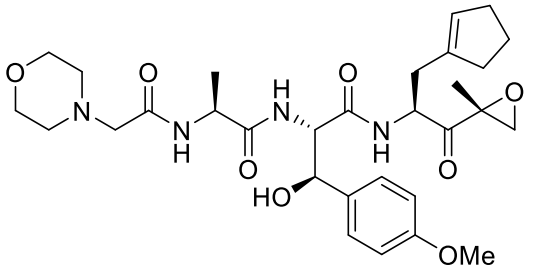
CLAIMS

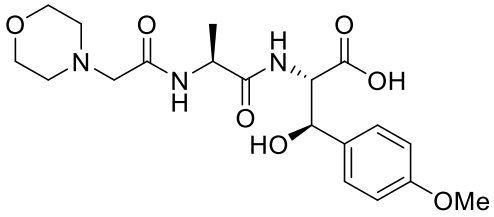
1. A method of preparing (2*S*,3*R*)-*N*-[(2S)-3-(cyclopent-1-en-1-yl)-1-[(2*R*)-2-methyloxiran-2-yl]-1-oxopropan-2-yl]-3-hydroxy-3-(4-methoxyphenyl)-2-[(2*S*)-2-[2-(morpholin-4-yl)acetamido]propanamido]propanamide (compound "G")



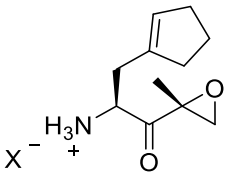
comprising:

(a) admixing a tertiary amine base and a suspension of:

(i) (2*S*,3*R*)-3-hydroxy-3-(4-methoxyphenyl)-2-((*S*)-2-(2-morpholino-acetamido)propanamido)propanoic acid (compound "E"):


(E), and

(ii) (*S*)-3-(cyclopent-1-en-1-yl)-1-((R)-2-methyloxiran-2-yl)-1-oxopropan-2-aminium salt (compound "F"):


(F), wherein X^- is a counterion;

in an aprotic solvent to form a mixture; and

(b) admixing a coupling agent and the mixture of step (a) to form compound G;

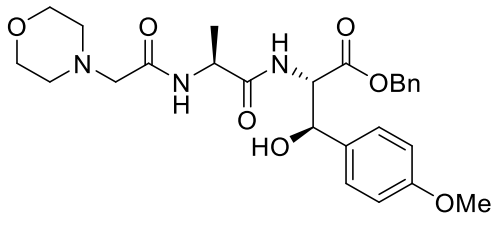
wherein the temperature of each admixing step is maintained at -20 °C to 5 °C.

2. The method of claim 1, wherein X^- is selected from the group consisting of tosylate, triflate, acetate, naphthalene sulfonate, 4-nitrobenzenesulfonate, sulfate, methylsulfate, nitrate, fluoride, chloride, bromide, and combinations thereof.

3. The method of any one of claims 1 to 2, wherein the aprotic solvent is selected from the group consisting of acetonitrile ("ACN"), dichloromethane ("DCM"), tetrahydrofuran ("THF"), dimethylacetamide ("DMAc"), ethyl acetate ("EtOAc"), isopropyl acetate ("iPrOAc"), dimethylformamide ("DMF"), and combinations thereof.

4. The method of any one of claims 1 to 3, wherein the tertiary amine base is selected from the group consisting of *N,N*-diisopropylethylamine ("DIPEA"), triethylamine ("TEA"), *N*-methylmorpholine ("NMM"), 2,2,6,6-tetramethylpiperidine ("TMP"), 2,4,6-trimethylpyridine ("collidine"), and combinations thereof.

5. The method of any one of claims 1 to 4, wherein compound E is prepared by admixing a reductant and benzyl (2*S*,3*R*)-3-hydroxy-3-(4-methoxyphenyl)-2-((S)-2-(2-morpholinoacetamido)propanamido)propanoate (compound "D")

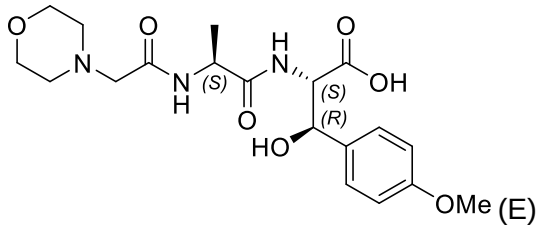


(D),

to form compound E.

6. The method of claim 5, wherein the reductant is selected from the group consisting of H_2, Pd/C; H_2, $Pd(OH)_2$/C; Li; Na; lithium 4,4′-di-tert-butylbiphenyl ("Li DTBBP"), and combinations thereof.

7. A crystalline form of (2*S*,3*R*)-3-hydroxy-3-(4-methoxyphenyl)-2-((*S*)-2-(2-morpholinoacetamido)propanamido)propanoic acid (compound "E"):



(E)

characterized by an X-ray powder diffraction pattern comprising peaks at 6.2, 8.5, 9.7, 12.7, 13.7, 16.0, 16.9 17.2, 18.4, 18.9, 19.2, 19.7, 22.5, 24.7, 25.4, 28.7, and 29.7 ± 0.2° 2θ using Cu Kα radiation.

8. The method of claim 1, wherein X^- is tosylate, the aprotic solvent comprises DCM, the tertiary amine base comprises DIPEA, or combinations thereof.

9. The method of claim 2, wherein X^- is is tosylate, naphthalene sulfonate, or 4-nitrobenzenesulfonate.

10. The method of any one of claims 1-4 and 8-9, wherein the molar ratio of the tertiary amine base to compound E is in a range of 1:1 to 4:1.

11. The method of any one of claims 1-4 and 8-10, wherein the coupling agent comprises a carbodiimide reagent, a phosphonium reagent, a uronium reagent, an immonium reagent, an imidazolium reagent, an organophosphorus reagent, an acid chloride reagent, a chloroformate reagent, or a pyridinium reagent.

12. The method of claim 11, wherein the uronium reagent is selected from the group 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate ("HATU"), O-(Benzotriazol-1-yl)-*N,N,N′,N′*-tetramethyluronium hexafluorophosphate ("HBTU"), and combinations thereof.

13. The method of any one of claims 1-4 and 8-12, wherein the molar ratio of coupling agent to compound E is 1 to 1.

14. The method of any one of claims 1-4 and 8-13, wherein the coupling reagent further comprises a coupling additive.

15. The method of claim 14, wherein the coupling additive is selected from the group consisting of a benzotriazole, a dicarboximide, a succinimide, and combinations thereof.

16. The method of any one of claims 1-4 and 8-15, wherein the temperature of each admixing step is maintained at -15 °C to 5 °C.

17. The method of any one of claims 1-4 and 8-16, wherein the admixing of step (a) comprises stirring the mixture for up to 10 minutes.

18. The method of claim 5 or 6, wherein the admixing of the reductant and compound D occurs under a nitrogen atmosphere.

19. The method of any one of claims 5-6 or 18, wherein the admixing of the reductant and compound D occurs for up to 4 hours.