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ABSTRACT

SYNTHESIS OF CORN-DERIVED CARBOHYDRATE DERIVATIVES AS EFFECTIVE MULTIFUNCTIONAL SUNSCREEN

by
Xianhong Feng

The eighty-years-old sunscreen industry is sustained by the growing incidence of skin cancer and the continual exploration of skin aging. From the UVB-induced erythema to the UVA-induced persistent pigment darkening, scientists have used versatile methods to reveal that not only does UVB damage skin but also that longer wavelengths such as UVAII (290nm~340nm) and UVAI rays (340nm~400nm) trigger skin cancer, premature skin aging and immunosuppression.

To meet a significant demand for improved photoprotection, a broad-spectrum sunscreen with a high extinction coefficient has been desired. As part of our ongoing studies on isosorbide-cinnamate derivatives, this work have found they have great promise as multifunctional sunscreens, based on the isosorbide molecule as a carrier and the cinnamate group's UV absorption.

In this study, a series of isosorbide derived UVB and UVA sunscreens of high extinction coefficient have been successfully synthesized. The combination of these two types of sunscreens covers the full UV-spectrum from 290 to 400nm. The high absorbance in the long wavelength UVA region of these synthetic UVA sunscreens magnifies their improved photoprotective properties, which is the deficient for most commercial sunscreens. Furthermore, these UVA sunscreens are highly photostable

under UVA radiation, which benefits their properties as UV stabilizers in cosmetic and pharmaceutical formulations.

The work described in this thesis also covers the synthesis of isosorbide-derived antioxidants and an isosorbide-derived single compound which functions as both UVB sunscreen and plasticizer. This compound can also increase the flow properties of polymers especially polyvinyl chloride (PVC) etc. Based on the different reactivities of the two -OH groups on the isosorbide, this work have demonstrated two synthetic routes to multifunctional single compounds such as a UV absorbing antioxidant. Continuing this idea, a full spectrum UV absorber, a UV absorbing thermal stabilizer and other multiple combinations could be made using the same synthetic route in the future.

**SYNTHESIS OF CORN-DERIVED CARBOHYDRATE DERIVATIVES AS
EFFECTIVE MULTIFUNCTIONAL SUNSCREEN**

by
Xianhong Feng

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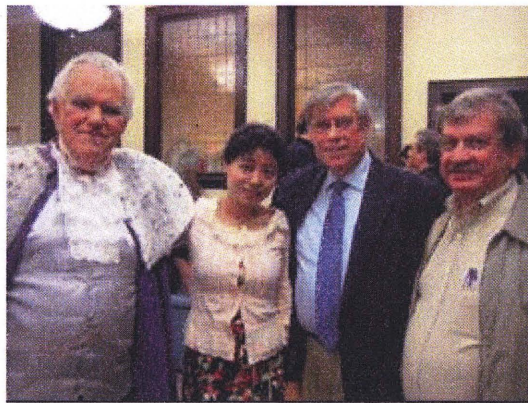
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CHAPTER 1

INTRODUCTION

1.1 Background Information

Nearly 40 years since the official launch of the "War on Cancer"[1] in 1971, the conflict shows no sign of ending. Based on the data of The National Institutes of Health, just skin cancer, the most common cancer in the USA, affects more than 1,000,000 Americans every year. It accounts for more than 10,000 deaths annually[2]. It's hard to believe that spending time in the sun increases our risk for the most common cancer and skin aging. However, Knowing is half the battle. Since 1983, scientists have found versatile methods to reveal that chronic sun exposure plays an important role in etiology of skin cancers[3],inflammation[4] and skin aging[5].

As is well known, the electromagnetic spectrum emitted by the sun ranges from the very short cosmic rays to the very long radio waves[6]. The ultraviolet (UV) rays which comprise the shortest of the non-ionizing rays are responsible for most of the photocutaneous changes. That is because the amount of energy in photons of the ultraviolet radiation can be absorbed by the photosensitizing molecules in the body to undergo degradation, chemical reaction and generate toxic radicals. The shorter the wavelength, the more damaging is the UV radiation. The damaging UV radiation is usually divided into three categories: UVC rays (100~290nm), UVB rays (290~320nm) and UVA rays (320~400nm). Even though all of them have potential to damage collagen fibers thereby accelerate aging of the skin, only the UVB and UVA are considered to be the main culprit who is responsible for the solar damage and skin disease[7].

The reason for this is that UVC is completely absorbed by the atmosphere and

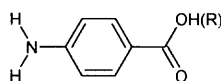
loses its highest energy before it reaches the ground. While the UVB and UVA rays can penetrate through the ozone and trigger photobiological event in the skin[5]. Prolonged UVB damages dermal connective tissues and is the primary carcinogenic stimulus for skin cancers through clinical formation of pyrimidine dimers[8]. As a rule, these rays do not pass through window glasses. In contrast, UVA rays **do** pass through window glass and produce a series of phototoxic events such as inducing DNA damage[9], generating reactive oxygen species[10] and triggering elastosis where elastic fibers decreases and premature skin-aging is initiated. Usually these changes remain for a full 12 weeks after exposure[8].

Increasing awareness of these damaging effects of sunlight had led to a significant demand for improved photoprotection by topical applied sunscreen agents. Several studies have shown that sunscreen not only protects against UV induced erythema in human and animal skin but also inhibits photo-carcinogenesis in animal skin. The first reported use of sunscreens in the world was in 1928, in the United States, with the commercial introduction of an emulsion containing two suncreening ingredients, benzyl salicylate and benzyl cinnamate[11]. Later on, p-aminobenzoic acid (PABA) was first patented in 1943, leading the way for the incorporation of several p-aminobenzoate derivatives in sunscreen formulations[12]. During World War II when red petrolatum was used by the U.S military, the extensive use of both physical and chemical ultraviolet filters was initiated. After 80 years evolution, multiple sunscreens have been desired based on the classic “structure-activity relationship” (SAR) studies.

1.2 Categories

In the United States, the UV filters include 2 categories: physical blockers and chemical absorbers. The two major component of physical blocker are titanium dioxide and zinc oxide. Because of their cellular and DNA damage in human skin cells and several other types of animal epithelial cell lines, some types of them are doubted whether are appropriate to use in sunscreen lotions[13]. For chemical UV filters in use throughout the world, they can be classified as derivates of the following: PABA and p-aminobenzoates, Salicylates, Cinnamates, Benzophenones, Anthranilates, Dibenzoylmethanes, Camphor derivates and other miscellaneous chemicals. Most of them will be introduced in this chapter.

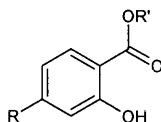
1.2.1 PABA and P-aminobenzoates



This chemical compound has maxima absorption at 296nm with a moderate molar extinction coefficient of 13600. The electron delocalization between electron releasing group (-NH₂) and an electron acceptor group (-COOH) corresponds to the electronic transitions associated with UVB region of the sunlight. Because its free amine tends to oxidize rapidly in the air and it is sensitive to pH, this compound is unstable and hard to formulate; the intermolecular hydrogen bonding between amine and carboxylic group producing a crystalline physical state make it hard to be dissolved in the formulation. And its hydrogen bond with solvent creates the solvent effect such as Hypsochromic shift in polar solvent [14] even if amine and carboxylic group are esterified.

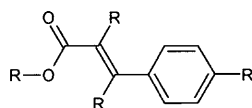
1.2.2 Salicylate

This chemical compound has UVB absorption around 300~310nm. Due to the ortho-position of this specific hydroxybenzoate, this compound can form intramolecular hydrogen bond which lowers the energy requirements for promoting excited state[15].



However, this crowding and strain position between two function groups leads them to deviate slightly from planarity, which lowers the extinction coefficient by considering its electronic dislocations. While this intramolecular hydrogen bondings make them less available for interaction with biological substrate on the skin. Therefore,, provide their safety and stability in both polar and nonpolar solvent.

1.2.3 Cinnamates

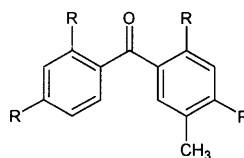


This class of compound belongs to be one of the earliest sunscreen protecting the UVB portion of the electromagnetic spectrum. Their extra unsaturation conjugating system from aromatic ring to carbonyl group permits the electron dislocalization to occur throughout the molecule[14]. The energy associated with this electron transition corresponds to a wavelength of about 305nm with strong molar extinction coefficient of 23000. Even if they are subject to some cis-trans isomerism, the literature report demonstrate their reasonable photostability[16]: only 4.5% loss in activity, compared with 15.5% loss of octyldimethyl PABA, and 36% loss of Parsol 1789 (Avobenzone, a FDA approved UVA absorber)[17]. Four of these derivatives have been proved by the

FDA including :Diethanolamin-p-methoxycinnamate,2-Ethylhexyl-p-methoxycinnamate, 2-Ethoxyethyl-p-methoxycinnamate, Ethylhexyl- α -cyano- β -phenylcinnamate.

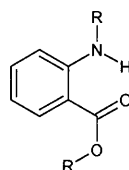
1.2.4 Benzophenones

This class of sunscreens is the only compound that belongs to aromatic ketone category. Their resonance delocalization is aided by the presence of an electron-releasing group in either the ortho or para-position to the electron-accepting carbonyl group. Aromatic ketones, unlike the benzoate esters, will resonate more easily.



That is because that the extra oxygen atom in ester destabilizes the electron transitions. Thereby benzophenone requires a lower quantum of energy to absorb longer UV wavelength. Since ketone structure is different from the ester which usually can be hydrolyzed in vivo and render the by-products that body can metabolize, benzophenones are hard to be metabolized and statistically generate allergic reactions to the patients [18]. And because some of the materials in this category have solid structure, they are hard to be solubilized in the solvent and have solvent effect.

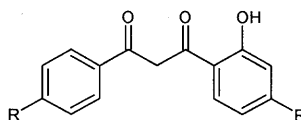
1.2.5 Anthranilates



Like the salicylate, anthranilate, an ortho-disubstituted aminobenzoate has easier electron delocalization activity with the “through space” assistance. It can absorb UV light down

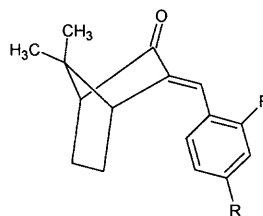
to the 336nm, compared with the PABA, a para-disubstitute aminobenzoate, with a λ_{max} of only 298nm. For the same reason with salicylate, the crowding structure of anthranilate produce a low extinction coefficient compared with PABA

1.2.6 Dibenzoylmethane



This class of substituted diketones received limited approval for use in the United States. Because their keto-enol tautomerism lead a significant loss of protective power when they shift to the keto form which posses a λ_{max} of only 260nm. .Therefore, even if it has exceptionally high molar extinction coefficient (>30000), its low photostability sacrifices utility.

1.2.7 Camphor Derivatives



None of this class of compound has been approved by FDA. They are UVB absorbers and have strong extinction coefficient above 20,000 and high photostability, only lose 2.5% activity under radiation.

1.3 Objectives

As described above, the UV-filtering ability of an organic sunscreen actually depends on its UV absorption property. The more the absorption, the better the photo-protective is the sunscreen. A parameter, extinction coefficient, is widely used here to measure how well a particular substance absorbs electromagnetic radiation. The higher the extinction coefficient, the stronger is the absorption. As part of our ongoing studies on isosorbide-cinnamate derivatives, this has found these materials have great promise as sunscreens of high extinction coefficient. Based on the isosorbide molecule as a carrier and the cinnamate group's UV absorption, synthesis of sunscreens with high extinction coefficient looks encouraging to us.

Isosorbide, which comes from glucose by reduction to sorbitol and acid-catalyzed cyclodehydration, is a stable, rigid, nature derived bisanhydrohexitol. This material has widely been used in pharmaceutical and food industries since its water soluble and harmless properties. It is increasingly becoming used as an intermediate for additives and stabilizers. After choosing it as nucleus, this work has proposed to attach different cinnamic derivatives to isosorbide to create a new series of UVB sunscreens with high extinction coefficient. 4-methoxycinnamic acid and 3,4,5-trimethoxycinnamic acid were chosen in this application as their ester forms hold photostability and highly stability potential against percutaneous diffusions[19]. Ferulic acid, which is derived from the plant cell wall, was also chosen in this application due to its significant health benefits through its antioxidant and anti-cancer activities.

On another hand, since solar irradiance studies have shown that somewhere between 10 and 15 times as much ultraviolet A radiation as ultraviolet B radiation

reaches the earth's surface each day[20], long wavelength UVA protection[21] becomes an important factor for chemists to design UVA sunscreens. However, from the list of FDA approved sunscreens in category 1, this work found that there was no approved cinnamate derivatives can cover the whole UVA region of electromagnetic spectrums. The most common used agents in this category are 2-Ethylhexyl-p-methoxycinnamate and cinoxate, both of which are just responsible for UVB and short wavelength UVA absorptions. The increasing understanding of the UVA rays in the suncreening application make us to consider about making a broad UVA especially long wavelength UVA absorbers derived from cinnamate, which can be better-suited to the cosmetics and medicine market.

Through attaching several kinds of hydroxycinnamic acid to the isosorbide's hydroxyl groups parallel with chemically modifying the backbone of the cinnamic acid, there should be some opportunities to synthesize a series of novel UVA filters as isosorbide-cinnamate derivatives of high extinction coefficient. They were expected to cover the full-UVA region especially the long wavelength UVA region. The mixture of these synthesized UVA sunscreens with the synthesized UVB sunscreens which have been desired above should cover both the UVB and UVA regions of electromagnetic spectrum. And the synthesized UVA sunscreens should be highly photostable under UVA radiations. Based on the same theory, an antioxidant as isosorbide derivatives can be synthesized. The combination of these isosorbide derivatives could generate a multifunctional sunscreen formulation which not only acts as a broad UV absorber but also an antioxidant.

Moreover, isosorbide, unlike its isomers isomannide and isoidide, has two hydroxyl groups with different topographies and chemical reactivity[22]. The 2-*exo* and 5-*endo* hydroxyl group lead isosorbide can be selectively esterified by use of appropriate synthetic routes. Following this method, several multifunctional single compounds can be made by attaching different functional moieties to the isosorbide. This biomass derived single multifunctional compound has strongly-perceived market in cosmetics and medicines. Because till now there is no commercially available single compound could cover both UVA and UVB region of the sunlight and there is no single agent which can have both UV absorption and antioxidant functions. By use of isosorbide as a carrier, this work can combine two different UV absorber chromophores to widen the spectral range or connect UV absorbers with antioxidant to make UV absorbing antioxidant. These UV absorbers should be highly photostable and stable against percutaneous diffusion by themselves. Continuing this idea, the plasticizers for materials such as PVC with additional stabilizer functions such as UV stabilizer, thermal stabilizer can be made and a sunscreen with additional surfactant function can be made. The possibility of this combination is wide.

CHAPTER 2

SYNTHESIS ROUTES

2.1 Preparation of Isosorbide Derived UVB Sunscreens With High Extinction Coefficient

In this part, the synthesis routes for preparation of isosorbide derived UVB sunscreens will be described. By attaching different cinnamic moieties to the isosorbide, several UVB sunscreens of notably high extinction coefficient have been desired. Different absorbances in the UVB region are expected for differently synthesized UVB sunscreens.

2.1.1 Synthetic route for Preparation of 4-Methoxycinnamic Acid (1)

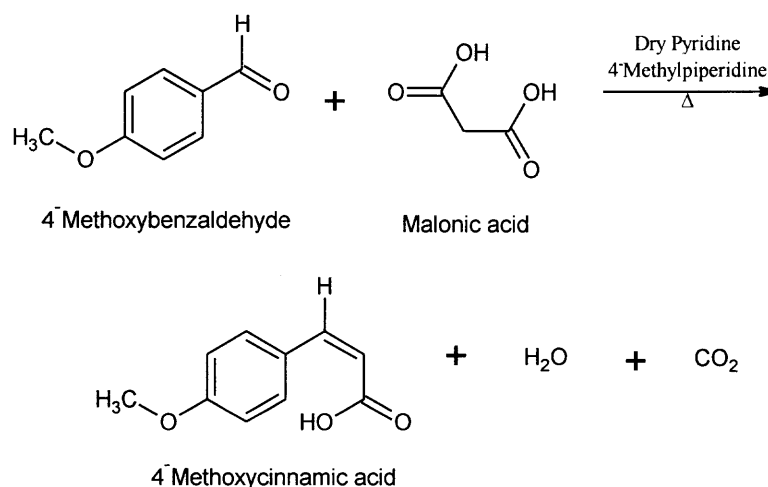


Figure 2.1 Synthetic route for synthesis of 4-methoxycinnamic acid.

This synthetic route is known as the Knoevenagel condensation, named after Emil Knoevenagel. It uses an active methylene compound such as malonic acid which reacts with a carbonyl group such as 4-methoxybenzaldehyde under nucleophilic conditions. Usually the catalyst in this reaction is a secondary amine such as piperidine (derived from pepper), but this work used 4-methylpiperidine, since it is more conveniently available.

At high temperatures, the malonic acid can lose one molecule of water and one molecule of carbon dioxide. Therefore, the loss of both water and carbon dioxide drives the reaction forward, rather than leaving it at equilibrium.

2.1.2 Material and Method

Materials:

- 1) 4-Methoxybenzaldehyde 90gm (0.66mole)
- 2) Malonic acid 150gm (1.44mole)
- 3) Dry pyridine 300ml
- 4) 4-Methylpiperidine a few drops

Method:

The reaction was run in a 3-neck 500 ml round bottom flask. A reflux condenser with a bubbler tube was set on the top of one neck and a long-stem thermometer carrying a Thermowatch™ sensor was set on another neck. The extra neck was stoppered. The prepared material was poured into the flask and stirred with a magnetic stirrer bar. The whole system was heated by means of a heating mantle. By use of the Thermowatch™, the temperature of the batch was kept around 100 °C. As soon as all materials had dissolved in the solution, carbon dioxide began to bubble off quickly from the flask. Then the Thermowatch™ was adjusted to keep the temperature of the batch around 95°C. Carbon dioxide was evolved steadily. After running for about 2~3 hours, carbon dioxide evolution stopped. Then the temperature was raised up to 120 °C in order to reflux the solution for about 5~10 minutes, which completed the de-carboxylation reaction whereby any excess malonic acid was degraded. When no more gas was evolved the flask was let cool. Meanwhile a 2000ml beaker was filled with 150ml de-ionized water and 350ml

concentrated hydrochloric acid. This acid solution was stirred with a paddle stirrer. When the flask had cooled to about 80 °C, the contents of the flask was poured in a thin stream into the dilute acid and a thick white precipitate of 4-methoxycinnamic acid came out. Then the solution was filtered through a big Buchner funnel using a # 4, 18.5cm filter paper and washed several times with de-ionized water. The pH of the filtrate was about 2.0 and the filter cake was pressed and sucked dry on the funnel for about 15 minutes. Then the solid was placed in a large crystallizing dish and dried at 17 millibar in a vacuum oven at 70~80°C overnight. The pale cream product weighed 111.1gm, 94.5% theoretical yield. The total solid was dissolved in boiling ethanol and let cool in the freezer. After standing overnight, colorless needle-like crystals came out from the ethanol solution. A Buchner funnel was used to filter off these crystals under vacuum. The solid was dried and recrystallized again from fresh ethanol. In this way 75gm well-crystallized 4-methoxycinnamic acid was generated, around 64% theoretical yield.

2.1.3 Synthetic Route for Preparation of Isosorbide Bis(4-methoxycinnamate)

Route 1:

This synthetic route is a Fischer esterification reaction, a well-known esterification process whereby a carboxylic acid is heated with an alcohol in the presence of an strongly acid catalyst. Our catalyst was toluene-4-sulfonic acid, which is readily soluble in organic solvents.

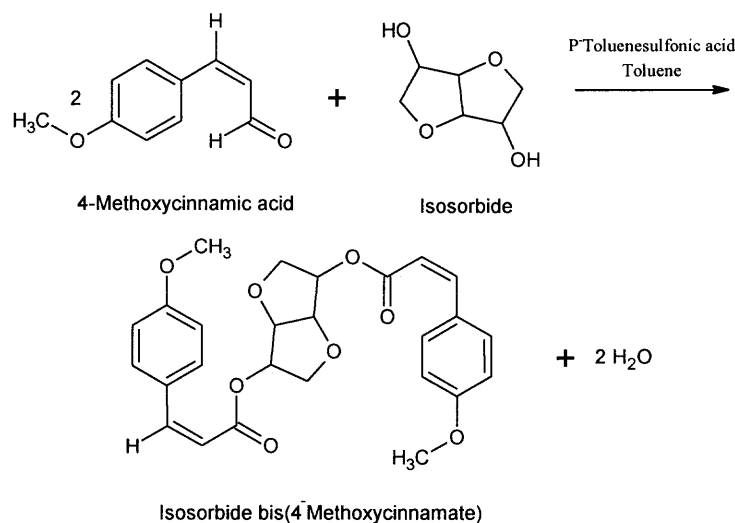


Figure 2.2 Synthetic route for isosorbide bis (4-methoxycinnamate).

This route involves 5 steps: (1) Proton transfer from acid catalyst to carbonyl oxygen to increase electrophilicity of carbonyl carbon; (2) The carbonyl carbon is then attacked by the nucleophilic oxygen atom of the alcohol, leading to the formation of an oxonium ion; (3) oxonium ion transfer to oxygen of the alcohol gives an activated complex; (4) Protonation of one of the hydroxyl groups gives a new oxonium ion; (5) Loss of water from this oxonium ion and subsequent loss of a proton gives the ester.

Route 2:

Step 1: Preparation of 4-methoxycinnamyl Chloride (2)

Route ①:

This reaction follows a synthetic route of internal nucleophilic substitution (S_Ni) reaction, in which thionyl chloride is used to convert the carboxylic acid to the acyl chloride. The initial reaction produces a cyclic intermediate or an intermediate complex with tight ion-pairing. Firstly, thionyl chloride reacts with the hydroxyl of the carboxylic acid to form a chlorosulfite, which re-arranges by a cyclic mechanism to form the acyl chloride

and displace sulfur dioxide. The side products from the reaction are the volatile SO_2 and hydrogen chloride gas, which enable the reaction to proceed.

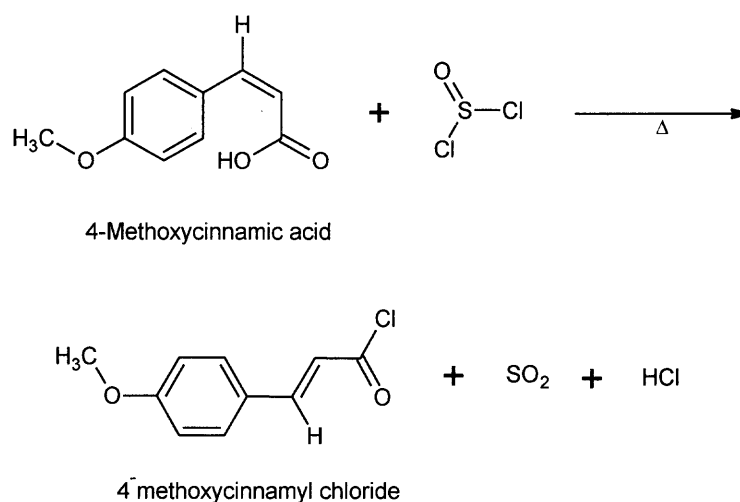


Figure 2.3 Synthetic route for synthesis of 4-methoxycinnamyl chloride.

Route □:

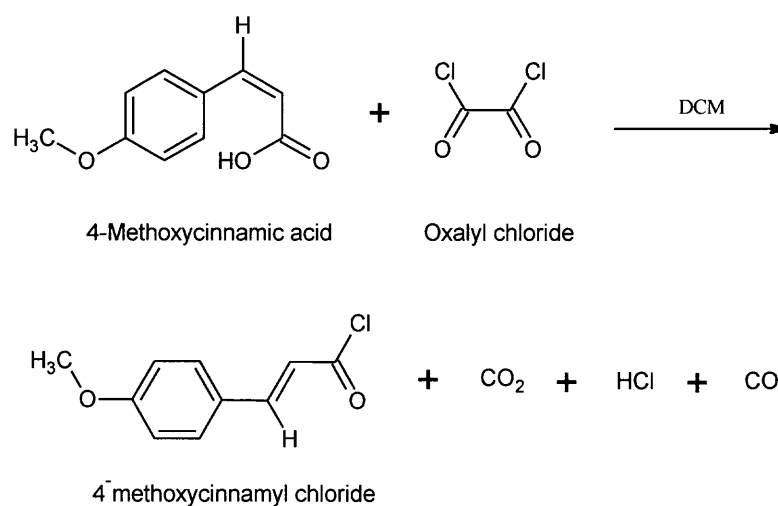


Figure 2.4 Synthetic route for 4-methoxycinnamyl chloride.

In this route, 4-methoxycinnamyl chloride is made using oxalyl chloride, which is a useful, if expensive, agent used to convert a carboxylic acid to its corresponding acid chloride. Although oxalyl chloride reacts in a similar way to thionyl chloride, it is milder and more selective. The side products are HCl , CO_2 and CO . Since oxalyl chloride can

react with water to release HCl, this reaction requires exclusion of water and the release of the volatile products drives the reaction forward.

Step 2: Preparation of Isosorbide Bis-(4-methoxycinnamate)(3)

In this route, the carboxylic acid halide is reacted with an alcohol to form the corresponding ester. Because of the high reactivity of the acyl halide, this reaction is often too vigorous to control and evolves excess heat, which results in a mixture of impure products. Therefore, this reaction should be kept cold, around 0°C.

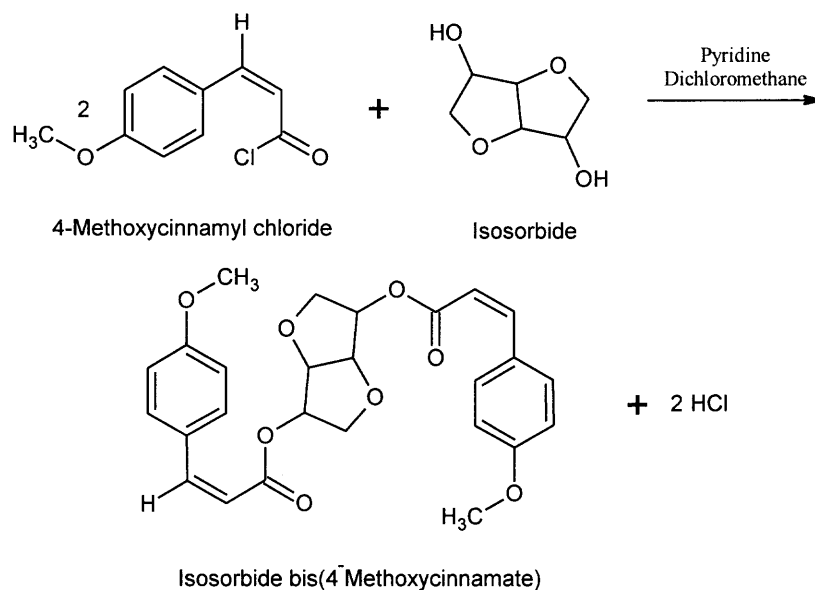


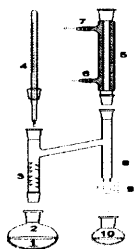
Figure 2.5 Synthetic route for synthesis of isosorbide bis (4-methoxycinnamate).

2.1.4 Material and Method

Route 1:

Materials:

- | | |
|---------------------------|-------------------|
| 1) 4-Methoxycinnamic acid | 44.5gm (0.25mole) |
| 2) Isosorbide | 14.6gm (0.1mole) |
| 3) p-Toluenesulfonic acid | 0.5gm(catalyst) |
| 4) Toluene | 500ml |

Method:

This reaction was first attempted using chloroform as a reaction medium but the cinnamic acid was insoluble, so toluene was substituted. It was run in a 1000ml three-neck flask with a magnetic stirrer. One of the necks was fitted with a Dean-Stark apparatus with a reflux condenser and a thermometer. The other two necks were fitted with a thermometer and a stopper. The whole system was heated on a heating mantle. After pouring all the ingredients into the flask and heating the mixture for a period of time, the 4-methoxycinnamic acid dissolved in the toluene. The latter is an aromatic hydrocarbon and is widely used as a solvent for the aromatic chemical reactions. The vapors containing an azeotrope of toluene and water travel out of the reaction flask up into the condenser and then drip into the distilling trap where the immiscible toluene and water separated into two layers. When the top layer of toluene reached the level of the side-arm, it could flow back to the reactor, while the lower water layer (with a higher density) would remain in the trap. The water was periodically collected in a measuring cylinder. After 2 days' running, no more water came out. The total volume of the water was 1.6ml. Then the heating was turned off and the toluene solution let cool. The cooled toluene solution was washed three times with 100ml of 15% saturated NaHCO_3 to neutralize the extra acid in a 1000ml Squibb funnel. Then two portions of 100ml saturated NaCl was used to wash off the NaHCO_3 and 100ml de-ionized water was used to wash away the last of the brine solution.. After that, magnesium sulfate was added into the toluene filtrate and the whole filtrate solution was put into the freezer. After 2 hours, the MgSO_4 was filtered through a Buchner funnel with #4, 7.7mm filter paper. The filtrate solution was taken to a vacuum rotary evaporator to

remove the toluene solvent. The residue was a yellow oil and weighed 50.61 gm (108% theoretical yield)

Route 2:

Step 1: Preparation of 4-methoxycinnamyl Chloride

Route ①:

Materials:

- 1) 4-Methoxycinnamic acid 44.5gm (0.25mole)
- 2) Thionyl chloride 30.6ml (0.42mole)

Method:

A 250ml one-neck round bottom flask with a heating mantle was used. In order to eliminate the acidic gases produced in the hood, a reflux condenser with a gas outlet tube was connected with the neck of the flask to lead the gases to a water trap. After the 4-methoxycinnamic acid, thionyl chloride and catalyst were poured into the flask, the mixture was gently stirred and heated for a few minutes. When the thionyl chloride started to reflux, a pale yellow solution was formed in the flask and the HCl and SO₂ gas started to evolve. After refluxing for about 2 hours, the color of the solution had turned from the initial orange, to darker and darker brown, and finally became a black oil, which illustrated that extensive decomposition had occurred.

Route ②:

Materials:

- 1) 4-Methoxycinnamic acid 44.14gm (0.248mole)
- 2) Oxalyl chloride 32,5gm (0.372mole)
- 3) Dichloromethane 400ml

Method:

This reaction was run in a 500ml one-neck round bottom flask with a condenser. A Drierite™ guard tube was connected to this condenser to prevent any moisture invading the flask. A mixture of 400ml methylene chloride, and the 4-methoxycinnamic acid was added to the flask, the solution was stirred at room temperature for a few minutes. When oxalyl chloride was poured into the flask down the condenser, the solution immediately became pale yellow and the gas started to evolve vigorously. After 30 minutes, the color of the solution had turned a bright lemon-yellow and HCl was coming off steadily, which was checked by use of strong ammonium hydroxide. When the ammonia gas and HCl came in contact, a dense white smoke of solid particles of NH₄Cl could be observed. When the HCl gas evolution ceased, the yellow solution became substantially but not entirely clear. The flask was warmed gently on a heating mantle to drive off the last traces of HCl. After one hours' running, the solution became clear and no more HCl came off. The flask was let cool and the solution taken down to dryness on a rotary evaporator. The product started to crystallize in the evaporator flask as a yellow waxy solid. The yield of it was 49.63gm (101.87 % theoretical yield). The recovered methylene chloride was mixed with water to kill the any un-reacted oxalyl chloride.

Step 2: Preparation of Isosorbide Bis-(4-methoxycinnamate)**Materials:**

- 1) 4-Methoxycinnamyl chloride 29gm (0.148mole)
- 2) Isosorbide 10gm (0.068mole)
- 3) Dry Pyridine 50ml
- 4) Dichloromethane 100ml

Method:

This reaction was run in a 500ml 3-neck round bottom flask with a magnetic stirrer. A 50ml Kontes "Bantam-Ware"TM pressure-equalizing (PE) tap funnel with a nitrogen inlet tube was fitted into of its necks. A reflux condenser with a bubbler tube was connected to the 2nd neck to measure the nitrogen flow and a thermometer was set in the third neck to measure the temperature of the flask. In order to control the reaction temperature the whole system was placed in an ice bath. After the flask was charged with isosorbide and dry pyridine, 4-methoxycinnamyl chloride in dichloromethane was added slowly into the flask through the PE funnel. The solution immediately started to form a yellow solid and some white fumes came out. In order to keep the reaction proceeding steadily, the flask temperature was kept below 5 °C. After 3 days' running, some brown solid was formed in the flask. To neutralize unreacted pyridine, the reaction mixture was poured into a beaker containing a little concentrated HCl and 250ml de-ionized water. The mixture was separated in a 1000ml Squibb funnel. The aqueous phase was washed with 100ml DCM three times to extract any traces of the organic-soluble products. The DCM layer was again shaken once with 200ml brine solution and once with 200ml de-ionized water. Anhydrous MgSO₄ was added to the DCM solution and the mixture left to dry 3 hours in the freezer. After that, the solution was filtered through a Buchner funnel with #4, 12cm filter paper. The filtrate was taken down on a Büchi RotovapTM to get rid of the methylene chloride. The crude product was a honey-colored thick oil weighing 45.8gm (144% theoretical yield). This showed the crude product still had some un-reacted starting materials in it. Therefore, the oil was taken to the RotovapTM again and heated at 60 °C /20millibar for about 30 minutes to distill off more volatiles. After this the weight of

the oil was 33.4gm (105% theoretical yield). The viscous oil spontaneously began to crystallize. After 3 days', it had completely solidified and became pale brown. From the NMR spectrum, it was shown that it was a mixture of ester and pyridine in a 1:1 ratio. Therefore, the pyridine was washed away with diethyl ether. After washing the brown crystals with 100 ml of ethyl ether three times, the crystals became white. This white solid was filtered from the ethyl ether and after drying weighed 24.02 gm (75.7% theoretical yield)

2.1.5 Synthetic Route for Isosorbide Bis(3,4,5-trimethoxycinnamate)

Step 1: Preparation of 3, 4, 5-trimethoxycinnamic Acid (4)

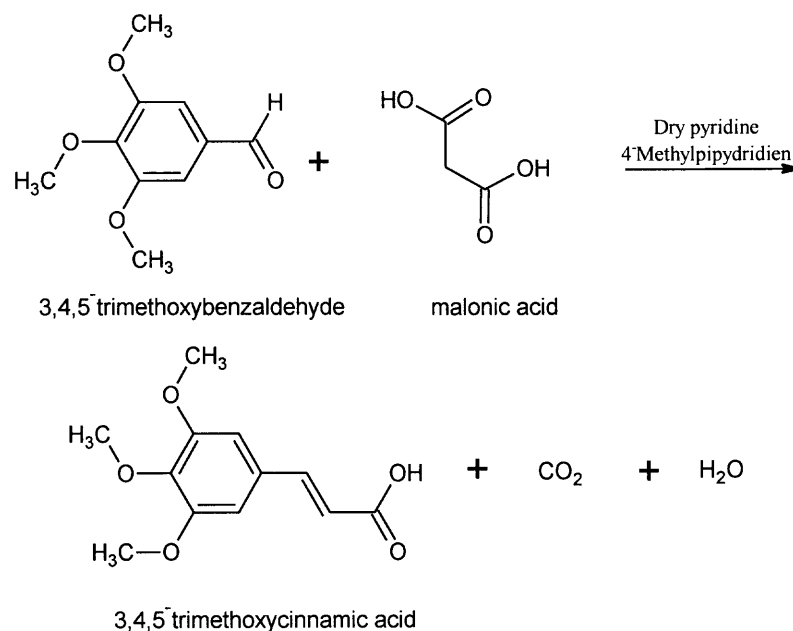


Figure 2.6 Synthetic route for synthesis of 3, 4, 5-trimethoxycinnamic acid.

This Synthetic route is another Knoevenagel condensation reaction and its mechanism is exactly the same as for 4-methoxycinnamic acid.

Step 2: preparation of 3, 4, 5-trimethoxycinnamyl chloride (5)

This Synthetic route was described in the preparation of 4-methoxycinnamyl chloride in section 2.1.3, step 1.

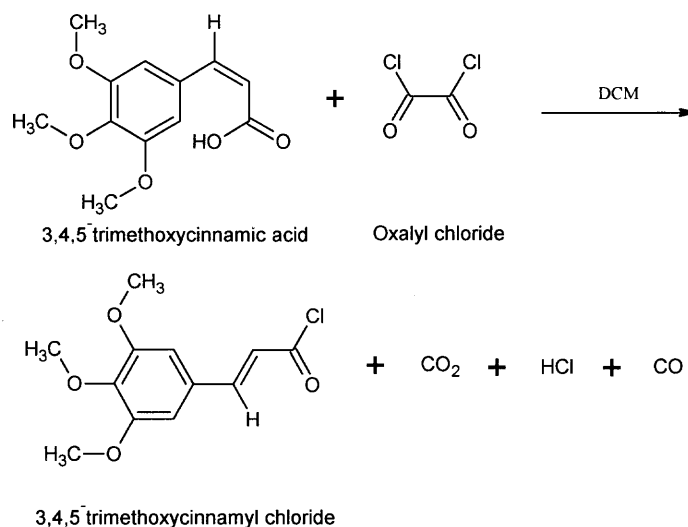


Figure 2.7 Synthetic route for synthesis of 3, 4, 5-trimethoxycinnamyl chloride.

Step 3: Preparation of Isosorbide Bis(3,4,5-trimethoxycinnamate)(6)

This Synthetic route was described in preparation of isosorbide bis (4-methoxycinnamate) in route II in section 2.1.3, step 2.

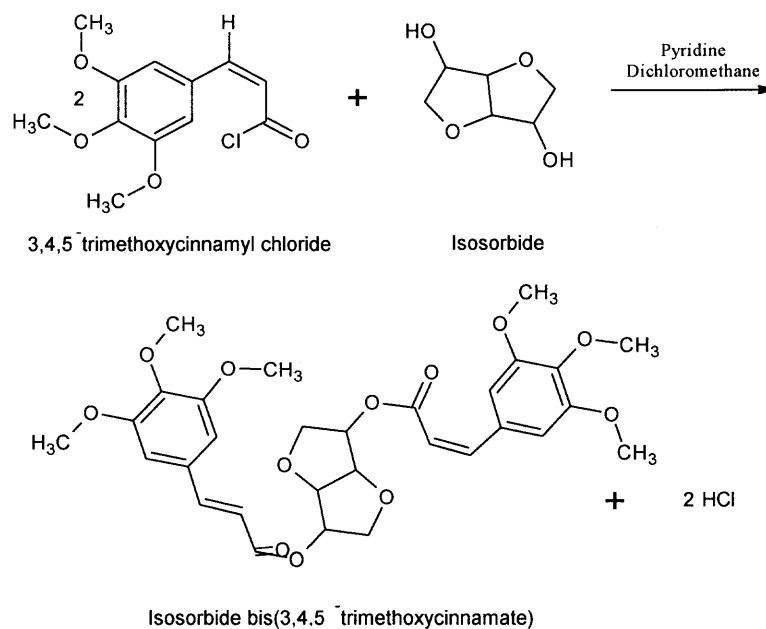


Figure 2.8 Synthetic route for synthesis of isosorbide bis (3, 4, 5-methoxycinnamate).

2.1.6 Material and Method

Step 1: Preparation of 3, 4, 5-trimethoxycinnamic acid

Materials:

1) Malonic acid	125gm	(1.2mole)
2) 3,4,5-Trimethoxybenzaldehyde	100gm	(0.51mole)
3) Dry pyridine	300ml	
4) 4-Methylpyridine	2ml	

Method:

The reaction was run in a 1000ml 3-neck flask with a paddle stirrer. A reflux condenser with a bubbler tube was set in one neck, a thermometer with a Thermowatch™ sensor was fitted to the second neck and the third neck was stoppered. The malonic acid was added first followed by the pyridine and the 3,4,5-trimethoxybenzaldehyde. When a clear solution had formed, the catalyst was added and the reaction temperature was set to 90°C. Carbon dioxide started to evolve immediately and came off steadily. After 4 hours, the solution had turned to a lemon yellow color. Then the pot temperature was raised to 115°C to reflux the pyridine and the rate of CO₂ started to slow down. The reaction was continued for another 20 minutes until no more gas come out. The reaction was let cool overnight. Next day in order to neutralize the excess pyridine, the reaction mixture was poured into a 1000ml beaker containing 1000ml de-ionized water and 220ml conc. HCl. An oily emulsion was formed at once. The mixture was cooled with cracked ice cubes. Suddenly a white precipitate was formed in the solution. The precipitate was stirred for about 30 minutes, then filtered through a Buchner funnel with #1, 15cm filter paper. The filtrate had pH about 1, which illustrated all the pyridine had been neutralized by the acid solution. Then the damp solid was weighed about 145.7gm (120%). After dried in a

1.3mm/60 °C vacuum oven to constant weight, the final product was weighed 83.95 gm (69% theoretical yield).

Step 2: Preparation of 3, 4, 5-trimethoxycinnamyl chloride

Materials:

- | | | |
|----------------------------------|---------------|-----------|
| 1) 3,4,5-Trimethoxycinnamic acid | 23.8gm | (0.1mole) |
| 2) Oxalyl chloride | 17.5ml=25.4gm | (0.2mole) |
| 3) Dichloromethane | 400ml | |

Method:

The method of this reaction was similar to the one which was described in the section 2.1.4, route 2, step 1. The product came out as nice yellow crystals. It was weighed 30.68gm (119% theoretical yield)

Step 3: Preparation of Isosorbide Bis(3,4,5-trimethoxycinnamate)

Material:

- | | | |
|--------------------------------------|---------|------------|
| 1) 3,4,5-Trimethoxycinnamyl chloride | 30.68gm | (0.12mole) |
| 2) Isosorbide | 4.38gm | (0.03mole) |
| 3) Dry Pyridine | 300ml | |
| 4) Dichloromethane | 100ml | |

Method:

The method of this reaction was similar to the one which was described in chapter 2.1.4 in route 2, step 2. The product formed a dark red solid from the ethyl ether. Recrystallization from ethanol gave the final product as a dark red crystalline solid (15gm, 85% theoretical yield).

2.1.7 Synthetic Route for Preparation of Isosorbide Bisferulate (7) (Contributed by Yi Zhang)

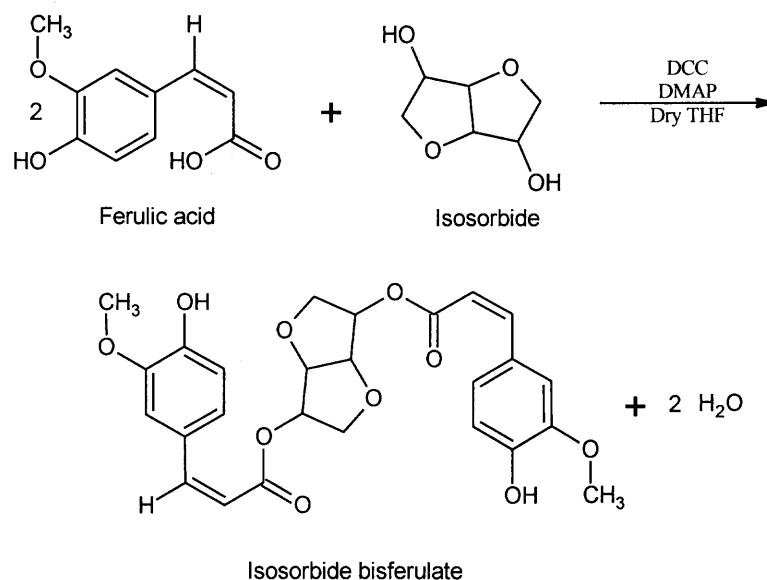


Figure 2.9 Synthetic route for synthesis of isosorbide bisferulate.

This Synthetic route is similar to preparation of isosorbide 2-(4-methoxycinnamate), which will be described in 2.3.1 route 2

2.1.8 Material and Method

Materials:

1) Ferulic acid	48.5	(0.1mole)
2) Isosorbide	14.6gm	(0.1mole)
3) Dicyclohexyl carbodiimide(DCC)	50gm	(0.24mole)
4) Dry THF	500ml	
5) 4-Dimethylaminopyridine (DMAP)	1gm	

Method:

The reaction was run in a 1000ml three-neck flask equipped with a magnetic stirrer, a condenser with a bubbler tube on its top, a nitrogen inlet adaptor and a thermometer.

The flask was charged with isosorbide, ferulic acid, dry THF and DMAP catalyst. This gave a clear, light yellow solution. The mixture was stirred for a few minutes under the nitrogen before the melted DCC was added to the reaction on a single portion. The reaction mixture immediately turned yellow. The temperature gradually rose to 38~40 °C and then fell back to the room temperature (25 °C). The reaction mixture became opaque and a precipitate was formed. The reaction mixture stood overnight under dry nitrogen gas. The next day, the dicyclohexylurea was filtered off (82gms) and the THF solvent was removed at a high vacuum rotovap. The crude product was a yellow solid (46.35gm, 93.1% theoretical yield).

2.2 Preparation of Isosorbide Derived UVA Sunscreens with High Extinction Coefficient and Long Wavelength UVA Absorption

In this part, the synthesis routes for preparation of isosorbide derived UVA sunscreens are described. Through appropriate chemical modification of cinnamic acids and attaching them to the isosorbide, several UVA sunscreens of extremely high extinction coefficient and long wavelength absorptions are desired. High photostability and different absorbances in the UVA region are expected for different synthesized UVA sunscreens.

2.2.1 Synthetic Route for Preparation of Isosorbide Biscyanoferualte

Step 1: Preparation of Isosorbide Biscyanoacetate(8)

Route I :

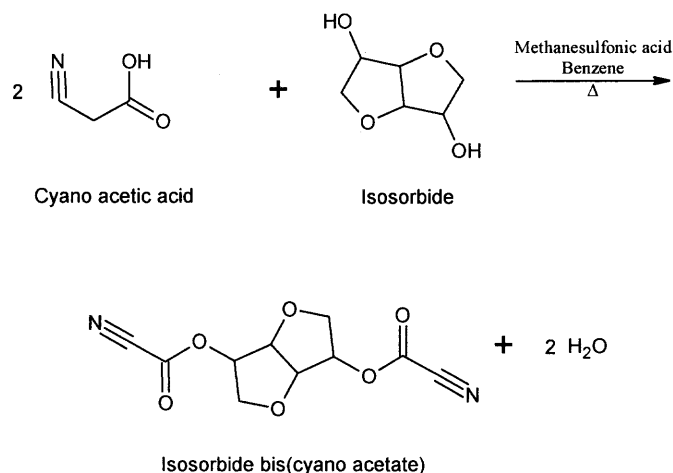


Figure 2.10 Synthetic route for synthesis of isosorbide biscyanoacetate.

This Synthetic route was described in preparation of isosorbide bis(4-methoxycinnamate) in route 1 of section 2.1.3. It gave a poor yield of very dark tarry product from which the desired material could not be isolate.

Route 2:

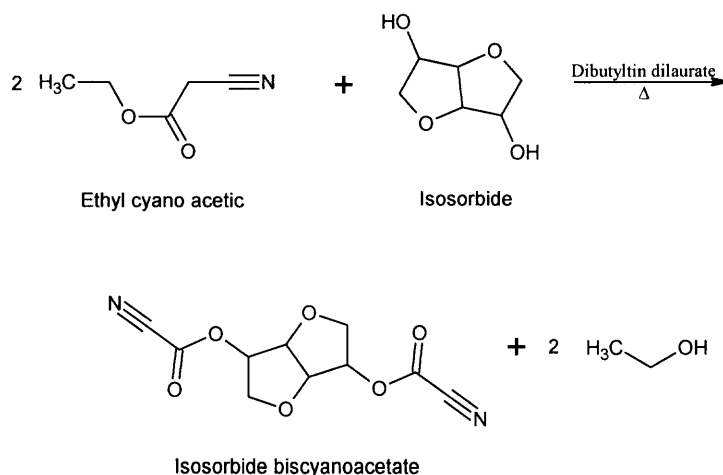


Figure 2.11 Synthetic route for synthesis of isosorbide biscyanoacetate.

Isosorbide biscyanoacetate was successfully prepared by the dibutyltin catalyzed transesterification of isosorbide with ethyl cyanoacetate.

Step 2: preparation of isosorbide biscyanoferulate (9)

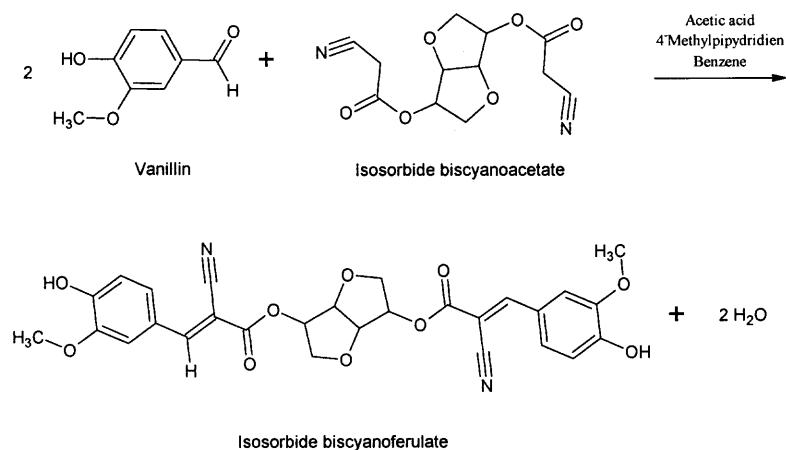


Figure 2.12 Synthetic route for synthesis of isosorbide biscyanoferulate.

This Synthetic route was described in preparation of isosorbide bis(3,4,5-trimethoxycinnamate) in step 1 of section 2.1.5. In this example, vanillin (3-methoxy-4-hydroxybenzaldehyde) was substituted for trimethoxybenzaldehyde and the Knoevenagel condensation was carried out on a cyanoacetate ester rather than a malonate ester to form the isosorbide biscyanoferulate.

2.2.2 Materials and Method

Step 1: Preparation of Isosorbide Biscyanoacetate

Route 1:

Materials:

- | | |
|---------------------|--------------------|
| 1) Cyanoacetic acid | 25.5gm (0.3mole) |
| 2) Isosorbide | 14.6gm (0.1mole) |
| 3) Methanesulfonic | 5 drops (catalyst) |
| 4) Benzene | 100ml |

Method:

A 500 ml 3-necked flask was equipped with a magnetic stirrer, a Dean Stark water separator and a thermometer. A heating mantle was used to heat the system. The flask was charged with isosorbide, cyanoacetic acid and benzene. The solution was heated to reflux for about 1 hour to remove residual water. Then 5 drops of methanesulfonic acid was added to catalyze the esterification. The mixture was refluxed overnight and water was removed with the Dean Stark trap. The total volume of recovered water was about 3ml (83% theoretical yield). The reaction was cooled to room temperature and the benzene was removed on a rotovap. The resulting brown oil was dissolved in 100ml DCM and washed four times with 100 ml of saturated aqueous NaHCO_3 to remove unreacted cyanoacetic acid. The DCM solution was washed twice with 100ml de-ionized water, anhydrous MgSO_4 was added and the DCM solution was stored in the freezer overnight. The DCM solution was filtered to remove the MgSO_4 and concentrated on a rotovap to give a brown oil (4.8gm, 17% theoretical yield).

Route II:**Materials:**

- 1) Ethyl cyanoacetate 133ml (1.25mole)
- 2) Isosorbide 36.5gm (0.25mole)
- 3) Dibutyltin dilaurate 3 drops (catalyst)

Method:

A 500 ml 3-necked flask was equipped with a magnetic stirrer, a distillation head and a thermometer. A heating mantle was used to heat the system. The flask was charged with isosorbide and ethyl cyanoacetate. The solution was heated under a slow stream of

N₂ gas. Three drops of dibutyltin dilaurate catalyst was added to the reaction mixture and heat was applied. The isosorbide dissolved at ca. 60 °C. The color of the solution was quickly changed from colorless to almond through pale straw to a golden yellow and eventually to a reddish-brown as the temperature rose to 150 °C. When the batch reached 210 °C the liquid started to boil. The temperature at the distill head rose to 70 °C and ethanol began to distill. After 2 hours, about 23ml of ethanol had collected (78.5% theoretical yield) and the distillation rate of ethanol slowed appreciably. The pot color became very dark and the temperature of it fell down to 117 °C. After about 3 hours, the head temperature had fallen down to 40 °C and no more ethanol was distilled. The final yield of ethanol was 25.5ml (87% theoretical yield). The mixture was cooled under a flow of N₂. Excess ethyl cyanoacetate was removed on the Rotovap™ (85 °C/0.5~1.0 mmHg). On cooling the product solidified to yield was 78.6 gm (112% theoretical yield).

Step 2: Preparation of Isosorbide Biscyanoferulate

Materials:

1) Vanillin	6.1 gm	(0.04 mole)
2) Isosorbide biscyanoacetate	5.6 gm	(0.02 mole)
3) 4-Methylpiperidine	3 drops=0.1 ml	(catalyst)
4) Acetic acid	5 drops=0.2 ml	(catalyst)
5) Benzene	100 ml	

Method:

A 250 ml 3-neck flask was equipped with a magnetic stirrer, a thermometer and Dean-Stark trap capped with a refluxing condenser and a drying tube. After adding all

the ingredients to the flask, the reaction mixture was heated to reflux at 78 °C with a heating mantle.. After refluxing for about 1.5 hours, a bright yellow solid began to form. Water was steadily collected in the Dean-Stark tube. After running for three hours about 0.7ml of water was collected (ca. 100% theoretical). After cooling, the yellow solid was collected by filtration and dried in a vacuum oven to constant weight to 8.75 gm (80% theoretical yield). The product was recrystallized from acetonitrile.

2.2.3 Synthetic Route for Preparation of Isosorbide Bis(3,4-dimethoxycinnamate) (10)

This Synthetic route has been described in section 2.2.1, step 2.

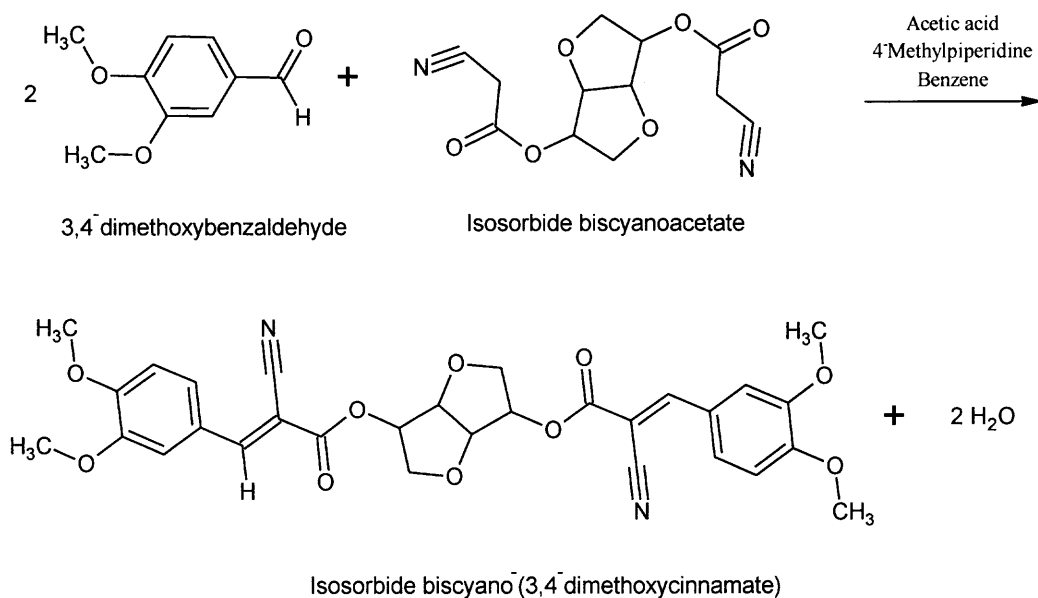


Figure 2.13 Synthetic route for synthesis of isosorbide 2,5-bis(3,4-dimethoxycinnamate).

2.2.4 Material and Method

Materials:

- | | | |
|-------------------------------|---------------|------------|
| 1) 3, 4-Dimethoxybenzaldehyde | 6.64gm | (0.04mole) |
| 2) Isosorbide biscyanoacetate | 5.6gm | (0.02mole) |
| 3) 4-Methylpiperidine | 3 drops=0.1ml | (catalyst) |
| 4) Acetic acid | 5 drops=0.2ml | (catalyst) |
| 5) Benzene | 100ml | |

Method:

This method was similar to the preparation of isosorbide biscyanoferulate which was described in section 2.14, step 2. The product came out as bright yellow solid, which weighed 17 gm (141% theoretical yield). It was recrystallized from ethanol.

2.2.5 Synthetic Route for Preparation of Isosorbide Biscyano (3,5-dimethoxy, 4-hydroxycinnamate) (11)

This Synthetic route has been described in section 2.2.1, step 2.

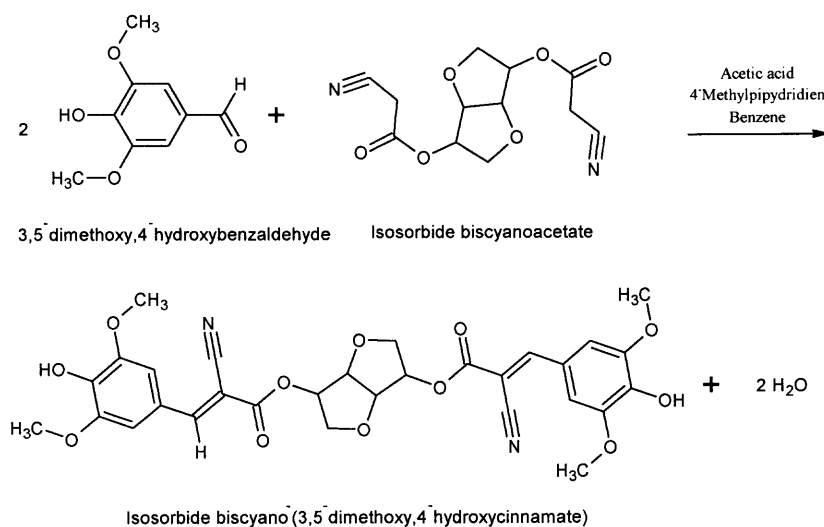


Figure 2.14 Synthetic route for synthesis of Isosorbide bis(3, 5-dimethoxy, 4-hydroxycinnamate).

2.2.6 Material and Method

Materials:

1) 3,5-dimethoxy-4-hydroxybenzaldehyde	6.64gm	(0.04mole)
2) Isosorbide biscyanoacetate	5.6gm	(0.02mole)
3) 4-Methylpiperidine	3 drops=0.1ml	(catalyst)
4) Acetic acid	5 drops=0.2ml	(catalyst)
5) Benzene	100ml	

Method:

This method was similar with preparation of isosorbide biscyanoferulate which was described in section 2.14, step 2. The product came out as bright yellow solid, which weighed 12.3gm (101% theoretical yield).

2.3 Preparation of Isosorbide Derived Multifunctional Single Compound

In this part, the synthetic routes to both an isosorbide-derived UVB absorbing plasticizer and an isosorbide-derived antioxidant are described.

2.3.1 Synthetic Route for Preparation of Isosorbide 2-(4-methoxycinnamate) (12)

Route 1:

This route used triethylamine as a base to prepare the ester from the acyl halide. Such reactions lead to the production of hydrogen chloride which combines with triethylamine to form the salt triethylamine hydrochloride, thus the HCl is removed and the reaction proceeds in a forward direction. For this reaction, the acyl halide is needed, which was already prepared by use of two Synthetic routes described in section 2.1.3, route 2, step 1.

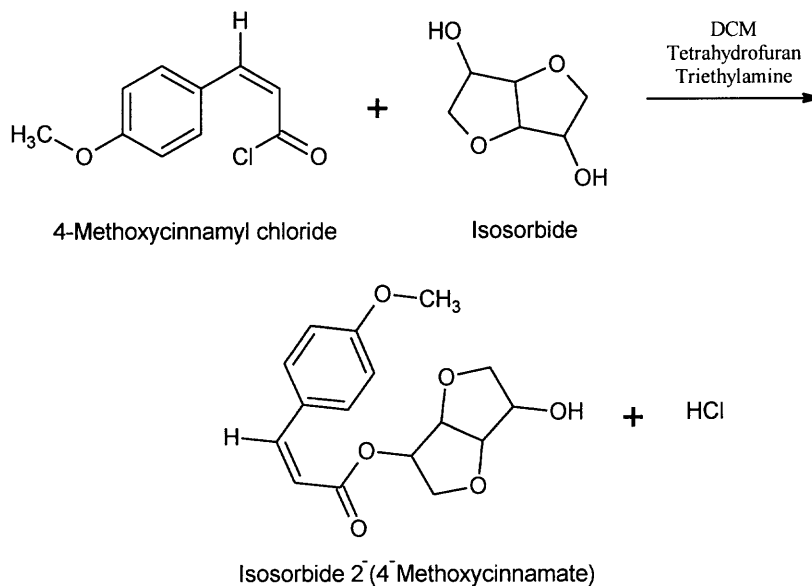


Figure 2.15 Synthetic route for synthesis of isosorbide 2-(4-Methoxycinnamate).

Route 2:

This route uses dicyclohexylcarbodiimide (DCC) as an intermediate to esterify acids (such as 4-methoxycinnamic acid) with an alcohol (such as isosorbide) to form an ester. DCC is primarily used in artificial peptide synthesis to react carboxylic acids with amines to form peptide linkages under mild conditions. Since isosorbide's 5-hydroxy group will form hydrogen bonds with the ring oxygen atom, it has a lower reactivity compared with the 2-hydroxy group of isosorbide. Therefore, DCC might selectively esterify the 2-*exo* hydroxyl group rather than the 5-*endo* hydroxyl group. This selective esterification reaction under mild conditions could provide a synthesis for isosorbide-5-hydroxy-2-(4-methoxycinnamate).

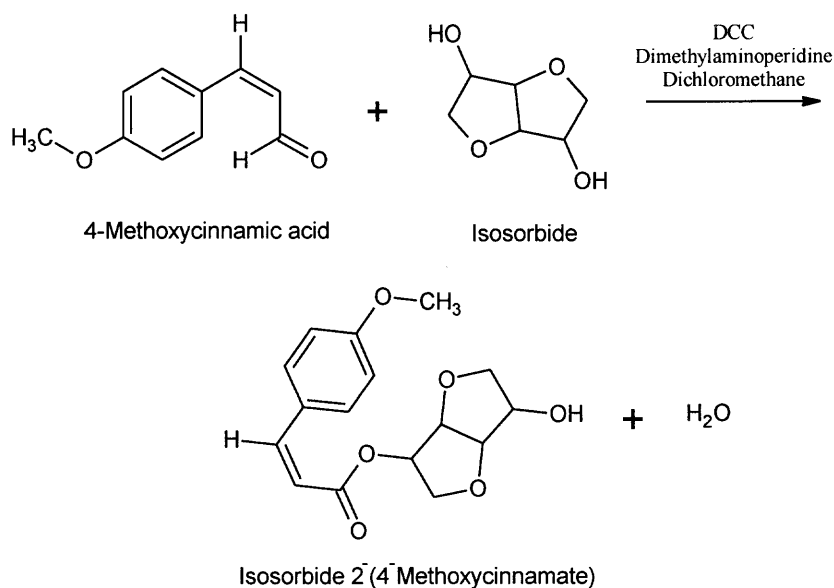


Figure 2.16 Synthetic route for synthesis of isosorbide 2-(4-Methoxycinnamate).

2.3.2 Material and Method

Route 1:

Materials:

1) 4-Methoxycinnamyl chloride	19.7gm	(0.1mole)
2) isosorbide	29.2gm	(0.2mole)
3) Tetrahydrofuran	100ml	
4) Triethylamine	14.5ml	
5) Dichloromethane	30ml	

Method:

This reaction was run in an identical apparatus to that described in **Section 2.1.4** for the preparation of isosorbide *bis* (4-methoxycinnamate). The system was placed in an ice-bath. The 500 ml flask was charged with isosorbide, tetrahydrofuran and triethylamine and a slow stream of nitrogen passed through the flask. The 4-methoxycinnamyl chloride, which was dissolved in dichloromethane, was added slowly

to the flask through the “Bantam-Ware”™ funnel. The solution immediately started to form bright yellow solid and some white fumes came out. In order to keep the reaction steady the flask temperature was kept below 5°C. After 5 hours, there was no more reaction. The flask was left to slowly warm up to the room temperature and stirred over night. The mixture was added to 400ml de-ionized water. Then the water layer and DCM were separated in a 1000ml Squibb separating funnel. The aqueous phase was washed with 50ml DCM two times to extract any last products from it in the separation funnel. The DCM extracts were shaken once with 200ml NaCl and once with 200ml of de-ionized water. Then the DCM solution was dried overnight over MgSO₄ in the freezer. After that, the solution was filtered through a Buchner funnel with #4, 7.7 cm filter paper. The filtrate was taken up to the Rotovap™ to remove methylene chloride. The crude product was a honey-colored thick oil, weighing 24.4gm (66% theoretical yield)

Route 2:**Materials:**

1) 4-Methoxycinnamic acid	17.8gm	(0.1mole)
2) Isosorbide	29.2gm	(0.2mole)
3) DCC (dicyclohexylcarbodiimide)	22.66gm	(0.11mole)
4) Dimethylaminopyridine	0.122gm	(0.1mole)
5) Dichloromethane	250ml	

Method:

The reaction was run in a one-neck 500ml round bottom flask with Drierite™ guard tube on top of its neck. A stirrer bar was used to agitate the flask. The whole system was immersed in an ice bath and the flask was charged with isosorbide and

4-methoxycinnamic acid in the dichloromethane solution. Then the DCC and dimethylaminopyridine (DMAP) were added slowly into the flask. The solution immediately became a clear yellow liquid. After running about 2 hours, some pale white precipitate, urea $(\text{NH}_2)_2\text{CO}$, came out from the solution. It was left to stir overnight till no more precipitate came out. The pale solution was filtered through a Buchner funnel with #4, 7 cm filter paper. The filtrate was washed with 100ml 5% acetic acid using a separation funnel. Deionized water (100ml) was added twice to wash off the acid from the organic phase, which caused more white precipitate to come out. The urea could come from two sources: excess DCC which was previously added to guarantee all the acid would react, or un-reacted DCC which was supposed to react with the acid. When the DCC came in contact with water, it would become dicyclohexylurea as a white precipitate. Therefore, we repeatedly washed the solution with de-ionized water until no more white precipitate came out. Then we added magnesium sulfate into the solution and put it into the freezer to dry for an hour. After that, the solution was filtered through a Buchner funnel with #4, 7 cm filter paper. The filtrate was taken up to the Rotovap™ to remove the solvent. The crude product weighed 25.17gm (82% yield). After recrystallization from methanol, the product came out as a pale cream solid.

2.3.3 Synthetic Route for Preparation of Isosorbide 2-(benzyl ether), 5-(4-methoxycinnamate)

Step 1: Preparation of Isosorbide 2-benzylether(13)

This synthetic route is called Williamson ether synthesis, and was developed by Alexander Williamson in 1850. This reaction converts alcohols (R-OH) into ethers (R-O-R). The first step in this reaction is to form the highly reactive conjugate base of the

alcohol (called an alkoxide). They are usually prepared immediately prior to the reaction, or are generated *in situ* by reacting the alcohol with sodium metal or in some cases (such as here) with strong aqueous sodium hydroxide. The alkoxide can then be added to a suitable alkyl halide (typically a primary halide) to form the ether via an S_N2 reaction which is known as a bimolecular nucleophilic substitution reaction. A typical Williamson reaction is conducted at 50-100°C and is complete in 1-8 hours. Often complete disappearance of the starting material is difficult to achieve, and side-reactions are common. Yields of 50-95% are generally achieved in the laboratory.

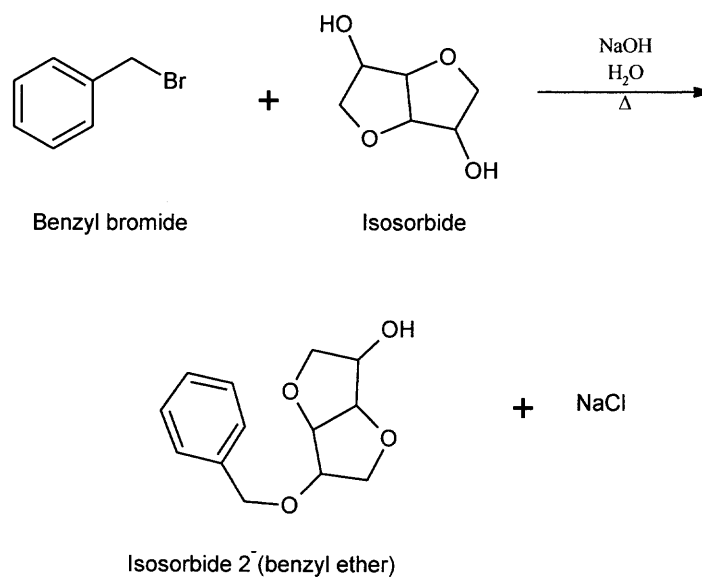


Figure 2.17 Synthetic route for isosorbide 2-(benzyl ether).

Step 2: Preparation of Isosorbide 2-(benzyl ether)- 5-(4-methoxycinnamate)(14)

This Synthetic route was described in preparation of isosorbide bis(4-methoxycinnamate) in route 2, step 2 in section 2.1.3.

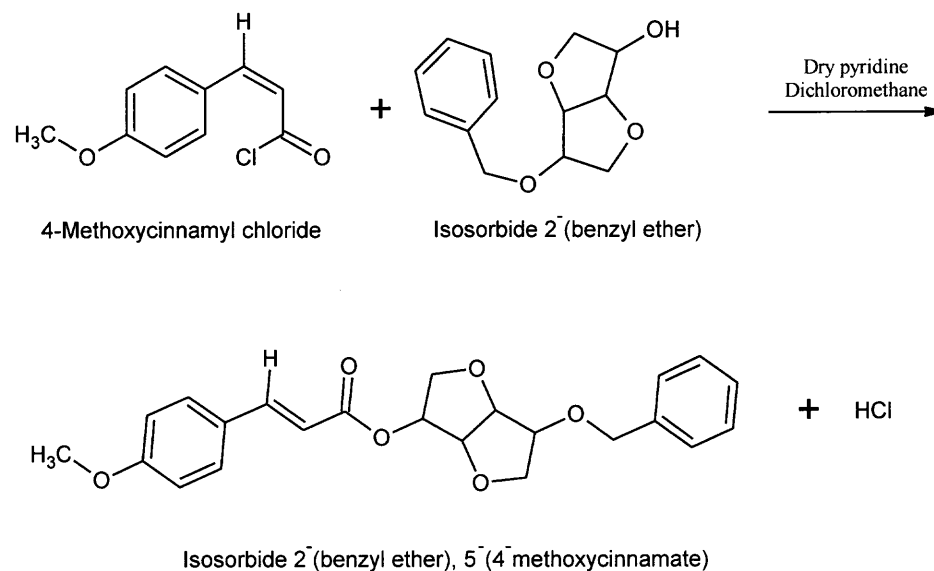


Figure 2.18 Synthetic route for synthesis of isosorbide 2-(benzyl ether), 5-(4-Methoxycinnamate).

2.3.4 Material and Method

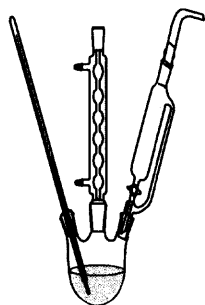
Step 1: preparation of isosorbide 2-(benzyl ether)

Materials:

1) Benzyl bromide	11.875gm	(0.1mole)
2) Isosorbide	29.2gm	(0.2mole)
3) Sodium hydroxide	4gm	(0.1mole)
4) Water	10ml	

Method:

This reaction was run in a 300ml three-neck round bottom flask with a magnetic stirrer. A reflux condenser was set in one of its necks with a bubbler tube to detect the nitrogen flow. A 50ml Kontes “Bantam-Ware”™ PE tap funnel with a nitrogen inlet tube was placed in another neck. The 3rd neck was capped by a thermometer. The flask was heated with a heating mantle. The flask was charged with isosorbide and benzyl bromide and



heated to 50 °C. Then 50% NaOH solution was added slowly into the flask and let it stir for about 4 hours. Then the heat was turned off and the flask was left to cool down to the room temperature. A mixture of 200ml of de-ionized water and 5ml concentrated hydrochloride was added to the flask to neutralize the un-reacted NaOH. Then 200ml methylene chloride was used to wash the solution using a 500ml Squibb separating funnel. The methylene chloride extracts were dried (MgSO₄) overnight in the freezer. The solution was filtered through a Buchner funnel with #4, 12 cm filter paper. The filtrate was taken up to the Rotovap™ to remove the methylene chloride. The yellow oil was weighed 17.04gm (66% theoretical yield). Then 150ml ether was added to the oil and left in the freezer for two days. The solution was taken down on the Rotovap™ to remove some of the ether and a white solid start to crystallize in the flask. The weight of the white solid was 8.2gm (32% theoretical yield) of isosorbide 2-benzyl ether.

Step 2: Preparation of Isosorbide 2-(benzyl ether), 5-(4-methoxycinnamate)

Materials:

- | | |
|-------------------------------|------------------|
| 1) Isosorbide 2(Benzyl ether) | 15gm (0.064mole) |
| 2) 4-methoxycinnmyl chloride | 15gm (0.076mole) |
| 3) Dry pyridine | 50ml |
| 4) Dry chloromethane | 150ml |

Method:

This reaction was run under nitrogen in a dry 500ml 3 neck flask with a magnetic stirrer, reflux condenser and 50ml PE tap funnel as described before. A thermometer was set in the 3rd neck. The flask was chilled in an ice bath. The flask was charged with 50ml dry

pyridine, 50ml dichloromethane and 15gm isosorbide-2-(benzyl ether). The mixture was stirred until a clear colorless solution was formed. Then 15gm yellow acid chloride in 50ml dry dichloromethane was added dropwise through the tap funnel to maintain the temperature of the solution below 5°C. Within a short time a yellow precipitate came out in the flask. The total addition of acid chloride took about 90 minutes. After all the acid chloride had been added, another 50ml DCM was added to wash in any acid chloride that had crystallized out in the tap funnel. The yellow suspension was stirred overnight and allowed to warm up to the room temperature. Then the solution was poured into 200 ml deionized water and 50ml concentrated HCl to neutralize the pyridine. The solution was left to cool down, and enough acid added to bring the pH to 1-2. A 1000ml Squibb funnel was used to separate the water and DCM layers. The aqueous phase was washed with 100ml DCM three times to extract any remaining products. The DCM extracts were shaken once with 200ml brine solution and once with 200ml of de-ionized water. Then MgSO₄ was added to the DCM solution and it was left to dry in the freezer for 3 hours. After that, the solution was filtered through a Buchner funnel with #4, 12 cm filter paper. The filtrate was taken down on the Rotovap™ (35 °C/40 millibar) to remove the solvent. A viscous oil was left, which was again heated up to 50°C/60 millibar to remove the last traces of solvent. The final weight of oil was 26gm (103% theoretical yield). After standing for several days, the oil started to crystallize. A mixture of cyclohexane and benzene was used to recrystallize it. The crystals came out as white platelets which weighed 19.42 gm (77% theoretical yield).

2.3.5 Synthetic Route for Preparation of Isosorbide 2-benzyl ether-5-cyanoferulate

Step 1: Preparation of Isosorbide 2-benzyl ether-5-cyanoacetate (15)

This Synthetic route has been described in section 2.2.1 in route 2.

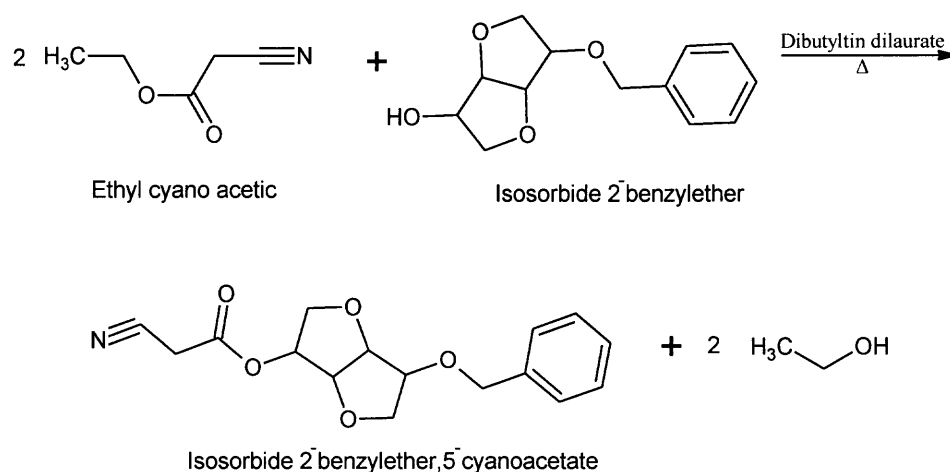


Figure 2.19 Synthetic route for synthesis of isosorbide 2-benzylether-5-cyanoacetate.

2.3.6 Material and Method

Materials:

1) Ethyl cyanoacetate	70ml	(0.66mole)
2) Isosorbide 2-benzylether	23.6gm	(0.1mole)
3) Dibutyltin dilaurate	3 drops	(catalyst)

Method:

This method was similar to preparation of isosorbide biscyanoferulate which was described in section 2.14 in route 2. The crude product came out as brown oil and weighed 34.85gm (115% theoretical yield), which means there was still some unreacted ethyl cyanoacetate left in the reaction. As before the Rotovap™ and distillation apparatus were used to get rid of the ethyl cyanoacetate. The residue was dissolved in diethyl ether.

However, both product and the impurity dissolved in ether to different extents, so this method could not be used to purify the product.

2.3.7 Synthetic Route for Preparation of Isosorbide Bis [3-(4-hydroxy-3,5-di-t-butylphenyl) propionate]

Step 1: Preparation of Methyl 3-(4-hydroxy-3,5-di-t-butylphenyl)propionate (16)

Route 1:

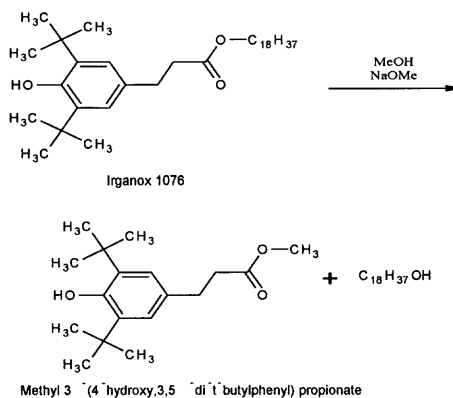


Figure 2.20 Synthetic route for methyl 3-(4-hydroxy, 3,5-di-t-butylphenyl) propionate.

This route is a methanolysis reaction, which is a reversed form of the trans-esterification reaction, in which the alkoxy group of an ester compound is replaced by methanol or its alkoxide anion.

Route 2:

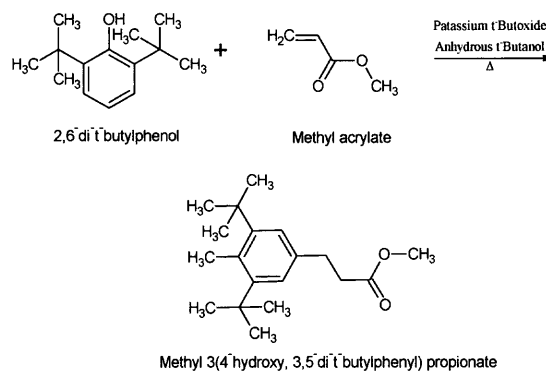


Figure 2.21 Synthesis route for methyl 3-(4-hydroxy-3, 5-di-t-butylphenyl) propionate.

This route is a Michael addition reaction, the nucleophilic addition of a carbanion to an alpha-beta unsaturated carbonyl compound. The base catalyst used in this reaction is potassium t-butoxide

Step 2: Preparation of Isosorbide Bis(3-(4-hydroxy-3,5-di-t-butylphenyl) propionate)(17)

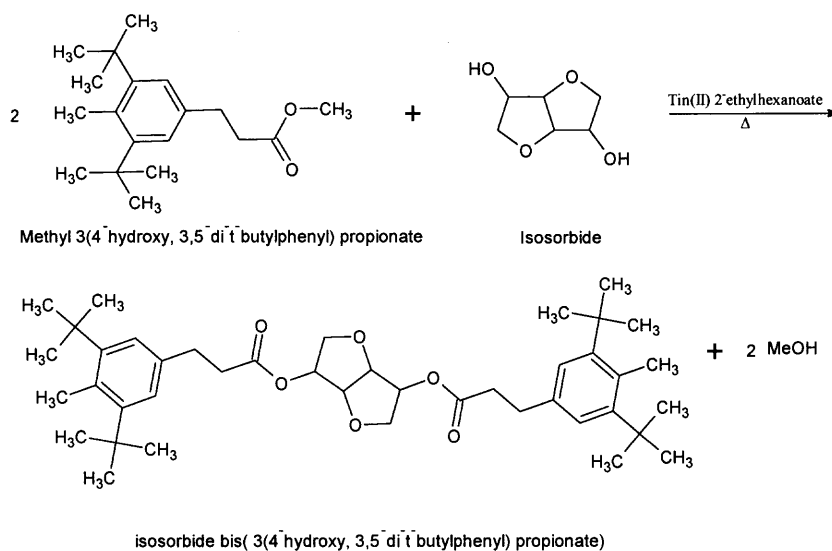


Figure 2.22 Synthetic route for isosorbide *bis* [3-(4-hydroxy, 3,5-di-t-butylphenyl) propionate]

This Synthetic route has been described in section 2.2.1 in route 2.

2.3.8 Material and method

Step 1: Preparation of Methyl 3-(4-hydroxy-3,5-di-t-butylphenyl) propionate

Route I :

Materials:

- | | | |
|------------------|--------|-------------|
| 1) Methanol | 1000ml | |
| 2) Irganox™ 1076 | 50gm | (0.097mole) |
| 3) Sodium | 1gm | |

Method:

The reaction was run in a 2000ml three-neck flask under the nitrogen. The flask was charged with methanol and sodium metal and allowed to react until all the sodium had dissolved. Then the Irganox™ 1076 was added. The solution was refluxed on the heating mantle for 4-5 hours. Gradually the color of solution was darkened from yellow to brown. After refluxing it was allowed to cool under the nitrogen. A brown-orange solid crystallized out on the top of the liquid. It was filtered through a Buchner funnel and washed with fresh methanol. The crystals were dried in the vacuum oven at 45 °C/10 milliBar. After 2 hours, it was recrystallized from the hexane and dried in the vacuum oven again. The final yellow-brown solid weighed 20.44gm (72.5% theoretical yield).

Route 2:**Materials:**

1) 2, 6-Di-t-butylphenol	37.3 gm	(0.181 mole)
2) Anhydrous t-butanol	50 ml	
3) Potassium-t-butoxide solution	54 ml	(0.054 mole)
4) Methyl acrylate	17.7 gm	(0.21mole)

Method:

A 500ml four-neck flask, with magnetic stirrer, was fitted with a reflux condenser with a bubbler tube on top, a thermometer with a Thermowatch™ sensor and a nitrogen inlet. The system was fitted with a heating mantle. The 2,6-di-t-butylphenol, anhydrous t-butanol (redistilled and dried over molecular sieves) and methyl acrylate were added to the flask and heated to 50 °C. After 2 hours, potassium t-butoxide solution was added. The reaction mixture became green immediately and gradually became went clear. It was

stirred overnight and the clear green solution was taken down on the Rotovap™ to remove the t-butanol. The resulting oil was added to a 1000ml beaker which containing 250ml deionized water and 20 ml concentrated HCl to bring the solution to pH ~ 2. After stirring this mixture for about 10 minutes, the solution turned into a thick orange-red oil and started to separate from the water. The oil was extracted three times with 100ml ethyl ether, and the ether layer sequentially washed with 100 ml brine solution and 100 ml de-ionized water. Finally it was dried with anhydrous MgSO₄ in the freezer. After drying overnight, it was taken down on the Rotovap™ to remove the ether. The product came out as thick oil and weighed 50.9 gm (94.6% theoretical yield).

Step 2: Preparation of Isosorbide bis [3-(4-hydroxy-3,5-di-t-butylphenyl)

propionate]

Materials:

1) Isosorbide	14.6gm
2) Methyl 3-(4-hydroxy,3,5-di-t-butylphenyl) propionate	50.4gm
3) Tin ^{II} 2-ethylhexanoate	1~2 drops (catalyst)
4) Toluene	200ml

Method:

The reaction was run in a four-neck flask with a paddle stirrer. A Dean-Stark apparatus with a reflux condenser, a thermometer with a Thermowatch™ sensor and an addition funnel with nitrogen inlet were fitted to the flask. It was charged with toluene and isosorbide and the mixture heated on the mantle to reflux the toluene and azeotrope out any water in the isosorbide (which is very hygroscopic) to prevent it hydrolyzing the tin catalyst. After heating until no more water came out, the temperature reached 110°C.

Methyl 3-(4-hydroxy-3,5-di-*t*-butylphenyl) propionate and the tin catalyst were added to the solution and the mixture was slowly refluxed and distilled for 4~5 hours. The temperature of the vapor fell to 65°C, which is the boiling point of the methanol. When the temperature of the distillate vapor suddenly rose to 110°C all the methanol had gone and the reaction had reached its end. By continuously adding catalyst and removing the toluene solvent, the reaction was driven to completion. After removing the excess toluene from the reaction mixture on the Rotovap™, the product came out as brown sticky solid.

CHAPTER 3

INSTRUMENT CHARACTERIZATION

3.1 DSC

Differential Scanning Calorimetry (DSC) is a thermo analytical technique which monitors heat effects such as phase transitions and chemical reactions of the sample as a function of temperature. There are two types of DSC: Heat flow DSC and Power compensate DSC. For the Heat flow DSC, it offers the same heat flow to the cell which contains the sample and the reference and detects the temperature difference between them. After converting the temperature difference to the heat flow difference, heat flow DSC can plot the heat flow as the function of the temperature it provides. And for the power compensate DSC, it maintains the same temperature for both the sample and the reference, then it plots the difference of the heat flow, which is required differently by the sample and the reference, as the function of temperature.

From the thermogram of DSC, the thermodynamic information about materials can be predicted, such as a materials' glass transition temperature: (when a material changes phase from a brittle state to a soft, rubbery state); crystallization point for the polymer; melting point such as crystalline polymer melts; ΔH_m (absorbed energy during melting); and ΔH_c (released energy during crystallization). Besides these important measurements, if the material is pure enough (>98%), the purity of the material can also be tested.

The theory of the purity test derives from the Freezing point depression equation, in which the melting point of sample will decrease with an increase of the impurities. It is defined by the following equation:

$$\Delta T = \left(\frac{RT^*2}{\Delta_{\text{fus}}H} \right) X_B$$

Where:

ΔT = Melting point depression

R=gas constant=1.9872 cal./mol° C

X_B =molar fraction of impurities

T^* =melting point of sample with zero impurity

$\Delta_{\text{fus}}H = \Delta H_{\text{sample}}/n$ =enthalpy of fusion per mole.

n =sample weight/sample molecular weight

When applying freezing point depression theory to a specific case, in which impurities in the sample are liquid -soluble, solid-insoluble, we can get the famous Van't Hoff equation:

$$\Delta T = (R T^*2 / \Delta_{\text{fus}}H) \times (X_0/F) = T^* - T$$

$$X_B = X_0/F$$

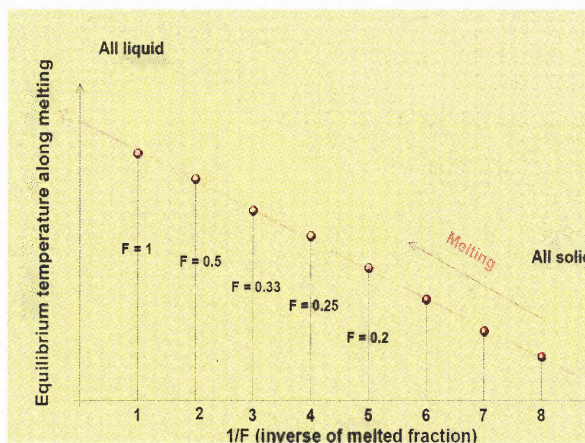
Where: X_0 =molar fraction of impurities in fully melted sample

X_B =instantaneous molar fraction of impurities in liquid

F=melted fraction of sample

In this case, all the impurities are confined in liquid and solid is perfectly pure. During melting, the molar fraction of impurity in liquid will decrease with the volume of the liquid phase increase. And because certain sample's R, T^* , $\Delta_{\text{fus}}H$ and impurity X_0 is constant, after plotting the sample's on-line T as the function of the 1/F, the slop of the

straight line which equals to coefficient of the $1/F$ could be calculated, which also equals to $(R T^{*2}/\Delta_{\text{fus}}H) \times X_0$. Since R is constant, $\Delta_{\text{fus}}H$ can be integrated from the thermogram. T^* is the intercept of the T axis. From the slope result, the sample's impurity X_0 could be calculated.



3.2 FTIR

This technique is based on a classic theory “Quantum Mechanics”, in which the energy states of a physical system are discrete. In 1900 Max Planck[23] hypothesized that any energy is radiated and absorbed in quantities divisible by discrete ‘energy elements’. Each of these energy elements is proportional to the oscillation frequency ν with which they individually radiate energy, as defined by the following formula:

$$\epsilon = h \cdot \nu$$

where h is Planck's Action Constant = 1.38×10^{-37} kcal*s (6.63×10^{-37} kj*s). Five years later, Albert Einstein extended Max Planck's theory to the light and mathematically explained the photoelectric effect. He proposed a model and equation to illustrate that

light is not only emitted but also absorbed in packets or photons[24]. Therefore, the energy of one light photon (ϵ) is equal to the frequency times Planck's constant or Planck's constant times the speed of light divided by the wavelength:

$$\epsilon = h\nu = hc/\lambda$$

Obviously besides photon, every element including atom could have its own quantum energy stored in molecules. Generally this total energy is divided into 4 categories:

$$\epsilon_{\text{TOT}} = \epsilon_{\text{TRANSLATION}} + \epsilon_{\text{ROTATION}} + \epsilon_{\text{VIBRATION}} + \epsilon_{\text{ELECTRONIC}}$$

At room temperature, most molecules are in the lowest vibrational energy level, which corresponds to the energy of infrared radiation of electromagnetic spectrum. Therefore, when the IR radiation passes through a sample, if the light energy matches to the energy separation between two vibration energy states of the sample, the IR light will be absorbed by the molecule causing it to jump to a higher vibration state. Because each vibrational level has a number of closely spaced rotational energy level, IR absorption appears as bands rather than lines. There are two types of vibrations which occur in molecules: stretches, where the distance between bonded atoms oscillates, and bends, where the bond angles oscillate. Generally an approximate value for the wavenumber, which is the reciprocal of wavelength for a particular IR transition, can be calculated from the following equation:

$$1/\lambda = \frac{c}{2\pi} \sqrt{\frac{k(m_1 + m_2)}{m_1 m_2}}$$

Where k is the force constant for the bond and is related to the bond strength. It is larger for bond-stretching vibrations than for bending vibrations. On the basis of this information, the following generalizations about the position of IR absorption can be made:

1. Because of the larger force constant, stronger bonds absorb at higher wavenumber than weaker bonds. For the same reason, bond stretches absorb at higher wavenumber than bending bonds.
2. Bonds involving light hydrogen atoms have smaller reduced masses. Therefore, they absorb at higher wavenumber than bonds involving only heavier atoms.
3. Polar bonds give rise to stronger absorption than non-polar bonds. Absorption due to symmetrical vibrations of very non-polar bonds is often weak and could be absent entirely.

Based on this information, it is possible to identify an unknown sample in terms of its specific function groups such as esters or alcohols. Specific covalent bond should have their absorption band in the consistent positions on the spectrum. However, it is not easy to record the amount of energy absorbed when the frequency of the infra-red light is varied. It challenges the sensitivity of the detector in the conventional (dispersive) infrared spectroscopy. Therefore, a cheaper and faster instrument, the Fourier Transform Spectroscopy, was developed. It is a measurement technique whereby spectra are collected based on measurements of the temporal coherence of a radiative source, using time-domain measurements of the electromagnetic radiation or other type of radiation. It uses a Michelson interferometer in which light from the source is split into two beams by a half-silvered mirror: one is reflected off a fixed mirror and one off a

moving mirror which introduces a time delay. When two beams interfere, it allows the temporal coherence of the light to be measured at each different time delay setting. By making measurements of the signal at many discrete positions of the moving mirror, the spectrum can be reconstructed using a Fourier transform of the temporal coherence of the light[25].

3.3 NMR

Nuclear magnetic resonance (NMR) is a physical phenomenon based upon the quantum mechanical magnetic properties of an atom's nucleus[26]. The nucleus of an atom is composed of neutrons and protons, both of which have the intrinsic quantum mechanical property of spin. If the overall spin in this nucleus is non-zero such as ^1H , the nuclear spin generates a small magnetic field in atoms. Different spin states could produce different energies in an external magnetic field. Some spin state has its magnetic field oriented in the same direction as the external magnetic field, B_0 , and is lower in energy than the other state that has its field oriented in opposition to the external field. The difference in energy between the two states is related to the strength of the external magnetic field by the equation:

$$\Delta E = \hbar \gamma B_0 / 2 \pi$$

Where B_0 is the strength of the external magnetic field and γ is the magnetogyric ratio, which differs for each kind of atomic nucleus. When electromagnetic radiation of the correct frequency matches this energy difference, the atom will absorb the energy of the radiation and is said to be in resonance. However, the exact field required for resonance depends on the local environment around the atom such as the electron density around the

^1H . The electrons in the molecule circulate and create magnetic field that oppose the external magnetic field. This reduces the magnetic field at the nucleus, which is what determines the NMR frequency. As a result the energy gap is reduced, and the frequency required to achieve resonance is also reduced. This shift of the NMR frequency due to the chemical environment is called the chemical shift which is referenced to a standard such as tetramethylsilane (TMS) for ^1H and ^{13}C nuclei

$$\delta = \frac{\text{Resonance frequency required by atom} - \text{Resonance frequency required by TMS}}{\text{Operating frequency of instrument (Hz)}} \times 10^6$$

Where: the chemical shift (δ) is called part per million (ppm), which do not depend on the operating frequency of the instrument. .Therefore, the more electronic shielding of the atom, its absorption appears at a more upfield chemical shift (lower δ).

Besides chemical shift, two other types of information are presented in a NMR spectrum: multiplicity and integral. Multiplicity is a phenomenon in which the absorption peak of absorbed signal is split into multiple peaks in the spectrum. It is generated due to the interaction with the nearby nuclei. The transmitting electrons between nucleus produce small magnetic fields to each other thereby shift the original signal into two opposite directions. A nucleus coupled to n identical neighbors of spin quantum number I is split into $(2nI + 1)$ peaks. For ^1H spectrum, the number of peaks equal to $n+1$ and the coupling constant J (Hz), which is size of the splitting, is between 0~20 Hz. .Based on this information, which hydrogens are near the hydrogen which is responsible for the signal could be measured. The area of a group of peaks is proportional to the number of nuclei that produce the signal and can be measured by integration.

3.4 UV/Visible Spectrum

The UV/VIS spectrometer uses the ultraviolet-visible light as the radiation source to pass through the sample. Its light source can generate rays in the UV region of the spectrum from 200nm~400nm and the visible region from 400nm to 800nm. The amount of energy available in this radiation ranges from 600 kJ/mol to 150 kJ/mol, which is enough to cause the electronic transitions in a molecule, that is, to excite an electron from an occupied molecular orbital to an unoccupied molecular orbital. The $\pi \rightarrow \pi^*$ transition of the conjugated pi bonds correspond to this energy. The more conjugated is the chromophore, the lower the energy it can absorb and a longer wavelength the maximum absorbance could move to. Therefore, it is routinely used in the quantitative determination of absorptions of highly conjugated organic compounds[27]. Besides detecting the absorption of the material; the UV/VIS spectrometer also could measure the concentration of the species in the solution. This is strongly related to a famous theory called Beer-Lambert law. The law states that there is a logarithmic dependence between the transmissivity of light through a substance and the concentration of the substance and path length of material that the light travels through. Thus if l and ϵ are known, the concentration of a substance can be deduced from the amount of light transmitted by it, calculated by the following equation:

$$1/T = A = \epsilon/c$$

Where, T is the transmittance

A is the absorbance of the sample

ϵ is the molar extinction coefficient

l is the distance that light travels through the sample (path length)

c is the absorbing species in the material

3.5 SPF

The Sun Protection factor (SPF) of a sunscreen is a laboratory measure of the effectiveness of sunscreen; the higher the SPF, the more protection a sunscreen offers against UV-B. The SPF indicates the time a person can be exposed to sunlight before getting sunburn with a sunscreen applied relative to the time they can be exposed without sunscreen[28]. It was defined as following equation:

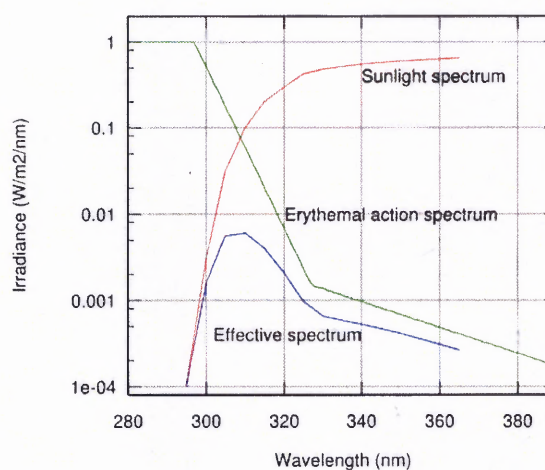
$$\text{SPF} = \frac{\text{Minimal erythema dose in sunscreen -protected skin}}{\text{Minimal erythema dose in nonsunscreen -protected skin}}$$

In the USA, the first guidelines for the formulation and evaluation of sunscreens marketed were published by the Federal Register in 1978[29]. These guidelines were reevaluated in 1988 and further revised in 1993[30]. The general measurement is to apply sunscreen to the skin of a volunteer and measure how long it takes before sunburn occurs when exposed to an artificial sunlight source. In the USA, such an *in vivo* test is required by the FDA. However, this *in vivo* test requires human volunteers to be subjected to potentially damaging and carcinogenic doses of ultraviolet radiation. Therefore, many *in vitro* tests have been proposed such as spectrometer method[31]. In this case, the actual transmittance of the sunscreen is measured, along with the degradation of the product due to being exposed to sunlight. The transmittance of the sunscreen is measured over all wavelengths in the UV-B range (290–350 nm), along with a table of how effective various wavelengths are in causing sunburn (the erythemal action spectrum) and the

actual intensity spectrum of sunlight[32]. Mathematically, the SPF is calculated from measured data as:

$$\text{SPF} = \frac{\int A(\lambda)E(\lambda)d\lambda}{\int A(\lambda)E(\lambda)/\text{MPF}(\lambda) d\lambda},$$

where $E(\lambda)$ is the solar irradiance spectrum, $A(\lambda)$ the erythemal action spectrum, and $\text{MPF}(\lambda)$ the monochromatic protection factor, all functions of the wavelength λ . The MPF is roughly the inverse of the transmittance at a given wavelength.



3.6 Critical Wavelength

On May 12, 1993, FDA issued its Notice of Proposed Rulemaking for OTC drug sunscreen products[30]. This proposal made many changes in the regulation of cosmetics containing sunscreens such as the maximum SPF allowed, sunscreen efficacy testing, the effectiveness against UVA and other claims in labeling. The proposed rule acknowledged the need for protection against UVA radiation (320-400nm) because there is much clinical evidence and theoretical consideration finding that the UVA radiation can penetrate the skin more efficiently than UVB radiation[33]: Bissett D L et al[34] and Harrison JA.[35] et al found that the exposure to UVA could introduce photodamage to

animals' skin. Later on, Lavker et al[36, 37], Lavker and Kaidbey[38], and Lowe et al[39] found the repeated exposure to an artificial source of long-wavelength UVA produces morphologic changes in human skin and it can trigger the skin tumors. This was further studied by Strickland PT[40] et al and Sterenborg HJCM[41] et al. However, the FDA thought that there are no appropriate, established testing methods could measure UVA protections till now. In their report they said that a sunscreen drug product may claim it protects against UVA radiation if it contains the active ingredients that absorb UVA radiation extending to 360nm or above. And it also should pass the testing procedures of the FDA before the sunscreen could finally be proposed as UVA protection[30]. Therefore, there is no official method which can test the UVA protection. This work adopts Brian L. Diffey's[42] method to test our sunscreen's broad-spectrum ultraviolet protection in vitro as their method is strongly consistent with in vivo measurement of UVA protection. In this method, a critical wavelength is determined by means of UV substrate spectrophotometry. In this work, a UV/VIS spectrometer was used as a UV detector to test the critical wavelength, which is defined as following equation:

$$\lambda_c = 400 - \frac{\int_{290}^{\lambda_c} A(\lambda) d\lambda}{0.9 \int_{290}^{400} A(\lambda) d\lambda}$$

Where A is absorption and λ is wavelength. The λ_c is critical wavelength which is the wavelength at which the integral of the spectral absorbance curve reached 90% of the integral from 290 to 400nm. Following this method, two claims were made: a broad-spectrum protection should cover the long-wavelength UVA (340~400nm) region

and the critical wavelength of it should be greater than or equal to 370nm These criteria must be met if a sunscreen is to be labeled as broad spectrum.

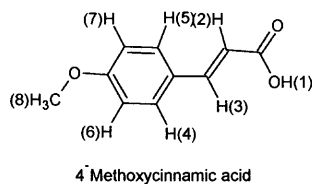
CHAPTER 4

RESULTS AND DISCUSSION

4.1 Results for Preparation of Isosorbide Derived UVB Sunscreens with High Extinction Coefficient

4.1.1 Results for Preparation of 4-methoxycinnamic Acid

From the DSC spectrum (Figure 6.1.1), this work found that this reaction provided a very pure product. Its purity even can reach 99.99%, which falls in the measurement range of the DSC. The FTIR (Figure 6.2.1) and NMR (Figure 6.3.1) spectra confirm that the material is the desired compound (1): In FTIR, the extremely broad and strong bond vibration centered near 3000 cm^{-1} illustrates this product has O-H group of carboxylic acid. And the weaker C-H absorption bands are superimposed on it from 3000 to 2850 cm^{-1} . Its carbonyl group C=O is shifted to lower wavenumbers 1687 cm^{-1} due to it is conjugated with benzene. The aromatic ring vibrations appear at 1598.709 , 1513.856 , 1511.927 and $1459,859\text{ cm}^{-1}$. This information is also consistent with NMR spectrum (Figure 6.3.1), where the three H(8) of $-\text{CH}_3$ group has chemical shift of 3.8 ppm and is shown as a singlet. H(2) and H(3) appear respectively at 6.377 and 7.552 ppm as doublets coupled with each other. The coupling constant for them is 16 Hz . H(4) and H(5) are identical and show as a doublet at 7.641 ppm as they are coupled with H(6) and H(7) which are also identical and appear as a doublet at 6.977 ppm with coupling constant of 8.72 Hz . H (6) and H(7) appear relatively at up-field because they near the $-\text{OCH}_3$ which push electrons to shield the external magnetic field .



And from DSC, this material has two melting peaks and two recrystallization peaks in the heating and cooling ramp respectively, both of which are located near the same place. This phenomenon illustrates this stiff, flat and small compound **(1)** is a liquid crystal which can flow like a liquid, but orient like a crystal. .Therefore, when we heat compound (1) from its solid crystal phase to its cloudy liquid phase or nematic phase, the arrangement of molecules is changed from 2D orientation to 1D orientation, which means its positional and long-range orientational order is reduced to be long-range orientational order. And if we continued to heat this cloudy liquid phase to its liquid phase, it loses all order at the second melting point. And following the similar orientation change, two re-crystallization points occurred during the cooling ramp.

From the UV/VIS spectrum(Figure 6.4.1), the maximum absorption of compound **(1)** appears at 288 nm with the extinction coefficient of 18300. It is not suitable as a UVB or UVA absorber.

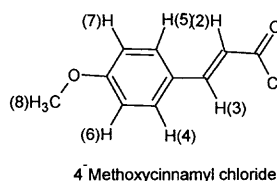
4.1.2 Results for Preparation of Isosorbide Bis(4-methoxycinnamate)

Route 1: The NMR spectrum shows the presence of 5-(4-methoxycinnamate), 2-(4-methoxycinnamate) and 2,5-bis(4-methoxycinnamate). Therefore a vacuum distillation at up to 200 °C and 3.5 mm Hg was attempted without success. Therefore this synthetic route was not suitable for isosorbide to make the ester.

Route 2:**Step 1: Results for Preparation of 4-methoxycinnamyl Chloride**

Route □: This reaction cannot cleanly make the 4-methoxycinnamyl chloride as its vigorous reaction conditions probably lead to HCl adding to the double bond of 4-methoxycinnamic acid and accelerate the decomposition of the chemical compound.

Route □:

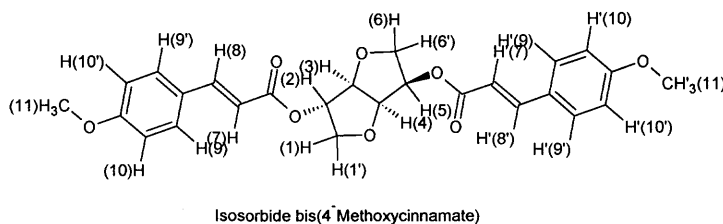


This reaction offered very pure 4-methoxycinnamyl chloride, which we can observe from the NMR spectrum (Figure 6.3.2). It has a similar structure with compound (2). The only difference for this compound is that the $-OH$ of 4-methoxycinnamic acid is replaced by the chloride. Therefore, the more electronegative chloride can attract electrons from the conjugation system to form a resonance structure. Through this resonance structure, H(3) is deshielded, causing a downfield shift. It appears at 7.829 ppm as a doublet since it coupled with H(2) which is located at 6.538 ppm with coupling constant of 15.39 Hz. H(7) and H(6) with the similar chemical environment are shown as doublet at 6.977 ppm as they are coupled with H(4) and H(5). Since H(4) and H(5) are not only coupled with H(6) and H(7) but also virtual coupled with themselves, they appear at 7.585, 7.583, 7.555 and 7.553 ppm as a complexity of peaks. 3 protons of H(3) are shown at 3.9 ppm as singlet.

Step 2: Results for Preparation of Isosorbide 2,5-Bis-(4-methoxycinnamate)

From the DSC (Figure 6.1.2), the product is around 96.6% pure. In FTIR (Figure 6.2.2), there is carbonyl group C=O of ester shown at 1720 cm^{-1} . The band for the C=C double bond appears at 1640 cm^{-1} . The aromatic ring vibrations appear at 1610, 1580, 1510 and 1460 cm^{-1} . The strong CH out-of-plane bending bands in benzene associated with para-substitution appear in $840\text{-}810\text{ cm}^{-1}$. And the C-H vibration bands appear at $3000\text{-}2850\text{ cm}^{-1}$. These illustrate the esterification between isosorbide and 4-methoxycinnamic acid happened in this reaction. And from the spectrum of NMR(Figure 6.3.3), the 1:1 ratio of H(2) and H(5) around the 5.332 and 5.303 ppm illustrates the esterification happened in both 2- and 5- OH groups of isosorbide. Therefore, the bis-compound is formed. A doublet peak for H(7) appear at 6.390 ppm and another doublet peak for H'(7) appear at 6.305 ppm due to near the asymmetric system of isosorbide and coupled with H(8) and H(8') respectively. For the same reason, H(8) and H(8') are also shown as two doublets at 7.714 ppm and 7.669 ppm with coupling constant of 16Hz. Since they are further from asymmetric isosorbide, the chemical shift for H(8) and H(8') are not so different. Therefore, two doublet peaks are overlapped with each other. H(10), H(10'), H'(10), H'(10') with identical chemical environment are coupled with H(9), H(9'), H'(9), H'(9') shown as a doublet at 6.374 ppm. H(9), H(9') and H(9), H(9') are shown at 7.514-7.47ppm as a complex peak system due to the asymmetric system and coupled with H(10), H(10'), H'(10), H'(10'). H(4) appear at 4.963 as a triplet due to coupled with H(5) and H(3) with similar coupling constant. H(3) appear at 4.629 and 4.613ppm as doublet due to coupled with H(4). H(1'), H(6) and H(6') appear at 4.1-4.0ppm. H(1) is shown at 3.95-3.87ppm. 6 of H(11) or H'(11) appear at 3.87-3.81ppm as a singlet due to far away from asymmetric system of

isosorbide. The information above demonstrates that the product is the desired compound **(3)**.

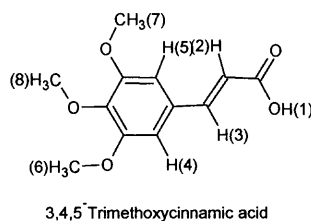


The UV/VIS Spectrum (Figure 6.4.2) shows that compound **(3)** has maximum absorption at 312 nm with the extinction coefficient of 44200. It suits to be a UVB absorber.

4.1.3 Results for Preparation of Isosorbide Bis(3,4,5-trimethoxycinnamate)

Step 1: Preparation of 3, 4, 5-trimethoxycinnamic Acid:

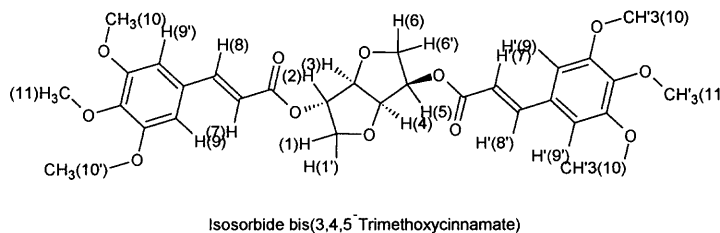
From NMR spectrum (Figure 6.3.4), this work found the product to be the pure desired compound (4): The 6 protons of H(7), H(6) and 3 protons of H(8) from $-\text{OCH}_3$ groups appear at 3.905 and 3.898 ppm as two singlet due to slight different chemical environment. H(2) and H(3) appear at 6.370 ppm and 7.719 ppm respectively as two doublets due to coupling with each other. The H(4) and H(5) appears at 6.789 ppm as a singlet since they have identical chemical environment. The H(1) are not shown as a strong peak in the spectrum as it undergoes quick exchange with proton of water, which always exists in the NMR solvent.



Step 2: Preparation of 3, 4, 5-trimethoxycinnamyl Chloride(5): From NMR spectrum(Figure 6.3.5), this work can confirm that the product in this reaction is the desired compound (5). It has similar structure with compound (4). H(2) and H(3) appear at 6.552 ppm and 7.759 ppm respectively as doublets due to coupling with each other. The H(4) and H(5) appears at 6.797 ppm as one peak since they have identical chemical environment. The difference between them is that 3 of H(8) appear downfield compared with 6 of H(7),H(6) rather than upfield compared with 6 of H(7),H(6). That is because the electronegative chloride withdraws the electrons from the conjugation system to form a resonance structure where the electrons on the para-position of benzene are pulled more than the meta-position. Therefore, H(8) are deshield more appearing at downfield.

Step 3: Preparation of Isosorbide Bis(3,4,5-trimethoxycinnamate)(6): From DSC(Figure 6.1.3), the purity of this product is around 96%. And it is the desired compound (6) which can be analyzed by FTIR and NMR spectra. In the FTIR spectrum (Figure 6.2.3), the carbonyl group C=O of ester appears at 1724 cm^{-1} . The band for the C=C double bond appears at 1641 cm^{-1} . The aromatic ring vibrations appear at 1585, 1506 and 1467 cm^{-1} . The strong CH out-of-plane bending bands in benzene associated with para-substitution appear in $840\text{-}810\text{ cm}^{-1}$. And in the NMR spectrum (Figure 6.3.6), the H (8) and H'(8) shown at 7.633 and 7.625 ppm as two doublets due to coupled with H(7) and H(7') which are shown at 6.742 and 6.813 ppm with the same coupling constant of 16 Hz. This large coupling constant confirms the α,β trans- conformation of the H(8) and H(7) or H'(8) or H'(7). And because of the asymmetric system of isosorbide, the doublet peaks of H(8) and H'(8) have slightly different chemical shift, .Therefore,, they overlapped with each other to form the quartet. For the same reason, H(7) and H'(7) are

also shown as quartet with distinct chemical shift as they are more influenced by the isosorbide' asymmetric system. The two singlets shown at 7.114, 7.107ppm relate to the 2 H(9) and 2 H'(9) in the slightly different chemical environment. And the 1:1 ratio of H(2) and H(5) around the 5.501 and 5.291 ppm as triplet and singlet illustrates the esterification happened in both 2- and 5- OH group of isosorbide .Therefore, the bis-compound is formed. H(4) and H(3) appear at 4.82 and 4.5ppm respectively as triplet and doublet. H(1), H'(1), H(6), H'(6) are shown at 3.85-4.0ppm region. 12 of H(10), H(10'), H(10), H'(10) are shown at 3.85-3.78ppm. The 6 hydrogens of H(11) and H'(11) appear at 3.71-3.65ppm. This information solidify that the product is the desired compound (6). Also from the NMR spectrum, some cinnamic acid impurities could be seen to exist in the material, which is consistent with the 4% impurity from the DSC.



The UV/VIS Spectrum (Figure 6.4.3) shows that compound (6) has maximum absorption at 304 nm with the extinction coefficient of 34655. It is suitable to be a UVB absorber.

4.1.4 Results for preparation of isosorbide bisferulate (7)

From DSC (Figure 6.1.4) , this work found the product is 96.7% pure. And in FTIR(Figure 6.2.4), the absorption band for the -OH bond appears at 3288 cm^{-1} . The carbonyl group C=O of ester appears at 1729 cm^{-1} . The band for the C=C double bond appears at 1658 cm^{-1} . The aromatic ring vibrations appear at 1604, 1575, 1513 and 1452

cm^{-1} . The strong CH out-of-plane bending bands in benzene associated with para-substitution appear in $840\text{-}810\text{ cm}^{-1}$. It means it is desired compound (7)

The UV/VIS Spectrum (Figure 6.4.4) shows that compound (7) has maximum absorption at 276 and 331 nm with the extinction coefficient of 39533 and 19535. It is suitable to be a UVB absorber.

4.2 Results for Preparation of Isosorbide Derived UVA Sunscreens with High Extinction Coefficient and Long Wavelength UVA Absorption

4.2.1 Results for preparation of isosorbide biscyanoferulate

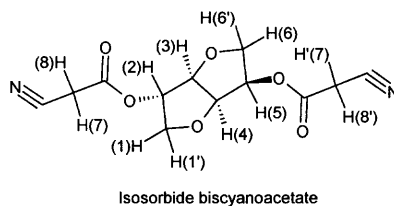
Step 1: preparation of isosorbide biscyanoacetate(8)

Route 1:

The experiment demonstrated that this synthetic route was not suitable for reacting cyanoacetic acid with isosorbide to form the ester because of its poor yield.

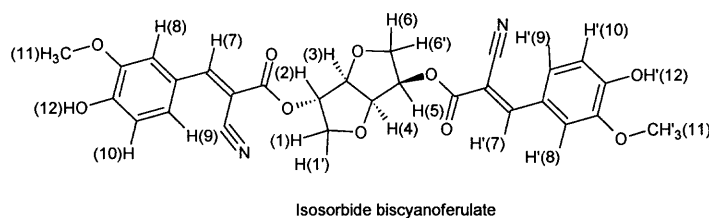
Route 2

In NMR(Figure 6.3.7) , the 1:1 ratio of H(2) and H(5) around the 5.3 and 5.25 ppm illustrates the esterification happened in both 2- and 5- OH group of isosorbide .Therefore,, the bis-compound is formed. The H(3) and H(4) appear at 4.53 and 4.9 ppm respectively as doublet and triplet. H(1), H(1'), H(6) and H(6') are shown at 4.1-3.88ppm. H(7),H(8) and H'(7), H'(8) appear at 3.55 and 3.5ppm respectively due to asymmetric system of isosorbide. The information in NMR spectrum illustrates the product is the desired compound (8)



Step 2: Preparation of Isosorbide Biscyanoferulate(9)

From the DSC(Figure 6.1.5), this work found that this synthetic route provides very pure product for us. Its purity can reach to 97%. In the FTIR spectrum (Figure 6.2.5), the strong absorption band for the -OH bond appears at 3370 cm^{-1} . The -CN triple-bond stretch occurs at 2220 cm^{-1} . The carbonyl group C=O of ester appears at 1740 cm^{-1} . The band for the C-O bond appears at 1230 cm^{-1} . The aromatic ring vibrations appear at 1580, 1520,



1460 and 1450 cm^{-1} . In NMR spectrum (FIGURE 6.3.8), the 1:1 ratio of H(2) and H(5) around the 5.3 and 5.25 ppm illustrates the esterification happened in both 2- and 5- OH group of isosorbide. A singlet peak appearing at 10.6ppm are H(12) and H'(12) of -OH group. H(3) and H(4) are also show at 4.6, 4.9 ppm respectively. H(7) ,H'(7) are shown as a two singlet at 8.288 and 8.259ppm due to asymmetric system of isosorbide. H(8) ,H(8') and H'(8) ,H.(8') coupled with H(9), H(9') and H'(9), H'(9') are shown at 6.990, 6.962ppm and 6.984,6.956 ppm as two doublet due to asymmetric system of isosorbide. For the same reason, H(9) ,H(9') and H'(9) H'(9') are coupled with H(10), H(10') and H'(10), H,(10') shown as two doublet overlapping with each other at 7.8, 7.77, 7.793 and 7.764 ppm. H(10), H(10') and H'(10), H(10') are coupled with H(9) ,H(9') and H'(9)

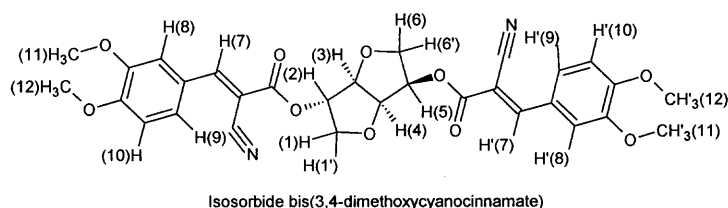
H'(9'), H(8), H(8') and H'(8), H.(8') form a complex peak system at 7.72-7.6ppm region. H(11) and H'(11) appear at 3.832 and 3.822 ppm as two singlet due to asymmetric system of isosorbide. H(1), H'(1) and H(6), H'(6) appear around 3.86-4.11ppm. These results demonstrate the product is the desired compound (9)

The UV/VIS Spectrum (Figure 6.4.5) shows that compound (9) has maximum absorption at 374 and 453 nm with the extinction coefficient of 48300 and 10100 . It is suitable to be a UVA absorber.

4.2.2 Results for Preparation of Isosorbide Bis (3,4-dimethoxycyanocinnamate)

From the DSC thermogram (FigureE 6.1.6), this work found that the product still contains some methanol which was the recrystallization solvent. The purity of it is only 94%. In FTIR (Figure 6.2.6), the strong absorption band for the -OH bond appears at 3370 cm^{-1} , which belongs to methanol. The -CN triple-bond stretch occurs at 2221 cm^{-1} . The carbonyl group C=O of ester appears at 1740 cm^{-1} . The band for the C-O bond appears at 1263 cm^{-1} . The aromatic ring vibrations appear at 1589, 1560, 1515 and 1465 cm^{-1} . In NMR (Figure 6.3.9), the 1:1 ratio of H(2) and H(5) around the 5.4 and 5.3 ppm illustrates the esterification happened in both 2- and 5- OH group of isosorbide. H(3) and H(4) are shown at 4.6, 5.0ppm respectively. H(7) and H'(7) appear at 8.356 and 8.324ppm as two singlet due to asymmetric system of isosorbide. H(8), H(8') and H'(8), H.(8') appear at 7.29-7.09 region as two doublet due to coupled with H(9), H(9') and H'(9), H.(9') and asymmetric system of isosorbide. H(9), H(9') and H'(9), H.(9') and H(10), H(10') are coupled with each other and H(8), H(8') and H'(8), H.(8') shown at 7.94-7.70ppm as a complex peak system. H'(1) and H(6), H'(6) appear around 3.86-4.11ppm. H(1) appear at 3.35ppm. 3 of H(11), 3 of H(12) and 3 of H'(11), 3 of

H'(12) appear at 3.888, 3.883 and 3.821, 3.810 ppm respectively as 4 singlet due to slight different chemical environment and asymmetric system of isosorbide. The information above illustrates the product is the desired compound **(10)**

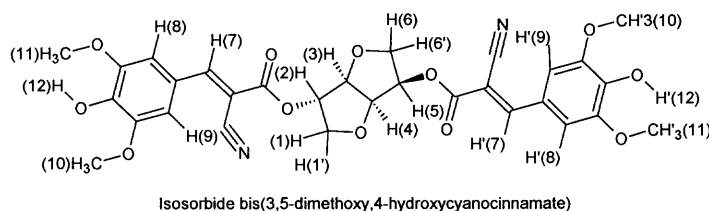


The UV/VIS Spectrum (Figure 6.4.6) shows that compound **(10)** has maximum absorption at 368 nm with the extinction coefficient of 45000. It is suitable to be a UVA absorber.

4.2.3 Results for Isosorbide Biscyano (3,5-dimethoxy, 4-hydroxycinnamate) **(11)**

From DSC (Figure 6.1.7), this work found the purity of the product is 97%. In FTIR (Figure 6.2.7), the strong absorption band for the -OH bond appears at 3494 cm^{-1} . The -CN triple-bond stretch occurs at 2219 cm^{-1} . The carbonyl group C=O of ester appears at 1714 cm^{-1} . The band for the C-O bond appears at 1249 cm^{-1} . The aromatic ring vibrations appear at 1600, 1581, 1513 and 1461 cm^{-1} . In NMR (Figure 6.3.10), the 1:1 ratio of H(2) and H(5) around the 5.4 and 5.3 ppm illustrates that esterification happened in both 2- and 5- OH group of isosorbide. H(3) and H(4) are shown at 4.6, 5.0 ppm respectively. H(7) or H'(7) appear at 8.304, 8.272 ppm as two singlet due to asymmetric system of isosorbide. For the same reason, H(8), H(9) and H'(8), H'(9) are shown at 7.561, 7.535 ppm respectively as two singlet. H(12) and H'(12) of -OH group are shown at 10.027 ppm as a singlet. H(1), H'(1) and H(6), H'(6) appear around 3.87-4.11 ppm region. H(10), H(11) or H'(10), H'(11) are shown at 3.83 and 3.82 ppm as two singlet due

to asymmetric system of isosorbide. The information above means the product is the desired compound **(11)**



The UV/VIS Spectrum (Figure 6.4.7) shows that compound **(11)** has maximum absorption at 388 and 408nm with the extinction coefficient of 49123. It is suitable to be a UVA absorber.

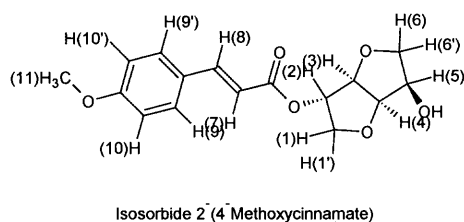
4.3 Results for Preparation of Isosorbide Derived Multifunctional Single Compound

4.3.1 Results for Preparation of Isosorbide 2-(4-methoxycinnamate)

Route 1:

This reaction did not give a very clean product even if excess isosorbide was used to favor the 4-methoxycinnamyl chloride just added to the 2 position of the isosorbide. Because from the spectrum of NMR, the H(2) and H(5) are showed at the 5.4, 5.3ppm region with the ratio of 4:6, which illustrates the esterification happened in both 2 position and 5 position of the -OH group in isosorbide and the ratio of them is 4:6. That maybe because the two hydroxy groups don't have enough selectivity to attach the 4-methoxycinnamyl chloride at one position, even if these two groups have some spatial and reactivity difference. Or it maybe because the 4-methoxycinnamyl chloride is so reactive that can disturb the isosorbide' original ability of selection. It tends to be difficult

to control, often resulting in a mixture of low purity products and a high percentage of by-products



Route 2:

This reaction can provide more selectivity for mono-esterification compared with route 1. However from the NMR, the isosorbide 5-(4-methoxycinnamate) was still existing since the H (5) next to ester group appearing as 30%. .Therefore, the column chromatograph was used to separate the isosorbide 5-(4-methoxycinnamate) and isosorbide 2-(4-methoxycinnamate) from each other. However, the effect was not encouraging. From the DSC (Figure 6.1.8), this work found there was about 20% isosorbide 5-(4-methoxycinnamate) left in the products. And from FTIR(Figure 6.2.8), some of compound (12) has been formed. The carbonyl group C=O of ester appears at 1716.346 cm^{-1} . The band for the C=C double bond appears at 1639 cm^{-1} . The aromatic ring vibrations appear at 1604, 1575, 1513 and 1463 cm^{-1} . The strong CH out-of-plane bending bands in benzene associated with para-substitution appear in 840-810 cm^{-1} . This information means some of the desired compound exists in the product. And from NMR spectrum(FIGURE 6.3.11), we can see H(7) appears at 7.670 ppm as a doublet due to coupled with H(8), which is located at 6.301 ppm as doublet with coupling constant of 16Hz. H(9) , H(9') and H(10) , H(10') coupled with each other are shown at 7.496ppm, 7.466ppm and 6.925, 6.896ppm as two doublet with coupling constant of 8.7Hz. H(5) exist at 5.3ppm illustrate the product is still not pure. And there are some peaks appearing

around 1.3ppm. That means some dicyclohexylurea is still in the sample, which is consistent with the result of the DSC. The existing of both isosorbide 2-(4-methoxycinnamate) and isosorbide 5-(4-methoxycinnamate) demonstrate the two synthetic routes are not clear and simple methods to make mono-ester of isosorbide.

From the UV/VIS spectrum (Figure 6.4.8), the maximum absorption of compound **(12)** locates at 312 nm with the extinction coefficient of 27700. It is suitable to be a UVB absorber.

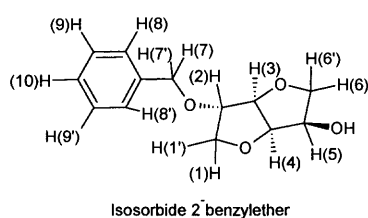
4.3.2 Results for Preparation of Isosorbide 2-(benzyl ether), 5-(4-methoxycinnamate)

Step 1: Preparation of Isosorbide 2-(benzyl ether)(13)

From the literature of carbohydrate research[43, 44], the two hydroxyl groups of the isosorbide can be alkylated selectively. Since the benzyl group can be removed by hydrogenation under very mild conditions, we choose to use it as a protecting group to selectively make 2- and 5-substituted isosorbide derivatives. Using literature procedures, the 2-benzyl ether of isosorbide was synthesized and recrystallized to high purity.

From DSC (Figure 6.1.10), this work found the product is very pure, even can reach 99.7%. And in FTIR (Figure 6.2.9), the absorption band for the -OH bond appears at 3421 cm^{-1} . The absorption due to the C-O bond of ether appears at 1114 cm^{-1} . The absorption due to aromatic ring skeletal vibration appears from $1498\text{--}1452\text{ cm}^{-1}$. In NMR (FIGURE 6.3.12), H(8), H(8'), H(9), H(9'), H(10) associated with benzene ring appear at 7.41-7.27ppm region. H(4) coupled with H(3) and H(5) with similar coupling constant is shown at 4.68-4.61ppm as triplet. H(7) and H(7') appear at 4.61-4.57 ppm as quartet due to coupled with each other. H(3) is shown at 4.57-4.50ppm region due to

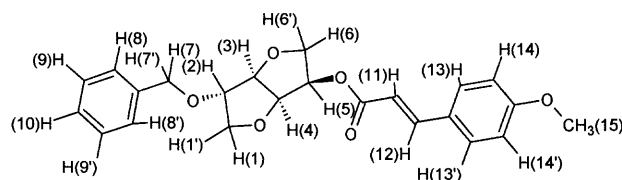
coupled with H(4) and it is overlapped with one peak of H(7), H(7') coupling. H(5) is coupled with H(4), H(6), H(6') to form a complicated peak system at 4.34-4.23ppm. H(2) and H(1') are overlapped at 4.15-4.06ppm region. H(6'), H(1') appear at 3.93-3.81ppm. H(6) is shown at 3.6-3.52ppm region. Proton of -OH group appear at 2.72-2.65ppm as doublet due to coupled with H(5). This information is consistent with the simulation of NMR program for isosorbide 2-(benzylether). That means that the product is the desired compound **(13)**.



Step 2: Preparation of Isosorbide 2-(benzyl ether), 5-(4-methoxycinnamate)(14)

From the DSC(Figure 6.1.10), this work found that the melting point this material is 62.64°C and its purity can reach about 95.56%. In FTIR(Figure 6.2.10), the absorption band for -OH bond has disappeared and a strong band at 1714 cm⁻¹ due to the carbonyl group of an ester appears. A band for the C=C double bond appears at 1641 cm⁻¹. The aromatic ring vibrations appear at 1600, 1585, 1513 and 1460 cm⁻¹. The strong absorption due to the C-O bond of the ether appears at 1176cm⁻¹. In the NMR spectrum (FIGURE 6.3.13), H(8), H(8'), H(9), H(9'), H(10) associated with the benzyl group appear at 7.4-7.28ppm. The two doublet peaks shown at 7.741 ppm and 6.393 ppm illustrate that the H(12) and H(11) are coupled with each other with a coupling constant of 16Hz. Two doublet peaks shown at 7.481 ppm and 6.905 ppm with a coupling constant of 8.8 Hz are consistent with the coupled H(13) with H(14) or H(13') with H(14'). H(2) showing at 5.3ppm means the *endo*- ester has been formed. H(4) appears at 4.884ppm as

triplet since it coupled with H(5) and H(3) with the similar coupling constant. H(3) shown as a doublet because it is coupled with H(4) and it is overlapped with A,B coupled H(7) and H(7') at 4.86ppm. H(1), H(1'),H(6) and H(6') appear at 4.2-3.9ppm. 3 of H(15) and H(5) appear at 3.7ppm as a singlet. The information above is consistent with the desired compound (14). And the presence of some cinnamic-acid related impurities are consistent with the result of DSC, where 4% of impurities are shown.

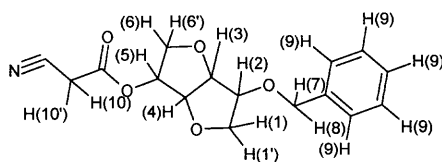


Isosorbide 2-benzylether,5-(4-methoxycinnamate)

The UV/VIS Spectrum (Figure 6.4.9) shows that compound (14) has maximum absorption at 310 nm with the extinction coefficient of 24561. It is suitable as a UVB absorber.

4.3.3 Results for preparation of isosorbide 2-benzyl ether, 5-cyanoferulate

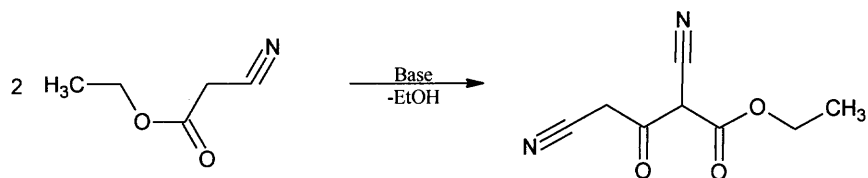
Step 1: Preparation of Isosorbide 2-benzyl ether, 5-cyanoacetate(15)



Isosorbide 2-benzylether,5-cyanoacetate

From the NMR spectrum (Figure 6.3.14), the 5 protons of H(9) are shown at 7.3pp. H(5) appears at 5.206ppm, which illustrates that some of the *endo*- ester has been formed. H(4) is shown at 4.885 as triplet. H(7) and H(8) appear at 4.561ppm as a singlet. H(3) is shown at 4.506 and 4.49ppm as a doublet. H(2) and H(1') are shown at 4.13-4.01ppm. H(6), H(6') and H(1) appear at 3.9-3.8ppm. H(10), H(10') are shown at 3.53-3.47ppm.

This information confirms that the major product is in the desired material. However, from the spectrum we still can see peaks for a methyl group and $-OCH_2$ group at 1.3ppm and 4.2ppm region. That means some ethyl cyanoacetate or ethyl cyanoacetate derived impurity is present in the material. That is probably because extra ethyl cyanoacetate was added in the reaction, which lead it to react with itself to undergo the following reaction:



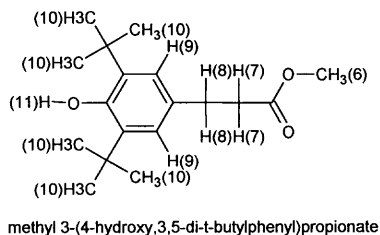
In the future one equivalent ethyl cyanoacetate would be tried and another chemical could be used as solvent to try this reaction.

4.3.4 Results for preparation of isosorbide 2,5-bis (3-(4-hydroxy,3,5-di-t-butylphenyl) propionate)

Step 1: Preparation of Methyl 3-(4-hydroxy,3,5-di-t-butylphenyl) propionate(16)

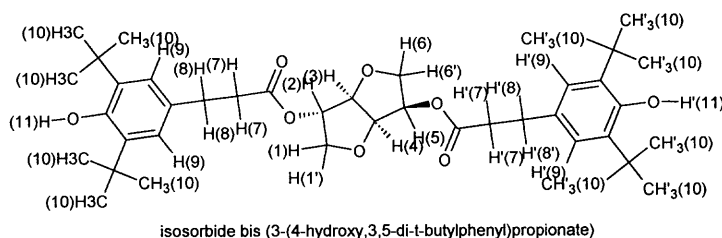
Route 2:

Since the route 1 did not give a good yield, this work switched the synthetic route to route 2. From the NMR spectrum (Figure 6.3.15), the 2 protons of H(9) and 1 proton of H(11) appear at 7.0 and 5.15ppm respectively as singlet. 3 protons of H(6) are appear at 3.7ppm as a singlet and two protons of H(8) are coupled with the two protons H(7) appearing at 2.8 and 2.6ppm respectively as a triplet. The 18 protons of the t-butyl group (10) appear in the spectrum at 1.4ppm as a singlet. This information is consistent with the product being the desired compound (16).



Step 2: Preparation of Isosorbide Bis(3-(4-hydroxy,3,5-di-t-butylphenyl) propionate)

From DSC (Figure 6.1.11), the material don't have melting point because it is the isotropic glass. In FTIR (Figure 6.2.11), we could see the strong absorption band for the -OH bond appears at 3644 cm^{-1} . The carbonyl group C=O of ester appears at 1743 cm^{-1} . The band for the C-O bond appears at 1236 and 1162 cm^{-1} . The aromatic ring vibrations appear at 1589 , 1484 and 1436 cm^{-1} . In the NMR spectrum (Figure 6.3.16), 2 protons of $\text{H}(9)$ and 2 protons of $\text{H}'(9)$ appear at 6.994 and 6.978 ppm as two singlets due to asymmetric system of isosorbide. $\text{H}(2)$, $\text{H}(5)$ appear at 5.25 and 5.2 ppm illustrating that both *exo*- and *endo*-esters have been formed. $\text{H}(11)$ and $\text{H}'(11)$ of -OH group appear at 5.2 ppm as a singlet. $\text{H}(3)$ and $\text{H}(4)$ are shown at 4.8 and 4.4 ppm respectively as triplet and doublet. $\text{H}(8)$, $\text{H}'(8)$ and $\text{H}(7)$, $\text{H}'(7)$ also appear at 2.8 and 2.6 ppm . They are coupled with each other and form a complexity of peaks due to the asymmetric system of isosorbide. This information in the NMR demonstrates this product is the desired compound (**17**).



4.4 Results of Critical Wavelength for All Synthetic UVA Absorbers

Based on the requirement of FDA, we selected our synthesized sunscreens which can absorb UVA radiation extending to 360nm or above as our UVA absorber. They are isororbide biscyanoferulate, isororbide bis(3,4-dimethoxycyanocinnamate) and isororbide bis(3,5-dimethoxy,5-hydroxycyanocinnamate). And following Brian L. Diffey's experiment, we have determined these UVA sunscreens' critical wavelength:

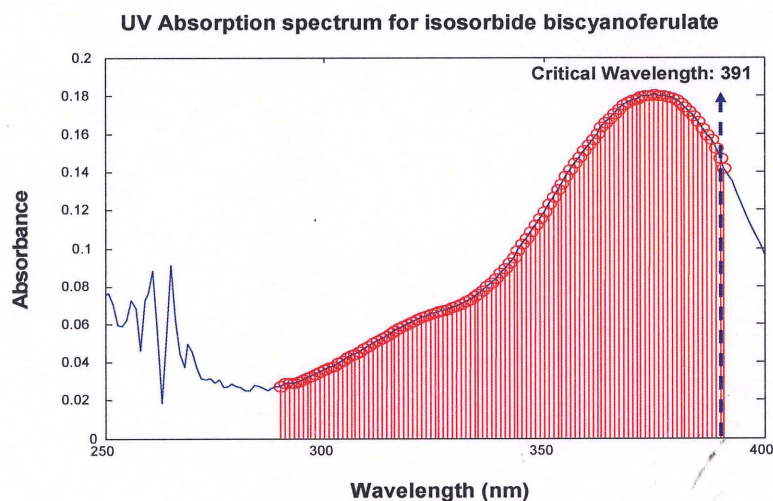


Figure 4.1 Critical wavelength of isororbide biscyanoferulate.

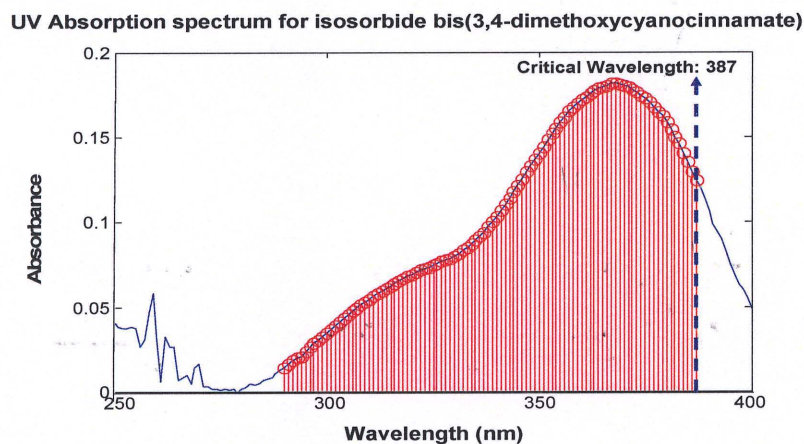


Figure 4.2 Critical wavelength of isororbide (3,4-dimethoxycyanocinnamate).

UV Absorption spectrum for isosorbide bis(3,5-dimethoxy, 4-hydroxycinnamate)

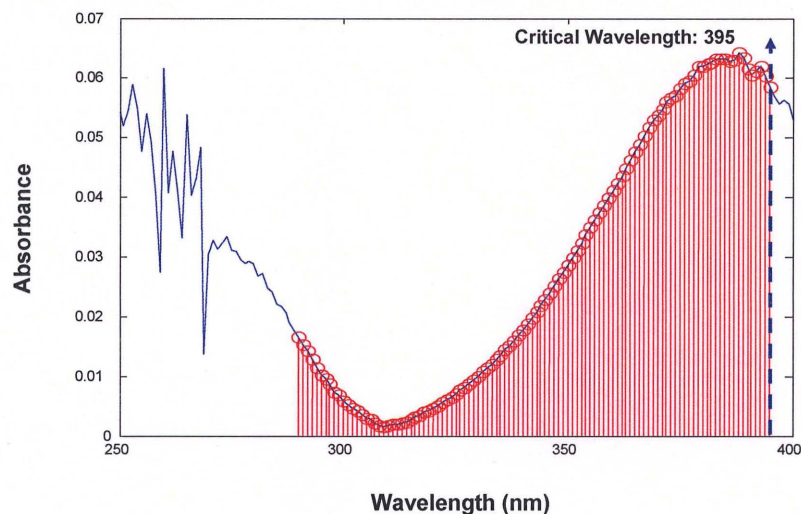


Figure 4.3 Critical wavelength of isosorbide bis(3,5-dimethoxy,4-hydroxycinnamate).

From the spectra, all the UVA absorbers we synthesized here can satisfy the minimum requirement as a broad UVA spectrum absorber which can be formulated to achieve a broad-spectrum sunscreen.

4.5 Results of Photostability for All Synthetic UVA Absorbers

After making sure of the UVA absorption properties of our synthesized UVA absorbers, we tested their photostability in our laboratory. The photostability testing was typically done at room temperature and in a sealed cardboard box where most of light exposure was delivered to the sunscreen solution. The light levels used in this testing were generally focused in the 375nm wavelength where the material has the strongest or relative strong absorbance. The material was dissolved in the HPLC grade ethanol and filled in a 10 mm quartz cuvette. The concentration of the radiated material was around $0.08 \times 10^{-3} \text{ mol/L}$, which is good enough to absorb almost 98% of radiation. The sample

was analyzed with a UV/Visible spectrometer before and after radiated after the appropriate dilution.

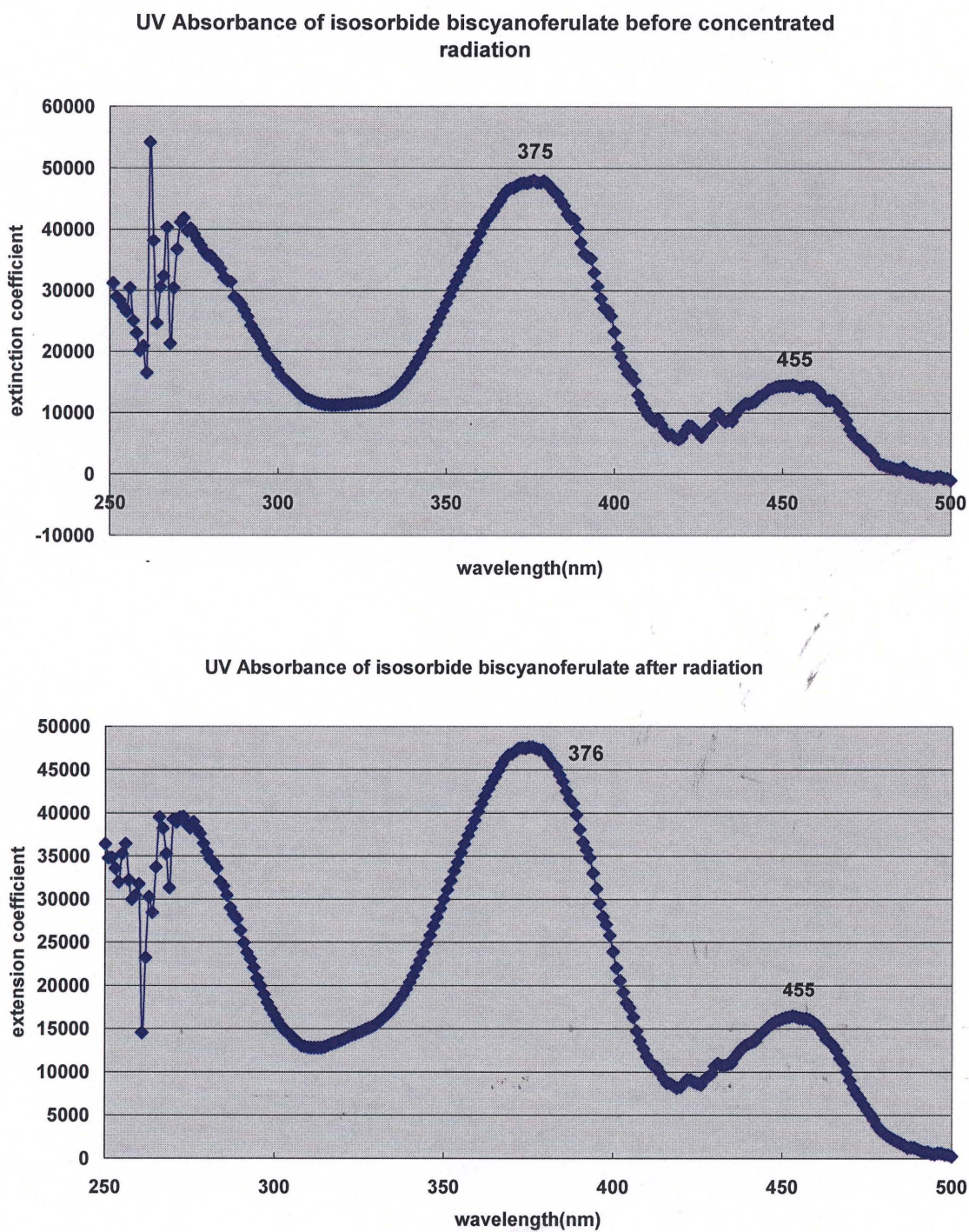
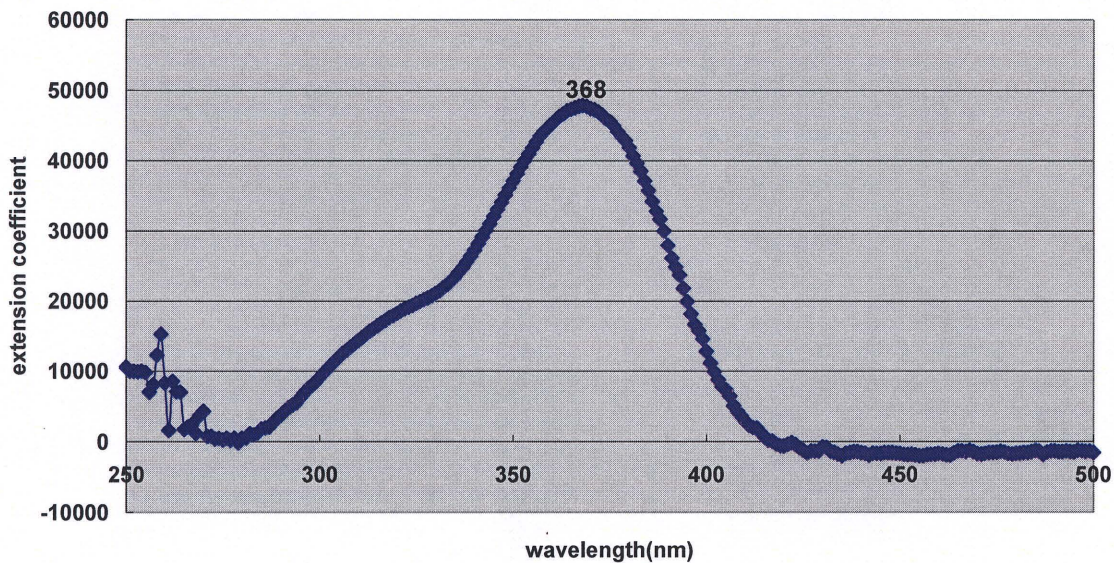


Figure 4.4 Photostability of isosorbide biscyanoferulate.

UV Absorbance of isosorbide bis(3,4-dimethoxycinnamate) before high concentrated radiation



UV Absorbance of isosorbide bis(3,4-dimethoxycinnamate) after high concentrated radiation

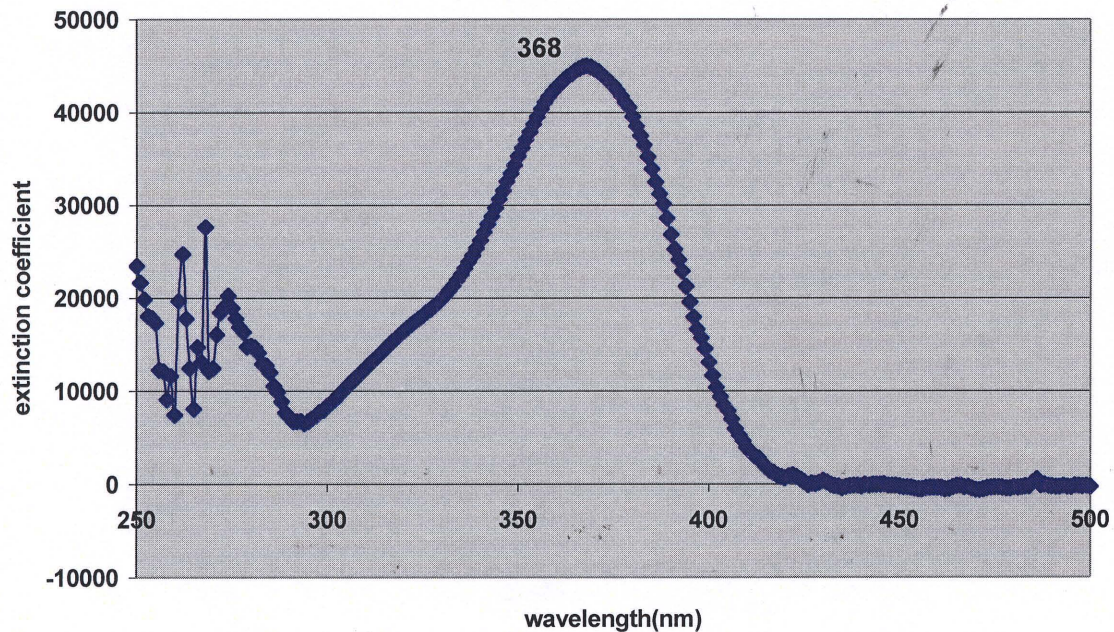


Figure 4.5 Photostability of isosorbide bis(3,4-dimethoxycinnamate).

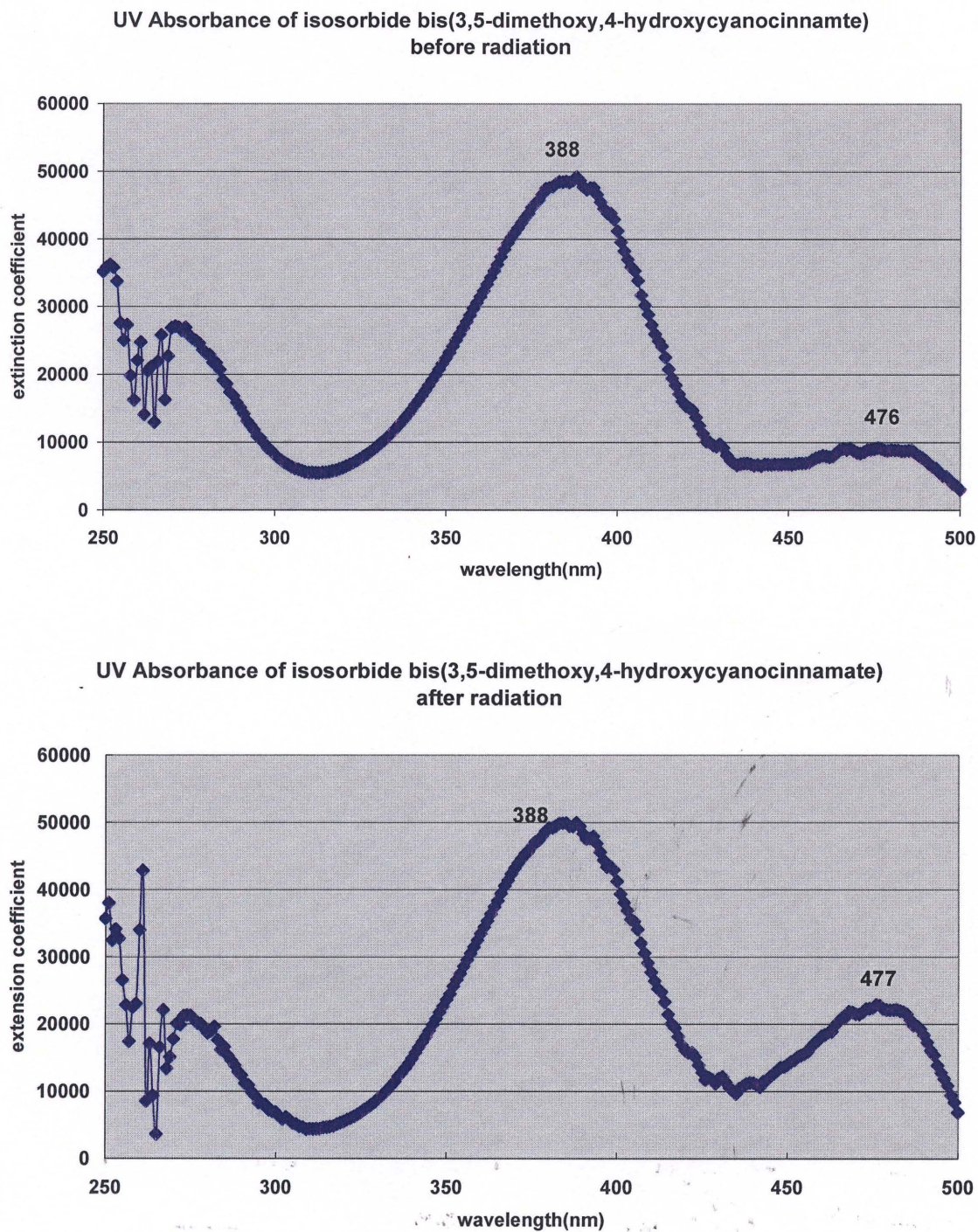


Figure 4.6 Photostability of isosorbide bis(3,5-dimethoxy,4-hydroxycinnamate).

From these series of UV spectra, this work found the λ_{max} of our material remained unchanged during irradiation and the shape of the absorption curve between

290~400nm in which it completely covers the whole UVA and part of UVB region did not change a lot. The area under the curve (AUC) in the spectrum was calculated for UVA1 (340–400 nm) and UVA2 (320–340 nm) before (AUC_{before}) and after (AUC_{after}) radiation. The AUC Index (AUCI) which is defined as $AUCI = AUC_{after}/AUC_{before}$ was calculated for each specific period of time. AUCI of our materials were all calculated and all of them were > 0.80 . Therefore, these materials are considered photostable in the ethanol at least for about 8 hours which is the normal exposure time of human skin under sunlight.

4.6 UV/Visible Absorption for mixture of synthetic UVB and UVA absorbers

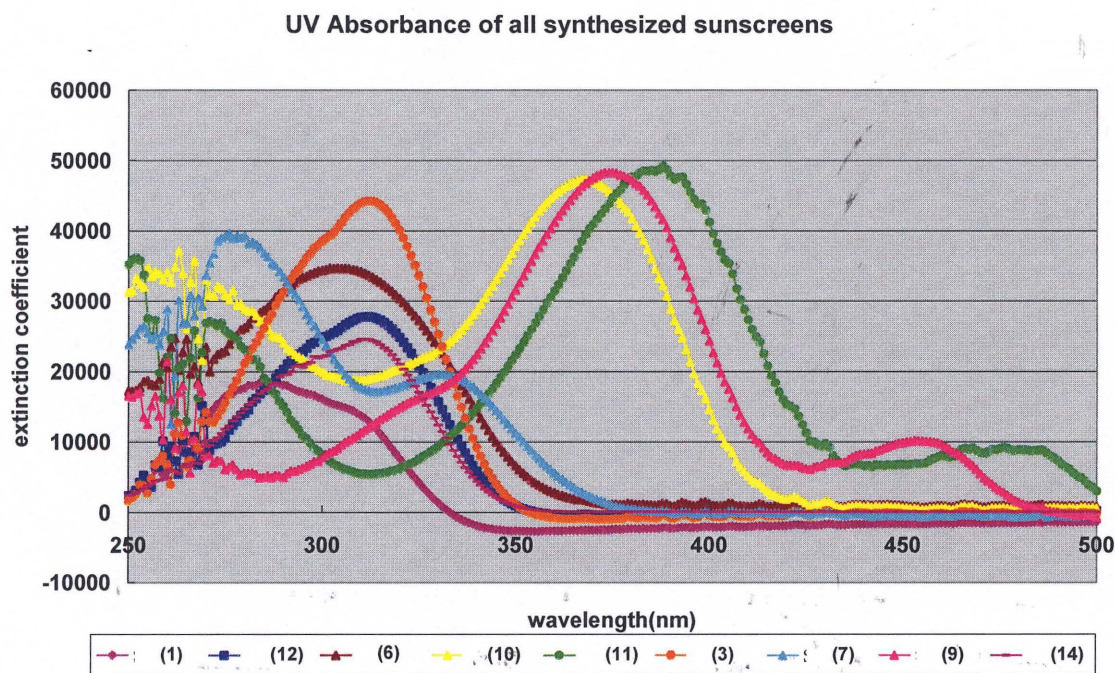


Figure 4.7 UV Absorbance of all synthesized sunscreen.

As Figure 4.7 shown, this work combined the UV absorbance spectra of all the synthesized sunscreen together and found the combination of them almost can cover the

whole UVA and UVB region. Only at 340nm the absorption of UV light is relative weaker than the absorptions at other wavelengths. However, these spectra are just the simple overlaying, the real mixture could show a different curve as the sunscreens in the mixture can have hydrogen binding and different concentration overlapping with each other in the solution. Therefore, following this idea, we mixed some of our synthesized UVA and UVB sunscreens together and dissolve them in the ethanol. Since the extension coefficient of every sunscreen is different, in order to view the spectrum in the available range the concentration of every sunscreen was adjusted. The absorbances of these mixtures are shown below:

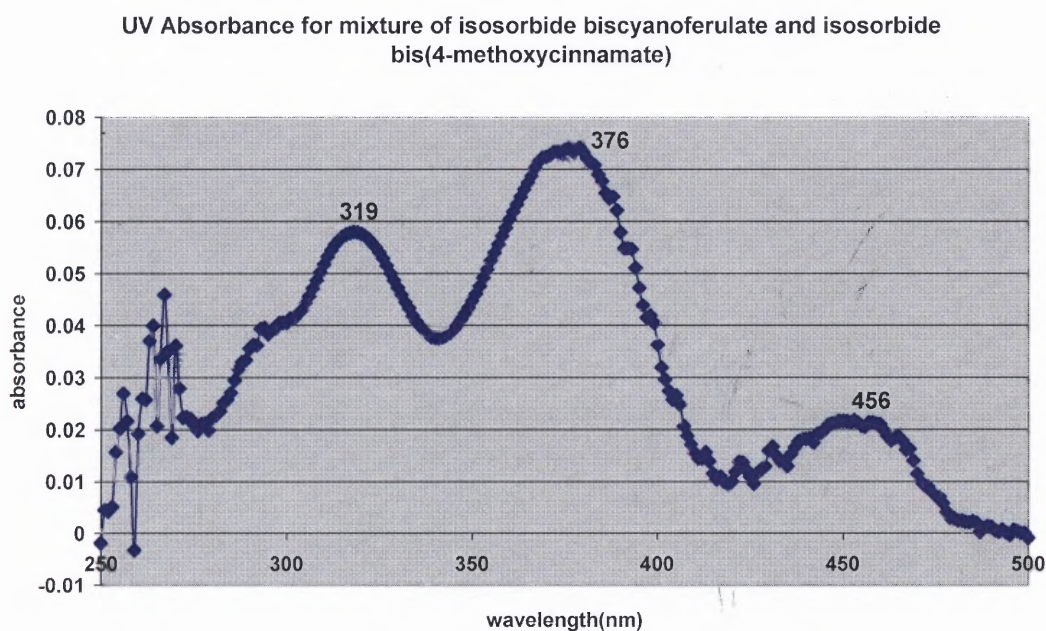


Figure 4.8 UV absorbance for mixture of isorbide bis(4-methoxycinnamate) with isorbide biscyanoferulate

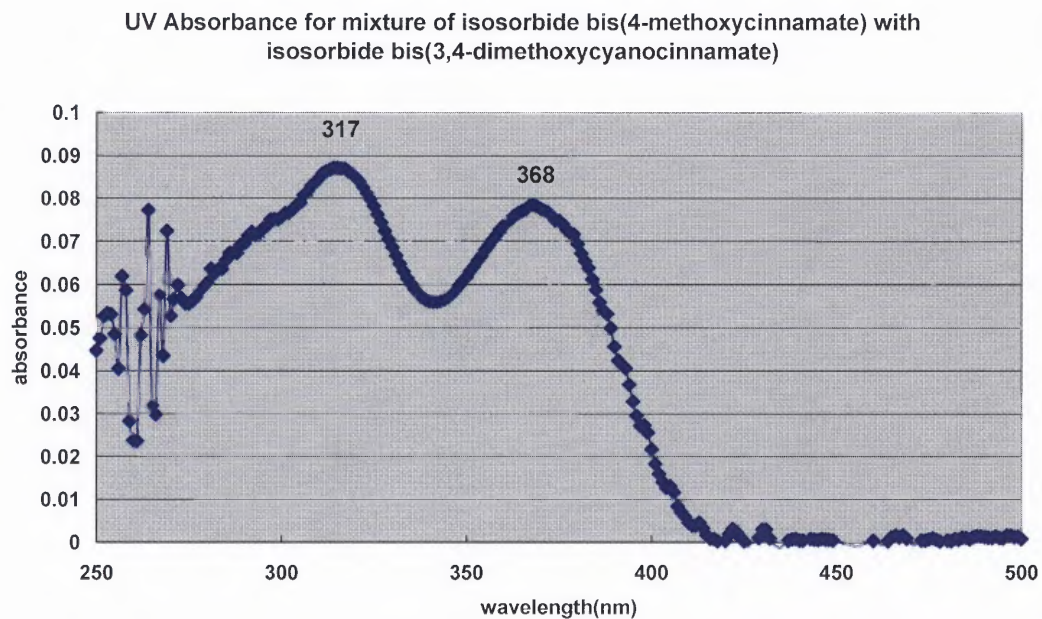


Figure 4.9 UV absorbance for mixture of isosorbide bis(4-methoxycinnamate) with isosorbide bis(3,4-dimethoxycyanoferulate).

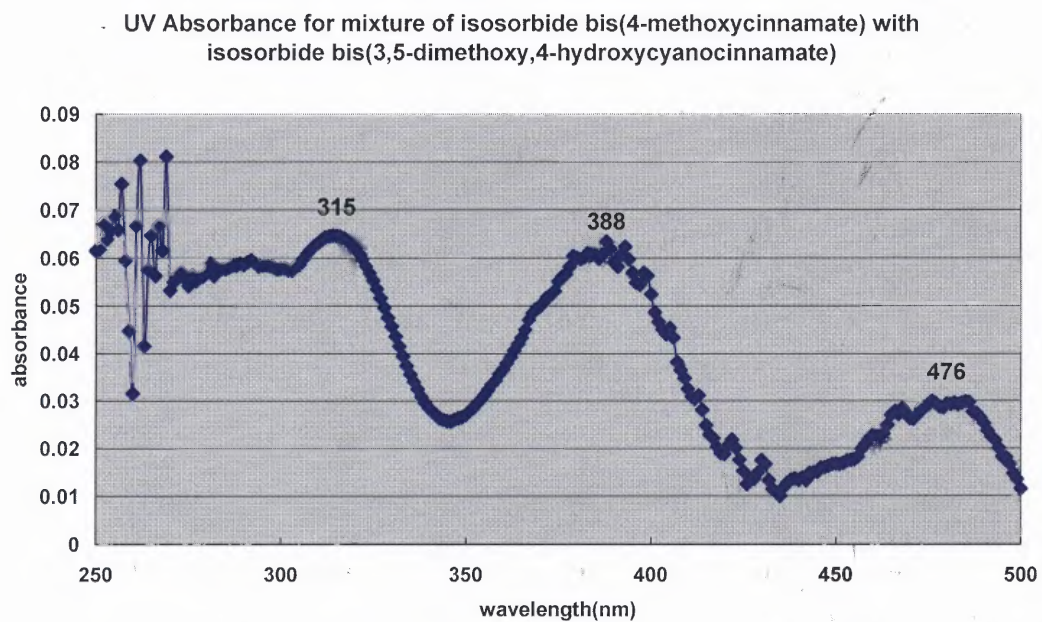


Figure 4.10 UV absorbance for mixture of isosorbide bis(4-methoxycinnamate) with isosorbide bis(3,5-dimethoxy,4-hydroxycyanocinnamate).

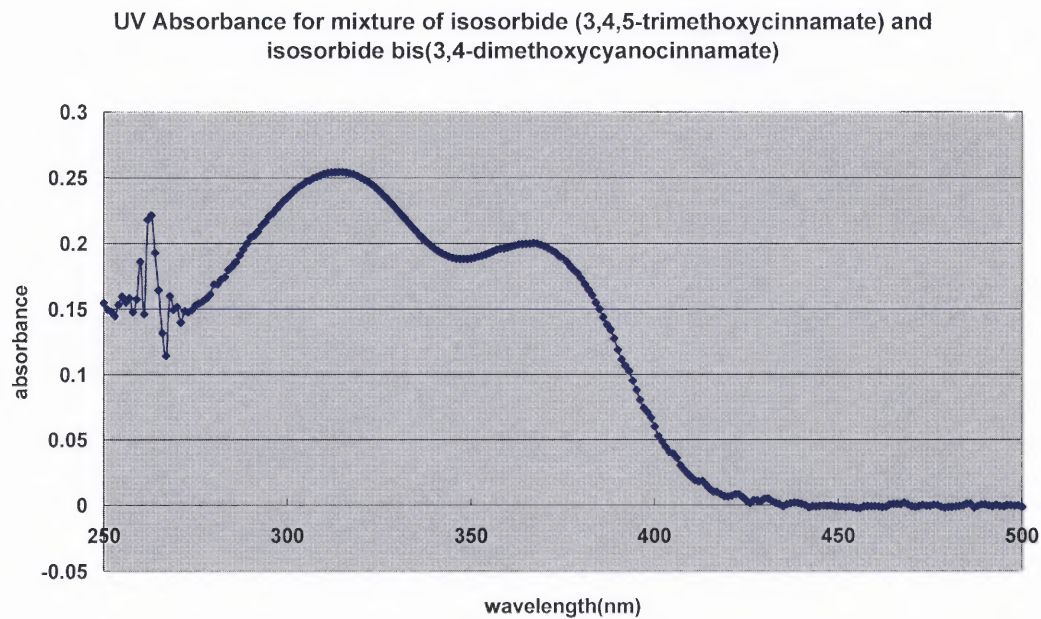


Figure 4.11 UV absorbance for mixture of isosorbide bis(3,4,5-trimethoxycinnamate) with isosorbide bis(3,4-dimethoxycinnamate).

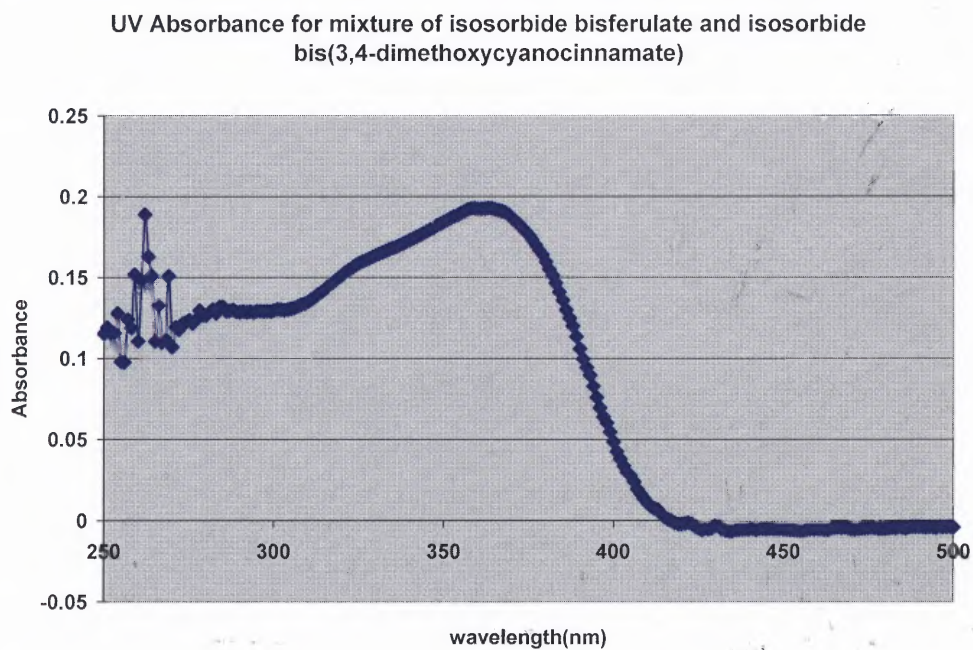


Figure 4.12 UV absorbance for mixture of isosorbide bisferulate with isosorbide bis(3,4-dimethoxycinnamate).

Based on these spectra this work found different combinations of sunscreens can provide different spectra. And each combination with different concentration also can

have different curve. It means the formulation of sunscreens is also important to achieve a broad-spectrum sunscreen such as choosing the ingredient and concentration to balance the effect of every component. In the formulation, the addition of other components such as surfactant and emollient need be considered. Because they not only can stabilize formulation but also can provide silky skinfeel. This part of work need to be finished in the future.

CHAPTER 5

CONCLUSION AND FUTURE WORK

In this study, several multifunctional isosorbide derivatives have been successfully synthesized. They are including a series of UVB, UVA sunscreens of high extinction coefficient and an isosorbide-derived antioxidant. The extinction coefficient of these sunscreens can reach twice the value of the original cinnamate. Based on the different modifications of cinnamic acid and different combinations of isosorbide with cinnamic acids, different sunscreens with different absorption properties have been synthesized. The combinations not only cover the UVB (290-320nm), the short wavelength UVA (320-340nm) but also the long wavelength UVA (340-400nm) regions, which is not the case in most commercial sunscreens, even if it has been emphasized widely in recent trade promotions for protection against skin cancer. Furthermore, these isosorbide derived sunscreens are natural-derived and photostable.

This work also finds that isosorbide as an intermediate in these sunscreens connects two chromophores together, allowing the electron delocalization throughout the whole molecule without disturbing their UV absorption properties. The combination of these two chromophores provides the high extinction coefficient. The addition of the cyano group in a modification of the cinnamate for the UVA sunscreens causes a bathochromic shift due to its electron withdrawing effect. The electron delocalization in each chromophore of these UVA sunscreens needs less energy to assist their electron transition process. Therefore, the long wavelength UVA rays with lower energy can correspond to their excitation process. And besides its bathochromic effect, the cyano

group also adds photostability to the cinnamyl moiety, which has been demonstrated by our own photostability test and the work of other groups.

The substituents on the benzene ring also provide photochemical influence. The hydroxyl group at the para- position of the benzene ring produces two band absorptions, which could come from some charge transferring or H-bonding in these chemicals. When the -OH group and -CN group are both added to the cinnamate backbone, the bathochromic effect of the -CN group moves the two band absorption curve from the UVB region to the longer wavelength UVA and into the visible region of electromagnetic spectrum, which generates the unexpected yellow color of the materials. And when the methoxyl group is added ortho- to the -OH group on the benzene ring, it can strengthen the electron delocalization through the conjugation system. Therefore, compound (11) can absorb at longer wavelengths compared with compound (9). While the 2-methoxyl groups are added next to a methoxyl group, a hypsochromic shift is generated. Therefore compound (6) absorbs at shorter wavelengths compared with compound (3).

An attempt was made to synthesize multifunctional compounds as asymmetric isosorbide derivatives. The known synthetic route to isosorbide 2-benzylether, 5-(4-methoxycinnmate) demonstrates this possibility. This specific material could be used in the polymer industry especially in PVC where it would function as both a plasticizer and UV stabilizer to decrease the polymer T_g, increase the flow properties and provide photostability to the polymer. Moreover, the 2-benzylether group of isosorbide 2-benzylether-5-(4-methoxycinnmate) could be removed by hydrogenation without destroying the 5-endo ester bond. Therefore, the newly-freed 2-*exo* hydroxyl group of isosorbide can react with another functional group to form an asymmetric functional

single compound. Following this idea, multiple functional groups can be sequentially added to 5-*endo* and 2-*exo* -OH groups of isosorbide to make many multifunctional compounds such as full-spectrum UV absorbers, UV absorbing antioxidants, and UV absorbing thermo-stabilizers. The combination of possibilities and applications is wide.

Recommendation

After completing the synthesis of these multifunctional sunscreens, some very important experiments need be finished in the future. The first thing is to formulate these sunscreens into actual preparations and lotions, which is always needed because most chemical compounds cannot be directly applied to human skin. The chemical stabilities of these synthetic sunscreens should be checked in order to make sure the chemical structure and function of them will not be destroyed by the formulation. Secondly, the photostability test needs to be completed after all the sunscreens have been synthesized. The purpose of this test is to make sure all the sunscreens can retain their functions and physical properties under the radiation of intense UV light for at least 8 hours. Finally, the percutaneous diffusion test should be finished in order to ensure the sunscreen will not diffuse into the *stratum corneum* (SC) of the human skin, where sunscreens could generate harmful molecules such as ROS (reactive oxygen species) which damage skin. Such tests could also examine different isosorbide derivatives: esters, ethers and other derivatives could be sorted into different classes based on their different hydrophilicity and molecular weight. Once the critical factors for their diffusion properties are found, multifunctional sunscreens more near to the ideal one could be synthesized in the future.

APPENDIX

The following diagrams are the DSC thermograms, FTIR spectra, NMR spectra and UV/VIS spectra mentioned in the chapters above.

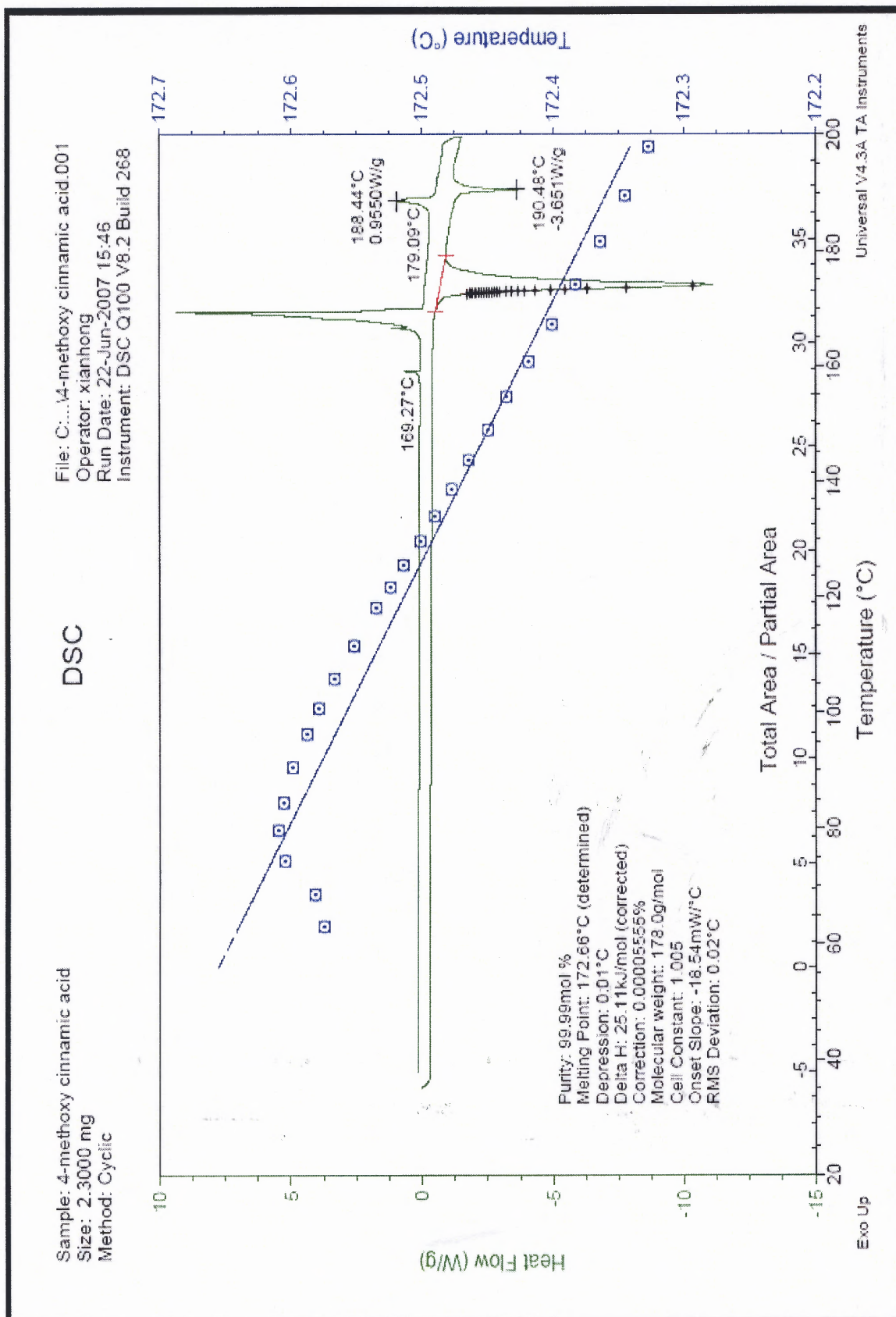


Figure 6.1.1 DSC of 4-methoxycinnamic acid.

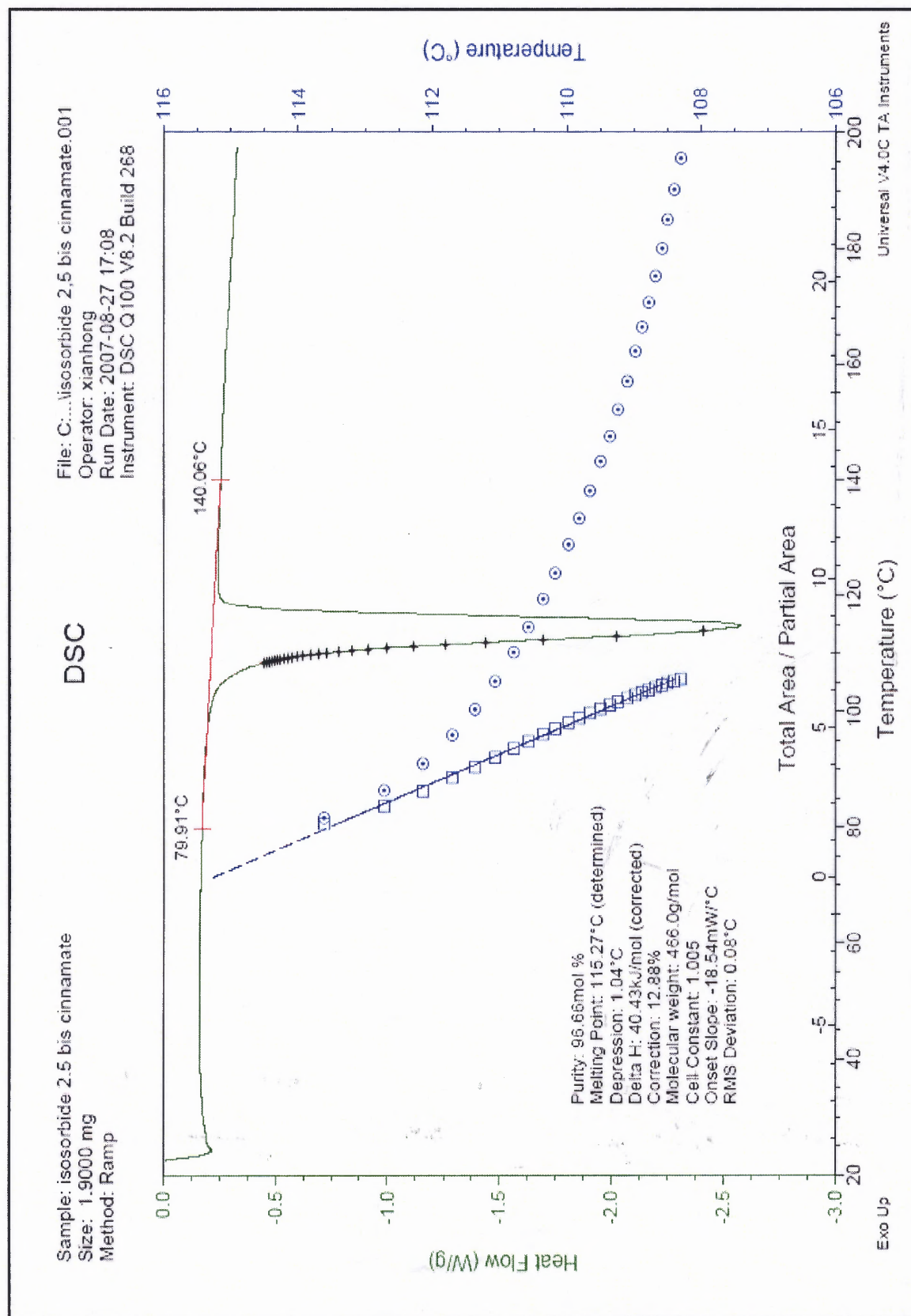


Figure 6.1.2 DSC of isororbide bis(4-methoxycinnamate).

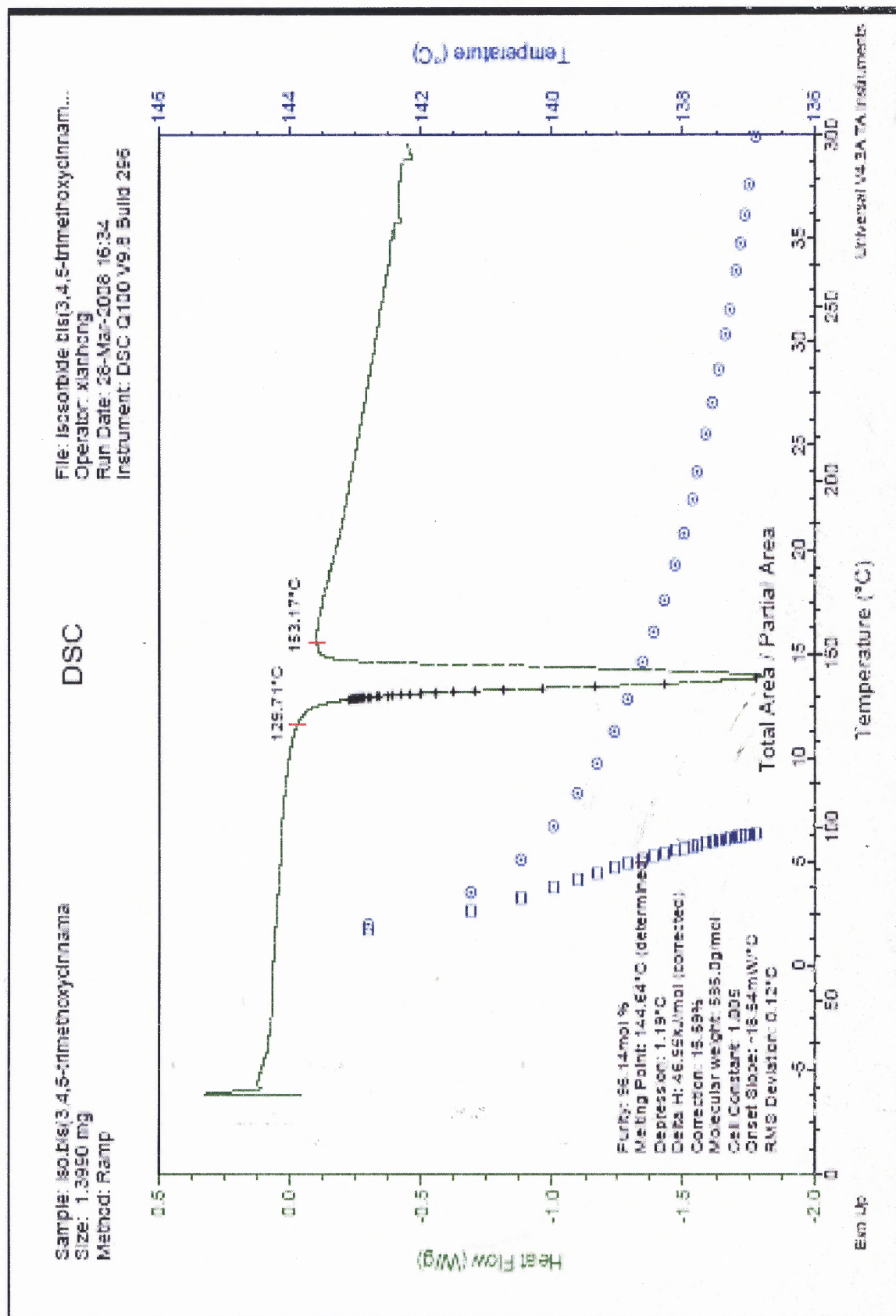


Figure 6.1.3 DSC of isosorbide bis(3,4,5-trimethoxycinnamate).

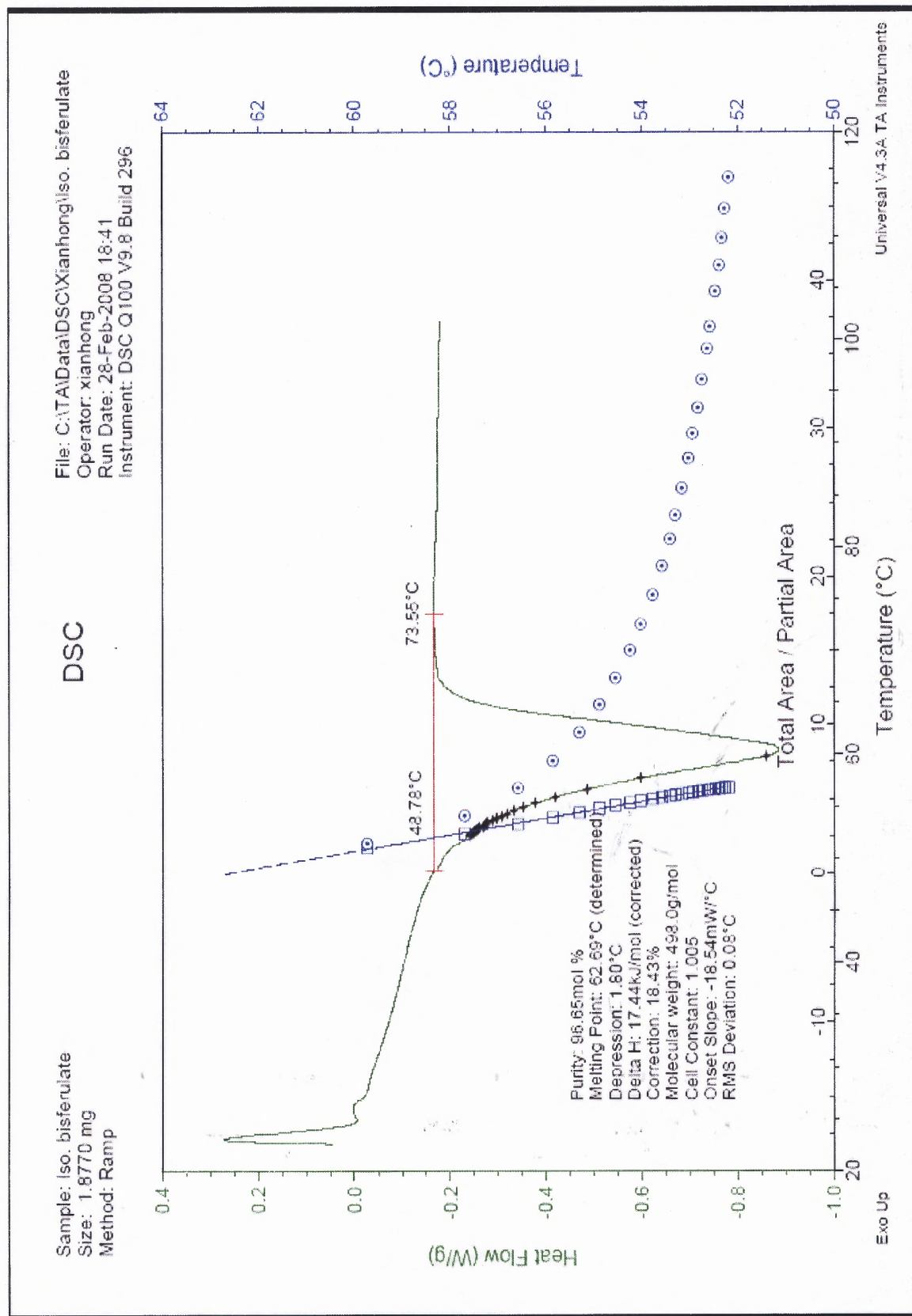


Figure 6.1.4 DSC of isosorbide bisferulate.

File: iso biscyanoferulate recrystallized fr...
Operator: xianhong
Run Date: 22-Feb-2008 10:19
Instrument: DSC Q100 V9.8 Build 296

DSC

Sample: isosorbide biscyanoferulate rec
Size: 1.9100 mg
Method: Ramp

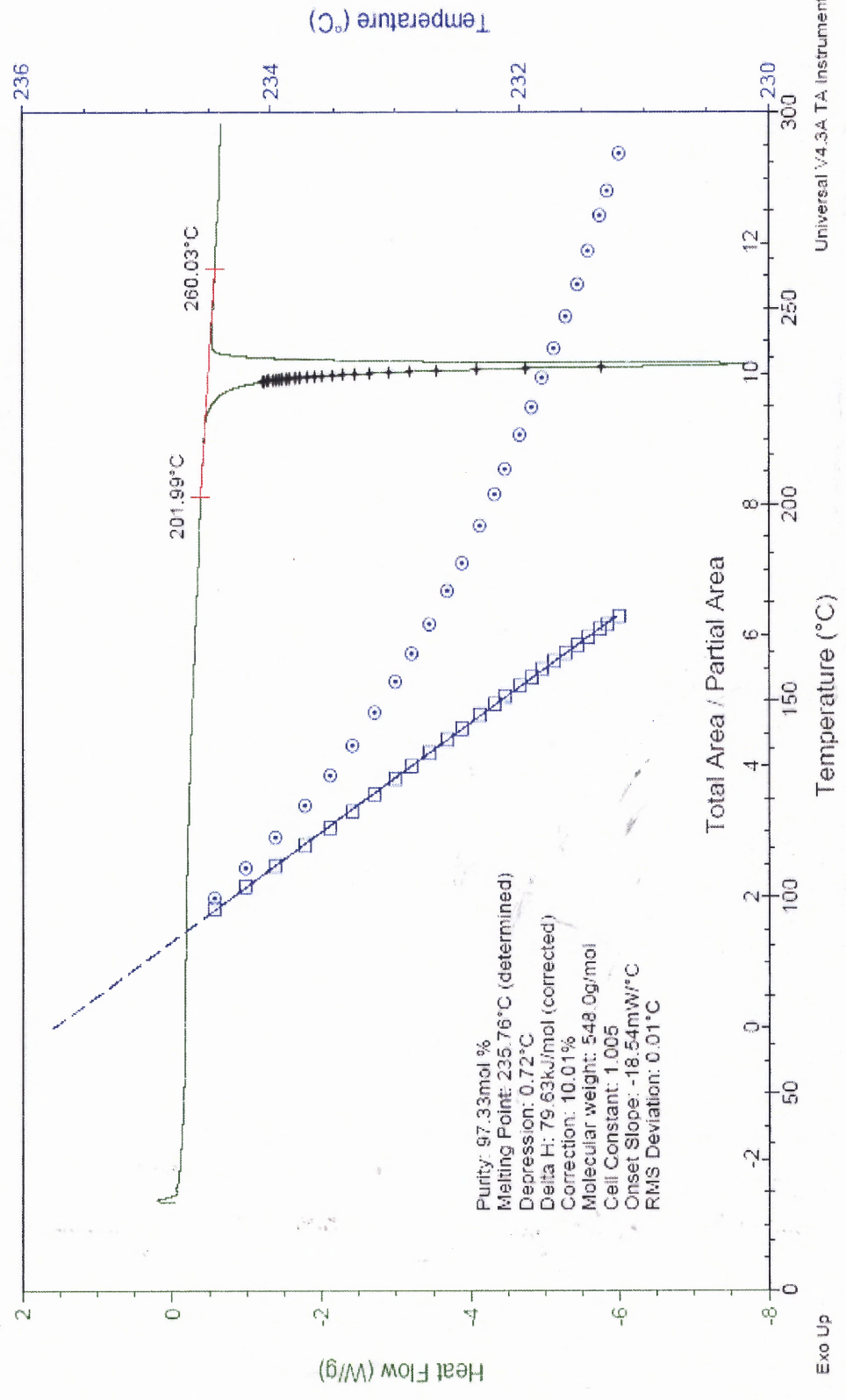


Figure 6.1.5 DSC of isosorbide biscyanoferulate.

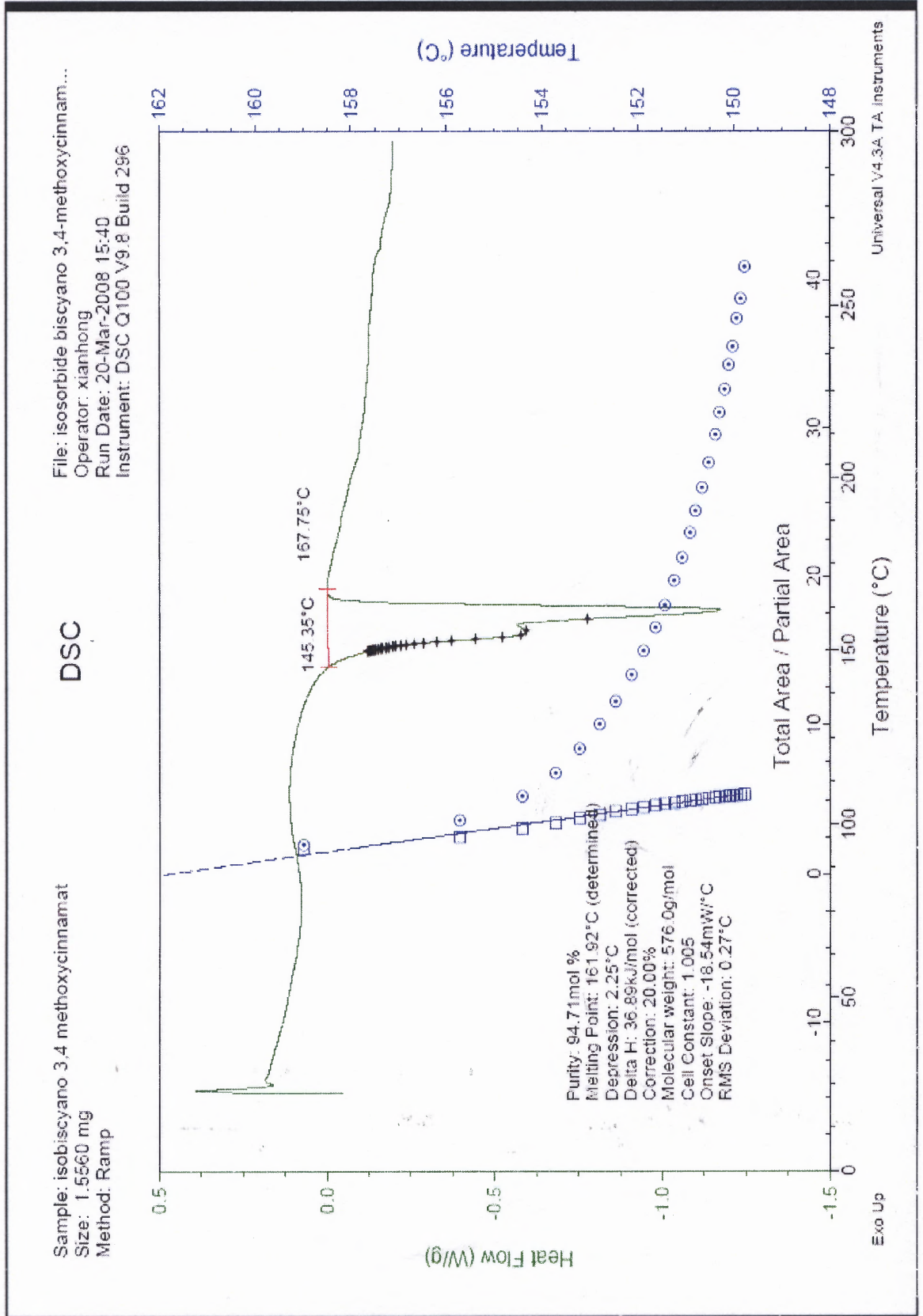


Figure 6.1.6 DSC of isosorbide bis(3,4-dimethoxycinnamate).

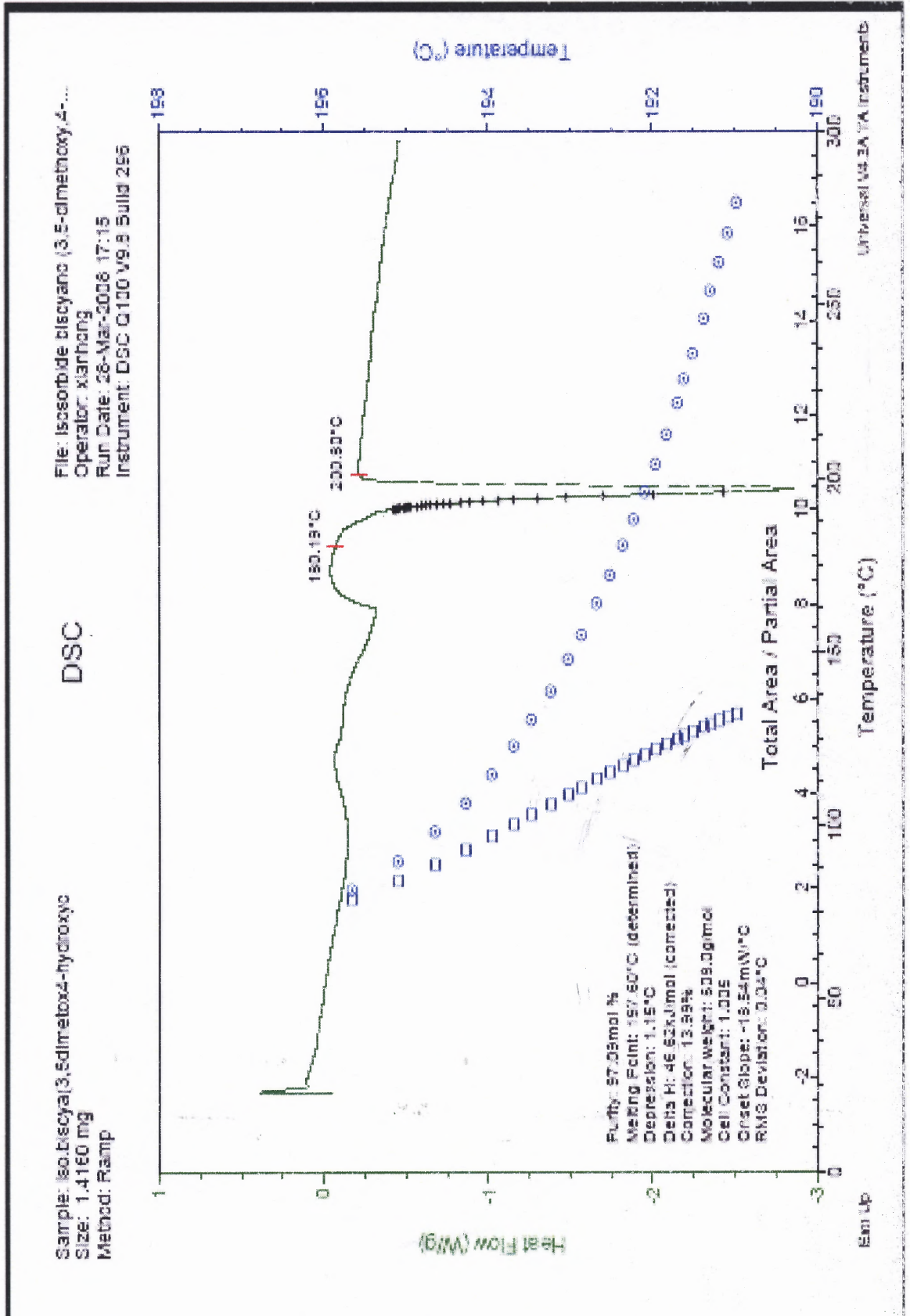


Figure 6.1.7 DSC of isosorbide bis(3,5-dimethoxy,4-hydroxycyanocinnamate).

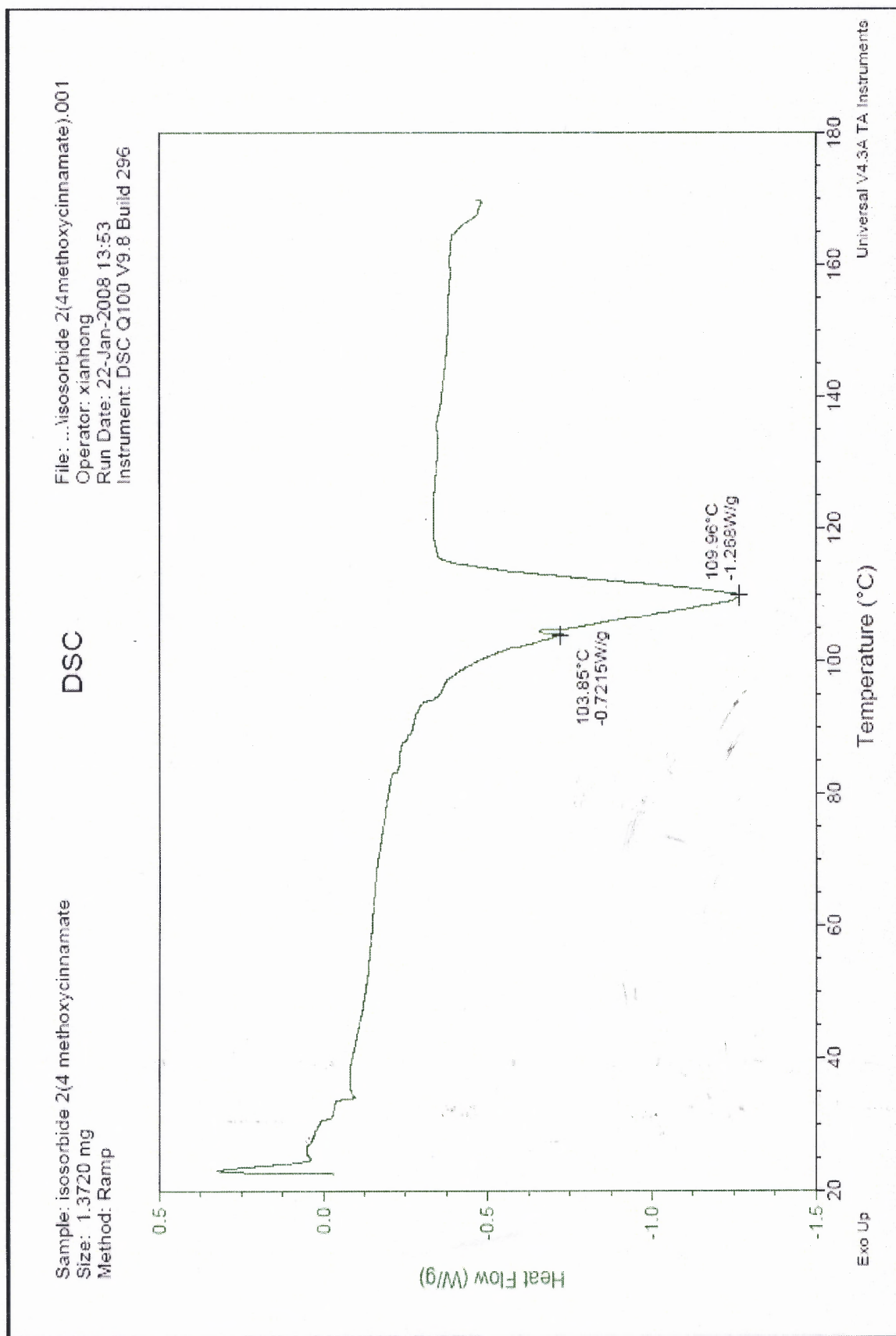


Figure 6.1.8 DSC of isorbide 2-(4-methoxycinnamate).

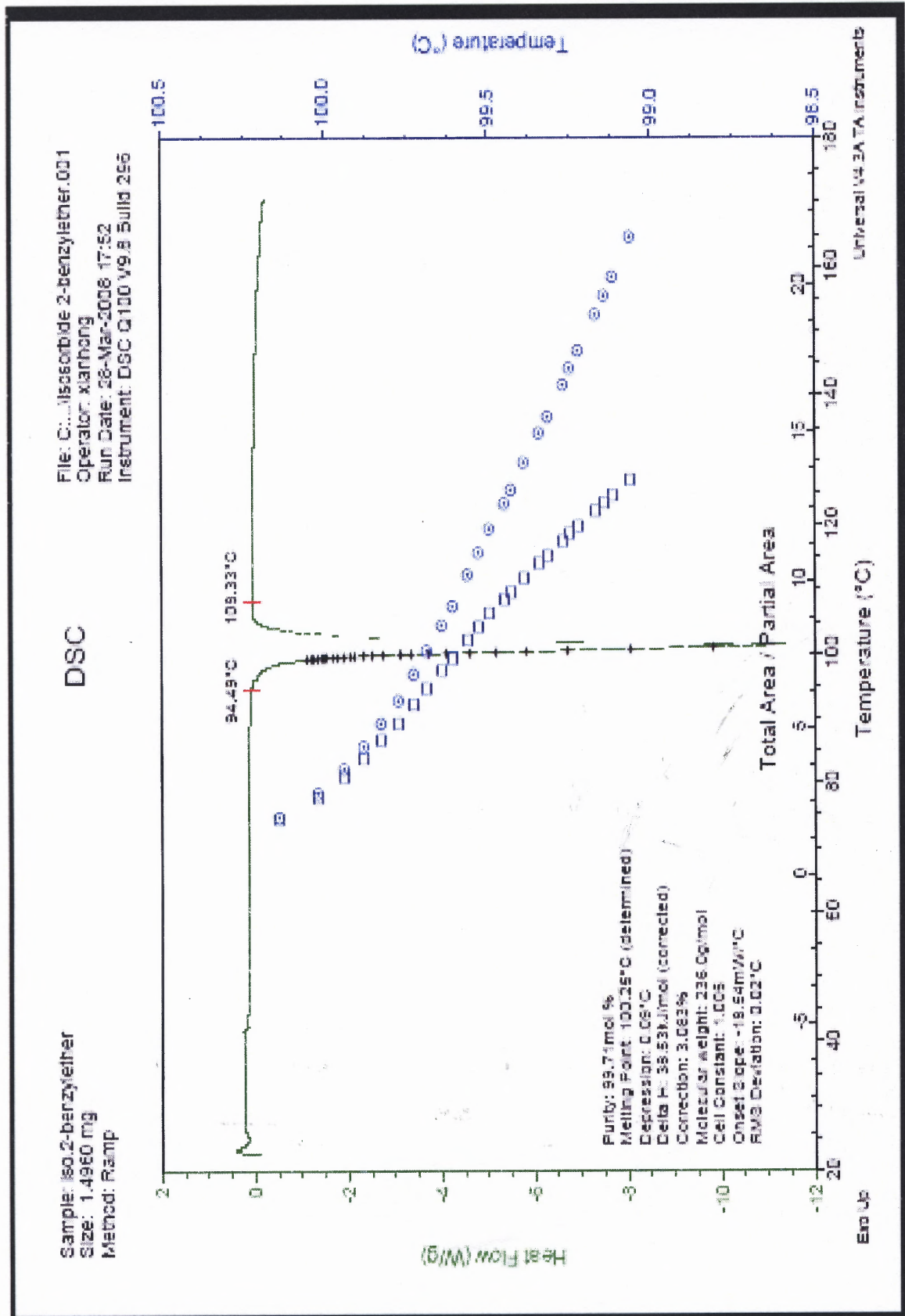


Figure 6.1.9 DSC of isosorbide 2-(benzylether).

File: iso. 2-benzyl ether 5(4-methoxycinnam...
 Operator: xianhong
 Run Date: 28-Feb-2008 19:21
 Instrument: DSC Q100 V9.8 Build 296

Sample: Iso. 2benzyl ether 5(4methoxyyci
 Size: 1.3200 mg
 Method: Ramp

DSC

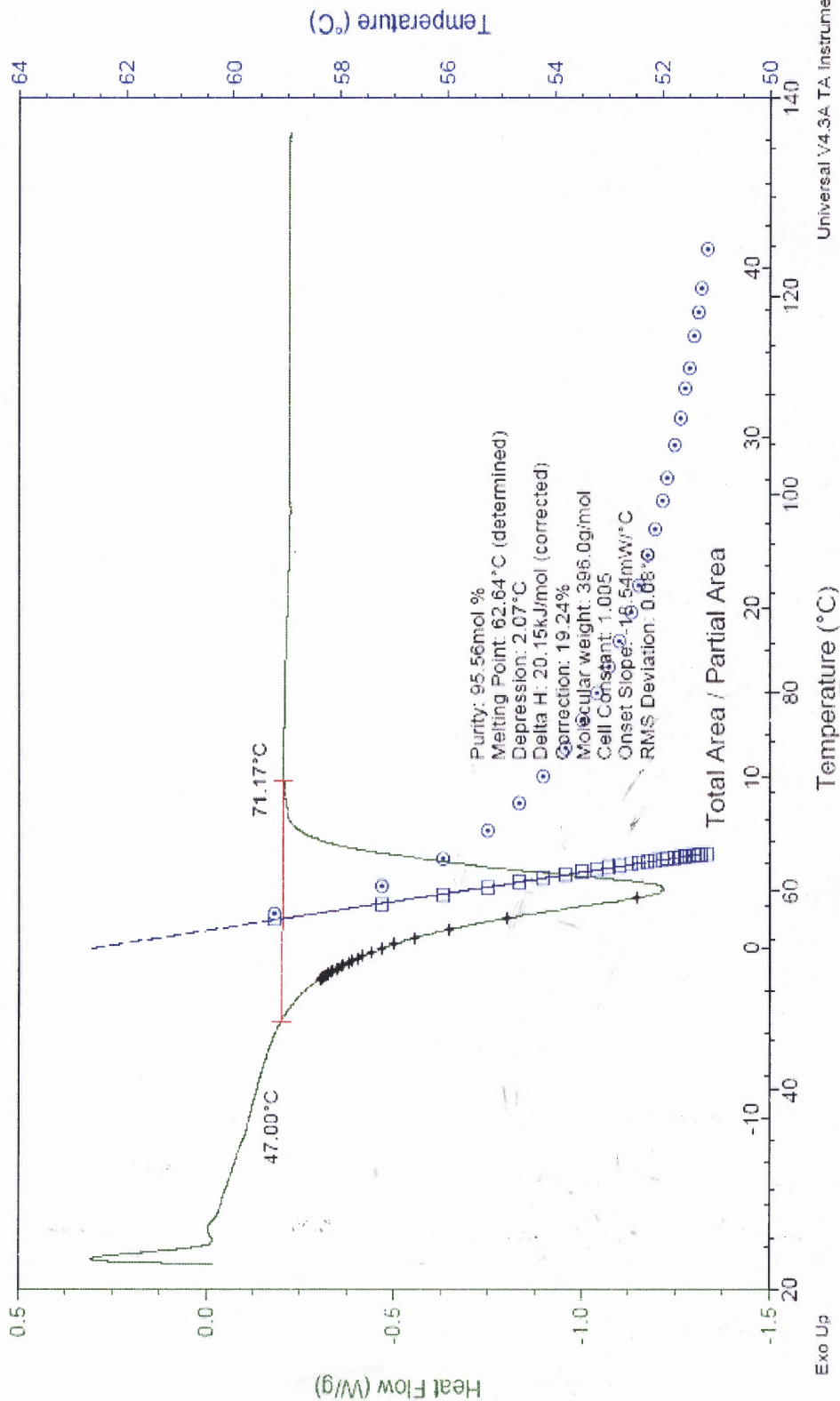


Figure 6.1.10 DSC of isosorbide 2-(benzylether), 5-(4-methoxycinnamate).

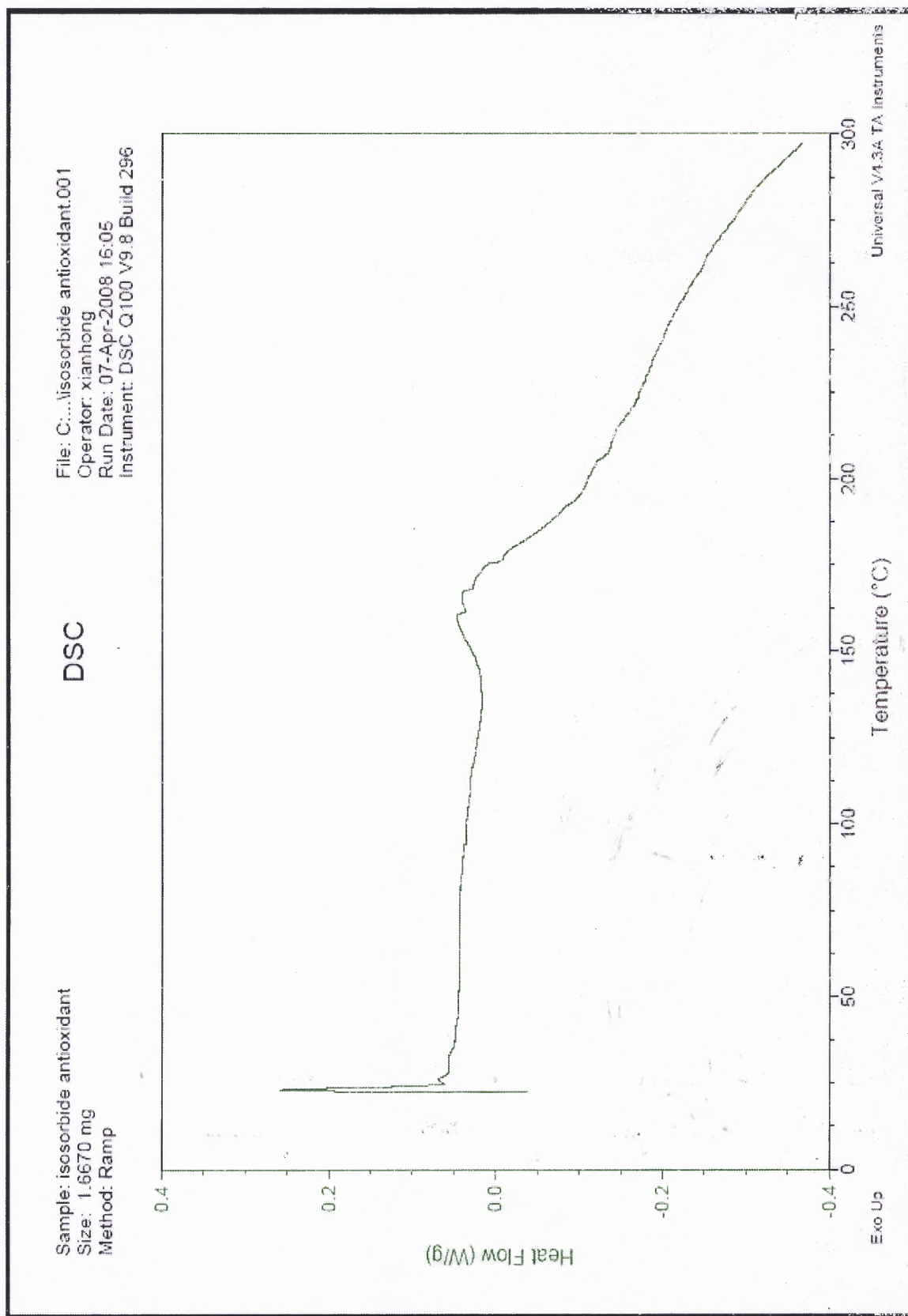


Figure 6.1.11 DSC of isosorbide antioxidant.

FTIR of 4-methoxycinnamic acid

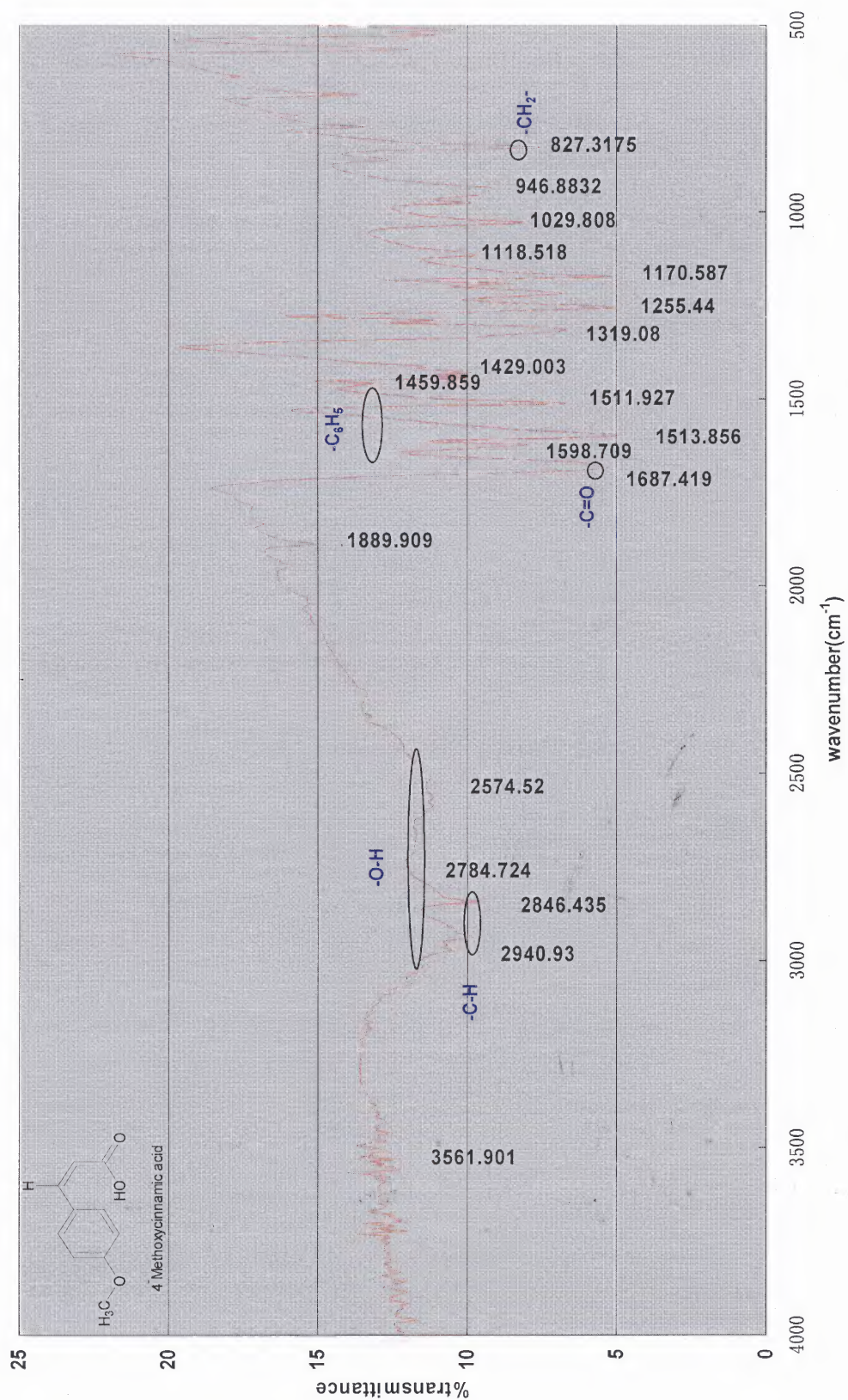


Figure 6.2.1 FTIR of 4-methoxycinnamic acid.

FTIR of isosorbide bis(4-methoxycinnamate)

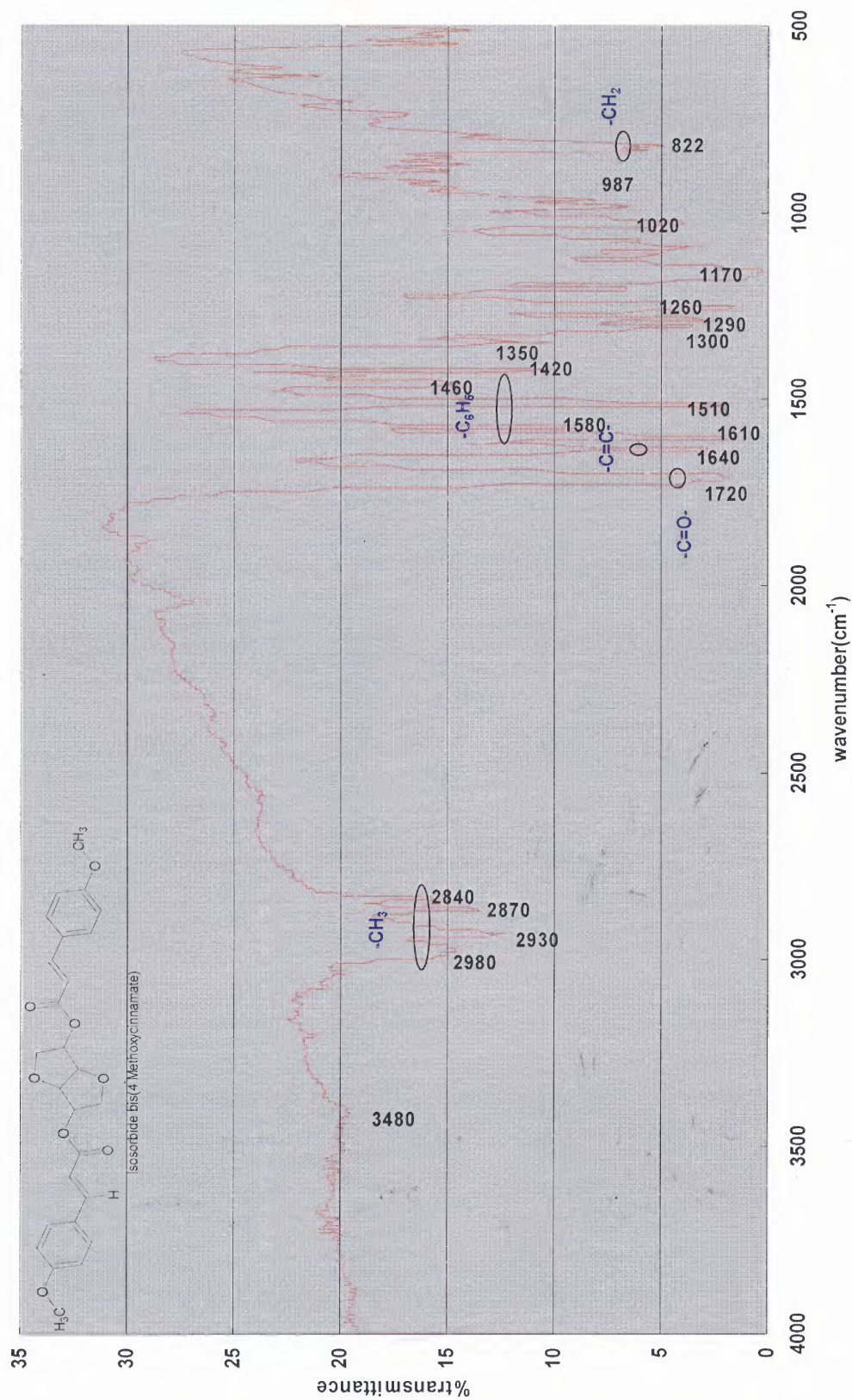


Figure 6.2.2 FTIR of isosorbide bis(4-methoxycinnamate).

FTIR of isosorbide bis(3,4,5-trimethoxycinnamate)

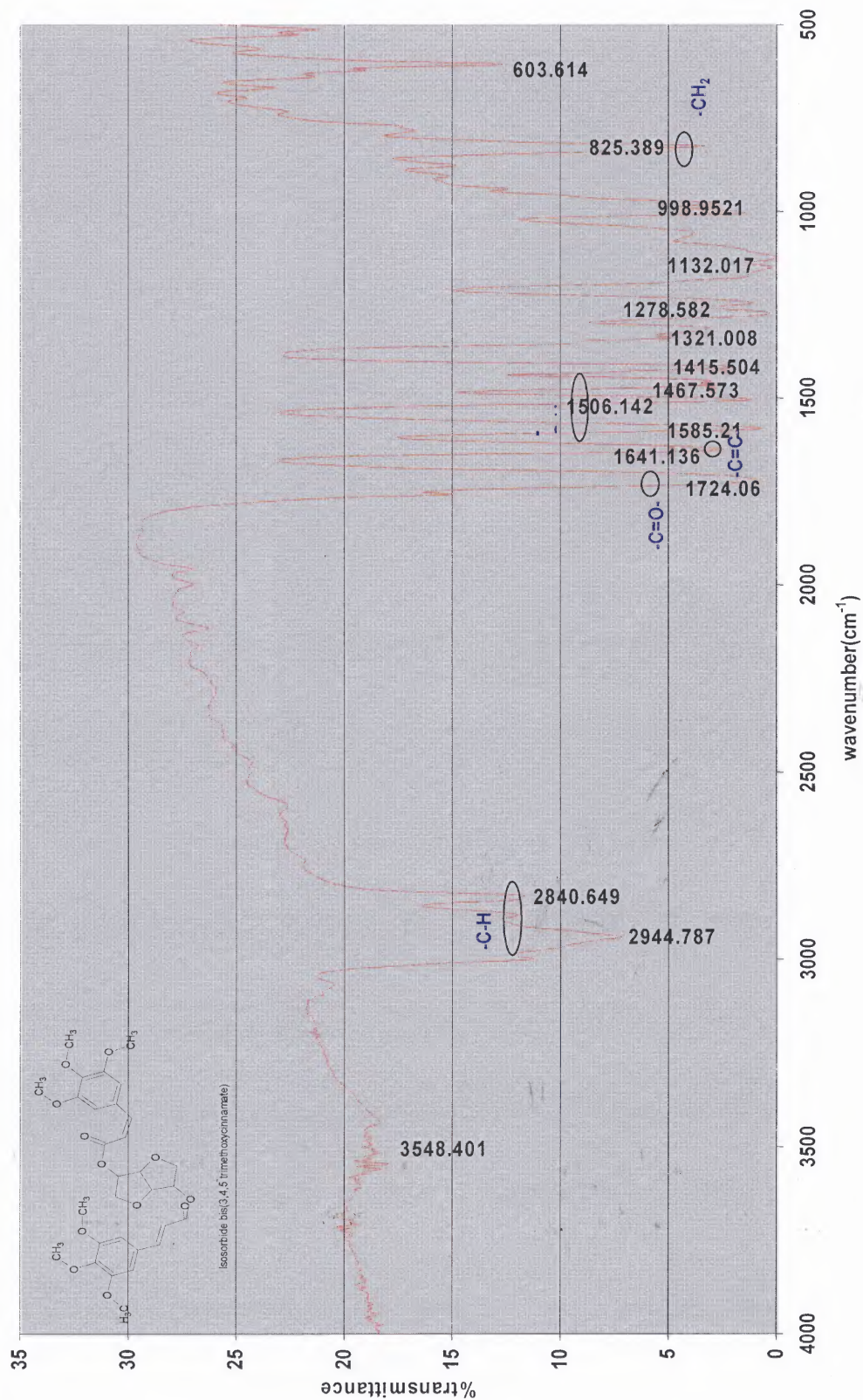


Figure 6.2.3 FTIR of isosorbide bis(3,4,5-trimethoxycinnamate).

FTIR of isosorbide bisferulate

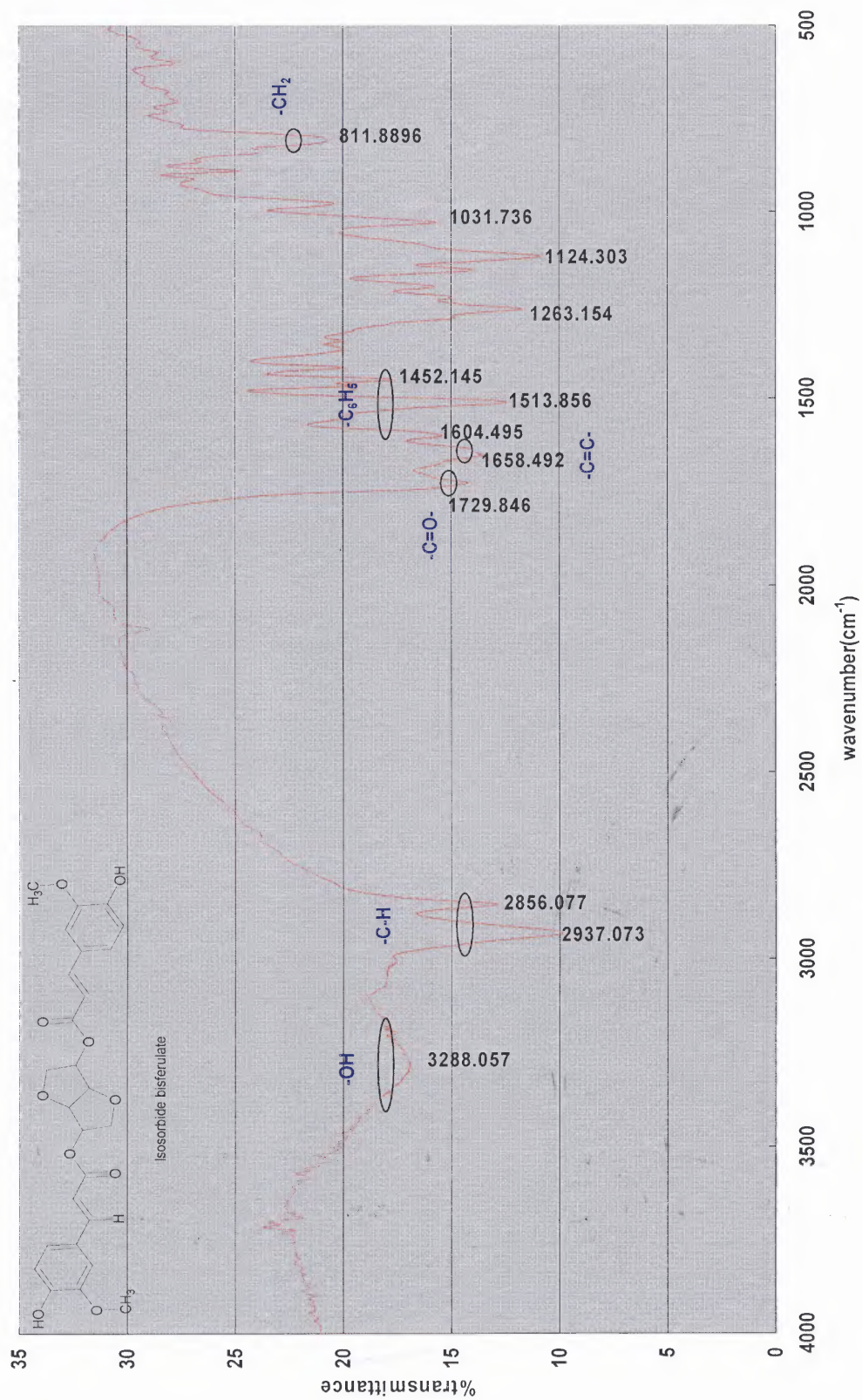


Figure 6.2.4 FTIR of isosorbide bisferulate.

FTIR of isosorbide biscyanoferulate

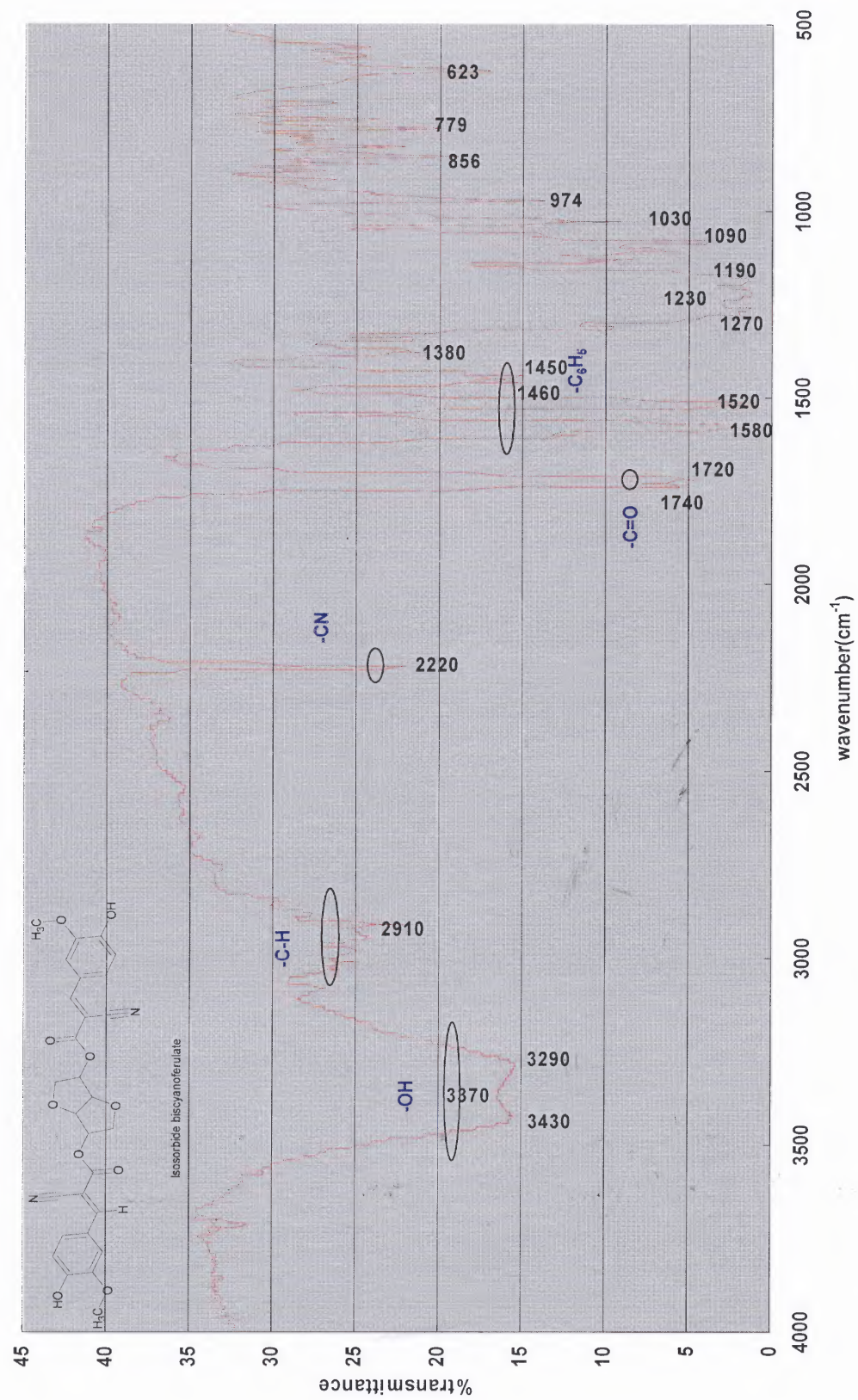


Figure 6.2.5 FTIR of isosorbide biscyanoferulate.

FTIR of isororbide bis(3,4-dimethoxycyanocinnamate)

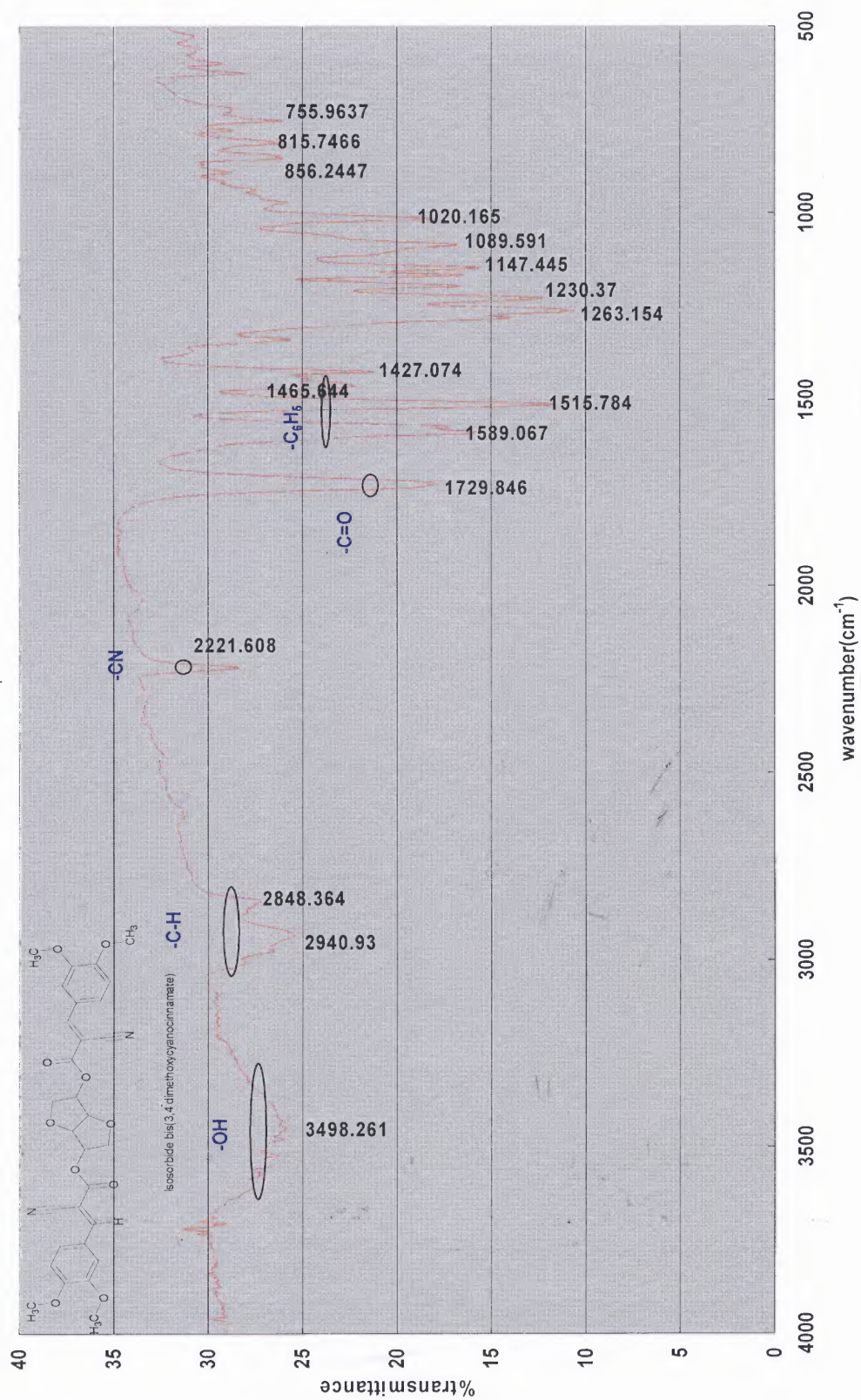


Figure 6.2.6 FTIR of isororbide bis (3, 4-dimethoxycyanocinnamate).

FTIR of isosorbide bis(3,5-dimethoxy,4-hydroxycyanocinnamate)

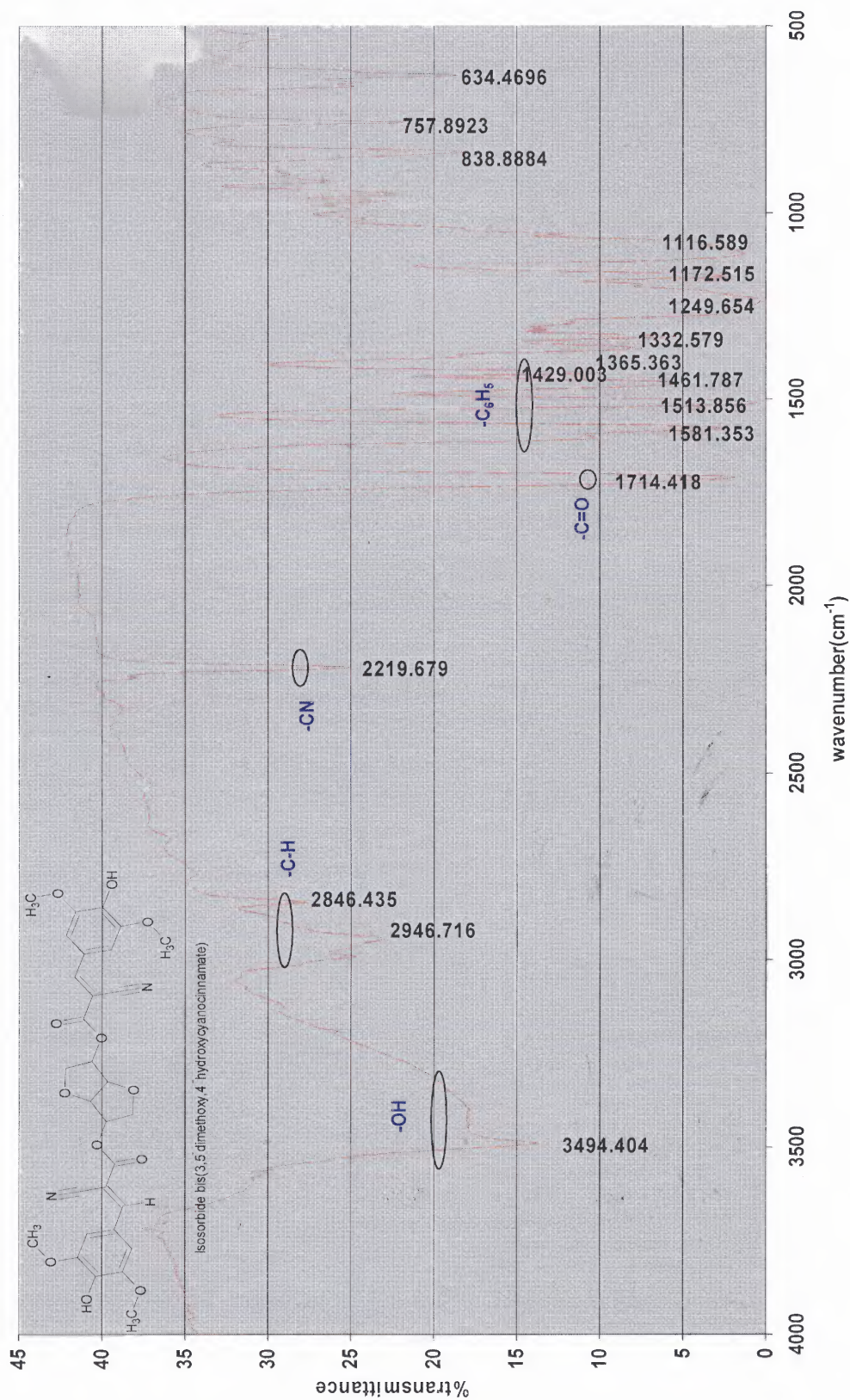


Figure 6.2.7 FTIR of isosorbide bis (3, 5-dimethoxy, 4-hydroxycyanocinnamate).

FTIR of isosorbide 2-(4-methoxycinnamate)

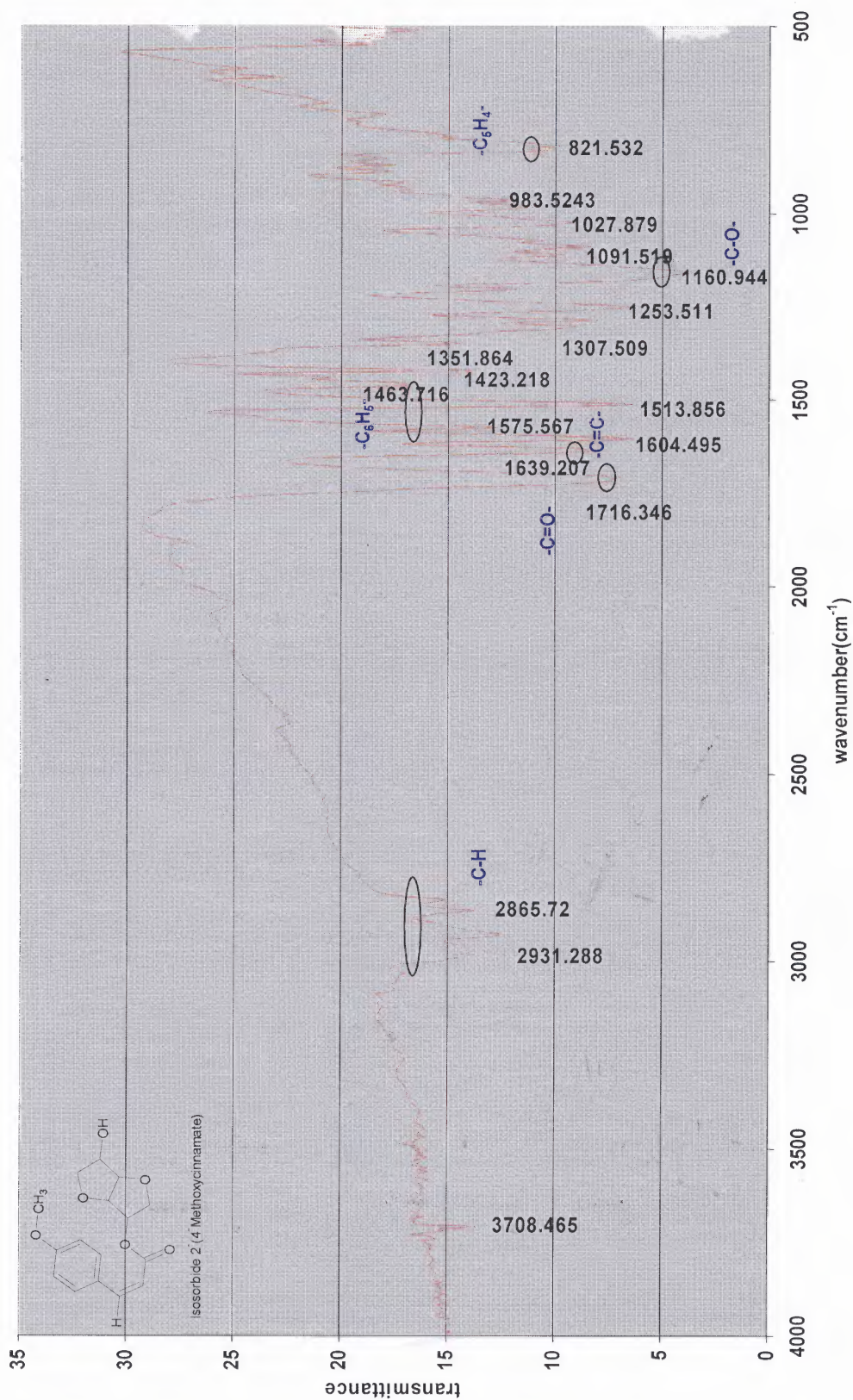


Figure 6.2.8 FTIR of isosorbide 2-(4-methoxycinnamate).

FTIR of isosorbide 2-benzylether

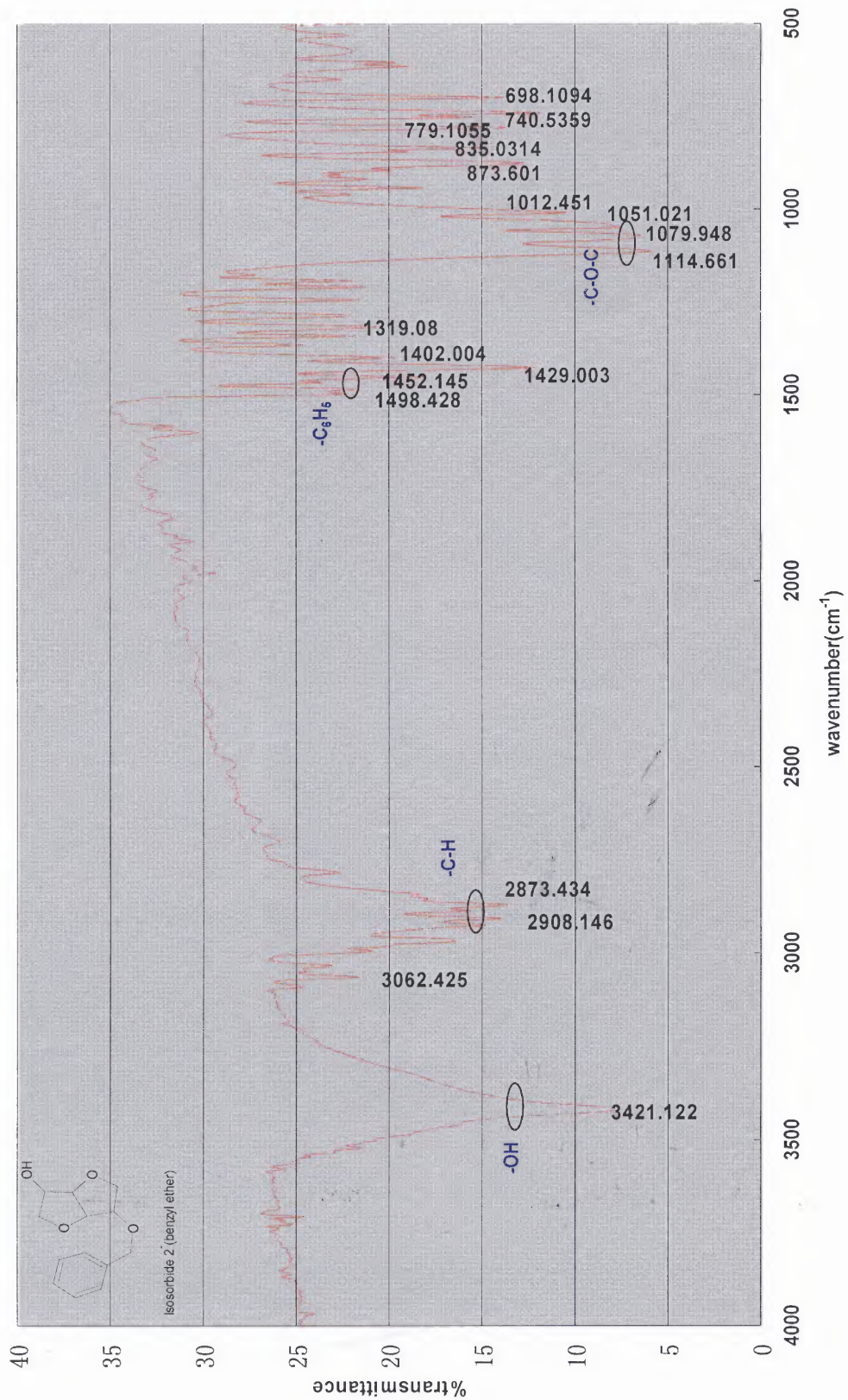


Figure 6.2.9 FTIR of isosorbide 2-benzylether.

FTIR of isosorbide 2-benzylether, 5-methoxycinnamate

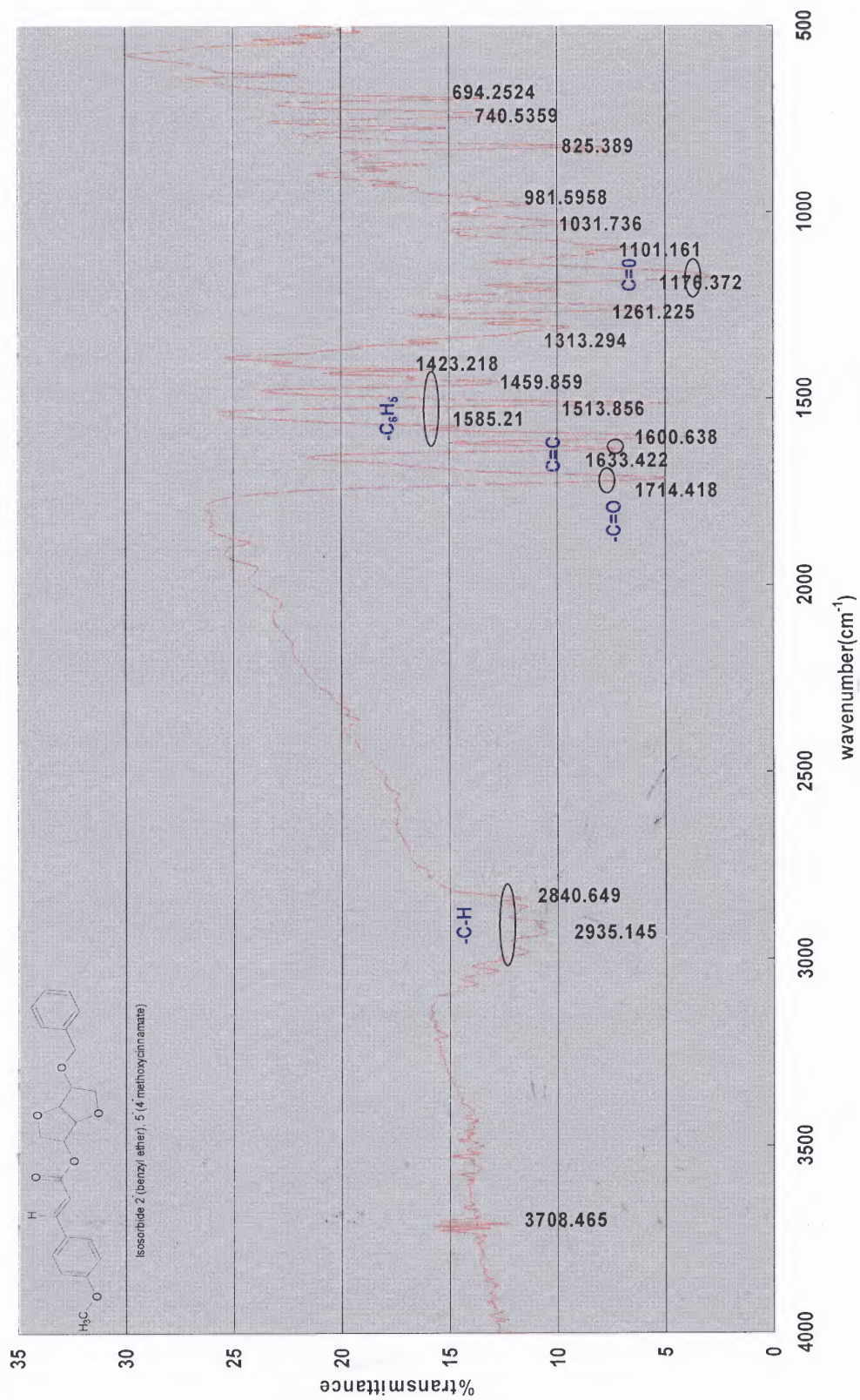


Figure 6.2.10 FTIR of isosorbide 2-(benzylether), 5-(4-methoxycinnamate).

FTIR for isorbide bis(3-(4-hydroxy,3,5-di-t-butylphenyl) propionate)

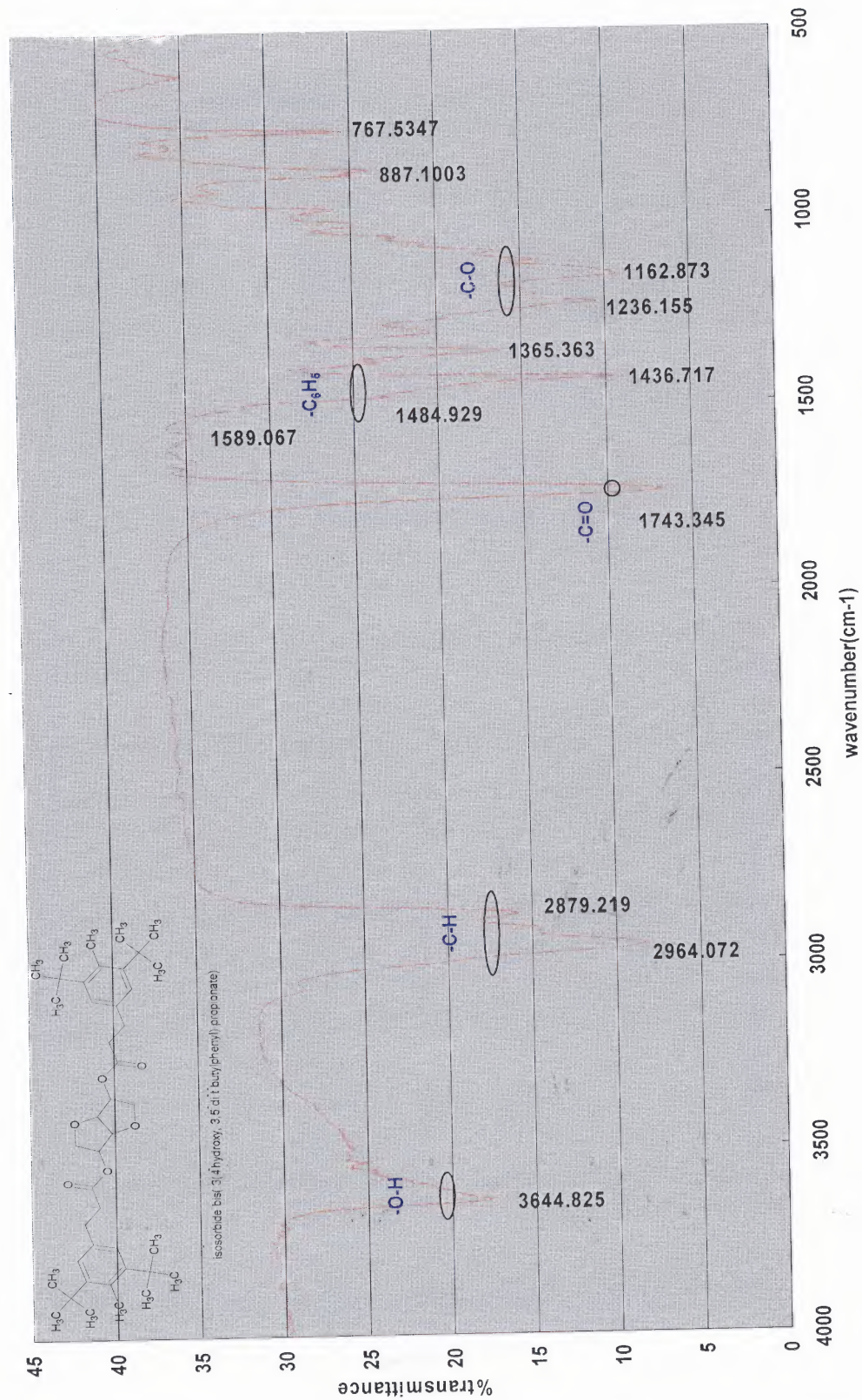


Figure 6.2.11 FTIR of isorbide bis(3-(4-hydroxy,3,5-di-t-butylphenyl) propionate).

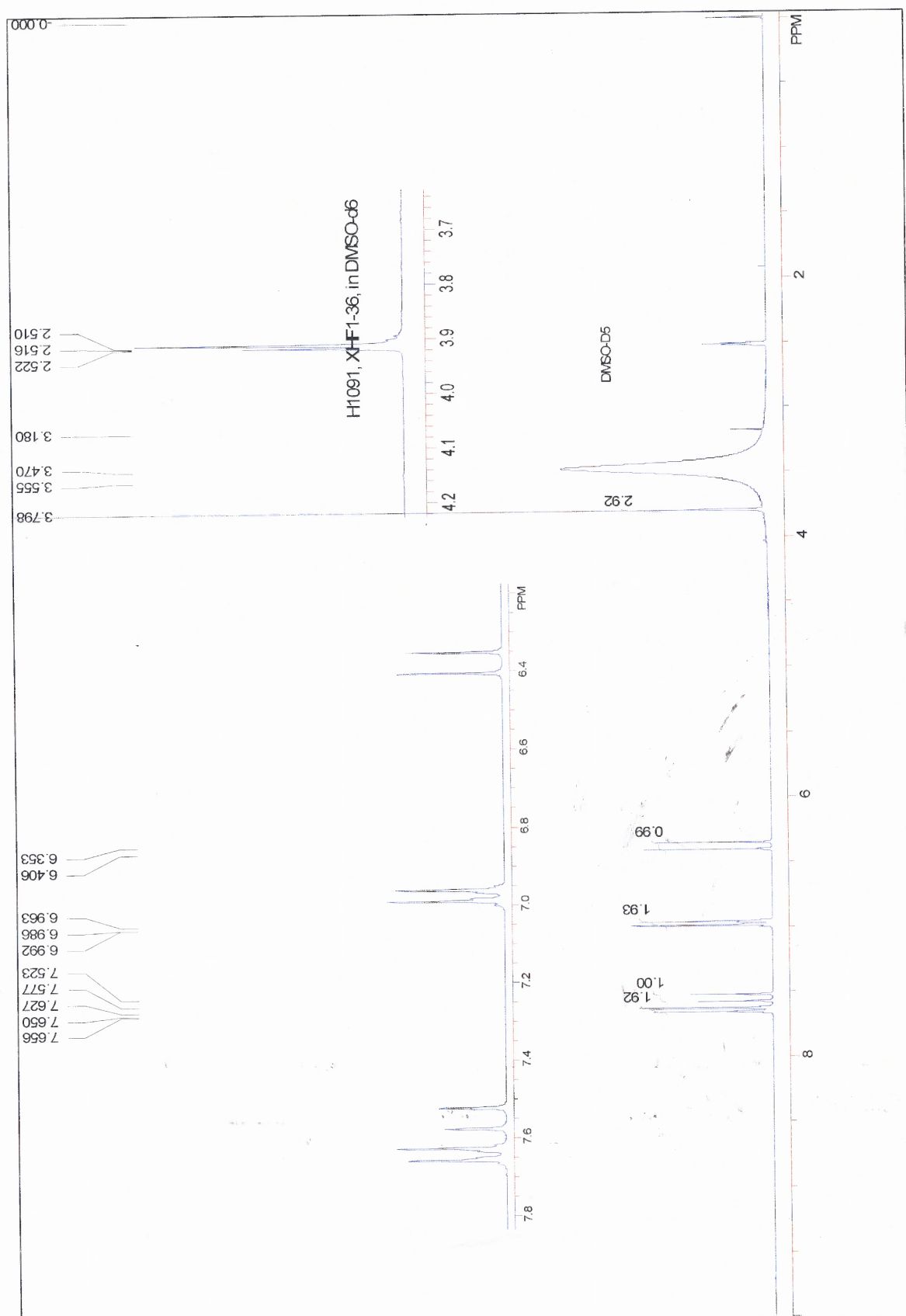


Figure 6.3.1 NMR of 4-methoxycinnamic acid in DMSO.

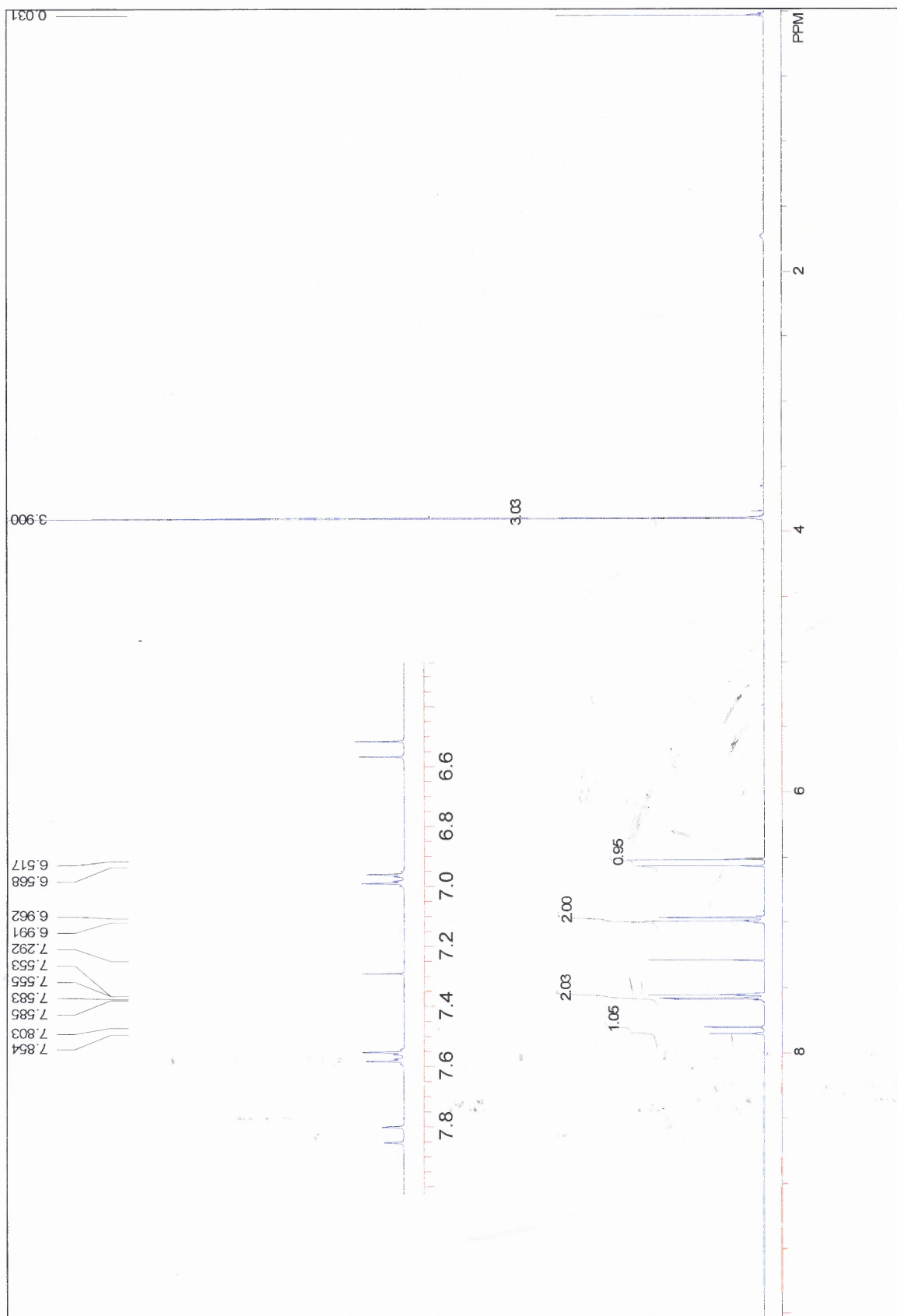


Figure 6.3.2 NMR of 4-methoxycinnamyl chloride in CDCl_3/TMS .

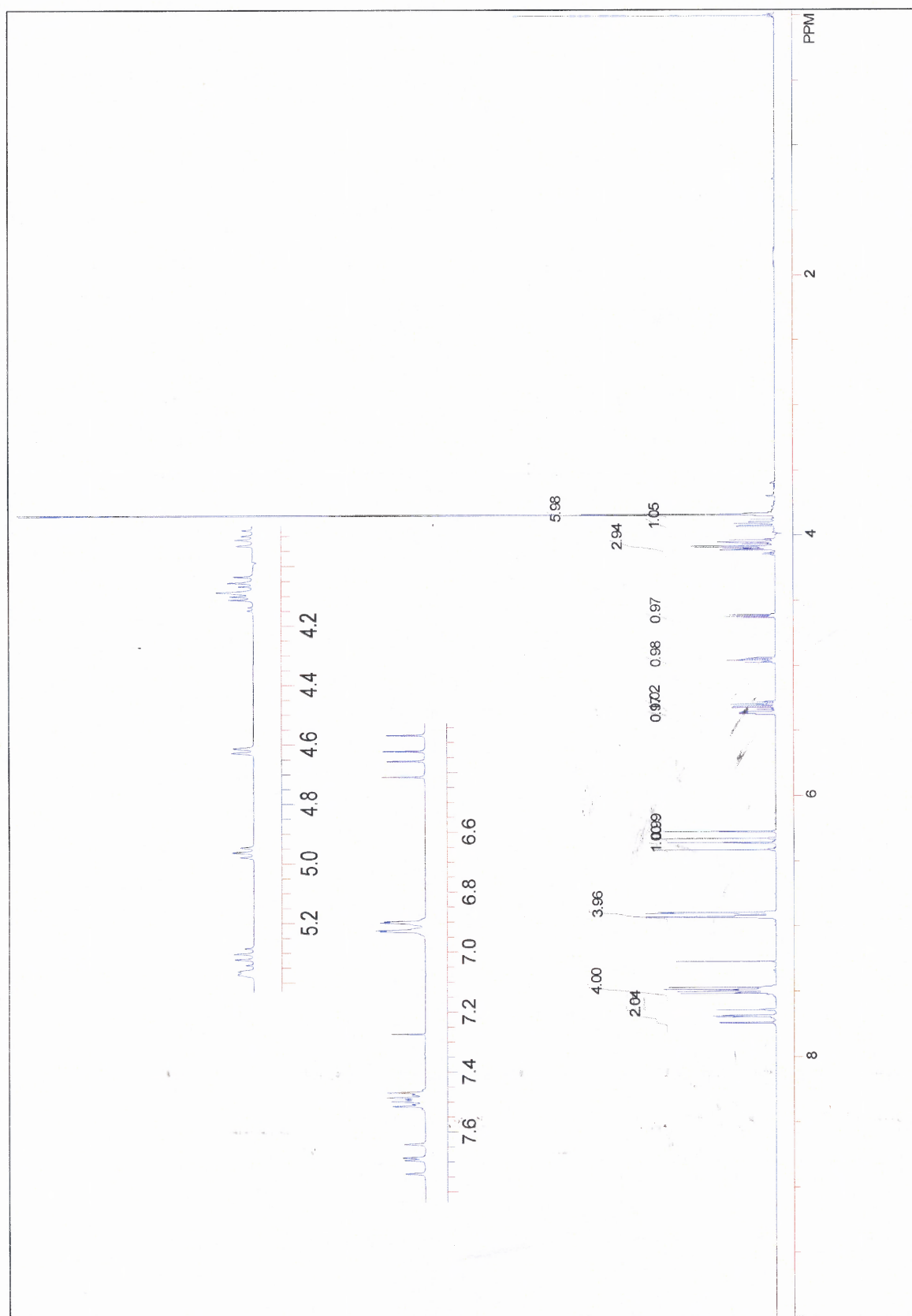


Figure 6.3.3 NMR of isosorbide bis(4-methoxycinnamate) in CDCl_3/TMS .

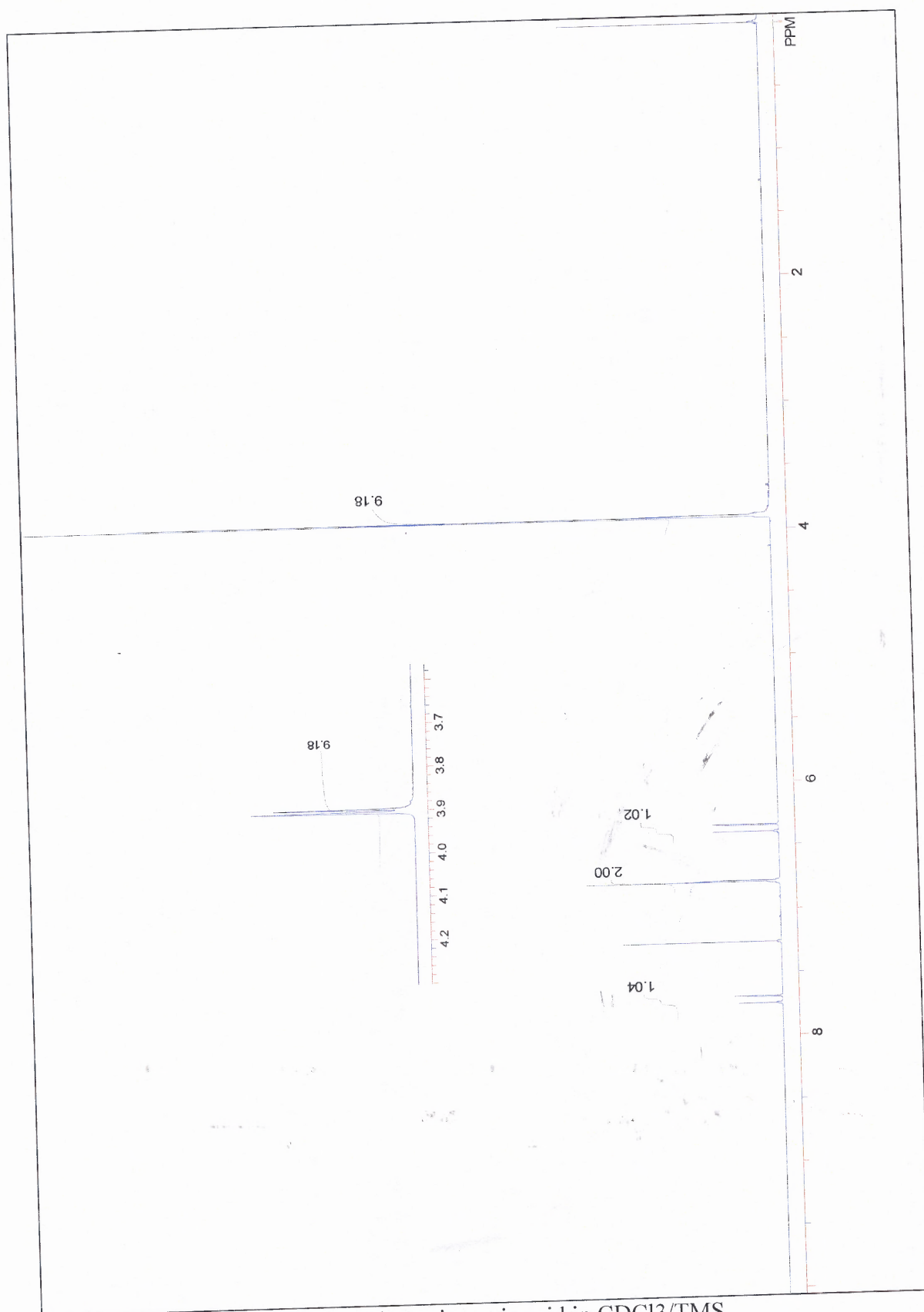


Figure 6.3.4 NMR of 3,4,5-trimethoxycinnamic acid in CDCl_3/TMS .

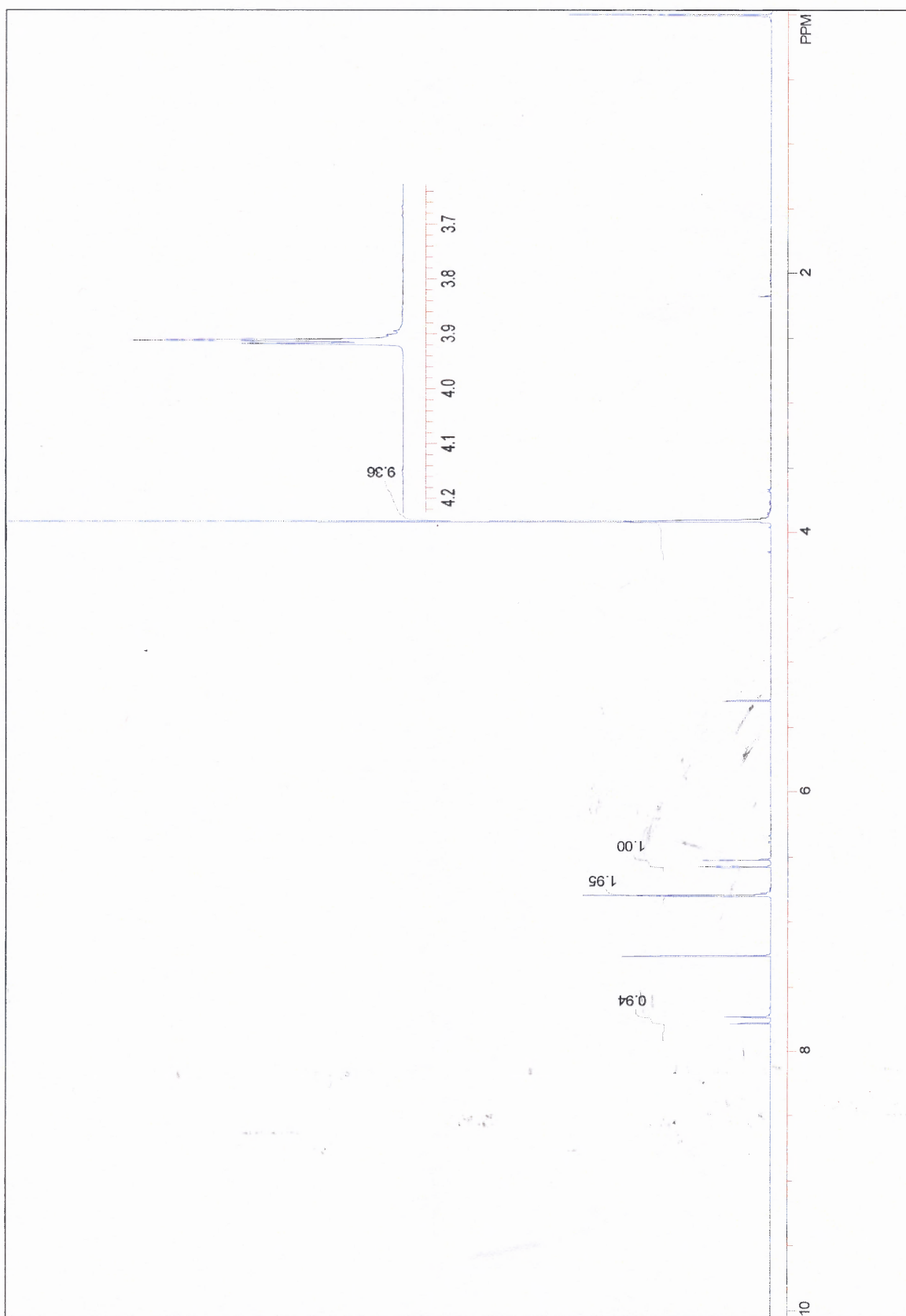


Figure 6.3.5 NMR of 3,4,5-trimethoxycinnamyl chloride in CDCl_3/TMS .

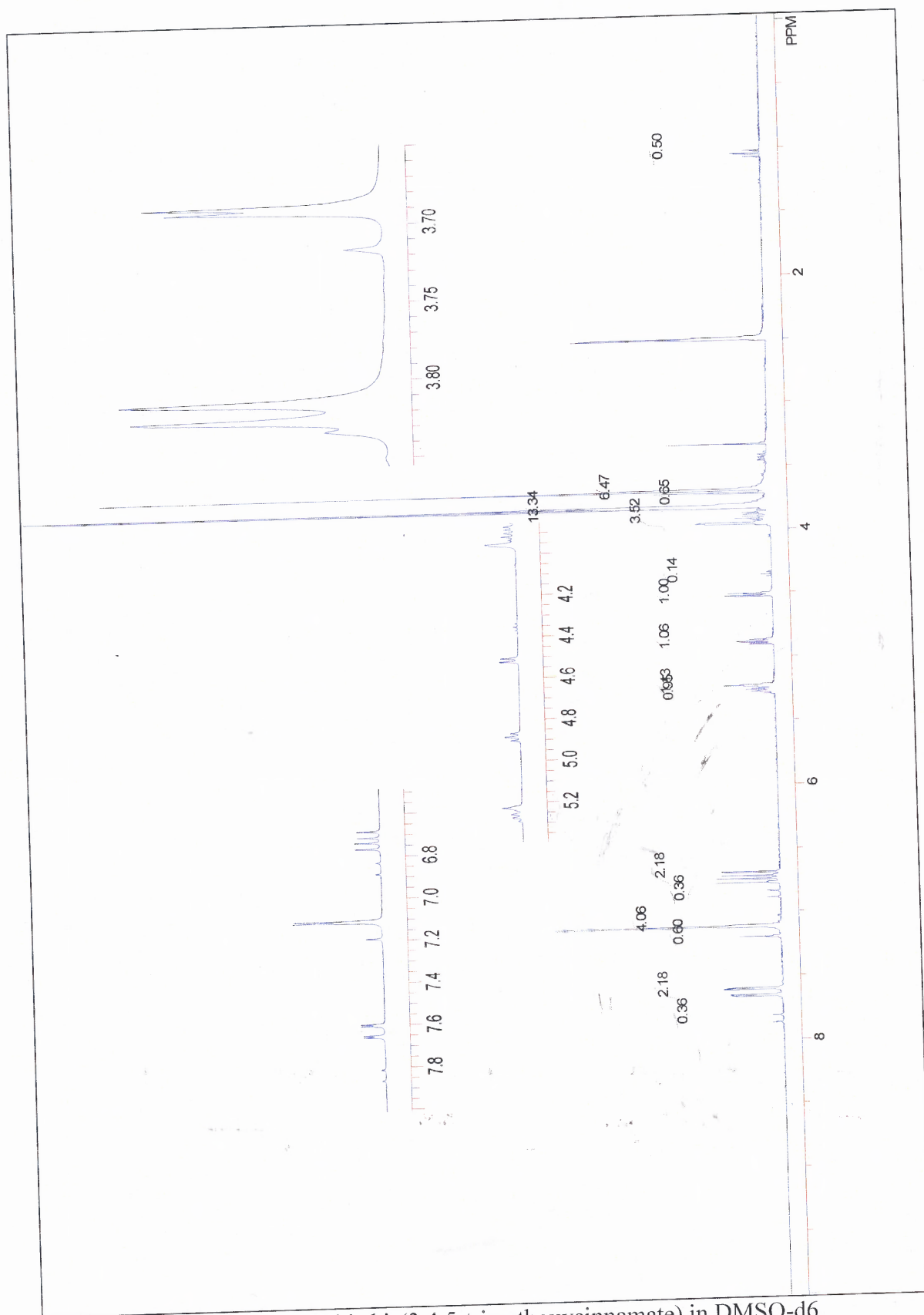


Figure 6.3.6 NMR of isororbide bis(3,4,5-trimethoxycinnamate) in DMSO-d₆.

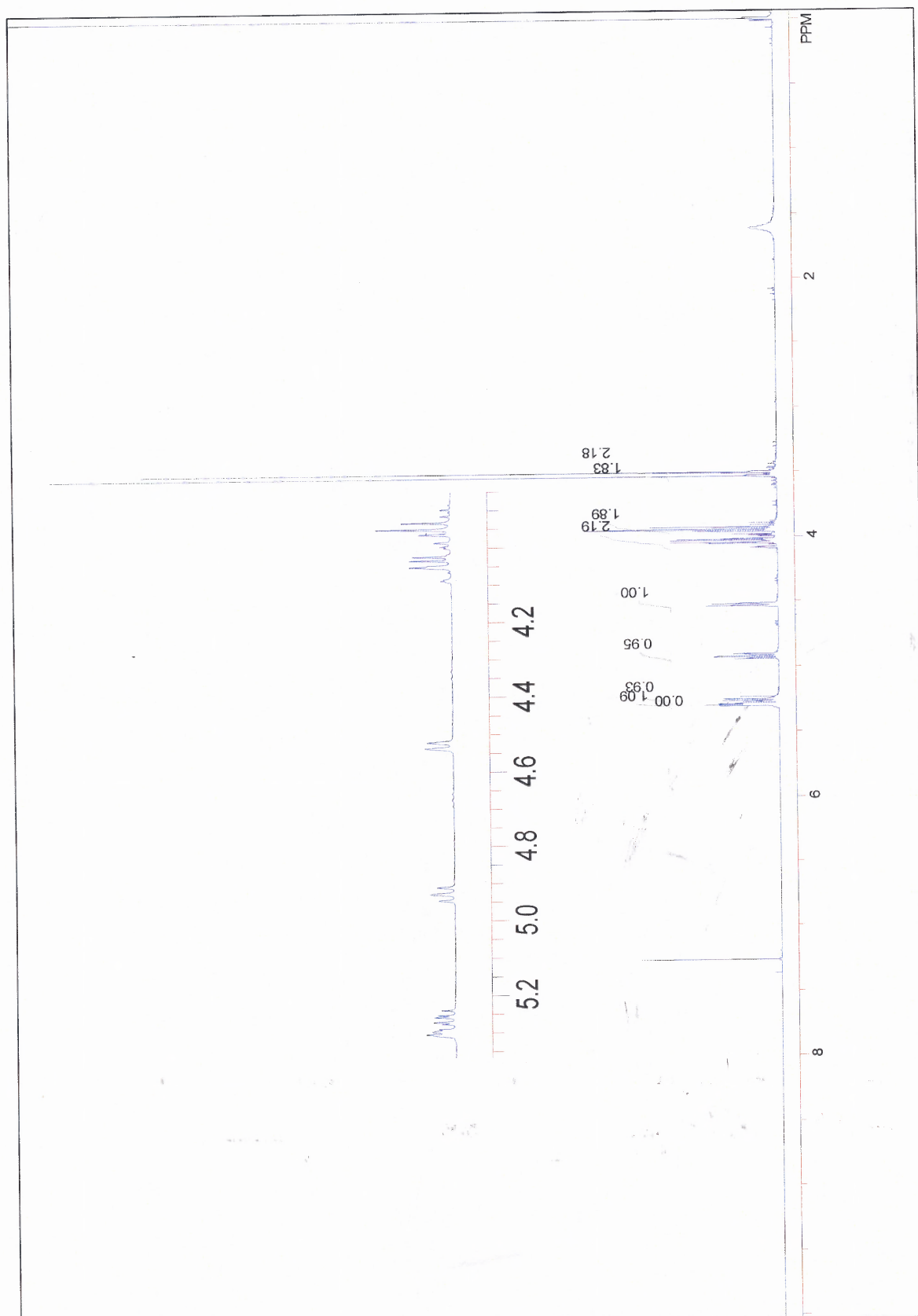


Figure 6.3.7 NMR of isosorbide biscyanoacetate in CDCl₃/TMS.

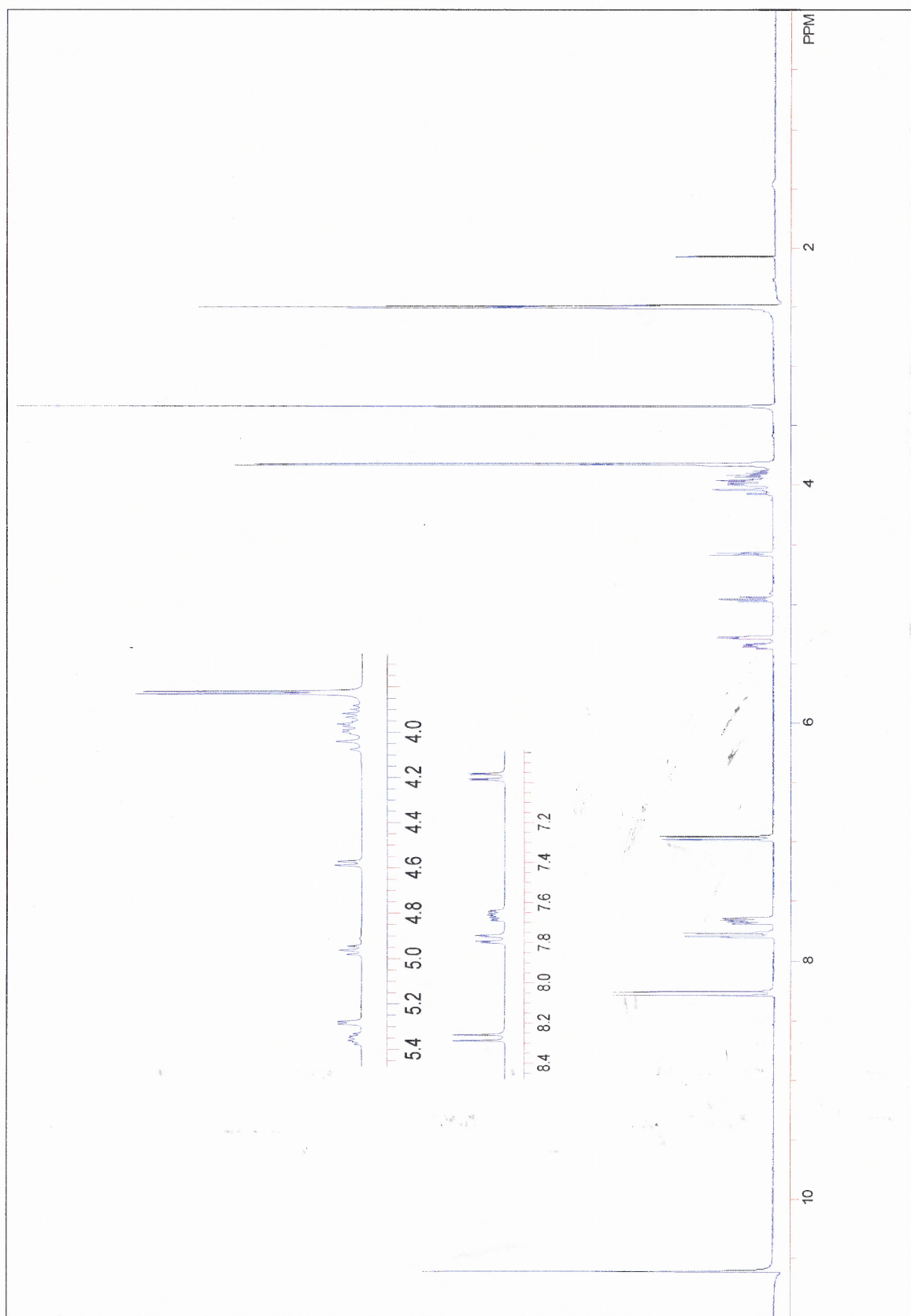


Figure 6.3.8 NMR of isosorbide biscyanoferrulate in DMSO-d6.

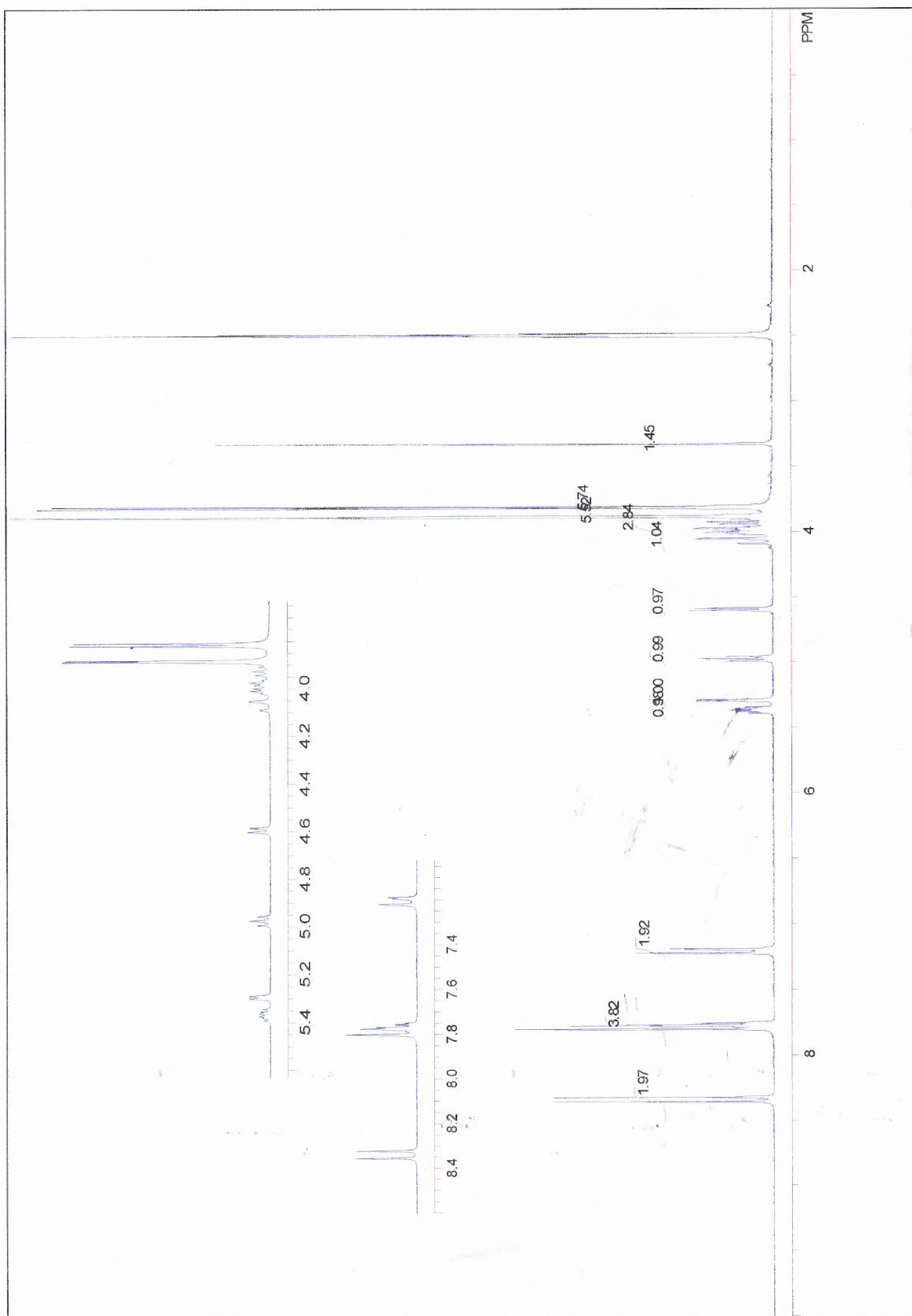


Figure 6.3.9 NMR of isosorbide bis(3,4-dimethoxycinnamate) in DMSO-d₆.

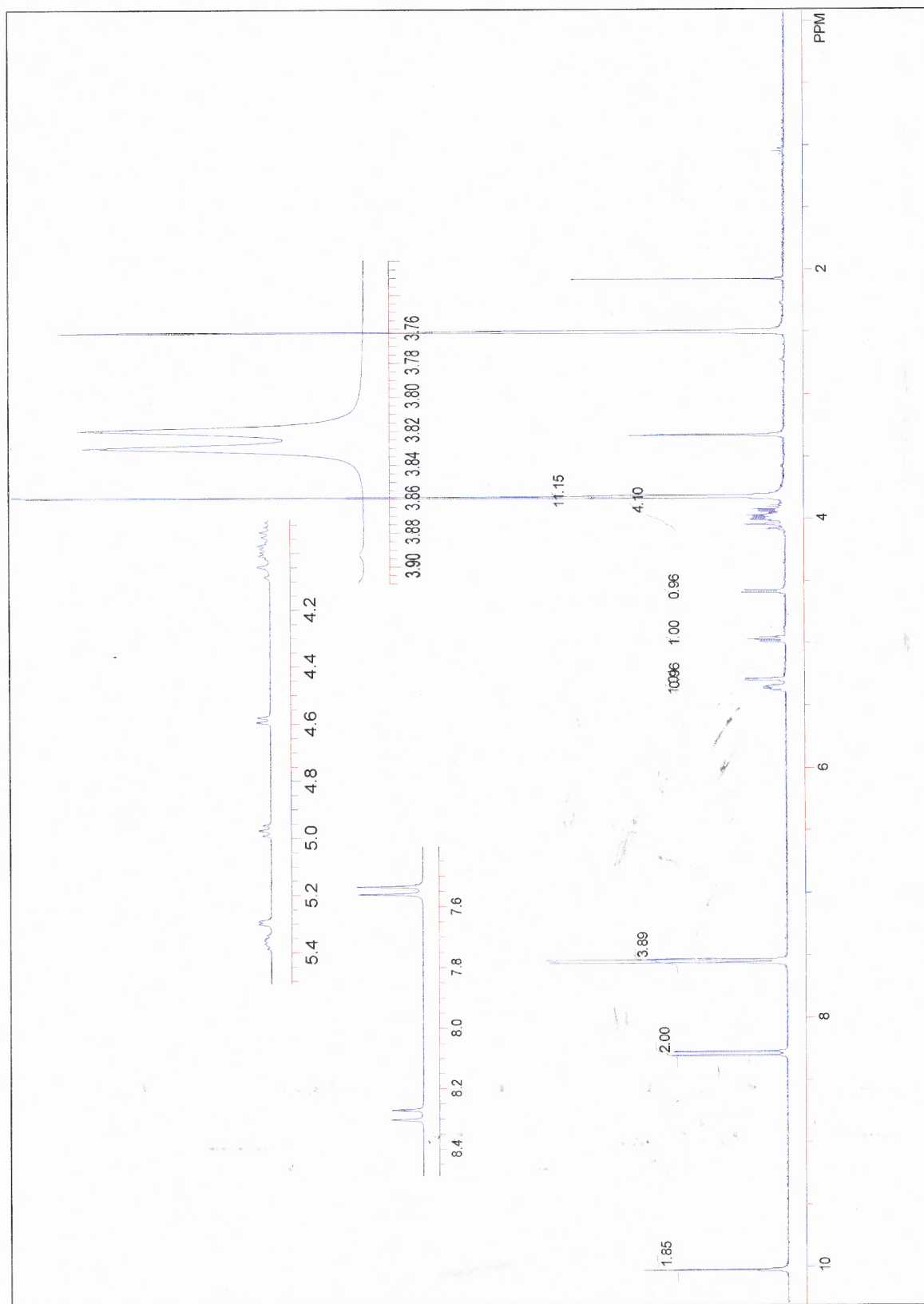


Figure 6.3.10 NMR of isororbide bis(3,5-dimethoxy,4-hydroxycinnamate) in DMSO--d6.

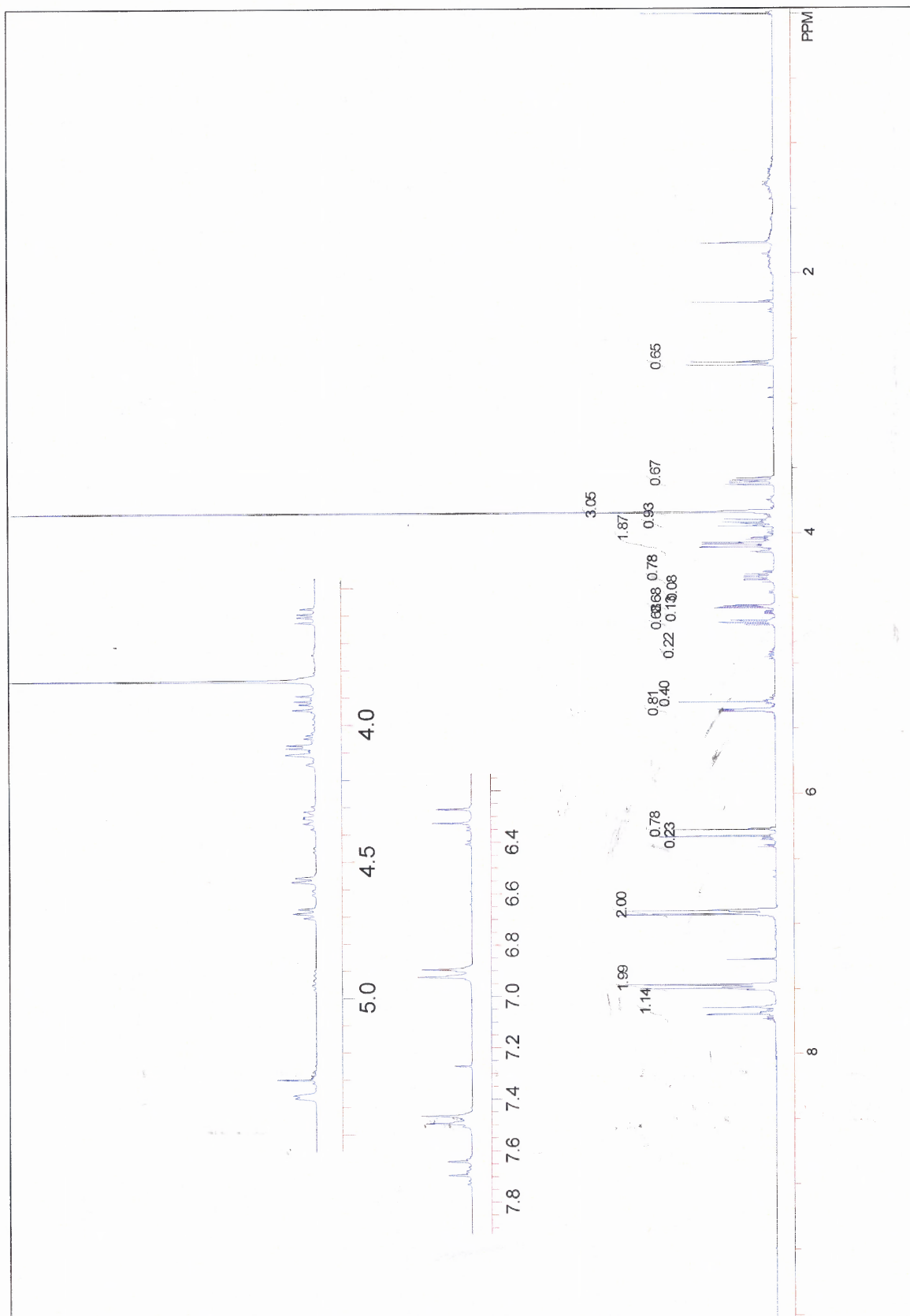


Figure 6.3.11 NMR of isosorbide 2-(4-methoxycinnamate) in CDCl_3/TMS .

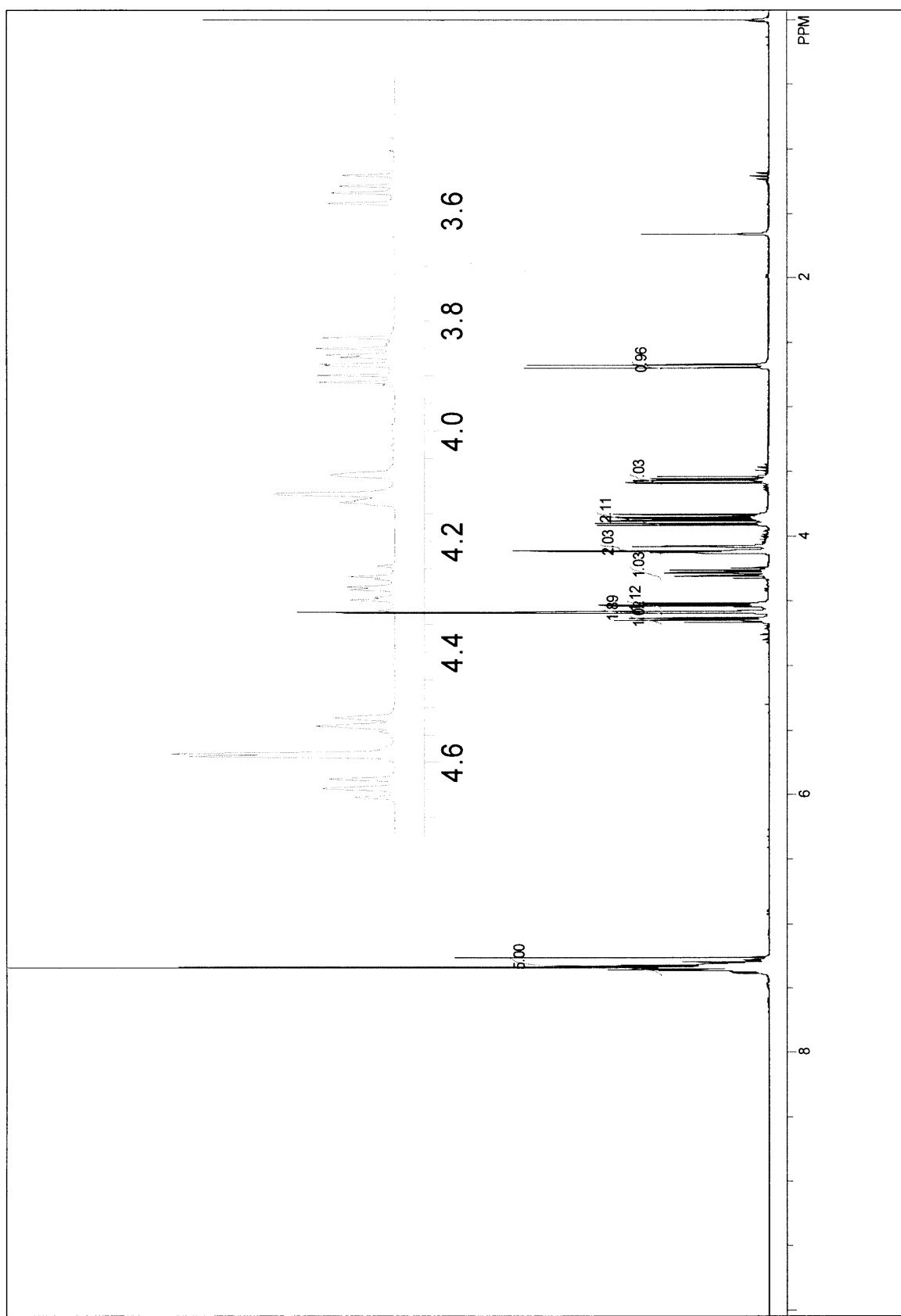


Figure 6.3.12 NMR of isosorbide 2-(benzylether) in CDCl_3/TMS .

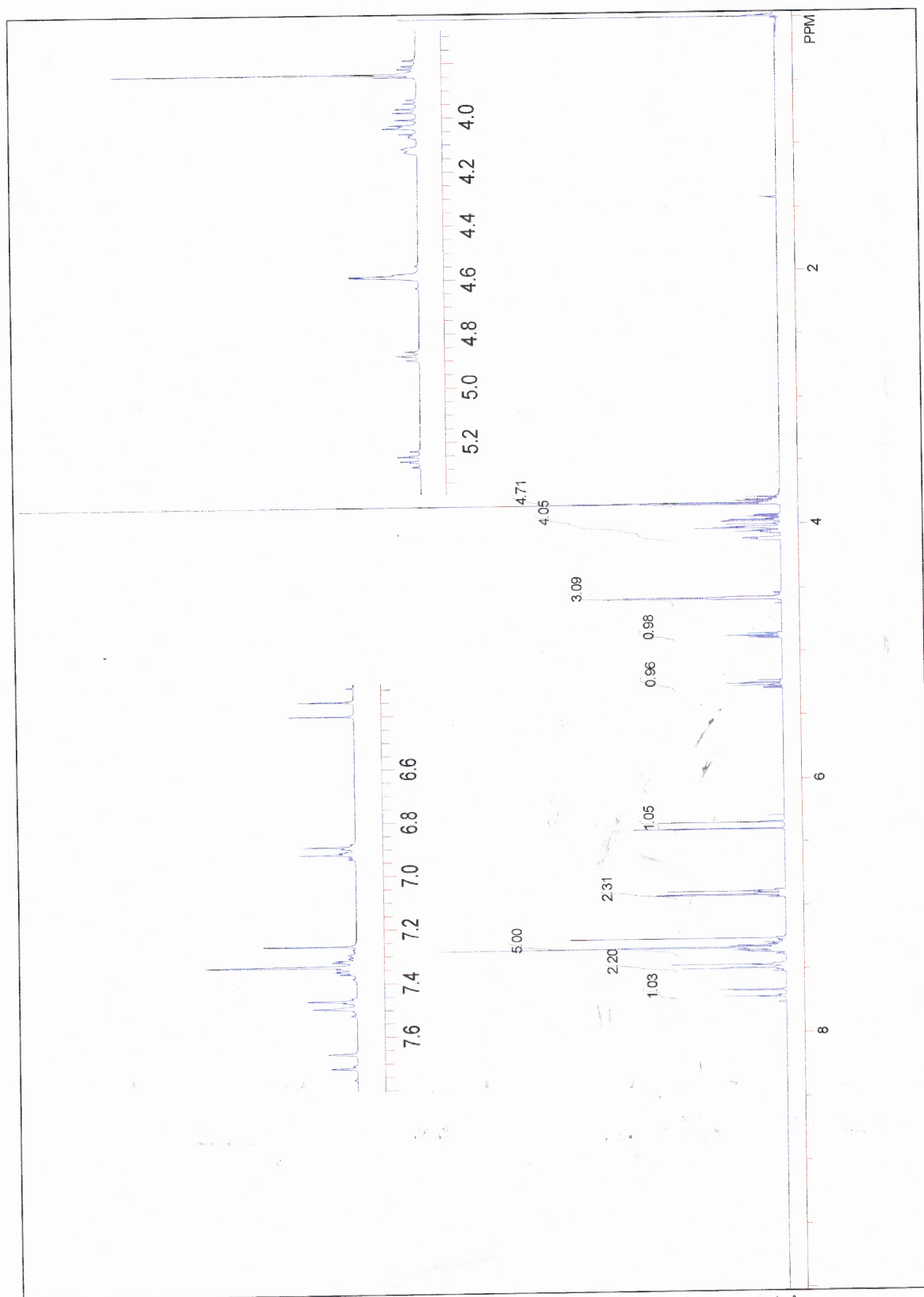


Figure 6.3.13 NMR of isoribide 2-(benzylether),5-(4-methoxycinnamate) in CDCl₃/TMS.

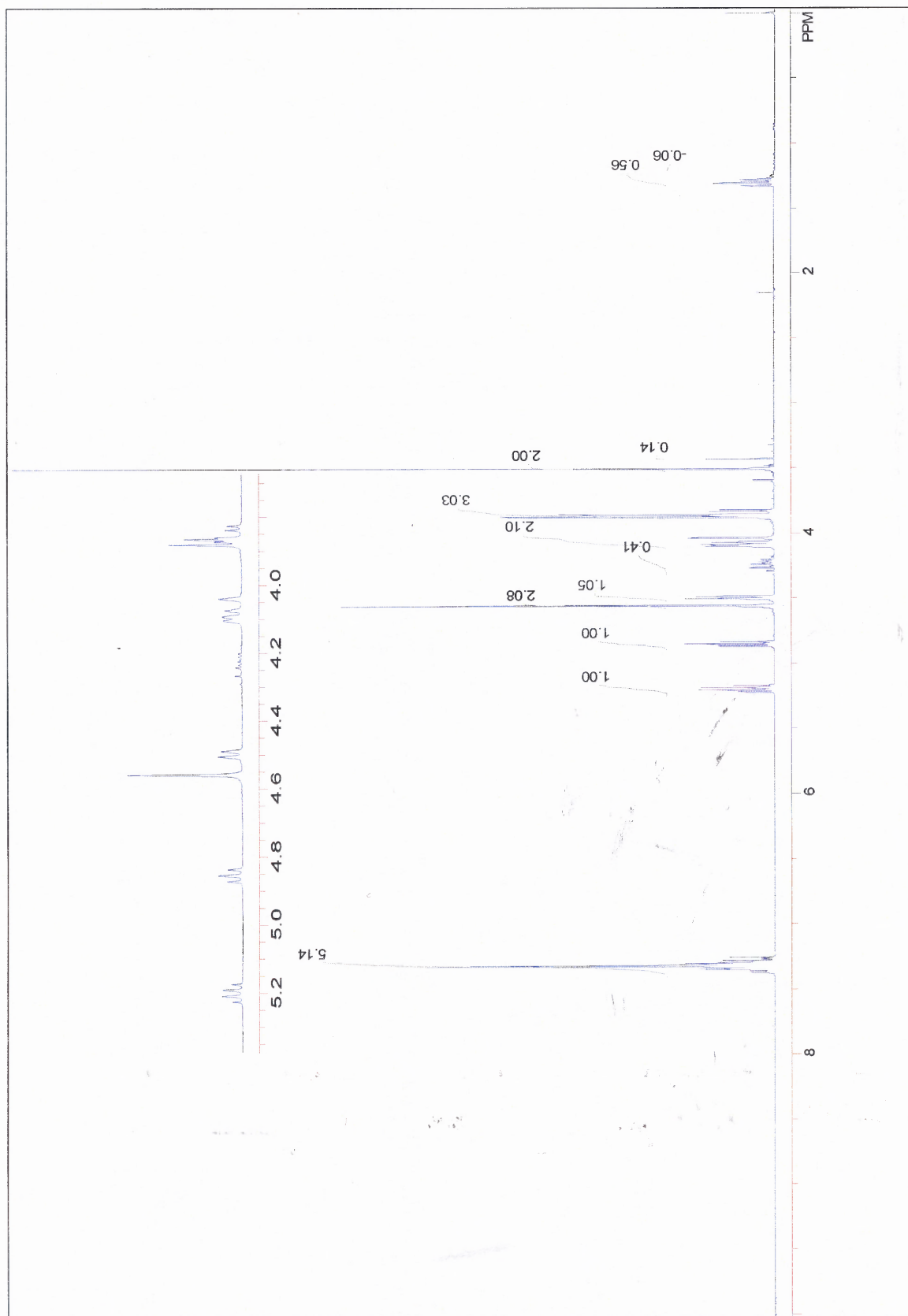


Figure 6.3.14 NMR of isosorbide 2-(benzylether), 5-(cyanoacetate) in CDCl₃/TMS.

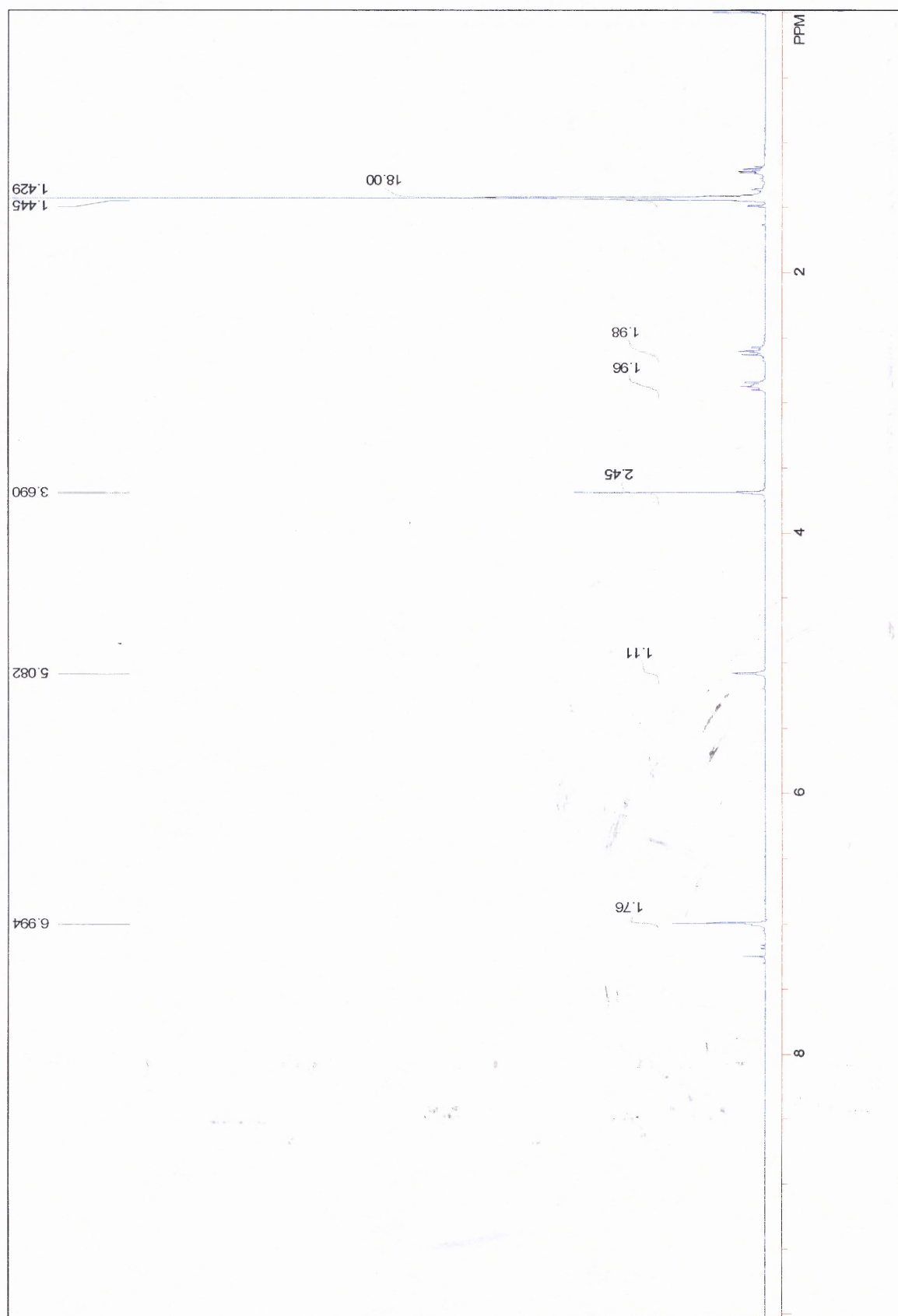


Figure 6.3.15 NMR of methyl 3-(4-hydroxy-3,5-di-t-butyl)propionate in CDCl₃/TMS.

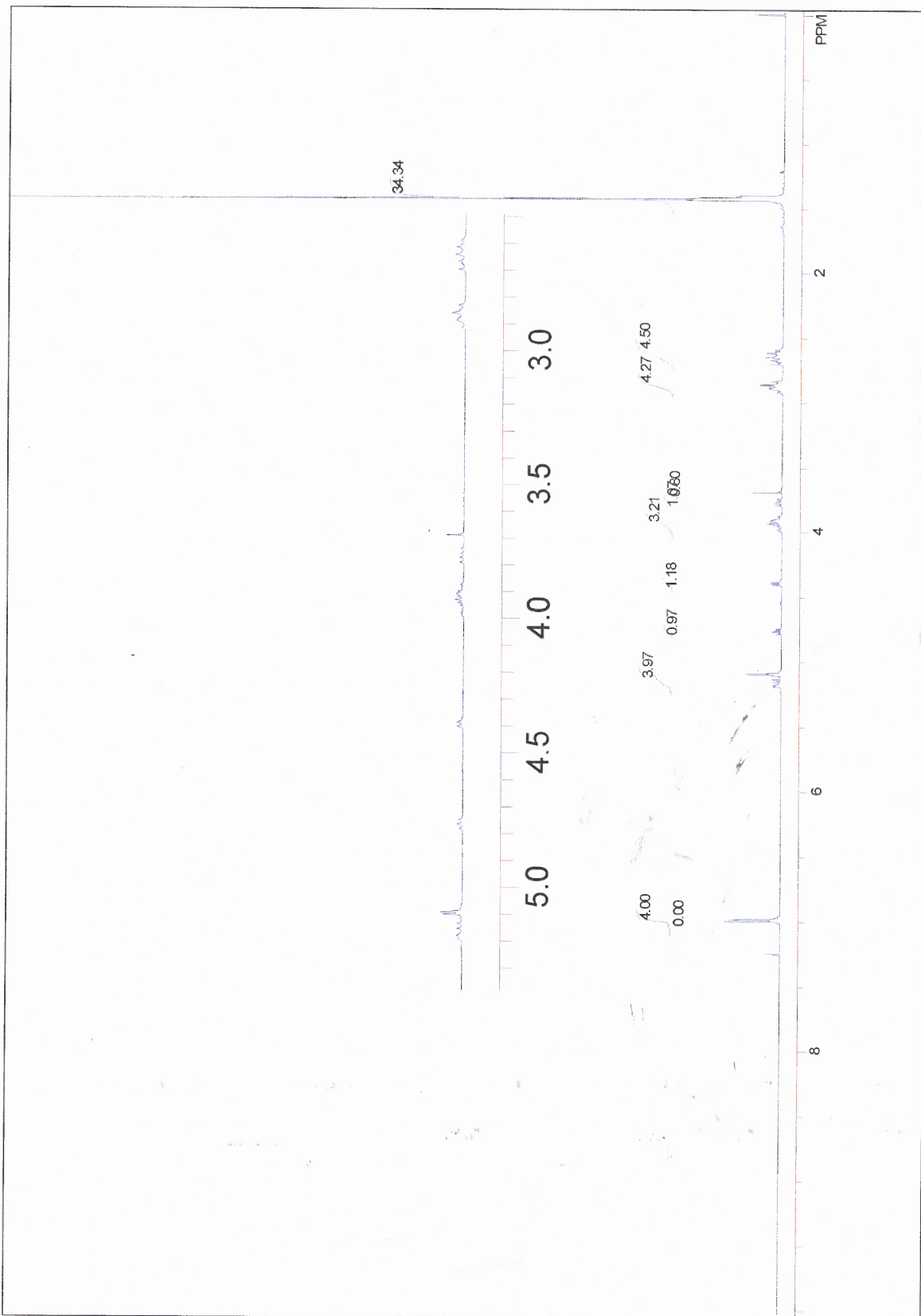


Figure 6.3.16 NMR of isosorbide bis(3-(4-hydroxy-3,5-di-t-butyl)propionate) in CDCl_3/TMS .

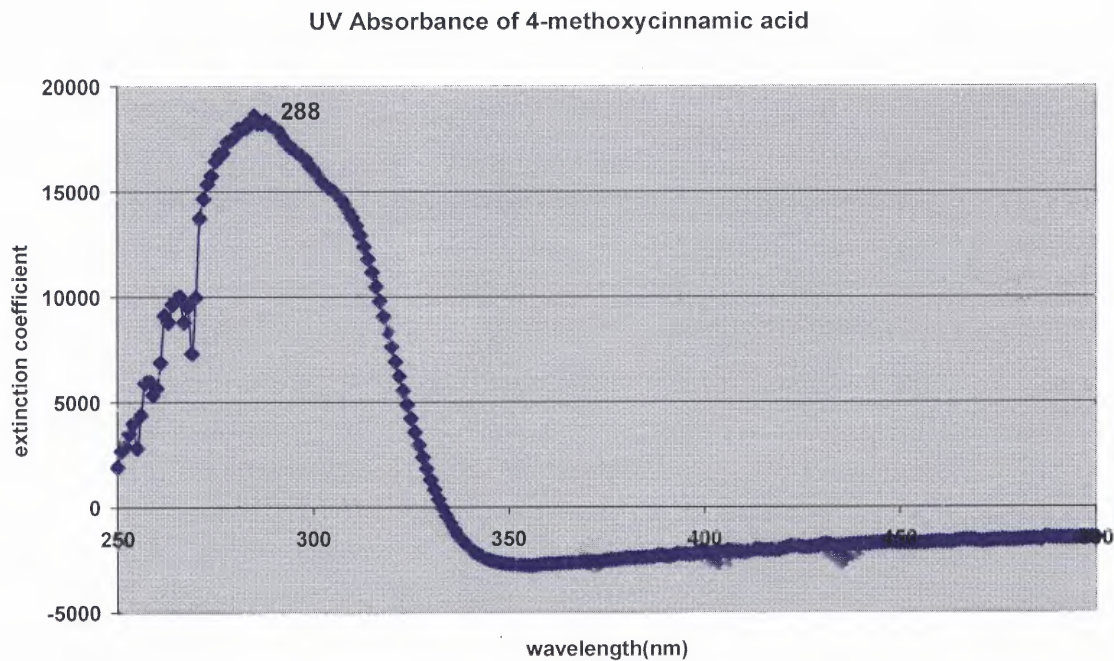


Figure 6.4.1 UV/VIS spectrum of 4-methoxycinnamic acid.

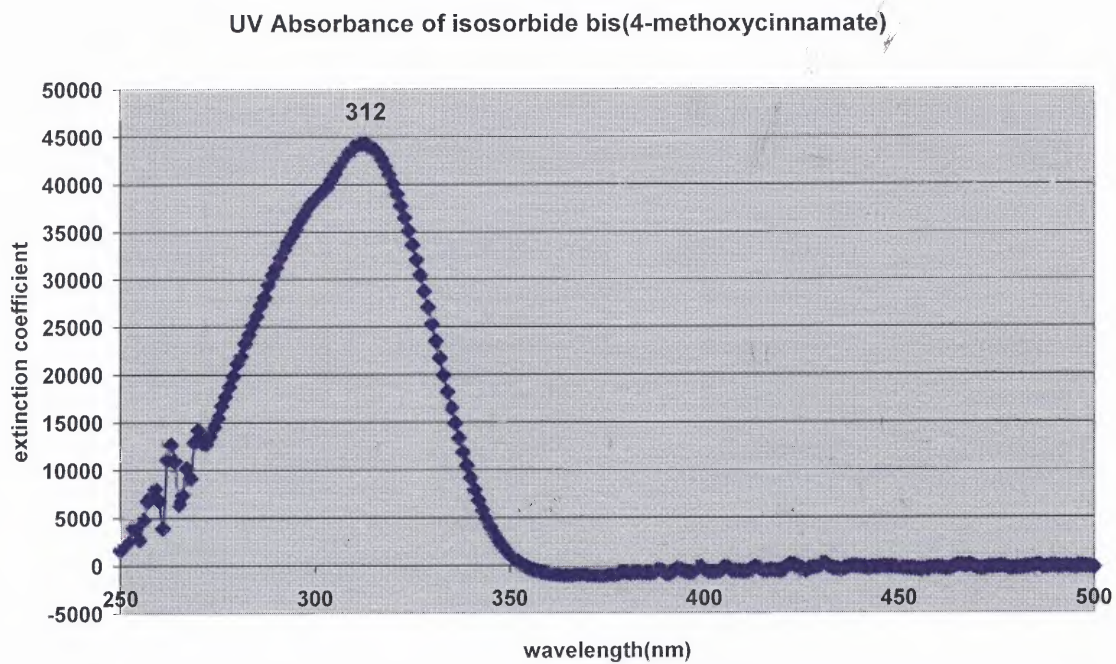


Figure 6.4.2 UVVIS spectrum of isosorbide bis(4-methoxycinnamate).

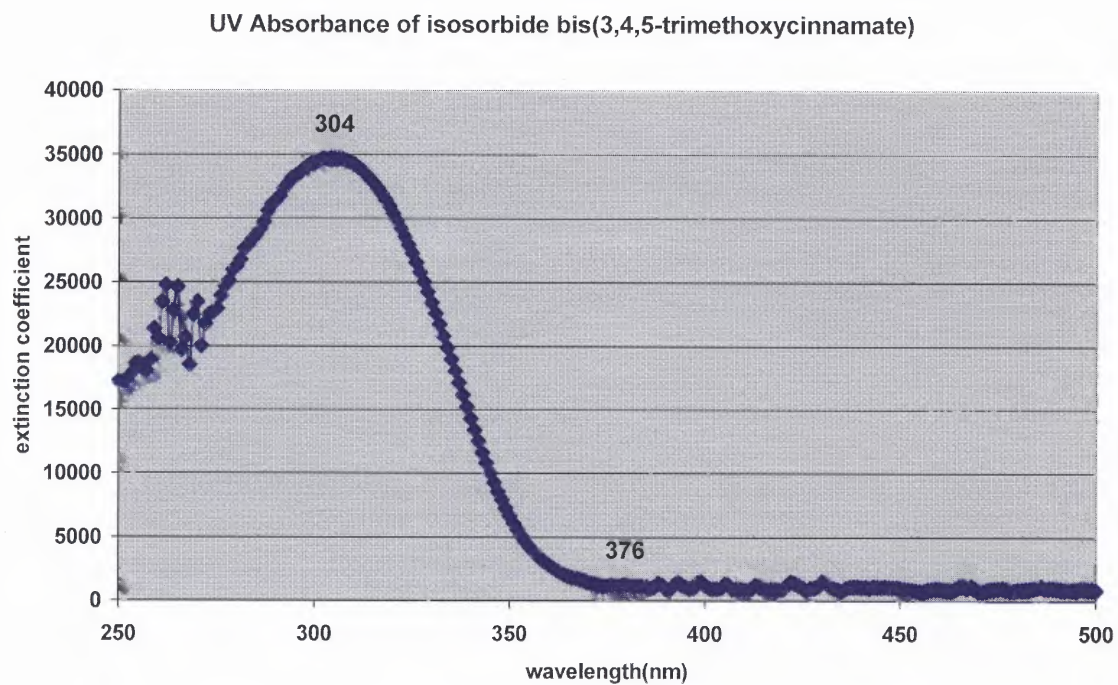


Figure 6.4.3 UV/VIS spectrum of isosorbide bis(3,4,5-trimethoxycinnamate).

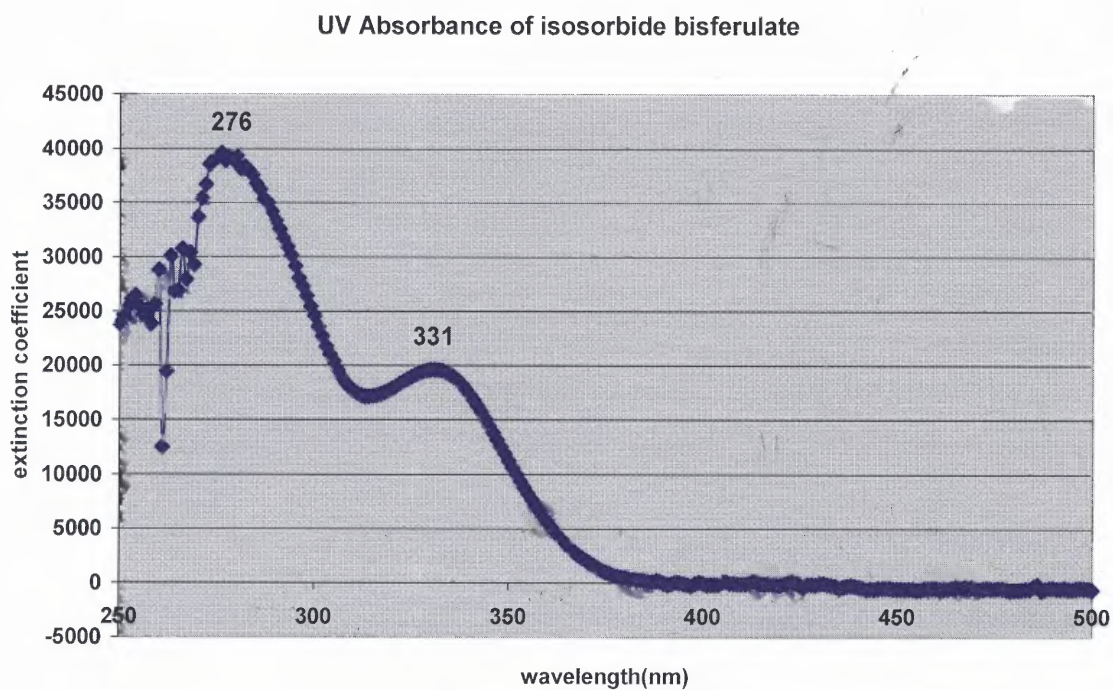


Figure 6.4.4 UV/VIS spectrum of isosorbide bisferulate.

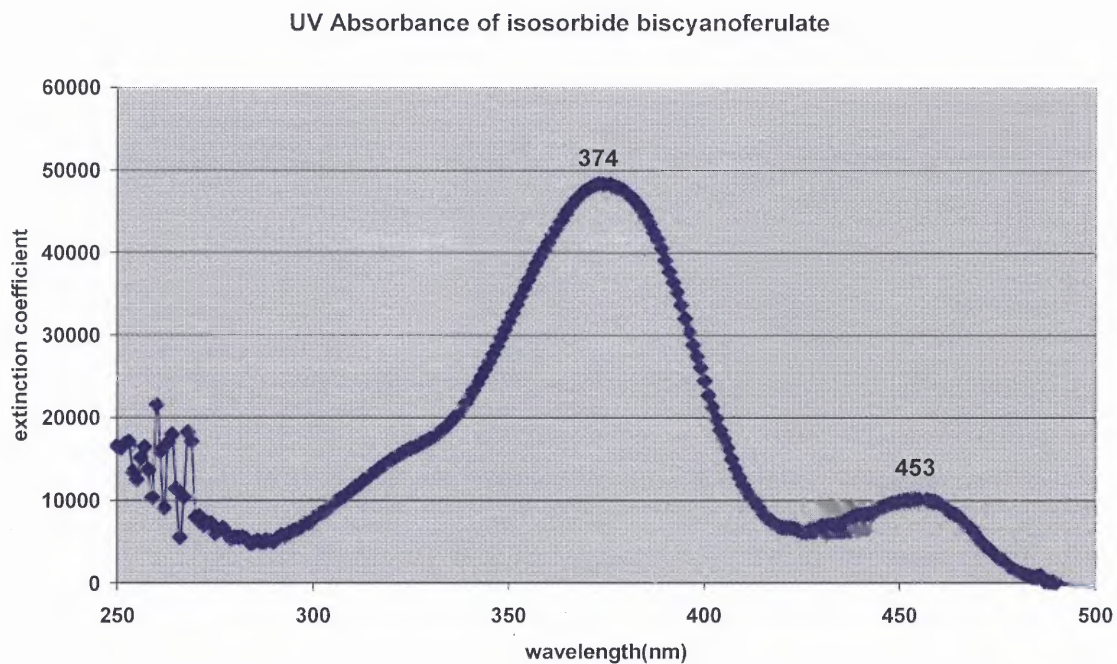


Figure 6.4.5 UV/VIS spectrum of isosorbide biscyanoferulate.

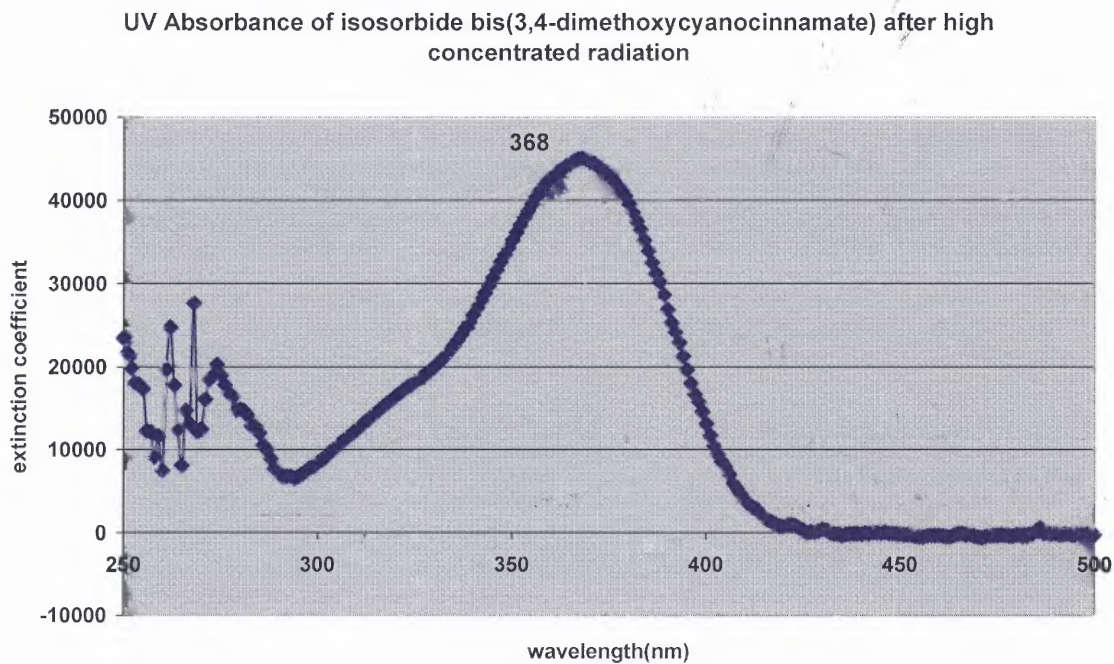


Figure 6.4.6 UV/VIS spectrum of isosorbide bis(3,4-dimethoxycyanocinnamate).

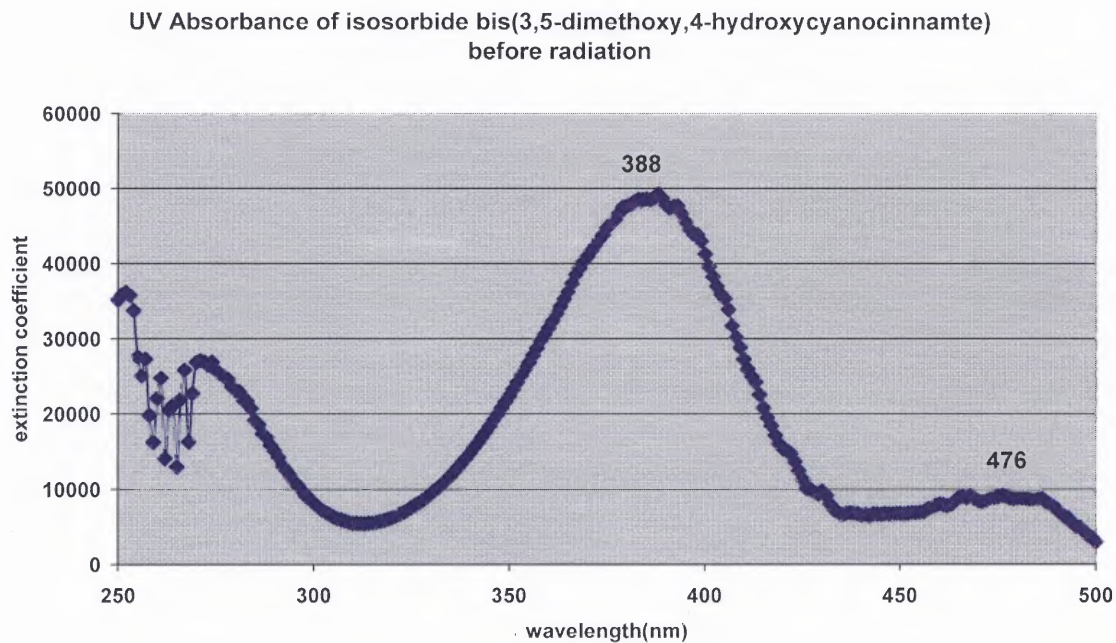


Figure 6.4.7 UV/VIS spectrum of isosorbide bis(3,5-dimethoxy,4-hydroxycinnamate).

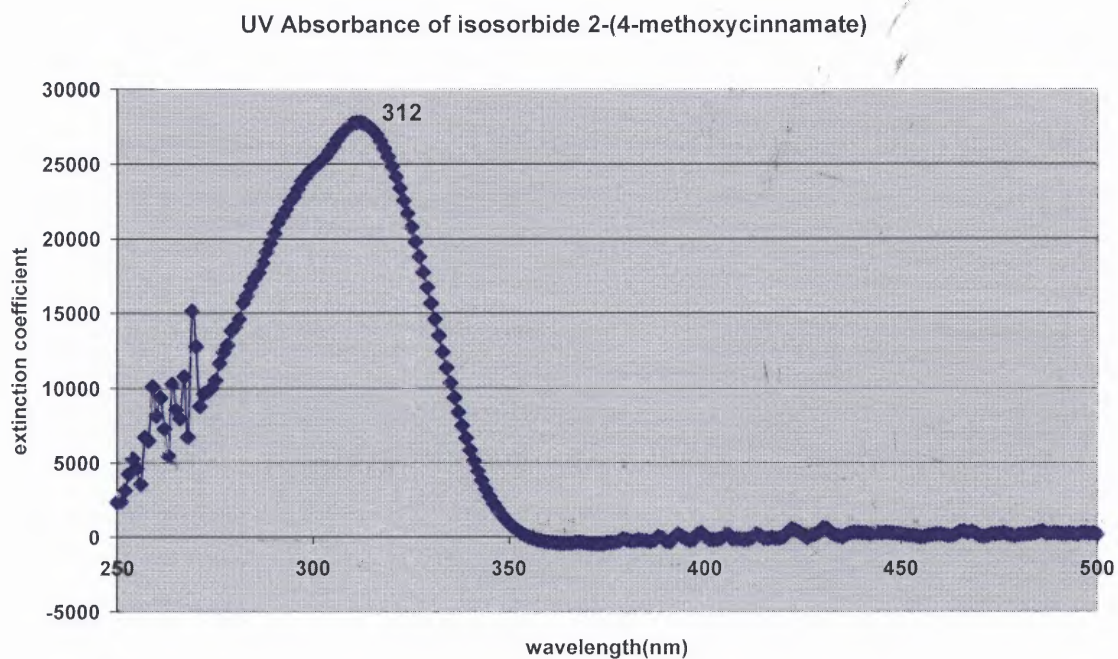


Figure 6.4.8 UV/VIS spectrum of isosorbide 2-(4-methoxycinnamate).

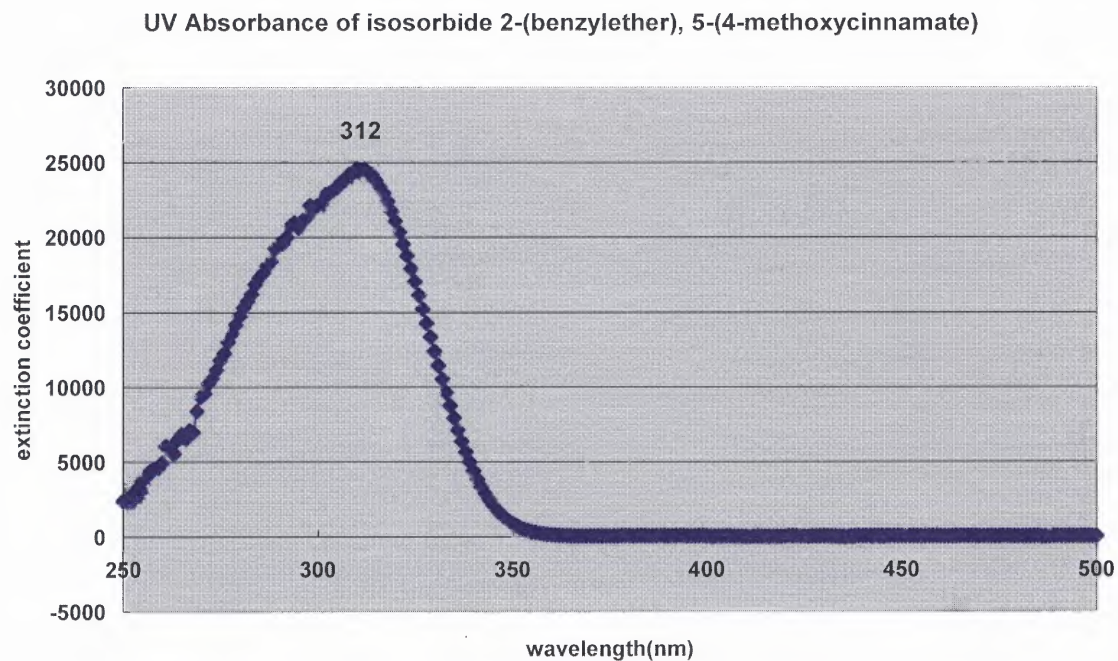


Figure 6.4.9 UV/VIS spectrum of isosorbide 2-(benzylether),5-(4-methoxycinnamate).

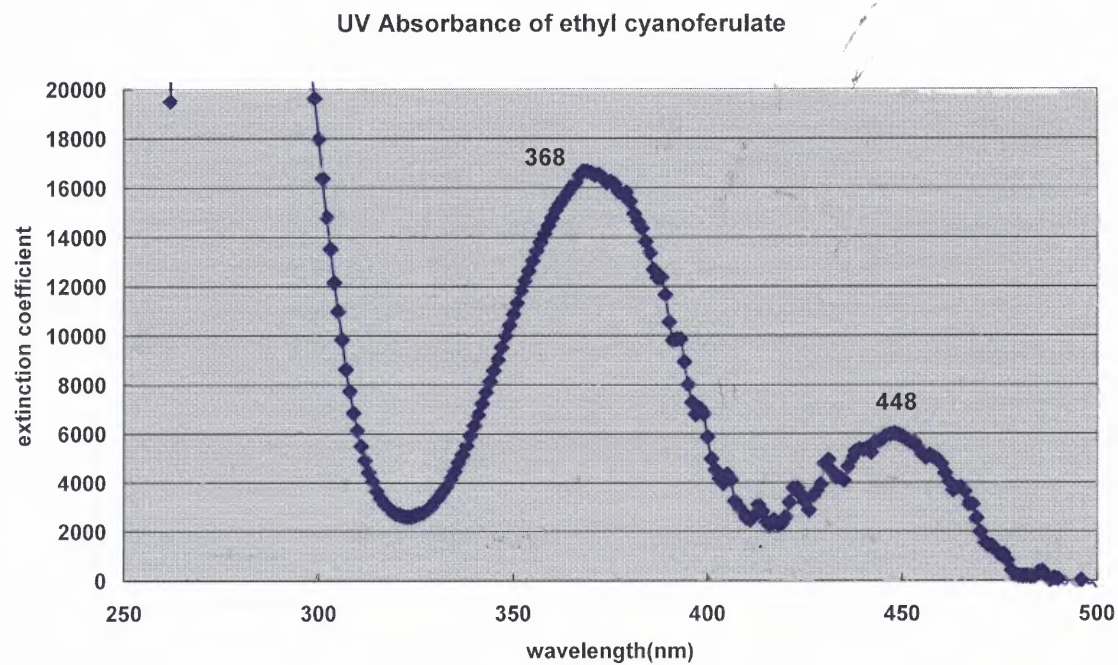


Figure 6.4.10 UV/VIS spectrum of ethyl cyanoferulate.

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