

UNIVERSITY OF CALIFORNIA

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Development of Asymmetric Alkylation Chemistry Using Chiral Lithium Amides and
Application to the Total Synthesis of (+)-Dragmacidin D

A dissertation submitted in partial satisfaction of the requirements for the
degree Doctor of Philosophy in Chemistry

by

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Jeffrey James Jackson

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2. Lu, P.; Jackson, J. J.; Eickhoff, J.; Zakarian, A. Direct Enantioselective Conjugate Addition of Carboxylic Acids with Chiral Lithium Amides as Traceless Auxiliaries. *J. Am. Chem. Soc.*, **2015**, *137*, 656-659.
3. Xiao, Q.; Jackson, J. J.; Basak, A.; Bowler, J. M.; Miller, B. G.; Zakarian, A. Enantioselective synthesis of tatanans A-C and reinvestigation of their glucokinase-activating properties. *Nature Chem.*, **2013**, *5*, 410-416.
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Abstract

Development of Asymmetric Alkylation Chemistry Using Chiral Lithium Amides and Application to the Total Synthesis of (+)-Dragmacidin D

by

Jeffrey James Jackson

Asymmetric alkylation of enolates has been the subject of vigorous investigation for several decades as researchers are constantly aiming to increase the efficiency of stereoselective C–C bond constructions, a cornerstone in asymmetric synthesis. Furthermore, Michael addition is a premier synthetic method for carbon–carbon and carbon–heteroatom bond formation. Our group has recently developed a procedure utilizing the chiral reactive enediolate–dilithium amide aggregate of aryl- and heteroaryl acetic acids in enantioselective Michael additions to α,β -unsaturated esters for asymmetric carbon-carbon bond formation, mediated by a dimeric chiral tetramine. A free carboxyl group in the product provides versatility for further functionalization, and the chiral reagent can be readily recovered by extraction with aqueous acid. The method has been applied in the enantioselective total synthesis of the purported structure of pulveraven B. In addition, our preliminary studies also reveal the potential expansion of alkylation scope towards the synthesis of quaternary stereocenters.

Dragmacidin D is a member of a family of heterocyclic bis-indolyl alkaloids isolated from deep-water Caribbean sponges of *Dragmacidon* and *Spongisorites* sp. Although

the initially isolated sample displayed no optical activity, subsequent reisolation provided a sample with an $[\alpha]_D$ of $+12^\circ$ (c 0.95, EtOH). These observations indicate a certain measure of ambiguity for the stereochemical identity and configurational stability of its sole stereogenic center. The asymmetric synthesis of (+)-dragmacidin D was completed in 10 steps. Its sole stereocenter was set by a direct asymmetric alkylation enabled by a C_2 -symmetric tetramine and lithium *N*-(trimethylsilyl)-*tert*-butylamide as the key enolization reagent. A central Larock indole synthesis was employed in a convergent assembly of the heterocyclic subunits. The 2-aminoimidazole heterocycle was installed in a concise manner via a copper mediated acyl cross coupling reaction. The stereochemical evidence from this work strongly supports the predicted *S* configuration at the 6''' position, which is consistent with other members of the dragmacidin family of natural products.

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List of Abbreviations

Abbreviation, symbol, or chemical formula	Term
$[\alpha]$	specific rotation
aq.	Aqueous
Bn	benzyl
BnBr	benzyl bromide
Boc	<i>tert</i> -butyl carbonate
Boc ₂ O	di- <i>tert</i> -butyl dicarbonate
br	broad
brsm	based on recovery of starting material
°C	degrees Celsius
c	concentration
calcd	calculated
CDCl ₃	deuteriochloroform
C ₆ D ₆	deuterobenzene
CD ₃ OD	deuteromethanol
δ	chemical shift(s)
d (NMR)	doublet
d (time)	days
DIPEA	di- <i>iso</i> -propylethylamine
DIBAL	diisobutylaluminum hydride
DMAP	<i>N,N</i> -4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	Dimethyl sulfoxide

DPPA	diphenyl phosphoryl azide
dr	diastereoseomeric ratio
<i>ee</i>	enantiomeric excess
EI	electron impact
equiv.	equivalent
ESI	electrospray ionization
g	gram(s)
h	hour(s)
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectroscopy
Hz	hertz
ImH	imidazole
<i>i</i>	iso
IR	Infrared Spectroscopy
<i>J</i>	coupling constant
L	liter(s)
LDA	lithium diisopropylamide
m	multiplet
M	molarity
<i>m/z</i>	mass/charge
mg	milligram(s)
MHz	megahertz
μL	microliter(s)
min	minute(s)

mL	milliliter(s)
mmol	millimole
mmHg	millimeters of mercury
NBS	<i>N</i> -bromosuccinimide
NIS	<i>N</i> -iodosuccinimide
NMP	<i>N</i> -methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
PMB	<i>para</i> -methoxybenzyl
ppm	parts per million
Py	pyridine
rt	room temperature
s	singlet
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBS	<i>tert</i> -butyldimethylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMS	trimethylsilyl
TMSCl	trimethylsilyl chloride
TMSCHN ₂	trimethylsilyldiazomethane
Ts	4-toluenesulfonyl
Z	zusammen

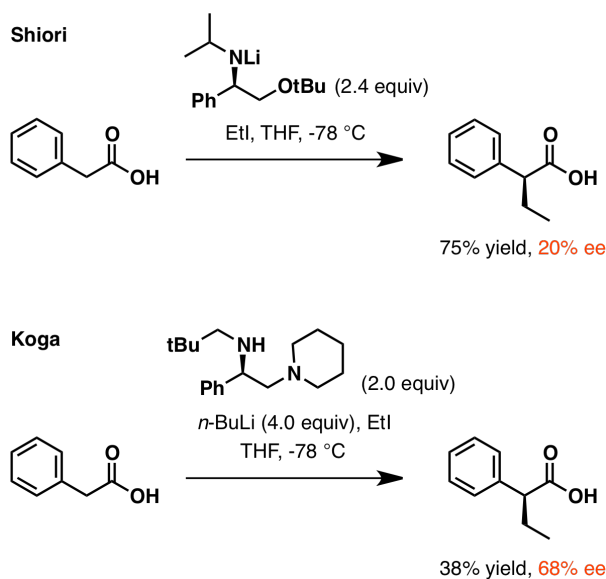
**Chapter 1: Direct Enantioselective Conjugate Addition of Arylacetic Acids with Chiral
Lithium Amides as Traceless Auxiliaries**

1.1 Introduction

Lithium enolates, and their subsequent reactions with electrophiles, have been the subject of rigorous investigation for many decades.¹ Researchers are constantly aiming to increase the efficiency of stereoselective C–C bond constructions, a cornerstone in asymmetric synthesis. Of the classic methods for α -functionalization of carboxylic acids, the traditional chiral auxiliary approach² has dominated the field. Evans' oxazolidinone³ and Myers' pseudoephedrine⁴ auxiliaries have gained widespread acceptance as premier methods for stereoselective enolate alkylation, finding utility from academic total synthesis project to industrial production of pharmaceuticals. These methods have set the benchmark for utility and truly broad generality in the field. Nevertheless, while commercially available, enantiopure auxiliaries are still relatively expensive. In addition, alkylation involves a three-step process: 1) attachment of the appropriate auxiliary, 2) diastereoselective alkylation, and 3) cleavage and recovery of the chiral auxiliary. These extra steps lower overall yields and generate additional waste. Furthermore, removal of the auxiliary must be achieved using conditions compatible with existing functionalities, a feat which becomes increasingly difficult when handling more complex molecules.

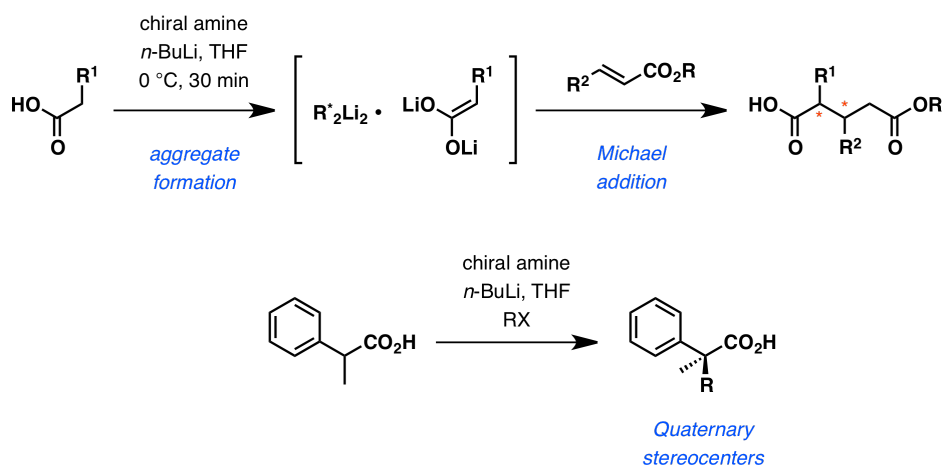
Current research has focused on accomplishing these transformations in the most efficient manner possible. The use of chiral lithium amides⁵ as traceless auxiliaries to stereoselectively alkylate enediolates is a relatively uninvestigated area. Shiori and Koga were among of the first to utilize monomeric chiral diamine bases in stereoselective alkylations of enediolates (Scheme 1).^{6,7} While their substrate scopes were limited, and yields and selectivities were generally poor to modest, these seminal publications demonstrated a proof of concept for this powerful approach.

Scheme 1. Shiori and Koga Precedents for Traceless Asymmetric Alkylation



Our group has recently developed a procedure utilizing the chiral reactive enediolate–dilithium amide aggregate of aryl- and hetero-aryl acetic acids in enantioselective Michael additions to α,β -unsaturated esters for asymmetric carbon-carbon bond formation, using a *dimeric* C_2 -symmetrical chiral tetramine (Scheme 2). Our preliminary studies also reveal the potential expansion of alkylation scope towards the synthesis of all-carbon quaternary stereocenters.

Scheme 2. Asymmetric Michael Addition and Quaternary Stereocenters

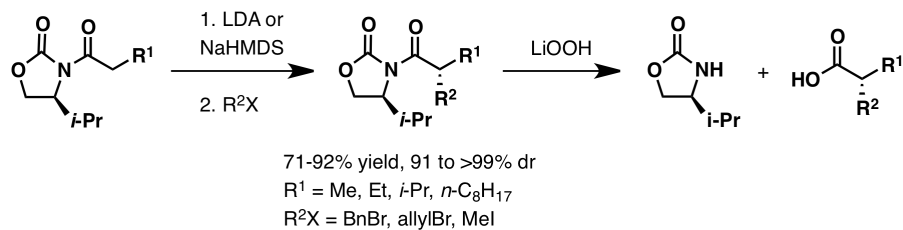


1.2 Traditional Auxiliary-Based Methods

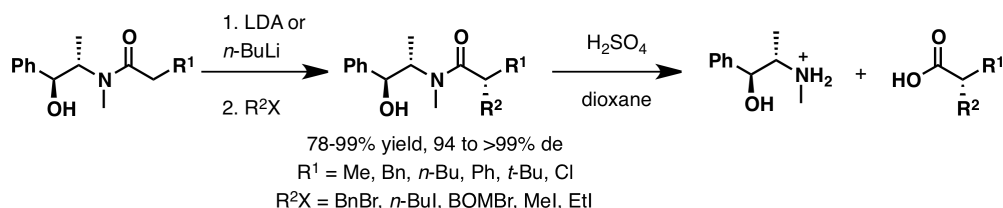
The use of chiral auxiliaries for the asymmetric construction of carbon stereocenters is an extremely important method in chemical synthesis. Although significant advances in the fields of asymmetric catalysis,⁸ biocatalysis,⁹ and chiral reagents have been made in recent years, chiral auxiliaries have remained the workhorses in asymmetric synthesis. The massive amount of research in the field has yielded a wealth of expertise providing a high level of predictability. Often, this knowledge can be utilized to install stereocenters in an incredibly time efficient manner because of this predictive power. Early examples involved diastereoselective alkylation and Diels-Alder reactions using menthol¹⁰ and camphor¹¹ derived directing groups. While many different chiral auxiliaries have been developed and demonstrated as chiral enolate synthons, Evans' oxazolidinone and Myers' pseudoephedrine, in particular, are among the most popular options. High diastereoselectivities from these methods stem from exceptionally selective enolization and the stereochemical properties of the auxiliary, which directs approach of the electrophile preferentially to one face of the nucleophilic enolate. Their outstanding versatility is demonstrated by their control in regards to both relative and absolute stereochemistry in asymmetric alkylation, aldol, and Diels-Alder reactions. For example, both methods generally provide access to α -alkylated products in good to excellent yield and excellent diastereoselectivities (Scheme 3). Additionally, the covalently bound auxiliaries can be cleaved using a variety of mild conditions without destruction of the newly generated stereocenter.

Scheme 3. Evans' and Myers' Auxiliaries for Diastereoselective Alkylation

Evans' Alkylation

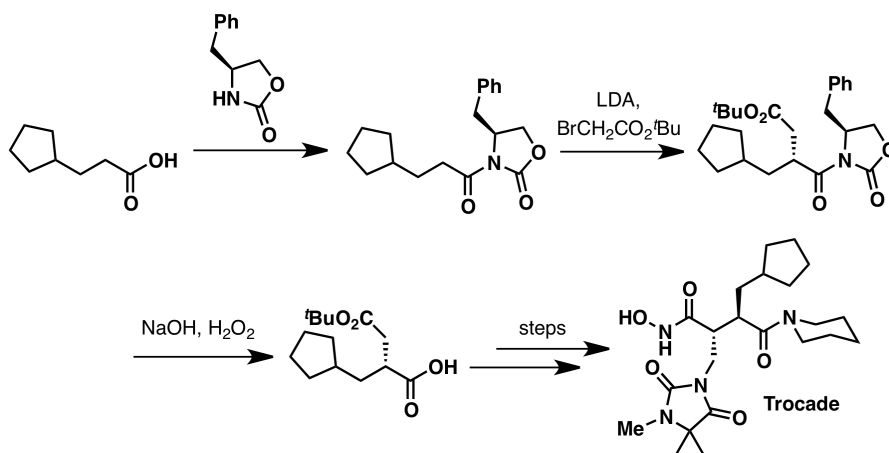


Myers' Alkylation



As mentioned earlier, there is significant exposure to chiral auxiliaries for industrial purposes. For example, the oxazolidinone auxiliary has been used in the asymmetric synthesis of Trocade (Scheme 4), a potential candidate for the treatment of rheumatoid and osteoarthritis.¹²

Scheme 4. Asymmetric Synthesis of Trocade



1.3 Enantioselective Alkylations Using Traceless Auxiliary

Our group has recently shown that *C*₂-symmetrical dimeric Koga-type chiral tetramine (*R*)-¹TA, readily accessible on a multi-kilogram scale from commercially

Table 1. Asymmetric Alkylation: Alkylating Agent Scope Summary

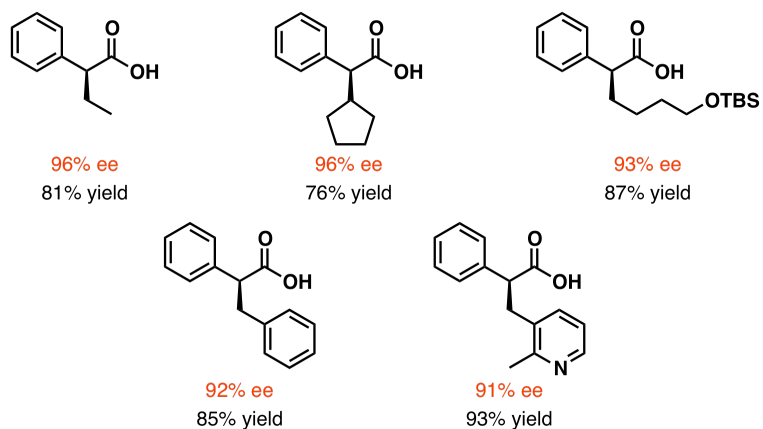
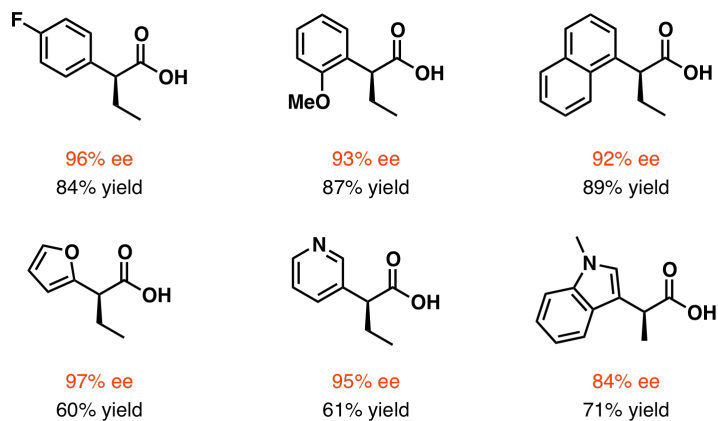
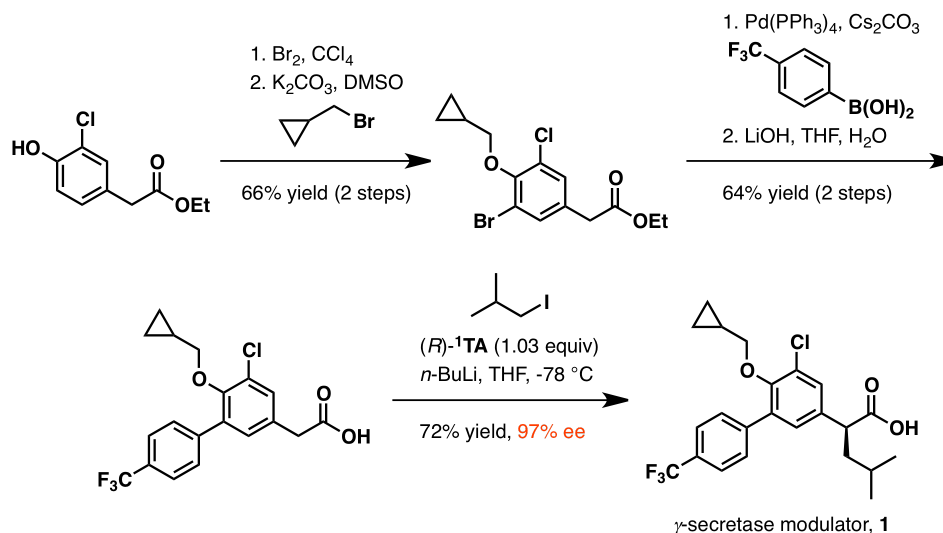


Table 2. Asymmetric Alkylation: Carboxylic Acid Scope Summary



This method is amenable to large-scale applications, illustrated by direct alkylation of 10 g of phenyl acetic acid with 2-iodopropane in 89% yield and 98% ee. Additionally, the technique was applied to the synthesis of the known γ -secretase modulator **1** (Scheme 7).¹⁶

Scheme 7. Synthesis of γ -Secretase Inhibitor **1** by Enantioselective Alkylation

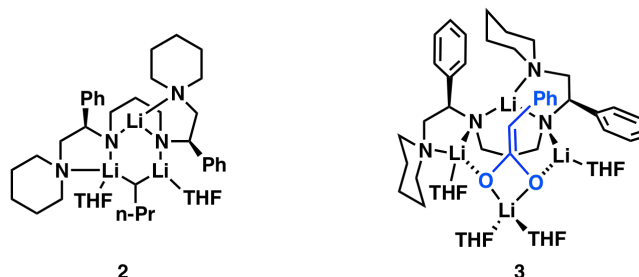


1.3.1 Mechanistic Studies

Evidence from mechanistic studies of enantioselective organolithium reactions has shown that high stereo control is sometimes correlated with high structural control of the reactive aggregates. Through a collaborative effort, the crystal structures of $n\text{-BuLi}$ with the bis(lithium)amide of (R) -**1TA** (**2**) and of (R) -**1TALi**₂ bound to the (bis)lithium enediolate of phenylacetic acid (**3**, Figure 1) have been elucidated.¹⁷ Both structures crystallize as dimers but are shown in monomeric form for simplification purposes. Bis(lithium)amide **2** crystallizes in the orthorhombic space group $P2_12_12_1$ with each piperidine-derived nitrogen atom coordinated to a single lithium cation, whereas each amide nitrogen atom is coordinated to two lithium cations. This orientation places both phenyl groups in the amine backbones pseudoequatorially. The enediolate–dilithiated amide mixed aggregate **3** crystallizes in the orthorhombic space group $P2_12_12_1$ as the THF solvate containing two chiral dilithiated amides and two enediolates. The most interesting feature of **3** is the incorporation of the enediolate, whose atoms are all

coplanar, suggesting strong π conjugation. Additionally, each oxygen atom is coordinated to three lithium cations.

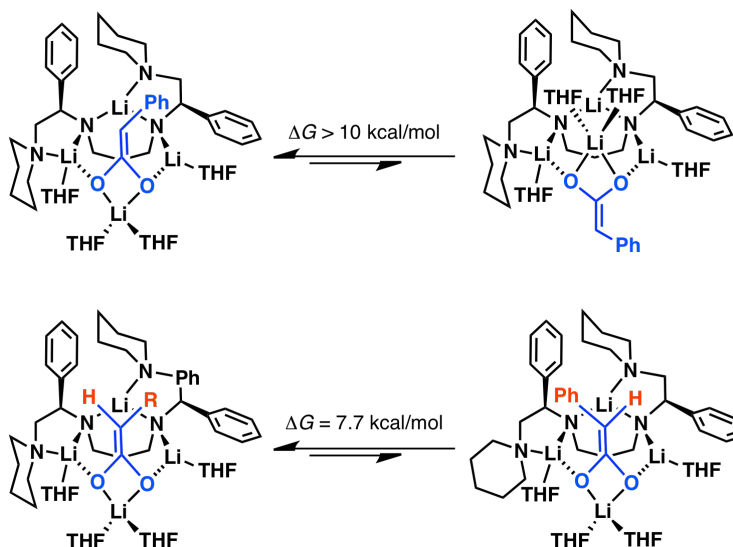
Figure 1. Aggregate Structures of (*R*)-¹TALi₂ and (*R*)-¹TALi₂-Enediolate



In solution, these reagents assume distinct aggregation states, which are supported by multinuclear solution NMR and *in silico* computations. The synthesis of a ¹⁵N-labeled (*R*)-¹TA from isotopically enriched ammonia, followed by ⁶Li and ¹⁵N two-dimensional NMR (2D-NMR) have allowed for systematic study of the active reagent aggregates in relation to structure, size, solvation, sterics, and reactivity. The assignment of trilithiated monomer **2** rather than the hexalithio dimer was established from ¹³C NMR spectrum splitting patterns. Similarly, tetralithio monomeric enediolate–dilithium amide mixed aggregate **3** is preferentially supported by observations via NMR and computational models, in comparison to its theoretical octalithio dimeric structure. A mechanistic model for the origin of, and in certain cases loss of, stereoselectivity has been established through the elucidation of these crystal structures, 2D-NMR data, and computations. The aggregate exhibits an immensely strong conformational preference for phenyl orientation to expose the *si* face of the enediolate derived from phenylacetic acid, resulting in exceedingly high selectivities (Figure 2). We believe the orientation of the phenyl ring of the enediolate is the variable that is most critical to enantioselectivity. It is noteworthy to mention that the level of enantioselectivity was dependent on the

quality of *n*-butyl lithium. Aged reagent bottles, likely contaminated with ionic lithium salts, resulted in drastically lower, inconsistent stereinduction.

Figure 2. Conformational Preferences of the Enediolate



1.4 Enantioselective Michael Addition

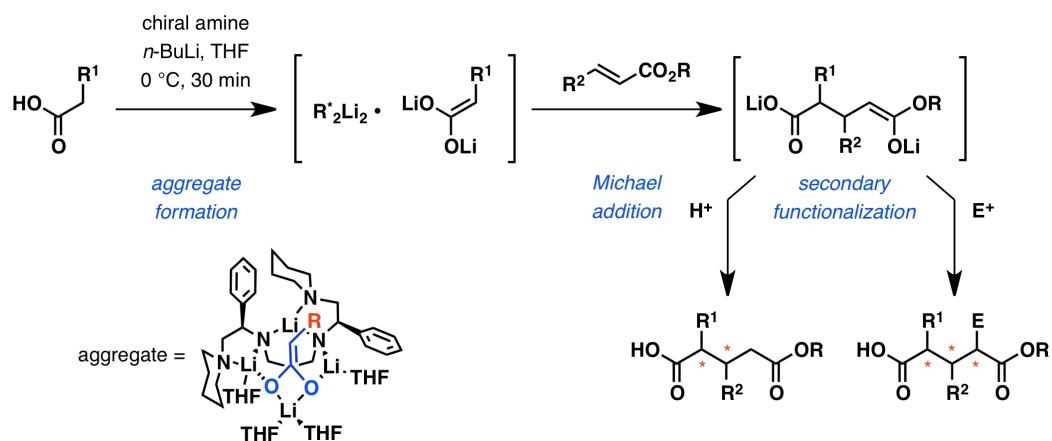
1.4.1 Introduction

Enantioselective Michael addition of lithium enolates is a process of significant utility. From simple precursors, this reaction has the potential to generate multiple consecutive stereocenters that are difficult to access by other methods. There has been considerable progress in methodology that has tapped into this potential,^{18,19} including several methods based on covalent chiral auxiliaries.^{20,21} Asymmetric transformations with lithium enolates derived from carboxylic acids are performed predominantly with covalently attached chiral auxiliaries. These reactions provide a broad arsenal of methods for enantioselective synthesis and are indispensable in the synthesis of many complex natural products and pharmaceuticals.²² We recently reported that high enantioselectivities could be achieved in the direct one-step alkylation of arylacetic acids using chiral lithium amides.¹⁴ In this process, the chiral C_2 -symmetric dilithium amide

functions as a chiral auxiliary within a mixed enediolate–dilithium amide aggregate formed in situ, thus bypassing the additional steps required to attach and remove covalently bound chiral auxiliaries. X-ray crystallography, ^6Li , ^{13}C , and ^{15}N NMR spectroscopy, and DFT calculations pointed to the structure of the aggregate.^{17,23}

A direct enantioselective Michael addition of carboxylic acids via enediolates mediated by chiral lithium amides is described (Scheme 8).^{24,25,26} The reaction occurs with high stereocontrol in both the relative and absolute sense, further highlighting the utility of chiral lithium amides as traceless auxiliaries for asymmetric synthesis.

Scheme 8. Asymmetric Michael Addition with Enediolate–Dilithium Amides



1.4.2 Reaction Optimization

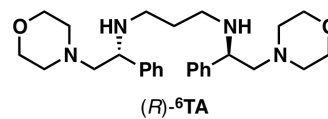
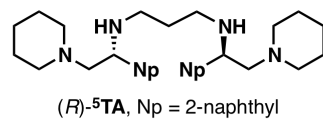
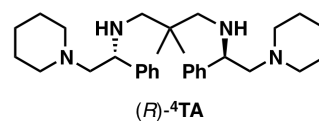
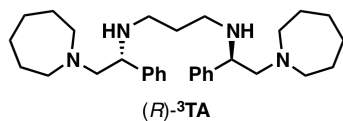
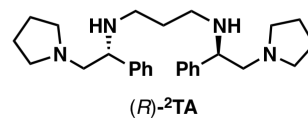
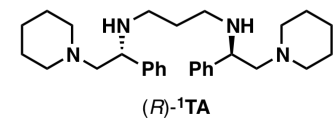
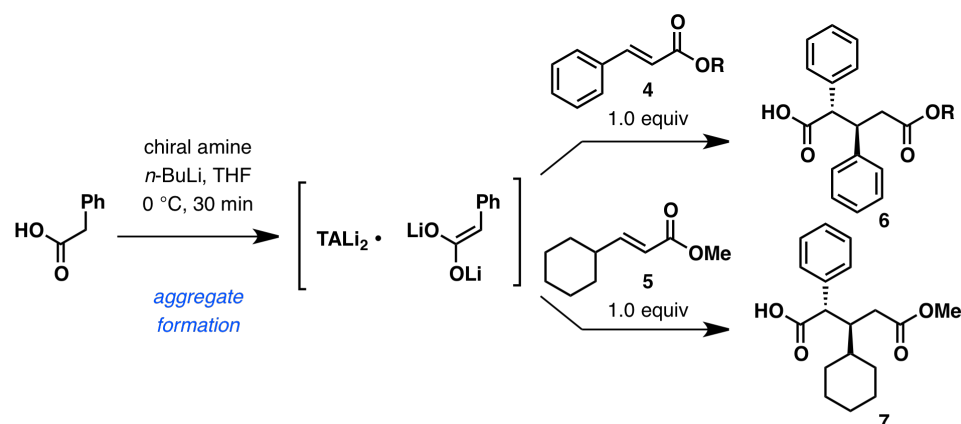
The addition of phenylacetic acid to alkyl cinnamates and methyl (*E*)-3-cyclohexylacrylate in the presence of dilithium amides from chiral *C*₂-symmetric tetramines ¹TA–⁶TA was investigated first (Table 3).²⁷ From the onset, the reactions were characterized by facile, highly anti-selective 1,4-additions with high conversions at -78 °C.²⁸ Piperidine-based tetramine (*R*)-¹TA,^{13,29} which was previously shown to be highly effective in asymmetric alkylations of arylacetic acids, again proved to be optimal (88% yield, >30:1 dr, 83% ee; entry 1). One of the most striking observations is that a seemingly minor adjustment in the structure of the base, i.e., replacing the

piperidine unit with pyrrolidine as in (*R*)-²TA, resulted in reversal of the enantiomeric preference, giving the opposite enantiomer *ent*-**6** as the major product with 84% ee and 17:1 dr (entry 2). The previously reported alkylation reaction showed the same sense of enantiofacial preferences for these two bases. The azepine base also displayed a reversal of selectivity, although at a lower level (46% ee; entry 3). Introduction of the gem-dimethyl substitution on the propylene bridge in (*R*)-⁴TA gave a diminished yield of the product with lower diastereoselectivity (entry 4). Replacing the phenyl group with 2-naphthyl ((*R*)-⁵TA) had a minor impact on the course of the reaction.

Variations in the ester group revealed that the enantioselectivity was higher for methyl cinnamate (**4**, R = Me) than for ethyl and *tert*-butyl cinnamate. Under optimal conditions, the addition product was formed in 88% yield with 93% ee as a single diastereomer (Table 3, entry 8). A larger-scale experiment was performed at -78 °C on 26 mmol scale, affording 5.97 g of **6** (R = CH₃) in 78% yield with 90% ee (entry 13). The product was isolated as a single diastereomer by recrystallization, and the reagent (*R*)-¹TA was recovered by extraction in 99% yield.

Similar selectivity trends were observed with methyl (*E*)-3-cyclohexylacrylate (**5**) (Table 3, entries 9–12). In this case, the pyrrolidine base (*R*)-²TA proved to be significantly more effective, giving adduct **7** in 74% isolated yield with 96% ee as a single anti diastereomer (cf. entries 9 and 10). The absolute and relative configurations of addition products **6** and **7** were established using X-ray crystallographic analysis as well as correlation with known compounds.

Table 3. Chiral Lithium Amides for the Enantioselective Conjugate Addition of PhCH₂CO₂H to Ester **4** and **5**^a



entry	ester, (<i>R</i>)	tetramine	yield	dr	ee
1	4 (Et)	(<i>R</i>)- 1TA	86%	>30:1	83%
2		(<i>R</i>)- 2TA	71%	17:1	-84%
3		(<i>R</i>)- 3TA	75%	25:1	-46%
4		(<i>R</i>)- 4TA	<74%	6:1	-
5		(<i>R</i>)- 5TA	74%	>30:1	80%
6 ^b		(<i>R</i>)- 1TA	77%	>30:1	90%
7 ^b	4 (<i>t</i> -Bu)	(<i>R</i>)- 1TA	71%	>30:1	83%
8 ^b	4 (Me)	(<i>R</i>)- 1TA	88%	>30:1	93%
9	5	(<i>R</i>)- 1TA	85%	>30:1	59%
10		(<i>R</i>)- 2TA	74%	>30:1	-96%
11		(<i>R</i>)- 3TA	81%	>30:1	-60%
12		(<i>R</i>)- 6TA	70%	>30:1	29%
13 ^c	4 (Me)	(<i>R</i>)- 1TA	78%	>30:1	90%

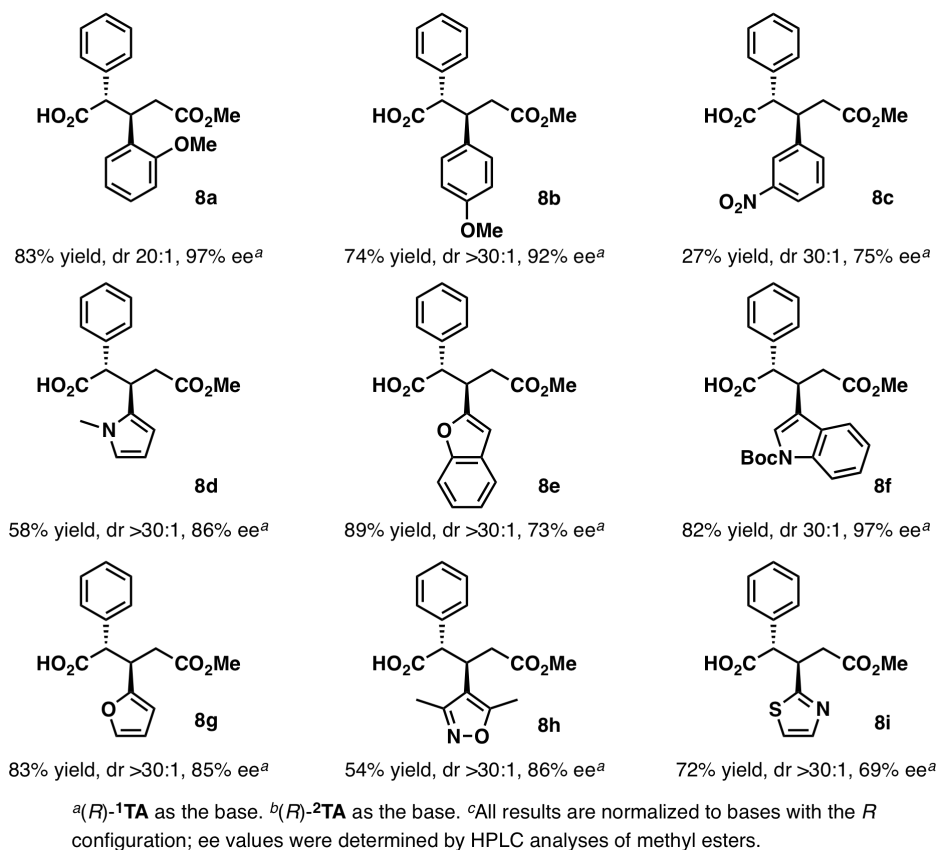
^aThe ee values were measured using chiral HPLC analysis of methyl esters after derivatization with Me₃SiCHN₂; all results are corrected to bases with the *R* configuration. ^bAddition at -90 °C. ^c26 mmol scale, 5.97 g of **4**; (*R*)-**1TA** was recovered in 99% yield.

1.4.3 Substrate Scope

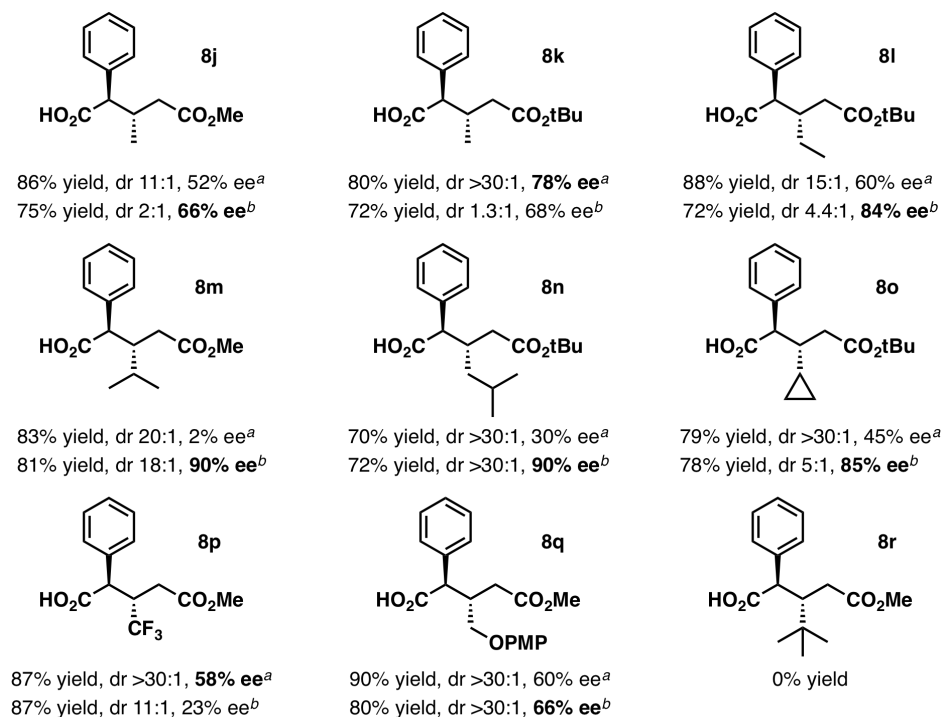
Guided by the initial experiments, we selected the piperidine base (*R*)-**1TA** and the

pyrrolidine base (*R*)-**2TA** for further investigations. The scope of Michael acceptors was examined first (Table 4). In all of the examples, ~1:1 stoichiometry between the Michael donor and acceptor was applied. Many aryl and heteroaryl substituents were suitable for the reaction using the piperidine base (*R*)-**1TA**. The diastereoselectivity was uniformly high for all of the α,β -unsaturated esters (>20:1), and the enantioselectivity was in the range of 69–97% ee, with the highest value observed for products **8a** and **8f** bearing 2-methoxyphenyl and 3-indolyl groups, respectively. The 3-nitroaryl substituent (**8c**) afforded a much lower yield of the addition product, likely because of the high reactivity of the substrate; however, high enantioselectivity was maintained. In our screening efforts, we placed an emphasis on heteroaryl substituents because of their relevance to medicinal chemistry (**8d–i**). Although the enantioselectivity was somewhat reduced, it was in the practical range of 70–97% ee for a variety of groups, including *N*-methyl-2-pyrrolyl (**8d**, 86% ee), 2-benzofuryl (**8e**, 73% ee), *N*-Boc-3-indolyl (**8f**, 97% ee), 2-furyl (**8g**, 85% ee), 3,5-dimethyl-4-isoxazolyl (**8h**, 86% ee), and 2-thiazolyl (**8i**), which gave the lowest ee of 69%. Notably, the potentially sensitive *N*-Boc group in **8f** was compatible with the reaction conditions; in fact, this was one of the best-performing reactions.

Table 4. Conjugate Addition: Scope of α,β -Unsaturated Esters^c



On the basis of the preliminary studies, aliphatic α,β -unsaturated esters were studied with both chiral bases, (*R*)-**1TA** and (*R*)-**2TA** (Table 5). With crotonates (**8j**, **8k**), we found that the best enantioselectivity of 78% was obtained with the tert-butyl ester using the original piperidine base (*R*)-**1TA**. For all of the other substrates except for methyl 4,4,4-trifluorocrotonate (**8p**, 58% ee), the enantioselectivity was superior with (*R*)-**2TA**. Ethyl (**8l**), isopropyl (**8m**), isobutyl (**8n**), cyclopropyl (**8o**), and (4-methoxyphenoxy)methyl (**8q**) substituents were effectively introduced. The enantioselectivities were in the range of 85–90%, except for **8q**, which was isolated with 66% ee. Under the conditions studied, no reactivity was observed with sterically demanding methyl (*E*)-4,4-dimethylpent-2-enoate (cf. **8r** in Table 5).

Table 5. Conjugate Addition: Aliphatic α,β -Unsaturated Esters^c

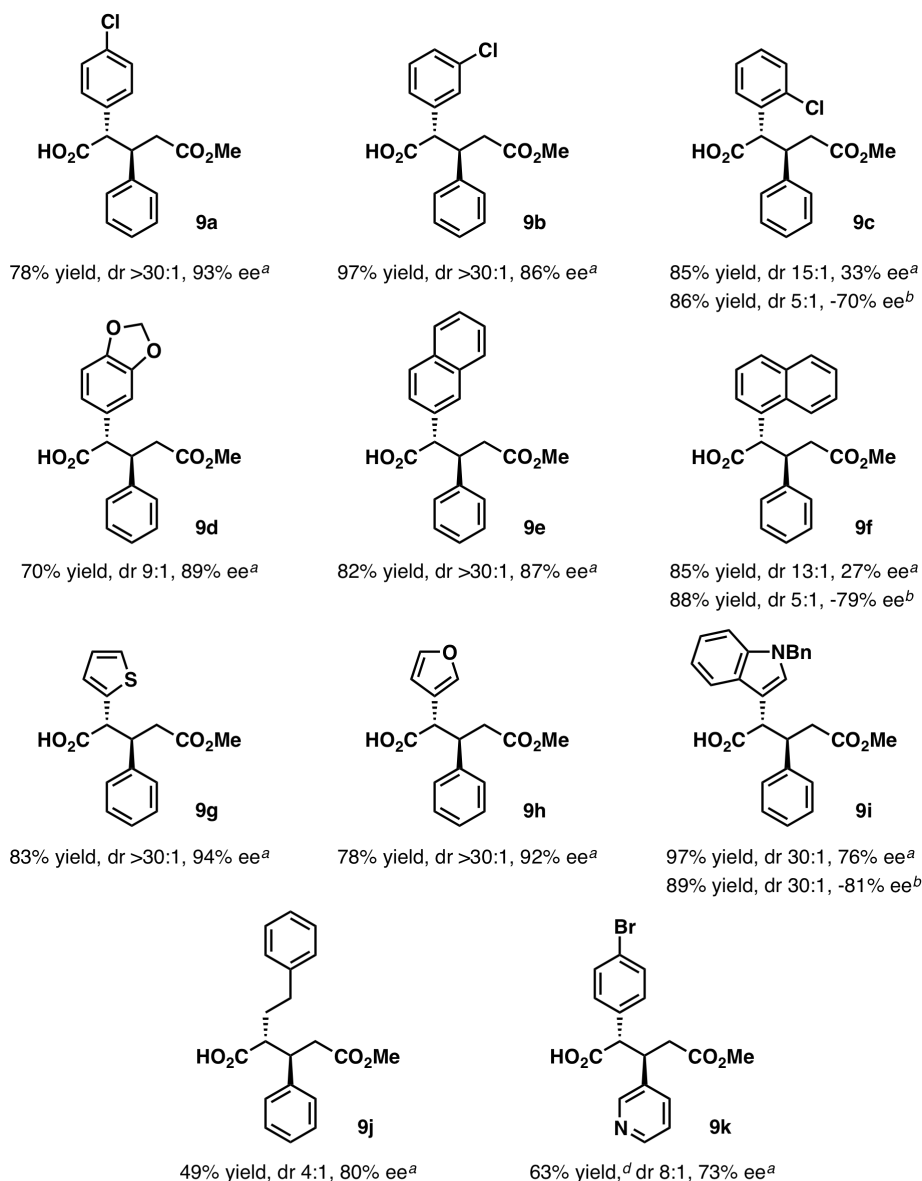
^a(*R*)-**1TA** as the base. ^b(*R*)-**2TA** as the base. ^cAll results are normalized to bases with the *R* configuration; ee values were determined by HPLC analyses of methyl esters.

The scope of carboxylic acids investigated as Michael donors with the piperidine base (*R*)-**1TA** is summarized in Table 6. Initially, variation of the position of the chlorine on the phenyl ring revealed that ortho substitution resulted in a drastic reduction of enantioselectivity. While 4- and 3-chlorophenylacetic acid afforded addition products with 93 and 86% ee, respectively, 33% ee was observed with 2-chlorophenylacetic acid. The selectivity could be substantially improved to 70% ee by using the alternative base (*R*)-**2TA** (**9c**). Again, the enantiomeric product was favored. Similar trends were observed for 2- and 3-naphthylacetic acid (**9e**, **9f**). The former afforded the addition product with 87% ee, while the selectivity with the latter was 33% ee, which could be enhanced to -79% ee using (*R*)-**2TA**. 2-(Benzo[d]dioxol-5-yl)acetic acid afforded **9d** with 89% ee.

The heteroarylacetic acids 2-thiophene- and 3-furanacetic acid afforded **9g** and **9h**

with high enantioselectivity (Table 6). Although *N*-Boc-3-indoleacetic acid proved to be a poor substrate in the addition reaction, *N*-benzyl-3-indoleacetic acid afforded **9i** in a very high yield with 76% ee. Improved selectivity was observed with (*R*)-**2TA** as the base, which again afforded the product with the opposite sense of enantioinduction.

Table 6. Conjugate Addition: Scope of Carboxylic Acids^c



^a(*R*)-**1TA** as the base. ^b(*R*)-**2TA** as the base. ^cAll results are normalized to bases with the *R* configuration; ee values were determined by HPLC analyses of methyl esters. ^dFor the dimethyl ester.

Although a systematic study of aliphatic carboxylic acids as Michael donors was

beyond the scope of this contribution, addition of 4-phenylbutyric acid was an important initial advance in this direction (**9j**; Table 6). In contrast to our previous work on alkylation reactions, a rather high ee of 80% (dr 4:1) was observed with (*R*)-¹**TA** as the base. Studies of enediolates from aliphatic acids continue and will be reported in due course. Variation in both coupling partners using more functionalized substrates is tolerated (**9k**).

1.4.4 Applications

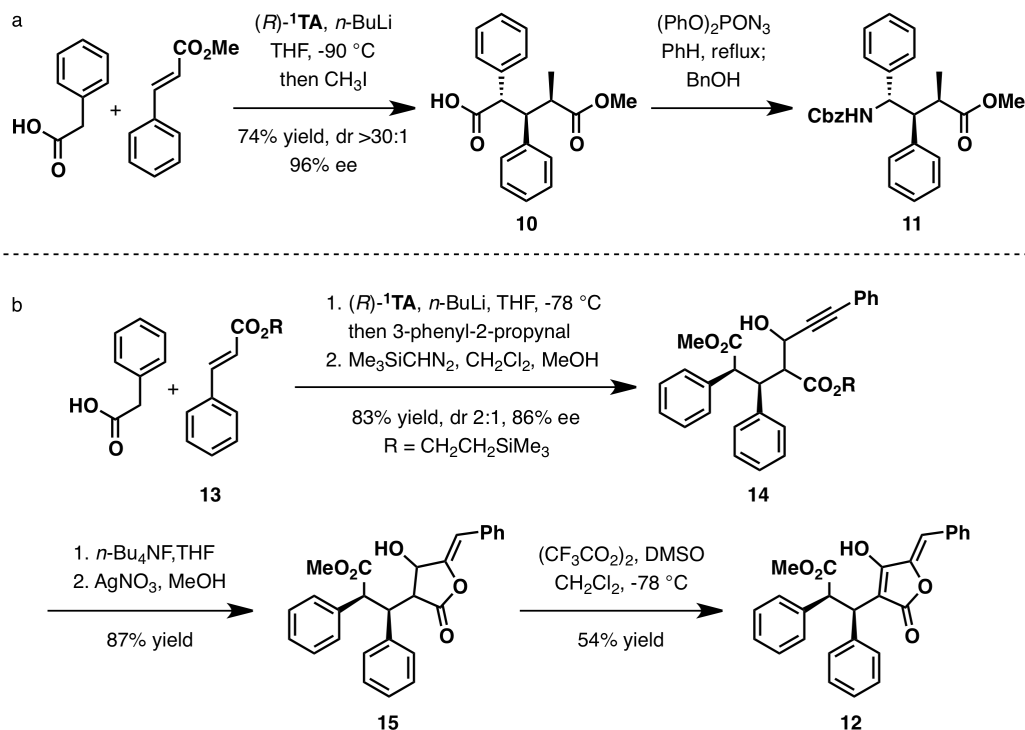
The versatility of the Michael addition methodology is illustrated by the applications depicted in Scheme 9. The first application capitalized on the reactivity of the initially formed enolate by exploiting it in a secondary alkylation reaction with iodomethane in one pot. This process enabled the formation of three consecutive tertiary stereocenters with excellent stereocontrol in 74% yield (Scheme 9a). The free carboxyl group is an exceptionally convenient surrogate for an amino group via the Curtius rearrangement transform. In the event, treatment of acid **10** with diphenylphosphoryl azide followed by benzyl alcohol delivered γ -amino acid derivative **11** in 53% unoptimized yield.

The second application was the enantioselective synthesis of the purported structure of pulveraven B (**12**) (Scheme 9b), reported as a constituent of the edible mushroom *Pulveroboletus ravenelii* in 2003.³⁰ It displayed selective inhibition of carcinogen-induced pre-neoplastic lesion formation in mouse mammary organ culture with IC₅₀ = 0.8 μ M. The potency was reduced 10-fold for its epimer pulveraven A.

In the synthesis described herein, the initial Michael adduct was subjected in situ to aldol coupling with 3-phenyl-2-propynal, affording a 2:1 mixture of aldol products **14** with 86% ee for both diastereomers (83% yield). After cleavage of the trimethylsilylethyl ester with *n*-Bu₄NF, a Ag-catalyzed cyclization afforded γ -lactone

15.³¹ Oxidation delivered the tetrionic acid with a structure proposed for pulveraven B. However, the optical rotation and NMR spectral data did not match those reported for the natural product.^{ref}

Scheme 9. Secondary Functionalization and Synthesis of Reported Pulveraven B Structure



1.4.5 Conclusions

In conclusion, we have developed a method for direct enantio- and diastereoselective conjugate addition of carboxylic acids to α,β -unsaturated esters. The stereoselectivity is imparted by a chiral lithium amide–enediolate aggregate formed from chiral C₂-symmetric Koga-type tetramines. The study revealed intriguing and unexpected patterns of stereoselectivity that are the subject of current mechanistic investigations.³² Multiple selective bond formations were illustrated (1) by a highly stereoselective one-pot alkylation with iodomethane and (2) by an aldol coupling within the context of the

enantioselective total synthesis of pulveraven B, which revealed that its structure appears to be misassigned.

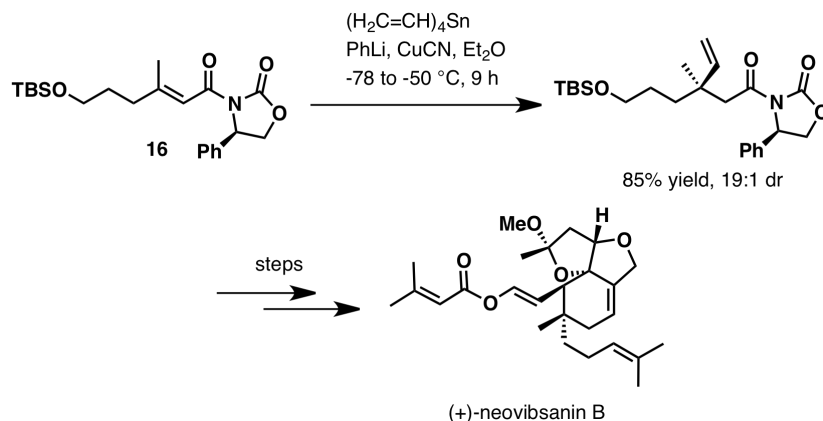
1.5 Asymmetric Alkylation for the Construction of Quaternary Stereocenters

1.5.1 Introduction

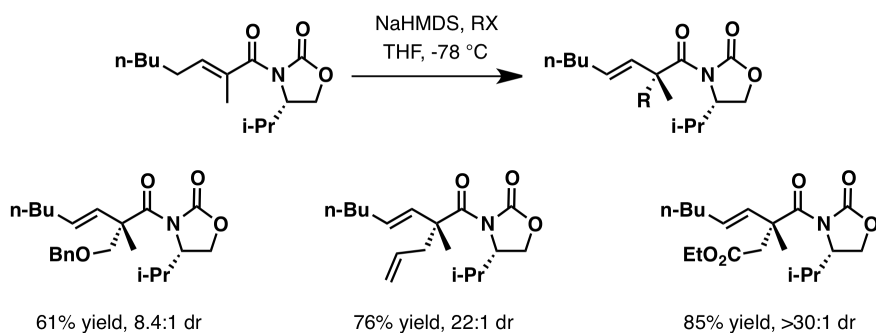
While countless methods have been developed in order to solve numerous obstacles in chemical synthesis, one problem that continues to elude organic chemists is the asymmetric synthesis of all-carbon quaternary stereocenters. Preparation of these centers is problematic due to the steric repulsions between the four carbon substituents. Despite this fact, many creative and elegant solutions have appeared in the literature making great strides towards this lofty goal, including, but not limited to: asymmetric Diels-Alder reactions, allylic substitution, chiral allylmetal electrophiles, intramolecular Heck reactions, conjugate additions, and desymmetrization reactions.³³ Once again, chiral auxiliaries have also been effectively utilized to overcome this challenge.

Esumi and Fukuyama prepared the C11 quaternary stereocenter of (+)-Neovibsanin by employing a 1,4-conjugate addition with the higher order organocuprate $(\text{H}_2\text{C}=\text{CH})_2\text{Cu}(\text{CN})\text{Li}_2$ to a trisubstituted α,β -unsaturated carboxylic acid derivative of (*R*)-4-phenyl-2-oxazolidinone (**16**, Scheme 10).³⁴ In the course of their total synthesis of madindolines, Kobayashi and co-workers developed a regio- and stereoselective α -alkylation of α,β -unsaturated chiral imides (Scheme 11).³⁵ Their alkylation is also compatible for the introduction of allyl and acetate fragments with excellent diastereoselectivities. Similarly, Myers and co-workers developed a one-pot conjugate addition, alkylation of α,β -unsaturated pseudoephedrine amides providing a variety of differentially substituted quaternary stereocenters in good yields and selectivities (Scheme 12).³⁶

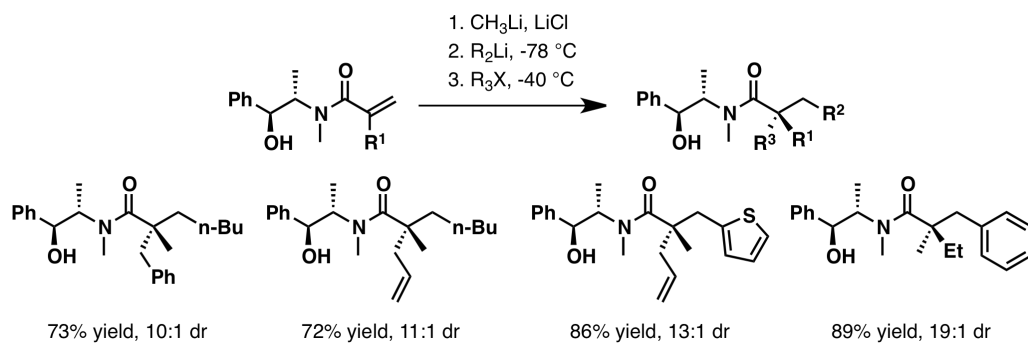
Scheme 10. Esumi's Formal Synthesis of (+)-neovibsanin B



Scheme 11. Kobayishi's Alkylation



Scheme 12. Myers' Conjugate Addition–Alkylation



1.5.2 Preliminary Results

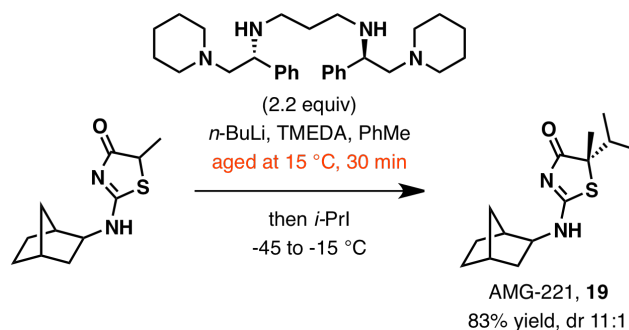
We have developed an alternative alkylation procedure to form quaternary stereocenters in high conversion and enantiomeric excess. The reaction was optimized by the alkylation of 2-phenylpropanoic acid (**17**) using excess iodoethane to produce 2-

methyl-2-phenylbutanoic acid (**18**, Table 7). Under the standard alkylation conditions, aggregation at 0 °C for 10 minutes, a modest yield was observed along with a modest stereoselectivity (Table 7, entry 1). An insightful publication from Amgen regarding their development of a diastereoselective alkylation to prepare the quaternary stereocenter of AMG-221 (**19**), a 11 β -hydroxysteroid dehydrogenase type 1 inhibitor, led to a revelation in our procedure.^{29c} Their aggregation conditions consisted of aging the reaction mixture, prior to alkylation, at 15 °C for 30 minutes (Scheme 13). We postulated it would be beneficial to the selectivity by extending the aggregation time and to increase the aggregation temperature. Consequently, increasing the aggregation time to 1 hr at 0 °C drastically improved enantioselectivity but, surprisingly, actually lowered conversion (Table 7, entry 2). We were delighted to find that by increasing aggregation temperature *and* time, an optimized 76% conversion and 90% ee was achieved (entry 3). Gentle heating of the aggregate mixture had a detrimental impact on the reaction (entry 4). We believe the rate of formation of the highly structured aggregate is more difficult, and therefore slower, due to the increased sterics from a disubstituted enediolate.

Table 7. Asymmetric Alkylation: Aggregation Optimization Studies

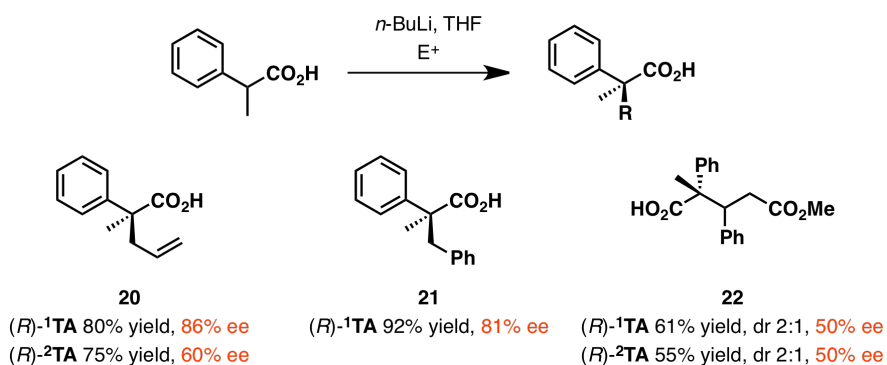
entry	temp	time	conversion	ee
1	0 °C	10 min	60	53
2	0 °C	1 h	45	90
3	23 °C	1 h	76	90
4	35 °C	2 h	61	30

Scheme 13. Amgen Diastereoselective Alkylation Towards AMG-221



Using the piperidine base (R)-**1TA**, ethylation (**18**), allylation (**20**), and benzylation (**21**) generate quaternary products in good yields and good enantioselectivities (Scheme 14). Allylation with pyrrolidine base (R)-**2TA** gave a slightly lower yield and modest enantioselectivity. Regrettably, conjugate addition to methyl cinnamate only provides **22** with modest stereoselectivity and yield.

Scheme 14. Alkylation Scope



Extension of this procedure is currently limited to 2-phenylpropanoic acid. Attempts to extend the protocol to 2-phenylbutanoic acid (**23**) results in good conversion but low enantioselectivity (Scheme 15). This outcome likely originates from lower energy differences (ΔG° calculated for mono-substituted substrates, $R_1 = \text{Ph}$, Me, $i\text{-Pr}$, cyclohexyl; $R_2 = \text{H}$) between stereo-conformations of the reactive aggregate (Figure 3).¹⁷ When disubstituted, the phenyl substituent of 2-phenylbutanoic acid is much closer in energy to an ethyl group, 7.7 kcal/mol and 1.3 – 4.2 kcal/mol, respectively, compared

to a methyl group, 1.3 kcal/mol. This leads to a higher probability for a conformational change exposing the *re* face, resulting in an erosion of enantioselectivity as a consequence. Another result of this structural change is a conformational flip of the piperidine ring, which may affect electrophilic approach.

Scheme 15. Asymmetric Alkylation of 2-Phenylbutanoic Acid (**23**)

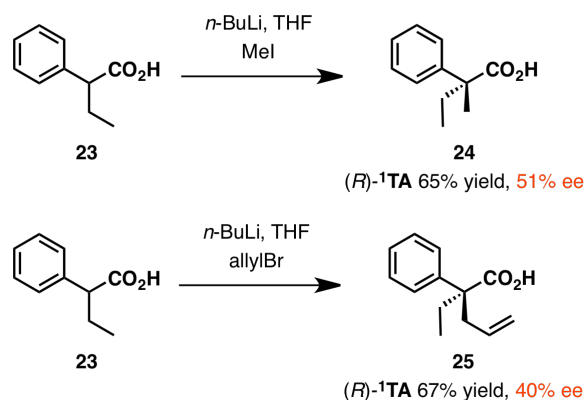
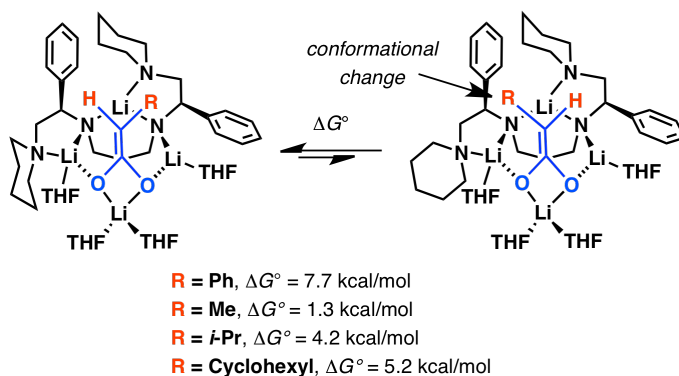


Figure 3. Calculated Conformation Energy Differences



1.5.3 Conclusions

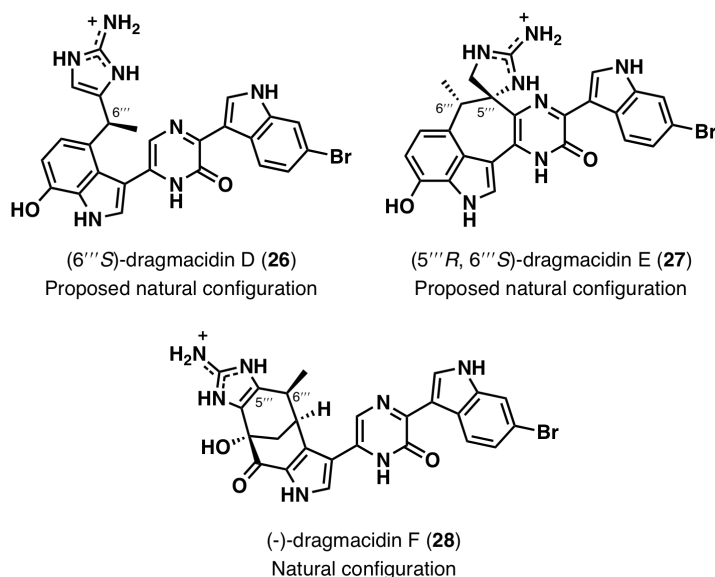
The development of asymmetric alkylation of enediolate—dilithium amide mixed aggregates with chiral tetramine (*R*)-1TA continues to yield fruitful results. The growth and expansion of this direct enantioselective alkylation methodology has the potential to continue to contribute to the chemical and scientific communities.

**Chapter 2: 10-Step Asymmetric Total Synthesis and Stereochemical Elucidation of (+)-
Dragmacidin D**

2.1 Introduction

Dragmacidin D (**26**) is a member of a family of heterocyclic bis(indole) natural products isolated from deep-water Caribbean sponges of *Dragmacidon* and *Spongosorites* sp. (Figure 4).³⁷ Although the initially isolated sample displayed no optical activity,³⁸ subsequent reisolation from a sponge specimen collected at 90 m depth along the coast of South Australia provided a sample of dragmacidin D with an $[\alpha]_D^{25}$ of $+12^\circ$ (c 0.95, EtOH).³⁹ These observations indicate a certain measure of ambiguity for the stereochemical identity of dragmacidin D and configurational stability of its sole stereogenic center.³⁷ Dragmacidin D, along with dragmacidin E (**27**), was found to be a potent inhibitor of serine-threonine phosphatases PP1 and PP2A (PP1, $IC_{50} = 21.0$ nM; PP2A₁, $IC_{50} = 3.0$ μ M; PP2A₂, $IC_{50} = 3.0$ μ M). Other biological activity reported for dragmacidins include antiviral, antibacterial, antifungal, and *in vitro* cytotoxicity against P388 murine leukemia, A549 human lung, HCT-8 human colon, and MDAMB human mammary cancer cell lines, in addition to selective inhibition of neural nitric oxide synthase (bNOS) with $EC_{50} = \sim 2.9$ μ M. The distinctive structure of dragmacidin D combines a reactive central pyrazinone core with flanking indole substituents, one of which is further elaborated with an aminoimidazole unit bound by a stereogenic methine linker at the 6''' position.

Figure 4. Pyrazinone Dragmacidins

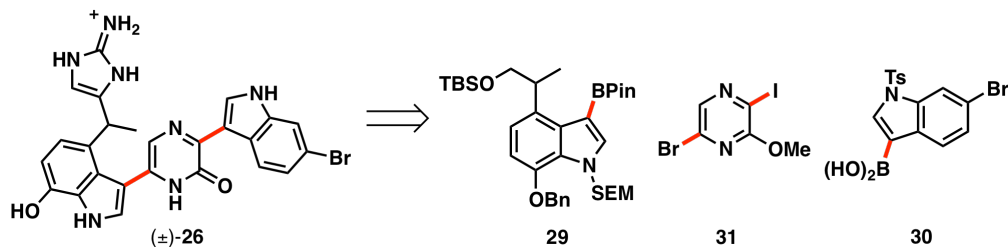


2.2 Previous Syntheses of Dragmacidin D

2.2.1 Stoltz' Synthesis of (±)-Dragmacidin D

In 2002, Stoltz and co-workers completed the first total synthesis of racemic dragmacidin D by effectively utilizing a series of sequential, temperature-controlled Suzuki cross-coupling reactions between organoboron reagents **29**, **30** and dihalopyrazine **31** (Scheme 16).⁴⁰ The synthesis was completed in 17 steps, which reflect many intricacies at the late-stage installation of the polar aminoimidazole substituent.

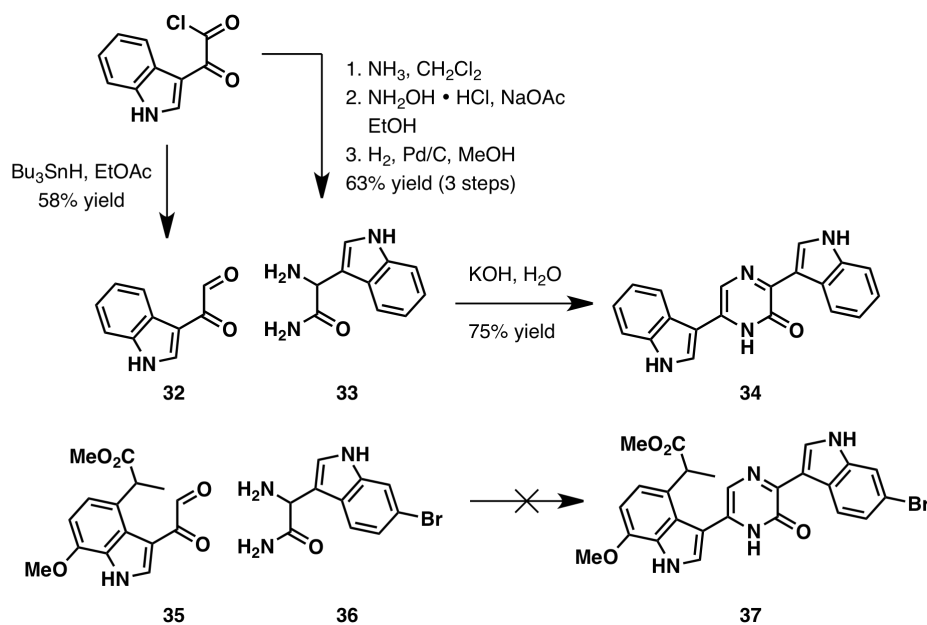
Scheme 16. Stoltz' Synthetic Plan



Although the Suzuki cross-coupling approach led to the successful synthetic route to dragmacidin D, Stoltz originally studied a cyclocondensative pyrazinone synthesis to assemble the bis-indolyl pyrazinone core structure, (Scheme 17). After identifying keto

aldehyde **32** and aminoamide **33** as simple model substrates, the authors were encouraged by facile condensation under basic conditions to form bis-indolyl pyrazinone **34**. Unfortunately, this approach was ineffective for producing the desired dragmaclidin framework **37** with more functionalized ketoaldehyde **35** and aminoamide **36**, likely due to the steric component of C4 substitution of the 3,4,7-trisubstituted indole.

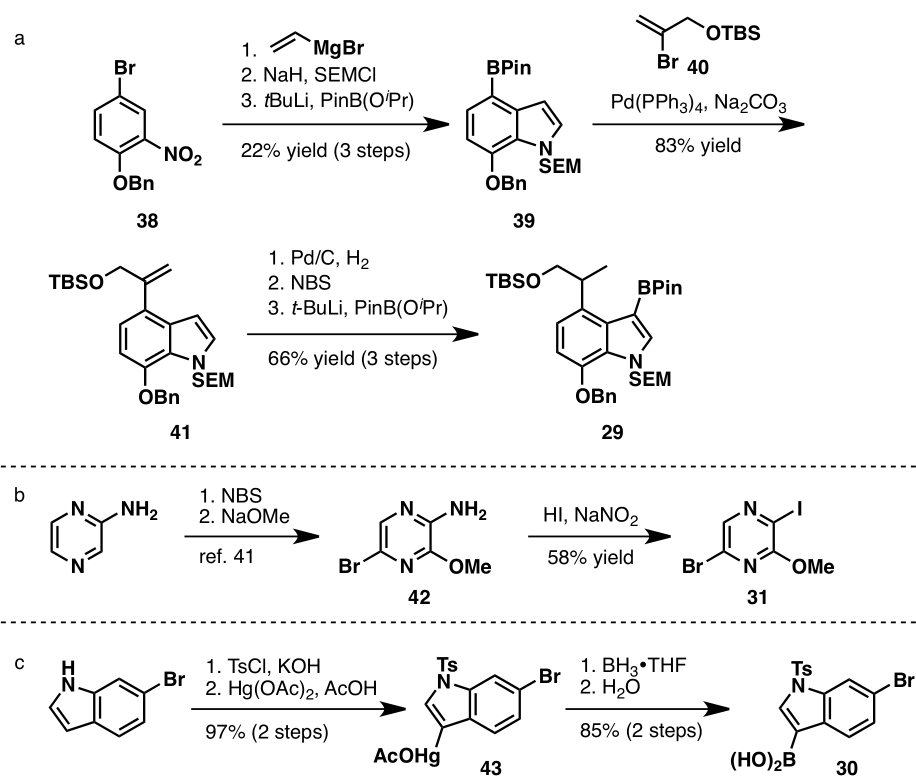
Scheme 17. Stoltz' Cyclocondensative Approach



Focusing on the Suzuki coupling approach, preparation of the 3,4,7-trifunctionalized indole boronate **29** began with a Bartoli indole synthesis from 1-(benzyloxy)-4-bromo-2-nitrobenzene (**38**) in a modest 33% yield (Scheme 18a). Initial protection of the indole nitrogen with a 2-(trimethylsilyl)ethoxymethyl (SEM) group was followed by lithium-halogen exchange and trapping as the pinacol ester. Suzuki coupling between indole **39** and vinyl bromide **40** provided silyl ether **41**. Synthesis of the fragment was accomplished via hydrogenation of the alkene, bromination of the indole at the C3 position, and finally lithium-halogen with subsequent trapping as the pinacol ester. Dihalopyrazine **31** was prepared via a Sandmeyer reaction from known amino pyrazine **42**,⁴¹ synthesized from 2-

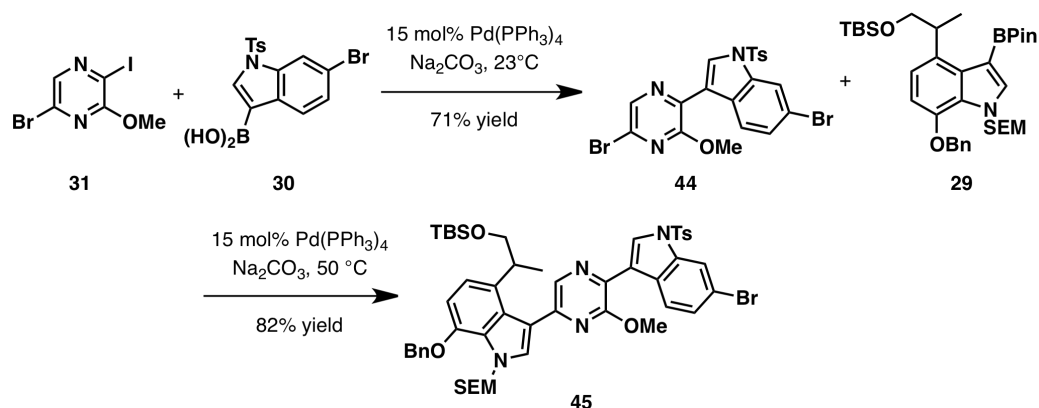
aminopyrazine in two steps (Scheme 18b). The bromoindole boronic acid **30** was prepared in 4 steps from 6-bromoindole through the organomercury indole **43** (Scheme 18c).⁴²

Scheme 18. Synthesis of Suzuki Precursors



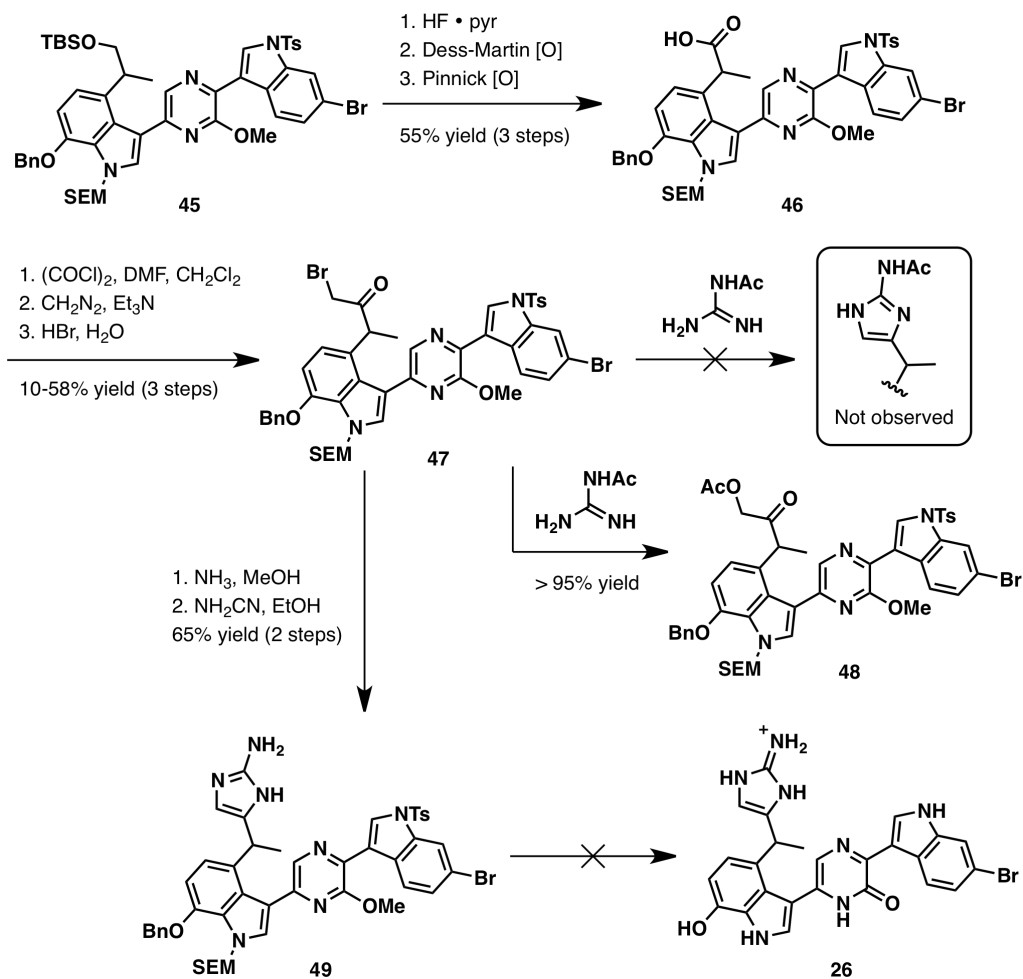
Next they turned their attention to the key sequential Suzuki couplings. After gaining insight regarding the reactivity of dihalopyrazines gathered from a model study, selective coupling between boronic acid **30** to the iodide of dihalopyrazine **31** was accomplished at room temperature in good yield (Scheme 19). The subsequent Suzuki coupling could be accomplished under carefully controlled reaction conditions, specifically restricting the reaction temperature at 50 °C, effectively coupling with the other indole boronate **29** to pyrazine **44** with minimal interference from the indolyl bromide.

Scheme 19. Temperature Controlled Sequential Suzuki Coupling



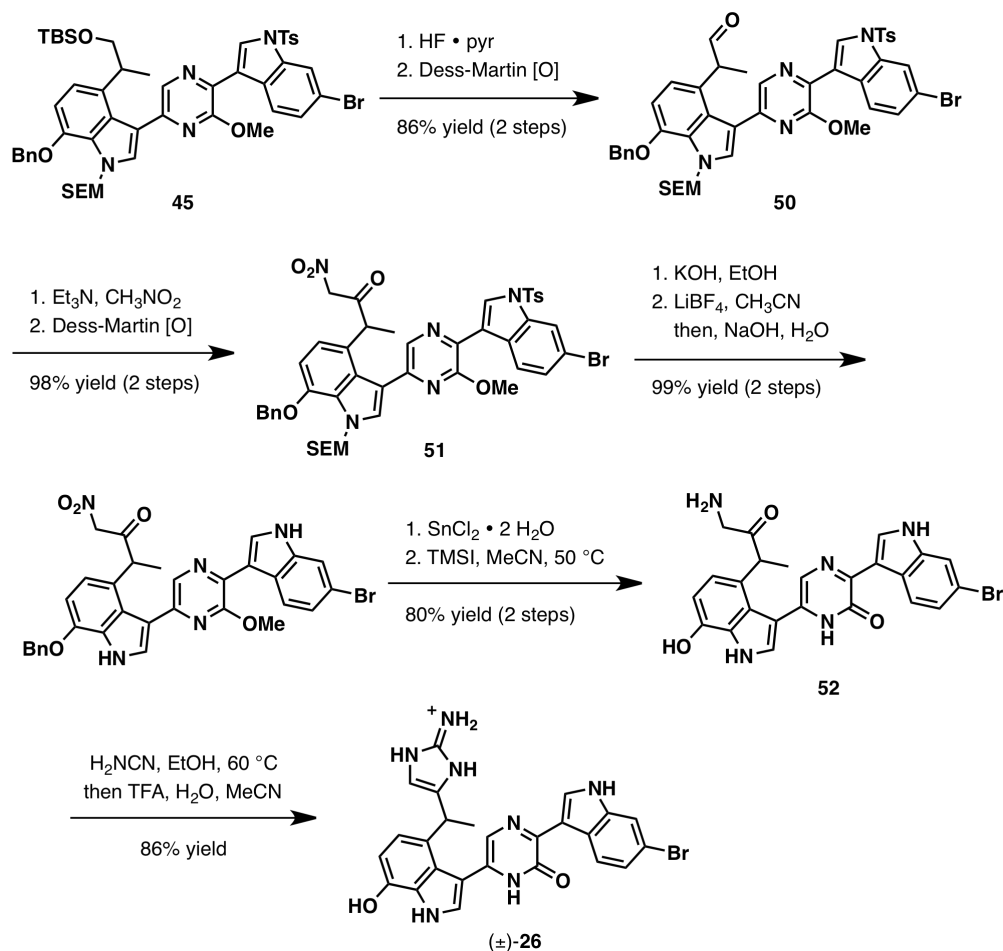
With the bis-indolylpyrazine core in hand, the authors attempted to convert **45** into drarmacidin D (Scheme 20). Silyl ether cleavage and two-step oxidation to carboxylic acid **46** was accomplished in good yield. An Arndt-Eistart homologation to α -bromo ketone was initially problematic, but after careful drying of the diazomethane, the transformation was accomplished in a good 58% yield. Treatment of bromoketone **47** with acetylguanidine did not produce the desired *N*-acetylaminoimidazole, but instead formed acetoxyketone **48** in nearly quantitative yield. Alternatively, condensation of the α -aminoketone with cyanamide in ethanol generated the desired aminoimidazole **49**. Sadly, all attempts to remove the remaining protecting groups resulting in nonspecific cleavage of the aminoimidazole heterocycle.

Scheme 20. Stoltz' Endgame Strategy 1



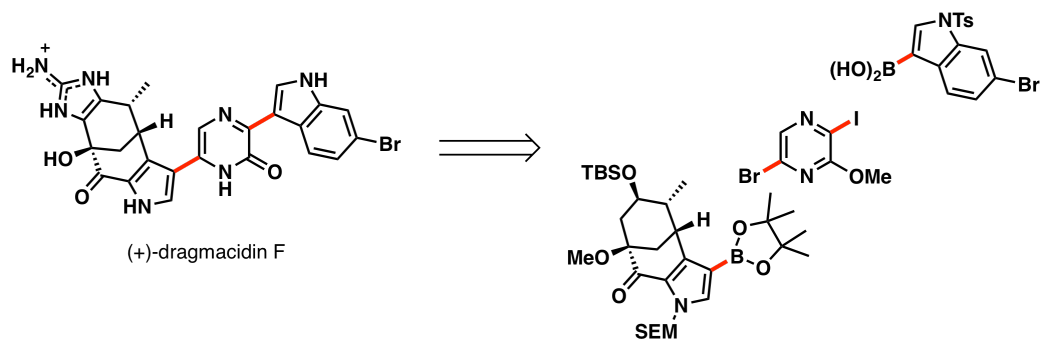
The authors decided to alter their final endgame strategy (Scheme 21). After silyl deprotection, Dess-Martin oxidation gave aldehyde **50**. Nitromethane addition followed by another Dess-Martin oxidation resulted in nitro ketone **51**. After deprotection, tin(II) promoted nitro reduction and dealkylation with TMSI gave amino ketone **52**. Finally, condensation of **52** with cyanamide in EtOH provided (±)-**26**, isolated as the trifluoroacetate salt, in 17 steps and 5.8% overall yield.

Scheme 21. Completion of (±)-Dragmacidin D

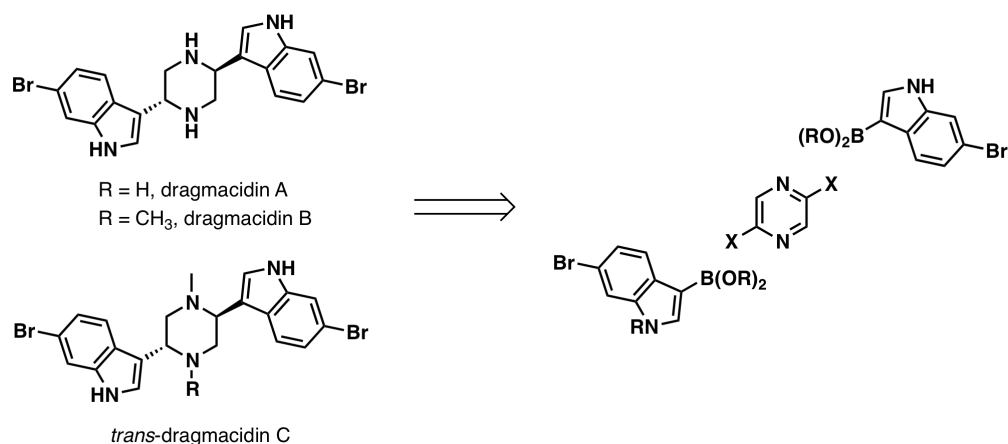


The key Suzuki coupling strategy was also utilized in the exceptional total synthesis of both enantiomers of dragmacidin F⁴³ as well as formal syntheses of dragmacidins A, B, and C.³⁷

Scheme 22. Stoltz' Synthetic Plan for (+)-Dragmacidin F

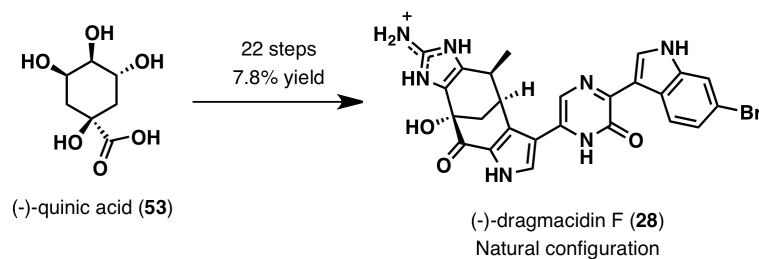


Scheme 23. Stoltz' Formal Syntheses of Dragmacidin A, B, and C

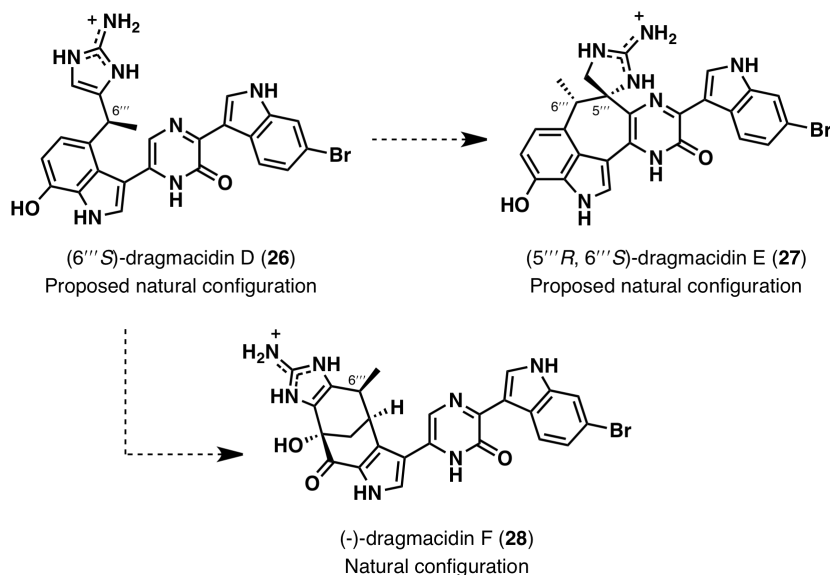


After completing the total synthesis of (–)-dragmacidin F (**28**) and thereby assigning its absolute configuration (Scheme 24),⁴³ the Stoltz group proposed the configuration of natural (+)-dragmacidin D (**26**) and (–)-dragmacidin E (**27**) to be 6'''*S* and 5'''*R*, 6'''*S*, respectively, postulating a common biogenesis (Scheme 25).³⁷

Scheme 24. Stoltz' Synthesis of (–)-Dragmacidin F (**28**)



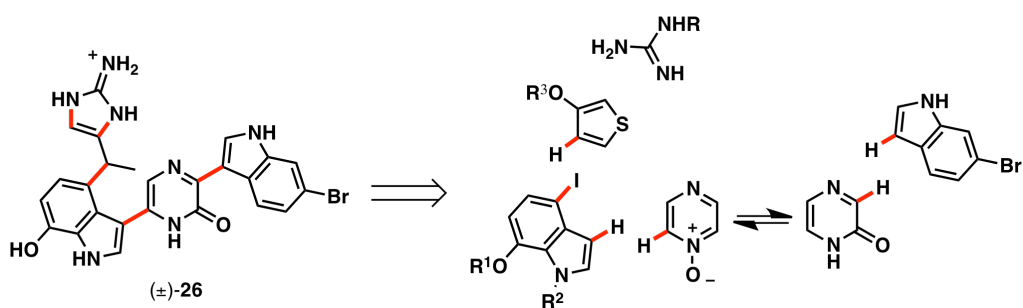
Scheme 25. Stoltz' Biosynthetic Proposal



2.2.2 Itami-Yamaguchi Synthesis of (±)-Dragmacidin D

In 2011, Yamaguchi and Itami et al. reported the second total synthesis of (±)-**26**, which was completed in 12 steps by using a series of C–H cross-coupling reactions.⁴⁴ This concise synthesis highlights the utility of C–H functionalization technology in complex total synthesis⁴⁵ and was accomplished by taking advantage of three sequential C–H coupling reactions and a tautomeric switch between pyrazinone and pyrazine *N*-oxide (Scheme 26).

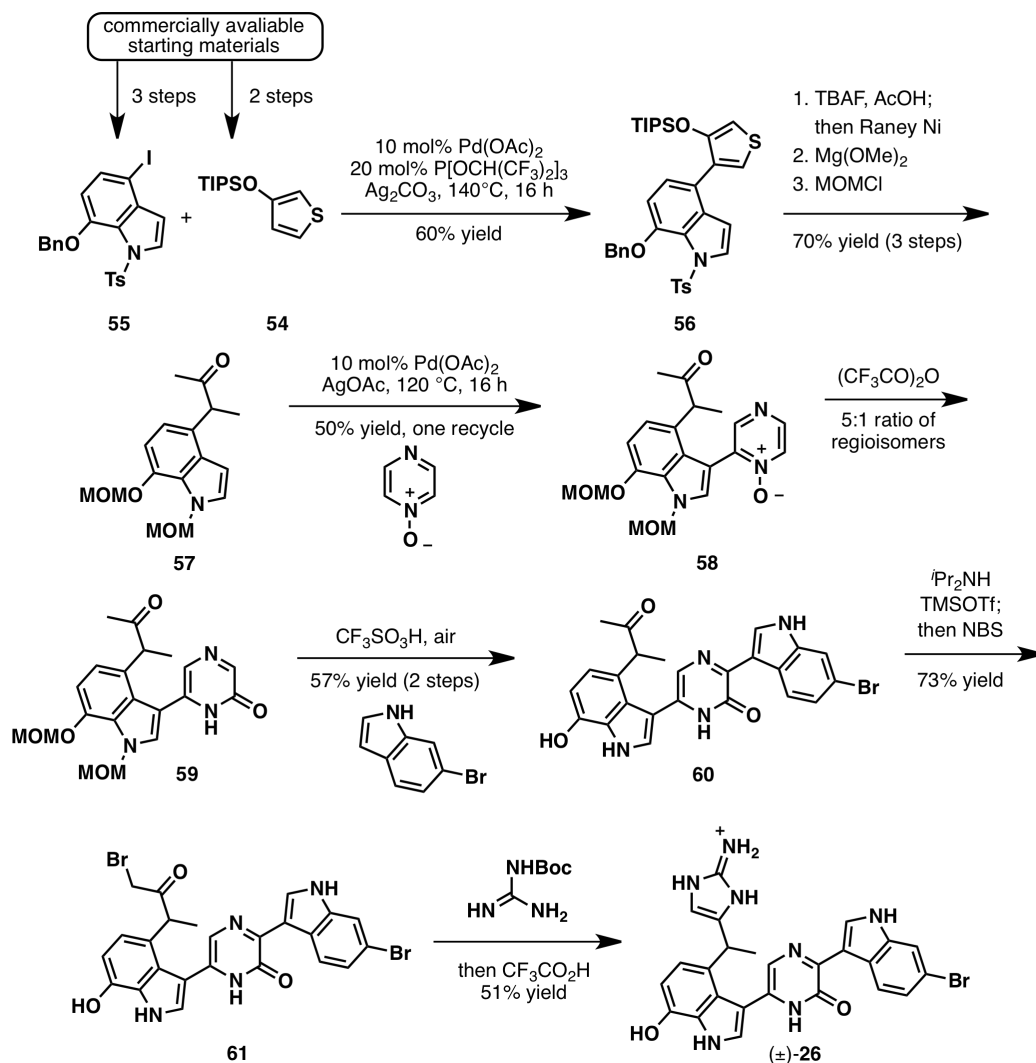
Scheme 26. Itami-Yamaguchi's Synthetic Plan



Utilizing methodology developed in their lab, Itami and co-workers employed a regioselective coupling at the C4 position of silyloxy thiophene **54** to 4-iodoindole **55** (Scheme 27).⁴⁶ The steric bulk of the silyloxy group was critical to achieve good

regioselectivity through directed palladium complexation to the C4/C5 double bond of **54**. Removal of the silyl ether, parallel thiophene and benzyl ether reduction, followed by protecting group exchange provided methyl ketone **57**. This substrate was used in a C–H/C–H coupling at the C3 indole position with pyrazine *N*-oxide catalyzed by Pd(OAc)₂ and stoichiometric AgOAc.⁴⁷ By recycling recovered starting material and resubmitting it to the reaction conditions, they were able to isolate coupled pyrazine *N*-oxide **58** in 50% yield. Tautomeric switch of the *N*-oxide **58** was induced by trifluoroacetic anhydride, affording pyrazinone **59** as a 5:1 mixture of regioisomers. It was reasoned that the steric bulk of the methyl ketone at the C4 position of the left-hand indole unit influenced the increase in regioselectivity favoring the desired regioisomer. Attachment of the 6-bromoindole unit was achieved through an oxidative C–H/C–H coupling reaction with pyrazinone **59** mediated by F₃CSO₃H with simultaneous MOM deprotection.⁴⁸ The synthesis of **26** was completed via α -bromination of **60** followed by nucleophilic attack and cyclocondensation of **61** with Boc-protected guanidine. Notably, the aminoimidazole installation was accomplished in a concise manner over 2 steps, compared to the 9 steps required by Stoltz and co-workers.

Scheme 27. Itami-Yamaguchi Synthesis

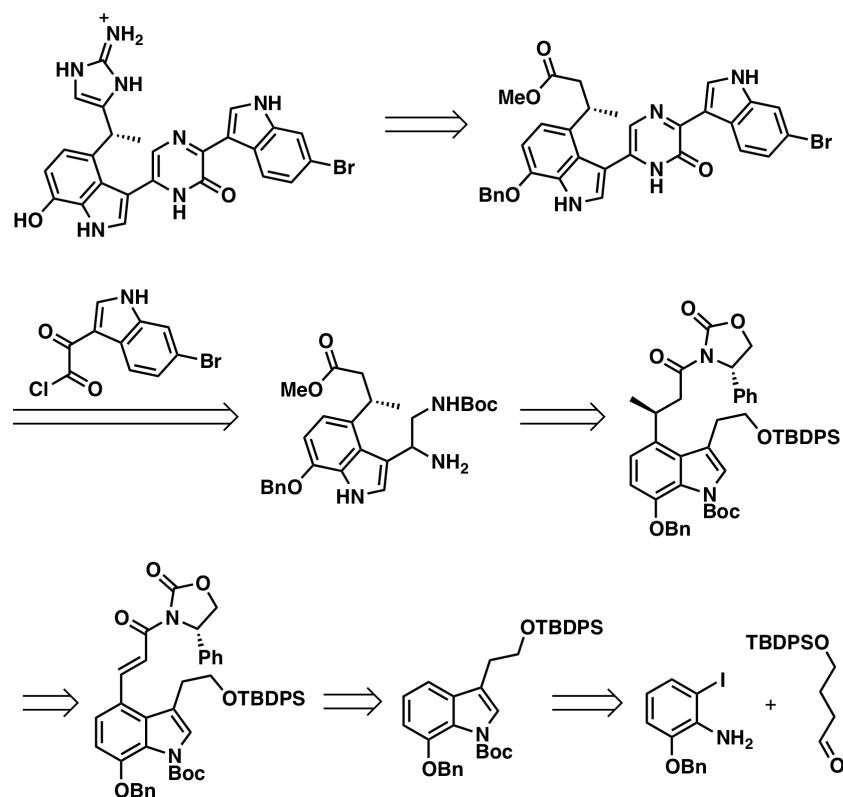


2.2.3 Jia-Capon Synthesis of (+)-Drarmacidin D

Recently, a collaborative effort by the Jia and Capon groups culminated in the asymmetric total synthesis of (+)-**26** in 26 steps.⁴⁹ This effort suggested a curious divergence in stereochemistry between drarmacidins D and F, and revises the stereochemistry of (+)-**26** to 6''*R*. The authors noted that **26** has never been co-isolated with drarmacidin F (**28**) but has been co-isolated with drarmacidin E (**27**), thus providing a plausible basis for this divergence, and reported that samples of **26** isolated by Capon and co-workers were either racemic or enantioenriched at 39% ee.

Retrosynthetically the authors opted, like the previous two syntheses, to install the aminoimidazole heterocycle at the end of the synthesis. They chose to use a modification of Chen's method.⁵⁰ The central pyrazinone ring would be constructed using a strategy similar to Stoltz' original approach via intermolecular cyclocondensation. The key 3,4,7-trisubstituted indole fragment, preinstalled with the stereogenic methyl group, would be prepared by an asymmetric conjugate addition directed by Evans' chiral oxazolidinone auxiliary. The indole heterocycle would be synthesized using a palladium-catalyzed heteroannulation reaction.

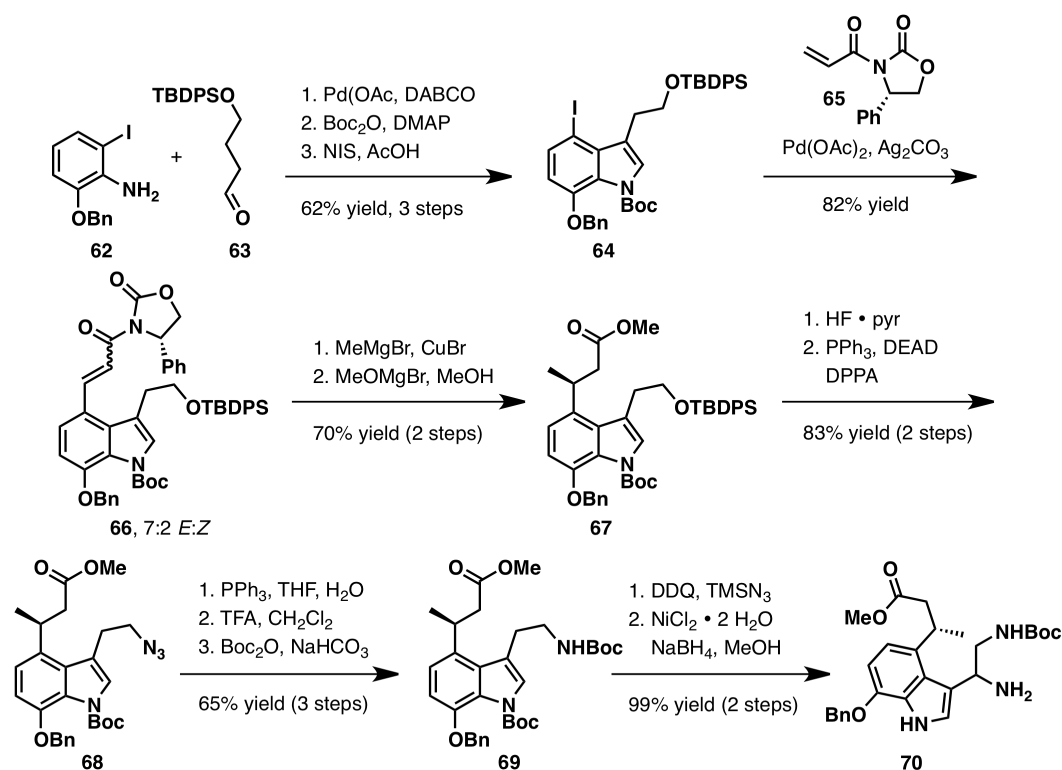
Scheme 28. Jia-Capon Synthetic Plan



The synthesis began with a palladium-catalyzed heteroannulation reaction from iodoaniline **62** and butyraldehyde **63** to prepare the tryptophol derivative (Scheme 29). Following *N*-Boc protection, chemoselective iodination at the C4 position with *N*-iodosuccinimide in the presence of acetic acid afforded iodide **64**. An intermolecular Heck

reaction with *N*-acyl oxazolidinone **65** gave indole **66** as a 7:2 ratio of *E:Z* isomers. Conjugate addition of methyl cuprate followed by methanolysis of Evan's auxiliary gave methyl ester **67** in 70% yield and a 7:2 ratio of diastereomers. After separation of the isomers via column chromatography, silyl ether deprotection, azide installation, Staudinger reduction, Boc deprotection, and Boc protection gave *N*-Boc tryptamine **69**. Treatment of **69** with a mixture of DDQ and TMSN₃ followed by azide reduction with NaBH₄ and NiCl₂ provided the amine **70** as a mixture of diastereomers.

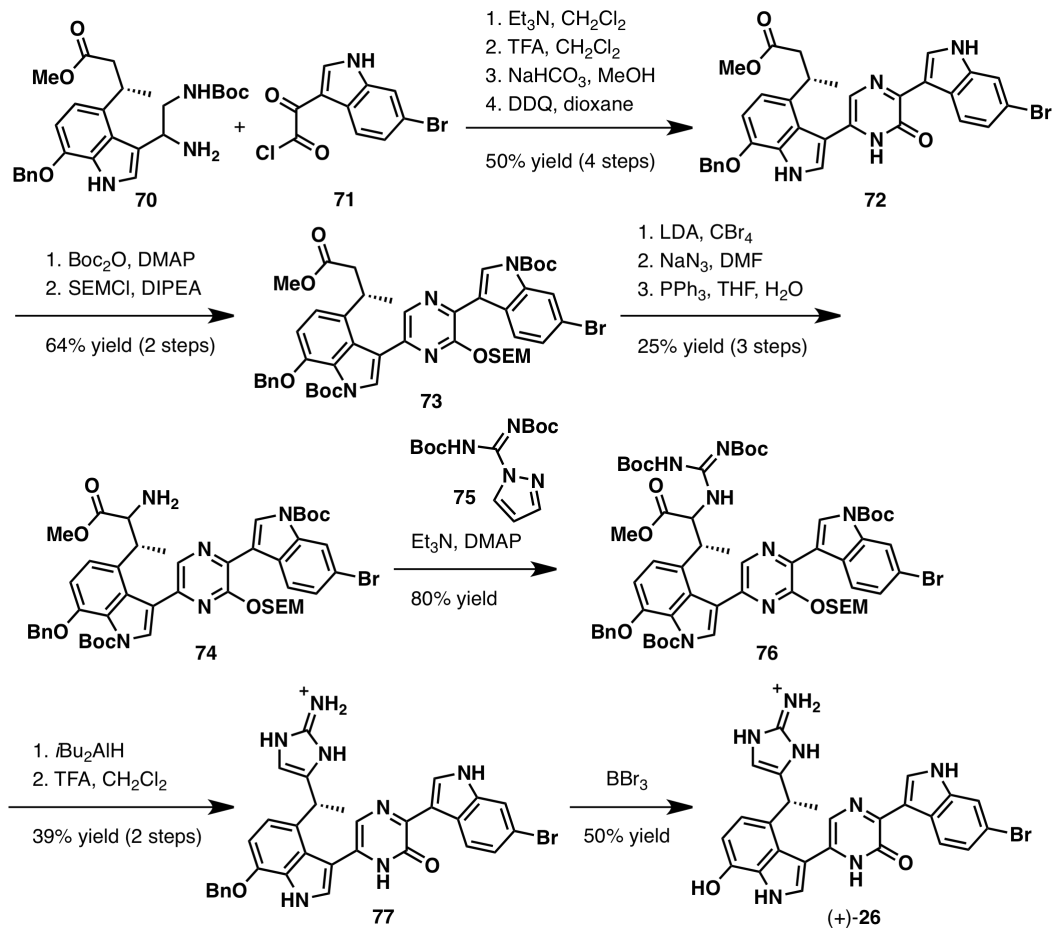
Scheme 29. Installation of Stereocenter and Synthesis of Left-Hand Fragment



The cyclocondensation strategy was completed in three-steps involving acylation of amine **70** with 6-bromoindole oxalyl chloride **71**, cyclization, and subsequent DDQ induced oxidative aromatization to pyrazinone **72** (Scheme 30). Protection of both indoles and pyrazinone provided methyl ester **73** in preparation for α -bromination. Azide substitution and Staudinger reduction generated α -amino ester **74**, which, after guanidine formation,

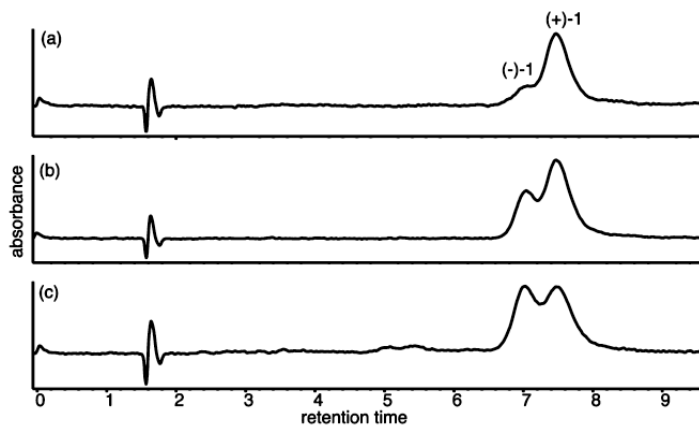
gave di-Boc guanidinyl methyl ester **76**. Reduction with *i*Bu₂AlH and TFA induced deprotection/cyclization gave aminoimidazole **77**. Finally, dealkylation with boron tribromide provided a synthetic sample of dragmacidin D with an $[\alpha]_D^{25}$ of +18.8° (*c* 0.10, EtOH).

Scheme 30. Cyclocondensation and Completion of Synthesis



Chiral HPLCs of both synthetic and natural dragmacidin D, isolated by Capon and co-workers, are represented in Figure 5. Synthetic dragmacidin D was without a doubt enantioenriched (ee unreported), while natural dragmacidin D possessed either a low enantiopurity of 39% ee or racemic.

Figure 5. Chiral HPLC Analysis. a) Synthetic (+)-Dragmacidin D. b) (+)-Dragmacidin D (39% ee) from RJC-91-011. and c) (±)-Dragmacidin D from RJC-98-305



The 6'''*R* stereochemistry, installed from the asymmetric organocuprate conjugate addition, was confirmed through derivitization of methyl ester **67** to known succinic benzyl ester **79**^{51,52} (Scheme 31) and chiral HPLC analysis (Figure 6).

Scheme 31. Confirmation of 6''' Stereochemistry

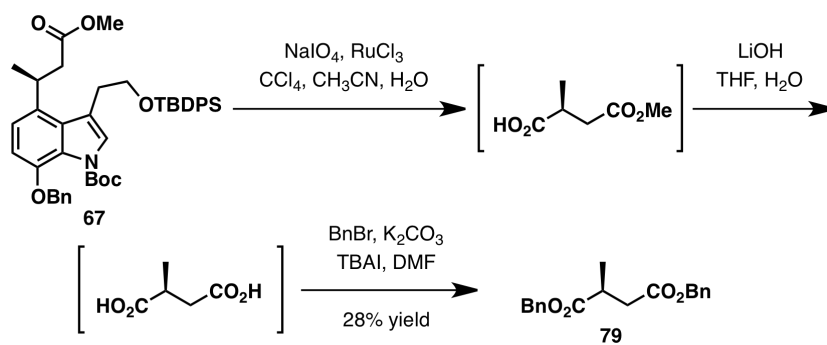
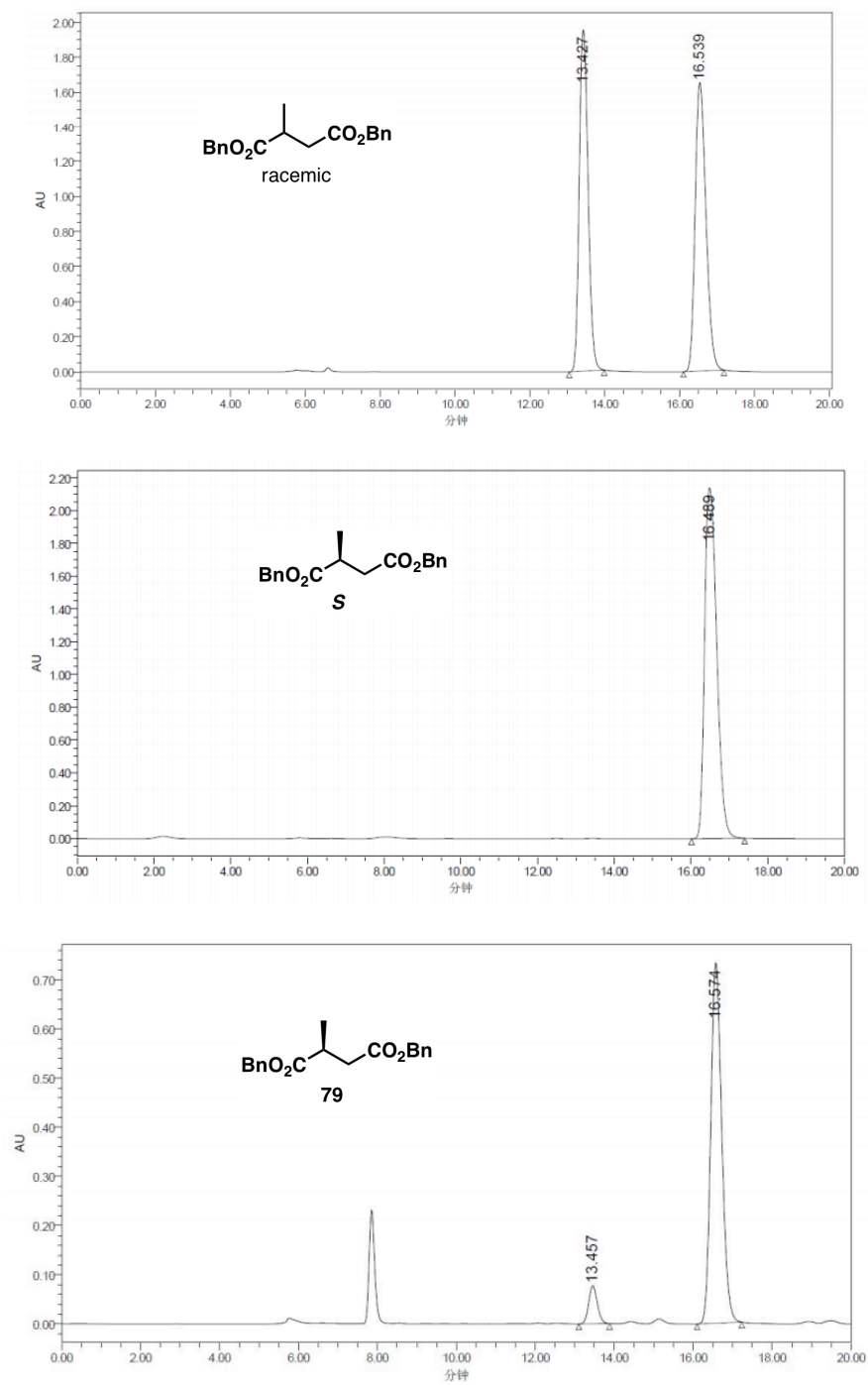


Figure 6. HPLC analysis of 79

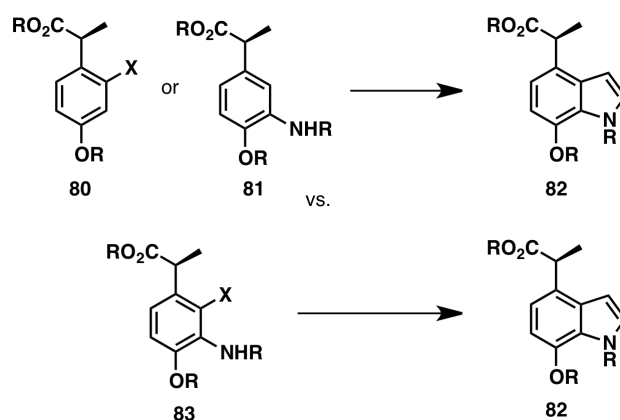


2.3 Zakarian Synthesis of (+)-Dragmacidin D

2.3.1 Early Strategies Towards the Total Synthesis of Dragmacidin D

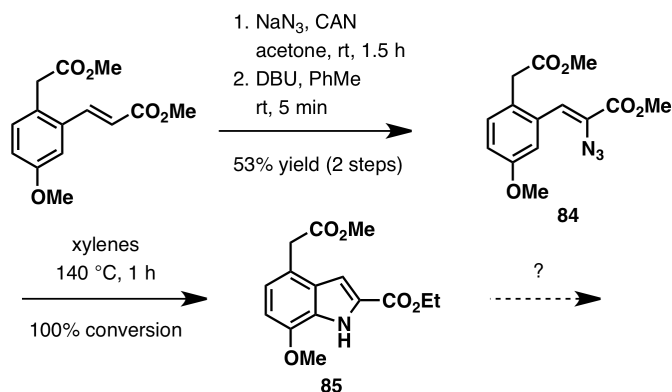
Our early synthetic strategy originally focused on employing a tri-substituted benzene ring, such as **80** or **81**, to manufacture the left-hand indole fragment **82**, avoiding the need to prepare a 1,2,3,4-tetrasubstituted benzene **83**, which would be much more difficult to synthesize efficiently (Scheme 32).

Scheme 32. Early Synthetic Strategy



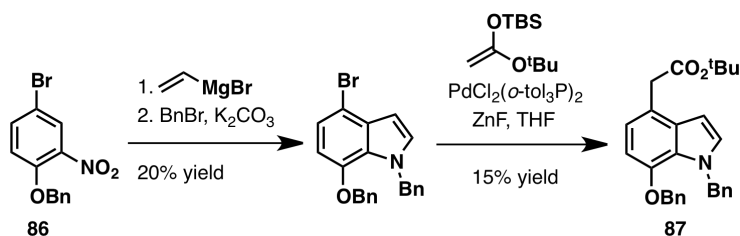
One initial strategy involved synthesis of alkenyl azide **84** through a ceric ammonium nitrate (CAN) mediated process followed by base promoted elimination (Scheme 33).⁵³ Subsequent thermal heating provided cyclized indole **85** with 100% conversion.⁵⁴ However, the need to remove the ethyl ester in the C2 position of the indole as well as the need to attach the pyrazinone heterocycle at the C3 position drastically reduced our enthusiasm towards this route.

Scheme 33. Azide Cyclization



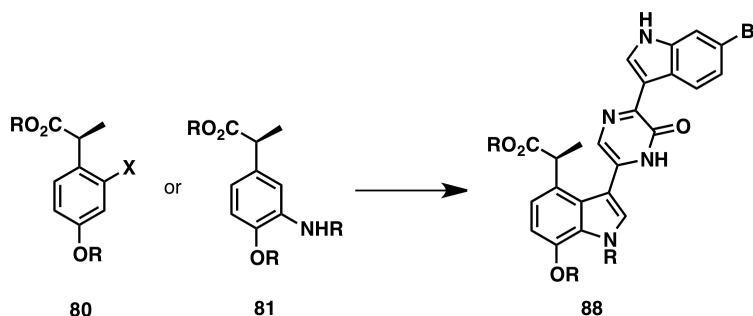
Another early strategy involved a Bartoli indole synthesis from nitro arene **86**,⁵⁵ followed by a palladium-catalyzed Hartwig enolate coupling to provide indolylacetate **87** (Scheme 34).⁵⁶ However, yields above 15% were never achieved and the issue of attaching the pyrazinone heterocycle regioselectively remained unsolved.

Scheme 34. Bartoli Synthesis–Hartwig Coupling Strategy



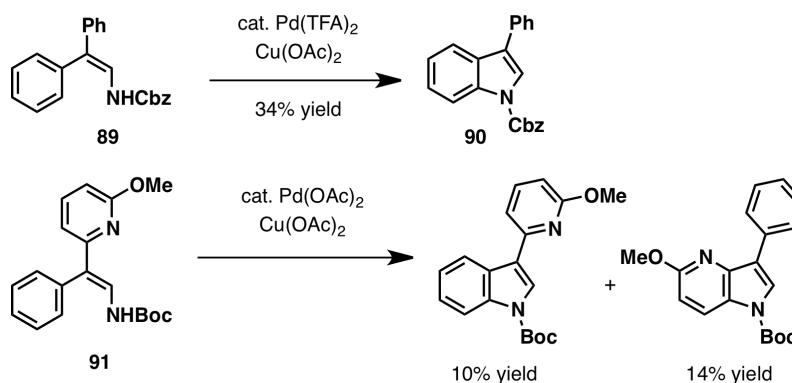
Adjusting our strategy, we wanted to form our left-hand indole **88** with simultaneous attachment of the pyrazinone and 6-bromoindole moieties (Scheme 35).

Scheme 35. Revised Left-Hand Indole Strategy



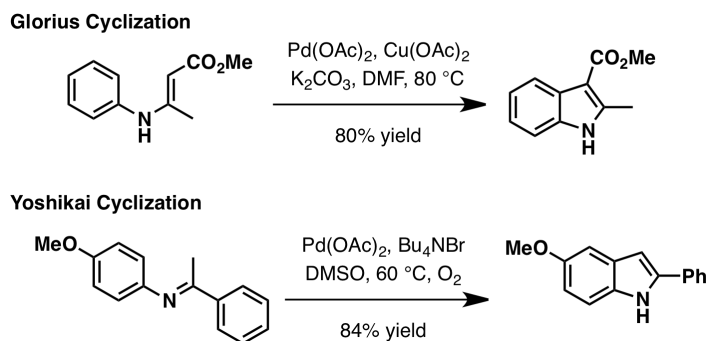
Using precedents by Inamoto and Queiroz, we attempted an intramolecular C–N cyclization of protected enamines (Scheme 36).⁵⁷ A model study showed the feasibility of this route using enamine **89** to provide 3-phenylindole **90** in modest yield. Unfortunately, the differentially substituted pyridine model **91** showed that the reaction was not regioselective. In addition, products were isolated in very poor yields.

Scheme 36. Intramolecular C–N Cyclization Strategy

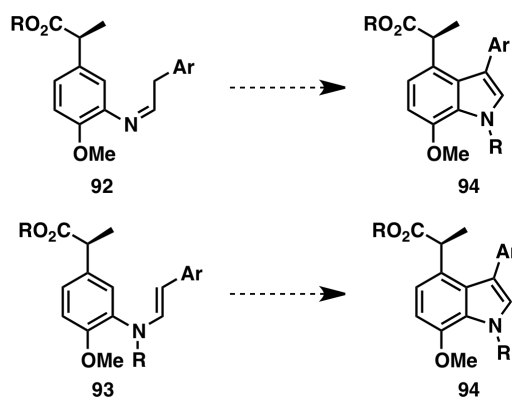


Inspired by the work of Glorius and Yoshikai (Scheme 37), we sought to oxidatively cyclize an *N*-aryl imine or enamine intermediate such as **92** or **93**, to form 3-arylindole **94** (Scheme 38).⁵⁸ An attempt to form imine **95** revealed that aryl acetaldehydes simply undergo a base catalyzed aldol polymerization so we decided to synthesize a carbamate protected *N*-aryl enamine (Scheme 39). Copper catalyzed Buchwald-Hartwig coupling to aryl iodide **96** provided Cbz-enamine **97** in modest yield.⁵⁹ Unfortunately, all cyclization attempts led to exclusive recovery of the starting material.

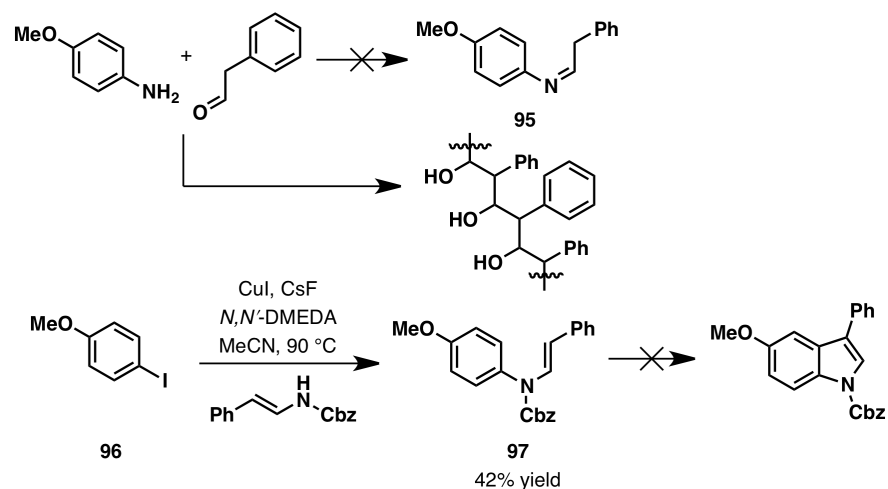
Scheme 37. Glorius' and Yoshikai's Oxidative Cyclization



Scheme 38. Cyclization Strategy

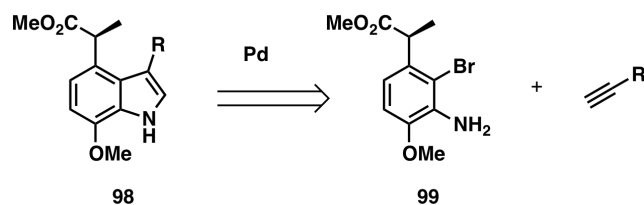


Scheme 39. Cyclization Attempts



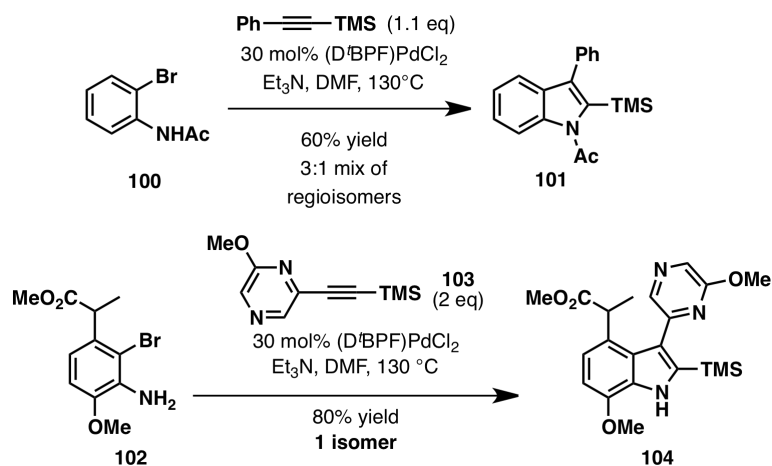
Conceding the option to pursue a route utilizing a tri-substituted benzene ring, we attempted to form our left hand indole **98**, with simultaneous pyrazine ring attachment, through a Larock heteroannulation from tetra-substituted bromoaniline **99** (Scheme 40).

Scheme 40. Larock Indole Synthesis Strategy

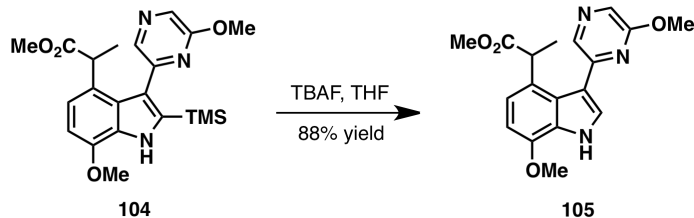


The most attractive feature of this method is the ability to regioselectively position aryl substituents in the C3 indole position through the use of silyl protected aryl alkynes. Heteroannulation between bromoanilide **100** and trimethylsilylphenyl acetylene confirmed our optimism by producing 3-phenyl indole **101** in moderate yield with acceptable selectivity (Scheme 41). We adjusted our strategy and decided to pursue this route. The reaction worked well between bromoaniline **102** and pyrazinyl alkyne **103** with complete regioselectivity. A quick optimization study revealed that 2 equivalents of alkyne **103** could produce indole **104** in 80% yield. Additionally, hydrodesilylation could be accomplished in good yield after treatment with TBAF providing indole **105** (Scheme 42).

Scheme 41. Testing the Larock Indole Synthesis



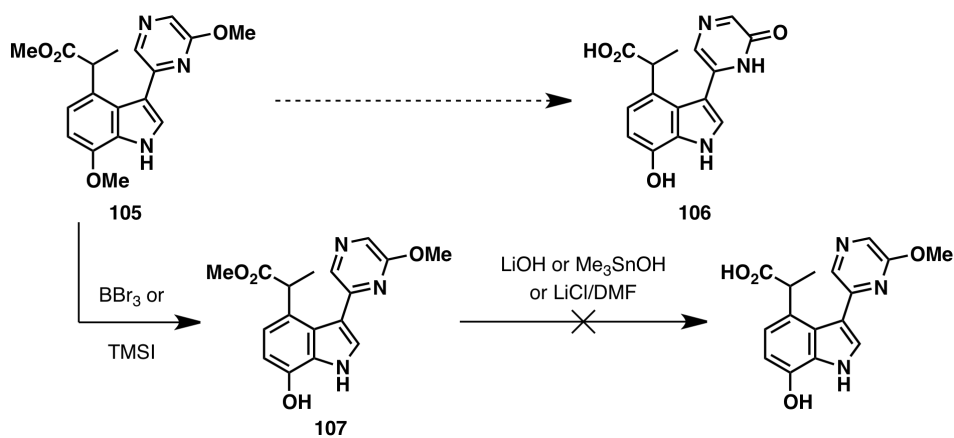
Scheme 42. Hydrodesilylation



2.3.2 Protecting Group Selection

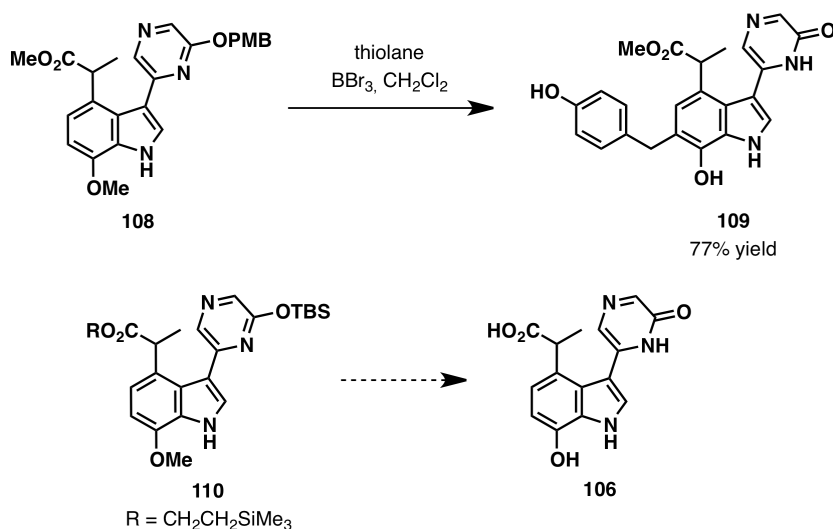
At this stage in the study, we began to investigate potential deprotection of the methyl ether and methyl ester protecting groups to expose pyrazinone **106** (Scheme 43). We were surprised to find that treatment of 3-pyrazinyl indole **105** with either BBr₃ or TMSI did not efficiently induce bis-demethylation. Additionally, we were unable to remove the methyl ester of **107** under a variety of the hydrolytic conditions.

Scheme 43. Protecting Group Issues



We attempted to switch the pyrazinyl methyl ether to a *para*-methoxybenzyl ether-protecting group (Scheme 44). After exposing **108** to boron tribromide, clean dealkylation was not observed; instead a very efficient Friedel–Crafts arylation took place yielding indole **109**, even in the presence of thiolane as a cation trap. After careful consideration, we decided to install a TBS ether and (2-trimethylsilyl)ethyl ester as protecting groups in **110**, which eventually led to the successful route.

Scheme 44. PMB Issues and Successful Protecting Groups

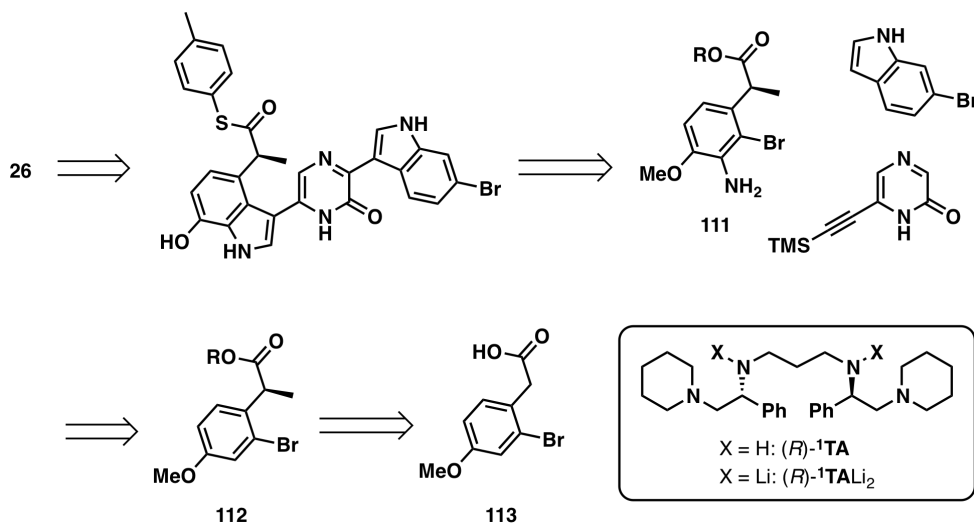


2.3.3 10-Step Asymmetric Synthesis and Stereochemistry of (+)-Drugmacidin D

Detailed herein is a 10-step asymmetric total synthesis of (+)-drugmacidin D and what appears to be compelling evidence that its absolute configuration is indeed $6'''S$, as originally forecasted by Stoltz, and is thus uniform with that of (-)-drugmacidin F. This short 10-step synthesis is enabled by direct early-stage enantioselective alkylation of commercially available 4-methoxy-2-bromophenylacetic acid, in an extension of the methodology recently developed in our laboratory.^{14,17} The final synthesis plan that unlocked the path to success is outlined in Scheme 45. A concise elaboration of the thioester to the aminoimidazole was projected for the final operations of the synthesis.⁶⁰ In contrast to all previous efforts that engaged a preassembled 7''-hydroxyindole found in **26**, we opted for the construction of the indole ring system by a Larock indole synthesis,⁶¹ thereby introducing a point of convergence in the synthesis plan. This transformation was to be followed by a Friedel–Crafts-type direct arylation with 6-bromoindole under acidic conditions, which was also utilized in the Itami/Yamaguchi synthesis. Bromoaniline **111** for the Larock indole synthesis was to be produced from precursor **112**, with 4-methoxy-2-

bromoacetic acid **113** identified as a straightforward starting material for its preparation by our direct alkylation method with the readily available tetramine (*R*)-**1**TA as the stereodirecting reagent (Scheme 45). One of the challenging objectives was preservation of the stereogenic center in **112** through the remaining operations of the synthesis.

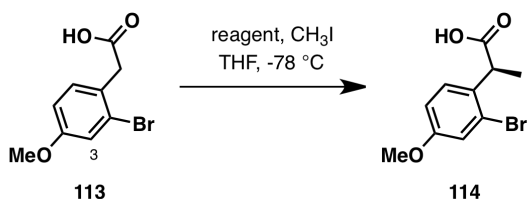
Scheme 45. Synthesis Plan for Dragmacidin D (**26**)



Direct α -alkylation of carboxylic acids occurs via dianionic enediolates as reactive intermediates. Our initial studies showed that **113** is a challenging substrate for this reaction. Attempts to obtain the α -methylation product with CH₃I and lithium diisopropylamide (LDA) or *n*-BuLi as the enolization reagents only led to decomposition of the starting material (Table 8, entries 1 and 2). Clean methylation was observed with LiN(SiMe₃)₂ (entry 3). We postulated that decomposition with the more basic reagents was due to competitive lithiation of the arene C–H bond of **113** at the C3 position to form benzyne species. This problem could be solved through careful choice of a base that would prevent the arene lithiation and yet be potent enough to be compatible with the asymmetric alkylation protocol. To our dismay, after enolization with LiN(SiMe₃)₂, alkylation with (*R*)-**1**TALi₂ resulted in racemic **114** (entry 4). It is likely that, after enolization, the higher acidity of

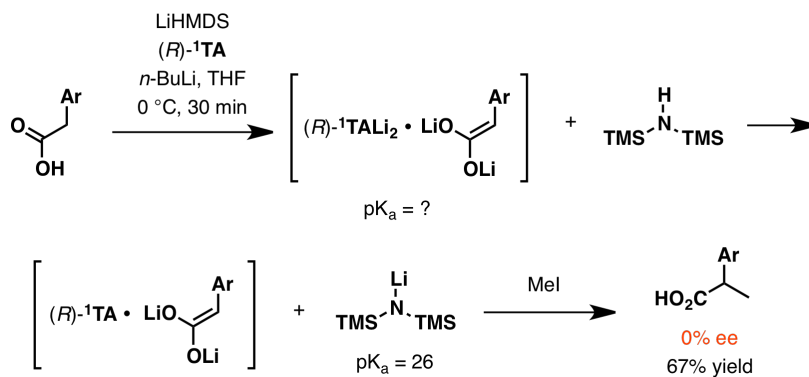
(Me₃Si)₂NH (pK_a=26) led to protonation of (*R*)-¹TALi₂ to give (*R*)-¹TA (Scheme 46). Intact lithium amide (*R*)-¹TALi₂ is a critical part of the chiral aggregate for stereoselective alkylation. Investigation of various readily available amines drew our attention to *t*-Bu(Me₃Si)NH, which in our assessment struck the right balance between steric bulk to prevent C3 lithiation, and basicity (pK_a=33 for *t*-BuNHSiMe₃; pK_a=37 for *i*Pr₂NH).⁶² A preliminary experiment supported this assessment (entry 5). We were delighted to discover that LiN(*t*Bu)SiMe₃ was an excellent choice, affording product **114** in 65% yield and 81% ee (entry 6).

Table 8. Development of the Direct Stereoselective α -Methylation of **113**



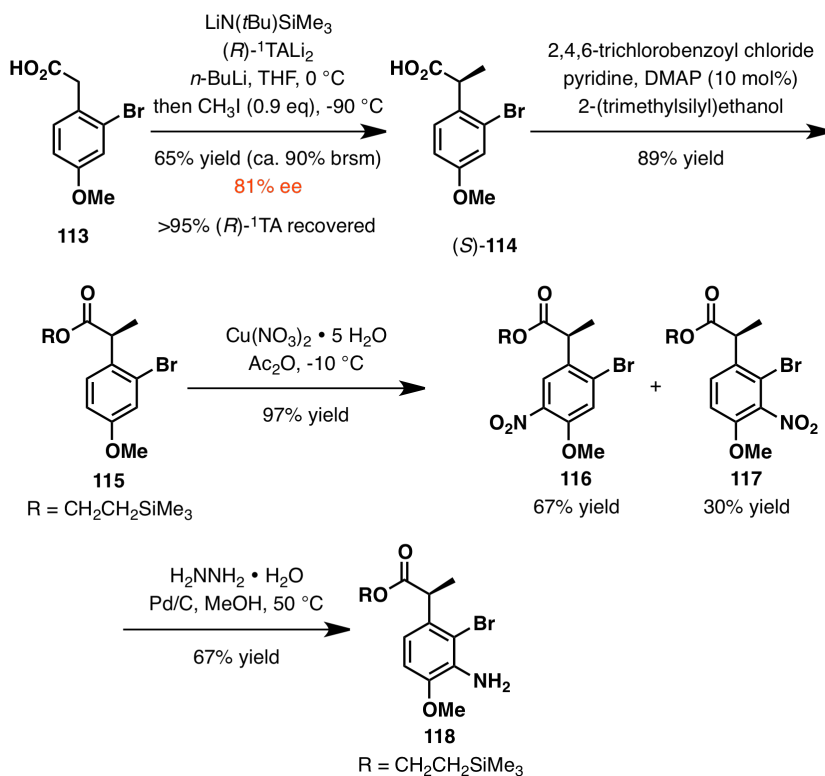
Entry	reagent	Result
1	nBuLi	decomposition
2	LDA	decomposition
3	LiN(SiMe ₃) ₂	78% conversion, clean
4	LiN(SiMe ₃) ₂ + (<i>R</i>)- ¹ TALi ₂	67% yield, 0% ee
5	LiN(<i>t</i> Bu)SiMe ₃	99% conversion, clean
6	LiN(<i>t</i> Bu)SiMe ₃ + (<i>R</i>)- ¹ TALi ₂	65% yield, 81% ee

Scheme 46. Postulation for Racemic Alkylation with LiHMDS

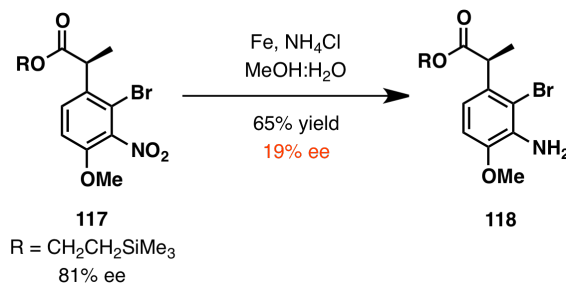


The synthesis of (+)-**26** began with direct asymmetric alkylation of **113** with 0.9 equiv of iodomethane mediated by (*R*)-**1TA** on scales up to 4.7 g, which afforded (*S*)-**114** in 65% yield and 81% ee (Scheme 47). We found that excess iodomethane was detrimental to enantioselectivity. Esterification of (*S*)-**114** with 2-(trimethylsilyl)ethanol was accomplished under Yamaguchi conditions in high yield with no racemization. Nitration of **115** was best achieved with $\text{Cu}(\text{NO}_3)_2 \cdot 5 \text{H}_2\text{O}$ in Ac_2O at $-10 \text{ }^\circ\text{C}$ ⁶³ to provide a mixture of nitration products **116** and **117** in 67% and 30% yield, respectively. The temperature of the reaction mixture had to be maintained at or below $-10 \text{ }^\circ\text{C}$ to avoid racemization. At this junction, we opted against further optimization of regioselectivity in favor of advancing the synthesis, given that multigram quantities of **117** could be produced in a concise fashion from **113** in 81% ee. Reduction of the nitro group to aniline was accomplished by treating **117** with $\text{N}_2\text{H}_4 \cdot \text{H}_2\text{O}$ and Pd/C in CH_3OH at $50 \text{ }^\circ\text{C}$. Careful control of temperature and N_2H_4 stoichiometry was necessary to minimize over-reduction. In this manner, **118** was obtained in 67% yield, along with its over-reduced product in 27% yield.⁶⁴ Metal mediated nitro reductions in acidic media lead to significant racemization of the stereocenter (Scheme 48).

Scheme 47. Synthesis of Precursor **118**



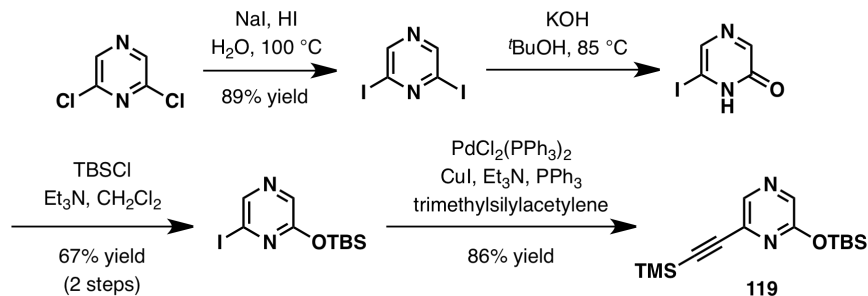
Scheme 48. Racemization Observed during Reduction with Fe



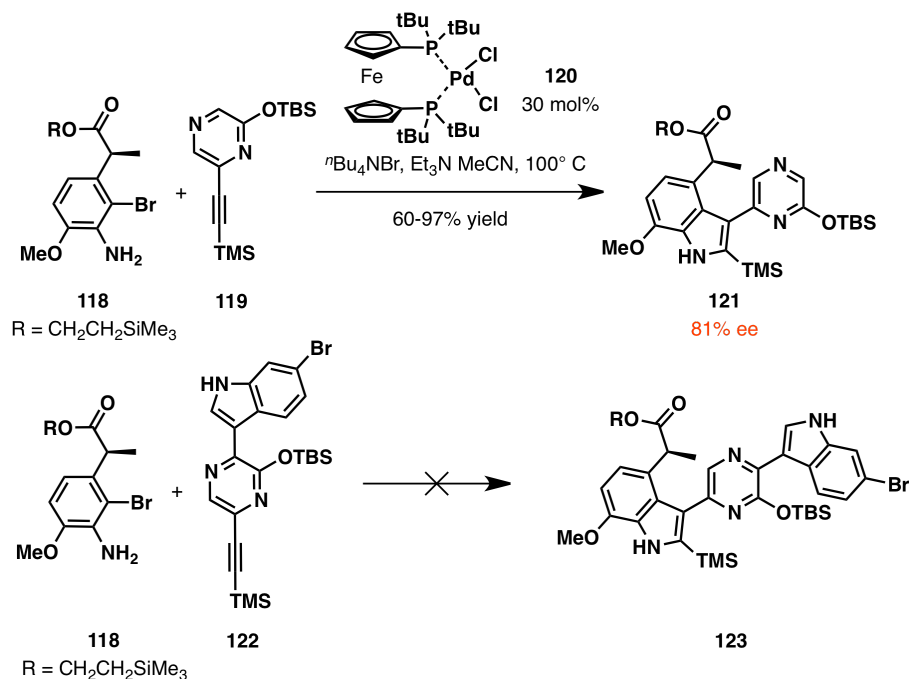
The alkynyl pyrazine precursor **119** was prepared in 4 steps from 2,6-dichloropyrazine (Scheme 49).⁶⁵ The central heteroannulation between **118** and **119** with the [1,1'-bis(di-tertbutylphosphino)ferrocene]PdCl₂ catalyst **120**[11] afforded the requisite 2,3,4,7-tetrasubstituted indole **121** in good yields and with no erosion of enantiomeric excess (Scheme 50). Yields were variable but the best results were obtained with freshly prepared substrates and freshly purified solvents. A dramatic improvement in reaction yield and

reproducibility was observed upon the addition of tetra-*n*-butylammonium bromide (TBAB) to prevent the formation of Pd black. A variant of the indole synthesis with an alkyne reagent analogous to **119** but bearing a preinstalled 6-bromoindole substituent (**122**) was unproductive (Scheme 50).

Scheme 49. Synthesis of Alkyne Precursor **119**



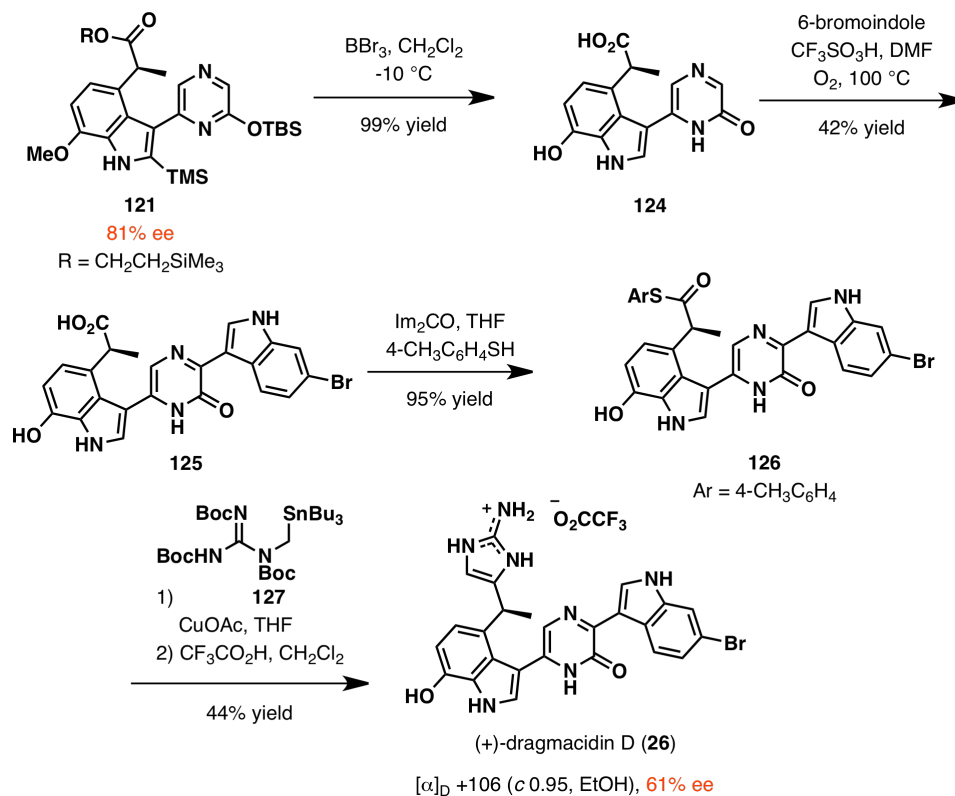
Scheme 50. Larock Indole Synthesis



The indole synthesis was followed by simultaneous cleavage of the 2-(trimethylsilyl)ethyl ester, indole C2 trimethylsilane, phenolic methyl ether, and pyrazine silyl ether upon exposure to BBr_3 in dichloromethane at $-10\text{ }^\circ\text{C}$ for 1 h (Scheme 51). The

resulting carboxylic acid **124** was isolated by reverse-phase column chromatography in a nearly quantitative yield. Since we could not identify a procedure to determine its enantiomeric excess, the material was advanced further. Friedel–Crafts-type arylation with 6-bromoindole was achieved in the presence of $\text{CF}_3\text{SO}_3\text{H}$ in DMF at 100 °C under an atmosphere of oxygen to deliver bis(indole) carboxylic acid **125** in 42% yield. Thioester **126** was produced in high yield with carbonyldiimidazole and 4-methylphenylthiol in tetrahydrofuran (THF). Again, we were unable to determine conditions to measure the ee of this compound. Therefore, the total synthesis was completed with two additional steps: 1) CuOAc-mediated acyl cross-coupling of thioester **126** with stannane **127**, which bears a guanidinyll substituent, and 2) cyclocondensation of the resulting guanidinyllmethyl ketone under acidic conditions with $\text{CF}_3\text{CO}_2\text{H}$ in CH_2Cl_2 at 23 °C for 3 h. After purification by reverse-phase preparative HPLC, 15 mg of the trifluoroacetic acid (TFA) salt of synthetic drarmacidin D was isolated as a brownish-red foam (44% overall yield from thioester **126**).

Scheme 51. Completion of the Total Synthesis of (+)-Dragmacidin D



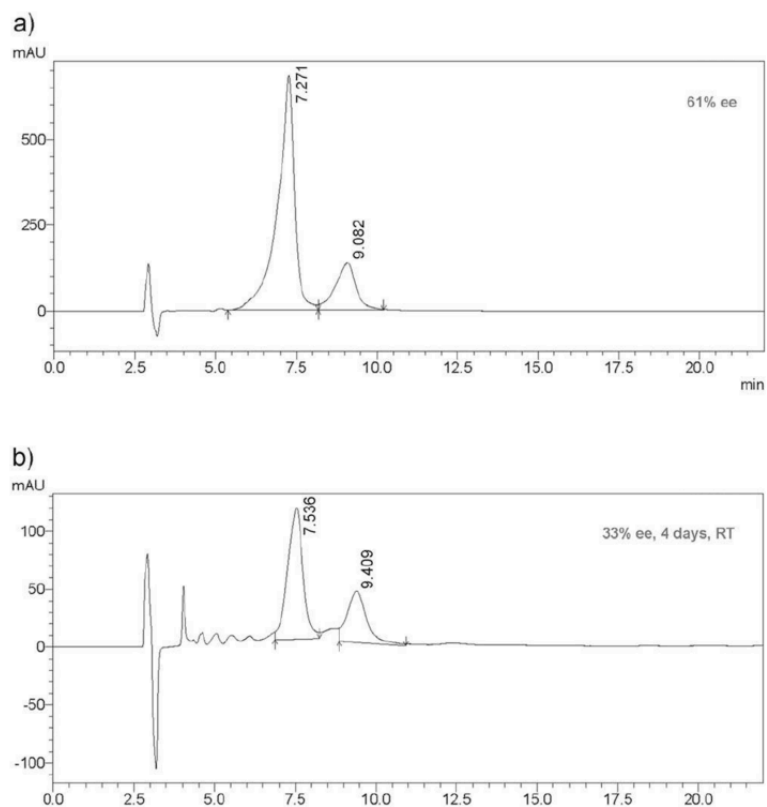
2.3.4 Stereochemistry of (+)-Dragmacidin D

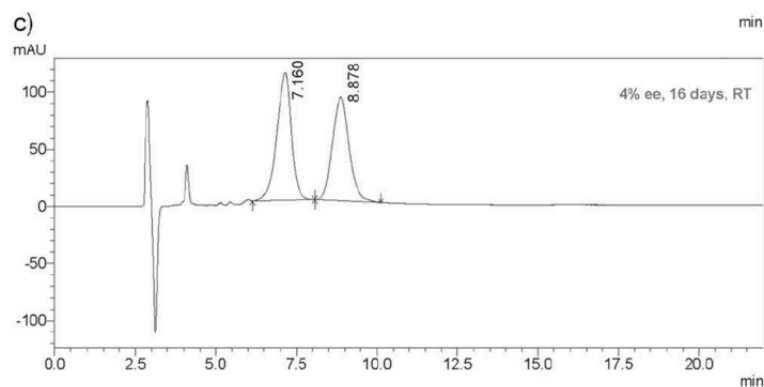
With **26** now available in sufficient supply (as well as the racemic sample prepared analogously), we were able to identify an effective chiral-phase HPLC method to measure its enantiomeric excess, which turned out to be 61% (Figure 7). Clearly there had been some erosion of ee between pyrazine-indole intermediate **121** and **26**. The most likely origins of the erosion in our assessment are either the multiple-group cleavage reaction with BBr₃, the Friedel–Crafts indolization, or, less likely, the final aminoimidazole formation with CF₃CO₂H. The potential instability of (+)-**26** to racemization could also be an issue (see below).

In light of uncertainties regarding the stereochemistry of **26**, as discussed in the literature, we measured the rate of racemization of a solution of (+)-dragmacidin D in water (Fisher Scientific W5-4, HPLC grade, pH 6.8, 1 mg mL⁻¹). The results reveal that **26** (61%

ee) undergoes slow but steady epimerization, reaching 33% ee after 4 days and 4% ee in approximately 16 days (Figure 7). Notably, the (+)-dragmacidin D TFA salt is configurationally stable upon storage at -20 °C as a mixture with benzene for at least 40 days with no change in enantiomeric excess. When aqueous **26** was exposed to light at 23 °C, rapid decomposition occurred.

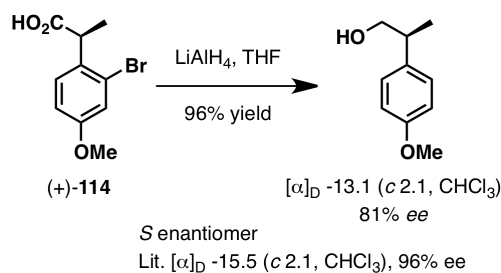
Figure 7. Enantiomeric excess of (+)-dragmacidin D trifluoroacetate solution in water at pH 6.8, as measured by chiral-phase HPLC. a) freshly prepared synthetic (+)-**26**, 61% ee. b) after 4 days at 23 °C, 33% ee. c) after 16 days, 4% ee.





Perhaps more intriguingly, our work provides evidence for the absolute configuration of (+)-dragmacidin D that appears to contradict the recent results of Jia, Capon, and co-workers.[8] First, the specific rotation of our sample at 61% ee ($[\alpha]_D +106$ (c 0.95, EtOH); $[\alpha]_D +95$ (c 0.10, EtOH) is notably higher at both concentrations than reported previously ($[\alpha]_D +12$ (c 0.95, EtOH) at 39% ee; ($[\alpha]_D +18$ (c 0.10, EtOH), ee not reported). Importantly, the precision of our enantiomeric excess measurement is supported by clear baseline separation in the HPLC traces (Figure 7). Second, the absolute configuration of (+)-**26** has been recently reassigned based on total synthesis to 6'''*R*, in contrast to the biosynthetic prediction by Stoltz and co-workers. The present work, however, clearly supports the 6'''*S* configuration, which is consistent with the known configuration of natural dragmacidin F. The evidence comes from correlation of the reduction product of carboxylic acid (+)-**114**, which was used as an intermediate in the total synthesis of (+)-**26** reported herein, to the well-characterized alcohol (-)-**128** (Scheme 52).⁶⁶

Scheme 52. Confirmation of the Absolute Stereochemistry of (+)-**114**



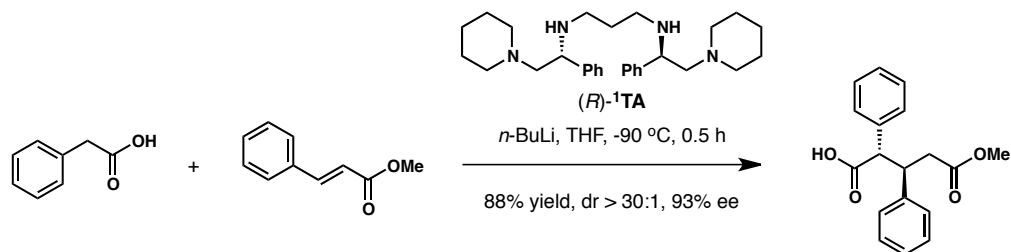
2.4 Conclusions

In summary, we have completed a 10-step asymmetric total synthesis of the marine alkaloid dragmacidin D (**26**). Key transformations include: 1) a direct asymmetric methylation of carboxylic acid **113** with CH₃I mediated by the reagent (*R*)-¹TA; 2) a Larock indole assembly at the convergence point of the total synthesis; and 3) a concise conversion of a thioester into an aminoimidazole at the concluding stage of the synthesis. As a result, 15 mg of (+)-dragmacidin D were produced in 61% ee, thus supporting the assignment of its sole stereogenic center at carbon 6''' as *S*. This result is in line with the original prediction by Stoltz and consistent with the absolute stereochemistry of dragmacidin F but contrasts with recent results by Jia, Capon, and co-workers. Additional studies revealed that dragmacidin D in solution in water at room temperature undergoes racemization within about 16 days and decomposes rapidly when exposed to light at room temperature. However, (+)-**26** is chemically and configurationally stable at -20 °C in the dark. Collectively, these observations provide an interesting context for the existence of this natural product in oceanic environments at high depth.

Experimental Procedures

General Information. All reactions were carried out under an inert atmosphere of dry argon in oven or flame-dried glassware, unless the reaction procedure states otherwise. Tetrahydrofuran (THF) and diethyl ether (Et₂O) were distilled from sodium-benzophenone in a continuous still under an atmosphere of argon. Dichloromethane, di-*iso*-propylamine, triethylamine, and acetonitrile were distilled from calcium hydride in a continuous still under an atmosphere of argon. Chlorotrimethylsilane was distilled from calcium hydride and stored over calcium hydride. Reaction temperature was controlled by IKA ETS-D4 fuzzy thermo couples. Room temperature reactions were carried out between 22-24 °C. Analytical

normal-phase thin-layer chromatography (TLC) was performed using pre-coated TLC plates with Silica Gel 60 F₂₅₄ (EMD no. 5715-7) and visualized using combinations of UV, anisaldehyde, ceric ammonium molybdate (CAM), potassium permanganate, and iodine staining. Normal-phase flash column chromatography was performed using 40-63 mm silica gel (EMD, Geduran, no. 1.11567.9026) as the stationary phase. Analytical reverse-phase thin-layer chromatography was performed using pre-coated TLC plates with Silica gel 60 RP-18 F_{254S} (Merck, no. 1.15685.0001). Reverse-phase flash column chromatography was performed using C₁₈-Reversed phase silica gel, fully end-capped (Fluka, no. 60756). Proton nuclear magnetic resonance spectra were recorded at 400, 500, and 600 MHz on Varian Unity Inova. Carbon nuclear magnetic resonance spectra were recorded at 101 MHz, 126 MHz, and 151 MHz on Varian Unity Inova, and Varian Unity Inova spectrometers. All chemical shifts were reported in δ units relative to tetramethylsilane. Optical rotations were measured on a Rudolph Autopol III polarimeter. High-resolution mass spectral data were obtained by the Mass Spectrometry laboratory at the University of California, Santa Barbara.

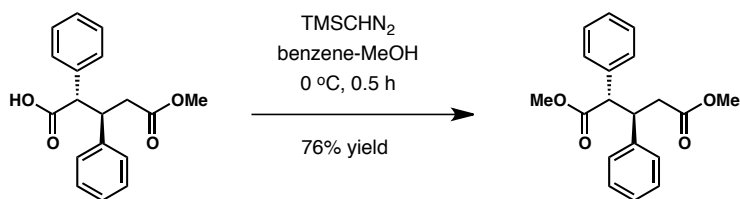


General Procedure I:

(2S,3R)-5-Methoxy-5-oxo-2,3-diphenylpentanoic acid. A solution of *n*-BuLi (0.81 mL, 2.46 M in hexanes, 1.99 mmol, 4.0 equiv) was added dropwise to a solution of phenylacetic acid (68.1 mg, 0.500 mmol) and (*R*)-¹TA (0.231 g, 0.515 mmol, 1.03 equiv) in THF (5.0 mL) at 0 °C and the reaction mixture was stirred at this temperature for 30 min.

The reaction mixture was then cooled to -90 °C and stirred for an additional 5 min. A solution of (*E*)-methyl cinnamate (81.1 mg, 0.500 mmol, 1.0 equiv) in THF (0.30 mL + 2 × 0.10 mL rinses) was added to the reaction mixture dropwise over 10 min. The resultant mixture was stirred for additional 20 min before a quench with a mixture of THF-MeOH (3:1, 0.64 mL) at -90 °C. After 5 min, the reaction mixture was acidified with 1 M aqueous solution of HCl and extracted with ethyl acetate. The combined organic phase was sequentially washed with 1 M aqueous solution of HCl and brine, dried over Na₂SO₄, concentrated, and the residue was purified by column chromatography on silica gel (2-4% methanol in dichloromethane) to afford the pure product (0.132 g, 0.442 mmol, 88% yield). $[\alpha]_D^{23} +25.8^\circ$ (*c* 1.2, CHCl₃). ¹H NMR (500 MHz, CDCl₃) δ (ppm): 7.43-7.39 (m, 2H), 7.37-7.29 (m, 3H), 7.27-7.21 (m, 4H), 7.20-7.16 (m, 1H), 3.87-3.78 (m, 2H), 3.37 (s, 3H), 2.42 - 2.33 (m, 2H). ¹³C NMR (125 MHz, CDCl₃) δ (ppm): 177.1, 171.9, 140.8, 135.9, 128.9, 128.7, 128.4, 128.2, 127.9, 127.2, 57.4, 51.4, 44.7, 38.5. HRMS-ESI (*m/z*): [M+Na]⁺ calcd for C₁₈H₁₈O₄Na, 321.1103; found, 321.1091.

Note: In most cases, ee values for the product were measured using the corresponding methyl ester due to low solubility of the free carboxylic acid in the HPLC eluent system (e.g. 1% *i*-PrOH in hexanes, 0.1% TFA).



(2*S*,3*R*)-Dimethyl 2,3-diphenylpentanedioate. A solution of TMSCHN₂ in hexane (0.10 mL, 1.76 M, 0.176 mmol) was added dropwise to a solution of carboxylic acid (9.3 mg, 31.2 μmol) in a mixture of benzene-MeOH (4:1, 1.0 mL) at 0 °C. The resultant mixture was stirred at the same temperature for 0.5 h. The solvent was removed on a rotary

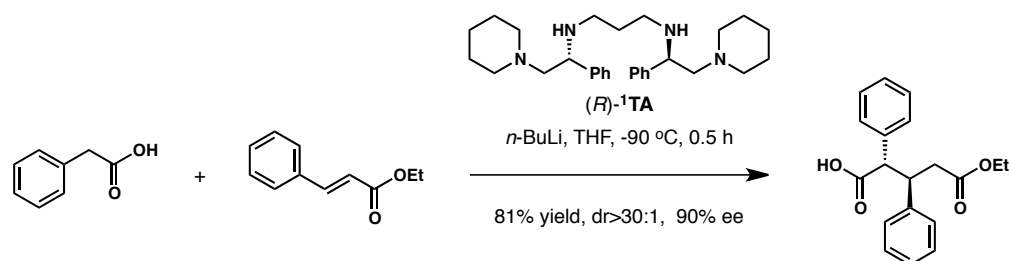
evaporator and the residue was purified by column chromatography on silica gel (8% ethyl acetate in hexanes) to afford the product (7.4 mg, 23.7 μ mol, 76% yield). Ee: 93% (Chiralcel® OD-H; 1% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 215 nm; $t_1=15.0$ min; $t_2=18.5$ min). $[\alpha]_D^{23} +15.9^\circ$ (c 0.57, CHCl_3). ^1H NMR (600 MHz, CDCl_3) δ (ppm): 7.47 (d, $J=7.4$ Hz, 2H), 7.37 (t, $J=7.4$ Hz, 2H), 7.34-7.27 (m, 5H), 7.25-7.19 (m, 1H), 3.91-3.83 (m, 2H), 3.39 (s, 3 H), 3.37 (s, 3 H), 2.47-2.35 (m, 2H). ^{13}C NMR (125 MHz, CDCl_3) δ (ppm): 172.6, 172.0, 141.2, 136.5, 128.9, 128.7, 128.4, 128.0, 127.9, 127.1, 57.7, 51.8, 51.4, 45.2, 38.6. LRMS-ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{19}\text{H}_{20}\text{O}_4\text{Na}$, 335; found 335.

Practical preparation at gram scale with recovery of the tetramine (*R*)- ^1TA .

To a 3-neck round-bottom flask was attached a gas-inlet adapter, glass-stopper, and thermometer adapter fitted with a low-temperature thermometer. After flame drying under vacuum and back filling with argon, the flask was charged with phenylacetic acid (3.50 g, 25.7 mmol), (*R*)- ^1TA (11.8 g, 26.4 mmol, 1.03 equiv), and THF (220 mL) under a positive pressure of argon gas. The reaction mixture was cooled in an ice-water bath to 0 $^\circ\text{C}$ and a solution of *n*-BuLi (39.0 mL, 2.65 M in hexanes, 103 mmol, 4.0 equiv) was added dropwise, keeping the internal reaction temperature below 15 $^\circ\text{C}$. The mixture was stirred at 0 $^\circ\text{C}$ for additional 15 min. The reaction mixture was then cooled to -78 $^\circ\text{C}$ and stirred for an additional 10 min. A solution of (*E*)-methyl cinnamate (4.59 g, 28.3 mmol, 1.1 equiv) in THF (50 mL + 15 mL rinse) was added to the reaction mixture dropwise over 30 min, maintaining the internal reaction temperature below -70 $^\circ\text{C}$. The resultant mixture was stirred for additional 30 min before a quench with a mixture of THF-MeOH (3:1, 32 mL) at -78 $^\circ\text{C}$. After 5 min, the reaction mixture was acidified to pH = 1 with a 1 M aqueous solution of HCl and extracted with ethyl acetate (400 mL X 3). The combined organic phase was sequentially washed with 1 M aqueous solution of HCl (300 mL) and brine, dried over

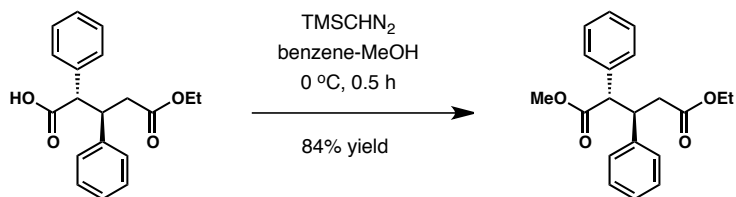
Na₂SO₄, concentrated. The crude product was obtained as a light yellow solid (8.09 g, 89% ee). The crude product was dissolved in a minimal amount of EtOAc (~30 mL) using heat and sonication to aid dissolution. The solution was cooled to room temperature and then to 0 °C in an ice-water bath. The formed precipitate was filtered through a medium-porosity sintered glass funnel and washed with ice-cold EtOAc to yield the pure product as a white solid (4.02 g, 13.5 mmol, 52% yield, 95% ee). A second recrystallization of the material recovered from the mother liquor of the first crystallization provided a second batch of pure product (1.95 g, 6.54 mmol, 25% yield, 80% ee). The two batches provided a total of 5.97 g (20.0 mmol, 78% yield, 90% ee).

Recovery of (*R*)-¹TA: The combined acidic aqueous layers were washed with diethyl ether then basified with sodium hydroxide to pH >12 at room temperature, and extracted with diethyl ether (400 mL X 3). The combined organic layers were washed with brine, dried over MgSO₄, filtered, and concentrated to recover pure (¹H NMR analysis) (*R*)-¹TA (11.8 g, 26.3 mmol, 99%).

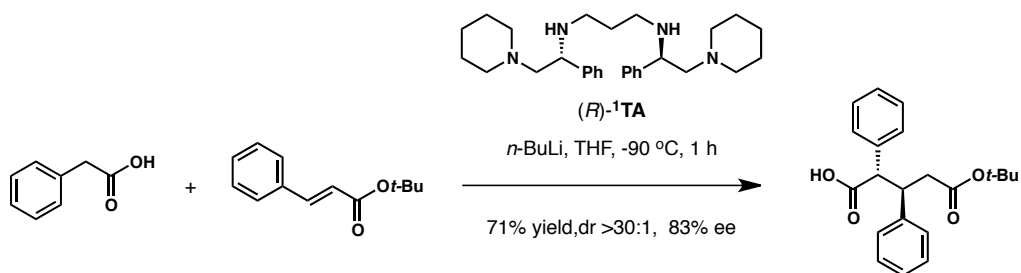


(2*S*,3*R*)-5-Ethoxy-5-oxo-2,3-diphenylpentanoic acid. The title compound was prepared according to general procedure I using phenylacetic acid (68.1 mg, 0.500 mmol), (*R*)-¹TA (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.81 mL, 2.46 M in hexanes, 1.99 mmol, 4.0 equiv) in THF (5.0 mL) followed by addition of a solution of (*E*)-ethyl cinnamate (85 μL, 89.2 mg, 0.506 mmol, 1.0 equiv) in THF (0.50 mL) at -90 °C. The reaction was quenched after 0.5 h and the product (0.126 g, 0.403 mmol, 81%) was obtained after

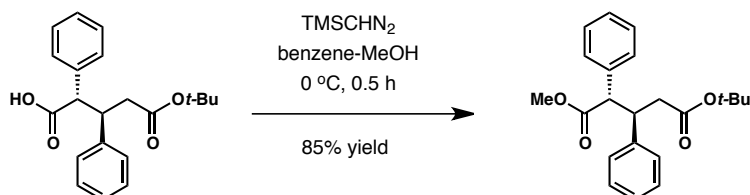
purification by column chromatography on silica gel (4% methanol in dichloromethane). $[\alpha]_D^{23} +28.2^\circ$ (*c* 0.54, CHCl₃). ¹H NMR (500 MHz, CDCl₃) δ (ppm): 7.45-7.39 (m, 2H), 7.39-7.28 (m, 3H), 7.28-7.20 (m, 4H), 7.20-7.15 (m, 1H), 3.86-3.76 (m, 4H), 2.42-2.31 (m, 2H), 0.97 (t, *J*=7.2 Hz, 3H). ¹³C NMR (125 MHz, CDCl₃) δ (ppm): 177.0, 171.5, 140.8, 136.0, 128.9, 128.7, 128.6, 128.4, 128.1, 128.0, 127.1, 60.2, 57.5, 44.7, 38.7, 13.9. HRMS-ESI (*m/z*): [M+Na]⁺ calcd for C₁₉H₂₀O₄Na, 335.1259; found, 335.1248.



(2S,3R)-5-Ethyl-1-methyl 2,3-diphenylpentanedioate. The title compound was prepared using carboxylic acid (14.2 mg, 45.5 μ mol), TMSCHN₂ in hexane (0.12 mL, 1.76 M, 0.211 mmol) in a mixture of benzene-MeOH (4:1, 1.0 mL) at 0 °C for 0.5 h. The solvent was removed and the residue was purified by column chromatography on silica gel (9% ethyl acetate in hexanes) to afford the product (12.4 mg, 38.0 μ mol, 84% yield). Ee: 90% (Chiralcel® OD-H; 1% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 215 nm; *t*₁=13.3 min; *t*₂=16.6 min). $[\alpha]_D^{23} +22.6^\circ$ (*c* 0.62, CHCl₃). ¹H NMR (500 MHz, CDCl₃) δ (ppm): 7.50-7.45 (m, 2H), 7.39-7.34 (m, 2H), 7.34-7.27 (m, 5H), 7.24-7.19 (m, 1H), 3.93-3.78 (m, 4H), 3.37 (s, 3H), 2.46-2.33 (m, 2H), 0.99 (t, *J*=7.1 Hz, 3H). ¹³C NMR (125 MHz, CDCl₃) δ (ppm): 172.6, 171.5, 141.2, 136.5, 128.9, 128.7, 128.4, 128.01, 127.95, 127.0, 60.2, 57.9, 51.8, 45.2, 38.8, 13.9. LRMS-ESI (*m/z*): [M+Na]⁺ calcd for C₂₀H₂₂O₄Na, 349; found 349.

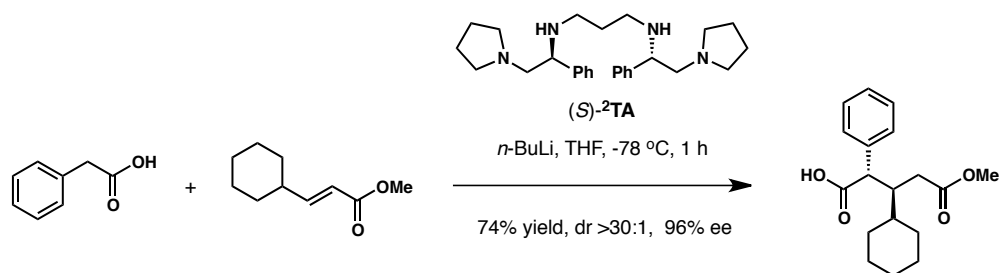


(2*S*,3*R*)-5-*tert*-Butoxy-5-oxo-2,3-diphenylpentanoic acid. The title compound was prepared according to general procedure I using phenylacetic acid (68.1 mg, 0.500 mmol), (*R*)-**1TA** (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.81 mL, 2.46 M in hexanes, 1.99 mmol, 4.0 equiv) in THF (5.0 mL) followed by addition of a solution of (*E*)-*tert*-butyl cinnamate (102 mg, 0.500 mmol, 1.0 equiv) in THF (0.50 mL) at -90 °C. The reaction was quenched after 1 h and the product (0.121 g, 0.355 mmol, 71%) was obtained after purification by column chromatography on silica gel (4% methanol in dichloromethane). $[\alpha]_D^{23} +24.6^\circ$ (*c* 0.50, MeOH). $^1\text{H NMR}$ (500 MHz, CDCl_3) δ (ppm): 7.42 (d, $J=6.7$ Hz, 2H), 7.35 (t, $J=7.2$ Hz, 2H), 7.34-7.27 (m, 1H), 7.27 (d, $J=7.2$ Hz, 2H), 7.22 (d, $J=7.9$ Hz, 2H), 7.18 (t, $J=6.8$ Hz, 1H), 3.81-3.70 (m, 2H), 2.27 (d, $J=6.8$ Hz, 2H), 1.12 (s, 9H). $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ (ppm): 177.2, 170.8, 140.7, 136.1, 128.9, 128.7, 128.22, 128.18, 128.0, 127.0, 80.3, 57.8, 45.0, 39.8, 27.7. HRMS-ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{21}\text{H}_{24}\text{O}_4\text{Na}$, 363.1572; found, 363.1562.



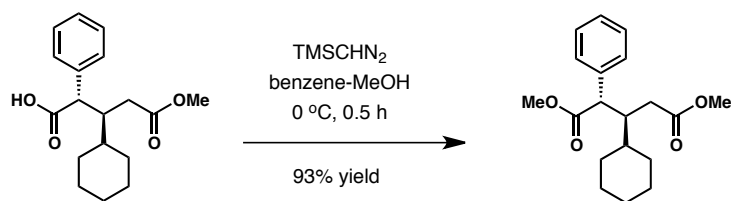
(2*S*,3*R*)-5-*tert*-Butyl-1-methyl 2,3-diphenylpentanedioate. The title compound was prepared using carboxylic acid (10.3 mg, 30.3 μmol), TMSCHN₂ in hexane (0.10 mL, 1.76 M, 0.176 mmol) in a mixture of benzene-MeOH (4:1, 1.0 mL) at 0 °C for 0.5 h. The solvent

was removed and the residue was purified by column chromatography on silica gel (6% ethyl acetate in hexanes) to afford the product (9.1 mg, 25.7 μmol , 85% yield). Ee: 83% (Chiralcel® OD-H; 1% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 215 nm; $t_1=6.0$ min; $t_2=7.2$ min). $[\alpha]_D^{23} +17.1^\circ$ (c 0.48, CHCl_3). ^1H NMR (500 MHz, CDCl_3) δ (ppm): 7.50-7.44 (m, 2H), 7.40-7.33 (m, 2H), 7.35-7.24 (m, 5H), 7.24-7.17 (m, 1H), 3.84-3.76 (m, 2H), 3.37 (s, 3H), 2.36-2.23 (m, 2H), 1.13 (s, 9H). ^{13}C NMR (125 MHz, CDCl_3) δ (ppm): 172.7, 170.8, 141.1, 136.6, 128.9, 128.6, 128.2, 127.9, 126.9, 80.3, 58.2, 51.7, 45.6, 39.9, 27.7. LRMS-ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{22}\text{H}_{26}\text{O}_4\text{Na}$, 377; found 377.

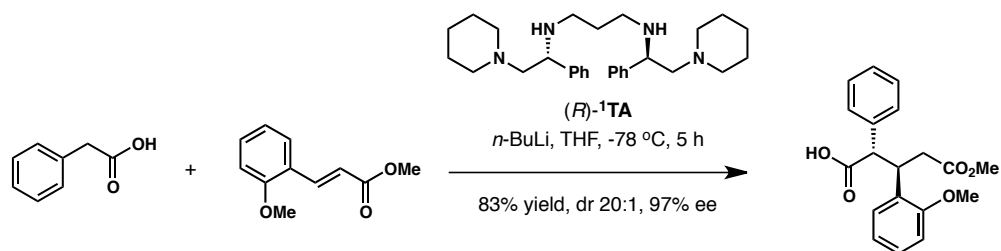


(2R,3R)-3-Cyclohexyl-5-methoxy-5-oxo-2-phenylpentanoic acid. The title compound was prepared according to general procedure I using phenylacetic acid (68.1 mg, 0.500 mmol), (*S*)- ^2TA (0.217 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.82 mL, 2.44 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (5.0 mL) followed by addition of a solution of (*E*)-methyl 3-cyclohexylacrylate (84.1 mg, 0.500 mmol, 1.0 equiv) in THF (0.50 mL) at -78 $^\circ\text{C}$. The reaction was quenched after 1 h and the product (0.113 g, 0.370 mmol, 74%) was obtained after purification by column chromatography on silica gel (4% methanol in dichloromethane). $[\alpha]_D^{23} +5.6^\circ$ (c 1.4, CHCl_3). ^1H NMR (500 MHz, CDCl_3) δ (ppm): 7.37 (d, $J=6.7$ Hz, 2H), 7.33-7.21 (m, 3H), 3.60 (d, $J=11.7$ Hz, 1H), 3.38 (s, 3H), 2.81 (*virt. dtd*, $J=11.7, 6.0, 2.9$ Hz, 1H), 2.16 (dd, $J=16.0, 6.2$ Hz, 1H), 1.92 (dd, $J=16.0, 5.7$ Hz, 1H), 1.80-1.71 (m, 3H), 1.70-1.62 (m, 2H), 1.58-1.48 (m, 1H), 1.32-1.05 (m, 4H), 1.02-0.92 (m, 1H). ^{13}C NMR (126 MHz, CDCl_3) δ (ppm): 179.1, 173.6, 136.4, 129.3, 128.6, 127.9, 54.7, 51.4,

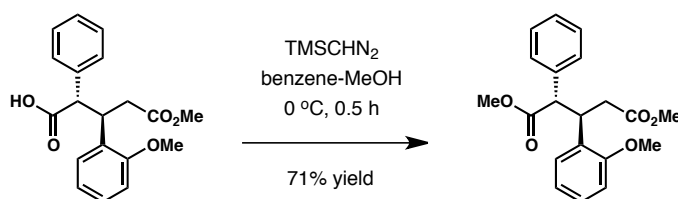
42.8, 40.8, 33.0, 31.6, 27.1, 26.8, 26.6, 26.5. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{18}H_{24}O_4Na$, 327.1572; found, 327.1556.



(2*R*,3*R*)-Dimethyl 3-cyclohexyl-2,3-diphenylpentanedioate. The title compound was prepared using carboxylic acid (28.7 mg, 94.3 μ mol), TMSCHN₂ in hexane (0.20 mL, 1.76 M, 0.352 mmol) in a mixture of benzene-MeOH (4:1, 2.0 mL) at 0 °C for 0.5 h. The solvent was removed and the residue was purified by column chromatography on silica gel (9% ethyl acetate in hexanes) to afford the product (27.9 mg, 87.6 μ mol, 93% yield). Ee: 96% (Chiralcel® OD-H; 1% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 215 nm; $t_1=6.7$ min; $t_2=7.5$ min). $[\alpha]_D^{23} +9.9^\circ$ (c 1.3, CHCl₃). ¹H NMR (500 MHz, CDCl₃) δ (ppm): 7.39-7.33 (m, 2H), 7.31-7.27 (m, 2H), 7.6-7.20 (m, 1H), 3.65 (s, 3H), 3.60 (d, $J=11.6$ Hz, 1H), 3.38 (s, 3H), 2.82 (*virt.* dtd, $J=11.6, 6.0, 3.0$ Hz, 1H), 2.15 (dd, $J=16.0, 6.4$ Hz, 1H), 1.93 (dd, $J=16.0, 5.7$ Hz, 1H), 1.81-1.71 (m, 3H), 1.70-1.63 (m, 2H), 1.44 (*virt.* td, $J=12.0, 3.0$ Hz, 1H), 1.32-1.04 (m, 4H), 1.01-0.91 (m, 1H). ¹³C NMR (126 MHz, CDCl₃) δ (ppm): 174.0, 173.6, 137.0, 129.2, 128.5, 127.6, 54.7, 51.9, 51.3, 43.1, 40.9, 33.1, 31.5, 27.2, 26.8, 26.7, 26.5. LRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{19}H_{26}O_4Na$, 341; found 341.

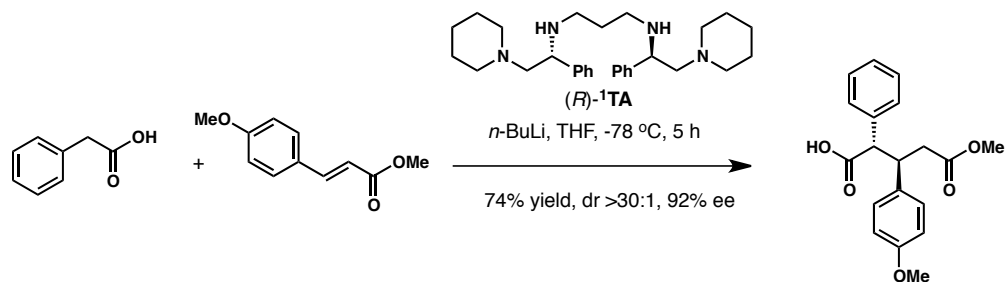


(2*S*,3*R*)-5-Methoxy-3-(2-methoxyphenyl)-5-oxo-2-phenylpentanoic acid. The title compound was prepared according to general procedure I using phenylacetic acid (68.1 mg, 0.500 mmol), (*R*)-¹TA (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.82 mL, 2.44 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (5.0 mL) followed by addition of a solution of methyl (*E*)-methyl-3-(2-methoxyphenyl)acrylate (101 mg, 0.525 mmol, 1.05 equiv) in THF (0.50 mL) at -78 °C. The reaction was quenched after 5 h and the product (0.136 g, 0.413 mmol, 83%) was obtained after purification by column chromatography on silica gel (25% ethyl acetate in hexanes then 4% methanol in dichloromethane). $[\alpha]_D^{23} +34.5^\circ$ (*c* 1.0, CHCl₃). ¹H NMR (500 MHz, CDCl₃) δ (ppm): 7.43-7.37 (m, 2H), 7.36-7.26 (m, 3H), 7.16 (d, *J*=7.4 Hz, 2H), 6.81 (d, *J*=7.4 Hz, 2H), 4.21 (d, *J*=11.2 Hz, 1H), 4.01 (ddd, *J*=11.2, 9.5, 4.6 Hz, 1H), 3.80 (s, 3H), 3.36 (s, 3H), 2.59 (dd, *J*=15.6, 9.5 Hz, 1H), 2.36 (dd, *J*=15.5, 4.6 Hz, 1H). ¹³C NMR (126 MHz, CDCl₃) δ (ppm): 178.2, 172.5, 157.4, 136.4, 130.2, 128.9, 128.6, 128.3, 128.2, 127.8, 120.4, 111.0, 55.3, 54.6, 51.2, 41.3, 36.1. HRMS-ESI (*m/z*): [M+Na]⁺ calcd for C₁₉H₂₀O₅Na, 351.1208; found, 351.1196.

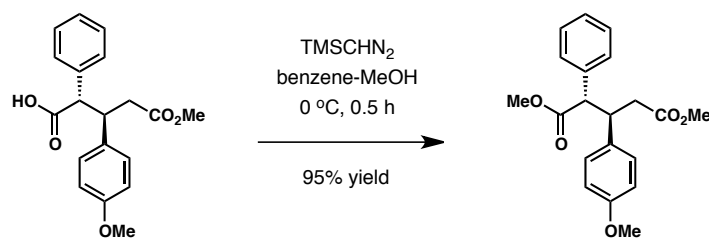


(2*R*,3*R*)-Dimethyl 3-(2-methoxyphenyl)-2-phenylpentanedioate. The title compound was prepared using carboxylic acid (16.4 mg, 49.9 μ mol), TMSCHN₂ in hexane (0.10 mL, 1.76 M, 0.176 mmol) in a mixture of benzene-MeOH (4:1, 1.0 mL) at 0 °C for 0.5 h. The solvent was removed and the residue was purified by column chromatography on silica gel (9% ethyl acetate in hexanes) to afford the product (12.1 mg, 35.3 μ mol, 71% yield). Ee: 97% (Chiralcel® OD-H; 1% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 215 nm; *t*₁=12.3 min; *t*₂=30.9 min). $[\alpha]_D^{23} +32.2^\circ$ (*c* 0.61, CHCl₃). ¹H NMR (500 MHz, CDCl₃) δ

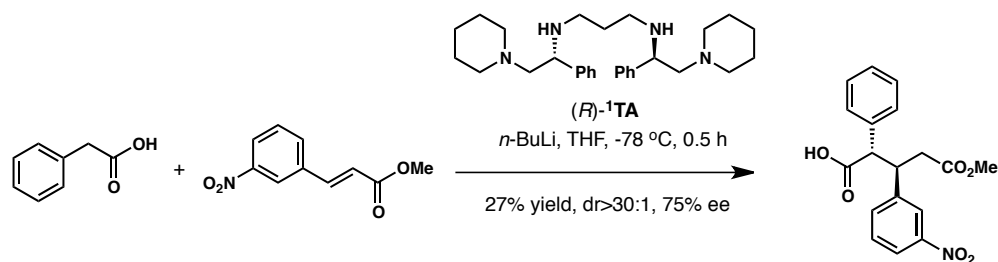
(ppm): 7.49-7.44 (m, 2H), 7.39-7.33 (m, 2H), 7.31-7.27 (m, 1H), 7.23 (dd, $J=7.9, 1.7$ Hz, 1H), 7.22-7.17 (m, 1H), 6.91-6.84 (m, 2H), 4.29 (d, $J=11.4$ Hz, 1H), 4.10-4.01 (m, 1H), 3.89 (s, 3H), 3.37 (s, 3H), 3.37 (s, 3H), 2.64 (dd, $J=15.5, 9.5$ Hz, 1H), 2.37 (dd, $J=15.5, 4.6$ Hz, 1H). ^{13}C NMR (126 MHz, CDCl_3) δ (ppm): 178.2, 172.5, 157.4, 136.4, 128.9, 128.7, 128.2, 127.8, 120.4, 111.0, 55.3, 54.6, 51.2, 36.1. LRMS-ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{20}\text{H}_{22}\text{O}_5\text{Na}$, 365; found, 365.



(2S,3R)-5-Methoxy-3-(4-methoxyphenyl)-5-oxo-2-phenylpentanoic acid. The title compound was prepared according to general procedure I using phenylacetic acid (68.1 mg, 0.500 mmol), (*R*)- ^1TA (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.82 mL, 2.44 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (5.0 mL) followed by addition of a solution of methyl (*E*)-methyl 3-(4-methoxyphenyl)acrylate (101 mg, 0.525 mmol, 1.05 equiv) in THF (0.50 mL) at -78 °C. The reaction was quenched after 5 h and the product (0.121 g, 0.369 mmol, 74%) was obtained after purification by column chromatography on silica gel (25% ethyl acetate in hexanes then 4% methanol in dichloromethane). $[\alpha]_{\text{D}}^{23} +24.4^\circ$ (c 0.30, CHCl_3). ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ (ppm): 7.47 (d, $J=7.3$ Hz, 2H), 7.39 (t, $J=7.3$ Hz, 2H), 7.31 (t, $J=7.3$ Hz, 1H), 7.28 (d, $J=8.5$ Hz, 2H), 6.85 (d, $J=8.5$ Hz, 2H), 3.89 (d, $J=11.7$ Hz, 1H), 3.73 (s, 3H), 3.59 (*virt. td*, $J=11.3, 4.0$ Hz, 1H), 3.30 (s, 3H), 2.41 (dd, $J=15.5, 10.9$ Hz, 1H), 2.13 (dd, $J=15.5, 4.0$ Hz, 1H). ^{13}C NMR (126 MHz, $\text{DMSO}-d_6$) δ (ppm): 173.2, 171.6, 157.9, 137.6, 133.8, 129.2, 128.7, 128.4, 127.6, 113.4, 56.7, 54.9, 51.1, 44.2, 38.4. HRMS-ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{19}\text{H}_{20}\text{O}_5\text{Na}$, 351.1208; found, 351.1198.

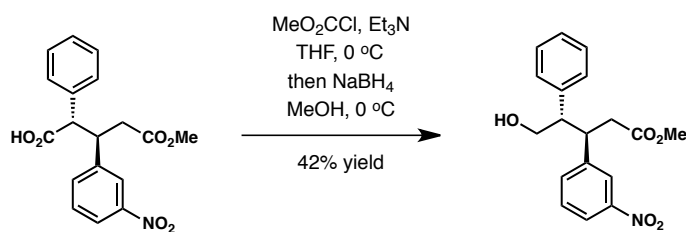


(2*R*,3*R*)-Dimethyl 3-(4-methoxyphenyl)-2-phenylpentanedioate. The title compound was prepared using carboxylic acid (7.2 mg, 21.9 μmol), TMSCHN₂ in hexane (0.10 mL, 1.76 M, 0.176 mmol) in a mixture of benzene-MeOH (4:1, 1.0 mL) at 0 °C for 0.5 h. The solvent was removed and the residue was purified by column chromatography on silica gel (9% ethyl acetate in hexanes) to afford the product (7.1 mg, 20.7 μmol , 95% yield). Ee: 97% (Chiralcel® AD-H; 1% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 215 nm; $t_1=59.8$ min; $t_2=74.5$ min). $[\alpha]_D^{23} +27.2^\circ$ (c 0.34, CHCl₃). ¹H NMR (500 MHz, CDCl₃) δ (ppm): 7.49-7.44 (m, 2H), 7.39-7.34 (m, 2H), 7.33-7.28 (m, 0H), 7.23 (d, $J=8.7$ Hz, 2H), 6.84 (d, $J=8.7$ Hz, 2H), 3.89-3.78 (m, 2H), 3.79 (s, 3H), 3.40 (s, 3H), 3.39 (s, 3H), 2.43-2.31 (m, 2H). ¹³C NMR (126 MHz, CDCl₃) δ (ppm): 172.7, 172.1, 158.5, 136.6, 133.1, 128.9, 128.9, 128.7, 127.9, 113.8, 58.0, 55.1, 51.8, 51.4, 44.4, 38.8. LRMS-ESI (m/z): [M+Na]⁺ calcd for C₂₀H₂₂O₅Na, 365; found, 365.



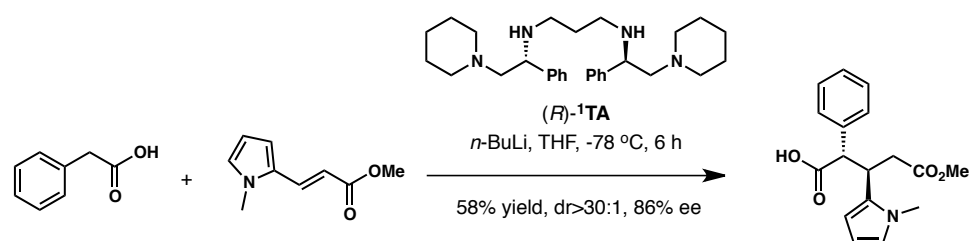
(2*S*,3*R*)-5-Methoxy-3-(3-nitrophenyl)-5-oxo-2-phenylpentanoic acid. The title compound was prepared according to general procedure I using phenylacetic acid (68.1 mg, 0.500 mmol), (*R*)-¹TA (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.51 M in hexanes, 2.01 mmol, 4.0 equiv) in THF (5.0 mL) followed by addition of a solution of

methyl (*E*)-methyl 3-(3-nitrophenyl)acrylate (0.114 g, 0.552 mmol, 1.1 equiv) in THF (0.50 mL) at -78 °C. The reaction was quenched after 0.5 h and product (46.1 mg, 0.114 mmol, 27%) was obtained after purification by column chromatography on silica gel (35% diethyl ether in hexanes with 0.5% AcOH). $[\alpha]_D^{23} +35.0^\circ$ (c 0.60, CHCl₃). ¹H NMR (400 MHz, CDCl₃) δ (ppm): 8.16 (t, $J=1.8$ Hz, 1H), 8.08-8.05 (m, 1H), 7.65-7.62 (m, 1H), 7.42-7.33 (m, 6H), 3.93 (dt, $J=11.8, 7.2$ Hz, 1H), 3.85 (d, $J=11.8$ Hz, 1H), 3.41 (s, 3H), 2.42 (d, $J=7.2$ Hz, 2H). ¹³C NMR (151 MHz, CDCl₃) δ (ppm): 176.4, 171.6, 148.5, 143.6, 135.5, 135.0, 129.6, 129.4, 128.8, 128.7, 123.0, 122.6, 57.2, 51.9, 44.5, 38.3. HRMS-ESI (m/z): $[M+Na]^+$ calcd for C₁₈H₁₇NO₆Na, 366.0954; found, 366.0941.



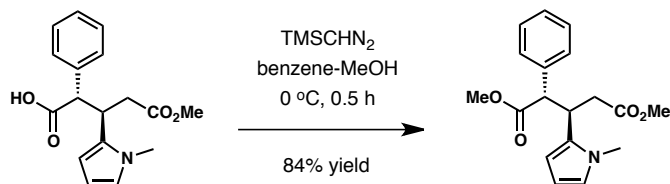
(3*R*, 4*S*)-Methyl 5-hydroxy-3-(3-nitrophenyl)-4-phenylpentanoate. Methyl chloroformate (9 μ L, 0.114 mol, 1.4 equiv) was added dropwise to a solution of carboxylic acid (28.0 mg, 0.0816 mmol) in THF (0.82 mL) and Et₃N (34 μ L, 0.244 mmol, 3.0 equiv) at 0 °C. The resultant mixture was stirred at the same temperature for 0.5 h. NaBH₄ (15.0 mg, 0.408 mmol, 5.0 equiv) was added to the crude reaction followed by MeOH (1.0 mL) at 0 °C. The reaction was stirred at the same temperature for 20 min. The solvent was removed by rotary evaporation and the crude reaction mixture was quenched with saturate aqueous NH₄Cl and extracted with ethyl acetate. The combined organic phase was washed with brine, dried over Na₂SO₄, concentrated, and the residue was purified by column chromatography on silica gel (70% diethyl ether in hexanes) to afford the product (8.0 mg, 24.3 μ mol, 42% yield). Ee: 75% (Chiralcel® OD-H; 10% *i*-PrOH in hexanes; flow rate = 1.0

mL/min; detection at 215 nm; $t_1=25.1$ min; $t_2=32.9$ min). $[\alpha]_D^{19} -0.59^\circ$ (c 0.60, CHCl_3). ^1H NMR (400 MHz, CDCl_3) δ (ppm): 8.18 (s, 1H), 8.13 (d, $J=8.2\text{Hz}$, 1H), 7.66 (d, $J=7.8$ Hz, 1H), 7.52 (t, $J=7.9$ Hz, 1H), 7.44-7.38 (m, 2H), 7.36-7.30 (m, 3H), 3.66 (*virt. dt*, $J=11.0$, 7.5 Hz, 1H), 3.57 (dd, $J=11.1$, 7.8 Hz, 1H), 3.47 (dd, $J=11.1$, 4.1 Hz, 1H), 3.42 (s, 3H), 3.04 (ddd, $J=11.5$, 7.8, 4.1 Hz, 1H), 2.54-2.47 (m, 2H). ^{13}C NMR (126 MHz, CDCl_3) δ (ppm): 171.9, 144.5, 139.5, 134.6, 129.6, 129.2, 128.6, 127.8, 122.6, 122.2, 64.9, 53.5, 51.6, 43.6, 39.2. LRMS-ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{18}\text{H}_{19}\text{NO}_5\text{Na}$, 352; found, 352.

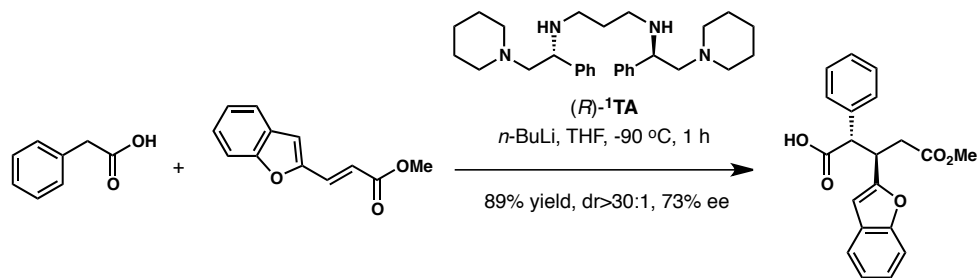


(2*S*,3*R*)-5-Methoxy-3-(1-methyl-1*H*-pyrrol-2-yl)-5-oxo-2-phenylpentanoic acid. The title compound was prepared according to general procedure I using phenylacetic acid (68.1 mg, 0.500 mmol), (*R*)-¹TA (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.82 mL, 2.44 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (5.0 mL) followed by addition of a solution of methyl (*E*)-methyl 3-(1-methyl-1*H*-pyrrol-2-yl)acrylate (86.7 mg, 0.525 mmol, 1.05 equiv) in THF (0.50 mL) at -78 °C. The reaction was quenched after 6 h and product (86.9 mg, 0.288 mmol, 58%) was obtained after purification by column chromatography on silica gel (25% ethyl acetate in hexanes then 4% methanol in dichloromethane). $[\alpha]_D^{23} +48.4^\circ$ (c 1.2, CHCl_3). ^1H NMR (500 MHz, CDCl_3) δ (ppm): 7.46-7.26 (m, 5H), 6.41 (dd, $J=2.7$, 1.6 Hz, 1H), 6.03 (dd, $J=3.6$, 2.7 Hz, 1H), 5.99 (dd, $J=3.6$, 1.6 Hz, 1H), 3.86 (ddd, $J=11.2$, 7.8, 5.9 Hz, 1H), 3.80 (d, $J=11.2$ Hz, 1H), 3.63 (s, 3H), 3.43 (s, 3H), 2.41-2.28 (m, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ (ppm): 177.8, 172.2, 136.2, 133.0, 128.9, 128.5, 128.0, 121.4, 106.7,

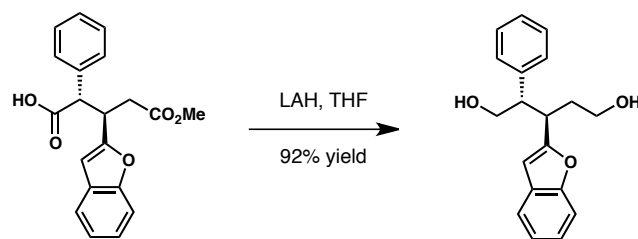
104.9, 57.8, 51.5, 39.0, 35.2, 33.6. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{17}H_{19}NO_4Na$, 324.1212; found, 324.1198.



(2*S*,3*R*)-Dimethyl 3-(1-methyl-1*H*-pyrrol-2-yl)-2-phenylpentanedioate. The title compound was prepared using carboxylic acid **5d** (18.0 mg, 59.7 μ mol), TMSCHN₂ in hexane (0.15 mL, 1.76 M, 0.264 mmol) in a mixture of benzene-MeOH (4:1, 1.0 mL) at 0 °C for 0.5 h. The solvent was removed and the residue was purified by column chromatography on silica gel (9% ethyl acetate in hexanes) to afford product (15.9 mg, 50.4 μ mol, 95% yield). Ee: 86% (Chiralcel® AD-H; 1% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 215 nm; t_1 =13.9 min; t_2 =16.1 min). $[\alpha]_D^{23} +53.0^\circ$ (c 0.76, CHCl₃). ¹H NMR (500 MHz, CDCl₃) δ (ppm): 7.42 (d, J = 6.9 Hz, 2H), 7.36 (t, J = 7.4 Hz, 2H), 7.30 (t, J = 7.2 Hz, 1H), 6.46 (dd, J = 2.7, 1.8 Hz, 1H), 6.04 (*virt.* t, J = 3.1 Hz, 1H), 6.00 (dd, J = 3.6, 1.8 Hz, 1H), 3.91 (ddd, J = 11.5, 8.5, 5.6 Hz, 1H), 3.81 (d, J = 11.5 Hz, 1H), 3.74 (s, 3H), 3.44 (s, 3H), 3.44 (s, 3H), 2.42-2.32 (m, 2H). ¹³C NMR (126 MHz, CDCl₃) δ (ppm): 173.0, 172.2, 136.7, 133.3, 128.9, 128.5, 128.0, 121.3, 106.7, 104.8, 57.9, 52.0, 51.5, 39.0, 35.7, 33.8. LRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{18}H_{21}NO_4Na$, 338; found, 338.

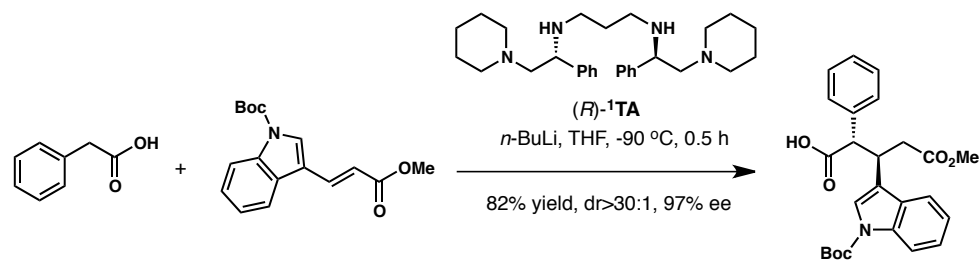


(2*S*,3*R*)-3-(Benzofuran-2-yl)-5-methoxy-5-oxo-2-phenylpentanoic acid. The title compound was prepared according to general procedure I using phenylacetic acid (68.1 mg, 0.500 mmol), (*R*)-¹TA (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.82 mL, 2.44 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (5.0 mL) followed by addition of a solution of methyl (*E*)-methyl 3-(benzofuran-2-yl)acrylate (0.106 g, 0.525 mmol, 1.05 equiv) in THF (0.50 mL) at -90 °C. The reaction was quenched after 1 h and product (0.150 g, 0.443 mmol, 89%) was obtained after purification by column chromatography on silica gel (25% ethyl acetate in hexanes then 4% methanol in dichloromethane). $[\alpha]_{\text{D}}^{23} +54.9^{\circ}$ (*c* 0.50, CHCl₃). ¹H NMR (400 MHz, CDCl₃) δ (ppm): 8.70 (brs, 1 H), 7.42 (d, *J*=7.3 Hz, 1H), 7.38-7.09 (m, 8H), 6.50 (s, 1H), 4.20-4.00 (m, 2H), 3.45 (s, 3H), 2.56-2.37 (m, 2H). ¹³C NMR (126 MHz, CDCl₃) δ (ppm): 177.7, 171.9, 157.2, 154.6, 135.3, 128.9, 128.8, 128.3, 128.1, 123.7, 122.6, 120.8, 111.0, 103.9, 54.6, 51.7, 38.4, 35.5. HRMS-ESI (*m/z*): [M+Na]⁺ calcd for C₂₀H₁₈O₅Na, 361.1044; found, 361.1043.



(2*S*,3*R*)-3-(Benzofuran-2-yl)-2-phenylpentane-1,5-diol. To a solution of carboxylic acid (13.9 mg, 39.4 μ mol) in THF (2 mL) was added lithium aluminum hydride (LAH, 20.1 mg, 0.529 mmol) at 0 °C. After stirring for 1 h at the same temperature, the reaction was carefully quenched by adding 20 μ L of water. After stirring for 5 min, 20 μ L of aqueous NaOH (15% w/w) solution was added and the mixture was stirred for 5 min. Water (60 μ L) was added and the mixture was stirred for additional 5 min. The white solid was filtered off, the filtrate was concentrated and the residue was purified by column chromatography on

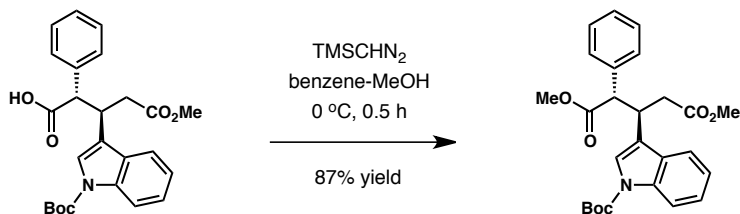
silica gel (50% of ethyl acetate in hexanes) to afford product (10.7 mg, 36.1 μmol , 92%). Ee: 73% (Chiralcel® OD-H; 10% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 215 nm; $t_1=19.0$ min; $t_2=34.0$ min). $[\alpha]_D^{23} +15.7^\circ$ (c 0.51, CHCl_3). ^1H NMR (500 MHz, CDCl_3) δ (ppm): 7.55-7.49 (m, 1H), 7.49-7.43 (m, 1H), 7.42-7.34 (m, 2H), 7.34-7.27 (m, 3H), 7.30-7.18 (m, 2H), 6.57 (d, $J=0.9$ Hz, 1H), 3.68 (dd, $J=11.2, 7.7$ Hz, 1H), 3.63 (dd, $J=11.2, 4.3$ Hz, 1H), 3.49 (ddd, $J=10.8, 6.6, 4.2$ Hz, 1H), 3.45-3.31 (m, 2H), 3.23 (ddd, $J=10.7, 7.7, 4.3$ Hz, 1H), 1.85 (dddd, $J=13.9, 11.3, 5.6, 4.3$ Hz, 1H), 1.70 (dddd, $J=13.9, 8.9, 6.6, 3.5$ Hz, 1H). ^{13}C NMR (126 MHz, CDCl_3) δ (ppm): 158.7, 154.8, 140.6, 129.0, 128.6, 128.3, 127.3, 123.6, 122.8, 120.5, 111.0, 104.4, 65.6, 60.6, 52.1, 38.2, 34.7. LRMS-ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{19}\text{H}_{20}\text{O}_3\text{Na}$, 319; found, 319.



(2*S*,3*R*)-3-(1-(*tert*-Butoxycarbonyl)-1*H*-indol-3-yl)-5-methoxy-5-oxo-2-

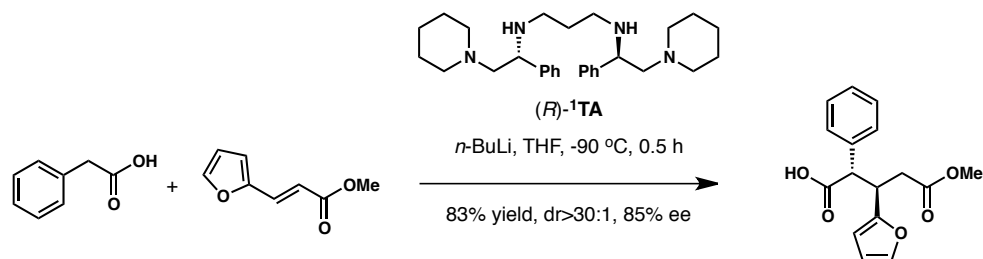
phenylpentanoic acid. The title compound was prepared according to general procedure I using phenylacetic acid (68.1 mg, 0.500 mmol), (*R*)-¹TA (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.82 mL, 2.44 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (5.0 mL) followed by addition of a solution of methyl (*E*)-*tert*-butyl 3-(3-methoxy-3-oxoprop-1-enyl)-1*H*-indole-1-carboxylate (0.158 g, 0.525 mmol, 1.05 equiv) in THF (0.50 mL) at -90 °C. The reaction was quenched after 0.5 h and product (0.180 g, 0.411 mmol, 82%) was obtained after purification by column chromatography on silica gel (25% ethyl acetate in hexanes then 4% methanol in dichloromethane). $[\alpha]_D^{23} +41.2^\circ$ (c 1.3, CHCl_3). ^1H NMR (500 MHz, CDCl_3) δ (ppm): 8.10 (brs, 1H), 7.65 (d, $J=7.8$ Hz, 1H), 7.46 (s, 1H), 7.42-7.36 (m, 2H), 7.38-7.25 (m,

4H), 7.25-7.18 (m, 1H), 4.16 (ddd, $J=10.9, 8.7, 4.8$ Hz, 1H), 4.06 (d, $J=10.9$ Hz, 1H), 3.36 (s, 3H), 2.50 (dd, $J=15.7, 4.8$ Hz, 1H), 2.43 (dd, $J=15.7, 8.7$ Hz, 1H), 1.65 (s, 9H). ^{13}C NMR (126 MHz, CDCl_3) δ (ppm): 177.5, 171.9, 149.5, 135.8, 129.4, 128.9, 128.8, 128.1, 124.4, 123.1, 122.4, 121.0, 119.3, 115.2, 83.6, 56.1, 51.4, 37.8, 35.3, 28.2. HRMS-ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{25}\text{H}_{27}\text{NO}_6\text{Na}$, 460.1736; found, 460.1718.

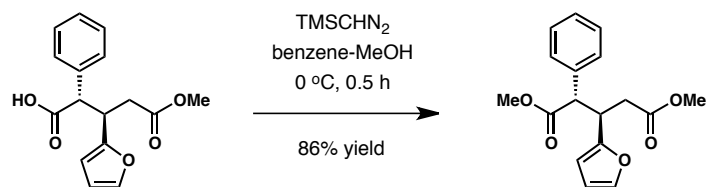


(2*S*,3*R*)-Dimethyl 3-(1-(*tert*-butoxycarbonyl)-1*H*-indol-3-yl)-2-phenylpentanedioate.

The title compound was prepared using carboxylic acid (15.9 mg, 36.3 μmol), TMSCHN_2 in hexane (0.1 mL, 1.76 M, 0.176 mmol) in a mixture of benzene-MeOH (4:1, 1.0 mL) at 0 °C for 0.5 h. The solvent was removed and the residue was purified by column chromatography on silica gel (9% ethyl acetate in hexanes) to afford product (14.2 mg, 31.5 μmol , 87% yield). Ee: 97% (Chiralcel® AD-H; 1% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 215 nm; $t_1=24.4$ min; $t_2=28.6$ min). $[\alpha]_{\text{D}}^{23} +41.3^\circ$ (c 0.71, CHCl_3). ^1H NMR (500 MHz, CDCl_3) δ (ppm): 8.11 (brs, 1H), 7.71 (d, $J=7.8$ Hz, 1H), 7.53-7.45 (m, 3H), 7.40-7.35 (m, 2H), 7.35-7.29 (m, 2H), 7.28-7.25 (m, 1H), 4.21 (ddd, $J=11.4, 8.1, 5.5$ Hz, 1H), 4.09 (d, $J=11.4$ Hz, 1H), 3.41 (s, 3H), 3.38 (s, 3H), 2.51 (dd, $J=15.9, 5.5$ Hz, 1H), 2.47 (dd, $J=15.9, 8.1$ Hz, 1H), 1.68 (s, 9H). LRMS-ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{26}\text{H}_{29}\text{NO}_6\text{Na}$, 474; found, 474.

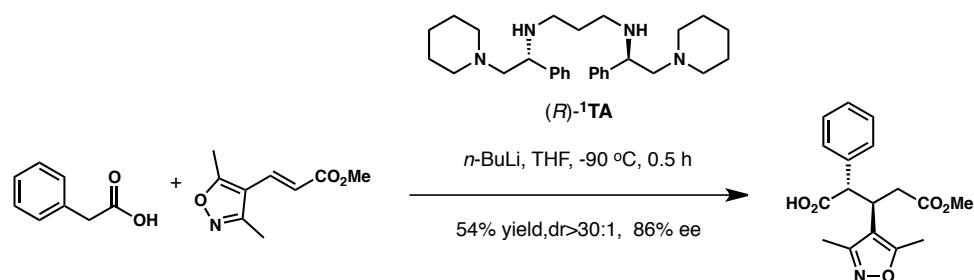


(2*S*,3*R*)-3-(Furan-2-yl)-5-methoxy-5-oxo-2-phenylpentanoic acid. The title compound was prepared according to general procedure I using phenylacetic acid (68.1 mg, 0.500 mmol), (*R*)-**1TA** (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.81 mL, 2.47 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (5.0 mL) followed by addition of a solution of methyl (*E*)-methyl 3-(furan-2-yl)acrylate (79.9 mg, 0.525 mmol, 1.05 equiv) in THF (0.50 mL) at -90 °C. The reaction was quenched after 0.5 h and product (0.120 g, 0.415 mmol, 83%) was obtained after purification by column chromatography on silica gel (2-5% methanol in dichloromethane). $[\alpha]_{\text{D}}^{23} +41.4^{\circ}$ (c 0.96, CHCl_3). ^1H NMR (500 MHz, CDCl_3) δ (ppm): 7.38-7.28 (m, 6H), 6.23 (dd, $J=3.2, 1.8$ Hz, 1H), 6.13 (d, $J=3.2$ Hz, 1H), 4.01 (ddd, $J=11.1, 9.2, 4.3$ Hz, 1H), 3.95 (d, $J=11.1$ Hz, 1H), 3.49 (s, 3H), 2.44 (dd, $J=15.8, 9.2$ Hz, 1H), 2.37 (dd, $J=15.8, 4.3$ Hz, 1H). ^{13}C NMR (126 MHz, CDCl_3) δ (ppm): 178.0, 171.8, 153.9, 141.7, 135.3, 128.9, 128.7, 128.2, 110.2, 106.9, 55.0, 51.6, 38.2, 35.9. HRMS-ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{16}\text{H}_{16}\text{O}_5\text{Na}$, 311.0895; found, 311.0881.



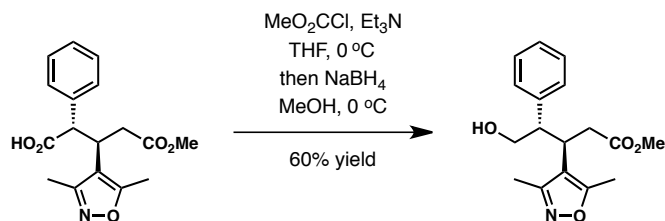
(2*S*,3*R*)-Dimethyl 3-(furan-2-yl)-2-phenylpentanedioate. The title compound was prepared using carboxylic acid (26.7 mg, 92.7 μmol), TMSCHN₂ in hexane (0.2 mL, 1.76 M, 0.352 mmol) in a mixture of benzene-MeOH (4:1, 2.0 mL) at 0 °C for 0.5 h. The solvent was removed and the residue was purified by column chromatography on silica gel (9%

ethyl acetate in hexanes) to afford product (24.2 mg, 80.0 μ mol, 86% yield). Ee: 85% (Chiralcel® OJ-H; 1% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 215 nm; $t_1=22.9$ min; $t_2=30.0$ min). $[\alpha]_D^{23} +41.7^\circ$ (c 1.2, CHCl_3). ^1H NMR (500 MHz, CDCl_3) δ (ppm): 7.40-7.37 (m, 2H), 7.37-7.32 (m, 3H), 7.32-7.27 (m, 1H), 6.27 (dd, $J=3.2, 1.8$ Hz, 1H), 6.15 (d, $J=3.2$ Hz, 1H), 4.04 (ddd, $J=11.3, 9.6, 4.4$ Hz, 1H), 3.96 (d, $J=11.3$ Hz, 1H), 3.54 (s, 3H), 3.49 (s, 3H), 2.46 (dd, $J=15.7, 9.6$ Hz, 1H), 2.37 (dd, $J=15.7, 4.4$ Hz, 1H). ^{13}C NMR (126 MHz, CDCl_3) δ (ppm): 172.7, 171.8, 154.3, 141.7, 135.9, 128.9, 128.7, 128.0, 110.2, 106.7, 55.2, 52.0, 51.5, 38.6, 36.0. LRMS-ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{17}\text{H}_{18}\text{O}_5\text{Na}$, 325; found, 325.

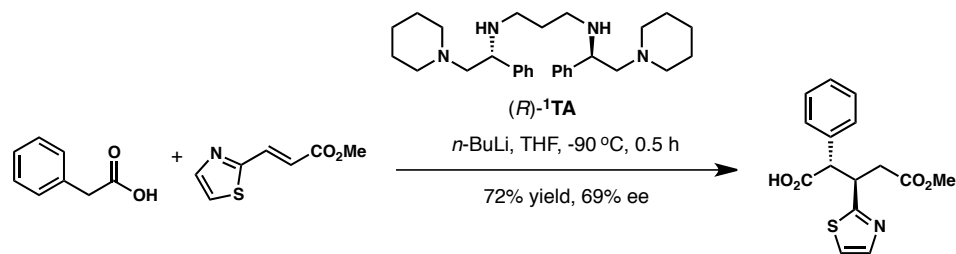


(2*S*,3*R*)-3-(3,5-Dimethylisoxazol-4-yl)-5-methoxy-5-oxo-2-phenylpentanoic acid. The title compound was prepared according to general procedure I using phenylacetic acid (68.1 mg, 0.500 mmol), (*R*)-¹TA (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.51 M in hexanes, 2.01 mmol, 4.0 equiv) in THF (5.0 mL) followed by addition of a solution of methyl (*E*)-methyl 3-(3,5-dimethylisoxazol-4-yl)acrylate (0.100 g, 0.552 mmol, 1.1 equiv) in THF (0.50 mL) at -90 °C. The reaction was quenched after 0.5 h and product (86.0 mg, 0.271 mmol, 54%) was obtained after purification by column chromatography on silica gel (50% diethyl ether in hexanes with 0.5% AcOH). $[\alpha]_D^{23} +2.2^\circ$ (c 1.0, CHCl_3). ^1H NMR (400 MHz, CDCl_3) δ (ppm): 7.43 (m, 5H), 3.78 (d, $J=11.8$ Hz, 1H), 3.71 (dt, $J=11.8, 3.7$ Hz, 1H), 3.46 (s, 3H), 2.39 (s, 3H), 2.33 (s, 3H), 2.42-2.24 (m, 2H). ^{13}C NMR (100 MHz,

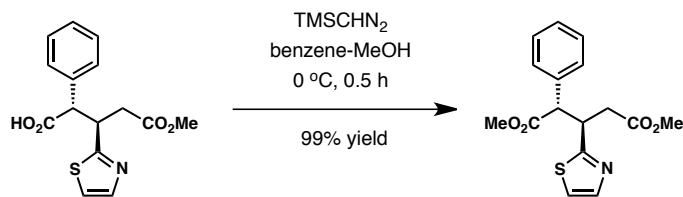
CDCl₃) δ (ppm): 176.0, 171.8, 171.7, 171.6, 135.5, 129.2, 128.5, 128.4, 112.8, 55.2, 51.7, 36.0, 33.9, 11.6, 10.9. HRMS-ESI (m/z): [M+Na]⁺ calcd for C₁₇H₁₉NO₅Na, 340.1161; found, 340.1153.



(2*S*,3*R*)-Methyl 3-(3,5-dimethylisoxazol-4-yl)-5-hydroxy-4-phenylpentanoate. Methyl chloroformate (15 μ L, 0.176 mmol, 1.4 equiv) was added dropwise to a solution of carboxylic acid (40.0 mg, 0.126 mmol) in THF (0.42 mL) and Et₃N (53 μ L, 0.378 mmol, 3.0 equiv) at 0 °C. The resultant mixture was stirred at the same temperature for 0.5 h. Then NaBH₄ (24.0 mg, 0.630 mmol, 5.0 equiv) was added followed by MeOH (1.0 mL) at 0 °C. The reaction was stirred at the same temperature for 20 min. The reaction mixture was quenched with saturated aqueous NH₄Cl and extracted with ethyl acetate. The combined organic phase was washed with brine, dried over Na₂SO₄, concentrated, and the residue was purified by column chromatography on silica gel (70% diethyl ether in hexanes) to afford the product (23.0 mg, 75.6 μ mol, 60% yield). Ee: 86% (Chiralcel® OD-H; 10% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 215 nm; t₁=21.2 min; t₂=27.1 min). $[\alpha]_D^{24}$ +30.2° (*c* 0.5, CHCl₃). ¹H NMR (600 MHz, DMSO) δ (ppm): 7.39-7.27 (m, 5H), 3.52-3.46 (m, 2H), 3.43 (s, 3H), 3.35-3.32 (m, 1H), 2.98-2.93 (m, 1H), 2.47 (dd, *J* = 15.6, 11.8 Hz, 1H), 2.31 (s, 3H), 2.30-2.26 (m, 1H), 2.21 (s, 3H). ¹³C NMR (126 MHz, DMSO) δ (ppm): 172.8, 165.9, 159.6, 142.8, 129.6, 129.1, 127.5, 113.8, 63.8, 52.1, 51.3, 37.3, 33.6, 12.0, 11.4. LRMS-ESI (m/z): [M+Na]⁺ calcd for C₁₇H₂₁NO₄Na, 326.14; found, 326.14.

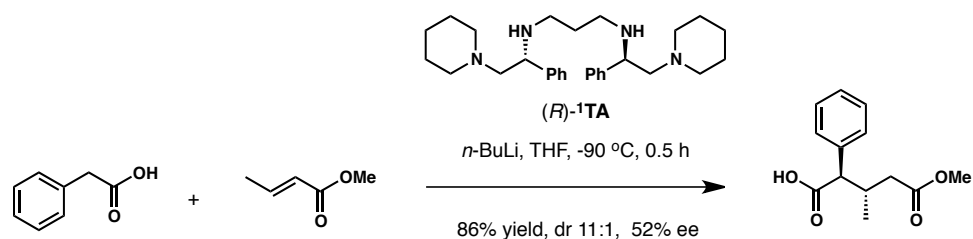


(2*S*,3*R*)-5-Methoxy-5-oxo-2-phenyl-3-(thiazol-2-yl)pentanoic acid. The title compound was prepared according to general procedure I using phenylacetic acid (68.1 mg, 0.500 mmol), (*R*)-¹TA (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.51 M in hexanes, 2.01 mmol, 4.0 equiv) in THF (5.0 mL) followed by addition of a solution of methyl (*E*)-methyl 3-(thiazol-2-yl)acrylate (93.0 mg, 0.552 mmol, 1.1 equiv) in THF (0.50 mL) at -90 °C. The reaction was quenched after 0.5 h and product (0.111 g, 0.361 mmol, 72% yield) was obtained after purification by column chromatography on silica gel (50% ethyl acetate in hexanes with 0.5% AcOH). $[\alpha]_D^{21} +33.5^\circ$ (*c* 1.0, CHCl₃). ¹H NMR (600 MHz, CDCl₃) δ (ppm): 7.66 (d, *J*=3.3 Hz, 1H), 7.37-7.30 (m, 5H), 7.16 (d, *J*=3.3 Hz, 1H), 4.32 (*virt. dt*, *J*=10.9, 3.8 Hz, 1H), 4.20 (d, *J*=11.0 Hz, 1H), 3.48 (s, 3H), 2.63 (dd, *J*=16.5, 10.1 Hz, 1H), 2.43 (dd, *J*=16.5, 3.8 Hz, 1H). ¹³C NMR (151 MHz, CDCl₃) δ (ppm): 176.0, 171.7, 171.0, 142.1, 135.8, 129.3, 128.9, 128.5, 119.2, 56.2, 51.9, 42.0, 37.9. HRMS-ESI (*m/z*): [M+Na]⁺ calcd for C₁₅H₁₅NO₄SNa, 328.0619; found, 328.0609.

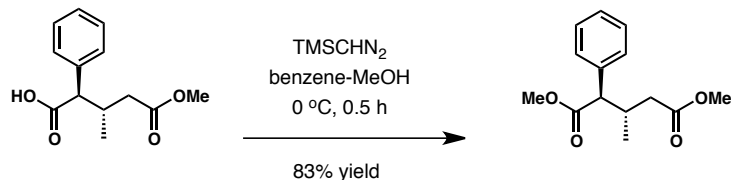


(2*S*,3*R*)-Dimethyl 2-phenyl-3-(thiazol-2-yl)pentanedioate. The title compound was prepared using carboxylic acid (10.0 mg, 32.7 μ mol), TMSCHN₂ in hexane (0.1 mL, 1.76 M, 0.176 mmol) in a mixture of benzene-MeOH (4:1, 1.0 mL) at 0 °C for 0.5 h. The solvent was removed and the residue was purified by column chromatography on silica gel (30-40%

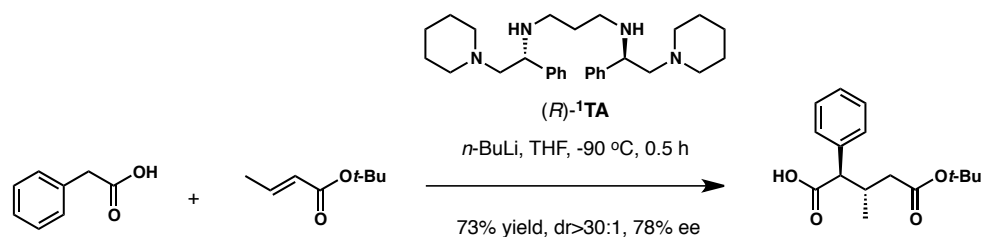
diethyl ether in hexanes) to afford product (10.3 mg, 32.4 μmol , 99% yield). Ee: 69% (Chiralcel® OD-H; 1% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 215 nm; $t_1=24.6$ min; $t_2=28.3$ min). $[\alpha]_D^{22} +63.4^\circ$ (c 1.0, CHCl_3). ^1H NMR (600 MHz, CDCl_3) δ (ppm): 7.72 (d, $J=2.8$ Hz, 1H), 7.44-7.30 (M, 5H), 7.23 (d, $J=2.8$ Hz, 1H), 4.38 (*virt. dt*, $J=10.9, 3.6$ Hz, 1H), 4.20 (d, $J=11.5$ Hz, 1H), 3.52 (s, 3H), 3.50 (s, 3H), 2.67 (dd, $J=16.4, 10.2$ Hz, 1H), 2.44 (dd, $J=16.4, 3.6$ Hz, 1H). ^{13}C NMR (151 MHz, CDCl_3) δ (ppm): 172.8, 171.8, 170.5, 142.4, 136.2, 129.3, 128.8, 128.4, 119.0, 56.3, 52.4, 51.9, 42.3, 37.9. LRMS-ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{16}\text{H}_{17}\text{NO}_4\text{SNa}$, 342; found, 342.



(2*R*,3*S*)-5-Methoxy-3-methyl-5-oxo-2-phenylpentanoic acid. The title compound was prepared according to general procedure I using phenylacetic acid (68.1 mg, 0.500 mmol), (*R*)-**1TA** (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.51 M in hexanes, 2.01 mmol, 4.0 equiv) in THF (5.0 mL) followed by addition of a solution of (*E*)-methyl crotonate (53 μL , 50.0 mg, 0.500 mmol, 1.0 equiv) in THF (0.50 mL) at -90 $^\circ\text{C}$. The reaction was quenched after 0.5 h and product (0.101 g, 0.429 mmol, 86% yield) was obtained after purification by column chromatography on silica gel (5% methanol in dichloromethane). $[\alpha]_D^{23} -23.1^\circ$ (c 1.1, CHCl_3). ^1H NMR (500 MHz, CDCl_3) δ (ppm): 7.36-7.27 (m, 5H), 3.58 (s, 3H), 3.39 (d, $J=10.7$ Hz, 1H), 2.79-2.66 (m, 1H), 2.17 (dd, $J=15.5, 4.0$ Hz, 1H), 1.92 (dd, $J=15.5, 9.3$ Hz, 1H), 1.13 (d, $J=6.4$ Hz, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ (ppm): 179.1, 172.8, 136.6, 128.8, 128.7, 127.9, 57.7, 51.4, 38.3, 33.4, 18.5. HRMS-ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{13}\text{H}_{16}\text{O}_4\text{Na}$, 259.0946; found, 259.0939.

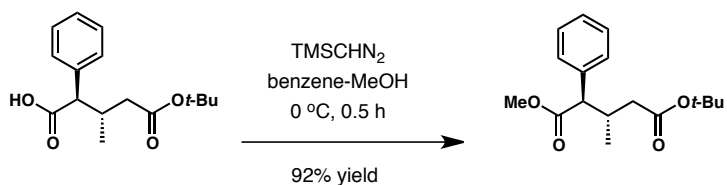


(2R,3S)-Dimethyl 3-methyl-2-phenylpentanedioate. The title compound was prepared using carboxylic acid (9.1 mg, 38.6 μmol), TMSCHN_2 in hexane (0.1 mL, 1.76 M, 0.176 mmol) in a mixture of benzene-MeOH (4:1, 1.0 mL) at 0 °C for 0.5 h. The solvent was removed and the residue was purified by column chromatography on silica gel (9% ethyl acetate in hexanes) to afford product (8.0 mg, 32.0 μmol , 83% yield). Ee: 52% (Chiralcel® OJ-H; 1% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 210 nm; *anti*: $t_1=18.9$ min; $t_2=22.7$ min; *syn*: $t_1=29.4$ min; $t_2=61.1$ min). $[\alpha]_{\text{D}}^{23}$ -26.9° (c 0.24, CHCl_3). ^1H NMR (500 MHz, CDCl_3) δ (ppm): 7.38-7.30 (m, 4H), 7.28-7.23 (m, 1H), 3.66 (s, 3H), 3.58 (s, 3H), 3.39 (d, $J=10.8$ Hz, 1H), 2.77-2.68 (m, 1H), 2.17 (dd, $J=15.5, 4.0$ Hz, 1H), 1.91 (dd, $J=15.5, 9.4$ Hz, 1H), 1.08 (d, $J=6.5$ Hz, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ (ppm): 173.7, 172.8, 137.2, 128.7, 128.6, 127.7, 57.7, 51.9, 51.4, 38.4, 33.8, 18.6. LRMS-ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{14}\text{H}_{18}\text{O}_4\text{Na}$, 273; found, 273.

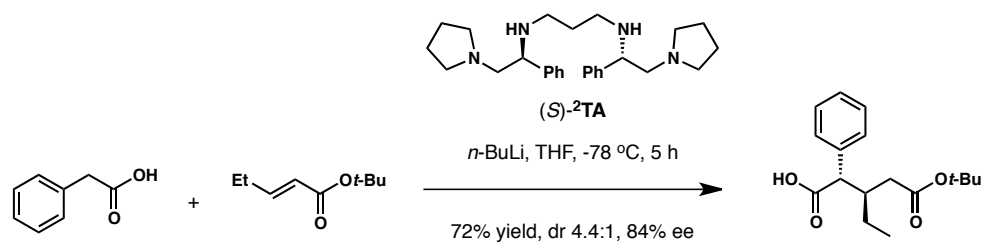


(2R,3S)-5-tert-Butoxy-3-methyl-5-oxo-2-phenylpentanoic acid. The title compound was prepared according to general procedure I using phenylacetic acid (0.136 g, 0.999 mmol), $(R)\text{-}^1\text{TA}$ (0.462 g, 1.03 mmol, 1.03 equiv), $n\text{-BuLi}$ (1.64 mL, 2.44 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (10 mL) followed by addition of a solution of $(E)\text{-tert}$ -butyl crotonate (0.171 g, 1.20 mmol, 1.2 equiv) in THF (1.0 mL) at -90 °C. The reaction was

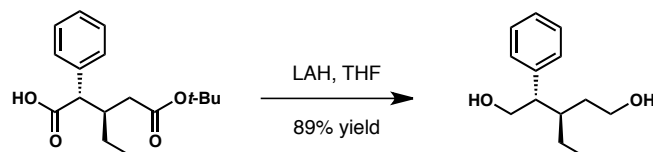
quenched after 0.5 h and product (0.203 g, 0.730 mmol, 73% yield) was obtained after recrystallization from ethyl acetate and hexanes. $[\alpha]_{\text{D}}^{23}$ -31.7° (c 1.1, CHCl_3). ^1H NMR (500 MHz, CDCl_3) δ (ppm): 7.38-7.24 (m, 5H), 3.38 (d, $J=10.8$ Hz, 1H), 2.72-2.61 (m, 1H), 2.09 (dd, $J=15.1$, 3.4 Hz, 1H), 1.80 (dd, $J=15.1$, 9.7 Hz, 1H), 1.40 (s, 3H), 1.13 (d, $J=6.4$ Hz, 9H). ^{13}C NMR (126 MHz, CDCl_3) δ (ppm): 179.4, 171.8, 136.7, 128.7, 128.6, 127.7, 80.4, 57.7, 39.7, 33.5, 28.0, 18.1. HRMS-ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{16}\text{H}_{22}\text{O}_4\text{Na}$, 301.1416; found, 301.1392.



(2R,3S)-5-tert-Butyl 1-methyl-3-methyl-2-phenylpentanedioate. The title compound was prepared using carboxylic acid **5k** (23.5 mg, 84.4 μmol), TMSCHN_2 in hexane (0.1 mL, 1.76 M, 0.176 mmol) in a mixture of benzene-MeOH (4:1, 1.0 mL) at 0 $^\circ\text{C}$ for 0.5 h. The solvent was removed and the residue was purified by column chromatography on silica gel (9% ethyl acetate in hexanes) to afford product (22.8 mg, 78.0 μmol , 92% yield). Ee: 78% (Chiralcel® OD-H; 1% *i*-PrOH in hexanes; flow rate = 0.5 mL/min; detection at 215 nm; $t_1=9.8$ min; $t_2=10.4$ min). $[\alpha]_{\text{D}}^{23}$ -41.8° (c 1.1, CHCl_3). ^1H NMR (500 MHz, CDCl_3) δ (ppm): 7.35-7.29 (m, 4H), 7.28-7.24 (m, 1H), 3.65 (s, 3H), 3.39 (d, $J=10.7$ Hz, 1H), 2.72-2.62 (m, 1H), 2.08 (dd, $J=15.1$, 3.8 Hz, 1H), 1.79 (dd, $J=15.1$, 9.6 Hz, 1H), 1.40 (s, 9H), 1.08 (d, $J=6.5$ Hz, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ (ppm): 173.8, 171.8, 137.4, 128.7, 128.6, 127.5, 80.3, 57.6, 51.9, 39.8, 33.9, 28.1, 18.2. LRMS-ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{17}\text{H}_{24}\text{O}_4\text{Na}$, 315; found, 315.

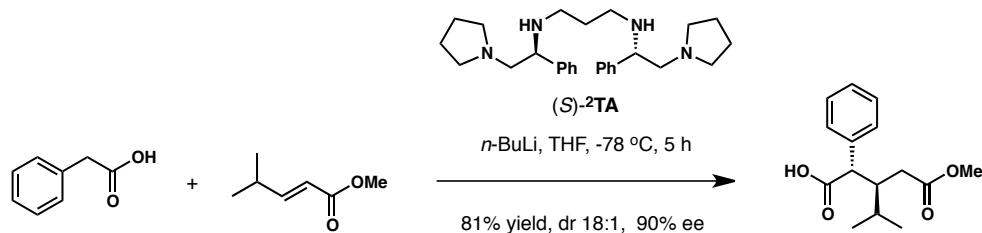


(2*S*,3*R*)-5-*tert*-Butoxy-3-ethyl-5-oxo-2-phenylpentanoic acid. The title compound was prepared according to general procedure I using phenylacetic acid (68.1 mg, 0.500 mmol), (*S*)-²TA (0.217 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.82 mL, 2.44 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (5.0 mL) followed by addition of a solution of (*E*)-*tert*-butyl pent-2-enoate (82.0 mg, 0.525 mmol, 1.05 equiv) in THF (0.50 mL) at -78 °C. The reaction was quenched after 5 h and product (0.105 g, 0.359 mmol, 72% yield) was obtained after purification by column chromatography on silica gel (20% ethyl acetate in hexanes, then 5% methanol in dichloromethane). $[\alpha]_D^{23} +29.1^\circ$ (*c* 1.6, CHCl₃). ¹H NMR (500 MHz, CDCl₃) δ (ppm): 7.37-7.22 (m, 5H), 3.59 (d, *J*=10.7 Hz, 1H), 2.61-2.50 (m, 1H), 2.10 (dd, *J*=15.6, 4.2 Hz, 1H), 1.90 (dd, *J*=15.6, 7.9 Hz, 1H), 1.64-1.54 (m, 1H), 1.53-1.46 (m, 1H), 1.38 (s, 9H), 0.95 (t, *J*=7.4 Hz, 3H). ¹³C NMR (126 MHz, CDCl₃) δ (ppm): 179.6, 171.9, 137.0, 128.9, 128.7, 127.6, 80.3, 55.4, 39.2, 35.8, 28.0, 24.7, 10.4. HRMS-ESI (*m/z*): [M+Na]⁺ calcd for C₁₇H₂₄O₄Na, 315.1572; found, 315.1561.



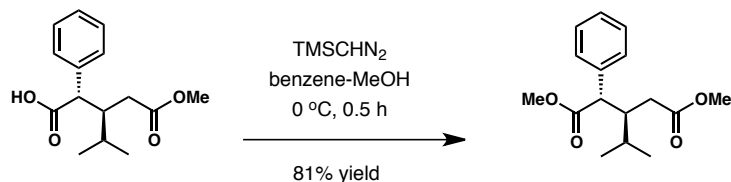
(2*S*,3*R*)-3-Ethyl-2-phenylpentane-1,5-diol. The title compound was prepared using carboxylic acid (11.2 mg, 36.6 μ mol), and lithium aluminum hydride (20.0 mg, 0.526 mmol) in THF (2.0 mL) at 0 °C. The reaction was quenched after 1 h, and product (6.8 mg, 32.6 μ mol, 89% yield) was obtained after purification by column chromatography on silica gel

(66% ethyl acetate in hexanes). Ee: 84% (Chiralcel® OJ-H; 10% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 215 nm; $t_1=11.7$ min; $t_2=14.0$ min). $[\alpha]_D^{23} +9.9^\circ$ (c 0.28, CHCl₃). ¹H NMR (500 MHz, CDCl₃) δ (ppm): 7.36-7.29 (m, 2H), 7.28-7.18 (m, 3H), 3.94 (dd, $J=11.0, 5.9$ Hz, 1H), 3.83 (dd, $J=11.0, 8.4$ Hz, 1H), 3.62 (ddd, $J=10.3, 7.4, 5.0$ Hz, 1H), 3.51 (ddd, $J=10.3, 7.8, 6.7$ Hz, 1H), 2.87 (*virt.* td, $J=8.2, 5.8$ Hz, 1H), 1.92-1.80 (m, 1H), 1.61-1.28 (m, 6H), 0.95 (t, $J=7.4$ Hz, 3H). ¹³C NMR (126 MHz, CDCl₃) δ (ppm): 141.1, 128.8, 128.6, 126.8, 64.7, 61.3, 50.6, 37.3, 33.3, 23.5, 10.4. LRMS-ESI (m/z): $[M+Na]^+$ calcd for C₁₃H₂₀O₂Na, 231; found, 231.

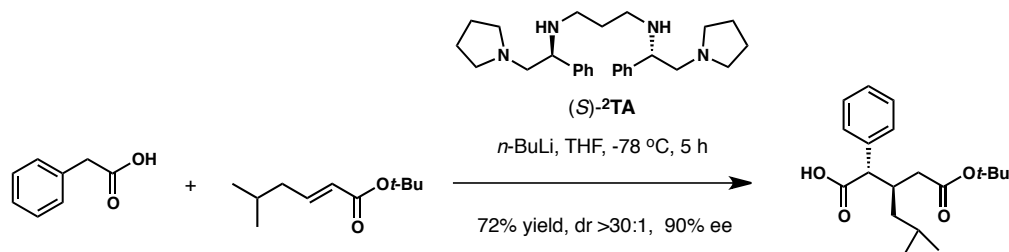


(2*R*,3*R*)-3-Isopropyl-5-methoxy-5-oxo-2-phenylpentanoic acid. The title compound was prepared according to general procedure I using phenylacetic acid (68.1 mg, 0.500 mmol), (*S*)-²TA (0.217 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.82 mL, 2.44 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (5.0 mL) followed by addition of a solution of (*E*)-methyl-4-methylpent-2-enoate (67.3 mg, 0.525 mmol, 1.05 equiv) in THF (0.50 mL) at -78 °C. The reaction was quenched after 5 h and product (0.107 g, 0.400 mmol, 81% yield) was obtained after purification by column chromatography on silica gel (10% ethyl acetate in hexanes, then 5% methanol in dichloromethane). $[\alpha]_D^{23} +8.2^\circ$ (c 1.0, CHCl₃). ¹H NMR (500 MHz, CDCl₃) δ (ppm): 7.40-7.35 (m, 2H), 7.32-7.23 (m, 3H), 3.52 (d, $J=11.7$ Hz, 1H), 3.36 (s, 3H), 2.91-2.77 (m, 1H), 2.13 (dd, $J=15.9, 5.8$ Hz, 1H), 2.00- 1.93 (m, 1H), 1.89 (dd, $J = 15.9, 6.0$ Hz, 1H), 0.98 (d, $J=6.8$ Hz, 3H), 0.90 (d, $J=7.0$ Hz, 3H). ¹³C NMR (126 MHz,

CDCl₃) δ (ppm): 178.9, 173.6, 136.3, 129.3, 128.6, 127.9, 55.5, 51.4, 43.1, 31.9, 29.7, 21.2, 16.1. HRMS-ESI (m/z): [M+Na]⁺ calcd for C₁₅H₂₀O₄Na, 287.1259; found, 287.1250.

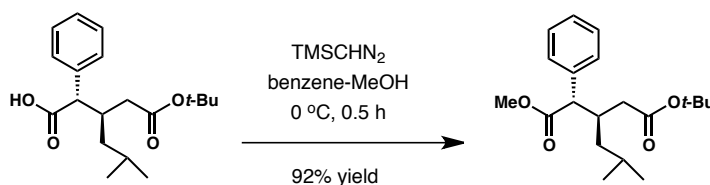


(2*R*,3*R*)-Dimethyl 3-isopropyl-2-phenylpentanedioate. The title compound was prepared using carboxylic acid (14.3 mg, 54.1 μ mol), TMSCHN₂ in hexane (0.1 mL, 1.76 M, 0.176 mmol) in a mixture of benzene-MeOH (4:1, 1.0 mL) at 0 °C for 0.5 h. The solvent was removed and the residue was purified by column chromatography on silica gel (9% ethyl acetate in hexanes) to afford product (12.2 mg, 43.8 μ mol, 81% yield). Ee: 90% (Chiralcel® AD-H; 1% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 215 nm; $t_1=10.3$ min; $t_2=13.2$ min). $[\alpha]_D^{23} +7.9$ (c 1.0, CHCl₃). ¹H NMR (500 MHz, CDCl₃) δ (ppm): 7.40-7.34 (m, 2H), 7.33-7.25 (m, 2H), 7.28-7.21 (m, 1H), 3.65 (s, 3H), 3.53 (d, $J=11.6$ Hz, 1H), 3.37 (s, 3H), 2.90-2.82 (m, 1H), 2.12 (dd, $J=15.9, 6.0$ Hz, 1H), 1.90 (dd, $J=15.9, 5.9$ Hz, 1H), 1.88-1.83 (m, 1H), 0.98 (d, $J=6.9$ Hz, 3H), 0.89 (d, $J=7.0$ Hz, 3H). ¹³C NMR (126 MHz, CDCl₃) δ (ppm): 173.9, 173.6, 136.9, 129.2, 128.5, 127.7, 55.4, 52.0, 51.4, 43.4, 32.2, 29.8, 21.1, 16.3. LRMS-ESI (m/z): [M+Na]⁺ calcd for C₁₆H₂₂O₄Na, 301; found, 301.



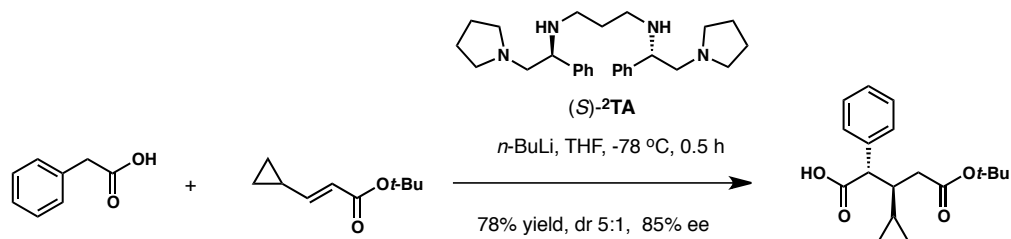
(2*S*,3*R*)-3-(2-*tert*-Butoxy-2-oxoethyl)-5-methyl-2-phenylhexanoic acid. The title compound was prepared according to general procedure I using phenylacetic acid (68.1 mg, 0.500 mmol), (*S*)-²TA (0.217 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.82 mL, 2.44 M in

hexanes, 2.00 mmol, 4.0 equiv) in THF (5.0 mL) followed by addition of a solution of (*E*)-*tert*-butyl 5-methylhex-2-enoate (96.7 mg, 0.525 mmol, 1.05 equiv) in THF (0.50 mL) at -78 °C. The reaction was quenched after 5 h and product (0.116 g, 0.362 mmol, 72% yield) was obtained after purification by column chromatography on silica gel (10% ethyl acetate in hexanes, then 4% methanol in dichloromethane). $[\alpha]_{\text{D}}^{23} +26.8^{\circ}$ (*c* 1.5, CHCl₃). ¹H NMR (500 MHz, CDCl₃) δ (ppm): 7.37-7.34 (m, 2H), 7.33-7.29 (m, 2H), 7.30-7.23 (m, 1H), 3.69 (d, *J*=10.1 Hz, 1H), 2.67-2.56 (m, 1H), 2.21 (dd, *J*=15.7, 4.6 Hz, 1H), 1.89 (dd, *J*=15.7, 5.8 Hz, 1H), 1.75-1.65 (m, 1H), 1.45-1.36 (m, 1H), 1.39 (s, 9H), 1.28-1.17 (m, 1H), 0.92 (d, *J*=6.6 Hz, 3H), 0.90 (d, *J*=6.5 Hz, 3H). ¹³C NMR (126 MHz, CDCl₃) δ (ppm): 179.6, 171.7, 136.8, 129.1, 128.6, 127.6, 80.3, 55.8, 41.8, 36.3, 36.1, 28.0, 25.4, 23.7, 21.5. HRMS-ESI (*m/z*): [M+Na]⁺ calcd for C₁₉H₂₈O₄Na, 343.1885; found, 343.1871.



(2*S*,3*R*)-5-*tert*-Butyl 1-methyl-3-isobutyl-2-phenylpentanedioate. The title compound was prepared using carboxylic acid (14.7 mg, 45.9 μ mol), TMSCHN₂ in hexane (0.14 mL, 1.76 M, 0.246 mmol) in a mixture of benzene-MeOH (4:1, 1.0 mL) at 0 °C for 0.5 h. The solvent was removed and the residue was purified by column chromatography on silica gel (9% ethyl acetate in hexanes) to afford product (14.1 mg, 42.2 μ mol, 92% yield). Ee: 90% (Chiralcel® OD-H; 1% *i*-PrOH in hexanes; flow rate = 0.5 mL/min; detection at 210 nm; *t*₁=7.6 min; *t*₂=8.8 min). $[\alpha]_{\text{D}}^{23} +7.9$ (*c* 1.0, CHCl₃). ¹H NMR (500 MHz, CDCl₃) δ (ppm): 7.37-7.34 (m, 2H), 7.34-7.27 (m, 2H), 7.28-7.23 (m, 1H), 3.69 (d, *J*=10.2 Hz, 1H), 3.65 (s, 3H), 2.67-2.54 (m, 1H), 2.19 (dd, *J*=15.6, 4.7 Hz, 1H), 1.88 (dd, *J*=15.6, 5.8 Hz, 1H), 1.72-1.63 (m, 1H), 1.43-1.35 (m, 1H), 1.39 (s, 9H), 1.15 (ddd, *J*=13.6, 9.4, 4.1 Hz, 1H), 0.91 (d,

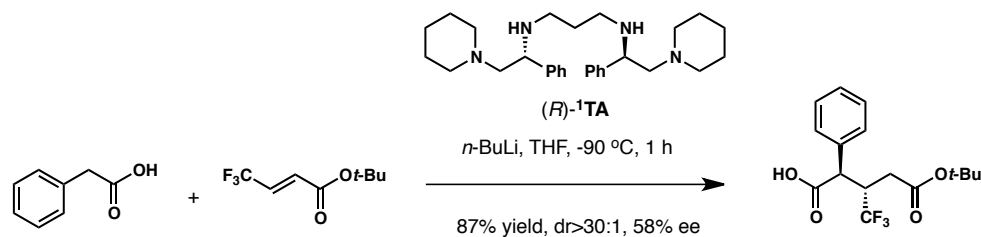
$J=6.3$ Hz, 3H), 0.90 (d, $J=6.3$ Hz, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ (ppm): 174.2, 171.7, 137.4, 128.9, 128.5, 127.4, 80.2, 55.8, 51.8, 41.9, 36.4, 36.4, 28.1, 25.4, 23.8, 21.6. LRMS-ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{20}\text{H}_{30}\text{O}_4\text{Na}$, 357; found, 357.



(2*S*,3*S*)-5-*tert*-Butoxy-3-cyclopropyl-5-oxo-2-phenylpentanoic acid. The title compound was prepared according to general procedure I using phenylacetic acid (68.1 mg, 0.500 mmol), (*S*)-²TA (0.217 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.82 mL, 2.44 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (5.0 mL) followed by addition of a solution of (*E*)-*tert*-butyl-3-cyclopropylacrylate (84.1 mg, 0.500 mmol, 1.0 equiv) in THF (0.50 mL) at -78 °C. The reaction was quenched after 0.5 h and product (0.119 g, 0.391 mmol, 78% yield) was obtained after purification by column chromatography on silica gel (4% methanol in dichloromethane). $[\alpha]_{\text{D}}^{23} +4.1^\circ$ (c 0.60, CHCl_3). ^1H NMR (500 MHz, CDCl_3) δ (ppm): 7.39-7.31 (m, 2H), 7.34-7.22 (m, 3H), 3.73 (d, $J=10.1$ Hz, 1H), 2.22 (dd, $J=15.0, 3.9$ Hz, 1H), 2.01 (dd, $J=15.0, 8.1$ Hz, 1H), 1.96-1.82 (m, 1H), 1.40 (s, 9H), 0.87-0.77 (m, 1H), 0.53-0.44 (m, 2H), 0.37-0.32 (m, 1H), 0.31-0.22 (m, 1H). ^{13}C NMR (126 MHz, CDCl_3) δ (ppm): 179.7, 171.9, 136.7, 128.9, 128.5, 127.6, 80.3, 56.6, 43.4, 38.9, 28.0, 15.2, 5.1, 3.5. HRMS-ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{18}\text{H}_{24}\text{O}_4\text{Na}$, 327.1572; found, 327.1560.

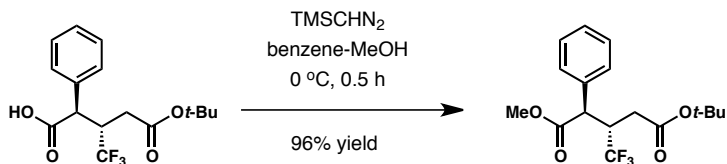


(2S,3S)-3-Cyclopropyl-2-phenylpentane diol. The title compound was prepared using carboxylic acid (29.1 mg, 95.7 μmol), and lithium aluminum hydride (36.4 mg, 0.957 mmol) in THF (3.0 mL) at 0 °C. The reaction was quenched after 1 h, and product (11.9 mg, 54.0 μmol , 56% yield) was obtained after purification by column chromatography on silica gel (55% ethyl acetate in hexanes). Ee: 85% (Chiralcel® OJ-H; 5% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 215 nm; $t_1=15.8$ min; $t_2=22.4$ min). $[\alpha]_D^{23} +7.7^\circ$ (*c* 0.55, CHCl_3). ^1H NMR (500 MHz, CDCl_3) δ (ppm): 7.35-7.28 (m, 2H), 7.27-7.20 (m, 3H), 4.11 (dd, $J=11.0, 6.0$ Hz, 1H), 3.91 (dd, $J=11.0, 8.3$ Hz, 1H), 3.78-3.58 (m, 2H), 2.96 (td, $J=8.0, 6.0$ Hz, 1H), 1.72-1.65 (m, 1H), 1.60-1.40 (m, 3H), 1.19-1.10 (m, 1H), 0.60-0.48 (m, 3H), 0.28-0.16 (m, 2H). ^{13}C NMR (126 MHz, CDCl_3) δ (ppm): 141.0, 128.8, 128.5, 126.8, 65.0, 61.2, 53.7, 42.5, 35.8, 14.9, 4.9, 4.7. LRMS-ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{14}\text{H}_{20}\text{O}_2\text{Na}$, 243; found, 243.

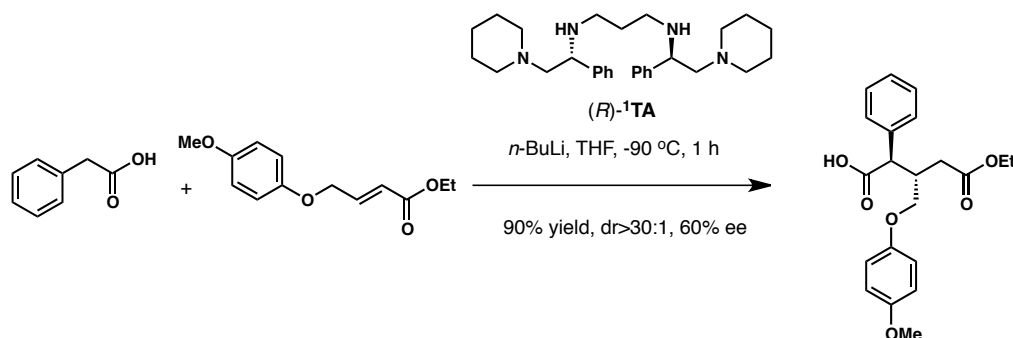


(2R,3S)-5-tert-Butoxy-5-oxo-2-phenyl-3-(trifluoromethyl)pentanoic acid. The title compound was prepared according to general procedure I using phenylacetic acid (68.1 mg, 0.500 mmol), (*R*)- ^1TA (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.82 mL, 2.44 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (5.0 mL) followed by addition of a solution of (*E*)-*tert*-butyl-3-trifluoromethylacrylate (0.103 g, 0.525 mmol, 1.05 equiv) in THF (0.50 mL) at -90 °C. The reaction was quenched after 1 h and product (0.144 g, 0.433 mmol, 87% yield) was obtained after purification by column chromatography on silica gel (4-6% methanol in dichloromethane). $[\alpha]_D^{23} +12.0$ (*c* 1.0, CHCl_3). ^1H NMR (500 MHz, CDCl_3) δ (ppm): 7.37-

7.29 (m, 5H), 3.82-3.69 (m, 2H), 2.25 (dd, $J=17.0$, 6.9 Hz, 1H), 2.09 (dd, $J=17.0$, 3.7 Hz, 1H), 1.33 (s, 9H). ^{13}C NMR (126 MHz, CDCl_3) δ (ppm): 176.8, 169.4, 133.75, 129.2, 129.1, 128.6, 127.1 (q, $J = 280.8$ Hz), 81.4, 50.2, 42.0 (q, $J=26.0$ Hz), 32.5 (q, $J = 2.2$ Hz), 27.8. ^{19}F NMR (376 MHz, CDCl_3) δ (ppm): -69.9 (d, $J=7.2$ Hz). HRMS-ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{16}\text{H}_{19}\text{F}_3\text{O}_4\text{Na}$, 355.1133; found, 355.1130.



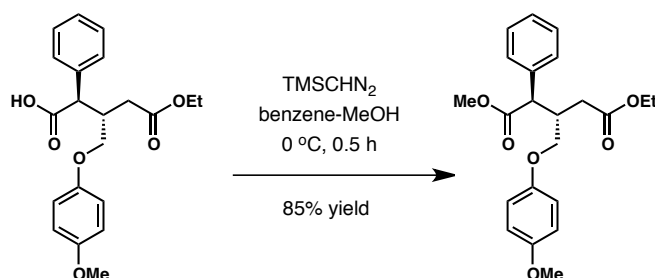
(2*R*,3*S*)-5-*tert*-Butyl 1-methyl-2-phenyl-3-(trifluoromethyl)pentanedioate. The title compound was prepared using carboxylic acid (15.4 mg, 46.3 μmol), TMSCHN_2 in hexane (0.15 mL, 1.76 M, 0.264 mmol) in a mixture of benzene-MeOH (4:1, 1.0 mL) at 0 °C for 0.5 h. The solvent was removed and the residue was purified by column chromatography on silica gel (9% ethyl acetate in hexanes) to afford product (15.4 mg, 44.5 μmol , 96% yield). Ee: 58% (Chiralcel® OD-H; 1% *i*-PrOH in hexanes; flow rate = 0.5 mL/min; detection at 215 nm; $t_1=8.7$ min; $t_2=9.5$ min). $[\alpha]_{\text{D}}^{23} +7.4^\circ$ (c 0.52, CHCl_3). ^1H NMR (500 MHz, CDCl_3) δ (ppm): 7.37-7.28 (m, 5H), 3.80-3.73 (m, 2H), 3.68 (s, 3H), 2.29-2.20 (m, 1H), 2.13-2.01 (m, 1H), 1.33 (s, 9H). ^{13}C NMR (126 MHz, CDCl_3) δ (ppm): 172.2, 169.4, 134.4, 129.1, 129.0, 127.2 (q, $J=281.0$ Hz), 81.3, 52.5, 50.3 (q, $J=2.2$ Hz), 42.2 (q, $J=25.8$ Hz), 32.7 (q, $J=2.2$ Hz), 27.9. ^{19}F NMR (376 MHz, CDCl_3) δ (ppm): -70.0 (d, $J=7.0$ Hz). LRMS-ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{17}\text{H}_{21}\text{F}_3\text{O}_4\text{Na}$, 369; found, 369.



(2*R*,3*S*)-5-Ethoxy-3-((4-methoxyphenoxy)methyl)-5-oxo-2-phenylpentanoic acid.

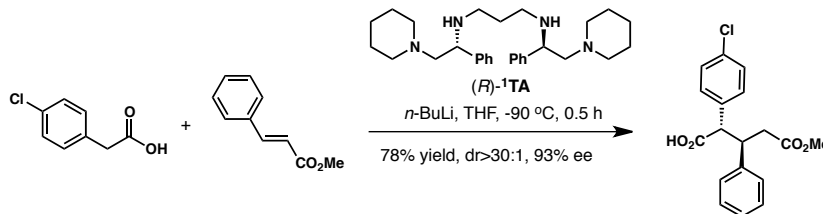
The title compound was prepared according to general procedure I using phenylacetic acid (68.1 mg, 0.500 mmol), (*R*)-¹TA (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.51 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (5.0 mL) followed by addition of a solution of (*E*)-ethyl 4-(4-methoxyphenoxy)but-2-enoate (0.124 g, 0.525 mmol, 1.05 equiv) in THF (0.50 mL) at $-90\text{ }^{\circ}\text{C}$. The reaction was quenched after 1 h and product (0.168 g, 0.452 mmol, 90% yield) was obtained after purification by column chromatography on silica gel (20% ethyl acetate in hexanes, then 4% methanol in dichloromethane). $[\alpha]_{\text{D}}^{23} +29.8$ (*c* 1.6, CHCl_3).

¹H NMR (500 MHz, CDCl_3) δ (ppm): 7.41-7.28 (m, 5H), 6.83 (d, $J=9.1$ Hz, 2H), 6.78 (d, $J=9.1$ Hz, 2H), 4.10 (dd, $J=9.6$, 4.9 Hz, 1H), 4.06-3.96 (m, 3H), 3.90 (d, $J=10.4$ Hz, 1H), 3.75 (s, 3H), 3.20-3.08 (m, 1H), 2.28 (d, $J=6.4$ Hz, 2H), 1.15 (t, $J=7.1$ Hz, 3H). ¹³C NMR (126 MHz, CDCl_3) δ (ppm): 178.6, 172.2, 153.9, 152.7, 135.9, 128.9, 128.8, 127.9, 115.4, 114.6, 68.9, 60.4, 55.6, 52.3, 37.8, 33.3, 14.0. HRMS-ESI (*m/z*): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{21}\text{H}_{24}\text{O}_6\text{Na}$, 395.1471; found, 395.1454.



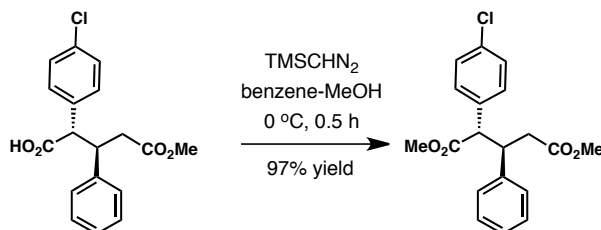
(2*R*,3*S*)-5-Ethyl 1-methyl-3-((4-methoxyphenoxy)methyl)-2-phenylpentanedioate.

The title compound was prepared using carboxylic acid (14.9 mg, 40.1 μ mol), TMSCHN₂ in hexane (0.15 mL, 1.76 M, 0.264 mmol) in a mixture of benzene-MeOH (4:1, 1.0 mL) at 0 °C for 0.5 h. The solvent was removed and the residue was purified by column chromatography on silica gel (9% ethyl acetate in hexanes) to afford product (13.1 mg, 33.9 μ mol, 85% yield). Ee: 60% (Chiralcel® OJ-H; 1% *i*-PrOH in hexanes; flow rate = 1 mL/min; detection at 215 nm; $t_1=77.7$ min; $t_2=95.4$ min). $[\alpha]_D^{23} +36.4^\circ$ (c 0.62, CHCl₃). ¹H NMR (500 MHz, CDCl₃) δ (ppm): 7.39-7.30 (m, 4H), 7.32-7.26 (m, 1H), 6.88-6.79 (m, 4H), 4.08-3.95 (m, 4H), 3.89 (d, $J=10.4$ Hz, 1H), 3.77 (s, 3H), 3.62 (s, 3H), 3.17-3.06 (m, 1H), 2.34-2.20 (m, 2H), 1.15 (t, $J=7.1$ Hz, 3H). ¹³C NMR (126 MHz, CDCl₃) δ (ppm): 173.5, 172.2, 154.0, 152.9, 136.5, 128.8, 128.8, 127.8, 115.5, 114.6, 68.9, 60.4, 55.7, 52.1, 52.1, 38.2, 33.4, 14.1. LRMS-ESI (m/z): $[M+Na]^+$ calcd for C₂₂H₂₆O₆Na, 409; found, 409.

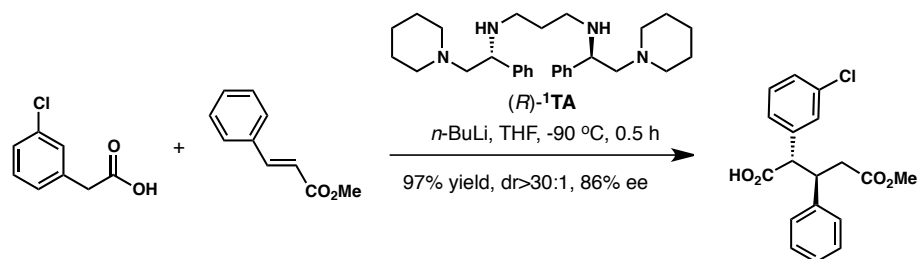


(2*S*,3*R*)-2-(4-Chlorophenyl)-5-methoxy-5-oxo-3-phenylpentanoic acid. The title compound was prepared according to general procedure I using 4-chlorophenylacetic acid (85.3 mg, 0.500 mmol), (*R*)-¹TA (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.51 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (5.0 mL) followed by addition of a solution of (*E*)-methyl cinnamate (83.5 mg, 0.515 mmol, 1.03 equiv) in THF (0.50 mL) at -90 °C. The reaction was quenched after 1 h and product (0.130 g, 0.392 mmol, 78% yield) was obtained after purification by column chromatography on silica gel (4% methanol in dichloromethane with 0.5% HOAc). $[\alpha]_D^{23} +39.3^\circ$ (c 0.25, MeOH). ¹H NMR (500 MHz, CDCl₃) δ (ppm): 7.37

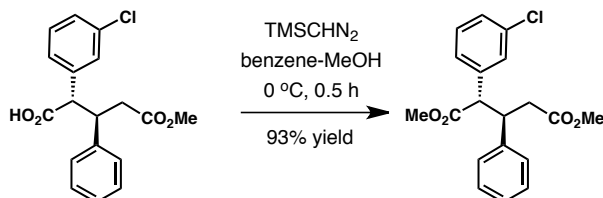
(d, $J = 8.3$ Hz, 2H), 7.33 (d, $J = 8.5$ Hz, 2H), 7.26-7.23 (m, 4H), 7.22-7.17 (m, 1H), 3.84 (d, $J = 11.4$ Hz, 1H), 3.77 (ddd, $J = 11.4, 8.8, 5.3$ Hz, 1H), 3.39 (s, 3H), 2.41 (dd, $J = 15.6, 8.8$ Hz, 1H), 2.41 (dd, $J = 15.6, 5.3$ Hz, 1H). ^{13}C NMR (126 MHz, CDCl_3) δ (ppm): 177.1, 171.7, 140.6, 134.5, 134.2, 130.1, 129.1, 128.5, 127.9, 127.3, 56.7, 51.5, 44.8, 38.4. HRMS-ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{18}\text{H}_{17}\text{ClO}_4\text{Na}$, 355.0713; found, 355.0704.



(2*S*,3*R*)-Dimethyl 2-(4-chlorophenyl)-3-phenylpentanedioate. The title compound was prepared using carboxylic acid (14.7 mg, 44.1 μmol), TMSCHN_2 in hexane (0.10 mL, 1.76 M, 0.176 mmol) in a mixture of toluene-MeOH (3:1, 1.0 mL) at 0 $^\circ\text{C}$ for 0.5 h. The solvent was removed and the residue was purified by column chromatography on silica gel (8% ethyl acetate in hexanes) to afford product (14.7 mg, 42.5 μmol , 97% yield). Ee: 93% (Chiralcel® OD-H; 1% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 215 nm; $t_1 = 11.6$ min; $t_2 = 14.8$ min). $[\alpha]_{\text{D}}^{23} +25.5^\circ$ (c 0.25, MeOH). ^1H NMR (500 MHz, CDCl_3) δ (ppm): 7.44-7.40 (m, 2H), 7.36-7.32 (m, 2H), 7.32-7.27 (m, 2H), 7.25-7.20 (m, 1H), 3.89-3.80 (m, 2H), 3.41 (s, 3H), 3.37 (s, 3H), 2.46-2.41 (m, 1H), 2.38 (dd, $J = 15.6, 4.3$ Hz, 1H). ^{13}C NMR (126 MHz, CDCl_3) δ (ppm): 172.3, 171.8, 140.8, 135.0, 134.0, 130.1, 129.0, 128.5, 127.9, 127.2, 57.0, 51.9, 51.4, 45.2, 38.5. LRMS-ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{19}\text{H}_{19}\text{ClO}_4\text{Na}$, 369; found, 369.

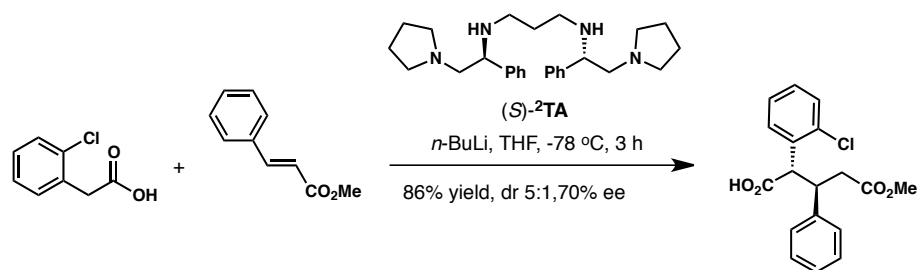


(2*S*,3*R*)-2-(3-Chlorophenyl)-5-methoxy-5-oxo-3-phenylpentanoic acid. The title compound was prepared according to general procedure I using 3-chlorophenylacetic acid (85.3 mg, 0.500 mmol), (*R*)-¹TA (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.51 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (5.0 mL) followed by addition of a solution of (*E*)-methyl cinnamate (83.5 mg, 0.515 mmol, 1.03 equiv) in THF (0.50 mL) at -90 °C. The reaction was quenched after 0.5 h and product (0.160 g, 0.487 mmol, 97% yield) was obtained after purification by column chromatography on silica gel (5% methanol in dichloromethane with 0.5% HOAc). $[\alpha]_D^{23} +26.9^\circ$ (*c* 0.47, MeOH). ¹H NMR (500 MHz, CDCl₃) δ (ppm): 7.48-7.45 (m, 1H), 7.37-7.27 (m, 7H), 7.24-7.19 (m, 1H), 3.87 (d, *J*=11.6 Hz, 1H), 3.86-3.75 (m, 1H), 3.41 (s, 3H), 2.43 (dd, *J*=15.0, 8.1 Hz, 1H), 2.38 (dd, *J*=15.0, 4.3 Hz, 1H). ¹³C NMR (126 MHz, CDCl₃) δ (ppm): 176.7, 171.7, 140.4, 137.9, 134.8, 130.2, 128.9, 128.5, 128.5, 127.9, 127.4, 127.0, 57.0, 51.5, 44.8, 38.5. HRMS-ESI (*m/z*): [M+Na]⁺ calcd for C₁₈H₁₇ClO₄Na, 355.0713; found, 355.0697.



(2*S*,3*R*)-Dimethyl 2-(3-chlorophenyl)-3-phenylpentanedioate. The title compound was prepared using carboxylic acid (14.0 mg, 42.1 μ mol), TMSCHN₂ in hexane (0.10 mL, 1.31 M, 0.131 mmol) in a mixture of toluene-MeOH (3:1, 1.0 mL) at 0 °C for 0.5 h. The

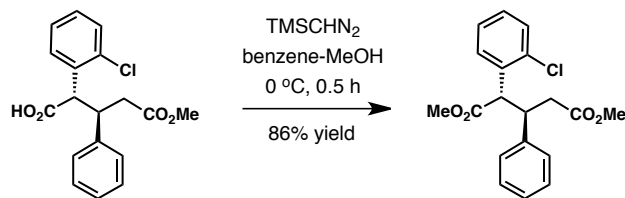
solvent was removed and the residue was purified by column chromatography on silica gel (8% ethyl acetate in hexanes) to afford product (13.5 mg, 39.0 μmol , 93% yield). Ee: 86% (Chiralcel® OD-H; 1% *i*-PrOH in hexanes flow rate = 1.0 mL/min; detection at 215 nm; $t_1=12.3$ min; $t_2=16.8$ min). $[\alpha]_D^{23} +13.6^\circ$ (c 0.50, CHCl_3). ^1H NMR (600 MHz, CDCl_3) δ (ppm): 7.50-7.47 (m, 1H), 7.39-7.35 (m, 1H), 7.33-7.28 (m, 6H), 7.23 (d, $J=6.1$ Hz, 1H), 3.88-3.81 (m, 2H), 3.41 (s, 3H), 3.38 (s, 3H), 2.48-2.37 (m, 2H). ^{13}C NMR (126 MHz, CDCl_3) δ (ppm): 172.2, 171.8, 140.9, 138.6, 134.8, 130.2, 128.9, 128.6, 128.4, 128.0, 127.4, 127.0, 57.4, 52.0, 51.6, 45.3, 38.6. LRMS-ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{19}\text{H}_{19}\text{ClO}_4\text{Na}$, 369; found, 369.



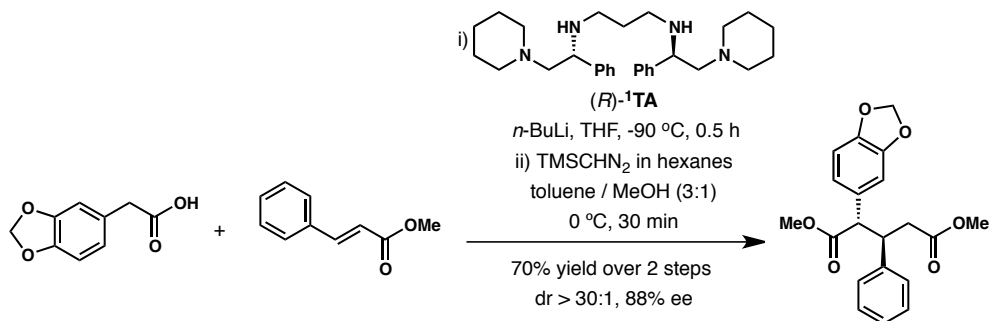
(2*S*,3*R*)-2-(2-Chlorophenyl)-5-methoxy-5-oxo-3-phenylpentanoic acid. The title compound was prepared according to general procedure I using 3-chlorophenylacetic acid (85.3 mg, 0.500 mmol), (*S*)-²TA (0.217 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.51 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (5.0 mL) followed by addition of a solution of (*E*)-methyl cinnamate (83.5 mg, 0.515 mmol, 1.03 equiv) in THF (0.50 mL) at -90 °C. The reaction was quenched after 3 h and products (0.143 g, 0.431 mmol, dr 5:1, 86% yield) together with inseparable 3-chlorophenylacetic acid (11.0 mg, 64.5 μmol , 13% yield) were obtained after purification by column chromatography on silica gel (4% methanol in dichloromethane). ^1H NMR (500 MHz, CDCl_3) δ (ppm): 7.64 (dd, $J=7.8, 1.8$ Hz, 1H), 7.43 (dd, $J=7.9, 1.5$ Hz, 1H), 7.34-7.14 (m, 7H), 4.61 (d, $J=11.5$ Hz, 1H), 3.82 (*virt.* td, $J=11.2,$

4.4 Hz, 1H), 3.37 (s, 3H), 2.53 (dd, $J=15.6, 10.9$ Hz, 1H), 2.31 (dd, $J=15.6, 4.4$ Hz, 1H).

LRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{18}H_{17}ClO_4Na$, 355; found, 355.

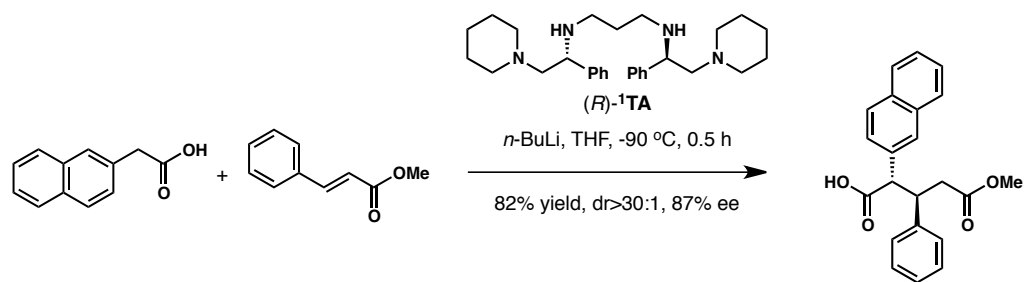


(2*S*,3*R*)-Dimethyl 2-(2-chlorophenyl)-3-phenylpentanedioate. The title compound was prepared using carboxylic acid (10.0 mg, 30.0 μ mol), TMSCHN₂ in hexane (0.10 mL, 1.31 M, 0.131 mmol) in a mixture of toluene-MeOH (3:1, 1.0 mL) at 0 °C for 0.5 h. The solvent was removed and the residue was purified by column chromatography on silica gel (6% ethyl acetate in hexanes) to afford product (9.0 mg, 26.0 μ mol, 86% yield). Ee: 70% (Chiralcel® OD-H; 1% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 215 nm; $t_1=9.6$ min; $t_2=12.8$ min). $[\alpha]_D^{23} +44.3^\circ$ (c 0.33, CHCl₃). ¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.72 (dd, $J=7.8, 1.7$ Hz, 1H), 7.42 (dd, $J=8.0, 1.4$ Hz, 1H), 7.39-7.28 (m, 5H), 7.25-7.19 (m, 2H), 4.61 (d, $J=11.6$ Hz, 1H), 3.86 (*virt.* td, $J=11.3, 4.4$ Hz, 1H), 3.38 (s, 3H), 3.37 (s, 3H), 2.56 (dd, $J=15.6, 11.0$ Hz, 1H), 2.32 (dd, $J=15.6, 4.4$ Hz, 1H). ¹³C NMR (126 MHz, CDCl₃) δ (ppm): 172.2, 172.0, 141.2, 135.0, 134.4, 129.9, 129.14, 129.09, 128.6, 128.2, 127.7, 127.3, 52.3, 52.0, 51.5, 45.9, 38.1. LRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{19}H_{19}ClO_4Na$, 369.0870; found, 369.0860.

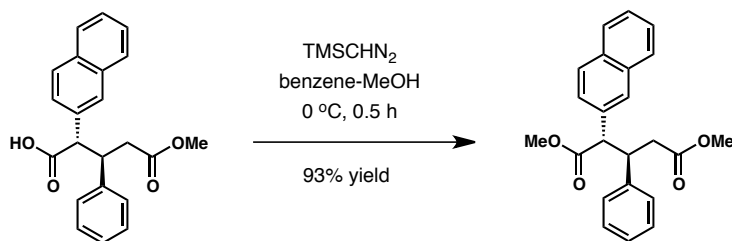


(2*S*,3*R*)-2-(1,3-Benzodioxol-5-yl)-5-methoxy-5-oxo-3-phenylpentanoic acid. The title compound was prepared according to general procedure I using 2-(1,3-benzodioxol-5-yl)-acetic acid (90.1 mg, 0.500 mmol), (*R*)-¹TA (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.51 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (5.0 mL) followed by addition of a solution of (*E*)-methyl cinnamate (83.5 mg, 0.515 mmol, 1.03 equiv) in THF (0.50 mL) at -90 °C. The reaction was quenched after 0.5 h and the crude product (0.168 g) was obtained after work up. Due to its extremely low solubility, no effort was attempted to purify by column chromatography, and the crude product was directly submitted to the next step.

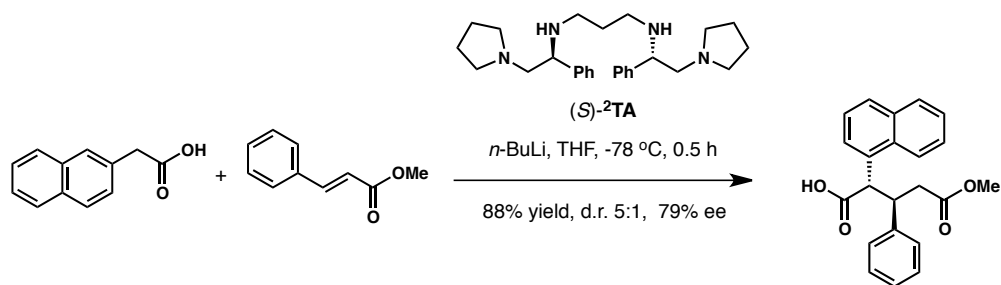
(2*S*,3*R*)-Dimethyl 2-(1,3-benzodioxol-5-yl)-3-phenylpentanedioate. The title compound was prepared using above crude acid (0.168 g), TMSCHN₂ in hexane (1.30 mL, 1.13 M, 1.47 mmol) in a mixture of toluene-MeOH (3:1, 16 mL) at 0 °C for 0.5 h. The solvent was removed and the residue was purified by column chromatography on silica gel (6% ethyl acetate in hexanes) to afford product (0.124 mg, 0.348 mmol, 70% yield over steps). Ee: 88 % (Chiralcel® OD-H; 1% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 215 nm; t₁=30.1 min; t₂=37.9 min). [α]_D²³ +21.6° (*c* 0.50, CHCl₃). ¹H NMR (500 MHz, CDCl₃) δ (ppm): 7.32-7.27 (m, 4H), 7.24-7.18 (m, 1H), 7.03 (d, *J*= 1.8Hz, 1H), 6.88 (dd, *J*=7.9, 1.8 Hz, 1H), 6.78 (d, *J*=7.9 Hz, 1H), 5.97 (d, *J*=1.5 Hz, 1H), 5.96 (d, *J*=1.5 Hz, 1H), 3.83-3.75 (m, 2H), 3.42 (s, 3H), 3.37 (s, 3H), 2.48-2.39 (m, 2H). ¹³C NMR (126 MHz, CDCl₃) δ (ppm): 172.6, 172.0, 148.1, 147.4, 141.1, 130.2, 128.4, 127.9, 127.1, 122.4, 108.5, 108.4, 101.2, 57.3, 51.8, 51.4, 45.4, 38.6. HRMS-ESI (*m/z*): [M+Na]⁺ calcd for C₂₀H₂₀O₆Na, 379.1158; found, 379.1146.



(2*S*,3*R*)-5-Methoxy-2-(naphthalen-2-yl)-5-oxo-3-phenylpentanoic acid. The title compound was prepared according to general procedure I using 2-naphthaleneacetic acid (93.1 mg, 0.500 mmol), (*S*)-²TA (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.51 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (5.0 mL) followed by addition of a solution of (*E*)-methyl cinnamate (85.1 mg, 0.525 mmol, 1.05 equiv) in THF (0.50 mL) at -90 °C. The reaction was quenched after 0.5 h and product (0.143 g, 0.410 mmol, 82% yield) was obtained after purification by column chromatography on silica gel (4% methanol in dichloromethane). $[\alpha]_D^{23} +33.9^\circ$ (*c* 0.38, CHCl₃). ¹H NMR (500 MHz CDCl₃) δ (ppm): 7.87 (d, *J*=1.8 Hz, 1H), 7.86-7.76 (m, 3H), 7.56 (dd, *J*=8.6, 1.8 Hz, 1H), 7.53-7.44 (m, 2H), 7.34-7.27 (m, 2H), 7.24 (t, *J*=7.5 Hz, 2H), 7.20-7.11 (m, 1H), 4.02 (d, *J*=11.6 Hz, 1H), 3.94 (ddd, *J*=11.6, 9.5, 5.0 Hz, 1H), 3.32 (s, 3H), 2.41 (dd, *J*=15.5, 9.5 Hz, 1H), 2.38 (dd, *J*=15.5, 5.0 Hz, 1H). ¹³C NMR (126 MHz, CDCl₃) δ (ppm): 176.6, 171.9, 140.8, 133.36, 133.35, 133.0, 128.8, 128.5, 128.2, 127.9, 127.6, 127.2, 126.4, 126.3, 125.9, 57.4, 51.4, 44.7, 38.6, 29.7. HRMS-ESI (*m/z*): [M+Na]⁺ calcd for C₂₂H₂₀O₄Na, 371.1259; found, 371.1249.

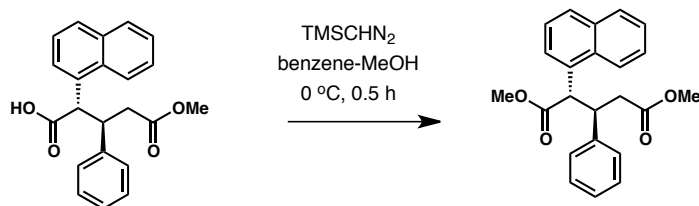


(2*S*,3*R*)-Dimethyl 2-(naphthalen-2-yl)-3-phenylpentanedioate. The title compound was prepared using carboxylic acid (18.6 mg, 53.4 μmol), TMSCHN₂ in hexane (0.15 mL, 1.76 M, 0.264 mmol) in a mixture of benzene-MeOH (4:1, 1.0 mL) at 0 °C for 0.5 h. The solvent was removed and the residue was purified by column chromatography on silica gel (9% ethyl acetate in hexanes) to afford product (18.0 mg, 49.7 μmol , 93% yield). Ee: 87% (Chiralcel® OD-H; 1% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 215 nm; $t_1=19.3$ min; $t_2=24.6$ min). $[\alpha]_D^{23} +33.7^\circ$ (c 0.86, CHCl₃). ¹H NMR (500 MHz, CDCl₃) δ (ppm): 7.92 (d, $J=1.7$ Hz, 1H), 7.90-7.82 (m, 3H), 7.65 (dd, $J=8.5, 1.8$ Hz, 1H), 7.53-7.46 (m, 2H), 7.40-7.36 (m, 2H), 7.35-7.31 (m, 2H), 7.27-7.22 (m, 1H), 4.06 (d, $J=11.6$ Hz, 1H), 4.01 (ddd, $J=11.6, 9.4, 4.3$ Hz, 1H), 3.39 (s, 3H), 3.34 (s, 3H), 2.47 (dd, $J=15.6, 9.4$ Hz, 1H), 2.41 (dd, $J=15.6, 4.3$ Hz, 1H). ¹³C NMR (126 MHz, CDCl₃) δ (ppm): 172.6, 171.9, 141.2, 134.0, 133.4, 133.0, 128.7, 128.5, 128.1, 128.0, 127.9, 127.6, 127.1, 126.4, 126.2, 126.0, 57.8, 51.8, 51.3, 45.1, 38.7. LRMS-ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for C₂₃H₂₂O₄Na, 385; found, 385.



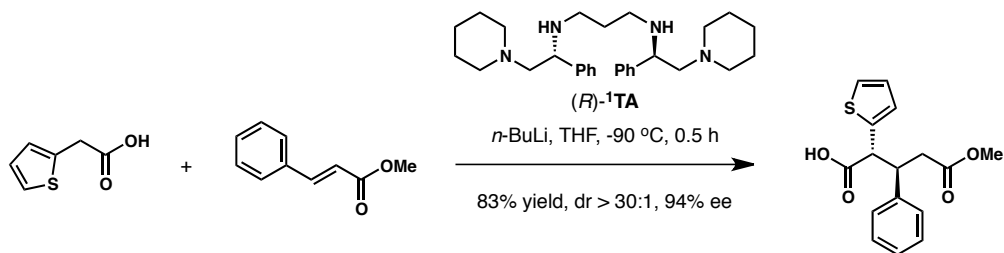
(2*S*,3*R*)-5-Methoxy-2-(naphthalen-1-yl)-5-oxo-3-phenylpentanoic acid. The title compound was prepared according to general procedure I using 1-naphthaleneacetic acid (93.1 mg, 0.500 mmol), (*S*)-²TA (0.217 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.51 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (5.0 mL) followed by addition of a solution of (*E*)-methyl cinnamate (85.1 mg, 0.525 mmol, 1.05 equiv) in THF (0.50 mL) at -78 °C. The reaction was quenched after 0.5 h and product (0.167 g, 0.478 mmol, dr 5:1, 88% yield) was

obtained after purification by column chromatography on silica gel (6% methanol in dichloromethane). Pure major diastereomer could be separated partially by column chromatography on silica gel (6% methanol in dichloromethane). $[\alpha]_D^{23} +71.4^\circ$ (c 1.2, CHCl_3). $^1\text{H NMR}$ (500 MHz, CDCl_3) δ (ppm): 8.24 (d, $J=8.5$ Hz, 1H), 7.89 (d, $J=8.1$ Hz, 1H), 7.81 (d, $J=8.0$ Hz, 1H), 7.76 (d, $J=7.4$ Hz, 1H), 7.58 (t, $J=7.4$ Hz, 1H), 7.56-7.49 (m, 1H), 7.48 (t, $J=7.7$ Hz, 1H), 7.35 (d, $J=7.3$ Hz, 2H), 7.23 (t, $J=7.5$ Hz, 2H), 7.16 (t, $J=7.3$ Hz, 1H), 4.77 (d, $J=9.9$ Hz, 1H), 4.10-3.98 (m, 1H), 3.32 (s, 3H), 2.41 (dd, $J=15.6, 10.7$ Hz, 1H), 2.30 (dd, $J=15.6, 4.2$ Hz, 1H). $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ (ppm): 177.1, 172.0, 141.0, 134.0, 132.2, 129.1, 128.5, 128.4, 128.1, 127.2, 126.7, 125.8, 125.7, 122.8, 51.3, 45.0, 38.3. HRMS-ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{22}\text{H}_{20}\text{O}_4\text{Na}$, 371.1259; found, 371.1244.

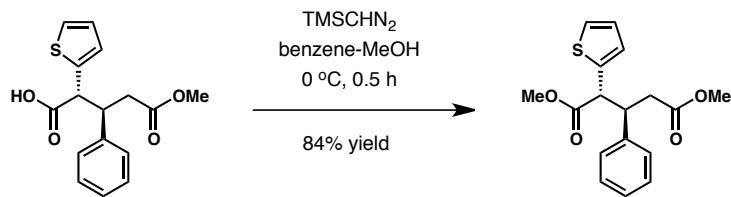


(2*S*,3*R*)-Dimethyl 2-(naphthalen-1-yl)-3-phenylpentanedioate. The title compound was prepared using the (18.2 mg, 52.3 μmol , dr 5:1), TMSCHN₂ in hexane (0.10 mL, 1.76 M, 0.176 mmol) in a mixture of benzene-MeOH (4:1, 1 mL) at 0 °C for 0.5 h. The solvent was removed and the residue was purified by column chromatography on silica gel (9% ethyl acetate in hexanes) to afford pure diastereomer product (11.4 mg, 31.5 μmol , 60% yield). Ee: 79% (Chiralcel® OD-H; 1% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 215 nm; $t_1=18.7$ min; $t_2=27.3$ min). $[\alpha]_D^{23} +89.3^\circ$ (c 1.9, CHCl_3). $^1\text{H NMR}$ (500 MHz, CDCl_3) δ (ppm): 8.34 (d, $J=8.5$ Hz, 1H), 7.94-7.87 (m, 2H), 7.85 (d, $J=8.1$ Hz, 1H), 7.63 (ddd, $J=8.4, 6.8, 1.4$ Hz, 1H), 7.58-7.51 (m, 2H), 7.51-7.45 (m, 2H), 7.41-7.33 (m, 2H), 7.31-7.24 (m, 1H), 5.00-4.69 (m, 1H), 4.22-4.13 (m, 1H), 3.37 (s, 3H), 3.35 (s, 3H), 2.49

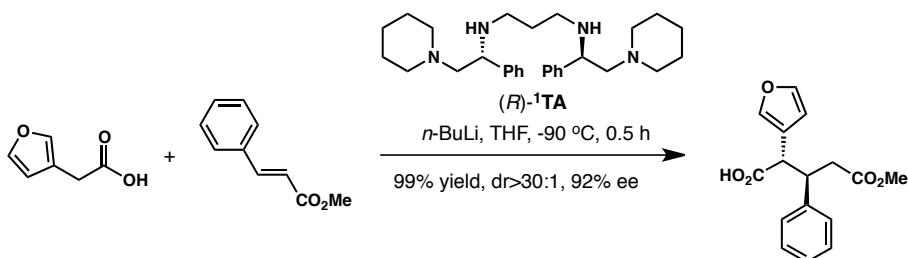
(dd, $J=15.6, 10.8$ Hz, 1H), 2.36 (dd, $J=15.6, 4.2$ Hz, 1H). ^{13}C NMR (126 MHz, CDCl_3) δ (ppm): 172.6, 171.9, 141.4, 134.0, 132.7, 132.2, 129.1, 128.4, 128.3, 128.1, 127.1, 126.7, 125.74, 125.71, 122.8, 51.8, 51.3, 45.5, 38.3. HRMS-ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{23}\text{H}_{22}\text{O}_4\text{Na}$, 385.1416; found, 385.1400.



(2*R*,3*R*)-5-Methoxy-5-oxo-3-phenyl-2-(thiophen-2-yl)pentanoic acid. The title compound was prepared according to general procedure I using 2-thiopheneacetic acid (71.1 mg, 0.500 mmol), (*R*)-**1TA** (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.51 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (5.0 mL) followed by addition of a solution of (*E*)-methyl cinnamate (85.1 mg, 0.525 mmol, 1.05 equiv) in THF (0.50 mL) at -90 °C. The reaction was quenched after 1 h and product (0.126 g, 0.414 mmol, 93% yield) was obtained after purification by column chromatography on silica gel (16% ethyl acetate in hexanes, then 4-6% methanol in dichloromethane). $[\alpha]_{\text{D}}^{23} +14.9$ (c 0.35, CHCl_3). ^1H NMR (500 MHz, CDCl_3) δ (ppm): 7.23 (d, $J=5.1$ Hz, 1H), 7.22-7.14 (m, 5H), 7.01 (d, $J=3.5$ Hz, 1H), 6.95 (dd, $J=5.1, 3.5$ Hz, 1H), 4.10 (d, $J=11.0$ Hz, 1H), 3.74 (*virt.* td, $J=10.4, 4.4$ Hz, 1H), 3.42 (s, 3H), 2.54 (dd, $J=15.6, 4.4$ Hz, 1H), 2.46 (dd, $J=15.6, 10.1$ Hz, 1H). ^{13}C NMR (126 MHz, CDCl_3) δ (ppm): 176.9, 172.1, 140.5, 138.2, 128.4, 127.9, 127.20, 127.17, 126.8, 125.5, 52.9, 51.5, 46.1, 38.3. HRMS-ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{16}\text{H}_{16}\text{O}_4\text{NaS}$, 327.0667; found, 327.0653.

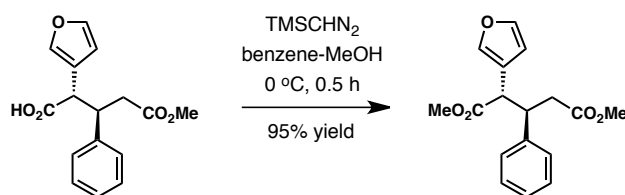


(2*R*,3*R*)-Dimethyl 3-phenyl-2-(thiophen-2-yl)pentanedioate. The title compound was prepared using carboxylic acid (10.3 mg, 33.8 μmol), TMSCHN₂ in hexane (0.10 mL, 1.76 M, 0.176 mmol) in a mixture of benzene-MeOH (4:1, 1.0 mL) at 0 °C for 0.5 h. The solvent was removed and the residue was purified by column chromatography on silica gel (9% ethyl acetate in hexanes) to afford product (9.1 mg, 28.6 μmol , 84% yield). Ee: 94% (Chiralcel® OD-H; 1% *i*-PrOH in hexanes; flow rate = 1 mL/min; detection at 215 nm; $t_1=22.2$ min; $t_2=23.1$ min). $[\alpha]_D^{23} +6.3$ (c 0.43, CHCl₃). ¹H NMR (500 MHz, CDCl₃) δ (ppm): 7.33-7.25 (m, 5H), 7.26-7.18 (m, 1H), 7.09 (dd, $J=3.5, 1.2$ Hz, 1H), 6.99 (dd, $J=5.2, 3.5$ Hz, 1H), 4.17 (d, $J=11.3$ Hz, 1H), 3.80 (ddd, $J=11.3, 10.0, 4.6$ Hz, 1H), 3.44 (s, 3H), 3.40 (s, 3H), 2.57 (dd, $J=15.7, 4.6$ Hz, 1H), 2.51 (dd, $J=15.7, 10.0$ Hz, 1H). ¹³C NMR (126 MHz, CDCl₃) δ (ppm): 171.9, 171.9, 140.6, 138.6, 128.5, 127.9, 127.3, 127.0, 126.8, 125.6, 52.9, 52.0, 51.5, 46.7, 38.5. LRMS-ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for C₁₇H₁₈O₄NaS, 341; found, 341.

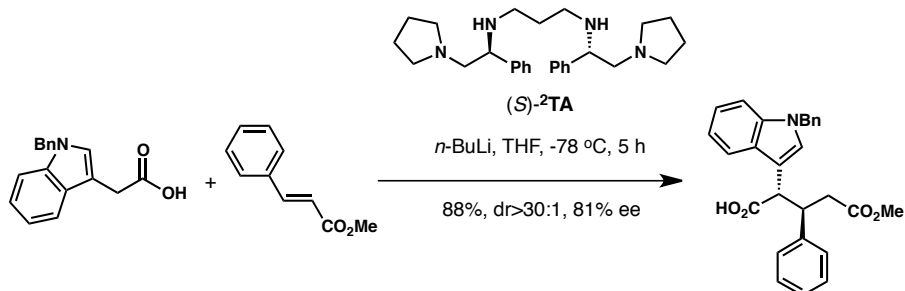


(2*S*,3*R*)-2-(Furan-3-yl)-5-Methoxy-5-oxo-3-phenylpentanoic acid. The title compound was prepared according to general procedure I using 3-furanacetic acid (63.1 mg, 0.500 mmol), (*R*)-¹TA (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.51 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (5.0 mL) followed by addition of a solution of (*E*)-

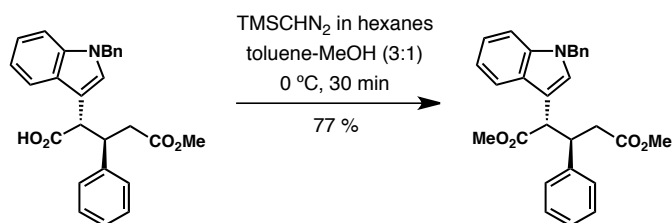
methyl cinnamate (85.1 mg, 0.525 mmol, 1.05 equiv) in THF (0.50 mL) at -90 °C. The reaction was quenched after 0.5 h and product (0.113 g, 0.442 mmol, 99% yield) was obtained after purification by column chromatography on silica gel (20% ethylacetate in hexanes with 1% AcOH). $[\alpha]_D^{23} +31.1^\circ$ (c 0.25, MeOH). $^1\text{H NMR}$ (500 MHz, CDCl_3) δ (ppm): 7.44-7.39 (m, 2H), 7.25-7.18 (m, 5H), 6.51-6.43 (m, 1H), 3.81 (d, $J = 10.0$ Hz, 1H), 3.69 (*virt. td*, $J = 10.0, 5.0$ Hz, 1H), 3.45 (s, 3H), 2.62 (dd, $J=15.7, 5.0$ Hz, 1H), 2.49 (dd, $J=15.7, 9.9$ Hz, 1H). $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ (ppm): 176.9, 172.0, 143.5, 141.2, 140.5, 128.5, 127.8, 127.3, 120.2, 110.2, 51.5, 48.0, 44.4, 38.3. HRMS-ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{16}\text{H}_{16}\text{O}_5\text{Na}$, 311.0895; found, 311.0881.



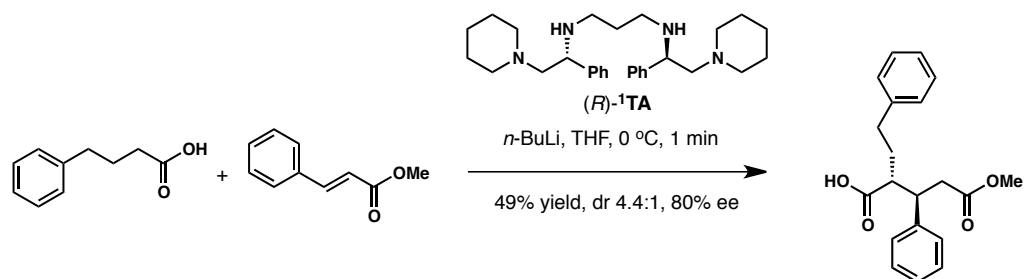
(2S,3R)-Dimethyl 2-(furan-3-yl)-3-phenylpentanedioate. The title compound was prepared using carboxylic acid (18.6 mg, 64.6 μmol), TMSCHN₂ in hexane (0.10 mL, 1.31 M, 0.131 mmol) in a mixture of toluene-MeOH (3:1, 1.0 mL) at 0 °C for 0.5 h. The solvent was removed and the residue was purified by column chromatography on silica gel (8% ethyl acetate in hexanes) to afford product (18.5 mg, 61.2 μmol , 95% yield). Ee: 92 % (Chiralcel® OD-H; 1% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 215 nm; $t_1=17.0$ min; $t_2=21.7$ min). $[\alpha]_D^{23} +9.6^\circ$ (c 1.0, CHCl_3). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ (ppm): 7.44-7.38 (m, 2H), 7.30-7.15 (m, 5H), 6.50 (m, 1H), 3.83 (d, $J=10.9$ Hz, 1H), 3.69 (*virt. td*, $J=10.4, 4.5$ Hz, 1H), 3.44 (s, 3H), 3.39 (s, 3H), 2.61 (dd, $J=15.6, 4.5$ Hz, 1H), 2.48 (dd, $J=15.6, 9.9$ Hz, 1H). $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ (ppm): 172.5, 172.1, 143.5, 141.0, 141.0, 128.5, 127.9, 127.3, 120.9, 110.3, 51.9, 51.6, 48.5, 45.0, 38.5. LRMS-ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{17}\text{H}_{18}\text{O}_5\text{Na}$, 325; found, 325.



(2*S*,3*R*)-2-(1-benzyl-1*H*-indol-3-yl)-5-methoxy-5-oxo-3-phenylpentanoic acid. The title compound was prepared according to general procedure I using *N*-benzyl-3-indolylacetic acid (0.133 g, 0.500 mmol), (*S*)- 2TA (0.217 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.51 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (5.0 mL) followed by addition of a solution of (*E*)-methyl cinnamate (85.1 mg, 0.525 mmol, 1.05 equiv) in THF (0.50 mL) at $-78\text{ }^\circ\text{C}$. The reaction was quenched after 5 h and product (0.189 g, 0.442 mmol, 88% yield) was obtained after purification by column chromatography on silica gel (8% methanol in dichloromethane with 1% AcOH). $[\alpha]_D^{23} +5.7^\circ$ (c 0.5, CHCl_3). ^1H NMR (500 MHz, CDCl_3) δ (ppm): 7.81-7.77 (m, 1H), 7.35-7.14 (m, 12H), 7.14-7.09 (m, 2H), 5.29 (s, 2H), 4.18 (d, $J=11.2$ Hz, 1H), 3.97 (*virt.* td, $J=10.5, 4.4$ Hz, 1H), 3.33 (s, 2H), 2.62 (dd, $J=15.7, 4.5$ Hz, 1H), 2.52 (dd, $J=15.6, 10.1$ Hz, 1H). ^{13}C NMR (126 MHz, CDCl_3) δ (ppm): 177.5, 172.3, 141.3, 137.1, 136.6, 128.8, 128.4, 127.9, 127.7, 127.7, 127.1, 126.8, 122.2, 119.9, 119.6, 110.0, 109.9, 51.3, 50.2, 48.8, 44.9, 38.8. HRMS-ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{27}\text{H}_{25}\text{NO}_4\text{Na}$, 450.1681; found, 450.1664.

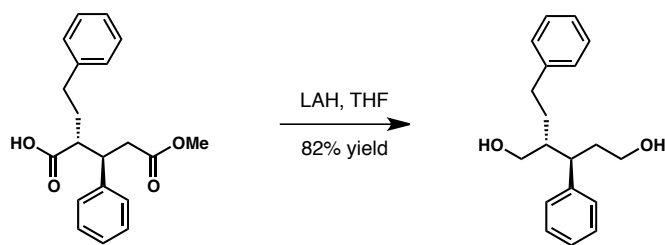


(2*S*,3*R*)-Dienmethyl 2-(1-benzyl-1*H*-indol-3-yl)-3-phenylpentanedioate. The title compound was prepared using carboxylic acid (10.0 mg, 23.4 μmol), TMSCHN₂ in hexane (0.10 mL, 1.31 M, 0.131 mmol) in a mixture of toluene-MeOH (3:1, 1.0 mL) at 0 °C for 0.5 h. The solvent was removed and the residue was purified by column chromatography on silica gel (6% ethyl acetate in hexanes) to afford product (7.9 mg, 17.9 μmol , 77% yield). Ee: 81% (Chiralcel® OD-H; 2% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 215 nm; t_1 =37.6 min; t_2 =68.9 min). $[\alpha]_D^{23}$ +12.2° (c 0.33, CHCl₃). ¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.84-7.77 (m, 1H), 7.36-7.25 (m, 9H), 7.24-7.16 (m, 3H), 7.15-7.11 (m, 2H), 5.30 (s, 2H), 4.18 (d, J =11.3 Hz, 1H), 3.99 (ddd, J =11.3, 10.1, 4.6 Hz, 1H), 3.36 (s, 3H), 3.32 (s, 3H), 2.61 (dd, J =15.7, 4.6 Hz, 1H), 2.52 (dd, J =15.6, 10.1 Hz, 1H). ¹³C NMR(126 MHz, CDCl₃) δ (ppm): 173.2, 172.3, 141.6, 137.2, 136.5, 128.8, 128.4, 127.9, 127.7, 127.5, 127.0, 126.8, 122.1, 119.8, 119.5, 110.5, 110.0, 51.7, 51.3, 50.2, 49.1, 45.4, 38.9. LRMS-ESI (m/z): $[M+Na]^+$ calcd for C₂₈H₂₇NO₄Na, 464; found, 464.



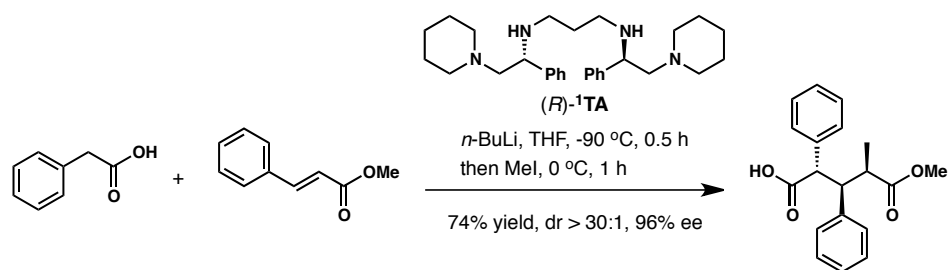
(2*R*,3*R*)-5-Methoxy-5-oxo-2-phenylethyl-3-phenylpentanoic acid. A solution of *n*-BuLi (0.80 mL, 2.51 M in hexanes, 2.01 mmol, 4.0 equiv) was added dropwise to a solution of *i*-Pr₂NH (0.14 mL, 0.101 g, 1.00 mmol) and (*R*)-¹TA (0.231 g, 0.515 mmol, 1.03 equiv) in THF (3.5 mL) at 0 °C and the reaction mixture was stirred at this temperature for 30 min. Then 4-phenylbutyric acid (82.1 mg, 0.500 mmol) in THF (1.0 mL + (0.2 + 0.3) mL rinses) was added dropwise. After additional 30 min, a solution of methyl cinnamate (81.1 mg, 0.500 mmol, 1.0 equiv) in THF (0.30 mL + 2×0.10 mL rinses) was added to the reaction

mixture dropwise over 1 min, immediately followed by a mixture of THF-MeOH (3:1, 0.64 mL). After 5 min, the reaction mixture was acidified with 1 M aqueous solution of HCl and extracted with ethyl acetate. The combined organic phase was sequentially washed with 1 M aqueous solution of HCl and brine, dried over Na₂SO₄, concentrated, and the residue was purified by column chromatography on silica gel (20-66% ethyl acetate in hexanes then 6% methanol in dichloromethane) to afford the pure major diastereomer product (65.3 mg, 0.200 mmol, 40% yield) together with minor diastereomer (15.1 mg, 46.3 mmol, 9% yield). $[\alpha]_D^{23} +9.9^\circ$ (*c* 1.1, CHCl₃). ¹H NMR (500 MHz, CDCl₃) δ (ppm): 7.30-7.23 (m, 4H), 7.22-7.11 (m, 6H), 3.53 (s, 3H), 3.49 (ddd, *J* = 9.4, 7.4, 5.8 Hz, 1H), 2.86 (dd, *J*=15.8, 5.6 Hz, 1H), 2.78-2.64 (m, 3H), 2.58-2.48 (m, 1H), 2.03-1.91 (m, 1H), 1.90 – 1.78 (m, 1H). ¹³C NMR (126 MHz, CDCl₃) δ (ppm): 179.4, 172.2, 141.1, 140.6, 128.40, 128.37, 128.35, 128.0, 127.1, 126.0, 51.6, 50.3, 43.7, 37.4, 33.7, 31.2. HRMS-ESI (*m/z*): [M+Na]⁺ calcd for C₂₀H₂₂O₄Na, 349.1416; found, 349.1406. Absolute configuration of this compound remained undetermined.



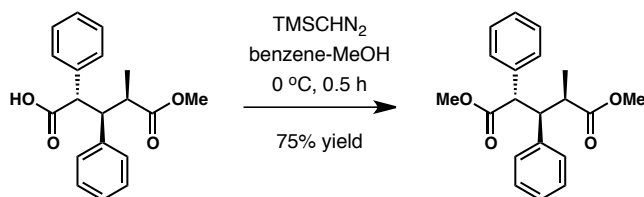
(2R,3R)-2-phenylethyl-3-phenylpentane diol. The title compound was prepared using carboxylic acid (31.4 mg, 96.3 μ mol), and lithium aluminum hydride (40.1 mg, 1.06 mmol) in THF (2.0 mL) at 23 °C. The reaction was quenched after 2 h, and product (22.5 mg, 79.1 μ mol, 82% yield) was obtained after purification by column chromatography on silica gel (50% ethyl acetate in hexanes). Ee: 80% (Chiralcel® OJ-H; 10% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 215 nm; *t*₁=20.0 min; *t*₂=30.7 min). $[\alpha]_D^{23} +17.8^\circ$ (*c* 1.2,

CHCl₃). ¹H NMR (500 MHz, CDCl₃) δ (ppm): 7.34-7.24 (m, 4H), 7.25-7.15 (m, 6H), 3.58 (dd, *J*=11.1, 4.9 Hz, 1H), 3.55-3.46 (m, 1H), 3.46-3.33 (m, 2H), 2.91 (ddd, *J*=11.0, 7.0, 3.9 Hz, 1H), 2.73 (ddd, *J*=13.8, 10.1, 5.5 Hz, 1H), 2.60 (ddd, *J*=13.8, 9.9, 5.6 Hz, 1H), 2.08 (dddd, *J*=14.3, 8.8, 7.0, 4.0 Hz, 1H), 1.92-1.62 (m, 6H). ¹³C NMR (126 MHz, CDCl₃) δ (ppm): 143.0, 142.4, 128.5, 128.3, 128.3, 126.4, 125.7, 62.9, 61.2, 45.6, 42.9, 34.9, 33.5, 30.2. HRMS-ESI (*m/z*): [M+Na]⁺ calcd for C₁₉H₂₄O₂Na, 307.1674; found, 307.1670. Absolute configuration of this compound remained undetermined.

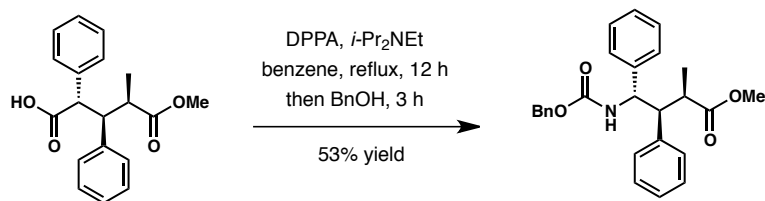


(2*S*,3*R*,4*R*)-5-Methoxy-4-methyl-5-oxo-2,3-diphenylpentanoic acid. A solution of *n*-BuLi (1.6 mL, 2.51 M in hexanes, 4.02 mmol, 4.0 equiv) was added dropwise to a solution of phenylacetic acid (136 mg, 1.00 mmol) and (*R*)-¹TA (0.462 g, 1.03 mmol, 1.03 equiv) in THF (10 mL) at 0 °C and the reaction mixture was stirred at this temperature for 30 min. The reaction mixture was then cooled to -90 °C and stirred for an additional 5 min. A solution of methyl cinnamate (162 mg, 1.00 mmol, 1.0 equiv) in THF (0.60 mL + 2×0.20 mL rinses) was added to the reaction mixture dropwise over 10 min. The resultant mixture was stirred for additional 20 min before a quench with a mixture of THF-MeOH (3:1, 1.3 mL) at -90 °C. After 5 min, the reaction mixture was acidified with 1 M aqueous solution of HCl and extracted with ethyl acetate. The combined organic phase was sequentially washed with 1 M aqueous solution of HCl and brine, dried over Na₂SO₄, concentrated, and the residue was purified by column chromatography on silica gel (15% ethyl acetate in hexanes with 0.5% HOAc) to afford the pure product (0.230 g, 0.736 mmol, 74% yield). [α]_D²³ +31.7

(*c* 1.2, CHCl₃). ¹H NMR (500 MHz, DMSO-*d*₆) δ (ppm): 7.54 (d, *J*=6.7 Hz, 2H), 7.41 (t, *J*=7.6 Hz, 2H), 7.36-7.27 (m, 3H), 7.28-7.21 (m, 3H), 4.21 (d, *J*=12.3 Hz, 1H), 3.92 (dd, *J*=12.3, 4.3 Hz, 1H), 3.41 (s, 3H), 2.33 (qd, *J*=7.0, 4.3 Hz, 1H), 0.78 (d, *J*=7.0 Hz, 3H). ¹³C NMR (126 MHz, DMSO-*d*₆) δ (ppm): 174.4, 173.3, 138.9, 137.3, 128.8, 128.7, 128.5, 127.9, 127.7, 126.8, 53.4, 51.2, 49.1, 40.2, 10.7. HRMS-ESI (*m/z*): [M+Na]⁺ calcd for C₁₉H₂₀O₄Na, 335.1259; found, 335.1246.

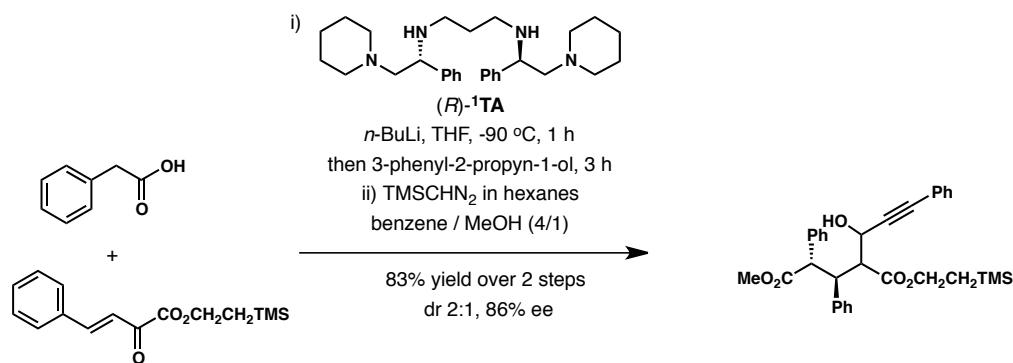


(2*R*,3*R*,4*S*)-Dimethyl-2-methyl-3,4-diphenylpentanedioate. The title compound was prepared using carboxylic acid (12.7 mg, 40.7 μmol), TMSCHN₂ in hexane (0.1 mL, 1.76 M, 0.176 mmol) in a mixture of benzene-MeOH (4:1, 1.0 mL) at 0 °C for 0.5 h. The solvent was removed and the residue was purified by column chromatography on silica gel (9% ethyl acetate in hexanes) to afford product (10.0 mg, 30.6 μmol, 75% yield). Ee: 96% (Chiralcel® AD-H; 1% *i*-PrOH in hexanes; flow rate = 1.0 ml/min; detection at 215 nm; *t*₁=20.5 min; *t*₂=26.8 min). [α]_D²³ +40.9° (*c* 0.48, CHCl₃). ¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.51 (d, *J*=6.9 Hz, 2H), 7.37 (t, *J*=7.4 Hz, 2H), 7.34-7.26 (m, 3H), 7.25-7.19 (m, 3H), 4.10 (d, *J*=12.1 Hz, 1H), 4.04 (dd, *J*=12.1, 4.9 Hz, 1H), 3.42 (s, 3H), 3.34 (s, 3H), 2.52 (qd, *J*=7.0, 4.9 Hz, 1H), 0.89 (d, *J* = 7.0 Hz, 3H). ¹³C NMR (126 MHz, CDCl₃) δ (ppm): 175.1, 172.7, 138.6, 136.3, 128.9, 128.8, 128.7, 128.2, 128.0, 127.2, 55.1, 51.8, 51.4, 49.6, 41.3, 11.9. LRMS-ESI (*m/z*): [M+Na]⁺ calcd for C₂₀H₂₂O₄Na, 349; found, 349.



(2*R*,3*S*,4*S*)-Methyl 4-(benzyloxycarbonylamino)-2-methyl-3,4-diphenylbutanoate. A solution of acid (78.1 mg, 0.250 mmol), diphenylphosphoryl azide (DPPA, 80 μ L, 0.102 g, 0.372 mmol) and *i*-Pr₂NEt (90 μ L, 66.8 mg, 0.517 mmol) in benzene was heated to reflux for 12 h. Then benzyl alcohol (80 μ L, 83.2 mg, 0.769 mmol) was added, and the reaction mixture was stirred at reflux for additional 5 h. After cooling, the reaction mixture was diluted with CH₂Cl₂, washed with 1 M aqueous solution of NaOH, extracted with CH₂Cl₂. The combined organic phase was washed with 10% aqueous solution of H₂SO₄ and brine, dried over Na₂SO₄, concentrated, and the residue was purified by column chromatography on silica gel (15% ethyl acetate in hexanes) to afford product (55.5 mg, 0.133 mmol, 53% yield). $[\alpha]_D^{23}$ -0.67° (*c* 1.4, CHCl₃). ¹H NMR (500 MHz, DMSO-*d*₆) δ (ppm): 7.71 (d, *J*=9.4 Hz, 1H), 7.50-7.45 (m, 2H), 7.41-7.33 (m, 2H), 7.32-7.22 (m, 7H), 7.20-7.16 (m, 2H), 7.08-7.02 (m, 2H), 5.03 (dd, *J*=11.4, 9.4 Hz, 1H), 4.92 (d, *J*=12.8 Hz, 1H), 4.76 (d, *J*=12.8 Hz, 1H), 3.66 (dd, *J*=11.4, 5.0 Hz, 1H), 3.39 (s, 3H), 2.35 (qd, *J*=7.0, 5.0 Hz, 1H), 0.82 (d, *J*=7.0 Hz, 3H). ¹³C NMR (126 MHz, CDCl₃) δ (ppm): 174.3, 155.2, 141.7, 138.1, 137.1, 129.0, 128.3, 128.2, 127.8, 127.5, 127.1, 126.6, 64.8, 56.3, 51.7, 51.2, 40.6, 11.5. HRMS-ESI (*m/z*): [M+Na]⁺ calcd for C₂₆H₂₇NO₄Na, 440.1838; found, 440.1817.

Synthesis of Proposed Structure of Pulveraven B.



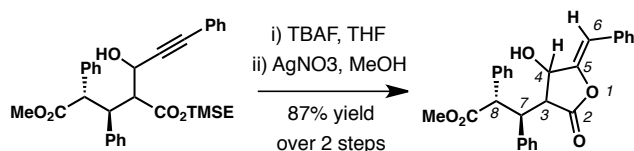
Alcohol. A solution of n -BuLi (0.80 mL, 2.51 M in hexanes, 2.01 mmol, 4.0 equiv) was added dropwise to a solution of phenylacetic acid (68.1 mg, 0.500 mmol) and (*R*)-¹TA (0.231 g, 0.515 mmol, 1.03 equiv) in THF (5.0 mL) at 0 °C and the reaction mixture was stirred at this temperature for 30 min. The reaction mixture was then cooled to -78 °C and stirred for an additional 5 min. A solution of (*E*)-2-(trimethylsilyl)ethyl 3-phenyl-2-butenate (0.149 g, 0.600 mmol, 1.2 equiv) in THF (0.30 mL + 2×0.10 mL rinses) was added to the reaction mixture dropwise over 10 min. After stirring for additional 50 min, a solution of 3-phenyl-2-propynal (0.325 g, 2.50 mmol) was added. The reaction mixture was stirred for additional 3 h before a quench with a mixture of THF-MeOH (3:1, 0.64 mL) at -78 °C. After 5 min, the reaction mixture was acidified with 1 M aqueous solution of HCl and extracted with ethyl acetate. The combined organic phase was sequentially washed with 1 M aqueous solution of HCl and brine, dried over Na₂SO₄, concentrated, and the residue was directly used for the next step.

The above crude acid was dissolved in a mixture of benzene-MeOH (4:1, 5.0 mL) and TMSCHN₂ in hexane (2.6 mL, 0.57 M in hexanes, 1.48 mmol) was added at 0 °C. The resultant mixture was stirred at the same temperature for 1 h. The solvent was removed on a

rotary evaporator and the residue was purified by column chromatography on silica gel (9-11% ethyl acetate in hexanes) to afford the product (0.221 g, 0.418 mol, dr 2:1, 83% yield).

Major diastereomer: Ee: 87% (Chiralcel® OD-H; 1% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 215 nm; major diastereomer $t_1=18.0$ min; $t_2=54.5$ min). $[\alpha]_D^{23} -5.2^\circ$ (c 0.5, CHCl_3). ^1H NMR (500 MHz, CDCl_3) δ (ppm): 7.52-7.46 (m, 2H), 7.43-7.37 (m, 2H), 7.38-7.28 (m, 6H), 7.29-7.23 (m, 5H), 4.21 (d, $J=11.2$ Hz, 1H), 4.15-4.05 (m, 1H), 3.78-3.66 (m, 1H), 3.51 (d, $J=10.5$ Hz, 1H), 3.44-3.33 (m, 1H), 3.28 (s, 3H), 2.97 (dd, $J=9.8, 3.9$ Hz, 1H), 0.88-0.75 (m, 2H), -0.04 (s, 9H). ^{13}C NMR (126 MHz, CDCl_3) δ (ppm): 173.6, 172.4, 139.0, 135.6, 131.6, 129.8, 128.9, 128.54, 128.46, 128.3, 128.2, 128.0, 127.5, 122.3, 88.1, 85.4, 63.3, 61.6, 57.2, 55.3, 51.7, 47.1, 17.2, -1.7. HRMS-ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{32}\text{H}_{36}\text{O}_5\text{NaSi}$, 551.2230; found, 551.2217.

Ee: 86% ee. (Chiralcel® OD-H; 1% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 215 nm; minor diastereomer $t_1=21.9$ min; $t_2=29.8$ min).



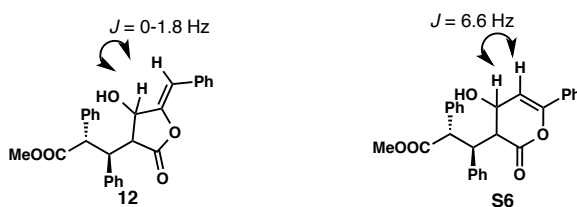
Lactone. To a solution of ester (51.8 mg, 98.0 μmol) in THF (2 mL) was added TBAF (1.0 M in THF, 0.25 mL, 0.250 mmol) at 23 °C. After stirring for 2 h, the reaction mixture was diluted with ethyl ether, quenched with water, and extracted with ethyl ether. The combined organic phase was washed with brine, dried over Na_2SO_4 , concentrated, and the crude acid was directly used for the next step.

To a solution of above crude acid in MeOH (2 mL) was added AgNO_3 (16.6 mg, 97.7 μmol) at 23 °C. Additional AgNO_3 (16.6 mg, 97.7 μmol) was added after 14 h, followed by third portion of AgNO_3 (33.2 mg, 0.195 mmol) after 10 h. The resultant mixture was stirred

for further 14 h. The solvent was removed on a rotary evaporator and the residue was purified by column chromatography on silica gel (25% ethyl acetate in hexanes) to afford the product (36.6 mg, 85.4 μ mol, dr 2:1, 87% yield over two steps.). The two diastereomers could be partially separated by column chromatography.

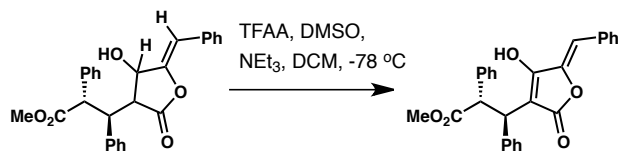
Major diastereomer: $[\alpha]_D^{23} +56.1$ (c 0.71, CHCl_3). ^1H NMR (500 MHz, CDCl_3) δ (ppm): 7.49-7.44 (m, 2H), 7.34-7.27 (m, 4H), 7.27-7.18 (m, 9H), 5.62 (s, 1H, H-6), 4.99 (d, $J=7.9$ Hz, 1H, H-8), 4.66 (*virt.* t, $J=5.7$ Hz, 1H, H-4), 3.87 (*virt.* t, $J=8.1$ Hz, 1H, H-7), 3.55 (s, 3H), 3.54 (dd, $J=8.0, 6.5$ Hz, 1 H, H-3), 1.88 (d, $J=5.3$ Hz, 1H, H-OH). ^{13}C NMR (126 MHz, CDCl_3) δ (ppm): 174.1, 172.8, 149.1, 138.0, 136.8, 132.9, 129.6, 129.2, 128.8, 128.6, 128.4, 128.2, 127.7, 127.6, 127.5, 106.8, 52.6, 51.9, 46.6, 46.1. LRMS-ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{27}\text{H}_{24}\text{O}_5\text{Na}$, 451; found, 451.

Minor diastereomer: $[\alpha]_D^{23} -89.7$ (c 0.75, CHCl_3). ^1H NMR (500 MHz, CDCl_3) δ (ppm): 7.71-7.65 (m, 2H), 7.48-7.38 (m, 4H), 7.39-7.32 (m, 1H), 7.29-7.12 (m, 7H), 7.11-7.03 (m, 1H), 5.40 (d, $J=1.8$ Hz, 1H, H-6), 4.87 (*virt.* td, $J=9.0, 1.8$ Hz, 1H, H-4), 4.63 (d, $J=12.2$ Hz, 1H, H-8), 4.06 (dd, $J=12.2, 3.6$ Hz, 1H, H-7), 3.33 (s, 3H), 2.82 (dd, $J=8.9, 3.5$ Hz, 1H, H-3), 2.06 (d, $J=9.1$ Hz, 1H, H-OH). ^{13}C NMR (126 MHz, CDCl_3) δ (ppm): 173.0, 172.5, 149.9, 138.1, 136.6, 132.9, 129.1, 129.0, 128.9, 128.8, 128.4, 128.19, 128.15, 128.10, 127.0, 104.5, 70.3, 54.4, 51.8, 46.1, 44.9. LRMS-ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{27}\text{H}_{24}\text{O}_5\text{Na}$, 451; found, 451.



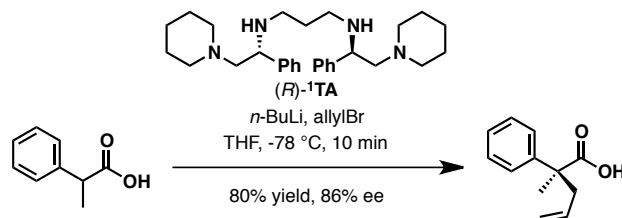
Scheme 1. Comparison of J -coupling constant

The regioselectivity of the Ag-mediated cyclization reaction was confirmed by *J*-coupling constant as shown in Scheme 1. Dihydro-2-pyrone **S6** was prepared using Hg(OAc)₂ (63%yield)⁶⁷ as catalyst instead of AgNO₃.



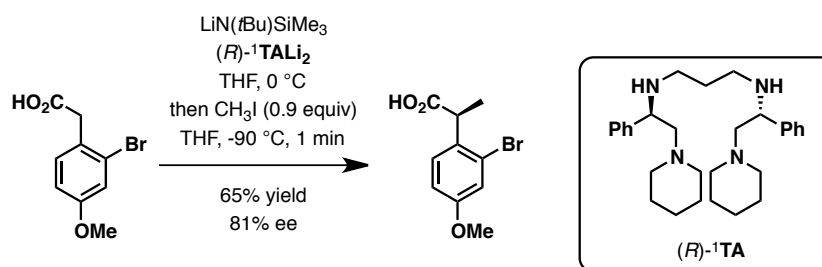
(2*S*,3*R*)-methyl 3-((*Z*)-5-benzylidene-4-hydroxy-2-oxo-2,5-dihydrofuran-3-yl)-2,3-diphenyl-propanoate.⁶⁸ Trifluoroacetic anhydride (TFAA, 40 μ L, 0.283 mmol) was added to a solution of DMSO (40 μ L, 0.563 mmol) in CH₂Cl₂ (1.5 mL) at -78 $^{\circ}$ C. After stirring for 0.5 h, alcohol (36.6 mg, dr 2:1, 85.5 μ mol) in CH₂Cl₂ (1.5 mL) was added dropwise. The reaction mixture was stirred at the same temperature for 2.5 h before NEt₃ (0.15 mL, 1.08 mmol) was added. After stirring for 2 h, the reaction mixture was quenched with water and extracted with CH₂Cl₂. The combined organic phase was washed brine, dried over Na₂SO₄, concentrated, and the residue was purified by column chromatography on silica gel (20% ethyl acetate in hexanes then 5% methanol in dichloromethane) to afford the pure product (19.7 mg, 46.2 μ mol, 54% yield). $[\alpha]_D^{23} +51.2^{\circ}$ (*c* 0.14, CHCl₃). ¹H NMR (500 MHz, Acetone-*d*₆) δ (ppm): 7.67-7.60 (m, 4H), 7.52-7.46 (m, 2H), 7.39-7.26 (m, 7H), 7.28-7.18 (m, 2H), 6.22 (s, 1H), 4.94 (d, *J*=12.2 Hz, 1H), 4.88 (d, *J*=12.2 Hz, 1H), 3.41 (s, 3H). ¹³C NMR (126 MHz, Acetone-*d*₆) δ (ppm): 206.2, 173.4, 169.2, 164.0, 143.3, 142.0, 138.4, 133.7, 131.0, 129.6, 129.5, 129.4, 129.3, 129.1, 129.0, 128.6, 127.9, 107.1, 104.5, 53.9, 52.1, 43.7, 30.2, 30.0, 29.8, 29.7, 29.5. HRMS-ESI (*m/z*): [M+Na]⁺ calcd for C₂₇H₂₂O₅Na, 449.1365; found, 449.1346.

HCl and extracted with ethyl acetate. The combined organic phase was sequentially washed with 1 M aqueous solution of HCl and brine, dried over Na₂SO₄, concentrated, and the residue was purified by column chromatography on silica gel (40% diethyl ether in hexanes with 0.5% acetic acid) to afford the pure product as a white crystalline solid (46 mg, 0.257 mmol, 76% yield). Ee: 90% (Chiralcel® OD-H; 1% *i*-PrOH in hexanes with 0.1% TFA; flow rate = 1.0 mL/min; detection at 215 nm; t₁=19.9 min; t₂=22.6 min). [α]_D²⁰ +24.2° (*c* 1.0, PhH). ¹H NMR (500 MHz, C₆D₆) δ (ppm): 7.23-7.20 (m, 2H), 7.05-7.01 (m, 2H), 6.98-6.94 (m, 1H), 2.00-1.92 (m, 1H), 1.83-1.75 (m, 1H), 1.36 (s, 3H), 0.64 (t, *J* = 7.4 Hz, 3H). ¹³C NMR (125 MHz, C₆D₆) δ (ppm): 183.4, 143.3, 128.7, 127.0, 126.6, 50.8, 32.0, 21.8, 9.2. LRMS-ESI (*m/z*): [M+Na]⁺ calcd for C₁₁H₁₄O₂Na, 201; found, 201.



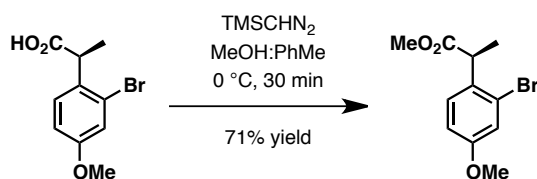
(S)-2-Methyl-2-phenyl-pent-4-enoic acid. A solution of *n*-BuLi (0.55 mL, 2.46 M in hexanes, 1.35 mmol, 4.0 equiv) was added dropwise to a solution of 2-phenylpropanoic acid (51 mg, 0.338 mmol) and (*R*)-¹TA (0.155 g, 0.346 mmol, 1.03 equiv) in THF (2.3 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 1 hour. The reaction mixture was then cooled to -78 °C and stirred for an additional 10 min. Allylbromide (0.12 ml, 1.35 mmol, 4.0 equiv) was added to the reaction mixture dropwise over 10 min. The resultant mixture was immediately quenched with a mixture of THF-MeOH (3:1, 1.0 mL) at -78 °C. After 5 min, the reaction mixture was acidified with 1 M aqueous solution of HCl and extracted with ethyl acetate. The combined organic phase was sequentially washed with 1 M aqueous solution of HCl and brine, dried over Na₂SO₄,

concentrated, and the residue was purified by column chromatography on silica gel (40% diethyl ether in hexanes with 0.5% acetic acid) to afford the pure product as a colorless film (51 mg, 0.270 mmol, 80% yield). Ee: 85% (Chiralcel® AD-H; 1% *i*-PrOH in hexanes with 0.1% TFA; flow rate = 1.0 mL/min; detection at 215 nm; $t_1=32.4$ min; $t_2=34.1$ min). $[\alpha]_D^{20} +50.5^\circ$ (*c* 1.0, EtOH). $^1\text{H NMR}$ (500 MHz, C_6D_6) δ (ppm): 7.23-7.18 (m, 2H), 7.05-7.00 (m, 2H), 6.98-6.93 (m, 1H), 5.52 (ddt, $J = 17.2, 10.1, 7.2$ Hz, 1H), 5.09 (m, 2H), 2.73 (ddt, $J = 13.8, 7.4, 1.2$ Hz, 1H), 2.52 (ddt, $J = 13.8, 17.1, 1.2$, 1H), 1.40 (s, 3H). $^{13}\text{C NMR}$ (125 MHz, C_6D_6) δ (ppm): 182.8, 142.8, 134.1, 128.7, 127.2, 126.5, 118.6, 50.0, 43.8, 22.2. LRMS-ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{12}\text{H}_{14}\text{O}_2\text{Na}$, 213; found, 213.

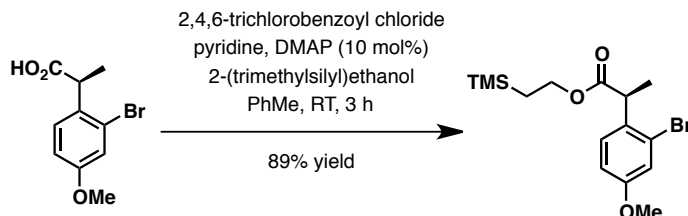


(S)-2-(2-bromo-4-methoxyphenyl)propanoic acid. A freshly titrated solution of *n*-BuLi (29.5 mL, 2.60 M in hexanes, 76.7 mmol, 4.0 eq) was added dropwise over 5 min to a solution of $(R)\text{-}^1\text{TA}$ (8.82 g, 19.7 mmol, 1.025eq) and *N*-(trimethylsilyl)-*tert*-butylamine⁷⁰ (7.35 mL, 38.4 mmol, 2.0 eq) in THF (100 mL) at -78°C and stirred 20 min. A solution of 2-bromo-4-methoxy phenylacetic acid (4.70 g, 19.2 mmol) in THF (22 mL) was added dropwise over 5 min and the reaction was stirred at -78°C for 20 min. The bright yellow solution was warmed to 0°C and stirred for 10 min. The resultant orange solution was cooled to -90°C and MeI (1.11 mL, 17.8 mmol, 0.9 eq) in THF (5 mL) was added dropwise over 1 min. The reaction was immediately quenched with a mixture of MeOH:THF (1:3, 25 mL) over 1 min at -90°C . After 5 min, the reaction mixture was warmed to room temperature, acidified with 1 M aqueous HCl to pH = 1, and extracted with EtOAc. The

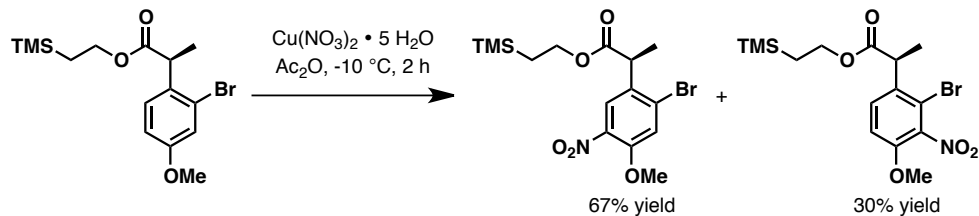
combined organic phase was sequentially washed with 1 M aqueous HCl and brine solution, dried over Na₂SO₄, concentrated, and the residue was purified by normal-phase column chromatography on silica gel (30% diethyl ether in hexanes with 0.5% AcOH) to afford the product as a light-orange solid (3.23 g, 12.5 mmol, 65% yield). $[\alpha]_D^{24} +40.7^\circ$ (*c* 1.0, CHCl₃). ¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.25 (d, *J* = 8.6 Hz, 1H), 7.12 (d, *J* = 2.7 Hz, 1H), 6.86 (dd, *J* = 8.6, 2.7 Hz, 1H), 4.21 (q, *J* = 7.2 Hz, 1H), 3.79 (s, 3H), 1.49 (d, *J* = 7.2 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃) δ (ppm): 179.5, 159.3, 131.6, 129.0, 124.9, 118.3, 114.3, 55.8, 43.8, 18.0. HRMS-EI⁺ (*m/z*): [M]⁺ calcd for C₁₀H₁₁BrO₃, 257.9892; found, 257.9890.



Methyl ester. A solution of TMSCHN₂ in hexanes (0.10 mL, 1.76 M in hexanes, 0.176 mmol, 4.6 eq) was added dropwise over 30 sec to a solution of acid (10.0 mg, 38.6 μ mol) in a mixture of MeOH:PhMe (1:3, 1.0 mL) at 0 °C. The resultant mixture was stirred for 30 min at this temperature and after concentrating, the residue was purified by normal-phase column chromatography on silica gel (10% EtOAc in hexanes) to afford methyl ester as a colorless oil (7.5 mg, 27.5 μ mol, 71% yield). Ee: 81% (Chiralcel® OD-H; 250mmx4.6mm, 1% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 210 nm; *t*₁ = 8.4 min; *t*₂ = 10.4 min). $[\alpha]_D^{21} +69.9^\circ$ (*c* 0.5, CHCl₃). ¹H NMR (500 MHz, CDCl₃) δ (ppm): 7.21 (d, *J* = 8.7 Hz, 1H), 7.11 (d, *J* = 2.6 Hz, 1H), 6.85 (dd, *J* = 8.7, 2.7 Hz, 1H), 4.15 (q, *J* = 7.2 Hz, 1H), 3.78 (s, 3H), 3.68 (s, 3H), 1.46 (d, *J* = 7.2 Hz, 3H). ¹³C NMR (126 MHz, CDCl₃) δ (ppm): 174.9, 159.2, 132.5, 128.9, 124.7, 118.4, 114.3, 55.8, 52.3, 44.0, 18.3. HRMS-EI⁺ (*m/z*): [M]⁺ calcd for C₁₀H₁₁BrO₃, 272.0048; found, 272.0058.



2-(Trimethylsilyl)ethyl ester. 2,4,6-trichlorobenzoyl chloride (3.86 mL, 24.7 mmol, 2.0 eq) was added to a solution of (*S*)-2-(2-bromo-4-methoxyphenyl)propanoic acid (3.20 g, 12.4 mmol) and pyridine (3.75 mL, 46.3 mmol, 3.75 eq) in PhMe (52 mL) at 0 °C. The solution was stirred for 1 h. Additional 2,4,6-trichlorobenzoyl chloride (1.35 mL, 8.65 mmol, 0.7 eq) and pyridine (3.75 mL, 46.3 mmol, 3.75 eq) were added and stirred another 1 h. A solution of DMAP (0.151 g, 1.24 mmol, 10 mol%) and 2-(trimethylsilyl)ethanol (8.85 mL, 61.8 mmol, 5.0 eq) in PhMe (10 mL) were added dropwise over 3 min and the solution was stirred at 0 °C for 15 min. The reaction was warmed up to room temperature and stirred for 3 h then it was diluted with brine solution and extracted with EtOAc. The combined organic phase was washed with brine, dried over Na₂SO₄, concentrated, and purified by normal-phase column chromatography on silica gel (5-10% EtOAc in hexanes) to afford the product as a colorless oil (3.95 g, 9.99 mmol, 89% yield). Ee: 81% (Chiralcel® OD-H; 250mmx4.6mm, 1% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 210 nm; *t*₁ = 6.2 min; *t*₂ = 6.7 min). [α]_D²⁰ +41.5° (*c* 1.0, CHCl₃). ¹H NMR (600 MHz, CDCl₃) δ (ppm): 7.22 (d, *J* = 8.6 Hz, 1H), 7.11 (d, *J* = 2.6 Hz, 1H), 6.84 (dd, *J* = 8.7, 2.6 Hz, 1H), 4.23-4.05 (m, 3H), 3.78 (s, 3H), 1.44 (d, *J* = 7.2 Hz, 3H), 1.00-0.90 (m, 2H), -0.01 (s, 9H). ¹³C NMR (151 MHz, CDCl₃) δ (ppm): 174.6, 159.1, 132.6, 128.9, 124.7, 118.2, 114.2, 63.4, 55.7, 44.2, 18.3, 17.4, -1.32. HRMS-EI⁺ (*m/z*): [M]⁺ calcd for C₁₅H₂₃BrO₃Si, 358.0600; found, 358.0609.

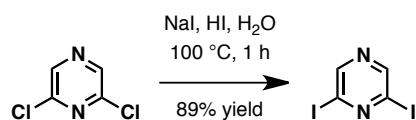


Ortho-nitrobromide. $\text{Cu}(\text{NO}_3)_2 \cdot 5 \text{H}_2\text{O}$ (1.13 g, 4.84 mmol, 1.2 eq) was added to Ac_2O (8.5 mL) under air atmosphere at 0°C and warmed up to RT. After 45 min, dissolution was complete and the bright blue mixture was cooled to -10°C . A solution of 2-(trimethylsilyl)ethyl ether (1.41 g, 4.04 mmol) in Ac_2O (5.0 mL) was added dropwise over 10 min, maintaining the reaction temperature below -5°C . The reaction mixture was stirred at -10°C for 2 h, quenched with H_2O and then extracted with EtOAc. The combined organic phase was dried over Na_2SO_4 and concentrated. The crude product was cooled to -10°C , dissolved in MeOH (50 mL), and stirred for 1 h at -10°C in order to remove the excess Ac_2O . After concentrating, the material was purified by normal-phase column chromatography on silica gel (5-15% EtOAc in hexanes) to afford the products.

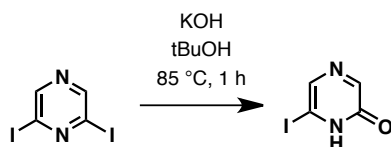
Para-nitrobromide: Isolated as a yellow oil that solidified upon standing (1.09 g, 2.70 mmol, 67% yield). ^1H NMR (500 MHz, CDCl_3) δ (ppm): 7.87 (s, 1H), 7.30 (s, 1H), 4.24-4.15 (m, 2H), 4.11 (q, $J = 7.2$ Hz, 1H), 3.96 (s, 3H), 1.51 (d, $J = 7.3$ Hz, 3H), 1.04-0.88 (m, 2H), 0.01 (s, 9H). ^{13}C NMR (126 MHz, CDCl_3) δ (ppm): 173.4, 152.1, 138.9, 133.1, 130.5, 125.6, 118.3, 63.9, 57.1, 44.3, 18.0, 17.5, -1.3. HRMS-EI⁺ (m/z): $[\text{M}]^+$ calcd for $\text{C}_{15}\text{H}_{22}\text{BrNO}_5\text{Si}$, 403.0451; found, 403.0449.

Ortho-nitrobromide: Isolated as a yellow oil that solidified upon standing (0.489 g, 1.21 mmol, 30% yield). Ee: 80% (Chiralcel® AD-H; 250mmx4.6mm, 1% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 210 nm; $t_1 = 12.1$ min; $t_2 = 16.7$ min). $[\alpha]_{\text{D}}^{20} +33.6^\circ$ (c 1.0, CHCl_3). ^1H NMR (500 MHz, CDCl_3) δ (ppm): 7.40 (d, $J = 8.9$ Hz, 1H), 7.00

Aniline: Isolated as a light-brown oil (46 mg, 0.267 mmol, 27% yield). ^1H NMR (500 MHz, CDCl_3); δ (ppm): 6.72 (d, $J = 8.2$ Hz, 1H), 6.68 (d, $J = 2.2$ Hz, 1H), 6.65 (dd, $J = 8.2$, 2.2 Hz, 1H), 4.23-4.04 (m, 2H), 3.82 (s, 3H), 3.72 (bs, 2H), 3.54 (q, $J = 7.1$ Hz, 1H), 1.43 (d, $J = 7.1$ Hz, 3H), 0.96-0.94 (m, 2H), 0.0 (s, 9H). ^{13}C NMR (126 MHz, CDCl_3); δ (ppm): 175.2, 146.6, 136.2, 133.6, 117.5, 114.3, 110.5, 63.0, 55.7, 45.2, 18.9, 17.4, -1.4. HRMS- EI^+ (m/z): $[\text{M}]^+$ calcd for $\text{C}_{15}\text{H}_{25}\text{NO}_3\text{Si}$, 295.1604; found, 295.1603.

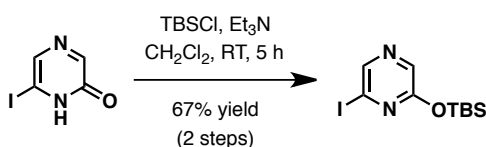


2,6-diiodopyrazine. Aqueous hydroiodic acid (15 mL, 47+%, ACS Reagent, stabilized with hypophosphorous acid) was added to 2,6-dichloropyrazine (3.0 g, 20.1 mmol) and sodium iodide (3.91 g, 26.1 mmol, 1.3 eq) in a 50 mL thick-walled Schlenk tube. The tube was sealed and it was heated at 100 °C for 1 h. After cooling, the reaction mixture was diluted with Et_2O and washed sequentially with water, sat. aq. NaHCO_3 , sat. aq. $\text{Na}_2\text{S}_2\text{O}_3$, and brine solutions. The organic phase was filtered through Na_2SO_4 and concentrated to yield 2,6-diiodopyrazine as a white solid (5.95 g, 17.9 mmol, 89% yield) that was used without further purification. ^1H NMR (500 MHz, CDCl_3) δ (ppm): 8.73 (s, 2H). ^{13}C NMR (126 MHz, CDCl_3) δ (ppm): 151.3, 116.8. HRMS- EI^+ (m/z): $[\text{M}]^+$ calcd for $\text{C}_4\text{H}_2\text{I}_2\text{N}_2$, 331.8307; found, 331.8309.

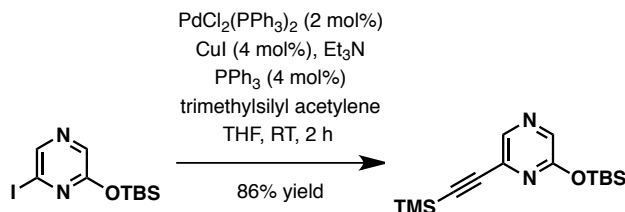


6-iodopyrazin-2-one. Potassium hydroxide (1.28 g, 22.9 mmol, 4.0 eq) was added to a solution of 2,6-diiodopyrazine (1.9 g, 5.72 mmol) in $t\text{BuOH}$ (19 mL) placed in a 50 mL thick-walled Schlenk tube at room temperature. The tube was sealed and heated at 85 °C for 1 h.

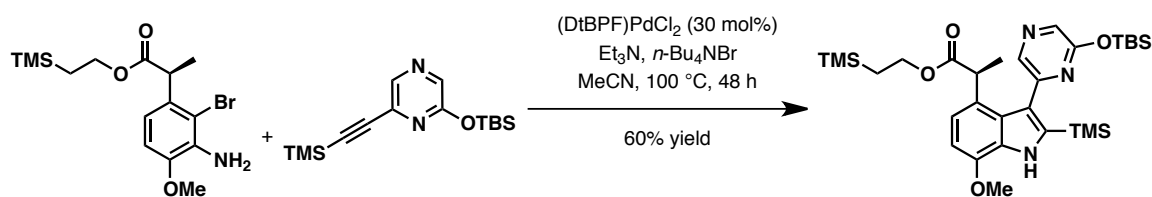
After cooling, the reaction mixture was acidified with 1M HCl and extracted with EtOAc (200 mL x 3). The combined organic phase was washed with brine, filtered through Na₂SO₄, and concentrated to yield an orange solid (~1.3 g). The crude pyrazinone was used in the subsequent reaction without further purification. ¹H NMR (500 MHz, DMSO-d₆) δ (ppm): 12.4 (bs, 1H), 8.33 (s, 1H), 8.10 (s, 1H). ¹³C NMR (126 MHz, DMSO-d₆) δ (ppm): 159.6, 141.7, 133.5, 112.5. HRMS-EI⁺ (*m/z*): [M]⁺ calcd for C₄H₃IN₂O, 221.9290; found, 221.9286.



Iodopyrazine. Triethylamine (3.3 mL, 23.4 mmol, 4.0 eq) and TBSCl (2.20 g, 14.6 mmol, 2.5 eq) were added sequentially to a solution of crude pyrazinone (1.3 g, 5.86 mmol) in CH₂Cl₂ (19.5 mL) at room temperature. The reaction mixture was stirred for 5 h at room temperature then diluted with water and extracted with CH₂Cl₂. The combined organic phase was washed with brine, filtered through Na₂SO₄, concentrated, and the residue was purified by normal-phase column chromatography on silica gel (5-10% EtOAc in hexanes) to afford the product as a colorless oil (1.28 g, 3.81 mmol, 67% yield). ¹H NMR (500 MHz, CDCl₃) δ (ppm): 8.37 (s, 1H), 8.04 (s, 1H), 0.97 (s, 9H), 0.32 (s, 6H). ¹³C NMR (126 MHz, CDCl₃) δ (ppm): 158.4, 144.5, 135.0, 112.6, 25.9, 18.3, 4.5. HRMS-EI⁺ (*m/z*): [M-C₄H₉]⁺ calcd for C₆H₈IN₂OSi, 278.9445; found, 278.9458.

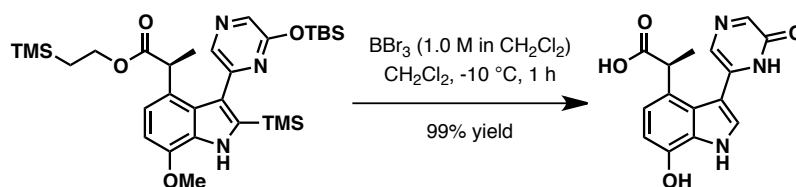


(Pyrazinyl)acetylene. Ethynyltrimethylsilane (0.58 mL, 4.10 mmol, 2.0 eq) was added to a solution of **S2.6** (2.30 g, 6.84 mmol), CuI (52 mg, 0.274 mmol, 4 mol%), PPh₃ (72 mg, 0.274 mmol, 4 mol%), PdCl₂(PPh₃)₂ (96 mg, 0.137 mmol, 2 mol%), and Et₃N (2.86 mL, 20.5 mmol, 3.0 eq) in THF (14 mL) at room temperature. The reaction was stirred for 2 h at room temperature and filtered through a 1 cm SiO₂ plug with EtOAc. After concentrating, the residue was purified by normal-phase column chromatography on silica gel (5% EtOAc in hexanes) to afford the product as a colorless oil (1.81 g, 5.89 mmol, 86% yield). Note: Store in freezer, decomposes slowly at room temperature on benchtop. ¹H NMR (500 MHz, CDCl₃) δ (ppm): 8.22 (s, 1H), 8.03 (s, 1H), 0.98 (s, 9H), 0.34 (s, 6H), 0.27 (s, 9H). ¹³C NMR (126 MHz, CDCl₃) δ (ppm): 158.4, 140.4, 136.5, 136.0, 101.3, 98.1, 25.9, 18.2, 0.13, -4.2. HRMS-EI⁺ (*m/z*): [M-C₄H₉]⁺ calcd for C₁₁H₁₇N₂OSi₂, 249.0874; found, 249.0883.



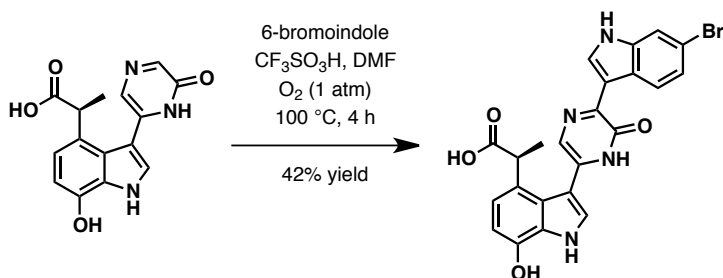
(Pyrazinyl)indole. A 1-dram vial was charged with freshly purified *ortho*-bromoaniline (45 mg, 0.120 mmol) and freshly purified (pyrazinyl)acetylene (90 mg, 0.295 mmol, 2.5 eq) without a stir bar. The 1-dram vial was placed in a glove-box and charged with PdCl₂(d'BPF) (23 mg, 35.3 μmol, 30 mol%) and *n*-tetrabutylammonium bromide (38 mg, 0.120 mmol, 1.0 eq). After removing from the glove-box, the reaction vial was charged with MeCN (1.2 mL) and Et₃N (84 μL, 0.60 mmol, 5.0 eq) through a Teflon-lined septa. The reaction was then sealed with a Teflon-lined cap and heated at 100 °C for 48 h. After cooling, the crude reaction mixture was filtered through a 1 cm silica gel plug with EtOAc, concentrated, and the residue was purified by normal-phase column chromatography on silica gel (7-12% EtOAc in hexanes) to deliver (pyrazinyl)indole as a light-brown foam (43

mg, 71.7 μmol , 60% yield). Ee: 81% (Chiralcel® AD-H; 250mmx4.6mm, 1% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 210 nm; t_1 = 8.6 min; t_2 = 12.2 min). $[\alpha]_D^{21} +94.9^\circ$ (*c* 1.0, CHCl_3). ^1H NMR (500 MHz, CDCl_3) δ (ppm): 8.45 (s, 1H), 8.23 (s, 1H), 8.14 (s, 1H), 6.93 (d, J = 8.0 Hz, 1H), 6.64 (d, J = 8.0 Hz, 1H), 4.06-3.87 (m, 2H), 3.98 (s, 3H), 3.78 (q, J = 7.1 Hz, 1H), 1.31 (d, J = 7.1 Hz, 3H), 1.00 (s, 9H), 0.84 (ddd, J = 9.7, 6.7, 2.4 Hz, 2H), 0.29 (s, 3H), 0.27 (s, 3H), 0.12 (s, 9H), -0.05 (s, 9H). ^{13}C NMR (126 MHz, CDCl_3) δ (ppm): 175.5, 158.2, 149.9, 145.1, 139.6, 136.9, 135.3, 129.0, 127.6, 126.3, 123.2, 118.5, 102.5, 62.8, 55.6, 40.5, 25.9, 18.8, 18.2, 17.3, -0.5, -1.4, -4.0, -4.2. HRMS- EI^+ (m/z): $[\text{M}]^+$ calcd for $\text{C}_{30}\text{H}_{49}\text{N}_3\text{O}_4\text{Si}_3$, 599.3031; found, 599.3043.

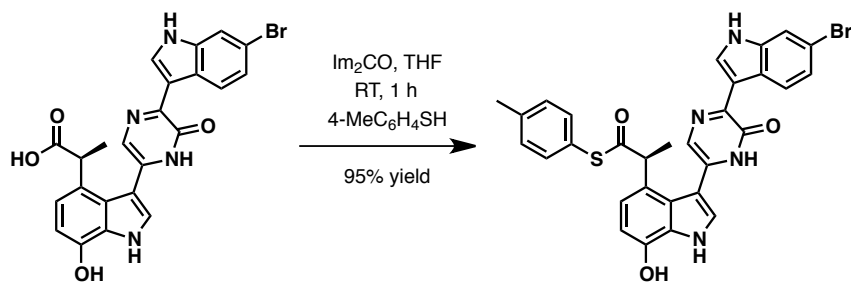


(Indolyl)pyrazinone. To a solution of (pyrazinyl)indole (190 mg, 0.317 mmol) in CH_2Cl_2 (3.2 mL) cooled to -10°C , was added BBr_3 (4.75 mL, 1.0 M in CH_2Cl_2 , 4.75 mmol, 15 eq) dropwise over 2 min. The deep purple reaction mixture was stirred at -10°C . After 1 h the reaction was quenched with H_2O (5 mL) and warmed to room temperature. After stirring approximately 30 min the solution color changed to dark red-orange. The CH_2Cl_2 was carefully removed via rotary evaporation and then the crude mixture was purified by reverse-phase column chromatography on silica gel (20% MeCN in H_2O with 0.1% TFA) to yield (indolyl)pyrazinone as a dark red solid (95 mg, 0.317 mmol, 99% yield). $[\alpha]_D^{23} +79.9^\circ$ (*c* 1.0, CH_3OH). ^1H NMR (500 MHz, CD_3OD) δ (ppm): 7.99 (s, 1H), 7.58 (s, 1H), 7.46 (s, 1H), 6.90 (d, J = 7.9 Hz, 1H), 6.60 (d, J = 8.0 Hz, 1H), 4.04 (q, J = 7.1 Hz, 1H), 1.42 (d, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, CD_3OD) δ (ppm): 179.0, 144.9, 144.4, 139.5, 128.6,

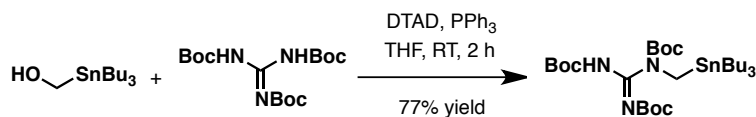
128.2, 127.0, 126.8, 125.1, 120.3, 108.5, 107.9, 107.6, 41.7, 18.6. HRMS-ESI⁺ (*m/z*): [M+Na]⁺ calcd for C₁₅H₁₃N₃O₄Na, 322.0804; found, 322.0797.



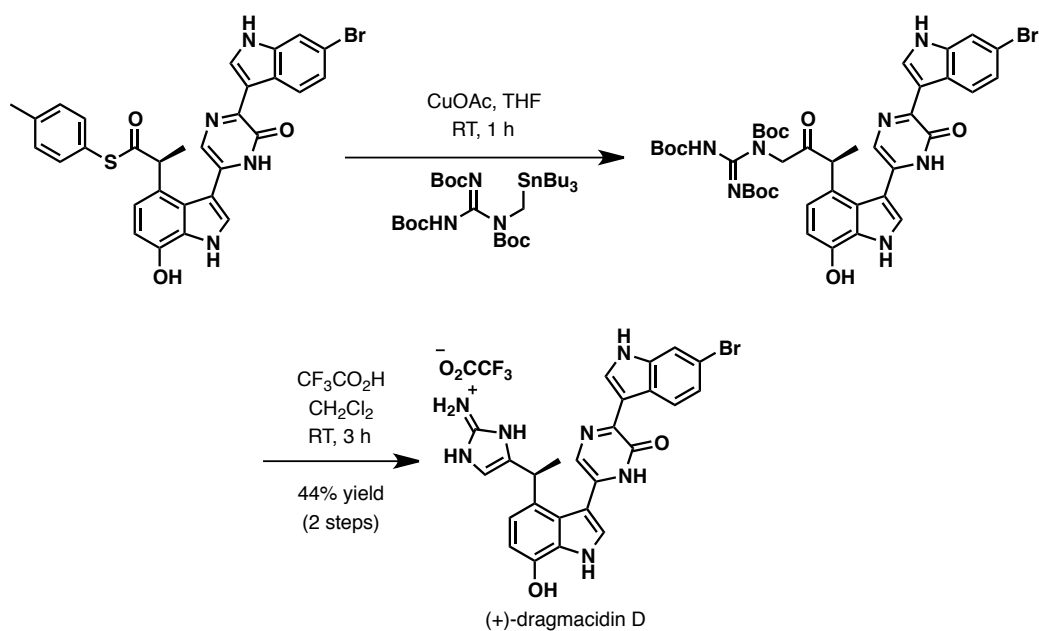
Bis-(indolyl)pyrazinone. A solution of TfOH in DMF (6.7 mL, 0.5 M in DMF, 3.34 mmol, 5.0 eq) was added to (indolyl)pyrazinone (95 mg, 0.317 mmol) and 6-bromoindole (0.262 g, 1.34 mmol, 2.0 eq) in a 25 mL round-bottom flask protected from light. The reaction mixture was placed under an atmosphere of O₂ and heated in the dark at 100 °C for 4 h. After cooling the crude reaction mixture was diluted with EtOAc, washed sequentially with water and brine, dried over Na₂SO₄, concentrated and purified by reverse-phase column chromatography on silica gel (50-60% MeCN in H₂O with 0.1% TFA) to deliver bis-(indolyl)pyrazinone as a orange-red solid (65 mg, 0.132 mmol, 42% yield). [α]_D²⁰ +83.4° (*c* 1.0, CH₃OH). ¹H NMR (500 MHz, CD₃OD) δ (ppm): 8.73 (s, 1H), 8.55 (d, *J* = 8.6 Hz, 1H), 7.62 (s, 1H), 7.61 (d, *J* = 1.8 Hz, 1H), 7.45 (s, 1H), 7.28 (dd, *J* = 8.6, 1.8 Hz, 1H), 6.90 (d, *J* = 7.9 Hz, 1H), 6.60 (d, *J* = 7.9 Hz, 1H), 4.13 (q, *J* = 7.1 Hz, 1H), 1.44 (d, *J* = 7.1 Hz, 3H). ¹³C NMR (126 MHz, CD₃OD) δ (ppm): 179.1, 157.2, 149.7, 144.3, 138.9, 132.8, 132.6, 128.5, 127.9, 127.2, 126.4, 125.3, 125.2, 125.1, 124.8, 120.0, 117.0, 115.4, 113.1, 108.6, 107.5, 41.6, 18.7. HRMS-ESI⁺ (*m/z*): [M+Na]⁺ calcd for C₂₃H₁₇BrN₄O₄Na, 515.0331; found, 515.0336.



Thioester. 1,1'-Carbonyldiimidazole (89 mg, 0.549 mmol, 5.0 eq) was added to a solution of bis-(indolyl)pyrazinone (54 mg, 0.110 mmol) in THF (3.6 mL) at room temperature. The reaction mixture was stirred 1 h at room temperature then 4-methylbenzenethiol (0.204 g, 1.64 mmol, 15 eq) was added and stirred was continued for an additional 2 h. The crude reaction mixture was diluted with water then extracted with EtOAc. The combined organic phase was washed with brine, dried over Na₂SO₄, concentrated and purified by reverse-phase column chromatography on silica gel (60% MeCN in H₂O with 0.1% TFA) to deliver thioester as a dark red solid (62 mg, 0.104 mmol, 95% yield). $[\alpha]_D^{24} +297.8^\circ$ (*c* 0.5, CH₃OH). ¹H NMR (500 MHz, CD₃OD) δ (ppm): 8.71 (s, 1H), 8.56 (d, *J* = 8.6 Hz, 1H), 7.61 (s, 1H), 7.59 (d, *J* = 1.8 Hz, 1H), 7.46 (s, 1H), 7.25 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.08 (s, 4H), 6.91 (d, *J* = 8.0 Hz, 1H), 6.63 (d, *J* = 7.9 Hz, 1H), 4.40 (q, *J* = 7.0 Hz, 1H), 2.27 (s, 3H), 1.56 (d, *J* = 7.1 Hz, 3H). ¹³C NMR (126 MHz, CD₃OD) δ (ppm): 202.2, 144.8, 140.4, 138.9, 135.5, 132.4, 132.0, 130.7, 128.4, 127.8, 127.7, 126.5, 126.4, 126.3, 126.1, 125.4, 124.7, 123.2, 121.1, 116.9, 115.3, 113.4, 108.7, 107.4, 106.4, 50.3, 21.2, 18.9. HRMS-ESI⁺ (*m/z*): [M+Na]⁺ calcd for C₃₀H₂₃BrN₄O₃SNa, 621.0572; found, 621.0567.

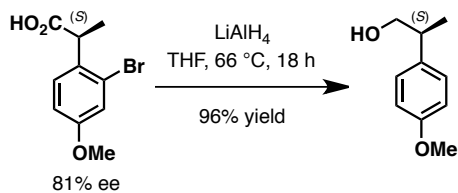


***N,N',N''*-tri-Boc-(tributylstannylmethyl)guanidine.** Di-tert-butyl azodicarboxylate (0.282 g, 1.22 mmol, 1.0 eq) was added portion wise to a mixture of tri-*n*-butylstannylmethanol (0.393 g, 1.22 mmol), tri-Boc-guanidine (0.440 g, 1.22 mmol, 1.0 eq), and PPh₃ (0.321 g, 1.22 mmol, 1.0 eq) in THF (5.0 mL) at room temperature. After stirring for 2 h, the reaction was quenched with water and extracted with EtOAc. The combined organic phase was washed with brine, filtered through Na₂SO₄, concentrated, and the residue was purified by normal-phase column chromatography on silica gel (2% EtOAc in hexanes) to afford the pure product as a colorless oil (0.623 g, 0.941 mmol, 77% yield). ¹H NMR (500 MHz, CDCl₃) δ (ppm): 10.64 (s, 1H), 3.42 (s, 2H), 1.56-1.39 (m, 33H), 1.33-1.22 (m, 6H), 0.96-0.79 (m, 15H). ¹³C NMR (126 MHz, CDCl₃) δ (ppm): 154.42, 151.4, 83.5, 82.2, 80.0, 34.5, 29.2, 28.3, 28.2, 27.6, 13.9, 10.4. HRMS-ESI⁺ (*m/z*): [M+Na]⁺ calcd for C₂₉H₅₇N₃O₆SnNa, 682.3163; found, 682.3161.



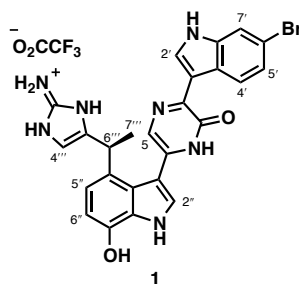
(+)-Dragmacidin D. A 25 mL round-bottomed flask, charged with *N,N',N''*-tri-Boc-(tributylstannylmethyl)guanidine (0.205 g, 0.309 mmol, 5.0 eq) was placed in a glove box and charged with CuOAc (38 mg, 0.309 mmol, 5.0 eq). The flask was removed from the

glove box and charged with a solution of thioester (37 mg, 61.9 μmol) in THF (6.2 mL) through a rubber septa. The orange heterogeneous solution was stirred at room temperature for 1.5 h. The reaction was quenched with saturated aqueous NH_4Cl and stirred for an additional 30 min at room temperature. The crude mixture was extracted with EtOAc, washed with brine, dried over Na_2SO_4 , concentrated and purified by normal-phase column chromatography on silica gel (3-4% MeOH in CH_2Cl_2) to deliver tri-Boc-guanidinyll ketone as a bright yellow solid (39 mg), which also contained inseparable tin by-products and was used without further purification. Note: tri-Boc-guanidinyll ketone begins to decompose rapidly at room temperature on benchtop after ~ 12 h. To a solution of crude tri-Boc-guanidinyll ketone (34 mg) in CH_2Cl_2 (2.0 mL) was added TFA (0.40 mL) at room temperature. The dark-red solution was stirred at room temperature for 3 h then concentrated and purified by reverse-phase HPLC (YMC-ODS-AM column, 250mmx20mm, 210 nm, 40% MeCN in H_2O with 0.1% TFA, 7 mL/min, $t = 15$ min) to deliver dragmacidin D as a bright red film (15 mg, 23.3 μmol , 44% yield). Ee: 61% (Lux® 5u Amylose-2; 250mmx4.6mm, 15% EtOH in hexanes with 0.1% TFA; flow rate = 1.0 mL/min; detection at 210 nm; $t_1 = 7.3$ min; $t_2 = 9.1$ min). $[\alpha]_{\text{D}}^{21} +69.1^\circ$ (c 1.0, CH_3OH), $+106.3^\circ$ (c 0.95, EtOH). ^1H NMR (500 MHz, CD_3OD) δ (ppm): 8.72 (s, 1H), 8.58 (d, $J = 8.6$ Hz, 1H), 7.60 (d, $J = 1.8$ Hz, 1H), 7.47 (s, 1H), 7.44 (s, 1H), 7.26 (dd, $J = 8.6, 1.8$ Hz, 1H), 6.83 (d, $J = 7.9$ Hz, 1H), 6.63 (d, $J = 7.9$ Hz, 1H), 5.97 (s, 1H), 4.34 (q, $J = 6.9$ Hz, 1H), 1.52 (d, $J = 6.9$ Hz, 3H). ^{13}C NMR (126 MHz, CD_3OD) δ (ppm): 157.0, 150.1, 148.6, 144.7, 138.9, 134.0, 132.4, 132.1, 128.6, 127.8, 127.1, 126.5, 126.0, 125.5, 125.4, 124.7, 120.0, 116.9, 115.3, 113.5, 110.0, 108.8, 107.2, 33.0, 20.6. HRMS-ESI⁺ (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{25}\text{H}_{21}\text{BrN}_7\text{O}_2$, 530.0935; found, 530.0941.



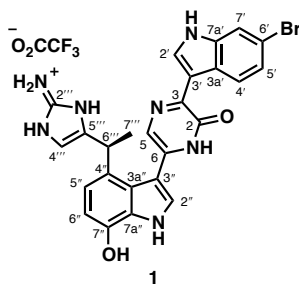
Alcohol.⁷¹ A solution of (*S*)-2-(2-bromo-4-methoxyphenyl)propanoic acid (0.167 g, 0.644 mmol) in THF (3.0 mL) was added dropwise over 1 min to a mixture of LiAlH₄ (49 mg, 1.29 mmol, 2.0 eq) in THF (3.4 mL) cooled to 0 °C. A reflux condenser was attached and the reaction was refluxed for 18 h. After cooling to 0 °C, 50 μL of H₂O was added, then 50 μL of 3M NaOH was added, followed by 0.150 mL H₂O. The solution was warmed to room temperature and filtered. After concentrating, the residue was purified by normal-phase column chromatography on silica gel (40% EtOAc in hexanes) to afford the pure product as a colorless oil (0.103 g, 0.620 mmol, 96% yield). $[\alpha]_D^{21} -13.1^\circ$ (*c* 2.1, CHCl₃). ¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.17 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 3.80 (s, 3H), 3.70-3.63 (m, 2H), 2.96-2.87 (m, 1H), 1.25 (d, *J* = 7.1 Hz, 3H). ¹³C NMR (126 MHz, CDCl₃) δ (ppm): 158.5, 135.8, 128.5, 114.2, 68.9, 55.4, 41.7, 17.9. HRMS-ESI⁺ (*m/z*): [M+Na]⁺ calcd for C₁₀H₁₄O₂Na, 189.0891; found, 189.0895.

Table S1. Comparison of ^1H NMR Data of Synthetic and Natural dragmaclidin D (CD_3OD)

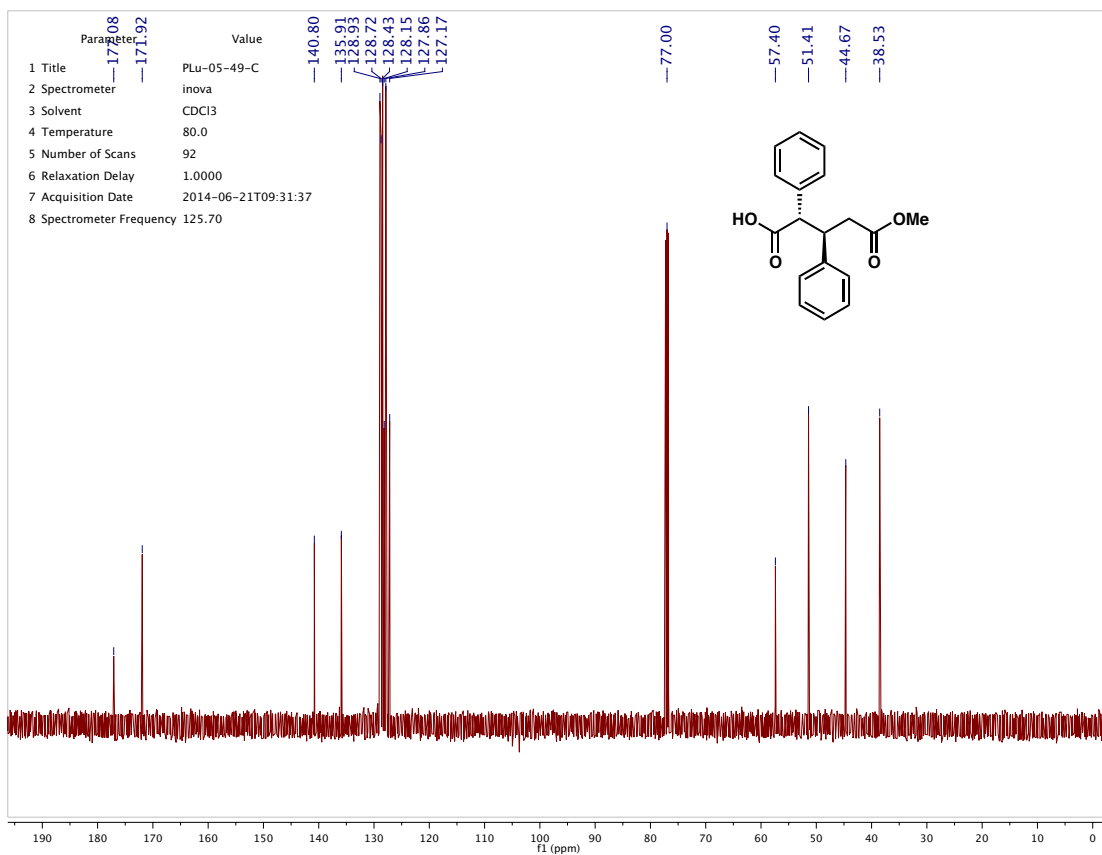
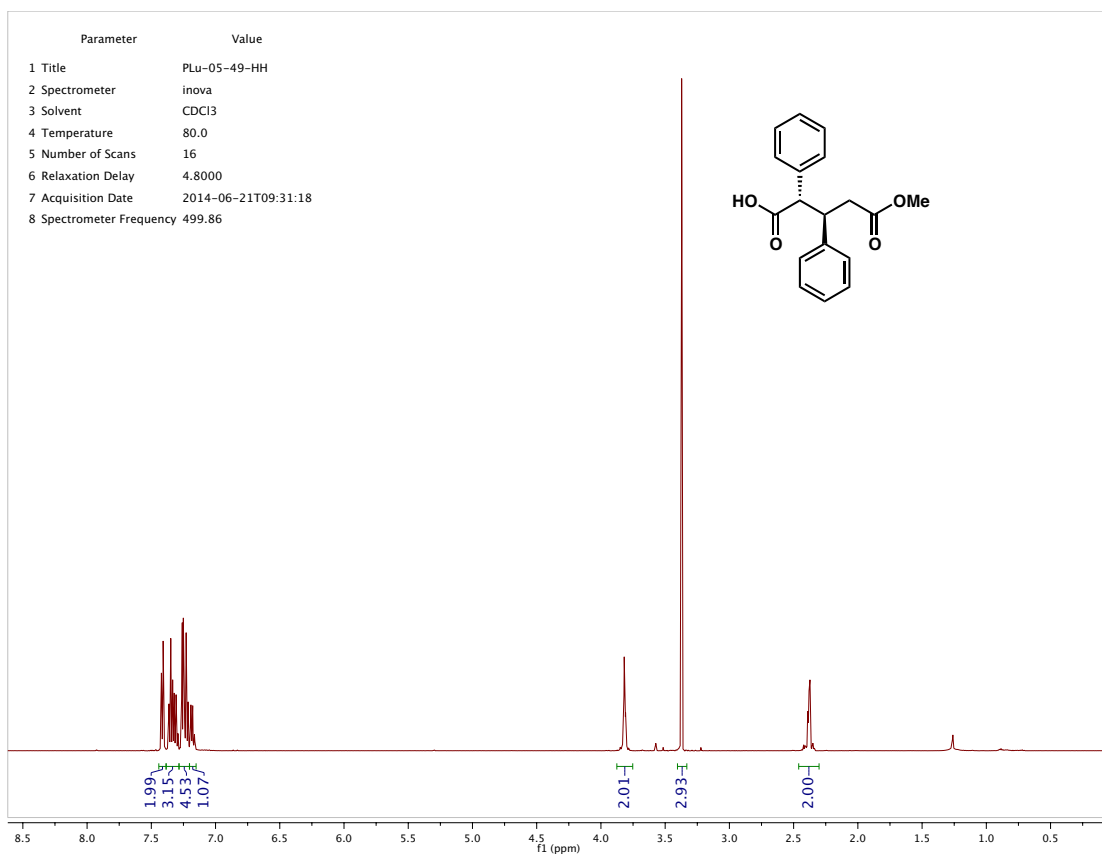


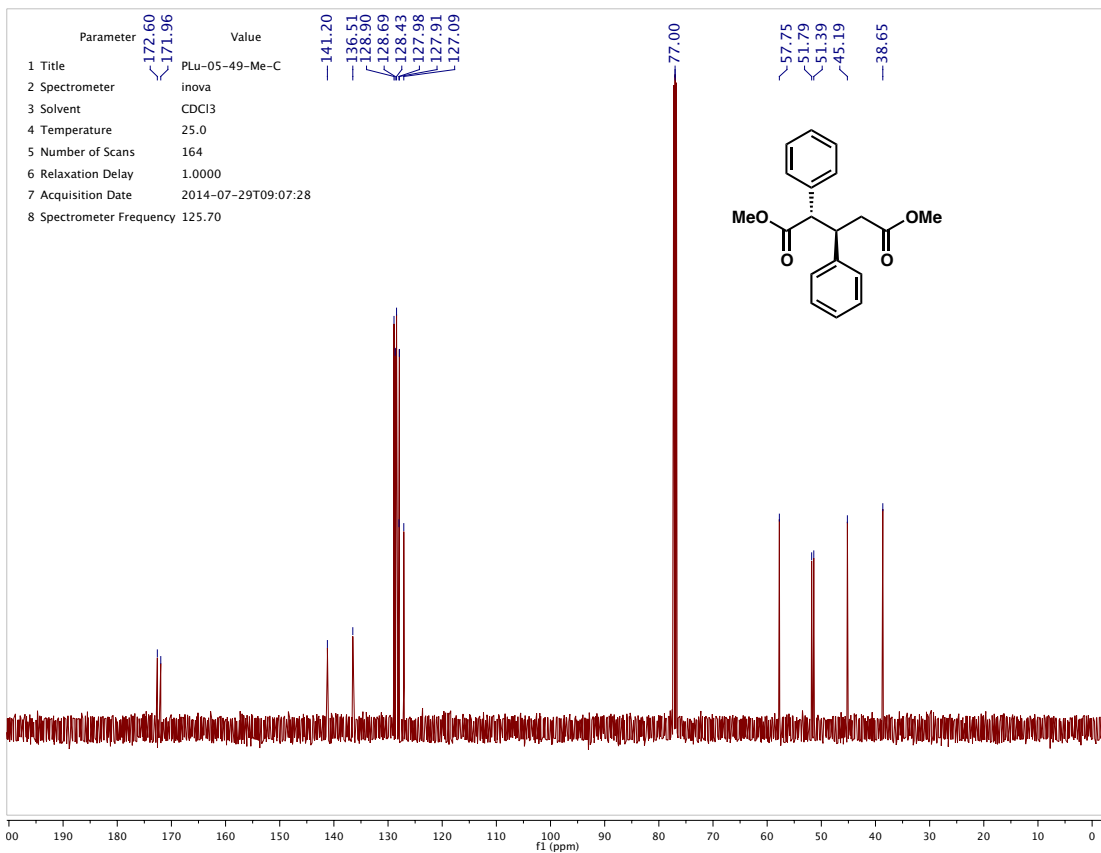
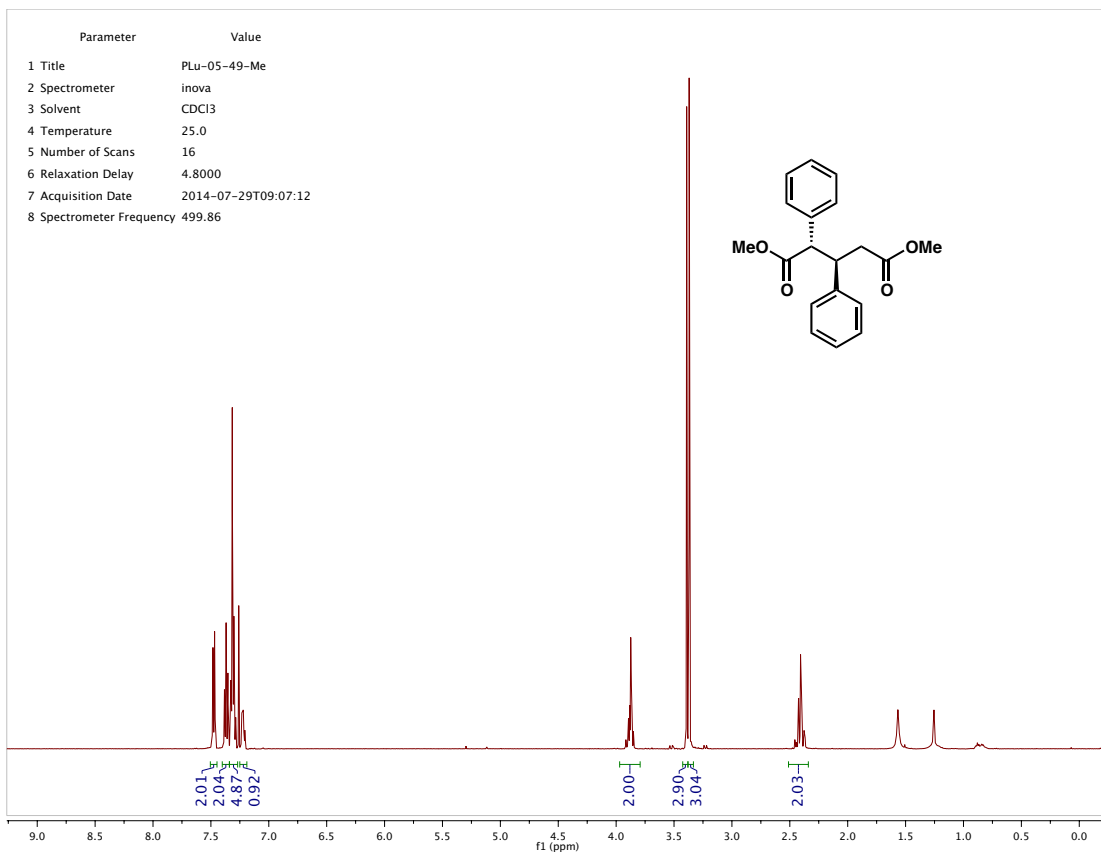
Position	Synthetic dragmaclidin D (600 MHz)	Reported for natural dragmaclidin D ⁷²
5	7.47 (s, 1H)	7.51 (s, 1H)
2'	8.72 (s, 1H)	8.67 (s, 1H)
4'	8.58 (d, $J = 8.6$ Hz, 1H)	8.55 (d, $J = 8.6$ Hz, 1H)
5'	7.26 (dd, $J = 8.6, 1.8$ Hz, 1H)	7.34 (dd, $J = 8.6, 1.8$ Hz, 1H)
7'	7.60 (d, $J = 1.8$ Hz, 1H)	7.68 (d, $J = 1.8$ Hz, 1H)
2''	7.44 (s, 1H)	7.43 (s, 1H)
5''	6.83 (d, $J = 7.9$ Hz, 1H)	6.85 (d, $J = 7.9$ Hz, 1H)
6''	6.63 (d, $J = 7.9$ Hz, 1H)	6.65 (d, $J = 7.9$ Hz, 1H)
4''	5.97 (s, 1H)	6.05 (s, 1H)
6'''	4.34 (q, $J = 6.9$ Hz, 1H)	4.35 (q, $J = 6.9$ Hz, 1H)
7'''	1.52 (d, $J = 6.9$ Hz, 3H)	1.54 (d, $J = 6.9$ Hz, 3H)

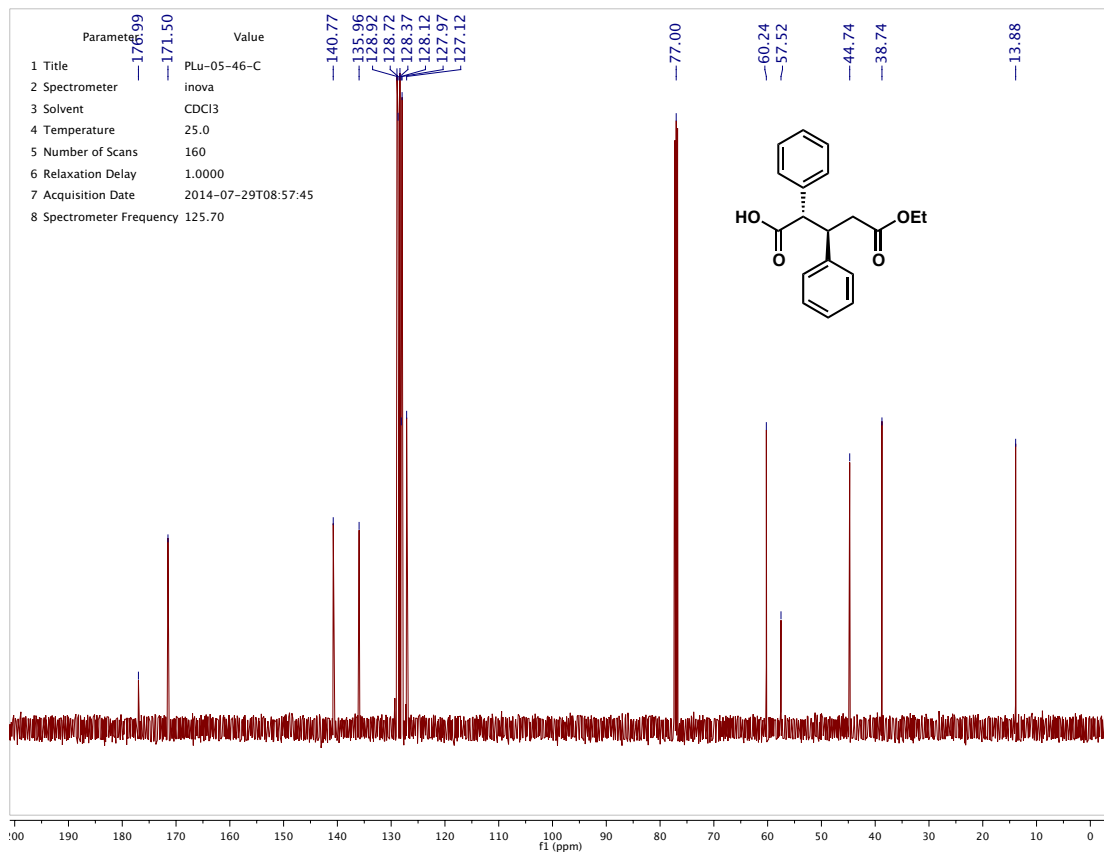
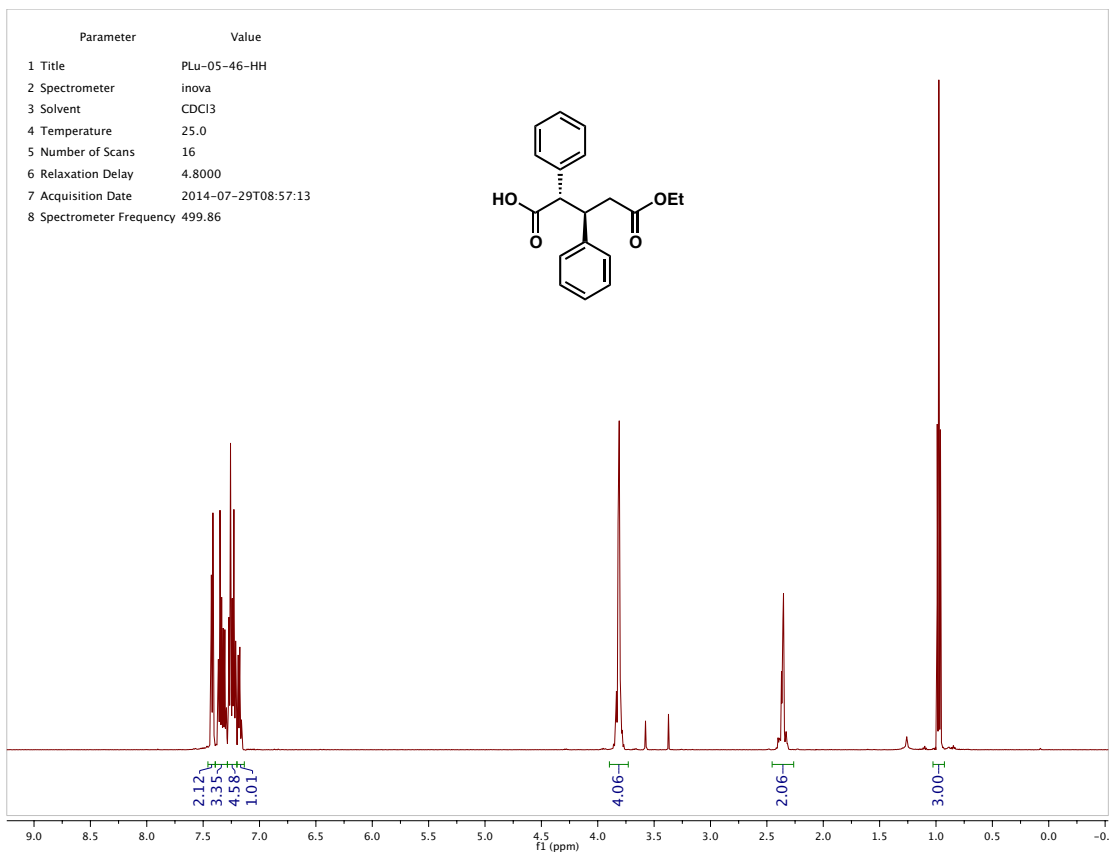
Table S2. Comparison of ^{13}C NMR Data of Synthetic and Natural dragmacidin D
(CD_3OD)

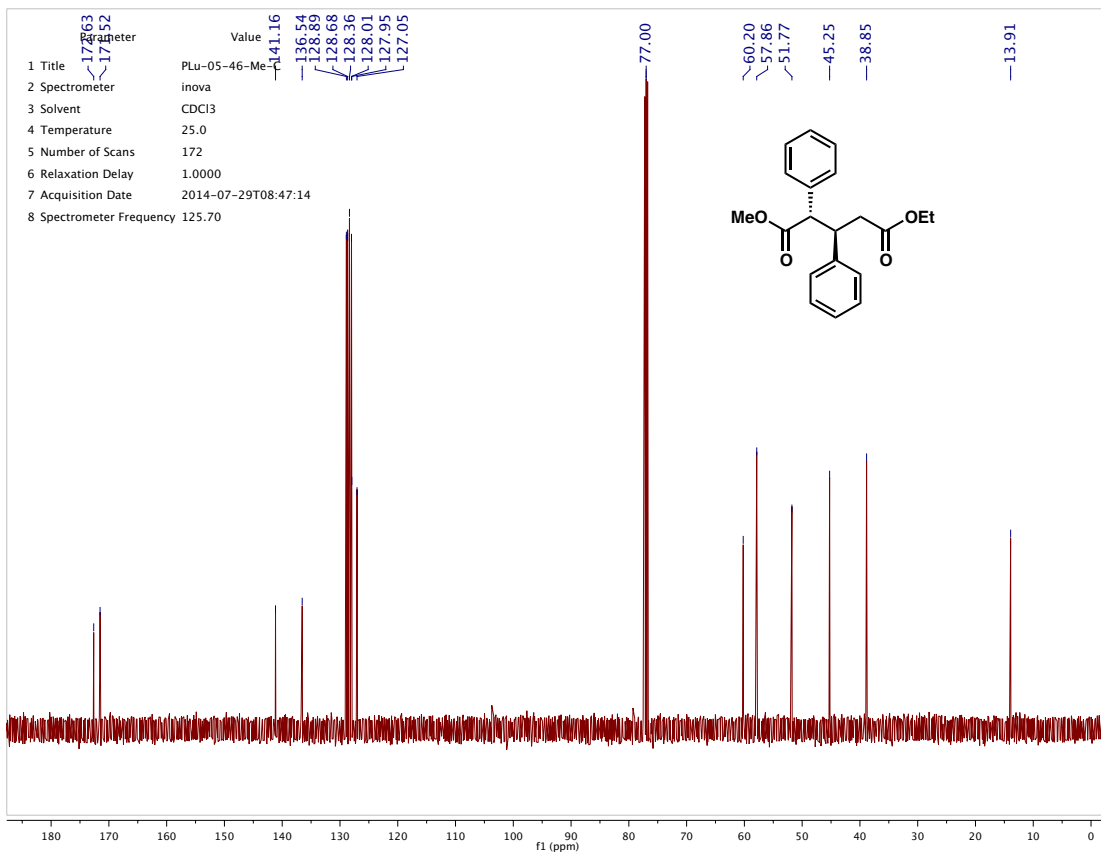
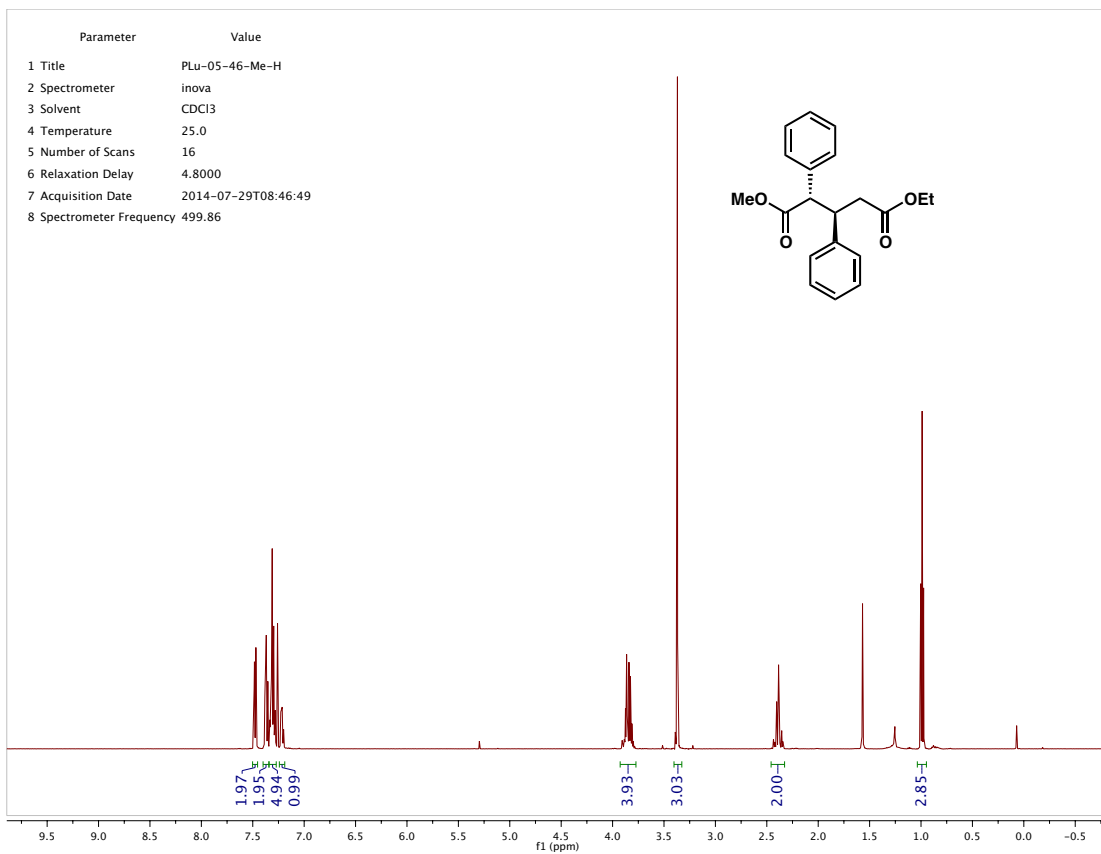


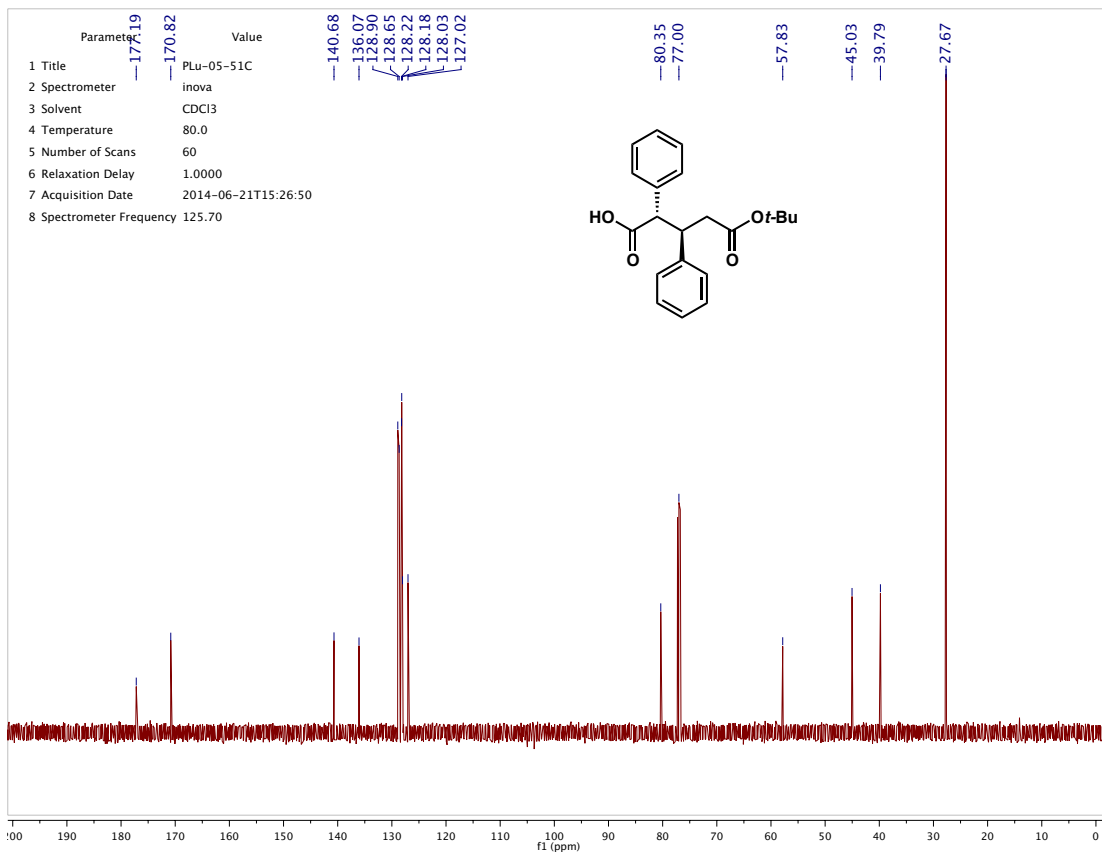
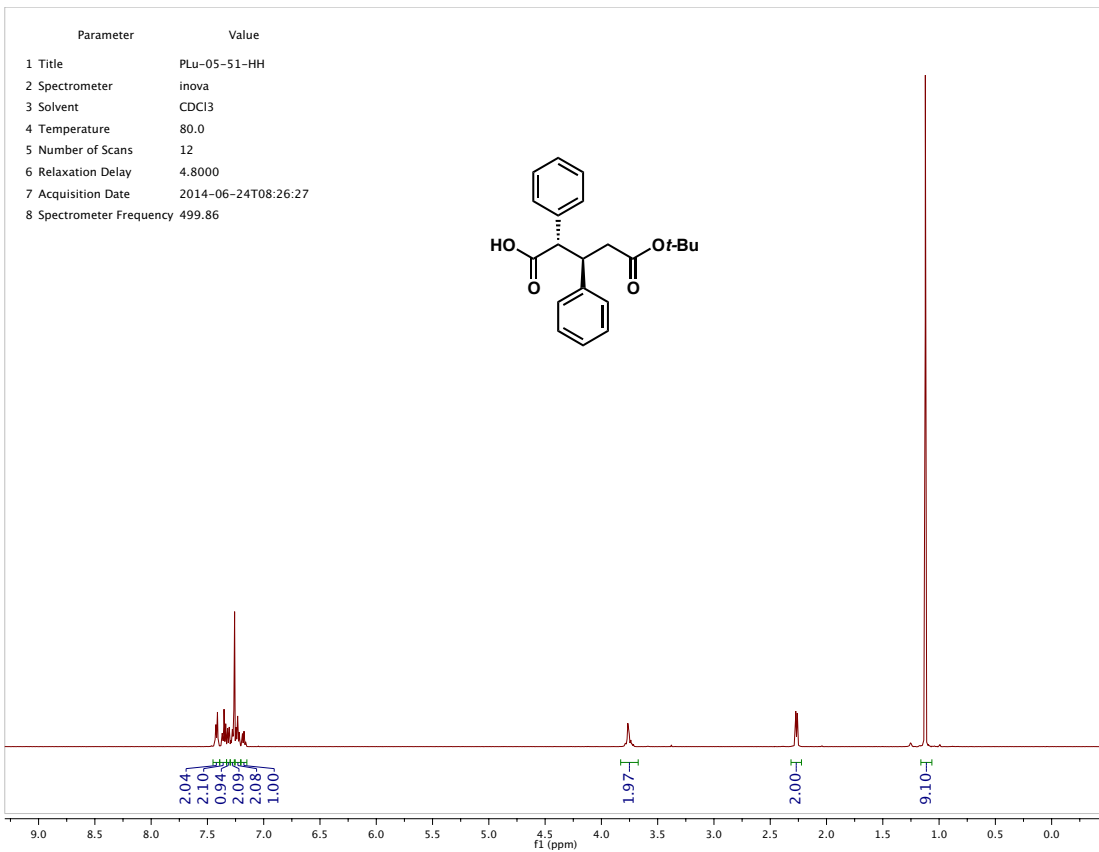
Position	Synthetic dragmacidin D (201 MHz)	Reported for natural dragmacidin D ³
2	157.0	157.0
3	150.1	149.8
5	125.5	125.4
6	132.1	132.2
2'	132.4	133.6
3'	113.5	113.1
3a'	126.5	126.3
4'	125.4	125.3
5'	124.7	124.8
6'	116.9	116.9
7'	115.3	115.3
7a'	138.9	138.8
2''	127.8	127.8
3''	108.7	108.5
3a''	127.1	126.9
4''	126.0	125.6
5''	120.0	120.0
6''	107.2	107.4
7''	144.7	144.4
7a''	128.6	128.5
2'''	148.6	148.5
4'''	110.0	109.9
5'''	134.0	133.8
6'''	33.0	33.0
7'''	20.6	20.6

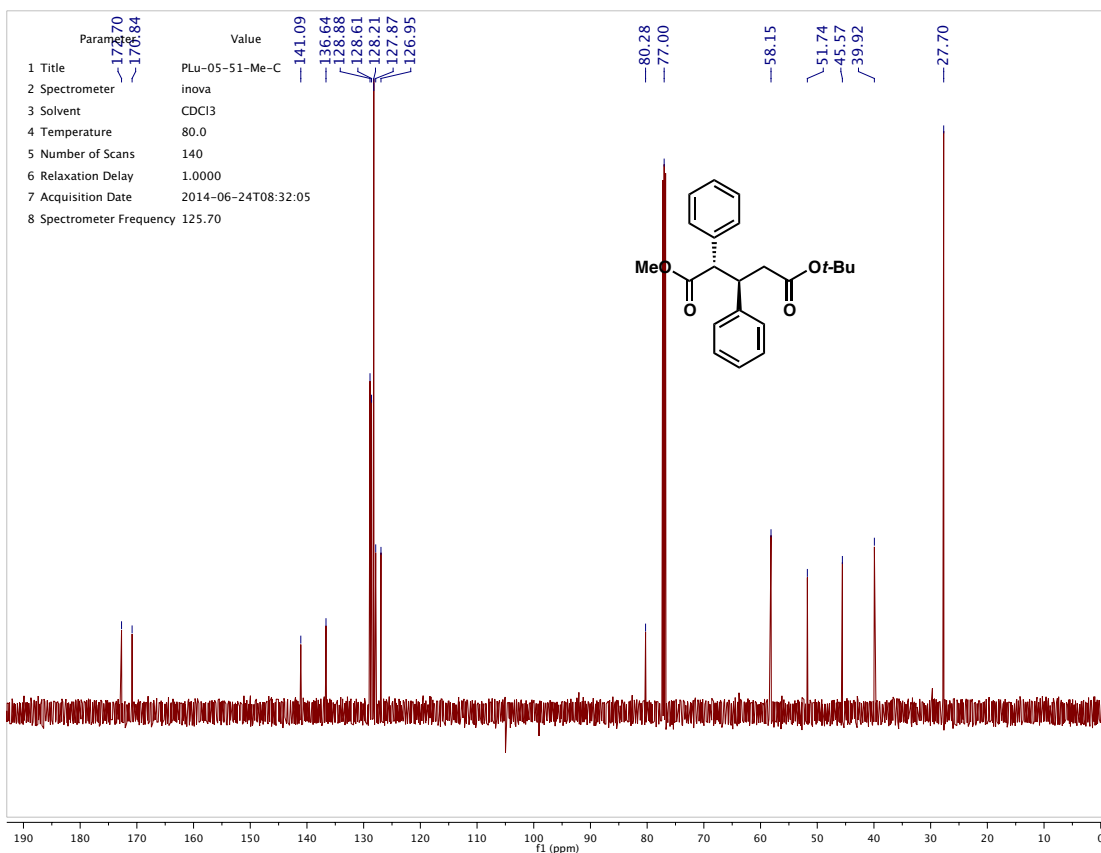
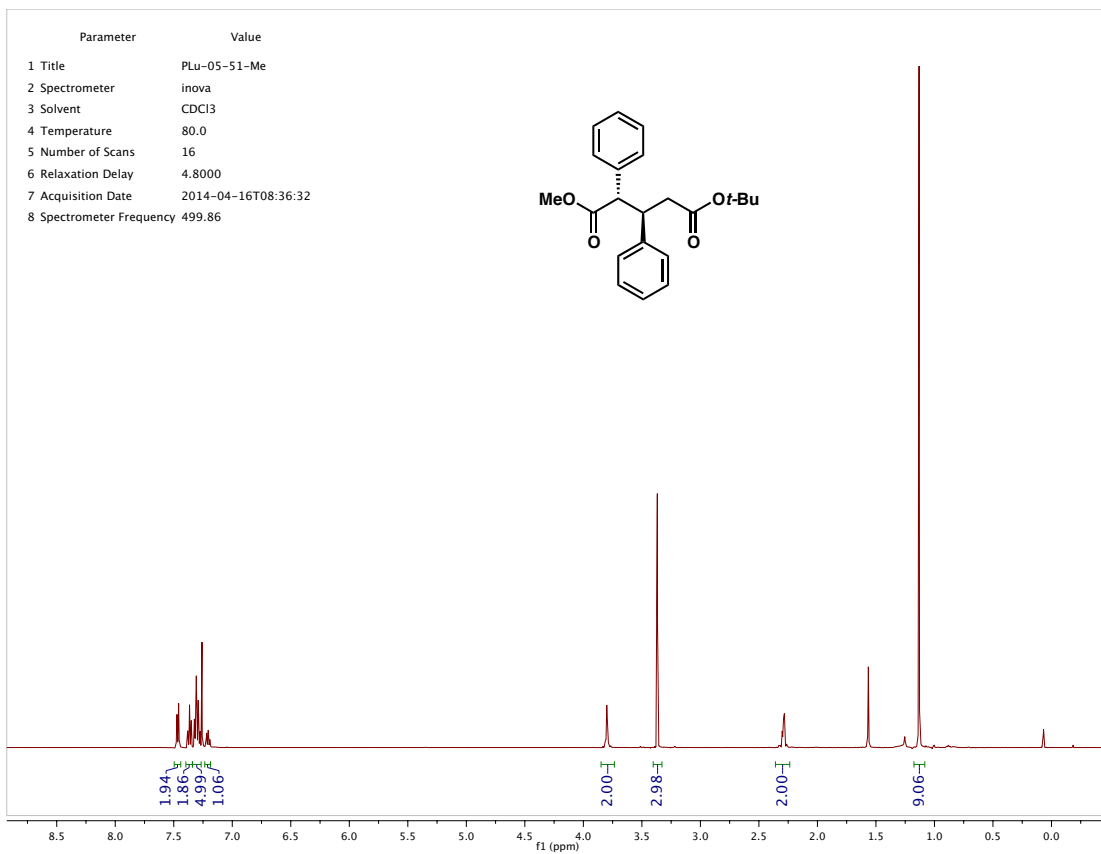


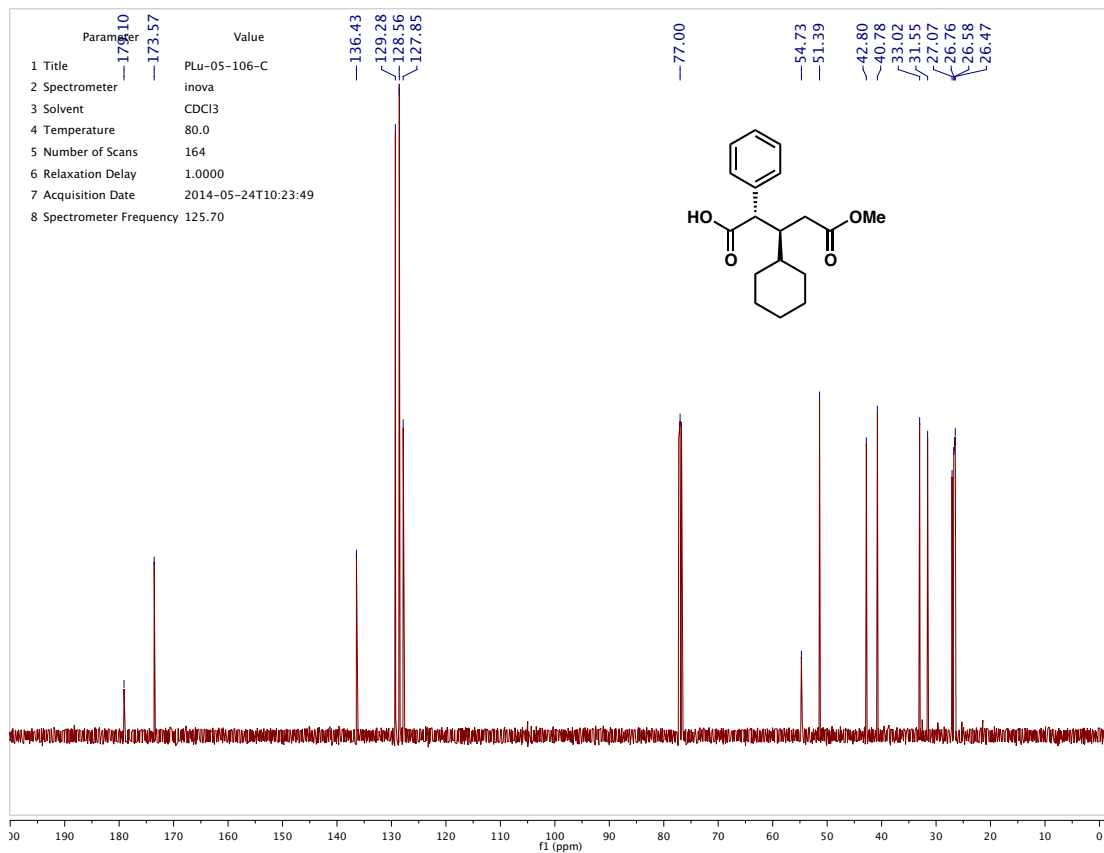
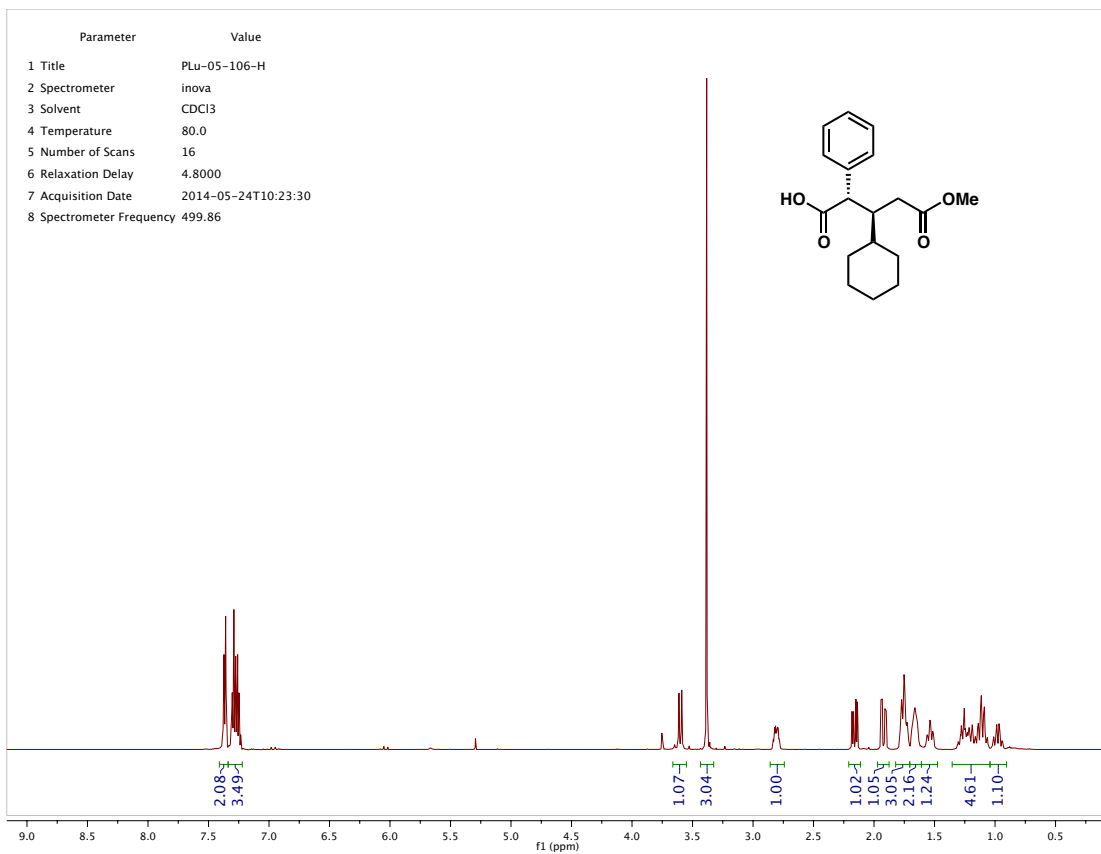


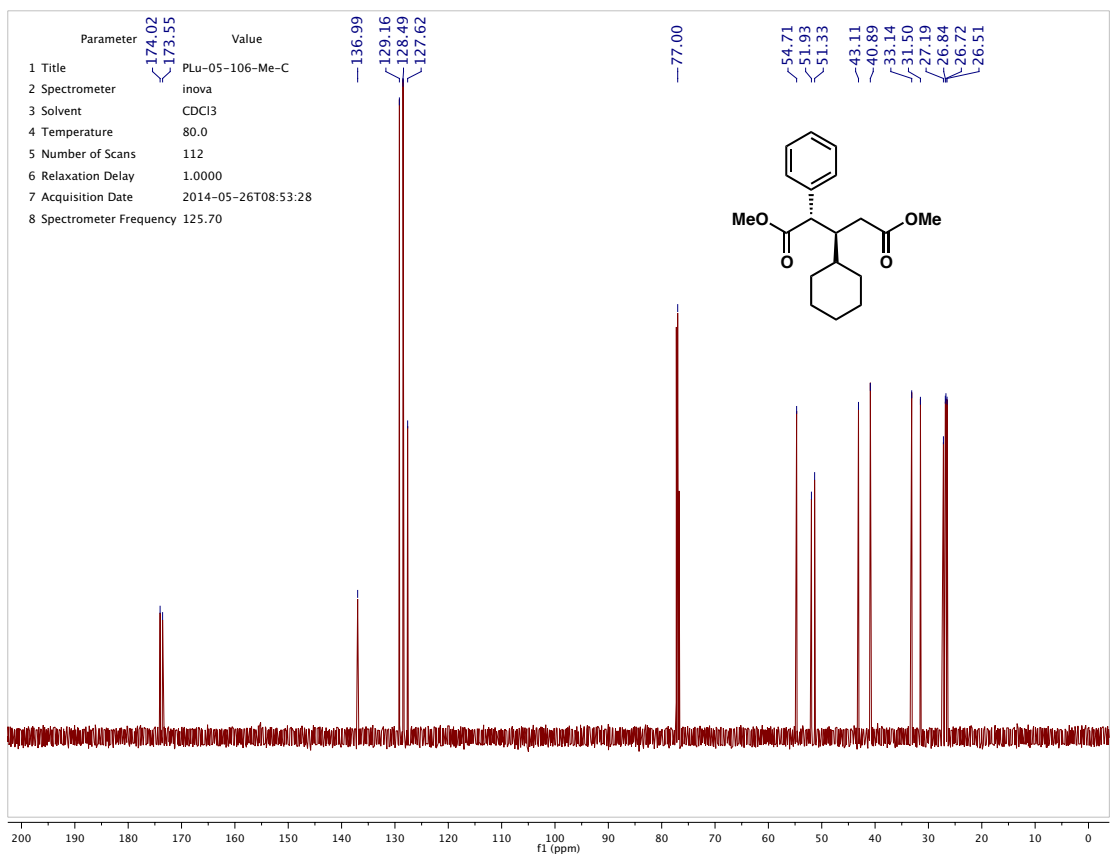
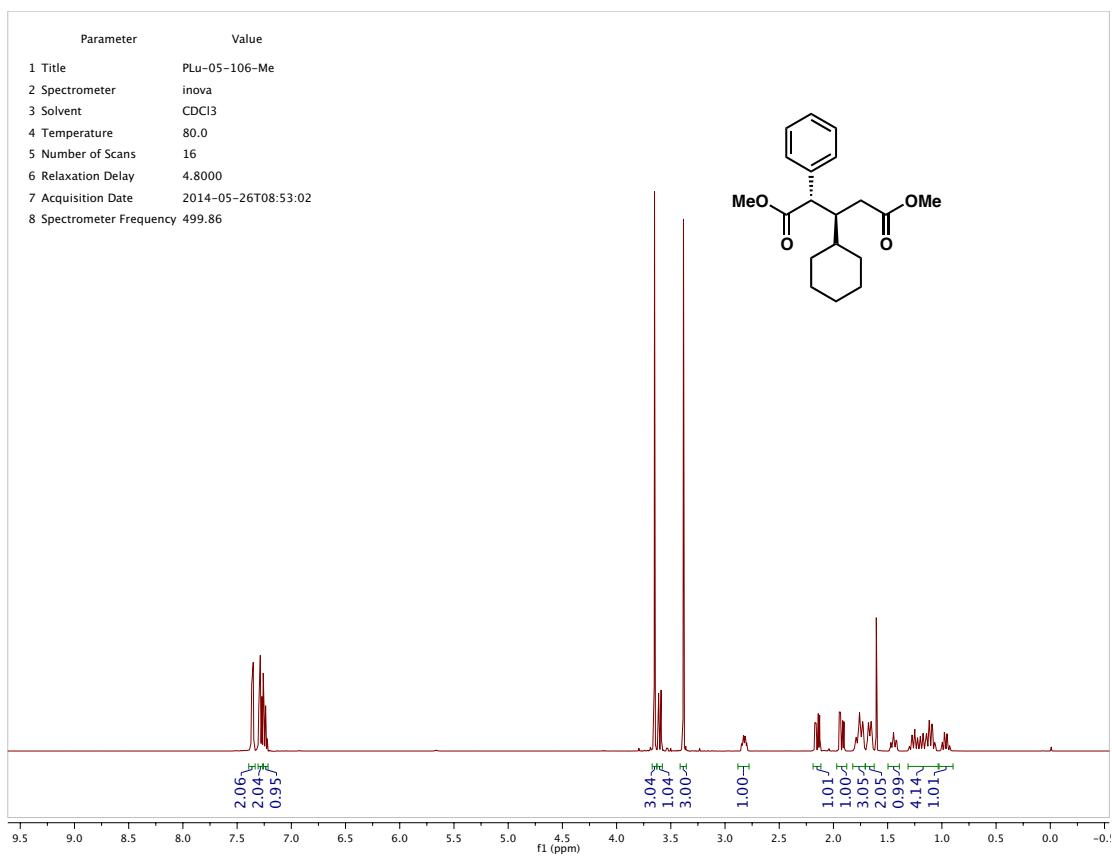


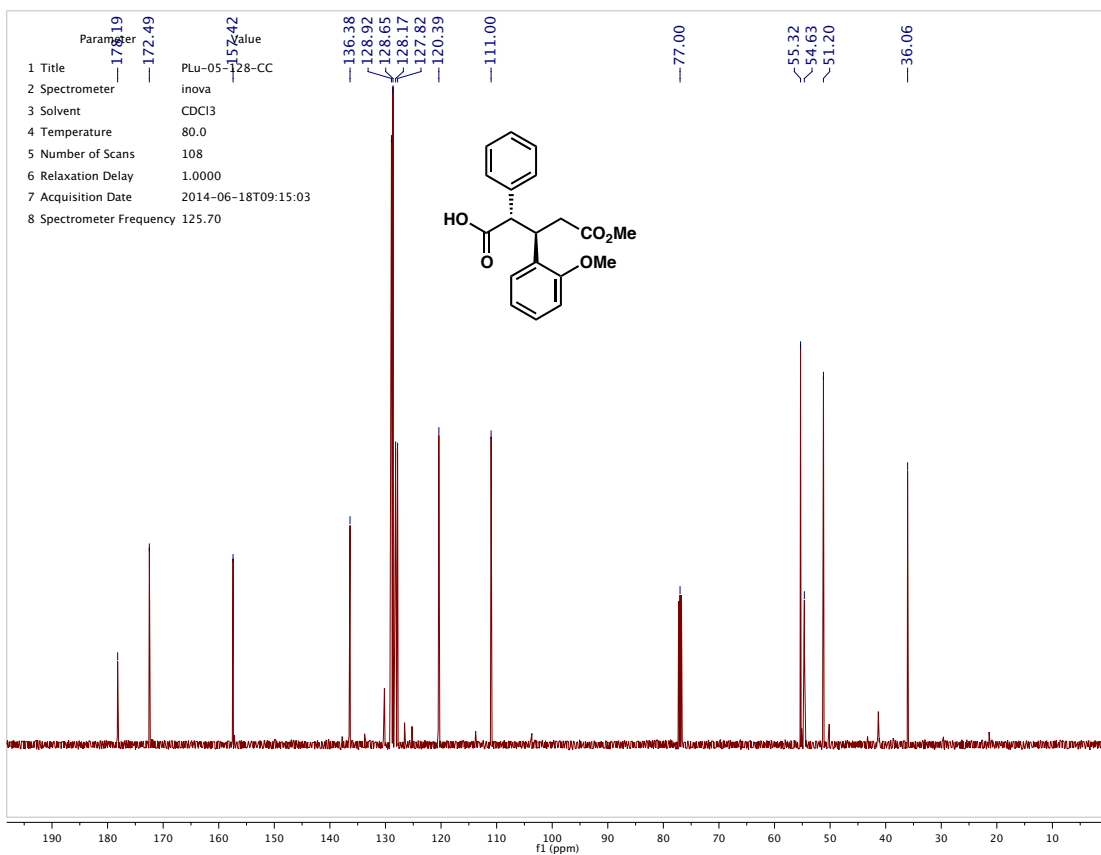
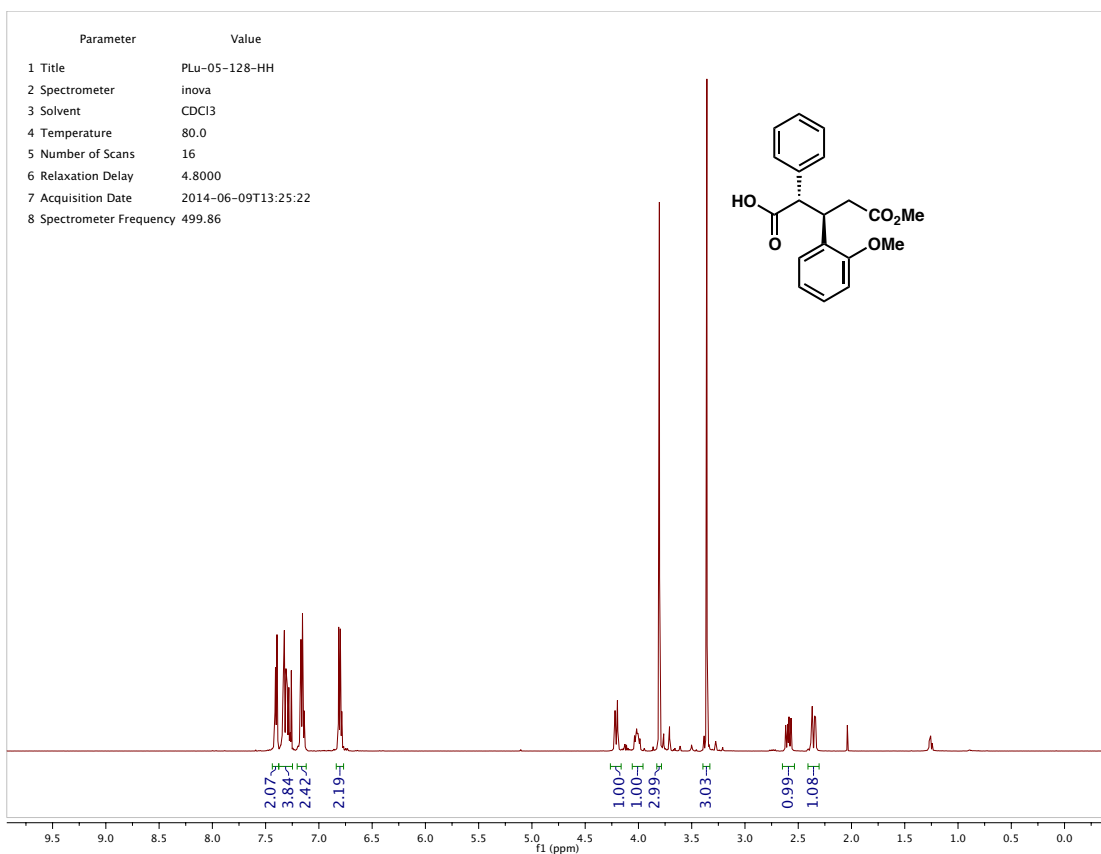


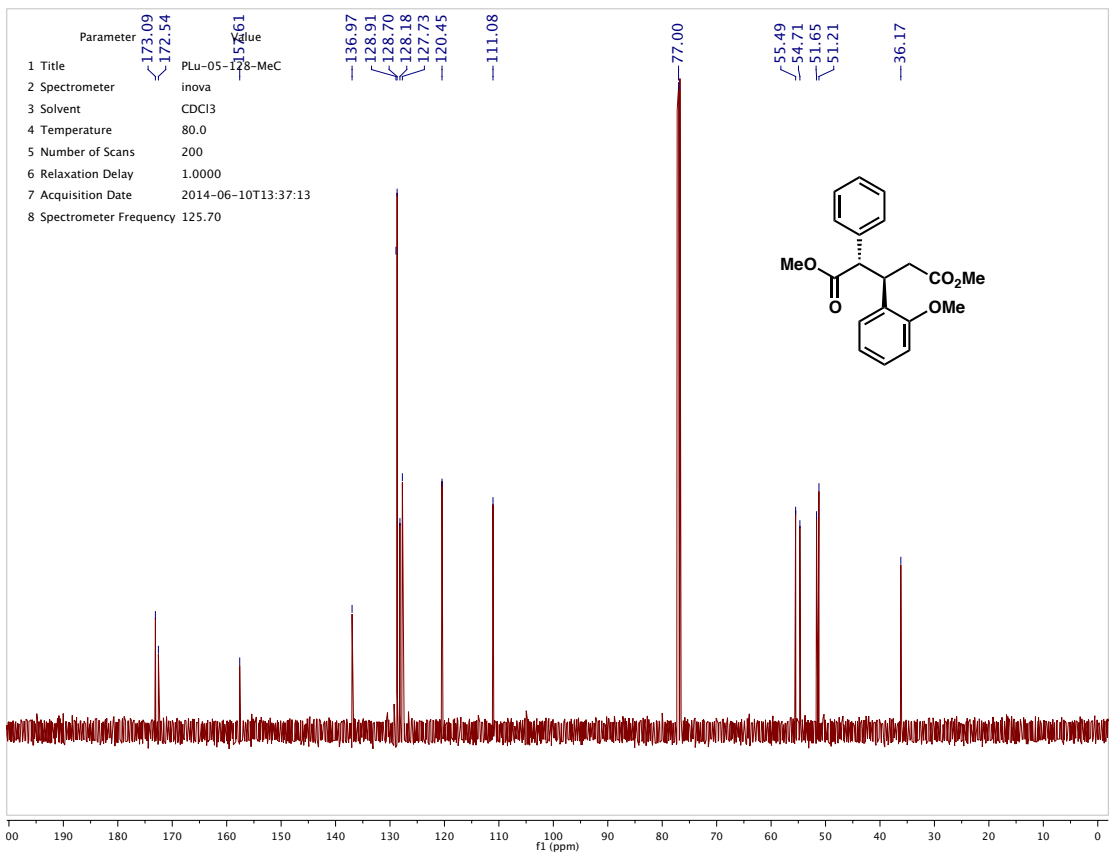
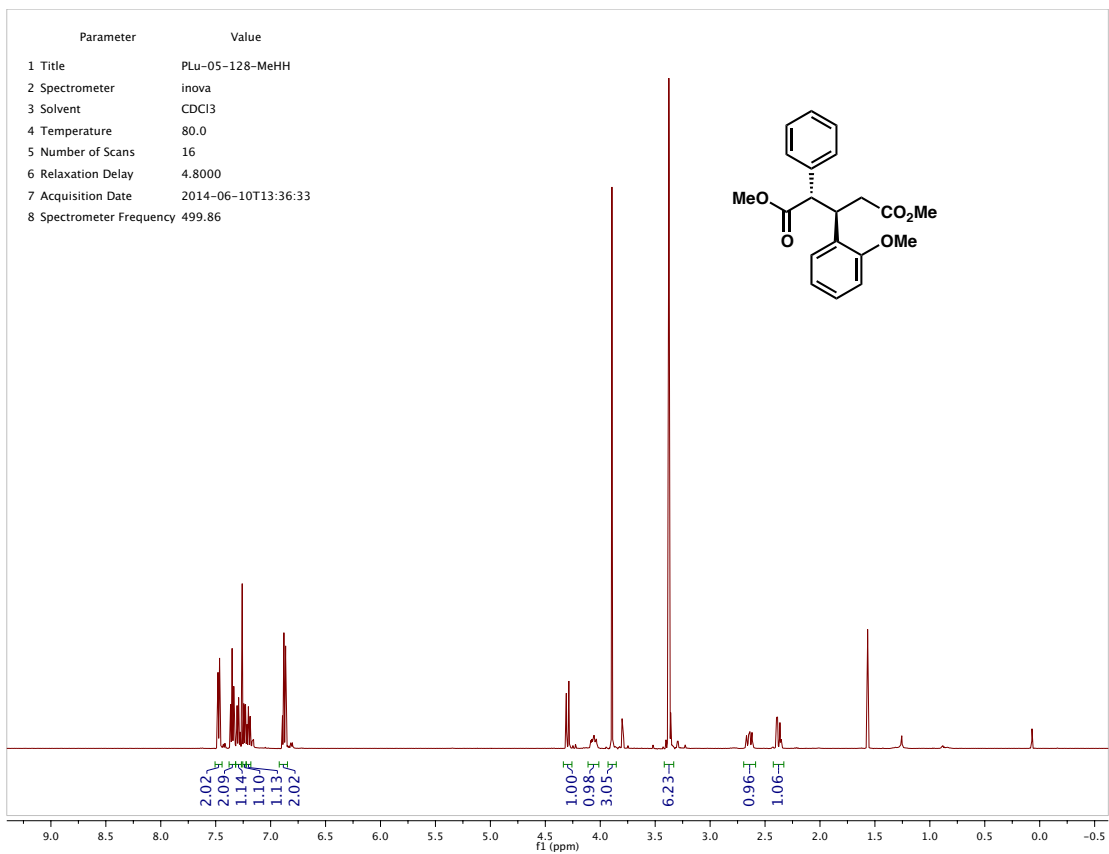


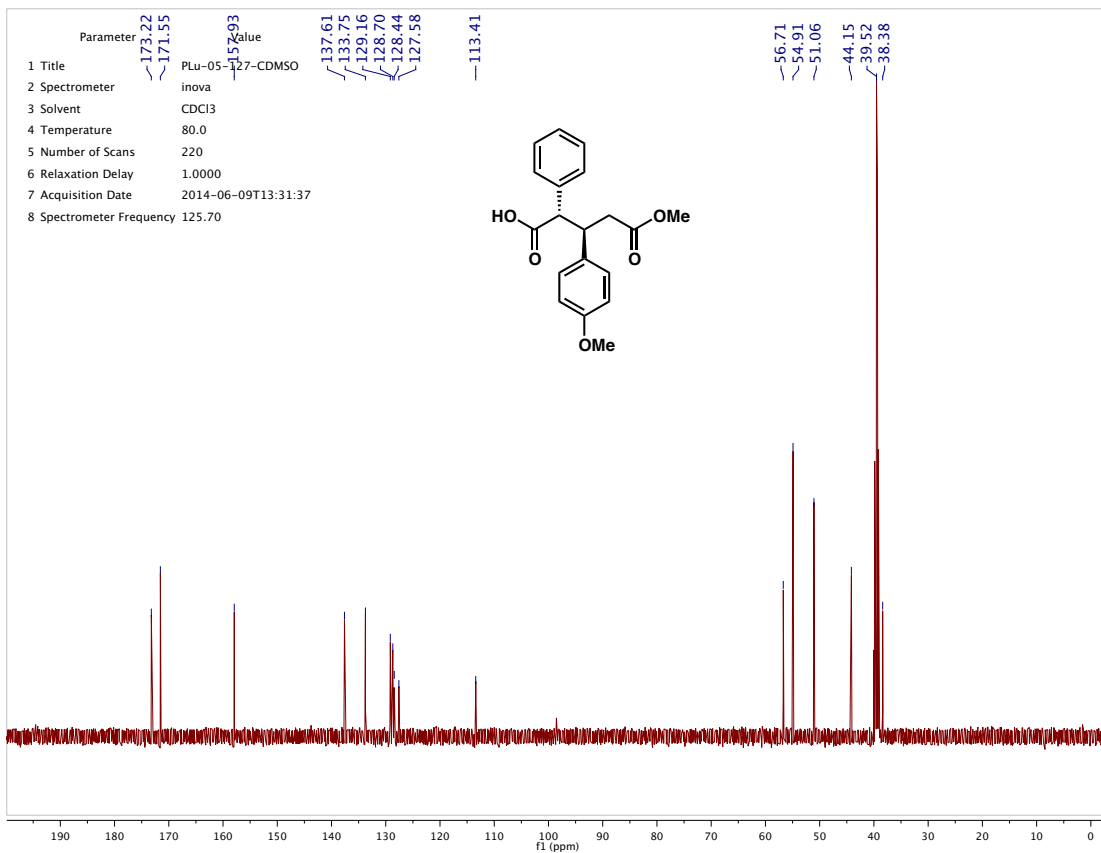
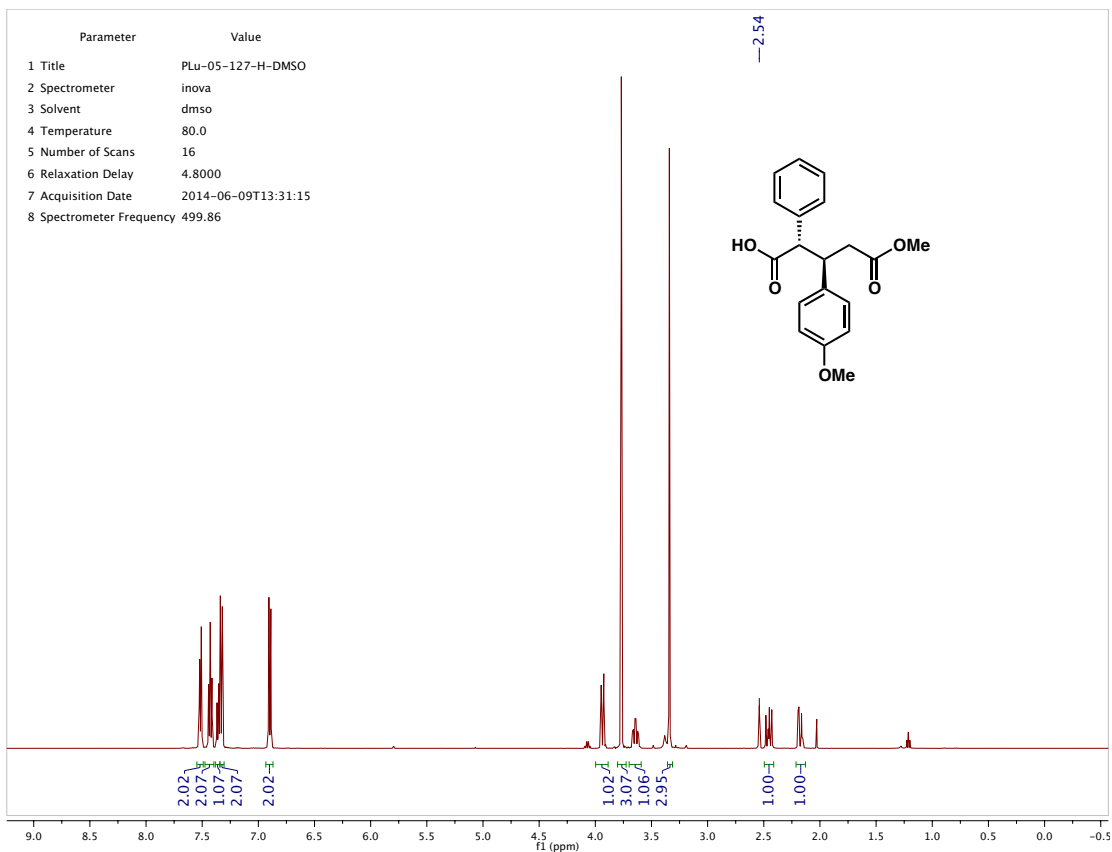


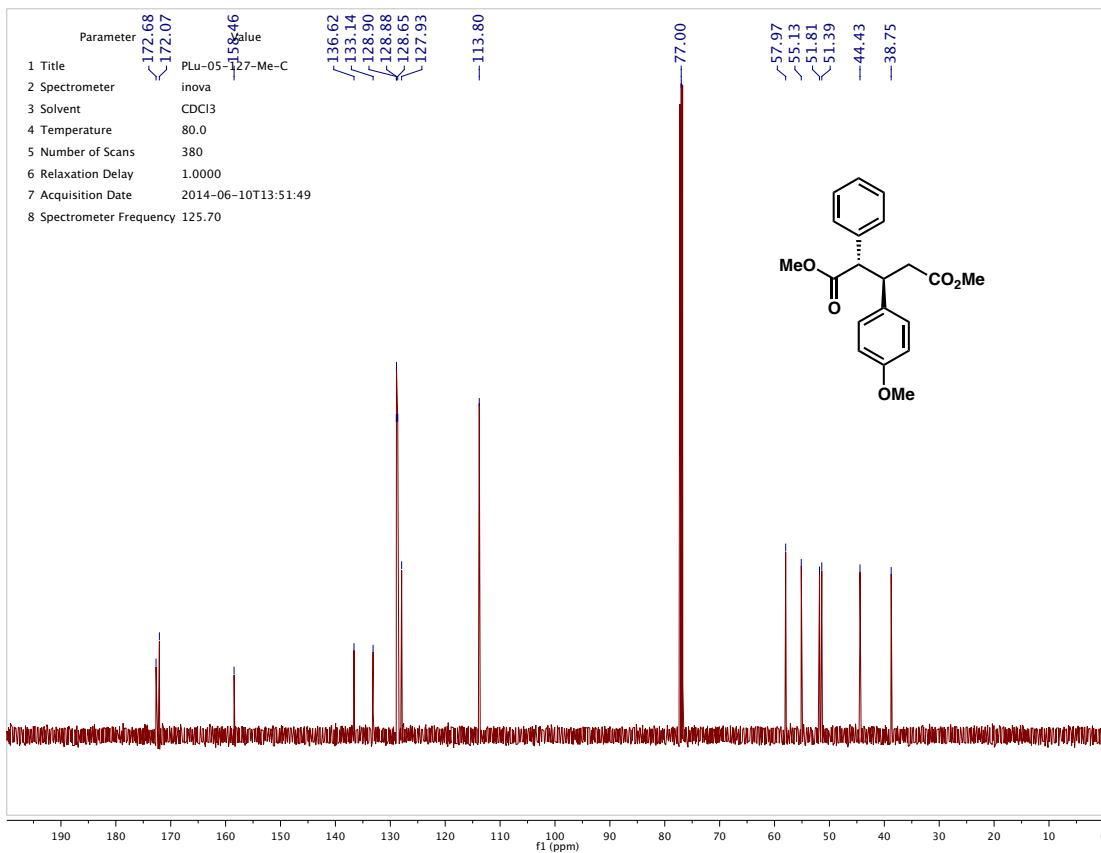
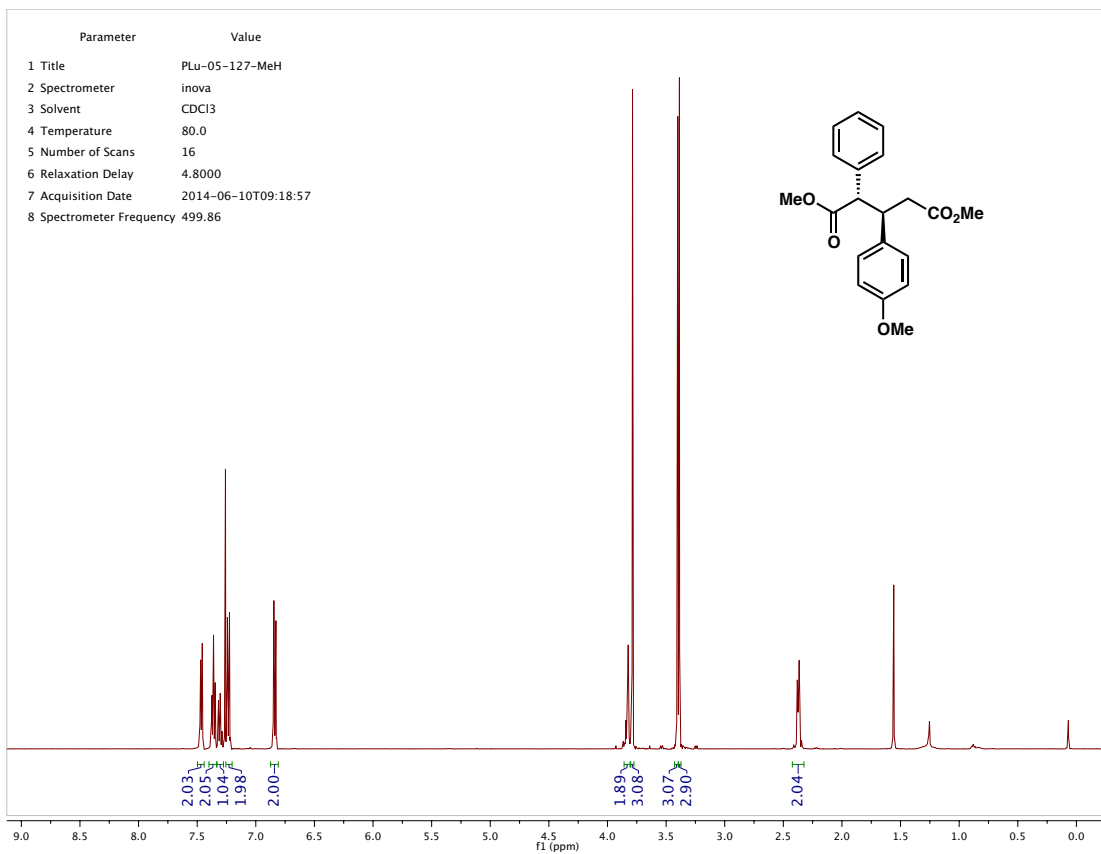


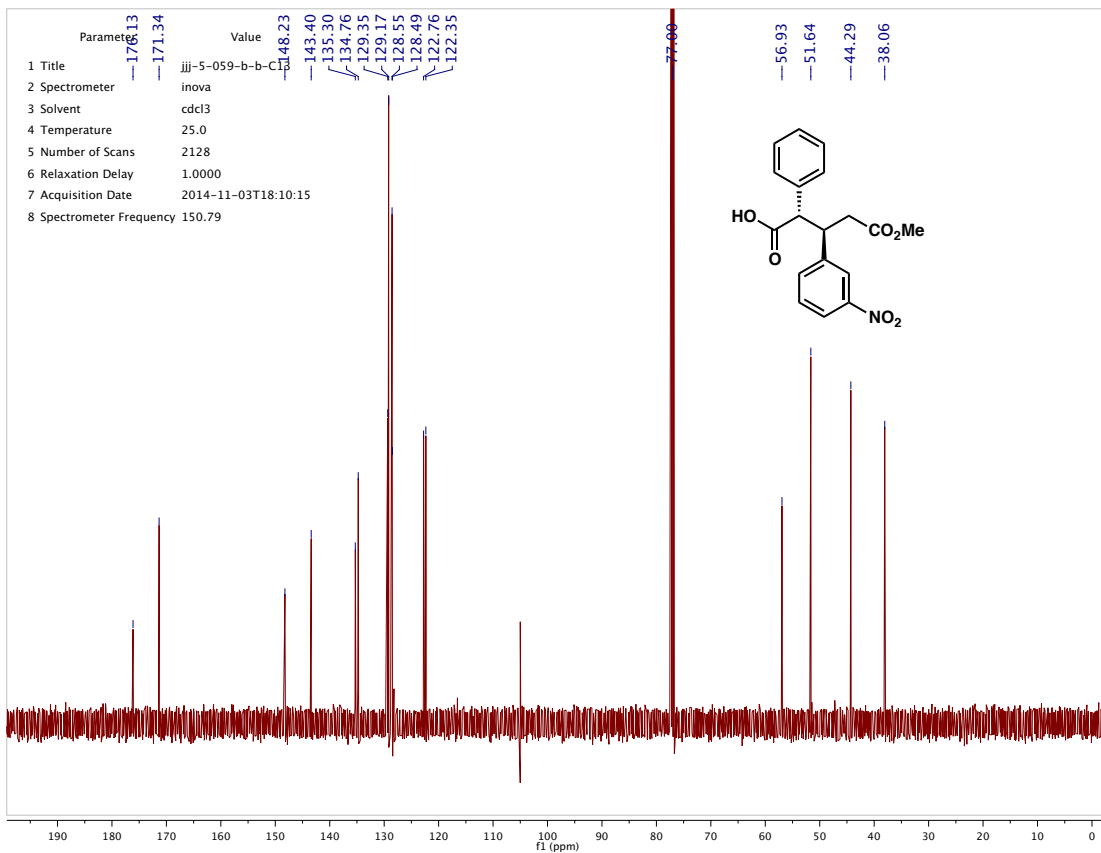
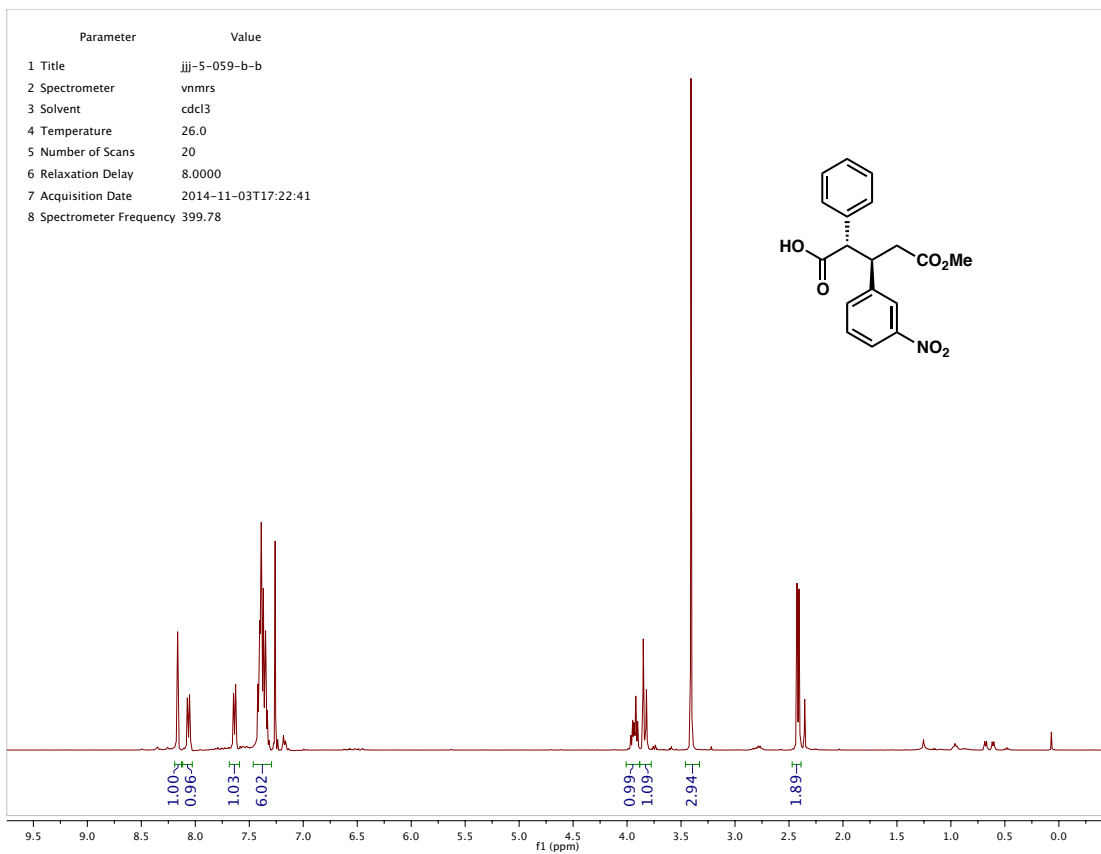


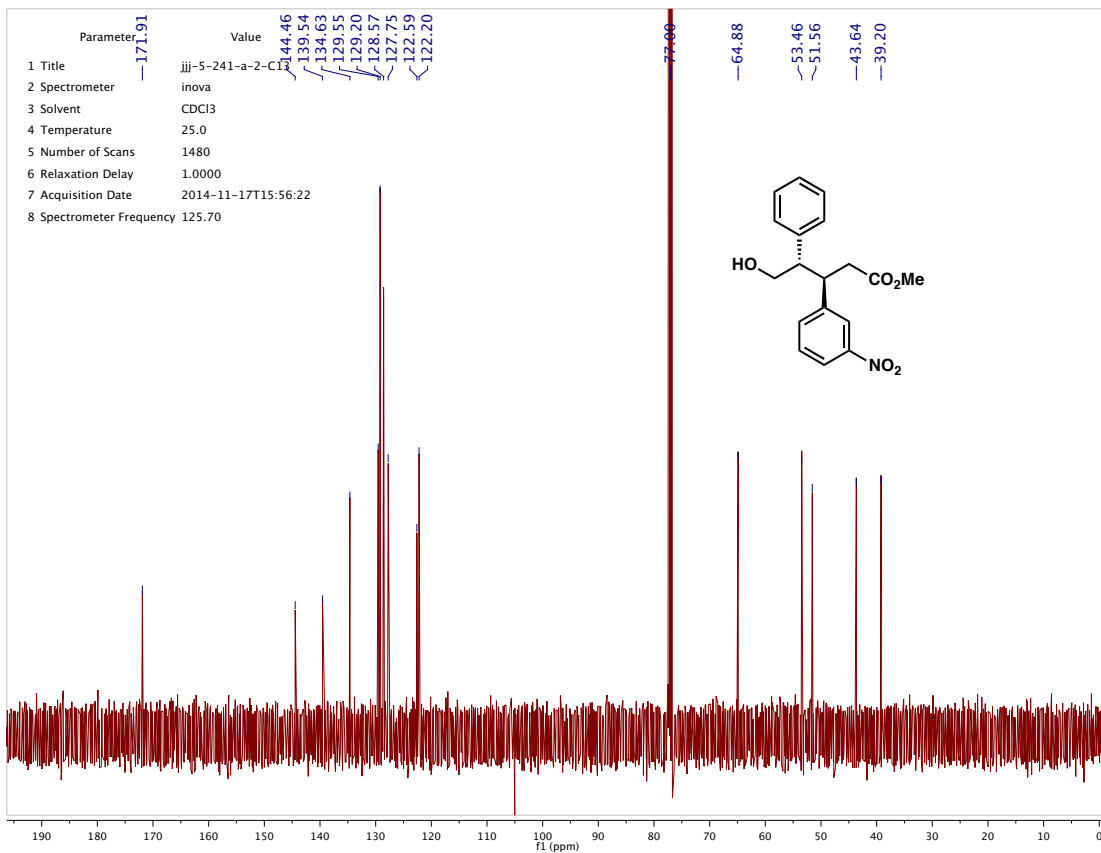
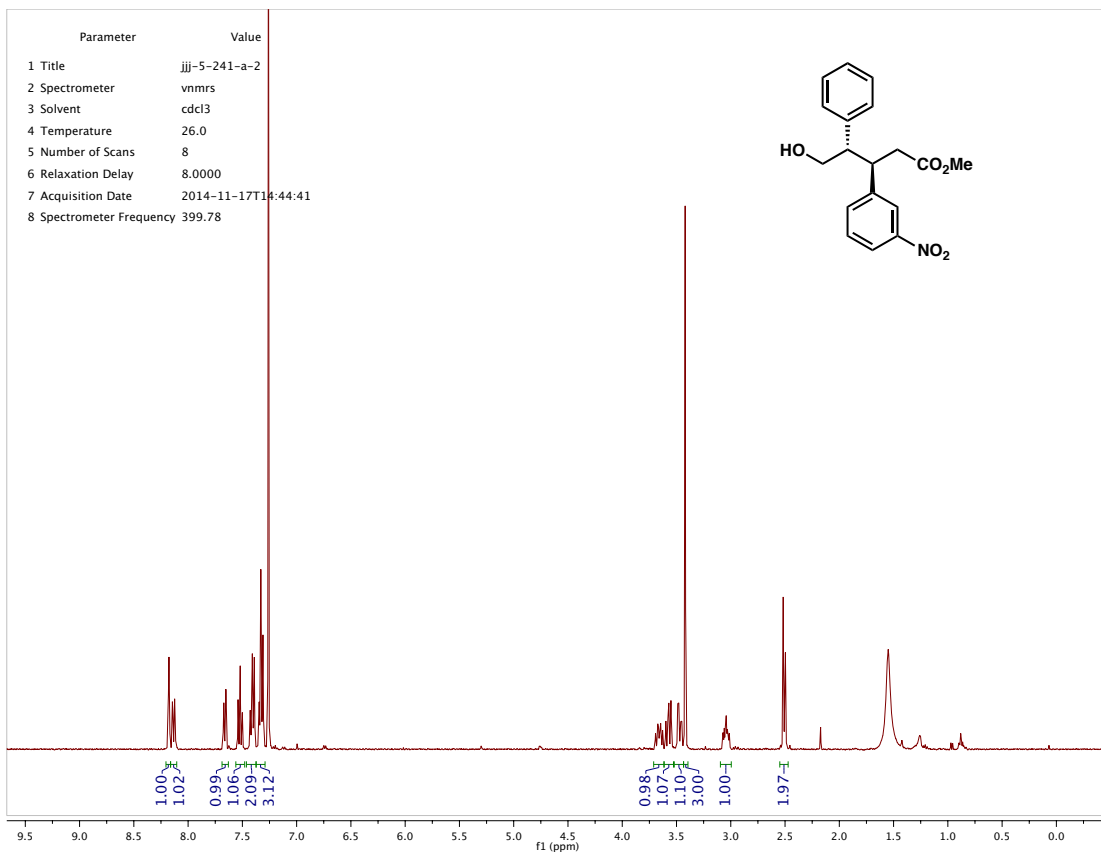


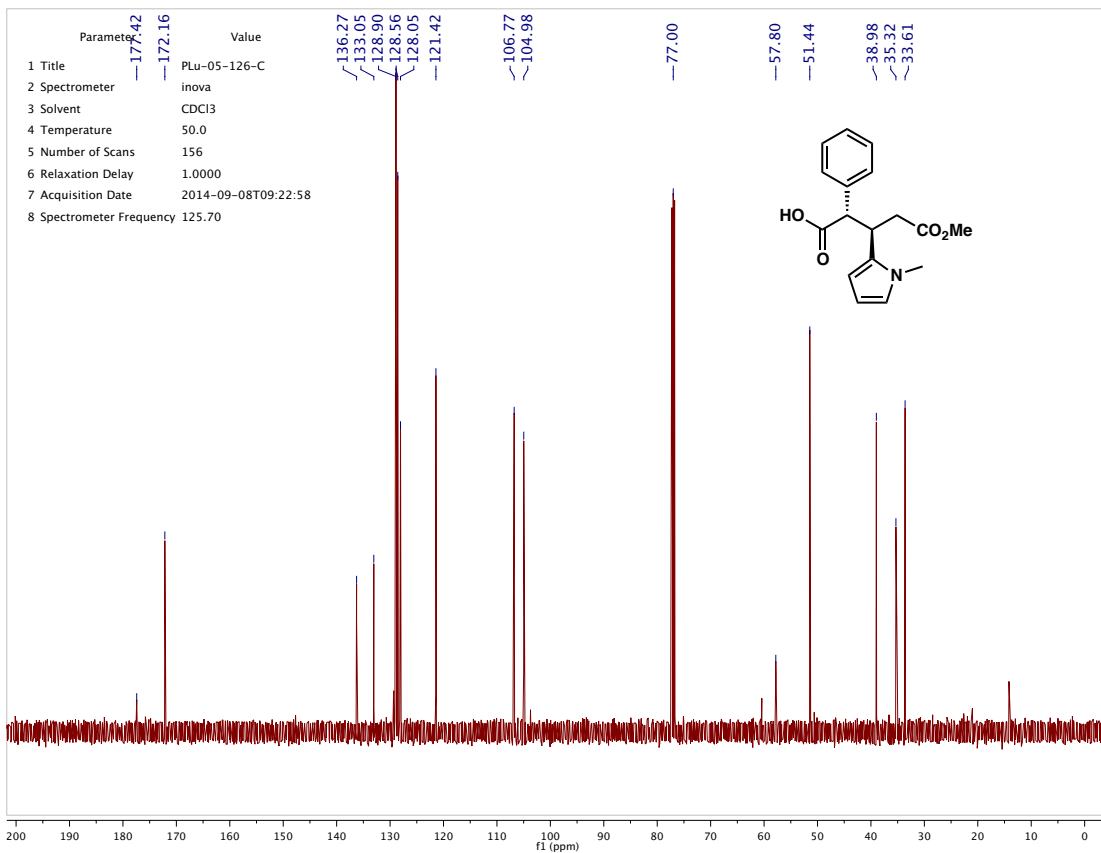
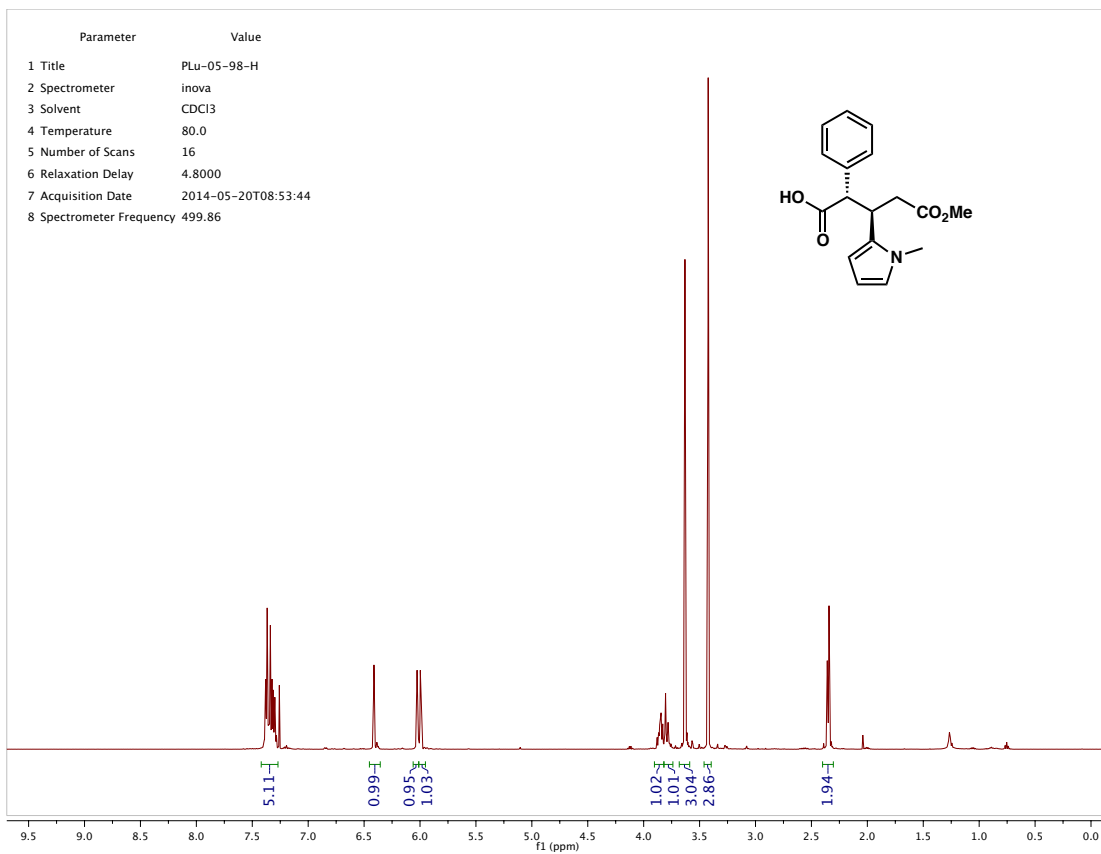


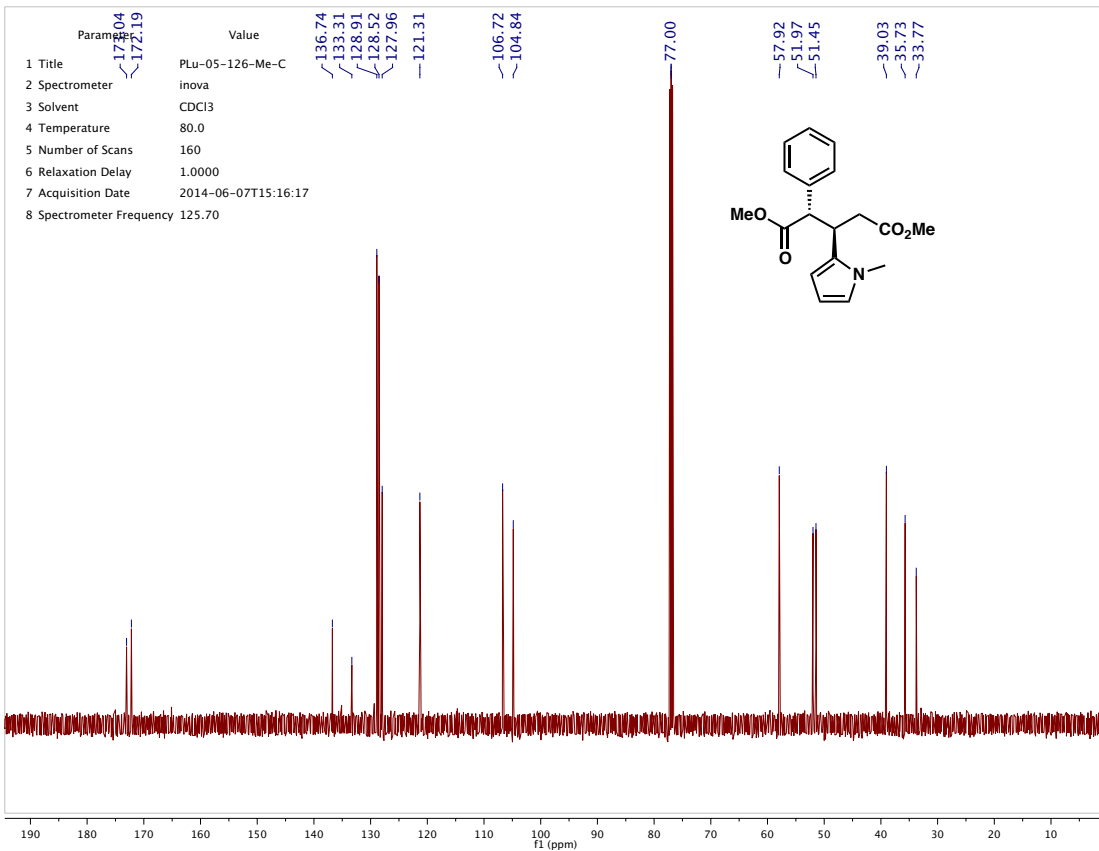
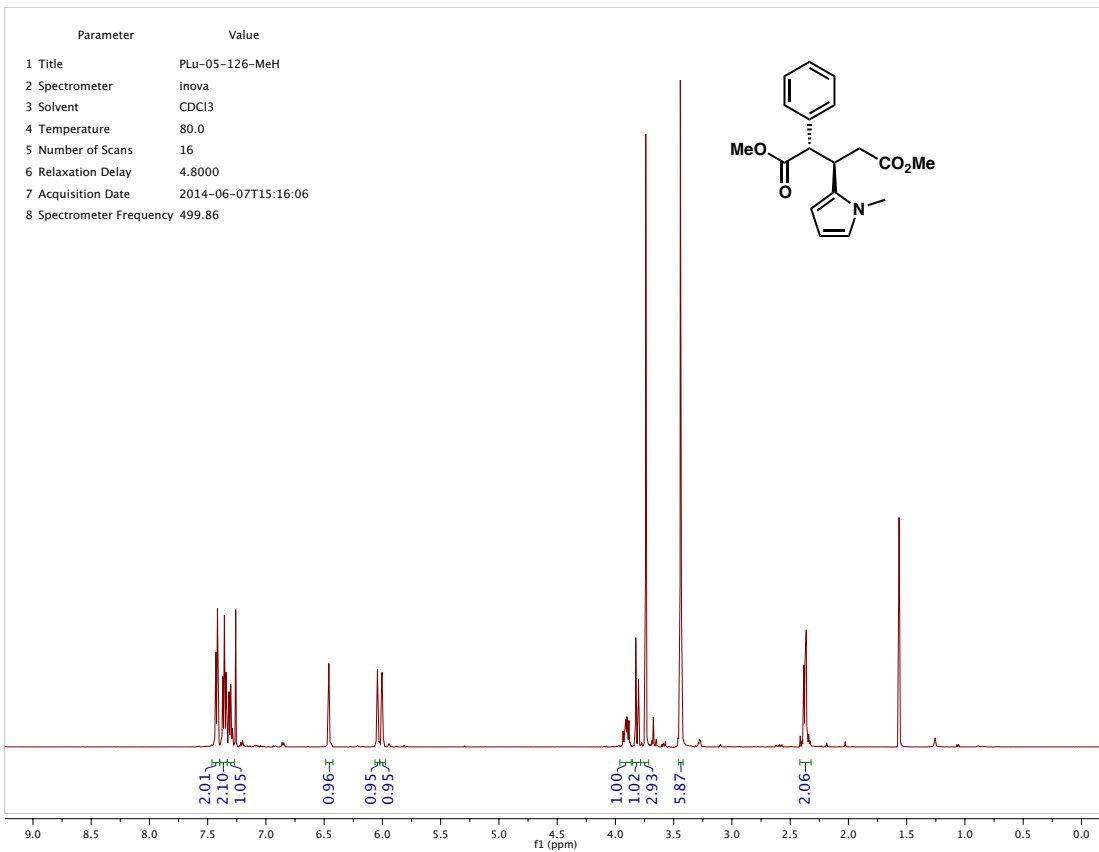


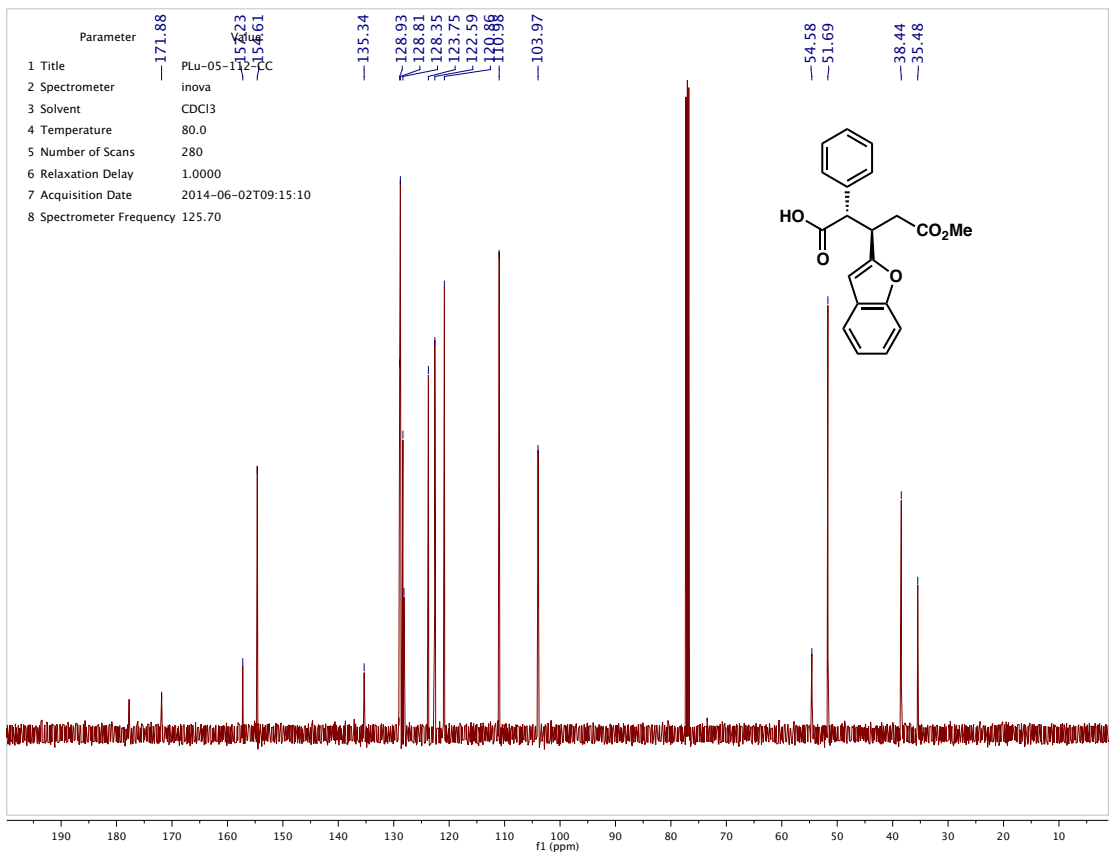
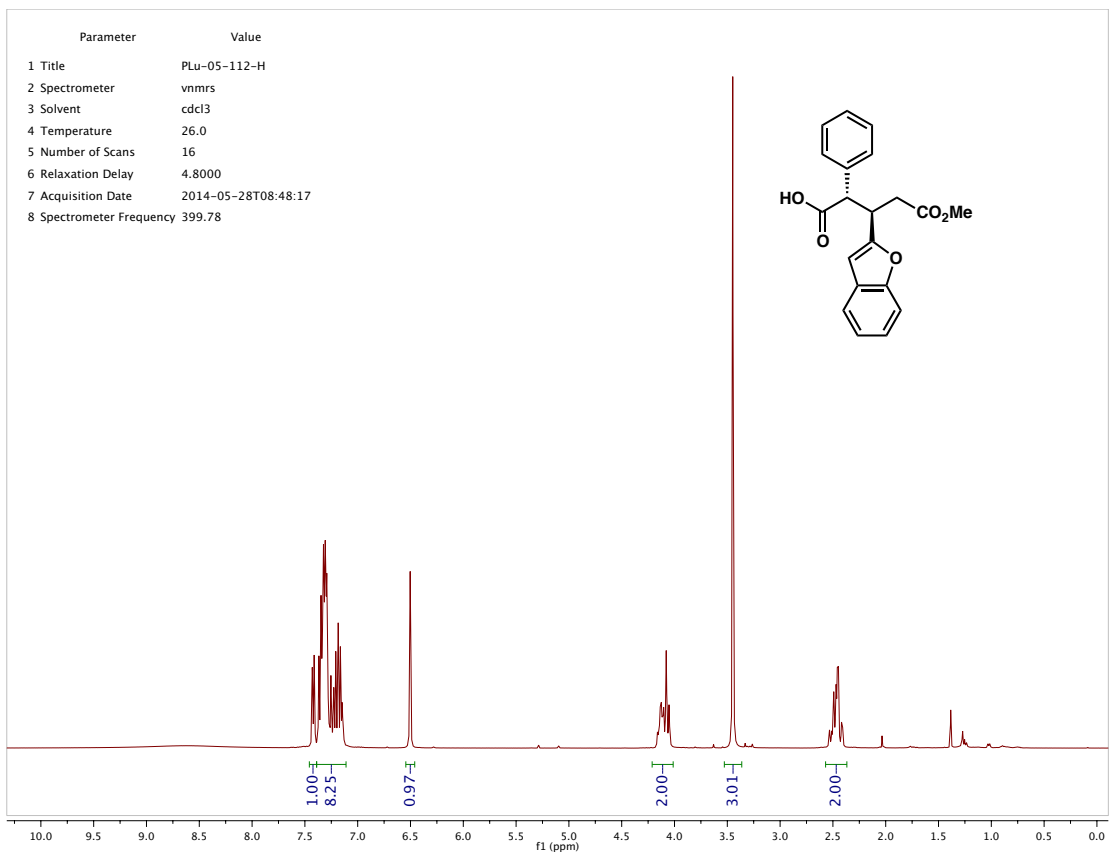


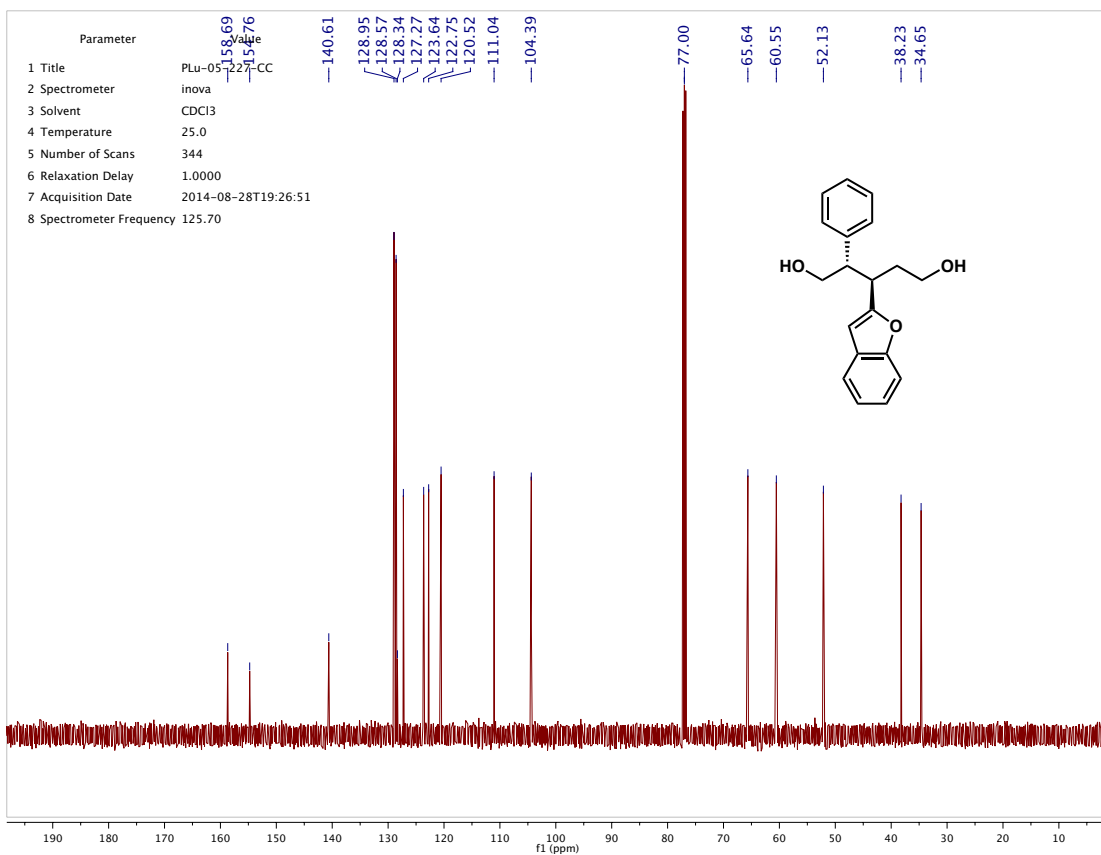
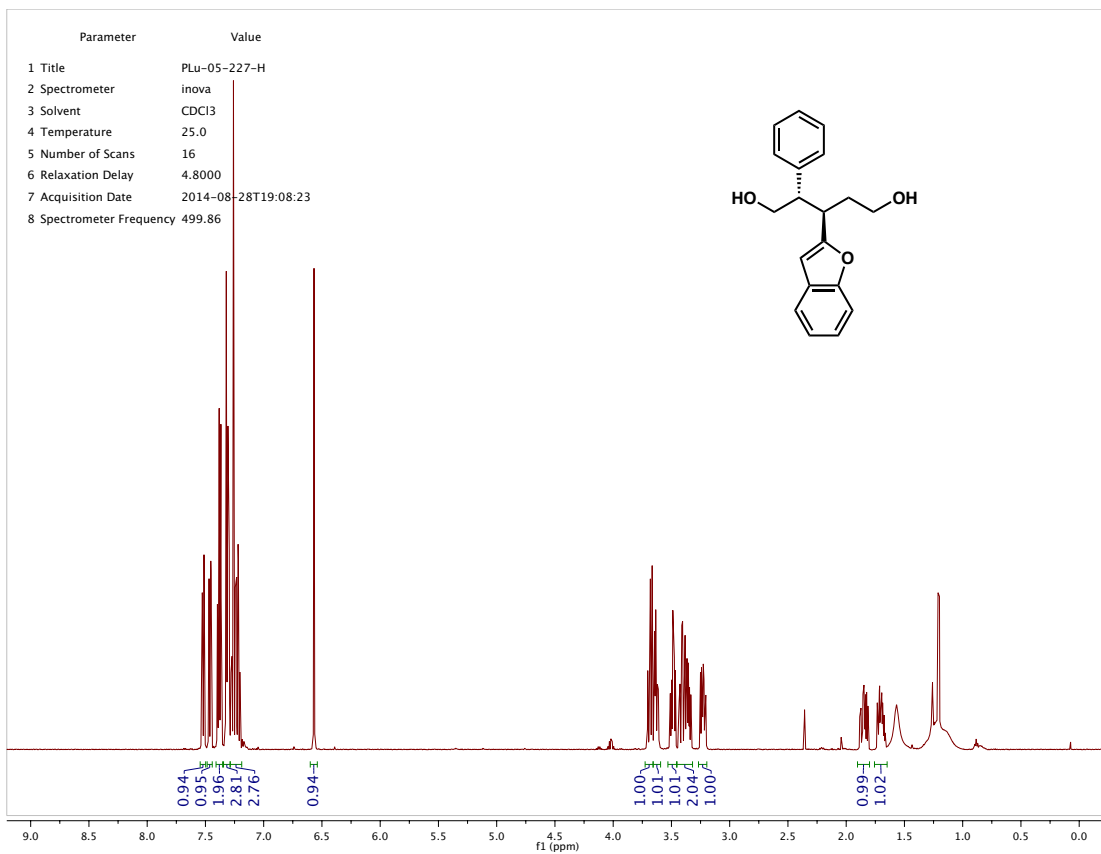


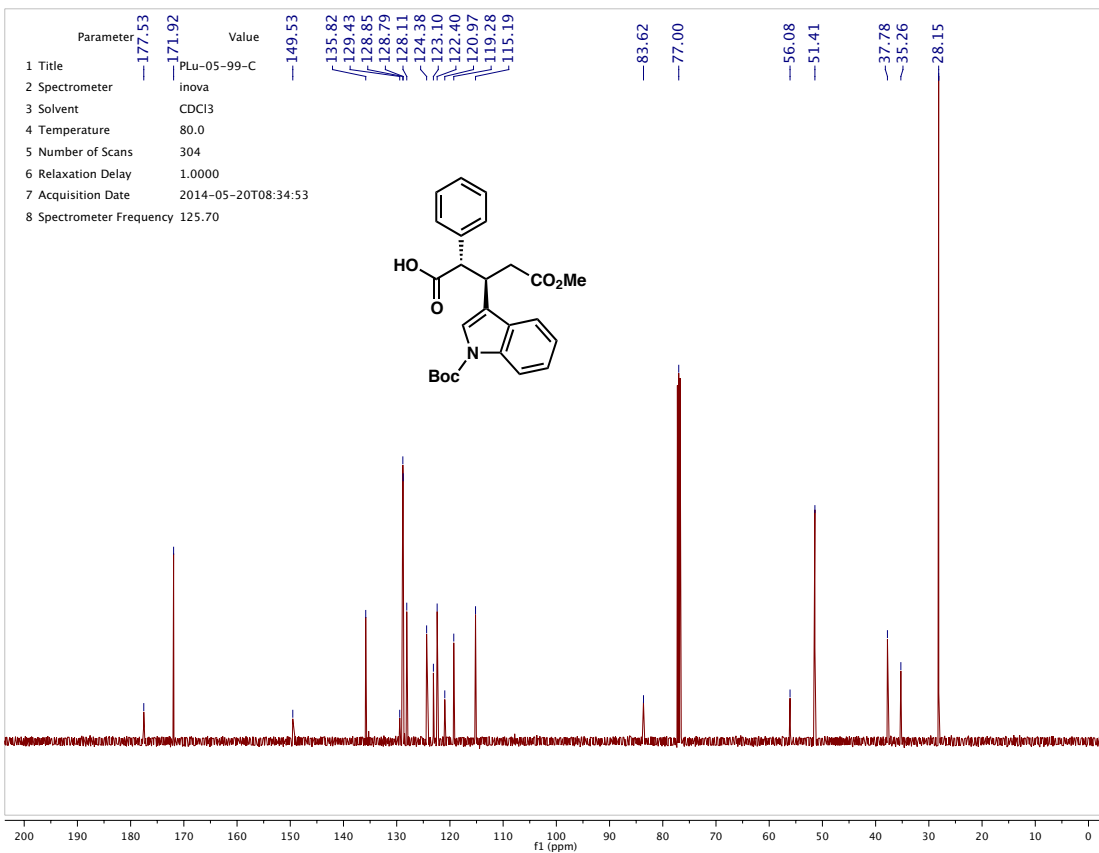
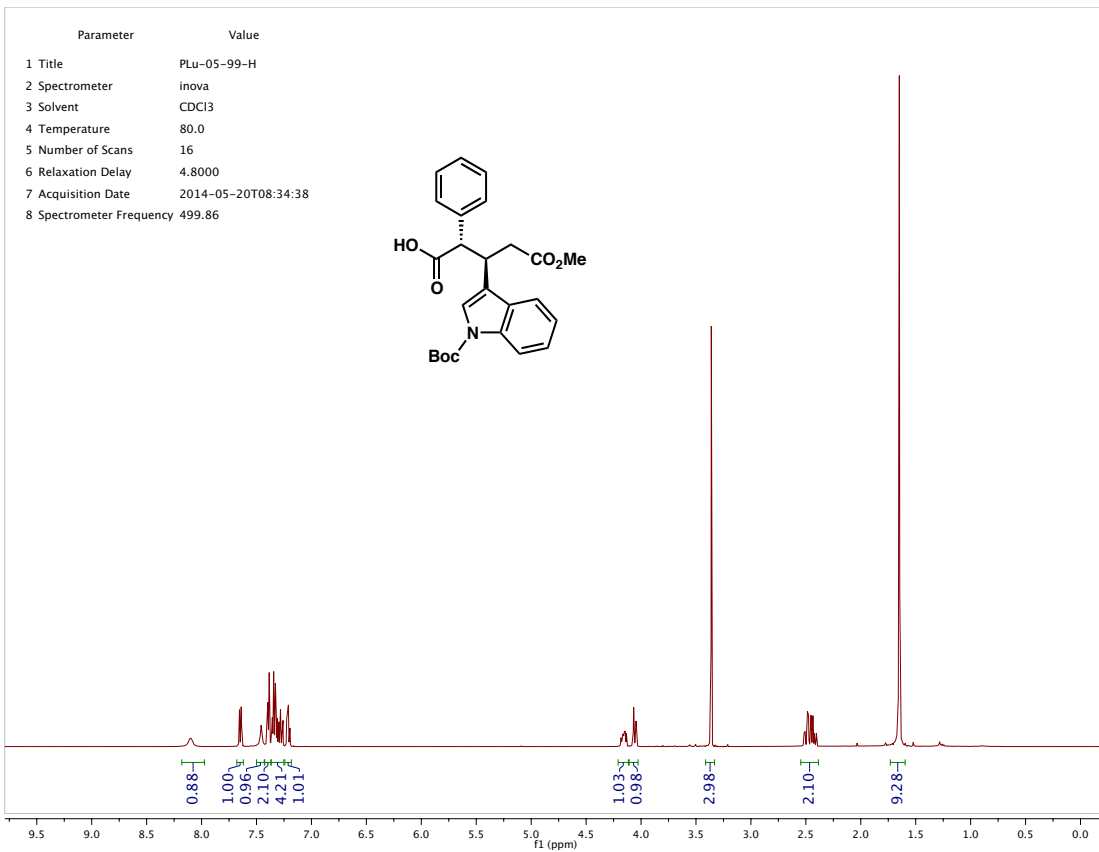


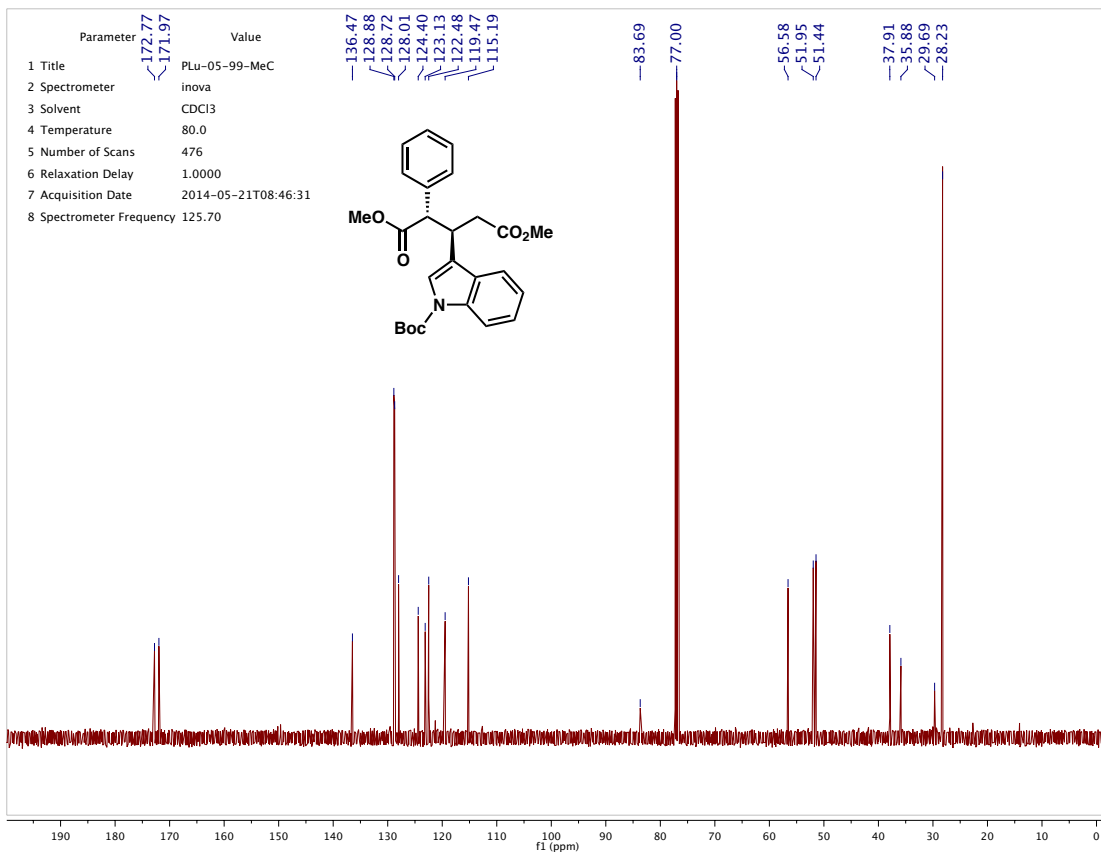
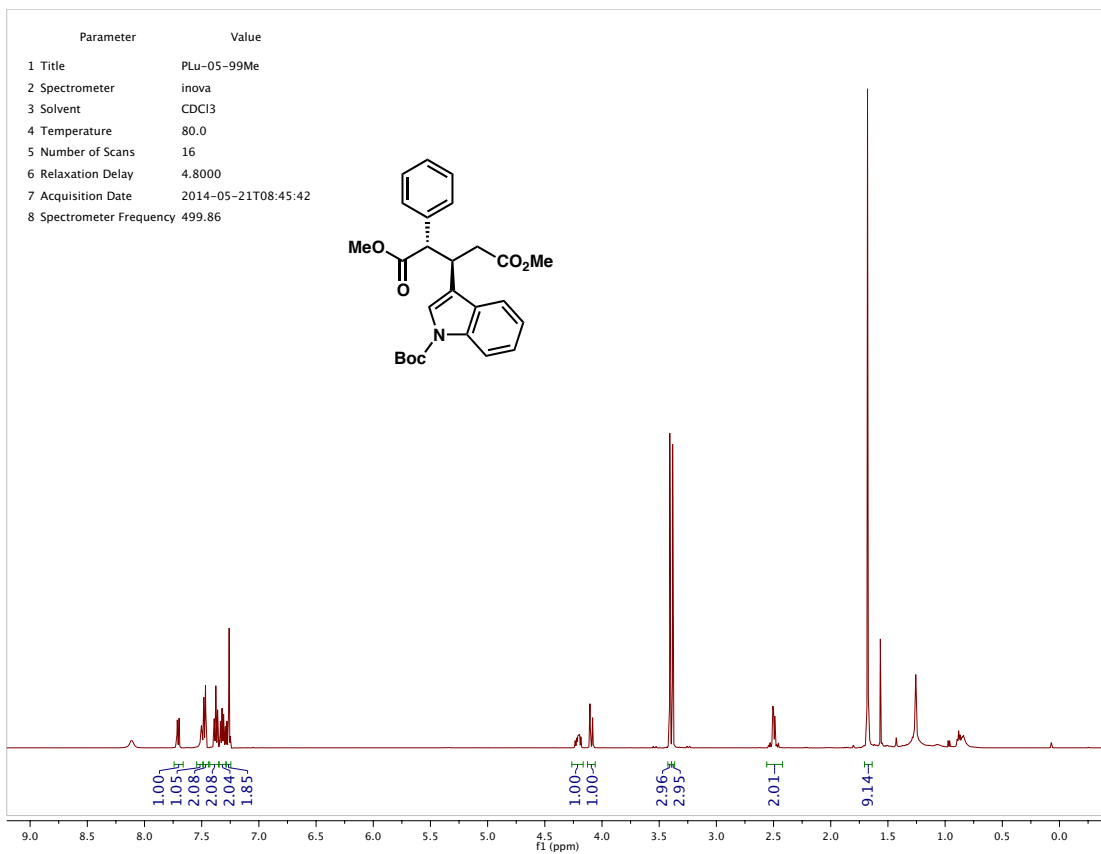


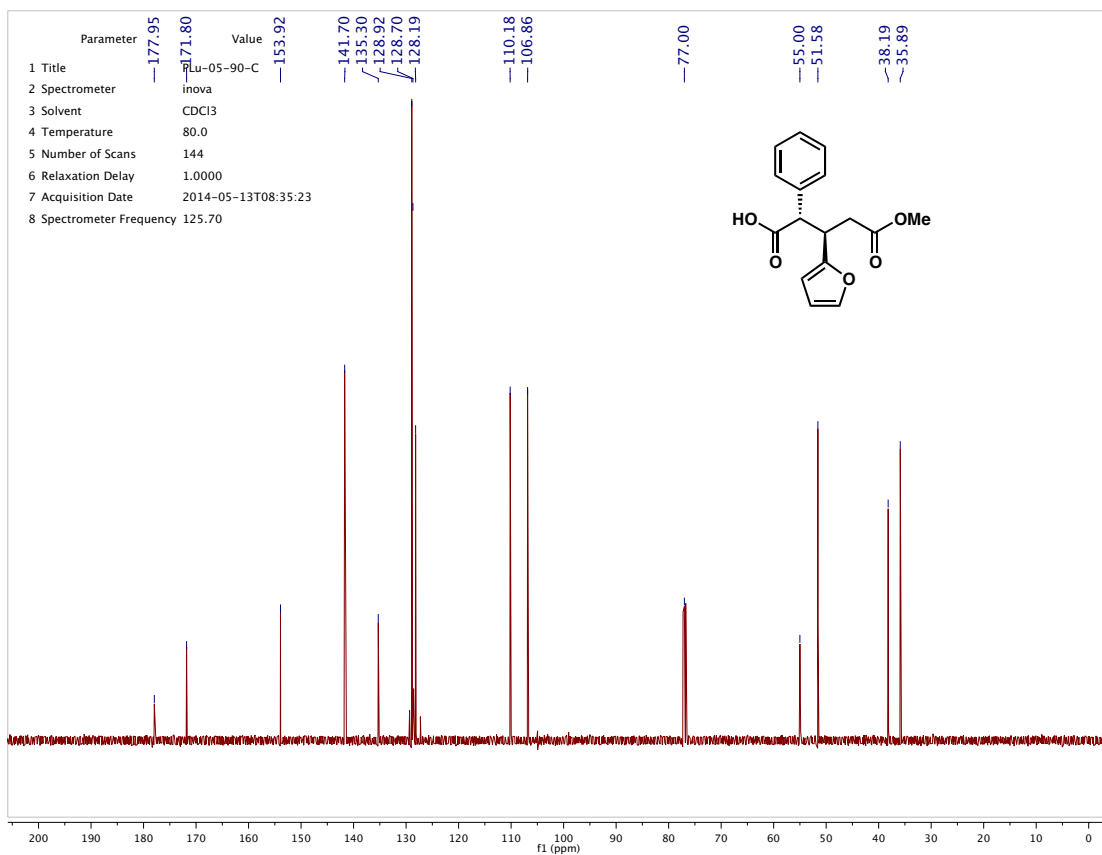
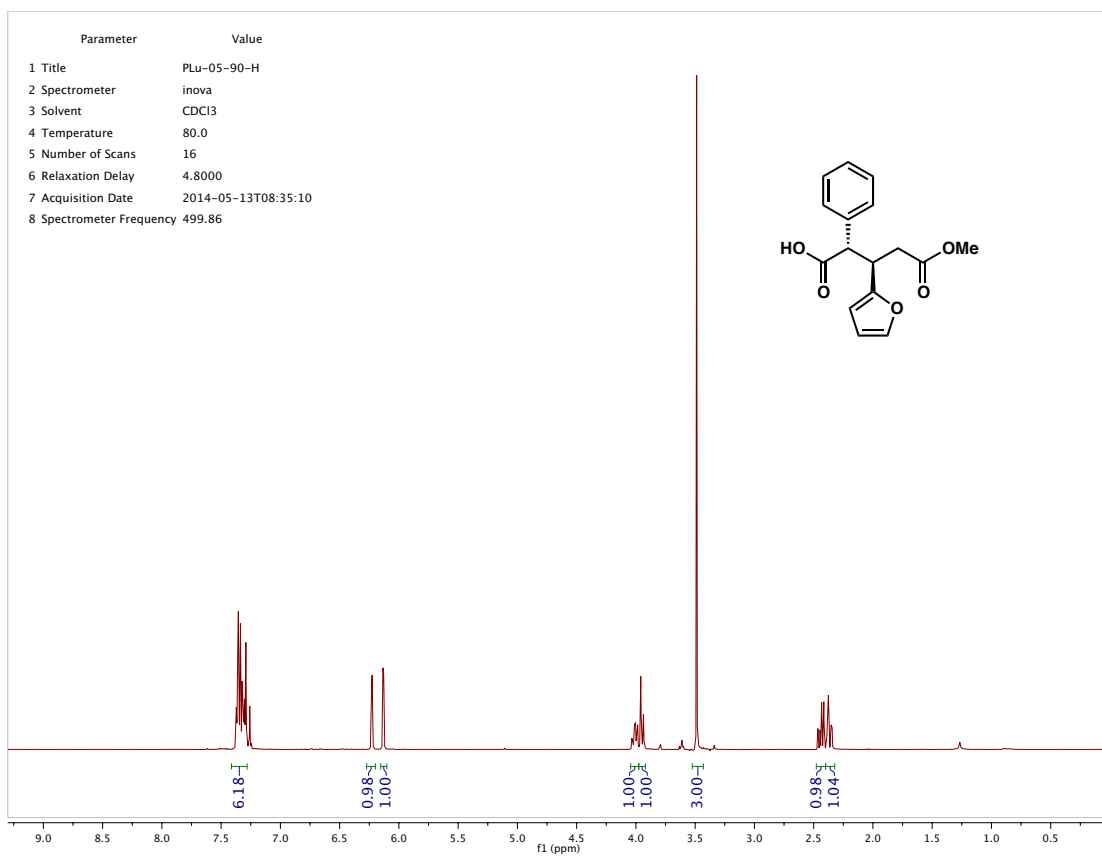


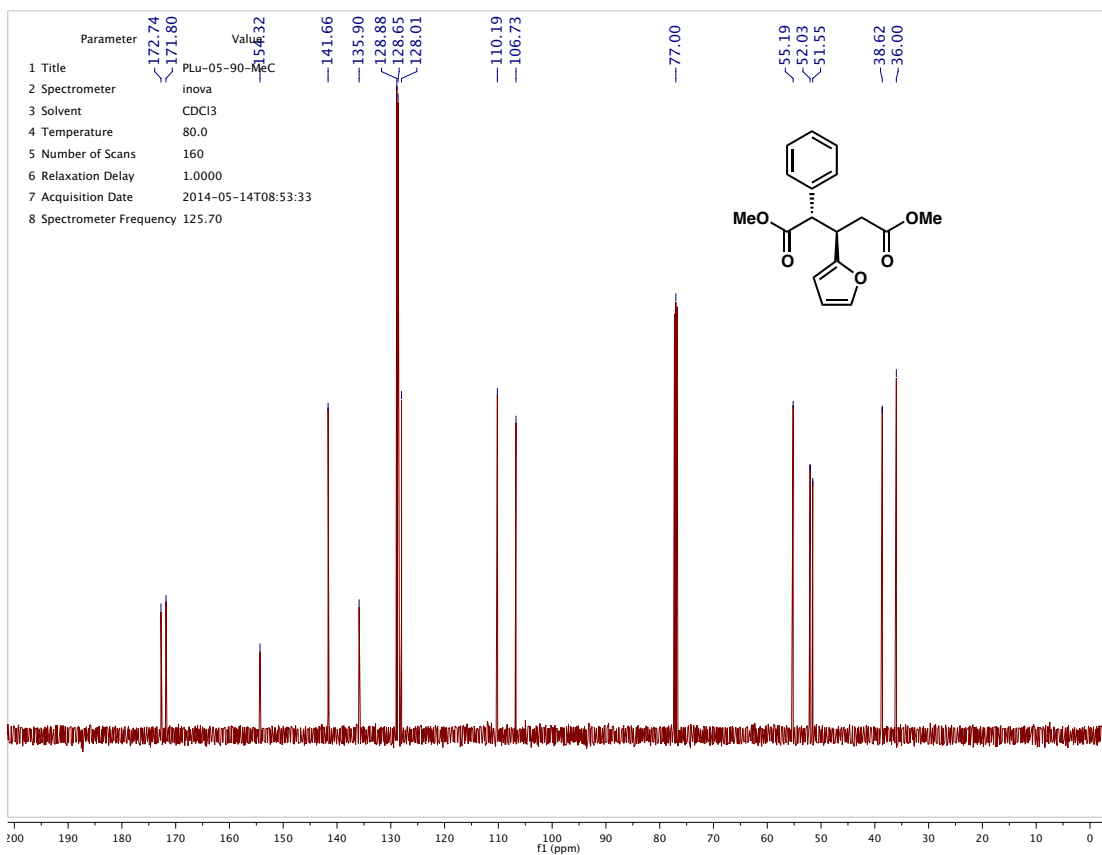
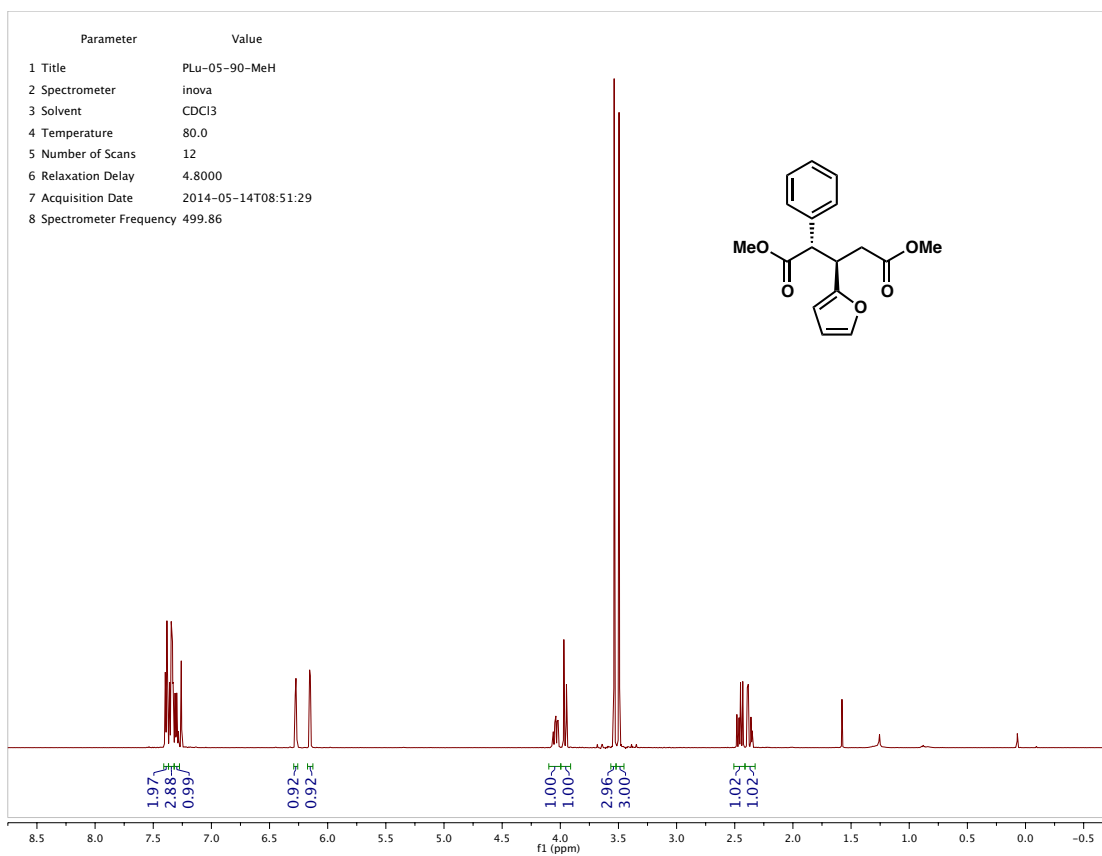


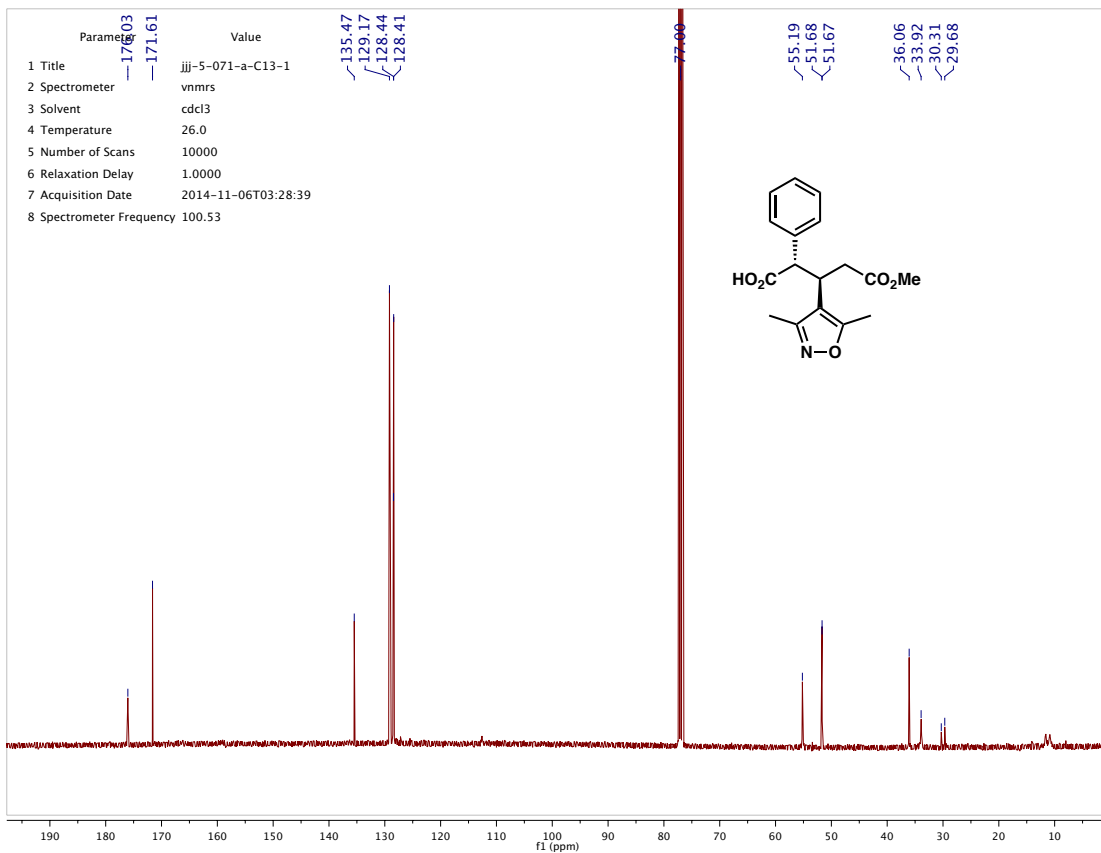
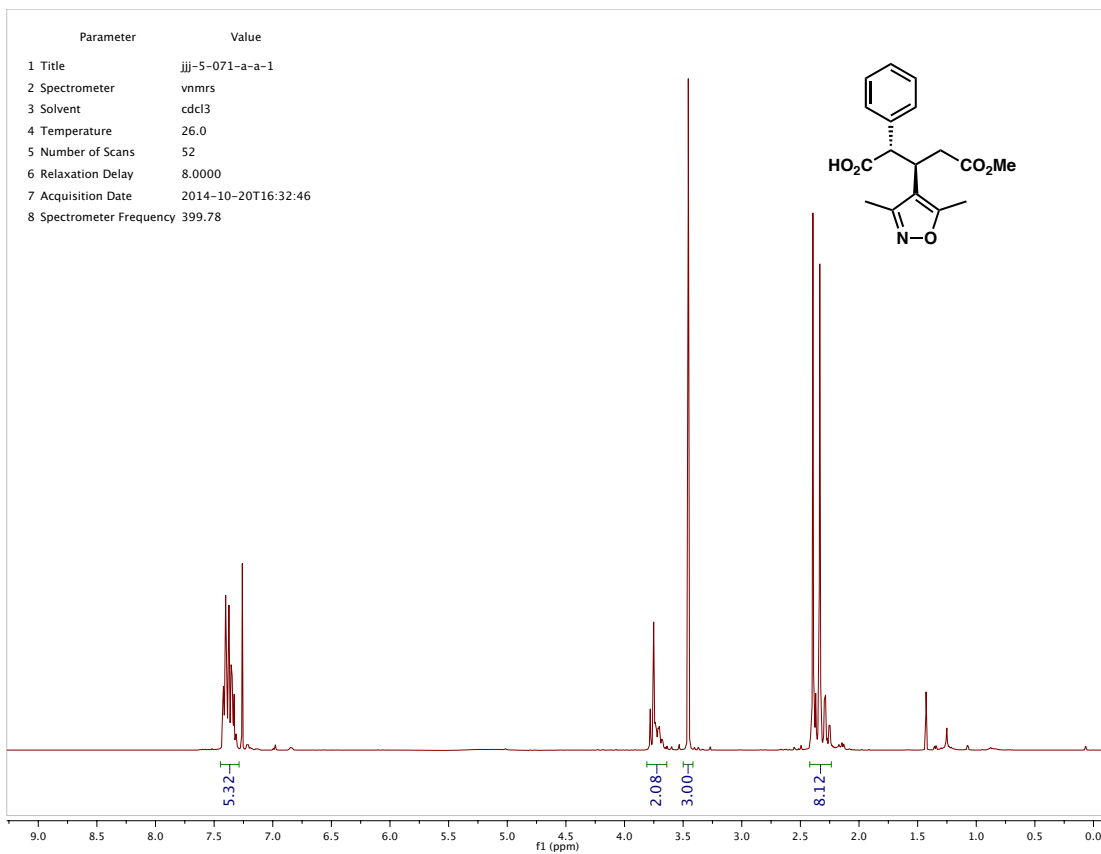


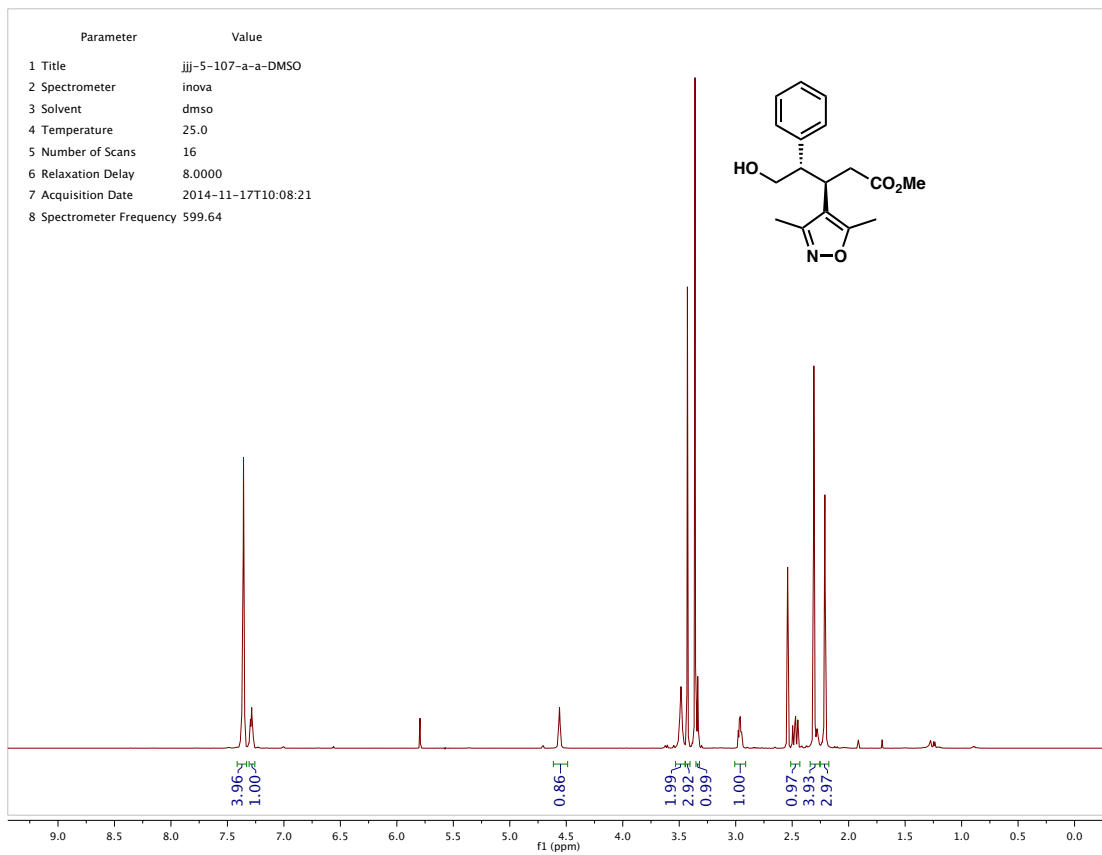
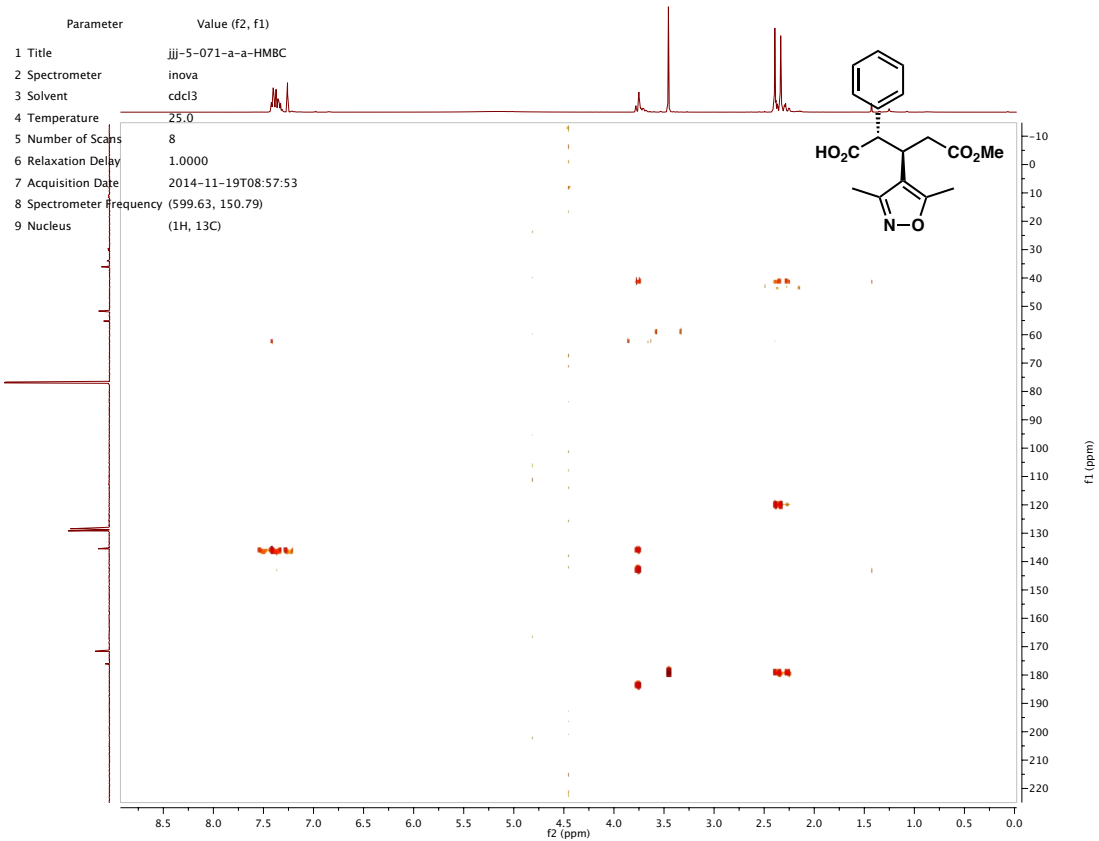


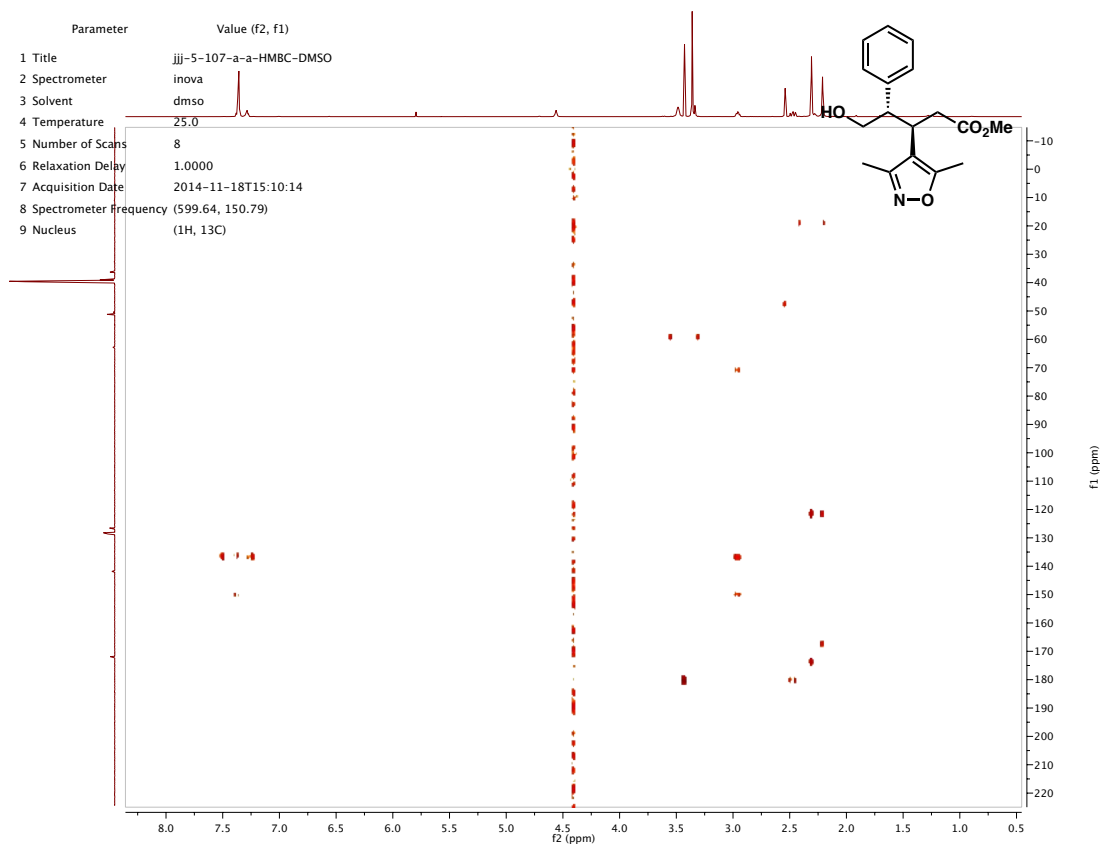
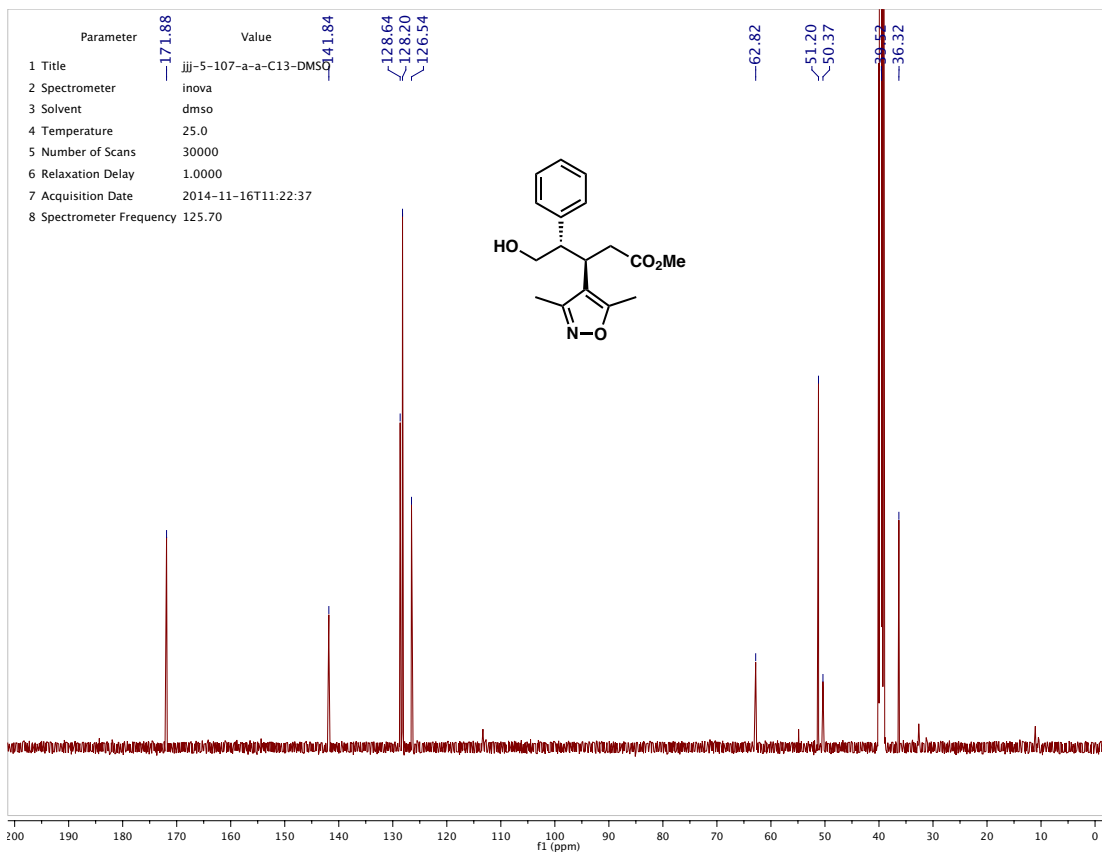


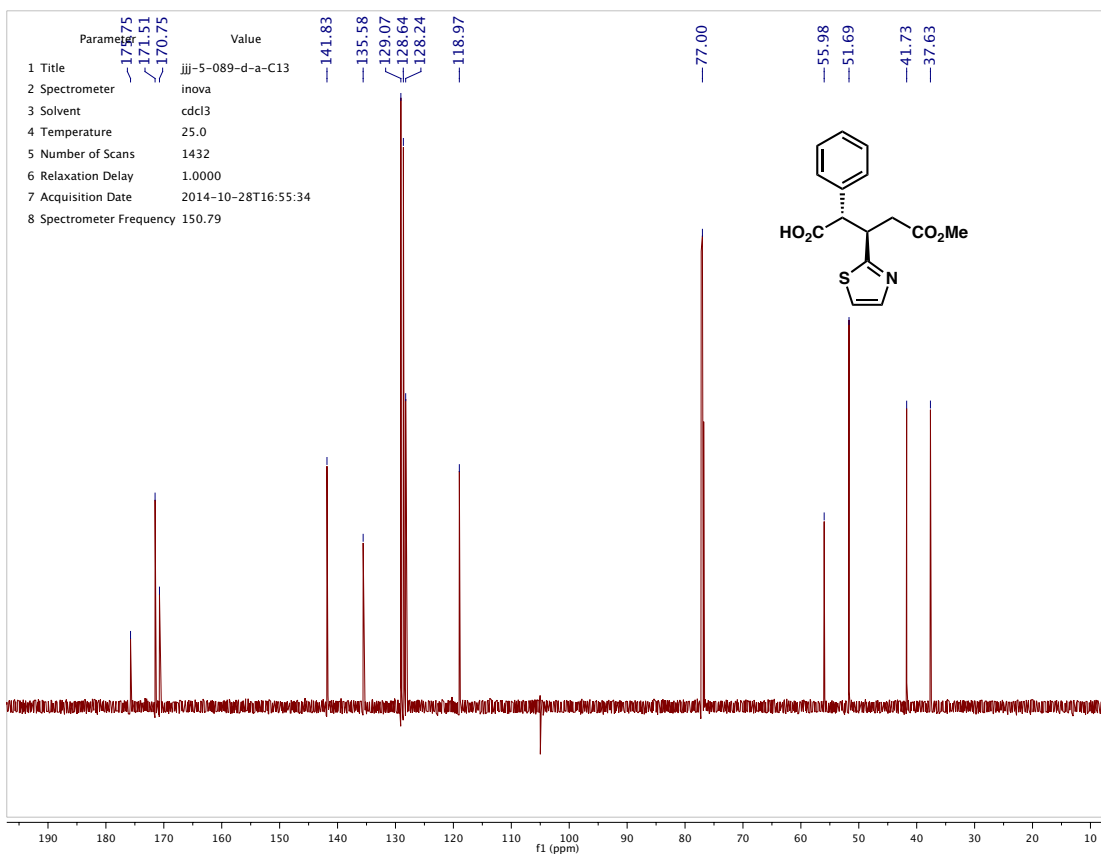
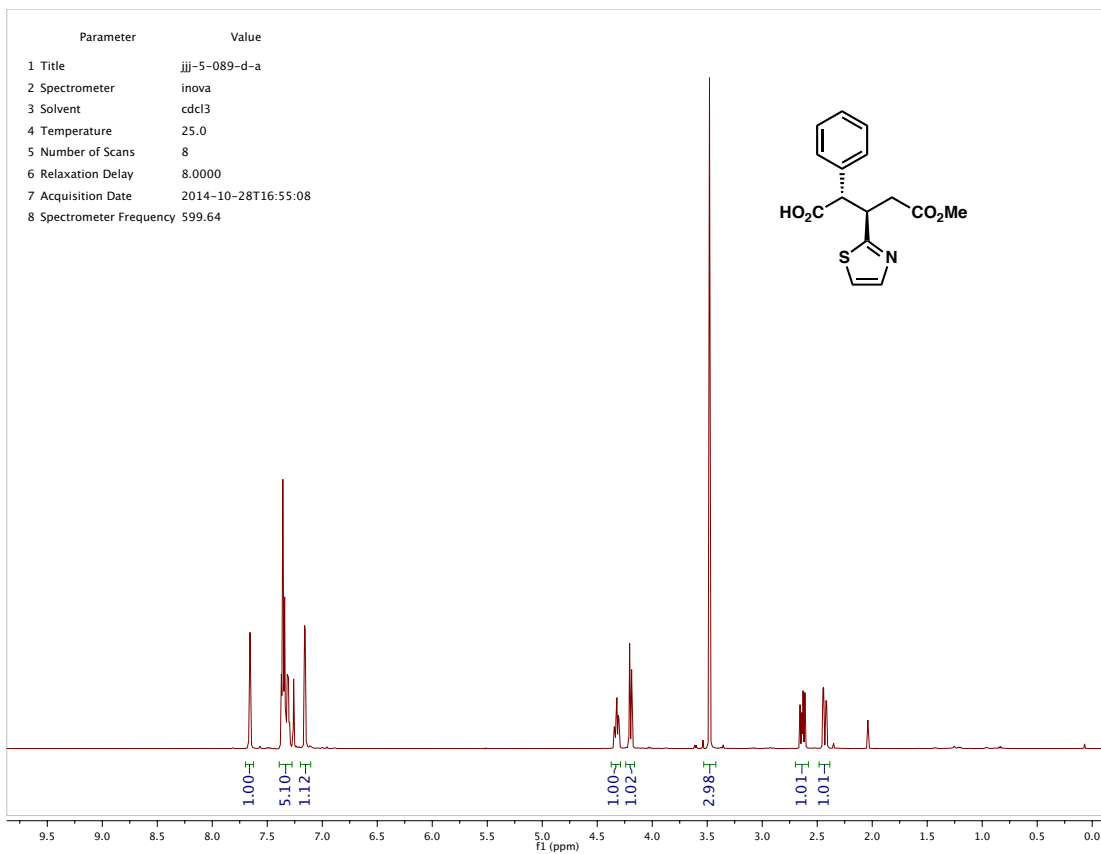


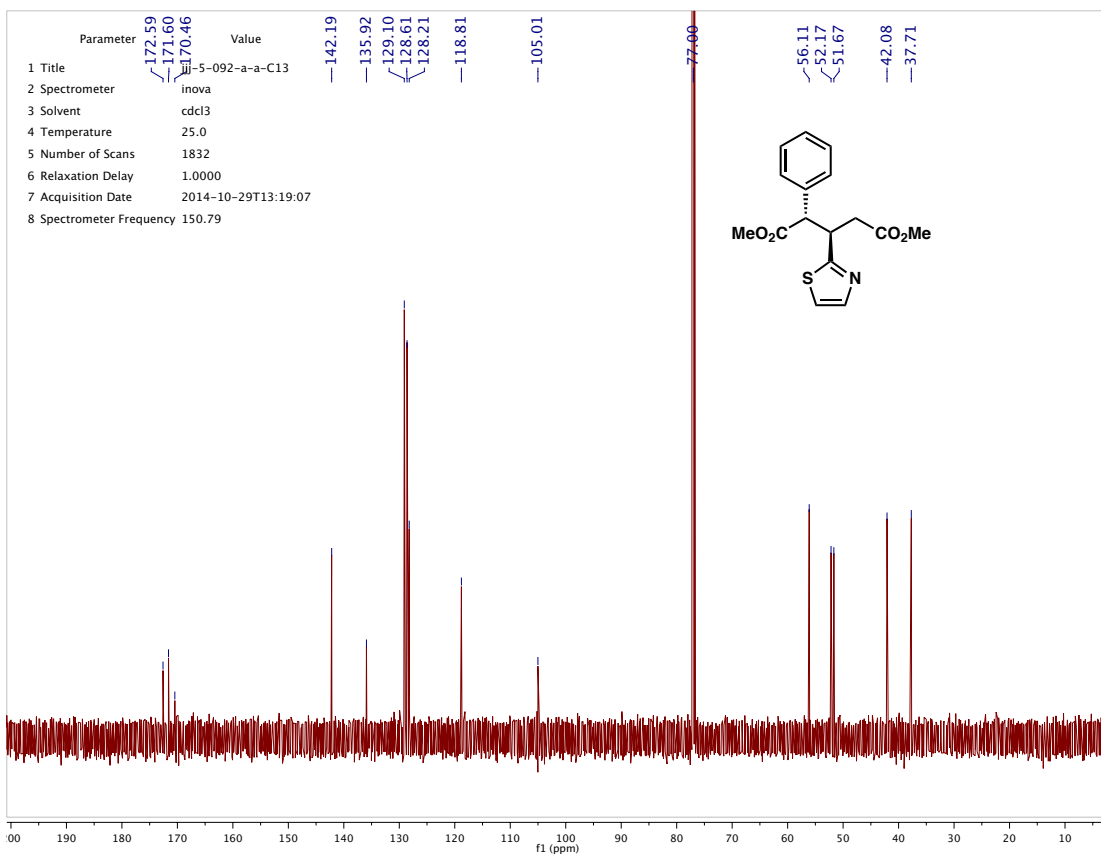
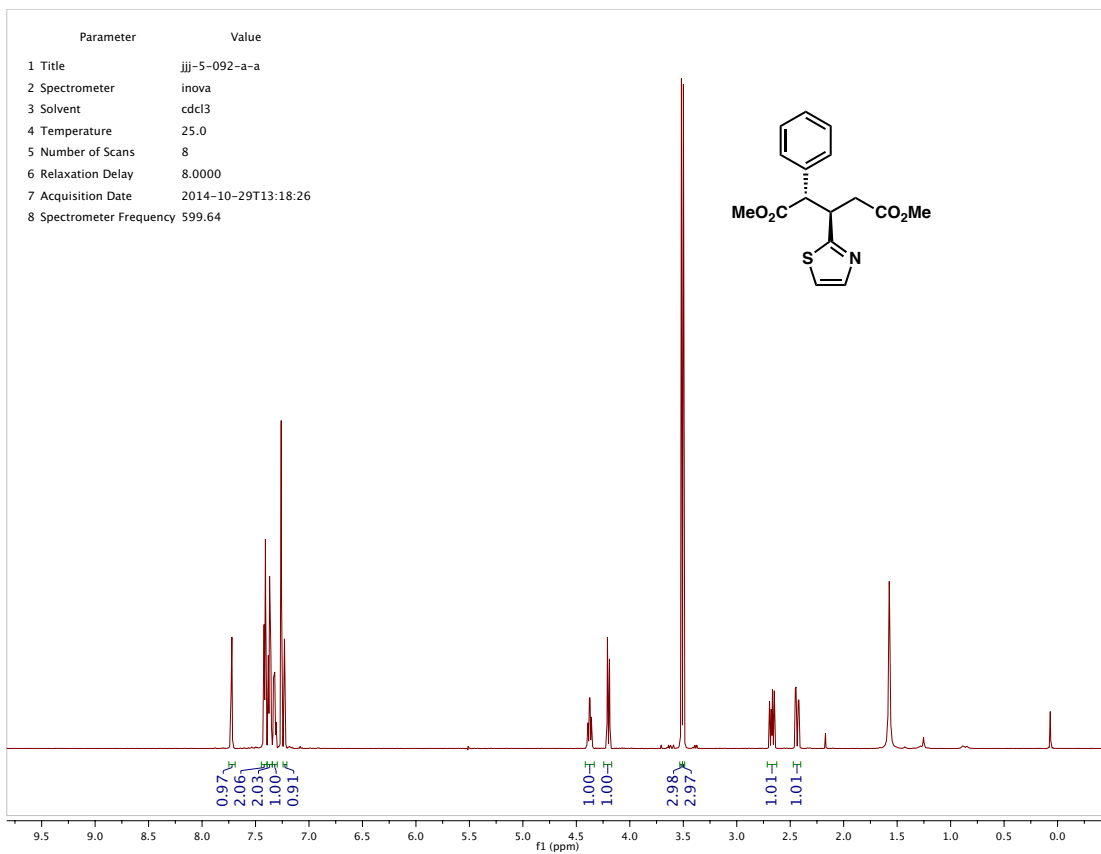


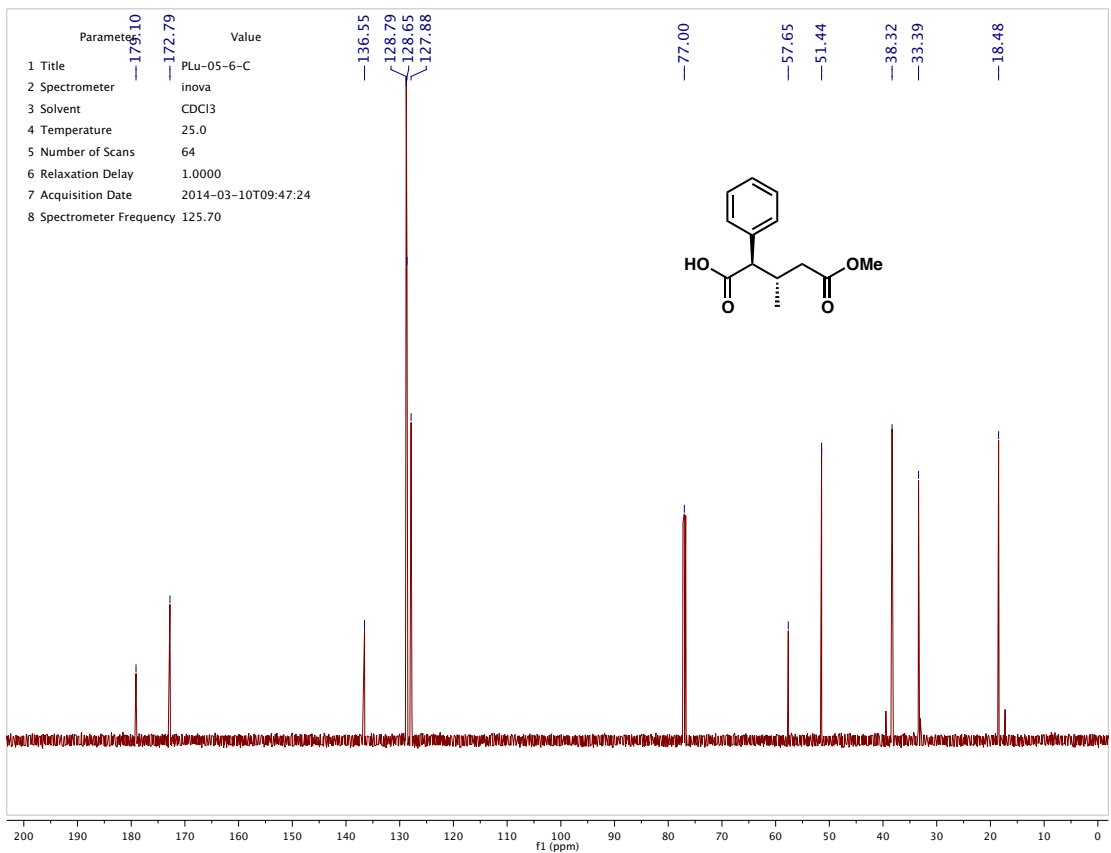
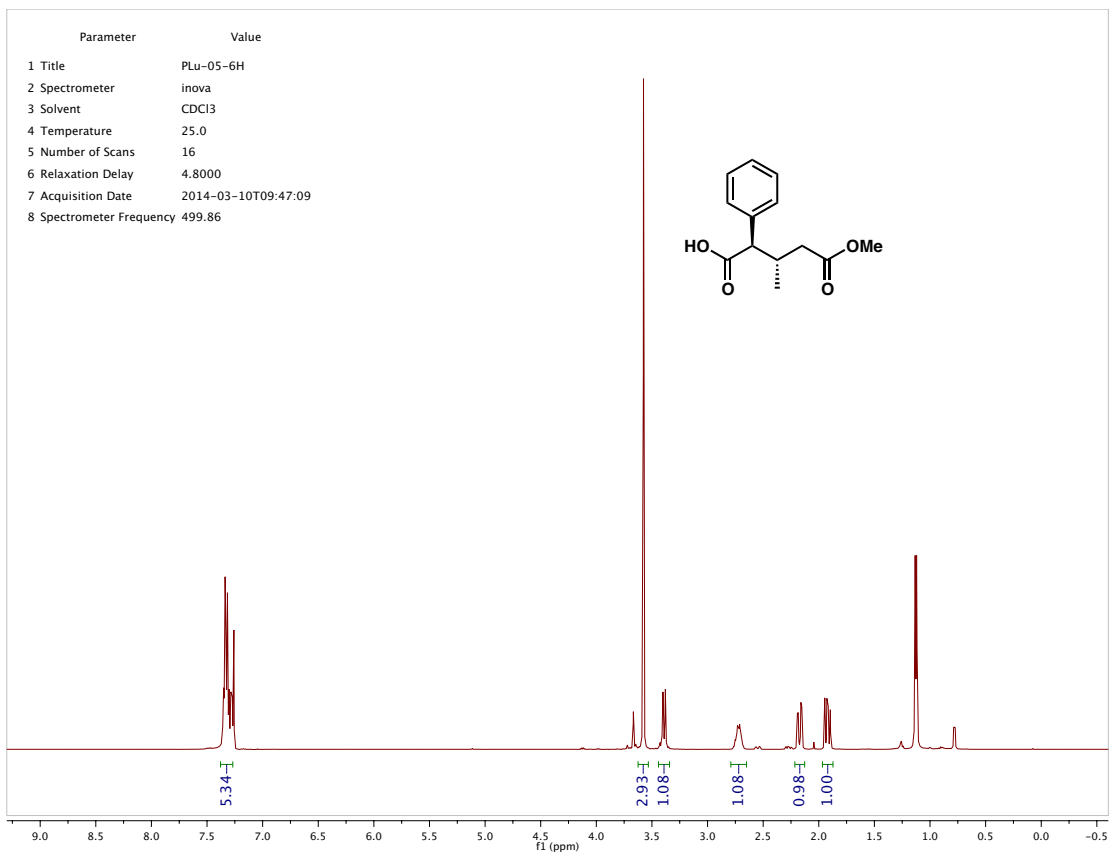


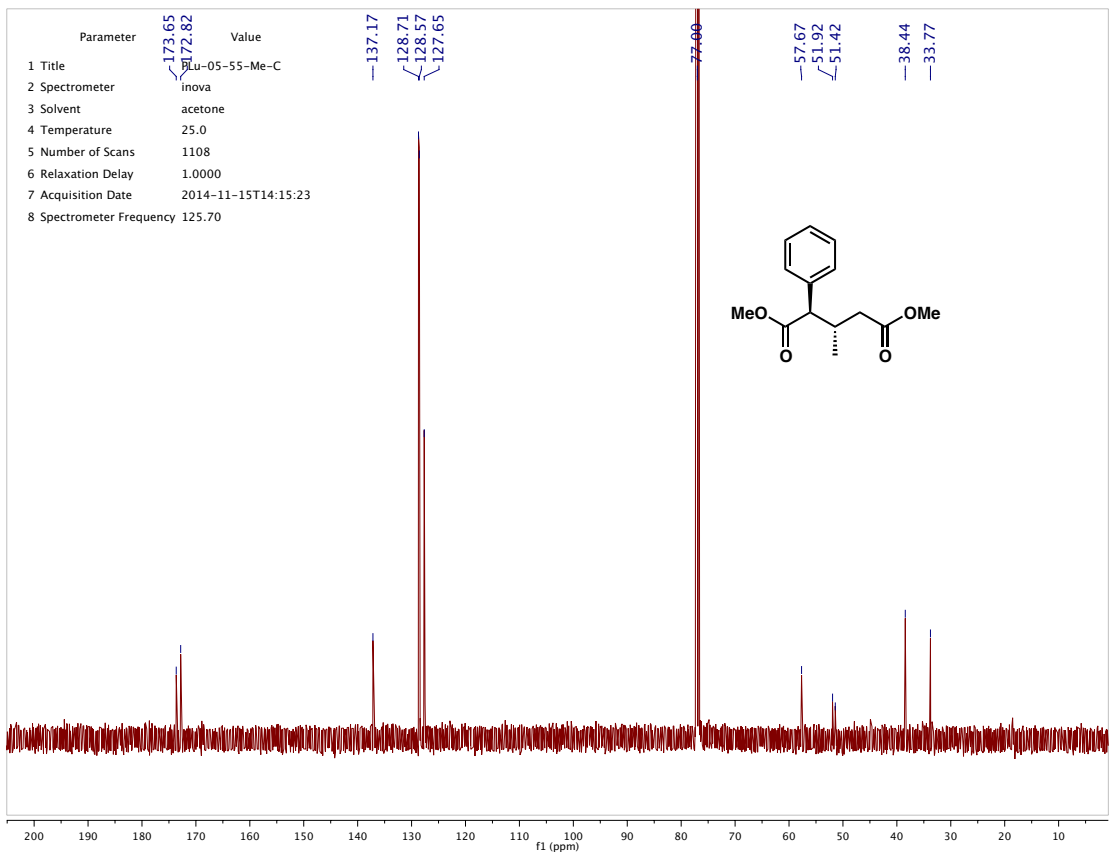
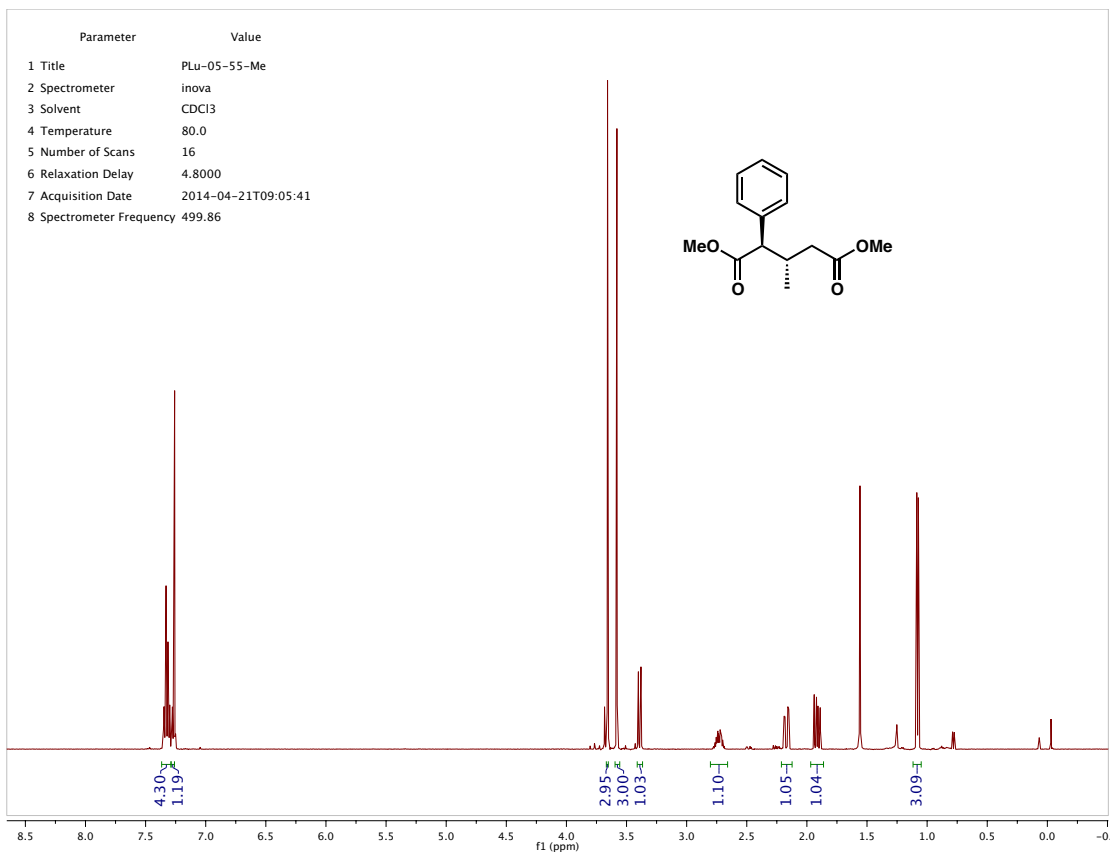


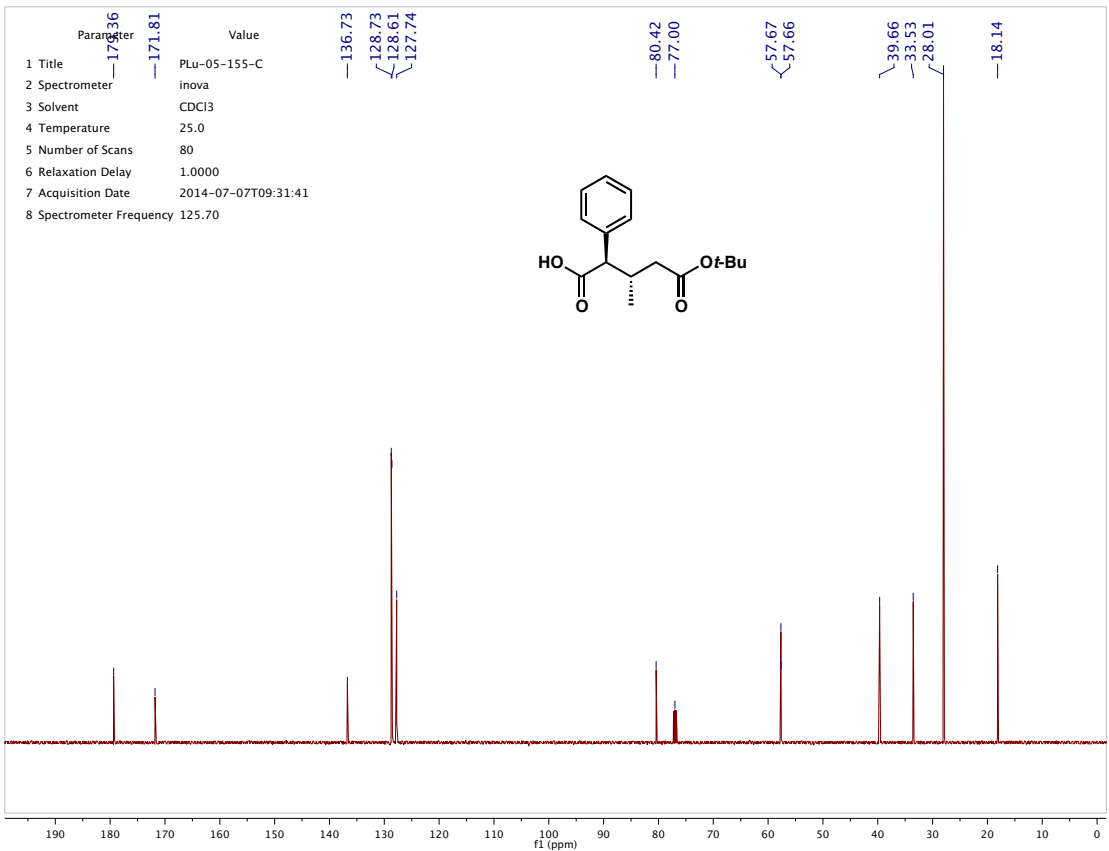
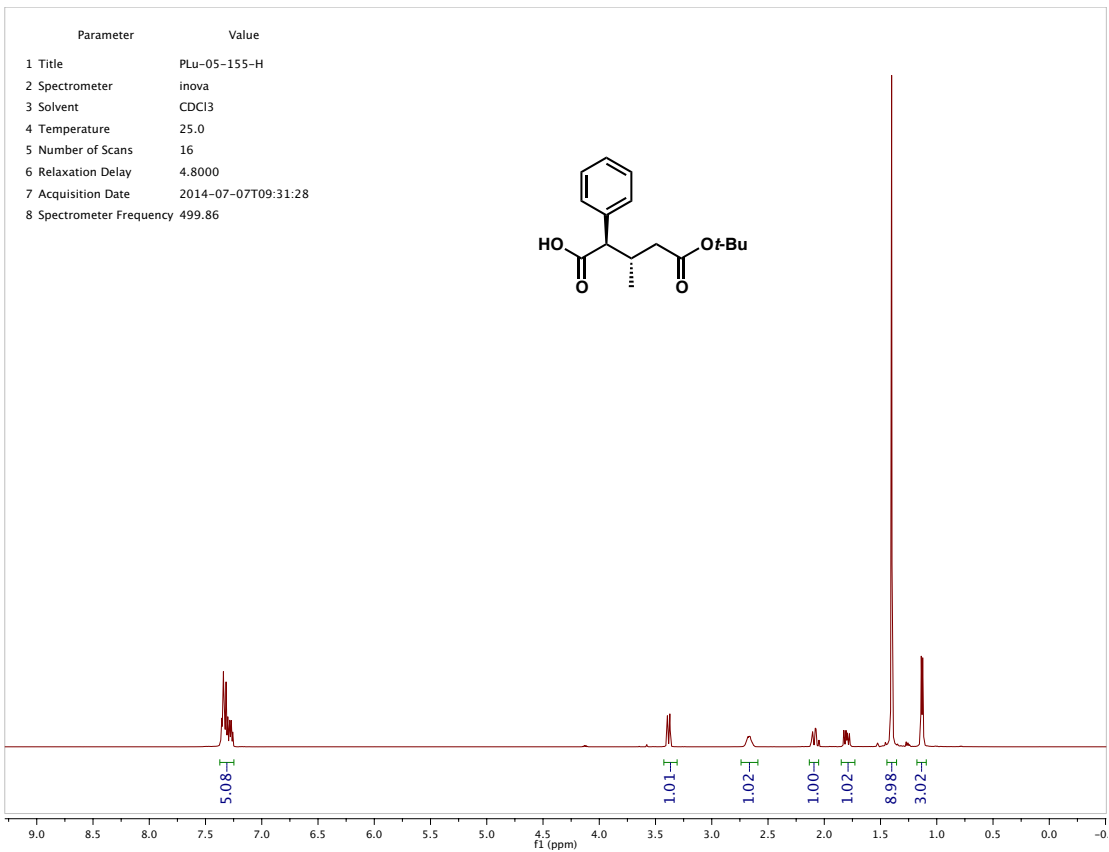


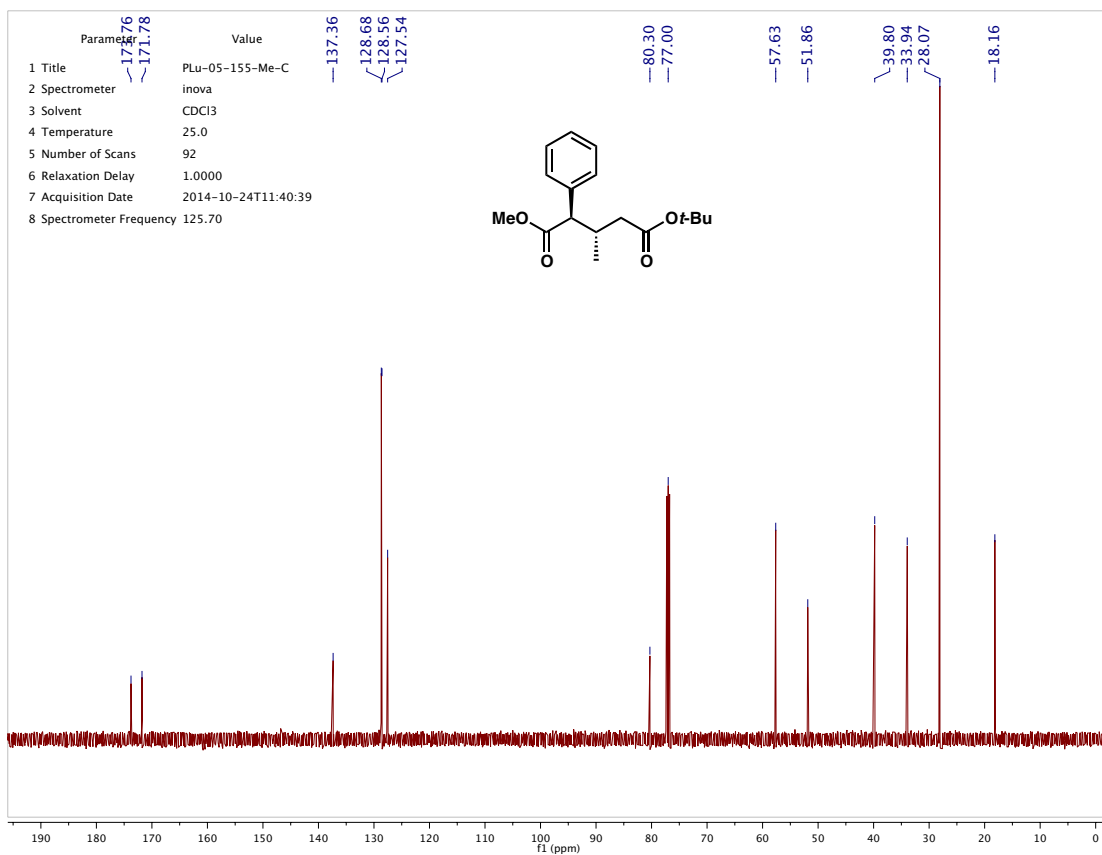
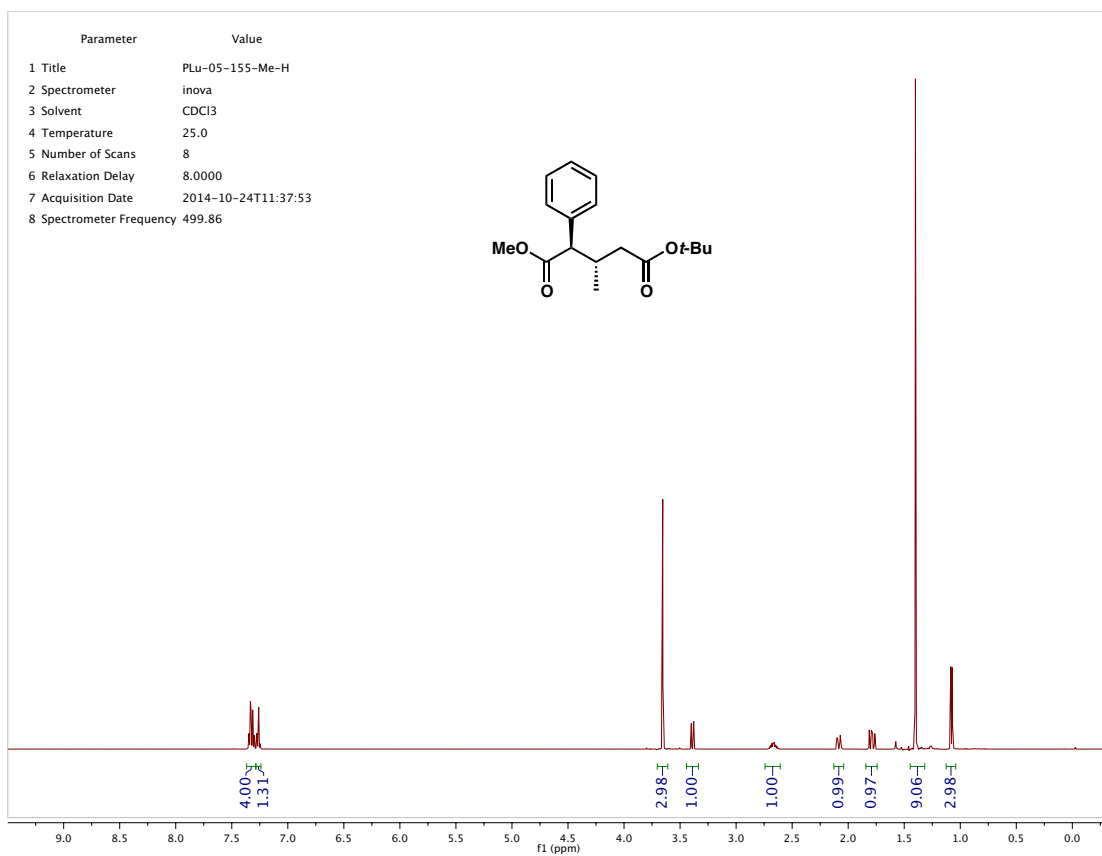


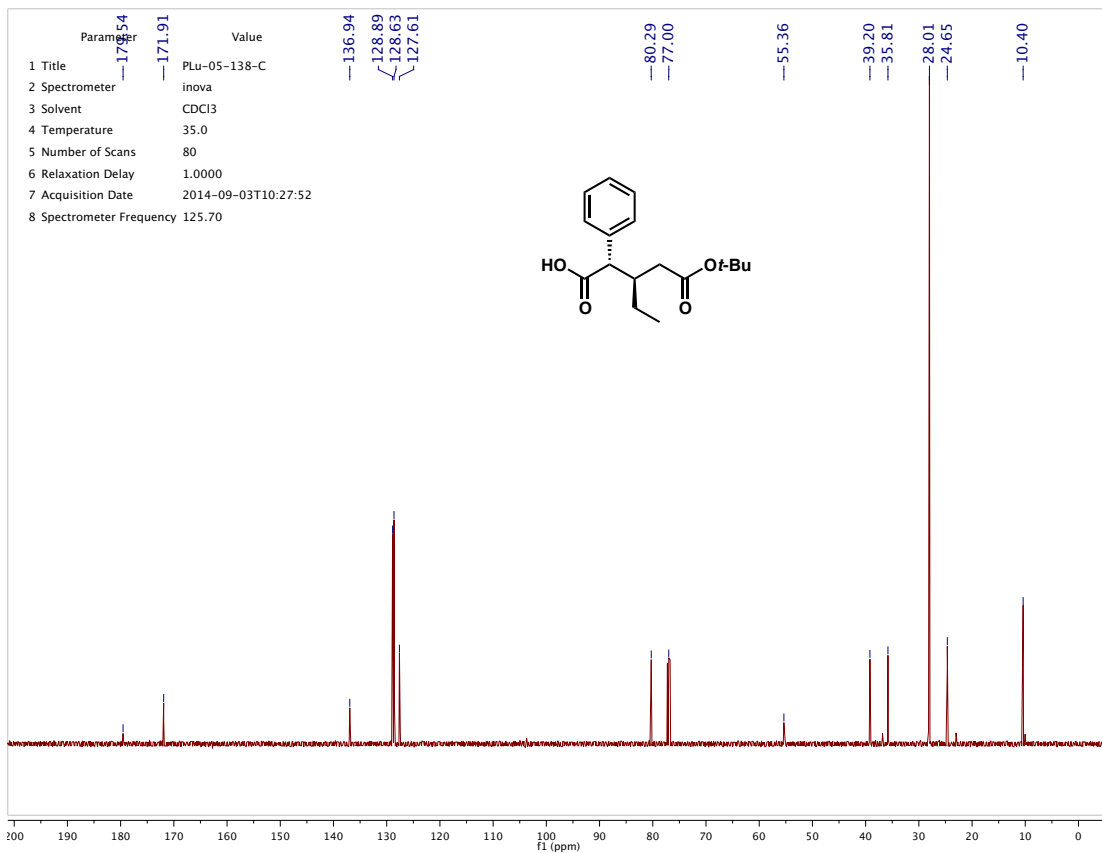
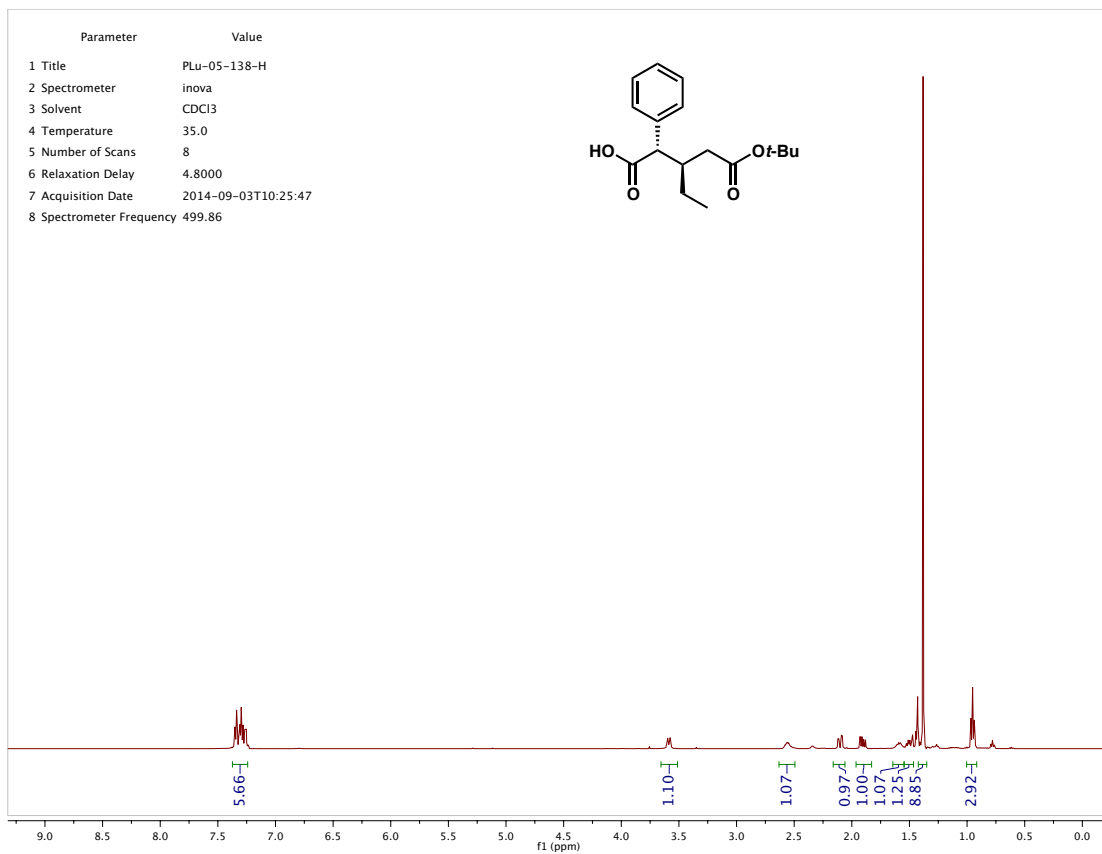


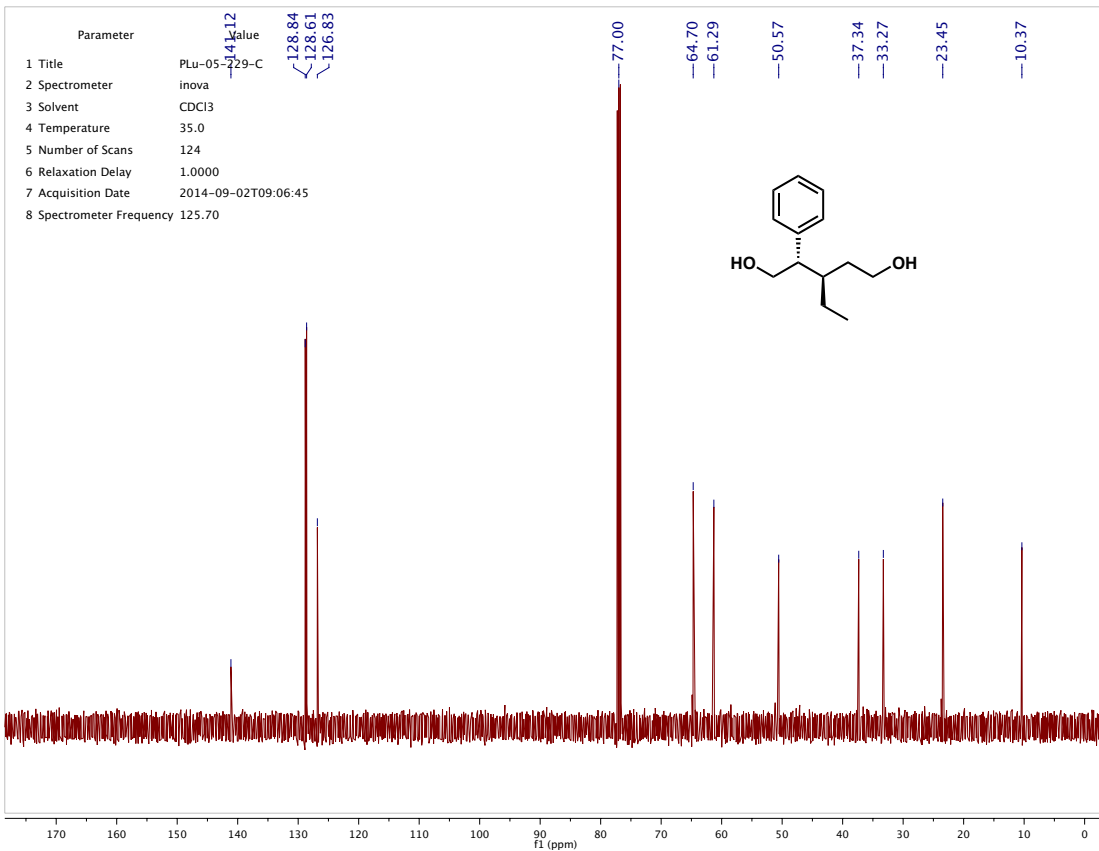
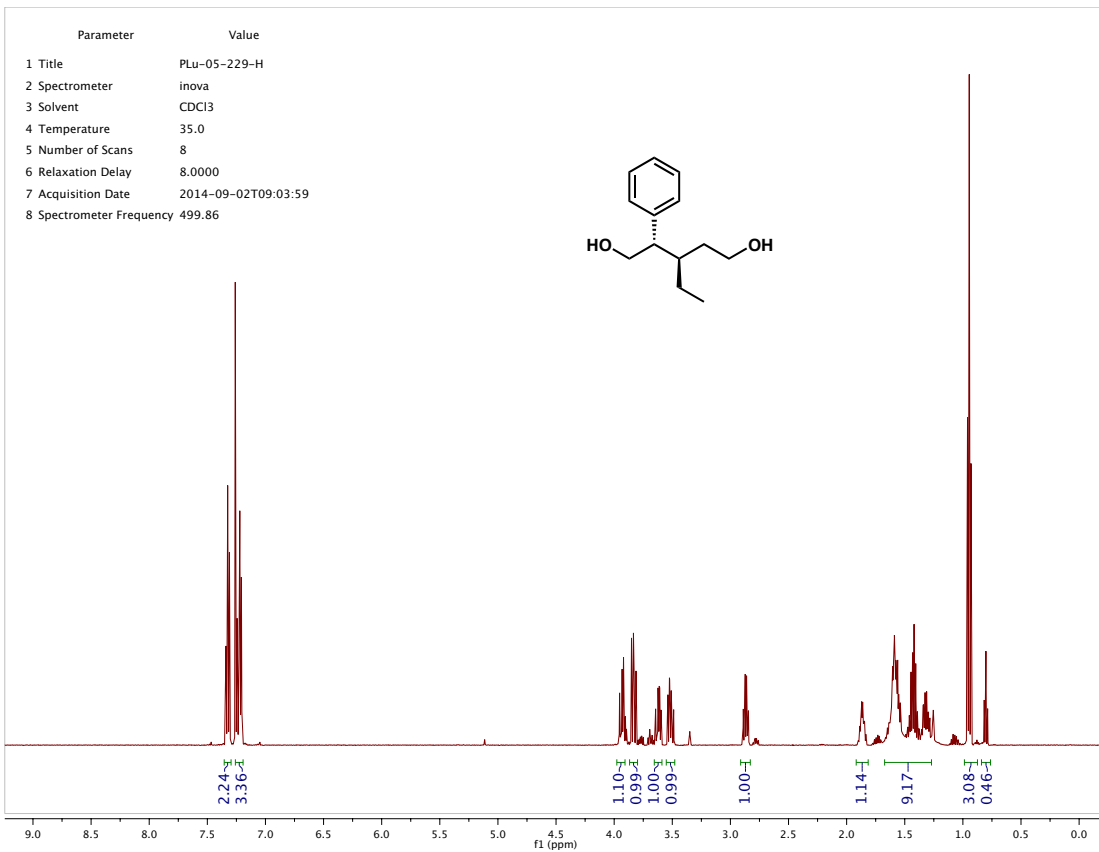


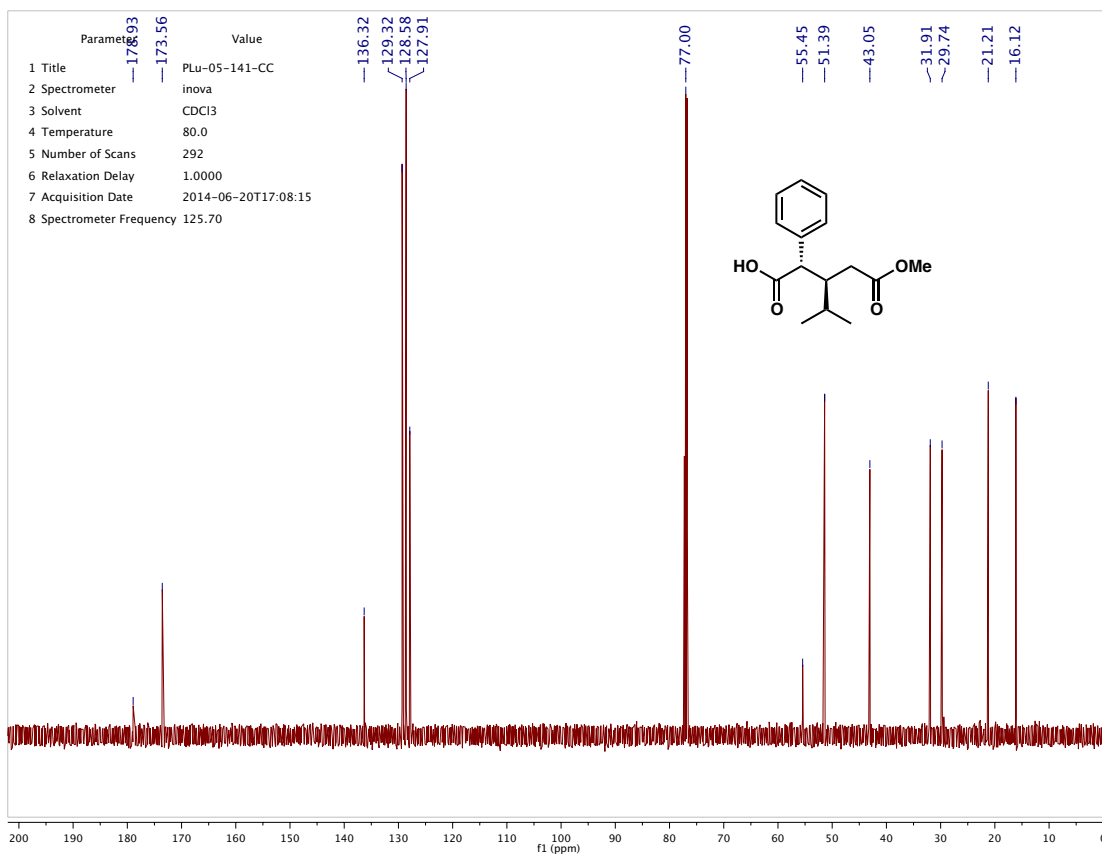
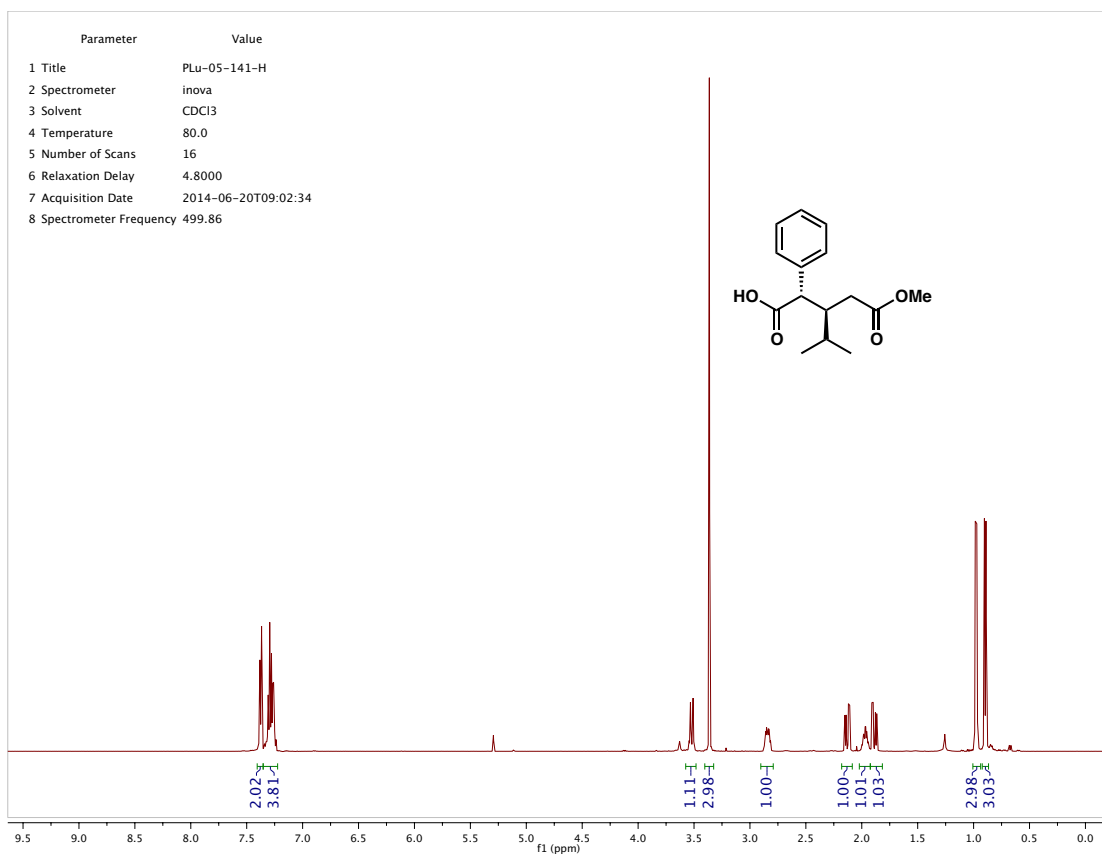


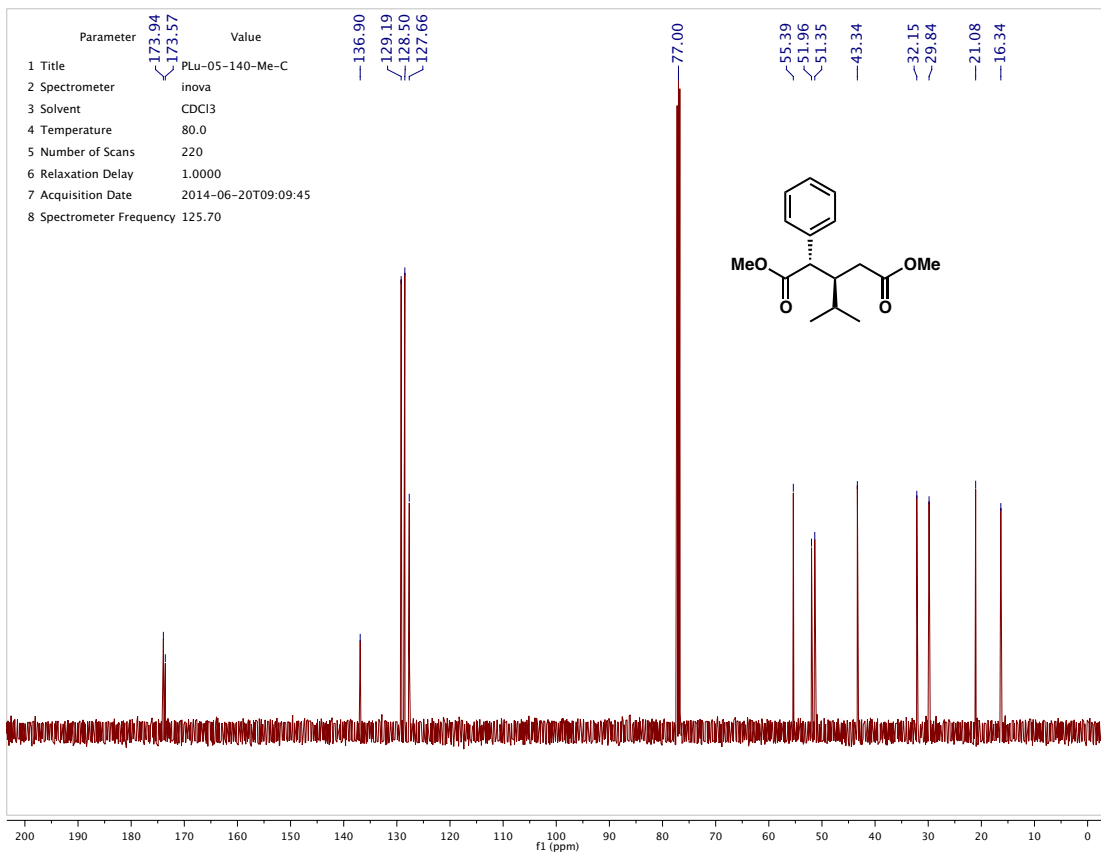
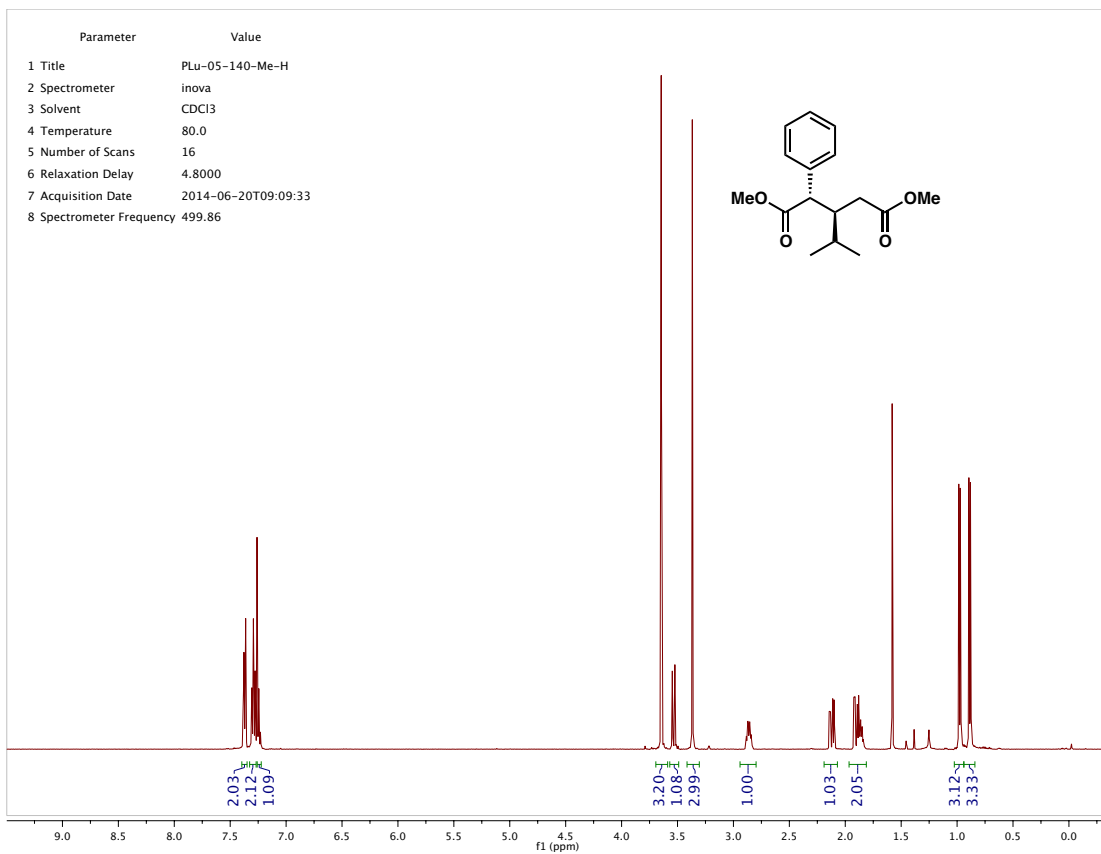


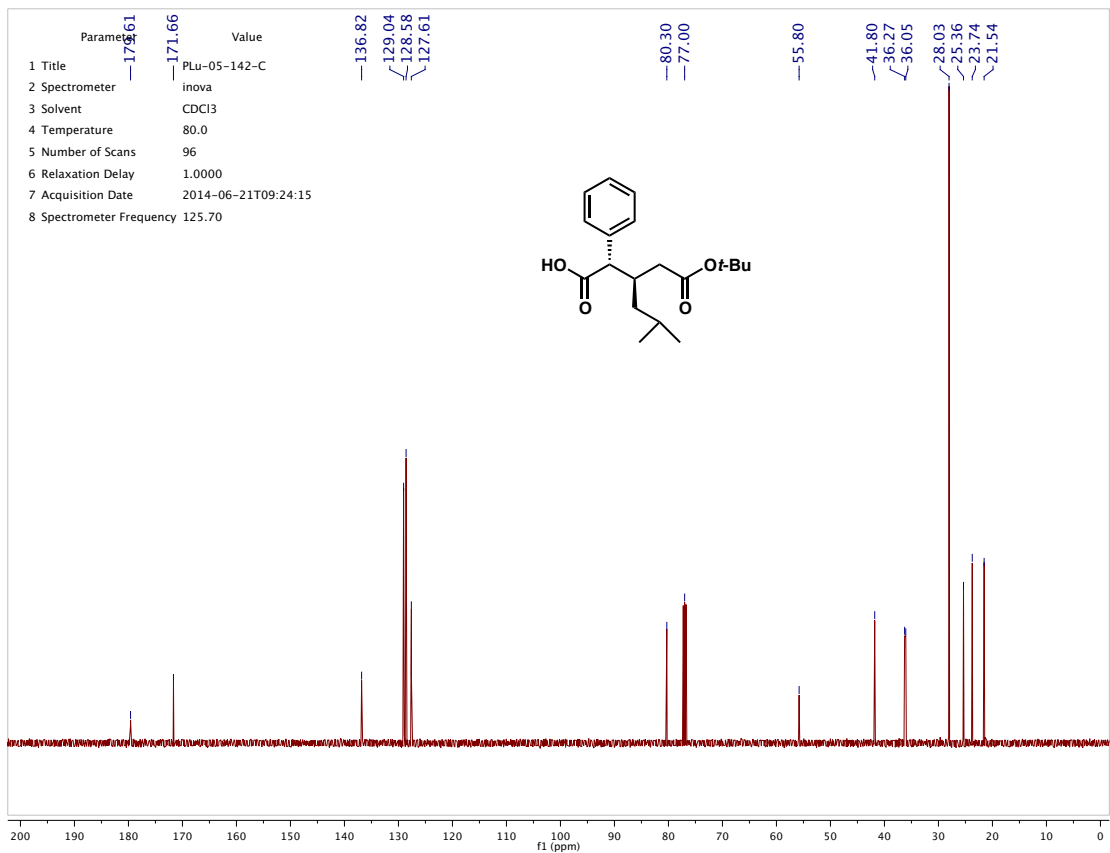
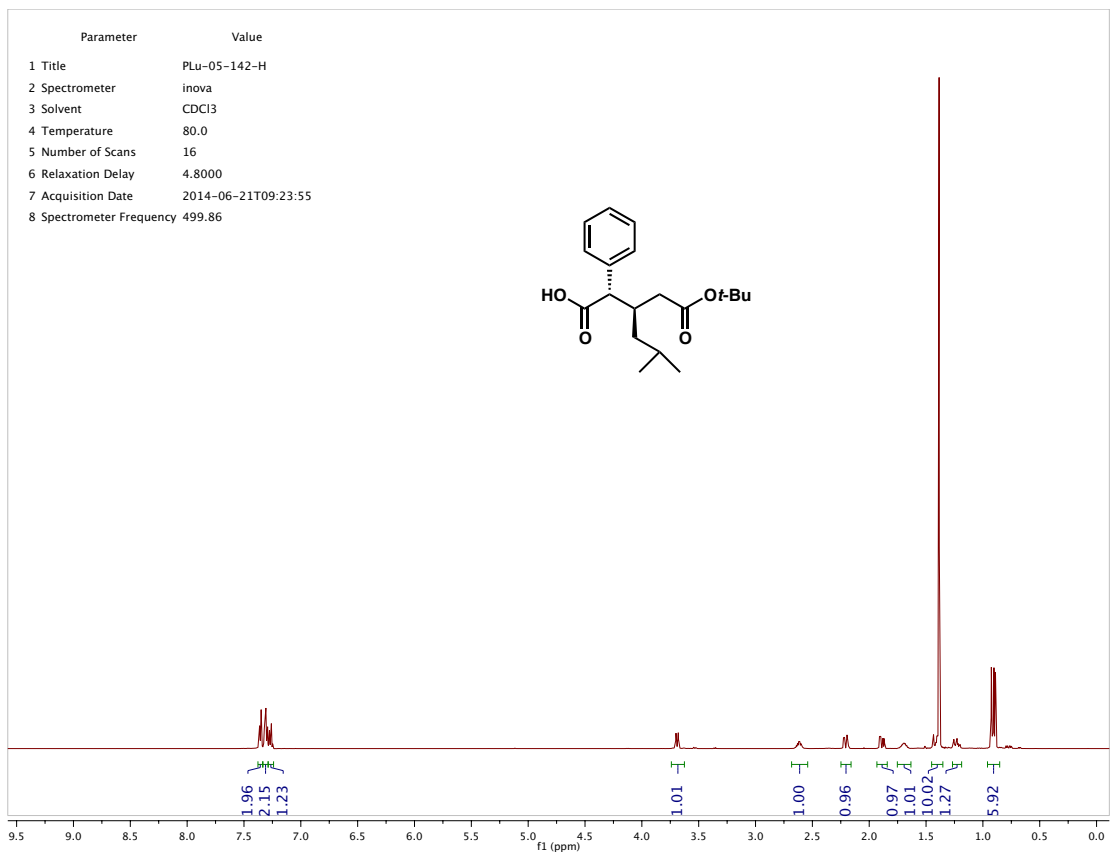


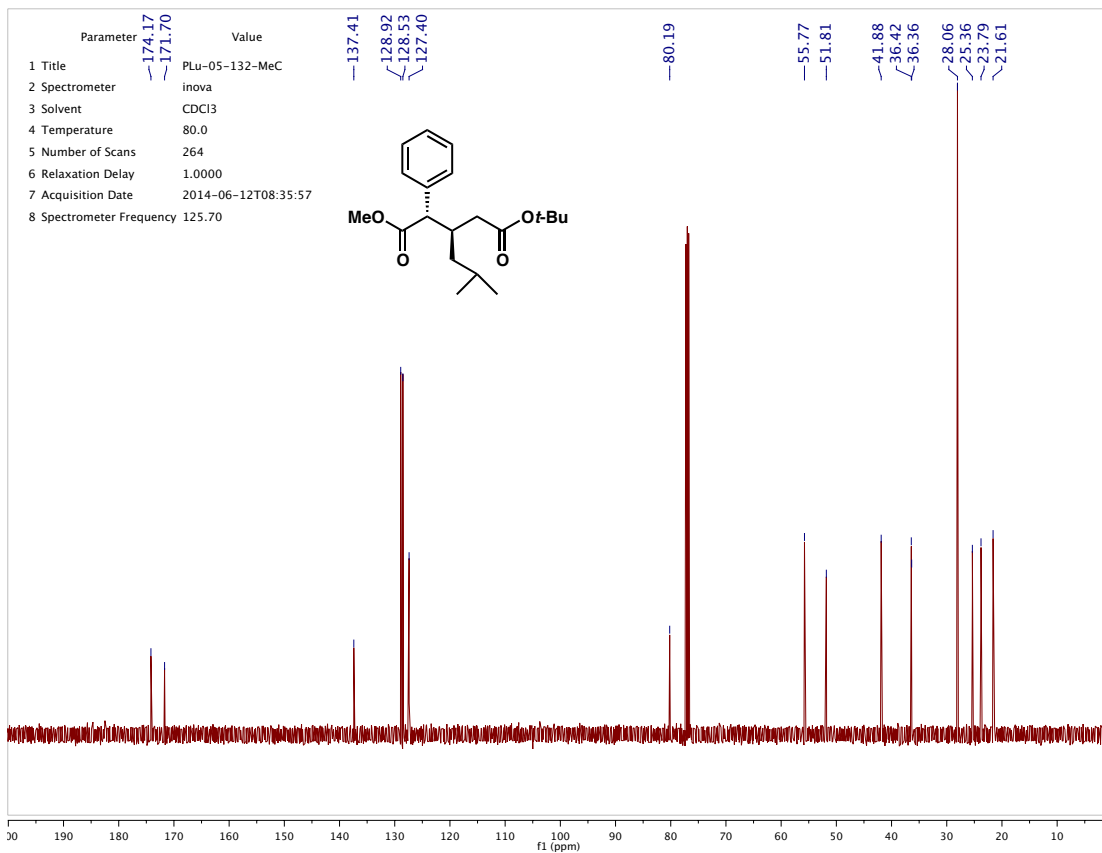
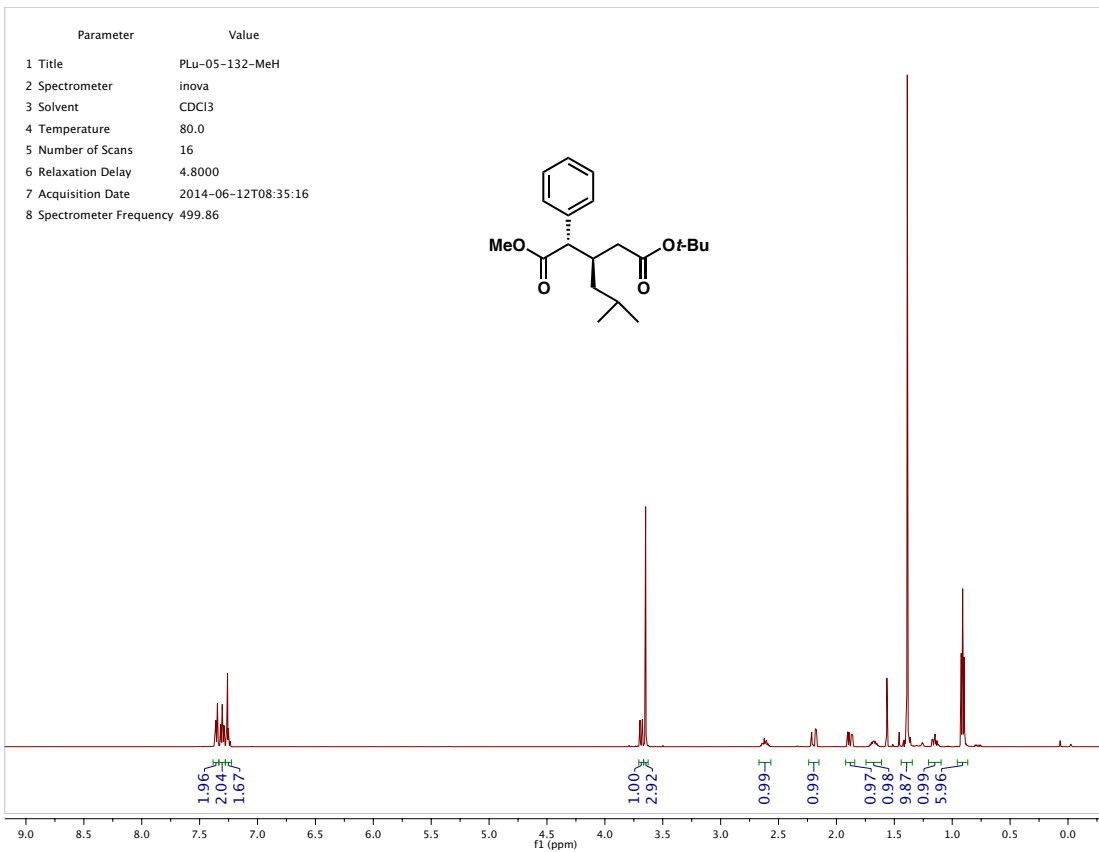


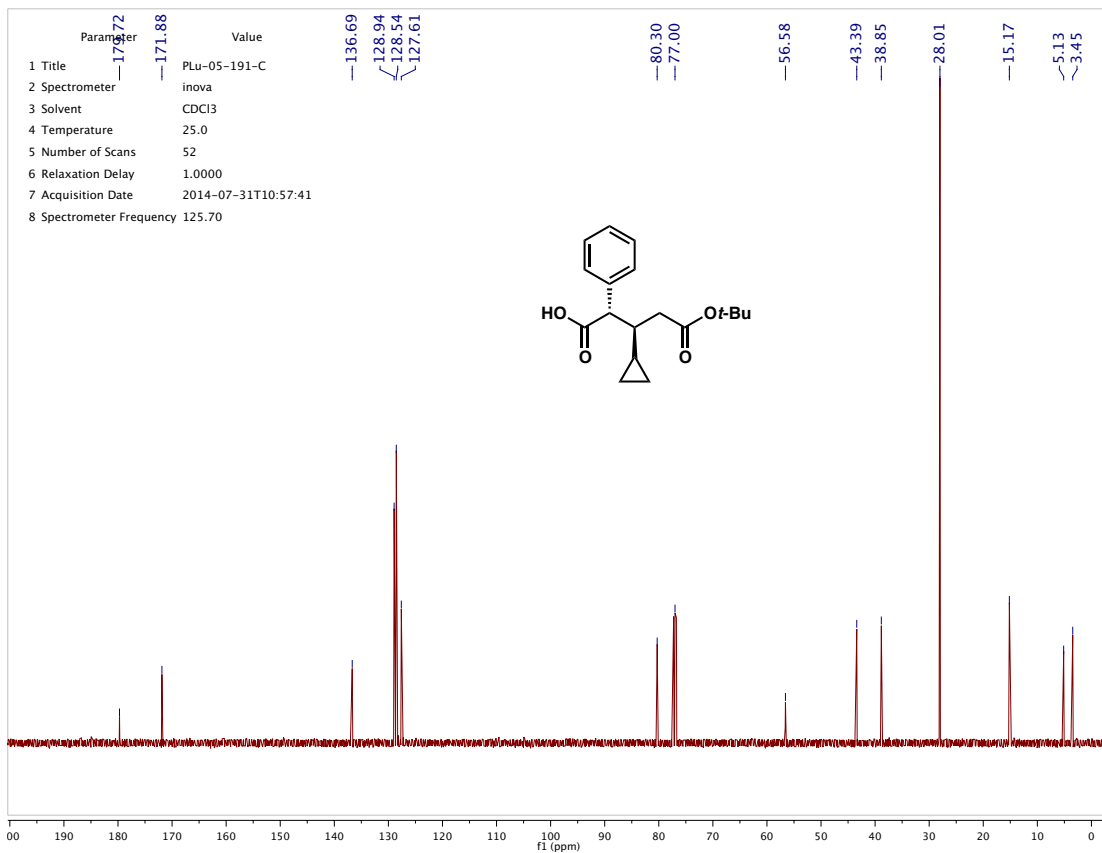
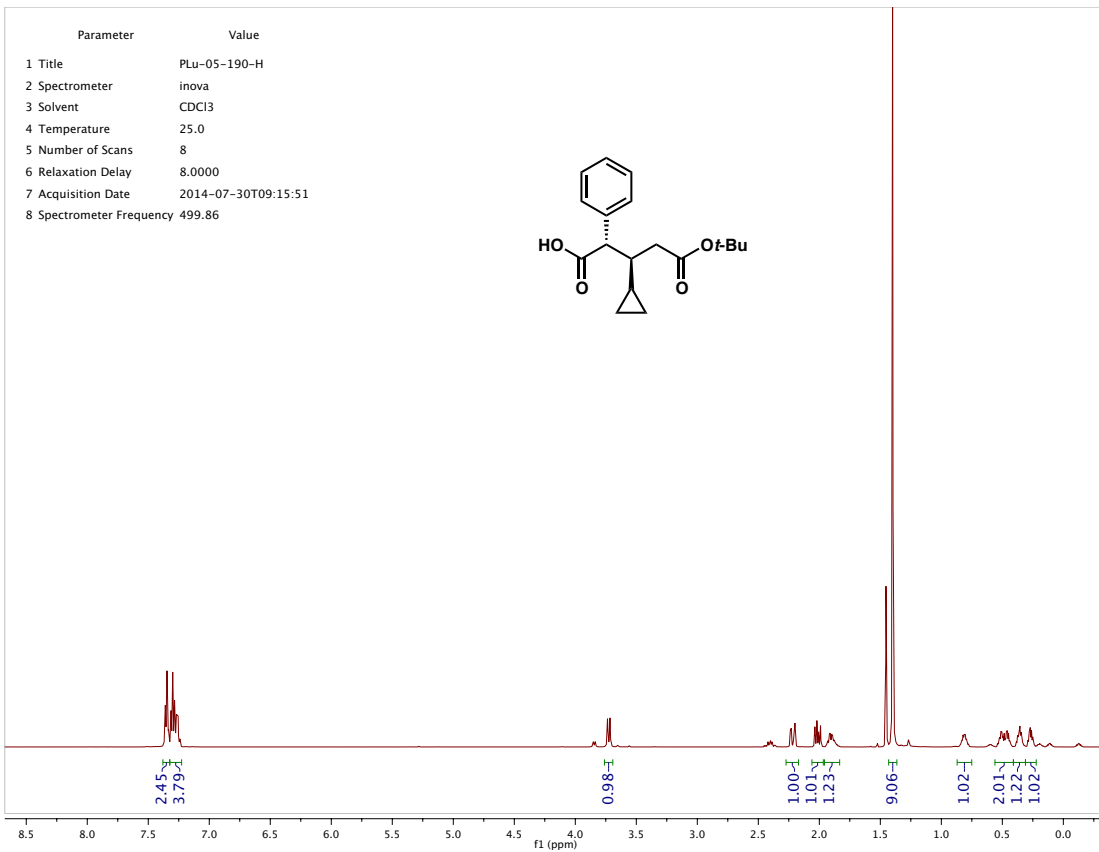


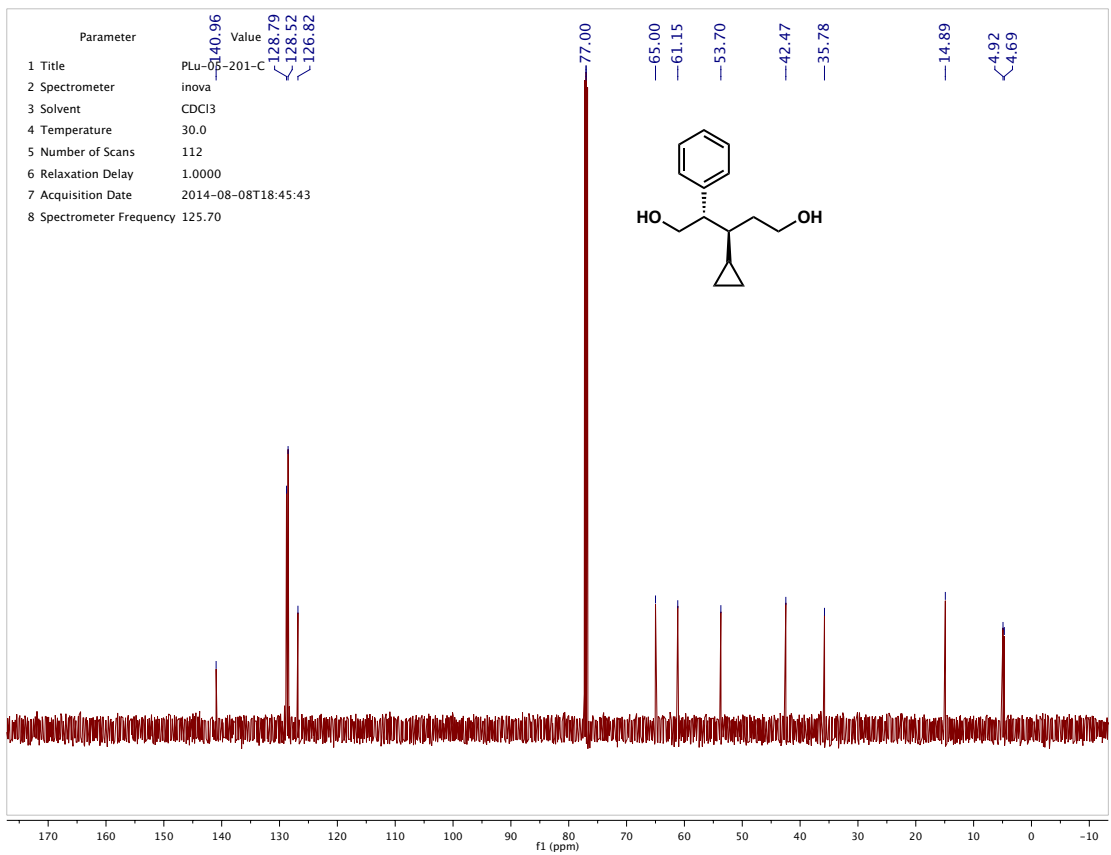
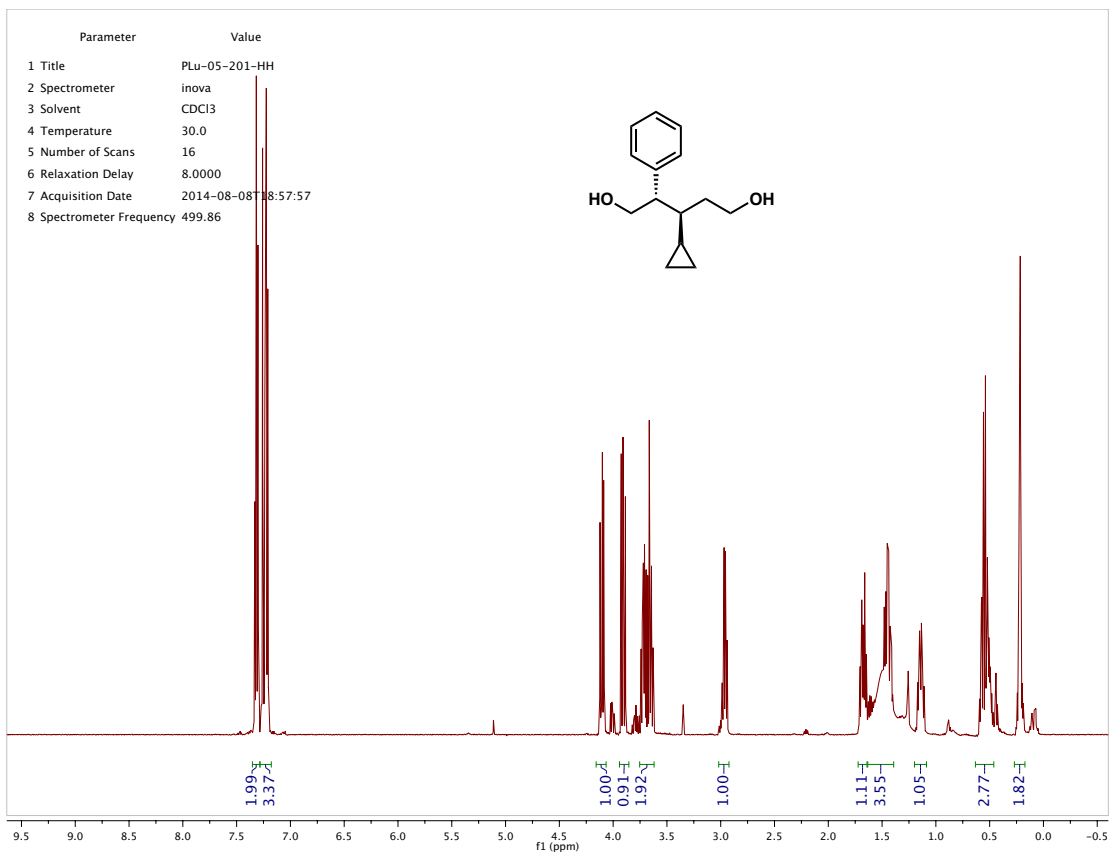


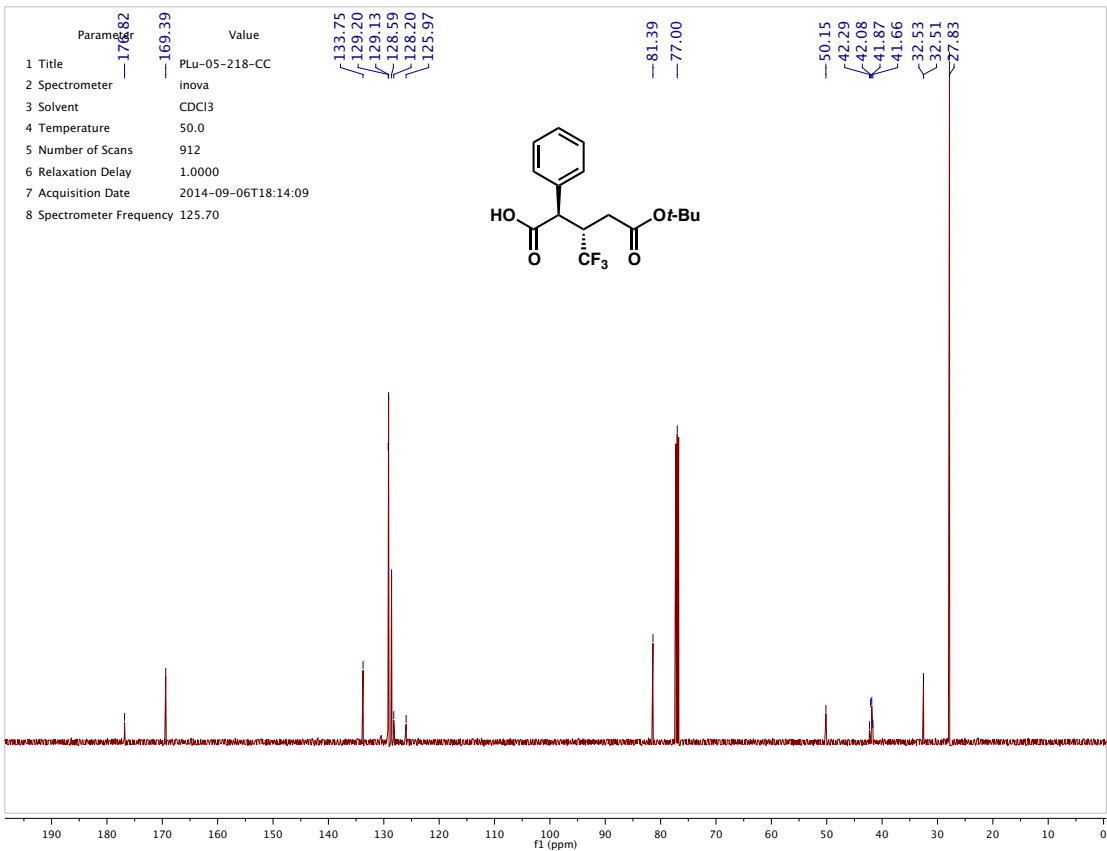
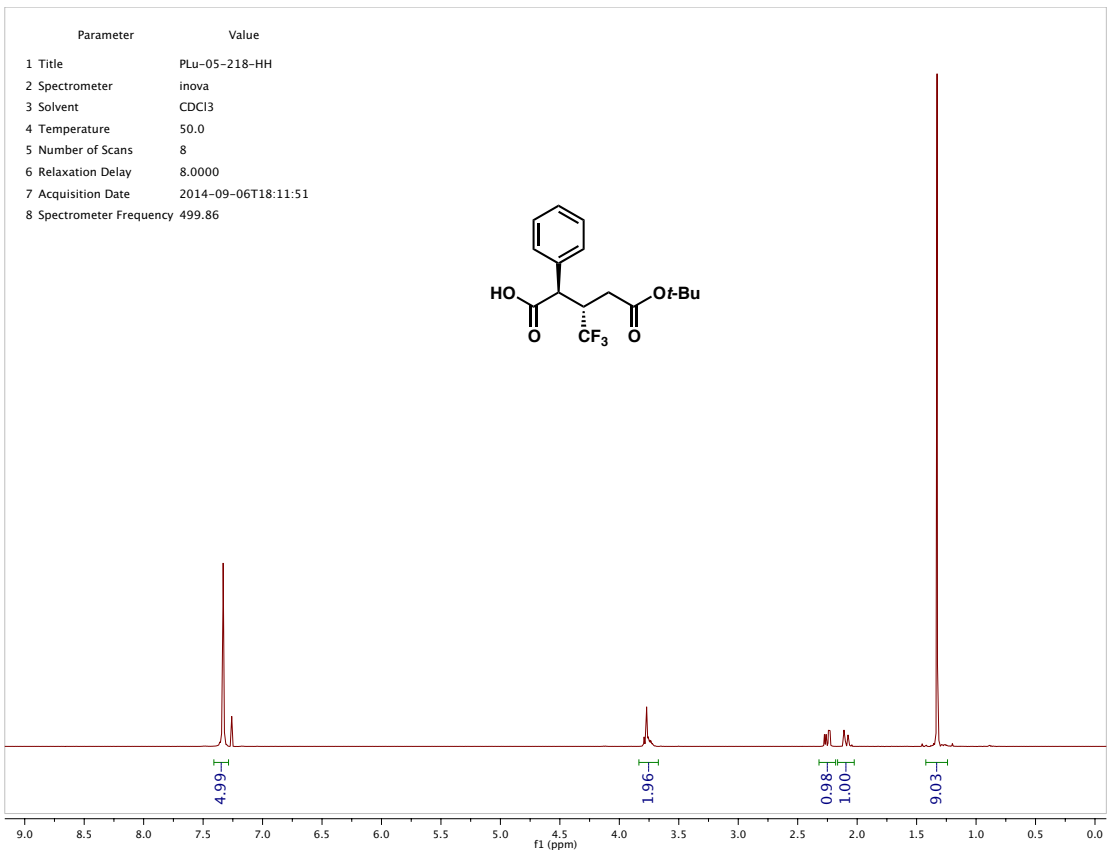


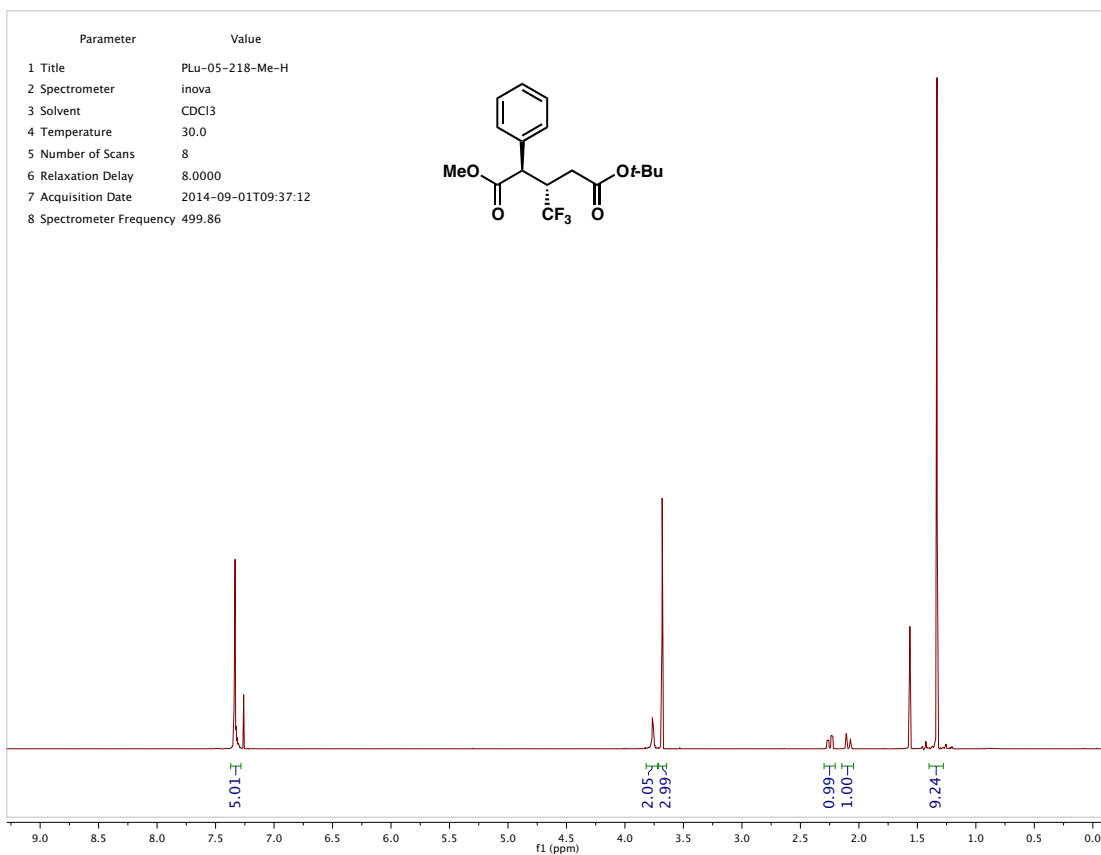
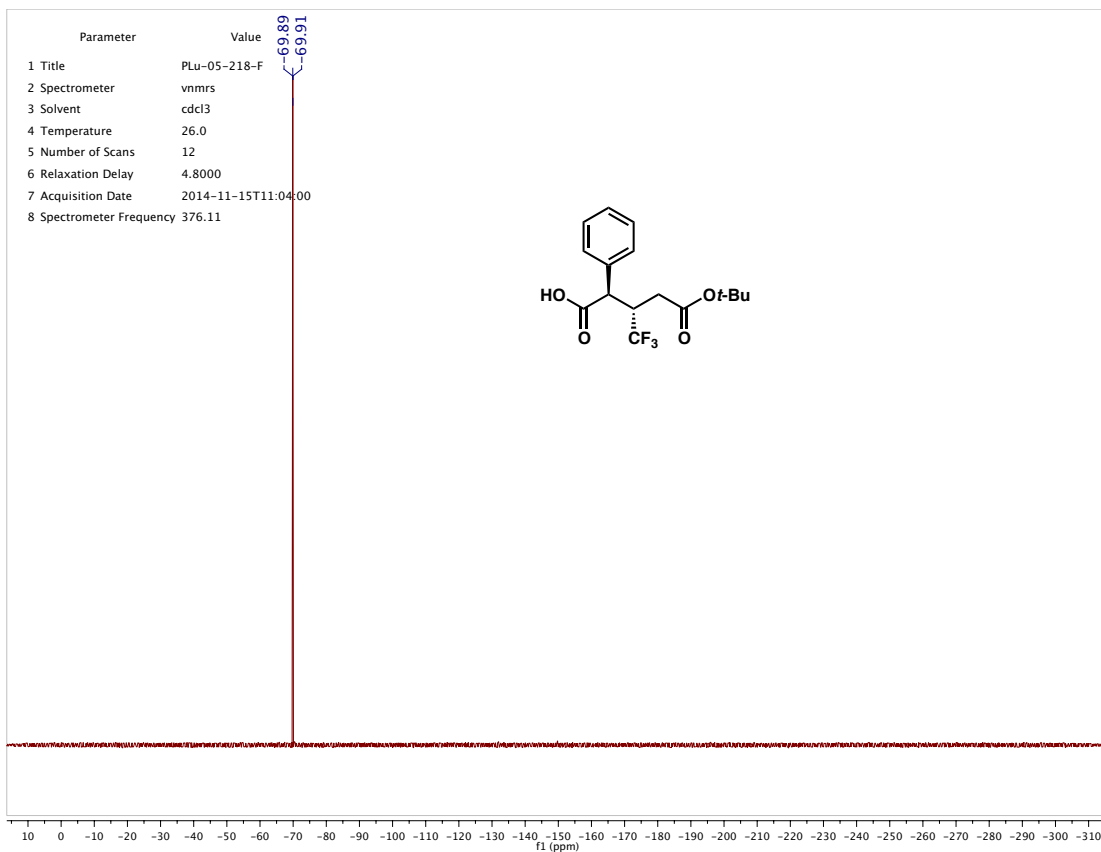


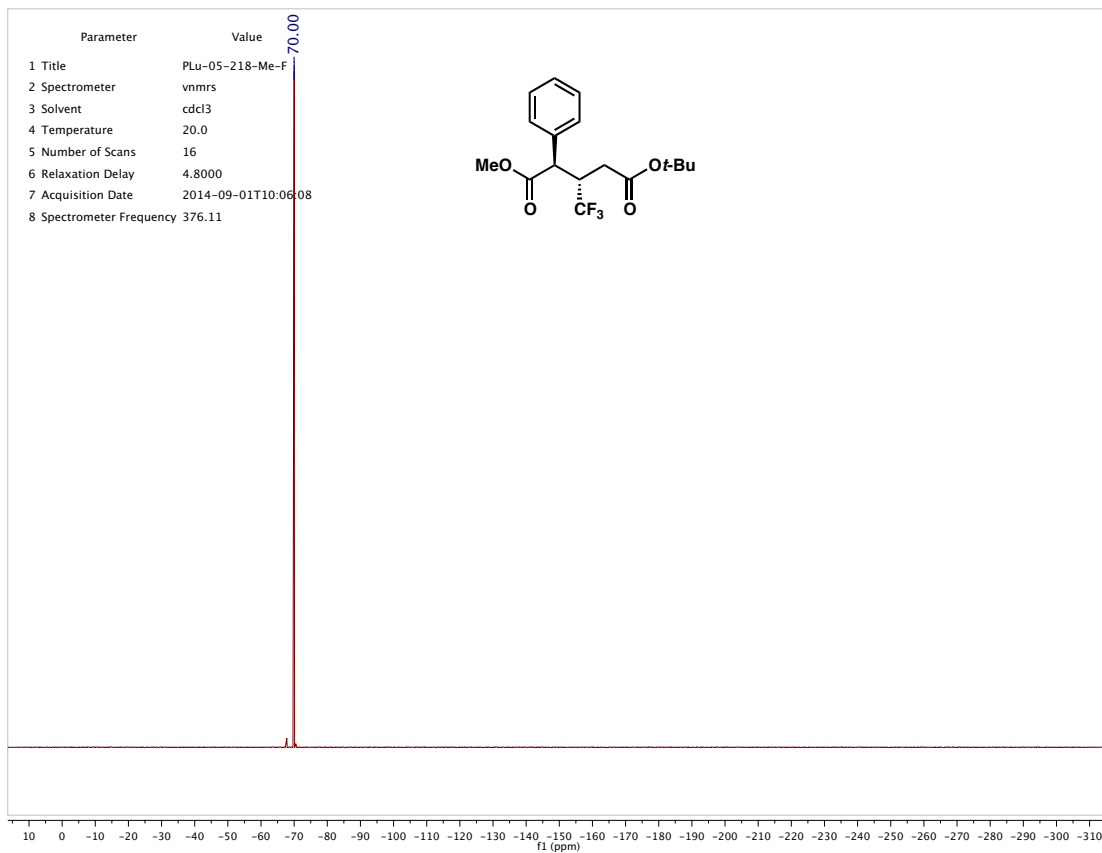
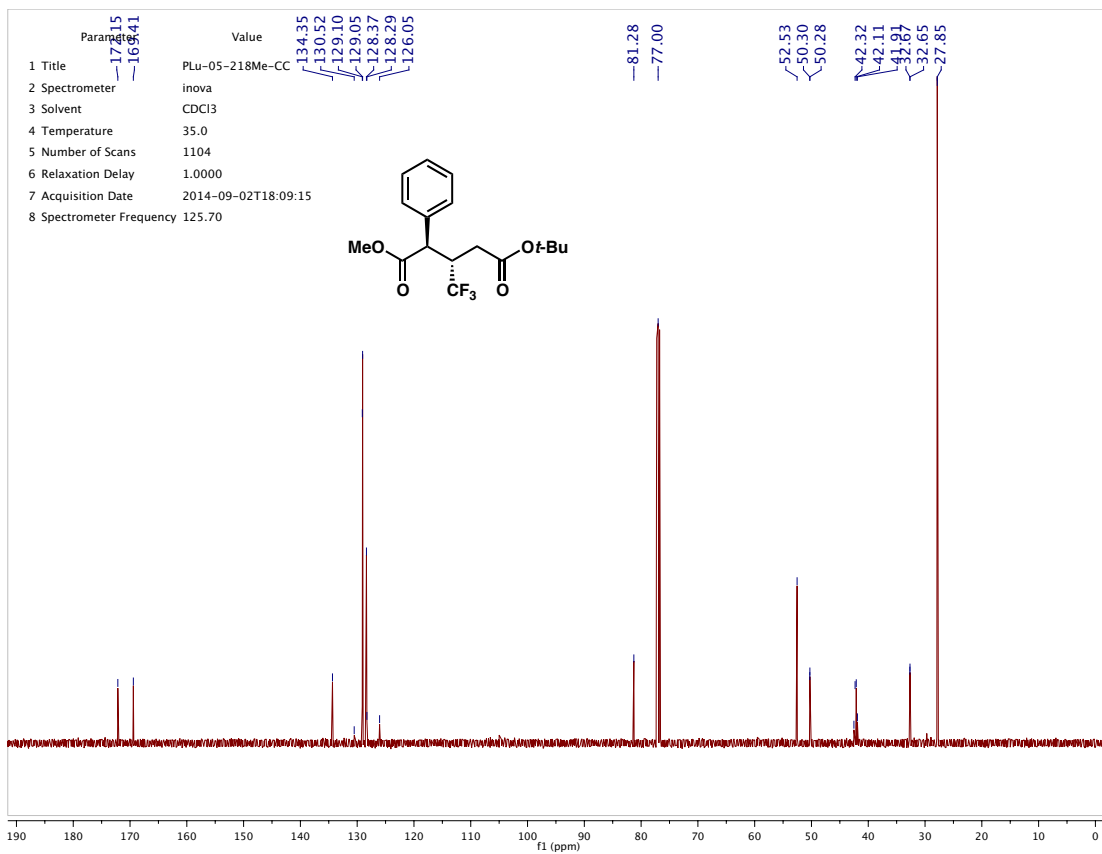


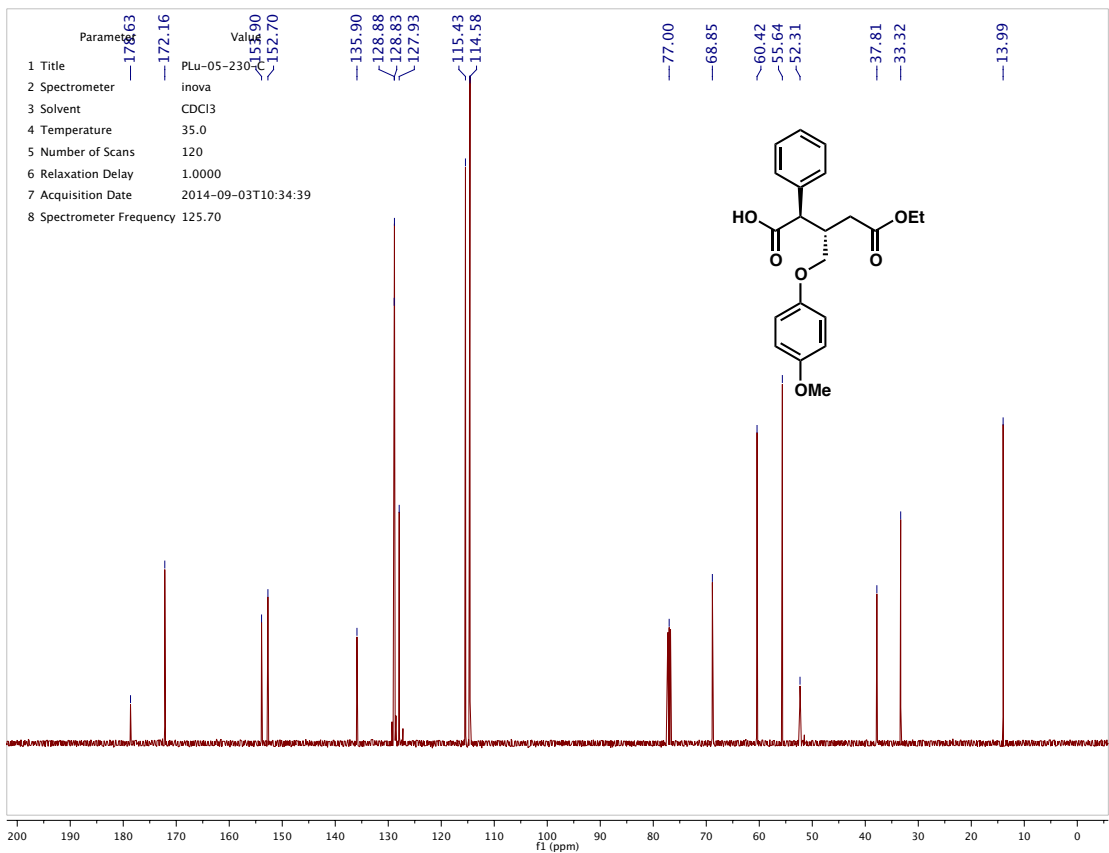
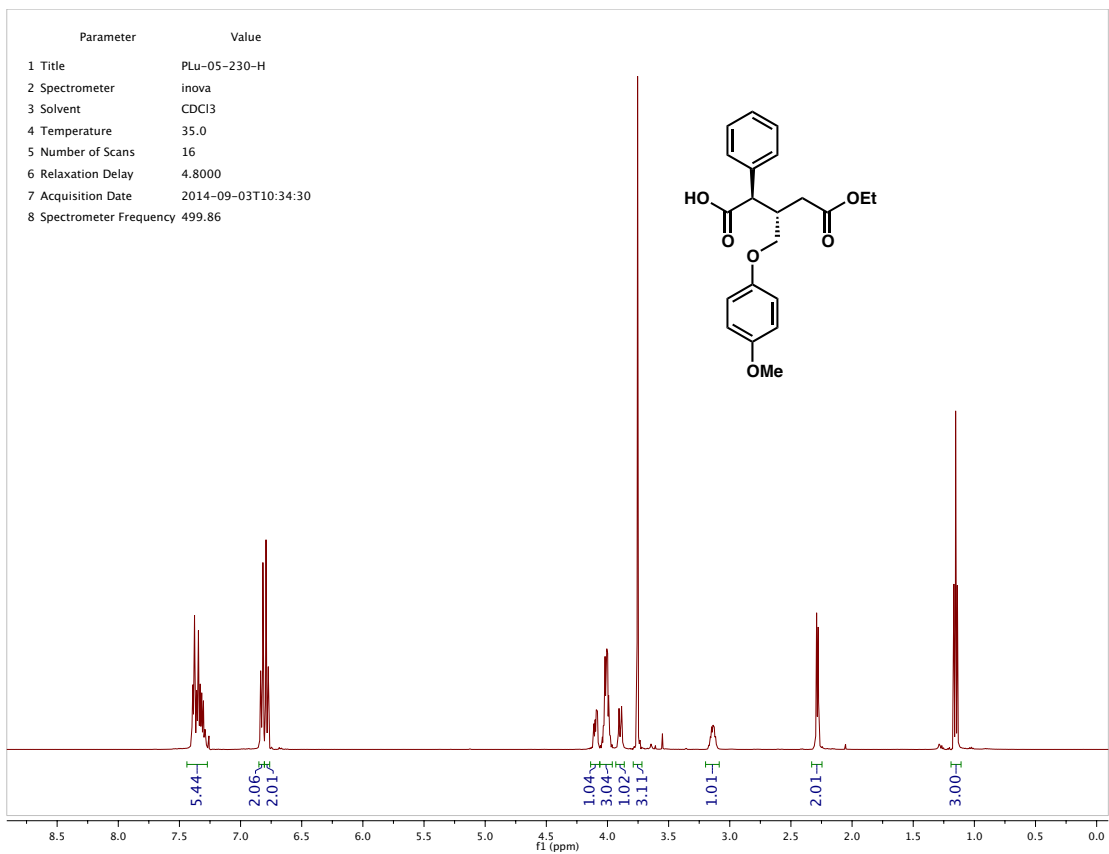


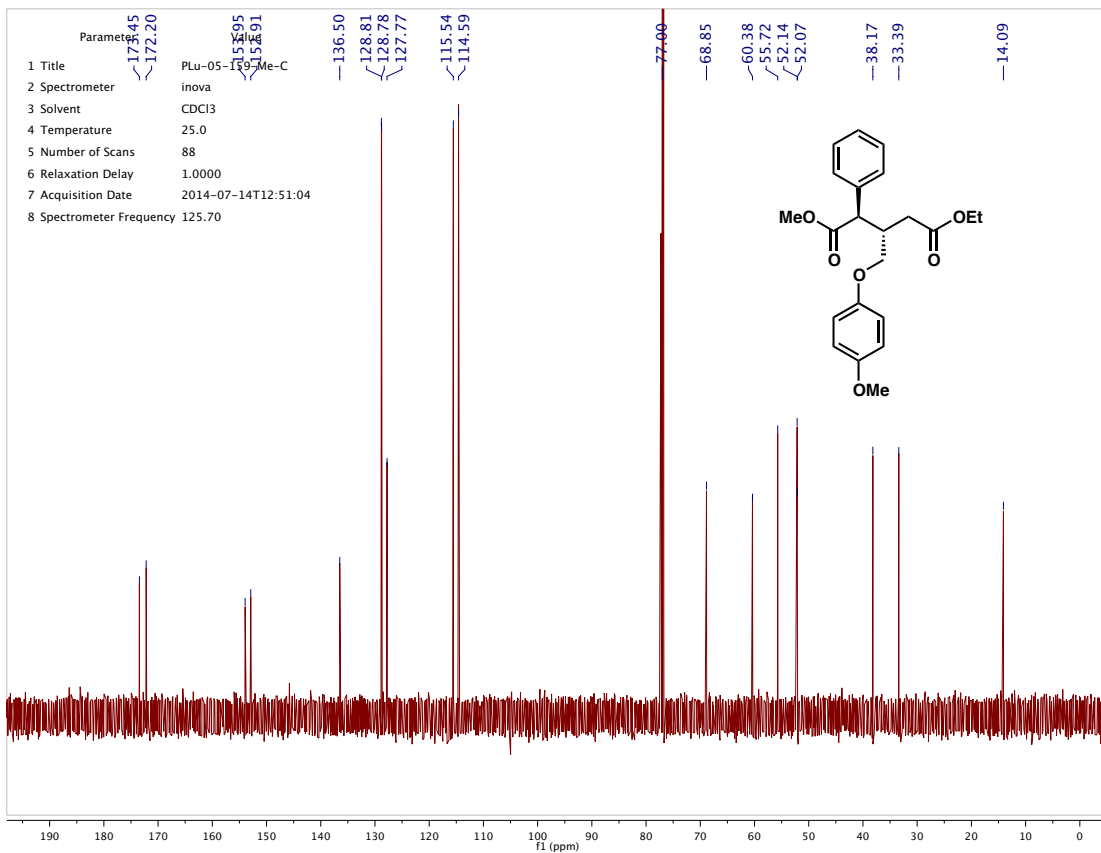
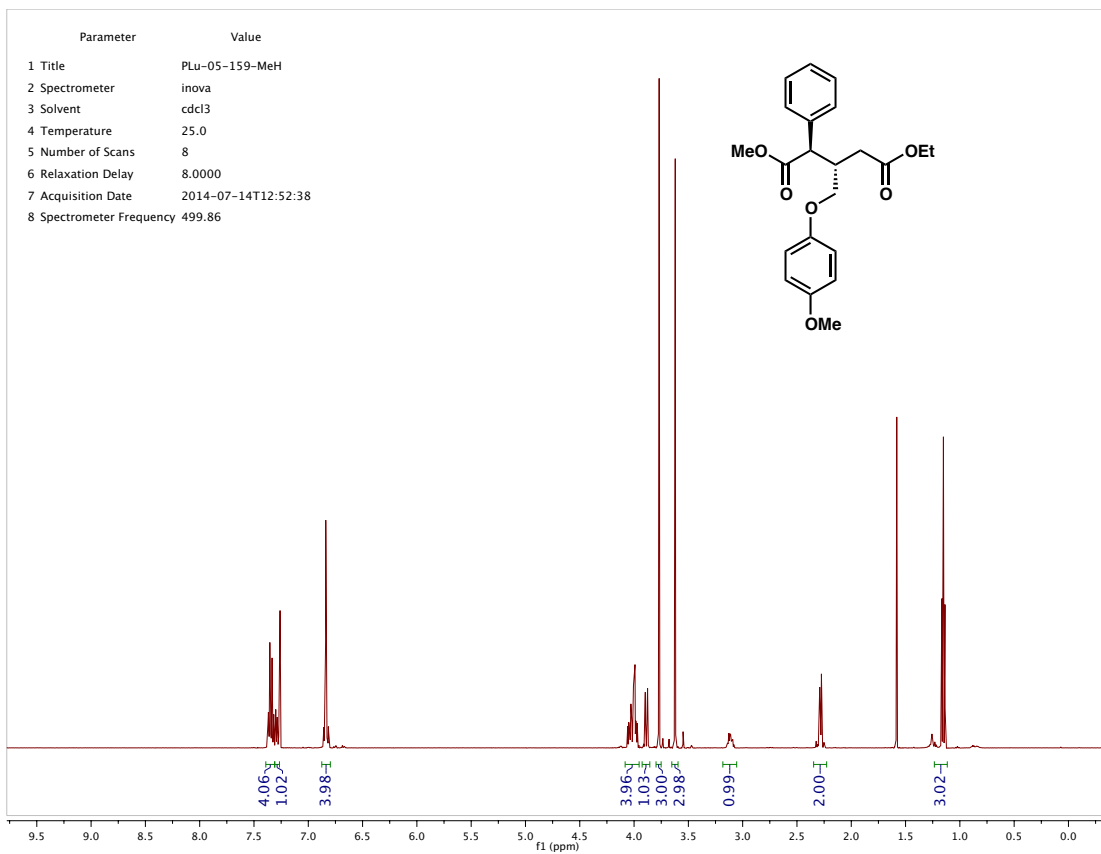


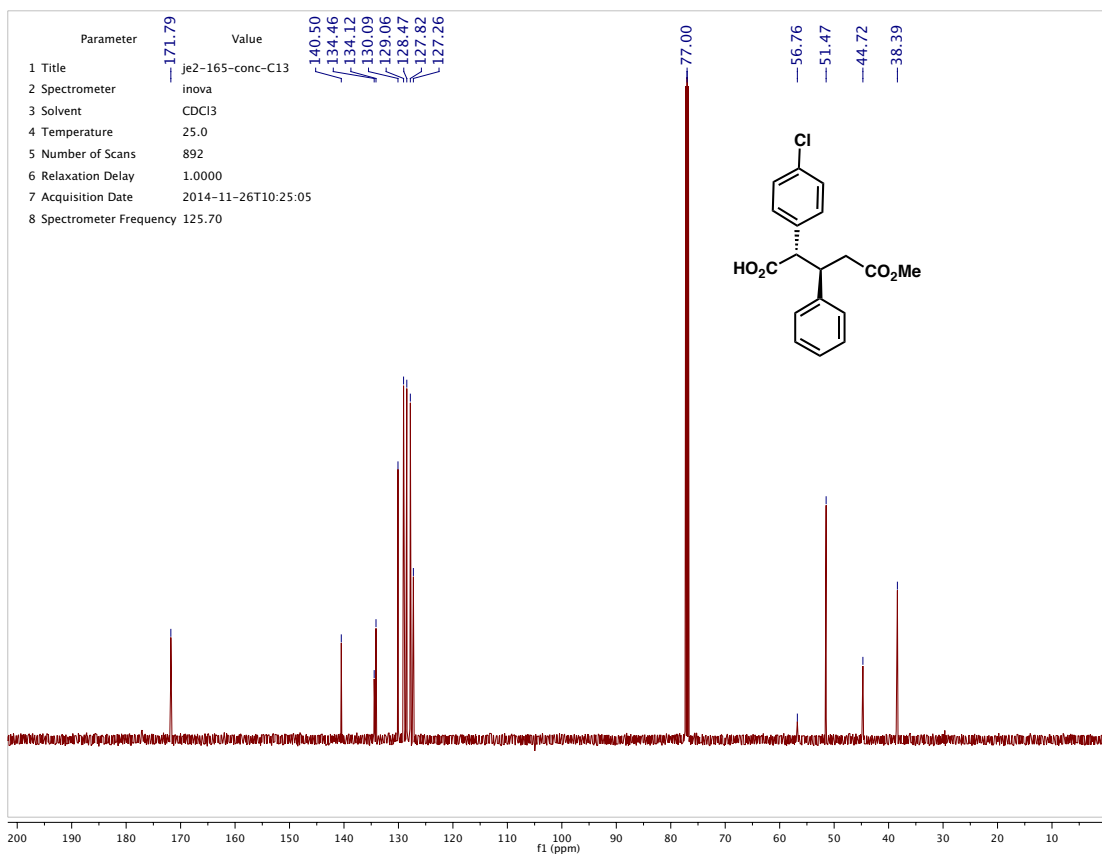
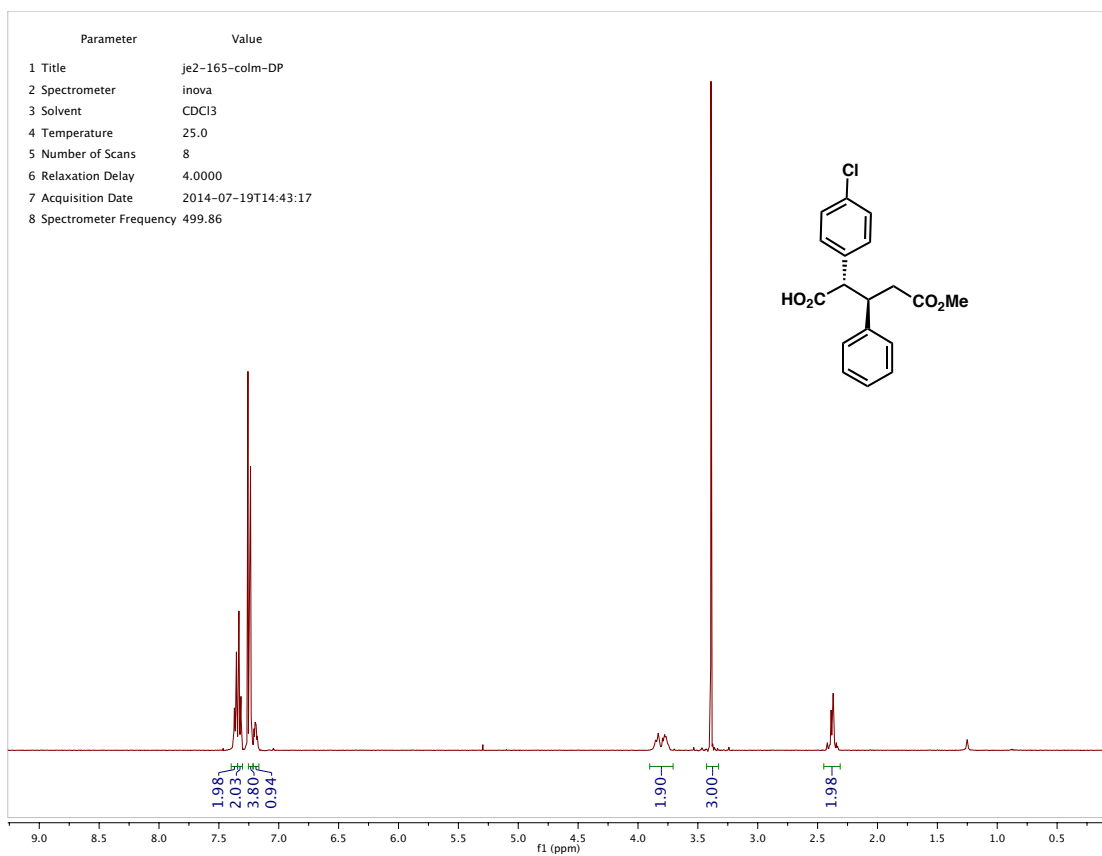


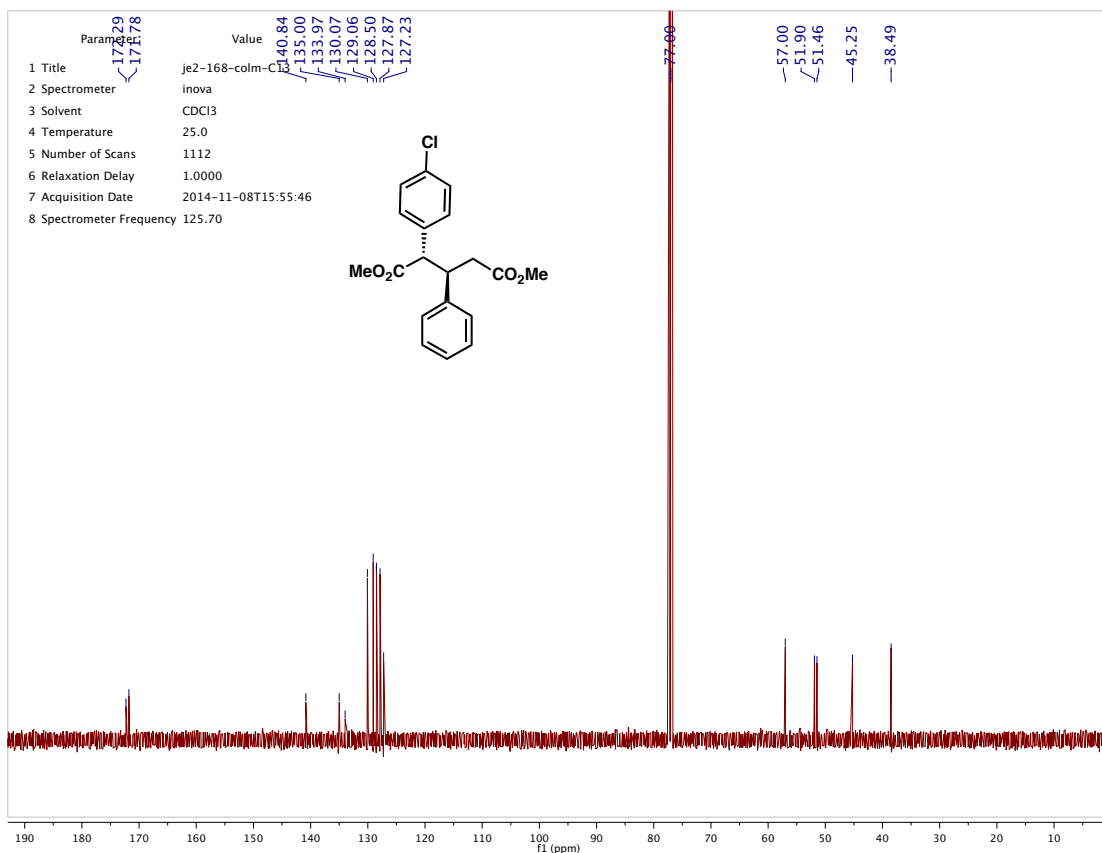
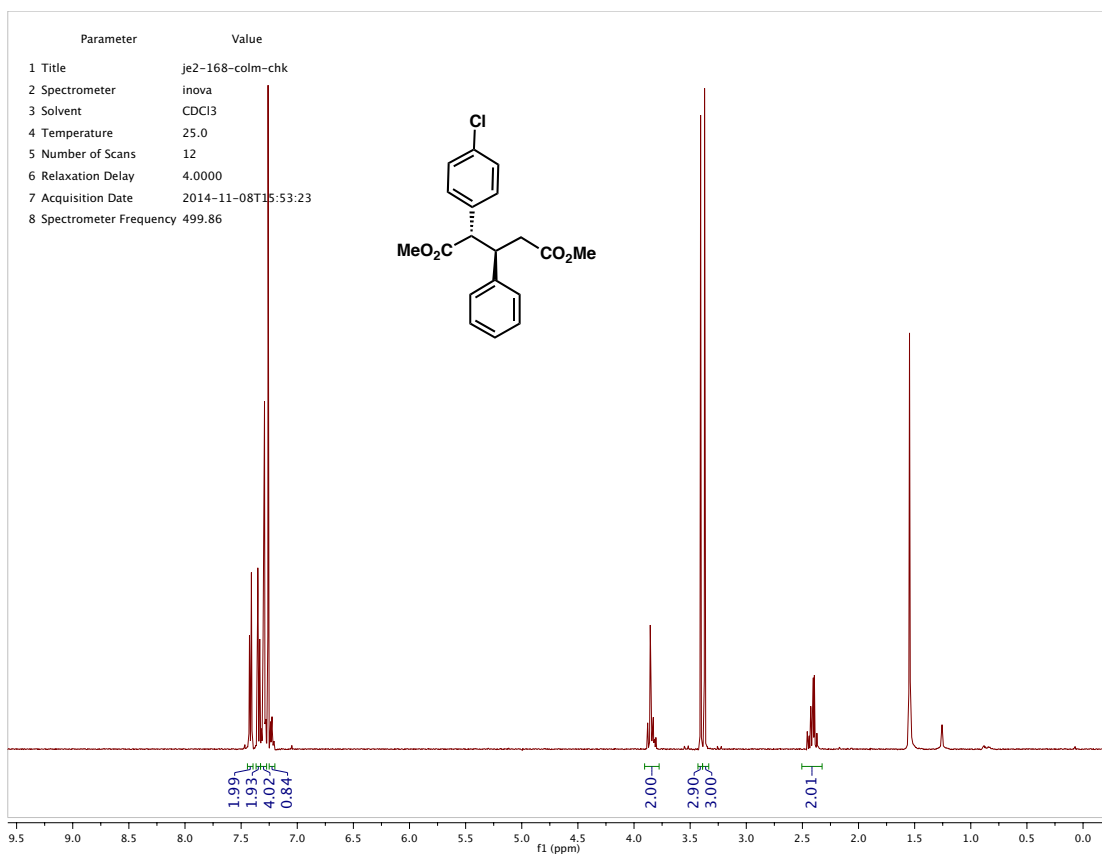


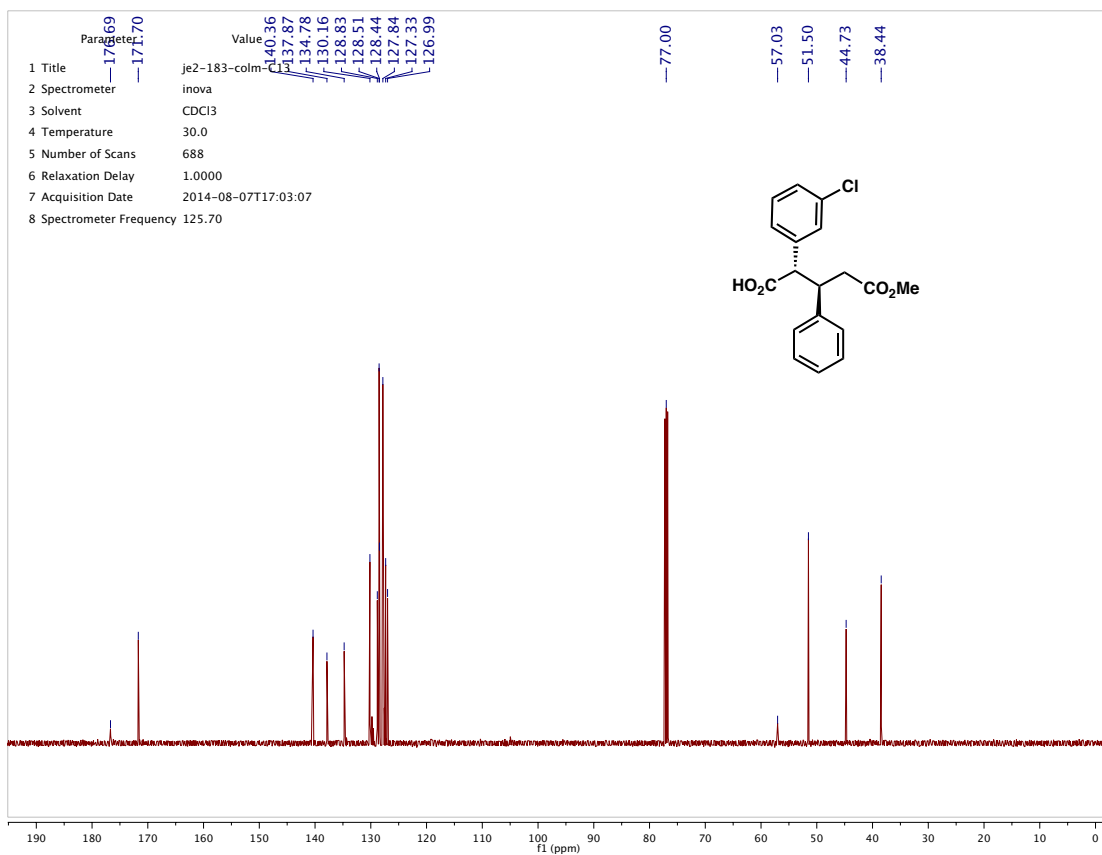
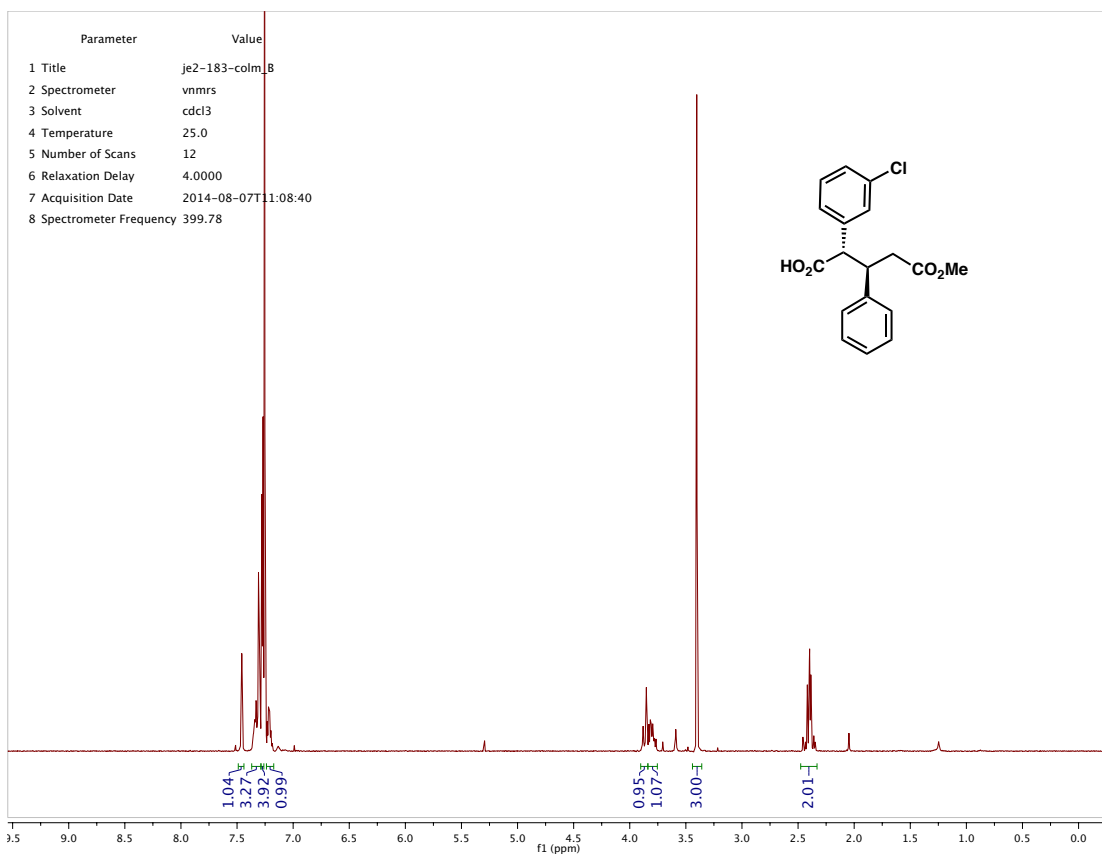


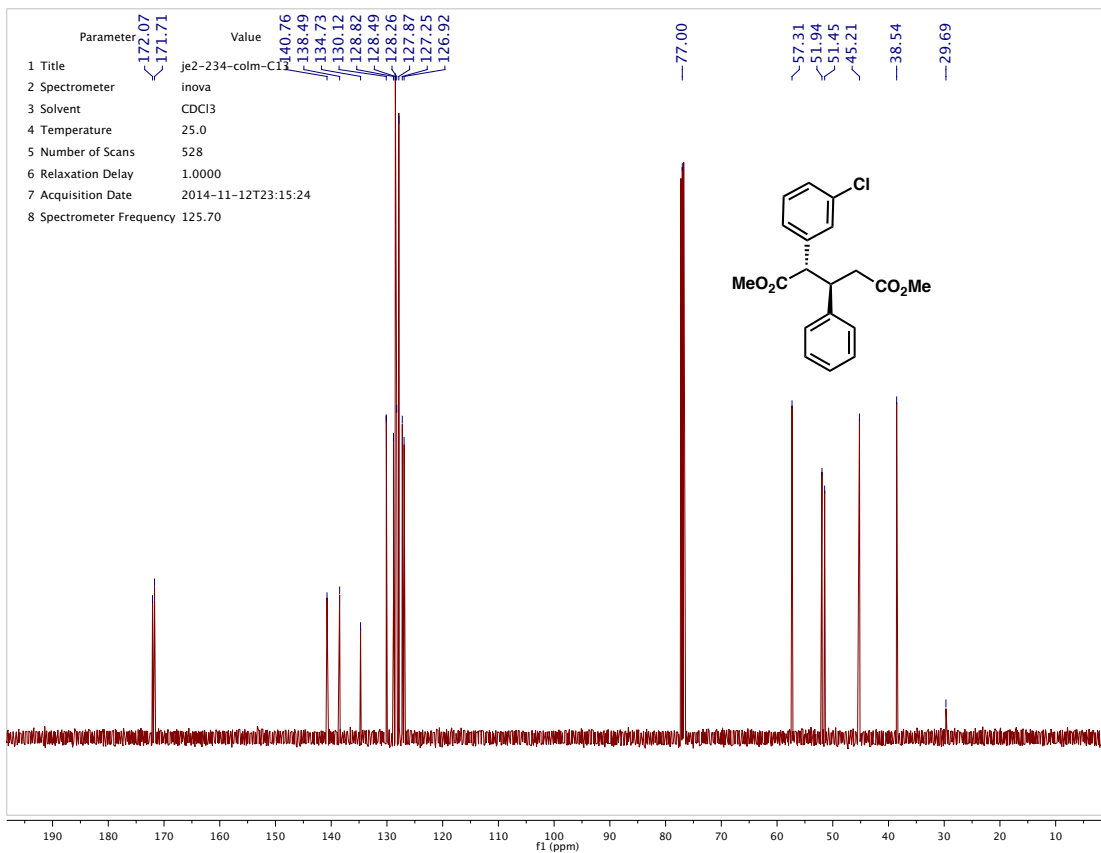
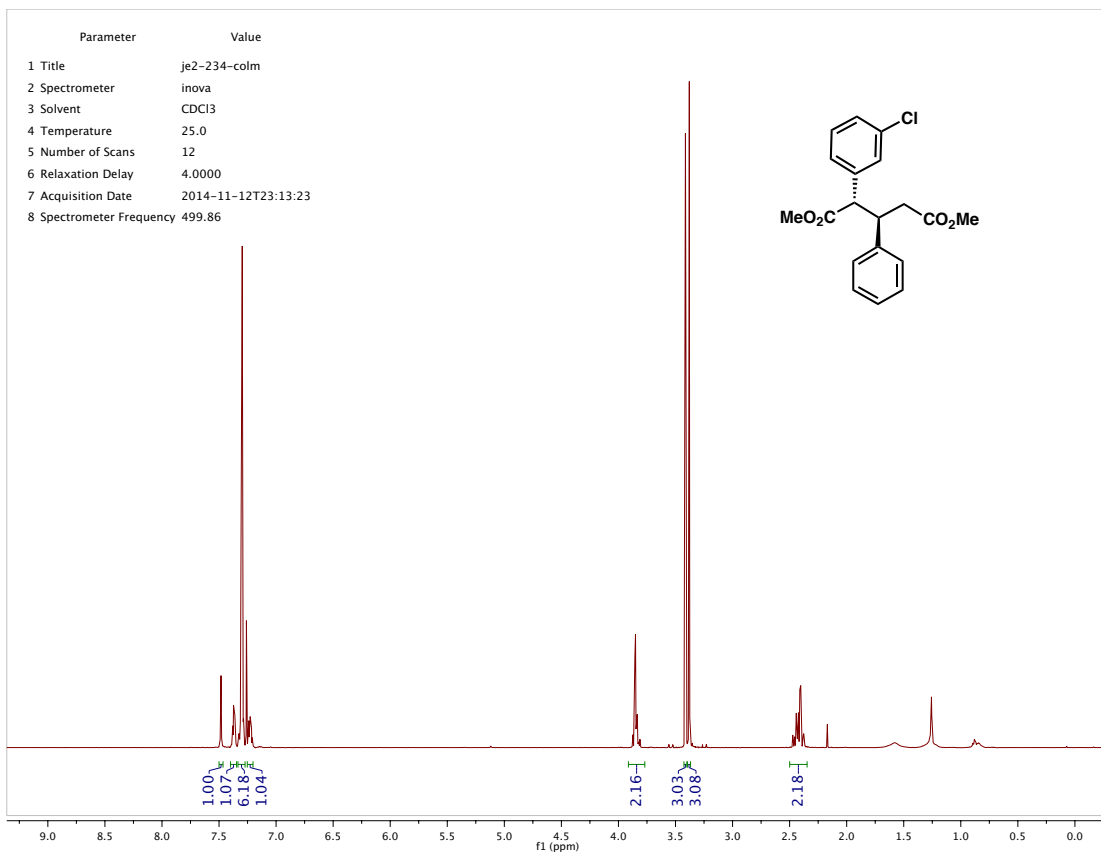


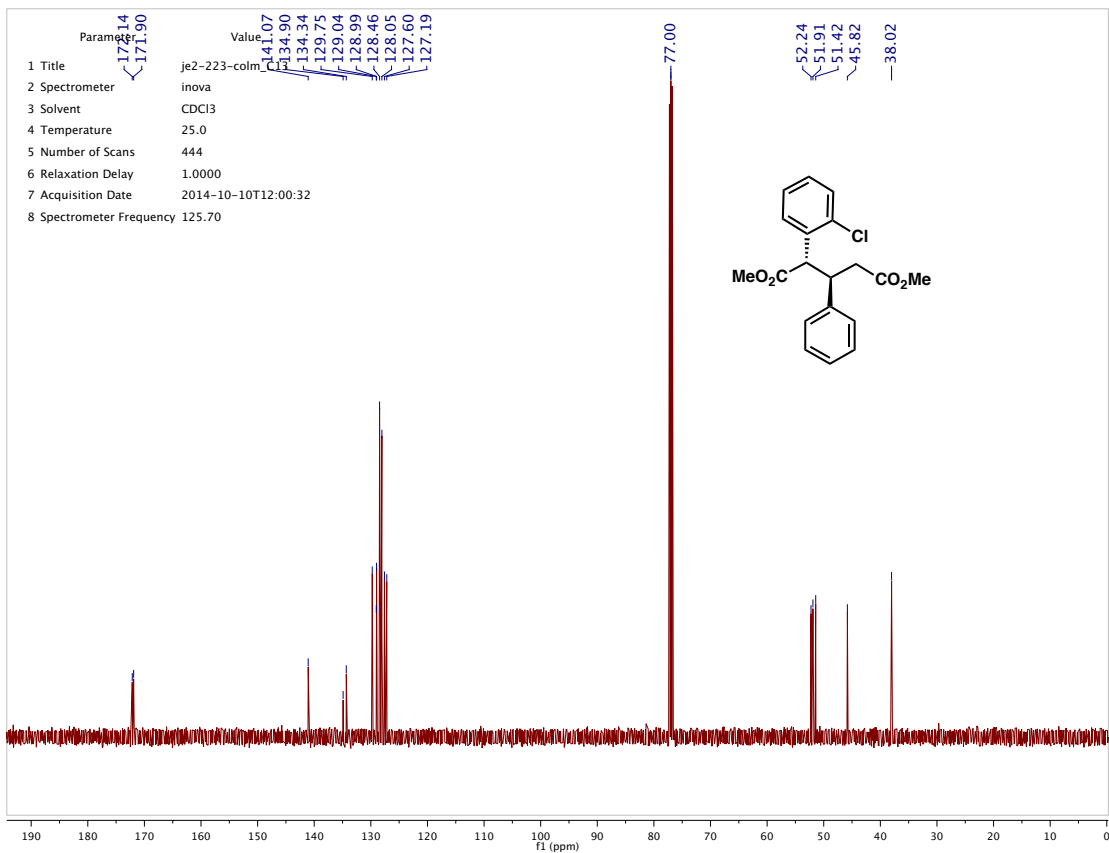
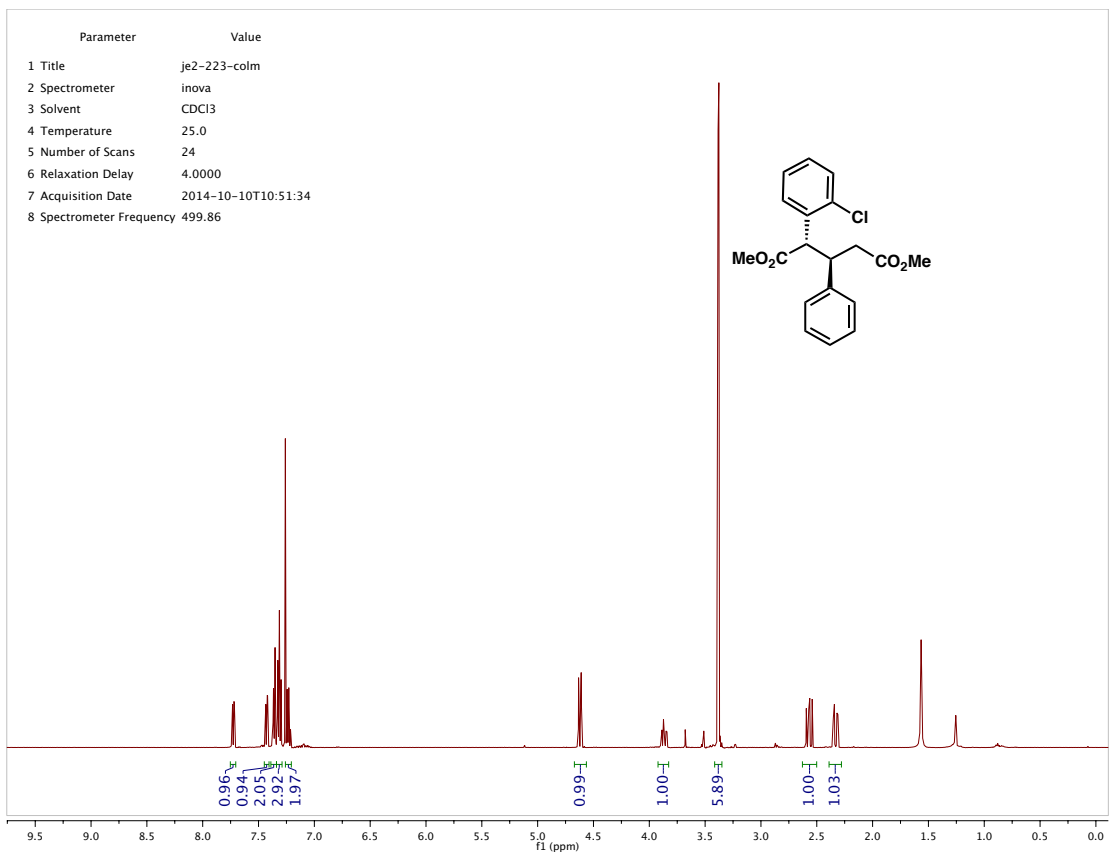


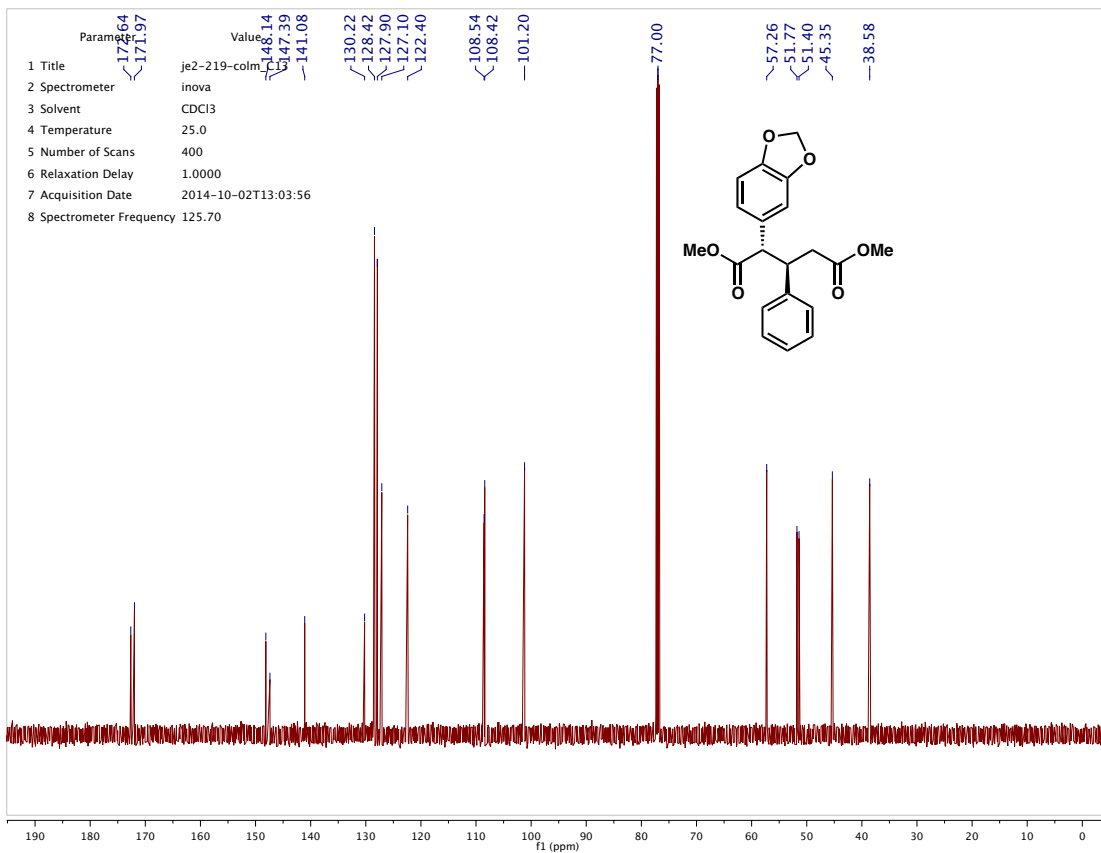
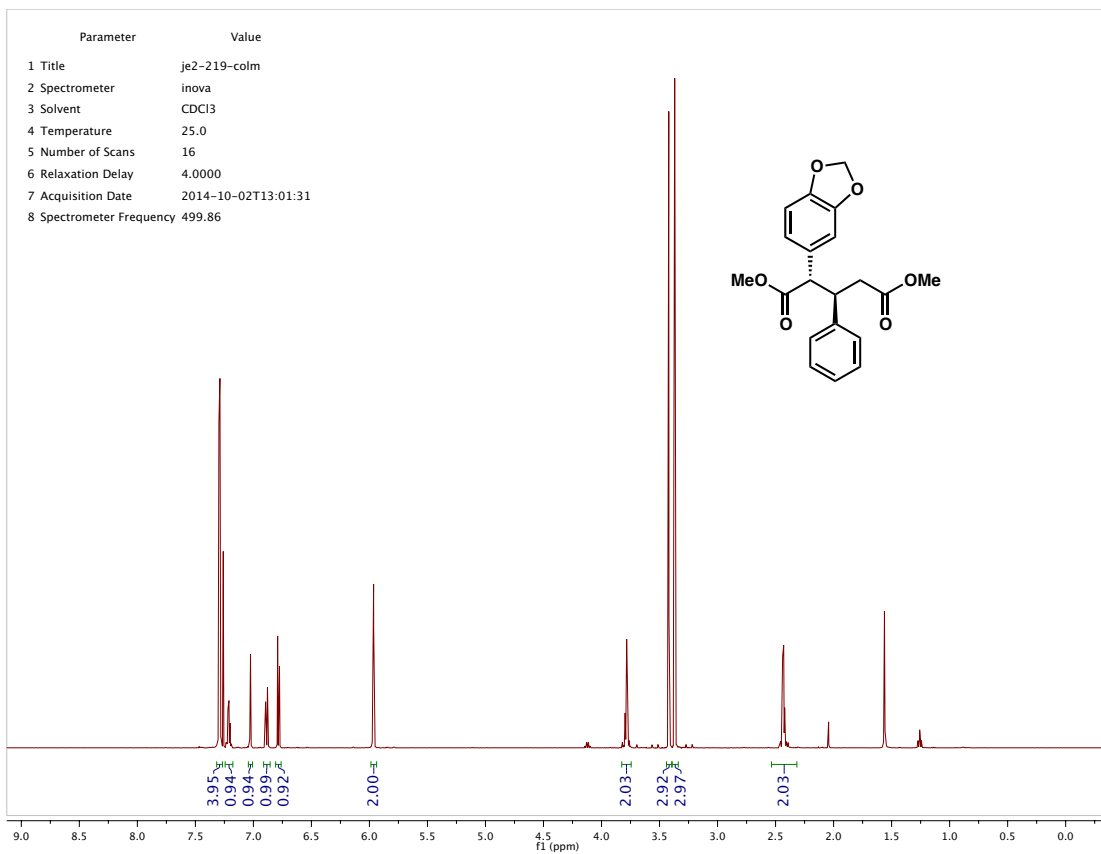


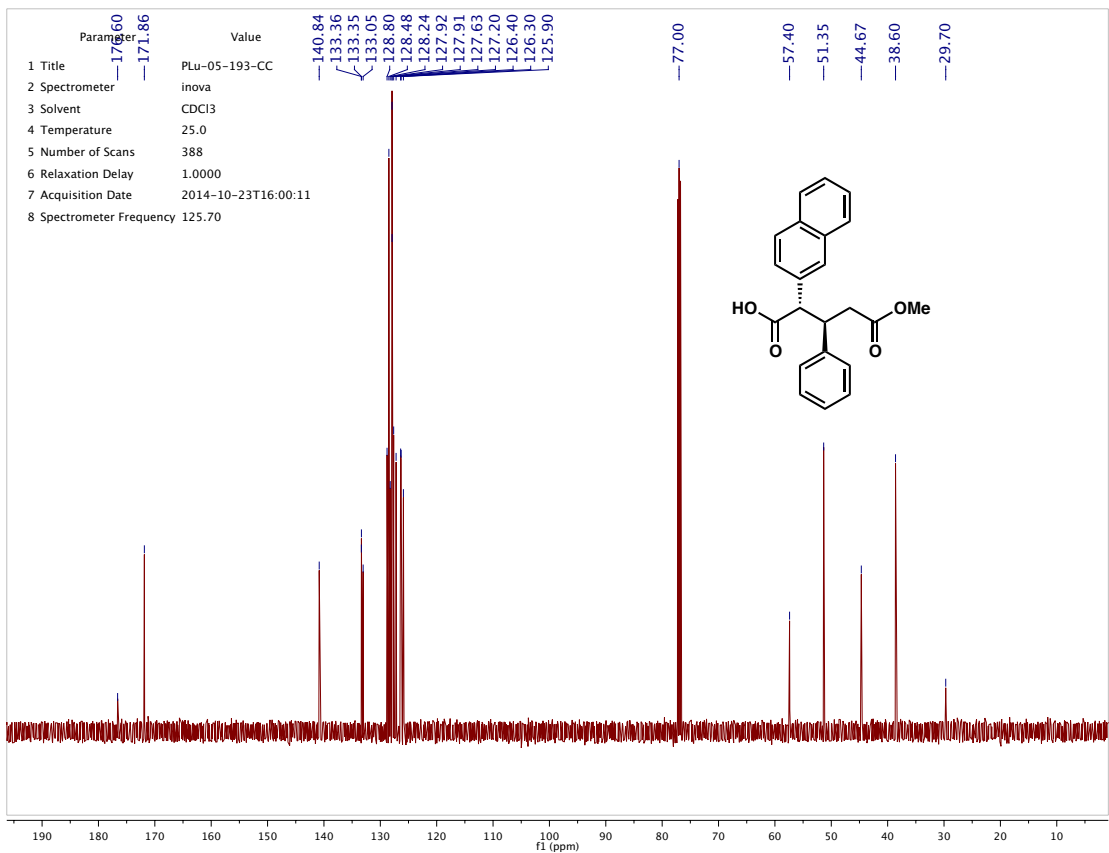
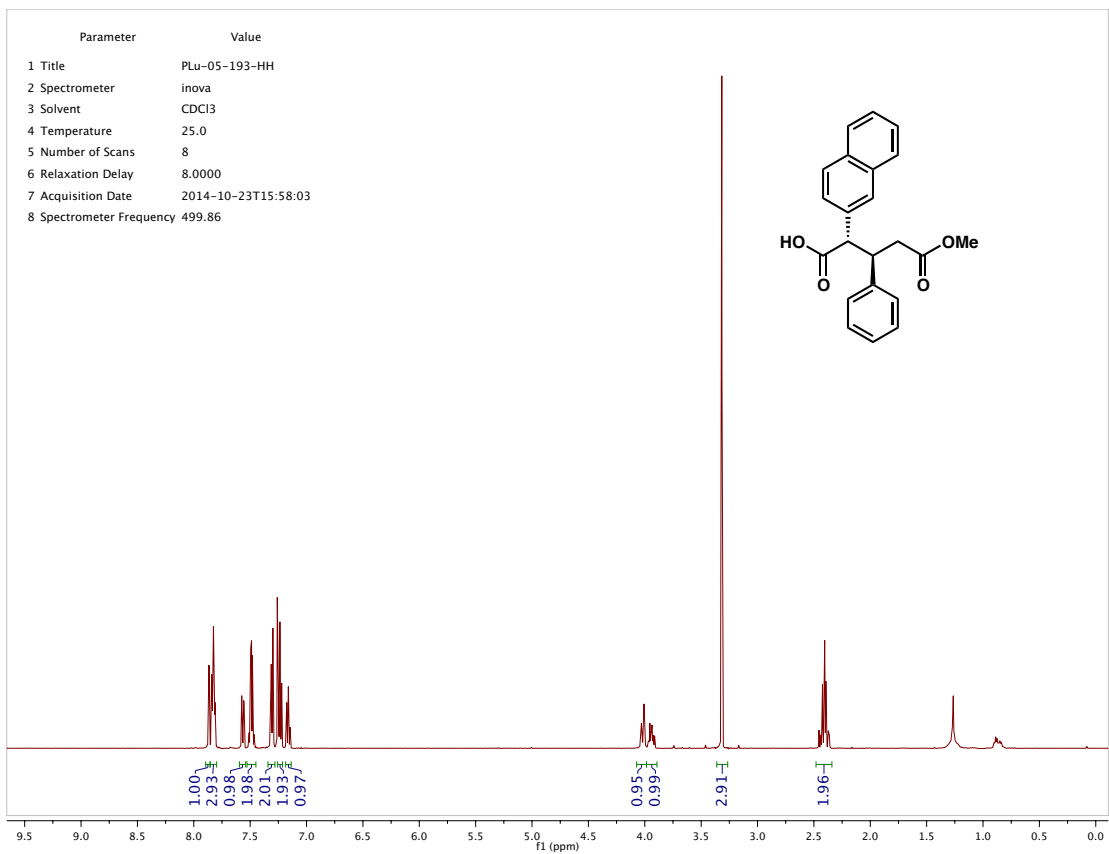


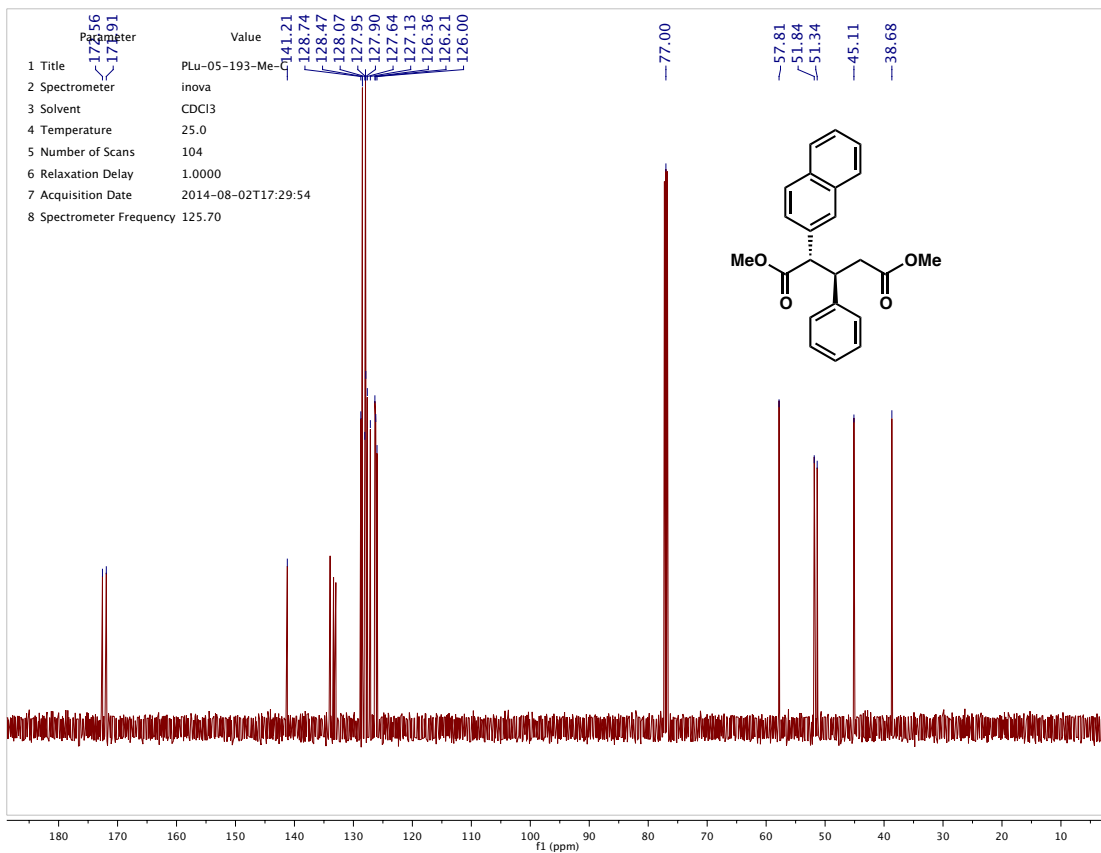
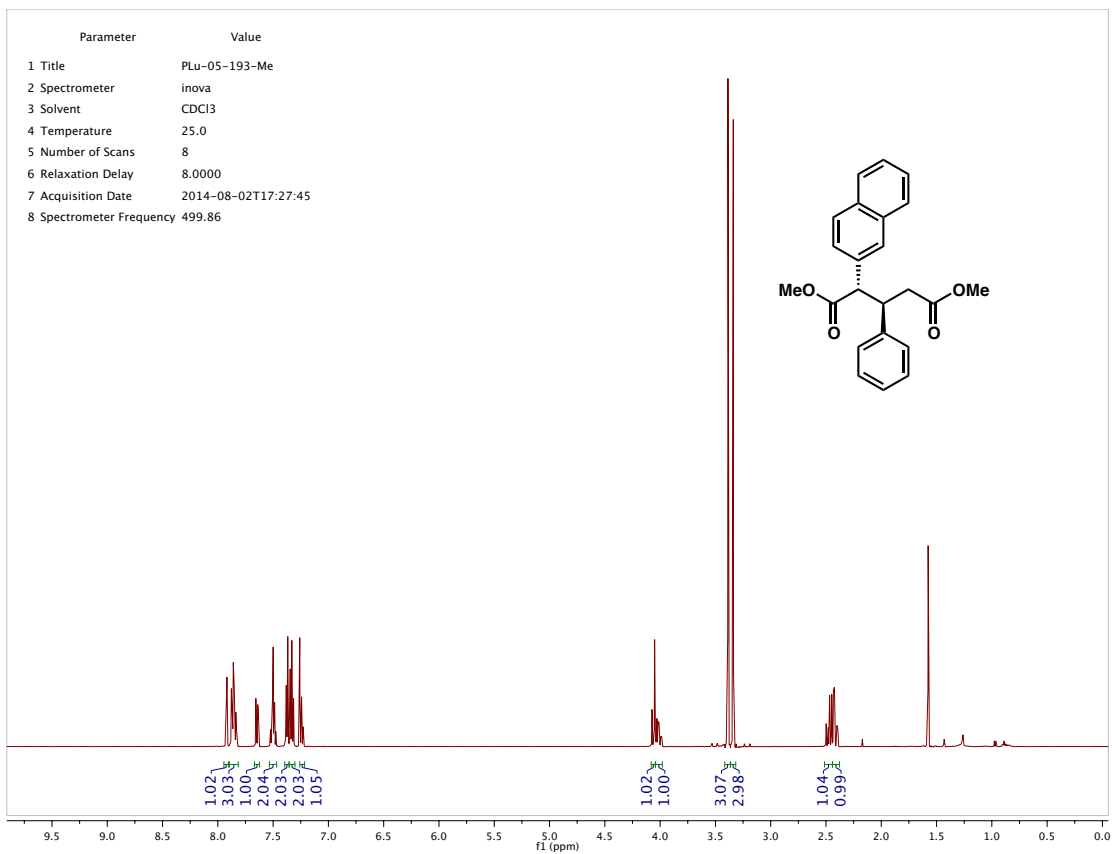


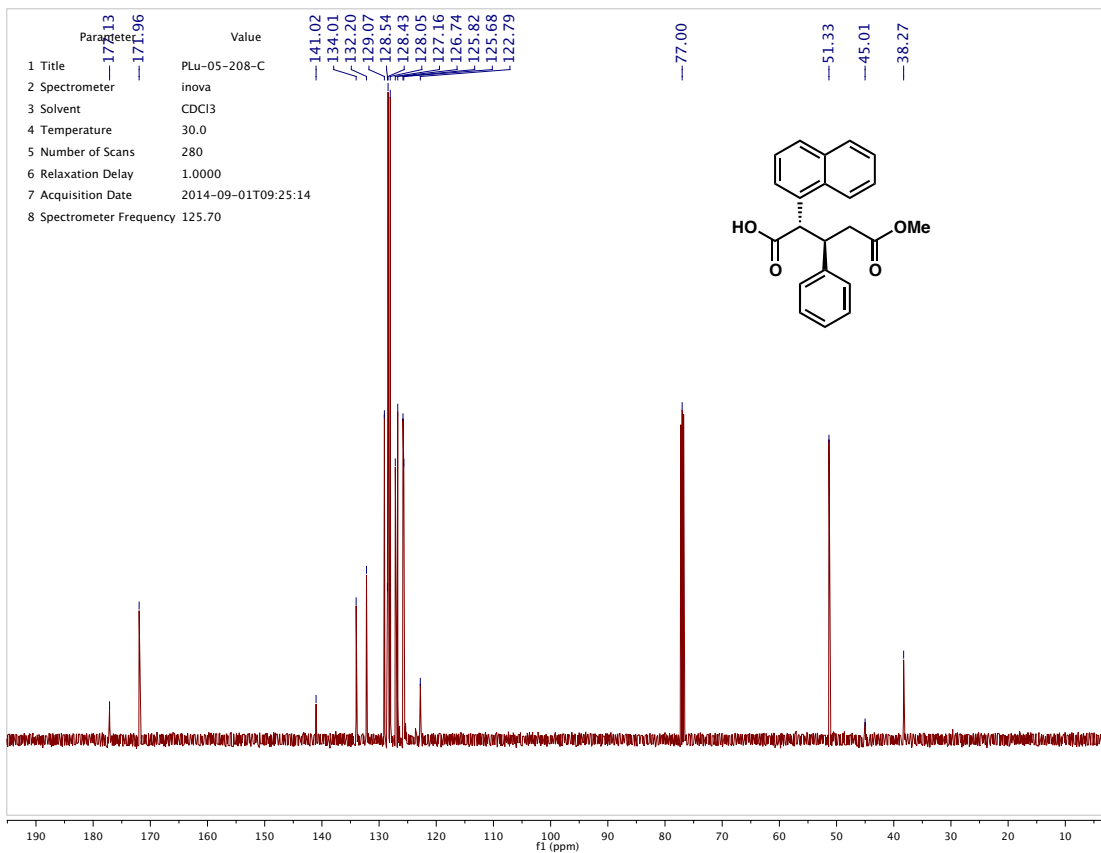
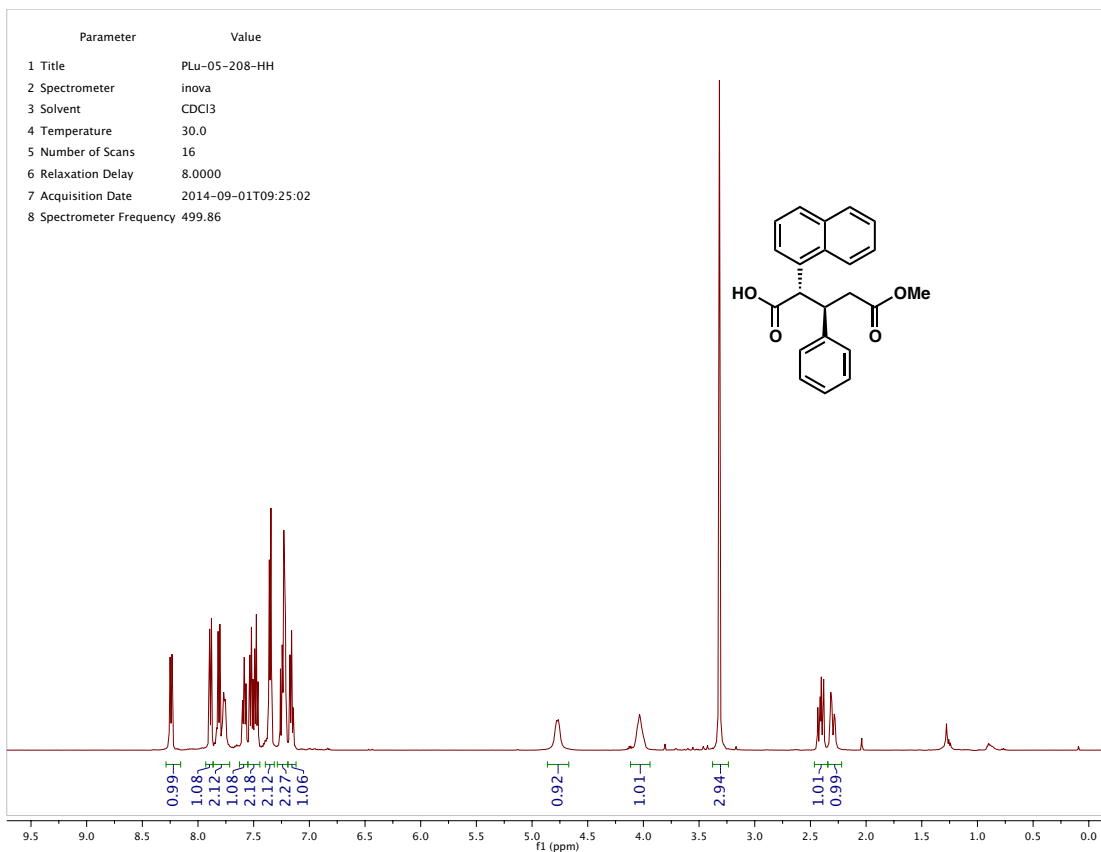


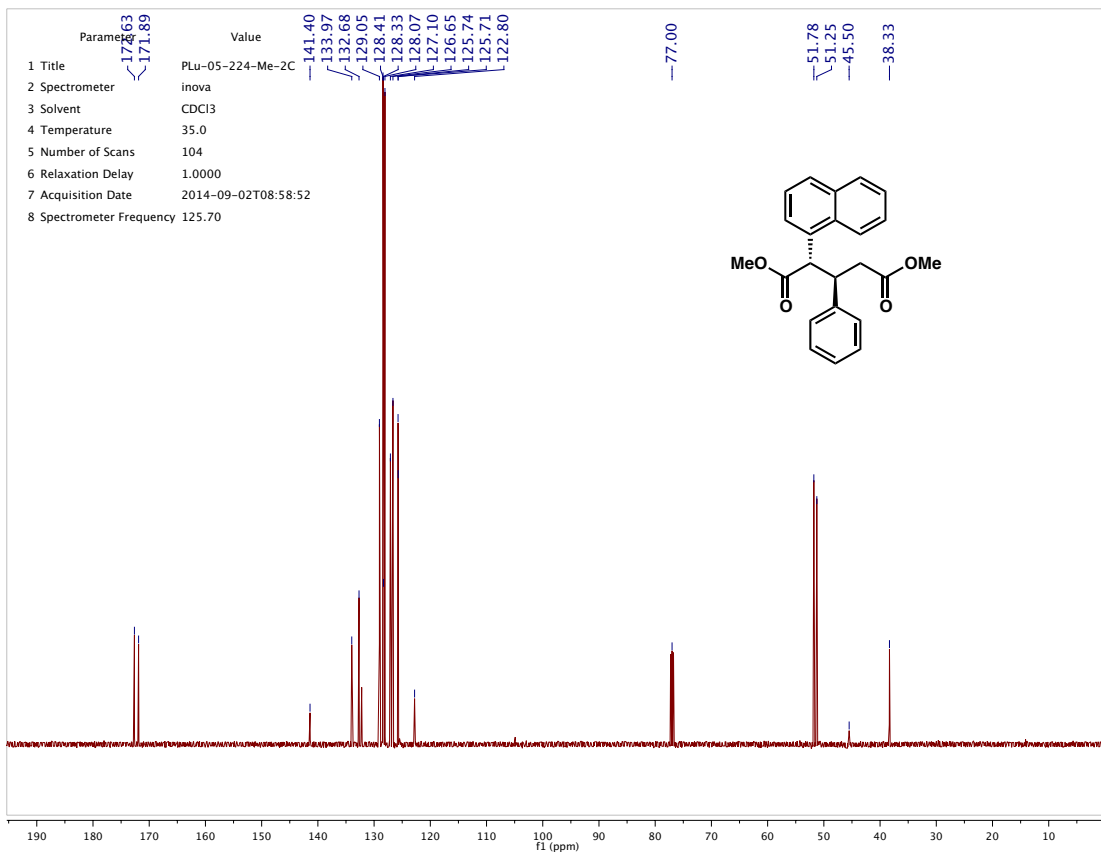
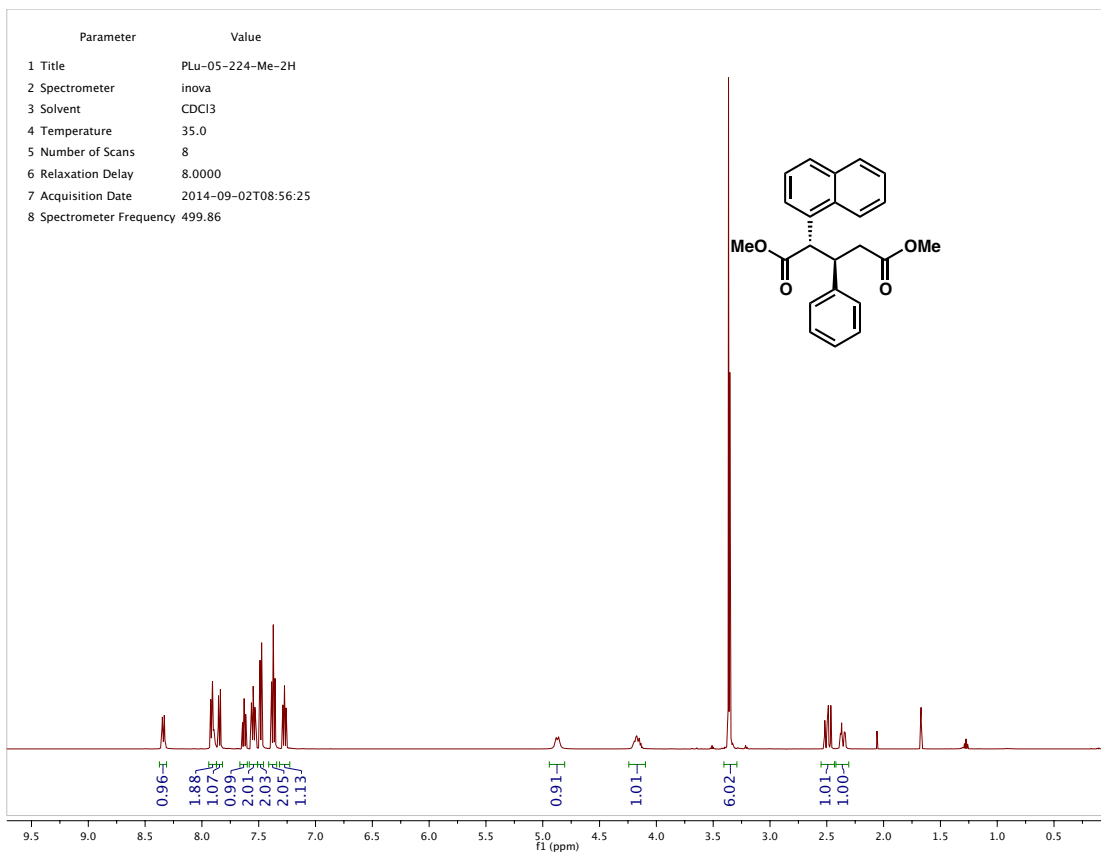


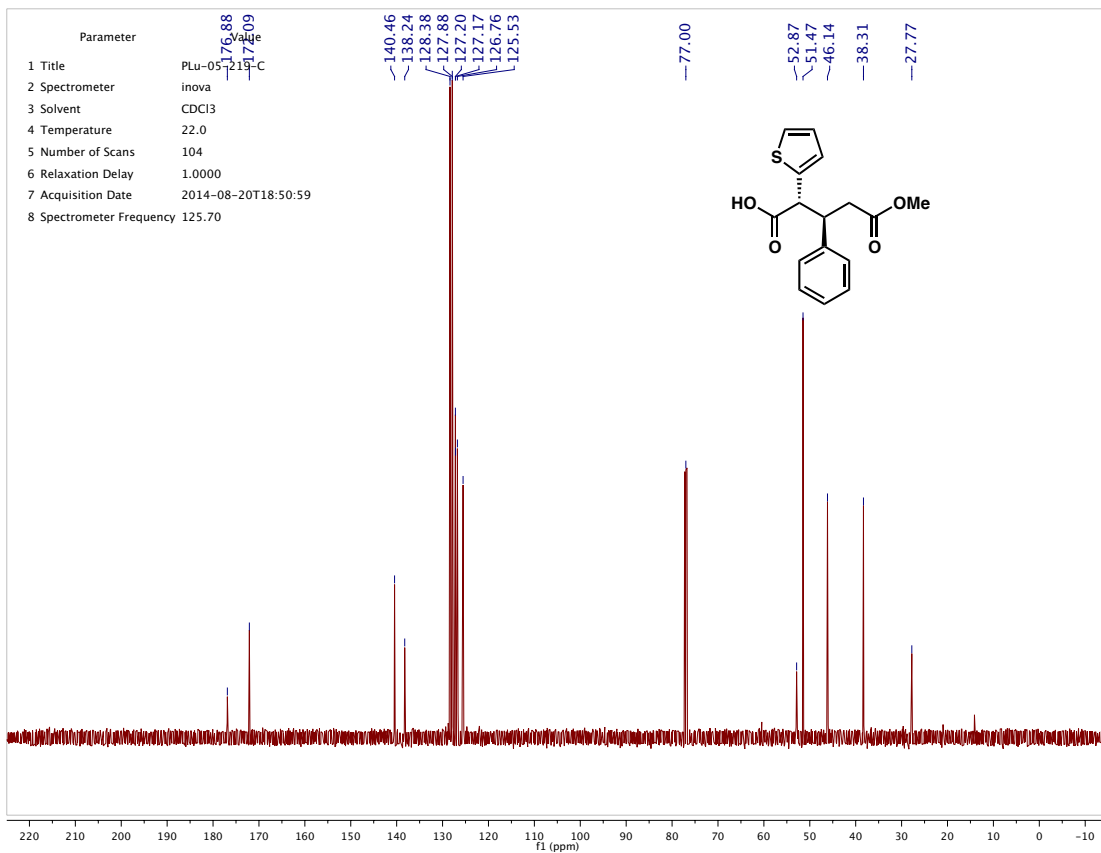
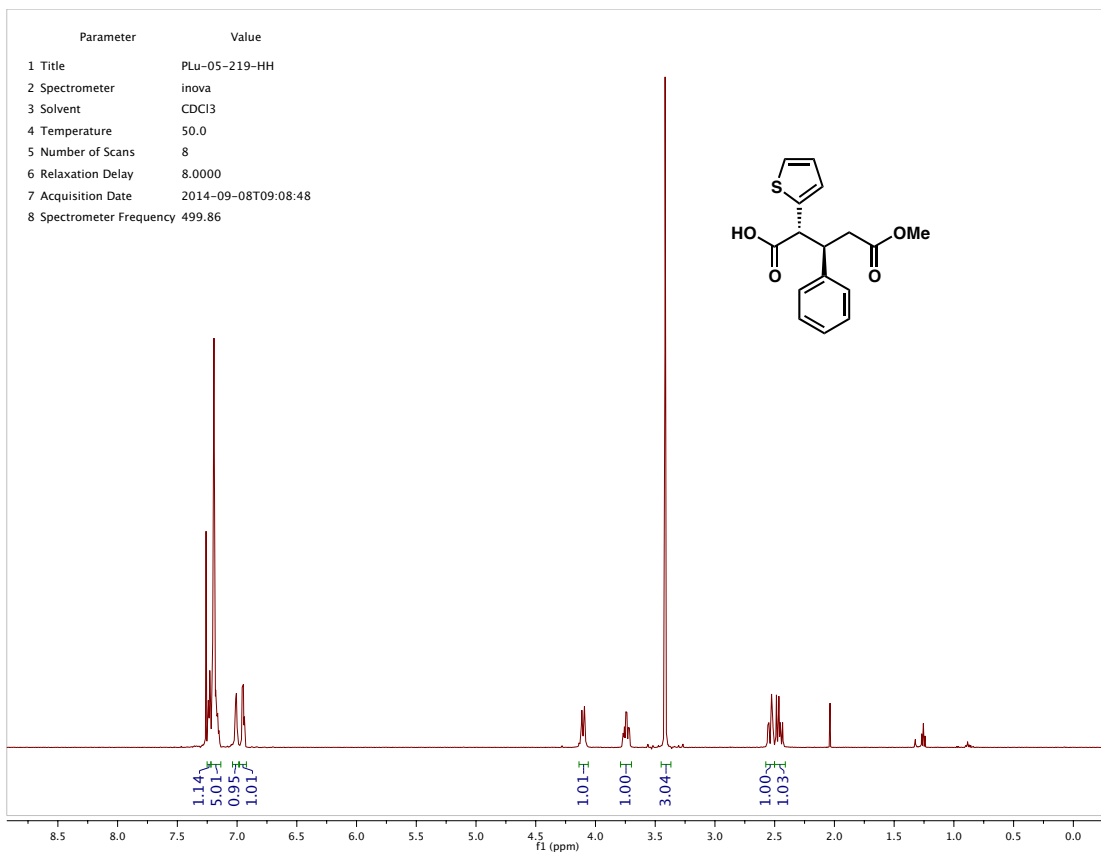


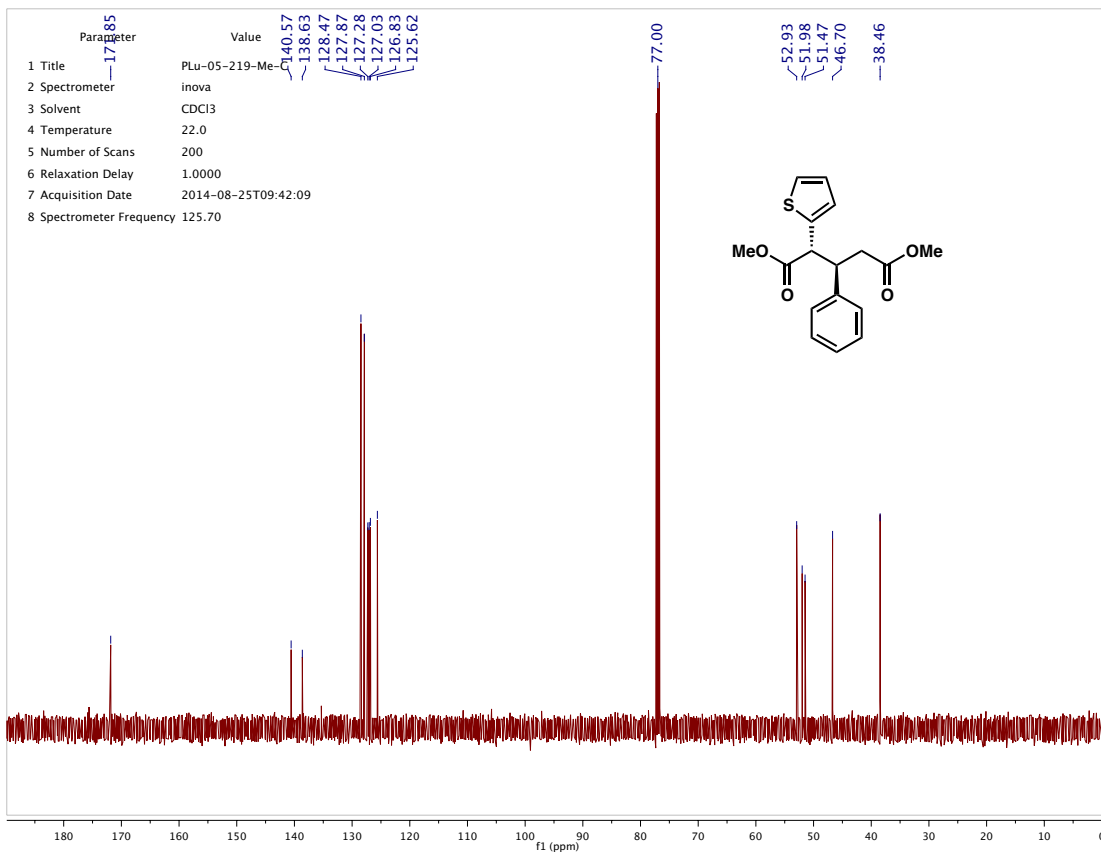
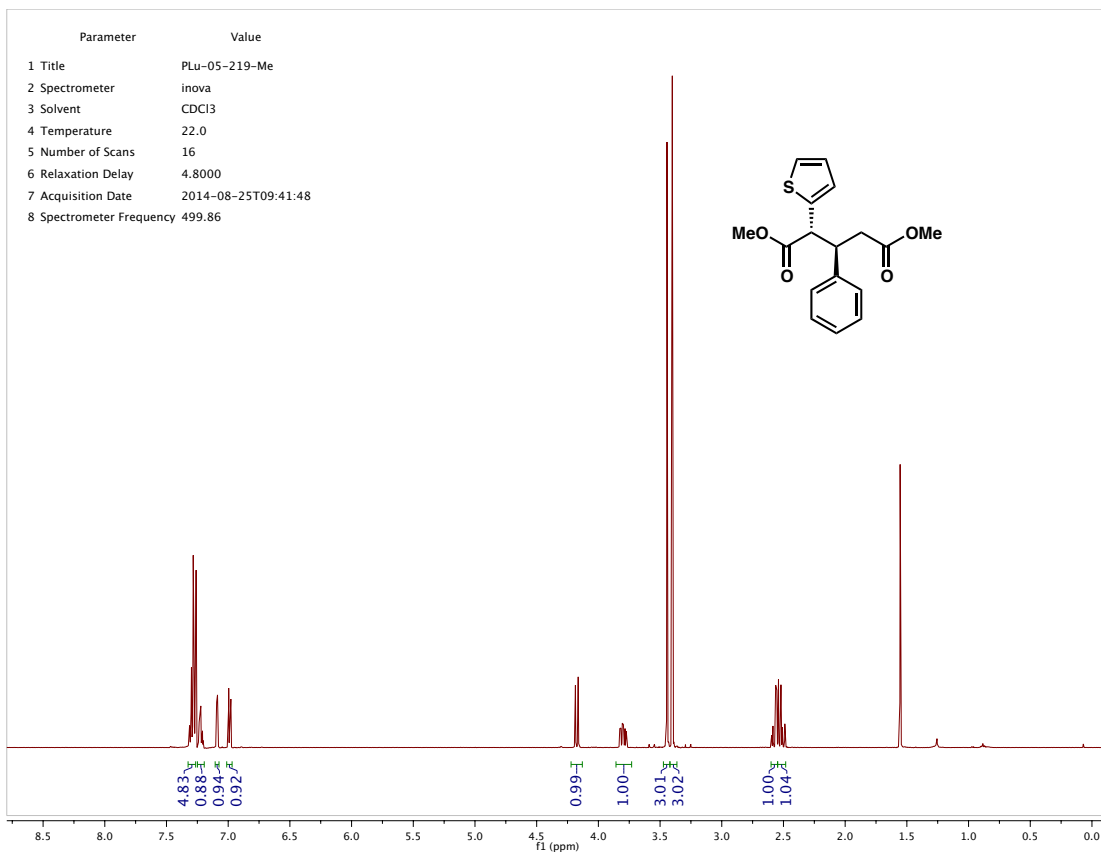


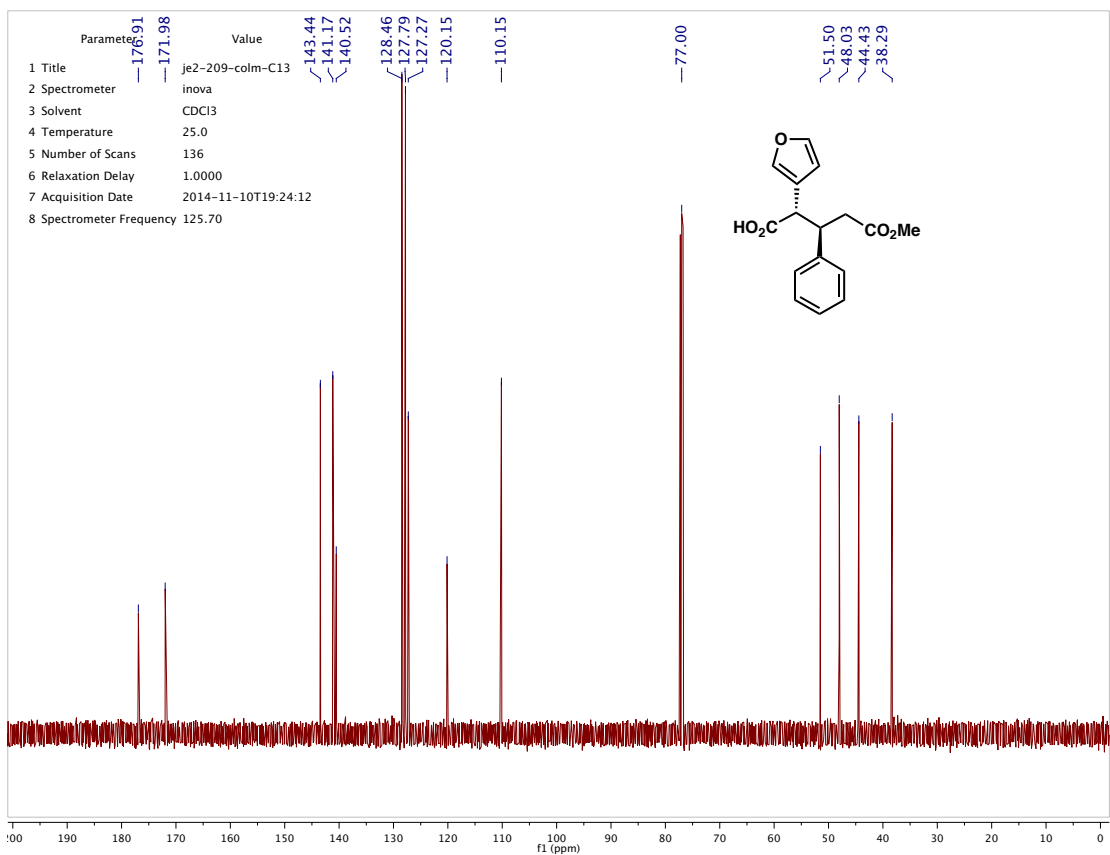
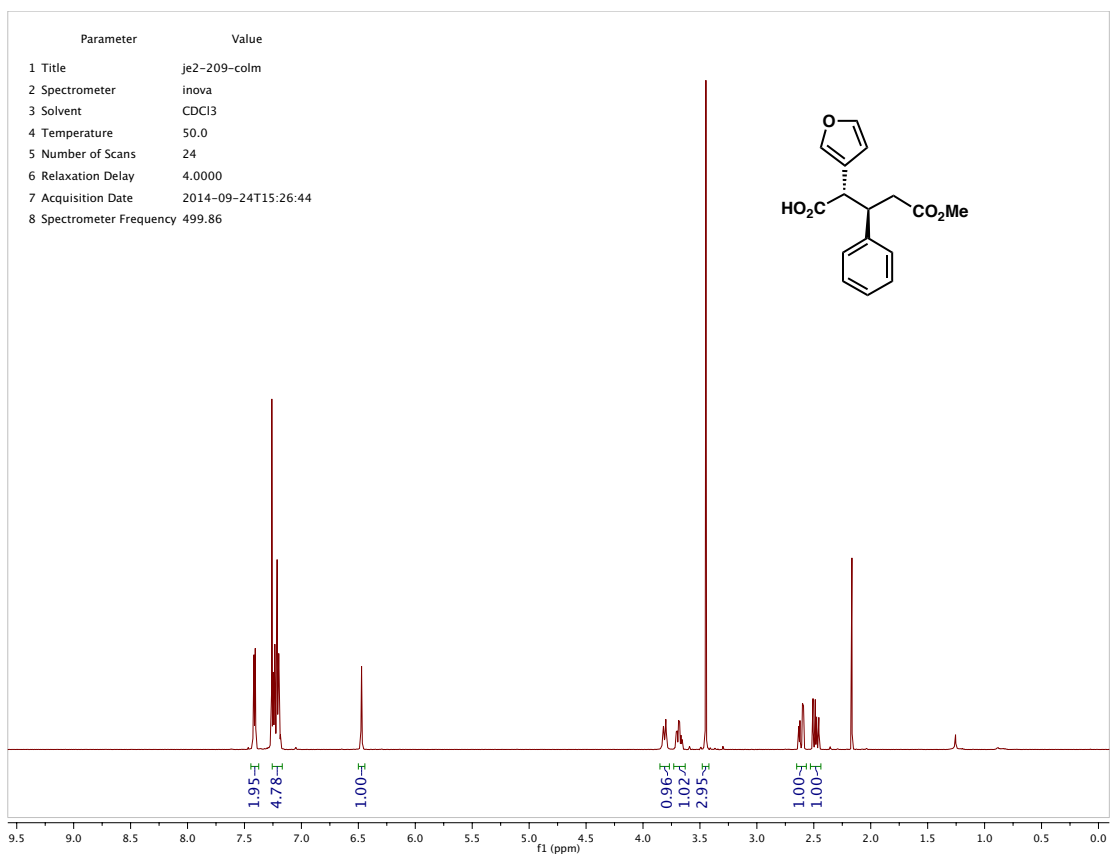


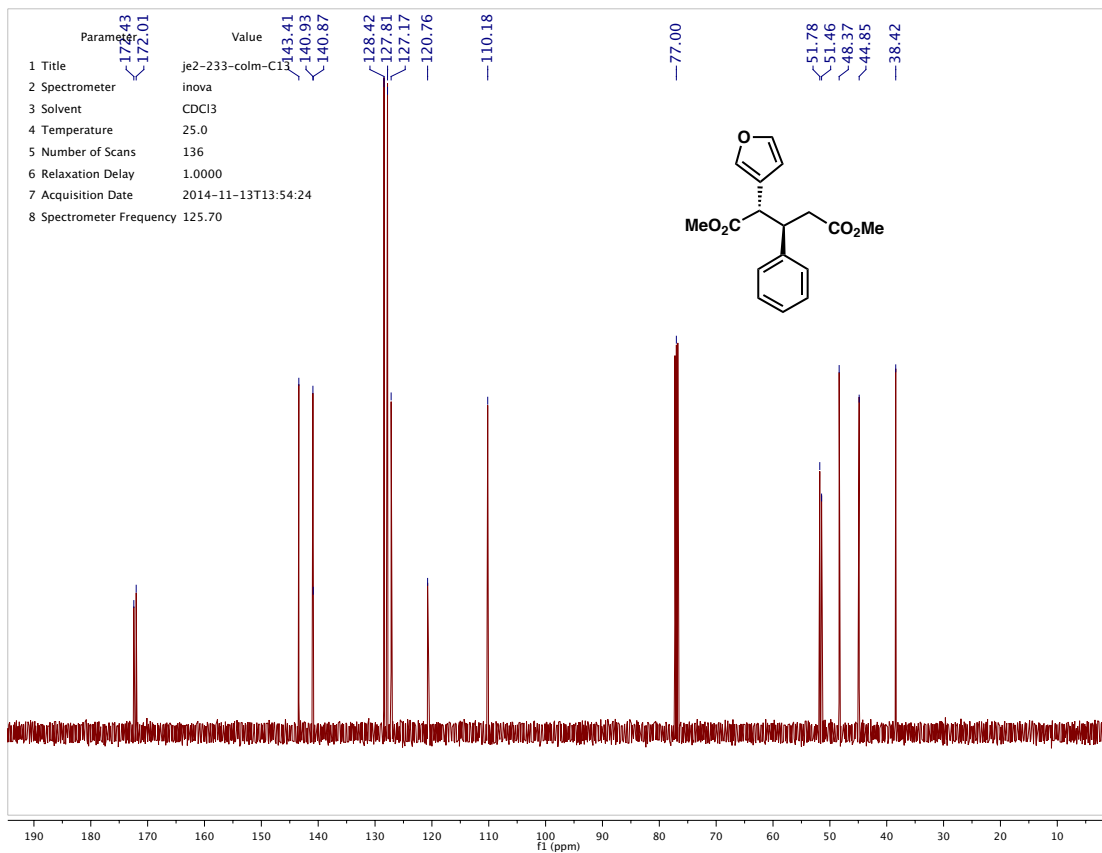
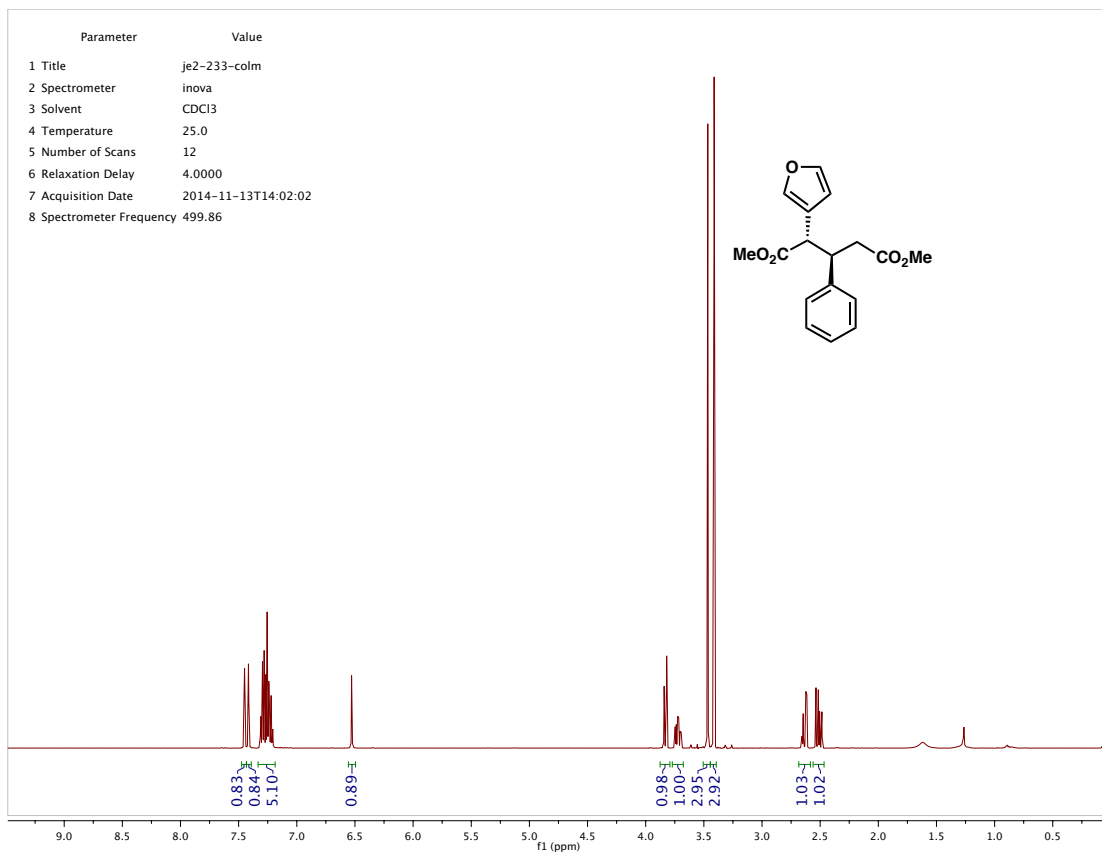


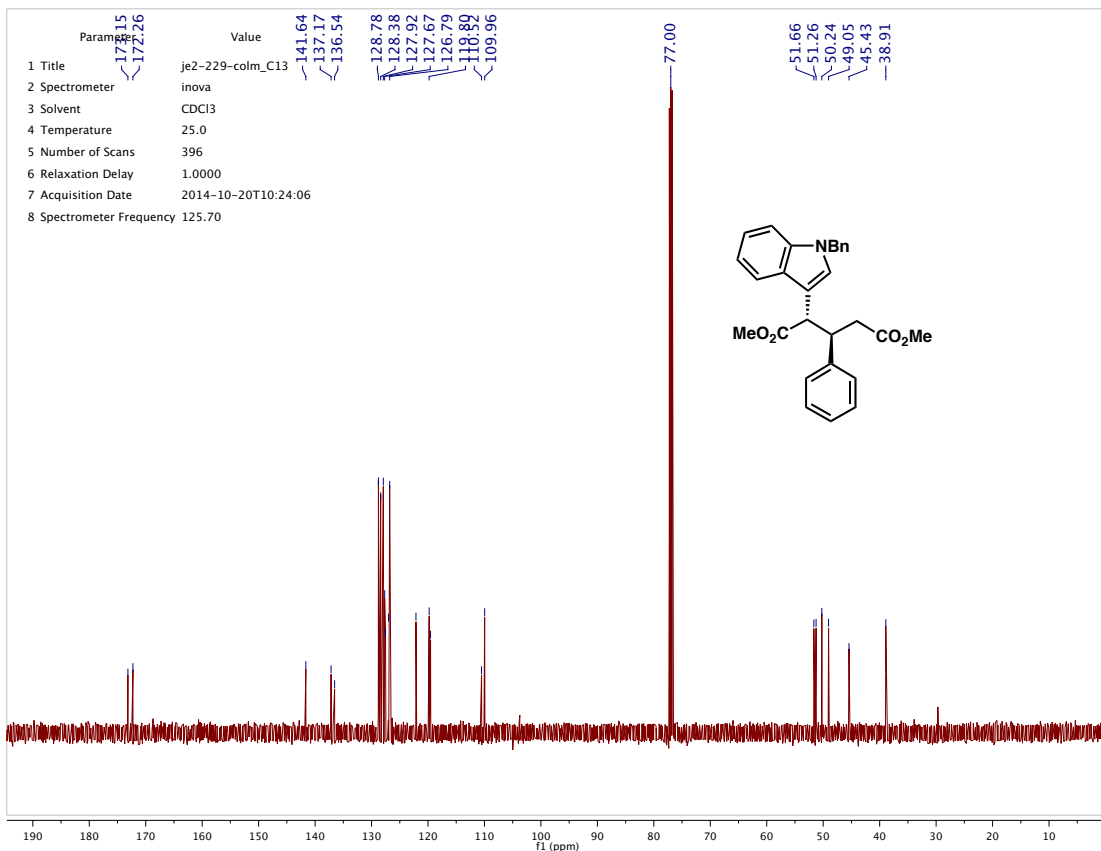
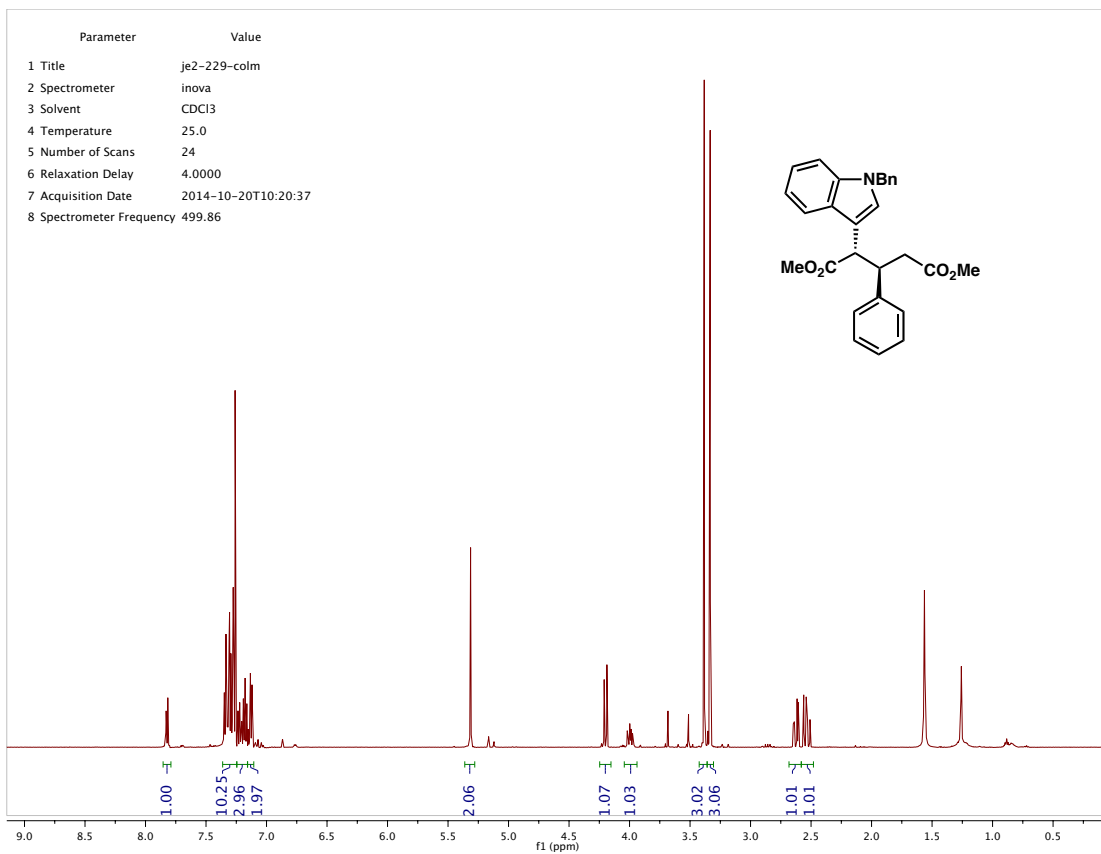


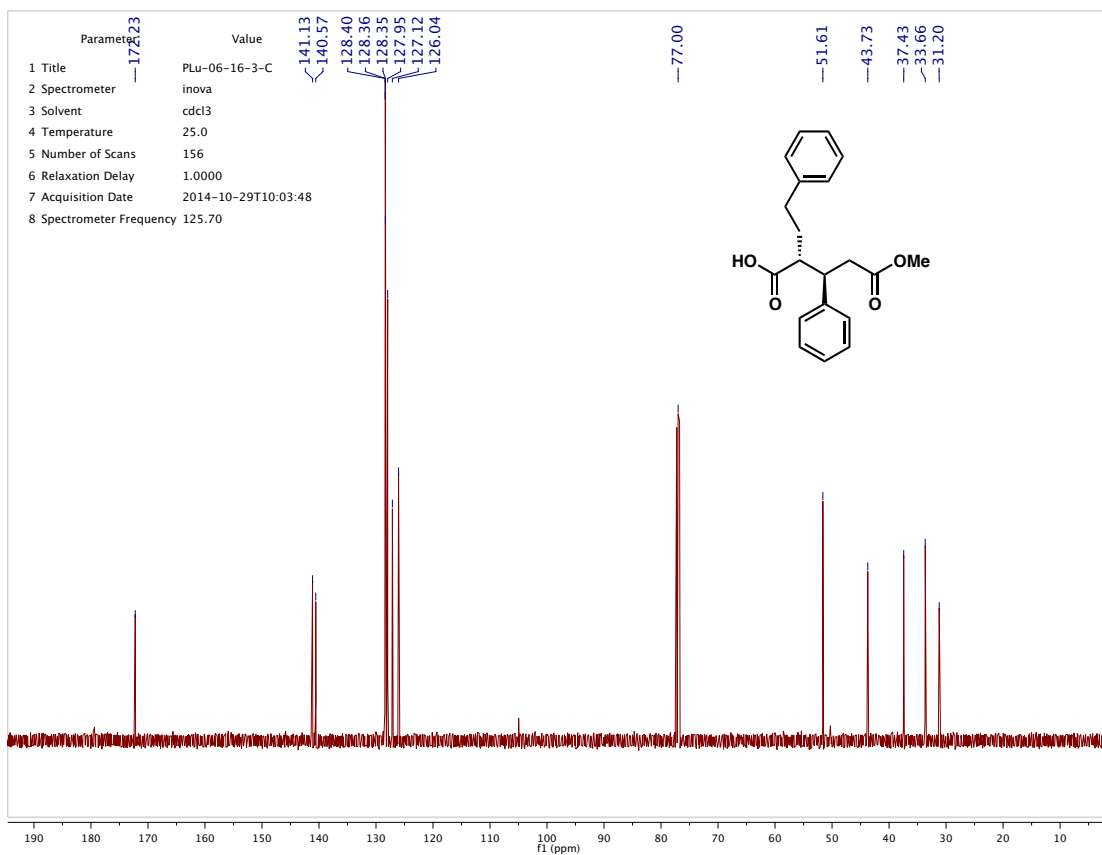
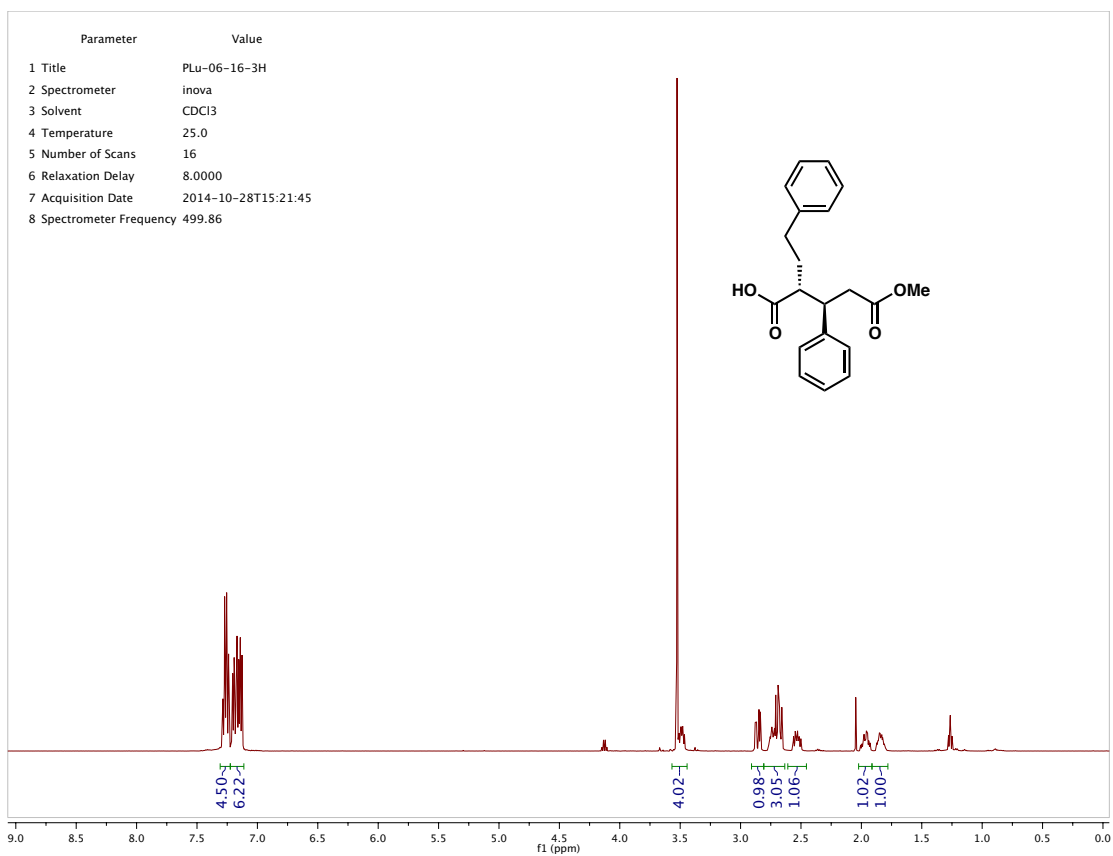


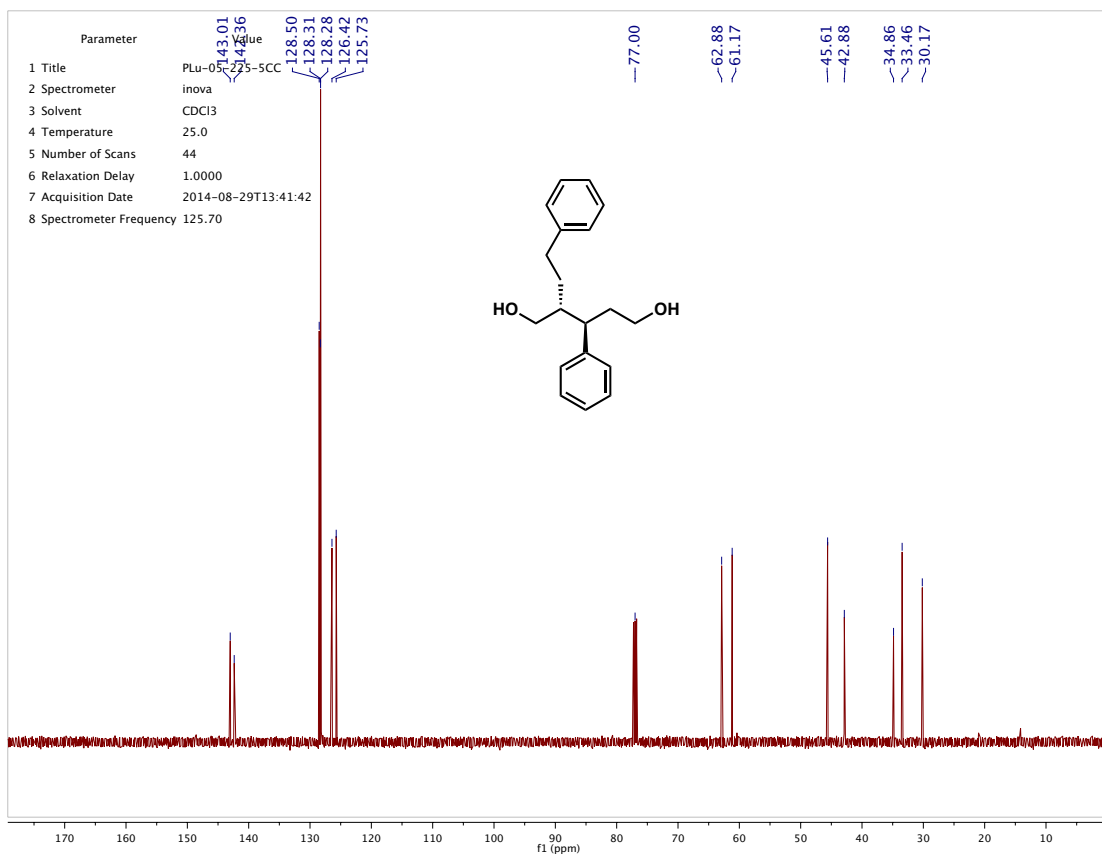
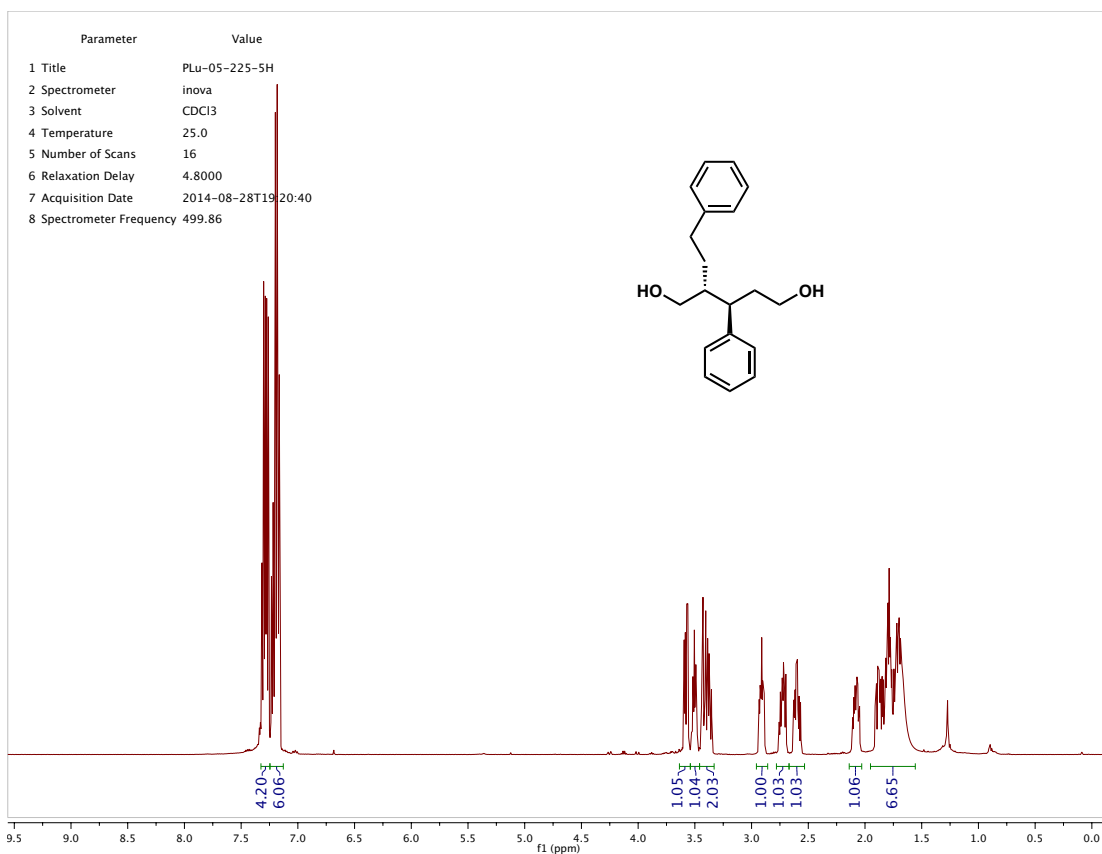


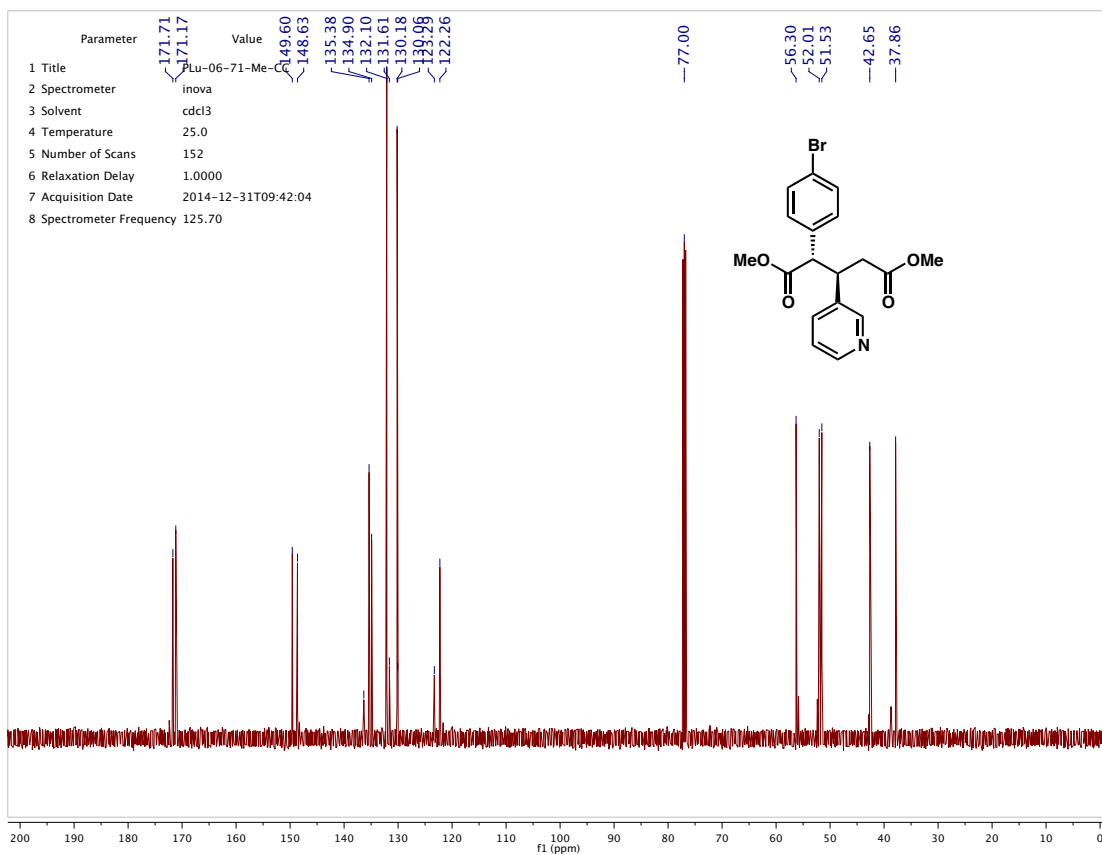
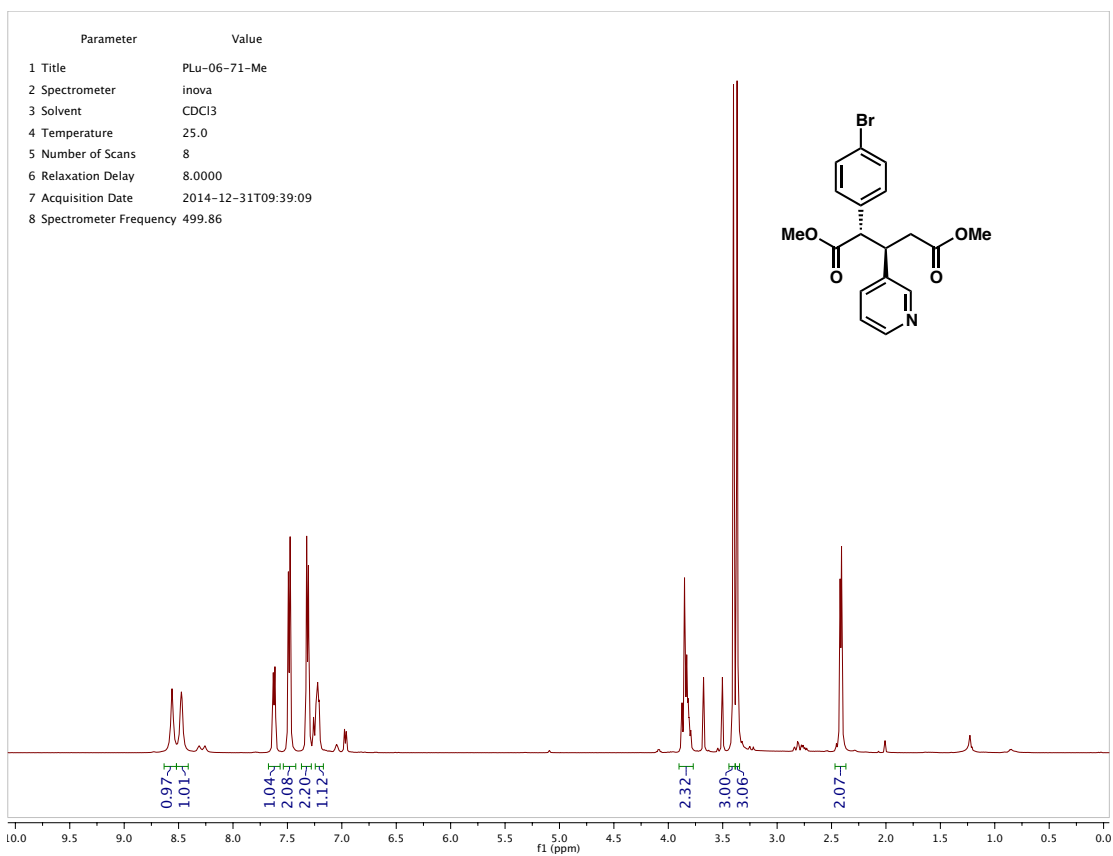


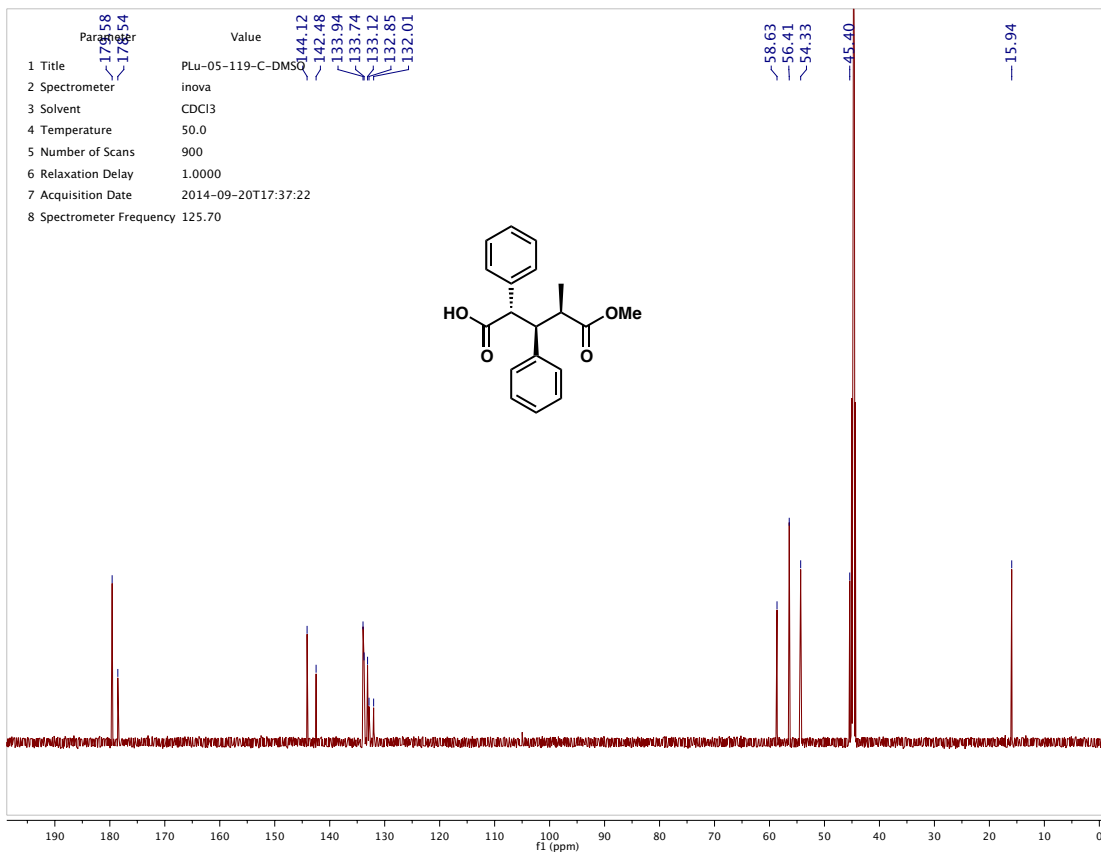
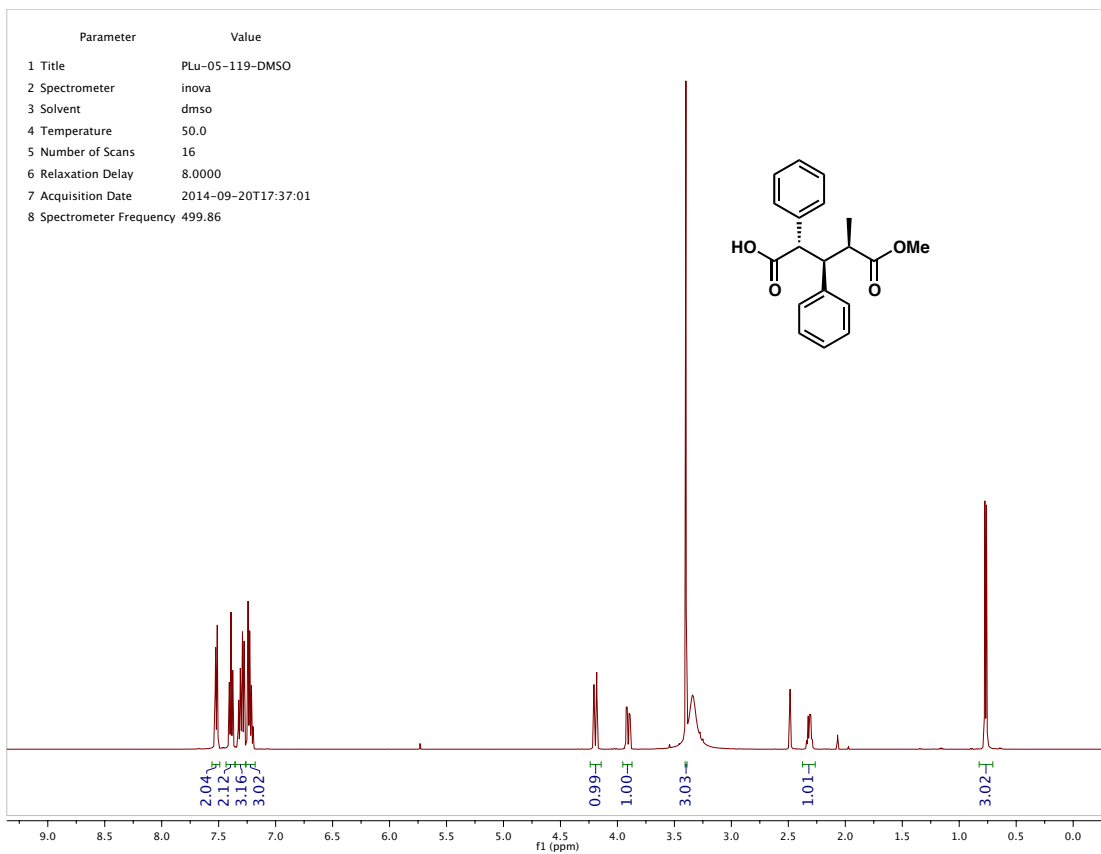


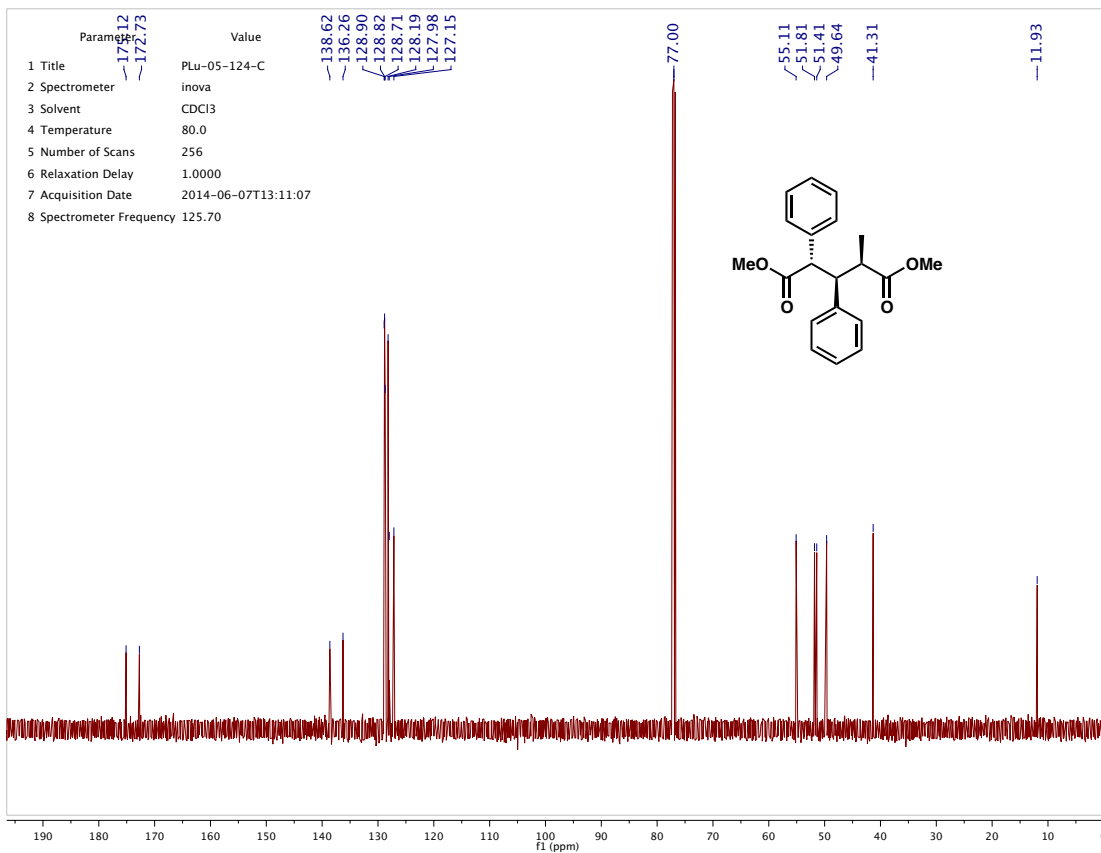
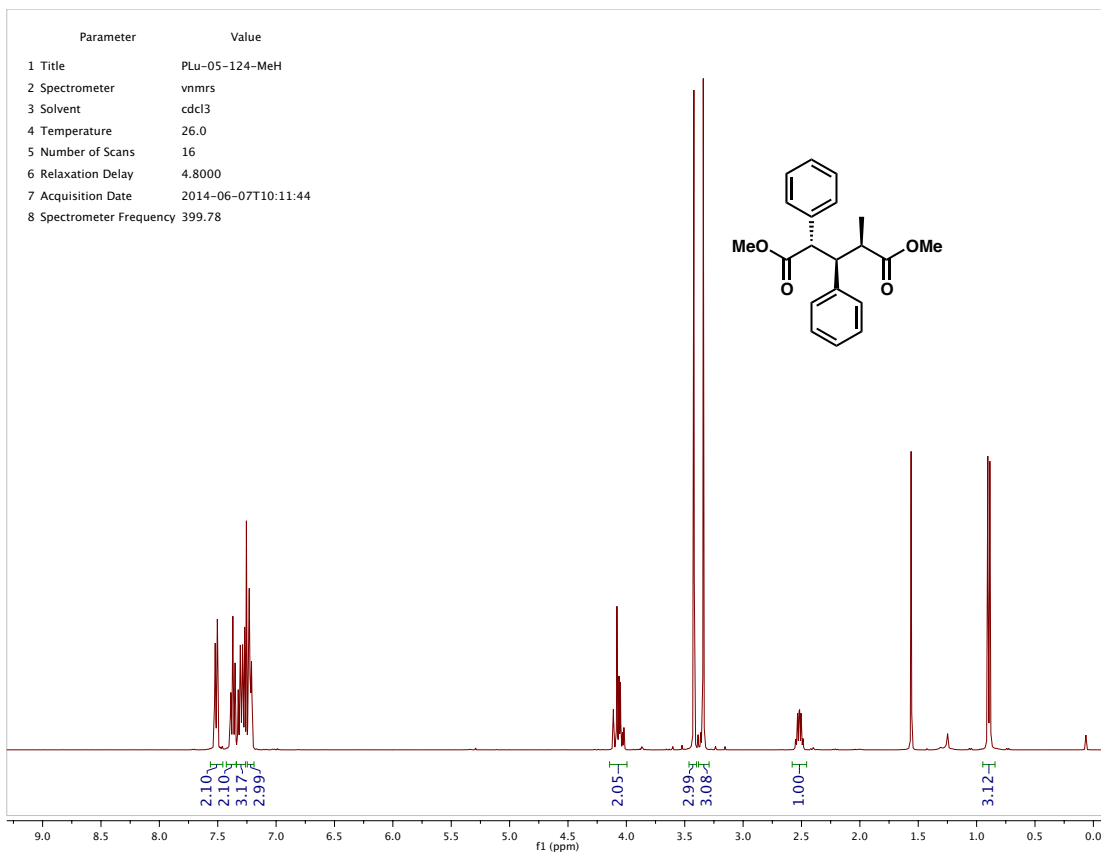


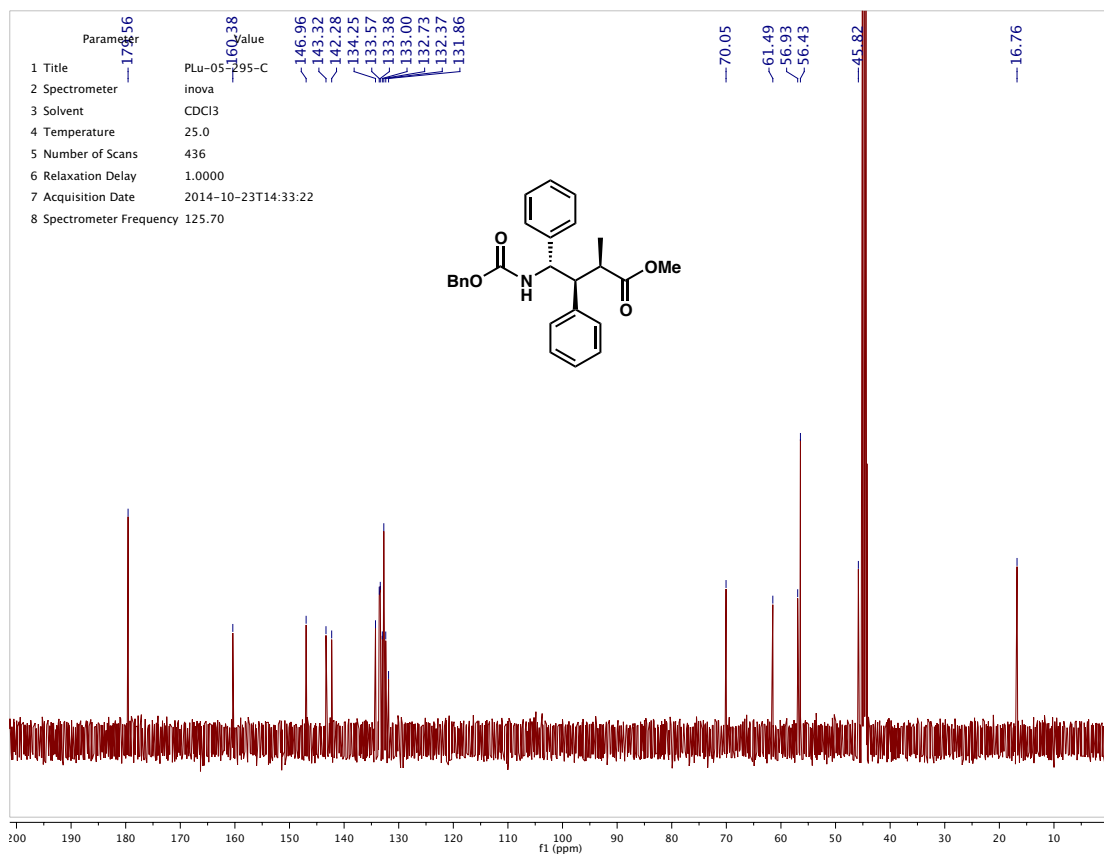
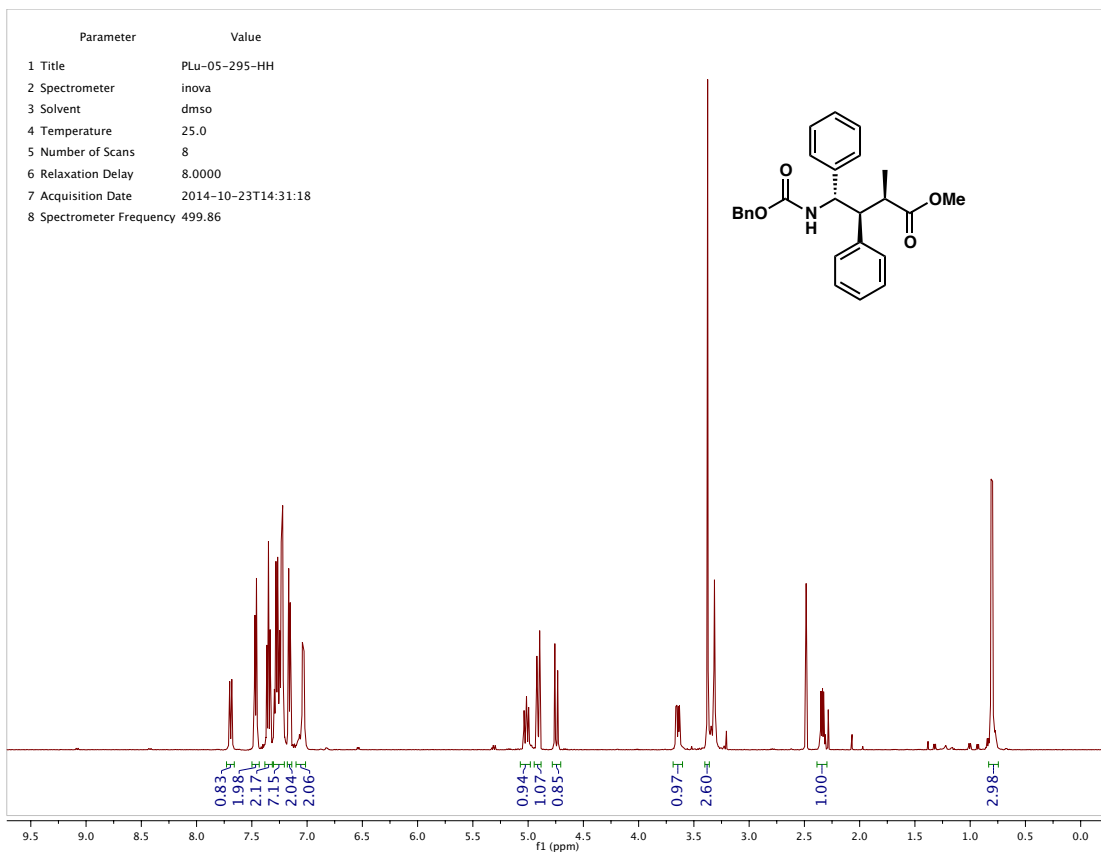


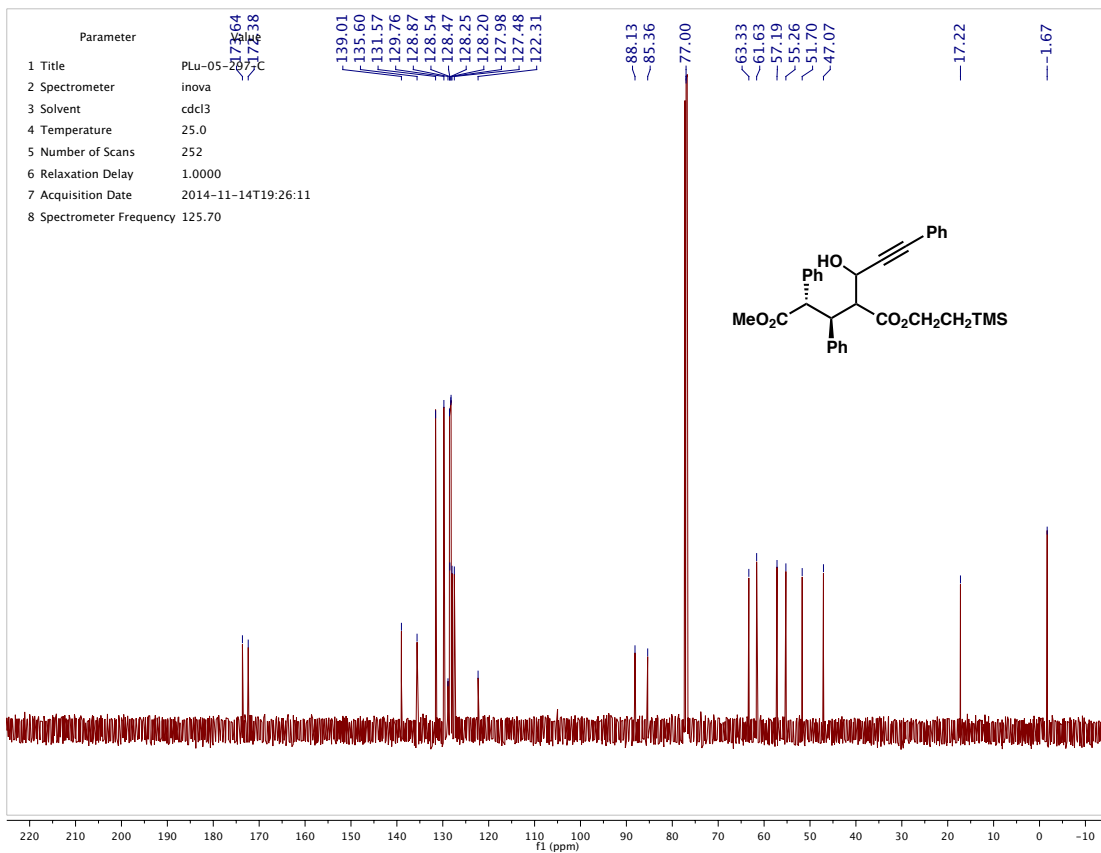
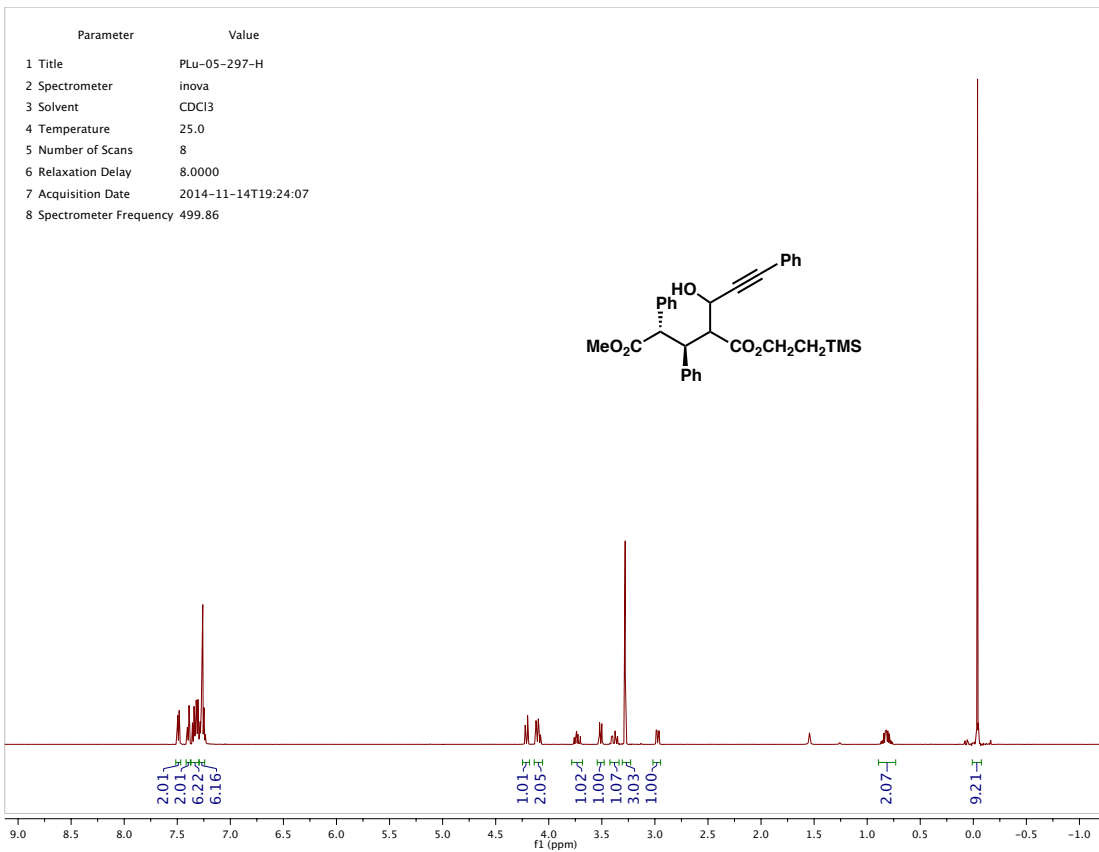


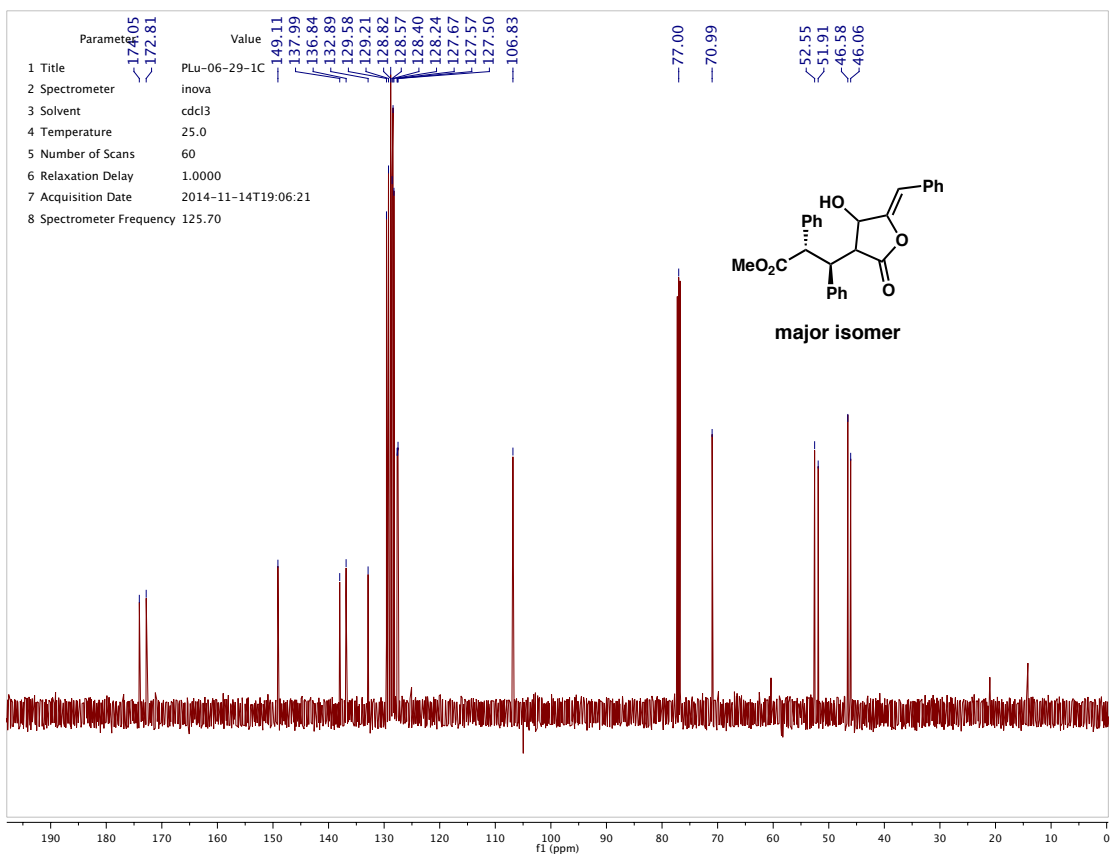
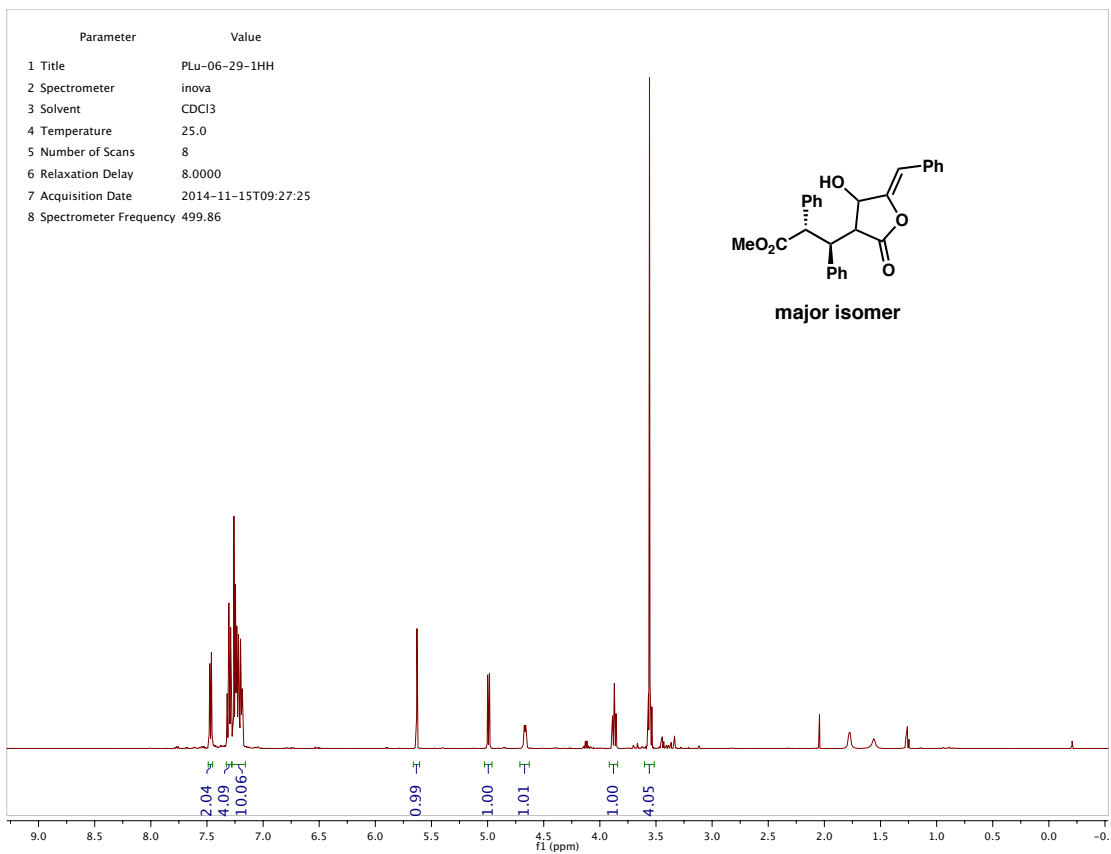


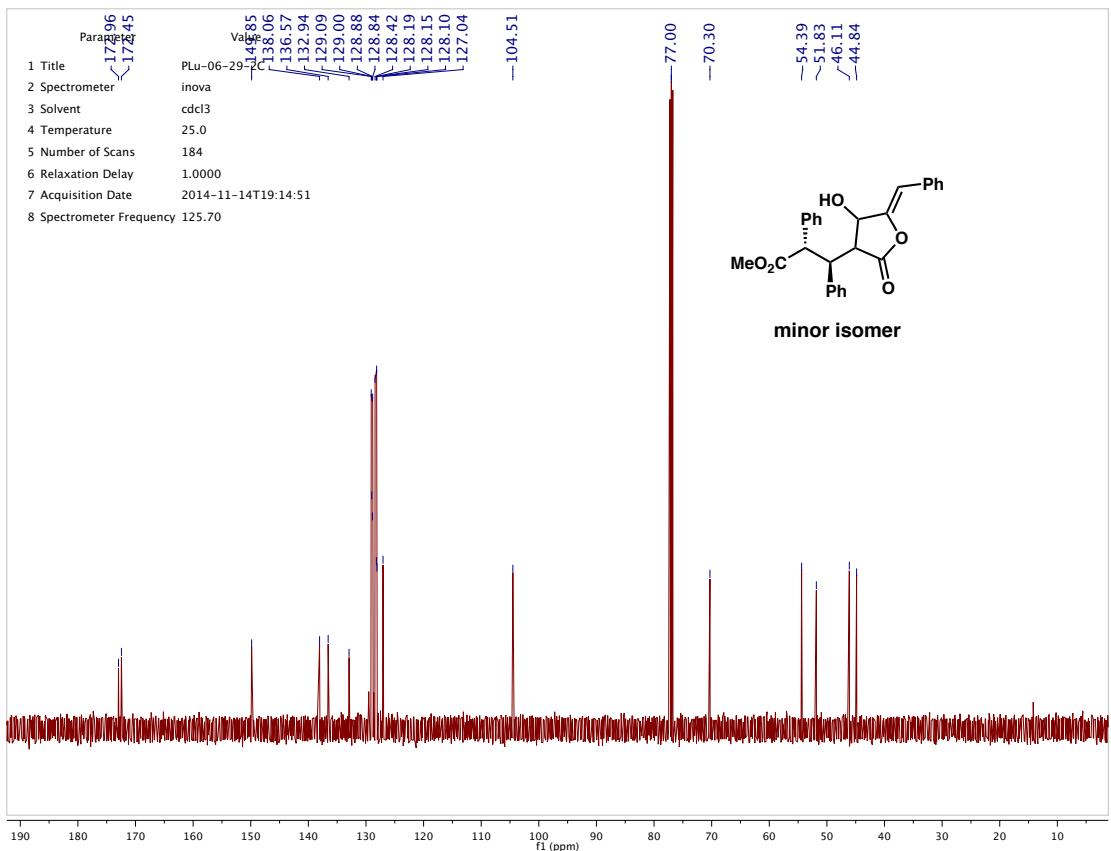
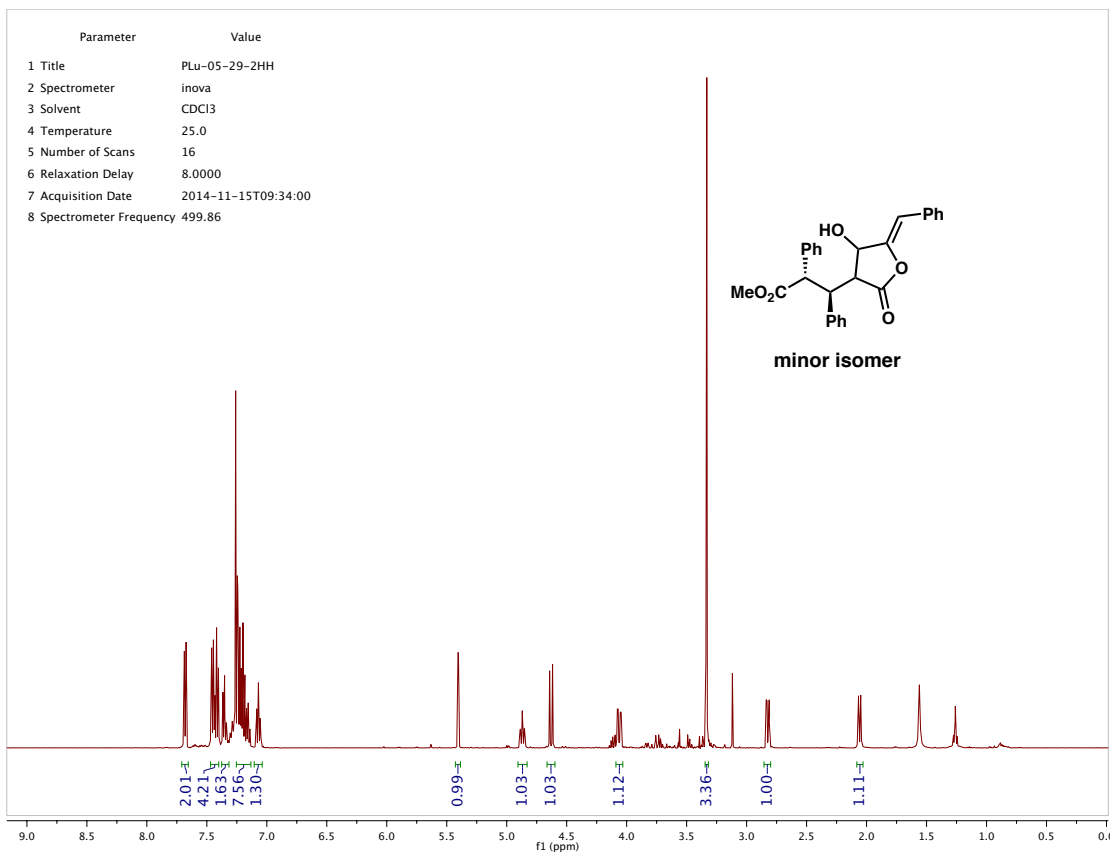


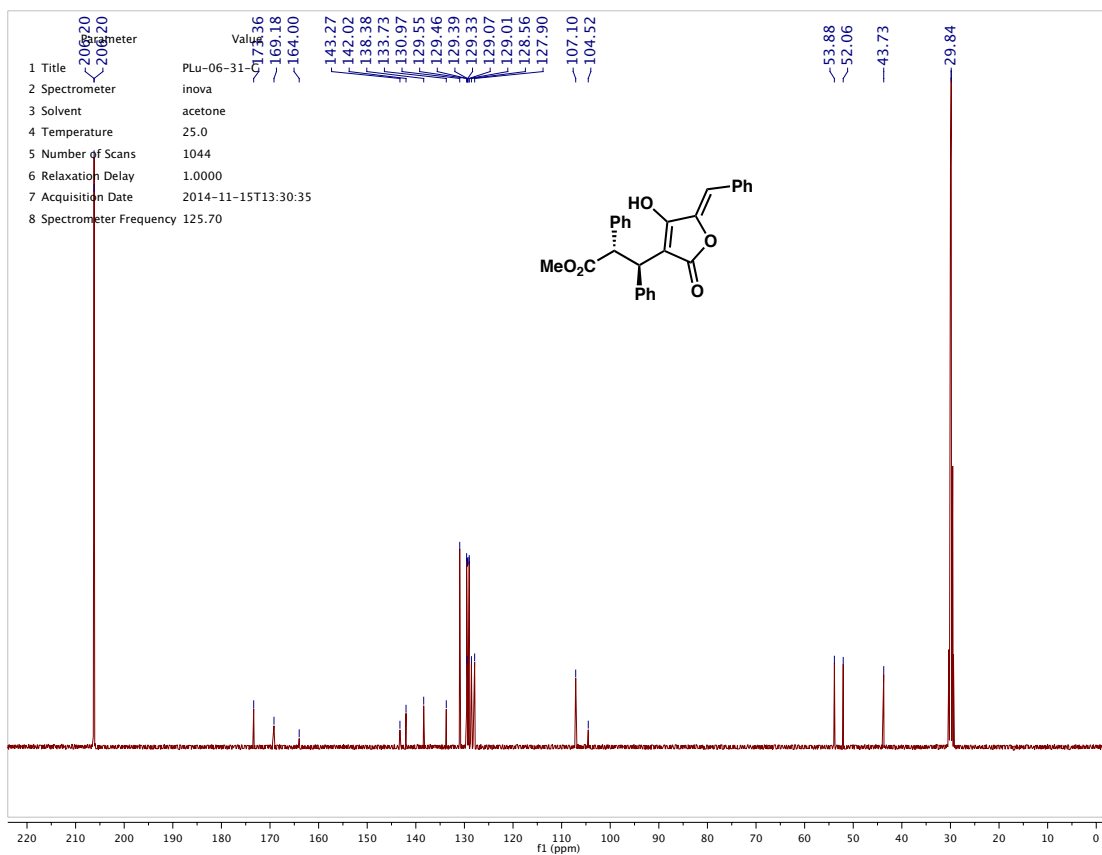
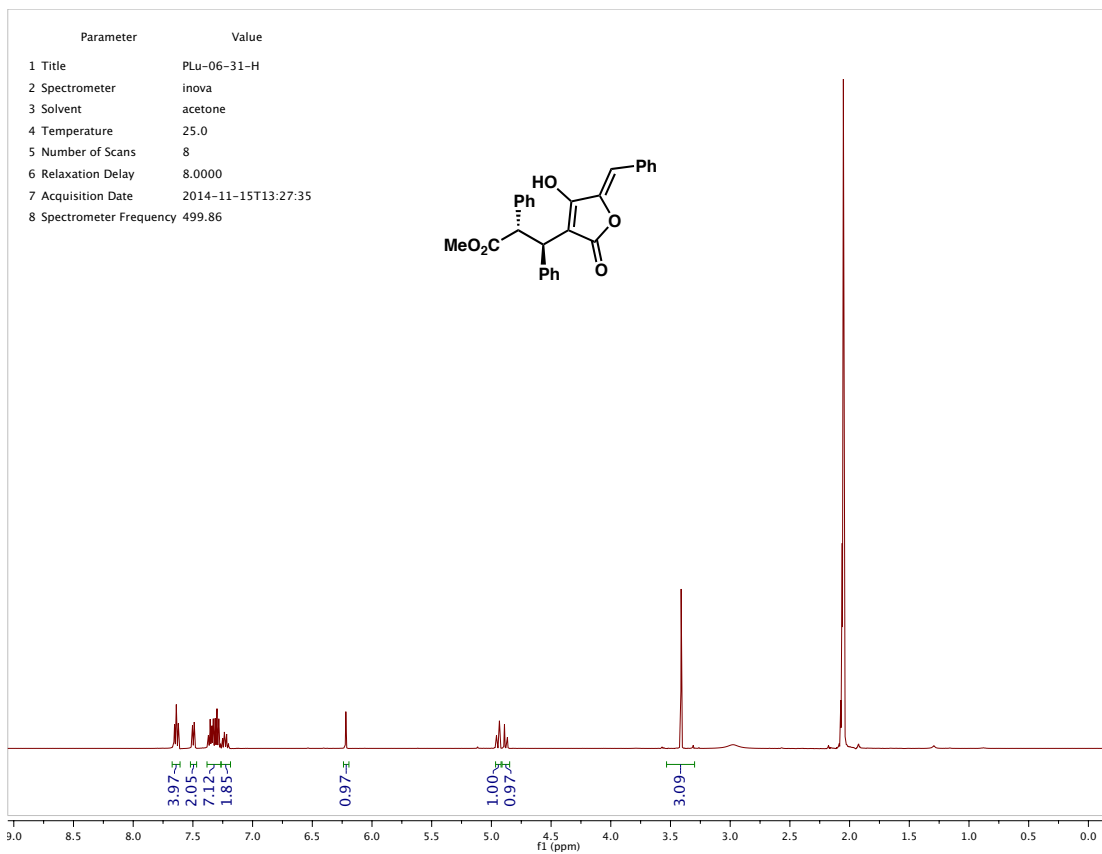








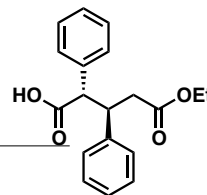




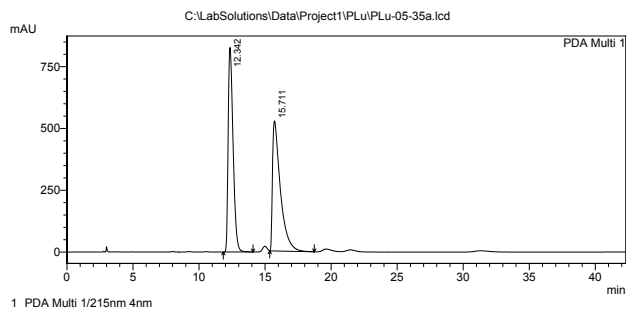
==== Shimadzu LCsolution Analysis Report ====

8/9/2014 17:30:13 1 / 1

Acquired by : Admin
 Sample Name : PLU-05-35
 Sample ID : PLU-05-35
 Vial # :
 Injection Volume : 20 uL
 Data File Name : PLU-05-35a.lcd
 Method File Name : ATH-OD-J-analytical-hplc.lcm
 Batch File Name :
 Report File Name : Default.lcr
 Data Acquired : 4/3/2014 6:54:56 PM
 Data Processed : 4/3/2014 7:37:17 PM



<Chromatogram>



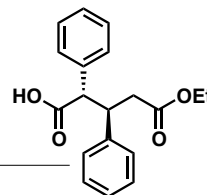
Peak#	Ret. Time	Area	Height	Area %	Height %
1	12.342	21412707	827543	49.560	61.130
2	15.711	21793027	526201	50.440	38.870
Total		43205734	1353744	100.000	100.000

C:\LabSolutions\Data\Project1\PLU\PLU-05-35a.lcd

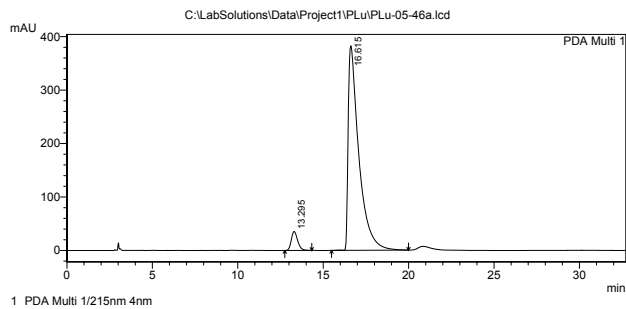
==== Shimadzu LCsolution Analysis Report ====

8/9/2014 17:28:53 1 / 1

Acquired by : Admin
 Sample Name : PLU-05-46
 Sample ID : PLU-05-46
 Vial # :
 Injection Volume : 10 uL
 Data File Name : PLU-05-46a.lcd
 Method File Name : ATH-OD-J-analytical-hplc.lcm
 Batch File Name :
 Report File Name : Default.lcr
 Data Acquired : 4/12/2014 1:18:40 PM
 Data Processed : 4/12/2014 1:51:24 PM



<Chromatogram>



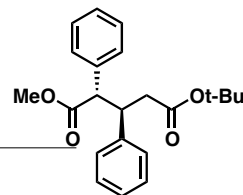
Peak#	Ret. Time	Area	Height	Area %	Height %
1	13.295	917124	35456	5.244	8.482
2	16.615	16572137	382547	94.756	91.518
Total		17489261	418003	100.000	100.000

C:\LabSolutions\Data\Project1\PLU\PLU-05-46a.lcd

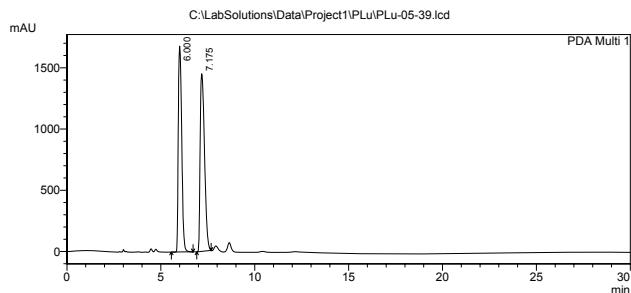
==== Shimadzu LCsolution Analysis Report ====

11/18/2014 09:41:52 1 / 1

Acquired by : Admin
 Sample Name : PLU-05-39
 Sample ID : PLU-05-39
 Vial # :
 Injection Volume : 20 uL
 Data File Name : PLU-05-39.lcd
 Method File Name : ATH-OD-J-analytical-hplc.lcm
 Batch File Name :
 Report File Name : Default.lcr
 Data Acquired : 4/4/2014 5:38:28 PM
 Data Processed : 4/4/2014 6:53:25 PM



<Chromatogram>



1 PDA Multi 1/215nm 4nm

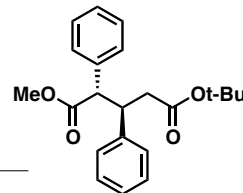
Peak#	Ret. Time	Area	Height	Area %	Height %
1	6.000	21354813	1681203	47.604	53.682
2	7.175	23504925	1450553	52.396	46.318
Total		44859738	3131756	100.000	100.000

C:\LabSolutions\Data\Project1\PLU\PLU-05-39.lcd

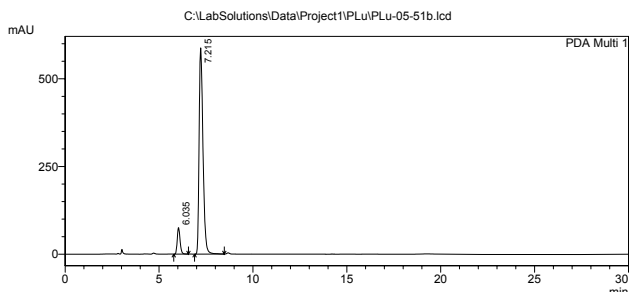
==== Shimadzu LCsolution Analysis Report ====

11/18/2014 09:44:26 1 / 1

Acquired by : Admin
 Sample Name : PLU-05-51
 Sample ID : PLU-05-51
 Vial # :
 Injection Volume : 10 uL
 Data File Name : PLU-05-51b.lcd
 Method File Name : ATH-OD-J-analytical-hplc.lcm
 Batch File Name :
 Report File Name : Default.lcr
 Data Acquired : 4/15/2014 5:42:42 PM
 Data Processed : 4/15/2014 6:19:20 PM



<Chromatogram>



1 PDA Multi 1/215nm 4nm

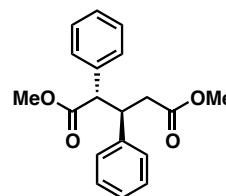
Peak#	Ret. Time	Area	Height	Area %	Height %
1	6.035	796193	75458	8.616	11.376
2	7.215	8444273	587839	91.384	88.624
Total		9240465	663297	100.000	100.000

C:\LabSolutions\Data\Project1\PLU\PLU-05-51b.lcd

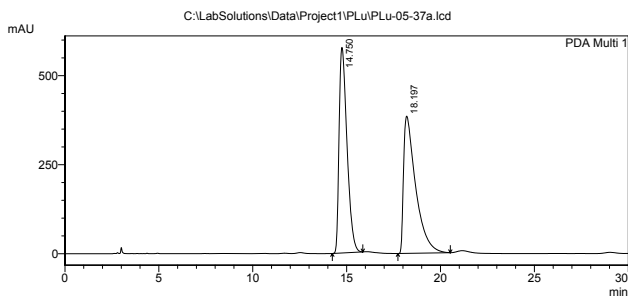
==== Shimadzu LCsolution Analysis Report ====

7/9/2014 10:35:36 1 / 1

C:\LabSolutions\Data\Project1\PLu\PLu-05-37a.lcd
 Acquired by : Admin
 Sample Name : PLu-05-37
 Sample ID : PLu-05-37
 Vial # :
 Injection Volume : 20 uL
 Data File Name : PLu-05-37a.lcd
 Method File Name : ATH-OD-J-analytical-hplc.lcm
 Batch File Name :
 Report File Name : Default.lcr
 Data Acquired : 4/4/2014 1:30:29 PM
 Data Processed : 7/8/2014 5:23:52 PM



<Chromatogram>



1 PDA Multi 1/215nm 4nm

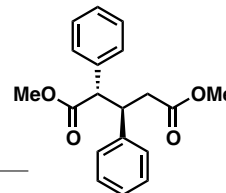
Peak#	Ret. Time	Area	Height	Area %	Height %
1	14.750	16879741	577355	49.432	59.970
2	18.197	17267500	385381	50.568	40.030
Total		34147240	962736	100.000	100.000

C:\LabSolutions\Data\Project1\PLu\PLu-05-37a.lcd

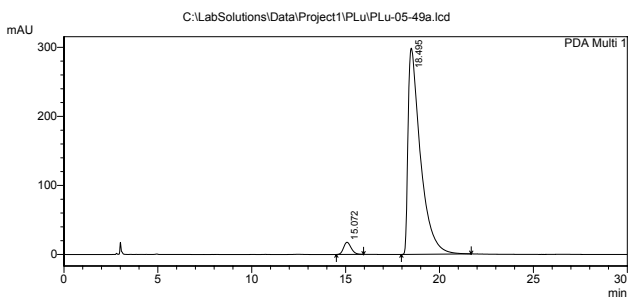
==== Shimadzu LCsolution Analysis Report ====

4/7/2016 15:00:24 1 / 1

C:\LabSolutions\Data\Project1\PLu\PLu-05-49a.lcd
 Acquired by : Admin
 Sample Name : PLu-05-49
 Sample ID : PLu-05-49
 Vial # :
 Injection Volume : 10 uL
 Data File Name : PLu-05-49a.lcd
 Method File Name : ATH-OD-J-analytical-hplc.lcm
 Batch File Name :
 Report File Name : Default.lcr
 Data Acquired : 4/14/2014 5:29:47 PM
 Data Processed : 4/14/2014 6:37:38 PM



<Chromatogram>



1 PDA Multi 1/210nm 4nm

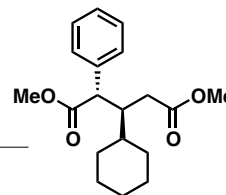
Peak#	Ret. Time	Area	Height	Area %	Height %
1	15.072	496602	17625	3.505	5.575
2	18.495	13672080	298532	96.495	94.425
Total		14168682	316157	100.000	100.000

C:\LabSolutions\Data\Project1\PLu\PLu-05-49a.lcd

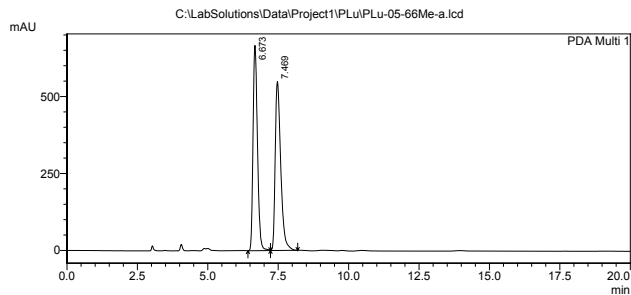
==== Shimadzu LCsolution Analysis Report ====

11/18/2014 09:46:16 1 / 1

C:\LabSolutions\Data\Project1\PLU\PLU-05-66Me-a.lcd
 Acquired by : Admin
 Sample Name : PLU-05-66Me
 Sample ID : PLU-05-66Me
 Vial # :
 Injection Volume : 10 uL
 Data File Name : PLU-05-66Me-a.lcd
 Method File Name : ATH-OD-J-analytical-hplc.lcm
 Batch File Name :
 Report File Name : Default.lcr
 Data Acquired : 4/29/2014 8:55:50 AM
 Data Processed : 5/6/2014 2:01:20 PM



<Chromatogram>



PeakTable

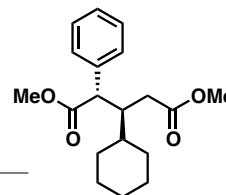
Peak#	Ret. Time	Area	Height	Area %	Height %
1	6.673	7274620	666845	49.339	54.864
2	7.469	7469594	548614	50.661	45.136
Total		14744213	1215459	100.000	100.000

C:\LabSolutions\Data\Project1\PLU\PLU-05-66Me-a.lcd

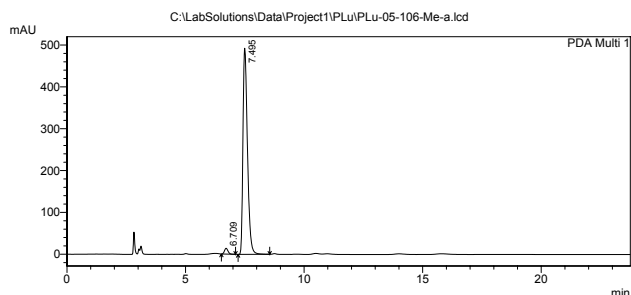
==== Shimadzu LCsolution Analysis Report ====

11/18/2014 09:48:38 1 / 1

C:\LabSolutions\Data\Project1\PLU\PLU-05-106-Me-a.lcd
 Acquired by : Admin
 Sample Name : PLU-05-106-Me
 Sample ID : PLU-05-106-Me
 Vial # :
 Injection Volume : 10 uL
 Data File Name : PLU-05-106-Me-a.lcd
 Method File Name : ATH-OD-J-analytical-hplc.lcm
 Batch File Name :
 Report File Name : Default.lcr
 Data Acquired : 5/24/2014 5:26:08 PM
 Data Processed : 5/24/2014 5:49:54 PM



<Chromatogram>



PeakTable

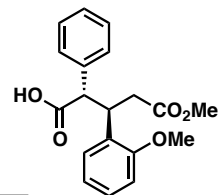
Peak#	Ret. Time	Area	Height	Area %	Height %
1	6.709	1411149	13303	2.128	2.725
2	7.495	6490632	492665	97.872	97.275
Total		6631780	506467	100.000	100.000

C:\LabSolutions\Data\Project1\PLU\PLU-05-106-Me-a.lcd

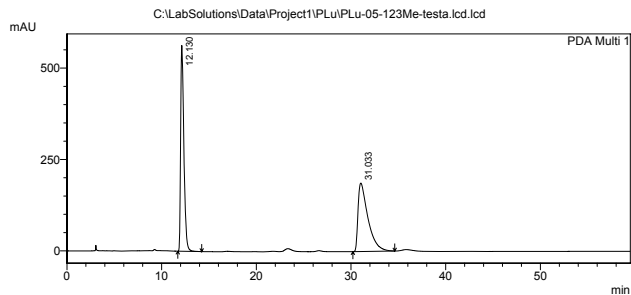
==== Shimadzu LCsolution Analysis Report ====

11/18/2014 09:53:52 1 / 1

C:\LabSolutions\Data\Project1\PLU\PLU-05-123Me-testa.lcd.lcd
 Acquired by : Admin
 Sample Name : PLU-05-123Me
 Sample ID : PLU-05-123Me
 Vial # :
 Injection Volume : 10 uL
 Data File Name : PLU-05-123Me-testa.lcd.lcd
 Method File Name : ATH-OD-J-analytical-hplc.lcm
 Batch File Name :
 Report File Name : Default.lcr
 Data Acquired : 6/11/2014 11:02:53 AM
 Data Processed : 6/11/2014 12:02:25 PM



<Chromatogram>



1 PDA Multi 1/215nm 4nm

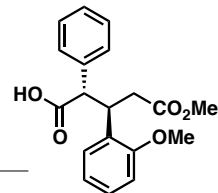
Peak#	Ret. Time	Area	Height	Area %	Height %
1	12.130	13370725	563118	49.532	75.050
2	31.033	13623258	187210	50.468	24.950
Total		26993983	750327	100.000	100.000

C:\LabSolutions\Data\Project1\PLU\PLU-05-123Me-testa.lcd.lcd

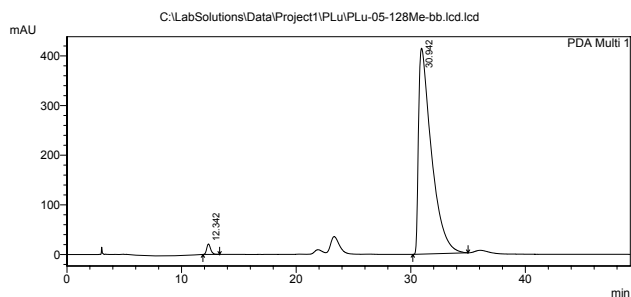
==== Shimadzu LCsolution Analysis Report ====

11/18/2014 09:55:31 1 / 1

C:\LabSolutions\Data\Project1\PLU\PLU-05-128Me-bb.lcd.lcd
 Acquired by : Admin
 Sample Name : PLU-05-128Me
 Sample ID : PLU-05-128Me
 Vial # :
 Injection Volume : 10 uL
 Data File Name : PLU-05-128Me-bb.lcd.lcd
 Method File Name : ATH-OD-J-analytical-hplc.lcm
 Batch File Name :
 Report File Name : Default.lcr
 Data Acquired : 6/11/2014 12:09:43 PM
 Data Processed : 6/11/2014 12:58:54 PM



<Chromatogram>



1 PDA Multi 1/215nm 4nm

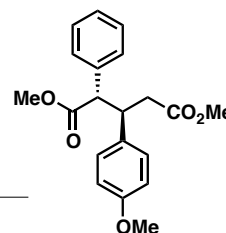
Peak#	Ret. Time	Area	Height	Area %	Height %
1	12.342	506154	20959	1.532	4.810
2	30.942	32523211	414762	98.468	95.190
Total		33029366	435721	100.000	100.000

C:\LabSolutions\Data\Project1\PLU\PLU-05-128Me-bb.lcd.lcd

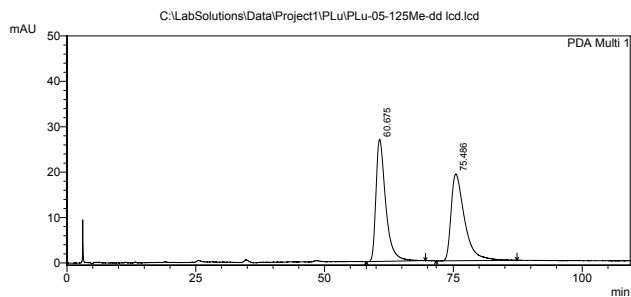
==== Shimadzu LCsolution Analysis Report ====

11/18/2014 10:04:17 1 / 1

Acquired by : Admin
 Sample Name : PLU-05-125Me
 Sample ID : PLU-05-125Me
 Vial # :
 Injection Volume : 10 uL
 Data File Name : PLU-05-125Me-dd lcd.lcd
 Method File Name : ATH-OD-J-analytical-hplc.lcm
 Batch File Name :
 Report File Name : Default.lcr
 Data Acquired : 6/10/2014 2:49:33 PM
 Data Processed : 6/10/2014 4:38:55 PM



<Chromatogram>



1 PDA Multi 1/215nm 4nm

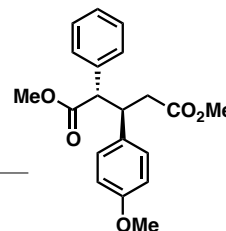
Peak#	Ret. Time	Area	Height	Area %	Height %
1	60.675	3521802	26908	50.222	58.446
2	75.486	3476735	19131	49.678	41.554
Total		6998536	46039	100.000	100.000

C:\LabSolutions\Data\Project1\PLU\PLU-05-125Me-dd lcd.lcd

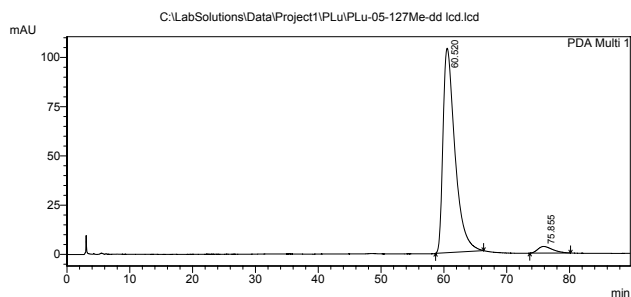
==== Shimadzu LCsolution Analysis Report ====

11/18/2014 09:59:45 1 / 1

Acquired by : Admin
 Sample Name : PLU-05-127Me
 Sample ID : PLU-05-127Me
 Vial # :
 Injection Volume : 10 uL
 Data File Name : PLU-05-127Me-dd lcd.lcd
 Method File Name : ATH-OD-J-analytical-hplc.lcm
 Batch File Name :
 Report File Name : Default.lcr
 Data Acquired : 6/10/2014 4:42:45 PM
 Data Processed : 6/10/2014 6:12:28 PM



<Chromatogram>



1 PDA Multi 1/215nm 4nm

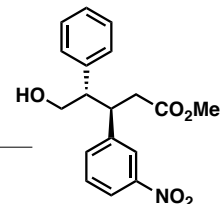
Peak#	Ret. Time	Area	Height	Area %	Height %
1	60.320	13724082	103829	96.158	96.871
2	75.855	548379	3353	3.842	3.129
Total		14272461	107182	100.000	100.000

C:\LabSolutions\Data\Project1\PLU\PLU-05-127Me-dd lcd.lcd

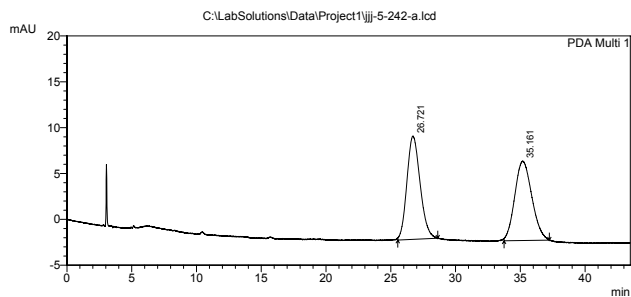
==== Shimadzu LCsolution Analysis Report ====

11/18/2014 19:00:10 1 / 1

C:\LabSolutions\Data\Project1\jij-5-242-a.lcd
 Acquired by : Admin
 Sample Name : jij-5-242-a
 Sample ID : jij-5-242-a
 Vial # :
 Injection Volume : 10 uL
 Data File Name : jij-5-242-a.lcd
 Method File Name : ATH-OD-J-analytical-hplc.lcm
 Batch File Name :
 Report File Name : Default.lcr
 Data Acquired : 11/18/2014 8:42:39 AM
 Data Processed : 11/18/2014 9:27:17 AM



<Chromatogram>



1 PDA Multi 1/210nm 4nm

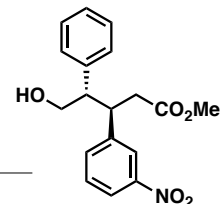
Peak#	Ret. Time	Area	Height	Area %	Height %
1	26.721	798582	11283	50.184	56.557
2	35.161	792717	8667	49.816	43.443
Total		1591299	19949	100.000	100.000

C:\LabSolutions\Data\Project1\jij-5-242-a.lcd

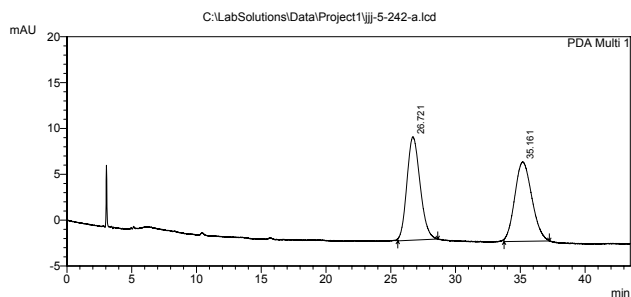
==== Shimadzu LCsolution Analysis Report ====

11/18/2014 19:00:10 1 / 1

C:\LabSolutions\Data\Project1\jij-5-242-a.lcd
 Acquired by : Admin
 Sample Name : jij-5-242-a
 Sample ID : jij-5-242-a
 Vial # :
 Injection Volume : 10 uL
 Data File Name : jij-5-242-a.lcd
 Method File Name : ATH-OD-J-analytical-hplc.lcm
 Batch File Name :
 Report File Name : Default.lcr
 Data Acquired : 11/18/2014 8:42:39 AM
 Data Processed : 11/18/2014 9:27:17 AM



<Chromatogram>



1 PDA Multi 1/210nm 4nm

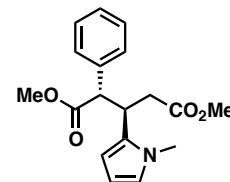
Peak#	Ret. Time	Area	Height	Area %	Height %
1	26.721	798582	11283	50.184	56.557
2	35.161	792717	8667	49.816	43.443
Total		1591299	19949	100.000	100.000

C:\LabSolutions\Data\Project1\jij-5-242-a.lcd

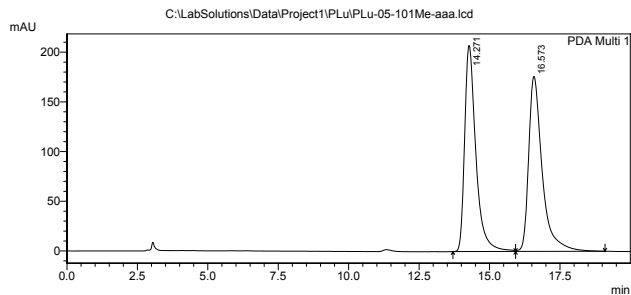
==== Shimadzu LCsolution Analysis Report ====

11/18/2014 10:05:59 1 / 1

C:\LabSolutions\Data\Project1\PLU\PLU-05-101Me-aaa.lcd
 Acquired by : Admin
 Sample Name : PLU-05-101Me
 Sample ID : PLU-05-101Me
 Vial # :
 Injection Volume : 10 uL
 Data File Name : PLU-05-101Me-aaa.lcd
 Method File Name : ATH-OD-J-analytical-hplc.lcm
 Batch File Name :
 Report File Name : Default.lcr
 Data Acquired : 6/7/2014 5:22:57 PM
 Data Processed : 6/7/2014 5:42:58 PM



<Chromatogram>



PeakTable

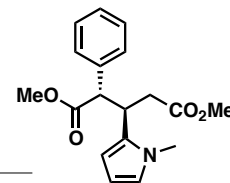
Peak#	Ret. Time	Area	Height	Area %	Height %
1	14.271	5737902	207418	49.389	54.085
2	16.573	5879821	176083	50.611	45.915
Total		11617723	383501	100.000	100.000

C:\LabSolutions\Data\Project1\PLU\PLU-05-101Me-aaa.lcd

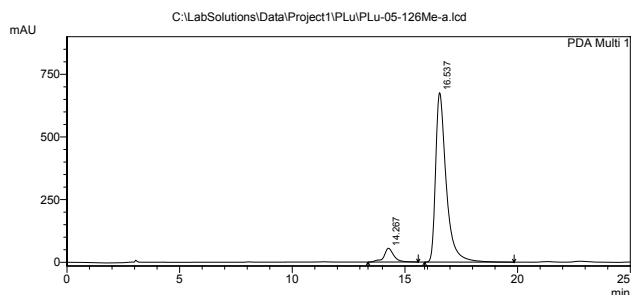
==== Shimadzu LCsolution Analysis Report ====

11/18/2014 10:08:13 1 / 1

C:\LabSolutions\Data\Project1\PLU\PLU-05-126Me-a.lcd
 Acquired by : Admin
 Sample Name : PLU-05-126Me
 Sample ID : PLU-05-126Me
 Vial # :
 Injection Volume : 10 uL
 Data File Name : PLU-05-126Me-a.lcd
 Method File Name : ATH-OD-J-analytical-hplc.lcm
 Batch File Name :
 Report File Name : Default.lcr
 Data Acquired : 6/7/2014 4:40:34 PM
 Data Processed : 6/7/2014 5:15:05 PM



<Chromatogram>



PeakTable

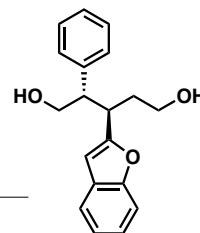
Peak#	Ret. Time	Area	Height	Area %	Height %
1	14.267	1676791	54964	7.054	7.519
2	16.537	22095373	676045	92.946	92.481
Total		23772163	731010	100.000	100.000

C:\LabSolutions\Data\Project1\PLU\PLU-05-126Me-a.lcd

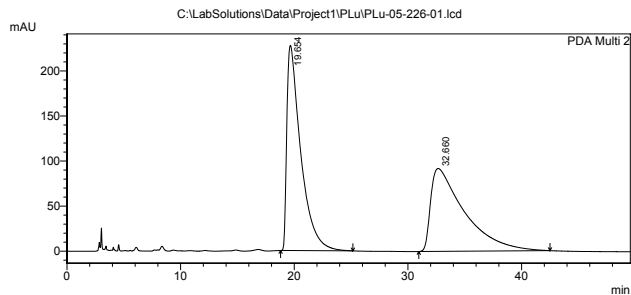
==== Shimadzu LCsolution Analysis Report ====

11/18/2014 10:12:32 1 / 1

Acquired by : Admin
 Sample Name : PLU-05-226
 Sample ID : PLU-05-226
 Vial # :
 Injection Volume : 10 uL
 Data File Name : PLU-05-226-01.lcd
 Method File Name : ATH-OD-J-analytical-hplc.lcm
 Batch File Name :
 Report File Name : Default.lcr
 Data Acquired : 8/27/2014 9:51:57 AM
 Data Processed : 8/27/2014 10:44:07 AM



<Chromatogram>



1 PDA Multi 2/215nm 4nm

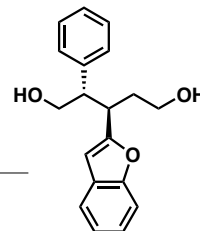
Peak#	Ret. Time	Area	Height	Area %	Height %
1	19.654	19377682	227621	50.573	71.226
2	32.660	18938853	91955	49.427	28.774
Total		38316535	319576	100.000	100.000

C:\LabSolutions\Data\Project1\PLU\PLU-05-226-01.lcd

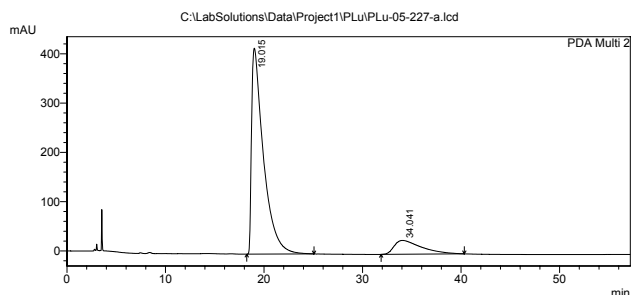
==== Shimadzu LCsolution Analysis Report ====

11/18/2014 10:14:16 1 / 1

Acquired by : Admin
 Sample Name : PLU-05-227
 Sample ID : PLU-05-227
 Vial # :
 Injection Volume : 10 uL
 Data File Name : PLU-05-227-a.lcd
 Method File Name : ATH-OD-J-analytical-hplc.lcm
 Batch File Name :
 Report File Name : Default.lcr
 Data Acquired : 8/28/2014 9:57:50 AM
 Data Processed : 11/17/2014 2:52:48 PM



<Chromatogram>



1 PDA Multi 2/215nm 4nm

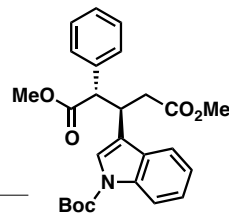
Peak#	Ret. Time	Area	Height	Area %	Height %
1	19.015	35055363	417781	86.634	93.707
2	34.041	5408577	28055	13.366	6.293
Total		40464341	445836	100.000	100.000

C:\LabSolutions\Data\Project1\PLU\PLU-05-227-a.lcd

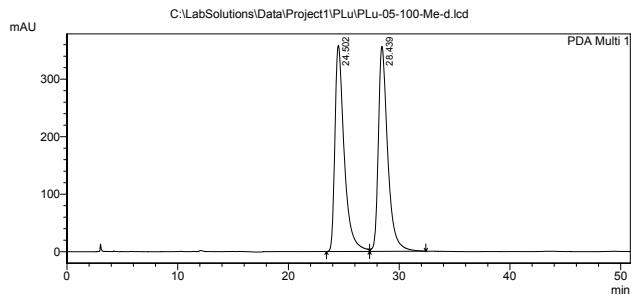
==== Shimadzu LCsolution Analysis Report ====

11/18/2014 10:17:40 1 / 1

C:\LabSolutions\Data\Project1\PLU\PLU-05-100-Me-d.lcd
 Acquired by : Admin
 Sample Name : PLU-05-100-Me
 Sample ID : PLU-05-100-Me
 Vial # :
 Injection Volume : 10 uL
 Data File Name : PLU-05-100-Me-d.lcd
 Method File Name : ATH-OD-J-analytical-hplc.lcm
 Batch File Name :
 Report File Name : Default.lcr
 Data Acquired : 5/20/2014 2:24:11 PM
 Data Processed : 5/20/2014 3:15:04 PM



<Chromatogram>



1 PDA Ch1 215nm 4nm

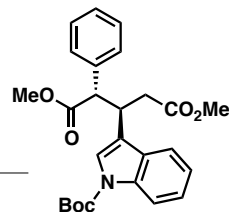
Peak#	Ret. Time	Area	Height	Area %	Height %
1	24.502	20916152	358421	50.059	50.128
2	28.439	20866982	356596	49.941	49.872
Total		41783133	715018	100.000	100.000

C:\LabSolutions\Data\Project1\PLU\PLU-05-100-Me-d.lcd

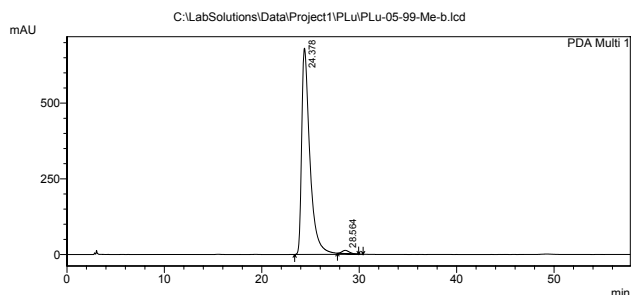
==== Shimadzu LCsolution Analysis Report ====

11/18/2014 10:16:40 1 / 1

C:\LabSolutions\Data\Project1\PLU\PLU-05-99-Me-b.lcd
 Acquired by : Admin
 Sample Name : PLU-05-99-Me
 Sample ID : PLU-05-99-Me
 Vial # :
 Injection Volume : 10 uL
 Data File Name : PLU-05-99-Me-b.lcd
 Method File Name : ATH-OD-J-analytical-hplc.lcm
 Batch File Name :
 Report File Name : Default.lcr
 Data Acquired : 5/20/2014 12:28:10 PM
 Data Processed : 5/20/2014 1:26:01 PM



<Chromatogram>



1 PDA Ch1 215nm 4nm

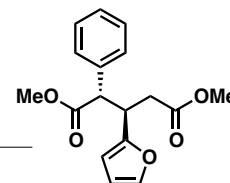
Peak#	Ret. Time	Area	Height	Area %	Height %
1	24.378	40158106	681092	98.723	98.497
2	28.564	519456	10396	1.277	1.503
Total		40677562	691488	100.000	100.000

C:\LabSolutions\Data\Project1\PLU\PLU-05-99-Me-b.lcd

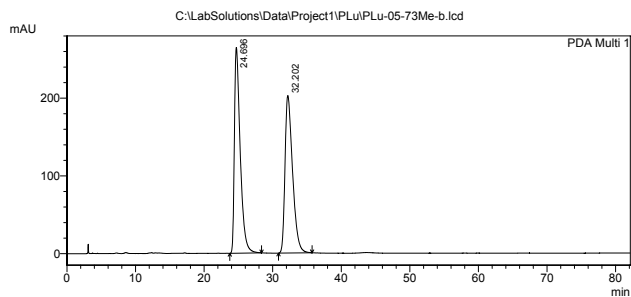
==== Shimadzu LCsolution Analysis Report ====

11/18/2014 10:20:51 1 / 1

C:\LabSolutions\Data\Project1\PLU\PLU-05-73Me-b.lcd
 Acquired by : Admin
 Sample Name : PLU-05-73Me
 Sample ID : PLU-05-73Me
 Vial # :
 Injection Volume : 10 uL
 Data File Name : PLU-05-73Me-b.lcd
 Method File Name : ATH-OD-J-analytical-hplc.lcm
 Batch File Name :
 Report File Name : Default.lcr
 Data Acquired : 5/2/2014 11:57:39 AM
 Data Processed : 5/2/2014 1:19:50 PM



<Chromatogram>



1 PDA Multi 1/215nm 4nm

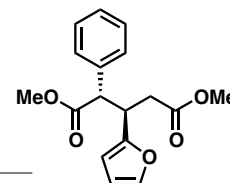
Peak#	Ret. Time	Area	Height	Area %	Height %
1	24.696	15582434	264704	50.196	56.648
2	32.202	15460821	202573	49.804	43.352
Total		31043255	467277	100.000	100.000

C:\LabSolutions\Data\Project1\PLU\PLU-05-73Me-b.lcd

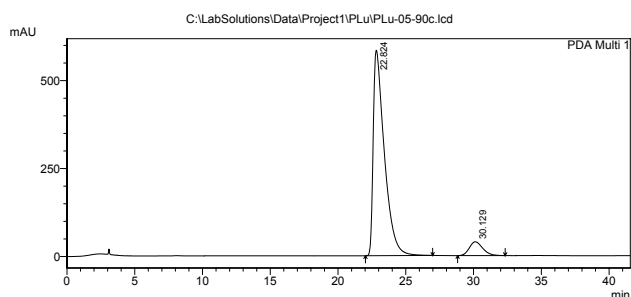
==== Shimadzu LCsolution Analysis Report ====

11/18/2014 10:19:44 1 / 1

C:\LabSolutions\Data\Project1\PLU\PLU-05-90c.lcd
 Acquired by : Admin
 Sample Name : PLU-05-90Me
 Sample ID : PLU-05-90Me
 Vial # :
 Injection Volume : 10 uL
 Data File Name : PLU-05-90c.lcd
 Method File Name : ATH-OD-J-analytical-hplc.lcm
 Batch File Name :
 Report File Name : Default.lcr
 Data Acquired : 5/13/2014 3:44:13 PM
 Data Processed : 5/13/2014 4:35:00 PM



<Chromatogram>



1 PDA Multi 1/215nm 4nm

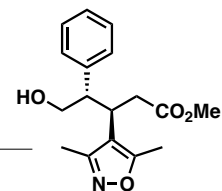
Peak#	Ret. Time	Area	Height	Area %	Height %
1	22.824	33336083	583990	92.500	93.706
2	30.129	2702862	39227	7.500	6.294
Total		36038946	623217	100.000	100.000

C:\LabSolutions\Data\Project1\PLU\PLU-05-90c.lcd

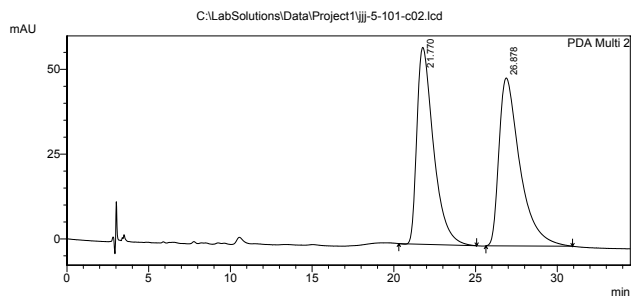
==== Shimadzu LCsolution Analysis Report ====

11/18/2014 10:24:42 1 / 1

Acquired by : Admin
 Sample Name : jji-5-101-c
 Sample ID : jji-5-101-c
 Vial # :
 Injection Volume : 10 uL
 Data File Name : jji-5-101-c02.lcd
 Method File Name : ATH-OD-J-analytical-hplc.lcm
 Batch File Name :
 Report File Name : Default.lcr
 Data Acquired : 8/27/2014 5:28:47 PM
 Data Processed : 8/27/2014 6:03:17 PM



<Chromatogram>



1 PDA Multi 2/215nm 4nm

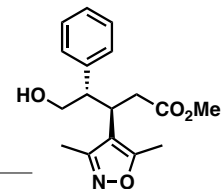
Peak#	Ret. Time	Area	Height	Area %	Height %
1	21.770	4105061	58063	48.236	53.962
2	26.878	4405385	49536	51.764	46.038
Total		8510346	107600	100.000	100.000

C:\LabSolutions\Data\Project1\jji-5-101-c02.lcd

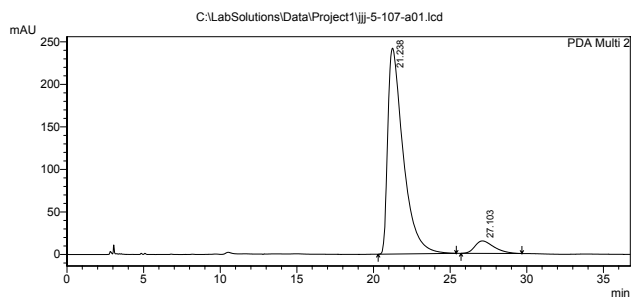
==== Shimadzu LCsolution Analysis Report ====

11/18/2014 10:23:26 1 / 1

Acquired by : Admin
 Sample Name : jji-5-107-a
 Sample ID : jji-5-107-a
 Vial # :
 Injection Volume : 10 uL
 Data File Name : jji-5-107-a01.lcd
 Method File Name : ATH-OD-J-analytical-hplc.lcm
 Batch File Name :
 Report File Name : Default.lcr
 Data Acquired : 8/29/2014 4:13:52 PM
 Data Processed : 11/3/2014 4:10:10 PM



<Chromatogram>



1 PDA Multi 2/215nm 4nm

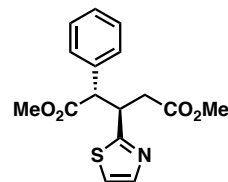
Peak#	Ret. Time	Area	Height	Area %	Height %
1	21.238	16940174	241991	93.005	94.294
2	27.103	1274041	14644	6.995	5.706
Total		18214214	256634	100.000	100.000

C:\LabSolutions\Data\Project1\jji-5-107-a01.lcd

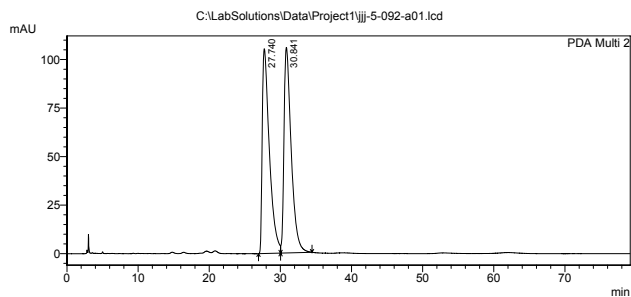
==== Shimadzu LCsolution Analysis Report ====

11/18/2014 10:25:42 1 / 1

Acquired by : Admin
 Sample Name : jijj-5-092-a
 Sample ID : jijj-5-092-a
 Vial # :
 Injection Volume : 10 uL
 Data File Name : jijj-5-092-a01.lcd
 Method File Name : ATH-OD-J-analytical-hplc.lcm
 Batch File Name :
 Report File Name : Default.lcr
 Data Acquired : 8/25/2014 9:14:31 AM
 Data Processed : 8/25/2014 10:33:45 AM



<Chromatogram>



1 PDA Ch2 215nm 4nm

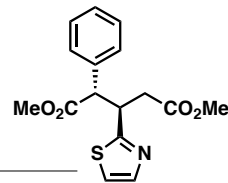
Peak#	Ret. Time	Area	Height	Area %	Height %
1	27.740	7354240	105481	49.592	49.902
2	30.841	7475392	105894	50.408	50.098
Total		14829632	211375	100.000	100.000

C:\LabSolutions\Data\Project1\jijj-5-092-a01.lcd

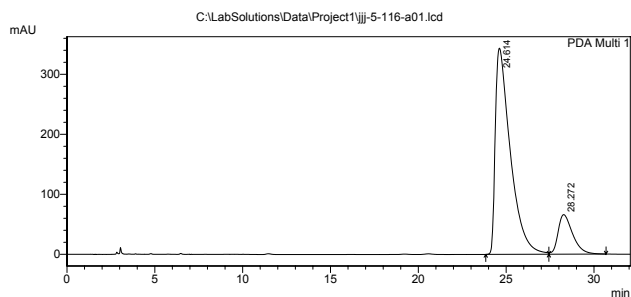
==== Shimadzu LCsolution Analysis Report ====

11/18/2014 10:37:37 1 / 1

Acquired by : Admin
 Sample Name : jijj-5-116-a
 Sample ID : jijj-5-116-a
 Vial # :
 Injection Volume : 10 uL
 Data File Name : jijj-5-116-a01.lcd
 Method File Name : ATH-OD-J-analytical-hplc.lcm
 Batch File Name :
 Report File Name : Default.lcr
 Data Acquired : 9/5/2014 5:18:49 PM
 Data Processed : 11/3/2014 4:11:24 PM



<Chromatogram>



1 PDA Ch1 215nm 4nm

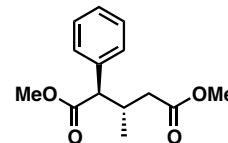
Peak#	Ret. Time	Area	Height	Area %	Height %
1	24.614	20444486	343598	84.316	83.911
2	28.272	3802862	65880	15.684	16.089
Total		24247348	409479	100.000	100.000

C:\LabSolutions\Data\Project1\jijj-5-116-a01.lcd

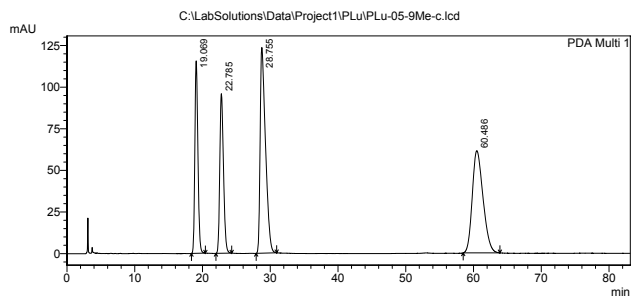
==== Shimadzu LCsolution Analysis Report ====

11/18/2014 10:35:09 1 / 1

Acquired by : Admin
 Sample Name : PLU-05-9Me
 Sample ID : PLU-05-9Me
 Vial # :
 Injection Volume : 10 uL
 Data File Name : PLU-05-9Me-c.lcd
 Method File Name : ATH-OD-J-analytical-hplc.lcm
 Batch File Name :
 Report File Name : Default.lcr
 Data Acquired : 4/20/2014 2:07:11 PM
 Data Processed : 4/20/2014 3:30:23 PM



<Chromatogram>



1 PDA Multi 1/215nm 4nm

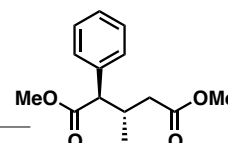
Peak#	Ret. Time	Area	Height	Area %	Height %
1	19.069	3619833	115637	17.437	29.171
2	22.785	3618619	95801	17.431	24.167
3	28.755	6758381	123600	32.555	31.180
4	60.486	6762800	61371	32.577	15.482
Total		20759634	396409	100.000	100.000

C:\LabSolutions\Data\Project1\PLU\PLU-05-9Me-c.lcd

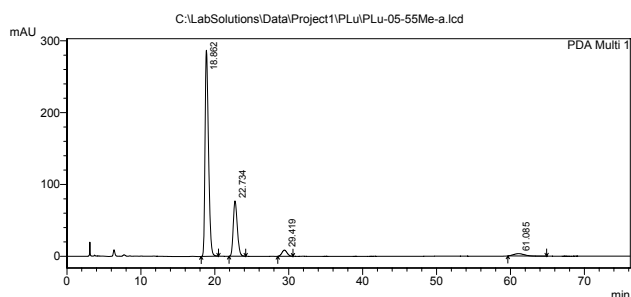
==== Shimadzu LCsolution Analysis Report ====

11/18/2014 10:36:26 1 / 1

Acquired by : Admin
 Sample Name : PLU-05-55Me
 Sample ID : PLU-05-55Me
 Vial # :
 Injection Volume : 10 uL
 Data File Name : PLU-05-55Me-a.lcd
 Method File Name : ATH-OD-J-analytical-hplc.lcm
 Batch File Name :
 Report File Name : Default.lcr
 Data Acquired : 4/20/2014 3:34:28 PM
 Data Processed : 4/20/2014 4:50:43 PM



<Chromatogram>



1 PDA Multi 1/215nm 4nm

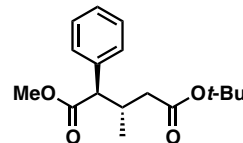
Peak#	Ret. Time	Area	Height	Area %	Height %
1	18.862	9330831	287018	71.760	76.369
2	22.734	2933770	76965	22.563	20.479
3	29.419	417480	8624	3.211	2.295
4	61.085	320711	3222	2.466	0.857
Total		13002792	375829	100.000	100.000

C:\LabSolutions\Data\Project1\PLU\PLU-05-55Me-a.lcd

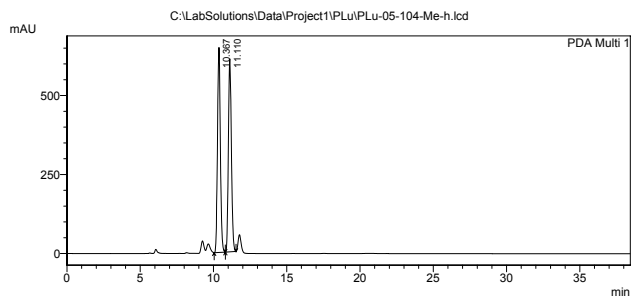
==== Shimadzu LCsolution Analysis Report ====

11/18/2014 10:39:57 1 / 1

C:\LabSolutions\Data\Project1\PLU\PLU-05-104-Me-h.lcd
 Acquired by : Admin
 Sample Name : PLU-05-104-Me
 Sample ID : PLU-05-104-Me
 Vial # :
 Injection Volume : 10 uL
 Data File Name : PLU-05-104-Me-h.lcd
 Method File Name : ATH-OD-J-analytical-hplc.lcm
 Batch File Name :
 Report File Name : Default.lcr
 Data Acquired : 5/23/2014 3:08:15 PM
 Data Processed : 5/23/2014 3:46:43 PM



<Chromatogram>



1 PDA Ch1 215nm 4nm

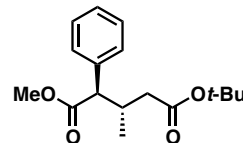
Peak#	Ret. Time	Area	Height	Area %	Height %
1	10.367	8843368	648961	50.257	51.512
2	11.110	8717836	610865	49.643	48.888
Total		17561204	1259826	100.000	100.000

C:\LabSolutions\Data\Project1\PLU\PLU-05-104-Me-h.lcd

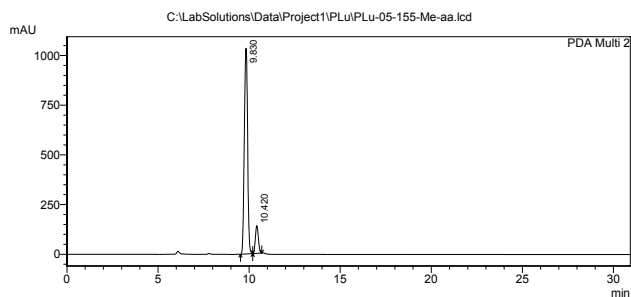
==== Shimadzu LCsolution Analysis Report ====

11/18/2014 10:41:34 1 / 1

C:\LabSolutions\Data\Project1\PLU\PLU-05-155-Me-aa.lcd
 Acquired by : Admin
 Sample Name : PLU-05-155-Me
 Sample ID : PLU-05-155-Me
 Vial # :
 Injection Volume : 5 uL
 Data File Name : PLU-05-155-Me-aa.lcd
 Method File Name : ATH-OD-J-analytical-hplc.lcm
 Batch File Name :
 Report File Name : Default.lcr
 Data Acquired : 7/14/2014 1:50:51 PM
 Data Processed : 7/14/2014 5:29:30 PM



<Chromatogram>



1 PDA Ch2 215nm 4nm

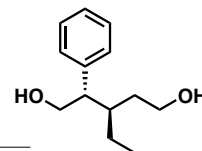
Peak#	Ret. Time	Area	Height	Area %	Height %
1	9.830	12935327	1035300	89.069	88.126
2	10.420	1587507	139492	10.931	11.874
Total		14522834	1174792	100.000	100.000

C:\LabSolutions\Data\Project1\PLU\PLU-05-155-Me-aa.lcd

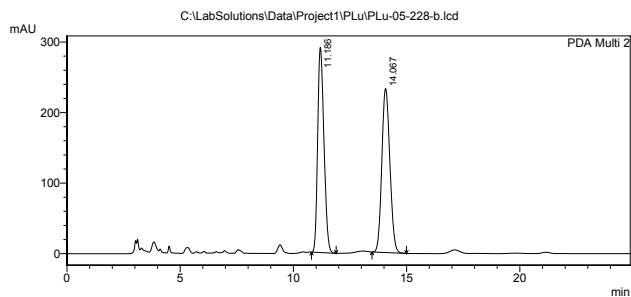
==== Shimadzu LCsolution Analysis Report ====

11/18/2014 10:44:06 1 / 1

Acquired by : Admin
 Sample Name : PLU-05-228
 Sample ID : PLU-05-228
 Vial # :
 Injection Volume : 10 uL
 Data File Name : PLU-05-228-b.lcd
 Method File Name : ATH-OD-J-analytical-hplc.lcm
 Batch File Name :
 Report File Name : Default.lcr
 Data Acquired : 8/29/2014 10:42:30 AM
 Data Processed : 8/29/2014 11:07:24 AM



<Chromatogram>



1 PDA Multi 2/215nm 4nm

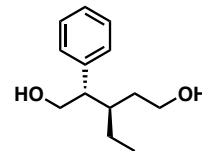
Peak#	Ret. Time	Area	Height	Area %	Height %
1	11.186	5592472	290782	49.251	55.568
2	14.067	5739619	232509	50.649	44.432
Total		11332091	523291	100.000	100.000

C:\LabSolutions\Data\Project1\PLU\PLU-05-228-b.lcd

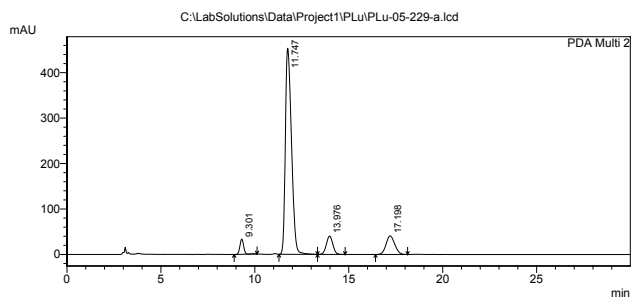
==== Shimadzu LCsolution Analysis Report ====

11/18/2014 10:45:31 1 / 1

Acquired by : Admin
 Sample Name : PLU-05-229
 Sample ID : PLU-05-229
 Vial # :
 Injection Volume : 10 uL
 Data File Name : PLU-05-229-a.lcd
 Method File Name : ATH-OD-J-analytical-hplc.lcm
 Batch File Name :
 Report File Name : Default.lcr
 Data Acquired : 9/2/2014 11:10:52 AM
 Data Processed : 9/2/2014 11:40:52 AM



<Chromatogram>



1 PDA Multi 2/215nm 4nm

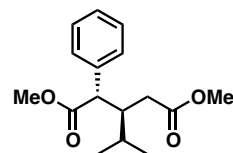
Peak#	Ret. Time	Area	Height	Area %	Height %
1	9.301	466571	33295	3.576	5.860
2	11.747	10290631	453524	78.878	79.819
3	13.976	970426	40441	7.438	7.118
4	17.198	1318644	40930	10.107	7.204
Total		13046273	568191	100.000	100.000

C:\LabSolutions\Data\Project1\PLU\PLU-05-229-a.lcd

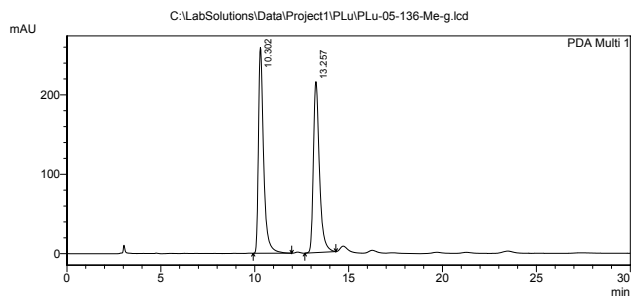
==== Shimadzu LCsolution Analysis Report ====

11/18/2014 10:48:50 1 / 1

C:\LabSolutions\Data\Project1\PLU\PLU-05-136-Me-g.lcd
 Acquired by : Admin
 Sample Name : PLU-05-136-Me
 Sample ID : PLU-05-136-Me
 Vial # :
 Injection Volume : 10 uL
 Data File Name : PLU-05-136-Me-g.lcd
 Method File Name : ATH-OD-J-analytical-hplc.lcm
 Batch File Name :
 Report File Name : Default.lcr
 Data Acquired : 6/17/2014 2:48:35 PM
 Data Processed : 6/17/2014 3:39:16 PM



<Chromatogram>



PeakTable

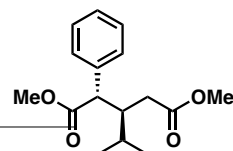
Peak#	Ret. Time	Area	Height	Area %	Height %
1	10.302	4950742	259193	50.791	54.620
2	13.257	4796524	215343	49.209	45.380
Total		9747266	474536	100.000	100.000

C:\LabSolutions\Data\Project1\PLU\PLU-05-136-Me-g.lcd

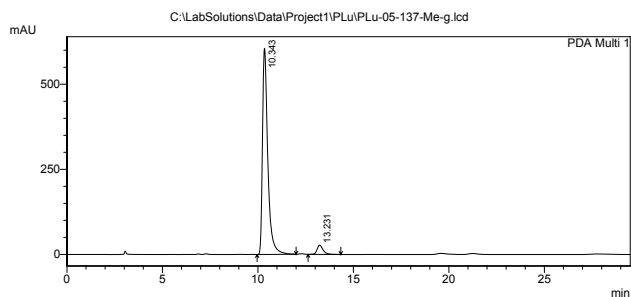
==== Shimadzu LCsolution Analysis Report ====

11/18/2014 10:47:37 1 / 1

C:\LabSolutions\Data\Project1\PLU\PLU-05-137-Me-g.lcd
 Acquired by : Admin
 Sample Name : PLU-05-137-Me
 Sample ID : PLU-05-137-Me
 Vial # :
 Injection Volume : 10 uL
 Data File Name : PLU-05-137-Me-g.lcd
 Method File Name : ATH-OD-J-analytical-hplc.lcm
 Batch File Name :
 Report File Name : Default.lcr
 Data Acquired : 6/17/2014 3:41:01 PM
 Data Processed : 6/17/2014 4:10:32 PM



<Chromatogram>



PeakTable

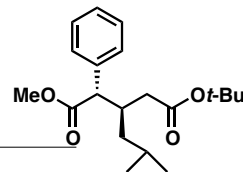
Peak#	Ret. Time	Area	Height	Area %	Height %
1	10.343	11734879	605961	95.08	95.713
2	13.231	603594	27144	4.892	4.287
Total		12338473	633105	100.000	100.000

C:\LabSolutions\Data\Project1\PLU\PLU-05-137-Me-g.lcd

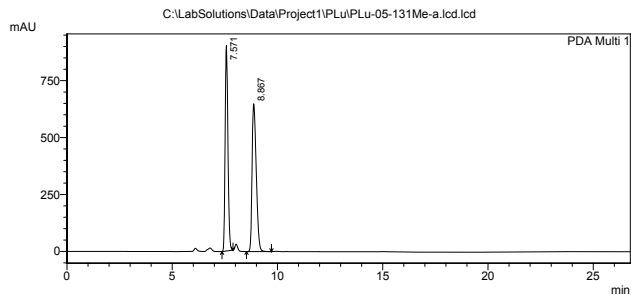
==== Shimadzu LCsolution Analysis Report ====

11/18/2014 10:54:50 1 / 1

Acquired by : Admin
 Sample Name : PLU-05-131Me
 Sample ID : PLU-05-131Me
 Vial # :
 Injection Volume : 10 uL
 Data File Name : PLU-05-131Me-a.lcd.lcd
 Method File Name : ATH-OD-J-analytical-hplc.lcm
 Batch File Name :
 Report File Name : Default.lcr
 Data Acquired : 6/11/2014 1:40:54 PM
 Data Processed : 6/11/2014 2:07:40 PM



<Chromatogram>



1 PDA Multi 1/215nm 4nm

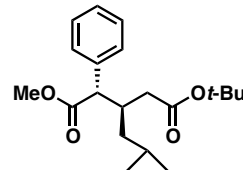
Peak#	Ret. Time	Area	Height	Area %	Height %
1	7.571	8320303	902814	48.172	58.170
2	8.867	8951858	649222	51.828	41.830
Total		17272161	1552036	100.000	100.000

C:\LabSolutions\Data\Project1\PLU\PLU-05-131Me-a.lcd.lcd

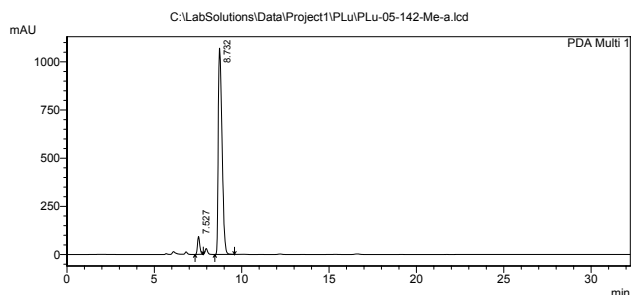
==== Shimadzu LCsolution Analysis Report ====

11/18/2014 10:55:44 1 / 1

Acquired by : Admin
 Sample Name : PLU-05-142-Me
 Sample ID : PLU-05-142-Me
 Vial # :
 Injection Volume : 10 uL
 Data File Name : PLU-05-142-Me-a.lcd
 Method File Name : ATH-OD-J-analytical-hplc.lcm
 Batch File Name :
 Report File Name : Default.lcr
 Data Acquired : 6/23/2014 2:46:39 PM
 Data Processed : 6/23/2014 3:18:55 PM



<Chromatogram>



1 PDA Multi 1/215nm 4nm

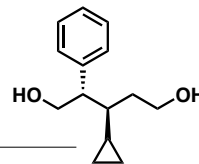
Peak#	Ret. Time	Area	Height	Area %	Height %
1	7.527	851620	92497	5.002	7.955
2	8.732	16173043	1070194	94.998	92.045
Total		17024663	1162691	100.000	100.000

C:\LabSolutions\Data\Project1\PLU\PLU-05-142-Me-a.lcd

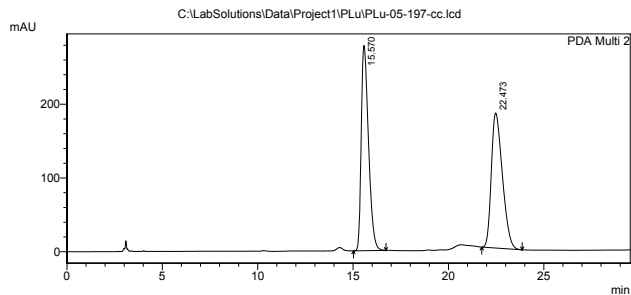
==== Shimadzu LCsolution Analysis Report ====

11/18/2014 11:02:38 1 / 1

Acquired by : Admin
 Sample Name : PLU-05-197
 Sample ID : PLU-05-197
 Vial # :
 Injection Volume : 20 uL
 Data File Name : PLU-05-197-cc.lcd
 Method File Name : ATH-OD-J-analytical-hplc.lcm
 Batch File Name :
 Report File Name : Default.lcr
 Data Acquired : 8/7/2014 5:44:51 PM
 Data Processed : 8/7/2014 6:14:25 PM



<Chromatogram>



1 PDA Multi 2/215nm 4nm

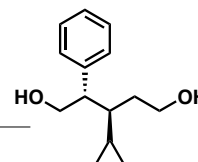
Peak#	Ret. Time	Area	Height	Area %	Height %
1	15.570	7341650	278382	49.915	60.228
2	22.473	7366742	183069	50.085	39.672
Total		14708393	461451	100.000	100.000

C:\LabSolutions\Data\Project1\PLU\PLU-05-197-cc.lcd

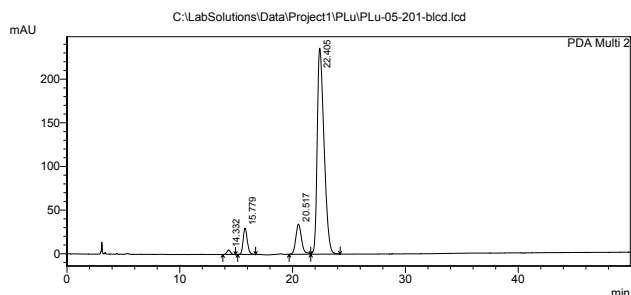
==== Shimadzu LCsolution Analysis Report ====

11/18/2014 10:58:24 1 / 1

Acquired by : Admin
 Sample Name : PLU-05-201
 Sample ID : PLU-05-201
 Vial # :
 Injection Volume : 20 uL
 Data File Name : PLU-05-201-bld.lcd
 Method File Name : ATH-OD-J-analytical-hplc.lcm
 Batch File Name :
 Report File Name : Default.lcr
 Data Acquired : 8/7/2014 4:52:59 PM
 Data Processed : 8/7/2014 5:42:58 PM



<Chromatogram>



1 PDA Multi 2/215nm 4nm

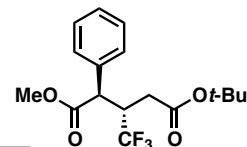
Peak#	Ret. Time	Area	Height	Area %	Height %
1	14.332	115213	5115	0.963	1.674
2	15.779	773262	30126	6.460	9.858
3	20.817	1217608	34469	10.173	11.279
4	22.405	9863297	235890	82.404	77.189
Total		11969381	305599	100.000	100.000

C:\LabSolutions\Data\Project1\PLU\PLU-05-201-bld.lcd

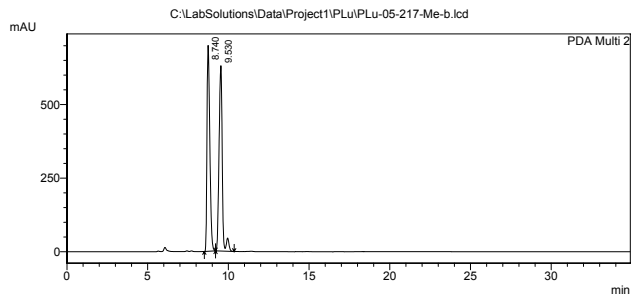
==== Shimadzu LCsolution Analysis Report ====

11/18/2014 11:05:27 1 / 1

C:\LabSolutions\Data\Project1\PLu\PLu-05-217-Me-b.lcd
 Acquired by : Admin
 Sample Name : PLu-05-217-Me
 Sample ID : PLu-05-217-Me
 Vial # :
 Injection Volume : 10 uL
 Data File Name : PLu-05-217-Me-b.lcd
 Method File Name : ATH-OD-J-analytical-hplc.lcm
 Batch File Name :
 Report File Name : Default.lcr
 Data Acquired : 8/20/2014 11:57:53 AM
 Data Processed : 8/20/2014 1:15:14 PM



<Chromatogram>



1 PDA Multi 2/215nm 4nm

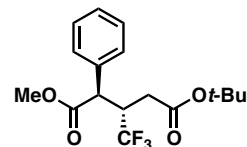
Peak#	Ret. Time	Area	Height	Area %	Height %
1	8.740	8583740	699512	49.386	52.623
2	9.530	8797193	629783	50.614	47.377
Total		17380933	1329295	100.000	100.000

C:\LabSolutions\Data\Project1\PLu\PLu-05-217-Me-b.lcd

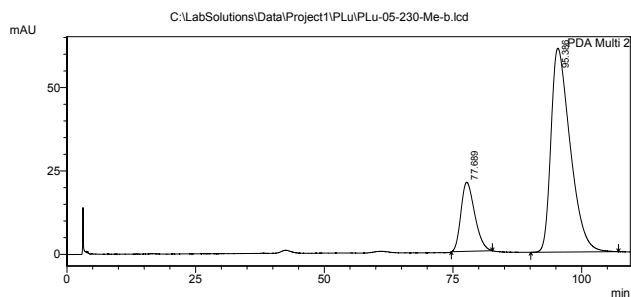
==== Shimadzu LCsolution Analysis Report ====

11/18/2014 11:10:11 1 / 1

C:\LabSolutions\Data\Project1\PLu\PLu-05-230-Me-b.lcd
 Acquired by : Admin
 Sample Name : PLu-05-230-Me
 Sample ID : PLu-05-230-Me
 Vial # :
 Injection Volume : 10 uL
 Data File Name : PLu-05-230-Me-b.lcd
 Method File Name : ATH-OD-J-analytical-hplc.lcm
 Batch File Name :
 Report File Name : Default.lcr
 Data Acquired : 9/4/2014 3:00:45 PM
 Data Processed : 11/17/2014 2:52:44 PM



<Chromatogram>



1 PDA Multi 2/215nm 4nm

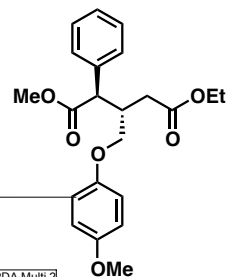
Peak#	Ret. Time	Area	Height	Area %	Height %
1	77.689	3864028	20735	19.606	23.329
2	95.386	15844264	61128	80.394	74.671
Total		19708292	81864	100.000	100.000

C:\LabSolutions\Data\Project1\PLu\PLu-05-230-Me-b.lcd

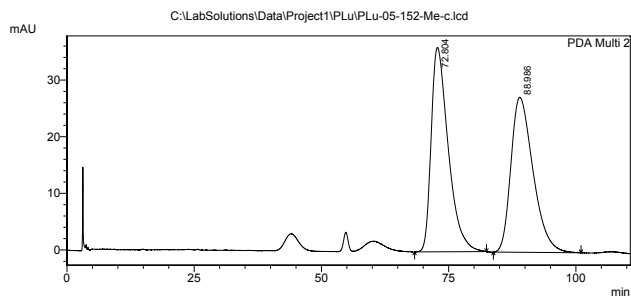
==== Shimadzu LCsolution Analysis Report ====

11/18/2014 11:12:25 1 / 1

C:\LabSolutions\Data\Project1\PLu\PLu-05-152-Me-c.lcd
 Acquired by : Admin
 Sample Name : PLu-05-152-Me
 Sample ID : PLu-05-152-Me
 Vial # :
 Injection Volume : 10 uL
 Data File Name : PLu-05-152-Me-c.lcd
 Method File Name : ATH-OD-J-analytical-hplc.lcm
 Batch File Name :
 Report File Name : Default.lcr
 Data Acquired : 7/5/2014 11:43:37 AM
 Data Processed : 9/4/2014 11:50:40 AM



<Chromatogram>



1 PDA Multi 2/215nm 4nm

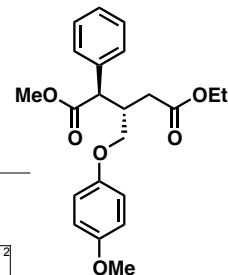
Peak#	Ret. Time	Area	Height	Area %	Height %
1	72.804	8427327	36087	50.435	56.881
2	88.986	8262036	27356	49.565	43.119
Total		16709364	63443	100.000	100.000

C:\LabSolutions\Data\Project1\PLu\PLu-05-152-Me-c.lcd

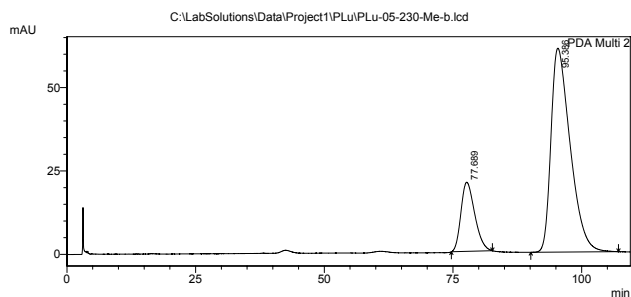
==== Shimadzu LCsolution Analysis Report ====

11/18/2014 11:10:11 1 / 1

C:\LabSolutions\Data\Project1\PLu\PLu-05-230-Me-b.lcd
 Acquired by : Admin
 Sample Name : PLu-05-230-Me
 Sample ID : PLu-05-230-Me
 Vial # :
 Injection Volume : 10 uL
 Data File Name : PLu-05-230-Me-b.lcd
 Method File Name : ATH-OD-J-analytical-hplc.lcm
 Batch File Name :
 Report File Name : Default.lcr
 Data Acquired : 9/4/2014 3:00:45 PM
 Data Processed : 11/17/2014 2:52:44 PM



<Chromatogram>



1 PDA Multi 2/215nm 4nm

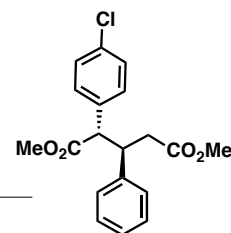
Peak#	Ret. Time	Area	Height	Area %	Height %
1	77.689	3864028	20735	19.606	23.329
2	95.386	15844264	61128	80.394	74.671
Total		19708292	81864	100.000	100.000

C:\LabSolutions\Data\Project1\PLu\PLu-05-230-Me-b.lcd

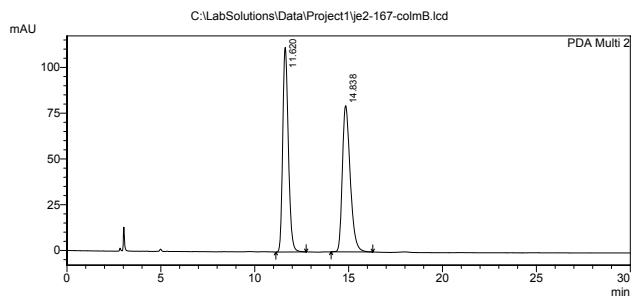
==== Shimadzu LCsolution Analysis Report ====

11/18/2014 11:56:11 / 1

Acquired by : Admin
 Sample Name : je2-167-colmB
 Sample ID : je2-167-colmB
 Vial # :
 Injection Volume : 10 uL
 Data File Name : je2-167-colmB.lcd
 Method File Name : ATH-OD-J-analytical-hplc.lcm
 Batch File Name :
 Report File Name : Default.lcr
 Data Acquired : 7/15/2014 10:15:53 AM
 Data Processed : 7/15/2014 11:26:46 AM



<Chromatogram>



PeakTable

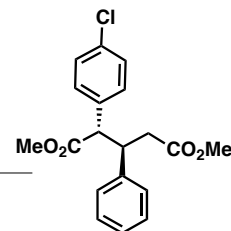
Peak#	Ret. Time	Area	Height	Area %	Height %
1	11.620	2322689	111759	49.969	58.316
2	14.838	2325606	79884	50.031	41.684
Total		4648295	191643	100.000	100.000

C:\LabSolutions\Data\Project1\je2-167-colmB.lcd

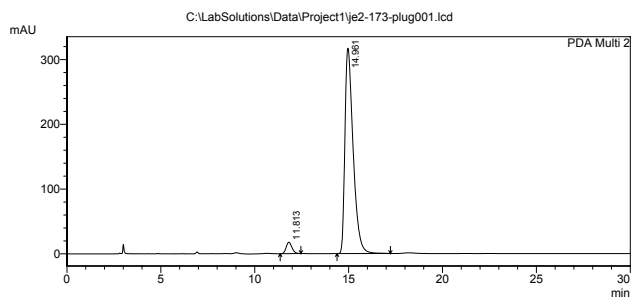
==== Shimadzu LCsolution Analysis Report ====

11/18/2014 11:55:36 / 1

Acquired by : Admin
 Sample Name : je2-173-plug
 Sample ID : je2-173-plug
 Vial # :
 Injection Volume : 10 uL
 Data File Name : je2-173-plug001.lcd
 Method File Name : ATH-OD-J-analytical-hplc.lcm
 Batch File Name :
 Report File Name : Default.lcr
 Data Acquired : 7/20/2014 8:18:26 PM
 Data Processed : 7/20/2014 10:14:43 PM



<Chromatogram>



PeakTable

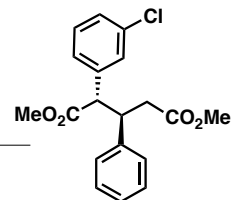
Peak#	Ret. Time	Area	Height	Area %	Height %
1	11.813	380351	17574	3.800	5.251
2	14.961	9629562	317082	96.200	94.749
Total		10009912	334656	100.000	100.000

C:\LabSolutions\Data\Project1\je2-173-plug001.lcd

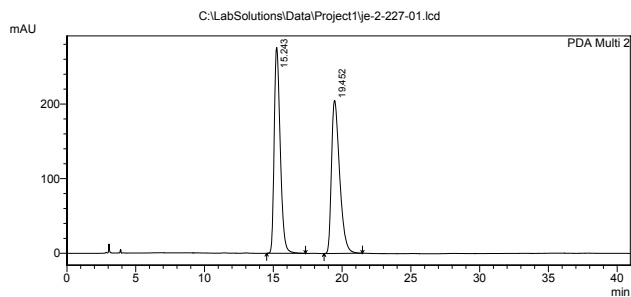
==== Shimadzu LCsolution Analysis Report ====

11/19/2014 11:13:09 1 / 1

C:\LabSolutions\Data\Project1\je-2-227-01.lcd
 Acquired by : Admin
 Sample Name : je-2-227
 Sample ID : je-2-227
 Vial # :
 Injection Volume : 10 uL
 Data File Name : je-2-227-01.lcd
 Method File Name : ATH-OD-J-analytical-hplc.lcm
 Batch File Name :
 Report File Name : Default.lcr
 Data Acquired : 11/19/2014 10:31:32 AM
 Data Processed : 11/19/2014 11:12:30 AM



<Chromatogram>



1 PDA Multi 2/215nm 4nm

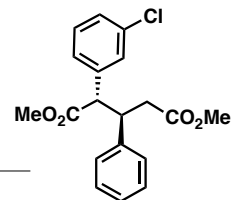
Peak#	Ret. Time	Area	Height	Area %	Height %
1	15.243	8417846	275903	49.908	57.344
2	19.452	8448715	205232	50.092	42.656
Total		16866561	481135	100.000	100.000

C:\LabSolutions\Data\Project1\je-2-227-01.lcd

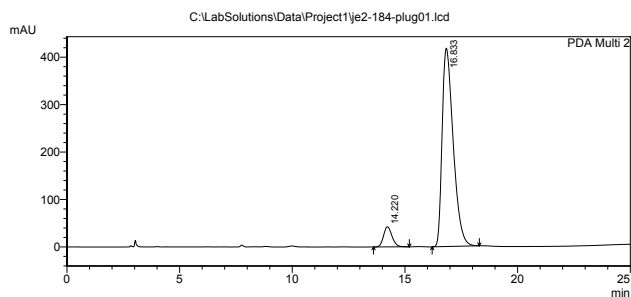
==== Shimadzu LCsolution Analysis Report ====

11/18/2014 11:59:10 1 / 1

C:\LabSolutions\Data\Project1\je2-184-plug01.lcd
 Acquired by : Admin
 Sample Name : je2-184-plug
 Sample ID : je2-184-plug
 Vial # :
 Injection Volume : 20 uL
 Data File Name : je2-184-plug01.lcd
 Method File Name : ATH-OD-J-analytical-hplc.lcm
 Batch File Name :
 Report File Name : Default.lcr
 Data Acquired : 8/8/2014 4:09:44 PM
 Data Processed : 8/8/2014 5:15:38 PM



<Chromatogram>



1 PDA Multi 2/215nm 4nm

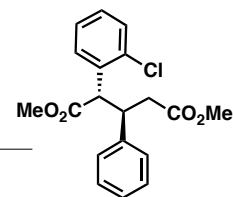
Peak#	Ret. Time	Area	Height	Area %	Height %
1	14.220	1108241	42468	7.196	9.219
2	16.833	14292751	418177	92.804	90.781
Total		15400992	460645	100.000	100.000

C:\LabSolutions\Data\Project1\je2-184-plug01.lcd

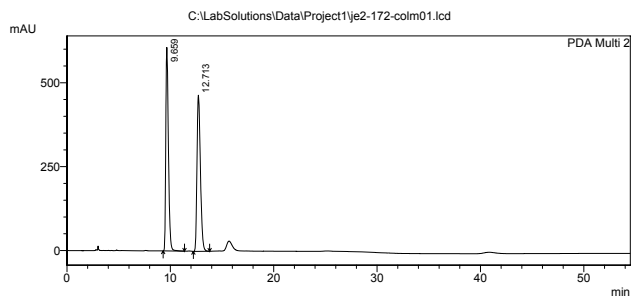
==== Shimadzu LCsolution Analysis Report ====

11/18/2014 12:11:53 1 / 1

Acquired by : Admin
 Sample Name : je2-172-colm
 Sample ID : je2-172-colm
 Vial # :
 Injection Volume : 10 uL
 Data File Name : je2-172-colm01.lcd
 Method File Name : ATH-OD-J-analytical-hplc.lcm
 Batch File Name :
 Report File Name : Default.lcr
 Data Acquired : 7/22/2014 7:35:08 AM
 Data Processed : 7/22/2014 8:29:40 AM



<Chromatogram>



1 PDA Multi 2/215nm 4nm

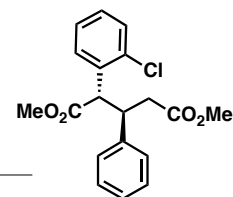
Peak#	Ret. Time	Area	Height	Area %	Height %
1	9.659	10760745	606292	50.035	56.582
2	12.713	10745704	465228	49.965	43.418
Total		21506449	1071520	100.000	100.000

C:\LabSolutions\Data\Project1\je2-172-colm01.lcd

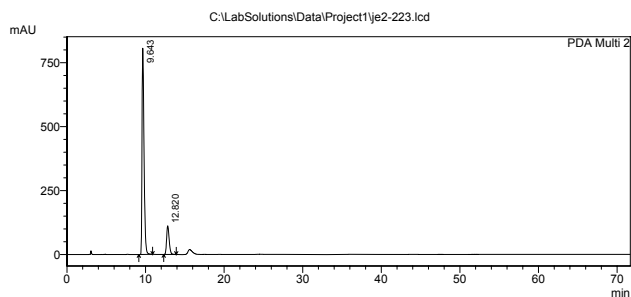
==== Shimadzu LCsolution Analysis Report ====

11/18/2014 12:11:02 1 / 1

Acquired by : Admin
 Sample Name : je2-223
 Sample ID : je2-223
 Vial # :
 Injection Volume : 10 uL
 Data File Name : je2-223.lcd
 Method File Name : ATH-OD-J-analytical-hplc.lcm
 Batch File Name :
 Report File Name : Default.lcr
 Data Acquired : 10/8/2014 5:30:25 PM
 Data Processed : 10/8/2014 6:42:07 PM



<Chromatogram>



1 PDA Multi 2/215nm 4nm

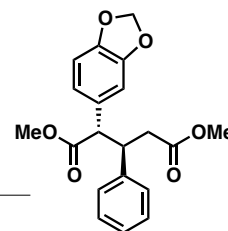
Peak#	Ret. Time	Area	Height	Area %	Height %
1	9.643	14349397	806296	85.046	87.797
2	12.820	2523082	112073	14.954	12.203
Total		16872480	918368	100.000	100.000

C:\LabSolutions\Data\Project1\je2-223.lcd

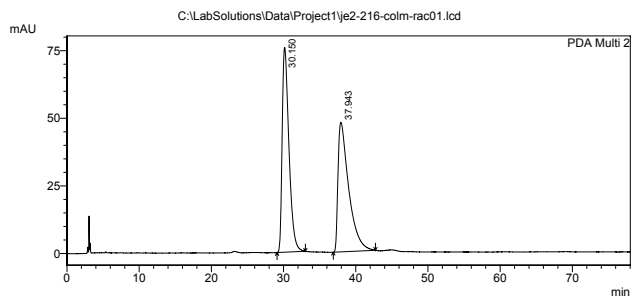
==== Shimadzu LCsolution Analysis Report ====

11/18/2014 12:19:17 1 / 1

C:\LabSolutions\Data\Project1\je2-216-colm-rac01.lcd
 Acquired by : Admin
 Sample Name : je2-214-colm-rac
 Sample ID : je2-214-colm-rac
 Vial # :
 Injection Volume : 10 uL
 Data File Name : je2-216-colm-rac01.lcd
 Method File Name : ATH-OD-J-analytical-hplc.lcm
 Batch File Name :
 Report File Name : Default.lcr
 Data Acquired : 10/4/2014 10:50:40 AM
 Data Processed : 10/4/2014 12:08:44 PM



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1 PDA Multi 2/215nm 4nm

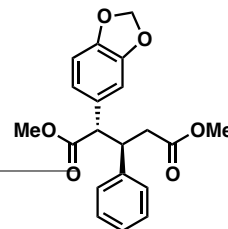
Peak#	Ret. Time	Area	Height	Area %	Height %
1	30.150	4914476	75717	49.859	61.249
2	37.943	4942323	47905	50.141	38.751
Total		9856799	123623	100.000	100.000

C:\LabSolutions\Data\Project1\je2-216-colm-rac01.lcd

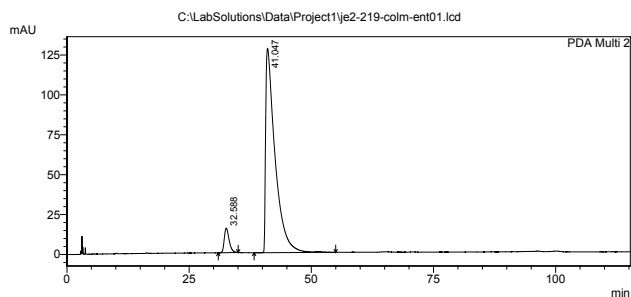
==== Shimadzu LCsolution Analysis Report ====

11/18/2014 12:14:22 1 / 1

C:\LabSolutions\Data\Project1\je2-219-colm-ent01.lcd
 Acquired by : Admin
 Sample Name : je2-219-colm-ent
 Sample ID : jji-5-156-a
 Vial # :
 Injection Volume : 10 uL
 Data File Name : je2-219-colm-ent01.lcd
 Method File Name : ATH-OD-J-analytical-hplc.lcm
 Batch File Name :
 Report File Name : Default.lcr
 Data Acquired : 10/2/2014 2:00:17 PM
 Data Processed : 10/2/2014 3:55:36 PM



<Chromatogram>



1 PDA Multi 2/215nm 4nm

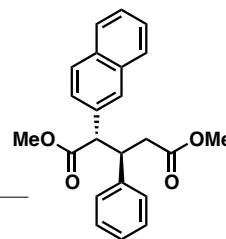
Peak#	Ret. Time	Area	Height	Area %	Height %
1	32.588	1070586	15419	5.369	10.741
2	41.047	17170183	128130	94.131	89.259
Total		18240769	143549	100.000	100.000

C:\LabSolutions\Data\Project1\je2-219-colm-ent01.lcd

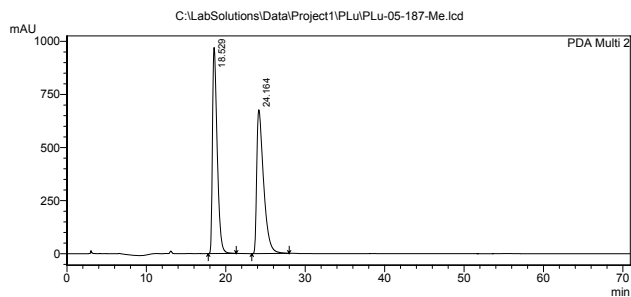
==== Shimadzu LCsolution Analysis Report ====

11/18/2014 11:37:25 1 / 1

C:\LabSolutions\Data\Project1\PLU\PLU-05-187-Me.lcd
 Acquired by : Admin
 Sample Name : PLU-05-187-Me
 Sample ID : PLU-05-187-Me
 Vial # :
 Injection Volume : 10 uL
 Data File Name : PLU-05-187-Me.lcd
 Method File Name : ATH-OD-J-analytical-hplc.lcm
 Batch File Name :
 Report File Name : Default.lcr
 Data Acquired : 7/29/2014 11:38:41 AM
 Data Processed : 7/30/2014 8:52:58 AM



<Chromatogram>



1 PDA Multi 2/215nm 4nm

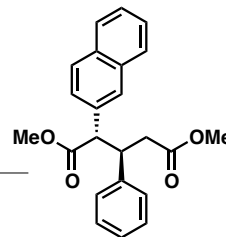
Peak#	Ret. Time	Area	Height	Area %	Height %
1	18.529	40020543	970681	49.602	58.897
2	24.164	40662801	677426	50.398	41.103
Total		80683344	1648106	100.000	100.000

C:\LabSolutions\Data\Project1\PLU\PLU-05-187-Me.lcd

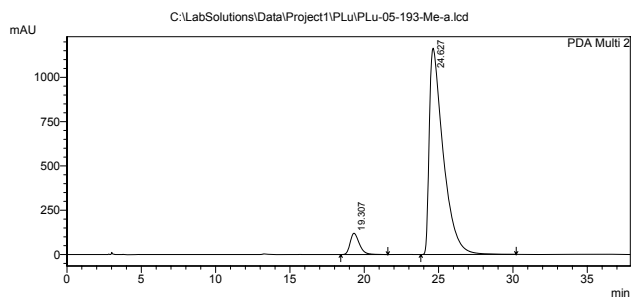
==== Shimadzu LCsolution Analysis Report ====

11/18/2014 11:36:41 1 / 1

C:\LabSolutions\Data\Project1\PLU\PLU-05-193-Me-a.lcd
 Acquired by : Admin
 Sample Name : PLU-05-193-Me
 Sample ID : PLU-05-193-Me
 Vial # :
 Injection Volume : 10 uL
 Data File Name : PLU-05-193-Me-a.lcd
 Method File Name : ATH-OD-J-analytical-hplc.lcm
 Batch File Name :
 Report File Name : Default.lcr
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 Data Processed : 8/2/2014 2:06:55 PM



<Chromatogram>



1 PDA Multi 2/215nm 4nm

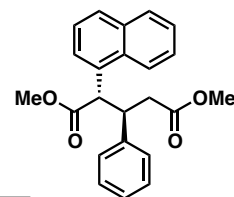
Peak#	Ret. Time	Area	Height	Area %	Height %
1	19.307	5133993	119983	6.344	9.344
2	24.627	75869004	1164131	93.656	90.656
Total		81007996	1284113	100.000	100.000

C:\LabSolutions\Data\Project1\PLU\PLU-05-193-Me-a.lcd

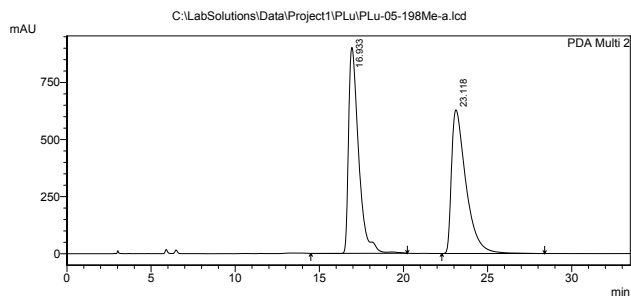
==== Shimadzu LCsolution Analysis Report ====

11/18/2014 11:35:35 1 / 1

C:\LabSolutions\Data\Project1\PLU\PLU-05-198Me-a.lcd
 Acquired by : Admin
 Sample Name : PLU-05-198Me
 Sample ID : PLU-05-198Me
 Vial # :
 Injection Volume : 10 uL
 Data File Name : PLU-05-198Me-a.lcd
 Method File Name : ATH-OD-J-analytical-hplc.lcm
 Batch File Name :
 Report File Name : Default.lcr
 Data Acquired : 8/6/2014 8:41:55 AM
 Data Processed : 8/6/2014 9:15:26 AM



<Chromatogram>



1 PDA Multi 2/215nm 4nm

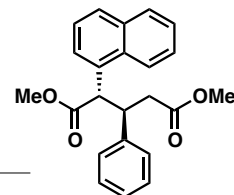
Peak#	Ret. Time	Area	Height	Area %	Height %
1	16.933	37343200	901742	49.865	58.907
2	23.118	37545465	629040	50.135	41.093
Total		74888665	1530781	100.000	100.000

C:\LabSolutions\Data\Project1\PLU\PLU-05-198Me-a.lcd

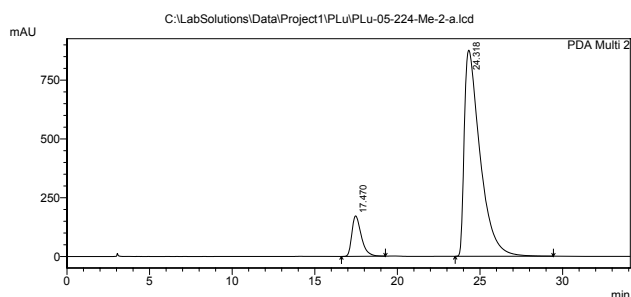
==== Shimadzu LCsolution Analysis Report ====

11/18/2014 11:33:19 1 / 1

C:\LabSolutions\Data\Project1\PLU\PLU-05-224-Me-2-a.lcd
 Acquired by : Admin
 Sample Name : PLU-05-224-Me-2
 Sample ID : PLU-05-224-Me-2
 Vial # :
 Injection Volume : 10 uL
 Data File Name : PLU-05-224-Me-2-a.lcd
 Method File Name : ATH-OD-J-analytical-hplc.lcm
 Batch File Name :
 Report File Name : Default.lcr
 Data Acquired : 9/2/2014 10:01:31 AM
 Data Processed : 9/2/2014 10:35:39 AM



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1 PDA Multi 2/215nm 4nm

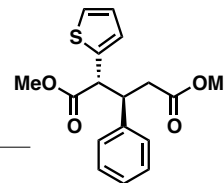
Peak#	Ret. Time	Area	Height	Area %	Height %
1	17.470	4833972	171837	10.524	16.400
2	24.318	58101912	875966	89.476	83.600
Total		64935884	1047803	100.000	100.000

C:\LabSolutions\Data\Project1\PLU\PLU-05-224-Me-2-a.lcd

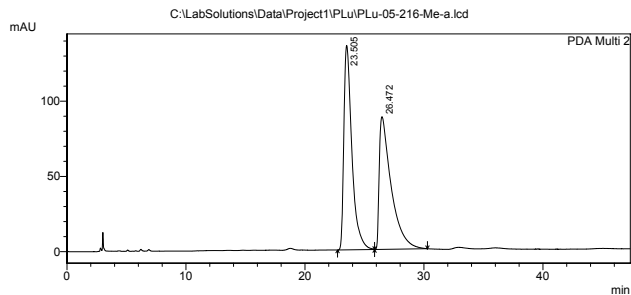
==== Shimadzu LCsolution Analysis Report ====

11/18/2014 11:38:21 1 / 1

C:\LabSolutions\Data\Project1\PLU\PLU-05-216-Me-a.lcd
 Acquired by : Admin
 Sample Name : PLU-05-216-Me
 Sample ID : PLU-05-216-Me
 Vial # :
 Injection Volume : 10 uL
 Data File Name : PLU-05-216-Me-a.lcd
 Method File Name : ATH-OD-J-analytical-hplc.lcm
 Batch File Name :
 Report File Name : Default.lcr
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 Data Processed : 8/20/2014 10:51:11 AM



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1 PDA Multi 2/215nm 4nm

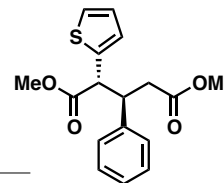
Peak#	Ret. Time	Area	Height	Area %	Height %
1	23.505	6373786	135920	50.938	60.644
2	26.472	6138927	88207	49.062	39.356
Total		12512713	224127	100.000	100.000

C:\LabSolutions\Data\Project1\PLU\PLU-05-216-Me-a.lcd

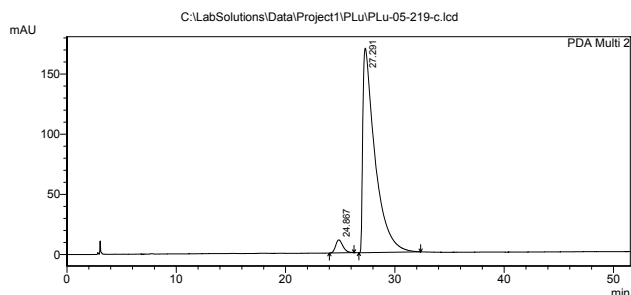
==== Shimadzu LCsolution Analysis Report ====

11/18/2014 11:39:27 1 / 1

C:\LabSolutions\Data\Project1\PLU\PLU-05-219-c.lcd
 Acquired by : Admin
 Sample Name : PLU-05-219
 Sample ID : PLU-05-219
 Vial # :
 Injection Volume : 10 uL
 Data File Name : PLU-05-219-c.lcd
 Method File Name : ATH-OD-J-analytical-hplc.lcm
 Batch File Name :
 Report File Name : Default.lcr
 Data Acquired : 8/23/2014 1:13:41 PM
 Data Processed : 8/23/2014 2:05:16 PM



<Chromatogram>



1 PDA Multi 2/215nm 4nm

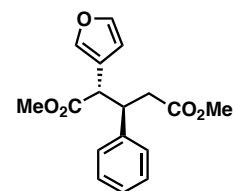
Peak#	Ret. Time	Area	Height	Area %	Height %
1	24.867	497932	10792	3.639	5.972
2	27.291	13183422	169923	96.361	94.028
Total		13681353	180715	100.000	100.000

C:\LabSolutions\Data\Project1\PLU\PLU-05-219-c.lcd

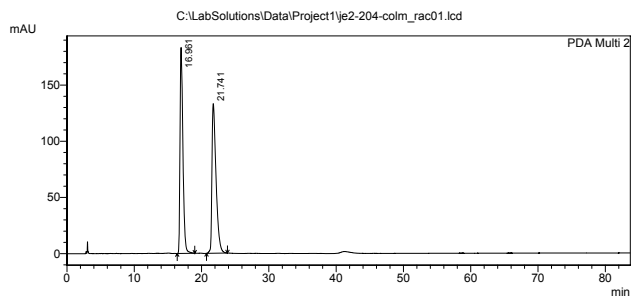
==== Shimadzu LCsolution Analysis Report ====

11/18/2014 12:03:15 1 / 1

C:\LabSolutions\Data\Project1\je2-204-colm_rac01.lcd
 Acquired by : Admin
 Sample Name : je2-204-colm_rac
 Sample ID : je2-204-colm_rac
 Vial # :
 Injection Volume : 10 uL
 Data File Name : je2-204-colm_rac01.lcd
 Method File Name : ATH-OD-J-analytical-hplc.lcm
 Batch File Name :
 Report File Name : Default.lcr
 Data Acquired : 9/15/2014 3:49:28 PM
 Data Processed : 9/15/2014 5:13:13 PM



<Chromatogram>



1 PDA Multi 2/215nm 4nm

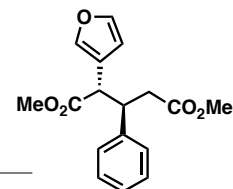
Peak#	Ret. Time	Area	Height	Area %	Height %
1	16.961	5484566	183282	49.404	57.940
2	21.741	5616925	133048	50.596	42.060
Total		11101491	316330	100.000	100.000

C:\LabSolutions\Data\Project1\je2-204-colm_rac01.lcd

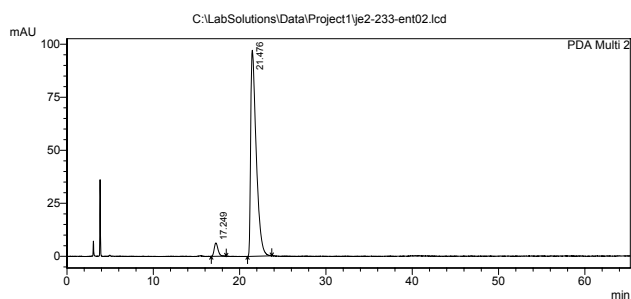
==== Shimadzu LCsolution Analysis Report ====

11/18/2014 12:06:04 1 / 1

C:\LabSolutions\Data\Project1\je2-233-ent02.lcd
 Acquired by : Admin
 Sample Name : je2-233-ent
 Sample ID : je2-233-ent
 Vial # :
 Injection Volume : 10 uL
 Data File Name : je2-233-ent02.lcd
 Method File Name : ATH-OD-J-analytical-hplc.lcm
 Batch File Name :
 Report File Name : Default.lcr
 Data Acquired : 11/12/2014 9:06:25 PM
 Data Processed : 11/12/2014 10:11:43 PM



<Chromatogram>



1 PDA Multi 2/215nm 4nm

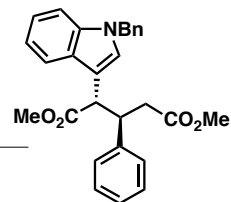
Peak#	Ret. Time	Area	Height	Area %	Height %
1	17.249	192881	6303	4.267	6.091
2	21.476	4322727	97175	95.733	93.909
Total		4515408	103478	100.000	100.000

C:\LabSolutions\Data\Project1\je2-233-ent02.lcd

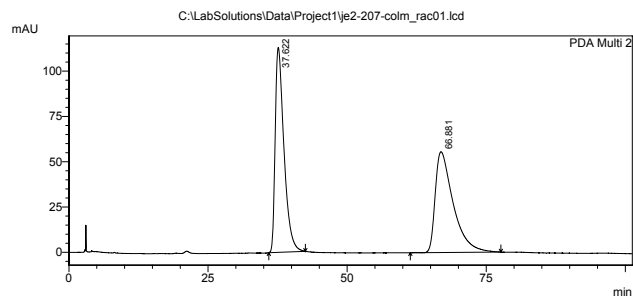
==== Shimadzu LCsolution Analysis Report ====

11/18/2014 12:08:30 1 / 1

C:\LabSolutions\Data\Project1\je2-207-colm_rac01.lcd
 Acquired by : Admin
 Sample Name : je2-207-colm_rac
 Sample ID : je2-207-colm_rac
 Vial # :
 Injection Volume : 10 uL
 Data File Name : je2-207-colm_rac01.lcd
 Method File Name : ATH-OD-J-analytical-hplc.lcm
 Batch File Name :
 Report File Name : Default.lcr
 Data Acquired : 9/15/2014 9:16:57 AM
 Data Processed : 9/15/2014 10:58:15 AM



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1 PDA Ch2 215nm 4nm

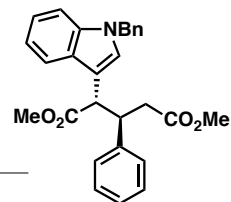
Peak#	Ret. Time	Area	Height	Area %	Height %
1	37.622	12401362	113128	49.864	67.041
2	66.881	12469076	55617	50.136	32.959
Total		24870438	168745	100.000	100.000

C:\LabSolutions\Data\Project1\je2-207-colm_rac01.lcd

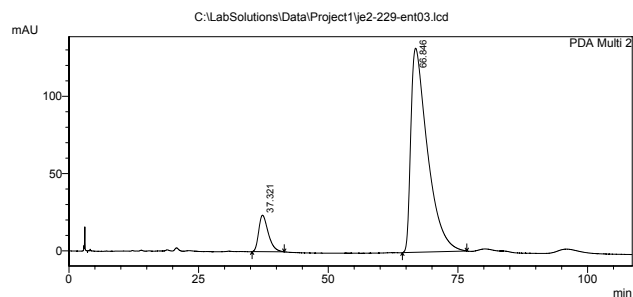
==== Shimadzu LCsolution Analysis Report ====

11/18/2014 12:07:33 1 / 1

C:\LabSolutions\Data\Project1\je2-229-ent03.lcd
 Acquired by : Admin
 Sample Name : je2-229-ent
 Sample ID : je2-229-ent
 Vial # :
 Injection Volume : 10 uL
 Data File Name : je2-229-ent03.lcd
 Method File Name : ATH-OD-J-analytical-hplc.lcm
 Batch File Name :
 Report File Name : Default.lcr
 Data Acquired : 10/20/2014 5:52:17 PM
 Data Processed : 10/20/2014 7:40:58 PM



<Chromatogram>



1 PDA Ch2 215nm 4nm

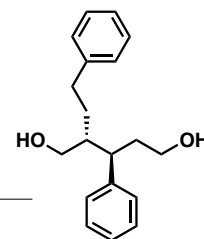
Peak#	Ret. Time	Area	Height	Area %	Height %
1	37.321	3011543	23575	9.261	15.148
2	66.846	29505404	132055	90.739	84.852
Total		32516947	155630	100.000	100.000

C:\LabSolutions\Data\Project1\je2-229-ent03.lcd

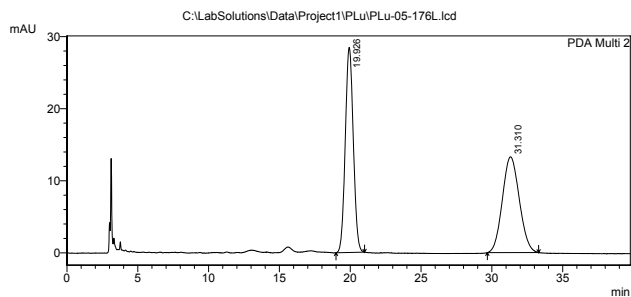
==== Shimadzu LCsolution Analysis Report ====

11/18/2014 11:42:33 1 / 1

Acquired by : Admin
 Sample Name : C:\LabSolutions\Data\Project1\PLU\PLU-05-176L.lcd
 Sample ID : PLU-05-176
 Vial # :
 Injection Volume : 10 uL
 Data File Name : PLU-05-176L.lcd
 Method File Name : ATH-OD-J-analytical-hplc.lcm
 Batch File Name :
 Report File Name : Default.lcr
 Data Acquired : 8/29/2014 11:09:42 AM
 Data Processed : 8/29/2014 11:49:29 AM



<Chromatogram>



1 PDA Multi 2/215nm 4nm

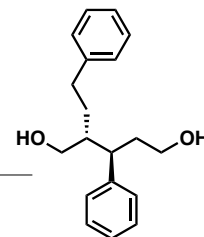
Peak#	Ret. Time	Area	Height	Area %	Height %
1	19.926	1116556	28452	50.279	68.183
2	31.310	1104174	13277	49.721	31.817
Total		2220731	41729	100.000	100.000

C:\LabSolutions\Data\Project1\PLU\PLU-05-176L.lcd

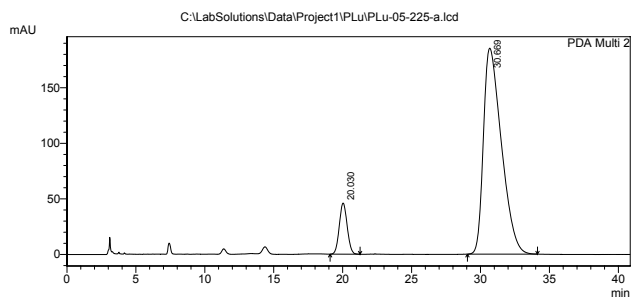
==== Shimadzu LCsolution Analysis Report ====

11/18/2014 11:41:34 1 / 1

Acquired by : Admin
 Sample Name : C:\LabSolutions\Data\Project1\PLU\PLU-05-225-a.lcd
 Sample ID : PLU-05-225
 Vial # :
 Injection Volume : 10 uL
 Data File Name : PLU-05-225-a.lcd
 Method File Name : ATH-OD-J-analytical-hplc.lcm
 Batch File Name :
 Report File Name : Default.lcr
 Data Acquired : 8/29/2014 9:59:29 AM
 Data Processed : 8/29/2014 12:51:14 PM



<Chromatogram>



1 PDA Multi 2/215nm 4nm

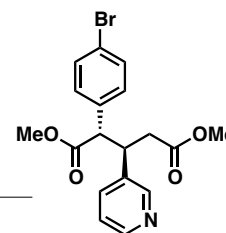
Peak#	Ret. Time	Area	Height	Area %	Height %
1	20.030	183446	45966	9.857	19.882
2	30.669	16779572	185230	90.143	80.118
Total		18614417	231196	100.000	100.000

C:\LabSolutions\Data\Project1\PLU\PLU-05-225-a.lcd

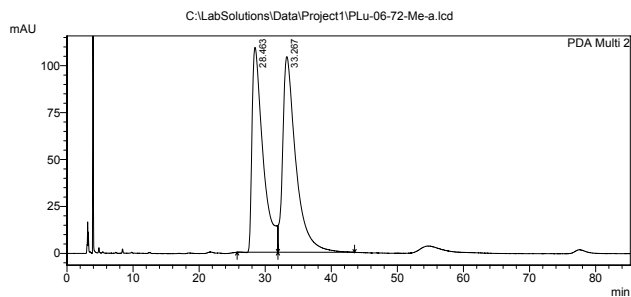
==== Shimadzu LCsolution Analysis Report ====

1/2/2015 13:20:44 1 / 1

C:\LabSolutions\Data\Project1\PLU-06-72-Me-a.lcd
 Acquired by : Admin
 Sample Name : PLU-06-72-Me
 Sample ID : PLU-06-72-Me
 Vial # :
 Injection Volume : 10 uL
 Data File Name : PLU-06-72-Me-a.lcd
 Method File Name : ATH-OD-J-analytical-hplc.lcm
 Batch File Name :
 Report File Name : Default.lcr
 Data Acquired : 1/2/2015 11:53:36 AM
 Data Processed : 1/2/2015 1:18:53 PM



<Chromatogram>



1 PDA Multi 2/210nm 4nm

PeakTable

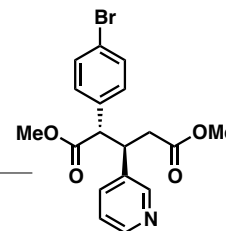
Peak#	Ret. Time	Area	Height	Area %	Height %
1	28.463	12585367	109122	46.545	51.154
2	33.267	14453549	104198	53.455	48.846
Total		27038917	213320	100.000	100.000

C:\LabSolutions\Data\Project1\PLU-06-72-Me-a.lcd

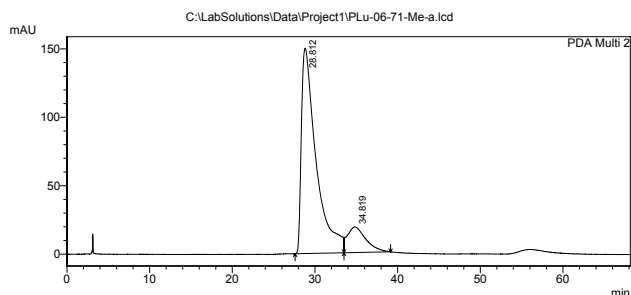
==== Shimadzu LCsolution Analysis Report ====

1/2/2015 13:21:07 1 / 1

C:\LabSolutions\Data\Project1\PLU-06-71-Me-a.lcd
 Acquired by : Admin
 Sample Name : PLU-06-71-Me
 Sample ID : PLU-06-71-Me
 Vial # :
 Injection Volume : 10 uL
 Data File Name : PLU-06-71-Me-a.lcd
 Method File Name : ATH-OD-J-analytical-hplc.lcm
 Batch File Name :
 Report File Name : Default.lcr
 Data Acquired : 1/2/2015 10:43:14 AM
 Data Processed : 1/2/2015 11:51:25 AM



<Chromatogram>



1 PDA Multi 2/210nm 4nm

PeakTable

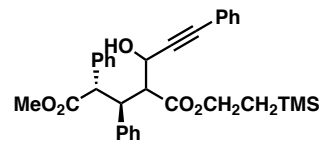
Peak#	Ret. Time	Area	Height	Area %	Height %
1	28.312	18469217	150011	86.337	88.922
2	34.319	2922714	18689	13.663	11.078
Total		21391931	168701	100.000	100.000

C:\LabSolutions\Data\Project1\PLU-06-71-Me-a.lcd

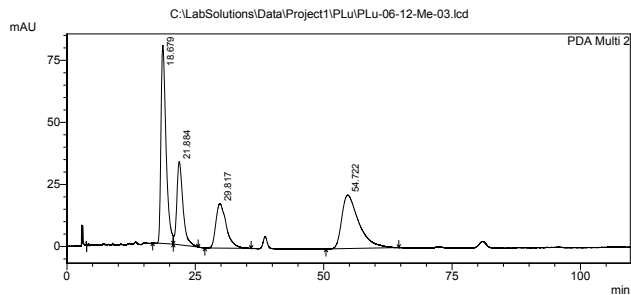
==== Shimadzu LCsolution Analysis Report ====

11/18/2014 11:52:42 1 / 1

C:\LabSolutions\Data\Project1\PLU\PLU-06-12-Me-03.lcd
 Acquired by : Admin
 Sample Name : PLU-06-12-Me
 Sample ID : PLU-06-12-Me
 Vial # :
 Injection Volume : 10 uL
 Data File Name : PLU-06-12-Me-03.lcd
 Method File Name : ATH-OD-J-analytical-hplc.lcm
 Batch File Name :
 Report File Name : Default.lcr
 Data Acquired : 10/31/2014 9:54:08 AM
 Data Processed : 10/31/2014 11:43:52 AM



<Chromatogram>



1 PDA Multi 2/210nm 4nm

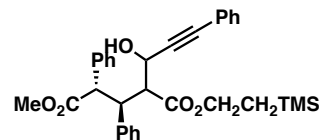
Peak#	Ret. Time	Area	Height	Area %	Height %
1	18.679	5473122	79790	34.795	52.200
2	21.884	2778905	33584	17.667	21.971
3	29.817	2521658	17965	16.031	11.753
4	54.722	4955859	21516	31.507	14.076
Total		15729545	152855	100.000	100.000

C:\LabSolutions\Data\Project1\PLU\PLU-06-12-Me-03.lcd

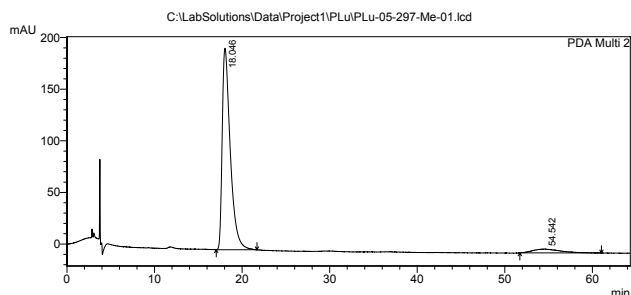
==== Shimadzu LCsolution Analysis Report ====

11/18/2014 11:44:40 1 / 1

C:\LabSolutions\Data\Project1\PLU\PLU-05-297-Me-01.lcd
 Acquired by : Admin
 Sample Name : PLU-05-297-Me
 Sample ID : PLU-05-297-Me
 Vial # :
 Injection Volume : 10 uL
 Data File Name : PLU-05-297-Me-01.lcd
 Method File Name : ATH-OD-J-analytical-hplc.lcm
 Batch File Name :
 Report File Name : Default.lcr
 Data Acquired : 10/31/2014 1:20:42 PM
 Data Processed : 10/31/2014 2:25:04 PM



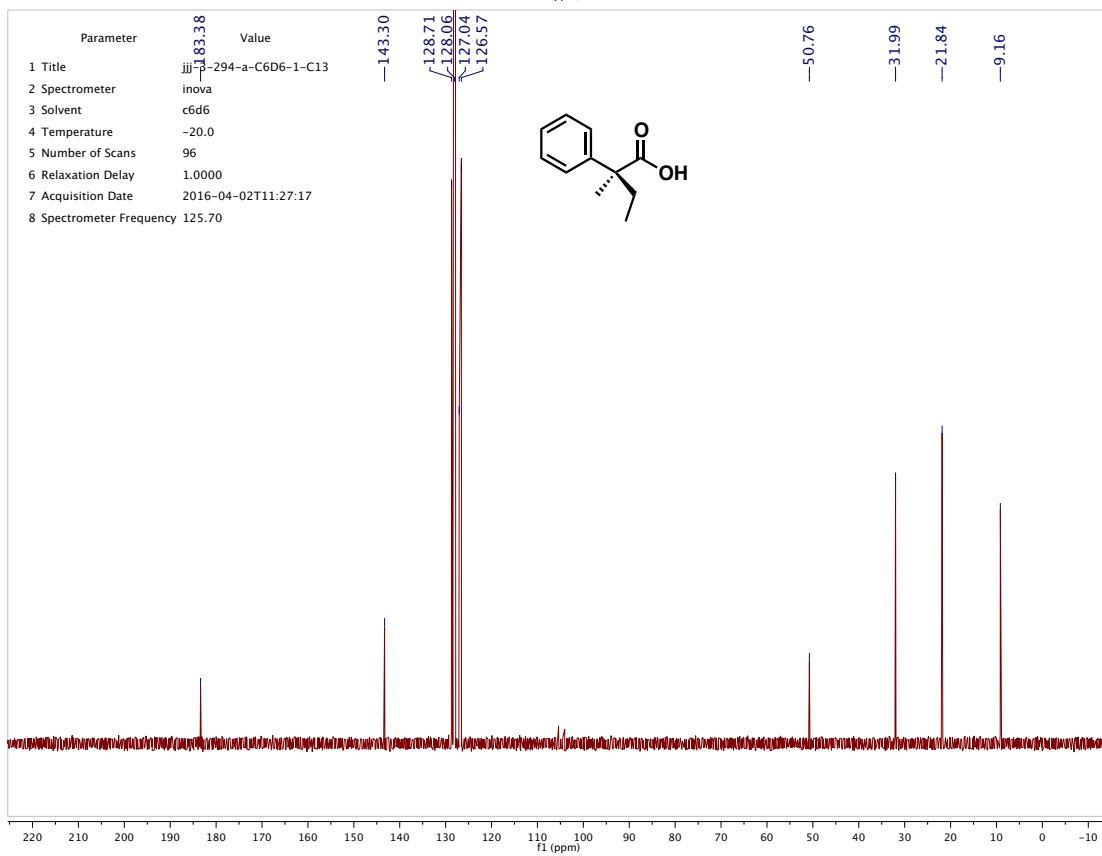
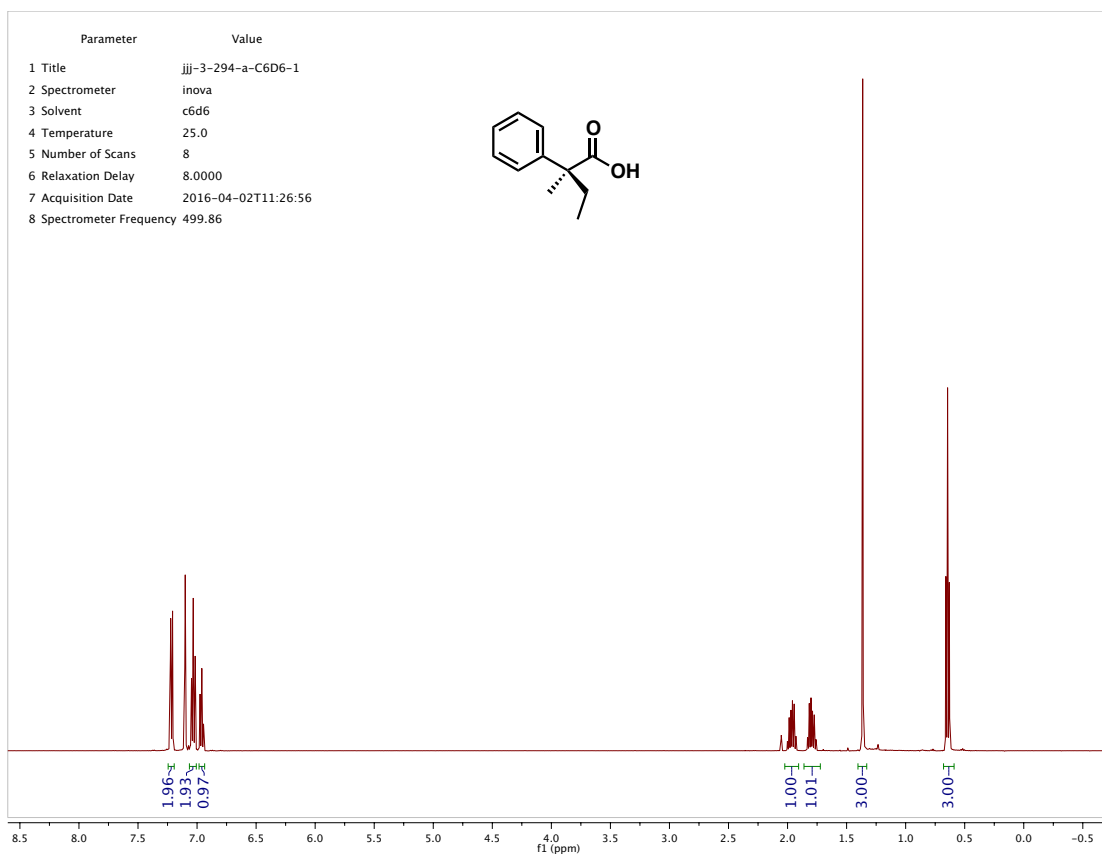
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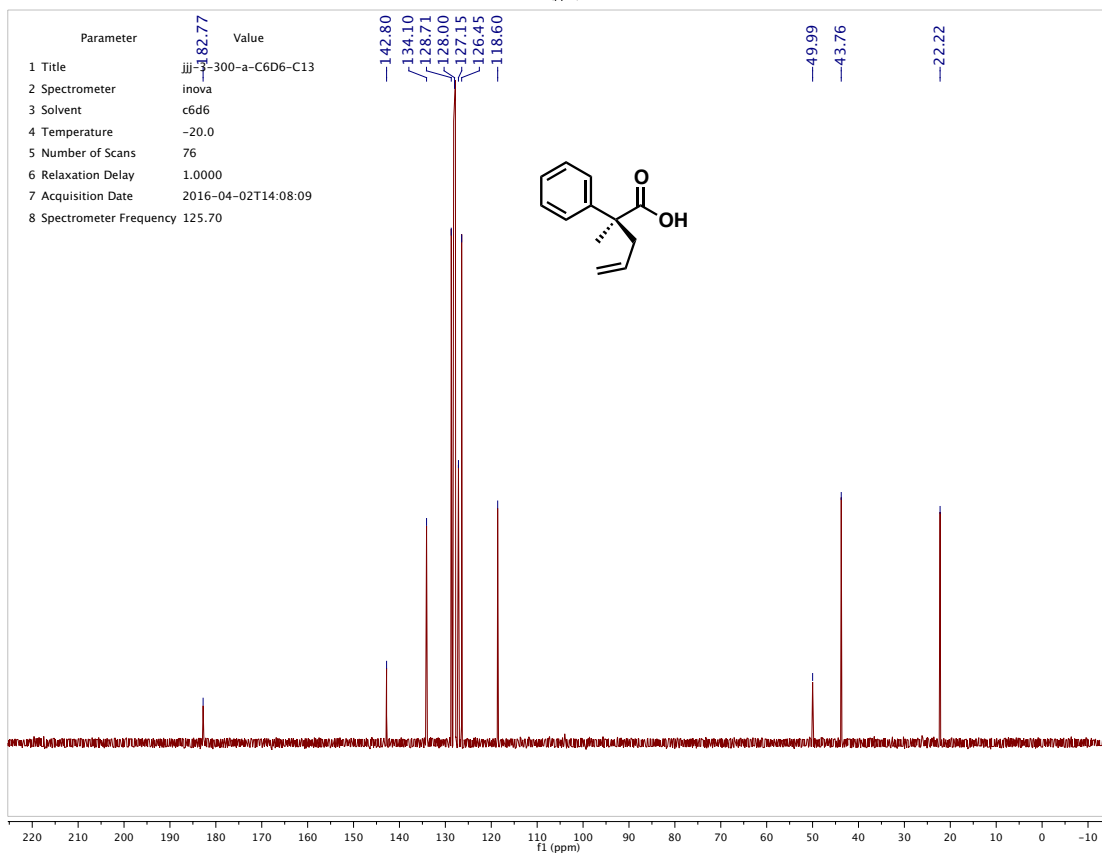
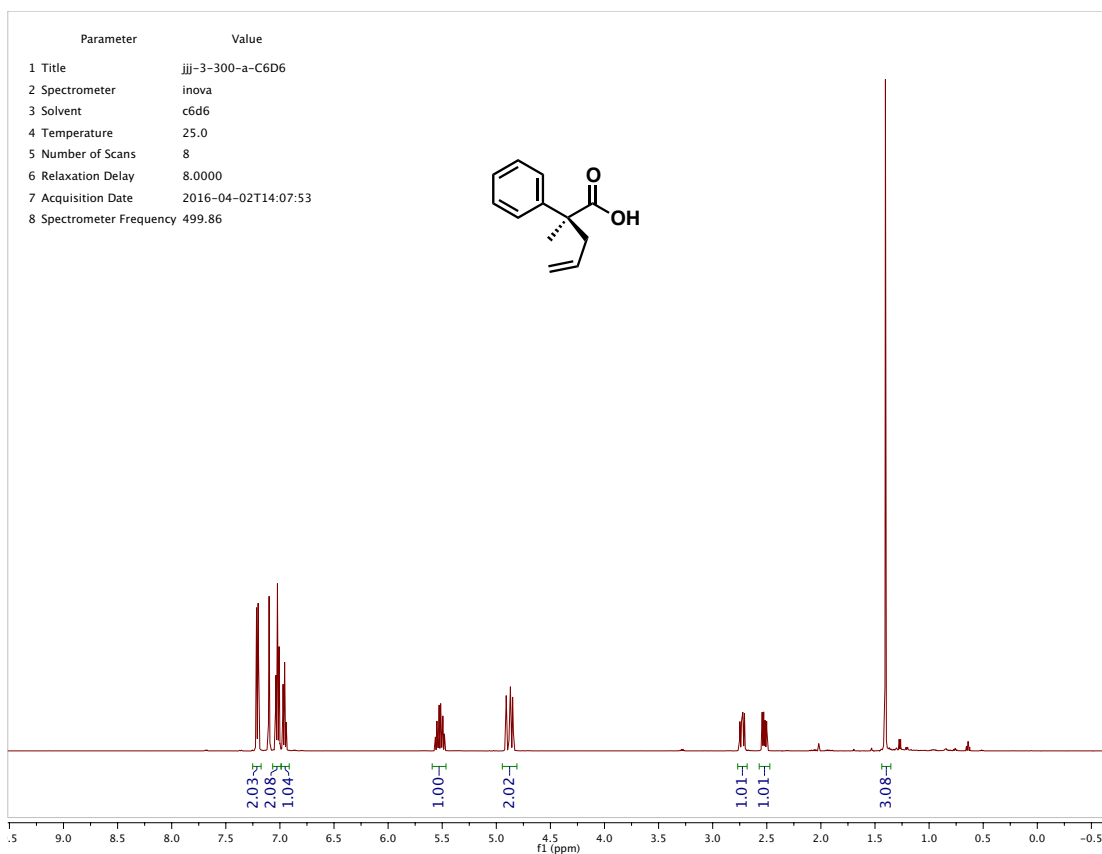


1 PDA Multi 2/215nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	18.046	12459047	195156	93.974	98.145
2	54.502	798981	3689	6.026	1.855
Total		13258028	198845	100.000	100.000

C:\LabSolutions\Data\Project1\PLU\PLU-05-297-Me-01.lcd

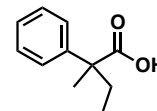




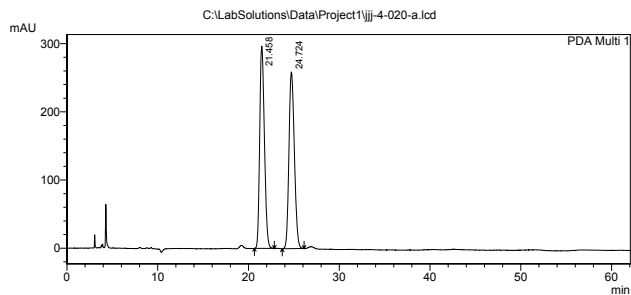
==== Shimadzu LCsolution Analysis Report ====

4/6/2016 12:27:41 1 / 1

Acquired by : Admin
 Sample Name : jijj-4-020-a
 Sample ID : jijj-4-020-a
 Vial # :
 Injection Volume : 10 uL
 Data File Name : jijj-4-020-a.lcd
 Method File Name : ATH-OD-J-analytical-hplc.lcm
 Batch File Name :
 Report File Name : Default.lcr
 Data Acquired : 4/6/2016 11:20:43 AM
 Data Processed : 4/6/2016 12:22:48 PM



<Chromatogram>



1 PDA Multi 1/210nm 4nm

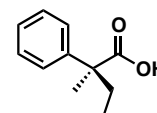
Peak#	Ret. Time	Area	Height	Area %	Height %
1	21.458	10689748	296791	49.845	53.392
2	24.724	10756050	259078	50.155	46.608
Total		21445797	555869	100.000	100.000

C:\LabSolutions\Data\Project1\jijj-4-020-a.lcd

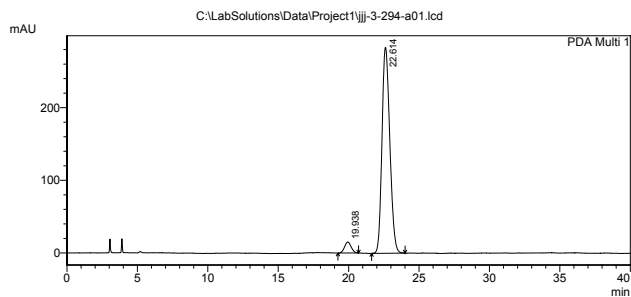
==== Shimadzu LCsolution Analysis Report ====

4/4/2016 11:11:45 1 / 1

Acquired by : Admin
 Sample Name : jijj-3-294-a
 Sample ID : jijj-3-294-a
 Vial # :
 Injection Volume : 10 uL
 Data File Name : jijj-3-294-a01.lcd
 Method File Name : ATH-OD-J-analytical-hplc.lcm
 Batch File Name :
 Report File Name : Default.lcr
 Data Acquired : 4/4/2016 9:23:39 AM
 Data Processed : 4/4/2016 11:09:54 AM



<Chromatogram>



1 PDA Multi 1/210nm 4nm

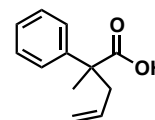
Peak#	Ret. Time	Area	Height	Area %	Height %
1	19.938	490267	15048	4.284	5.038
2	22.614	10955179	283650	95.716	94.962
Total		11445445	298698	100.000	100.000

C:\LabSolutions\Data\Project1\jijj-3-294-a01.lcd

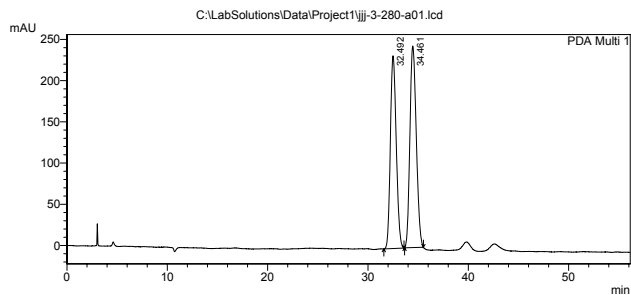
==== Shimadzu LCsolution Analysis Report ====

4/6/2016 16:14:46 1 / 1

Acquired by : Admin
 Sample Name : jji-3-280-a
 Sample ID : jji-3-280-a
 Vial # :
 Injection Volume : 10 uL
 Data File Name : jji-3-280-a01.lcd
 Method File Name : ATH-OD-J-analytical-hplc.lcm
 Batch File Name :
 Report File Name : Default.lcr
 Data Acquired : 4/6/2016 2:53:56 PM
 Data Processed : 4/6/2016 3:51:38 PM



<Chromatogram>



1 PDA Multi 1/210nm 4nm

PeakTable

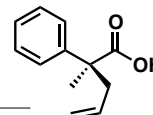
Peak#	Ret. Time	Area	Height	Area %	Height %
1	32.492	9527730	233865	46.960	48.893
2	34.461	10761223	244454	53.040	51.107
Total		20288952	478319	100.000	100.000

C:\LabSolutions\Data\Project1\jji-3-280-a01.lcd

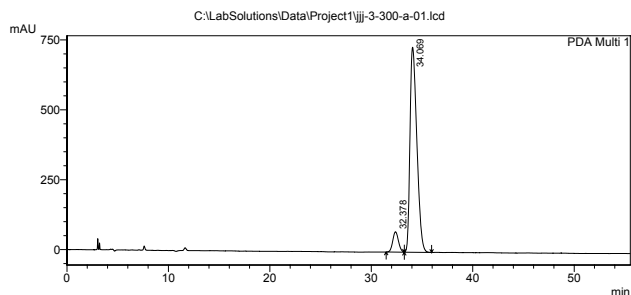
==== Shimadzu LCsolution Analysis Report ====

4/6/2016 15:52:34 1 / 1

Acquired by : Admin
 Sample Name : jji-3-300-a
 Sample ID : jji-3-300-a
 Vial # :
 Injection Volume : 10 uL
 Data File Name : jji-3-300-a-01.lcd
 Method File Name : ATH-OD-J-analytical-hplc.lcm
 Batch File Name :
 Report File Name : Default.lcr
 Data Acquired : 4/6/2016 1:57:34 PM
 Data Processed : 4/6/2016 2:53:08 PM



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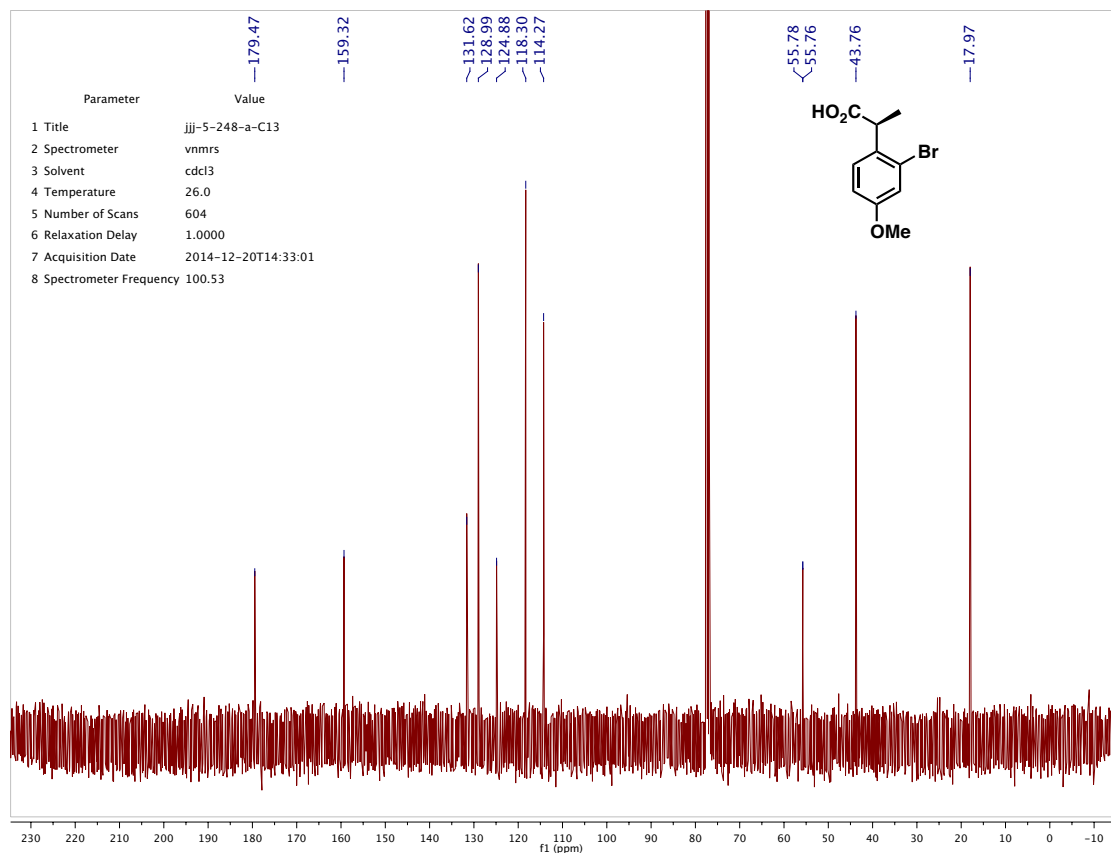
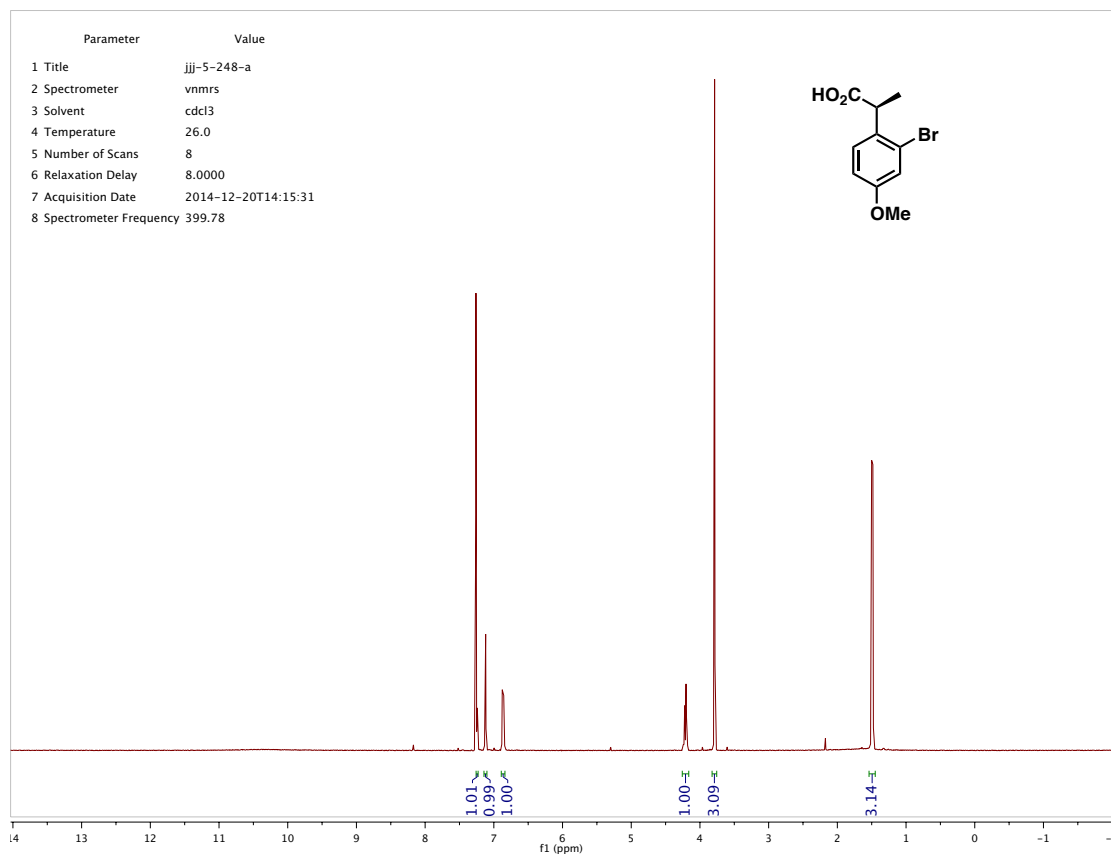


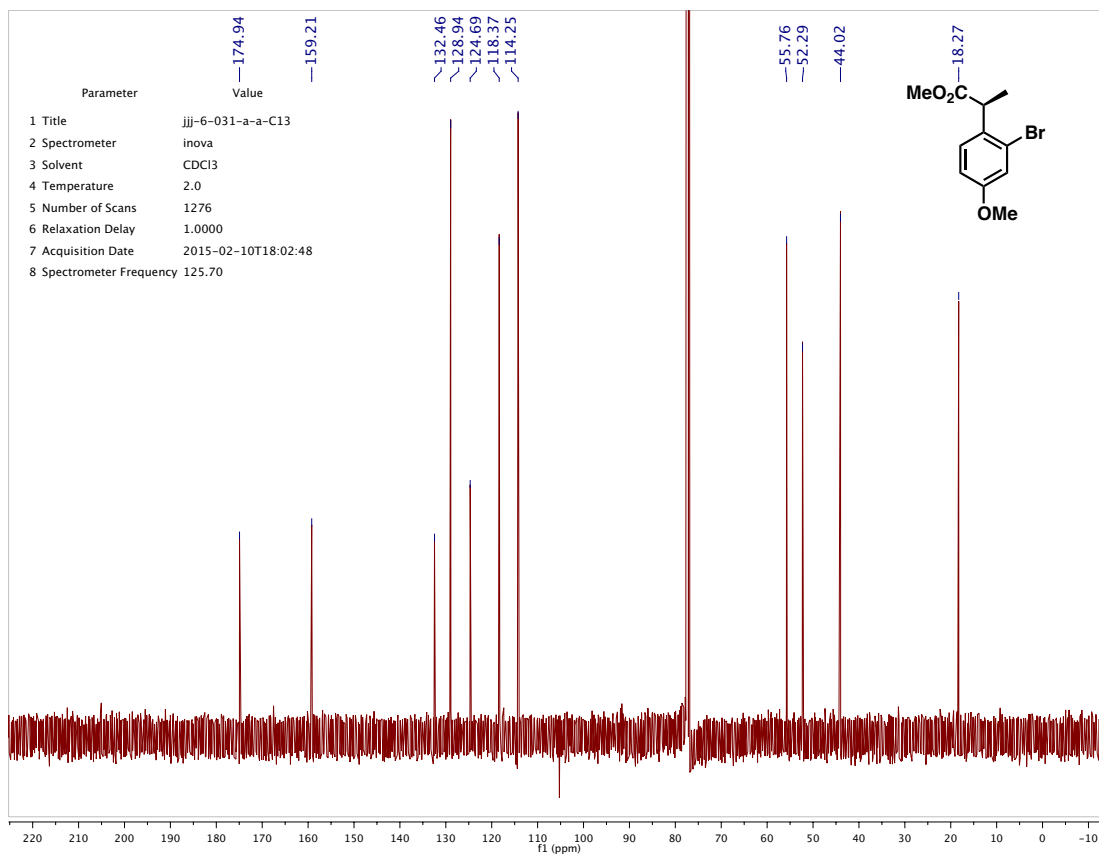
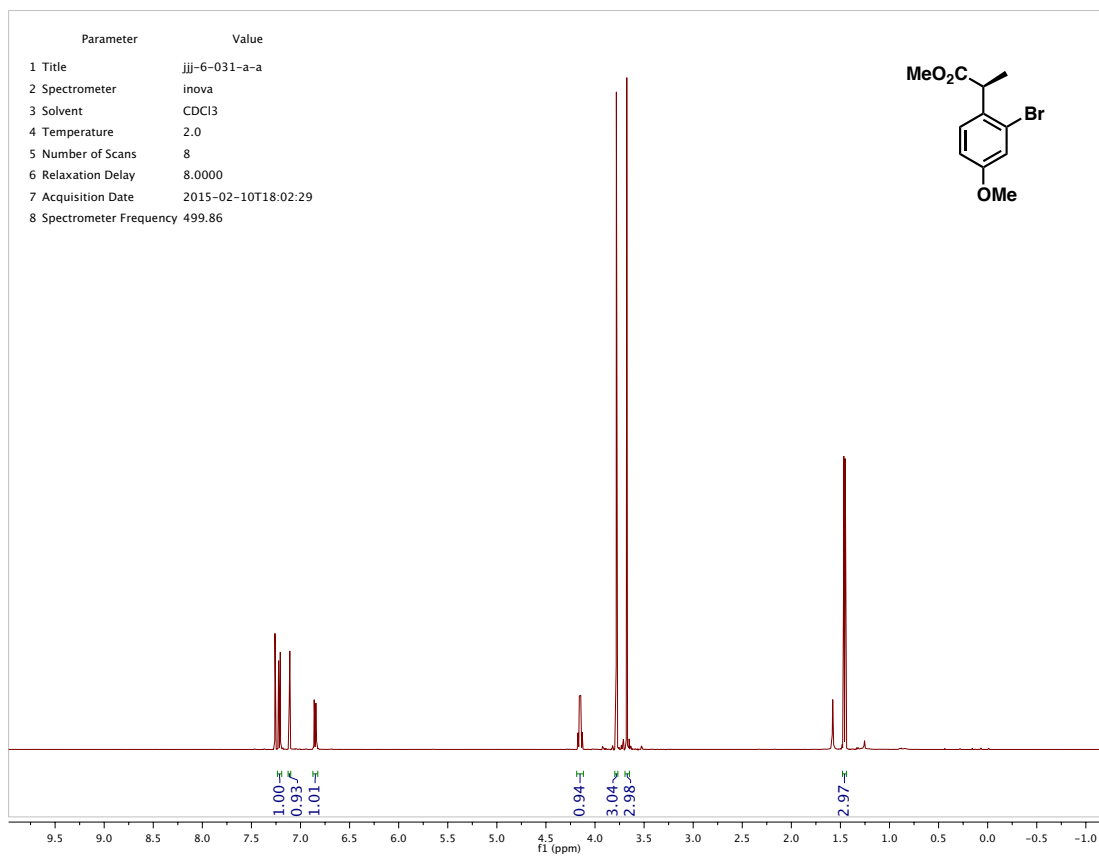
1 PDA Multi 1/210nm 4nm

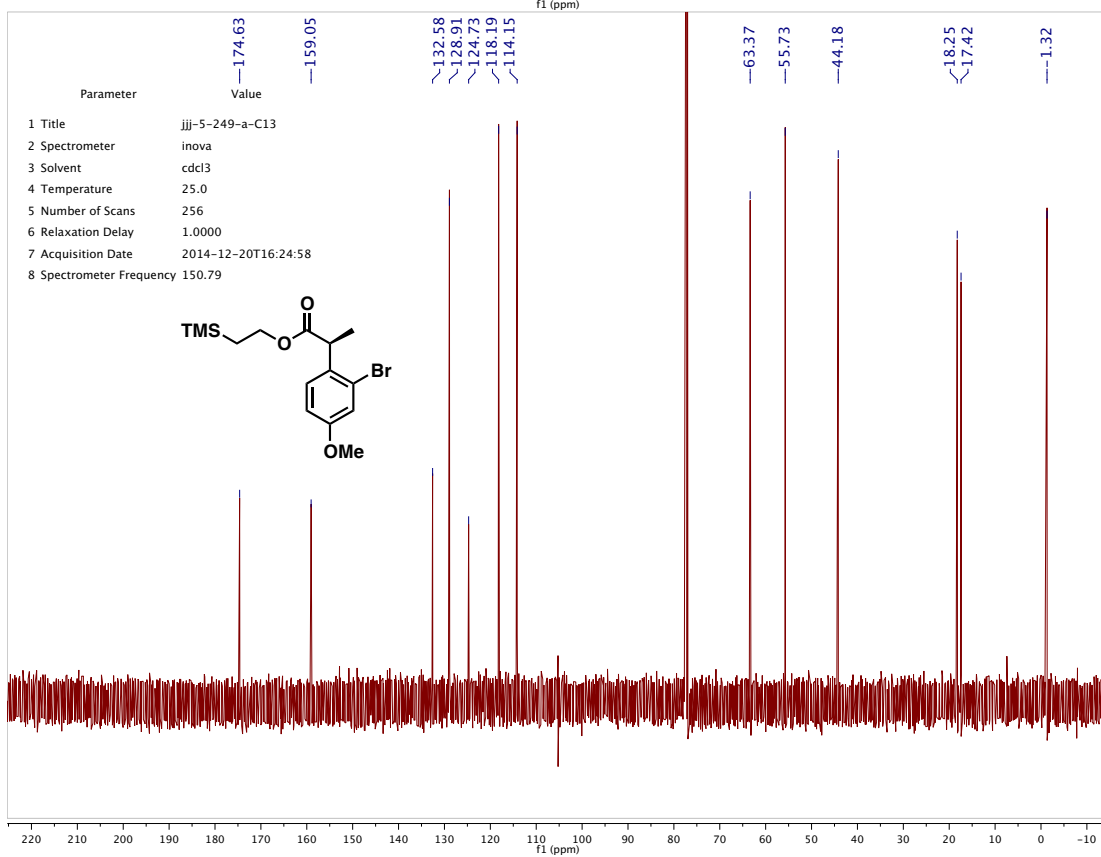
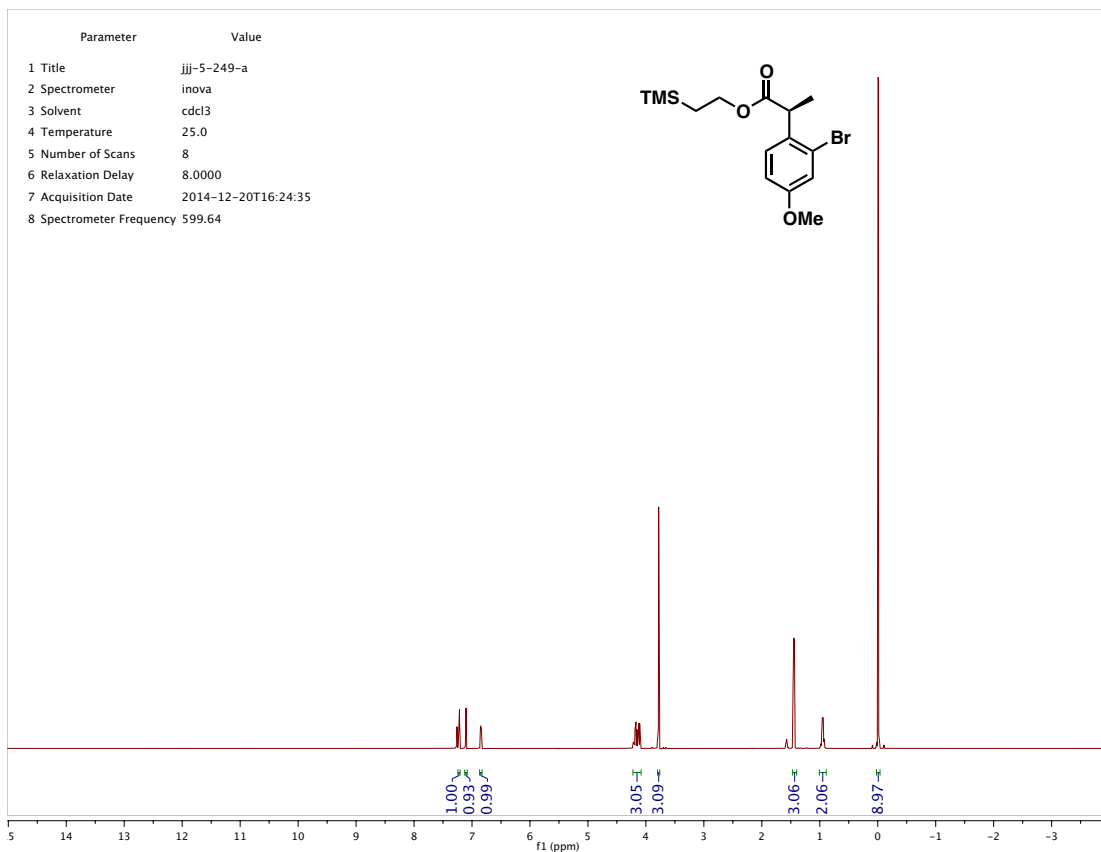
PeakTable

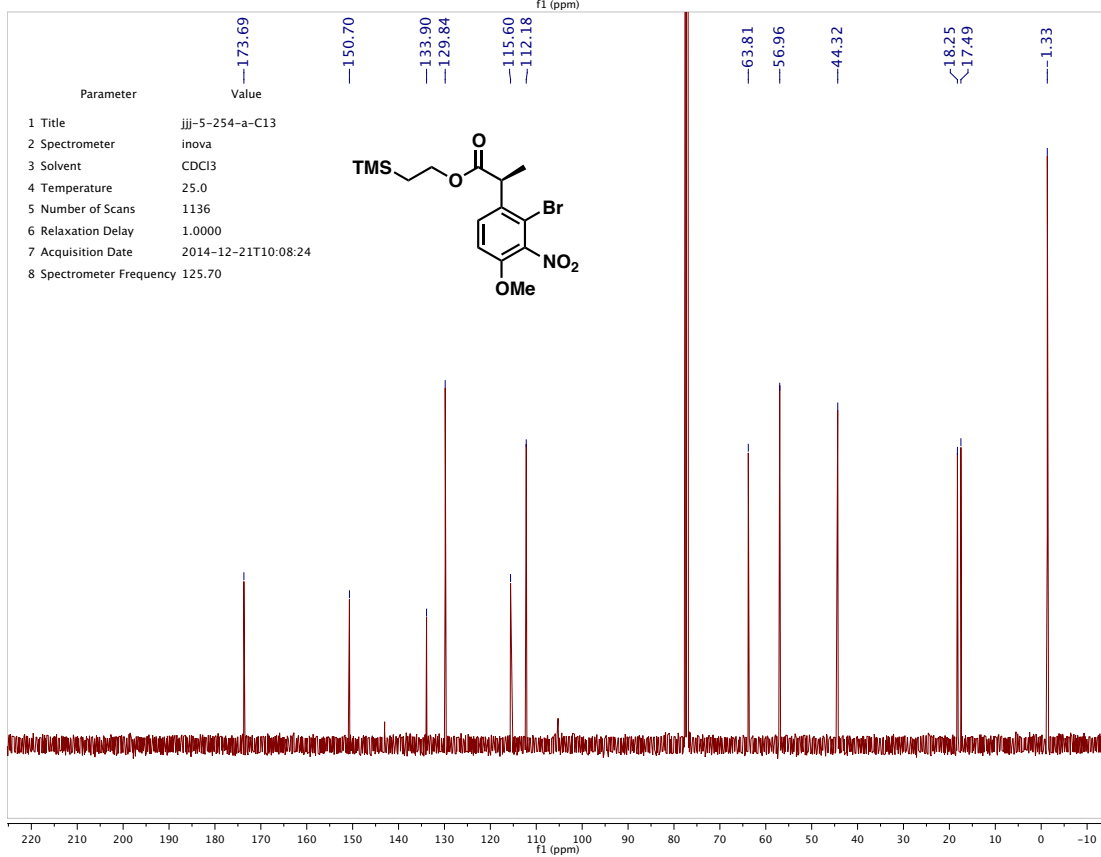
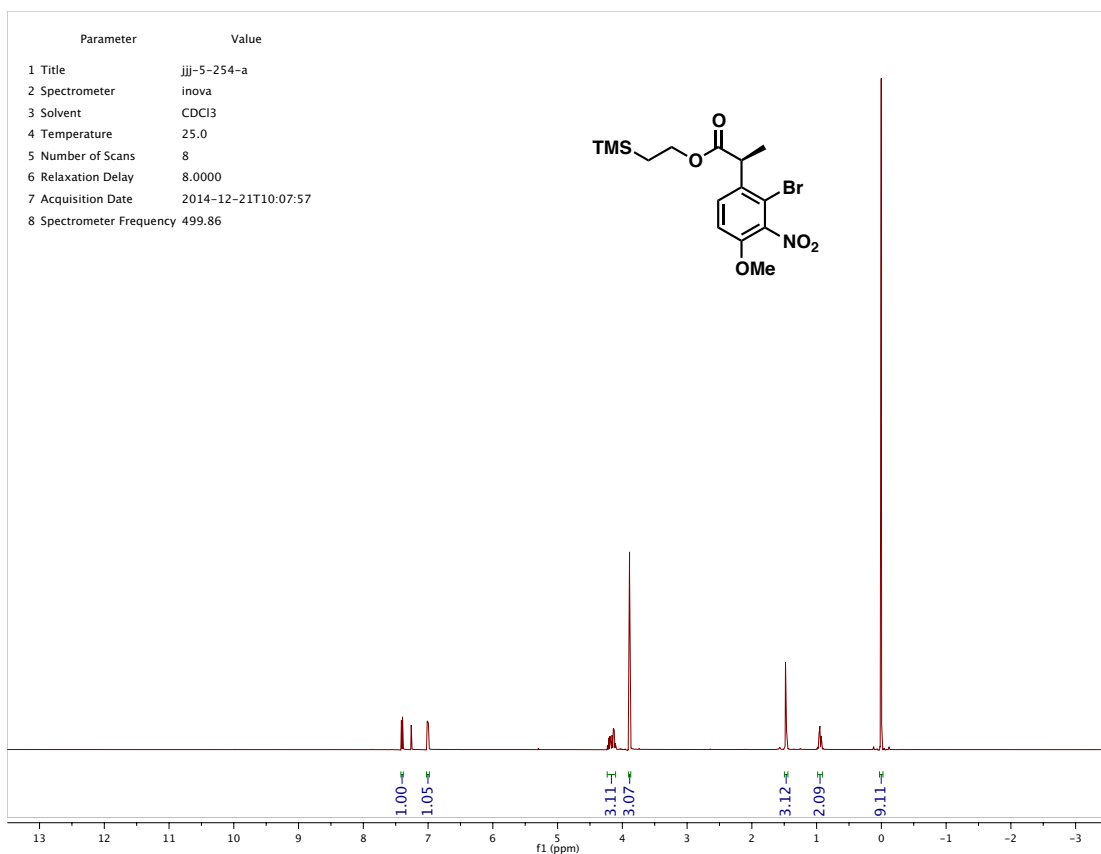
Peak#	Ret. Time	Area	Height	Area %	Height %
1	32.378	2844624	72743	7.633	9.023
2	34.069	34425231	733411	92.367	90.977
Total		37269855	806155	100.000	100.000

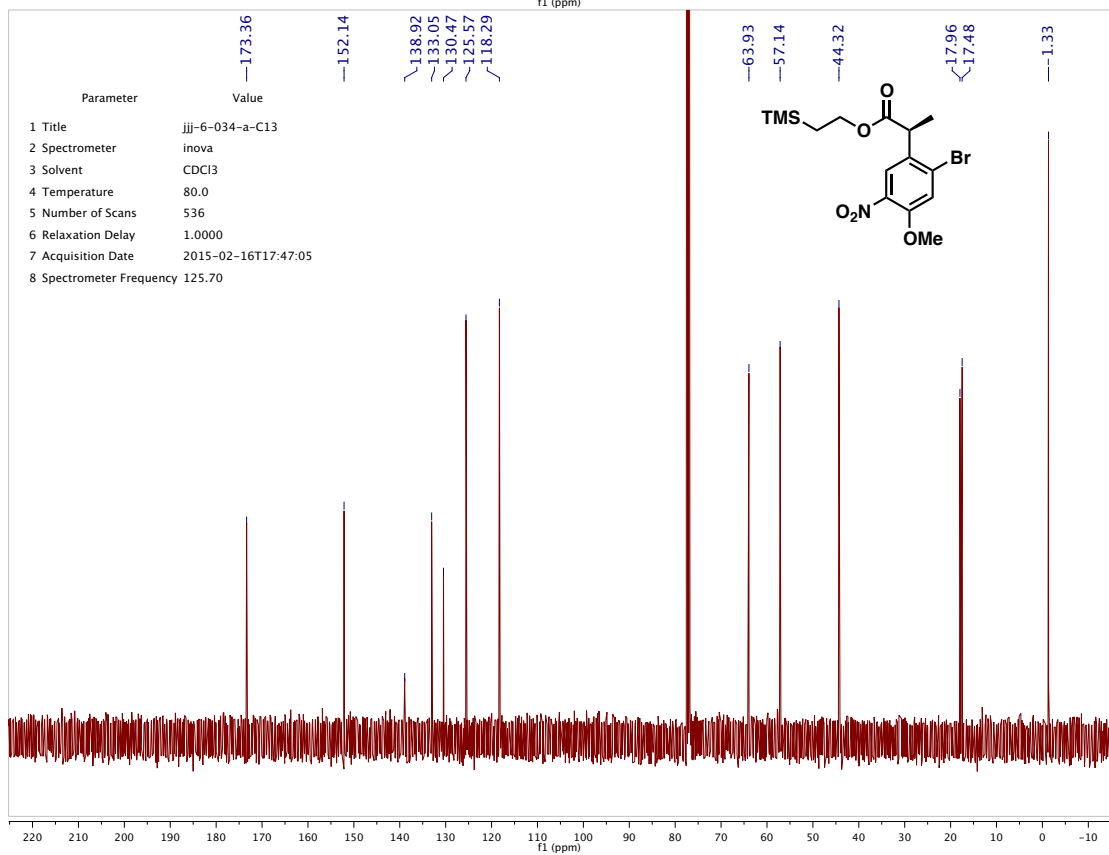
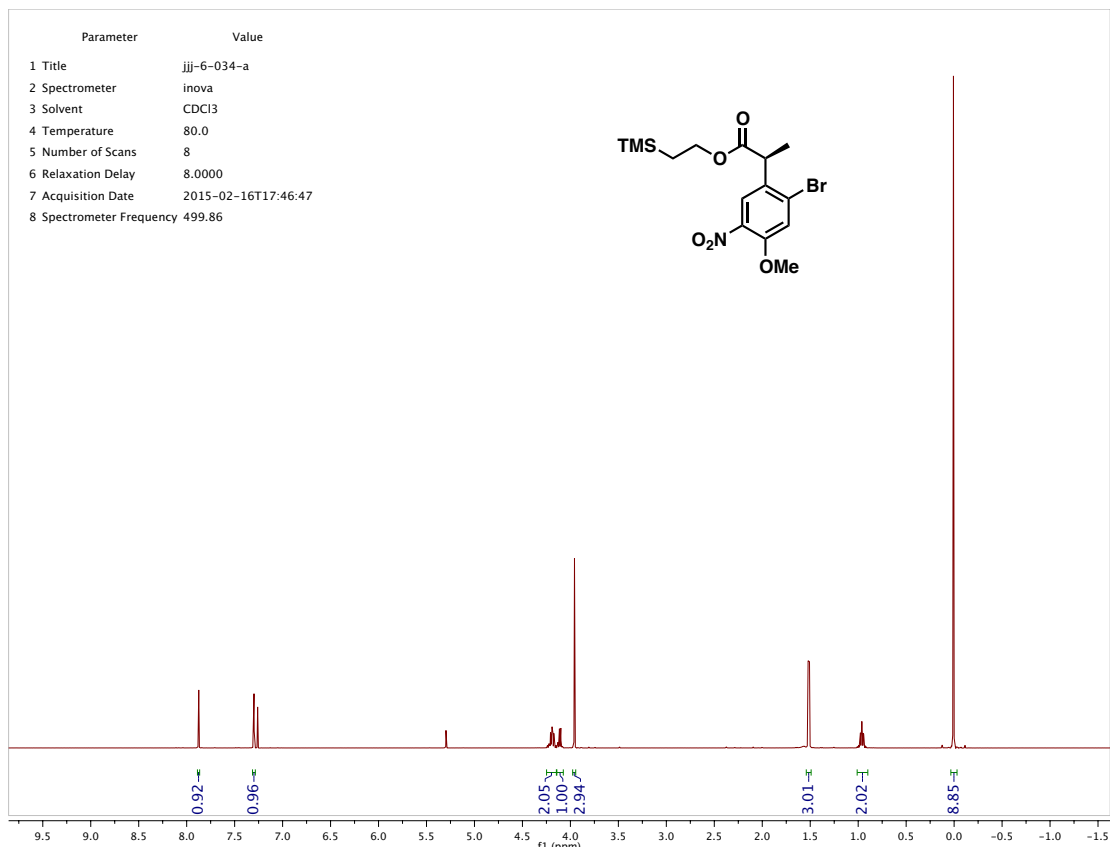
C:\LabSolutions\Data\Project1\jji-3-300-a-01.lcd

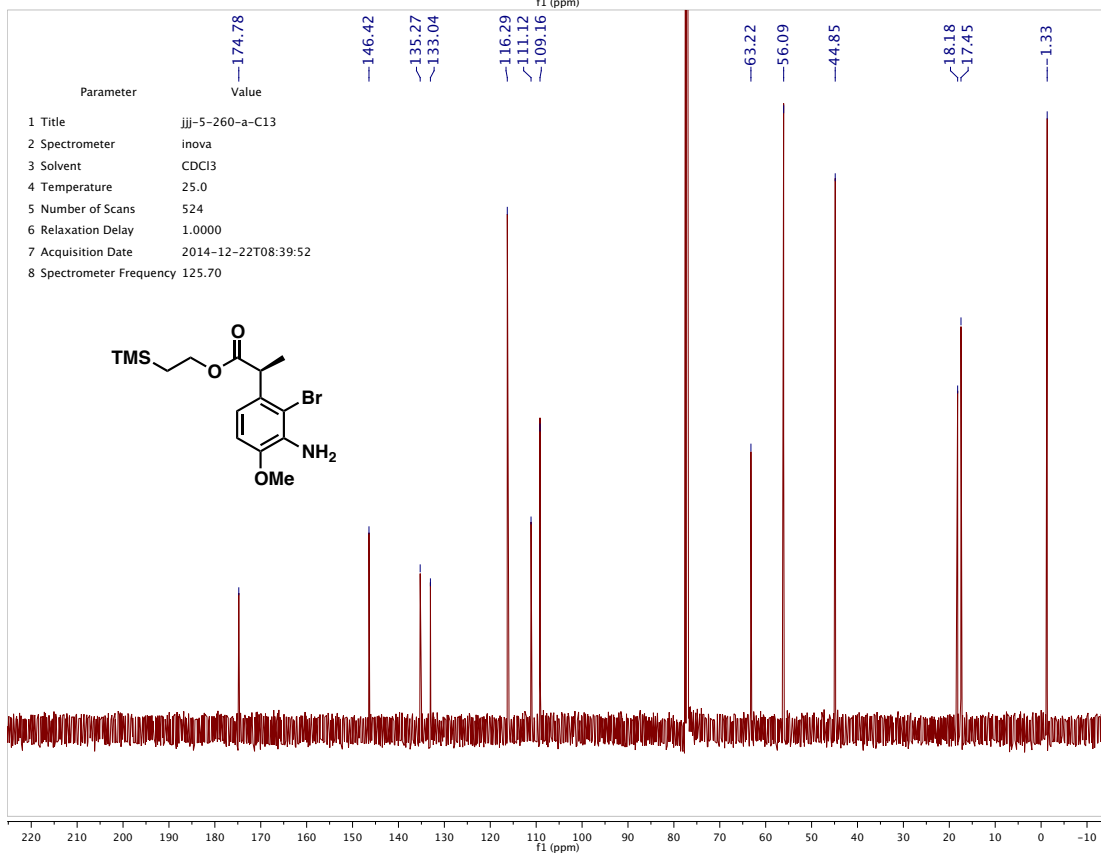
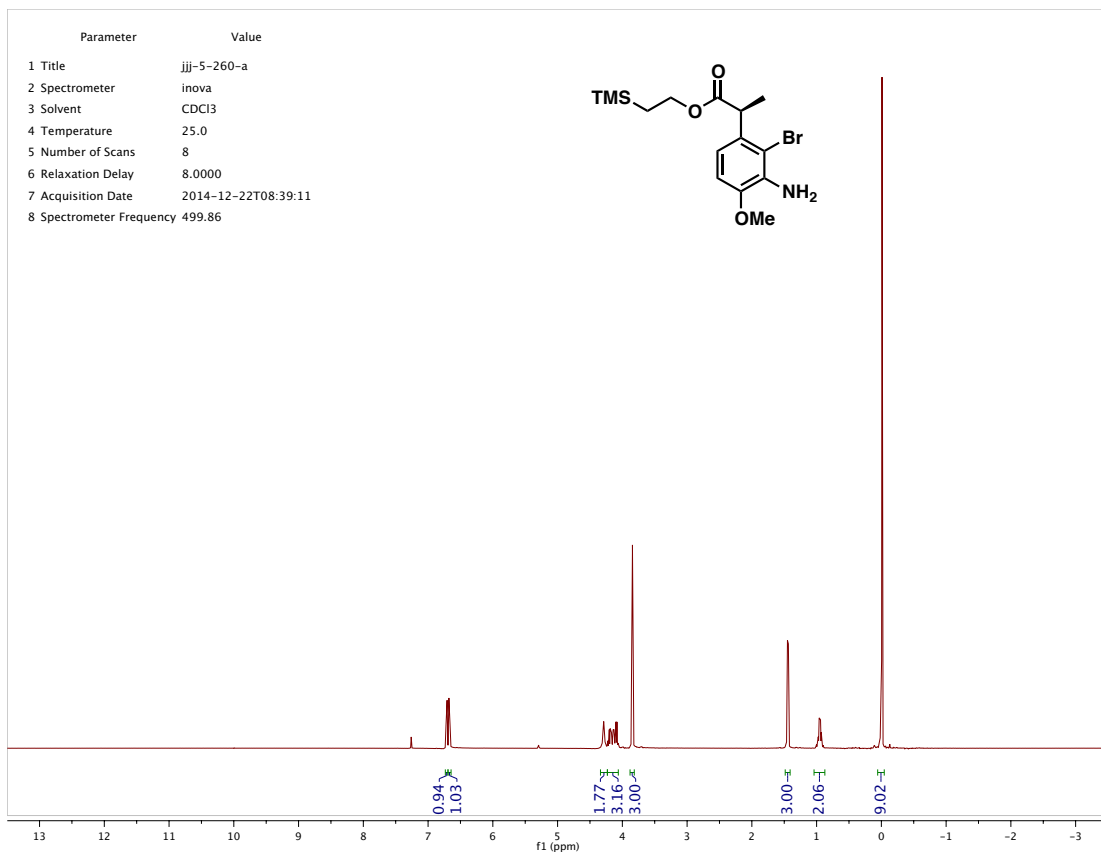


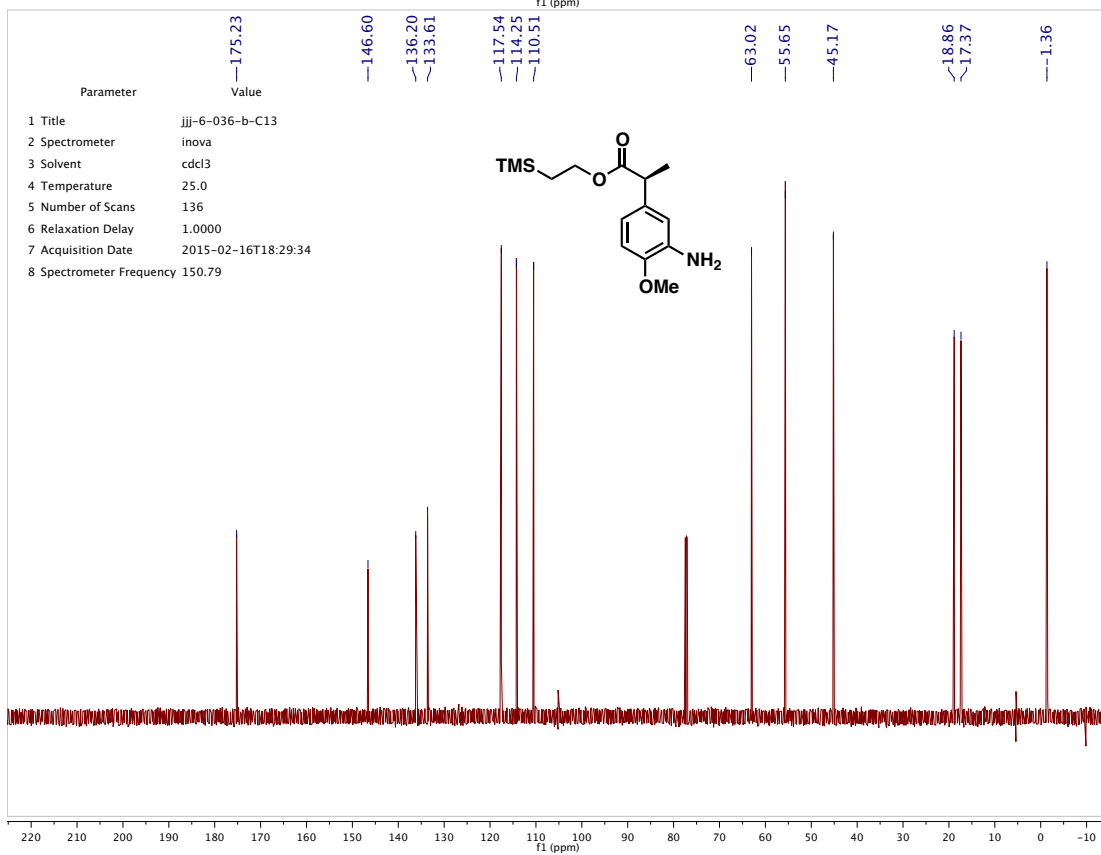
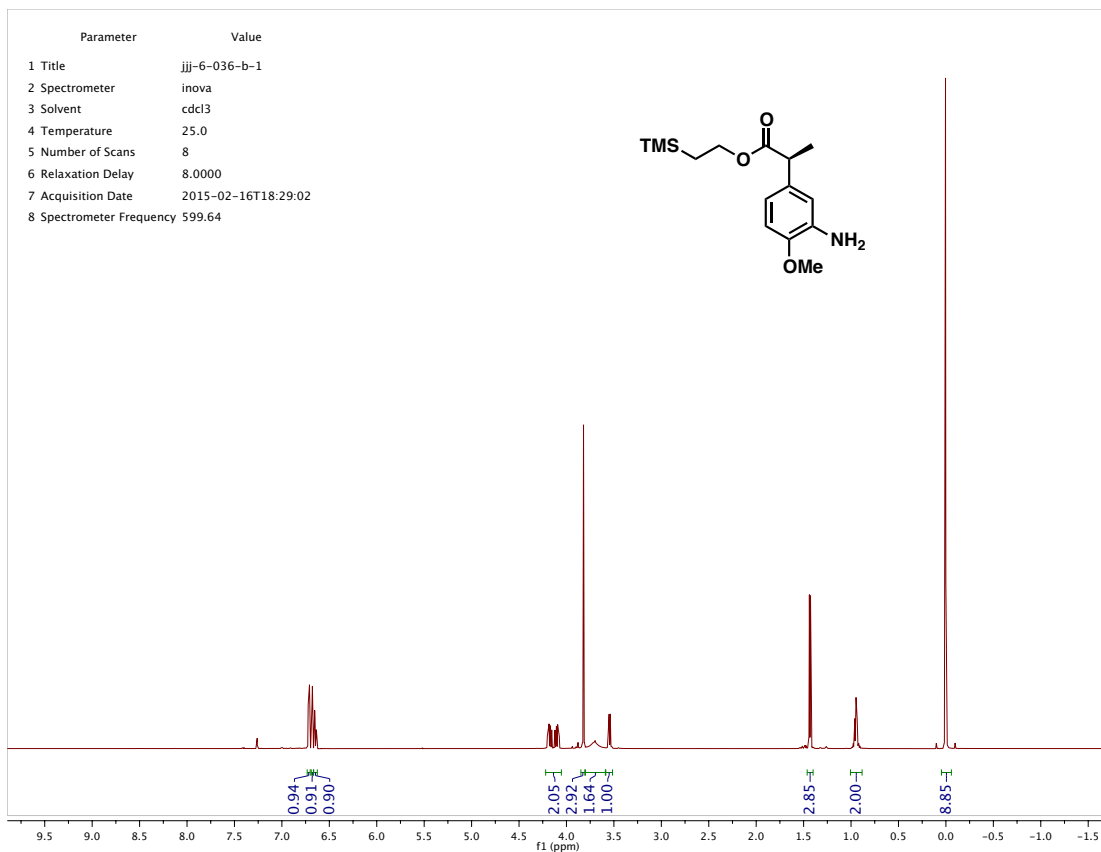


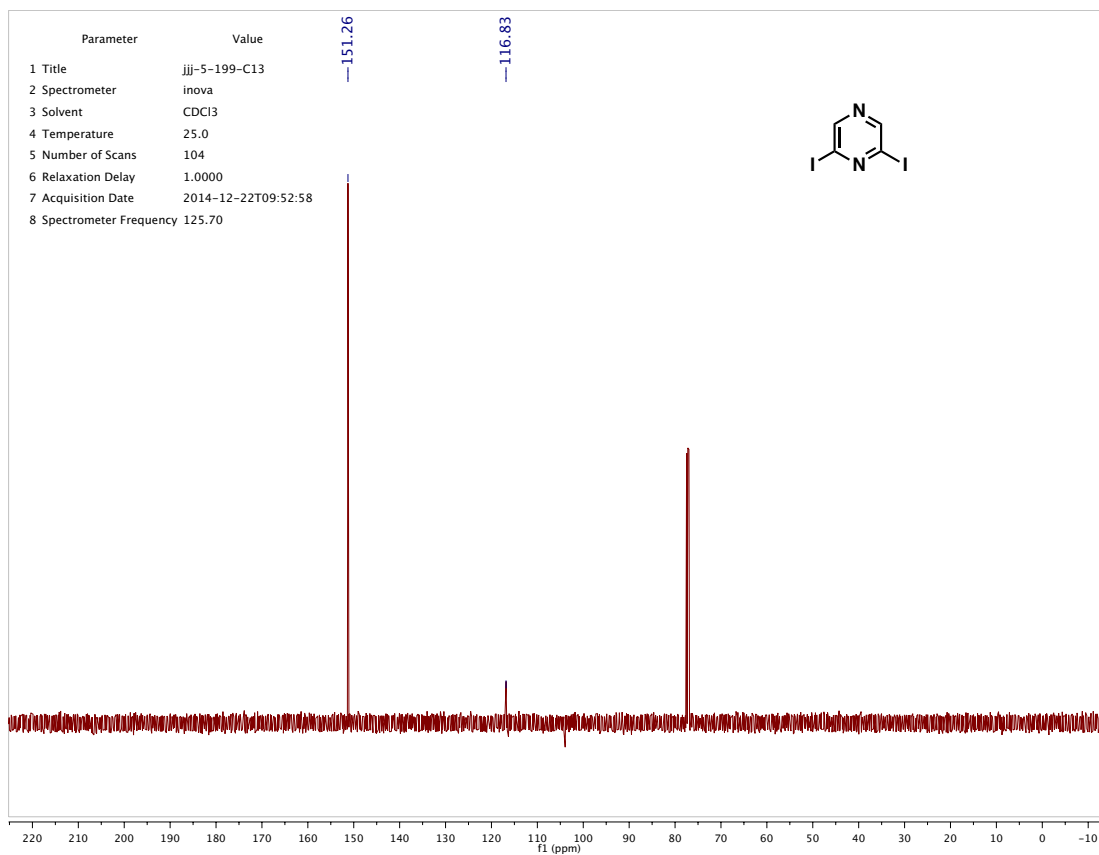
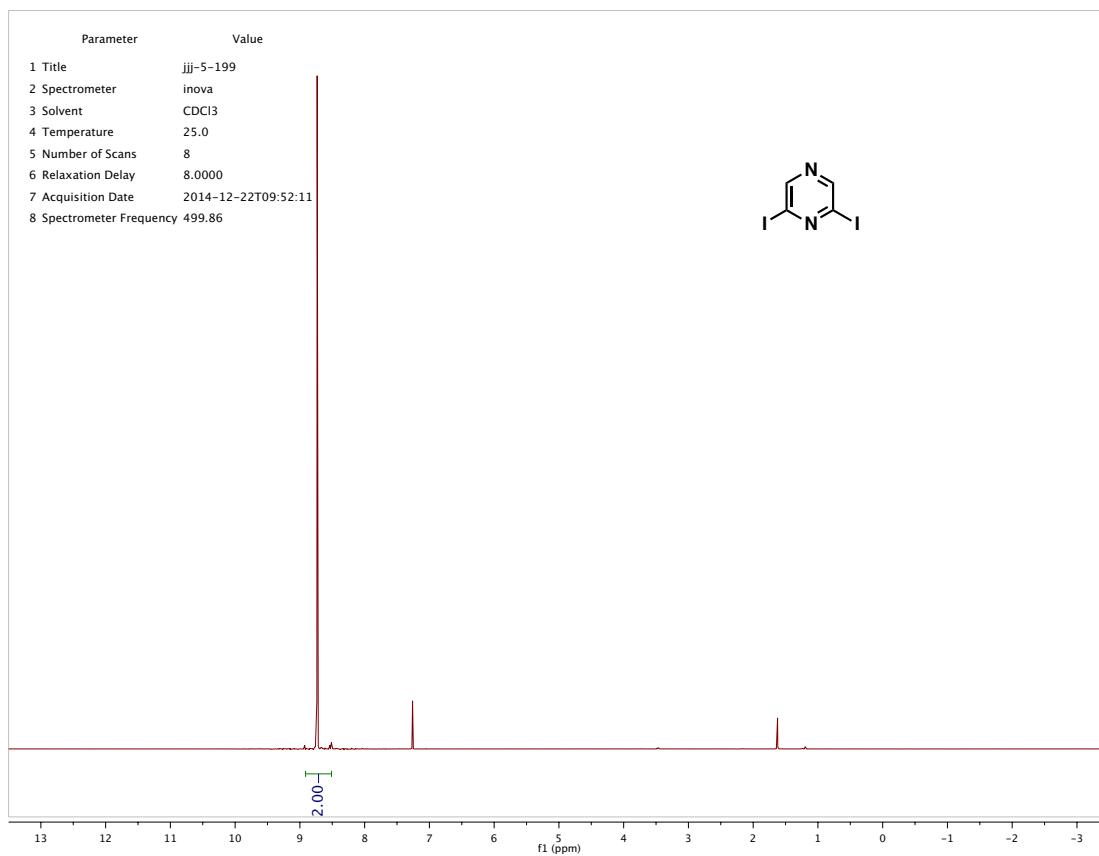


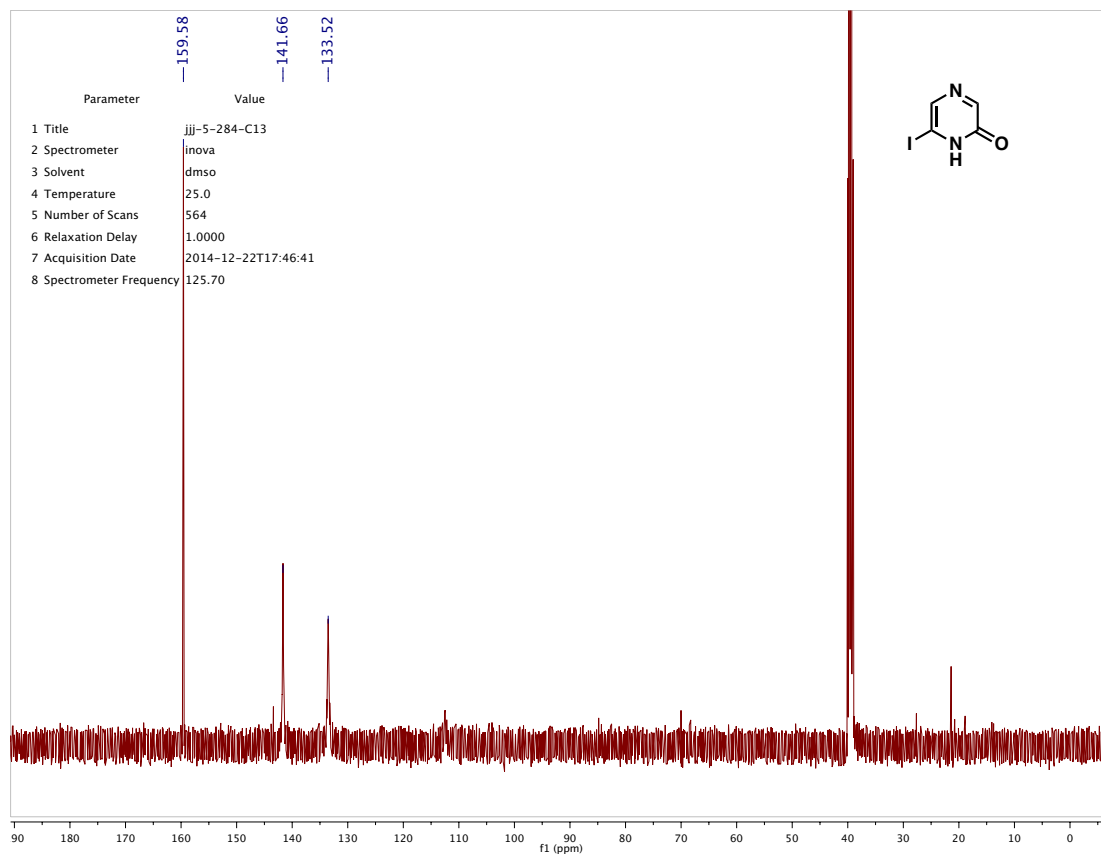
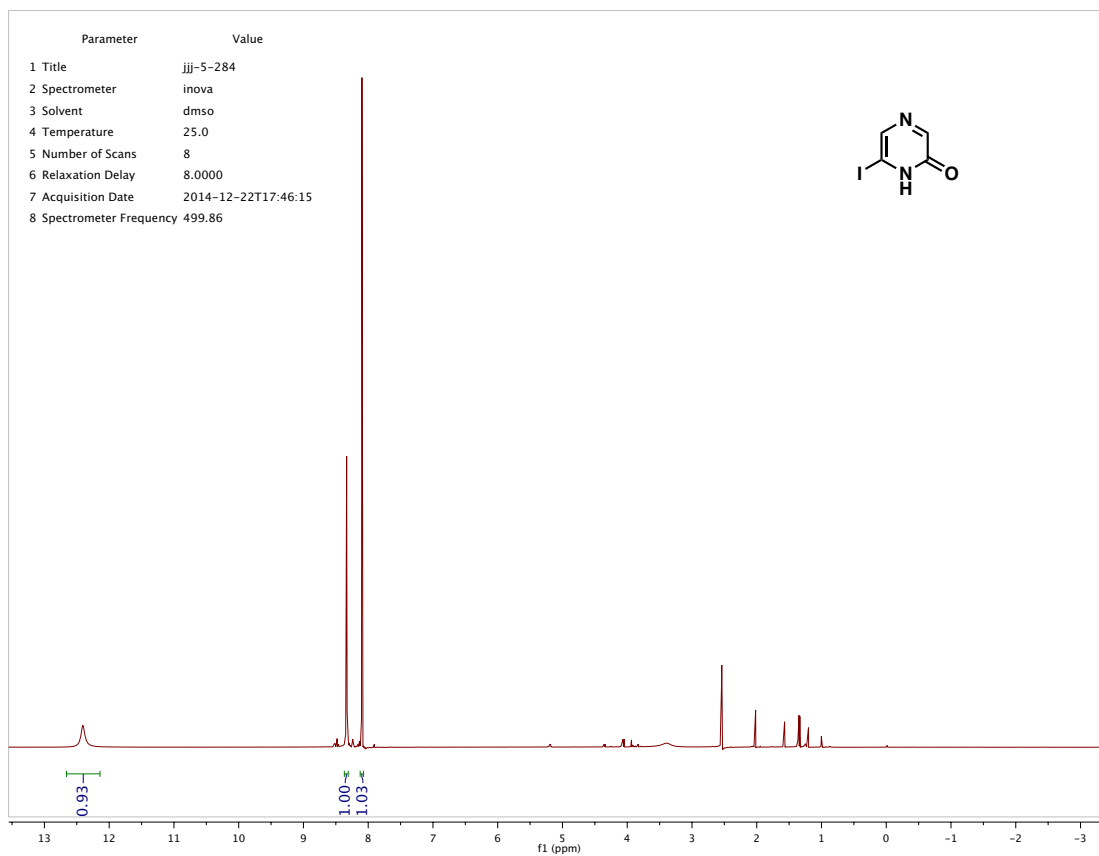


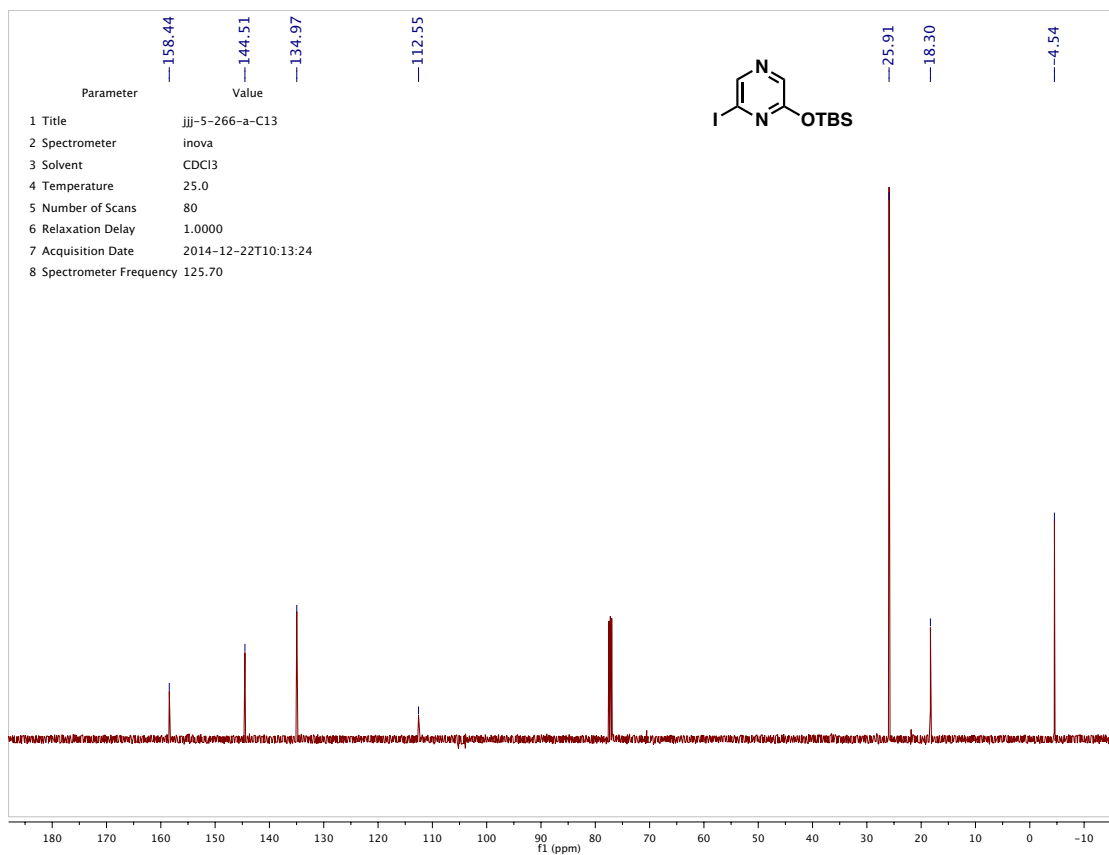
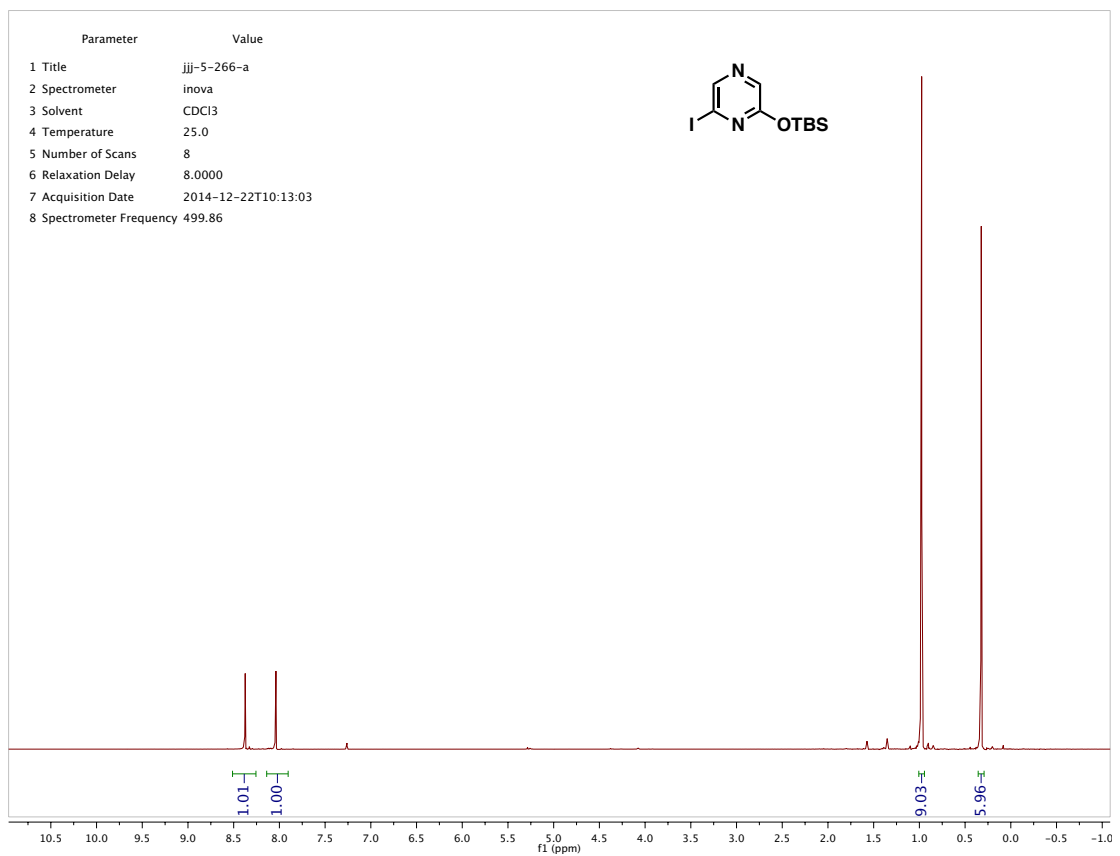


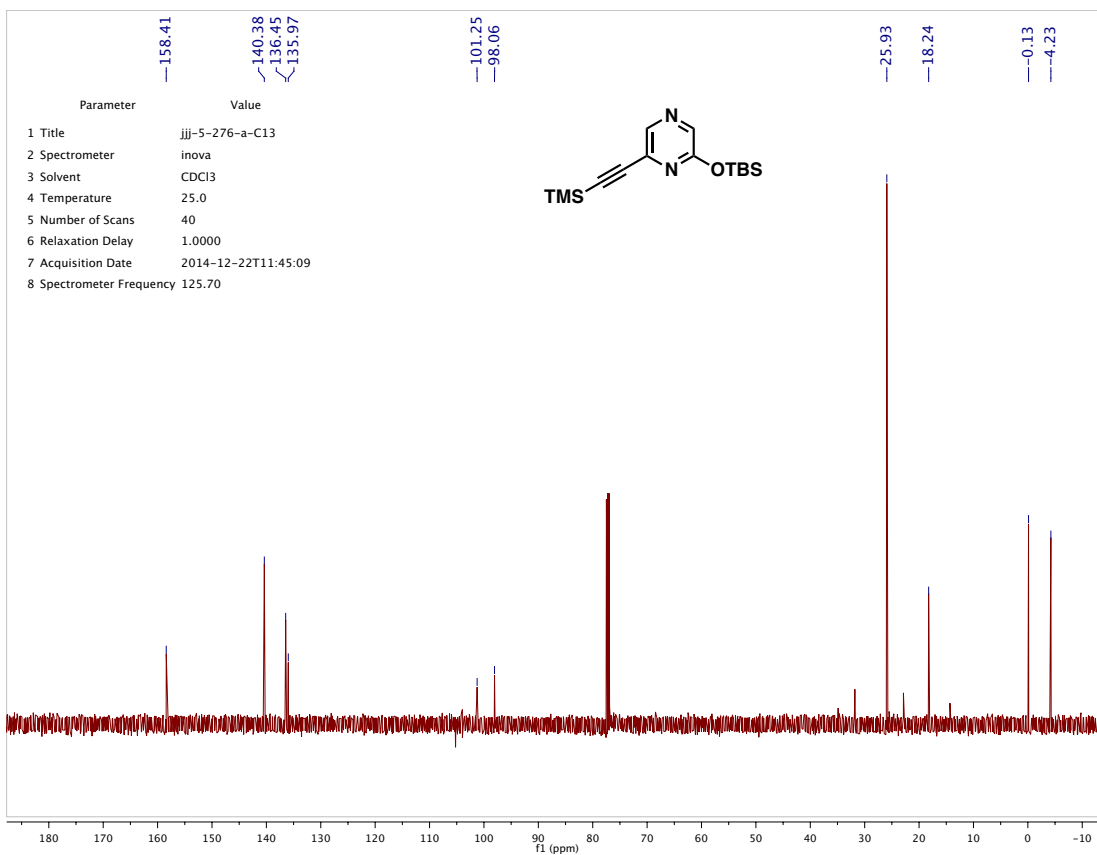
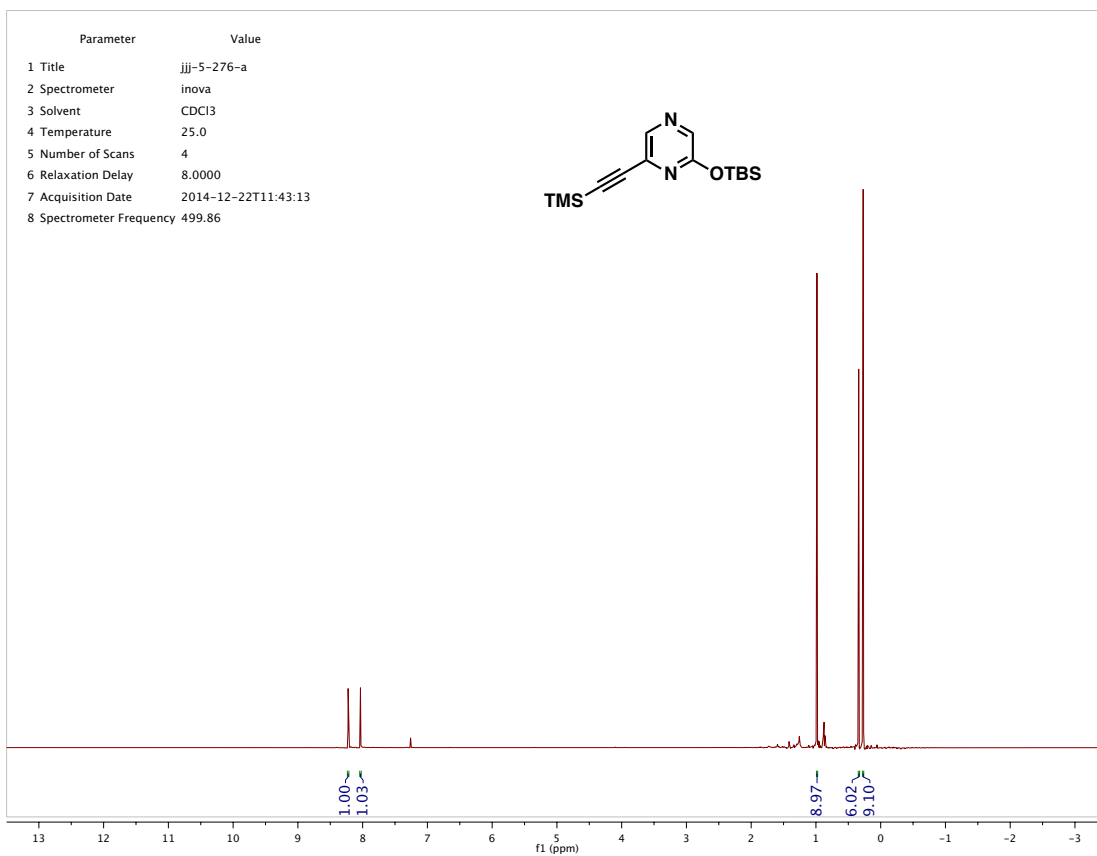


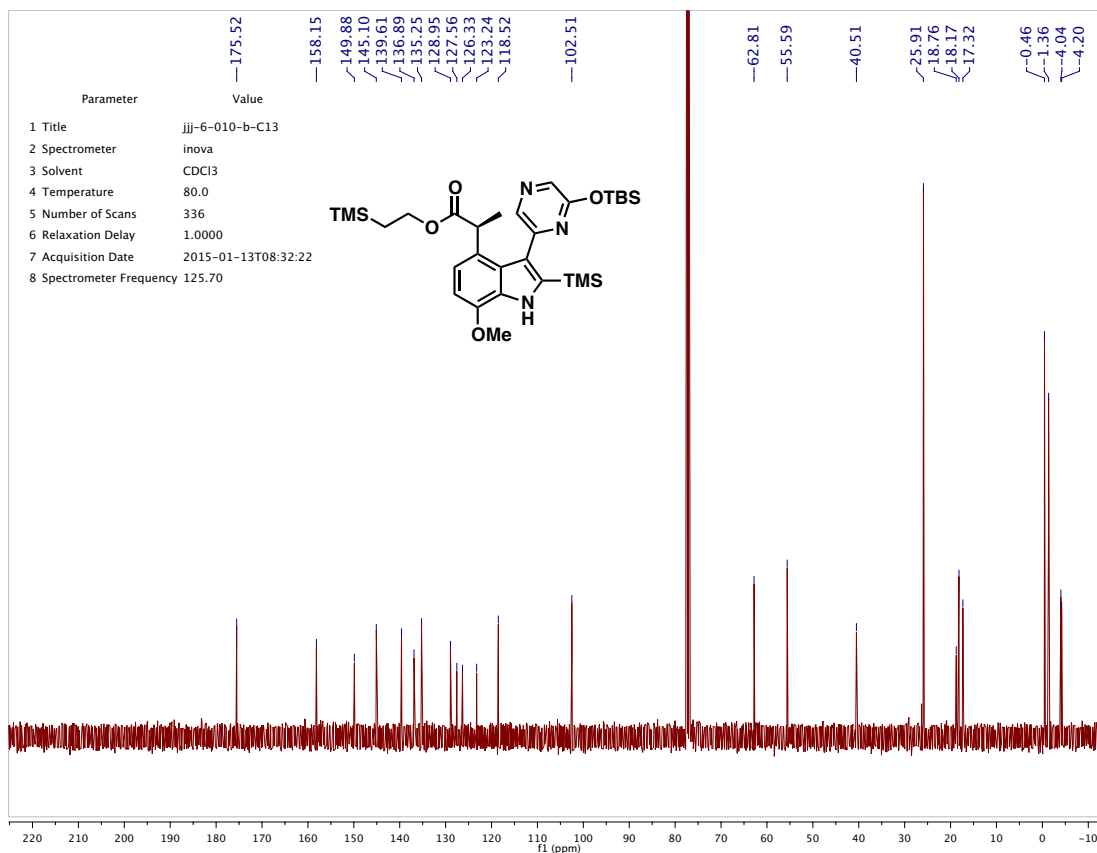
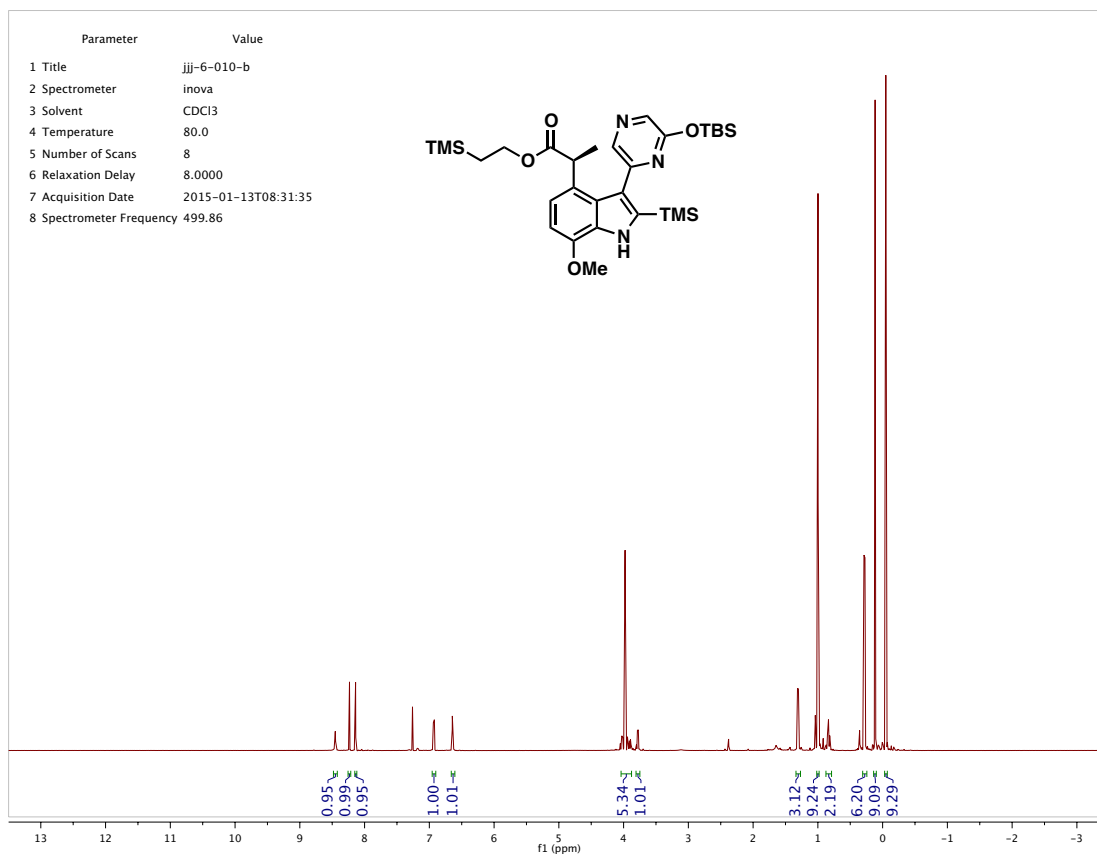


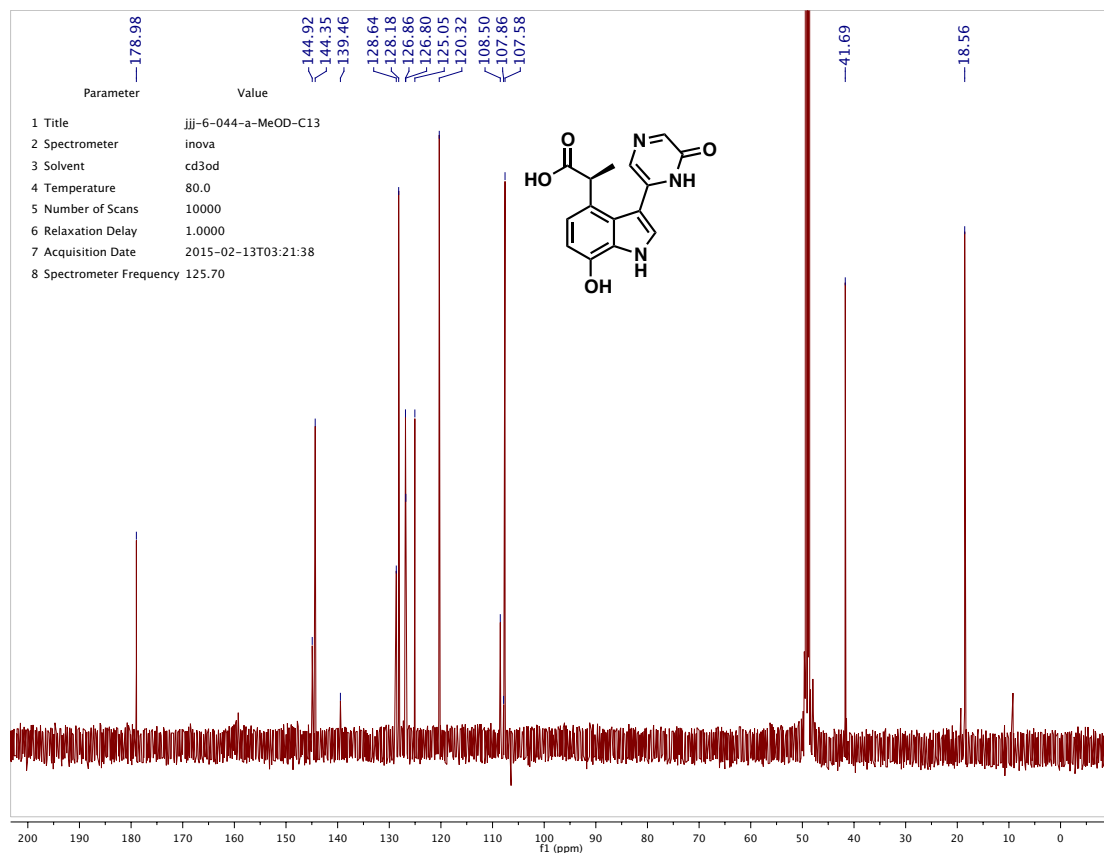
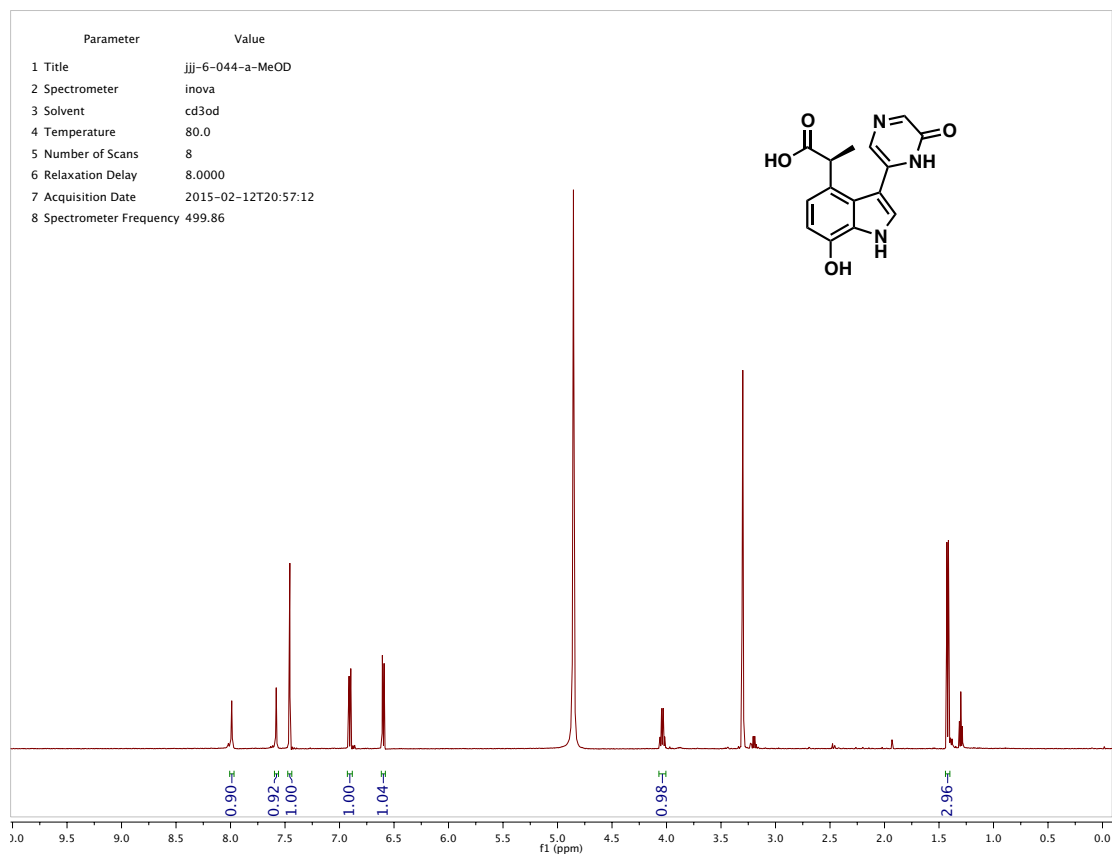


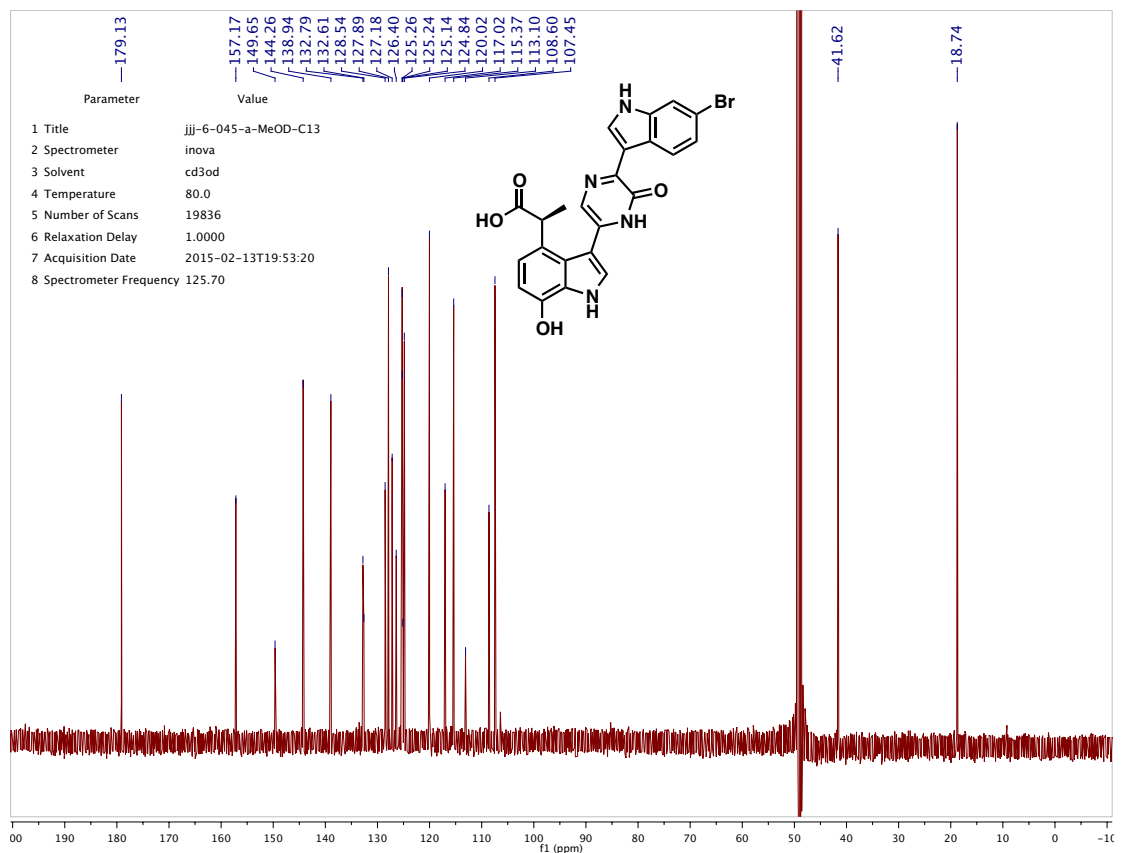
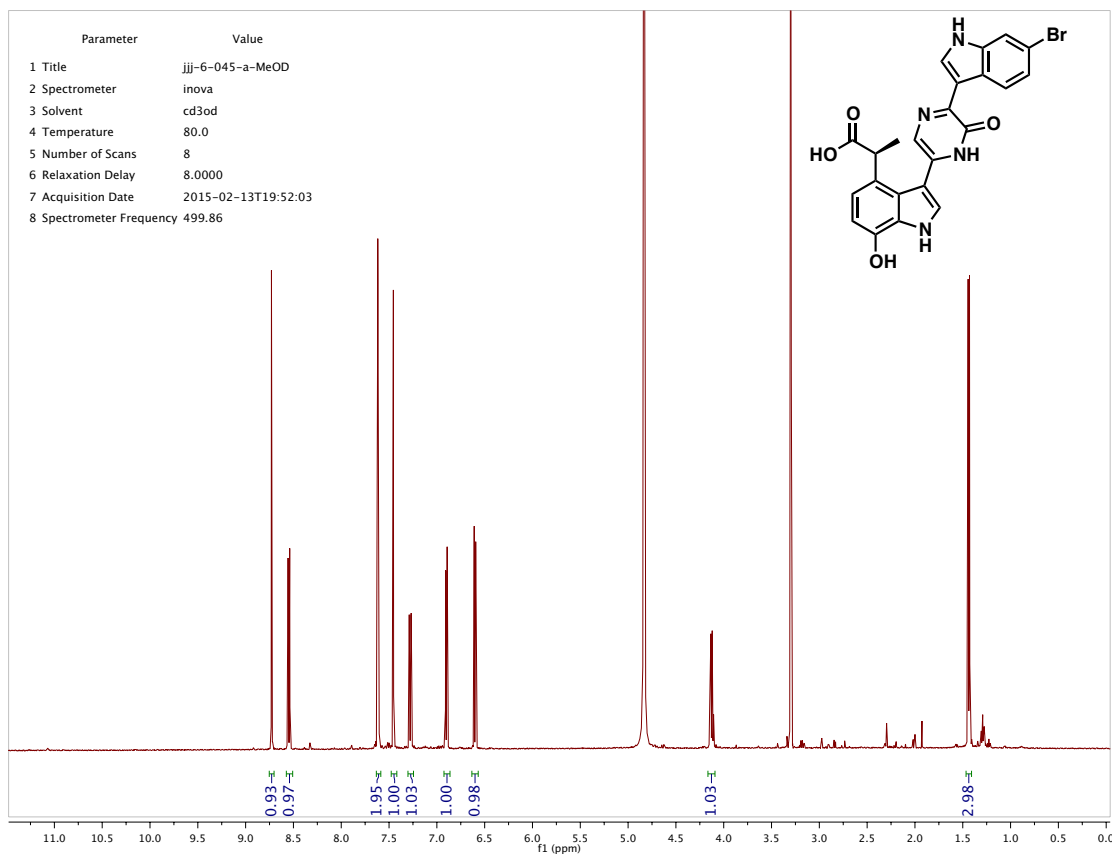


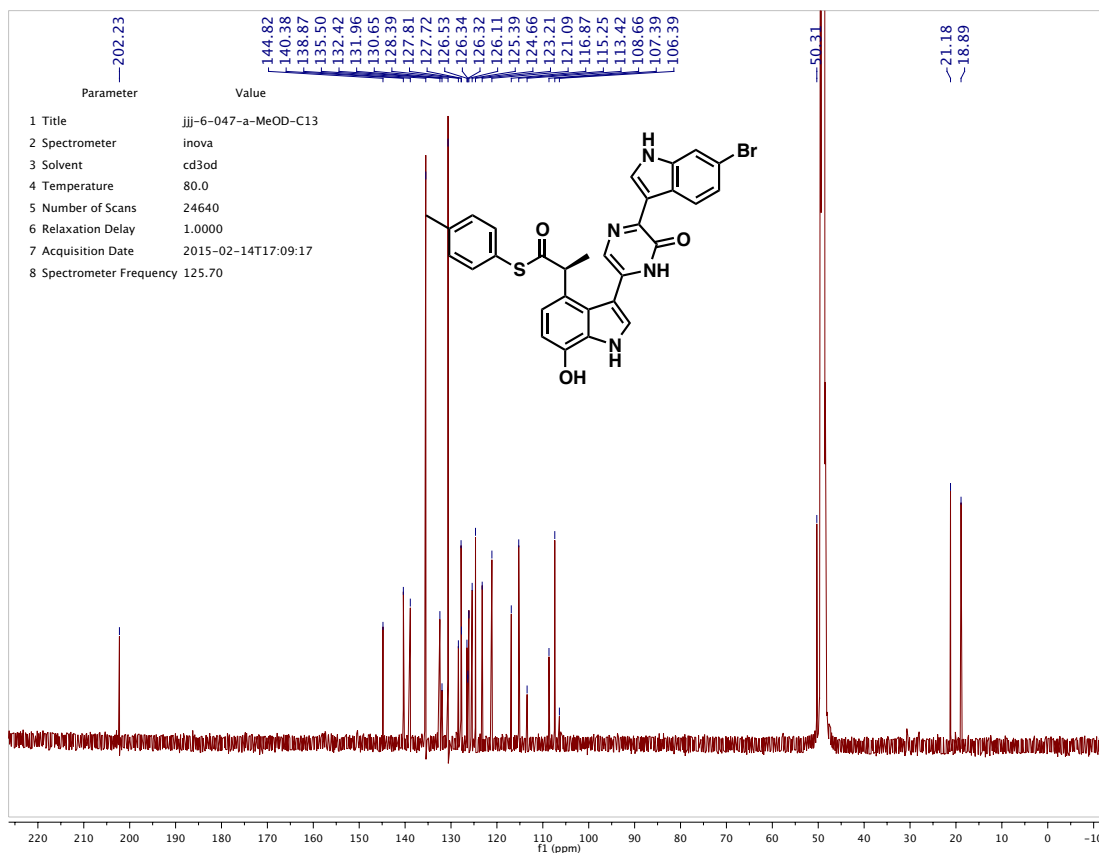
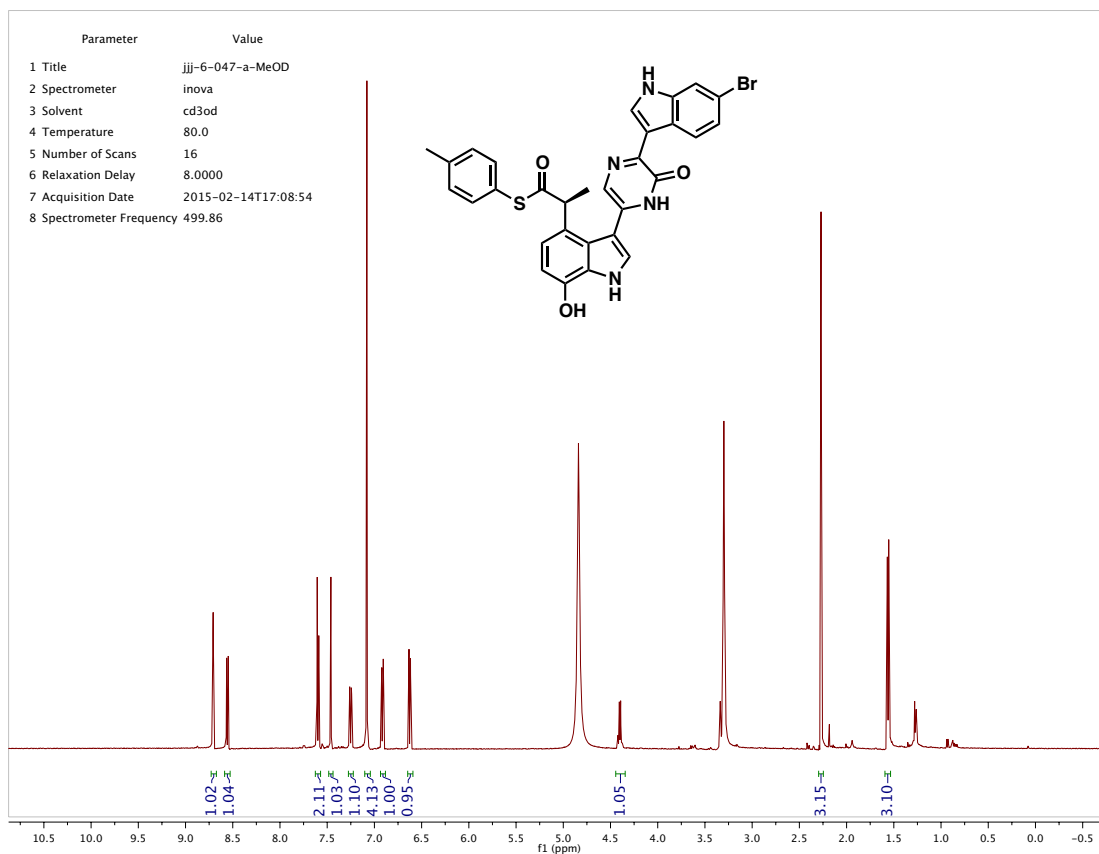


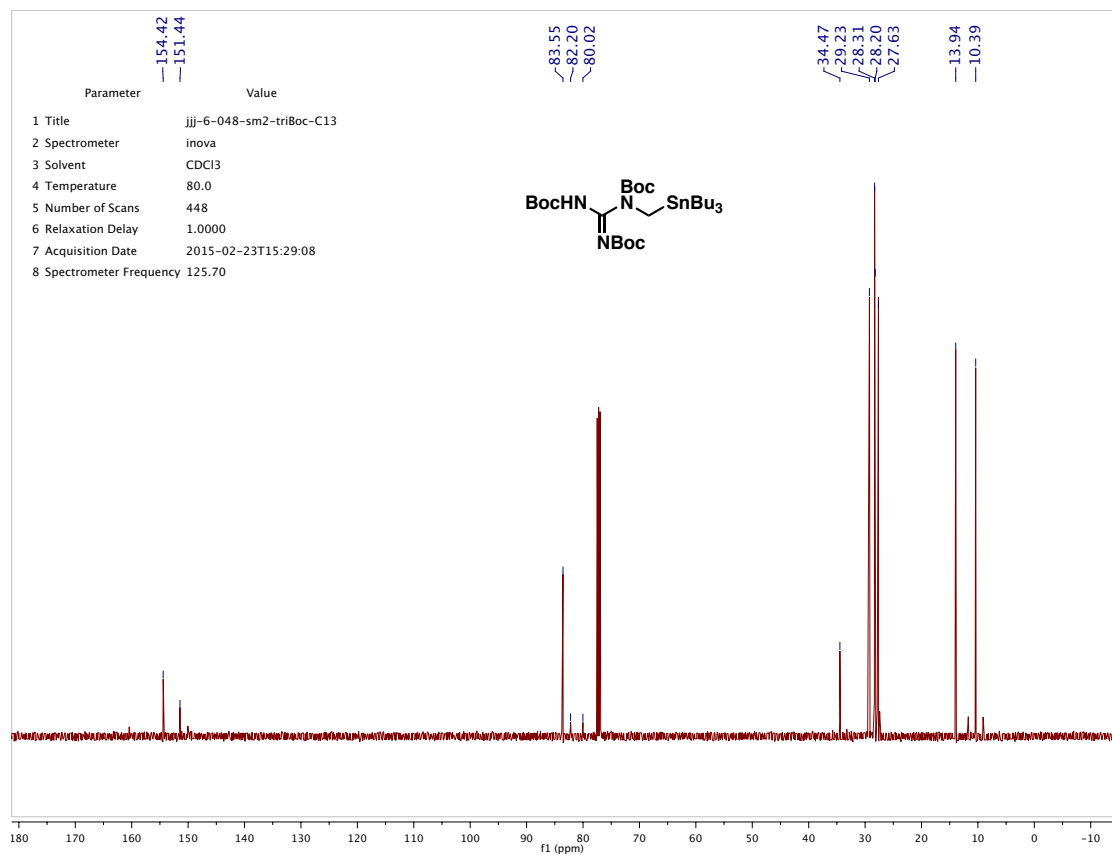
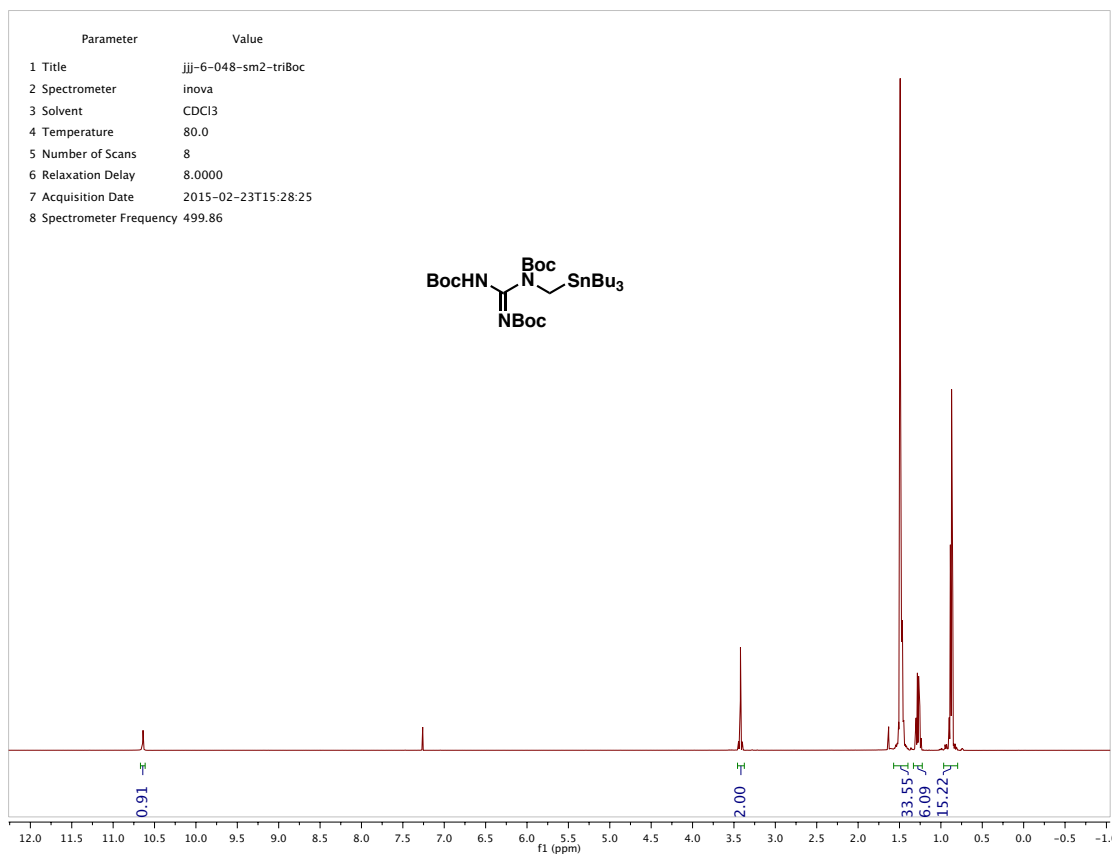


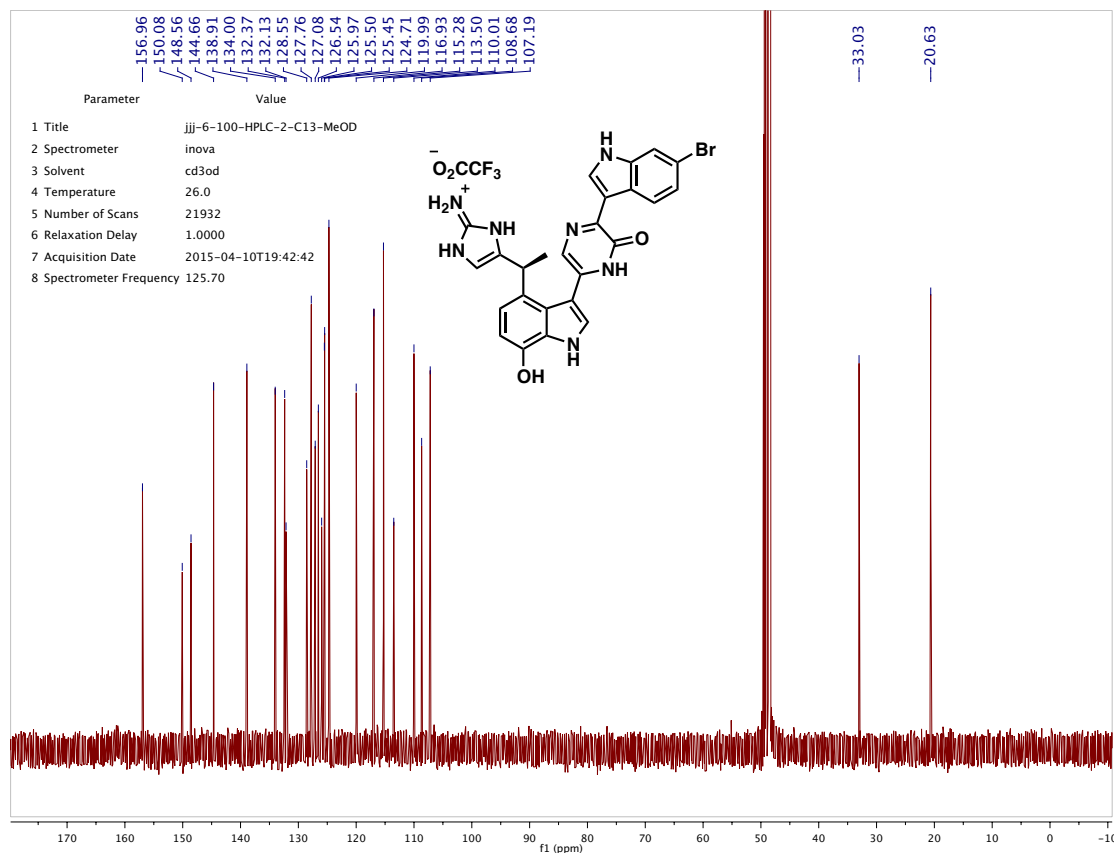
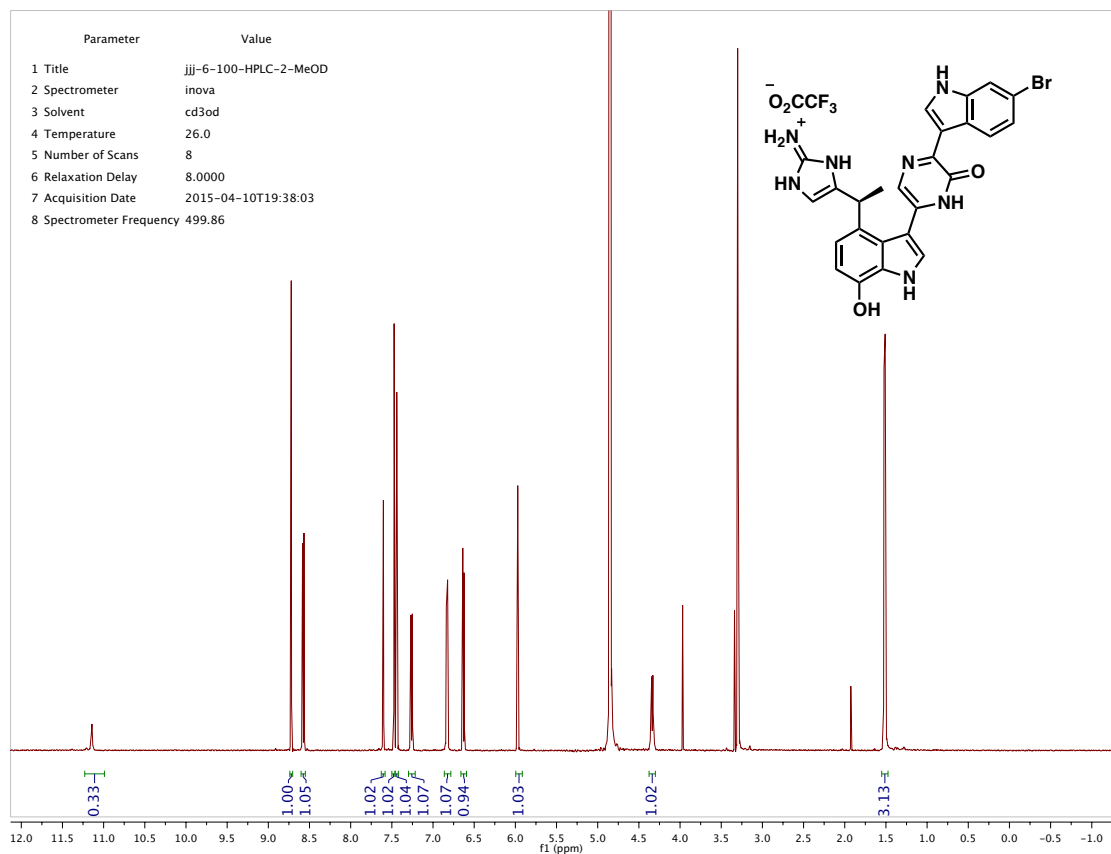


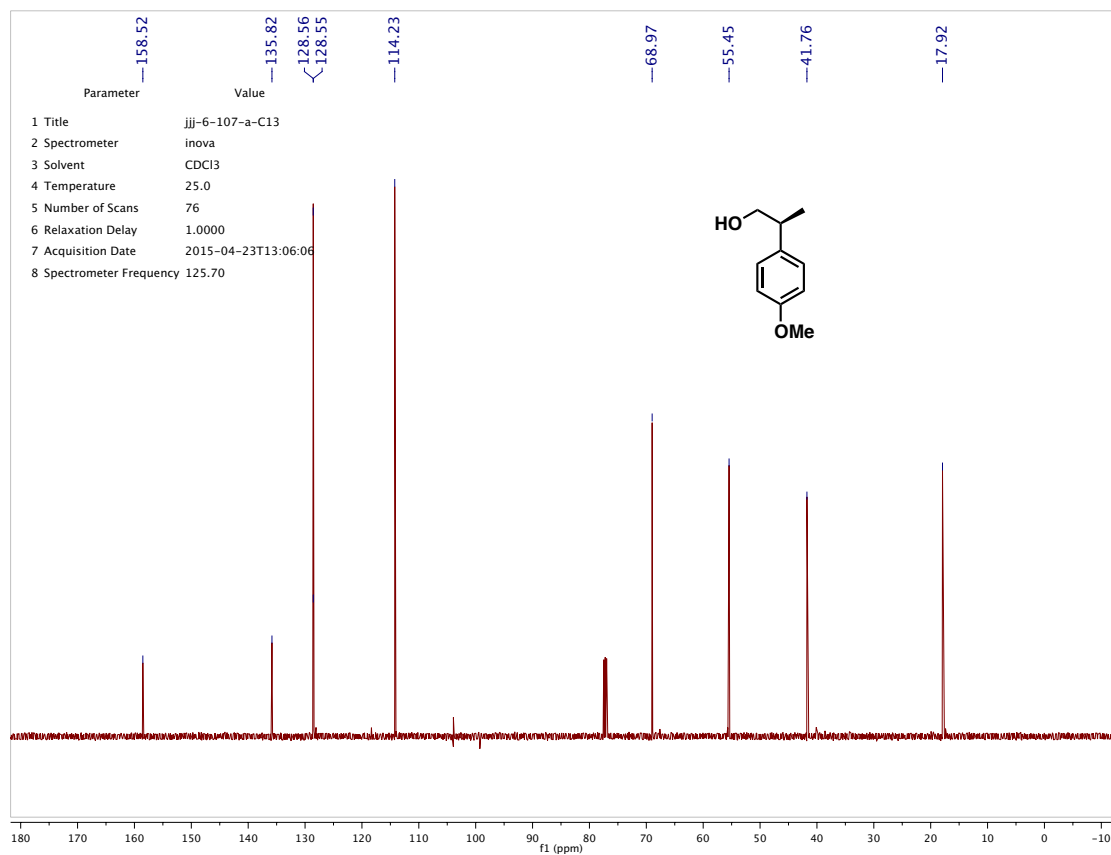
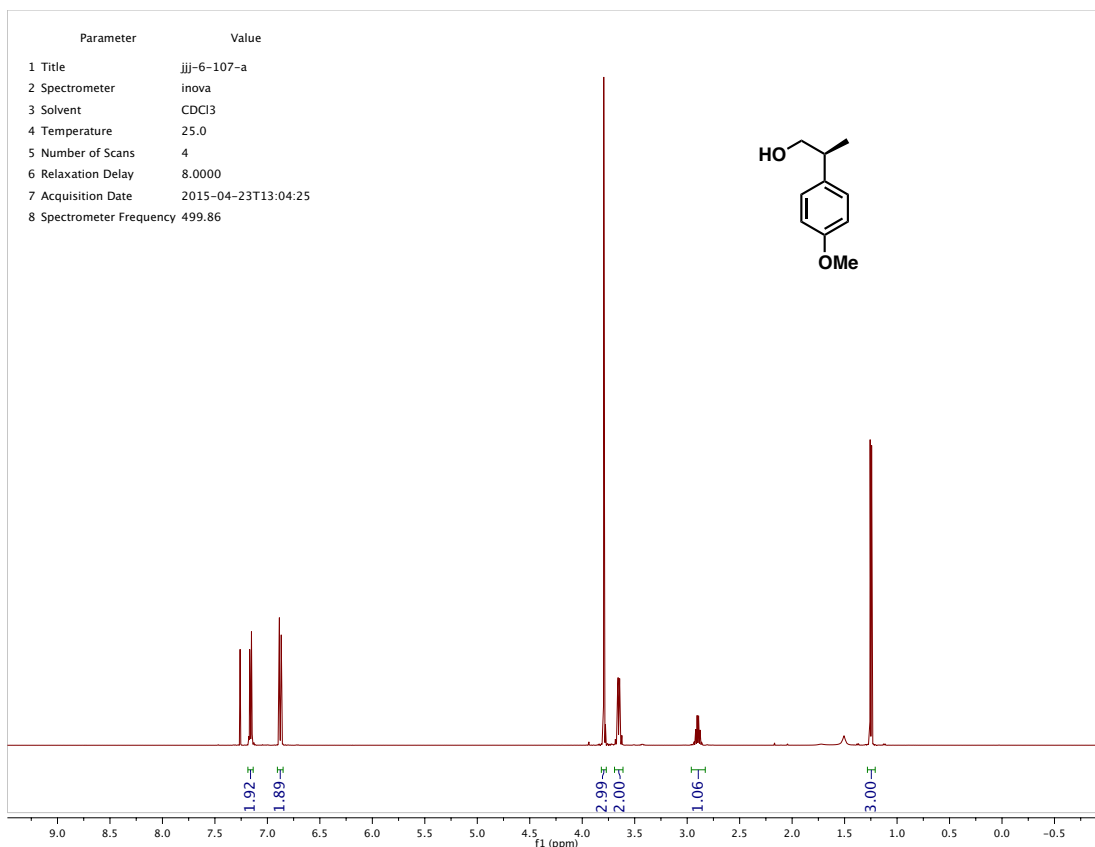








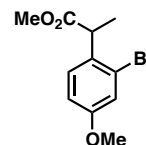




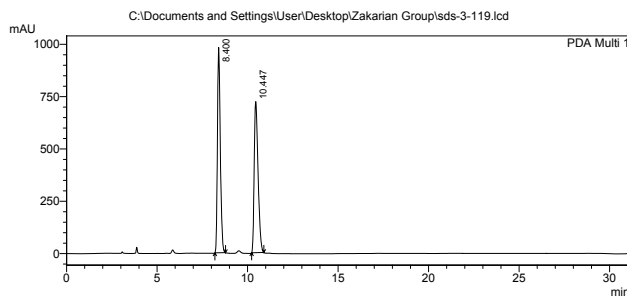
==== Shimadzu LCsolution Analysis Report ====

2/3/2015 16:43:00 1 / 1

Acquired by : Admin
 Sample Name : sds-3-119
 Sample ID : sds-3-119
 Vial # :
 Injection Volume : 10 uL
 Data File Name : sds-3-119.lcd
 Method File Name : ATH-OD-J-analytical-hplc.lcm
 Batch File Name :
 Report File Name : Default.lcr
 Data Acquired : 11/5/2014 5:31:35 PM
 Data Processed : 12/11/2014 11:49:51 AM



<Chromatogram>



1 PDA Multi 1/210nm 4nm

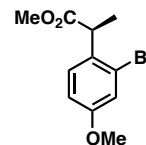
Peak#	Ret. Time	Area	Height	Area %	Height %
1	8.400	10848176	981236	50.400	57.619
2	10.447	10675859	721739	49.600	42.381
Total		21524035	1702974	100.000	100.000

C:\Documents and Settings\User\Desktop\Zakarian Group\sds-3-119.lcd

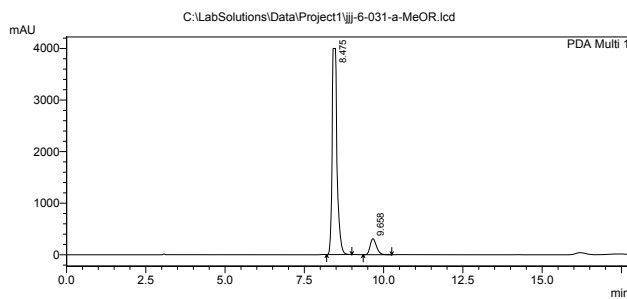
==== Shimadzu LCsolution Analysis Report ====

2/2/2015 16:46:32 1 / 1

Acquired by : Admin
 Sample Name : jij-6-031-a-MeOR
 Sample ID : jij-6-031-a-MeOR
 Vial # :
 Injection Volume : 10 uL
 Data File Name : jij-6-031-a-MeOR.lcd
 Method File Name : ATH-OD-J-analytical-hplc.lcm
 Batch File Name :
 Report File Name : Default.lcr
 Data Acquired : 2/2/2015 3:55:25 PM
 Data Processed : 2/2/2015 4:18:38 PM



<Chromatogram>



1 PDA Multi 1/210nm 4nm

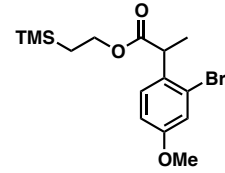
Peak#	Ret. Time	Area	Height	Area %	Height %
1	8.475	43114143	3995989	90.903	92.796
2	9.658	4314810	310219	9.097	7.204
Total		47428953	4306208	100.000	100.000

C:\LabSolutions\Data\Project1\jij-6-031-a-MeOR.lcd

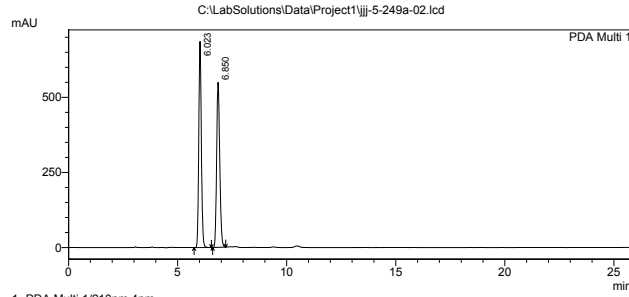
==== Shimadzu LCsolution Analysis Report ====

2/3/2015 16:29:15 1 / 1

Acquired by : Admin
 Sample Name : jji-5-249a-02
 Sample ID : jji-5-249a-02
 Vial # :
 Injection Volume : 10 uL
 Data File Name : jji-5-249a-02.lcd
 Method File Name : ATH-OD-J-analytical-hplc.lcm
 Batch File Name :
 Report File Name : Default.lcr
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 Data Processed : 12/2/2014 4:18:38 PM



<Chromatogram>



PeakTable

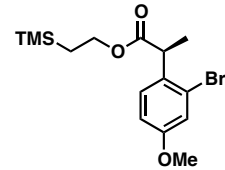
Peak#	Ret. Time	Area	Height	Area %	Height %
1	6.023	5570227	686193	50.588	55.547
2	6.850	5440694	549136	49.412	44.453
Total		11010922	1235339	100.000	100.000

C:\LabSolutions\Data\Project1\jji-5-249a-02.lcd

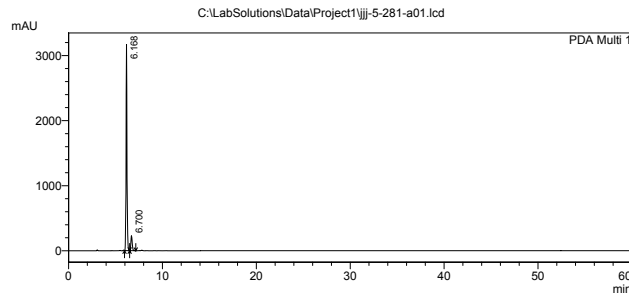
==== Shimadzu LCsolution Analysis Report ====

2/3/2015 16:33:56 1 / 1

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 Injection Volume : 10 uL
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 Method File Name : ATH-OD-J-analytical-hplc.lcm
 Batch File Name :
 Report File Name : Default.lcr
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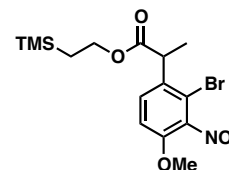
Peak#	Ret. Time	Area	Height	Area %	Height %
1	6.168	21744743	3167839	90.411	93.250
2	6.700	2306363	229308	9.589	6.750
Total		24051106	3397147	100.000	100.000

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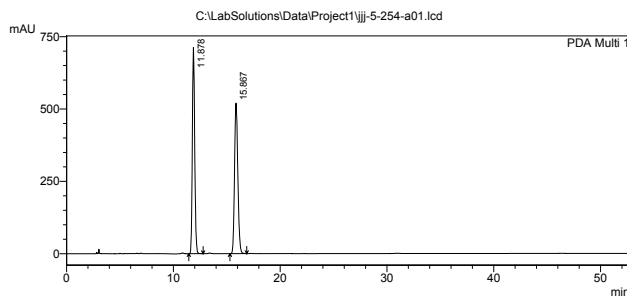
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2/3/2015 16:35:33 1 / 1

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 Sample ID : jji-5-254-a
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 Injection Volume : 10 uL
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 Method File Name : ATH-OD-J-analytical-hplc.lcm
 Batch File Name :
 Report File Name : Default.lcr
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1 PDA Multi 1/210nm 4nm

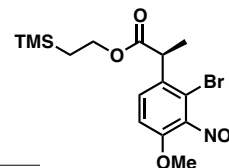
Peak#	Ret. Time	Area	Height	Area %	Height %
1	11.878	11040959	712748	49.750	57.798
2	15.867	11151705	520412	50.250	42.202
Total		22192664	1233160	100.000	100.000

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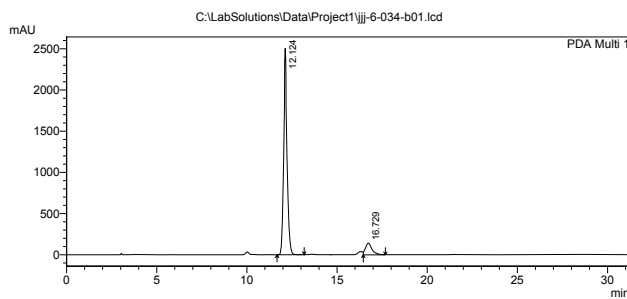
==== Shimadzu LCsolution Analysis Report ====

2/16/2015 13:23:53 1 / 1

Acquired by : Admin
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 Sample ID : jji-6-033-b
 Vial # :
 Injection Volume : 10 uL
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 Method File Name : ATH-OD-J-analytical-hplc.lcm
 Batch File Name :
 Report File Name : Default.lcr
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1 PDA Multi 1/210nm 4nm

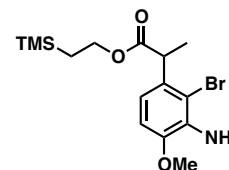
Peak#	Ret. Time	Area	Height	Area %	Height %
1	12.124	31972163	2503189	89.783	94.630
2	16.729	3638442	142041	10.217	5.370
Total		35610605	2645230	100.000	100.000

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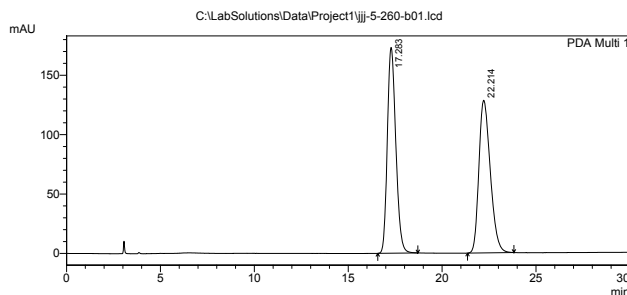
==== Shimadzu LCsolution Analysis Report ====

5/2/2015 13:01:50 1 / 1

Acquired by : Admin
 Sample Name : jji-5-260-b
 Sample ID : jji-5-260-b
 Vial # :
 Injection Volume : 10 uL
 Data File Name : jji-5-260-b01.lcd
 Method File Name : ATH-OD-J-analytical-hplc.lcm
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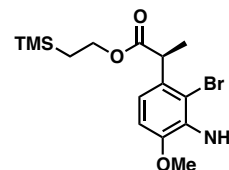
Peak#	Ret. Time	Area	Height	Area %	Height %
1	17.283	5418173	173238	49.977	57.425
2	22.214	5423260	128438	50.023	42.575
Total		10841433	301675	100.000	100.000

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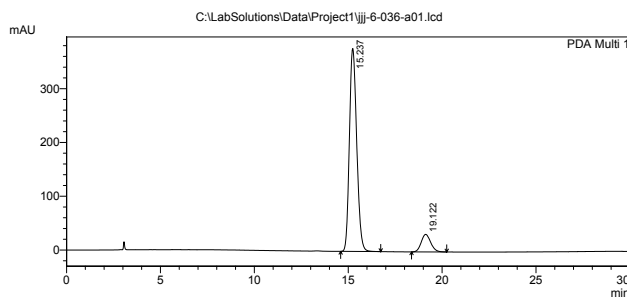
==== Shimadzu LCsolution Analysis Report ====

5/2/2015 13:00:38 1 / 1

Acquired by : Admin
 Sample Name : jji-6-036-a
 Sample ID : jji-6-036-a
 Vial # :
 Injection Volume : 10 uL
 Data File Name : jji-6-036-a01.lcd
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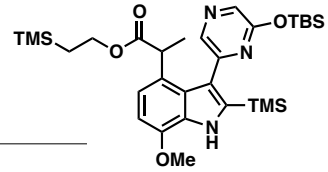
Peak#	Ret. Time	Area	Height	Area %	Height %
1	15.237	10194748	377334	89.904	92.057
2	19.122	1144867	32558	10.096	7.943
Total		11339614	409892	100.000	100.000

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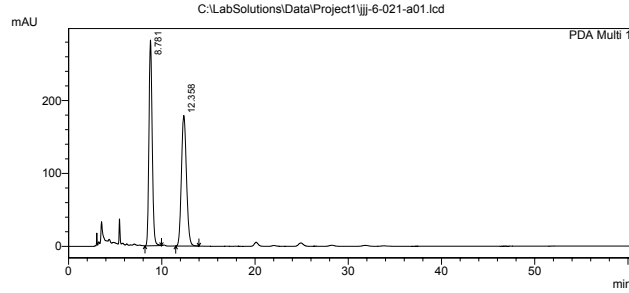
==== Shimadzu LCsolution Analysis Report ====

2/20/2015 10:44:01 1 / 1

Acquired by : Admin
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 Sample ID : jji-6-021-a
 Vial # :
 Injection Volume : 10 uL
 Data File Name : jji-6-021-a01.lcd
 Method File Name : ATH-OD-J-analytical-hplc.lcm
 Batch File Name :
 Report File Name : Default.lcr
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1 PDA Multi 1/210nm 4nm

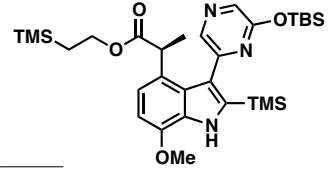
Peak#	Ret. Time	Area	Height	Area %	Height %
1	8.781	6829457	282132	50.306	61.158
2	12.358	6746417	179186	49.694	38.842
Total		13575874	461318	100.000	100.000

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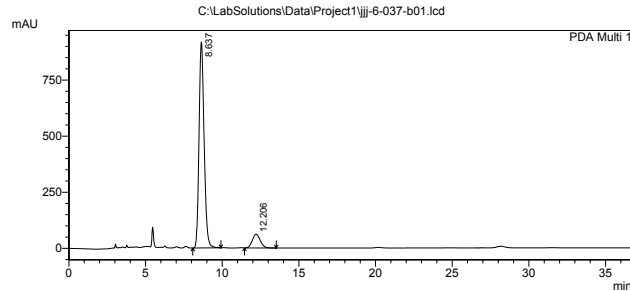
==== Shimadzu LCsolution Analysis Report ====

2/9/2015 11:28:32 1 / 1

Acquired by : Admin
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 Sample ID : jji-6-037-b
 Vial # :
 Injection Volume : 10 uL
 Data File Name : jji-6-037-b01.lcd
 Method File Name : ATH-OD-J-analytical-hplc.lcm
 Batch File Name :
 Report File Name : Default.lcr
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<Chromatogram>



1 PDA Multi 1/210nm 4nm

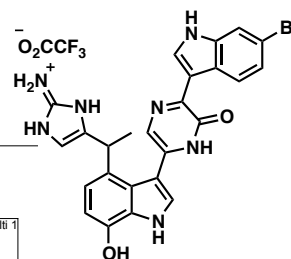
Peak#	Ret. Time	Area	Height	Area %	Height %
1	8.637	21103427	918192	90.529	93.771
2	12.208	2207709	60995	9.471	6.229
Total		23311136	979187	100.000	100.000

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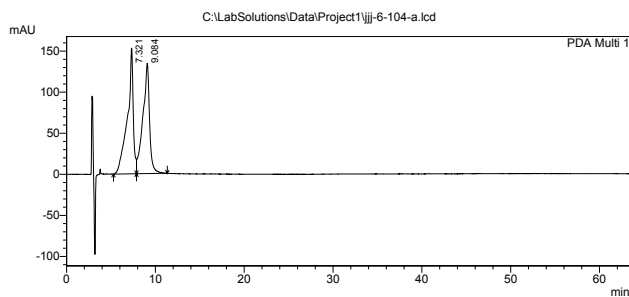
==== Shimadzu LCsolution Analysis Report ====

4/13/2015 16:30:38 1 / 1

Acquired by : Admin
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 Sample ID : jji-6-104-a
 Vial # :
 Injection Volume : 10 uL
 Data File Name : jji-6-104-a.lcd
 Method File Name : ATH-OD-J-analytical-hplc.lcm
 Batch File Name :
 Report File Name : Default.lcr
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1 PDA Multi 1/210nm 4nm

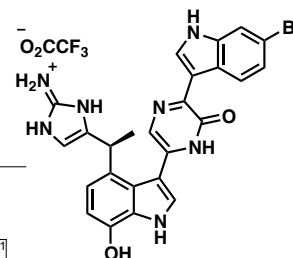
Peak#	Ret. Time	Area	Height	Area %	Height %
1	7.321	7050077	153133	50.038	53.292
2	9.084	7039247	134211	49.962	46.708
Total		14089323	287345	100.000	100.000

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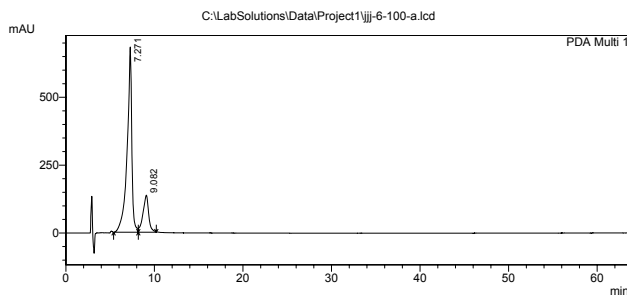
==== Shimadzu LCsolution Analysis Report ====

4/13/2015 16:31:32 1 / 1

Acquired by : Admin
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 Sample ID : jji-6-100-a
 Vial # :
 Injection Volume : 10 uL
 Data File Name : jji-6-100-a.lcd
 Method File Name : ATH-OD-J-analytical-hplc.lcm
 Batch File Name :
 Report File Name : Default.lcr
 Data Acquired : 4/10/2015 12:01:52 PM
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<Chromatogram>



1 PDA Multi 1/210nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	7.271	24975213	682450	80.441	83.338
2	9.082	6072785	136440	19.559	16.662
Total		31047998	818890	100.000	100.000

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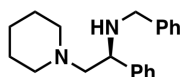
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