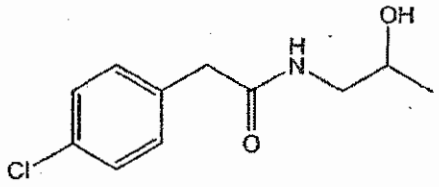
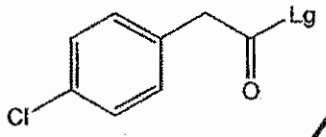
What is claimed is:

1. A process for preparing an amide compound of Formula 1-3:



1-3

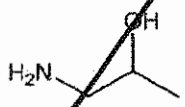
comprising reacting a phenylacetic acid derivative compound of Formula 1-1:



1-1

or salt thereof, wherein Lg is a leaving group,

with an amine compound of Formula 1-2:



1-2

or salt thereof, in the presence of a coupling reagent to afford said amide compound of Formula 1-3.

2. The process according to claim 1, wherein Lg is OH.

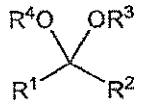
3. The process according to claim 1 or 2, wherein said coupling reagent comprises phenylboronic acid, boric acid, or mixture thereof.

4. The process according to claim 1 or 2, wherein said coupling reagent comprises 2,5,6-trifluorophenylboronic acid.

5. The process according to claim 1 or 2, wherein said coupling reagent comprises a boron-containing acid, a carbodiimide, or a ketal.

6. The process according to claim 5, wherein said carbodiimide is 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (EDC).

7. The process according to claim 5, wherein said ketal has the formula:



wherein R^1, R^2, R^3, and R^4 are C_{1-6} alkyl.

8. The process according to claim 7, wherein R^1, R^2, R^3, and R^4 are independently selected from methyl and ethyl.

9. The process according to claim 5, wherein said ketal comprises 2,2-dimethoxypropane.

10. The process according to any one claims 7 to 9, wherein said reacting is carried out in the presence of an acid catalyst.

11. The process according to any one claims 7 to 9, wherein said catalyst comprises a sulfonic acid.

12. The process according to any one claims 7 to 9, wherein said catalyst comprises an optionally substituted arylsulfonic acid.

13. The process according to any one claims 7 to 9, wherein said catalyst comprises *p*-toluenesulfonic acid.

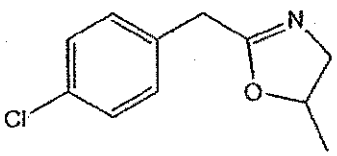
14. The process according to claim 1, wherein Lg is halo.

15. The process according to claim 1 or 14, wherein said coupling reagent comprises a base.

16. The process according to claim 15, wherein said base comprises a tri(C_{1-6})alkylamine.

17. The process according to claim 15, wherein said base is triethylamine.

18. The process according to claim 1, further yielding a dihydrooxazole compound of Formula 1-4:



or salt thereof.

19. The process according to any one of claims 1 to 18, wherein the molar ratio of said phenylacetic acid derivative compound of Formula 1-1 to said coupling reagent is about 1:1 to about 20:1.

20. The process according to any one of claims 1 to 18, wherein said reacting is carried out in the presence of a solvent.

21. The process according to claim 20, wherein said solvent is an aromatic solvent or an alcohol solvent.

22. The process according to claim 20, wherein said solvent comprises toluene.

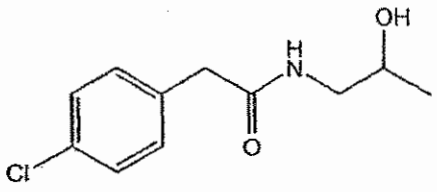
23. The process according to claim 20, wherein said solvent comprises methanol, ethanol, or isopropanol.

24. The process according to any one of claims 1 to 23, wherein said reacting is carried out at about room temperature.

25. The process according to any one of claims 1 to 23, wherein said reacting is carried out at elevated temperature.

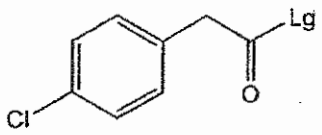
26. The process according to claim 25, wherein said elevated temperature is about 80 °C to about 140 °C.

27. A process for preparing an amide compound of Formula 1-3:



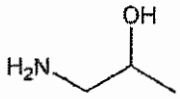
1-3

comprising reacting, in a solvent comprising toluene and at elevated temperature, a phenylacetic acid derivative compound of Formula 1-1:



1-1

or salt thereof, wherein Lg is OH, with an amine compound of Formula 1-2:



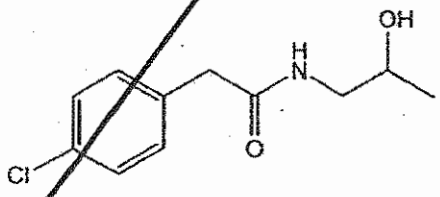
1-2

or salt thereof, in the presence of at least one boron-containing acid to afford said amide compound of Formula 1-3.

28. The process according to claim 27, wherein said reacting is carried out in the presence of phenylboronic acid, boric acid, or mixture thereof.

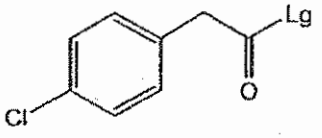
29. The process according to claim 27, wherein said reacting is carried out in the presence of 2,5,6-trifluorophenylboronic acid.

30. A process for preparing an amide compound of Formula 1-3:



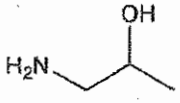
1-3

comprising reacting, in a solvent comprising isopropyl alcohol and at about room temperature, a phenylacetic acid derivative compound of Formula 1-1:



1-1

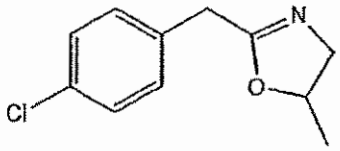
or salt thereof, wherein Lg is OH, with an amine compound of Formula 1-2:



1-2

or salt thereof, in the presence of 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride to afford said amide compound of Formula 1-3.

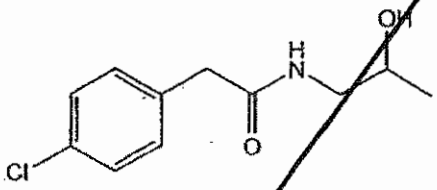
31. The process according to claim 30, further affording a dihydrooxazole compound of Formula 1-4:



1-4

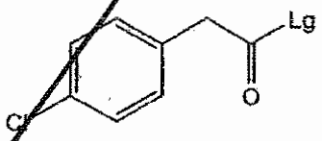
or salt thereof.

32. A process for preparing an amide compound of Formula 1-3:



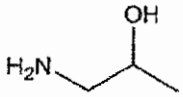
1-3

comprising reacting, in an alcohol solvent and optionally in the presence of an acid catalyst, a phenylacetic acid derivative compound of Formula 1-1:



1-1

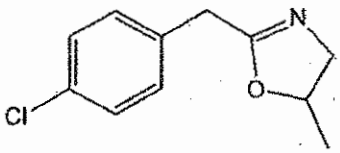
or salt thereof, wherein Lg is OH, with an amine compound of Formula 1-2:



1-2

or salt thereof, in the presence of 2,2-dimethoxypropane to afford said amide compound of Formula 1-3.

33. The process according to claim 32 further affording a dihydrooxazole compound of Formula 1-4:



1-4

or salt thereof.

34. The process according to claim 32 or 33 further comprising combining said 2,2-dimethoxypropane with said phenylacetic acid derivative compound of Formula 1-1 prior to said reacting with said amine compound of Formula 1-2, or salt thereof.

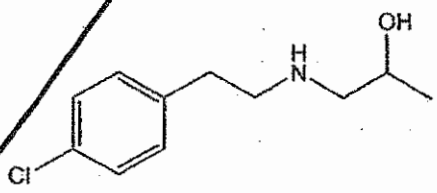
35. The process according to claim 34, wherein said combining affords 2-(4-chlorophenyl)acetic acid methyl ester.

36. The process according to claim 34, wherein said combining is carried out at elevated temperature.

37. The process according to claim 36, wherein said elevated temperature is about 60 °C to about 120 °C.

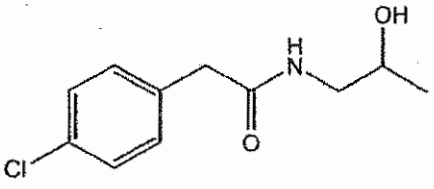
38. The process according to any one of claims 32 to 37, wherein conversion of said phenylacetic acid derivative compound of Formula 1-1 to said 2-(4-chlorophenyl)acetic acid methyl ester is about 90% or greater.

39. A process for preparing an amino alcohol compound of Formula 2-1:



2-1

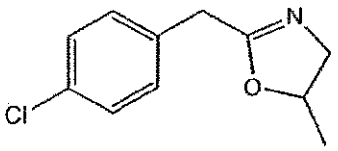
or salt thereof, comprising reacting an amide compound of Formula 1-3:



1-3

with a reducing agent to afford said amino alcohol compound of Formula 2-1, or salt thereof.

40. The process according to claim 39 further comprising reacting a dihydrooxazole compound of Formula 1-4:



1-4

or salt thereof, with said reducing agent.

41. The process according to claim 39 or 40, wherein said reducing agent comprises a borane, dialkylborane, alkali metal trialkylboron hydride, alkali metal aluminum hydride, alkali metal borohydride, alkali metal trialkoxyaluminum hydride, dialkylaluminum hydride, or H_2 optionally in the presence of a catalyst.

42. The process according to claim 39 or 40, wherein said reducing agent comprises BH_3.

43. The process according to claim 42, wherein said BH_3 is generated in situ.

44. The process according to claim 39 or 40, wherein said reducing agent comprises a borane tetrahydrofuran complex.

45. The process according to claim 39 or 40, wherein said reducing agent comprises a borane methylsulfide complex.

46. The process according to any one of claims 39 to 45, wherein said reducing agent is provided in molar excess relative to the amount of said amide compound of Formula 1-3.

47. The process according to any one of claims 39 to 45, wherein the molar ratio of said reducing agent to said amide compound of Formula 1-3 is about 1:1 to about 10:1.

48. The process according to any one of claims 39 to 45, wherein the molar ratio of said reducing agent to said amide compound of Formula 1-3 is about 1:1 to about 5:1.

49. The process according to any one of claims 39 to 45, wherein the molar ratio of said reducing agent to said amide compound of Formula 1-3 is about 3.5:1.

50. The process according to claim 39 or 40, wherein said reducing agent comprises $NaBH_4$ in the presence of iodine.

51. The process according to claim 50, wherein the molar ratio of $NaBH_4$ to iodine to said amide compound of Formula 1-3 is about 10:1:1.

52. The process according to claim 50, wherein the molar ratio of $NaBH_4$ to iodine to said amide compound of Formula 1-3 is about 5:1:1.

53. The process according to claim 50, wherein the molar ratio of $NaBH_4$ to iodine to said amide compound of Formula 1-3 is about 2.5:1:1.

54. The process according to any one of claims 39 to 53, wherein said reacting is carried out at elevated temperature.

55. The process of claim 54, wherein said elevated temperature is about 30 °C to about 80 °C.

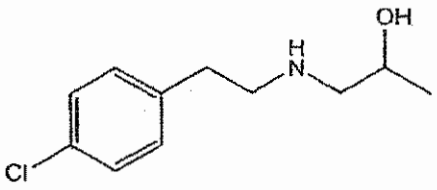
56. The process of claim 54, wherein said elevated temperature is about 40 °C to about 70 °C.

57. The process of claim 54, wherein said elevated temperature is about 50 °C to about 60 °C.

58. The process according to any one of claims 39 to 57, wherein conversion of said amide compound of Formula 1-3 to said amino alcohol compound of Formula 2-1, or salt thereof, is about 90% or greater.

59. The process according to any one of claims 39 to 58, wherein said amide compound of Formula 1-3 is prepared by the process of any one of claims 1-38.

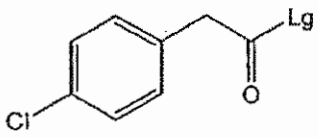
60. A process for preparing an amino alcohol compound of Formula 2-1:



2-1

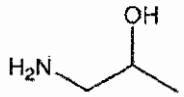
or salt thereof, comprising:

a) reacting a phenylacetic acid derivative compound of Formula 1-1:



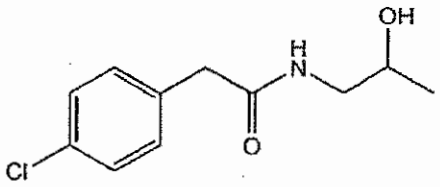
1-1

or salt thereof, wherein Lg is a leaving group, with an amine compound of Formula 1-2:

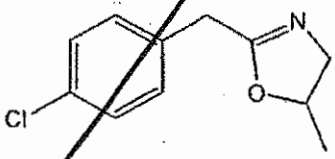


1-2

or salt thereof, in the presence of a coupling reagent to afford an amide compound of Formula 1-3 and optionally a dihydrooxazole compound of Formula 1-4, or salt thereof:



1-3

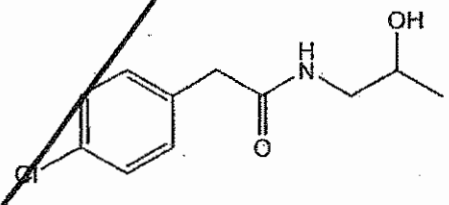


1-4

and

b) reacting said amide compound of Formula 1-3 and optionally said dihydrooxazole compound of Formula 1-4, or salt thereof, with a reducing agent to afford said amino alcohol compound of Formula 2-1, or salt thereof.

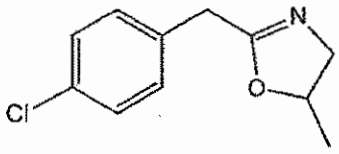
61. A compound of Formula 1-3:



1-3.

62. The compound of claim 61 that is substantially isolated.

63. A compound of Formula 1-4:



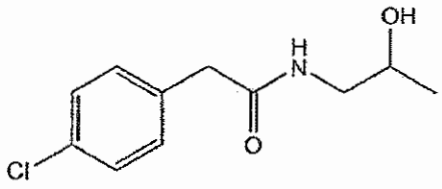
1-4

or salt thereof.

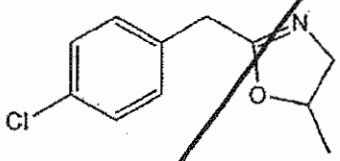
64. The compound of claim 63, or salt thereof, that is substantially isolated.

65. A composition comprising a compound of claim 61 or 63, or salt thereof.

66. A composition comprising a compound of Formula 1-3 and a compound of Formula 1-4, or salt thereof:

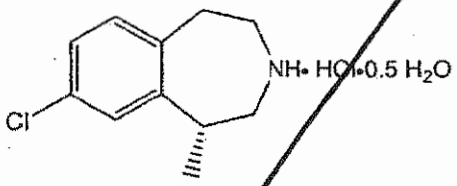


1-3



1-4.

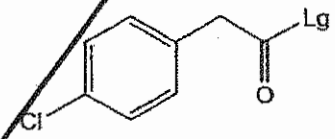
67. A process for preparing a compound of Formula 3-5:



3-5

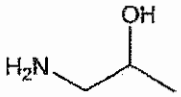
comprising:

a) reacting a phenylacetic acid derivative compound of Formula 1-1:



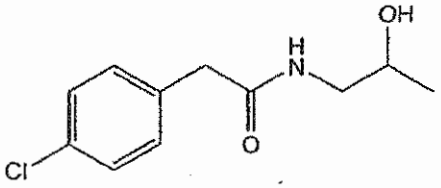
1-1

or salt thereof, wherein Lg is a leaving group, with an amine compound of Formula 1-2:

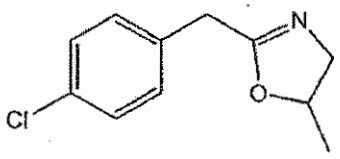


1-2

or salt thereof, in the presence of a coupling reagent to afford an amide compound of Formula 1-3 and optionally a dihydrooxazole compound of Formula 1-4, or salt thereof:

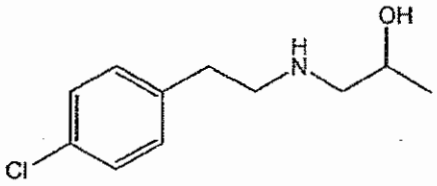


1-3



1-4

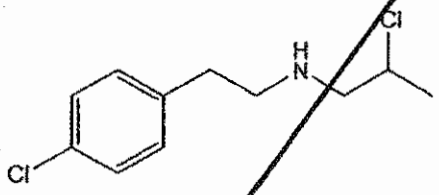
b) reacting said amide compound of Formula 1-3 and optionally said dihydrooxazole compound of Formula 1-4, or salt thereof, with a reducing agent to afford an amino alcohol compound of Formula 2-1:



2-1

or salt thereof;

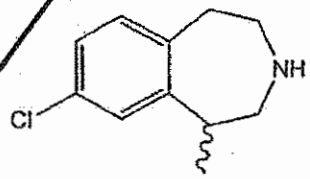
c) reacting said amino alcohol compound of Formula 2-1, or salt thereof, with a chlorinating reagent to afford a dichloro compound of Formula 3-1:



3-1

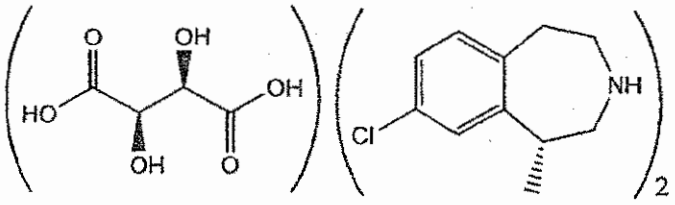
or salt thereof;

d) reacting said dichloro compound of Formula 3-1 with a cyclizing reagent to afford a 3-benzazepine compound of Formula 3-2:



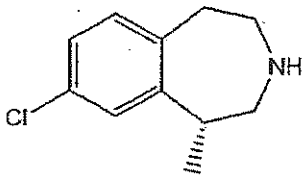
3-2

e) contacting said 3-benzazepine compound of Formula 3-2 with L-(+)-tartaric acid to afford a tartrate salt of Formula 3-3:



3-3

f) reacting said tartrate salt of Formula 3-3 with a base to afford the optically active compound of Formula 3-4:



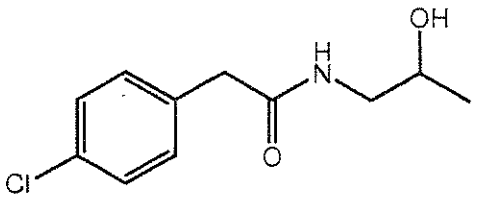
3-4

and

g) reacting said optically active compound of Formula 3-4 with HCl to afford said compound of Formula 3-5.

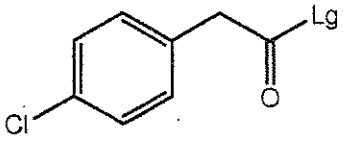
Claims

1. A process for preparing an amide compound of Formula 1-3:



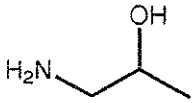
1-3

comprising reacting a phenylacetic acid derivative compound of Formula 1-1:



1-1

or salt thereof, wherein Lg is a leaving group,
with an amine compound of Formula 1-2:



1-2

or salt thereof, in the presence of a coupling reagent to afford said amide compound of Formula 1-3.

2. A process according to claim 1, wherein Lg is OH.

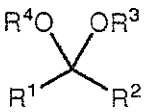
3. A process according to claim 1 or 2, wherein said coupling reagent comprises a boron-containing acid, a carbodiimide, or a ketal.

4. A process according to claim 1 or 2, wherein said coupling reagent comprises phenylboronic acid, boric acid, or mixture thereof.

5. A process according to claim 1 or 2, wherein said coupling reagent comprises 2,5,6-trifluorophenylboronic acid.

6. A process according to claim 3, wherein said carbodiimide is 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (EDC).

7. A process according to claim 3, wherein said ketal has the formula:



wherein R^1, R^2, R^3, and R^4 are C_{1-6} alkyl.

8. A process according to claim 3, wherein said ketal comprises 2,2-dimethoxypropane.

9. A process according to claim 7 or 8, wherein said reacting is carried out in the presence of an acid catalyst.

10. A process according to claim 7 or 8, wherein said catalyst comprises *p*-toluenesulfonic acid.

11. A process according to claim 1, wherein Lg is halo.

12. A process according to claim 1 or 11, wherein said coupling reagent comprises a base.

13. A process according to claim 12, wherein said base is triethylamine.

14. A process according to any one of claims 1 to 12, wherein the molar ratio of said phenylacetic acid derivative compound of Formula 1-1 to said coupling reagent is about 1:1 to about 20:1.

15. A process according to any one of claims 1 to 12, wherein said reacting is carried out in the presence of a solvent.

16. A process according to claim 15, wherein said solvent comprises toluene.

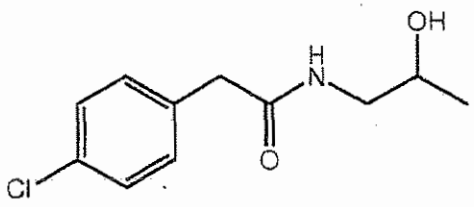
17. A process according to claim 15, wherein said solvent comprises methanol, ethanol, or isopropanol.

18. A process according to any one of claims 1 to 17, wherein said reacting is carried out at about room temperature.

19. A process according to any one of claims 1 to 17, wherein said reacting is carried out at elevated temperature.

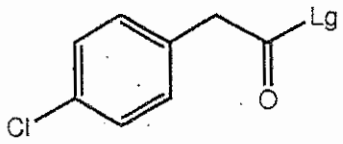
20. A process according to claim 19, wherein said elevated temperature is about 80 °C to about 140 °C.

21. A process according to claim 1, for preparing an amide compound of Formula 1-3:



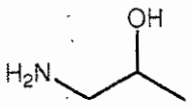
1-3

comprising reacting, in a solvent comprising toluene and at elevated temperature, a phenylacetic acid derivative compound of Formula 1-1:



1-1

or salt thereof, wherein Lg is OH, with an amine compound of Formula 1-2:



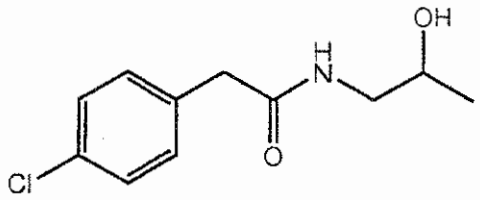
1-2

or salt thereof, in the presence of at least one boron-containing acid to afford said amide compound of Formula 1-3.

22. A process according to claim 21, wherein said reacting is carried out in the presence of phenylboronic acid, boric acid, or mixture thereof.

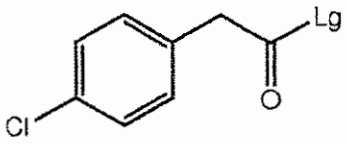
23. A process according to claim 21, wherein said reacting is carried out in the presence of 2,5,6-trifluorophenylboronic acid.

24. A process according to claim 1, for preparing an amide compound of Formula 1-3:



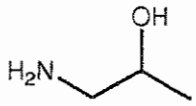
1-3

comprising reacting, in a solvent comprising isopropyl alcohol and at about room temperature, a phenylacetic acid derivative compound of Formula 1-1:



1-1

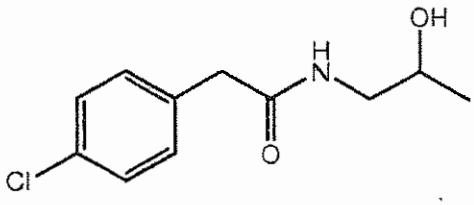
or salt thereof, wherein Lg is OH, with an amine compound of Formula 1-2:



1-2

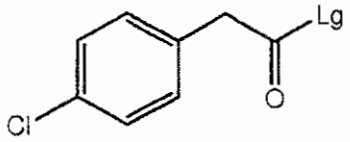
or salt thereof, in the presence of 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride to afford said amide compound of Formula 1-3.

25. A process according to claim 1, for preparing an amide compound of Formula 1-3:



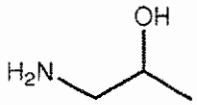
1-3

comprising reacting, in an alcohol solvent and optionally in the presence of an acid catalyst, a phenylacetic acid derivative compound of Formula 1-1:



1-1

or salt thereof, wherein Lg is OH, with an amine compound of Formula 1-2:



1-2

or salt thereof, in the presence of 2,2-dimethoxypropane to afford said amide compound of Formula 1-3.

26. A process according to claim 25, further comprising combining said 2,2-dimethoxypropane with said phenylacetic acid derivative compound of Formula 1-1 prior to said reacting with said amine compound of Formula 1-2, or salt thereof.

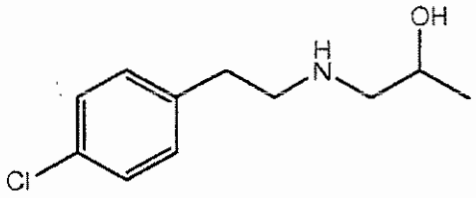
27. A process according to claim 26, wherein said combining affords 2-(4-chlorophenyl)acetic acid methyl ester.

28. A process according to claim 26, wherein said combining is carried out at elevated temperature.

29. A process according to claim 28, wherein said elevated temperature is about 60 °C to about 120 °C.

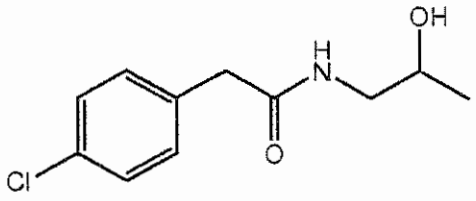
30. A process according to any one of claims 25 to 29, wherein conversion of said phenylacetic acid derivative compound of Formula 1-1 to said 2-(4-chlorophenyl)acetic acid methyl ester is about 90% or greater.

31. A process for preparing an amino alcohol compound of Formula 2-1:



2-1

or salt thereof, comprising reacting an amide compound of Formula 1-3:



1-3

with a reducing agent to afford said amino alcohol compound of Formula 2-1, or salt thereof.

32. A process according to claim 31, wherein said reducing agent comprises a borane, dialkylborane, alkali metal trialkylboron hydride, alkali metal aluminum hydride, alkali metal borohydride, alkali metal trialkoxyaluminum hydride, dialkylaluminum hydride, or H_2 optionally in the presence of a catalyst.

33. A process according to claim 31, wherein said reducing agent comprises BH_3.

34. A process according to claim 33, wherein said BH_3 is generated in situ.

35. A process according to claim 31, wherein said reducing agent comprises a borane tetrahydrofuran complex.

36. A process according to claim 31, wherein said reducing agent comprises a borane methylsulfide complex.

37. A process according to any one of claims 31 to 36, wherein said reducing agent is provided in molar excess relative to the amount of said amide compound of Formula 1-3.

38. A process according to any one of claims 31 to 36, wherein the molar ratio of said reducing agent to said amide compound of Formula 1-3 is about 1:1 to about 5:1.

39. A process according to claim 31, wherein said reducing agent comprises $NaBH_4$ in the presence of iodine.

40. A process according to claim 39, wherein the molar ratio of $NaBH_4$ to iodine to said amide compound of Formula 1-3 is about 2.5:1:1.

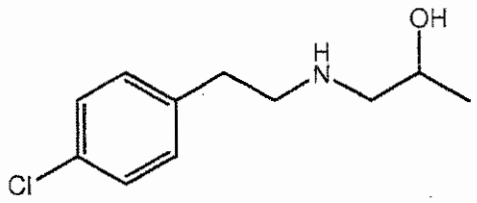
41. A process according to any one of claims 31 to 40, wherein said reacting is carried out at elevated temperature.

42. A process of claim 41, wherein said elevated temperature is about 30 °C to about 80 °C.

43. A process according to any one of claims 31 to 42, wherein conversion of said amide compound of Formula 1-3 to said amino alcohol compound of Formula 2-1, or salt thereof, is about 90% or greater.

44. A process according to any one of claims 31 to 43, wherein said amide compound of Formula 1-3 is prepared by the process of any one of claims 1-38.

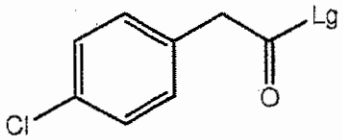
45. A process according to claim 31, for preparing an amino alcohol compound of Formula 2-1:



2-1

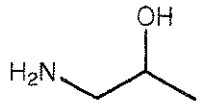
or salt thereof, comprising:

a) reacting a phenylacetic acid derivative compound of Formula 1-1:



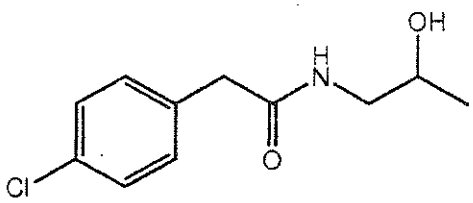
1-1

or salt thereof, wherein Lg is a leaving group, with an amine compound of Formula 1-2:

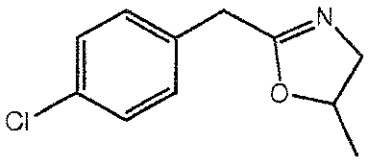


1-2

or salt thereof, in the presence of a coupling reagent to afford an amide compound of Formula 1-3 and optionally a dihydrooxazole compound of Formula 1-4, or salt thereof:



1-3

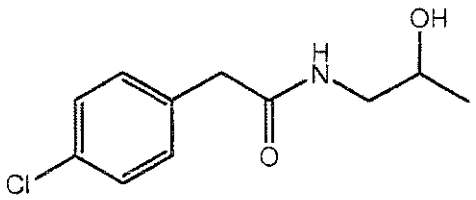


1-4

and

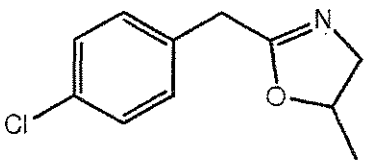
b) reacting said amide compound of Formula 1-3 and optionally said dihydrooxazole compound of Formula 1-4, or salt thereof, with a reducing agent to afford said amino alcohol compound of Formula 2-1, or salt thereof.

46. A compound of Formula 1-3:



1-3.

47. A compound of Formula 1-4:

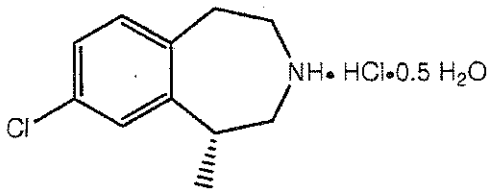


1-4

or salt thereof.

48. A composition comprising a compound of claim 46 or 47, or salt thereof.

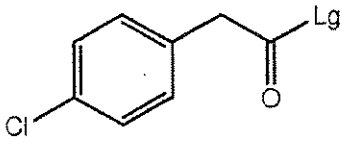
49. A process for preparing a compound of Formula 3-5:



3-5

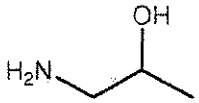
comprising:

a) reacting a phenylacetic acid derivative compound of Formula 1-1:



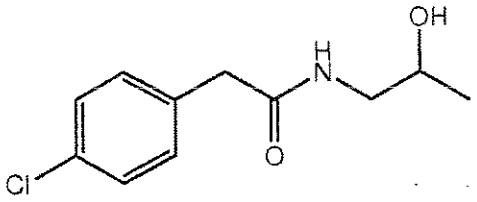
1-1

or salt thereof, wherein Lg is a leaving group, with an amine compound of Formula 1-2:

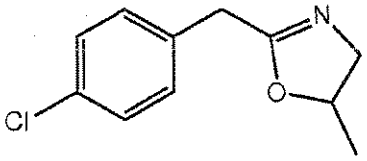


1-2

or salt thereof, in the presence of a coupling reagent to afford an amide compound of Formula 1-3 and optionally a dihydrooxazole compound of Formula 1-4, or salt thereof:

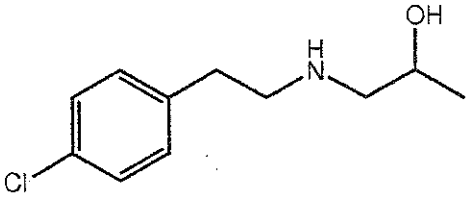


1-3



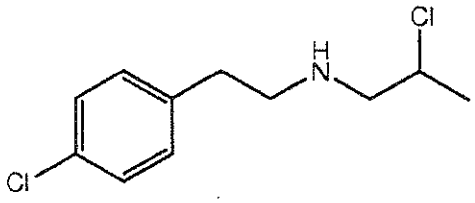
1-4

b) reacting said amide compound of Formula 1-3 and optionally said dihydrooxazole compound of Formula 1-4, or salt thereof, with a reducing agent to afford an amino alcohol compound of Formula 2-1:



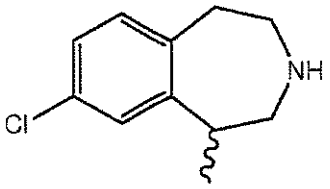
2-1

or salt thereof;
c) reacting said amino alcohol compound of Formula 2-1, or salt thereof, with a chlorinating reagent to afford a dichloro compound of Formula 3-1:



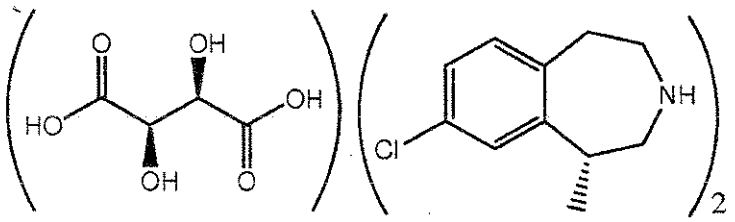
3-1

or salt thereof;
d) reacting said dichloro compound of Formula 3-1 with a cyclizing reagent to afford a 3-benzazepine compound of Formula 3-2:



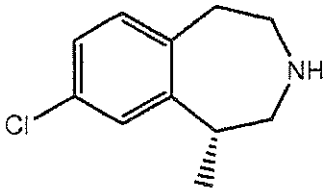
3-2

e) contacting said 3-benzazepine compound of Formula 3-2 with L-(+)-tartaric acid to afford a tartrate salt of Formula 3-3:



3-3

f) reacting said tartrate salt of Formula 3-3 with a base to afford the optically active compound of Formula 3-4:



and
g) reacting said optically active compound of Formula 3-4 with HCl to afford said compound of Formula 3-5.

50. A process according to claim 49, wherein:

Lg is OH;
said coupling reagent comprises phenylboronic acid, boric acid, or mixture thereof; and
said reducing agent comprises $NaBH_4$ in the presence of iodine.