CLEAN, HIGH-YIELD PREPARATION OF S,S AND R,S AMINO ACID ISOSTERES

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References Cited

U.S. PATENT DOCUMENTS

5,684,176 A 11/1997 Hilpert
5,847,144 A 12/1998 Hilpert


OTHER PUBLICATIONS


* cited by examiner

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ABSTRACT

The present invention provides compounds and methods that can be used to convert the intermediate halomethyl ketones (HMKs), e.g., chloromethyl ketones, to the corresponding S,S- and R,S-diastereomers. More particularly, the present invention provides: (1) reduction methods; (2) inversion methods; and (3) methods involving the epoxidation of alkenes. Using the various methods of the present invention, the R,S-epoxide and the intermediary compounds can be prepared reliably, in high yields and in high purity.

36 Claims, 4 Drawing Sheets
Figure 1
Figure 3
Figure 4
CLEAN, HIGH-YIELD PREPARATION OF S,S AND RS AMINO ACID ISOSTERES

BACKGROUND OF THE INVENTION

Human immunodeficiency virus (HIV), the causative agent of acquired immunodeficiency syndrome (AIDS), encodes three enzymes, including the well-characterized protease belonging to the aspartic protease family, the HIV protease. Inhibition of this enzyme has been regarded as a promising approach for treating AIDS. Hydroxyethylene amine isosteres have been extensively utilized in the synthesis of potent and selective HIV protease inhibitors. However, this modern generation of HIV protease inhibitors has created an interesting challenge for the synthetic organic chemist. Advanced x-ray structural analysis has allowed for the design of molecules that fit closely into active sites on enzymes creating very effective drug molecules. Unfortunately, these molecules, designed by molecular shape, are often difficult to produce using conventional chemistry.

The modern generation of HIV inhibitors has structural similarities in a central three-carbon piece containing two chiral carbons that link two larger groups on each side (see, e.g., Parkes, et al., J. Org. Chem., 59:3656-3664 (1994). Numerous synthetic routes to these isosteres have been developed. As illustrated below, a common strategy to prepare the linking group starts with an amino acid, such as phenylalanine, to set the chirality of the first carbon. Then, the linking group is completed by a series of reactions including a one-carbon homologation during which the old amino acid carbon is transformed into a hydroxy-functionalized carbon having the correct chirality. However, the commercial production of isosteres by this method presents serious challenges, generally requiring low-temperature organometallic reactions (Ghosh, et al., J. Org. Chem., 62:6080-6082 (1997) or the use of exotic reagents.

The most useful amino acid isosteres are based on phenylalanine. The key intermediate in the synthesis of Sequinivir® (Roche) and Aprenavir® (Glaxo Wellcome) is the (S,S)-N-t-butoxycarbonyl-1,2-epoxy-4-phenyl-3-butanamine (called “CMK”). Several other protease inhibitors, such as those described in Chen, et al. (J. Med. Chem., 39:1991-2007 (1996) or those under development (e.g., BMS-234475 or BMS-232623), use the diastereomeric (R,S)-N-t-butoxycarbonyl-1,2-epoxy-4-phenyl-3-butanamine.


OTHER ROUTES THAT HAVE BEEN PUBLISHED, BUT NOT COMMERCIALIZED ARE ILLUSTRATED IN FIG. 1.

One of the best reagents that can be used to add a single carbon to amino acids is diazomethane because it gives high yields and few side-products. In addition, diazomethane reactions are very clean, generating only nitrogen as a by-product. HIV inhibitor molecules need high purity because of the high daily doses required. As such, diazomethane is an ideal reagent for making high purity compounds. In spite of the documented hazards of diazomethane, processes have recently been developed that permit the commercial scale use of diazomethane to convert amino acids into the homologous chloromethyl ketones (see, U.S. Pat. No. 5,817,778, which issued to Archibald, et al. on Oct. 6, 1998; and U.S. Pat. No. 5,854,405, which issued to Archibald, et al. on Dec. 29, 1998). FIG. 2 illustrates examples of HIV protease inhibitors wherein the central linking group can be synthesized by the commercial use of diazomethane. FIG. 3 illustrates a general reaction scheme that can be used to prepare the SS-epoxide compound using diazomethane.

A second approach, which is illustrated below, is to convert the amino acid to an aldehyde and to add the carbon by use of a Wittig reaction to give an olefin (see, Luly, et al., J. Org. Chem., 52:1487-1492 (1987). The olefin is then epoxidized. Alternatively, the aldehyde can be reacted with
SUMMARY OF THE INVENTION

The present invention provides compounds and methods that can be used to convert the intermediate halomethyl ketones (HMKs), e.g., chloromethyl ketones, to the corresponding S,S- and R,S-diastereomers. It is these chiral centers that determine the chiral centers in the HIV protease inhibitor and, thus, the efficacy of the drug. As explained herein, the present invention provides (1) reduction methods; (2) inversion methods; and (3) methods for preparing alkenes that, in turn, can undergo epoxidation reactions to form the desired R,S-epoxide. Using the various methods of the present invention, the R,S-epoxide and the intermediary compounds can be prepared reliably, in high yields and in high purity.

As such, in one embodiment, the present invention provides a method for selectively preparing an R,S-halomethyl alcohol (R,S-HMA) compound having the following general formula:

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(I)
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with a reducing agent to form an S,S-halomethyl alcohol (S,S-HMA) compound having the following general formula:

```
(II)
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The method comprising: reducing a compound having the following general formula:

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(III)
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with a non-chelating, bulky reducing agent to form the R,S-HMA compound. In the above formulae, R is an amino acid side chain (e.g., a benzyl group, an S-phenyl group, an alkyl group and a para-nitrobenzene group, etc.); X is a blocking or protecting group (e.g., Boc, Cbz, Moc, etc.); and X is a leaving group (e.g., a halo group, such as chloro). In a presently preferred embodiment, the non-chelating, bulky reducing agent is a member selected from the group consisting of lithium aluminum t-butoxyhydride (LATBH), sodium tris-t-butoxyborohydride (STBH). In another presently preferred embodiment, the reduction is carried out in a solvent such as diethyl ether. Once formed, the R,S-HMA can be reacted with an alkali metal base to form an R,S-epoxide.

In another aspect, the present invention provides inversion methods that can be used to selectively prepare the R,S-epoxide. In one embodiment of the inversion method, the R,S-epoxide is prepared by a four step process. More particularly, in one embodiment of the inversion method, the present invention provides a method for preparing an R,S-epoxide having the following general formula:

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(IV)
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and (d) contacting the R,S-HMA compound of Formula IV with an alkali metal base to form the R,S-epoxide. In the above formulae, R is an amino acid side chain (e.g., a benzyl group, an S-phenyl group, an alkyl group, a para-nitrobenzene group, etc.); X is a blocking or protecting group; X is a leaving group (i.e., a halo group, such as chloro); R is a functional group including, but not limited to, arylsulfonyls and alkylsulfonyls (e.g., a mesyl group, a tosyl group, a triflate group, a nosyl group, etc.); and R is an acyl group derived from the acetate (e.g., an acetyl group).

In another embodiment of the inversion method, the present invention provides a method for preparing an R,S-epoxide compound having the following general formula:
US 6,605,732

BRIEF DESCRIPTION OF THE DRAWINGS


FIG. 2 illustrates examples of HIV protease inhibitors where the central linking group can be synthesized by commercial use of diazomethane.

FIG. 3 illustrates a general reaction scheme that can be used to prepare the epoxide compound.

FIG. 4 illustrates the two diastereomers that can be formed from the common chloroketone starting material, i.e., S,S-epoxide and R,S-epoxide.

DETAILED DESCRIPTION OF THE INVENTION AND PREFERRED EMBODIMENTS

The present invention provides various compounds and methods that can be used to prepare both reliable and in high yields either diastereomer, i.e., the S,S- or the R,S-, from the common halo methyl ketone (e.g., chloromethyl ketone) starting material. More particularly, as explained herein in greater detail, the present invention provides (1) reduction methods; (2) inversion methods, and (3) methods involving the epoxidation of alkenes.

A. THE REDUCTION METHODS

A variety of reducing agents can be used to reduce a halo methyl ketone (HMK) to a halo methyl alcohol (HMA) (see, Table I). However, under most conditions, the predominant diastereomer is the 2S,3S-HMA. For instance, reduction of HMK with sodium borohydride in ethanol (Chen, et al., J. Med. Chem., 39:1991–2007 (1996) produces a 1:4 mixture of R,S:S,S HMA in near quantitative yield. Moreover, the reduction of HMK with aluminium isopropanoxide in isopropanol can give ratios as high as 1:18 in favor of the S,S-isomer (see, U.S. Pat. Nos. 5,684,176 and 5,847,144, both of which issued to Hilpert). Thus, commercial routes to S,S-HMA are easily achieved.

In contrast, the preparation of the R,S-isomer is much more difficult. A slight increase in the R,S-HMA:S,S-HMA ratio is achieved when the reaction solvent, ethanol, is replaced with THF. Further enhancement in the R,S-HMA:S,S-HMA ratio is obtained when the reaction is carried out in the presence of CeCl₃ (Barluenga, et al., J. Org. Chem., 62:5974(1997); but even then the ratio of...
R,S-HMA:S,S-HMA is <1:1. Other reducing agents, such as LAH, sodium cyanoborohydride, potassium borohydride, etc., under a variety of reaction conditions, also fail to provide >1:1 R,S-HMA:S,S-HMA. In fact, a perusal of the scientific and patent literature, it has now been discovered that the reduction of IMK proceeds with high R,S-diastereoselectivity when lithium aluminum t-butoxyhydride (LATBH) is used as the reducing agent. Quite surprisingly and in contrast to the findings of the prior art, it has been found that the reduction of IMK with LATBH in, for example, diethyl ether provides a 8:1 mixture of R,S-HMA:S,S-HMA in 97% yield. This high diastereofacial selectivity of the LATBH reducing agent is unusual since reduction of IMK with similar reducing agents, such as lithium aluminum hydride or sodium borohydride, do not favor R,S-diastereoselectivity (see, U.S. Pat. Nos. 5,684,176 and 5,847,144, both of which issued to Hilpert).

In contrast to the teachings of both the scientific and patent literature, it has now been discovered that the reduction of IMK proceeds with high R,S-diastereoselectivity when lithium aluminum t-butoxyhydride (LATBH) is used as the reducing agent. Quite surprisingly and in contrast to the findings of the prior art, it has been found that the reduction of IMK with LATBH in, for example, diethyl ether provides a 8:1 mixture of R,S-HMA:S,S-HMA in 97% yield. This high diastereofacial selectivity of the LATBH reducing agent is unusual since reduction of IMK with similar reducing agents, such as lithium aluminum hydride or sodium borohydride, do not favor R,S-diastereoselectivity (see, U.S. Pat. Nos. 5,684,176 and 5,847,144, both of which issued to Hilpert).

TABLE 1

<table>
<thead>
<tr>
<th>Reagent(s)</th>
<th>Solvent(s)</th>
<th>Temp</th>
<th>Time</th>
<th>R:S:S:S</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li(OtBu)3AIH</td>
<td>THF</td>
<td>RT</td>
<td>2 Hrs</td>
<td>0.2:1</td>
</tr>
<tr>
<td>(+)-Dip Chloride 1:4</td>
<td>THF</td>
<td>5C-RT</td>
<td>12 Hrs</td>
<td>5:1</td>
</tr>
<tr>
<td>K-Selectride ®</td>
<td>THF</td>
<td>Reflux</td>
<td>2 Hrs</td>
<td>2:1</td>
</tr>
<tr>
<td>K-Selectride ®</td>
<td>THF</td>
<td>25 C</td>
<td>30 Min</td>
<td>2:1</td>
</tr>
<tr>
<td>KN-Selectride ®</td>
<td>THF</td>
<td>30 C</td>
<td>2 Hrs</td>
<td>2:1</td>
</tr>
<tr>
<td>K-Select/MgBr2=OEt2</td>
<td>THF</td>
<td>30 C</td>
<td>2 Hrs</td>
<td>2:1</td>
</tr>
<tr>
<td>R-Alpine Bonne®(Conc.)</td>
<td>THF</td>
<td>Reflux</td>
<td>9 Dys</td>
<td>1:1</td>
</tr>
<tr>
<td>L-Selectride ®</td>
<td>THF</td>
<td>R.T.</td>
<td>1 Hr</td>
<td>0.9:1</td>
</tr>
<tr>
<td>NaBH4/C4C3(anh.)</td>
<td>THF</td>
<td>RT</td>
<td>2 Hrs</td>
<td>0.6:1</td>
</tr>
<tr>
<td>N-Selectride ®</td>
<td>THF</td>
<td>25 C</td>
<td>30 Min</td>
<td>0.6:1</td>
</tr>
<tr>
<td>NaBH4/C4C3=H2O</td>
<td>THF</td>
<td>25 C</td>
<td>18 Hrs</td>
<td>0.7:1</td>
</tr>
<tr>
<td>NaBH4/EDTA(N=2=2H2O)</td>
<td>THF</td>
<td>RT</td>
<td>30 Min</td>
<td>0.7:1</td>
</tr>
<tr>
<td>NaCNBH3</td>
<td>THF</td>
<td>RT</td>
<td>36 Hrs</td>
<td>0.7:1</td>
</tr>
<tr>
<td>(+)-2-Butanol/NaBH4</td>
<td>THF</td>
<td>RT</td>
<td>1 Hr</td>
<td>0.6:1</td>
</tr>
<tr>
<td>Cp2TBH4</td>
<td>Glyme</td>
<td>R.T.</td>
<td>30 Min</td>
<td>0.6:1</td>
</tr>
<tr>
<td>NaBH4</td>
<td>THF</td>
<td>25 C</td>
<td>2 Hrs</td>
<td>0.6:1</td>
</tr>
<tr>
<td>NaBH4/-/-2-Butanol</td>
<td>THF</td>
<td>RT</td>
<td>30 Min</td>
<td>0.6:1</td>
</tr>
<tr>
<td>NaBH4/AI(OiPr)4</td>
<td>THF</td>
<td>Reflux</td>
<td>2 Hrs</td>
<td>0.6:1</td>
</tr>
<tr>
<td>NaBH4/Disaccharide Glucose</td>
<td>THF</td>
<td>RT</td>
<td>12 Hrs</td>
<td>0.6:1</td>
</tr>
<tr>
<td>NaBH4/EDTA</td>
<td>THF</td>
<td>RT</td>
<td>12 Hrs</td>
<td>0.6:1</td>
</tr>
<tr>
<td>NaBH4/L-Tartaric Acid</td>
<td>THF</td>
<td>5 C</td>
<td>1 Hr</td>
<td>0.6:1</td>
</tr>
<tr>
<td>NaBH4/MgBr2-OEt2</td>
<td>THF</td>
<td>RT</td>
<td>1 Hr</td>
<td>0.6:1</td>
</tr>
<tr>
<td>BH3/l-butylamine</td>
<td>THF</td>
<td>RT</td>
<td>1 Hr</td>
<td>0.5:1</td>
</tr>
<tr>
<td>L-BH</td>
<td>THF</td>
<td>25 C</td>
<td>1 Hr</td>
<td>0.5:1</td>
</tr>
<tr>
<td>L-Selectride ®</td>
<td>THF</td>
<td>RT</td>
<td>1 Hr</td>
<td>0.5:1</td>
</tr>
<tr>
<td>NaBH4/D-Trinitic Acid</td>
<td>THF</td>
<td>RT</td>
<td>30 Min</td>
<td>0.5:1</td>
</tr>
<tr>
<td>(+)-2-Butanol * BH3</td>
<td>THF</td>
<td>RT</td>
<td>1 Hr</td>
<td>0.4:1</td>
</tr>
<tr>
<td>NaBH4/C4C32</td>
<td>MeOH</td>
<td>R.T.</td>
<td>1 Hr</td>
<td>0.4:1</td>
</tr>
<tr>
<td>Amino Alcohol Borane</td>
<td>THF</td>
<td>25 C</td>
<td>12 Hrs</td>
<td>0.3:1</td>
</tr>
<tr>
<td>Na(PFG)2BH2</td>
<td>THF</td>
<td>30</td>
<td>30 Min</td>
<td>0.3:1</td>
</tr>
<tr>
<td>THP-BH</td>
<td>THF</td>
<td>10% THF</td>
<td>5 Dys</td>
<td>0.5:1</td>
</tr>
<tr>
<td>Al(OiPr)3</td>
<td>IPA</td>
<td>70C</td>
<td>5 Dys</td>
<td>0.5:1</td>
</tr>
<tr>
<td>Na HB(OCH3)2</td>
<td>MeOH</td>
<td>RT</td>
<td>1 Hr</td>
<td>1:1</td>
</tr>
</tbody>
</table>

As such, in one embodiment, the present invention provides a method for preparing an R,S-halomethyl alcohol (R,S-HMA) compound having the following general formula:

[R,R'HN]X1

the method comprising: reducing a compound having the following general formula:

The above method can be reacted with an alkali metal base to form an R,S-epoxide. An exemplar embodiment of the above method is illustrated by the following reaction scheme:

Synthesis of R,S-Boc-Epoxide by LATBH Reduction
In this embodiment, the reduction is preferably carried out in a solvent. It will be readily apparent to those of skill in the art that numerous solvents can be used. Exemplar solvents include, but are not limited to, the following: diethyl ether, tetrahydrofuran (THF) and methyl t-butyl ether (MTBE) and mixtures thereof. Quite surprisingly, it has been found that the reduction of LATBH is dependent on the solvent employed. For instance, when diethyl ether is used as the solvent, a 8:1 mixture of R,S-HMA:S,S-HMA is obtained. However, when THF or MTBE is used as the solvent the ratio of R,S-HMA:S,S-HMA is less than or equal to about 2:1. Based on these results, it is thought that a variety of factors, such as steric, solvation and chelation, are responsible for the high R,S diastereoselectivity observed in LATBH reduction of HMK. Thus, when LATBH is used as the reducing agent, diethyl ether is preferably used as the solvent.

LATBH is commercially available as a white powder and is used as a suspension in diethyl ether. Alternately, LATBH can be prepared in situ by the reaction of LAH with 3 equivalents of t-butylalcohol in diethylether and then reacted with HMK. The best solvent, as judged on basis of R,S-diastereoselectivity, is diethyl ether. However, the solubility of HMK in diethyl ether is relatively low and a large amount of diethyl ether is needed to dissolve CMK, thereby reducing reactor efficiency to some extent. The reactor efficiency can be improved by either adding HMK as a solid or, alternatively, as a solution in a secondary solvent (e.g., THF, toluene, ethyl acetate, etc.) to a suspension of LATBH in diethyl ether. The reaction rate is not affected, but the diastereoselectivity can be reduced from 8:1 in pure diethyl ether to about 5:1 with the above modifications.

In this embodiment, the reduction can be carried out at a temperature ranging from about _30° C. to about 25° C. In a presently preferred embodiment, the reduction is carried out at a temperature ranging from about _5° C. to about 5° C. At lower temperatures, larger amounts of solvent are needed to maintain homogeneity; whereas at high temperatures, formation of the epoxide, resulting from intramolecular cyclization, is observed. At 0° C., the reduction reaction is rapid and is complete in less than about 30 minutes. It will be readily apparent to those of skill in the art that the progress of the reduction reaction can be monitored by, for example, HPLC, and the reaction is deemed complete when the amount of unreacted HMK is less than about 1%.

In another embodiment, the present invention provides a method for preparing an R,S-halomethyl alcohol (R,S-HMA) compound having the following general formula:

```
<table>
<thead>
<tr>
<th>H</th>
<th>R'HN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cl</td>
<td>X'</td>
</tr>
</tbody>
</table>
```

the method comprising: reducing a halomethyl ketone (HMK) compound having the following general formula:

```
<table>
<thead>
<tr>
<th>H</th>
<th>R'HN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cl</td>
<td>X'</td>
</tr>
</tbody>
</table>
```

with a reducing agent selected from the group consisting of sodium cyanoborohydride, cerium chloride/sodium borohydride, K-Selectride®, KS-Selectride® and (4-)Dip Chloride™ to form the R,S-HMA compound. In this method, R¹ is an amino acid side chain; R² is a blocking group; and X¹ is a leaving group. It will be readily apparent to those of skill in the art that the foregoing discussions relating to R¹, R² and X¹ and their preferred embodiments are fully applicable to this method and, thus, will not be repeated.

As with the previously described method, the reduction is preferably carried out in a solvent. It will be readily apparent to those of skill in the art that numerous solvents can be used. Exemplar solvents include, but are not limited to, the following: diethyl ether, THF, MTBE and mixtures thereof. In a preferred embodiment, diethyl ether or THF is employed as the solvent. Methods similar to the previously described method, the reduction can be carried out at a temperature ranging from about ~30° C. to about 25° C. In a presently preferred embodiment, the reduction is carried out at a temperature ranging from about ~5° C. to about 5° C.

In yet another embodiment, the present invention provides a method for isolating an R,S-halomethyl alcohol (R,S-HMA) from a mixture of R,S-HMA and S,S-HMA. S,S-HMA is crystalline and is relatively easy to purify. In contrast, the R,S-HMA is soluble in hot hexanes, whereas the crystalline diastereomer, S,S-HMA, is not. As such, the present invention provides a method for isolating an R,S-halomethyl alcohol (R,S-HMA) from a mixture of R,S-HMA and S,S-HMA, the method comprising: combining the mixture of R,S- and S,S-HMAs with hexane and heating to a temperature ranging from about 30° C. to about 60° C. to produce a hexane extractant; cooling the hexane extractant to a temperature ranging from about 0° C. to about 10° C.; filtering the hexane extractant to form a first retentate and recovering the first retentate; combining the first retentate with hexane to form a hexane solution, heating the hexane solution to a temperature ranging from about 30° C. to about 40° C. to produce a suspension; and filtering the suspension to form a second retentate and recovering the second retentate, wherein the R,S-HMA is present in the second retentate.

For instance, a crude reaction mixture, consisting of 50–90% R,S-HMA, 10–50% S,S-HMA and 0–10% Me-ester, was extracted with hot hexane and the resulting hexane extractant was cooled to 10° C. and filtered to provide about 94% pure R,S-HMA in 74% yield (based on HMK); the major contaminant was S,S-HMA (5%). Attempts to purify the 94% pure material by differential solubility (above treatment) or by recrystallization from a variety of solvent/solvent mixtures were not completely successful. However, it has been determined that the best
way to purify the 94% pure R,S-HMA is to dissolve it in hot hexane (about 60° C.), cool to about 40° C., and then allowing the mixture to crystallize at about 35° C. to about 37° C. for at least 2 h. The crystallized product is then filtered at about 30° C. to about 35° C. to provide about 99.5% pure R,S-HMA in 83% recovery. Interestingly, it has been found that if the mixture is cooled to 25° C. and filtered, a mixture consisting of about 94.5% R,S-HMA and 5.5% S,S-HMA, is obtained. This result is surprising because S,S-HMA is more crystalline and is not soluble in hexane, thus suggesting that S,S-HMA, not R,S-HMA, should be the first to crystallize. Although a variety of solvent/solvent mixtures, such as methanol, methanol/water, toluene, dibutyl ether, etc., have been used to purify 94% pure R,S-HMA, the highest degree of purity/recovery is obtained with the hot hexane method of the present invention.

Once prepared and purified, the R,S-HMA can be converted into an R,S-epoxide. As such, in another embodiment, the present invention provides a method for preparing an R,S-epoxide compound having the following general formula:

![Chemical Structure]

the method comprising: reducing a haloketone (HMK) compound having the following general formula:

![Chemical Structure]

with a non-coordinating reducing agent to form an R,S-haloalcohol (R,S-HMA) compound having the following general formula:

![Chemical Structure]

and contacting the R,S-HMA compound of Formula II with an alkali metal base to form the R,S-epoxide compound. It will be readily apparent to those of skill in the art that the foregoing discussions relating to R¹, R² and X¹ and their preferred embodiments are fully applicable to this method and, thus, will not be repeated. In a presently preferred embodiment, the non-coordination reducing agent is LiATBH and the reduction is carried out in diethyl ether. In another presently preferred embodiment, the alkali metal base is selected from the group consisting of NaOH, KOH, LiOH, NaOCH₃, NaOCH₂CH₃, and KOHBr. In a further preferred embodiment, KOH is the alkali metal base used. In another embodiment, calcium hydroxide can be used.

**B. THE INVERSION METHOD**

In one embodiment of the inversion method, R,S-epoxide is prepared by a four step process illustrated below. More particularly, in one embodiment of the inversion method, the present invention provides a method for preparing an R,S-epoxide having the following general formula:

![Chemical Structure]

the method comprising: (a) reducing a haloketone (HMK) compound having the following general formula:

![Chemical Structure]

with a reducing agent to form an S,S-haloalcohol (S,S-HMA) compound having the following general formula:

![Chemical Structure]

(b) contacting the S,S-HMA compound of Formula II with a member selected from the group consisting of arylsulfonyl halides and alkylsulfonyl halides in the presence of an amine to form an S,S-halomethyl sulfonyl (S,S-HMS) compound having the following general formula:

![Chemical Structure]

(c) contacting the S,S-HMS compound of Formula III with an acetate in the presence of a phase transfer catalyst and water to form an R,S-halomethyl acetate (R,S-HMAc) compound having the following general formula:

![Chemical Structure]

(d) contacting the R,S-HMAc compound of Formula IV with an alkali metal base to form the R,S-epoxide. It will be readily apparent to those of skill in the art that the foregoing discussions relating to R¹, R² and X¹ and their preferred embodiments are fully applicable to this method and, thus, will not be repeated. In the above formulas, R³ is a functional group including, but not limited to, arylsulfonyls and alkylsulfonyls. In a presently preferred embodiment, R³ is a member selected...
from the group consisting of a methylsulfonyl group (i.e., a mesyl group), a toluenesulfonyl group (i.e., a tosyl group), a trifluoromethanesulfonyl group (i.e., a triflate group) and a para-nitrobenzene sulfonyl group (i.e., a nosyl group). It will be readily apparent to those of skill in the art that other leaving groups can be used as R_3 in place of the arylsulfonyl and alkylsulfonyl groups. R_4, in the above formulae, is an acyl group derived from the acetic acid. In a presently preferred embodiment, R_4 is an acetyl group.

In the first step, i.e., step (a), a HMK is reduced with a reducing agent to form an S,S-HMA. In a preferred embodiment, the reducing agent is selected from the group consisting of sodium borohydride, lithium aluminum hydride and sodium cyanoborohydride. In another preferred embodiment, step (a) is carried out in a solvent. Suitable solvents include, but are not limited to, ethanol, methanol, isopropanol, THF, diethyl ether, etc. The reduction can be carried out at a temperature ranging from about from about 10°C to about 70°C. In a presently preferred embodiment, the reduction step is carried out using sodium borohydride in ethanol to provide greater than 95% pure S,S-HMA in near quantitative yield. The S,S-isomer is highly crystalline and can be easily purified by recrystallization to provide >99.8% pure S,S-HMA in 80% yield.

In the second step, i.e., step (b), an S,S-HMA is reacted with an arylsulfonyl halide or an alkylsulfonyl halide in the presence of triethylamine to provide greater than 95% pure S,S-CMA Mesylate in near quantitative yield. Presumably, under these conditions, the reduction occurs under chelation control and a mixture of S,S-HMA:S,S-HMAr:S,S-HMAc with ratios as high as 20:1 is obtained (see, U.S. Pat. Nos. 5,684,176 and 5,847,144, both of which issued to Hilpert).

In a particularly preferred embodiment of step (b), the S,S-HMA is reacted with an arylsulfonyl halide or an alkylsulfonyl halide in the presence of an equivalent amount of triethylamine to give the corresponding 2S,3S-CMA Mesylate in 98% yield. The reaction is exothermic and is best conducted at a temperature ranging from from about 30°C to about 100°C to provide greater than 95% pure S,S-CMA Mesylate in near quantitative yield. However, in the preferred process, S,S-CMA Mesylate is not isolated and the solution of crude S,S-CMA mesylate in toluene is used, without purification, in the next step, i.e., step (c). Although this mesylation step can be conducted in a variety of solvents, toluene is the preferred solvent because it can be used in the next step, thereby eliminating a solvent exchange step from the process.

In the third step, i.e., step (c), the S,S-HMS is reacted with an acetate in the presence of a phase transfer catalyst and water to from a HMAc. Suitable acetates for use in the present method include, but are not limited to, the following: cesium acetate, potassium acetate, tetrabutylammonium acetate and sodium acetate. In a presently preferred embodiment, the acetate is cesium acetate. A variety of phase transfer catalysts (PTCs) can be used in carrying out step (c). Exemplar phase transfer catalysts include, but are not limited to, crown ethers (e.g., 18-crown-6, dibenzo crown ether, etc.), quaternary ammonium salts and quaternary phosphonium salts (e.g., tetrabutylammonium bromide (TBAB), alaq. 336, etc.). In a presently preferred embodiment, the phase transfer catalyst is a crown ether. The crown ether 18-crown-6 is particularly preferred because it allows for the production of R,S-HMAc with least amount of side product. Moreover, the rate of reaction with 18-crown-6 is much faster than with any of the other phase transfer catalysts. In addition, 18-crown-6 can be easily removed from the product by a simple water wash.

In a particularly preferred embodiment, toluene is used as the solvent because it can be used for both steps (b) and (c), and it can be used as a crystallization solvent for the R,S-HMAc. In addition, toluene is commercially available from a variety of sources and can be recycled in high efficiency. The displacement reaction, i.e., step (c) can be carried out at a temperature ranging from about 20°C to about 100°C. In a presently preferred embodiment, the displacement reaction is carried out at a temperature ranging from about 20°C to about 100°C.

In addition to the foregoing, HMA can also be prepared by Merwin Pondroff Verley reduction of HMK. In this process, HMK is reacted with aluminum isopropoxide in refluxing isopropyl alcohol (IPA) to give S,S-CMA in high diastereoselectivity. Presumably, under these conditions, the reduction occurs under chelation control and a mixture of S,S-HMA:R,S-HMA with ratios as high as 20:1 is obtained (see, U.S. Pat. Nos. 5,684,176 and 5,847,144, both of which issued to Hilpert).
the method comprising: (a) contacting an S,S-halomethyl sulfonyl (S,S-HMS) compound having the following general formula:

\[
\text{R}^1 \text{R}^2 \backslash \text{O}^3 \text{R}^4
\]

and (b) contacting the cyclic carbamate with an alkali metal base to form the R,S-epoxide.

As with the previously described methods, step (a) can be carried out in a variety of solvents, such as hydrocarbons (e.g., hexane, heptane, etc.), aromatic hydrocarbons (e.g., toluene, xylene, benzene, etc.) and chlorinated solvents (e.g., \( \text{CCl}_4 \), dichloroethane, chlorotoluenes, etc.). In a preferred embodiment, the solvent is toluene. In step (b) of the above method, the cyclic carbamate is reacted with an alkali metal base to form the R,S-epoxide. In a presently preferred embodiment, the alkali metal base is selected from the group consisting of \( \text{NaOH} \), \( \text{KOH} \), \( \text{LiOH} \), \( \text{NaOCH}_3 \), \( \text{NaOCH}_2 \text{CH}_3 \) and \( \text{KOH} \). In another preferred embodiment, step (b) is carried out in a solvent. Suitable solvents include, but are not limited to, hydrocarbons, aromatic hydrocarbons, chlorinated solvents and ethers (e.g., THF). In a presently preferred embodiment, the solvent is a mixture of THF and ethanol.

In connection with the above method, the present invention provides a cyclic carbamate compound having the following general formula:

\[
\text{R}^1 \text{R}^2 \backslash \text{O}^3 \text{R}^4
\]

Using this method of the present invention, greater than 99.5% pure R,S-epoxide can be prepared in 95–97% yields. The R,S-epoxide prepared by this process can be characterized by NMR, HPLC, TLC and differential scanning calorimetry (DSC). Moreover, despite difficulties encountered in the prior art relating to the purification of the R,S-epoxide, it has now been discovered that the R,S-epoxide can be purified by recrystallization from petroleum ether. This is an important discovery because traditional purification techniques, such as chromatography, are not applicable due to instability of the R,S-epoxide towards silica gel and alumina. As such, in a preferred embodiment, the above method further comprises: purifying the R,S-epoxide by recrystallization with petroleum ether. An exemplar embodiment of the above method is illustrated by the following reaction scheme:

**Preparation of the R,S-Epoxide Using One Embodiment of the Inversion Method**

In another embodiment of the inversion method, the present invention provides a method for preparing an R,S-epoxide compound having the following general formula:

\[
\text{R}^1 \text{R}^2 \backslash \text{O}^3 \text{R}^4
\]

In the above formula, \( \text{R}^1 \) is an amino acid side chain (e.g., benzyl); \( \text{R}^2 \) is hydrogen or a blocking/protecting group (e.g., butyloxycarbonyl (Boc), methoxycarbonyl (Moc), benzylloxycarbonyl (Cbz), etc.); and \( \text{X}^1 \) is a leaving group (e.g., a bromomethylalcohol was dehalohydroxylated to give the olefin (i.e., the compound of Formula V) by zinc metal...
In another embodiment, the present invention provides a method for preparing an alkene having the following general formula:

\[
\begin{align*}
&\text{R}\text{CH} \quad \text{H} \\
&\text{R}\text{C} = \text{O} \\
&\text{OH} \\
&\text{H} \\
&\text{N}\text{H}_2
\end{align*}
\]

the method comprising: (a) contacting a compound having the following general formula:

\[
\begin{align*}
&\text{R}\text{CH} \quad \text{H} \\
&\text{R}\text{C} = \text{O} \\
&\text{N}_2 + \\
&\text{R}\text{H}_2 \text{N}
\end{align*}
\]

with a hydrohalo acid to form a compound having the following general formula:

\[
\begin{align*}
&\text{R}\text{CH} \quad \text{H} \\
&\text{R}\text{C} = \text{O} \\
&\text{OH} \\
&\text{H} \\
&\text{N}\text{H}_2
\end{align*}
\]

(b) reducing a compound of Formula II with a reducing agent to form a compound having the following general formula:

\[
\begin{align*}
&\text{R}\text{CH} \quad \text{H} \\
&\text{R}\text{C} = \text{O} \\
&\text{N}\text{H}_2 \\
&\text{BMK}
\end{align*}
\]

and (c) dehalohydroxylating a compound of Formula III to form the alkene. It will be readily apparent to those of skill in the art that the foregoing discussions relating to R, R, and X and their preferred embodiments are fully applicable to this method and, thus, will not be repeated.

In step (a), a compound of Formula I is reacted with a hydrohalo acid to form a compound of Formula II. Suitable hydrohalo acids include, but are not limited to, hydrobromic acid, hydrochloric acid and hydroiodic acid. In a presently preferred embodiment, the hydrohalo acid is hydrobromic acid or hydrochloric acid. Step (b) can be carried out using any of a variety of reducing agents. In a presently preferred embodiment, sodium borohydride is the reducing agent employed in step (b). Finally, in step (c), compound III is dehalohydroxylated to form the desired alkene. Suitable dehalohydroxylating compounds include, but are not limited to, zinc (0) metals (e.g., zinc dust), nickel metals, zinc mercury amalgan, etc. Step (c) can be carried out in a number of different solvents. Suitable solvents include, but are not limited to, methanol, ethanol, isopropanol, THF, MTBE, toluene, etc. In a presently preferred embodiment, zinc dust in ethanol is used in step (c).

Once prepared, the alkene can be converted to the R,S-epoxide using, for example, m-chloroperbenzoic acid as illustrated below.

In one particularly preferred embodiment of this method, reaction of the diazoketone (i.e., the compound of Formula I), which is prepared from phenylalanine using diazo methane, with hydrobromic acid gives the bromoketone (i.e., the compound of Formula II) in 77% yield. Reduction of the bromoketone with sodium borohydride under conditions similar to those used for the chloroketone gave high selectivity for the S,S-bromomethylalcohol (i.e., the compound of Formula III) over the R,S-diastereomer. The desired S,S-isomer was isolated in 85% yield after recrystallization (see, Parkes, et al., J. Org. Chem., 59:3656–3664 (1994)).

The bromomethylalcohol was dehalohydroxylated to give the olefin (i.e., the compound of Formula V) by zinc metal in ethanol. Upon work up, the tert-butyloxycarbonyl (t-BOC) protected S-3-amino-4-phenyl-1-butene was isolated in 77% yield. Using this method of the present invention, very pure material was prepared without the problems of racemization associated with the reaction of the t-BOC protected S-phenylalanal route. The alkene was converted to the R,S-epoxide using, for example, a published route using m-chloroperbenzoic acid. An exemplar embodiment of the above method is illustrated by the following reaction scheme:
The invention will be described in greater detail by way of specific examples. The following examples are offered for illustrative purposes, and are not intended to limit the invention in any manner. Those of skill in the art will readily recognize a variety of noncritical parameters that can be changed or modified to yield essentially the same results.

EXAMPLES

A. Example I

This example illustrates the preparation of S,S-CMA and R,S-CMA using the reduction methods of the present invention.

1. Preparation of S,S-CMA by Reduction

A 500 mL, 3-necked round bottom flask was fitted with a condenser, thermocouple temperature probe, dry nitrogen inlet, and magnetic stirring. A stirred solution of chloromethylketone (CMK) (19.22 g, 0.0645 mol) and Isopropanol (200 mL) was heated to 50° C. and aluminum isopropoxide (6.87 g, 0.0337 mol, 1.5 eq) was charged to the reactor. The reaction mixture was heated at 50° C. for three hours at which point HPLC analysis indicated 0.4% CMK remained. After heating for 1 additional hour and cooling to room temperature, the reaction was quenched with water (200 mL) and glacial acetic acid (~50 mL) to adjust the pH to 4. The reaction was transferred to a separatory funnel and the organic solids were extracted into ethyl acetate, resulting in two clear phases. The phases were split and the organic phase was evaporated to 18.63 g (97% yield) off-white solid.

S,S-Chloromethylalcohol (S,S-CMA): 1H NMR (CDCl3): δ 1.37 (s, 9H), 2.97 (m, 2H, J=5.1 Hz), 3.20 (br d, 1H), 3.55–3.69 (m, 2H), 3.83–3.93 (m, 2H), 4.59 (br d, 1H, J=6.6 Hz), 7.21–7.34 (m, 5H). HPLC (Short) tR 3.55–3.69 (m, 2H, J=5.1 Hz), 3.20 (br d, 1H), 3.55–3.69 (m, 2H), 3.83–3.93 (m, 2H), 4.59 (br d, 1H, J=6.6 Hz), 7.21–7.34 (m, 5H), HPLC (Long) tR 13.26 min=99.50%, 17.42 min=0.50%.

Proton NMR analysis of final product indicated 37:1 ratio of S,S:R,S Boc-phenylalanine Chloromethylalcohol (CMA), and traces of acetic acid. HPLC analysis indicated 32:1 ratio of S,S:R,S CMA (95.1% S,S CMA, 3.0% R,S CMA, 0.6% CMK, and 1.3% impurities from the starting material e.g. methyl ester, boc-phenylalanine). Further purification was accomplished by recrystallization from heptane.

2. Sodium Cyanoborohydride Reduction of CMK

To a solution of sodium cyanoborohydride (5.28 g, 84.0 mmol, 1.0 eq) in THF (25 mL) was added a solution of CMK (25.0 g, 0.672 mol) in THF (716 g) was added over 90 min maintaining an internal temperature of less than 5° C. After the addition was complete, the mixture was stirred for 30 min at which point HPLC analysis indicated no starting material remaining. The reaction was slowly quenched with water (1000 mL) and then acetylated with glacial acetic acid (1000 mL) at a rate such the temperature was below 10° C. The reaction was warmed to ambient and the organic phase was separated, washed with water and was evaporated in vacuo to give 175 g (96% yield) of a white solid.

Lithium tri-t-butoxylaminohydride (LATBH) (93.87 g, 0.369 mol, 1.1 eq) and anhydrous diethyl ether (500 mL) were placed in a reactor and cooled to 2° C. A solution of CMK (99.84 g, 0.355 mol) and anhydrous diethyl ether (2000 mL) was added over 90 min maintaining an internal temperature of less than 5° C. After the addition was complete, the mixture was stirred for 30 min at which point HPLC analysis indicated no starting material remaining. The reaction was slowly quenched with water (1500 mL) and then acetylated with glacial acetic acid (1000 mL) at a rate such the temperature was below 10° C. The reaction was warmed to ambient and the organic phase was separated, washed with water and was evaporated in vacuo to give an orange oil (100.12 g). Hexanes (500 mL) was added to the flask and evaporated on the rotary evaporator to remove residual t-butanol and isobutanol; the evaporation yielded an orange oil/solid (97.34 g, 97% yield).

HPLC and 1H NMR analysis indicated approximately 65:1 ratio of R,S:SS CMA. The R,S-isomers was purified by extraction into refluxing hexanes (300 mL), filtration while hot to remove the less soluble S,S-isomer, and slow cooling overnight. After filtration and drying, 74.5 g (62.3% yield) of a product that was 92.1% R,S CMA and 5.4% S,S CMA by HPLC and 1H NMR analysis.
5. Purification of Mixtures of S,S- and R,S-CMA

CMA (170 g of a mixture of 0.6 to 1 isomers) and hexanes (800 g) were charged to the flask and heated to reflux for 1 hour. The less soluble isomer mix (90% S,S-CMA, 9% R,S-CMA) (99.6 g, 58% yield) was removed by filtration of the hot mixture. The filtrate was evaporated to 75% volume, cooled and filtered to give the more soluble isomer mix (94% R,S CMA, 3% S,S CMA) 36.7 g (22% yield) were removed by cold filtration through a 600 mL coarse, sintered glass funnel. The residual filtrate was dried in vacuo to give a yellow oil (18.6 g, 11% yield) containing a mixture of isomers.

A mixture of 32 g of the crude solid (93% R,S-CMA and 6% S,S-CMA) from the hot hexane recrystallization and hexanes (600 mL) was heated to 60°C. The resulting solution was slowly allowed to cool to 33°C and seeded with R,S-CMA crystals. Further crystallization was observed at 37°C at which point significant amount of white needles had formed in solution. The internal temperature was allowed to range between 35-40°C for 1.5 h, at which point the mixture was hot filtered to provide 25.7 g (80% recovery) of R,S-CMA as white needles. HPLC analyses revealed that R,S-CMA was 99.8% pure and contained ca. 0.2% S,S-CMA. Concentration of hexane filtrate on a rotary evaporator afforded 6.1 g of a white solid which based on HPLC analysis was found to be consist of 99.1% R,S-CMA and 0.4% S,S-CMA.

R,S-Chloromethylalcohol (R,S-CAL4): 1H NMR (CDCl3): δ 1.36 (s, 9H), 2.54 (m, 2H, J=7.3 Hz), 3.54 (d, 2H, J=4.6 Hz), 3.77 (m, 1H, J=2.1 Hz), 3.94 (m, 1H, J=7.3 Hz), 4.99 (d, 1H, J=8.8 Hz), 7.24 (br m, 5H); HPLC (Short) tR 3.87 min=0.21 %, 4.69 min=99.79%.

B. Example II

This example illustrates the preparation of R,S-Epoxide using two different inversion methods. In NMR: Varian 300 MHz; HPLC: Hewlett Packard 1100, column C18 reverse phase using acetonitrile/water with phosphate buffer; melting points were measured by DSC.

1. Preparation of R,S-Epoxide by the Inversion

Route Via An Acetate

a. Step 1: Mesylation A 3 L jacketed reactor equipped with a mechanical stirrer, addition funnel, reflux condenser, temperature probe, and a nitrogen gas inlet was charged with S,S-CMA (150.3 g, 0.501 mol) and toluene (1.5 L). The system was flushed with nitrogen and triethylamine (62 g, 0.613 mol) was added. The resulting mixture was treated, dropwise, with methanesulfonyl chloride (69 g, 0.595 mol). The rate of addition of methanesulfonyl chloride was maintained so as to control the reaction temperature below 50°C. When the addition was complete, the reaction mixture was stirred for 1 h, sampled and analyzed by HPLC which indicated that the reaction was complete. The reaction mixture was slowly quenched into 35-40°C aqueous potassium bicarbonate solution, and the organic phase was separated and washed with water. The organic layer containing the mesylate derivative was then dried azeotropically and used without isolation in the displacement reaction. In order to obtain yield/purity data, a sample of reaction mixture was withdrawn and stripped off solvent under reduced pressure to give S,S-CMA mesylate, a pale yellow solid: mp 117-121°C; 1H NMR (CDCl3): δ 1.35 (s, 9H), 2.79 (br t, 1H, J=1.1 Hz), 3.04 (dd, 1H, J=14.4,4.8 Hz), 3.17 (s, 3H), 3.73 (m, 2H, J=4.5 Hz), 4.15 (ddd, 1H, J=5.1, 4.8, 3.6 Hz) 4.69 (br d, 1H, J=6.6 Hz), 5.04 (br s, 1H), 7.20-7.24 (m, 5H); HPLC revealed that the product was 99.7% (area %) pure.

b. Step 2: Displacement

A second reactor was charged with cesium acetate (241.7 g, 1.125 mol) and 18-crown-6 (33 g, 0.125 mol) in toluene (400 mL) and the mixture was heated to 70°C. Next, a solution of S,S-CMA mesylate in toluene was added over 1 h and the resulting mixture was heated at 70°C for an additional 9 hrs at which time TLC analysis indicated the reaction was complete. The reactor was cooled to 35°C, and water (1 L) was added. The organic layer was separated and washed with water and the solvent was evaporated until the concentration of the product was 20% by weight as determined by 1H NMR analysis. Heptane (1350 g) was added and the mixture heated to 55°C. For 30 min, and cooled to ambient over 1 h. The mixture was then cooled to 15°C, filtered, and the white solid was dried in vacuo to give 131.5 g (77% yield) of (2R,3S)-N-butoxycarbonyl-1-chloro-2-acetoxy-4-phenylbutanamine, a white solid: mp 105-106°C; 1H NMR (CDCl3): δ 1.39 (s, 9H), 2.13 (s, 3H), 2.75 (br d, 2H, J=7.5 Hz), 3.56 (br d, 2H, J=6.3 Hz), 4.24 (dd, 2H, J=7.4, 2.2 Hz), 4.52 and 4.67 (both br d, 1H, J=1.5 Hz), 5.03-5.12 (m, 1H, J=6, 2.1 Hz), 7.17-7.33 (m, 5H); TLC (silica gel, 30% EtOAc/Hexane) Rr 0.75%; HPLC analysis revealed that the product was 99.7% pure.

c. Step 3: Hydrolysis and Ring Closure

A 1 L flask fitted with a mechanical stirrer, addition funnel, temperature probe, and a nitrogen inlet was charged with R,S-CMA Acetate (34.3 g, 0.104 mmol), THF (156 mL), ethanol (90 mL) and water (30 mL). The mixture was cooled to 0-3°C and a 43% aq. KOH solution (13.3 g of 86% potassium hydroxide dissolved in 13.3 mL of water) was added dropwise to the reaction mixture so as to maintain an internal temperature of 5°C. The reaction mixture was stirred at 0-3°C for 1.5 h and then quenched with 6% aq. Na2SO4 filtered, and the white solid was dried in vacuo to give a yellow solid (18.6 g, 11% yield) containing a mixture of 2R,3S-Chloromethylacetate. Recrystallization of the crude product was warmed at 10% hexane and the residue was dissolved in ethyl acetate (1.2 L) and the precipitated solid was collected by filtration and dried under reduced pressure to provide 25.4 g (96%) of the title compound, a white solid: mp (DSC): 51.56°C; 1H NMR (CDCl3): δ 1.39 (s, 9H), 2.59 (s, 1H), 2.70 (dd, 1H, J=3.9 Hz), 2.91 (m, 2H, J=6.0 Hz), 3.01 (m, 1H, J=3.6 Hz), 4.13 (d, 1H, J=7.8 Hz), 4.49 (d, 1H, J=7.2 Hz), 7.27 (br m, 5H). The purity, as determined by HPLC analysis, was 99.5%.
d. Alternate Process for Preparation of 2R,3S-Chloromethylacetate

A 4 L jacketed reactor equipped with a mechanical stirrer, reflux condenser, temperature probe, and a nitrogen gas inlet was charged with S,S-CMA Mesylate (246.5 g, 0.65 mol) and 18-crown-6 (43.4 g, 0.16 mol), cesium acetate (322.8 g, 1.685.7 mol) and toluene (3.2 L). The resulting mixture was heated to 72°C for 11 hours, at which point TLC analysis (silica gel, 30% EtOAc/Hexane) indicated the starting material had been consumed. The organic phase was separated and concentrated under reduced pressure to provide a white solid. The residue was dissolved in ethyl acetate (1.2 L) and the resulting solution was washed with H2O (2×550 mL), dried (Na2SO4), filtered, and stripped off solvent under reduced pressure to give a clear oil. Hexane (130 mL) was added and the resulting mixture was concentrated on a rotary evaporator till <10% hexane remained and the residue was seeded with crystals of pure R,S-Epoxide. The mixture was then stored at room temperature for 16 h and the precipitated solid was collected by filtration and dried under reduced pressure to provide 25.4 g (96%) of the title compound, a white solid: mp (DSC): 51.56°C; 1H NMR (CDCl3): δ 1.39 (s, 9H), 2.59 (s, 1H), 2.70 (dd, 1H, J=3.9 Hz), 2.91 (m, 2H, J=6.0 Hz), 3.01 (m, 1H, J=3.6 Hz), 4.13 (d, 1H, J=7.8 Hz), 4.49 (d, 1H, J=7.2 Hz), 7.27 (br m, 5H). The purity, as determined by HPLC analysis, was 99.5%.
on rotary evaporator, treated with water, and chilled to 5°C. to provide an additional 22 g of 98.2% pure product, thus increasing the total yield of R,S-CMA Acetate to 76%.

2. Preparation of R,S-Epoxide by the Inversion Route Via Trichloroacetic Acid

a. Step 1: Preparation of 'Cyclic Carbamate'

A 250 mL round-bottom flask equipped with a magnetic stir bar, reflux condenser, temperature probe, and a nitrogen gas inlet was charged with 9.98 g (26.4 mmol) of S,S-chloromethyl mesylates (CMMs), 0.434 g (1.35 mmol) of tetrabutylammonium bromide (TBAB), 7.46 g (40.2 mmol) of sodium trichloroacetate, and washed vigorously with N₂. Toluene (104 mL, 90 g) was added under a steady stream of N₂ and the resulting slurry was heated to ~45°C. The reaction mixture was stirred at 45°C overnight, at which point TLC analysis (silica gel, 30% EtOAc:Hexane) indicated the starting material had been consumed. The toluene phase was transferred from the reaction vessel into a 500 mL separatory funnel and EtOAc:H2O (50 mL/100 mL) used to rinse the reactor, was combined with the organic layer. After separating the two layers, the organic layer was washed with H₂O (1x100 mL), dried over Na₂SO₄, filtered, and removed under vacuum. The resulting crude solid was dried in a vacuum oven (45°C) overnight to provide a yield of 92% (7.92 g, 24.3 mmol, ~90% pure).

This product was combined with the crude cyclic carbamate (1.67 g, 5.13 mmol) from a previous small scale synthesis (CP078-24) and crystallized from MeOH:H₂O as (due to solubility problems in desired eluent) and purified (~99.42% pure).

b. Step 2: Preparation of R,S-Epoxide

To a 50 mL round-bottom flask equipped with a magnetic stir bar, temperature probe, and a nitrogen gas inlet was added a 43% aqueous KOH solution (0.73 g soln., 5.82 mmol) and 1.0 g of H₂O. The contents of the flask were cooled to 0-3°C. with the aid of an ice-bath. A separate flask was charged with 5.07 (d, 1H, 1.5 Hz), 7.10-7.31 (br m, 5H).

The reaction mixture was stirred at 0-3°C for ~1 hour, at which point the reaction was quenched with addition of sodium trichloroacetate, and flushed vigorously with N₂. Toluene (104 mL, 90 g) was added under a steady stream of N₂ and the resulting slurry was heated to ~45°C. The reaction mixture was stirred at 45°C overnight, at which point TLC analysis (silica gel, 30% EtOAc:Hexane) indicated the starting material had been consumed. The reaction mixture was quenched with water (20 mL). The organic layer was separated and washed with 3x20 mL) until the pH of the final water wash was ~6. The organic layer was concentrated to ~1 mL, and the crude product was added to 43% aqueous KOH solution (0.73 g soln., 5.82 mmol) and 1.0 g of H₂O. The contents of the flask were cooled to 0-3°C. with the aid of an ice-bath. A separate flask was charged with 5.07 (d, 1H, 1.5 Hz), 7.10-7.31 (br m, 5H).

The reaction mixture was stirred at 0-3°C for ~1 hour, at which point the reaction was quenched by addition of sodium biphosphate solution (0.448 g Na₂HPO₄. 6.8 g H₂O). The reaction quench was conducted at such a rate as to keep the internal temperature <10°C. (Note: The reaction was analyzed for completion via TLC after a 30 min. post-stir and found to contain the desired epoxide.) The cloudy reaction mixture was diluted with 10 mL of Et₂O and the layers were separated. The clear organic layer was dried over Na₂SO₄, filtered, and the solvent was removed under vacuum to afford a clear oil (0.8 g).

The crude product was taken up in 20% EtOAc/hexanes (due to solubility problems in desired eluent) and purified via column chromatography (silica gel, 10% EtOAc/hexanes). RS-epoxide, as well as a small amount of a nonpolar impurity, were collected prior to running a gradient to 50% EtOAc/hexanes to collect the deblocked impurity. The two fractions were evaporated of solvent to obtain clear oils: RS-epoxide: 0.444 g (solidified under vacuum; HPLC: ~90%). The identity of the RS-epoxide was confirmed by 3H NMR, HPLC, and TLC.

2. Preparation of R,S-Epoxide by the Inversion Route Via Trichloroacetic Acid

a. Step 1: Preparation of 'Cyclic Carbamate'

A 250 mL round-bottom flask equipped with a magnetic stir bar, reflux condenser, temperature probe, and a nitrogen gas inlet was charged with 9.98 g (26.4 mmol) of S,S-chloromethyl mesylates (CMMs), 0.434 g (1.35 mmol) of tetrabutylammonium bromide (TBAB), 7.46 g (40.2 mmol) of sodium trichloroacetate, and washed vigorously with N₂. Toluene (104 mL, 90 g) was added under a steady stream of N₂ and the resulting slurry was heated to ~45°C. The reaction mixture was stirred at 45°C overnight, at which point TLC analysis (silica gel, 30% EtOAc:Hexane) indicated the starting material had been consumed. The reaction mixture was quenched with water (20 mL). The organic layer was separated and washed with 3x20 mL) until the pH of the final water wash was ~6. The organic layer was concentrated to ~1 mL, and the crude product was added to 43% aqueous KOH solution (0.73 g soln., 5.82 mmol) and 1.0 g of H₂O. The contents of the flask were cooled to 0-3°C. with the aid of an ice-bath. A separate flask was charged with 5.07 (d, 1H, 1.5 Hz), 7.10-7.31 (br m, 5H).

The reaction mixture was stirred at 0-3°C for ~1 hour, at which point the reaction was quenched by addition of sodium biphosphate solution (0.448 g Na₂HPO₄. 6.8 g H₂O). The reaction quench was conducted at such a rate as to keep the internal temperature <10°C. (Note: The reaction was analyzed for completion via TLC after a 30 min. post-stir and found to contain the desired epoxide.) The cloudy reaction mixture was diluted with 10 mL of Et₂O and the layers were separated. The clear organic layer was dried over Na₂SO₄, filtered, and the solvent was removed under vacuum to afford a clear oil (0.8 g).

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The reaction mixture was stirred at 0-3°C for ~1 hour, at which point the reaction was quenched by addition of sodium biphosphate solution (0.448 g Na₂HPO₄. 6.8 g H₂O). The reaction quench was conducted at such a rate as to keep the internal temperature <10°C. (Note: The reaction was analyzed for completion via TLC after a 30 min. post-stir and found to contain the desired epoxide.) The cloudy reaction mixture was diluted with 10 mL of Et₂O and the layers were separated. The clear organic layer was dried over Na₂SO₄, filtered, and the solvent was removed under vacuum to afford a clear oil (0.8 g).

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and the filtrate was concentrated in vacuo to give an oil. This oil was dissolved in ethyl acetate (100 mL) and washed with 2% aqueous acetic acid (50 mL). The organic layer was separated, dried (Na$_2$SO$_4$), filtered and evaporated to give 7.5 g of crude product, an oil; this oil solidified on standing at room temperature to give a white solid. The solid was dissolved in methylene chloride (50 mL) and the solution was filtered through 10 g of silica gel. Evaporation of the solvent gave 6.0 g (77% yield) of the desired olefin. HPLC analysis showed the olefin was >99% pure. BOC-alkene: $^1$H NMR (CDCl$_3$): δ 1.40 (s, 9H), 2.83 (br d, 2H, J=6.6 Hz), 4.43 (br s, 2H), 4.65 (br s, 2H), 5.06–5.13 (m, 2H, J=17.4, 10.5, 1.2 Hz), 5.8 (ddd, 2H, J=17.1, 10.5, 5.4 Hz), 7.20–7.31 (m, 5H); IR (thin film): ν 3359 (NH), 1686 (CO), 1645 (alkene); HPLC (Short) $t_R$ 3.87 min=0.65%, 4.01 min=0.04%, 4.69 min=0.19%, 8.58 min=99.12%; MS, m/e MH$^+$ 248.1661.

4. **R,S-Epoxide by Alkene Route**

A mixture of BOC-alkene (0.498 g, 2.02 mmol), meta-chloroperbenzoic acid (1.93 g, 8.1 mmol) and dichloromethane (22 mL) was stirred at ambient temperature for 3 h at which time HPLC analysis indicated the starting material had been consumed. The reaction mixture was quenched with aqueous 10% Na$_2$SO$_3$ (60 mL), and diluted with diethyl ether. The organic layer was washed with cold saturated Na$_2$CO$_3$ (60 mL), brine (60 mL), dried over Na$_2$SO$_4$, and the solvent evaporated to provide a clear oil that solidified on standing. A white solid (0.49 g, 1.86 mmol) was isolated in 92% yield and was shown to be a 5.2:1 mixture of R,S- and S,S-epoxide, respectively (HPLC, 96.5% pure combined). Analysis of the product mixture by proton NMR spectroscopy indicated an approximate 5.7:1 ratio of diastereomeric epoxides and no alkene starting material.

It is to be understood that the above description is intended to be illustrative and not restrictive. Many embodiments will be apparent to those of skill in the art upon reading the above description. The scope of the invention should, therefore, be determined not with reference to the above description, but should instead be determined with reference to the appended claims, along with the full scope of equivalents to which such claims are entitled. The disclosures of all articles and references, including patent applications and publications, are incorporated herein by reference for all purposes.

What is claimed is:

1. A method for preparing an R,S-epoxide compound having the following general formula:

   ![R,S-Epoxide](image)

   said method comprising:

   (a) reducing a halomethyl ketone (HMK) compound having the following general formula:

   ![HMK](image)

   with a non-chelating, bulky reducing agent to form an R,S-halomethyl alcohol (R,S-HMA) compound having the following general formula:

   ![R,S-HMA](image)

2. The method in accordance with claim 1, wherein R$^1$ is an amino acid side chain having a benzyl group; R$^2$ is a BOC blocking group; and X$^1$ is chloro or bromo.

3. The method in accordance with claim 1, wherein said non-chelating, bulky reducing agent is a member selected from the group consisting of lithium aluminum t-butoxyhydride (LATBH) and sodium tris-t-butoxyborohydride (STBH).

4. The method in accordance with claim 1, wherein the reduction is carried out in diethyl ether.

5. The method in accordance with claim 1, wherein said alkali metal base is a member selected from the group consisting of NaOH, KOH, LiOH, NaOCH$_3$, NaOCH$_2$CH$_3$ and KO$_t$Eu.

6. A method for preparing an R,S-epoxide compound having the following general formula:

   ![R,S-Epoxide](image)

   said method comprising:

   (a) reducing a halomethyl ketone (HMK) compound having the following general formula:

   ![HMK](image)

   with a reducing agent to form an S,S-halomethyl alcohol (S,S-HMA) compound having the following general formula:

   ![S,S-HMA](image)

(b) contacting said R,S-HMA compound of Formula II with an alkali metal base to form said R,S-epoxide compound;

   wherein:

   R$^1$ is an amino acid side chain;

   R$^2$ is a blocking group; and

   X$^1$ is a leaving group.

7. The method in accordance with claim 1, wherein said alkali metal base is a member selected from the group consisting of NaOH, KOH, LiOH, NaOCH$_3$, NaOCH$_2$CH$_3$ and KO$_t$Bu.

8. A method for preparing an R,S-epoxide compound having the following general formula:

   ![R,S-Epoxide](image)

   said method comprising:

   (a) reducing a halomethyl ketone (HMK) compound having the following general formula:

   ![HMK](image)

   with a reducing agent to form an S,S-halomethyl alcohol (S,S-HMA) compound having the following general formula:

   ![S,S-HMA](image)

(b) contacting said S,S-HMA compound of Formula II with a member selected from the group consisting of arylsulfonyl halides and alkylsulfonyl halides in the presence of an amine to form an S,S-halomethyl sulfonyl (S,S-HMS) compound having the following general formula:
17. The method in accordance with claim 6, wherein step (b) is carried out at a temperature ranging from about 10°C to about 70°C.

18. The method in accordance with claim 6, wherein said acetate is a member selected from the group consisting of cesium acetate, potassium acetate, tetrabutylammonium acetate and sodium acetate.

19. The method in accordance with claim 6, wherein step (c) is carried out at a temperature ranging from about 20°C to about 100°C.

20. The method in accordance with claim 6, wherein step (c) is carried out at a temperature ranging from about 65°C to about 75°C.

21. The method in accordance with claim 6, wherein step (c) is carried out in a solvent selected from the group consisting of hydrocarbons and chlorinated solvents.

22. The method in accordance with claim 6, wherein step (c) is carried out in toluene.

23. The method in accordance with claim 6, wherein said phase transfer catalyst is a member selected from the group consisting of crown ethers, quaternary ammonium salts and quaternary phosphonium salts.

24. The method in accordance with claim 6, wherein said phase transfer catalyst is a crown ether.

25. The method in accordance with claim 24, wherein said phase transfer catalyst is a crown ether.

26. The method in accordance with claim 6, wherein step (d) is carried out in a solvent selected from the group consisting of hydrocarbons and chlorinated solvents.

27. The method in accordance with claim 6, wherein step (d) is carried out in a solvent selected from the group consisting of hydrocarbons and chlorinated solvents.

28. The method in accordance with claim 6, wherein said solvent is a mixture of toluene and THE.

31. The method in accordance with claim 6, further comprising purifying said R,S-epoxide compound by recrystallization with petroleum ether.

32. The method in accordance with claim 1, wherein said non-chelating, bulky reducing agent is a member selected from the group consisting of (+)-Dip Chloride™, K-Selectride®, KS-Selectride®.

33. The method in accordance with claim 21, wherein said solvent is a hydrocarbon.

34. The method in accordance with claim 33, wherein said hydrocarbon is an aromatic hydrocarbon.

35. The method in accordance with claim 29, wherein said solvent is a hydrocarbon.

36. The method in accordance with claim 35, wherein said hydrocarbon is an aromatic hydrocarbon.