Synthesis of 2-oxo-16-(3', 4'-methylenedioxyphenyl)-trans-15-hexadecene

Adelajda Zorba
Colby College

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Synthesis of 2-oxo-16-(3', 4'-methylenedioxyphenyl)-trans-15-hexadecene

By Adelajda Zorba

A Thesis Presented to the Department of Chemistry, Colby College, Waterville, ME
In Partial Fulfillment of the Requirements for Graduation With Honors in Chemistry

Submitted May, 2006
Synthesis of 2-oxo-16-(3', 4'-methylenedioxyphenyl)-trans-15-hexadecene

By Adelajda Zorba

Approved:

(Mentor, Dasan M. Thamattoor, Associate Professor of Chemistry)

Date

(Reader, Thomas Shattuck, Professor of Chemistry)

Date
Adelajda Zorba was born in Durrës, Albania on July 27, 1984 to Ali Zorba and Luiza Omari. In primary school Adelajda reluctantly committed to memory the standard communist verses that praised the leader of the country the same way she tried to resist studying Italian and English a few years later. These languages later became the secret means of communication with her sister, Anjeza, and brother, Ardit, and urged Adelajda to study French and Spanish in high school.

After the second year of study at the Gjergj Kastrioti High School, Adelajda took part in a national competition where she was ranked first and was offered a scholarship for the Armand Hammer United World College in Montezuma, NM. The liberal arts education offered in US colleges appealed to Adelajda who entered Colby College on a Davis Scholarship. Despite her initial interest in languages and International Studies, she devoted herself to Chemistry being inspired by her organic chemistry professor Dasan Thamattor. She began research with Prof. Thamattoor the summer after her first year. Her passion for research urged her to intern in different laboratories around the world – The Pasteur Institute (Paris, France), Cambridge University (Cambridge, UK) and University of Tsukuba (Tsukuba, Japan) – where she worked on structural biology, organic chemistry and molecular biology projects.

In August 2006, Adelajda will attend the University of Pittsburgh as a Molecular Biophysics and Structural Biology PhD candidate.
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I also thank the Davis family for generously providing the funds for my college education and for allowing me to spend four wonderful years at Colby.

Lastly, I would like to thank my family and friends whose smiles and good words, especially this past year, have made my work in lab enjoyable and rewarding.
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ABSTRACT

This work presents the progress made towards synthesizing 2-oxo-16-(3', 4' - methylenedioxyphenyl)-trans-15-hexadecene, an antimycobacterial compound that was originally isolated from the leaves of Piper Sanctum. The hydrocarbon chain of the molecule was synthesized first by opening a 15-pentadecanolactone ring by means of HI, and performing an E2 elimination reaction on the molecule followed by an organolithium reaction with CH₃Li. Hexadec-15-en-2-one that was afforded this way was later reacted with 5-bromobenzo[d][1,3]dioxole following the appropriate Heck reaction protocol that allows for the formation of a palladium catalyzed carbon-carbon bond.

The modes of action of 2-oxo-16-(3', 4' - methylenedioxyphenyl)-trans-15-hexadecene are comparable to the ones of rifampicin, a marketable drug that has been successfully used in the treatment of tuberculosis in the past. Additionally, this compound can serve as an intermediate towards the synthesis of 2-oxo-16-(3', 4' - methylenedioxyphenyl)-hexadecane and 2-oxo-14-(3', 4' - methylenedioxyphenyl)-tetradecane, both strong inhibitors of the growth of Mycobacterium tuberculosis. Lastly, due to Multi-Drug Resistant tuberculosis, there has been an increasing need to find alternative cures for tuberculosis. Therefore, the work on 2-oxo-16-(3', 4' - methylenedioxyphenyl)-trans-15-hexadecene is not only chemically interesting but it is also biologically important.
INTRODUCTION

In 2004, the World Health Organization and the International Union Against Tuberculosis and Lung Disease reported multiple cases of patients suffering from Multi-Drug Resistant tuberculosis (MDR TB), a form of tuberculosis that is resistant to two or more of the primary drugs used for the treatment of the disease. This report was the last of a series of comprehensive global surveys that monitored the spread of MDR TB in 77 different countries during the 1994-2002 periods. WHO expressed in this account its fears of a major MDR TB outbreak at a time when the number of immuno compromised, and thus MDR TB susceptible, people is continuously increasing. Hence, several studies were conducted on the mode of action and prevention of MDR TB.

Tuberculosis is caused by *Mycobacterium tuberculosis*, an aerobic bacterium of the genus *Mycobacterium* that has a distinctly rod-like, slender shape (figure 1). A strain of MDR TB originally develops when a case of drug-susceptible tuberculosis is improperly or incompletely treated. This occurs when a physician does not prescribe proper treatment regimens or when a patient is unable to adhere to therapy. In either case, improper treatment allows individual TB bacilli that have natural resistance to a drug to multiply. Eventually the majority of bacilli in the body are resistant. Once a strain of MDR TB develops it can be transmitted to others just like a normal drug-susceptible strain. Airborne transmission has been the cause of several well-publicized cases of nosocomial outbreaks of MDR TB in New York City and Florida. These outbreaks were responsible for the deaths of several patients and health care workers, a majority of whom were coinfecte...
In perspective, the deaths in New York City and Florida account for only a small number of the 4% of the world population that is presently infected with MDR TB. The number of hosts that are resistant to at least one anti-TB drug that is commercially available can be as high as 20% in the TB hotspots. Therefore, there is an urgent demand for effective solutions to the MDR TB problem.

There are currently two modes of action that can be taken: either use short-course chemotherapy (SCC) while testing the patient for the drugs he/she is resistant to, or develop a new drug that the bacilli has not yet been resistant to. In the first case, the short-course chemotherapy is similar to cancer therapy but it lasts for at least two years instead of six months and is thus very damaging to the patient. Hence, SCC is not a very desirable route of action against MDR TB. Similarly, tests to determine the resistance of a particular strain to various drugs are equally unattractive since they take several weeks to complete. During the delay the patient may be treated with a drug regimen that is ineffective and might cause further gain in immunity of the MDR TB strains. The success of this latter treatment

Figure 1. Scanning electron micrograph of *Mycobacterium tuberculosis.*
depends upon how quickly a case of TB is identified as drug resistant and whether an effective drug therapy is available. Hence, this method is very time and cost ineffective. On the other hand, the development of new anti TB drugs presents an efficient and long-term solution to the MDR TB problem.

In our lab we became interested in the chemical synthesis of antimycobacterial compounds recently isolated from the leaves and roots of *Piper Sanctum* and found to have anti-TB activity that is comparable to one of the TB drugs. Of the twenty-four compounds isolated from *Piper Sanctum*, we are aiming to synthesize only compounds 1, 2 and 3 since they can be prepared using fast, clean reactions and have shown significant antimycobacterial activity.

<table>
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<th>Cytotoxic activity (µg/mL)</th>
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<tr>
<td>2-oxo-16-(3’, 4’ - methylenedioxyphenyl)-trans-15-hexadecene (1)</td>
<td>32</td>
<td>N/D</td>
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<tr>
<td>2-oxo-16-(3’, 4’ - methylenedioxyphenyl)-hexadecane (2)</td>
<td>6.25</td>
<td>&gt;102</td>
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<tr>
<td>2-oxo-14-(3’, 4’ - methylenedioxyphenyl)-tetradecane (3)</td>
<td>6.25</td>
<td>&gt;102</td>
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*Figure 2. Antimycobacterial and cytotoxic activity of compounds 1, 2 and 3 isolated from *Piper Sanctum*.***
Compounds 2 and 3 are approximately 5 fold more powerful than compound 1 and their *M. tuberculosis* Growth Inhibition (MTGI) value of 6.25 μg/mL is comparable to the 0.25-μg/mL value of rifampicin, one of the commercially available anti-TB drugs. Additionally, compounds 2 and 3 show a cytotoxic activity that is comparable to and even slightly better than that of rifampicin (less than 102 μg/mL vs. 104.2 μg/mL). Furthermore, since compound 1 was synthesized in small amounts, its cytotoxic activity could not be determined. Lastly, the fact that these compounds are obtained from a plant that has traditionally been used in the treatment of tuberculosis is a good indication of their potential strength of becoming future anti-TB drugs. In fact, for centuries, the root and leaves of *Piper Sanctum* in Mexico were boiled and used as medicinal teas in the treatment of TB as well as stomach cramps, cough, bronchitis, asthma and colds.

We undertook two different synthetics routes for preparing compound 1. The first route (figure 3) involved the conversion of the commercially available 15-pentadecanolactone (4) to 15-iodopentadecanoic acid (5) in the presence of HI and acetic acid through a known procedure. An E2 type elimination in the presence of potassium tert-butoxide afforded pentadec-14-enoic acid (6) that was later reacted with methyllithium to yield hexadec-15-en-2-one (7). The final step that included the reaction of 7 with 5-bromobenzo[d][1,3]dioxole in the presence of a palladium catalyst aimed at preparing the final compound, 1. The compound thus produced could later be reduced to 2-oxo-16-(3', 4'-methylenedioxyphenyl)-hexadecane (2) in the presence of hydrogen and a palladium catalyst. 2-oxo-14-(3',4' - methylenedioxyphenyl)-tetradecane (3) could be produced in a similar way to 2; the only difference between the two compounds is that 3 lacks an extra C2H4 group that is present in 2.
Figure 3. First proposed synthetic route for the preparation of compound 1.
The second route (figure 4) involves the conversion of 15-pentadecanolacone to its corresponding methyl ester through the reaction of NaOCH₃ and MeOH. The product thus generated, 15-hydroxypentadecanoic acid methyl ester (8), can react with a dehydrating agent to yield pentadec-14-enoic acid methyl ester (9). Compound 9 can later on react with methyllithium in a way that is similar to the reaction of 7 (above) with MeLi. The ketone obtained this way can then undergo a Heck reaction in the presence of 5-bromobenzo[d][1,3]dioxole to yield compound 1. As it was mentioned above, compound 1 could easily afford 2 through a reduction in the presence of H₂ and a palladium catalyst.
Figure 4. Alternative synthetic route for the preparation of compound 1.
RESULTS AND DISCUSSION

ROUTE I

Step 1

Hydrolysis of lactone 1 to its corresponding carboxylic acid occurred in the presence of hydriodic acid and 57% acetic acid (the reaction scheme is shown below).

![Reaction Scheme]

**Figure 5.** Iodination of 15-pentadecanolactone (4).

After the mixture was refluxed for 6 hours, the organic acid and hydriodic acid were distilled to make it easier to separate the solvents from the organic layer. However, distillation proved to be ineffective since most of the product distilled off with the solvents.

To account for this problem, we used an alternative separation method: we added dilute
NaOH to the mixture hoping that an exposure to the alkaline environment would induce the formation of the salt of 5. Due to its long hydrocarbon chain, the salt of 5 did not dissolve in the aqueous layer and it was easily filtered and thus separated from the unreacted starting material. Subsequent acidification of the salt with dilute HCl gave rise to compound 5 at a significantly higher yield than the one previously achieved from distillation.

The organic solvent used during the work-up was ether. The work-up involved several washes of the organic layer with aqueous sodium thiosulfate pentahydrate (Na$_2$S$_2$O$_3$.5H$_2$O). Sodium thiosulfate is a colorless, crystalline compound that has traditionally been used in iodometry, a method of volumetric chemical analysis, a titration where the appearance or the disappearance of elementary iodine indicates the end point. $^9$ Na$_2$S$_2$O$_3$, quickly reduces iodine according to the following reaction.

$$I_2(g) + 2S_2O_3^{2-}(aq) \rightarrow 2 I(aq) + S_4O_6^{2-}(aq)$$

In a typical iodometry titration starch is initially added to form a blue complex with iodine that is later titrated with thiosulfate until the color vanishes. In Step 1, the presence of iodine, I$_2$, was observed by the purple color of the organic layer: when iodine crystals form they quickly sublime into gaseous iodine that has a distinctive purple color and does not dissolve in the aqueous layer. At first it seems like it would be hard to remove acetic acid from the organic layer. But, in fact, acetic acid is not even part of the organic layer, even though it is an organic compound. Being a polar protic solvent, acetic acid dissolves in water and is thus easily separated from the organic layer.

After addition of ether and the separation of the organic layers from HI and acetic acid, the combined organic extracts were dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. Recrystallization using a mixture of solvent
(ether:hexanes) was the suggested route towards product purification. However, because recrystallization had proven to yield low percent recovery and because the product had successfully been separated from unreacted starting material in the form of the 15-iodopentadecanoic salt, the recrystallization step was not carried out.

To successfully carry out the reaction of step 1, hydriodic acid is needed. HI, being a strong acid can easily open up the lactone ring and, being a strong leaving group, it can just as easily be removed from 5 to yield alkene 6 through an E2 elimination reaction. Hydriodic acid is the strongest among the common acids and was thus chosen as one of the reactants for the experiment. Despite the weak electronegativity of iodine, HI is a stronger acid than HCl or HBr because of the dispersal of the negative charge on iodide. Being a much larger atom than chloride, for example, the negative charge on iodide is spread over a much larger space, leading to a weaker interaction between the iodide and the proton. Hence, HI dissociates with greater ease that HCl and has a much higher pKa (-10). Additionally, the fact that HI is in a highly polar solvent such as acetic acid, leads to full ionization of the HI making iodide an excellent nucleophile in this S_N2 reaction. The percent yield for the reaction was 58%.
Figure 6. Elimination reaction of 15-iodopentadecanoic acid (5).

Compound 6 was obtained through addition of potassium tert-butoxide, KOTBu, to 5. THF was added to KOTBu and the reaction mixture was exposed to an argon atmosphere. The mixture thus obtained was cooled to 0°C and 15-iodopentadecanoic acid dissolved in dry ether was added to the flask. After one hour the ice bath was removed and the mixture was worked up. The combined organic layers were washed with water, brine and dried over anhydrous sodium sulfate. The solvents (ether and THF) were later removed under reduced pressure. This procedure allowed for a 67% yield.

Potassium tert-butoxide is a bulkier group than primary and secondary alkoxides. Due to steric reasons, (CH₃)₃COK is unable to attack 5 from the rear in an SN₂ fashion. However, the E2 reaction is relatively unhindered and takes precedence over the SN₂ reaction to
afford 6. Potassium tert-butoxide is thus the base of choice for this reaction since it demonstrates high specificity and selectivity for the E2 reaction.

Exposure of potassium tert-butoxide to atmospheric moisture deactivates the base. Potassium tert-butoxide reacts violently with the water and carbon dioxide in the air to afford potassium hydroxide, potassium carbonate and t-butanol that forms a cloudy solution in water. Hence, to retain the reactivity of (CH₃)₃COK, the solution medium should be exposed to a continuous atmosphere of inert gas, in our case, argon.
Step 3

\[
\text{CH}_3\text{Li deprotonation}
\]

\[
\text{addition}
\]

\[
\text{H}_3\text{O}^-/\text{H}_2\text{O}
\]

\[
\text{Hydrate}
\]

\[
\text{Ketone 7}
\]

**Figure 7.** Formation of hexadec-15-en-2-one (7).
Compound 6 was dissolved in ether and added to a flask that was previously under an argon atmosphere and cooled to 0°C. The inert atmosphere was maintained throughout the experiment. Drop wise addition of a little over 2 equivalents of methyllithium followed over a period of 20 minutes. The ice bath was removed 20 minutes after the completion of addition. The reaction mixture was allowed to stir overnight at room temperature.

The work-up involved addition of 12M HCl that helped dissolve the organic salt into the organic layer. The combined organic extracts dissolved in ether were washed with water and brine, dried over sodium sulfate and the solvent was removed under reduced pressure. To purify the product dilute NaOH was used to precipitate any starting material in the form of the salt of 6. The solid salt did not dissolve in the aqueous layer and was later removed through filtration, acidified and converted into 6 that was finally recycled in various reactions of step 3 and step 4. While the aqueous layer contained the salt of 6, the organic layer contained compound 7. After the standard separation procedures (washes with brine, use of anhydrous sodium sulfate and solvent removal) compound 7 was obtained, even though at a low yield of 18%.

The first step in the conversion of 6 to 7 was the formation of the carboxylate dianion (figure 7). One equivalent of MeLi was used to deprotonate the carboxylic acid and the second equivalent attacked the carbon at the carbonyl position thus generating a lithium salt of 6. MeLi was chosen because we needed a methyl group to be added to 6 and organolithium reagents have traditionally been used in the conversion of carboxylic acids to ketones. Excessive care was needed in avoiding exposure of MeLi to air. MeLi, being a very potent base, reacts violently with water to yield methane gas and lithium hydroxide according to the following equation:
\[
\text{CH}_3^- + \text{Li}^+ + \text{H}_2\text{O} \rightarrow \text{CH}_4 + \text{Li}^+ + \text{OH}^-
\]

Addition of aqueous HCl constituted the second step of the reaction. The hydrate thus produced had two strongly electronegative groups on a quaternary carbon and was thus unstable relative to the ketone.

An alternative route towards the production of 7 could be the conversion of 6 into pentadec-14-enoic chloride.\(^\text{10}\) The reaction of pentadec-14-enoic chloride with N,O-dimethylhydroxylammonium chloride could then afford the Weinreb Amide. Then MeLi is added. Once the organometallic adducts of the Weinreb amides are formed they are quite stable as it can be seen in figure 8. Finally, aqueous work-up would liberate the desired ketone (7).\(^\text{11}\)
Figure 8. Alternative synthetic route for the preparation of 7.
The palladium-catalyzed C-C coupling between aryl halides or vinyl halides and activated alkenes in the presence of a base is referred to as the "Heck Reaction". A schematic representation of the reaction mechanism is shown in figure 9.12

Figure 9. The mechanism of the Heck Reaction.12

The Heck reaction requires the presence of a palladium(0) catalyst (Pd(0)L₂) that is usually created in situ by the reduction of a palladium(II) compound Pd(II)X₂ by a ligand. This is followed by an oxidative addition of the palladium species into the aryl halide bond to form PdRXL₂. Afterwards, the activated aryl-Pd compound forms a π-complex with the alkene (in our case, the alkene could be either 6 or 7). Elimination follows this step that leads to the formation of the coupled product and the Pd(II) species that in turn is further reduced by a strong base to yield the Pd(0) species. This latter compound can enter the
cycle again and produce more of the coupled alkene product. The product is often the (E) isomer even though recent cases of the (Z) product have been reported.\textsuperscript{13} Hence, for the proper functioning of the Heck reaction, several compounds need to be present: an organopalladium catalyst, a halide or triflate group attached to an aryl, benzyl or vinyl compound, an alkene, a ligand and a strong base.

In this step we used two different procedures in order to couple the commercially available aryl bromide to either alkene 6 or 7. In the first case, Pd(OAc)\textsubscript{2} served as the catalyst, aryl bromide and 6 were the compounds that would be coupled, the solvent was acetonitrile and the base was CsCO\textsubscript{3}.\textsuperscript{14} All of the above compounds were added to the reaction mixture that was stirred at 100°C for 3 hours (figure 10).

![Figure 10. The Heck Reaction – first attempt.\textsuperscript{d}](image)

The work-up involved dilution with dichloromethane that was followed by several washes with brine. The combined organic layers, dissolved in ether, were dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure. A \textsuperscript{1}H NMR spectrum revealed that the final product was just a mixture of starting materials; the coupling had not occurred.
The second attempt towards producing 1 was reacting 7 with the aryl bromide following a procedure published in 2002. In this procedure Pd(OAc)$_2$ was again the catalyst, aryl bromide and 7 were the compounds that would be coupled, the base was triethylamine and the solvent medium was poly(ethylene glycol) (PEG). It is believed that PEG could serve as the ligand in this reaction. All of the above compounds were placed in a pressure vessel and heated at 80°C for 8 hours (figure 11).

\[
\begin{align*}
\text{7} & \quad \text{Pd(OAc)$_2$} & \quad \text{Et$_3$N} & \quad \text{PEG(1500), 80°C} \\
\end{align*}
\]

**Figure 11.** Second attempt at the Heck Reaction.

Initially, PEG with a molecular weight of 8000 g/mol was used as the solvent medium, but the reaction was unsuccessful. It was believed that a shorter polymer would be less viscous and would therefore allow for better mixing of the starting materials in solution. Hence, PEG of 1500 g/mol was used.

The work-up involved cooling the reaction down to 0°C in order to allow for PEG (1500) to precipitate out of solution. The liquid medium was then diluted with ether and washed with brine. The organic layer was dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure. The $^1$H NMR spectrum, however, showed that there was no coupled product present in the organic layer.

Final notes on this reaction regard the choice of the halide group on the aryl ring and the choice of the palladium catalyst. It was observed that the oxidative addition, the
first step of the Heck reaction (figure 9), proceeded at an accelerated rate when an electron withdrawing group was present on the aryl structure.\textsuperscript{13} We considered this fact while choosing a leaving group that had to be associated with the benzodioxole structure. Even though iodine is a better leaving group than bromine, 5-bromobenzo[d][1,3]dioxole was more readily available for purchase than the analogous iodine compound and was thus used in this experiment. Lastly, we were limited by the choice of the palladium catalyst. Most of the catalysts that were reported to have worked well in Heck couplings of linear alkenes and aryl halides were not available for purchase. Because of time constraints, it was not possible to synthesize these catalysts. Therefore, palladium acetate that was more readily available and had worked for some linear alkenes, was used in this experiment.
ROUTE II

The second synthetic route proved to be unsuccessful since several difficulties were faced while trying to synthesize 8. Because 8 was the first product in the chain of reactions that would eventually yield 1, none of the other reactions could be carried out. When trying to synthesize 8, it was not possible to find a solvent where the organic layer could fully dissolve. The first time the reaction was carried out, 8 (crude) was obtained at 42% yield. The second time we ran the reaction, it was not possible to successfully separate the organic and aqueous layers. In the interest of time it was decided to focus on route 1 and focus on route 2 at a later time.
CONCLUSION

We are one step away from successfully completing the synthesis of 1 (2-oxo-16-(3',4',methylenedioxyphenyl)-trans-15-hexadecene), a compound extracted from Piper Sanctum and found to have antimycobacterial activity. The first step of the synthesis involved the opening of 15-pentadecanolactone by means of HI in the presence of acetic acid. This was a previously known reaction and gave a 58% yield of the pure compound. The second step was an E2 type elimination with potassium tert-butoxide. The compound thus produced was pentadec-14-enoic acid (6) in a 67% yield. In the third step, 6 was reduced in the presence of methyllithium and gave rise to 7 in a 18% yield. The Heck reaction that followed used aryl halide and either 6 or 7 as the starting material. Two different reaction conditions were tested. In the first one, we reacted 5-bromobenzo[d][1,3]dioxole and 6 in the presence of Pd(OAc)$_2$, CsCO$_3$ and acetonitrile. The second attempt at synthesizing 1 aimed at coupling 5-bromobenzo[d][1,3]dioxole and 7 in the presence of Pd(OAc)$_2$, Et$_3$N and PEG(1500) or PEG(8000). Unfortunately, both attempts at the Heck coupling were unsuccessful.

Future work should therefore include the completion of the last step towards synthesizing 1 (2-oxo-16-(3',4',methylenedioxyphenyl)-trans-15-hexadecene). Once 1 is obtained, its more interesting derivatives, 2 and 3 could be obtained. These latter compounds have proven to be more powerful than 1 in inhibiting the growth of the tuberculosis bacterium. Compound 2 can be obtained by a simple hydrogenation of the alkene bond in 1. Meanwhile, compound 3, being 2 carbons shorter than 2, can be synthesized in a similar way to 2; this time a lactone that is 2 carbons less than 4 needs to be used.
MATERIALS AND METHODS

$^1$H NMR spectra were taken at 400MHz using a Bruker Avance 400 spectrometer. GC/MS analysis was performed on a Hewlett Packard 5890 Gas Chromatograph/5891 MSD; the GC part used a Supelco 2-4028 SPB-1 fused silica column measuring 30m x 0.25mm. IR spectra were recorded on a Mattson 4020 Galaxy series FT-IR (3500-400 cm$^{-1}$).

Preparation of 15-Iodopentadecanoic acid (5). 15-Pentadecanolactone (4) (10.1g, 42.0mmol) and 57% hydroiodic acid in water (3.5mL, 46.0mmol) and acetic acid (295mL) were added to a 500mL three-necked round-bottomed flask and refluxed for 6 hours. The color of the reaction went from bright yellow to brown to dark purple with reaction completion. The reaction mixture was dissolved in ether washed with anhydrous sodium thiosulfate. The combined organic layers were then dried over sodium sulfate. Purification of the final product involved the formation of the 15-iodopentadecanoic salt that precipitated into the solution as a white solid, insoluble in neither water nor ether. To this goal, 100mL of dilute 35%NaOH were added to the reaction mixture. The salt was then acidified, dissolved in ether and separated from the aqueous layer. The organic layer was dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. The residue gave 15-iodopentadecanoic acid (5) (8.9g, 58%) as a flaky white solid. mp 74-77°C; IR (some significant peaks) 2929, 1705 cm$^{-1}$; $^1$H NMR (CDCl$_3$) δ 12.18 (broad s, 1H), 3.13 (t, 2H), 2.30 (m, 2H), 1.29-1.86 (broad m, 24H); $^1$H NMR (DMSO) δ 11.98 (s, 1H), 3.23 (t, 2H), 2.18 (m, 2H), 1.7-1.8 (broad m, 2H), 1.2-1.5 (broad m, 22H); $^{13}$C NMR (CDCl$_3$) δ 178.7, 32.4, 31.9, 28.8, 27.9, 27.8, 27.7, 27.5, 27.3, 26.8, 23.0, 5.7.
Preparation of Pentadec-14-enoic acid (6). Potassium tert-butoxide (2.7 g, 23.0 mmol) was dissolved in dry tetrahydrofuran (165 mL) and added through a syringe to a 300 mL three-necked round-bottomed flask placed under an argon atmosphere. The mixture was cooled to 0°C. 15-Iodopentadecanoic acid (5) (4 g, 10.9 mmol) dissolved in dry ether (30 mL) was added through a syringe to the flask and the reaction mixture was left to stir for 15 minutes. The ice-bath was removed and the solution was then allowed to stir for 1 hour at room temperature. The color of the reaction went from colorless to milky white with reaction completion. The solution was diluted with ether, washed with water, and dried over sodium sulfate. The solvent was evaporated under reduced pressure and the residue gave pentadec-14-enoic acid (6) (1.75 g, 67%) as a flaky white solid, mp 54-65°C; IR (some significant peaks) 2931, 1713 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 12.18 (broad s, 1H), 5.82 (m, 1H), 5.07 (d of d, 1H), 5.02 (d of d, 1H), 2.30 (m, 2H), 2.18 (m, 2H), 1.29-1.52 (broad m, 20H); \(^1\)H NMR (DMSO) \(\delta\) 11.98 (s, 1H), 5.7-5.9 (m, 1H), 4.85-4.95 (d of d, 1H), 4.95-5.05 (d of d, 1H), 2.18 (m, 2H), 1.7-1.8 (broad m, 2H), 1.2-1.5 (broad m, 22H); \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 179.8, 139.3, 114.1, 34.0, 30.5, 29.2, 24.7, 7.4 (the last signal seems to come from some starting material, 5 impurity).

Preparation of Hexadec-15-en-2-one (7). Pentadec-14-enoic acid (6) (2.5 g, 10 mmol) dissolved in ether (50 mL) was added to a 200 mL three-necked round-bottomed flask placed under an argon atmosphere. Drop-wise addition of 1.6 M solution of MeLi (15 mL, 20 mmol) followed during the next 20 minutes, after the solution had cool down to 0°C. The ice-bath was removed and the solution was allowed to stir overnight. The color of the reaction went from colorless to milky white with reaction completion. The mixture was
acidified through the addition of 50mL of 12M HCl diluted in water. The organic layer was
separated from the aqueous layer through several washes with water and then it was dried
over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and the
residue gave hexadec-15-en-2-one (7) (480mg, 18%) as a flaky white solid, mp 46-60°C;
IR (some significant peaks) 2933, 1716 cm⁻¹ water is present, water peak is at 3439 cm⁻¹;
¹H NMR (CDCl₃) δ 5.82 (m, 1H), 5.07 (d of d, 1H), 5.02 (d of d, 1H), 2.38 (m, 2 H), 2.12
(s, 3H), 2.0-2.1 (m, 2H), 1.21-1.52 (broad m, 18H); ¹³C NMR (CDCl₃) δ 208.5, 138.2,
113.0, 61.9, 42.8, 32.8, 31.8, 28.4, 24.7, 23.4.

Preparation of 2-oxo-16-(3',4',methylenedioxyphenyl)-trans-15-hexadecene (1a)). To a
solution of 4-bromo-1, 2-(methylenedioxy)benzene (420mg, 2.1mmol) in acetonitrile
(6mL), CsCO₃ (290g, 0.9mmol), Pd(OAc)₂ (220mg, 0.1mmol) and pentadec-14-enoic acid
(6) (1g, 4.2mmol) were added. The reaction mixture was heated to 100°C for 3 hours while
being constantly exposed to an argon atmosphere. The work-up involved dilution of the
organic layer with dichloromethane and several washes with brine. The combined organic
layers were then dried over anhydrous magnesium sulfate and the solvent was removed
from the solution under reduced pressure. The ¹H NMR spectra showed that only starting
material was present.

Preparation of 2-oxo-16-(3',4',methylenedioxyphenyl)-trans-15-hexadecene (1). 4-
bromo-1,2-(methylenedioxy)benzene (210mg, 1mmol), poly(ethylene glycol) (PEG 1500)
(1.5g, 1mmol), Et₃N (104mg, 1mmol), Pd(OAc)₂ (290mg, 1mmol) and hexadec-15-en-2-one (7) (250mg, 0.9mmol) were all added to a pressure vessel and heated to 80°C for 15
hours. The reaction mixture was then cooled to 0°C to allow PEG to precipitate out and it was extracted with ether (3 x 10mL). However, further analysis showed that the desired product was not obtained.
REFERENCES


(2) Thakker, H.; Shah, J. R. “Multi-Drug Resistant Pulmonary Tuberculosis,” The Indian Journal of Tuberculosis 1998; 45 (131); 4-12.


$^{1}H$ NMR in DMSO
$^1$H NMR in DMSO

![NMR Spectrum](image)
$^{13}$C NMR in CDCl$_3$
$^{13}$C NMR in CDCl$_3$