การแยกอิแนนทิโอเมอร์ของแอลกอฮอล์ด้วยแก๊สโครมาโทกราฟีที่ใช้อนุพันธ์บีตาไซโคลเดกซ์ทรินเป็นเฟสคงที่

นางสาวมรกต จงจิตรวัฒนา

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรมหาบัณฑิต
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ENANTIOMERIC SEPARATION OF ALCOHOLS BY GAS CHROMATOGRAPHY USING BETA-CYCLODEXTRIN DERIVATIVE AS STATIONARY PHASE

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มรกต จงจิตรวัฒนา : การแยกอิแนนทิโอเมอร์ของแอลกอฮอล์ด้วยแก๊สโครมาโทกราฟีที่ใช้อนุพันธ์บีตาไซโคลเดกซ์ทรินเป็นเฟสคงที่ (ENANTIOMERIC SEPARATION OF ALCOHOLS BY GAS CHROMATOGRAPHY USING BETA-CYCLODEXTRIN DERIVATIVE AS STATIONARY PHASE) อ.ที่ปรึกษาวิทยานิพนธ์หลัก: ผศ. ดร.อรุณศิริ ชิตางกูร, 87 หน้า.

ศึกษาการแยกอิแนนทิโอเมอร์ของแอลกอฮอล์กลุ่ม 1-ฟีนิลเอทานอล รวม 40 ชนิดด้วยแก๊สโครมาโทกราฟีที่ใช้เฮปตะคิส(2,3-ได-โอ-แอซีทิล-6-โอ-เทอร์ต-บิวทิลไดเมทิลไซลิล)บีตาไซโคลเดกซ์ทริน (หรือ BSiAc) เป็นเฟสคงที่ชนิดไครัล ศึกษาปัจจัยที่มีผลต่อค่ารีเทนชันและค่าการแยกอิแนนทิโอเมอร์ ได้แก่ อุณหภูมิคอลัมน์ โครงสร้างของแอลกอฮอล์ (ชนิดและตำแหน่งของหมู่แทนที่) รวมถึงชนิดของอนุพันธ์แอลกอฮอล์ (ไตรฟลูออโรแอซีทิล (TFA) และไตรเมทิลไซลิล (TMS)) พบว่าหากวิเคราะห์ในรูปแอลกอฮอล์โดยตรงสามารถแยกอิแนนทิโอเมอร์ของสารได้จำนวนมากชนิดกว่าแอลกอฮอล์ในรูปอนุพันธ์ อุณหภูมิมีผลต่อค่าการแยกอิแนนทิโอเมอร์ของแอลกอฮอล์ที่มีหมู่แทนที่ในตำแหน่งเมตามากกว่าพาราและออร์โธ แต่อุณหภูมิมีผลต่อค่าการแยกอิแนนทิโอเมอร์ของอนุพันธ์แอลกอฮอล์ที่มีหมู่แทนที่ในตำแหน่งพารามากกว่า อย่างไรก็ตาม การวิเคราะห์แอลกอฮอล์ในรูปอนุพันธ์สามารถปรับปรุงการแยกของสารบางชนิดได้ และอาจให้พีกที่สมมาตรกว่าการวิเคราะห์ในรูปแอลกอฮอล์ นอกจากนี้ยังแยกแอลกอฮอล์ในรูปอนุพันธ์ TFA หลายชนิดได้สมบูรณ์โดยใช้เวลาน้อยกว่าการวิเคราะห์ในรูปแอลกอฮอล์ จากแอลกอฮอล์ที่นำมาศึกษาทั้งหมดพบว่าสามารถแยกอิแนนทิโอเมอร์ของสารได้ทุกชนิด อาจอยู่ในรูปแอลกอฮอล์หรือในรูปอนุพันธ์ และแยก 18-TFA ได้สมบูรณ์ภายในเวลาน้อยที่สุด

ภาควิชา เคมี ลายมือชื่อนิสิต .....

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MORRAKOT JONGJITWATTANA: ENANTIOMERIC SEPARATION OF ALCOHOLS BY GAS CHROMATOGRAPHY USING BETA-CYCLODEXTRIN DERIVATIVE AS STATIONARY PHASE. ADVISOR: ASST. PROF. AROONSIRI SHITANGKOON, Ph.D., 87 pp.

Enantiomeric separation of forty alcohols based on 1-phenylethanol was studied by gas chromatography using heptakis(2,3-di-*O*-acetyl-6-*O*-*tert*-butyldimethylsilyl)-β-CD (or BSiAc) as a chiral stationary phase. Factors affecting analyte retentions and enantioselectivities were studied: column temperature, alcohol structure (type and position of substitution) as well as type of alcohol derivatization (trifluoroacetyl (TFA) and trimethylsilyl (TMS)). The number of underivatized alcohols that could be separated into their enantiomers was higher than those of derivatized forms. Temperature affected enantioselectivities of *meta*-substituted underivatized alcohols more than *para*- or *ortho*-isomers, while it affected enantioselectivities of *para*-substituted derivatized alcohols more than other isomers. However, derivatization could improve enantioseparation of some alcohols and may provide more symmetrical peak shapes. In addition, many TFA derivatives showed complete enantioseparation in shorter analysis time than their corresponding underivatized alcohols. In this study, enantiomeric separation of all analytes, either underivatized or derivatized form, could be observed. The shortest analysis time for complete enantioseparation was observed for 18-TFA.

Department: Chemistry Student's Signature .....
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CONTENTS

Page

Page

LIST OF TABLE

LIST OF FIGURES

CHAPTER I

Introduction

Due to the development of science and technology, organic compounds, both natural and synthetic, are unavoidably utilized in human daily lives. Markedly, enantiomeric compounds are important products in drugs, food additives, perfumes and pesticides [1-5]. Enantiomers are optical isomers which are mirror images of each other. The pair of enantiomers has similar chemical and physical properties. However, each enantiomer may show different bioactivity, clinical activity or toxicity than its pair. For instance, (*S*,*S*)-enantiomer of ethambutol (Figure 1.1) is used to treat tuberculosis (an infectious disease of tissue by mycobacterium) while its (*R*,*R*)-enantiomer may result in blindness [6]. Another example is salbutamol (Figure 1.1), a drug for asthma (allergy or disorder of respiration system), (*R*)-enantiomer is more active than its (*S*)-enantiomer [7].

(*S*,*S*)-ethambutol (*R*,*R*)-ethambutol

(*S*)-salbutamol (*R*)-salbutamol

Figure 1.1 Structures of ethambutol and salbutamol.

In recent years, the consumption of chiral products is increasing continuously [8]. According to the need for pure enantiomers, techniques such as asymmetric synthesis towards a particular enantiomer and separation of racemates were constantly developed. At each step of production process towards the final products, the monitoring of purity of enantiomer is essential.

Chromatography and electrophoresis are popular analytical techniques used to separate compound mixtures. Gas chromatography (GC) is suitable for volatile and thermally stable organic compounds. The success of GC separation depends on the difference in partition (solubility) of gaseous analytes between the stationary phase and the mobile phase. For enantiomeric separation, either direct or indirect analysis can be used [9]. The indirect method requires a change of enantiomers into diastereomers by a chemical reaction using a chiral reagent. The diastereomeric form of analytes can then be separates on a regular stationary phase. However, the direct method is based on the separation of enantiomers directly on a chiral stationary phase. The direct method is widely applied in routine because it saves time and expense for chiral reagents [1].

Chiral selectors used as GC stationary phase include amino acid or peptide derivatives, chiral transition metal complexes, and cyclodextrin (CD) derivatives [9, 10]. Up to now, CD derivatives are more widely used as chiral stationary phases (CSPs) for GC than the others [11]. Previously, CD derivatives with diverse functional groups substituted at C2, C3 and C6 of glucose unit have been synthesized and applied as CSP for GC with varied enantioselectivity [12-17]. The results rely on several factors such as size of CD, type and position of substituent on CD, column temperature and structure of analytes. Nonetheless, the prediction for successful enantioseparation is still ambiguous.

In this work, 1-phenylethanols are the analytes of interest. 1-Phenylethanol with substituent on the aromatic ring is the core structure of precursor or product in the manufacturing adrenergic drugs such as sotalol, nifenalol, isoprenaline [18-20]. Previous studies related to the enantiomeric separation of 1-phenylethanols were done by GC using 2,3-di-*O*-methyl-6-*O*-tert-butyldimethylsilyl derivative of α-, β- and γ-CDs as chiral stationary phases and found that β-CD derivative provided better enantioseparation for most analytes than other derivatives [21-23]. Furthermore, 1-phenylethanols with *ortho*-substitution mostly showed higher enantioselectivity than *meta*- or *para*-isomers.

For this study, enantiomers of forty 1-phenylethanols and other alcohols of related structures were further examined as a function of temperature by GC using heptakis(2,3-di-*O*-acetyl-6-*O*-*tert*-butyldimethylsilyl)-β-CD (BSiAc) as a chiral stationary phase. To study the effect of derivatization on enantioseparation, chiral alcohols were analyzed as trifluoroacetyl (TFA) and trimethylsilyl (TMS) derivatives and compared to those obtained from direct analyses without derivatization. Hopefully, the information from this study would benefit the selection of derivatization and CD derivative for enantiomeric separation of new alcohols.

CHAPTER II

Theory

2.1 Enantiomeric separation by gas chromatography

Generally, there are two methods for the differentiation of enantiomers in chromatography [9-11]. The first method is indirect: enantiomers were changed to diastereomers by a chemical reaction using a chiral reagent. Diastereomers, having different physical or chemical properties, were then separated by chromatography using common stationary phases and mobile phases. The limitations of this indirect method are the available functional groups of analytes for the reaction and the availability of pure chiral reagents. In addition, the reaction should be complete, fast and reproducible. The other method is direct separation involving the use of chiral selectors as mobile phase additives or stationary phases. Each enantiomer forms a temporary diastereomeric complex with the chiral selector. The enantioseparation using the direct method are preferred and new chiral selectors have been continuously reported [12-17].

Analysis of chiral compounds to determine their purities was realized in diverse fields. Normally, gas chromatography (GC) is used for the analyses of volatile and thermally stable organic compounds. GC offers high sensitivity, high efficiency and good reproducibility. In high efficient capillary GC, liquid phases are coated on the wall inside the capillary column. The commonly used chiral stationary phases are classified by intermolecular interaction between analytes and stationary phases such as hydrogen bonding with chiral amino acid derivatives, complexation with chiral metal coordination and inclusion complex with cyclodextrin derivatives [9, 10]. Among them, cyclodextrin derivatives were the most commonly used chiral stationary phases for GC [11, 17].

2.2 Cyclodextrin [24, 25]

Cyclodextrins (CDs) are supramolecule made from the digestion of starch by emzyme “cyclodextrin glucanosyltransferase” from bacillus. The CD subunits are D-glucoses connected by α-(1,4)-glucosidic bonds to form a cyclic molecule (Figure 2.1). The secondary hydroxyl groups at C2 and C3 positions of CD molecule are at the wider rim, whereas the primary hydroxyl groups at C6 position are at the narrower rim. The CD has a shape of truncated cone with the relatively hydrophobic property inside the cavity due to the hydrogen atoms at C3 and C5 positions and the lone pair electron from oxygen atoms of α-(1,4)-glucosidic bond at C1 and C4 positions. This characteristic provides the inclusion of apolar compound (guest) inside the cavity of CD (host). Thus, CD can increase the solubility of apolar compound in polar solvent through the inclusion complex. In addition, the CD-analyte inclusion complex can change the properties of substances for example stability, toxicity, spectral properties, etc. Therefore, CDs offer widespread applications in diverse fields.

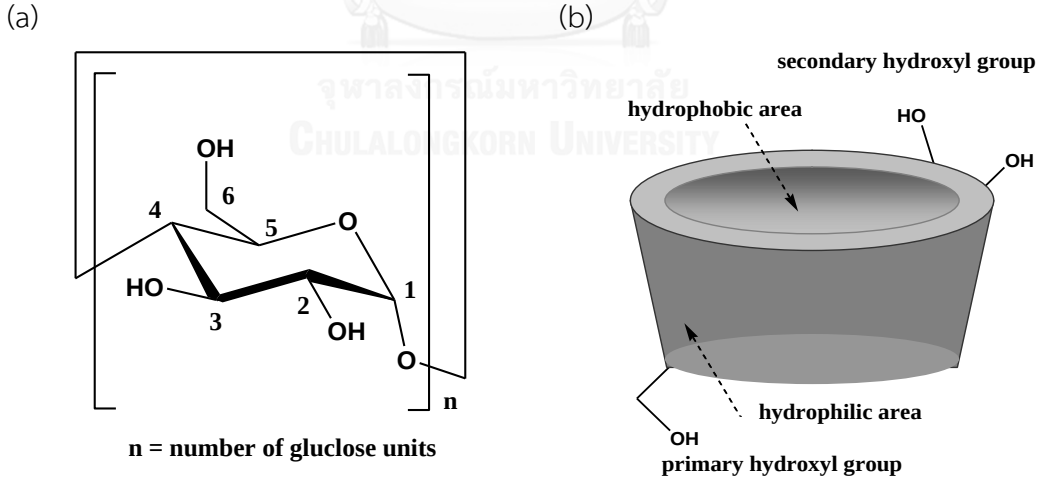


Figure 2.1 (a) Structure of CD subunit and (b) shape of CD.

The size of CD depends on the number of glucose units in its molecule. The most frequently used CDs are composed of six, seven and eight D-glucoses and are called α-, β-, and γ-CDs, respectively. Their properties are compared in Table 2.1.

Table 2.1 Properties of α-, β-, and γ-CDs [24, 25].

properties	cyclodextrin (CD)		
	α	β	γ
number of glucose units	6	7	8
molecular weight	972.86	1135.01	1291.15
external diameter (Å)	14.6 ± 0.4	15.4 ± 0.4	17.5 ± 0.4
internal diameter (Å)	4.7 – 5.3	6.0 – 6.5	7.5 – 8.3
height of torus (Å)	7.9 ± 0.1	7.9 ± 0.1	7.9 ± 0.1
volume of cavity ($Å^3$)	174	262	427
solubility in water at room temp (g/100 mL)	14.50	1.85	23.20
decomposition and melting point (K)	551	572	540

From distinct characteristic of each CD, an analyte can selectively form an inclusion complex with each CD. In the same way, each enantiomer of a chiral compound can form a temporary diastereomeric complex with a CD differently. Thus, CDs could be utilized as chiral stationary phase in chromatography. Since native CDs are polar and solid at room temperature and decompose at high temperature, they cannot be coated onto a capillary wall of GC column or an inefficient column will be obtained. As a result, CD derivatives with proper polarity and improved thermal stability were synthesized and used in enantiomeric separation of chiral compounds by GC.

2.3 Cyclodextrin derivatives as chiral stationary phases in GC

CD derivatives were synthesized from native CD by chemical reaction such as alkylation, acylation, silylation, etc [24, 26, 27]. The reactions mostly occur at the hydroxyl groups on C2, C3 and/or C6 positions of CD. The obtained CD derivatives may possess different functional groups, sizes and shapes from their native CDs, resulting in different interactions between analytes and CD derivatives which affect enantioselectivity [10, 24]. Furthermore, substitution at hydroxyl groups with

nonpolar groups could improve the solubility in nonpolar diluent, improve the ability to coat on a column wall and extend the operating temperature range. Some previous literatures showing the influence of substitution at different positions of CD as well as the size of CD on enantioseparation by GC will be mentioned.

In 1996, Shitangkoon and Vigh [27] studied the enantioseparation of 35 analytes of different functional groups (hydrocarbons, lactones, epoxides, alcohols, amines, hydroxyl acid esters, amides, etc) by GC. The (2,3-di-*O*-methyl)-β-CDs with different types of substitution at C6 position, including methyl, pentyl, deoxy-fluoro, *tert*-butyldimethylsilyl, propyldimethylsilyl and triisopropylsilyl, were mixed in polysiloxane and used as chiral stationary phases. It was found that (2,3-di-*O*-methyl-6-*O*-*tert*-butyldimethylsilyl)-β-CD could separate the largest numbers of chiral analytes. In addition, it also provided a column with high efficiency and broad operating temperature range.

In 2000 [13], two new CD derivatives with different alkyl chain length at C2 and C6 position on CDs were prepared: 2,6-di-*O*-nonyl-3-*O*-trifluoroacetyl-β-CD (DNTBCD) and 2,6-di-*O*-dodecyl-3-*O*-trifluoroacetyl-β-CD (DDTBCD). They were then used as chiral stationary phases for the enantioseparation of amines, amino acids, carboxylic acids, alcohols, diols, epoxides, halohydrocarbons and ketones. It was found that DNTBCD could separate almost all chiral analytes in their studies with higher enantioselectivity than DDTBCD. These results indicated the effect of alkyl chain length on enantioselectivity.

In 2005, Takahisa and coworkers [15, 16] synthesized 2,3-di-*O*-methoxymethyl-6-*O*-*tert*-butyldimethylsilyl-β- and γ-CDs and employed as chiral stationary phases for the enantioseparation of more than 100 organic compounds from various classes. It was found that the γ-CD derivative was suitable for a very broad functional groups, except for tertiary alcohols and their esters, bicyclic compounds and less volatile esters. It showed high enantioselectivities for hydroxyketone, cyclic enolones and acyclic methyl branched ketones. The number of compounds enantioseparated by β-CD derivative was limited and their enantioselectivities were generally lower than those of γ-CD derivative.

In addition to the size and the structure of CD derivatives, the structure of chiral analytes also influences enantioselectivity. Alcohols are the analytes of interest as they are precursors or products with extensive applications in various fields. Examples on the investigation of enantiomeric separation of alcohols are discussed.

In 1992, Smith and Simpson [12] examined the effect of alcohol structures on the separation of enantiomers using 2,6-di-*O*-pentyl-3-*O*-trifluoroacetyl-γ-CD as a stationary phase. More than 30 alcohols were directly analyzed without derivatization using isothermal condition between 35-70 °C. It was found that enantioselectivity depended on the alkyl chain length attached to the stereogenic center, the relative position of methyl and hydroxyl substituents, and the effects of multiple bonds in the molecule of alcohol. Alcohols with a chain length of 4 carbon atoms gave the highest enantioselectivity. The 2-hydroxy alkanes showed higher enantioselectivity values than the 3-hydroxy alkanes with the same number of carbon atoms in the longer chain. Alcohols with multiple bonds (alkenes or alkynes) showed improved enantioselectivities. It was probably caused by the increased rigidity of the molecule compared with the fully unsaturated analog.

In 2002, Iamsam-ang [21] studied the separation of enantiomers of 1-phenylethanols with different types and positions of substituents on the aromatic ring using 2,3-di-*O*-methyl-6-*O*-*tert*-butyldimethylsilyl-β-CD (BSiMe) and 2,3,6-tri-*O*-methyl-β-CD (BMe) as stationary phases. All alcohols were directly analyzed without derivatization using isothermal conditions. The results showed that the position of substituent had more influences on the enantioselectivity than the type of substituent. All enantiomers of *ortho*-substituted analytes were much better separated than those of *meta*- and *para*-substituted analytes. The results from both CD derivatives were in agreement. However, BSiMe provided better peak shapes and better enantioselectivities than BMe. This was probably due to the bulky *tert*-butyldimethylsilyl group substituted at C6 position of BSiMe could change the conformation of the CD cavity, resulting in better enantioselectivities.

Later, the separation of enantiomers of 1-phenylethanols were investigated using 2,3-di-*O*-methyl-6-*O*-*tert*-butyldimethylsilyl-α- and γ-CDs [22, 23]. In most cases,

enantiomers of *ortho*-substituted analytes were much better separated than those of *meta*- and *para*-substituted analytes. Comparing the effect of CD size, the enantioselectivities of CD derivatives toward 1-phenylethanols were in the order: $\beta > \alpha > \gamma$.

2.4 Analyte derivatization on enantioselectivity

Analyses of polar compounds, capable of hydrogen bonding with the stationary phase such as –COOH, –OH, –NH, or –SH group, may result in asymmetrical peaks, poor separation or low detector responses [28]. Derivatization is thus required to convert an analyte using a chemical reaction into a new compound with suitable properties, such as volatility and thermal stability. In addition, it may improve detector response and improve resolution between peaks.

Alkylation, acylation and silylation are common derivatization reactions for alcohols prior to GC analyses. Alkylation is a substitution of the active hydrogen atom with an aliphatic or aromatic alkyl group. Acylation and silylation are substitutions with acyl group and silyl group, respectively. The reactions generally increase the volatility of non-volatile or less volatile compounds and reduce adsorption of polar compounds. Furthermore, in many cases derivatization could change the enantioselectivity of analytes. The effect of derivatization on enantioselectivity of alcohols will be discussed.

In 1993, Smith and Simpson [12] studied the separation of enantiomers of 32 chiral alcohols by GC using 2,6-di-*O*-pentyl-3-*O*-trifluoroacetyl- γ-CD as a stationary phase. Saturated and unsaturated alcohols were analyzed using isothermal conditions as underivatized alcohols, acyl derivatives and fluoroacyl derivatives. Enantioselectivities obtained from underivatized and derivatized alcohols were significantly different. For all analytes, enantiomers of acyl derivatives (acetyl and trimethylacetyl) were not separated. For most analytes, at least one of the fluoroacyl derivatives (trifluoroacetyl, pentafluoropropionyl and heptafluorobutyryl) could be separated into their enantiomers. Reversal of elution order was also observed for

some fluoroacyl derivatives. For most cases, fluoroacyl derivatives gave shorter retention times, better peak shapes and improved enantioseparation compared to alcohols.

In 1994, Krupčík et al. [29] studied the separation of enantiomers of short chain secondary alcohols (2-butanol, 2-pentanol, 2-hexanol and 3-hexanol) by GC using a mixture of OV-1701 and 2,3-di-*O*-acetyl-6-*O*-*tert*-butyldimethylsilyl-β-CD as a stationary phase. All alcohols were analyzed using isothermal conditions as underivatized alcohols and methyl, pentyl, acetyl and trifluoroacetyl derivatives. Enantiomers of all alcohols could be separated at 40 ℃ at varying degree of separation: 3-hexanol > 2-butanol and 2-hexanol > 2-pentanol. All derivatives showed lower retention than their alcohols. Enantiomers of alkyl derivatives (methyl and pentyl) were not separated or poorly separated, while those of acetyl or trifluoroacetyl derivatives were better separated.

In 1998, Szöllösi et al. [30] studied the separation of enantiomers of several 2- and 3-alkanols, 1-phenylalkanols and diols by GC using a Cyclodex-B column. Alcohols were analyzed both as underivatized alcohols and trimethylsilyl derivatives. For most analytes, silylation improved the separation of enantiomers, decreased peak tailing and decreased the analysis times.

In 2003, Ghanam et al. [14], synthesized a new permethyl-mono-undec-10-enyl-β-CD (C11-Chirasil-β-Dex) and used as a chiral stationary phase for the separation of enantiomers by GC. Analytes were 16 underivatized secondary alcohols and their corresponding acetyl derivatives. For most cases, enantiomers of acetyl derivatives were better separated with more symmetrical peaks and shorter analysis times than underivatized alcohols. For some analytes, a reversal in elution order was observed.

In 2004, Juvancz et al. [31] used Chirasil-Dex (permethylated-β-CD bonded to the polysiloxane) as a chiral GC stationary phase for the separation of enantiomers of arylalkyl amines and alcohols. Amines were analyzed as *N*-Ac (*N*-acetyl) and *N*-TFA (*N*-trifluoroacetyl) derivatives, while alcohols were analyzed as underivatized form

and as *O*-Ac (*O*-acetyl) and *O*-TFA (*O*-trifluoroacetyl) derivatives. The results showed that acetyl derivatives provided higher enantioselectivity than their trifluoroacetyl derivatives for both alcohols and amines. Enantioselectivity for most alcohols were in the order of *O*-Ac > alcohol > *O*-TFA. The opposite elution order was observed for the *N*-Ac and *N*-TFA amines and for the *O*-Ac and underivatized alcohols.

In 2012, Oromí-Farrús et al. [32] used Chirasil-Dex (permethylated-β-CD bonded to the polysiloxane) as a chiral GC stationary phase for the separation of enantiomers of acyclic and cyclic alcohols and diols in both underivatized form and acetyl derivatives. For most cases, enantiomers of acetyl derivatives were separated with higher selectivity, more symmetrical peaks and shorter analysis times than underivatized alcohols.

2.5 Thermodynamic studies for enantioseparation by GC [10, 33]

Although certain mechanisms related to enantiomeric differentiation by CDs are not clear, some features could be obtained from thermodynamic investigation through GC experiments. Generally, it is realized that the direct chiral recognition occurs via the formation of a temporary reversible diastereomeric complex between enantiomers and a chiral selector. Temperature is an important factor affecting retention factor, enantioselectivity and resolution of analytes. The equilibrium associated between an enantiomer and a chiral selector can be explained by thermodynamic values as follow:

$$-\Delta G = -\Delta H + T \cdot \Delta S \quad (1)$$

$$-\Delta G = RT \cdot \ln K \quad (2)$$

$$\ln K = -\frac{\Delta H}{RT} + \frac{\Delta S}{R} \quad (3)$$

where

ΔG = Gibbs free energy (kcal/mol)

ΔH = enthalpy change (kcal/mol) resulting from the interaction between an analyte (enantiomer) and a stationary phase. It

indicates the strength of interaction between an analyte and a stationary phase.

ΔS = entropy change (cal/mol·K) resulting from the interaction between an analyte (enantiomer) and a stationary phase. It indicates the degree of freedom between an analyte and a stationary phase.

T = absolute temperature (K)

R = gas constant (1.987 cal/mol·K)

K = distribution coefficient of an analyte (enantiomer) between the gas and the liquid phases

As the distribution coefficient is related to the retention factor, thermodynamic parameters can be determined from retention factors and retention times obtained from GC experiments, according to equation (4).

$$\ln k' = -\frac{\Delta H}{RT} + \frac{\Delta S}{R} - \ln \beta \qquad (4)$$

where

k′ = retention factor of each analyte (enantiomer) calculated from the retention time according to

$$k' = \left(\frac{t_R - t_M}{t_M} \right)$$

k′ is related to the distribution coefficient according to

$$K = k' \cdot \beta$$

t_R = retention time of an analyte (enantiomer)

t_M = time for the mobile phase or unretained compound to pass the column

β = phase ratio (a ratio between volume of the mobile phase and volume of the stationary phase)

Plots of ln k′ and 1/T for each enantiomer are linear. When a chiral compound is separated into it enantiomers, the ΔH and ΔS values for the less and

the more retained enantiomers are obtained. Thus, the corresponding $\Delta\Delta H$ and $\Delta\Delta S$ values for a pair of enantiomers could be calculated.

CHAPTER III

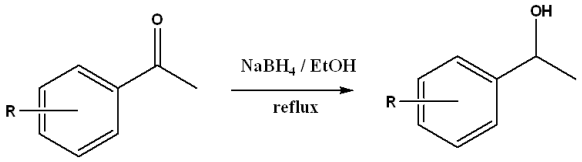
Experiment

3.1 Chiral alcohols

Chiral alcohols used in this work were previously prepared by Iamsam-ang [21] and Konghuirob [22]. Some alcohols were commercially available. Additional thirteen alcohols were newly synthesized from their corresponding ketones. Chemicals, reagents, and solvents were mostly purchased from Aldrich, Fluka, Merck and J.T. baker and were used without further purification. Ketones used as starting materials for this work are as follow:

- 1-acetonaphthone, [941-98-0], ≥96% (Fluka)
- 4′-bromopropiophenone, [10342-83-3], 99% (Aldrich)
- butyrophenone, [495-40-9], ≥99% (Aldrich)
- 4′-chloropropiophenone, [6285-05-8], 98% (Aldrich)
- 4′-fluoropropiophenone, [456-03-1], 98% (Aldrich)
- 2′-methoxyacetphenone, [579-74-8], 99% (Fluka)
- 4′-methoxyacetophenone, [100-06-1], 99% (Fluka)
- 4′-methoxypropiophenone, [204-512-7], 99% (Aldrich)
- 4′-methylacetophenone, [122-00-9], 95% (Fluka)
- 4′-methylpropiophenone, [5337-93-9], 90% (Aldrich)
- 2′-(trifluoromethyl)acetophenone, [17408-14-9], 99% (Aldrich)
- 3′-(trifluoromethyl)acetophenone, [349-76-8], 99% (Aldrich)
- 4′-(trifluoromethyl)propiophenone, [711-33-1], 99% (Aldrich)

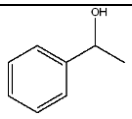
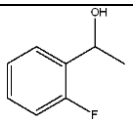
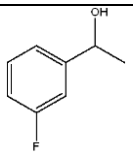
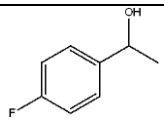
3.1.1 Syntheses of alcohols

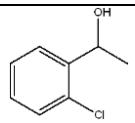
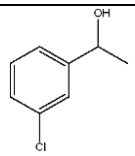
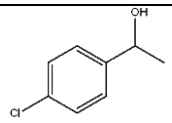
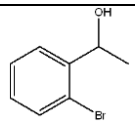
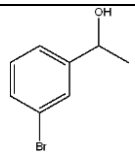
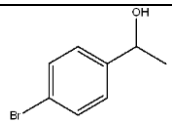
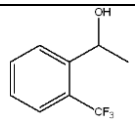
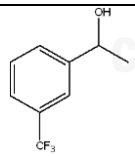
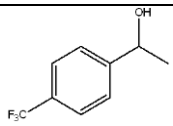
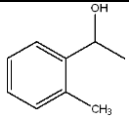
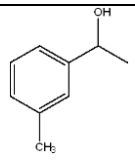


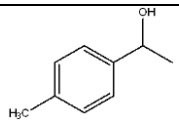
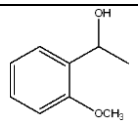
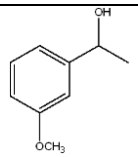
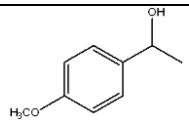
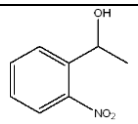
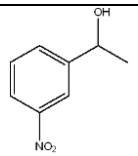
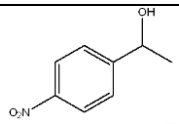
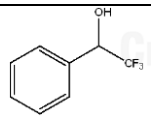
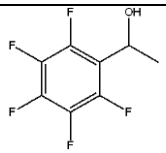
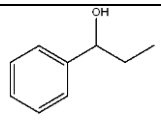
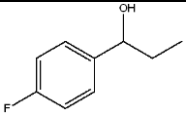
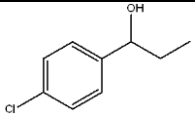
The ketone (2 mmol) was dissolved in 10 mL ethanol and sodium borohydride ($NaBH_4$, 4 mmol) was added into the solution. The reaction mixture was refluxed for 3 hours. The progress of reaction was monitored by thin layer chromatography (TLC) using TLC aluminum sheet coated with silica gel F_{254}, and then visualized under UV light. After that, the solution was cooled down and the solvent was evaporated under vacuum to obtain white precipitate. The solid was redissolved in 2 M hydrochloric acid. The solution was extracted with dichloromethane (2 x 25 mL). Organic layers were combined, dried with anhydrous sodium sulfate, and evaporated to dryness to obtain the corresponding alcohol. Some alcohols was purified by column chromatography using hexane : ethyl acetate (3:1) as an eluent. The structure of the product was confirmed by ^1H NMR spectrometer (Bruker AV-400 or Varian Mercury Plus 400 spectrometer at 400 MHz) using deuterated chloroform ($CDCl_3$) as a solvent.

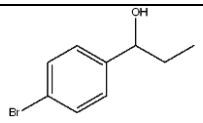
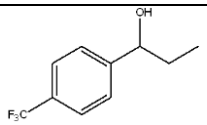
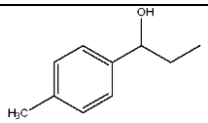
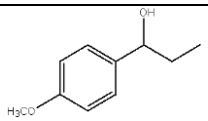
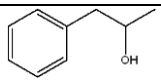
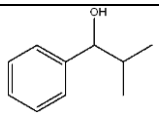
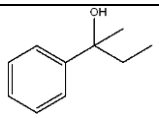
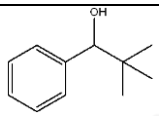
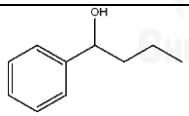
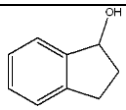
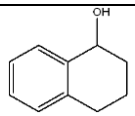
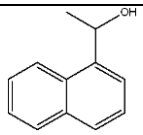
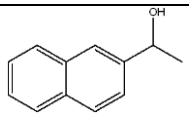
The structures of all alcohols used in this study are shown in Table 3.1.

Table 3.1 Structure, abbreviation, and name of chiral alcohols

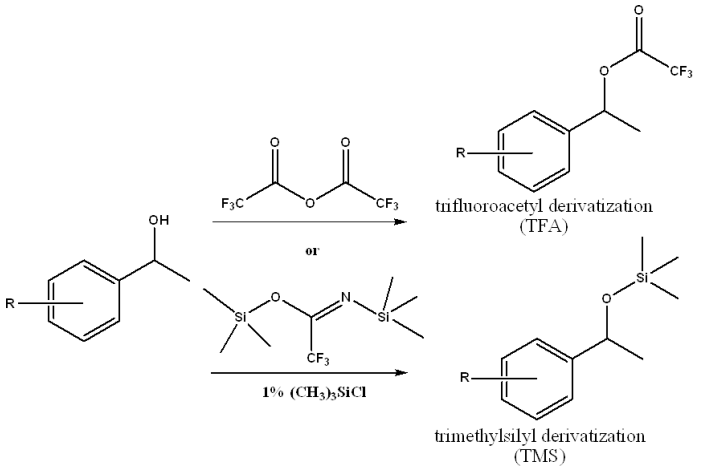
no.	structure	abbreviation	name
1		**1**	1-phenylethanol
2		**2o**	1-(2-fluorophenyl)ethanol
3		**2m**	1-(3-fluorophenyl)ethanol
4		**2p**	1-(4-fluorophenyl)ethanol

no.	structure	abbreviation	name
5		**3o**	1-(2-chlorophenyl)ethanol
6		**3m**	1-(3-chlorophenyl)ethanol
7		**3p**	1-(4-chlorophenyl)ethanol
8		**4o**	1-(2-bromophenyl)ethanol
9		**4m**	1-(3-bromophenyl)ethanol
10		**4p**	1-(4-bromophenyl)ethanol
11		**5o**	1-(2-(trifluoromethyl)phenyl)ethanol
12		**5m**	1-(3-(trifluoromethyl)phenyl)ethanol
13		**5p**	1-(4-(trifluoromethyl)phenyl)ethanol
14		**6o**	1-(2-methylphenyl)ethanol
15		**6m**	1-(3-methylphenyl)ethanol

no.	structure	abbreviation	name
16		**6p**	1-(4-methylphenyl)ethanol
17		**7o**	1-(2-methoxyphenyl)ethanol
18		**7m**	1-(3-methoxyphenyl)ethanol
19		**7p**	1-(4-methoxyphenyl)ethanol
20		**8o**	1-(2-nitrophenyl)ethanol
21		**8m**	1-(3-nitrophenyl)ethanol
22		**8p**	1-(4-nitrophenyl)ethanol
23		**9**	2,2,2-trifluoro-1-phenylethanol
24		**10**	1-(pentafluorophenyl)ethanol
25		**11**	1-phenyl-1-propanol
26		**12p**	1-(4-fluorophenyl)propanol
27		**13p**	1-(4-chlorophenyl)propanol

no.	structure	abbreviation	name
28		**14p**	1-(4-bromophenyl)propanol
29		**15p**	1-(4-(trifluoromethyl)phenyl)propanol
30		**16p**	1-(4-methylphenyl)propanol
31		**17p**	1-(4-methoxyphenyl)propanol
32		**18**	1-phenyl-2-propanol
33		**19**	2-methyl-1-phenyl-1-propanol
34		**20**	2-phenyl-2-butanol
35		**21**	2,2-dimethyl-1-phenyl-1-propanol
36		**22**	1-phenyl-1-butanol
37		**23**	1-indanol
38		**24**	1,2,3,4-tetrahydro-1-naphthol
39		**25**	1-(1-naphthyl)ethanol
40		**26**	1-(2-naphthyl)ethanol

3.1.2 Derivatization of alcohols



Each alcohol was separately derivatized into trimethylsilyl (TMS) and trifluoroacetyl (TFA) derivatives. The identity of the products was confirmed by ^{1}H NMR spectrometry using deuterated chloroform ($CDCl_3$) as a solvent.

TMS derivatization: An alcohol (20 μL) was dissolved in tetrahydrofuran (THF, 20 μL) in a vial (2 mL), then a solution of *N,O*-bis(trimethylsilyl) trifluoroacetamide + 1% trimethylchlorosilane (BSTFA + 1% TMCS, 100 μL) was added. The solution was left for an hour at room temperature and then heated for 2 hours at 50 °C. Excess reagents were purged with nitrogen gas to dryness.

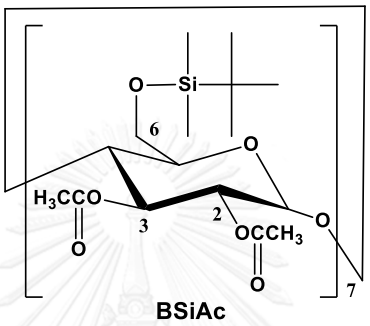
TFA derivatization: An alcohol (20 μL) was dissolved in tetrahydrofuran (THF, 20 μL) in a vial (2 mL), then trifluoroacetic anhydride (TFAA, 100 μL) was added. The solution was left for an hour at room temperature and then heated for 2 hours at 50 °C. Excess reagents were purged with nitrogen gas to dryness.

3.2 Gas Chromatographic separation

3.2.1 Coating a capillary column

Heptakis(2,3-di-*O*-acetyl-6-*O*-*tert*-butyldimethylsilyl)-β-CD (or BSiAc) was received from Professor Gyula Vigh (Texas A & M University, USA) and used as a chiral selector. A mixture of 33.5 % BSiAc and polysiloxane OV-1701 (7 % phenyl, 7 % cyanopropyl, 86 % dimethyl polysiloxane, Supelco) was dissolved in 10 mL

dichloromethane. A deactivated fused silica capillary column (16 m long, 0.25 mm I.D., Agilent) was filled with the stationary phase solution. A 0.25 μm film thickness of stationary phase on column wall was achieved after solvent evaporation. The coated capillary column was conditioned at 220 °C until a flat baseline was achieved. The performance of coated column was evaluated by Grob test and column efficiency over a temperature range of 50-220 °C was also determined using *n*-alkanes before usage.



BSiAc

3.2.2 Instrumentation and GC conditions

All analyses were performed on a gas chromatograph (Agilent 6890 series) with the following conditions:

carrier gas:	hydrogen at an average linear velocity of 50 cm/s
injector:	split, 250 °C, split ratio of 100:1
detector:	flame ionization detector, 250 °C
column:	15 m long, 0.25 mm I.D., 0.25 μm film thickness
stationary phase:	33.5% BSiAc in OV-1701

All analytes were diluted in dichloromethane to obtain final concentration of 0.01 mg/mL. Each analyte solution (0.1-0.2 μL) was separately injected using a microsyringe (SGE). Analysis was performed isothermally at different 5-7 temperatures of 10 °C intervals at least in duplicate. Retention times and peak widths obtained from chromatograms for each run were used to calculated retention factor (k′), selectivity (α), and resolution (Rs). These values leaded to thermodynamic

parameters via van't Hoff plot which described temperature dependent on retention and selectivity of each analyte.

CHAPTER IV

Results and discussions

4.1 Syntheses of alcohols and derivatizations

Thirteen alcohols were synthesized from reduction of ketone by $NaBH_4$ and were obtained in 60-90 % yield. Small amount of each alcohol was separately reacted to form trimethylsilyl (TMS) and trifluoroacetyl (TFA) derivatives. Characterization of both types of derivatives was done by ^{1}H NMR spectroscopy. The presence of TMS derivative was confirmed by the disappearance of OH peak and the presence of a singlet peak (9H, s, Si(C<u>H</u>$_3$)$_3$) at δ 0.00 ppm (Figure 4.1). The presence of TFA derivative was confirmed by the disappearance of OH peak and the downfield shift of proton at the stereogenic center (1H, m, C<u>H</u>O) at δ 6.01 – 5.83 ppm due to TFA group (Figure 4.2).

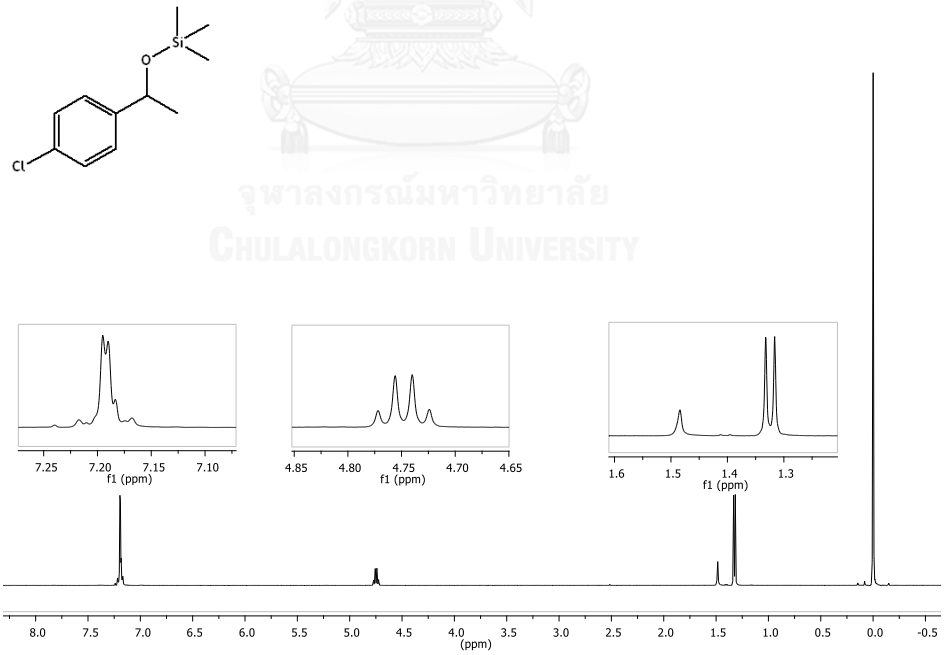


Figure 4.1 ^{1}H NMR spectrum of **3p-TMS**.

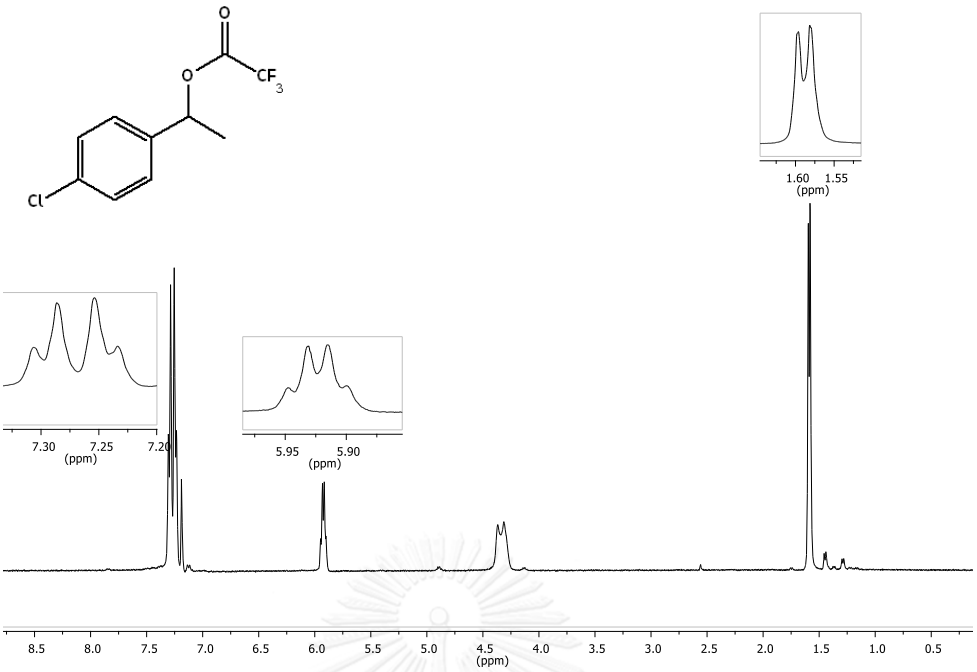


Figure 4.2 ^{1}H NMR spectrum of **3p-TFA**.

Derivatization of some alcohols in this study was not successful. 2-Phenyl-2-butanol (**20**) could not be derivatized into either TMS or TFA derivatives. This might be from the steric hindrance around hydroxyl group of **20**. For other five alcohols (**7o**, **7p**, **17p**, **23** and **24**), pure TFA products could not be obtained; therefore, their enantioseparations were not studied.

4.2 Properties of a coated capillary column

A capillary column of 16 m long, 0.25 mm I.D. coated with a mixture of BSiAc and polysiloxane OV-1701 as a stationary phase was characterized. Its efficiency was tested isothermally at various temperature ranging from 50-220 °C using *n*-alkanes and was found to be good, having 3,000-4,500 plates/m at k′ ≥ 5. The column was then subjected to the Grob test under a temperature program and the obtained chromatogram is shown in Figure 4.3.

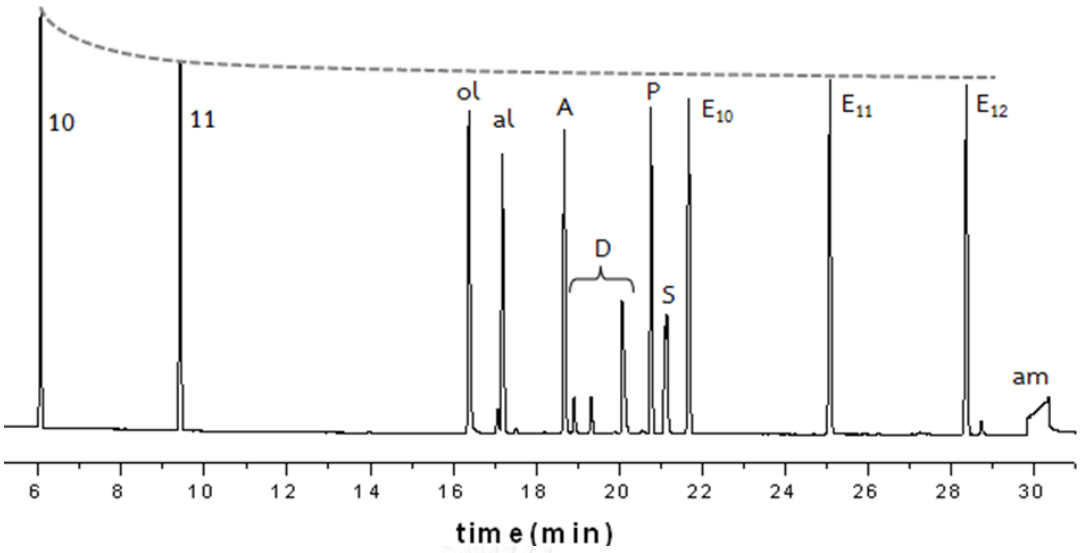


Figure 4.3 Grob test of the BSiAc column.

The elution order of the Grob mixture was *n*-decane (10), *n*-undecane (11), 1-octanol (ol), nonanal (al), 2,6-dimethylaniline (A), 2,3-butanediol (D), 2,6-dimethylphenol (P), 2-ethylhexanoic acid (S), methyl decanoate (E_{10}), methyl undecanoate (E_{11}), methyl dodecanoate (E_{12}), and dicyclohexylamine (am), respectively. Column efficiency under temperature program condition was determined from the average TZ values of E_{10}-E_{11} and E_{11}-E_{12} peak pairs and was found to be 27.9. Aldehyde and alcohols could be analyzed using this column because al, ol and D peak were quite symmetrical and no serious tailing was observed. The acid-base property of this column was evaluated from weak acid (P) – weak base (A) peak pair and strong acid (S) – strong base (am) peak pair. P and A peaks were symmetrical with similar peak height, indicating no strong acid-base property. However, the column was slightly acidic because am peak was severely tailing, indicating strong adsorption with the stationary phase. In addition, BSiAc column showed chiral property towards S and D as they could be separated into their enantiomers and isomers (incomplete separation for S). In all, this column shows good efficiency and is suitable for analysis of different compound types including alcohols (the analytes of interest for this study), except for direct analysis of strong amines.

4.3 Enantiomer separation of alcohols and their derivatives

Enantiomer separation was studied on BSiAc for 40 alcohols of different structures, based on 1-phenylethanol, in the form of underivatized alcohols and their corresponding TMS and TFA derivatives. The effects of temperature, alcohol structure and type of derivatization were studied. The comparison was expressed in terms of thermodynamic parameters over a temperature range because alcohols and their derivatives have different physical properties and direct comparison of chromatographic parameters among analytes at the same temperature was not possible.

Thermodynamic parameters related to chromatographic separation by GC could be obtained through van't Hoff equation [33].

$$\ln k' = -\frac{\Delta H}{RT} + \frac{\Delta S}{R} - \ln \beta$$

Relationships of ln k′ versus 1/T for each enantiomer for all analytes were linear with correlation coefficient (R^2) greater than 0.9968. Enthalpy change (ΔH) and entropy change (ΔS) associated with the interaction between each enantiomer and stationary phase could be determined from its corresponding slope and y-intercept, respectively. More negative ΔH value indicated a strong increase in intermolecular forces between analyte and stationary phase when the temperature decreased. More negative ΔS value indicated fewer freedom of motion of analyte molecule on stationary phase. When the separation of enantiomers were observed, ΔH and ΔS values for two enantiomers were different and the difference in enthalpy change (ΔΔH) and difference in entropy change (ΔΔS) for the enantioseparation could be obtained. Large difference in thermodynamic terms indicated that the separation of analyte was high temperature dependent and the separation could be easily improved with a decrease in temperature.

Figures 4.4-4.5 show the comparison of ΔH and ΔS values of the more retained enantiomers of all analytes in three forms (underivatized alcohol, TFA derivative and TMS derivative). From Figure 4.4, it can be seen that $-\Delta H_2$ values of all analytes were in the order of alcohol > TFA > TMS. The decrease of interaction

strength as a function of temperature of alcohol to TMS derivatives was probably due to the decrease in analyte polarity as well as the increase in analyte volatility. The variation in $-\Delta H_2$ values was more noticeable for alcohols and TFA derivatives than the least polar TMS derivatives. However, the trends for $-\Delta H_2$ values of three types of analytes were quite similar. The $-\Delta H_2$ values of analytes with mono-substitution on the aromatic ring showed a slight increase from *ortho*- < *meta*- < *para*-position, regarding the type of substitution. Analytes with nitro-substitution showed the highest $-\Delta H_2$ values compared to other types of substitution. Analytes with naphthyl group (**25**, **26**) showed higher $-\Delta H_2$ values than that of phenyl group without substitution (**1**). Other analytes with different alkyl substitution at the stereogenic center (**18**-**22**) or with different core structure (**23**-**24**) showed small variation in their $-\Delta H_2$ values but no clear conclusion could be made. The trends for $-\Delta S_2$ values of three types of analytes were also similar (Figure 4.5).

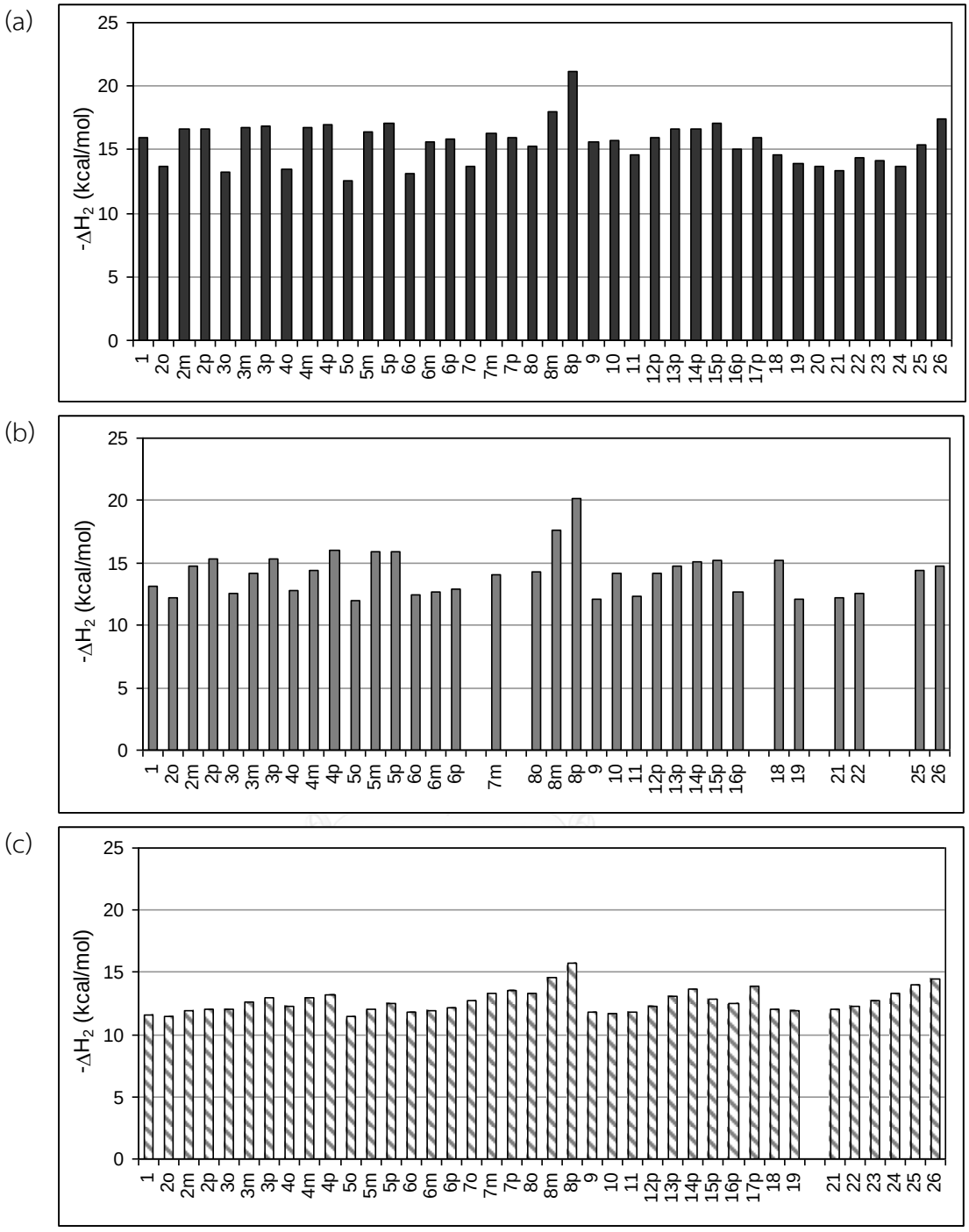


Figure 4.4 Enthalpy change (-ΔH, kcal/mol) of the more retained enantiomers of (a) underivatized, (b) TFA and (c) TMS alcohols on BSiAc column.

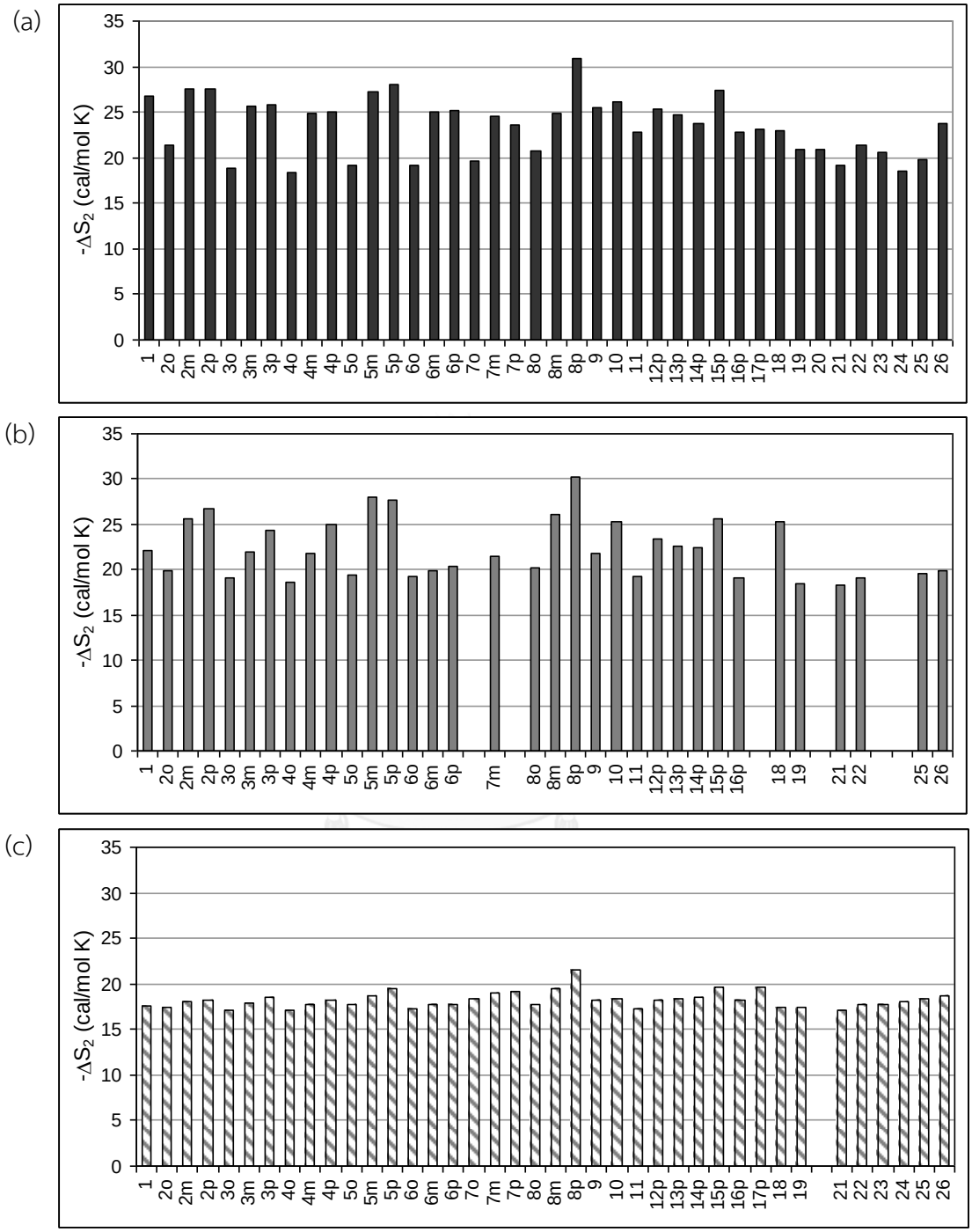


Figure 4.5 Entropy change (-ΔS, cal/mol·K) of the more retained enantiomers of (a) underivatized, (b) TFA and (c) TMS alcohols on BSiAc column.

Figures 4.6-4.7 show -ΔΔH and -ΔΔS values of all three types of analytes separated on BSiAc column. Both -ΔΔH and -ΔΔS values for each type of alcohol analytes showed similar trend, but were different from their corresponding $-\Delta H_2$ and $-\Delta S_2$ values. These results suggested that strength of interaction did not necessarily relate to its enantioselectivity. Because -ΔΔH and -ΔΔS values showed similar trend, the results will be discussed based on -ΔΔH values only.

From Figure 4.6, it was clear that the number of underivatized alcohols separated into their enantiomers was higher than those of derivatized forms, either TFA or TMS form. From 40 underivatized alcohols, 37 analytes could be separated into their enantiomers. Only three analytes could not be enantioseparated: **6o**, **8m** and **19**. When alcohols were derivatized before analyses, 29 of 34 TFA derivatives and only 21 of 39 TMS derivatives could be separated into their enantiomers. The -ΔΔH values of all separable enantiomers were quite varied and the discussion will be made according to analyte structure.

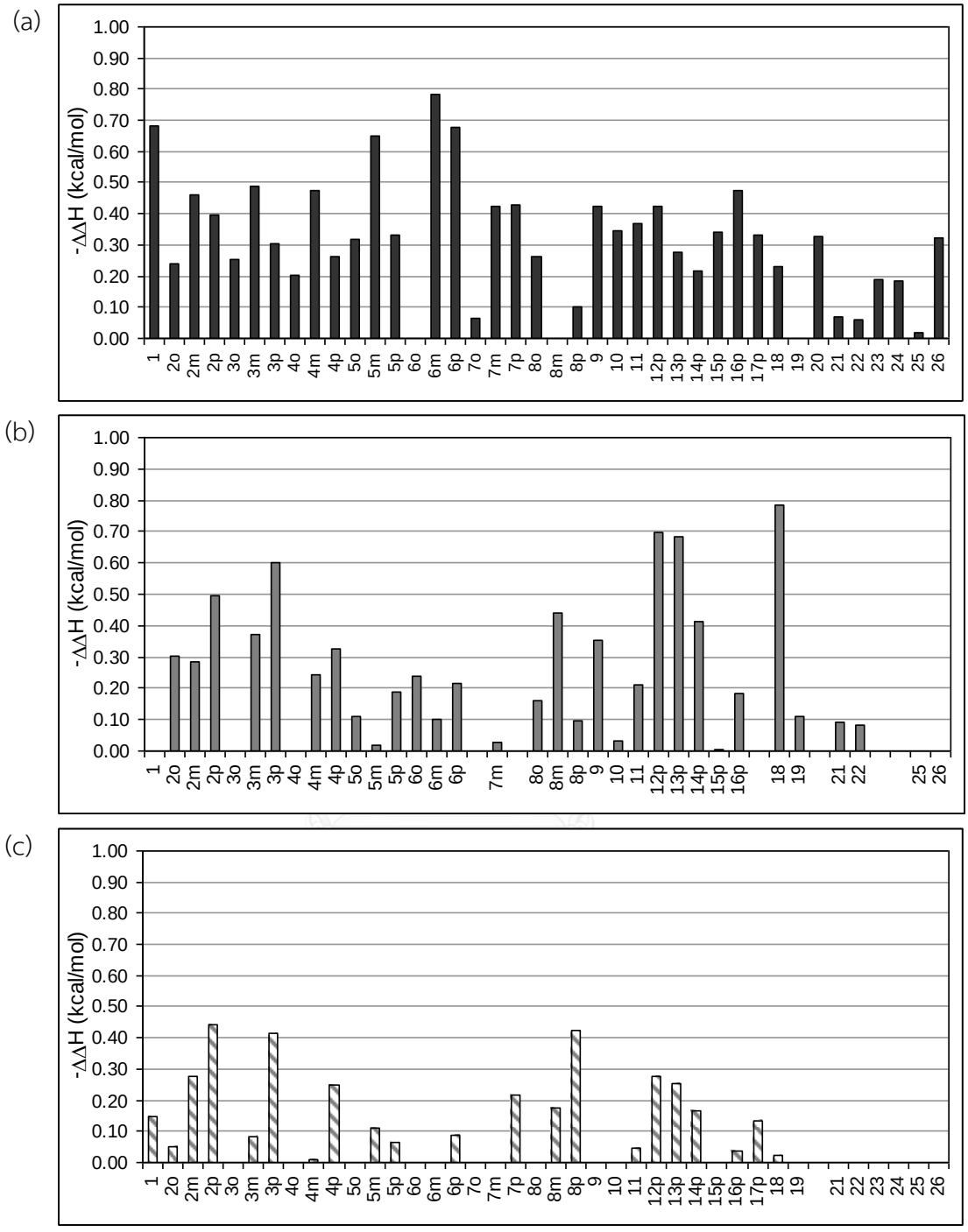


Figure 4.6 Enthalpy difference (-ΔΔH, kcal/mol) of (a) underivatized, (b) TFA and (c) TMS alcohols on BSiAc column.

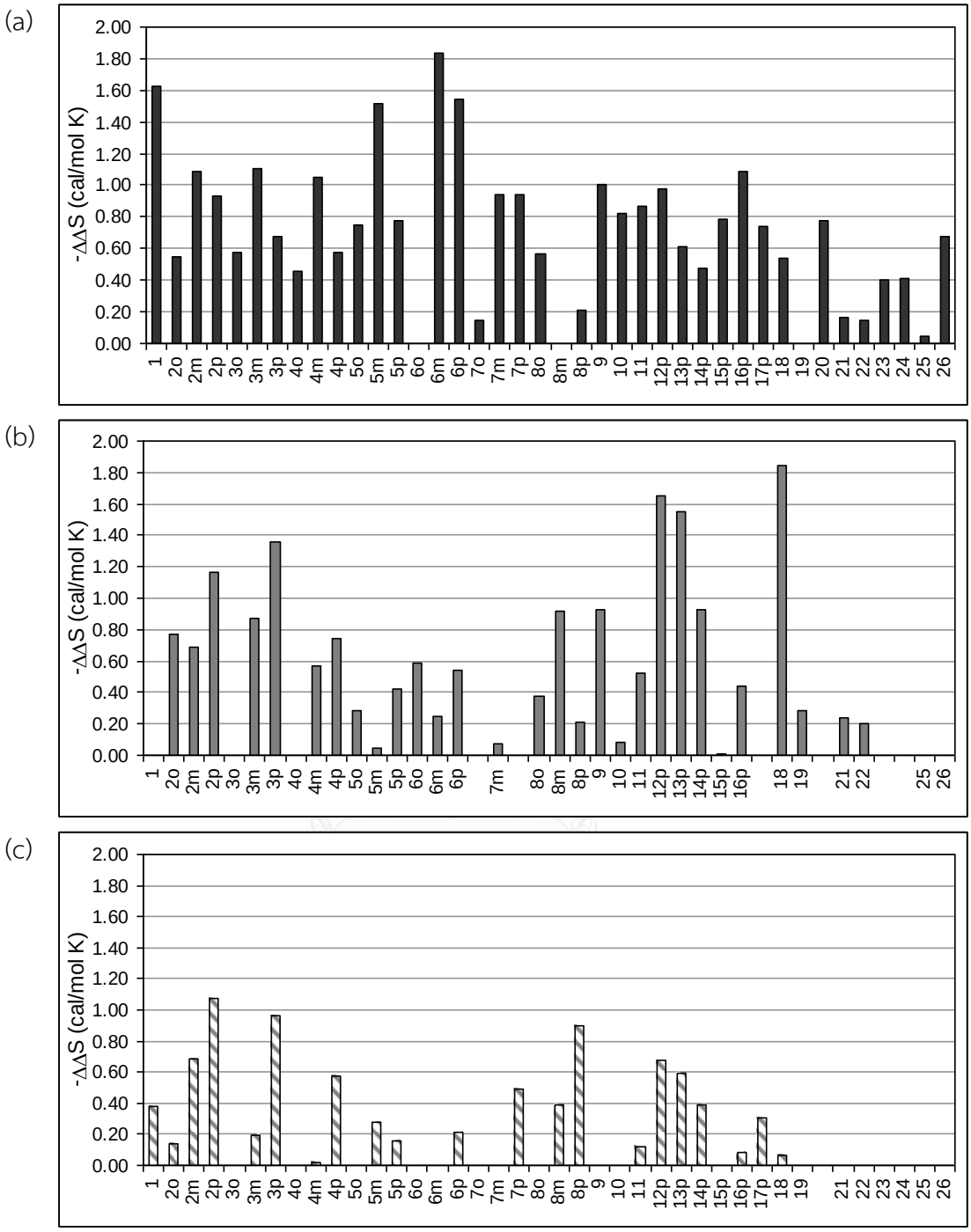
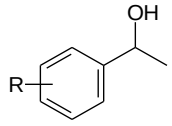


Figure 4.7 Entropy difference (-ΔΔS, cal/mol·K) of (a) underivatized, (b) TFA and (c) TMS alcohols on BSiAc column.

Effect of type and position of substitution on the aromatic ring



Effects of type and position of substitution on the aromatic ring of 1-phenylethanols on the enantioseparation were studied as a function of temperature. 1-Phenylethanol (**1**) was used as a reference compound. Other alcohols were 1-phenylethanols with mono-substitution of fluoro (**2**), chloro (**3**), bromo (**4**), trifluoromethyl (**5**), methyl (**6**), methoxy (**7**) and nitro (**8**) at *ortho-*, *meta-* and *para-*positions.

Retention and enantioselectivity of **1** were compared in Figures 4.8-4.9 respectively. It can be seen from Figure 4.8 that **1-OH** was more retained (higher k'_2) on BSiAc than its two derivatives at the same temperature. The enantiomer separation of **1-OH** could be noticed at high temperature. In addition, enantioselectivity of **1-OH** was more temperature dependent (high $-\Delta\Delta H$ value); therefore, its value could be easily improved with a decrease in temperature. For **1-TFA** and **1-TMS**, they showed similar retention on this column, but only **1-TMS** could be enantioseparated at very low temperature and the decrease in temperature resulted in a small increase of enantioselectivity. Chromatograms for the separation of enantiomers of **1-OH** and **1-TMS** were shown in Figure 4.10. Enantiomers of **1-OH** could be completely separated at 120 °C within 3 minutes with slightly tailing peaks. **1-TMS** offered more symmetrical peak shapes due to the derivatization with less polar group. However, Enantiomers of **1-TMS** could be completely separated at 70 °C within 8.5 minutes (longer analysis time).

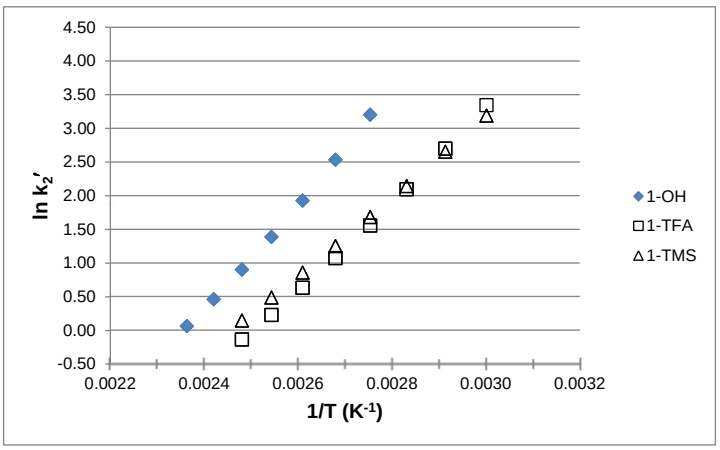


Figure 4.8 Plots of ln k'_2 versus 1/T of **1-OH**, **1-TFA** and **1-TMS**.

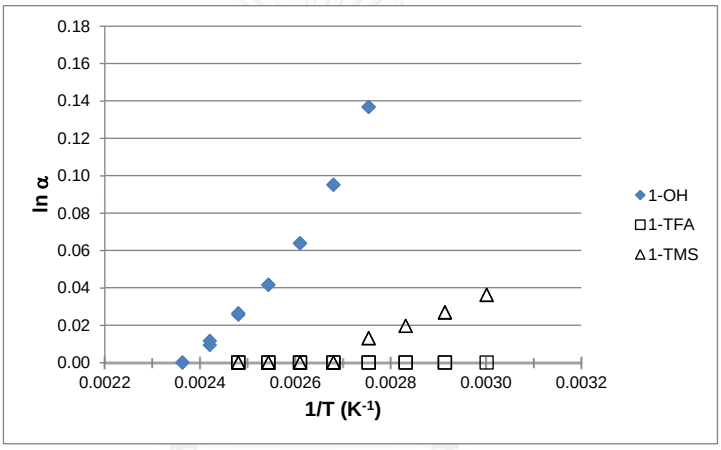


Figure 4.9 Plots of ln α versus 1/T of **1-OH**, **1-TFA** and **1-TMS**

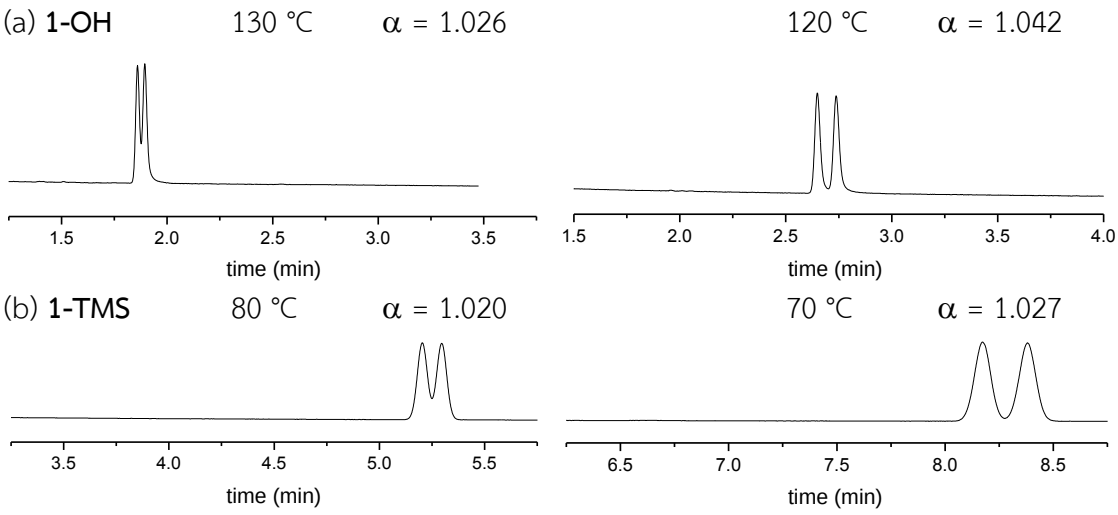


Figure 4.10 Chromatograms of (a) **1-OH** and (b) **1-TMS**.

For mono-substituted 1-phenylethanols (analytes **2**-**8**), most alcohols could be enantioseparated and showed lower -ΔΔH values than **1-OH**. Only two alcohols that could not be enantioseparated (-ΔΔH and -ΔΔS = 0) were **6o-OH** and **8m-OH**. The -ΔΔH values were varied depending on type and position of substitution. It was quite clear that the position of substitution had more influence toward -ΔΔH values than the type of substitution (Figure 4.11). The -ΔΔH values of most analytes were in the order of *meta*- ≥ *para*- > *ortho*-. Among 21 alcohols, methyl-substituted alcohol at *meta*-position (**6m-OH**) showed the highest -ΔΔH value. Nitro-substituted analytes were the only exception: their -ΔΔH values were in the order of *ortho*- > *para*- > *meta*-.

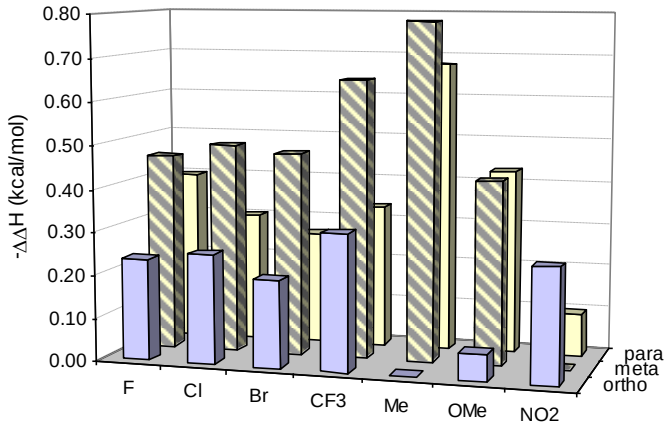


Figure 4.11 Enthalpy difference (-ΔΔH, kcal/mol) of alcohols **2**-**8**.

To demonstrate the influence of the position of substitution, plots of ln k′ versus 1/T and ln α versus 1/T of three isomers of alcohols **5** are shown in Figures 4.12-4.13, respectively. From Figure 4.12, **5o-OH** was the least retained and the least enantioselective on BSiAc among three isomers at the same temperature. While **5m-OH** not only showed highest enantioselectivity at the same temperature, but also showed largest increase in enantioselectivity as the temperature decrease (highest -ΔΔH value) as in Figure 4.13. Nonetheless, **5m-OH** was less retained than **5p-OH**. Their corresponding chromatograms are shown in Figure 4.14. Enantiomers of **5m-OH**

could be completely separated with the shortest analysis time (within 4 minutes at 120 °C).

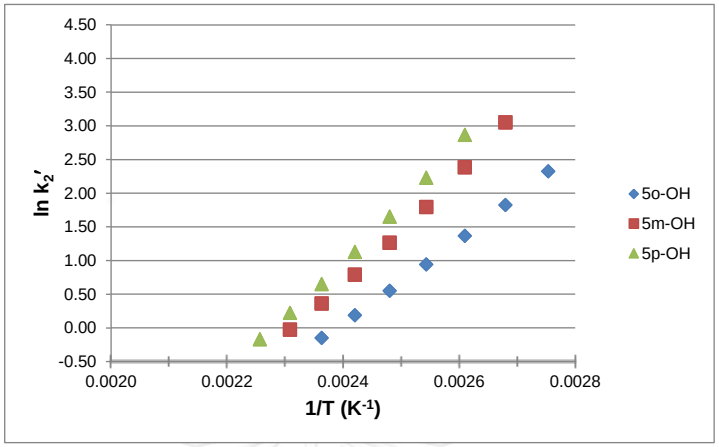


Figure 4.12 Plots of ln k'_2 versus 1/T of **5o-OH**, **5m-OH** and **5p-OH**.

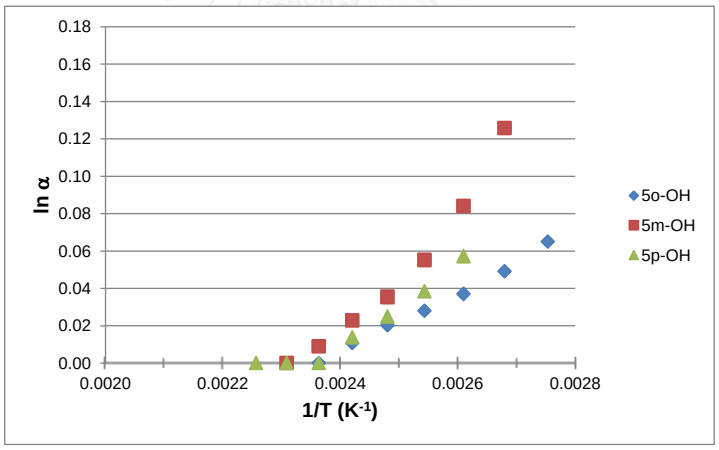


Figure 4.13 Plots of ln α versus 1/T of **5o-OH**, **5m-OH** and **5p-OH**.

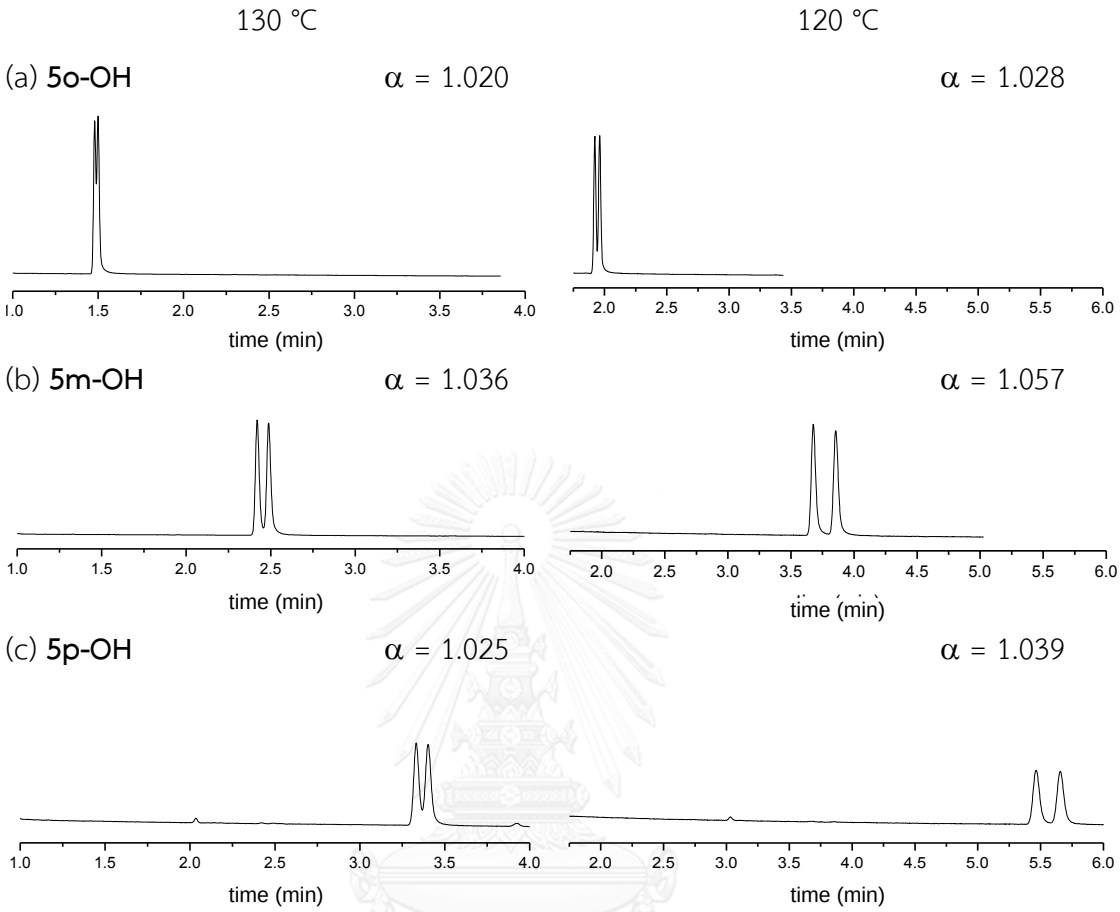


Figure 4.14 Chromatograms of (a) **5o-OH**, (b) **5m-OH** and (c) **5p-OH**.

The effect of type of substitution on the aromatic ring on enantioseparation was also studied. For *meta*-substituted analytes, their -ΔΔH values were in the order of **Me** > **CF_3** > (**Cl** ~ **Br** ~ **F** ~ **OMe**). However, the effect of type of substitution on enantioseparation was changed as the position of substitution changed (Figure 4.11).

Derivatization of hydroxyl group of analytes mostly resulted in poorer or complete loss of enantioseparation (Figure 4.11). Most *ortho*-substituted TMS and TFA derivatives showed lower -ΔΔH values than their corresponding alcohols. This was possible that larger-size TMS or TFA might sterically hinder the interaction around the stereogenic center and lower -ΔΔH values were obtained. Interestingly, **6o-TFA** could be enantioseparated while its alcohol could not. Better improvement in enantioseparation observed with derivatization was *para*-substituted TFA

derivatives, e.g. **2p-TFA**, **3p-TFA** and **4p-TFA**. Although most TMS derivatives showed poorer enantioseparation than alcohols, all 7 *para*-substituted TMS analytes could be enantioseparated (Figure 4.15) and **8p-TMS** was the only TMS derivative that showed better enantioseparation than its corresponding alcohol or TFA derivative. Chromatograms of **6o-TFA** and **8p-TMS** are shown in Figure 4.16.

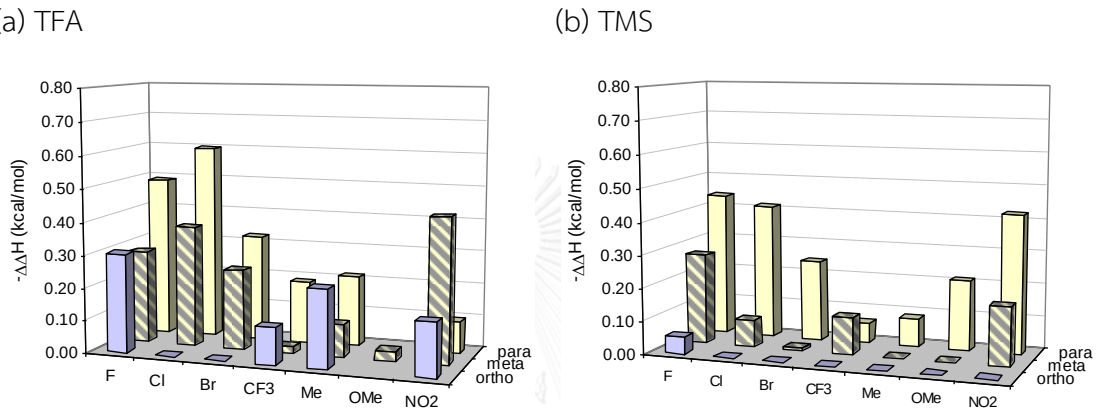


Figure 4.15 Enthalpy difference (-ΔΔH, kcal/mol) of (a) TFA and (b) TMS derivatives of alcohols **2**-**8**.

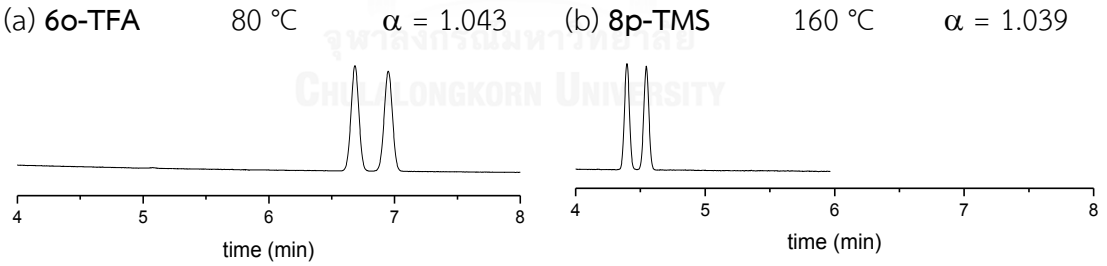
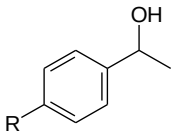


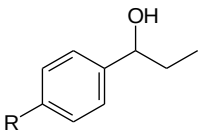
Figure 4.16 Chromatograms of (a) **6o-TFA** and (b) **8p-TMS**.

Effect of the type of substitution at the stereogenic center or the core structure



phenylethanol

PE



phenylpropanol

PP

R	PE	PP
H	**1**	**11**
F	**2p**	**12p**
Cl	**3p**	**13p**
Br	**4p**	**14p**
CF3	**5p**	**15p**
Me	**6p**	**16p**
OMe	**7p**	**17p**

Other alcohols based on the core structure of 1-phenylethanol were investigated. Enantioseparation of 1-phenylpropanol and its *para*-substituted derivatives were compared to those of 1-phenylethanols. Their -ΔΔH values were compared as shown in Figure 4.17. For most alcohols and TMS derivatives, PEs showed higher -ΔΔH values than PPs (Figure 4.17 (a) and (c)).

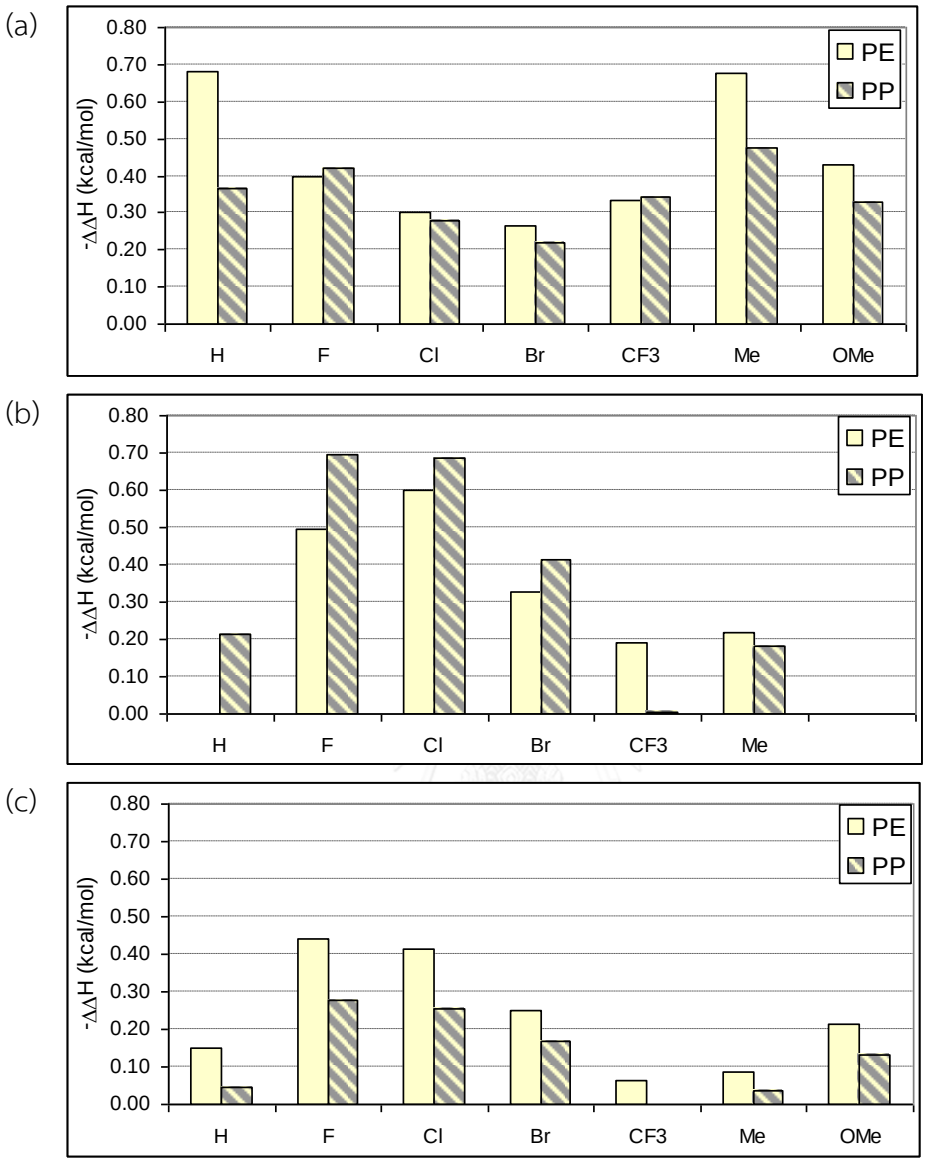


Figure 4.17 Enthalpy difference (-ΔΔH, kcal/mol) of (a) underivatized, (b) TFA and (c) TMS phenylethanols (PEs) and phenylpropanols (PPs).

For TFA derivatives with no substitution or halogen substitution, PPs showed better enantioseparation than PEs (Figure 4.17 (b)). Chromatograms of *para*-fluoro substituted **2p-TFA** and **12p-TFA** were compared in Figure 4.18. Nevertheless, *para*-trifluoromethyl substituted **15p-TFA** showed very low -ΔΔH value compared to **5p-TFA**. Plots of ln k′ versus 1/T and ln α versus 1/T of both **5p-TFA** and **15p-TFA** are

shown in Figures 4.19-4.20, respectively. It can be seen that the retention and enantioselectivity of **5p-TFA** increased as the temperature decreased. However, temperature had almost no effect on enantioselectivity of **15p-TFA**. As the temperature decreased, the enantioselectivity increased to a maximum (α = 1.011). A further decrease in temperature resulted in a decrease in enantioselectivity and resolution (Figure 4.21). This is probably caused by multiple interaction types between the analyte and the stationary phase as the temperature changed [34]. Thus, a complete resolution of **15p-TFA** could not be obtained.

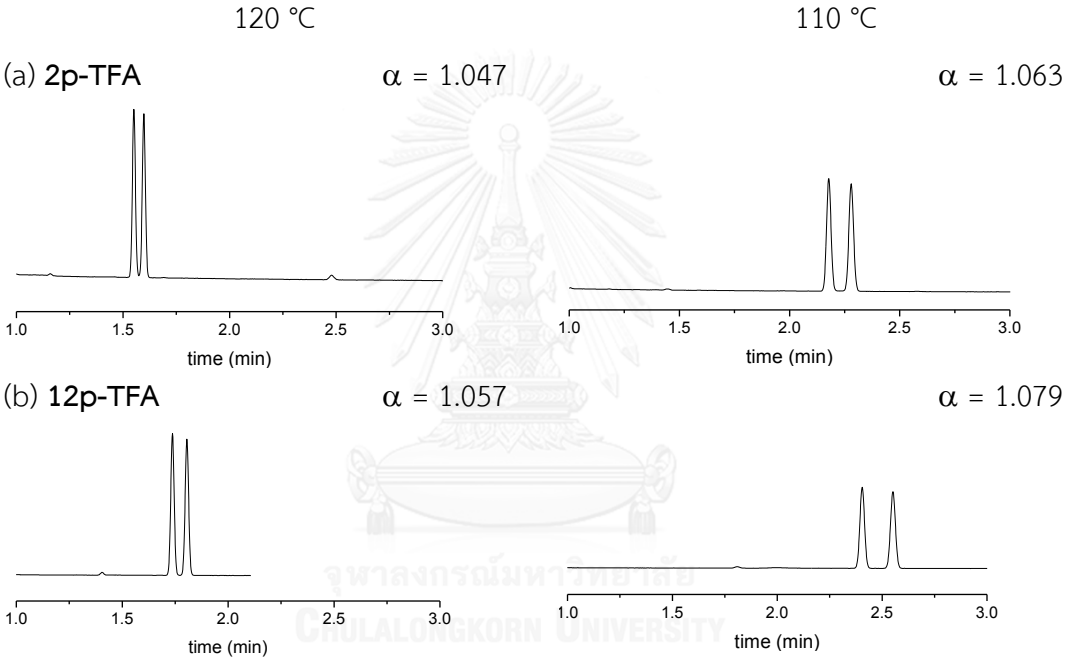


Figure 4.18 Chromatograms of (a) **2p-TFA** and (b) **12p-TFA**.

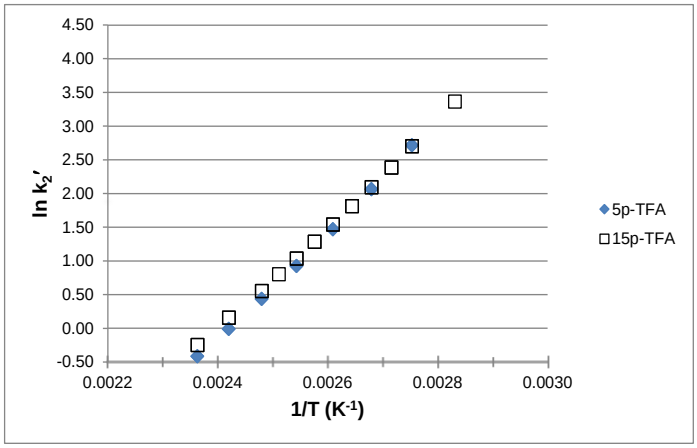


Figure 4.19 Plots of ln k'_2 versus 1/T of **5p-TFA** and **15p-TFA**.

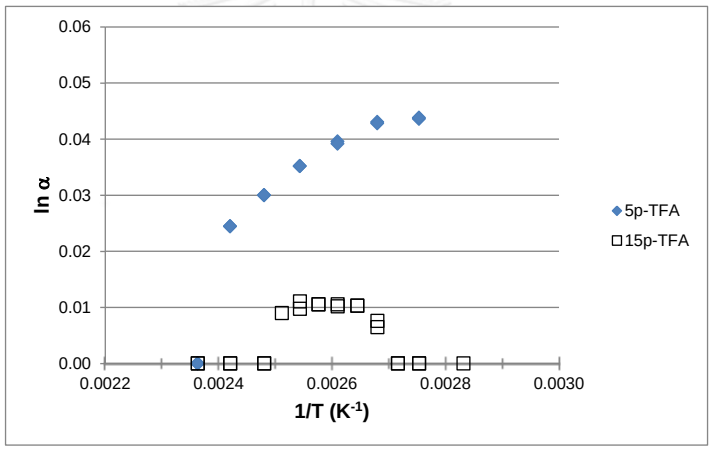


Figure 4.20 Plots of ln α versus 1/T of **5p-TFA** and **15p-TFA**.

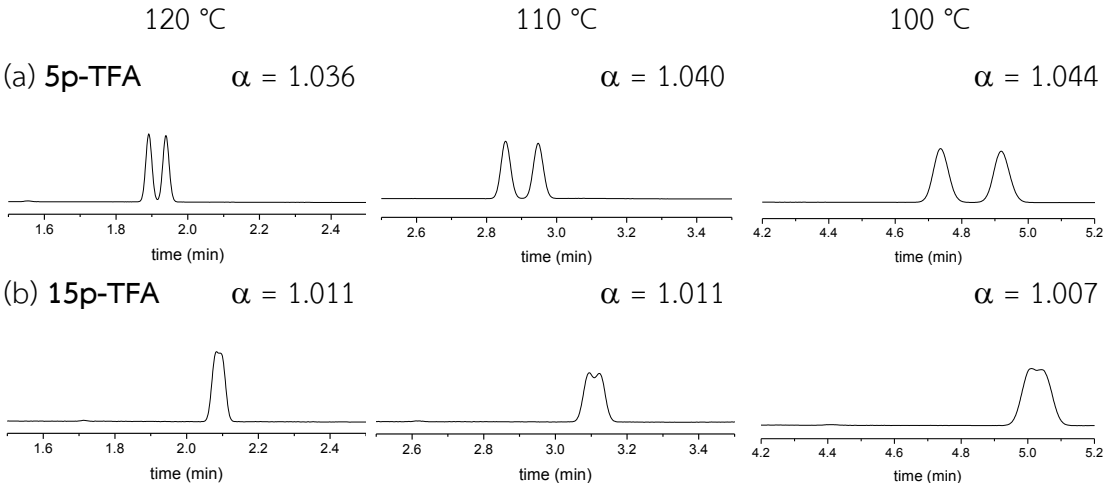


Figure 4.21 Chromatograms of (a) **5p-TFA** and (b) **15p-TFA**.

Other twelve alcohols with different type of substitution at the stereogenic center or the core structure were further investigated. Their -ΔΔH values were compared to alcohol **1** as shown in Figure 4.22.

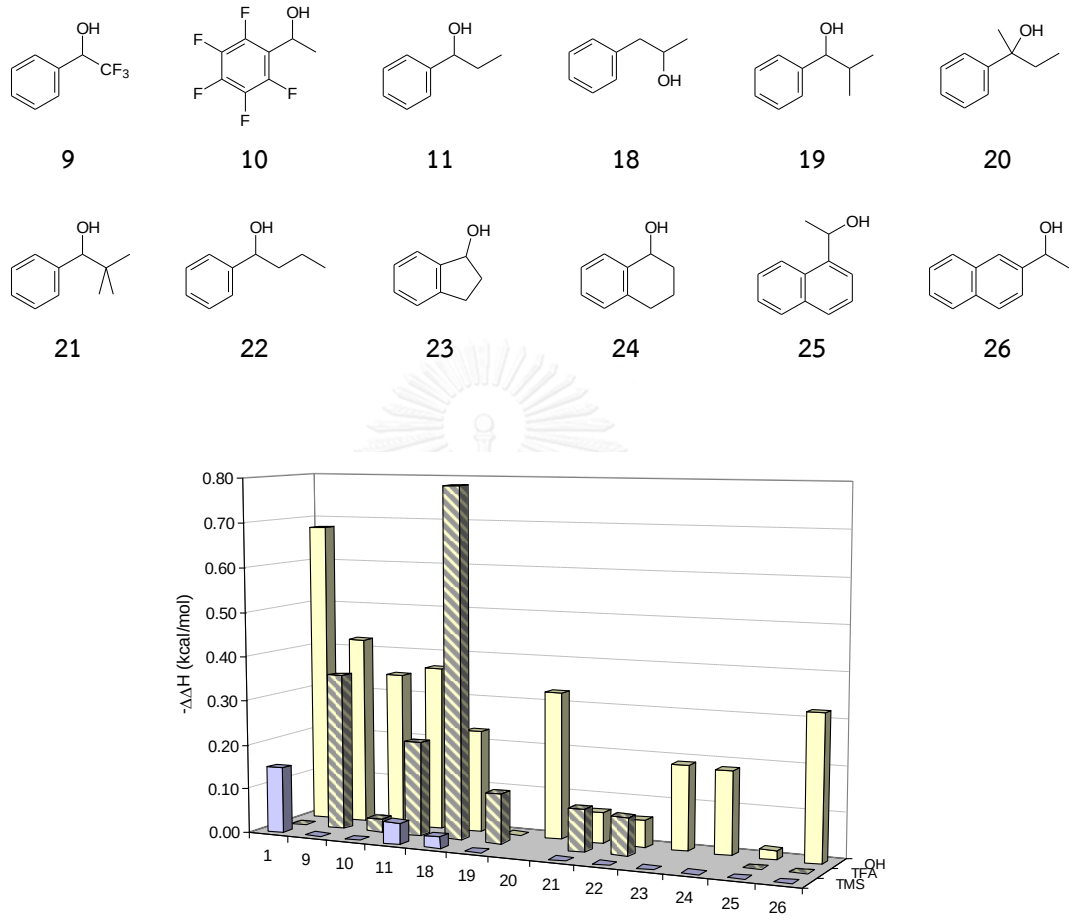


Figure 4.22 Enthalpy difference (-ΔΔH, kcal/mol) of underivatized, TFA and TMS alcohols with different type of substitution at the stereogenic center or core structure.

For most cases, all analytes in underivatized alcohol form could be enantioseparated except for **19-OH**. The -ΔΔH values of other twelve alcohols were much lower than **1-OH**. The results indicated that longer or bulkier alkyl group or less flexible cyclic structure (**23**, **24**) at the stereogenic center did not benefit the enantioseparation of alcohol. Larger alcohols such as naphthylethanols (**25**, **26**) did

not show good enantioseparation either. However, a small change in the substitution position on the naphthyl ring could result in a big change in enantioseparation.

Derivatization of alcohols in this group resulted in poorer or no enantioseparation. For TMS derivatives, enantioseparation could only be observed for **11-TMS** and **18-TMS**. However, their -ΔΔH values were rather small. For TFA derivatives, enantioseparation could be observed for 7 analytes. Most of their -ΔΔH values were similar or smaller than those of corresponding alcohols but higher than TMS derivatives. Unexpectedly, **18-TFA** showed much higher -ΔΔH value than **18-OH** and gave the highest -ΔΔH value among all 40 analytes studied. Chromatograms of alcohol **18** are shown in Figure 4.23.

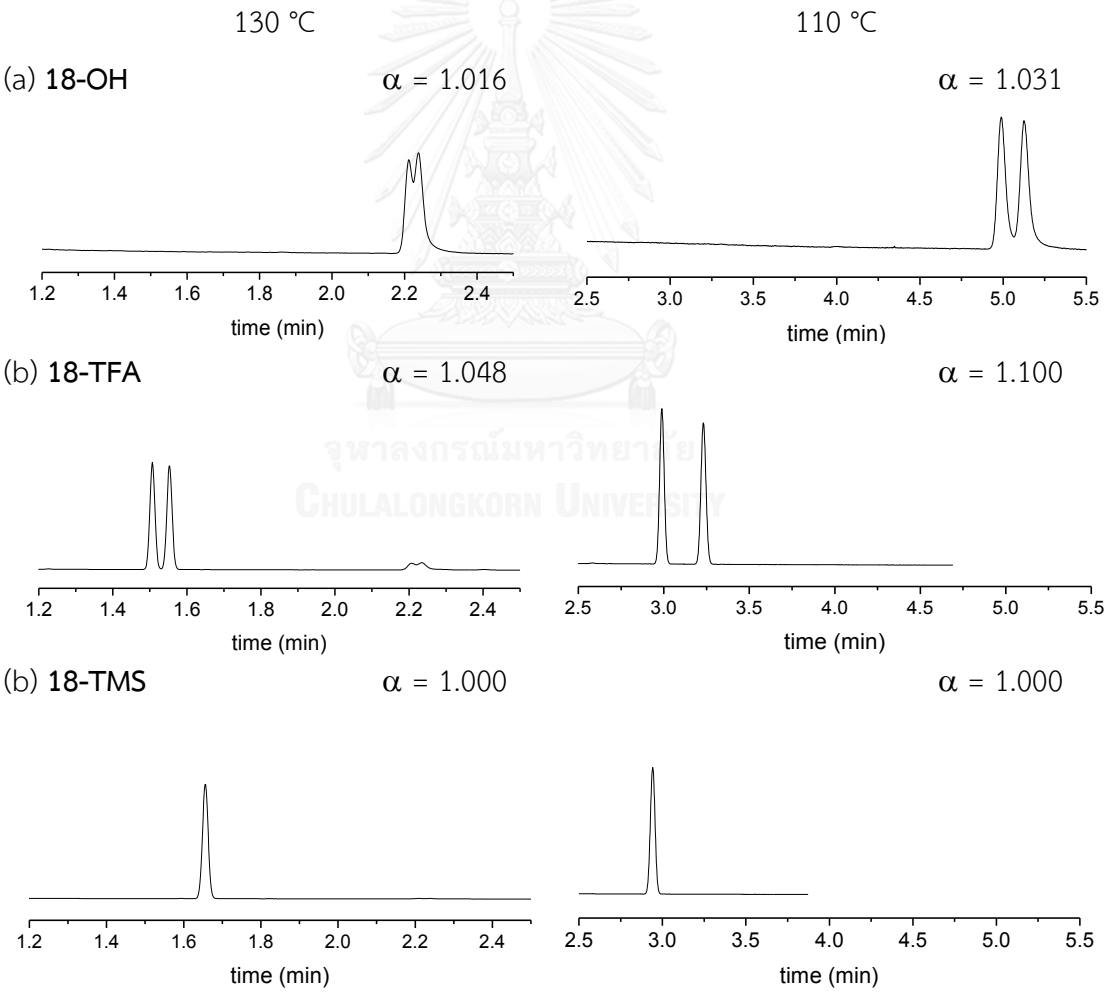


Figure 4.23 Chromatograms of (a) **18-OH**, (b) **18-TFA** and (c) **18-TMS**.

For analyses of chiral analytes, complete separations between enantiomeric peak pairs are preferred for accurate results. In addition, short analysis times are desirable. Previously, it can be seen that temperature is an important operating parameter for successful separation by GC. However, a decrease in temperature normally results in a better enantioselectivity as well as an increased analysis time. To compare the effect of temperature towards both enantioselectivity and retention, retention factors of the more retained enantiomer (k'_2) of all analytes that provided complete baseline separation of enantiomers (at Rs = 1.5) were compared and shown in Figure 4.24. Since the experiments were performed at predetermined temperatures, resolution (Rs) values of exactly 1.5 and their corresponding retention (k'_2) may not be obtained. Therefore, the Rs values were obtained from plots of Rs vs. k'_2. For some analytes, where their enantioselectivities were very low and k'_2 values were very large (> 30), complete separations could not be obtained and the data were not shown.

Although almost all alcohols could be enantioseparated and most alcohols showed higher $-\Delta\Delta H$ values than their TFA or TMS derivatives, complete enantioseparation for many alcohols required longer analysis time than their TFA or TMS derivatives. Eleven TFA derivatives showed complete enantioseparation with $k'_2 \leq 5$ (**2o-TFA**, **2m-TFA**, **2p-TFA**, **3m-TFA**, **3p-TFA**, **4p-TFA**, **5p-TFA**, **8m-TFA**, **9-TFA**, **12p-TFA**, **13p-TFA** and **18-TFA**) and the shortest analysis time was observed for **18-TFA** (k'_2 = 1.5).

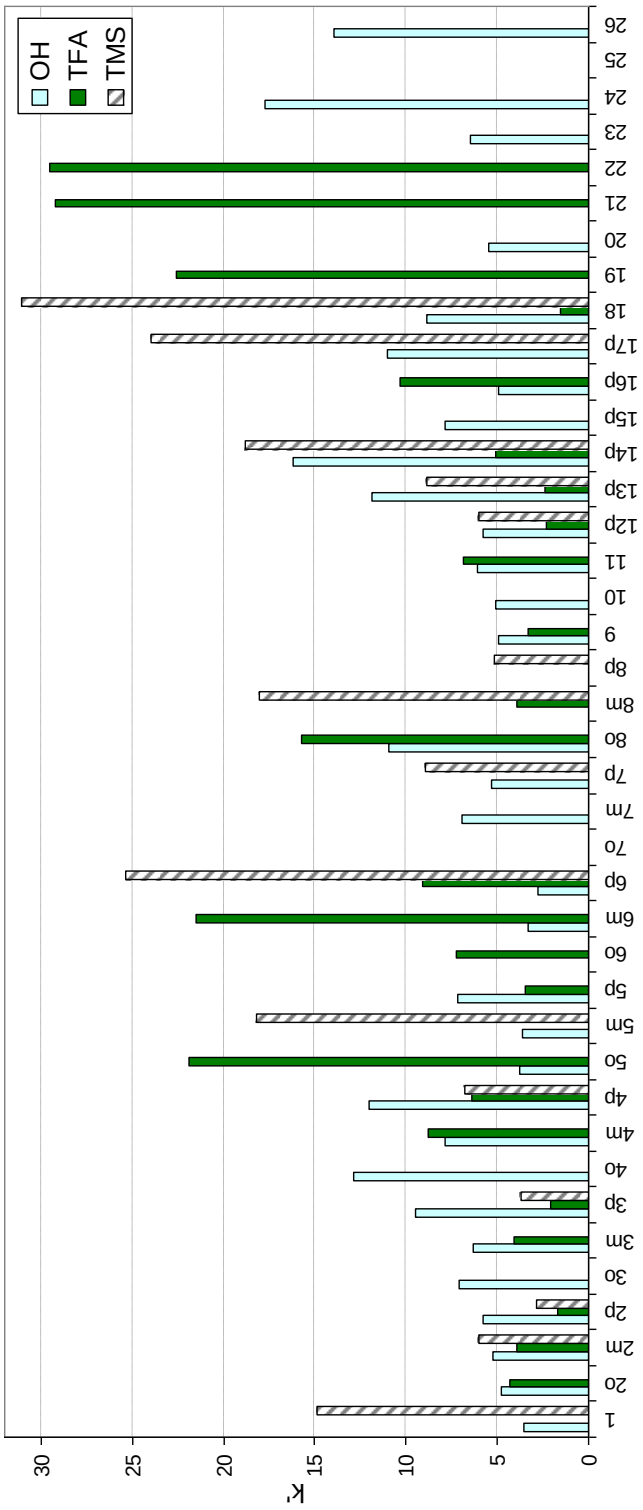


Figure 4.24 Retention factors of the more retained enantiomers (k'_2) of underivatized, TFA and TMS alcohols at resolution of 1.5. Analytes that could not be separated or separated with $k'_2 > 30$ are not shown.

In several cases, alcohols or derivatives having similar thermodynamic values may provide different separation results. An example was selected for alcohol **9**. Plots of ln k′ versus 1/T and ln α versus 1/T of **9** were compared in Figures 4.25-4.26. From Figure 4.25, it was clear that, at the same temperature, k′ values were in the order of **9-OH** > **9-TMS** > **9-TFA**. The effect of temperature on retention was higher for **9-OH** (sharper slope). The effect of temperature on enantioselectivity was similar for both **9-OH** and **9-TFA** (Figure 4.26). In this case, complete enantioseparation of **9-TFA** could be achieved at lower temperature and shorter analysis time (Figure 4.27).

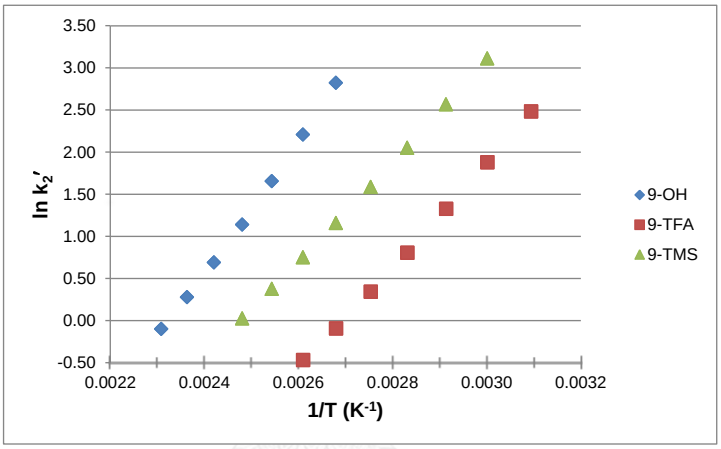


Figure 4.25 Plots of ln k'_2 versus 1/T of **9-OH, 9-TFA** and **9-TMS**.

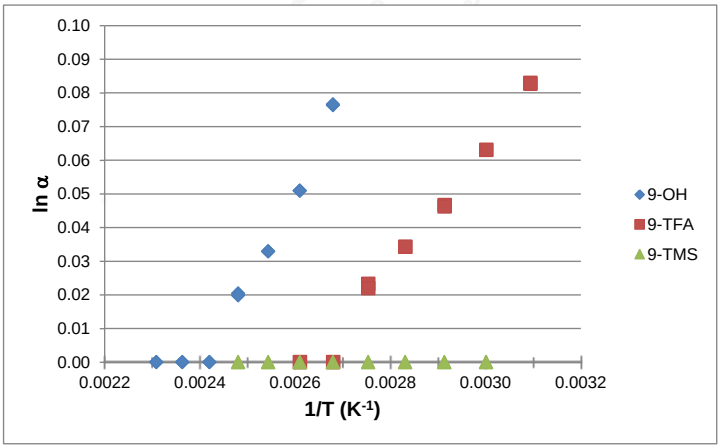


Figure 4.26 Plots of ln α versus 1/T of **9-OH, 9-TFA** and **9-TMS**.

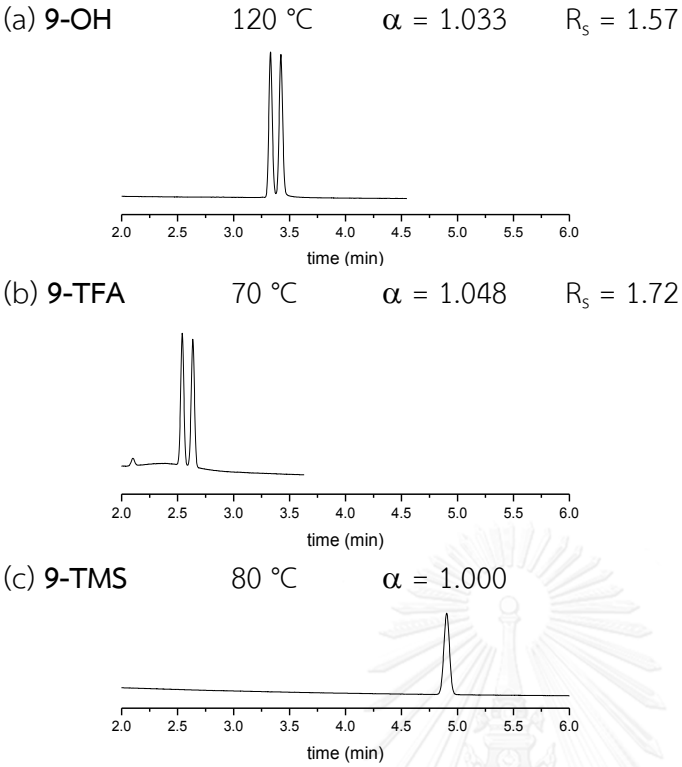


Figure 4.27 Chromatograms of (a) **9-OH**, (b) **9-TFA** and (c) **9-TMS**.

4.4 Comparison on enantiomeric separation with other β-CD derivatives

The enantioseparations of underivatized alcohols by GC using BSiAc column were compared with previous reports [21] using heptakis(2,3-di-O-methyl-6-O-*tert*-butyldimethylsilyl)-β-CD (or BSiMe) and heptakis(2,3,6-tri-O-methyl)-β-CD (or BMe) as chiral selectors. For substituted 1-phenylethanols, it was shown that the position of substitution on the aromatic ring strongly affect enantioseparation of analytes on all three columns. For BSiAc, *meta*- and *para*-substitutions gave better enantioseparation (higher -ΔΔH values) than their *ortho*-isomers. In contrast, both BSiMe and BMe provided much better enantioseparation for all *ortho*-substituted analytes and similar or poorer enantioseparation for *meta*- and *para*-substitutions. However, BSiMe provided better enantioselectivities and peak shapes than BMe. The difference in enantioseparation would come from the different type of functional group at the C2 and C3 chiral carbons of glucose units in CD ring.

CHAPTER V

Conclusion

Forty racemic alcohols were acquired or prepared from reduction of their corresponding ketones using sodium borohydride. They were independently derivatized into trifluoroacetyl (TFA) and trimethylsilyl (TMS) derivatives. Enantiomeric separations of all underivatized and derivatized alcohols were studied by gas chromatography using heptakis(2,3-di-*O*-acetyl-6-*O*-*tert*-butyldimethylsilyl)-β-CD (or BSiAc) mixed in polysiloxane OV-1701 as a chiral stationary phase. Factors affecting analyte retentions and enantioselectivities were studied including column temperature, alcohol structure (type and position of substitution) as well as type of alcohol derivatization (TFA vs. TMS).

The influence of analyte derivatization of the strength of interaction between analyte and stationary phase was shown. As expected, underivatized alcohols were more retained in the column than their derivatized forms. In addition, the $-\Delta H_2$ values of all analytes were in the order of alcohol > TFA > TMS. The $-\Delta H_2$ values of analytes with mono-substitution on the aromatic ring showed a slight increase from *ortho*- < *meta*- < *para*-position, regarding the type of substitution. Analytes with nitro-substitution showed the highest $-\Delta H_2$ values compared to other types of substitution. The trends for $-\Delta H_2$ values of three forms of analytes were quite similar.

Enantiomers of all analytes, as either underivatized or derivatized form, could be separated. Analyte structure and derivatization strongly influence their enantioseparation. From 40 underivatized alcohols, enantioseparation of 37 analytes could be observed. Three analytes that could not be enantioseparated were **6o**, **8m** and **19**. After derivatization, 29 of 34 TFA derivatives and only 21 of 39 TMS derivatives could be separated into their enantiomers. The degree of enantioseparation was varied depending on analyte structure.

For mono-substituted 1-phenylethanols, most alcohols could be enantioseparated but showed lower -ΔΔH values than **1-OH**. The -ΔΔH values of most alcohol analytes were in the order of *meta*- ≥ *para*- > *ortho*- with **6m-OH** showing the highest -ΔΔH value. While nitro-substituted alcohols showed different trend: their -ΔΔH values were in the order of *ortho*- > *para*- > *meta*-. The effect of type of substitution on enantioseparation was not apparent. TFA and TMS derivatives mostly resulted in poorer -ΔΔH values or complete loss of enantioseparation.

Effect of the type of substitution at the stereogenic center of 1-phenylethanol was also studied. Enantioseparations of *para*-substituted 1-phenylpropanols (PPs) were compared to *para*-substituted 1-phenylethanols (PEs). For most alcohols and TMS derivatives, PEs showed higher -ΔΔH values than PPs. For TFA derivatives with halogen substitution, PPs showed better enantioseparation than PEs. Other alcohols with different type of substitution at the stereogenic center or different core structure were also examined. Most underivatized alcohols could be enantioseparated but the introduction of longer or bulkier alkyl group or less flexible cyclic structure at the stereogenic center resulted in lower -ΔΔH values compared to 1-phenylethanol. Derivatization of alcohols in this group resulted in poorer or no enantioseparation. Only a few TFA derivatives (**18-TFA**, **19-TFA**, and **21-TFA**) showed higher -ΔΔH values than its alcohols.

Although TFA and TMS derivatives mostly resulted in poorer -ΔΔH values or complete loss of enantioseparation, derivatization could improve enantioseparation of some alcohols. For example, **6o-TFA**, **8p-TMS** and **19-TFA** could be enantioseparated while their corresponding alcohols could not. In addition, derivatization could provide more symmetrical peak shapes and sometimes offer complete enantioseparation in shorter analysis time than their corresponding underivatized alcohols. Among all analytes in this study, the shortest analysis time for complete enantioseparation was observed for **18-TFA**. Further study with larger number of analytes should be made.

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APPENDIX

NMR spectra

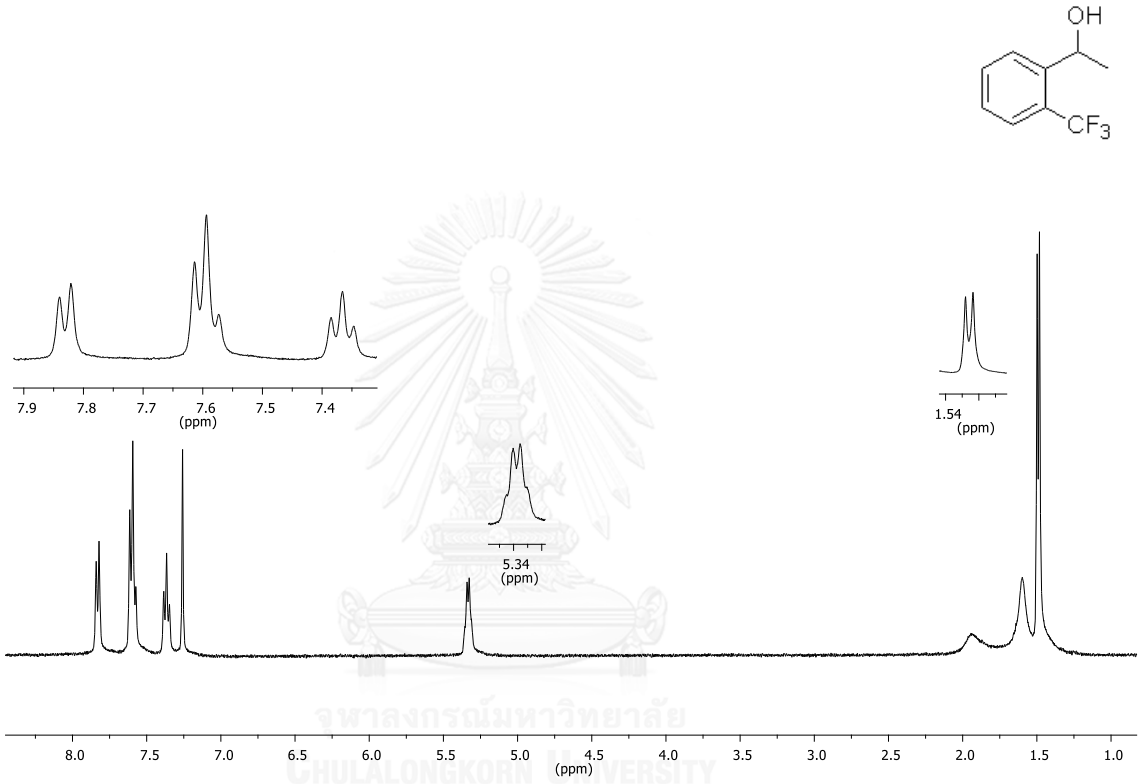

Figure A1 NMR spectrum of **5o**; ^{1}H NMR ($CDCl_3$, 400 MHz) **δ**(ppm); 1.49 (3H, d, *J* = 6.3 Hz, $CH_2C\underline{H}_3$), 1.94 (1H, s, O<u>H</u>), 5.33 (1H, dd, *J* = 11.0, 5.1 Hz, C<u>H</u>OH), 7.57 (4H, ddd, *J* = 90.8, 53.0, 7.7 Hz, Ar<u>H</u>).

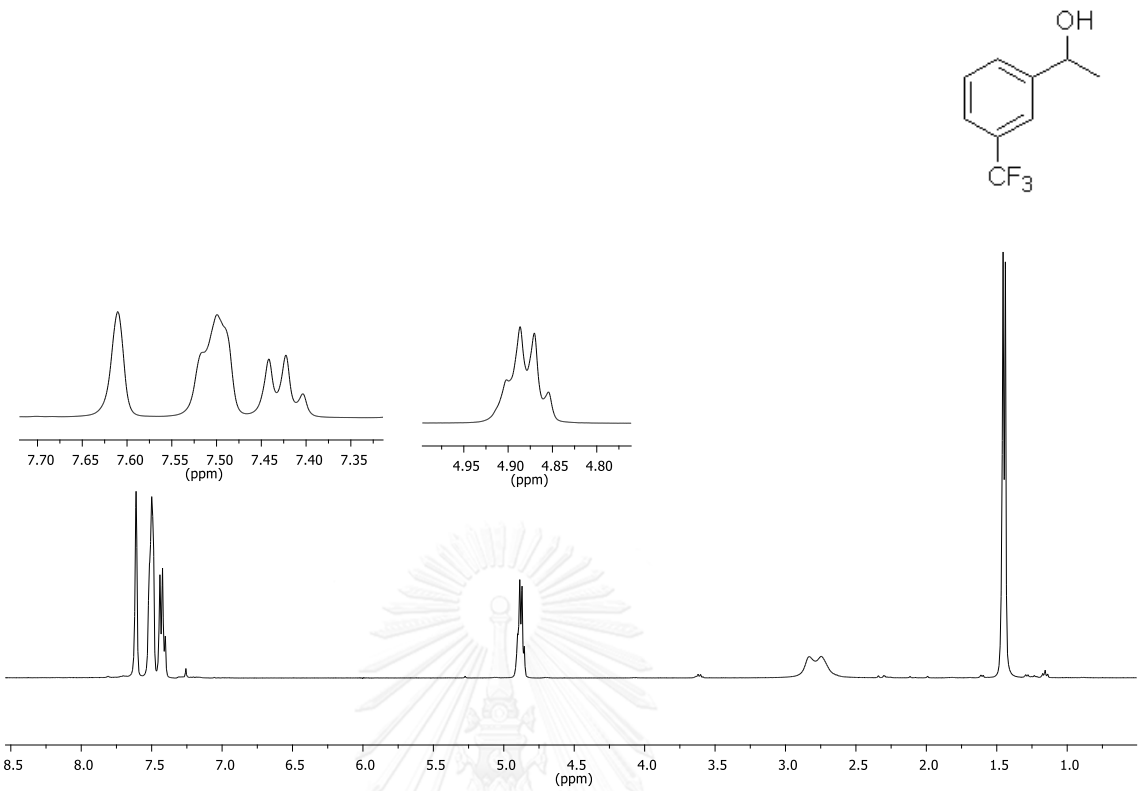

Figure A2 NMR spectrum of **5m**; ^{1}H NMR ($CDCl_3$, 400 MHz) **δ**(ppm); 1.45 (3H, d, *J* = 6.5 Hz, $CH_2C\underline{H}_3$), 2.79 (1H, d, *J* = 33.9 Hz, O<u>H</u>), 4.88 (1H, dd, *J* = 12.7, 6.3 Hz, C<u>H</u>OH), 7.65 – 7.38 (4H, m, Ar<u>H</u>).

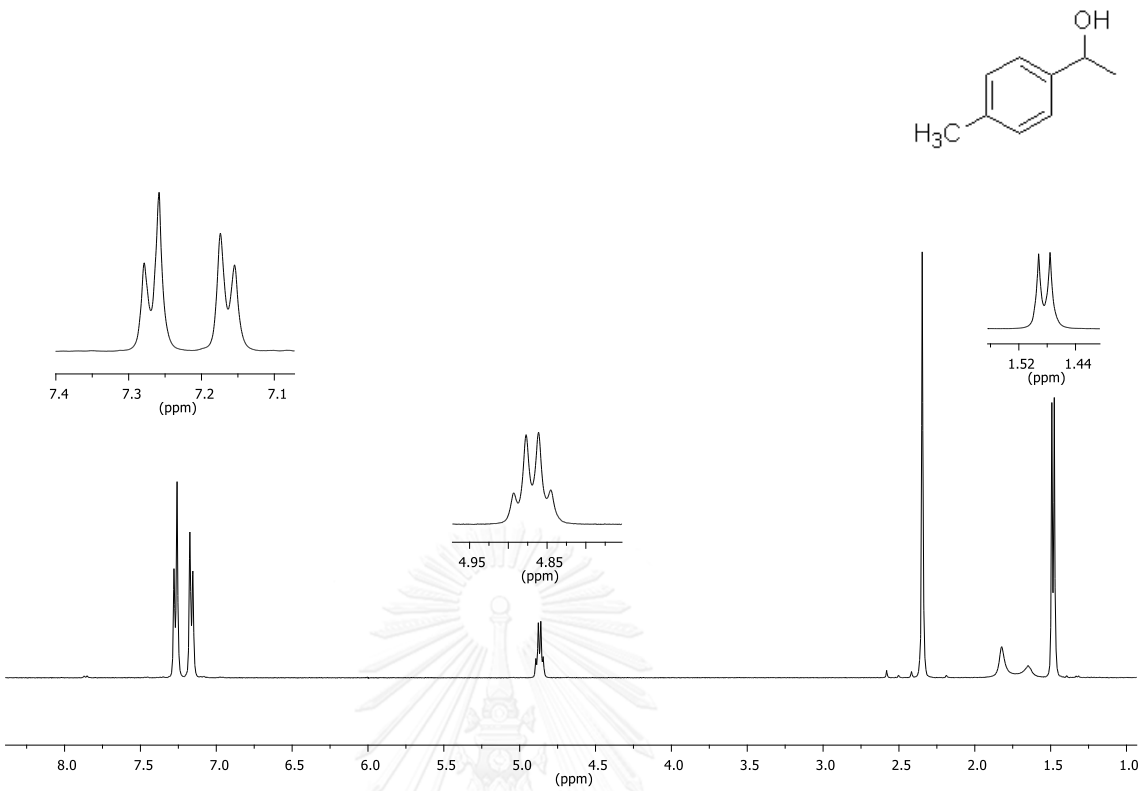

Figure A3 NMR spectrum of **6p**; ^{1}H NMR ($CDCl_3$, 400 MHz) **δ**(ppm); 1.48 (3H, d, *J* = 6.5 Hz, $CH_2C\underline{H}_3$), 1.82 (1H, s, O<u>H</u>), 2.35 (3H, s, $ArC\underline{H}_3$), 4.87 (1H, q, *J* = 6.3 Hz, C<u>H</u>OH), 7.22 (4H, dd, *J* = 41.6, 8.0 Hz, Ar<u>H</u>).

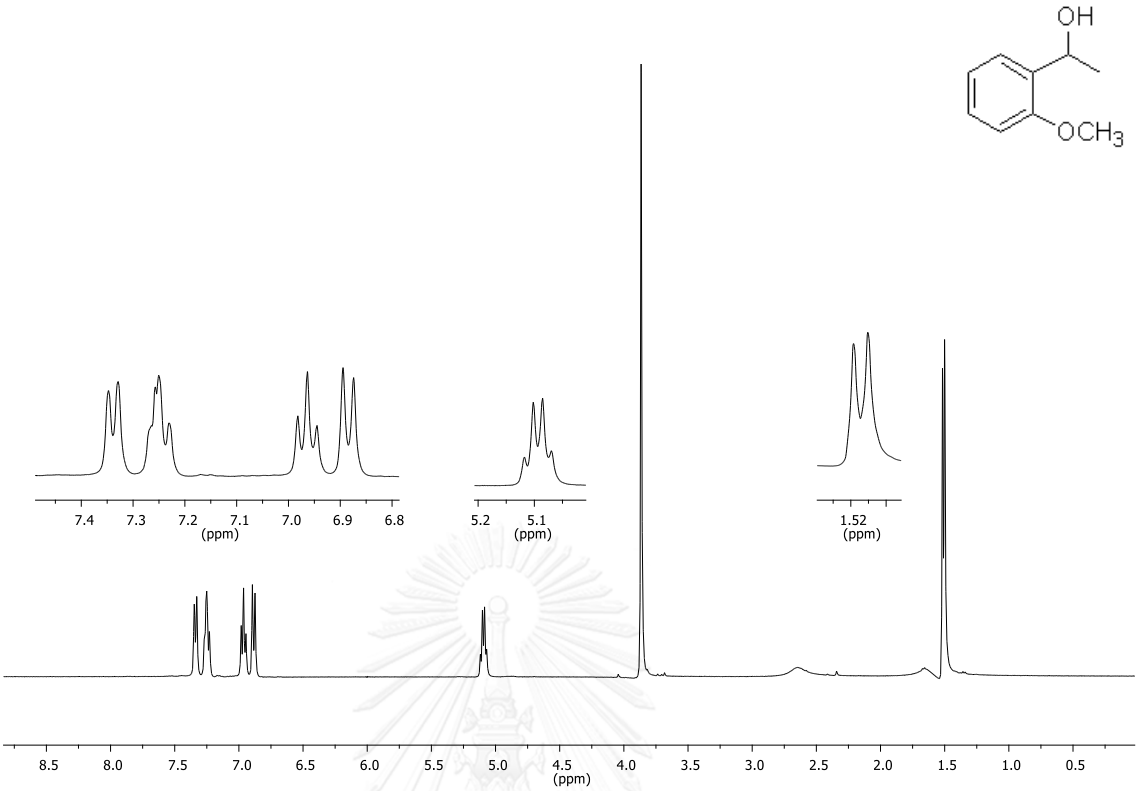

Figure A4 NMR spectrum of **7o**; ^{1}H NMR ($CDCl_3$, 400 MHz) **δ**(ppm) 1.51 (3H, d, *J* = 6.5 Hz, CHC<u>H</u>$_3$), 3.87 (3H, s, OC<u>H</u>$_3$), 5.09 (1H, q, *J* = 6.4 Hz, C<u>H</u>OH), 7.53 – 6.70 (4H, m, Ar<u>H</u>).

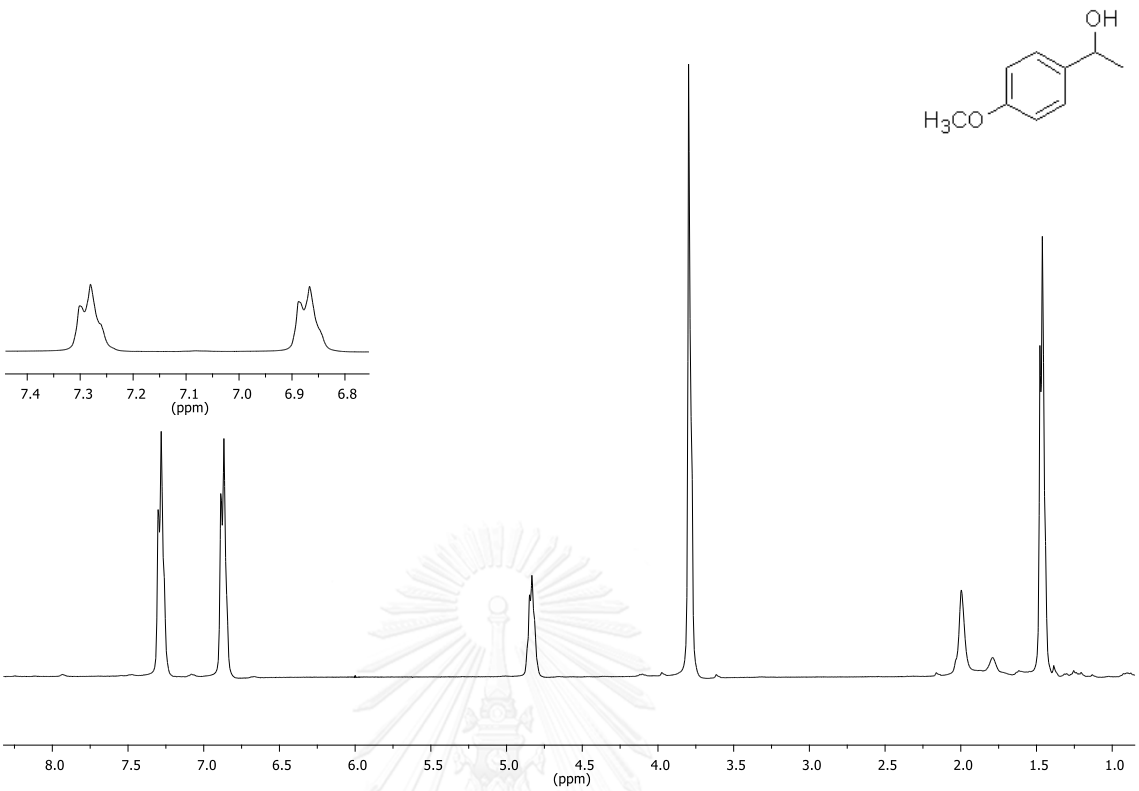

Figure A5 NMR spectrum of **7p**; ^{1}H NMR ($CDCl_3$, 400 MHz) **δ**(ppm) 1.44 (3H, t, *J* = 18.3 Hz, CHC<u>H</u>$_3$), 2.00 (1H, s, O<u>H</u>), 3.79 (3H, d, *J* = 7.6 Hz, OC<u>H</u>$_3$), 4.84 (1H, d, *J* = 6.2 Hz, C<u>H</u>OH), 7.08 (4H, dd, *J* = 164.9, 7.8 Hz, Ar<u>H</u>).

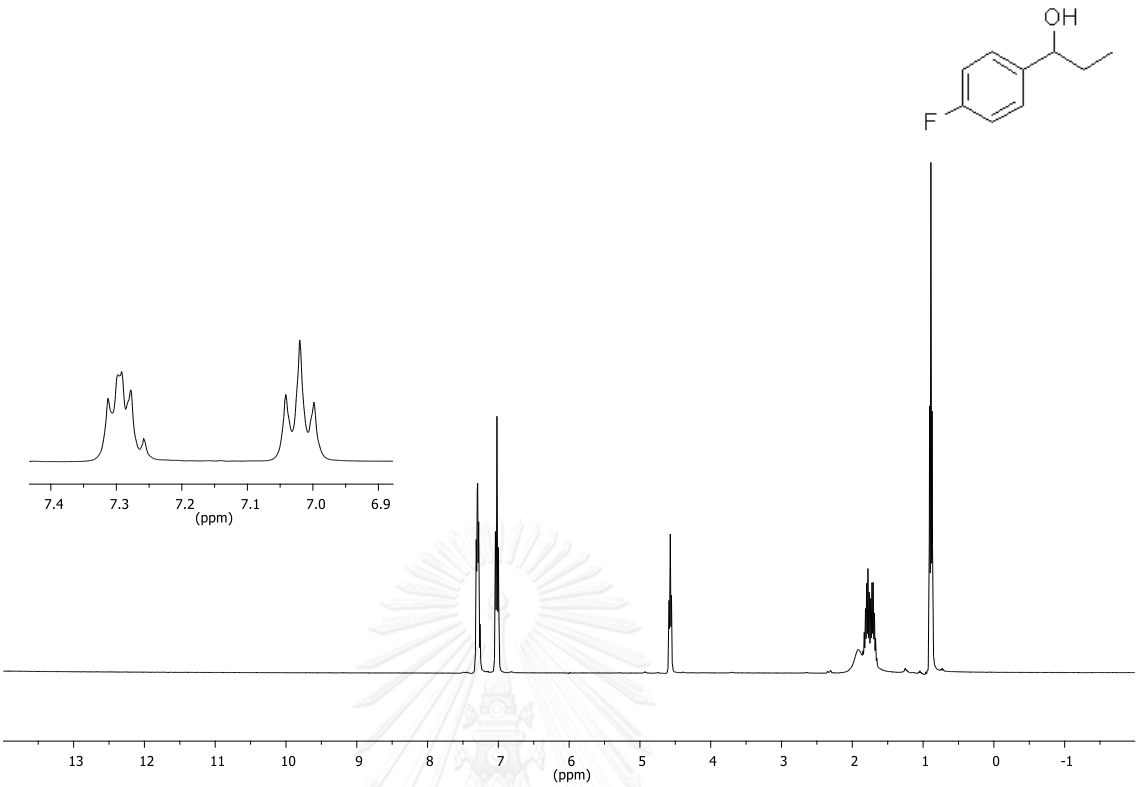

Figure A6 NMR spectrum of **12p**; ^{1}H NMR ($CDCl_3$, 400 MHz) **δ**(ppm): 0.89 (3H, t, *J* = 7.4 Hz, $CH_2C\underline{H}_3$), 1.86 – 1.61 (2H, m, $C\underline{H}_2CH_3$), 1.92 (1H, s, OH), 4.57 (1H, t, *J* = 6.5 Hz, C<u>H</u>OH), 7.02 (2H, t, *J* = 8.6 Hz, Ar<u>H</u>), 7.29 (2H, dt, *J* = 13.5, 6.9 Hz, Ar<u>H</u>).

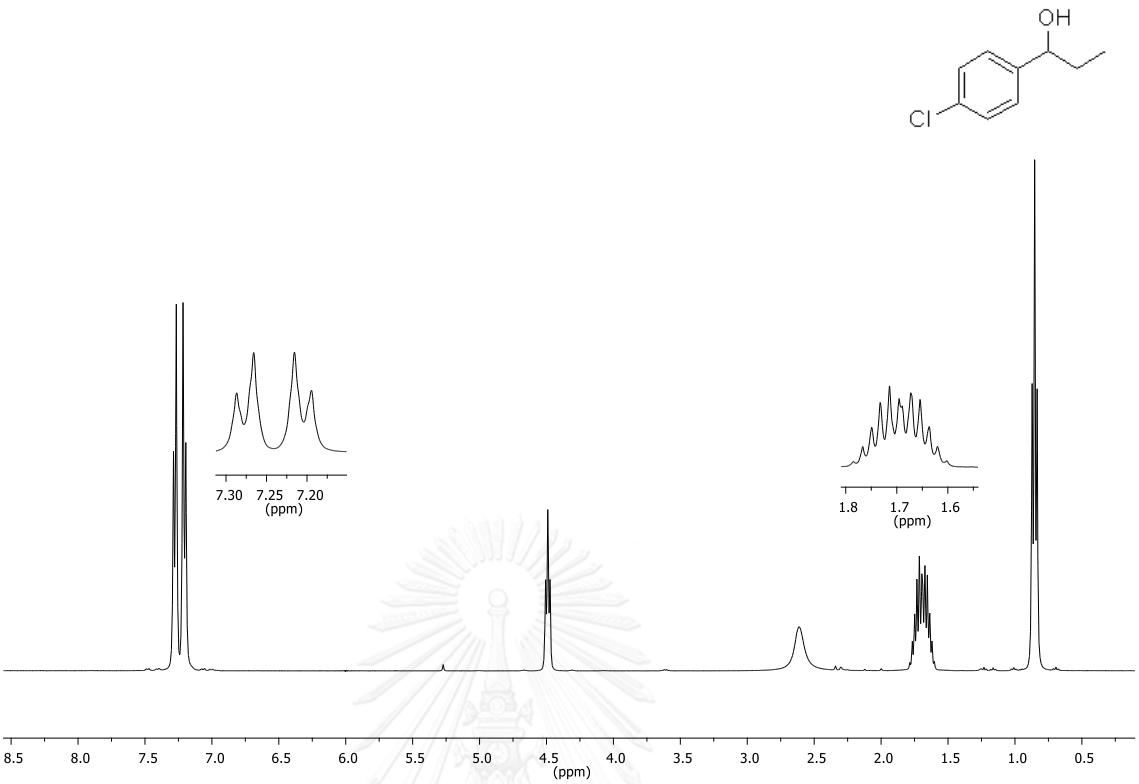

Figure A7 NMR spectrum of **13p**; ^{1}H NMR ($CDCl_3$, 400 MHz) **δ**(ppm): 0.85 (3H, t, *J* = 7.4 Hz, $CH_2C\underline{H}_3$), 1.92 – 1.43 (2H, m, $C\underline{H}_2CH_3$), 2.61 (1H, s, O<u>H</u>), 4.49 (1H, t, *J* = 6.5 Hz, C<u>H</u>OH), 7.24 (4H, dd, *J* = 28.5, 8.4 Hz, Ar<u>H</u>).

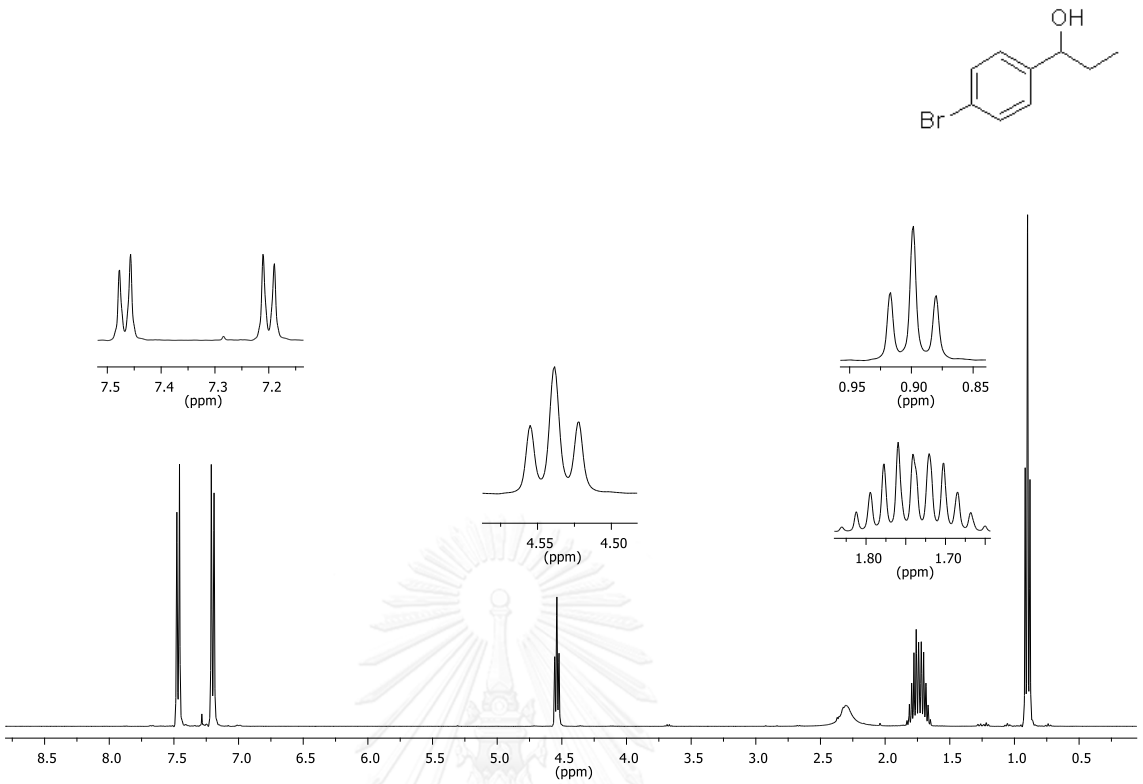

Figure A8 NMR spectrum of **14p**; ^{1}H NMR ($CDCl_3$, 400 MHz) **δ**(ppm): 0.90 (3H, t, *J* = 7.4 Hz, $CH_2C\underline{H}_3$), 1.88 – 1.60 (2H, m, $C\underline{H}_2CH_3$), 2.48 – 2.11 (1H, s, O<u>H</u>), 4.54 (1H, t, *J* = 6.5 Hz, C<u>H</u>OH), 7.33 (4H, d, *J* = 106.9, 8.3 Hz, ArH).

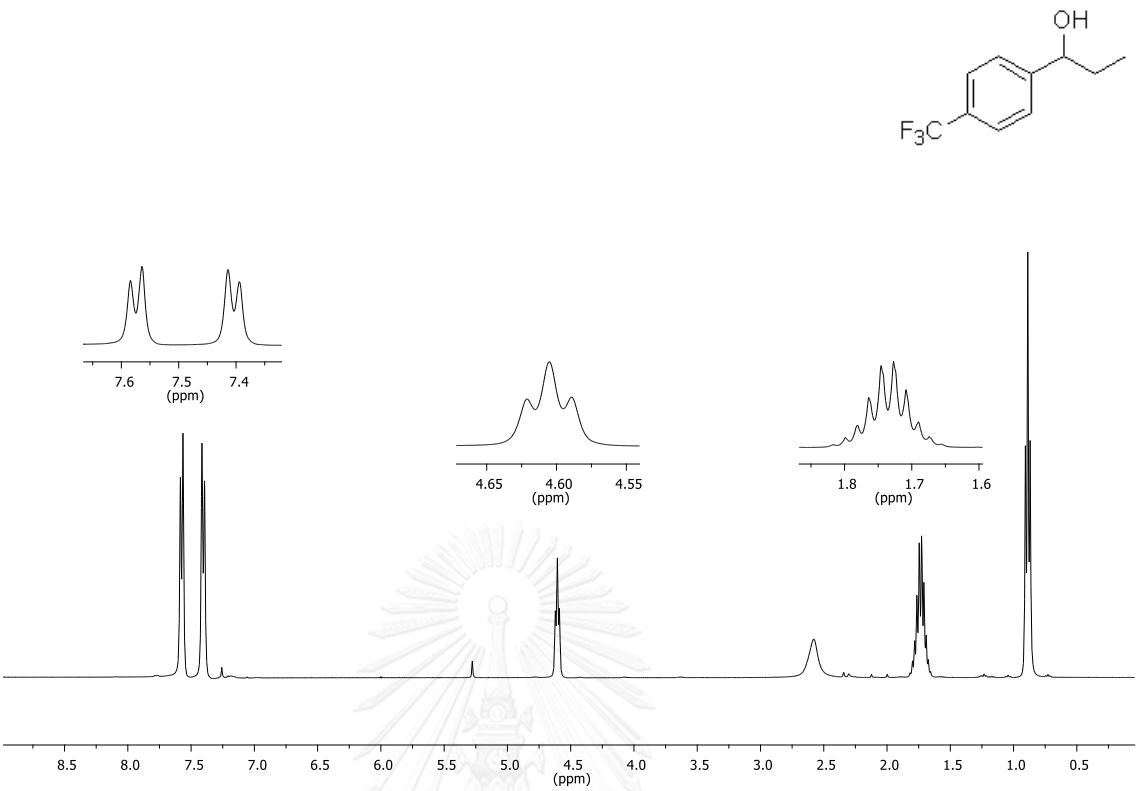

Figure A9 NMR spectrum of **15p**; ^{1}H NMR ($CDCl_3$, 400 MHz) **δ**(ppm); 0.89 (t, *J* = 7.4 Hz, CH_2CH_3, 1.89 – 1.54 (2H, m, CH_2CH_3), 2.58 (1H, s, OH), 4.61 (1H, t, *J* = 6.4 Hz, CHOH), 7.49 (4H, dd, *J* = 68.1, 8.0 Hz, ArH).

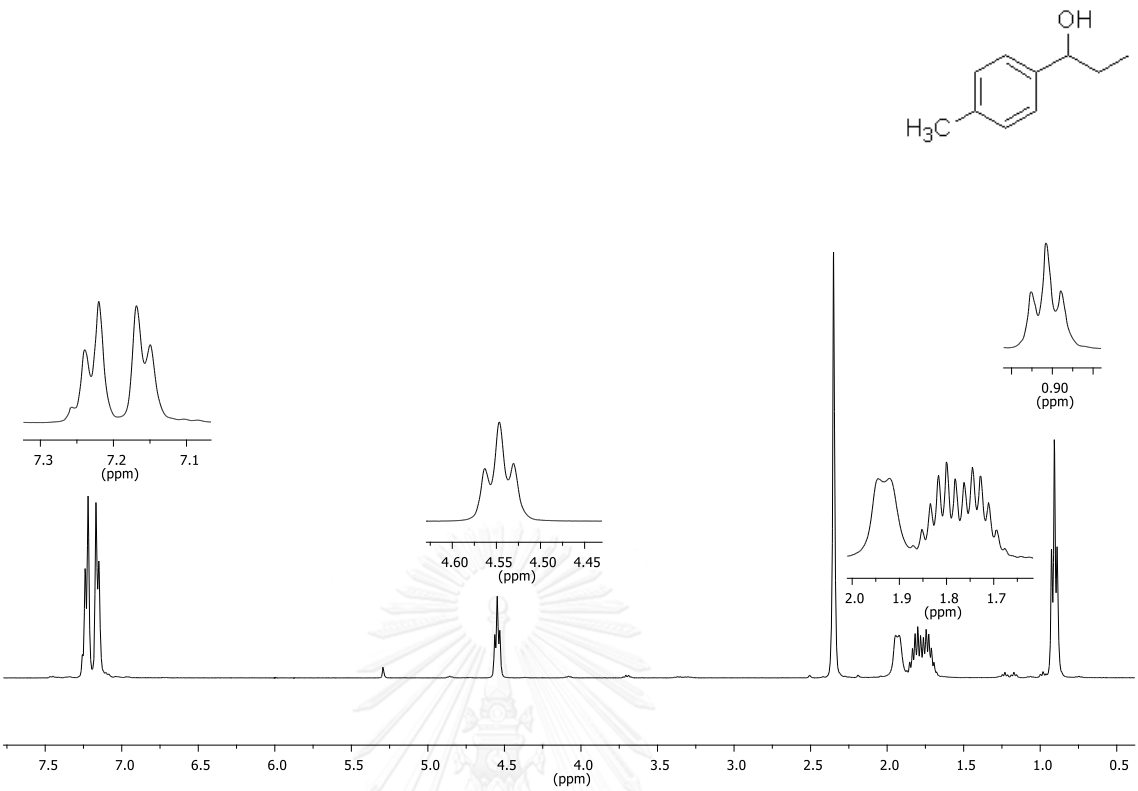

Figure A10 NMR spectrum of **16p**; ^{1}H NMR ($CDCl_3$, 400 MHz) **δ**(ppm); 0.91 (3H, t, *J* = 7.3 Hz, $CH_2C\underline{H}_3$), 1.77 (2H, dtd, *J* = 27.8, 13.9, 7.0 Hz, $C\underline{H}_2CH_3$), 1.93 (1H, d, *J* = 9.9 Hz, O<u>H</u>), 2.35 (3H, s, $ArC\underline{H}_3$), 4.55 (1H, t, *J* = 6.5 Hz, C<u>H</u>OH), 7.19 (4H, dd, *J* = 28.2, 7.6 Hz, Ar<u>H</u>).

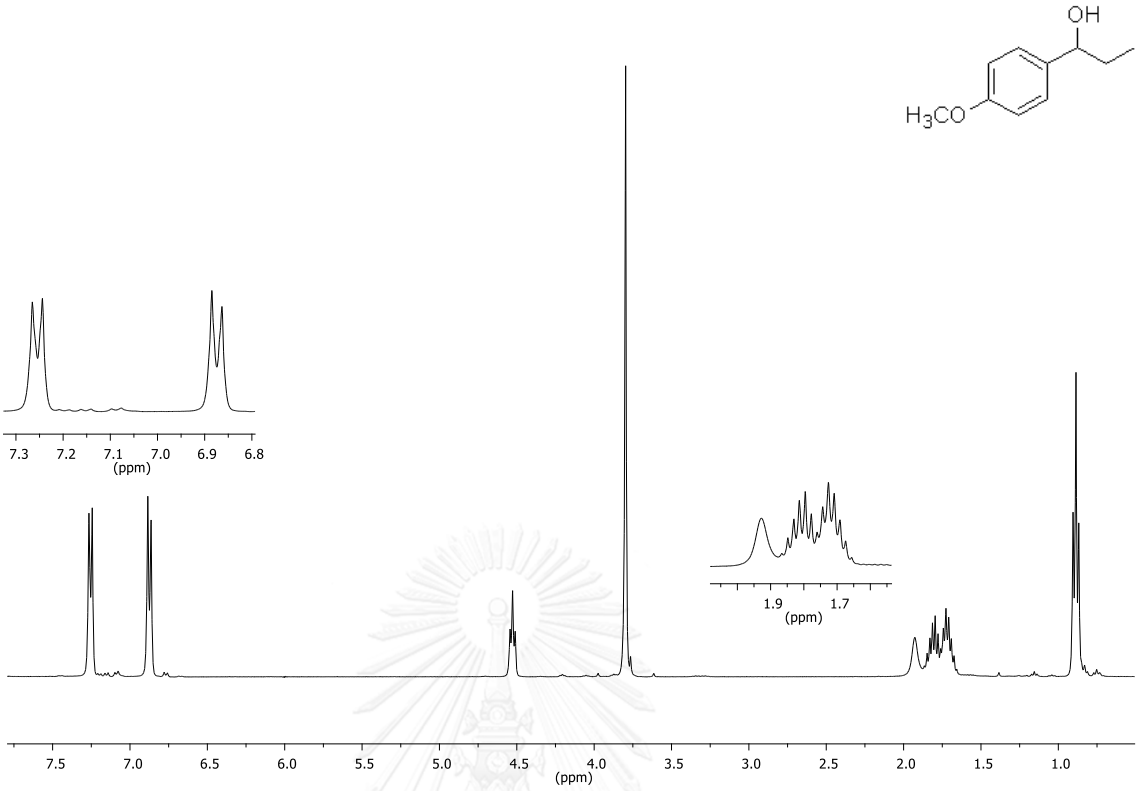

Figure A11 NMR spectrum of **17p**; ^{1}H NMR ($CDCl_3$, 400 MHz) **δ**(ppm); 0.89 (3H, t, *J* = 7.4 Hz, $CH_2C\underline{H}_3$). 1.87 – 1.65 (m, 2H, $C\underline{H}_2CH_3$), 1.93 (1H, s, O<u>H</u>), 3.80 (3H, s, $OC\underline{H}_3$), 4.53 (1H, t, *J* = 6.6 Hz, C<u>H</u>OH), 7.06 (4H, d, *J* = 152.1, 8.5 Hz, Ar<u>H</u>).

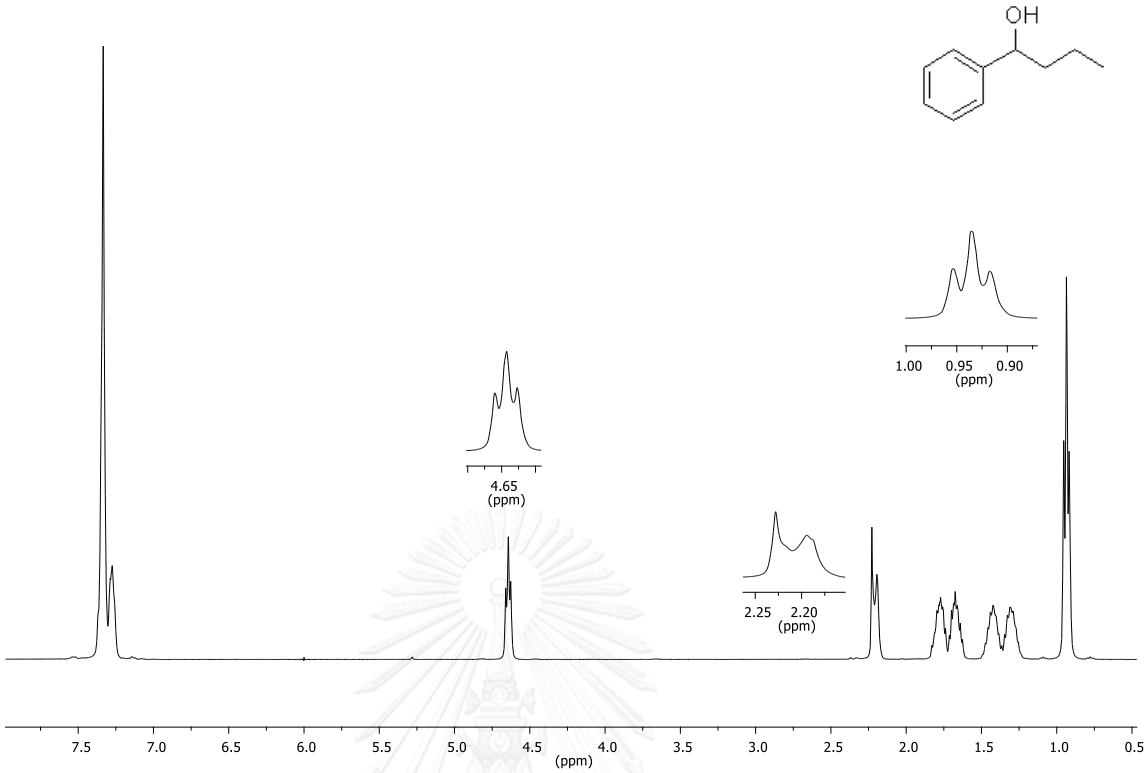

Figure A12 NMR spectrum of **22**; ^{1}H NMR ($CDCl_3$, 400 MHz) **δ**(ppm): 0.94 (3H, t, *J* = 7.2 Hz, $CH_2C\underline{H}_3$), 1.53 – 1.21 (2H, m, $CH_2C\underline{H}_2CH_3$), 1.89 – 1.57 (2H, m, $CHC\underline{H}_2CH_2$), 2.21 (1H, d, *J* = 13.4 Hz, $CHO\underline{H}$), 4.64 (1H, t, *J* = 6.6 Hz, $C\underline{H}OH$), 7.33 (4H, s, Ar$\underline{H}$).

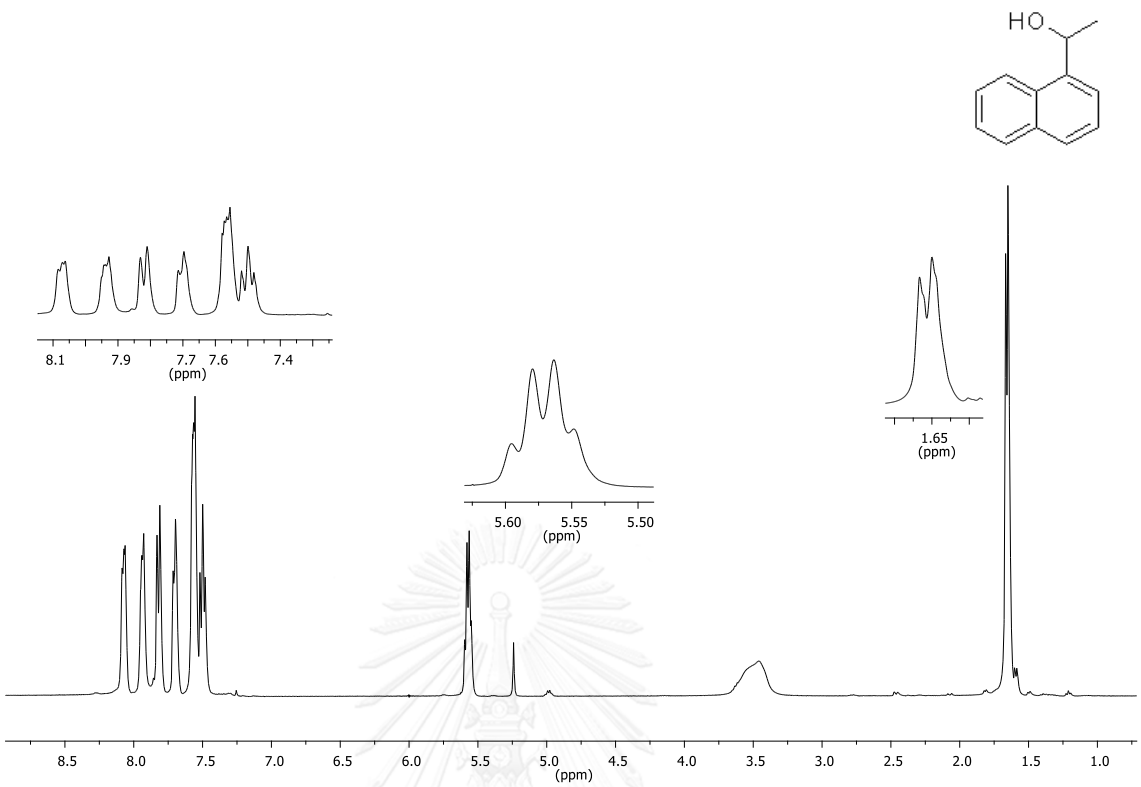

Figure A13 NMR spectrum of **25**; ^{1}H NMR ($CDCl_3$, 400 MHz) **δ**(ppm): 1.66 (3H, d, *J* = 6.6 Hz, CHC<u>H</u>$_3$), 3.46 (1H, s, O<u>H</u>), 5.58 (1H, q, CHO<u>H</u>), 7.50 (1H, t, *J* = 7.6 Hz, Ar<u>H</u>), 7.59 – 7.53 (2H, m, Ar<u>H</u>), 7.71 (1H, d, *J* = 6.8 Hz, Ar<u>H</u>), 7.82 (1H, d, *J* = 8.2 Hz, Ar<u>H</u>), 7.98 – 7.88 (1H, m, Ar<u>H</u>), 8.10 – 8.03 (1H, m, Ar<u>H</u>).

Table A1 Slope and y-intercept from ln k′ versus 1/T plots of 40 alcohols on the BSiAc column.

analyte	temperature range (°C)	less retained enantiomer			more retained enantiomer		
		ln k′ = m(1/T)+C		R^2	ln k′ = m(1/T)+C		R^2
		m	C		m	C	
1	90-150	7687.1	-18.164	0.9983	8029.3	-18.983	0.9978
2o	90-160	6751.6	-16.024	0.9983	6871.2	-16.302	0.9985
2m	100-160	8114.9	-18.821	0.9979	8346.6	-19.366	0.9974
2p	100-160	8140.9	-18.881	0.9984	8341.5	-19.352	0.9981
3o	110-170	6551.5	-14.694	0.9996	6679.2	-14.984	0.9996
3m	120-180	8151.2	-17.882	0.9981	8398.0	-18.438	0.9975
3p	120-190	8337.6	-18.155	0.9975	8489.9	-18.493	0.9971
4o	120-180	6667.2	-14.519	0.9996	6769.0	-14.748	0.9995
4m	120-190	8187.2	-17.487	0.9976	8426.1	-18.016	0.9968
4p	130-200	8417.1	-17.841	0.9981	8550.0	-18.131	0.9977
5o	90-150	6172.0	-14.764	0.9994	6330.9	-15.139	0.9994
5m	100-160	7949.1	-18.440	0.9981	8275.7	-19.205	0.9975
5p	110-170	8416.6	-19.214	0.9985	8584.6	-19.603	0.9982
6o	90-160	6613.6	-15.205	0.9991	6613.6	-15.205	0.9991
6m	100-160	7437.5	-17.151	0.9980	7832.1	-18.075	0.9971
6p	110-170	7623.0	-17.417	0.9981	7964.5	-18.196	0.9976
7o	90-170	6877.9	-15.307	0.9994	6909.3	-15.381	0.9993
7m	120-190	7995.0	-17.388	0.9975	8208.9	-17.863	0.9968
7p	130-190	7824.2	-16.932	0.9984	8040.5	-17.407	0.9980
8o	130-200	7573.8	-15.706	0.9993	7706.7	-15.990	0.9992
8m	150-220	9057.9	-18.052	0.9981	9057.9	-18.052	0.9981
8p	150-220	10620.0	-20.942	0.9982	10670.0	-21.047	0.9980
9	100-160	7657.5	-17.825	0.9986	7870.5	-18.329	0.9982
10	90-160	7721.8	-18.290	0.9981	7896.5	-18.703	0.9978

analyte	temperature range (°C)	less retained enantiomer			more retained enantiomer		
		ln k′ = m(1/T)+C		R^2	ln k′ = m(1/T)+C		R^2
		m	C		m	C	
11	100-160	7150.4	-16.533	0.9983	7335.1	-16.971	0.9976
12p	100-170	7795.4	-17.744	0.9978	8008.2	-18.237	0.9971
13p	120-190	8226.3	-17.640	0.9978	8365.5	-17.948	0.9974
14p	130-200	8272.3	-17.258	0.9981	8382.1	-17.497	0.9977
15p	110-170	8406.3	-18.915	0.9980	8578.2	-19.312	0.9977
16p	110-170	7327.3	-16.462	0.9982	7565.8	-17.010	0.9976
17p	120-190	7885.9	-16.796	0.9984	8052.4	-17.167	0.9978
18	100-160	7247.1	-16.824	0.9980	7362.7	-17.095	0.9979
19	80-160	6978.5	-16.006	0.9982	6978.5	-16.006	0.9982
20	100-160	6741.1	-15.612	0.9983	6906.5	-16.003	0.9978
21	90-160	6669.3	-15.053	0.9993	6703.8	-15.137	0.9991
22	100-170	7191.4	-16.212	0.9985	7221.8	-16.284	0.9983
23	110-170	7009.1	-15.673	0.9987	7104.1	-15.875	0.9989
24	120-180	6793.3	-14.664	0.9993	6886.0	-14.870	0.9993
25	130-210	7712.0	-15.482	0.9995	7721.8	-15.503	0.9994
26	140-220	8580.8	-17.163	0.9978	8742.8	-17.504	0.9972

Table A2 Thermodynamic parameters of 40 alcohols on the BSiAc column.

analyte	enthalpic term (kcal/mol)			entropic term (cal/mol·K)		
	$-\Delta H_1$	$-\Delta H_2$	$-\Delta\Delta H$	$-\Delta S_1$	$-\Delta S_2$	$-\Delta\Delta S$
1	15.27	15.95	0.68	25.12	26.75	1.63
2o	13.42	13.65	0.24	20.87	21.42	0.55
2m	16.12	16.58	0.46	26.43	27.51	1.08
2p	16.18	16.57	0.40	26.55	27.48	0.94
3o	13.02	13.27	0.25	18.23	18.80	0.58
3m	16.20	16.69	0.49	24.56	25.67	1.10
3p	16.57	16.87	0.30	25.10	25.77	0.67
4o	13.25	13.45	0.20	17.88	18.33	0.46
4m	16.27	16.74	0.47	23.78	24.83	1.05
4p	16.72	16.99	0.26	24.48	25.06	0.58
5o	12.26	12.58	0.32	18.36	19.11	0.75
5m	15.79	16.44	0.65	25.67	27.19	1.52
5p	16.72	17.06	0.33	27.21	27.98	0.77
6o	13.14	13.14	0.00	19.24	19.24	0.00
6m	14.78	15.56	0.78	23.11	24.94	1.84
6p	15.15	15.83	0.68	23.64	25.18	1.55
7o	13.67	13.73	0.06	19.44	19.59	0.15
7m	15.89	16.31	0.43	23.58	24.52	0.94
7p	15.55	15.98	0.43	22.67	23.62	0.94
8o	15.05	15.31	0.26	20.24	20.80	0.56
8m	18.00	18.00	0.00	24.90	24.90	0.00
8p	21.10	21.20	0.10	30.64	30.85	0.21
9	15.22	15.64	0.42	24.45	25.45	1.00
10	15.34	15.69	0.35	25.37	26.19	0.82
11	14.21	14.57	0.37	21.88	22.75	0.87
12p	15.49	15.91	0.42	24.29	25.27	0.98
13p	16.35	16.62	0.28	24.08	24.69	0.61

analyte	enthalpic term (kcal/mol)			entropic term (cal/mol·K)		
	$-\Delta H_1$	$-\Delta H_2$	$-\Delta\Delta H$	$-\Delta S_1$	$-\Delta S_2$	$-\Delta\Delta S$
14p	16.44	16.66	0.22	23.32	23.80	0.47
15p	16.70	17.04	0.34	26.61	27.40	0.79
16p	14.56	15.03	0.47	21.74	22.83	1.09
17p	15.67	16.00	0.33	22.40	23.14	0.74
18	14.40	14.63	0.23	22.46	23.00	0.54
19	13.87	13.87	0.00	20.83	20.83	0.00
20	13.39	13.72	0.33	20.05	20.83	0.78
21	13.25	13.32	0.07	18.94	19.11	0.17
22	14.29	14.35	0.06	21.24	21.39	0.14
23	13.93	14.12	0.19	20.17	20.57	0.40
24	13.50	13.68	0.18	18.17	18.58	0.41
25	15.32	15.34	0.02	19.79	19.83	0.04
26	17.05	17.37	0.32	23.13	23.81	0.68

Table A3 Slope and y-intercept from ln k′ versus 1/T plots of 34 TFA alcohols on the BSiAc column.

analyte	temperature range (°C)	less retained enantiomer			more retained enantiomer		
		ln k′ = m(1/T)+C		R^2	ln k′ = m(1/T)+C		R^2
		m	C		m	C	
1	60-130	6626.9	-16.644	0.9981	6626.9	-16.644	0.9981
2o	70-130	5984.1	-15.123	0.9992	6136.7	-15.509	0.9990
2m	80-140	7292.8	-18.033	0.9977	7436.8	-18.380	0.9979
2p	80-140	7473.0	-18.376	0.9984	7722.1	-18.962	0.9983
3o	70-140	6319.2	-15.097	0.9993	6319.2	-15.097	0.9993
3m	100-160	6939.5	-16.173	0.9987	7125.9	-16.610	0.9985
3p	110-170	7433.7	-17.107	0.9980	7736.0	-17.791	0.9979
4o	80-150	6412.4	-14.859	0.9996	6412.4	-14.859	0.9969
4m	100-170	7150.0	-16.193	0.9987	7273.4	-16.479	0.9984
4p	110-170	7906.7	-17.726	0.9984	8070.6	-18.100	0.9983
5o	60-130	5978.5	-15.157	0.9994	6034.7	-15.302	0.9993
5m	70-140	7964.5	-19.622	0.9975	7974.1	-19.646	0.9974
5p	90-150	7929.3	-19.226	0.9980	8024.9	-19.439	0.9985
6o	70-140	6117.1	-14.933	0.9993	6236.4	-15.230	0.9990
6m	70-140	6312.1	-15.425	0.9992	6362.4	-15.551	0.9990
6p	70-140	6380.9	-15.490	0.9991	6490.0	-15.761	0.9989
7o	ND	ND	ND	ND	ND	ND	ND
7m	80-160	7070.1	-16.305	0.9988	7085.0	-16.341	0.9986
7p	ND	ND	ND	ND	ND	ND	ND
8o	110-180	7093.7	-15.521	0.9993	7175.5	-15.708	0.9991
8m	140-200	8673.7	-18.185	0.9980	8894.2	-18.649	0.9981
8p	150-220	10078.0	-20.658	0.9978	10127.0	-20.762	0.9975
9	50-110	5939.0	-16.012	0.9992	6115.9	-16.479	0.9992
10	60-130	7128.9	-18.173	0.9985	7144.0	-18.213	0.9983
11	70-140	6090.3	-14.949	0.9994	6196.9	-15.213	0.9993

analyte	temperature range (°C)	less retained enantiomer			more retained enantiomer		
		ln k′ = m(1/T)+C		R^2	ln k′ = m(1/T)+C		R^2
		m	C		m	C	
12p	80-150	6779.4	-16.438	0.9984	7129.5	-17.267	0.9981
13p	110-170	7087.4	-16.107	0.9987	7432.1	-16.888	0.9984
14p	110-180	7388.0	-16.306	0.9985	7595.6	-16.773	0.9981
15p	80-150	7639.0	-18.371	0.9982	7642.1	-18.374	0.9985
16p	80-150	6295.0	-14.942	0.9997	6387.2	-15.165	0.9996
17p	ND	ND	ND	ND	ND	ND	ND
18	90-150	7230.4	-17.343	0.9977	7625.7	-18.270	0.9971
19	70-140	6047.6	-14.668	0.9995	6103.9	-14.809	0.9994
20	ND	ND	ND	ND	ND	ND	ND
21	70-140	6097.0	-14.585	0.9997	6144.0	-14.703	0.9996
22	70-150	6279.4	-14.989	0.9995	6321.5	-15.092	0.9993
23	ND	ND	ND	ND	ND	ND	ND
24	ND	ND	ND	ND	ND	ND	ND
25	110-190	7270.2	-15.389	0.9994	7270.2	-15.389	0.9994
26	120-190	7411.3	-15.566	0.9995	7411.3	-15.566	0.9995

Note: ND = Not determined.

Table A4 Thermodynamic parameters of 34 TFA alcohols on the BSiAc column.

analyte	enthalpic term (kcal/mol)			entropic term (cal/mol·K)		
	$-\Delta H_1$	$-\Delta H_2$	$-\Delta\Delta H$	$-\Delta S_1$	$-\Delta S_2$	$-\Delta\Delta S$
1	13.17	13.17	0.00	22.10	22.10	0.00
2o	11.89	12.19	0.30	19.08	19.85	0.77
2m	14.49	14.78	0.29	24.86	25.55	0.69
2p	14.85	15.34	0.49	25.54	26.71	1.16
3o	12.56	12.56	0.00	19.03	19.03	0.00
3m	13.79	14.16	0.37	21.16	22.03	0.87
3p	14.77	15.37	0.60	23.02	24.38	1.36
4o	12.74	12.74	0.00	18.55	18.55	0.00
4m	14.21	14.45	0.25	21.20	21.77	0.57
4p	15.71	16.04	0.33	24.25	24.99	0.74
5o	11.88	11.99	0.11	19.15	19.43	0.29
5m	15.83	15.84	0.02	28.02	28.07	0.05
5p	15.76	15.95	0.19	27.23	27.65	0.42
6o	12.15	12.39	0.24	18.70	19.29	0.59
6m	12.54	12.64	0.10	19.68	19.93	0.25
6p	12.68	12.90	0.22	19.81	20.35	0.54
7o	ND	ND	ND	ND	ND	ND
7m	14.05	14.08	0.03	21.43	21.50	0.07
7p	ND	ND	ND	ND	ND	ND
8o	14.10	14.26	0.16	19.87	20.24	0.37
8m	17.23	17.67	0.44	25.16	26.08	0.92
8p	20.02	20.12	0.10	30.08	30.28	0.21
9	11.80	12.15	0.35	20.84	21.77	0.93
10	14.17	14.20	0.03	25.14	25.22	0.08
11	12.10	12.31	0.21	18.73	19.26	0.52
12p	13.47	14.17	0.70	21.69	23.34	1.65
13p	14.08	14.77	0.68	21.03	22.59	1.55

analyte	enthalpic term (kcal/mol)			entropic term (cal/mol·K)		
	$-\Delta H_1$	$-\Delta H_2$	$-\Delta\Delta H$	$-\Delta S_1$	$-\Delta S_2$	$-\Delta\Delta S$
14p	14.68	15.09	0.41	21.43	22.36	0.93
15p	15.18	15.18	0.01	25.53	25.54	0.01
16p	12.51	12.69	0.18	18.72	19.16	0.44
17p	ND	ND	ND	ND	ND	ND
18	14.37	15.15	0.79	23.49	25.33	1.84
19	12.02	12.13	0.11	18.17	18.45	0.28
20	ND	ND	ND	ND	ND	ND
21	12.11	12.21	0.09	18.01	18.24	0.23
22	12.48	12.56	0.08	18.81	19.02	0.20
23	ND	ND	ND	ND	ND	ND
24	ND	ND	ND	ND	ND	ND
25	14.45	14.45	0.00	19.61	19.61	0.00
26	14.73	14.73	0.00	19.96	19.96	0.00

Note: ND = Not determined.

Table A5 Slope and y-intercept from ln k′ versus 1/T plots of 39 TMS alcohols on the BSiAc column.

analyte	temperature range (°C)	less retained enantiomer			more retained enantiomer		
		ln k′ = m(1/T)+C		R^2	ln k′ = m(1/T)+C		R^2
		m	C		m	C	
1	60-130	5770.9	-14.201	0.9996	5845.6	-14.392	0.9995
2o	60-130	5740.2	-14.224	0.9997	5766.6	-14.292	0.9996
2m	70-140	5859.3	-14.295	0.9995	5999.0	-14.642	0.9993
2p	80-140	5817.1	-14.178	0.9997	6040.0	-14.719	0.9995
3o	70-150	6029.0	-14.136	0.9995	6029.0	-14.136	0.9995
3m	80-160	6291.6	-14.411	0.9997	6332.5	-14.510	0.9996
3p	100-160	6297.7	-14.328	0.9997	6506.0	-14.814	0.9995
4o	80-160	6187.6	-14.101	0.9997	6187.6	-14.101	0.9997
4m	90-170	6498.3	-14.450	0.9997	6502.0	-14.459	0.9996
4p	110-170	6543.0	-14.433	0.9998	6667.7	-14.721	0.9997
5o	50-130	5785.9	-14.423	0.9995	5785.9	-14.423	0.9995
5m	70-140	6010.8	-14.748	0.9996	6066.6	-14.889	0.9994
5p	70-140	6279.0	-15.262	0.9994	6311.0	-15.342	0.9993
6o	70-140	5963.8	-14.217	0.9997	5963.8	-14.217	0.9997
6m	70-140	6028.7	-14.410	0.9997	6028.7	-14.410	0.9997
6p	70-150	6062.3	-14.382	0.9996	6105.5	-14.488	0.9995
7o	80-160	6432.9	-14.764	0.9996	6432.9	-14.764	0.9996
7m	90-170	6701.7	-15.084	0.9995	6701.7	-15.084	0.9995
7p	110-170	6704.0	-14.950	0.9997	6812.0	-15.199	0.9997
8o	100-180	6673.5	-14.488	0.9997	6673.0	-14.487	0.9997
8m	120-200	7263.5	-15.104	0.9995	7352.0	-15.298	0.9993
8p	140-200	7732.4	-15.877	0.9992	7945.1	-16.327	0.9991
9	60-130	5917.5	-14.683	0.9996	5917.5	-14.683	0.9996
10	50-130	5860.3	-14.790	0.9995	5860.3	-14.790	0.9995
11	70-140	5906.5	-14.189	0.9998	5930.4	-14.249	0.9998

analyte	temperature range (°C)	less retained enantiomer			more retained enantiomer		
		ln k′ = m(1/T)+C		R^2	ln k′ = m(1/T)+C		R^2
		m	C		m	C	
12p	80-150	6015.0	-14.332	0.9998	6154.5	-14.671	0.9996
13p	100-170	6481.9	-14.473	0.9996	6609.5	-14.769	0.9994
14p	100-180	6767.1	-14.679	0.9995	6851.3	-14.873	0.9993
15p	70-140	6466.4	-15.418	0.9996	6466.4	-15.418	0.9996
16p	80-150	6294.0	-14.660	0.9998	6311.6	-14.704	0.9997
17p	100-170	6933.2	-15.241	0.9996	7000.1	-15.397	0.9995
18	70-150	6027.8	-14.243	0.9995	6040.4	-14.274	0.9993
19	70-140	6005.0	-14.251	0.9997	6005.0	-14.251	0.9997
20	ND	ND	ND	ND	ND	ND	ND
21	70-150	6035.3	-14.144	0.9995	6035.3	-14.144	0.9995
22	80-150	6180.8	-14.443	0.9997	6180.8	-14.443	0.9997
23	90-160	6392.6	-14.416	0.9997	6392.6	-14.416	0.9997
24	100-170	6698.8	-14.617	0.9998	6698.8	-14.617	0.9998
25	120-190	7071.7	-14.729	0.9997	7071.7	-14.729	0.9997
26	120-200	7265.7	-14.954	0.9997	7265.7	-14.954	0.9997

Note: ND = Not determined.

Table A6 Thermodynamic parameters of 39 TMS alcohols on the BSiAc column.

analyte	enthalpic term (kcal/mol)			entropic term (cal/mol·K)		
	$-\Delta H_1$	$-\Delta H_2$	$-\Delta\Delta H$	$-\Delta S_1$	$-\Delta S_2$	$-\Delta\Delta S$
1	11.47	11.62	0.15	17.25	17.63	0.38
2o	11.41	11.46	0.05	17.29	17.43	0.14
2m	11.64	11.92	0.28	17.43	18.12	0.69
2p	11.56	12.00	0.44	17.20	18.28	1.07
3o	11.98	11.98	0.00	17.12	17.12	0.00
3m	12.50	12.58	0.08	17.66	17.86	0.20
3p	12.51	12.93	0.41	17.50	18.46	0.97
4o	12.29	12.29	0.00	17.05	17.05	0.00
4m	12.91	12.92	0.01	17.74	17.76	0.02
4p	13.00	13.25	0.25	17.71	18.28	0.57
5o	11.50	11.50	0.00	17.69	17.69	0.00
5m	11.94	12.05	0.11	18.33	18.61	0.28
5p	12.48	12.54	0.06	19.35	19.51	0.16
6o	11.85	11.85	0.00	17.28	17.28	0.00
6m	11.98	11.98	0.00	17.66	17.66	0.00
6p	12.05	12.13	0.09	17.61	17.82	0.21
7o	12.78	12.78	0.00	18.36	18.36	0.00
7m	13.32	13.32	0.00	19.00	19.00	0.00
7p	13.32	13.54	0.21	18.73	19.23	0.49
8o	13.26	13.26	0.00	17.82	17.81	0.00
8m	14.43	14.61	0.18	19.04	19.43	0.39
8p	15.36	15.79	0.42	20.58	21.47	0.89
9	11.76	11.76	0.00	18.20	18.20	0.00
10	11.64	11.64	0.00	18.42	18.42	0.00
11	11.74	11.78	0.05	17.22	17.34	0.12
12p	11.95	12.23	0.28	17.51	18.18	0.67
13p	12.88	13.13	0.25	17.79	18.37	0.59

analyte	enthalpic term (kcal/mol)			entropic term (cal/mol·K)		
	$-\Delta H_1$	$-\Delta H_2$	$-\Delta\Delta H$	$-\Delta S_1$	$-\Delta S_2$	$-\Delta\Delta S$
14p	13.45	13.61	0.17	18.20	18.58	0.39
15p	12.85	12.85	0.00	19.66	19.66	0.00
16p	12.51	12.54	0.03	18.16	18.25	0.09
17p	13.78	13.91	0.13	19.31	19.62	0.31
18	11.98	12.00	0.03	17.33	17.39	0.06
19	11.93	11.93	0.00	17.35	17.35	0.00
20	ND	ND	ND	ND	ND	ND
21	11.99	11.99	0.00	17.13	17.13	0.00
22	12.28	12.28	0.00	17.73	17.73	0.00
23	12.70	12.70	0.00	17.67	17.67	0.00
24	13.31	13.31	0.00	18.07	18.07	0.00
25	14.05	14.05	0.00	18.30	18.30	0.00
26	14.44	14.44	0.00	18.74	18.74	0.00

Note: ND = Not determined.

Table A7 The highest operating column temperature and chromatographic parameters for all alcohols and derivatives where enantiomers are baseline separated (Rs ≥ 1.5) on the BSiAc column.

NO.	alcohol				TFA				TMS			
	T	k_2'	α	R_s	T	k_2'	α	R_s	T	k_2'	α	R_s
1	120	3.987	1.042	1.73	60	28.285	1.000	NS	60	24.200	1.037	2.27
2o	110	4.962	1.036	1.58	80	6.412	1.047	2.17	60	21.060	1.016	0.94
2m	120	6.222	1.040	1.79	100	4.501	1.040	1.70	90	6.376	1.034	1.63
2p	120	6.202	1.036	1.63	120	1.900	1.047	1.66	100	4.260	1.050	2.22
3o	120	7.404	1.034	1.55	70	29.347	1.000	NS	80	19.013	1.000	NS
3m	130	10.865	1.056	2.60	120	4.388	1.034	1.65	80	32.079	1.025	1.84
3p	130	13.099	1.040	2.02	140	2.423	1.045	1.80	120	5.574	1.039	1.97
4o	120	12.076	1.032	1.48	80	28.278	1.000	NS	80	31.740	1.000	NS
4m	140	10.417	1.043	2.00	110	12.263	1.036	1.98	90	32.664	1.000	NS
4p	140	13.042	1.033	1.61	130	6.546	1.030	1.58	120	9.362	1.030	1.62
5o	110	3.915	1.039	1.59	60	17.341	1.027	1.38	50	34.027	1.000	NS
5m	130	3.540	1.036	1.52	70	41.548	1.012	NS	70	16.955	1.028	1.45
5p	120	9.285	1.039	1.90	110	4.348	1.040	1.75	70	22.098	1.015	0.90
6o	90	21.448	1.000	NS	80	11.433	1.043	2.22	70	24.647	1.000	NS
6m	130	3.646	1.043	1.70	70	20.995	1.025	1.48	70	24.568	1.000	NS
6p	140	2.800	1.042	1.49	80	13.803	1.040	2.15	70	28.873	1.024	1.74
7o	100	23.424	1.013	0.84	ND	ND	ND	ND	80	33.011	1.000	NS
7m	140	7.084	1.036	1.57	90	24.482	1.000	NS	90	30.608	1.000	NS
7p	150	4.753	1.032	1.46	ND	ND	ND	ND	110	13.508	1.036	2.00
8o	140	14.493	1.038	1.87	110	21.471	1.032	1.94	100	30.946	1.000	NS
8m	150	30.658	1.000	NS	170	3.965	1.032	1.54	130	18.953	1.027	1.59
8p	160	36.483	1.011	0.85	150	25.931	1.019	1.27	160	7.296	1.039	2.06
9	120	5.233	1.033	1.57	70	3.767	1.048	1.72	60	22.453	1.000	NS
10	110	6.545	1.042	1.95	60	27.721	1.012	0.78	50	29.851	1.000	NS
11	110	8.742	1.044	2.23	80	10.333	1.039	2.00	70	21.234	1.014	0.83
12p	120	8.198	1.044	2.19	120	2.282	1.057	1.54	100	6.094	1.032	1.54
13p	130	16.384	1.037	2.01	140	2.908	1.047	2.00	110	12.009	1.037	2.00
14p	140	16.435	1.028	1.53	130	7.558	1.043	2.24	110	20.448	1.028	1.65
15p	120	12.262	1.041	2.18	150	6.109	1.010	0.55	70	31.687	1.000	NS
16p	130	5.499	1.037	1.74	90	11.312	1.031	1.62	80	24.326	1.010	0.71
17p	130	16.434	1.043	2.32	ND	ND	ND	ND	100	29.762	1.027	1.85
18	100	14.808	1.041	2.10	130	1.834	1.048	1.72	70	29.752	1.018	1.29
19	90	25.688	1.000	NS	70	20.481	1.025	1.48	70	26.859	1.000	NS
20	110	7.497	1.040	2.09	ND	ND	ND	ND	ND	ND	ND	ND

NO.	alcohol				TFA				TMS			
	T	k_2'	α	R_s	T	k_2'	α	R_s	T	k_2'	α	R_s
21	90	29.501	1.022	1.45	70	25.434	1.022	1.34	80	19.229	1.000	NS
22	100	22.955	1.012	0.79	70	29.787	1.023	1.53	80	22.013	1.000	NS
23	120	8.969	1.041	1.73	ND	ND	ND	ND	90	24.950	1.000	NS
24	120	14.556	1.030	1.36	ND	ND	ND	ND	100	28.910	1.000	NS
25	130	40.201	1.008	NS	110	38.201	1.000	NS	120	26.746	1.000	NS
26	160	14.083	1.031	1.61	120	27.898	1.000	NS	120	21.738	1.000	NS

Note: ND = Not determined.

NS = No enantioseparation or baseline separation could not be observed.

Table A8 Relationship between Rs (y) versus k'_2 (x) for alcohols and the calculated k'_2 values at baseline separation.

analyte	polynomial equation (order = 2) $y = ax^2+bx+c$			x (k'_2)
	a	b	c	
1	-0.0035	0.4487	-0.0477	3.547
2o	-0.0098	0.3126	0.2283	4.786
2m	-0.0048	0.3369	-0.1395	5.261
2p	-0.0036	0.2698	0.0625	5.773
3o	-0.0068	0.2599	-0.0032	7.104
3m	0.0005	0.2291	0.0391	6.290
3p	0.0003	0.1289	0.2493	9.493
4o	-0.0033	0.1505	0.1115	12.842
4m	0.0001	0.1820	0.0659	7.846
4p	-0.0005	0.1182	0.1468	12.064
5o	-0.0088	0.4048	0.0891	3.799
5m	-0.0074	0.4888	-0.1737	3.623
5p	-0.0041	0.2576	-0.1409	7.194
6o	NS	NS	NS	NS
6m	-0.0065	0.5762	-0.3481	3.333
6p	-0.0154	0.6822	-0.2675	2.763
7o	-0.0008	0.0658	-0.2768	NS
7m	0.0019	0.1555	0.3304	6.934
7p	-0.0053	0.3121	-0.0020	5.287
8o	-0.0009	0.1202	0.2924	10.943
8m	NS	NS	NS	NS
8p	-0.0007	0.0923	-1.5462	NS
9	-0.0069	0.3838	-0.2345	4.962
10	-0.0039	0.2796	0.1773	5.092
11	-0.0054	0.3473	-0.4116	6.079

analyte	polynomial equation (order = 2) $y = ax^2+bx+c$			x (k'_2)
	a	b	c	
12p	-0.0005	0.2246	0.2201	5.773
13p	-0.0004	0.1211	0.1151	11.904
14p	-0.0002	0.1003	-0.0729	16.206
15p	-0.0016	0.1916	0.0878	7.890
16p	-0.0048	0.3877	-0.2956	4.933
17p	0.0005	0.1338	-0.0360	11.026
18	-0.0047	0.2021	0.0813	8.835
19	NS	NS	NS	NS
20	-0.0075	0.3878	-0.4033	5.491
21	-0.0028	0.1875	-1.6496	NS
22	-0.0055	0.2212	-1.3931	NS
23	-0.0046	0.1839	0.5001	6.491
24	-0.0012	0.085	0.3714	17.701
25	NS	NS	NS	NS
26	-0.0007	0.1339	-0.2327	13.959

Note: NS = No enantioseparation or baseline separation could not be observed.

Table A9 Relationship between Rs (y) versus k'_2 (x) for TFA alcohols and the calculated k'_2 values at baseline separation.

analyte	polynomial equation (order = 2) $y = ax^2+bx+c$			x (k'_2)
	a	b	c	
1	NS	NS	NS	NS
2o	-0.0136	0.4592	-0.2279	4.314
2m	-0.0108	0.3509	0.2799	3.960
2p	-0.0171	0.6532	0.4256	1.722
3o	NS	NS	NS	NS
3m	-0.0115	0.4544	-0.1744	4.113
3p	-0.0305	0.8972	-0.2193	2.061
4o	NS	NS	NS	NS
4m	-0.0024	0.1923	-0.0038	8.783
4p	-0.0040	0.2403	0.1263	6.398
5o	-0.0016	0.0911	0.2719	21.918
5m	NS	NS	NS	NS
5p	-0.0101	0.2510	0.7456	3.498
6o	-0.0035	0.2387	-0.0419	7.225
6m	-0.0023	0.1327	-0.2892	21.480
6p	0.0006	0.1283	0.2866	9.073
7o	ND	ND	ND	ND
7m	NS	NS	NS	NS
7p	ND	ND	ND	ND
8o	-0.0009	0.1050	0.0720	15.717
8m	-0.0081	0.3698	0.1771	3.913
8p	-0.0046	0.2206	-1.4387	NS
9	-0.0159	0.4818	0.0877	3.288
10	NS	NS	NS	NS
11	-0.0040	0.2259	0.1323	6.897

analyte	polynomial equation (order = 2) $y = ax^2+bx+c$			x (k'_2)
	a	b	c	
12p	-0.0125	0.7308	-0.1197	2.307
13p	-0.0278	0.9474	-0.6046	2.389
14p	-0.0041	0.3202	-0.0289	5.109
15p	NS	NS	NS	NS
16p	-0.0016	0.1508	0.1168	10.297
17p	ND	ND	ND	ND
18	-0.0259	1.0030	0.0082	1.549
19	-0.0010	0.0782	0.2425	22.629
20	ND	ND	ND	ND
21	-0.0001	0.0464	0.2297	29.217
22	-0.0006	0.0661	0.0711	29.536
23	ND	ND	ND	ND
24	ND	ND	ND	ND
25	NS	NS	NS	NS
26	NS	NS	NS	NS

Note: ND = Not determined.

NS = No enantioseparation or baseline separation could not be observed.

Table A10 Relationship between Rs (y) versus k'_2 (x) for TMS alcohols and the calculated k'_2 values at baseline separation.

analyte	polynomial equation (order = 2) $y = ax^2+bx+c$			x (k'_2)
	a	b	c	
1	-0.0006	0.0990	0.1583	14.898
2o	-0.0051	0.2129	-1.3083	NS
2m	-0.0039	0.2773	-0.0235	6.000
2p	-0.0135	0.6210	-0.1691	2.866
3o	NS	NS	NS	NS
3m	0.0007	0.0290	0.1857	27.313
3p	0.0076	0.4308	-0.2102	3.725
4o	NS	NS	NS	NS
4m	NS	NS	NS	NS
4p	0.0034	0.2229	-0.1647	6.769
5o	NS	NS	NS	NS
5m	-0.0033	0.1558	-0.2426	18.204
5p	-0.0074	0.2817	-1.6900	NS
6o	NS	NS	NS	NS
6m	NS	NS	NS	NS
6p	0.0006	0.0288	0.3836	25.363
7o	NS	NS	NS	NS
7m	NS	NS	NS	NS
7p	-0.0055	0.2325	-0.1439	8.977
8o	NS	NS	NS	NS
8m	0.0007	0.0545	0.2882	18.050
8p	-0.0050	0.3186	-0.0038	5.134
9	NS	NS	NS	NS
10	NS	NS	NS	NS
11	-0.0029	0.1470	-0.9817	NS

analyte	polynomial equation (order = 2) $y = ax^2+bx+c$			x (k'_2)
	a	b	c	
12p	-0.0055	0.3123	-0.1821	6.026
13p	-0.0016	0.1926	-0.0796	8.852
14p	0.0011	0.0452	0.2569	18.853
15p	NS	NS	NS	NS
16p	NS	NS	NS	NS
17p	-0.0005	0.0743	0.0048	24.000
18	0.0046	-0.1183	0.7330	31.082
19	NS	NS	NS	NS
20	ND	ND	ND	ND
21	NS	NS	NS	NS
22	NS	NS	NS	NS
23	NS	NS	NS	NS
24	NS	NS	NS	NS
25	NS	NS	NS	NS
26	NS	NS	NS	NS

Note: ND = Not determined.

NS = No enantioseparation or baseline separation could not be observed.

VITA

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