Synthesis of 2-Alkyl Chromane-4-ones Using Hydrogen Bond Donor Catalysis

A Major Qualifying Project Report
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Approved

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Abstract

The total synthesis of biologically active natural product phomoxanthone A has been impeded due to the difficulty in synthesizing its 2-alkyl chromane-4-one core with a stereogenic center. Investigations into chromanone functionalization has revealed that hydrogen bond donor catalysis using silanediols has enabled the enantioselective addition of silyl ketene acetals to benzopyrylium triflates, creating chromanones with one stereogenic center with promising levels of enantiocontrol. The previous success of silanediol-catalyzed functionalization of benzopyrylium ions has inspired us to pursue the enantioselective and diastereoselective synthesis of 2-alkyl chroman-4-ones containing two stereocenters using hydrogen bond donor catalysis. The data collected during this study suggest that the influence of hydrogen bond donor catalyst, base, and silyl ketene acetal lead to moderate changes in the diastereomer ratio of the reaction product.

Introduction

Phomoxanthone A

Phomoxanthone A (**1**) offers an intriguing avenue of research with potential application in the pharmaceutical industry. This naturally occurring organic molecule (as depicted in Figure 1A) is a tetrahydroxanthone dimer and secondary metabolite that was isolated from the *Phomopsis* sp. BCC 1323 in 2001.[1] This initial study by Tanticharoen and co-workers found **1** to have antimalarial and antitubercular activity, as well as cytotoxicity toward two cancer cell lines; KB (IC_{50}=9.9 µM) and BC-1 (IC_{50} =5.1 µM) (Table 1). In 2013, Ronsberg and co-workers further demonstrated **1**'s powerful anticancer activity, showing it to be effective against cisplatin resistant cell lines: tongue cancer, Cal27 CisR (IC_{50} =5.6 µM); esophageal cancer, Kyse510 (IC_{50} =0.8 µM); ovarian cancer, A2780 (IC_{50} =0.9 µM); and suggested that it selectively induces apoptosis (Table 1).[2] This data implies potential medicinal applications of **1**: it may have the potential to be derivatized into a therapy to combat cis-platin resistant cancers, including ovarian cancer, which are among the most aggressive and fatal to those who acquire it.

Figure 1: Phomoxanthone A

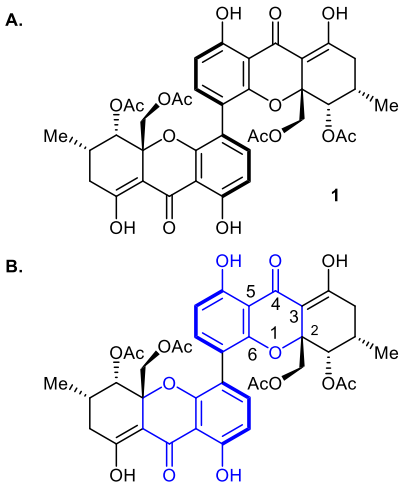


Figure 1 Phomoxanthone A a)The overall structure b) Chromanone components highlighted in blue

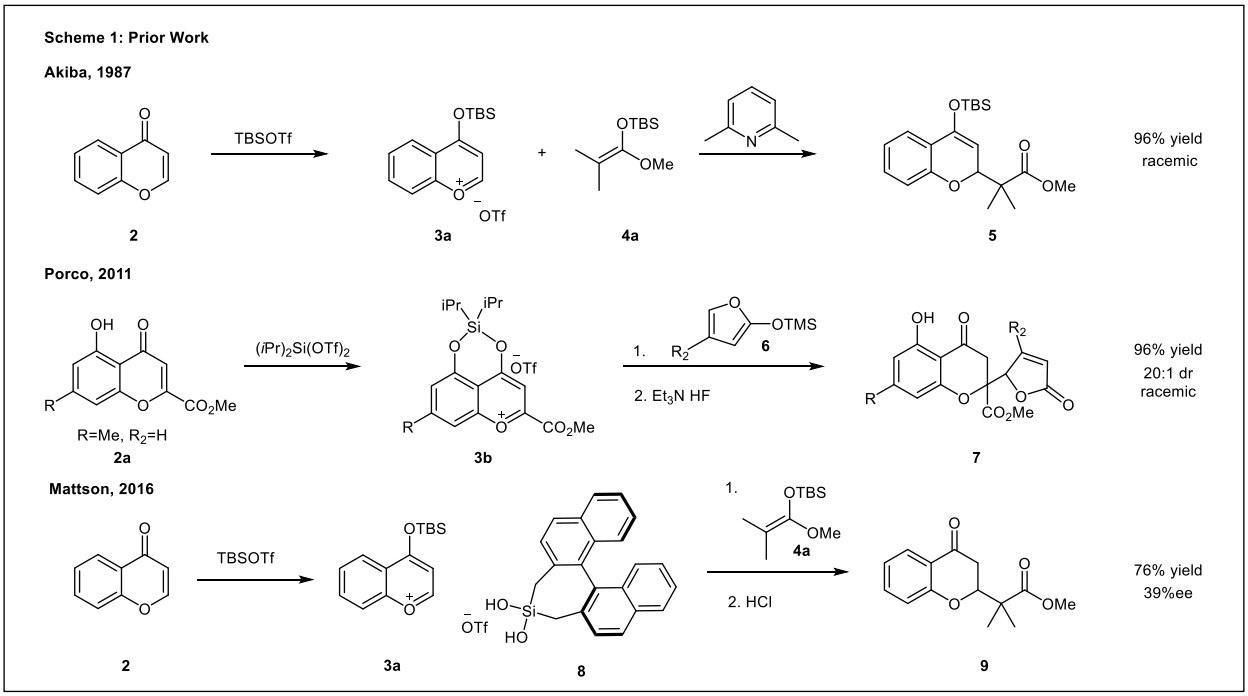
Table 1: Phomoxanthone Activity

	Cytotocicity	
Cell Line	IC_{50} (µM)	Cisplatin IC_{50} (µM)
KB	9.9	
BC-1	5.1	
Cal27 sens	5.2	57.8
Cal27 CisR	5.6	41.4
Kyse510 sens	0.8	2.5
Kyse510 CisR	0.8	8.4
A2780 sens	0.7	1.2
As2780 CisR	0.9	10.2

Phomoxanthone A (**1**) possesses a synthetically challenging molecular architecture and it has not yet been prepared by chemical synthesis. There are several synthetically demanding aspects to consider when synthesizing **1**, including (1) the sterically encumbered biaryl bond joining the two tetrahydroxanthone units and (2) the 2-alkyl chromane-4-one core (highlighted in blue, Figure 1B) containing a stereogenic center at the 2-position which is particularly difficult to generate. While there are a few literature approaches for the enantioselective synthesis of 2-alkyl chromanones, they are not applicable for our needs. Specifically, they are limited in number, typically confined to a specific substructure, and often do not result in highly enantiopure products.[3] The paucity of suitable methods for the enantioselective construction of 2-alkyl chroman-4-ones is a significant gap in knowledge as it renders the investigations of **1** as a therapeutic agent nearly impossible. To offer a solution for the enantioselective synthesis of 2-alkyl chroman-4-ones, the Mattson group has initiated the study of new catalyst systems for the

stereoselective functionalization of benzopyrylium triflates, a reactive species generated *in situ* from chromenones.

Chromanone Synthesis from Benzopyrylium Ions



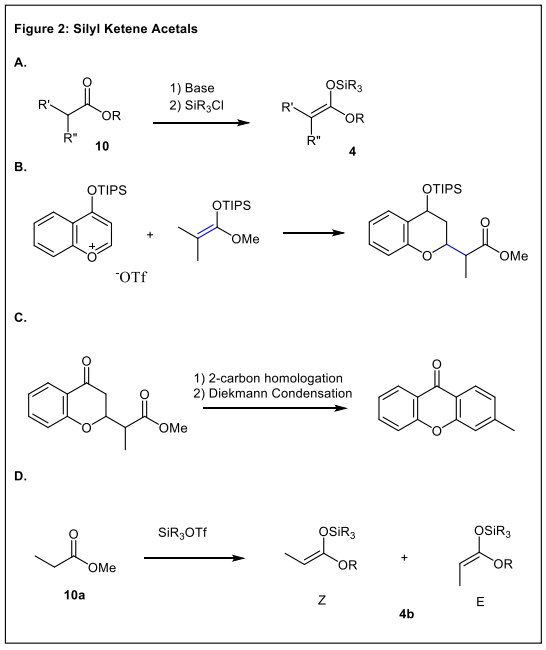
Functionalized chromanones are viable precursors of the tetrahydroxanthones found in many bioactive natural products and therefore, are a common target of many synthetic organic research projects. One lucrative approach, pioneered by Akiba and co-workers, relies on the synthesis of chromanones via the functionalization of benzopyrylium triflates (**3a**), a reactive species generated *in situ* from the corresponding chromenone (**2**) and a silyl triflate (Scheme 1). Their studies found a number of carbon-based nucleophiles, such as alkyl silanes and silyl ketene acetals (**4a**), could undergo addition to **3a** with high yields (Scheme 1).[1] While they did not functionalize the chromanone with enantioselectivity, this proof of concept inspired future research programs capitalizing on benzopyrylium ion functionalization.

In 2011, Porco and co-workers expanded on Akiba's early work with their investigations of the functionalization of benzopyrylium triflates (**3b**) using siloxy furans (**6**).[5] Specifically, the vinylogous addition of **6** to **3b** was employed to form chromone lactones (**7**, Scheme 1). When optimized, the products were produced in 96% yield as a racemic mixture with a 20:1 diastereomer ratio. Porco and co-workers then directly applied this synthetic method to the synthesis of tetrahydroxanthone natural products, such as (±)-blennolides B and C. Such promising results demonstrated the potential for chromanone functionalization to be applied to the demands of tetrahydroxanthone natural products. However, this approach still lacked enantioselectivity and was limited to specific classes of compounds. Therefore, the challenge still remained to develop an enantioselective method for functionalizing chromenones for tetrahydroxanthone production.

Akiba's and Porco's investigations inspired Mattson and co-workers, in 2016, to use silanediol anion binding catalysis to encourage enantioselectivity in the addition of carbonyl containing nucleophiles to chromenones.[5] This method utilized silanediol catalysts (**8**) to add **4a** to **2** through **3a** (Scheme 1). Using this method, they obtained moderate levels of enantiocontrol, ranging from 16-56% ee, depending upon the substituents on **2.** This was the first instance of enantioselective functionalization of silyl triflate activated chromenones.

Throughout the experiments detailed in their 2016 report, Mattson and co-workers used the same silyl ketene acetal, **4a**: triisopropyl ((1-methoxy-2-methyl prop-1-en-1-yl)oxy) silane. We became interested in exploring how this method of chromenone functionalization would translate using a different silyl ketene acetal, one that already has an intrinsic stereochemical element. Specifically, we hypothesized that improved enantiomeric excess and diastereocontrol would be observed if silyl ketene acetals derived from methyl propionate were employed in the silanediol catalyzed functionalization of benzopyrylium triflates. The results of these studies are described next.

Silyl Ketene Acetals



Silyl ketene acetals are attractive nucleophiles for reaction with benzopyryliuim triflates in the pursuit of tetrahydroxanthones scaffolds, such as **1**. Silyl ketene acetals are enols of esters where an organosilicon is attached to the oxygen alpha to an alkoxy group (**4**, Figure 2A). These nucleophilic substrates will readily form C-C bonds with appropriate reaction partners which will result in the formation of an ester (Figure 2B). The ester functional group is a good synthetic handle that can be further functionalized through standard manipulations, including ring closing reactions. For example, a silyl ketene acetal made from a methyl ester that is added to a chromanone will produce a methyl ester which, after a 2-carbon homologation, is capable of undergoing cyclization to produce a xanthone (Figure 2C). Moreover, silyl ketene acetals are highly customizable. They are created by the deprotonation of esters followed by silylation by a silyl chloride in the presence of base (Figure A). The properties are dependent upon the composition of the original ester.

Our investigations used a silyl ketene acetal (**4b**) derived from methyl propionate (**10a**, Figure 2D). In 1985, Duntiz and co-workers found that the deprotonation of **10a** with lithium diisopropyl amide followed by silylation with TBSCl gave rise to a 9:91 ratio of the Z:E silyl ketene acetal. [6] Armstrong and co-workers in 1991 demonstrated the effect of solvent on the creation of the E and Z isomers of silyl ketene acetals.[7] They found that changing the solvent

system to a THF/23% HMPA mixture will give silyl ketene acetal in an 84:16 Z:E ratio. Armstrong and co-workers also found that by using bulkier amide bases slightly increases the Z:E ratio to 95:5. Based upon these results, the silyl ketene acetals used in the following investigation was prepared using LDA/THF/DMPU system in order to obtain silyl ketene acetals with the highest levels of diastereocontrol possible to be used in chromanone additions.

Benzopyrylium Triflate

It is proposed that our addition of silyl ketene acetals to chromenones proceeds via a benzopyrylium triflate intermediate. The benzopyrylium triflate (**3a**) requires that the ketone group becomes a siloxy group which, in turn, encourages the oxygen to adopt a positive charge that is stabilized by triflate. As previously mentioned, Akiba's and Porco's reactions using **3** were effective but racemic (Scheme 1). Mattson and co-workers' were able to install enantioselectivity by utilizing a BINOL-based silanediol anion binding catalyst (**8**), which is thought to associated with **3a** so that the addition would be forced to occur in an enantioselective fashion. These results suggest great promise for the utilization of the benzopyrylium triflate intermediate to functionalize chromanones with enantiocontrol when coupled with an appropriate catalyst.

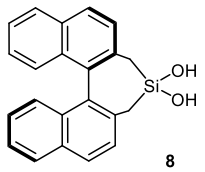
Catalyst

Our investigations utilize BINOL-based silanediol (**8**) as the catalyst (Figure 4). A silanediol is characterized by its silicon atom bonded to two hydroxyl groups. Silanediols can be classified as a hydrogen-bond donor (HBD) anion-binding catalyst. This means that the catalyst is thought to function by binding to the anion component of an ion pair which then strategically positions the cationic component for reaction.[8] Silanediols are just one class of a larger family catalysts proposed to proceed through anion binding, including thioureas (**11**) and squaramides (**12**).

The choice to use predominantly employ silanediols in this work was informed by a previous research study we conducted that revealed that silanediols are uniquely suited to induce enantioselective reaction on benzopyrylium triflates.[9] Specifically, we analytically compared the anion-binding affinity of **11**, **12**, and **8**. This was done, in part, through titrations using ultraviolet-visible light (UV-Vis) and a nuclear magnetic resonance (NMR) spectroscopy. These investigations were used to determine how well an anion (the guest) was binding to the catalyst (the host) which was quantified by an association constant. Our initial hypothesis focused on the premise that a higher association constant correlates to better catalytic activity because the catalyst

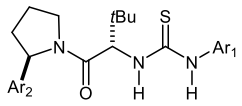
Figure 4: HBD Catalysts

A. Silanediol



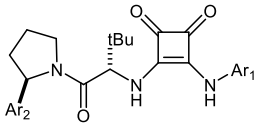
8

B. Thiourea



11: Ar_1= 3, 5- difluoromethyl benzene
Ar_2=2-pyrene

C. Squaramide



12: Ar_1= 3, 5- difluoromethyl benzene
Ar_2=2-pyrene

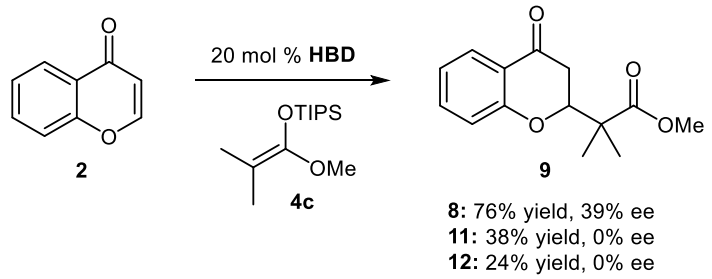
would form a stronger attachment to the anion and therefore, more reliably expose the cation for reaction. As shown in Figure 5A, **8** has a significantly lower association constant with the triflate anion than either **11** or **12**; suggesting that **11** and **12** are associating more tightly with the anion. However, **8** was the only HBD catalyst of those investigated to give rise to enantiomeric excess in the reaction as detailed in Figure 5B, thereby suggesting that **8** may be engaging with the anion differently than the other HBD catalysts. Therefore, **8** has been chosen as the primary catalyst in this investigation as it is known to interact in a unique and favorable manor to catalyze the enantioselective functionalization of **3**.

Figure 5: Anion Binding Activity of HBD Catalysts

A. Association Constants Determined for **8**, **11**, and **12** with Triflate (M^{-1})

Host	Uv-Vis
8	2.8×10^3
11	6.5×10^4
12	3.8×10^5

B.

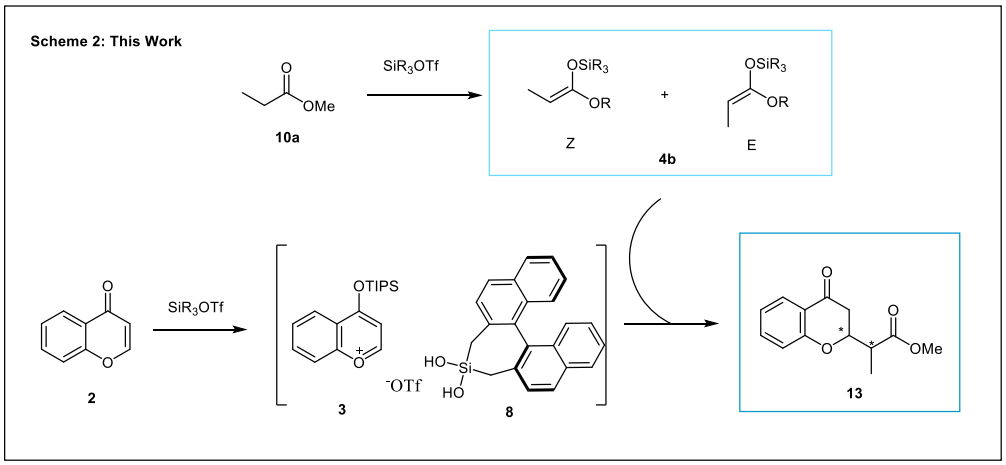


8: 76% yield, 39% ee
11: 38% yield, 0% ee
12: 24% yield, 0% ee

Project Goal

The goal of our project was to effect the enantioselective and diastereoselective synthesis of 2-alkyl chroman-4-ones containing two stereocenters under the influence of silanediol anion binding catalysis (Scheme 2). Prior studies revealed that that silyl ketene acetals can be added with promising levels of enantiocontrol to chromanones in the 2 position via a benzopyrylium intermediate in the presence of a BINOL-based silanediol catalysts. This reaction results in a stereocenter at the 2 position. However, at the onset of our investigations, it was unknown the additions of methyl propionate-derived silyl ketene acetals to benzopyrylium ions will give rise to a chromanone product with two stereocenters with enantiocontrol and diasterecontrol. Therefore, our investigations focused on the enantioselective addition the methyl propionate derived silyl ketene acetal to chromanones in order to

Scheme 2: This Work



investigate if 1) the reaction is possible, 2) the reaction can be obtained with enantiomeric excess at one and/or both of the stereocenters and 3) the stereochemistry (e.g., E to Z ratio) of the silyl ketene acetal influences the results.

Results and Discussion

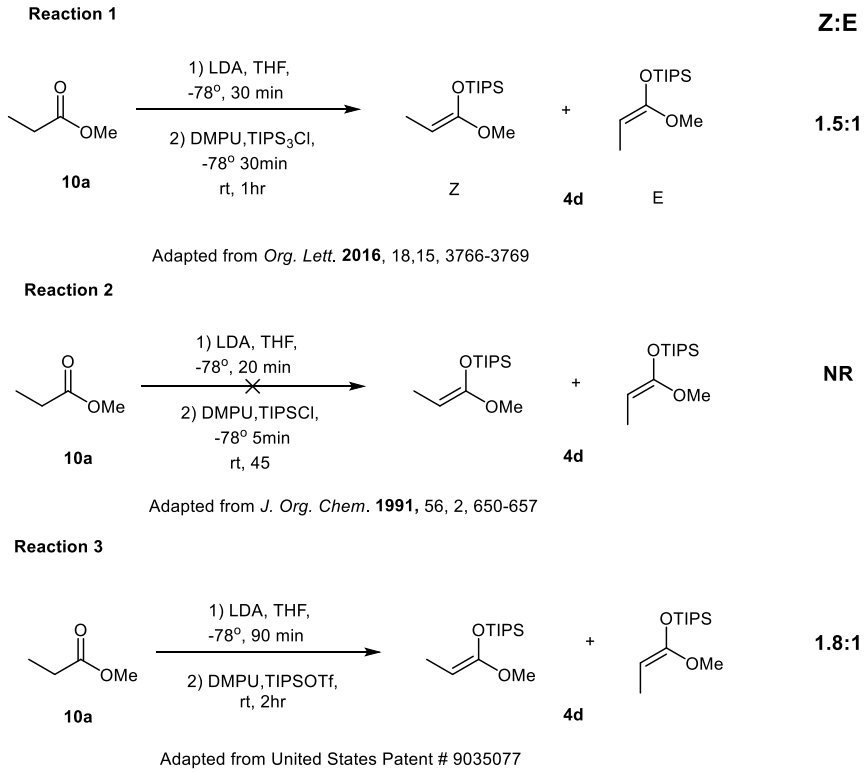
Triisopropylsilyl Ketene Acetals

Table 2: Triisopropylsilyl Ketene Acetal

Method	dr	Addition dr
Reaction 1	1:1.5	1:1.2
Reaction 2	-	-
Reaction 3	1:1.8	1:1.4

The silyl ketene acetals (**4d**) were synthesized using three different reactions (Scheme 3, See Appendix 1A, B, and C for procedures). No yields were obtained for these reactions because all products were used as crude reaction mixtures. Therefore, in order to determine which method we would use to make **4d** for the addition reactions, we first compared the diastereomer ratios of the products. Reaction 2 failed to make the desired product as indicated by ^{1}H NMR spectroscopy. Reaction 1 produced the desired product with a slightly lower diastereomer ratio than Reaction 3 (Table 2, Reaction 1 and 3). However, the ^{1}H NMR spectrum suggested the presence of more impurities in Reaction 1 than in 3. Therefore, an additional comparison was made through a preliminary assessment of how the products from

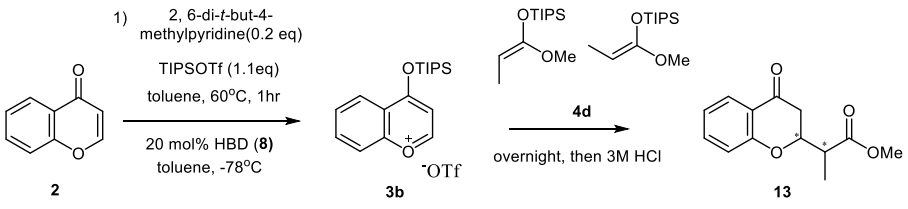
Scheme 3: Triisopropyl Silyl Ketene Acetal Synthesis



each method would perform when used to functionalize chromenones (see Appendix 1D for procedure). The silyl ketene acetal from Reaction 3 functionalized the chromenone with more diastereocontrol than the silyl ketene acetal from Reaction 1 could achieve (Table 2, Reaction 1 and 3). Therefore, **4d** for the following investigations was synthesized using the method as described in Reaction 3 (Scheme 3).

Triisopropylsilyl Activated Benzopyrylium Ions

Table 3: Triisopropylsilyl Activated Benzopyrylium Ions



Entry	Catalyst	Deviation	Yield(%)	dr	ee
JH-127	-	-	45	1.5:1	racemic
JH-130	8	-	27	4:1	racemic
JH-133	8	2x catalyst	27	6:1	racemic
JH-136	8	2x base	38	5:1	racemic

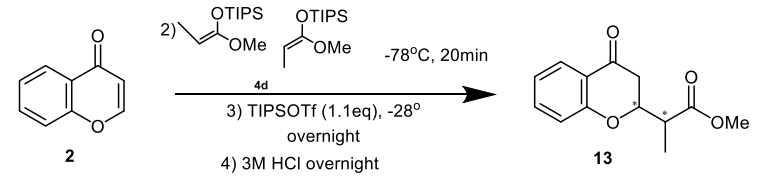
Initially, the chromenone (**2**) was activated with triisopropylsilyl (TIPS) triflate in heat and in the presence of 2,6-di-*tert*-butyl-4-methylpyridine to form the benzopyrylium ion intermediate (**3b**) prior to the addition of the silyl ketene acetal (**4d,** See Appendix 1D). Using this protocol, without any variations, JH-127 produced the functionalized chromenone (**13**) in a moderate yield and with a slightly lower ratio of diastereomers than the silyl ketene acetal had of its isomers (JH-127, Table 2). With the addition of silanediol (**8**), the diastereoselectivity increased significantly, however, at the cost of the yield (JH-130). Unfortunately, the additional **8** did not cause any enantioselectivity in the process. By doubling the catalyst loading, **13** was still isolated as a racemic mixture with slightly increased diastereoselectivity (6:1 dr), but not enough to warrant additional investigations using excess **8** (JH-133). The same diastereoselectivity was also achieved by doubling the amount of base used in this reaction (JH-136). JH-136 also had an increase in yield, however, it still did not match the yield of JH-127.

Previous unpublished experiments of the Mattson group found that the enantioselectivity of dimethyl malonate additions to chromenones using silanediols could be improved by generating the reactive intermediate **3b** not with heat, but at –78°C in the presence of the other reactants. Therefore, we proposed that by generating **3b** at –78°C rather than at 60°C may improve diastereoselectivity and/or enantioselectivity in the addition of **4d** as well (See Appendix 1E). Unfortunately, no additions using this protocol caused an enantiomeric excess. However, when using the non-heating protocol in reaction conditions stoichiometrically analogous to JH-127, slightly higher diastereoselectivity was achieved (2:1 dr) but in a lower yield (JH-128, Table 4). With the use of **8**, both the yield and the diastereoselectivity increased significantly (Table 4, JH-131). However, when the catalyst loading was doubled, the yield

decreased by 30% (Table 4, JH-134). Therefore, despite the positive effect on diastereoselectivity, increased catalyst loading was not pursued further. Additionally, when the equivalents of base added to the reaction was double that which was described in the procedure, the yield returned to the mid 40% with a slight increase in diastereoselectivity as compared to JH-131. (Table 4, JH-137) However, without enantiomeric excess, changes in the equivalents of base used did not warrant further investigations. Overall, by generating **3b** *in situ* at –78°C rather than at 60°C, the functionalized chromanone could be produced with equivalent or improved diastereoselctivity and with the exception of JH-134, improved yields as compared to additions where the **3b** in generated in heat prior to the addition of the other reactants.

With no selectivity observed with **8**, we expanded our survey of reaction conditions to other well-established anion-binding catalysts, including thiourea (**11**) and squaramide (**12**) (Figure 4). The different catalysts were tested on a 0.5 scale where **3b** was generated at –78°C. Neither **11** nor **12** improved the diastereoselectivity of the functionalized chromanone more so than what had been achieved when using **8** as the catalyst (JH-138 and JH-139, Table 4). Also, neither catalyst produced the product in an enantiomeric excess. This data confirmed that neither the squaramide or thiourea were worth additional pursuits in these investigations.

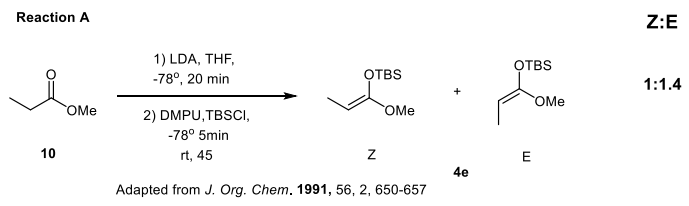
Table 4: Triisopropylsilyl Modified Procedure



Entry	Catalyst	Deviation	Yield*(%)	dr	ee
JH-128	-	-	38	2:1	racemic
JH-131	8	-	47	4:1	racemic
JH-134	8	2x catalyst	17	6:1	racemic
JH-137	8	2x base	44	5:1	racemic
JH-138	11	0.5 scale	26	3.3:1	racemic
JH-139	12	0.5 scale	32	3.74:1	racemic

Tert-Butyldimethylsilyl Ketene Acetals

Scheme 4: Tert-butyldimethyl Silyl Ketene Acetal Synthesis



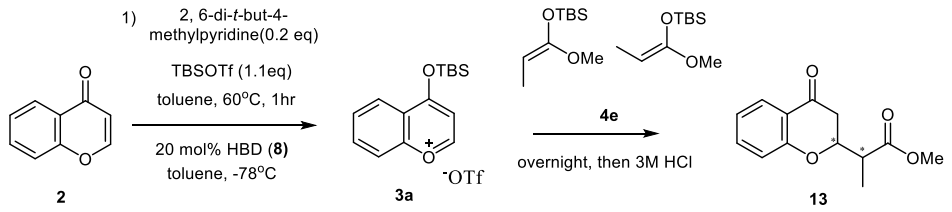
In an effort to improve enantioselectivity and diastereoselectivity, we turned our attention to silyl ketene acetals with *tert*-butyldimethylsilyl (TBS) groups. We hypothesized that the size of the TBS group would allow access to a transition state that would improve stereocontrol. Initially, silyl ketene acetals containing *tert*-

butyldimethylsilyl (**4e**) were synthesized using two methods (Scheme 4, See Appendix 1Fand 1G for procedures). Despite its lack of success in the triisopropylsilyl variation, the method used for Reaction 2A was originally designed for *tert*-butyldimethylsilyl use and therefore, was of interest. As in the reactions in Scheme 2, no yields were obtained and therefore the Z:E ratio of **4e** were compared. No additional comparisons were necessary because **4e** from Reaction B only produced a signal diastereomer whereas Reaction A had a mixture. (Scheme 3) Therefore, following investigations used the method from Reaction B to synthesize **4e**.

Tert-Butyldimethylsilyl activated Benzopyrylium Ions

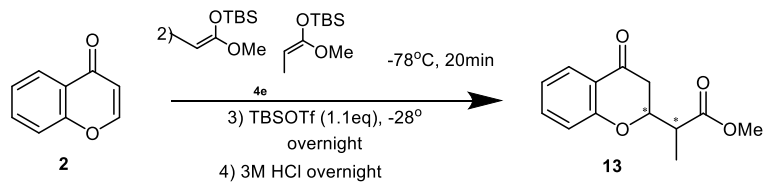
Initially, the chromenone was activated with TBS triflate in the presence of 2,6-di-*tert*-butyl-4-methylpyridine to form the benzopyrylium ion intermediate (**3a**, See Appendix 1H). The addition occurred in a moderate yield with a diastereoselectivity significantly higher than the equivalent reaction when activated by triisopropylsily triflate (JH-151, Table 5). When the reaction was tested with 1,4-diazabicyclo[2.2.2]octane (DABCO), the product (**13**) was obtained in a higher yield and but a lower diastereomer ratio (JH-153). With the addition of **8**, **13** was produced as a racemic mixture with a slightly higher yield but, surprisingly, with less diastereoselectivity (JH-156).

Table 5: Tert-Butyldimethylsilyl Activated Benzopyrylium Ions



Entry	Catalyst	Deviation	Yield*(%)	dr	ee
JH-151	-	-	30	5:1	racemic
JH-153	-	DABCO	42	2.9:1	racemic
JH-156	8	DABCO	44	2.5:1	racemic

Table 6: Tert-Butyldimethylsilyl Modified Procedure



Entry	Catalyst	Deviation	Yield*(%)	dr	ee
JH-152	-	-	38	2.7:1	racemic
JH-154	-	DABCO	46	2.7:1	racemic
JH-155	Silanediol	DABCO	29	3.3:1	racemic

We then altered the protocol so that the TBS derived benzopyrylium intermediate (**3a**) was generated at –78°C as opposed to 60°C (See Appendix 1I). When using 2,6-di-*tert*-butylmethyl pyridine as the base, the yield was slightly higher than that obtained in JH-151, where analogous conditions were investigated in the protocol that produces **3a** using heat (JH-152, Table 6). However, JH-152 had a significantly smaller diastereomer ratio than JH-151.

Nonetheless, when comparing the TBS activated protocol where the benzopyrylium was generated in colder conditions to the same protocol using TIPS, the TBS version, JH-152, produced the product (**13**) with higher distereoselectivity than JH-128, the TIPS version. Using DABCO in this protocol, increased the yield, but had no impact on the diastereoselectivity (JH-154). The addition of silanediol (**8**) improved the diastereoselectivity of **13** but lowered the yield and did not produce **13** in enantiomeric excess (JH-155).

Conclusions

2-Alkyl chroman-4-ones containing a stereogenic center at the 2-position are highly desirable and yet synthetically challenging targets for drug discovery investigations. Previous work has demonstrated that 2-alkyl chroman-4-ones may be synthesized using silyl ketene acetals and benzopyrylium ions. Our laboratory has found that silanediols are able to catalyze this reaction to proceed in good yields with promising levels of enantiocontrol. These past results motivated this study to investigate how additional complexity in the silyl ketene may influence the enantioselectivity and diastereoselectivity of the addition product. Herein, a silanediol catalyst was demonstrated to afford desirable products in the addition of methyl propionate derived silyl ketene acetals to activated chromenones.

Our studies found 2-alkyl chroman-4-ones could be synthesized using methyl propionate derived silyl ketene acetals with moderate diastereoselectivity but no enantiomeric excess. The silyl ketene acetals were produced as a mixture of the Z/E isomers, with slight favoritism towards the Z isomer. The addition product, in all investigations, demonstrated moderate preference to the same orientation of the methyl group as in the Z silyl ketene acetal, as indicated by the diastereoselectivity favoring R at that position. The diastereocontrol and yields were also found to be responsive to the variation of other reaction conditions, such as the temperature at which the benzopyrilium ion is generated, the catalyst, and the amount of base. However, silanediol was unable to catalyze the enantioselective synthesis of 2-alkyl chroman-4-ones. Ongoing studies in our laboratory are exploring different hydrogen bond donor catalysts in this reaction in an effort to obtain a highly diastereoselective and enantioselective process.

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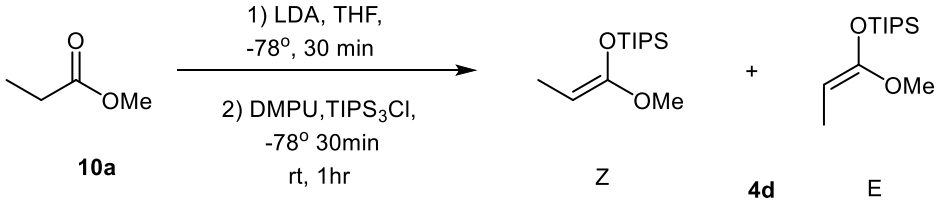
Appendix 1: Procedures

General Methods

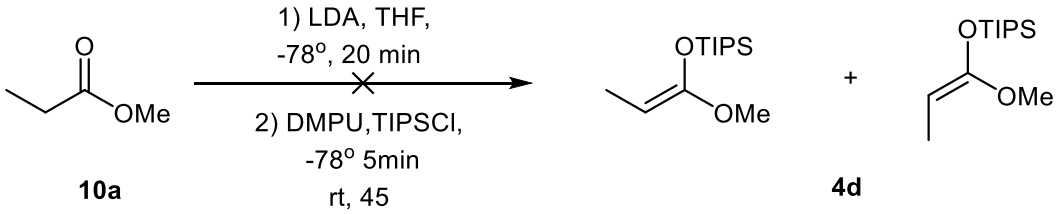
Tetrahydrofuran, hexanes, ethyl acetate, and toluene were used as received. Diisopropylamine was distilled with sodium hydroxide prior to use. The silanediol catalyst, thiourea catalyst, and squaramide were prepared according to literature method. [9] Unless otherwise noted, all other commercially available reagents and solvents were used without further purification. Analytical thin layer chromatography was performed using Analtech 250 µm silica gel HLF plates and visualized under UV 254nm. All ^{1}H NMR spectra were acquired using a Bruker BioSpin 500MHz Avance III Digital NMR spectrometer and calibrated using the solvent signal (CDCl3 7.26 ppm). ^{1}H NMR splitting patterns are designated as singlet (s), doublet (d), or multiplet (m). Chiral HPLC analysis was performed using an Agilent 1260 equip with a diode array detector.

A



(4d) Triisopropyl ((1-methoxyprop-1-en-1-yl)oxy)silane was prepared according to an established procedure. [5] A 50 mL round bottom equipped with a stir bar was flame dried and purged with $N_{2(g)}$. The round bottom was placed under positive pressure of $N_{2(g)}$. Anhydrous THF (10mL) was added followed by distilled diisopropylamine (0.83mL , 6 mmol, 1.2 eq). The round bottom was placed in an ice bath and allowed to cool to 0° C. N-BuLi (2.25 mL of 2.44M in hexanes, 5.5 mmol, 1.1 eq) was added dropwise. The reaction mixture was allowed to stir for 20 min at 0º C. The round bottom was then placed in an acetone/dry ice bath and allowed to cool to -78º C. Methyl propionate **10a** (0.481 mL, 5 mmol, 1 eq) was added drop wise. The reaction mixture was allowed to stir at -78ºC for 30 min. DMPU (0.9mL, 7.5 mmol, 1.5 eq) was added followed by TIPSCl (1.285 mL, 6 mmol, 1.2 eq). The reaction mixture stirred at -78º C for 30 min before being removed from the bath and stir at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure and diluted with hexanes. The crude was washed with DI H_2O (20mL), saturated Cu(II)SO_4 solution (20mL), saturated sodium bicarbonate solution (20mL) and brine (20mL). The crude was dried using sodium sulfate and concentrated under reduced pressure. The resulting yellow oil was used without further purification as the title compound **4d**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.54, 3.69(s, 3H), 1.55,1.80 (d, 3H), 1.07-1.17, 1.14-1.21 (m, 6H), 0.95-1.07, 1.14-1.17 (m, 3H).

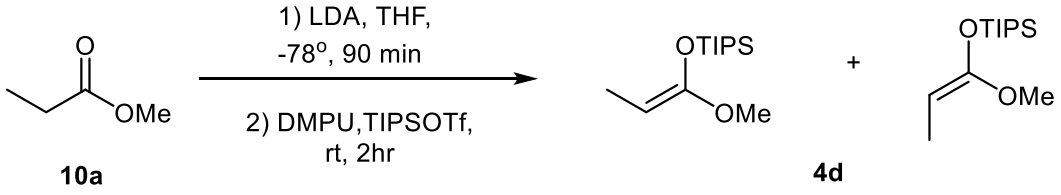
B



10a **4d**

(4d) Triisopropyl ((1-methoxyprop-1-en-1-yl)oxy)silane was prepared according to an established procedure. [7] A 50 mL round bottom equipped with a stir bar was flame dried and purged with $N_{2(g)}$. The round bottom was placed under positive pressure of $N_{2(g)}$. Anhydrous THF (5mL) was added followed by distilled diisopropylamine (0.70mL , 5 mmol, 1 eq). The round bottom was placed in an ice bath and allowed to cool to 0º C. N-BuLi (2.05 mL of 2.44M in hexanes, 5 mmol, 1 eq) was added dropwise. The reaction mixture was allowed to stir for 3 min at 0º C. The round bottom was then placed in an acetone/dry ice bath and allowed to cool to -78º C. THF (5mL) was added followed by methyl propionate **10a** (0.481 mL, 5 mmol, 1 eq) was added drop wise. The reaction mixture was allowed to stir at -78º C for 20 min. DMPU (3.975 mL, 33 mmol, 6.6 eq) was added followed by TIPSCl (1.177 mL, 5.5 mmol, 1.1 eq). The reaction mixture stirred at -78º C for 5 min before being removed from the bath and stir at room temperature for 45 min. The reaction mixture was quenched with saturated sodium bicarbonate solution (10 mL) and diluted with hexanes. The reaction mixture was extracted with DI H_2O (4 x 50mL). The resulting solution was dried using sodium sulfate and concentrated under reduced pressure. No product **4d** was observed by ^{1}H NMR spectroscopy.

C

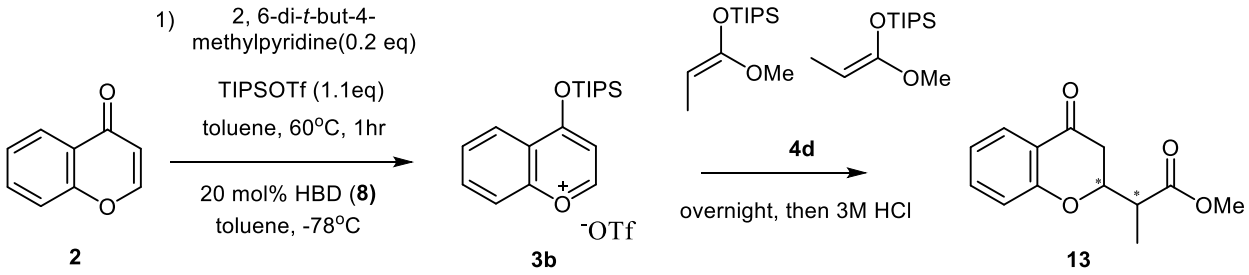


10a **4d**

(4d) Triisopropyl ((1-methoxyprop-1-en-1-yl)oxy)silane was prepared according to an established procedure. [10] A 50 mL round bottom equipped with a stir bar was flame dried and purged with $N_{2(g)}$. The round bottom was placed under positive pressure of $N_{2(g)}$. Anhydrous THF (10mL) was added followed by distilled diisopropylamine (1.05mL, 7.5 mmol, 1.5 eq). The round bottom was placed in an ice bath and allowed to cool to 0º C. N-BuLi (2.87 mL of 2.44M in hexanes, 7 mmol, 1.4 eq) was added dropwise. The reaction mixture was allowed to stir for 30 min at 0º C. The round bottom was then placed in an acetone/dry ice bath and allowed to cool to

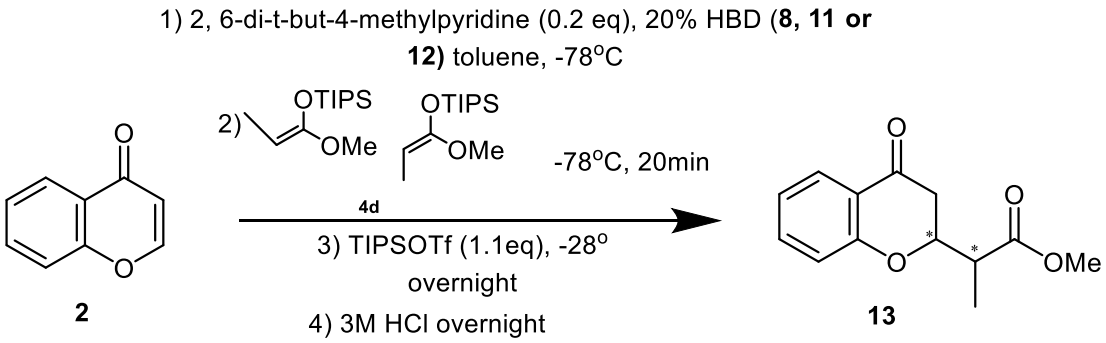
-78º C. Methyl propionate **10a** (0.481 mL, 5 mmol, 1 eq) was added drop wise. The reaction mixture was allowed to stir at -78º C for 90 min. TIPSOTf (1.34mL, 5.5 mmol, 1.1 eq) was added and the round bottom was removed from the bath and stir at room temperature for 2 h. The reaction mixture was filtered through celite with hexanes. The resulting solution was dried using sodium sulfate and concentrated under reduced pressure. The resulting yellow oil was used without further purification as the title compound **4d**.[1]H NMR (500 MHz, $CDCl_3$) δ 3.59, 3.63(s, 3H), 1.57, 1.82 (d, 3H), 1.11-1.15, 1.24-1.32 (m, 6H), 0.85-0.92, 1.21-1.25 (m, 3H).

D



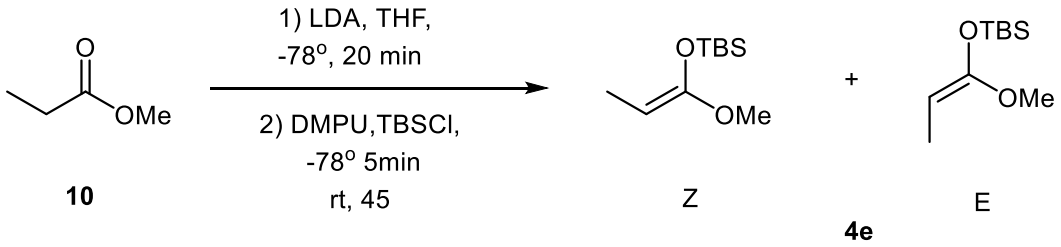
(13) Methyl 2-(4-ocochroman-en-yl) propanoate was prepared according to an established procedure. [5] Chromanone **2** (0.0146 g, 0.1 mmol, 1 eq) and 2,6- di-*t*-Bu-4-methyl pyridine (0.0065 g, 0.03 mmol, 0.3eq) were added to a flame dried vial with a stir bar. The vial was purged with $N_{2(g)}$ and toluene (0.2 mL) were added. TIPSOTf (0.03 mL, 0.11 mmol, 1.1 eq) was added and the vial was heated at 60ºC for 1 h. The vial was removed from the heat and allowed to cool to room temperature. Toluene (1.8 mL) was added. The reaction mixture was the placed in a dry ice/acetone bath and allowed to cool to -28º C. A solution of the silanediol catalyst **8** (12.6mg, 0.02mmol, 0.2eq) in 0.5mL toluene was added slowly down the sides of the vial. After 10 min, Silyl ketene acetal **4d** (0.125 mL of 1 M in toluene, 0.125 eq) was added to the vial. The vial was removed from the acetone/dry ice bath and placed in the freezer to stir at -28º C overnight. The reaction mixture was removed from the freezer, HCl (0.2 mL of 3M, 6eq) was added, and the reaction was allowed to stir at room temperature overnight. The reaction mixture was diluted with H_2O (1mL) and extracted with ethyl acetate (1mL x 3). Dried with sodium sulfate and concentrated under reduced pressure. Product collected via preparative TLC plates (20:80 ethyl acetate:hexanes solvent system). The yield of the desired product **13** was determined by [1]H NMR spectroscopy using 1,3,5-trimethoxy benzene as the reference. [1]H NMR (500 MHz, $CDCl_3$) δ 7.87, 7.88(m, 1H), 7.47, 7.48 (m, 2H), 6.95, 6.98 (d, 1H), 4.12, 4.68 (d, 1H), 3.74, 3.75 (s, 3H), 2.75-2.83, 2.88-2.97 (m, 1H), 2.68, 2.70 (d, 2H), 1.26, 1.38 (d, 1H).

E



(13) Methyl 2-(4-ocochroman-2-yl) propanoate was prepared according to an established procedure. [5] Chromanone **2** (0.0146 g, 0.1 mmol, 1 eq) and 2,6- di-*t*-Bu-4-methyl pyridine (0.0065 g, 0.03 mmol, 0.3eq) were added to a flame dried vial with a stir bar. The vial was placed in an acetone/dry ice bath and allowed to cool to -78º C. Silyl ketene acetal **4d** (0.125 mL of 1 M in toluene, 0.125 eq) was added to the vial and allowed to stir for 10 min. A solution of the hydrogen bond donor catalyst **(8**, **12**, or **13)** (12.6mg, 0.02mmol, 0.2eq) in 0.5mL toluene was added slowly down the sides of the vial. After 10 min, TIPSOTf (0.03 mL, 0.11 mmol, 1.1 eq) was added. The vial was removed from the acetone/dry ice bath and placed in the freezer to stir at -28º C overnight. The reaction mixture was removed from the freezer, HCl (0.2 mL of 3M, 6eq) was added, and the reaction was allowed to stir at room temperature overnight. The reaction mixture was diluted with H_2O (1mL) and extracted with ethyl acetate (1mL x 3). Dried with sodium sulfate and concentrated under reduced pressure. Product collected via preparative TLC plates (20:80 ethyl acetate:hexanes solvent system). The yield of the desired product 13 was determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxy benzene as the reference. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87, 7.88(m, 1H), 7.47, 7.48 (m, 2H), 6.95, 6.98 (d, 1H), 4.12, 4.68 (d, 1H), 3.74, 3.75 (s, 3H), 2.75-2.83, 2.88-2.97 (m, 1H), 2.68, 2.70 (d, 2H), 1.26, 1.38 (d, 1H).

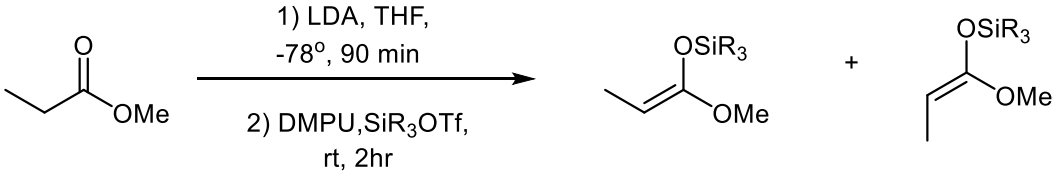
F



(4e) *Tert*- butyl ((1-methoxyprop-1-en-1-yl)oxy)dimethylsilane was prepared according to an established procedure. [7] A 50 mL round bottom equipped with a stir bar was flame dried and purged with $N_{2(g)}$. The round bottom was placed under positive pressure of $N_{2(g)}$.

Anhydrous THF (5mL) was added followed by distilled diisopropylamine (0.70mL , 5 mmol, 1 eq). The round bottom was placed in an ice bath and allowed to cool to 0º C. N-BuLi (2.05 mL of 2.44M in hexanes, 5 mmol, 1 eq) was added dropwise. The reaction mixture was allowed to stir for 3 min at 0º C. The round bottom was then placed in an acetone/dry ice bath and allowed to cool to -78º C. THF (5mL) was added followed by methyl propionate **10** (0.481 mL, 5 mmol, 1 eq) was added drop wise. The reaction mixture was allowed to stir at -78º C for 20 min. DMPU (3.975 mL, 33 mmol, 6.6 eq) was added followed by TIPSCl (1.177 mL, 5.5 mmol, 1.1 eq). The reaction mixture stirred at -78º C for 5 min before being removed from the bath and stir at room temperature for 45 min. The reaction mixture was quenched with saturated sodium bicarbonate solution (10 mL) and diluted with hexanes. The reaction mixture was extracted with DI H_2O (4 x 50mL). The resulting solution was dried using sodium sulfate and concentrated under reduced pressure. The resulting yellow oil was used without further purification as the title compound **4e**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.49, 3.47(s, 3H), 3.27,3.34 (s, 1H), 1.59, 1.51 (d, 3H), 1.11-1.15, 1.24-1.32 (m, 6H), 0.21-0.35, 0.36-0.51 (m, 3H).

G

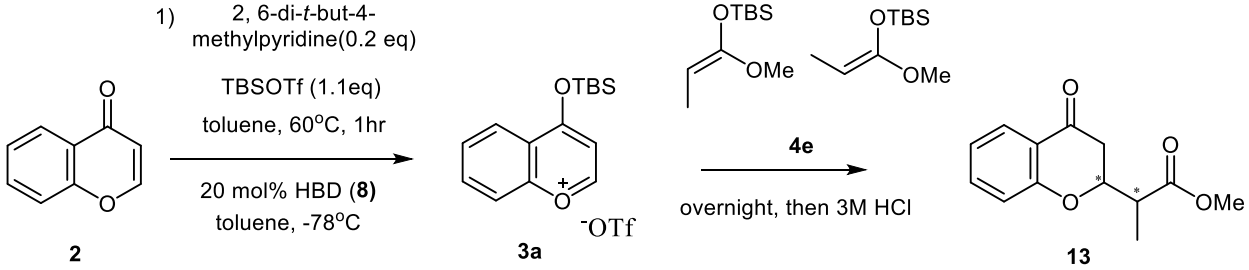


Adapted from United States patent. #9035077

(4e) *Tert*- butyl ((1-methoxyprop-1-en-1-yl)oxy)dimethylsilane was prepared according to an established procedure. [10] A 50 mL round bottom equipped with a stir bar was flame dried and purged with $N_{2(g)}$. The round bottom was placed under positive pressure of $N_{2(g)}$. Anhydrous THF (10mL) was added followed by distilled diisopropylamine (1.05mL, 7.5 mmol, 1.5 eq). The round bottom was placed in an ice bath and allowed to cool to 0º C. N-BuLi (2.87 mL of 2.44M in hexanes, 7 mmol, 1.4 eq) was added dropwise. The reaction mixture was allowed to stir for 30 min at 0º C. The round bottom was then placed in an acetone/dry ice bath and allowed to cool to -78º C. Methyl propionate **10** (0.481 mL, 5 mmol, 1 eq) was added drop wise. The reaction mixture was allowed to stir at -78º C for 90 min. TIPSOTf (1.34mL, 5.5 mmol, 1.1 eq) was added and the round bottom was removed from the bath and stir at room temperature for 2 h. The reaction mixture was filtered through celite with hexanes. The resulting solution was dried using sodium sulfate and concentrated under reduced pressure. The resulting

yellow oil was used without further purification as the title compound **4e**. ^{1}H NMR (500 MHz, CDCl3) δ 3.36 (s, 3H), 3.29 (s, 1H), 1.32 (d, 3H), 0.69-0.76 (m, 6H), 0.02-0.13 (m, 3H).

H



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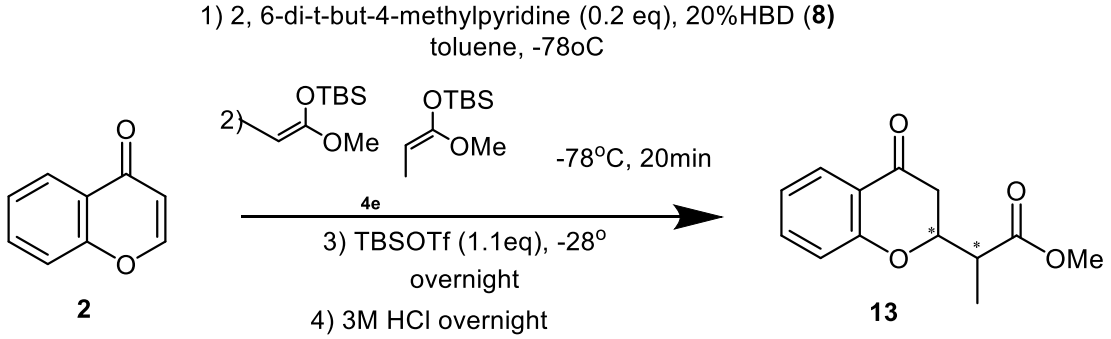
I



(13) Methyl 2-(4-ocochroman-2-yl) propanoate was prepared according to an established procedure.[5] Chromanone **2** (0.0146 g, 0.1 mmol, 1 eq) and 2,6- di-*t*-Bu-4-methyl pyridine

(0.0065 g, 0.03 mmol, 0.3eq) were added to a flame dried vial with a stir bar. The vial was placed in an acetone/dry ice bath and allowed to cool to -78º C. Silyl ketene acetal **4e** (0.125 mL of 1 M in toluene, 0.125 eq) was added to the vial and allowed to stir for 10 min. A solution of the silanediol catalyst **8** (12.6mg, 0.02mmol, 0.2eq) in 0.5mL toluene was added slowly down the sides of the vial. After 10 min, TBSOTf (0.03 mL, 0.11 mmol, 1.1 eq) was added. The vial was removed from the acetone/dry ice bath and placed in the freezer to stir at -28º C overnight. The reaction mixture was removed from the freezer, HCl (0.2 mL of 3M, 6eq) was added, and the reaction was allowed to stir at room temperature overnight. The reaction mixture was diluted with H_2O (1mL) and extracted with ethyl acetate (1mL x 3). Dried with sodium sulfate and concentrated under reduced pressure. Product collected via preparative TLC plates (20:80 ethyl acetate:hexanes solvent system). The yield of the desired product **13** was determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxy benzene as the reference. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87, 7.88(m, 1H), 7.47, 7.48 (m, 2H), 6.95, 6.98 (d, 1H), 4.12, 4.68 (d, 1H), 3.74, 3.75 (s, 3H), 2.75-2.83, 2.88-2.97 (m, 1H), 2.68, 2.70 (d, 2H), 1.26, 1.38 (d, 1H).

Appendix 2: Analytical Techniques

Characterization of Compounds

^{1}H NMR spectroscopy was primarily used to confirm the composition of the starting materials and products. ^{1}H NMR (Proton Nuclear Magnetic Resonance) spectroscopy uses magnetic fields to verify the organization of hydrogens within a molecule.[11] The organic molecules of interest in this investigation could be reliably identified using characteristics of the spectra such as number of peaks, chemical shift, and splitting patterns (See Appendix 1 for the identification of the protons in each compound). All ^{1}H NMR spectra were obtained in $CDCl_3$ solutions.

^{1}H NMR spectroscopy was also used to determine the yield of the addition reaction. A known quantity (between 0.005-0.010 g) of the internal standard, 1, 3, 5-trimethoxy benzene, was added to the crude of the product prior to purification via preparative TLC. This standard produces a peak representing 3 protons in the ^{1}H NMR spectra at 6ppm. The integration of that signal was calibrated to 3. A peak known to be only corresponding to the desired product was subsequently integrated. The following values were entered into an "NMR assay" excel sheet that then calculated the yield of the desired product: mass of internal standard, integration of product peak, number of protons the product peak represents.

Determination of isomer ratio

After confirming the identity of the products, the orientation of the methyl group needed to be determined. This orientation established the E:Z ratio of the silyl ketene acetal and the ratios of diastereomers in the chromanone. ^{1}H NMR spectroscopy was also used to elucidate these ratios. The presence of the two diastereomers or isomers presented themselves as multiplicities in the spectra. The compounds of interest in this investigation showed the most distinct multiplicity at approximately 3.66ppm. When the purified compound exists as a mixture

of isomers, there are two peaks representing the singlet. This phenomenon was noted by Ireland and co-workers. They found that, in silyl ketene acetals, the E isomer resulted in a peak present at a slightly higher ppm than the Z isomer.[7] This trend is assumed to apply to the compounds of this investigation as well. The diastereomers reflect a similar pattern in which one isomer (the S) produces a peak at a slightly higher ppm than the other. The S was determined to be the higher peak because the J coupling constant between the proportionally sized peaks in the rest of the molecule were found to be larger than that of the peaks proportional to the other diastereomer peak. This indicates that the hydrogens attached to adjacent carbons would be closer to each other in the dominant isomer than how they would be in the non-dominant isomer.[12] The S isomer positions the groups in this way and therefore, is represented by the larger peak at the same position as the peak of the Z isomer. The ratio between the isomers is then determined as the ratio of the integrated values of each peak.

Determination of Enantioselectivity

The enantioselectivity of the addition at the 2 position of the chromenone was determined using High Performance Liquid Chromatography (HPLC). In this method, the purified product is flushed through the HPLC using a 10% pentanol in hexane mixture in a OD-H column. After approximately 10 minutes, both enantiomers and diastereomers become separated. This is evident in the spectra that shows four separate and distinct peaks as shown in figure 4. Peaks 1 and 2 correspond to the R isomer. Peak 1 represents R,R and Peak 2 represents R,S. Peaks 3 and 4 correspond to the S isomer, in which Peak 3 is S,S and Peak 4 is S,R.

Figure 7

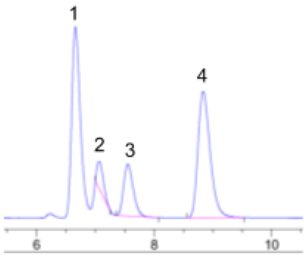
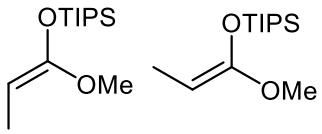


Figure 7 depicts the peaks representing the different enantiomers and diastereomers of the product: Peak 1- R,R; Peak 2-R,S, Peak 3-S,S, Peak 4-S,R

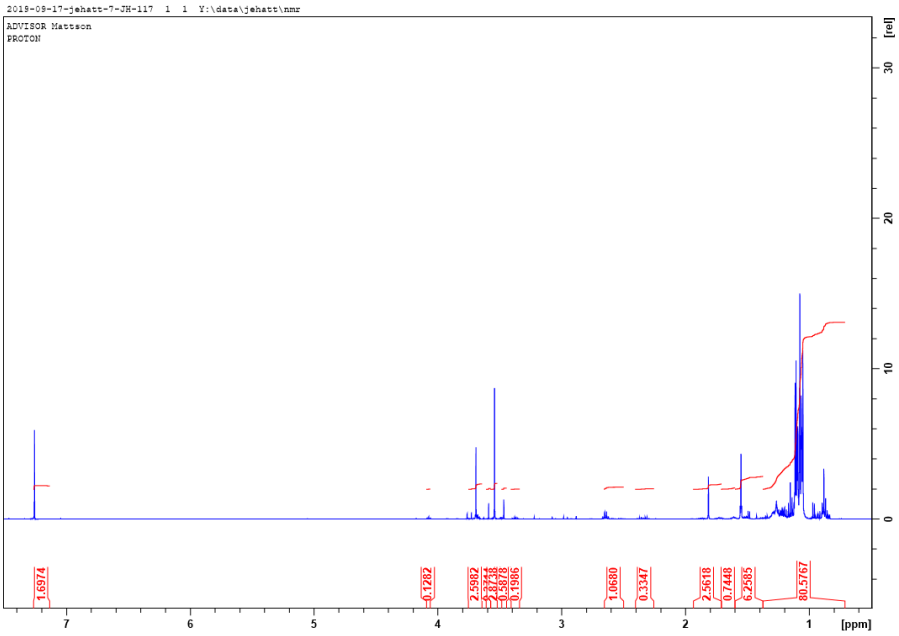
Appendix 3: ^{1}H NMR

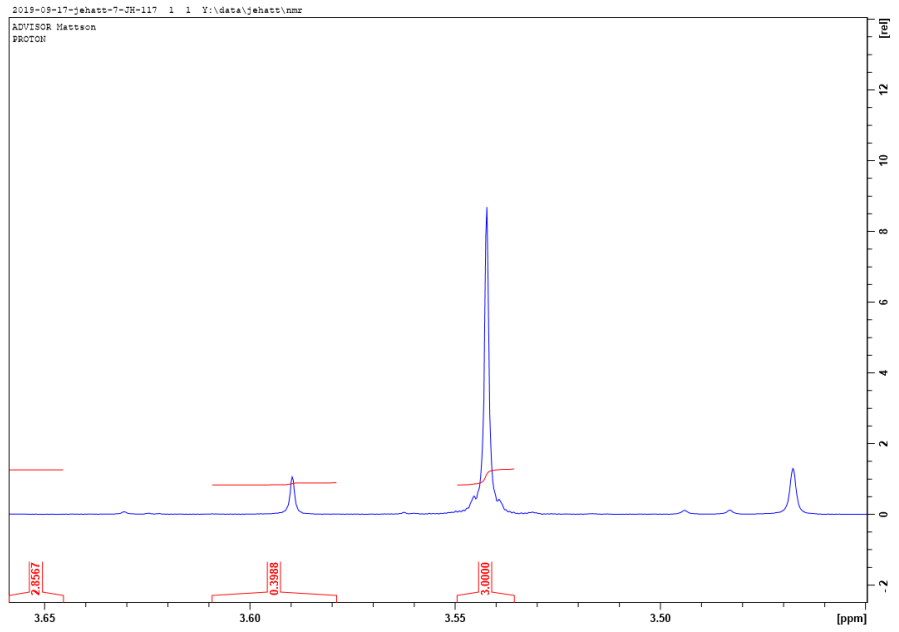
Triisopropylsilyl Ketene Acetals



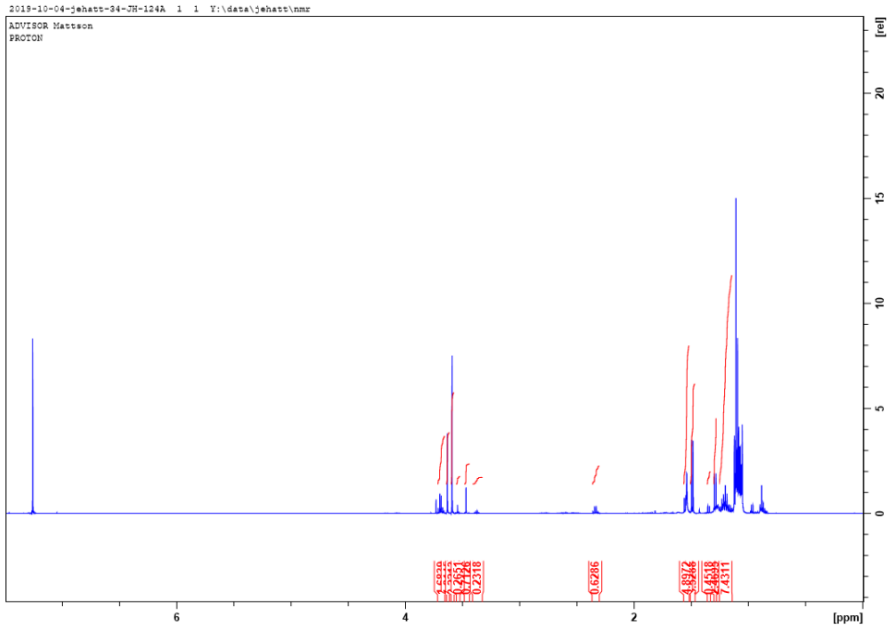
4d

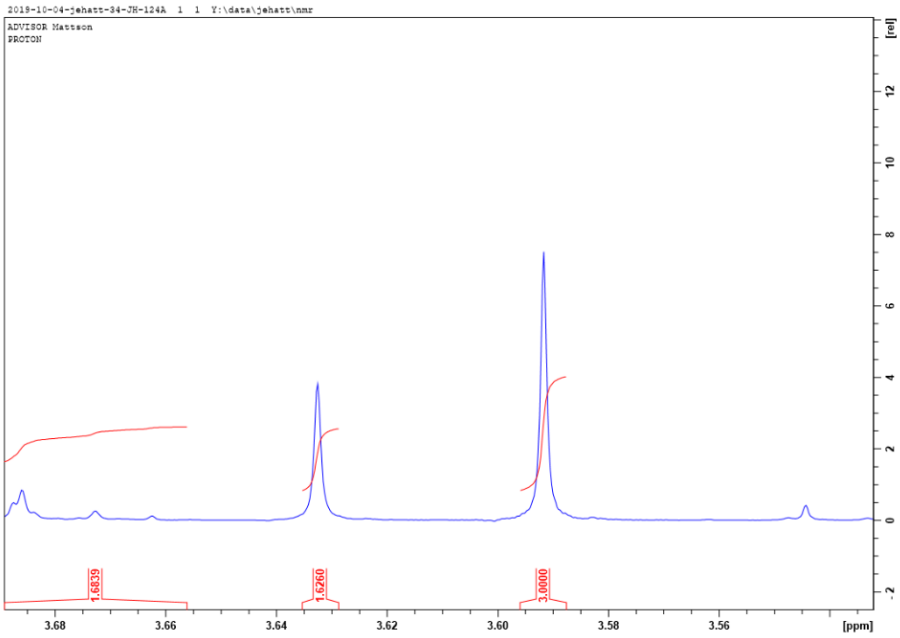
JH-117 (Reaction 1)



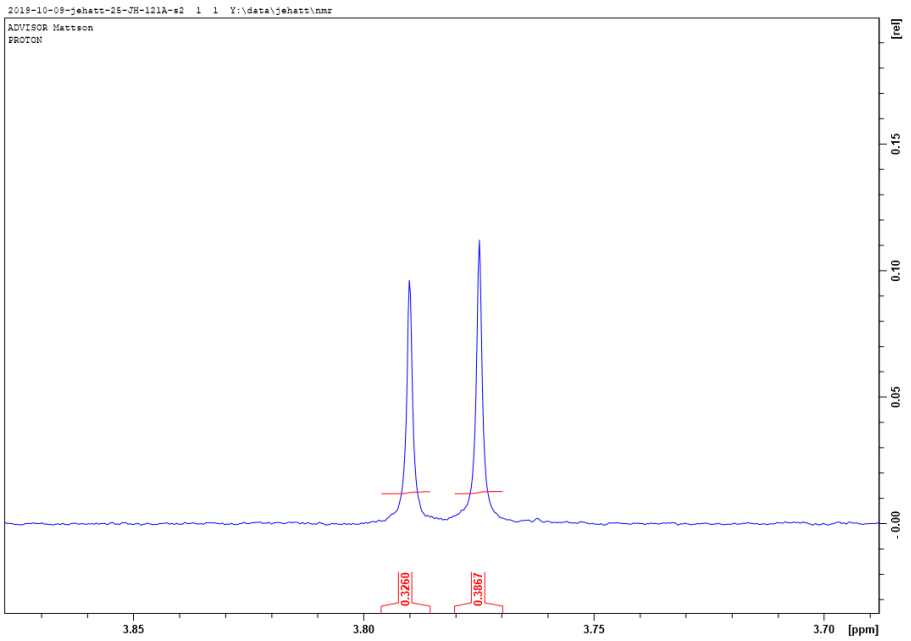


JH-124 (Reaction 3)

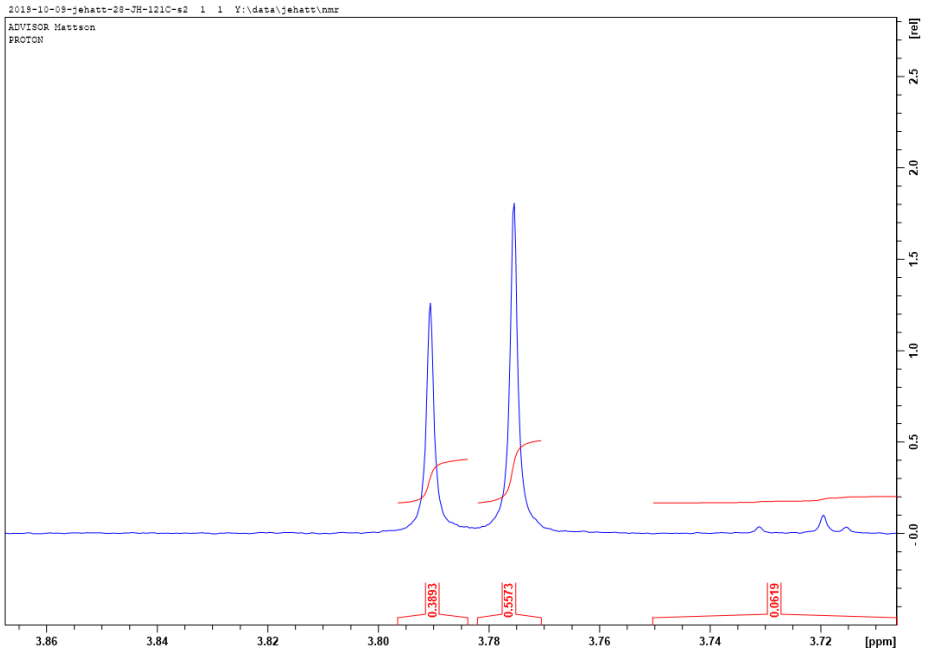




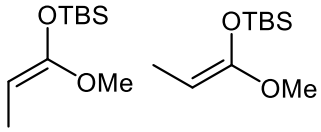
Comparison of the addition products when using Reaction 1 vs Reaction 2 silyl ketene acetals
Reaction 1 product



Reaction 2 product

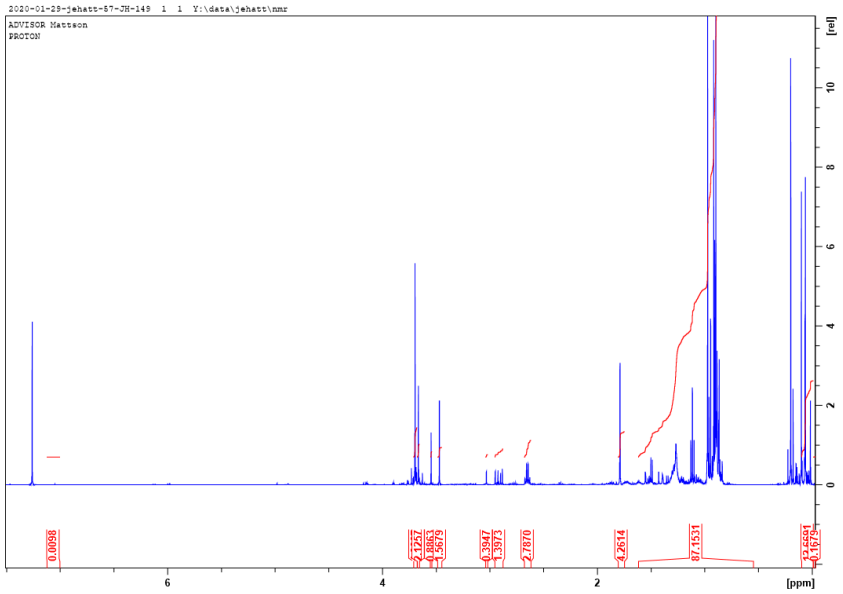


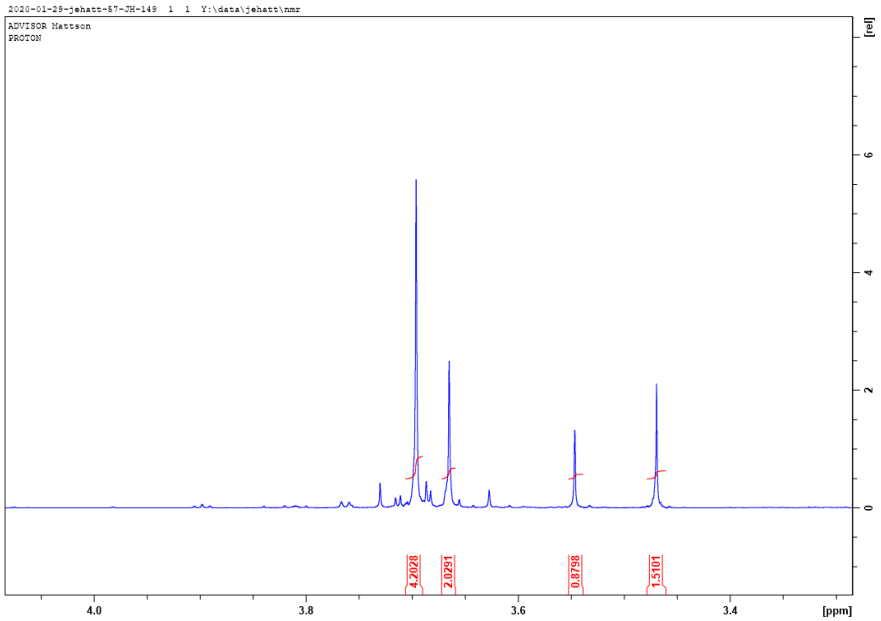
Tert-Butyldimethylsilyl ketene acetals



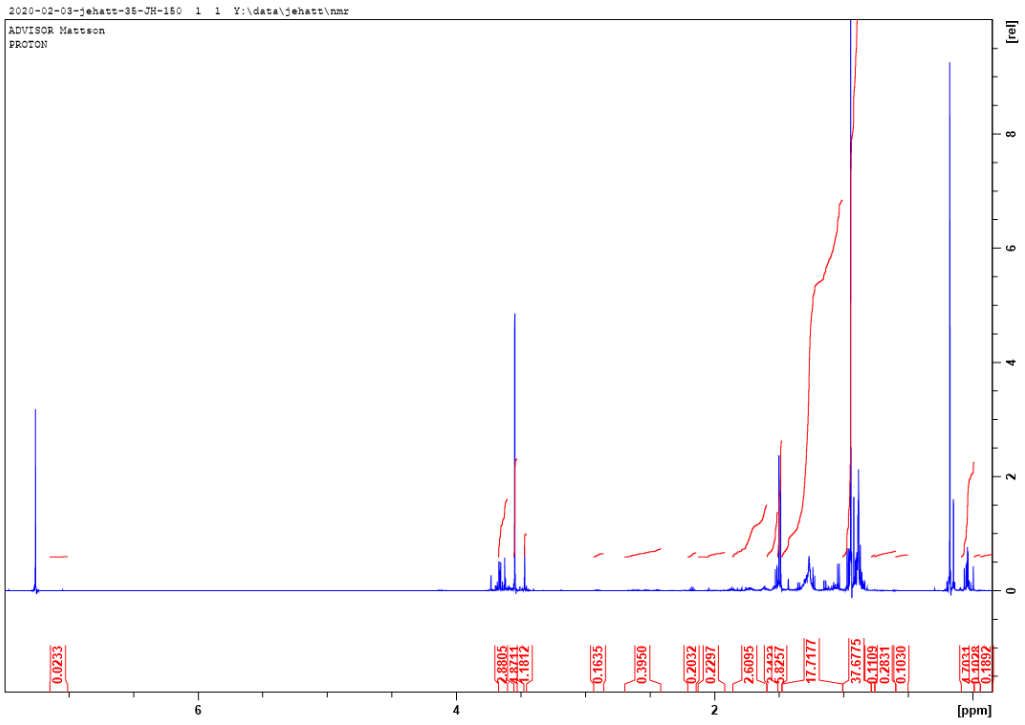
4e

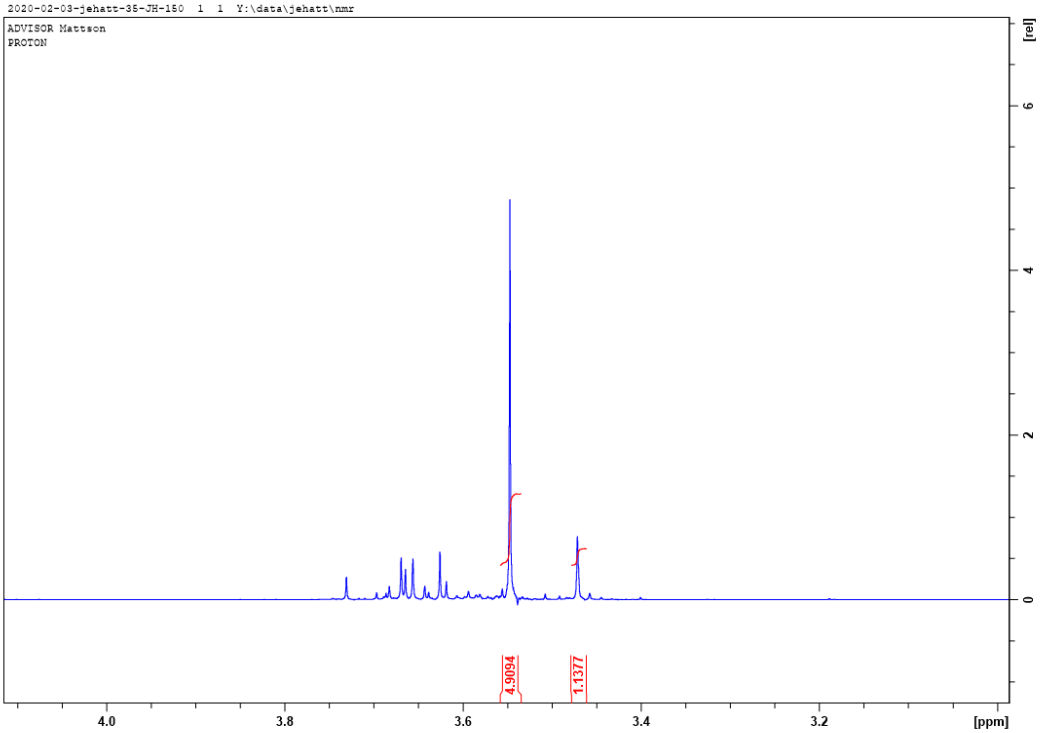
JH- 149 (Reaction A)



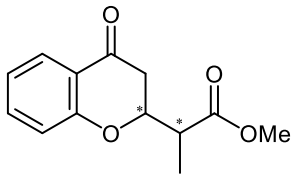


JH-150 (Reaction B)

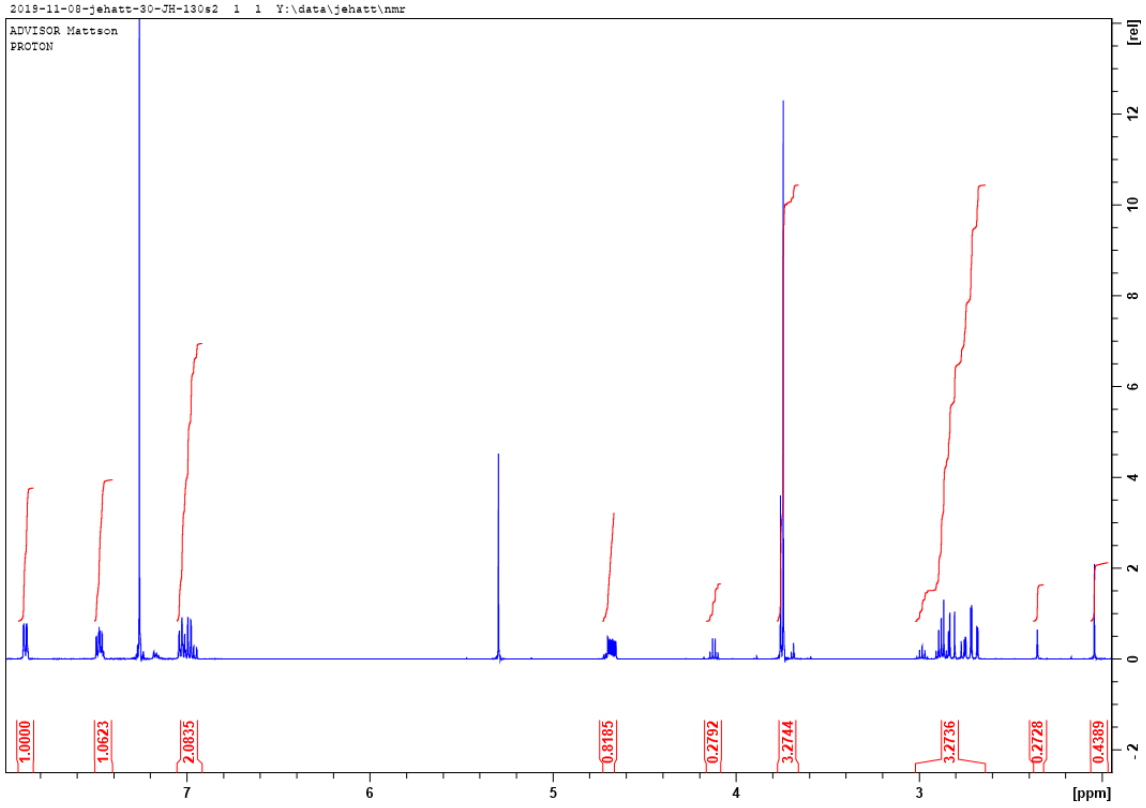




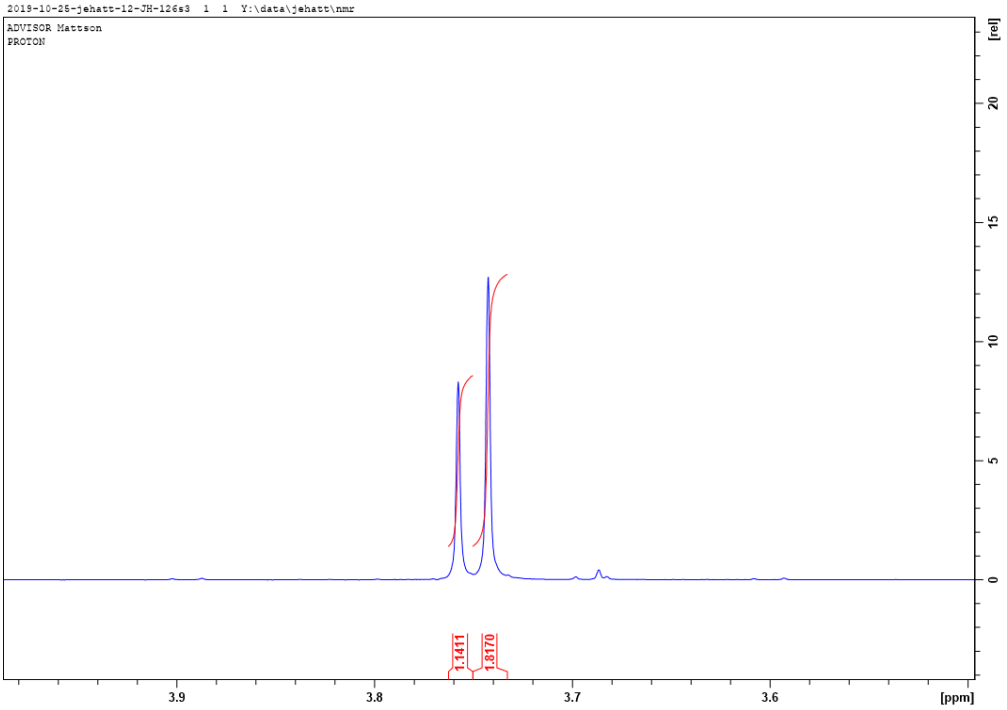
Functionalized Chromanone



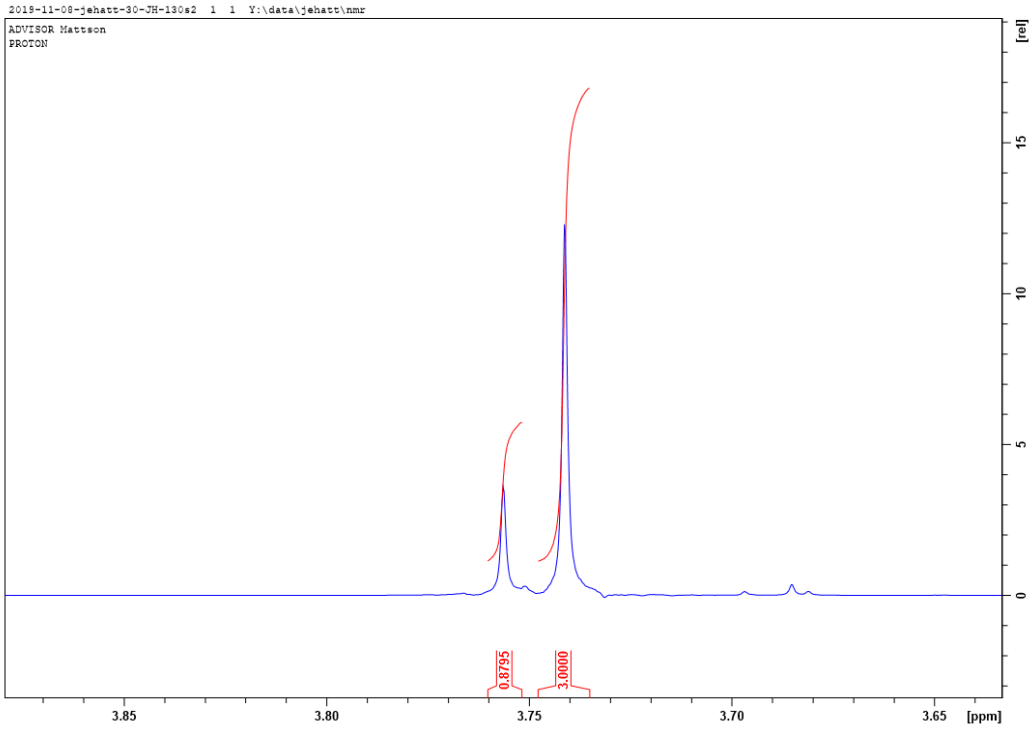
13



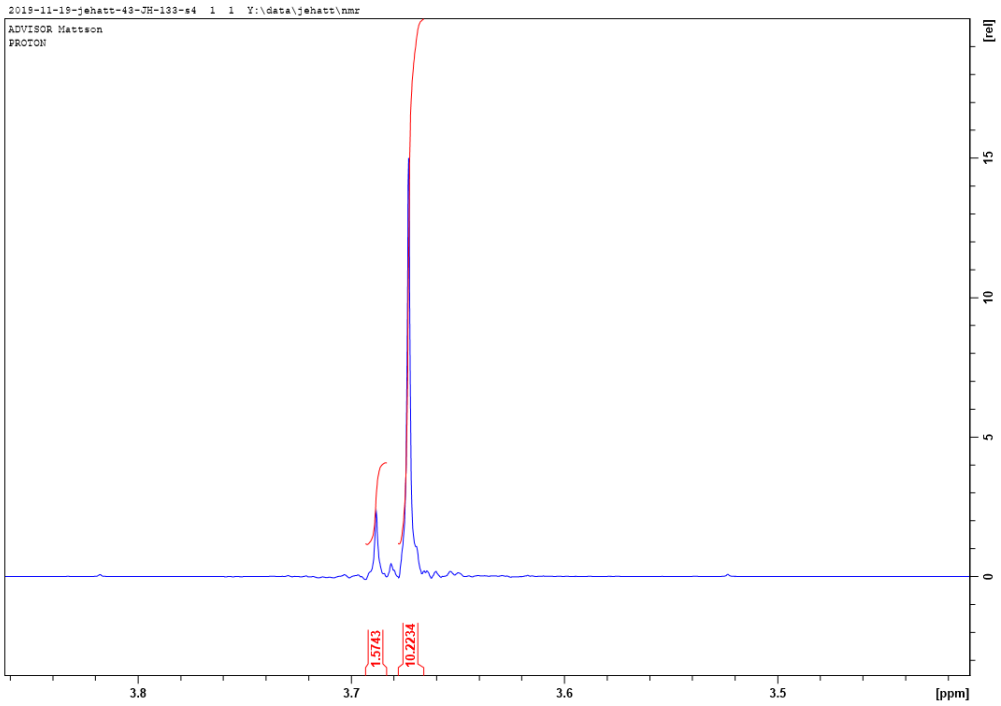
JH-126


2019-10-25-jehatt-12-JH-126s3 1 1 Y:\data\jehatt\nmr
ADVISOR Mattson
PROTON
[rel]
20
15
10
5
0
1.1411
1.8170
3.9
3.8
3.7
3.6
[ppm]

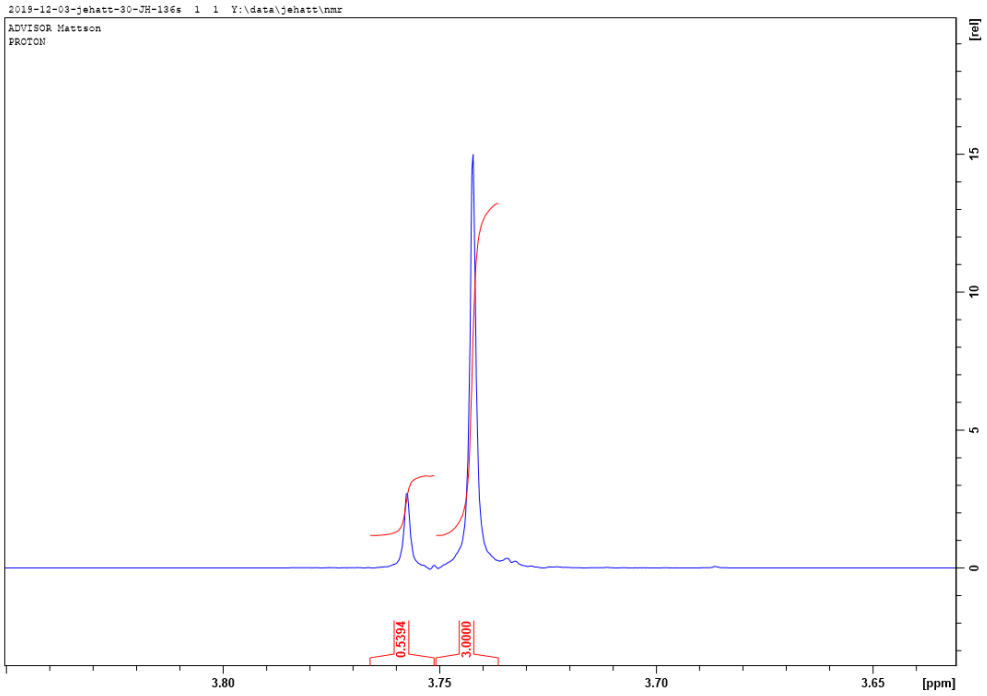
JH-130


2019-11-08-jehatt-30-JH-130s2 1 1 Y:\data\jehatt\nmr
ADVISOR Mattson
PROTON
[rel]
15
10
5
0
0.8795
3.0000
3.85
3.80
3.75
3.70
3.65
[ppm]

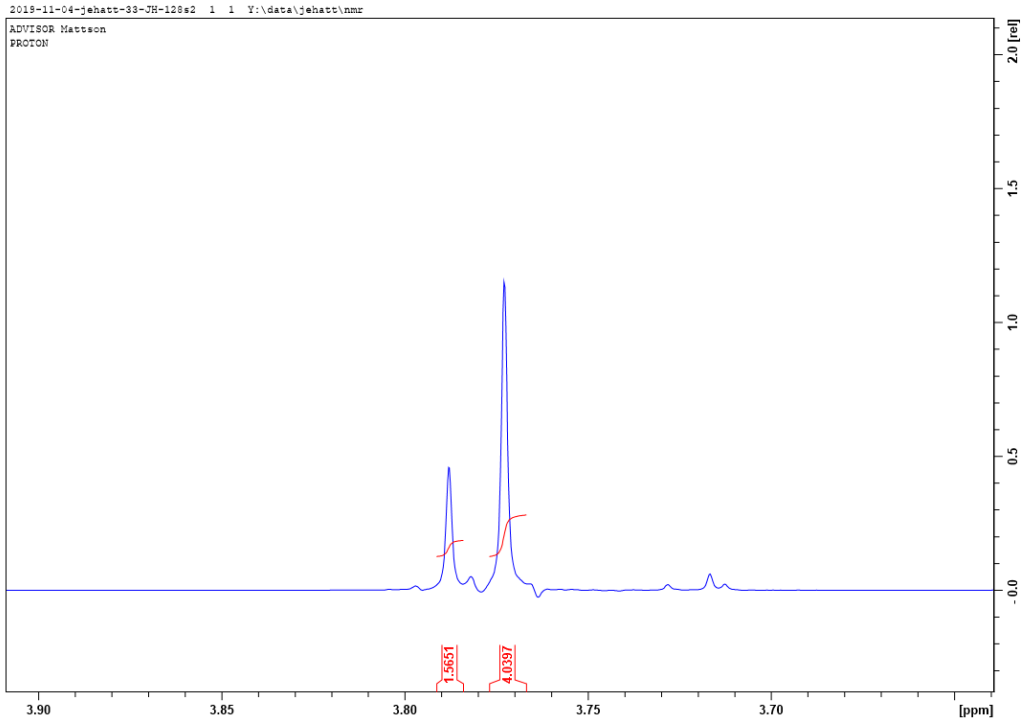
JH-133


2019-11-19-jehatt-43-JH-133-s4 1 1 Y:\data\jehatt\nmr
ADVISOR Mattson
PROTON
[rel]
15
10
5
0
1.5743
10.2234
3.8
3.7
3.6
3.5
[ppm]

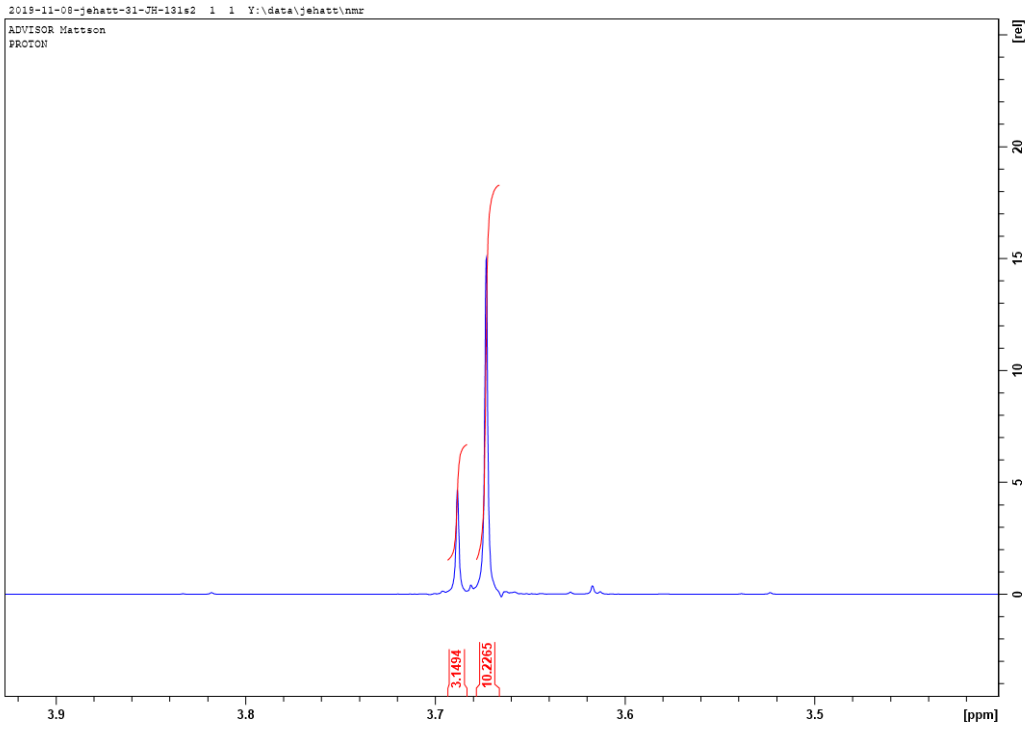
JH-136


2019-12-03-jehatt-30-JH-136s 1 1 Y:\data\jehatt\nmr
ADVISOR Mattson
PROTON
[rel]
15
10
5
0
0.5394
3.0000
3.80
3.75
3.70
3.65
[ppm]

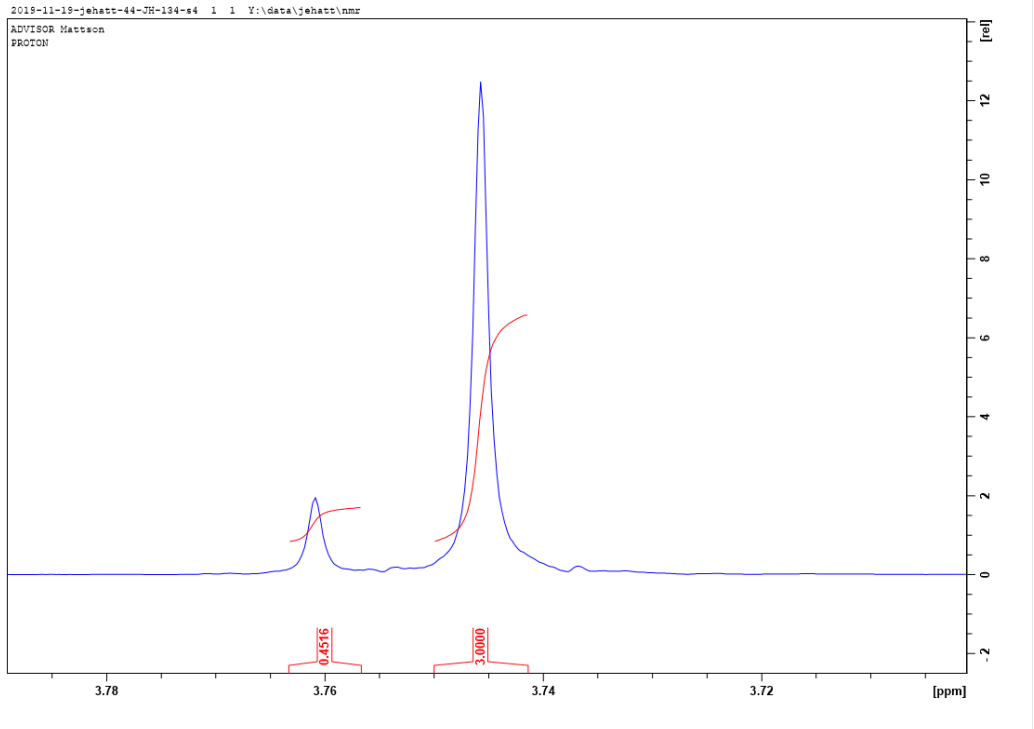
Triisopropylsilyl Modified Procedure
JH-128



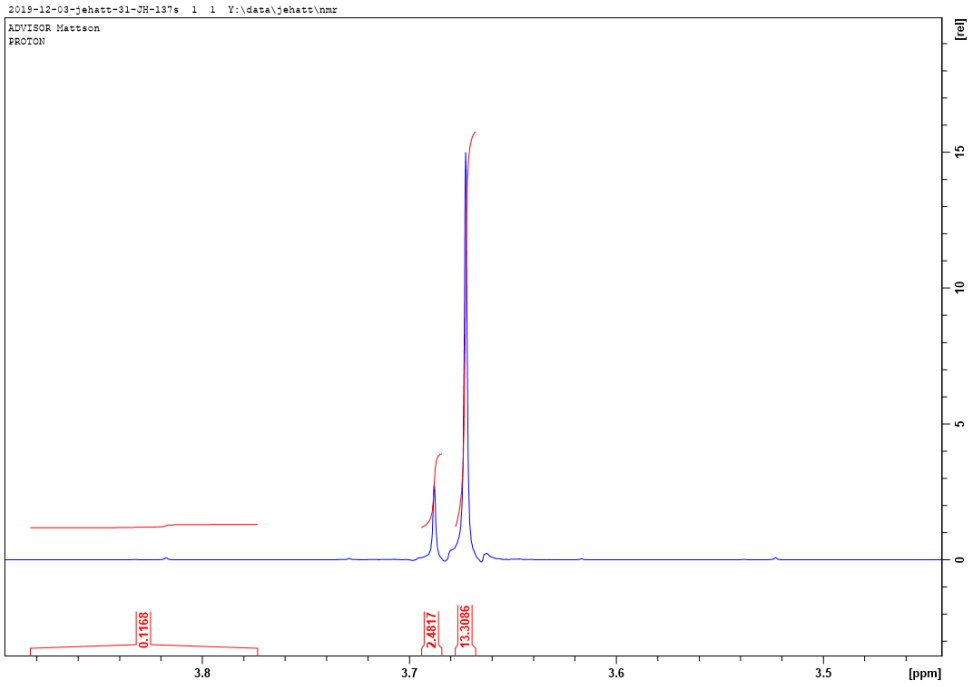
JH-131


2019-11-08-jehatt-31-JH-131s2 1 1 Y:\data\jehatt\nmr
ADVISOR Mattson
PROTON
[rel]
20
15
10
5
0
3.1494
10.2265
3.9
3.8
3.7
3.6
3.5
[ppm]

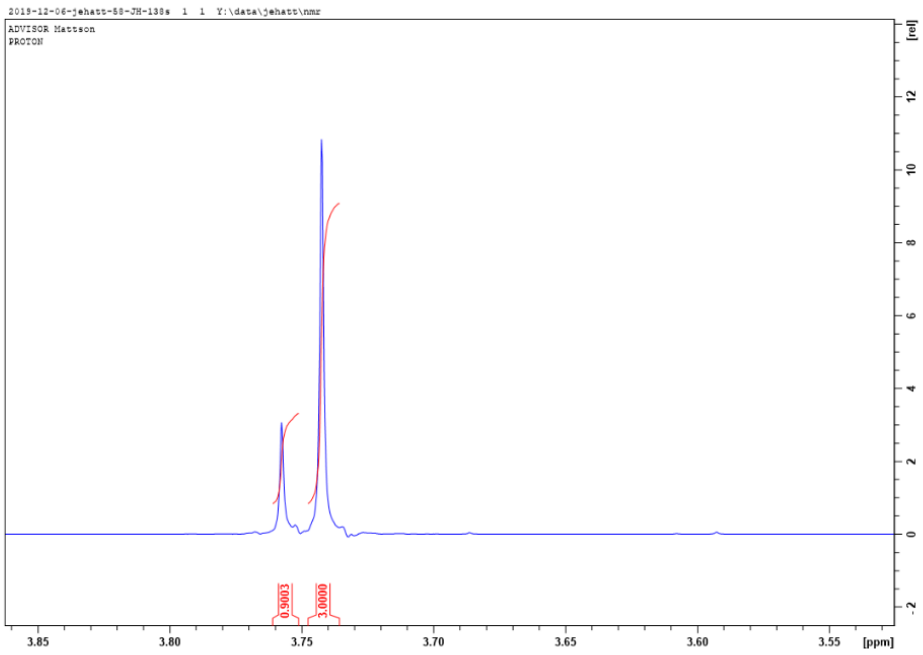
JH-134


2019-11-19-jehatt-44-JH-134-s4 1 1 Y:\data\jehatt\nmr
ADVISOR Mattson
PROTON
[rel]
12
10
8
6
4
2
0
-2
0.4516
3.0000
3.78
3.76
3.74
3.72
[ppm]

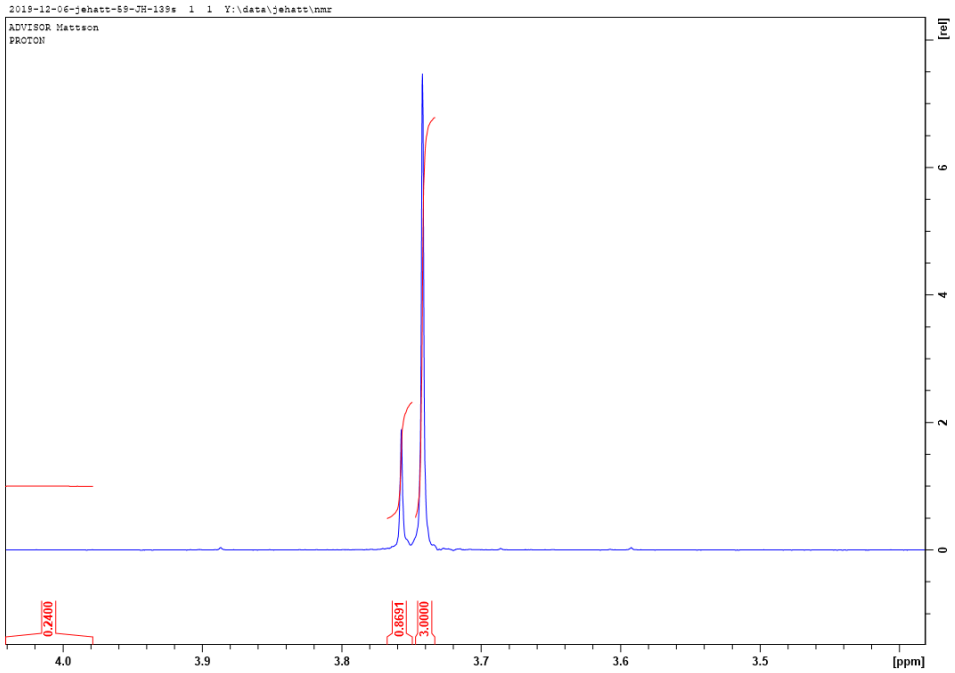
JH-137


2019-12-03-jehatt-31-JH-137s 1 1 Y:\data\jehatt\nmr
ADVISOR Mattson
PROTON
[rel]
15
10
5
0
0.1168
2.4817
13.3086
3.8
3.7
3.6
3.5
[ppm]

JH-138

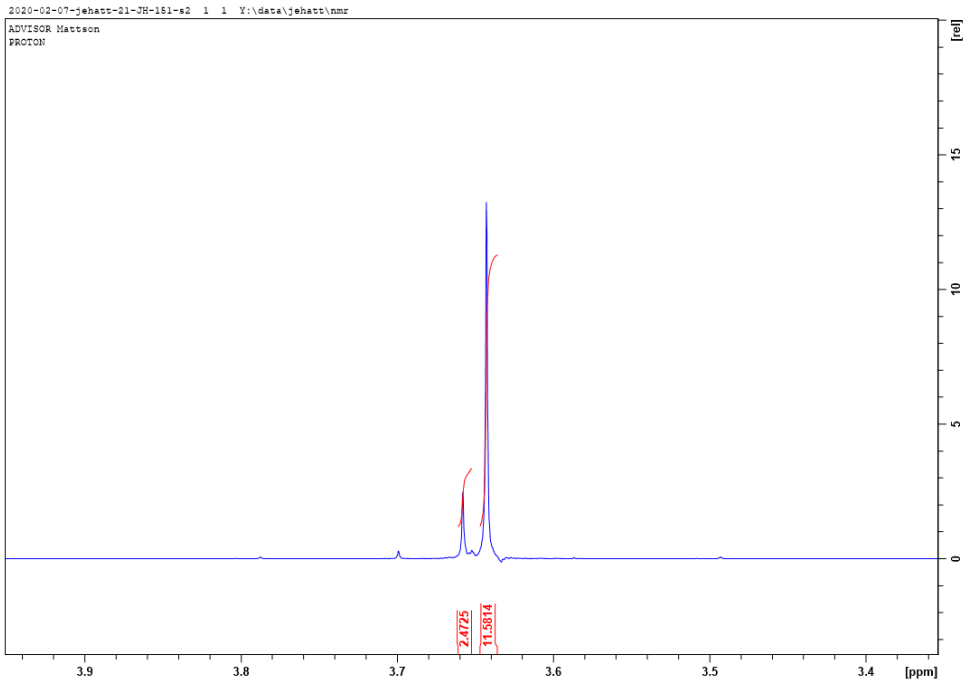

2019-12-06-jehatt-58-JH-138s 1 1 Y:\data\jehatt\nmr
ADVISOR Mattson
PROTON
[rel]
12
10
8
6
4
2
0
-2
0.9003
3.0000
3.85
3.80
3.75
3.70
3.65
3.60
3.55
[ppm]

JH-139

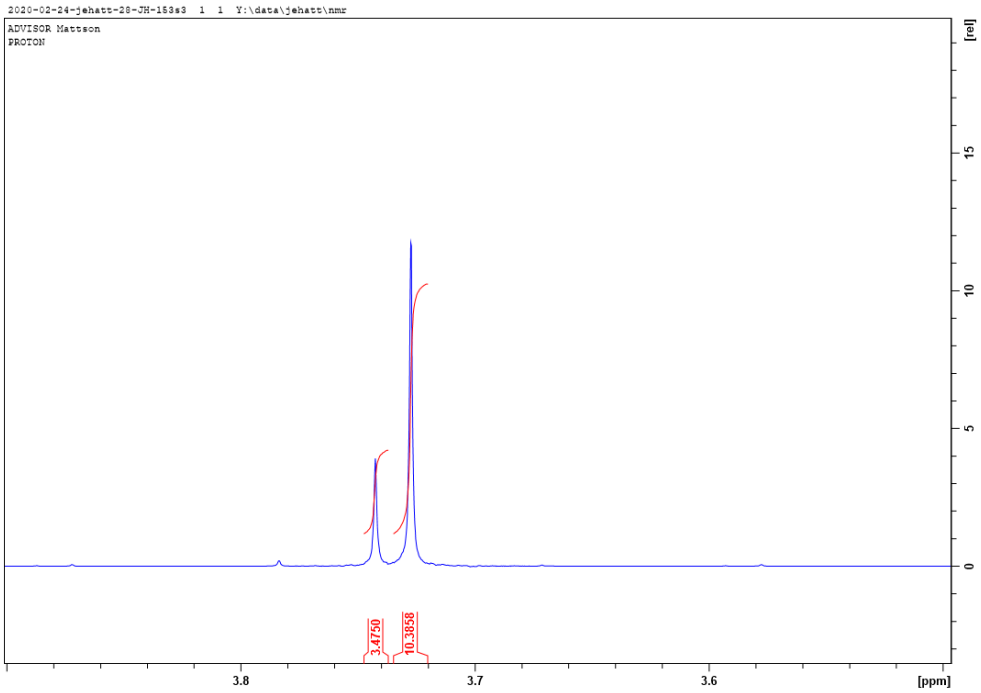


Tert-Butyldimethylsilyl Activated Benzopyrylium Ions

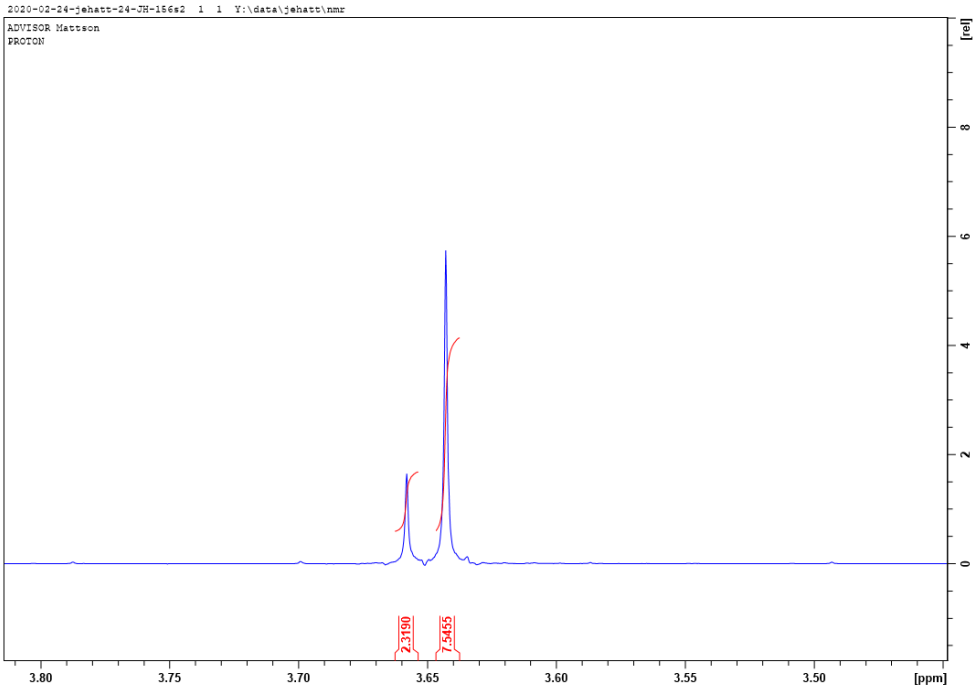
JH-151



JH-153

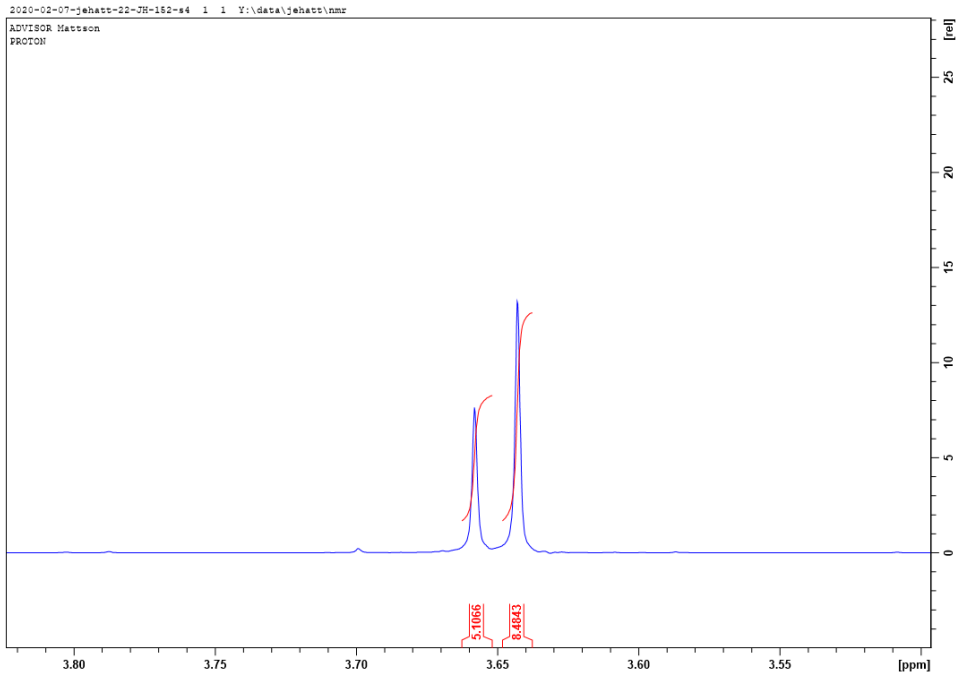

2020-02-24-jehatt-28-JH-153s3 1 1 Y:\data\jehatt\nmr
ADVISOR Mattson
PROTON
[rel]
15
10
5
0
3.4750
10.3658
3.8
3.7
3.6
[ppm]

JH-156

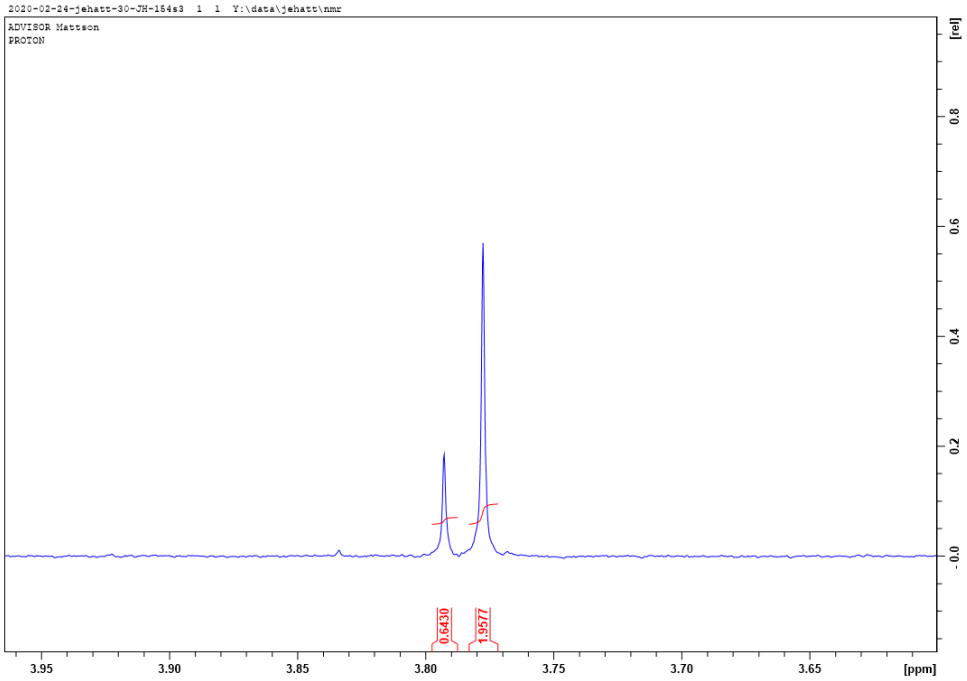

2020-02-24-jehatt-24-JH-156s2 1 1 Y:\data\jehatt\nmr
ADVISOR Mattson
PROTON
[rel]
8
6
4
2
0
2.3190
7.5455
3.80
3.75
3.70
3.65
3.60
3.55
3.50
[ppm]

Tert-Butyldimethylsilyl Modified Procedure

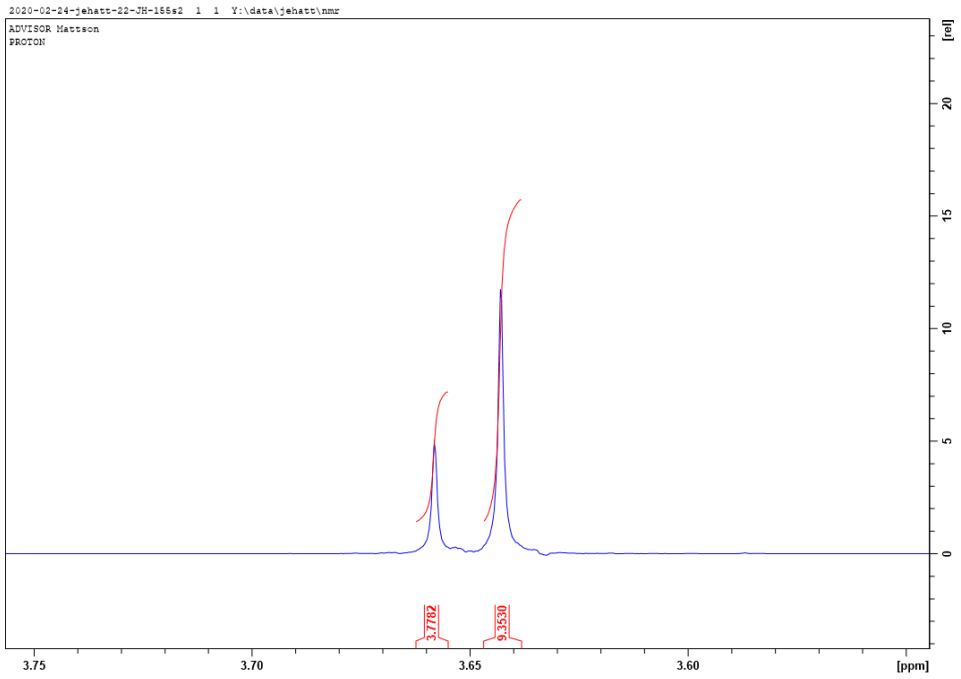
JH-152



JH-154



JH-155


2020-02-24-jehatt-22-JH-155s2 1 1 Y:\data\jehatt\nmr
ADVISOR Mattson
PROTON
[rel]
20
15
10
5
0
3.7782
9.3530
3.75
3.70
3.65
3.60
[ppm]

Appendix 4: HPLC

Entry	Area %			
	R,R	R,S	S,S	S,R
JH-126	31.4	17.5	19.7	31.2
JH-129	41.0	9.4	10.1	39.4
JH-130	42.4	8.7	10.1	38.8
JH-131	43.3	9.4	10.2	37.2
JH-133	47.8	4.1	4.5	43.7
JH-134	48.0	4.4	6.1	41.5
JH-135	40,8	6.2	6.4	46.6
JH-136	44.0	6.1	7.0	42.8
JH-137	44.9	5.5	7.2	42.3
JH-138	41.2	8.5	9.7	40.5
JH-139	41.3	7.9	8.7	42.0
JH-151	43.0	6.6	6.3	44.1
JH-152	31.3	18.2	18.5	31.9
JH-153	38.8	10.9	11.6	38.7
JH-154	33.0	16.9	16.6	33.5
JH-155	37.4	13.3	13.7	35.6
JH-156	37.7	8.7	10.2	43.4