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[54] SUBSTITUTED PHENYL SULFONAMIDES AS SELECTIVE β 3 AGONISTS FOR THE TREATMENT OF DIABETES AND OBESITY

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[21] Appl. No.: **168,105**

[22] Filed: **Dec. 15, 1993**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 15,689, Feb. 9, 1993, abandoned.

[51] **Int. Cl.**[6] **C07D 455/00**; C07D 307/10; C07C 311/01

[52] **U.S. Cl.** **546/138**; 546/290; 548/316.4; 548/469; 548/541; 549/33; 549/416; 549/475; 564/80; 564/82; 564/83; 564/84; 564/85; 564/86; 564/87; 564/88; 564/89; 564/90; 564/92; 564/96; 564/99

[58] **Field of Search** 514/604, 605; 564/80, 564/82, 83, 84, 85, 86, 87, 88, 89, 90, 92, 96, 99; 546/290, 138; 548/469, 541, 316.4; 549/33, 475, 416

[56] **References Cited**

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[57] **ABSTRACT**

Substituted phenylsulfonamides are selective β_3 adrenergic receptor agonists with very little β_1 and β_2 adrenergic receptor activity and as such the compounds are capable of increasing lipolysis and energy expenditure in cells. The compounds thus have potent activity in the treatment of Type II diabetes and obesity. The compounds can also be used to lower triglyceride levels and cholesterol levels or raise high density lipoprotein levels or to decrease gut motility. In addition, the compounds can be used to reduced neurogenic inflammation or as antidepressant agents. The compounds are prepared by coupling an aminoalkylphenyl-sulfonamide with an appropriately substituted alkyl epoxide. Compositions and methods for the use of the compounds in the treatment of diabetes and obesity and for lowering triglyceride levels and cholesterol levels or raising high density lipoprotein levels or for increasing gut motility are also disclosed.

18 Claims, No Drawings

SUBSTITUTED PHENYL SULFONAMIDES AS SELECTIVE β 3 AGONISTS FOR THE TREATMENT OF DIABETES AND OBESITY

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of our application Ser. No. 08/015,689 filed Feb. 9, 1993, abandoned on May 12, 1994.

BACKGROUND OF THE INVENTION

β-Adrenoceptors have been subclassified as β_1 and β_2 since 1967. Increased heart rate is the primary consequence of β_1-receptor stimulation, while bronchodilation and smooth muscle relaxation typically result from β_2 stimulation. Adipocyte lipolysis was initially thought to be solely a β_1-mediated process. However, more recent results indicate that the receptor-mediating lipolysis is atypical in nature. These atypical receptors, later called β_3-adrenoceptors, are found on the cell surface of both white and brown adipocytes where their stimulation promotes both lipolysis (breakdown of fat) and energy expenditure.

Early developments in this area produced compounds with greater agonist activity for the stimulation of lipolysis (β_3 activity) than for stimulation of atrial rate (β_1) and tracheal relaxtion (β_2)- These early developments disclosed in Ainsworth et al., U.S. Pat. Nos. 4,478,849 and 4,396,627, were derivatives of phenylethanolamines.

Such selectivity for β_3-adrenoceptors could make compounds of this type potentially useful as antiobesity agents. In addition, these compounds have been reported to show antihyperglycemic effects in animal models of non-insulin-dependent diabetes mellitus.

A major drawback in treatment of chronic diseases with β_3 agonists is the potential for stimulation of other β-receptors and subsequent side effects. The most likely of these include muscle tremor (β_2) and increased heart rate (β_1). Although these phenylethanolamine derivatives do possess some β_3 selectively, side effects of this type have been observed in human volunteers. It is reasonable to expect that these side effects resulted from partial β_1 and/or β_2 agonism.

More recent developments in this area are disclosed in Ainsworth et al., U.S. Pat. No. 5,153,210, Caulkett etal., U.S. Pat. No. 4,999,377, Alig et al., U.S. Pat. No. 5,017,6 19, Lecount et al., European Patent 427480 and Bloom et al., European Patent 455006.

Even though these more recent developments purport to describe compounds with greater β_3 selectively over the β_1 and β_2 activities, this selectively was determined using rodents, in particular, rats as the test animal. Because even the most highly selective compounds, as determined by these assays, still show signs of side effects due to residual β_1 and β_2 agonist activity when the compounds are tested in humans, it has become apparent that the rodent is not a good model for predicting human β_3 selectivity.

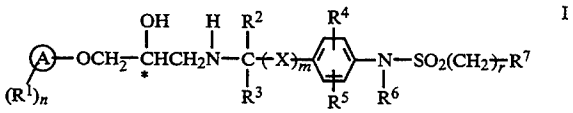
Recently, assays have been developed which more accurately predict the effects that can be expected in humans. These assays utilize cloned human β_3 receptors which have been expressed in Chinese hamster ovary cells. The agonist and antagonist effects of the various compounds on the cultivated cells provide an indication of the antiobesity and antidiabetic effects of the compounds in humans.

SUMMARY OF THE INVENTION

The instant invention is concemed with substituted phenyl sulfonamides which are useful as antiobesity and antidiabetic compounds. Thus, it is an object of this invention to describe such compounds. It is a further object to describe the specific preferred stereoisomers of the substituted phenylsulfonamides. A still further object is to describe processes for the preparation of such compounds. Another object is to describe methods and compositions which use the compounds as the active ingredient thereof. Further objects will become apparent from reading the following description.

DESCRIPTION OF THE INVENTION

The compounds of the instant invention are best realized in the following structural formula:



I

where

n is 0to 7;

m is 0or 1;

r is 0to 3;

A is phenyl, naphthyl, a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur or nitrogen, a benzene ring fused to a C_3-C_8 cycloalkyl ring, a benzene ting fused to a 5 or 6-membered heterocyclic ring with from 1 to 3 heteroatoms selected from oxygen, sulfur or nitrogen or a 5 or 6-membered heterocyclic ring with from 1 to 3 heteroatoms selected from oxygen, sulfur or nitrogen fused to a 5 or 6-membered heterocyclic ting with from 1 to 3 heteroatoms selected from oxygen, sulfur or nitrogen;

R^1 is hydroxy, oxo, halogen, cyano, nitro, NR^8R^8, SR^8, trifluoromethyl, C_1–C_6 alkyl, C_1–C_6 alkoxy, C_3–C_8 cycloalkyl, phenyl, SO_2R^9, NR^8COR^9, COR^9, $NR^8SO_2R^9$, $NR^8CO_2R^8$ or C_1–C_6 alkyl substituted by hydroxy, nitro, halogen, cyano, NR^8R^8, SR^8, trifluoromethyl, C_1–C_6 alkoxy, C_3–C_8 cycloalkyl, phenyl, NR^8COR^9, COR^9, SO_2R^9, $NR^8SO_2R^9$, $NR^8CO_2R^8$, or R^1 is a 5 or 6-membered heterocycle with from 1 to 3 heteroatoms selected from oxygen, sulfur or nitrogen;

R^2 and R^3 are independently hydrogen, C_1–C_6 alkyl or C_1–C_6 alkyl substituted by 1 to 3 of hydroxy, C_1–C_6 alkoxy, or halogen;

X is —CH_2—, —CH_2—CH_2—, —CH═CH— or —CH_2O—;

R^4 and R^5 are independently hydrogen, C_1–C_6 alkyl, halogen, NHR_8, OR_8, SO_2R^9 or $NHSO_2R^9$;

R^6 is hydrogen or C_1–C_6 alkyl;

R^7 is C_1–C_6 alkyl, C_3–C_8 cycloalkyl, or B-(RI)n;

B is phenyl, naphthyl, a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur or nitrogen, a benzene ring fused to a C_3–C_8 cycloalkyl ring, a benzene ting fused to a 5 or 6-membered heterocyclic ring with from 1 to 3 heteroatoms selected from oxygen, sulfur or nitrogen or a 5 or 6-membered heterocy-

clic ring with from 1 to 3 heteroatoms selected from oxygen, sulfur or nitrogen fused to a 5 or 6-membered heterocyclic ring with from 1 to 3 heteroatoms selected from oxygen, sulfur or nitrogen;

R^8 is hydrogen, C_1–C_{10} alkyl, C_3–C_8 cycloalkyl, phenyl optionally substituted by 1 to 3 of halogen, C_1–C_6 alkyl or C_1–C_6 alkoxy, or C_1–C_{10} alkyl substituted by 1 to 3 of hydroxy, halogen, CO_2H, CO_2—C_1—C_6 alkyl, C_3–C_8 cycloalkyl, C_1–C_6 alkoxy, or phenyl optionally substituted by from 1 to 3 of halogen, C_1–C_6 alkyl or C_1–C_6 alkoxy;

R^9 is R^8, NHR^8 or NR^8R^8.

In the above structural formula and throughout the instant specification, the following terms have the indicated meanings:

The alkyl groups specified above are intended to include those alkyl groups of the designated length in either a straight or branched configuration. Exemplary of such alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tertiary butyl, pentyl, isopentyl, hexyl, isohexyl, and the like.

The alkoxy groups specified above are intended to include those alkoxy groups of the designated length in either a straight or branched configuration. Exemplary of such alkoxy groups are methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tertiary butoxy, pentoxy, isopentoxy, hexoxy, isohexoxy and the like.

The term "halogen" is intended to include the halogen atoms fluorine, chlorine, bromine and iodine.

Certain of the above defined terms may occur more than once in the above formula and upon such occurrence each term shall be defined independently of the other.

The preferred 5 and 6-membered heterocycles and fused heterocycles of A, B and R_1 are those heterocycles with from 1 to 4 heteroatoms independently selected from one of oxygen or sulfur or 1 to 4 nitrogen atoms.

The preferred values of A and B are phenyl, naphthyl or the foregoing preferred 5 and 6-membered heterocycles and fused heterocycles.

The more preferred values of A are phenyl, naphthyl, pyridyl, quinolinyl, pyrimidinyl, pyrrollyl, thienyl, imidazolyl, and thiazolyl.

The more preferred values of B are phenyl, naphthyl, quinolinyl, thienyl, benzimidazolyl, thiadiazolyl, benzothiadiazolyl, indolyl, indolinyl, benzodioxolyl, benzodioxanyl, benzothiophenyl, benzofuranyl, benzisoxazolyl, benzothiazolyl, tetrahydronaphthyl, dihydrobenzofuranyl, and tetrahydroquinolinyl.

Further preferred compounds of the instant invention are s realized when in the above structural formula:

R^2 and R^3 are hydrogen or methyl;

X is —CH_2—

m is 1;

r is 0–2; and

R^4, R^5 and R^6 are hydrogen.

Still further preferred compounds of the instant invention are realized when in the above structural formula:

A is phenyl, quinolinyl, or a 6-membered heterocyclic ring with 1 or 2 nitrogen atoms;

B is phenyl or quinolinyl;

R^1 is NH_2, hydroxy, halogen, cyano, trifluoromethyl, phenyl, NR^8COR^9, $NR^8CO_2R^8$, C_1–C_6 alkyl optionally substituted by hydroxy; and

r is 0or2.

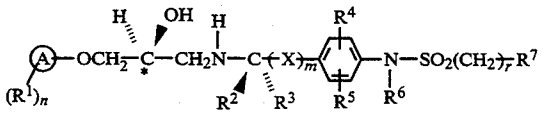
Representative preferred antiobesity and antidiabetic compounds of the present invention include the following: N-[4-[2-[[2-hydroxy-3-(4-hydroxyphenoxy)propyl-]amino]ethyl]phenyl]benzenesulfonarnide N-[4-[2-[[2-hydroxy-3-(4-hydroxyphenoxy)propyl]amino]ethyl]-phenyl]-4-iodobenzenesulfonamide N-[4-[2-[[2-hydroxy-3-(4-hydroxyphenoxy)propyl]amino]ethyl]-phenyl]-2-naphthalenesulfonamide N-[4-[2-[[2-hydroxy-3-(4-hydroxyphenoxy)propyl]amino]ethyl]phenyl]4-(benzo-2,1,3-thiadiazole)sulfonamide N-[4-[2-[[2-hydroxy-3-(4-hydroxyphenoxy)propyl]amino]ethyl]-phenyl]-2-phenylethanesulfonamide N-[4-[2-[[3-(4-fluorophenoxy)-2-hydroxypropyl]amino]ethyl]phenyl]-4-benzenesulfonamide N-[4-[2-[[3-[(2-amino-5-pyridinyl)oxy]-2-hydroxyptopyl]amino]ethyl]phenyl]-2-naphthalenesulfonamide N-[4-[2-[[2-hydroxy-3-(4-hydroxyphenoxy)propyl]amino]ethyl]phenyl]-3-quinolinesulfonamide N-[4-[2-[[2-hydroxy-3-(4-hydroxyphenoxy)propyl]amino]ethyl]phenyl]-4-[(5-methoxycarbonyl)pentanoyl]amino]benzenesulfonamide N-[4-[2-[[2-hydroxy-3-(4-hydroxyphenoxy)propyl]amino]ethyl]phenyl]-4-[(5-hydroxycarbonyl)pentanoyl]amino]-benzenesulfonamide N-[4-[2-[[2-hydroxy-3-(4-hydroxyphenoxy)propyl]amino]ethyl]phenyl]-4-(hexylaminocarbonylamino)benzenesulfonamide N-[4-[2-[(2-hydroxy-3-phenoxypropyl)amino]ethyl]phenyl]-4-chlorobenzenesulfonamide N-[4-[2-[[2-hydroxy-3-(3-cyanophenoxy)propyl]amino]ethyl]phenyl]-3-quinolinesulfonamide N-[4-[2-[[3-(4-amino-3-cyanophenoxy)-2-hydroxypropyl]amino]ethyl]phenyl]-3-quinolinesulfonamide N-[4-[2-[[2-hydroxy-3-[(3-hydroxymethyl)phenoxy]propyl]amino]ethyliphenyl]-3-quinolinesulfonamide N-[4-[2-[[2-hydroxy-3-(3-pyridyloxy)propyl]amino]ethyl]phenyl]-3-quinolinesulfonamide N-[4-[2-[[2-hydroxy-3-(3-pyridyloxy)propyl-lamino]ethyl]phenyl]-4-iodobenzenesulfonamide N-[4-[2-[[3-[(2-amino-5-pyridinyl)oxy]-2-hydroxypropyl-]amino]ethyl]phenyl]-4-isopropylbenzenesulfonamide.

The compounds of the instant invention all have at least one asymmetric center as noted by the asterisk in structural Formulae I and Ia. Additional asymmetric centers may be present on the molecule depending upon the nature of the various substituents on the molecule, in particular, R_2 and R_3. Each such asymmetric center will produce two optical isomers and it is intended that all such optical isomers, as separated, pure or partially purified optical isomers or racemic mixtures thereof, be included within the ambit of the instant invention. In the case of the asymmetric center represented by the asterisk in Formula I, it has been found that the compound in which the hydroxy substituent is above the plane of the structure, as seen in Formula Ia, is more active and thus more preferred over the compound in which the hydroxy substituent is below the plane of the structure.

Compounds of the general Formula I may be separated into diastereoisomeric pairs of enantiomers by, for example, fractional crystallization from a suitable solvent, for example methanol or ethyl acetate or a mixture thereof. The pair of enantiomers thus obtained may be separated into individual stereoisomers by conventional means, for example by the use of an optically active acid as a resolving agent.

Alternatively, any enantiomer of a compound of the general Formula I may be obtained by stereospecific synthesis using optically pure starting materials of known configuration.

The following stereospecific structure represents the preferred stereoisomers of the instant invention.

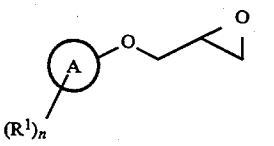


Ia

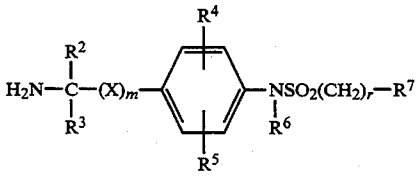
pos where the various substituents are as defined above.

The instant compounds can be isolated in the form of their pharmaceutically acceptable acid addition salts, such as the salts derived from using inorganic and organic acids. Examples of such acids are hydrochloric, nitric, sulfuric, phosphoric, formic, acetic, trifluoroacetic, propionic, maleic, succinic, malonic and the like. In addition, certain compounds containing an acidic function such as a carboxy or tetrazole, can be isolated in the form of their inorganic salt in which the counterion can be selected from sodium, potassium, lithium, calcium, magnesium and the like, as well as from organic bases.

The compounds (I) of the present invention can be prepared from epoxide intermediates such as those of formula II and amine intermediates such as those of formula III. The preparation of these intermediates is described in the following schemes.



II

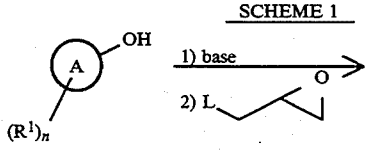


III

where n, m, r, A, R_1, R_2, R_3, R_4, R_5, R_6, R_7 and X are as defined above.

Compounds II can be conveniently prepared by a variety of methods familiar to those skilled in the art. One common route is illustrated in Scheme 1. Alcohol **1** is treated with base such as sodium hydride or potassium t-butoxide in a polar solvent such as anhydrous dimethylformamide. The resultant anion is alkylated with epoxide derivative **2**, wherein "L" is a leaving group such as a sulfonate ester or a halide, for 0.5 to 24 hours at temperatures of 20°–100° C. to provide compound II. The epoxide derivative **2** is conveniently the commercially available, enantiomerically pure (2S)or (2R)-glycidyl 3-nitrobenzene sulfonate or (2R) or (2S)-glycidyl 4-toluenesulfonate, thus both the (S) and (R) enantiomers of epoxide II are readily available.

SCHEME 1



1 2

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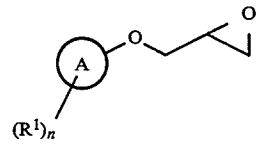
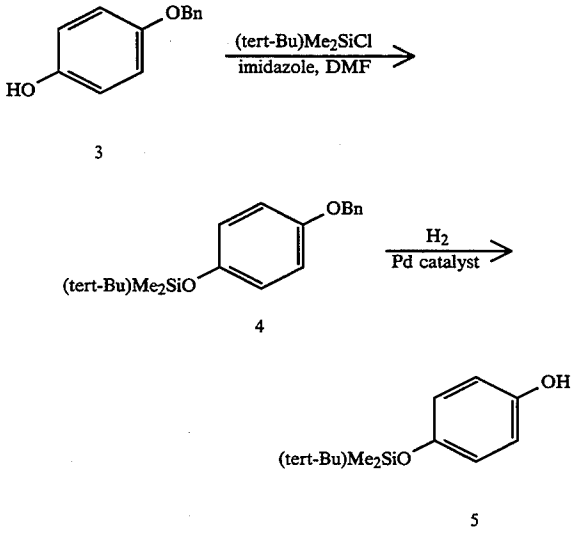
SCHEME 1



II

Many of the alcohols **1** are commercially available or readily prepared by methods described in the literature and known to those skilled in the art. R^1 substituents on the alcohol **1** may need to be protected during the alkylation and subsequent procedures. A description of such protecting groups may be found in: *Protective Groups in Organic Synthesis,* 2nd Ed., T. W. Greene and P. G. M. Wuts, John Wiley and Sons, New York, 1991. A useful method for protecting the preferred alchohol **1** wherein A $(R^1)_n$ is 4-hydroxyphenyl as its tert-butyldimethylsilyl (TBS) derivative is illustrated in Scheme 2. Commercially available phenol **3** is treated with a silylating agent such as tert-butyldimethylsilyl chloride in the presence of a base such as imidazole in an aprotic solvent such as dimethylformamide. The benzyl group is then removed by catalytic hydrogenation to give the desired alcohol **5**.

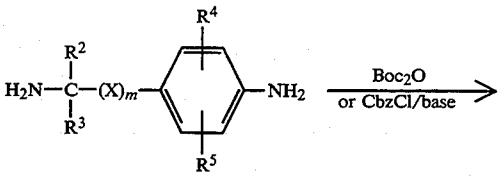
SCHEME 2



3 4 5

Compounds III can be conveniently prepared by a variety of methods familiar to those skilled in the art. A convenient route for their preparation when R^6 is hydrogen is illustrated in Scheme 3. Compound **6** is selectively protected as a suitable carbamate derivative **6a** with, for example, di-tert-butyl dicarbonate or carbobenzyloxy chloride. This compound is then treated with a sulfonyl halide, preferably the sulfonyl chloride **7**, and a base such as pyridine in an anhydrous solvent such as dichloromethane or chloroform for 0.5 to 24 hours at temperatures of −20° to 50° C., preferably 0° C., to provide the sulfonamide **8**. The protecting group is then removed with, for example, trifluoracetic acid in the case of Boc or catalytic hydrogenation in the case of Cbz, to give the desired amine **9**.

SCHEME 3



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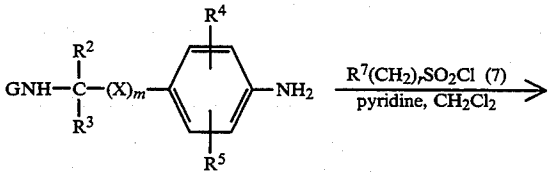
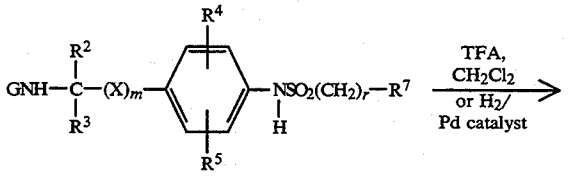


6a

G = Boc or Cbz



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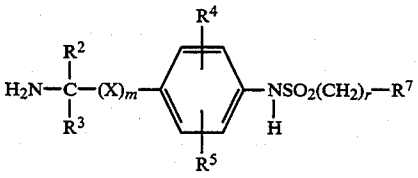

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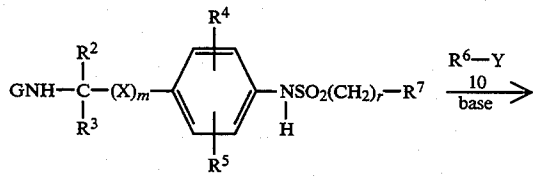
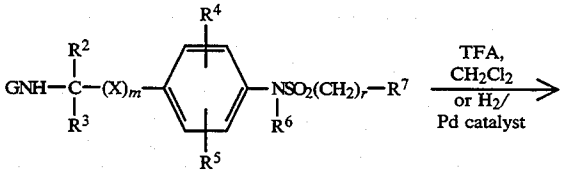
Compounds III where R^6 is not hydrogen may be conveniently prepared as illustrated in Scheme 4. Sulfonamide **8**, prepared as described above, is alkylated with an appropriate alkylating agent **10** in the presence of base to provide sulfonamide **11**. Removal of the protecting group as above gives the desired compound III.

SCHEME 4



8



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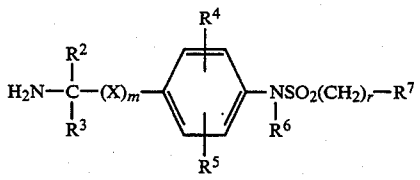
SCHEME 4



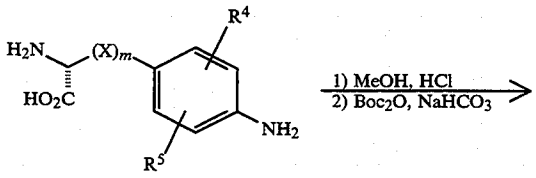
G = Boc or Cbz
Y = Cl, Br, or I

III

The sulfonyl chlorides **7**, many of which are commercially available, can also be readily prepared by a number of methods familiar to those skilled in the art. One suitable method involves the addition of an organolithium reagent or a Grignard reagent to sulfuryl chloride following the procedure of S. N. Bhattacharya, et. al., J. Chem. Soc. (C), 1265–1267 (1968). Another convenient method involves the treatment of a thiol with sulfuryl chloride and a metal nitrate according to the procedure of Y. J. Park, et. al., Chemistry Letters, 1483–1486 (1992). Sulfonic acids are also conveniently converted to the corresponding sulfonyl chloride by treatment with PCl_5, PCl_3 or $SOCl_2$ (J. March, *Advanced Organic Chemistry,* 4th Ed., John Wiley and Sons, New York: 1992, p 1297 and references cited therein). Alternatively, aromatic compounds may be treated with chlorosulfonic acid according to the procedure of Albert, et. al., *J. Het. Chem.* 15, 529 (1978), to provide the sulfonyl chlorides.

The diamines **6** are commercially available or readily prepared by methods described in the literature or known to those skilled in the art. Compound **6** where R^2 or R^3 is methyl can be prepared from the corresponding amino acid following the method of J. D. Bloom, et. al., *J. Med. Chem.*, 35, 3081–3084 (1992). As illustrated in Scheme 5 for R^3=methyl, the appropriate (R) amino acid **12** is esterified, conveniently by treatment with methanolic hydrochloric acid, and then treated with di-tert-butyl dicarbonate to give compound **13**. The ester group is reduced with a hydride source such as lithium borohydride and the resultant alcohol is converted to a leaving group such as a mesylate. Removal of the Boc protecting groups gives diamine **14**. This compound is subjected to catalytic hydrogenation in the presence of base such as sodium acetate to give the desired a-methyl amine **15**. The other enantiomer is available through an analogous sequence starting with the corresponding (S) amino acid.

SCHEME 5



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