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# A kinetic study of the elimination of various 1,2 diols

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**Abstract**

The cyclopropyl moiety is a useful structure for drug performance. In recent years, these structures have appeared in pharmaceuticals with greater frequency given benefits such as enhancing drug potency, increasing brain permeability, and reducting off-target defects. Cyclopropanone acetals provide a functional source of cycloproyl groups for incorporation into drugs and have been synthesized through the reaction of a dioxacarbene and an alkene. However, current dioxacarbenes are limited and rely on reactive precursors. The Corey-Winter olefination involves the conversion of a 1,2 diol to a thiocarbonate by thiocarbonyldiimidazole, followed by the elimination of the thiocarbonate by trimethylphosphite. The dioxacarbene is a hypothesized intermediate in the elimination, offering a dioxacarbene source to synthesize a cyclopropanone acetal.

The aim of this study was to synthesize a series of diols, convert them to carbonate or thiocarbonate, and compare their rates of elimination to infer the relative stability of the dioxacarbene intermediate. To synthesize the diols, a novel, green one-pot dihydroxylation of the alkenes of cinnamates was developed. Diols were synthesized with the addition of electron donating and electron withdrawing groups to observe their relative ability to stabilize a carbene intermediate. The reaction of carbonates and thiocarbonates with trimethylphosphite was monitored by GC/MS every 15 minutes and the abundance of product was plotted over time. Trendline slopes were compared and peliminary results of the elimination of 4-methoxy-5-(4-methylphenyl)-1,3-dioxolan-2-one and 4-methoxy-5-(4-methylphenyl)-1,3-dioxolan-2-thione suggest the thiocarbonate eliminates faster than the carbonate, with slopes of $1\times10^{7}$ and $3\times10^{6}$, respectively.

**Acknowledgements**

I would like to sincerely thank Dr. Timothy Troyer for granting me the freedom to be curious, make mistakes, and create a project that I am truly proud to take ownership of. I am deeply grateful for his intellectual guidance and ceaseless encouragement as my research advisor, academic advisor, and professor. I would also like to thank Dr. Peter Kuhlman as both my second reader and my first professor in the department. He is steadfast in his dedication to teaching others how to learn, and his CHEM 131 course was the inspiration for my pursuing the Biochemistry major.

I extend additional gratitude to the professors of the department, whether they served as educators or simply cheerleaders, as well as Dr. Quentin Cheek, Jodi Cambraia, and Cathy Romei. Finally, I would like to thank the RC & EM Miller Summer Scholars Endowment, J.R. & P.V. Anderson Endowment, and the Lisska Center for funding this project as well as the Department of Chemistry and Biochemistry at Denison University for the opportunity to hone my skills as a learner, a researcher, and a scientist.

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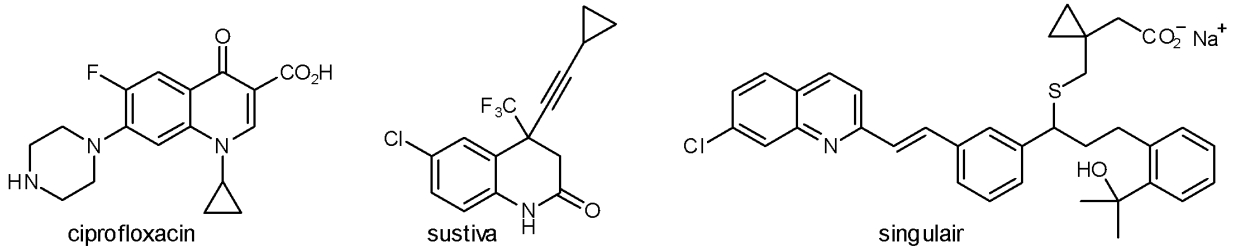
## GENERAL INTRODUCTION

Prescription drug spending per capita is greater in the United States than any other country.[1] One of the contributing factors to the high cost of prescription drugs is the high cost associated with drug development. Developing novel methodlogies for drug manufacturing can contribute to lowered cost of prescriptions. Moreover, developing diverse arrays of medicinal compounds can lead to more specialized treatment. The cyclopropyl moiety is useful for drug performance. In recent years, cyclopropyl rings have been incorporated into pharmaceuticals with greater frequency. The coplanarity of the carbon atoms, shorter and stronger C-C and C-H bonds compared to alkanes, and pi-bond character of the C-C bonds contribute to the usefulness of these structures. Benefits of incorporating cyclopropyl rings include enhancing drug potency, reduction of off-target defects, increasing brain permeability, and increasing metabolic stability[2]. Cyclopropyl groups are found in several currently marketed drugs including the antibiotic Ciproflaxin, the antiviral Sustiva, and the asthma treatment Singulair (Figure 1).

**Figure 1.** Currently marketed drugs which contain a cycopropyl group.

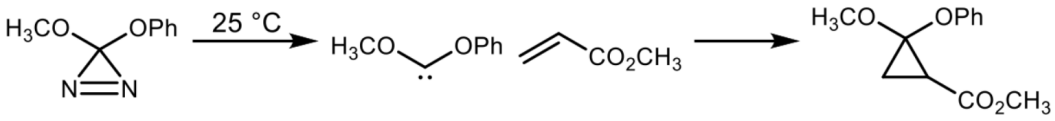



However, cyclopropanes present drawbacks of high cost and a relatively small array of variants. Cyclopropanone acetals are a functional and desirable alternative given the reactivity of ketones to synthesize cyclopropanes containing substituents. This presents an avenue for creating novel medicinal compounds.

[1] Kesselheim A.S.; Avorn J.; Sarpatwari A. *JAMA*. **2016**, *32,* 858-71
[2] Talele, T. T. *J. Med. Chem.* **2016** 59 (19), 8712-8756

The reaction of carbenes with alkenes is well known[3]. A study by Moss reports successfully synthesizing a cyclopropenone acetal through the reaction of a dioxacarbene with an olefin (scheme 1).[4]

**Scheme 1.** Moss's synthesis of cyclopropanone acetal through a dioxacarbene and olefin.

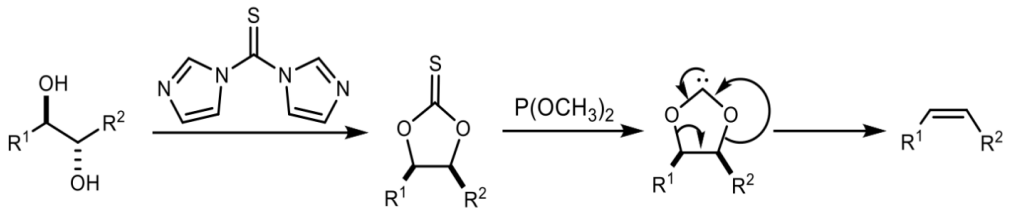



Another study by Warkentin prepared 2,5-dihydro-1,3,4-oxadiazoles to afford a dioxacarbene.[5] However, these current dioxacarbenes are limited and derived from highly reactive precursors. A refined synthesis of a dioxacarbene is desired before proceeding in any attempt to synthesize the cyclopropenone acetal. Developing a new synthetic methodology for the dioxacarbenes can lead to a safer, more reliable, and more accessible procedure, potentially resulting in a larger array of compounds.

The Corey-Winter olefination (scheme 2) involves the conversion of a vicinal diol to a thiocarbonate by thiocarbonyldiimidazole, followed by the elimination of the thiocarbonate to an olefin by trimethylphosphite.[6] The dioxacarbene is a hypothesized intermediate in the elimination of the thiocarbonate, based on reaction outcome and presents a potential source of a dioxacarbene for use in the synthesis of the cyclopropenone acetal.

[3] Harvey, D.F.; Sigano, D.M. *Chem. Rev.* **1996**, *96* (1), 271-288.
[4] Moss, R.A.; Wlostowski, M.; Terpinksi, J.; Kmiecik-Lawrynowicz, G.; Krogh-Jerpersen, K. *J. Am. Chem. Soc.* **1987** *109,* 3811-3812.
[5] Warkentin, J. *Acc. Chem. Res.* **2009**, *42*, 205-212.
[6] Corey, E. J.; Winter, Roland A. E. *J. Am. Chem. Soc.* **1963** *85* (17), 2677-2678.

**Scheme 2.** The Corey-Winter Olefination




A study by Horton found supporting evidence for the dioxacarbenene intermediate in the Corey-Winter olefination, when using a thiocarbonate that cannot eliminate resulted in dimerization.[7] There is no record of others attempting to trap and exploit the dioxacarbene from the Corey-Winter olefination for use.

The evidence for a carbene intermediate in the Corey-Winter olefination, as well as the subsequent reaction of a carbene with an olefin to yield a cyclopropanone acetal is underwhelming and circumstantial, supported only by singular examples in each case. The Troyer group hopes to develop a reliable synthesis for a series of cyclopropanone acetals by trapping and reacting the dioxacarbene intermediate with an alkene.

## PROJECT INTRODUCTION

Previous work has focused on using 2,2-dimethyl-3-phenyl-1,3-propanediols, which cannot eliminate, to form the dioxacarbene. The dioxacarbene has not been observed thus far. However, phosphorus-NMR has indicated formation of the phosphonate when trimethylphosphite is reacted with carbonates and thiocarbonates which confirms reaction of the phosphite with the carbonate or thiocarbonate. By shifting the focus to diols that can eliminate to form the olefin, a study of the kinetics of elimination can provide insight into the relative stability

[7] Horton, D.; Tindall, C. G. *J. Org. Chem.* **1970**, *35*, 3558-3559.

of their dioxacarbenes. Diols with slower eliminations suggest a more stable dioxacarbene that may be better able to react with the olefin. In turn, a kinetic study will inform the design of the carbonates, thiocarbonates, and alkenes used to attempt the synthesis of the cyclopropanone acetal. The focus of this senior research project is to synthesize a series of 1,2-diols, convert them to carbonates and thiocarbonates, and study the kinetics of their elimination with the addition of trimethylphosphite.

To design and synthesize the diols, we planned to develop a new procedure for the dihydroxylation of alkenes of methyl cinnamates. The dihydroxylation of alkenes is a well-established procedure. The Sharpless asymmetric dihydroxylation is perhaps the most prominent, as it is enantioselective in producing vicinial diols.[8] However, the use of toxic osmium makes it undesirable due to environmental cost. [9] The procedure has also shown to be less effective on cis olefins. Less toxic procedures have been developed without osmium but rely on other metals including iron[10] and manganese[11]. In recent years, metal-free dihydroxylation procedures have been developed. These procedures present drawbacks, however, using peroxides, diselenides[12], and iodine. Furthermore, there are still a limited number of metal-free procedures available. We sought to develop a metal-free, green dihydroxylation of alkenes at lower cost to synthesize the diols for this kinetic study. Additionally, we did not need our procedure to be enantioselective. To synthesize the diols, we planned to first convert the alkene of the methyl cinnamate to a bromohydrin by *N*-Bromosuccinimide in water. From there, we hoped to develop a new synthetic methodology to hydrolyze the bromohydrin to the diol.

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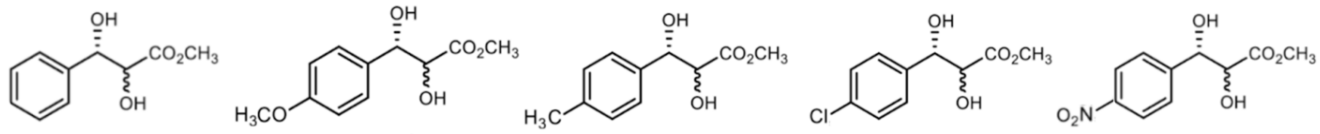
[8] Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, 94, 2483-2547.
[9] Wang, L.; Sharpless, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 7568-7570.
[10] Costas, M.; Tipton, A. K.; Chen, K.; Jo, D.-H.; Que, L., Jr. *J. Am. Chem. Soc*. **2001**, *123*, 6722.
[11] de Boer, J. W.; Browne, W. R.; Harutyunyan, S. R.; Bini, L.; Tiemersma-Wegman, T. D.; Alsters, P. L.; Hage, R.; Feringa, B. L. *Chem. Commun.* **2008**, *44*, 3747-3749.
[12] Santi, C.; Di Lorenzo, R.; Tidei, C.; Bagnoli, L.; Wirth, T. *Tetrahedron* **2012**, *68*, 10530-10535.

To study and attempt to control the elimination of the carbonates and thiocarbonates, the phenyl ring can be manipulated to be either electron donating or electron withdrawing. The electron donating or electron withdrawing character of the phenyl ring may ultimately contribute to the relative stability of the dioxacarbene intermediate.

**Figure 2.** Diols of methyl cinnamates with varying electron donating and electron withdrawing groups on the phenyl ring.



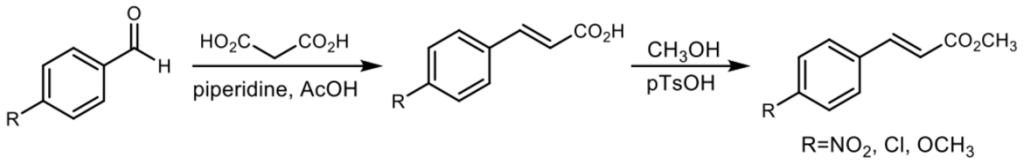

The diols for this project will be synthesized to include varying electron donating (methyl, methoxy) and electron withdrawing (chlorine, nitro) groups attached to the phenyl ring.

## EXPERIMENTAL

*Materials*

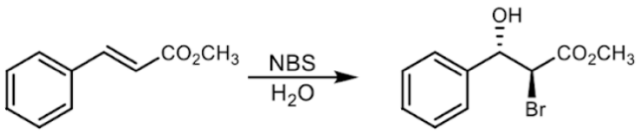
All reagents were purchased from Sigma-Aldrich.

*Synthesizing the methyl cinnamates*




The methyl cinnamates were synthesized using the Doebner-Verlag modification of the Knoevenagel condensation of malonic acids and a benzaldehyde.[13] All cinnamates and their derivatives were synthesized by Olivia R. Mahaffey.

*Synthesizing the bromohydrin*



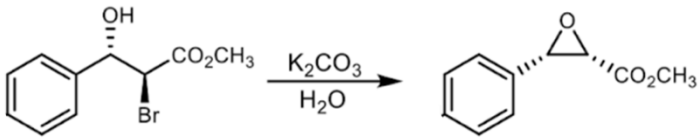

**Methyl-2-bromo-3-hydroxy-3-phenylpropanoate**

To a 250-mL flask, methyl *trans* cinnamate (10.5813 g, 65 mmol), *N*-Bromosuccinimide (11.5619 g, 65 mmol), and water (65 mL) was added. The reaction stirred at reflux for 16 hours. The aqueous layer was extracted 3 times with ethyl acetate, and the organic layer was dried with magnesium sulfate, gravity filtered, and condensed to afford an amber-colored oil (17.74 g, 105.4%).

[13] Stabile, R. G.; Dicks, A. P. *J. Chem. Ed.* **2004**, *81*, 1488-1491.

Data: $R_f$=0.77 (40% EtOAc/hexanes). $^1$H NMR (400 MHz, $CDCl_3$) 7.37-7.40 (m, 6 H), 5.10 (d, *J*= 8.0 Hz, 1 H), 4.40 (d, *J*=8.80 Hz, 1 H), 3.75 (s, 1 H).

*Synthesizing the epoxide*

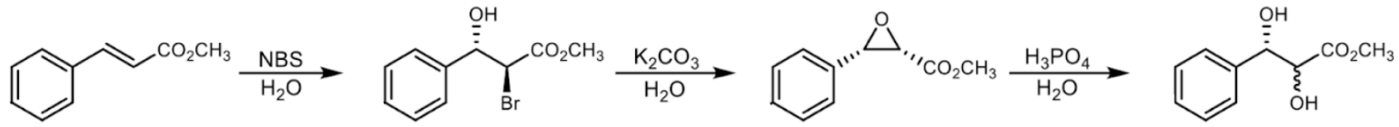



**Methyl 2-phenyloxirane-2-carboxylate**

To a 250 mL flask, Methyl 3-hydroxy-2-methyl-3-phenylpropanoate (5.1023 g. 20 mmol), potassium carbonate (2.7563 g, 20 mmol), acetonitrile (40 mL), and water (20 mL) was added. The reaction stirred at ambient temperature for 2 hours. The aqueous layer was extracted 3 times with ethyl acetate, dried with magnesium sulfate, gravity filtered, and condensed to afford an amber-colored oil. The epoxide was purified by silica gel column chromatography (2.2751 g, 71.23%).

Data: $R_f$=0.26 (2% $CH_2Cl_2$/methanol). $^1$H NMR (400 MHz, $CDCl_3$) 7.16-7.30 (m, 5 H), 4.01 (s, 1 H), 3.78 (s, 5 H), 3.42 (s, 1H).

*Synthesizing the diols*

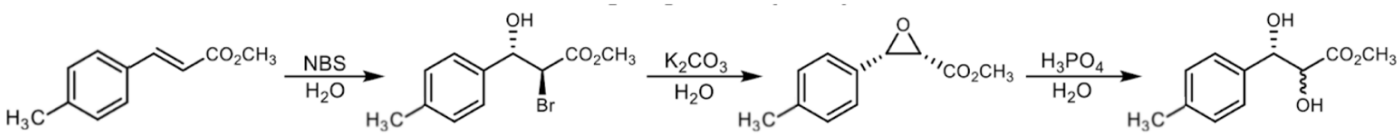



**Methyl 2,3-dihydroxy-3-phenylpropanoate**

To a 15-mL flask, methyl *trans* cinnamate (0.5627 g, 3.5 mmol) was added, with *N*-Bromosuccinimide (0.6245 g, 3.5 mmol) and water (3.5 mL). The reaction refluxed overnight

for 14 hours. The reaction was cooled to ambient temperature and potassium carbonate (0.5550 g, 3.5 mmol) was added to the flask, stirring. After 2 hours, 85% phosphoric acid (1.69 mL) was added, and the reaction stirred at ambient temperature for 2 hours. The aqueous layer was extracted 3 times with ethyl acetate and the organic layer was dried with magnesium sulfate, gravity filtered, and condensed to afford an amber-colored oil (0.8683 g, 127.6%). The diol was then purified by silica gel column chromatography (0.0969 g, 14.2%).

Data: $R_f$=0.41 (40% EtOAc/hexanes). $^1$H NMR (400 MHz, $CDCl_3$) 7.31-7.42 (m, 27 H), 5.02 (d, *J*= 6.40 Hz, 5H), 4.52 (d, *J*= 4.0 Hz, 2 H), 3.83 (s, 9 H), 3.22 (s, 1H), 2.77 (s, 1 H).

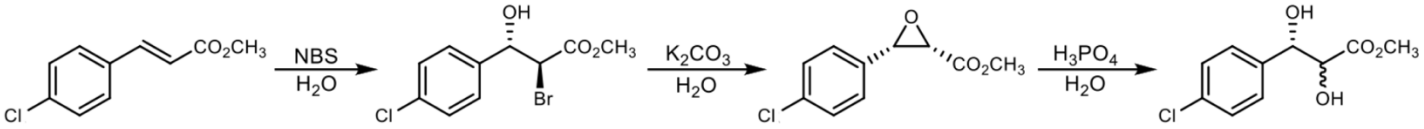



**Methyl 3-(4-methylphenyl)-2,3 dihydroxypropanoate**

To a 25-mL flask, methyl (*E*)-3-(4-methylphenyl) acrylate (1.4528 g, 8.24 mmol) was added, with *N*-Bromosuccinimide (1.4933 g, 8.24 mmol) and water (8.2 mL). The reaction refluxed overnight for 14 hours. The reaction was cooled to ambient temperature and potassium carbonate (1.1520 g, 8.24 mmol) was added to the flask, stirring. After 2 hours, 85% phosphoric acid (3.9 mL) was added, and the reaction stirred at ambient temperature for 2 hours. The aqueous layer was extracted 3 times with ethyl acetate and the organic layer was dried with magnesium sulfate, gravity filtered, and condensed to afford an amber-colored oil (1.2602 g, 72.71%). The diol was then purified by silica gel column chromatography (0.5283 g, 30.48%).

***Syn*-methyl 3-(4-methylphenyl)-2,3 dihydroxypropanoate**

Data: $R_f$=0.44 (40% EtOAc/hexanes). $^1$H NMR (400 MHz, $CDCl_3$) 7.20-7.30 (m, 6 H), 5.06 (m, 2 H), 4.38 (d, *J*=8.0 Hz, 2 H), 3.82 (s, 8 H), 3.04 (d, *J*= 5.2 Hz, 2 H), 2.35 (m, *J*= 6.4 Hz, 6 H); $^{13}$C NMR (100 MHz, $CDCl_3$) ppm 169.997, 138.786, 136.069, 129.385, 126.918,77.433, 77.112, 76.795, 75.200, 53.260, 47.539, 21.316.



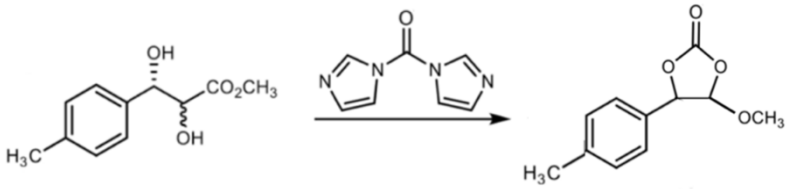

**Methyl 3-(4-chlorophenyl)-2,3 dihydroxypropanoate**

To a 15-mL flask, methyl (*E*)-3-(4-chlorophenyl)acrylate (0.5247 g, 3.5 mmol) was added, with *N*-Bromosuccinimide (0.4776 g, 3.5 mmol) and water (3.5 mL). The reaction refluxed overnight for 14 hours. The reaction was cooled to ambient temperature and potassium carbonate (0.4771 g, 3.5 mmol) was added to the flask, stirring. After 2 hours, 6 M phosphoric acid (1.65 mL) was added, and the reaction stirred at ambient temperature for 2 hours. The aqueous layer was extracted 3 times with ethyl acetate and the organic layer was dried with magnesium sulfate, gravity filtered, and condensed to afford an amber-colored oil. The diol was purified by silica gel column chromatography (0.0503 g, 8.13%).

Data: $R_f$=0.66 (40% EtOAc/hexanes).$^1$H NMR (400 MHz, $CDCl_3$) 7.31-7.39 (m, 48 H), 5.088 (s, 3 H), 4.70 (s, 6 H), 3.71 (s, 3 H), 3.23 (d, 2 H), 3.10 (m, 6 H).

*Synthesizing the carbonates and thiocarbonates*

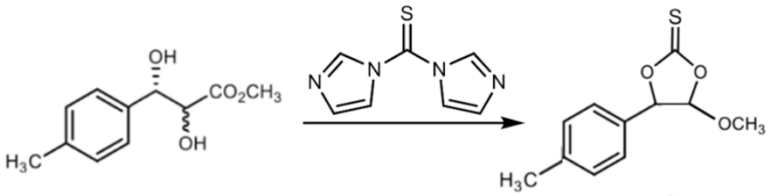
The carbonates/thiocarbonates were synthesized from the diols following the first step of the Corey-Winter olefination (scheme 2).



**4-methoxy-5-(4-methylphenyl)-1,3-dioxolan-2-one**

To a 15-mL flask, 1-(4-methylphenyl)-1,2-dihydroxycinnamate (0.2178 g, 1.04 mmol), CDI (0.1786 g, 1.04 mmol) and dichloromethane (3 mL) was added. The reaction stirred at ambient temperature for 1 hour. The reaction was vacuum filtered through a 30 mL Kimble Buchner funnel containing silica gel, flushing with ethyl acetate. Reactions were condensed to afford an amber-colored oil.

Data: $R_f$=0.79 (40% EtOAc/hexanes). $^1$H NMR (400 MHz, $CDCl_3$) 7.19-7.40 (m, 30 H), 6.03 (d, *J*=19.6 Hz , 1H), 5.97 (d, *J*=8.8 Hz, 5 H), 3.40 (s, 4 H), 2.34 (s, 83 H).



**4-methoxy-5-(4-methylphenyl)-1,3-dioxolan-2-thione**

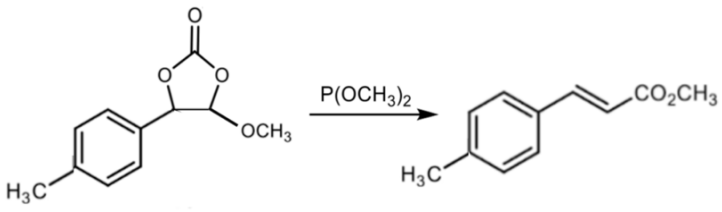
To a 25-mL flask, 1-(4-methylphenyl)-1,2-dihydroxycinnamate (0.1541 g, 0.720 mmol), TCDI (0.1213 g, 0.720 mmol) and dichloromethane (3 mL) was added. The reaction stirred at ambient temperature for 1 hour. The reaction was vacuum filtered through a 30 mL Kimble Buchner

funnel containing silica gel using ethyl acetate. Reactions were condensed to afford an amber-colored oil.

Data: $R_f$=0.79 (40% EtOAc/hexanes). $^1$H NMR (400 MHz, $CDCl_3$) 7.29-7.36 (m, 18 H), 5.86 (d, *J*=6.0 Hz, 8 H), 5.11 (d, *J*=6.0 Hz, 8 H), 3.39 (s, 4 H), 2.05 (s, 35 H).

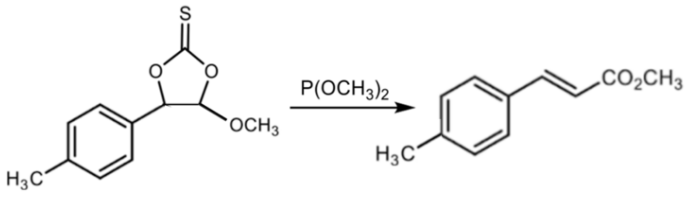
*Olefination of the carbonates and thiocarbonates*

This procedure was performed following the second step of the Corey-Winter olefination (scheme 2).




**Methyl (*E*)-3-(4-methylphenyl)acrylate**

A 5 mL vial was sealed with a rubber stopper, and all air was removed using a vacuum pump. The vial was heated to remove vapors. The vial was backfilled with nitrogen gas. To the vial, 4-methoxy-5-(4-methylphenyl)-1,3-dioxolan-2-one (0.0879 g, 0.372 mmol) was added by quickly unsealing and resealing the vial. Nitrogen flow was restored before attaching a balloon to maintain a nitrogen atmosphere. Using a syringe, $P(OCH_3)_3$ (0.375 mL) was added to the vial. The reaction stirred in an oil bath at 70°C for 2.5 hours to afford a cloudy white solution. Reaction progress was monitored every 15 minutes by injecting 1μL of solution into the GC/MS. Reactions were monitored for a total of 135 minutes.




**Methyl (*E*)-3-(4-methylphenyl)acrylate**

A 5 mL vial was sealed with a rubber stopper, and all air was removed using a vacuum pump. The vial was heated to remove vapors and backfilled with nitrogen gas. To the vial, 4-methoxy-5-(4-methylphenyl)-1,3-dioxolan-2-thione (0.0945 g, 0.375 mmol) was added by quickly unsealing and resealing the vial. Nitrogen flow was restored before attaching a balloon to maintain a nitrogen atmosphere. Using a syringe, $P(OCH_3)_3$ (0.375 mL) was added to the vial. The reaction stirred in an oil bath at 70°C for 2.5 hours to afford a cloudy white solution. Reaction progress was monitored every 15 minutes by injecting 1μL of solution into the GC/MS. Reactions were monitored for a total of 135 minutes.

*NMR Spectra Collection*

All $^{1}H$ NMR spectra were collected using a Bruker Avance 400 MHz spectrometer at 25°C. All $^{13}C$ NMR spectra were collected using a Bruker Avance 100 MHz spectrometer at 25°C.

*PuriFlash Chromatography Conditions*

All flash chromatography purification was performed using an Interchim puriFlash XS520 Plus. Mobile phase was run through the column in a gradient of 15% ethyl acetate in hexanes followed by 25% ethyl acetate in hexanes at a flow rate of 15 mL/min.

*Gas Chromatography/Mass Spectrometry Conditions*

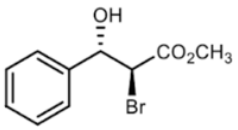
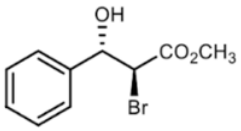
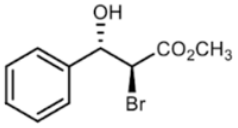
All GC/MS spectra data were collected using an Agilent 6850 Series GC system and 5973 Network Mass Selective Detector. The initial temperature of the GC was set to 100°C with a ramp rate of 10°C/minute to reach a final temperature of 250°C. The detector temperature was 250°C and pressure was set to 7.00 psi for a flow rate of 1.57 mL/min.

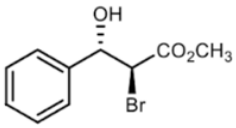
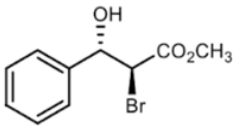
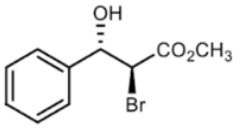
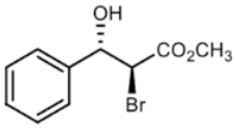
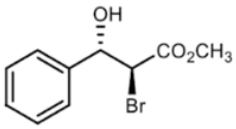
## RESULTS AND DISCUSSION

*Synthesis of the diols*

The first steps to develop a synthesis for the diols included synthesizing the bromohydrin on a large scale (65 mmol) to use in attempts for hydrolysis to the diol. Initial attempts to hydrolyze the bromohydrin to diol included varying base and solvent conditions, summarized in Table 1.

**Table 1.** Summary of attempts at hydrolysis of the bromohydrin.

| Bromohydrin | Base | Solvent | Temperature | Time (hr) |
|---|---|---|---|---|
|  | LiOH | $THF/H_2O$ | Ambient | 1 |
|  | LiOH | $THF/H_2O$ | Ambient | 2 |
|  | | $H_2O$ | Reflux | 2 |

| | | | | |
|---|---|---|---|---|
|  | LiOAc | THF/$H_2O$ | Ambient | 2 |
|  | | Acetonitrile/ $H_2O$ | Reflux | 1 |
|  | LiOAc after 2 hr | Acetonitrile/ $H_2O$ | Reflux | 4 |
|  | $K_2CO_3$ | Acetonitrile/ $H_2O$ | Ambient | 2 |
|  | $K_2CO_3$ | Acetonitrile/ $H_2O$ | Ambient | 2 |

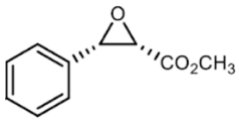
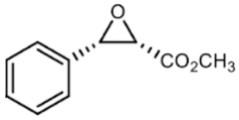
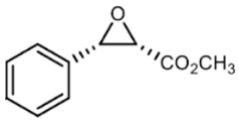
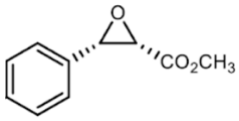
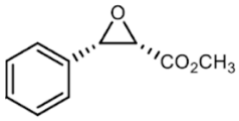
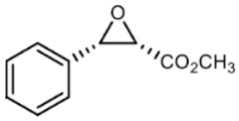
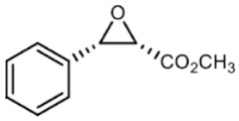
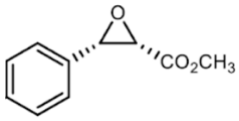
Reaction progress was monitored by TLC (2% dichloromethane in methanol) in all cases. When a change in $R_f$ from the bromohydrin was observed, reactions were stopped, condensed, and $^1H$ NMR was taken. We first attempted hydrolysis using lithium hydroxide in THF and water for 1 hour and observed no change from the bromohydrin. We then attempted the same reaction for 2 hours, adding an additional equivalent of lithium hydroxide after 3 hours when TLC revealed no change. Again, no change from starting material was observed. Attempts to use water or water in acetonitrile, both without any base present, at reflux led to no change in starting material. We began using lithium acetate in both THF/water or acetonitrile water at ambient temperature and found that the bromohydrin cyclized to epoxide. However, conversion was incomplete. Next

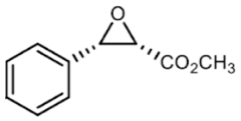
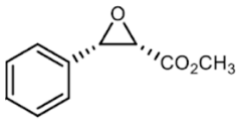
attempts involved adding potassium carbonate in acetonitrile water at ambient temperature. Better conversion was observed via $^{1}$H NMR. Potassium carbonate was thus used in subsequent attempts to synthesize the epoxide.

After consistently seeing epoxide forming rather than diol, we shifted our focus to instead hydrolyzing epoxide to yield the diol. Because converting the alkene of the methyl cinnamate to bromohydrin and the subsequent conversion of bromohydrin to epoxide are performed in water, we attempted to complete both reactions in one flask, without isolation between steps. We also wanted to attempt the reaction without acetonitrile. We refluxed the methyl cinnamate for 2 hours with *N*-Bromosuccinimide and potassium carbonate in water but observed no reaction occurring. Next, we tried refluxing the methyl cinnamate with *N*-Bromosuccinimide in water for 2 hours and then adding potassium carbonate for 2 hours. The epoxide was successfully synthesized. We attempted the reaction again, this time cooling the flask to ambient temperature before adding potassium carbonate. The epoxide was synthesized with greater percent conversion, and this procedure was used moving forward.

After observing that we could convert the alkene of the methyl cinnamate to epoxide in one reaction flask, we focused on hydrolyzing the epoxide to diol. We first synthesized epoxide from the bromohydrin on a large-scale (20 mmol) using potassium carbonate in acetonitrile water (yield: 71.23%). From there, we attempted hydrolysis of the epoxide using a series of acids and acidic ion exchange resins (Table 2).

**Table 2.** Summary of attempts at hydrolysis of the epoxide.

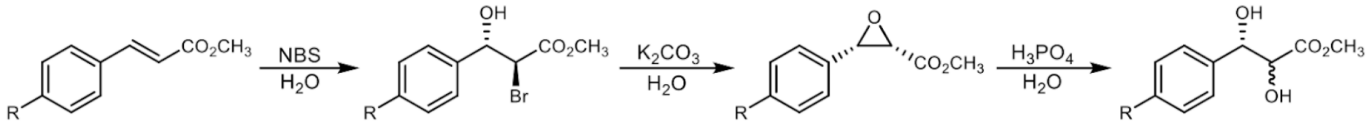
| Epoxide | Acid/Ion Exchange Resin | Solvent | Temperature | Time (hr) |
|---|---|---|---|---|
|  | 1M HCl | | Ambient | 1 |
|  | 1M HCl | Acetonitrile | Ambient | 1 |
|  | 1M $H_3PO_4$ | | Ambient | 1.5 |
|  | 6M $H_3PO_4$ | | Ambient | 1.5 |
|  | 1M $CH_3COOH$ | THF/$H_2O$ | Ambient | 1.5 |
|  | 6M $CH_3COOH$ | | Ambient | 1.5 |
|  | Dowex | $H_2O$ | Ambient | 1.5 |
|  | PPTs | $H_2O$ | Ambient | 1.5 |

| | | | | |
|---|---|---|---|---|
|  | AmberLite IRC 120 | $H_2O$ | Ambient | 1.5 |
|  | AmeberLyst-15 | $H_2O$ | Ambient | 1.5 |

Initial attempts using 1M hydrochloric acid led to hydrolysis of the ester. We then shifted our focus to acids weaker than hydrochloric acid and acidic ion exchange resins. We found that Dowex, AmberLite-15, and phosphoric acid all afforded the diol, but 6M phosphoric gave the most complete conversion with the greatest crude recovery.

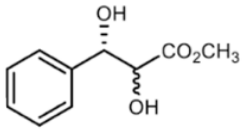
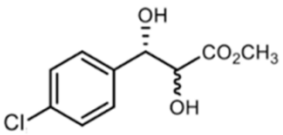
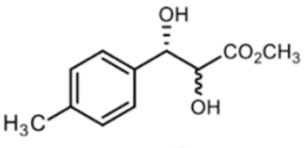
After successfully hydrolyzing the diol from the epoxide, we attempted the reaction in one consolidated reaction flask without isolation between steps. The methyl cinnamate was first converted to bromohydrin by refluxing for 14 hours with *N*-Bromosuccinimide in water. The reaction was cooled to ambient temperature and cyclized to epoxide by potassium carbonate. Finally, the epoxide was hydrolyzed to diol by adding 85% phosphoric acid to achieve a final solution concentration of 6 M, again, at ambient temperature. The diol was successfully synthesized (Figure A3). Initially, the epoxide was synthesized from bromohydrin in a solution of acetonitrile water. Upon comparing the one-pot procedure with and without acetonitrile, we found that the presence of acetonitrile did not affect the formation of diol. In future syntheses, acetonitrile was omitted from the procedure. After optimizing conditions, this synthesis was extended to other cinnamates with variable R-groups on the phenyl ring (scheme 3).

**Scheme 3.** A novel green dihydroxylation of alkenes.




After synthesis and purification, current and most optimal yields for all diols were determined.

**Table 3.** Percent yield of different diol derivatives. Diols were synthesized using the procedure in scheme 3, starting with different cinnamates. All diols were purified by silica gel column chromatography.

| Diol | Purified Yield (%) |
|---|---|
|  | 14.2 |
|  | 8.13 |
|  | 30.48 |

The yields for all purified diols were consistently below 50% (Table 3). These data are inconsistent, however, with anticipated yields based on crude recovery and $^{1}$H NMR. We suspect material loss is largely occurring during silica gel column chromatography. Because of the polarity of alcohols, the diols interact with the polar silica gel more compared to the bromohydrin and epoxide. During a purification, the bromohydrin would elute off the column first, followed by epoxide, diol, and then finally, succinimide. The succinimide always eluted last, given the two carbonyls that are more polar than the alcohols. Mobile phase was run through

on a gradient of 20% ethyl acetate in hexanes, 40% ethyl acetate in hexanes, and 60% ethyl acetate in hexanes at a 2:2:1 volume ratio. For diols synthesized on a 10 mmol scale, we used 250 mL, 250 mL, and 125 mL of each mobile phase type, respectively. The diols began eluting in 20% ethyl acetate in hexanes, after the bromohydrin and epoxide had eluted, and stopped eluting once 60% ethyl acetate in hexanes was added to the column. We found that once 60% ethyl acetate in hexanes was added, only succinimide eluted. At first, we assumed that all our material was eluting off the column because succinimide alone appeared after adding 60% ethyl acetate in hexanes as the mobile phase. However, after consistently seeing low yields for all diol derivatives, we began increasing the volume of both 20% ethyl acetate in hexanes and 40% ethyl acetate in hexanes added by a factor of 1.25. After making this adjustment, we still only saw succinimide eluting in 60% ethyl acetate in hexanes but noticed an increase in yield. This suggests that the diols stop eluting in 60% ethyl acetate in hexanes, and a greater volume of 20% ethyl acetate in hexanes and 40% ethyl acetate in hexanes is required all desired material has eluted from the column.

However, even as we increased volume of mobile phase used, the greatest purified yield of any diol observed was 30.48%, in a synthesis of the 1-(4-methylphenyl)-1,2 dihydroxycinnamate (Table 3). This yield is still inconsistent with trends in crude recovery and percent conversion suggested by $^{1}$H NMR, suggesting material is still being lost on the column. In addition to the polarity of the diols, they are also able to hydrogen bond with the silica gel, contributing to their tendency to remain on the column. This hydrogen bonding is also more extensive given the multiple alcohol groups. Furthermore, we suspect the silica gel may be coordinating between the two alcohols. Because of the 1,2 positioning of the alcohols on the diols, and the favorable interactions between the diols and the silica gel, the silicon can

coordinate between the two lone pairs on the oxygens of the diols. Neither ethyl acetate nor hexanes provide a replacement in this hydrogen bonding between the silica gel and the alcohols. Thus, we suspect this interaction also plays a significant role in the tendency for the diols to remain on the column.

After successfully developing the dihydroxylation procedure, we tested options for mobile phase in column chromatography by performing thin-layer chromatography in 10% ethyl acetate in hexanes, 20% ethyl acetate in hexanes, 40% ethyl acetate in hexanes, and 2% dichloromethane in methanol. The TLC plates with 2% dichloromethane in methanol showed high $R_f$ values for all samples tested. These results guided the decision to proceed using ethyl acetate in hexanes as mobile phase in chromatography. However, given current yield data, attempting chromatography in 2% dichloromethane in methanol may improve purified yields. As an alcohol, methanol will be better able to disrupt the interactions between the diols and the silica gel. This may provide better results with yield and should be considered as a next step.

After successfully and consistently synthesizing the diols on a small scale, we attempted a large-scale (~60 mmol) synthesis of both the 1-phenyl-1,2-dihydroxycinnamate and 1-(4-methylphenyl)-1,2 dihydroxycinnamate. After purification, we were observing several fractions containing product of interest. Each fraction had to be subsequently repurified by either silica gel column chromatography or flash chromatography. When purifying by flash chromatography, we found that we could separate the two diastereomers of the diol (Figure A4).

*The kinetics of the elimination of the carbonates and thiocarbonates*

The carbonates and thiocarbonates were not purified before reacting with trimethylphosphite. We were unconcerned with yield, only that enough material was present to

study the kinetics of elimination. Additionally, previous work showed the carbonates and thiocarbonates were fairly unstable and prone to hydrolysis. The kinetics of the elimination of all carbonates and thiocarbonates was monitored by GC/MS by injecting 1μL of solution every 15 minutes. Reactions were monitored for a total of135 minutes. The first carbonates and thiocarbonates studied were those with a methyl group on the phenyl ring given the amount of material at hand and higher purity compared to the other diols. The GC/MS of the methyl cinnamate with a methyl on the phenyl ring revealed methyl cinnamate has a retention time of 5.30 and 11.32 minutes (Figure B.1). However, the peak at 11.32 minutes showed a sharper peak with greater abundance and was used as a reference for the analysis of the elimination of carbonates and thiocarbonates.

To compare the rate of elimination of the carbonates and thiocarbonates, the presence and area of the cinnamate peaks were monitored over the course of the reaction and plotted.

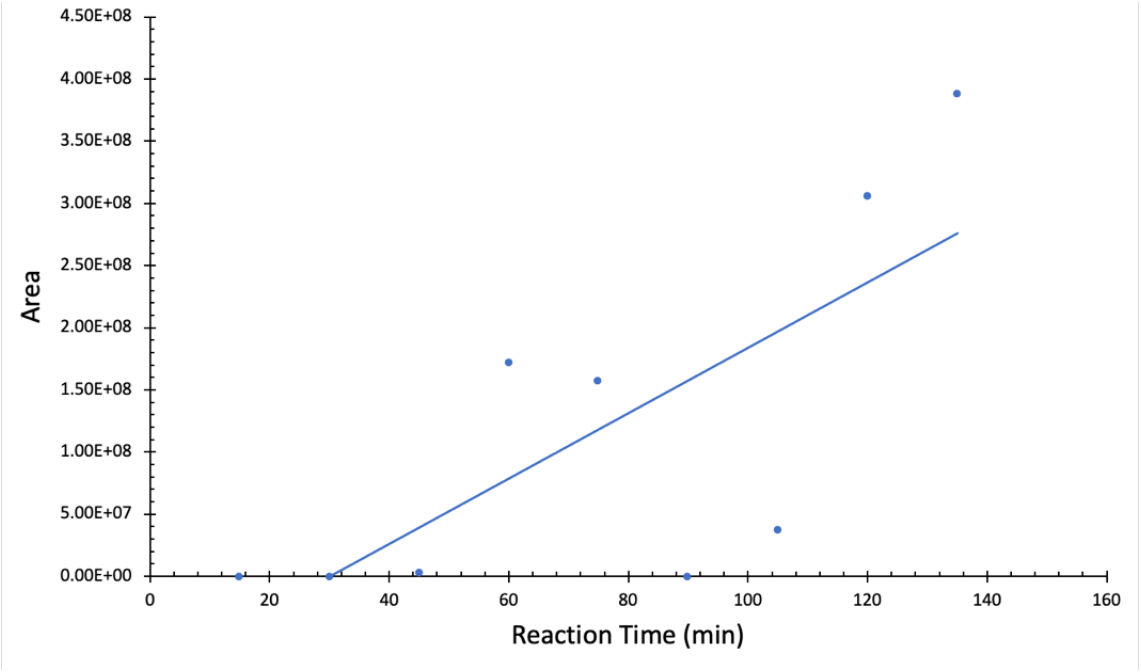



**Figure 3.** The kinetics of the elimination of 4-methoxy-5-(4-methylphenyl)-1,3-dioxolan-2-one with the addition of trimethylphosphite. Every 15 minutes, 1 μL of reaction was injected, and the area under the GC peaks corresponding to product was observed over time. The equation of the trendline is $y = (3\times10^{6})x - (8\times10^{7})$.

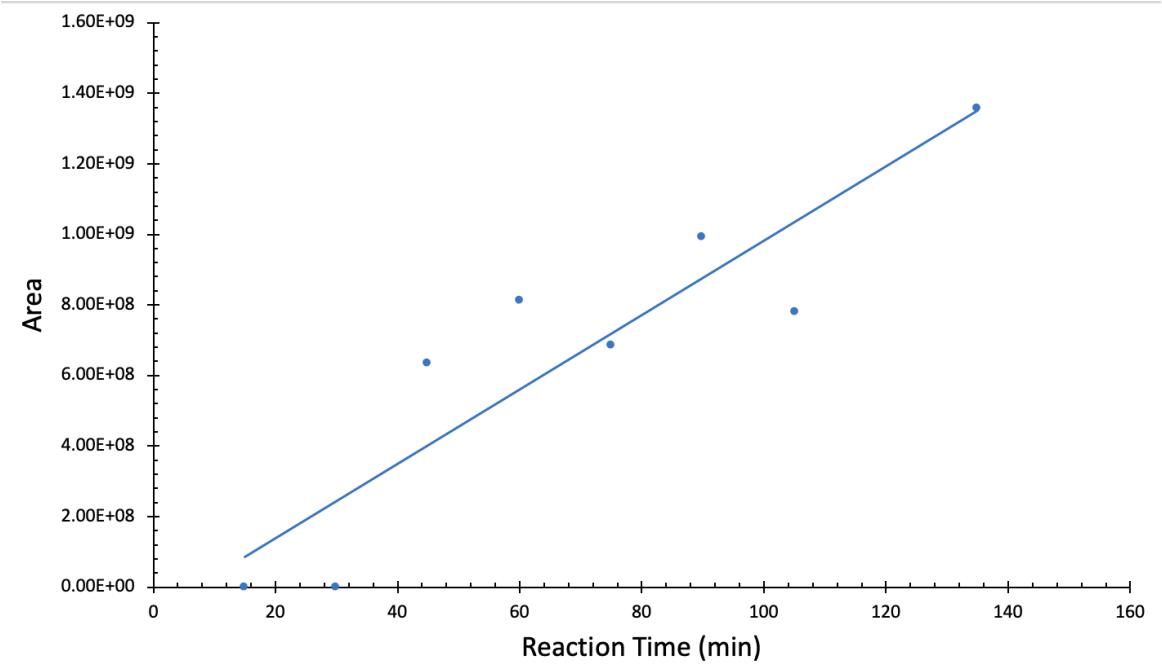



**Figure 4.** The kinetics of the elimination of4-methoxy-5-(4-methylphenyl)-1,3-dioxolan-2-thione with the addition of trimethylphosphite. Every 15 minutes, 1 μL of reaction was injected, and the area under the GC peaks corresponding to product was observed over time. The equation of the trendline is $y = (1\times10^{7})x - (7\times10^{7})$.

Comparing the slope of each trendline, the elimination of the thiocarbonate to product showed a steeper slope, indicating a faster rate of elimination (Figure 4). Furthermore, the product of the elimination of the thiocarbonate first appears after 45 minutes. With the carbonate, product first appears after 60 minutes. These results further support a faster elimination with the thiocarbonate than the carbonate. However, it is important to note the absence of a cinnamate peak at 90 minutes in the elimination of the carbonate. This is followed by minimal cinnamate detected at 105 minutes and a sharp increase in cinnamate detected at 120 minutes. It is unlikely that no cinnamate was present in the reaction mixture at these times, given its presence before and after these measurements. Omitting these data gives a trendline of $y = (3\times10^{6})x - (9\times10^{7})$ for the elimination of the carbonate. This rate is still less than that of the thiocarbonate by almost a factor of 10, further supporting a faster elimination of the thiocarbonate.

The thiocarbonates may be more reactive than the carbonates because of differences in the partial positive character of the carbon in the carbon-sulfur or carbon-oxygen double bond. The carbon-sulfur double bond can be more reactive than the carbon-oxygen double bond. Despite oxygen's stronger electronegativity, sulfur has a larger atomic radius. The electrons in its valence are farther from the positively charged nucleus and thus more available to react with the trimethyphosphite. The GC/MS data of the reactions also shows numerous peaks indicating the formation of tangential products. This is likely a result of high temperatures. Monitoring reaction progress by $^{1}H$ NMR may provide an alternative method for observing rates of elimination without generating thermal products.

## CONCLUSIONS AND FUTURE WORK

To study the rate of the elimination of the carbonates and thiocarbonates synthesized from various diols, we developed a novel, green, one-pot procedure for the dihydroxylation of alkenes. The alkene of a methyl cinnamate is converted to bromohydrin by refluxing for 14 hours with *N*-Bromosuccinimide in water. The bromohydrin is then cyclized to epoxide by adding potassium carbonate for 2 hours at ambient temperature. Finally, the epoxide is hydrolyzed to diol with the addition of 85% phosphoric acid for 2 hours at ambient temperature. This procedure represents an unprecedented, non-enatioselective dihydroxylation of alkenes

Preliminary data of the elimination of the carbonates and thiocarbonates indicates the thiocarbonate eliminating faster than the carbonate. Through monitoring the reaction of 4-methoxy-5-(4-methylphenyl)-1,3-dioxolan-2-one versus 4-methoxy-5-(4-methylphenyl)-1,3-dioxolan-2-thione with the addition of trimethylphosphite, 4-methoxy-5-(4-methylphenyl)-1,3-dioxolan-2-thione showed a faster onset of elimination, with product detected after 45 minutes. Furthermore, comparing the rates of elimination by appearance of product over time, the thicoarbonate displayed a faster rate of elimination compared to the carbonate with trendline slopes of $1\times10^7$ and $3\times10^6$, respectively.

Future work includes optimizing chromatography conditions for purification and synthesizing all diol derivatives. Throughout this project, we were consistently seeing yields under 50% (Table 3). Performing silica gel column chromatography using 2% dichloromethane in methanol as the mobile phase may disrupt the interactions between the diols and the silica gel. Thus, potentially leading to a decrease in material loss. Furthermore, flash chromatography can be used to separate and collect data on both diastereomers of the diols. After optimizing

purification technique, the one-pot synthesis of the diols can be extended to include all diol derivatives.

After synthesizing the full series of diol derivatives with more optimal purity, the diols can be converted to both carbonate and thiocarbonate. From there, the kinetics of their elimination with the addition of trimethylphosphite can be studied by GC/MS. By conducting multiple analyses for each diol derivative, reaction evolution can be compared to infer the relative stability of the dioxacarbene intermediate in each case. In addition to studying the appearance of product over time, the disappearance of the carbonates and thiocarbonates can also be studied to follow reaction progress. Once the more stable dioxacarbenes are identified, these molecules can be tested as a dioxacarbene source in the synthesis of the cyclopropenone acetals. Furthermore, the carbonates and thiocarbonates appear to have higher thermal reactivity, based on the appearance of tangential product formation on GC/MS spectra. To avoid formation of unintended product, reactions may also be monitored by $^{1}$H NMR. To do so, the carbonates and thiocarbonates can be reacted with trimethylphosphite, and $^{1}$H NMR samples can be taken every 15 minutes to follow reaction progress.

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## APPENDICES

*Appendix A: NMR spectra*

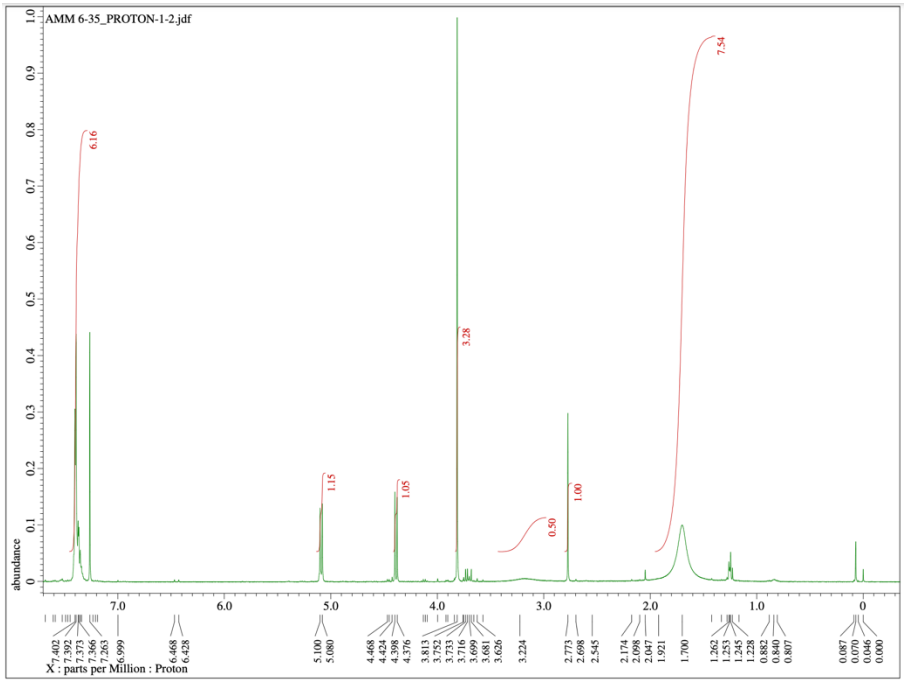


**Figure A1.** [1]H NMR spectrum of the methyl-2-bromo-3-hydroxy-3-phenylpropanoate. Spectrum collected using a Bruker Avance 400 MHz spectrometer at 25°C.

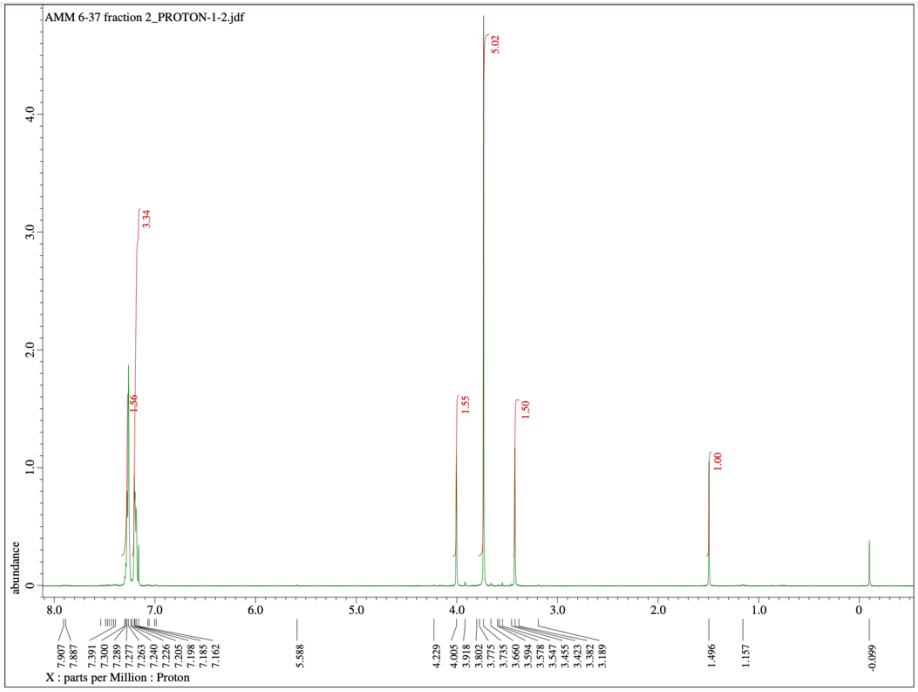


**Figure A2.** [1]H NMR spectrum of the methyl 2-phenyloxirane-2-carboxylate. Spectrum collected using a Bruker Avance 400 MHz spectrometer at 25°C.

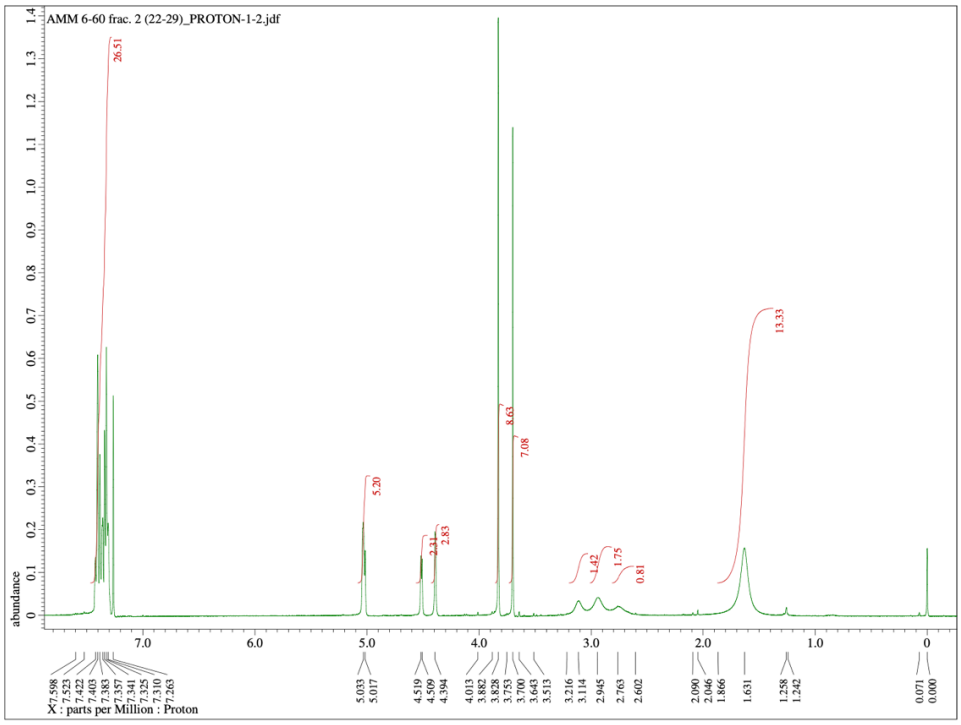


**Figure A3.** [1]H NMR spectrum of the methyl 2,3-dihydroxy-3-phenylpropanoate. Spectrum collected using a Bruker Avance 400 MHz spectrometer at 25°C.

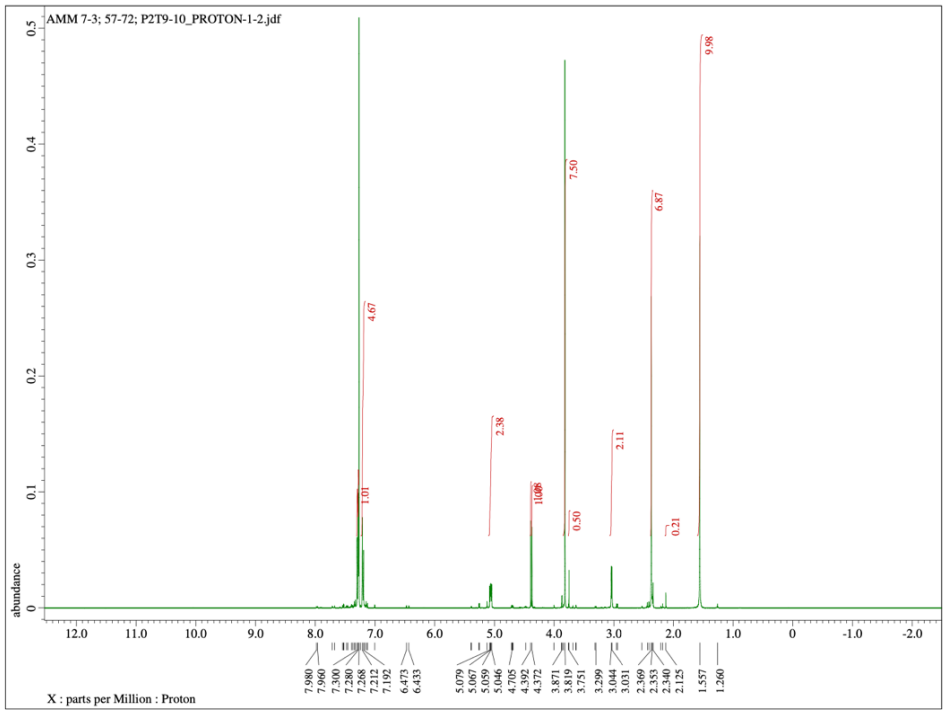


**Figure A4.** [1]H NMR spectrum of the *syn*-methyl 3-(4-methylphenyl)-2,3 dihydroxypropanoate. Spectrum collected using a Bruker Avance 400 MHz spectrometer at 25°C.

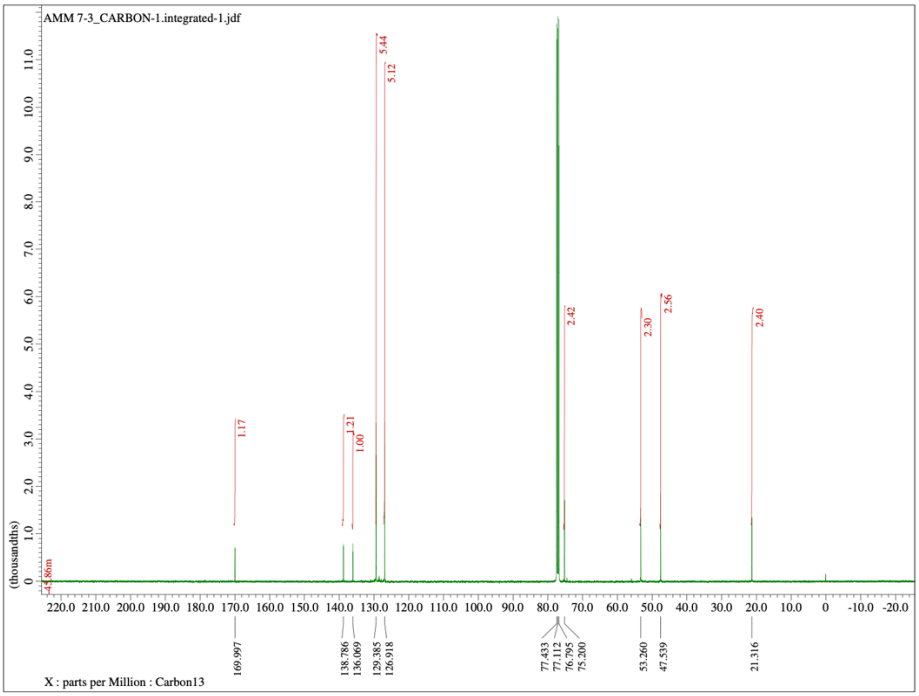


**Figure A5.** $^{13}$C NMR spectrum of the *syn*-methyl 3-(4-methylphenyl)-2,3 dihydroxypropanoate. Spectrum collected using a Bruker Avance 100 MHz spectrometer at 25°C.

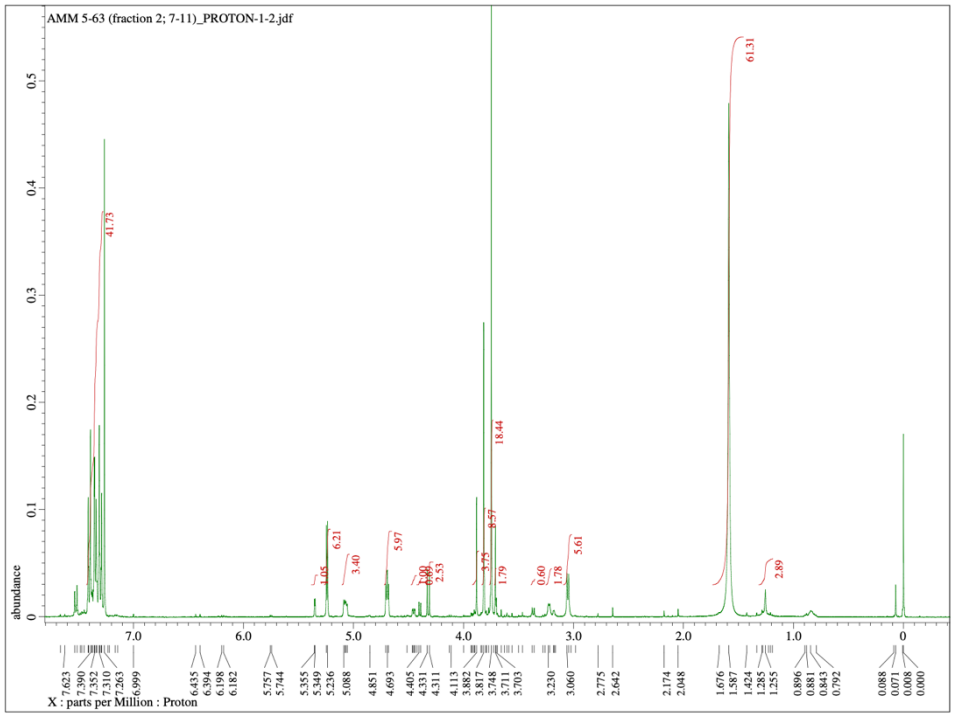


**Figure A6.** $^{1}$H NMR spectrum of the methyl 3-(4-chlorophenyl)-2,3 dihydroxypropanoate . Spectrum collected using a Bruker Avance 100 MHz spectrometer at 25°C.

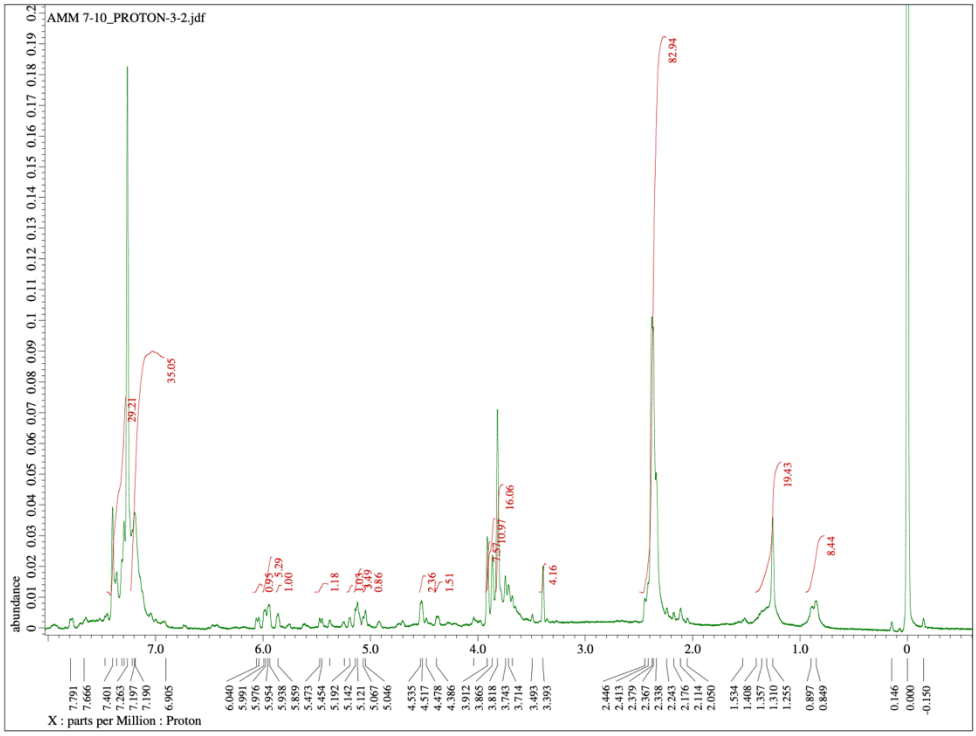


**Figure A7.** $^{1}$H NMR spectrum of the 4-methoxy-5-(4-methylphenyl)-1,3-dioxolan-2-one. Spectrum collected using a Bruker Avance 100 MHz spectrometer at 25°C.

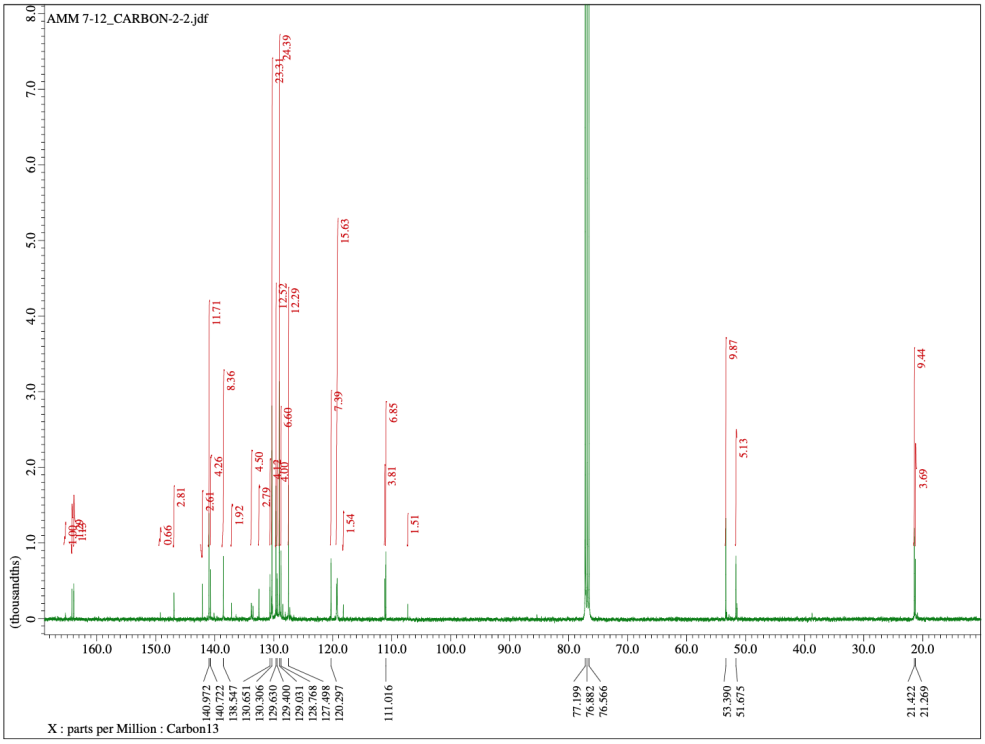


**Figure A8.** $^{13}$C NMR spectrum of the 4-methoxy-5-(4-methylphenyl)-1,3-dioxolan-2-one. Spectrum collected using a Bruker Avance 100 MHz spectrometer at 25°C.

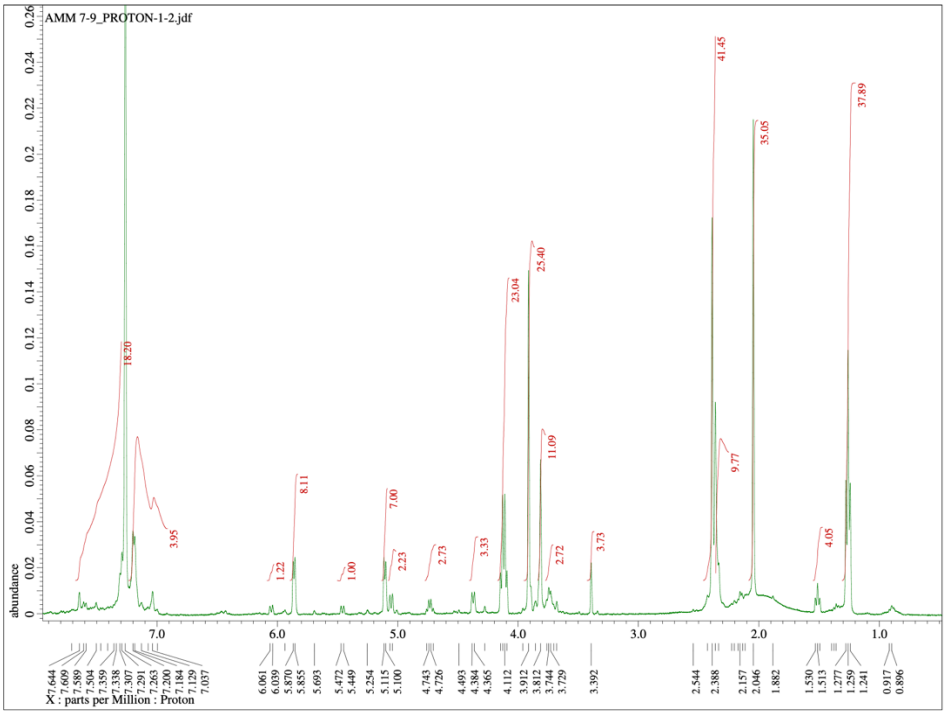


**Figure A9.** [1]H NMR spectrum of the 4-methoxy-5-(4-methylphenyl)-1,3-dioxolan-2-thione. Spectrum collected using a Bruker Avance 100 MHz spectrometer at 25°C.

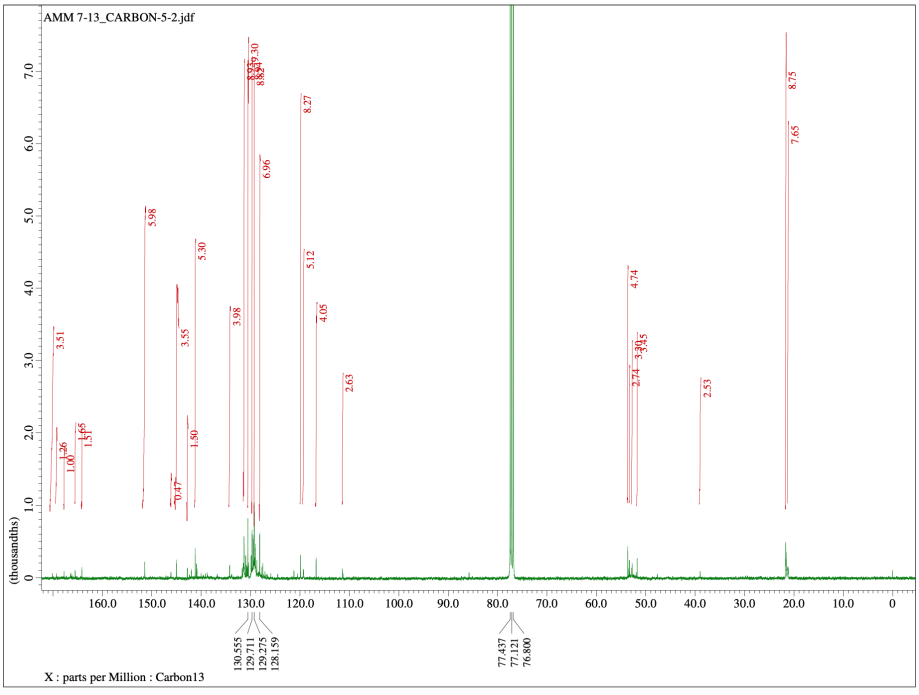


**Figure A10.** [12]C NMR spectrum of the 4-methoxy-5-(4-methylphenyl)-1,3-dioxolan-2-thione. Spectrum collected using a Bruker Avance 100 MHz spectrometer at 25°C.

*Appendix B: Gas Chromatography/MassSpectrometry*

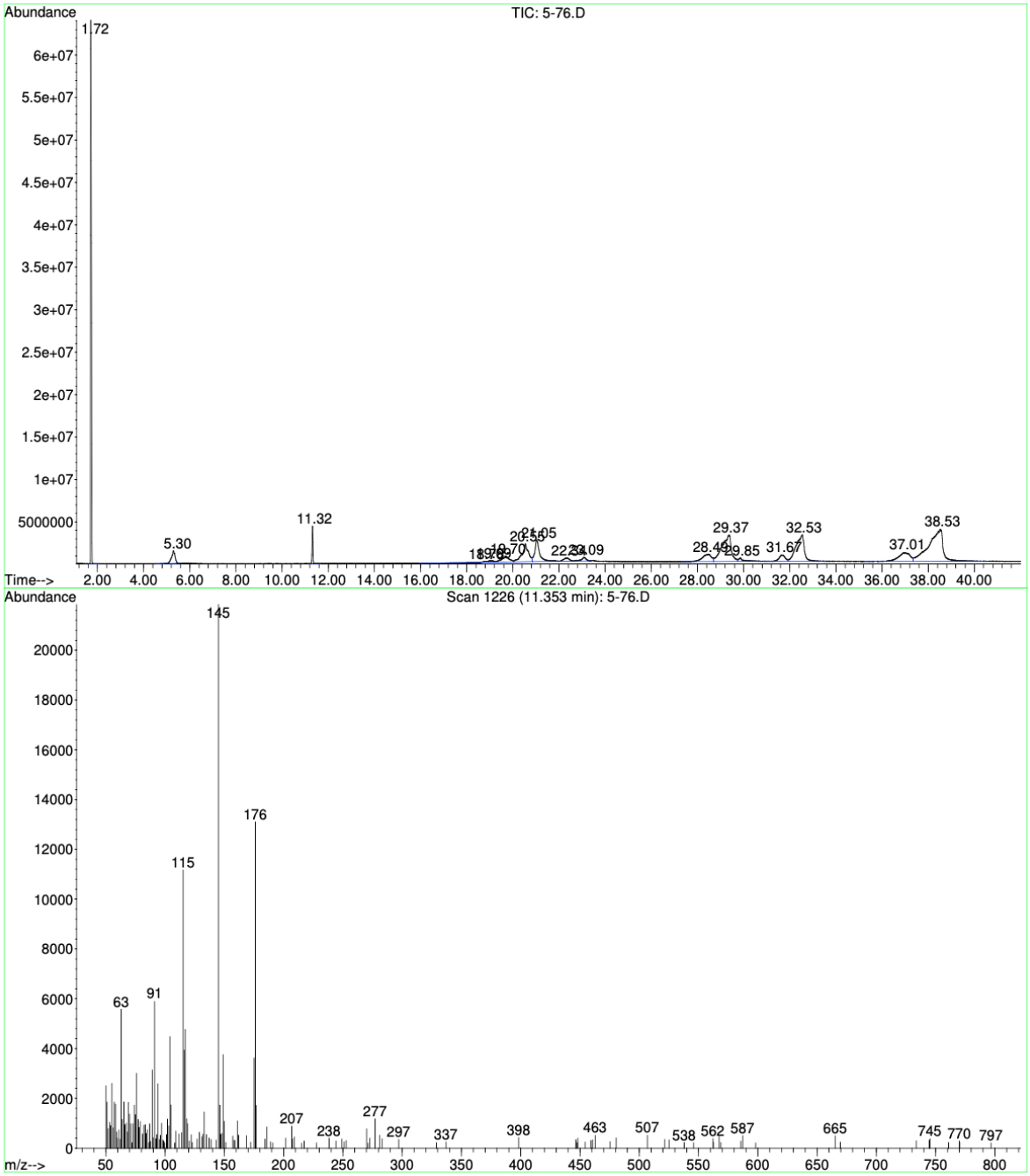


**Figure B.1** Gas chromatography/mass spectrometry spectra of the 1-(4-methylphenyl)-cinnamate. Spectra collected using an Agilent 6850 Series GC system and 5973 Network Mass Selective Detector.

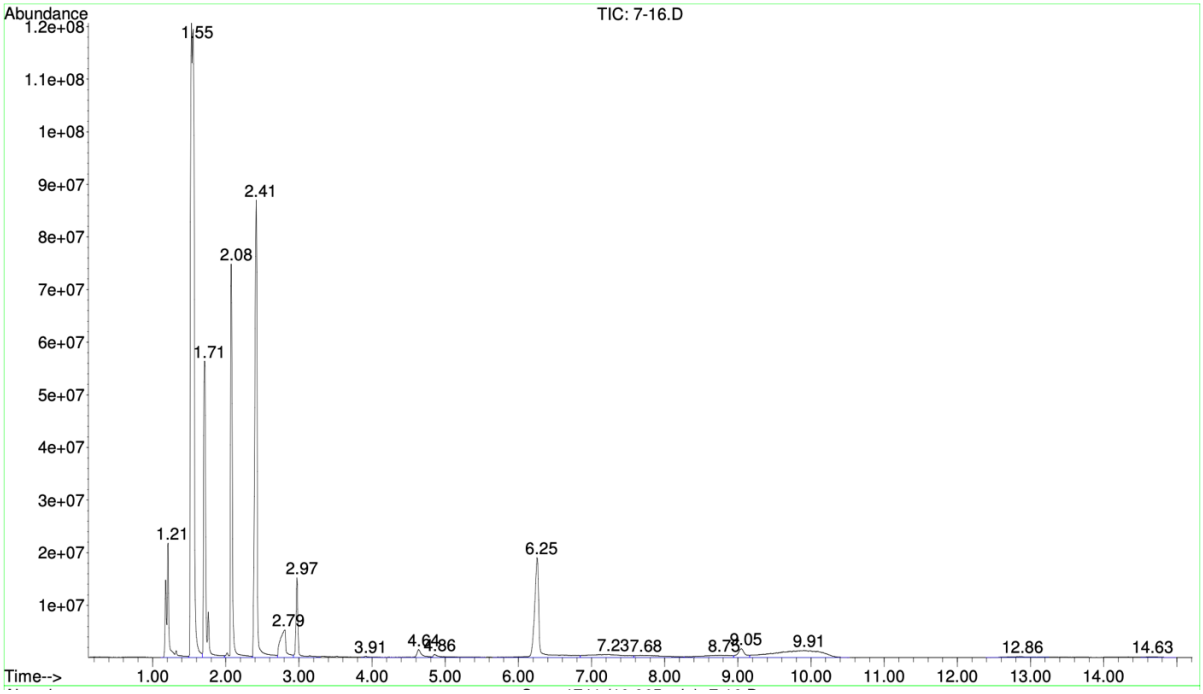


**Figure B2.** Gas chromatography spectra of the elimination of the 4-methoxy-5-(4-methylphenyl)-1,3-dioxolan-2-one after the addition of trimethylphosphite. Spectra collected after 15 minutes using an Agilent 6850 Series GC system and 5973 Network Mass Selective Detector.

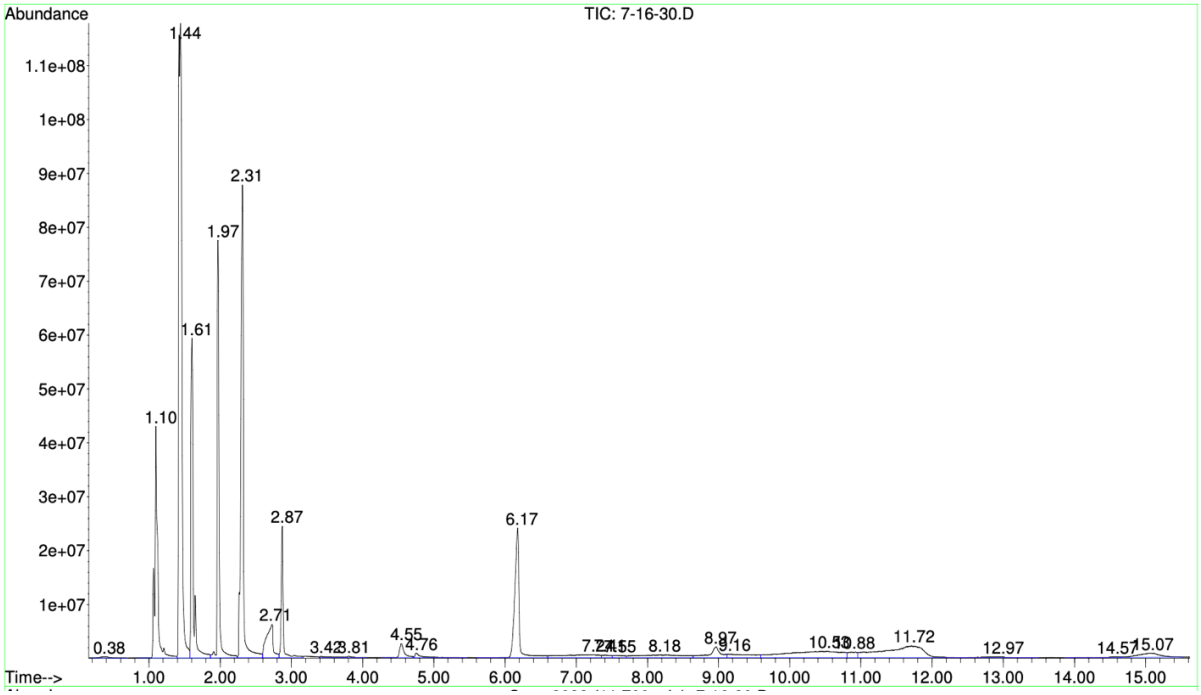


**Figure B3.** Gas chromatography spectra of the elimination of the 4-methoxy-5-(4-methylphenyl)-1,3-dioxolan-2-one after the addition of trimethylphosphite. Spectra collected after 30 minutes using an Agilent 6850 Series GC system and 5973 Network Mass Selective Detector.

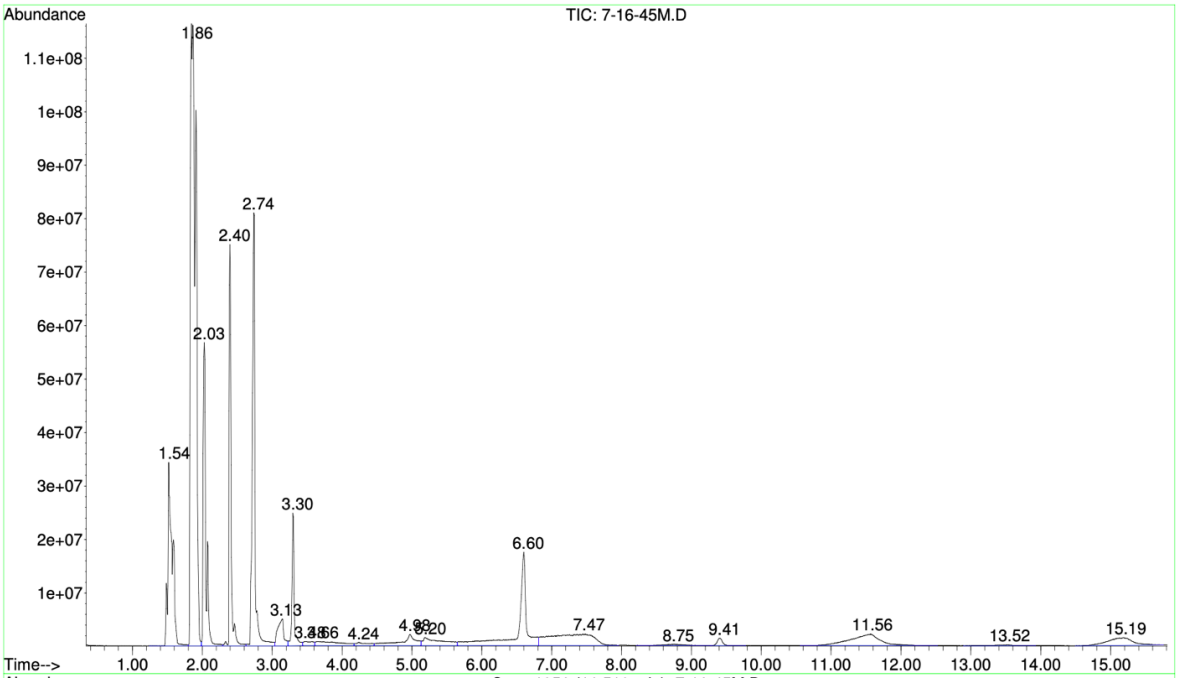


**Figure B4.** Gas chromatography spectra of the elimination of the 4-methoxy-5-(4-methylphenyl)-1,3-dioxolan-2-one after the addition of trimethylphosphite. Spectra collected after 45 minutes using an Agilent 6850 Series GC system and 5973 Network Mass Selective Detector.

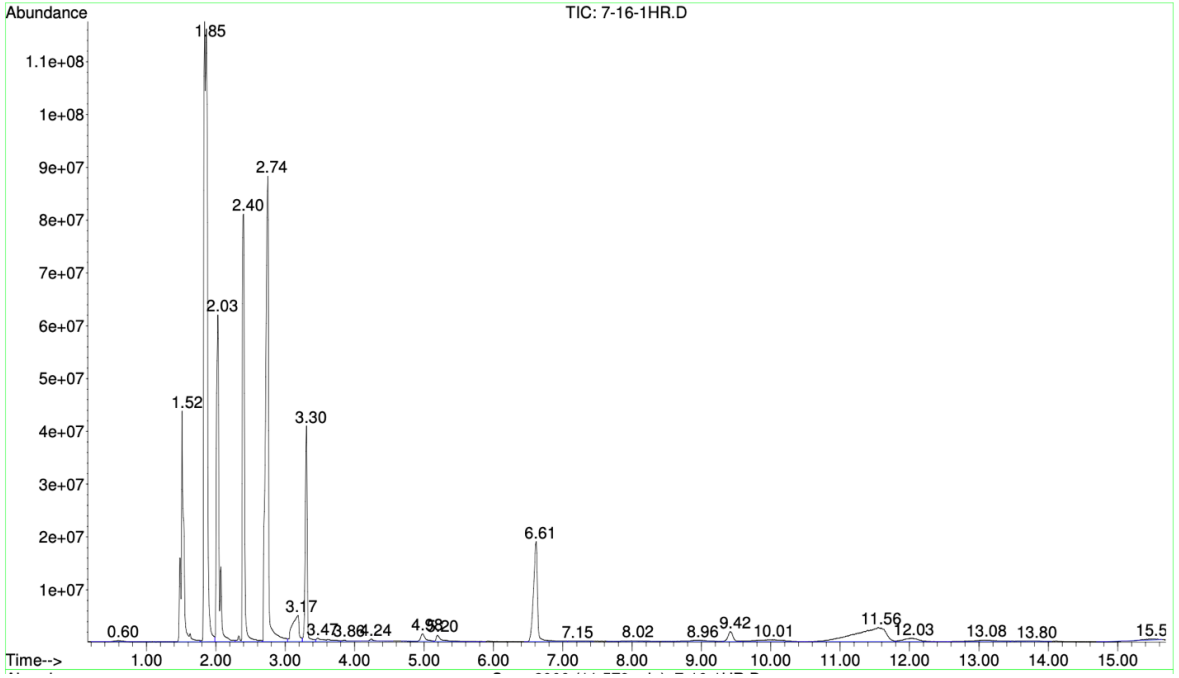


**Figure B5.** Gas chromatography spectra of the elimination of the 4-methoxy-5-(4-methylphenyl)-1,3-dioxolan-2-one after the addition of trimethylphosphite. Spectra collected after 60 minutes using an Agilent 6850 Series GC system and 5973 Network Mass Selective Detector.

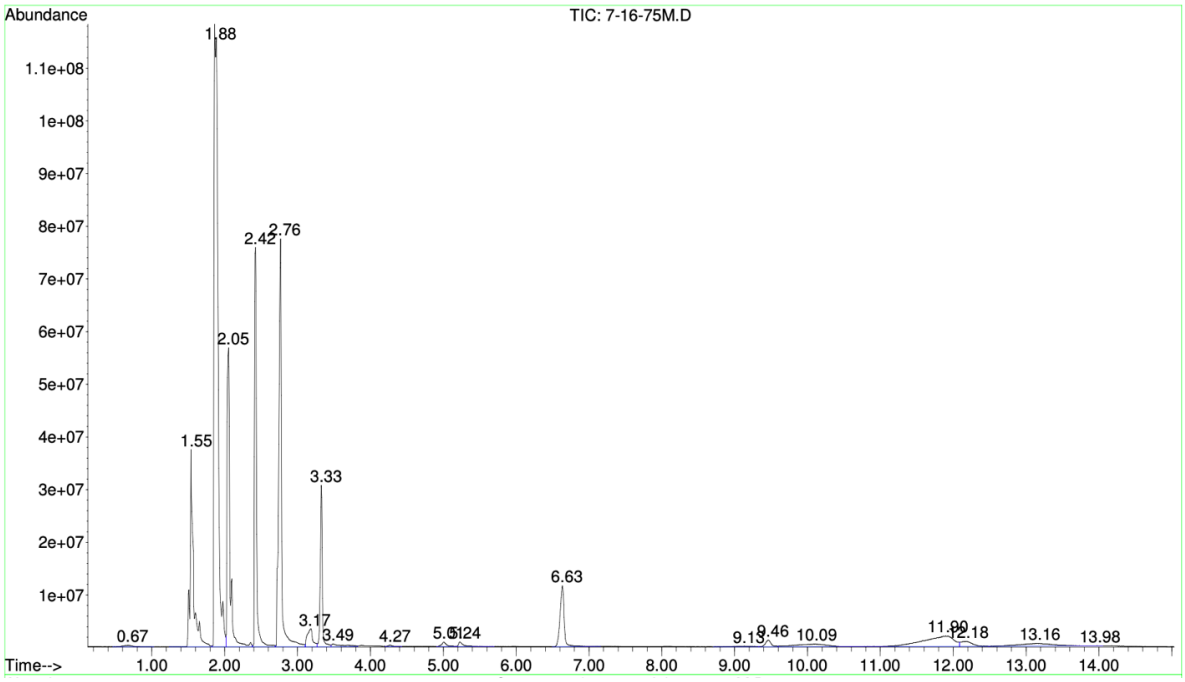


**Figure B6.** Gas chromatography spectra of the elimination of the 4-methoxy-5-(4-methylphenyl)-1,3-dioxolan-2-one after the addition of trimethylphosphite. Spectra collected after 75 minutes using an Agilent 6850 Series GC system and 5973 Network Mass Selective Detector.

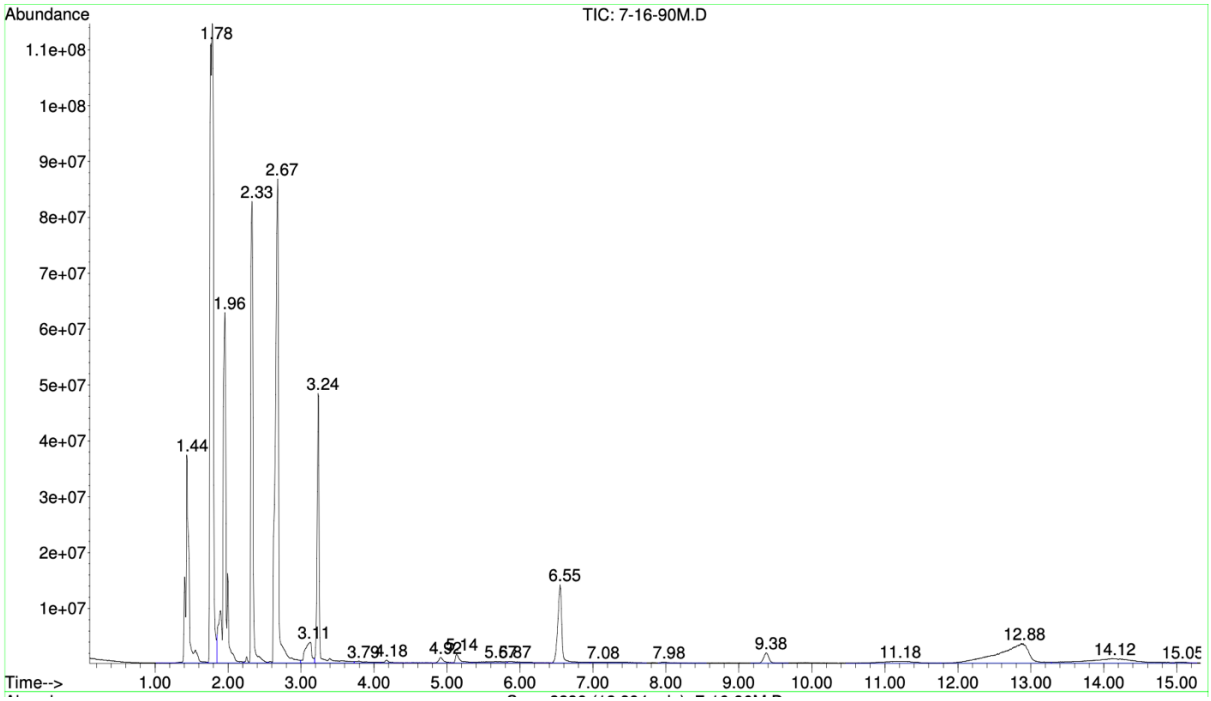


**Figure B7.** Gas chromatography spectra of the elimination of the 4-methoxy-5-(4-methylphenyl)-1,3-dioxolan-2-one after the addition of trimethylphosphite. Spectra collected after 90 minutes using an Agilent 6850 Series GC system and 5973 Network Mass Selective Detector.

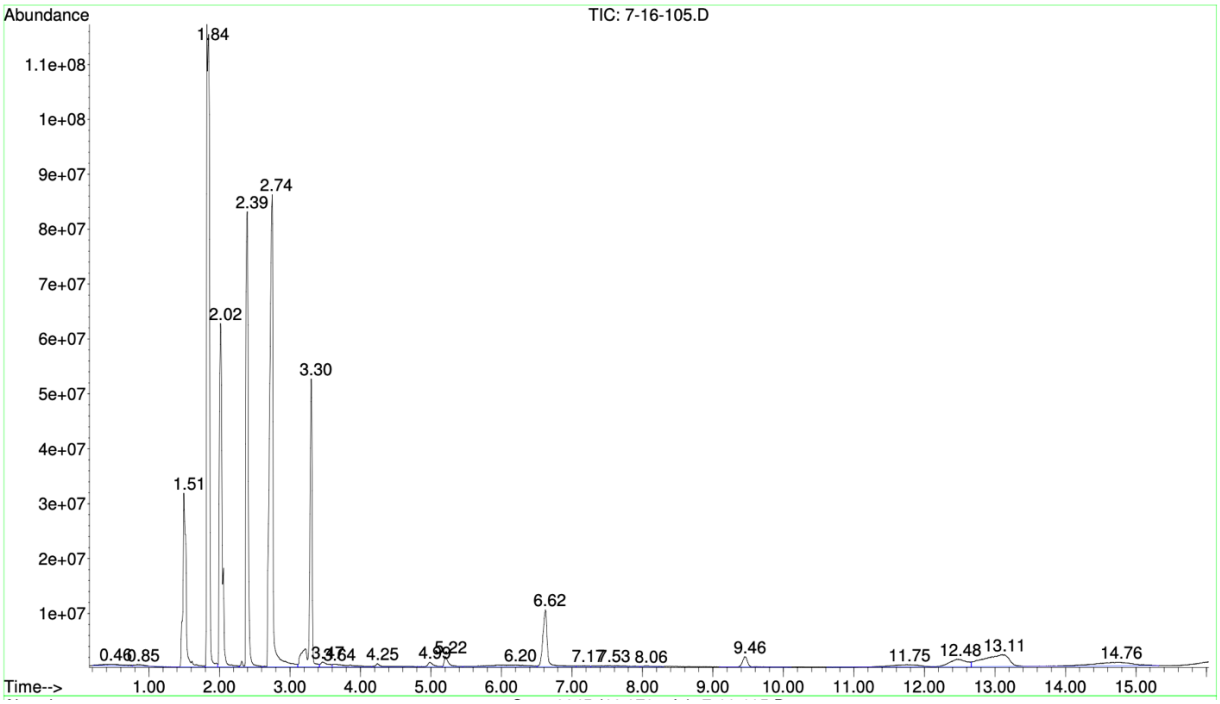


**Figure B8.** Gas chromatography spectra of the elimination of the 4-methoxy-5-(4-methylphenyl)-1,3-dioxolan-2-one after the addition of trimethylphosphite. Spectra collected after 105 minutes using an Agilent 6850 Series GC system and 5973 Network Mass Selective Detector.

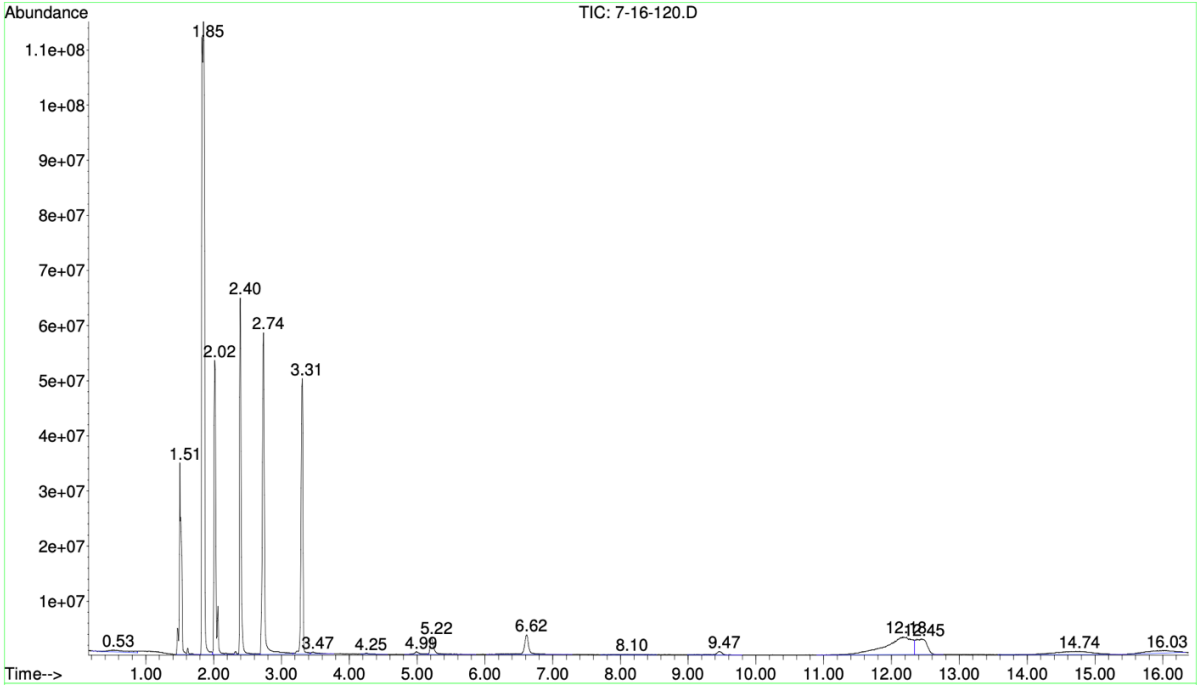


**Figure B9.** Gas chromatography spectra of the elimination of the 4-methoxy-5-(4-methylphenyl)-1,3-dioxolan-2-one after the addition of trimethylphosphite. Spectra collected after 120 minutes using an Agilent 6850 Series GC system and 5973 Network Mass Selective Detector.

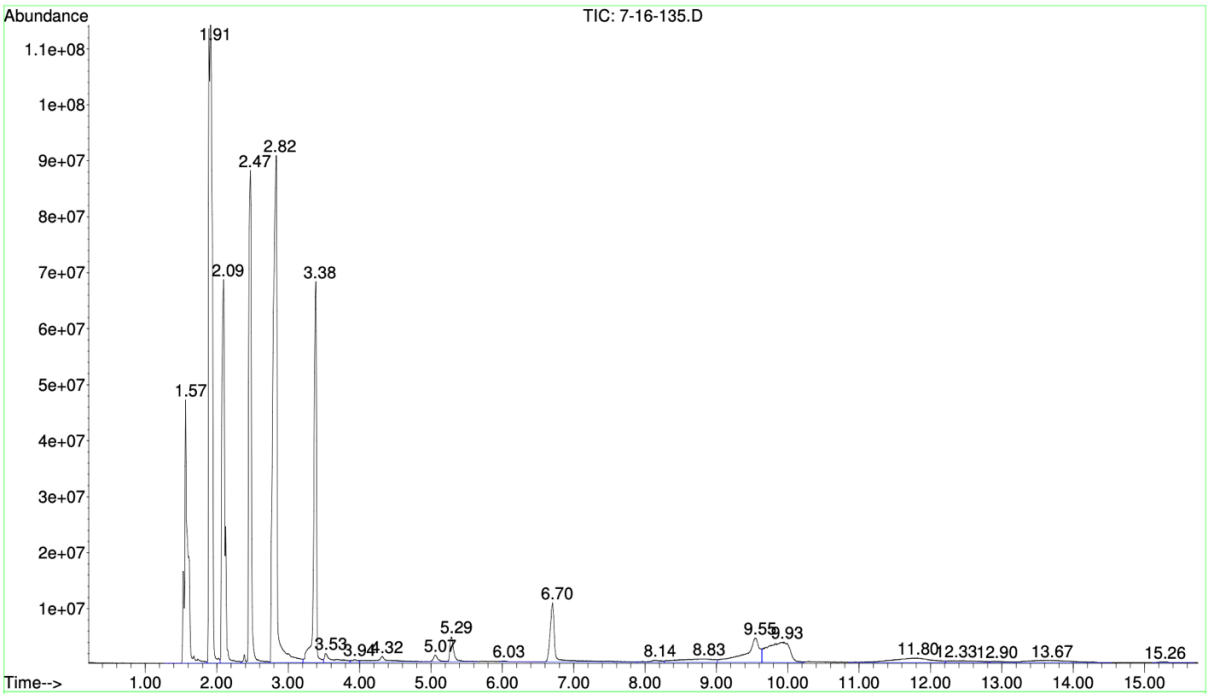


**Figure B10.** Gas chromatography spectra of the elimination of the 4-methoxy-5-(4-methylphenyl)-1,3-dioxolan-2-one after the addition of trimethylphosphite. Spectra collected after 135 minutes using an Agilent 6850 Series GC system and 5973 Network Mass Selective Detector.

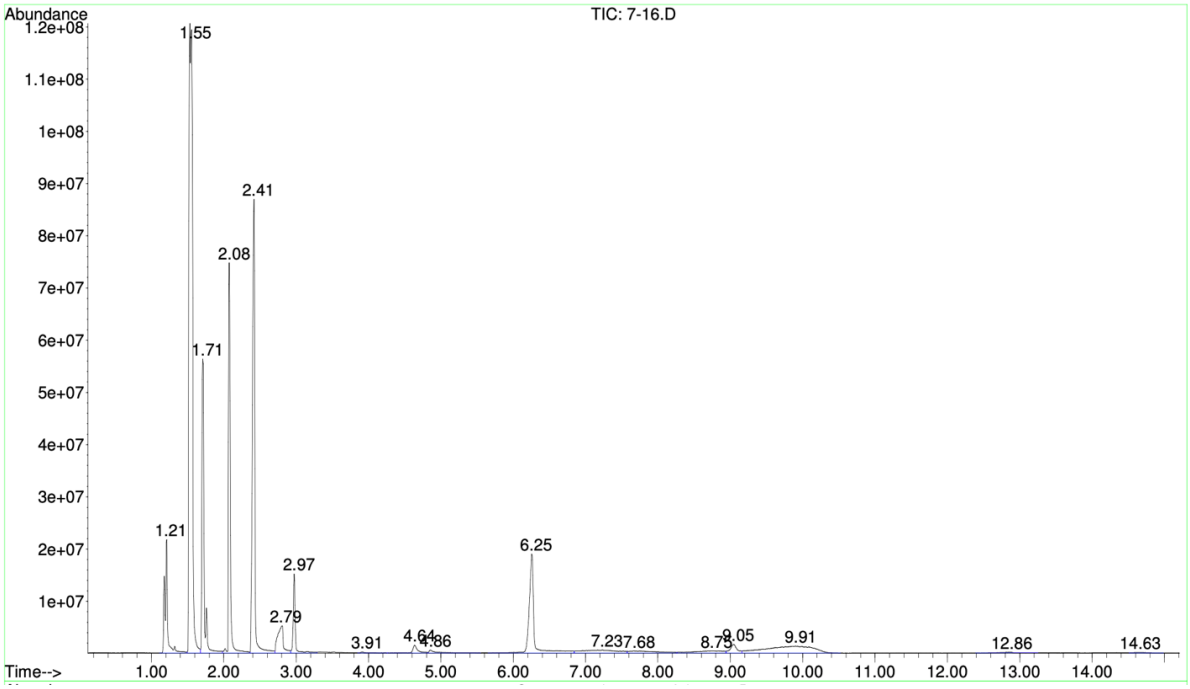


**Figure B11.** Gas chromatography spectra of the elimination of the 4-methoxy-5-(4-methylphenyl)-1,3-dioxolan-2-thione after the addition of trimethylphosphite. Spectra collected after 15 minutes using an Agilent 6850 Series GC system and 5973 Network Mass Selective Detector.

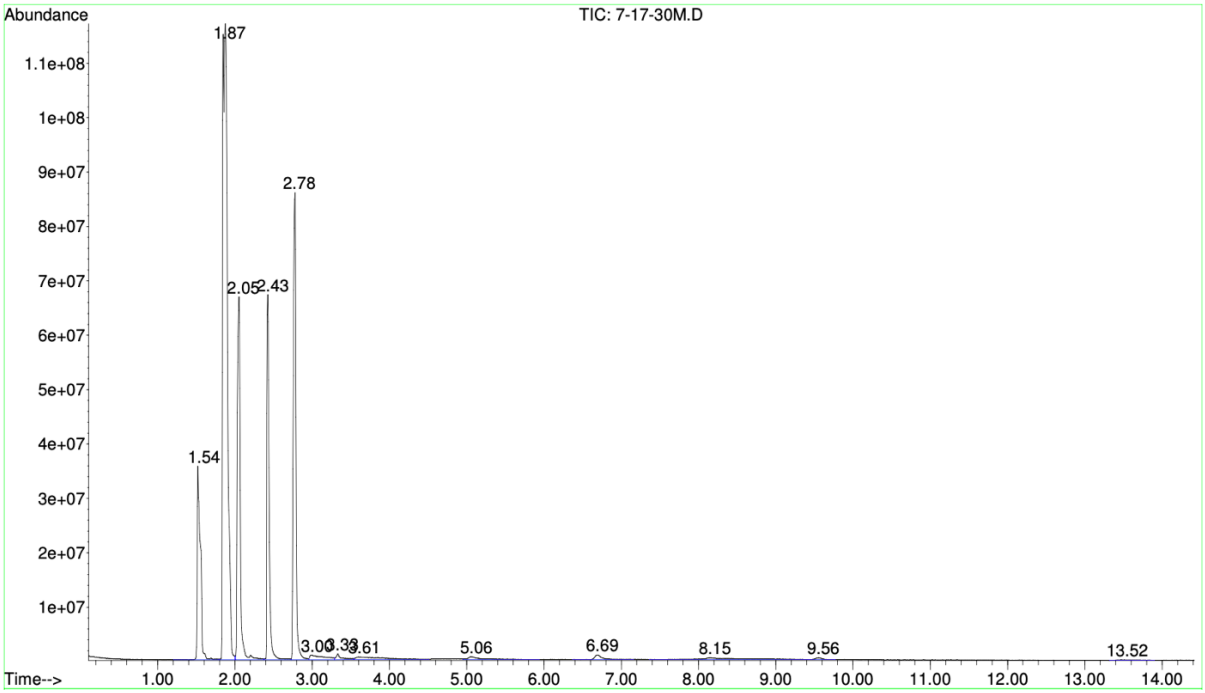


**Figure B12.** Gas chromatography spectra of the elimination of the 4-methoxy-5-(4-methylphenyl)-1,3-dioxolan-2-thione after the addition of trimethylphosphite. Spectra collected after 30 minutes using an Agilent 6850 Series GC system and 5973 Network Mass Selective Detector.

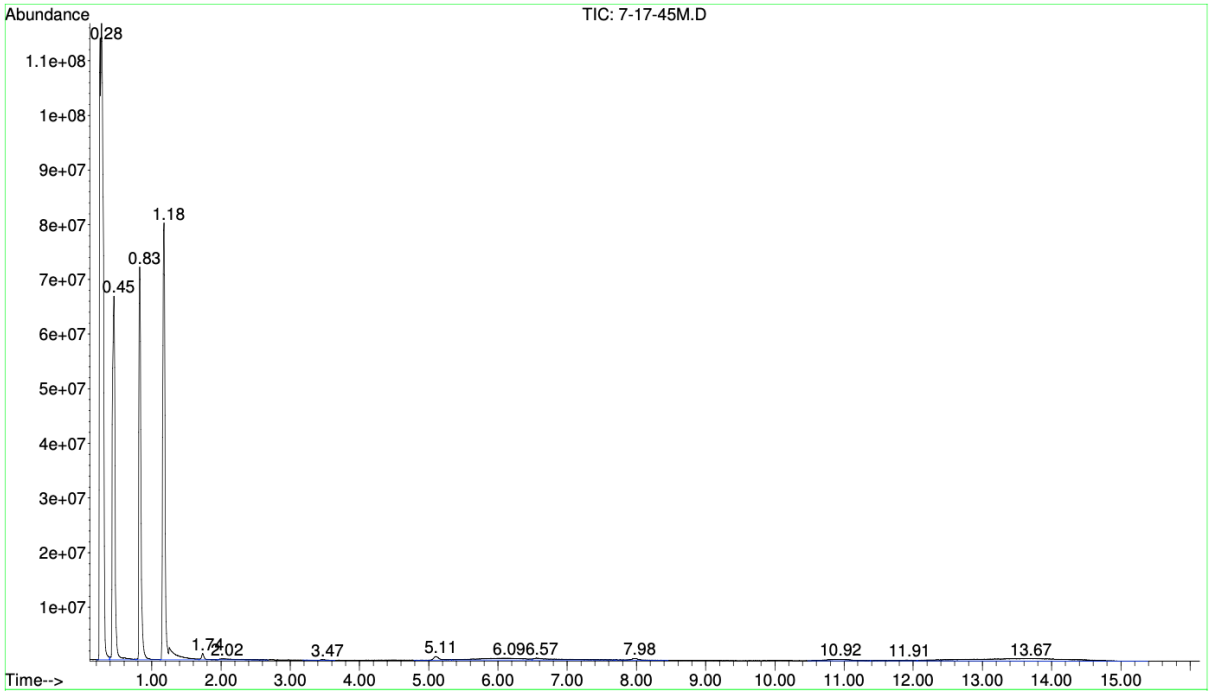


**Figure B13.** Gas chromatography spectra of the elimination of the 4-methoxy-5-(4-methylphenyl)-1,3-dioxolan-2-thione after the addition of trimethylphosphite. Spectra collected after 45 minutes using an Agilent 6850 Series GC system and 5973 Network Mass Selective Detector.

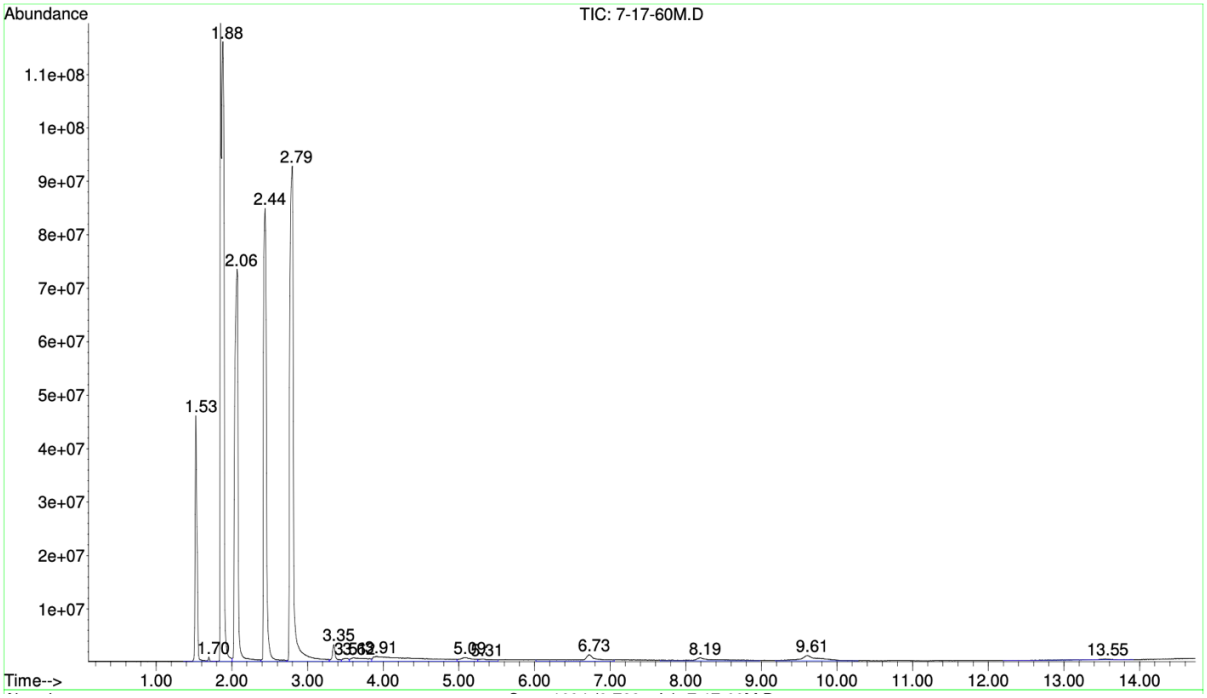


**Figure B14.** Gas chromatography spectra of the elimination of the 4-methoxy-5-(4-methylphenyl)-1,3-dioxolan-2-thione after the addition of trimethylphosphite. Spectra collected after 60 minutes using an Agilent 6850 Series GC system and 5973 Network Mass Selective Detector.

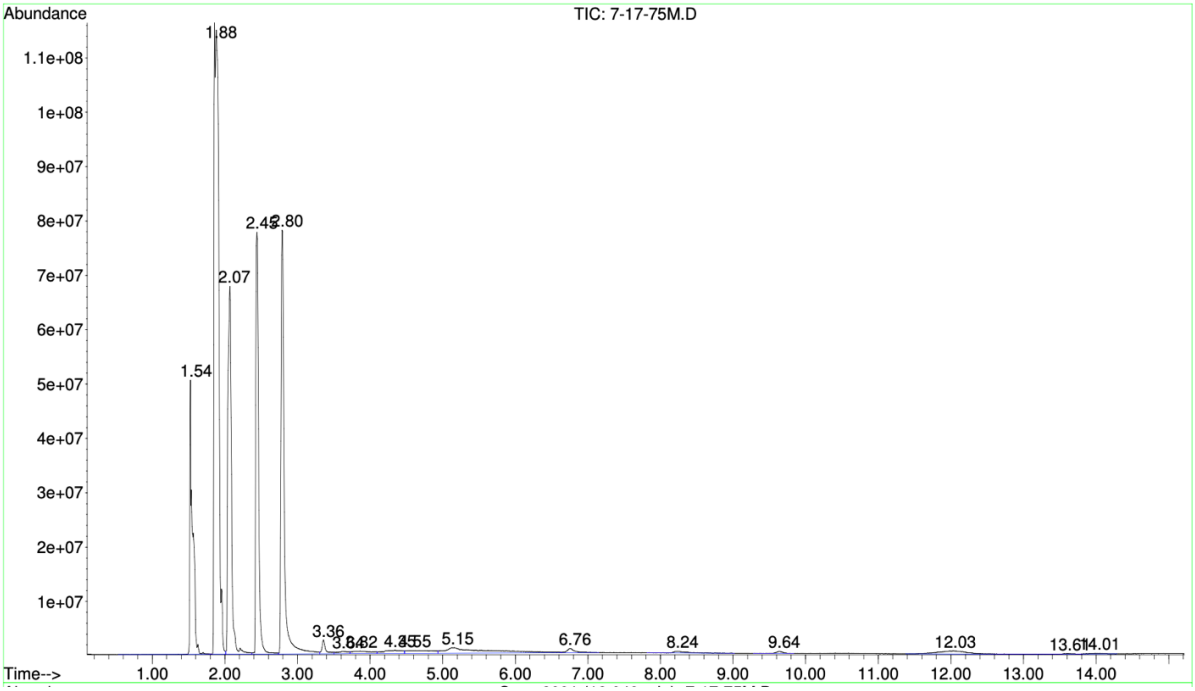


**Figure B15.** Gas chromatography spectra of the elimination of the 4-methoxy-5-(4-methylphenyl)-1,3-dioxolan-2-thione after the addition of trimethylphosphite. Spectra collected after 75 minutes using an Agilent 6850 Series GC system and 5973 Network Mass Selective Detector.

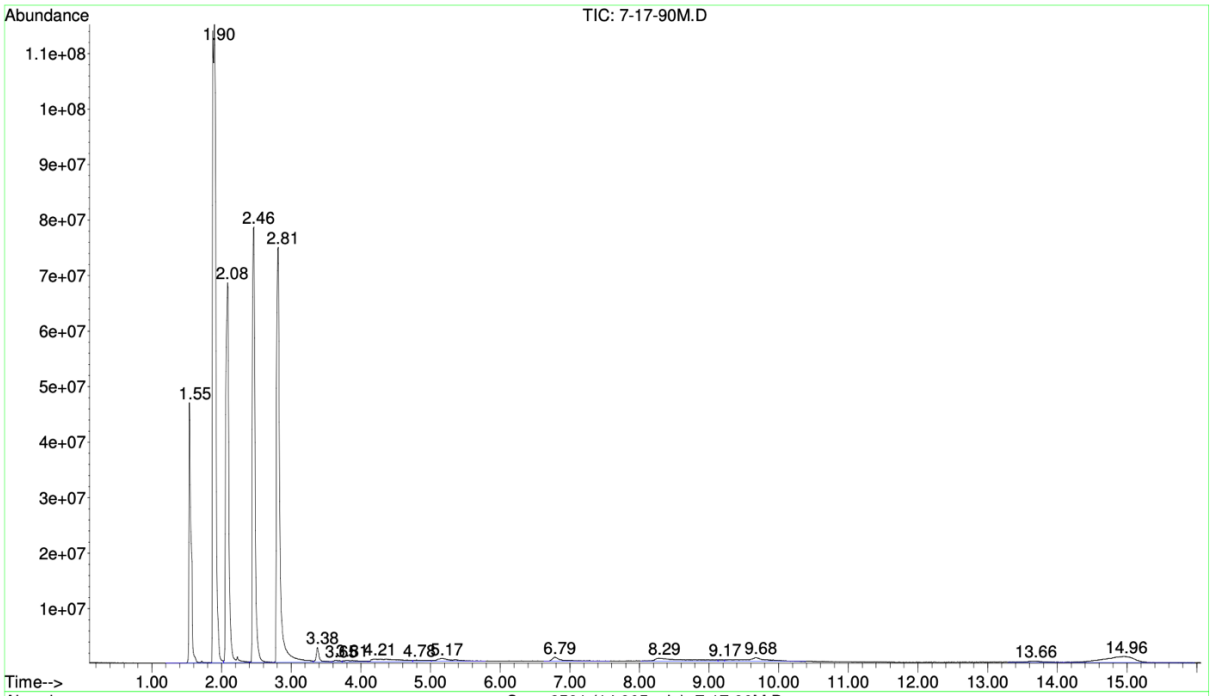


**Figure B16.** Gas chromatography spectra of the elimination of the 4-methoxy-5-(4-methylphenyl)-1,3-dioxolan-2-thione after the addition of trimethylphosphite. Spectra collected after 90 minutes using an Agilent 6850 Series GC system and 5973 Network Mass Selective Detector.

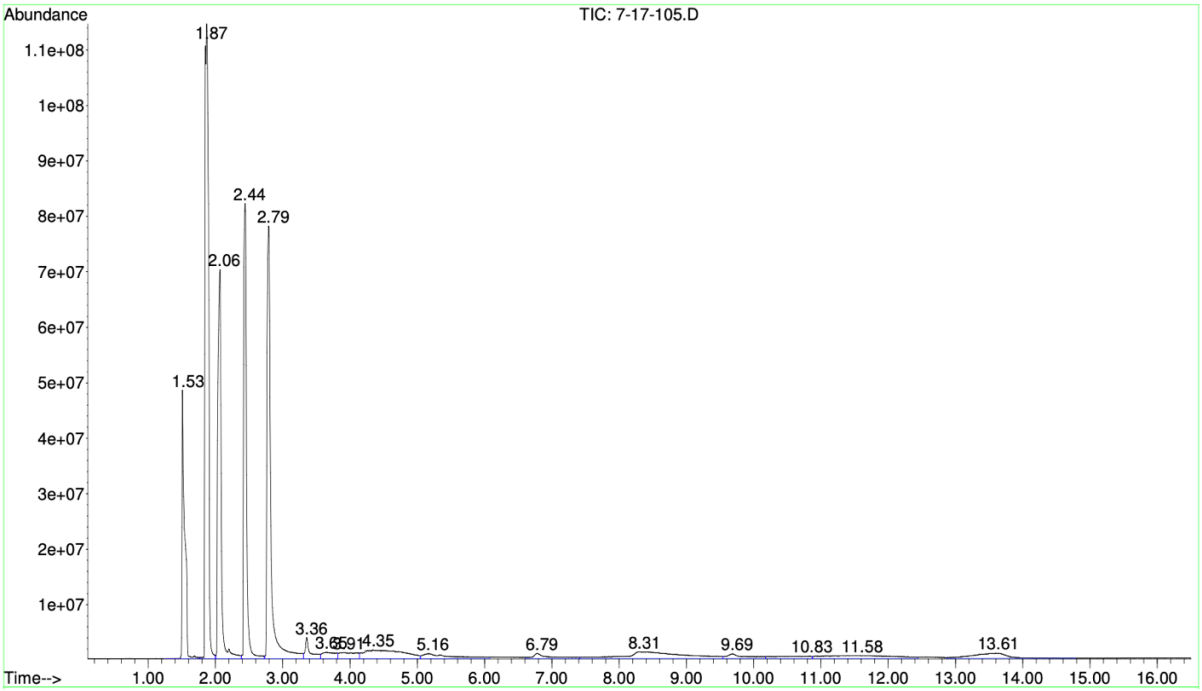


**Figure B17.** Gas chromatography spectra of the elimination of the 4-methoxy-5-(4-methylphenyl)-1,3-dioxolan-2-thione after the addition of trimethylphosphite. Spectra collected after 105 minutes using an Agilent 6850 Series GC system and 5973 Network Mass Selective Detector.

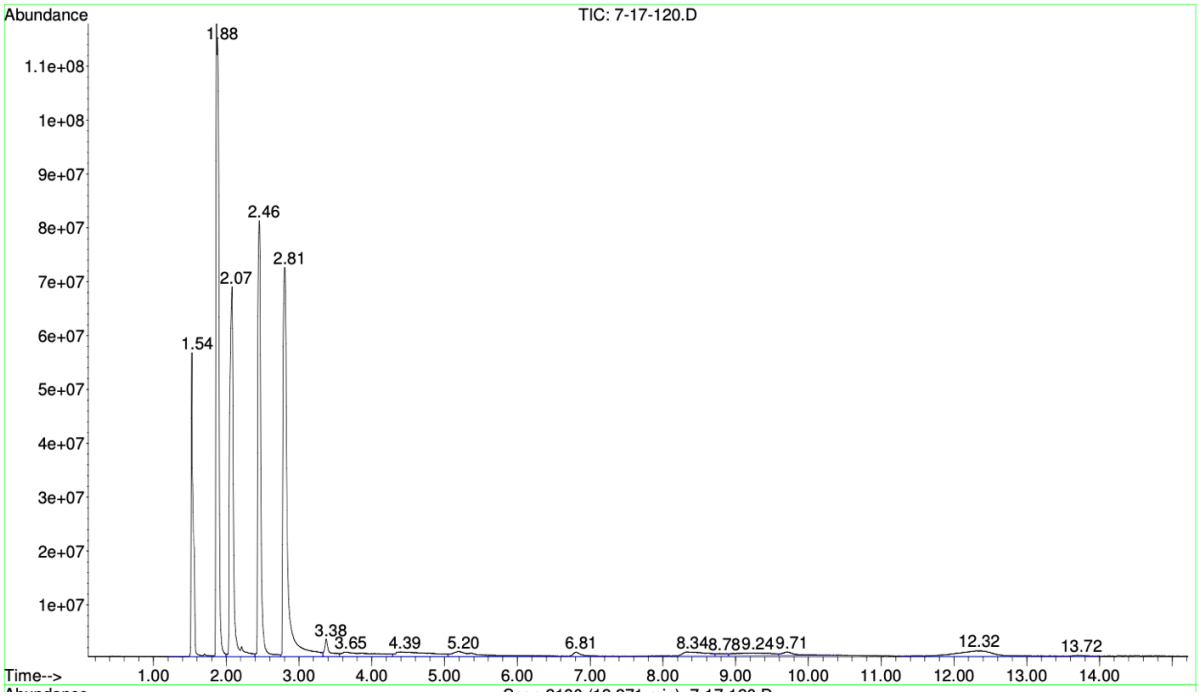


**Figure B18.** Gas chromatography spectra of the elimination of the 4-methoxy-5-(4-methylphenyl)-1,3-dioxolan-2-thione after the addition of trimethylphosphite. Spectra collected after 120 minutes using an Agilent 6850 Series GC system and 5973 Network Mass Selective Detector.

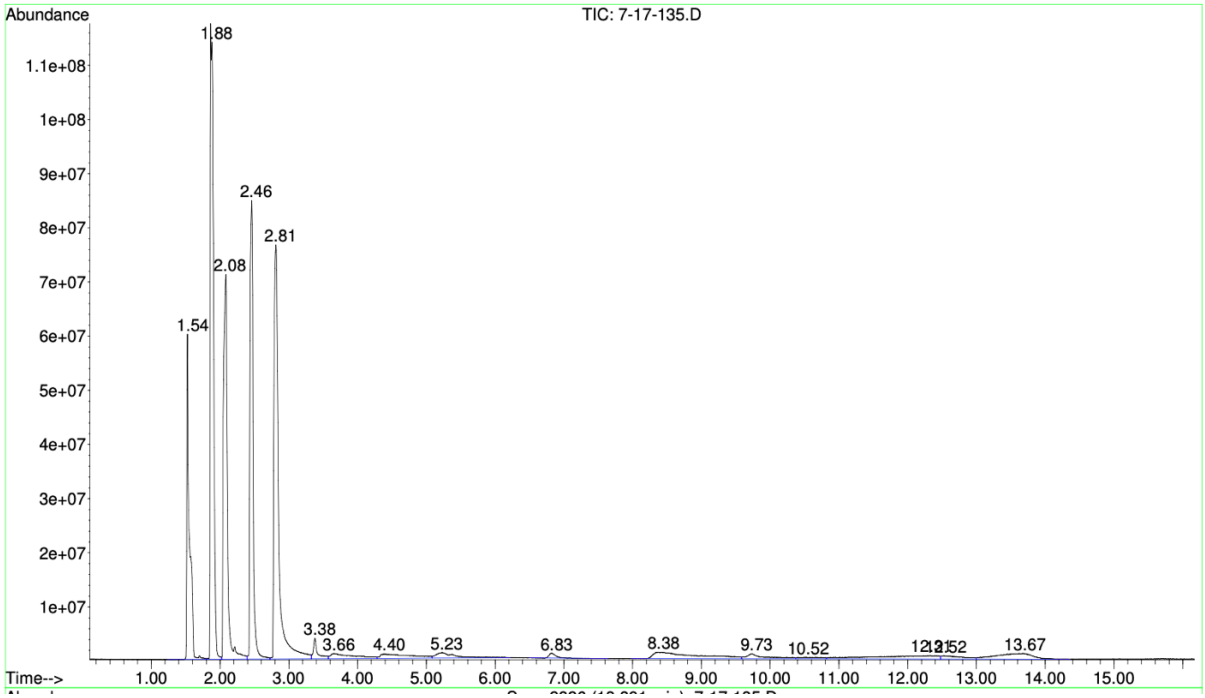


**Figure B19.** Gas chromatography spectra of the elimination of the 4-methoxy-5-(4-methylphenyl)-1,3-dioxolan-2-thione after the addition of trimethylphosphite. Spectra collected after 135 minutes using an Agilent 6850 Series GC system and 5973 Network Mass Selective Detector.