CHAPTER IV

RESULTS AND DISCUSSION

4.1 Synthesis of alcohol derivatives

Most of alcohol derivatives used in this study were prepared by reduction of their corresponding ketones with sodium borohydride as a reducing agent. Further purification by column chromatography was performed, if needed. The products were characterized by ^{1}H-NMR. The yield of all synthesized alcohols was greater than 70%, except for **24Me**, **34Me** and **11** were obtained in 30-50%.

4.2 Evaluation of coated column performance

The performance of three capillary columns used in this study was evaluated by means of Grob test [29-30]. The Grob test mixture contains decane (**C10**); undecane (**C11**); nonanal (**al**); 1-octanol (**ol**); 2,3-butanediol (**D**); 2,6-dimethylaniline (**A**); 2,6-dimethylphenol (**P**); 2-ethylhexanoic acid (**S**); dicyclohexylamine (**am**); and three methyl esters of fatty acids C10-C12 (**E10-E12**). A single chromatographic run of the test mixture gives the information on column characteristics in terms of column efficiency, inertness, acidity and basicity. Column efficiency was evaluated from the average separation number (SN) values of methyl ester peaks (**E10-E12**). Column inertness was observed through the adsorption of alcohol (**ol** and **D**) and aldehyde (**al**) peaks. Acidity and basicity of column was judged from the peak height ratio of acids and bases (**A**, **P**, **S** and **am**). Test chromatograms attained from OV-1701, BSiMe, and GSiMe columns were demonstrated in figures 4.1-4.3, respectively.

As illustrated in figure 4.1, OV-1701 column has high separation efficiency (an average SN value of 29.6). This column is suitable for quantitative analysis of monoalcohols due to no adsorption of **ol**. Nonetheless, diol (**D**) and aldehyde (**al**) are slightly adsorbed and their analyses with this column might not be appropriate. The peak height of **P** and **A** are rather equivalent, indicating the

neutrality of the column. However, this column is very active to strong acid (**S**) and strong base (**am**). Therefore, underivatized carboxylic acids and amines could not be analyzed on OV-1701 column.

For both chiral columns (figures 4.2-4.3), the separation efficiencies are also high with an average SN value of 26.9 and 29.4 for BSiMe and GSiMe, respectively. The adsorption of **ol** was not observed but **D** and **al** were moderately adsorbed, indicating that columns are inert to monoalcohols but active to alcohols with many hydroxyl groups and aldehydes. Column neutralities are good as seen from the equivalent height of weak acid (**P**) and weak base (**A**) peaks. Nevertheless, both columns are not appropriate for the separation of underivatized carboxylic acids and amines as **S** and **am** were strongly adsorbed. Both columns also displayed their ability to separate isomers and enantiomers as shown on **D** and **S** peaks.

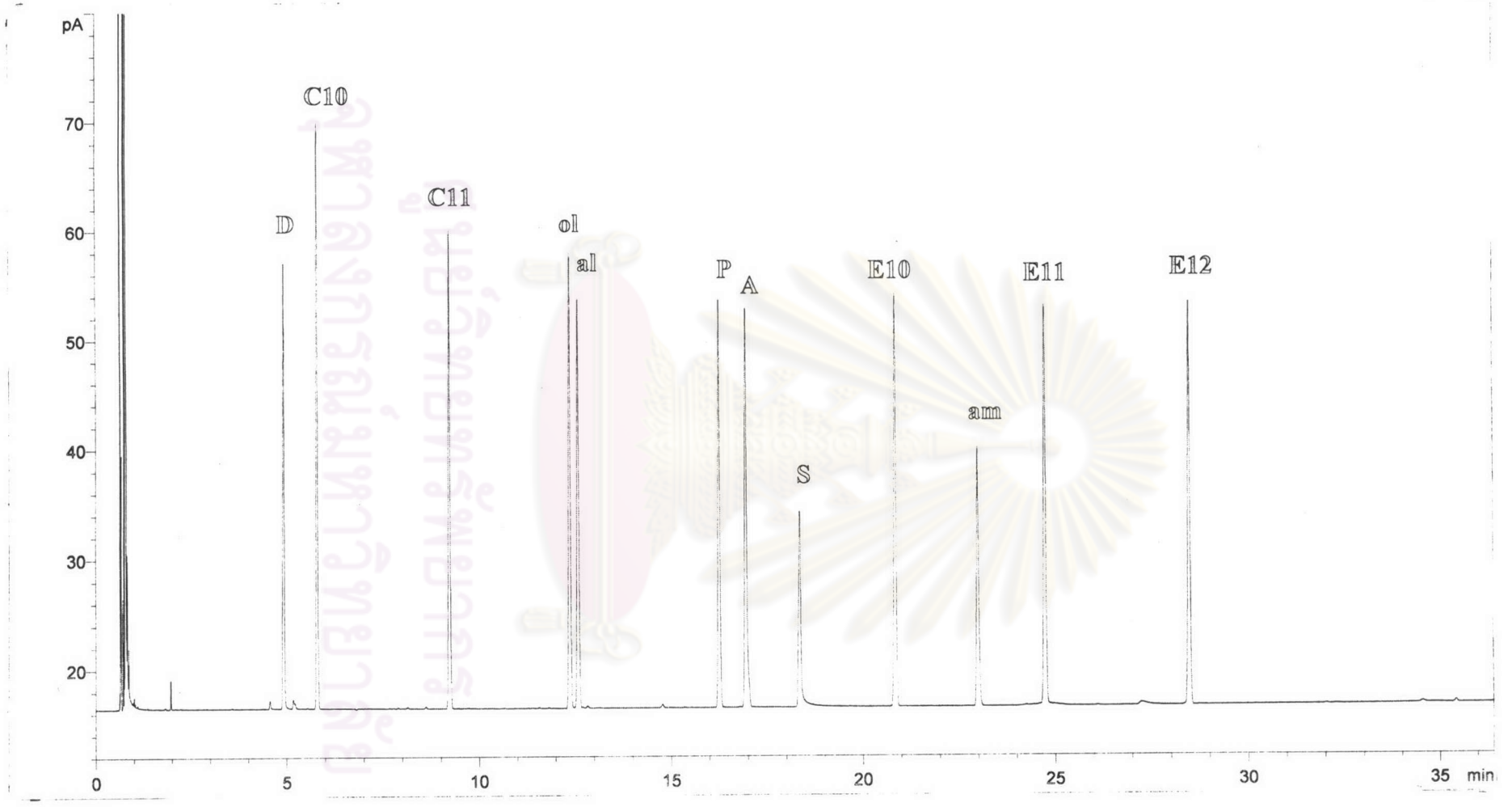


Figure 4.1 Chromatogram of Grob test on OV-1701 column (16.53 m × 0.25 mm i.d. × 0 .25 µm film thickness); temperature program: 40 to 150 °C at 3.02 °C/min.

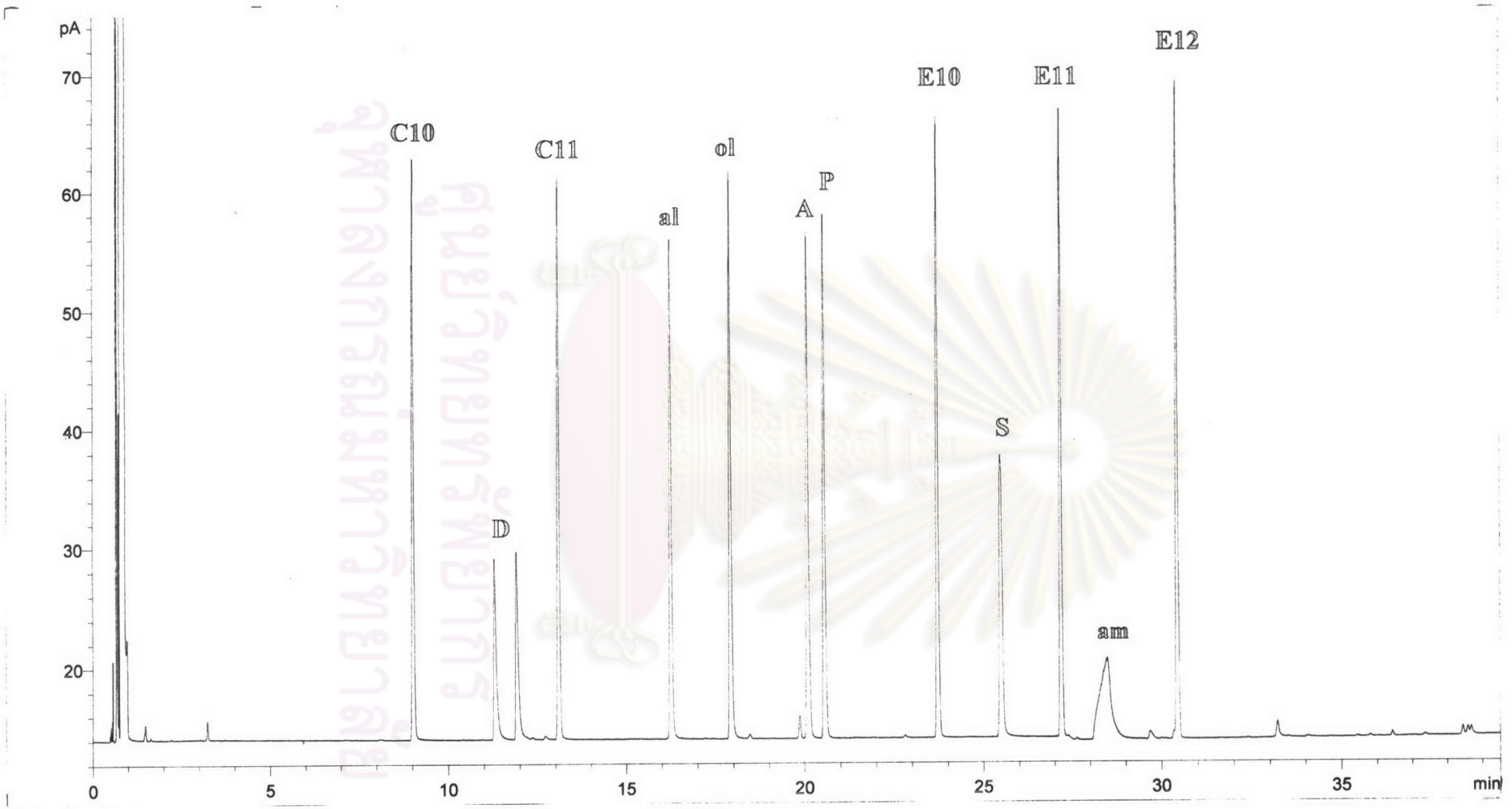


Figure 4.2 Chromatogram of Grob test on BSiMe column (15.22 m × 0.25 mm i.d. × 0.25 µm film thickness); temperature program: 40 to 170 °C at 3.29 °C/min.

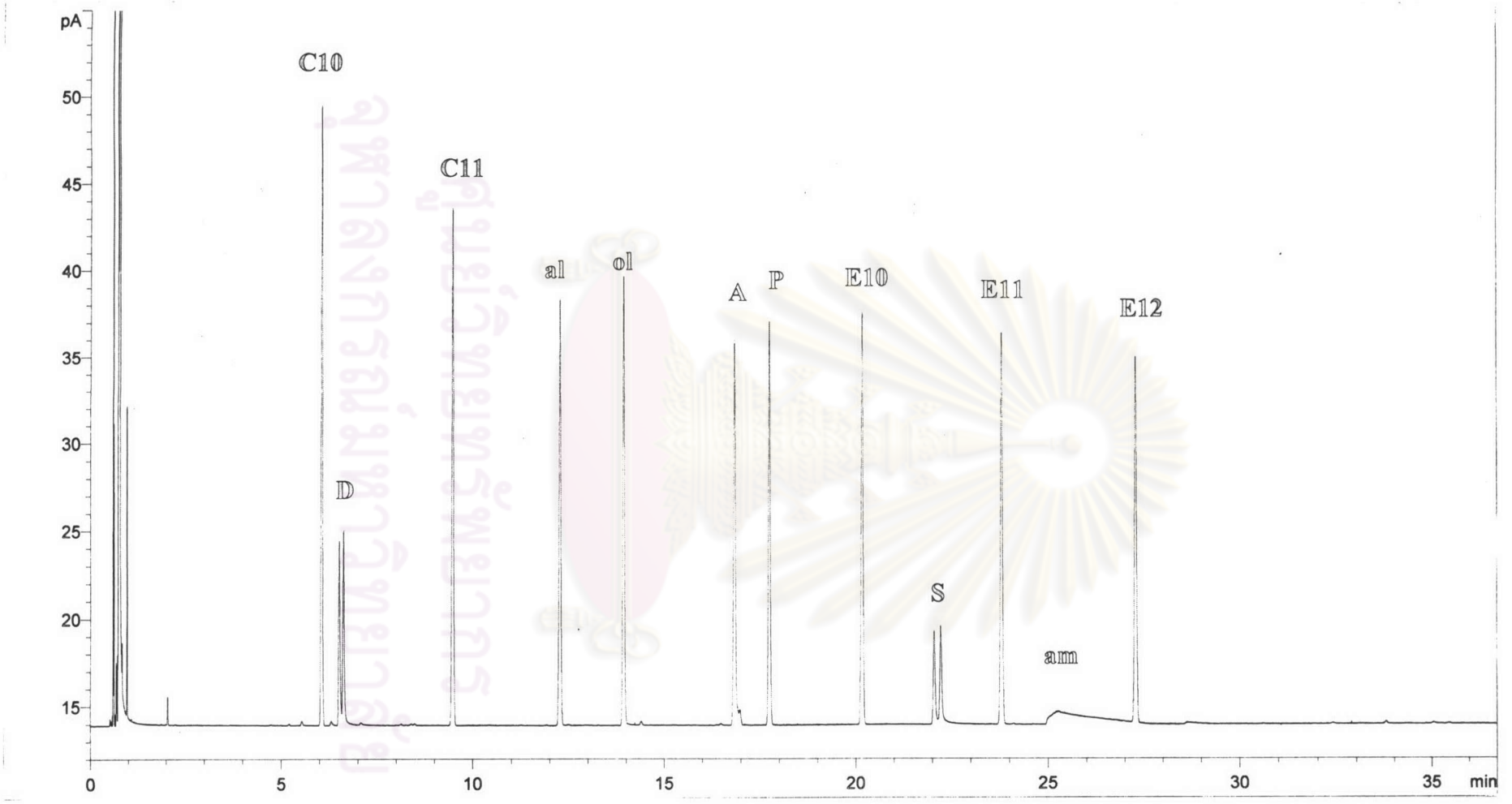


Figure 4.3 Chromatogram of Grob test on GSiMe column (15.84 m × 0.25 mm i.d. × 0.25 µm film thickness); temperature program: 40 to 150 °C at 3.26 °C/min.

4.3 Gas chromatographic separation of alcohol derivatives

All chiral alcohols were isothermally analyzed on three columns in the temperature range of 60-230 °C at 10 °C interval. The retention factors (k′) of represented alcohol racemates on three columns at 150 °C are compared and illustrated in figures 4.4-4.5. It can be observed that the retention factors of analytes on each column vary significantly depending on their molecular weight; boiling point; type, number, and position of substituents. It is apparent that most analytes show higher retention on two chiral columns than on the polysiloxane OV-1701 column and retain more strongly on the BSiMe column than on the GSiMe chiral column. These results indicate that the increased interactions come from cyclodextrin derivatives as all columns contain polysiloxane as a major component and have identical film thickness. Additionally, β-cyclodextrin derivative interacts more strongly with the alcohol analytes than the γ-cyclodextrin derivative. It is interesting to note that only **pentaF** provided lower retention (k′) on both chiral columns than on nonchiral column.

All racemic alcohols, except **35F** and **2oct**, could be resolved into their enantiomers on at least one chiral column used. The enantioselectivities of represented alcohol analytes at 150 °C are compared in figure 4.6. Most compounds could be enantioselectively separated by BSiMe derivative and with higher degree of separation than by GSiMe derivative. Generaliy, on BSiMe column the separation of monosubstituted alcohols was better as the substituent size became larger (**2Br** > **2Cl** > **2F**). Nevertheless, the position of substituent seemed to have a stronger effect on selectivity than the substituent size. Monosubstituted analytes with substituent on *ortho* position exhibited much superior enantioselectivities than those with substituent on *meta* and *para* positions (**2Br** > **3Br**, **4Br**). Nonetheless, due to the difference in physical properties of analytes at a particular temperature, the retention factors and enantioselectivities could not be directly compared. Therefore, thermodynamic studies over a temperature range should be determined to provide better understanding about the interactions between analytes and gas chromatographic stationary phases.

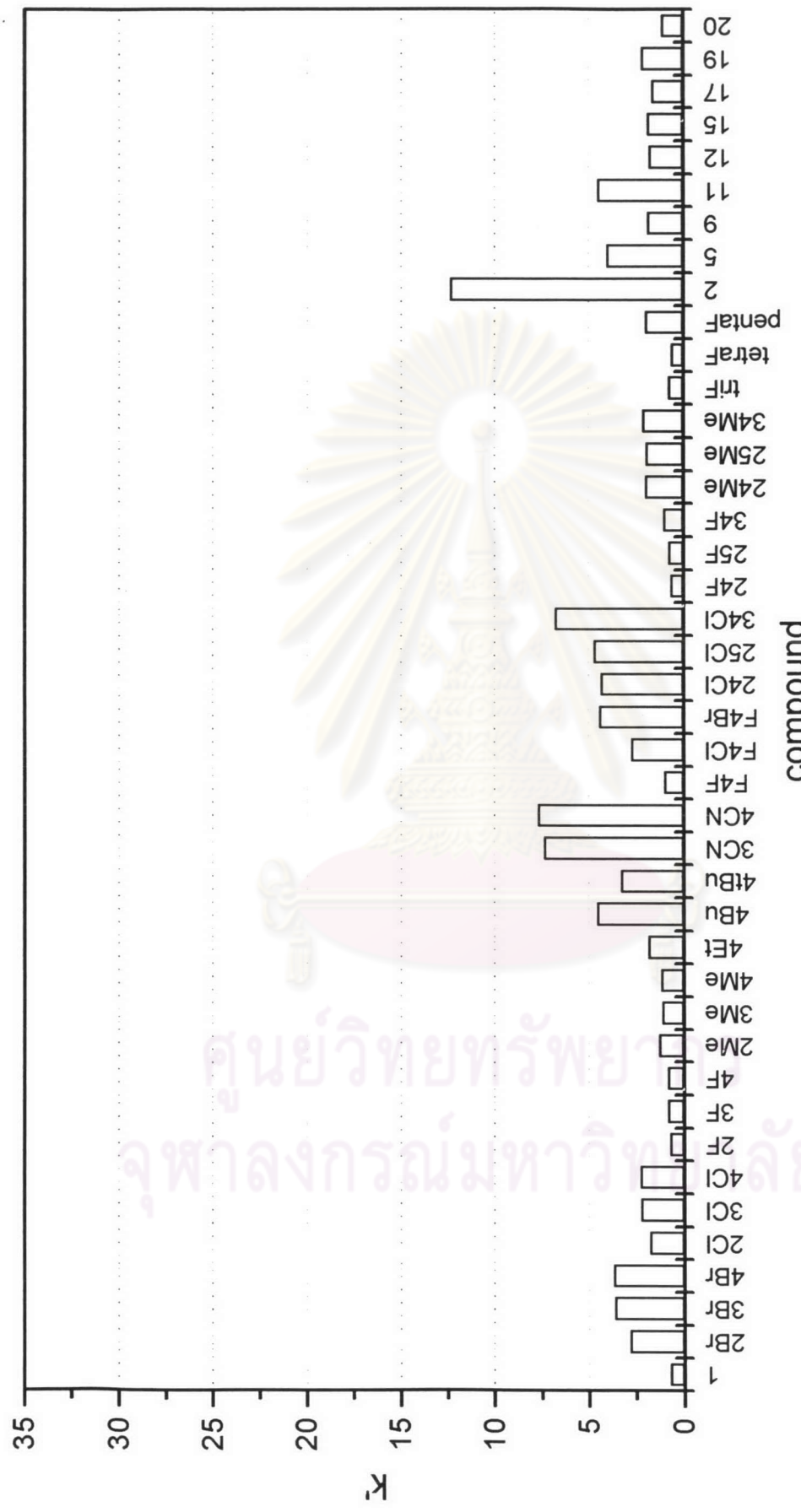


Figure 4.4 Retention factors (k') of represented alcohols on OV-1701 column at 150 °C.

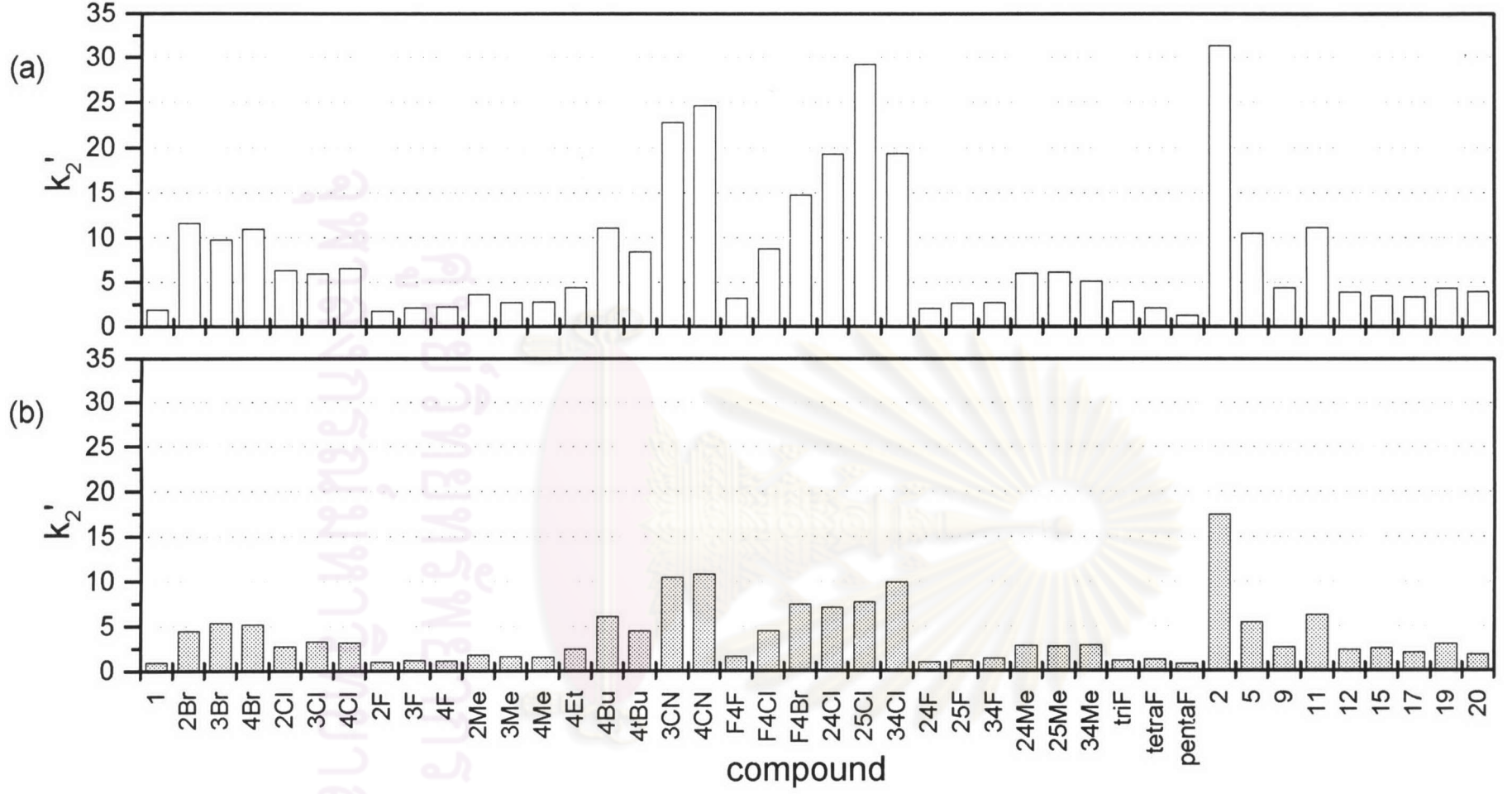


Figure 4.5 Retention factors (k_2') of the more retained enantiomers of represented alcohols on (a) BSiMe and (b) GSiMe columns at 150 °C.

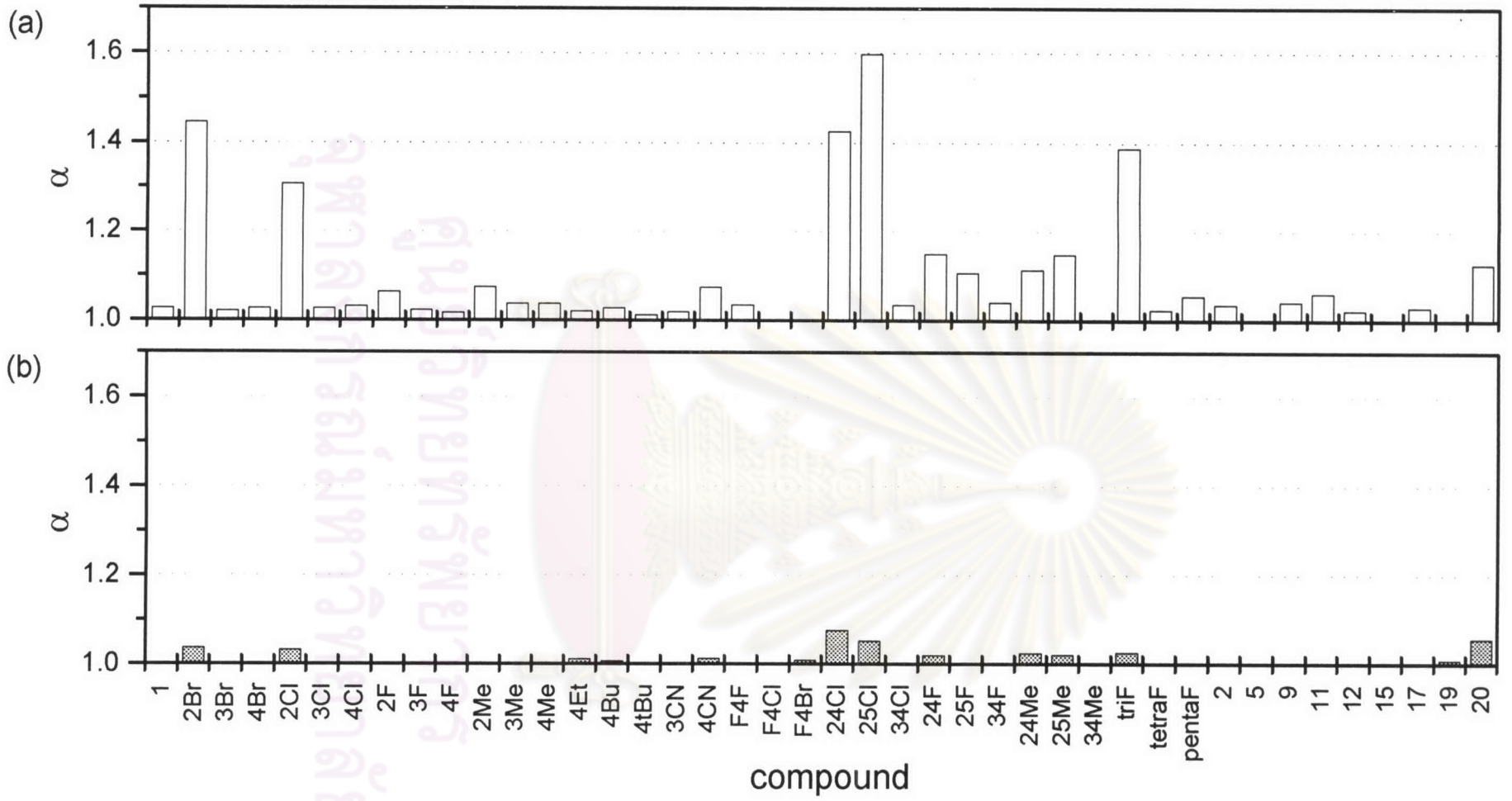


Figure 4.6 Enantioselectivity values (α) of the enantiomers of represented alcohols on (a) BSiMe and (b) GSiMe columns at 150 °C.

4.4 Thermodynamic investigation by van't Hoff approach

To investigate the influence of analyte structure on the strength of interaction and enantioresolution, thermodynamic parameters associated with the interactions between alcohol analytes and stationary phases were acquired through the construction of van't Hoff plots. Almost all ln k′ versus 1/T plots exhibited linear relationship with correlation coefficient values (R^2) greater than 0.998. From these plots, enthalpy (ΔH) and entropy (ΔS) values could be calculated. When enantiomeric pairs were separated, the enthalpy and entropy differences ($\Delta(\Delta H)$ and $\Delta(\Delta S)$) could be determined from the relationship between ln α and 1/T. Theoretically, the ln α and 1/T plots should be linear; however, curvatures were detected for some analytes. The nonlinearity may be an indicator for a change in the interaction mechanism between analytes and chiral stationary phase as the temperature changed [31]. The determination of $\Delta(\Delta H)$ and $\Delta(\Delta S)$ values in this study were, therefore, calculated from the differences in ΔH and ΔS values of two enantiomers.

4.4.1 Enthalpy change ($-\Delta H$) and entropy change ($-\Delta S$)

The enthalpy value ($-\Delta H$) indicated the strength of interaction between an analyte and a stationary phase: the larger the value (more negative value), the stronger the interaction. While the entropy value ($-\Delta S$) symbolized the loss of degree of freedom associated with the interaction between an analyte and a stationary phase. Enthalpy and entropy values of all alcohols studied obtained from OV-1701 column were illustrated in figures 4.7-4.8. It can be seen that the enthalpy values ($-\Delta H$) of most alcohol analytes were very similar and close to the average value of 12.27 kcal/mol. This indicated that major analyte contribution towards the interaction would come from the hydroxyl group. A small increase in the interaction from *ortho-* < *meta-* < *para*-isomers was also noticed. A similar trend was also observed for the entropy values (figure 4.8). Noticeably, analytes with α-(trifluoromethyl) substituents (**F4Br**, **F4Cl**, **F4F**, **20**, **21**) displayed the highest $-\Delta S$ values.

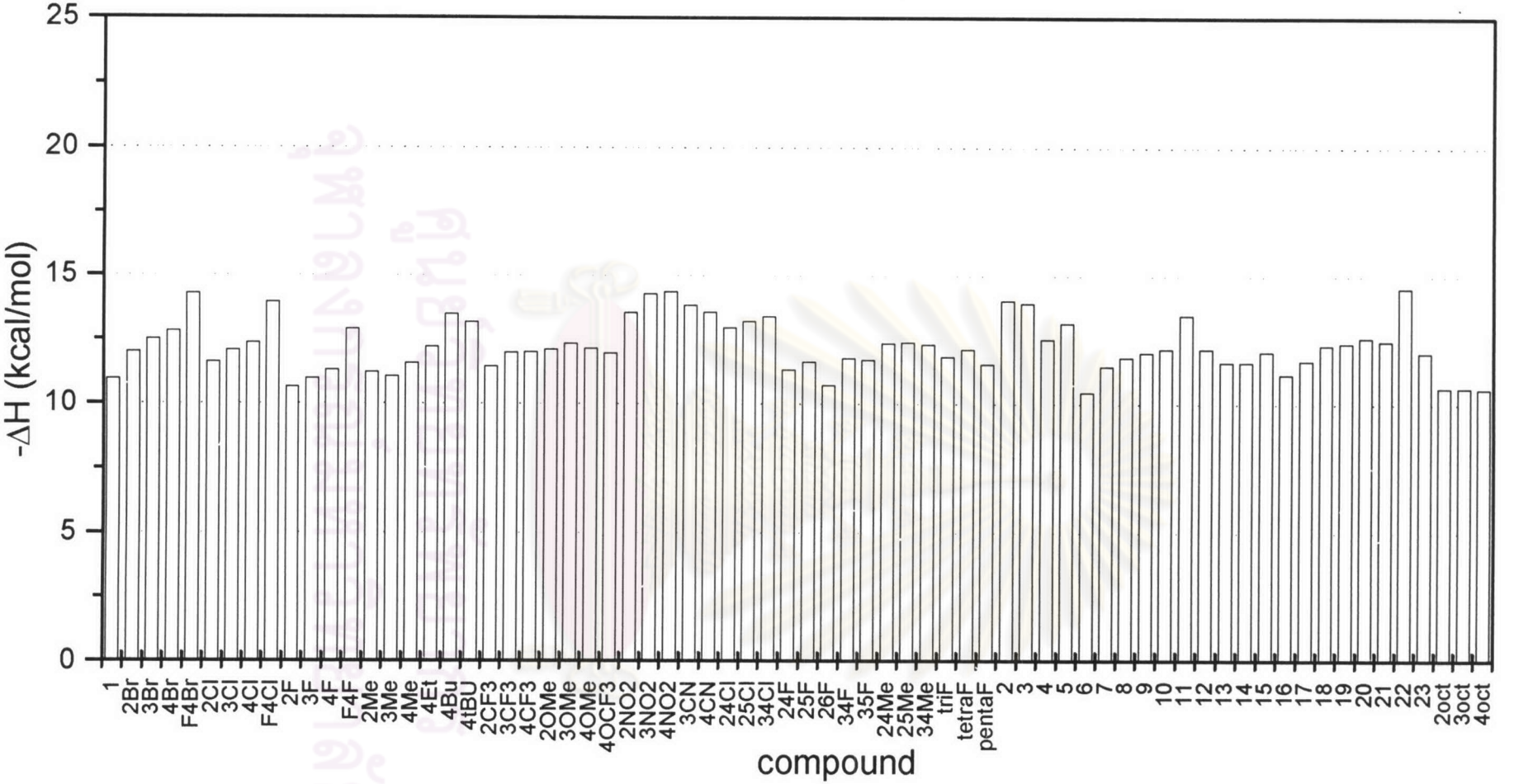


Figure 4.7 Enthalpy values (-ΔH, kcal/mol) of alcohol analytes on OV-1701 column obtained from van't Hoff approach ($\bar{x}$ = 12.27; SD = 1.01).

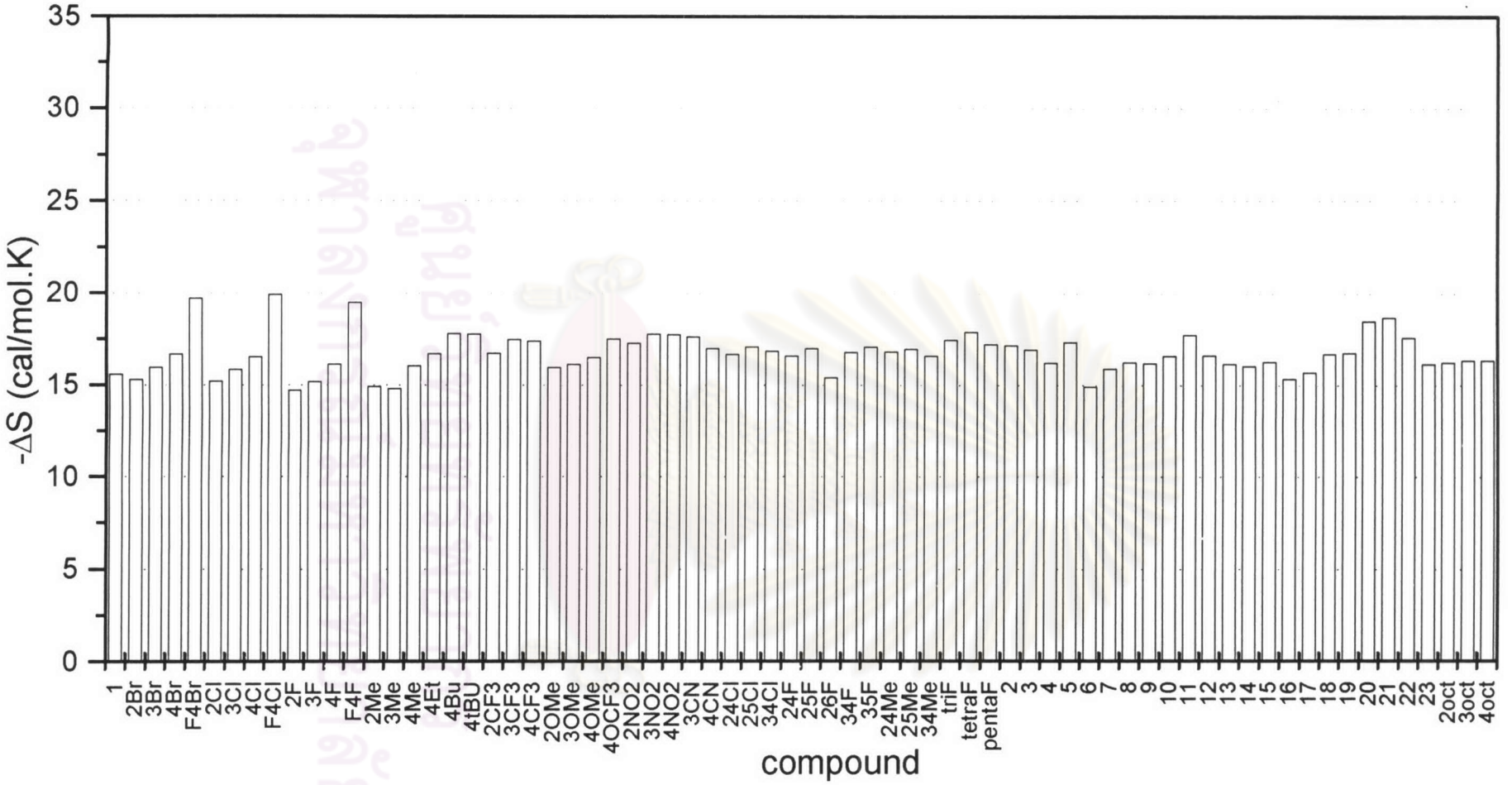


Figure 4.8 Entropy values (-ΔS, cal/ mol · K) of alcohol analytes on OV-1701 column obtained from van't Hoff approach ($\bar{x}$ = 16.74; SD = 1.08).

Both enthalpy and entropy values of the more retained enantiomers of all analytes on each chiral column (figures 4.9-4.12) were not significantly different from each other within the same column. The average $-\Delta H_2$ and $-\Delta S_2$ values obtained from all three columns increased in the order of OV-1701 < GSiMe < BSiMe, which would result from the increased interaction between analytes and cyclodextrin derivatives. Nonetheless, the average $-\Delta H_2$ and $-\Delta S_2$ values obtained from BSiMe were approximately 20% higher than values obtained from GSiMe, even both cyclodextrin derivatives possess similar functional groups. This indicated that the structure of β-cyclodextrin derivative was probably more suitable for the interaction with analytes, which mostly are aromatic alcohols, than the γ-derivative.

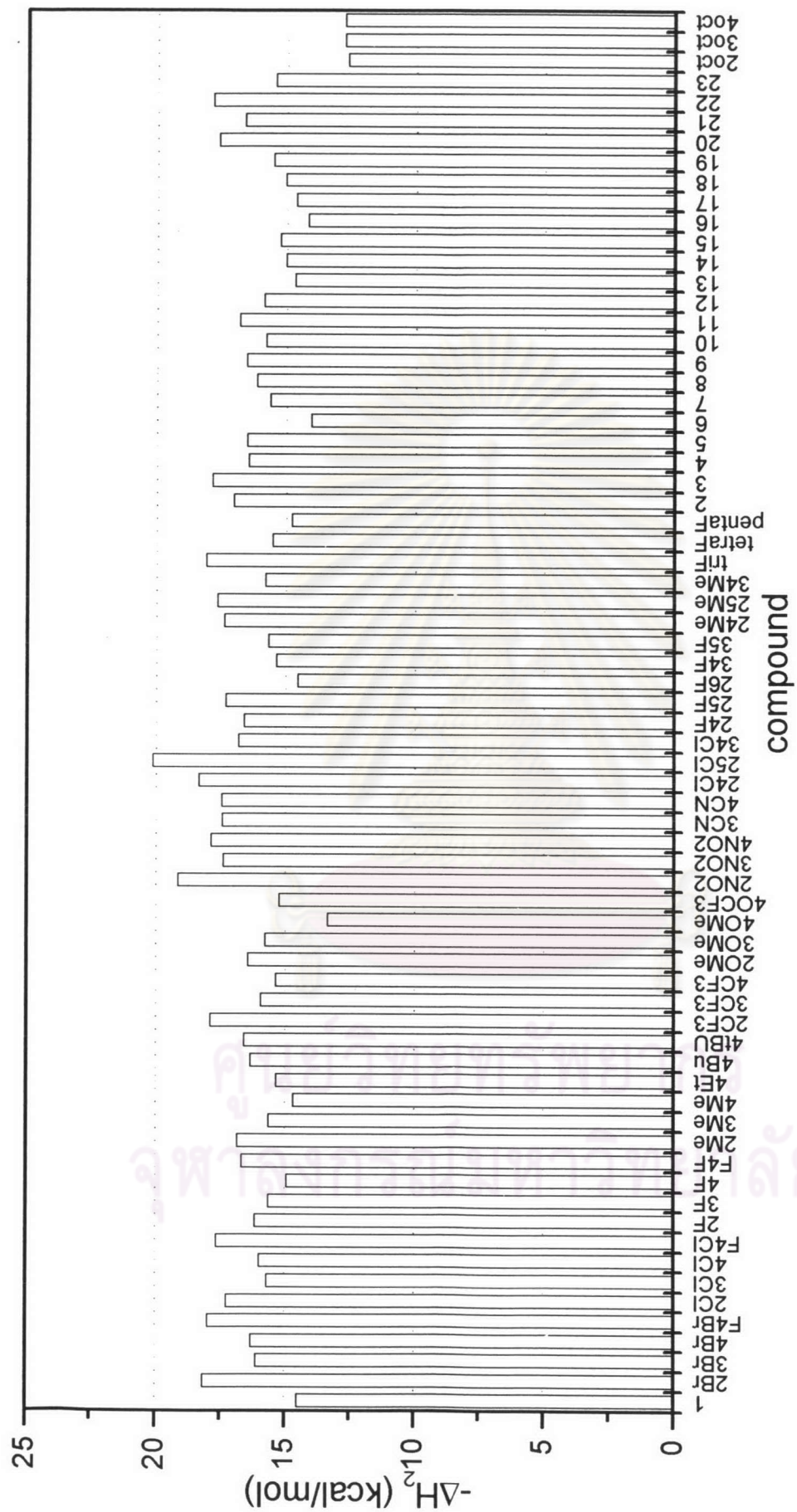


Figure 4.9 Enthalpy values ($-\Delta H_2$, kcal/mol) of the more retained enantiomers of alcohol analytes on BSiMe column obtained from van't Hoff approach ($\bar{x}$ = 16.74; SD = 1.08).

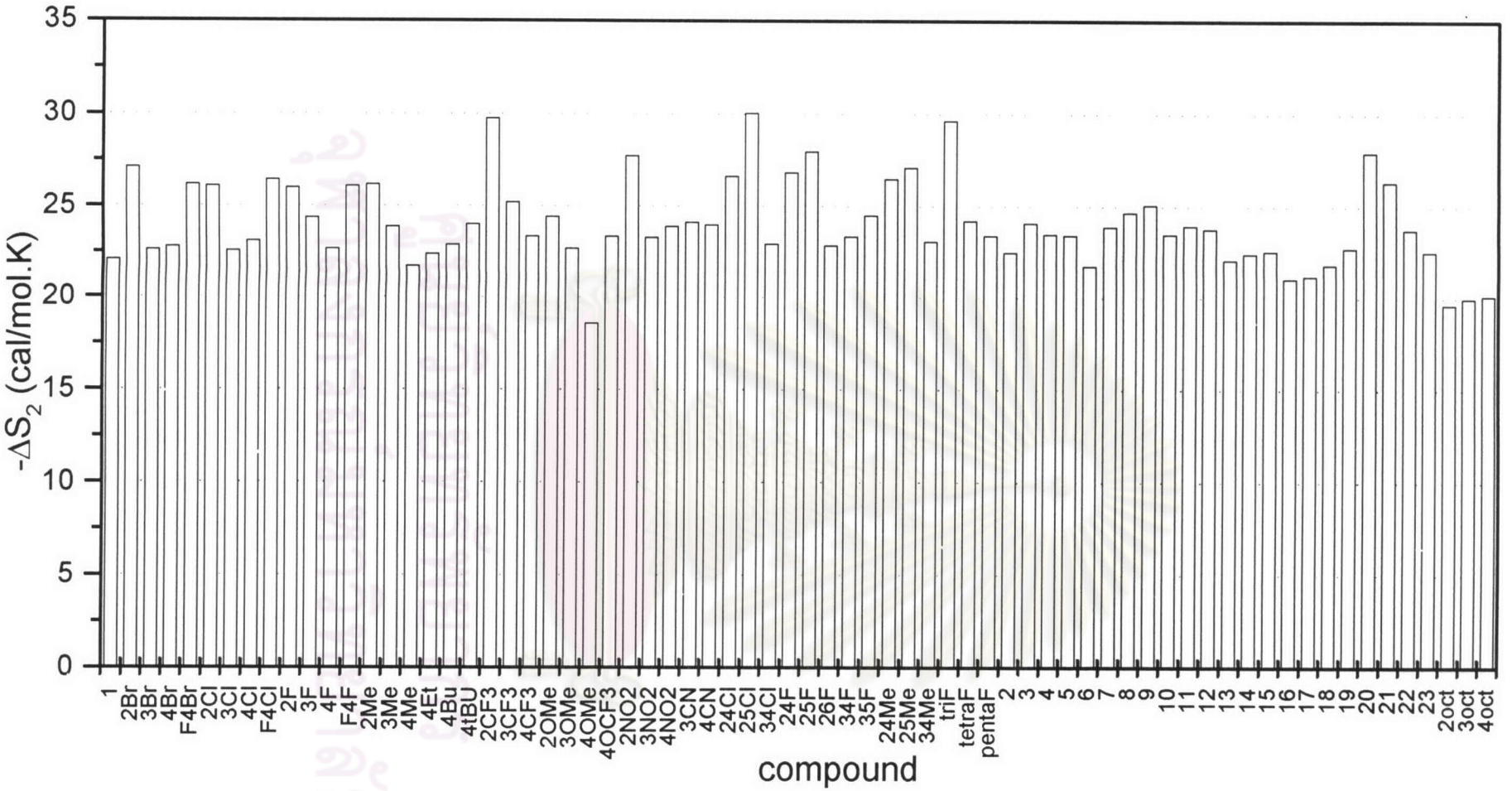


Figure 4.10 Entropy values ($-\Delta S_2$, cal/ mol · K) of the more retained enantiomers of alcohol analytes on BSiMe column obtained from van't Hoff approach ($\bar{x}$ = 24.07; SD = 2.33).

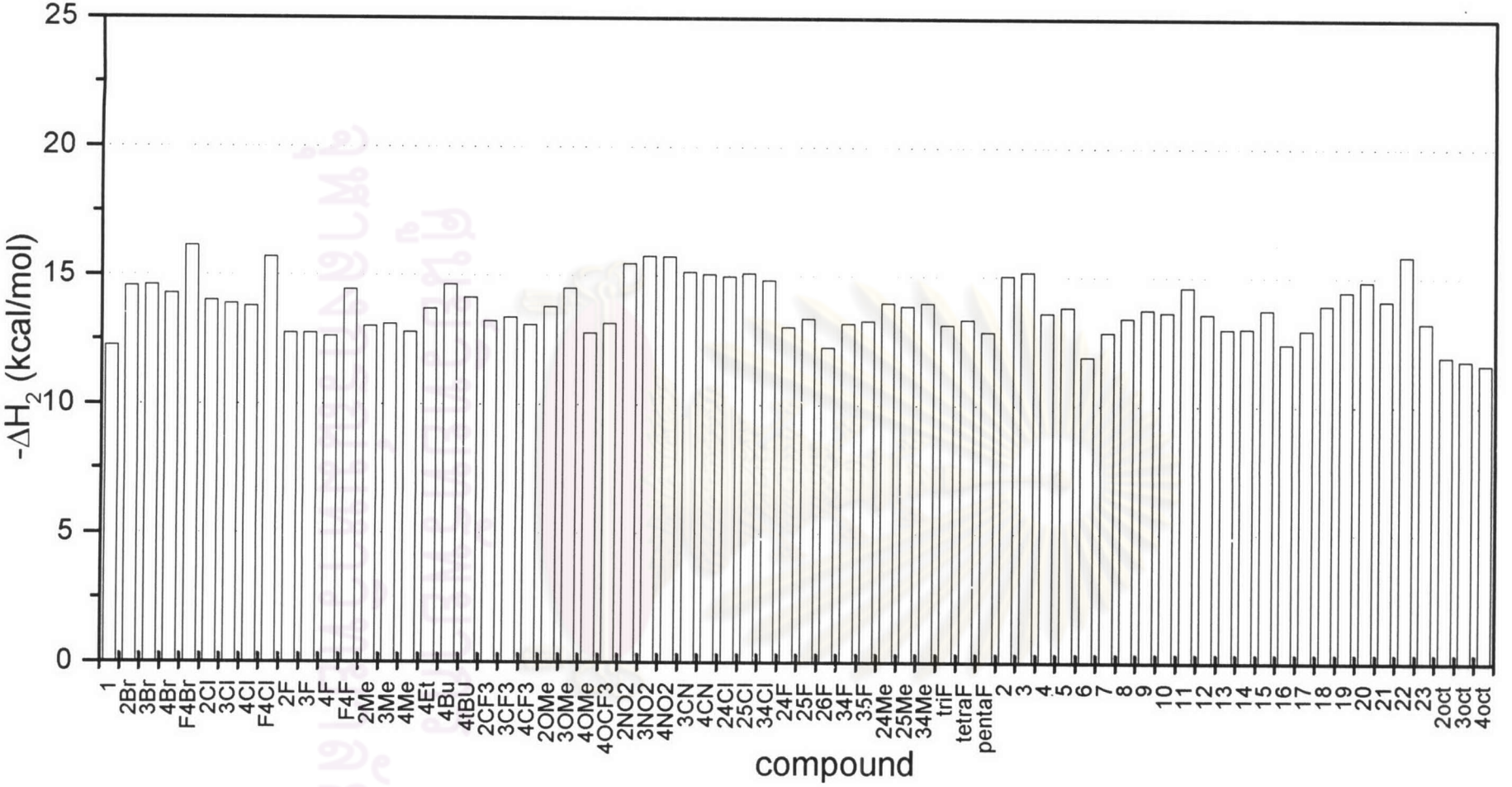


Figure 4.11 Enthalpy values ($-\Delta H_2$, kcal/mol) of the more retained enantiomers of alcohol analytes on GSiMe column obtained from van't Hoff approach ($\bar{x}$ = 13.78; SD = 1.06).

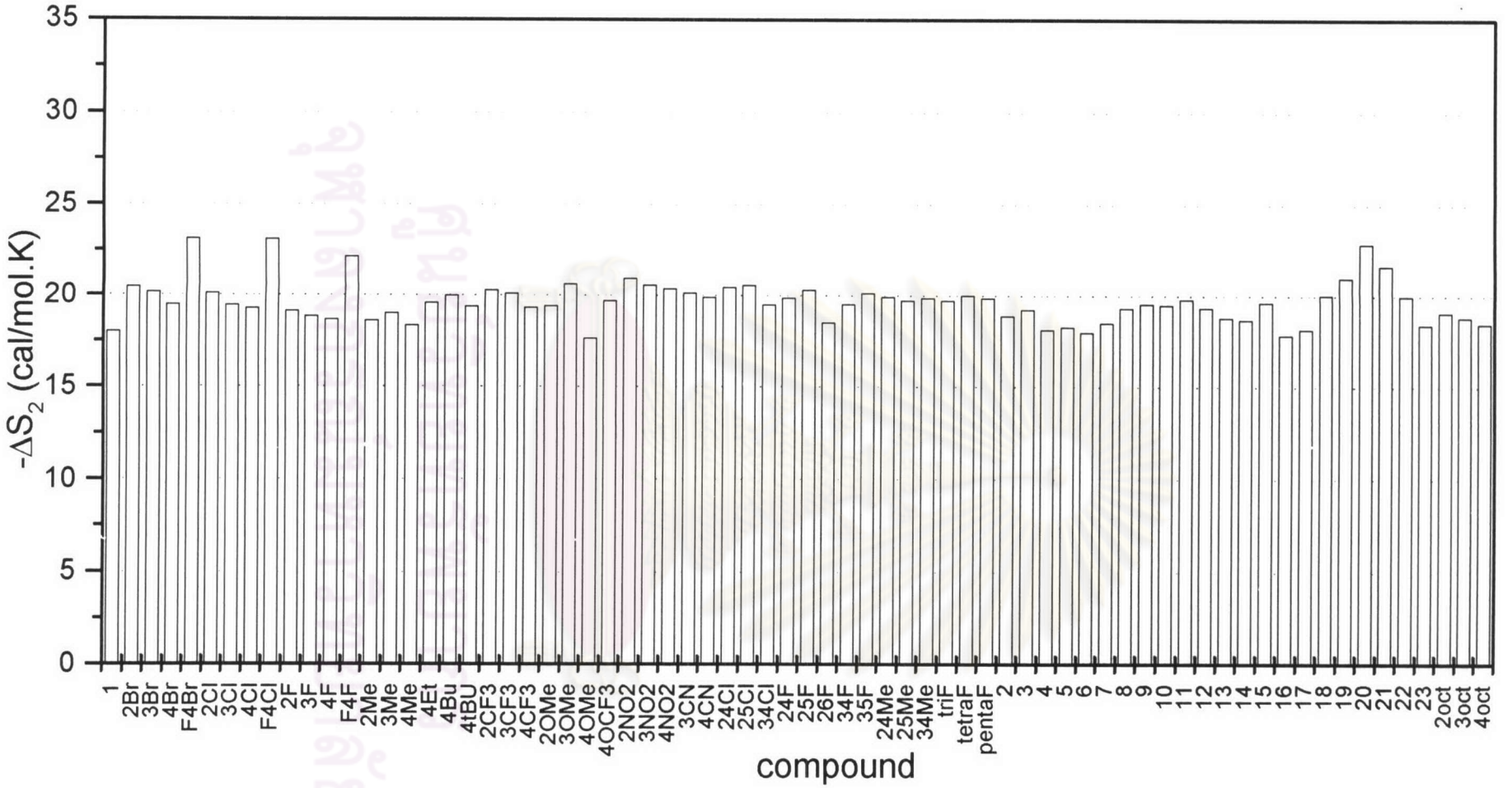
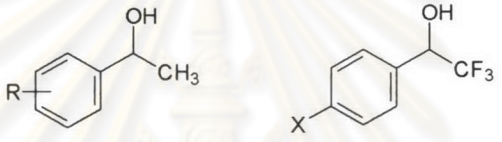


Figure 4.12 Entropy values ($-\Delta S_2$, cal/ mol · K) of the more retained enantiomers of alcohol analytes on GSiMe column obtained from van't Hoff approach ($\bar{x}$ = 19.67; SD = 1.13).

4.4.2 Enthalpy difference (-Δ(ΔH)) and entropy difference (-Δ(ΔS))

The differences in thermodynamic values from chiral BSiMe column for all alcohol analytes were significantly different, even though -Δ(ΔH) and -Δ(ΔS) values showed similar trend. Additionally, the values from BSiMe column were generally much higher than values from GSiMe column. In this study, 1-phenylethanol was selected as a reference analyte. The influence of analyte structure and substituents on enantioseparation will be discussed and classified according to the similarity of analyte structure.

Series 1: Alcohols with mono-substitution on the aromatic ring



R = Br, Cl, F, Me, Et, Bu, tBu, OMe, CN, NO_2, CF_3, OCF_3

X = Br, Cl, F

Racemic alcohols in this series are 1-phenylethanol derivatives with mono-substitution on the aromatic ring as shown above. The type of substituent includes bromo, chloro, fluoro, methyl, ethyl, butyl, *tert*-butyl, methoxy, cyano, nitro, trifluoromethyl, and trifluoromethoxy at *ortho*-, *meta*-, or *para*-position. The enthalpy differences (-Δ(ΔH) values) and entropy differences (-Δ(ΔS) values), representing the enantioseparation, for the separation of enantiomers of these alcohols on BSiMe column display similar trend and are shown in figures 4.13-4.14.

It can be seen that the -Δ(ΔH) values of each analyte obtained from BSiMe column are notably different but a trend is detected. In most cases, the -Δ(ΔH) values of substituted analytes are in the order of *ortho* >> *para* > *meta*, except for methoxy-substituted 1-phenylethanols where the order is *ortho* >> *meta* > *para*. The -Δ(ΔH) values of *ortho*-substituted analytes are also much larger than that of 1-phenylethanol, while those of *meta*- or *para*-substituted analytes are closed to or lower than that of 1-phenylethanol. Comparing -Δ(ΔH) values of analytes with

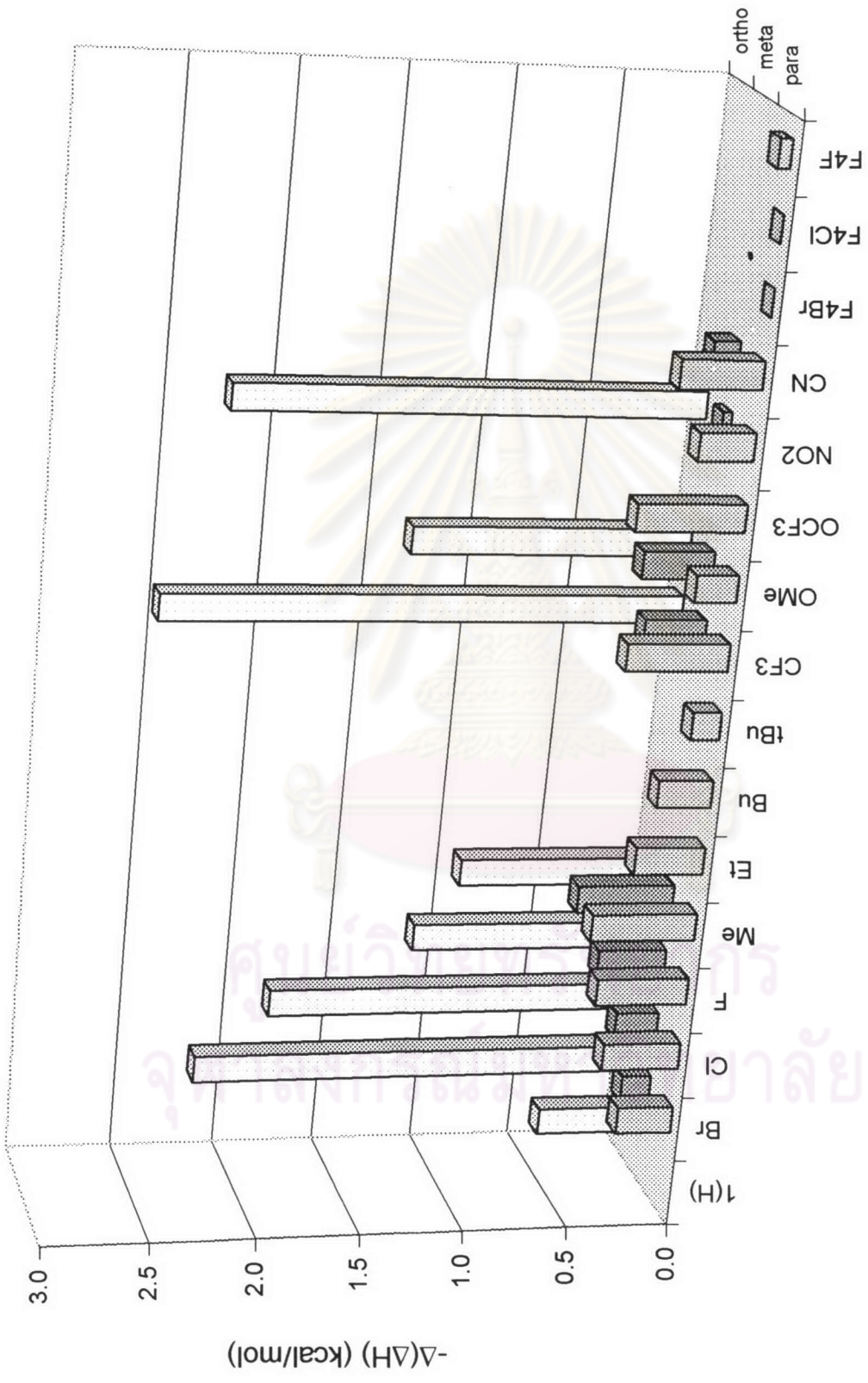


Figure 4.13 Difference in enthalpy values (-Δ(ΔH), kcal/mol) of the enantiomers of mono-substituted 1-phenylethanol derivatives on BSiMe column.

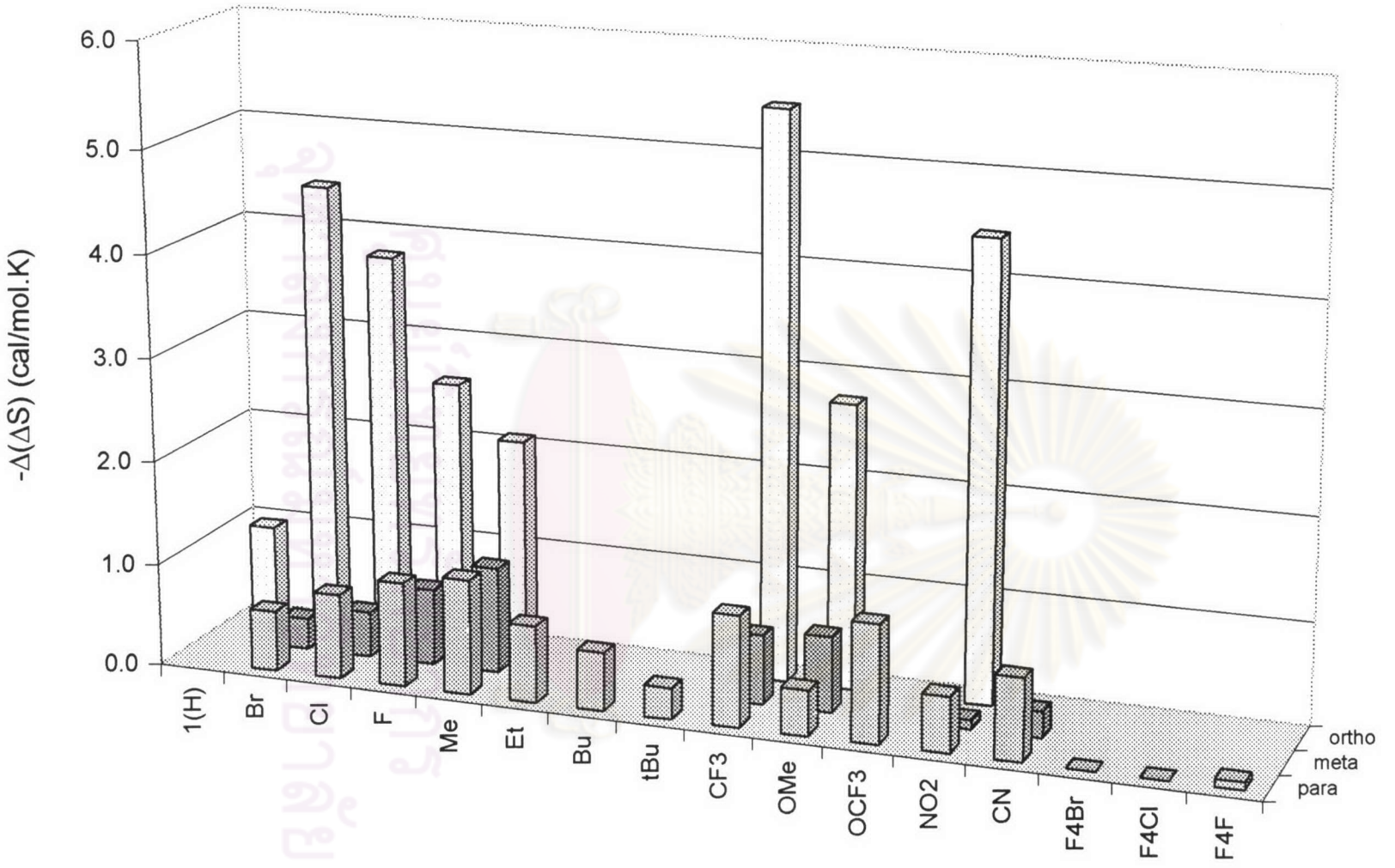


Figure 4.14 Difference in entropy values (-Δ(ΔS), cal/ mol · K) of the enantiomers of mono-substituted 1-phenylethanol derivatives on BSiMe column.

different type of substitution at the same position, it is found that values of *meta*- and *para*-substituted analytes are very similar at ~ 0.5 kcal/mol or lower. In contrast, values of *ortho*-substituted analytes vary significantly depending on the type of substitution. These results indicate that the position of substituent has much stronger influence to enantioseparation than the type of substituent.

Comparing the effect of substituent type, the -Δ(ΔH) values for *ortho*-substituted alcohols decrease in the order of **2CF$_3$** > **2NO$_2$** > **2Br** > **2Cl** > **2OMe** > **2F** > **2Me**. The results are almost reversed for the *meta*- and *para*-substituted analytes. For *para*-substituted alcohols, longer or bulkier alkyl substituents (as in **4Et**, **4Bu**, **4tBu**) decrease enantioseparation. Among the mono-substituted analytes used in this study, 1-(2-trifluoromethylphenyl)ethanol (**2CF$_3$**) shows the greatest -Δ(ΔH) value. Interestingly, when the substitution is changed from trifluoromethyl to methyl as in 1-(2-methylphenyl)ethanol (**2Me**), the -Δ(ΔH) value is the lowest among the *ortho*-substituted analytes. The enantioseparation of **2CF$_3$** and **2Me** are compared in figure 4.15. It is clear that the resolution of **2CF$_3$** is superior in shorter time. Even though the trifluoromethyl group showed superior improvement in enantioseparation at *ortho*-position, the replacement of methyl group with trifluoromethyl group at the α-carbon of **4Br**, **4Cl**, and **4F** exhibited the opposite effect as in **F4Br**, **F4Cl**, and **F4F**.

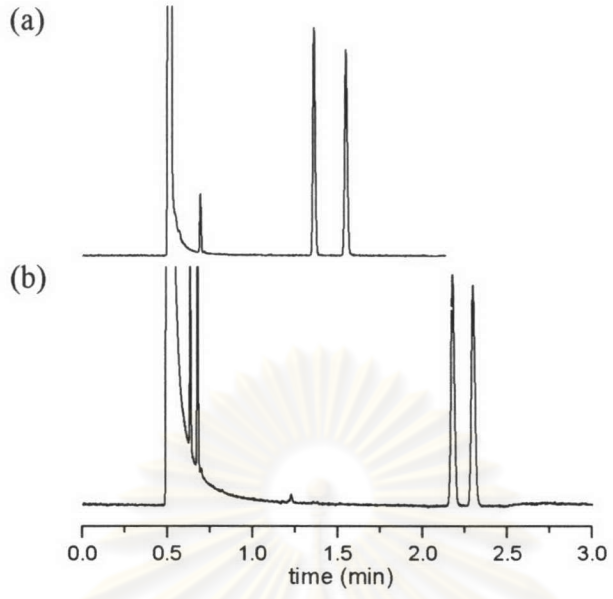


Figure 4.15 Chromatograms of (a) **2CF$_3$** and (b) **2Me** on BSiMe column at 150 °C.

The enthalpy differences (-Δ(ΔH) values) for the separation of enantiomers of alcohols series 1 on GSiMe are illustrated in figure 4.16. In all cases, the -Δ(ΔH) values acquired from GSiMe column were much lower than those from BSiMe column, except for **F4Br** and **F4Cl** where separation were observed only on GSiMe column. The -Δ(ΔH) values of substituted analytes are in the order of *ortho* > *para* > *meta*, except for methoxy-substituted 1-phenylethanols where the order is *para* > *meta* > *ortho*. Furthermore, it should be noted that the GSiMe is not suitable for the enantioseparation of *meta*-substituted alcohols as only a few can be separated with very small degree of separation. The same trend was also noticed for the entropy differences (-Δ(ΔS) values). The enantioseparation abilities of both cyclodextrin derivatives for the separation of chloro-substituted 1-phenylethanols were compared as displayed in figure 4.17.

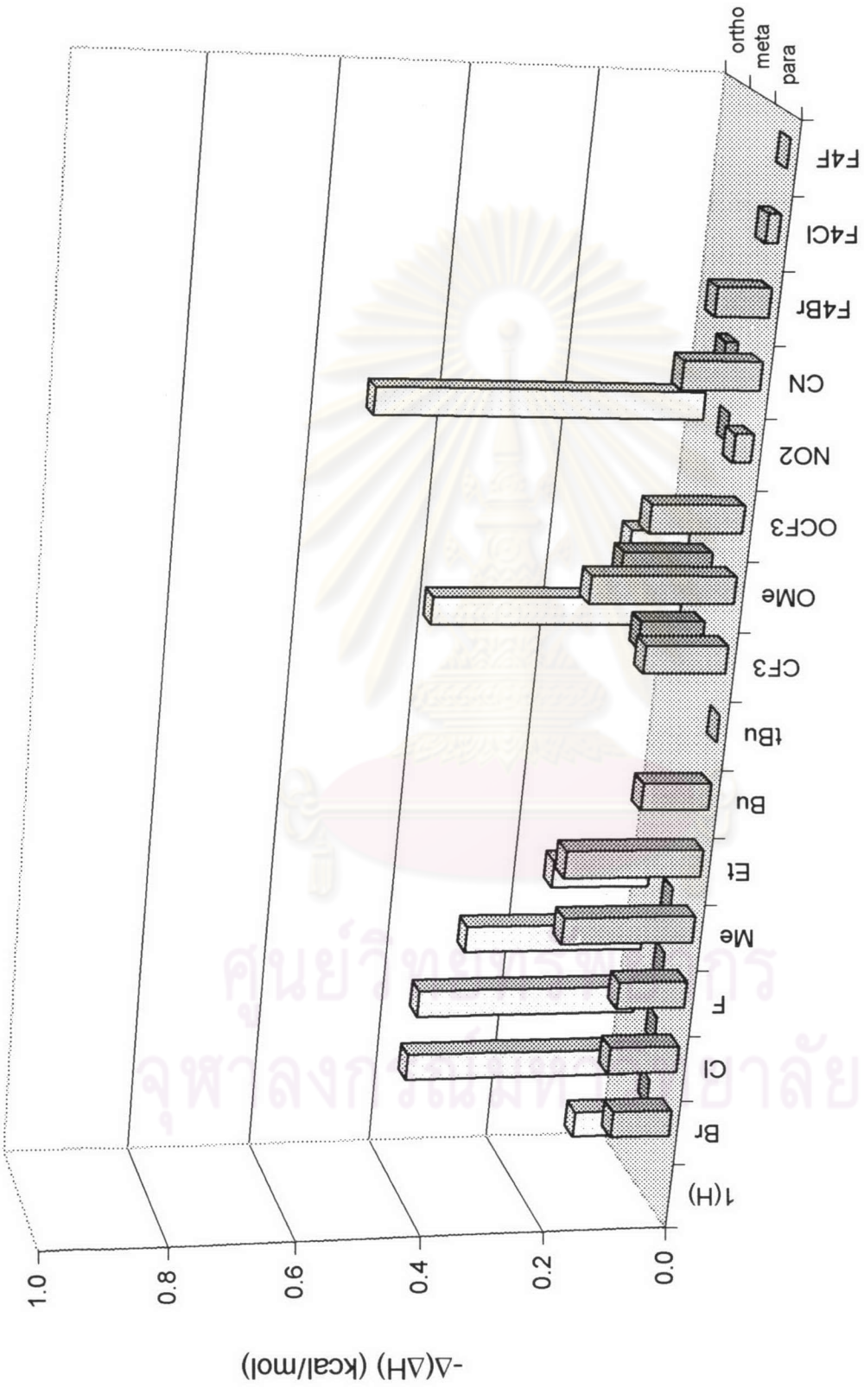
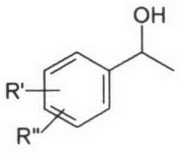


Figure 4.16 Difference in enthalpy values (-Δ(ΔH), k cal/mol) of the enantiomers of mono-substituted 1-phenylethanol derivatives on GSiMe column.

Figure 4.17 Chromatograms of **2Cl**, **3Cl**, and **4Cl** on (a) BSiMe and (b) GSiMe columns at 150 °C.

Series 2: Alcohols with di-substitution on the aromatic ring



R' = R'' = Cl, F, Me

Racemic alcohols in series 2 comprise of 1-phenylethanol derivatives with dichloro-, difluoro-, and dimethyl-substitutions at different position of the aromatic ring. The enthalpy differences for the enantioseparation of di-substituted 1-phenylethanols on BSiMe and GSiMe columns are presented in figure 4.18. The entropy differences from each column also showed similar trend as enthalpy differences.

On BSiMe column, analytes with *ortho*-substitution show enhanced enantioseparation, as in **24Cl**, **25Cl**, **24Me, 25Me, 24F, 25F,and 26F**, compared to those without *ortho*-substitution, as in **34Cl**, **34Me** and **35F**, except for **34F**. These results correspond with the findings from series 1 that *ortho*-substitution provides the largest enantiomer separation. Type of substituent also affects the separation to some extent. In this study, the $-\Delta(\Delta H)$ values have a tendency to decrease as the substitution is changed from chloro or fluoro to methyl, similar to the tendency of *ortho*-substituted analyted in series 1. Among all series 2 analytes tested on BSiMe column, the highest enantioseparation was observed for 1-(2,5-dichlorophenyl)ethanol (**25Cl**), while the separation of **35F** could not be achieved.

It is evident that BSiMe exhibits better chiral recognition towards di-substituted 1-phenylethanols than GSiMe, as seen from the larger $-\Delta(\Delta H)$ values on BSiMe column. On GSiMe column, where the cavity size of selector is larger, the enantiorecognition is relatively small and very similar. Among all series 2 analytes tested on GSiMe column, the highest enantioseparation was observed for 1-(2,4-dichlorophenyl)ethanol (**24Cl**). The separation of three dichloro-substituted 1-phenylethanols on BSiMe and GSiMe columns at 160 °C is demonstrated in figure 4.19.

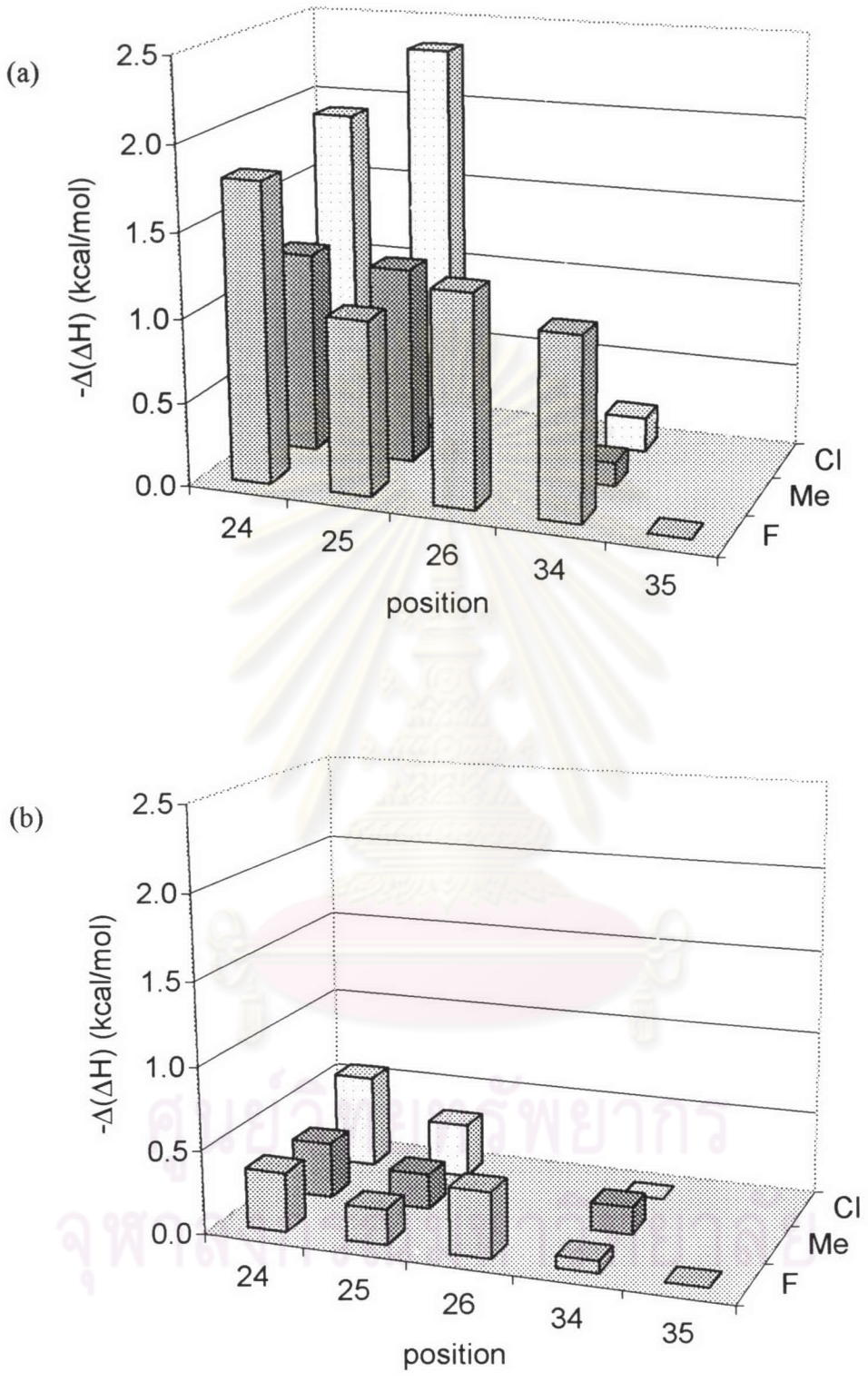


Figure 4.18 Difference in enthalpy values (-Δ(ΔH), kcal/mol) of the enantiomers of di-substituted 1-phenylethanol derivatives on (a) BSiMe and (b) GSiMe columns.

Figure 4.19 Chromatograms of **24Cl**, **25Cl**, and **34Cl** on (a) BSiMe and (b) GSiMe columns at 160 °C.

Series 3: Other alcohols

Other alcohols with diversed structures were also investigated. Similar to previous study, the $-\Delta(\Delta H)$ and $-\Delta(\Delta S)$ values on each column displayed similar trend. The $-\Delta(\Delta H)$ values of alcohols in series 3 on both columns are compared in figure 4.20. Largely, the enantioseparation of these alcohols was satisfactorily achieved with BSiMe phase. However, compared to analyte **1**, substitution on the side chain of alcohols tends to reduce enantiodifferentiation on BSiMe. For the simplicity of discussion, alcohols in series 3 are further subdivided into 4 subgroups according to the similarity of their structures and only the $-\Delta(\Delta H)$ values will be shown.

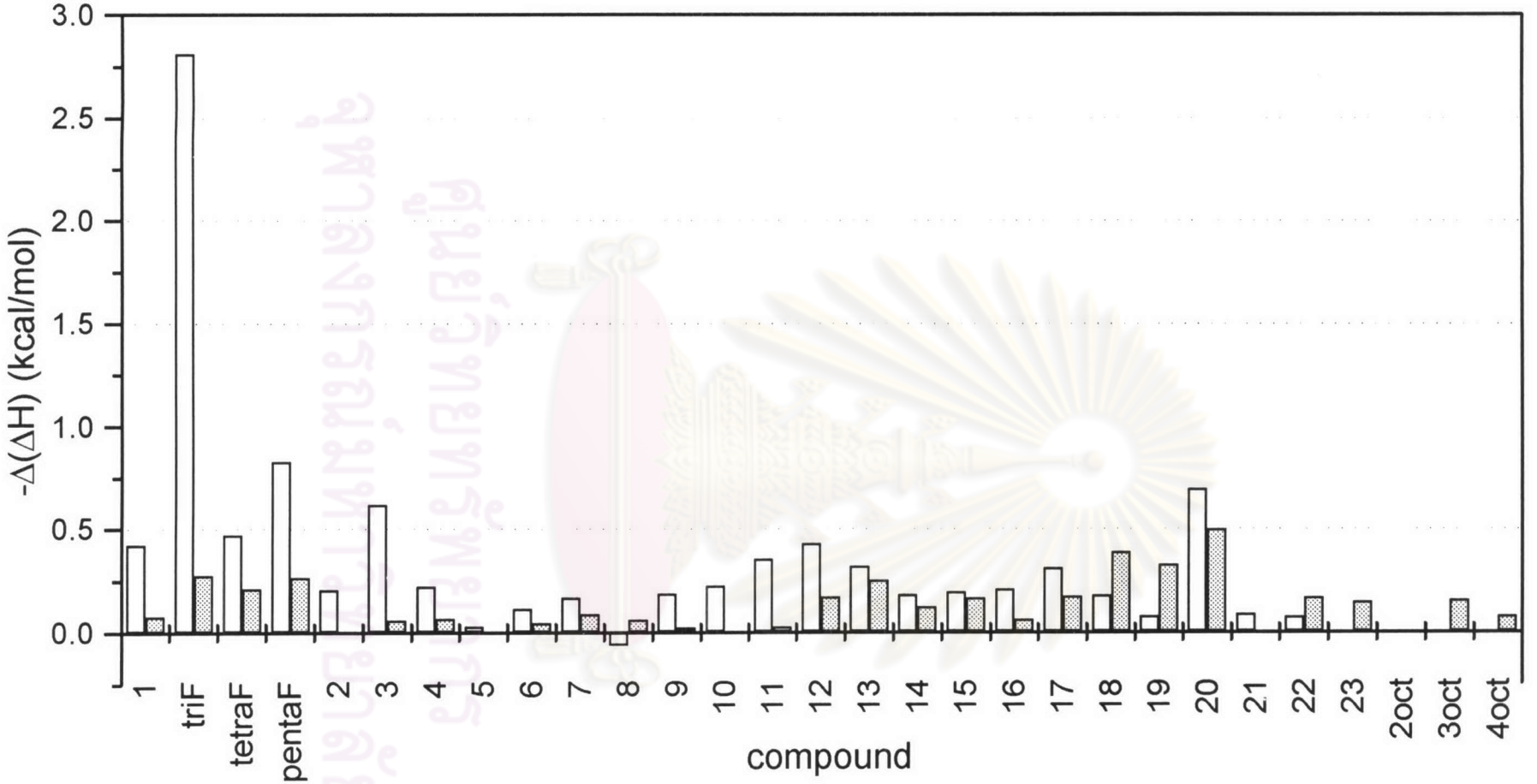
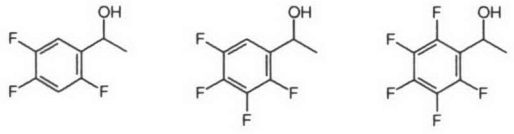


Figure 4.20 Difference in enthalpy values (-Δ(ΔH), kcal/mol) of the enantiomers of alcohols in series 3 on BSiMe (white bar) and GSiMe (gray bar) columns.

Series 3.1: Polyfluoro-substituted 1-phenylethanols



triF **tetraF** **pentaF**

Alcohols in this subgroup compose of 1-(2,4,5-trifluorophenyl)ethanol (**triF**), 1-(2,3,4,5-tetrafluorophenyl)ethanol (**tetraF**), and 1-(pentafluorophenyl) ethanol (**pentaF**). Their thermodynamic parameters are evaluated against other monofluoro- and difluoro-substituted 1-phenylethanols. Their -Δ(ΔH) values are presented in figure 4.21. Similar trend was attained for the -Δ(ΔS) values.

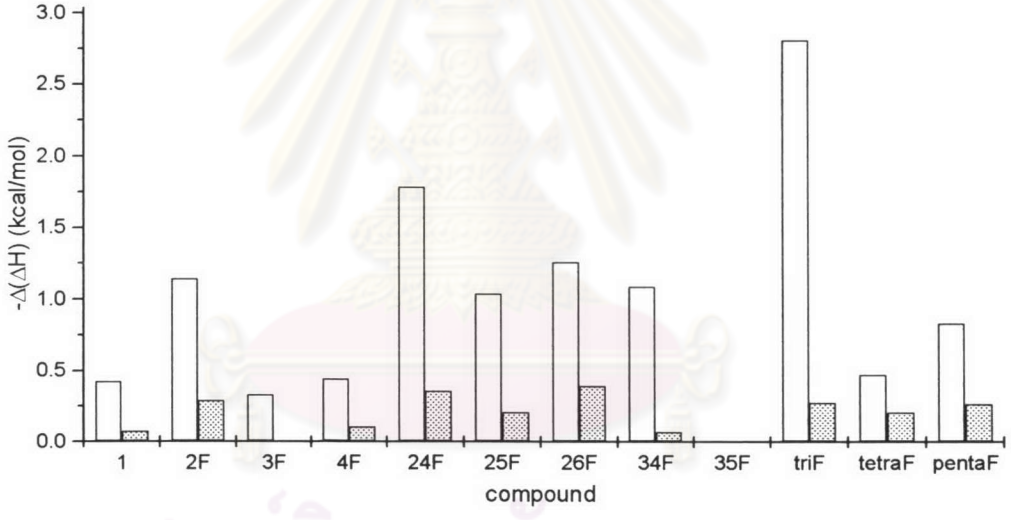


Figure 4.21 Difference in enthalpy values (-Δ(ΔH), kcal/mol) of the enantiomers of alcohols in series 3.1 on BSiMe (white bar) and GSiMe (gray bar) columns.

According to figure 4.21, BSiMe phase offers superior enantiorecognition towards all analytes than GSiMe phase. The -Δ(ΔH) values on GSiMe phase are relatively small and are not significantly different. On the other hand, the -Δ(ΔH) values on BSiMe column vary considerably. In all cases, except for **3F** and **35F**, replacing hydrogen atom(s) on the aromatic ring with fluorine atom(s) improves enantiorecognition. However, the degree of enhancement varies depending on the number and position of fluoro-substitution. Among all analytes examined on BSiMe column, **triF** presents the best enantioseparation and the resolution is displayed in figure 4.22. Unfortunately, other isomers of trifluoro-substituted 1-phenylethanol are not available to study the effect of position of fluoro-substituent.

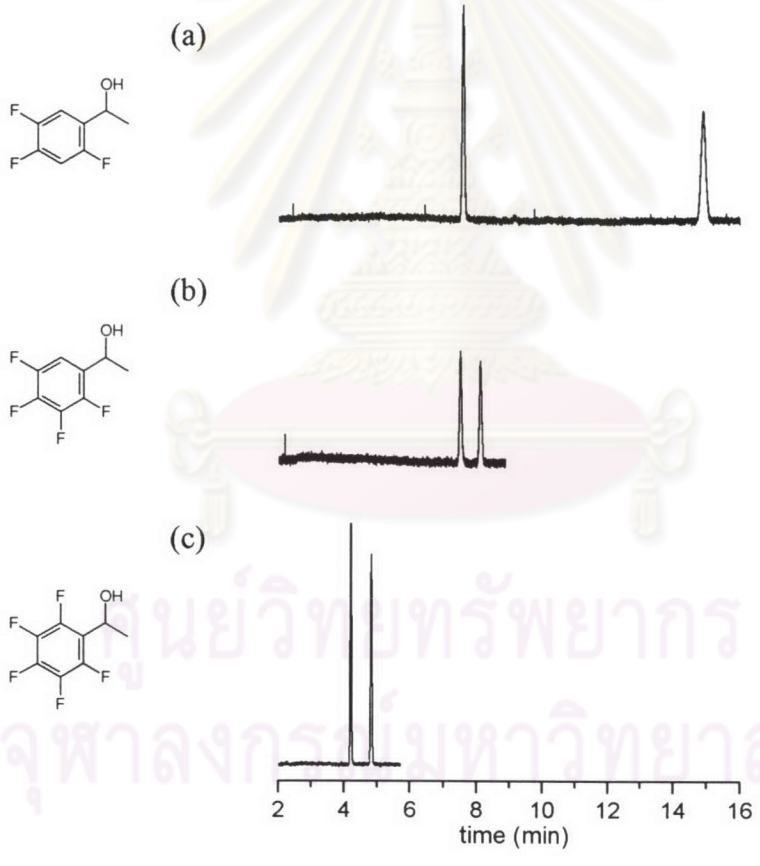
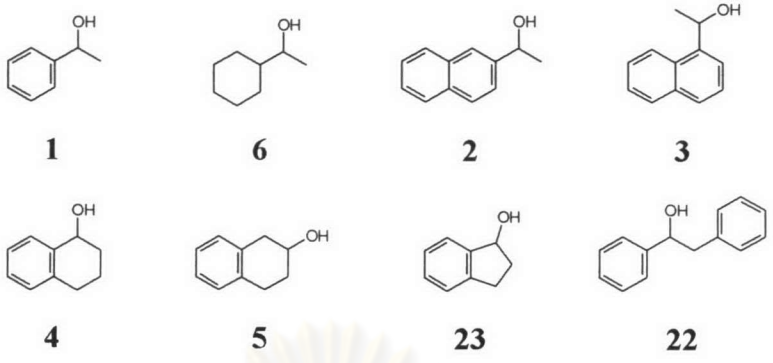


Figure 4.22 Chromatograms of (a) **triF**, (b) **tetraF**, and (c) **pentaF** on BSiMe column at 110 °C.

Series 3.2: Alcohols with different structures



This subgroup is composed of alcohols with different structure based on 1-phenylethanol (**1**). Thermodynamic data for the separation of these alcohols on BSiMe and GSiMe columns are demonstrated in figures 4.23.

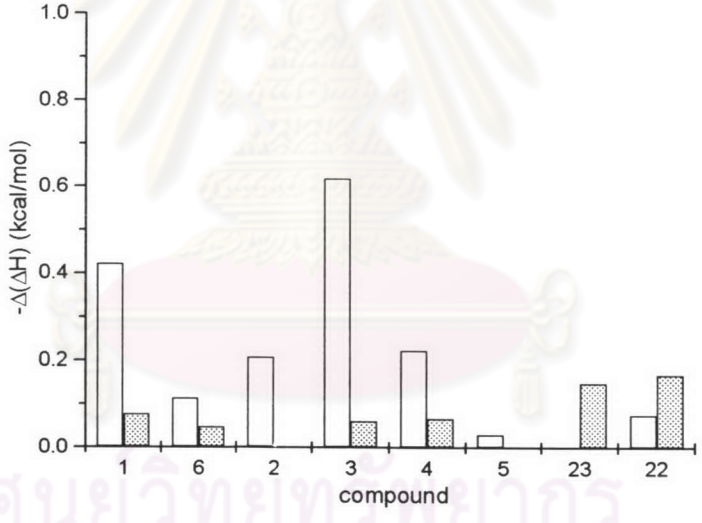


Figure 4.23 Difference in enthalpy values (-Δ(ΔH), kcal/mol) of the enantiomers of alcohols in series 3.2 on BSiMe (white bar) and GSiMe (gray bar) columns.

Similar to other discovery, the enantioseparation of series 3.2 alcohols with GSiMe phase are generally small and the -Δ(ΔH) values are very closed to each other. Nonetheless, GSiMe provides better enantioseparation for some analytes than BSiMe phase as in **22** and **23**. It could be explained that the larger size cyclodextrin,

GSiMe, would be more suitable to accommodate larger analyte as **22** and provide proper interactions, thus, yield better separation and in shorter analysis time. The separation of **22** on both columns is shown in figure 4.24.

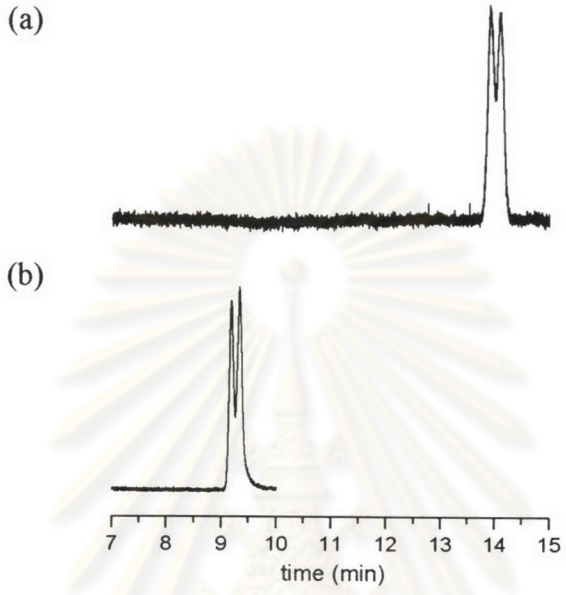


Figure 4.24 Chromatograms of **22** on (a) BSiMe and (b) GSiMe columns at 160 °C.

On BSiMe column, the enantiorecognition decreases when the structure is changed from an aromatic (as in **1**) to a cyclohexane ring (as in **6**) or when the structure contains cycloalkyl moiety (as in **4**, **5**, and **23**). When the structure contains a naphthyl moiety (as in **2** and **3**), the separation is obviously affected by the position of 1-ethanoyl substituent, as the enantioseparation of **3** is much better than **2** (figure 4.25). Similar result for the separation of **2** and **3** on BSiMe phase was also obtained by Kobor et al. [20, 21]. They proposed that the dipole-dipole interaction between analyte **2** and cyclodextrin could be weakened by steric hindrance, leading to reduced separation [20]. Additionally, they investigated the enantioselectivity of 2,3-di-*O*-methyl-6-*O*-*tert*-butyldimethylsilyl derivative of α-, β-, and γ-cyclodextrins dissolved in nonpolar SE-54 (3-5% phenyl, 1% vinyl, 94-96% methyl polysiloxane) towards the enantiomers of **2** and **3** at 180 °C. Their data indicated that the enantioseparation of 1-(2-naphthyl)ethanol, **2**, could only be achieved with

β-derivative, while **3** could be resolved with either α- or β-derivatives. γ-Derivative was the poorest chiral selector among the three derivatives for 29 test analytes [21].

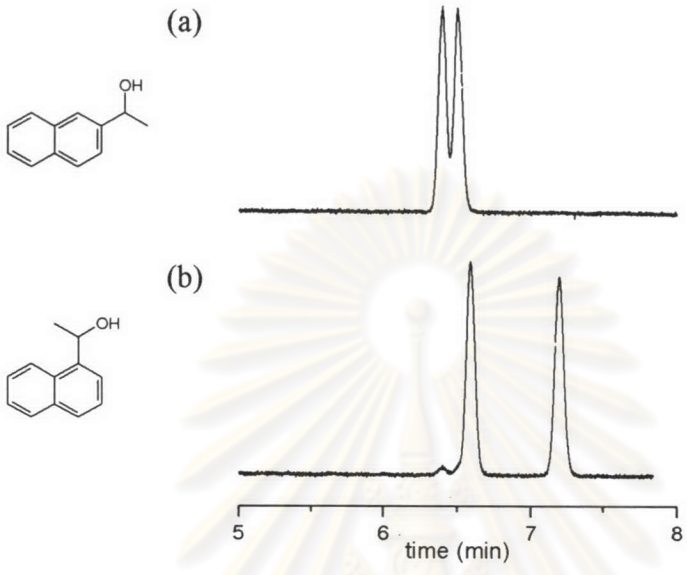
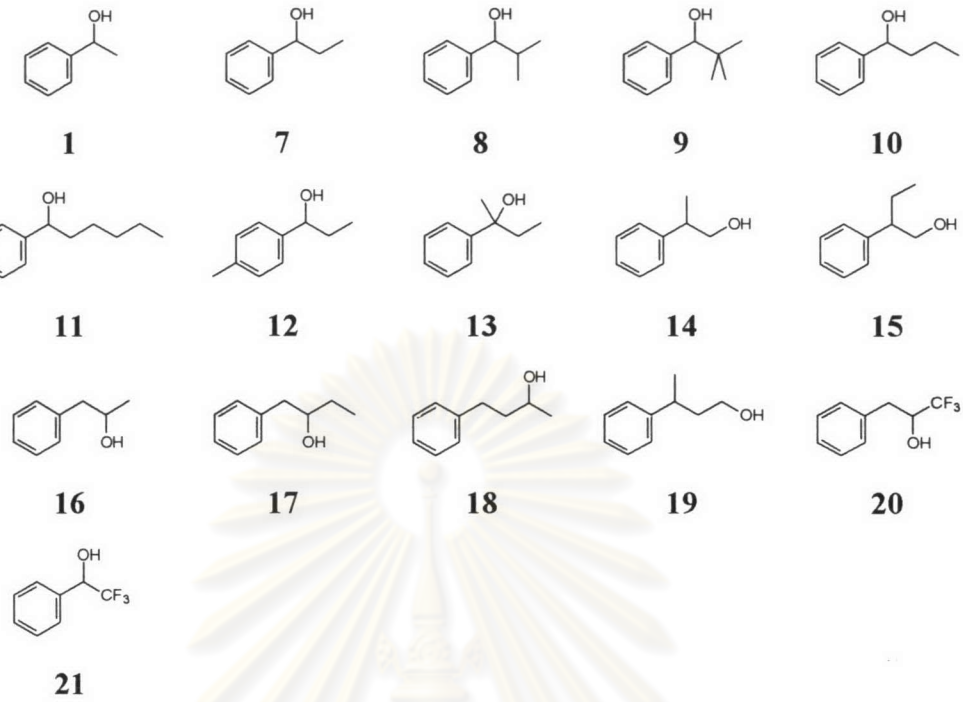


Figure 4.25 Chromatograms of (a) **2** and (b) **3** on BSiMe column at 170 °C.

The enantioseparation of **4** was also examined by Armstrong and coworkers using dipentyl-β-cyclodextrin as stationary phase, without dilution in polysiloxane, at 100 °C with the enantioselectivity value (α) of 1.05 [10]. However, analyte **4** could be separated with similar α value on diluted BSiMe column at 120 °C. The improved separation is expected at lower temperature. This indicates the greater enantioseparation power of BSiMe over dipentyl-β-cyclodextrin for analyte **4**.

Series 3.3: Alcohols with different alkyl chain



Alcohols in series 3.3 include derivatives of 1-phenylethanols with different alkyl substituent on the α-carbon (as in 7, **8**, **9**, **10**, **11**, **12**, **13**); aromatic alcohols with different position of chiral center or hydroxyl group (as in **14**, **15**, **16**, **17**, **18**, **19**, **20**); and aromatic alcohols with trifluoromethyl substituent at the chiral center (as in **20**, **21**). Enthalpy differences responsible for chiral discrimination of alcohols in series 3.3 are depicted in figure 4.26.

The enantioseparation of alcohols in series 3.3 is relatively low on both columns. Surprisingly, both the $-\Delta(\Delta H)$ and $-\Delta(\Delta S)$ values of alcohol **8** on BSiMe show opposite values to those on GSiMe column. A plot of ln α versus 1/T for alcohol **8** on BSiMe column (figure 4.27) displays a separation selectivity maxima. It is possible that compound **8** interacts with BSiMe by multiple mechanisms and there is a change in the interaction mechanism between analyte and cyclodextrin derivative in this temperature range [31].

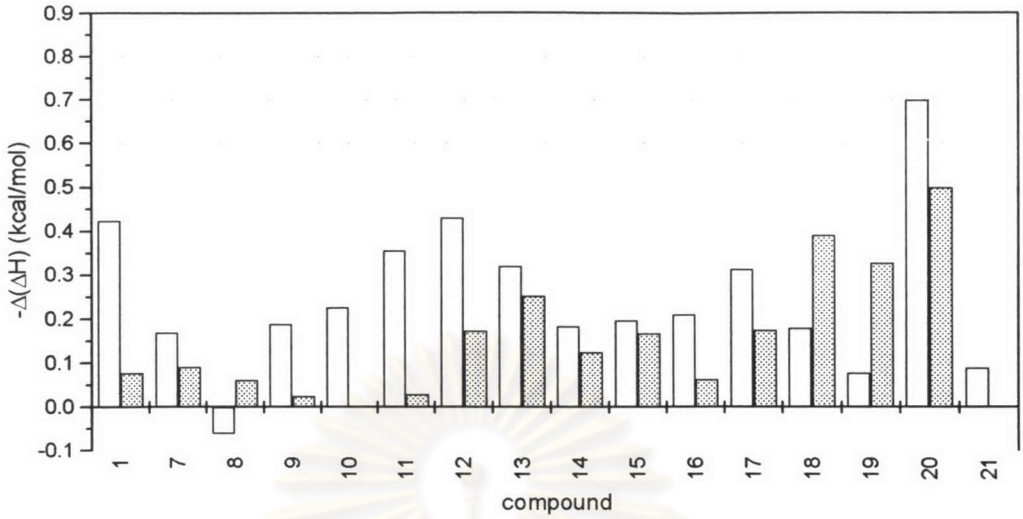


Figure 4.26 Difference in enthalpy values (-Δ(ΔH), kcal/mol) of the enantiomers of alcohols in series 3.3 on BSiMe (white bar) and GSiMe (gray bar) columns.

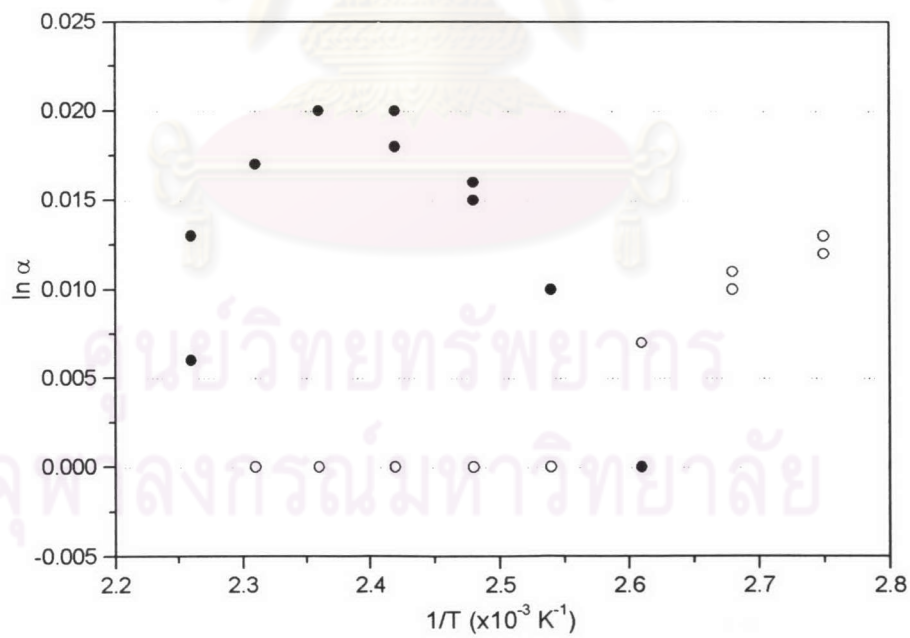


Figure 4.27 Ln α versus 1/T plots for the enantiomers of alcohol **8** on BSiMe (●) and GSiMe (○) columns.

On BSiMe column, substitution on the side chain of analytes tends to decreased enantioselectivities compared to alcohol **1**. All compounds, except **20**, exhibit lower enantiodifferentiation on BSiMe than **1**. On the contrary, the opposite is observed on GSiMe column as most analytes show better enantioseparation than **1**. This is probably due to the larger size of γ-cyclodextrin derivative.

The effect of position of chiral center and hydroxyl group on the analyte molecule towards the enantioseparation is not apparent, as the thermodynamic values are not significantly different. The effect of trifluoromethyl group on chiral recognition is worthy of note. As previously observed on the results from mono-substituted 1-phenylethanol derivatives (series 1), the substitution of methyl with trifluoromethyl group at the α-carbon tremendously deteriorates the separation as in **F4Br**, **F4Cl**, and **F4F**. Similar results were noticed for the separation of **21** on both columns. Nevertheless, when the alkyl chain of **21** was extended by one carbon as in **20**, the enantiorecognition on both columns improves enormously, as demonstrated in figure 4.28.

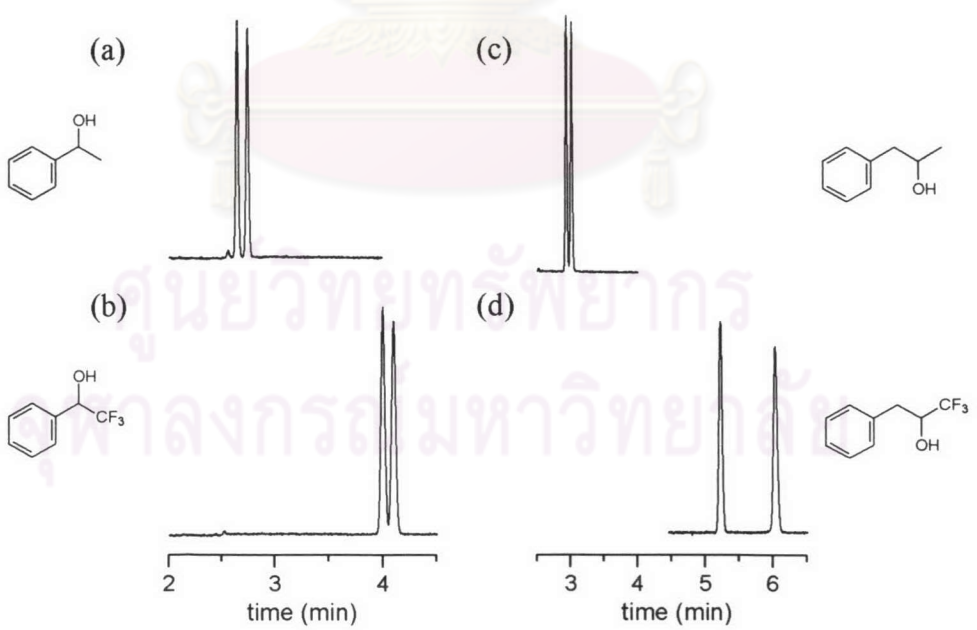


Figure 4.28 Chromatograms of (a) **1**, (b) **21**, (c) **16**, and (d) **20** on BSiMe column at 130 °C.

For a group of isomers (analytes **8**, **10**, **12**, **13**, **15**, **17**, **18** and **19**), the best enantioseparation on GSiMe column is for compound **18**, which contains a long side chain with the furthest chiral hydroxyl group. On the contrary, the greatest enantioseparation observed on BSiMe column is for compound **12**, which possesses a *para*-methyl, aromatic substituent. Comparing of ln α versus 1/T plots of compounds **10** and **12** (figure 4.29), it can be realized that the enantioseparation of **12** improves faster with the decrease in temperature, along with an inevitably increase in analysis time. Below 130 °C, the enantioselectivity of **12** is better than **10**. However, the reverse situation is observed above 130 °C. Therefore, several aspects must be considered in choosing the optimum separation condition.

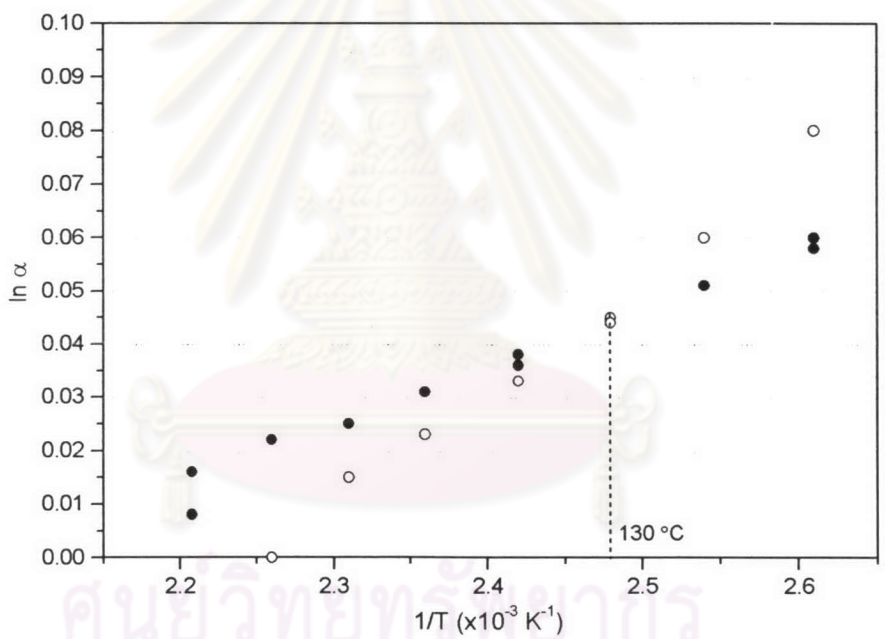
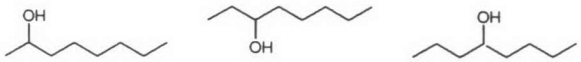


Figure 4.29 Ln α versus 1/T plots for the enantiomers of alcohols **10** (●) and **12** (○) on BSiMe column.

Series 3.4: Aliphatic alcohols



2oct **3oct** **4oct**

A preliminary study on the enantioseparation of aliphatic alcohols was also explored. Three aliphatic alcohols with different position of chiral center were selected. Their separation will be compared with analytes **1** and **6**, since they both have identical number of carbons in the molecule. Enthalpy differences responsible for chiral discrimination of alcohols in series 3.4 are compared to those of **1** and **6** in figure 4.30.

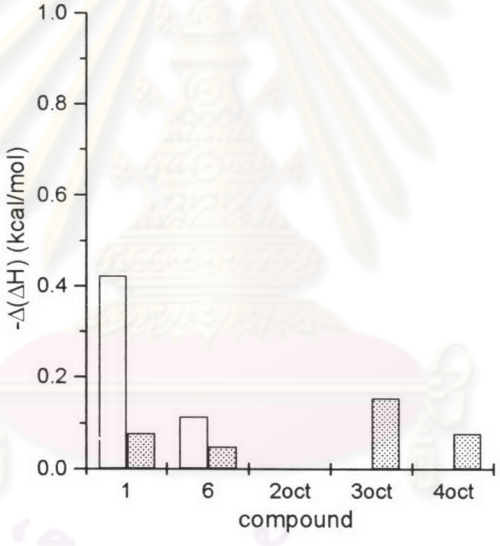


Figure 4.30 Difference in enthalpy values (-Δ(ΔH), kcal/mol) of the enantiomers of alcohols in series 3.4 on BSiMe (white bar) and GSiMe (gray bar) columns.

It is evident that BSiMe is not suitable for the separation of aliphatic alcohols, as none of them could be resolved on this column. Interestingly, larger cyclodextrin derivative GSiMe could separate enantiomers of **3oct** and **4oct** with higher degree than the cyclic (**6**) and aromatic (**1**) analytes. The position of chiral center shows an influence to the enantioseparation on GSiMe as well. Nonetheless, a

definite conclusion cannot be drawn in view of the fact that the enthalpy difference values are relatively small and only three aliphatic alcohols are exploited in this study.