SYNTHESIS OF CURCUMIN-BASED LIGANDS FOR MOLECULAR KNOTS

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SYNTHESIS OF CURCUMIN-BASED LIGANDS FOR MOLECULAR KNOTS

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ABSTRACT

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SYNTHESIS OF CURCUMIN-BASED LIGANDS FOR MOLECULAR KNOTS

(85 pages)

Director of Thesis: Jared A. Butcher, Jr.

The aesthetics of molecular knots have been a strong interest for organic chemists. In this thesis, curcumin\((\text{1E, 6E)}-1,7\)-bis \(4\)-hydroxy-\(3\)\,-methoxyphenyl)-1,6-heptadiene-3,5-dione} was used as a substrate towards molecular knots. Its fascinating molecule possesses several attractive features that are useful in designing a synthesis of knots, catenanes, or braided polymer chains.

A commercial way of purifying curcumin from curcuminoids was studied and some curcumin-based ligands were synthesized. The chemistry of ligands with ester and ether linkages to curcumin was investigated. It was shown that the ester linkage to curcumin is vulnerable and those ligands were not suitable for the synthesis of molecular knots. The ether linkage is promising.

Approved: __________________________________________________________

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LIST OF ABBREVIATIONS

Bdmc---Bisdemethoxycurcumin

Dmc----Demethoxycurcumin
CHAPTER I. INTRODUCTION

1. **Statement of purpose**

Knots and interlocked rings have fascinated people for a long time.\(^1\) The trefoil knot, which is the simplest nontrivial knot,\(^2\) was the first to be studied by chemists. The first molecular trefoil knot was synthesized in 1988.\(^3\)

Our task is to use curcumin as the basis for ligand to facilitate the synthesis of curcumin analogs suitable for molecular knot. Curcumin possesses several attractive features that are useful in designing a synthesis of knots, catenanes, or braided polymer chains. Its two phenol groups on either end could form ester and/or ether linkage with other substrates. Through remodeling the structure of curcumin analogs, some promising compounds could be synthesized for further use in making molecular knots. In general, these compounds must be stable in some circumstances acidic or basic. In the course of this investigation, monoacetylcurcumin was shown to be vulnerable to hydrolysis under basic condition. Curcumin derivatives containing an ether linkage showed promising results.

2. **Definition of terms**

a. **Molecular knots**

Molecular knot is also called knotane, which is a mechanically-interlocked molecular structure.\(^2\) The trefoil knot, which is the simplest nontrivial knot, was the first to be studied by chemists.\(^3\) A trefoil knot is chiral in topology. One could see their
topological properties from a, b and c from Figure 1.\textsuperscript{2,3} Although they may contain the same atoms, they are topological stereoisomers. It is impossible to interconvert them by any transfiguration in space. In this figure, the compounds b and a are topological enantiomers because their mirror images are non-superimposable.\textsuperscript{2}

\textbf{b. Curcumin and its analogues}

Curcumin (Figure 2) (1E, 6E)-1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione, is a natural product found as major pigment in the Indian spice turmeric.\textsuperscript{4} Curcumin and some of its derivatives have several pharmacological properties, such as antioxidation, antimutation, antitumor, and anti-inflammatory.\textsuperscript{5-11} In the present project, a metal complex to a modified curcumin, used as a ligand, forms the basis for the synthesis of a trefoil knot. Analogues could be synthesized through remodeling its phenol groups to form the ether or ester linkage at each end.

\textbf{c. The isolation of curcumin from curcuminoids}

The commercial curcumin is the mixture of curcuminoids. Besides curcumin (around 70\%), commercial material also contains demethoxycurcumin (Dmc) and bisdemethoxycurcumin (Bdmc) (Figure 3). The isolation of curcumin from curcuminoids could be accomplished by using flash chromatography or recrystallization.
d. Flash chromatography

Column chromatography was discovered by Tswett in 1906. It is a separation technique in which the stationary phase is packed within a vertical glass column. The mobile phase, a liquid is added to the top and flow through the whole column. Column chromatography allows multiple components to be separated and it is one of the most useful methods for the separation and purification of both solids and liquids when carrying out chemical experiments. Depending on how the solvent flows down the column, it could be divided into two categories. If the solvent flows down the column by gravity, it is called “gravity column chromatography”. If the solvent is forced to flow down the column under air pressure, it is called “flash chromatography”. The first application of flash application was reported by Cawley in 1944. In his apparatus, the pressure chromatography was used to handle the slow-flowing adsorbents.

Flash chromatography was further developed by Still, et al. of Columbia University as an alternative to slow, tedious and inefficient gravity chromatography. The differences between flash chromatography and conventional technique are: first, it uses slightly smaller silica gel particles (250-400 mesh). Secondly, pressurized air is used to press the solvent through the column quickly. Nowadays, the technique of flash chromatography has become universal in chemical labs. As for the purification of some air-sensitive compounds, Kremer and Helquist developed a modified form of the flash chromatography.

Before carrying out the flash chromatography, thin layer chromatography (TLC) is often used for choosing a suitable solvent system and for testing the purity of the
Based on the Δ Rf value from TLC, the diameter and length of column, the quantity of sample and the volume of eluant could be selected.

Modern technology makes separation of compounds much easier and faster than before. In the current state-of-the-art flash chromatography system, glass columns are replaced with pre-packed plastic cartridges, which are much more efficient and also more reproducible. These improvements should make flash chromatography the technique of choices for separating compounds for years to come.

Figure 1. Trefoil knots

Reprinted with permission from Molecular Catenanes, Rotaxanes and Knots, page 112, Copyright 1999 Wiley-VCH.
Figure 2. Structure of curcumin 1.
Figure 3. Structures of curcuminoids: 2 is demethoxycurcumin (Dmc); 3 is bisdemethoxycurcumin (Bdmc)
CHAPTER II. HISTORICAL BACKGROUND

1. The history of knots

Knots and interlocked rings have fascinated people for a long time.\(^1\) The aesthetics of the beauty of these structures have been, and still are, a strong interest for many chemists.\(^2\) One could find knots everywhere in daily lives (Chinese knots, ties, ropes, shoelaces, sculptures, etc.). They are beautiful and also very useful.

The knot theory was originated and developed in chemistry. It began as a result of Lord Kelvin’s hypothesis in the 1880’s.\(^4\) According to Kelvin’s model, atoms were rings knotted in different ways to produce different elements. While Kelvin’s hypothesis has long been disproved, mathematicians are more interested in the knot theory. Nowadays, knot theory has been applied in chemistry and biology, these form new sub-disciplines such as chemical topology, biochemical topology, and topological stereochemistry.\(^5\)\(^-\)\(^7\)

The first application of knot theory was the recognition of their existence in biology. Electron microscopy established that DNA could form beautiful catenanes and knots.\(^6\)\(^,\)\(^8\) In 1976, Liu and his coworkers reported the first single-stranded DNA knot.\(^9\)

2. Early strategies of making a molecular knot

Besides the application of knot theory in biology, chemists also made some experimental and theoretical progress towards the production of molecular knots.\(^10\) A molecular knot has the mechanically-interlocked molecular structure. Early strategies for making a molecular knot involved: a) the Mobius strip approach\(^11\) b) Schill’s directed strategy based on covalent template\(^12\) c) templated strategy based on metal coordination\(^3\)\(^-\)\(^5\)
The first successful synthesis of trefoil molecular knot was completed by Dietrich-Buchecker and Sauvage in 1989.\textsuperscript{3,36} As illustrated in Figure 5, the dimeric complex composed of two bisphenanthroline ligands and two Cu\textsuperscript{I} cations. They were linked by oligoethyleneglycol chains. The structure was confirmed by X-ray structure analysis. Later Dietrich-Buchecker and his co-workers also made some attempts to improve the yield of the reaction.\textsuperscript{34}

Inspired by Dietrich-Buchecker and Sauvage’s success, other chemists also tried different strategies to synthesize trefoil knot. In 1997, Stoddart and his co-workers isolated a trefoil knot. In his approach, the \(\pi\)-donor/\(\pi\)-acceptor interaction between amine units was used.\textsuperscript{37} In 2001, Hunter and coworkers reported the synthesis of open loop. This open knot is an important intermediate for a range of topologically complex molecules. \textsuperscript{38}
a) the Mobius strip approach

b) Directed syntheses covalent template

c) Templated synthesis approach

Figure 4. Early strategies of making molecular knots

Reprinted with permission from Molecular Catenanes, Rotaxanes and Knots, page 114, Copyright 1999 Wiley-VCH.
Figure 5. Synthesis of the first trefoil knot by Dietrich-Buchecker and his coworkers\textsuperscript{2}

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3. Chemistry of curcumin

Butcher’s research group is working on the synthesis of curcumin analogs that can serve as ligands in the synthesis of molecular knots.\(^{39}\)

Curcumin is a fascinating molecule possessing several attractive features that are useful in designing a synthesis of knots, catenanes, or braided polymer chains: (1) It could be viewed as an “oversized” ligand possessing a \(\beta\) diketone moiety in the center and two hydroxyl groups at each end. (2) It can be viewed as a molecule having \(sp^2\) carbons. (3) The \(\beta\) diketone moiety could be used to coordinate with some transition metal ions \(Al^{3+}, Cu^{2+}, Ni^{2+}, Zn^{2+}, Pd^{2+}, Fe^{3+}\).\(^{40,41}\) (4) The phenol group on either end can be used to as the starting point of further attachment in making ester and/or ether linkages. Taken together, these properties make curcumin a logical candidate for making octahedral metal complexes that can be used to study a variety of methods for making knotted, linked, or woven structures found in knots and catenanes.

a. Protecting group of curcumin

There are two functional groups in curcumin molecule, phenolic hydroxyl group and carbonyl group in \(\beta\) dikeone.

1. Phenolic hydroxyl group: For the protection of phenolic hydroxyl group, there are several options. The most commonly used methods are forming ethers or esters. But ether is not suitable in our case since there is another methoxy group in the structure and it could be also cleaved upon deprotection. Aryl esters is easily prepared from phenol and acid chloride or anhydride in the presence of base and readily cleaved by saponification.\(^{42}\) (Figure 6)
2. Carboxyl group: The most useful protective groups for carbonyl group in curcumin is acyclic and cyclic ketals. Alcohol, diol are commonly used protective reagents. Cyclic and acyclic ketals are stable to basic solution and some nucleophiles. Deprotection of these ketals are also readily accomplished.\textsuperscript{42} (Figure 7)

b. Reactions of curcumin

Curcumin has an interesting structure and it has been studied for a long time on its application in medicine and biology. There are a lot of reports on the reactions curcumin, which are very useful guides to designing the synthetic strategies. (Figures 8-10). In Butcher’s group, some analogues of curcumin have been synthesized\textsuperscript{39}. These analogues are promising ligands for making molecular knots. (Figures 11-13)

![Figure 6](image.png)

**Figure 6.** The protection of phenolic hydroxyl groups\textsuperscript{42}
Figure 7. The protection of carbonyl groups\textsuperscript{42}
**Figure 8.** Reaction of phenolic hydroxyl groups

Synthesis of di-acetate derivative of curcumin I: (a) 10% NaOH/crushed ice/acetic anhydride;\textsuperscript{[43]} synthesis of di-methyl derivative of curcumin II: (b) KOH/acetone/NaHSO\textsubscript{4}/(n-Bu)\textsubscript{4}I/CH\textsubscript{3}I;\textsuperscript{[44]} synthesis of di-methyl derivative of curcumin III: (c) KOH/acetone/NaHSO\textsubscript{4}/(n-Bu)\textsubscript{4}I/benzyl bromide\textsuperscript{[44]}
Figure 9. Reaction of β diketone/hydrogenation of curcumin: MeOH/Pd/C\textsuperscript{45}
Figure 10. Reaction on β diketone/synthesis of pyrazole derivative of curcumin: EtOH/histidine hydrazide/HOAc/TsOH$^{45}$
Figure 11. Synthesis of curcumin diacetate$^{39}$
Figure 12. Synthesis of curcumin ditoluate
Figure 13. Synthesis of curcumin ethers.
CHAPTER III. RESULTS AND DISCUSSION

1. The isolation of curcumin from a commercial mixture of curcuminoids

The commercial curcumin is the mixture of curcuminoids. Besides curcumin (around 70%), commercial material also contains demethoxycurcumin (Dmc) and bisdemethoxycurcumin (Bdmc). The available method of isolation of curcumin from curcuminoids could be fulfilled by flash chromatography. Considering potential application of demethoxycurcumin and bisdemethoxycurcumin in pharmacology, a more effective and commercial method to separate curcuminoids in bulk at a low price was sought as part of this research project.

Direct crystallization of the neutral compounds in commercial mixture yields no separation, but there are interesting hints. For example, attempted crystallization from hot cyclohexane yields an amorphous solid that contains the mixture of curcuminoids, but curcumin is highly enriched in the solution.

One could argue that there is a network of curcuminoids forms in the solvent and that the curcuminoids are preferentially incorporated into it and this leaves curcumin as the sole component in solution. If this is true, then a number of properties of curcumin must be explored, all of which have to do with the acidity of protons in the molecule and their ability to participate in hydrogen bonding, dipole-dipole, and other intermolecular interactions. These are the forces that permit chromatography to separate the compounds; perhaps they can be exploited to give separation by other means as well.
In the course of work described in this thesis, it was found that various bases can be used to effect a separation of curcumin from the commercial mixture (Figure 14):

Cross-linked polyvinylpyridine powder mixed with Celite in a column “filters” the curcuminoids out of the mixture in a dichloromethane solution. The result is that pure curcumin comes out first. Presumably, the basicity of pyridine is sufficient to deprotonate the curcuminoids to greater extent than curcumin. This would indicate that the acidities of demethoxycurcumin and bisdemethoxycurcumin are greater than curcumin itself.

**Figure 14.** The isolation of curcumin from curcuminoids with cross-linked polyvinylpyridine/Celite mixture (1:1), CH$_2$Cl$_2$ as mobile phase.
2. Synthesis of curcumin analogues containing an ester linkage

In this research, the emphasis was focused on modeling the structure of curcumin. The hydroxyl group on the ends of curcumin molecule could be used to as the starting point of further attachment. Through modifying the curcumin molecule and synthesize curcumin analogues, we could evaluate if the analogues are valuable or not for further use in the formation of molecular knots.

4-Chlorobenzoic acid 11 is one key starting substrate to form molecular knot. This compound could be converted to anhydride\textsuperscript{49} 12 or ester\textsuperscript{50} 13 (Figure 15), and then be attached to curcumin through either an ester or ether linkage.

Monoacetylcurcumin 14 is a very important intermediate in synthesizing other curcumin analogues. (Figure 16) The acetyl group could be regarded as a protecting group on one of hydroxyl group of curcumin molecule. With the acetyl group on one side of curcumin molecule, some other functional groups could be attached to the other side to make curcumin analogues.
Figure 15. The derivatives of 4-(chloromethyl)benzoic acid$^{49,50}$
Figure 16. Monoacetylcurcumin 14

a. The synthesis of unsymmetrical curcumin ester

With the acetyl group forming the ester linkage to one hydroxyl group of curcumin, we could use another anhydride to react with the monoacetyl curcumin to form unsymmetrical ester accordingly. Here unsymmetrical curcumin ester means that there are two different functional groups on either end of curcumin molecule.

i. Synthesis of monoacetyl curcumin 14

Considering the symmetry of curcumin molecule and its hydroxyl groups on each end, it is not surprising that the product of reaction between curcumin and acetic
anhydride would be mixture of diacetyl curcumin, monoacetyl curcumin and unreacted curcumin. If one controls the ratio of acetic anhydride and reaction time, then the monoacetyl curcumin could be the major product. Then monoacetyl curcumin 14 could then be separated through column chromatography. (Figure 17)

ii. Synthesis of acetyl-(4-chloromethyl)benzoyl-curcumin 15

4-(Chloromethyl)benzoic anhydride 12 was prepared through the dehydration of 4-(chloromethyl)benzoic acid with the presence of P$_2$O$_5$. 49 With one acetyl group on the one side of curcumin, the reaction of monoacetyl curcumin with excess 4-(chloromethyl)benzoic anhydride was clean and complete. (Figure 18)

iii. Synthesis of acetyl-toluyl curcumin 16

4-Toluic anhydride was prepared through dehydration of 4-toluic acid with the presence of P$_2$O$_5$. 39 Then mono-acetyl curcumin was reacted with excess 4-toluic anhydride to get acetyl-toluyl curcumin. (Figure 19)

iv. Synthesis of Acetyl-benzoyl curcumin 17

Similar with the previous one, benzoic anhydride was prepared through dehydration of benzoic acid with the presence of P$_2$O$_5$. 49 Monoacetyl curcumin was reacted with excess benzoic anhydride to get acetyl-benzoyl curcumin. (Figure 20)
Figure 17. The synthesis of monoacetyl curcumin 14
Figure 18. The synthesis of acetyl-(4-chloromethyl)benzoyl curcumin 15
Figure 19. The synthesis of acetyl-toluyl curcumin 16
Figure 20. The synthesis of acetyl-benzoyl curcumin 17
b. The synthesis of symmetrical curcumin ester

Hydroxyl groups on each end of curcumin could react with anhydrides to form esters. Here symmetrical curcumin ester means that functional groups attached to each end of the curcumin molecule are the same.

i. Synthesis of curcumin dibenzoate 18

Benzoic anhydride was prepared through dehydration of benzoic acid with the presence of \( \text{P}_2\text{O}_5 \). Curcumin was then reacted with excess benzoic anhydride to get curcumin dibenzoate 18. (Figure 21)

ii. Synthesis of curcumin 4-(chloromethyl)benzoyl diester 19

4-(Chloromethyl)benzoic anhydride was prepared through dehydration of 4-(chloromethyl)benzoic acid with the presence of \( \text{P}_2\text{O}_5 \). Then curcumin was reacted with excess benzoic anhydride to give curcumin 4-(chloromethyl)benzoyl diester 19 (Figure 22)
Figure 21. The synthesis of curcumin dibenzoate 18
Figure 22 The synthesis of curcumin 4-(chloromethyl)benzoyl diester 19
c. Synthesis of curcumin ether based on curcumin ester

Compound 20 is one of desired products in this research project, which was supposed to used to coordinate with transition metal and then form a molecular knot (Figure 23). There is no direct way to synthesize compound 20 since some kind of polymers w formed instead when the reaction was run between curcumin and epichlorohydrin. Actually one could also see the phenomenon from the production of epoxy resin. Bisphenol A (Figure 24), which has similiar structure to curcumin in that both of them have hydroxyl groups on each end, reacts with epichlorohydrin to yield epoxy.51

It was supposed that through monoacetylcurcumin, one might prevent the polymerization reaction between curcumin and epichlorohydrin, but, the acetyl group was removed when running the reaction of monoacetyl curcumin with epichlorohydrine and the final product was a mixture (Figure 25). This proved that the ester linkage is very vulnerable and could not withstand the reacting conditions needed for etherification.
Figure 23. The approach to molecular knot from compound 20
Figure 24. The reaction between Bisphenol A and epichlorohydrin $^{51}$
**Figure 25.** The etherification of monoacetyl curcumin
3. Synthesis of curcumin analogues containing an ether linkage

The hydroxyl groups of curcumin could form the ether linkage through Williamson etherification.\textsuperscript{52} Methyl 4-(chloromethyl) benzoate (Figure 26) and some other long chain difunctional compounds were used for the reaction.

The nucleophilic properties of curcumin present a contradiction. It is quite reactive with benzyl chloride in that both mono- and di-substituted curcumin derivatives form readily in 30 min, but the yields are low. Extending the time and increasing the temperature and concentration of substrates does not improve the yield beyond 25\%. The most likely explanation for this behavior are (1) low reactivity, or (2) equilibrium formation. However, increasing the time and temperature and increasing the concentration did nothing on low reactivity and equilibrium. This leads to the conclusion that there is a third, undocumented alternative. If one were to consider curcumin as analogous to hydroquinone, then this alternative might be formation of a radical intermediate, similar to semihydroquinone formation. On work up, this intermediate would have to revert to curcumin, because no other products were detected. Initial attempts to reduce an undetected radical by using sodium bisulfite produced no measurable change in the reaction rate or the yield of products. While this does not prove whether a radical is involved, it does make finding the answer more intriguing.
Figure 26 Methyl 4-chloromethyl benzoate 13

a. The synthesis of curcumin ester containing curcumin monoether

Butcher’s group has synthesized some curcumin ethers. The products of the etherification were always the mixture of curcumin diether, monoether and unreacted curcumin. Column chromatography was used to separate the mixture. In this project, curcumin 4-(carboxymethyl) benzyl monoether 21, which was obtained from the reaction of curcumin with methyl 4-(chloromethyl) benzoate, was used. (Figure 27)
i. Synthesis of curcumin 4-(carboxymethyl) benzyl ether-acetyl ester 22

Curcumin 4-(carboxymethyl) benzyl monoether was reacted with excess acetic anhydride. Sodium acetate was used as the base. The reaction was very complete and all monoether was converted to the final product curcumin 4-(carboxymethyl) benzyl ether-acetyl ester 22 (Figure 28).

ii. Synthesis of curcumin 4-(carboxymethyl) benzyl ether-toluic ester 23

Similar with the previous reaction, curcumin 4-(carboxymethyl) benzyl monoether was reacted with excess 4-(chloromethyl)benzoic anhydride. Pyridine was used as the base. The reaction was very complete and all monoether was converted to the final product curcumin 4-(carboxymethyl) benzyl ether-4-(chloromethyl)benzoyl ester 23 (Figure 29).
Figure 27. Curcumin 4-(carboxymethyl) benzyl monoether \(^{39}\) 21
Figure 28. Synthesis of curcumin 4-(carboxymethyl) benzyl ether-acetyl ester 22
Figure 29. Synthesis of curcumin 4-(carboxymethyl) benzyl ether-4-(chloromethyl) benzoyl ester 23
b. The synthesis of curcumin with long chain difunctional compounds

Butcher’s group has synthesized a series of long-chain molecules containing benzoic acid, alcohol or benzyl chloride moieties at each end as shown in Figure 30.\textsuperscript{53,54}

Theoretically, these compounds might react with curcumin to form a closed loop directly (Figure 31). This curcumin analogue loop showed a rapid entry to the making of a molecular knot. When this reaction was attempted by using the standard condition developed for other benzyl chlorides (DMF/K\textsubscript{2}CO\textsubscript{3}, 60-70 °C for 4 hr), polymeric mixture was obtained. this curcumin analogue loop was never separated from the final products in our research. Some kind of polymer was evidently formed in the reaction.
**Figure 30.** Long-chain difunctional compounds from Butcher’s group$^{53,54}$
Figure 31. The curcumin analogue towards molecular knot 24
4. **Conclusions**

The separation method of curcumin from curcuminoid was investigated. Recrystallization did not work as proposed. Column chromatography was used temporarily but not recommended because of its costliness and it is time-consuming.

Some curcumin analogues based on ester and ether linkages were synthesized. It proved that the ester linkage to curcumin is vulnerable to hydrolyze and not suitable for further synthesis of a molecular knot. Ether-linkage curcumin analogues were more robust and provide promising precursors for making molecular knots. The products of long chain difunctional compounds with curcumin could not be used to make a knot because of the formation of polymers.
CHAPTER IV. EXPERIMENTAL SECTION

Curcumin was purchased from Aldrich—Sigma Company as a mixture containing around 70% curcumin and purified by flash chromatography (CH$_2$Cl$_2$/silica 200-400 mesh). All other chemicals, solvents and reagents were of available purity and used without any further purification.

Elemental analyses were conducted by Desert Analytics Laboratories, Tucson, Arizona. $^1$H NMR spectra were recorded on a Bruker 300 ultra shield system. Fresh CDCl$_3$ was used as solvent for NMR. Infrared (IR) spectra were recorded on a FTIR 8400 system.

Thin-layer chromatography (TLC) was performed on Merck silica gel (Item No.: 60F$_{254}$) aluminum-backed sheets (5%MeOH/ CH$_2$Cl$_2$). Products were purified by column chromatography on Fisher chromatographic silica gel (200-400 mesh) as the stationary phase (CH$_2$Cl$_2$/Hexane=70:30). Melting points (mp) were determined by using an electrothermal MEL-TEMP II apparatus.
1. Synthesis of 4-(chloromethyl)benzoic anhydride\textsuperscript{49} 12

A mixture of 4-chlorobenzoic acid (5 g, 29.4 mmol) and anhydrous P\textsubscript{2}O\textsubscript{5} (2.0 g, 14.1 mmol) in CH\textsubscript{2}Cl\textsubscript{2} was refluxed for 12 h. After filtering the solid residue, the product was washed with Na\textsubscript{2}CO\textsubscript{3} solution and dried over anhydrous MgSO\textsubscript{4}. After evaporating the solvent, white crystal was obtained. Yield = 4.3 g (90%).

2. Synthesis of methyl 4-(chloromethyl)benzoate\textsuperscript{50} 13

4-Chlorobenzoic acid (5 g, 29.4 mmol) was dissolved in methanol (200 mL). Six drops of concentrated sulfuric acid were added dropwise to a stirred solution. The solution was then stirred at room temperature for 24 h. The solvent methanol was evaporated. Then the product was dissolved in 100 mL CH\textsubscript{2}Cl\textsubscript{2} and was washed with Na\textsubscript{2}CO\textsubscript{3} solution. Then dried with anhydrous MgSO\textsubscript{4}. After evaporating the solvent, white crystal compound was obtained. Yield = (4.3 g, 80%).

3. Synthesis of (1E, 6E)-1-(4’-acetoxy-3’-methoxyphenyl)-7-(4’’-hydroxy-3’’-methoxyphenyl)-1,6-heptadiene-3,5-dion 14

Curcumin (200 mg, 0.54 mmol) was dissolved in 100 mL of dry acetone, mixed with acetic anhydride (83 mg, 0.82 mmol) was mixed together. 10 mg of sodium acetate (0.12 mmol) was added. The mixture was stirred at 50 °C for 15 min. The reaction progress was monitored by TLC experiments. After completion of the reaction, the product was poured into 20 mL CH\textsubscript{2}Cl\textsubscript{2} and washed with water for several times. Then
the product was dried with anhydrous MgSO$_4$. The crude product was purified by flash column chromatography (CH$_2$Cl$_2$/hexane=70:30). 65 mg (29%) Toluene/cyclohexane was used to recrystallize the product and yellow crystal was obtained. mp 81.8-82.4 °C; IR (KBr) 2850, 1780, 1640, 1600, 120, 1475, 1450, 1375, 1200, 960 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): δ 7.54 (d, 1H, J = 15.78 Hz), 7.53 (d, 1H, J = 15.84 Hz), 6.84-7.10 (m, 6H), 6.48 (d, H, J = 15.9), 6.43 (d, 1H, J = 15.84 Hz), 5.76 (s, 1H), 3.84 (s, 3H), 3.81 (s, 3H), 2.26 (s, 3H). Anal. Calc. for C$_{23}$H$_{22}$O$_7$: C, 67.31; H, 5.40. Found: C, 67.00; H, 5.87.

The $^1$H NMR and IR spectra of 14 are given in the Appendix on pages 70 and 78.

4. Synthesis of (1E, 6E)-1-(4’-acetoxy-3’-methoxyphenyl)-7-(4’’)-(4’’’- Chloromethylbenzoyloxy-3’’’-methoxyphenyl)-1,6-heptadiene-3,5-dion 15

A mixture of monoacetyl curcumin (25 mg, 0.06 mmol), 4-(chloromethyl)benzoic anhydride (30 mg, 0.09 mmol) was mixed together and dissolved in 5 mL of dry acetone. One drop of pyridine was added. The mixture was stirred for 1.5 h at 50 °C. The reaction progress was monitored by TLC experiments. After completion of the reaction, the product was poured into water. After 2 mL CH$_2$Cl$_2$ was added, the solution was washed three times with water and dried over anhydrous MgSO$_4$. After filtration and concentration of the solution, the residue was purified by column chromatography on silica gel (CH$_2$Cl$_2$/hexane=70:30). 31 mg (90%)

Toluene/cyclohexane was used to recrystallize the product and yellow crystal was obtained. mp 83.9-84.3 °C; IR (KBr) 2850, 1750, 1640, 1600, 1475, 1450, 1375, 1200,
$\nu\text{-}1100, 980, 730 \text{ cm}^{-1}$. $^1\text{H NMR (300 MHz, CDCl}_3\text{): } \delta 8.12(\text{d, 2H, } J=8.13) 7.58(\text{d, 1H, } J=15.78), 7.56(\text{d, 1H, } J=15.78), 7.46(\text{d, 2H, } J=8.19), 6.98-7.13(\text{m, 6H}), 6.53(\text{d, 1H, } J=15.81), 6.50(\text{d, 1H, } J=15.81), 5.80(\text{s, 1H}), 4.58(\text{s, 2H}), 3.81(\text{s, 3H}), 3.79(\text{s, 3H}), 2.26(\text{s, 3H}).$ Anal. Calc. for C$_{31}$H$_{27}$ClO$_8$: C, 66.13; H, 4.83. Found: C, 65.74; H, 5.00.

The $^1\text{H NMR and IR spectra of 15 are given in the Appendix on pages 71 and 79.}$

5. Synthesis of (1E, 6E)-1-((4'-acetoxy-3'-methoxyphenyl)-7-((4'')-(4''')-methylbenzoyloxy-3''-methoxyphenyl)-1,6-heptadiene-3,5-dion 16

A mixture of pure monoacetyl curcumin (25 mg, 0.06 mmol), 4-toluic anhydride (23 mg, 0.09 mmol) was mixed together and dissolved in 5 mL of dry acetone. One drop of pyridine was added. The mixture was stirred for 1.5 h at 50 °C. The reaction progress was monitored by TLC experiments. After completion of the reaction, the product was poured into water. After 2 mL CH$_2$Cl$_2$ was added, the solution was washed three times with water and dried over anhydrous MgSO$_4$. After filtration and concentration of the solution, the residue was purified by column chromatography on silica gel (CH$_2$Cl$_2$/hexane=70:30). 28 mg (87%)

Toluene/cyclohexane was used to recrystallize the product and yellow crystal was obtained. mp 87.4-87.8 °C; IR (KBr) 2880, 2360, 1760, 1640, 1600, 1520, 1475, 1280, 1200, 1100, 1080 cm$^{-1}$. $^1\text{H NMR (300 MHz, CDCl}_3\text{): } \delta 8.02(\text{d, 2H, } J=8.22), 7.58(\text{d, 1H, } J=15.81), 7.56(\text{d, 1H, } J=15.75), 7.23(\text{d, 2H, } J=8.07), 6.98-7.13(\text{m, 6H}), 6.53(\text{d, 1H, }$
J=15.81), 6.50(d, 1H, J=15.81), 5.80(s, 1H), 3.82(s, 3H), 3.79(s, 3H), 2.39(s, 3H), 2.26(s, 3H) Anal. Calc. for C\textsubscript{31}H\textsubscript{28}O\textsubscript{8}: C, 70.44; H, 5.34. Found: C, 70.42; H, 5.46.

The \textsuperscript{1}H NMR and IR spectra of 16 are given in the Appendix on pages 72 and 80.

6. Synthesis of (1E, 6E)-1-(4’-acetoxy-3’-methoxyphenyl)-7-(4”’-(4”’’-benzoyloxy-3’’’-methoxyphenyl)-1,6-heptadiene-3,5-dion 17

A mixture of pure monoacetyl curcumin (25 mg, 0.06 mmol), benzoic anhydride (21 mg, 0.09 mmol) was mixed together and dissolved in 5 mL of dry acetone. One drop of pyridine was added. The mixture was stirred for 1.5 h at 50 °C. The reaction progress was monitored by TLC experiments. After completion of the reaction, the product was poured into water. After 2 mL CH\textsubscript{2}Cl\textsubscript{2} was added, the solution was washed three times with water and dried over anhydrous MgSO\textsubscript{4}. After filtration and concentration of the solution, the residue was purified by column chromatography on silica gel (CH\textsubscript{2}Cl\textsubscript{2}/hexane=70:30). 28 mg (89%)

Toluene/cyclohexane was used to recrystallize the product and yellow crystal was obtained mp 102.8-103.2 °C; IR (KBr) 2860, 2360, 1760, 1640, 1600, 1500, 1475, 1450, 1375, 1260, 1200, 1100 cm\textsuperscript{-1}. \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): δ 8.14(d, 2H, J=7.14), 7.59(d, 1H, J=15.84), 7.56(t, 1H) 7.56(d, 1H, J=15.78), 7.45(t, 2H), 6.98-7.14(m, 6H), 6.53(d, 1H, J=15.81), 6.50(d, 1H, J=15.84), 5.80(s, 1H), 3.82(s, 3H), 3.75(s, 3H), 2.26(s, 3H) Anal. Calc. for C\textsubscript{30}H\textsubscript{26}O\textsubscript{8}: C, 70.03; H, 5.40. Found: C, 68.79; H, 5.15.

The \textsuperscript{1}H NMR and IR spectra of 17 are given in the Appendix on pages 73 and 81.
7. Synthesis of (1E, 6E)-1,7-Bis(4’-(4”-benzoyloxy-3’-methoxyphenyl)-1,6-heptadiene-3,5-dion 18

A mixture of pure curcumin (25 mg, 0.07 mmol), benzoic anhydride (46 mg, 0.20 mmol) was mixed together and dissolved in 5 mL of dry acetone. One drop of pyridine was added. The mixture was stirred for 1.5 h at 50 °C. The reaction process was monitored by TLC experiments. After completion of the reaction, the product was poured into water. After 2 mL CH₂Cl₂ was added, the solution was washed three times with water and dried over anhydrous MgSO₄. After filtration and concentration of the solution, the residue was purified by column chromatography on silica gel (CH₂Cl₂/hexane=70:30). 29 mg (82%)

Toluene/cyclohexane was used to recrystallize the product and yellow crystal was obtained mp 215.9-216.3 °C; IR (KBr) 2880, 2370, 1760, 1680, 1600, 1500, 1475, 1250, 1200, 1100, 760 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ 8.14(d, 2H, J=7.14), 7.60(m, 1H), 7.57(d, 2H, J=15.78), 7.45(t, 2H), 7.11-7.14(m, 6H), 6.53(d, 2H, J=15.84), 5.82(s, 1H), 3.82(s, 3H). Anal. Calc. for C₃₅H₂₈O₈: C,72.91, H, 4.89. Found: C, 72.88; H, 4.82.

The ¹H NMR and IR spectra of 18 are given in the Appendix on pages 74 and 82.

8. Synthesis of (1E, 6E)-1,7-Bis(4’-(4”-chloromethylbenzoyloxy-3’-methoxyphenyl)-1,6-heptadiene-3,5-dion 19

A mixture of pure curcumin (25 mg, 0.07 mmol), 4-(chloromethyl)benzoic anhydride (65 mg, 0.20 mmol) was mixed together and dissolved in 5 mL of dry acetone.
One drop of pyridine was added. The mixture was stirred for 1.5 h at 50 °C. The reaction process was monitored by TLC experiments. After completion of the reaction, the product was poured into water. After 2 mL CH$_2$Cl$_2$ was added, the solution was washed three times with water and dried over anhydrous MgSO$_4$. After filtration and concentration of the solution, the residue was purified by column chromatography on silica gel (CH$_2$Cl$_2$/hexane=70:30). 39 mg (85%)

Toluene/cyclohexane was used to recrystallize the product and yellow crystal was obtained mp 181.7-182.1°C; IR (KBr) 2880, 2380, 1740, 1680, 1600, 1500, 1475, 1250, 1200, 650 cm$^{-1}$. $^1$H NMR (300 MHz, CDCl$_3$): δ 8.14 (d, 4H, J = 8.37 Hz), 7.57 (d, 2H, J = 15.81 Hz), 7.47 (d, 4H, J = 8.4 Hz), 7.11-7.14 (m, 6H), 6.51 (d, 2H, J = 15.81 Hz), 5.82 (s, 1H), 4.59 (s, 4H) 3.80 (s, 6H). Anal. Calc. for C$_{37}$H$_{30}$Cl$_2$O$_8$: C, 65.98; H, 4.49. Found: C, 65.85; H, 4.87.

The $^1$H NMR and IR spectra of 19 are given in the Appendix on pages 75 and 83.

9. **Synthesis of (1E, 6E)-1-(4'-acetoxy-3'-methoxyphenyl)-7-(4''-(4''''-methylbenzoatemethoxy-3'''-methoxyphenyl)-1,6-heptadiene-3,5-dion 22**

A mixture of pure monocurcumin ether (1,6-Heptadiene-1-[3-methoxy-4-(4-methylbenzoate-methoxy)]-7-(4-hydroxy-3-methoxyphenyl)- 3,5-dion) (50 mg, 0.10 mmol), acetic anhydride (15 mg, 0.15 mmol) and sodium acetate(5 mg) was dissolved in 5 mL of dry acetone. The mixture was stirred for 1.5 h at 50 °C. The reaction process was monitored by TLC experiments. After completion of the reaction, the product was poured into water. Adding of 2 mL CH$_2$Cl$_2$, the solution was washed three times with
water and dried over anhydrous MgSO$_4$. After filtration and concentration of the solution, the residue was purified by column chromatography on silica gel (CH$_2$Cl$_2$/hexane=70:30). 48mg (88%)

Toluene/cyclohexane was used to recrystallize the product and yellow crystal was obtained. mp 158.8-159.2°C; IR (KBr) 2880, 2380, 1780, 1720, 1680, 1640, 1500, 1475, 1280, 1200, 1120 and 720 cm$^{-1}$. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.97 (d, 2H, J = 8.4 Hz), 7.53 (d, 2H, J = 15.87 Hz), 7.42 (d, 2H, J = 8.43 Hz), 6.75-7.09 (m, 6H), 6.47 (d, 1H, J = 15.75 Hz), 6.43 (d, 1H, J = 15.72 Hz), 5.76 (s, 1H), 5.18(s, 2H), 3.88(s, 3H), 3.84(s, 3H), 3.81(s, 3H), 2.26(s, 3H). Anal. Calc. for C$_{32}$H$_{30}$O$_9$: C, 68.81; H, 5.41. Found: C, 68.64; H, 5.75.

The $^1$H NMR and IR spectra of 22 are given in the Appendix on pages 76 and 84.

10. Synthesis of (1E, 6E)-1-(4'-acetoxy-3'-methoxyphenyl)-7-(4''-(4''''-methylbenzoatemethoxy-3''''-methoxyphenyl)-1,6-heptadiene-3,5-dion 23

A mixture of pure monocurcumin ether (1,6-Heptadiene-1-[3-methoxy-4-(4-methylbenzoate-methoxy)]-7-(4-hydroxy-3-methoxyphenyl)-3,5-dion) (50 mg, 0.01 mmol), acetic 4-chloromethylbenzoic anhydride (47 mg, 0.15 mmol) was dissolved in 5 mL of dry acetone. One drop of pyridine was added. The mixture was stirred for 1.5 h at 50 °C. The reaction process was monitored by TLC experiments. After completion of the reaction, the product was poured into water. After 2 mL CH$_2$Cl$_2$ was added, the solution was washed three times with water and dried over anhydrous MgSO$_4$. After filtration and
concentration of the solution, the residue was purified by column chromatography on silica gel (CH$_2$Cl$_2$/hexane=70:30). 55mg (85%)

Toluene/cyclohexane was used to recrystallize the product and yellow crystal was obtained. Toluene/cyclohexane was used to recrystallize the product and yellow crystal was obtained. mp 189.2-189.6°C; IR (KBr) 2880, 2380, 1780, 1700, 1680, 1550, 1500, 1250, 1180, 1080, 1000, and 760 cm$^{-1}$. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 8.14(d, 2H, J=8.31), 7.98(d, 2H, J=8.34), 7.57 (d, 2H, J = 15.84 Hz), 7.54(d, 2H, J=15.87), 7.47 (d, 2H, J =8.58 Hz), 7.43(d, 2H, J=4.62), 6.76-7.13(m, 6H), 6.50 (d, 2H, J = 15.81 Hz), 6.44 (d, 2H, J = 15.81 Hz), 5.78 (s, 1H), 5.18(s, 2H), 4.58(s, 2H) 3.88(s, 3H), 3.84(s, 3H), 3.81(s, 3H). Anal. Calc. for C$_{38}$H$_{33}$ClO$_9$: C, 68.21; H, 4.97. Found: C, 68.00; H, 5.00.

The $^1$H NMR and IR spectra of 23 are given in the Appendix on pages 77 and 85.
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Figure 32. 300 MHz 1H NMR spectrum of (1E, 6E)-1-(4’-acetoxy-3’-methoxyphenyl)-7-(4’’-hydroxy-3’’-methoxyphenyl)-1,6-heptadiene-3,5-dion 14
Figure 33. 300 MHz 1H NMR spectrum of (1E, 6E)-1-(4'-acetoxy-3'-methoxyphenyl)-7-(4''-(4'''-Chloromethylbenzoyloxy-3'''-methoxyphenyl)-1,6-heptadiene-3,5-dion 15
Figure 34. 300 MHz 1H NMR spectrum of (1E, 6E)-1-(4'-acetoxy-3’-methoxyphenyl)-7-(4''-(4'''-methylbenzoyloxy-3''-methoxyphenyl)-1,6-heptadiene-3,5-dion 16
Figure 35. 300 MHz 1H NMR spectrum of (1E, 6E)-1-(4'-acetoxy-3'-methoxyphenyl)-7-(4''-(4''''-benzoyloxy-3''''-methoxyphenyl)-1,6-heptadiene-3,5-dion 17

Offset: 15.79 ppm.
Figure 36. 300 MHz 1H NMR spectrum of (1E, 6E)-1,7-Bis(4’-(4''-benzoyloxy-3’-methoxyphenyl)-1,6-heptadiene-3,5-dion 18
Figure 37. 300 MHz 1H NMR spectrum of (1E, 6E)-1,7-Bis(4’-(4’’-Chloromethyl)benzoyloxy-3’-methoxyphenyl)-1,6-heptadiene-3,5-dion 19
Figure 38. 300 MHz 1H NMR spectrum of (1E, 6E)-1-(4'-acetoxy-3''-methoxyphenyl)-7-(4'''-methylbenzoatemethoxy-3'''-methoxyphenyl)-1,6-heptadiene-3,5-dion 22
Figure 39. 300 MHz 1H NMR spectrum of (1E, 6E)-1-(4’-acetoxy-3’-methoxyphenyl)-7-(4’’-(4’’’-methylbenzoatemethoxy-3’’’-methoxyphenyl)-1,6-heptadiene-3,5-dion 23
Figure 40. FT-IR spectrum of (1E, 6E)-1-(4’-acetoxy-3’-methoxyphenyl)-7-(4’’-hydroxy-3’’-methoxyphenyl)-1,6-heptadiene-3,5-dion 14
Figure 41. FT-IR spectrum of (1E, 6E)-1-(4'-acetoxy-3'-methoxyphenyl)-7-(4'')-(4'''-Chloromethylbenzoyloxy-3'''-methoxyphenyl)-1,6-heptadiene-3,5-dion 15
Figure 42. FT-IR spectrum of (1E, 6E)-1-(4'-acetoxy-3'-methoxyphenyl)-7-(4'"- (4'''-methylbenzoyloxy-3'''-methoxyphenyl)-1,6-heptadiene-3,5-dion 16
Figure 43. FT-IR spectrum of 1E, 6E)-1-(4’-acetoxy-3’-methoxyphenyl)-7-(4’’-(4’’’-benzoyloxy-3’’’-methoxyphenyl)-1,6-heptadiene-3,5-dion 17
Figure 44. FT-IR spectrum of (1E, 6E)-1,7-Bis(4′-(4″'-benzoyloxy-3″'-methoxyphenyl)-1,6-heptadiene-3,5-dion 18
Figure 45. FT-IR spectrum of (1E, 6E)-1,7-Bis(4’-(4’’-Chloromethyl)benzoyloxy-3’-methoxyphenyl)-1,6-heptadiene-3,5-dion 19
Figure 46. FT-IR spectrum of 1E, 6E)-(4’-acetoxy-3’-methoxyphenyl)-7-(4”’-(4”’’-methylbenzoatemethoxy-3’’’-methoxyphenyl)-1,6-heptadiene-3,5-dion
Figure 47. FT-IR spectrum of $(1E, 6E)-1-(4'-acetoxy-3'-methoxyphenyl)-7-(4''-(4'''-methylbenzoatemethoxy-3''-methoxyphenyl)-1,6-heptadiene-3,5-dion$ 23