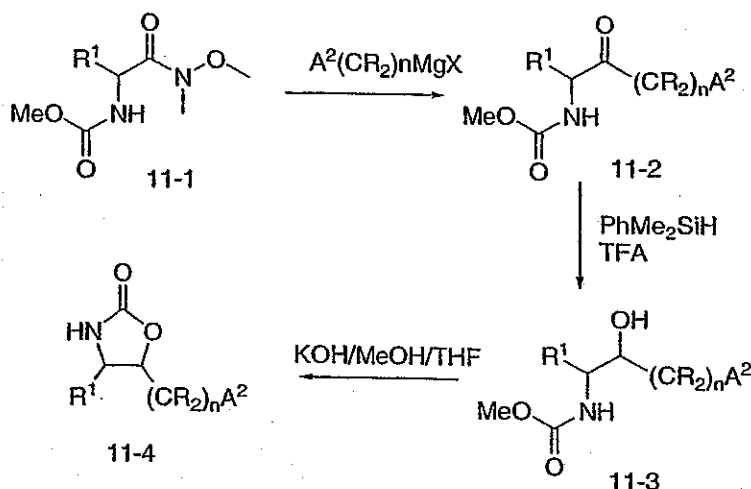
Intermediates 9-3 and 9-4 wherein R^a , p , and A^3 are as defined in the claims utilized in the present invention can be prepared as shown in Scheme 9. An appropriately substituted benzyl nitrile 9-1 prepared as shown in Scheme 2 can be heated with a base such as sodium hydroxide or potassium hydroxide or the like in an appropriate aqueous alcohol such as ethanol, propanol or the like to afford the appropriately substituted benzoic acid 9-2 (See: Smith, M. B. and March, J. "March's Advanced Organic Chemistry", 5th Ed., John Wiley and Sons, New York, pp. 1179-1180 (2001) and references therein). Benzoic acids 9-2 can be reduced to benzyl alcohols 9-3 with reducing agents such as borane in solvents such as tetrahydrofuran or the like (See: Smith, M. B. and March, J. "March's Advanced Organic Chemistry", 5th Ed., John Wiley and Sons, New York, pp. 1549 (2001) and references therein). Alternatively, 9-2 can be esterified by known methods including treatment with trimethylsilyldiazomethane and the resulting ester reduced to alcohol 9-3 with $LiAlH_4$ or the like. Intermediates 9-3 can be transformed into benzyl bromides 9-4 using reagents such as triphenylphosphine and carbon tetrabromide in solvents such as dichloromethane, dichloroethane or the like (See: Smith, M. B. and March, J. "March's Advanced Organic Chemistry", 5th Ed., John Wiley and Sons, New York, pp. 518-519 (2001) and references therein).

SCHEME 10



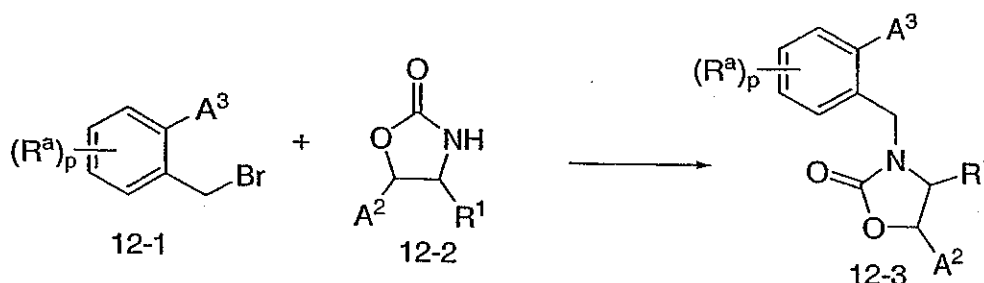
Intermediates 10-4 of the present invention wherein R, R^1 , A^2 , p, and n are as defined in the claims can be prepared as shown in Scheme 10 from an appropriately substituted benzaldehyde 10-1 by
 5 condensation with a nitroalkane to afford the substituted nitroalcohol 10-2. This reaction may be catalyzed by aqueous bases such as sodium hydroxide or the like in solvents such as ethanol, methanol or the like. Nitroalcohols 10-2 can be reduced to aminoalcohols 10-3 with reductants such as Raney nickel, palladium on activated carbon or platinum oxide in the presence of hydrogen gas and aqueous acid in alcoholic solvents such as methanol, ethanol or the like (See: Langer, O., *et al.*, *Bioorg. Med. Chem.*,
 10 2001, 9, 677-694). Aminoalcohols 10-3 can be cyclised to oxazolidinones 10-4 using reagents such as phosgene ($\text{Y}=\text{Cl}$), triphosgene ($\text{Y}=\text{OCCl}_3$) or carbonyl diimidazole ($\text{Y}=\text{imidazole}$) with bases such as triethylamine, diisopropylethylamine or the like in solvents like dichloromethane, dichloroethane, tetrahydrofuran, dimethoxyethane or the like.

SCHEME 11



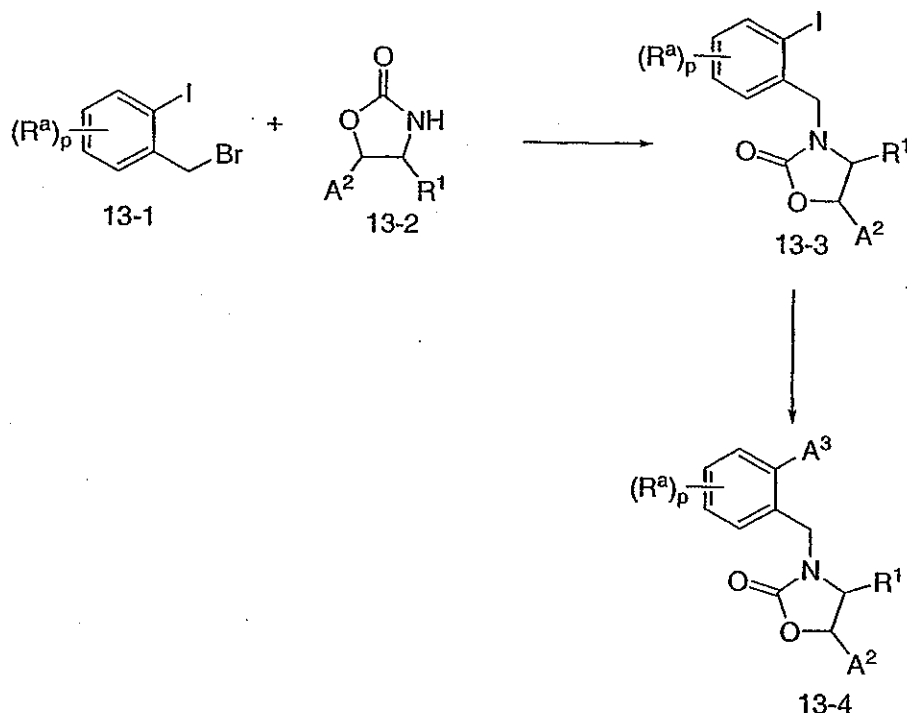
Intermediates 11-4 of the present invention wherein R, R¹, A², p and n are as defined in the claims can be prepared as shown in scheme 11. Treatment of an N-carbamoyl-(N-methoxy-N-methyl)amide of an amino acid 11-1 which can be purchased or prepared by known methods with a Grignard or other organometallic reagent such as an organolithium affords the corresponding ketone 11-2. Reduction of the ketone with sodium borohydride or zinc borohydride in alcoholic solvents or THF or the like or with other reducing agents such as phenyldimethyl silane in THF affords alcohol 11-3 which can be cyclized to oxazolidinone 11-4 upon treatment with base such as KOH in solvents such as MeOH, EtOH or the like and THF, dioxane, dimethoxyethane or the like.

SCHEME 12



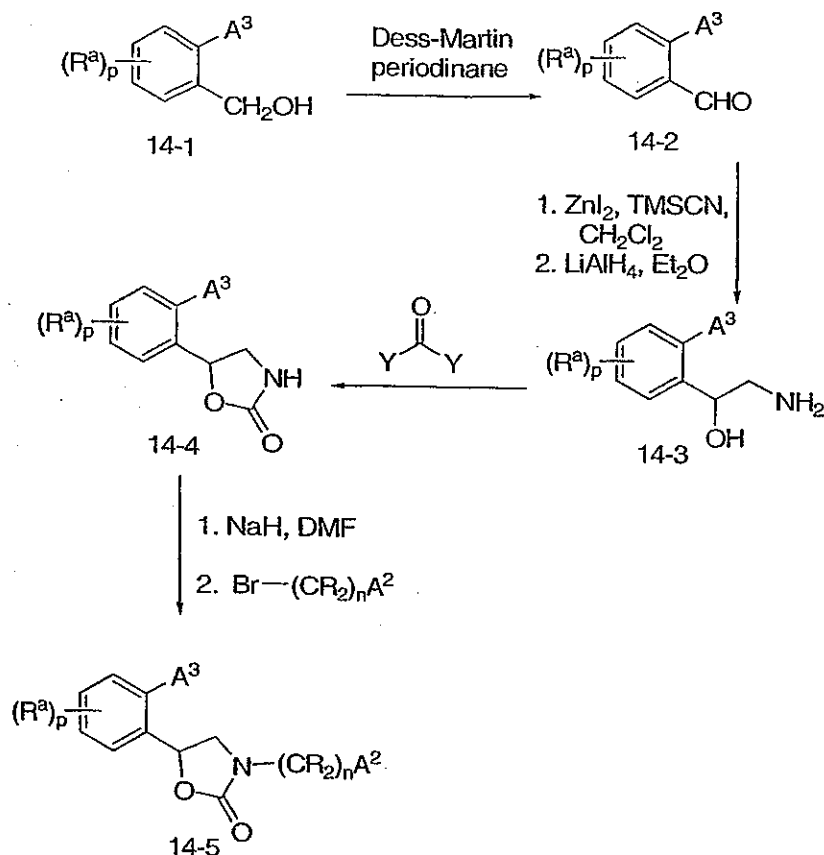
Compounds of the present invention 12-3 wherein R, R¹, R^a, A², A³, p and n are as defined in the claims can be prepared as shown in Scheme 12. Oxazolidinones 12-2, prepared as shown in Schemes 10 and 11 can be alkylated with benzyl bromides 12-1 which is prepared as shown in Scheme 9 using bases such as sodium hexamethyldisilazide or sodium hydride in solvents like tetrahydrofuran, dimethoxyethane, diethyl ether, dimethylformamide, dimethylacetamide, or the like to afford products 12-3.

SCHEME 13



Compounds of the present invention 13-4 wherein R, R^1 , R^a , A^2 , A^3 , p and n are as defined in the claims can be prepared as shown in Scheme 13. Oxazolidinones 13-2, prepared as shown in Schemes 10 and 11 can be alkylated with benzyl bromides 13-1 which can be prepared as shown in Scheme I using bases such as sodium hexamethyldisilazide or sodium hydride in solvents like tetrahydrofuran, dimethoxyethane, diethyl ether or the like to afford products 13-3. Compounds 13-4 are then prepared via a Suzuki or Stille reaction or variation thereof employing palladium catalyzed cross coupling of iodide 13-3 with an appropriately substituted aryl- or heteroaryl-boronic acid, -boronate ester or -trialkyl tin as described in Miyaura et al., *Chem. Rev.* 95, 2457 (1995) and references cited within and as described in Smith, M. B. and March, J. "March's Advanced Organic Chemistry", 5th Ed., John Wiley and Sons, New York, pp. 868-869 (2001) and references cited therein.

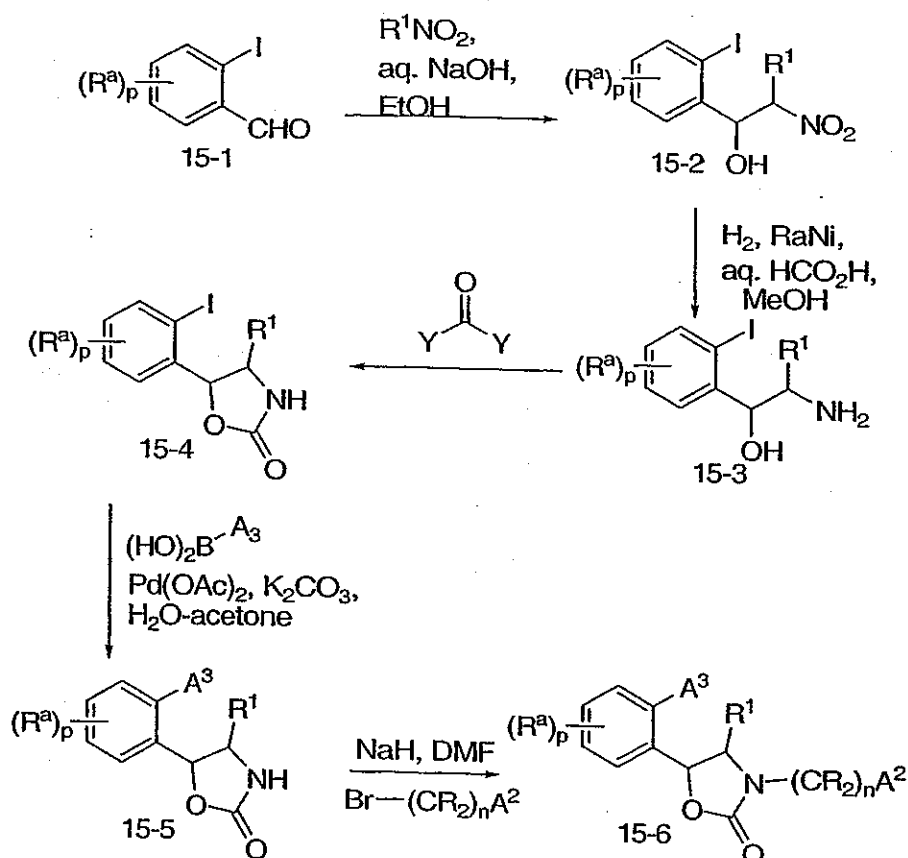
SCHEME 14



Compounds 14-5 of the present invention wherein R, R^a, A², A³, p and n are as defined in the claims can be prepared as shown in Scheme 14. Benzyl alcohols 14-1 can be purchased or prepared according to the procedure outline in Scheme 9. Reaction of 14-1 with the Dess-Martin periodinane affords the corresponding benzaldehydes 14-2. Other methods for oxidizing a primary hydroxyl group to an aldehyde can also be used, for example, Swern oxidation conditions, tetrapropylammonium perruthenate, pyridinium chlorochromate, sulfur trioxide-pyridine, or the like. 2-Amino-1-phenylethanols 14-3 can be prepared from 14-2 via the corresponding silylated cyanohydrin by treatment with trimethylsilyl cyanide and catalytic zinc iodide followed by reduction with lithium aluminum hydride or the like reducing agent. Alternatively, 2-amino-1-phenylethanols 14-3 can be prepared from 14-2 via the corresponding cyanohydrin by treatment with potassium cyanide followed by reduction. 2-Amino-1-phenylethanols 14-3 can be cyclized to oxazolidinones 14-4 using reagents such as phosgene (Y=Cl), triphosgene (Y=OCCl₃) or carbonyl diimidazole (Y=imidazole) with bases such as triethylamine, diisopropylethylamine or the like in solvents like dichloromethane, dichloroethane, tetrahydrofuran, dimethoxyethane or the like. Oxazolidinones 14-4 can be alkylated with alkyl, heteroalkyl, aryl, or heteroaryl bromides using bases such as sodium hexamethyldisilazide or sodium hydride in solvents like

tetrahydrofuran, dimethoxyethane, diethyl ether or the like to afford products 14-5. Enantiopure products may be obtained via chiral chromatography.

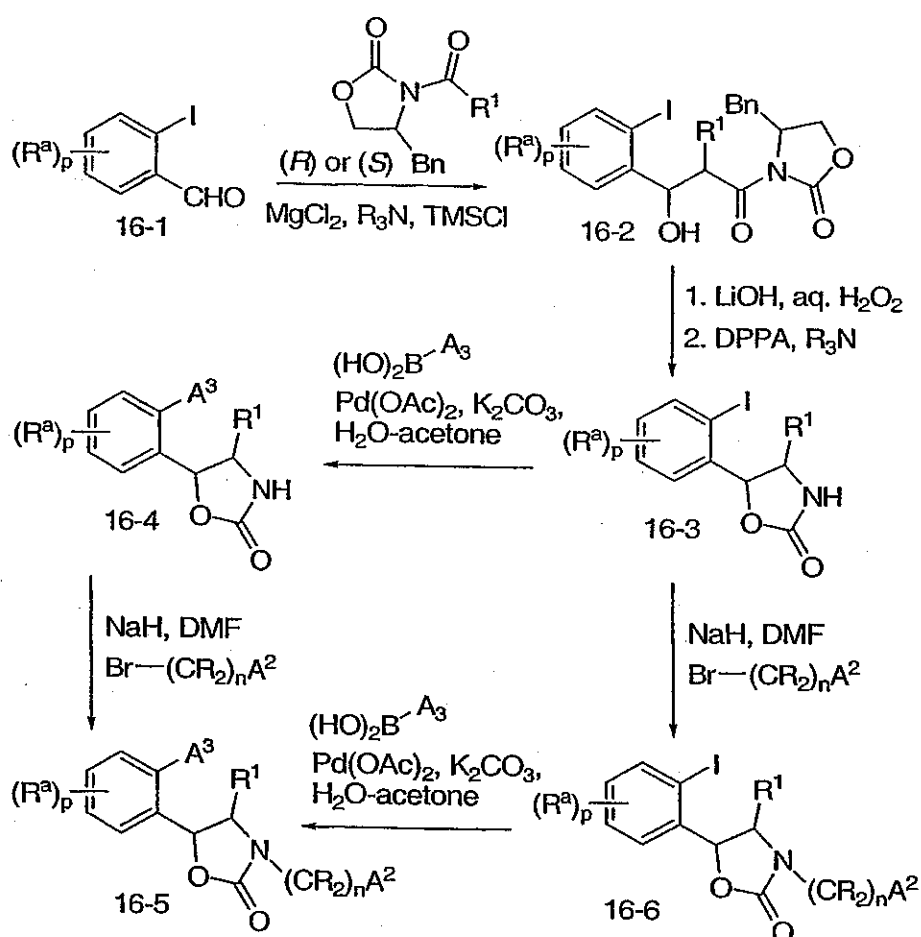
SCHEME 15



Compounds 15-6 of the present invention wherein R, R¹, R^a, A², A³, p and n are as defined in the claims can be prepared as shown in Scheme 15. Aldehydes 15-1 can be purchased or prepared according to the procedure outline in Scheme 1. Condensation of 15-1 with a nitroalkane affords the substituted nitroalcohols 15-2. This reaction may be catalyzed by aqueous bases such as sodium hydroxide or the like in solvents such as ethanol, methanol, or the like. Nitroalcohols 15-2 can be reduced to aminoalcohols 15-3 with reductants such as Raney nickel, palladium on activated carbon, or platinum oxide in the presence of hydrogen gas and aqueous acid in alcoholic solvents such as methanol, ethanol or the like (See: Langer, O., et al., *Bioorg. Med. Chem.*, 2001, 9, 677-694). Aminoalcohols 15-3 can be cyclized to oxazolidinones 15-4 using reagents such as phosgene (Y=Cl), triphosgene (Y=OCCl₃) or carbonyl diimidazole (Y=imidazole) with bases such as triethylamine, diisopropylethylamine or the like in solvents like dichloromethane, dichloroethane, tetrahydrofuran, dimethoxyethane or the like. Oxazolidinones 15-5 are prepared via a Suzuki or Stille reaction or variation thereof employing

palladium catalyzed cross coupling of iodides 15-4 with appropriately substituted aryl- or heteroaryl-boronic acids, -boronate esters or -trialkyl tin compounds, as described in Miyaura et al., *Chem. Rev.* 95, 2457 (1995) and references cited within, and as described in Smith, M. B. and March, J. "March's Advanced Organic Chemistry", 5th Ed., John Wiley and Sons, New York, pp. 868-869 (2001) and references cited therein. Oxazolidinones 15-5 can be alkylated with alkyl, heteroalkyl, aryl, or heteroaryl bromides using bases such as sodium hexamethyldisilazide or sodium hydride in solvents like tetrahydrofuran, dimethoxyethane, diethyl ether or the like to afford products 15-6. Enantiopure products may be obtained via chiral chromatography.

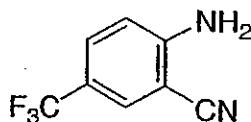
SCHEME 16



- 5 Compounds 16-5 of the present invention wherein R , R^1 , R^a , A^2 , A^3 , p and n are as defined in the claims can be prepared as shown in Scheme 16. Aldehydes 16-1 can be purchased or prepared according to the procedure outline in Scheme 1. Condensation of 16-1 with chiral *N*-acyloxazolidinones affords the aldol

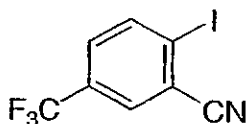
adducts 16-2, as described in Evans, D.A. *et al.*, *J. Am. Chem. Soc.*, **2002**, *124*, 392-3. The chiral *N*-acyloxazolidinones can be purchased or prepared as described in Ager, D.J.; Allen, D.A.; Schaad, D.R. *Synthesis* **1996**, 1283-5. Compounds 16-2 can be hydrolyzed to the corresponding acids and then treated with diphenylphosphorazidate and a trialkylamine base to effect a Curtius rearrangement, affording chiral oxazolidinones 16-3. Oxazolidinones 16-4 are prepared via a Suzuki or Stille reaction or variation thereof employing palladium catalyzed cross coupling of iodides 16-3 with appropriately substituted aryl- or heteroaryl-boronic acids, -boronate esters or -trialkyl tin compounds, as described in Miyaura *et al.*, *Chem. Rev.* **95**, 2457 (1995) and references cited within, and as described in Smith, M. B. and March, J. "March's Advanced Organic Chemistry", 5th Ed., John Wiley and Sons, New York, pp. 868-869 (2001) and references cited therein. Oxazolidinones 16-4 can be alkylated with alkyl, heteroalkyl, aryl, or heteroaryl bromides using bases such as sodium hexamethyldisilazide or sodium hydride in solvents like tetrahydrofuran, dimethoxyethane, diethyl ether or the like to afford products 16-5. Alternatively, oxazolidinones 16-3 are alkylated with the appropriate bromides to afford compounds 16-6, which are subjected to a Suzuki or Stille reaction or variation thereof with appropriately substituted aryl- or heteroaryl-boronic acids, -boronate esters or -trialkyl tin compounds to afford products 16-5.

EXAMPLE 1

2-Amino-5-(trifluoromethyl)benzonitrile

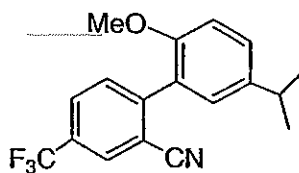
A 2-liter flask was charged with 100g (0.348 mol) of 4-amino-3-iodobenzotrifluoride, 40 g of CuCN and 750 mL of DMF. The mixture was heated to and then maintained at reflux for 1 hour. The reaction was cooled and poured into 3L of water containing 300 mL of concentrated ammonium hydroxide. To the mixture was added 1L CH₂Cl₂. The mixture was then filtered through celite. The layers were separated and the aqueous layer was back extracted with CH₂Cl₂. The organic extracts were combined and the solvent removed under reduced pressure. The residue was dissolved in 1.5 L of ether and the resulting solution was washed with 1N ammonium hydroxide, aqueous sodium bisulfite, 1N aqueous HCl and brine. The solution was dried over anhydrous MgSO₄ and filtered through a silica gel plug containing a layer of MgSO₄ on top. The plug was washed with .5L ether. The ether solutions were combined and concentrated to 750 mL and let stand at room temperature. After 2 days the resulting solids were collected, washed with hexanes and dried under reduced pressure to afford 2-amino-5-(trifluoromethyl)benzonitrile: ¹H NMR (CDCl₃, 500 MHz) δ 7.68 (s, 1H), 7.58 (d, *J* = 8.5 Hz, 1H), 6.81 (d, *J* = 8.5 Hz, 1H), 4.80 (br s, 2H).

EXAMPLE 2

2-Iodo-5-(trifluoromethyl)benzonitrile

To a solution of 2-amino-5-(trifluoromethyl)benzonitrile (15.1 g) and diiodomethane (24 mL) in acetonitrile (150 mL) at 35°C was added *t*-butyl nitrite (21 mL) dropwise. The reaction was maintained at 30 – 35°C during the addition. The reaction was aged for 30 min and then was heated to 60°C for 30 minutes. The reaction mixture was cooled, diluted with ether and washed 2x with water, 2x with aqueous sodium bisulfite, water and then brine. The solution was dried over anhydrous MgSO₄, filtered through a silica gel plug and then concentrated giving 100 g of a red oil. The product was purified by silica gel chromatography eluting sequentially with hexanes, 3:1 hexanes/CH₂Cl₂ and 1:1 hexanes/CH₂Cl₂ to afford 2-iodo-5-(trifluoromethyl)benzonitrile. ¹H NMR (CDCl₃, 500 MHz) δ 8.10 (d, *J* = 8.5 Hz, 1H), 7.85 (d, *J* = 1.8 Hz, 1H), 7.52 (dd, *J* = 8.5, 1.8 Hz, 1H).

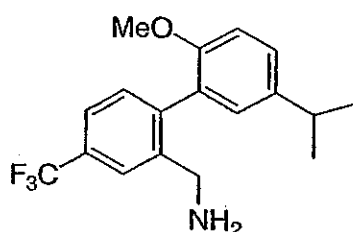
EXAMPLE 3

5'-Isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-carbonitrile

To a solution of 2-iodo-5-(trifluoromethyl)benzonitrile (2.0 g, 6.7 mmol) and (5-isopropyl-2-methoxyphenyl)boronic acid (1.6 g, 8.4 mmol) in dimethyl ethylene glycol (30.4 mL) was added 2M Na₂CO₃ (6.8 mL), ethanol (9.6 mL), and water (10 mL). The solution was degassed with nitrogen for 2 minutes. Pd(PPh₃)₄ (774 mg, 0.67 mmol) was added and the solution was degassed with nitrogen again for 2 minutes. The solution was divided equally into two 40 mL microwave tubes. Each tube was degassed with nitrogen for 1 minute, sealed, and placed in a microwave reactor. The wattage was set for 200 W until the temperature reached 150°C and then the temperature was held at 150°C for ten minutes. The tubes were then cooled to room temperature, combined, poured into H₂O (50 mL), and extracted

with EtOAc (100 mL). The organic layer was washed with brine (50 mL), dried over Na₂SO₄, filtered, and concentrated. Purification by flash chromatography with 15% CH₂Cl₂/hexanes afforded 5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-carbonitrile as a light yellow oil. R_f = 0.65 (25% EtOAc/hexanes). ¹H NMR (CDCl₃, 500 MHz) δ 7.97 (s, 1H), 7.85 (d, J = 8.0 Hz, 1H), 7.63 (d, J = 8.0 Hz, 1H), 7.31 (dd, J = 8.5, 2.0 Hz, 1H), 7.12 (d, J = 2.0 Hz, 1H), 6.97 (d, J = 8.5 Hz, 1H), 3.82 (s, 3H), 2.93 (m, 1H), 1.27 (d, J = 7.0 Hz, 6H).

EXAMPLE 4

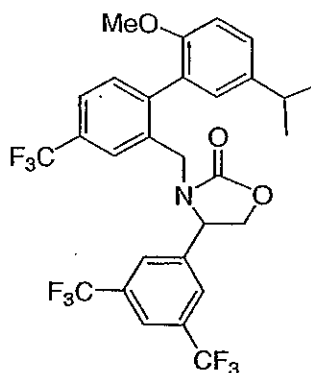
10 1-[5'-Isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methanamine

5'-Isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-carbonitrile (996.2 mg, 3.12 mmol) was dissolved in Et₂O (33 mL) and cooled to 0°C. LAH (12.49 mL of a 1 M solution in Et₂O, 12.49 mmol) was added dropwise by syringe. After stirring at 0°C for 10 minutes, the reaction was warmed to room temperature and stirred at room temperature for 6 hours. The reaction was then quenched by slow dropwise addition of 1.5 mL of H₂O (vigorous evolution of gas), followed by 1.5 mL of 30% NaOH, followed by 3.0 mL of H₂O. The resulting gelatinous precipitate was washed with 5 x 20 mL of CH₂Cl₂; the organic washes were dried over Na₂SO₄, filtered and concentrated. Purification of the residue by flash chromatography with 2% MeOH/CH₂Cl₂ containing 0.1% Et₃N afforded 1-[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methanamine. R_f = 0.30 (10% MeOH/CH₂Cl₂). LCMS = 324.3 (M+1)⁺.

20 ¹H NMR (CDCl₃, 500 MHz) δ 7.77 (s, 1H), 7.55 (d, J = 6.8 Hz, 1H), 7.32 (d, J = 7.8 Hz, 1H), 7.25 (dd, J = 8.3, 2.1 Hz, 1H), 7.00 (d, J = 2.1 Hz, 1H), 6.92 (d, J = 8.4 Hz, 1H), 3.66-3.74 (m, 5H), 2.91 (m, 1H), 1.26 (d, J = 6.9 Hz, 6H).

EXAMPLE 5

25



4-[3,5-bis(trifluoromethyl)phenyl]-3-({[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl}-1,3-oxazolidin-2-one

Step A: methyl [3,5-bis(trifluoromethyl)phenyl](hydroxy)acetate

To solution of [3,5-bis(trifluoromethyl)phenyl](hydroxy)acetic acid (510 mg, 1.77 mmol) in benzene (10 mL) was added MeOH (1.5 mL) followed by (trimethylsilyl)diazomethane (1.06 mL of a 2M solution in hexanes, 2.12 mmol). After 10 minutes, the reaction was quenched with several drops of HOAc (add until yellow color disappears). The reaction was concentrated and purified by flash chromatography with 10 to 80% EtOAc/hexanes to afford methyl [3,5-bis(trifluoromethyl)phenyl](hydroxy)acetate. ¹H NMR (CDCl₃, 500 MHz) δ 7.94 (s, 2H), 7.85 (s, 1H), 5.32 (s, 1H), 3.83 (s, 3H), 3.68 (bs, 1H).

Step B: methyl [3,5-bis(trifluoromethyl)phenyl](bromo)acetate

Methyl [3,5-bis(trifluoromethyl)phenyl](hydroxy)acetate (300 mg, 0.993 mmol) was dissolved in CH₂Cl₂ (10 mL). The solution was cooled to 0°C and CBr₄ (659 mg, 1.986 mmol) was added followed by PPh₃ (521 mg, 1.986 mmol). After 1 hour, the reaction was warmed to room temperature and stirred at room temperature for 1 hour. The reaction was filtered through a short plug of silica gel with CH₂Cl₂. The filtrate was concentrated and the residue was purified by flash chromatography with 5% EtOAc/hexanes to afford methyl [3,5-bis(trifluoromethyl)phenyl](bromo)acetate. R_f = 0.24 (5% EtOAc/hexanes). ¹H NMR (CDCl₃, 500 MHz) δ 8.02 (s, 2H), 7.87 (s, 1H), 5.41 (s, 1H), 3.83 (s, 3H).

Step C: methyl[3,5-bis(trifluoromethyl)phenyl]({[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl}amino)acetate

To a flask containing methyl [3,5-bis(trifluoromethyl)phenyl](bromo)acetate (237.7 mg, 0.651 mmol) was added 1-[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methenamine (102.1 mg, 0.316 mmol) in CH₂Cl₂ (4 mL). The reaction was stirred at room temperature for 5 hours and then diluted with EtOAc (50 mL). The organic solution was washed with water and brine (15 mL each). The organic extract was dried over Na₂SO₄, filtered, and concentrated. Purification of the residue by flash

chromatography (5 to 15% EtOAc/hexanes) afforded methyl[3,5-bis(trifluoromethyl)phenyl]([5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl)methyl]amino)acetate. $R_f = 0.33$ (15% EtOAc/hexanes). LCMS = 608.4 (M+1)⁺. ¹H NMR (CDCl₃, 500 MHz) δ 7.76-7.79 (m, 3H), 7.62 (s, 1H), 7.56 (d, $J = 7.8$ Hz, 1H), 7.31 (d, $J = 7.8$ Hz, 1H), 7.23 (dd, $J = 8.2, 1.9$ Hz, 1H), 6.96 (m, 1H), 6.89 (d, $J = 8.5$ Hz, 1H), 4.30 (m, 1H), 3.54-3.70 (m, 8H), 2.87 (m, 1H), 1.21-1.23 (m, 6H).

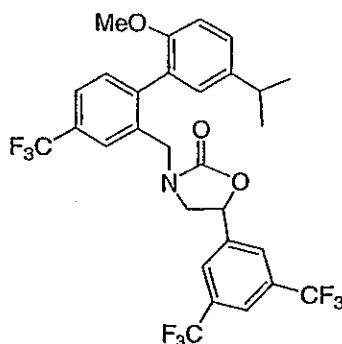
Step D: 2-[3,5-bis(trifluoromethyl)phenyl]-2-([5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl)methyl]amino)ethanol

A solution of methyl[3,5-bis(trifluoromethyl)phenyl]([5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl)methyl]amino)acetate (13.2 mg, 0.0217 mmol) was dissolved in Et₂O (1.5 mL) and cooled to 0°C. LAH (108.5 μ L of a 1 M solution in LAH, 0.1085 mmol) was added dropwise by syringe. The reaction was warmed to room temperature and stirred at room temperature for 1 hour. The reaction was then quenched by addition of H₂O (100 μ L) followed by 1 N NaOH (100 μ L), followed by H₂O (300 μ L). The gelatinous precipitate was washed several times with CH₂Cl₂. The organic washes were filtered through a plug of silica gel with 2% MeOH/CH₂Cl₂ and the filtrate was concentrated. Purification of the residue by PTLC with 25% EtOAc/hexanes afforded 2-[3,5-bis(trifluoromethyl)phenyl]-2-([5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl)methyl]amino)ethanol. $R_f = 0.27$ (25% EtOAc/hexanes). LCMS = 580.4 (M+1)⁺. ¹H NMR (CD₂Cl₂, 500 MHz) δ 7.79 (s, 1H), 7.75 (s, 2H), 7.63-7.68 (m, 1H), 7.55 (d, $J = 7.8$ Hz, 1H), 7.31 (d, $J = 7.8$ Hz, 1H), 7.23 (m, 1H), 6.94 (m, 1H), 6.89 (m, 1H), 3.43-3.76 (m, 9H), 2.86 (m, 1H), 1.90 (bs, 1H), 1.20 (d, $J = 6.8$ Hz, 6H).

Step E: 4-[3,5-bis(trifluoromethyl)phenyl]-3-([5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl)methyl]-1,3-oxazolidin-2-one

To a solution of phosgene (21 μ L of a 20% solution in toluene, ~ 0.0535 mmol) in CH₂Cl₂ (0.5 mL) was added 2-[3,5-bis(trifluoromethyl)phenyl]-2-([5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl)methyl]amino)ethanol (3.1 mg, 0.00535 mmol) in CH₂Cl₂ (0.5 mL), followed by DIPEA (19 μ L, 0.107 mmol). After stirring for 5 minutes, the reaction was poured into water (1 mL) and the mixture was extracted with EtOAc (20 mL). The organic extract was washed with H₂O, saturated NaHCO₃, and brine (5 mL each). The organic layer was then dried over Na₂SO₄, filtered, and concentrated. The residue was purified by PTLC to afford 4-[3,5-bis(trifluoromethyl)phenyl]-3-([5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl)methyl]-1,3-oxazolidin-2-one. $R_f = 0.27$ (25% EtOAc/hexanes). LCMS = 606.3 (M+1)⁺. ¹H NMR (CD₂Cl₂, 500 MHz) (Doubling of some peaks observed; atropisomers present in 1:1 ratio) δ 7.84 (s, 1H), 7.19-7.60 (m, 6H), 6.80-6.87 (m, 2H), 3.84-4.68 (m, 5H), 3.68 & 3.64 (2 singlets, 3H), 2.82 (m, 1H), 1.17-1.21 (m, 6H).

EXAMPLE 6



5-[3,5-bis(trifluoromethyl)phenyl]-3-([5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl)-1,3-oxazolidin-2-one

Step A: 2-[3,5-bis(trifluoromethyl)phenyl]oxirane

In a dry flask was placed NaH (1.09 g of 60% NaH, 27.27 mmol). DMSO (90 mL) was added followed by trimethylsulfoxonium iodide (7.0 g, 31.82 mmol). The reaction was stirred for 5 minutes and then 3,5-bis(trifluoromethyl)benzaldehyde (1.5 mL, 9.09 mmol) was added as a solution in DMSO (15 mL). The reaction was stirred at room temperature for 1 hour and then poured into ice/water (300 mL). The mixture was extracted with pentanes (3 x 150 mL). The pentane extracts were combined and filtered through a short plug of silica gel with 10% Et₂O/pentanes. The filtrate was concentrated and the residue was purified by flash chromatography with 10% Et₂O/pentanes to give 2-[3,5-bis(trifluoromethyl)phenyl]oxirane. *R_f* = 0.42 (10% Et₂O/pentanes). ¹H NMR (CDCl₃, 500 MHz) 7.82 (s, 1H), 7.74 (s, 2H), 3.99 (dd, *J* = 3.9, 2.5 Hz, 1H), 3.23 (dd, *J* = 5.2, 4.1 Hz, 1H), 2.79 (dd, *J* = 5.5, 2.5 Hz, 1H).

Step B: 1-[3,5-bis(trifluoromethyl)phenyl]-2-([5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl)amino)ethanol

A solution of 1-[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methenamine (300 mg, 0.929 mmol) and 2-[3,5-bis(trifluoromethyl)phenyl]oxirane (297 mg, 1.161 mmol) in 2-propanol (9 mL) was heated at reflux for 15 hours and then cooled to room temperature. The solution was concentrated, and purification of the residue by flash chromatography with 10 to 80% EtOAc/hexanes afforded 1-[3,5-bis(trifluoromethyl)phenyl]-2-([5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl)amino)ethanol. *R_f* = 0.24 (25% EtOAc/hexanes). LCMS = 580.3 (M+1)⁺. ¹H NMR (CDCl₃, 500 MHz) δ 7.75-7.76 (m, 3H), 7.69 (s, 1H), 7.58 (d, *J* = 7.8 Hz, 1H), 7.34 (d, *J* = 7.7 Hz, 1H), 7.25 (m,

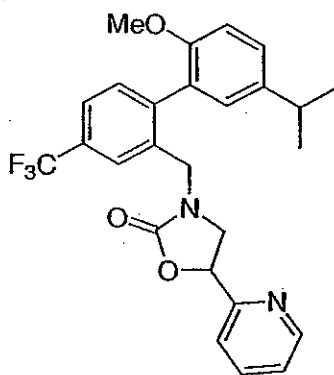
1H), 6.98 (bs, 1H), 6.92 (d, $J = 8.5$ Hz, 1H), 4.62 (m, 1H), 3.65-3.82 (m, 5H), 2.89 (m, 1H), 2.79 (dd, $J = 12.4, 3.0$ Hz, 1H), 2.48 (m, 1H), 1.23 (d, $J = 6.8$ Hz, 6H).

Step C: 5-[3,5-bis(trifluoromethyl)phenyl]-3-([5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl)-1,3-oxazolidin-2-one

To a solution of 1-[3,5-bis(trifluoromethyl)phenyl]-2-([5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl)amino)ethanol (31.9 mg, 0.0551 mmol) in CH_2Cl_2 (5 mL) at 0°C was added DIPEA (67 μL , 0.386 mmol), followed by triphosgene (8.2 mg, 0.0276 mmol). The reaction was stirred at 0°C for 30 minutes. The reaction was then poured into saturated NaHCO_3 (15 mL) and the mixture was extracted with EtOAc (50 mL). The organic layer was washed with brine (15 mL), dried over Na_2SO_4 , filtered, and concentrated. Purification of the residue by flash chromatography (20% EtOAc/hexanes) afforded 5-[3,5-bis(trifluoromethyl)phenyl]-3-([5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl)-1,3-oxazolidin-2-one. $R_f = 0.32$ (25% EtOAc/hexanes). LCMS = 606.3 ($\text{M}+1$)⁺. ^1H NMR (CD_2Cl_2 , 500 MHz) (atropisomers present in 1:1 ratio, doubling of some peaks) δ 7.90 (s, 1H), 7.77 (s, 2H), 7.57-7.62 (m, 2H), 7.37 (d, $J = 8.0$ Hz, 1H), 7.27 (m, 1H), 6.98 (s, 1H), 6.93 (dd, $J = 8.4, 3.2$ Hz, 1H), 5.42-5.53 (m, 1H), 4.15-4.59 (m, 2H), 3.72 & 3.73 (2 singlets, 3H), 3.05-3.65 (m, 2H), 2.88 (m, 1H), 1.19-1.23 (m, 6H).

The 2 enantiomers could be separated by chiral HPLC using 15% IPA/heptanes and an AD chiral column.

EXAMPLE 7



3-([5'-Isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl)-5-pyridin-2-yl-1,3-oxazolidin-2-one

Step A: 2-([5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl)amino)-1-pyridin-2-ylethanol

A solution of 1-[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methenamine (300 mg, 0.929 mmol) and 2-oxiran-2-ylpyridine (640 mg) [prepared by reaction of 2-pyridine carboxaldehyde with NaH and trimethylsulfoxonium iodide in DMSO] in 2-propanol (9 mL) was heated at reflux for 5 hours and then cooled to room temperature. The solution was concentrated, and the residue was purified by flash chromatography with 50 to 100% EtOAc/hexanes containing 0.5% Et₃N to afford 2-([5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl)amino)-1-pyridin-2-ylethanol. Analysis by LCMS showed the desired product contaminated with several minor impurities. This material was used in the next reaction without further purification or analysis.

Step B: Benzyl (2-hydroxy-2-pyridin-2-ylethyl){[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl}carbamate

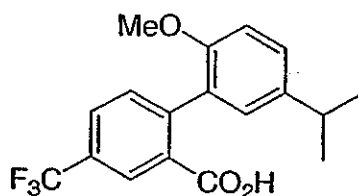
A solution of (PhCH₂OCO)₂O (103 mg, 0.360 mmol) in dry CH₂Cl₂ (2 mL) was added by cannula to a stirred solution of 2-([5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl)amino)-1-pyridin-2-ylethanol (160 mg, 0.360 mmol) in dry CH₂Cl₂ (10 mL) at room temperature under N₂. The reaction was stirred for 2 h at room temperature and concentrated *in vacuo* to give the crude product.

This was purified by flash chromatography (Si, 25 x 160 mm, 0-50% EtOAc in hexanes gradient) to afford benzyl (2-hydroxy-2-pyridin-2-ylethyl){[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl}carbamate. *R_f* = 0.63 (50% EtOAc/hexanes). LCMS calc. = 579.25; found = 579.2 (M+1)⁺.

Step C: 3-([5'-Isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl)-5-pyridin-2-yl-1,3-oxazolidin-2-one

A solution of potassium bis(trimethylsilyl)amide (464 μL of a 0.5M solution in toluene, 0.232 mmol) was added dropwise to a stirred solution of benzyl (2-hydroxy-2-pyridin-2-ylethyl){[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl}carbamate (134.3 mg, 0.232 mmol) in dry THF (10 mL) at room temperature under N₂. After stirring at room temperature for 1 h, the reaction was quenched with saturated NH₄Cl (10 mL) and extracted with EtOAc (3 x 20 mL). The combined extracts were dried (Na₂SO₄) and concentrated *in vacuo* to give the crude product. This was purified by flash chromatography (Si, 25 x 160 mm, 0-70% EtOAc in hexanes gradient) to afford 3-([5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl)-5-pyridin-2-yl-1,3-oxazolidin-2-one. *R_f* = 0.58 (50% EtOAc/hexanes). LCMS calc. = 471.19; found = 471.2 (M+1)⁺.

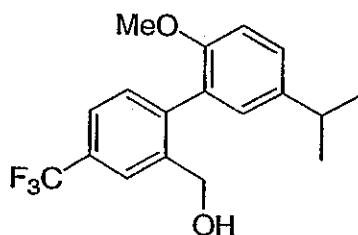
EXAMPLE 8



5'-Isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-carboxylic acid

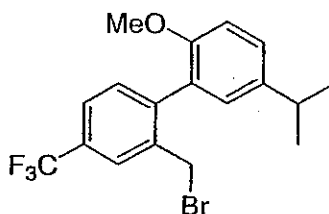
A solution of 5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-carbonitrile (727 mg, 2.28 mmol) and KOH (767 mg, 13.7 mmol) in H₂O (7.70 mL) and *i*-PrOH (11.55 mL) was subjected to microwave irradiation (300W 130°C, 4 h) in a sealed tube. The reaction mixture was concentrated *in vacuo* to remove the *i*-PrOH. The aqueous slurry obtained was diluted with water (50 mL) and extracted with EtOAc (50 mL). The organic extract was dried (Na₂SO₄) and concentrated *in vacuo* to afford 5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-carboxamide. The aqueous layer was acidified with concentrated HCl and extracted with EtOAc (3 x 50 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated *in vacuo* to give 5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-carboxylic acid as a colorless solid. ¹H NMR (CDCl₃, 500 MHz) δ 8.01 (s, 1H), 7.71 (d, *J* = 7.8 Hz, 1H), 7.41 (d, *J* = 7.8 Hz, 1H), 7.14 (d, *J* = 8.1 Hz, 1H), 7.04 (s, 1H), 6.77 (d, *J* = 8.1, 1H), 3.68 (s, 3H), 2.84 (septet, *J* = 6.7 Hz, 1H), 1.19 (d, *J* = 6.7 Hz, 6H).

EXAMPLE 9

[5'-Isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methanol

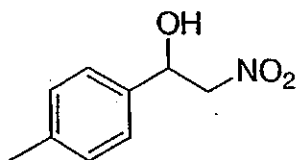
A solution of borane in THF (1 M, 859 μL, 0.859 mmol) was added dropwise to a stirred solution of 5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-carboxylic acid and 5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-carboxamide (3:1, 96.8 mg, 0.286 mmol) in dry THF at room temperature under N₂. The reaction was stirred at room temperature for 3 h and carefully quenched with water (10 mL). The mixture was extracted with EtOAc (3 x 20 mL) and the combined extracts were washed with brine, dried (Na₂SO₄) and concentrated *in vacuo* to give the crude product. This was purified by flash chromatography (Si, 125 x 160 mm, 0-30% EtOAc in hexanes gradient) to afford [5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methanol as a colorless oil. *R_f* = 0.27 (10% EtOAc/hexanes). ¹H NMR (CDCl₃, 500 MHz) δ 7.89 (br s, 1H), 7.62 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.29 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.03 (d, *J* = 2.3 Hz, 1H), 6.96 (d, *J* = 8.5, 1H), 4.51 (m, 2H), 3.74 (s, 3H), 2.93 (septet, *J* = 7.0 Hz, 1H), 2.51 (s, 1H), 1.29 (d, *J* = 7.0 Hz, 6H).

EXAMPLE 10

2-(Bromomethyl)-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl

CBr₄ (112 mg, 0.211 mmol) and Ph₃P (55 mg, 0.211 mmol) were added successively to a stirred solution of [5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methanol (57.1 mg, 0.176 mmol) in dry CH₂Cl₂ (1 mL) at 0°C under N₂. The solution was stirred at room temperature for 1 h and the reaction mixture was concentrated *in vacuo* to afford the crude product. This was purified by flash chromatography (Si, 12 x 160 mm, 0-20% EtOAc in hexanes gradient) to give 2-(bromomethyl)-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl as a colorless oil. *R_f* = 0.95 (20% EtOAc/hexanes). LCMS calc. = 387.05; found = 387.0 (M+1)⁺. ¹H NMR (CDCl₃, 500 MHz) δ 7.83 (br s, 1H), 7.60 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.37 (d, *J* = 8.0 Hz, 1H), 7.29 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.14 (d, *J* = 2.3 Hz, 1H), 6.95 (d, *J* = 8.5, 1H), 4.45 (d, *J* = 10.6 Hz, 1H), 4.33 (d, *J* = 10.6 Hz, 1H), 3.76 (s, 3H), 2.94 (septet, *J* = 6.9 Hz, 1H), 1.29 (d, *J* = 6.9 Hz, 6H).

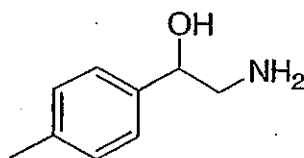
EXAMPLE 11

1-(4-Methylphenyl)-2-nitroethanol

A stirred solution of 4-methylbenzaldehyde (325 mg, 319 μL, 2.71 mmol) and nitromethane (531 μL, 9.89 mmol) in absolute EtOH (20 mL) at 0°C was treated with 10% aq. NaOH (m/v) (1.14 mL, 2.84 mmol), stirred for 1 h and treated with 2% aq. acetic acid (m/v) (8.54 mL, 2.84 mmol). The reaction was stirred for 1 h at room temperature then partitioned between water (50 mL) and EtOAc (50 mL). The aqueous layer was extracted with EtOAc (2 x 50 mL) and the combined organic extracts were washed with saturated NaHCO₃ (50 mL) and brine (50 mL), dried (Na₂SO₄) and concentrated *in vacuo* to afford 1-(4-methylphenyl)-2-nitroethanol as a colorless oil. ¹H NMR (CDCl₃, 500 MHz) δ 7.28 (d, *J* = 8.1 Hz,

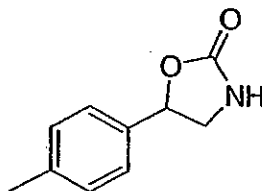
2H), 7.21 (d, $J = 8.1$ Hz, 2H), 5.42 (dt, $J = 9.6, 3.3$ Hz, 1H), 4.60 (dd, $J = 13.3, 9.7$ Hz, 1H), 4.49 (dd, $J = 13.3, 3.1$ Hz, 1H), 2.79 (d, $J = 3.7$, 1H), 2.36 (s, 3H).

EXAMPLE 12

2-Amino-1-(4-methylphenyl)ethanol

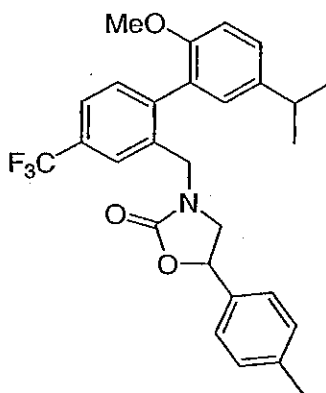
A suspension of 10% Pd/C (24 mg) in a solution of 1-(4-methylphenyl)-2-nitroethanol (50 mg, 0.276 mmol) in absolute EtOH (1 mL) was stirred overnight at room temperature under 15 psi of H₂. The reaction mixture was filtered through a pad of Celite and the filtrate was concentrated *in vacuo* to afford 2-amino-1-(4-methylphenyl)ethanol as an oil. LCMS calc. = 152.10; found = 152 (M+1)⁺. ¹H NMR (CDCl₃, 500 MHz) δ 7.20 (d, $J = 8.0$ Hz, 2H), 7.13 (d, $J = 8.0$ Hz, 2H), 4.57 (dd, $J = 7.9, 3.9$ Hz, 1H), 2.86 (dd, $J = 12.7, 3.9$ Hz, 1H), 2.76 (dd, $J = 12.7, 7.9$ Hz, 1H), 2.33 (s, 3H).

EXAMPLE 13

5-(4-Methylphenyl)-1,3-oxazolidin-2-one

Diisopropylethylamine (181 mg, 244 μ L, 1.40 mmol) and triphosgene (138 mg, 0.466 mmol) were added successively to a stirred solution of 2-amino-1-(4-methylphenyl)ethanol (35.2 mg, 0.233 mmol) in dry CH₂Cl₂ (22 mL) at 0°C under N₂. The reaction was stirred at 0°C for 1 h then concentrated *in vacuo* to a volume of about 5 mL. The mixture was diluted with water (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated *in vacuo* to give the crude product. This was purified by flash chromatography (Si, 12 x 160 mm, 0-80% EtOAc in hexanes gradient) to afford 5-(4-methylphenyl)-1,3-oxazolidin-2-one. $R_f = 0.41$ (50% EtOAc/hexanes). LCMS calc. = 178.08; found = 178.1 (M+1)⁺. ¹H NMR (CDCl₃, 500 MHz) δ 7.25 (d, $J = 7.4$ Hz, 2H), 7.19 (d, $J = 7.4$ Hz, 2H), 6.69 (br s, 1H), 5.55 (t, $J = 7.8$ Hz, 1H), 3.93 (t, $J = 8.6$ Hz, 1H), 3.52 (t, $J = 8.1$ Hz, 1H), 2.35 (s, 3H).

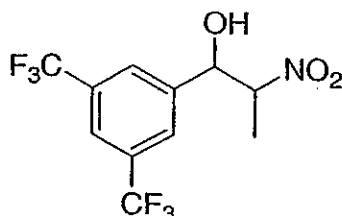
EXAMPLE 14



3-([5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl)-5-(4-methylphenyl)-1,3-oxazolidin-2-one

Sodium hydride (6.4 mg of a 60% dispersion in mineral oil, 0.161 mmol) was added to a stirred solution of 5-(4-methylphenyl)-1,3-oxazolidin-2-one (37.7 mg, 0.0973 mmol) in dry THF (1 mL) at room temperature under N₂. The reaction was stirred for 30 min and a solution of 2-(bromomethyl)-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl (19.0 mg, 0.107 mmol) in dry THF (2 mL) was added by cannula. The reaction was stirred at room temperature for 3 days. The reaction was quenched with saturated NH₄Cl (10 mL) and extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine (10 mL), dried (Na₂SO₄) and concentrated *in vacuo* to give the crude product. This was purified by flash chromatography (Si, 12 x 160 mm, 0-80% EtOAc in hexanes gradient) to afford 3-([5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl)-5-(4-methylphenyl)-1,3-oxazolidin-2-one as a colorless oil. *R_f* = 0.37 (20% EtOAc/hexanes). LCMS calc. = 484.21; found = 484.2 (M+1)⁺. ¹H NMR (benzene-*d*₆, 500 MHz, 1:1 mixture of atropisomers) δ 7.76 (s, 0.5H), 7.65 (s, 0.5H), 7.31 (d, *J* = 7.7 Hz, 1H), 7.08 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.05 (br d, *J* = 7.8 Hz, 1H), 6.95-6.86 (m, 5H), 6.58 (t, *J* = 7.7 Hz, 1H), 4.74 (t, *J* = 8.0 Hz, 0.5H), 4.70 (t, *J* = 8.0 Hz, 0.5H), 4.50 (d, *J* = 15.7 Hz, 0.5H), 4.42 (d, *J* = 15.7 Hz, 0.5H), 4.25 (d, *J* = 15.7 Hz, 0.5H), 4.11 (d, *J* = 15.7 Hz, 0.5H), 3.26 (s, 1.5H), 3.21 (s, 1.5H), 2.81 (t, *J* = 8.6 Hz, 0.5H), 2.76 (septet, *J* = 7.0 Hz, 1H), 2.68 (t, *J* = 8.6 Hz, 0.5H), 2.55 (t, *J* = 8.6 Hz, 0.5H), 2.53 (t, *J* = 8.6 Hz, 0.5H), 2.04 (s, 3H), 1.20 (t, *J* = 7.0 Hz, 3H), 1.19 (t, *J* = 7.0 Hz, 3H).

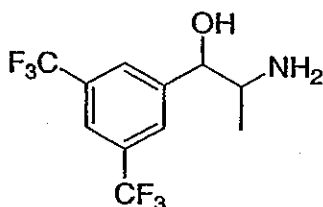
EXAMPLE 15

1-[3,5-Bis(trifluoromethyl)phenyl]-2-nitropropan-1-ol

A stirred solution of 3,5-bis(trifluoromethyl)benzaldehyde (1.00g, 4.13 mmol) and nitroethane (1.13 g, 1.08 mL, 15.1 mmol) in absolute EtOH (20 mL) at 0°C was treated with 10% aq. NaOH (m/v) (1.73 mL, 4.34 mmol), stirred for 1 h and treated with 2% aq. acetic acid (m/v) (13.0 mL, 4.32 mmol). The reaction was stirred for 1 h at room temperature then partitioned between water (50 mL) and EtOAc (50 mL).

The aqueous layer was extracted with EtOAc (2 x 50 mL) and the combined organic extracts were washed with saturated NaHCO₃ (50 mL) and brine (50 mL), dried (Na₂SO₄) and concentrated *in vacuo* to afford a 1.5:1 mixture of *threo*- and *erythro*- 1-[3,5-bis(trifluoromethyl)phenyl]-2-nitropropan-1-ol as a colorless oil. ¹H NMR (CDCl₃, 500 MHz) *threo*-diastereoisomer: δ 7.88 (br s, 1H), 7.86 (br s, 2H), 5.22 (d, *J* = 8.4 Hz, 1H), 4.77 (dq, *J* = 8.4, 6.9 Hz, 1H), 3.03 (br s 1H), 1.42 (d, *J* = 6.9 Hz, 3H), *erythro*-diastereoisomer: δ 7.90 (br s, 1H), 7.86 (br s, 2H), 5.59 (d, *J* = 3.2 Hz, 1H), 4.72 (dq, *J* = 3.2, 6.9 Hz, 1H), 3.03 (br s 1H), 1.50 (d, *J* = 6.9 Hz, 3H).

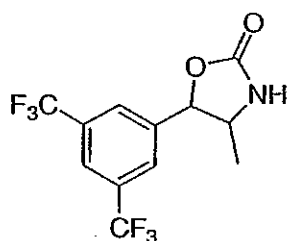
EXAMPLE 16

2-Amino-1-[3,5-bis(trifluoromethyl)phenyl]propan-1-ol

A suspension of Raney Nickel (50 mg) in a solution of a 1.5:1 mixture of *threo*- and *erythro*- 1-[3,5-bis(trifluoromethyl)phenyl]-2-nitropropan-1-ol (50 mg, 0.158 mmol) in 30%(v/v) aqueous HCO₂H (0.75 mL) and MeOH (10 mL) was stirred overnight at room temperature under 15 psi of H₂. The reaction mixture was filtered through a pad of Celite and the filtrate was concentrated *in vacuo* to remove the MeOH. The aqueous slurry was adjusted to pH 9-10 with 28% aq NH₄OH, diluted with water (20 mL)

and extracted with EtOAc (3 x 20 mL). The combined extracts were washed with brine (10 mL), dried (Na₂SO₄) and concentrated *in vacuo* to afford a mixture of *threo*- and *erythro*-2-amino-1-[3,5-bis(trifluoromethyl)phenyl]propan-1-ol as colorless solid. LCMS calc. = 288.08; found = 288.1 (M+1)⁺. ¹H NMR (CDCl₃, 500 MHz) *threo*-diastereoisomer: δ 7.79 (br s, 3H), 4.35 (br s, 1H), 3.25 (br s, 1H), 2.59 (br s, 3H), 0.86 (d, *J* = 6.1 Hz, 3H), *erythro*-diastereoisomer: δ 7.79 (br s, 3H), 4.71 (br s, 1H), 3.00 (br s, 1H), 2.59 (br s, 3H), 1.06 (d, *J* = 5.0 Hz, 3H).

EXAMPLE 17

5-[3,5-Bis(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one

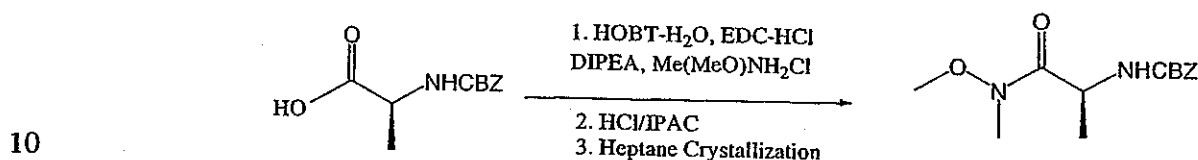
Diisopropylethylamine (106 mg, 142 μL, 0.817 mmol) and triphosgene (20.2 mg, 0.068 mmol) were added successively to a stirred solution of 2-Amino-1-[3,5-bis(trifluoromethyl)phenyl]propan-1-ol (39.1 mg, 0.136 mmol) in dry CH₂Cl₂ (10 mL) at 0°C under N₂. The reaction was stirred at 0°C for 1 h then concentrated *in vacuo* to a volume of about 5 mL. The mixture was diluted with water (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated *in vacuo* to give the crude product. This was purified by flash chromatography (Si, 12 x 160 mm, 0-70% EtOAc in hexanes gradient) to afford *threo*-5-[3,5-bis(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one (17.5 mg) and *erythro*-5-[3,5-bis(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one (14.4 mg) as colorless solids. *threo*-diastereoisomer: *R_f* = 0.63 (50% EtOAc/hexanes). LCMS calc. = 314.06; found = 314.1 (M+1)⁺. ¹H NMR (CDCl₃, 600 MHz) δ 7.90 (br s, 1H), 7.83 (br s, 2H), 6.71 (br s, 1H), 5.17 (d, *J* = 7.0 Hz, 1H), 3.86 (br pentet, *J* = 6.2 Hz, 1H), 1.48 (d, *J* = 6.2 Hz, 1H). This compound was separated into its enantiomers (4*R*, 5*R*)-5-[3,5-bis(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one and (4*S*, 5*S*)-5-[3,5-bis(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one using chiral HPLC (AS column, 20 x 250 mm, 20% *i*-PrOH in heptane). *erythro*-diastereoisomer: *R_f* = 0.38 (50% EtOAc/hexanes). LCMS calc. = 314.06; found = 314.1 (M+1)⁺. ¹H NMR (CDCl₃, 600 MHz) δ 7.90 (br s, 1H), 7.79 (br s, 2H), 5.83 (d, *J* = 8.0 Hz, 1H), 5.34 (br s, 1H), 4.31 (br pentet, *J* = 7.0 Hz, 1H), 0.84 (d, *J* = 6.6 Hz, 1H). This compound was separated into its two enantiomers (4*S*, 5*R*)-5-[3,5-bis(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one and (4*R*, 5*S*)-5-[3,5-

bistrifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one using chiral HPLC (AS column, 20 x 250 mm, 15% *i*-PrOH in heptane).

Chiral Synthesis of (4S,5R)-5-[3,5-Bis(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one

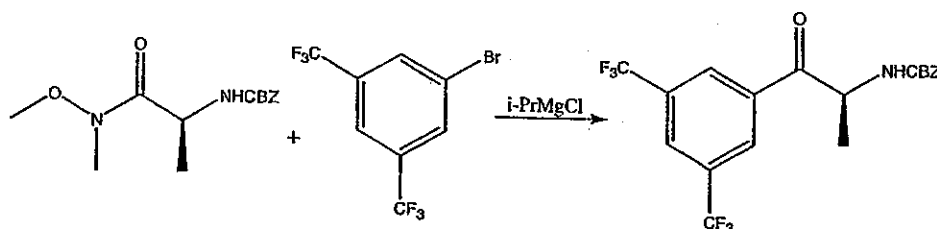
- 5 This intermediate can be made directly from the chiral starting material CBZ-L-alanine by the 3-step route shown below. The compound (4R,5S)-5-[3,5-bis(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one can be made by an analogous route starting from CBZ-D-alanine.

Step 1



- CBZ-L-Alanine (6.5 kg, 28.5 mol), HOBT-hydrate (4.8 kg, 34.8 mol), Weinreb amine-HCl salt (3.4 kg, 36.2 mol) and THF (32 L) are charged to a clean flask under nitrogen. The mixture is cooled to 0-10°C and then DIPEA (12.4L) is slowly added at a temperature less than 20°C. EDC-HCl (7Kg, 36.2 mol) is then added slowly with slight cooling at 15°-25°C. The slurry is aged overnight at 20°-25°C. The mixture is then cooled to 0°-10°C and 3 N HCl (13L) is added slowly. Then IPAC (45.5 L) is added and the layers are separated. The organic layer is washed once with HCl (13L) and twice with 8% NaHCO₃ (13L). The organic layer is then concentrated under vacuum to <20L at 50°C. The clear solution is cooled slowly to room temperature, allowing the product to crystallize. Heptane (~70L) is then added slowly. The slurry is filtered, washed with heptane (18L), and dried at room temperature on the filter pot. Product is obtained with >99.9%ee measured by chiral HPLC.
- 15
- 20

Step 2

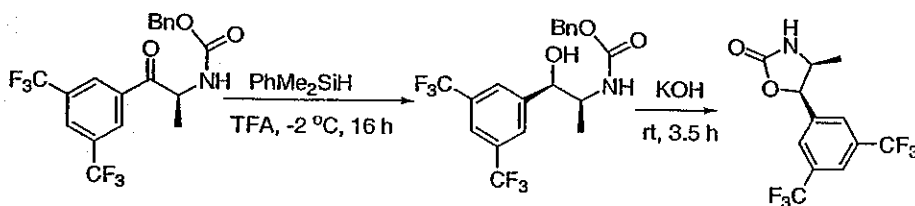


The Weinreb amide from Step 1 (6kg, 22.5 mol) and 3,5-bis(trifluoromethyl)bromobenzene (4.85L, 28.1 mol) are dissolved in anhydrous THF (24L). The solution is purged with nitrogen to remove distilled oxygen. The solution is cooled to -10°C and iso-PrMgCl in THF (56.4 mol) is slowly added (2 hours) to the reaction via addition funnel, maintaining a reaction temperature ≤ -5 °C. The solution is allowed to

warm to 20°C and aged overnight at 20°C. The reaction is then cooled to -10°C under nitrogen and is quenched slowly over 2 hours into 5N HCl (14L) that is maintained at 0-5°C. MTBE (60L) is added and the biphasic mixture is agitated for 5 min. After warming to 20°-25°C, it is allowed to settle for 30 min, and then the layers are separated. The organic layer is washed with water twice (12L).

The organic layer is vacuum transferred through a 1-micron in-line PTFE filter into a distillation flask and is then concentrated to ~12L under vacuum (internal temperature <40°C). Heptane is added and the distillation is continued under vacuum at 40°-55°C until the final volume is 40L. The solution is cooled to 35°-37°C, seeded (~0.5%, 30gms) and then aged for 30min to allow for a full seed bed to grow. The slurry is cooled to 10°C over 2-3 hrs. The slurry is then filtered, washed with 5°C heptane (18L), and allowed to dry fully on the filter pot using a vacuum/nitrogen sweep overnight. The dried solid is obtained with >99.9ee%. The amide can be recrystallized from straight heptane if the optical purity is not sufficient.

Step 3



TFA (9L) is added to a 100 L Buchi reactor under an inert atmosphere and is cooled to -5°C. The ketone product from Step 2 (5.50 kg, 13.1 mol) is added as a solid followed by a TFA rinse (2 L). The solution is cooled to -5°C and is stirred until all the solid dissolves. The silane (2.18 kg, 15.7 mol) is added slowly over ~1 h (in two portions) while keeping the temperature at <0°C. The reaction is aged at -2 to -6°C for 15-20 h, at which time LC reveals <2% of the ketone remains. A 50w/w% KOH solution is prepared by adding 13.6kg of KOH pellets (87w%) slowly to 10 L water while keeping the highly exothermic dissolution at <30 °C. The solution is stored in a refrigerator.

The reaction is quenched with ~2 L of the 50w/w% KOH solution with vigorous stirring and cooling, keeping temp at ~20 °C. Cold THF (16.5L, previously stored in freezer) is added, followed by slow addition of the remainder of the KOH solution (~13.7 L), followed by a 2 L water rinse while keeping temp <20 °C. After complete addition of KOH, the reaction is aged at room temperature. The reaction is quenched after 3 h with 27.5 L IPAC and 20 L 20%w/v aq NaCl.

The aqueous and organic layers are separated. The organic layer is washed with 26 L of 20%w/v aq NaCl, then with 36 L water, then with 31 L 0.5 N HCl, and finally with 32 L of water. The

organic layer is concentrated to ~10 L. Heptane (20 L) is added, yielding crystals. The organic layer is concentrated to ~10 L. Heptane (20L) is added again, and the organic layer is concentrated to ~10 L. Heptane (22 L) is added and the slurry is aged at rt. The solid is filtered and washed with 24 L heptane. A solid product is obtained (98.8% purity, >99.95%ee, by LC). The solid is then re-dissolved in 12.5 L MeOH (endothermic). At rt, 3 L water is added, and the mixture is aged to initiate crystallization. Water (9.5 L) is added over ~60min at rt. After aging for 60min, the slurry is filtered and the solid is washed with 5 L MeOH/water (1/1.5), 5 L MeOH/water (1/4) and then 4 L water. The solid product is dried at 50° C under vacuum (99.9% pure by LC, >99.95%ee).

10 HPLC Method for assays used in Step 3:

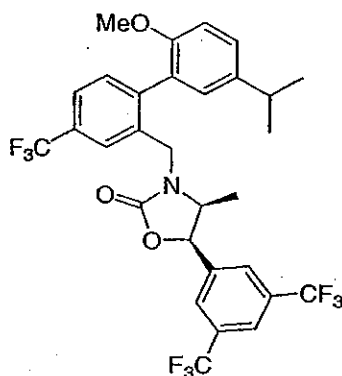
Ace-C8 column 250 x 4.6 mm A: MeCN; B: 0.1% H₃PO₄ in H₂O;

Gradient: 5A:95B at 0 min to 95A:5B at 9 min; hold 95A:5B until 13 min; return to 5A:95B 13-15 min.

Conditions: 35 °C, 1.5 mL/min, 210 nm

15

EXAMPLE 18

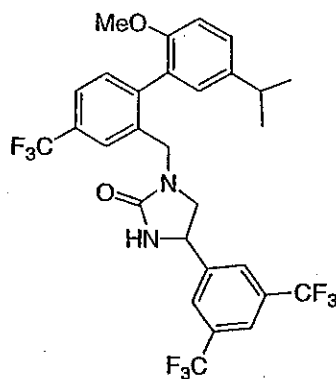


20 erythro-5-[3,5-Bis(trifluoromethyl)phenyl]-3-([5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl)-4-methyl-1,3-oxazolidin-2-one

Sodium bis(trimethylsilyl)amide (172 µL of a 1M solution in THF, 0.172 mmol) was added to a stirred solution of erythro-5-[3,5-bis(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one (50 mg, 0.129 mmol) in dry THF (1 mL) at room temperature under N₂. The reaction was stirred for 15 min and a solution of 2-(bromomethyl)-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl (27.0 mg, 0.0861 mmol) in dry THF (2 mL) was added by cannula. The reaction was stirred at room temperature for 3 days. The reaction was quenched with saturated NH₄Cl (10 mL) and extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine (10 mL), dried (Na₂SO₄) and concentrated *in vacuo* to give the crude product. This was purified by flash chromatography (Si, 12 x 160 mm, 0-40% EtOAc in hexanes gradient) to afford erythro-5-[3,5-bis(trifluoromethyl)phenyl]-3-([5'-isopropyl-2'-

methoxy-4-(trifluoromethyl)biphenyl-2-yl)methyl}-4-methyl-1,3-oxazolidin-2-one as a colorless oil. R_f = 0.64 (20% EtOAc/hexanes). LCMS calc. = 620.18; found = 620.2 (M+1)⁺. ¹H NMR (benzene-*d*₆, 600 MHz, 1:1 mixture of atropisomers) δ 7.94 (s, 0.5H), 7.72 (s, 0.5H), 7.64 (s, 0.5H), 7.63 (s, 0.5H), 7.39-7.34 (m, 3H), 7.12-7.04 (m, 2H), 6.95 (d, J = 2.1 Hz, 0.5H), 6.86 (d, J = 1.7 Hz, 0.5H), 6.64 (d, J = 8.5 Hz, 0.5H), 6.56 (d, J = 8.5 Hz, 0.5H), 4.99 (d, J = 15.9 Hz, 0.5H), 4.93 (d, J = 15.9 Hz, 0.5H), 4.73 (d, J = 7.9 Hz, 0.5H), 4.61 (d, J = 7.9 Hz, 0.5H), 3.88 (d, J = 15.9 Hz, 0.5H), 3.82 (d, J = 15.9 Hz, 0.5H), 3.35 (s, 1.5H), 3.24 (s, 1.5H), 3.05 (septet, J = 6.9 Hz, 0.5H), 3.01 (septet, J = 6.9 Hz, 0.5H), 2.75 (m, 1H), 1.19 (dd, J = 6.9, 2.7 Hz, 3H), 1.17 (dd, J = 10.9, 6.9 Hz, 3H), -0.18 (d, J = 6.4 Hz, 1.5H), -0.33 (t, J = 6.4 Hz, 1.5H). This compound was separated into its two enantiomers (4*R*,5*S*)-5-[3,5-bis(trifluoromethyl)phenyl]-3-{{[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl)methyl}-4-methyl-1,3-oxazolidin-2-one and (4*S*,5*R*)-5-[3,5-bis(trifluoromethyl)phenyl]-3-{{[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl)methyl}-4-methyl-1,3-oxazolidin-2-one using chiral HPLC (AD column, 20 x 250 mm, 3% *i*-PrOH in heptane).

EXAMPLE 19



4-[3,5-bis(trifluoromethyl)phenyl]-1-{{[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl)methyl}imidazolidin-2-one.

Step A: *tert*-butyl{2-[3,5-bis(trifluoromethyl)phenyl]-2-hydroxyethyl}{{[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl)methyl}carbamate

To a solution of 1-[3,5-bis(trifluoromethyl)phenyl]-2-({[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl)methyl}amino)ethanol (Example 6 Step B, 325.0 mg, 0.561 mmol) in CH₂Cl₂ (15 mL) was added BOC₂O (122 mg, 0.561 mmol) and DIPEA (98 μ L, 0.561 mmol). The reaction was stirred at room temperature. After 5 hours, additional BOC₂O (50 mg, 0.229 mmol) and DIPEA (50 μ L, 0.287 mmol) were added. The reaction was stirred at room temperature for 48 hours. The reaction was then concentrated to ~ 2 mL, diluted with hexanes (8 mL) and purified by flash chromatography with 10 to 20% EtOAc/hexanes to afford *tert*-butyl{2-[3,5-bis(trifluoromethyl)phenyl]-

2-hydroxyethyl}{[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl}carbamate. R_f = 0.38 (25% EtOAc/hexanes). LCMS = 580.3 ($M+1$ -BOC)⁺. ¹H NMR (CD₂Cl₂, 500 MHz) δ 7.78 (s, 1H), 7.54-7.67 (m, 4H), 7.23-7.33 (m, 2H), 6.90-6.95 (m, 2H), 3.15-4.82 (m, 9H), 2.87 (m, 1H), 1.19-1.43 (m, 15 H).

5

Step B: 1-[3,5-bis(trifluoromethyl)phenyl]-2-((tert-butoxycarbonyl){[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl}amino)ethyl methanesulfonate

To a solution of *tert*-butyl{2-[3,5-bis(trifluoromethyl)phenyl]-2-hydroxyethyl}{[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl}carbamate (350.1 mg, 0.516 mmol) in CH₂Cl₂ (15 mL) was
 10 added DIPEA (450 μ L, 2.58 mmol). The solution was cooled to 0°C and MsCl (100 μ L, 1.29 mmol) was added. After 45 minutes of stirring at 0°C, the reaction was diluted with EtOAc (100 mL) and washed with saturated NaHCO₃ (25 mL), brine (25 mL), 1N HCl (25 mL), and brine (2 x 25 mL). The organic layer was dried over Na₂SO₄, filtered, and concentrated. The residue was put through a short plug of
 15 silica gel with 25% EtOAc/hexanes and concentrated. The product, 1-[3,5-bis(trifluoromethyl)phenyl]-2-((tert-butoxycarbonyl){[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl}amino)ethyl methanesulfonate, was used immediately in the next reaction without further characterization. R_f = 0.33 (25% EtOAc/hexanes).

Step C: *tert*-butyl{2-azido-2-[3,5-bis(trifluoromethyl)phenyl]ethyl}{[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl}carbamate

The 1-[3,5-bis(trifluoromethyl)phenyl]-2-((tert-butoxycarbonyl){[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl}amino)ethyl methanesulfonate from the previous reaction was dissolved in DMPU (15 mL) and treated with NaN₃ (140 mg, 2.15 mmol). The reaction was stirred at room temperature for 15 hours and then diluted with EtOAc (75 mL). The solution was washed with H₂O
 25 (5 x 40 mL) and brine (40 mL). The organic layer was dried over Na₂SO₄, filtered, and concentrated. The residue was purified with 20% EtOAc/hexanes to afford *tert*-butyl{2-azido-2-[3,5-bis(trifluoromethyl)phenyl]ethyl}{[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl}carbamate. R_f = 0.52 (15% EtOAc/hexanes). LCMS = 605.3 ($M+1$ -BOC)⁺. ¹H NMR (C₆D₆, 500 MHz, 70°C) δ 7.80 (s, 1H), 7.67 (s, 1H), 7.48 (s, 2H), 7.36 (d, J = 7.8 Hz, 1H), 7.01-7.11 (m, 2H),
 30 6.89 (m, 1H), 6.64 (d, J = 8.6 Hz, 1H), 4.22-4.69 (m, 3H), 3.28 (s, 3H), 2.61-3.16 (m, 3H), 1.34 (s, 9H), 1.13-1.18 (m, 6H).

Step D: mixture of *tert*-butyl{2-amino-2-[3,5-bis(trifluoromethyl)phenyl]ethyl}{[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl}carbamate and *tert*-butyl{1-[3,5-

bis(trifluoromethyl)phenyl]-2-([5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl)methyl]amino)ethyl]carbamate

To a solution of *tert*-butyl {2-azido-2-[3,5-bis(trifluoromethyl)phenyl]ethyl} {[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl)methyl]carbamate (300 mg, 0.426 mmol) in EtOAc (15 mL) was added 10% Pd on C (100 mg). The reaction was placed under H₂ and stirred at room temperature for 5 hours. At this time the reaction was complete to give a mixture of two products, *tert*-butyl {2-amino-2-[3,5-bis(trifluoromethyl)phenyl]ethyl} {[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl)methyl]carbamate and *tert*-butyl [1-[3,5-bis(trifluoromethyl)phenyl]-2-([5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl)methyl]amino)ethyl]carbamate. The catalyst was filtered off and the filtrate was concentrated to afford the product mixture. LCMS = 679.3 (M+1)⁺. The products were used in the next reaction without further purification or characterization.

Step E: 1-[3,5-bis(trifluoromethyl)phenyl]-N²-{[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl)methyl]ethane-1,2-diamine

To a solution of 283.5 mg (0.418 mmol) of the mixture of *tert*-butyl {2-amino-2-[3,5-bis(trifluoromethyl)phenyl]ethyl} {[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl)methyl]carbamate and *tert*-butyl [1-[3,5-bis(trifluoromethyl)phenyl]-2-([5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl)methyl]amino)ethyl]carbamate in CH₂Cl₂ (15 mL) was added TFA (1.5 mL). The reaction was stirred at room temperature for 5 hours and then poured into 1 N NaOH (50 mL). The mixture was extracted with CH₂Cl₂ (3 x 50 mL) and the organic extracts were combined, dried over Na₂SO₄, filtered, and concentrated. Purification of the residue by flash chromatography with 5 to 10% MeOH/CH₂Cl₂ gave 1-[3,5-bis(trifluoromethyl)phenyl]-N²-{[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl)methyl]ethane-1,2-diamine. R_f = 0.46 (10% MeOH/CH₂Cl₂). LCMS = 579.2 (M+1)⁺. ¹H NMR (CD₂Cl₂, 500 MHz) δ 7.83 (s, 2H), 7.77 (s, 2H), 7.55 (d, *J* = 7.8 Hz, 1H), 7.31 (d, *J* = 8.1 Hz, 1H), 7.24 (dd, *J* = 8.4, 2.3 Hz, 1H), 6.99 (d, *J* = 2.0 Hz, 1H), 6.92 (d, *J* = 8.5 Hz, 1H), 4.06 (m, 1H), 3.59-3.76 (m, 2H), 3.69 (s, 3H), 2.88 (m, 1H), 2.67 (dd, *J* = 11.9, 4.3 Hz, 1H), 2.51 (m, 1H), 1.22 (d, *J* = 6.9 Hz, 6H).

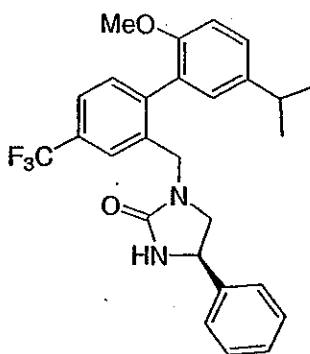
Step F: 4-[3,5-bis(trifluoromethyl)phenyl]-1-[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl)methyl]imidazolidin-2-one

A solution of 1-[3,5-bis(trifluoromethyl)phenyl]-N²-{[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl)methyl]ethane-1,2-diamine (125.2 mg, 0.217 mmol) in CH₂Cl₂ (30 mL) was cooled to 0°C and DIPEA (227 μL, 1.30 mmol) was added. Next, triphosgene (32.2 mg, 0.109 mmol) was added. The reaction was stirred at 0°C for 45 minutes and then poured into saturated NaHCO₃ (20 mL). The mixture was extracted with EtOAc (100 mL) and the organic layer was washed

with brine (25 mL), dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography with 40% EtOAc/hexanes to afford 4-[3,5-bis(trifluoromethyl)phenyl]-1-([5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl)methyl]imidazolidin-2-one. *R_f* = 0.22 (40% EtOAc/hexane). LCMS = 605.2 (M+1)⁺. ¹H NMR (CDCl₃, 500 MHz) (atropisomers present in 1:1 ratio; doubling of some peaks observed) δ 7.83 (s, 1H), 7.78 (s, 2H), 7.55-7.62 (m, 2H), 7.32 (d, *J* = 7.8 Hz, 1H), 7.22 (m, 1H), 6.94 (s, 1H), 6.88 (d, *J* = 8.3 Hz, 1H), 5.33 & 5.24 (2 singlets, 1H), 4.80-4.88 (m, 1H), 4.00-4.61 (m, 2H), 3.72 & 3.70 (2 singlets, 3H), 3.55-3.59 (m, 1H), 2.83-2.93 (m, 2H), 1.17-1.23 (m, 6H).

The two enantiomers of this compound could be separated using an AD chiral column with 5% IPA/heptanes.

EXAMPLE 20



(4R)-1-([5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl)methyl]-4-phenylimidazolidin-2-one

Step A: *tert*-butyl [(1R)-2-hydroxy-1-phenylethyl]carbamate

To a solution of (2R)-2-amino-2-phenylethanol (400 mg, 2.91 mmol) in CH₂Cl₂ (15 mL) was added BOC₂O (636 mg, 2.91 mmol) and DIPEA (507 μL, 2.91 mmol). The reaction was stirred at room temperature for 18 hours, diluted with EtOAc (75 mL) and washed with H₂O, brine, 1N HCl, brine, saturated NaHCO₃, and brine (25 mL each). The organic layer was dried over Na₂SO₄, filtered, and concentrated. Purification of the residue by flash chromatography with 50% EtOAc/hexanes afforded *tert*-butyl [(1R)-2-hydroxy-1-phenylethyl]carbamate. *R_f* = 0.23 (40% EtOAc/hexane). ¹H NMR (CDCl₃, 600 MHz) δ 7.27-7.37 (m, 5H), 5.27 (bs, 1H), 4.78 (bs, 1H), 3.83 (bs, 2H), 2.46 (bs, 1H), 1.44 (bs, 9H).

Step B: *tert*-butyl [(1R)-2-oxo-1-phenylethyl]carbamate

To a solution of *tert*-butyl [(1*R*)-2-hydroxy-1-phenylethyl]carbamate (200 mg, 0.844 mmol) in CH₂Cl₂ (20 mL) at 0°C was added Dess-Martin periodinane (447 mg, 1.05 mmol). The reaction was stirred at 0°C for 15 minutes and then at room temperature for 30 minutes. The reaction was then diluted with EtOAc (75 mL) and washed rapidly with 10% K₂CO₃ (2 x 30 mL). The organic layer was dried over Na₂SO₄, filtered, and concentrated. Purification of the residue on a short column of silica gel with 50% EtOAc/hexanes gave *tert*-butyl [(1*R*)-2-oxo-1-phenylethyl]carbamate. ¹H NMR (CDCl₃, 600 MHz) (a major and a minor conformer observed). Data for major conformer given) δ 9.53 (s, 1H), 7.29-7.40 (m, 5H), 5.80 (bs, 1H), 5.31 (m, 1H), 1.42 (s, 9H). This material was used immediately in the following reaction.

Step C: *tert*-butyl[(1*R*)-2-([5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl)amino]-1-phenylethyl]carbamate

To a solution of *tert*-butyl[(1*R*)-2-oxo-1-phenylethyl]carbamate (113.8 mg, 0.484 mmol) in MeOH (7 mL) was added 1-[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methenamine (98 mg, 0.303 mmol), followed by NaCNBH₃ (30 mg, 0.477 mmol) and HOAc (2 drops). The reaction was stirred overnight at room temperature, diluted with EtOAc (75 mL), and washed with 1 N NaOH (25 mL) and brine (25 mL). The organic layer was dried over Na₂SO₄, filtered, and concentrated. Purification of the residue by flash chromatography with 5 to 25% EtOAc/hexanes gave *tert*-butyl[(1*R*)-2-([5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl)amino]-1-phenylethyl]carbamate. *R*_f = 0.30 (25% EtOAc/hexane). LCMS = 543.4 (M+1)⁺.

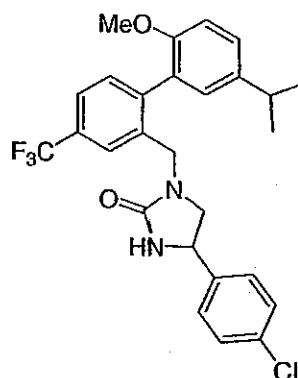
Step D: (1*R*)-*N*²-([5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl)-1-phenylethane-1,2-diamine

To a solution of *tert*-butyl[(1*R*)-2-([5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl)amino]-1-phenylethyl]carbamate (150 mg, 0.277 mmol) containing minor impurities in CH₂Cl₂ (10 mL) was added TFA (1 mL). The reaction was stirred at room temperature for 2 hours and then poured into 1 N NaOH (25 mL). The mixture was extracted with CH₂Cl₂ (3 x 25 mL). The combined organic extracts were dried over Na₂SO₄, filtered, and concentrated. Purification of the resulting residue by flash chromatography with 0 to 10% MeOH/CH₂Cl₂ afforded (1*R*)-*N*²-([5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl)-1-phenylethane-1,2-diamine. *R*_f = 0.27 (10% MeOH/CH₂Cl₂). LCMS = 443.4 (M+1)⁺.

Step E: (4*R*)-1-[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]-4-phenylimidazolidin-2-one

A solution of (1*R*)-*N*2-([5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl)-1-phenylethane-1,2-diamine (96.0 mg, 0.22 mmol) in CH₂Cl₂ (15 mL) was cooled to 0°C and DIPEA (230 μL, 1.32 mmol) was added followed by triphosgene (32.6 mg, 0.11 mmol). After 45 minutes, the reaction was poured into saturated NaHCO₃ (25 mL). The mixture was extracted with EtOAc (75 mL).
 5 The organic layer was washed with brine, dried over Na₂SO₄, filtered, and concentrated. Purification of the residue by flash chromatography with 10 to 60% EtOAc/hexanes afforded (4*R*)-1-([5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl)-4-phenylimidazolidin-2-one. The minor enantiomer was removed by chiral HPLC using an AD chiral column and 15% IPA/heptanes to afford enantiomerically pure product. *R*_f = 0.16 (40% EtOAc/hexanes). LCMS = 469.3 (M+1)⁺. ¹H NMR (CDCl₃, 500 MHz) (atropisomers present in 1:1 ratio, doubling of some peaks observed) δ 7.65 (m, 1H), 7.54 (d, *J* = 7.7 Hz, 1H), 7.21-7.36 (m, 7H), 6.87-6.94 (m, 2H), 4.65-4.77 (m, 2H), 4.10-4.49 (m, 2H), 3.71 & 3.72 (2 singlets, 3H), 3.49-3.53 (m, 1H), 2.94-2.97 (m, 1H), 2.87 (m, 1H), 1.19-1.24 (m, 6H).

EXAMPLE 21



4-(4-chlorophenyl)-1-([5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl)imidazolidin-2-one

20 Step A: 1-(4-chlorophenyl)-2-([5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl)amino)ethanol

A solution of 1-[5'-isopropyl-2'-methoxy-5-(trifluoromethyl)biphenyl-2-yl]methanamine (300 mg, 1.1 mmol) and 2-(4-chlorophenyl)oxirane (143 μL, 1.2 mmol) in isopropyl alcohol (10.5 mL) was heated to reflux for 24 hours. The reaction was concentrated and purified by flash chromatography with 5% to
 25 80% EtOAc/hexanes to afford 1-(4-chlorophenyl)-2-([5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl)amino)ethanol. *R*_f = 0.37 (50% EtOAc/hexanes). LCMS = 478.1 (M+1)⁺. ¹H NMR (CDCl₃, 500 MHz) δ 7.70 (s, 1H), 7.55 (d, *J* = 7.5 Hz, 1H), 7.33-7.19 (m, 6H), 6.97 (s, 1H), 6.90 (d, *J* = 8.5 Hz, 1H), 4.52 (m, 1H), 3.77-3.62 (m, 5H), 2.89 (m, 1H), 2.71 (m, 1H), 2.51 (m, 1H), 1.24 (d, *J* = 7.0 Hz, 6H).

Step B: benzyl [2-(4-chlorophenyl)-2-hydroxyethyl][5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl} carbamate

To a solution of 1-(4-chlorophenyl)-2-([5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl)amino)ethanol (40 mg, 0.08 mmol) in CH₂Cl₂ (2 mL) was added dibenzyl dicarbonate (24 mg, 0.08 mmol). The reaction was stirred at room temperature for 24 hours and then poured into H₂O (15 mL). The resultant mixture was extracted with EtOAc (50 mL) and the organic layer was washed with brine (15 mL), dried over Na₂SO₄, filtered, and concentrated. Purification of the residue by flash chromatography with 5% to 60% EtOAc/hexanes afforded benzyl [2-(4-chlorophenyl)-2-hydroxyethyl][5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl} carbamate. *R_f* = 0.20 (25% EtOAc/hexanes). LCMS = 612.2 (M+1)⁺. ¹H NMR (C₆D₆, 600 MHz, peaks broadened and/or doubled; rotamers and/or atropisomers present) δ 7.98-6.45 (m, 15H), 5.00-3.46 (m, 6H), 3.20-2.96 (m, 5H), 2.72 (m, 1H), 1.20-1.15 (m, 6H).

Step C: benzyl [2-azido-2-(4-chlorophenyl)ethyl][5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl} carbamate

A solution of benzyl [2-(4-chlorophenyl)-2-hydroxyethyl][5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl} carbamate (44 mg, 0.07 mmol) in CH₂Cl₂ (6 mL) was cooled to 0°C and *N,N* diisopropylethylamine (63 μL, 0.36 mmol) was added followed by methanesulfonyl chloride (14 μL, 0.18 mmol). The reaction was stirred at 0°C for 30 minutes and then poured into saturated NaHCO₃ (15 mL). The resultant mixture was extracted with EtOAc (50 mL) and the organic layer was washed with brine (15 mL), dried over Na₂SO₄, filtered through a short plug of silica gel, and concentrated. The residue was redissolved in DMPU (6 mL) and sodium azide (12 mg, 0.18 mmol) was added. The reaction was stirred at room temperature for 24 hours and then poured into H₂O (15 mL). The resultant mixture was extracted with EtOAc (50 mL) and the organic layer was washed with H₂O (2 x 15 mL) and brine (15 mL), dried over Na₂SO₄, filtered, and concentrated. Purification of the residue by flash chromatography with 25% EtOAc/hexanes afforded benzyl [2-azido-2-(4-chlorophenyl)ethyl][5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl} carbamate. *R_f* = 0.66 (25% EtOAc/hexanes). LCMS = 637.3 (M+1)⁺. ¹H NMR (C₆D₆, 600 MHz, peaks doubled; rotamers and/or atropisomers present) δ 8.03-6.52 (m, 15 H), 5.00-5.08 (m, 2H), 4.76-4.12 (m, 3H), 3.28-2.86 (m, 5H), 2.77 (m, 1H), 1.23-1.18 (m, 6H).

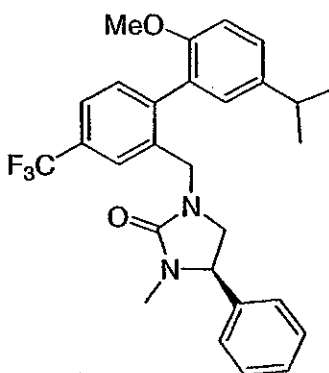
Step D: benzyl [2-amino-2-(4-chlorophenyl)ethyl][5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl} carbamate

To a solution of benzyl [2-azido-2-(4-chlorophenyl)ethyl][{5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl)methyl}carbamate (30 mg, 0.05 mmol) in THF (1 mL) was added PtO₂ (8 mg) and the reaction was stirred at room temperature under hydrogen for 1 hour. The catalyst was removed by filtration through a plug of Celite with 100% EtOAc and the filtrate was concentrated to afford crude benzyl [2-amino-2-(4-chlorophenyl)ethyl][{5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl)methyl}carbamate. $R_f = 0.66$ (25% EtOAc/hexanes). LCMS = 611.3 (M+1)⁺.

Step E: 4-(4-chlorophenyl)-1-{{5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl)methyl}imidazolidin-2-one

To a solution of benzyl [2-amino-2-(4-chlorophenyl)ethyl][{5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl)methyl}carbamate (30 mg, 0.05 mmol) in THF (2 mL) was added potassium bis(trimethylsilyl)amide (295 μ L of a 0.5M solution in toluene, 0.147 mmol). The reaction was stirred at room temperature for 30 minutes and then quenched with saturated NH₄Cl (15 mL). The resultant mixture was extracted with EtOAc (25 mL) and the organic layer was washed with H₂O (15 mL) and brine (15 mL), dried over Na₂SO₄, filtered, and concentrated. Purification of the residue by flash chromatography with 5% to 60% EtOAc/hexanes afforded 4-(4-chlorophenyl)-1-{{5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl)methyl}imidazolidin-2-one. $R_f = 0.46$ (5% MeOH/CH₂Cl₂). LCMS = 503.1 (M+1)⁺. ¹H NMR (C₆D₆, 600 MHz, atropisomers observed; doubling of peaks.) δ 7.90 – 7.03 (m, 6H), 6.89–6.20 (m, 4H), 4.69–3.88 (m, 3H), 3.16 (s, 3H), 2.88–2.30 (m, 3H), 1.18–1.13 (m, 6H).

EXAMPLE 22



(4R)-1-{{5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl)methyl}-3-methyl-4-phenylimidazolidin-2-one

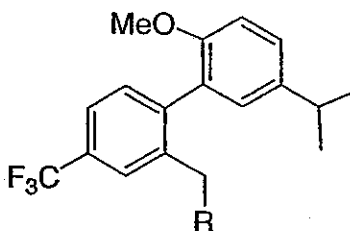
To a solution of (4R)-1-{{5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl)methyl}-4-phenylimidazolidin-2-one (12.6 mg, 0.0269 mmol) in THF (1.5 mL) was added MeI (10 μ L, 0.162

mmol), followed by KHMDS (162 μ L of a 0.5 M solution in toluene, 0.081 mmol). The reaction was stirred at room temperature for 10 minutes, and then poured into water (10 mL). The mixture was extracted with EtOAc (30 mL) and the organic layer was washed with brine (10 mL), dried over Na_2SO_4 , filtered, and concentrated. Purification of the residue by flash chromatography with 50%

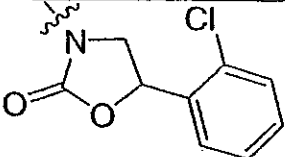
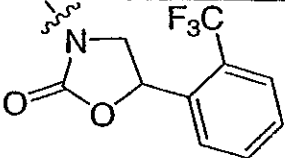
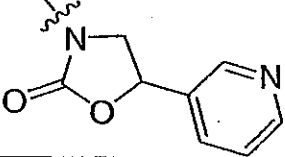
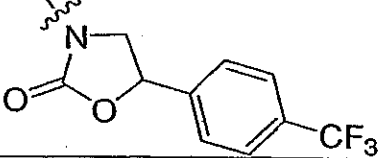
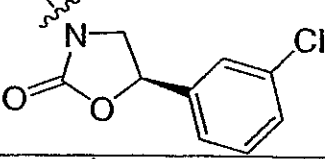
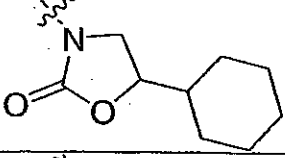
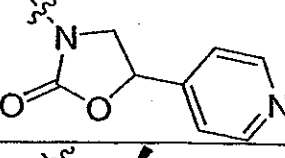
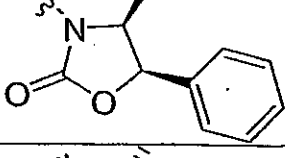
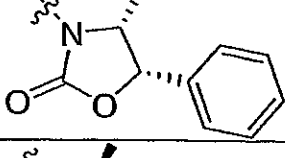
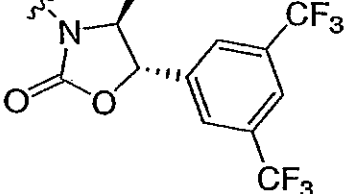
EtOAc/hexanes afforded (4*R*)-1-{[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl}-3-methyl-4-phenylimidazolidin-2-one. R_f = 0.26 (40% EtOAc/hexanes). LCMS = 483.2 ($M+1$)⁺. ¹H NMR (CDCl_3 , 500 MHz, atropisomers observed; doubling of peaks.) δ 7.68 – 7.53 (m, 2H), 7.21-7.36 (m, 7H), 6.87-6.94 (m, 2H), 4.08-4.56 (m, 3H), 3.72 & 3.71 (2 singlets, 3H), 3.34-3.38 (m, 1H), 2.77-2.89 (m, 2H), 2.67 & 2.63 (2 singlets, 3H), 1.18-1.26 (m, 6H).

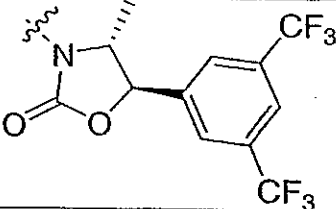
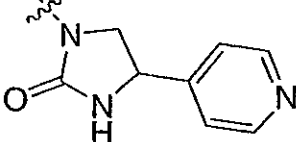
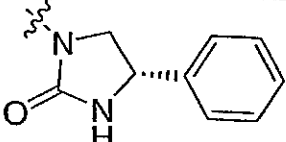
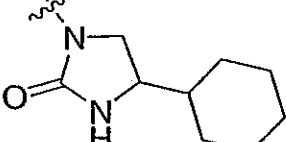
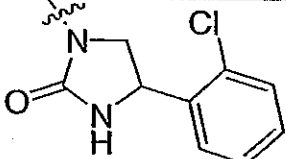
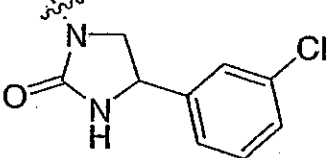
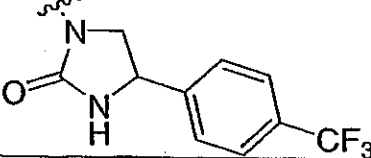
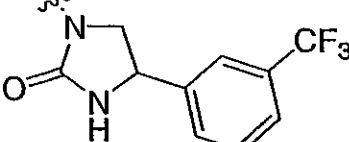
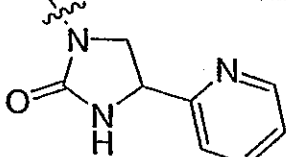
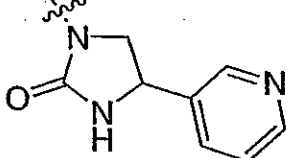
Following the procedures outlined in EXAMPLES 1-22 the compounds listed in Table 1 were prepared:

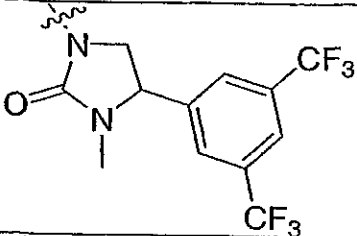
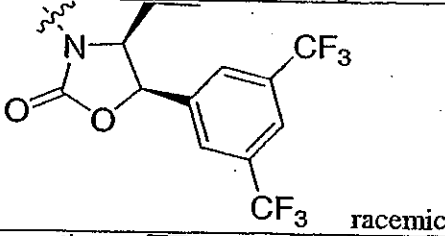
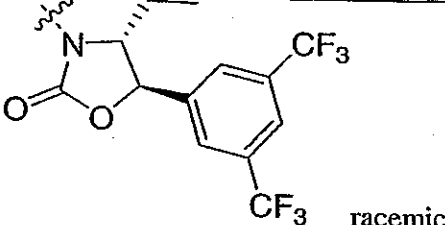
Table 1



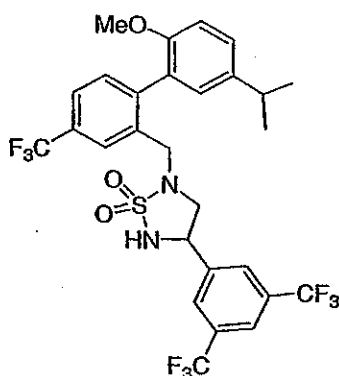
Example	R	LCMS ($M+1$) ⁺
23		618.1
24		470.2
25		470.4
26		538.2

27		504.1
28		538.2
29		471.2
30		538.2
31		504.2
32		476.2
33		471.2
34		484.2
35		484.2
36		620.2

37		620.2
38		470.2
39		469.2
40		475.2
41		503.1
42		503.1
43		537.2
44		537.2
45		470.2
46		470.2

47		619.2
48	 racemic	634.1
49	 racemic	634.1

EXAMPLE 50

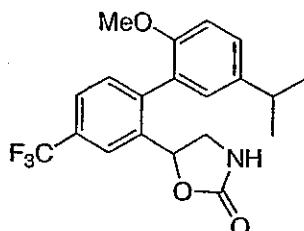


4-[3,5-bis(trifluoromethyl)phenyl]-2-[[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]-1,2,5-thiadiazolidine 1,1-dioxide

A solution of 1-[3,5-bis(trifluoromethyl)phenyl]-N 2-[[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]ethane-1,2-diamine (8.0 mg, 0.014 mmol) and sulfamide (2.0 mg, 0.021 mmol) in pyridine (300 μ L) was heated to 120°C in a sealed tube. After 3 hours, the reaction was cooled to room temperature and diluted with 25 mL of EtOAc. The organic solution was washed with 1 N HCl (2 x 5 mL) and brine (1 x 5 mL), dried over Na₂SO₄, filtered, and concentrated. Purification of the residue by PTLC with 25% EtOAc/hexanes afforded 4-[3,5-bis(trifluoromethyl)phenyl]-2-[[5'-

isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl)methyl}-1,2,5-thiadiazolidine 1,1-dioxide. R_f = 0.29 (25% EtOAc/hexanes). LCMS = 641.1 (M+1)⁺. ¹H NMR (CDCl₃, 500 MHz; atropisomers present) δ 7.58-7.85 (m, 5H), 7.35-6.86 (m, 4H), 4.82-4.94 (m, 2H), 3.54-4.42 (m, 6H), 2.71-2.91 (m, 2H), 1.11-1.26 (m, 6H).

EXAMPLE 51



5-[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]-1,3-oxazolidin-2-one

Step A: [5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methanol

- To a solution of 1.08 g of 5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-carbonitrile (EXAMPLE 3) in 25 mL of *n*-PrOH, was added 0.97 g of KOH. The mixture was heated to reflux and stirred at this temperature for 36 h, then cooled and concentrated to a clear oil. This oil was partitioned between 15 mL of water and 10 mL of Et₂O. The aqueous phase was extracted with 10 mL of Et₂O. The combined organics were washed with brine (15 mL), dried over Na₂SO₄, and concentrated. The residue was purified by flash chromatography on a Biotage Horizon 40S column, eluting with 1 CV of 95% hexanes-5% of a mixture of 5% formic acid in acetone, followed by a linear gradient of the acetone mixture in hexanes from 5 to 100% over 10 CV. The resulting white solid was dissolved in 10 mL of 9:1 benzene-MeOH and excess TMSCH₂N₂ was added. The mixture was stirred for 10 min at room temperature, then quenched with trifluoroacetic acid and concentrated. The residue was dissolved in 15 mL of Et₂O and cooled to 0°C. A 1-M solution of LiAlH₄ in Et₂O (5.4 mL) was added dropwise via addition funnel. The cooling bath was removed once the addition was complete, and the mixture was stirred 2 h at room temperature, then recooled to 0°C and quenched by dropwise addition of 0.2 mL of water, 0.2 mL of 15% aqueous NaOH, and 0.5 mL of water. The cooling bath was removed once the addition was complete, and the mixture was stirred 30 min at room temperature, filtered (washing the solids liberally with Et₂O), and concentrated. Flash chromatography on a Biotage Horizon, 40S column, eluting with 1 CV of 4% EtOAc in hexanes, followed by a linear gradient of EtOAc in hexanes from 4 to 100% over 10 CV provided the title compound. Mass spectrum (ESI) 307.2 (M-17). ¹H NMR (500 MHz, CDCl₃): δ 7.85 (s, 1H), 7.60 (d, J=8 Hz, 1H), 7.33 (d, J=8 Hz, 1H), 7.25 (dd, J=2 Hz, 9 Hz, 1H), 6.99 (d, J=2.5 Hz, 1H), 6.93 (d, J=8.5 Hz, 1H), 4.49 (m, 2H), 3.74 (s, 3H), 2.90 (septet, J=7 Hz, 1H), 1.25 (d, J=7 Hz, 6H).

Step B: 5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-carbaldehyde

To a solution of 0.725 g of [5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methanol in 10 mL of CH₂Cl₂ was added 1.14 g of Dess-Martin periodinane. The mixture was stirred at room temperature for 30 min, then filtered and concentrated. The residue was purified by flash chromatography on a Biotage Horizon, 40S column, eluting with 1 CV of 1% EtOAc in hexanes, followed by a linear gradient of EtOAc in hexanes from 1 to 100% over 10 CV to provide the title compound. Mass spectrum (ESI) 323.2 (M+1). ¹H NMR (500 MHz, CDCl₃): δ 9.81 (s, 1H), 8.28 (s, 1H), 7.88 (dd, J=1.5 Hz, 8 Hz, 1H), 7.54 (d, J=8 Hz, 1H), 7.33 (dd, J=2 Hz, 8 Hz, 1H), 7.16 (d, J=2.5 Hz, 1H), 6.95 (d, J=8.5 Hz, 1H), 3.74 (s, 3H), 2.95 (septet, J=7 Hz, 1H), 1.29 (d, J=7 Hz, 6H).

Step C: 2-amino-1-[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]ethanol

To a solution of 0.679 g of 5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-carbaldehyde in 1.5 mL of CH₂Cl₂ was added ca. 5 mg of ZnI₂, then 0.23 g of trimethylsilyl cyanide. The mixture was stirred at room temperature for 3 h, and then partitioned between 15 mL of water and 10 mL of Et₂O. The aqueous phase was extracted with 2 x 10 mL of Et₂O. The combined organics were dried over Na₂SO₄ and concentrated. The residue was dissolved in 15 mL of Et₂O and cooled to 0°C. A 1-M solution of LiAlH₄ in Et₂O (4.2 mL) was added dropwise via addition funnel. The cooling bath was removed once the addition was complete, and the mixture was stirred overnight at room temperature, then recooled to 0°C and quenched by dropwise addition of 0.15 mL of water, 0.15 mL of 15% aqueous NaOH, and 0.4 mL of water. The cooling bath was removed once the addition was complete, and the mixture was stirred 30 min at room temperature, filtered (washing the solids liberally with Et₂O), and concentrated to provide the title compound, which was used without further purification. Mass spectrum (ESI) 354.2 (M+1). Some ¹H NMR signals are doubled because of atropoisomerism. ¹H NMR (500 MHz, CDCl₃): δ 7.88 (s, 1H), 7.55 (app t, J=7.5 Hz, 1H), 7.22-7.28 (m, 2H), 6.99, 6.95 (d, J=2.5 Hz, 1H), 6.92, 6.90 (sm 1H), 4.52 (m, 1H), 3.70 (s, 3H), 2.90 (septet, J=7 Hz, 1H), 2.81 (m, 1H), 2.60-2.70 (m, 2H), 1.23-1.28 (m, 6H).

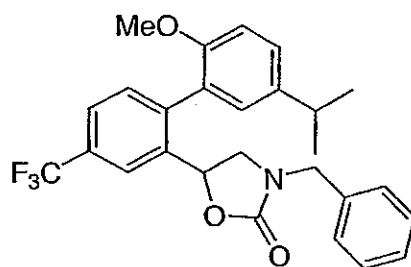
Step D: 5-[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]-1,3-oxazolidin-2-one

To a 0°C solution of 0.44 g of 2-amino-1-[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]ethanol in 15 mL of CH₂Cl₂ was added 0.241 g of diisopropylethylamine, then 0.185 g of triphosgene. The mixture was stirred at 0°C for 30 min, and then diluted with 30 mL of EtOAc and 20 mL of saturated NaHCO₃. The phases were separated and the organic phase was washed with 20 mL of brine, dried (Na₂SO₄), and concentrated. The residue was purified by flash chromatography on a Biotage Horizon, 40S column, eluting with 1 CV of 5% EtOAc in hexanes, followed by a linear gradient of EtOAc in hexanes from 5 to 100% over 10 CV to provide the title compound. Mass spectrum (ESI) 380.2 (M+1). ¹H NMR signals are doubled because of atropoisomerism ¹H NMR (500 MHz, CDCl₃): δ 7.90, 7.86 (s, 1H), 7.66 (d, J=8 Hz, 1H), 7.35 (d, J=8 Hz, 1H), 7.27 (dd, J=2.5 Hz, 8.5 Hz 1H), 7.03 (d, J=2.5 Hz, 0.5H), 6.87-6.93 (m, 1.5H), 5.65, 5.50 (t, J=8 Hz, 1H), 5.23, 5.09 (s, 1H), 3.75 (s, 1.5H), 3.69

(s, 1.5H), 3.68, 3.51 (t, J=9 Hz, 1H), 3.31, 3.19 (t, J=8.5 Hz, 0.5H), 2.90 (septet, J=7 Hz, 1H), 1.25, 1.24 (d, J=7 Hz, 6H).

Further purification by HPLC on Chiralpak AD 2 x 25 cm, eluting with 10% isopropanol in heptane at 9 mL/min, provided two enantiomers: enantiomer A, t_R =15.1 min; enantiomer B, t_R =17.4 min.

EXAMPLE 52

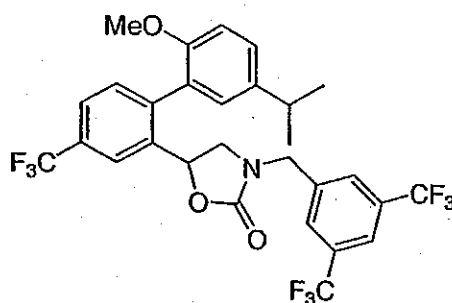


3-Benzyl-5-[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]-1,3-oxazolidin-2-one

To a 0°C solution of 44 mg of 5-[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]-1,3-oxazolidin-2-one in 1 mL of DMF was added 10 mg of sodium hydride. The mixture was stirred 10 min at room temperature, and then 24 mg of benzyl bromide was added. The mixture was stirred overnight at room temperature, then diluted with 15 mL of EtOAc and 5 mL of water. The phases were separated and the organic phase was washed with 5 mL each of water and brine, dried (Na₂SO₄), and concentrated.

The residue was purified by flash chromatography on a Biotage Horizon, 25S column, eluting with 1 CV of hexanes, followed by a linear gradient of EtOAc in hexanes from 0 to 50% over 10 CV to provide the title compound. Mass spectrum (ESI) 470.1 (M+1). ¹H NMR (500 MHz, CDCl₃): δ 7.86, 7.76 (s, 1H), 7.62 (d, J=8 Hz, 1H), 7.14-7.40 (m, 7H), 7.01, 6.77 (d, J=2.5 Hz, 1H), 6.87, 6.83 (d, J=8.5 Hz, 1H), 5.45, 5.53 (m, 1H), 4.30-4.53 (m, 2H), 3.73, 3.55 (s, 3H), 3.48, 3.30 (m, 1H), 3.10, 2.96 (t, J~8.5 Hz, 1H), 2.89, 2.82 (septet, J=7 Hz, 1H), 1.24, 1.16 (m, 6H).

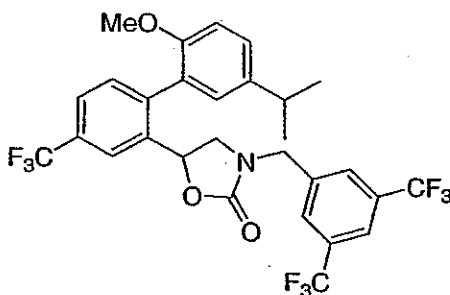
EXAMPLE 53



3-[3,5-bis(trifluoromethyl)benzyl]-5-[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]-1,3-oxazolidin-2-one (racemic)

Following the procedure described in EXAMPLE 50, 43 mg of 5-[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]-1,3-oxazolidin-2-one and 43 mg of 3,5-bis(trifluoromethyl)benzyl bromide gave the title compound. Mass spectrum (ESI) 606.1 (M+1). ¹H NMR signals are doubled because of atropoisomerism. ¹H NMR (500 MHz, CDCl₃): δ 7.58-7.88 (m, 5H), 7.34 (d, J=8 Hz, 1H), 7.23 (m, 1H), 7.02, 6.79 (d, J=2 Hz, 1H), 6.88, 6.85 (d, J= 8.5 Hz, 1H), 5.45, 5.42 (m, 1H), 4.52-4.64 (m, 1.5H), 4.36 (d, J=15.5 Hz, 0.5 H), 3.74, 3.57 (s, 3H), 3.49, 3.34 (m, 1H), 3.09, 2.99 (t, J~8.5 Hz, 1H), 2.89, 2.81 (septet, J=7 Hz, 1H), 1.24, 1.12 (m, 6H).

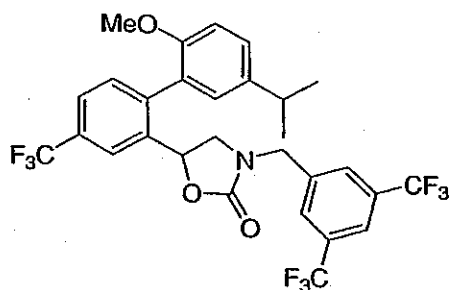
EXAMPLE 54



3-[3,5-bis(trifluoromethyl)benzyl]-5-[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]-1,3-oxazolidin-2-one (enantiomer A)

Following the procedure described in EXAMPLE 50, 43 mg of 5-[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]-1,3-oxazolidin-2-one, enantiomer A, and 43 mg of 3,5-bis(trifluoromethyl)benzyl bromide gave the title compound. Analytical HPLC on Chiralpak AS 4.6 x 250 mm, eluting with 5% isopropanol in heptane at 0.5 mL/min: t_R=9.9 min

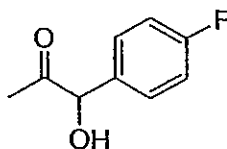
EXAMPLE 55



3-[3,5-bis(trifluoromethyl)benzyl]-5-[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]-1,3-oxazolidin-2-one (enantiomer B)

Following the procedure described in EXAMPLE 50, 44 mg of 5-[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]-1,3-oxazolidin-2-one, enantiomer B, and 43 mg of 3,5-bis(trifluoromethyl)benzyl bromide gave the title compound. Analytical HPLC on Chiralpak AS 4.6 x 250 mm, eluting with 5% isopropanol in heptane at 0.5 mL/min: t_R =11.0 min

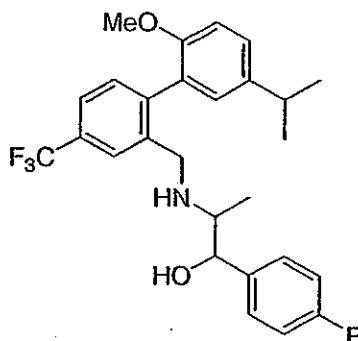
EXAMPLE 56



1-(4-Fluorophenyl)-1-hydroxyacetone

A suspension of ground LaCl_3 (26 mg, 0.104 mmol) in dry THF (7.8 mL) under N_2 was cooled to -78°C and stirred for 15 min. A solution of $n\text{-BuLi}$ (1.6 M in hexanes, 195 μL , 0.312 mmol) was added and stirring was continued for 15 min. The reaction was warmed to 0°C and stirred for 30 min. Trimethylsilyl cyanide (31 mg, 42 μL , 0.312 mmol) was added and the reaction was stirred for 30 min at 0°C and warmed to room temperature over 30 min. A solution of acetyltrimethylsilane (Cunico, R. F., Kuan, C. -P., *J. Org. Chem.*, 1985, 50, 5410-5413) (121 mg, 1.04 mmol) and 4-fluorobenzaldehyde (142 mg, 1.14 mmol) in dry THF (19 mL) was added by cannula and the reaction was stirred at room temperature for 2 h. After this time 1N HCl (24 mL) was added and the reaction was stirred for 1 h. Et_2O (25 mL) was added and the organic layer was separated and washed with H_2O (2 x 25 mL). The combined aqueous layers were extracted with Et_2O (3 x 50 mL). The combined organic extracts were dried (MgSO_4) and concentrated in vacuo to give the crude product. This was purified by flash chromatography (Si, 25 x 160 mm, 0-50% EtOAc in hexanes gradient) to give 1-(4-fluorophenyl)-1-hydroxyacetone as a colorless solid. R_f = 0.31 (20% EtOAc/hexanes). ^1H NMR (CDCl_3 , 500 MHz) δ 7.29 (m, 2H), 7.08-7.04 (m, 2H), 5.06 (d, J = 3.6 Hz, 1H), 4.35 (t, J = 6.5 Hz, 1H), 2.05 (s, 3H).

EXAMPLE 57

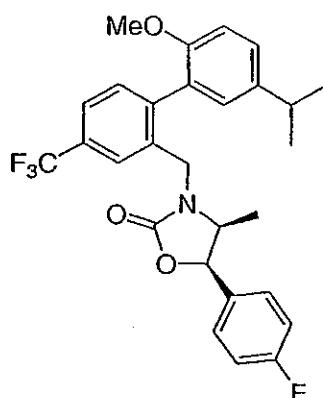


erythro- and threo-1-(4-Fluorophenyl)-2-((5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl)methyl)amino)propan-1-ol

NaCNBH₃ (19 mg, 0.306 mmol) was added to a solution of {[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl}amine (67 mg, 0.204 mmol) and 1-(3,5-dichlorophenyl)-1-hydroxyacetone (45 mg, 0.204 mmol) in MeOH at room temperature followed by acetic acid (2 drops). The reaction was stirred for 5 h at room temperature. The reaction mixture was diluted with EtOAc (20 mL), H₂O (20 mL and brine (5 mL). The aqueous layer was extracted with EtOAc (2 x 20 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated *in vacuo* to give the crude product.

This was purified by flash chromatography (Si, 12 x 160 mm, 0-50% EtOAc in hexanes gradient) to give the two possible diastereoisomers, *erythro*-1-(4-fluorophenyl)-2-((5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl)methyl)amino)propan-1-ol (68.4 mg) and *threo*-1-(4-fluorophenyl)-2-((5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl)methyl)amino)propan-1-ol (48.9 mg) as colorless oils. *erythro*-diastereoisomer: *R_f* = 0.40 (20% EtOAc/hexanes). LCMS calc. = 476.22; found = 476.2 (M+1)⁺. ¹H NMR (500 MHz, CDCl₃) δ 7.72 (s, 1H), 7.60 (d, *J* = 7.8 Hz, 1H), 7.36 (m, 1H), 7.27 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.19 (m, 2H), 7.04-6.92 (m, 4H), 4.63-4.56 (m, 1H), 3.85-3.65 (m, 7H), 2.92 (m, 1H), 2.72 (m, 1H), 1.26 (t, *J* = 8.0 Hz, 6H), 0.64 (t, *J* = 5.4 Hz, 3H). *threo*-diastereoisomer: *R_f* = 0.20 (20% EtOAc/hexanes). LCMS calc. = 476.22; found = 476.2 (M+1)⁺. ¹H NMR (500 MHz, CDCl₃) δ 7.73 (d, *J* = 9.0 Hz, 1H), 7.58 (d, *J* = 7.9 Hz, 1H), 7.32 (m, 1H), 7.24 (m, 3H), 7.07-6.97 (m, 3H), 6.92 (d, *J* = 8.5 Hz, 1H), 4.05 (d, *J* = 7.9 Hz, 1H), 3.82-3.70 (m, 5H), 3.59 (d, *J* = 13 Hz, 1H), 3.51 (d, *J* = 13 Hz, 1H), 2.90 (m, 1H), 2.51 (m, 1H), 1.25 (m, 6H), 0.73 (d, *J* = 6.4 Hz, 3H).

EXAMPLE 58



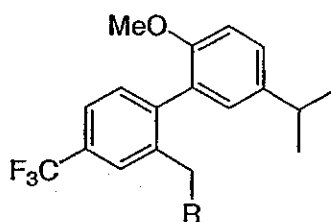
erythro-5-(4-Fluorophenyl)-3-{[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl}-4-methyl-1,3-oxazolidin-2-one

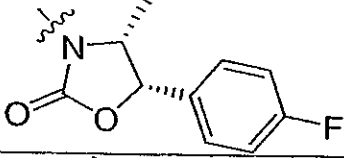
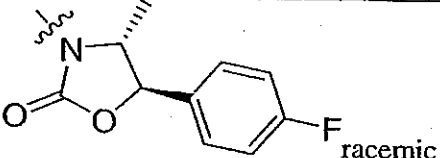
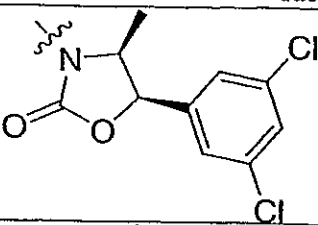
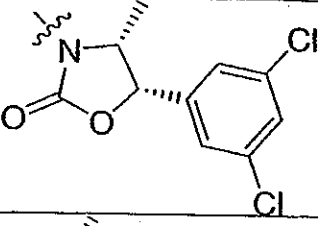
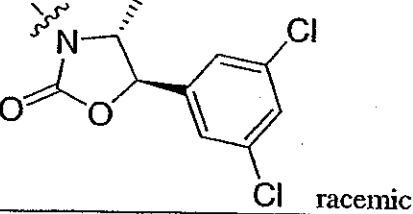
As for EXAMPLE 7 Step 3. $R_f = 0.38$ (20% EtOAc/hexanes). LCMS calc. = 502.20; found = 502.2 (M+1)⁺. ¹H NMR (500 MHz, benzene-d₆, 1:1 mixture of atropisomers) δ 7.96 (s, 0.5H), 7.75 (s, 0.5H),

7.35 (d, $J = 7.7$ Hz, 1H), 7.10-7.06 (m, 2H), 6.94 (d, $J = 2.1$ Hz, 0.5H), 6.88 (d, $J = 2.1$ Hz, 0.5H), 6.69-6.62 (m, 4.5H), 6.55 (d, $J = 8.4$ Hz, 0.5H), 4.95 (d, $J = 15.9$ Hz, 0.5H), 4.86 (d, $J = 15.8$ Hz, 0.5H), 4.80 (d, $J = 7.9$ Hz, 0.5H), 4.70 (d, $J = 7.8$ Hz, 0.5H), 4.04 (d, $J = 15.8$ Hz, 0.5H), 3.93 (d, $J = 15.9$ Hz, 0.5H), 3.36 (s, 1.5H), 3.22 (s, 1.5H), 3.14 (m, 0.5H), 3.05 (m, 0.5H), 2.79-2.71 (m, 1H), 1.18 (m, 6H), 0.02 (d, $J = 6.5$ Hz, 1.5H), -0.04 (d, $J = 6.5$ Hz, 1.5H). This compound was separated into its two enantiomers (4*R*,5*S*)- 5-(4-Fluorophenyl)-3-{[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl}-4-methyl-1,3-oxazolidin-2-one and (4*S*,5*R*)- 5-(4-Fluorophenyl)-3-{[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl}-4-methyl-1,3-oxazolidin-2-one using chiral HPLC (AD column, 20 x 250 mm, 3% EtOH in heptane).

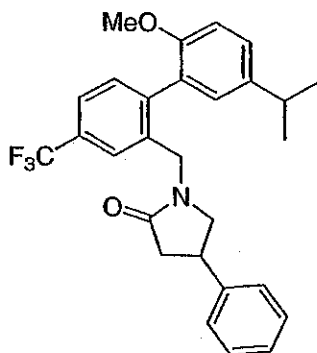
Following the procedures outlined in EXAMPLE 58 the compounds listed in Table 2 were prepared:

Table 2



Example	R	LCMS (M+1) ⁺
59		502.2
60		502.2
61		552.2
62		552.2
63		552.1

EXAMPLE 64



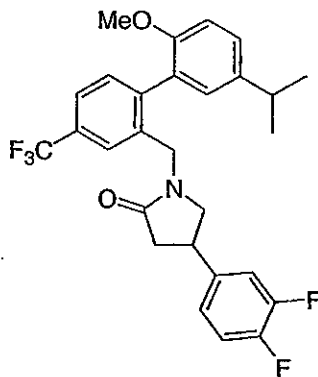
5

1-([5'-Isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl)-4-phenylpyrrolidin-2-one

Sodium bis(trimethylsilyl)amide (114 μ L of a 1M solution in THF, 0.114 mmol) was added to a stirred solution of 4-phenylpyrrolidin-2-one (Winans, C. F., Adkins, H., *J. Am. Chem. Soc.*, **1933**, 55, 4167-

4176) (17 mg, 0.103 mmol) in dry THF (1 mL) at room temperature under N₂. The reaction was stirred for 5 min and a solution of 2-(bromomethyl)-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl (20 mg, 0.0516 mmol) in dry THF (2 mL) was added by cannula. The reaction was stirred at room temperature for 3 days. The reaction was quenched with saturated NH₄Cl (10 mL) and extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine (10 mL), dried (Na₂SO₄) and concentrated *in vacuo* to give the crude product. This was purified by flash chromatography (Si, 12 x 160 mm, 0-90% EtOAc in hexanes gradient) to afford 1-([5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl)-4-phenylpyrrolidin-2-one as a colorless oil. *R*_f = 0.11 (20% EtOAc/hexanes). LCMS calc. = 468.22; found = 468.2 (M+1)⁺. ¹H NMR (600 MHz, benzene-d₆, 1:1 mixture of atropisomers) δ 7.79 (s, 0.5H), 7.73 (s, 0.5H), 7.33 (d, *J* = 7.7 Hz, 1H), 7.08-7.04 (m, 4H), 6.99 (m, 1H), 6.92 (s, 0.5H), 6.88 (s, 0.5H), 6.76 (dd, *J* = 16.0, 7.4 Hz, 2H), 6.60 (dd, *J* = 8.5, 3.1 Hz, 1H), 4.58 (d, *J* = 15.4 Hz, 1H), 4.38 (t, *J* = 13.9 Hz, 1H), 3.29 (s, 1.5H), 3.26 (s, 1.5H), 2.85-2.73 (m, 3H), 2.63-2.57 (m, 1H), 2.38-2.28 (m, 1H), 2.21-2.11 (m, 1H), 1.20-1.16 (m, 6H).

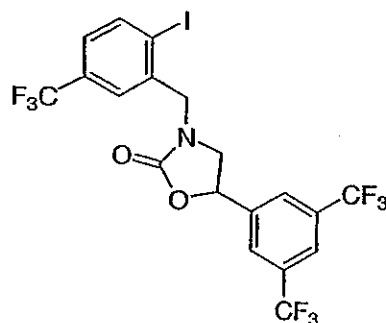
EXAMPLE 65



4-(3,4-Difluorophenyl)-1-([5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl)pyrrolidin-2-one

Prepared by a similar method as EXAMPLE 64 starting with 4-(3,4-difluorophenyl)pyrrolidin-2-one (prepared by a similar method as in Marivet, M. C., Bourguignon, J. -J.; Lugnier, C., Mann, A., Stoclet, J. -C., Wermuth, C. -G. *J. Med. Chem.*, **1989**, 32, 1450-1457). LCMS calc. = 504.20; found = 504.2 (M+1)⁺.

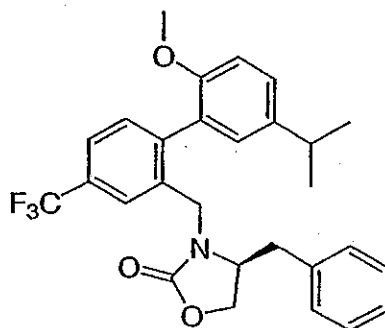
EXAMPLE 66

5-[3,5-bis(trifluoromethyl)phenyl]-3-[2-iodo-5-(trifluoromethyl)benzyl]-1,3-oxazolidin-2-one

A stirred suspension of sodium hydride (60% in oil, 167 mg, 4.18 mmol) in THF (5 mL) was treated at 0°C with 5-[3,5-bis(trifluoromethyl)phenyl]-1,3-oxazolidin-2-one (500 mg, 1.67 mmol) dissolved in THF (1 mL), under an atmosphere of N₂. The reaction was stirred for 20 min and a solution of 2-

(bromomethyl)-1-iodo-4-(trifluoromethyl)benzene (610 mg, 1.67 mmol) in THF (1 mL) was added dropwise. The reaction was stirred at room temperature for 18 h. The reaction was quenched with H₂O (1 mL) and partitioned between EtOAc (80 mL) and H₂O (25 mL). The aqueous phase was re-extracted with EtOAc (2 x 20 mL) and the combined organic extracts were washed with brine (30 mL), dried (MgSO₄) and concentrated *in vacuo* to give the crude product. This was purified by flash silica-gel chromatography (0-30% EtOAc in hexanes gradient) to afford 5-[3,5-bis(trifluoromethyl)phenyl]-3-[2-iodo-5-(trifluoromethyl)benzyl]-1,3-oxazolidin-2-one. R_f = 0.55 (51:5% EtOAc/hexanes). LCMS 584 (M+1)⁺. ¹H NMR (CDCl₃, 500 MHz) δ 8.05 (d, J = 8.2 Hz, 1H), 7.95 (br s, 1H), 7.85 (br s, 2H), 7.51 (br s, 1H), 7.32 (m, 1H), 5.72 (t, J = 8.0 Hz, 1H), 4.74 (d, J = 15.5 Hz, 1H), 4.64 (d, J = 15.3 Hz, 1H), 4.14 (t, J = 7.1 Hz, 1H), 3.47 (dd, J = 7.1, 1.6 Hz).

EXAMPLE 67



(4S)-4-benzyl-3-([5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl)-1,3-oxazolidin-2-one.

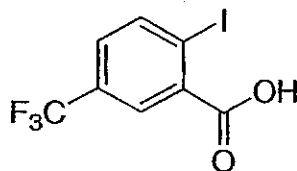
Step A: (4S)-4-benzyl-3-[2-iodo-5-(trifluoromethyl)benzyl]1,3-oxazolidin-2-one

A stirred suspension of sodium hydride (60% in oil, 27 mg, 0.68 mmol) in THF (3 mL) was treated at 0°C with (S)-4-benzyl-2-oxazolidinone (49 mg, 0.27 mmol) dissolved in THF (1 mL), under an atmosphere of N₂. The reaction was stirred for 20 min and a solution of 2-(bromomethyl)-1-iodo-4-(trifluoromethyl)benzene (100 mg, 0.27 mmol) in THF (1 mL) was added dropwise. The reaction was stirred at room temperature for 18 h. The reaction was quenched with H₂O (1 mL) and partitioned between EtOAc (80 mL) and H₂O (25 mL). The aqueous phase was re-extracted with EtOAc (2 x 20 mL) and the combined organic extracts were washed with brine (30 mL), dried (MgSO₄) and concentrated *in vacuo* to give the crude product. This was purified by flash silica-gel chromatography (0-30% EtOAc in hexanes gradient) to afford (4S)-4-benzyl-3-[2-iodo-5-(trifluoromethyl)benzyl]1,3-oxazolidin-2-one. *R_f* = 0.45 (15% EtOAc/hexanes). LCMS 462 (M+1)⁺. ¹H NMR (CDCl₃, 500 MHz) δ 8.04 (d, *J* = 8.2 Hz, 1H), 7.54 (br s, 1H), 7.33-7.27 (m, 5H), 7.11-7.10 (m, 2H), 7.32 (m, 1H), 4.80 (d, *J* = 16.0 Hz, 1H), 4.49 (d, *J* = 16.1 Hz), 4.28 (t, *J* = 8.7 Hz, 1H), 4.25 (t, *J* = 9.1, 4.8 Hz, 1H), 3.94 (m, 1H), 3.16 (dd, *J* = 13.5, 4.8 Hz, 1H), 2.73 (dd, *J* = 9.1, 4.4 Hz, 1H).

Step B: (4S)-4-benzyl-3-([5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl)-1,3-oxazolidin-2-one.

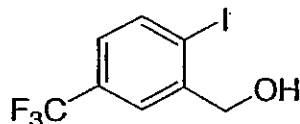
A stirred suspension of (4S)-4-benzyl-3-[2-iodo-5-(trifluoromethyl)benzyl]1,3-oxazolidin-2-one (63 mg, 0.137 mmol), 2-methoxy-5-isopropylphenyl boronic acid (52 mg, 0.274 mmol), K₂CO₃ (47 mg, 0.34 mmol) and Pd(OAc)₂ (9.2 mg, 0.0137 mmol) in acetone:H₂O (5:1) (6 mL) was heated at reflux for 1 h. The reaction mixture was concentrated *in vacuo*, diluted with H₂O (15 mL) and extracted with EtOAc (3 x 30 mL). The combined organic extracts were washed with brine (30 mL), dried (MgSO₄), filtered and concentrated. The crude product was purified by silica-gel flash chromatography (0-20% EtOAc in hexanes gradient) to (4S)-4-benzyl-3-([5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl)-1,3-oxazolidin-2-one. *R_f* = 0.35 (15% EtOAc/hexanes). LCMS 484 (M+1)⁺. ¹H NMR (CDCl₃, 500 MHz) (atropisomers present; doubling of some peaks observed in ¹H NMR) δ 7.72 (br s 1H), 7.65 (br s, 1H), 7.42 (m, 1H), 7.32-7.22 (m, 3H), 7.08 (d, *J* = 2.3 Hz, 1H), 6.90-6.84 (m, 3H), 4.80 (d, *J* = 15.8 Hz, 1H), 4.35 (d, *J* = 15.8 Hz), 4.28 (t, *J* = 8.7 Hz, 1H), 3.96-3.92 (m, 3H), 3.78 (s, 3H), 3.62-3.52 (m, 1H), 2.94-2.86 (m, 1H), 2.82 (dd, *J* = 9.4, 3.9 Hz, 1H), 2.42 (dd, *J* = 9.6, 3.9 Hz), 1.26 (s, 3H), 1.10 (s, 3H).

EXAMPLE 68

2-Iodo-5-(trifluoromethyl)benzoic acid

Potassium hydroxide (3.78 g; 0.0673 mol) was added to a stirred solution of 2-iodo-5-(trifluoromethyl)benzonitrile (EXAMPLE 2; 4 g; 0.0135 mol) in a 1:1 isopropanol:H₂O solution (60 mL). The reaction was heated at reflux for 14 h and then partitioned between H₂O (50 mL) and EtOAc (50 mL). The aqueous layer was extracted with EtOAc (50 mL) and acidified to pH 5 with 6N HCl. The aqueous layer was further extracted with EtOAc (4 x 50 mL) and the combined extracts were washed with brine (50 mL), dried over MgSO₄, filtered, and concentrated *in vacuo* to afford 2-iodo-5-(trifluoromethyl)benzoic acid as a yellow solid. LCMS = 317.0 (M+1)⁺. ¹H NMR (CDCl₃, 500 MHz): δ 8.27 (d, *J* = 1.6 Hz, 1 H), 8.25 (d, *J* = 8.2 Hz, 1 H), 7.47 (dd, *J* = 8.2, 1.8 Hz, 1 H).

EXAMPLE 69

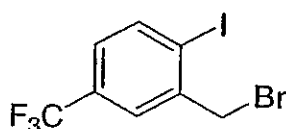
[2-Iodo-5-(trifluoromethyl)phenyl]methanol

Borane-THF (1.0M solution in THF; 94 mL; 94 mmol) was added to a stirred solution of 2-iodo-5-(trifluoromethyl)benzoic acid (2.97g; 9.4 mmol) in THF (300 mL) at 0°C under N₂. The reaction was heated at reflux for 90 min and then carefully quenched with 6N HCl until no further gas evolution. The reaction was diluted with H₂O (250 mL) and extracted with EtOAc (3 x 250 mL). The combined extracts were washed with brine (300 mL), dried over MgSO₄, filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography (0-25% EtOAc/hexanes gradient) to afford [2-iodo-5-(trifluoromethyl)phenyl]methanol as a white solid. LCMS = 285.0 (M - 17)⁺. ¹H NMR (CDCl₃, 500 MHz): δ 7.97 (d, *J* = 8.3 Hz, 1 H), 7.79 (s, 1 H), 7.28 (d, *J* = 8.4 Hz, 1 H), 4.75 (s, 2 H).

An alternative procedure is as follows: To a solution of 2-Iodo-5-(trifluoromethyl)benzaldehyde (EXAMPLE 80, Step A, 9g) in THF (100 mL) and water (10 mL) at 0°C was added NaBH₄ (0.5 g). The reaction was stirred 30 minutes. To the reaction mixture was added dilute aqueous HCl (cautiously).

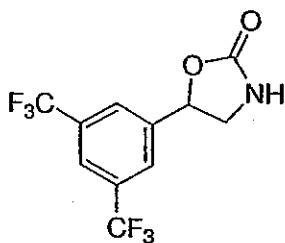
The mixture was extracted with ether and the ether layer was washed with water, then brine. The ether layer was then dried over anhydrous MgSO_4 , filtered and concentrated. The material is chromatographed on SiO_2 using a step gradient of 1:3 CH_2Cl_2 /hexanes, then 1:1 CH_2Cl_2 /hexanes, then 100% CH_2Cl_2 to afford [2-iodo-5-(trifluoromethyl)phenyl]methanol as a white solid.

EXAMPLE 70

2-(Bromoethyl)-1-iodo-4-(trifluoromethyl)benzene

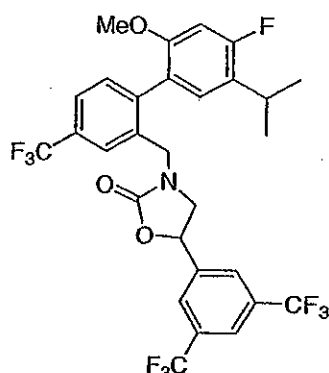
Carbon tetrabromide (1.86 g; 5.6 mmol) and triphenylphosphine (1.47 g; 5.6 mmol) were added successively to a stirred solution of [2-iodo-5-(trifluoromethyl)phenyl]methanol (1.13 g; 3.74 mmol) in CH_2Cl_2 (25 mL) at 0°C under N_2 . The reaction was stirred at room temperature for 48 h. A second equivalent of carbon tetrabromide (1.2 g; 3.74 mmol) and triphenylphosphine (0.98 g; 3.74 mmol) was added and the reaction was stirred an additional 14 h. The solvent was removed *in vacuo* and the residue was purified by flash chromatography (0-25% EtOAc/hexanes gradient) to afford 2-(bromoethyl)-1-iodo-4-(trifluoromethyl)benzene as a clear oil. ^1H NMR (CDCl_3 , 500 MHz): δ 8.02 (d, $J = 8.2$ Hz, 1 H), 7.73 (d, $J = 1.8$ Hz, 1 H), 7.26 (dd, $J = 8.3, 1.8$ Hz, 1 H), 4.64 (s, 2 H).

EXAMPLE 71

5-[3,5-bis(trifluoromethyl)phenyl]-1,3-oxazolidin-2-one

Following the procedure described in EXAMPLE 13, 5.46 g of 2-amino-1-[3,5-bis(trifluoromethyl)phenyl]ethanol yielded 5-[3,5-bis(trifluoromethyl)phenyl]-1,3-oxazolidin-2-one as an off-white solid. LCMS = 300.1 ($\text{M}+1$) $^+$. ^1H NMR (CDCl_3 , 500 MHz): δ 7.94 (s, 1 H), 7.89 (s, 2 H), 5.81-5.77 (m, 1 H), 5.29 (s, 1 H), 4.17-4.12 (m, 1 H), 3.59-3.55 (m, 1 H).

EXAMPLE 72



5-[3,5-bis(trifluoromethyl)phenyl]-3-[[4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]-1,3-oxazolidin-2-one

A mixture of 5-[3,5-bis(trifluoromethyl)phenyl]-3-[2-iodo-5-(trifluoromethyl)benzyl]-1,3-oxazolidin-2-one (60 mg; 0.103 mmol), (4-fluoro-5-isopropyl-2-methoxyphenyl)boronic acid (27 mg; 0.129 mmol), palladium acetate (7 mg; 0.0103 mmol), and potassium carbonate (36 mg; 0.257 mmol) in 5:1 acetone/water (6 mL) was heated at reflux for 1 h. Acetone was removed *in vacuo* and the residue was diluted with H₂O (10 mL) and extracted with CH₂Cl₂ (3 x 10 mL). The combined extracts were washed with brine (10 mL), dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (0-25% EtOAc/hexanes gradient) to afford 5-[3,5-

bis(trifluoromethyl)phenyl]-3-[[4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]-1,3-oxazolidin-2-one as a clear glass. LCMS = 624.2 (M+1)⁺. ¹H NMR (benzene-d₆, 500 MHz, 1:1 mixture of atropisomers): δ 7.60 (s, 1.5 H), 7.45 (s, 0.5 H), 7.31-7.25 (m, 3 H), 6.98-6.94 (m, 1 H), 6.87-6.82 (m, 1 H), 6.43-6.37 (m, 1 H), 4.54 (d, J = 15.6 Hz, 0.5 H), 4.40-4.36 (m, 1 H), 4.47 (d, J = 15.6 Hz, 0.5 H), 3.96 (d, J = 15.5 Hz, 0.5 H), 3.80 (d, J = 15.8 Hz, 0.5 H), 3.24-3.15 (m, 1 H), 3.02 (s, 3 H), 2.62-2.58 (m, 0.5 H), 2.53-2.48 (m, 0.5 H), 2.12-2.07 (m, 0.5 H), 2.04-2.00 (m, 0.5 H) 1.22-1.11 (m, 6 H).

The racemic material was separated by chiral HPLC using 15% IPA/heptane and an OD column into its two enantiomers.

(5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[[4'-fluoro-5'-isopropyl-2'-methoxy-4-

(trifluoromethyl)biphenyl-2-yl]methyl]-1,3-oxazolidin-2-one: LCMS = 624.2 (M+1)⁺. ¹H NMR (benzene-d₆, 500 MHz, 1:1 mixture of atropisomers): δ 7.62 (s, 1.5 H), 7.47 (s, 0.5 H), 7.34-7.27 (m, 3 H), 6.99-6.95 (m, 1 H), 6.88-6.83 (m, 1 H), 6.44-6.39 (m, 1 H), 4.54 (d, J = 15.5 Hz, 0.5 H), 4.47-4.41 (m, 1 H), 4.33 (d, J = 15.6 Hz, 0.5 H), 3.98 (d, J = 15.7 Hz, 0.5 H), 3.82 (d, J = 15.8 Hz, 0.5 H), 3.24-

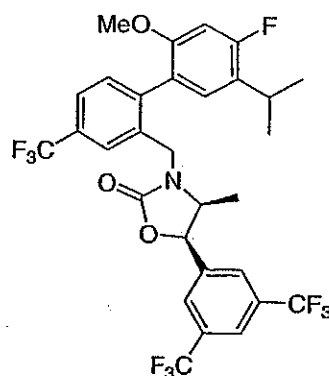
3.15 (m, 1 H), 3.05 (s, 3 H), 2.67-2.62 (m, 0.5 H), 2.57-2.52 (m, 0.5 H), 2.16-2.11 (m, 0.5 H), 2.09-2.04 (m, 0.5 H) 1.22-1.11 (m, 6 H).

(5*S*)-5-[3,5-bis(trifluoromethyl)phenyl]-3-{[4'-fluoro-5'-isopropyl-2'-methoxy-4-

(trifluoromethyl)biphenyl-2-yl]methyl}-1,3-oxazolidin-2-one: LCMS = 624.2 (M+1)⁺. ¹H NMR

(benzene-d₆, 500 MHz, 1:1 mixture of atropisomers): δ 7.63 (s, 1.5 H), 7.48 (s, 0.5 H), 7.35-7.27 (m, 3 H), 7.00-6.95 (m, 1 H), 6.88-6.83 (m, 1 H), 6.44-6.38 (m, 1 H), 4.54 (d, *J* = 15.8 Hz, 0.5 H), 4.48-4.42 (m, 1 H), 4.34 (d, *J* = 15.8 Hz, 0.5 H), 3.99 (d, *J* = 15.8 Hz, 0.5 H), 3.83 (d, *J* = 15.8 Hz, 0.5 H), 3.25-3.15 (m, 1 H), 3.05 (s, 3 H), 2.68-2.63 (m, 0.5 H), 2.58-2.53 (m, 0.5 H), 2.18-2.12 (m, 0.5 H), 2.10-2.05 (m, 0.5 H) 1.23-1.11 (m, 6 H).

EXAMPLE 73



Step 1: (4*S*,5*R*)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[2-iodo-5-(trifluoromethyl)benzyl]-4-methyl-1,3-oxazolidin-2-one

To a stirred suspension of sodium hydride (60% dispersion in mineral oil; 1.3 g; 0.0325 mol) in THF (60 mL) at 0 °C under N₂ was added dropwise a solution of (4*S*,5*R*)-5-[3,5-bis(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one (Example 17) (4.077 g; 0.013 mol) in THF (50 mL). Gas evolution was observed. The resultant mixture stirred at 0 °C for 30 min prior to addition of a solution of 2-(bromomethyl)-1-iodo-4-(trifluoromethyl)benzene (4.754 g; 0.013 mol) in THF (20 mL). The reaction was allowed to warm to room temperature and stirred for 14 h. The reaction was carefully quenched with H₂O (15 mL) and partitioned between EtOAc (250 mL) and H₂O (75 mL). The aqueous layer was extracted with EtOAc (3 x 100 mL). Combined organic layers were washed with brine (100 mL), dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (0-20% EtOAc/hexanes gradient) to afford 6.4 g (82.5%) of (4*S*,5*R*)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[2-iodo-5-(trifluoromethyl)benzyl]-4-methyl-1,3-oxazolidin-2-one as a white solid. LCMS = 598.1 (M+1)⁺. ¹H NMR (CDCl₃, 500 MHz): δ 8.03 (d, *J* = 8.2 Hz, 1 H), 7.90 (s, 1 H), 7.79 (s, 2 H), 7.58 (s, 1H), 7.30

(dd, $J = 8.2$ Hz, $J = 2.0$ Hz, 1 H), 5.76 (d, $J = 8$ Hz, 1 H), 4.88 (d, $J = 15.8$ Hz, 1 H), 4.37 (d, $J = 15.8$ Hz, 1 H), 4.09-4.02 (m, 1 H), 0.8 (d, $J = 6.6$ Hz, 3 H).

Step 2: (4*S*,5*R*)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[[4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]-4-methyl-1,3-oxazolidin-2-one

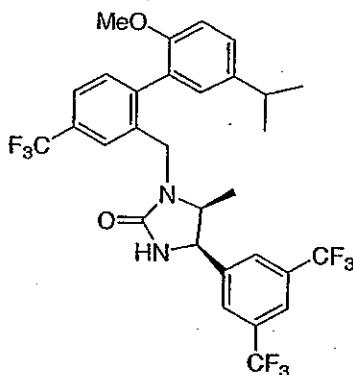
A stirred mixture of (4*S*,5*R*)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[2-iodo-5-(trifluoromethyl)benzyl]-4-methyl-1,3-oxazolidin-2-one (4.29 g; 7.19 mmol), (4-fluoro-5-isopropyl-2-methoxyphenyl)boronic acid (Example 78) (4.57 g; 21.57 mmol), *tetrakis*(triphenylphosphine)palladium (0) (1.0 g; 0.86 mmol), and sodium carbonate (6.35 g) in C_6H_6 /EtOH/ H_2O (120 mL/17 mL/51 mL) was heated at reflux (100°C) under N_2 for 14 h. The reaction was partitioned between EtOAc (200 mL) and H_2O (100 mL). The aqueous phase was extracted with EtOAc (3 x 200 mL). The combined organic phases were washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by silica-gel flash chromatography (0-25% EtOAc/hexanes gradient) to afford (4*S*,5*R*)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[[4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]-4-methyl-1,3-oxazolidin-2-one as a yellow solid. To remove the yellow impurity, 2.7 g were dissolved in 165 mL EtOH and 275 mg decolorizing charcoal was added (activated carbon, Darco, G-60, 100 mesh powder, Aldrich). The mixture was stirred at room temperature for 40 min, filtered, and concentrated *in vacuo*. Trituration with *ca.* 25 mL hexanes afforded 2.46 g of the title compound as a white solid. 1H NMR indicated trace impurities which were removed by silica gel flash chromatography (0-15% EtOAc/hexanes gradient). Residual solvent was removed by lyophilization from acetonitrile. LCMS = 638.3 ($M+1$)⁺. 1H NMR (benzene- d_6 , 500 MHz, 1:1 mixture of atropisomers): δ 7.82 (s, 0.5 H), 7.60 (s, 0.5 H), 7.57 (s, 1 H), 7.33 (d, $J = 8$ Hz, 1H), 7.27 (d, $J = 9.9$ Hz, 2 H), 7.02-6.98 (m, 1 H), 6.89 (d, $J = 8.5$ Hz, 0.5 H), 6.82 (d, $J = 8.5$ Hz, 0.5 H), 6.45 (d, $J = 12.1$ Hz, 0.5 H), 6.35 (d, $J = 11.9$ Hz, 0.5 H), 4.94 (d, $J = 16.0$ Hz, 0.5 H), 4.87 (d, $J = 15.8$ Hz, 0.5 H), 4.54 (d, $J = 8.0$ Hz, 0.5 H), 4.50 (d, $J = 7.8$ Hz, 0.5 H), 3.74-3.66 (m, 1 H), 3.23-3.15 (m, 1 H), 3.12 (s, 1.5 H), 2.99 (s, 1.5 H), 2.97-2.92 (m, 0.5 H), 2.89-2.84 (m, 0.5 H), 1.21-1.09 (m, 6 H), -0.27 (d, $J = 6.7$ Hz, 1.5 H), -0.40 (d, $J = 6.7$ Hz, 1.5 H).

Alternate procedure for making (4*S*,5*R*)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[[4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]-4-methyl-1,3-oxazolidin-2-one:

A mixture of (4*S*,5*R*)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[2-iodo-5-(trifluoromethyl)benzyl]-4-methyl-1,3-oxazolidin-2-one (50 mg; 0.084 mmol), (4-fluoro-5-isopropyl-2-methoxyphenyl)boronic acid (EXAMPLE 78, 22 mg; 0.105 mmol), palladium acetate (6 mg; 0.0103 mmol), and potassium carbonate (29 mg; 0.257 mmol) in 5:1 acetone/water (6 mL) was heated at reflux for 1 h. Acetone was removed *in vacuo* and the residue was diluted with H_2O (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined extracts were washed with brine (10 mL), dried over Na_2SO_4 , filtered, and concentrated *in*

vacuo. The residue was purified by flash chromatography (0-25% EtOAc/hexanes gradient) to afford (4*S*,5*R*)-5-[3,5-bis(trifluoromethyl)phenyl]-3-{[4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl}-4-methyl-1,3-oxazolidin-2-one as a clear glass.

EXAMPLE 74



(4*R*,5*S*)-4-[3,5-bis(trifluoromethyl)phenyl]-1-{[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl}-5-methylimidazolidin-2-one.

Step A: (4*S*,5*S*)-5-[3,5-bis(trifluoromethyl)phenyl]-3-{[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl}-4-methyl-1,3-oxazolidin-2-one.

((4*S*,5*S*)-5-[3,5-bis(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one) (46.2 mg, 0.148 mmol) was placed in a dry flask and DMA (3 mL) was added. NaHMDS (296 μ L of a 1M solution in THF, 0.296 mmol) was added and the reaction was stirred for 5 min. At this time, 2'-(bromomethyl)-5-isopropyl-4'-(trifluoromethyl)biphenyl-2-yl methyl ether (80.0 mg, 0.207 mmol) was added by cannula in DMA (2 mL). After 30 min, the reaction was quenched with saturated NH_4Cl (2 mL). The mixture was diluted with EtOAc (40 mL). The organic layer was washed with water (15 mL), and brine (15 mL), dried over Na_2SO_4 , filtered, and concentrated. Purification of the residue by flash chromatography with 25% EtOAc/hexanes afforded (4*S*,5*S*)-5-[3,5-bis(trifluoromethyl)phenyl]-3-{[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl}-4-methyl-1,3-oxazolidin-2-one. R_f = 0.27 (25% EtOAc/hexanes). LCMS = 620.2 ($M+1$)⁺. ^1H NMR (CDCl_3 , 500 MHz; atropisomers present) δ 6.90-7.88 (m, 9H), 4.04-5.05 (m, 3H), 3.25-3.74 (m, 4H), 2.88 (m, 1H), 1.19-1.24 (m, 6H), 0.99-1.07 (m, 3H).

Step B: (1*S*,2*S*)-1-[3,5-bis(trifluoromethyl)phenyl]-2-([5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl)amino)propan-1-ol.

To a solution of (4*S*,5*S*)-5-[3,5-bis(trifluoromethyl)phenyl]-3-{[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl}-4-methyl-1,3-oxazolidin-2-one (147.7 mg, 0.239 mmol) in EtOH (7.5 mL) was added H_2O (1.5 mL) and KOH (150 mg, 2.67 mmol). The solution was heated to 75°C for 30 h and then cooled to room temperature. EtOAc (75 mL) was added and the organic layer was washed

with H₂O (15 mL) and brine (2 x 15 mL). The organic layer was dried over Na₂SO₄, filtered, and concentrated. The residue was purified by flash chromatography to afford (1*S*,2*S*)-1-[3,5-bis(trifluoromethyl)phenyl]-2-([5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl)methyl]amino)propan-1-ol. *R*_f = 0.44 (40% EtOAc/hexanes). LCMS = 594.2 (M+1)⁺. ¹H NMR (CDCl₃, 500 MHz) δ 6.93-7.78 (m, 9H), 3.51-4.20 (m, 6H), 2.91 (m, 1H), 2.49 (m, 1H), 1.22-1.26 (m, 6H), 0.79-0.81 (m, 3H).

Step C: *tert*-butyl{(1*S*,2*S*)-2-[3,5-bis(trifluoromethyl)phenyl]-2-hydroxy-1-methylethyl}{[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl)methyl]carbamate}.

To a solution of (1*S*,2*S*)-1-[3,5-bis(trifluoromethyl)phenyl]-2-([5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl)methyl]amino)propan-1-ol (135.5 mg, 0.228 mmol) in CH₂Cl₂ (5 mL) was added BOC₂O (49.7 mg, 0.228 mmol). The reaction was stirred at room temperature for 2 days; during this time, 2 additional portions of BOC₂O (25 mg each) were added. After 2 days, the reaction was concentrated, and the residue was purified by flash chromatography with 20% EtOAc/hexanes to afford *tert*-butyl{(1*S*,2*S*)-2-[3,5-bis(trifluoromethyl)phenyl]-2-hydroxy-1-methylethyl}{[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl)methyl]carbamate. *R*_f = 0.41 (40% EtOAc/hexanes). LCMS = 594.2 (M+1-BOC)⁺.

Step D: *tert*-butyl{(1*S*,2*R*)-2-azido-2-[3,5-bis(trifluoromethyl)phenyl]-1-methylethyl}{[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl)methyl]carbamate}.

A dry flask was charged with THF (1 mL) diethyl azodicarboxylate (DEAD) (11 μL, 0.0698 mmol) and diphenylphosphoryl azide (DPPA) (15 μL, 0.0698 mmol). *tert*-butyl{(1*S*,2*S*)-2-[3,5-bis(trifluoromethyl)phenyl]-2-hydroxy-1-methylethyl}{[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl)methyl]carbamate (20.7 mg, 0.0698 mmol) was added by cannula in THF (1 mL). Next Ph₃P (18.3 mg, 0.0698 mmol) was added. The reaction was stirred at room temperature for 30 min, and then additional DEAD (11 μL, 0.0698 mmol), DPPA (15 μL, 0.0698 mmol), and Ph₃P (18.3 mg, 0.0698 mmol) were added. After an additional 30 min, the reaction was diluted with EtOAc (40 mL) and washed with water and brine (15 mL each). The organic layer was dried over Na₂SO₄, filtered, and concentrated. Purification of the residue by flash chromatography with 15% EtOAc/hexanes afforded *tert*-butyl{(1*S*,2*R*)-2-azido-2-[3,5-bis(trifluoromethyl)phenyl]-1-methylethyl}{[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl)methyl]carbamate. *R*_f = 0.60 (25% EtOAc/hexanes). LCMS = 619.3 (M+1-BOC)⁺.

Step E: (1*R*, 2*S*)-1-azido-1-[3,5-bis(trifluoromethyl)phenyl]-*N*-{[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl)methyl]propan-2-amine}.

To a solution of *tert*-butyl{(1*S*,2*R*)-2-azido-2-[3,5-bis(trifluoromethyl)phenyl]-1-methylethyl}{[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl)methyl]carbamate (21.7 mg, 0.030 mmol) in CH₂Cl₂ (2 mL) was added TFA (200 μL). The reaction was stirred at room temperature for 1 hour and

then diluted with CH₂Cl₂ (25 mL). The CH₂Cl₂ solution was washed with 1 N NaOH (15 mL) and the aqueous phase was re-extracted with CH₂Cl₂ (25 mL). The organic extracts were combined, washed with brine (20 mL), dried over Na₂SO₄, filtered, and concentrated. Purification of the residue by flash chromatography with 15% EtOAc/hexanes afforded (1*R*, 2*S*)-1-azido-1-[3,5-bis(trifluoromethyl)phenyl]-*N*-{[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)bi phenyl-2-yl]methyl}propan-2-amine. *R*_f = 0.45 (15% EtOAc/hexanes). LCMS = 619.2 (M+1)⁺.

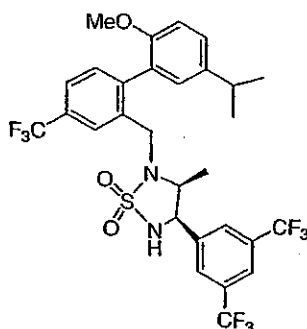
Step F: (1*R*, 2*S*)-1-[3,5-bis(trifluoromethyl)phenyl]-*N*²-{[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl}propane-1,2-diamine.

To a solution of (1*R*, 2*S*)-1-azido-1-[3,5-bis(trifluoromethyl)phenyl]-*N*-{[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)bi phenyl-2-yl]methyl}propan-2-amine (17.8 mg, 0.0288 mmol) in THF (3 mL) was added PtO₂ (12 mg, 0.053 mmol). The reaction was placed under hydrogen balloon atmosphere and stirred at room temperature for 3 h. The catalyst was removed by filtration and the filtrate was concentrated. The residue was put through a short plug of silica gel with 0-10% MeOH/CH₂Cl₂ to give (1*R*, 2*S*)-1-[3,5-bis(trifluoromethyl)phenyl]-*N*²-{[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl}propane-1,2-diamine. LCMS = 619.2 (M+1)⁺.

Step G: (4*R*, 5*S*)-4-[3,5-bis(trifluoromethyl)phenyl]-1-{[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl}-5-methylimidazolidin-2-one.

A solution of (1*R*, 2*S*)-1-[3,5-bis(trifluoromethyl)phenyl]-*N*²-{[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl}propane-1,2-diamine (8.0 mg, 0.0135 mmol) in CH₂Cl₂ (2 mL) was cooled to 0°C and DIPEA (14 μL, 0.081 mmol) was added followed by triphosgene (2 mg, 0.00657 mmol). The reaction was stirred at 0°C for 30 min and then diluted with EtOAc (30 mL). The reaction was washed with saturated NaHCO₃ (10 mL) and brine (10 mL). The organic layer was dried over Na₂SO₄, filtered, and concentrated. Purification of the residue by flash chromatography with 40% EtOAc/hexanes afforded (4*R*, 5*S*)-4-[3,5-bis(trifluoromethyl)phenyl]-1-{[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl}-5-methylimidazolidin-2-one. *R*_f = 0.24 (40% EtOAc/hexanes). LCMS = 619.2 (M+1)⁺. ¹H NMR (CD₂Cl₂, 600 MHz; atropisomers present) δ 6.91-7.84 (m, 9H), 3.84-4.94 (m, 4H), 3.64-3.80 (m, 4H), 2.88 (m, 1H), 1.18-1.26 (m, 6H), 0.27-0.42 (m, 3H).

EXAMPLE 75

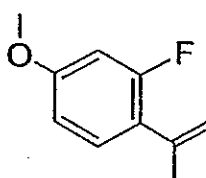


(3S,4R)-4-[3,5-bis(trifluoromethyl)phenyl]-2-[[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]-3-methyl-1,2,5-thiadiazolidine 1,1-dioxide.

- 5 A glass reaction tube was charged with (1R,2S)-1-[3,5-bis(trifluoromethyl)phenyl]-N²-[[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]propane-1,2-diamine (15.9 mg, 0.0269 mmol), sulfamide (4 mg, 0.0403 mmol), and pyridine (600 μ L). The tube was flushed with N₂, sealed, and heated at 120°C for 2 h. The reaction was then cooled to room temperature, diluted with EtOAc (40 mL) and washed with H₂O, 1N HCl, and brine (10 mL each). The organic layer was dried over Na₂SO₄,
10 filtered, and concentrated. Purification of the residue by flash chromatography with 25% EtOAc/hexanes afforded (3S,4R)-4-[3,5-bis(trifluoromethyl)phenyl]-2-[[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]-3-methyl-1,2,5-thiadiazolidine 1,1-dioxide. R_f = 0.27 (25% EtOAc/hexanes). LCMS = 655.2 (M+1)⁺. ¹H NMR (C₆D₆, 500 MHz; atropisomers present) δ 6.51-8.19 (m, 9H), 3.64-4.53 (m, 4H), 3.00-3.18 (m, 4H), 2.73 (m, 1H), 1.13-1.20 (m, 6H), -0.03-0.09 (m, 3H).

15

EXAMPLE 76



- 20 2-fluoro-1-isopropenyl-4-methoxybenzene

Step A: 2-(2-fluoro-4-methoxyphenyl)propan-2-ol

- To a solution of 2'-fluoro-4'-methoxyacetophenone (4.45 g, 26.5 mmol) in THF (50 mL) at 0°C, a solution of 2.4 M MeMgBr (11.6 mmol, 27.8 mmol) was added. The mixture was stirred at 0°C and then room temperature for 4 h. The reaction was quenched with saturated ammonium chloride solution. The
25 organic was extracted with ethyl acetate (3 x 50 mL). The combined ethyl acetate layers were washed with brine and dried over sodium sulfate. The resulting alcohol was obtained as an oil after flash column using EtOAc:hexane = 2:8 as the elute.

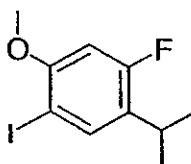
Step B: 2-fluoro-1-isopropenyl-4-methoxybenzene

To a solution of 2-(2-fluoro-4-methoxyphenyl)propan-2-ol from Step A (3.89 g, 21.14 mmol) in methylene chloride (50 ml) at 0°C, MsCl (1.95 ml, 25.4 mmol) and triethylamine (6.52 ml, 46.5 mmol) were added. The solution was stirred at 0°C and then room temperature for 2 h. The solution was diluted with methylene chloride (100 ml), washed with water, and dried over sodium sulfate. The title compound was obtained as an oil after flash column using EtOAc:hexane = 1:9 as the elute. ¹H NMR (CDCl₃, 500 MHz) δ 7.25 (t, *J* = 9.0 Hz, 1H), 6.68 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.63 (dd, *J* = 13, 2.5 Hz, 1H), 5.20 (d, *J* = 17.0 Hz, 2H), 3.82 (s, 3H), 2.18 (s, 3H).

Alternate route to make 2-fluoro-1-isopropenyl-4-methoxybenzene:

A solution of sodium bis(trimethylsilyl)-amide, 1.0M in tetrahydrofuran (714ml, 0.714m) was added to a suspension of methyltriphenylphosphonium bromide (255g, 0.714m) in THF (2.50L) cooled with an ice bath. The resultant yellow colored suspension was stirred for 30 minutes at ice bath temperature and then cooled to -78°C. A total of 2-fluoro-4-methoxyacetophenone (100g, 0.595m) in THF (200ml) was added dropwise and stirred at -78°C for 1.5 hours. Reaction mixture was allowed to warm to room temperature for one hour, quenched with acetic acid (~80ml) where color change was observed from yellow to off white and stirred for 30 minutes (pH~7)(slight exotherm noted). The mixture was concentrated to a slush, diluted with 7:2 hexane:ethyl acetate, and was allowed to sit overnight. Solids were removed by filtration and the filtrate was concentrated to yellow oil. The title compound was obtained after flash column using 9:1 hexane:ethyl as the eluant.

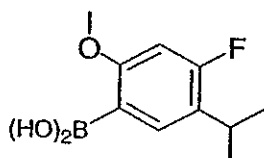
EXAMPLE 77

1-fluoro-4-iodo-2-isopropyl-5-methoxybenzene

A solution of the 2-fluoro-1-isopropenyl-4-methoxybenzene (Example 76, 1.96 g, 11.81 mmol) in MeOH (30 ml) was charged with hydrogen at 1 atm with catalytic amount of Pd/C. The mixture was stirred at room temperature for 1 h. The mixture was filtered through Celite. The filtrate was then added to a mixture of silver sulfate (3.68 g, 11.81 mmol) and Iodine (3.00 g, 11.81 mmol) in MeOH (10 ml). The mixture was stirred at room temperature for 3 h until the color of solution became light yellow. The mixture was filtered and the filtrate was concentrated. The title compound was obtained after flash

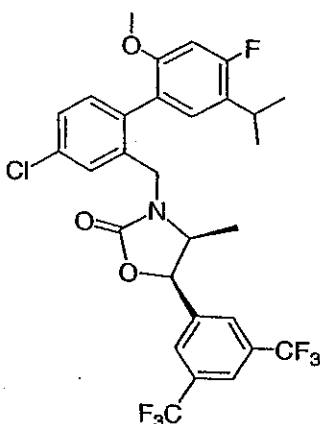
column using EtOAc:hexane 5:95 as the elute. ^1H NMR (CDCl_3 , 500 MHz) δ 7.61 (d, $J = 8.0$ Hz, 1H), 6.56 (d, $J = 12.5$ Hz, 1H), 3.90 (s, 3H), 3.18 (m, 1H), 1.28 (m, 6H).

EXAMPLE 78

(4-fluoro-5-isopropyl-2-methoxyphenyl)boronic acid

To a solution of 1-fluoro-4-iodo-2-isopropyl-5-methoxybenzene (Example 77, 2.61 g, 8.88 mmol) in THF at -78°C , $n\text{-BuLi}$ (4.26 ml, 10.65 mmol, 2.5 M) was added dropwise. The solution was stirred at -78°C for 30 min. Trimethyl borate (2.98 ml, 26.6 mmol) was added. The solution was then stirred at -78°C for 3 h. The reaction was quenched at -78°C with saturated ammonium chloride and the mixture was warmed to room temperature. The organic was extracted with ethyl acetate (3 x 50 ml). The combined ethyl acetate layers were washed with brine and dried over sodium sulfate. The title compound was obtained as a solid pure enough for next step. Further purification with silica gel caused decomposition of product. ^1H NMR (CDCl_3 , 500 MHz) δ 7.74 (d, $J = 10.0$ Hz, 1H), 6.62 (d, $J = 12.5$ Hz, 1H), 5.65 (br s, 2H), 3.92 (s, 3H), 3.20 (m, 1H), 1.22 (m, 6H).

EXAMPLE 79

(4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[(4-chloro-4'-fluoro-5'-isopropyl-2'-methoxybiphenyl-2-yl)methyl]-4-methyl-1,3-oxazolidin-2-one

Step A: 1-bromo-2-(bromomethyl)-4-chlorobenzene

A mixture of 2-bromo-5-chloro-toluene (2.00 g, 9.75 mmol), NBS (2.08 g, 11.7 mmol) and catalytic amount of AIBN in carbon tetrachloride (50 ml) was stirred under refluxing conditions for 4 h. TLC (EtOAc:hexane = 5:95) showed no starting material. The mixture was filtered and the filtrate was concentrated. The title compound was obtained as a white solid after flash column using EtOAc:hexane = 5:95 as the elute. ¹H NMR (CDCl₃, 500 MHz) δ 7.53 (d, *J* = 9.0 Hz, 1H), 7.47 (d, *J* = 2.5 Hz, 1H), 7.18 (dd, *J* = 8.5, 2.5 Hz, 1H), 4.60 (s, 2H).

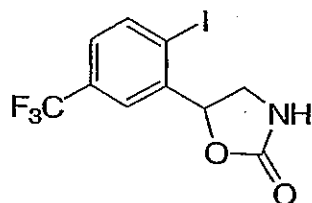
Step B. (4*S*,5*R*)-5-[3,5-bis(trifluoromethyl)phenyl]-3-(2-bromo-5-chlorobenzyl)-4-methyl-1,3-oxazolidin-2-one

To a solution of (4*S*,5*R*)-5-[3,5-bis(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one (0.050 g, 0.16 mmol) in THF (1 ml) at 0°C, NaH (7.6 mg, 0.19 mmol, 60%) was added. The mixture was stirred at 0°C for 30 min. The title compound from Step A (0.059 g, 0.21 mmol) was added. The whole mixture was stirred at 0°C for 1 h and warmed to room temperature for 4 h. The reaction was quenched with saturated ammonium chloride. The organic was extracted with ethyl acetate (3 x 15 ml). The combined ethyl acetate layers were washed with brine and dried over sodium sulfate. The title compound was obtained after preparative TLC purification using EtOAc:hexane = 2:8 as the elute. ¹H NMR (CDCl₃, 500 MHz) δ 7.92 (s, 1H), 7.82 (s, 2H), 7.55 (d, *J* = 8.5 Hz, 1H), 7.43 (d, *J* = 2.5 Hz, 1H), 7.23 (dd, *J* = 8.5, 2.5 Hz, 1H), 5.77 (d, *J* = 8.0 Hz, 1H), 4.86 (d, *J* = 16.0 Hz, 1H), 4.36 (d, *J* = 16.0 Hz, 1H), 4.11 (m, 1H), 0.82 (d, *J* = 6.5 Hz, 3H).

Step C. (4*S*,5*R*)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[(4-chloro-4'-fluoro-5'-isopropyl-2'-methoxybiphenyl-2-yl)methyl]-4-methyl-1,3-oxazolidin-2-one

A mixture of (4*S*,5*R*)-5-[3,5-bis(trifluoromethyl)phenyl]-3-(2-bromo-5-chlorobenzyl)-4-methyl-1,3-oxazolidin-2-one (44 mg, 0.085 mmol), (4-fluoro-5-isopropyl-2-methoxyphenyl)boronic acid (Example 78, 23 mg, 0.11 mmol), potassium carbonate (25 mg, 0.18 mmol) and catalytic amount of PdOAc in a 4:1 mixture of acetone/water was heated to reflux for 1 h. Acetone was removed and water was added. The organic was extracted with methylene chloride (3 x 15 ml). The combined methylene chloride layers were washed with brine and dried over sodium sulfate. The title compound was obtained as a solid after preparative reverse phase HPLC. ¹H NMR (CDCl₃, 500 MHz) a 1:1 mixture of rotamer δ 7.90 (s, 1H), 7.73 (s, 2H), 7.49 (m, 1H), 7.40 (m, 1H), 7.20 (m, 1H), 7.00 (m, 1H), 6.68 (dd, *J* = 12.0, 3.0 Hz, 1H), 5.63 (d, *J* = 8.0 Hz, ½ H), 5.44 (d, *J* = 8.0 Hz, ½ H), 4.85 (d, *J* = 10.0 Hz, ½ H), 4.82 (d, *J* = 10.0 Hz, ½ H), 4.03 (d, *J* = 16.0 Hz, ½ H), 3.84 (m, 1½ H), 3.80 (s, 3H), 3.20 (m, 1H), 1.20 (m, 6H), 0.56 (d, *J* = 6.5 Hz, 3/2 H), 0.38 (d, *J* = 6.5 Hz, 3/2 H). LC-MS (*M*+1): 604.3, 4.61 min.

EXAMPLE 80



5-[2-iodo-5-(trifluoromethyl)phenyl]-1,3-oxazolidin-2-one

Step A: 2-iodo-5-(trifluoromethyl)benzaldehyde

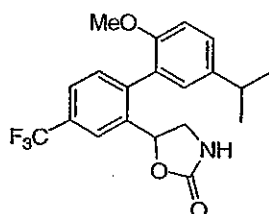
To a solution of 2-iodo-5-(trifluoromethyl)benzonitrile (EXAMPLE 2, 42 g) in CH_2Cl_2 (300 mL) at -78°C was added a solution of DIBAL in CH_2Cl_2 (175 mL, 1M) over 30 minutes. A precipitate formed. The reaction was warmed to 0°C . An additional 25 mL of the DIBAL solution was added dropwise over 30 minutes. The reaction was poured into 200 mL 2N aqueous HCl, diluted with ether and stirred 1 hour. TLC analysis indicates imine still present and an additional 100 mL 2N aqueous was added and the reaction stirred overnight. Imine was still present by TLC analysis and 200 mL 2N aqueous HCl was added and the mixture stirred 2 hours. The layers were separated and the aqueous layer back extracted with ether. The ether extracts were combined, washed with brine, dried over anhydrous MgSO_4 , filtered and concentrated. The product was purified by silica gel chromatography eluting with 95:5 hexanes/EtOAc to give 2-Iodo-5-(trifluoromethyl)benzaldehyde as a white solid. ^1H NMR (500 MHz, CDCl_3): δ 10.00 (s, 1H), 8.12 (s, 1H), 8.11 (d, $J=8$ Hz, 1H), 7.53 (dd, $J=2$ Hz, 8 Hz, 1H).

Step B: 5-[2-iodo-5-(trifluoromethyl)phenyl]-1,3-oxazolidin-2-one

To a 0°C solution of 0.2 g of 2-iodo-5-(trifluoromethyl)benzaldehyde in 3 mL of EtOH was added 0.13 mL of nitromethane, then 0.28 mL of a 2.5 N solution of NaOH. The mixture was stirred at 0°C for 3 h, and then neutralized by addition of 2.1 mL of a 0.33 N aqueous solution of AcOH. The mixture was partitioned between 10 mL of water and 10 mL of EtOAc. The aqueous phase was extracted with 2 x 5 mL of EtOAc. The combined organics were washed with 10 mL of brine, dried over Na_2SO_4 , and concentrated. The residue was dissolved in 4 mL of MeOH and 0.5 mL of 88% aqueous formic acid was added. Approximately 200 mg of a Raney nickel slurry was added and the mixture was flushed with H_2 , and stirred under an H_2 balloon for 4 h. The mixture was filtered through a pad of Celite, washing with MeOH, and the filtrate was concentrated. The residue was partitioned between 10 mL of 10% aqueous NH_4OH and 20 mL of EtOAc. The aqueous phase was extracted with 2 x 10 mL of EtOAc. The combined organics were washed with 10 mL of brine, dried over Na_2SO_4 , and concentrated. The residue was dissolved in 2 mL of CH_2Cl_2 . To the solution was added 0.114 mL of diisopropylethylamine, then 0.065 g of triphosgene. The mixture was stirred at 0°C for 30 min, then diluted with 10 mL of EtOAc and 10 mL of saturated NaHCO_3 . The aqueous phase was extracted with 2 x 10 mL of EtOAc. The combined organics were washed with 10 mL of brine, dried over Na_2SO_4 , and concentrated. The residue was purified by flash chromatography on a Biotage Horizon, 25S column, eluting with 1 CV of 4% EtOAc in hexanes, followed by a linear gradient of EtOAc in hexanes from 4 to

100% over 10 CV to provide the title compound. Mass spectrum (ESI) 350.0 (M+1). ^1H NMR (500 MHz, CDCl_3): δ 8.00 (d, $J=8$ Hz, 1H), 7.74 (br s, 1H), 7.33 (br d, $J=8$ Hz, 1H), 5.80 (dd, $J=7$ Hz, 9 Hz, 1H), 5.05-5.50 (br, 1H), 4.28 (t, $J=9$ Hz, 1.5H), 3.36 (dd, $J=7$ Hz, 9 Hz, 1H).

EXAMPLE 81

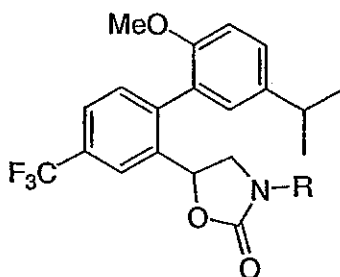


5-[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]-1,3-oxazolidin-2-one

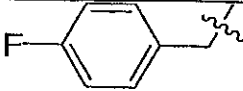
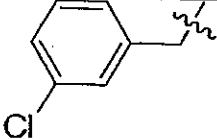
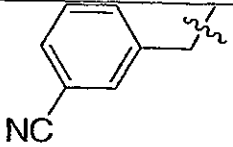
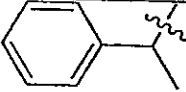
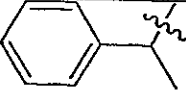
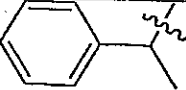
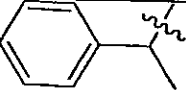
To a solution of 65 mg of 5-[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]-1,3-oxazolidin-2-one, 45 mg of (5-isopropyl-2-methoxyphenyl)boronic acid, and 66 mg of potassium carbonate in 6 mL of acetone and 1.5 mL of water was added ca. 5 mg of palladium acetate. The mixture was heated to reflux and stirred at this temperature for 1.5 h. Acetone was removed by rotary evaporation and the residue was diluted with 10 mL of EtOAc and 10 mL of water. The aqueous phase was extracted with 10 mL of EtOAc. The combined organics were washed with 10 mL of brine, dried over Na_2SO_4 , and concentrated. The residue was purified by flash chromatography on a Biotage Horizon, 25S column, eluting with 1 CV of 10% EtOAc in hexanes, followed by a linear gradient of EtOAc in hexanes from 10 to 100% over 10 CV to provide the title compound. Spectral data are provided in EXAMPLE 49.

Following the procedures outlined in EXAMPLE 52 the compounds listed in Table 2 were prepared:

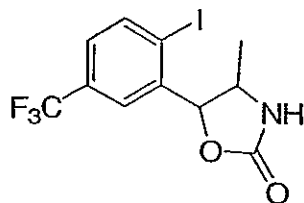
Table 3



EXAMPLE	R	LC/MS Data (M+1)
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82	 ent A	488.1
83	 ent A	504.1
84	 ent A	495.1
85	 ent A	476.2
86	 ent A, diast A	484.2
87	 ent A, diast B	484.2
88	 ent B, diast A	484.2
89	 ent B, diast B	484.2

EXAMPLE 90



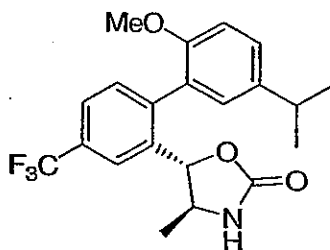
5-[2-iodo-5-(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one

Following the procedure described in EXAMPLE 80 and using nitroethane, 0.2 g of 2-iodo-5-(trifluoromethyl)benzaldehyde provided 0.102 g of the desired product, which was separated into the cis and trans diastereomers by flash chromatography Biotage Horizon, 25S column, eluting with 1 CV of 10% EtOAc in hexanes, followed by a linear gradient of EtOAc in hexanes from 10 to 100% over 10 CV.

trans-5-[2-iodo-5-(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one: Mass spectrum (ESI) 372.1 (M+1). ¹H NMR (500 MHz, CDCl₃): δ 8.02 (d, J=8 Hz, 1H), 7.61 (d, J=1.5 Hz, 1H), 7.32 (dd, J=2 Hz, 8 Hz, 1H), 6.16 (s, 1H), 5.39 (d, J=4 Hz, 1H), 3.76 (dq, J= 6 Hz, 4.5 Hz, 1H), 1.62 (d, J=6 Hz, 3H).

cis-5-[2-iodo-5-(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one: Mass spectrum (ESI) 372.1 (M+1). ¹H NMR (500 MHz, CDCl₃): δ 7.98 (d, J=8 Hz, 1H), 7.60 (br s, 1H), 7.33 (dd, J=1.5 Hz, 8 Hz, 1H), 6.25 (s, 1H), 5.85 (d, J=8 Hz, 1H), 3.76 (dq, J= 8 Hz, 7 Hz, 1H), 0.81 (d, J=7 Hz, 3H).

EXAMPLE 91

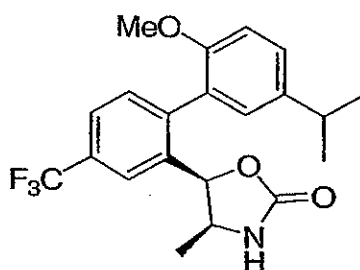


trans-5-[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]-4-methyl-1,3-oxazolidin-2-one (racemic)

To a solution of 0.036 g of trans-5-[2-iodo-5-(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one, 0.024 g of (5-isopropyl-2-methoxyphenyl)boronic acid, and 0.04 g of potassium carbonate in 2 mL of acetone and 0.5 mL of water was added ca. 2 mg of palladium acetate. The mixture was heated to reflux and stirred at this temperature for 1.5 h. Acetone was removed by rotary evaporation and the residue was diluted with 10 mL of EtOAc and 10 mL of water. The aqueous phase was extracted with 10 mL of EtOAc. The combined organics were washed with 10 mL of brine, dried over Na₂SO₄, and

concentrated. The residue was purified by flash chromatography on a Biotage Horizon, 25S column, eluting with 1 CV of 10% EtOAc in hexanes, followed by a linear gradient of EtOAc in hexanes from 10 to 100% over 10 CV to provide the title compound. Mass spectrum (ESI) 394.2 (M+1). ¹H NMR signals are doubled because of atropoisomerism. ¹H NMR (500 MHz, CDCl₃): δ 7.80, 7.78 (s, 1H), 7.64, 7.63 (d, J=8 Hz, 1H), 7.35 (d, J=7.5 Hz, 1H), 7.27, 7.26 (d, J=8 Hz 1H), 7.00, 6.95 (d, J=2.5 Hz, 1H), 6.93, 6.92 (d, J=8 Hz, 1H), 5.87, 5.81 (s, 1H), 5.16, 5.10 (d, J=5 Hz, 1H), 3.70-3.78 (m, 3.5H), 3.49 (m, 0.5H), 2.89 (m, 1H), 1.24 (m, 6H), 0.90, 0.70 (d, J=6.5 Hz, 3H).

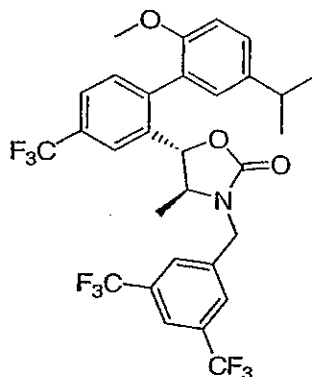
EXAMPLE 92



cis-5-[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]-4-methyl-1,3-oxazolidin-2-one (racemic)

Following the procedure described in EXAMPLE 91, 0.046 g of cis-5-[2-iodo-5-(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one provided the desired product. Mass spectrum (ESI) 394.2 (M+1). ¹H NMR signals are doubled because of atropoisomerism. ¹H NMR (500 MHz, CDCl₃): δ 7.89, 7.88 (s, 1H), 7.65, 7.64 (d, J=7.5 Hz, 1H), 7.34, 7.32 (d, J=8 Hz, 1H), 7.26 (d, J=8.5 Hz, 1H), 6.98, 6.86 (d, J=2.5 Hz, 1H), 6.91, 6.89 (d, J=8 Hz, 1H), 5.83, 5.75 (s, 1H), 5.69, 5.61 (d, J=8 Hz, 1H), 3.75 (s, 1.8H), 3.58-3.70 (m, 2H), 3.32 (m, 0.6H), 2.88 (m, 1H), 1.23 (m, 6H), 0.89, 0.71 (d, J=6.5 Hz, 3H).

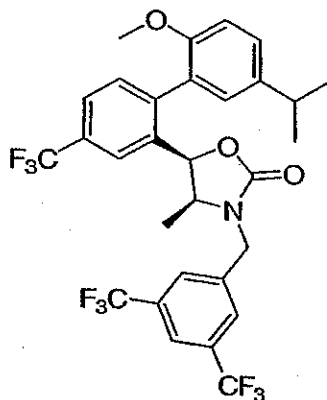
EXAMPLE 93



trans-3-[3,5-bis(trifluoromethyl)benzyl]-5-[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]-4-methyl-1,3-oxazolidin-2-one (racemic)

To a 0°C solution of 30 mg of trans-5-[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]-4-methyl-1,3-oxazolidin-2-one in 1 mL of DMF was added 8 mg of sodium hydride. The mixture was stirred 10 min at room temperature, and then 32 mg of 3,5-bis(trifluoromethyl)benzyl bromide was added. The mixture was stirred overnight at room temperature, then diluted with 10 mL of EtOAc and 10 mL of water. The phases were separated and the aqueous phase was extracted with 5 mL of EtOAc. The combined organics were washed with 5 mL of brine, dried (Na₂SO₄), and concentrated. The residue was purified by flash chromatography on a Biotage Horizon, 25S column, eluting with 1 CV of 4% EtOAc in hexanes, followed by a linear gradient of EtOAc in hexanes from 4 to 100% over 10 CV to provide the title compound. Mass spectrum (ESI) 620.2 (M+1). ¹H NMR signals are doubled because of atropoisomerism. ¹H NMR (500 MHz, CDCl₃): δ 7.53-7.80 (m, 5H), 7.33 (d, J=8 Hz, 1H), 7.21-7.29 (m, 1H), 7.00, 6.76 (d, J=2.5 Hz, 1H), 6.91, 6.86 (d, J= 8.5 Hz, 0.4H), 5.15, 5.10 (d, J=4.5 Hz, 1H), 4.80, 4.74 (d, J=16 Hz, 1H), 4.25, 4.21 (d, 16 Hz, 1H), 3.76 (s, 2H), 3.49 (s, 1H), 3.43 (m, 0.4H), 3.18 (m, 0.5H), 2.77-2.98 (m, 1H), 1.24 (m, 3H), 1.16 (m, 3H), 0.78, 0.61 (d, J=6.5 Hz, 3H).

EXAMPLE 94

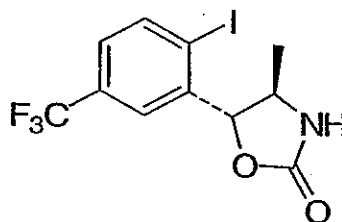


cis-3-[3,5-bis(trifluoromethyl)benzyl]-5-[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]-4-methyl-1,3-oxazolidin-2-one (racemic)

Following the procedure described in EXAMPLE 93, 40 mg of cis-5-[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]-4-methyl-1,3-oxazolidin-2-one and 42 mg of 3,5-

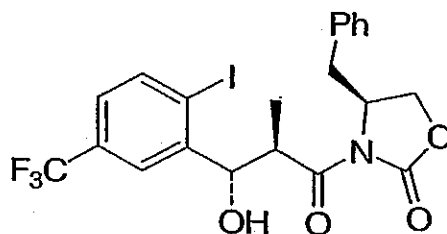
bis(trifluoromethyl)benzyl bromide gave the title compound. Mass spectrum (ESI) 620.2 (M+1). ¹H NMR signals are doubled because of atropoisomerism. ¹H NMR (500 MHz, CDCl₃): δ 7.82-7.94 (m, 2H), 7.62-7.74 (m, 3H), 7.39, 7.37 (d, J=8 Hz, 1H), 7.25, 7.17 (br d, J=8.5 Hz, 1H), 7.00, 6.78 (s, 1H), 6.87, 6.84 (d, J=8.5 Hz, 1H), 5.59, 5.56 (d, J=4.5 Hz, 1H), 4.96 (d, J=16 Hz, 1H), 4.22, 4.11 (d, J=16 Hz, 1H), 3.76 (s, 2H), 3.58 (s, 1H), 3.40 (m, 0.4H), 2.85-3.00 (m, 1H), 2.78 (m, 0.5H), 1.23 (d, J=7 Hz, 3H), 1.06 (m, 3H), 0.88, 0.69 (d, J=6.5 Hz, 3H).

EXAMPLE 95



(4R,5R)-5-[2-iodo-5-(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one

Step A: (4S)-4-benzyl-3-[(2R,3S)-3-hydroxy-3-[2-iodo-5-(trifluoromethyl)phenyl]-2-methylpropanoyl]-1,3-oxazolidin-2-one



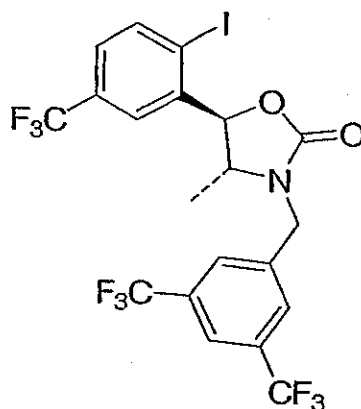
A mixture of 1.8 g of 5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-carbaldehyde (EXAMPLE 80, Step A), 1.16 g of (4S)-4-benzyl-3-propionyl-1,3-oxazolidin-2-one, 0.048 g of magnesium chloride, 1.40 mL of triethylamine, and 0.91 mL of chlorotrimethylsilane in 10 mL of EtOAc was stirred at r.t. for 24 h, then filtered through a 10 x 10 cm plug of silica gel, eluting with 400 mL of Et₂O. The filtrate was concentrated, and 10 mL of MeOH was added along with 2 drops of trifluoroacetic acid. This solution was stirred at r.t. for 30 min and concentrated to a pale yellow oil. The residue was purified by flash

chromatography on a Biotage Horizon, 65i column, eluting with 15 CV of 10% acetone in hexanes to provide 1.42 g (53%) of the title compound. Mass spectrum (ESI) 516.2 (M-OH). ¹H NMR (500 MHz, CDCl₃): δ 8.00 (d, J=8.5 Hz, 1H), 7.76 (d, J=2 Hz, 1H), 7.22-7.32 (m, 4H), 7.07 (br d, J=6.5 Hz, 2H), 5.18 (dd, J=6.5 Hz, 7.5 Hz, 1H), 4.67 (m, 1H), 4.46 (dq, J= 6.5 Hz, 7.5 Hz, 1H), 4.17 (t, J=9 Hz, 1H), 4.11 (dd, J=3 Hz, 9 Hz, 1H), 3.97 (d, J=8 Hz, 1H), 3.19 (dd, J=7 Hz, 13.5 Hz, 1H), 2.57 (dd, J=9.5 Hz, 13.5 Hz, 1H), 1.34 (d, J=7.5 Hz, 3H).

Step B: (4*R*,5*R*)-5-[2-iodo-5-(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one

- To a 0°C solution of 0.65 g of (4*S*)-4-benzyl-3-[(2*R*,3*S*)-3-hydroxy-3-[2-iodo-5-(trifluoromethyl)phenyl]-2-methylpropanoyl]-1,3-oxazolidin-2-one in 6 mL of 3:1 tetrahydrofuran-water was added 0.102 g of lithium hydroxide in 1.5 mL of water, then 0.554 mL of a 30% aqueous solution of hydrogen peroxide. The solution was stirred 1 h at 0°C, at which point LC/MS analysis showed no starting material. A 1.5 M solution of sodium sulfite (3.7 mL) was added to the cold solution, which was then poured into a separatory funnel and extracted with 2 x 10 mL of CH₂Cl₂. The combined CH₂Cl₂ extracts were back-extracted with 20 mL of 3:1 water-saturated aqueous NaHCO₃. The combined aqueous layers were acidified (pH < 1) with 6 N HCl and extracted with 4 x 10 mL of EtOAc. The combined EtOAc extracts were washed with 10 mL of brine, dried over Na₂SO₄, and concentrated. The residue was dissolved in 10 mL of toluene. Diphenylphosphoryl azide (0.315 mL) and 0.24 mL of triethylamine were added and the mixture was stirred overnight at 100°C, then cooled and concentrated. The residue was purified by flash chromatography on a Biotage Horizon, 40S column, eluting with 1 CV of 5% EtOAc in hexanes, followed by a linear gradient of EtOAc in hexanes from 5 to 100% over 10 CV to provide 0.302 g (67%) of the title compound. Mass spectrum (ESI) 372.1 (M+1). ¹H NMR (500 MHz, CDCl₃): δ 8.02 (d, J=8 Hz, 1H), 7.61 (d, J=1.5 Hz, 1H), 7.32 (dd, J=2 Hz, 8 Hz, 1H), 6.16 (s, 1H), 5.39 (d, J=4 Hz, 1H), 3.76 (dq, J= 6 Hz, 4.5 Hz, 1H), 1.62 (d, J=6 Hz, 3H). Analytical HPLC on Chiralpak AD 4.6 x 250 mm, eluting with 4% ethanol in heptane at 0.75 mL/min (*t*_R=21.56 min for *R,R*; *t*_R=18.00 min for *S,S*) showed 98% e.e.

EXAMPLE 96



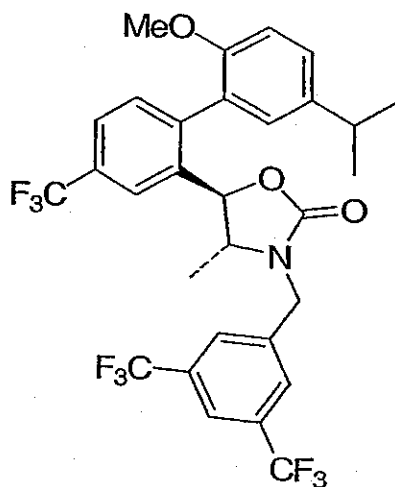
(4R,5R)-3-[3,5-bis(trifluoromethyl)benzyl]-5-[2-iodo-5-(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one

5

To a 0°C solution of 95 mg of (4R,5R)-5-[2-iodo-5-(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one in 1 mL of DMF was added 20 mg of sodium hydride. The mixture was stirred 10 min at 0°C; then 94 mg of 3,5-bis(trifluoromethyl)benzyl bromide was added. The mixture was stirred 10 min at 0°C, then diluted with 10 mL of EtOAc and 10 mL of water. The phases were separated and the aqueous phase was
 10 extracted with 10 mL of EtOAc. The combined organic phases were washed with 10 mL of brine, dried over Na₂SO₄, and concentrated. The residue was purified by flash chromatography on a Biotage Horizon, 25M column, eluting with 1 CV of 2% EtOAc in hexanes, followed by a linear gradient of EtOAc in hexanes from 2 to 100% over 10 CV to provide 0.121 g (79%) of the title compound. Mass spectrum (ESI) 598.1 (M+1). ¹H NMR (500 MHz, CDCl₃): δ 8.00 (d, J=8.5 Hz, 1H), 7.77 (s, 1H), 7.58 (br s, 3H), 7.34 (dd, J=1.5 Hz, 8 Hz, 1H), 5.36 (d, J=4 Hz, 1H), 4.89 (d, J=16 Hz, 1H), 4.31 (d, J=16 Hz, 1H), 4.48 (dq, J= 6 Hz, 4 Hz, 1H), 1.55 (d, J=6.5 Hz, 3H).

15

EXAMPLE 97



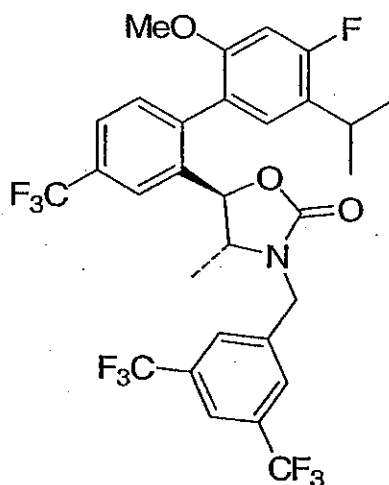
20

(4*R*,5*R*)-3-[3,5-bis(trifluoromethyl)benzyl]-5-[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]-4-methyl-1,3-oxazolidin-2-one

Following the procedure described in EXAMPLE 81, 41 mg of (4*R*,5*R*)-3-[3,5-

bis(trifluoromethyl)benzyl]-5-[2-iodo-5-(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one and 17 mg of (5-isopropyl-2-methoxyphenyl)boronic acid gave 39 mg of the title compound (95%). Mass spectrum (ESI) 620.4 (M+1). ¹H NMR signals are doubled because of atropoisomerism. ¹H NMR (500 MHz, CDCl₃): δ 7.53-7.80 (m, 5H), 7.33 (d, J=8 Hz, 1H), 7.21-7.29 (m, 1H), 7.00, 6.76 (d, J=2.5 Hz, 1H), 6.91, 6.86 (d, J=8.5 Hz, 0.4H), 5.15, 5.10 (d, J=4.5 Hz, 1H), 4.80, 4.74 (d, J=16 Hz, 1H), 4.25, 4.21 (d, 16 Hz, 1H), 3.76 (s, 2H), 3.49 (s, 1H), 3.43 (m, 0.4H), 3.18 (m, 0.5H), 2.77-2.98 (m, 1H), 1.24 (m, 3H), 1.16 (m, 3H), 0.78, 0.61 (d, J=6.5 Hz, 3 Hz).

EXAMPLE 98

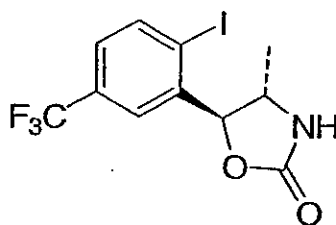


(4*R*,5*R*)-3-[3,5-bis(trifluoromethyl)benzyl]-5-[4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]-4-methyl-1,3-oxazolidin-2-one

Following the procedure described in EXAMPLE 81, 38.5 mg of (4*R*,5*R*)-3-[3,5-

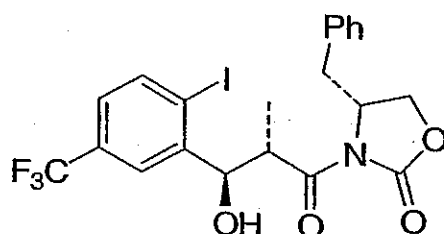
bis(trifluoromethyl)benzyl]-5-[2-iodo-5-(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one and 18 mg of (4-fluoro-5-isopropyl-2-methoxyphenyl)boronic acid (EXAMPLE 78) gave 27 mg of the title compound (66%). Mass spectrum (ESI) 638.3 (M+1). ¹H NMR signals are doubled because of atropoisomerism. ¹H NMR (500 MHz, CDCl₃): δ 7.55-7.80 (m, 5H), 7.29 (d, J=8 Hz, 1H), 7.00, 6.77 (d, J=8.5 Hz, 1H), 6.68, 6.63 (d, J~12 Hz, 1H), 5.08, 5.04 (d, J~5 Hz, 1H), 4.81, 4.75 (d, J=16 Hz, 1H), 4.26, 4.23 (d, 15.5 Hz, 1H), 3.75 (s, 2H), 3.50 (s, 1H), 3.43 (m, 0.5H), 3.12-3.24 (m, 1.5H), 1.24, 1.22 (d, J~5 Hz, 3H), 1.17, 1.06 (d, J=7 Hz, 3H), 0.84, 0.70 (d, J=6 Hz, 3H).

EXAMPLE 99



(4S,5S)-5-[2-iodo-5-(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one

- 5 Step A: (4R)-4-benzyl-3-[(2S,3R)-3-hydroxy-3-[2-iodo-5-(trifluoromethyl)phenyl]-2-methylpropanoyl]-1,3-oxazolidin-2-one

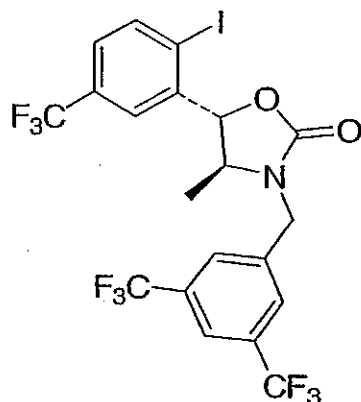


- 10 Following the procedure described in EXAMPLE 95, Step A, 0.72 g of 5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-carbaldehyde (EXAMPLE 80, Step A), 0.466 g of (4R)-4-benzyl-3-propionyl-1,3-oxazolidin-2-one, 0.02 g of magnesium chloride, 0.56 mL of triethylamine, and 0.38 mL of chlorotrimethylsilane provided 0.554 g (52%) of the title compound. Mass spectrum (ESI) 516.2 (M-OH). ¹H NMR (500 MHz, CDCl₃): δ 8.00 (d, J=8.5 Hz, 1H), 7.76 (d, J=2 Hz, 1H), 7.22-7.32 (m, 4H),
15 7.07 (br d, J=6.5 Hz, 2H), 5.18 (dd, J=6.5 Hz, 7.5 Hz, 1H), 4.67 (m, 1H), 4.46 (dq, J= 6.5 Hz, 7.5 Hz, 1H), 4.17 (t, J=9 Hz, 1H), 4.11 (dd, J=3 Hz, 9 Hz, 1H), 3.97 (d, J=8 Hz, 1H), 3.19 (dd, J=7 Hz, 13.5 Hz, 1H), 2.57 (dd, J=9.5 Hz, 13.5 Hz, 1H), 1.34 (d, J=7.5 Hz, 3H).

Step B: (4S,5S)-5-[2-iodo-5-(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one

- 20 Following the procedure described in EXAMPLE 95, Step B, 0.214 g of (4R)-4-benzyl-3-[(2S,3R)-3-hydroxy-3-[2-iodo-5-(trifluoromethyl)phenyl]-2-methylpropanoyl]-1,3-oxazolidin-2-one, 0.034 g of lithium hydroxide, 0.16 mL of a 30% aqueous solution of hydrogen peroxide, 0.1 mL of diphenylphosphoryl azide, and 0.072 mL of triethylamine provide 0.118 g (79%) of the title compound.
25 Mass spectrum (ESI) 372.1 (M+1). ¹H NMR (500 MHz, CDCl₃): δ 8.02 (d, J=8 Hz, 1H), 7.61 (d, J=1.5 Hz, 1H), 7.32 (dd, J=2 Hz, 8 Hz, 1H), 6.16 (s, 1H), 5.39 (d, J=4 Hz, 1H), 3.76 (dq, J= 6 Hz, 4.5 Hz, 1H), 1.62 (d, J=6 Hz, 3H). Analytical HPLC on Chiralpak AD 4.6 x 250 mm, eluting with 4% ethanol in heptane at 0.75 mL/min (*t*_R=21.56 min for *R,R*; *t*_R=18.00 min for *S,S*) showed 99% e.e.

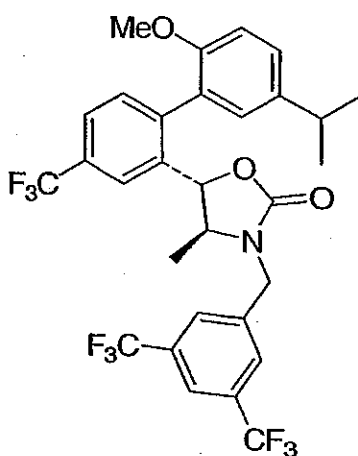
EXAMPLE 100



(4S,5S)-3-[3,5-bis(trifluoromethyl)benzyl]-5-[2-iodo-5-(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one

Following the procedure described in EXAMPLE 96, 0.108 g of (4S,5S)-5-[2-iodo-5-(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one, 23 mg of sodium hydride, and 107 mg of 3,5-bis(trifluoromethyl)benzyl bromide provided 0.151 g (87%) of the title compound. Mass spectrum (ESI) 598.1 (M+1). ¹H NMR (500 MHz, CDCl₃): δ 8.00 (d, J=8.5 Hz, 1H), 7.77 (s, 1H), 7.58 (br s, 3H), 7.34 (dd, J=1.5 Hz, 8 Hz, 1H), 5.36 (d, J=4 Hz, 1H), 4.89 (d, J=16 Hz, 1H), 4.31 (d, J=16 Hz, 1H), 4.48 (dq, J=6 Hz, 4 Hz, 1H), 1.55 (d, J=6.5 Hz, 3H).

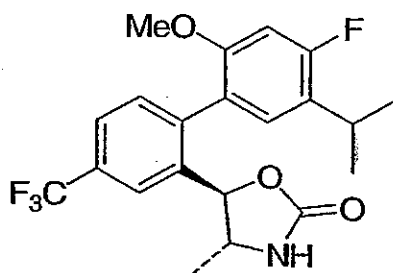
EXAMPLE 101



(4S,5S)-3-[3,5-bis(trifluoromethyl)benzyl]-5-[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]-4-methyl-1,3-oxazolidin-2-one

Following the procedure described in EXAMPLE 81, 40 mg of (4*S*,5*S*)-3-[3,5-bis(trifluoromethyl)benzyl]-5-[2-iodo-5-(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one and 17 mg of (5-isopropyl-2-methoxyphenyl)boronic acid gave 39 mg of the title compound (95%). Mass spectrum (ESI) 620.4 (M+1). ¹H NMR signals are doubled because of atropoisomerism. ¹H NMR (500 MHz, CDCl₃): δ 7.53-7.80 (m, 5H), 7.33 (d, J=8 Hz, 1H), 7.21-7.29 (m, 1H), 7.00, 6.76 (d, J=2.5 Hz, 1H), 6.91, 6.86 (d, J= 8.5 Hz, 0.4H), 5.15, 5.10 (d, J=4.5 Hz, 1H), 4.80, 4.74 (d, J=16 Hz, 1H), 4.25, 4.21 (d, 16 Hz, 1H), 3.76 (s, 2H), 3.49 (s, 1H), 3.43 (m, 0.4H), 3.18 (m, 0.5H), 2.77-2.98 (m, 1H), 1.24 (m, 3H), 1.16 (m, 3H), 0.78, 0.61 (d, J=6.5 Hz, 3 Hz).

EXAMPLE 102

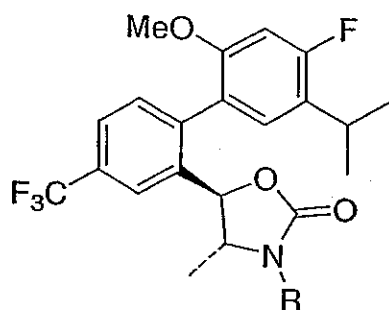


15 (4*R*,5*R*)-5-[4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]-4-methyl-1,3-oxazolidin-2-one

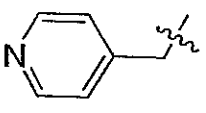
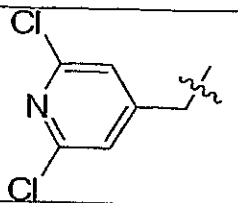
Following the procedure described in EXAMPLE 81, 240 mg of (4*R*,5*R*)-5-[2-iodo-5-(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one and 171 mg of (4-fluoro-5-isopropyl-2-methoxyphenyl)boronic acid (EXAMPLE 78) gave 241 mg of the title compound (91%). Mass spectrum (ESI) 412.3 (M+1). ¹H NMR signals are doubled because of atropoisomerism. ¹H NMR (500 MHz, CDCl₃): δ 7.79, 7.77 (s, 1H), 7.64, 7.62 (dd, J~2.5 Hz, 8 Hz, 1H), 7.32, 7.31 (d, J~8 Hz, 1H), 7.00, 6.95 (d, J=8.5 Hz, 1H), 6.70, 6.67 (d, J= 12 Hz, 1H), 6.47, 6.43 (s, 1H), 5.08, 5.04 (d, J=5 Hz, 0.1H), 3.68-3.80 (m, 3.5H), 3.53 (m, 0.5H), 3.21 (m, 1H), 1.19-1.30 (m, 6H), 0.95, 0.77 (d, J=6 Hz, 3H).

25 Following the procedures outlined in EXAMPLE 96 the compounds listed in Table 4 were prepared from (4*R*,5*R*)-5-[4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]-4-methyl-1,3-oxazolidin-2-one:

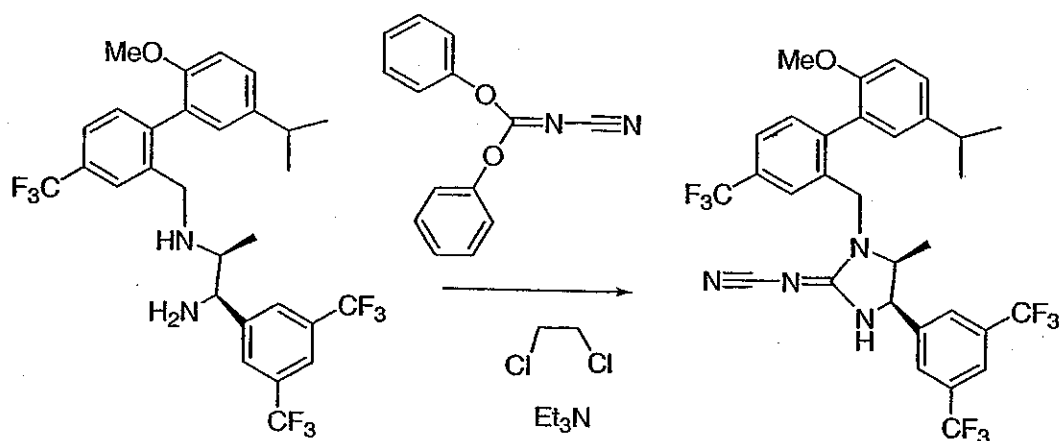
Table 4



EXAMPLE	R	LC/MS Data (M+1)
103		520.3
104		520.3
105		520.3
106		538.4
107	 diastereomer A	516.4
108	 diastereomer B	516.4

109		503.3
110		571.4

EXAMPLE 111

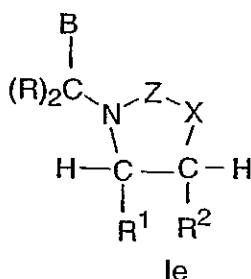


((4*R*,5*S*)-4-[3,5-bis(trifluoromethyl)phenyl]-1-{[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl}-5-methylimidazolidin-2-ylidene)cyanamide.

To a solution of (1*R*,2*S*)-1-[3,5-bis(trifluoromethyl)phenyl]-*N*²-{[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl}propane-1,2-diamine (25.1 mg, 0.0424 mmol) in dichloroethane (1.5 mL) was added triethylamine (15 μL, 0.105 mmol) and diphenyl cyanocarbonimidate (13 mg, 0.053 mmol). The reaction was heated at 60°C overnight, cooled to room temperature, filtered, and loaded directly onto a silica gel column for purification by flash chromatography with 10 to 40% EtOAc/hexanes to afford 21.6 mg (79%) of ((4*R*,5*S*)-4-[3,5-bis(trifluoromethyl)phenyl]-1-{[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl}-5-methylimidazolidin-2-ylidene)cyanamide. *R*_f = 0.20 (25% EtOAc/hexanes). LCMS = 643.3 (M+1)⁺. ¹H NMR (C₆D₆, 500 MHz; atropisomers present, doubling of some peaks) δ 6.53-8.83 (m, 10H), 3.61-4.91 (m, 3H), 3.28-2.70 (m, 5H), 1.14-1.25 (m, 6H), -0.39-0.26 (m, 3H).

WE CLAIM:

1. A compound having Formula Ie, or a pharmaceutically acceptable salt thereof, wherein

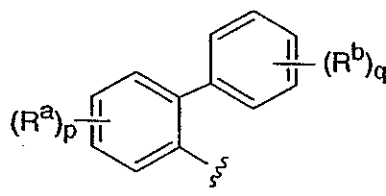


X is selected from the group consisting of -O-, -NH-, -N(C₁-C₅alkyl)- and -(CH₂)_n-;

Z is selected from the group consisting of -C(=O)-, -S(O)₂-, and -C(=N-R⁹)-, wherein R⁹ is selected from the group consisting of H, -CN, and C₁-C₅alkyl optionally substituted with 1-11 halogens;

Each R is independently selected from the group consisting of H and -CH₃;

B is selected from the group consisting of A¹ and A², wherein A¹ has the structure:



R¹ is selected from the group consisting of H, -C₁-C₅ alkyl, and -(C(R)₂)_nA², wherein -C₁-C₅ alkyl is optionally substituted with 1-11 halogens;

R² is selected from the group consisting of H, -C₁-C₅ alkyl, A¹, and -(C(R)₂)_nA², wherein -C₁-C₅alkyl is optionally substituted with 1-11 halogens;

Wherein one of B and R² is A¹; and one of B, R¹, and R² is A² or -(C(R)₂)_nA²; so that the compound of Formula Ie comprises one group A¹ and one group A²;

A² is selected from the group consisting of phenyl, cyclohexyl, and pyridyl, wherein A² is optionally substituted with 1-2 substituent groups independently selected from halogen, -C₁-C₄ alkyl, and -CN, wherein -C₁-C₄ alkyl is optionally substituted with 1-3 halogens;

Each R^a is independently selected from the group consisting of -C₁-C₃ alkyl and halogen, wherein -C₁-C₃ alkyl is optionally substituted with 1-3 halogens;

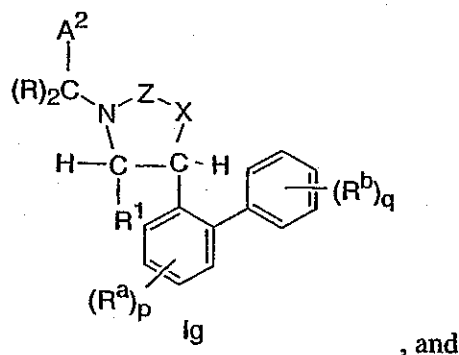
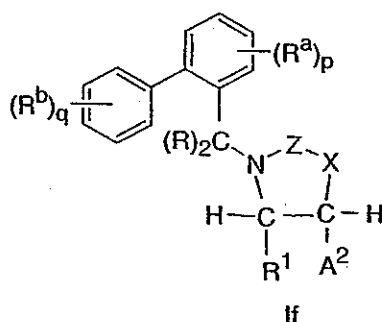
Each R^b is independently selected from the group consisting of Cl, F, -C₁-C₄ alkyl, and -OC₁-C₄ alkyl, wherein -C₁-C₄ alkyl and -OC₁-C₄ alkyl are optionally substituted with 1-5 F;

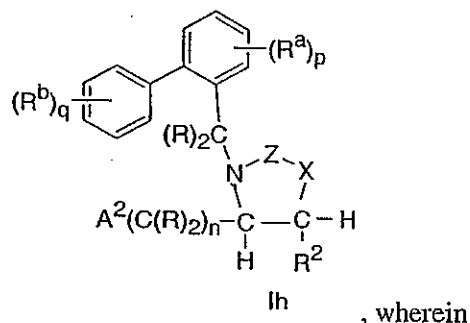
n is 0 or 1;

p is an integer from 0-2; and

q is an integer from 0-3.

2. The compound of Claim 1, selected from the group consisting of compounds having Formula If, Ig, and Ih, or a pharmaceutically acceptable salt thereof:





R^1 and R^2 are each independently selected from the group consisting of H and -C₁-C₅ alkyl, wherein -C₁-C₅ alkyl is optionally substituted with 1-11 halogens.

3. The compound of Claim 2 having Formula If, Ig, or 1h, or a pharmaceutically acceptable salt thereof, wherein

A^2 is selected from the group consisting of phenyl, cyclohexyl, and pyridyl, wherein A^2 is optionally substituted with 1-2 substituent groups independently selected from halogen, -CH₃, -CF₃, and -CN;

Each R^a is independently selected from the group consisting of -CF₃ and Cl;

Each R^b is independently selected from the group consisting of -C₁-C₃ alkyl, -OCH₃, and F;

R^1 and R^2 are each independently selected from the group consisting of H and -C₁-C₂ alkyl;

X is selected from the group consisting of -O-, -NH-, -N(CH₃)-, and -CH₂-;

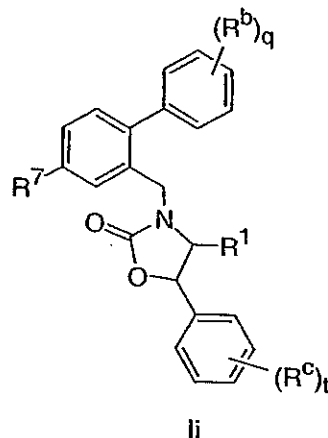
Z is selected from the group consisting of -C(=O)-, -S(O)₂-, and -C(=N-CN)-;

n is 0 or 1;

p is 1; and

q is 2 or 3.

4. The compound of Claim 3 having Formula Ii, or a pharmaceutically acceptable salt thereof, wherein:

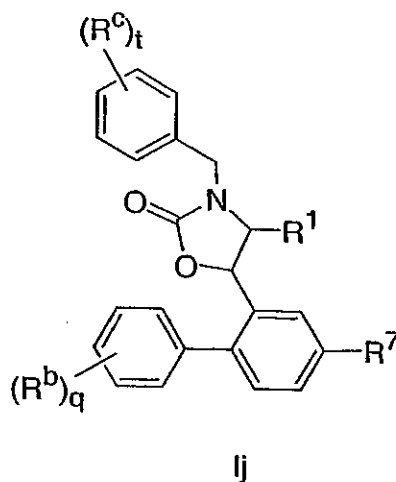


R^7 is selected from the group consisting of Cl and $-CF_3$;

R^c is selected from the group consisting of halogen, $-CH_3$, $-CF_3$, and $-CN$; and

t is an integer from 0-2.

5. The compound of Claim 3 having Formula Ij, or a pharmaceutically acceptable acceptable salt thereof, wherein:



R^7 is selected from the group consisting of Cl and $-CF_3$;

R^c is selected from the group consisting of halogen, $-CH_3$, $-CF_3$, and $-CN$; and

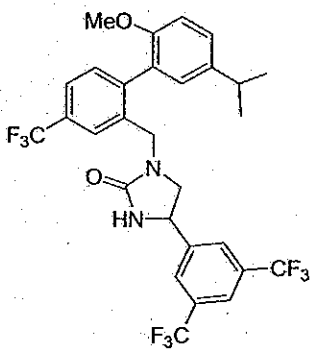
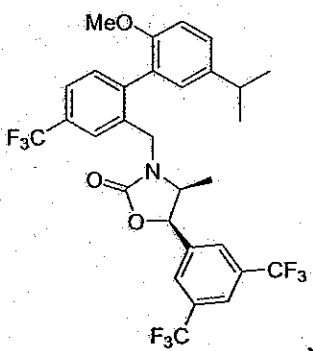
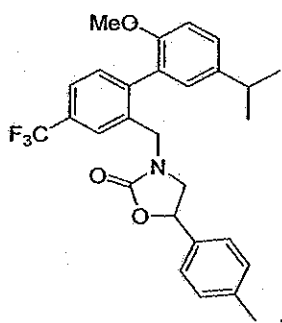
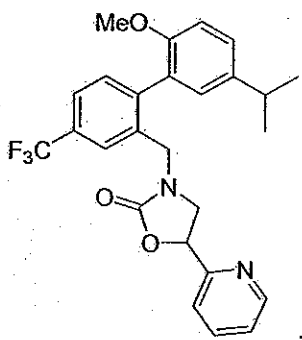
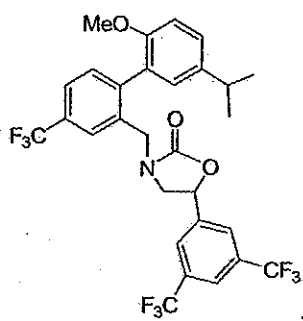
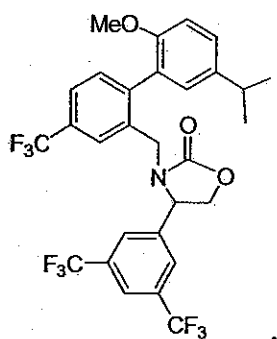
t is an integer from 0-2.

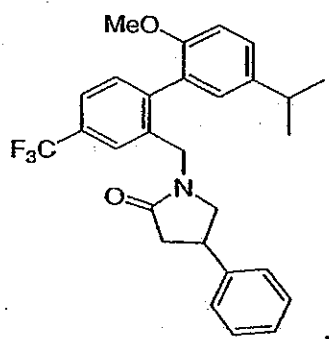
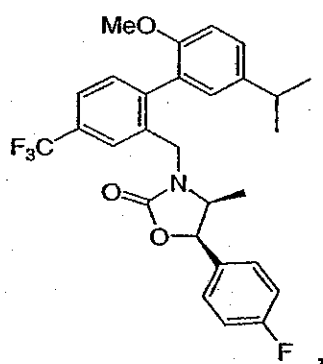
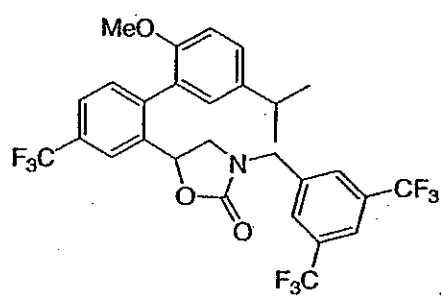
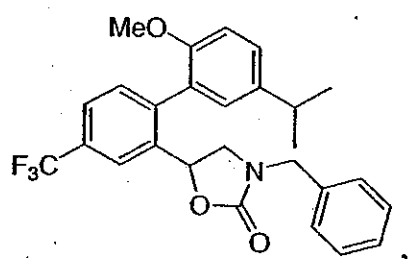
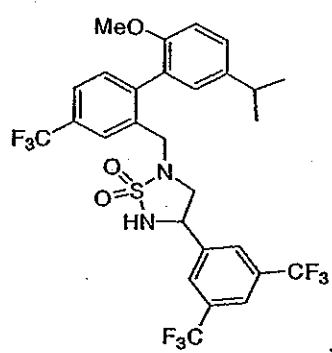
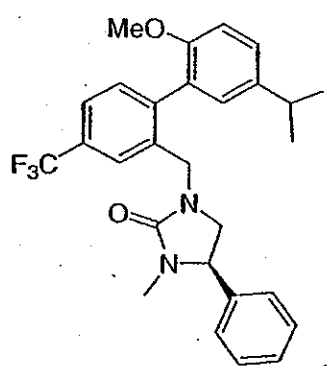
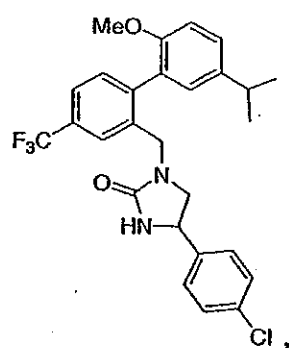
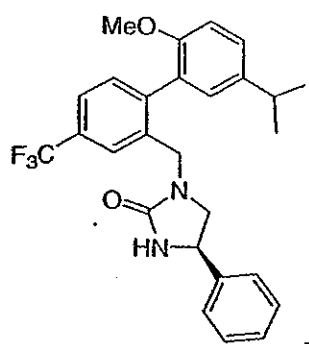
6. The use of the compound of Claim 1 or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for raising HDL-C in a patient in need of such treatment.

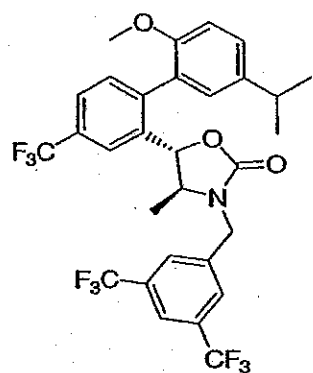
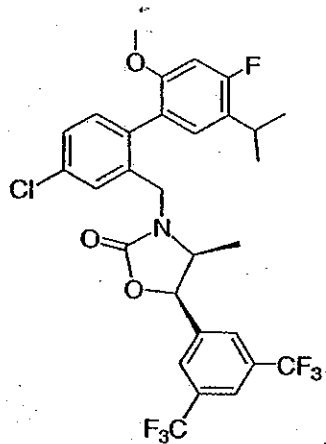
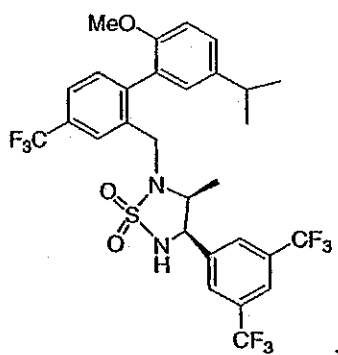
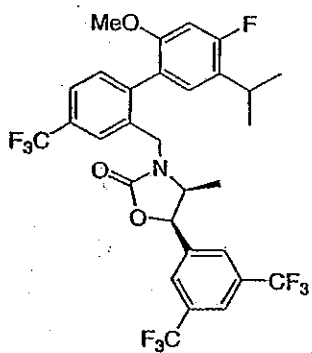
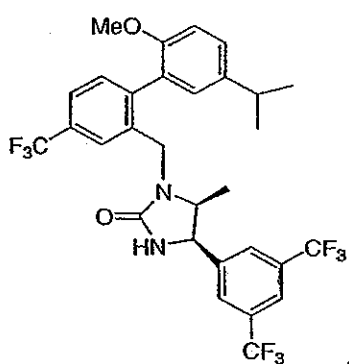
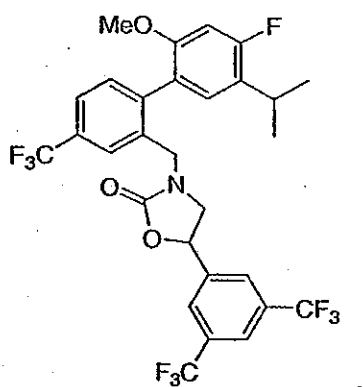
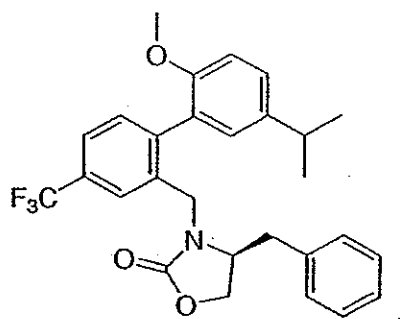
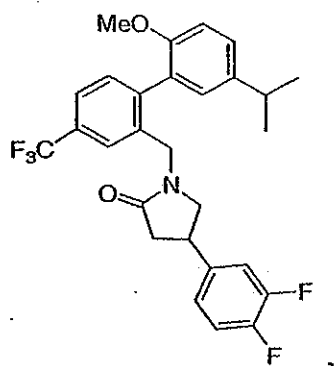
7. The use of the compound of Claim 1 or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of atherosclerosis.

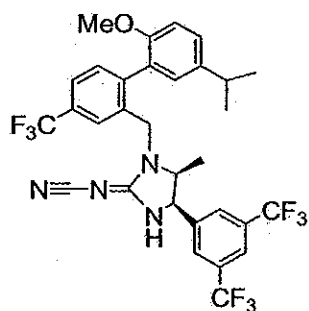
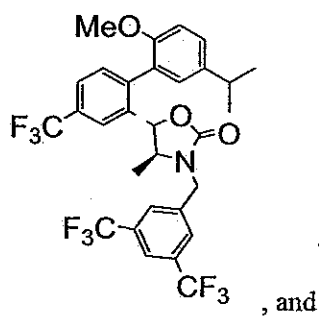
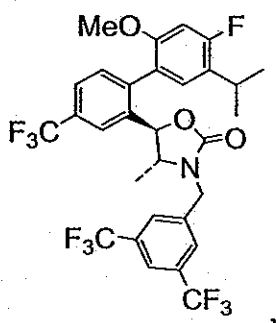
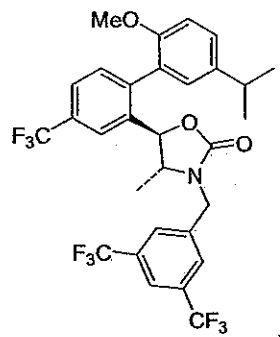
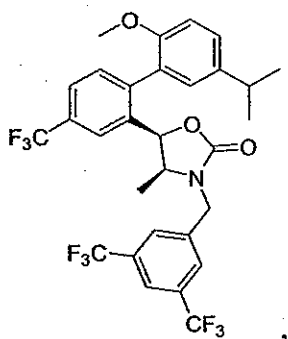
8. A pharmaceutical composition comprising the compound of Claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

9. The compound of Claim 3, selected from the following compounds, or a pharmaceutically acceptable salt thereof:

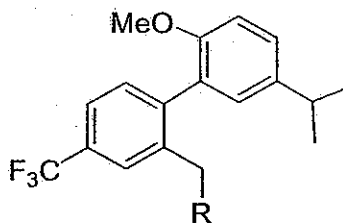




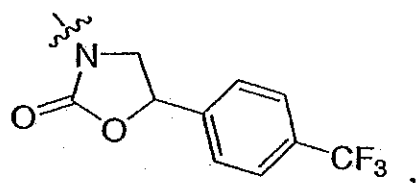
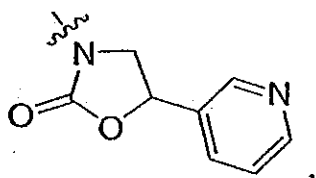
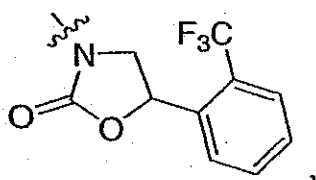
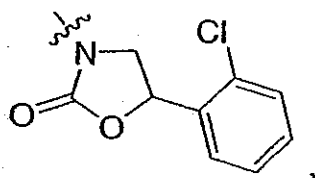
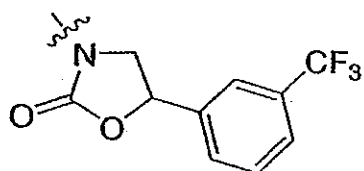
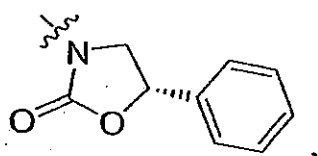
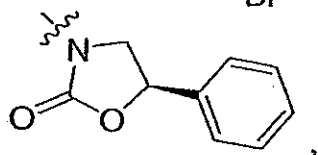
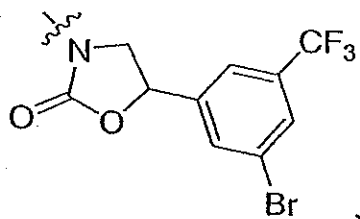


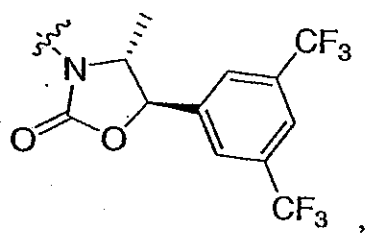
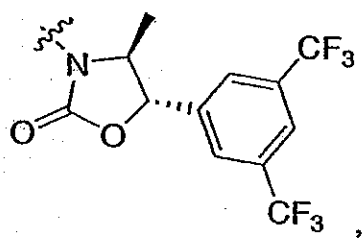
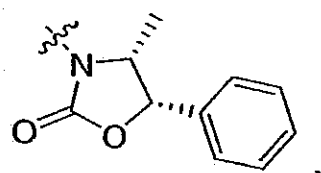
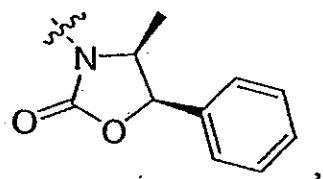
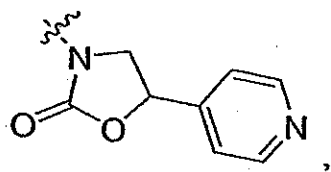
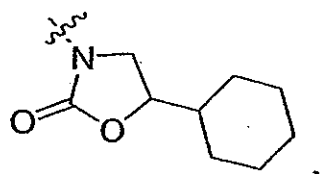
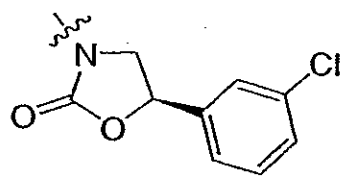


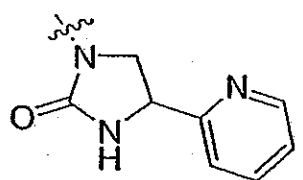
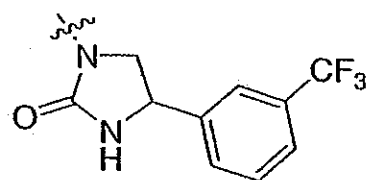
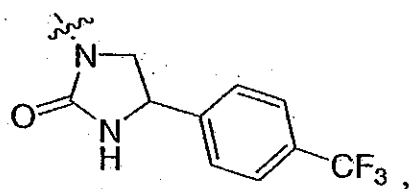
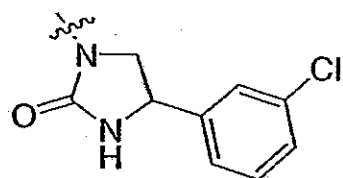
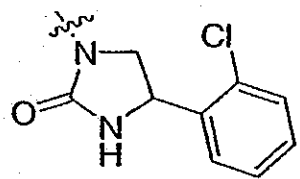
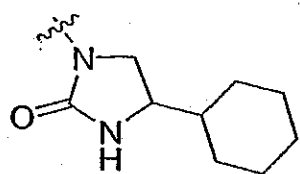
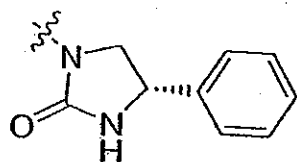
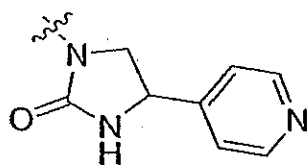
10. The compound of Claim 3, or a pharmaceutically acceptable salt thereof:

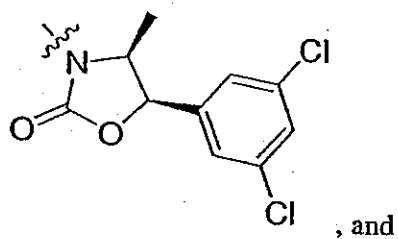
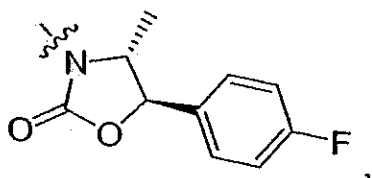
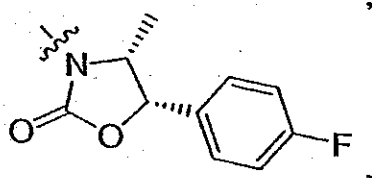
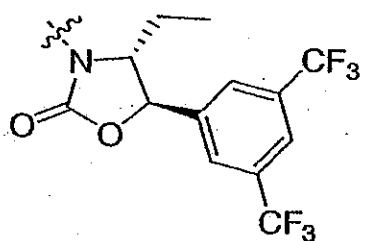
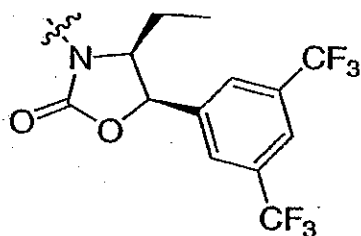
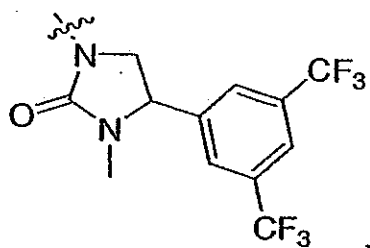
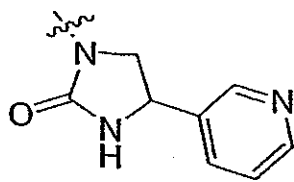


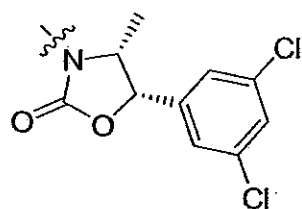
Wherein R is selected from the group consisting of



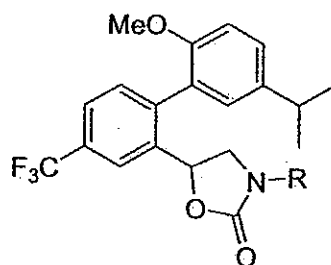




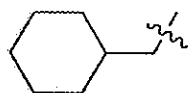
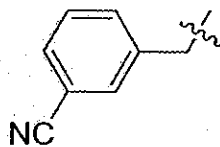
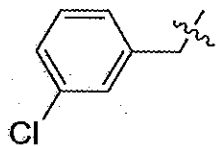
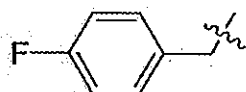




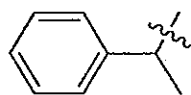
11. The compound of Claim 3, or a pharmaceutically acceptable salt thereof:



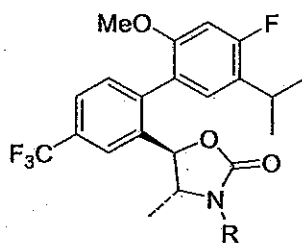
wherein R is selected from the group consisting of



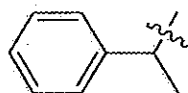
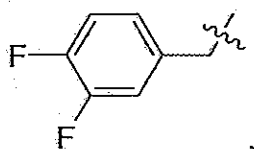
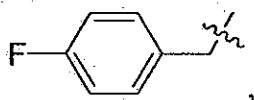
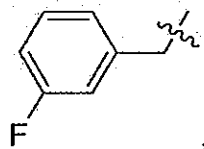
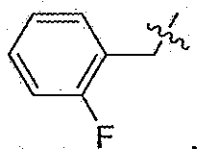
, and

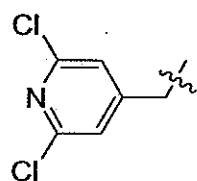
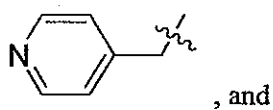


12. The compound of Claim 3, or a pharmaceutically acceptable salt thereof:

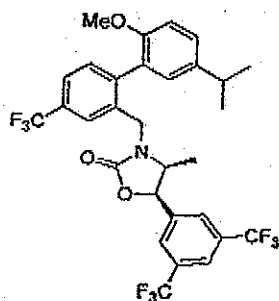


wherein R is selected from the group consisting of

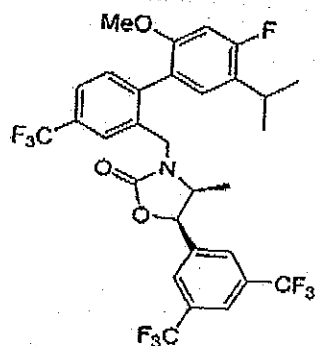




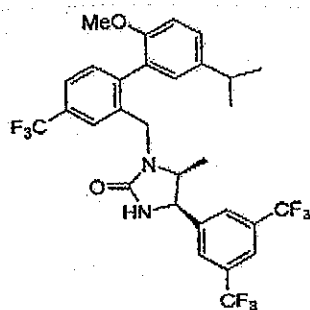
13. The compound of Claim 9, or a pharmaceutically acceptable salt thereof:



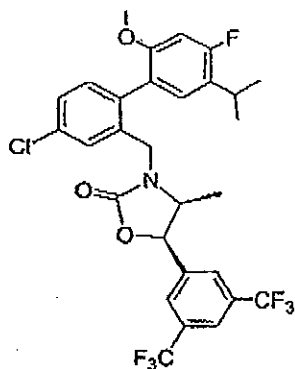
14. The compound of Claim 9, or a pharmaceutically acceptable salt thereof:



15. The compound of Claim 9, or a pharmaceutically acceptable salt thereof:



16. The compound of Claim 9, or a pharmaceutically acceptable salt thereof:



17. The compound of Claim 9, or a pharmaceutically acceptable salt thereof:

