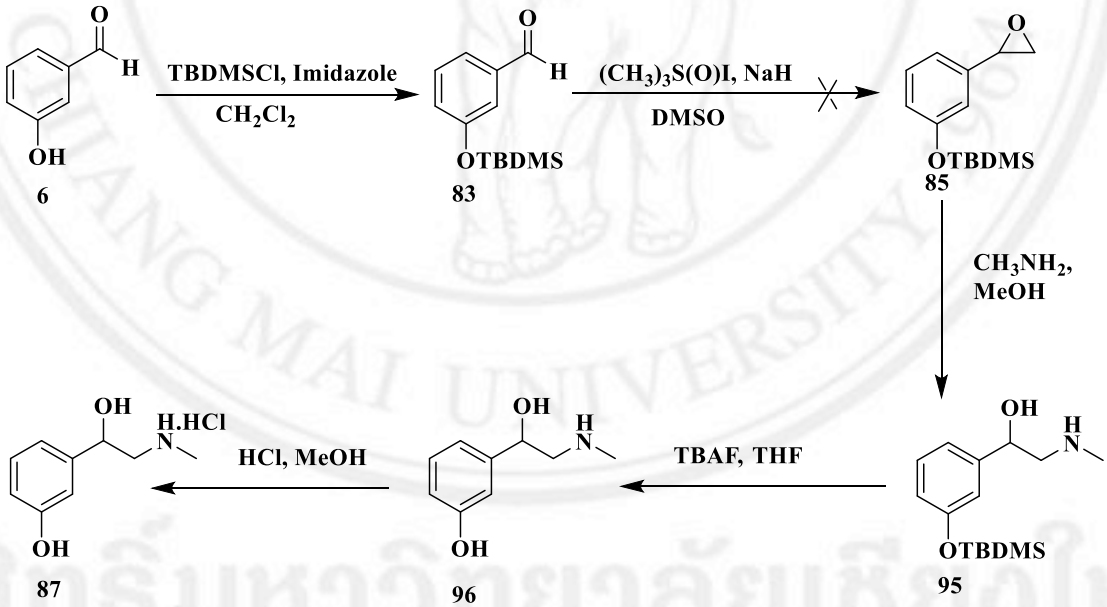
CHAPTER 3

RESULTS AND DISCUSSION

3.1 The synthesis of (±)-phenylephrine

The initial synthetic plan has five steps, which involved protection of hydroxyl group, epoxidation, epoxide ring opening and deprotection as shown in Scheme 29. It was believed that this route is a simple condition, low cost and considered a short pathway for (±)-phenylephrine.



6 83 85 87 96 95

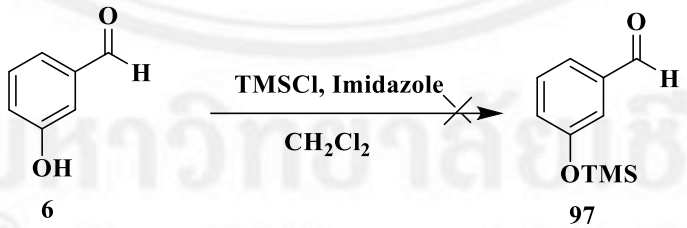
Scheme 29 The first attempt for (±)-phenylephrine pathway

Protection of *m*-hydroxybenzaldehyde **(6)** with *t*-butyldimethylsilyl chloride under basic imidazole in dichloromethane was done at room temperature for 24 hours in order to afford protected aldehyde **(83)** with quantitative yield. The IR

spectra of aldehyde **(83)** showed strong C=O stretching at a wavelength of 1705 cm^{-1} and HRMS found $C_{13}H_{21}O_2Si$ $[M+H]^+$ 237.1313 (calculated 237.1311). The ^{1}H-NMR spectra of aldehyde **(83)** showed the methyl protons (6H) which are adjacent to the silicon atom, as a singlet at δ = 0.22 ppm and the *t*-butyl protons (9H) as a singlet at δ = 0.99 ppm.

Epoxide formation of aldehyde **(83)** with trimethylsulfoxonium iodide and sodium hydride and dimethylsulfoxide was not successful due to the cleavage of the *t*-butyldimethylsilyl group. The obtained product showed no signal of the *tert*-butyl group, 9 protons at δ = 0.99 ppm and dimethylsilyl group, 6 protons at δ = 0.22 ppm in the ^{1}H-NMR spectrum. Since cleavage of the protecting group occurred, several protecting groups were studied *i.e.* trimethylsilyl chloride (TMSCl), *t*-butyl chloride (*t*-BuCl) and benzyl bromide (BnBr) in order to achieve the protected aldehyde that was stable enough in the epoxidation step.

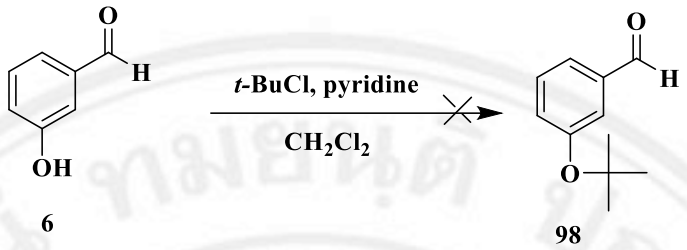
Protection of hydroxyl group with trimethylsilyl chloride (TMSCl) was shown in Scheme 30. It was found that the protecting group was lost in silica gel column chromatography, the compound **(97)** was converted to the starting material.



6 97

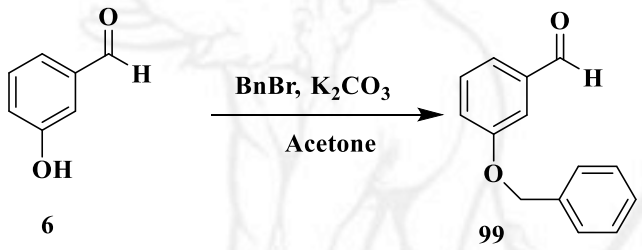
Scheme 30 The protection of hydroxyl group with trimethylsilyl chloride

After that the *t*-butyl chloride was used to protect the hydroxyl group in basic pyridine in dichloromethane at room temperature for overnight (Scheme 31). The compound **(98)** did not show on TLC.



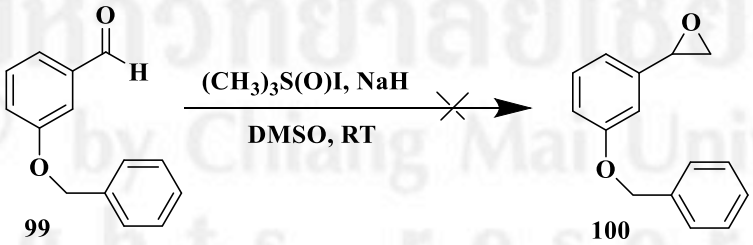
Scheme 31 The protection of hydroxyl group with *t*-butyl chloride

Benzyl bromide was chosen in other conditions for the protection of the hydroxyl group as shown in Scheme 32. The reaction was refluxed in acetone for 5 hours which afforded the aldehyde **(99)** in 87% yield.



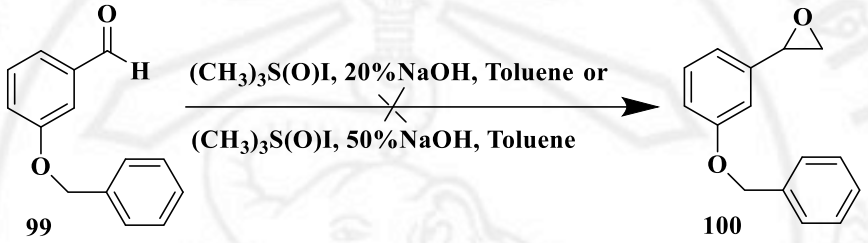
Scheme 32 The protection of hydroxyl group with benzyl bromide

Then the aldehyde **(99)** was epoxidized with trimethylsulfoxonium iodide under basic sodium hydride in dimethylsulfoxide at room temperature for 30 min[76] as shown in Scheme 33. It was found that aldehyde **(99)** could not be epoxidized to epoxide **(100)**.



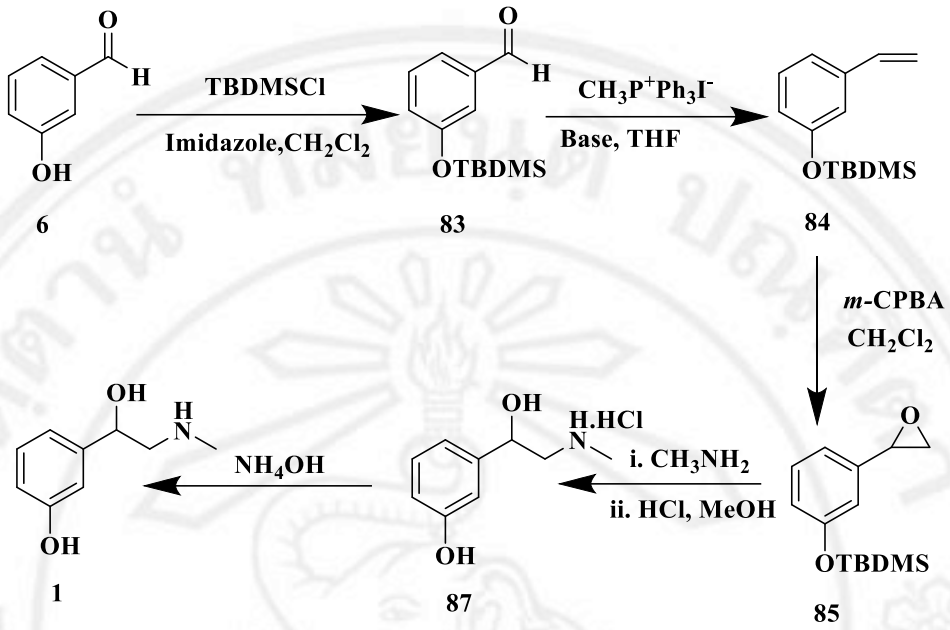
Scheme 33 The epoxidation of aldehyde with trimethylsulfoxonium iodide and sodium hydride

Moreover attempts to prepare epoxide **(100)** using other condition such as trimethylsulfoxonium iodide in 20% sodium hydroxide in toluene and trimethylsulfoxonium iodide in 50% sodium hydroxide in toluene[77] (Scheme 34), were not successful in affording epoxide **(100)**. Only starting material was left in the reaction mixture.



Scheme 34 The epoxidation of aldehyde with trimethylsulfoxonium iodide and sodium hydroxide

With the prior failure in epoxide formation, another route was explored. The plan was to achieve Wittig reaction of aldehyde **(83)** with phosphonium salt under basic conditions to form alkene **(84)**, followed by epoxidation of alkene **(84)** to give epoxide **(85)**, and the ring opening of epoxide **(85)** with methylamine gas. In the last step, the deprotection of *t*-butyldimethylsilyl group with hydrochloric solution to afford (±)-phenylephrine hydrochloride **(87)** and basicify of salts with ammonium hydroxide TS solution to give (±)-phenylephrine **(1)**, as shown in Scheme 35.



Scheme 35 (±)-Phenylephrine synthesis pathway *via* epoxide

Synthesis of (±)-phenylephrine **(1)** through Wittig reaction of aldehyde **(83)** with 1.2 equivalents of phosphonium salt (synthesized from methyl iodide and triphenylphosphine in hexane at room temperature for overnight) and 1.2 equivalents of *n*-butyl lithium in tetrahydrofuran[78,79] gave alkene **(84)** in low yield (12%) as a colorless oil. The disappearance of an aldehyde proton at δ = 9.94 (1H) and the occurrence of olefinic protons at δ = 6.77 (1H), 5.82 (1H) and 5.32 (1H) confirmed that the alkene **(84)** was occurred, as shown in Figure 1. The IR spectrum of alkene **(84)** did not show strong C=O stretching at a wavelength of 1705 cm^{-1}, as shown in Figure 2 and HRMS found $C_{14}H_{23}O_2Si$ $[M+H]^+$ 235.1512 (calculated 235.1518). The reason behind the low yield might be the moisture-sensitive nature of *n*-butyl lithium.

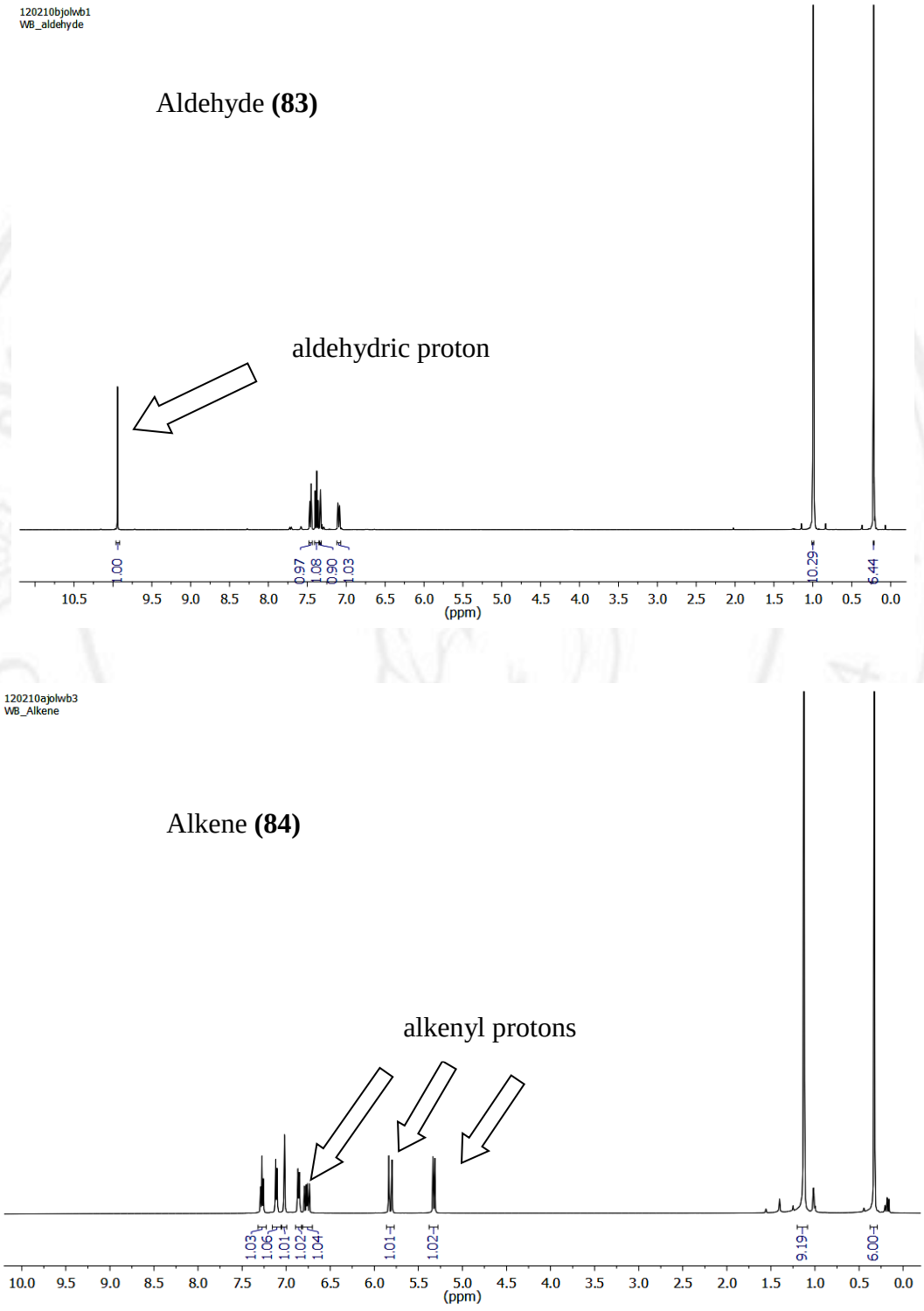


Figure 1 The ^{1}H-NMR spectra of aldehyde (83) and alkene (84)

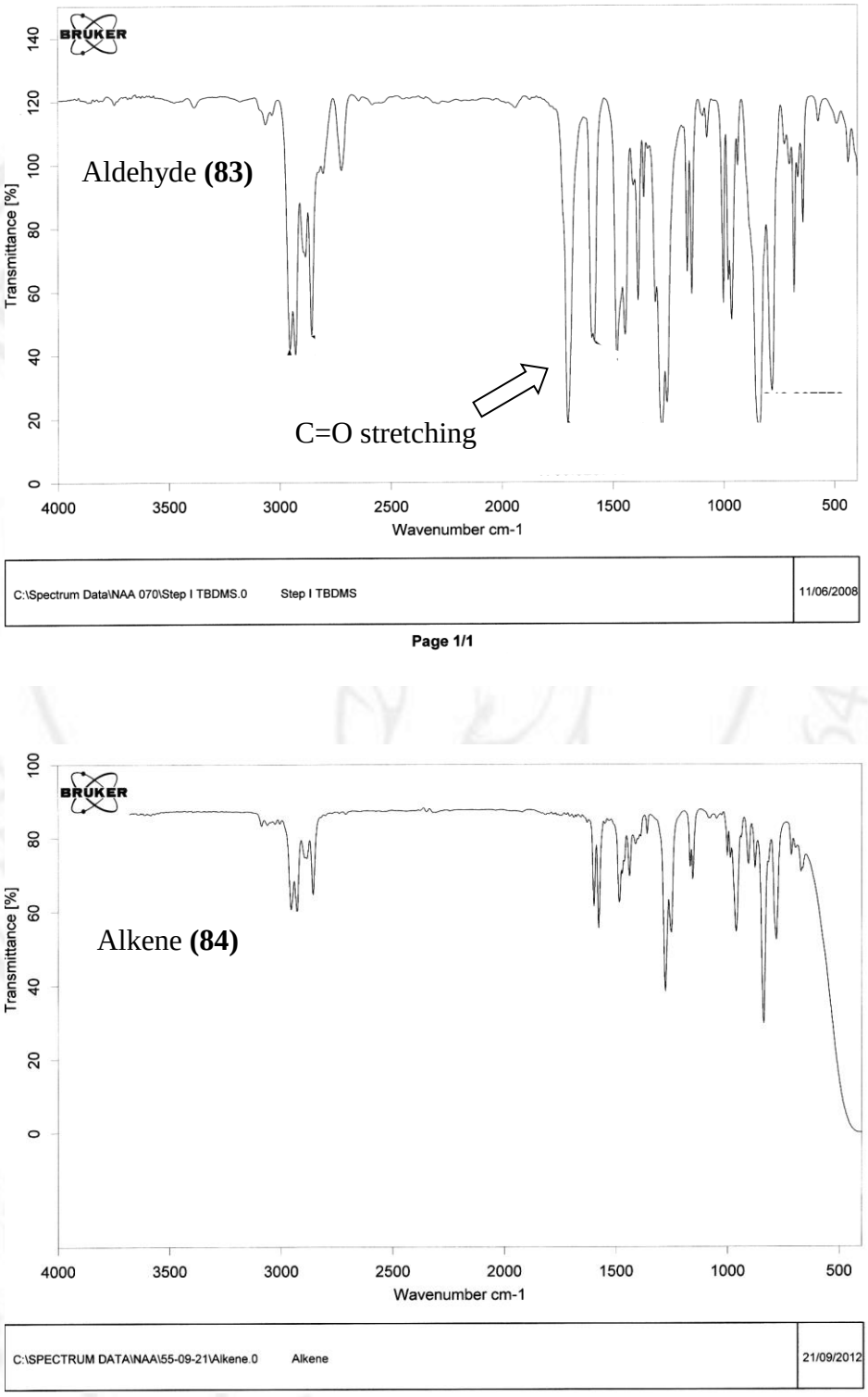
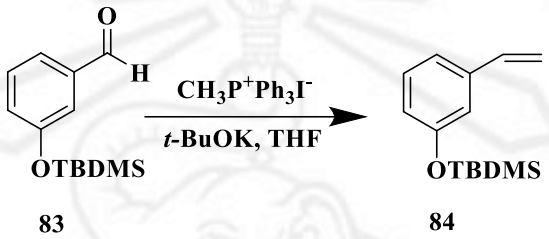


Figure 2 The IR spectra of aldehyde (83) and alkene (84)

Improvement of Wittig reaction of aldehyde **(83)** with phosphonium salt has been achieved using potassium *t*-butoxide instead of *n*-butyl lithium. The reaction employed 1.2 equivalents of phosphonium salt and 1.2 equivalents of potassium *t*-butoxide in the presence of tetrahydrofuran[80] at room temperature for 2 hours to produce alkene **(84)** in 97% yield, as shown in Scheme 36.

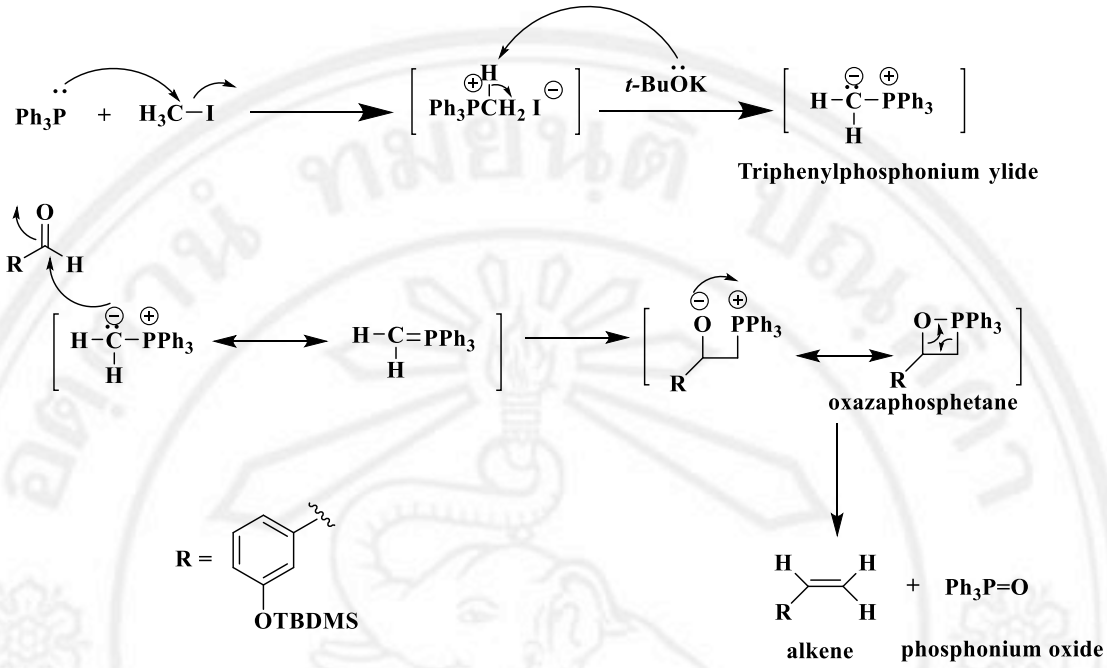


83 84

Scheme 36 Wittig reaction of aldehyde (83) with phosphonium salt and *t*-BuOK

The alkene **(84)** was confirmed by IR, ^{1}H-NMR and HRMS. The IR spectrum did not show strong C=O stretching at a wavelength of 1705 cm^{-1} and the ^{1}H-NMR spectrum showed the occurrence of olefinic protons at δ = 6.77 (1H), 5.82 (1H) and 5.32 (1H) . The HRMS found $C_{14}H_{23}O_2Si$ $[M+H]^+$ 235.1512 (calculated 235.1518).

The mechanism of Wittig reaction was proposed as shown in Scheme 37.[81, 82] In the first step, triphenylphosphine reacted with methyl iodide to form phosphonium salt, then the salt proton was abstracted by potassium *t*-butoxide to give triphosphonium ylide. After that, the nucleophilic phosphorus of ylide attacked the carbonyl group of the aldehyde to form a four-membered intermediate (oxazaphosphetane) from which the alkene product and the by-product triphenylphosphine oxide were released.



Scheme 37 The proposed mechanism of Wittig reaction

The resulting alkene **(84)** was epoxidized with *m*-chloroperoxybenzoic acid in dichloromethane at room temperature for 3 hours. The epoxide **(97)** occurred in high yield (81%) as a colorless liquid, the 1H-NMR spectrum showed the occurrence of protons at δ = 3.79 (1H), 3.09 (1H) and 2.24 (1H) as shown in Figure 3 and IR spectra of epoxide **(97)** showed strong C-O stretching at wavelength of 1284 cm^{-1} and disappearance of strong C=O stretching at a wavelength of 1705 cm^{-1} (Figure 4) and HRMS found $C_{14}H_{23}O_2Si$ $[M+H]^+$ found 251.1465 (calculated 251.1467).

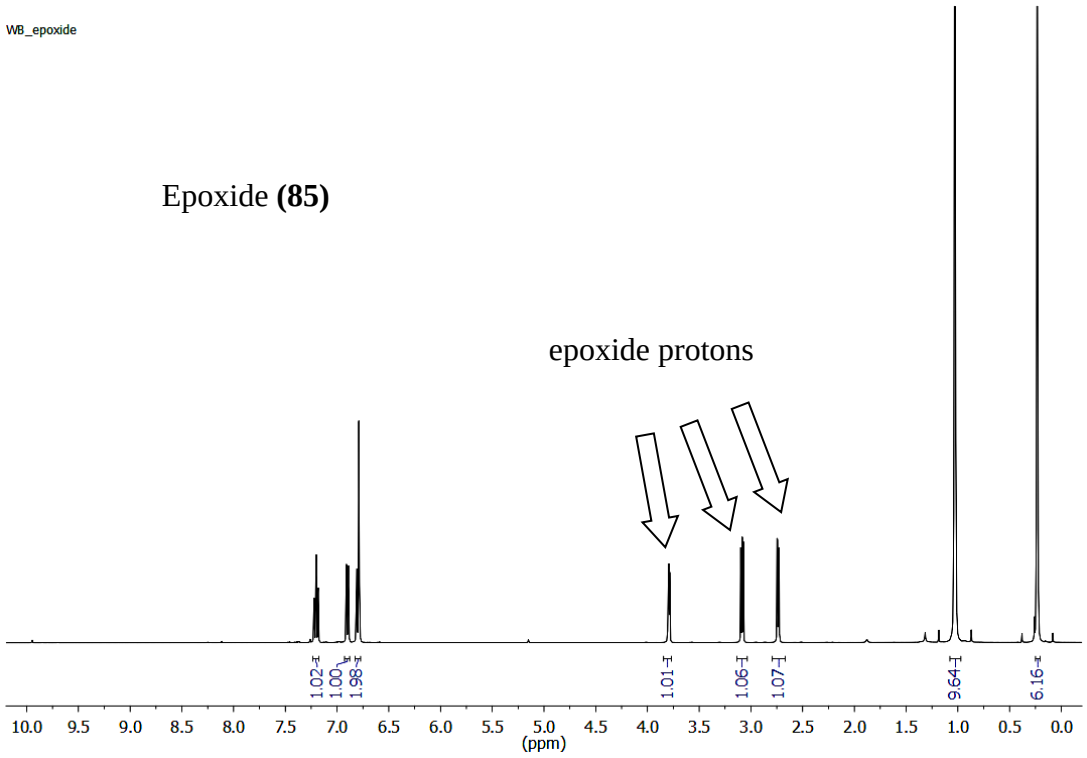


Figure 3 The ^{1}H-NMR spectrum of epoxide (85)

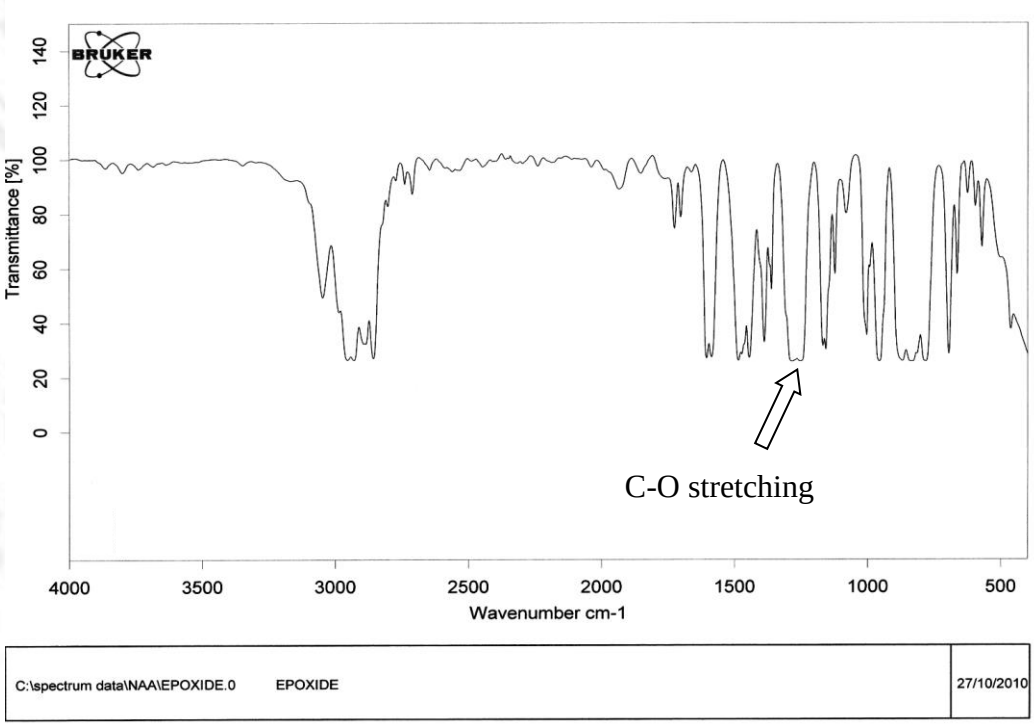
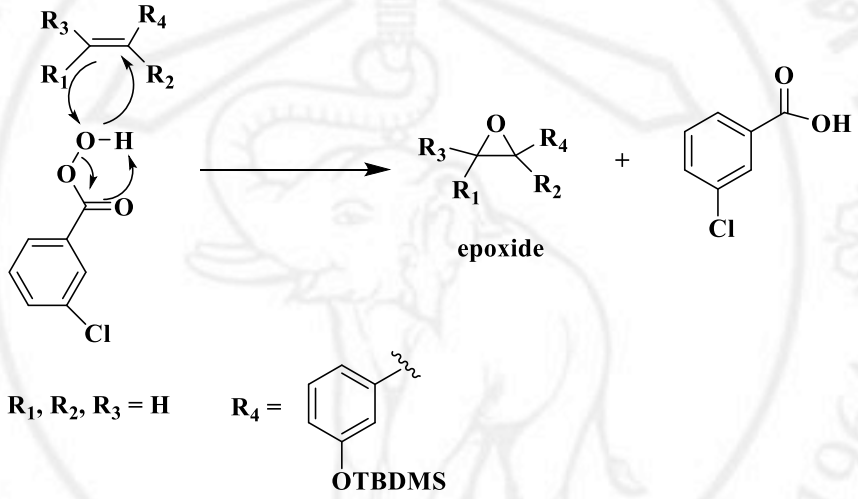


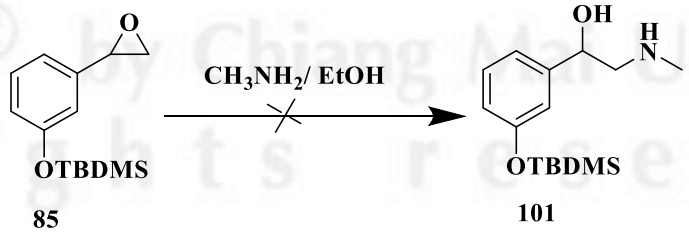
Figure 4 The IR spectrum of epoxide (85)

The mechanism of epoxidation with *m*-chloroperoxybenzoic was proposed as shown in Scheme 38.[83,84] The epoxidation of alkene by peroxyacid was believed to be a one step transfer of oxygen to the double bond. The reaction took place at the terminal oxygen atom of peroxyacid, and π-electrons of the olefin approaches the σ-electrons of the O-O bond.



Scheme 38 The proposed mechanism of epoxidation reaction

The ring opening of epoxide **(85)** was achieved by treating the epoxide with 5 equivalents of methylamine in ethanol solution (8 M), as shown in Scheme 39. After 24 hours, the reaction mixture was checked with TLC. It was fund that there were more than five spots on TLC chromatogram. The separation of the amino alcohol **(101)** from the crude mixture by column chromatography was, however, unsucessful.



Scheme 39 The epoxide ring opening with methylamine in ethanol solution

In the failure condition for epoxide ring opening, the ethanolic solution of methylamine was changed to anhydrous methylamine gas. The resulting epoxide **(85)** was opened with excess methylamine gas in the presence of dry methanol at room temperature for 2 hours, followed by the deprotection of *t*-butyldimethylsilyl group with 6 M hydrochloric solution[85,86] to afford (±)-phenylephrine hydrochloride **(87)** in 90% yield (over two steps) as a white solid. The ^{1}H-NMR spectrum disclosed the methyl protons (3H) as a singlet at δ = 2.53, methylene protons (2H) which are adjacent to the nitrogen atom, as a doublet of doublet at δ = 2.89-3.01, methine proton (1H) which are adjacent to the hydroxyl group as a doublet at δ = 4.85 and bezene ring protons (4H) as a multiplet at δ = 6.69-7.12. In addition, the ^{1}H-NMR spectrum was compared with standard (±)-phenylephrine hydrochloride to confirm the structure, as shown in Figure 5, which served as assurance that the formation of (±)-phenylephrine hydrochloride **(87)** had been achieved. Moreover, HRMS found $C_9H_{14}NO_2$ $[M+H]^+$ 168.0852 (calculated 168.0980) and mp.141-143^{o}C (Lit[18] mp 141 ^{o}C).

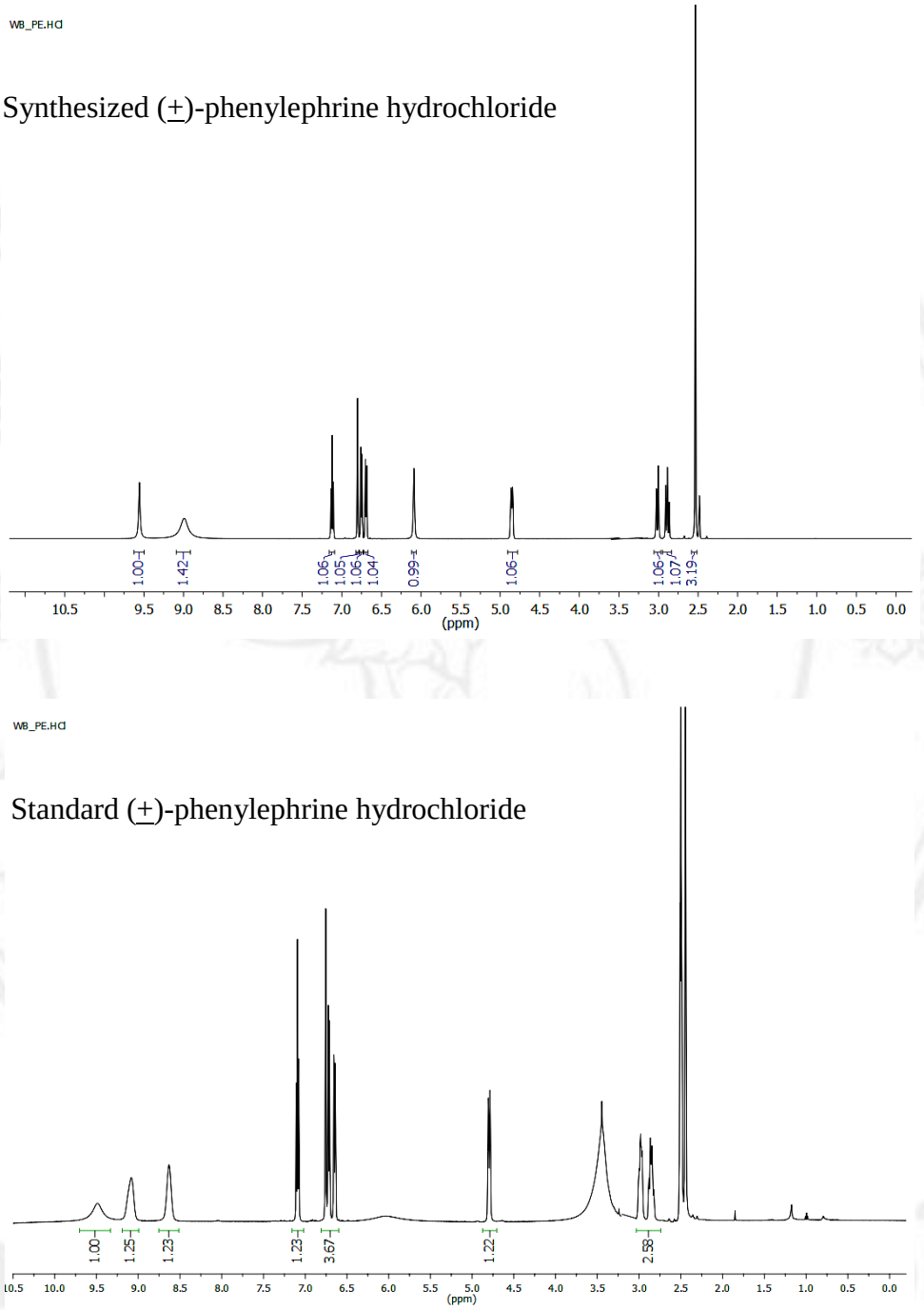
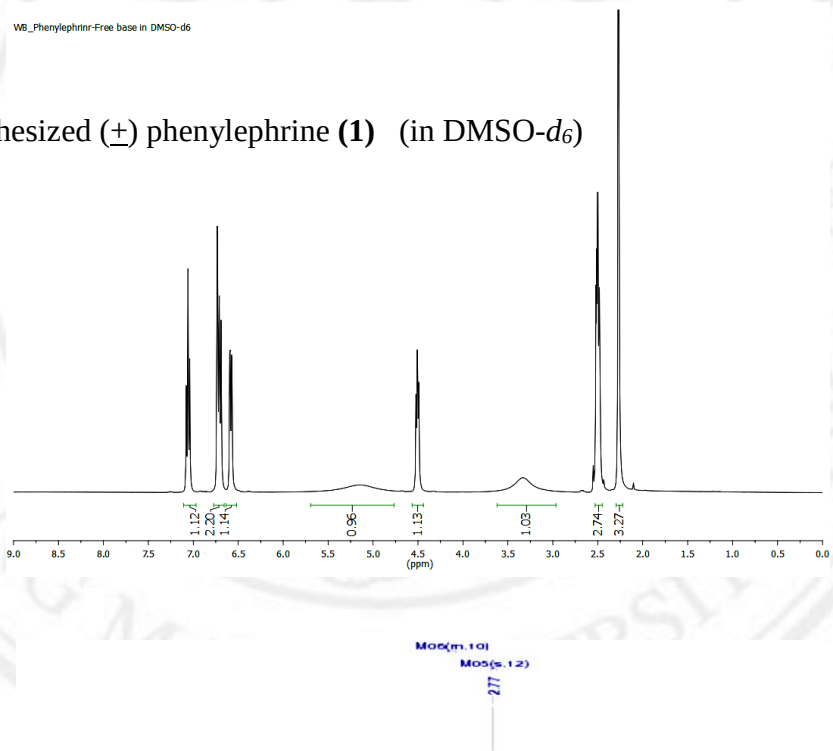


Figure 5 The ^{1}H-NMR spectra of synthesized (±)-phenylephrine hydrochloride and its standard

The final step for synthesis of (±)-phenylephrine was carried on. (±)-phenylephrine hydrochloride **(87)** was basified with ammonium hydroxide TS solution (ammonium hydroxide : water = 2:3). The precipitate was collected and washed with a few drops of ice-cold water and dried at 105°C for 2 hours to give (±)-phenylephrine **(1)** as a white solid. The ^{1}H-NMR spectrum was shown in Figure 6 and mp 170-172°C (Lit[87] mp 171 °C).



Synthesized (±) phenylephrine **(1)** (in DMSO-d_6)

Standard (±) phenylephrine **(1)** (in H_2O)

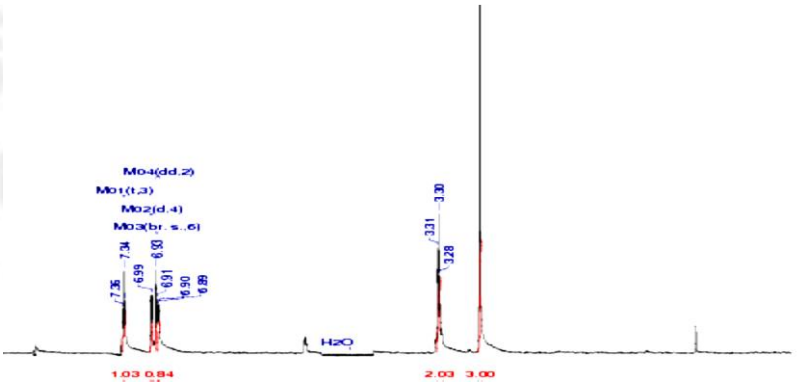
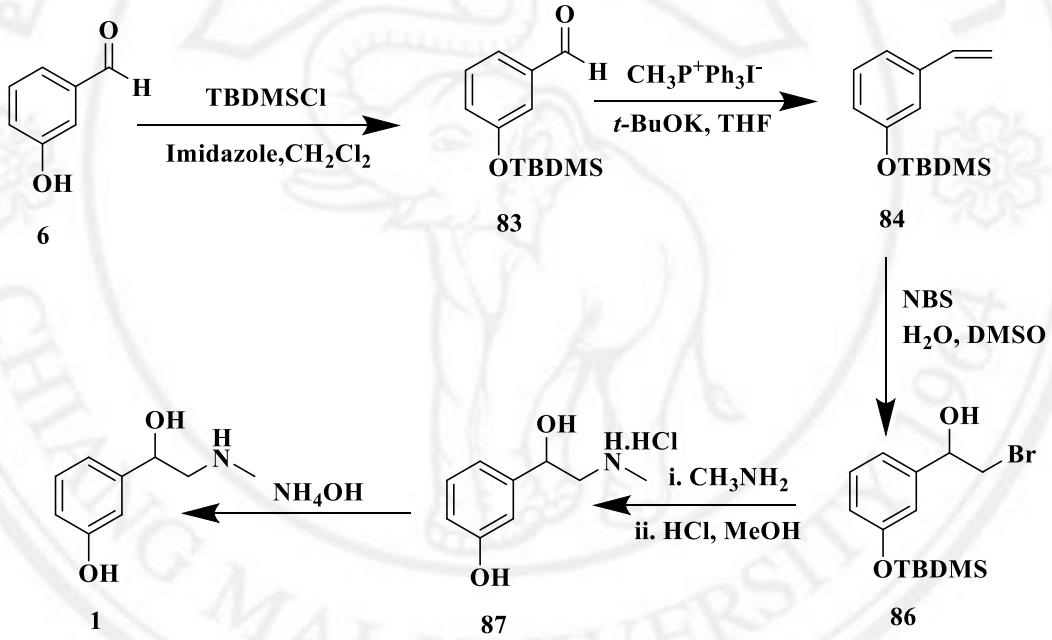


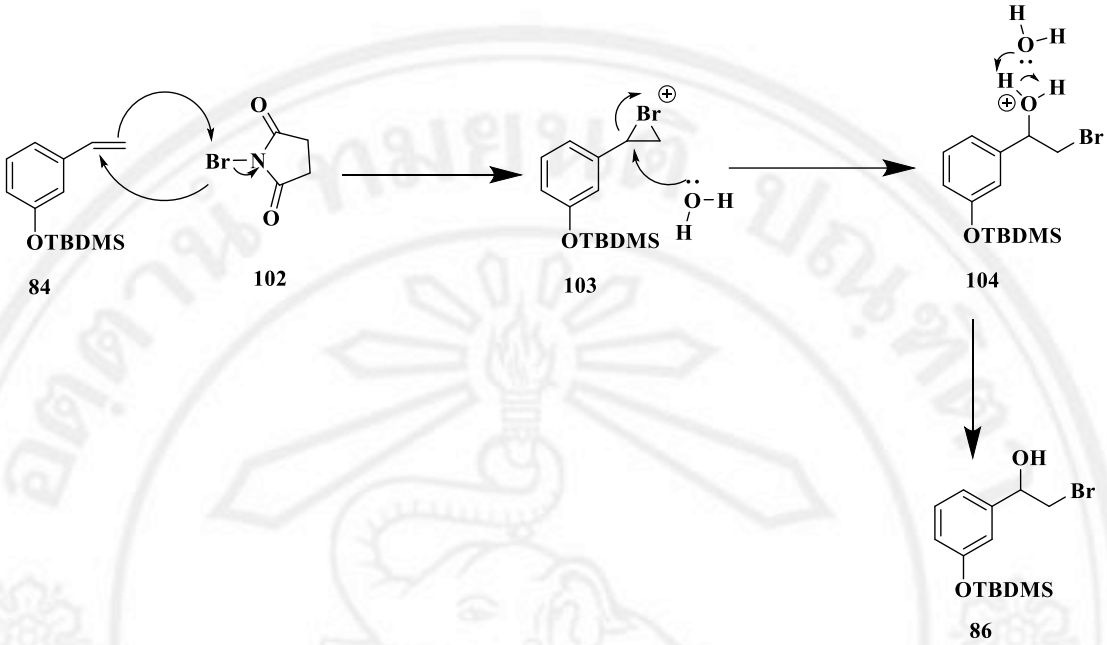
Figure 6 The ^{1}H-NMR spectra of (±)-phenylephrine and its standard

As an alternative pathway, (±)-phenylephrine **(1)** could be synthesized *via* bromohydrin formation as shown in Scheme 40. The alkene **(84)** was treated with 2 equivalents of *N*-bromosuccinimide in the presence of dimethylsulfoxide and water. The reaction mixture was stirred at room temperature for 45 minutes. The purification and elucidation of product were then conducted. The bromohydrine **(86)** was obtained in 80% yield as a colorless liquid.



Scheme 40 (±)-Phenylephrine synthesis pathway *via* bromohydrin

The mechanism of bromohydrin formation has been proposed as shown in Scheme 41.



Scheme 41 The proposed mechanism of bromohydrin formation

Although the reaction occurs in a single step, three mechanistic steps are thought to be involved. In the initial mechanistic step, the π electrons of the carbon-carbon double bond of alkene **(84)** interact with the electrophilic bromine of *N*-bromosuccinimide **(103)**. The intermediate formed in this first reaction is a cyclic bromonium cation **(104)**. In the second step, the oxygen atom of water displaces bromine and picks up the formal positive charge. In the third step, a proton is lost to H_2O, leaving a bromine atom and a hydroxyl group to give bromohydrin **(86)**.

The structure of bromohydrin **(86)** was confirmed by IR, ^{1}H-NMR, and HRMS. The IR spectrum of bromohydrin showed strong OH stretching at a wavelength of 3422 cm^{-1} and HRMS found $C_{14}H_{23}O_1SiBr$ $[M+H-OH]^+$ 315.0346 (calculated 315.0630). The ^{1}H-NMR spectrum showed the methine proton (1H) adjacent to the hydroxyl group as a doublet at $\delta = 4.85$, as shown in Figure 7.

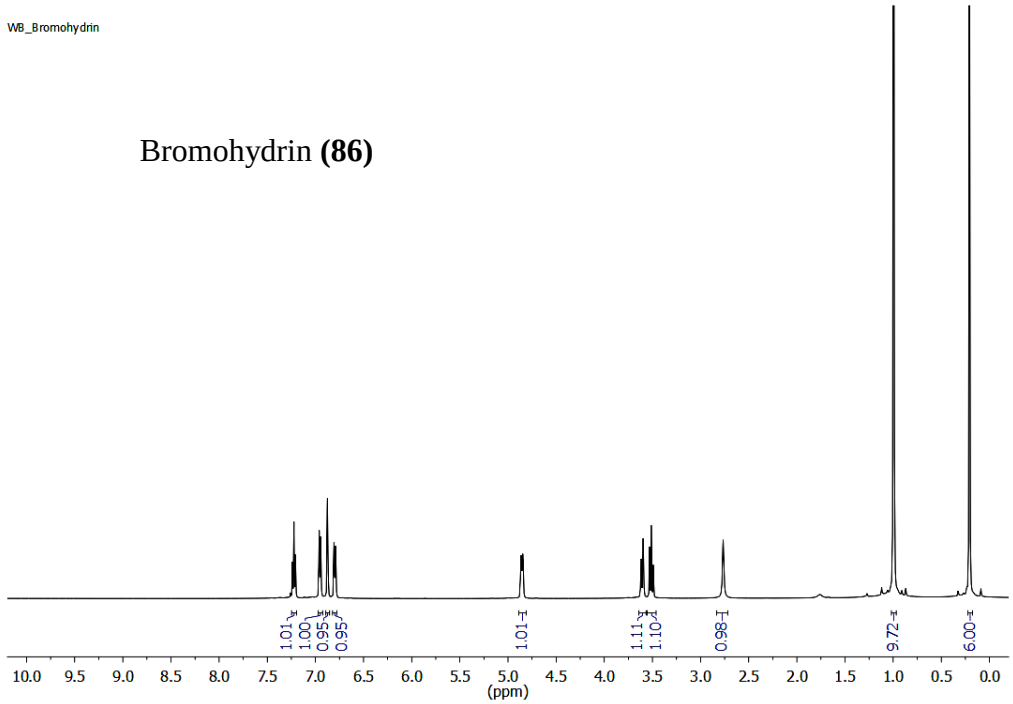
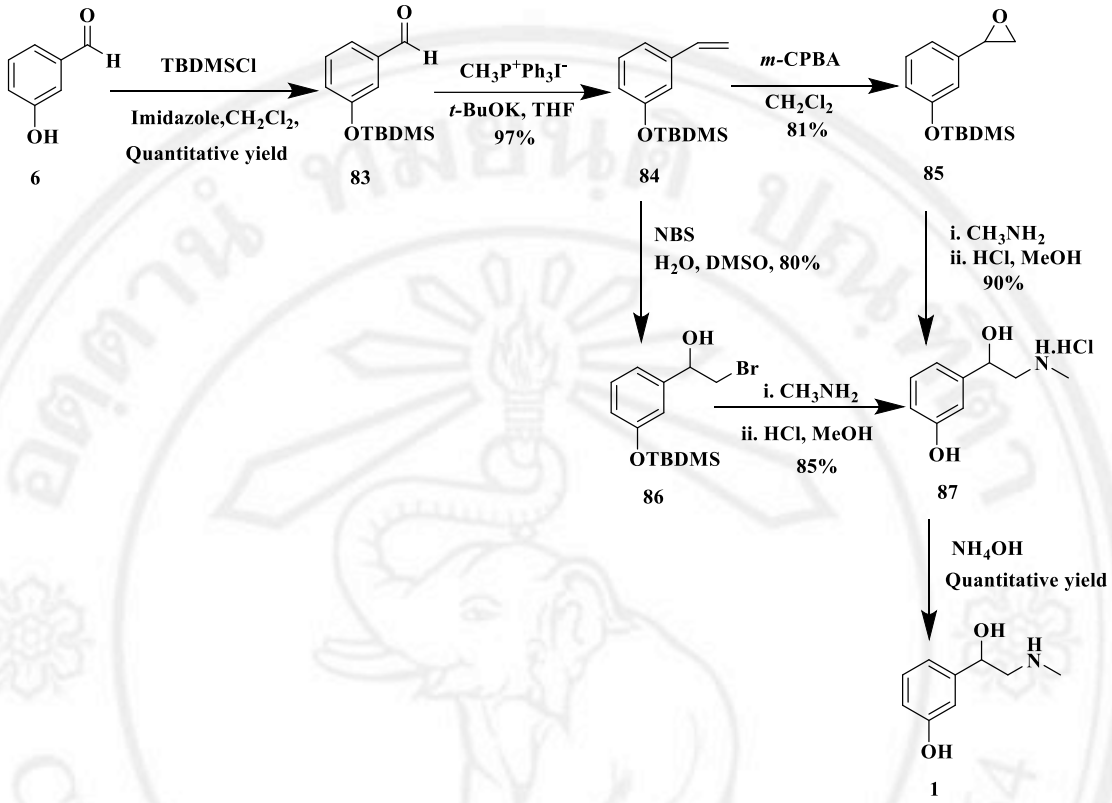


Figure 7 The ^{1}H-NMR spectrum of bromohydrin (86)

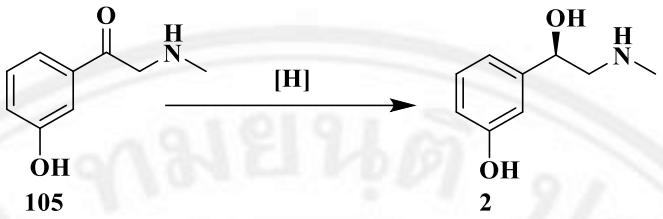
By the synthesis of (±)-phenylephrine **(1)** can be accomplished in five steps and two separate pathways *i.e.* epoxidation and bromohydrin formation, were studied, as shown in Scheme 42. The overall yields were 71% and 66%, respectively. Although, this pathway could not be shortened, but good to excellent yield were obtained in every steps.



Scheme 42 The (±)-phenylephrine synthesis pathways

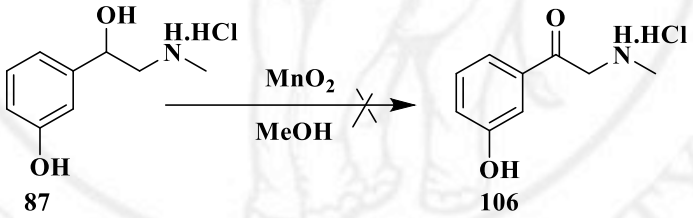
3.2 The synthesis of (R)-phenylephrine

The synthesis of *(R)*-phenylephrine **(2)** would be carried out from (±)-phenylephrine hydrochloride **(87)**. The racemate phenylephrine hydrochloride would be oxidized to obtain the amino ketone **(105)**. The key step in this synthesis is the asymmetric reduction of the amino ketone **(105)** to *(R)*-phenylephrine **(2)** as shown in Scheme 43.



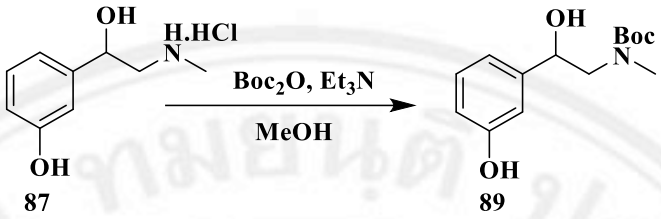
Scheme 43 The key step of *(R)*-phenylephrine synthesis

The initial reaction involves an oxidation of (±)-phenylephrine hydrochloride **(87)** as the model of this study with appropriate oxidizing agent. Firstly, manganese (IV) oxide was used to oxidize (±)-phenylephrine hydrochloride **(87)** because it was a simple and inexpensive oxidizing agent (Scheme 44).[88] However, this reaction was not successful.



Scheme 44 The oxidation of (±)-phenylephrine hydrochloride (87) with MnO_2

Then the amino group of (±)-phenylephrine hydrochloride was protected with di-*t*-butyldicarbonate in the presence of triethylamine in methanol. The reaction mixture was stirred at room temperature for 2.5 hours to give amino alcohol **(89)** in a quantitative yield as shown in Scheme 45.



Scheme 45 The protection of (±)-phenylephrine hydrochloride

The mass spectrum showed the fragmentations of amino alcohol **(89)**, as shown in Figure 8. The IR spectrum of amino alcohol **(89)** showed strong OH stretching at a wavelength of 3363 cm^{-1} and strong C=O stretching at wavelength of 1666 cm^{-1} (Figure 9) and HRMS found $C_{14}H_{21}NO_4Na$ $[M+Na]^+$ found 290.1374 (calculated 290.1368). The ^{1}H-NMR spectrum showed the signal of *t*-butyl protons (9H) adjacent to the carboxylate group, as doublet at δ = 1.39 ppm, as shown in Figure 10.

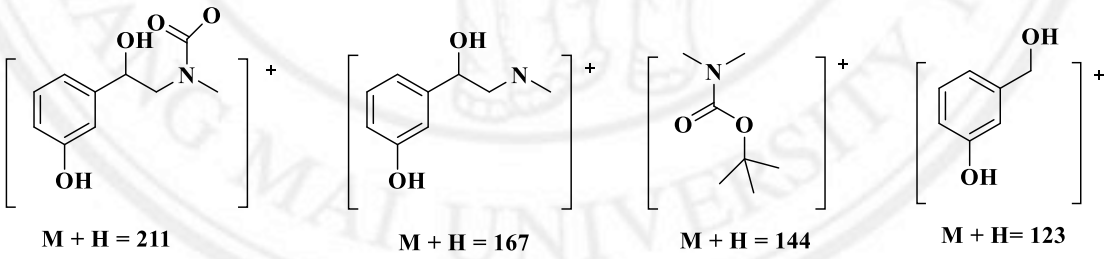


Figure 8 The fragmentation of amino alcohol (89) in the mass spectrum

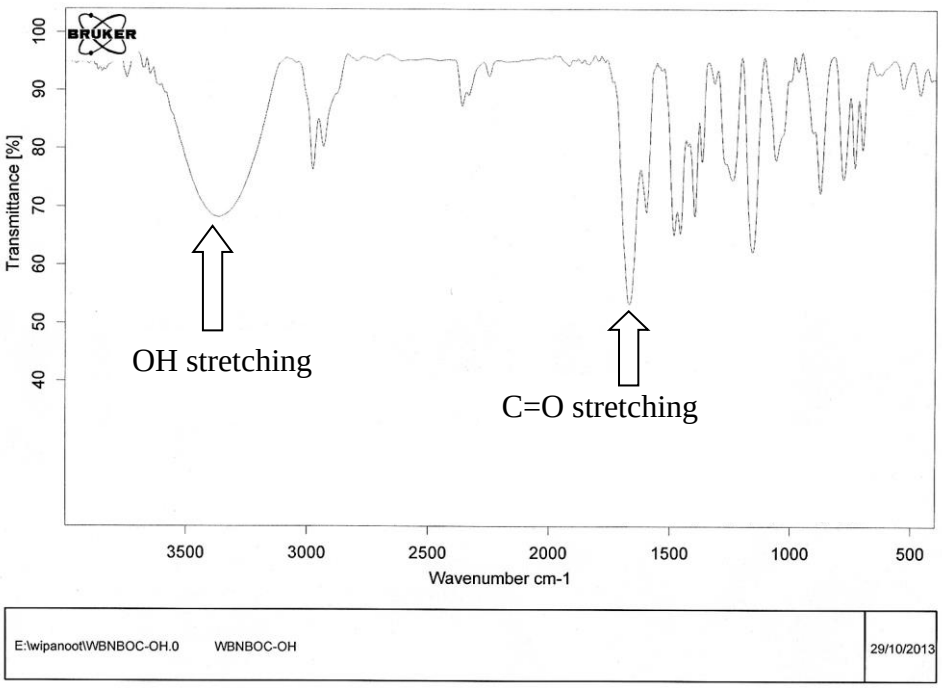


Figure 9 The IR spectrum of amino alcohol (89)

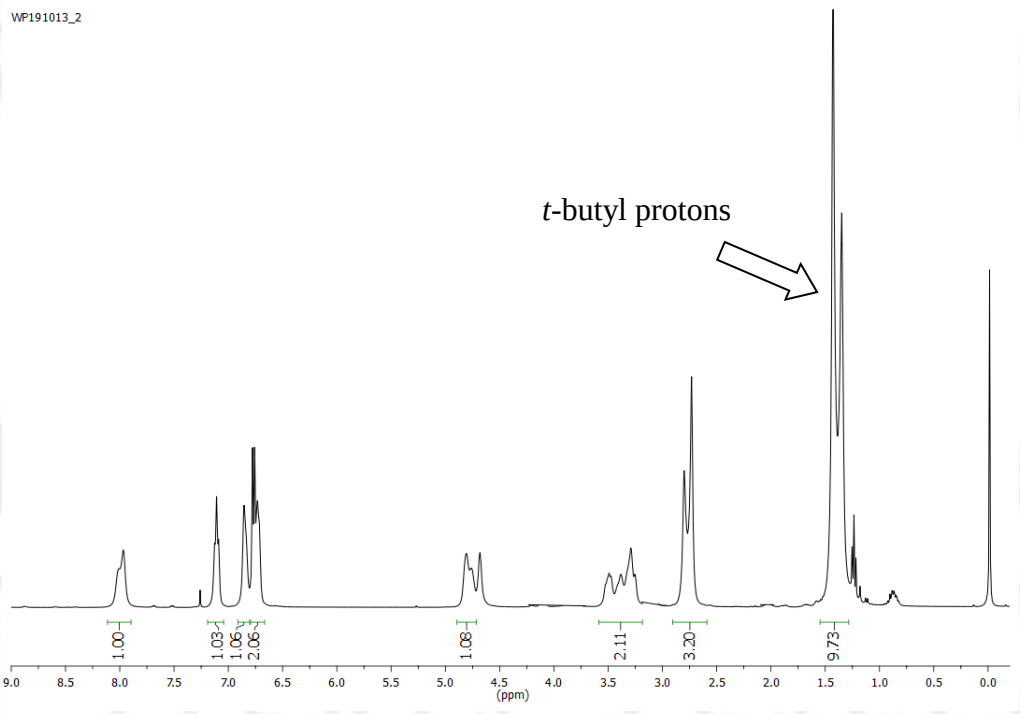
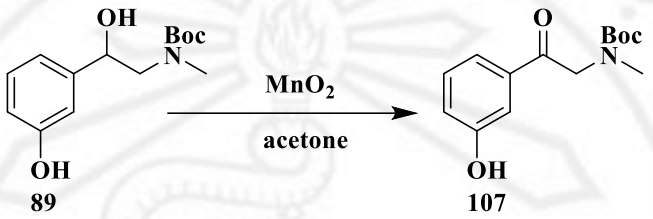


Figure 10 The ^{1}H-NMR spectrum of amino alcohol (89)

The amino alcohol **(89)** was oxidized with manganese (IV) oxide in acetone at room temperature for 20 hours to give amino ketone **(107)** in low yield (18.5%) and decomposed to several components at room temperature (Scheme 46). The mass spectrum showed the fragmentations of amino ketone **(107)**, as shown in Figure 11.



Scheme 46 The oxidation of amino alcohol (89) with MnO_2

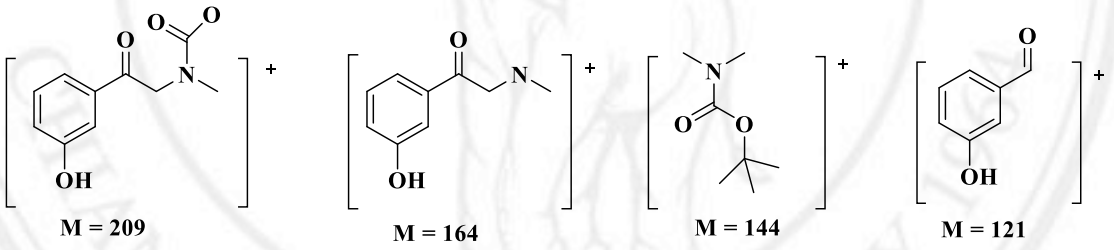
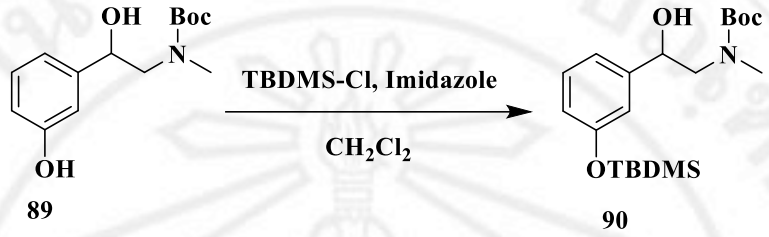


Figure 11 The fragmentations of amino ketone (107) in the mass spectrum

Having been unsuccessful in oxidation of amino alcohol **(89)** and the amino ketone **(107)** was unstable, *t*-butyldimethylsilyl chloride was, therefore, used to protect the hydroxyl group at phenolic position as shown in Scheme 47. Protection of amino alcohol **(89)** with *t*-butyldimethylsilyl chloride under basic imidazole in dichloromethane was done at room temperature for overnight in order to afford protected amino alcohol **(90)** in 86% yield as a white solid. The obtained product showed signal of *t*-butyl protons of (9H) which is adjacent to the silicon atom, as singlet at $\delta = 0.96$ ppm and methyl protons (6H) which is adjacent to the silicon atom,

as singlet at δ = 0.17 ppm as shown in Figure 12. The HRMS found $C_{20}H_{36}NO_4Si$ $[M+H]^+$ found 382.2415 (calculated 382.2414).



Scheme 47 The protection of hydroxyl group at phenolic position with *t*-butyldimethylsilyl chloride

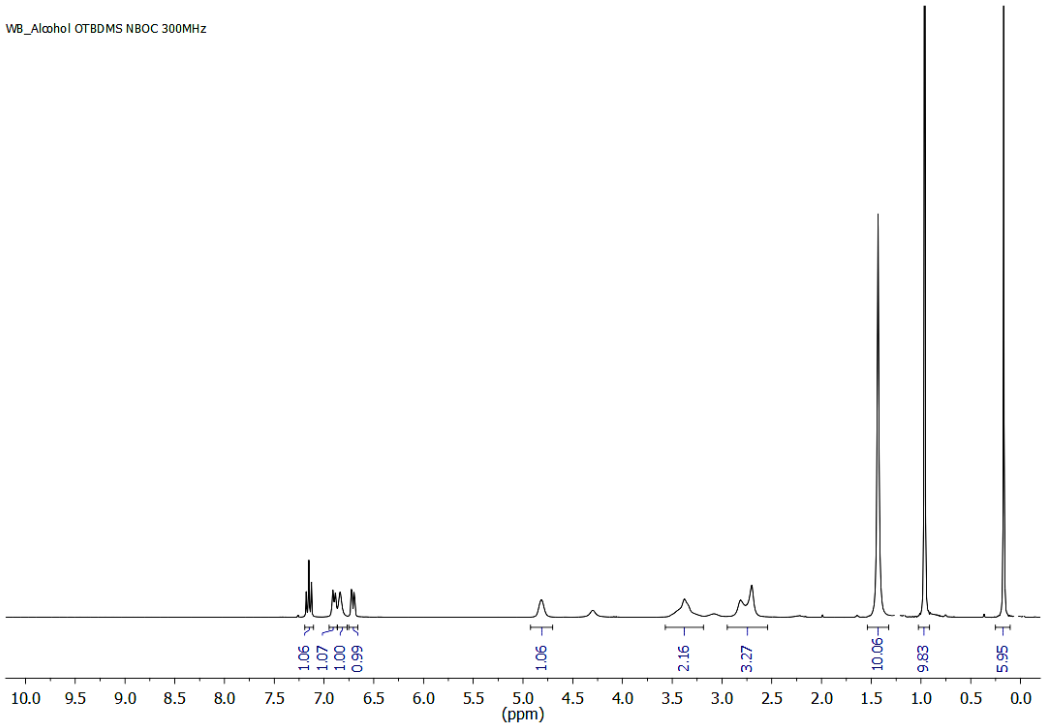
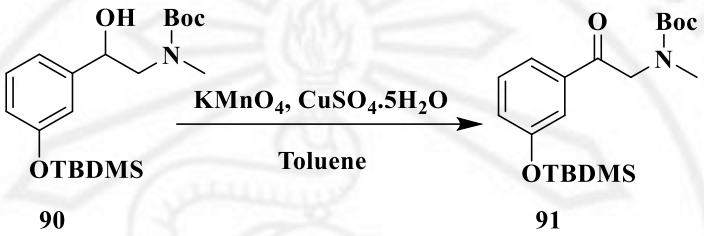


Figure 12 The ^{1}H-NMR spectrum of protected amino alcohol (90)

The oxidation of protected amino alcohol **(90)** with various amounts of manganese(IV) oxide (20 and 50 equivalents) in acetone was not successful due to low yield (25% and 32%, respectively) was obtained. Improvement of oxidation of

protected amino alcohol **(90)** has been achieved using potassium permanganate and copper (II) sulfate instead of manganese(IV) oxide in toluene.[89] The reaction mixture was stirred at room temperature for 24 hours to produce protected amino ketone **(91)** in 86% yield as a pale yellow oil (Scheme 48).



90 91

Scheme 48 The oxidation of protected amino alcohol (90) with potassium permanganate and copper (II) sulfate

The IR spectrum of protected amino ketone **(91)** showed disappearance of OH stretching at a wavelength of 3432 cm^{-1} (Figure 13) and HRMS found $C_{20}H_{33}NO_4NaSi$ $[M+Na]^+$ found 402.2074 (calculated 402.2077).

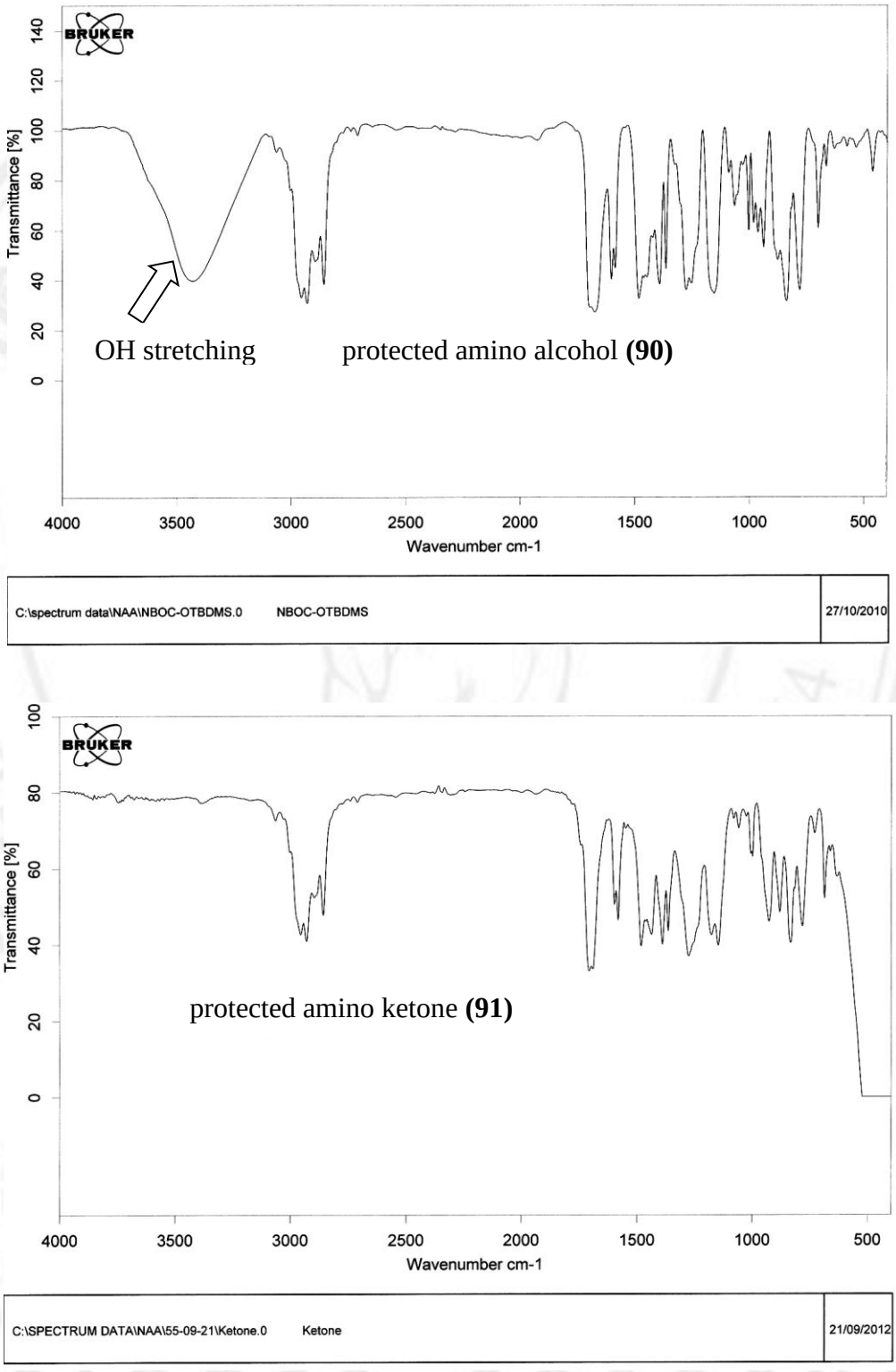


Figure 13 The IR spectra of protected amino alcohol (90) and protected amino ketone (91)

Moreover, the ^{1}H-NMR spectrum of protected amino ketone **(91)** showed the methyl protons (6H) which is adjacent to the silicon atom δ = 0.00 ppm, *t*-butyl protons of (9H) which is adjacent to the silicon atom at δ = 0.78 ppm and methylene protons at δ = 4.33-4.44 ppm, into 2 groups, of which the peak was a singlet, but the spectrum showed the peak alike two sets of singlet. This phenomenon might have been affected by the fluxional inversion, which means the pyramidal structure of an amine flips back and forth, much like an umbrella inverting in a windstorm, as shown in Figure 14.

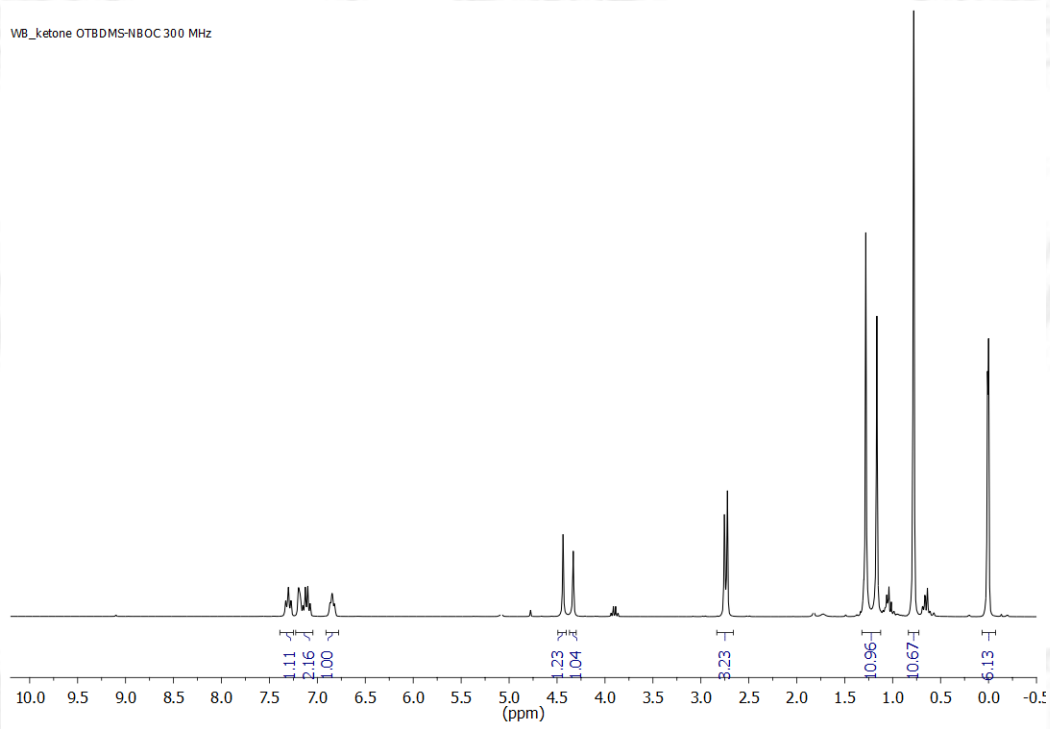
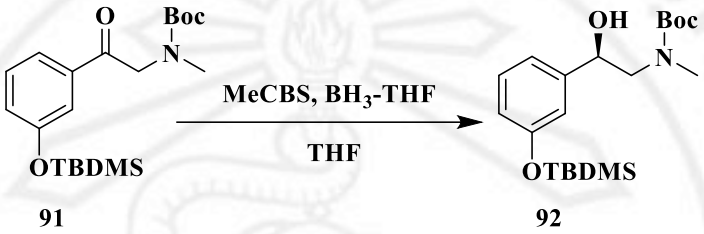


Figure 14 The ^{1}H-NMR spectrum of protected amino ketone (91)

The study of asymmetric reduction of amino ketone **(91)** started with *(R)*-2-methyl-CBS-oxazaborolidine and borane-tetrahydrofuran complex as a reducing agent (Scheme 49).The reduction of the amino ketone **(91)** was done with *(R)*-2-Methyl-

CBS-oxazaborolidine and borane-tetrahydrofuran complex under various amounts of *(R)*-2-methyl-CBS-oxazaborolidine (0.10 eq, 0.25 eq, 0.50 eq and 1.00 eq) at various temperature (-78 °C, -40 °C, -20 °C, 0 °C and room temperature) with 0.1 eq of *(R)*-2-methyl-CBS-oxazaborolidine. The data of this step is presented in Table 3.



91 92

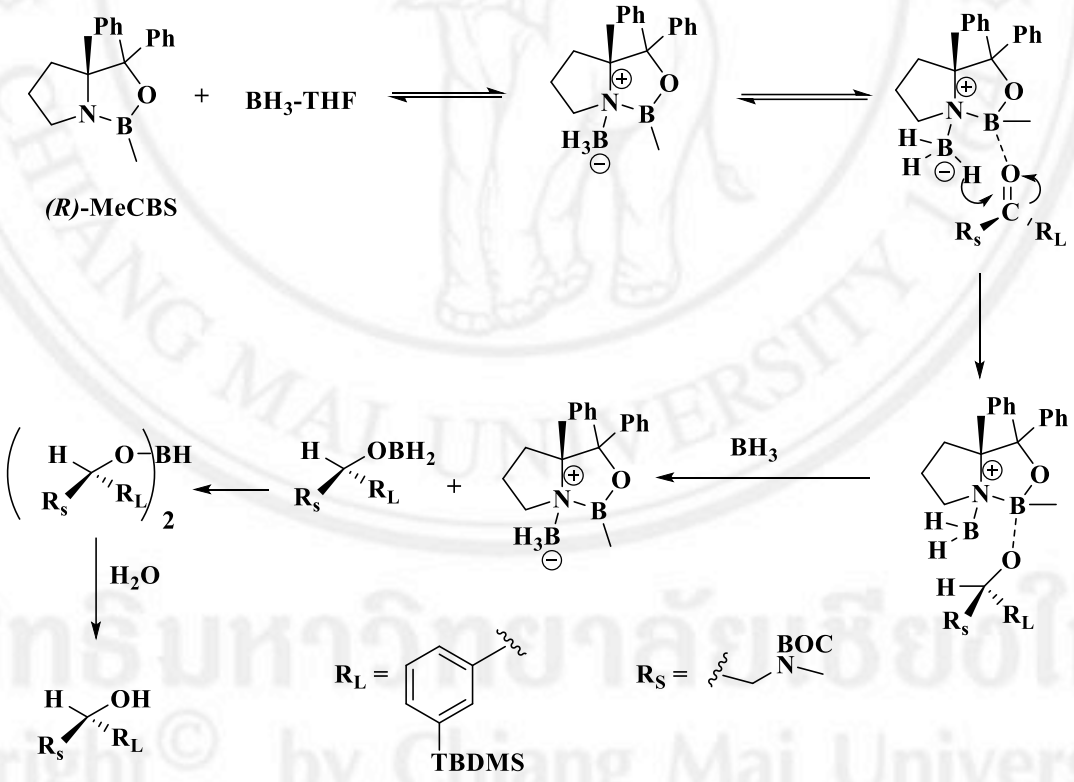
Scheme 49 The reduction of amino ketone (91) with *(R)*-MeCBS and BH_3-THF

Table 3 The reduction of amino ketone (91) with *(R)*-2-Methyl-CBS-Oxazaborolidine and borane-tetrahydrofuran complex

Entry	Amount of *(R)*-2-Methyl-CBS-oxazaborolidine (eq.)	Temperature (°C)	%yield	%ee*(R)*
1	0.10	-78	72	21
2	0.10	-40	36	41
3	0.10	-20	64	44
4	0.10	0	75	77
5	0.10	RT	81	64
6	0.25	RT	77	71
7	0.50	RT	66	84
8	1.00	RT	81	90

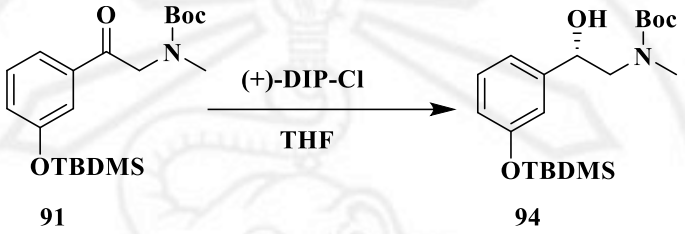
This table showed that as the amount of *(R)*-2-methyl-CBS-oxazaborolidine and temperature decreased, the enantiomeric excess decreased too. It means the amount of *(R)*-2-methyl-CBS-oxazaborolidine and temperature had effects on the reduction of amino ketone **(91).** The best conditions was 1.0 equivalents of *(R)*-2-methyl-CBS-oxazaborolidine and the reaction was stirred at room temperature to give the amino alcohol **(92)** in 81% as a white solid and 90% ee*(R).*

The mechanism of reduction of amino ketone **(91)** with *(R)*-2-methyl-CBS-oxazaborolidine and borane-tetrahydrofuran complex was proposed as shown in Scheme 50.[90]



Scheme 50 The proposed mechanism of reduction of amino ketone (91) with *(R)*-2-methyl-CBS-oxazaborolidine and borane-THF complex

The second procedure for the reduction of amino ketone **(91)** used (+)-*B*-chlorodiisopinocampheylborane as a chiral reducing agent (Scheme 51). The reaction was stirred at -78°C for 4 hours and allowed to warm up to room temperature for overnight to afford the animo alcohol **(94)** in 55% yield and 99%ee. Disappointingly, it was the *(S)*-form.



91 94

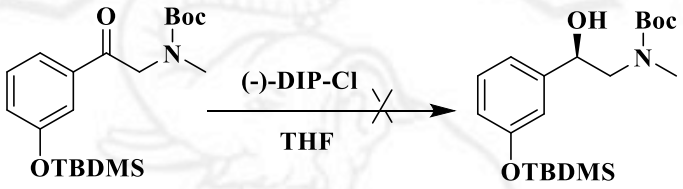
Scheme 51 The reduction of amino ketone (91) with (+)-*B*-chlorodiisopino-campheylborane

The mechanism of the reduction of amino ketone **(91)** with (+)-*B*-chlorodi isopinocampheylborane was proposed as shown in Scheme 52. It was believed to be one step transfer of hydrogen atom through the more favored intermediate.[40]

favored disfavored

Scheme 52 The proposed mechanism of reduction of amino ketone (91) with (+)-*B*-chlorodiisopinoampheylborane

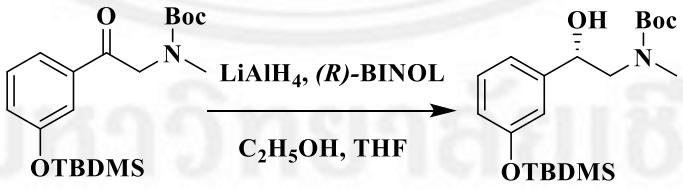
Since the use of (+)-*B*-chlorodiisopinocampheylborane as reducing agent resulted in good yield of *(S)*-amino alcohol **(94)**, it was believed that the (-)-*B*-chlorodiisopinocampheylborane would give the enantiomeric analog in good yield too. However, the reduction of amino ketone **(91)** using (-)-*β*-chlorodiisopino campheylborane did not occurred. This might be due to the air and moisture sensitivity, and thus difficult to handle of (-)-*β*-chlorodiisopinocam pheylborane.



91 **92**

Scheme 53 The reduction of amino ketone (91) with (-)-*B*-chlorodiisopino-campheylborane

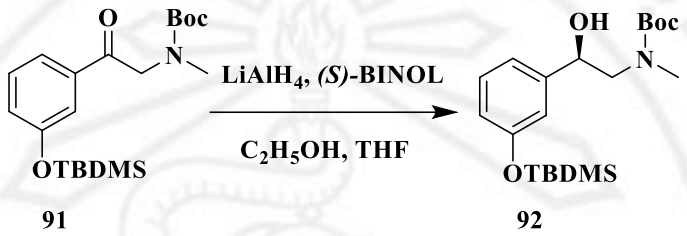
The third procedure for reduction of amino ketone **(91)** was the employment of lithium aluminium hydride with *(R)*-1,1-binaphthol and *(S)*-1,1-binaphthol as a reducing agent as shown in Scheme 54 and Scheme 55, respectively.



91 **94**

Scheme 54 The reduction of amino ketone (91) with lithium aluminium hydride with *(R)*-1,1-binaphthol

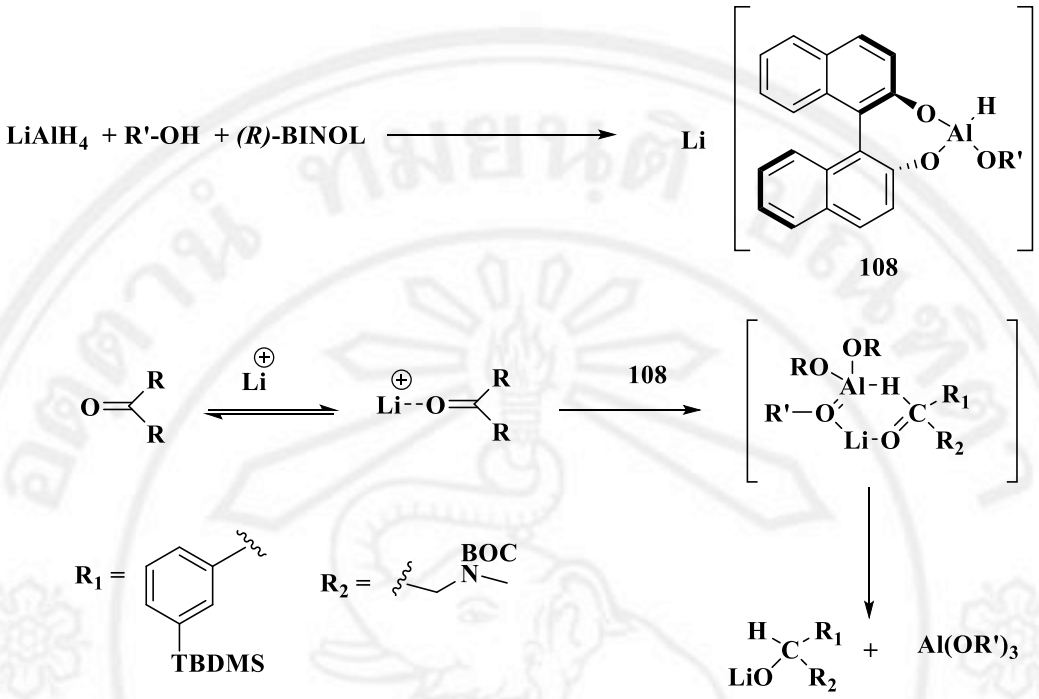
The reduction of amino ketone **(91)** with lithium aluminium hydride with *(R)*-1,1-binaphthol and *(S)*-1,1-binaphthol in the presence of ethanol and tetrahydrofuran resulted in the amino alcohol **(92)** in 68% yield (>99%ee*(S)*) and 66% yield (75%ee*(R)*), respectively.



91 **92**

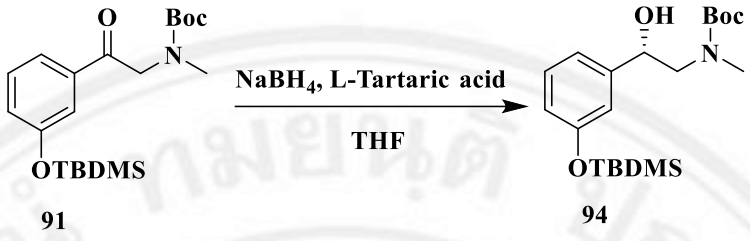
Scheme 55 The reduction of amino ketone (91) with lithium aluminium hydride with *(S)*-1,1-binaphthol

The mechanism of reduction of amino ketone **(91)** with lithium aluminium hydride with *(R)*-1,1-binaphthol has been proposed as shown in Scheme 56.[27] In the first step, lithium aluminium hydride was modified with *(R)*-1,1-binaphthol and ethanol to give the chiral reducing agent **(108)**. Then the ketone **(91),** complexed with lithium ion, was attracted by the chiral reducing agent (**108)** and the by-product was released to produce the *(S)*-amino alcohol **(92).**



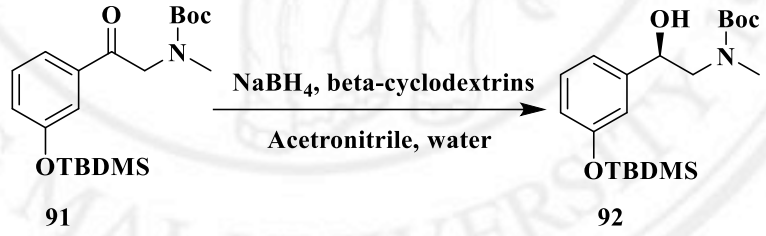
Scheme 56 The proposed of mechanism of reduction of amino ketone (91) with lithium aluminium hydride with *(R)*-1,1-binaphthol

The fourth procedure for reduction of amino ketone **(91)** used sodium borohydride and L-tartaric acid as a reducing agent (Scheme 57). Sodium borohydride was modified with L-tartaric acid in tetrahydrofuran, the reaction was refluxed for 5 hours. Afetr that, the amino ketone **(91)** was added and stirred at room temperature for 60 hours to afford the *(S)*-amino alcohol **(94)** in high yield (84%) but low %ee (13%).



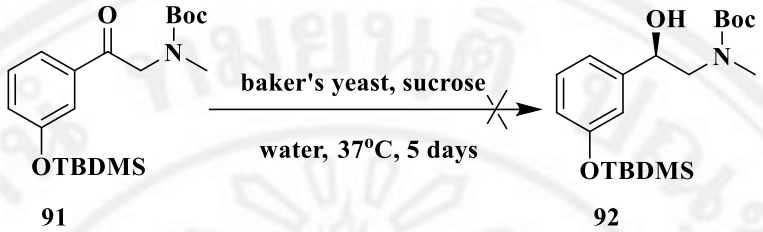
Scheme 57 The reduction of amino ketone (91) with sodium borohydride and L-tartaric acid

In addition, the reduction of amino ketone **(91)** with sodium borohydride and *beta*-cyclodextrins as a reducing agent was also studied (Scheme 58). It was found that the enantioselectivities observed was frequently low (19% ee*(R)*) and low yield (8%). This could be attributed to the prochiral center assuming an incorrect orientation in the cavity.



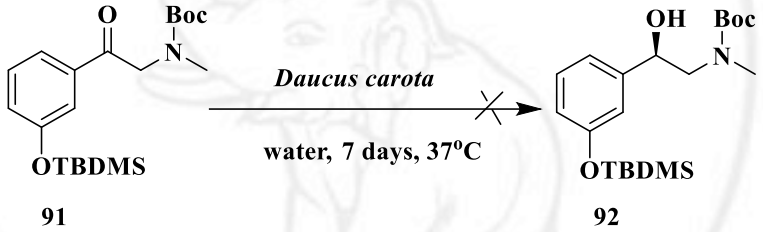
Scheme 58 The reduction of amino ketone (91) with sodium borohydride and *β*-cyclodextrins

The final procedure for asymmetric reduction (amino ketone **(91)**) is use of enzymes as reducing agents such as baker's yeast (*Saccharomyces cerevisiae*), and *Daucus carota* (from carrot). Disappointingly the reduction of amino ketone **(91)** with neither baker's yeast nor *Daucus carota* were successful. It was found that only the starting amino ketone **(91)** was detected on TLC after the reaction period. The reaction Schemes are shown in Scheme 59 and 60, respectively.



91 92

Scheme 59 The reduction of amino ketone (91) with baker's yeast



91 92

Scheme 60 The reduction of amino ketone (91) with *Daucus carota* from carrot

From several trials on asymmetric reduction, it was found that with *(R)*-2-methyl-CBS-oxazaborolidine (1.0 equivalent) at room temperature gave the best result *i.e.* 81% and 90%ee *(R).*

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)*

Entry	Reducing agent	%yield	%ee
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	

The next step is the deprotecting of the blocking groups, which has been achieved with 6 M hydrochloric acid. The amino alcohol **(92)** was stirred in excess hydrochloric acid at room temperature for 4 hours to give *(R)*-phenylephrine hydrochloride **(3)** in quantitative yield. The ^{1}H-NMR spectrum showed no signal at 0-2 ppm suggesting that all the protecting group have been completely removed as shown in Figure 15. The HRMS found $C_9H_{14}NO_2$ $[M+H]^+$ 168.1019 (calculated 168.0980) and mp 141-143ºC (Lit. mp 141 ºC)[18], $[\alpha]_D$ = -44.5º (c = 2.15 , H_2O), Lit[18] $[\alpha]_D$ = -45.2º (c = 2.0 , H_2O).

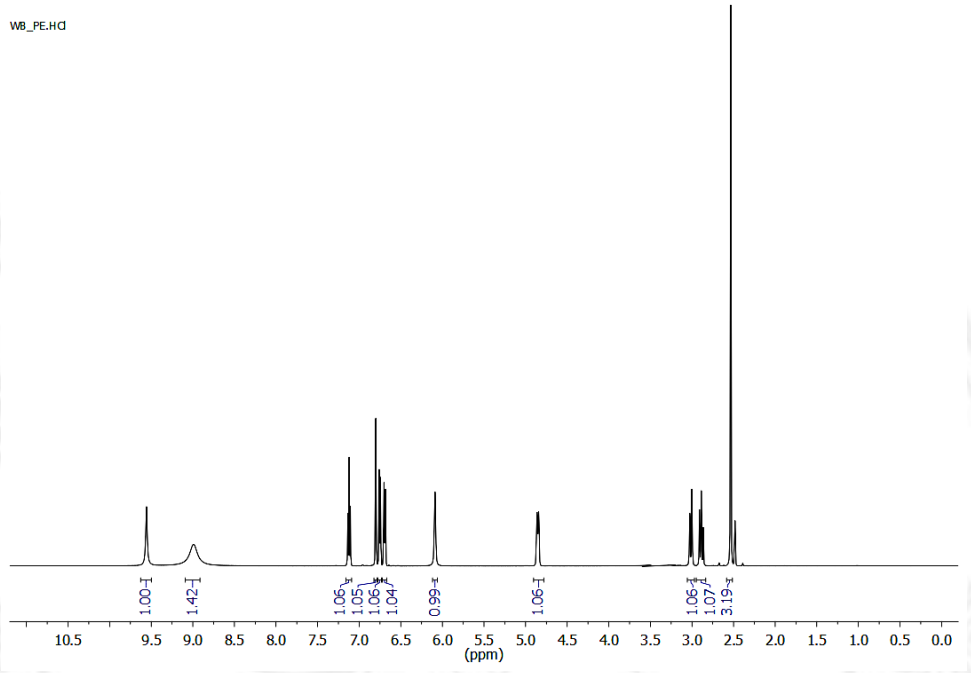


Figure 15 The ^{1}H-NMR spectrum of *(R)*-phenylephrine hydrochloride

The final step for synthesis of *(R)*-phenylephrine **(2)** was carried on. *(R)*-phenylephrine hydrochloride **(3)** was basified with ammonium hydroxide TS solution (ammonium hydroxide : water = 2:3). The precipitate was collected and washed with a few drops of ice-cooled water and dried at 105^{o}C for 2 hours to give *(R)*-phenylephrine **(2)** as a white solid which has mp 170-172^{o}C (Lit. mp 171 ^{o}C) (the ^{1}H-NMR spectrum is shown in Figure 16).

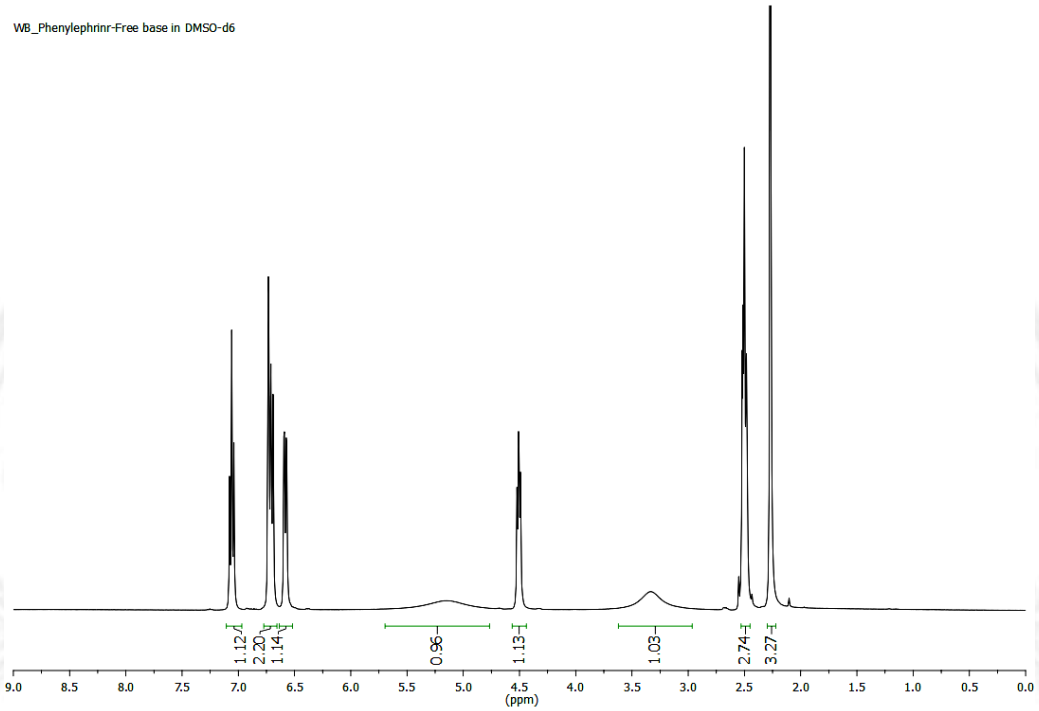
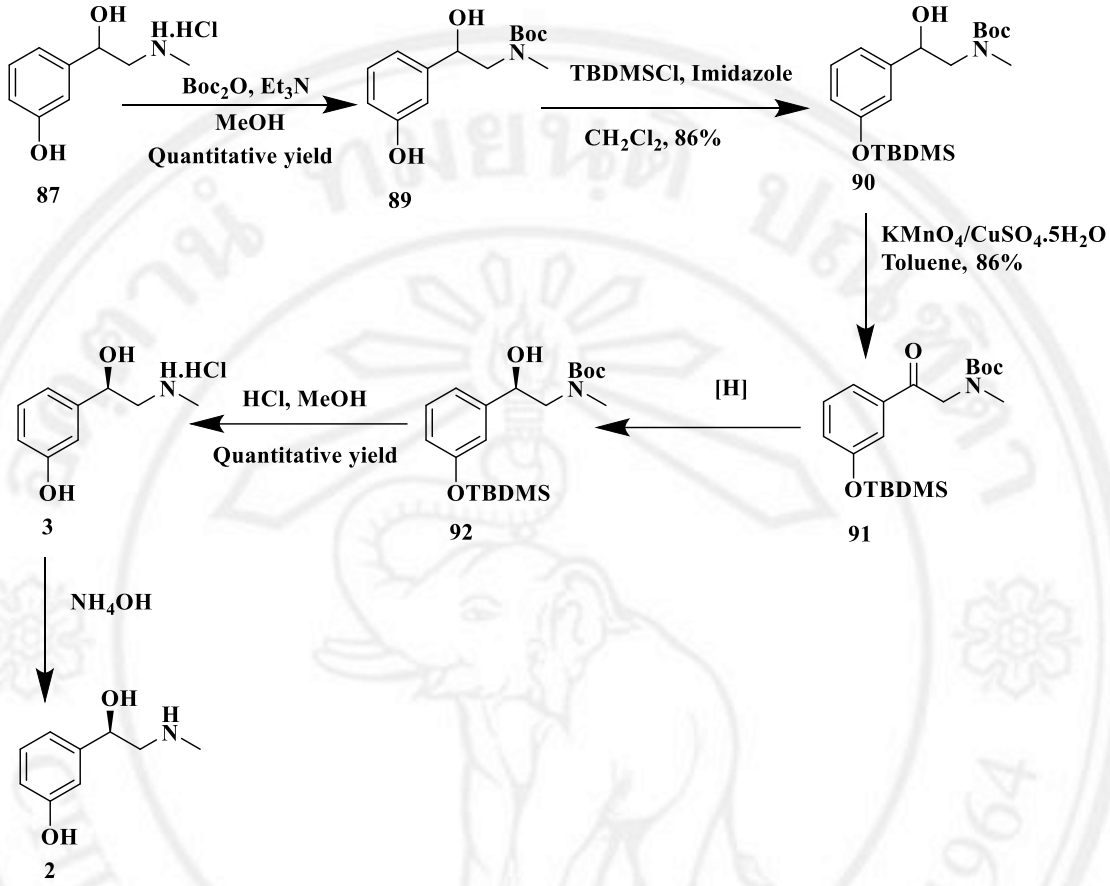


Figure 16 The ^{1}H-NMR spectrum of *(R)*-phenylephrine

It has been shown that the synthesis of *(R)*-phenylephrine **(2)** from the racemate has been accomplished in six steps as shown in Scheme 61. Every step gave good to quantitative yields with a high stereoselectivity and environmentally benign.



Scheme 61 The (*R*)-phenylephrine synthesis pathway