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Studies into the synthesis of alkyne dienophiles with η^6-Ruthenium Arene Complex Substituents

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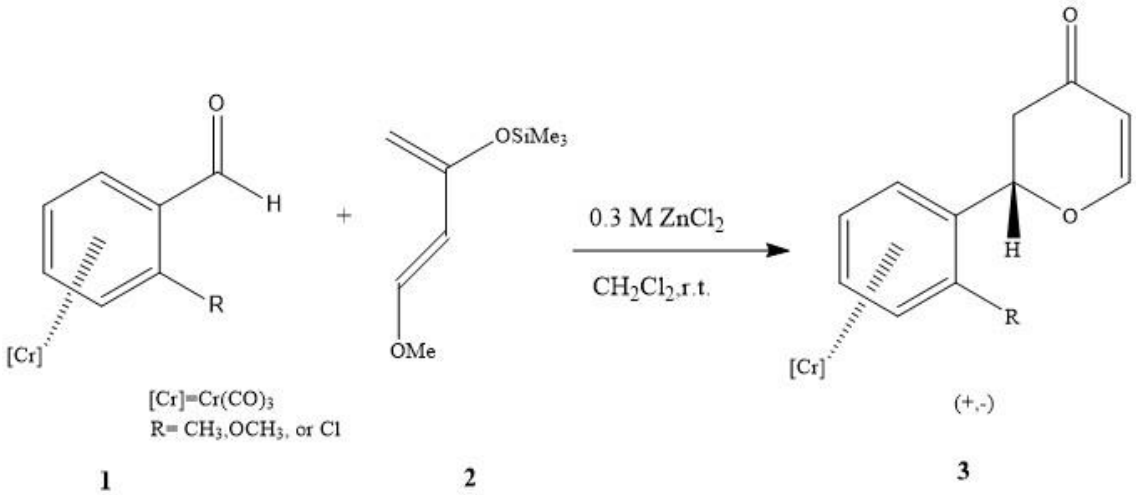
Abstract

In organic chemistry, η^6-metal arene complexes constitute a class of valuable intermediates in organic synthesis due to the metals ability to act as a strong electron withdrawing group.[1-9] While known for being an electron withdrawing group, little research regarding their ability to accelerate the Diels-Alder (DA) reaction - which is known to be accelerated by electron-withdrawing dienophile substituents -has been done. Previous work by the Hitt research group has strongly suggested that the DA reaction can be accelerated by an alkene dienophile with a η^6 -ruthenium arene substituent.[10] However, the effects of using an alkyne dienophile with a η^6 -ruthenium arene substituent have not been explored. Herein we report the synthesis of model dienophile precursor 3-phenyl-2-propenoic acid ethyl ester via an acyl substitution reaction. We also report our three attempts at synthesizing the alkyne dienophile [CpRu(η^6-(3-phenyl-2-propenoic acid ethyl ester))]PF_6. Unfortunately, after these three attempts, no product was obtained. It was thought that the alkyne in 3-phenyl-2-propenoic acid ethyl ester acted is a strong ligand to the $CpRu^+$ moiety thus inhibiting complexation to the aryl ring.

Introduction

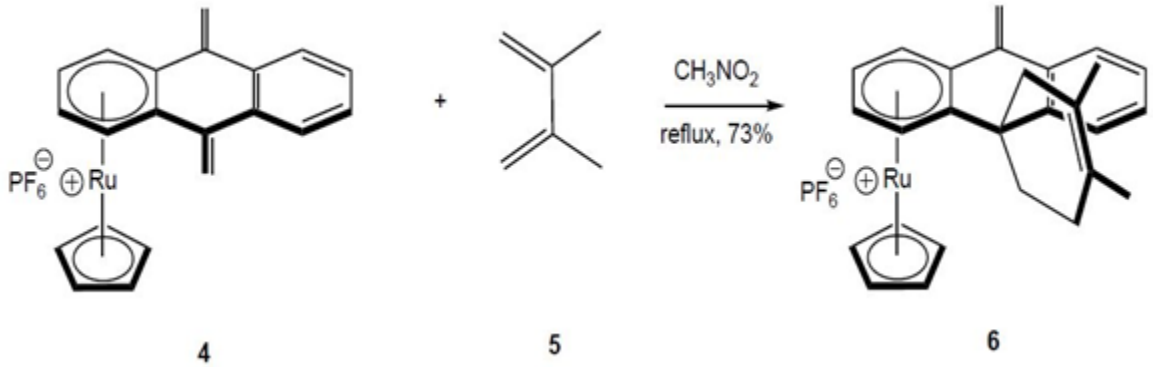
η^6-Metal arene complexes constitute a class of valuable intermediates in organic synthesis due to the ability of the metal to act as powerful electron-withdrawing group. [1-9] This property allows them to make aromatic reactions such as nucleophilic aromatic substitution and deprotonation of benzylic and aromatic positions facile. These reactions would otherwise normally happen only under very harsh conditions.

An application of the increased reactivity that η^6-metal arene complexes bestow is their use as a dienophile substituent in the DA reaction, leading to accelerated rates of reaction. A well-known instance of this involves the use of (η^6-arene)$Cr(CO)_3$ complexes as dienophile substituents.[2,5-6,11-18] For example, the research group led by Baldoli showed that the cycloaddition of *ortho*-substituted benzaldehyde–$Cr(CO)_3$ complexes (**1,** Scheme 1) to Danishefsky's diene (**2**) is an efficient method to synthesize the corresponding 2-aryl pyranone (**3)** as a single diastereomer.[7] Structures such as **3** serve as integral units of biooligomers and biopolymers that can be used in the synthesis of biologically relevant molecules.



Scheme 1: Lewis acid-promoted stereoselective hetero Diels–Alder reaction between Danishefsky's diene (**2**) and benzaldehyde chromium tricarbonyl complexes (**1**) to give corresponding 2-aryl pyranone(**3**) as a single diasteromer .[7]

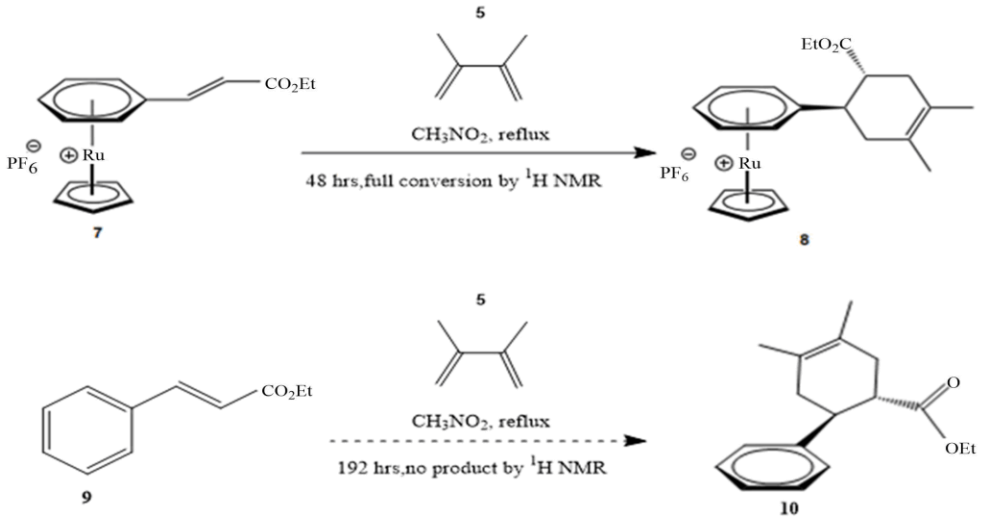
An alternative to (η^6 -arene)$Cr(CO)_3$ complexes is the less popular cationic η^6-cyclopentadienylruthenium(II) group ($CpRu^+$). The $CpRu(arene)^+$ complexes commonly exist as air-stable ion pairs with a non-coordinating anion (e.g. BF_4, PF_6, OTf). Despite proven to be valuable in organic synthesis,[9] there have only been three reported instances of research regarding the effectiveness of $CpRu^+$ complexes as dienophile substituents. The Glatzhofer research group was the first to observe the formation of DA adducts via the use of $CpRu^+$ as a dienophile substituent. Glatzhofer's research group showed that DA adduct (**6**, Scheme 2) could be formed as the sole diastereomer when the $CpRu^+$(arene) **4** was reacted with 2,3-dimethyl-1,3-butadiene (**5**) . The stereoselectivity was explained by a mechanism where the $CpRu^+$ moiety acts as a steric directing group, allowing the diene to successfully attack solely from the face anti to the metal fragment.[8]



Scheme 2: Previous work by the Glatzhofer research group using a dienophile with a $CpRu^+$ moiety (**4**)

In the second instance, Lindel and coworkers saw the formation of two stereoisomer DA products during the one-pot synthesis of [Cp*Ru(η^6- arene)]PF_6 sandwich complexes from ruthenium(III) chloride and ethyl *trans*-cinnamate.[19] These DA products were thought to have arose from DA cycloaddition of the ancillary ligand precursor, pentamethylcyclopentadiene (Cp*H), to the olefinic double bond of the complexed arene, ethyl *trans*-cinnamate. These DA products were seen as coincidental byproducts by Lindel's group and were not studied further after spectral characterization.

In the research involving DA reactions with η^6-metal ruthenium arene complex substituents, Glatzhofer [8] and Lindel[19] made no direct rate comparisons of dienophiles with η^6-ruthenium arene moieties to non-complexed dienophiles. Based on the powerful electron withdrawing properties of η^6-metal arene complexes, it could be hypothesized that a difference in reaction rate would be seen as it is well known that normal electron-demand DA reactions are accelerated by electron-deficient dienophiles. Previous research by the Hitt group has contributed to the gap of knowledge in this area by directly comparing the DA reaction rate of free ethyl *trans*-cinnamate (**9**) to [CpRu(η^6-(ethyl *trans*-cinnamate))]PF_6 (**7**) with dienophile **5**.[10] The reaction involving the non-complexed dienophile did not produce any product after eight days while the reaction involving the metal-arene substitued dienophile went to completion in 48 hours, demonstrating the ability of the η^6-metal ruthenium arene complex to markedly accelerate the reaction.

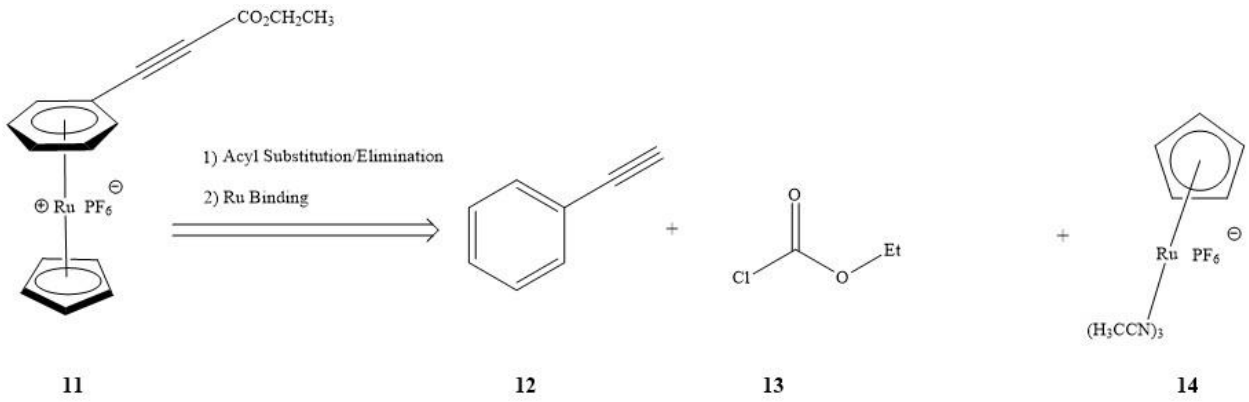


Scheme 3: Previous work by the Hitt research group showing the DA accelerating abilities of the [CpRu(η^6-arene)]PF_6 dienophile (**7**)

The goal of this study is to explore the effect that an alkyne [CpRu(η^6-arene)]PF_6 dienophile would have on the rate of the DA reaction. The work done previously in our group

has shown that the use of a [CpRu(η^6-arene)]PF_6 alkene-based dienophile (**7**) greatly accelerates the DA reactions as compared to the metal-free dienophile. Based on these results, we hypothesize that the use of an [CpRu(η^6-arene)]PF_6 alkyne-based dienophile would accelerate the DA reaction to an even greater extent. An alkene [CpRu(η^6-arene)]PF_6 dienophile has the issue of greater steric interactions during the DA reaction because one of its substituents will always be situated underneath the diene in the transition state, leading to steric repulsion (assuming some stabilization by secondary orbital overlap – *endo* effect).[20] Because of the bond angles that the alkyne dienophile exhibits, steric hindrance should be decreased as the substituents would be in a pseudo-linear geometry during the transition state. The use of an alkyne dienophile also eliminates the possibility for diastereomer formation or isomerization once the cycloaddition has occurred thus eliminating any need for purification after the DA reaction and simplifying spectral analysis of the crude material – a necessary requirement for more quantitative rate studies. In this study, we plan to investigate the effect that an alkyne dienophile (**11,** Scheme 5) has on the rate of the DA reaction. It should also be noted that all reported η^6-metal-arene substituted dienophiles have been alkene-based, thus making this research the first attempt at studying the alkyne as a dienophile in this context.

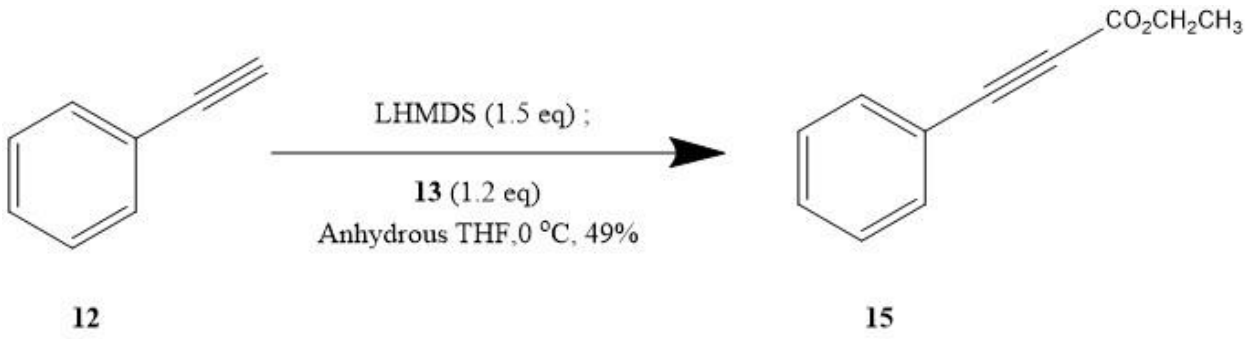
Results and Discussion



11 **12** **13** **14**

Scheme 4: Proposed retrosynthesis of model dienophile substrate

To begin our research, Ru-arene complex **(11),** containing Cp and phenylpropiolic acid, methyl ester aryl ligands, was chosen as the model alkyne-based dienophile substrate for the DA rate comparison study. Complex **11** was envisioned to form by first reacting phenylacetylene (**12**) with ethyl chloroformate (**13**) via an acyl-substitution reaction then complexing the resulting product with [CpRu$(NCMe)_3$]PF_6 (**14**).



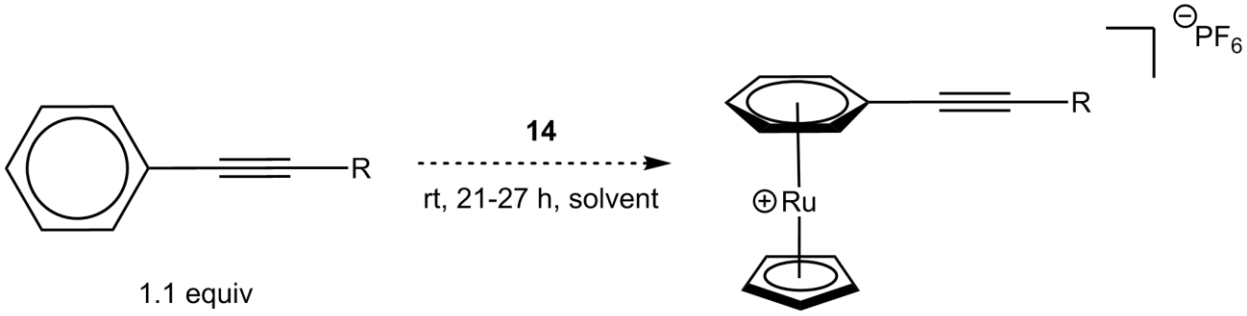
Scheme 5: Synthesis of free arene dienophile (**15**).

The synthesis of the Ru-arene complex was initiated by the acyl substitution reaction of reaction between **12** and **13**. Lithium hexamethyldisilylamide (LHMDS) was used to deprotonate the acetylenic hydrogen from **12** thus making the necessary acetylide nucleophile. This resulted in successful isolation of the free-arene **15** after purification via column chromatography. Analysis of the isolated product by GC-MS showed the molecular ion peak at 174 m/z in the mass spectrum and a single peak in the chromatogram, indicating a high level of purity. Analysis of the IR spectrum showed the appearance of a carbonyl stretch at 1701.66 cm^{-1}, and symmetrical and asymmetrical C≡C stretches at 2235.04 and 2208.59 cm^{-1}, which was in close agreement with literature.[21] Analysis of the ^{1}H NMR spectrum showed the appearance of the added ethyl group from a quartet at δ 4.30 and triplet at δ 1.36 in a 2:3 ratio, respectively. These NMR signals were also observed to integrate accordingly to the aromatic hydrogen signals.

The next step in the synthetic pathway was to attach the $CpRu^{+}$ moiety to the precursor benzenoid **15** via reaction with **14** (Table 1). The first attempt was conducted in dichloromethane using a slight excess of **15** to **14** (trial 1). Unfortunately, analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed no appearance of the Cp proton signal between the typical range of δ 5 - 6. Furthermore, the diagnostic upfield shift of the aryl hydrogen signals in ruthenium-arene complexes between δ 7 – 5.5 was also not observed

Two additional attempts were made at synthesizing the Ru-arene complex **(11)** using identical stoichiometries to the first attempt between the arene and metal precursor**.** The second trial was conducted in a different solvent, acetone, which was thought to be more coordinating than dichloromethane and might help to stabilize the metal complex. In a third attempt (trial 3), the free arene was changed to phenylacetylene (**12)** as it was thought that the ester present on the alkyne in **15** may bind the metal very strongly due to the electron-deficient nature of the π-system (increased back-bonding between the metal d electrons and the low-lysing π* orbital on the ligand). Unfortunately, spectral analysis of the crude products from this final attempt also showed no evidence for successful attachment of the CpRu cation.

Table 1: Trials for attempted synthesis of an alkyne-substituted [CpRu(η^6-arene)]PF_6 complex.



Trial	R	solvent
1	CO_2Et	CH_2Cl_2
2	CO_2Et	acetone
3	H	CH_2Cl_2

We hypothesize that the complexation reactions failed due to strong coordination of the alkyne to the metal thus inhibiting arene complexation. Both the Liu and Jordan research groups have observed that when **15** was reacted with Cp*RuCl(COD) (**16**), the metal binds to the alkyne to form isolable complex **17**[22,23] Although the metal precursor is different, we propose that a similar process may be occurring in our system to form a related species (**Figure 1**); however, we believe that the η^2-alkyne complex decomposes when exposed to air, thus inhibiting our ability to isolate it.

Scheme 6: Ruthenium catalyzed association of **16** with **15** as observed by Liu and Jordan

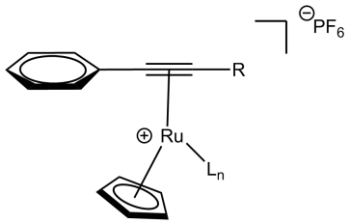


Figure 1: Proposed intermediate alkyne complex.

Conclusion

We have proposed and attempted to synthesize a model alkyne dienophile (**11**), consisting in part of a η^6 -ruthenium arene complex, in order to be used in a Diels Alder reaction. However, synthesis of the dienophile was unsuccessful and was thought to have failed due to the alkyne acting as a strong ligand for the $CpRu^+$ moiety. Further studies will be focused on developing different methods to attach the $CpRu^+$ fragment to an alkyne precursor as well as identification of other η^6-metal arene complexes that may bind alkyne precursors.

Experimental

General Information. All reagents used were purchased from chemical suppliers and used as received. Flash column chromatographic purification of synthetic intermediates and substrates was performed using silica gel (60 Å, particle size 43-60 m, 230-400 mesh) or activated neutral alumina (50-200 micron, Acros Organics).

Instrumentation. NMR spectra were recorded on a Bruker BioSpin Ascend Aeon 400 (^{1}H, 400 MHz; ^{13}C 100 MHz) spectrometer. ^{1}H and ^{13}C NMR chemical shifts (δ) were reported in parts per million (ppm) relative to tetramethylsilane (1H and 13C, δ0.00 ppm), with reference to the residual proton or carbon resonance for CDCl3 (^{1}H, δ 7.26 ppm; 13C δ 77.16 ppm). Infrared (IR) spectra were recorded on a ThermoFisher Nicolet Smart iTR iS10 FTIR. Mass Spectra were recorded on a Hewlett Packard 5973 Mass Selective Detector using Electronic Ionization coupled to a Hewlett Packard 6890 Series GC System equipped with a 5% Phenyl polysilphenylene-siloxane column (Trajan, P/N 054310).

Synthesis of (13)

A solution of LHMDS (2.8 mL, 2.94 mmol, 1.06 M in hexanes) was added to a flask containing phenylacetylene (0.215 mL, 1.96 mmol) and stirred for 10 minutes in a water-ice bath under a nitrogen atmosphere. Anyhydrous THF (19.6 mL) was then added. After stirring for 5 minutes in an ice bath, ethyl chloroformate (0.22 mL, 2.35 mmol) was added dropwise and the reaction mixture was stirred for 30 minutes in ice bath then poured over a saturated solution of ammonium chloride (70 mL). The resulting mixture was partitioned and the aqueous layer was washed with ethyl ether (2 x 70 mL). The combined organic layer was washed with brine (12 mL), dried over anhydrous $MgSO_4$, concentrated under reduced pressure, and purified by silica column chromatography (10:1 silica/crude, hexanes then 95:5 hexanes / EtOAc) to afford **(13)** as a yellow oil (0.168 mg,0.964 mmol, 49 % yield). IR (ZnSe,neat): 2235.04 & 2208.59 (C≡C), 1701.66 (C=O) cm^{-1}. ^{1}H NMR: δ 1.36 (t, $^3J_{HH}$ = 7.2 Hz, 3H, CH_3), δ 4.3 (q , $^3J_{HH}$ =7.2 Hz, 2H,

CH_2), δ 7.37 (t, $^3J_{HH}$ =7.6 Hz , 2 H, *meta*-$C_{Ar}H$), δ 7.44 (t, $^3J_{HH}$ =7.6 Hz, 1 H, *para*-$C_{Ar}H$), δ 7.58 (d, $^3J_{HH}$ = 7.8 Hz, 2 H, *ortho*-$C_{Ar}H$).

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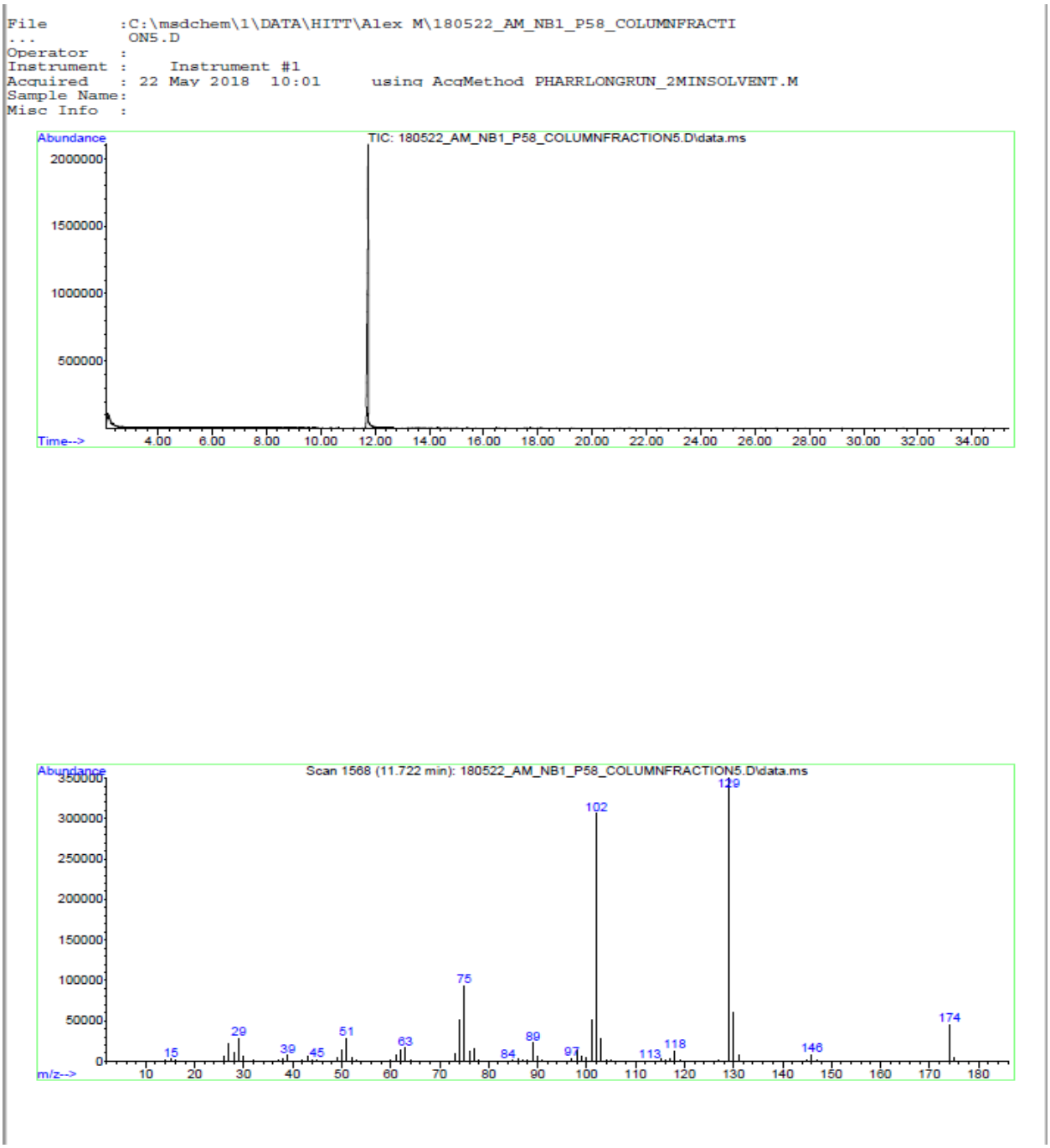
Table of Appendices



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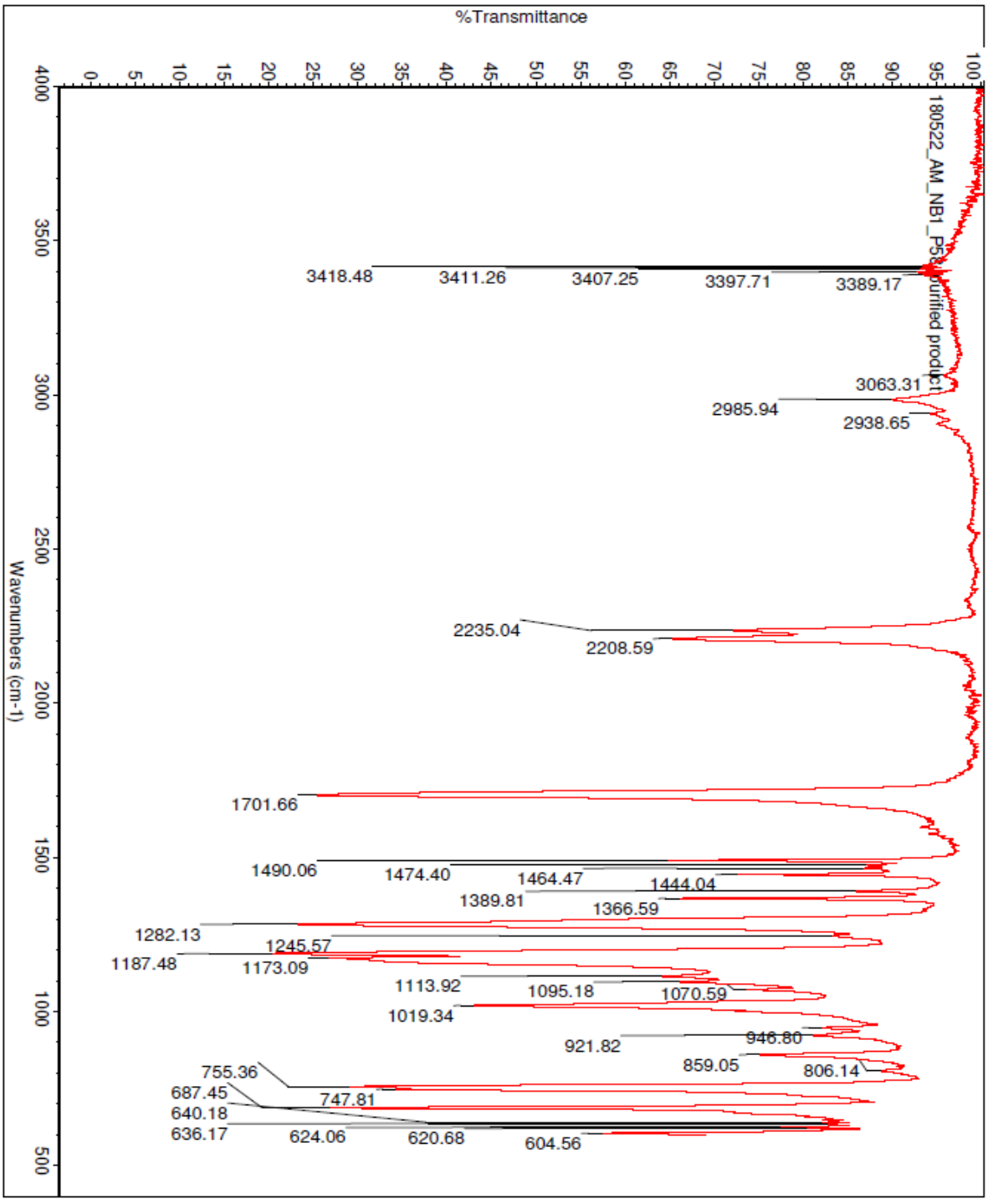

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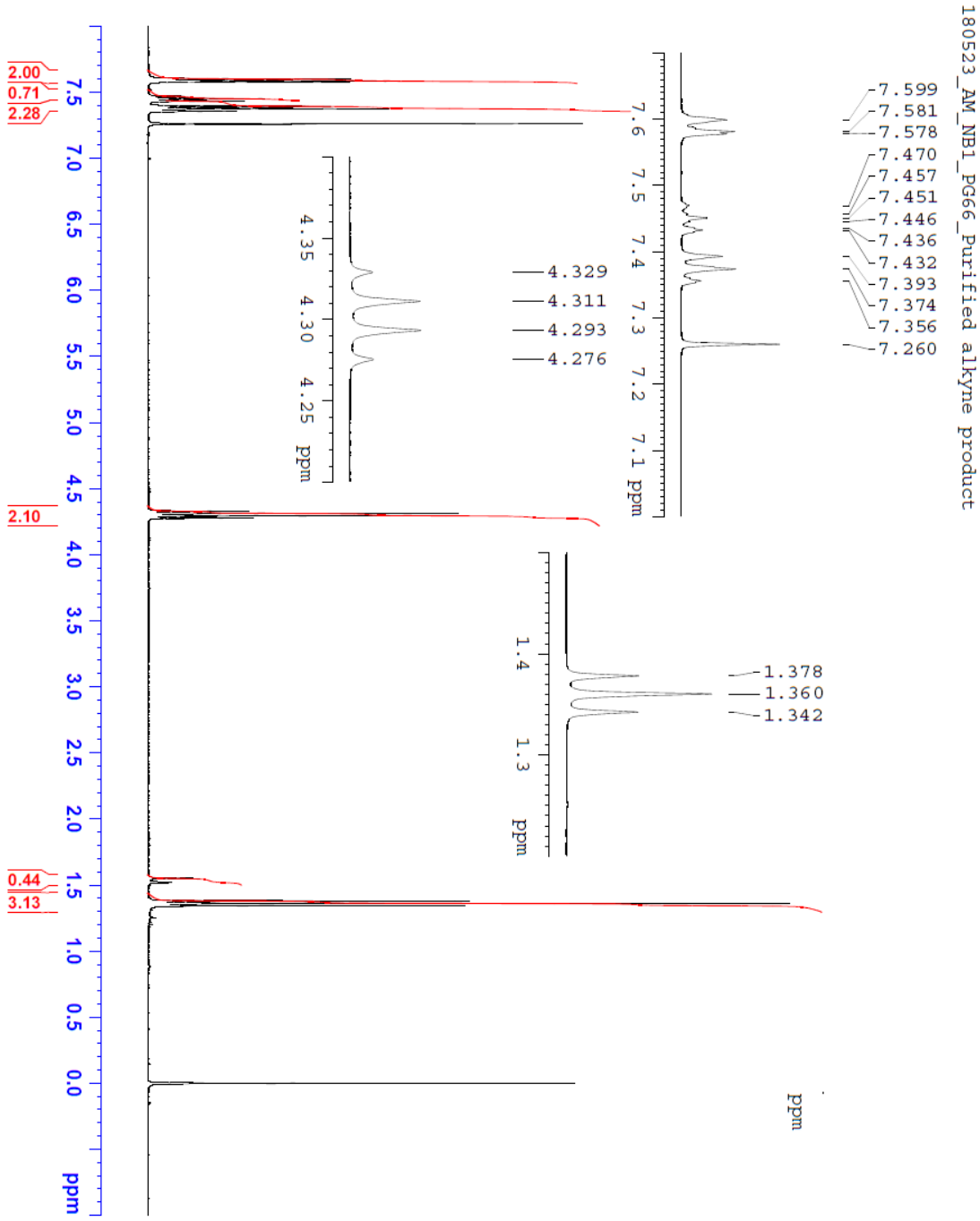

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