CATALYTIC, ENANTIOSELECTIVE OXYALLYLATION OF ACTIVATED CARBONYL COMPOUNDS

by

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APPROVAL

of a thesis submitted by

Bradley Earl Reaman

This thesis has been read by each member of the thesis committee and has been found to be satisfactory regarding content, English usage, format, citation, bibliographic style, and consistency and is ready for submission to The Graduate School.

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April 2012

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Thanks to my friends who, when in a desperate situation, snuck into my house and stocked my shelves full of much needed food. This isn't the only thing I am grateful for but it's an apt example to summarize my feelings for you. Couldn't have asked for better if I picked myself.

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ABSTRACT

Stereoselective alkylations are a very useful tool in synthetic chemistry and, specifically, natural product synthesis. One such reaction, named the Tsuji-Trost allylation, is a palladium-catalyzed substitution with the overall transformation being the replacement of an allylic leaving group with a nucleophile. First observed in 1965 with the allylation of diethyl malonate[1], and in 1973 made asymmetric with the use of chiral phosphine ligands by B. M. Trost[2], the reaction has been studied and utilized extensively over the years. While there have been many examples of this reaction in the literature, few explore functionalizing the allylic electrophile.

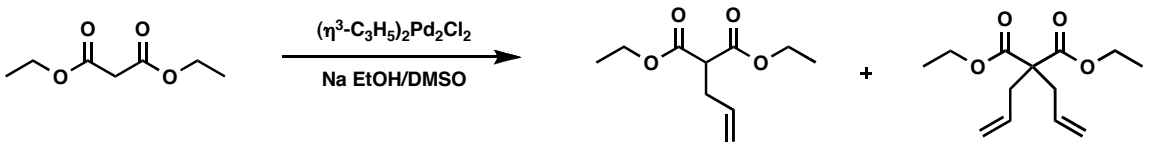
Functionalizing the "2" position of an allylic acetate or carbonate could prove to be a useful synthetic tool. Allylic acetates, chlorides and carbonates bearing a methoxymethyl group at this middle position were synthesized. β-carbonyl ketones which work well under the Tsuji-Trost conditions were also synthesized. Phosphine ligands that provided enantiomeric excess with a variety of nucleophiles in allylic alkylations were used. Upon reaction with a palladium (0) source, the pro-nucleophiles were successfully alkylated in a stereospecific manner.

The work described herein investigates modification of the Tsuji-Trost allylation in which oxy-allylation is carried out with a high yield and high degree of enantioselectivity.

CHEMISTRY OF ALLYLATION

Tsuji-Trost Allylic Alkyaltion

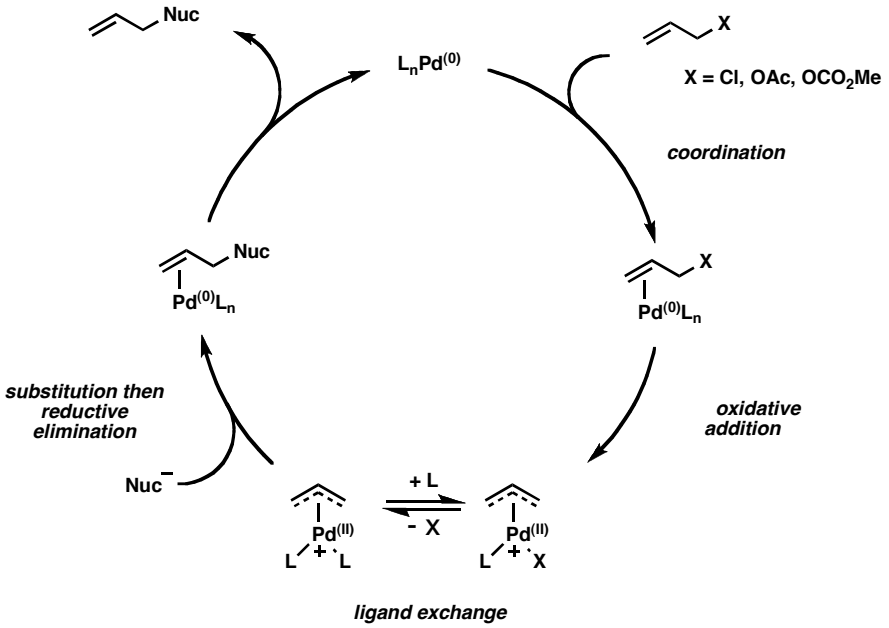
The Tsuji-Trost Reaction has been studied in great depth ever since it's discovery by Jiro Tsuji in 1965. Tsuji reacted diethyl malonate with palladium allyl chloride dimer and sodium ethoxide to create mono- and diallylated products (Scheme 1.1).[1] The ability to construct carbon-carbon bonds to form secondary and tertiary centers is a powerful tool in synthetic chemistry.



Scheme 1.1 Allylation of Diethyl Malonate

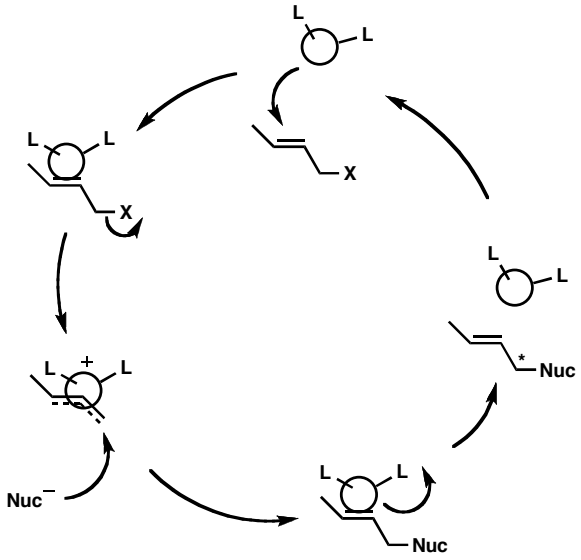
B. M. Trost later made this reaction asymmetric with the introduction of chiral phosphine ligands in 1973.[2] Mechanistically, the reaction involves an allylic leaving group—typically an acetate, chloride or carbonate. This undergoes coordination to a palladium(0) source (Scheme 1.2), which can be used directly or created in situ from a palladium(II) source, followed by oxidative addition. At this point the leaving group is expelled and a π-allyl palladium intermediate is created with inversion of stereochemistry. The nucleophile then attacks, in an outer sphere or inner sphere mechanism at either the distal or proximal carbon of the allylic group. Dissociation of the Pd(0) catalyst then turns the catalytic cycle over. This reaction has been shown to

work with a variety of metal complexes including nickel, platinum, rhodium, ruthenium, tungsten and iron.



Scheme 1.2 Tsuji-Trost Catalytic Cycle

A hard nucleophile, defined as one with a conjugate acid that has a pKa greater than 25, attaches the nucleophile to the metal center followed by "inner sphere" nucleophilic attack and reductive elimination. Conversely, a soft nucleophile, one who's conjugate acid has a pKa less than 25 follows a process in which the nucleophile attacks one enantiotopic end of the π - allyl palladium complex in an "outer sphere" fashion. The present chiral ligand forces preference of the nucleophile to one face over the other (Scheme 1.3). [3]



Scheme 1.3 Outer Sphere Nucleophilic Attack

As previously stated, use of a chiral ligand dictates the stereochemical outcome of the product by forcing nucleophilic attack to one face of the π - allyl palladium complex . Although ligands concentrating on phosphorous-phosphorous bidentate ligands such as CHIRAPHOS and DIOP displayed incredible results in catalytic hydrogenation, less than remarkable results for allylic alkylation were witnessed.[10], [11] Computational means of constructing ligands are currently underway and many other interesting ligands have been discovered, empiracally, which give impressive stereocontrol. These include amino acid derived chirality and ligands utilizing phosphorous-nitrogen, nitrogen-nitrogen and even nitrogen-selenium bidentate chelation (Figure 1.1). The use of ferrocene ligands has also afforded products with impressive selectivity.

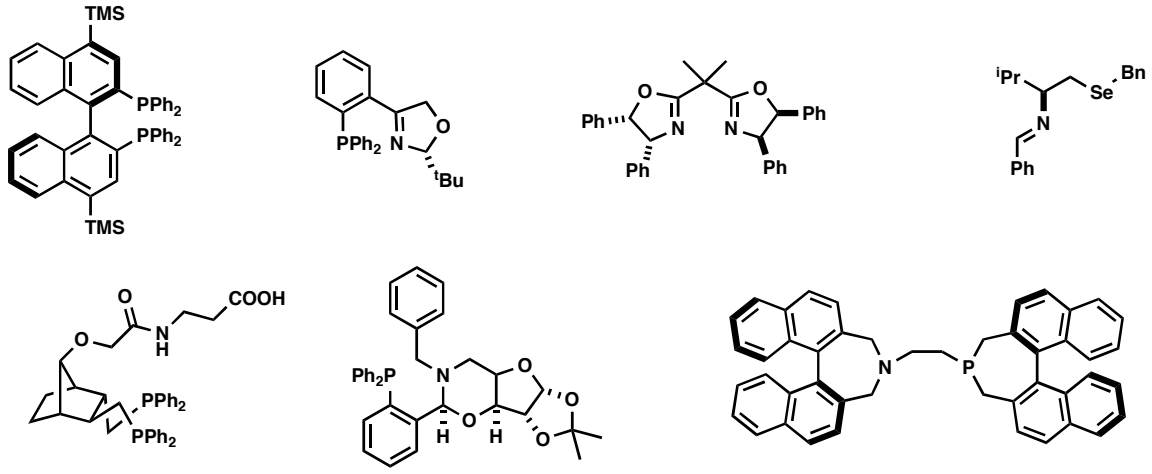


Figure 1.1 Ligands for Asymmetric Allylation

The allylic metal intermediate has been shown to react with a vast number of nucleophiles to form carbon-carbon bonds as well as carbon-oxygen, -nitrogen and -sulfur bonds. This reaction also tolerates a wide range of functional groups and has been used in the construction of many natural products including horsfiline, nigellamine and broussonetine G. [4],[5],[6] The total synthesis of Horsfiline involves the direct allylation of a silyl enol ether indole moiety in a 96% yield and 84% *ee*. Subsequent cyclization and deprotection forms a single stereocenter spirocycle. The total synthesis of Nigellamine incorporates an intramolecular Tsuji-Trost allylation to stereoselectively create a five membered ring with 100% conversion and 95% enantiomeric excess. Broussonetine G utilizes the nitrogen of an oxazolidone as a nucleophile to attack the palladium intermediate of an allylic epoxide.

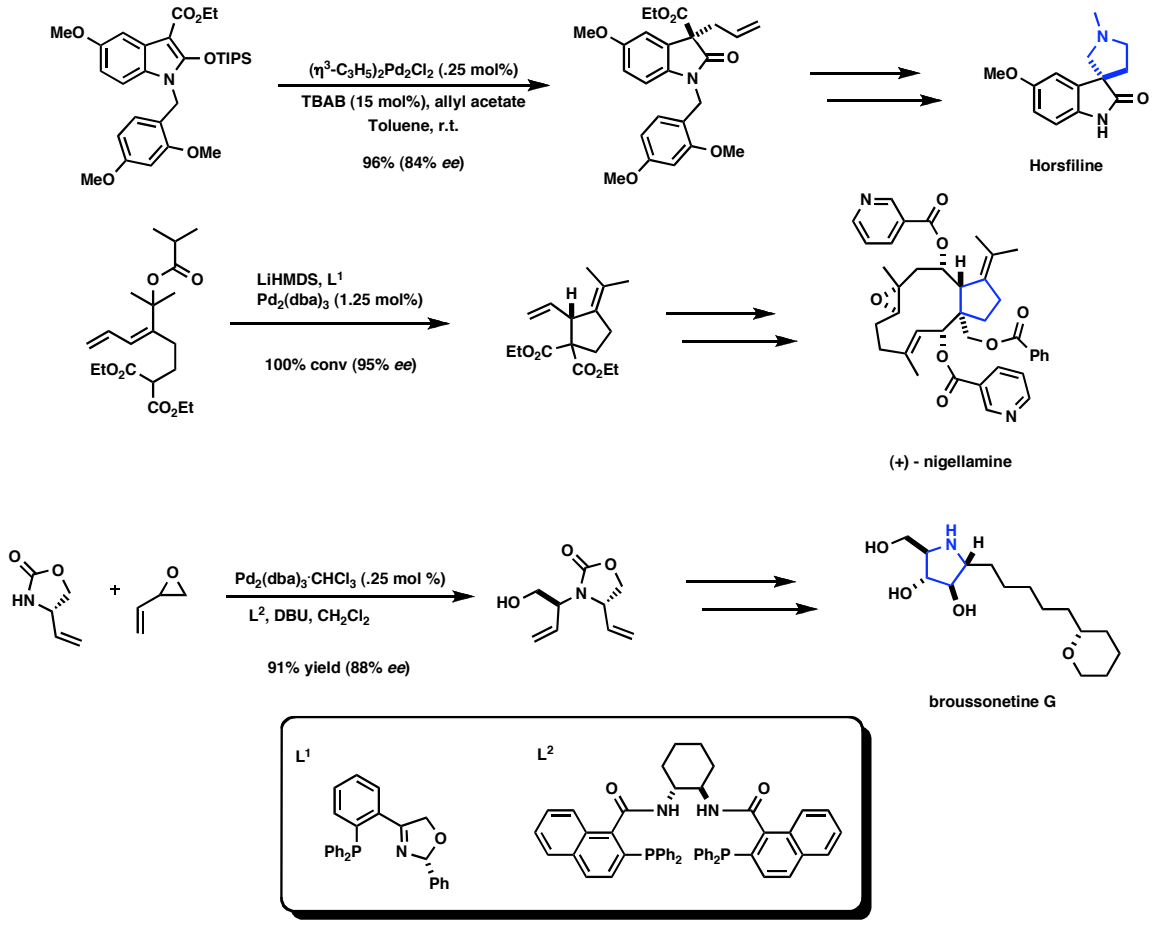
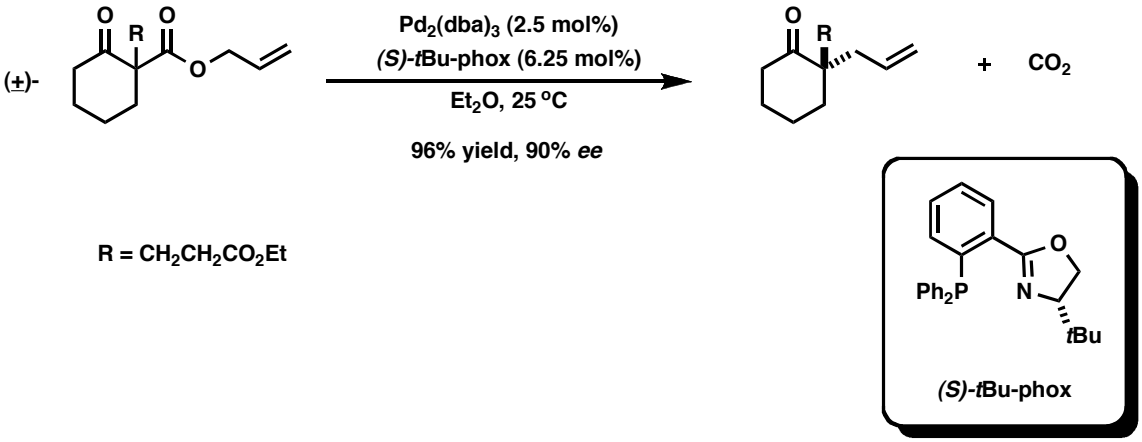


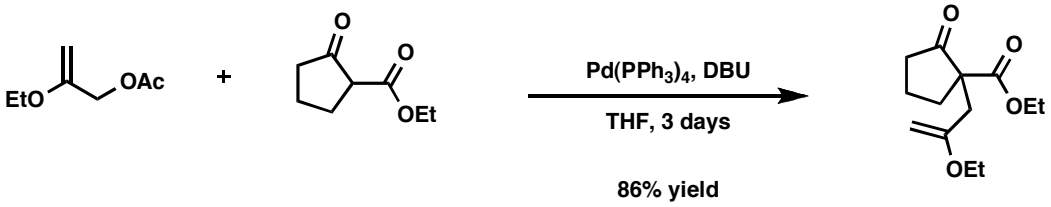
Figure 1.2 Tsuji-Trost Allylation in Natural Product Synthesis

Another facet concerning this type of palladium (0) chemistry is the catalytic enantioconvergent decarboxylative allylation of α-substituted 2-carboxyallylcyclohexanones. Racemic compounds containing a quaternary center are typically poor substrates for enantioselective deracemization. However, Stoltz et. al. have deracemized these quaternary stereocenters by using Pd(0) and chiral phosphine ligands and achieve products in high yield and enantiomeric excess (Scheme 1.4).[23]



Scheme 1.4 Enantioconvergent Decarboxylative Allylation

Considering the ubiquitous nature of this kind of reaction and how much research has been done concerning ligands, substrates and conditions, surprisingly little has been done with respect to modifying the allylic species. One notable example is the addition of 2-ethoxyallyl acetate to ethyl-2-cylopentanone carboxylate (Scheme 1.5).[7]



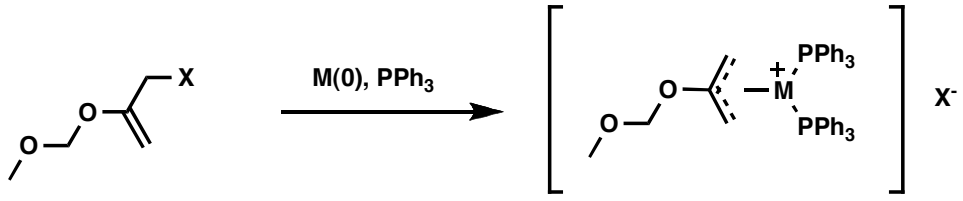
Scheme 1.5 Trost Functionalization

Catalytic Enantioselective Oxyallylation

Functionalization of the allylic leaving group prior to oxidative addition could prove to be a useful synthetic method. Often, during a natural product synthesis and after stereoselective allylation, the new olefin moiety is manipulated to set up for subsequent reactions, i.e., oxidation, hydroxylation, amination, hydroboration etc. A disadvantage of

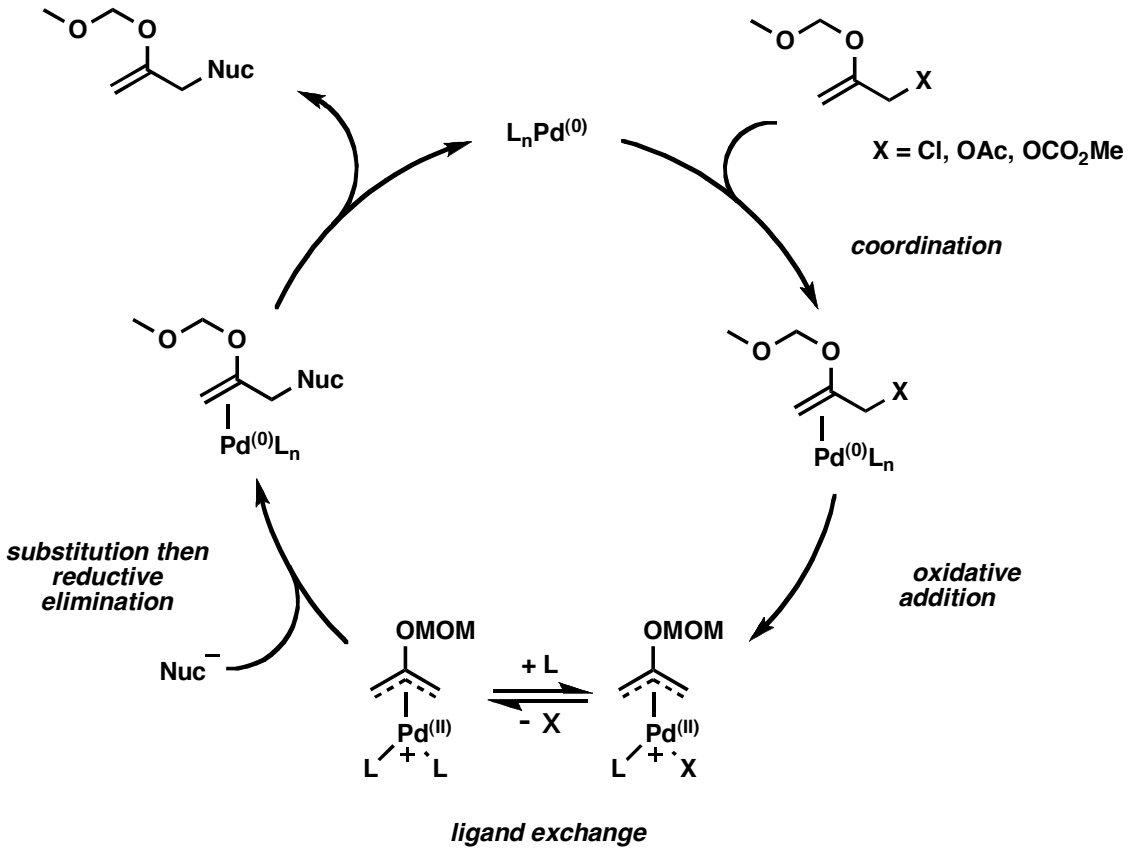
this strategy is that the requisite chemistry may be incompatible with other functionality on the molecule To have this structurally modified prior to attachment to the nucleophile could circumvent any undesirable functionality changes.

Ikeda et. al. studied the formation and eventual reactivity of oxodimethylenemethane-transition metal complexes and their reactivity towards cyclopropanation (Scheme 1.6).[8]



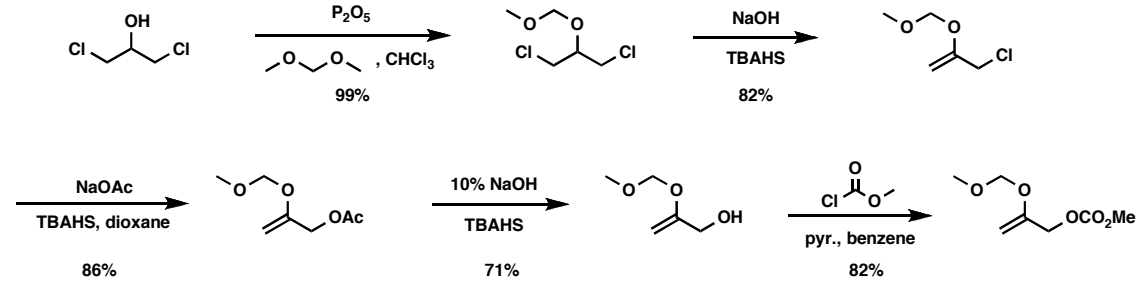
Scheme 1.6 Oxidative Addition to Methoxymethyl-enolethers

The ability to use the aforementioned research and adapt it to a modified Tsuji-Trost allylation was the goal of this research. The fact that these methoxymethyl-enolethers underwent oxidative addition meant that, using the right nucleophile, catalyst and ligand, an “oxyallylation” could be envisioned with a high yield and high degree of stereoselectivity. The proposed catalytic cycle for a such a reaction is similar to the typical Tsuji-Trost Reaction (Scheme 1.7).



Scheme 1.7 Modification of Tsuji-Trost Catalytic Cycle

If this reaction proceeds with a palladium (0) source, providing a racemic mixture of products, then it is simply a matter of finding the best ligand in order to provide and enantioselective variant of the reaction. Construction of the allylic leaving group compounds is straightforward, provides products in high yields and provides a route to three target compounds, allyl acetate, chloride and carbonate, that could be used in the oxyallylation (Scheme 1.8).



Scheme 1.8 Synthesis of Allylic Species

Initially, substrates that display a high degree of selectivity towards the Tsuji-Trost allylation were used to determine whether congruous results would be observed.[12] Ethyl-2-cyclopentanone carboxylate was successfully reacted with the allylic carbonate in 6 hours at room temperature. Using three ligands that have literature precedence for allylation (L1, L3, L4) and a phosphine ligand that was available (L2), the reaction afforded products in average yields with no significant enantiomeric excess (Figure 1.3).

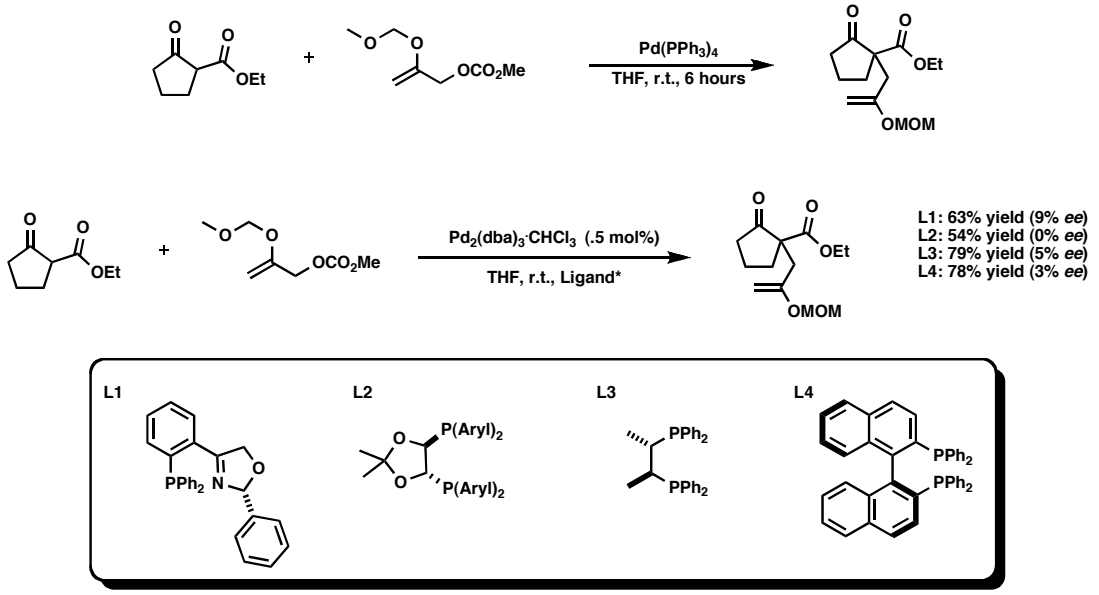


Figure 1.3 Initial Attempts at Oxyallylation

While these results were disappointing, knowing that the reaction worked in a racemic environment, it was a reasonable assumption that enantioselective product formation could be induced if the correct ligand could be identified. Ligands were selected due to literature reports of a high degree of selectivity with β-keto compounds.[8] The following bidentate chiral P,P ligands are quite general ligands for the reaction of many nucleophiles including carbon (pro)nucleophiles such as β-keto esters, nitrogen nucleophiles such as phthalimide or $TsNH_2$ and even oxygen nucleophiles (Figure 1.4).[8]

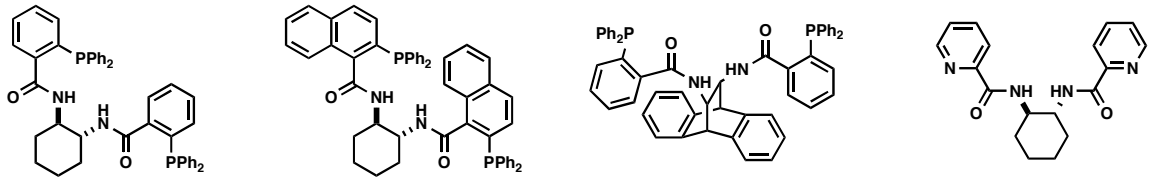
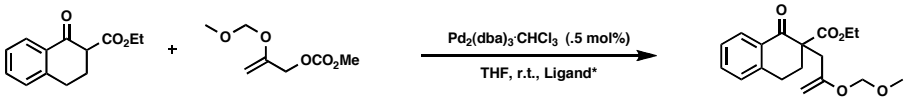
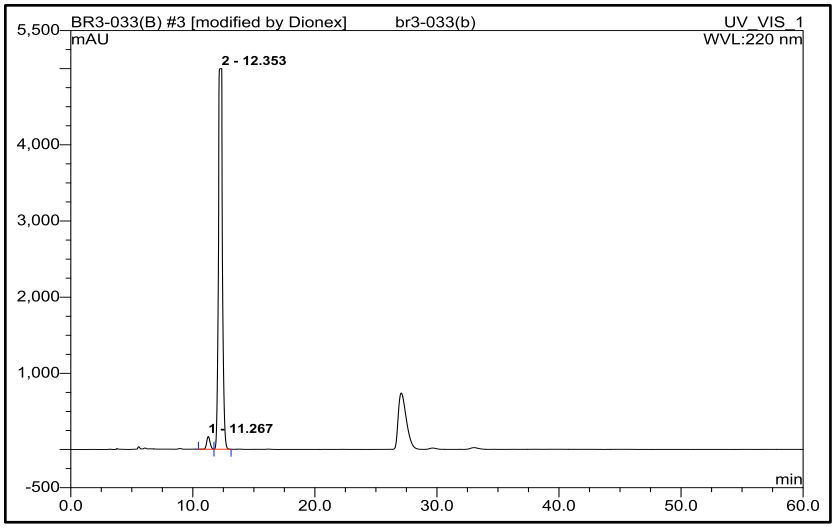
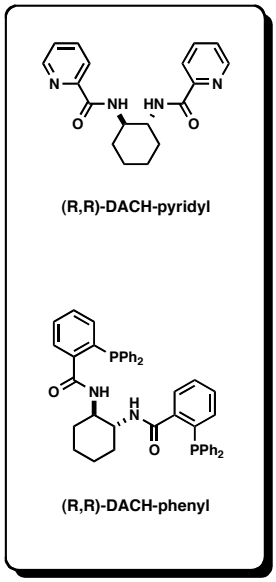


Figure 1.4 Versatile Ligands

(R,R) DACH-pyridyl, an N-N bidentate ligand, provided no stereoselection upon oxyallylation. However, the (R,R) DACH-naphthyl ligand gave a 94% enantiomeric excess upon the first try (Figure 1.5).







No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	11.27	n.a.	166.298	53.363	2.71	n.a.	BM *
2	12.35	n.a.	4995.459	1918.326	97.29	n.a.	MB*
Total:			5161.757	1971.689	100.00	0.000	

Figure 1.5 Enatioselective Oxyallylation HPLC

With the knowledge that these reactions could be carried out in a stereoselective manner using the appropriate ligand, a class of substrates was synthesized that should present similar or improved results. Ethyl esters have a good history for allylation reactions and typically, changing the ethyl to a benzyl or a *tert*-butyl group has a significant impact on the resultant enantioselectivity. Therefore, most of the ethyl esters that were constructed were also modified to benzyl esters to test selectivity. Malonates were also synthesized to demonstrate the application on more "linear" products. To

show the versatility of oxyallylation, substrates in which the β substituent is something other than an ester were also synthesized. This included benzyl, methyl, nitro and nitrile functionality (Figure 1.6).

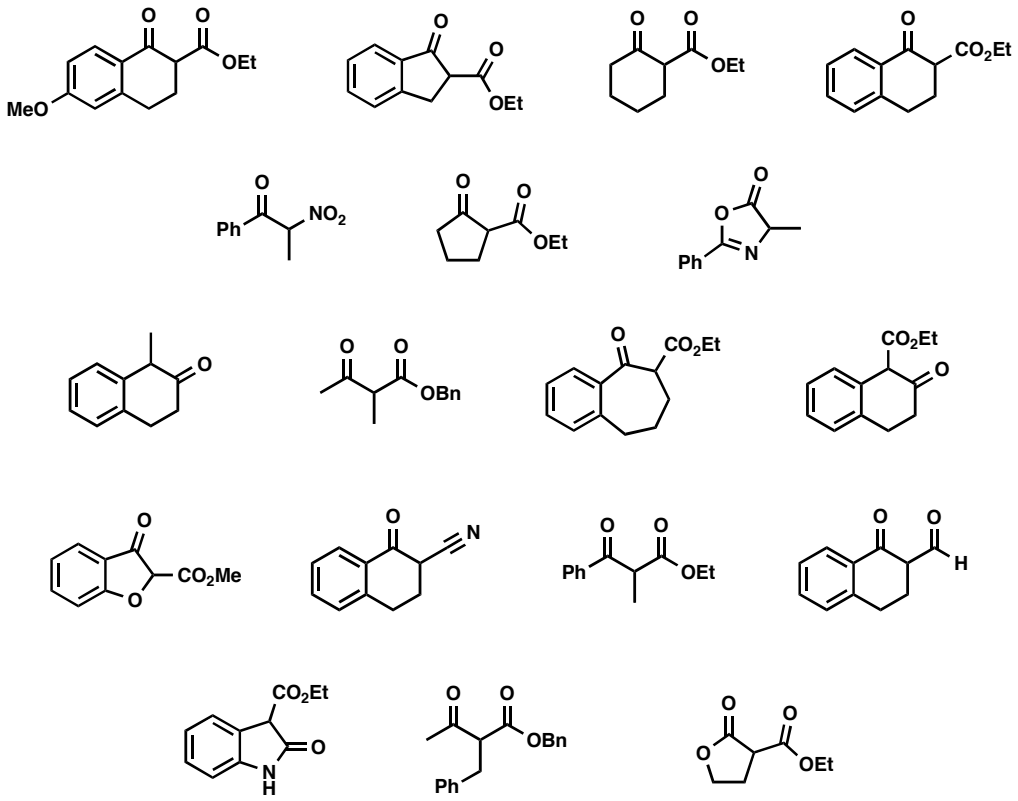
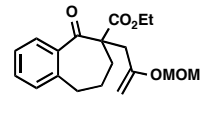
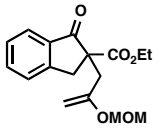
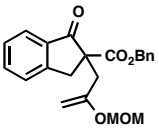
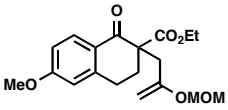
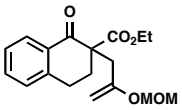


Figure 1.6 Substrates

Results

After optimization of conditions for allylation of the substrates, excellent results were obtained with respect to enantioselectivity and yield in many cases (Figure 1.7).

product	yield (%)	% ee
 13(c)	88%	81%
 13(a)	92%	87%
 13(b)	93%	89%
 13(d)	79%	97%
 13(e)	93%	97%

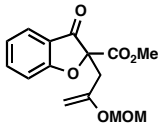
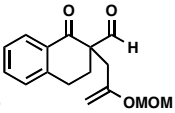
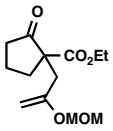
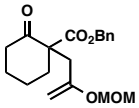
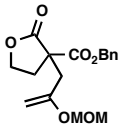
product	yield (%)	% ee
 13(g)	88%	71%
 13(j)	77%	71%
 13(f)	83%	74%
 13(h)	91%	89%
 13(i)	67%	15%

Figure 1.7 Results Table

The tetralone ethyl ester 13(e) displayed the best yield and enantiomeric excess, while the benzyl ester 13(i) of ϒ-butyrolactone displayed the worst in both categories. The aldehyde of tetralone showed surprising results, as literature concerning allylation of β-ketones and aldehydes displayed very poor results with respect to streoselection. These results suggest that the core structure of the β-carbonyl substrate greatly effects the enantiofidelity of the reaction, specifically the size of the ring. Looking at the table, it is easy to see that a six-membered ring containing the ketone gives the best results followed by the five-member ring and then even less so with the seven-membered ring. The presence of an aromatic ring attached to the ring bearing the ketone also seems to

improve the enantiomeric excess of product formation. This could suggest that the ligand participates in a π stacking interaction with the substrate's aromatic ring. Conversion from an ethyl to a benzyl ester did not significantly increase in enatioselectivity. Differences in enatiomeric excess between the two ranged from 0% to 5% with a 2% difference in ee for the indanone ester.

Some of the cyclic substrates displayed inconsistent stereoselection or their product formation lacked stereospecificity (Figure 1.8).

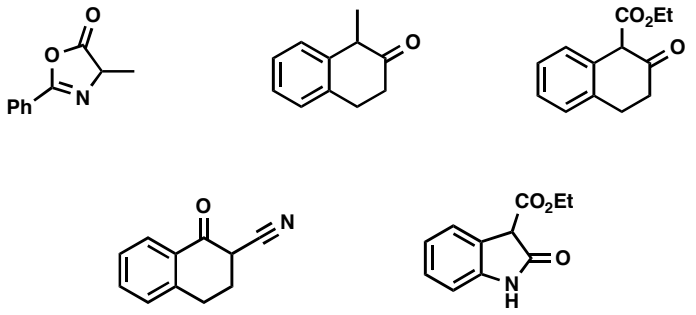


Figure 1.8 Cyclic Substrates without Stereoselection

The compound shown in Figure 1.8 reacted with good yields. However, the only substrate that showed any enantioselectivity was the aza-lactone but the observed ee was inconsistent, preventing it from being included in the previous table. Further optimization using these substrates should allow for stereoselective product formation .

Contrary to expectations based on literature precedence, the acyclic substrates did not react (Figure 1.9). These substrates proceeded in a stereospecific manner when run at room temperature under the traditional Tsuji-Trost allyl alkylation. However, even when subjected to heat, these reactions would not proceed using the oxy-allylcarbonate.

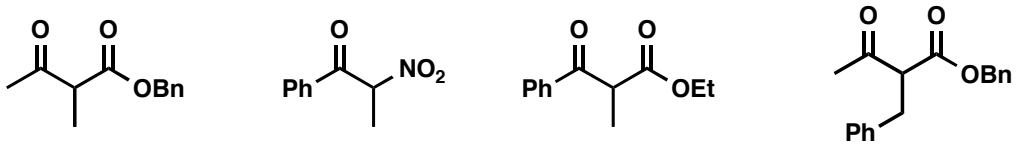
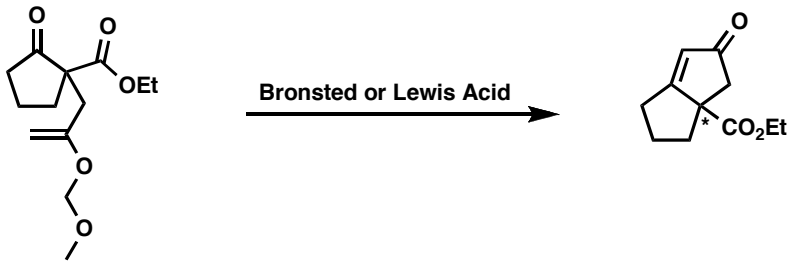


Figure 1.9 Acyclic Substrates

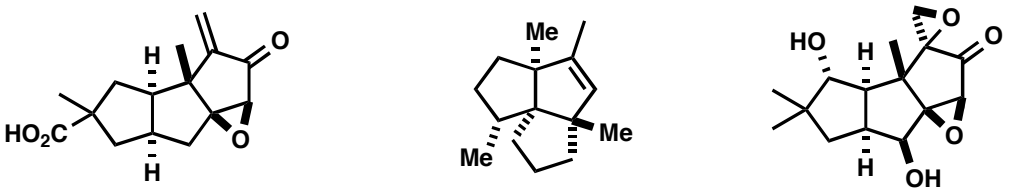
Synthetic Application

In order for this research to be useful, a realistic application must be envisioned. These substrates display a unique moiety in which there is an enol connected at the α-position of the carbonyl. Lewis or Bronsted acid catalyzed reaction should be an efficient route to access stereospecific 5,5 bicycles (Scheme 1.9).



Scheme 1.9 Annulation

One way in which this method may be used is in the total synthesis of natural products. Many biologically active natural products possess fused five membered rings that are not easily accessed using existing methodology. A few of these include hirsutic acid, isocomene and coriolin (Figure 1.10).

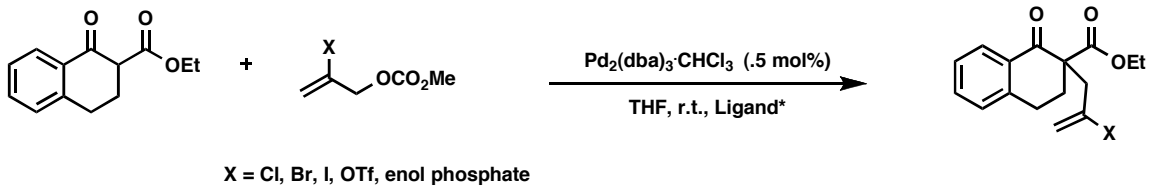


Hirsutic Acid **Isocomene** **Coriolin**

Figure 1.10 Biologically Active Fused Rings

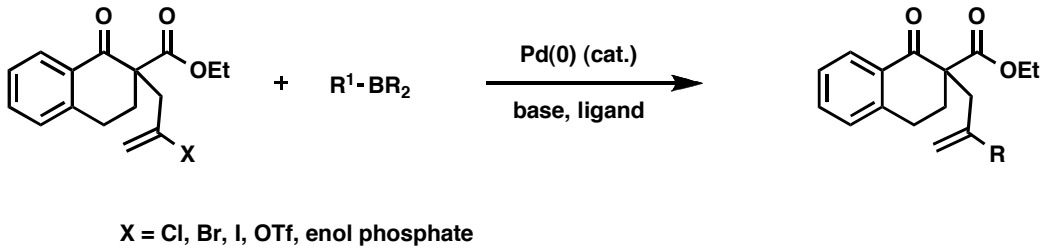
Natural product synthesis continues to be a difficult yet very important aspect of research in drug design.

Yet another application may lie in the manipulation of the enol ether itself to provide a functionality that may be used in subsequent reactions. Experimentation has been started to change the enol to a vinyl halide, triflate or phosphate. Stereoselective alkylation of these compounds provide very interesting products (Scheme 1.10).



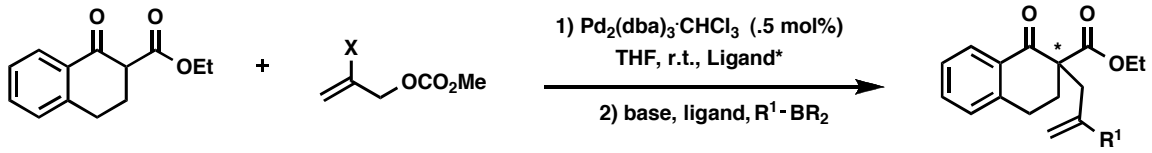
Scheme 1.10 Functionalization of the Allylic Carbonate

Vinyl halides, triflates and enol phosphates are commonly used as substrates in the Suzuki-Cross Coupling reaction, a reaction for which Suzuki was awarded the Nobel Prize in Chemistry in 2010. During this palladium (0) catalyzed reaction, these compounds are reacted with aryl or vinyl boronic acids to create new carbon-carbon bonds (Scheme 1.11).



Scheme 1.11 Suzuki Cross Coupling

As this reaction is also catalyzed by a palladium (0) source, one could conceive a one-pot synthesis in which the first step is an oxyallylation, followed by the addition of a boronic acid for a subsequent cross coupling reaction (Scheme 1.12).

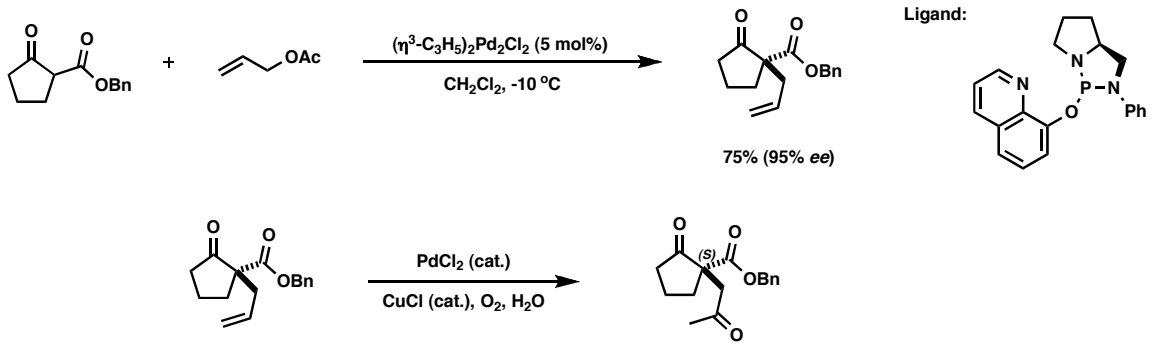


Scheme 1.12 One Pot Allylation/Suzuki Cross Coupling

This tandem reaction sequence could be an incredibly powerful tool since one carbon-carbon bond would be constructed stereospecifically and then followed by a second carbon-carbon bond formation in a one-pot synthesis.

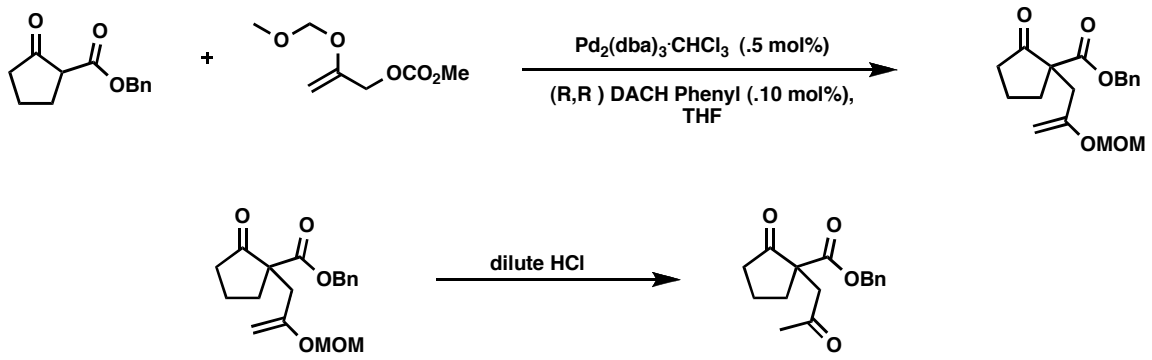
Determination of Absolute Stereochemistry

At this point, while it is clear that stereoselcetive products are being obtained, the absolute stereochemistry is still in undetermined. The proposed, short term solution for this is the creation of a product in which the absolute stereochemisty is known followed by a Wacker oxidation to provide the corresponding ketone (Scheme 1.13).



Scheme 1.13 Wacker Oxidation

Simultaneously, the same substrate that was used in the modified synthesis will be created and subsequently deprotected (Scheme 1.14).



Scheme 1.14 Acidic Deprotection

Running concurrent HPLC analyses on both samples will enable the determination of the absolute stereochemistry of our target compound.

EXPERIMENTAL

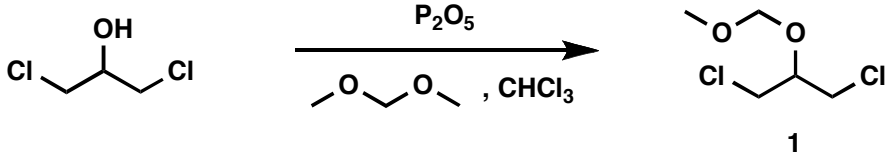
General Information

Commercial reagents were purified prior to use following the guidelines of Perrin and Armarego.[13] Et_2O and THF were distilled from sodium benzophenone ketyl under a positive pressure of argon. All other solvents were obtained from commercial vendors and used as received unless otherwise noted. $Pd_2(dba)_3{\cdot}CHCl_3$, $Pd_2(dba)_3$, $Pd(PPh_3)_4$, and all chiral ligands (Aldrich), were purchased from commercial vendors and used as received. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Chromatographic purification of products was accomplished using forced-flow chromatography on Silicycle SiliaFlash® F60 40–63 μm, 60 Å silica gel according to the method of Still.[14] Thin-layer chromatography (TLC) was performed on Silicycle SiliaPlate® G, 250 μm plates. Visualization of the developed chromatogram was performed by fluorescence quenching, staining with ceric ammonium molybdate, or by $KMnO_4$ stain.

^{1}H NMR spectra (300 or 500 MHz) and ^{13}C NMR (75 or 125 MHz) spectra were recorded on Bruker DPX 300 or AVANCE-500 spectrometers in $CDCl_3$ and are internally referenced to residual protio solvent signals (δ 7.26 and δ 77.16, respectively). Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constant (Hz) and assignment. Data for ^{13}C NMR are reported in terms of chemical shift. IR spectra were recorded on a JASCO 4100 spectrometer as thin films on a NaCl plate and are reported in

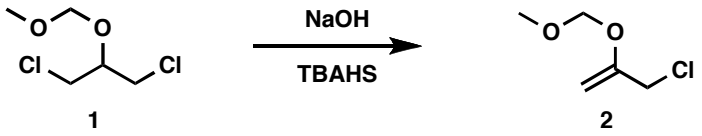
terms of frequency of absorption (cm^{-1}). Mass spectra were obtained from the Montana State University Mass Spectral facility using a Bruker micrOTOF (ESI-TOF) with Agilent 1100 HPLC system. High performance liquid chromatography (HPLC) was performed on a DIONEX UltiMate 3000 chromatograph using either a Daicel Chiralcel® AD-H column (25 x 0.46 cm) and AD-H guard cartridge (0.4 cm x 1 cm) or a Daicel Chiralcel® AS-H column (25 x 0.46 cm) and AS-H guard cartridge (0.4 cm x 1 cm) as noted. Optical rotations were measured using a Jasco P-1020 polarimeter (WI lamp, 589 nm, 25 °C), and $[\alpha]_D$ values are reported in 10^{-1} dg cm^2 g^{-1}; concentration (c) is in g/100 mL.

Experimental Conditions and Compound Information



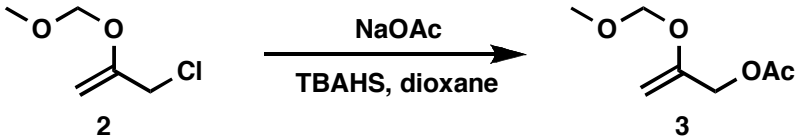
1

1,3-dichloro-2-(methoxymethoxy)propane (1). To a solution of 6.0 g (46.6 mmol) dichloropropanol, (10 mL) chloroform and 9.26 mL (0.105 mol) dimethoxymethane was added 3.96 g (27.9 mmol) P_2O_5 with vigorous stirring at 45 °C. The resulting solution was then stirred at room temperature for 18 h after which the supernatant was decanted, washed with DI water, sat. aq. $NaHCO_3$ and once more with water. The oily material was fractionally distilled to give 8.02 g (99% yield) of **2.** NMR data was consistent with literature values.[16]



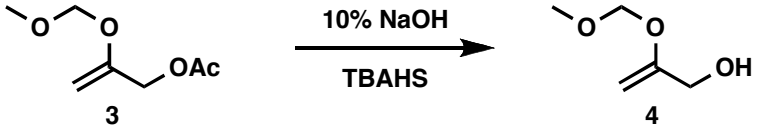
1 2

3-chloro-2-(methoxymethoxy)prop-1-ene (2). To a flame dried round bottom flask equipped with a stir bar and charged with 23.04 g (0.133 mol) of **1** was added 7.99 g (0.1997 mol) of NaOH followed by 2.26 g (6.65 mmol) tetrabutylammonium hydrogen sulfate. The resulting solution was heated to 90 °C and the product was slowly distilled under reduced pressure (~30 Torr) into a receiving flask using a vigreux column equipped with condenser to give 15.0 g (82% yield) of **2** with a small amount of water present. NMR data was consistent with literature values.[16]



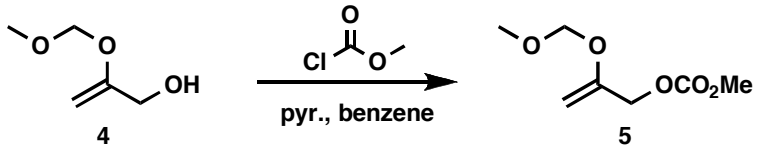
2 3

2-(methoxymethoxy)allyl acetate (3). To a solution of 12.0 g (87.9 mmol) of 2 in dioxane (1.9 M) was added 8.07 g (98.4 mmol) of sodium acetate followed by 1.49 g (4.4 mmol) tetrabutylammonium hydrogen sulfate. The resulting solution was refluxed for 6 h and then the solvent was removed by distillation and the generated solid materials were removed by filtration. The crude product was distilled on the Kugelrohr (105 °C, ~20 Torr) to give 12.1 g (86% yield) of 3. NMR data was consistent with literature values.[17]

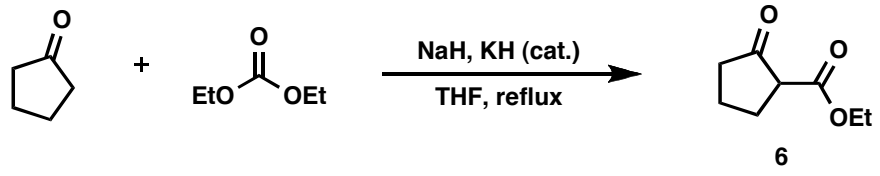


3 4

2-(methoxymethoxy)prop-2-en-1-ol (4). 31.38 g (78.5 mmol) of a 10% aqueous NaOH solution and 0.89 g (2.62 mmol) of tetrabutylammonium hydrogen sulfate was mixed with 8.38 g (52.3 mmol) of allyl acetate **3** and then stirred at 80 °C for 1 hour. After cooling to room temperature, the crude oily mixture was extracted with CH_2Cl_2 (3X). The crude product was then distilled on the Kugelrohr (105 °C, ~ 20 Torr) to give 4.4 g (71% yield) of pure compound **4**. NMR data was consistent with literature values.[17]

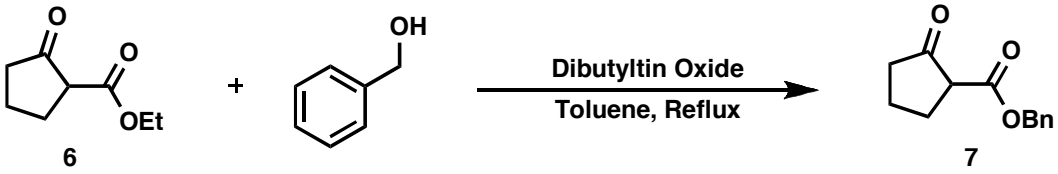


2-(methoxymethoxy)allyl methyl carbonate (5). 4.18 g (35.4 mmol) of allyl alcohol **4** was dissolved in 17.7 mL of benzene (2 M) and 12.2 mL (2.9 M) of pyridine in a round bottom flask equipped with a stir bar under argon. The solution was cooled to 0 °C and 2.73 g (35.4 mmol) of methyl chloroformate was added dropwise over 5 min. The reaction was stirred for another 5 min. at which point the precipitate was removed by filtration and the low boiling solvent was removed by evaporation. The crude product was distilled by Kugelrohr (110 °C, ~20 Torr) to afford 5.11 g (82% yield) of pure compound **5.** NMR data was consistent with literature values.[17]

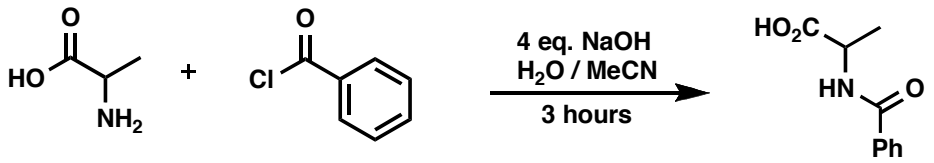


General procedure for the formation of β- keto ethyl ester compounds. To a dry three-necked round bottom flask equipped with a dropping funnel, condenser, and a

magnetic stir bar was added 11.2 g (0.28 mol) NaH (60% dispersion in oil), a few drops of KH (35% dispersion in oil), 24.23 mL (0.2 mol) of diethyl carbonate and 50 mL of toluene. The resulting mixture was heated to reflux and a solution of 8.4 g (0.1 mol) of cyclopentanone dissolved in 50 mL of toluene was added via the dropping funnel over the course of 2 hours. After addition, the solution was refluxed until the evolution of hydrogen ceased. The reaction was then cooled to room temperature and glacial acetic acid was added very slowly until a dense pasty solid appeared. Ice water was added until the solid dissolved completely. The toluene layer was removed and the water layer was extracted with toluene (3x). The toluene layers were combined, washed with brine and dried over $MgSO_4$. Column chromatography afforded pure β- keto ethyl ester, and all NMR results were consistent with the literature.[18]

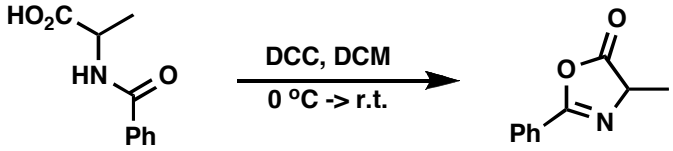


General procedure for the formation of β- keto-benzylester compounds from β-keto-ethylester compounds. A mixture of 0.750 g (3.44 mmol) of ethyl cyclopentanone 2-carboxylate, 0.712 mL (6.87 mmol) of benzyl alcohol, and 0.086 g (0.344 mmol) of dibutyltin oxide was refluxed in toluene for 18 hours before it was concentrated in vacuo and purified via column chromatography to afford benzyl cyclopentanone-2-carboxylate. NMR data was consistent with literature values.[18]



8

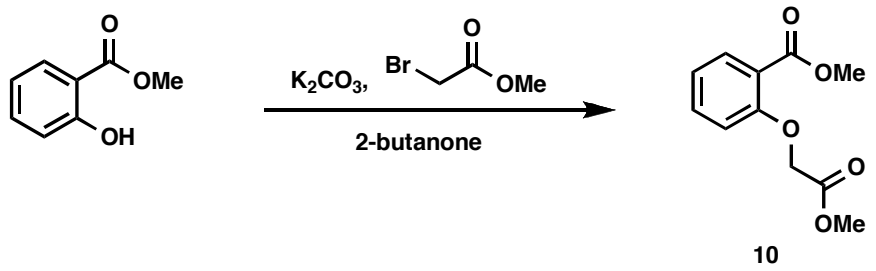
2-benzamidopropanoic acid (8). 3.0 g (33.7 mol) of L-alanine and 5.39 g (0.135 mol) of NaOH were dissolved in a mixture of 75 mL of water and 25 mL of acetonitrile. After cooling to 0 °C, benzoyl chloride was added dropwise. After the addition was complete, the mixture was stirred for an additional 2 hours at 0 °C and then 1 hour at room temperature after which all volatiles were removed under reduced pressure before concentrated HCl was added to cause precipitation. The mixture was filtered and the filter cake was washed with ice cold diethyl ether. The resulting product was purified via column chromatography to afford 4.03 g (62% yield) of pure 8. NMR data was consistent with literature values.[19]



8 9

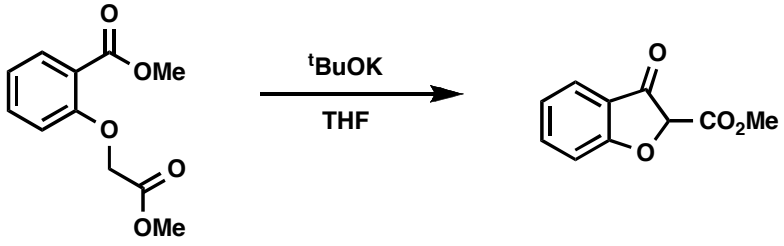
4-methyl-2-phenyloxazol-5(4H)-one (9). 2.50 g (12.9 mmol) of N-benzoyl-alanine **8** was suspended in 50 mL of anhydrous dichloromethane, the mixture was cooled to 0 °C and 2.79 g (13.5 mmol) of DCC was added portionwise. After complete addition, the mixture was allowed to warm to room temperature and stirred for an additional 20 hours. A precipitate was filtered off and the filtrate was concentrated under vacuum. The

product was purified by column chromatography to give 1.8 g (80% yield) of pure **9** as a colorless solid. NMR data was consistent with literature values.[19]



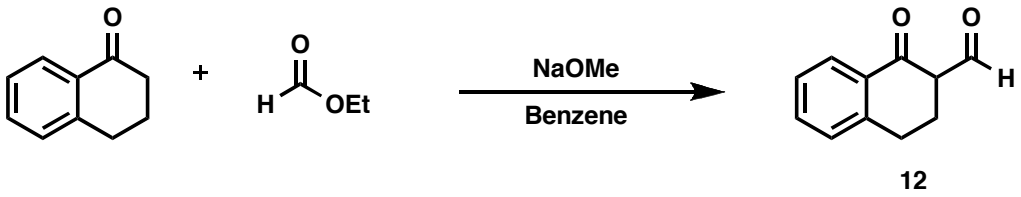
10

methyl 2-(2-methoxy-2-oxoethoxy)benzoate (10). 3.31 g (21.8 mol) of methyl salicylate was dissolved in anhydrous 2-butanone in a 100 mL round bottom flask equipped with a stir bar under argon. To this was added 3.16g (22.8 mmol) of K_2CO_3 and 2.52 mL (22.8 mmol) ethyl bromoacetate. The mixture was refluxed for 18 hours at the end of which it was cooled to 0 ^oC and quenched with DI water. To this was added 10% HCl, diluted with dichloromethane and extracted (3x). After concentrating in vacuo, the crude product was purified via column chromatography to give 3.4 g (70% yield). NMR data was consistent with literature values.[22]



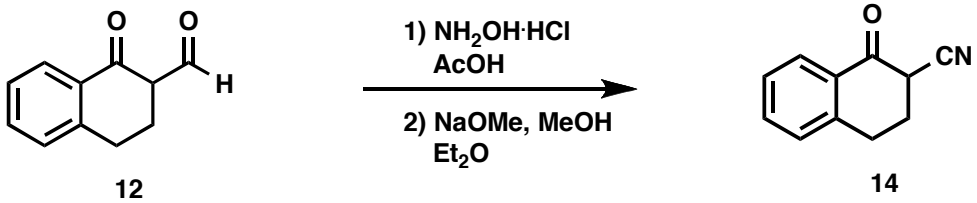
methyl 3-oxo-2,3-dihydrobenzofuran-2-carboxylate (11). A suspension of 4.53g (40.3 mmol) of potassium tert butoxide and 4.58 g (19.2 mmol) of diester **10** in 100 mL of dry THF was stirred at room temperature for two hours. 10% aqueous HCl was added to stop the reaction and the mixture was extracted with ethyl acetate (3x). the combined organic

extracts were washed with brine, dried over anhydrous $MgSO_4$ and concentrated in vacuo. The crude mixture was purified by column chromatography to give 2.8 g (89% yield) of **11.** NMR data was consistent with literature values.[22]



12

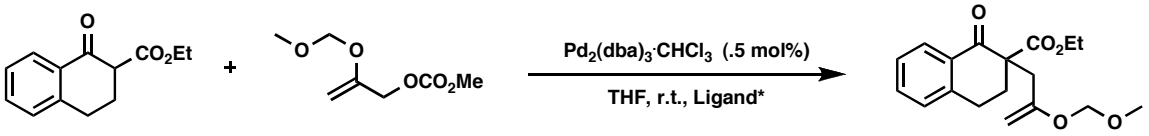
1-oxo-1,2,3,4-tetrahydronaphthalene-2-carbaldehyde (12). 1.48 g (27.4 mmol) of sodium methoxide was added to a stir bar equipped round bottom flask with 2.21 mL (27.4 mmol) of ethyl formate and benzene (.42 M). The solution was cooled to 0 °C and tetralone was a added. The reaction was monitored for the formation of a precipitate. After 5 hours, the solution was hydrolized with cool water. The organic layer was then washed with DI water then dilute NaOH. The aqueous portions were combined, washed with ether, and then acidified with ice and HCl. The resulting product was purified via column chromatography to give 2.2 g (92% yield) of compound **12.**[20]



12 14

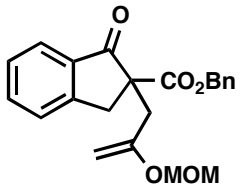
1-oxo-1,2,3,4-tetrahydronaphthalene-2-carbonitrile (14). .500 g (2.87 mmol) of **12** was dissolved in 2.4 mL (0.82 M) of AcOH. To this added .399 g (5.74 mmol) of $NH_4OH{\cdot}HCl$ and the reaction was stirred vigorously for 8 hours at 80 °C. The reaction was cooled to room temperature and the acetic acid was removed under reduced pressure

after which the residue was diluted with H_2O and extracted with diethyl ether. The organic layer was washed with dilute $NaHCO_3$. to remove any acetic acid and unreacted starting material, and then washed with water and brine. The organic layer was then dried over $MgSO_4$, filtered and the solvent was removed under vacuum. The crude product was then purified using column chromatography to give 0.411 g (84% yield) of compound **14**.[21]



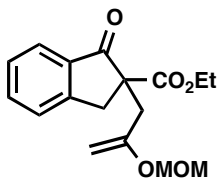
Typical procedure for the allylation reaction A two-dram vial was charged with chiral phosphine ligand (6.9 mg, 0.01 mmol) and dissolved in .5 mL of THF. To this was added allyl carbonate (21.1 mg, 0.12 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (5.2 mg, 0.005 mmol) and indanone benzyl ester (25.2 mg, 0.1 mmol) and the resultant mixture was stirred at -40 ^oC for 24 hours at which time the solvent was removed under vacuum and the crude product was loaded directly onto a column for purification.

Racemic products for HPLC assay were obtained by by using 10 mol% $Pd(PPh_3)_4$ in THF and stirring for 24 hours at room temperature.

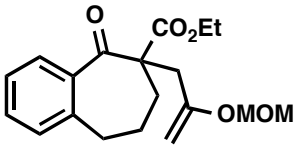


13(a): Obtained as a yellow oil (93% yield), [α]21D = +89.81 (*c* 0.107, CH_2Cl_2); ee = 89%, **HPLC**: Daicel CHIRALCEL OD-H column, 5% IPA in hexanes, 1.0 mL/min, λ=

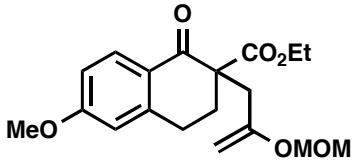
220 nm, t_R(major) = 10.0 min, t_R(minor) = 11.7 min; **IR** (CH_2Cl_2, film): 2980, 2959, 1745, 1713, 1637, 1605, 1264 cm^{-1}; ^1H NMR (500 MHz, Chloroform-d) δ 7.75 (d, *J* = 7.7 Hz, 1H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.44 (d, *J* = 7.7 Hz, 1H), 7.35 (t, *J* = 7.5 Hz, 1H), 7.32 – 7.19 (m, 5H), 5.12 (q, *J* = 12.5 Hz, 2H), 4.53 (t, *J* = 4.6 Hz, 2H), 4.14 (d, *J* = 2.2 Hz, 1H), 4.02 (d, *J* = 2.1 Hz, 1H), 3.66 (d, *J* = 17.4 Hz, 1H), 3.31 (d, *J* = 17.3 Hz, 1H), 3.05 (s, 1H), 3.03 (s, 4H), 2.86 (d, *J* = 14.5 Hz, 1H) ^{13}C NMR (126 MHz, Chloroform-d) δ 201.33 , 170.41 , 156.86 , 153.19 , 135.67 , 135.24 , 135.03 , 128.42 , 128.04 , 127.77 , 127.53 , 126.27 , 124.65 , 93.55 , 88.13 , 67.16 , 59.24 , 55.87 , 39.66 , 35.44



13(b): Obtained as a pale yellow oil (92% yield), [α]21D = +110.52 (*c* 0.097, CH_2Cl_2); ee = 84%, **HPLC**: Daicel CHIRALCEL OD-H column, 5% IPA in hexanes, 1.0 mL/min, λ=220 nm, t_R(minor) = 7.4 min, t_R(major) = 8.5 min; **IR** (CH_2Cl_2, film): 2980, 2962, 2934, 2897, 1741, 1716, 1207, 1012 cm^{-1}; ^1H NMR (500 MHz, Chloroform-d) δ 7.76 (d, *J* = 7.7 Hz, 1H), 7.67 – 7.50 (m, 1H), 7.50 – 7.43 (m, 1H), 7.43 – 7.31 (m, 1H), 4.72 – 4.43 (m, 3H), 4.20 – 4.08 (m, 3H), 4.06 (d, *J* = 2.0 Hz, 1H), 3.66 (d, *J* = 17.3 Hz, 1H), 3.32 (d, *J* = 17.4 Hz, 1H), 3.07 (s, 4H), 3.01 (d, *J* = 14.5 Hz, 1H), 2.87 (d, *J* = 14.5 Hz, 1H), 1.21 (t, *J* = 7.1 Hz, 3H) ^{13}C NMR (126 MHz, Chloroform-d) δ 157.00 , 153.27 , 135.32 , 134.94 , 127.45 , 126.24 , 124.60 , 93.58 , 88.08 , 76.91 , 61.70 , 55.88 , 39.66 , 35.51 , 14.00

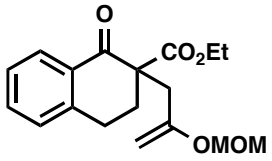


13(c): Obtained as a clear oil (88% yield), [α]20D = -90.6 (*c* 0.033, CH_2Cl_2); ee = 83%, **HPLC**: Daicel CHIRALCEL OD-H column, 5% IPA in hexanes, 1.0 mL/min, λ=220 nm, t_R(minor) = 6.4 min, t_R(major) = 7.4 min; **IR** (CH_2Cl_2, film): 2987, 2926, 1734, 1680, 1637, 1264, 1153 cm^{-1}; ^1H NMR (500 MHz, Chloroform-d) δ 7.40 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.32 (td, *J* = 7.4, 1.6 Hz, 1H), 7.23 (t, *J* = 7.5 Hz, 1H), 7.11 (d, *J* = 7.6 Hz, 1H), 4.79 (s, 2H), 4.20 (d, *J* = 2.0 Hz, 1H), 4.05 (d, *J* = 2.0 Hz, 1H), 3.99 (dqd, *J* = 10.7, 7.1, 3.6 Hz, 1H), 3.30 (s, 3H), 3.06 (ddd, *J* = 14.8, 10.5, 3.7 Hz, 1H), 2.92 – 2.74 (m, 3H), 2.45 (qd, *J* = 7.8, 6.6, 4.6 Hz, 1H), 2.07 (ddt, *J* = 14.4, 8.2, 3.0 Hz, 1H), 1.90 – 1.70 (m, 2H), 1.04 (t, *J* = 7.1 Hz, 3H) ^{13}C NMR (126 MHz, Chloroform-d) δ 203.88 , 171.58 , 156.58 , 139.92 , 138.96 , 130.73 , 129.07 , 129.03 , 125.96 , 93.59 , 88.26 , 60.94 , 56.16 , 42.59 , 33.03 , 31.86 , 24.14 , 13.64

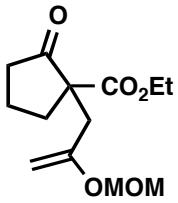


13(d): Obtained as a clear oil (79% yield), [α]19.5D = -38.08 (*c* 0.026, CH_2Cl_2); ee = 97%, **HPLC**: Daicel CHIRALCEL AD-H column, 5% IPA in hexanes, 1.0 mL/min, λ= 220 nm, t_R(minor) = 14.3 min, t_R(major) = 15.8 min; **IR** (CH_2Cl_2, film): 2987, 2872, 1730, 1676, 1597, 1418, 1264 cm^{-1}; ^1H NMR (500 MHz, Chloroform-d) δ 8.01 (d, *J* = 8.8 Hz, 1H), 6.82 (dd, *J* = 8.9, 2.5 Hz, 1H), 6.71 – 6.57 (m, 1H), 4.83 (q, *J* = 6.2 Hz, 2H),

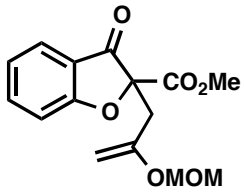
4.21 (d, *J* = 2.0 Hz, 1H), 4.17 – 4.05 (m, 2H), 3.85 (s, 3H), 3.31 (s, 3H), 3.17 (ddd, *J* = 16.4, 11.1, 4.8 Hz, 1H), 3.02 (d, *J* = 14.3 Hz, 1H), 2.89 (dt, *J* = 17.4, 4.8 Hz, 1H), 2.76 (d, *J* = 14.3 Hz, 1H), 2.61 (dt, *J* = 13.8, 4.5 Hz, 1H), 2.11 (ddd, *J* = 13.9, 11.0, 4.8 Hz, 1H), 1.19 (t, *J* = 7.1 Hz, 3H) ^{13}C NMR (126 MHz, Chloroform-d) δ 192.87 , 170.95 , 163.48 , 156.88 , 145.74 , 130.52 , 125.45 , 113.26 , 112.14 , 93.56 , 88.06 , 61.21 , 56.19 , 55.91 , 55.32 , 39.80 , 29.95 , 26.24 , 13.97



13(e): Obtained as a pale yellow oil (93% yield), [α]21D = -60.66 (*c* 0.091, CH_2Cl_2); ee = 97%, **HPLC**: Daicel CHIRALCEL AD-H column, 2% IPA in hexanes, 1.0 mL/min, λ =220 nm, t_R(minor) = 14.5 min, t_R(major) = 15.7 min; **IR** (CH_2Cl_2, film): 2984, 2962, 2937, 2905, 1726, 1684, 1457 1299, 1156., 1020 cm^{-1}; ^{1}H NMR (500 MHz, Chlororform-d) δ 8.00 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.42 (td, *J* = 7.5, 1.5 Hz, 1H), 7.30 – 7.22 (m, 1H), 7.17 (d, *J* = 7.7 Hz, 1H), 4.84 – 4.73 (m, 2H), 4.19 (d, *J* = 2.0 Hz, 1H), 4.16 – 4.01 (m, 3H), 3.25 (s, 3H), 3.15 (ddd, *J* = 16.6, 11.1, 4.8 Hz, 1H), 2.96 (d, *J* = 14.3 Hz, 1H), 2.90 (dt, *J* = 17.3, 4.7 Hz, 1H), 2.78 (d, *J* = 14.3 Hz, 1H), 2.67 – 2.48 (m, 1H), 2.11 (ddd, *J* = 13.9, 11.1, 4.9 Hz, 1H), 1.14 (t, *J* = 7.1 Hz, 3H) ^{13}C NMR (126 MHz, Chloroform-d) δ 195.03 , 172.04 , 166.05 , 154.04 , 138.06 , 124.70 , 122.41 , 119.63 , 113.39 , 93.69 , 88.82 , 55.80 , 53.24 , 47.19 , 39.48, 39.03

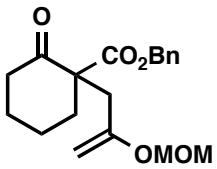


13(f): Obtained as a clear oil (83% yield), [α]21D = +297.9 (*c* 0.012, CH_2Cl_2); ee = 75%, **HPLC**: Daicel CHIRALCEL OD-H column, 2% IPA in hexanes, 1.0 mL/min, λ=220 nm, t_R(major) = 8.8 min, t_R(major) = 10.5 min; **IR** (CH_2Cl_2, film): 3055, 2980, 2868 1730, 1701, 1630, 1422, 1267 cm^{-1}; ^1H NMR (500 MHz, Chloroform-d) δ 4.84 (s, 2H), 4.24 – 4.16 (m, 1H), 4.15 (t, *J* = 2.0 Hz, 1H), 4.14 – 4.07 (m, 1H), 4.02 (d, *J* = 2.0 Hz, 1H), 3.36 (s, 3H), 3.05 (d, *J* = 14.4 Hz, 1H), 2.78 (d, *J* = 8.3 Hz, 3H), 2.60 – 2.53 (m, 2H), 2.34 (d, *J* = 14.4 Hz, 1H), 2.30 (t, *J* = 7.0 Hz, 3H), 1.97 – 1.81 (m, 1H), 1.25 (t, *J* = 7.1 Hz, 3H) ^{13}C NMR (126 MHz, Chloroform-d) δ 93.75 , 87.39 , 61.42 , 56.38 , 40.04 , 34.82 , 33.12 , 28.98 , 26.99 , 26.71 , 25.37 , 14.29 .

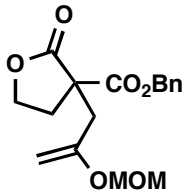


13(g): Obtained as a clear oil (88% yield), [α]21D = -228.9 (*c* 0.009, CH_2Cl_2); ee = 73%, **HPLC**: Daicel CHIRALCEL AD-H column, 2% IPA in hexanes, 1.0 mL/min, λ=220 nm, t_R(major) = 17 min, t_R(minor) = 19 min; **IR** (CH_2Cl_2, film): 2984, 2955, 1752, 1726, 1612, 1465, 1264, 1153, 1045, 1012 cm^{-1}; ^1H NMR (500 MHz, Chloroform-d) δ 7.66 (d, *J* = 7.7 Hz, 2H), 7.65 – 7.60 (m, 2H), 7.21 (d, *J* = 8.1 Hz, 2H), 7.10 (t, *J* = 7.4 Hz, 2H), 4.64 (s, 4H), 4.22 (s, 1H), 4.12 (s, 1H), 3.76 (s, 5H), 3.16 (d, *J* = 14.9 Hz, 2H), 3.13 (s,

3H), 3.02 (d, *J* = 14.9 Hz, 2H) ^{13}C NMR (126 MHz, Chloroform-d) δ 172.04 , 154.04 , 138.06 , 124.70 , 122.41 , 119.63 , 113.39 , 93.69 , 88.82 , 55.80 , 53.24 , 39.48

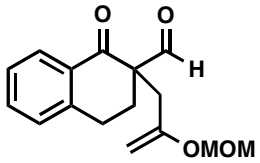


13(h): Obtained as a yellow oil (91% yield), [α]21D = -94.0 (*c* 0.02, CH_2Cl_2); ee = 90%, **HPLC**: Daicel CHIRALCEL OD-H column, 5% IPA in hexanes, 1.0 mL/min, λ=220 nm, t_R(major) = 7.6 min, t_R(minor) = 8.9 min; **IR** (CH_2Cl_2, film): 2944, 2868, 1738, 1713, 1637, 1454, 1293, 1178, 1156 cm^{-1}; ^{1}H NMR (500 MHz, Chloroform-d) δ 7.37 – 7.25 (m, 5H), 2.67 – 2.56 (m, 1H), 5.12 (s, 2H), 4.72 (d, *J* = 0.9 Hz, 2H), 4.22 – 4.08 (m, 1H), 3.97 – 3.86 (m, 1H), 3.31 (s, 1H), 2.93 (d, *J* = 14.3 Hz, 1H), 2.39 (dt, *J* = 13.7, 4.0 Hz, 1H), 2.32 (d, *J* = 14.3 Hz, 1H), 2.25 (td, *J* = 13.3, 5.8 Hz, 1H), 1.98 (ddp, *J* = 12.7, 6.7, 3.6 Hz, 1H), 1.81 (ddt, *J* = 16.7, 12.3, 3.9 Hz, 1H), 1.72 (dp, *J* = 11.8, 4.1 Hz, 1H), 1.60 (ddq, *J* = 17.8, 8.8, 4.4 Hz, 1H), 1.48 – 1.34 (m, 1H) ^{13}C NMR (126 MHz, Chloroform-d) δ 206.69 , 170.66 , 156.87 , 135.68 , 128.66 , 128.40 , 93.93 , 88.15 , 67.00 , 59.88 , 56.40 , 41.12 , 40.49 , 35.60 , 27.83 , 22.47 .



13(i): Obtained as a clear oil (67% yield), [α]21D = -5.18 (*c* 0.112, CH_2Cl_2); ee = 15%, **HPLC**: Daicel CHIRALCEL AS-H column, 5% IPA in hexanes, 1.0 mL/min, λ=220

nm, t_R(major) = 25.5 min, t_R(minor) = 47.4 min; **IR** (CH_2Cl_2, film): 2955, 2922, 1774, 1730, 1210, 1163 cm^{-1}; ^1H NMR (500 MHz, Chloroform-d) δ 7.45 – 7.26 (m, 5H), 5.18 (s, 2H), 4.79 (q, *J* = 6.3 Hz, 2H), 4.34 – 4.26 (m, 2H), 4.21 (d, *J* = 2.3 Hz, 1H), 4.07 (d, *J* = 2.2 Hz, 1H), 3.32 (s, 3H), 2.97 (d, *J* = 14.5 Hz, 1H), 2.74 – 2.67 (m, 2H), 2.39 (dt, *J* = 13.4, 8.8 Hz, 1H) ^{13}C NMR (126 MHz, Chloroform-d) δ 174.36 , 168.93 , 155.62 , 135.11 , 128.59 , 128.41 , 128.12 , 93.63 , 88.61 , 67.80 , 66.32 , 56.36 , 52.99 , 39.23 , 30.50 .



13(j): Obtained as a yellow oil (77% yield), [α]21D = -55.71 (*c* 0.189, CH_2Cl_2); ee = 70%, **HPLC**: Daicel CHIRALCEL AD-H column, 2% IPA in hexanes, 1.0 mL/min, λ= 220 nm, t_R(major) = 12 min, t_R(minor) = 17.8 min; **IR** (CH_2Cl_2, film): 3055, 2980, 2959, 2934, 1726, 1670, 1153 cm^{-1}; ^1H NMR (500 MHz, Chloroform-d) δ 9.84 (s, 1H), 7.97 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.47 (td, *J* = 7.5, 1.5 Hz, 1H), 7.33 – 7.26 (m, 1H), 7.21 (d, *J* = 7.7 Hz, 1H), 4.85 – 4.74 (m, 3H), 4.25 (d, *J* = 2.2 Hz, 1H), 4.07 (d, *J* = 2.2 Hz, 1H), 3.29 (s, 3H), 3.10 – 3.01 (m, 2H), 2.95 (ddd, *J* = 17.1, 7.8, 4.8 Hz, 1H), 2.63 (d, *J* = 14.4 Hz, 1H), 2.51 (ddd, *J* = 14.1, 7.8, 4.9 Hz, 1H), 2.04 (ddd, *J* = 13.5, 8.1, 4.8 Hz, 1H) ^{13}C NMR (126 MHz, Chloroform-d) δ 200.87 , 196.00 , 155.73 , 143.53 , 133.91 , 131.51 , 128.59 , 127.73 , 126.78 , 93.61 , 88.36 , 60.24 , 56.34 , 39.13 , 25.44 , 25.14

^{13}C and ^{1}H Nuclear Magnetic Resonance Data

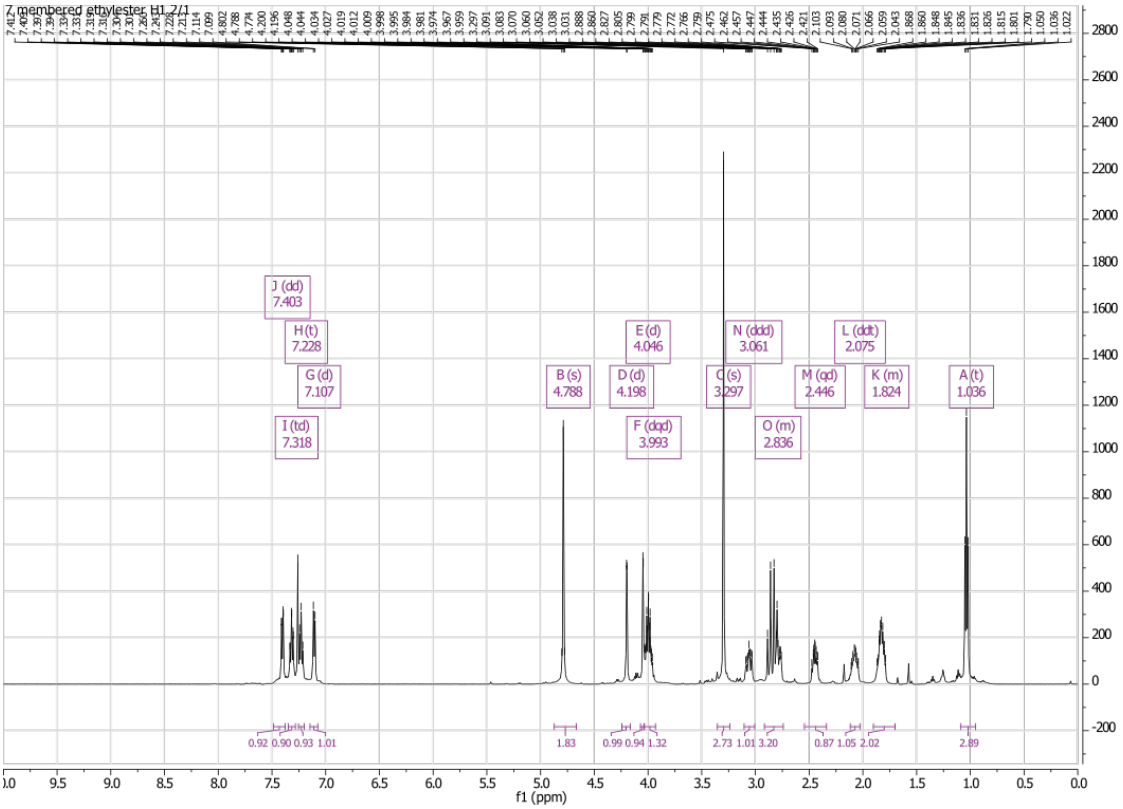


Figure 1.11 ^{1}H NMR spectrum of compound 13(c) in $CDCl_3$

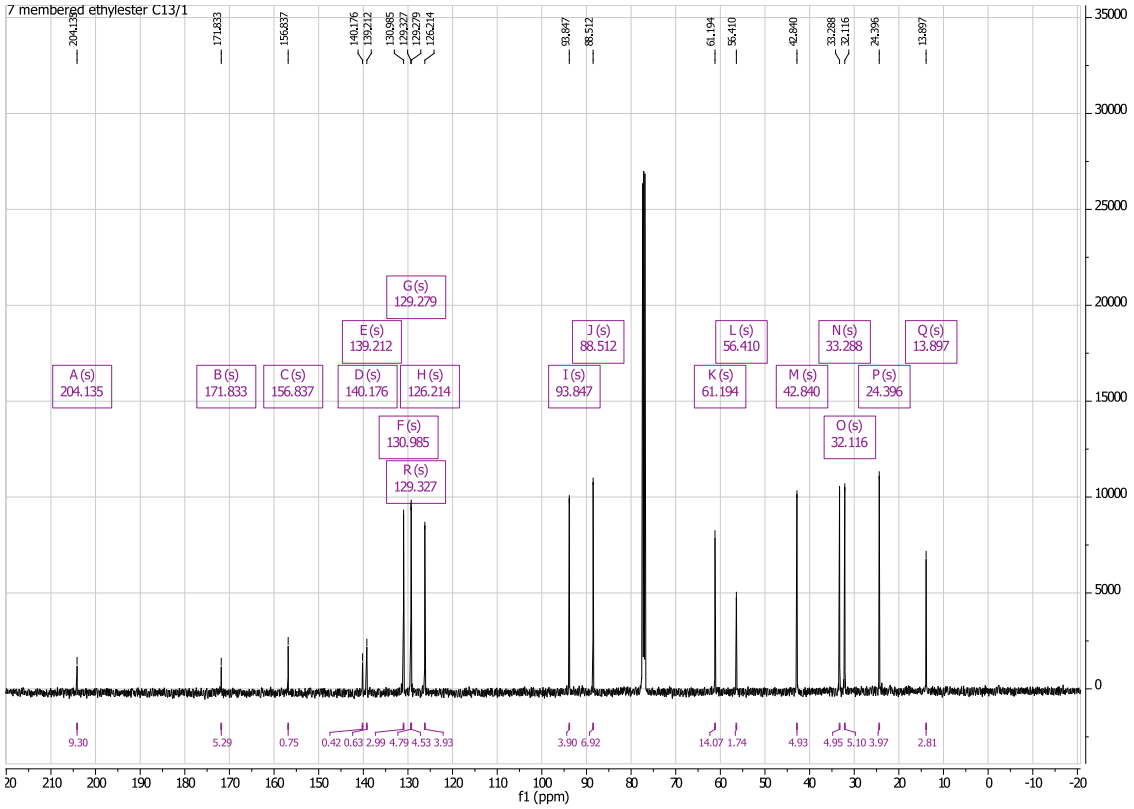


Figure 1.12 ^{13}C NMR spectrum of compound 13(c) in $CDCl_3$

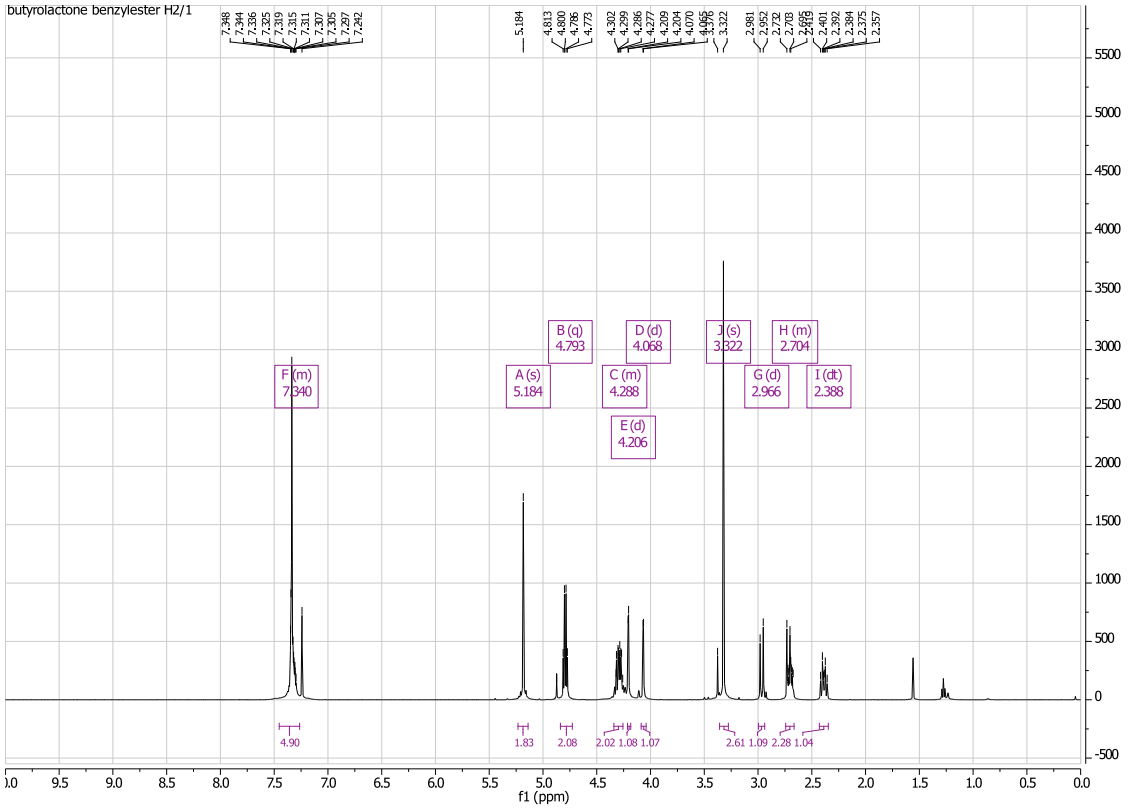


Figure 1.13 ^{1}H NMR spectrum of compound 13(i) in $CDCl_3$

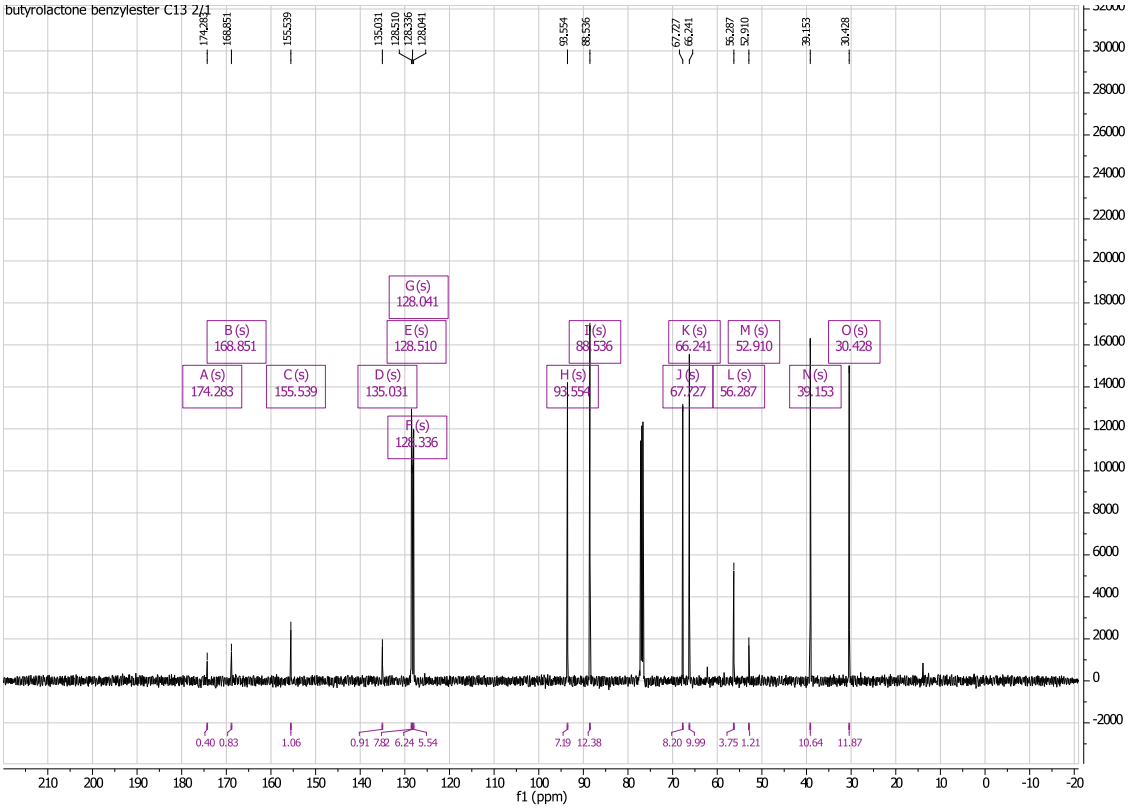


Figure 1.14 ^{13}C NMR spectrum of compound 13(i) in $CDCl_3$

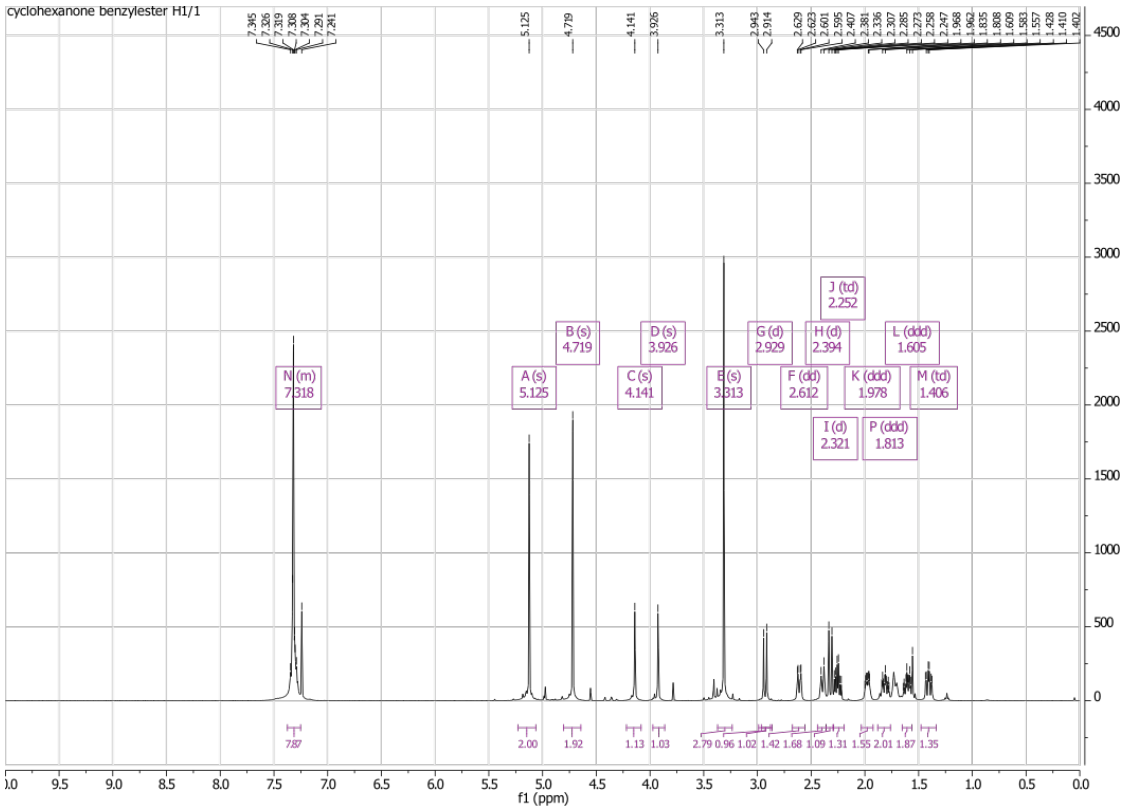


Figure 1.15 ^{1}H NMR spectrum of compound 13(h) in $CDCl_3$

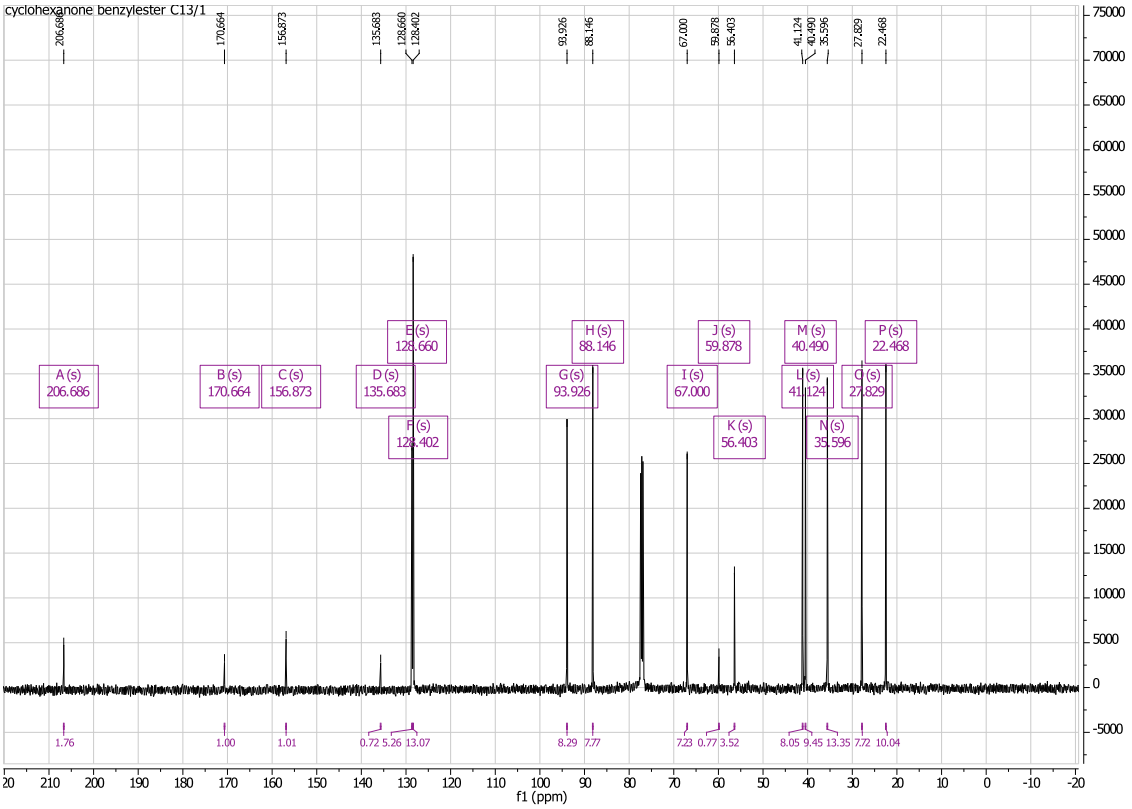


Figure 1.16 ^{13}C NMR spectrum of compound 13(h) in $CDCl_3$

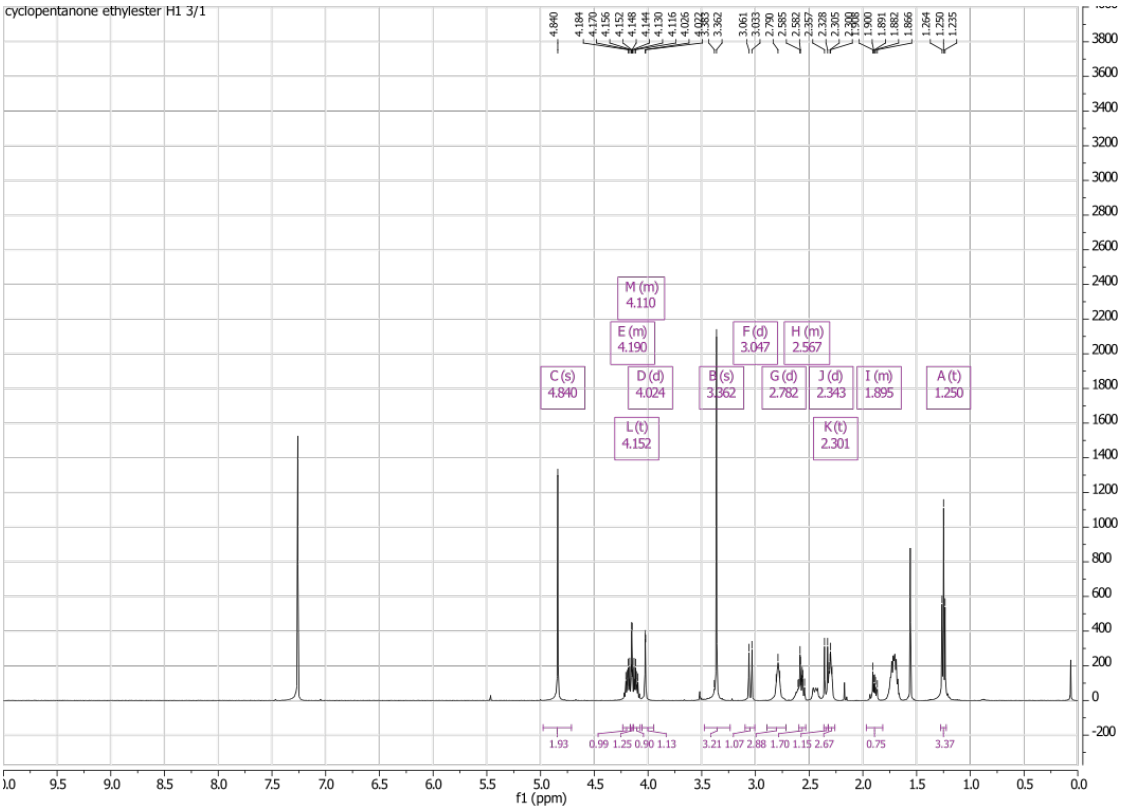


Figure 1.17 ^{1}H NMR spectrum of compound 13(f) in $CDCl_3$

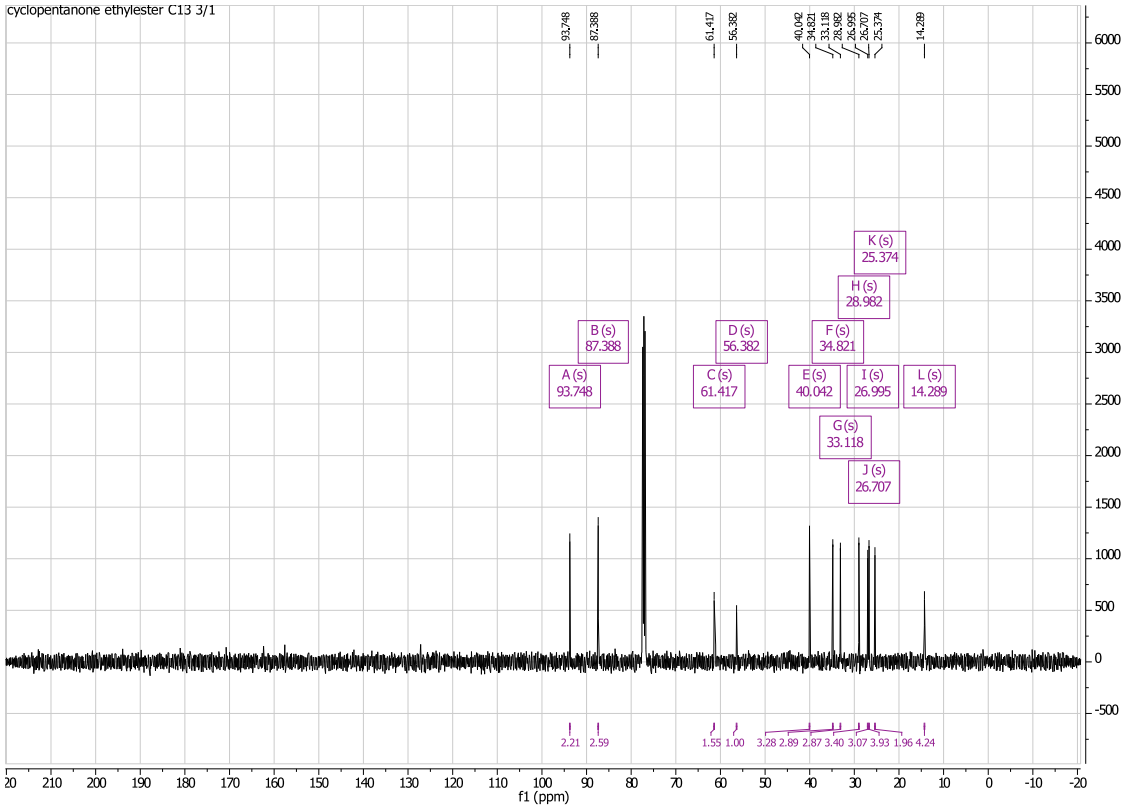


Figure 1.18 ^{13}C NMR spectrum of compound 13(f) in $CDCl_3$

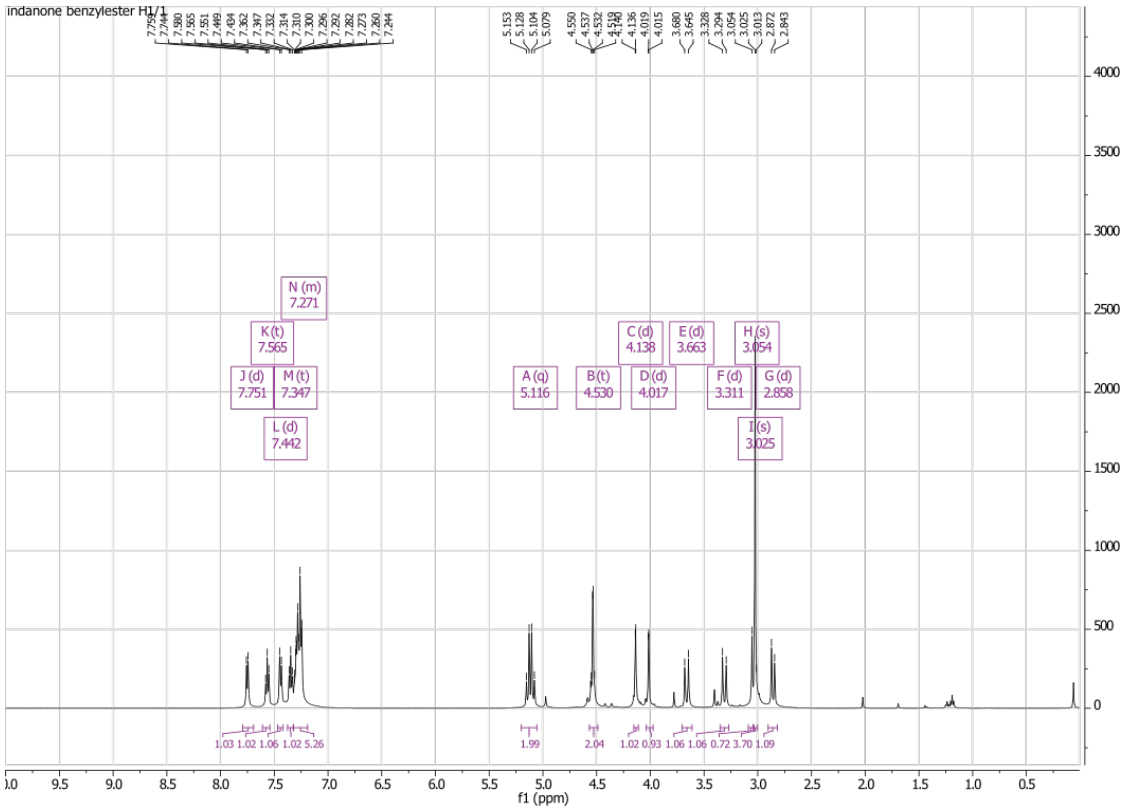


Figure 1.19 ^{1}H NMR spectrum of compound 13(a) in $CDCl_3$

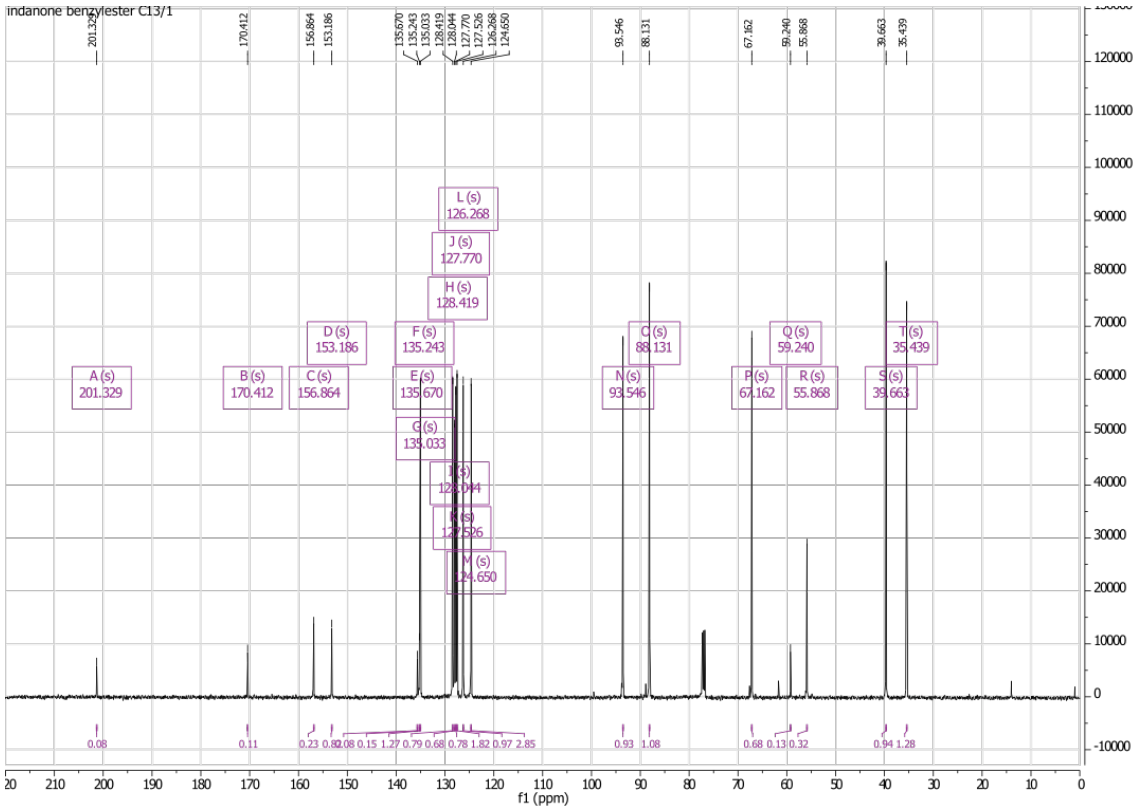


Figure 1.20 ^{13}C NMR spectrum of compound 13(a) in $CDCl_3$

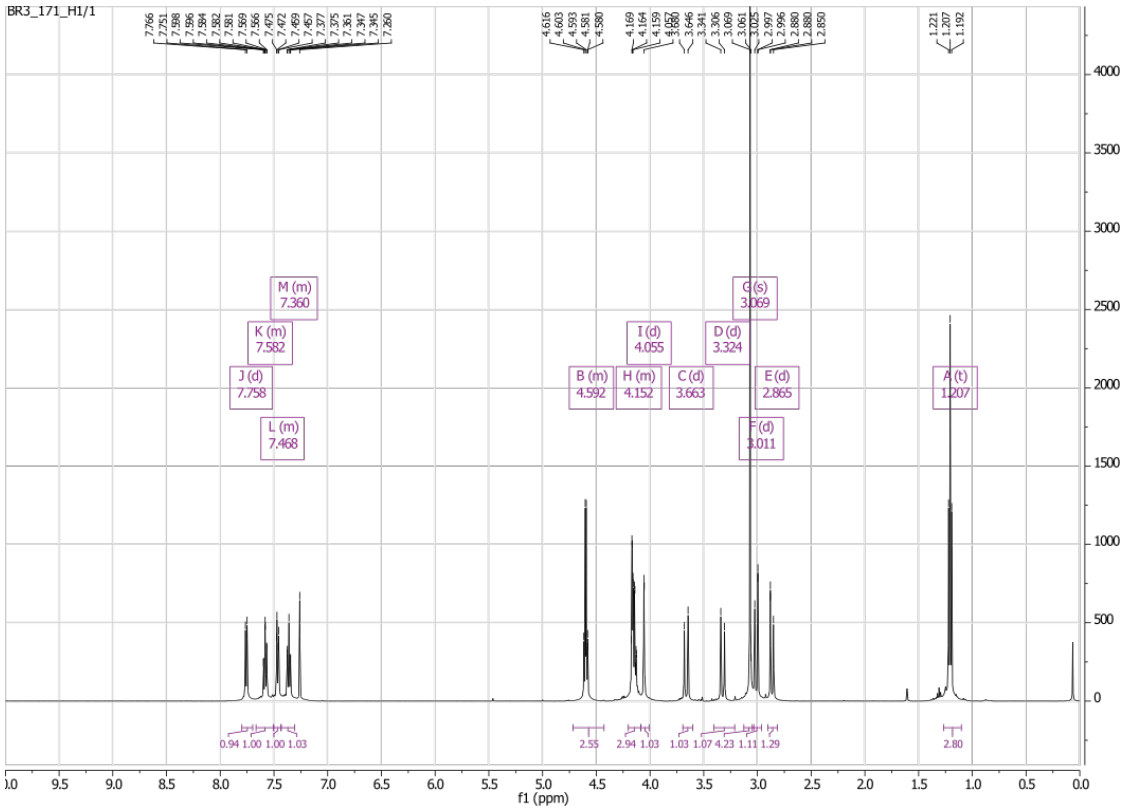


Figure 1.21 ^{1}H NMR spectrum of compound 13(b) in $CDCl_3$

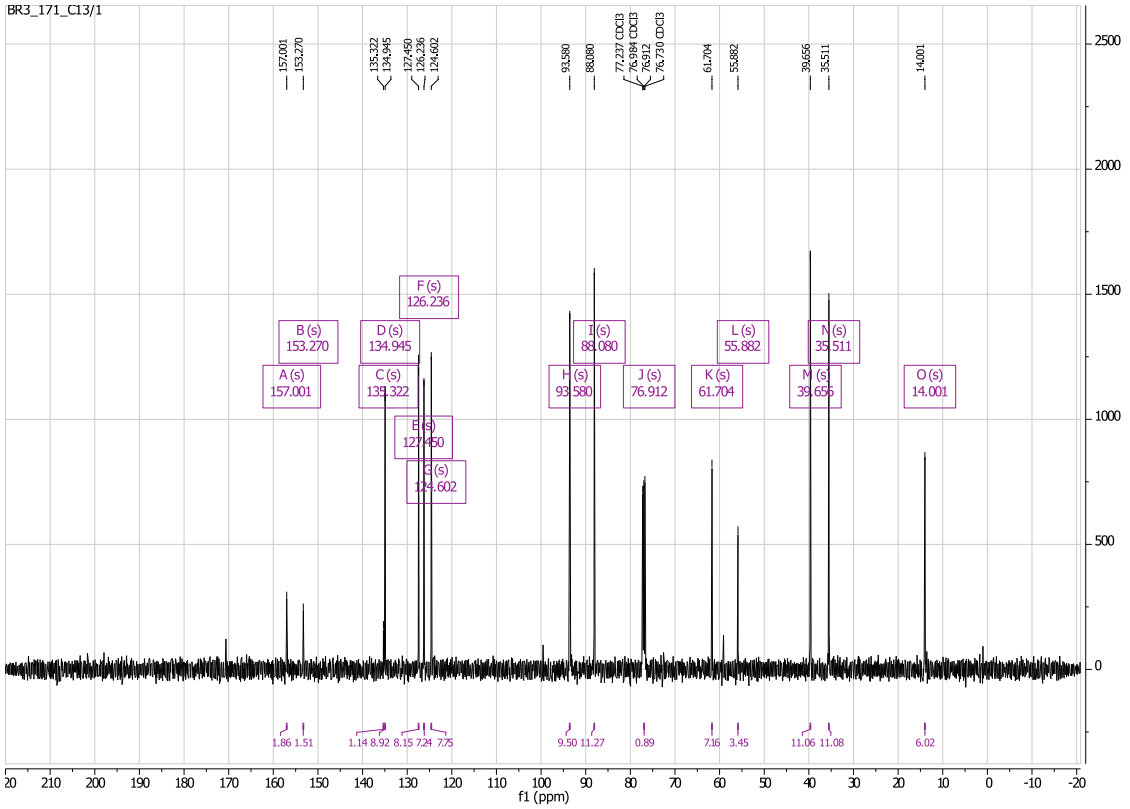


Figure 1.22 ^{13}C NMR spectrum of compound 13(b) in $CDCl_3$

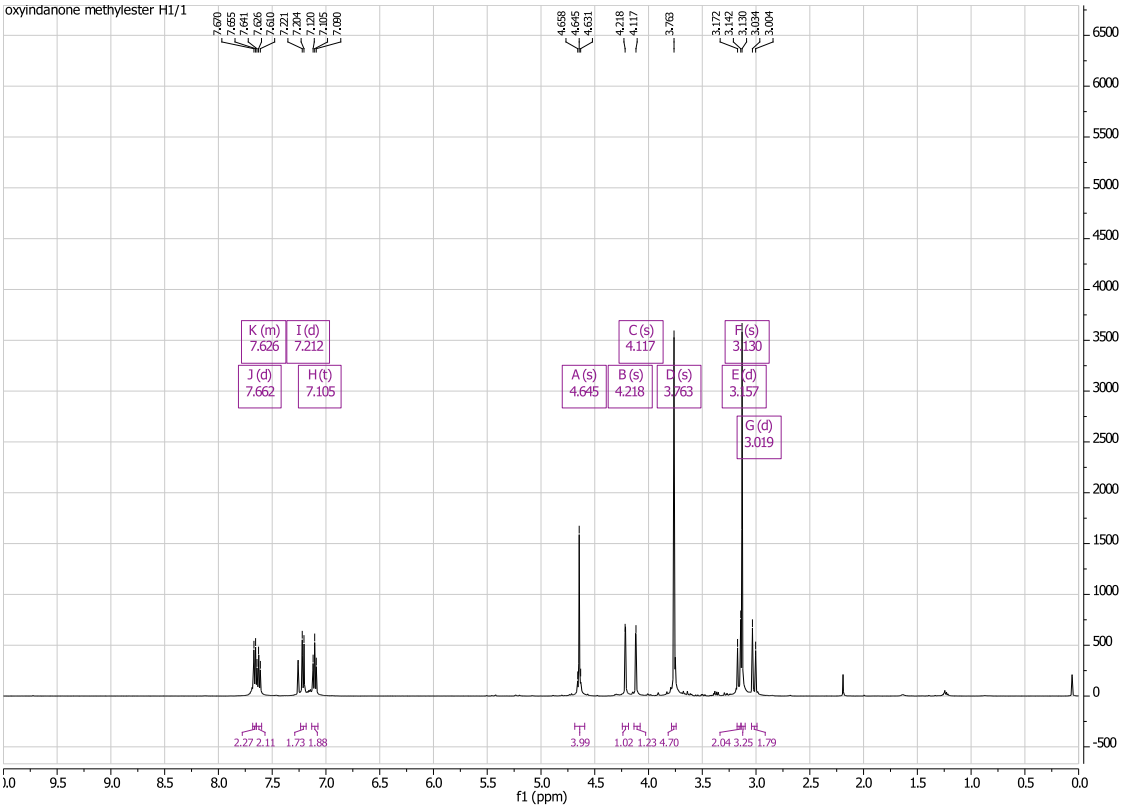


Figure 1.23 ^{1}H NMR spectrum of compound 13(g) in $CDCl_3$

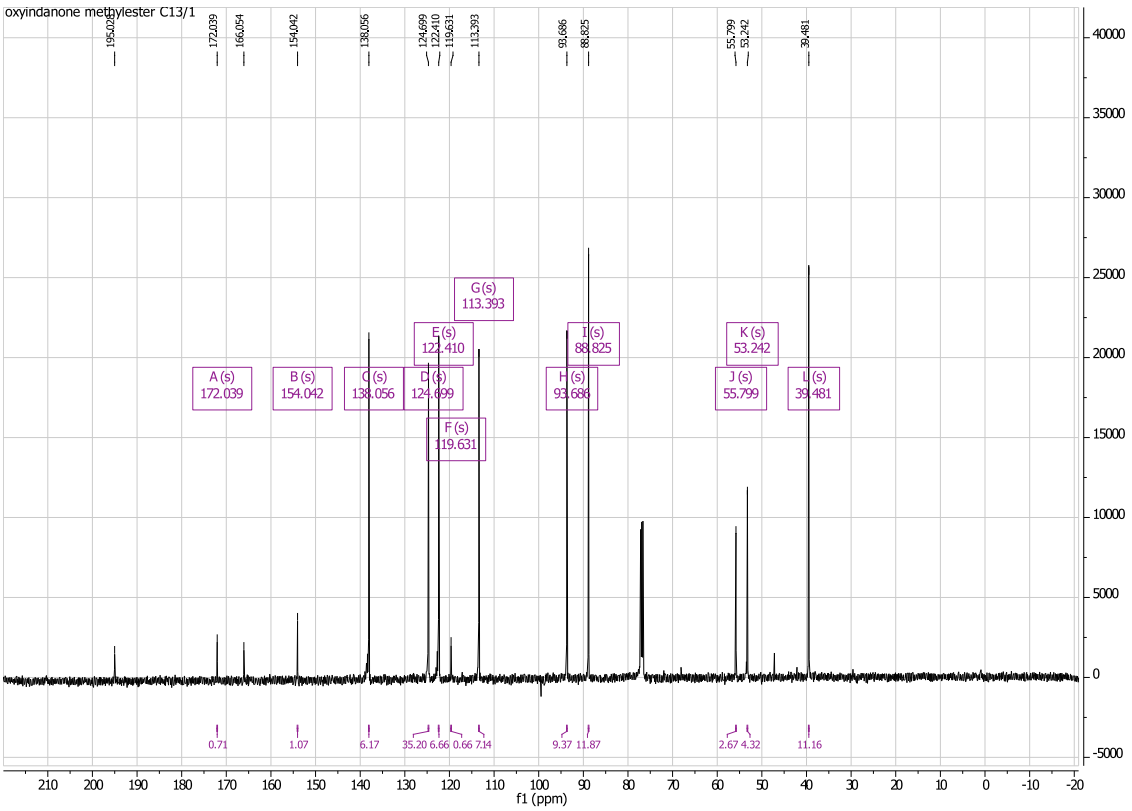


Figure 1.24 ^{13}C NMR spectrum of compound 13(g) in $CDCl_3$

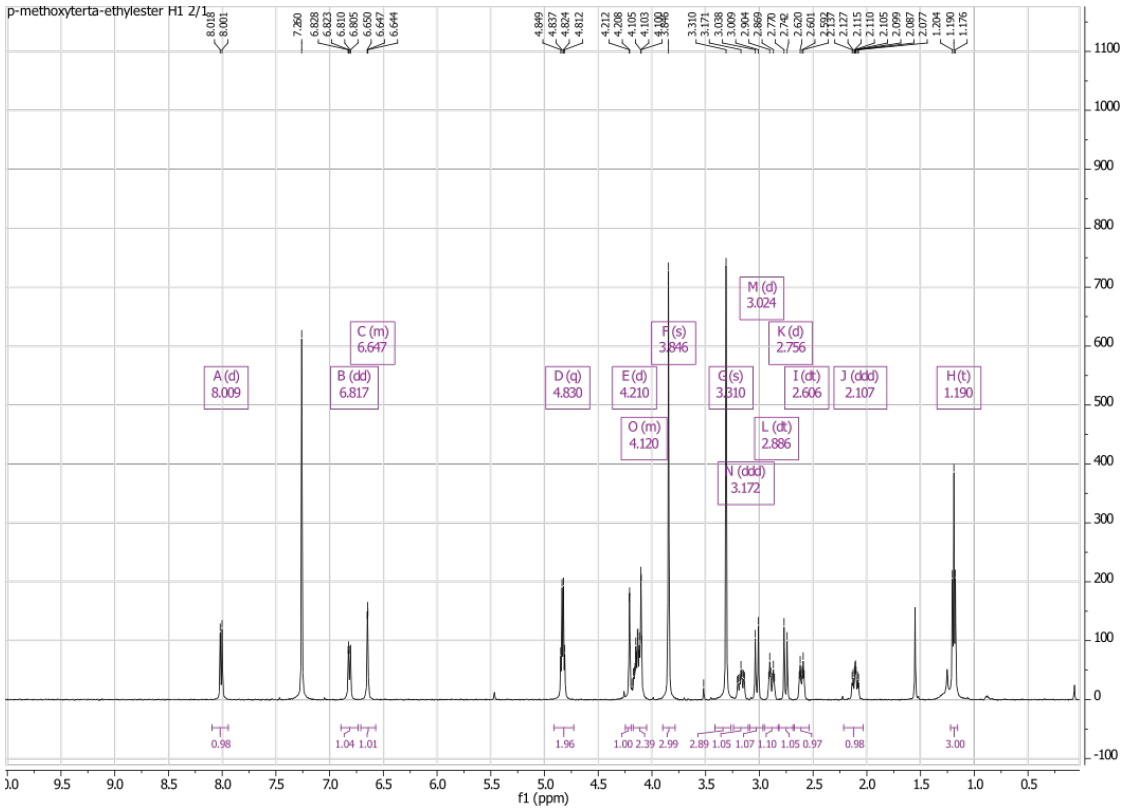


Figure 1.25 ^{1}H NMR spectrum of compound 13(d) in $CDCl_3$

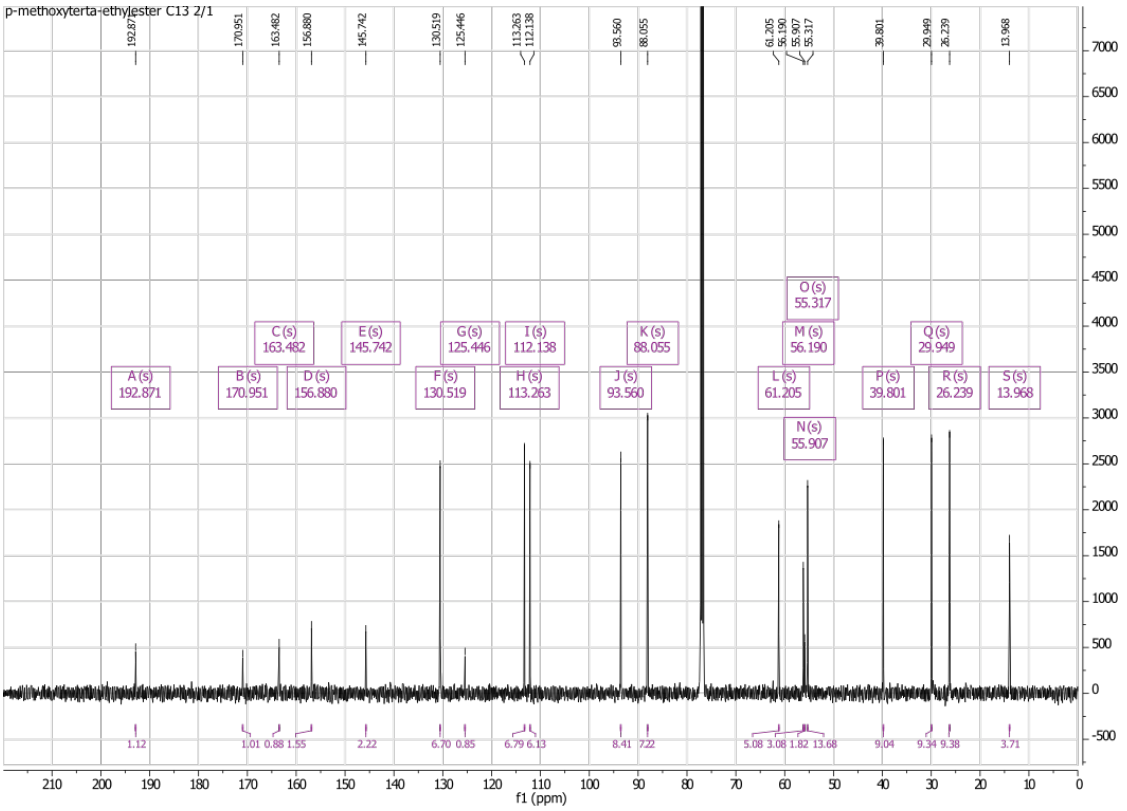


Figure 1.26 ^{13}C NMR spectrum of compound 13(d) in $CDCl_3$

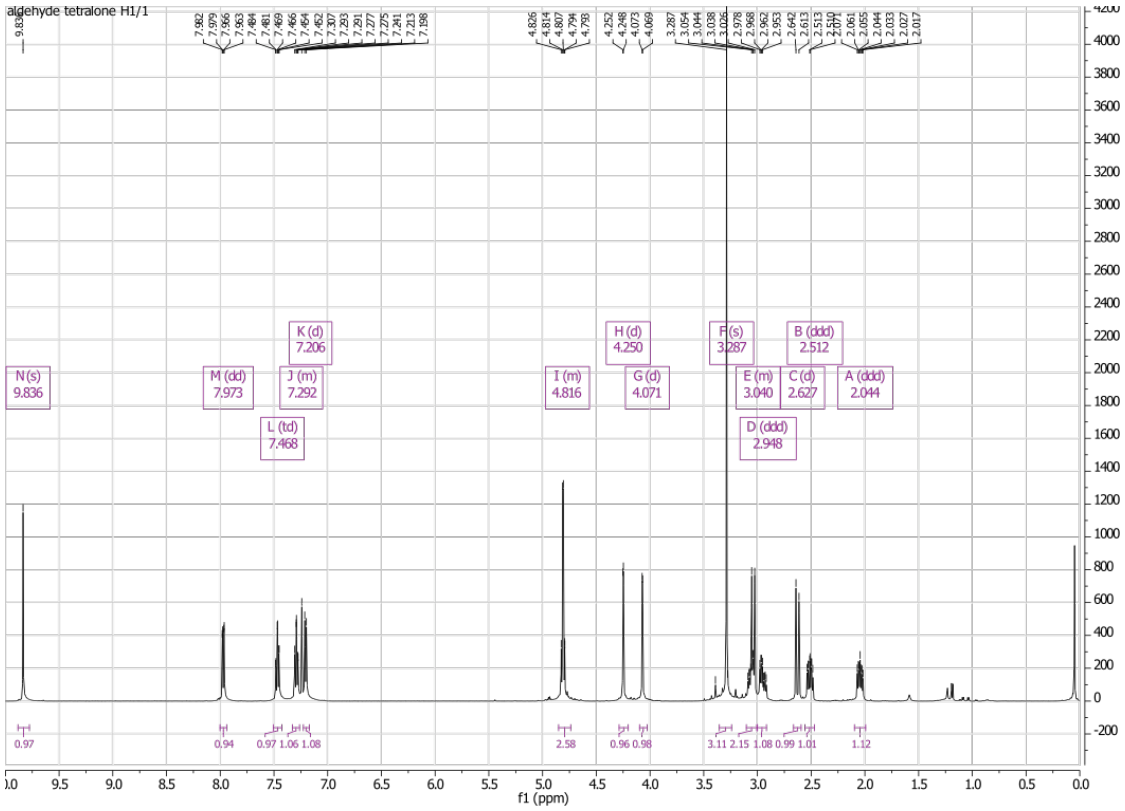


Figure 1.27 ^{1}H NMR spectrum of compound 13(j) in $CDCl_3$

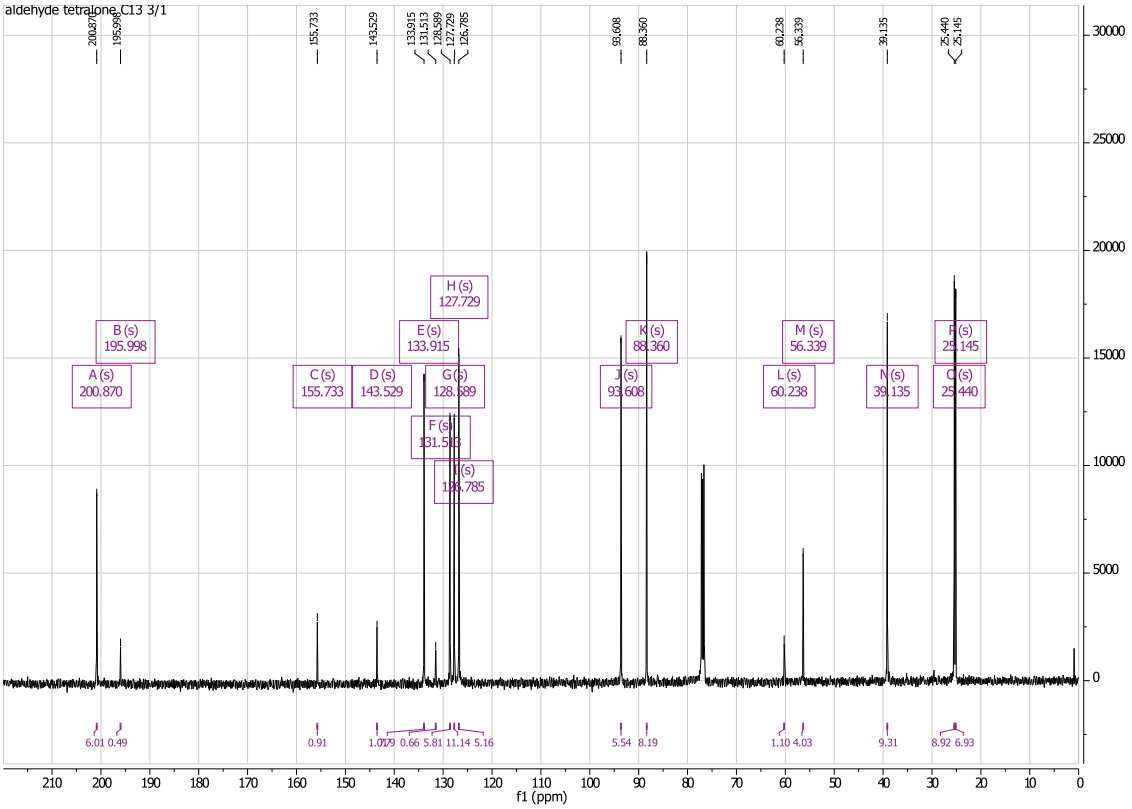


Figure 1.28 ^{13}C NMR spectrum of compound 13(j) in $CDCl_3$

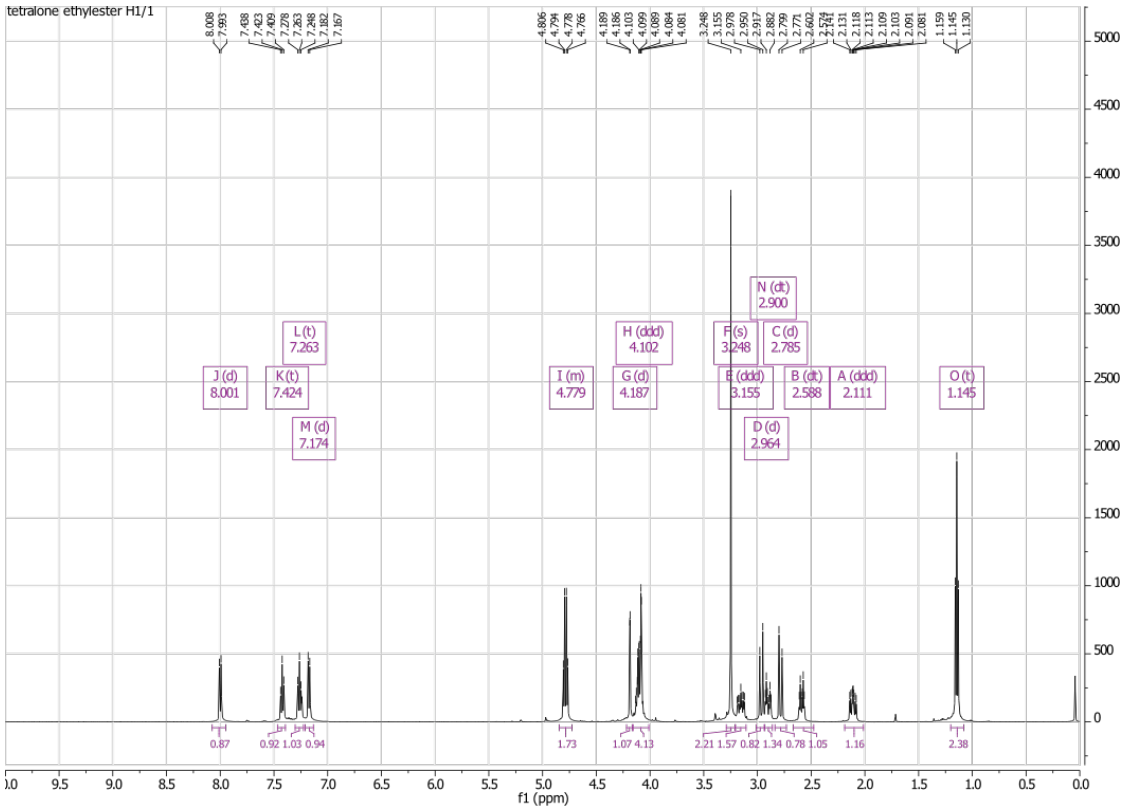


Figure 1.29 ^{1}H NMR spectrum of compound 13(e) in $CDCl_3$

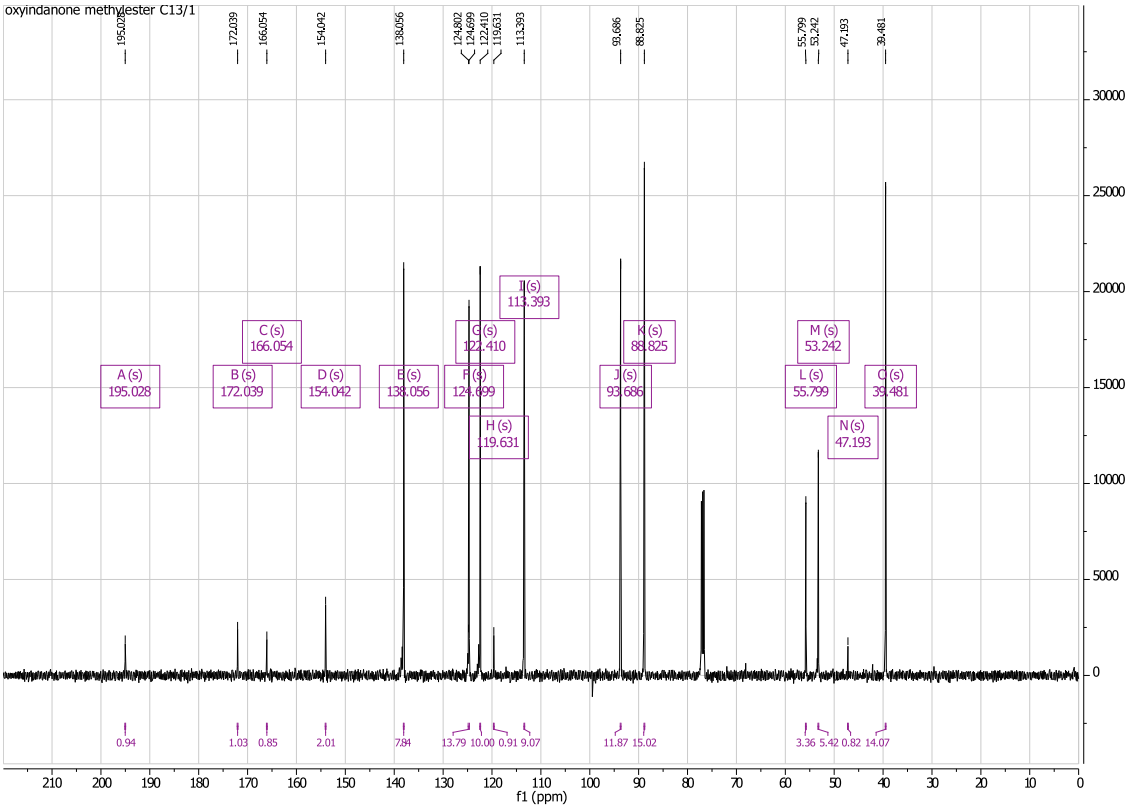
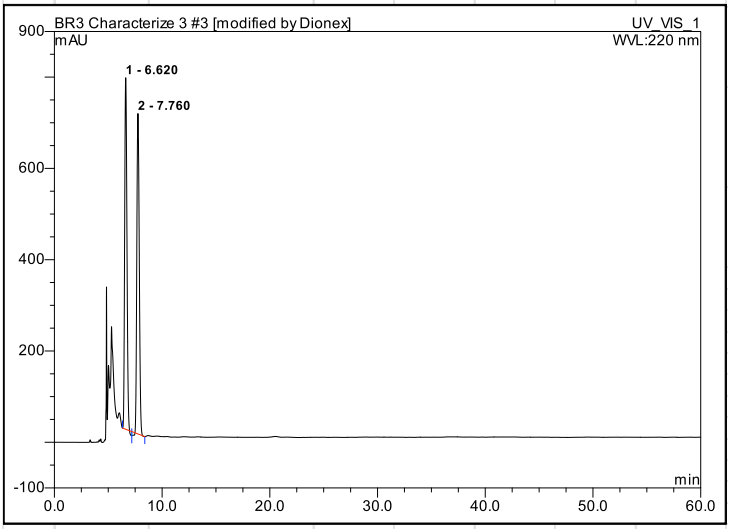
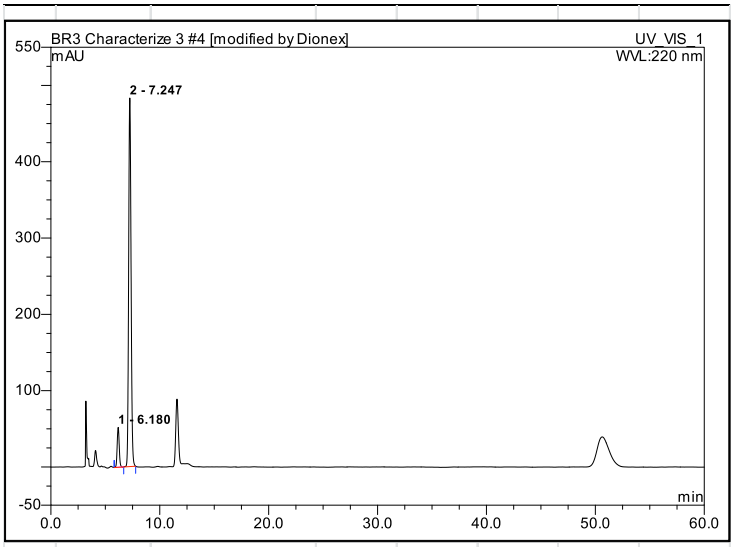


Figure 1.30 ^{13}C NMR spectrum of compound 13(e) in $CDCl_3$

HPLC Data

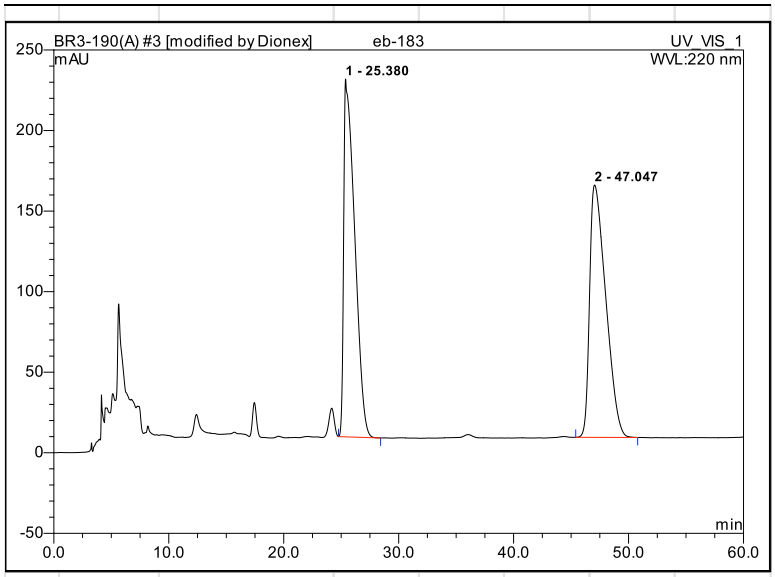


No.	Ret.Time	Peak Name	Height	Area	Rel.Area	Amount	Type
	min		mAU	mAU*min	%		
1	6.62	n.a.	770.068	187.252	50.45	n.a.	BM *
2	7.76	n.a.	702.079	183.881	49.55	n.a.	MB*
Total:			1472.147	371.133	100.00	0.000	

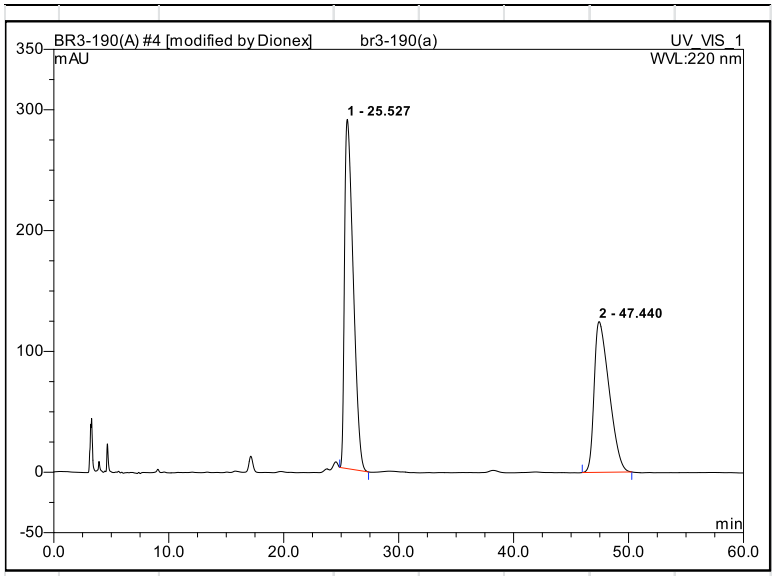


No.	Ret.Time	Peak Name	Height	Area	Rel.Area	Amount	Type
	min		mAU	mAU*min	%		
1	6.18	n.a.	52.180	11.297	8.36	n.a.	Ru*
2	7.25	n.a.	482.990	123.781	91.64	n.a.	BMB*
Total:			535.170	135.077	100.00	0.000	

Figure 1.31 Racemic and Stereoselective HPLC for compound 13(c)

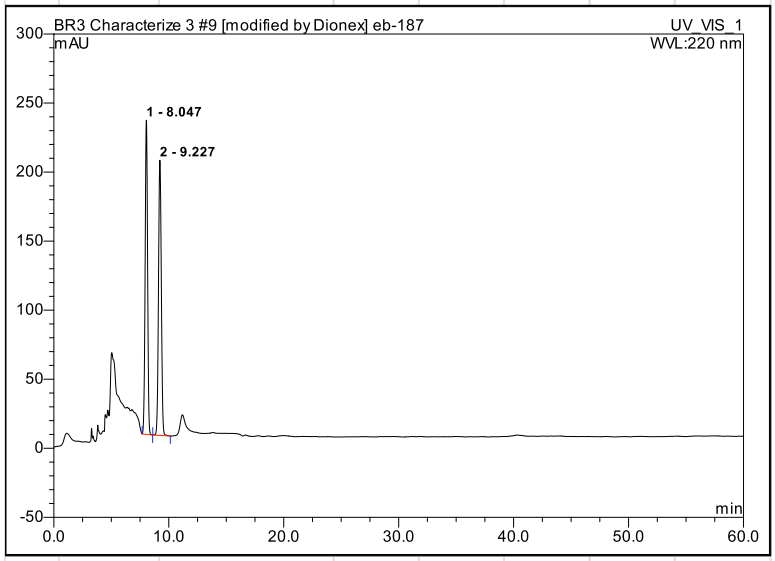


No.	Ret.Time	Peak Name	Height	Area	Rel.Area	Amount	Type
	min		mAU	mAU*min	%		
1	25.38	n.a.	222.080	246.636	49.20	n.a.	BMB*
2	47.05	n.a.	156.633	254.695	50.80	n.a.	BMB
Total:			378.714	501.331	100.00	0.000	

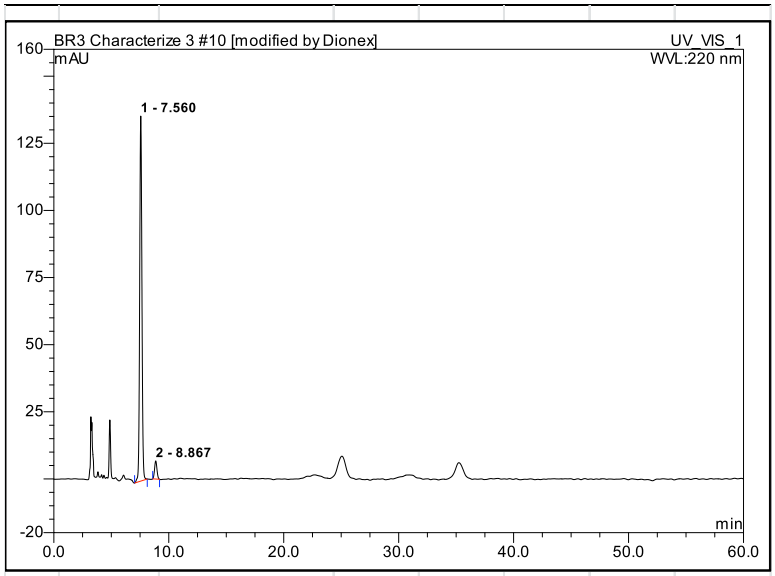


No.	Ret.Time	Peak Name	Height	Area	Rel.Area	Amount	Type
	min		mAU	mAU*min	%		
1	25.53	n.a.	288.999	253.971	57.45	n.a.	BMB*
2	47.44	n.a.	124.732	188.121	42.55	n.a.	BMB*
Total:			413.731	442.092	100.00	0.000	

Figure 1.32 Racemic and Stereoselective HPLC for compound 13(i)

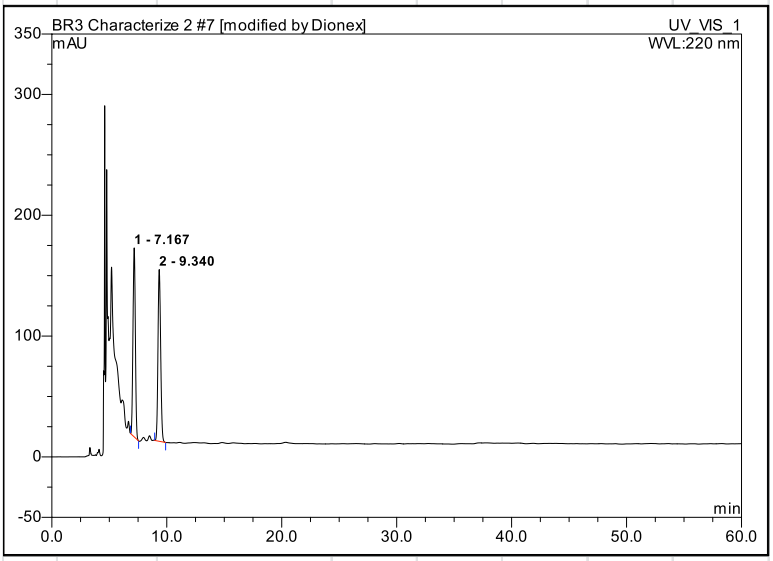


No.	Ret.Time	Peak Name	Height	Area	Rel.Area	Amount	Type
	min		mAU	mAU*min	%		
1	8.05	n.a.	227.514	56.115	49.71	n.a.	BMB
2	9.23	n.a.	199.320	56.773	50.29	n.a.	BMB
Total:			426.834	112.888	100.00	0.000	

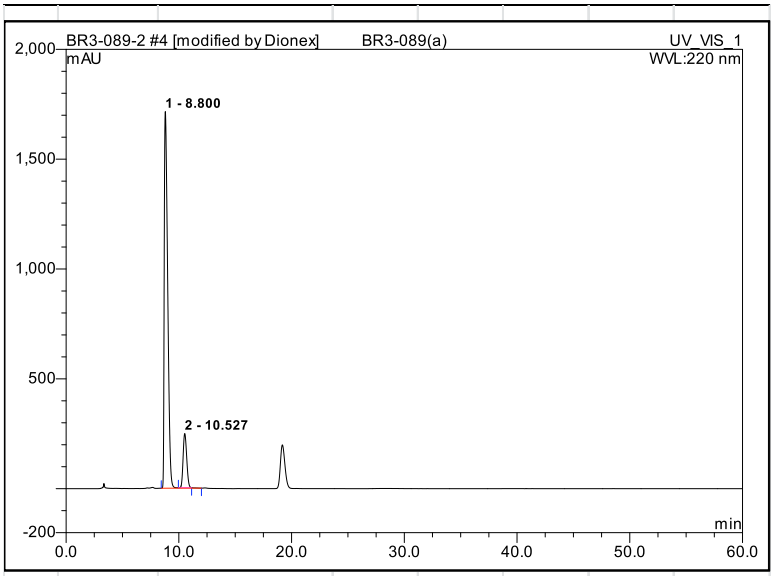


No.	Ret.Time	Peak Name	Height	Area	Rel.Area	Amount	Type
	min		mAU	mAU*min	%		
1	7.56	n.a.	135.965	30.562	94.97	n.a.	BMB*
2	8.87	n.a.	6.742	1.620	5.03	n.a.	BMB*
Total:			142.706	32.181	100.00	0.000	

Figure 1.33 Racemic and Stereoselective HPLC for compound 13(h)

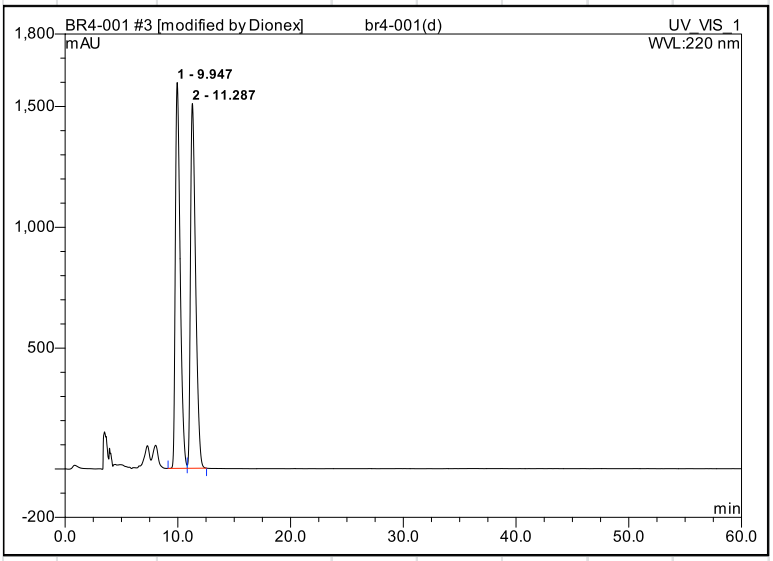


No.	Ret.Time	Peak Name	Height	Area	Rel.Area	Amount	Type
	min		mAU	mAU*min	%		
1	7.17	n.a.	156.420	37.486	49.42	n.a.	BMB
2	9.34	n.a.	142.138	38.365	50.58	n.a.	BMB
Total:			298.558	75.851	100.00	0.000	

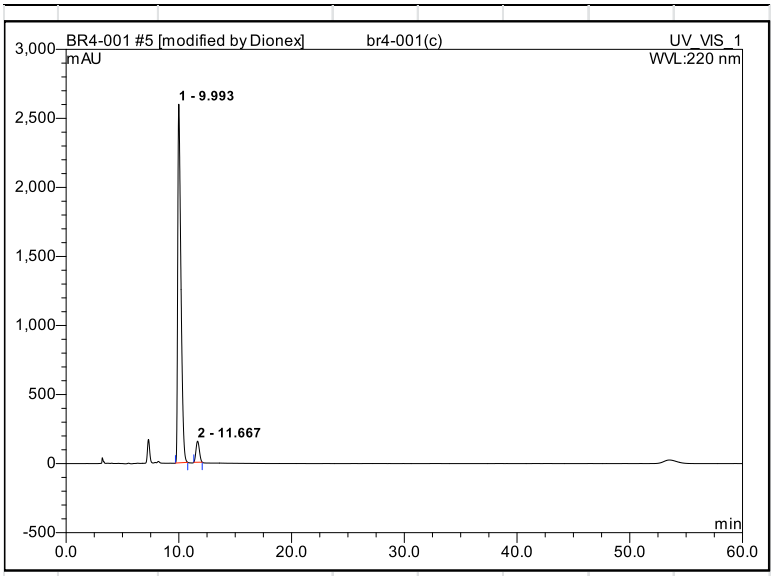


No.	Ret.Time	Peak Name	Height	Area	Rel.Area	Amount	Type
	min		mAU	mAU*min	%		
1	8.80	n.a.	1714.275	609.910	87.05	n.a.	BMB*
2	10.53	n.a.	246.855	90.759	12.95	n.a.	Rd*
Total:			1961.130	700.669	100.00	0.000	

Figure 1.34 Racemic and Stereoselective HPLC for compound 13(f)

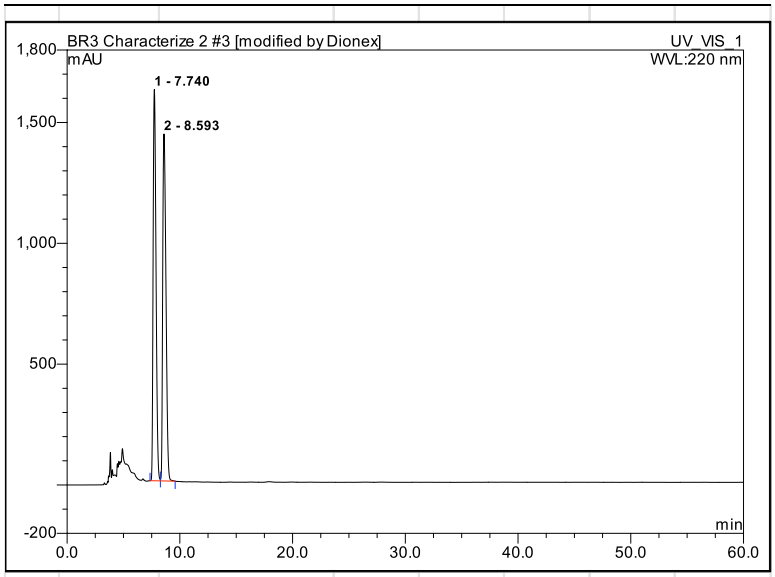


No.	Ret.Time	Peak Name	Height	Area	Rel.Area	Amount	Type
	min		mAU	mAU*min	%		
1	9.95	n.a.	1596.705	794.469	49.87	n.a.	BM *
2	11.29	n.a.	1509.421	798.585	50.13	n.a.	MB*
Total:			3106.126	1593.054	100.00	0.000	

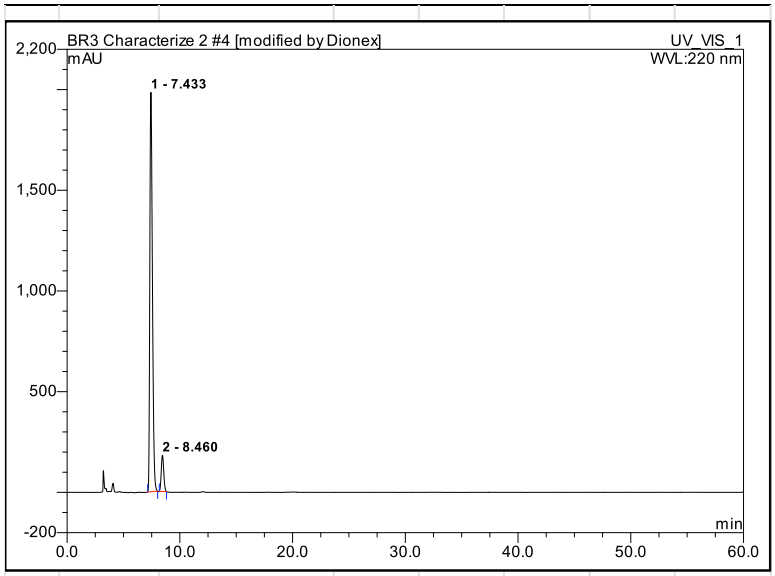


No.	Ret.Time	Peak Name	Height	Area	Rel.Area	Amount	Type
	min		mAU	mAU*min	%		
1	9.99	n.a.	2597.305	856.067	94.15	n.a.	BMB*
2	11.67	n.a.	152.413	53.192	5.85	n.a.	BMB*
Total:			2749.717	909.259	100.00	0.000	

Figure 1.35 Racemic and Stereoselective HPLC for compound 13(a)

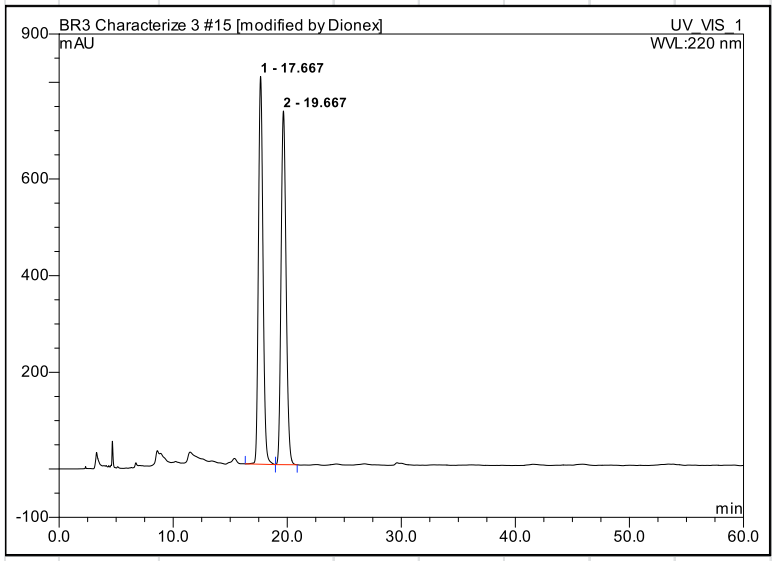


No.	Ret.Time	Peak Name	Height	Area	Rel.Area	Amount	Type
	min		mAU	mAU*min	%		
1	7.74	n.a.	1619.212	477.035	49.91	n.a.	BM *
2	8.59	n.a.	1435.974	478.756	50.09	n.a.	MB*
Total:			3055.186	955.791	100.00	0.000	

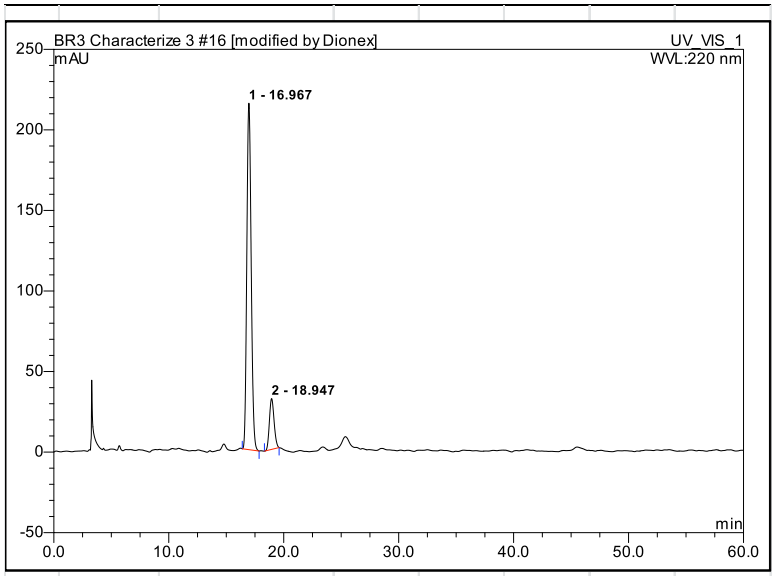


No.	Ret.Time	Peak Name	Height	Area	Rel.Area	Amount	Type
	min		mAU	mAU*min	%		
1	7.43	n.a.	1983.135	531.284	92.10	n.a.	BMB*
2	8.46	n.a.	179.601	45.579	7.90	n.a.	BMB*
Total:			2162.737	576.863	100.00	0.000	

Figure 1.36 Racemic and Stereoselective HPLC for compound 13(b)

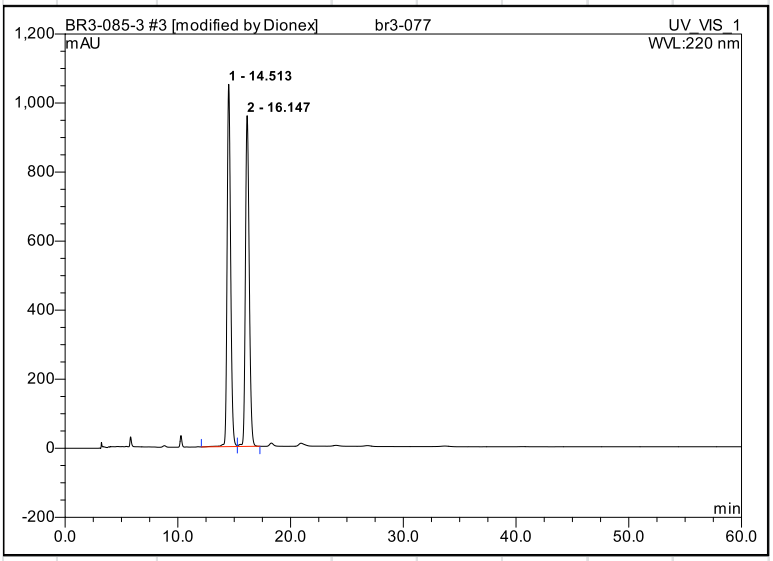


No.	Ret.Time	Peak Name	Height	Area	Rel.Area	Amount	Type
	min		mAU	mAU*min	%		
1	17.67	n.a.	802.476	373.820	49.99	n.a.	BMB*
2	19.67	n.a.	731.810	374.005	50.01	n.a.	BMB*
Total:			1534.285	747.825	100.00	0.000	

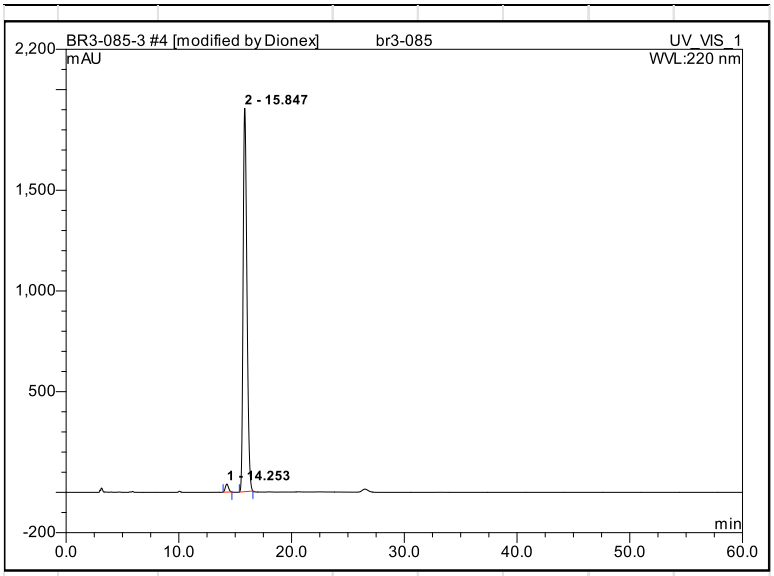


No.	Ret.Time	Peak Name	Height	Area	Rel.Area	Amount	Type
	min		mAU	mAU*min	%		
1	16.97	n.a.	215.019	94.761	86.40	n.a.	BMB
2	18.95	n.a.	31.557	14.912	13.60	n.a.	BMB*
Total:			246.576	109.673	100.00	0.000	

Figure 1.37 Racemic and Stereoselective HPLC for compound 13(g)

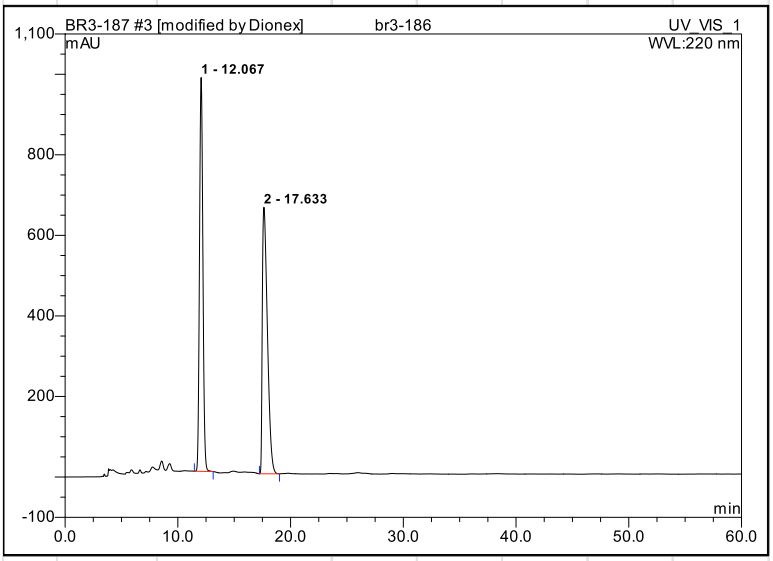


No.	Ret.Time	Peak Name	Height	Area	Rel.Area	Amount	Type
	min		mAU	mAU*min	%		
1	14.51	n.a.	1049.451	379.783	50.23	n.a.	BM *
2	16.15	n.a.	957.990	376.272	49.77	n.a.	MB*
Total:			2007.442	756.055	100.00	0.000	

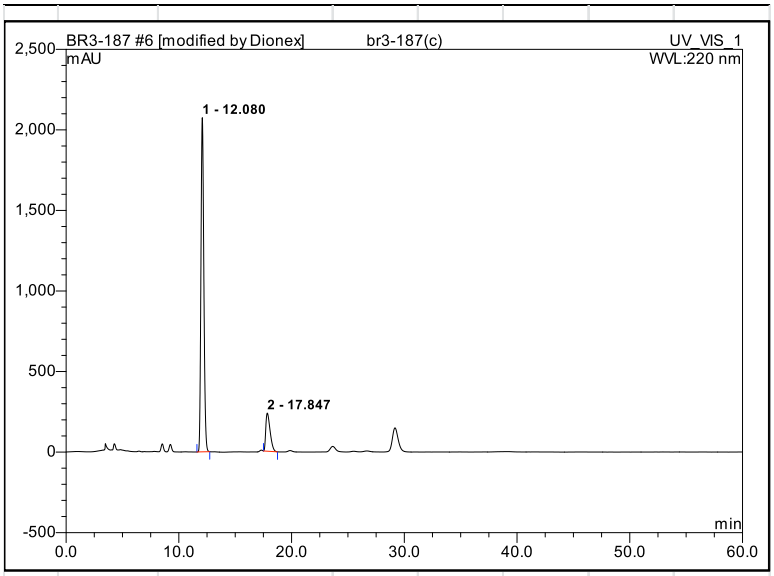


No.	Ret.Time	Peak Name	Height	Area	Rel.Area	Amount	Type
	min		mAU	mAU*min	%		
1	14.25	n.a.	39.582	13.059	1.72	n.a.	BMB*
2	15.85	n.a.	1904.275	746.382	98.28	n.a.	BMB*
Total:			1943.857	759.441	100.00	0.000	

Figure 1.38 Racemic and Stereoselective HPLC for compound 13(d)

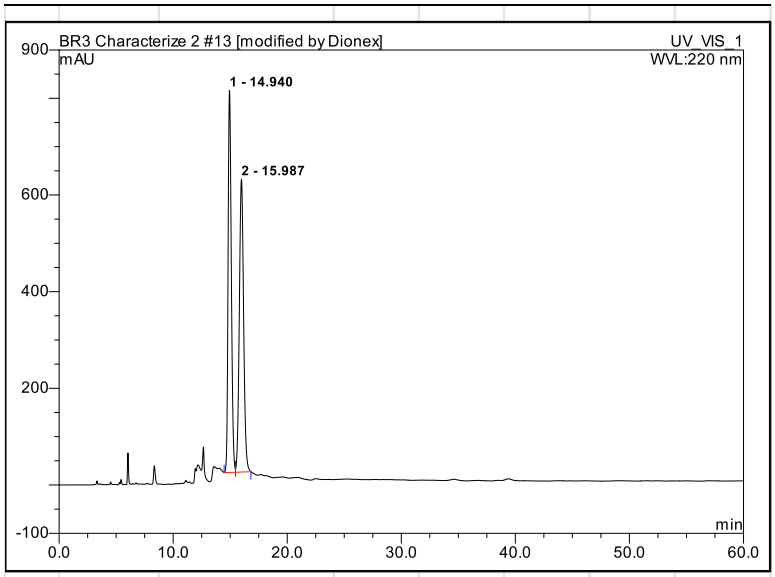


No.	Ret.Time	Peak Name	Height	Area	Rel.Area	Amount	Type
	min		mAU	mAU*min	%		
1	12.07	n.a.	977.697	340.837	49.55	n.a.	BMB*
2	17.63	n.a.	661.788	347.027	50.45	n.a.	BMB*
Total:			1639.485	687.864	100.00	0.000	

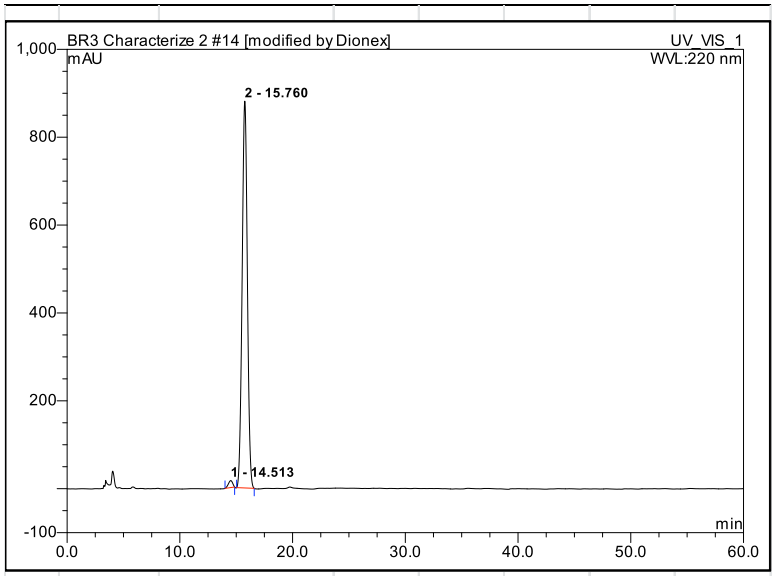


No.	Ret.Time	Peak Name	Height	Area	Rel.Area	Amount	Type
	min		mAU	mAU*min	%		
1	12.08	n.a.	2074.072	614.204	85.39	n.a.	BMB*
2	17.85	n.a.	236.519	105.092	14.61	n.a.	BMB*
Total:			2310.591	719.297	100.00	0.000	

Figure 1.39 Racemic and Stereoselective HPLC for compound 13(j)



No.	Ret.Time	Peak Name	Height	Area	Rel.Area	Amount	Type
	min		mAU	mAU*min	%		
1	14.94	n.a.	790.886	259.048	49.52	n.a.	BM *
2	15.99	n.a.	606.180	264.114	50.48	n.a.	MB*
Total:			1397.065	523.161	100.00	0.000	



No.	Ret.Time	Peak Name	Height	Area	Rel.Area	Amount	Type
	min		mAU	mAU*min	%		
1	14.51	n.a.	15.854	6.900	1.44	n.a.	BMB*
2	15.76	n.a.	880.344	473.204	98.56	n.a.	BMB*
Total:			896.197	480.103	100.00	0.000	

Figure 1.40 Racemic and Stereoselective HPLC for compound 13(e)

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