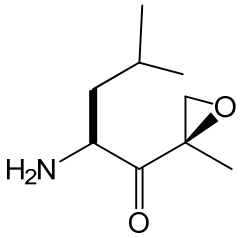
corresponding ketone. This process effectively reduces the ketone then re-oxidizes the same ketone. Thus, while the diastereoselectivity may be improved relative to *Sin*, this process is synthetically inefficient thereby increasing associated costs, time, waste generation and labor of production.

The process taught in WO2009045497 utilized bleach to accomplish the epoxidation reaction avoiding the inefficient reduction/oxidation cycle of the adjacent ketone. However, this epoxidation reaction results in about a 1:1 ratio of (*R*) and the (*S*) stereoisomers at the epoxide carbon. In addition, the oxidation reaction with bleach is an exothermic reaction to the extent of being a potential safety hazard, particularly when conducted on a larger, manufacturing scale. To this end, this process requires costly and time consuming chromatographic separation and re-crystallizations to isolate the desired stereoisomeric product, resulting in significant waste.

The process taught in *Wang* provides diastereoselective epoxidation reaction favoring the undesired epoxide stereochemistry. The desired epoxide diastereomer only accounts for 12% of the crude reaction mixture. Therefore, use of this process is overall low yielding, and would require a laborious column chromatography setp resulting in increased time and expense, as well as to the potential of having to dispose of additional chemical waste. To this end, the literature teaches epoxidation processes that are simply not very efficient and/or sub-optimal for large scale production of the commercial drug product carfilzomib. Therefore, there is a need to identify alternative synthetic methods, of increased efficiency and effectiveness, to prepare key intermediate 5 for the manufacture of carfilzomib.

SUMMARY

In one aspect, the present disclosure refers to a method of making compound 5

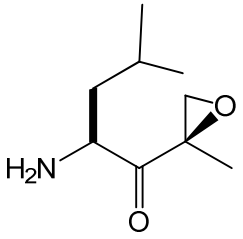


5

or a pharmaceutically acceptable salt thereof, the method comprising steps 1-5 according to scheme 1

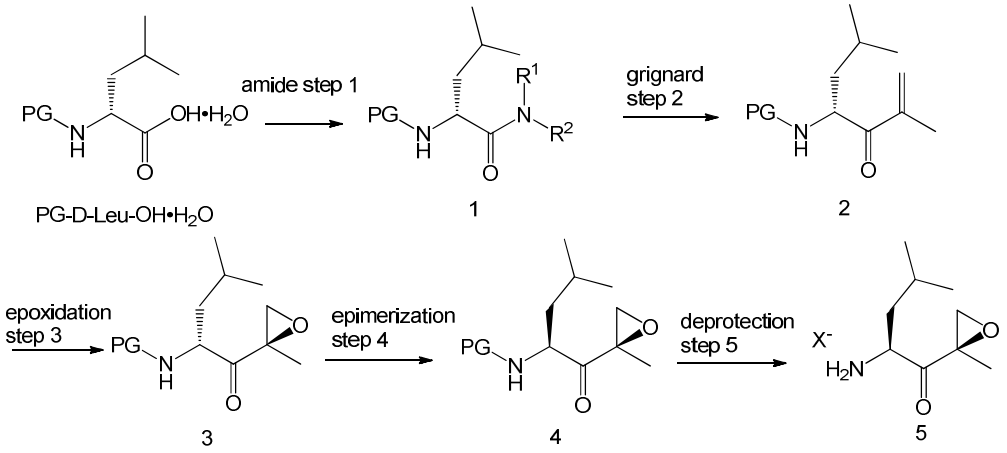
What is claimed is:

1. A method of making compound 5



5

or a pharmaceutically acceptable salt thereof, the method comprising steps 1-5 according to scheme 1



Scheme I

wherein

PG is a protecting group selected from t-butoxycarbonyl (Boc) and carboxybenzyl (cbz);

R^1 is CH_3 and R^2 is $–OCH_3$ or R^1 and R^2 taken together with the nitrogen atom to which they are attached form a morpholine ring;

X^- is absent or X^- is an addition salt anion selected from TFA, Cl, Br, I and mesylate;

the amide step 1 comprises use of an acid activating agent and a basic amine selected from $(CH_3)NH(OCH_3)$ and morpholine;

the Grignard step 2 comprises use of isopropyl magnesiumchloride, Mg and 2-bromopropene or isopropenylmagnesium bromide;

the epoxidation step 3 comprises use of an oxidizing agent and a manganese catalyst;

the epimerization step 4 comprises the use of a base; and
the deprotection step 5 comprises use of a catalyst or an acid.

2. The method of claim 1 wherein PG is boc.

3. The method of claim 1 wherein PG is carboxybenzyl.

4. The method of any one of claims 1, 2 and 3 wherein amide step 1 comprises use of morpholine and an acid activating agent selected from CDI, DCC, TBTU, HATU, PyBOP, TCTU, EDCI, pivaloyl chloride, isobutylchloroformate, propylphosphnic anhydride, triphenylphosphine and *N,N*-diisopropylcarbodiimide.

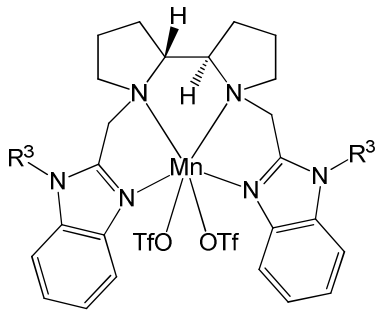
5. The method of any one of claims 1, 2, 3 and 4 wherein activating agent used in the amide step 1 is CDI.

6. The method of any one of claims 1 - 5 wherein the Grignard step 2 comprises use of isopropyl magnesiumchloride, Mg and 2-bromopropene.

7. The method of any one of claims 1 - 6 wherein the oxidizing agent used in the epoxidation step 3 is hydrogen peroxide, peracetic acid, t-BuOOH and PhIO.

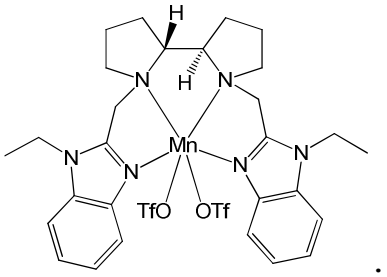
8. The method of any one of claims 1- 7 wherein the oxidizing agent used in the epoxidation step 3 is hydrogen peroxide.

9. The method of any one of claims 1 - 8 wherein manganese catalyst used in the epoxidation step 3 has a structure of



wherein each R^3, independently, is methyl or ethyl.

10. The method of any one of claims 1 - 9 wherein manganese catalyst used in the epoxidation step 3 has a structure of



.

11. The method of any one of claims 1 - 10 wherein the base used in the epimerization step 4 is selected from DBU, triazabicyclodecene (TBD), pyrrolidine, potassium carbonate and sodium hydroxide.

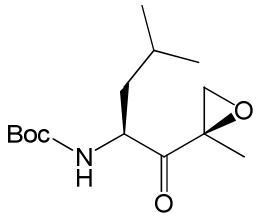
12. The method of any one of claims 1 - 11 wherein the base used in the epimerization step 4 is DBU.

13. The method of any one of claims 1 - 11 wherein the base used in the epimerization step 4 is TBD.

14. The method of any one of claims 1 - 13 further comprising a solvent swap involving a switch to an alcohol solvent or a basic solvent.

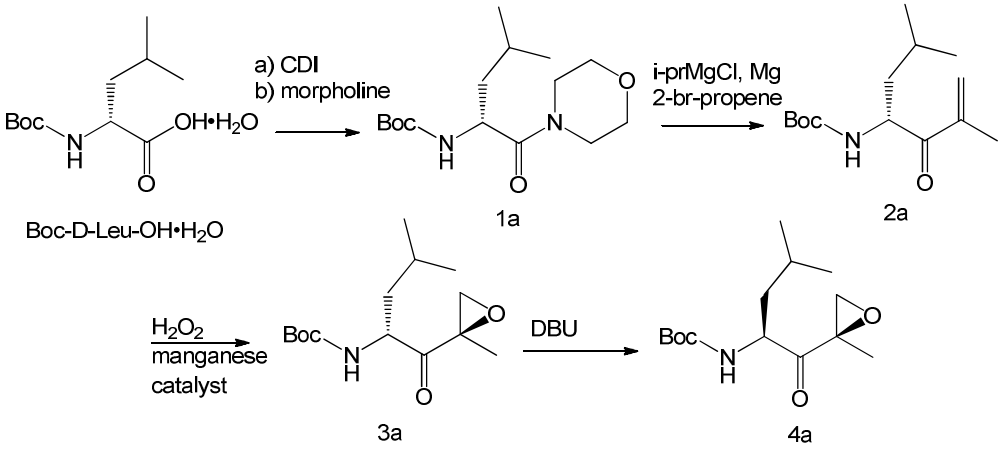
15. The method of any one of claims 1 - 13 further comprising a solvent swap involving a switch to methanol, isopropanol or N-methylpyrrolidinone.

16. A method of making compound 4a



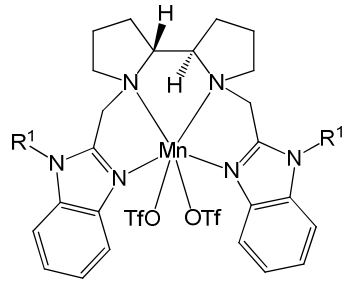
4a

the method comprising steps 1-4 according to scheme 1-a



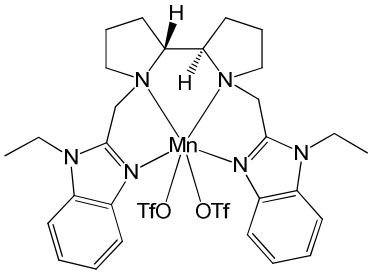
Scheme 1-a

wherein the manganese catalyst has a structure of



wherein R^1 is methyl or ethyl.

17. The method of claim 16 wherein manganese catalyst has a structure of



.

18. The method of any one of claims 16 and 17, wherein

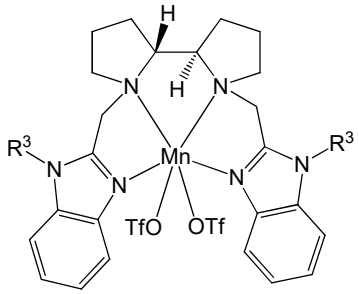
CDI is used in an amount ranging from 1.0 equivalents to 2.5 equivalents;

morpholine is used in an amount ranging from 1.2 equivalents to 2.0 equivalents;

2-bromopropene is used in an amount ranging from.5 equivalents to 3.5 equivalents;

hydrogen peroxide is used in an amount ranging from 1.5 equivalents to 3.0 equivalents;

the manganese catalyst has a structure of



wherein each R^3, independently, is methyl or ethyl, and used in an amount ranging from 0.0002 equivalents to 0.001 equivalents; and

triazabicyclodecene is used in an amount ranging from 0.01 to 0.1 equivalents.

19. The method of any one of claims 1-17 wherein the manganese catalyst is used in a amount ranging from 0.0001 to 0.002 molar equivalents to the moles of the starting material compound 2a.

20. The method of any one of claims 1-17 and 19 wherein the manganese catalyst is used in an amount ranging from 0.0002 to 0.001 molar equivalents to the moles of the starting material compound 2a.

.

21. The method of any one of claims 1-20 wherein the manganese catalyst is used in a amount of 0.001 molar equivalents to the moles of the starting material 2 or 2a.

22. The method of any one of claims 14-15 and 20-21 wherein the solvent swap comprises a switch from ACN to methanol between the Grignard step and the epoxidation step.

23. The method of any one of claims 1-13 and 16-22 further comprising a solvent swap involving a switch to methanol, isopropanol or N-methylpyrrolidinone.