การเตรียมกลีเซอรอลโมโนเอสเทอร์โดยใช้ไทรเฟนิลฟอสฟีนและแฮโลจีเนทิงรีเอเจนต์

นายมาโนช รัตนคุณ

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรมหาบัณฑิต
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PREPARATION OF GLYCEROL MONOESTER USING TRIPHENYLPHOSPHINE AND HALOGENATING REAGENTS

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A Thesis Submitted in Partial Fulfillment of the Requirements

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Field of Study	Petrochemistry and Polymer Science
Advisor	Assistant Professor Warinthorn Chavasiri, Ph.D.

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มาโนช รัตนคุณ : การเตรียมกลีเซอรอลโมโนเอสเทอร์โดยใช้ไทรเฟนิลฟอสฟีนและแฮโลจีเนทิงรีเอเจนต์. (PREPARATION OF GLYCEROL MONOESTER USING TRIPHENYLPHOSPHINE AND HALOGENATING REAGENTS) อ.ที่ปรึกษาวิทยานิพนธ์หลัก: ผศ.ดร.วรินทร ชวศิริ, 46 หน้า.

ศึกษาวิธีการเตรียมกลีเซอรอลโมโนเอสเทอร์ ด้วยปฏิกิริยาเอสเทอริฟิเคชันของกรดคาร์บอกซิลิกกับ 1,2-โอ-ไอโซโพรพิลิดีนกลีเซอรอล โดยใช้ไทรเฟนิลฟอสฟีนและแฮโลจีเนทิงเอเจนต์ ได้หาผลของชนิดของแฮโลจิเนตทิงเอเจนต์ ปริมาณของรีเอเจนต์ ปริมาณของไทรเฟนิลฟอสฟีน ปริมาณของ 1,2-โอ-ไอโซโพรพิลิดีนกลีเซอรอล ระบบของตัวทำละลายและเวลาในการทำปฏิกิริยา เพื่อได้ภาวะที่เหมาะสม พบว่าเอทิลไทรคลอโรแอซีเทตร่วมกับไทรเฟนิลฟอสฟีน เป็นรีเอเจนต์ที่ดีสำหรับการเตรียม (2,2-ไดเมทิล-1,3-ไดออกโซเลน-4-อิล)เมทิล เบนโซเอต จากกรดเบนโซอิกและ 1,2-โอ-ไอโซโพรพิลิดีนกลีเซอรอล ในไดคลอโรมีเทนที่อุณหภูมิรีฟลักซ์เป็นเวลา 5 ชั่วโมง ได้ปริมาณผลิตภัณฑ์ 84% ปฏิกิริยานี้ใช้ได้ดีกับกรดคาร์บอกซิลิกทุกชนิดที่เลือก เช่น กรดคาร์บอกซิลิกอิ่มตัว กรดคาร์บอกซิลิกไม่อิ่มตัว และกรดคาร์บอกซิลิกแอโรมาทิก สามารถดีโพรเทกชันผลิตภัณฑ์ตัวอย่างโดยใช้กรดไฮโดรคลอริก เพื่อเปลี่ยน (2,2-ไดเมทิล-1,3-ไดออกโซแลน-4-อิล) เมทิล เบนโซเอต ไปเป็น 2,3-ไดไฮดรอกซีโพรพิล-1-เบนโซเอต สำเร็จได้ปริมาณผลิตภัณฑ์ 94% วิธีใหม่สำหรับการเตรียมกลีเซรอลโมโนเอสเทอร์นี้ให้ผลิตภัณฑ์ปริมาณสูงภายใต้ภาวะที่ไม่รุนแรงและปราศจากกรด

สาขาวิชา ...ปิโตรเคมีและวิทยาศาสตร์พอลิเมอร์... ลายมือชื่อนิสิต.....

ปีการศึกษา.....2551..... ลายมือชื่อ อ.ที่ปรึกษาวิทยานิพนธ์หลัก.....

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MANOCH RATANACOON: PREPARATION OF GLYCEROL MONOESTER USING TRIPHENYLPHOSPHINE AND HALOGENATING REAGENTS. THESIS ADVISOR: ASSIT. PROF. WARINTHORN CHAVASIRI, Ph.D., 46 pp.

The preparation of glycerol monoester by esterification of carboxylic acids with 1,2-*O*-isopropylideneglycerol using triphenylphosphine and halogenating agents was studied. The effects of type of halogenating agents, amount of reagents, amount of PPh_3, amount of 1,2-*O*-isopropylideneglycerol, solvent system and reaction time were investigated to optimize the reaction conditions. Ethyl trichloroacetate as a combination with triphenylphosphine was a good reagent for the preparation of (2,2-dimethyl-1,3-dioxolan-4-yl)methyl benzoate from benzoic acid and 1,2-*O*-isopropylideneglycerol in dichloromethane at reflux temperature within 5 hours, the product yield is 84%. This reaction worked well for all selected carboxylic acids: *i.e.* saturated carboxylic acid, unsaturated carboxylic acid and aromatic carboxylic acid. The deprotection of (2,2-dimethyl-1,3-dioxolan-4-yl)methyl benzoate using hydrochloric acid to transform to 2,3-dihydroxypropyl-1-benzoate was accomplished, the product yield is 94%. This new methodology to prepare the glycerol monoester gave high product yield under mild and acid free condition.

Field of study Petrochemistry and Polymer Science Student's signature.....
Academic year.....2008..... Advisor's signature.....

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As well as all other persons, whose names the author is unable to print there names here in this page for a whole, which he would like to send his sincere gratefulness. Without them, the author would difficult to achieve this goal.

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LIST OF ABBREVIATIONS

δ	chemical shift (NMR)
cm^{-1}	wave number (IR)
°C	degree Celsius
$CDCl_3$	deuterated chloroform
CH_2Cl_2	dichloromethane
$Cl_3CCOOEt$	ethyl trichloroacetate
DMSO- d_6	deuterated dimethylsulfoxide
d	doublet (NMR)
dd	doublet of doublet (NMR)
EtOAc	ethyl acetate
g	gram(s)
Hz	hertz
h	hour
J	coupling constant (NMR)
MeOH	methanol
mL	milliliter(s)
mmol	millimole
m	multiplet (NMR)
NMR	nuclear magnetic resonance
s	singlet (NMR)
THF	tetrahydrofuran
t	triplet (NMR)
w	watt

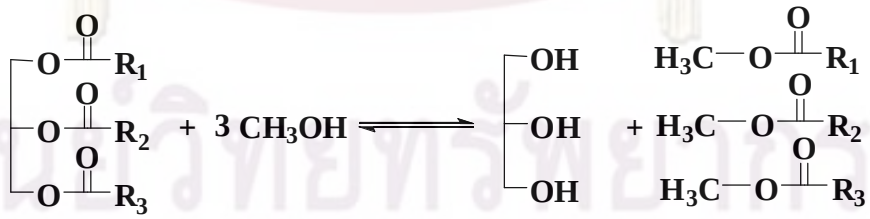
CHAPTER I

INTRODUCTION

With the first worldwide oil shortage in the 1970s, a number of researchers began working earnestly in an attempt to develop the biofuel market. Several shortcomings related to the direct use of plant oils and their total incompatibility with petrodiesel fuel pushed the researchers into the direction of chemically modified forms of plant oils and animal fats known as biodiesel.

Biodiesel is a renewable, relatively clean-burning, carbon-neutral fuel that can be obtained from a variety of oilseed plants, waste oils, and rendered animal fats. These unprocessed materials (collectively referred to as feedstock oils) can be converted into petrodiesel-compatible fuel using a process known as chemical transesterification.

Chemical *trans*esterification of feedstock oils is a well-known process which solves the problem of feedstock viscosity. The process was first described in 1852 when it was originally used as a means of producing high-quality soaps, and with a bit of retooling in the production of biodiesel. Simply stated, biodiesel is produced by the reaction of feedstock oils with an alcohol in the presence of a catalyst to produce fatty acid methyl esters (FAME) or biodiesel and by-product glycerol. The typical process is demonstrated below.

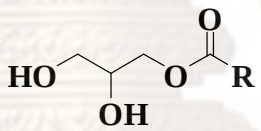


feedstock oil methanol glycerol fatty acid methyl ester

Every 150 lites batch of vegetable oil that is converted into biodiesel generates approximately 30 lites of raw glycerol. Glycerol (common name glycerin) is an alcohol which has three hydroxyl groups that can combine with up to three acids to form glycerol mono, di, and triester [1].

Nowadays, the world energy crisis made petroleum fuel prices even higher. In 2006, petroleum consumption of Thailand was more than 40,000 million liters and estimated to increase by 1.7% in next year [2]. Like many other countries, Thailand has begun to use biodiesel. The government of Thailand has the potential to develop biofuel set alternative energy usage as national agenda by encouraging the production and usage of alternative energy, particularly biofuel and bio-mass such as gasohol and biodiesel [3]. Vegetable oil such as soybean, palm oil can be used to manufacture biodiesel that replace diesel from petroleum. In November 2008, demand for biodiesel in Thailand was more than 1.5 million liters a day [4]. In 2012, Thailand government aims to use 8 million liters of biodiesel a day which means that around 1.6 million liters of glycerol will be produced per day. If this could be utilized for the production of higher valued derivatives of glycerol, such as glycerol monoester (monoglyceride or monoacylglycerol), the economic viability of the biodiesel process might improve.

1.1 Introduction to glycerol monoester



glycerol monoester

Glycerol monoester is a glycerol that combines with acids. The interest in glycerol monoester resides in their structure comprising an aliphatic lipophilic chain and two hydroxyl groups in the hydrophilic part. This structure causes surfactant action, which stabilizes emulsions. Their abilities to form stable emulsions make the glycerol monoester suitable as internal and external lubricants in fiber and textile technologies. In addition, glycerol monoester is an important emulsifier used in food, pharmaceutical, and cosmetic industries. Glycerol monoester and their derivatives represent 75% of the world production of food emulsifiers [5]. Glycerol monoester is used in the food and drug industry (Table 1.1) because they have better emulsifying properties than a mixture of different acylglycerols (*e.g.* glycerol diester, glycerol triester).

Table 1.1 Derivatives of glycerol monoester

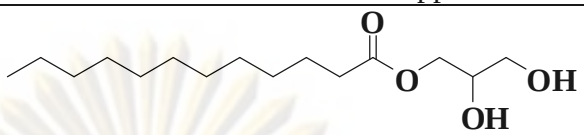
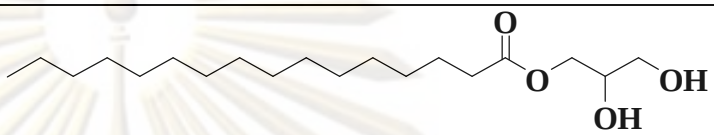
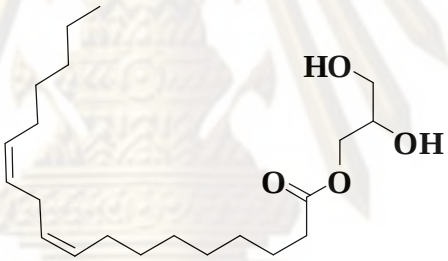
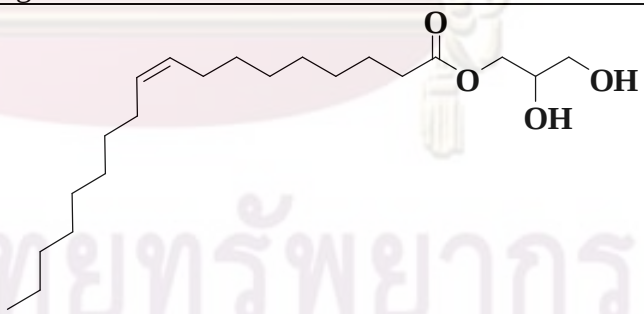
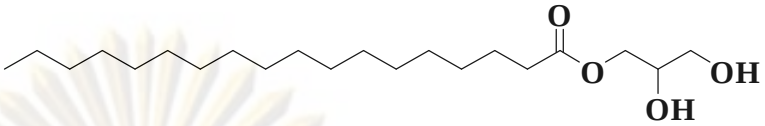
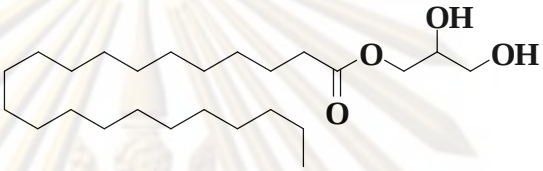
Glycerol monoester	Structure and application
Glycerol monolaurate $C_{15}H_{30}O_4$	 Commonly used as naturally occurring surfactants, emulsifier in the food and cosmetics industries.
Glycerol monopalmitate $C_{19}H_{38}O_4$	 Primary and auxiliary emulsifiers. Lubricants and spreading agents in bath oils. Pigment dispersants in make-up. Slip agents in vanishing and moisturizing creams. Emollients in suppositories and vaginal creams. Major uses include creams, lotions, hair rinses, make-up, shaving preparations, conditioners and toiletries.
Glyceol monolinoleate $C_{21}H_{38}O_4$	 Skin-conditioning agent, emollient, surfactant, emulsifying agent.
Glycerol monooleate $C_{21}H_{40}O_4$	 Used as emulsifiers or oiling agents for foods, spin finishes and textiles; antifoaming and antistatic agents for plastics; and lubricants, water treatment, metal working fluids, and dispersing agents. End applications include cosmetics, foods, personal care products, medicine, pesticides, paper making, plastics and paints.

Table 1.1 (cont.)

Glycerol monoester	Structure and application
Glycerol Monostearate $C_{21}H_{42}O_4$	 Used as an emulsifier, emulsion stabilizer, emollient, moisturizer, surface active agent in food or cosmetics, lubricant for PVC, transparent grain and viscosity builder in creams and lotions. It is also used as an opacifying and pearlizing agent in cosmetics.
Glycerol monobehenate $C_{25}H_{50}O_4$	 Drug stabilizer, drug delivery, homogenizing agent.

Glycerol monoester is a non-ionic surfactant with important applications in pharmaceutics, food and cosmetics production. Because of their non-toxic nature and known biochemical metabolism pathway, monoglycerides are recognized as a new class of safe chemicals and are under extensive studies due to its high antimicrobial activity. The three most important processes for the preparation of monoglycerides are glycerolysis, hydrolysis of triglycerides and direct esterification of glycerol with fatty acids.

1.2. Synthesis of glycerol monoester

The most common method used for the production of glycerol monoester is an enzymatic glycerolysis reaction and esterification reaction. The finished product generally contains 35-50% glycerol monoester and the rest are mostly glycerol diester, some unreacted triglycerides, residual glycerol, and free fatty acid [6].

The utilization of esterification reaction has been continuously developed in organic synthesis. This reaction could be adopted to prepare many classes of organic compounds such as glycerol monoester. This research is focused in producing glycerol monoester. When the production of a high-purity-degree monoglyceride is desired, the most viable route is the direct esterification. Moreover, esterification reaction can be used with a variety of catalysts such as acid and base.

1.3 Literature reviews

1.3.1 Synthesis of glycerol monoester

The methodologies for the preparation of glycerol monoester by esterification reactions have been extensively studied in many research groups. For instance, commercial production of glycerol monoester is described in details by Gupta (1996) "Monoglyceride (glycerol monoester) are made by reacting triglycerides with excess glycerol in presence of a NaOH catalyst". The finished product generally contains 35-50% monoglycerides [6].

In 2000 Pouilloux [7] and co-workers addressed the preparation of glycerol monoester by esterification reaction using glycerol, stearic acid and basic catalysts (MgO, ZnO, Na_2CO_3). The use of a well chosen solvent and catalyst increased the activity and the glycerol monoester selectivity. However, the esterification reaction of glycerol with fatty acid with non-selective catalysts lead to a mixture of glycerol mono-, di- and triesters.

In 2000 Machado [8] and co-workers studied the selective synthesis of glycerol monolaurate from lauric acid and glycerol as starting materials employing commercial Beta, Y and Mordenite zeolites with different Si/Al ratio as catalysts. Zeolite Beta exhibited the best results as catalyst to obtain the mono-derivative, presenting selectivities higher than 60% at 20% yield. Zeolite Y presented 55% selectivities at 16% yield and Mordenite exhibited 55% selectivities at 13% yield.

In 2001 Bancquart [9] and co-workers reported the methodology to prepare glycerol monoester from fatty acid or fatty methyl esters and glycerol using several solid basic catalyst (MgO, ZnO, La_2O_3, and CeO_2). From the comparison of the catalytic properties, the activity order is as follows: La_2O_3 > MgO >> ZnO > CeO_2. Indeed, at 80% conversion, the selectivity to mono-, di- or triesters are similar to that obtained in using homogenous basic catalysts (*i.e.* 40% monoester, 50% diester and 10% triester).

In 2004 Barrault [10] and co-workers developed a method for preparing glycerol monoester from transesterification of glycerol with several methyl esters using mesoporous catalysts, MCM-41 derivatives. This study clearly shows that porous solids such as MCM-41 promoted with magnesium species can be efficient catalysts for clean synthesis processes, particularly when the synthesis of the porous

material and the experimental conditions are finely tuned to the reagents. Here glycerol monoesters were synthesized with a yield up to 80%, which is higher than 40% monoglycerides obtained with homogeneous catalysts.

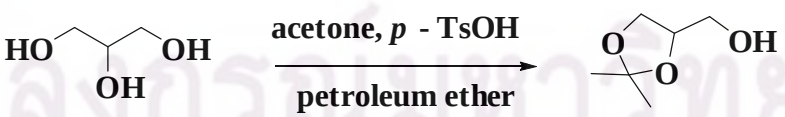
In 2008 H-Kittikun [11] and co-workers developed a packed-bed reactor (PBR) system using immobilized lipase PS (*Pseudomonas*) as biocatalyst for continuous monoacylglycerols (MAG) production. The yield of MAG increased with increasing residence time. At a residence time of 7.5 h led to highest yield of MAG of 60%.

In 2008 Chetpattanacodh and Tongurai [5] reported the optimum conditions for the glycerolysis of palm stearin and crude glycerol derived from biodiesel process: a reaction temperature of 200 °C with a molar ratio of crude glycerol to palm stearin of 2.5:1, and a reaction time of 20 minutes. At the optimum conditions for glycerolysis of crude glycerol about 61% yield and 62% purity of glycerol monoester was obtained.

1.3.2 Protection and deprotection of glycerol hydroxyl group

The difficulty in achieving high yields of glycerol monoester by esterification of glycerol with acid lies in the three hydroxyl groups of glycerol that can consist of fatty acid in every site. Multiple products can result from this reaction which includes the glycerol mono-, di-, and triester. To produce only glycerol monoester, the researcher must transform glycerol to 1,2-*O*-isopropylideneglycerol that contains only one hydroxyl group. The common method of synthesizing 1,2-*O*-isopropylidene glycerol from glycerol is the use of acetone and an acidic catalyst in petroleum ether.

In 1955, Renoll and Newman [12] prepared 1,2-*O*-isopropylideneglycerol (protected hydroxyl group) from glycerol using acetone and *p*-toluenesulfonic acid.

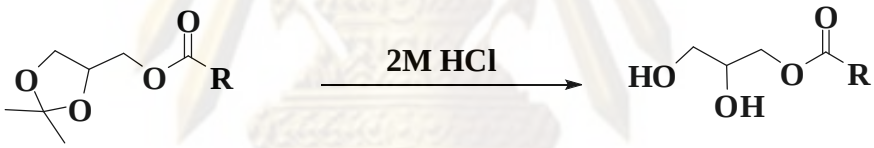


In 2003, Yu [13] and co-workers synthesized glycerol monoester from the transesterification of 1,2-*O*-isopropylideneglycerol with methyl stearate. The protected glycerol prevented the formation of diglyceride and triglyceride at higher

temperatures. In this three-step process, each purification procedure is very simple and the yield and purity (97%) are very high (overall yield: 92%). The selective and efficient deprotection of the acetonide was accomplished using the strongly acidic wet resin (Amberlyst-15)-ethanol (95%) system in which the purification procedure was very simple (filtration and concentration). This procedure can be applied to the production of monoglycerides of other fatty acids in industry.

Acetonide groups are the most frequently used protecting groups for 1,2-diols in organic synthesis. The deprotection of acetonide groups is an important transformation in the synthesis of biologically active natural products and in the field of drugs and pharmaceuticals [14].

In 2008 Swift and Sutherland [15] addressed the deprotection of acetonide group using 2M HCl. The present procedure for the synthesis of 1,2-diols has the advantage of short reaction time, high yield of products (over 90% yield) and simple experimental work-up procedure.



1.3.3 Triphenylphosphine and halogenating agents

The utilization of halogenated agents and triphenylphosphine (PPh_3) has been continuously developed as a versatile reagent in organic synthesis. These reagents could be adopted to prepare organic halides such as alkyl or acyl halides. Acyl chlorides generated could be used as a reliable intermediate for the synthesis of other classes of organic compounds such as amides, sulfonamides and esters [16].

In 1966 Lee [17] reported that the combination of CCl_4 and PPh_3 could be utilized to replace $SOCl_2$, PCl_3, or oxalyl chloride in the preparation of acyl chlorides or alkyl chlorides due to their strong acidic conditions. This method is not compatible for the acid-sensitive molecules.

In 2003 Chayaripongkal [18] developed a new methodology to synthesize amides and esters using Cl_3CCONH_2 and PPh_3 at reflux temperature of CH_2Cl_2. This combined reagent was attractive since it could be utilized under mild and acid-free condition using short reaction time.

In 2005 Chantarasriwong [16] introduced the new system for the synthesis of amides, esters and sulfonamides using Cl_3CCONH_2/PPh_3 and Cl_3CCN/PPh_3. For the ester formation, this new system showed a good yield percentage at 66%-98% depends on the type of alcohol and carboxylic acid. Moreover, the system also provided a mild reaction condition by using a short time of reaction.

1.5 The goal of this research

This research aims to study on the preparation of glycerol monoester and specifically focuses on the methodologies which will eventually arrive at the development of a system for synthesizing glycerol monoester from glycerol using PPh_3 and halogenating agents under mild and acid-free conditions. Moreover, this research is conducted to find out the optimum conditions required for the synthesis of glycerol monoester and applied systems for the synthesis of the derivatives of glycerol monoester.

CHAPTER II

EXPERIMENTAL

2.1 Instruments and equipments

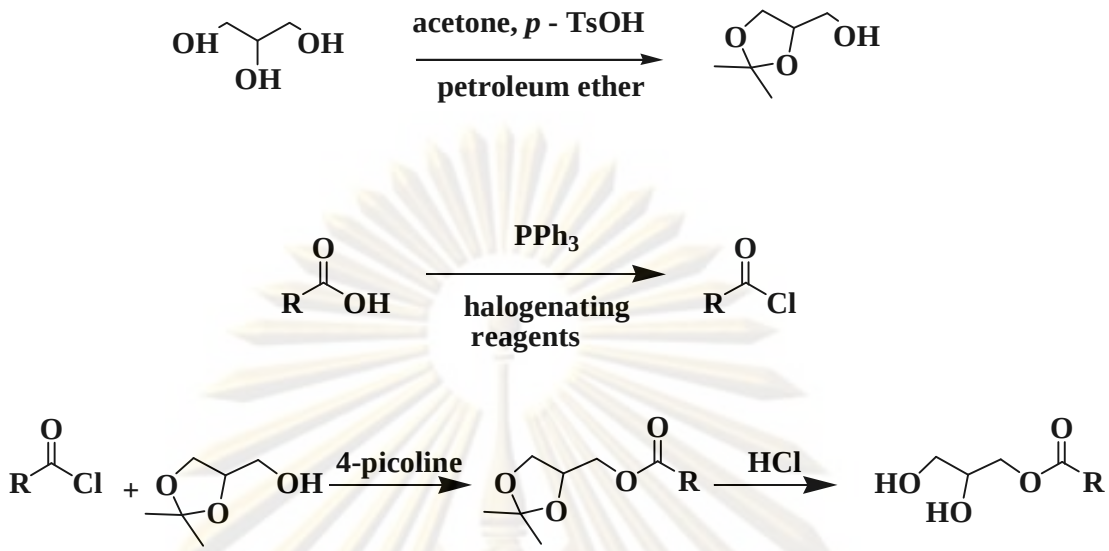
Spectrometer: The ^{1}H-NMR and ^{13}C-NMR spectra were obtained in $CDCl_3$ or otherwise stated, with Fourier transform nuclear magnetic resonance spectrometer of Varian model Mercury+400 spectrometer which operated at 399.84 MHz for ^{1}H and 100.54 MHz for ^{13}C nuclei. The chemical shifts (δ) are assigned by comparison with residue solvent protons.

Chromatography: Thin layer chromatography (TLC) was carried out on aluminium sheets precoated with silica gel (Merck's, Kieselgel 60 PF_{254}). Column chromatography was performed on silica gel (Merck's, Kieselgel 60G Art 7734 (70-230 mesh) or Art 9385(230-400 mesh)) and aluminium oxide 90 (70-230 mesh ASTM).

2.2 Chemicals

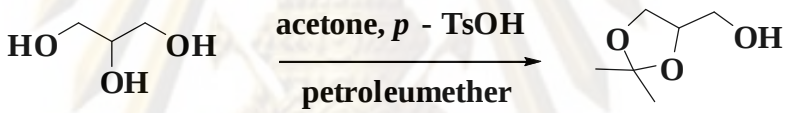
For all solvents: CH_2Cl_2, $CHCl_3$, Hexane, $(C_2H_5)_2O$, C_4H_8O, $CH_3COOC_2H_5$ and MeOH, were purified by a standard methodology except for those which were reagent grades. For *p*-TsOH, PPh_3, CCl_4, Cl_3CCCl_3, $Cl_3CCOCCl_3$, Cl_3CCN, Cl_3CCONH_2 and $Cl_3CCOOEt$, which were utilized in synthesizing of glycerol monoester, and all the organic substrates: acetone, glycerol, 1,2-*O*-isopropylideneglycerol, benzoic acid, 1-naphthoic acid, lauric acid, palmitic acid, linoleic acid, oleic acid, stearic acid and behenic acid, were purchased from Merck and Fluka chemical company, they were used without any additional purification.

The new methodology for the preparation of glycerol monoester by esterification reactions with glycerol and carboxylic acid using PPh3 and halogenating agents is displayed in scheme 2.1.



Scheme 2.1 Methodology for the preparation of glycerol monoester

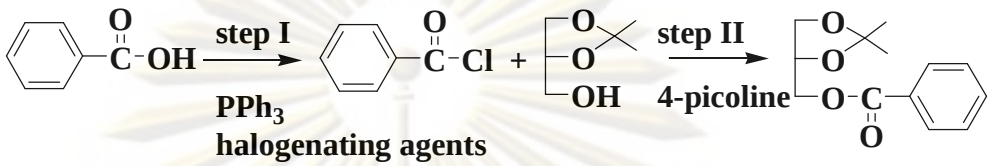
2.3 General procedure for synthesis of 1,2-*O*-isopropylideneglycerol



A mixture of glycerol 1 eq (10 mmol) and acetone 4 eq (40 mmol) was prepared at reflux temperature with Dean stark. *p*-Toluenesulfonic acid 0.015 eq (*p*-TsOH 0.15 mmol) with petroleum ether 3 mL was added. The solution was stirred at reflux temperature and the stirring and refluxing were continued until no more water collected in the trap of the separating head. The mixture was cooled to room temperature and freshly saturated aqueous $NaHCO_3$ was added. The mixture was then filtered, petroleumether and excess acetone were removed by distillation under reduced pressure. The fraction boiling at 80-82 °C/11 mm was collected. The yield of colorless oil 1,2-*O*-isopropylidene glycerol (78%), ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.36 (3H, *s*, C*H*$_3$-), 1.43 (3H, *s*, C*H*$_3$-), 3.58 (1H, *dd*, *J* = 11.7 and 5.2 Hz, glycerol-*H*), 3.70-3.80 (2H, *m*, glycerol-*H*), 4.03 (1H, *t*, *J* = 7.4 Hz, glycerol-*H*) and 4.20-4.26 (1H, *m*, glycerol-*H*).

2.4 General procedure for the esterification of carboxylic acid with alcohol using PPh_3 and halogenating agents.

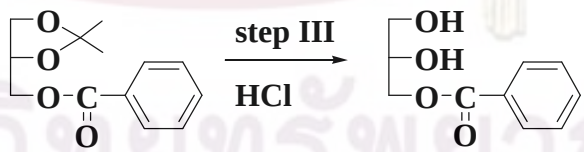
2.4.1 General procedure for the synthesis of (2,2-dimethyl-1,3-dioxolan-4-yl) methyl benzoate.



Step I: PPh_3 2 eq (6 mmol) in CH_2Cl_2 3 mL was added to a mixture of benzoic acid 1 eq (3 mmol) and $Cl_3CCOOEt$ 2 eq (6 mmol) in CH_2Cl_2 3 mL at reflux temperature. The mixture was stirred for 1 h.

Step II: A mixture of 1,2-*O*-isopropylideneglycerol 1 eq (3 mmol) and 4-picoline 3 eq (9 mmol) was added to the above mixture. The reaction was refluxed and continued stirring for another 1 h. When the reaction was completed, the organic layer was extracted with 10% HCl and saturated aqueous $NaHCO_3$, respectively, dried over anhydrous Na_2SO_4 and evaporated *in vacuo*. The mixture was separated with silica gel column eluting with hexane/EtOAc (9/1) (84%).

2.4.2 General procedure for deprotection of acetonide groups



Step III: A solution of (2,2-dimethyl-1,3-dioxolan-4-yl)methyl benzoate (0.175 g 0.75 mmol) was dissolved in MeOH (5 mL). HCl (2 M, 0.75 mL) was then added and the solution was stirred at room temperature for 3 h. The reaction was quenched by the addition of small lumps of $NaHCO_3$ (1.0 g). Insoluble material was then removed by filtration and the mixture was concentrated *in vacuo*. Further insoluble material was removed by filtration and the solution was dried over

anhydrous $NaSO_4$. Purification by filtration through a pad of silica gel gave 2,3-dihydroxyl-1-benzoate after concentration (94%).

2.5 Study on the optimum conditions for esterification of carboxylic acid and 1,2-*O*-isopropylidene glycerol (in step I,II)

2.5.1 Effect of reaction time in step II

The esterification was carried out as described in the general procedure, but the reaction time in step II was varied: 1, 2, 3, 4 and 5 h.

2.5.2 Effect of halogenating agents

The esterification was carried out as described in the general procedure, but the different type of halogenating agents was varied: none, CCl_4, Cl_3CCCl_3, $Cl_3CCOCCl_3$, Cl_3CCN**,** Cl_3CCONH_2 and $Cl_3CCOOEt$.

2.5.3 Effect of amount of reagents

The esterification was carried out as described in the general procedure, but the ratios of $Cl_3CCOOEt$ and PPh_3 was varied (benzoic acid was fixed at 1 eq): 1:1, 1:2, 2:1, 2:2 and 2:3.

2.5.4 Effect of amount of 1,2-*O*-isopropylideneglycerol

The esterification was carried out in the same manner as described above but the different equivalent of 1,2-*O*-isopropylideneglycerol was varied: 0.5, 1 and 2.

2.5.5 Effect of solvent system

The esterification was carried out in the same manner as described above but the different solvent was varied: CH_2Cl_2, $CHCl_3$, $(C_2H_5)_2O$, C_4H_8O and $CH_3COOC_2H_5$.

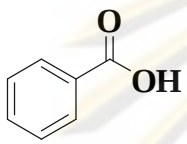
2.5.6 Effect of reaction temperature in step II

The esterification was carried out in the same manner as described above but the different reaction temperature in step II was varied: at room temperature and solvent reflux temperature.

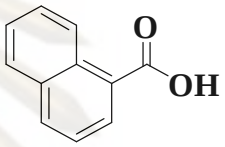
2.6 Applications of developed procedures for the synthesis of glycerol monoester derivatives.

2.6.1 Variation of carboxylic acids on the formation of ester

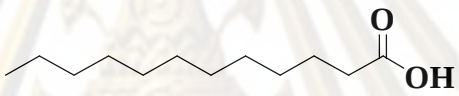
The developed procedures for the synthesis of selected glycerol monoester were performed according to the general procedure under the optimum conditions but using different carboxylic acids: 1-naphthoic acid, lauric acid, palmitic acid, linoleic acid, oleic acid, stearic acid and behenic acid instead of benzoic acid.



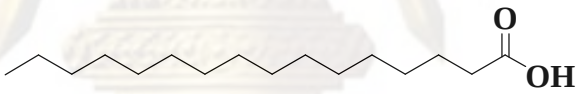
benzoic acid



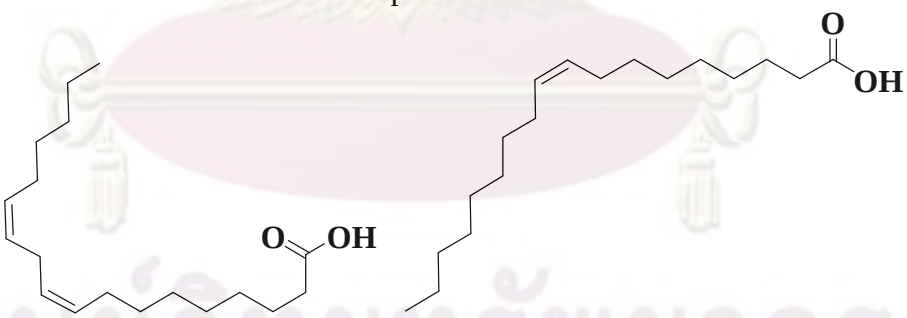
1-naphthoic acid



lauric acid

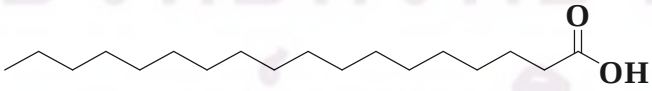


palmitic acid

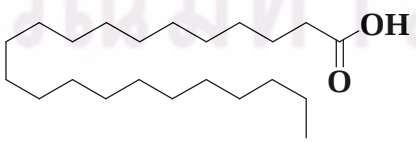


linoleic acid

oleic acid

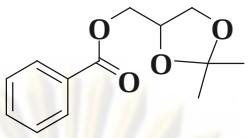


stearic acid



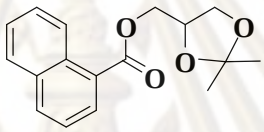
behenic acid

(2,2-dimethyl-1,3-dioxolan-4-yl)methyl benzoate:



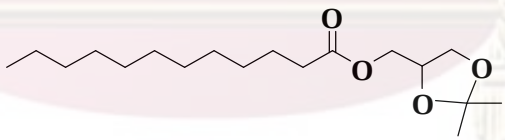
colorless oil (85%), ^{1}H NMR ($CDCl_3$) : 1.39 (3H, s, C*H*$_3$-), 1.45 (3H, s, C*H*$_3$-), 3.88 (1H, t, *J* = 8.46 Hz, glycerol-*H*), 4.14 (1H, t, *J* = 8.37 Hz, glycerol-*H*), 4.33-4.47 (3H, m, glycerol-*H*), 7.44 (2H, t, *J* = 7.60 Hz, Ph*H*), 7.56 (1H, t, *J* = 7.36 Hz, Ph*H*), 8.05 (2H, d, *J* = 7.35 Hz, Ph*H*).

(2,2-dimethyl-1,3-dioxolan-4-yl)methyl-1-naphthoate:



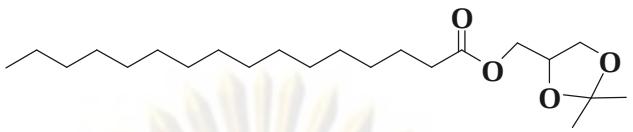
colorless oil (65%), ^{1}H NMR ($CDCl_3$) : 1.41 (3H, s, C*H*$_3$-), 1.48 (3H, s, C*H*$_3$-), 3.92 (1H, t, *J* = 8.28 Hz, glycerol-*H*), 4.18 (1H, t, *J* = 8.20 Hz, glycerol-*H*), 4.43-4.55 (3H, m, glycerol-*H*), 7.48-7.64 (3H, m, Ar*H*), 7.89 (1H, d, *J* = 8.11 Hz, Ar*H*), 8.03 (1H, d, *J* = 8.18 Hz, Ar*H*), 8.23 (1H, d, *J* = 7.25 Hz, Ar*H*), 8.92 (1H, d, *J* = 8.65 Hz, Ar*H*).

(2,2-dimethyl-1,3-dioxolan-4-yl)methyl laurate:



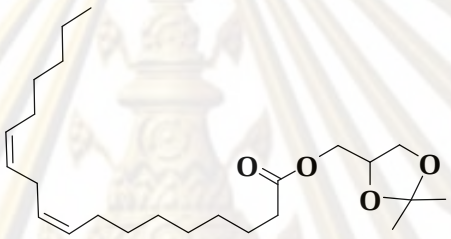
colorless oil (75%), ^{1}H NMR ($CDCl_3$) : 0.87 (3H, t, *J* = 6.80 Hz, C*H*$_3$-), 1.25-1.28 (16H, m, -(C*H*$_2$)$_8$-), 1.37 (3H, s, C*H*$_3$-), 1.43 (3H, s, C*H*$_3$-), 1.60-1.63 (2H, m, -C*H*$_2$-CH$_2$CO-), 2.34 (2H, t, , *J* = 7.55 Hz, -C*H*$_2$CO-), 3.73 (1H, t, *J* = 8.42 Hz, glycerol-*H*), 4.05-4.18 (3H, m, glycerol-*H*), 4.28-4.34 (1H, m, glycerol-*H*).

(2,2-dimethyl-1,3-dioxolan-4-yl)methyl palmitate:



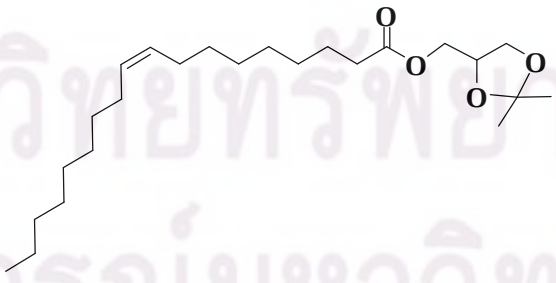
white solid (69%), ^{1}H NMR ($CDCl_3$) : 0.87 (3H, t, *J* = 6.75 Hz, C*H*$_3$-), 1.24-1.27 (24H, m, -(C*H*$_2$)$_{12}$-), 1.36 (3H, s, C*H*$_3$-), 1.42 (3H, s, C*H*$_3$-), 1.58-1.63 (2H, m, -C*H*$_2$-CH$_2$CO-), 2.33 (2H, t, , *J* = 7.57 Hz, -C*H*$_2$CO-), 3.72 (1H, t, *J* = 8.42 Hz, glycerol-*H*), 4.05-4.17 (3H, m, glycerol-*H*), 4.28-4.33 (1H, m, glycerol-*H*).

(2,2-dimethyl-1,3-dioxolan-4-yl)methyl linoleate:



colorless oil (73%), ^{1}H NMR ($CDCl_3$) : 0.97 (3H, t, *J* = 7.54 Hz, C*H*$_3$-), 1.30 (14H, m, -(C*H*$_2$)$_4$- and -(C*H*$_2$)$_3$-), 1.36 (3H, s, C*H*$_3$-), 1.43 (3H, s, C*H*$_3$-), 1.58-1.64 (2H, m, -C*H*$_2$-CH$_2$CO-), 2.02-2.11 (4H, m, -C*H*$_2$-CH=CH-), 2.34 (2H, t, , *J* = 7.57 Hz, -C*H*$_2$CO-), 2.74-2.81 (2H, m, -CH=CH-C*H*$_2$-CH=CH-), 3.73 (1H, t, *J* = 8.44 Hz, glycerol-*H*), 4.05-4.18 (3H, m, glycerol-*H*), 4.28-4.34 (1H, m, glycerol-*H*), 5.27-5.42 (4H, m, -C*H*=C*H*-).

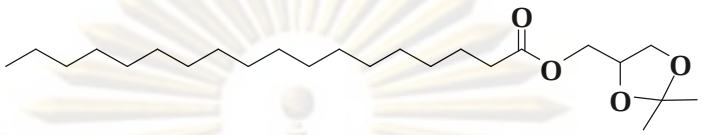
(2,2-dimethyl-1,3-dioxolan-4-yl)methyl oleate:



colorless oil (76%), ^{1}H NMR ($CDCl_3$) : 0.87 (3H, t, *J* = 6.65 Hz, C*H*$_3$-), 1.24-1.29 (20H, m, -C*H*$_2$-), 1.36 (3H, s, C*H*$_3$-), 1.43 (3H, s, C*H*$_3$-), 1.60-1.67 (2H, m, -C*H*$_2$-CH$_2$CO-), 1.99-2.06 (4H, m, -C*H*$_2$-CH=CH- C*H*$_2$-), 2.32-243 (2H, m, -C*H*$_2$CO-),

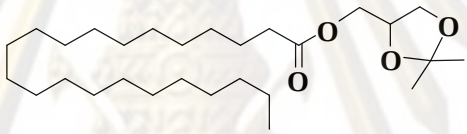
3.71-3.75 (1H, m, glycerol-*H*), 4.05-4.33 (4H, m, glycerol-*H*), 5.29-5.41 (2H, m, -C*H*=C*H*-).

(2,2-dimethyl-1,3-dioxolan-4-yl)methyl stearate:



white solid (65%), ^{1}H NMR ($CDCl_3$) : 0.88 (3H, t, *J* = 6.79 Hz, CH_3-), 1.25-1.28 (28H, m, -(CH_2)$_{14}$-), 1.37 (3H, s, CH_3-), 1.43 (3H, s, CH_3-), 1.58-1.64 (2H, m, -CH_2-CH_2CO-), 2.34 (2H, t, , *J* = 7.57 Hz, -CH_2CO-), 3.73 (1H, t, *J* = 8.34 Hz, glycerol-*H*), 4.06-4.18 (3H, m, glycerol-*H*), 4.28-4.34 (1H, m, glycerol-*H*).

(2,2-dimethyl-1,3-dioxolan-4-yl)methyl beheate:

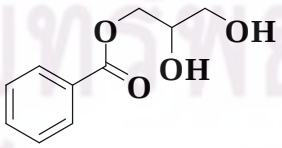


colorless oil (63%), ^{1}H NMR ($CDCl_3$) : 0.88 (3H, t, *J* = 6.78 Hz, CH_3-), 1.25-1.28 (36H, m, -(CH_2)$_{12}$-), 1.37 (3H, s, CH_3-), 1.43 (3H, s, CH_3-), 1.58-1.64 (2H, m, -CH_2-CH_2CO-), 2.34 (2H, t, , *J* = 7.56 Hz, -CH_2CO-), 3.74 (1H, t, *J* = 8.43 Hz, glycerol-*H*), 4.06-4.18 (3H, m, glycerol-*H*), 4.28-4.34 (1H, m, glycerol-*H*).

2.6.2 Deprotection of acetonide in selected monoester(step III)

The deprotection was carried out in the same manner as described.

2,3-dihydroxylpropyl-1-benzoate:



colorless oil(94%), ^{1}H-NMR (DMSO-d_6) δ (ppm): 3.41-3.44 (2H, *m*, glycerol-*H*), 3.74-3.81 (1H, *m*, glycerol-*H*), 4.15 (1H, *dd*, *J* = 11.15 and 6.29 Hz, glycerol-*H*), 4.29 (1H, *dd*, *J* = 11.15 and 3.95 Hz, glycerol-*H*), 4.72 (1H, *t*, *J* = 5.65 Hz, -O*H*), 5.04 (1H, *d*, *J* = 6.45 Hz, -O*H*), 7.51 (2H, *t*, *J* = 7.64 Hz, Ar*H*), 7.64 (1H, *t*, *J* = 7.40 Hz, Ar*H*), 7.98 (2H, *d*, *J* = 8.40 Hz, Ar*H*).

CHAPTER III

RESULTS AND DISCUSSION

3.1 Synthesis of 1,2-*O*-isopropylideneglycerol

1,2-*O*-Isopropylideneglycerol [22-24] could be synthesized from glycerol and acetone with *p*-TsOH or other acids. The time required was varied between 24 and 48 hours. The effect of reaction time was investigated and the results are reported in Table 3.1.

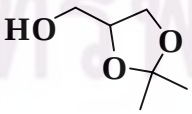
Table 3.1 Effect of reaction time on synthesis of 1,2-*O*-isopropylideneglycerol

Entry	Reaction time (h)	%Isolated yield
1	24	52
2	36	70
3	48	78

Reaction conditions: glycerol 2.37 g (3 mL, 40.9 mmol), acetone 1 g (10.9 mmol), petroleum ether (3.0 mL), *p*-TsOH 30 mg at reflux temperature.

It can be seen that the reaction time was essential for this reaction. The reaction time of 36 h gave good yield of the desired product (entry 2). Indeed when reaction time is prolonged to 48 h, the yield of 1,2-*O*-isopropylideneglycerol was increased (entry 3). The ^{1}H-NMR spectrum of the desired 1,2-*O*-isopropylideneglycerol is depicted in Figure A1.

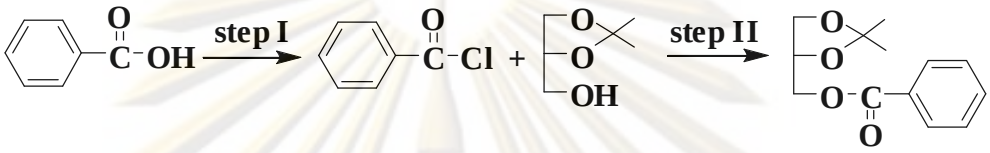
1,2-*O*-isopropylideneglycerol



The ^{1}H-NMR spectrum of 1,2-*O*-isopropylideneglycerol displayed two singlet signals at d_H 1.36 and 1.43 ppm, indicating the presence of two methyl groups. The multiplet of five glycerol protons signified at d_H 3.58, 3.70-3.80, 4.03 and 4.20-4.26.

3.2 Study on the optimum conditions for esterification of carboxylic acid and 1,2-*O*-isopropylidene glycerol (steps I and II) using PPh_3 and halogenating agents

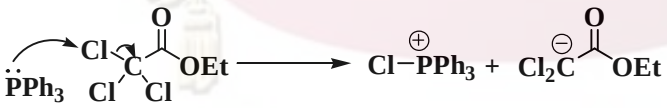
The efficient synthesis for 1,2-*O*-isopropylideneglycerol using the combination of halogenating agents and PPh_3 was demonstrated as a novel and facile method. The general equation can be simplified as shown below.

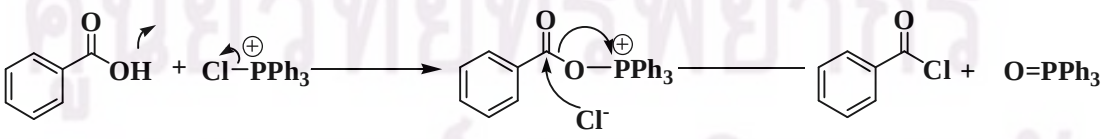


In the present study, various factors were scrutinized to search for new appropriate chemical reagents and to evaluate for the optimal conditions for the preparation of monoester. The standard chemical reaction involves the reaction of benzoic acid with halogenating agents to form an acid chloride intermediate, which was consequently trapped with 1,2-*O*-isopropylideneglycerol to furnish the desired product. Variable parameters studied included type of halogenating agents, reaction time, temperature and solvent system. Moreover, under the optimized conditions, this protocol was then applied for the synthesis of potential compounds.

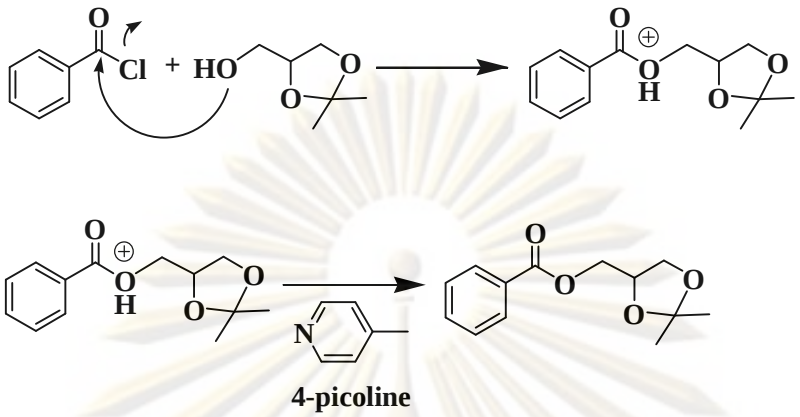
A proposed mechanistic pathway of esterification reaction using PPh_3 and $Cl_3CCOOEt$ is displayed below.

Step I:





Step II:



4-picoline

3.2.1 Effect of reaction time in step II

To optimize the reaction conditions, the benzoic acid and 1,2-*O*-isopropylideneglycerol esterification was used as the model substrates. At the first step, to treat the former by the selected halogenating agents and PPh_3 in CH_2Cl_2 at reflux temperature for 1 h. The next step, to treat it by the latter in the presence of 4-picoline as a base, and follow by 1,2-*O*-isopropylideneglycerol. After that, the reaction was refluxed and to be stirred continuously for 1 h. Then, the desired product would be obtained. The effect of reaction time in step II was investigated and the results are accumulated in Table 3.2.

Table 3.2 Effect of reaction time in step II on the esterification of benzoic acid with 1,2-*O*-isopropylideneglycerol

Entry	Reaction time in step II (h)	%Isolated yield
1	1	51
2	2	62
3	3	75
4	4	84
5	5	86

Reaction conditions: benzoic acid (3 mmol), 1,2-*O*-isopropylideneglycerol (3 mmol), CH_2Cl_2 (3.0 mL), PPh_3 (6 mmol), $Cl_3CCOOEt$ (6 mmol), 4-picoline (9 mmol), reflux temperature, reaction time: step I 1 h, step II (vary).

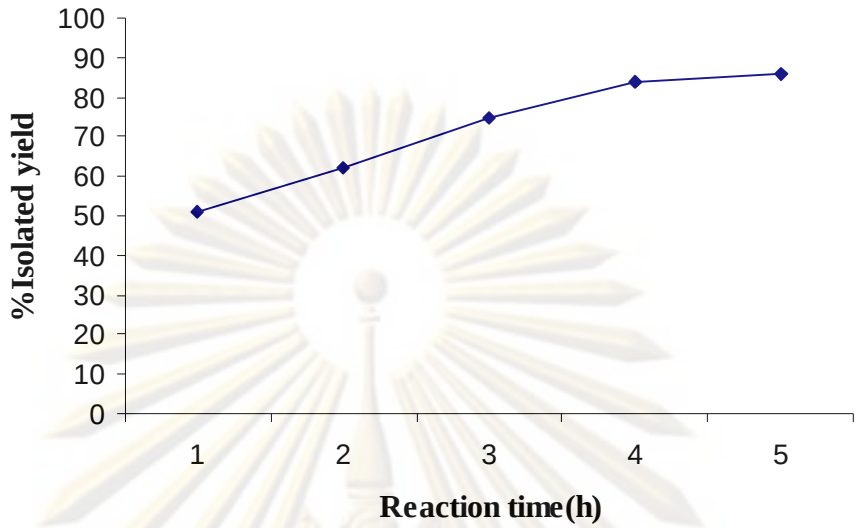


Figure 3.1 %Isolated yield of (2,2-dimethyl-1,3-oxolan-4-yl)methyl benzoate with various reaction time in step II

It was clearly found that benzoic acid could be transformed to the desired ester in higher yield if the reaction conditions were altered. This could be seen from the outcome of the experiment. Factors that controlled the yield of the desired product included the reaction time in step 2. The first parameter implied that the formation of monoester in this particular case was greatly depended upon the period for the reaction. The yield of product ranged from 51% (entry 1) to 84 and 86% under modified reaction conditions (entries 4 and 5). From the result at the reaction time is increased, the yield of the product was consistent. The comparison between the reaction at 4 h and the reaction at 5 h, found that the 4 h reaction was better than another for working continue to the next step, and it gave a higher yield by using a shorter time.

3.2.2 Effect of halogenating agents

The synthesis method of the desired glycerol monoester by a chemical route is difficult and expensive, as shown in recent work [25]. To use the combination of halogenating agents and PPh_3 is a good alternative and interested [26,27]. The esterification of benzoic acid with 1,2-*O*-isopropylidene glycerol was completely performed within 5 h under mild condition to get the desired product, (2,2-dimethyl-

1,3-dioxolan-4-yl)methyl benzoate. The problem of unavailable purchasing of the halogenating agents that would be used with the esterification process of benzoic acid with 1,2-*O*-isopropylidene glycerol were thoroughly carried out, the outcome is presented in Table 3.3.

Table 3.3 Effect of halogenating agents on the esterification of benzoic acid with 1,2-*O*-isopropylideneglycerol

Entry	Halogenating agents	%Isolated yield
1	none	trace
2	CCl_4	65
3	Cl_3CCCl_3	84
4	$Cl_3CCOCCl_3$	15
5	Cl_3CCN	24
6	Cl_3CCONH_2	74
7	$Cl_3CCOOEt$	84

Reaction conditions: benzoic acid (3 mmol), 1,2-*O*-isopropylideneglycerol (3 mmol), CH_2Cl_2 (3.0 mL), PPh_3 (6 mmol), halogenating agents (6 mmol), 4-picoline (9 mmol) at reflux temperature, reaction time: step I 1 h, step II 4 h.

The halogenating agents employed in this experiment are commercially available. Considering the effect of halogenating agents on the formation of monoester, it was observed that when the reaction was carried out in the absence of halogenating agents (entry 1), the desired product was obtained only in trace amount. This was clearly demonstrated that the halogenating agents was essential for this reaction. The latter reagents bearing more affinity electron-withdrawing group that revealed the influence to provide the desired product in higher yield, for example, $Cl_3CCOOEt$ and Cl_3CCCl_3 (entries 3 and 7) gave 84% yield. Other reagents containing electron-withdrawing group were chosen to prove this assumption. For instance, $Cl_3CCOONH_2$ and CCl_4 provided the moderate yield (entries 2 and 5). In addition, a type of the substitutent on halogenating agents also revealed the profound effect on the reactivity of the reaction. Either $Cl_3CCOCCl_3$ or Cl_3CCN (entries 4 and 5) did not good yield of the desired product probably because of their low affinity

electron-withdrawing group that may make the reaction become acidic and thus not appropriate for further reaction to take place.

The efficiency of halogenating agents providing (2,2-dimethyl-1,3-dioxolan-4-yl) methyl benzoate could be arranged as shown below.

$Cl_3CCOOEt \sim Cl_3CCCl_3 > Cl_3CCOONH_2 > CCl_4 > Cl_3CCN > Cl_3CCOCCl_3 >$ none

It should be worth noting here that the use of $Cl_3CCOOEt$, Cl_3CCCl_3 and $Cl_3CCOONH_2$ as effective reagents for the aids of converting carboxylic acid and glycerol to monoester has never been addressed in the chemical literature.

3.2.3 Effect of amount of reagents

Table 3.3 clearly reveals that $Cl_3CCOOEt$ was an efficient reagents for the esterification of benzoic acid with 1,2-*O*-isopropylideneglycerol. For optimizing the reaction conditions, it would then be curious whether a mixture of $Cl_3CCOOEt$ and PPh_3 would affect on this reaction. Various ratios of $Cl_3CCOOEt$ and PPh_3 as 1:1, 2:1, 1:2, 2:2 and 2:3 were therefore examined. The results are accumulated as shown in Table 3.4.

Table 3.4 Effect of equivalent of reagents on the esterification of benzoic acid with 1,2-*O*-isopropylideneglycerol

Entry	$Cl_3CCOOEt$: PPh_3 (eq)	%Isolated yield
1	1 : 1	59
2	2 : 1	26
3	1 : 2	78
4	2 : 2	84
5	2 : 3	75

Reaction conditions: benzoic acid (3 mmol), 1,2-*O*-isopropylideneglycerol (3 mmol), CH_2Cl_2 (3.0 mL), PPh_3 (vary), $Cl_3CCOOEt$ (vary), 4-picoline (9 mmol), reflux temperature, reaction time: step I 1 h, step II 4 h.

According to the aforementioned results, it could be concluded that the ratio of halogenating agents and PPh_3 had effect on the efficiency of the reaction. A mixture of $Cl_3CCOOEt$ and PPh_3 2:2 seemed to be a right choice of combination. Reaction

carried out in this matrix gave (2,2-dimethyl-1,3-dioxolan-4-yl)methyl benzoate in surprisingly quite good yield (84%, entry 4). Increasing amount of PPh_3 more than 2 equivalents (entry 5), the yield of product was decreased. This might be caused from the excess PPh_3 that is able to react with the substrate and the products. Moreover, the excess PPh_3 was difficult to be removed at purification state.

3.2.4 Effect of amount of 1,2-*O*-isopropylideneglycerol

A variety of amount of 1,2-*O*-isopropylideneglycerol is reported. Thus, amount of 1,2-isopropylideneglycerol was another parameter that needs to be evaluated for optimizing reaction conditions. The effect of the amount of 1,2-*O*-isopropylideneglycerol is shown in Table 3.5.

Table 3.5 Effect of the amount of 1,2-*O*-isopropylideneglycerol on the esterification of benzoic acid with 1,2-*O*-isopropylideneglycerol

Entry	Amount of 1,2-*O*-isopropylideneglycerol (mmol)	%Isolated yield
1	1.5	46
2	3	84
3	6	89

Reaction conditions: benzoic acid (3 mmol), 1,2-*O*-isopropylideneglycerol (vary), CH_2Cl_2 (3.0 mL), PPh_3 (6 mmol), $Cl_3CCOOEt$ (6 mmol), 4-picoline (9 mmol), reflux temperature, reaction time: step I 1 h, step II 4 h.

In the present study, employing 6 mmol of 1,2-*O*-isopropylideneglycerol gave the highest yield of product (89%, entry 3). When 1,2-*O*-isopropylideneglycerol was used less than 6 mmol (entries 1-2), the desired product was decreased. However, at 3 mmol of 1,2-*O*-isopropylideneglycerol could be obtained in high yield (84%, entry 2). The yield of the desired product based on the more substrate was used. That may provide higher opportunity to have collision between substrate and reagents when the amount of substrate was increased.

3.2.5 Effect of solvent system

From the experimental conditions described above, CH_2Cl_2 was used as a homogeneous medium. Several solvents were chosen to evaluate their compatibility in the reaction and to observe whether they could replace CH_2Cl_2. The results of the variation of solvents such as $CHCl_3$, $(C_2H_5)_2O$, C_4H_8O and $CH_3COOC_2H_5$ in the esterification of benzoic acid with 1,2-*O*-isopropylideneglycerol using $Cl_3CCOOEt$ as a reagent are presented in Table 3.6.

Table 3.6 The effect of solvent on the esterification of benzoic acid with 1,2-*O*-isopropylideneglycerol

Entry	Solvent	%Isolated Yield
1	CH_2Cl_2	84
2	$CHCl_3$	77
3	$(C_2H_5)_2O$	21
4	C_4H_8O	40
5	$CH_3COOC_2H_5$	39

Reaction conditions: benzoic acid (3 mmol), 1,2-*O*-isopropylideneglycerol (3 mmol), solvent (3.0 mL), PPh_3 (6 mmol), $Cl_3CCOOEt$ (6 mmol), 4-picoline (9 mmol), reflux temperature, reaction time: step I 1 h, step II 4 h.

Among several diverse solvents studied, CH_2Cl_2 was chosen as a reaction medium because it could dissolve both reagents and a substrate. Four common solvents were selected to examine whether they could use to replace CH_2Cl_2 in this reaction. It was found that CH_2Cl_2 was superior in terms of producing the highest yield of (2,2-dimethyl-1,3-dioxolan-4-yl)methyl benzoate. However, some specific cases, $CHCl_3$ (chloroform) (entry 2) is used as another alternative instead of CH_2Cl_2. In opposite way, C_4H_8O (tetrahydrofuran), $CH_3COOC_2H_5$ (ethylacetate) and $(C_2H_5)_2O$ (diethylether) is not good solvent for the esterification of benzoic acid with 1,2-*O*-isopropylideneglycerol because these 3 solvents have high polarity index. The polarity index is a cause of a non-homogeneous mixture, which is appeared like oil drop. It was observed that it became oil droplets when the polar solvent was used.

3.2.6 Effect of reaction temperature in step II

Another important factor for condition optimization on the esterification of benzoic acid with 1,2-*O*-isopropylideneglycerol was the effect of reaction temperature. The temperature in the reaction was varied between room temperature and reflux temperature in order to search for the most felicitous temperature that accommodated the highest yield. The results are demonstrated in Table 3.7.

Table 3.7 The effect of reaction temperature in step II on the esterification of benzoic acid with 1,2-*O*-isopropylideneglycerol

Entry	Reaction temperature in step II	%Isolated yield
1	Room temp(28-30°C)	39
2	Reflux temp(40-42°C)	84

Reaction conditions: benzoic acid (3 mmol), 1,2-*O*-isopropylideneglycerol (3 mmol), CH_2Cl_2 (3.0 mL), PPh_3 (6 mmol), $Cl_3CCOOEt$ (6 mmol), 4-picoline (9 mmol), temperature (vary), reaction time: step I 1 h, step II 4 h.

The highest yield of product was accomplished at reflux temperature (84%, entry 2). It could be obviously seen that when the reaction temperature was rasied up from room temperature (28-30°C) to refluxing dichloromethane temperature, the yield of (2,2-dimethyl-1,3-dioxolan-4-yl)methyl benzoate was significantly increased. In addition, the advantage of this reaction carried out at elevated temperature was the better solubility for some carboxylic acid substrates, which in some cases not totally dissolve at room temperature.

From this studies, the optimum conditions were disclosed:

Step I: Triphenylphosphine 2 eq (6 mmol) in CH_2Cl_2 3 mL was added to a mixture of benzoic acid 1 eq (3 mmol) and $Cl_3CCOOEt$ 2 eq (6 mmol) in CH_2Cl_2 3 mL at reflux temperature. The mixture was stirred for 1 hr.

Step II: A mixture of 1,2-*O*-isopropylideneglycerol 1 eq (3 mmol) and 4-picoline 3 eq (9 mmol) was added to the above mixture. The reaction was refluxed and continued stirring for another 4 hr. When the reaction was completed, the organic layer was extracted with 10% HCl and saturated aqueous $NaHCO_3$, respectively, dried over Na_2SO_4 and evaporated *in vacuo*. The mixture was separated with silica gel column eluting with hexane/EtOAc (9/1).

3.3 Applications of the developed procedures for the synthesis of glycerol monoester derivatives.

3.3.1 Variation of carboxylic acids on the formation of ester

To explore the scope of the esterification utilizing this developed protocol, the relationship between the structures of carboxylic acid with 1,2-*O*-isopropylidene glycerol was examined. The results of the effect of types of carboxylic acids on the esterification are presented in Table 3.8.

Table 3.8 Effect of types of carboxylic acids

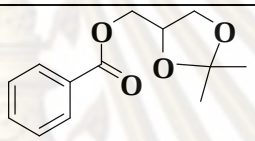
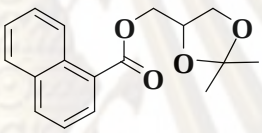
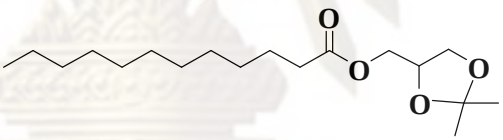
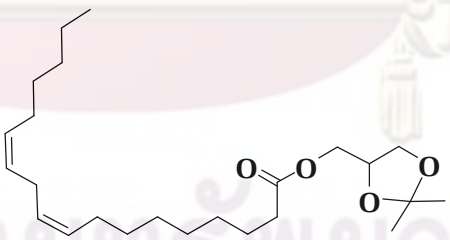
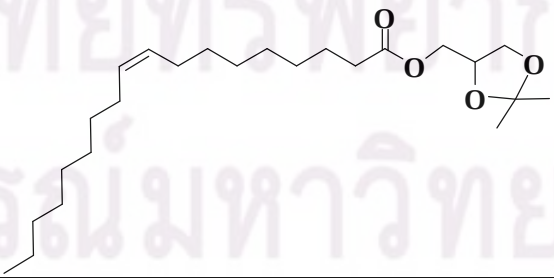
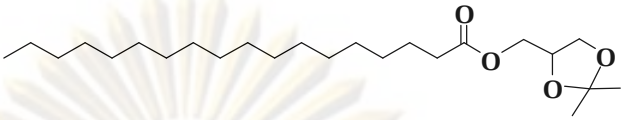
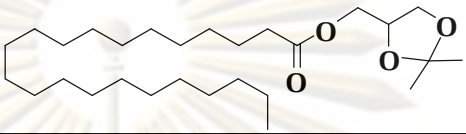
Entry	Carboxylic acid	Ester	%Isolated yield
1	Benzoic acid		84
2	1-naphthoic acid		65
3	Lauric acid		75
4	Palmitic acid		69
5	Linoleic acid		73
6	Oleic acid		76

Table 3.8 (cont.)

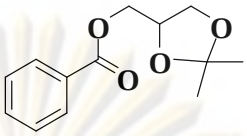
Entry	Carboxylic acid	Ester	%Isolated yield
7	Stearic acid		65
8	Behenic acid		63

Reaction conditions: carboxylic acid (3 mmol), 1,2-*O*-isopropylideneglycerol (3 mmol), CH_2Cl_2 (3.0 mL), PPh_3 (6 mmol), $Cl_3CCOOEt$ (6 mmol), 4-picoline (9 mmol), reflux temperature, reaction time: step I 1 h, step II 4 h.

The above results indicated that the order of the reactivity upon the glycerol monoester formation relied greatly on types of carboxylic acids. In the present work, aromatic carboxylic acids could be accomplishly obtained in high yield (84%, entry 1). The ester yield decreased with the increment of a carbon chain. It was observed that the desired ester manipulated using short chain aliphatic carboxylic acids could be achieved in higher yield than that derived from the long chain ones (entries 3,4 and 7). This may be because of the solubility of the longer carbon chain aliphatic acids. To illustrate this, the long chain aliphatic acid had low capability to dissolve in medium and it was likely hindering the progress of the esterification. Xinzhong *et al.* addressed that with the increasing of carbon chain of aliphatic acids the yields of esters were decreased [28]. This present method in addition could apply for the preparation of long chain carboxylic acid. In the case of linoleic acid, a carboxylic acid with an 18 carbon chain and two *cis* double bonds and oleic acid, a monounsaturated fatty acid the corresponding glycerol monoester were obtained in good yield 73-76% (entries 5-6). Nevertheless, the method introduced here has proven to be very useful for the molecule with steric hindrance such as steric acid and behenic acid, the desired product were gained in around 65% (entries 7-8).

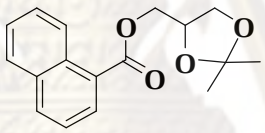
^{1}H-NMR spectra of the desired glycerol monoester are depicted in Figures A2-A9.

(2,2-dimethyl-1,3-dioxolan-4-yl)methyl benzoate



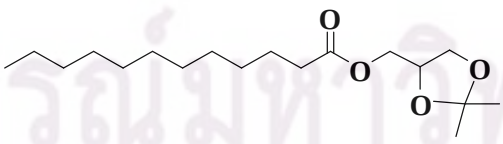
The ^{1}H-NMR spectrum of (2,2-dimethyl-1,3-dioxolan-4-yl)methyl benzoate showed two singlet signal at d_H 1.39 and 1.45 ppm, indicating the presence of two methyl groups. The five glycerol protons were observed from tree signals around d_H 3.88-4.47 ppm. The signals around δ_H 7.51-7.98 ppm were assigned five aromatic protons.

(2,2-dimethyl-1,3-dioxolan-4-yl)methyl-1-naphthoate



The ^{1}H-NMR spectrum of (2,2-dimethyl-1,3-dioxolan-4-yl)methyl naphthoate showed a two singlet signal at d_H 1.41 and 1.48 ppm, indicating the presence of two methyl groups. The five glycerol protons were observed from tree signals at d_H 3.92, 4.18 and 4.43-4.55 ppm. The signals around d_H 7.25-8.92 ppm were assigned for seven aromatic protons.

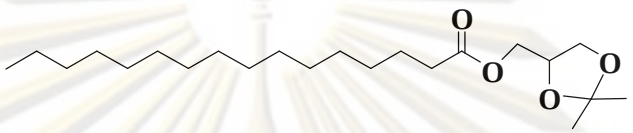
(2,2-dimethyl-1,3-dioxolan-4-yl)methyl laurate



The ^{1}H-NMR spectrum of (2,2-dimethyl-1,3-dioxolan-4-yl)methyl laurate presented two singlet signal at d_H 1.37 and 1.47 ppm, indicating the presence of two

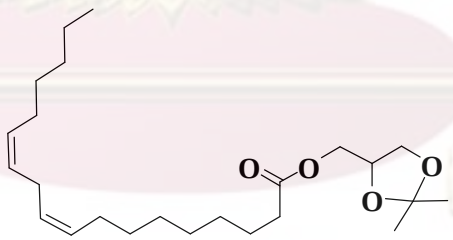
methyl groups. The five glycerol protons were observed from tree signals at d_H 3.73, 4.05-4.18 and 4.28-4.34 ppm. The triplet signal at d_H 2.34, multiplet signal at d_H 1.60-1.64, 1.25-1.28 and triplet signal at d_H 0.87, were appropriated for the undecyl chain.

(2,2-dimethyl-1,3-dioxolan-4-yl)methyl palmitate



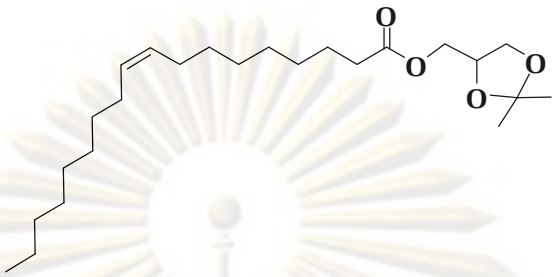
The ^{1}H-NMR spectrum of (2,2-dimethyl-1,3-dioxolan-4-yl)methyl palmitate displayed two singlet signals at d_H 1.36 and 1.42 ppm, indicating the presence of two methyl groups. The five glycerol protons were observed from three signals at d_H 4.28-4.33 and 4.05-4.17 ppm. The triplet signal at d_H 2.33, multiplet signal at d_H 1.58-1.63, 1.24-1.27 and triplet at d_H 0.87, were appropriated for the pentadecyl chain.

(2,2-dimethyl-1,3-dioxolan-4-yl)methyl linoleate



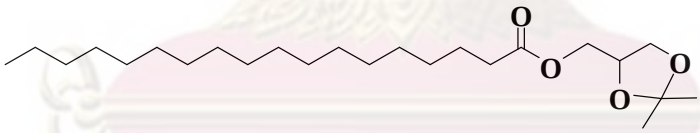
The ^{1}H-NMR spectrum of (2,2-dimethyl-1,3-dioxolan-4-yl)methyl linoleate displayed two singlet signals at d_H 1.36 and 1.43 ppm, indicating the presence of two methyl groups. The multiplet of five glycerol proton signified at d_H 3.73-4.34. The multiplet signal at d_H 5.27-5.42 was assigned to the four protons at two C=C bond. The triplet signal at d_H 0.97, 2.34 and three multiplet signal at d_H 1.58-1.64, 2.74-2.81, 1.30, were appropriated for the two C=C unsaturated hydrocarbon chain.

(2,2-dimethyl-1,3-dioxolan-4-yl)methyl oleate



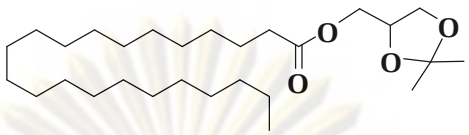
The ^{1}H-NMR spectrum of (2,2-dimethyl-1,3-dioxolan-4-yl)methyl oleate displayed two singlet signals at d_H 1.36 and 1.43 ppm, indicating the presence of two methyl groups. The multiplet of five glycerol protons signified at d_H 3.71-4.33. The multiplet signal at d_H 5.29-5.41 was assigned to the two protons at C=C bond. Four multiplet signal at d_H 2.32-2.43, 1.60-1.67, 1.60-1.67, 1.24-1.29 and triplet at d_H 0.87, were appropriated for the one C=C unsaturated hydrocarbon chain.

(2,2-dimethyl-1,3-dioxolan-4-yl)methyl stearate



The ^{1}H-NMR spectrum of (2,2-dimethyl-1,3-dioxolan-4-yl)methyl stearate displayed two singlet signals at d_H 1.37 and 1.43 ppm, indicating the presence of two methyl groups. The multiplet of five glycerol protons signified at d_H 3.73-4.34. Two triplet signal at d_H 0.87, 2.34 and two multiplet signals at d_H 1.58-1.64, 1.25-1.28, were appropriated for the heptadecyl chain.

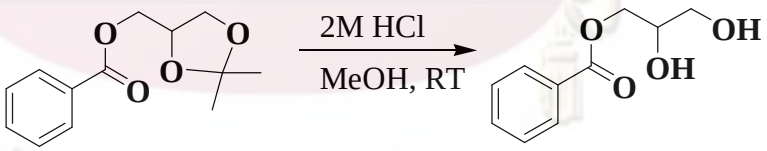
(2,2-dimethyl-1,3-dioxolan-4-yl)methyl behenate



The ^{1}H-NMR spectrum of (2,2-dimethyl-1,3-dioxolan-4-yl)methyl behenate displayed two singlet signals at d_H 1.37 and 1.43 ppm, indicating the presence of two methyl groups. The multiplet of five glycerol protons signified at d_H 3.47-4.34. Two triplet signal at d_H 0.88, 2.34 and two multiplet signals at d_H 1.58-1.64, 1.25-1.28, were appropriated for the henicosyl chain.

3.3.2 Deprotection of acetonide group in selected monoester [29]

A variety of reagents have been employed for deprotection of acetonide group including acids [30] such as aq HCl, aq HBr, 60% aq acetic acid and 0.8% H_2SO_4 in MeOH. Other Lewis acid reagents such as $FeCl_3 \cdot 6H_2O/SiO_2$, $CuCl_2 \cdot 2H_2O$ in EtOH, $Zn(NO_3)_2 \cdot 6H_2O$, and $CeCl_3 \cdot 7H_2O$ $(COOH)_2$ are also known to deprotect acetonides [14]. However, HCl was considered to deprotect acetonide group in (2,2-dimethyl-1,3-dioxolan-4-yl)methyl benzoate, because this procedure is a common method that gives a high %yield.



(2,2-dimethyl-1,3-dioxolan-4-yl)methyl benzoate

2,3-dihydroxypropyl benzoate

Reaction time and temperature in general-deprotection procedure were altered in order to find out the relationship between time and temperature, which provide selected glycerol monoester in high yield. (2,2-Dimethyl-1,3-dioxolan-4-yl)methyl benzoate was used as model substrates. The suitable time must give the highest yield of the desired product. The result of % yield of 2,3-dihydroxypropyl-1-benzoate when time and temperature were altered are displayed in Table 3.9.

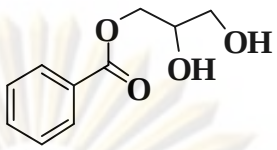
Table 3.9 Deprotection of acetonide group in (2,2-dimethyl-1,3-dioxolan-4-yl) methyl benzoate

Entry	Temp	Time (h)	%Isolated yield	%Conversion	
				1,2-*O*-isopropylidene glycerol	methyl benzoate
1	Room temp	1	78	-	-
2	Room temp	2	90	-	-
3	Room temp	3	94	-	-
4	Reflux temp	1	trace	26	62

Reaction condition: Substrate (0.75 mmol), 2M HCl (0.75 mL), dried MeOH (5 mL), stired at room temp. and vary reaction time.

At room temperature (28-30 °C), when the reaction time was prolonged from 1 to 3 h, the maximum yield of 2,3-dihydroxypropyl-1-benzoate was obtained (entries 1-3). At solvent reflux temperature (65-70 °C), 2,3-dihydroxypropyl-1-benzoate was attained in only trace amount. An unwanted product as methyl benzoate was detected in medium yield (entry 4), probably at high temperature *trans*esterification reaction [31] could be taken place. Thus, deprotecttion with HCl 3 h at room temperature was considered as the most fitting condition. The yield of colorless oil(94%), ^{1}H-NMR (DMSO-d_6) δ (ppm): 3.41-3.44 (2H, *m*, glycerol-*H*), 3.74-3.81 (1H, *m*, glycerol-*H*), 4.15 (1H, *dd*, *J* = 11.15 and 6.29 Hz, glycerol-*H*), 4.29 (1H, *dd*, *J* = 11.15 and 3.95 Hz, glycerol-*H*), 4.72 (1H, *t*, *J* = 5.65 Hz, -O*H*), 5.04 (1H, *d*, *J* = 6.45 Hz, -O*H*), 7.51 (2H, *t*, *J* = 7.64 Hz, Ph*H*), 7.64 (1H, *t*, *J* = 7.40 Hz, Ph*H*), 7.98 (2H, *d*, *J* = 8.40 Hz, Ph*H*). The ^{1}H-NMR 2,3-dihydroxylpropyl-1-benzoate are depicted in Figures A10.

2,3-dihydroxypropyl-1-benzoate



The ^{1}H-NMR spectrum of 2,3-dihydroxypropyl-1-benzoate contained a triplet signal at δ_H 4.72 and a doublet signal at 5.04 of two hydroxyl groups. The five glycerol protons were observed from three signals around δ_H 3.41-4.29 ppm. The signals around δ_H 7.51-7.98 ppm were assigned five aromatic protons.

CHAPTER IV

CONCLUSION

Esterification reaction of carboxylic acid and 1,2-*O*-isopropylideneglycerol was used to produce glycerol monoester product.

The objectives of this research are focused on the suitable halogenated reagent for the transforming of carboxylic acid and 1,2-*O*-isopropylideneglycerol to glycerol monoester. The optimal conditions are also investigated. This developed methodology was carried out under the mild conditions. The high yield of desired product was obtained by this method. The synthesis processes are given as below.

The mixture of reagent was prepared by using triphenylphosphine an benzoic acid dissolve in CH_2Cl_2, then to add $Cl_3CCOOEt$ in the mixture. All prepared solutions were mixed in the volumetric flask, after that to do a further stirring for 1h at solvent reflux temperature. A mixture of 1,2-*O*-isopropylideneglycerol and 4-picoline was mixed to the above prepared solution as well. The whole mixture was refluxed and was done a further stirring for 4 hr. After that, the organic layer was extracted by 10% HCl and saturated aqueous $NaHCO_3$ respectively, dried over Na_2SO_4 and evaporated *in vacuo.* The mixture was separated by silica gel column chromatography using hexane/ethyl acetate to an eluting (9/1).

Various carboxylic acids were determined to verify this developed procedure. Evidently, this method is suitable for aromatic carboxylic acid and long chain aliphatic acids. The long chain aliphatic carboxylic acids are responsible for the high yield of the desired product.

The deprotected acetonide group in product was fruitfully achieved, by using 2M HCl and stirring 3h at room temperature. The application of this developed method by using the acetonide groups could not be suppressed.

This developed protocol is useful for converting the carboxylic acid and1,2-*O*-isopropylideneglycerol to produce the glycerol monoester product. The cost of the reagents used in this method is cheaper than other related methods, which are cited in the literature. The high selectivity of monoester products is abundantly productive.

Suggestion for the further work

This research provided many prospective points for the future work. For instance, other potential halogenating agents such as *p*-nitrophenyl trichloroacetate are still waiting for further investigate. The developed system for synthesis of other valuable glycerol ester such as glycerol β-monoester and glycerol diester should be verified.

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APPENDICES

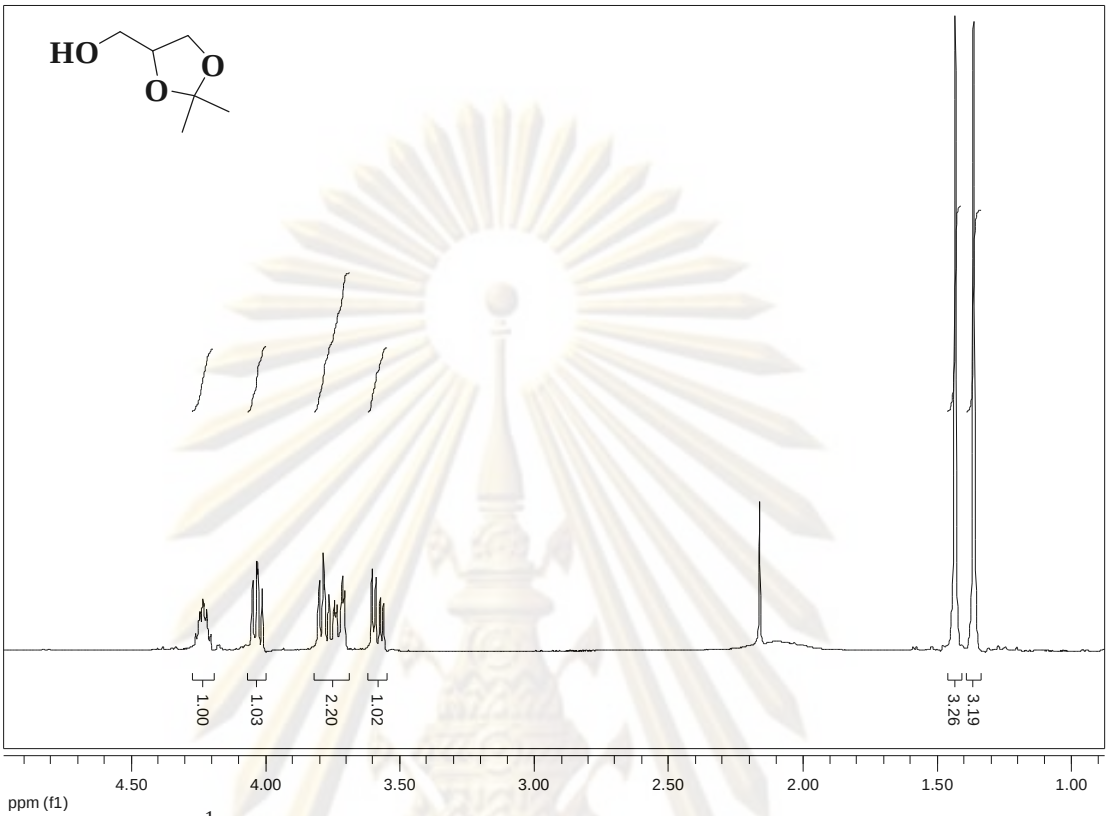

Figure A1 The ^{1}H-NMR spectrum of 1,2-*O*-isopropylideneglycerol.

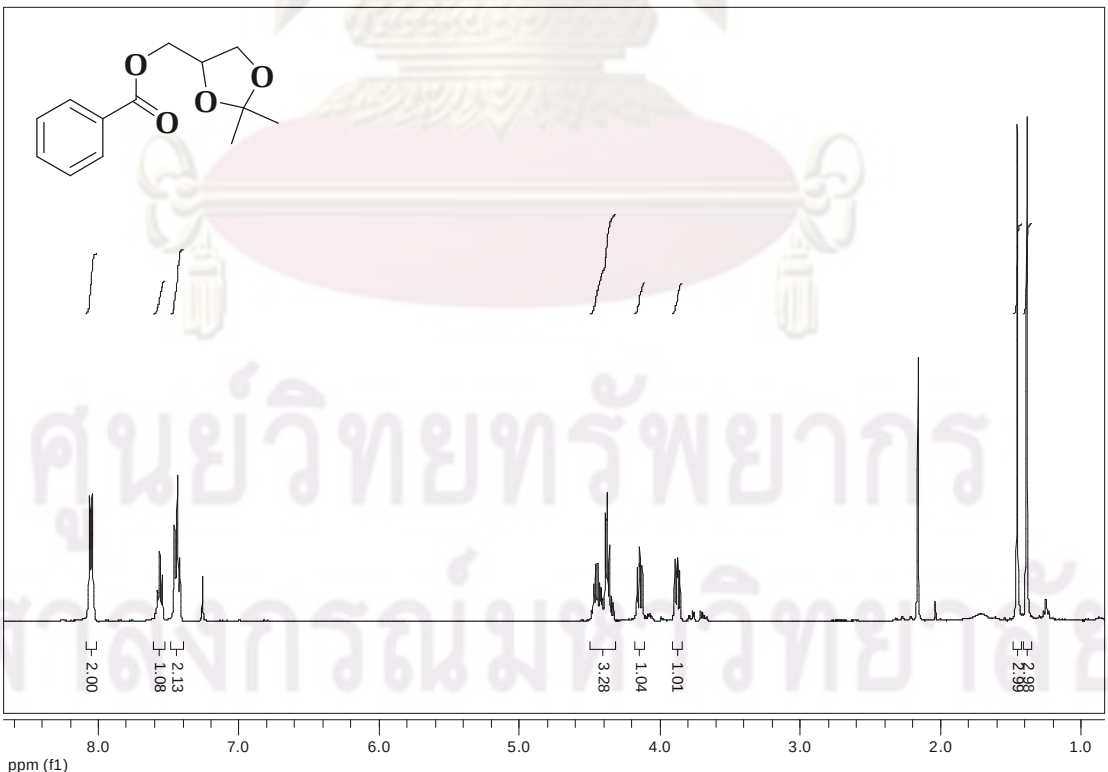

Figure A2 The ^{1}H-NMR spectrum of (2,2-dimethyl-1,3-dioxolan-4-yl)methyl benzoate.

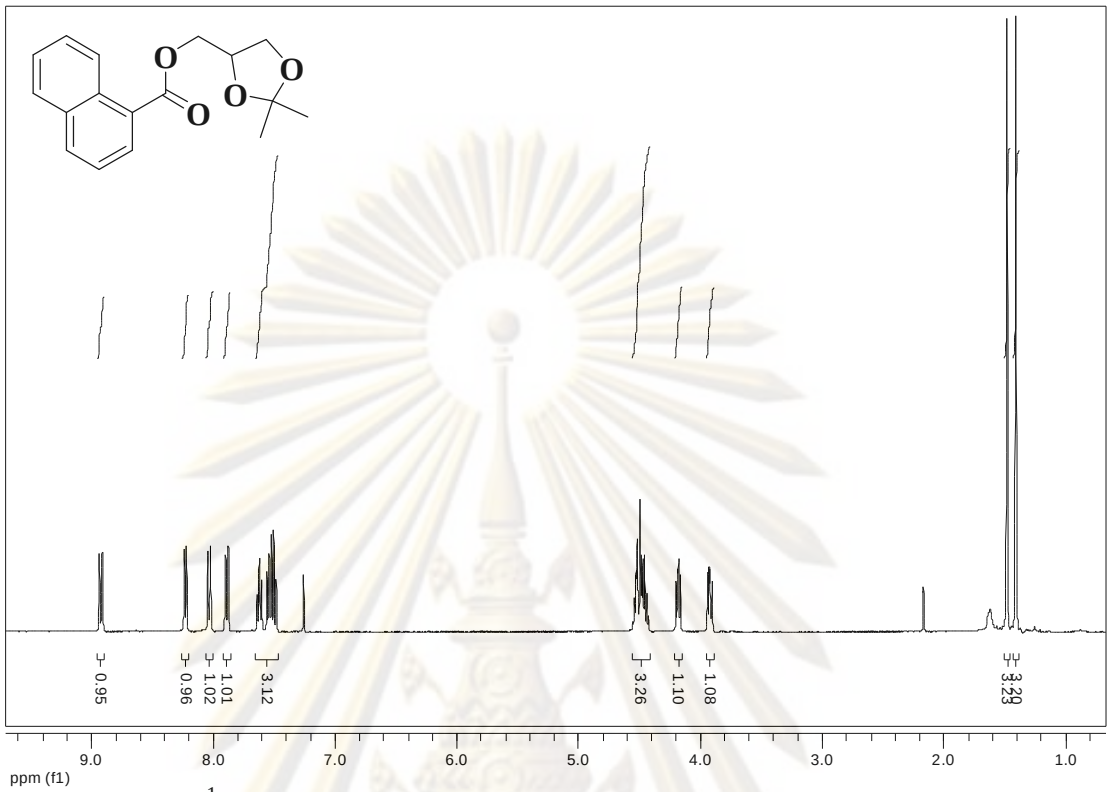

Figure A3 The ^{1}H-NMR spectrum of (2,2-dimethyl-1,3-dioxolan-4-yl)methyl-1-naphthoate.

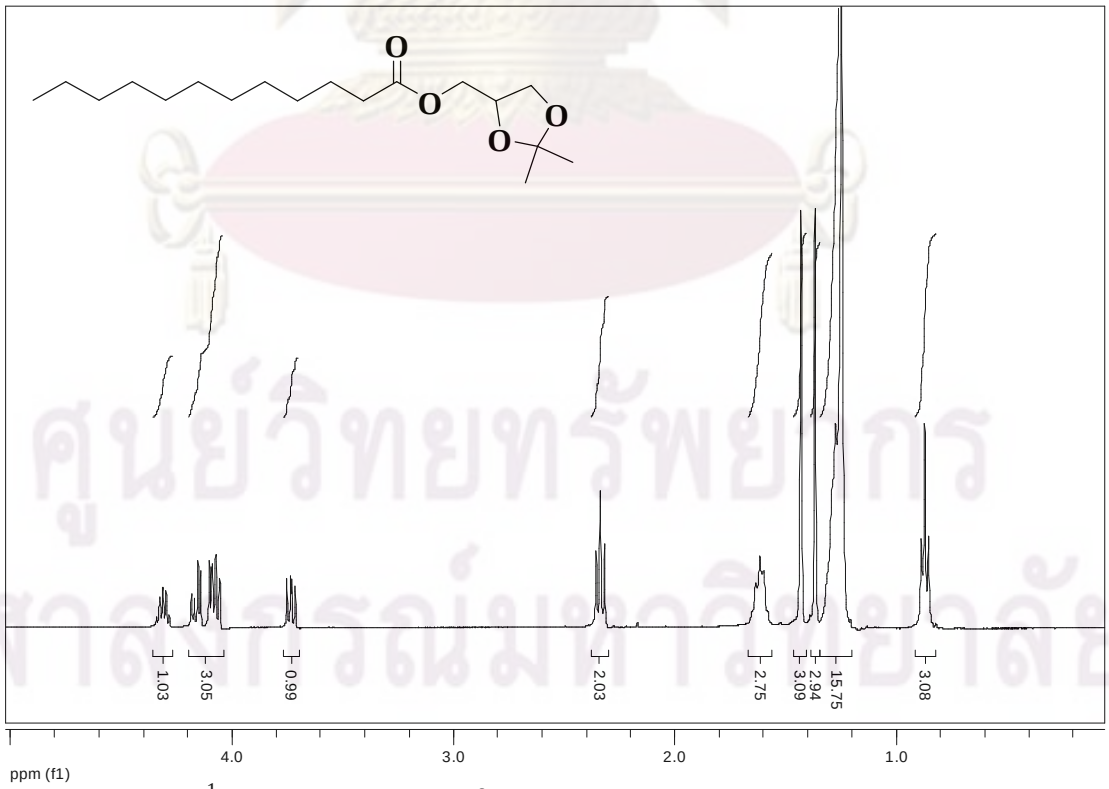

Figure A4 The ^{1}H-NMR spectrum of (2,2-dimethyl-1,3-dioxolan-4-yl)methyl laurate.

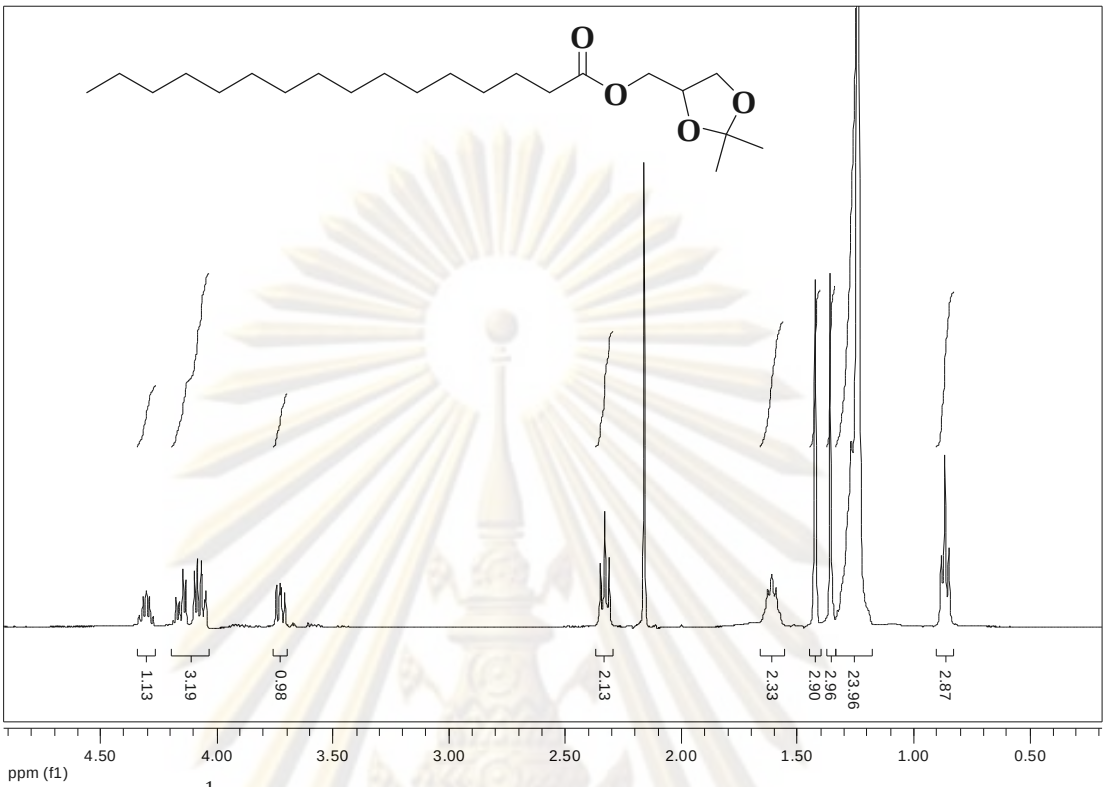

Figure A5 The ^{1}H-NMR spectrum of (2,2-dimethyl-1,3-dioxolan-4-yl)methyl palmitate.

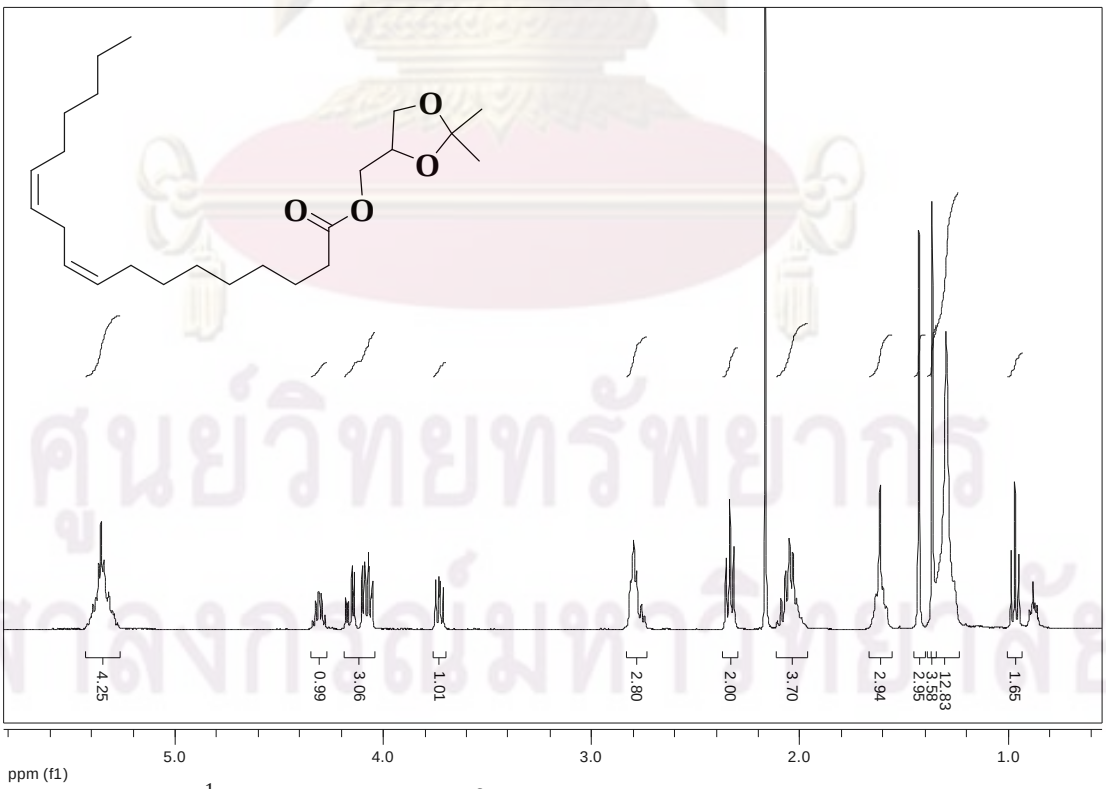

Figure A6 The ^{1}H-NMR spectrum of (2,2-dimethyl-1,3-dioxolan-4-yl)methyl linoleate.

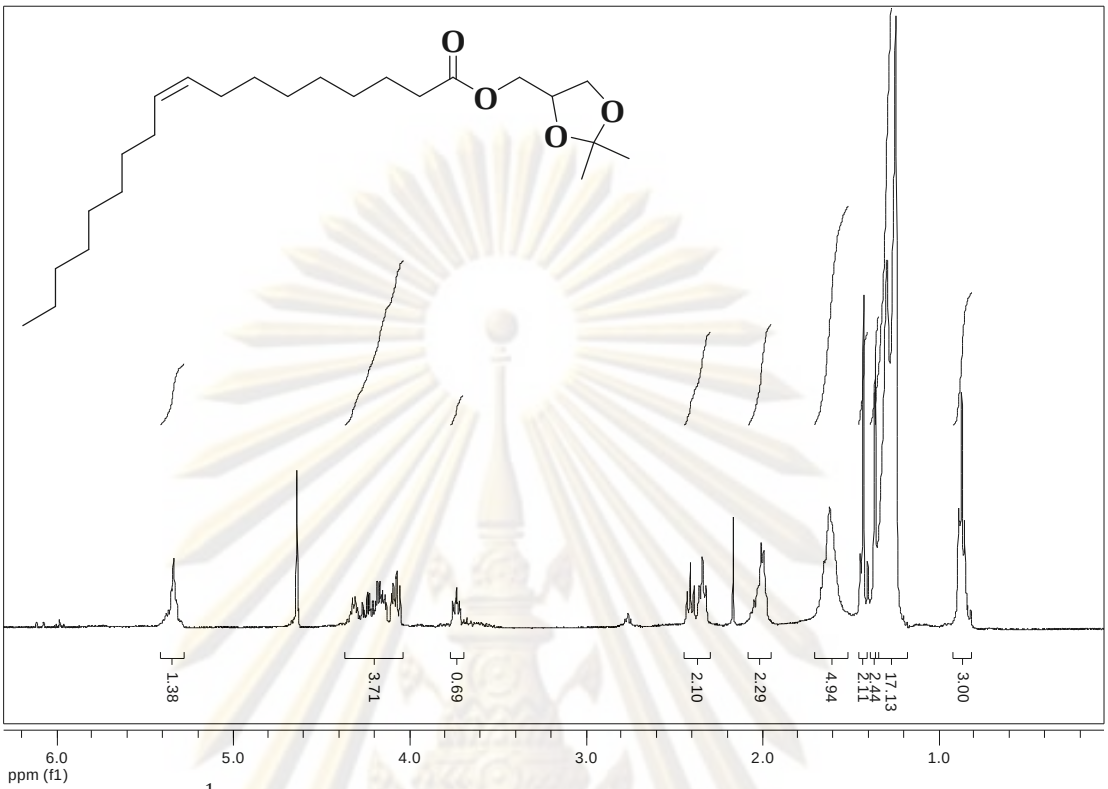

Figure A7 The ^{1}H-NMR spectrum of (2,2-dimethyl-1,3-dioxolan-4-yl)methyl oleate.

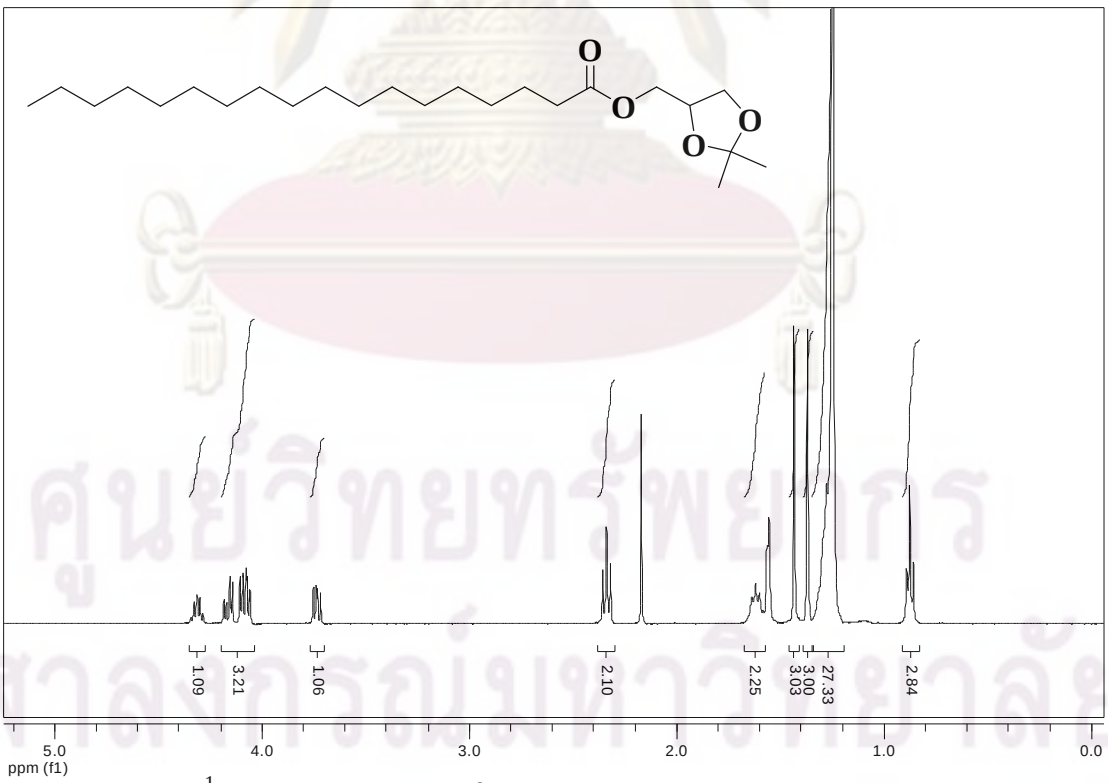

Figure A8 The ^{1}H-NMR spectrum of (2,2-dimethyl-1,3-dioxolan-4-yl)methyl stearate.

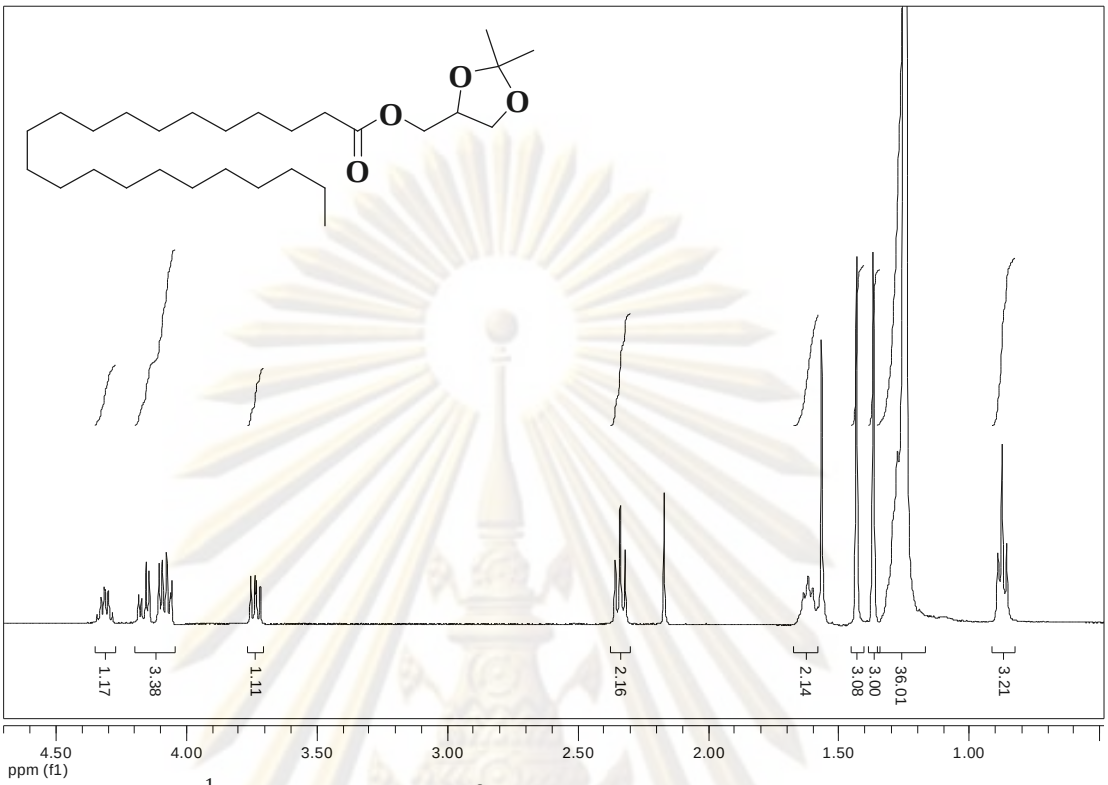

Figure A9 The ^{1}H-NMR spectrum of (2,2-dimethyl-1,3-dioxolan-4-yl)methyl behenate.

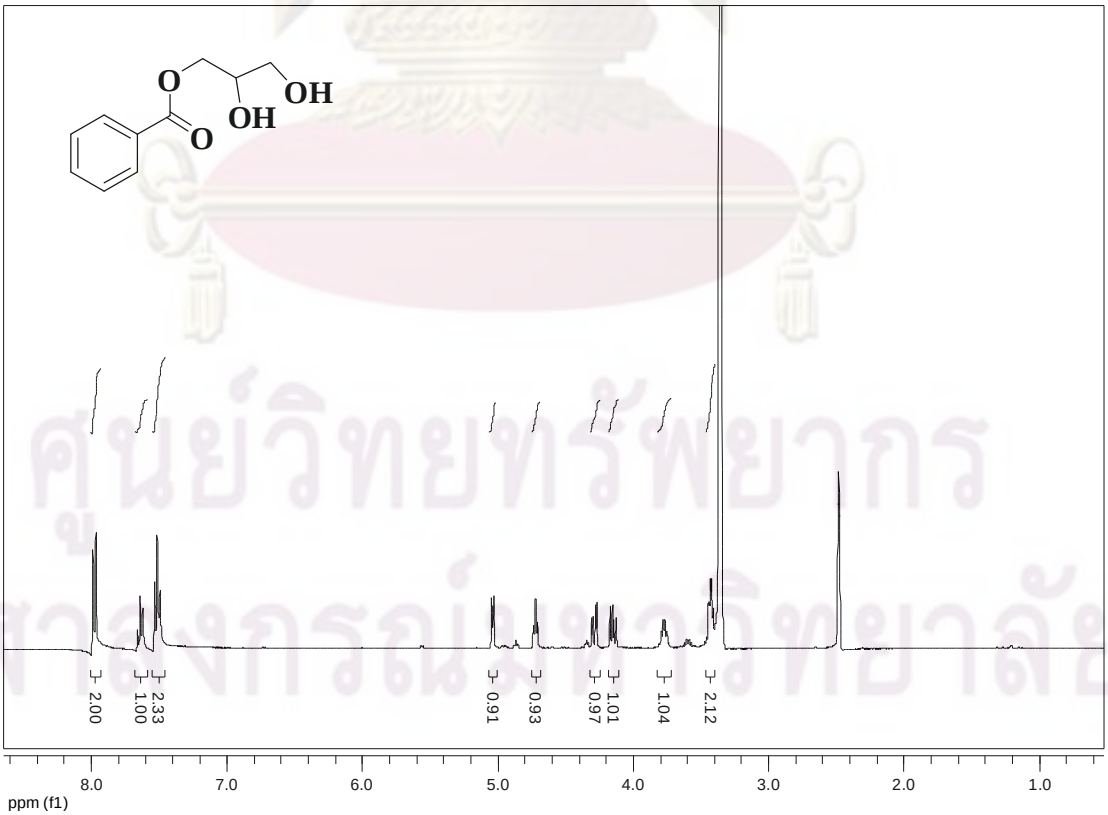

Figure A10 The ^{1}H-NMR spectrum of 2,3-dihydroxypropyl-1-benzoate.

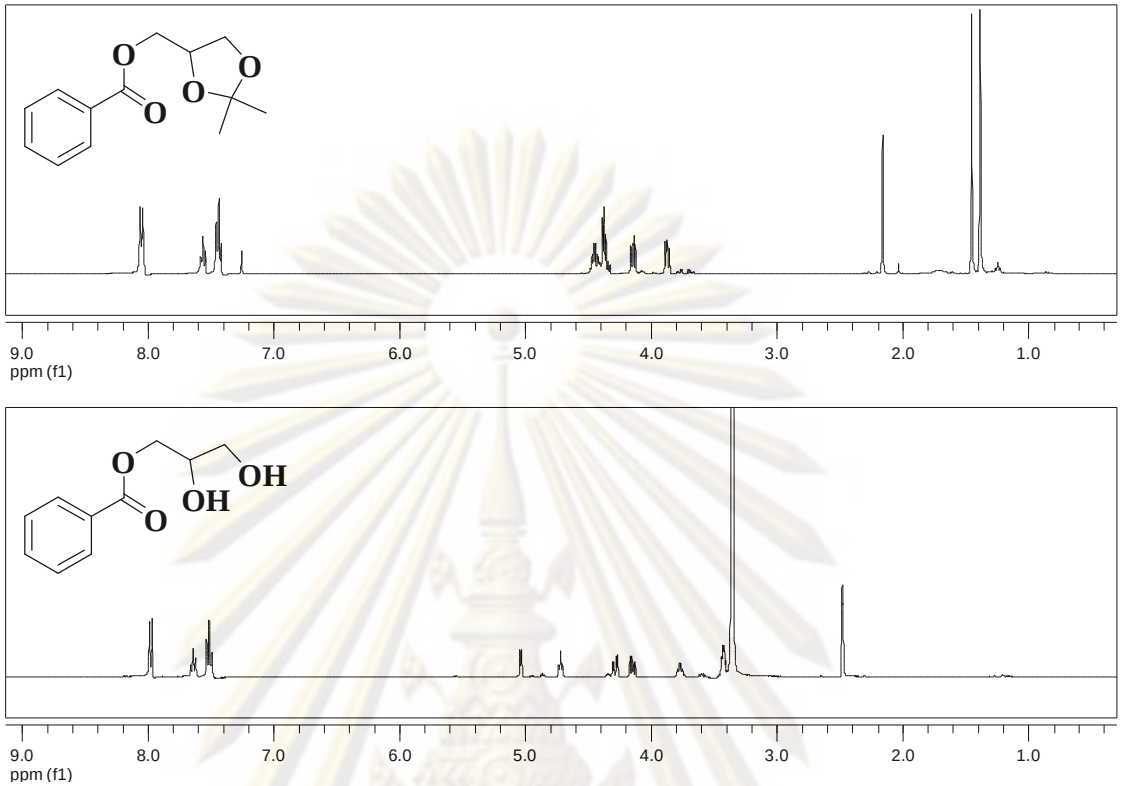

Figure A11 The ^{1}H-NMR spectrum of (2,2-dimethyl-1,3-dioxolan-4-yl)methyl benzoate($CDCl_3$) compare with 2,3-dihydroxyl-1-benzoate(DMSO-d_6).

VITA

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