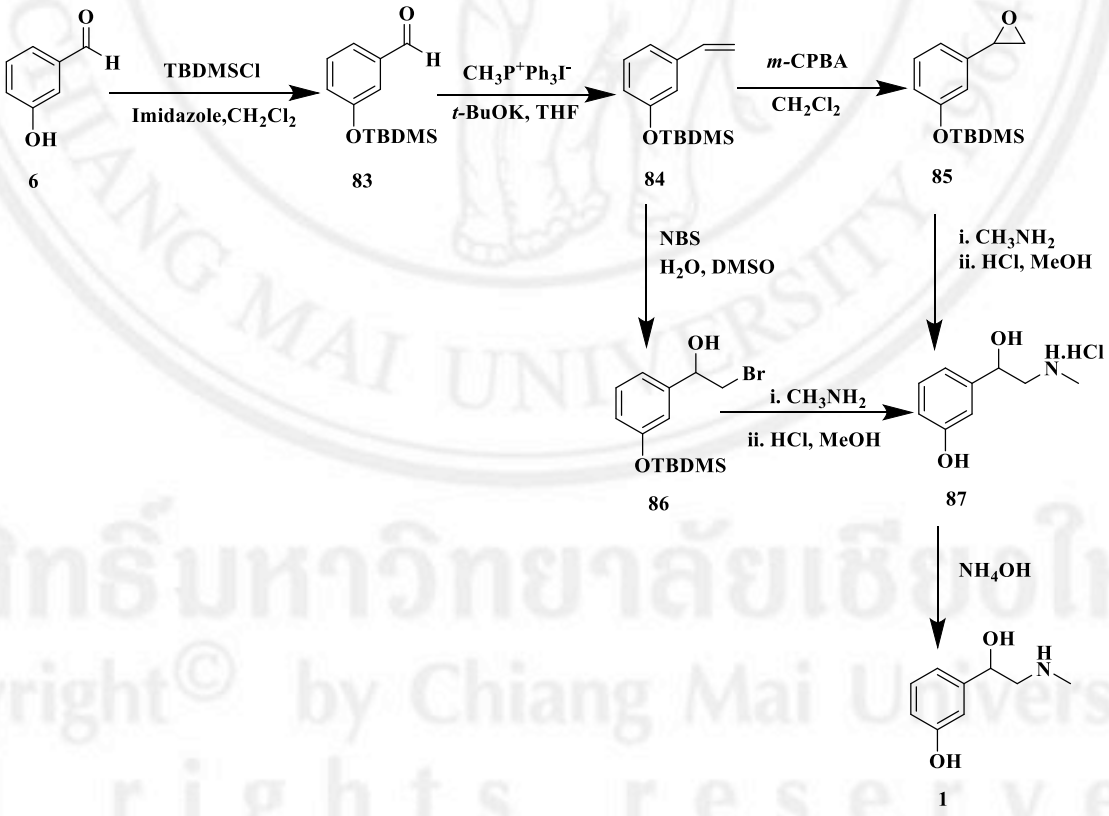
CHAPTER 4

CONCLUSIONS

In conclusion, we have developed alternative routes for the synthesis of racemic phenylephrine and *(R)*-phenylephrine including their hydrochloride salts. These routes provide good yields, short reaction times and could be performed entirely at room temperature. The complete pathway for the synthesis of racemic phenylephrine is in accordance with Scheme 62.

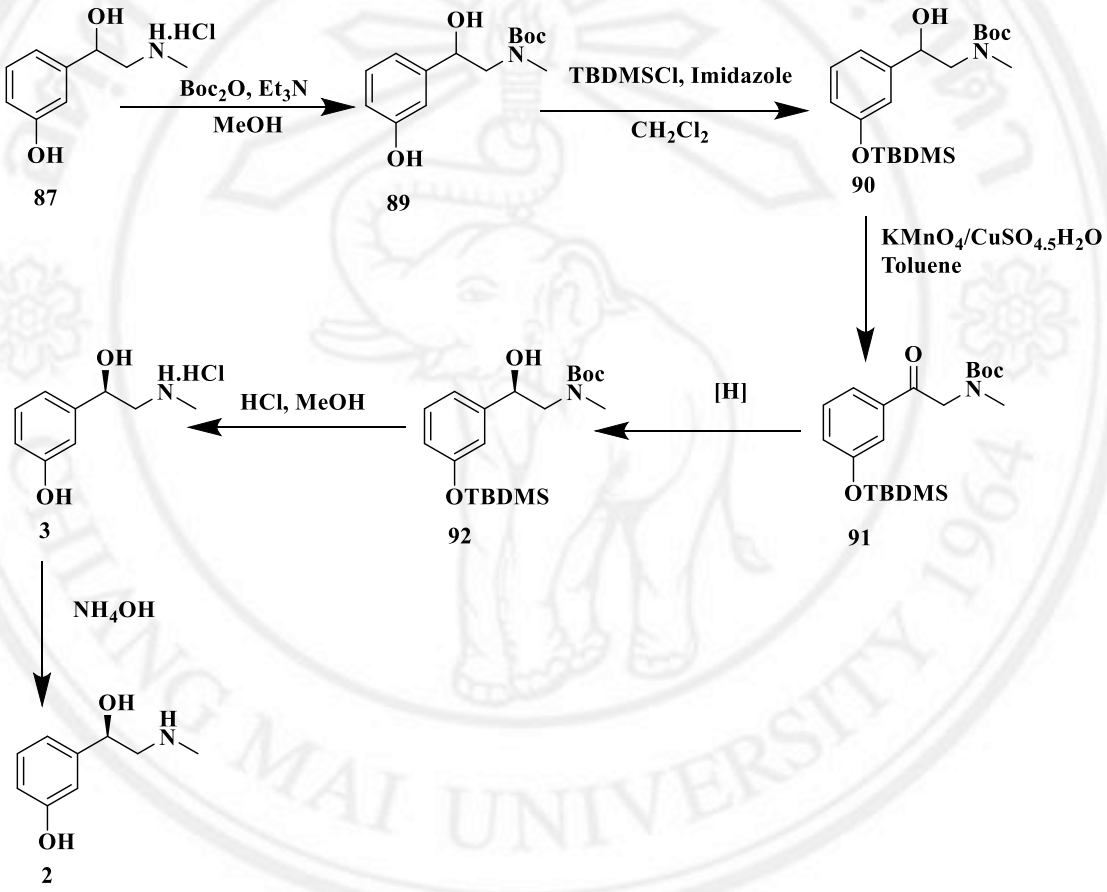


Scheme 62 The synthesis pathway for racemic phenylephrine and racemic phenylephrine hydrochloride

This pathway started with the protection of the hydroxyl group with tert-butyldime- thylsilyl chloride (TBDMSCl) in the presence of imidazole and CH_2Cl_2, followed by Wittig olefination of aldehyde **83** with phosphonium salt under basic conditions to afford alkene **84**. After these steps, the synthesis could be performed using two pathways. The alkene **84** was epoxidized with *m*-chloroperoxybenzoic acid to give epoxide **85**. Alternatively, the treatment of alkene **84** with *N*-bromosuccinimide (NBS) in the presence of H_2O and DMSO produced bromohydrin **86**. In the final step, the epoxide **85** and bromohydrine **86** were treated with methylamine gas, followed by removal of *t*-butyldimethylsilyl group with hydrochloric acid solution to produce racemic phenylephrine hydrochloride **(87)**. Basicify of the salt **87** with ammonium hydroxide TS solution gave racemic phenylephrine **(1)**. The overall yield of racemic phenylephrine hydrochloride from epoxide **85** and bromohydrin **86** were 71% and 66%, respectively.

The synthesis of *(R)*-phenylephrine **(2)** from the racemate is as follow, the direct oxidation of (±)-phenylephrine hydrochloride can not be achieved, to avoid this problem, (±)-phenylephrine hydrochloride was protected with di-*t*-butyldicarbonate and *tert*-butyldimethylsilyl chloride to give amino alcohol **(90)**. Then the simple oxidation of amino alcohol **(90)** with potassium permanganate in the presence of copper (II) sulfate pentahydrate was developed to afford amino ketone **(91)** in high yield (86%). Asymmetric reduction of ketone with Chiral reagents (modified lithium aluminium hydride with *(R)*-BINOL and *(S)*-BINOL, (+)-*β*-chlodiisopinocampheylborane (DIP-Cl, Ipc_2BCl), enzymic reducing agents (Baker's yeast and *Daucus carota*)) and chiral catalysts (*Corey-Bakshi-Shibata (CBS) reduction*, *β*-cyclodextrins and L-tartaric acid) was shown in Scheme 63. Reduction of

amino ketone **(91)** was shown in Table 4. In final step, the deprotection with hydrochloric solution was developed to afford *(R)*-phenylephrine hydrochloride **(3)**. *(R)*-Phenylephrine **(2)** could be obtained after basification of salt **3** with ammonium hydroxide TS solution.



Scheme 63 The synthesis pathway for *(R)*-phenylephrine (2) and *(R)*-phenylephrine hydrochloride (3)

Table 4 Asymmetric reduction of amino ketone (91)

Entry	Reducing agent	%yield	%ee
1	Borane-THF and *(R)*-2-methyl-CBS-oxazaborolidine	36-81	21-90 *(R)*
2	(+)-*β*-Chlodiisopinocampheylborane	55	99 *(S)*
3	(-)-*β*-Chlodiisopinocampheylborane	No reaction	
4	Lithium aluminium hydride and *(R)*-BINOL	68	>99 *(S)*
5	Lithium aluminium hydride and *(S)*-BINOL	66	75 *(R)*
6	Sodium borohydride and L-tartaric acid	84	13 *(S)*
7	Sodium borohydride and *β*-cyclodextrins	8	19 *(R)*
8	Baker's yeast	No reaction	
9	*Daucus carota* from carrot	No reaction	

It is shown in this table that the percentage yield had a wide range from 8% to 84% and the enantiomeric excess was 19-90%*(R)* and 13-99%*(S)*. Moreover, the reduction of amino ketone **(91)** with enzymic reducing agent could not be occurred and could be explored for more information. The reduction of amino ketone **(91)** with (-)-*β*-Chlodiisopinocampheylborane could not occurr because (-)-*β*-chlodiisopino campheylborane was air and moisture sensitive and difficult to handle.

Furthermore, *(R)*-phenylephrine was prepared by asymmetric reduction of amino ketone **(91)** with borane-THF complex and *(R)*-2-methyl-CBS-oxazaborolidine (1 eq.) at room temperature, lithium aluminium hydride and *(S)*-BINOL and sodium borohydride and *β*-cyclodextrins. The yields were 81%, 66%, and 8%, respectively. The enantiomeric excess were 90%, 75% and 19%, respectively.

In conclusion, the synthesis of racemic phenylephrine **(1)** and *(R)*-phenylephrine **(2)** in this study has been achieved. These synthetic routes are convenient and economical enough for further applications.