

**STUDIES IN SIMULTANEOUS GENERATION OF CENTRAL AND AXIAL  
CHIRALITY VIA THE BUCHWALD-HARTWIG REACTION**

by

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## Abstract

# STUDIES IN SIMULTANEOUS GENERATION OF CENTRAL AND AXIAL CHIRALITY VIA THE BUCHWALD-HARTWIG REACTION

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The Buchwald-Hartwig reaction has been investigated previously by the Viirre group to show that intramolecular cyclization using palladium and (R)-(+)-2-(diphenylphosphino)-2'-methoxy-1,1'-binaphthyl, can instill enantioselectivity. This system was continued to show that steric bulk on the 2' position on the phenyl ring attached to the nitrogen malonamide can lock the rotation ending in a chiral axis. The diastereomers resulting from this chiral axis can be selectively formed when the substrate is 2-(2-bromobenzyl)-*N*1,*N*3-bis(2-(tert-butyl)phenyl)-2-methylmalonamide and using a similar ligand (*R*)-dicyclohexyl(2'-methoxy-[1,1'-binaphthalen]-2-yl)phosphane with enantio- and diastereoselectivities of 88% and 99% respectively. The work presented in this thesis continues on this class of substrates to include *N*,1-Di([1,1'-biphenyl]-2-yl)-3-methyl-2-oxo-1,2,3,4-tetrahydroquinoline-3-carboxamide, as well as a newer class of monoamide substrates. The monoamide substrates allowed the interpretation of events occurring in the Buchwald-Hartwig reaction, ultimately showing that the chiral center on the substrate has some control as to the outcome of the chiral axis. Lastly, a timed sampling kinetics experiment was done to investigate if the enantiomers of the starting material were being consumed at different rates or if one diastereomeric product was being produced favourably. The kinetics experiment shows that the system does not have a preference as to the starting material or product being produced.

## **Acknowledgements**

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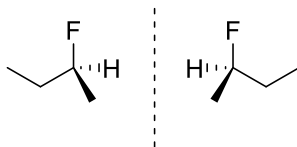
## 1 Introduction

### 1.1 Stereochemistry

Stereochemistry is an area of chemistry devoted to understanding the differences between molecules which have the same atoms and bonds but differ in their three-dimensional structures. Isomers that differ in this way are known as stereoisomers.<sup>1</sup> This thesis deals with issues of stereochemistry and will therefore begin with a brief introduction into the matter.

#### 1.1.1 Chirality

Chirality is a property of certain organic molecules that arises from not being superimposable on their mirror image, as seen in Figure 1.



**Figure 1 - Mirror Images of 2-Fluorobutane**

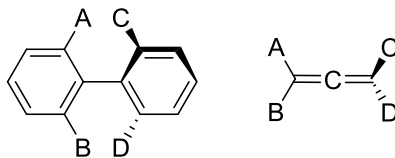
##### 1.1.1.1 Point Chirality

Point chirality exists when having four different groups bonded to a central tetrahedral carbon atom.<sup>1</sup> As in Figure 1, the carbon atom bonded to F, H, ethyl and methyl is at the center of the chirality. This is known as the chiral center.<sup>1</sup>

##### 1.1.1.2 Axial Chirality

When the chiral element is not on a single atom, but along a bond between two atoms, this is known as axial chirality.<sup>2</sup> Generally, bonds are allowed to rotate freely, but when this

rotation is restricted by steric hindrance or  $\pi$  bonds, this creates an element of chirality, as in Figure 2.



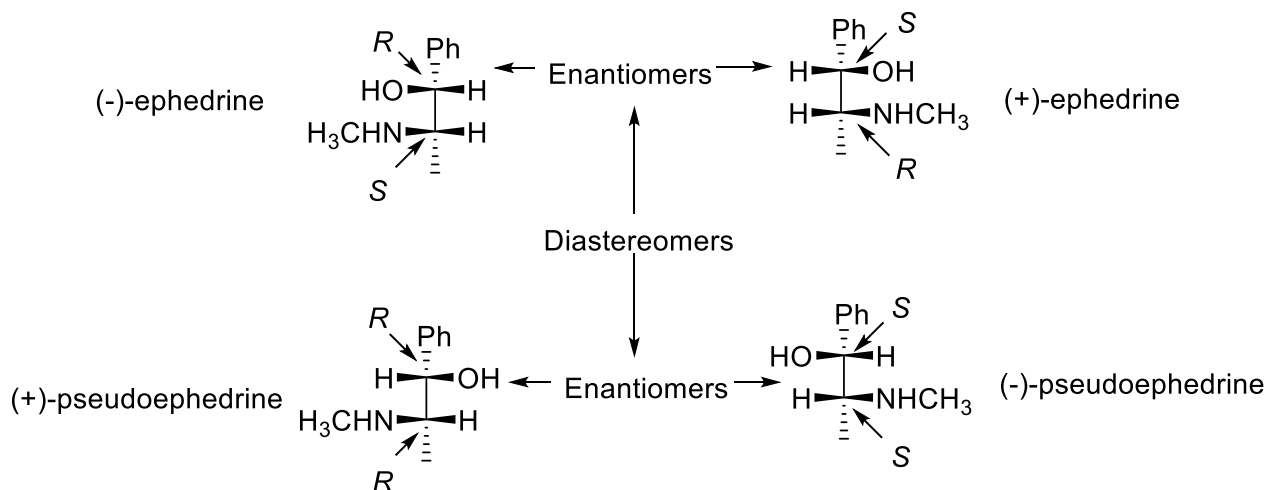
**Figure 2 – Axial Chirality Due to Restricted Rotation Both Sterically  
and by  $\pi$  Bonds**

### 1.1.2 Enantiomers

Referring back to Figure 1, the two molecules differ only in the arrangement of the substituents bonded on the chiral center. These give rise to the nonsuperimposable mirror images as seen. The pair that is represented in this figure are known as enantiomers.<sup>1</sup> Enantiomers have identical physical and chemical properties in achiral environments. Enantiomers behave differently in chiral environments, i.e. chiral reactions and biological activities, and can be separated by chiral means, i.e. chiral salts, chiral HPLC, etc.

### 1.1.3 Diastereomers

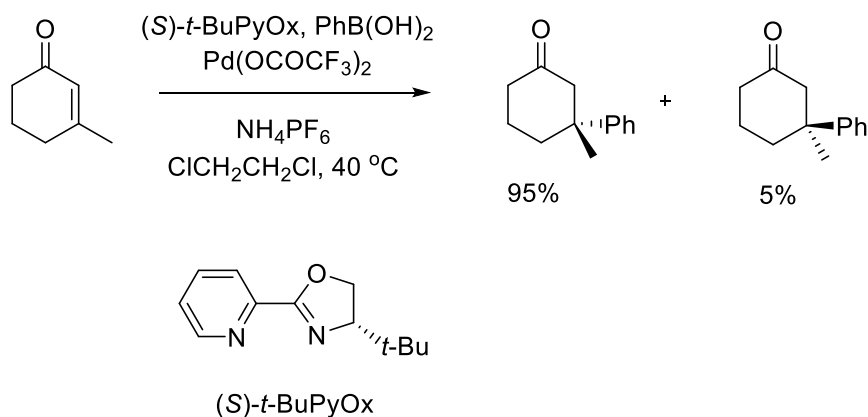
Molecules that have  $n$  chiral centers or elements typically have  $2^n$  different stereoisomers. For instance, the four possible arrangements in a molecule that has two chiral centers or elements are, *RR*, *SS*, *SR*, *RS*. When both chiral elements are switched to the opposite configuration, those molecules are enantiomers. This means, *RR* is the enantiomer of *SS*, and *SR* is the enantiomer of *RS*. A diastereomer is when at least one chiral element is different, while at least one is the same.<sup>1</sup> For instance, in this case *SR* and *RS* are diastereomers of *RR* and *SS*. This is depicted by the stereoisomers of ephedrine and pseudoephedrine in Figure 3.



**Figure 3 – The Four Configurations in Molecules with Two Chiral Centers**

#### 1.1.4 Stereoselectivity

Reactions that have achiral reagents and produce a chiral product always produce equal amounts of *R* and *S*. This is known as a racemic mixture. When one or more reagents or catalyst, used in a reaction is chiral, then there can be a preference for one enantiomer over another, as depicted in the reaction given in Figure 4.<sup>3</sup>



**Figure 4 – Enantioselective Palladium Catalyzed Arylation**

Stereoselectivity is measured in enantiomeric excess or %ee. The enantiomeric excess is calculated by the difference of the enantiomers divided by the sum of the enantiomers. The ee for the reaction in Figure 4 is 90% ee.

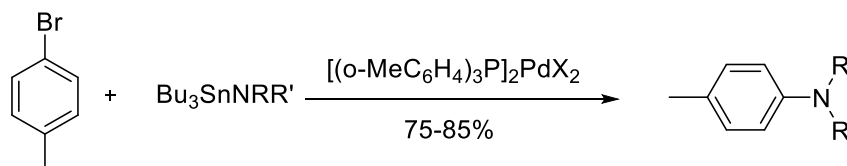
$$\frac{|R - S|}{|R + S|} \times 100 = \frac{|95-5|}{|95+5|} \times 100 = 90\% \text{ ee}$$

**Figure 5 – Enantiomeric Excess Equation**

An enantiomeric excess of 100% would mean only one of the enantiomers was produced, or enantiopure. An enantiomeric excess of 0% would be equal parts of each enantiomer, or racemic.

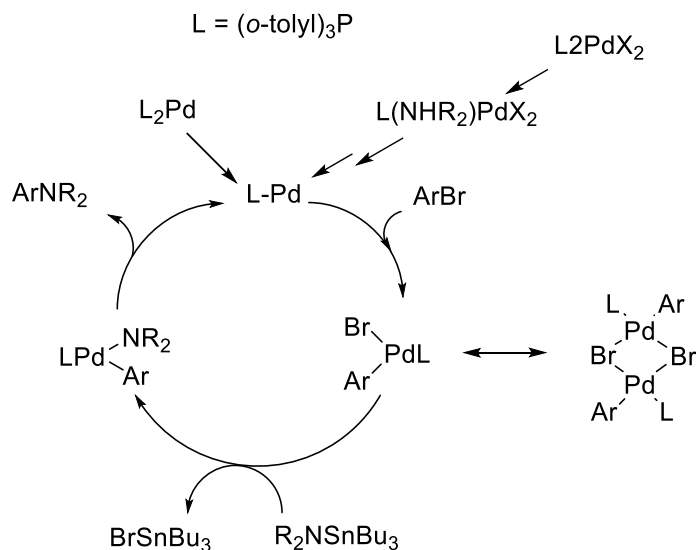
## 1.2 Buchwald – Hartwig Cross-coupling Reactions

In the early 1990's, Buchwald<sup>4</sup> and Hartwig<sup>5,6</sup> started working on palladium catalyzed nitrogen arylation. The overall reaction is seen in Figure 6.



**Figure 6 - General Buchwald-Hartwig Reaction**

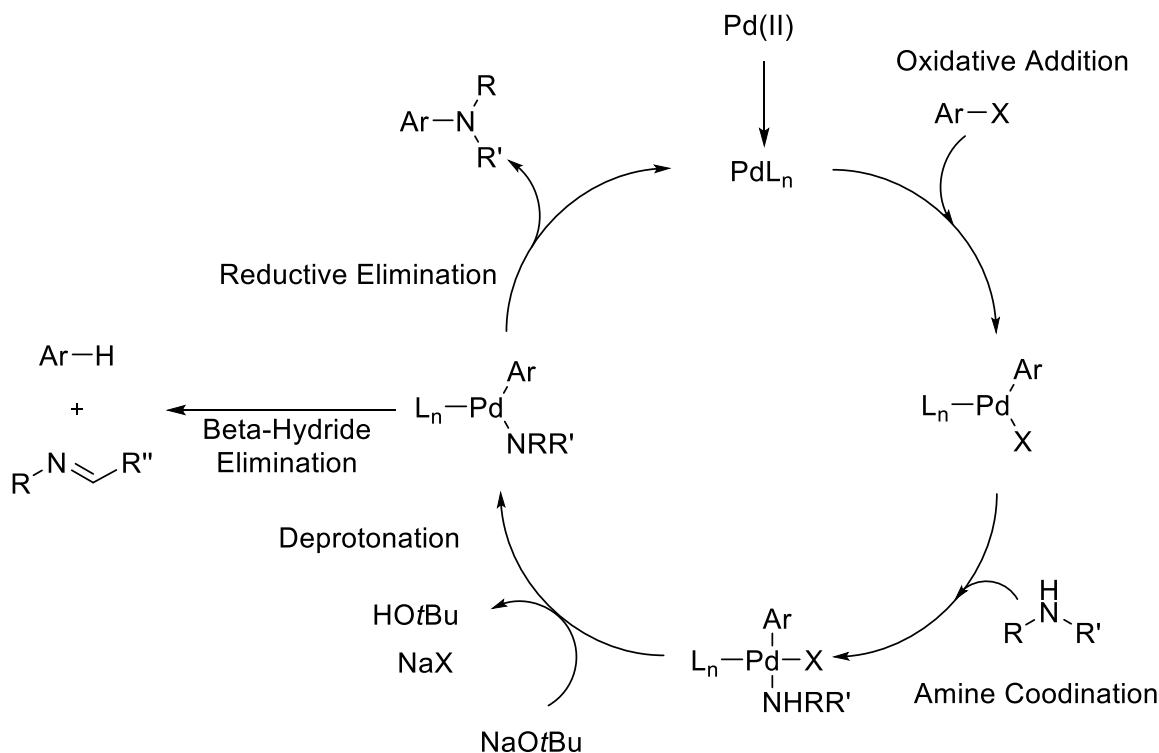
The mechanism originally proposed by both Buchwald and Hartwig had a step to make tin amides which would enter into the catalytic cycle, but this was found to be unnecessary as the palladium is able to coordinate the secondary amine without the tin treatment. However, it was found that certain cases might require tin amide formation to increase yields (as seen in Scheme 1.)<sup>6</sup>



**Scheme 1 - Original Mechanism Of the Buchwald-Hartwig Using Tin Amides**

The reaction mechanism, as seen in Scheme 2, works with either monodentate or bidentate ligands forming 3- or 4-coordinate palladium complexes, respectively. If the palladium source used is Pd(II) it then must be reduced to a Pd(0) complex before it can enter into the catalytic cycle. There are several ways in which it can be reduced within the reaction mixture. The first example of reduction is beta-hydride elimination of the amine species present.<sup>7</sup> The palladium species can also be reduced by the phosphine ligand, in which case the phosphine is oxidized to a phosphine oxide, with the assistance of water.<sup>8</sup> The next step in the cycle is the oxidative addition of the aryl halide to the palladium forming a 3 or 4 coordinate complex. Then the amine coordinates to the palladium, followed by deprotonation of the amine and release of the palladium bound halide as a salt.<sup>6</sup> The final step is the reductive elimination of the substrate forming the C-N bond and regeneration of the Pd(0) catalyst. There is also a potential side

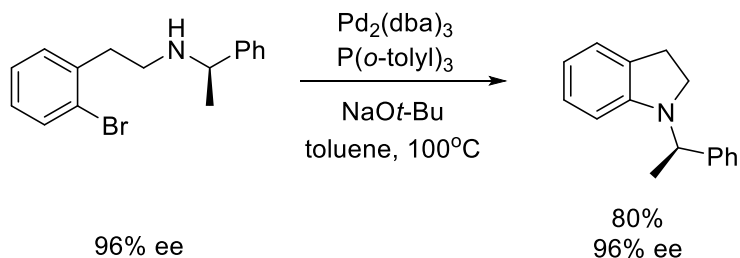
reaction that can happen at this stage where reductive elimination does not occur but beta-hydride elimination occurs, forming the debrominated arene product, and an imine.



**Scheme 2 - Buchwald-Hartwig Cross-Coupling Mechanism**

### 1.3 Preservation of Enantiopurity

In 1997, Wagaw *et al.* had shown that coupling an optically active amine with an aryl halide can be done without the racemization of the product (Figure 7.)<sup>9</sup> This discovery is critical to the pharmaceutical industry, as optically pure drugs have proven to be generally more active than their racemic counterparts.<sup>10</sup>

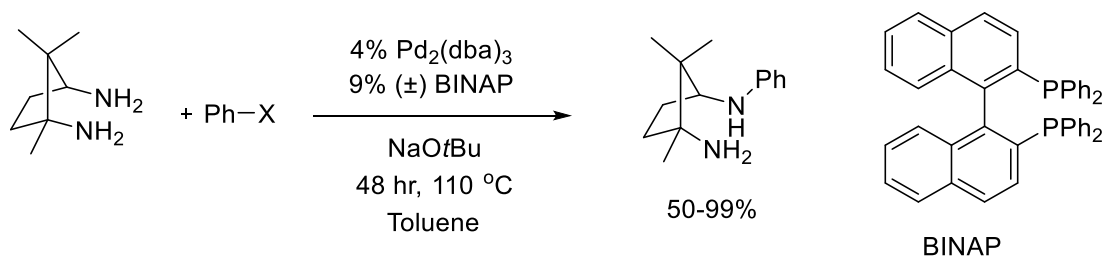


**Figure 7 - Preservation of Optical Purity after Amination**

#### 1.4 Regioselective Buchwald-Hartwig Amination

Differentiation of similar amine groups with the use of the Buchwald-Hartwig amination reaction can be done with (i) the use of a chiral ligand, or (ii) by taking advantage of halide reactivity in the reaction.

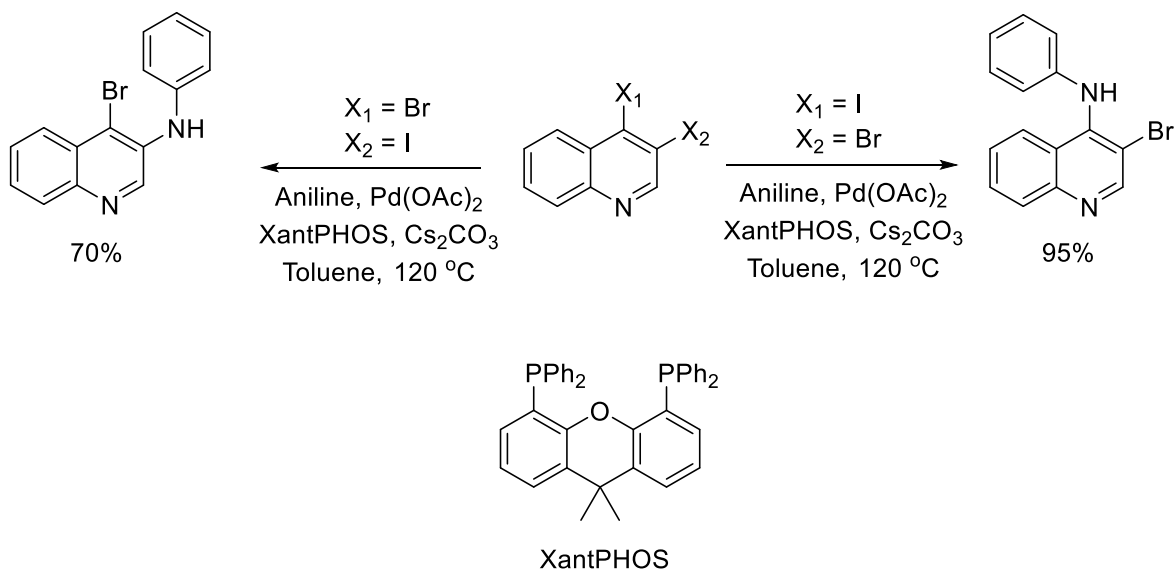
Uzarewicz-Baig *et al.* demonstrated that camphor diamines can be selectively arylated at the primary amine attached to a 2° carbon as opposed to primary amine attached to a 3° carbon in the presence of  $\text{Pd}_2(\text{dba})_3$  and racemic BINAP, as seen in Figure 8. Yields range from moderate to excellent and can tolerate many different types of arenes.<sup>11</sup> This is selective due to the ligand in the catalyst, (±) BINAP. The steric bulk of the ligand selectively arylated the less bulky nitrogen.



**Figure 8 - Regioselective Arylation with BINAP**



Another example of regioselective Buchwald-Hartwig reaction involves differentiation at the oxidative addition step. It was observed that, given a choice for the palladium to react with either a naphthyl bromide or a naphthyl iodide, the iodide was chosen with good to excellent yields (70-95%). The ligand used is the achiral Xantphos with palladium acetate and cesium carbonate, as seen in Figure 9.<sup>12</sup>



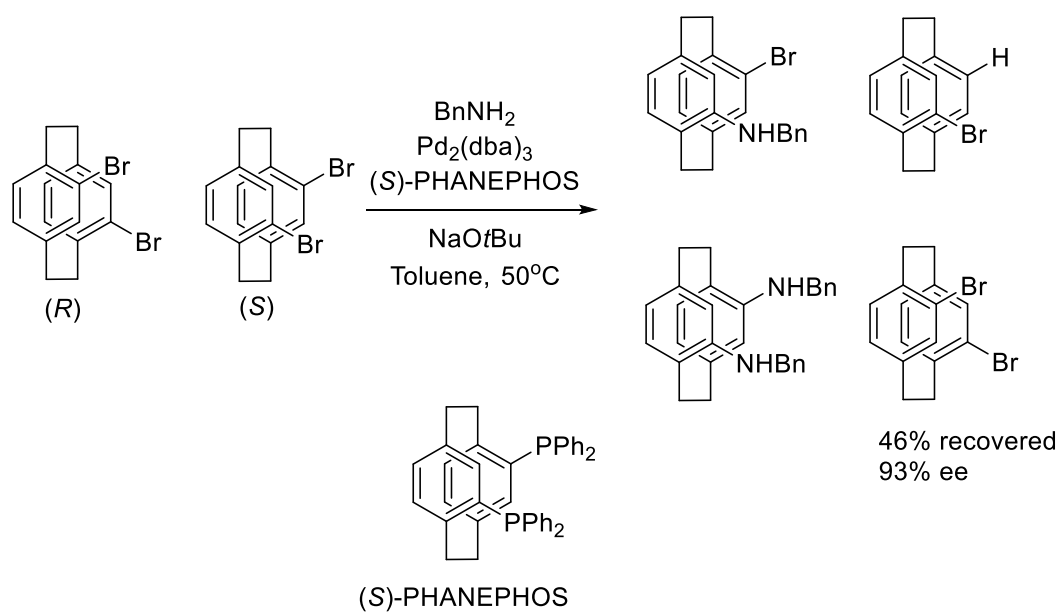
**Figure 9 - Regioselective Amination by Aryl Halide Selectivity**

### 1.5 Enantioselective Amination

Since the Buchwald-Hartwig amination is the formation of an aryl-nitrogen bond, it is generally not thought to be able to have enantioselective properties. The only cases to date have been either when the amination is selecting a single enantiomer to react with, thus derivatizing only one enantiomer and thus making them separable, or when the substrate has a plane of symmetry that is being broken by the amination usually through regioselection.

### 1.5.1 Chiral Resolution

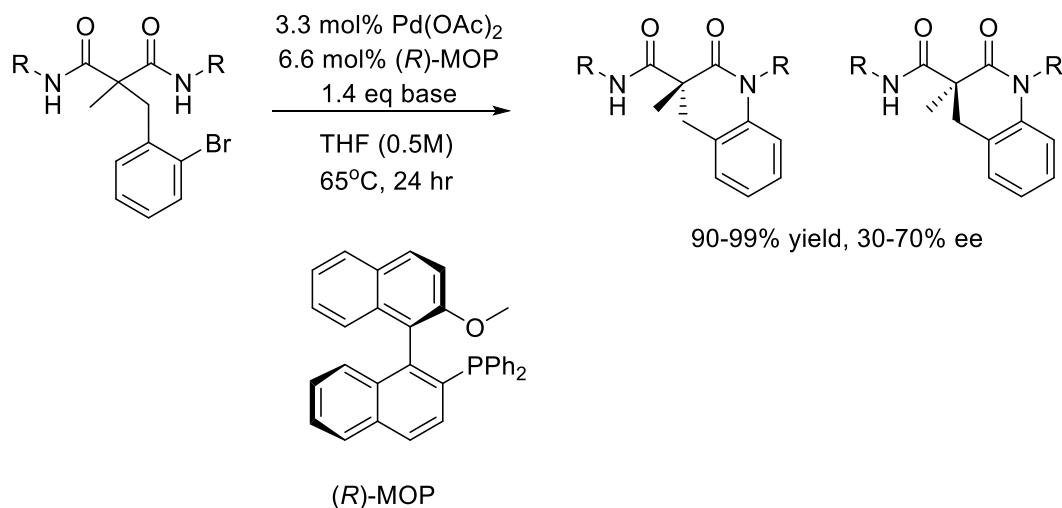
Researchers at Merck were able to selectively resolve 4,12-dibromo-[2.2]-paracyclophane with the use of  $\text{Pd}_2(\text{dba})_3$  and (*S*)-PHANEPHOS, Figure 10. The reaction takes place more favourably (about 3 to 4 times more) on the *S* enantiomer of the substrate. The reaction produces a complex mixture of compounds but leaves the *R* enantiomer of the starting material in a 93% ee. It is interesting to point out that this resolution discriminates at the aryl halide oxidative addition stage of the mechanism.



**Figure 10 - Kinetic Resolution Via Buchwald-Hartwig Amination**

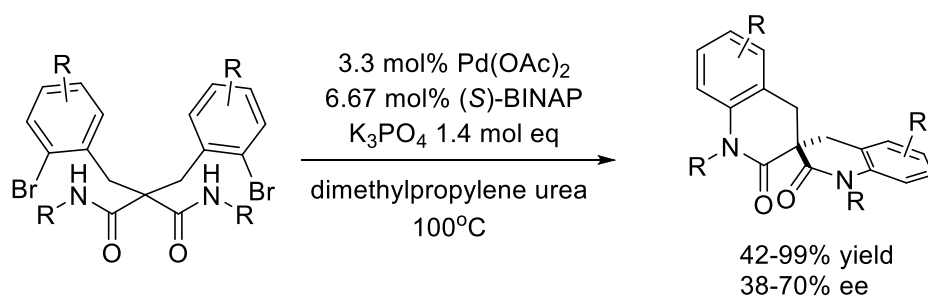
### 1.5.2 Asymmetric Amination

In the case of desymmetrization of a molecule by amination, the selectivity is given preference to a single enantiomer, also with the use of chiral ligands. Porosa and Viirre, had shown in 2009, that with a substituted malonamide substrate, they were able to produce optically active quinolinone moieties in excellent yields and good enantiomeric selectivities, Figure 11.<sup>13</sup>



**Figure 11 - Desymmetrization of Malonamides with (*R*)-MOP**

Following on this asymmetric amination, Sasai *et al.* have designed a similar malonamide substrate, but in this case they have made the central prochiral carbon doubly substituted with bromobenzyl groups in which case both amides was arylated (Figure 12).<sup>13,14</sup> They use the same catalyst loading but with (*S*)-BINAP which is similar to (*R*)-MOP in structure. They also achieve similar yields and enantioselectivities as Porosa and Viirre.

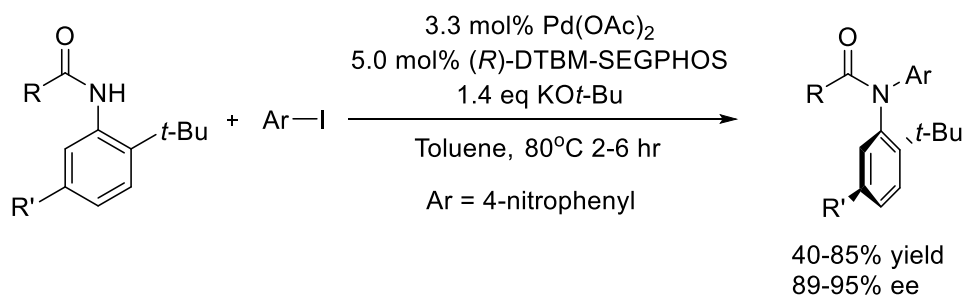


**Figure 12 - Double N-Arylation of Malonamide Substrate with Pd/(*S*)-BINAP**

### 1.5.3 Enantioselective Formation of a Chiral Axis

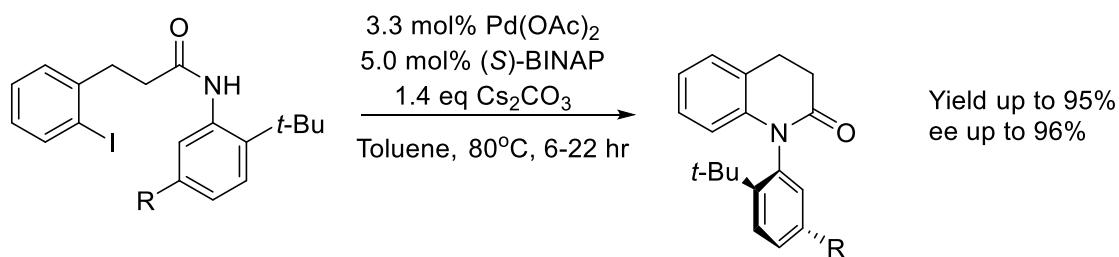
Another form of enantioselectivity that can be brought on by the Buchwald-Hartwig amidation is with the formation of a chiral axis. Generally C-N single bonds can freely rotate and it is rare that there is a chiral axis formed by this reaction due to nitrogen's ability to invert.

Taguchi *et al.* in 2005 presented a reaction in which the amine was attached to a 2-(*t*-butyl)phenyl group, thus post arylation the *t*-butyl group sterically locked free rotation forming a chiral axis as shown in Figure 13.<sup>15</sup>



**Figure 13 - Generation of a Chiral Axis by Arylation**

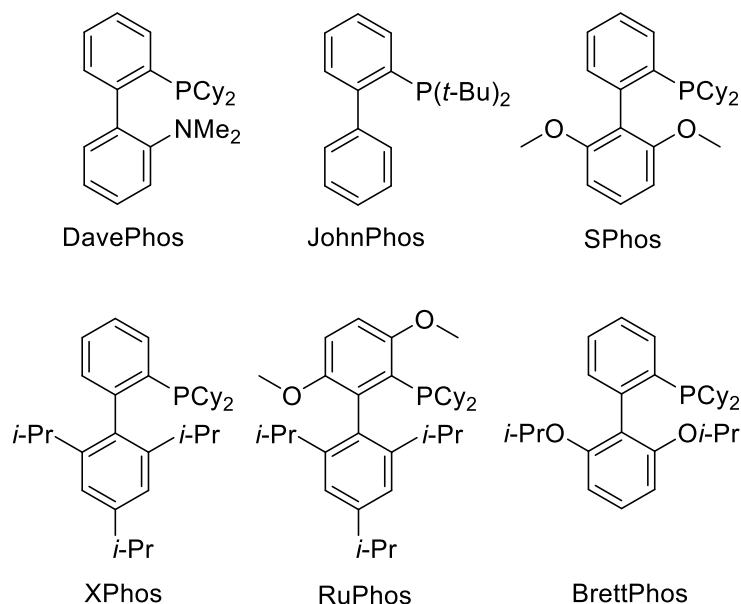
The group extended this concept to intramolecular reactions (Figure 14) and were able to drive the reaction to excellent yields and enantioselectivities, 95% and 96%, respectively. In this case they have switched to using (*S*)-BINAP and a weak base Cs<sub>2</sub>CO<sub>3</sub>. The reaction also takes a considerable amount of time longer than previous trials.



**Figure 14 - Intramolecular Amidation Forming a Chiral Axis**

## 1.6 Biphenyl Based Ligands

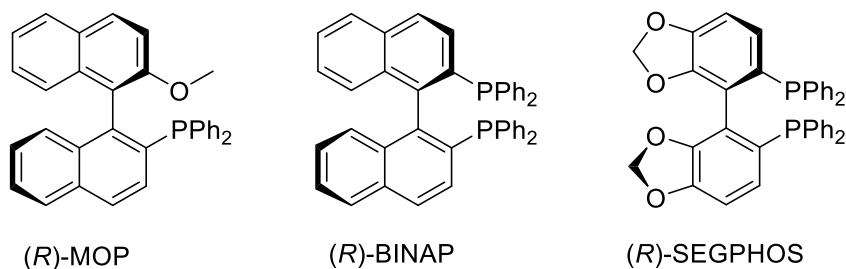
Over the years since the Buchwald-Hartwig amination was first reported, there have been efforts devoted to making better more robust or selective ligands. Modifications have shown drastic changes to the scope of the reaction. Originally the ligands were simple monophosphine biphenyl compounds with bulky alkyl groups on the phosphine, DavePhos and JohnPhos, depicted in Figure 15. Larger, bulky groups were attached onto this scaffold to create greater reactivity and diversity among the Buchwald-Hartwig reactions. The robustness of these catalyst systems have improved as well, catalyst loadings are seen as low as 0.05 mol% and are still able to drive reactions to near completion. A select few examples of the ligands employed are depicted in Figure 15. All of these ligands pictured are achiral.<sup>16</sup>



**Figure 15 - Several Achiral Ligands for Buchwald-Hartwig Amination**

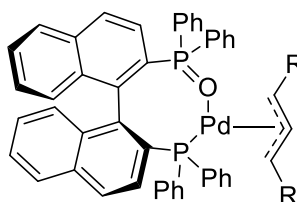
### 1.6.1 Binaphthyl Base Ligands

The binaphthyl ring system unlike the biaryl ring system, has an extra benefit of being chiral. The phosphine is still bound to the bulky dialkyl/biaryl groups as this aspect aids in both the oxidative addition and the reductive elimination steps.<sup>16</sup> Generally without substituents the rings can freely rotate about the C-C bridge, but when a substituted phosphorus, nitrogen or oxygen is attached at the 2 and 2' position, that rotation is locked, forming a chiral axis.<sup>17,18</sup> The most notable binaphthyl phosphine ligands are (*R*)-BINAP and (*R*)-MOP.<sup>19</sup>



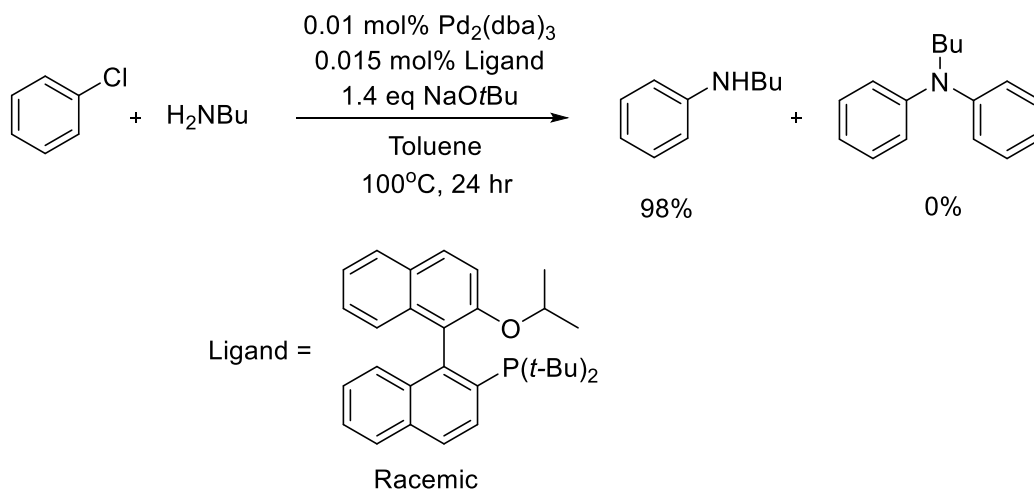
**Figure 16 - Common Binaphthyl Phosphine Ligands**

Oxidation of the phosphorus has been thought to deactivate the ligand rendering it incapable of coordinating to the palladium. In cases like BINAP where there are two phosphorus atoms, if one atom is oxidized to P=O the oxygen has been shown to coordinate the palladium along with the pre-existing P(III) atom, as seen in Figure 17.<sup>20</sup>



**Figure 17 - (S)-BINAPO Complex with Palladium**

Most modifications to the MOP-type ligands have been at the 2,2' position on the binaphthyl scaffold, since the commercially available BINOL has two alcohol groups for facile derivatization. Generally the modifications are other bulky alkyl groups to increase the selectivity. Zhang *et al.* created several ligands, through an 8 step synthesis, containing bulky alkyl group such as; Cy, *t*-Bu, Me, *i*Pr and Bn, to investigate simple amination. Interestingly, they found one of their ligands was particularly effective for monoarylation of primary amines as depicted in Figure 18.<sup>21</sup>

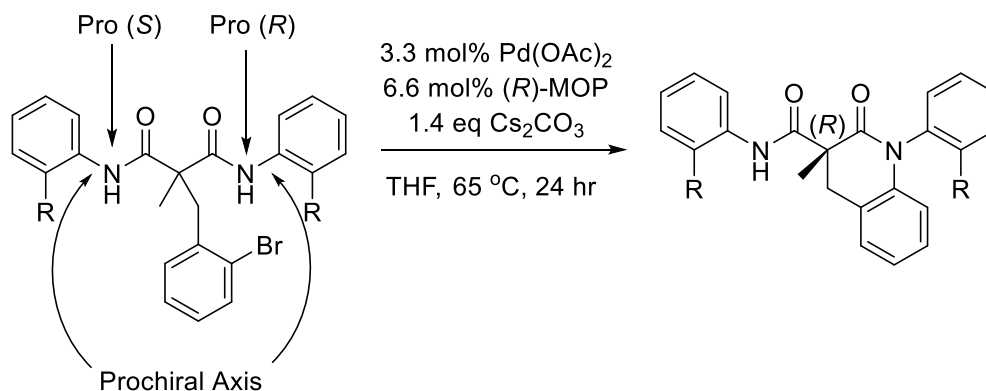


**Figure 18 - Selective Monoamination with MOP-type Ligand**

## 1.7 Research Goals

The objective of this thesis is to extend the previous work of desymmetrization of malonamides reported by the Viirre group to include bulky *ortho*-substituted phenyl substituents on the malonamide nitrogen atoms. This class of substrates possess both a prochiral centre and axis, with the possibility of setting both selectively in a single Buchwald-Hartwig event, as seen in Scheme 3.<sup>13</sup>





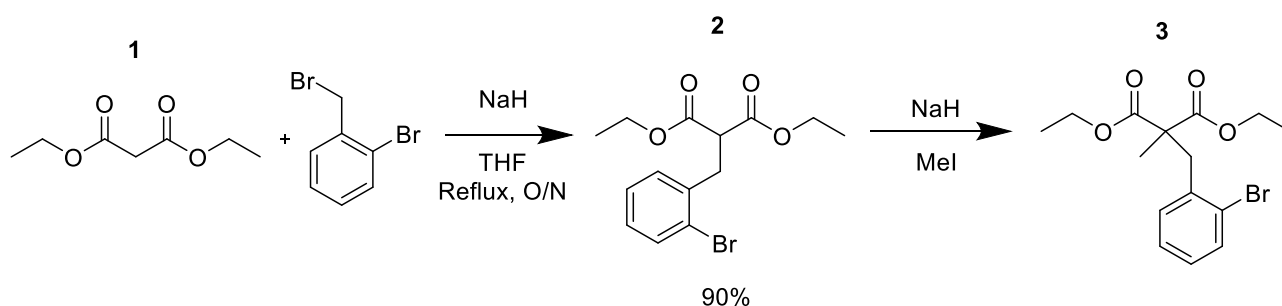
**Scheme 3 - Previous Work Published by the Viirre Group**

Previous work in the Viirre group completed by Augusto Matarazzo, preliminarily reported that (*R*)-dicyclohexyl(2'-methoxy-[1,1'-binaphthalen]-2-yl)phosphane, which will henceforth be referred to as (*R*)-Cy<sub>2</sub>MOP, was more effective ligand for this transformation than phenyl substituted MOP used in earlier desymmetrizations. Matarazzo had completed the cyclization of the 2-*t*-butylphenyl malonamide compound, the sample that was sent for crystallographic data was not enantiopure, meaning the absolute configuration observed cannot be linked to the major peak in the HPLC as there is a chance that it was compound producing the minor peak in the HPLC.<sup>22</sup> This is where the thesis will begin. Also, as the ligand is not commercially available, a secondary goal of the project was to develop a practical method for the synthesis of (*R*)-Cy<sub>2</sub>MOP.

## 2 Results and Discussion

### 2.1 Synthesis Towards Substituted Malonamides

To determine the absolute configuration of the cyclized product **8** that was previously carried out by Matarazzo,<sup>22</sup> the substrate **6** needed to be prepared. Although the original synthesis was carried out using diethyl methylmalonate, starting with diethyl malonate would allow for further customizability of the alkyl group at the alpha carbon.

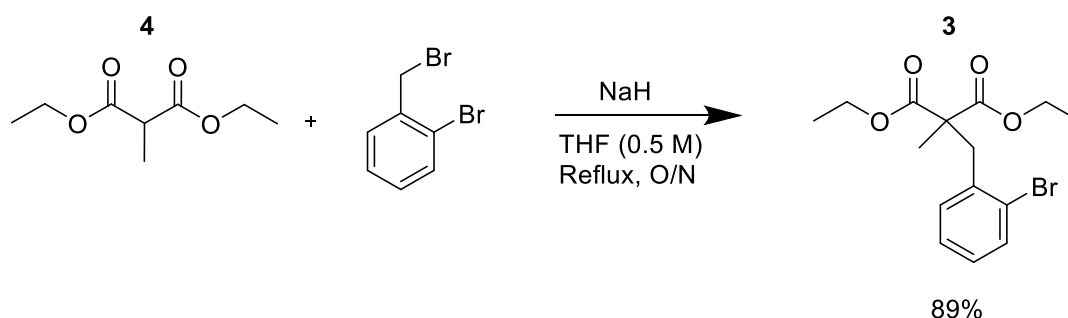


**Scheme 4 - Synthesis of Diethyl 2-(2-Bromobenzyl)malonate from Diethyl Malonate**

The first step from **1** to **2** is a substitution step in which a 2-bromobenzyl group is added to diethyl malonate. Sodium hydride was used since it deprotonates the central carbon irreversibly. The reaction proceeded smoothly and the resulting diethyl 2-bromobenzylmalonate was obtained in a good yield. The following methylation step converting **2** into **3** proved to be challenging. The reaction did not go to completion and would require column chromatography to separate the starting material from the product. The problem was that under the solvent systems; hexanes/EtOAc, hexanes/Et<sub>2</sub>O, EtOAc/Et<sub>2</sub>O, neat DCM, DCM/hexanes, and CHCl<sub>3</sub>, a good enough separation was not attainable for chromatography. The difference in polarity imparted by the addition of only a methyl group on this already non-polar compound was not large enough to separate **2** from **3**. Other forms of separation were not options either. For instance, the starting

material and the product are both oils at room temperature and thus cannot be purified by crystallization. The next reaction is a hydrolysis reaction and the reactivity of the esters on the starting material and the product are comparable, leading to a more complex mixture of compounds. Thus, starting material of this reaction could not have been carried over and then separated at a later step. After several attempts at trying to purify this compound or drive the reaction to completion, was prepared using the original synthesis as reported by Matarazzo.

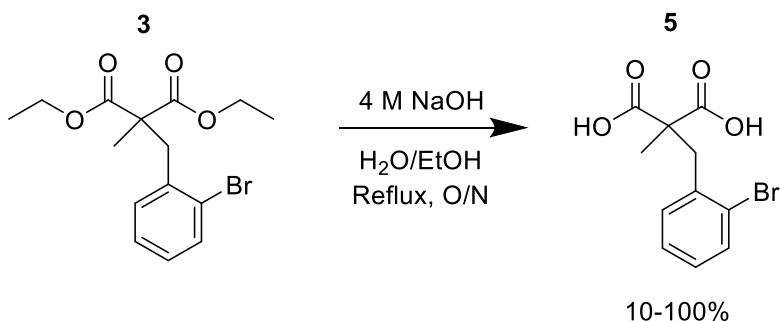
The synthesis that was carried out previously uses diethyl methylmalonate **4** as a starting material in order to obtain compound **3**, as seen in Scheme 5.



**Scheme 5 - Synthesis of Diethyl 2-(2-Bromobenzyl)-2-methylmalonate from Diethyl 2-Methylmalonate**

Scheme 4 would have allowed for customizability of the alkyl position at the alpha carbon. This could have led to the investigation of the electronic and steric properties that position has on the cyclization of the malonamide end product. Unfortunately due to the separation issues, the starting material was switched to **4** for the ease of synthesis as seen in Scheme 5. The substitution reaction in Scheme 5 to produce **3** in 89% yield uses NaH in THF.

The next reaction in the synthesis of **8** was the saponification of **3** affording the substituted malonic acid **5**, as seen in Scheme 6.



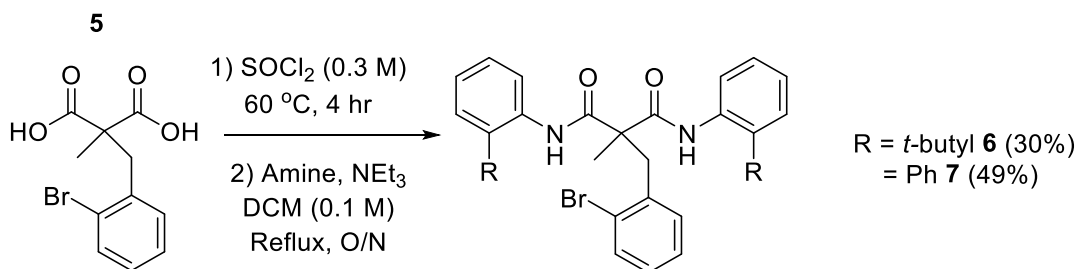
### Scheme 6 - Hydrolysis of Diethyl 2-(2-bromobenzyl)-2-methylmalonate

Both reaction and workup conditions needed to be carefully controlled in order to obtain good yield. During early attempts, the reaction was heated to reflux overnight in accordance to similar syntheses, but this high temperature and caustic conditions led to decarboxylation of the product.

The workup includes an initial extraction with Et<sub>2</sub>O while the aqueous phase remains basic to recover any starting material that had not reacted. This is followed by protonation of the carboxylic acid groups with 1 M HCl, which produces **5** and is no longer soluble in the water/EtOH mixture. The product **5** was believed to be soluble in DCM/CHCl<sub>3</sub>, and so this was chosen as an extraction solvent. Visibly the precipitate had disappeared. Upon concentration under vacuum, there was nothing left in the flask. Since after concentrating the Et<sub>2</sub>O phase only produced trace amounts of unreacted **3**, the original thought was that compound **5** was undergoing decarboxylation during the concentration step of the workup, but there was no evidence of by product. Replicating this reaction, proved to yield the same result, of an absence of anything in any flask.

The successful attempt at the isolation of **5** was due to filtering out the precipitate after acidification and realizing the compound is not soluble in DCM but EtOAc instead. Switching

the extraction solvents was able to isolate **5** in a 91.5% yield. This reaction is 100% based on recovered starting material.



### Scheme 7 - Malonamide Formation from Malonic Acid

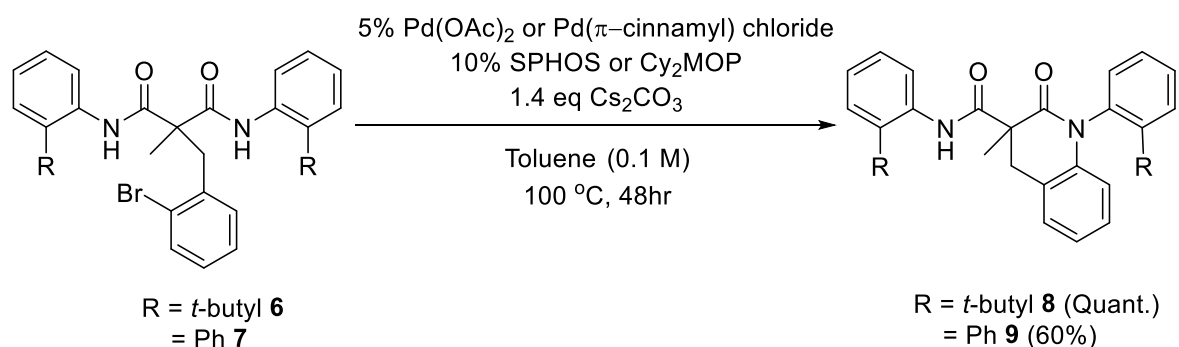
The formations of different malonamides were done under identical reaction conditions, as shown in Scheme 7. The malonic acid was taken up in thionyl chloride and heated to  $60\text{ }^\circ\text{C}$  for four hours to convert to the acid chloride. It is difficult to monitor this reaction by TLC because the thionyl chloride creates large dark spots on the silica plate. The acid chloride was not isolated because it can decompose easily back to the starting material **5**, after prolonged exposure to moisture. After the four hours at elevated temperature, the product was worked up and carried through. The reaction was evaporated under vacuum to remove extra thionyl chloride, redissolved in chloroform and further concentrated several times to remove any traces of thionyl chloride. After this brief work up there was still a slight thionyl chloride smell that was apparent but further evaporation did not dissipate the smell. The acid chloride was dissolved in DCM (0.1 M), and the desired amine (2-*t*-butyl aniline or 2-biphenylamine) was added slowly over ice. The reaction was warmed to room temperature and allowed to stir for an hour before being cooled again and having the base added. The reaction was heated to reflux overnight and the work up consisted of an acid extraction to remove extra amine and base. The yields are generally poor to moderate for this reaction with the best yields being 30% and 49% for the bis(*t*-butylphenyl)

malonamide and bis(biphenyl) malonamide, respectively. The poor yields could be due to the low nucleophilicity of anilines. Also the amines that are used are sterically hindered by the bulky ortho substituents. With the difficulty these bulky amines have forming the amide, it is statistically challenging to form an acid chloride and subsequent nucleophilic displacement twice on the same molecule. For example, if the amide formation proceeds with a moderate yield of 65%, then having this happen twice on the same molecule the yields are multiplicative resulting in an overall yield of 42%.

## 2.2 Cyclization of Substituted Malonamides

As in the amide formation, each malonamide was cyclized via the Buchwald-Hartwig C-N cross-coupling using SPHOS (achiral) or Cy<sub>2</sub>MOP (chiral) as the ligand. The general procedure for the reaction, as seen in Scheme 8, was adding the malonamide, palladium source and ligand to a Schlenk flask while evacuating and back filling with nitrogen in between each addition. Ensuring the nitrogen backfilling in between each addition seemed to be the best route to exclude oxygen from the reaction mixture. Previous work in the lab had added all the solids and then evacuated and backfilled three times in a row lead to irreproducible results. Better reproducibility was found when all solids excluding the base were dissolved in anhydrous toluene (0.1 M) and heated to 100 °C to obtain a clear solution. This generally happened within 20-30 seconds but the reaction was given three minutes to ensure complete solvation. Upon cooling to room temperature, the base was added and the reaction was sealed for 48 hours at 100 °C, under N<sub>2</sub>. During the 48 hours, some of the reactions turned black and some did not. This black precipitate is the palladium catalyst becoming inactive and precipitating. This was not an indication of completion as some reactions would have the reaction go to completion before the catalyst decomposed and some would not. Moderate to great yields were observed, with the better yields

stemming from the *t*-butyl substituted compounds. This could be due to the inherent steric bulk causing issues in allowing the coupling of the palladium to the nitrogen and aromatic group at the same time while still being bound to the bulky ligand. The difference in yields among the substrates could be due to differences in which each bulky substituent interacts with the catalyst, electronic differences of the two amides (i.e. pKa or nucleophilicity) or by agostic interactions that result from the *t*-butyl C-H bond interacting with the palladium atom's empty d orbital, assisting in the coordination of the amine. The sp<sup>2</sup> nature of the C-H bond present in the biphenylamine is less nucleophilic and thus has a lower yield. Further study into the interaction of these types of substrates with the catalyst is underway in the Viirre group.

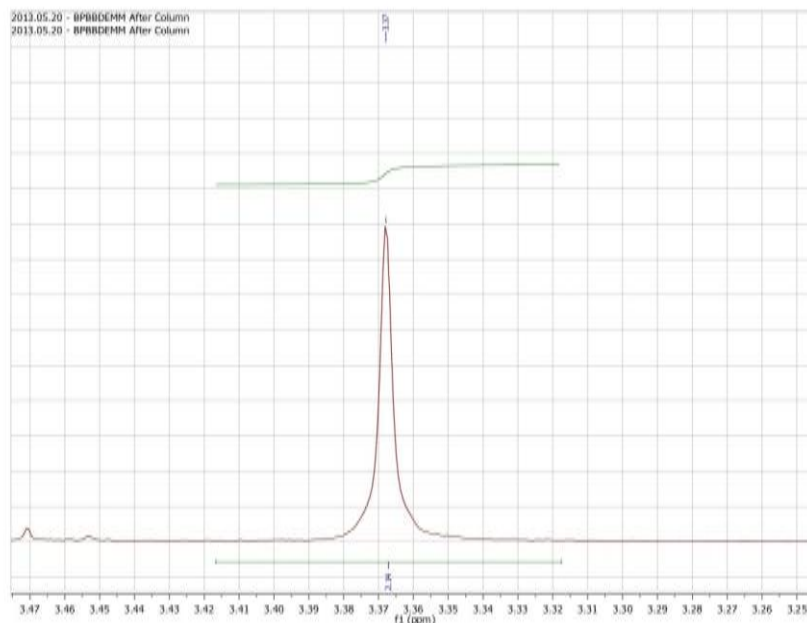


**Scheme 8 – General Reaction for the Cyclization of Malonamides**

### 2.2.1 Analyzing Enantioselectivity and Diastereoselectivity of Cyclized Substituted Malonamides

There are two ways in which diastereoselectivity is calculated, by NMR and HPLC. Enantioselectivity can only be analyzed by HPLC, since enantiomers are magnetically equivalent. The way that the diastereomeric ratio is calculated by <sup>1</sup>H NMR is observing the ratio

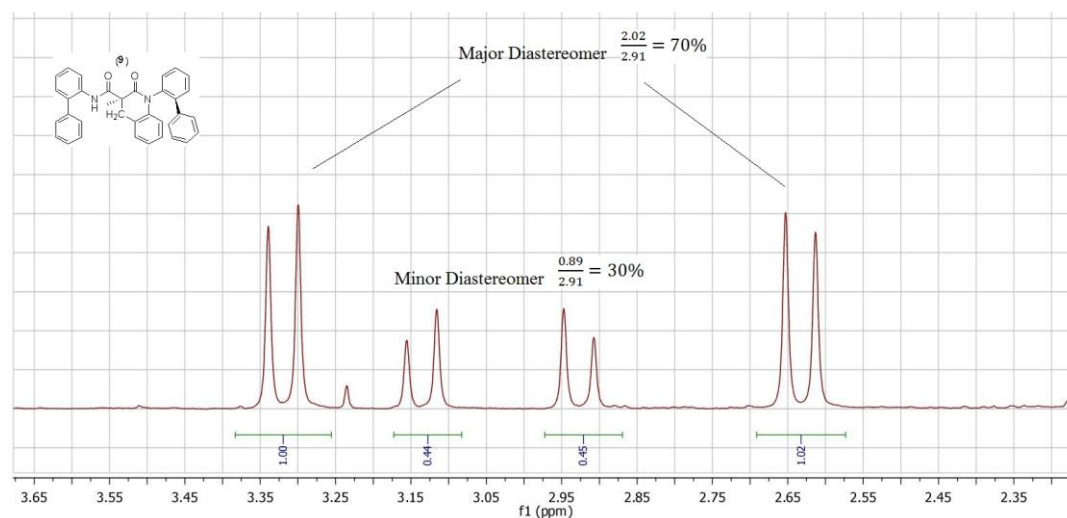
and splitting pattern of the benzylic CH<sub>2</sub> peaks. In the starting materials **6** and **7** the protons are equivalent and produce a singlet for two protons, as seen in Figure 19.



**Figure 19 - CH<sub>2</sub> Singlet Peak of 6**

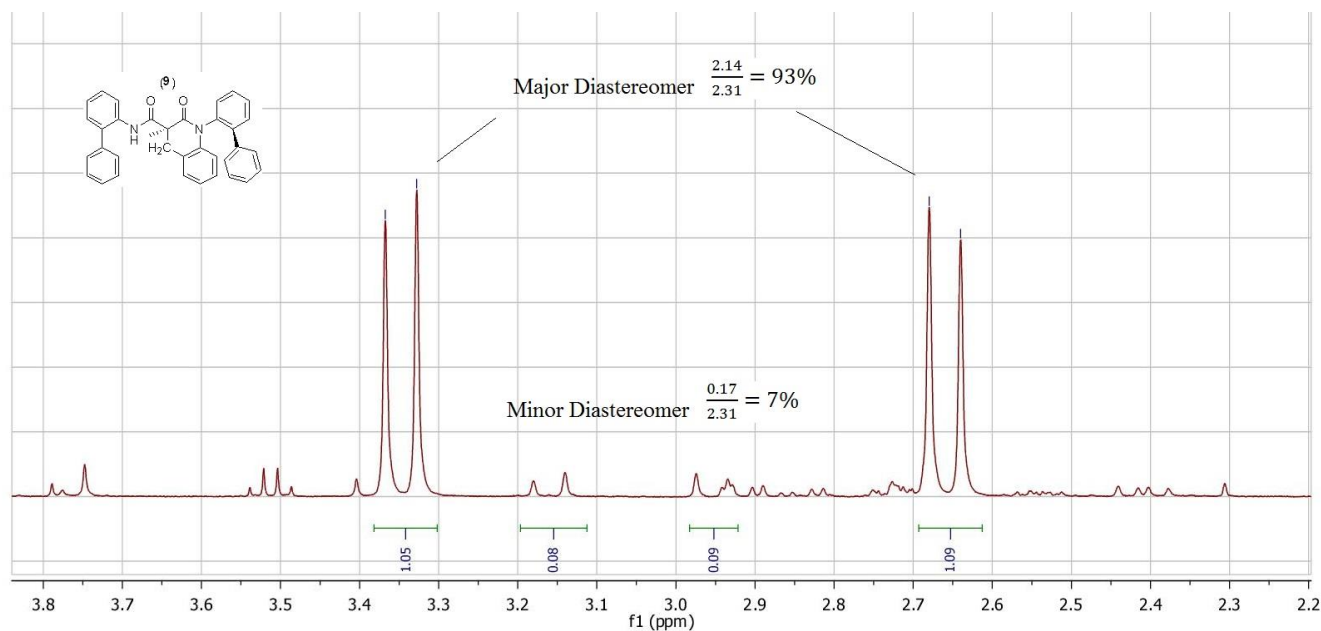
When the cyclization reaction forming the chiral products **8** and **9**, the two protons are no longer magnetically equivalent, they are diastereotopic. The two protons couple to each other, forming two doublets leaning towards each other, and integrate for one proton each. Since diastereomers are not magnetically equivalent, each set of diastereomers give rise to a pair of leaning doublets that are well resolved in the <sup>1</sup>H NMR spectrum. The diastereomeric ratio is calculated by dividing the integration of one pair of doublets by the integration of the combined 4 doublets. The four doublets can be observed easily in the <sup>1</sup>H NMR spectrum of **9** when cyclized with the Pd/SPHOS catalyst system, Figure 20.





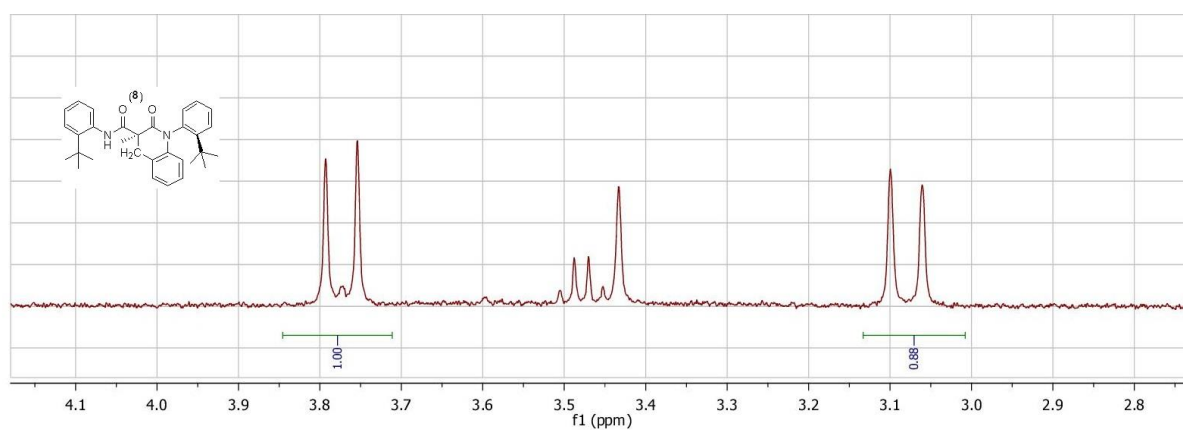
**Figure 20 - Diastereotopic Protons of **9** via Pd/SPHOS**

Using the protons in Figure 20 as an example, the integration all of the doublets total 2.91. It is clear which protons are on the same diastereomer as the doublets are paired in integration and amount of leaning towards one another. Totaling the integration of the two major diastereomeric protons is 2.02, and dividing by the total integration yields a diastereomeric ratio of 70%. The diastereoselectivity of **9** when cyclized with Pd/SPHOS can be compared to the cyclization of **9** when cyclized with Pd/(*R*)-Cy<sub>2</sub>MOP as in Figure 21.



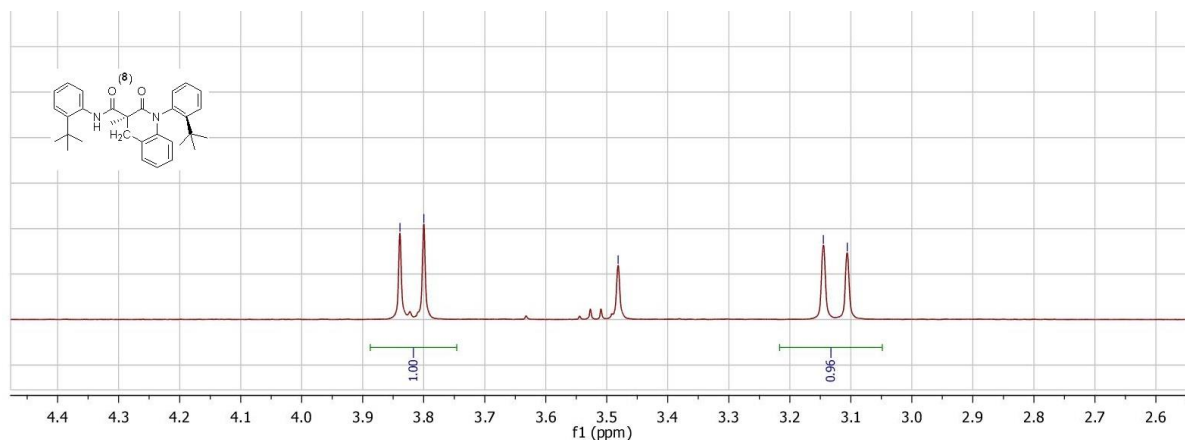
**Figure 21 - Diastereotopic Protons of **9** via Pd/(*R*)-Cy<sub>2</sub>MOP**

The <sup>1</sup>H NMR spectra of **8** when cyclized with Pd/SPHOS (Figure 22) and Pd/(*R*)-Cy<sub>2</sub>MOP (Figure 23) show only one set of doublets meaning that there is only one diastereomer formed in the reaction. This was later confirmed by HPLC.



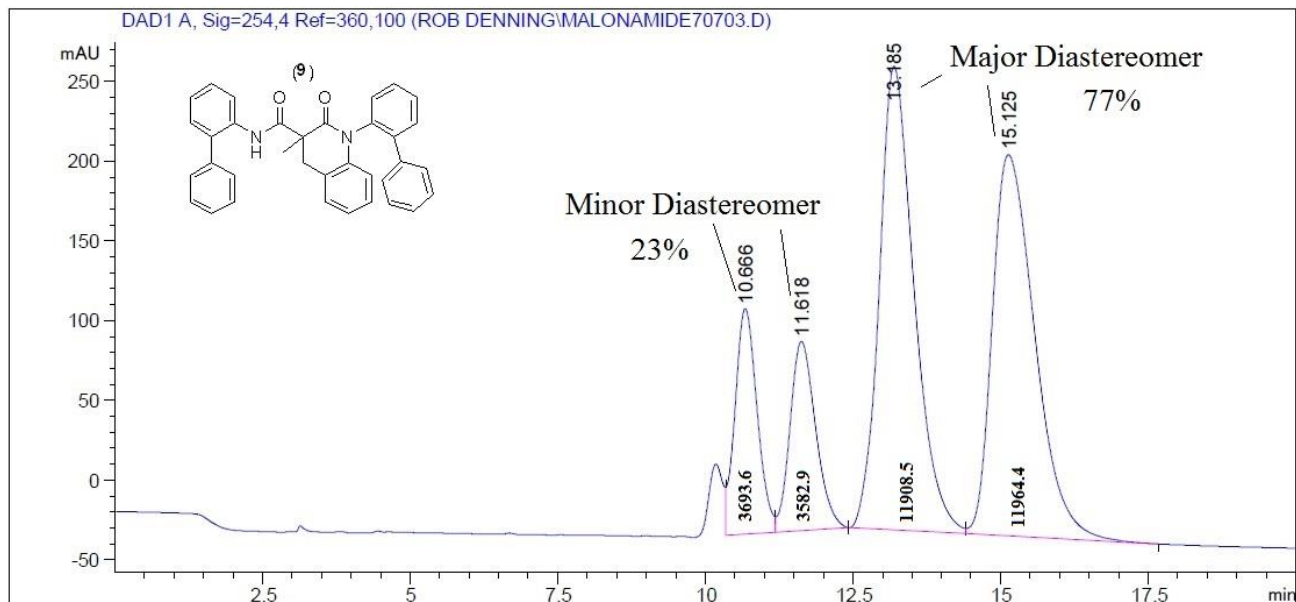
**Figure 22 - Single Diastereomer of **8** via Pd/SPHOS**

There is an impurity peak seen at 3.48, but it is quite evident that there is only one set of doublets meaning that there is only one diastereomer produced in this reaction. A comparable spectrum is seen in Figure 23, when the Pd/(*R*)-Cy<sub>2</sub>MOP catalyst system was used.



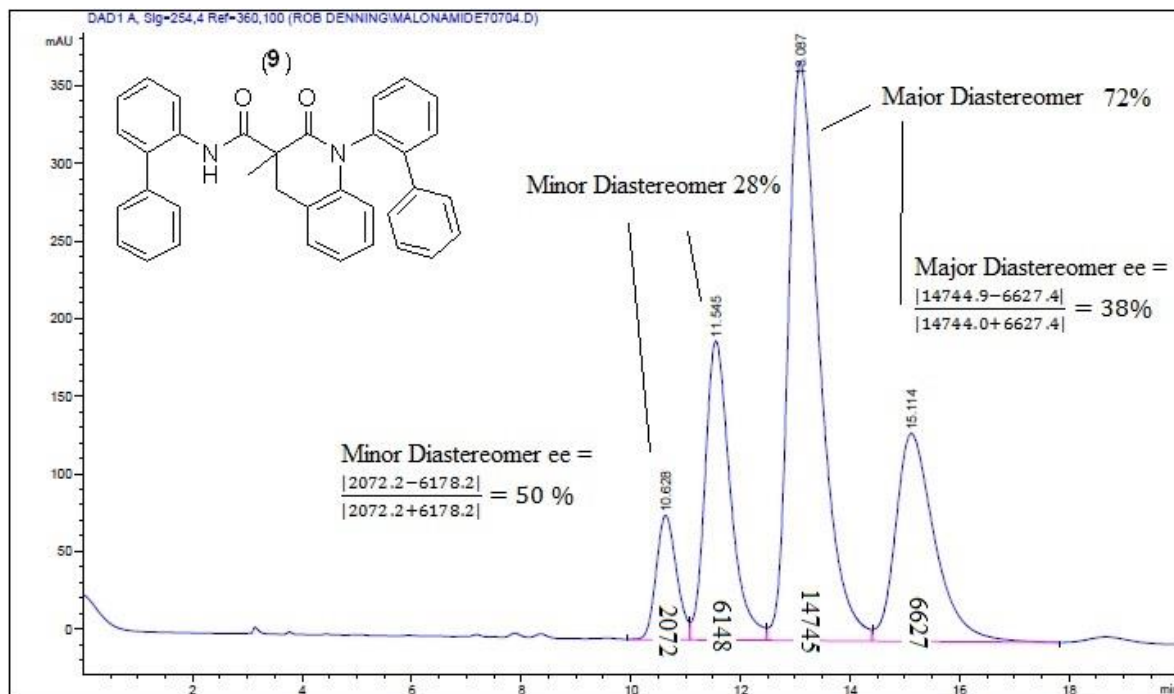
**Figure 23 - Single Diastereomer of 8 via Pd/(*R*)-Cy<sub>2</sub>MOP**

The diastereomeric ratio and enantiomeric excess of the compounds **8** and **9** can be calculated by HPLC. Using a Chiralpak OD-H column, each of the four diastereomers are separated and integrated based on the area of each peak. To understand which two peaks correlate to a set of diastereomers, the product formed from the Pd/SPHOS reaction analyzed by HPLC first. Since the SPHOS is achiral, there cannot be any enantioselectivity, resulting in two pairs of peaks that can be seen to have the same areas, as seen in Figure 24.



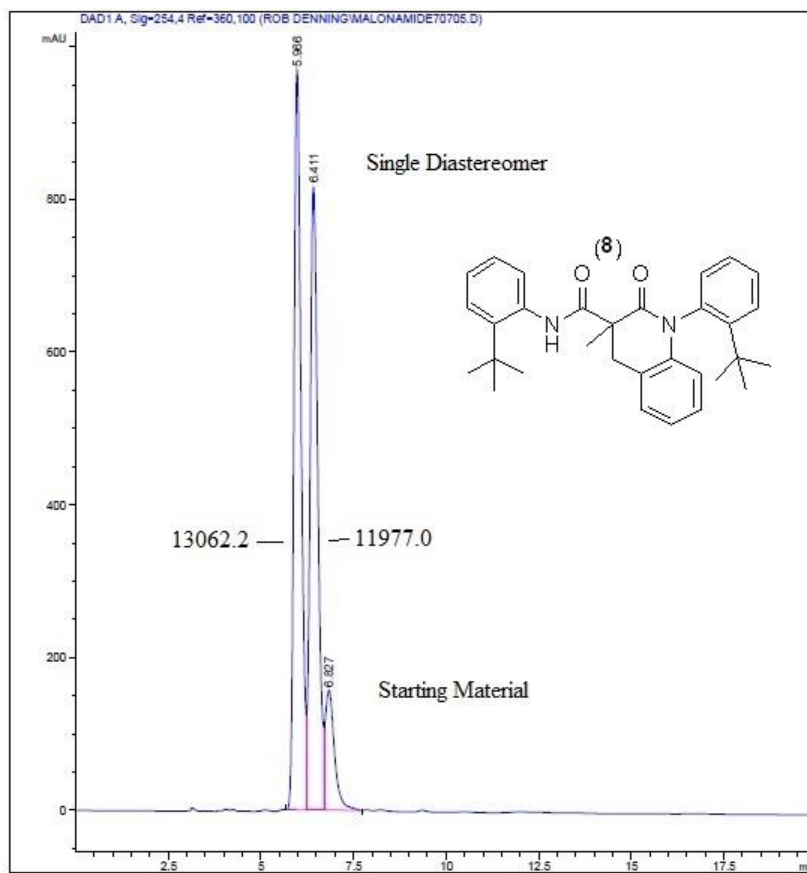
**Figure 24 - HPLC Chromatogram of **9** via Pd/SPHOS**

With the identification of the diastereomers as seen in the Figure 24, analysis of the HPLC chromatogram of **9** as cyclized by Pd/(*R*)-Cy<sub>2</sub>MOP shows enantioselectivity. In Figure 25, the peak area in increasing order is 2072.2, 6148.2, 14744.9, 6627.4, which totaled is 29592.7. The diastereomeric ratio as per the HPLC is 72% which differs from the results seen in the <sup>1</sup>H NMR spectra. The enantiomeric excess is 38% and 49.5% for the major and minor diastereomers, respectively.



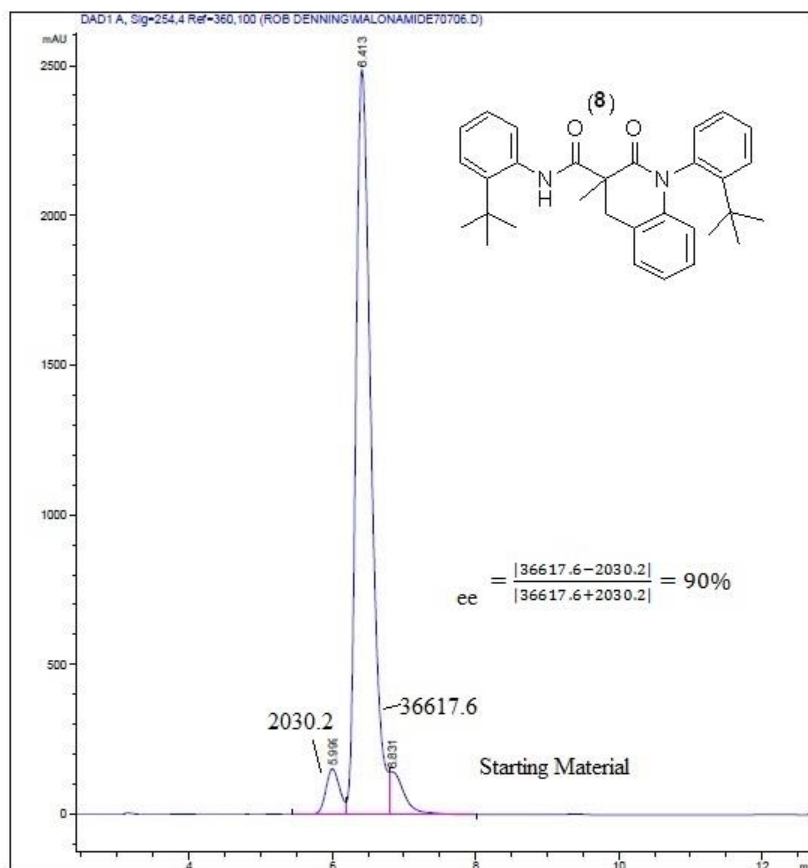
**Figure 25 - HPLC Chromatogram of **9** via Pd/(*R*)-Cy<sub>2</sub>MOP**

The HPLC chromatograms of **8** are not as well resolved but there is only one diastereomer that is seen. There is a contaminant of starting material seen but it does not interfere with the analysis, the Pd/SPHOS reaction forming **8** is shown in Figure 26.



**Figure 26 - Product 8 via Pd/SPHOS**

Once again, with the identification of the enantiomeric peaks established, the chromatogram of the reaction forming product **8** with Pd/(*R*)-Cy<sub>2</sub>MOP can be done, shown in Figure 27. With the NMR and HPLC data, the reaction forming product **8** with Pd/(*R*)-Cy<sub>2</sub>MOP, is 100% diastereoselective and 90% enantioselective. This means that out of four possible conformations, one is being highly selected for.



**Figure 27 - HPLC Chromatogram of **8** via Pd/(R)-Cy<sub>2</sub>MOP**

The two compounds **8** and **9** were cyclized with SPHOS and (*R*)-Cy<sub>2</sub>MOP as the ligand. Since SPHOS is achiral the reaction won't exhibit enantioselectivity but the reaction is able to show diastereoselectivity. The results for the four reactions are summarized in Table 1.

	NMR dr	HPLC dr	Major Diastereomer ee	Minor Diastereomer ee
Cyclized <b>8</b> by SPHOS	100%	100%	4%	NA
Cyclized <b>8</b> by ( <i>R</i> )-Cy <sub>2</sub> MOP	100%	100%	90%	NA
Cyclized <b>9</b> by SPHOS	70%	77%	NA	NA
Cyclized <b>9</b> by ( <i>R</i> )-Cy <sub>2</sub> MOP	93%	72%	38%	50%

**Table 1 - Enantioselectivity and Diastereoselectivity of the Cyclization of **6** and **7** by SPHOS and (*R*)-Cy<sub>2</sub>MOP**

From Table 1, it is clear to see that the enantioselectivity and diastereoselectivity are favoured in the cyclization reaction that forms **8**. Although there is a slight enantioselectivity seen in the SPHOS reaction forming **8**, this is within the margin of error for the instrument; as only the chiral ligand, (*R*)-Cy<sub>2</sub>MOP, can result in enantioselectivity. In both reactions forming **8** involving SPHOS and (*R*)-Cy<sub>2</sub>MOP, the diastereoselectivity is preserved, which is reflected in the NMR and HPLC results. The diastereoselectivity then could be caused by either the ligand, in the catalyst system or it can be potentially directed by the substrate.

The overall cyclization reaction to form **9** shows poorer enantio- and diastereoselectivity when using Pd/SPHOS and Pd/(*R*)-Cy<sub>2</sub>MOP. The reaction using (*R*)-Cy<sub>2</sub>MOP does show greater diastereoselectivity, as by NMR (Figure 21) but when viewing the HPLC chromatogram (Figure 25) there seems to be the same amount of selectivity for one diastereomer as seen with the

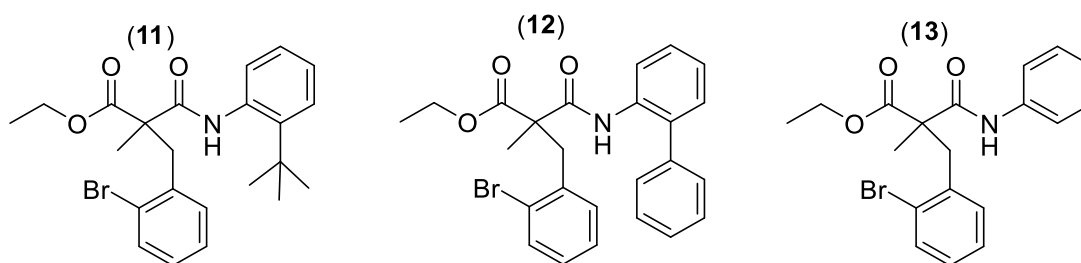


Pd/SPHOS system. Also there is only moderate selectivity seen in the (*R*)-Cy<sub>2</sub>MOP reaction at 36% and 50% ee for the major and minor diastereomers respectively.

The different bulky R substituent, phenyl (**9**) as opposed to *t*-butyl (**8**), is impacting the cyclization negatively. For reasons stated earlier, the nature of the biphenyl substrate produces poorer reactivities and selectivities.

## 2.3 Synthesis Towards Monoamide Compounds

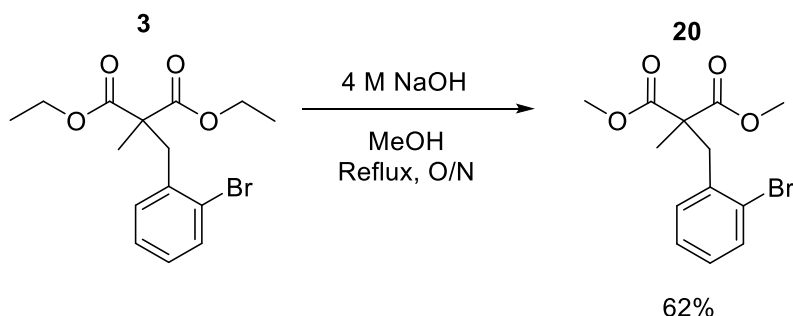
Further investigation into the mechanics of this cycle needed to be done, thus the next system looked at were the monoamide compounds **11-13**, as seen in Figure 28.



**Figure 28 - Monoamide Compounds Used to Understand Enantio- and Diastereoselectivity within the Buchwald-Hartwig Reaction**

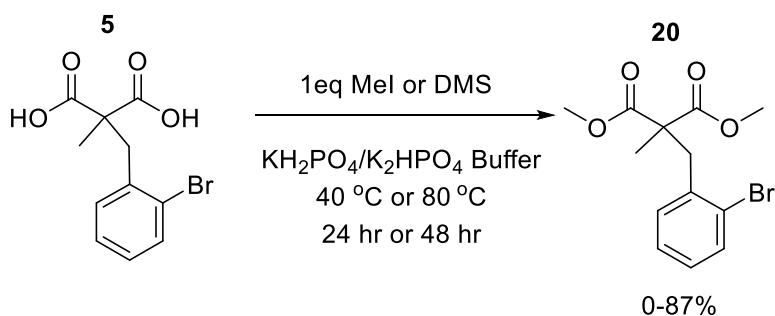
Since these compounds only have one potentially reactive amide functional group and begin the reaction mixture as a racemic mixture, they offer the possibility of determining whether it is the substrate or the catalyst that influences axial chirality. Starting from **3** the first step was a monohydrolysis of the malonate, Scheme 12. This proved to be very difficult since both esters have the same reactivity and reaction temperatures required for the hydrolysis to occur were high, which would encourage both esters to hydrolyze. Failed attempts include; room temperature for seven days, 0.5 M NaOH and 0.25 M KOH, slight heating at 40 °C, different

solvent systems (THF, EtOH, EtOH/water, MeOH/water), phase transfer catalysts (tetrabutylammonium hydroxide), which all either resulted in no reaction or dihydrolysis. Once MeOH was used instead of EtOH, but this only resulted in transesterification and the dimethyl malonate **20**, was recovered in 62% yield, Scheme 9 .



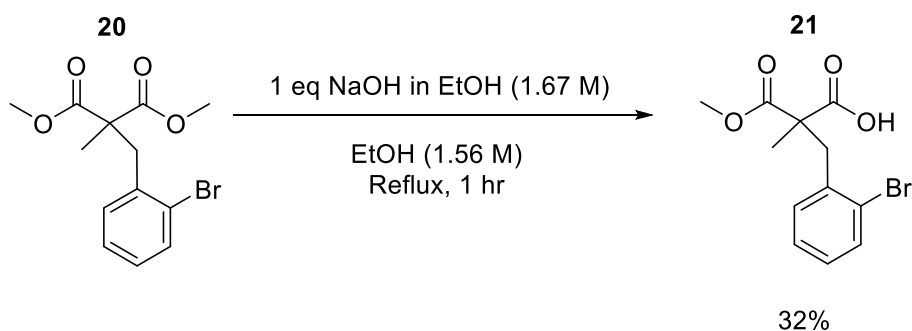
**Scheme 9 - Transesterification of Diethyl Malonate to Dimethyl Malonate**

Mono methylation of the diacid **5** was also attempted with methyl iodide or dimethyl sulphate in a phosphate buffer but the reactions either did not work or formed the dimethyl ester **20**, Scheme 10.



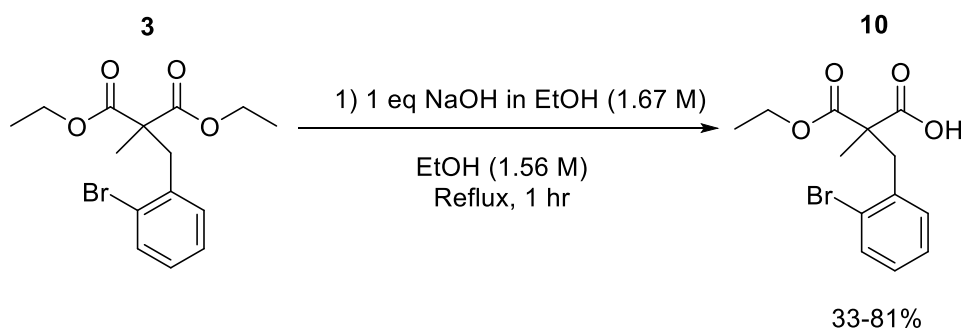
**Scheme 10 - Monomethylation Attempts on Substituted Malonic Acid**

With a sizable amount of the dimethyl malonate **20**, it was considered for future derivatization. Monohydrolysis reactions were attempted and proved to be successful by solubilizing the base as well as the substrate separately, followed by a slow addition of the base solution to the substrate solution over ice. A quick one hour reflux with a subsequent acid workup afforded the monoacid compound **21** in 32% yield, Scheme 11. Compound **21** was carried through to both the 2-(*t*-butyl)phenylamide and 2-biphenylamide. The issue with this route was that there was not enough material to continue through, considering diethyl 2-methylmalonate was the original starting material. Also it was different from our other models, so this route was not pursued further.



**Scheme 11 - Monohydrolysis of Substituted Dimethyl Malonate**

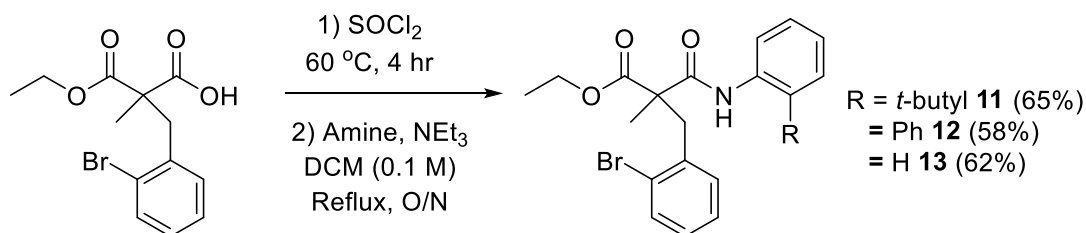
The reaction conditions that were used for the monohydrolysis of the derivatized dimethyl malonate, were used to achieve a monohydrolysis of the diethyl malonate, as seen in Scheme 12.



**Scheme 12 - Monohydrolysis of Diethyl 2-(2-bromobenzyl)-2-methylmalonate**

The large fluctuation in yield for the reaction is likely due to greater difficulty in achieving very slow addition of the NaOH on smaller scales, thus smaller attempts ended up in poorer yields. Mechanical addition with a motorized syringe would make this addition simpler in the future.

With a reliable method to produce the monohydrolyzed product on hand, the next step was to make the 2-(*t*-butyl)phenylamide and 2-biphenylamide analogs. The same conditions that were used for the conversion of the malonic acids, **6** and **7**, to the malonamides, **8** and **9**, were used for the mono acid mono ester conversion, as seen in Scheme 13.

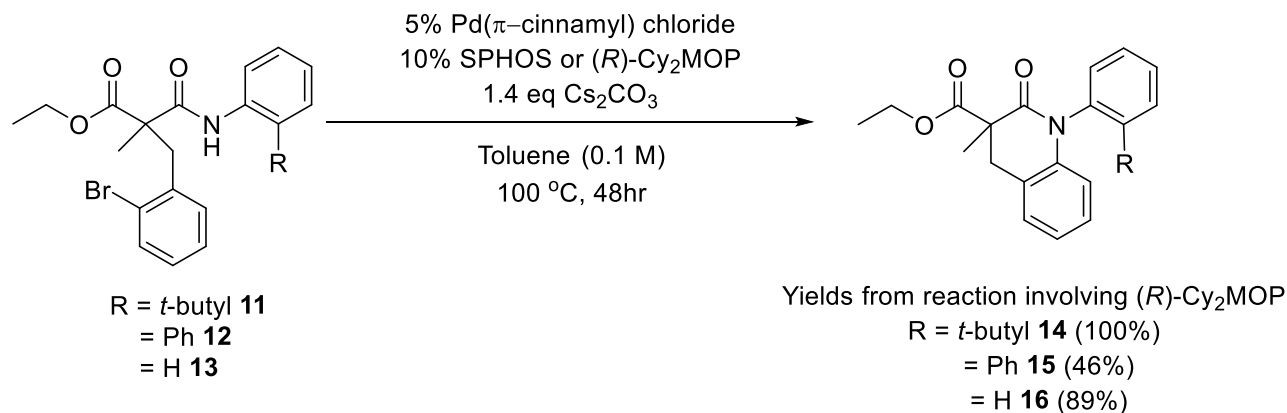


**Scheme 13 - Conversion of Mono Acid to Mono Amide**

The reactions forming monoamides, **11-13**, were still plagued by the problems that occurred in the formation of compounds **8** and **9**. There is still the use of aniline compounds which have lower nucleophilicity and the formation of the acid chloride is difficult to monitor by TLC. The yields of the reactions forming **11-13**, are higher than reactions that form **8** and **9**, could be attributed to the fact that only one acid chloride and subsequent nucleophilic attack needs to occur and thus poor yields are not amplified. Also in the reaction to form the malonamide compounds, **8** and **9**, the second amine attack might be impeded sterically after the first amide is formed.

## 2.4 Cyclization of Substituted Mono Amide Compounds

The final step would be to cyclize compounds, **11-13**, with catalyst systems including SPHOS and (*R*)-Cy<sub>2</sub>MOP. The cyclization reactions were conducted in the same manner as the malonamide compounds. Each reaction was run for 48 hours, except compound **13**. Since **13** has no bulky substituent on the *ortho* position of the phenyl ring, a chiral axis is not possible and thus the reaction can only lead to two enantiomeric products. The idea was that if the reaction was stopped early enough, prior to completion there may be some selectivity either for one enantiomer. The general reaction is represented in Scheme 14.

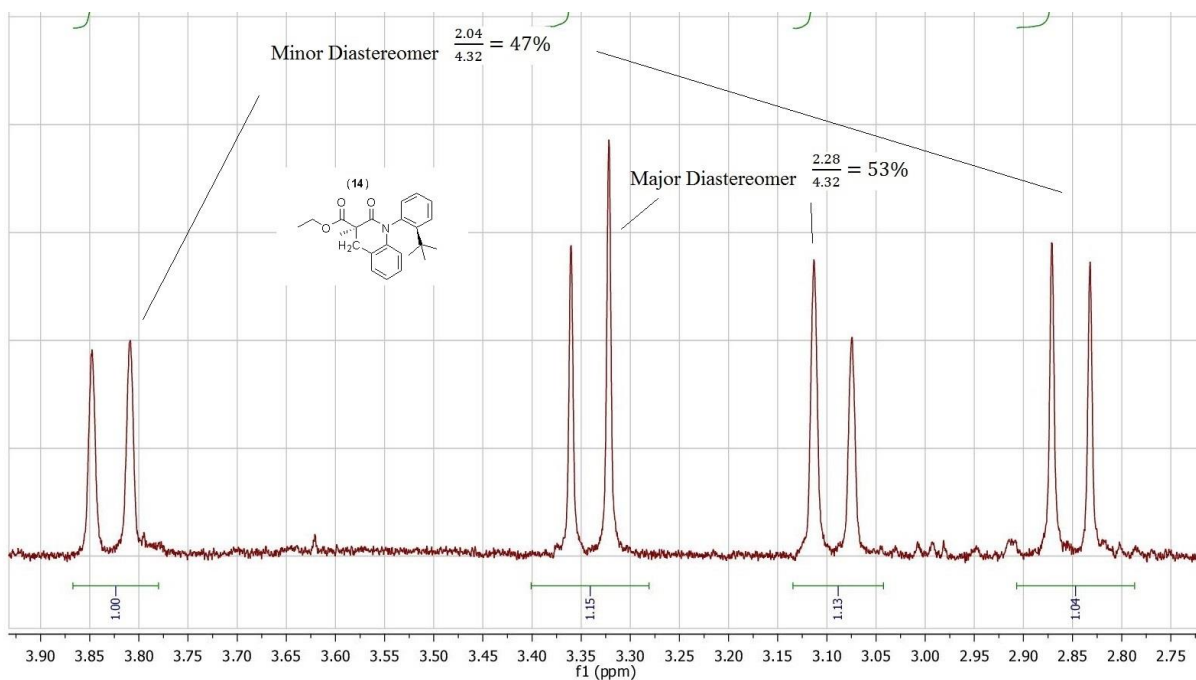


### Scheme 14 - Cyclization of Monoamide Compounds

The reaction forming **15** produced the lowest yield of all monoamide compounds **14-16** which was analogous to cyclized malonamide reactions forming **9**. Both products **9** and **15** have the 2-biphenylamide substituent which again is poorer in reactivity and selectivity for reasons stated earlier. The compound **16** does not have a comparable malonamide to be measured against but it is interesting to note that without any bulky ortho substituent, the reaction does not go to completion whereas the reaction to form **14** does. Similar to compound **8**, the 2-*t*-butylphenylamide substituted **14** goes to completion showing that the catalyst system is complimented very well by the ortho *t*-butyl group.

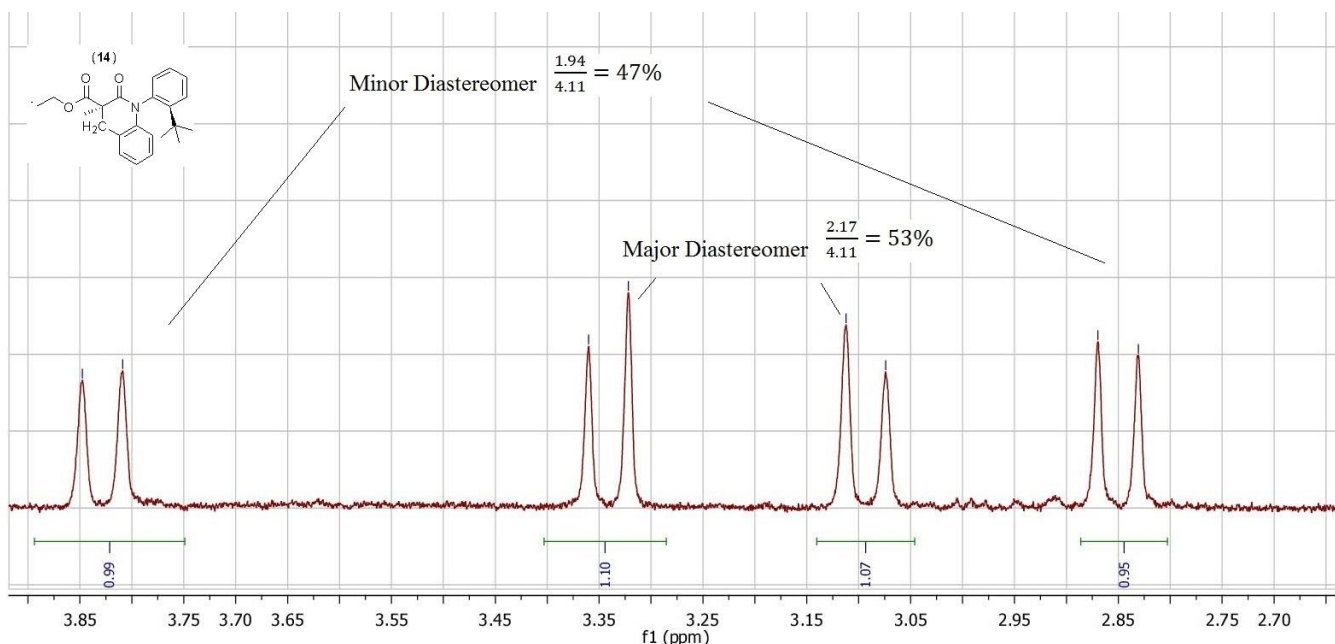
#### 2.4.1 Analyzing Enantioselectivity and Diastereoselectivity of Cyclized Monoamide Compounds

The enantio- and diastereoselectivity of the cyclized monoamide compounds **14-16** were analyzed in the same manner as the malonamide compounds **8** and **9**. The <sup>1</sup>H NMR of compound **11** when cyclized with the Pd/SPHOS catalyst system shows poor diastereoselective control compared to previous malonamide reactions, as seen in Figure 29.



**Figure 29 - Diastereotopic Protons of 14 via Pd/SPHOS**

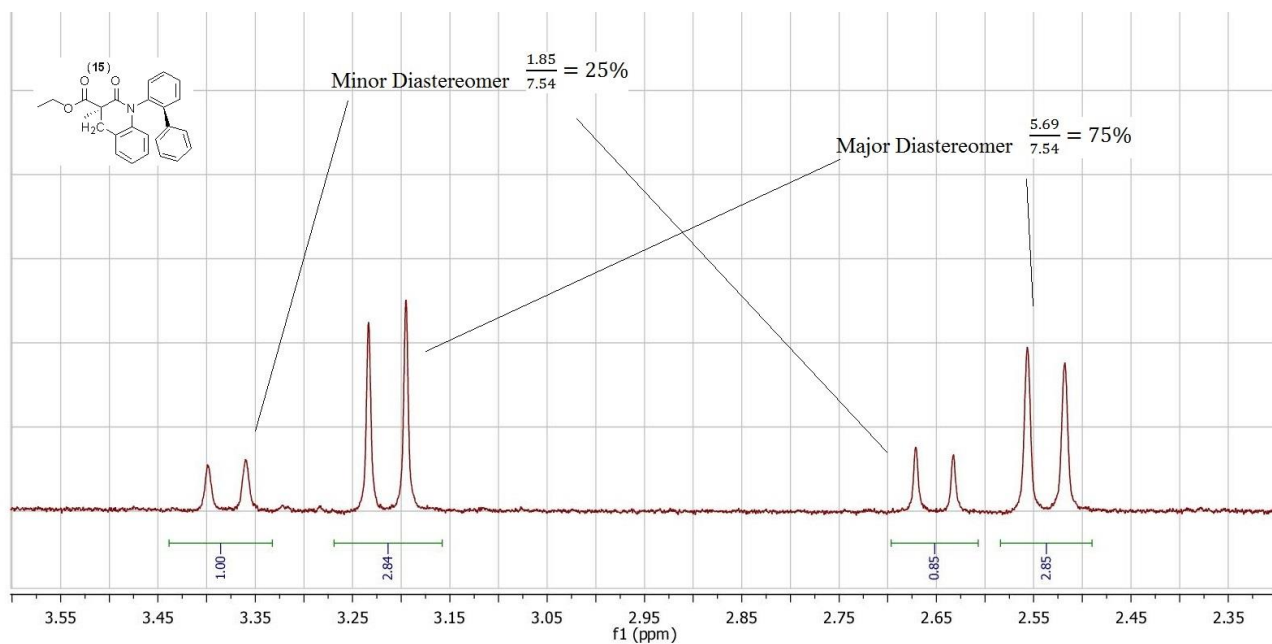
The same reaction forming product **14** with the Pd/(*R*)-Cy<sub>2</sub>MOP catalyst produced just as good of diastereomer control as the Pd/SPHOS containing reaction, as seen in Figure 30. Throughout this project the diastereomeric ratio is the same for the reactions involving the same substrate but differ in catalyst makeup. This means that the diastereomeric ratio is more dependent on the substrate than on the catalyst.



**Figure 30 - Diastereotopic Protons for **14** via Pd/(*R*)-Cy<sub>2</sub>MOP**

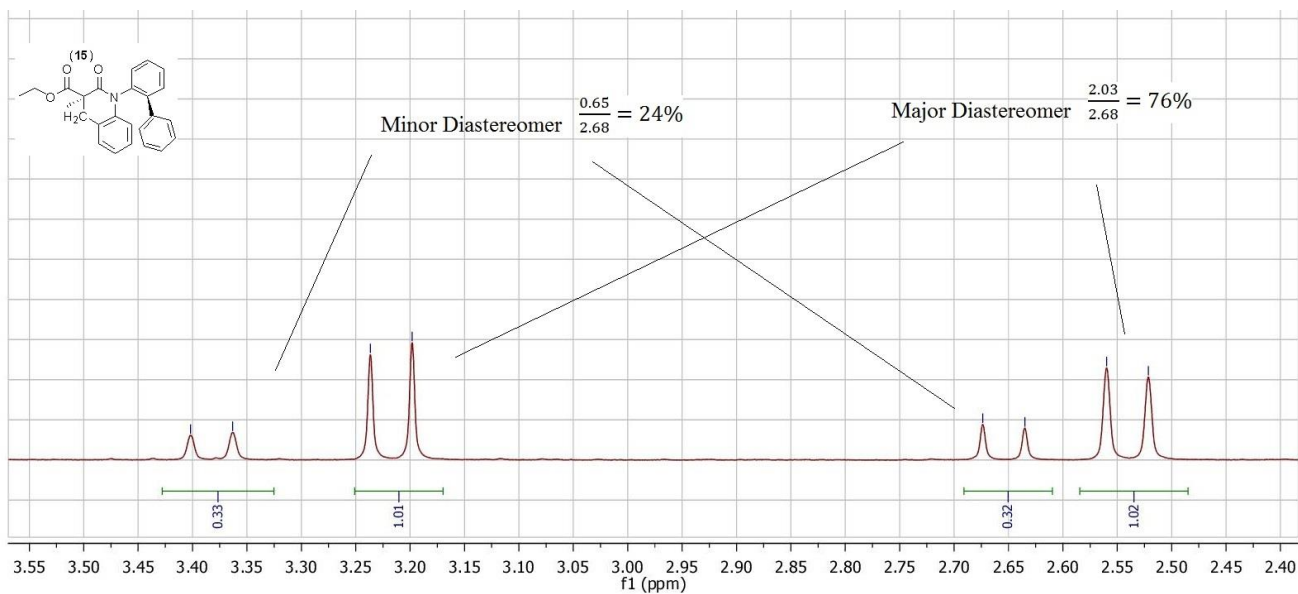
There is an improvement when comparing the diastereomeric ratio of product **14** to that of product **15**. The diastereomeric ratio is 75:25 for **12** when cyclized with either Pd/SPHOS, as seen in Figure 31. Once again, it might be due to the substrate and how it interacts with the catalysts to produce the diastereomer. Future research into precatalyst systems could shed light on the interactions of the catalyst and the substrate.





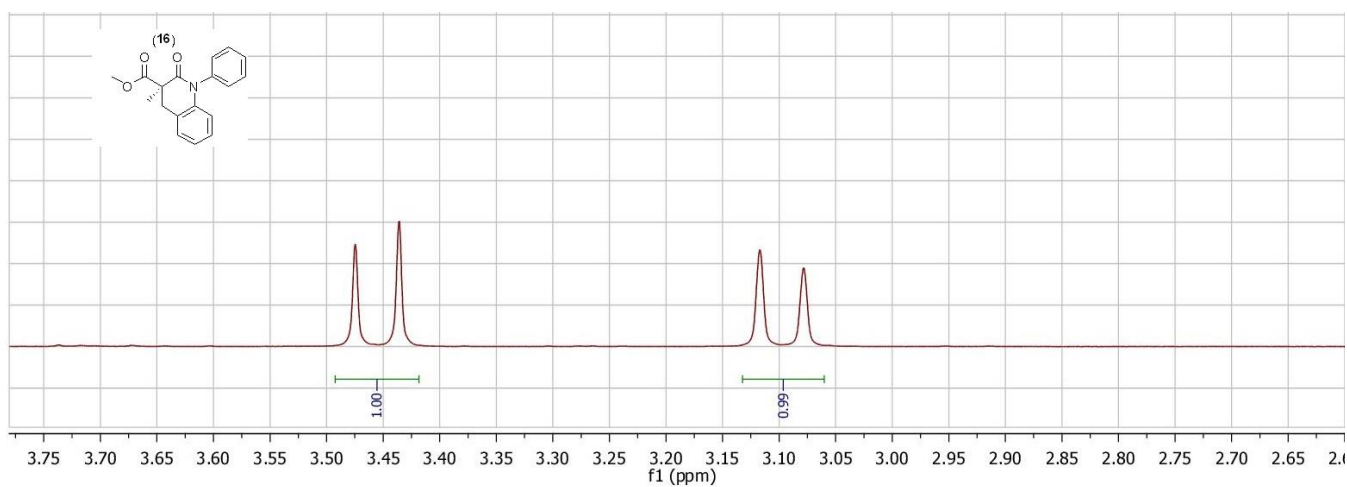
**Figure 31 - Diastereotopic Protons for **15** via Pd/SPHOS**

Diastereomeric enrichment seen in Figure 31, is reproduced when compound **15** is synthesized by the Pd/(*R*)-Cy<sub>2</sub>MOP catalyst, as in Figure 13.



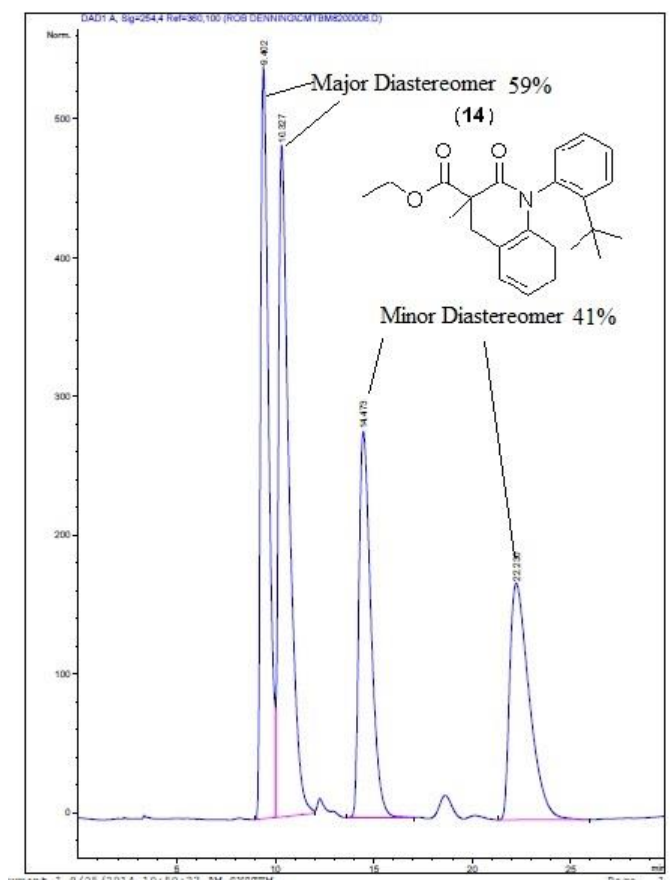
**Figure 32 - Similar Diastereoselectivity Seen Producing **15** via Pd/(*R*)-Cy<sub>2</sub>MOP**

Since the substrate **13** does not have the potential to form and not a chiral axis, there are no diastereomers that are present and thus only a single set of doublets are produced in the <sup>1</sup>H NMR of both the Pd/SPHOS and Pd/(*R*)-Cy<sub>2</sub>MOP reactions, as seen in Figure 33.



**Figure 33 - Cyclization Forming **16** Only Produces Enantiomers**

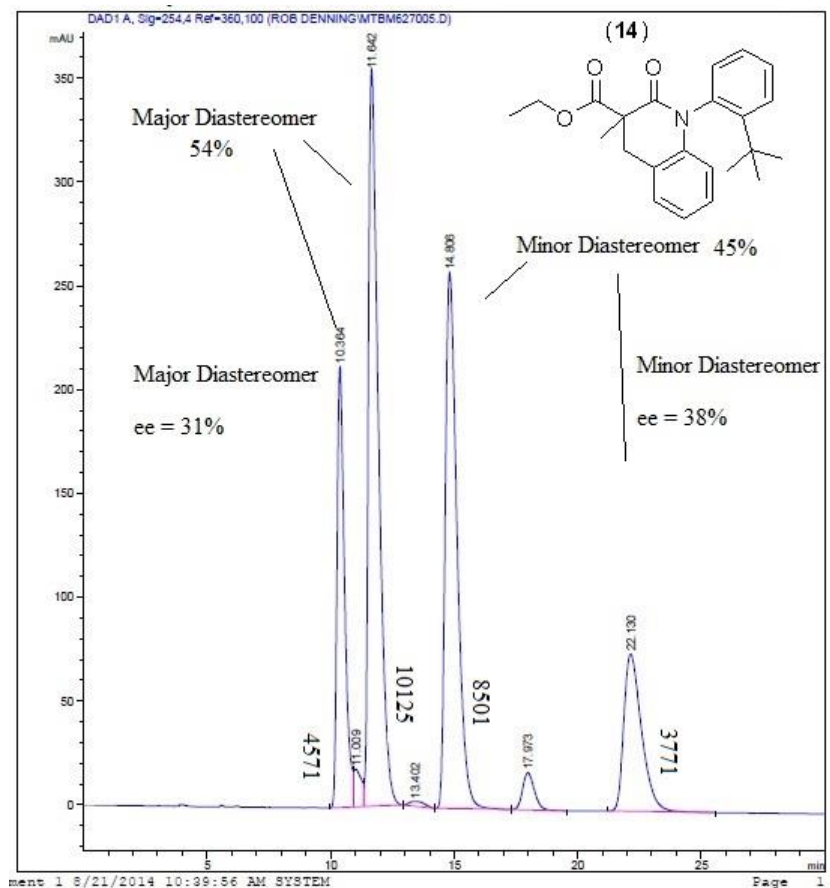
Analysis of the cyclized monoamide compounds **14-16** with HPLC has proven to be difficult. HPLC conditions in order to separate all four diastereomers of **14** have been found. But conditions to successfully separate all four diastereomers of **15** and enantiomers of **16** have not yet been discovered. Once again, the product **14** cyclized by Pd/SPHOS allows the identification of the diastereomeric peaks in the chromatogram, as seen in Figure 34.



**Figure 34 - HPLC Chromatogram of 14 via Pd/SPHOS**

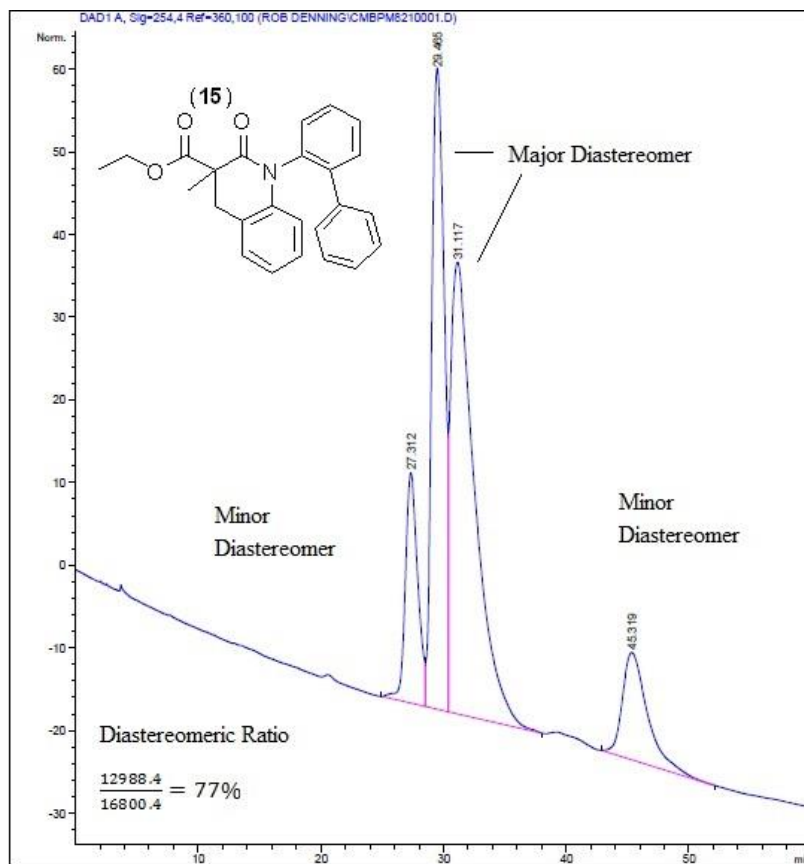
It is evident that the first two peaks represent the major diastereomer and the last two peaks represent the minor diastereomer. Using this information the analysis of the reaction forming **15**

with Pd/(*R*)-Cy<sub>2</sub>MOP can be done to calculate both the diastereomeric ratio and enantiomeric excess, the HPLC chromatogram is seen in Figure 35.



**Figure 35 - HPLC Chromatogram forming Product 14 via Pd/(*R*)-Cy<sub>2</sub>MOP**

As stated earlier, the HPLC conditions to fully resolve the four diastereomers of **15** could not be found. However, the diastereomeric ratio can be calculated since the diastereomers are separated, shown in Figure 36.



**Figure 36 - Unresolved Chromatogram of 15 via Pd/SPHOS**

This monoamide reaction scheme was pursued to show the potential substrate directing effects on the overall diastereomeric and enantiomeric selectivity of the reaction. Unfortunately, to date, HPLC conditions to resolve enantiomers of **16** have not been found. Also there seems to be some inconsistent results creating non-comparable chromatograms for compound **15** cyclized by Pd/(*R*)-Cy<sub>2</sub>MOP. The results for the dr (by NMR and HPLC) and er (by HPLC) are shown in Table 2.

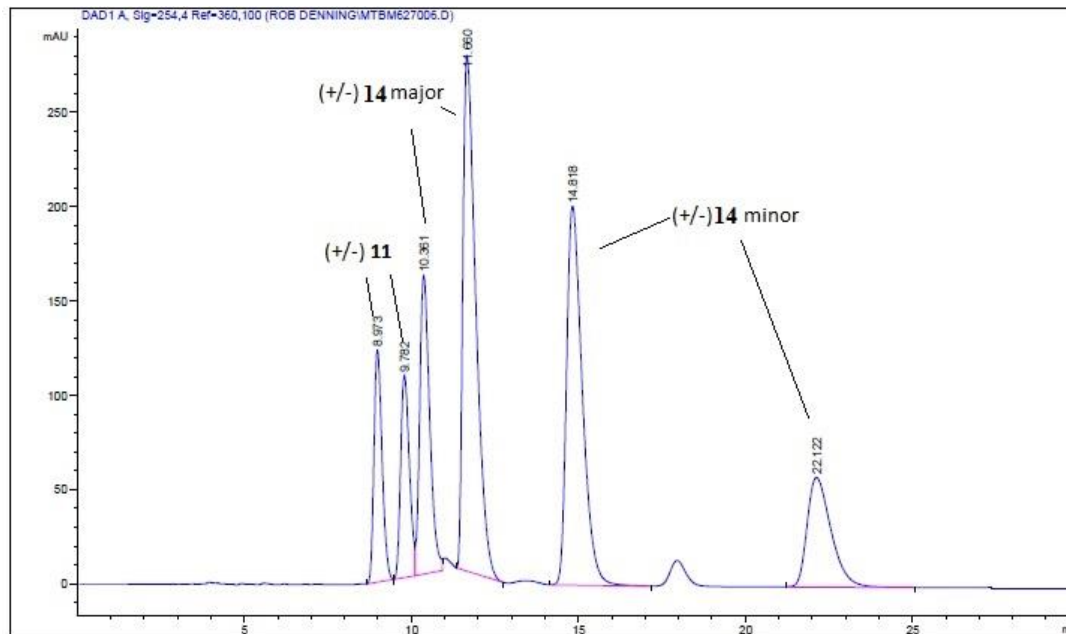
Product	NMR dr	HPLC dr	Major Diastereomer ee	Minor Diastereomer ee
<b>14</b> via SPHOS	53%	59%	NA	NA
<b>14</b> via (R)-Cy <sub>2</sub> MOP	53%	54%	31%	38%
<b>15</b> via SPHOS	75%	77%	NA	NA
<b>15</b> via (R)-Cy <sub>2</sub> MOP	75%			
<b>16</b> via SPHOS	NA	NA	NA	NA
<b>16</b> via (R)-Cy <sub>2</sub> MOP	NA	NA		

**Table 2 - Enantioselectivity and Diastereoselectivity of the Cyclization of **14**, **15** and **16** by SPHOS and (R)-Cy<sub>2</sub>MOP**

Comparing Table 2 with Table 1 with respect to the dr of the compounds, previously it was the compound with the *t*-butyl substituent **8** that had complete diastereoselectivity, but in the case with mono amide compounds the diastereoselectivity for the biphenyl compound **15** has held constant but is now much higher than the *t*-butyl compound **14**. It is also evident by the HPLC that there is degradation in the enantioselectivity of the compounds as well. This would give the impression that either the steric nature of the distant amide is directing the enantioselectivity or impacting the catalyst in a way that helps it form one enantiomer.

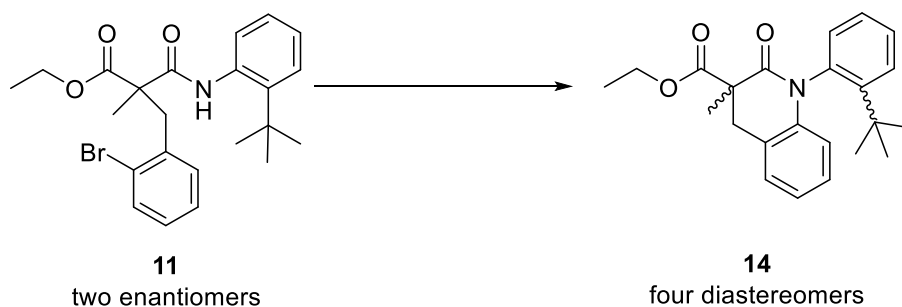
#### **2.4.2 Kinetics Experiment of the Cyclization Reaction of **11** with (R)-Cy<sub>2</sub>MOP and (R)-BINAP**

The kinetics of the cyclization reaction of **11** was studied to investigate if there was a preference towards consuming a single enantiomer of **11** or producing a single diastereomer/enantiomer of **14**. HPLC conditions were optimized so the peaks for the starting material did not overlap with the peaks for the product. Figure 37 shows an example chromatogram a mixture of **11** and **14**.



**Figure 37 - Optimized HPLC Conditions to Identify 11 and 14**

The reaction was done according to the condition in Scheme 14, with samples of the reaction being taken at time intervals; 15 min, 30 min, 45 min, 1 hr, 2 hr, 4 hr, 6 hr, 24 hr, and 48 hr. The drops were then diluted in 1 mL of 10% IPA/Hexanes and analyzed by HPLC. At the time of the experiments the absorption coefficients of all compounds in the reaction were not known. Thus quantification of the drop was not done, which could have led to the determination of the amounts of each compound present. Since the drop was not quantified, percent areas are shown in Table 3 to understand the amount of consumption/production as the reaction progresses. This reaction was not monitored by NMR since the enantiomers of the starting material, **11**, and the two sets of enantiomers of the product, **14**, cannot be seen since they are magnetically equivalent.



Relative Peak Area (%)

				14							
				Major Diastereomer			Minor Diastereomer				
Reaction Time Interval	Identified Peak	(±) 11 (8.973 min)	(±) 11 (9.782 min)	ee 11	Minor Enantiomer (10.361 min)	Major Enantiomer (11.660 min)	ee	Major Enantiomer (14.818 min)	Minor Enantiomer (22.122 min)	ee	dr
	15 min	50	50	0	0	0	0	0	0	0	0
	30 min	50	50	0	0	0	0	0	0	0	0
	45 min	41	40.5	0.6	0	0.7	100	6.2	0	100	79.7
	1 hr	44	41	3.5	0	2	100	9	0	100	63.6
	2 hr	39	37	2.6	2.5	5	33.3	11	1.4	77.4	24.6
	4 hr	35	33.7	1.9	4.8	10.2	36	11.5	3.8	50.3	0.9
	6 hr	29.5	28	2.6	6.7	14.7	37.4	14.4	5.5	44.7	3.6
	24 hr	3.8	2.6	18.8	14.4	32.4	38.5	29.4	13.9	35.8	3.8
	48 hr	0	0	0	14.5	31.2	36.5	27.3	11.8	39.6	7.7

**Table 3 - Reaction Kinetics of the Cyclization of 14 with (R)-Cy<sub>2</sub>MOP**

The first two peaks mentioned (8.973 min and 9.782 min) are the enantiomers of the starting material **11**, where the last 4 peaks (10.361, 11.660, 14.818 and 22.122 min) are the four diastereomers of the product. Over the course of 48 hours each enantiomer of **11** is consumed at roughly the same rate. Looking at the (±) **14** major diastereomer peaks, there is an initial selectivity seen at the 45 min mark, but there is only a small amount of major enantiomer present. The major enantiomer has an overall percentage of 31.2 percent at 48 hours, giving a 36.5% ee. With the (±) **14** minor peaks, the last peak takes a while before it is seen in the HPLC,

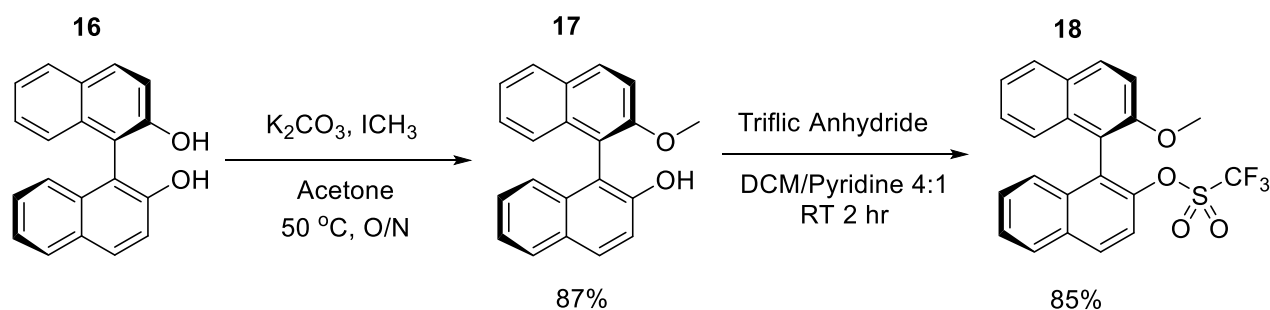


two hours after the reaction has started. The ee for the ( $\pm$ ) **14** minor peaks, which is 39.6% ee, is similar to the ( $\pm$ ) **14** major peaks.

The kinetics experiment was also repeated with (*R*)-BINAP and (*R*)-DTBM-SEGPHOS but by HPLC analysis no reaction had occurred.

## 2.5 Synthesis of (*R*)-Cy<sub>2</sub>MOP

The ligand of choice for our studies, (*R*)-Cy<sub>2</sub>MOP, is not commercially available. The source of the chirality comes from the starting material, (*R*)-BINOL. The BINOL is methylated as in Scheme 15.



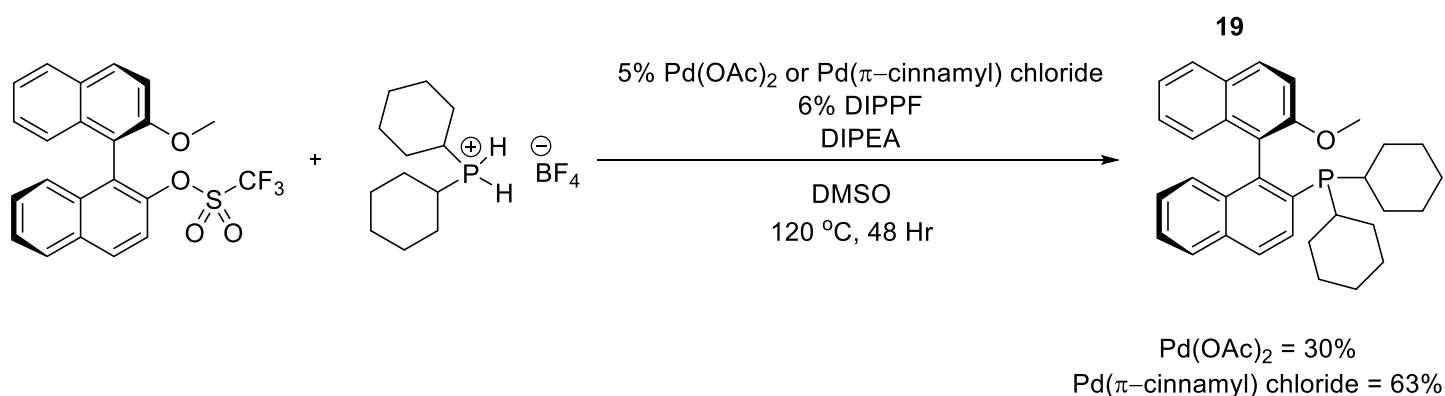
**Scheme 15 - Methylation and Triflation of (*R*)-BINOL**

This reaction was a difficult one to make the desired product, as a lot of dimethylated byproduct can be created. The extremely slow addition of the iodomethane with high stirring helped this reaction achieve the good yield observed.

The following reaction to form **18** also proceeded with good yields. Previous attempts required stirring overnight to achieve good results, but the slow addition of the triflic anhydride and maintaining a concentrated solution allowed this reaction to consume all of the starting

material in two hours. With a usable amount of (*R*)-**18** on hand a large scale reaction was done to prepare the active ligand (*R*)-Cy<sub>2</sub>MOP.

The reaction conditions to make (*R*)-Cy<sub>2</sub>MOP are similar to that of the Buchwald-Hartwig cross-coupling reaction studied in this thesis. The Buchwald-Hartwig reaction involves an aryl-halide and an amine, whereas the reaction to produce (*R*)-Cy<sub>2</sub>MOP involves the aryl-triflate and a phosphine, both reactions use a phosphorus bound palladium catalyst. The reaction is shown in Scheme 16.



### Scheme 16 - Synthesis of (*R*)-Cy<sub>2</sub>MOP from (*R*)-Me-BINOL-Otf

The range in yield can be attributed to the switch to the Pd( $\pi$ -cinnamyl) chloride from the palladium acetate. The largest scale this reaction was ran at was 1.16 mmol with a yield of 350 mg (63%) there was more than enough to carry out the remainder of the cyclization experiments. The (*R*)-Cy<sub>2</sub>MOP was compared by HPLC against the racemic Cy<sub>2</sub>MOP that was kindly prepared by Ms. Nande Wright following the same procedure outlined here but starting with racemic BINOL. When the ( $\pm$ )-Cy<sub>2</sub>MOP was analyzed by HPLC, there are two peaks observed, at retention times 17.065 and 19.374 min. Allowing the analysis of the enantiopurity of the (*R*)-Cy<sub>2</sub>MOP, which only has one peak at 19.186 min, ensuring a *R* enantiopure conformer.

### 3 Conclusion

With the use of (*R*)-dicyclohexyl(2'-methoxy-[1,1'-binaphthalen]-2-yl)phosphane, (*R*)-Cy<sub>2</sub>MOP in the Buchwald-Hartwig, excellent enantio- and diastereoselectivity of substituted malonamides can be seen (up to 90% and 100%, respectively). The selectivity seen is attributed to the effect of the steric bulk on the ligand playing a key role. This system was expanded to the substrate *N*1,*N*3-di([1,1'-biphenyl]-2-yl)-2-(2-bromobenzyl)-2-methylmalonamide but lower selectivity was observed in this case.

To investigate the mechanism further, monoamide malonamide compounds were synthesized. Cyclization of the monoamide compounds would determine if the (*R*)-Cy<sub>2</sub>MOP ligand or the substrate's chiral center is influencing the stereochemistry of the chiral axis. Once the cyclization reactions were done, there was a lot of loss in enantio- and diastereoselectivities as this could be due to the lack of steric bulk further away from the catalytic site. HPLC analysis of the molecules proved to be difficult, and only ethyl 1-(2-(*tert*-butyl)phenyl)-3-methyl-2-oxo-1,2,3,4-tetrahydroquinoline-3-carboxylate was fully resolved.

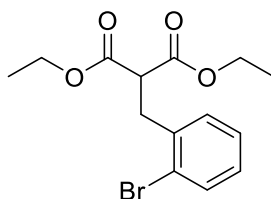
Finally, the synthesis of (*R*)-Cy<sub>2</sub>MOP was done in a three step process, compared to the 8 step process as seen in the literature. Successful characterization and HPLC analysis showed that the chirality of the molecule was retained completely throughout the synthesis.

Future work should isolate the precatalyst systems of the catalyst with these groups of substrates to better understand the interaction occurring. The kinetics reaction of cyclized malonamide compounds needs to be done to fully understand the selectivities that have been seen, or develop models that better reflect the initial findings of Matarazzo.

## 4 Experimental

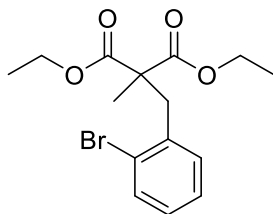
Chemicals and solvents were purchased from Sigma-Aldrich. All  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR,  $^{19}\text{F}$  NMR and  $^{31}\text{P}$  NMR spectra were collected on a Bruker 400 MHz NMR. All HPLC chromatograms were recorded on an Agilent 1260 Infinity machine using a photo diode array and a 4.6 mm x 250 mm Chiralpak OD-H column.

### 4.1 Synthesis Towards Substituted Malonamides



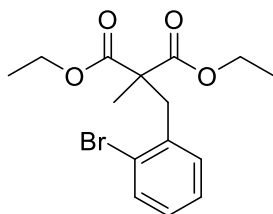
#### 4.1.1 Diethyl 2-(2-bromobenzyl)malonate (2)

Sodium hydride (0.6075 g, 15.188 mmol) was suspended in dry THF (30 mL, 0.5 M). The reaction was cooled to 0 °C and diethyl malonate (2.31 mL, 15.188 mmol) was added. After 30 minutes of stirring at 0 °C, there was no more elution of  $\text{H}_2$  gas. 2-Bromobenzyl bromide (4.1757 g, 16.7068 mmol) was added and the reaction was heated to reflux overnight. The reaction was cooled to room temperature and concentrated under vacuum. The crude mixture was redissolved in EtOAc (60 mL), and washed with water (3 x 30 mL). Once dried over magnesium sulphate and concentrated under vacuum, the crude mixture was purified via flash chromatography eluting with 15% EtOAc:Hexanes. The reaction yielded a colourless oil in 90% TLC (20% EtOAc:Hex )  $R_f = 0.23$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  7.53-7.51 (m, 1H, Ar), 7.25-7.18 (m, 2H, Ar), 7.10-7.06 (m, 1H, Ar), 4.18-4.12 (m, 4H,  $\text{CH}_2\text{CH}_3$ ), 3.84 (t,  $J = 8$  Hz, 1H,  $\text{CHCH}_2$ ) 3.33 (d,  $J = 8$  Hz, 2H,  $\text{CH}_2\text{CH}$ ) 1.20 (t,  $J = 8$  Hz, 6H,  $\text{CH}_2\text{CH}_3$ ).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 101 MHz)  $\delta$  168.62, 137.10, 132.91, 131.44, 128.57, 127.39, 124.55, 61.45, 51.48, 41.63, 35.02, 14.02, 13.97.



#### 4.1.2 Diethyl 2-(2-bromobenzyl)-2-methylmalonate (3)

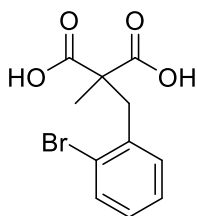
Sodium hydride (2.4359 g, 60.92 mmol) was suspended in dry THF (120 mL, 0.5 M). The reaction was cooled to 0 °C and diethyl 2-(2-bromobenzyl)malonate (4.0108 g, 12.184 mmol) was added slowly. After 30 minutes of stirring at 0 °C, there was no more elution of H<sub>2</sub> gas. Iodo methane (3.79 mL, 60.92 mmol) was added and the mixture was heated to reflux overnight. The reaction was quenched with a drop of ethanol, and concentrated under vacuum. The crude oil was redissolved in EtOAc (48 mL) and washed with water (3 x 24 mL). The crude product was dried over magnesium sulphate and concentrated under vacuum. It was not possible to isolate the crude product from its starting material via flash chromatography or crystallization.



#### 4.1.3 Diethyl 2-(2-bromobenzyl)-2-methylmalonate (3)

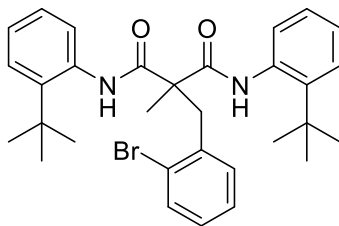
Sodium hydride (1.2823 g, 32.054 mmol) was suspended in dry THF (60 mL, 0.5 M). The reaction was cooled to 0 °C and diethyl 2-methylmalonate (4.97 mL, 29.14 mmol) was added slowly. Once there was no more elution of H<sub>2</sub> gas, 2-bromobenzyl bromide was added. The solution was heated to reflux overnight, cooled and concentrated under vacuum. The mixture was diluted in EtOAc (120 mL), and washed with water (3 x 60 mL). Once dried over magnesium sulphate and concentrated under vacuum, the crude product was purified via flash

chromatography eluting 10% EtOAc:Hexanes. The reaction gave a colourless oil with a mass of 8.5374 g, 89%. TLC (15% EtOAc:Hexanes )  $R_f = 0.20$ .  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.56-7.54 (m, 1H, Ar), 7.24 – 7.15 (m, 2H, Ar), 7.12 – 7.05 (m, 1H, Ar), 4.32 – 4.13 (m, 4H,  $\text{CH}_2\text{CH}_3$ ), 3.53 (s, 2H,  $\text{CH}_2$ ), 1.40 (s, 3H,  $\text{CH}_3$ ), 1.27 (t,  $J = 7.1$  Hz, 6H,  $\text{CH}_2\text{CH}_3$ ).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  171.83, 136.41, 133.07, 131.37, 128.44, 127.26, 126.26, 61.45, 55.06, 39.34, 19.36, 13.97.



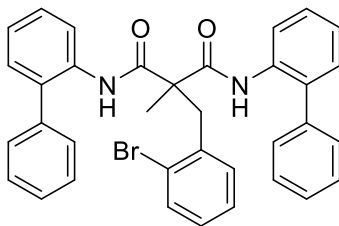
#### 4.1.4 2-(2-Bromobenzyl)-2-methylmalonic acid (5)

Diethyl 2-(2-bromobenzyl)-2-methylmalonate (5.0 g, 15.18 mmol) was dissolved in a minimum amount of MeOH. While stirring, aqueous 4M sodium hydroxide (15.2 mL, 60.74 mmol) was added and the solution was heated to reflux overnight. The reaction was cooled and diluted with water (15.2 mL). The reaction was extracted with  $\text{Et}_2\text{O}$  (3 x 15 mL), acidified with 6N HCl to pH 3 over ice and the remaining solution was extracted with EtOAc (3 x 15 mL). The organic phase was dried over magnesium sulphate and concentrated under vacuum to yield a white solid (3.7914 g, 91.5%) The  $\text{Et}_2\text{O}$  extracts were concentrated under vacuum to afford 0.643 g of starting material (effectively 100% based on recovered starting material). TLC (20% EtOAc:Hexanes)  $R_f = 0.30$   $^1\text{H}$  NMR (400 MHz, Acetone)  $\delta$  7.63-7.61 (m, 1H, Ar), 7.40-7.37 (m, 1H, Ar), 7.32-7.28 (m, 1H, Ar), 7.20-7.16 (m, 1H, Ar), 3.55 (s, 2H,  $\text{CH}_2$ ), 1.36 (s, 3H,  $\text{CH}_3$ ).  $^{13}\text{C}$  NMR (101 MHz, Acetone)  $\delta$  172.36, 136.70, 132.95, 131.43, 128.66, 127.55, 125.90, 54.37, 38.99, 18.60.



#### 4.1.5 2-(2-Bromobenzyl)-N1,N3-bis(2-(tert-butyl)phenyl)-2-methylmalonamide (6)

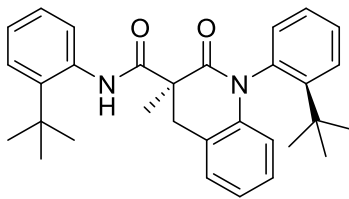
A round bottom flask was charged with a solution of 2-(2-bromobenzyl)-2-methylmalonic acid (1.8957 g, 6.94 mmol) in thionyl chloride (23 mL, 0.3 M) and was sealed and heated to 60 °C for 4 hours. The solution was cooled and concentrated under vacuum. The residual mixture was redissolved in  $\text{CHCl}_3$  (23 mL) and concentrated under vacuum a total of three times. The crude mixture was redissolved in DCM (70 mL, 0.1 M) and cooled to 0 °C. Once 2-(tert-butyl)aniline (2.38 mL, 15.27 mmol) was added slowly over ice, the reaction was stirred at room temperature for an hour. The mixture was then cooled to 0 °C, and triethylamine (2.13 mL, 15.27 mmol) was added dropwise and the mixture was heated to reflux overnight. The reaction was cooled to room temperature, washed with 1M HCl (4 x 70 mL), dried over magnesium sulphate and concentrated under vacuum. The crude mixture was purified via flash chromatography eluting at 20% EtOAc:Hexanes to yield 1.1213g (30%) of an off white solid. TLC (EtOAc:Hexanes)  $R_f$  = 0.45.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.64 (s, 2H, NH), 7.65 – 7.55 (m, 3H, Ar), 7.48-7.39 (m, 3H, Ar), 7.25 – 7.14 (m, 5H, Ar), 7.12-7.08 (m, 1H, Ar), 3.78 (s, 2H,  $\text{CH}_2$ ), 1.71 (s, 3H,  $\text{CH}_3$ ), 1.37 (s, 18H,  $\text{C}(\text{CH}_3)_3$ ).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  170.66, 142.81, 136.22, 134.84, 133.30, 131.54, 128.77, 127.70, 127.41, 126.73, 126.72, 126.40, 126.10, 56.29, 42.90, 34.56, 30.58, 18.52, 1.02.



#### 4.1.6 *N1,N3*-Di([1,1'-biphenyl]-2-yl)-2-(2-bromobenzyl)-2-methylmalonamide (7)

A round bottom flask was charged with a solution of 2-(2-bromobenzyl)-2-methylmalonic acid (1.8957 g, 6.94 mmol) in thionyl chloride (23.1 mL, 0.3 M) and was sealed and heated to 60 °C for 4 hours. The solution was cooled and concentrated under vacuum. The residual mixture was redissolved in  $\text{CHCl}_3$  (23.1 mL) and concentrated under vacuum a total of three times. The crude mixture was redissolved in DCM (69.4 mL, 0.1 M) and cooled to 0 °C. Once [1,1'-biphenyl]-2-amine (2.5840 g, 15.27 mmol) was added slowly over ice, the reaction was stirred at room temperature for an hour. Once cooled to 0 °C, triethylamine (2.13 mL, 15.27 mmol) was added dropwise and the mixture was heated to reflux overnight. The reaction was cooled to room temperature, washed with 1M HCl (4 x 70 mL), dried over magnesium sulphate and concentrated under vacuum. The crude mixture was purified via flash chromatography eluting 20% EtOAc:Hexanes to yield 2.0188 g (49.3%) of a light yellow compound. TLC (20% EtOAc:Hexanes)  $R_f$  = 0.33  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.44 (s, 2H, NH), 8.13-8.11 (m, 2H, Ar), 7.58 – 7.52 (m, 1H, Ar), 7.43 – 7.32 (m, 9H, Ar), 7.25 – 7.04 (m, 13H, Ar), 3.37 (s, 2H,  $\text{CH}_2$ ), 1.06 (s, 3H,  $\text{CH}_3$ ).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  169.89, 137.69, 136.20, 134.43, 133.31, 133.12, 131.24, 130.02, 129.25, 129.01, 128.61, 128.26, 128.04, 127.57, 126.18, 124.76, 121.68, 56.64, 42.59, 17.11.

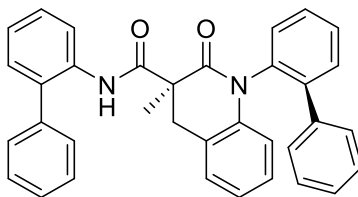




#### 4.1.7 *N*,1-Bis(2-(tert-butyl)phenyl)-3-methyl-2-oxo-1,2,3,4-tetrahydroquinoline-3-carboxamide (8)

A 10 mL Schlenk flask was charged with 2-(2-bromobenzyl)-*N*1,*N*3-bis(2-(tert-butyl)phenyl)-2-methylmalonamide (100 mg, 0.182 mmol), palladium( $\pi$ -cinnamyl) chloride dimer (2.4 mg, 0.00455 mmol) and dicyclohexyl(2'-methoxy-[1,1'-binaphthalen]-2-yl)phosphane (8.7 mg, 0.0182 mmol), with the flask being evacuated and backfilled with N<sub>2</sub> in between each addition. Anhydrous toluene (1.8 mL, 0.1 M) was added and the solution was evacuated and backfilled with N<sub>2</sub> three times. The mixture was heated to 100 °C for three minutes to dissolve the compounds and cooled to room temperature. Cs<sub>2</sub>CO<sub>3</sub> (83.0 mg, 0.2548 mmol) was added under N<sub>2</sub> and the solution was heated to 100 °C for 24 hours. The reaction was cooled, and diluted with EtOAc (5.4 mL). The solution was filtered through celite and concentrated under vacuum. The crude product was purified via flash chromatography, eluting with 5% EtOAc:Hexanes, to afford 84.3 mg (quantitative) of a white solid. TLC (20% EtOAc:Hexanes) R<sub>f</sub> = 0.40. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.41 (s, 1H, NH), 7.69-7.66 (m, 1H, Ar), 7.54 – 7.24 (m, 7H, Ar), 7.24 – 6.96 (m, 6H, Ar), 6.25 (m, 1H, Ar), 3.82 (d, *J* = 15.6 Hz, 1H, CH<sub>2a</sub>), 3.13 (d, *J* = 15.6 Hz, 1H, CH<sub>2b</sub>), 1.82 (s, 3H, CH<sub>3</sub>), 1.40 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>), 1.29 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  173.28, 168.29, 147.41, 142.37, 140.69, 135.93, 135.21, 132.22, 129.44, 129.01, 128.71, 127.57, 127.20, 127.07, 126.65, 126.49, 125.91, 123.99, 123.89, 116.63, 50.73, 35.77, 35.23, 34.48, 31.46, 30.57, 24.15. HPLC (Flow rate = 1.0 mL/min, 1% IPA:Hexanes) t<sub>R</sub> minor = 5.999 min

(area = 2030.1)(single diastereomer),  $t_R$  major = 6.413 min (area = 36617.6)(single diastereomer),  $t_R$  minor = 6.831 min (area 1998.5) (starting material)

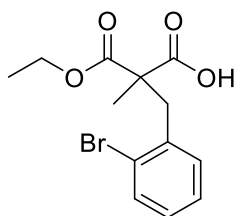


#### 4.1.8 *N*,1-Di([1,1'-biphenyl]-2-yl)-3-methyl-2-oxo-1,2,3,4-tetrahydroquinoline-3-carboxamide (9)

A 10 mL Schlenk flask was charged with *N*1,*N*3-di([1,1'-biphenyl]-2-yl)-2-(2-bromobenzyl)-2-methylmalonamide (200 mg, 0.339 mmol), palladium( $\pi$ -cinnamyl) chloride dimer (4.4 mg, 0.0169 mmol, 5%) and dicyclohexyl(2'-methoxy-[1,1'-binaphthalen]-2-yl)phosphane (16.2 mg, 0.0339 mmol, 10%), with the flask being evacuated and backfilled with  $N_2$  in between each addition. Anhydrous toluene (3.4 mL, 0.1 M) was added and the solution was evacuated and backfilled with  $N_2$  three times. The mixture was heated to 100 °C for three minutes to dissolve the compounds and cooled to room temperature.  $Cs_2CO_3$  (154.8 mg, 0.475 mmol) was added under  $N_2$  and the solution was heated to 100 °C for 24 hours. The reaction was cooled, and diluted with EtOAc (10.2 mL). The solution was filtered through celite and concentrated under vacuum. The crude product was purified via flash chromatography, eluting 10% EtOAc:Hexanes, to afford a white solid with a mass of 103.44 mg (60%), as a mixture of diastereomers.  $R_f$  = 0.25 (20% EtOAc:Hexanes)  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  8.83 (s, 1H, NH), 8.12-8.10 (m, 1H, Ar), 7.64 – 6.83 (m, 24H, Ar), 6.29-6.27 (m, 1H, Ar), 3.35 (d,  $J$  = 15.9 Hz, 1H,  $CH_{2a}$ ), 2.66 (d,  $J$  = 15.9 Hz, 1H,  $CH_{2b}$ ), 1.60 (s, 1H,  $CH_3$ ), 1.15 (s, 3H,  $CH_3$ ).  $^{13}C$  NMR (101 MHz,  $CDCl_3$ )  $\delta$  171.10, 169.20, 141.41, 139.76, 138.46, 138.19, 135.70, 134.67, 133.88, 131.22, 130.25, 129.76, 129.22, 128.87, 128.83, 128.79, 128.38, 128.28, 128.12, 127.79, 127.74, 127.42,

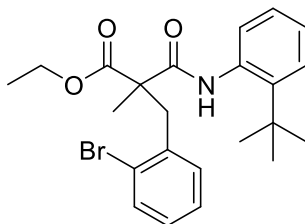
127.00, 124.71, 123.57, 122.50, 116.48, 49.27, 35.02, 22.74. HPLC (Flow rate 1.0 ml/min, 1% IPA:Hexanes)  $t_R$  minor, minor diast. = 10.628 min (area = 2072.2),  $t_R$  major, minor diast. = 11.545 min (area = 6178.2),  $t_R$  major, major diast. = 13.087 min (area = 14744.9),  $t_R$  minor, major diast. = 15.114 min (area = 6627.4).

## 4.2 Synthesis Towards Monoamide Compounds



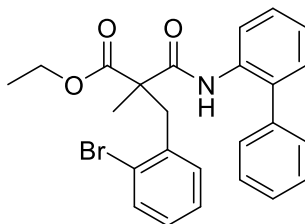
### 4.2.1 2-(2-Bromobenzyl)-3-ethoxy-2-methyl-3-oxopropanoic acid (10)

Diethyl 2-(2-bromobenzyl)-2-methylmalonate (4.0 g, 11.65 mmol) was dissolved in EtOH (7.5 mL, 1.56 M). A separate solution of NaOH (0.5594 g, 13.986 mmol) in EtOH (8.37 mL, 1.67M) was prepared. The reaction mixture was cooled to 0 °C and the base solution was added slowly over ice. The reaction was heated to reflux for an hour, then concentrated under vacuum. The residual reaction mixture was dissolved in water (10 mL) and extracted with Et<sub>2</sub>O (3 x 5 mL). The aqueous layer was acidified to pH 3 with 1 M HCl. The product was extracted out of the aqueous layer with EtOAc (3 x 5 mL). The organic layer was dried over magnesium sulphate and concentrated under vacuum to afford 3.0 g (81%) of a colourless oil. TLC (20% EtOAc:Hexanes)  $R_f$  = 0.19 <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.57-7.55 (m, 1H, Ar), 7.22-7.21 (m, 2H, Ar), 7.13 – 7.06 (m, 1H, Ar), 4.25 (qd,  $J$  = 7.1, 1.3 Hz, 2H, CH<sub>2a/b</sub>CH<sub>3</sub>), 3.54 (dd,  $J$  = 20, 16 Hz, 2H, CH<sub>2a/b</sub>), 1.45 (s, 3H, CH<sub>3</sub>), 1.28 (t,  $J$  = 7.1 Hz, 3H, CH<sub>2</sub>CH<sub>3</sub>). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  177.54, 172.10, 135.81, 133.20, 131.31, 128.71, 127.44, 126.23, 55.03, 52.90, 39.54, 19.41, 13.91.



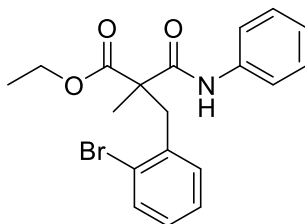
#### 4.2.2 Ethyl 2-(2-bromobenzyl)-3-((2-(tert-butyl)phenyl)amino)-2-methyl-3-oxopropanoate (11)

A round bottom flask was charged with a solution of 2-(2-bromobenzyl)-3-ethoxy-2-methyl-3-oxopropanoic acid (3.0 g, 9.5 mmol) in thionyl chloride (32.0 mL, 0.3 M) and was sealed and heated to 60 °C for 4 hours. The solution was cooled and concentrated under vacuum. The residual mixture was redissolved in CHCl<sub>3</sub> (30.0 mL) and concentrated under vacuum a total of three times. The crude mixture was redissolved in DCM (95.0 mL, 0.1 M) and cooled to 0 °C. Once 2-(tert-butyl)aniline (1.63 mL, 10.45 mmol) was added slowly over ice, the reaction was stirred at room temperature for an hour. Once cooled to 0 °C, triethylamine (1.46 mL, 10.45 mmol) was added dropwise and the mixture was heated to reflux overnight. The reaction was cooled to room temperature, washed with 1 M HCl (4 x 50 mL), dried over magnesium sulphate and concentrated under vacuum. The crude mixture was purified via flash chromatography eluting with 20% EtOAc:Hexanes to yield 2.7322 g (65%) of a light yellow oil. TLC (20% EtOAc:Hexanes) R<sub>f</sub> = 0.38 <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.85 (s, 1H, NH), 7.66-7.64 (m, 1H, Ar), 7.60 – 7.55 (m, 1H, Ar), 7.44-7.41 (m, 1H, Ar), 7.35-7.32 (m, 1H, Ar), 7.30 – 7.15 (m, 3H, Ar), 7.12-7.07 (m, 1H, Ar), 4.27 (m, 2H, CH<sub>2</sub>CH<sub>3</sub>), 3.72 (d, *J* = 14.4 Hz, 1H, CH<sub>2a</sub>), 3.61 (d, *J* = 14.4 Hz, 1H, CH<sub>2b</sub>), 1.66 (s, 3H, CH<sub>3</sub>), 1.41 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>), 1.27 (t, *J* = 7.1 Hz, 3H, CH<sub>3</sub>CH<sub>2</sub>). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 174.72, 169.19, 142.70, 136.85, 135.20, 133.16, 131.00, 128.50, 127.50, 127.48, 126.73, 126.64, 126.14, 126.01, 62.18, 55.36, 41.69, 34.59, 30.55, 21.50, 13.99.



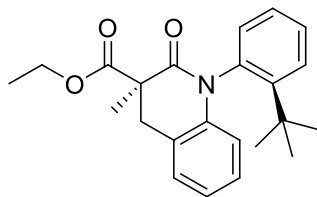
#### 4.2.3 Ethyl 3-([1,1'-biphenyl]-2-ylamino)-2-(2-bromobenzyl)-2-methyl-3-oxopropanoate (12)

A round bottom flask was charged with a solution of 2-(2-bromobenzyl)-3-ethoxy-2-methyl-3-oxopropanoic acid (1.5 g, 4.75 mmol) in thionyl chloride (15.8 mL, 0.3 M) and was sealed and heated to 60 °C for 4 hours. The solution was cooled and concentrated under vacuum. The residual mixture was redissolved in CHCl<sub>3</sub> (15 mL) and concentrated under vacuum a total of three times. The crude mixture was redissolved in DCM (47.5 mL, 0.1 M) and cooled to 0 °C. Once [1,1'-biphenyl]-2-amine (0.8842 g, 5.225 mmol) was added slowly over ice, the reaction was stirred at room temperature for an hour. Once cooled to 0 °C, triethylamine (0.7 mL, 5.225 mmol) was added dropwise and the mixture was heated to reflux overnight. The reaction was cooled to room temperature, washed with 1 M HCl (4 x 25 mL), dried over magnesium sulphate and concentrated under vacuum. The crude mixture was purified via flash chromatography eluting with 20% EtOAc:Hexanes to yield 1.2992 g (58.8%) of a light yellow oil. TLC (20% EtOAc:Hexanes) R<sub>f</sub> = 0.35 <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.37 (s, 1H, NH), 7.58-7.56 (m, 1H, Ar), 7.44-7.40 (m, 5H, Ar), 7.29 – 7.26 (m, 3H, Ar), 7.23-7.17 (m, 3H, Ar), 7.13 – 7.04 (m, 1H, Ar), 4.09 (q, *J* = 7.1 Hz, 2H, CH<sub>2</sub>CH<sub>3</sub>), 3.52 (d, *J* = 3.5 Hz, 2H, CH<sub>2</sub>), 1.38 (s, 3H, CH<sub>3</sub>), 1.18 (t, *J* = 7.1 Hz, 3H, CH<sub>3</sub>CH<sub>2</sub>). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 173.18, 168.78, 137.88, 136.56, 134.67, 133.06, 132.95, 131.14, 130.04, 129.32, 129.25, 129.02, 128.96, 128.49, 128.41, 127.98, 127.43, 126.14, 124.57, 121.54, 61.87, 56.00, 41.04, 19.97, 13.90.



#### 4.2.4 Ethyl 2-(2-bromobenzyl)-2-methyl-3-oxo-3-(phenylamino)propanoate (13)

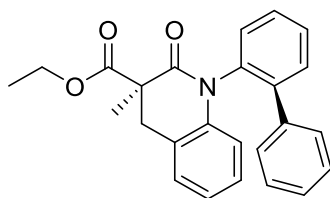
A solution of 2-(2-bromobenzyl)-3-ethoxy-2-methyl-3-oxopropanoic acid (1.5 g, 4.75 mmol) in thionyl chloride (15.8 mL, 0.3 M) was heated to 60 °C for 4 hours. The solution was cooled and concentrated under vacuum. The residual mixture was redissolved in  $\text{CHCl}_3$  (15 mL) and concentrated under vacuum a total of three times. The crude mixture was redissolved in DCM (47.5 mL, 0.1 M) and cooled to 0 °C. Once aniline (0.477 mL, 5.225 mmol) was added slowly over ice, the reaction was stirred at room temperature for an hour. Once cooled to 0 °C, triethylamine (0.7 mL, 5.225 mmol) was added dropwise and the mixture was heated to 60 °C overnight. The reaction was cooled to room temperature, washed with 1 M HCl (4 x 25 mL), dried over magnesium sulphate and concentrated under vacuum. The crude mixture was purified via flash chromatography with eluting 20% EtOAc:Hexanes to yield 1.1567 g (62.6%) of a light yellow oil. TLC (20% EtOAc:Hexanes)  $R_f$  = 0.28  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.20 (s, 1H, NH), 7.60 – 7.46 (m, 3H, Ar), 7.35-7.31 (m, 2H, Ar), 7.20 – 7.01 (m, 4H, Ar), 4.29 – 4.15 (m, 2H,  $\text{CH}_{2\text{a/b}}$ CH<sub>3</sub>), 3.58 (d,  $J$  = 14.2 Hz, 1H,  $\text{CH}_{2\text{a}}$ ), 3.51 (d,  $J$  = 14.2 Hz, 1H,  $\text{CH}_{2\text{b}}$ ), 1.60 (s, 3H, CH<sub>3</sub>), 1.25 (t,  $J$  = 7.1 Hz, 3H,  $\text{CH}_3\text{CH}_2$ ).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  174.86, 168.80, 137.71, 136.41, 133.04, 130.78, 128.97, 128.54, 127.37, 125.83, 124.49, 120.24, 62.20, 54.99, 42.59, 21.25, 13.89.



#### 4.2.5 Ethyl 1-(2-(tert-butyl)phenyl)-3-methyl-2-oxo-1,2,3,4-tetrahydroquinoline-3-carboxylate (14)

A 10 mL Schlenk flask was charged with ethyl 2-(2-bromobenzyl)-3-((2-(tert-butyl)phenyl)amino)-2-methyl-3-oxopropanoate (200 mg, 0.448 mmol), palladium( $\pi$ -cinnamyl) chloride dimer (5.8 mg, 0.0224 mmol, 5%) and dicyclohexyl(2'-methoxy-[1,1'-binaphthalen]-2-yl)phosphane (21.4 mg, 0.0448 mmol, 10%), with the flask being evacuated and backfilled with  $N_2$  in between each addition. Anhydrous toluene (4.5 mL, 0.1 M) was added to the solution under a stream of  $N_2$ . The mixture was heated to 100 °C for three minutes to dissolve the compounds and cooled to room temperature.  $Cs_2CO_3$  (204.4 mg, 0.627 mmol) was added under  $N_2$  and the solution was heated to 100 °C for 24 hours. The reaction was cooled, and diluted with EtOAc (13.5 mL). The solution was filtered through celite and concentrated under vacuum. The crude product was purified via flash chromatography, eluting at 20% EtOAc:Hexanes, to afford 160 mg (quant.) of a yellow oil, as a mixture of diastereomers. TLC (20% EtOAc:Hexanes)  $R_f$  = 0.22  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.69 – 7.58 (m, 2H, Ar), 7.47 – 7.30 (m, 4H, Ar), 7.26 – 7.12 (m, 3H, Ar), 7.12 – 6.93 (m, 4H, Ar), 6.91-6.89 (m, 1H, Ar), 6.25-6.18 (m, 2H, Ar), 4.39 – 3.92 (m, 4H,  $CH_2CH_3$ ), 3.83 (d,  $J$  = 15.5 Hz, 1H,  $CH_2$ , minor diastereomer), 3.34 (d,  $J$  = 15.3 Hz, 1H,  $CH_2$ , major diastereomer), 3.09 (d,  $J$  = 15.3 Hz, 1H,  $CH_2$ , major diastereomer), 2.85 (d,  $J$  = 15.6 Hz, 1H,  $CH_2$ , minor diastereomer), 1.66 (s, 3H,  $CH_3$ , major diastereomer), 1.48 (s, 3H,  $CH_3$ , minor diastereomer), 1.28 (s, 9H,  $C(CH_3)_3$ , minor diastereomer), 1.21 (s, 9H,  $C(CH_3)_3$ , major diastereomer), 1.03 (t,  $J$  = 7.1 Hz, 3H,  $CH_3CH_2$ ).  $^{13}C$  NMR (101 MHz,  $CDCl_3$ )  $\delta$  172.29, 169.53,

141.22, 136.22, 131.45, 131.20, 130.23, 130.08, 128.86, 128.69, 128.41, 128.26, 128.25, 127.72, 127.71, 127.69, 127.31, 127.23, 127.06, 123.33, 122.88, 116.44, 61.38, 50.53, 49.91, 36.87, 20.33, 13.92. HPLC (Flow Rate = 1.0 mL/min, 1% IPA:Hexanes)  $t_R$  minor = 10.364 min (area = 4571.8),  $t_R$  major = 11.542 min (area = 10125.5),  $t_R$  minor = 14.806 min (area = 8501.1),  $t_R$  minor = 22.130 min (area = 3771.7)

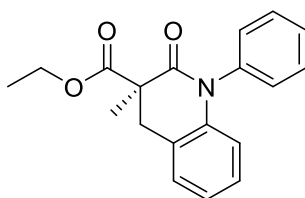


#### 4.2.6 Ethyl 1-([1,1'-biphenyl]-2-yl)-3-methyl-2-oxo-1,2,3,4-tetrahydroquinoline-3-carboxylate (15)

A 10 mL Schlenk flask was charged with ethyl 3-([1,1'-biphenyl]-2-ylamino)-2-(2-bromobenzyl)-2-methyl-3-oxopropanoate (200 mg, 0.4298 mmol), palladium( $\pi$ -cinnamyl) chloride dimer (5.7 mg, 0.02149 mmol, 5%) and dicyclohexyl(2'-methoxy-[1,1'-binaphthalen]-2-yl)phosphane (20.5 mg, 0.04298 mmol, 10%), with the flask being evacuated and backfilled with  $N_2$  in between each addition. Anhydrous toluene (4.30 mL, 0.1 M) was added to the solution under a stream of  $N_2$ . The mixture was heated to 100 °C for three minutes to dissolve the compounds and cooled to room temperature.  $Cs_2CO_3$  (196.1 mg, 0.6017 mmol) was added under  $N_2$  and the solution was heated to 100 °C for 24 hours. The reaction was cooled, and diluted with EtOAc (12.9 mL). The solution was filtered through celite and concentrated under vacuum. The crude product was purified via flash chromatography, eluting with 20% EtOAc:Hexanes, to afford 76.5 mg (46%) of a yellow oil, as a mixture of diastereomers. TLC (20% EtOAc:Hexanes)



$R_f = 0.22$   $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.59 – 7.39 (m, 5H, Ar), 7.27 – 7.10 (m, 7H, Ar), 7.00–6.98 (m, 3H, Ar), 6.91–6.85 (m, 1H, Ar), 6.32–6.29 (m, 1H, Ar), 4.31 – 3.93 (m, 4H,  $\text{CH}_2\text{CH}_3$ ), 3.38 (d,  $J = 15.5$  Hz, 1H,  $\text{CH}_2$ , minor diastereomer), 3.22 (d,  $J = 15.4$  Hz, 1H,  $\text{CH}_2$ , major diastereomer), 2.65 (d,  $J = 15.5$  Hz, 1H,  $\text{CH}_2$ , minor diastereomer), 2.54 (d,  $J = 15.3$  Hz, 1H,  $\text{CH}_2$ , major diastereomer), 1.45 (s, 1H,  $\text{CH}_3$ , minor diastereomer), 1.41 (s, 3H,  $\text{CH}_3$ , major diastereomer), 1.24 (t,  $J = 7.1$  Hz, 1H,  $\text{CH}_3\text{CH}_2$ , minor diastereomer), 1.07 (t,  $J = 7.1$  Hz, 3H,  $\text{CH}_3\text{CH}_2$ , major diastereomer).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  172.29, 141.22, 136.22, 131.20, 130.08, 128.86, 128.69, 128.41, 128.26, 128.25, 127.81, 127.72, 127.69, 127.31, 127.23, 123.33, 122.88, 116.44, 61.38, 49.91, 36.87, 20.33, 13.92.

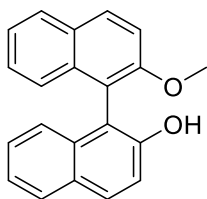


#### 4.2.7 Ethyl 3-methyl-2-oxo-1-phenyl-1,2,3,4-tetrahydroquinoline-3-carboxylate (16)

A 10 mL Schlenk flask was charged with Ethyl 2-(2-bromobenzyl)-2-methyl-3-oxo-3-(phenylamino)propanoate (200 mg, 0.5125 mmol), palladium( $\pi$ -cinnamyl) chloride dimer (6.6 mg, 0.0256 mmol, 5%) and dicyclohexyl(2'-methoxy-[1,1'-binaphthalen]-2-yl)phosphane (24.5 mg, 0.05125 mmol, 10%), with the flask being evacuated and backfilled with  $\text{N}_2$  in between each addition. Anhydrous toluene (5.1 mL, 0.1M) was added to the solution under a stream of  $\text{N}_2$ . The mixture was heated to  $100^\circ\text{C}$  for three minutes to dissolve the compounds and cooled to room temperature.  $\text{Cs}_2\text{CO}_3$  (233.7 mg, 0.7175 mmol) was added under  $\text{N}_2$  and the solution was heated to  $100^\circ\text{C}$  for 24 hours. The reaction was cooled, and diluted with EtOAc (15.4 mL). The

solution was filtered through celite and concentrated under vacuum. The crude product was purified via flash chromatography, eluting with 20% EtOAc:Hexanes, to afford 141.6 mg (89.2%) of a yellow oil. TLC (20% EtOAc:Hexanes)  $R_f = 0.18$ .  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.53-7.51 (m, 2H, Ar), 7.46-7.42 (m, 1H, Ar), 7.29-7.21 (m, 2H, Ar), 7.22-7.21 (m, 1H, Ar), 7.08-7.04 (m, 1H, Ar), 6.99-6.98 (m, 1H, Ar), 6.36-6.33 (m, 1H, Ar), 4.15 (dq,  $J = 10.8, 7.1$  Hz, 1H,  $\text{CH}_2\text{CH}_3$ ), 4.06 (dq,  $J = 10.8, 7.1$  Hz, 1H,  $\text{CH}_2\text{CH}_3$ ), 3.46 (d,  $J = 15.5$  Hz, 1H,  $\text{CH}_{2a}$ ), 3.10 (d,  $J = 15.5$  Hz, 1H,  $\text{CH}_{2b}$ ), 1.63 (s, 3H,  $\text{CH}_3$ ), 1.10 (t,  $J = 7.1$  Hz, 3H,  $\text{CH}_3\text{CH}_2$ ).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  172.29, 169.70, 141.15, 138.69, 129.82, 128.79, 128.17, 128.10, 127.50, 123.54, 123.10, 116.67, 61.50, 49.96, 37.20, 20.52, 13.95.

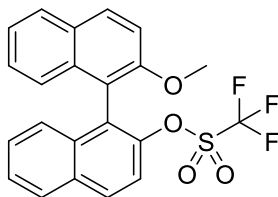
### 4.3 Synthesis Towards $\text{Cy}_2\text{MOP}$



#### 4.3.1 (*R*)-2'-Methoxy-[1,1'-binaphthalen]-2-ol (17)

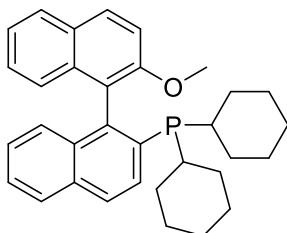
A solution of  $\text{K}_2\text{CO}_3$  (3.459 g, 25.025 mmol) in acetone (182 mL) was stirred for 30 minutes at room temperature. (*R*)-(+)-1,1'-Bi(2-naphthol) (6.514 g, 22.75 mmol) was added and the solution was cooled to 0 °C. Iodomethane (1.407 mL, 22.75 mmol) was added extremely slowly over ice. The solution was heated to 50 °C overnight. The reaction was cooled and filtered through celite with the celite being washed with  $\text{Et}_2\text{O}$ . The crude mixture was concentrated under vacuum and purified via flash chromatography eluting in neat DCM to afford the target compound in 5.944 g (87%) yield. The product is a light yellow solid. TLC (neat DCM)  $R_f = 0.42$ .  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.13 – 7.03 (m, 12H, Ar), 4.98 (s, 1H, OH), 3.83 (s, 3H,  $\text{CH}_3$ ).  $^{13}\text{C}$  NMR (101 MHz,

CDCl<sub>3</sub>)  $\delta$  156.02, 151.26, 134.07, 133.80, 131.07, 129.81, 129.46, 129.17, 128.17, 128.15, 127.35, 126.42, 124.94, 124.84, 124.20, 123.25, 117.50, 115.40, 115.04, 113.86, 56.70.



#### 4.3.2 (R)-2'-Methoxy-[1,1'-binaphthalen]-2-yl trifluoromethanesulfonate (18)

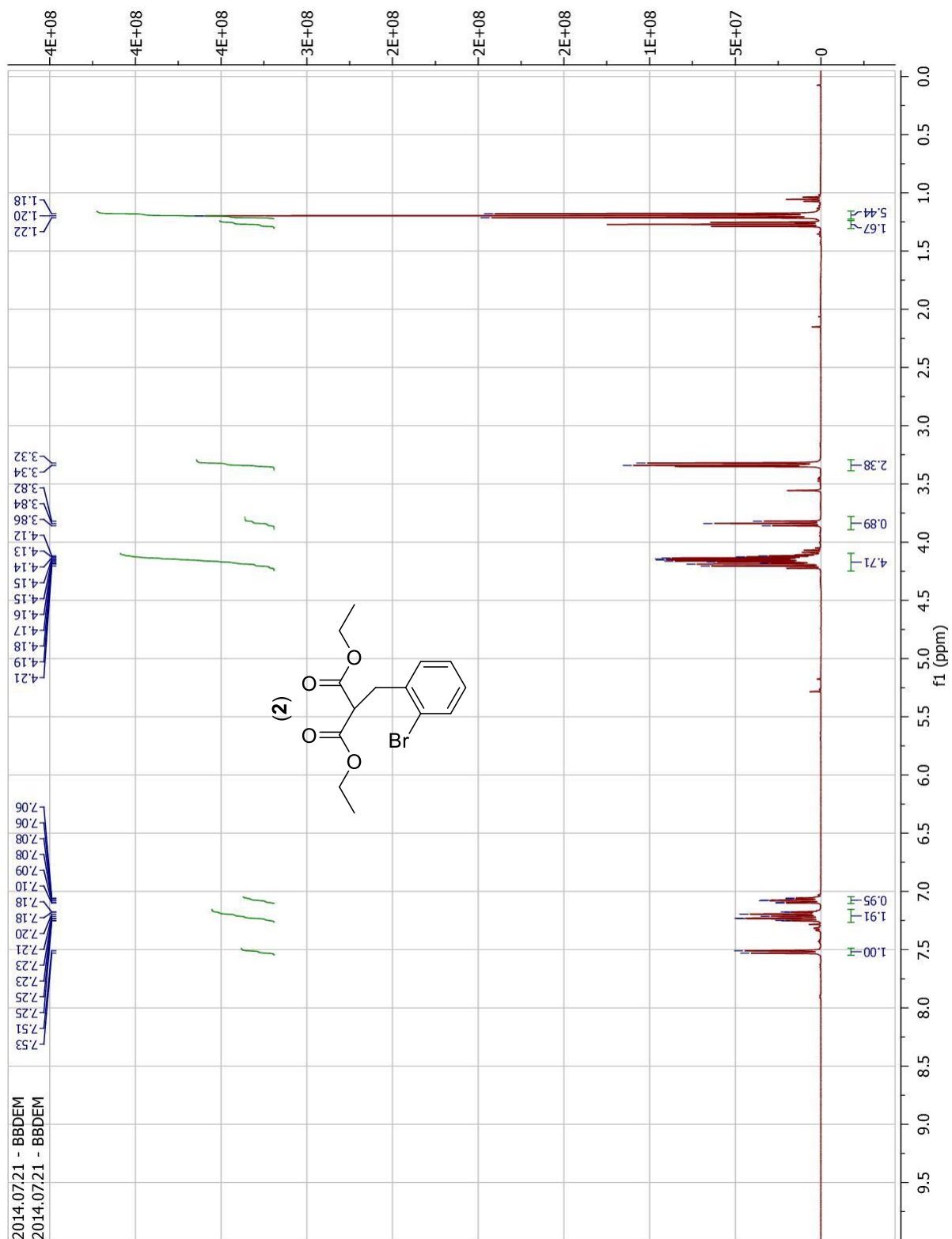
(R)-2'-Methoxy-[1,1'-binaphthalen]-2-ol (3.0 g, 9.9916 mmol) was dissolved in DCM (30 mL). Pyridine (2.40 mL, 4.16 M) was added and the mixture was cooled to 0 °C. Triflic anhydride (5.55 mL, 32.97 mmol) was added dropwise over 10 minutes. An extra portion of DCM (70 mL) was needed to maintain stirring since a precipitate was forming. The reaction was stirred for 30 minutes at 0 °C. The organic phase was washed with 1M HCl (50 mL), saturated NaHCO<sub>3</sub> (50 mL) and brine (50 mL), in sequential order. The crude mixture was concentrated under vacuum and purified via flash chromatography, eluting with 50% DCM:Hexanes to afford the white solid product (3.6959 g, 85.5%). TLC (50% DCM:Hexanes)  $R_f$  = 0.36 <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.16 – 6.98 (m, 12H, Ar), 3.87 (s, 3H, CH<sub>3</sub>). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  155.23, 145.69, 133.70, 133.61, 132.61, 131.11, 130.25, 128.88, 128.28, 128.15, 127.42, 127.33, 126.96, 126.91, 126.87, 124.84, 123.73, 119.90, 119.57, 116.72, 115.17, 112.97, 56.20. <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>)  $\delta$  -74.89.



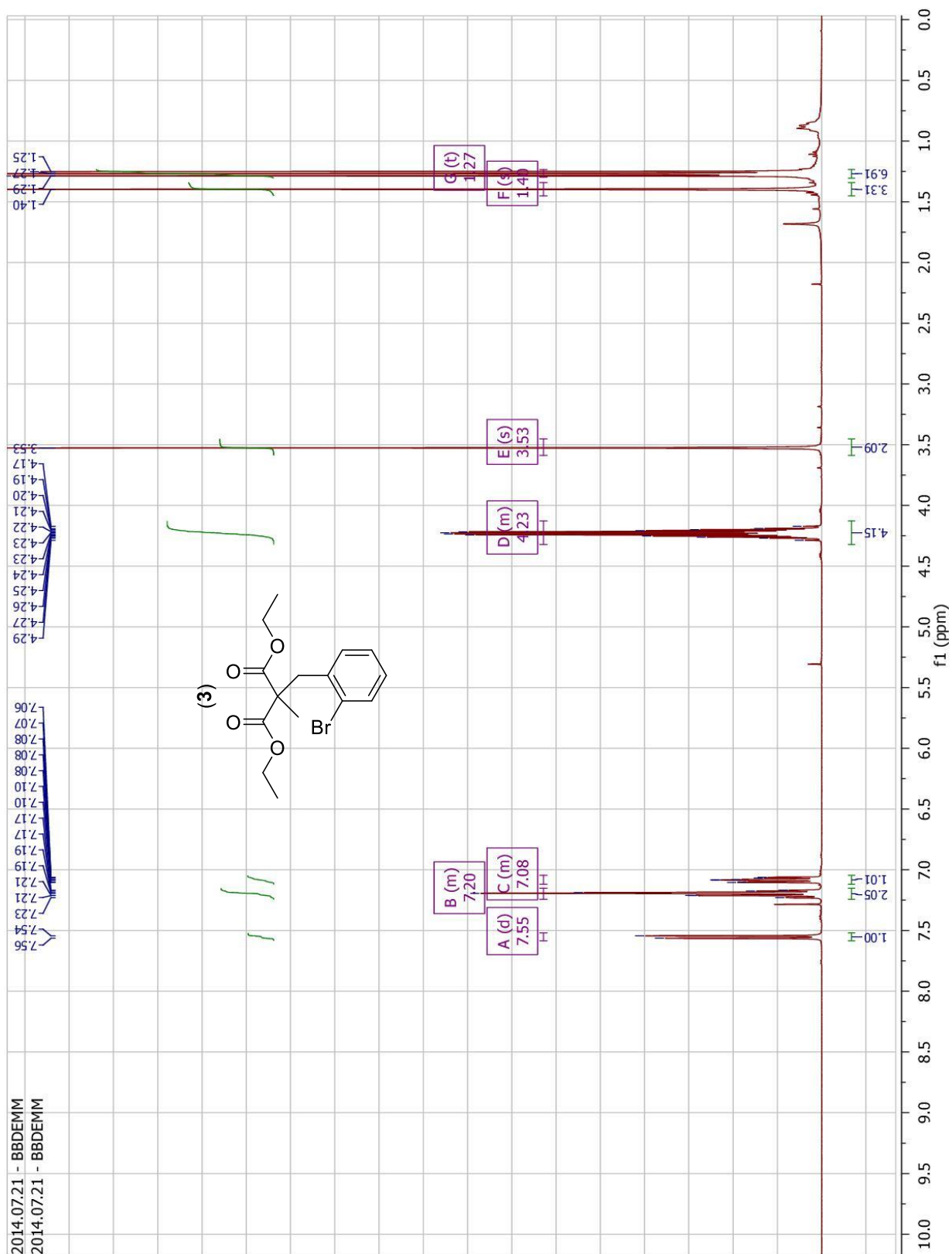
#### 4.3.3 (*R*)-Dicyclohexyl(2'-methoxy-[1,1'-binaphthalen]-2-yl)phosphane (19)

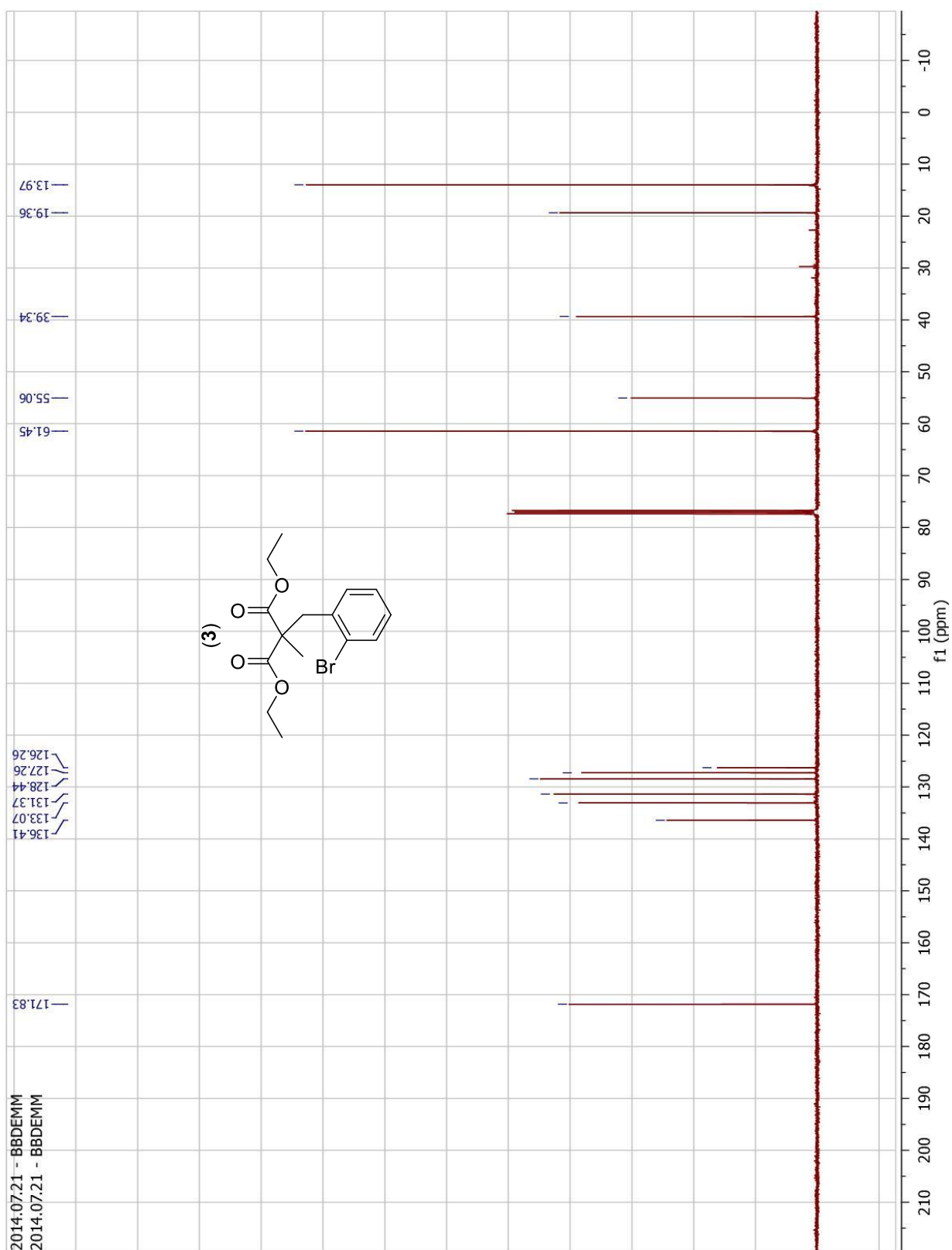
A Schlenk flask was charged with (*R*)-2'-methoxy-[1,1'-binaphthalen]-2-yl trifluoromethanesulfonate (500 mg, 1.156 mmol), dicyclohexylphosphonium tetrafluoroborate (363.8 mg, 1.2716 mmol), palladium( $\pi$ -cinnamyl) chloride dimer (15 mg, 0.0289 mmol, 5%), and 1,1'-bis(di-*i*-propylphosphino)ferrocene (29.0 mg, 0.06936 mmol, 6%). The flask was evacuated and backfilled with N<sub>2</sub> three times. Under a stream of N<sub>2</sub>, DMSO (6.60 mL, 0.1735M) and diisopropyl ethyl amine (2.00 mL, 191.7 mmol) were added. The reaction was heated to 120 °C for 48 hours. The reaction was cooled and diluted with EtOAc (132 mL). The organic phase was washed with water (5 x 66 mL). The organic phase was dried over magnesium sulphate and concentrated under vacuum. The crude product was purified via flash chromatography eluting with 10% EtOAc:Hexanes, to afford a white solid (346.6 mg, 62.5%). TLC (20% EtOAc:Hexanes) R<sub>f</sub> = 0.55 <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.05 – 6.83 (m, 12H, Ar), 3.75 (s, 3H, CH<sub>3</sub>), 1.90 – 0.70 (m, 20H, CH<sub>2</sub>). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  154.40, 143.59, 143.27, 135.06, 134.30, 133.57, 133.36, 133.29, 129.62, 129.19, 128.55, 127.89, 127.83, 126.99, 126.73, 126.27, 126.19, 125.99, 125.81, 123.20, 122.51, 112.30, 55.53, 35.47, 35.32, 34.57, 34.43, 30.70, 30.61, 30.45, 30.03, 29.92, 27.65, 27.40, 27.32, 27.20, 26.59, 26.41. <sup>31</sup>P NMR (162 MHz, CDCl<sub>3</sub>)  $\delta$  -8.82. HPLC (Flow Rate = 0.5 mL/min, 0.1% IPA:Hexanes) t<sub>R</sub> major = 19.217 min (area = 6083.8)

## 5 Appendix

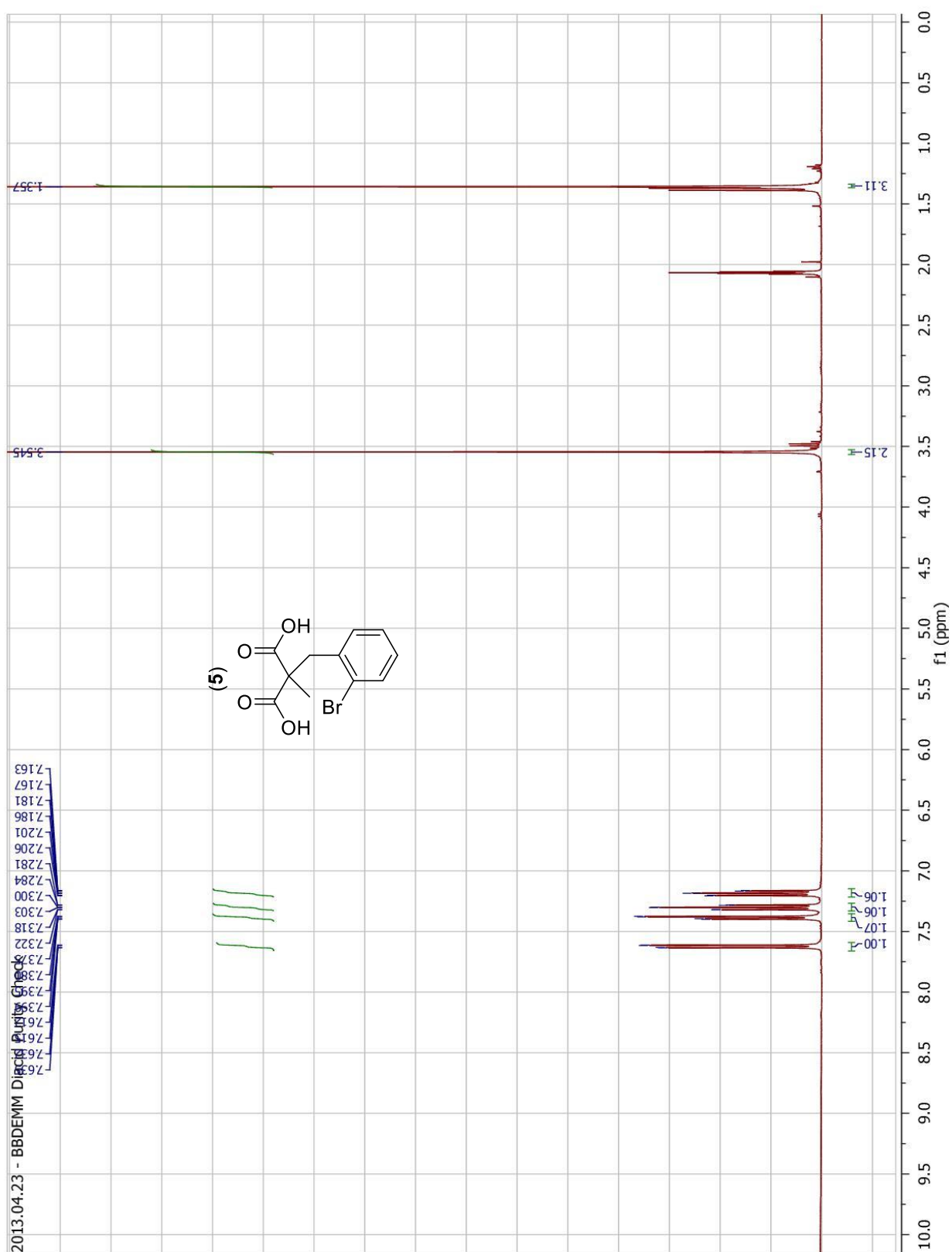


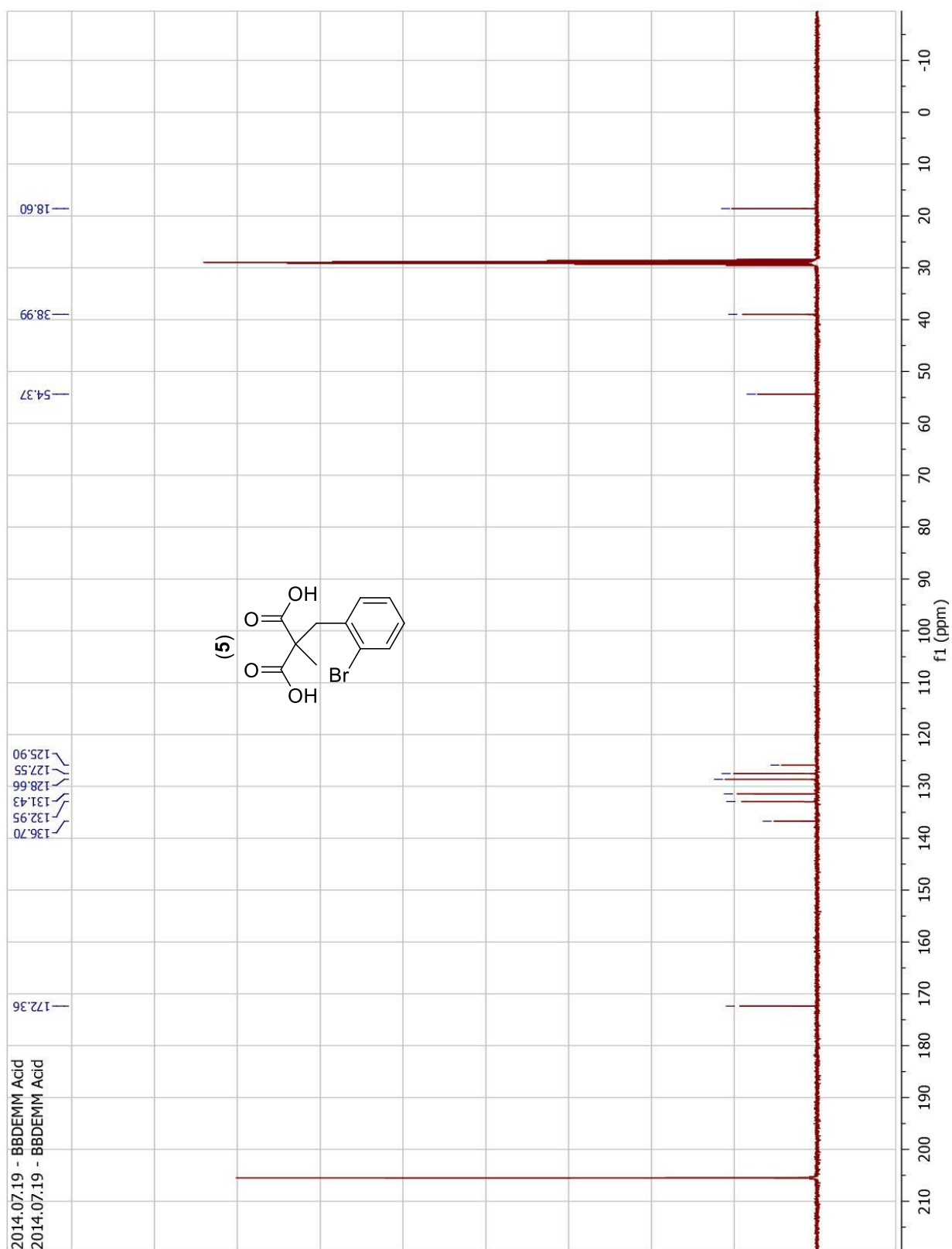


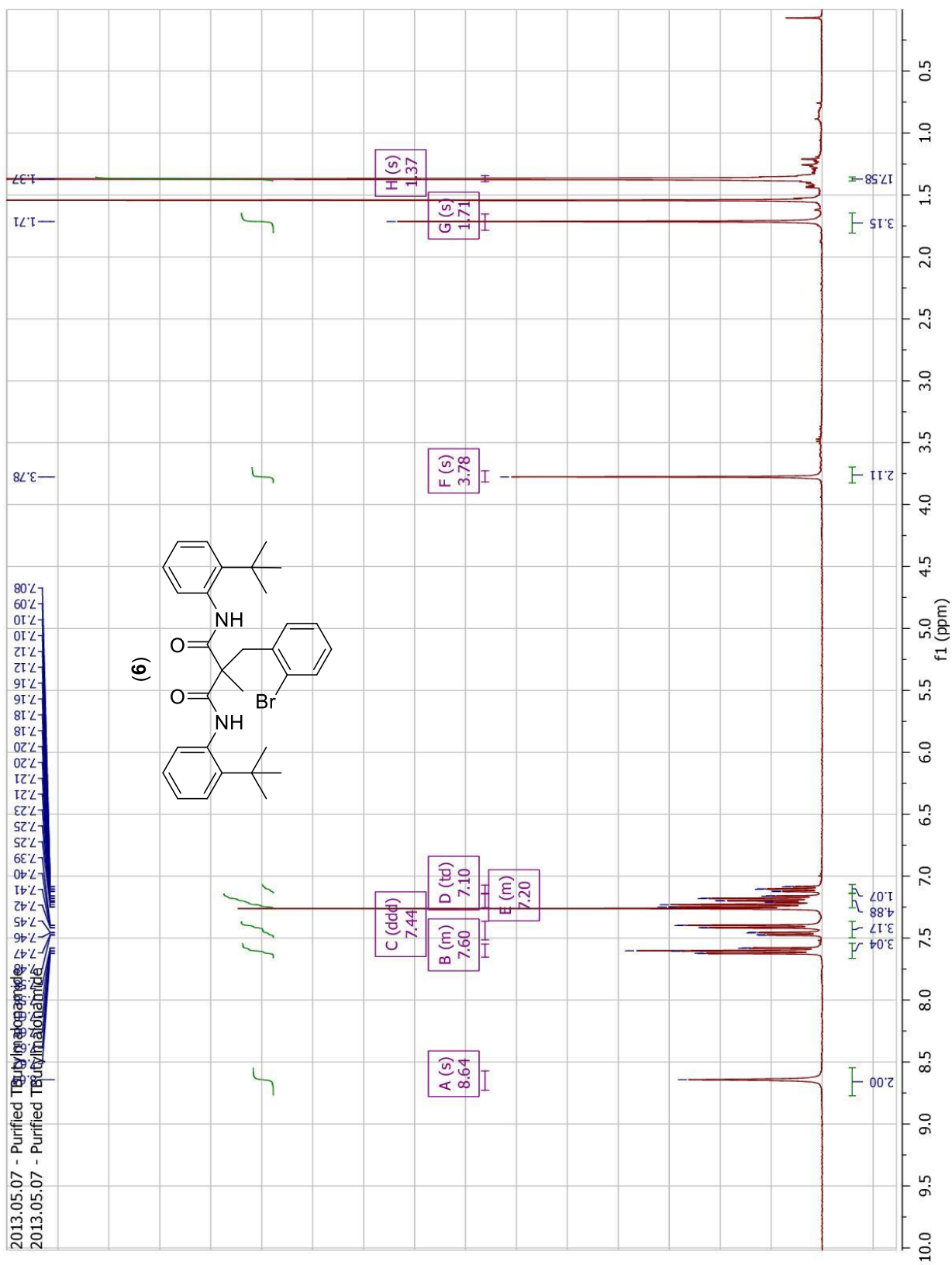


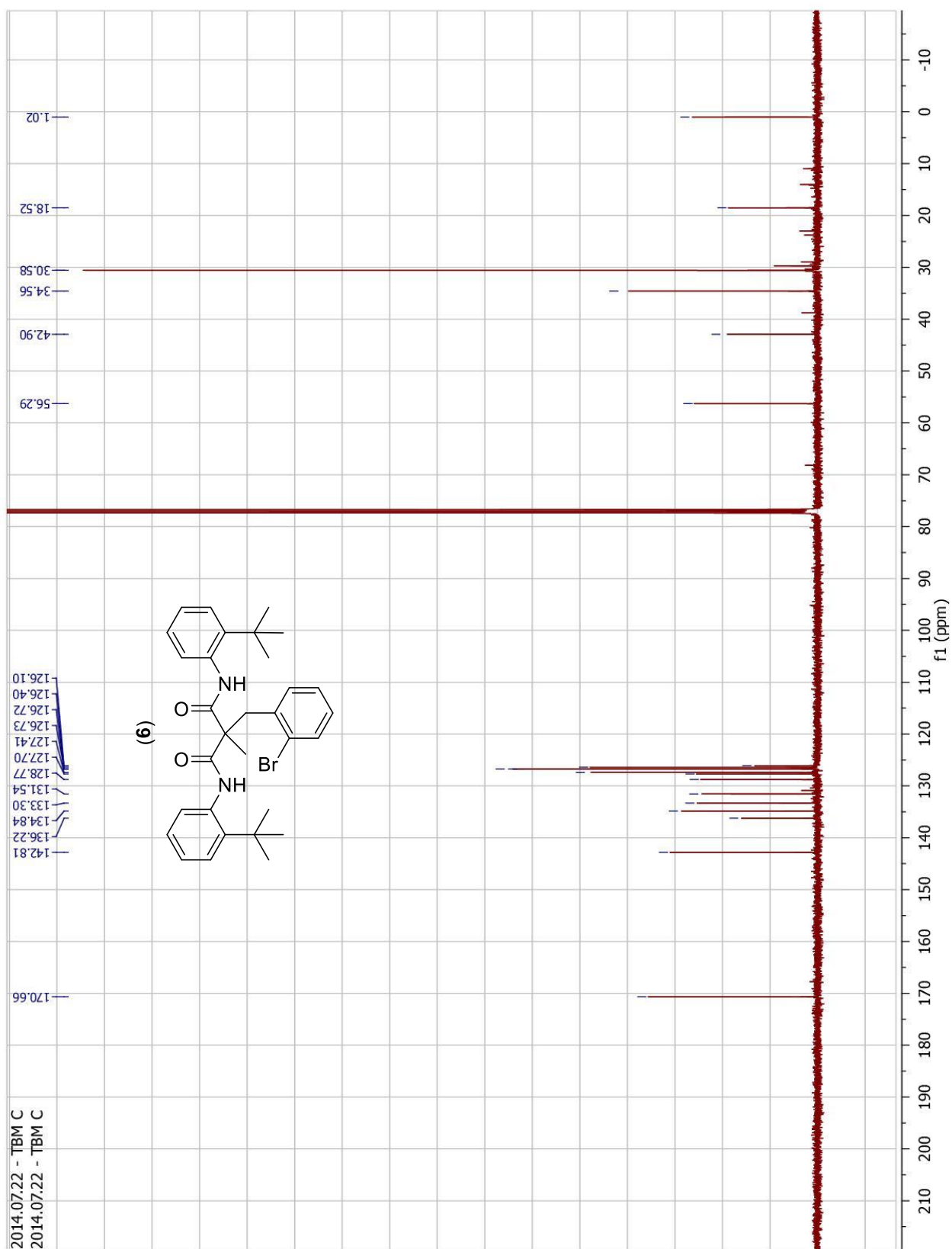


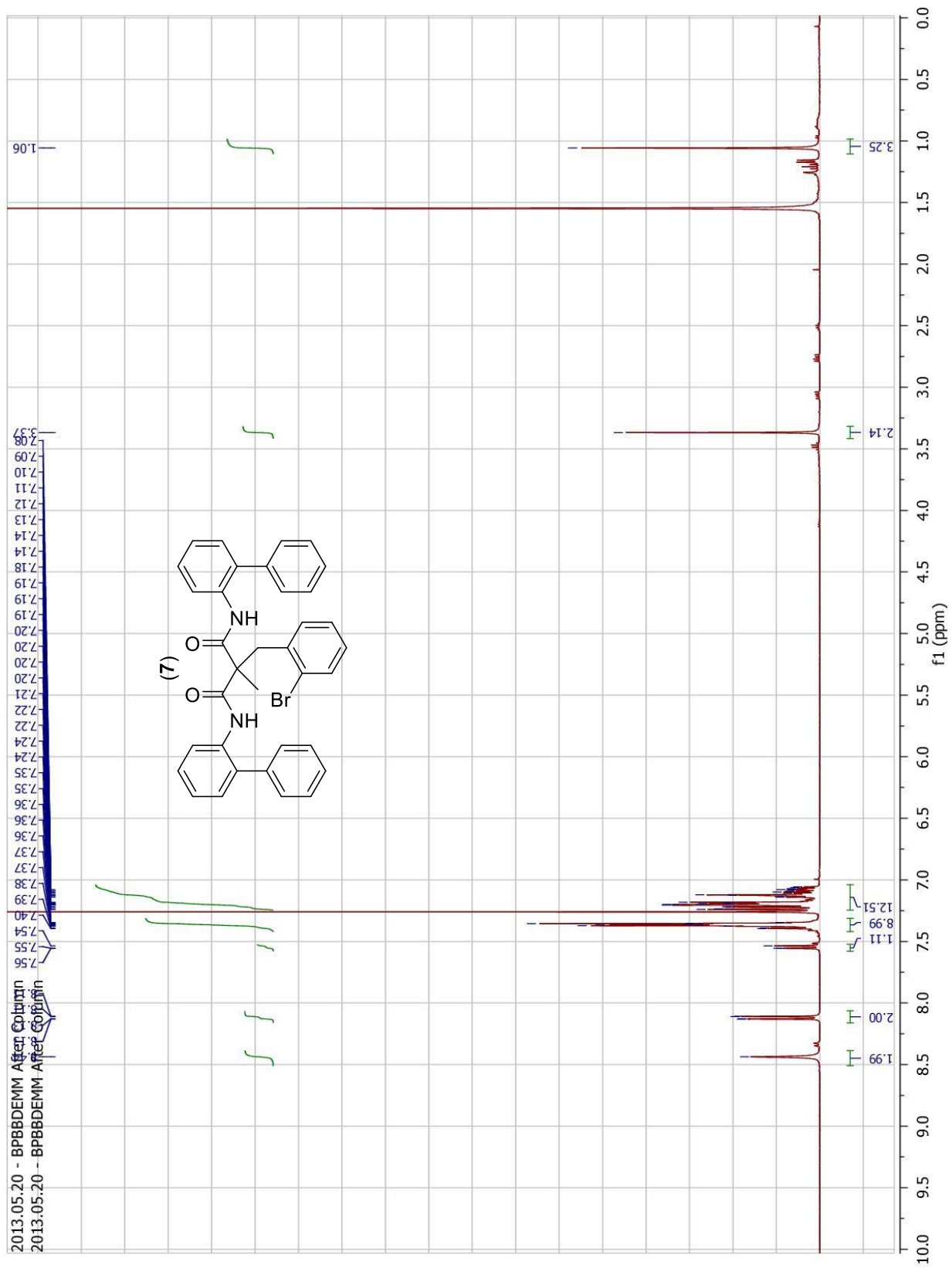


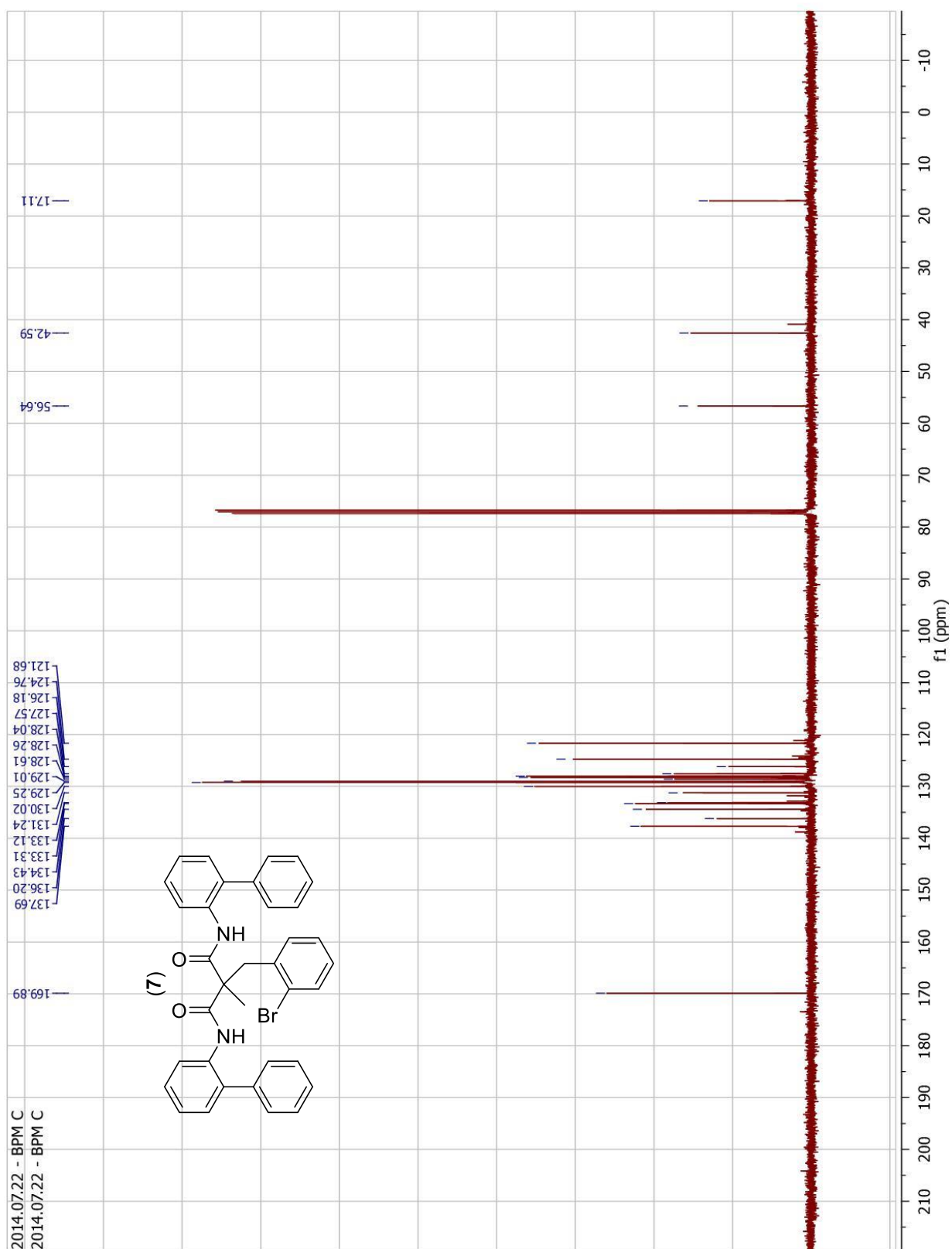


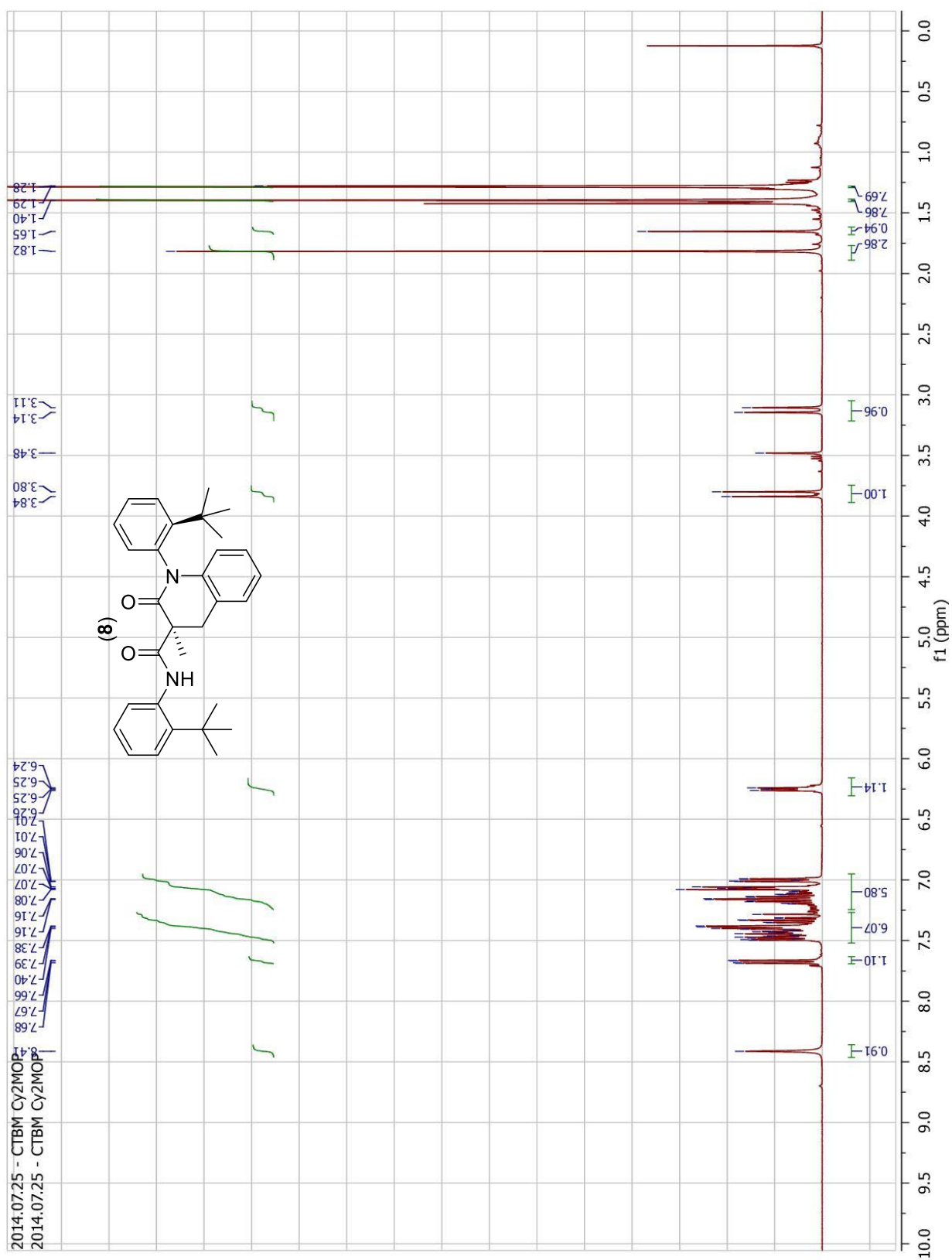


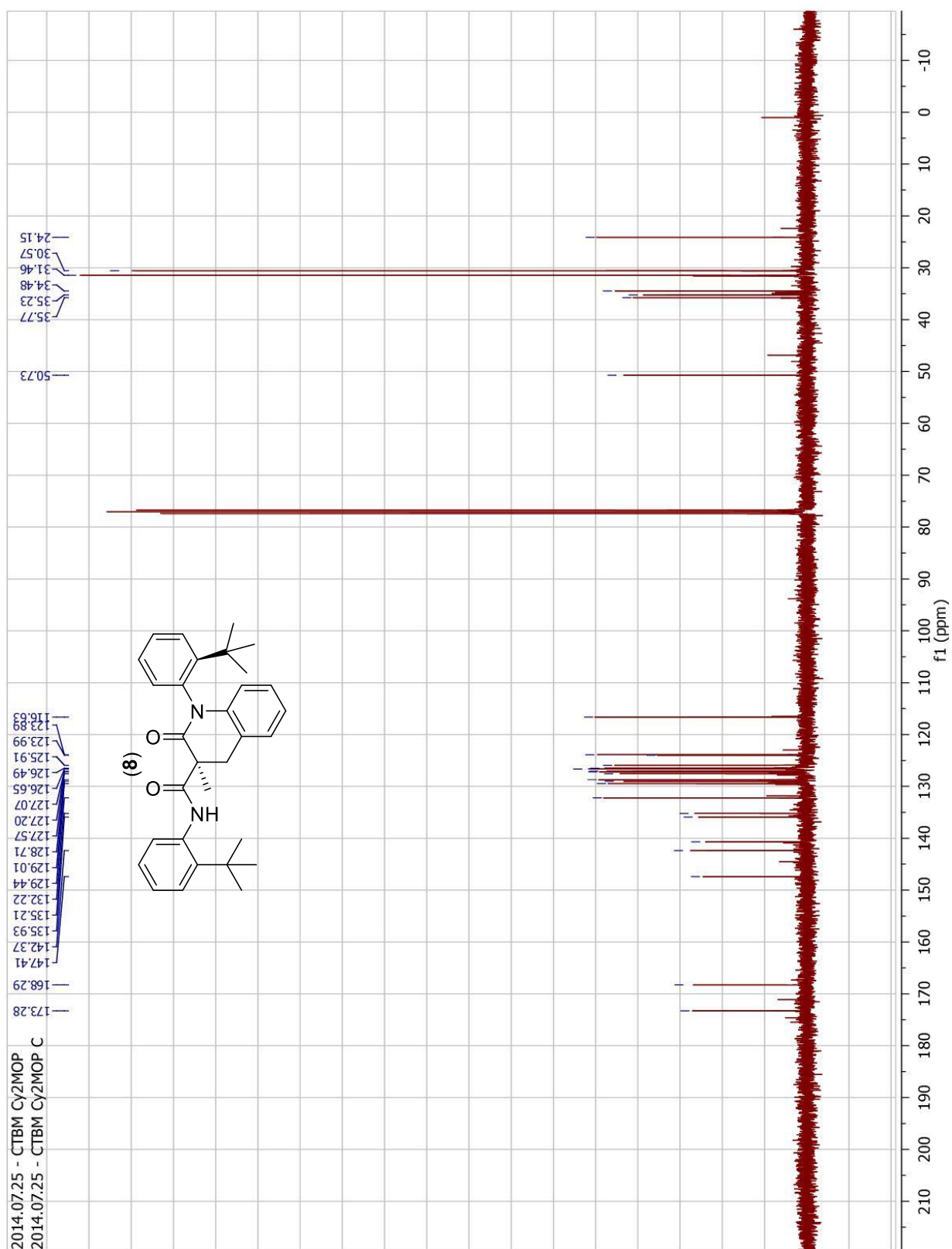




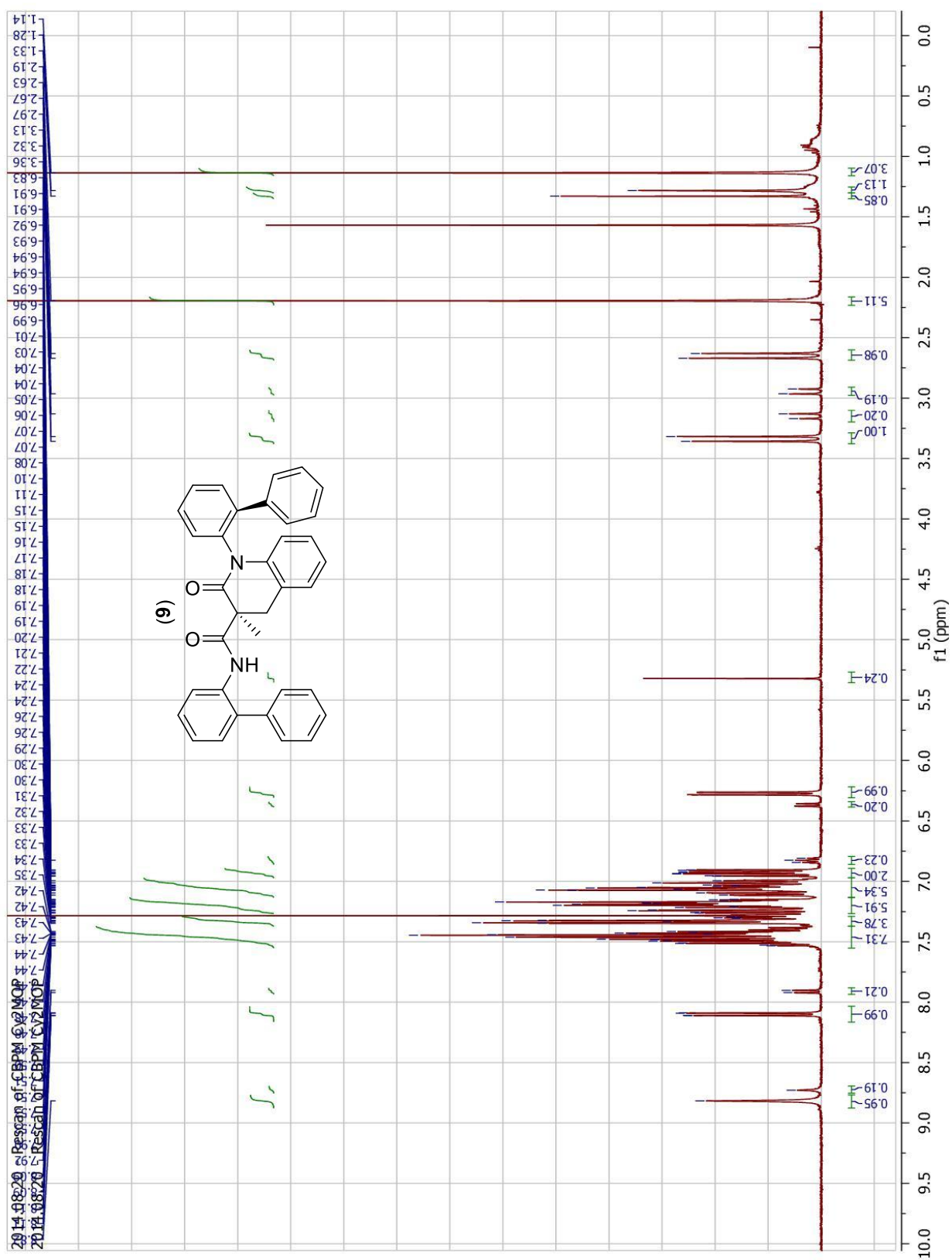


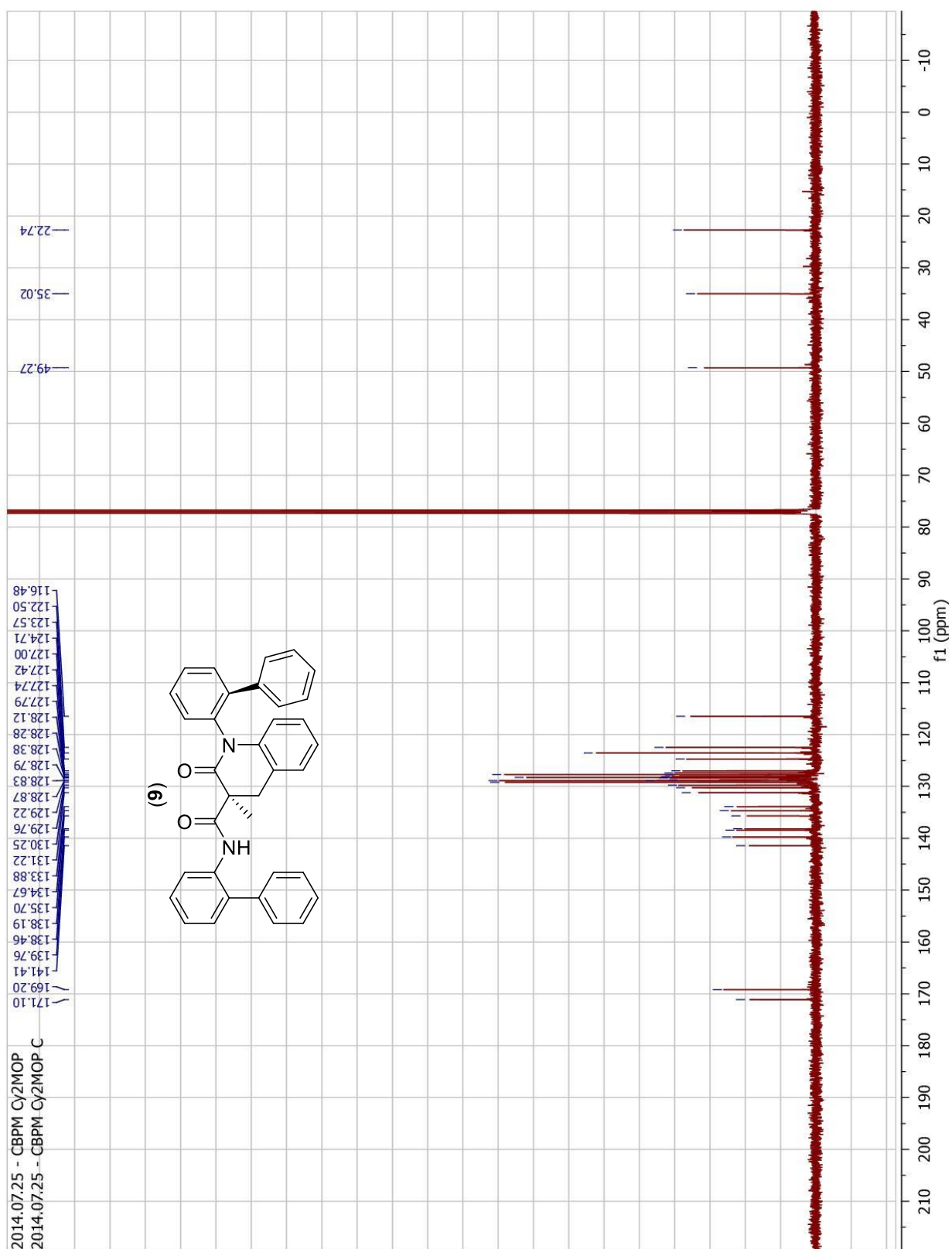


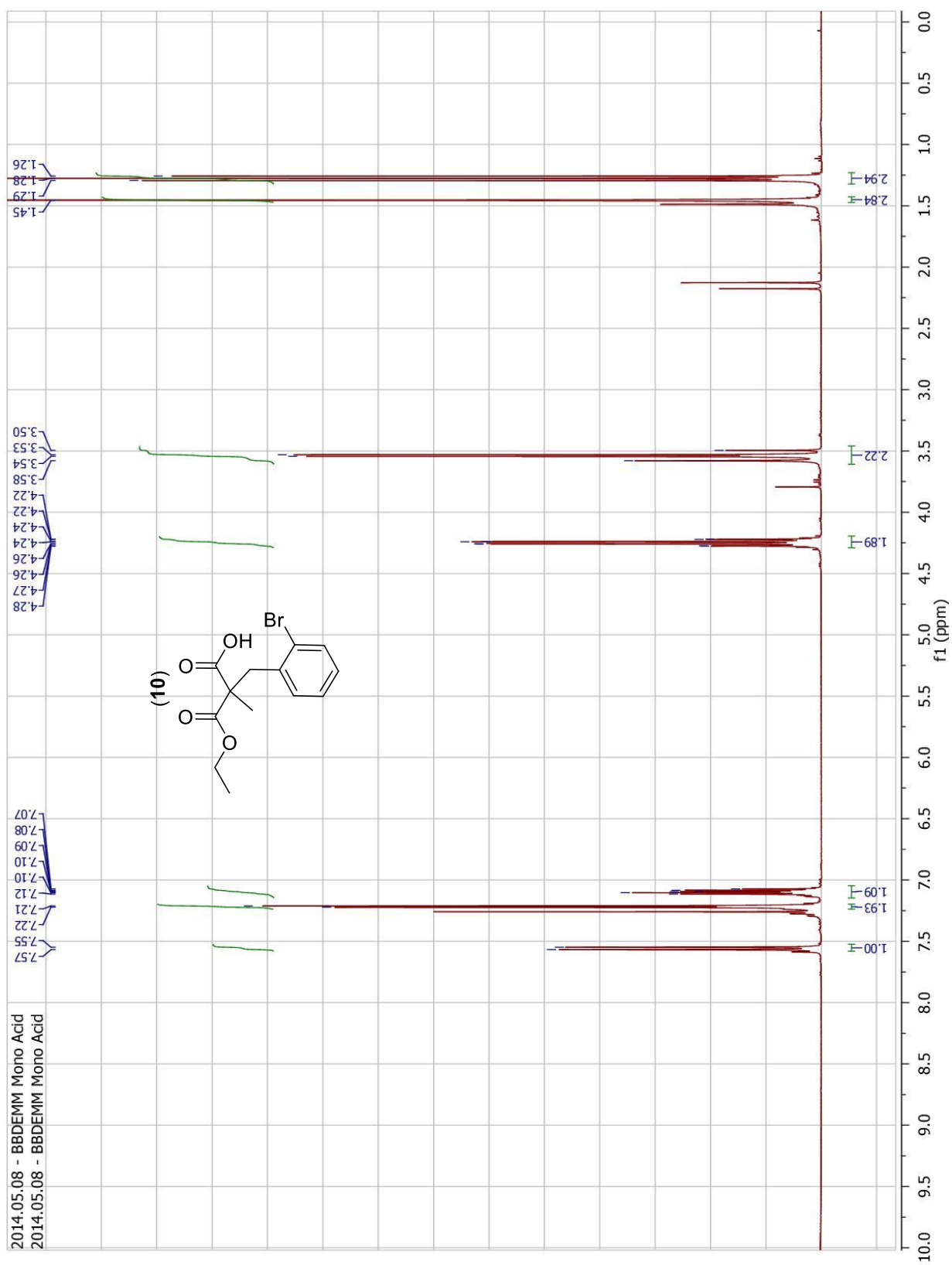


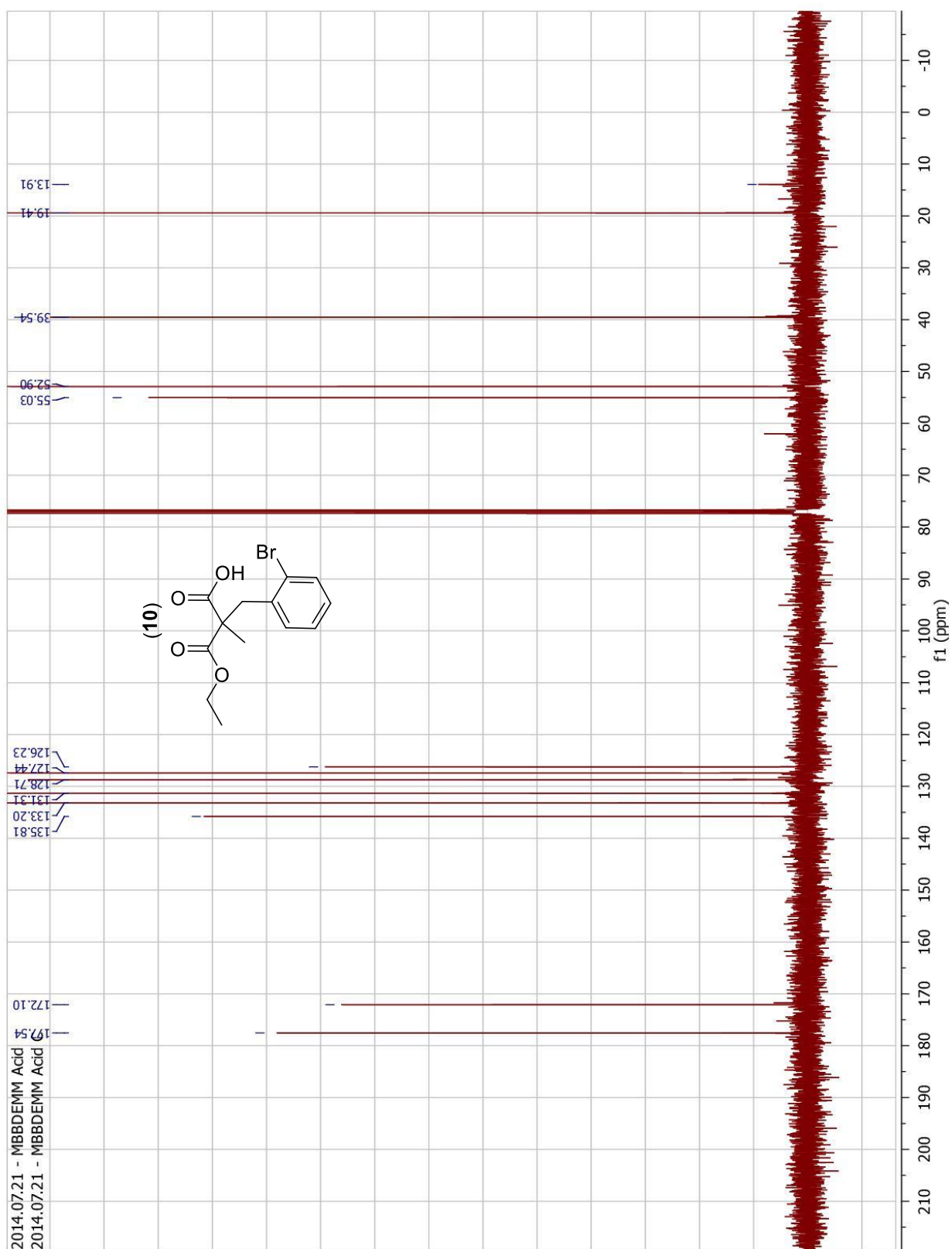


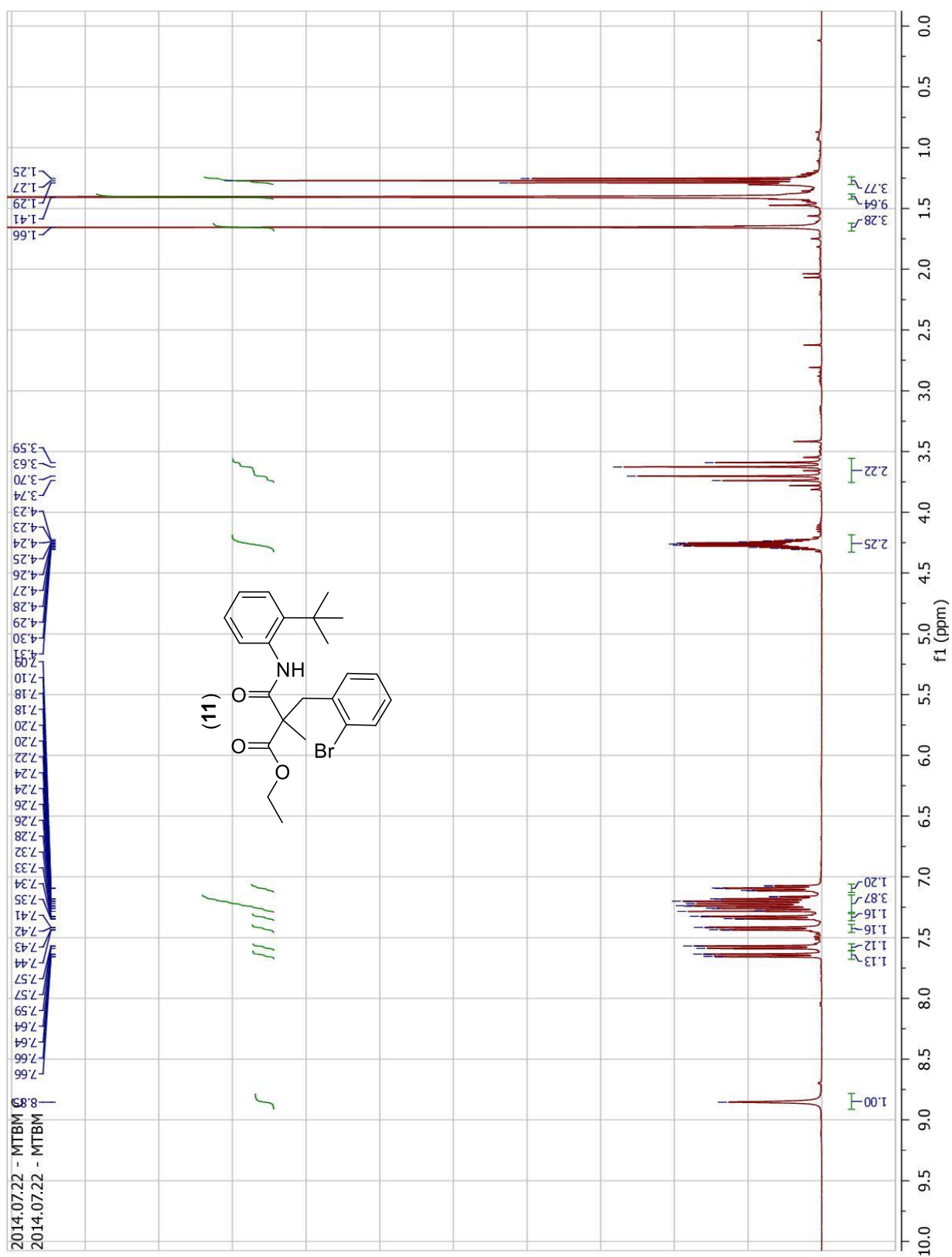


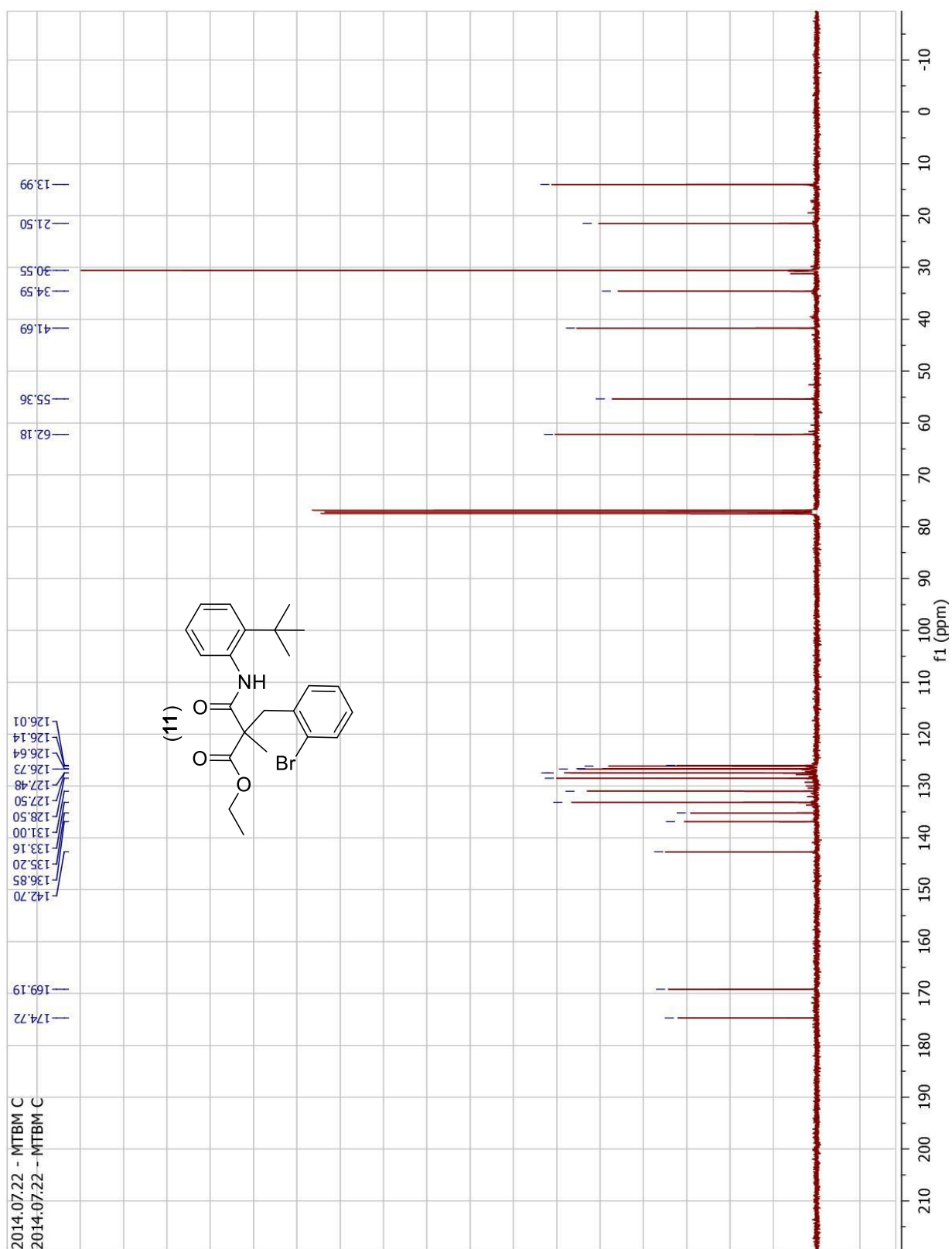


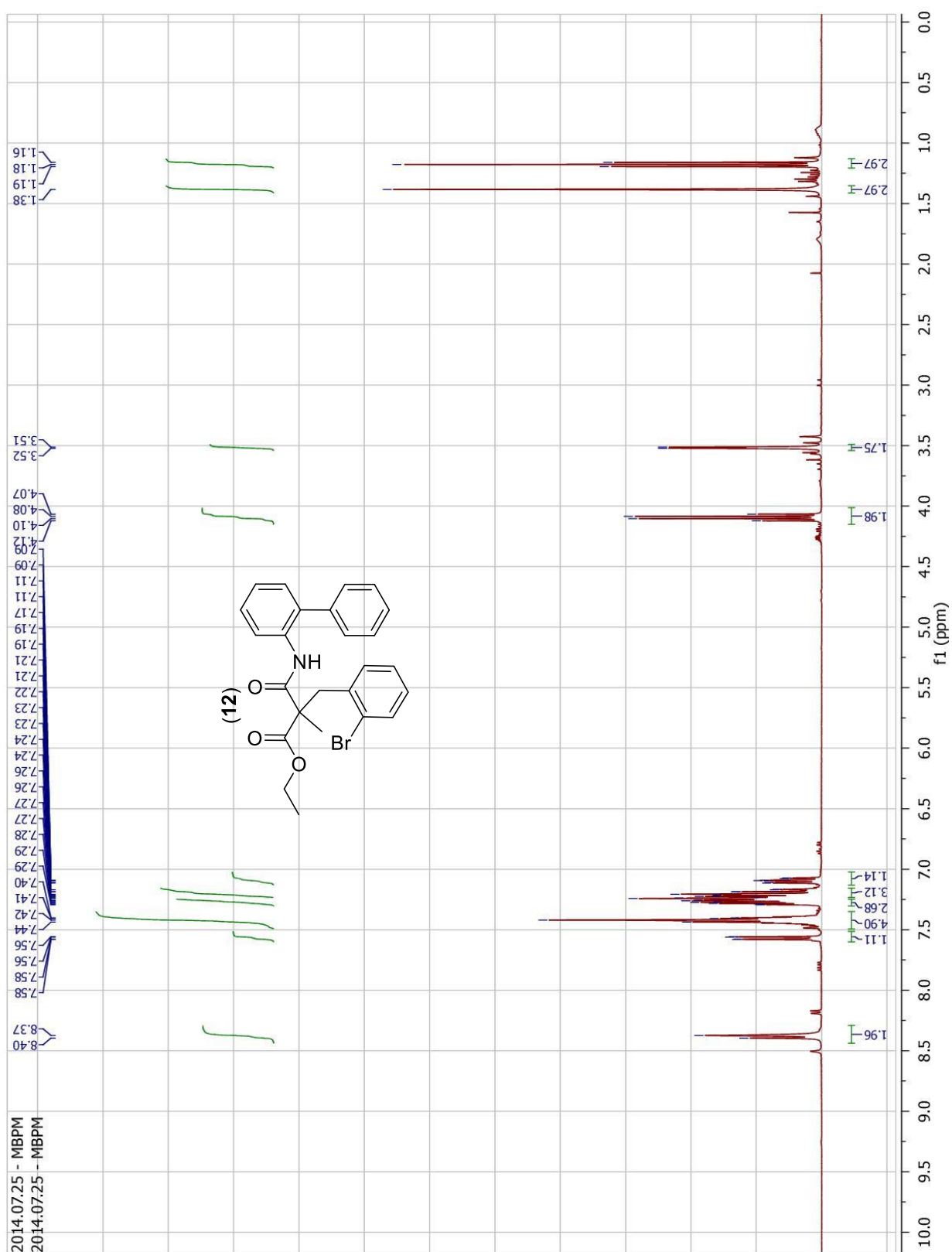


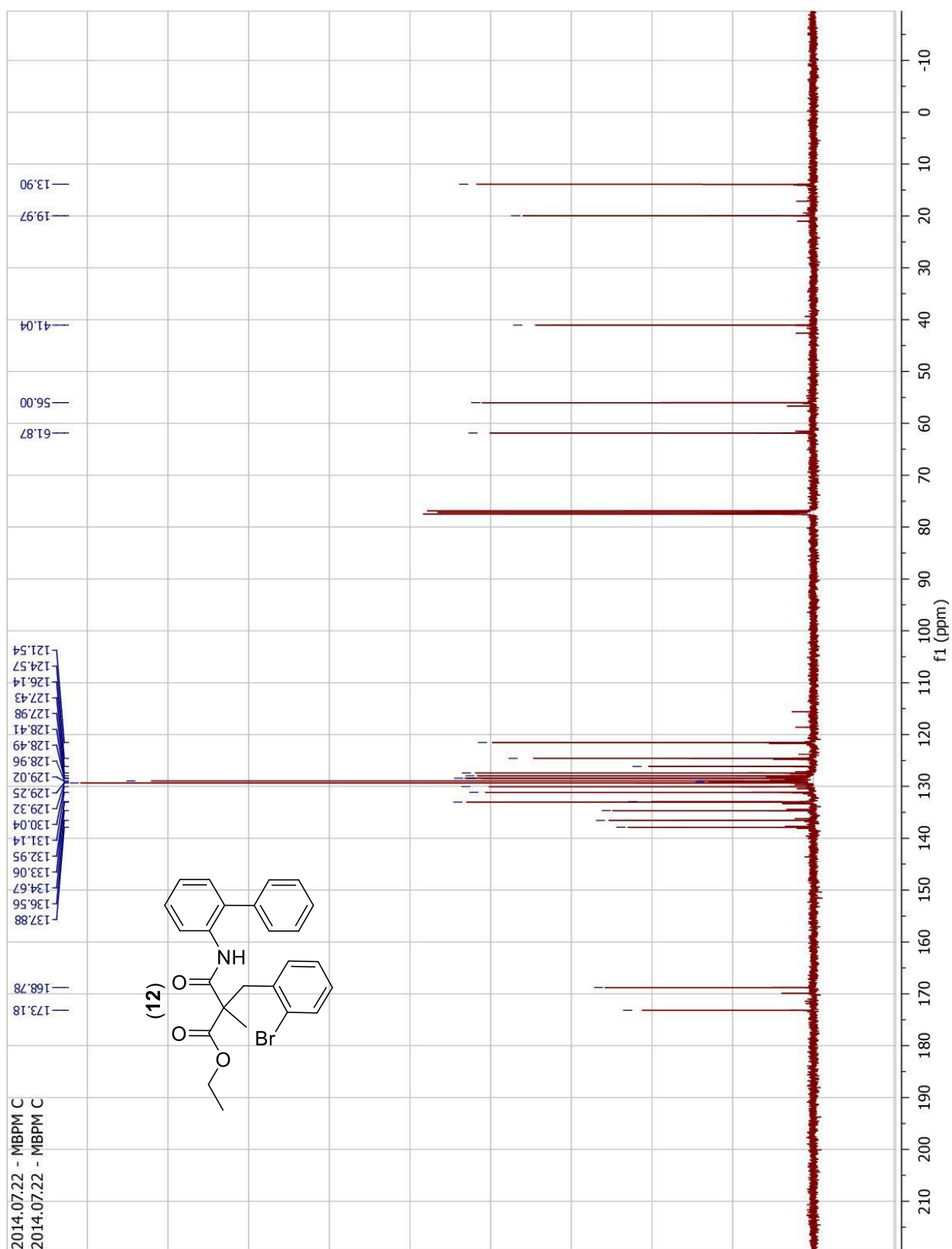




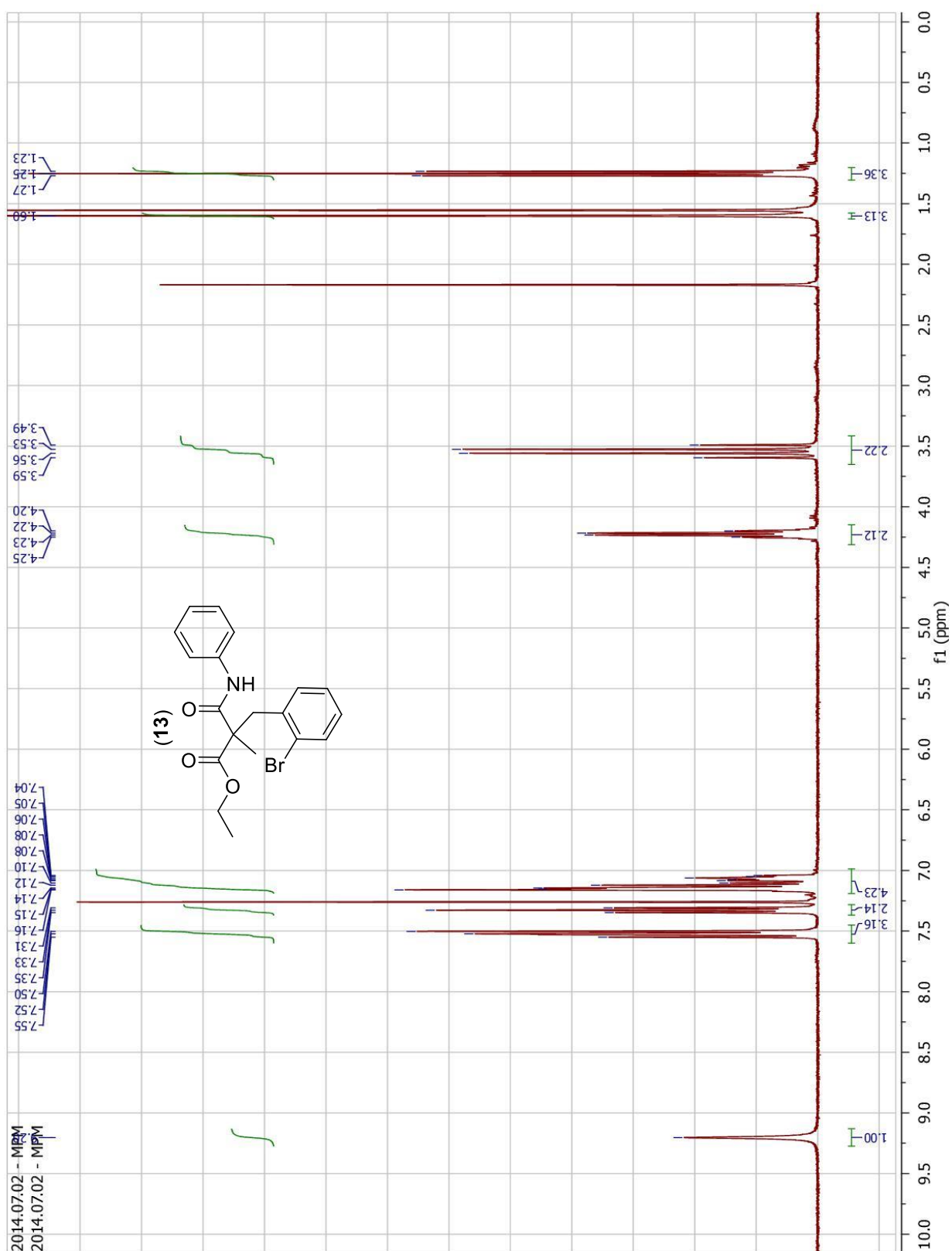


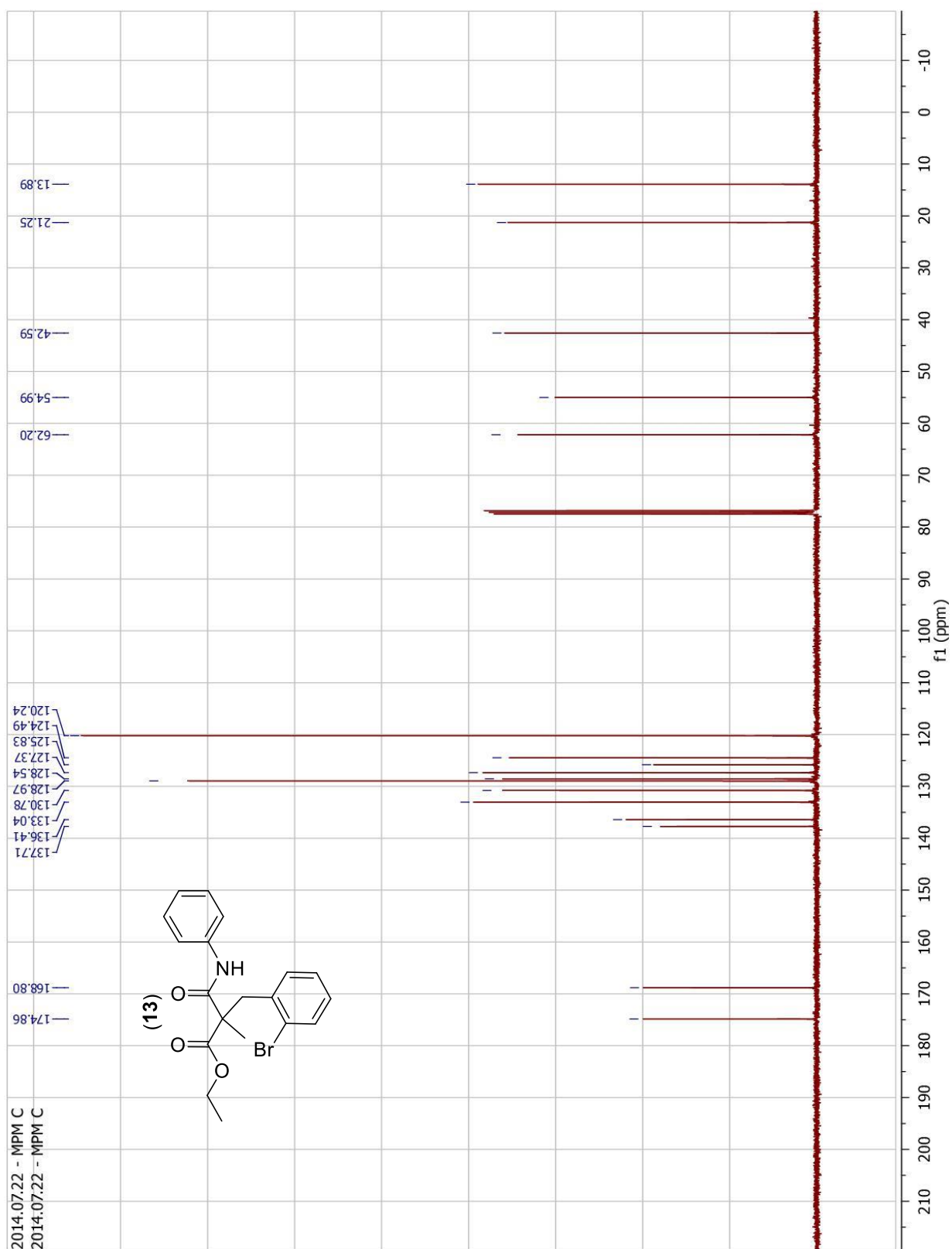


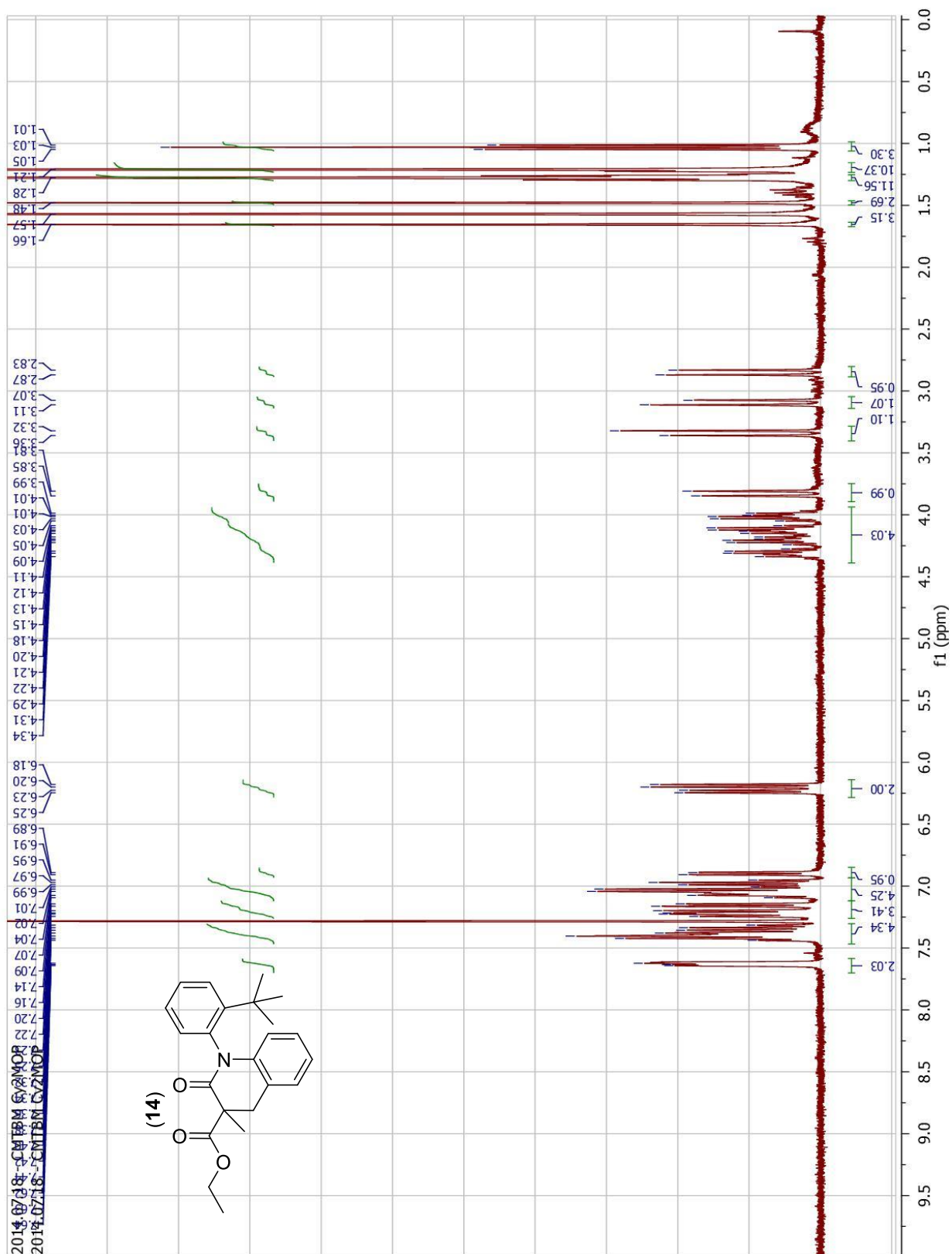


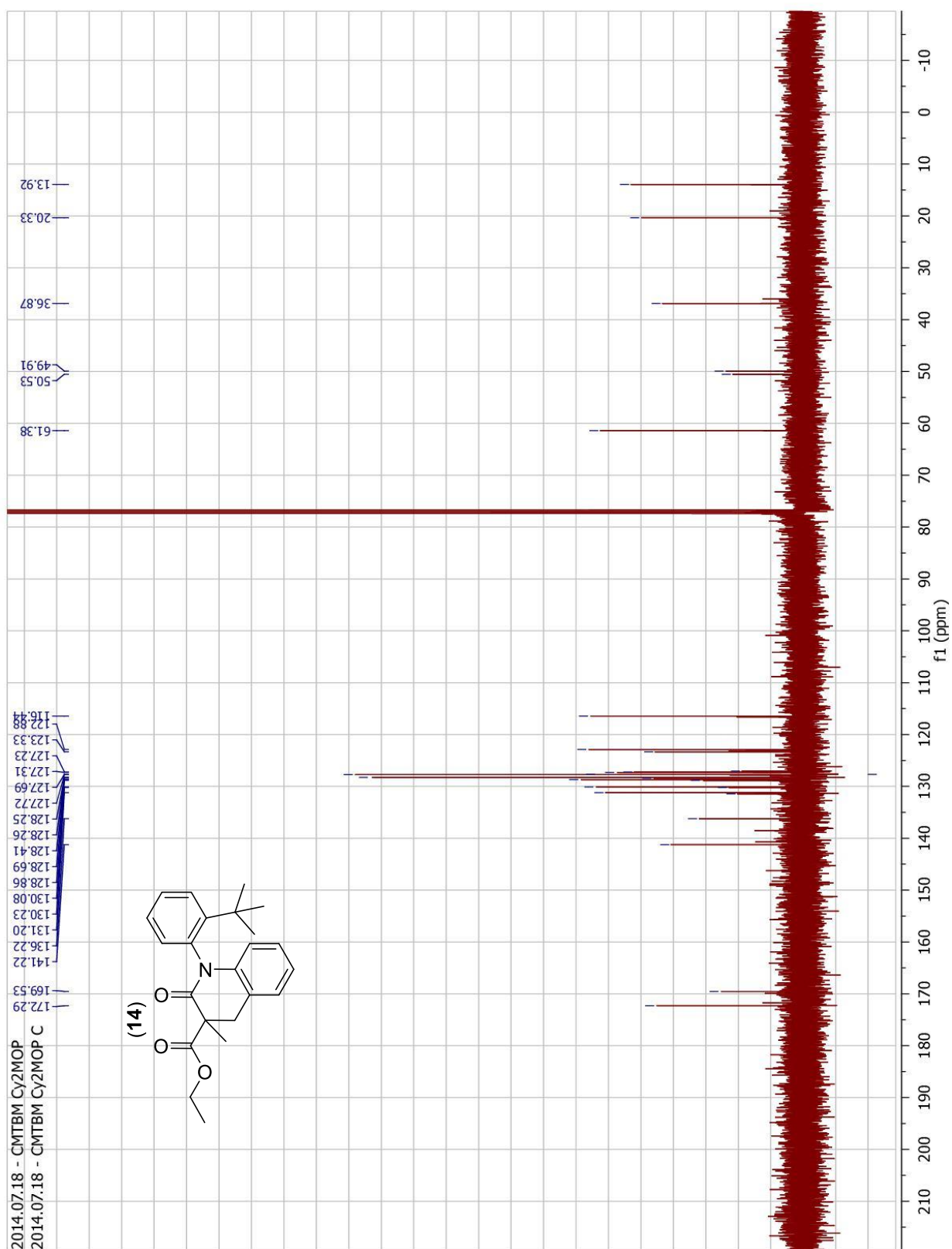


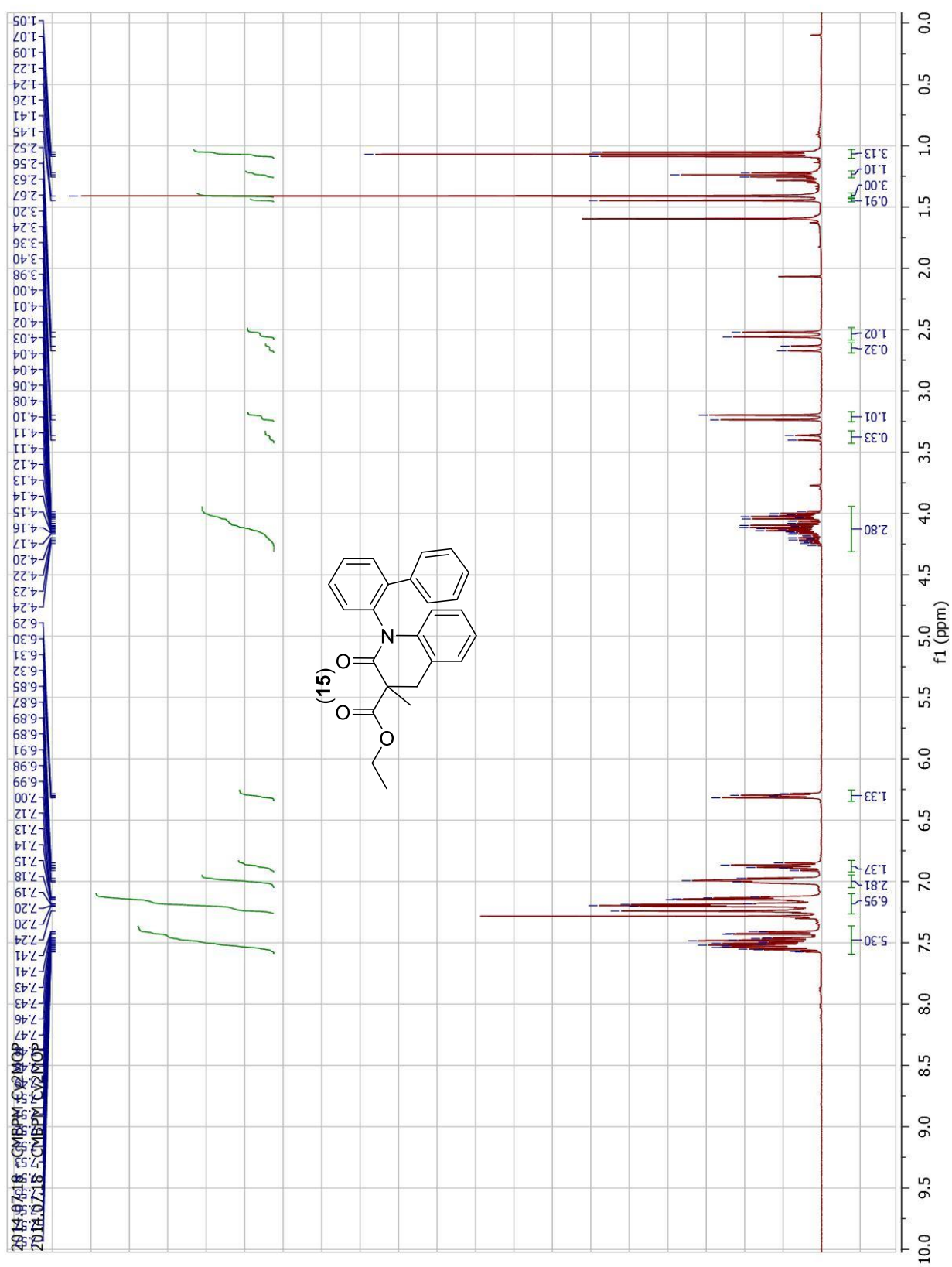


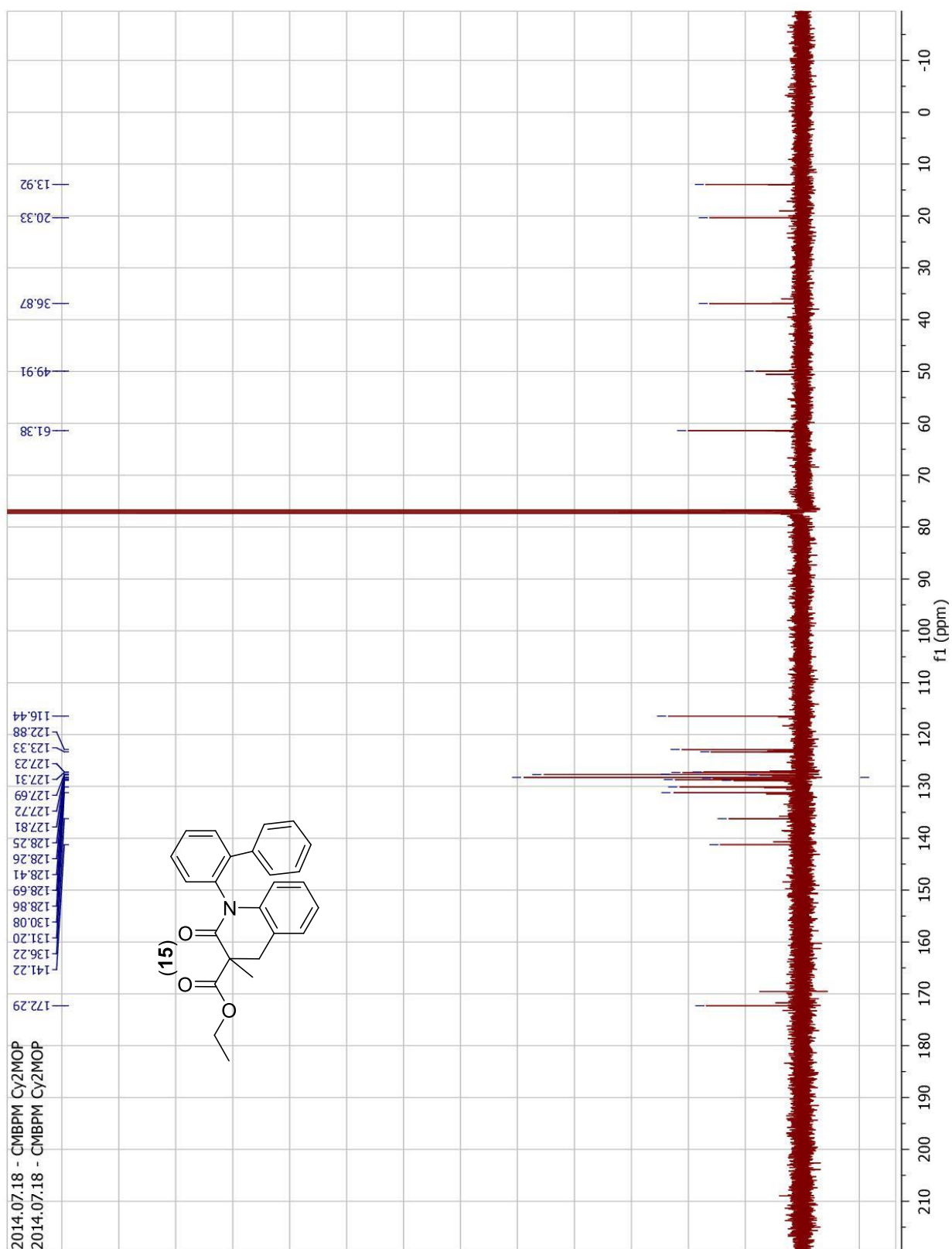


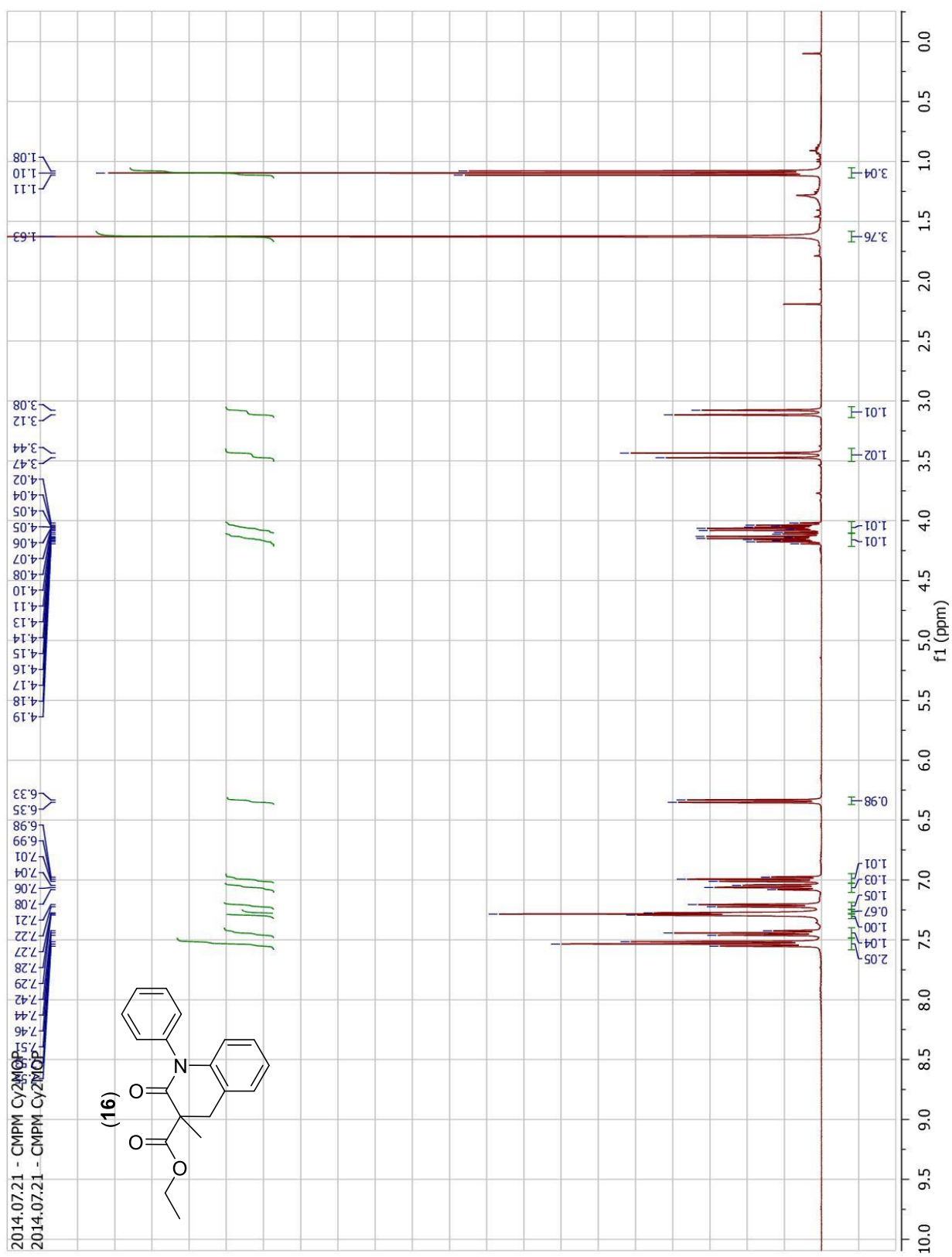




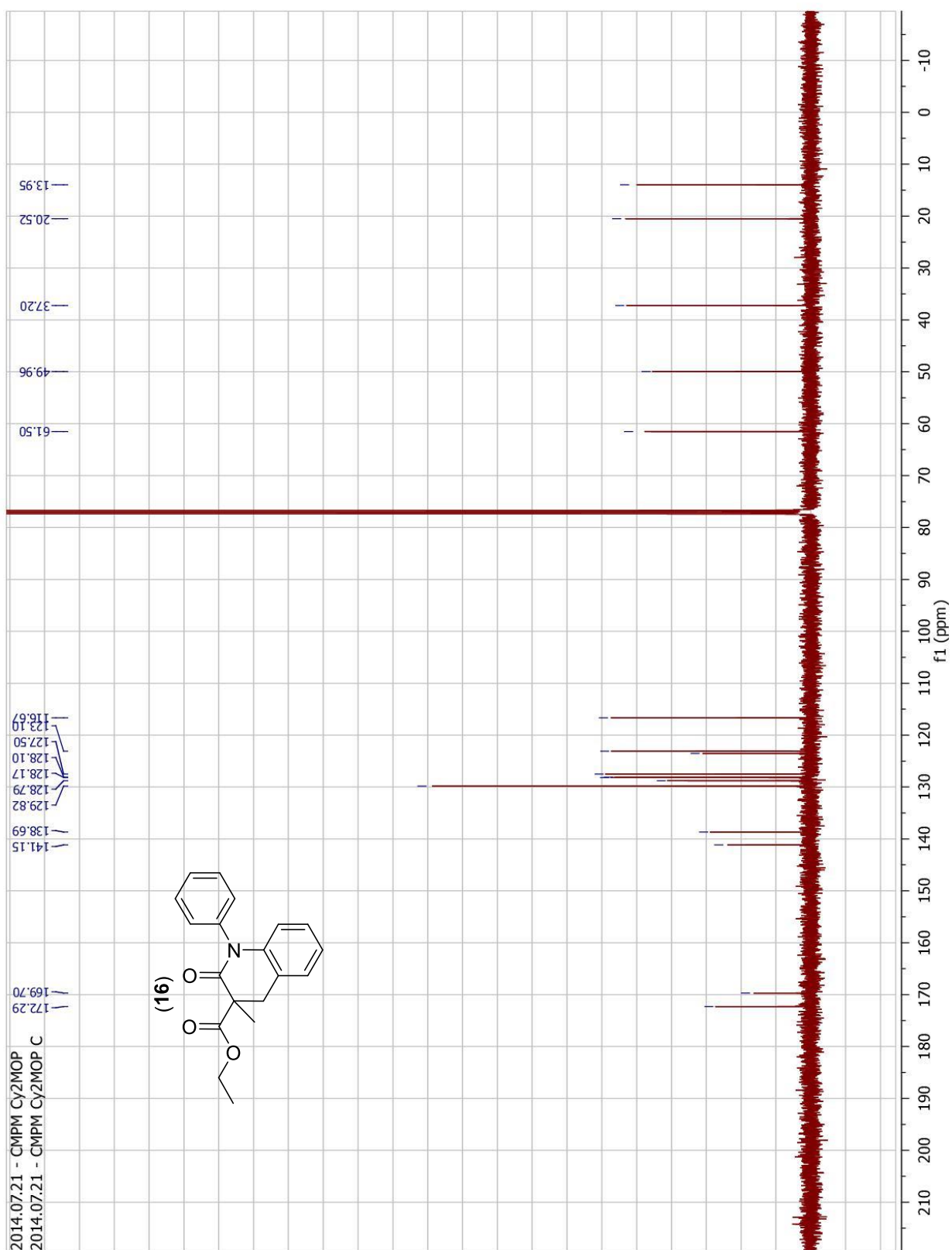




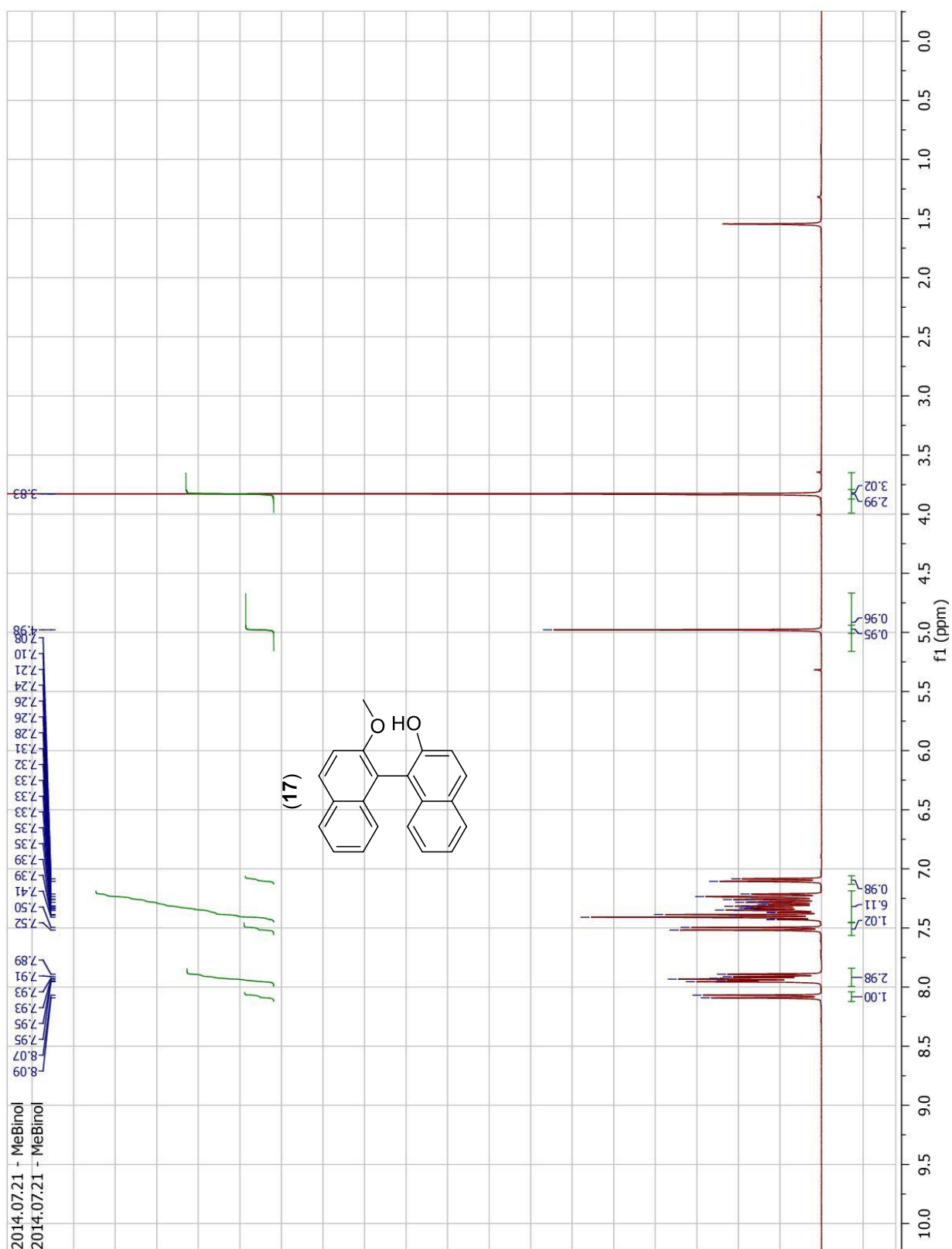


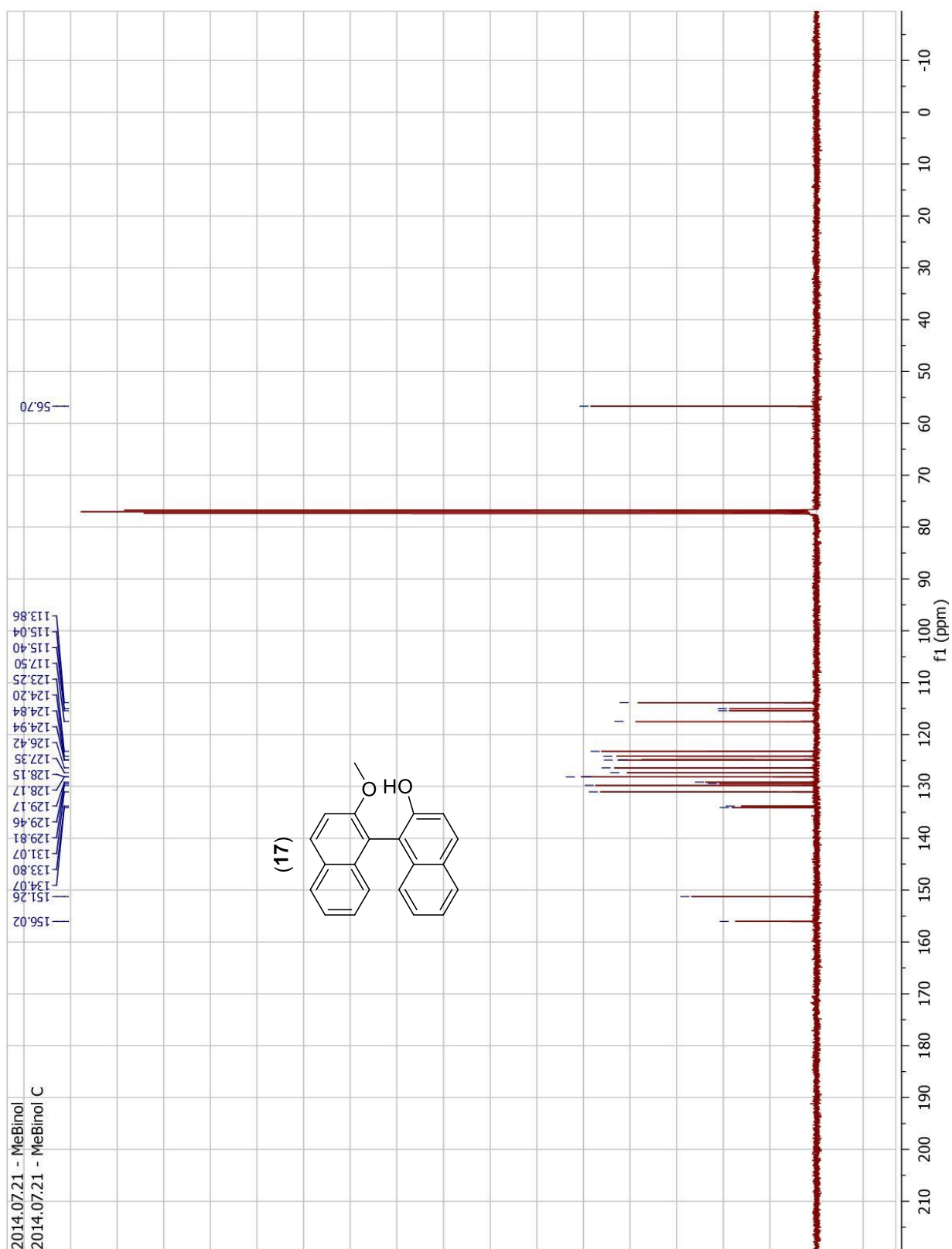


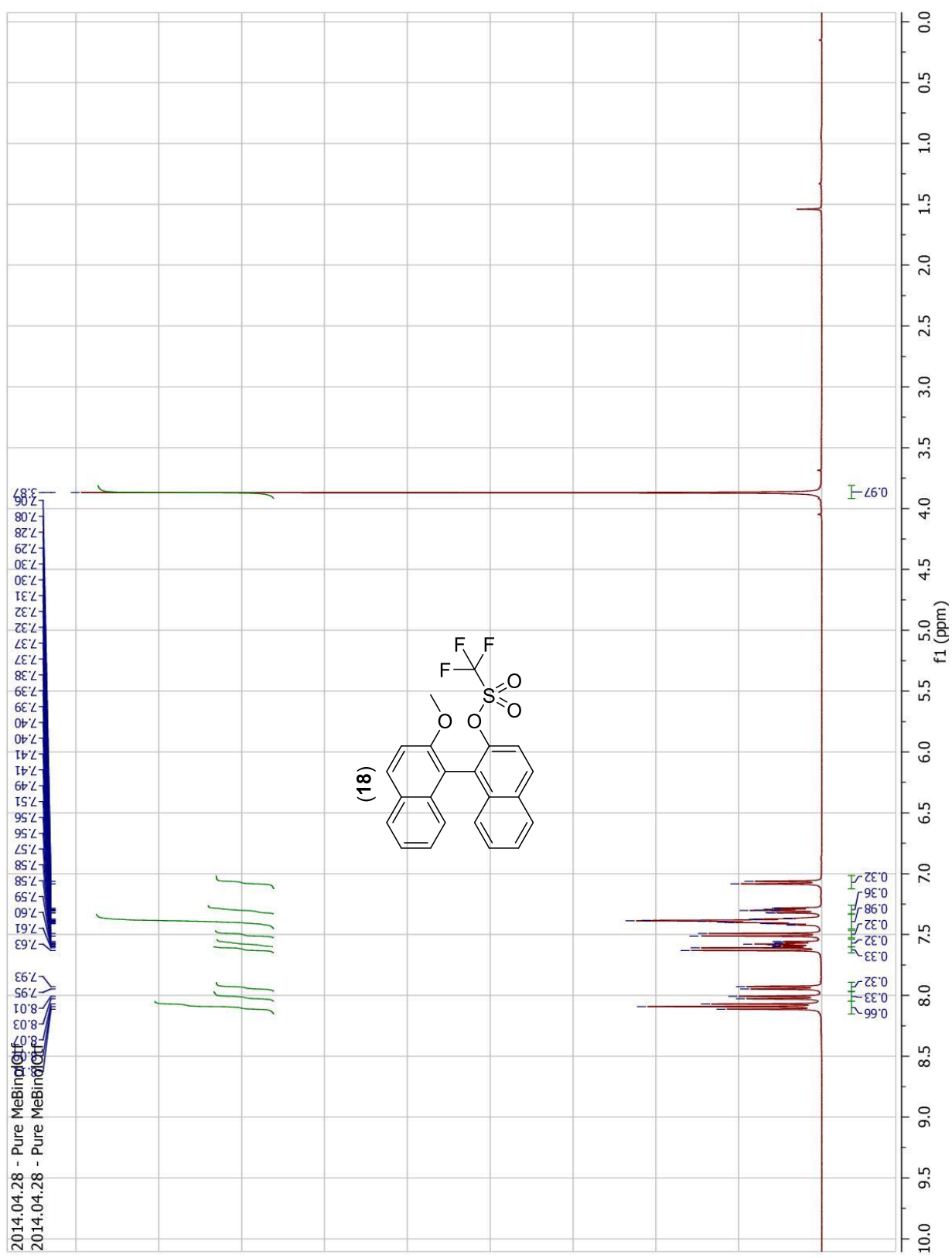


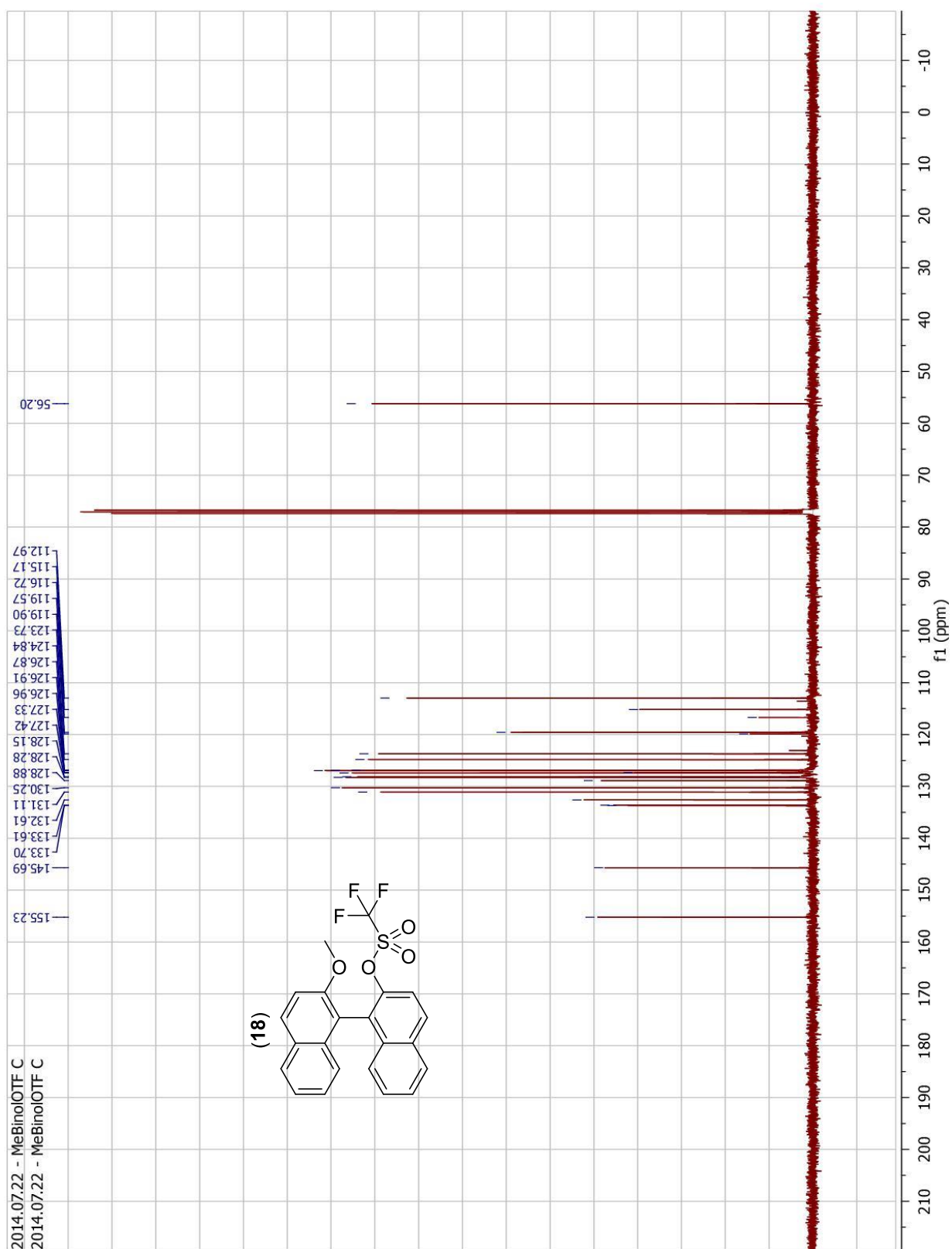


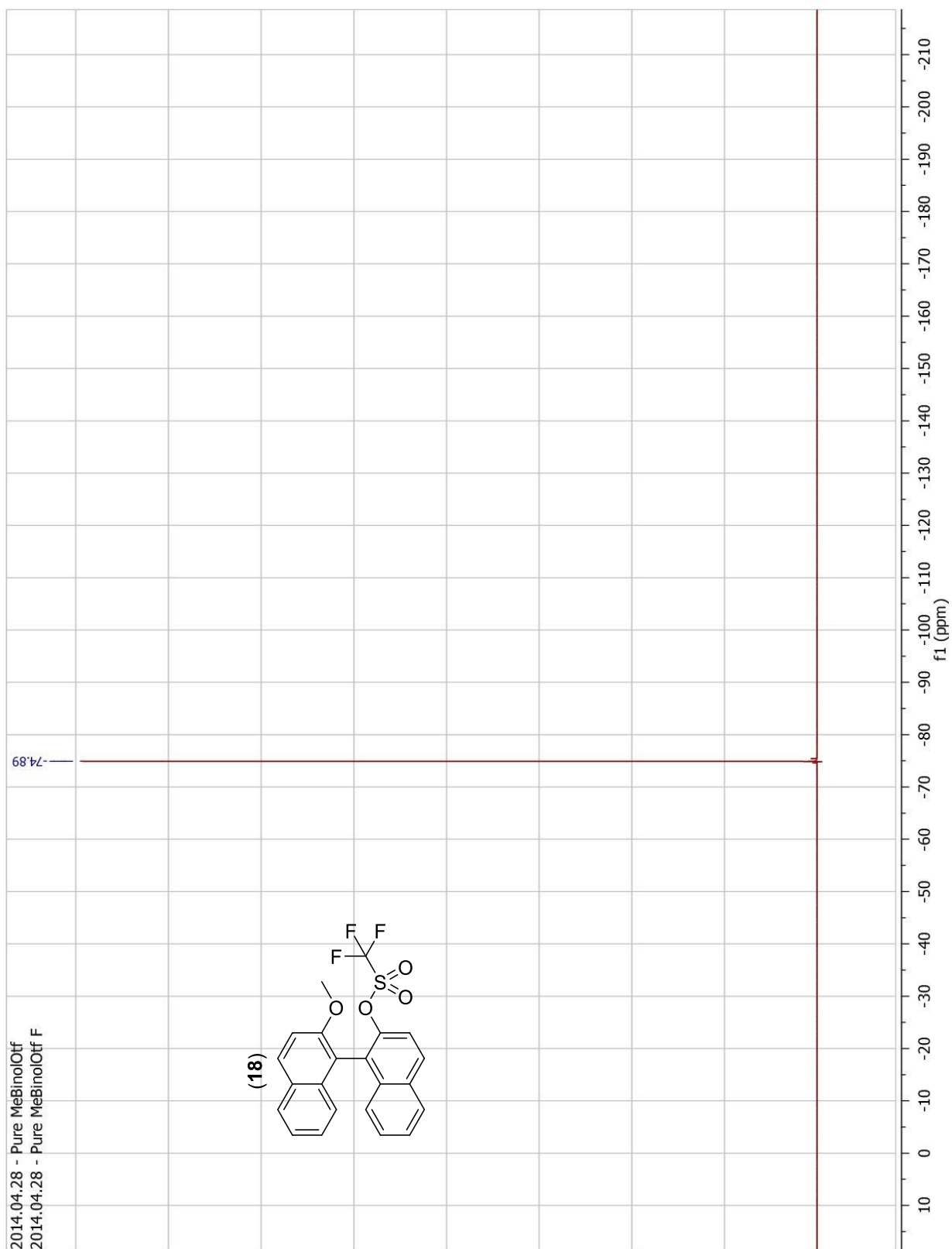


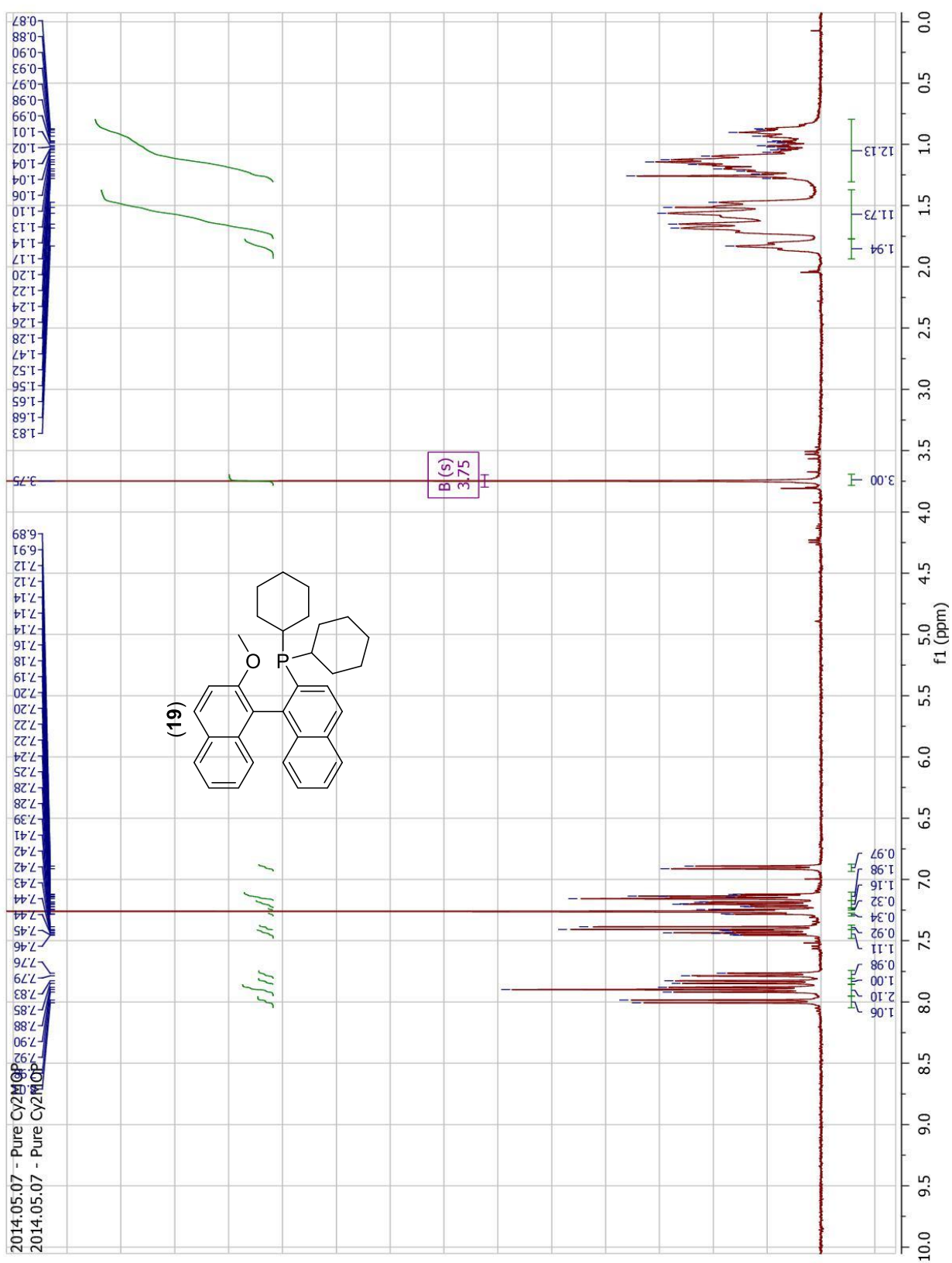


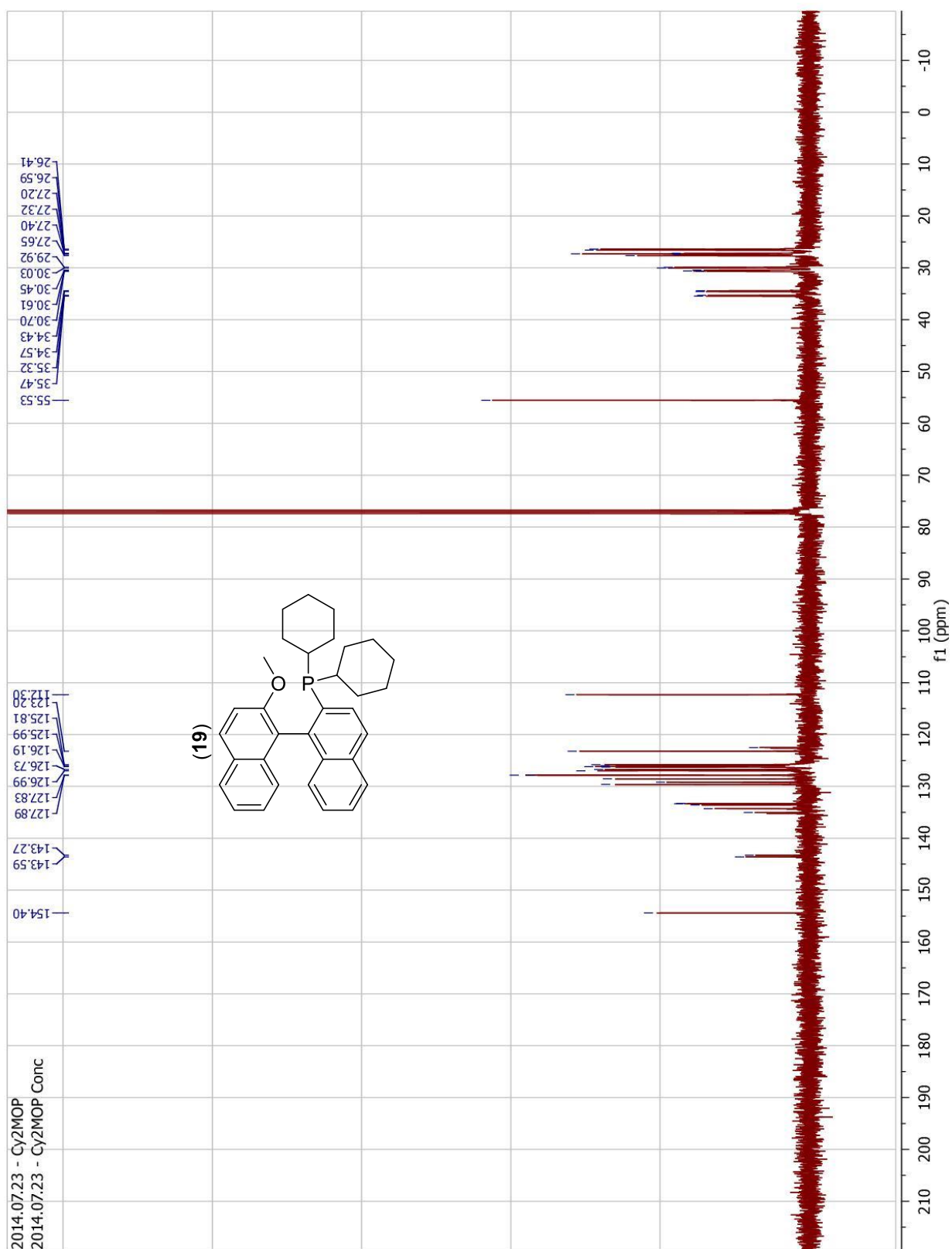


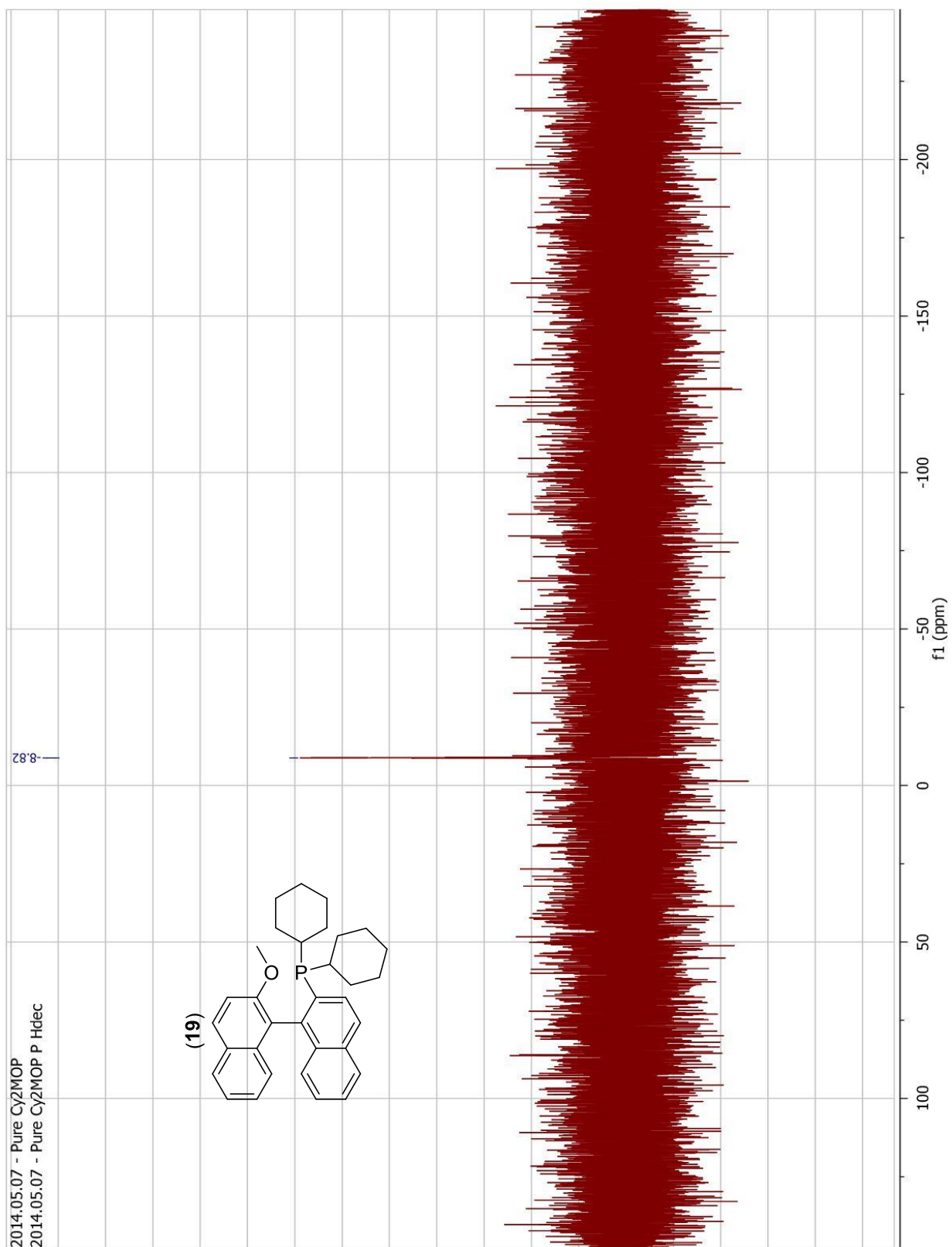












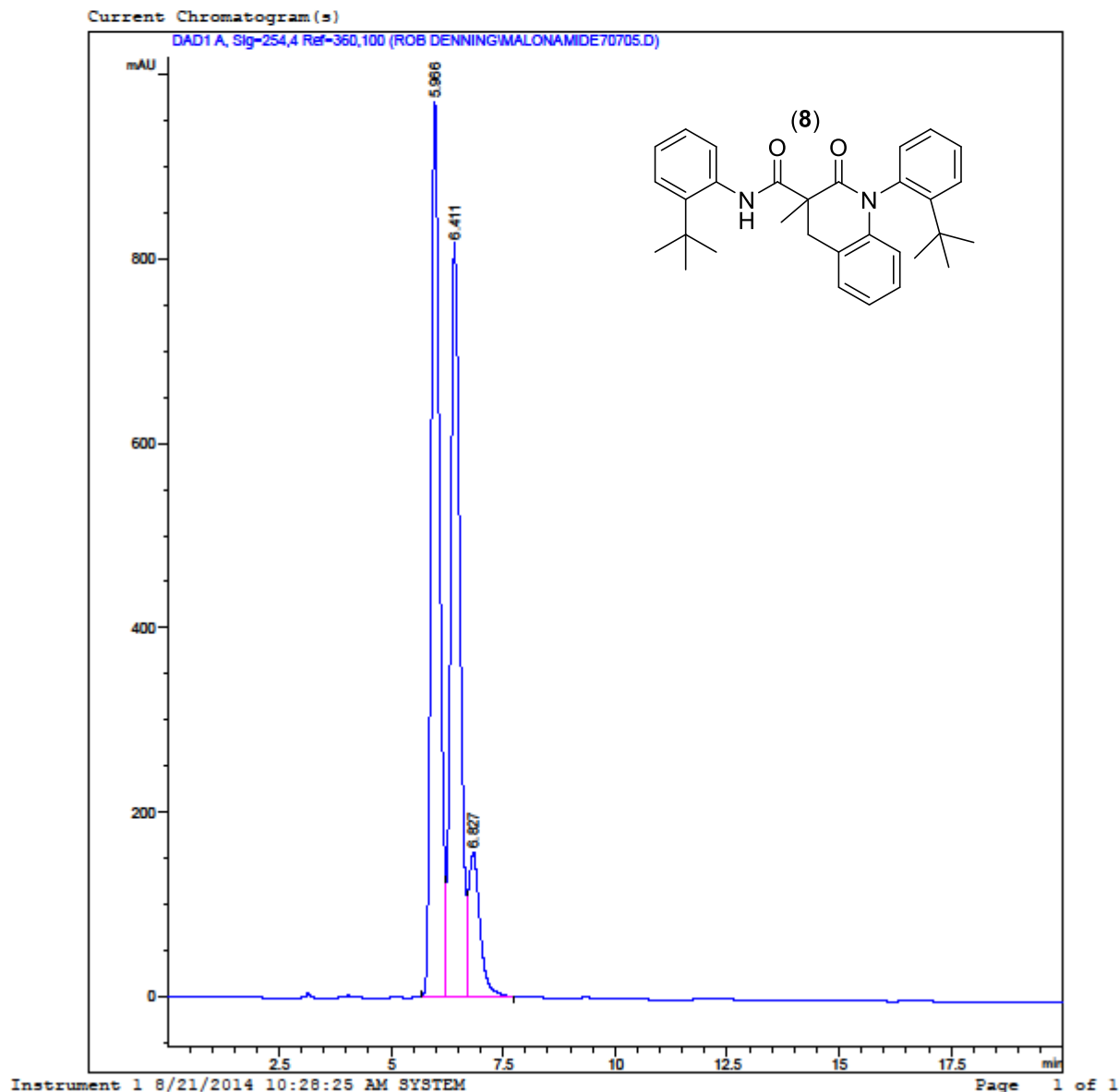


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Sample Name : CTBM SPHOS

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		Inj Volume	: 10.000 µl

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Additional Info : Peak(s) manually integrated



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Integration Results  
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3	6.827	VB	2768.18359	157.07123	0.2596	6.693	7.711

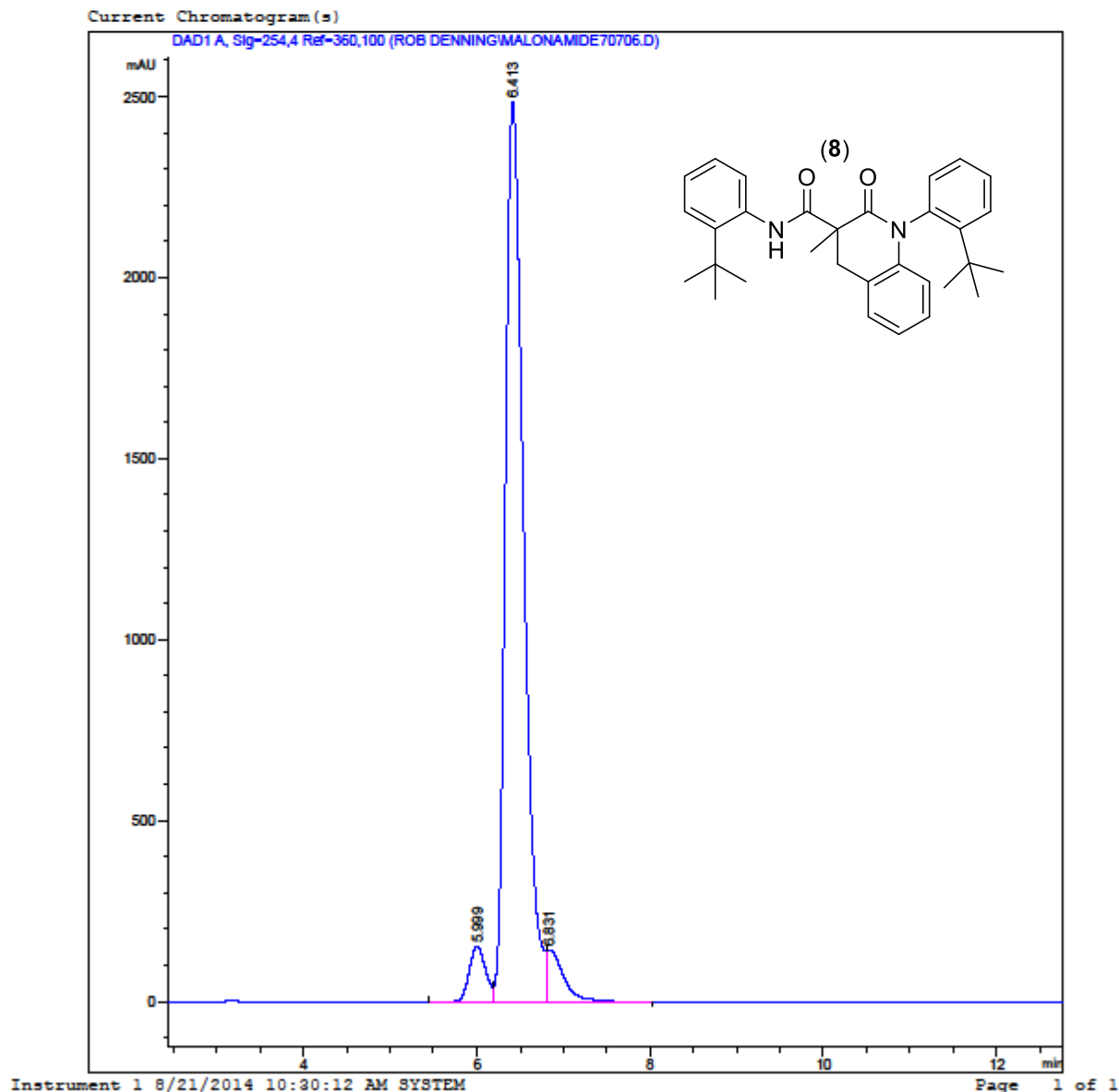
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Sample Name : CTBM CY2

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		Inj Volume	: 10.000 µl

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Integration Results  
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2	6.413	VV	3.66176e4	2486.60107	0.2258	6.185	6.800
3	6.831	VB	1998.51538	142.45128	0.2097	6.800	8.023

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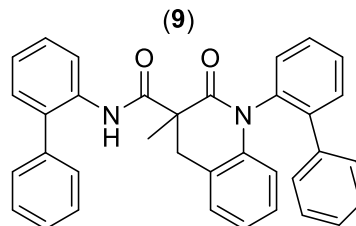
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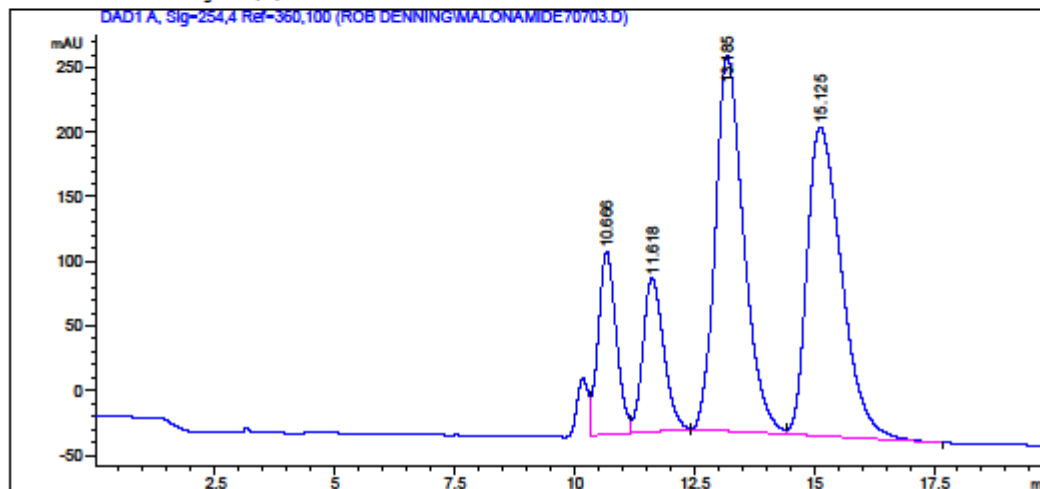
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Current Chromatogram(s)



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Integration Results  
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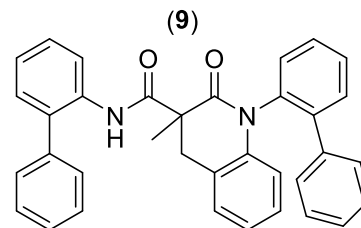
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3	13.185	BV	1.19085e4	290.71176	0.6179	12.420	14.405
4	15.125	VBA	1.19644e4	239.17972	0.7856	14.405	17.676

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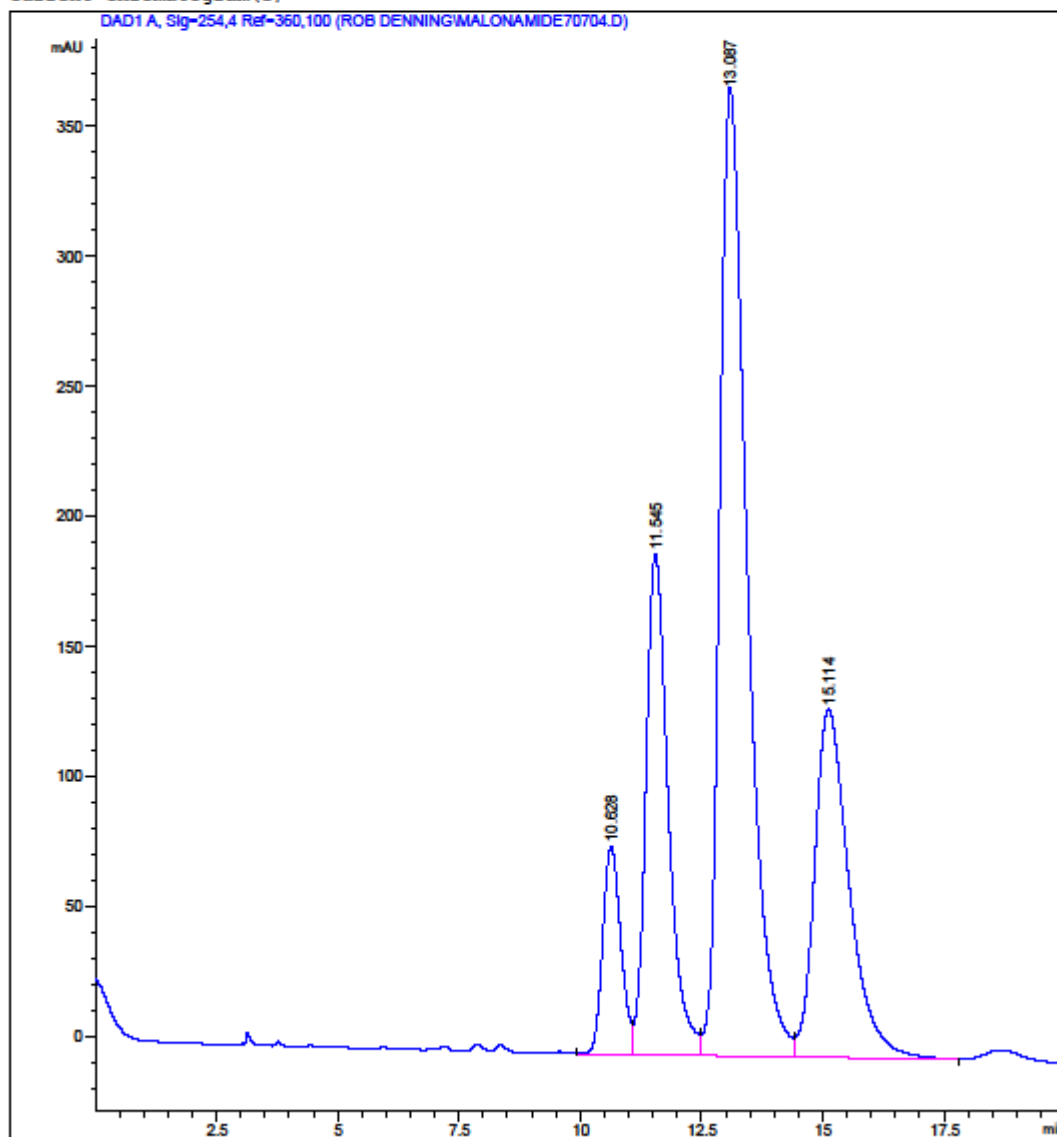
Print of window 38: Current Chromatogram(s)  
Data File : C:\CHEM32\1\DATA\ROB DENNING\MALONAMIDE70704.D  
Sample Name : CBPM CY2

=====

Acq. Operator	: SYSTEM	Seq. Line	: 2
Acq. Instrument	: Instrument 1	Location	: Vial 14
Injection Date	: 7/3/2014 1:08:23 PM	Inj	: 1
		Inj Volume	: 10.000 µl
Acq. Method	: C:\CHEM32\1\METHODS\RDMTBM.M		
Last changed	: 7/3/2014 12:46:13 PM by SYSTEM		
Analysis Method	: C:\CHEM32\1\METHODS\RDANALYSIS.M		
Last changed	: 8/21/2014 10:20:31 AM by SYSTEM		
Additional Info	: Peak(s) manually integrated		



Current Chromatogram(s)



Instrument 1 8/21/2014 10:27:02 AM SYSTEM

Page 1 of 1

Data File C:\CHEM32\1\DATA\ROB DENNING\MALONAMIDE70704.D  
Sample Name: CBPM CY2

=====  
Integration Results  
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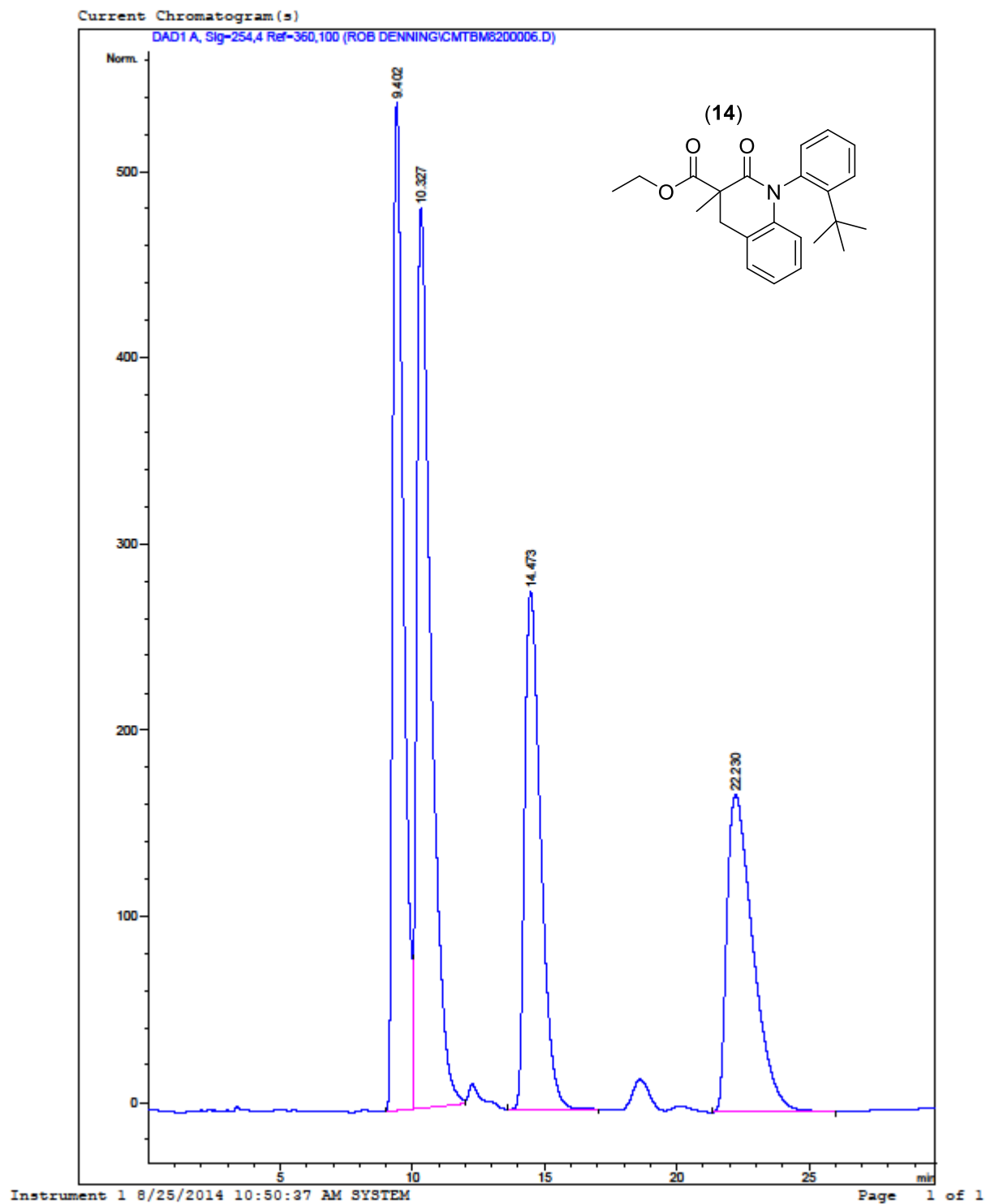
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	Time [min]	Type	Area [mAU*s]	Height [mAU]	Width [min]	Start [min]	End [min]
1	10.628	BV	2072.21118	80.13913	0.3997	9.935	11.076
2	11.545	VV	6178.20801	192.70490	0.4860	11.076	12.472
3	13.087	VV	1.47449e4	372.27863	0.6001	12.472	14.399
4	15.114	VB	6627.40869	133.83157	0.7477	14.399	17.808

=====



Print of window 38: Current Chromatogram(s)



Print of window 38: Current Chromatogram(s)

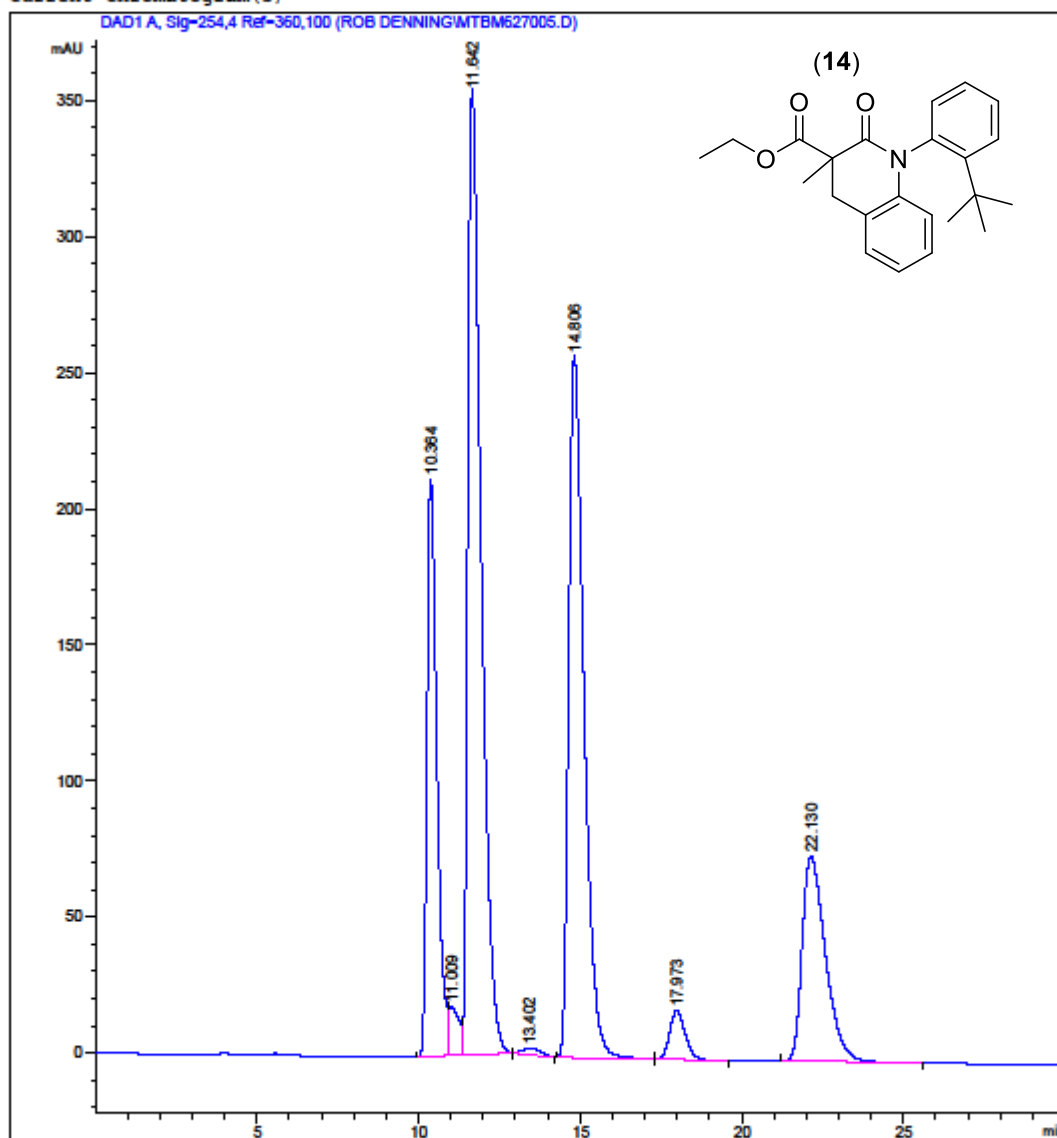
Data File : C:\CHEM32\1\DATA\ROB DENNING\MTBM627005.D

Sample Name : CMTEM

=====

Acq. Operator	: SYSTEM	Seq. Line	: 2
Acq. Instrument	: Instrument 1	Location	: Vial 2
Injection Date	: 6/27/2014 1:13:57 PM	Inj	: 1
		Inj Volume	: 5.000 µl
Acq. Method	: C:\CHEM32\1\METHODS\RDMTBM.M		
Last changed	: 6/27/2014 12:42:01 PM by SYSTEM		
Analysis Method	: C:\CHEM32\1\METHODS\RDANALYSIS.M		
Last changed	: 8/21/2014 10:39:03 AM by SYSTEM		
	(modified after loading)		

Current Chromatogram(s)



Instrument 1 8/21/2014 10:39:56 AM SYSTEM

Page 1 of 1

Data File C:\CHEM32\1\DATA\ROB DENNING\MTBM627005.D  
Sample Name: CMTEM

=====  
Integration Results  
=====

Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	Time [min]	Type	Area [mAU*s]	Height [mAU]	Width [min]	Start [min]	End [min]
1	10.364	BV	4571.75439	212.26962	0.3293	9.955	10.919
2	11.009	VV	381.17456	18.00923	0.2929	10.919	11.330
3	11.642	VB	1.01255e4	354.96542	0.4328	11.330	12.906
4	13.402	BB	99.05111	2.28091	0.7146	12.909	14.209
5	14.806	BB	8501.06445	258.04272	0.5024	14.235	17.269
6	17.973	BB	591.14038	17.90004	0.5113	17.295	19.569
7	22.130	BBA	3771.65088	75.69991	0.7633	21.215	25.582

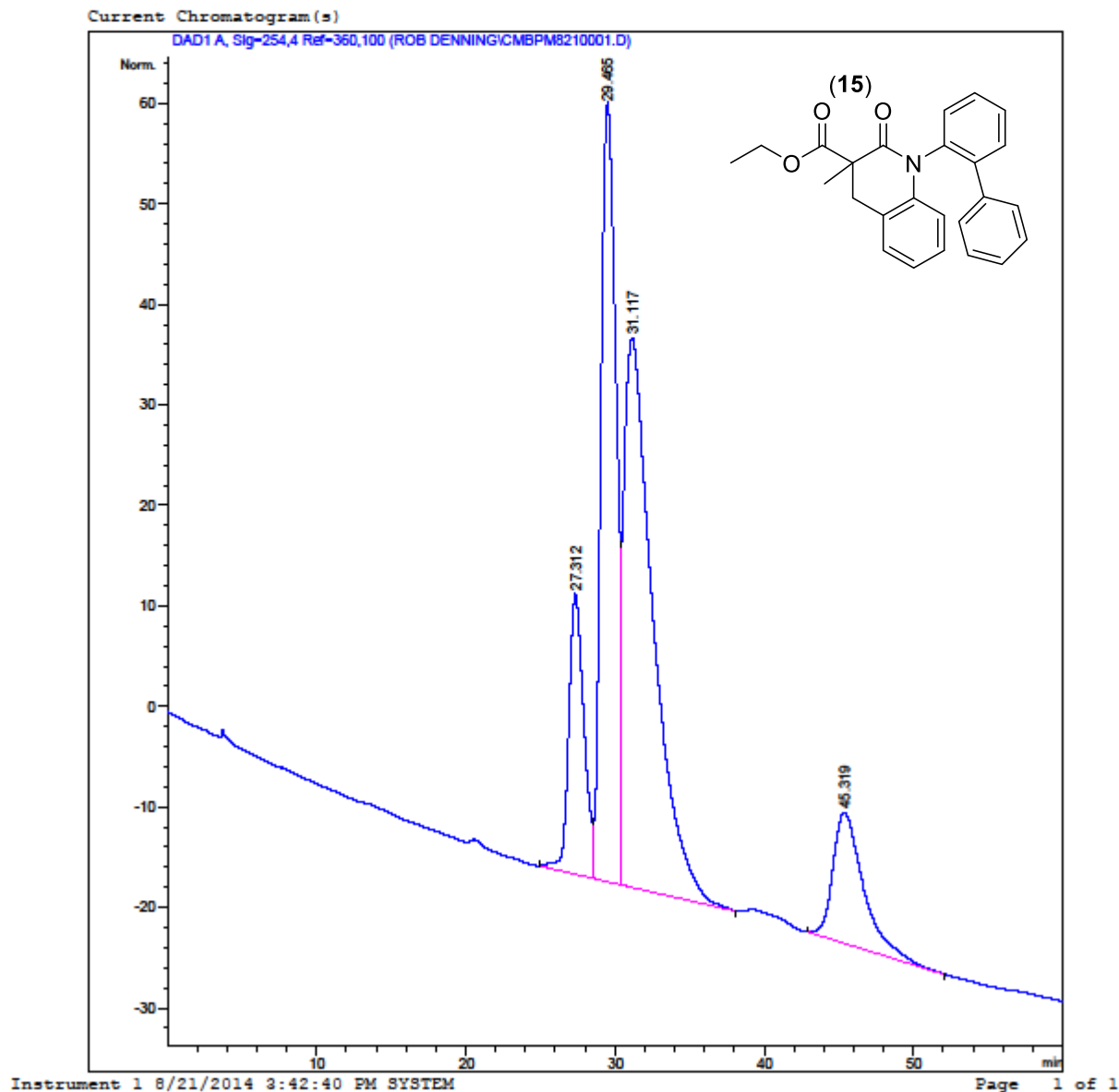
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Print of window 38: Current Chromatogram(s)  
Data File : C:\CHEM32\1\DATA\ROB DENNING\CMBPM8210001.D  
Sample Name : CMBPM SPHOS

=====

Acq. Operator	: SYSTEM	Seq. Line	: 1
Acq. Instrument	: Instrument 1	Location	: Vial 6
Injection Date	: 8/21/2014 12:57:00 PM	Inj	: 1
		Inj Volume	: 10.000 µl

Acq. Method : C:\CHEM32\1\METHODS\RDCMBPM.M  
Last changed : 8/21/2014 12:55:54 PM by SYSTEM  
Analysis Method : C:\CHEM32\1\METHODS\RDANALYSIS.M  
Last changed : 8/21/2014 2:45:54 PM by SYSTEM  
(modified after loading)



Data File C:\CHEM32\1\DATA\ROB DENNING\CMBPM8210001.D  
Sample Name: CMBPM SPHOS

=====  
Integration Results  
=====

Signal 1: DAD1 H, Sig=250,4 Ref=360,100

Peak #	Time [min]	Type	Area [mAU*s]	Height [mAU]	Width [min]	Start [min]	End [min]
1	27.311	BV	2166.86206	30.71970	1.0669	24.855	28.493
2	29.466	VV	5966.80225	84.18759	1.1229	28.493	30.386
3	31.116	VB	8140.27637	59.35410	1.9241	30.386	38.089
4	45.319	BBA	2021.15308	14.24312	2.0015	42.915	51.915

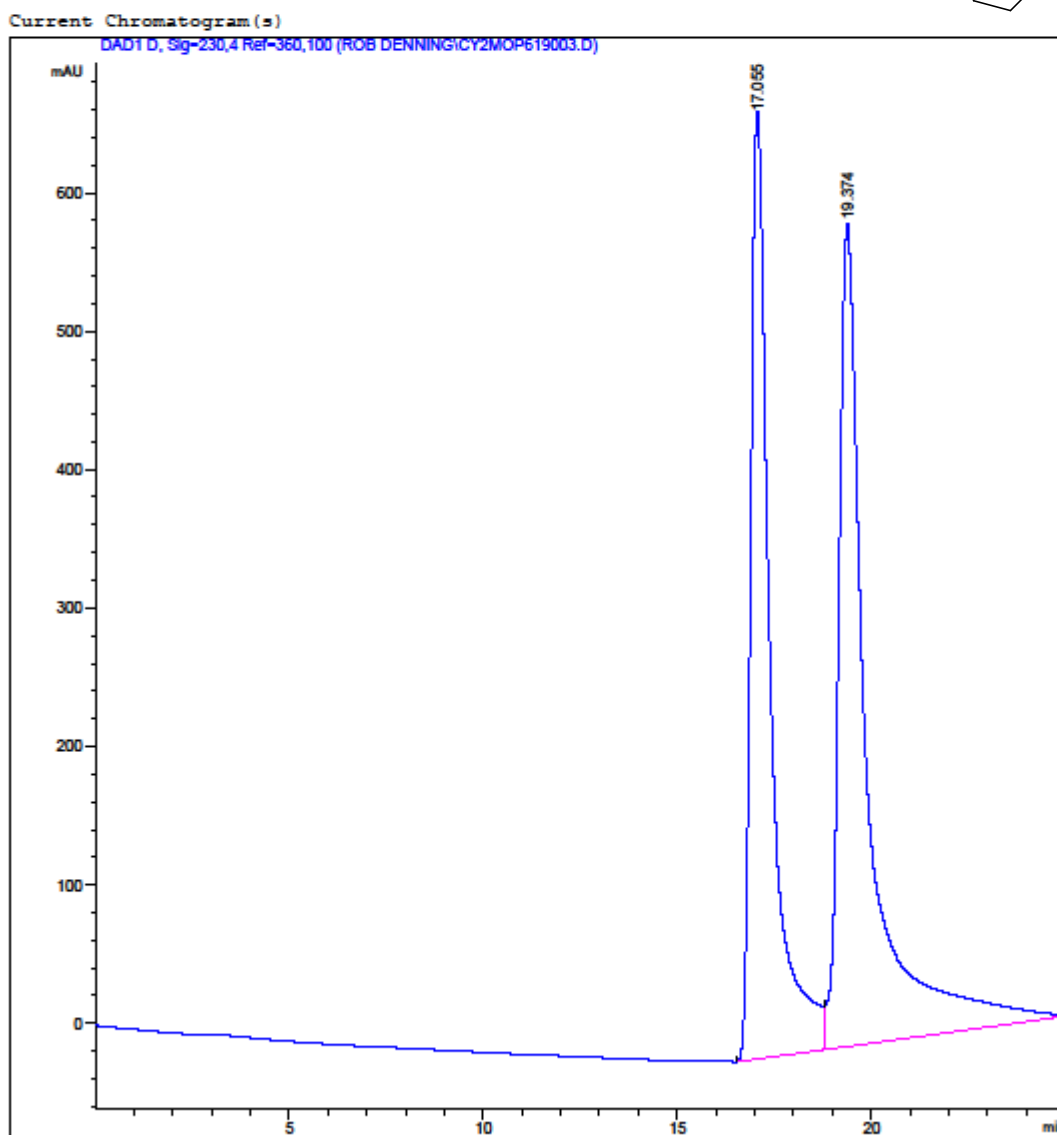
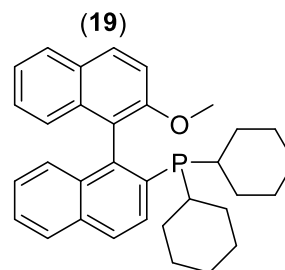
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Print of window 38: Current Chromatogram(s)  
Data File : C:\CHEM32\1\DATA\ROB DENNING\CY2MOP619003.D  
Sample Name : RacCy2MOP

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Acq. Operator	: SYSTEM	Seq. Line	: 1
Acq. Instrument	: Instrument 1	Location	: Vial 1
Injection Date	: 6/19/2014 2:47:05 PM	Inj	: 1
		Inj Volume	: 4.000 µl

Acq. Method : C:\CHEM32\1\METHODS\ROBDENNINGSUMCOLUMN.M  
Last changed : 6/19/2014 2:46:15 PM by SYSTEM  
Analysis Method : C:\CHEM32\1\METHODS\RDANALYSIS.M  
Last changed : 8/21/2014 10:32:26 AM by SYSTEM  
(modified after loading)  
Additional Info : Peak(s) manually integrated



Instrument 1 8/21/2014 10:33:10 AM SYSTEM

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Data File C:\CHEM32\1\DATA\ROB DENNING\CY2MOP619003.D  
Sample Name: RacCy2MOP

=====  
Integration Results  
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Signal 1: DAD1 D, Sig=230,4 Ref=360,100

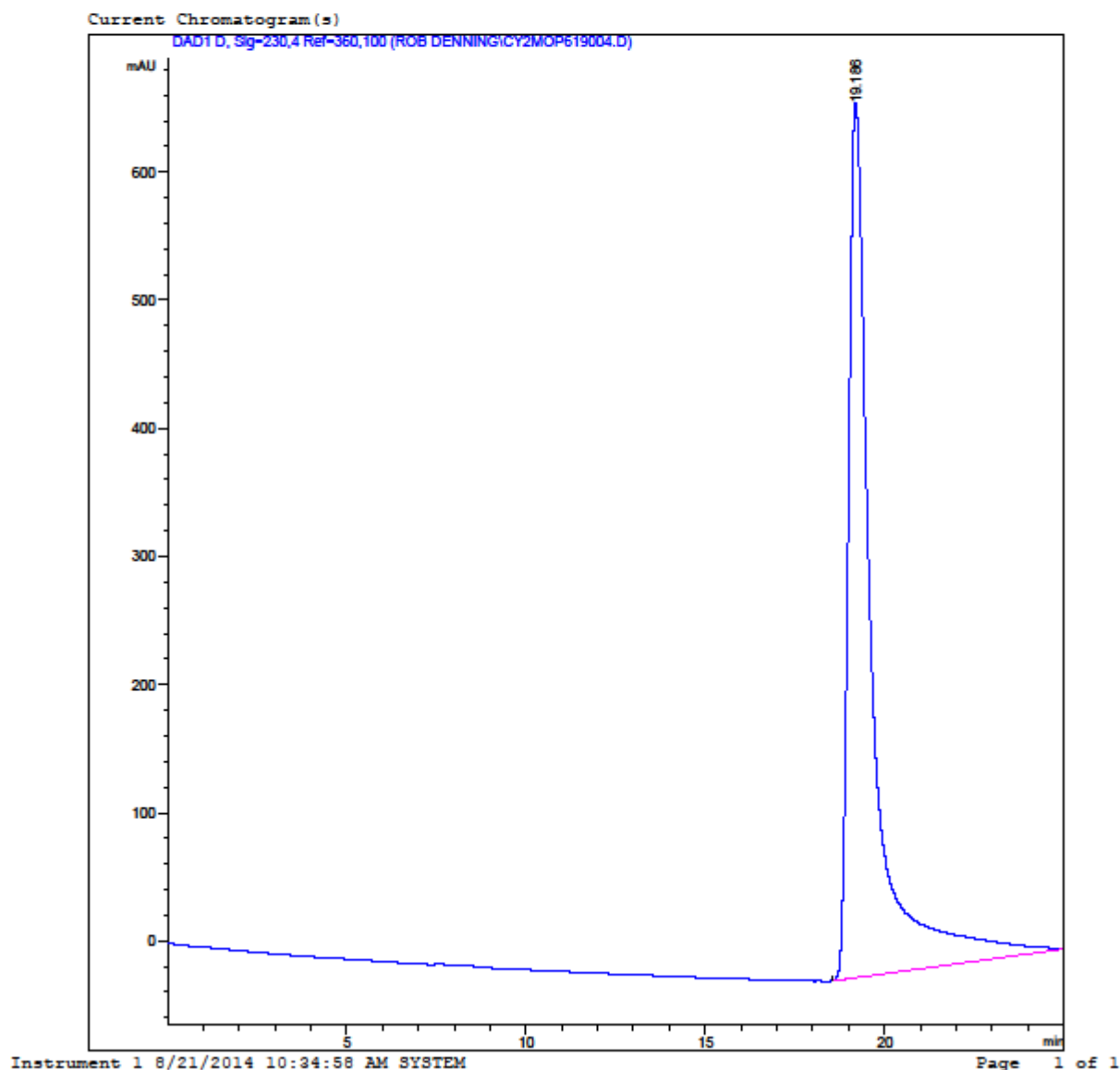
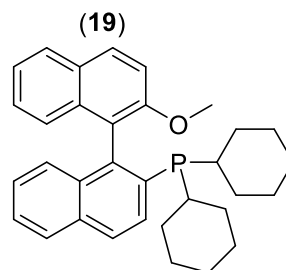
Peak #	Time [min]	Type	Area [mAU*s]	Height [mAU]	Width [min]	Start [min]	End [min]
1	17.055	BV	2.41876e4	684.73065	0.5151	16.507	18.765
2	19.374	VBA	3.09856e4	594.95740	0.7336	18.765	25.000

=====

Print of window 38: Current Chromatogram(s)  
Data File : C:\CHEM32\1\DATA\ROB DENNING\CY2MOP619004.D  
Sample Name : Cy2MOP

=====

Acq. Operator	: SYSTEM	Seq. Line	: 2
Acq. Instrument	: Instrument 1	Location	: Vial 2
Injection Date	: 6/19/2014 3:12:56 PM	Inj	: 1
		Inj Volume	: 4.000 µl
Acq. Method	: C:\CHEM32\1\METHODS\ROBDENNINGSUMCOLUMN.M		
Last changed	: 6/19/2014 2:46:15 PM by SYSTEM		
Analysis Method	: C:\CHEM32\1\METHODS\RDANALYSIS.M		
Last changed	: 8/21/2014 10:32:26 AM by SYSTEM		
	(modified after loading)		
Additional Info	: Peak(s) manually integrated		





Data File C:\CHEM32\1\DATA\ROB DENNING\CY2MOP619004.D  
Sample Name: Cy2MOP

=====  
Integration Results  
=====

Signal 1: DAD1 D, Sig=230,4 Ref=360,100

Peak #	Time [min]	Type	Area [mAU*s]	Height [mAU]	Width [min]	Start [min]	End [min]
1	19.186	BBA	3.18221e4	682.95551	0.6676	18.538	25.001

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## 6 Bibliography

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