CHAPTER 2

EXPERIMENTAL

2.1 Instruments

1. ^{1}H- Nuclear Magnetic Resonance (^{1}H-NMR) spectrometor; AVANCE DPX 200; Bruker; 200.13 MHz
2. ^{13}C- Nuclear Magnetic Resonance (^{13}C-NMR) spectrometor; AVANCE DPX 200; Bruker; 50.32 MHz
3. ^{1}H- Nuclear Magnetic Resonance (^{1}H-NMR) spectrometor; AVANCE DPX 300; Bruker; 300.13 MHz
4. ^{13}C- Nuclear Magnetic Resonance (^{13}C-NMR) spectrometor; AVANCE DPX 300; Bruker; 75.47 MHz
5. ^{1}H- Nuclear Magnetic Resonance (^{1}H-NMR) spectrometor; AVANCE DPX 400; Bruker; 400.13 MHz
6. ^{13}C- Nuclear Magnetic Resonance (^{13}C-NMR) spectrometor; AVANCE DPX 400; Bruker; 100.61 MHz
7. ^{1}H- Nuclear Magnetic Resonance (^{1}H-NMR) spectrometor; AVANCE DPX 500; Bruker; 500.13 MHz

8. ^{13}C- Nuclear Magnetic Resonance (^{13}C-NMR) spectrometor; AVANCE DPX 500; Bruker; 125.76 MHz
9. Fourier Transform Infrared Spectrometer (FT-IR); Tensor 27
10. High Resolution Mass Spectra (HRMS); Q-TOF 2™ mass spectrometer; Z-spray™ ES source; Micromass, Manchester, UK
11. Mel-Temp II; Laboratory Devices INC USA
12. Perkin Elmer precisely Model 341 polarimeter
13. Reduce pressure Rotary Evaporator; Buchi
14. High Performance Liquid Chromatography (HPLC); Waters™ 410

2.2 Chemicals

1. Absolute ethanol [C_2H_6O] 99% Merck
2. Acetone [C_3H_6O] 99.7% J.T.Baker
3. Acetonitrile [C_2H_3N] 99.9% Aldrich
4. *(R)*-Alpine-Borane solution [$C_{18}H_{31}B$] (0.5 M in THF) Aldrich
5. Ammonium chloride [NH_4Cl] 99.9% Aldrich
6. *(R)*-1,1-Binaphthol [$C_{20}H_{14}O_2$] 99% Aldrich
7. *(S)*-1,1-Binaphthol [$C_{20}H_{14}O_2$] 99% Aldrich
8. Borane tetrahydrofuran complex solution (1.0 M in THF) [$C_4H_{11}OB$] Aldrich
9. *N*-Bromosuccinimide [$C_4H_4BrNO_2$] 99% Organic

10. *t*-Butyldimethylsilyl chloride [$C_6H_{15}ClSi$] 98% Acros

11. *n*-Butyllithium solution [C_4H_9Li] (1.6 M in Hexane) Fluka

12. Calcium chloride [$CaCl_2$] 92% Carlo Erba

13. Celite® 545 Aldrich

14. (+)-*B*-Chlorodiisopinocampheylborane [$C_{20}H_{34}BCl$] 99-105% Aldrich

15. (-)-*B*-Chlorodiisopinocampheylborane [$C_{20}H_{34}BCl$] Aldrich

16. *m*-chloroperoxybenzoic acid [$C_7H_5ClO_3$] 70% Fluka

17. Copper (II)sulfate pentahydrate [$CuSO_4.5H_2O$] 98.5% Merck

18. *beta*-Cyclodextrins [$C_{42}H_{70}O_{35}$] 97% Aldrich

19. *N*,*N'*-Dicyclohexylcarbodiimide [$C_{13}H_{22}N_2$] 99% Fluka

20. *N*,*N'*-Dimethylaminopyridine [$C_7H_{10}N_2$] 98% Fluka

21. Deuterated chloroform-*d* [$CDCl_3$] 99.8% Aldrich

22. Deuterated dimethylsulfoxide-d_6 [C_2D_6OS] 99.9% Aldrich

23. Dichloromethane [CH_2Cl_2] Commercial Grade

24. Diethanolamine [$C_4H_{11}NO_2$] 99% Eastman

25. Diethyl ether [$C_4H_{10}O$] Commercial Grade

26. Dimethylsulfoxide [C_2H_6OS] 99.5% Aldrich

27. Di-*t*-butyl dicarbonate [$C_{10}H_{18}O_5$] 98% Fluka

28. Ethyl acetate [$C_2H_8O_2$] Commercial Grade

29. Europium (III) tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorate]

$[C_{42}H_{42}EuF_{21}O_6]$ 99.9% Fluka

30. Glacial acetic acid $[C_2H_4O_2]$ 99.8% Aldrich

31. Hexane $[C_6H_{14}]$ Commercial Grade

32. Hydrochloric acid [HCl] 37% Lab Acan

33. *m*-Hydroxybenzaldehyde $[C_7H_6O_2]$ 98.5% Acros

34. Imidazole $[C_3H_4N_2]$ 99% Acros

35. Lithium aluminium hydride $[LiAlH_4]$ 95% Aldrich

36. Methanol $[CH_3OH]$ Commercial Grade

37. *(R)*-(+)-α-Methoxy-α-trifluoromethylphenylacetic acid $[C_{10}H_9F_3O_3]$ 99.9% Fluka

38. Methylamine anhydrous $[CH_5N]$ 98% Aldrich

39. Methylamine solution $[CH_5N]$ (33% in Ethanol) Fluka

40. Methylamine solution $[CH_5N]$ (2M in Methanol) Acros

41. *(R)*-2-Methyl-CBS-oxazaborolidine $[C_{18}H_{20}BNO]$ 95% Aldrich

42. Methyl iodide $[CH_3I]$ 99% Fluka

43. Molecular Sieve 4 A^o Fluka

44. *(R)*-Phenylephrine hydrochloride $[C_9H_{13}NO_2.HCl]$ 99.9%, Aldrich

45. Potassium carbonate $[K_2CO_3]$ 99% Ajax

46. Potassium permanganate $[KMnO_4]$ 99% BDH

47. Potassium-*t*-butoxide $[C_4H_9KO]$ 97% Aldrich

48. Silica gel (0.063-0.200 mm.) for column chromatography; Merck

49. Silica gel 60 for thin layer chromatography; Merck

50. Sodium borohydride [$NaBH_4$] 97% Labscan

51. Sodium chloride [NaCl] 99.5% Carlo Erba

52. Sodium hydrogencarbonate [$NaHCO_3$] 99.8% Carlo Erba

53. Sodium hydrogenphosphate [Na_2HPO_4] 99% Aldrich

54. Sodium hydroxide [NaOH] 99 % Thasco

55. Sodium sulfate anhydrous [Na_2SO_4] 99% Fisher

56. Sodium thiosulfate [$Na_2S_2O_3$] 99.5% Carlo Erba

57. Sucrose [$C_{12}H_{22}O_{11}$] commercial grade

58. L-Tartaric acid [$C_4H_6O_6$] 97% Aldrich

59. Tetrabutylammonium fluoride solution [$C_{16}H_{36}NF$] (1.0 M in THF) Fluka

60. Tetrahydrofuran [C_4H_8O] AR Grade 99.9% J.T.Baker

61. TLC Aluminium Sheet 20x20 cm Merck

62. Toluene [C_7H_8] 99.5% Panreac

63. Triethylamine [$C_6H_{15}N$] 99% Merck

64. Trifluoroacetic acid [$C_2HF_3O_2$] 99% Aldrich

65. Trimethylsulfoxonium iodide [C_3H_9SOI] 98% Acros

66. Triphenylphosphine [$C_{18}H_{15}P$] 98% Fluka

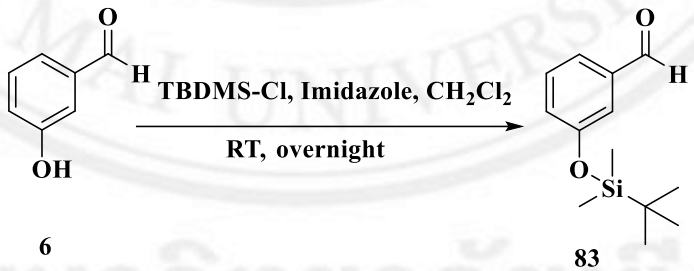
67. Yeast from *Saccharomyces cerevisiae*, Type II Aldrich

Melting point were measured using a Mel-temp II apparatus and were uncorrected. Optical rotations were performed using a Perkin Elmer precisely model 341 polarimeter using the indicated spectroscopic grade solvents. ^{1}H nuclear magnetic resonance spectra were recorded using a Bruker Avance DPX 500 at a frequency of 500.13 MHz, a Bruker Avance DPX 400 at a frequency of 400.13 MHz, a Bruker Avance DPX 300 at a frequency 300.13 MHz, or a Bruker Avance DPX 200 at a frequency of 200.13 MHz are reported as parts per million (ppm) downfield shift from tetramethylsilane (δ_H 0.00 ppm), with deuterochloroform ($CDCl_3$, δ_H 7.26 ppm) or deuterodimethyl- sulfoxide (DMSO-d_6, δ_H 2.50 ppm) as internal references, unless otherwise stated. The data is reported as chemical shift (δ), multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (*J* Hz) and relative integral. ^{13}C nuclear magnetic resonance spectra were recorded using a Bruker Avance DPX 500 at a frequency of 125.76 MHz, a Bruker Avance DPX 400 at a frequency of 100.61 MHz, a Bruker Avance DPX 300 at a frequency 75.47 MHz, or a Bruker Avance DPX 200 at a frequency of 50.32 MHz are reported as parts per million (ppm) downfield shift with deuterochloroform (δ_c 77.16 ppm) or deuterodimethylsulfoxide (δ_c 39.52 ppm) as internal references, unless otherwise stated. High Resolution Mass Spectra (HRMS) were recorded on a Q-TOF 2™ mass spectrometer with a Z-spray™ ES source. Electron impact mass spectra were measured with Agilent-HP 5973 Mass Spectrometer. FT-IR spectra were recorded by a FT-IR, Tensor 27 spectrometer on the wave length, ν (cm^{-1}). Analytical thin layer chromatography (TLC) was performed using precoated silica gel plates (Merck Kieselgel 60 F_{254}). Preparative column chromatography was carried out using either Merck Kieselgel 60 silica gel (SiO_2; 0.040-0.063 mm and 0.063-0.200 mm), with the

indicated solvents which were mixed v/v as specified. Analytical high performance liquid chromatography (HPLC) was performed on a Waters^{TM} 410 consisting of chiral OD-H column at flow rate of 0.5 mL/min. Compounds were eluted in a mobile phase consisting of 0.5% (v/v) isopropanol in hexane. The chromatograms were detected at wavelength 270 nm. Reactions were performed under a positive pressure of dry nitrogen. Dichloromethane, methanol and triethylamine were distilled from calcium hydride before used. THF was distilled from sodium metal and benzophenone before used. All other reagents were commercially available and were used as supplied and all solid chemicals were recrystallized before use. All other solvents were distilled prior to used.

2.3 Synthesis of (±)-Phenylephrine hydrochloride

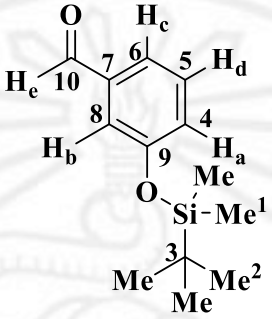
2.3.1 Preparation of 3-((tert-butyldimethylsilyl)oxy)benzaldehyde (83)



6 **83**

Imidazole (4.21 g, 61.8 mmol) and *t*-butyldimethylsilyl chloride (9.31 g, 61.7 mmol) was added to a stirred solution of *m*-hydroxybenzaldehyde **(6)** (5.04 g, 41.3 mmol) in dry dichloromethane (50 mL) at 0^{o}C, then allowed to warm up to room temperature. After 24 h, water (30 mL) was added. The organic layer was washed with brine (10 mL) and dried with anhydrous sodium sulfate. The organic layer was

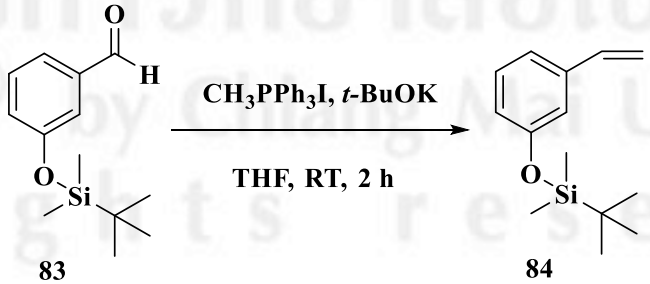
concentrated under reduced pressure and the residue was purified on silica gel by eluting with ethyl acetate:hexane (1:4) to give 3-((*tert*-butyldimethylsilyl)-oxy)benzaldehyde **(83)** (10.13 g, quantitative yield) as a pale yellow liquid.



83

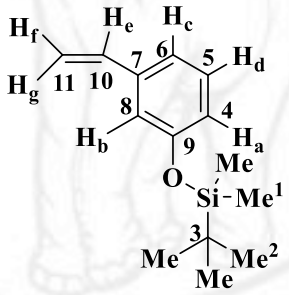
Compound 83: FT-IR (neat), ν_{max} 2958, 2927, 2860,2750, 1705, 1581, 1275, 840 cm^{-1}; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 9.94 (s, 1H, H_e), 7.46 (dt, *J* = 7.5, 1.3 Hz, 1H, H_d), 7.38 (t, *J* = 7.8 Hz, 1H, H_c), 7.33 (dd, *J* = 2.3, 1.6 Hz, 1H, H_b), 7.10 (m, 1H, H_a), 0.99 (s, 9H, Me_2), 0.22 (s, 6H, Me_1); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 191.85 (C-10), 156.27 (C-9), 137.85 (C-7), 129.95 (C-5), 126.37 (C-4), 123.43 (C-6), 119.69 (C-8), 25.52 (C-3), 18.05 (C-2), -4.58 (C-1); **HRMS** calcd for $C_{13}H_{21}O_2Si$ $[M+H]^+$ 237.1311, found 237.1313.

2.3.2 Preparation of tert-Butyldimethyl(3-vinylphenoxy)silane (84)



83 **84**

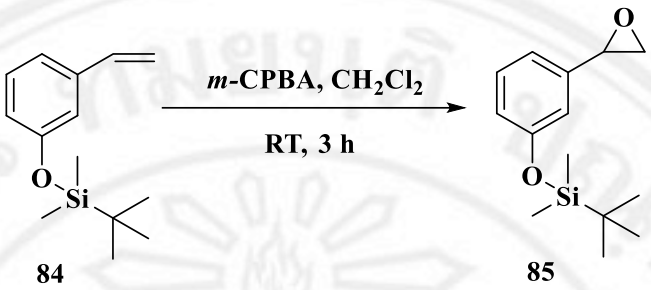
Potassium-*t*-butoxide (2.90 g, 25.9 mmol) was added to a stirred suspension of methylenetriphenylphosphonium iodide (10.32 g, 25.5 mmol) in dry tetrahydrofuran (50 mL) at 0°C. The reaction was stirred at room temperature for 1 h, then aldehyde **(83)** (5.01 g, 21.2 mmol) was added portionwise to the mixture. The reaction was stirred for 2 h at room temperature, after that diluted with water (40 mL). The aqueous layer was extracted with ethyl acetate (2 × 40 mL). The combined organic layer was washed with brine (10 mL), dried with anhydrous sodium sulfate and concentrated under reduced pressure. The crude was purified on silica gel eluting with ethyl acetate:hexane (1:19), followed by concentration to furnish *tert*-butyldimethyl(3-vinylphenoxy)silane **(84)** (4.82 g, 97% yield) as a colorless liquid.



84

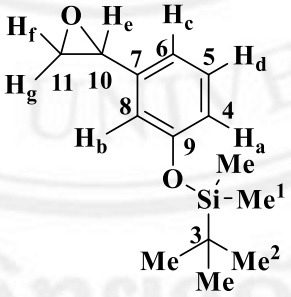
Compound 84: FT-IR (neat), ν_{max} 2957, 2930, 2858, 1578, 1485, 1279, 839 cm^{-1}; **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.27 (t, *J* = 7.8 Hz, 1H, H_d), 7.11 (d, *J* = 7.6 Hz, 1H, H_c), 7.02 (s, 1H, H_b), 6.86 (d, *J* = 8.0 Hz, 1H, H_a), 6.77 (dd, *J* = 17.5, 10.8 Hz, 1H, H_e), 5.82 (d, *J* = 17.6 Hz, 1H, H_g), 5.32 (d, *J* = 10.8 Hz, 1H, H_f), 1.12 (s, 9H, Me_2), 0.33 (s, 6H, Me_1); **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 155.84 (C-9), 139.06 (C-7), 136.75 (C-10), 129.36 (C-5), 119.51 (C-4), 119.49 (C-8), 117.72 (C-6), 113.78 (C-11), 25.69 (C-3), 18.17 (C-2), -4.42 (C-1); **HRMS** calcd for $C_{14}H_{23}O_2Si$ $[M+H]^+$ 235.1518, found 235.1512.

2.3.3 Preparation of tert- Butyldimethyl(3-(oxiran-2-yl)phenoxy)silane (85)



84 **85**

m-Chloroperoxybenzoic acid (1.01 g, 5.83 mmol) was added to a stirred solution of compound **(84)** (0.65 g, 2.76 mmol) in dichloromethane (15 mL) at room temperature. After 3 h, the reaction mixture was washed with saturated sodium thiosulfate solution (5 mL) and saturated sodium hydrogencarbonate solution (5 mL). The organic layer was washed with brine (5 mL), dried with anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified on silica gel and washed with ethyl acetate:hexane (1:19) to produce *tert*- butyldimethyl(3-(oxiran-2-yl)phenoxy)silane **(85)** (0.56 g, 81% yield) as a colorless liquid.

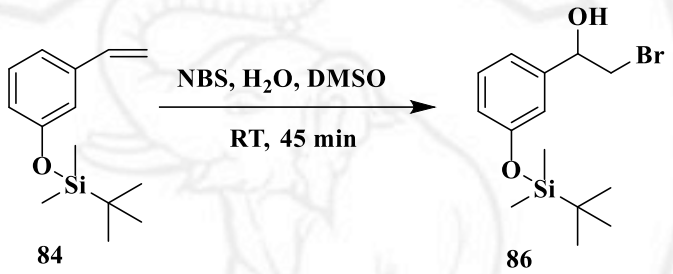


85

Compound 85: FT-IR (neat), ν_{max} 3048, 2931, 2858, 1606, 1486, 1284, 957, 833 cm^{-1}; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.20 (t, *J* = 8.0 Hz, 1H, H_d), 6.90 (d, *J* = 7.6 Hz, 1H, H_b), 6.80 (d, *J* = 7.3 Hz, 2H, H_a), 3.79 (dd, *J* = 4.0, 2.6 Hz, 1H, H_e), 3.09 (dd, *J* = 5.6, 4.1 Hz, 1H, H_f or H_g), 2.74 (dd, *J* = 5.6, 2.5 Hz, 1H, H_f or H_g), 1.03 (s, 9H,

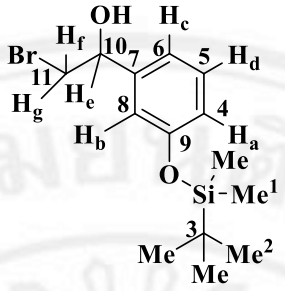
Me_2), 0.23 (s, 6H, Me_1); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 155.80 (C-9), 139.24 (C-7), 129.30 (C-5), 119.64 (C-4), 118.42 (C-6), 116.74 (C-8), 51.87 (C-10), 50.82 (C-11), 25.51 (C-3), 17.99 (C-2), -4.60 (C-1); **HRMS** calcd for $C_{14}H_{23}O_2Si$ $[M+H]^+$ 251.1467, found 251.1465.

2.3.4 Preparation of 2-Bromo-1-(3-(tert-butyldimethylsilyloxy)phenyl)ethanol (86)



84 **86**

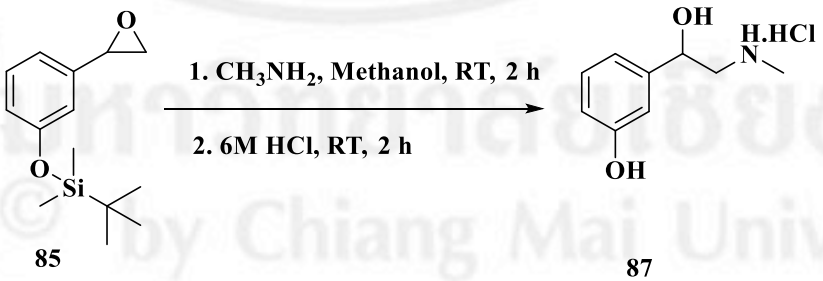
N-Bromosuccinimide (1.14 g, 6.43 mmol) and water (0.25 mL) was added to a stirred solution of compound **(84)** (0.52 g, 2.22 mmol) in dimethylsulfoxide (8 mL) at 0^oC. After 45 min, ice-cooled water (10 mL) was added. The aqueous phase was extracted with ethyl acetate (2 × 10 mL). The combined organic layer was washed with brine (5 mL), dried with anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified on silica gel and eluted with ethyl acetate:hexane (1:19) to produce 2-Bromo-1-(3-(*tert*-butyldimethylsilyloxy)phenyl)-ethanol **(86)** (0.59 g, 80% yield) as a colorless liquid.



86

Compound 86: FT-IR (neat), ν_{max} 3422, 3032, 2956, 2858, 1602, 1485, 1065, 1278, 835 cm^{-1}; **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.22 (t, *J* = 7.8 Hz, 1H, H_d), 6.95 (d, *J* = 7.6 Hz, 1H, H_c), 6.88 (br, 1H, H_b), 6.80 (d, *J* = 8.0 Hz, 1H, H_a), 4.85 (d, *J* = 8.3 Hz, 1H, H_e), 3.61 (d, *J* = 9.3 Hz, 1H, H_f or H_g), 3.51 (t, *J* = 9.7 Hz, 1H, H_f or H_g), 2.77 (s, 1H, OH), 1.00 (s, 9H, Me_2), 0.21 (s, 6H, Me_1); **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 155.85 (C-9), 141.89 (C-7), 129.59 (C-5), 119.98 (C-4), 118.79 (C-6), 117.69 (C-8), 73.51 (C-10), 40.04 (C-11), 25.62 (C-3), 18.12 (C-2), -4.45 (C-1); **HRMS** calcd for $C_{14}H_{23}O_1SiBr$ $[M+H-OH]^+$ 315.0630, found 315.0346.

2.3.5 Preparation of (±)-Phenylephrine hydrochloride (87) via epoxide compound (85)

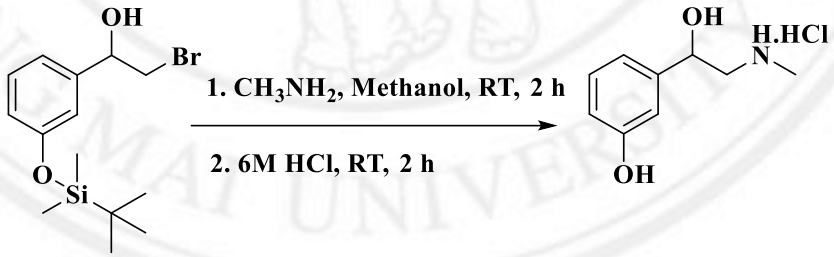


85 **87**

A solution of epoxide **(85)** (0.51 g, 2.05 mmol) in dry methanol (5 mL) was saturated with methylamine gas and left stirred at room temperature for 2 h. The solution was concentrated to give the crude mixture. Hydrochloric acid (6M, 0.50 mL)

was added to the solution of crude in methanol (5 mL). The solution was stirred at room temperature for 2 h. The solution was concentrated under reduced pressure and the residue was purified on silica gel by eluting with methanol:dichloromethane (1:19). This was then concentrated to produce racemic phenylephrine hydrochloride **(87)** (0.38 g, 90% yield) as a white solid. Then dissolved racemic phenylephrine hydrochloride **(87)** (0.38 g, 1.87 mmol) in water (3 mL). Ammonia TS solution (ammonium hydroxide : water = 2:3) (1 mL) was added and rub the inner side of the test tube with glass rod. The precipitate was collected and washed with a few drops of ice-cold and dried at 105°C for 2 h to give racemic phenylephrine **(1)**.

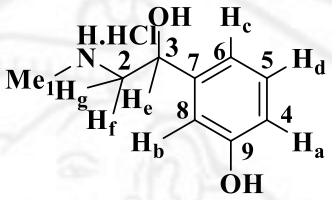
2.3.6 Preparation of (±)-Phenylephrine hydrochloride (87) via bromohydrin compound (86)



86 **87**

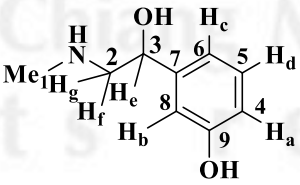
A solution of bromohydrin **(86)** (0.53 g, 1.60 mmol) in dry methanol (5 mL) was saturated with methylamine gas and left stirred at room temperature for 2 h. The solution was concentrated to give the crude mixture. Hydrochloric acid (6M, 0.50 mL) was added to the solution of crude in methanol (5 mL). The mixture solution was stirred at room temperature for 2 h. The solution was concentrated under reduced pressure and the residue was purified on silica gel by eluting with methanol:dichloromethane (1:19). This was then concentrated to produce racemic

phenylephrine hydrochloride **(87)** (0.29 g, 85% yield) as a white solid. Then dissolved racemic phenylephrine hydrochloride **(87)** (0.29 g, 1.42 mmol) in water (3 mL). Ammonia TS solution (ammonium hydroxide : water = 2:3) (1 mL) was added and rub the inner side of the test tube with glass rod. The precipitate was collected and washed with a few drops of ice-cooled water and dried at 105ºC for 2 h to give racemic phenylephrine **(1)**.



87

Compound 87: mp. 141-143ºC (Lit[18] mp 141 ºC); **FT-IR** (KBr), ν_{max} 3419, 2963, 2798, 1593, 1462, 1274, 1083, 879 cm^{-1}; **^{1}H-NMR** (500 MHz, DMSO-d_6) δ 9.56 (s, 1H,OH or NH), 8.99 (br, 1H, OH or NH), 7.15 (t, J = 7.8 Hz, 1H, H_d), 6.81 (br, 1H, H_b), 6.78 (d, J = 7.7 Hz, 1H, H_c), 6.70 (d, J = 8.0 Hz, 1H, H_a), 6.11 (s, 1H, OH), 4.83 (d, J = 8.3 Hz, 1H, H_e), 3.05 (d, J = 12.5 Hz, 1H, H_f or H_g), 2.91 (d, J = 12.4 Hz, 1H, H_f or H_g), 2.53 (s, 3H, Me_1); **^{13}C-NMR** (125 MHz, DMSO-d_6) δ 157.99 (C-9), 143.71 (C-7), 129.78 (C-5), 116.74 (C-6), 115.12 (C-4), 113.22 (C-8), 68.49 (C-3), 55.37 (C-2), 33.14 (C-1); **HRMS** calcd for $C_9H_{14}NO_2$ $[M+H]^+$ 168.0980, found 168.1019.

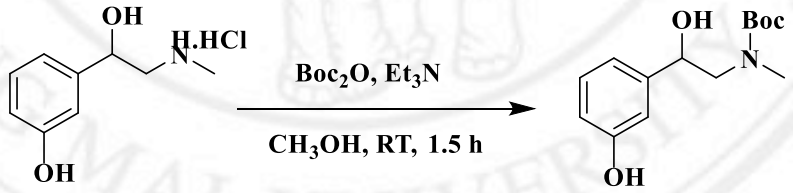


1

Compound 1: mp. 170-172°C (Lit. mp 171 °C); **FT-IR** (KBr), ν_{max} 3050, 2720, 2500, 1590, 1468, 1266, 1129, 869 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.06 (t, J = 7.7 Hz, 1H, H_d), 6.73 (br, 1H, H_b), 6.70 (d, J = 7.6 Hz, 1H, H_c), 6.58 (d, J = 7.7 Hz, 1H, H_a), 5.47 (br,1H, OH or NH), 4.69 – 4.38 (m, 1H, H_e), 3.33 (br, 1H, OH or NH), 2.50 (dd, J = 9.9, 5.4 Hz, 2H, H_f, H_g), 2.27 (s, 3H, Me_1);**^{13}C NMR** (100 MHz, DMSO-d_6) δ 157.65 (C-9), 146.64 (C-7), 129.30 (C-5), 116.93 (C-6), 114.14 (C-4), 113.25 (C-8), 71.41 (C-3), 60.23 (C-2), 36.34 (Me_1); **HRMS** calcd for $C_9H_{14}NO_2$ $[M+H]^+$ 168.0980, found 168.1019.

2.4 Synthesis of (R)-Phenylephrine hydrochloride

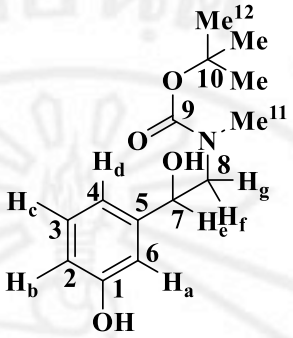
2.4.1 Preparation of tert-butyl(2-hydroxy-2(3-hydroxyphenyl)ethyl)(methyl)-carbamate (89)



87 **89**

To (±)-phenylephrine hydrochloride **(87)** (1.05 g, 5.17 mmol) and triethylamine (0.90 mL, 6.46 mmol) in methanol (20 mL) at 0 °C, di-*t*-butyl dicarbonate (1.20 mL, 5.22 mmol) was added. The mixture was warmed to room temperature and stirred for 1.5 h. The reaction was washed with 10% sodium hydroxide solution and the extraction was performed with ethyl acetate (3x50 mL). The organic layer was dried with anhydrous sodium sulfate and then concentrated under reduced pressure. The residue was purified by column chromatography with

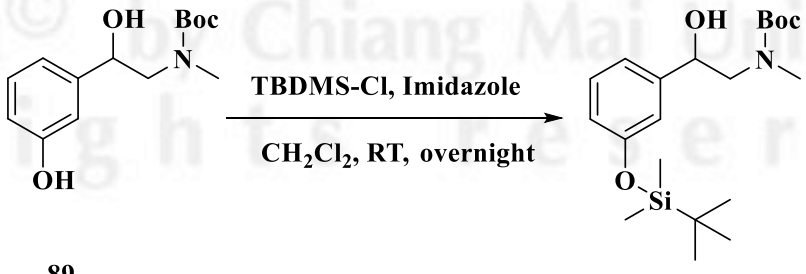
ethyl acetate:hexane (1:4) as an eluent to give *tert*-butyl(2-hydroxy-2(3-hydroxyphenyl)ethyl(methyl)carbamate **(89)** (1.53 g, quantitative yield) as a pale yellow oil.



89

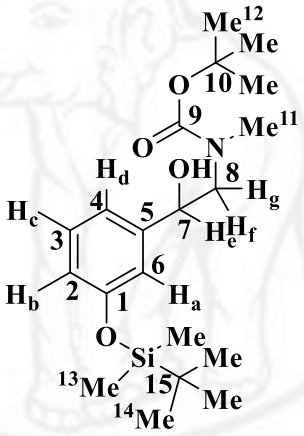
Compound 89: FT-IR (neat), ν_{max} 3363, 2976, 1666, 1485, 1399, 1241, 1156, 1060, 876 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.99 (br, 1H, OH), 7.11 (t, *J* = 7.2 Hz, 1H, H_c), 6.85 (br, 1H, H_b), 6.77 (d, *J* = 7.6 Hz, 1H_d), 6.73 (s, 1H, H_a), 4.78 (d, *J* = 18.6 Hz, 1H, H_e), 3.64 – 3.19 (m, 2H, H_f, H_g), 2.77 (d, *J* = 27.3 Hz, 3H, Me_{11}), 1.39 (d, *J* = 32.0 Hz, 9H, Me_{12}); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 157.71 (C-1), 156.51 (C-9), 143.39 (C-5), 129.48 (C-3), 117.52 (C-4), 114.91 (C-2), 112.87 (C-6), 80.58 (C-10), 73.06 (C-7), 56.85 (C-8), 36.35 (C-11), 28.25 (C-12); **HRMS** calcd for $C_{14}H_{21}NO_4Na$ $[M+Na]^+$ 290.1368, found 290.1374.

2.4.2 Preparation of tert-butyl(2-(3-((tert-butyldimethylsilyl)oxy)phenyl)-2-hydroxyethyl)(methyl)carbamate (90)



89 **90**

Imidazole (0.35 g, 5.10 mmol) and *t*-butyldimethylsilyl chloride (0.78 g, 5.14 mmol) was added to a stirred solution of compound **(89)** (0.91 g, 3.40 mmol) in dry dichloromethane (25 mL) at 0°C, then allowed to warm up to room temperature. After 24 h, water (15 mL) was added. The organic layer was washed with brine (5 mL) and dried with anhydrous sodium sulfate. The organic layer was concentrated under reduced pressure and the residue was purified on silica gel by eluting with ethyl acetate:hexane (1:9) to give *tert*-butyl(2-(3-((*tert*-butyldimethylsilyl)oxy)phenyl)-2-hydroxyethyl)(methyl)carbamate **(90)** (1.12 g, 86% yield) as a white solid.

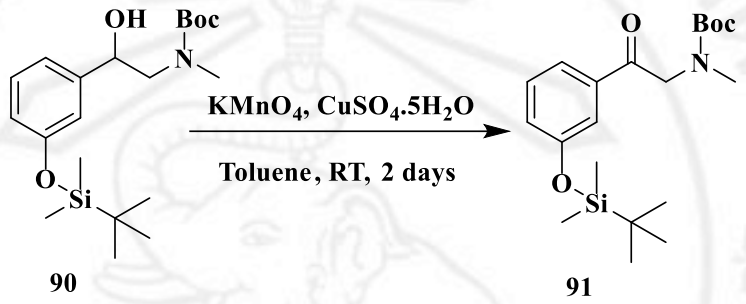


90

Compound 90: mp 74-76°C; **FT-IR** (KBr), ν_{max} 3432, 2957, 2931, 2859, 1675, 1483, 1393, 1277, 1155, 877, 781 cm^{-1}; **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.15 (t, *J* = 7.8 Hz, 1H, H_c), 6.90 (d, *J* = 7.4 Hz, 1H, H_d), 6.84 (s, 1H, H_a), 6.71 (d, *J* = 7.9 Hz, 1H, H_b), 4.81 (br, 1H, H_e), 3.38 (s, 2H, H_f, H_g), 2.76 (s, 3H, Me_{11}), 1.43 (s, 9H, Me_{12}), 0.96 (s, 9H, Me_{14}), 0.17 (s, 6H, Me_{13}); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 157.78 (C-1), 155.62 (C-9), 144.03 (C-5), 129.17 (C-3), 118.96 (C-2), 118.72 (C-4), 117.54 (C-6), 80.09 (C-10), 73.17 (C-7), 57.30 (C-8), 36.35 (C-11), 28.27 (C-15), 25.57 (C-12),

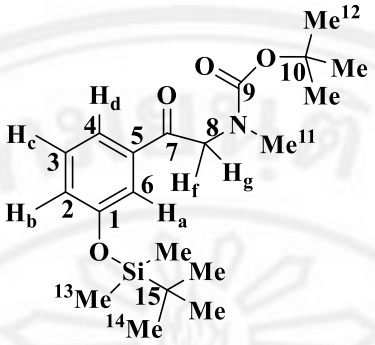
18.04 (C-14), -4.52 (C-13); **HRMS** calcd for $C_{20}H_{36}NO_4Si$ $[M+H]^+$ 382.2414, found 382.2415.

2.4.3 Preparation of tert-butyl(2-(3-((tert-butyldimethylsilyl)oxy)phenyl)-2-oxoethyl)(methyl)carbamate (91)



90 **91**

A solution of *tert*-butyl(2-(3-((*tert*-butyldimethylsilyl)oxy)phenyl)-2-hydroxy-ethyl)(methyl)carbamate **(90)** (1.05 g, 2.75 mmol) in toluene (20 mL) was cooled at 0°C. The mixture of potassium permanganate (5.34 g, 68 mmol) and copper (II) sulfate pentahydrate (2.74 g, 22 mmol) was added in the solution, then allowed to warm up to room temperature. After completion (24 h), the mixture was filtered and concentrated under reduced pressure. The crude mixture was purified by column chromatography with gradient ethyl acetate:hexane (1:19) to give *tert*-butyl(2-(3-((*tert*-butyldimethylsilyl)oxy)phenyl)-2-oxoethyl)(methyl)carbamate **(91)** (0.90 g, 86%) as a pale yellow oil.

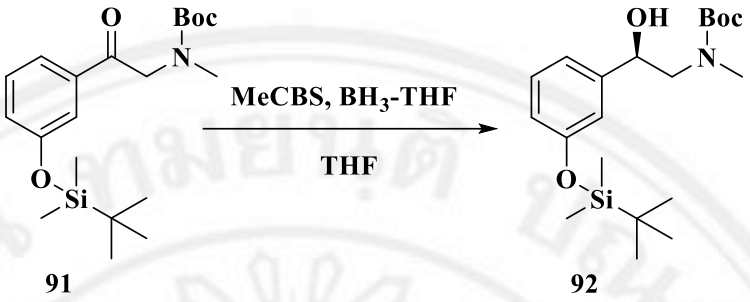


91

Compound 91: FT-IR (KBr), ν_{max} 2931, 2859, 1708, 1482, 1390, 1277, 1147, 834, 783 cm^{-1}; **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.30 (t, *J* = 8.2 Hz, 1H, H_c), 7.20 (s, 1H, H_a), 7.11 (q, *J* = 7.5 Hz, 1H, H_d), 6.84 (t, *J* = 6.1 Hz, 1H, H_b), 4.44 (s, 1H, H_f or H_g), 4.33 (s, 1H, H_f or H_g), 2.74 (s, 3H, Me_{11}), 1.25 (s, 9H, Me_{12}), 0.78 (s, 9H, Me_{14}), 0.00 (d, *J* = 3.2 Hz, 6H, Me_{13}); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 194.65 (C-7), 155.97 (C-1), 155.62 (C-9), 136.66 (C-5), 129.72 (C-3), 125.26 (C-2), 120.86 (C-4), 119.02 (C-6), 79.87 (C-10), 55.06 (C-8), 35.61 (C-11), 28.28 (C-15), 25.53 (C-12), 18.09 (C-14), -4.53 (C-13); **HRMS** calcd for $C_{20}H_{33}NO_4NaSi$ $[M+Na]^+$ 402.2077, found 402.2074.

2.4.4 Preparation of (R)-tert-butyl-(2-(3-((tert-butyldimethylsilyl)oxy)phenyl) 2-hydroxyethyl)(methyl)carbamate (92) from asymmetric reduction of tert-butyl(2-(3-((tert-butyldimethylsilyl)oxy)phenyl)-2-oxoethyl)(methyl)carbamate (91)

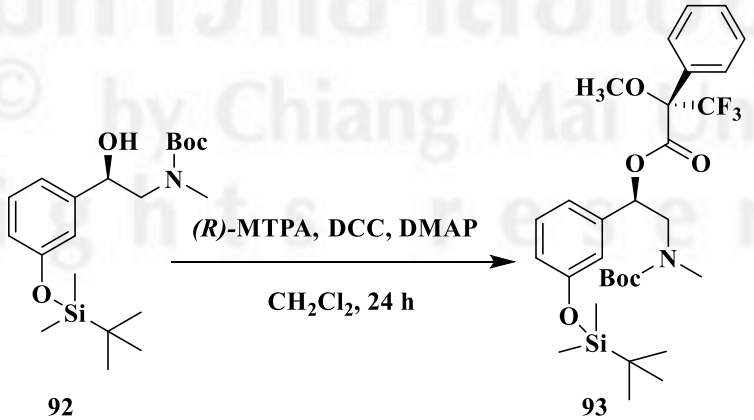
<u>Procedure 1</u> via (R)-2-methyl-CBS-oxazaborolidine (MeCBS) and borane-tatrahydofuran complex (BH_3-THF)



91 **92**

(R)-2-Methyl-CBS-oxazaborolidine (0.03 g, 0.11 mmol) and borane-tetrahydrofuran complex (0.87 mL, 0.80 mmol) was stirred at 0°C for 1 h, *tert*-butyl(2-(3-((*tert*-butyldimethylsilyl)oxy)phenyl)2-oxoethyl)(methyl)carbamate **(91)** (0.10 g, 0.27 mmol) was added portionwise to the mixture. The reaction was stirred for 4 h at 0°C, after that methanol (5 mL) and 1 M hydrochloric acid (0.5 mL) was added. The mixture reaction was concentrated under reduce pressure. The crude mixture was extracted with ethyl acetate (3 × 2 mL). The combined organic layer was washed with brine (10 mL), dried with anhydrous sodium sulfate and concentrated under reduced pressure. The crude was purified on silica gel eluting with ethyl acetate:hexane (1:9), followed by concentration to furnish *(R)-tert*-butyl(2-(3-((*tert*-butyldimethylsilyl)oxy)phenyl)-2-hydroxyethyl)(methyl)carbamate **(92)** (0.09 g, 87% yield) as a white solid.

General modified Mosher's method to calculated % enantiomeric excess (%ee)



92 **93**

To a stirred solution of *(R)*-*tert*-butyl(2-(3-((*tert*-butyldimethylsilyl)oxy)-phenyl)-2-hydroxyethyl)(methyl)carbamate **(92)** (0.01 g, 0.03 mmol) and *(R)*-(+)-α-Methoxy-α-trifluoromethylphenylacetic acid (0.03 g, 0.13 mmol) in dry dichloromethane (1 mL) was added *N,N'*-dicyclohexylcarbodiimide (0.04 g, 0.17 mmol) and *N,N'*-dimethylaminopyridine (a catalytic amount). The above mixture was stirred at room temperature for 24 h and the precipitated urea was then filtered off. The filtrate was washed with 1.0 M hydrochloric acid solution, saturated sodium hydrogen carbonate solution, brine and then dried over anhydrous sodium sulfate followed by concentrated under reduced pressure to give the crude of *(S)-(R)*-2-((*tert*-butoxycarbonyl)(methyl)amino)-1-(3-((*tert*-butyldimethylsilyl)oxy)phenyl)ethyl-3,3,3 - trifluoro-2-phenylpropanoate **(93)** as a white solid.

Asymmetric reduction of tert-butyl(2-(3-((tert-butyldimethylsilyl)oxy)phenyl)-2-oxoethyl)(methyl)carbamate (91)

The reduction of the ketone **(91)** was done with *(R)*-2-Methyl-CBS-oxazaborolidine and borane-tetrahydrofuran complex under various amount of *(R)*-2-Methyl-CBS-oxazaborolidine (0.10 eq, 0.25 eq, 0.50 eq and 1.00 eq) at room tempera- ture and temperature (-78^{o}C, -40 ^{o}C, -20^{o}C, 0 ^{o}C and room temperature) with 0.1 eq of *(R)*-2-Methyl-CBS-oxazaborolidine. The data of this step are presented in Table 1 and Table 2, respectively.

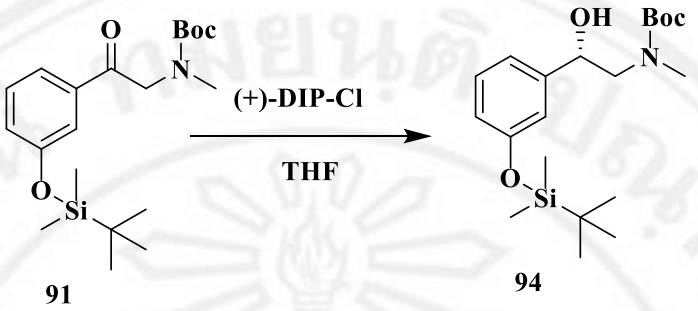
Table 1 Asymmetric reduction of ketone **(91)** at various the amount of *(R)*-2-Methyl-CBS-oxazaborolidine at room temperature.

Entry	Amount of *(R)*-MeCBS-oxazaborolidine	%Yield	%ee*(R)*
1	0.10	81	64
2	0.25	77	71
3	0.50	66	84
4	1.00	81	90

Table 2 Asymmetric reduction of ketone **(91)** at various temperature with 0.1 eq of *(R)*-2-Methyl-CBS-oxazaborolidine

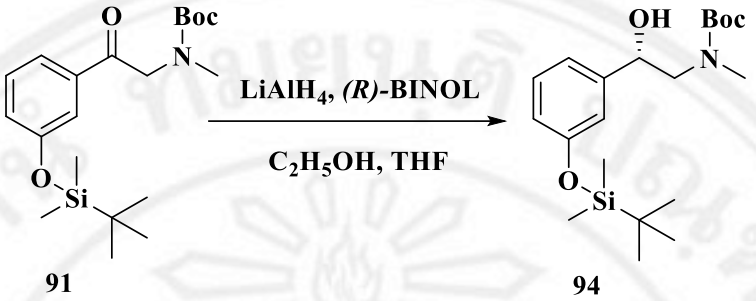
Entry	Temperature (^{o}C)	%Yield	%ee*(R)*
1	-78	72	21
2	-40	36	41
3	-20	64	44
4	0	75	77
5	RT	81	64

<u>Procedure 2</u> via (+)-B-Chlorodiisopinocampheyl borane



(+)-*B*-Chlorodiisopinocampheylborane (0.29 g, 0.90 mmol) in anhydrous tetrahydrofuran (1 mL) at -78ºC under nitrogen gas was added with the solution of ketone **(91)** (0.10 g, 0.25 mmol) in tetrahydrofuran (1 mL), and stirred for 4 h, then allowed to warm up to room temperature for overnight. Work up of the reaction was initiated by the addition of tetrahydrofuran (2 mL), followed by diethanolamine (0.30 mL) and the mixture was stirred at room temperature for 2 h when the boron components precipitated as a complex. This precipitate was filtered and washed with ethyl acetate. The combined filtrates were concentrated and purified by column chromatography with gradient 3-10% ethyl acetate in hexane to give *(S)-tert*-butyl(2-(3-((*tert*-butyldimethylsilyl)oxy)phenyl)-2-hydroxyethyl)(methyl)carbamate **(94)** (0.05 g, 55% yield, 99% ee*(S)*) as a white solid.

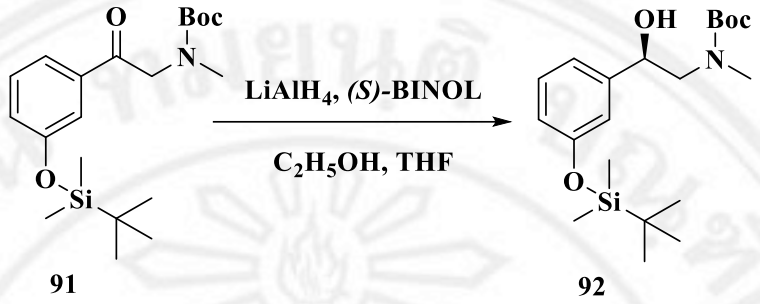
<u>Procedure 3</u> via (R)-1,1-Binaphthol and lithium aluminium hydride



91 **94**

The suspension of lithium aluminium hydride powder (0.04 g, 1.11 mmol) in 2 mL of anhydrous tetrahydrofuran was stirred at room temperature under nitrogen gas. The solution of ethanol (0.04 mL, 0.69 mmol) in 0.10 mL of tetrahydrofuran was added dropwise with vigorous evolution of hydrogen gas. The mixture was stirred for 20 min and a solution of *(R)*-1,1-binaphthol (0.16 g, 0.57 mmol) in 0.60 mL of tetrahydrofuran was added by means of a cannula. The resulting cloudy, milky solution was refluxed for 2 h. The solution was cooled to -78^{o}C and solution of ketone **(91)** (0.18 g, 0.48 mmol) in 0.30 mL of tetrahydrofuran was added by means of a cannula. The reaction mixture was stirred for overnight as the bath slowly warms to room temperature. The reaction was quenched by the careful addition of 5 mL of saturated ammonium chloride solution and diluted with water (5 mL) and ether (10 mL). The layers were separated. The organic layers were combined and washed with aqueous saturated sodium hydrogencarbonate (10 mL), dried over anhydrous sodium sulfate, filtered and the solvent was removed under reduced pressure. Purification by preparation thin layer chromatography plate to give *(S)-tert*-butyl(2-(3-((*tert*-butyldimethylsilyl)oxy)phenyl)-2-hydroxyethyl)(methyl)carbamate **(94)** (0.13 g, 68% yield, >99% ee*(S)*) as a white solid.

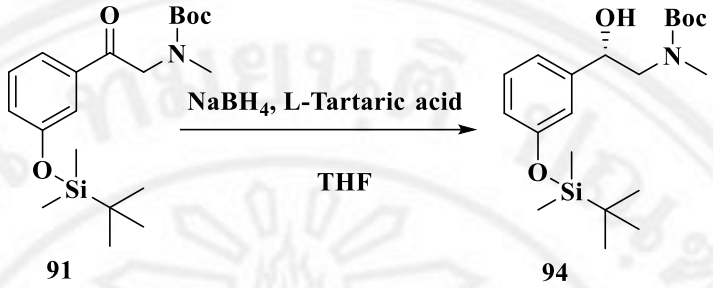
<u>Procedure 4</u> via (S)-1,1-Binaphthol and lithium aluminium hydride



91 **92**

The suspension of lithium aluminium hydride powder (0.06 g, 1.48 mmol) in 2 mL of anhydrous tetrahydrofuran was stirred at room temperature. The solution of ethanol (0.04 mL, 0.69 mmol) in 0.10 mL of tetrahydrofuran was added dropwise with vigorous evolution of hydrogen gas. The mixture was stirred for 20 min and a solution of *(S)*-1,1-binaphthol (0.16 g, 0.57 mmol) in 0.60 mL of tetrahydrofuran was added by means of a cannula. The resulting cloudy, milky solution was refluxed for 2 h. The solution was cooled to -78^{o}C and solution of ketone **(91)** (0.18 g, 0.48 mmol) in 0.30 mL of tetrahydrofuran was added by means of a cannula. The reaction mixture is stirred for overnight as the bath slowly warms to room temperature. The reaction was quenched with 5 mL of aqueous saturated ammonium chloride solution and diluted with water (5 mL) and ether (10 mL). The layers were separated. The organic layers were combined and washed with aqueous saturated sodium hydrogencarbonate (10 mL), dried over anhydrous sodium sulfate, filtered and the solvent was removed under reduced pressure. Purification by preparation thin layer chromatography plate to give *(R)*-*tert*-butyl(2-(3-((*tert*-butyldimethylsilyl)oxy)phenyl)-2-hydroxyethyl)(methyl)carbamate **(92)** (0.12 g, 66% yield, 75% ee*(R)*) as a white solid.

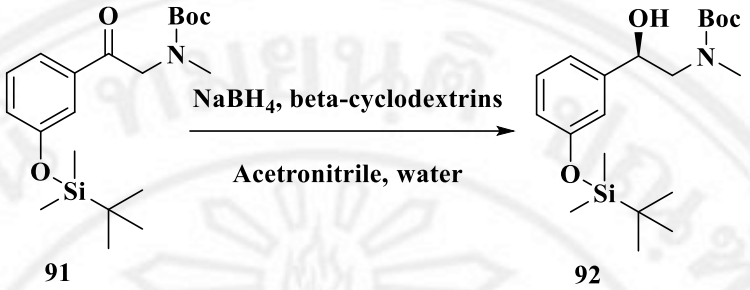
Procedure 5 via sodium borohydride and L-tartaric acid



91 **94**

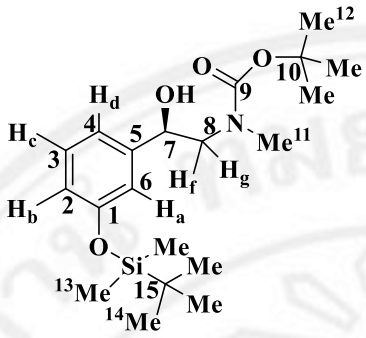
L-tartaric acid (0.16 g, 1.10 mmol) and sodium borohydride (0.04 g, 1.18 mmol) in anhydrous tetrahydrofuran (1 mL) was added to the flask, and the reaction mixture was heated at reflux for 5 h. The mixture was slowly cooled to -78^{o}C. A solution of ketone **(91)** (0.09 g, 0.24 mmol) in 1 mL of tetrahydrofuran was added dropwise to the reaction mixture while maintaining the temperature at -78^{o}C. The mixture was warmed slowly to room temperature, stirred for 60 h and treated dropwise with water (5 mL) at 0^{o}C. The mixture was warmed at room temperature, and tetrahydrofuran was removed under reduced pressure. To the mixture was charged with 10 mL of diethyl ether and 1 mL of 1.0 M hydrochloric, the organic layer was separated with diethyl ether (2 × 10 mL). The combined organic layers were washed with 10 mL of water, 10 mL of brine and then dried over anhydrous sodium sulfate. The organic layer was concentrated under reduced pressure. Purification of the crude products by silica gel column chromatography (eluent : hexane-ethyl acetate; 19:1 to 17:3) to give *(S)-tert*-butyl(2-(3-((*tert*-butyldimethylsilyl)oxy) phenyl)-2-hydroxyethyl)(methyl)carbamate **(94)** (0.07 g, 84% yield, 13%ee*(S)*) as a white solid.

<u>Procedure 6</u> via sodium borohydride and β-cyclodextrins

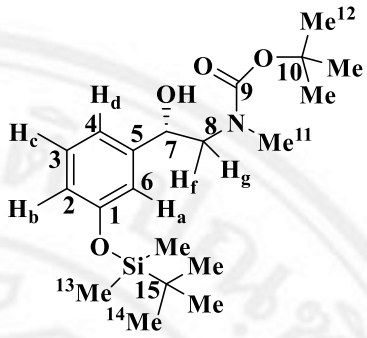


91 **92**

β-Cyclodextrin (3.01 g, 2.66 mmol) was suspended in 50 mL of 0.1 M aqueous potassium carbonate solution. The ketone **(91)** (0.10 g, 0.27 mmol) dissolved in 1 mL of acetronitrile was added and the mixture was stirred for a day at 35°C. After 24 h, a mixture of sodium borohydride (0.08 g, 2.05 mmol) and potassium carbonate (0.06 g, 0.45 mmol) in water (5 mL) was added and stirred for 16 h. Diethyl ether (50 mL) was added to the reaction mixture and stirred for 0.5 h. After the precipitated *β*-Cyclodextrin was removed, two layers were separated and the aqueous layer was extracted with diethyl ether (3 × 25 mL). The filtered *β*-Cyclodextrin was suspended in 50 mL of warm water and extracted was above with diethyl ether. The combined diethyl ether layers were dried with anhydrous sodium sulfate, concentrated and purified by column chromatography to afford *(R)-tert*-butyl(2-(3-((*tert*-butyldimethyl silyl)oxy)phenyl)-2-hydroxyethyl)(methyl)carbamate **(92)** (0.008 g, 8% yield, 19%ee *(R)*) as a white solid.



92

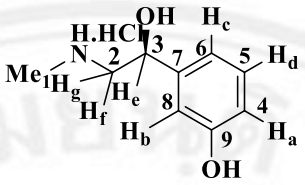


94

Compound 92, 94: mp 74-76°C; **FT-IR** (KBr), ν_{max} 3432, 2957, 2931, 2859, 1675, 1483, 1393, 1277, 1155, 877, 781 cm^{-1}; **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.15 (t, *J* = 7.8 Hz, 1H, H_c), 6.90 (d, *J* = 7.4 Hz, 1H, H_d), 6.84 (s, 1H, H_a), 6.71 (d, *J* = 7.9 Hz, 1H, H_b), 4.81 (br, 1H, H_e), 3.38 (s, 2H, H_f, H_g), 2.76 (s, 3H, Me_{11}), 1.43 (s, 9H, Me_{12}), 0.96 (s, 9H, Me_{14}), 0.17 (s, 6H, Me_{13}); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 157.78 (C-1), 155.62 (C-9), 144.03 (C-5), 129.17 (C-3), 118.96 (C-2), 118.72 (C-4), 117.54 (C-6), 80.09 (C-10), 73.17 (C-7), 57.30 (C-8), 36.35 (C-11), 28.27 (C-15), 25.57 (C-12), 18.04 (C-14), -4.52 (C-13); **HRMS** calcd for $C_{20}H_{36}NO_4Si$ $[M+H]^+$ 382.2414, found 382.2415.

2.4.5 Preparation of (R)-Phenylephrin hydrochloride (3)

The excess amount of hydrochloric acid (6M, 0.20 mL) was added to the solution of *(R)-tert*-butyl(2-(3-((*tert*-butyldimethylsilyl)oxy)phenyl)-2-hydroxyethyl) (methyl) carbamate **(92)** (0.10 g, 0.26 mmol) in dry methanol (5 mL). The mixture solution was stirred at room temperature for 4 h. The solution was concentrated under reduced pressure and the residue was purified on silica gel by eluting with methanol:dichloromethane (1:19). This was then concentrated to produce *(R)*-phenylephrin hydrochloride **(3)** in quantitative yield as a white solid.



3

Compound 3: mp. 141-143°C (Lit[18] mp 141 °C); **FT-IR** (KBr), ν_{max} 3419, 2963, 2798, 1593, 1462, 1274, 1083, 879 cm^{-1}; **^{1}H-NMR** (500 MHz, DMSO-d_6) δ 9.56 (s, 1H,OH or NH), 8.99 (br, 1H, OH or NH), 7.15 (t, J = 7.8 Hz, 1H, H_d), 6.81 (br, 1H, H_b), 6.78 (d, J = 7.7 Hz, 1H, H_c), 6.70 (d, J = 8.0 Hz, 1H, H_a), 6.11 (s, 1H, OH), 4.83 (d, J = 8.3 Hz, 1H, H_e), 3.05 (d, J = 12.5 Hz, 1H, H_f or H_g), 2.91 (d, J = 12.4 Hz, 1H, H_f or H_g), 2.53 (s, 3H, Me_1); **^{13}C-NMR** (125 MHz, DMSO-d_6) δ 157.99 (C-9), 143.71 (C-7), 129.78 (C-5), 116.74 (C-6), 115.12 (C-4), 113.22 (C-8), 68.49 (C-3), 55.37 (C-2), 33.14 (C-1); **HRMS** calcd for $C_9H_{14}NO_2$ $[M+H]^+$ 168.0980, found 168.1019.