I. APPLICATION OF CHIRAL α,β-UNSATURATED ACYLAMMONIUM SALTS FOR EFFICIENT CATALYTIC TRANSFORMATIONS

II. STUDIES TOWARD THE TOTAL SYNTHESIS OF RAMESWARALIDE

A Dissertation

by

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DOCTOR OF PHILOSOPHY

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ABSTRACT

The developments of novel catalytic transformations are just as important as the discoveries of new reactions. In the most common way, catalysts provide more efficient and economical alternatives to known reactions. Arguably, sometimes, catalysts enable new and amazing transformations. Described herein are methodologies that expand the field of chiral tertiary amine catalysis. In the past few decades, chiral tertiary amine-catalyzed reactions have become one of the most versatile and useful methodologies in organic transformations. Among several modes of activation by chiral tertiary amines, the α,β-unsaturated acylammonium salts is the most underexplored despite its potential to reveal three reactive sites. Two projects focusing on novel transformations of α,β-unsaturated acylammonium salts are described. The first development showed the potential of a conjugated acylammonium species in a multicomponent process, namely a Michael Michael aldol β-lactonization cascade. Three achiral (52-72% yield) and ten enantioselective (19-61% yield) examples have been demonstrated with this methodology, with excellent dr (>19:1) in the optically active examples. In parallel, an expansion of a nucleophile-catalyzed Michael proton-transfer lactamization is described with a focus on the syntheses of chiral piperidi-2-ones and a dihydropiperidinone. The NMR study of the intermediate α,β-unsaturated acylammonium salts gave us an insight into decreased 1,2-reactivity which promoted addition at the β-carbon of these reactive intermediates.

Natural products continue to be an inspiration for drug discovery and development. Due to its potent biological activity in a variety of inflammatory assays,

the synthesis of rameswaralide is highly desirable, as it would enable sufficient quantities of the natural product that could be used to elucidate its mechanism of action along with a full structure activity relationship investigation.

In the second part, an approach to access the core structure of rameswralide is proposed, where the complexity is increased with each synthesized fragment. The bicyclic AD core of rameswaralide was obtained *via* a 6-step process from inexpensive commercially available starting materials. The tricyclic ABD and the tetracyclic core are being constructed involving either ring closing metathesis or organometallic coupling as a key step.

DEDICATION

To my parents, Phuong Ngoc Van and Anh-Thu Tran Thi, my grandmother, Lan Thi Nguyen, my sister, Quynh-Nhu Ngoc Van and my significant other, Samantha Lynn Kristufek

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Contributors

Transformation of β-lactone **2.14k** to **2.20** in Chapter II was finished by Mr. Martin Sevrin (former TAMU, 2013 REU student). Compounds **3.5a** and **3.6a** in Chapter III were prepared by Dr. Sreekumar Vellalath (post-doctoral scholar in the Daniel Romo's research group). Preparation of **4.57** in Chapter IV was assisted by Ms. Lauren Freeman (Baylor Chemistry Graduate Student), Mr. Kevin Gayler (Baylor Chemistry Graduate Student) and Mr. Javier Hernandez (Baylor Undergraduate Student).

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NOMENCLATURE

BTM	benzotetramisole
CDI	carbodiimidazole
DMAP	4-(dimethylamino)pyridine
HBTM	homobenzotetramisole
HOBt	1-Hydroxybenzotriazole
LA	Lewis acid
LB	Lewis base
NFSI	*N*-fluorobenzenesulfonimide
PMP	1,2,2,6,6-pentamethylpiperidine
PPY	4-pyrrolidinopyridine
TM	tetramisole·hydrochloride
TMSQD	*O*-trimethylsilylquinidine
TMSQN	*O*-trimethylsilylquinine

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CHAPTER I

INTRODUCTION*

1.1 Chiral α,β-Unsaturated Acylammonium Salts As Underexplored Intermediates for Organocatalysis

In the past few decades, organocatalysis has become a more centralized focus in organic transformations. The use of small, chiral organic molecules to catalyze a reaction has provided the chemical community with a complimentary alternative to transition metal catalyzed methods.[1] In this field, chiral tertiary amine-catalyzed reactions have become one of the most versatile and useful methodologies.[2] Several modes of activation by chiral tertiary amines are shown in scheme 1.1. While chiral ammonium enolate **1.1**[2-3] and acylammonium **1.2**[4] are the most commonly explored, the conjugated ammonium dienolate **1.3**[5] has recently been described in formal [4+2] cyclization. However, among these reactive intermediates, the α,β-unsaturated acylammonium[6] **1.4** is the most underexplored despite its potential to reveal three reactive sites.

The use of α,β-unsaturated acylammonium salts as intermediates was first described for the racemic synthesis of dihydropyrones **1.12** and **1.14** by Yamamura group in the 1960's (Scheme 1.2).[7] In this process, α,β-unsaturated acylammonium salts,

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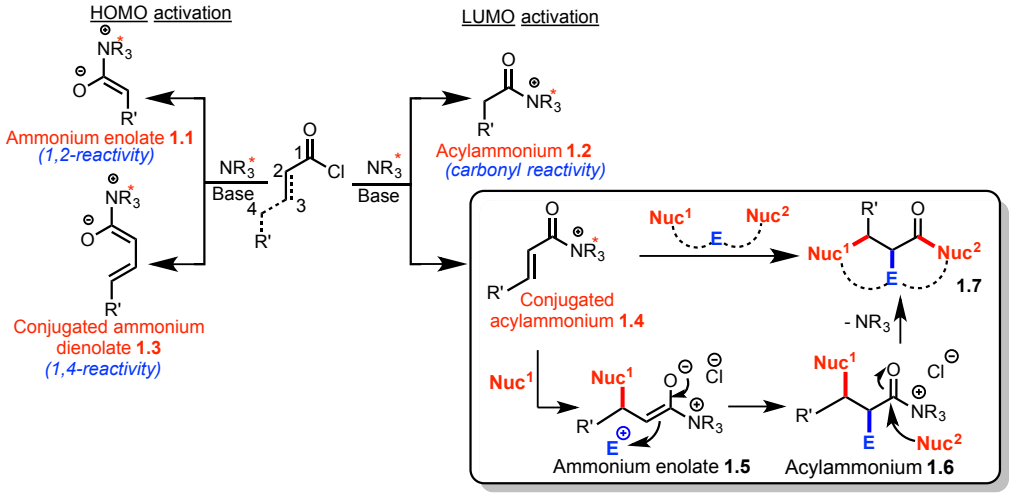
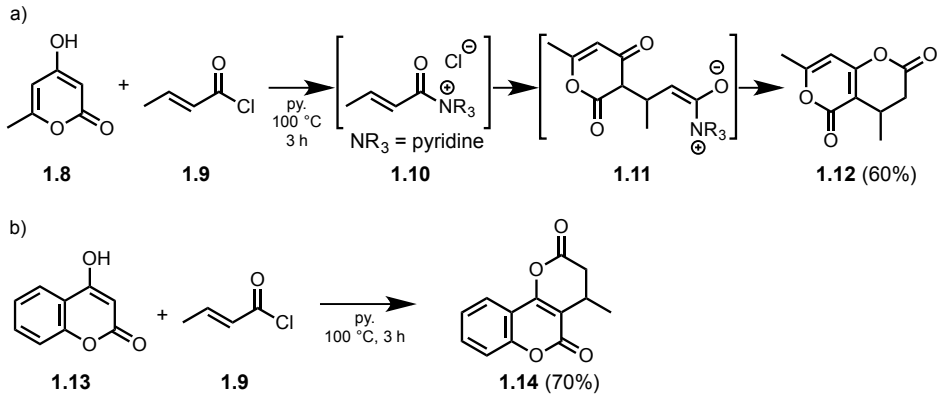
generated *in situ* by reaction of crotonoyl chloride **1.9** and pyridine, reacted with triacetic acid lactone **1.8** and coumarin **1.13** through an initial Michael addition followed by enol lactonization to form dihydropyrones **1.12**, and **1.14**, respectively.



Scheme 1.1 Generic modes of activation commonly used in chiral amine catalysis

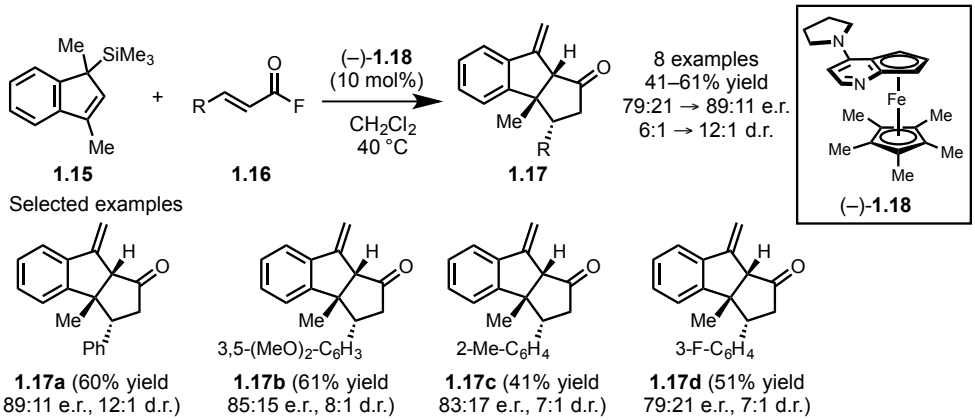


Scheme 1.2 Initial studies on α,β-unsaturated acylammonium salts by Yamamura

1.1.1 Fu's formal [3+2] annulation

More than 40 years later, the reactivity of α,β-unsaturated acylammonium salts was revisited by Fu and coworkers.[8] A formal [3+2] annulation was designed between a

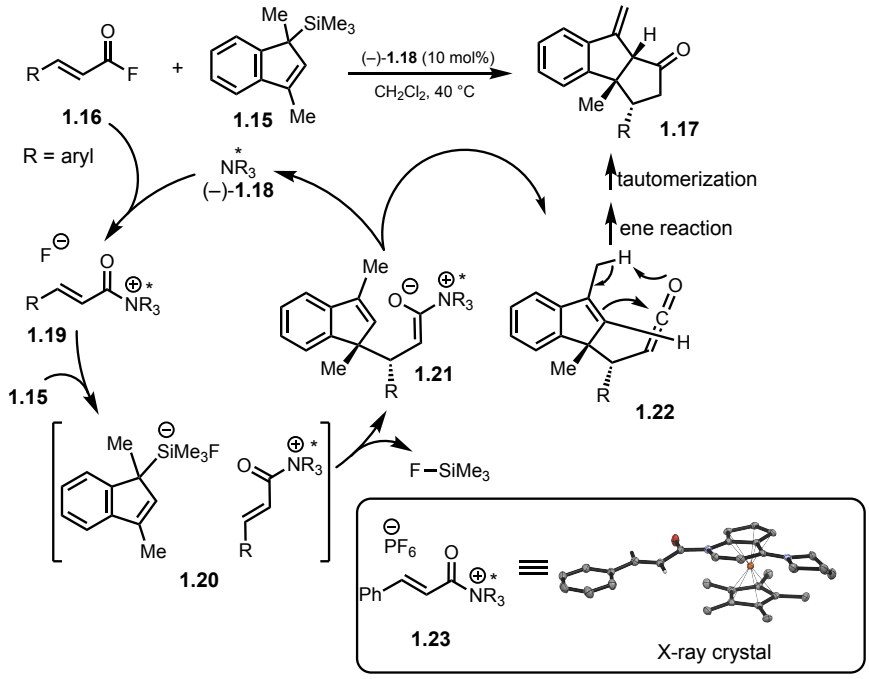
silylated indene **1.15** and an α,β-unsaturated acid fluoride. The enantioselective process made use of chiral PPY-based catalysts, **1.18**, previously developed and studied extensively by the Fu group. Several unsaturated acid derivatives were studied and the best results were obtained with acid fluoride **1.16**. A variety of aryl-substituted acid fluorides **1.16**, including those with diverse electronic properties and heteroaryl substitution, were tolerated in this transformation (Scheme 1.3).



Scheme 1.3 Fu's formal [3+2] annulation of α,β-unsaturated acylfluorides **1.16** with silylindene **1.15**

Under the optimized conditions, *in situ* formation of unsaturated acylammonium fluoride salt **1.19** is presumably followed by activation of the silylindene through attack by fluoride ion to generate ion pair **1.20**. Subsequent Michael addition by the allylsilane nucleophile and elimination of the catalyst from ammonium enolate **1.21** leads to ketene **1.22**, which undergoes an ene reaction with the pendant alkene to provide tricyclic adduct **1.17** in moderate yield and enantioselectivity (Scheme 1.3). Thus, a key step in this transformation is activation of silicon by fluoride at the appropriate time and location. One possibility is C-C bond formation at the stage of the silicate ammonium

ion pair **1.20**, involving the polarized C-Si bond as the nucleophile or as the precursor of an allylic carbanion. In addition, the Fu group provided the first information regarding the structure of an unsaturated acylammonium salt intermediate through X-ray analysis of the acylammonium **1.23** derived from cinnamoyl chloride and catalyst (+)-**1.18** (Scheme 1.4, inset). According to the X-ray crystal structure, the π system of **1.23** exists as an extended planar structure with the *s-cis* conformation. Across the carbonyl carbon-nitrogen system, the oxygen atom lies on the same side with the more bulky cyclopentadienyl ring of the catalyst, suggesting favored *si*- face nucleophilic addition. This seminal work was the beginning of a new era for the applications of α,β-unsaturated acylammonium salts in organocatalysis.

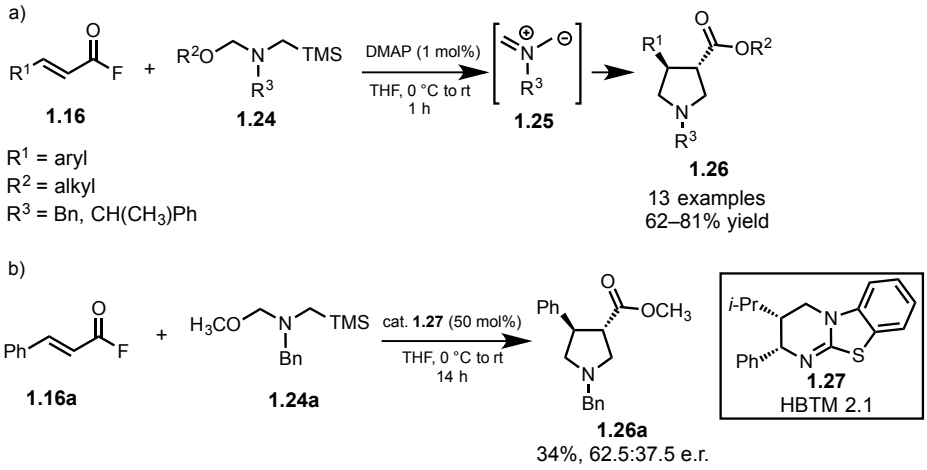


Scheme 1.4 Proposed mechanism for the formal [3+2] annulation of α,β-unsaturated acylammonium fluorides **1.19** and silylindenes **1.15**. Inset contains X-ray of unsaturated acylammonium salt **1.23**; PF_6^- anion and most of the hydrogens are omitted for clarity

1.1.2 Lupton's [3+2] annulation

In 2012, Lupton and coworkers utilized α,β-unsaturated acylammonium salts, again derived from acid fluorides, to react with *in situ* generated 1,3-dipoles through the action of liberated fluoride to form disubstituted pyrrolidines.[9] However, preliminary studies of a catalytic, enantioselective 1,3-dipolar cycloadditions employing unstabilized azomethine ylides did not provide high enantiomeric ratios, most likely due to a rapid background reaction of stoichiometrically formed azomethine ylides.[10,11] To address this issue, the authors hypothesized that catalytic amounts of azomethine ylide **1.25** could be

generated *via* fluoride ion mediated synthesis of the required 1,3-dipole. Thus, analogous to the work of Fu, liberated fluoride activates the nucleophile required for subsequent bond forming events, in this case [3+2] cycloaddition with the chiral unsaturated acylammonium salt. The authors first studied the reaction of acid fluoride **1.16** and azomethine ylide precursor **1.24** in the presence of the achiral Lewis base DMAP, resulting in formation of racemic pyrrolidines **1.26**. Screening of several Lewis bases demonstrated that DMAP was quite effective even with low catalyst loading (1 mol%). The ether moiety in precursor **1.24** was determined to be important for catalytic turnover. A variety of R^2 groups could be used ranging from methyl to *tert*-butyl. Diverse electronic properties of the R^1 β-aryl group of the acid fluoride **1.16** are also tolerated. The authors investigated the enantioselective variant of this reaction using a variety of chiral Lewis bases. Unfortunately, only modest yields and enantiomeric ratios were obtained, even with high catalyst loadings (50 mol%) of homobenzotetramisole (HBTM) 2.1 **1.27** (Scheme 1.5).[12]

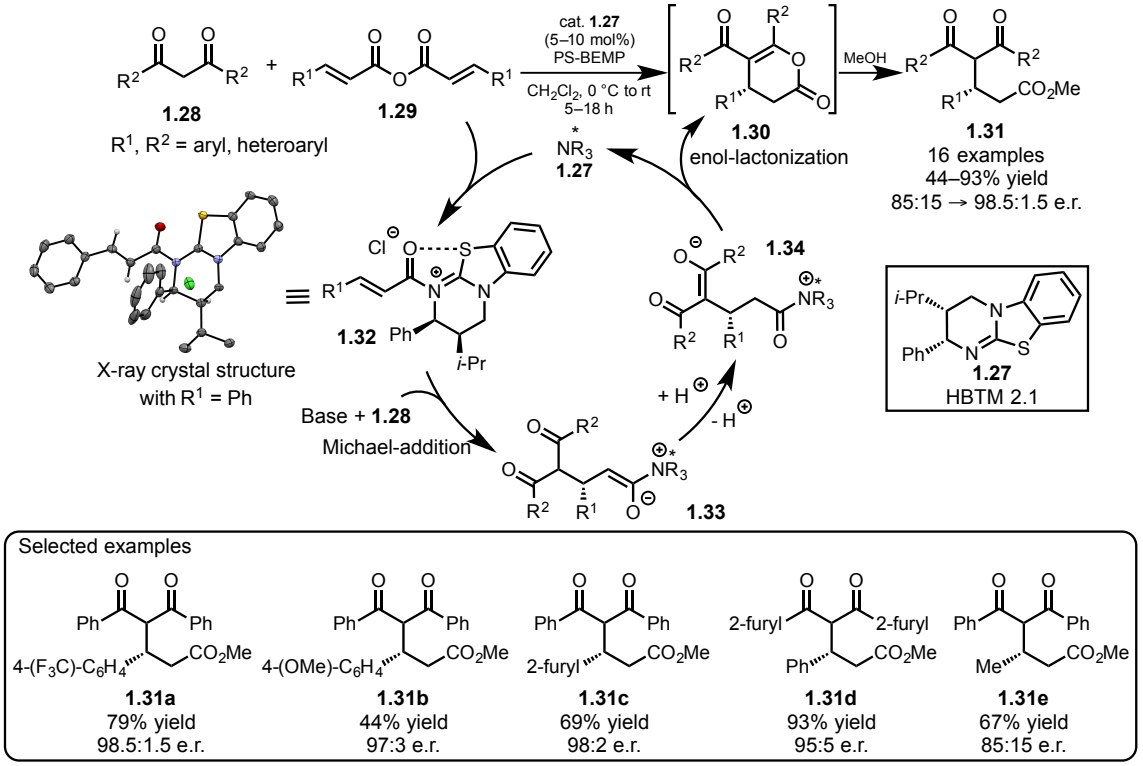


Scheme 1.5 Lupton's [3+2] annulation

1.1.3 Smith's Michael proton-transfer enol lactonization

In 2013, a flurry of activity detailing the broader utility of α,β-unsaturated acylammonium salts for highly enantioselective organocascade processes was reported independently by the groups of Smith and Romo with subsequent contributions by Matsubara. Smith and coworkers introduced the use of α,β-unsaturated acylammonium salts for enantioselective syntheses of dihydropyranones and dihydropyridones building on the earlier work of Yamamura.[13] The Smith group found that symmetrical acid anhydrides **1.29** were the optimal substrates for generation of α,β-unsaturated acylammonium salts *in situ* for subsequent Michael-proton transfer-enol lactonization (Scheme 1.6). The combination of an isothiourea catalyst **1.27** and the polymer-supported Brønsted base, PS-BEMP (polymer-supported 2-*t*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine), in CH_2Cl_2 proved optimal for this process. In this organocascade process, the α,β-unsaturated acylammonium salt **1.32**, generated from an (*E,E*)-unsaturated anhydride **1.29**, serves as a Michael acceptor with 1,3-diketone Michael donors **1.28** leading to an intermediate ammonium enolate **1.33**. Following proton transfer to the intermediate ammonium enolate **1.33**, enol lactonization ensues with the pendant acylammonium salt **1.34** to deliver dihydropyranone **1.30**, which was typically not isolated but subjected directly to methanolysis delivering a variety of esters **1.31** with excellent enantioselectivity. The reaction works best with anhydrides containing electron poor aryl groups vs. electron rich ones. Additionally, this reaction is stereospecific with respect to the olefin geometry of anhydrides **1.29** since enantiomeric products were obtained when the (*Z,Z*)-anhydride starting material was

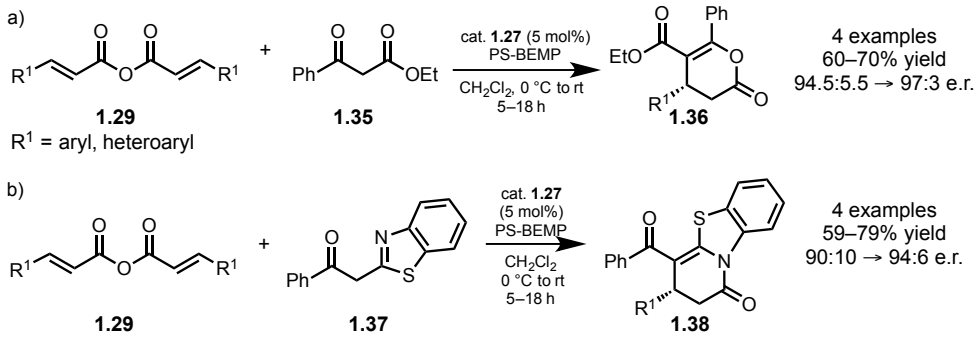
utilized, albeit with greatly reduced yield and enantioselectivity (65:35 e.r., for $R^1 = R^2 =$ Ph, not shown).



Scheme 1.6 Smith's Michael-proton transfer-enol lactonization with subsequent methanolysis delivering esters **1.31** and X-ray structure of an unsaturated HBTM-derived acylammonium salt **1.32** (R^1 = Ph)

The intermediate dihydropyranones **1.36** could also be isolated in uniformly excellent enantioselectivity with the use of β-ketoesters **1.35** as Michael donors (Scheme 1.7a). Use of more reactive benzothiazole ketone **1.37** as Michael donor delivered dihydropyridones **1.38** in good yields and uniformly high enantiomeric ratios even with

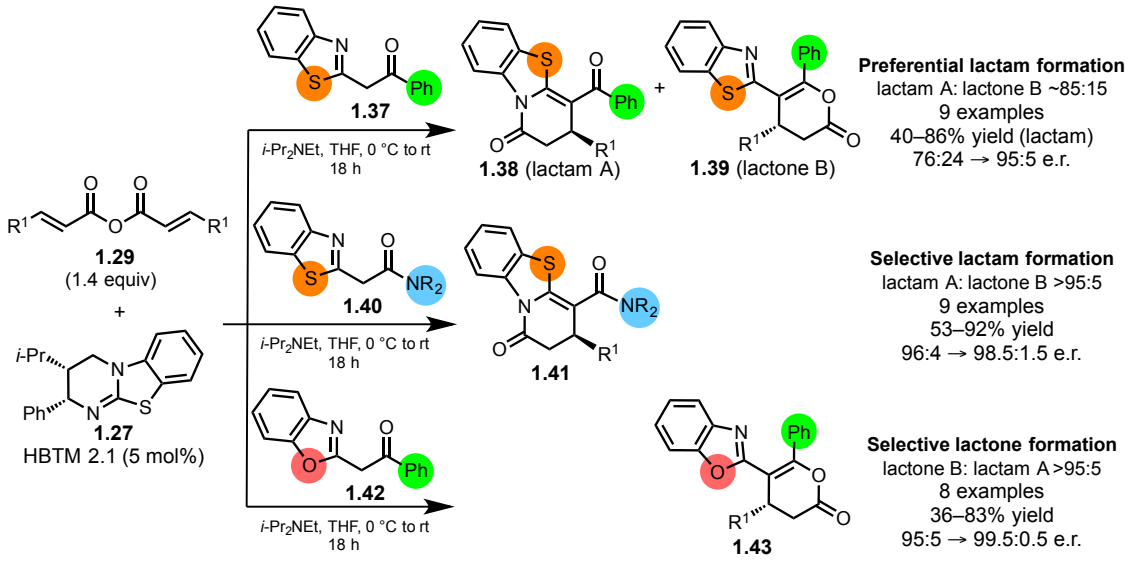
electron rich aromatic and aliphatic anhydrides, which were modestly tolerated in reactions with diketones **1.28** (Scheme 1.7b).



Scheme 1.7 Smith's use of 1,3-diketones and benzothiazole ketones as Michael donors

Recently, to further understand the selective formation of lactam **1.38** in the presence of benzothiazole **1.37**, Smith and coworkers investigated the analogous reaction of anhydride **1.29** and a variety of benzothiazoles and benzoxazoles (Scheme 1.8).[14] As reported in the earlier study,[13] 2-phenacylbenzothiazole **1.37** preferentially delivered lactam **1.38** to lactone **1.39** (~85:15 lactam **1.38** : lactone **1.39**) when reacted with anhydride **1.29**. The incorporation of electron donating benzothiazole amide **1.40** yielded lactam **1.41** as a single constitutional isomer. On a contrary, lactone **1.43** was obtained exclusively when benzoxazole **1.42** was employed as a Michael donor. In the case of benzothiazole nucleophiles **1.37** and **1.40**, an S-O interaction (see 1.1.5 for more information about S-O interaction) was invoked leading to the *s-trans* conformation of the corresponding enolates. In this conformation, the alkoxy moiety interacted with the sulfur atom on the benzothiazole moiety, resulting in a more exposed nitrogen

nucleophile to deliver the lactams as the preferred product. In all cases, the products were obtained in good to excellent enantioselectivity.



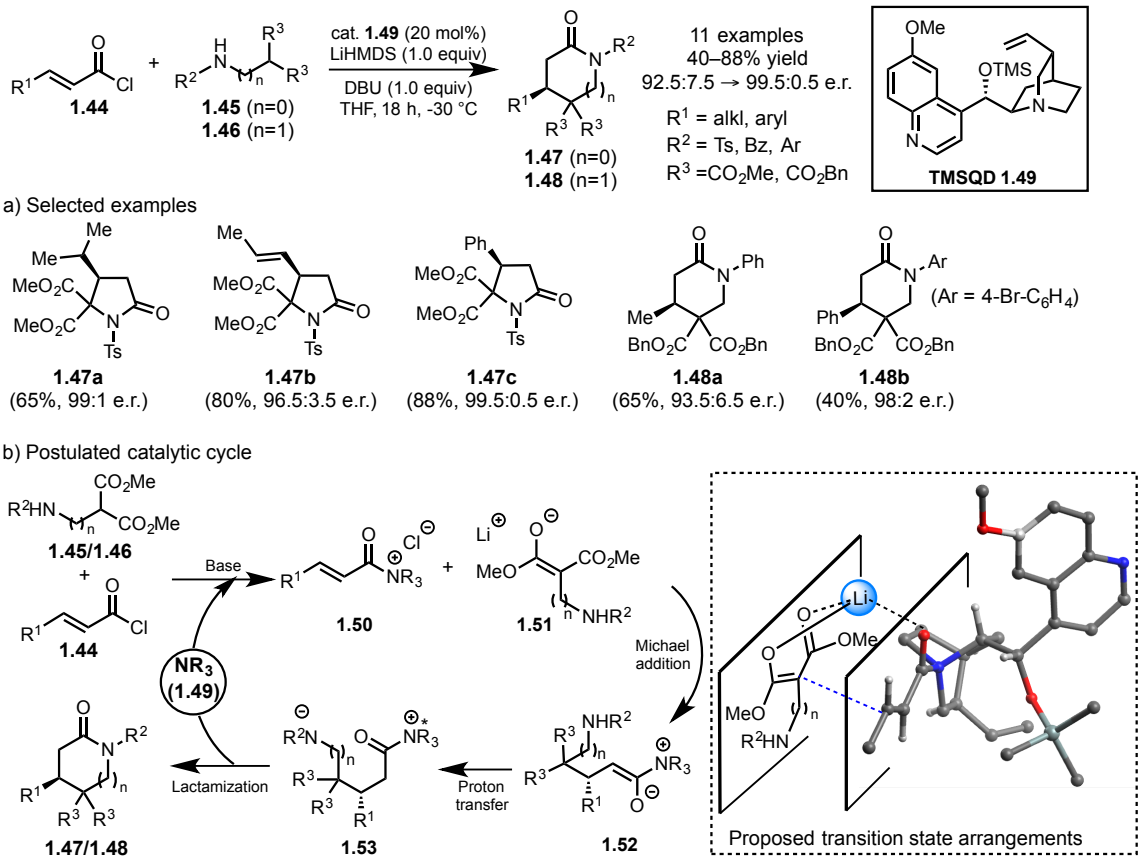
Scheme 1.8 Smith's extended study toward the chemo- and enantioselective, isothiourea-catalyzed annulation of anhydrides and benzoxazoles

1.1.4 Vellalath/Romo's Michael proton-transfer lactonization or lactamization (NCMPL)

In 2013, two consecutive publications by Romo and coworkers demonstrated the great utility of α,β-unsaturated acylammonium chlorides derived from commodity acid chlorides for organocascade processes, leading to pyrrolidinones[15] as well as both bi- and tricyclic-β-lactones.[16]

In the first organocascade process, a nucleophile (Lewis base)-catalyzed Michael proton-transfer lactonization (NCMPL) process provides facile access to pyrrolidinones, piperidin-2-ones, dihydropyranones and dihydropyridinones on gram scale. A highlight

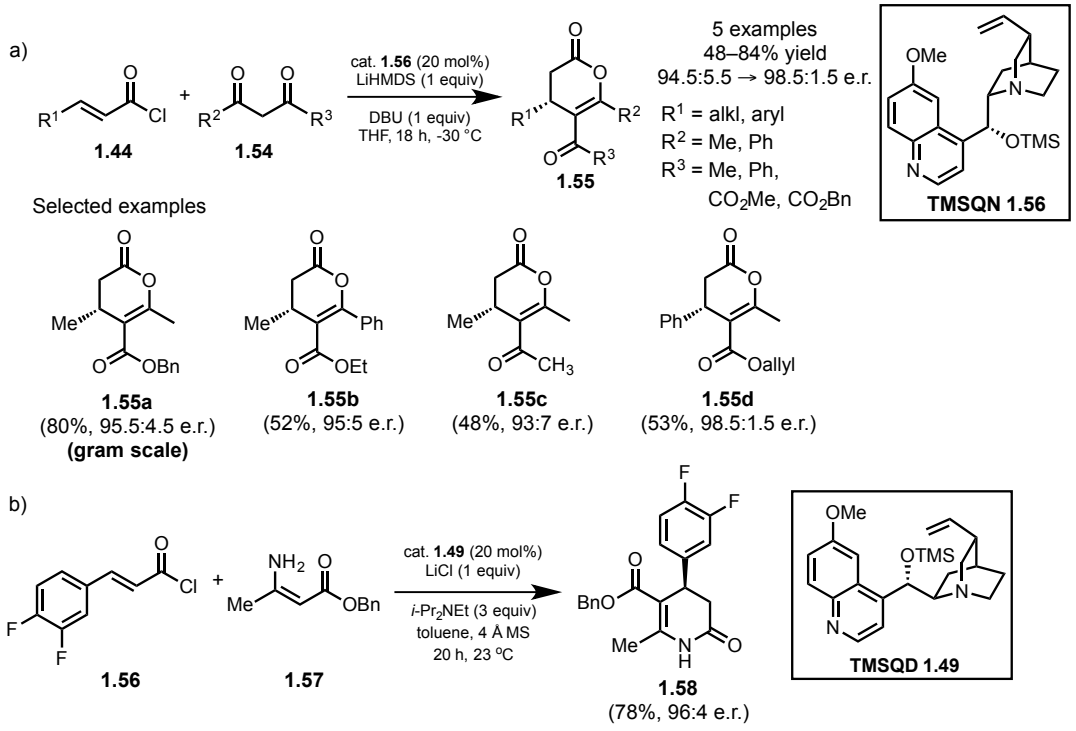
of this methodology is the ability to use commercially available acid chlorides and readily available cinchona alkaloids as Lewis bases, rendering this a highly practical method. The reaction partners in this process are readily accessible α- or β-aminomalonates **1.45** and **1.46** leading to pyrrolidinones **1.47** and piperidin-2-ones **1.48** with excellent enantioselectivity (Scheme 1.9).



Scheme 1.9 Romo's syntheses of pyrrolidinones and piperidinones through a nucleophile-catalyzed, Michael proton-transfer lactamization (NCMPL) organocascade

The proposed mechanistic pathway involves generation of a malonate enolate **1.51** with LiHMDS which undergoes a Michael addition with the α,β-unsaturated

acylammonium chloride **1.50**, derived from acylation of the quinidine catalyst **1.49**, to produce ammonium enolate **1.52**. Following proton transfer, the nitrogen anion undergoes lactamization with the pendant acylammonium **1.53** to deliver pyrrolidinones **1.47** and piperidones **1.48**. The lithium cation was found to play an important role in achieving high enantioselectivity, while the use of NaHMDS led to greatly reduced enantioselectivities (65:35 e.r.).



Scheme 1.10 Romo's syntheses of dihydropyranones and a dihydropyridone through Michael proton-transfer lactonization/lactamization

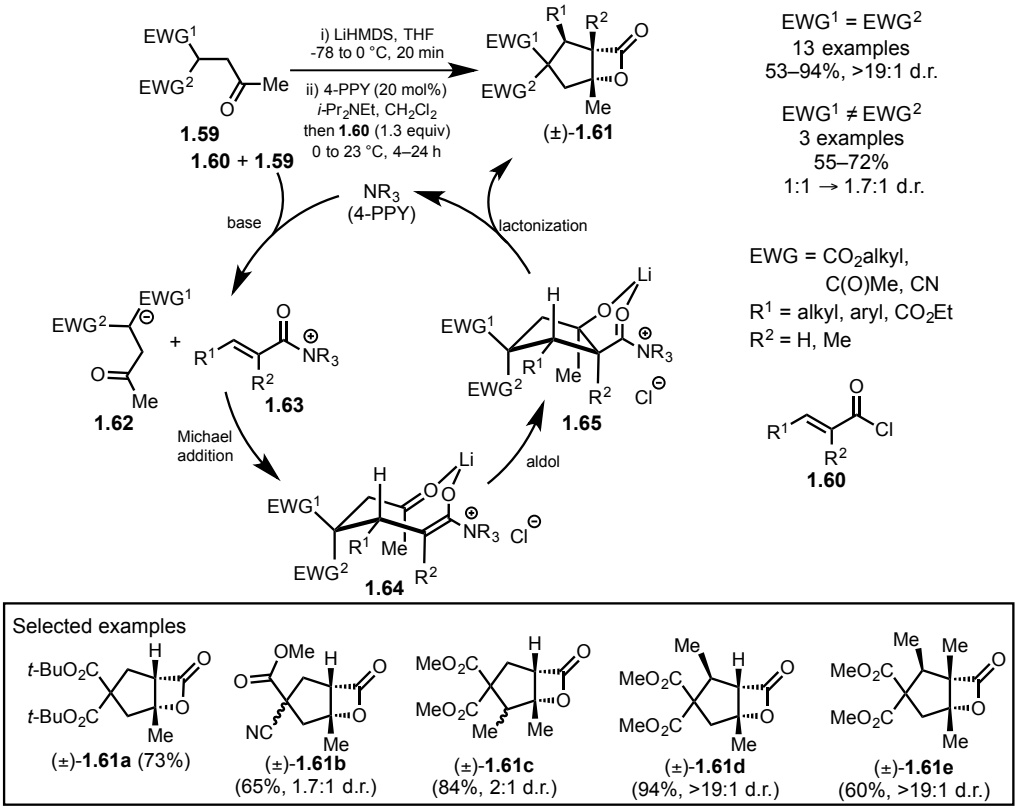
1,3-Dicarbonyl compounds such as β-ketoesters and 1,3-diketones **1.54** also resulted in the production of dihydropyranones **1.55** (Scheme 1.10) in a manner analogous to that previously described by Smith but with the direct use of commodity

acid chlorides. Another class of heterocyclic compounds, dihydropyridones, could be accessed *via* enamine **1.57** as Michael donor to deliver dihydropyridone **1.58**, but required modified reaction conditions (the hindered Bronsted base *i*-Pr_2NEt with LiCl and 4Å MS in toluene) for optimal enantioselectivity and yield. It is worth noting that dihydropyridone **1.58** was used in the synthesis of an α_{1a} adrenergic receptor antagonist.[17]

1.1.5 Liu/Romo's Michael aldol β-lactonization (NCMAL)

Building on an extensive body of work that enables rapid construction of bi- and tricylic β-lactones by a nucleophile (Lewis base)-catalyzed aldol-lactonization (NCAL) from ketoacid and ketoaldehyde substrates through ammonium enolate intermediates,[18] the Romo group developed an organocascade process for the rapid construction of related polycylic fused β-lactones from commodity α,β-unsaturated acid chlorides.[16] The Romo group initially developed an achiral nucleophile (Lewis base)-catalyzed, Michael aldol β-lactonization (NCMAL) reaction leading to good yields of bicyclic β-lactones **1.61** with generally high diastereoselectivity (Scheme 1.11). It was hypothesized that an ammonium enolate could be accessed *in situ* by Michael reaction between a malonate anion **1.62** and the α,β-unsaturated acylammonium chloride **1.63**. The derived ammonium enolate **1.64** can then undergo lactonization, in analogy to extensive previous aldol-lactonization studies, with the pendant ketone to deliver bicyclic β-lactone **1.61**. As previously observed, a β-substituent ($R^1 \neq H$) results in high diastereoselectivity (>19:1 d.r.) during the aldol step due to minimization of $A^{1,3}$-strain.[18m] When $EWG^1 \neq$

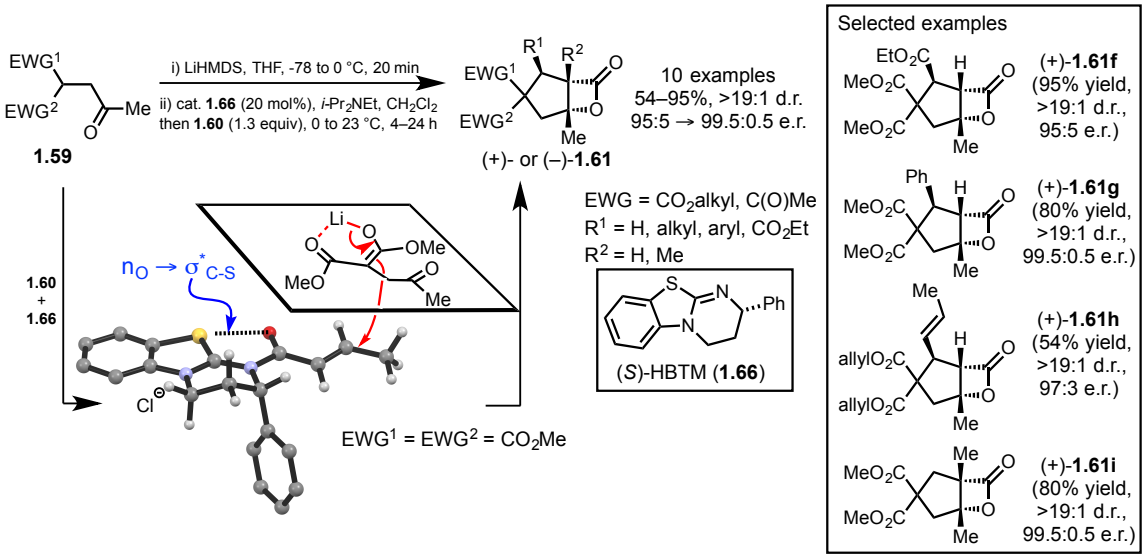
EWG^2, as expected, a mixture of diastereomers at the carbon bearing the EWGs is obtained (~1:1 d.r.).



Scheme 1.11 Romo's NCMAL strategy toward racemic, fused bicylic β-lactones

An enantioselective NCMAL was also realized with excellent enantiomeric ratios obtained using the isothiourea catalysts developed and popularized by Birman (Scheme 1.12). The facial selectivity was explained in a similar fashion as for the previous NCAL process[18j] and also as described by Smith.[13] The α,β-unsaturated acylammonium structure derived from HBTM **1.66** adopts a lower energy boat conformation for the pyrimidine ring and is expected to exist in the extended *s-cis* configuration, owing to the minimization of non-bonded interactions and the proposed $n_o \rightarrow \sigma^*_{C\text{-}S}$ interaction[13-14,19]

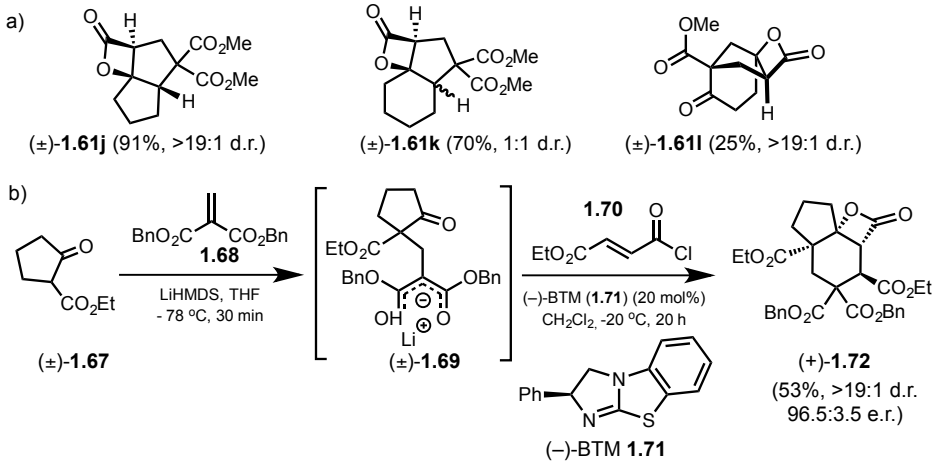
between the acyl oxygen and the sulfur atom of the catalyst, initially proposed by Birman[19d] for isothiourea catalysts. This conformation leads to a pseudoaxial orientation of the phenyl group in catalyst **1.66**, effectively blocking one face of the unsaturated acylammonium intermediate leading to the observed facial selectivity and absolute stereochemistry of the adducts.



Scheme 1.12 Enantioselective NCMAL with proposed rationale for the observed facial selectivity

The potential of the NCMAL process for rapidly generating molecular complexity was demonstrated through several examples leading to fused and bridged tricyclic β-lactones (*e.g.* **1.61j-l**, Scheme 1.13a). In addition, the use of carboxylic acids activated *in situ* with TsCl broadens the scope of useful substrates for the NCMAL process. As a further extension of this organocascade, a multi-component process was developed with ketoester **1.67**, alkene **1.68**, and acid chloride **1.70**, involving a Michael

Michael aldol lactonization process to deliver the tricyclic β-lactone **1.72**. The initially formed racemic enolate **1.69** presumably undergoes kinetic resolution during the subsequent NCMAL process to deliver tricyclic-β-lactone with high enantioselectivity (Scheme 1.13b).

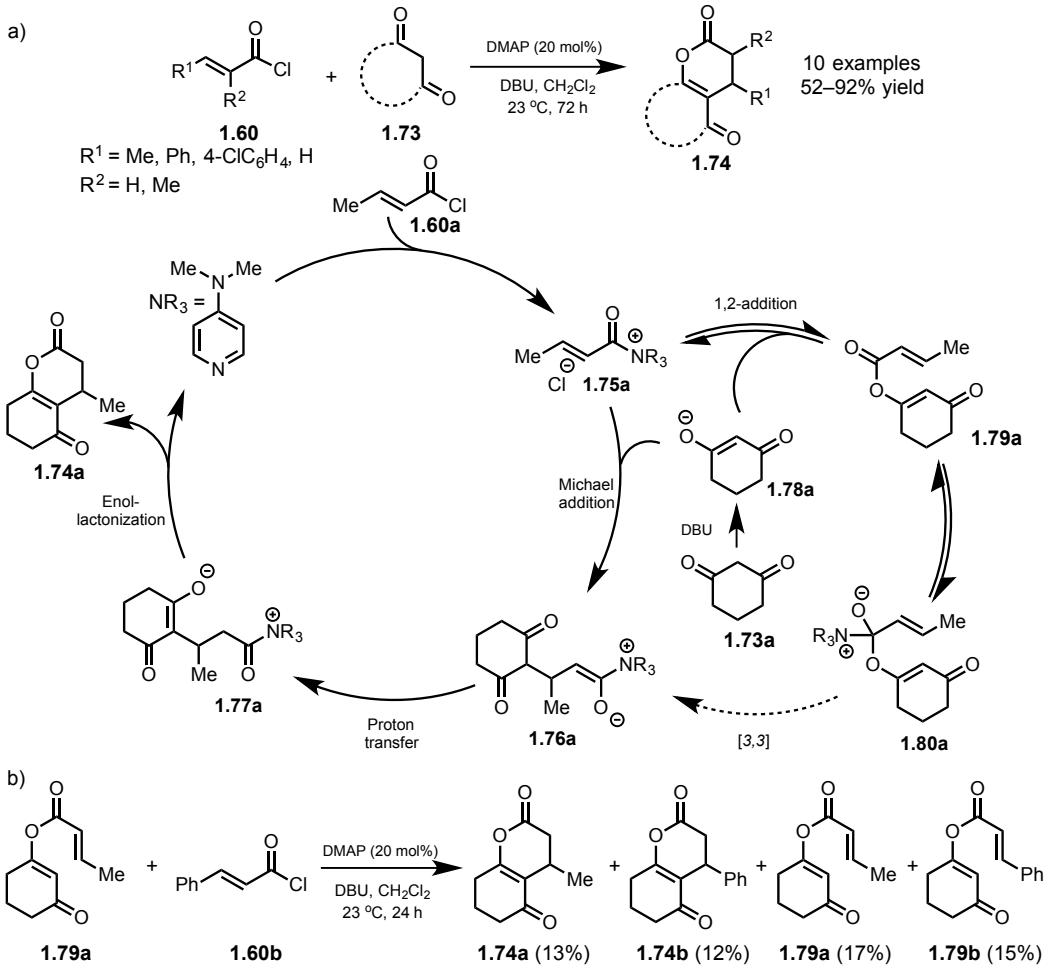


Scheme 1.13 a) Linearly fused and bridged tricyclic-β-lactones accessed through the NCMAL organocascade process; b) Development of a multicomponent, organocascade Michael Michael aldol lactonization delivering the tricyclic β-lactone through an α,β-unsaturated acylammonium salt

1.1.6 Michael proton-transfer lactonization process (NCMPL) delivering polycyclic enol lactones

As a follow-up study, the Romo group investigated the reaction of *cyclic* 1,3-diketones **1.73** as Michael donors,[13,15] substrates that had not been explored previously, and that provide access to polycyclic dihydropyranones and dihydropyridones (Scheme 1.14a).[20] At first glance, these *cyclic* Michael donors appear similar to *acyclic* 1,3-

diketone **1.28** and β-ketoesters **1.35** described by Smith, but conditions that worked well for *acyclic* Michael donors provided unsatisfactory yields with **1.73,** likely due to the inability to generate cyclic chelates with Li cations (see Scheme 1.9). Ultimately, optimal conditions for cyclic β-diketones and β-ketolactones involved using two equivalents of the Michael donor, DBU as a Brønsted base and DMAP as an achiral Lewis base. Prolonged reaction times (72 h) were necessary for optimal yields of adduct **1.74**. This was determined to be a result of formation of an enol ester by-product **1.79a**, which only slowly re-enters the catalytic cycle (Scheme 1.14a)**.** A variety of both substituted acid chlorides **1.60** and diketones **1.73**, including aliphatic and aromatic substitutents were tolerated providing 52–92% yields of polycyclic enol lactones. While both α- or β-monosubstituted acid chlorides participated in this NCMPL process, α, β-disubtituted acid chlorides were unreactive. Acid chlorides containing electron rich aromatic (4-methoxyphenyl) substituents at the β-position were also unreactive. The proposed mechanism involves Michael addition of enolate **1.78** to the unsaturated acylammonium chloride **1.75** leading to ammonium enolate **1.76**. A proton-transfer is then followed by an enol-lactonization process to deliver adducts **1.74** with regeneration of the Lewis base promoter, DMAP (Scheme 1.14a). As mentioned above, an enol ester by-product **1.79** could be isolated and is presumably derived from direct acylation of enolate **1.78** with acylammonium salt **1.75** or acid chloride **1.60**. However, a cross-over experiment suggested that this enol-esterification is reversible under the reaction conditions since both cross-over products **1.74b** and **1.79b** were isolated (Scheme 1.14b).

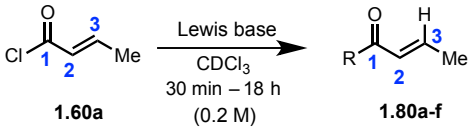


Scheme 1.14 a) Proposed mechanism for Romo's Michael enol-lactonization as shown for crotonoyl chloride **1.60a** and 1,3-cyclohexanedione (**1.73a**); b) cross-over experiment with ester **1.79a** and cinnamoyl chloride (**1.60b**).

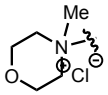
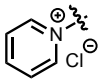
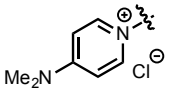
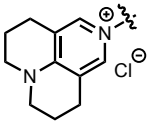
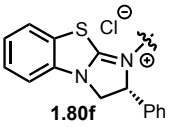
To gain further insights into the reactivity of unsaturated acylammonium salts, the Romo group analyzed the ^{13}C NMR chemical shifts of the C3-carbon (β-carbon) of various unsaturated acylammonium salts and compared those with the acid chloride (Table 1.1) in analogy to studies previously undertaken to study Lewis acid activation of

unsaturated carbonyls to gain information regarding relative Lewis acid strengths.[21] In the case of *N*-methylmorpholine and pyridine, the derived acylammonium salts **1.80b** and **1.80c** exhibited upfield shifts ($\Delta\delta \sim +3$) of the β-carbon and it was noted that formation of the acylammonium was not complete even after 18 h since starting acid chloride was detected. This also suggests a likely rapid equilibrium between the acylammonium salt and the starting acid chloride.[22] When DMAP and 9-azajulolidine were used as Lewis bases to generate the corresponding acylammonium salts, a downfield shift of the β-carbon compared to the acid chloride was observed ($\Delta\delta \sim -3$) suggesting an increase in electrophilicity at the β-carbon consistent with their reactivity as Michael acceptors. On the other hand, acylammonium salt **1.80f** formed with BTM **1.71** which rapidly proceeded to completion (< 2 min) and did not exhibit significant chemical shift differences ($\Delta\delta \sim +0.5$). Based on this evidence, it was proposed that while formation of the unsaturated acylammonium salt may not provide an activation of the acid chloride *per se*, formation of the acylammonium salt provides a steric impediment to the otherwise rapid 1,2-addition to the carbonyl carbon. Thus, formation of chiral unsaturated acylammonium salts enables 1,4 addition to become the predominant pathway and provides a chiral environment for enantioselective Michael additions while at least retaining the activity of the starting acid chloride.

Table 1.1 ^{13}C NMR comparison of acylammonium salts with an acid chloride and amide



1.60a **1.80a-f**

Entry	Lewis base	R	^{13}C NMR δ (ppm) C3	Δδ C3[a]
1	-	Cl	152.9	-
2	morpholine	 **1.80a**	142.0	+10.9
3	*N*-methyl morpholine	 **1.80b**	149.6	+3.3
4	pyridine[b]	 **1.80c**	149.6	+3.3
5	DMAP	 **1.80d**	156.8	-3.9
6	9-azajulolidine	 **1.80e**	155.6	-2.7
7	(+)-BTM **1.71**	 **1.80f**	152.4	+0.5

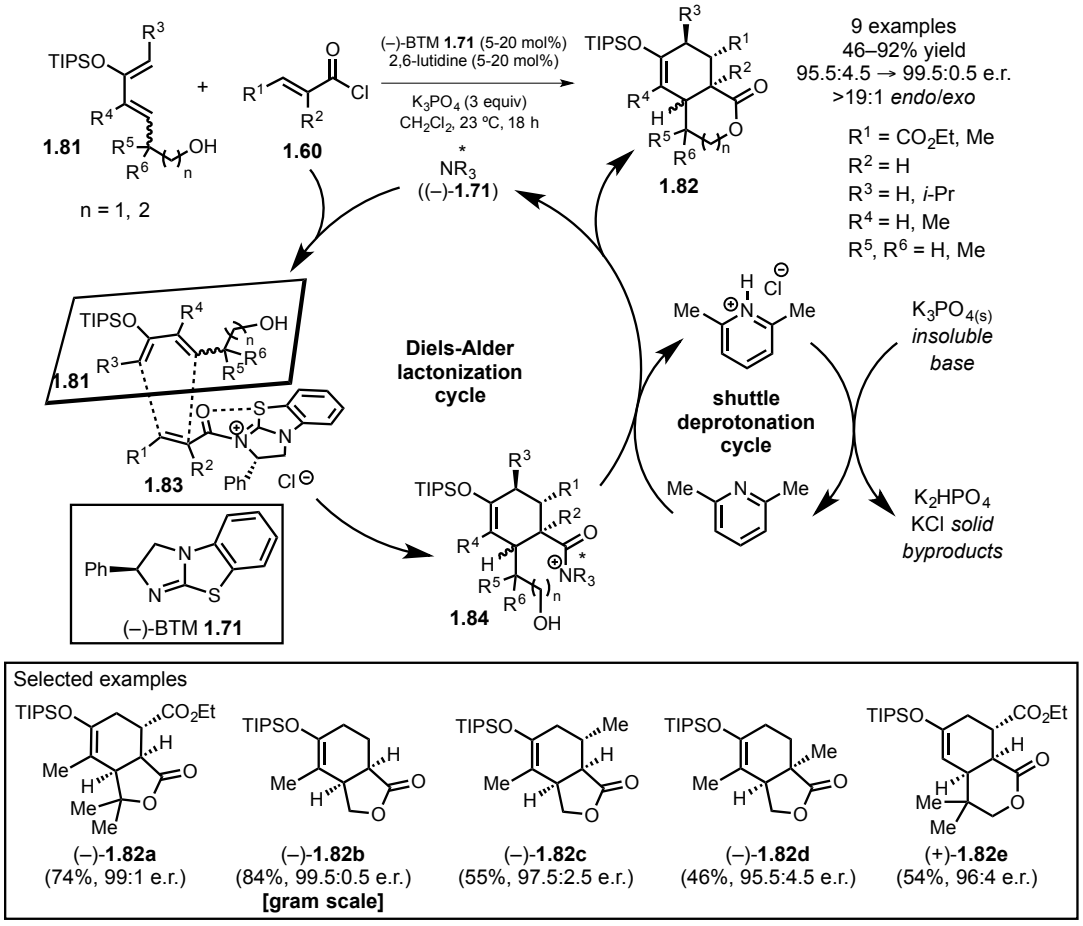
[a]Change in chemical shift for ^{13}C of C3 in the acylammonium salt relative to C3 of acid chloride; [b]The use of pyridine led to slow formation of the acylpyridinium requiring 18 h to reach only 30% completion, compared to other Lewis bases.

1.1.7 Abbasov/Romo's Diels-Alder lactonization (DAL)

In 2014, the Romo group described the first use of α,β-unsaturated acylammonium salts as dienophiles in enantioselective Diels-Alder lactonization (DAL) organocascade processes.[23] *Cis* and *trans* bicyclic γ- and δ-lactones were targeted due to their presence in bioactive terpenoids and pharmaceuticals. This plan was executed by

the use of the Danishefsky diene with a tethered alcohol. An *in situ*-generated α,β-unsaturated acylammonium **1.83** undergoes cycloaddition with diene **1.81** followed by lactonization of the derived acylammonium **1.84** to ultimately afford bicyclic cycloadducts **1.82** (Scheme 1.15). Building on Letcka's concept of shuttle bases,[24] 2,6-lutidine and K_3PO_4 were found to be optimal as HCl scavengers in the DAL process. Optimization revealed several important facts about this reaction. First, chiral isothioureas are superior Lewis base catalysts compared to cinchona alkaloids and chiral 4-PPY in this reaction. Second, the Brønsted base used in the reaction dictates the *endo*/*exo* selectivity! Finally, chlorinated solvents (such as CH_2Cl_2) led to the highest diastereo- and enantioselectivities. Computational studies in collaboration with the Tantillo group indicated that the *endo* transition state leading to intermediate **1.84** was 1.3 kcal/mol lower in energy compared to the *exo* transition state, agreeing with the observed *endo*/*exo* ratios. The facial selectivity of the Diels-Alder step was also favored by >5 kcal/mol based on computation and this was consistent with the observed high enantioselectivities. The acid chlorides that participate in the DAL process include a wide range of different electronic properties as seen in the derived cycloadducts **1.82**. The reaction is stereospecific with *cis*- and *trans*-fused bicyclic lactones **1.82** accessible through the use of (*Z, E*) or (*Z, Z*)-dienes **1.81**. Both primary and tertiary pendant alcohols were tolerated in the cascade. This may seem surprising, but it is known that ester formation from alcohols and *N*-acylammonium acyl donors analogous to **1.83** depends on the basicity of the anion. In the present example, the relatively non-basic chloride in **1.83** would provide minimal assistance for proton-transfer from hydroxyl in

1.81, a prerequisite for facile acyl transfer. A further detailed study of this work was later published.[22]

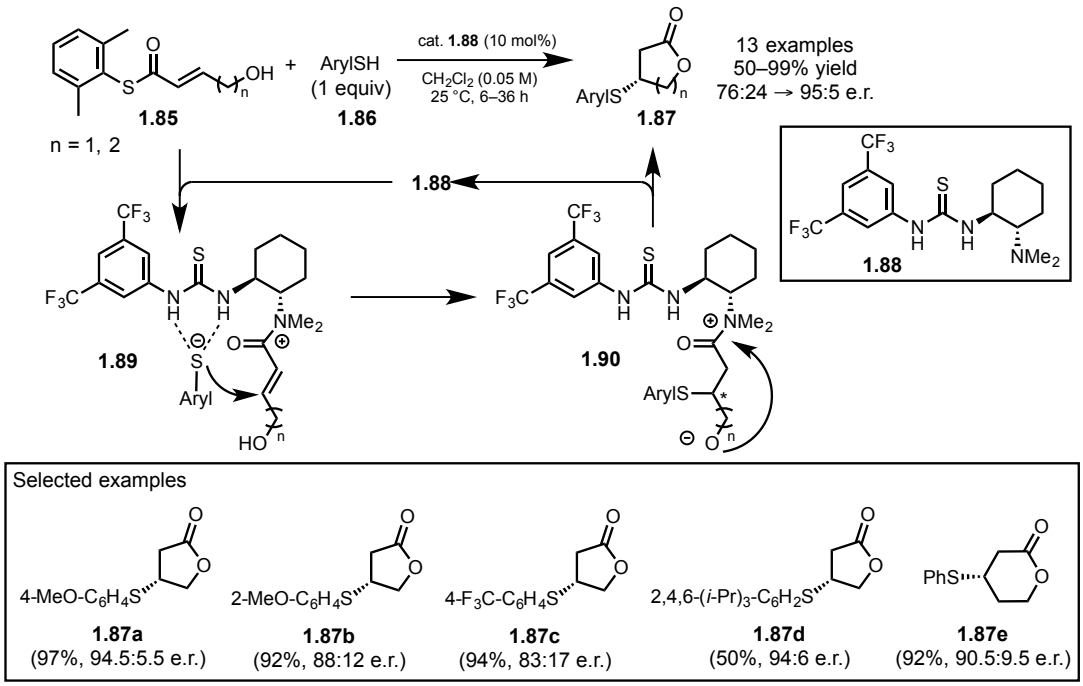


Scheme 1.15 α,β-Unsaturated acylammonium salts as dienophiles in Diels-Alder lactonization (DAL) organocascade developed by Romo and coworkers.

1.1.8 Matsubara's thia-Michael proton-transfer lactonization or lactamization

In 2014, β-mercaptolactones were synthesized by Matsubara and co-workers *via* α,β-unsaturated acylammonium salts using unsaturated thioester **1.85** as a substrate.[25] The concept was to use a bifuntional catalyst (such as **1.88**) with both a tertiary amine

and a thiourea functionality (Scheme 1.16). Following formation of the α,β-unsaturated acylammonium salt **1.89**, the thiourea moiety of the catalyst can direct the thia-Michael addition leading to thioether intermediate **1.90**. Subsequently, the hydroxyl group of this intermediate lactonizes to release the catalyst. To this end, a variety of β-mercaptolactones **1.87** were prepared in good yields and moderate to good enantioselectivity employing thiophenol **1.86** as the Michael donor. In the absence of thiophenol **1.86**, the corresponding lactone product is formed in lower enantioselectivity and required much longer reaction time.

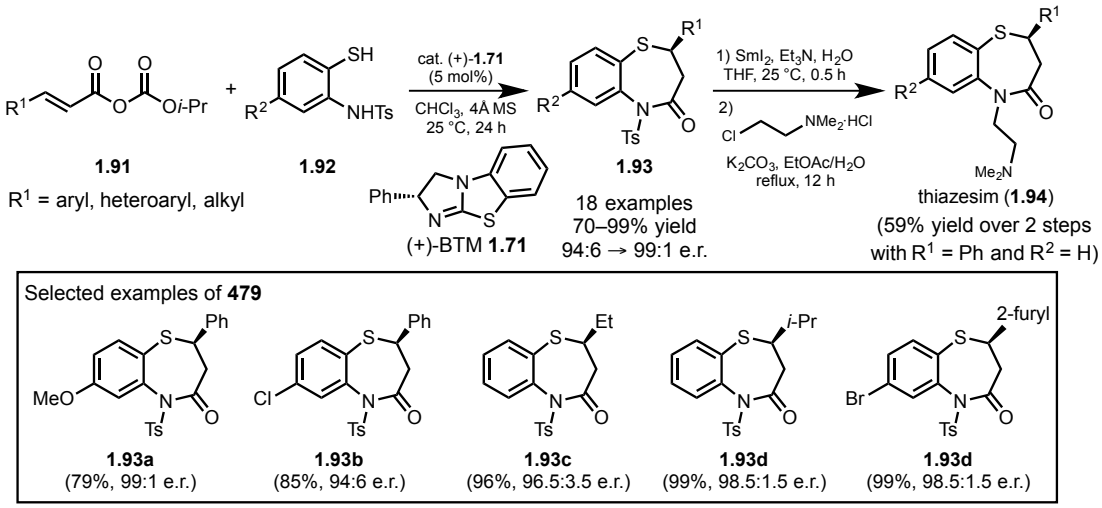


Scheme 1.16 β-mercaptolactones accessed *via* α,β-unsaturated acylammonium salt using a bifunctional catalyst by Matsubara

A variety of thiophenol starting materials **1.86** could be employed in this process. However, electron-rich thiophenols generally led to higher enantiomeric ratios than electron-poor derivatives. Additionally, *ortho*-substituted thiophenols diminished the enantioselectivity. While achieving good enantiocontrol, bulky thiophenols usually gave lower yields of the desired product likely due to the slower thia-Michael process. In contrast to thiophenol, aliphatic thiols afforded much lower yields and enantiomeric ratios of the product.

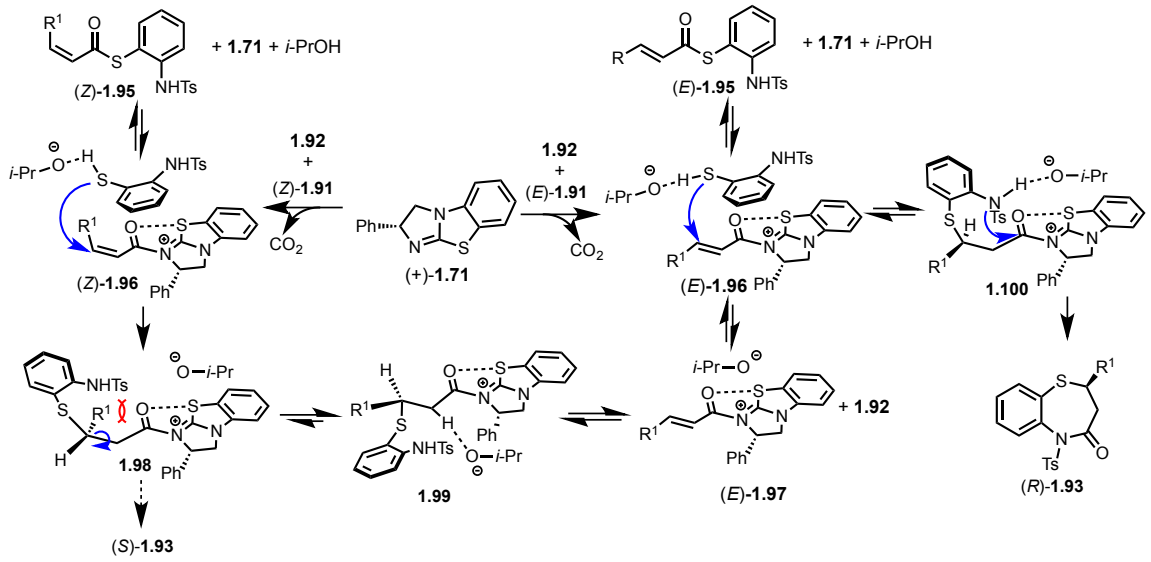
In 2015, following on their earlier work with thia-nucleophiles, Matsubara described the enantioselective synthesis of 1,5-benzothiazepines using unsaturated acylammonium salts.[26] This structural motif is found in antidepressant agents and in potential drugs for treatment of hypertension and angina. Mixed anhydride **1.91** was combined with aminothiophenol **1.92** to yield the desired benzothiazepines **1.93** in high yield and excellent enantioselectivity (Scheme 1.17). Screening of various catalysts including cinchona alkaloid and cinchona-alkaloid thiourea derivatives revealed the superiority of BTM **1.71** in this reaction. High enantioselectivity was observed in $CHCl_3$ and addition of 4Å molecular sieves gave optimal yields of desired product. Surprisingly, while the reactions in toluene, benzene and CH_2Cl_2 gave similar yields as that of in $CHCl_3$, the reaction in THF delivered undesired 1,2-addition products (such as **1.95**, see Scheme 1.18). Interestingly, a bulky *i*-Pr on the carbonic anhydride **1.91** and a tosyl group on the nitrogen of aminothiophenol **1.92** were necessary to ensure high yield of the desired adduct **1.93**. A variety of unsaturated anhydrides **1.91** with varying electronic and steric properties were tolerated providing moderate to excellent yield and

typically high enantioselectivity. On the other hand, electron-rich thiophenols **1.92** gave higher enantioselectivities compared to electron-poor analogues. The utility of the benzothiazepines accessible by this methodology was demonstrated by a concise 2-step, enantioselective synthesis of the antidepressant, thiazesim (**1.94**).



Scheme 1.17 Asano and Matsubara's synthesis of 1,5-benzothiazepines

Based on their mechanistic study, the authors proposed the catalytic cycle shown in Scheme 1.18. Unsaturated acylammonium salt **1.96** is formed when anhydride **1.91** reacts with catalyst **1.71**. As in previous reactions involving isothiourea catalysts, formation of the unsaturated acylammonium salt directs the conjugate addition of thiophenol **1.92** to deliver either diastereomeric sulfide intermediate **1.100** or **1.98**. Due to steric strain, **1.98** may interconvert with a more stable conformer **1.99**. Conjugated acylammonium salt (*E*)-**1.97** may then be generated *via* reversible deprotonation and elimination, followed by reversible thia-Michael addition to form **1.100** and finally, cyclization to deliver adduct **1.93**.

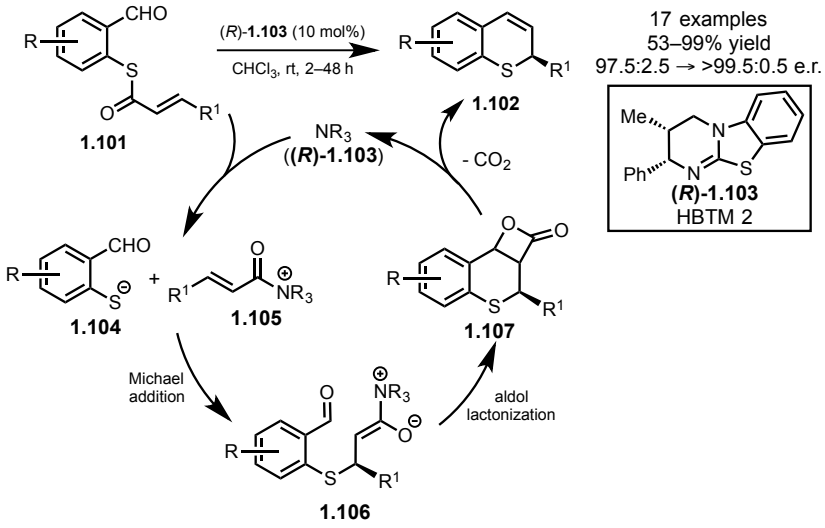


Scheme 1.18 Proposed reaction pathway for the Matsubara's thia-Michael lactamization process

1.1.9 Birman's thia-Michael aldol β-lactonization decarboxylation delivering thiochromenes

Recently, thiochromene compounds attracted attention from the synthetic community due to their potential in drug design. An enantioselective synthesis has been reported by Birman and coworkers, employing α,β-unsaturated acylammonium salt as the intermediate (Scheme 1.19).[27] In the presence of HBTM 2 (**1.103**), thioester **1.101** bearing an adjacent aldehyde was converted to enantio-enriched thiochromene **1.102** in high yield. Substrate **1.101** includes both electron withdrawing- and electron donating-aromatic R^1 substituents. Aromatic heterocyclic and saturated cyclic alkyl groups R^1 were also effective as substrates in this transformation. Variants on the benzothio moiety (R group) were also tolerated albeit generally gave lower yield compared to their

substituent free (R = H) counterpart. The proposed mechanism started with the elegant generation of unsaturated acylammonium **1.105** and thiolate **1.104** *via* the interaction of the thioester **1.101** and the catalyst **1.103**, followed by a thia-Michael reaction. The subsequent ammonium enolate adduct **1.106** undergoes an intramolecular aldol β-lactonization process to form **1.107**, which readily eliminates CO_2 to deliver thiochromene **1.102**.

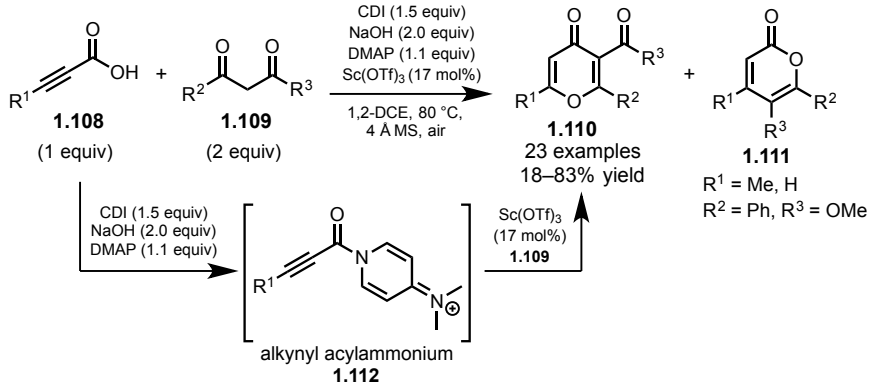


Scheme 1.19 Birman's sysnthesis of thiochromene

1.1.10 Alkynyl acylammonium salts as reactive intermediates

While unsaturated acylammonium salts were exclusively generated from alkenyl carboxylic derivatives up to this point, Lu, Du and coworkers introduced a new type of unsaturated acylammonium, the alkynyl acylammonium (Scheme 1.20).[28] In this study, propiolic acid **1.108** was activated *in situ* by carbodiimidazole (CDI) and subsequently formed alkylnyl acylammonium **1.112** in the presence of DMAP. The reactive intermediate **1.112**, as an electrophilic 3C synthon, underwent a formal [3+3] annulation

with 1,3-dicarbonyl compound **1.109** to deliver pyran-4-ones **1.110**. This reaction tolerates a diverse array of β-keto esters **1.109** (R^2 = aryl, alkyl; and R^3 = *O*-alkyl), however, aromatic R^2-containing **1.109** generally gave higher yields than the alkyl R^2-analogues. β-keto ester also showed better reactivity than 1,3-diketones as nucleophiles in this reaction. Interestingly, cyclic 1,3-diketones such as 1,3-cyclohexanedione was not compatible in this reaction under the optimized conditions, which was also observed by Romo, Vellalath, and coworkers[20] (see section 1.1.6). Various substituents on propiolic acid **1.108** (R^1) are tolerated with aromatic R^1 groups generally giving higher yields of **1.110** than those with aliphatic R^1, except for when R^1 = 2-furyl and 1-napthyl. Surprisingly, when R^1 = Me and H, pyran-2-ones **1.111** were also obtained.



Scheme 1.20 Alkynyl acylammonium

CHAPTER II

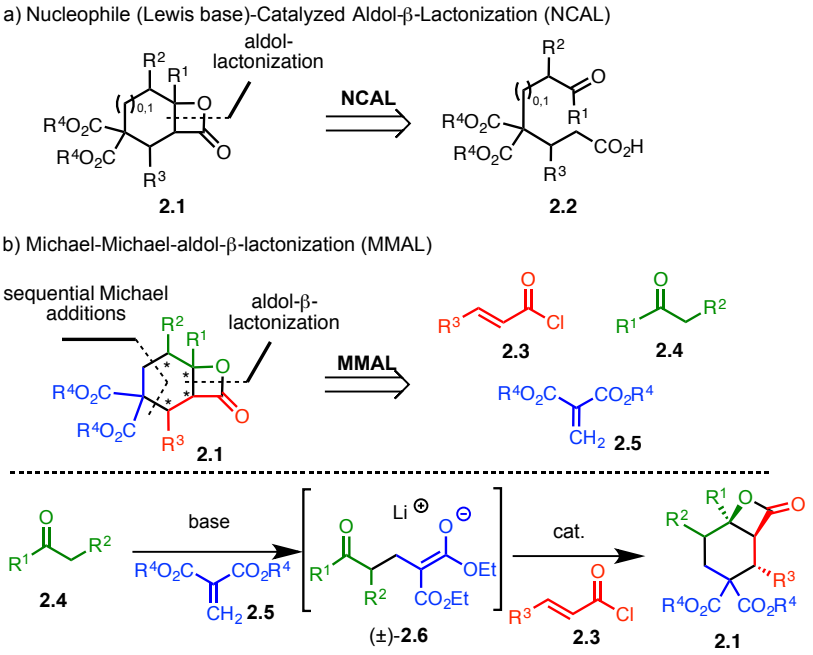
MULTICOMPONENT, CATALYTIC, ENANTIOSELECTIVE MICHAEL MICHAEL ALDOL β-LACTONIZATION (MMAL)

2.1 Introduction

Multicomponent reactions (MCRs) are atom economical transformations in which three or more substrates are combined to form a product in one pot without isolation of intermediates.[29] Compared to traditional sequential syntheses, MCRs can quickly deliver complex scaffolds by multiple-bond formations while significantly reducing the time of preparation, purification, as well as labor and cost which explains their great utility for chemists in a time when sustainable synthesis is sought.[30] Development of new MCRs, substantially increases the numbers of accessible products by simply varying each component making these processes popular for medicinal chemistry and drug discovery.[31] Despite these advantages, relatively few multicomponent processes have emerged since their initial development nearly 100 years ago, and asymmetric MCRs are even more limited.[29,32] The field of organocatalysis has recently increased dramatically,[33] with applications increasing tremendously owing to their varied benefits.[34] Not surprisingly, the marriage of organocatalysis and MCRs is highly desirable.[35]

Because the carbonyl moiety, particularly ketones and aldehydes, are ubiquitous components of MCRs, iminium catalysis is one of the most common strategies employed for organocatalytic MCRs.[29,31-32,35] Seminal work in this area employing secondary amines includes the groups of Barbas,[36] MacMillan,[37] Jørgensen,[38] and Enders.[39]

However, to the best of our knowledge, MCRs utilizing tertiary amine catalysis remain elusive.[29]



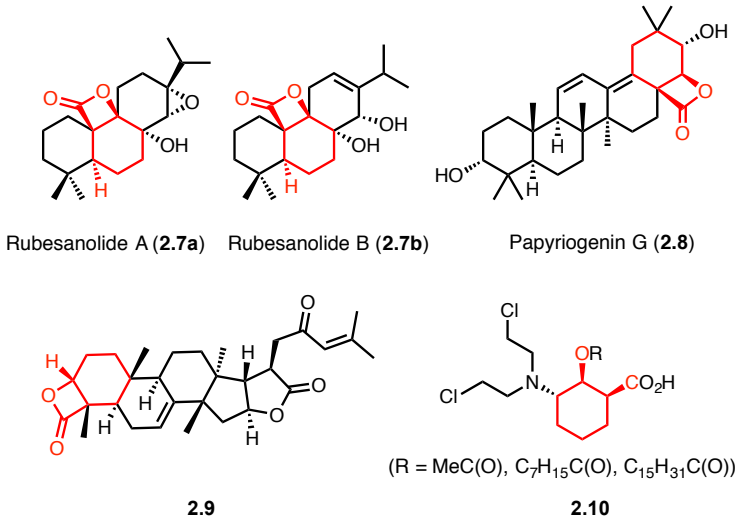
Scheme 2.1 a) The intramolecular Nucleophile (Lewis base)-Catalyzed Aldol-Lactonization (NCAL) process toward bicyclic-β-lactones. b) The described multi-component approach toward bicyclic-β-lactones *via* a Michael Michael aldol lactonization (MMAL).

Previously we prepared bicyclic-β-lactones (*e.g.* β-lactone **2.1**) employing the intramolecular nucleophile-catalyzed aldol β-lactonization (NCAL) that relies on the intermediacy of chiral ammonium enolate intermediates (Scheme 2.1a).[18c,18d] We recently described several organocascade processes that utilize chiral nucleophiles (Lewis bases) to generate chiral unsaturated acylammonium salts[6] from unsaturated acid chlorides as key intermediates for Michael proton-transfer lactamizations (MPTL),[15]

Michael aldol β-lactonizations (NCMAL),[16] Michael enol-lactonizations,[15,20] Diels-Alder lactonizations,[22-23] and lactamizations (DAL).[40] The groups of Smith,[13-14,41] Lupton,[9] Matsubara,[25-26] and Birman[27] have also made significant contributions toward demonstrating the vast potential of these chiral intermediates for organocascade processes. Despite the efficiency of generating three bonds in one operation using commodity acid chlorides, the NCMAL methodology requires the preparation of a malonate substrate bearing a pendant ketone or aldehyde. A potential solution we envisioned was the *in situ* generation of the required malonate substrate via a Michael reaction between ketone **2.4** and an alkylidene malonate **2.5** that would also directly deliver the required malonate anion for a subsequent Michael reaction (*e.g.* **2.6**). In the course of our studies of the NCMAL process,[16] a single example of a MCR involving a Michael Michael aldol β-lactonization of an acid chloride, an alkylidene malonate, and a β-ketoester to deliver a tricyclic β-lactone was described (Scheme 2.1b). Herein, we describe our full study including the scope of this kinetic resolution MCR organocascade that delivers complex tricyclic products **2.1** through formation of 3 C-C bonds, 1 C-O bond, 3 rings, and up to 4 stereocenters from either commercially available or readily available components **2.3**-**2.5**.

The [4.2.0] bicyclic β-lactone motif is found in several bioactive natural products and is also a useful intermediate to access other structural motifs. The natural products such as rubesanolides A and B[42] and papyriogenin G,[43] which were isolated from plant species used in traditional medicine to treat bacterial infections, inflammation and cancer (Scheme 2.2). In addition, the unnamed β-lactone **2.9** has shown thrombin inhibitory

activity, and the acyloxy acids **2.10**, which could be obtained through hydrolysis of a [4.2.0] bicyclic β-lactone, exhibits anticancer activity.[44]



Scheme 2.2 Natural products and bioactive molecules containing or potentially derived from [4.2.0] bicyclic-β-lactones (highlighted in red)

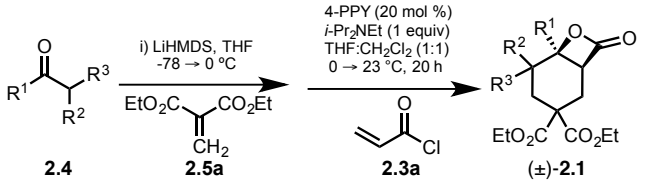
2.2 Results and Discussion

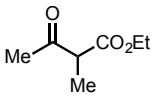
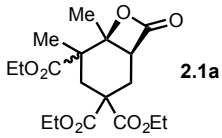
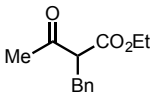
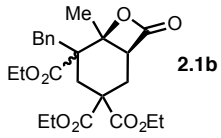
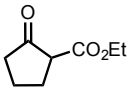
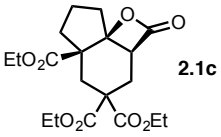
2.2.1 Screening Michael donors

We initially explored suitable Michael donors by studying simple ketones and both cyclic and acyclic β-ketoesters employing the achiral Lewis base, 4-pyrrolidinopyridine. The process involved the deprotonation of the Michael donor with LiHMDS, followed by the addition of alkylidene **2.5a** followed by 4-PPY, Hünig's base, and slow addition of acryloyl chloride (**2.3a**). Simple ketones including cyclohexanone, 3,3,5,5-tetramethylcyclohexanone, and β-tetralone were found to be poor initial Michael donors, only giving a trace amount of β-lactone adduct, as determined by crude IR analysis (β-lactone C=O stretch *c.a.* 1820 cm^{-1}). Hypothesizing a mismatch between the

hard nucleophiles, namely the enolates of the aforementioned ketones, and a soft electrophile, alkylidene malonate **2.5a**, we moved to softer nucleophiles such as 1,3-diketones and β-ketoesters. 2,4-Pentandione and 2-methylcyclohexane-1,3-dione did not provide any improvement over monoketones. However, β-ketoester **2.4a** delivered the desired β-lactone **2.1a** in moderate yield (Table 2.1, entry 1). α-Substitution of ethyl acetoacetate was also tolerated in this reaction providing β-lactone **2.1b** in good yield (75%, Table 2.1, entry 2). While acyclic β-ketoesters **2.4a** and **2.4b** gave a mixture of diastereomers of the respective lactones **2.1a** and **2.1b**, cyclic β-ketoester **2.4c** rendered the desired adduct as a single diastereomer, presumably due to the higher ring strain associated with the *trans* 6,5-bicyclic system (Table 2.1, entry 3). Attempt to increase the CH_2Cl_2 ratio in the solvent mixture diminished the yield of the desired product **2.1c** (58% to 44%) (Table 1, footnote).

Table 2.1 Screening Michael donors in the MMAL reaction



entry	carbonyl **2.4**	product **2.1**	result
1	 **2.4a**	 **2.1a**	54% yield dr 1:1
2	 **2.4b**	 **2.1b**	75% yield dr 1:1
3	 **2.4c**	 **2.1c**	58% yield [a] dr > 19:1

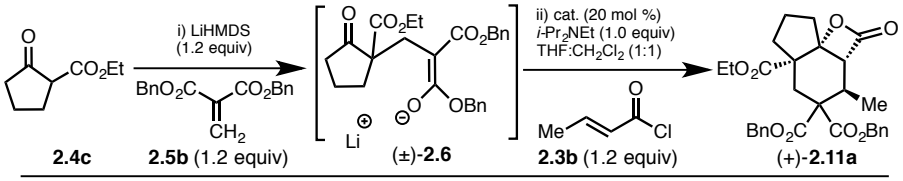
[a] Product **2.1c** was obtained in 44% yield, dr >19:1 when THF:CH_2Cl_2 (1:3) was used.

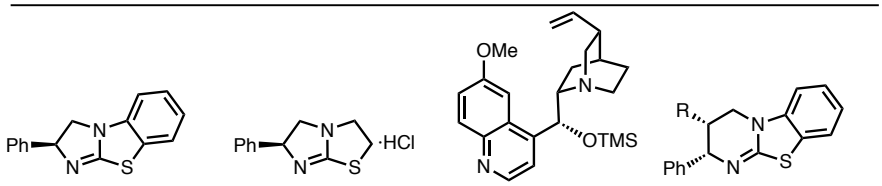
2.2.2 Optimization of the enantioselective MMAL

With the working conditions for the racemic reaction in place, we decided to focus on the enantioselective variant of this methodology (Table 2.2). Cyclic β-ketoester **2.4c** was selected to be the substrate for this study as it delivered a single diastereomer of the β-lactone **2.1c**. Additionally, dibenzyl methylenemalonate **2.5b** was used in place of **2.5a** for enhanced stability and increased UV sensitivity for the convenient determination of enantiomeric ratio. It is worth noting that without equilibrium of the first Michael reaction, the maximum yield should be 50% under kinetic resolution control, due to the fact that only one enantiomer of the racemic mixture **2.6** could form the product **2.11** as a single diastereomer. With crotonoyl chloride (**2.3b**), several chiral

tertiary amine catalysts were screened. Employing commercially available isothiourea catalysts BTM (**2.12**) and tetramisole (**2.13**), the desired lactones were obtained in moderate enantioselectivity (Table 2.2, entries 1-3). Readily available cinchona alkaloid TMSQN (**2.14**) delivered the product with good enantiomeric excess (93:7 er) in 18% yield (Table 2.2, entry 4). Improvement in both yield and enantioselectivity was observed when the isothiourea catalysts HBTM (**2.15**), HBTM 2.1 (**2.16**), and HBTM 2.2 (**2.17**) were employed (Table 2.2, entries 5-10). More specifically, up to 94:6 er was obtained in all of these cases with yield varying from 13-43%. The optimal condition was found with HBTM 2.1[45] (**2.16**) to deliver desired β-lactone **2.11a** in 43% yield and 93.5:6.5 er (Table 2.2, entry 7). Neither increasing the amount of acid chloride **2.3b** (Table 2.2, entry 8) nor reversing the stoichiometry of the reagents (Table 2.2, entry 9) led to any improvement in yields and enantioselectivity of the desired β-lactone **2.11a**.

Table 2.2 Optimization of the enantioselective MMAL





(–)-**2.12**, (*S*)-(–)-BTM | **2.13**, (–)-tetramisole.HCl | **2.14**, TMSQN | **2.15**, R = H, HBTM; **2.16**, R = *i*-Pr, HBTM 2.1; **2.17**, R = Ph, HBTM 2.2

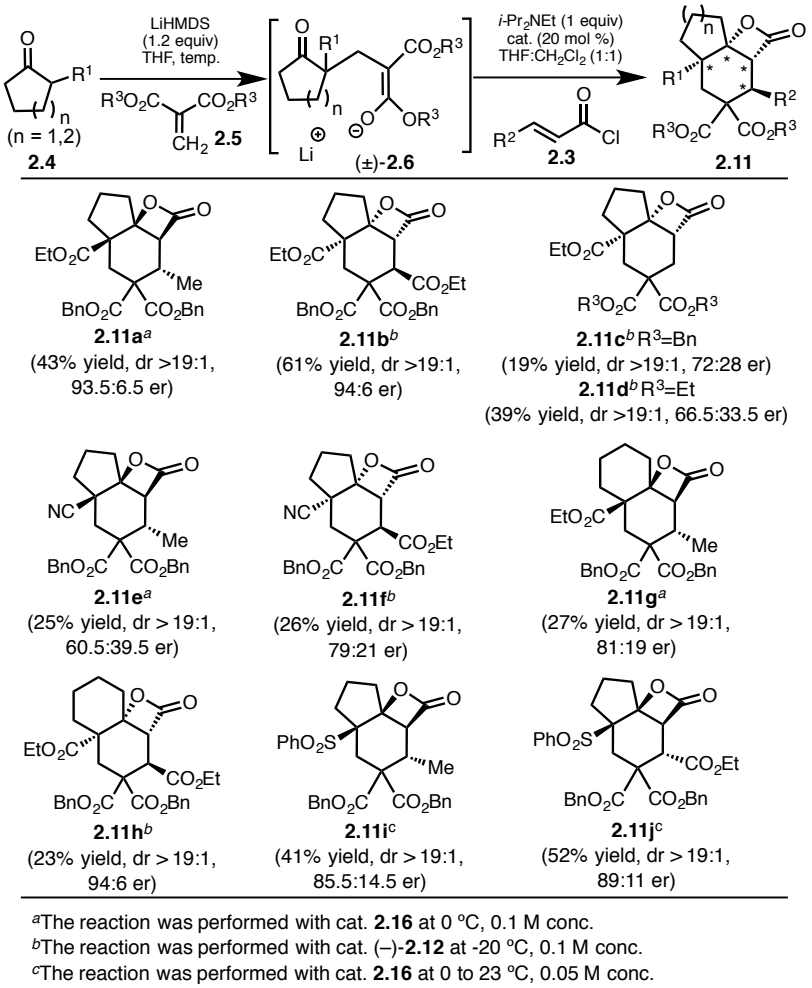
entry	cat. (20 mol %)	temp	yield (%)	dr	er
1	(–)-**2.12**	-20 °C	18	>19:1	88:12
2	(+)-**2.12**	-20 °C	22	>19:1	20:80
3	**2.13**	-20 °C	12	>19:1	79:21
4	**2.14**	-20 °C	18	>19:1	93:7
5	**2.15**	-20 °C	31	>19:1	76.5:13.5
6	**2.15**	0 → 23 °C	13	>19:1	93.5:6.5
7	**2.16**	**0 °C**	**43**	**>19:1**	**6.5:93.5**
8[a]	**2.16**	0 °C	41	>19:1	6:94
9[b]	**2.16**	0 °C	41	>19:1	6:94
10	**2.17**	0 °C	35	>19:1	6:94

[a]The reaction was performed with 2.0 equiv of acid chloride **2.3b**
[b]The reaction was performed with 2.0 equiv of **2.4c**, 2.1 equiv of **2.5b** and 1.0 equiv of **2.3b**

2.2.3 Scope of the enantioselective MMAL

Having found the optimal conditions for the enantioselective Michael Michael aldol β-lactonization reaction, we sought to further expand the scope of this reaction (Scheme 2.3). To our delight, the use of more reactive ethyl fumaroyl chloride (**2.3c**, R^2 = CO_2Et) provided 61% yield of the desired product **2.11b** with comparable enantioselectivity. When acryloyl chloride **2.3a** (R^3 = H) was used, the enantioselectivity reduced dramatically to 72:28 er and 66.5:33.5 er for **2.11c** and **2.11d**, respectively,

presumably due to less sterically congested environment. The reduced enantioselectivity was also observed in **2.11e** and **2.11f** when α-cyanocyclopentanone (R^1 = CN) was employed as the nucleophile **2.4**. It was hypothesized that the inability to coordinate with the Li cation of these corresponding enolates of the substrates leads to the eroded enantiomeric excess. The importance of the coordination between the Li cation and enolate was also observed in the Michael proton-transfer enol-lactamization/lactonization, developed in our group.[15] Larger ring size (6-membered) was also tolerated albeit providing lower yields of the desired products **2.11g** and **2.11h**, presumably due to the higher steric strain associated with these 6,6,4-tricyclic adducts. α-Sulfone containing **2.4** (R^1 = SO_2Ph) was also a compatible substrate in this reaction producing **2.11i** and **2.11j** in good yield and enantioselectivity. Generally, BTM (**2.12**) was the superior catalyst for ethyl fumaroyl chloride (**2.3c**) (R^2 = CO_2Et) while HBTM 2.1 (**2.16**) was better suited for less reactive crotonoyl chloride (**2.3b**) (R^2 = Me).



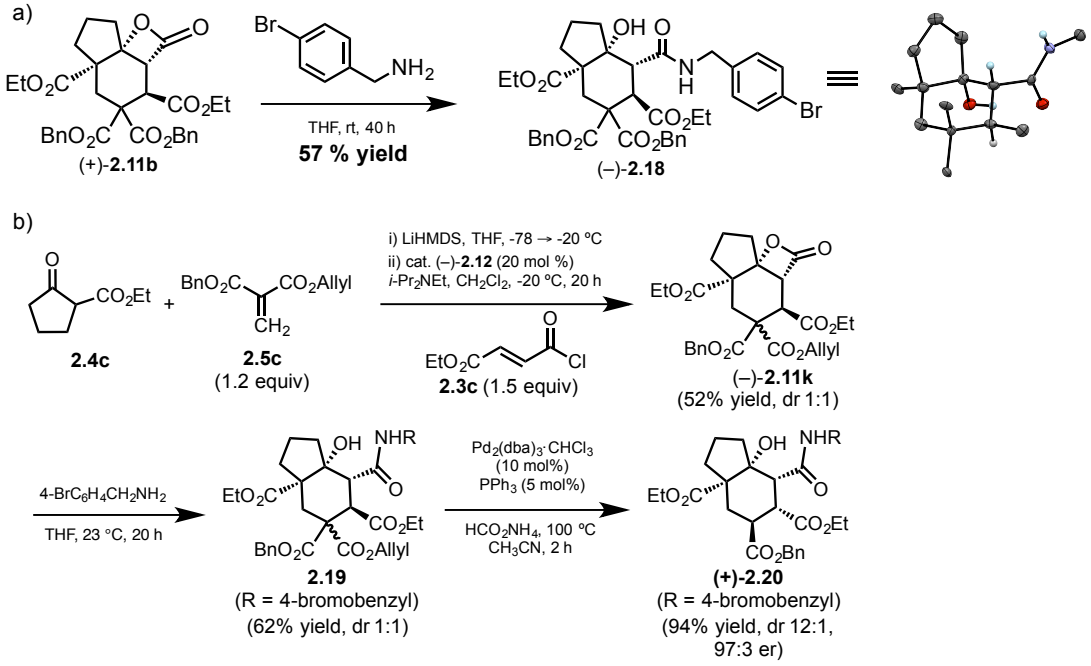
[a]The reaction was performed with cat. **2.16** at 0 ºC, 0.1 M conc.
[b]The reaction was performed with cat. (–)-**2.12** at -20 ºC, 0.1 M conc.
[c]The reaction was performed with cat. **2.16** at 0 to 23 ºC, 0.05 M conc.

Scheme 2.3 Substrate scope of the enantioselective MMAL cascade

2.2.4 Further applications of the MMAL cascade

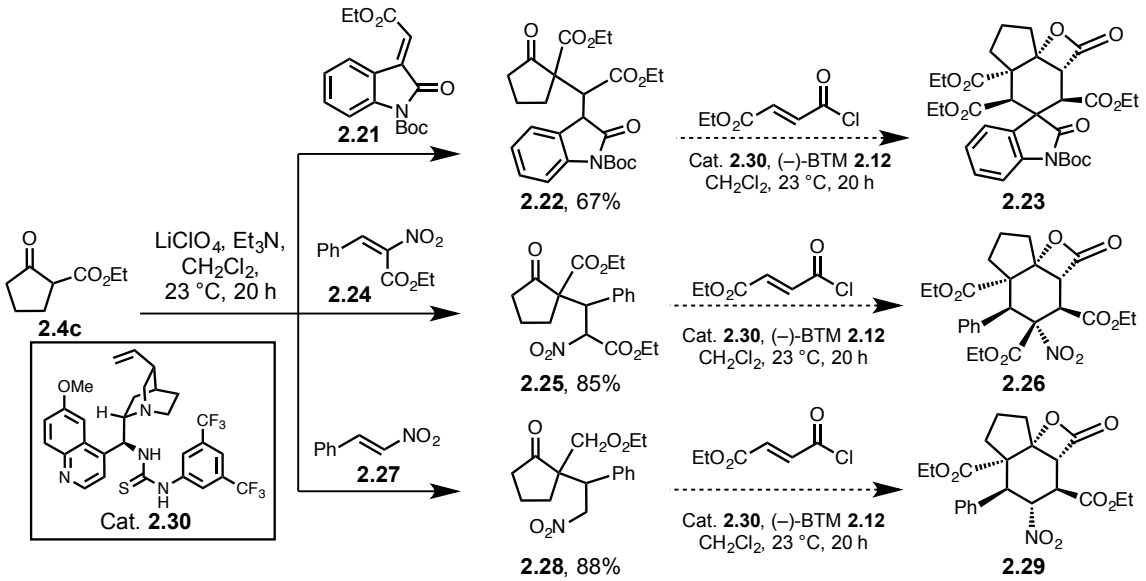
The absolute stereochemistry of β-lactone **2.11b** was confirmed by X-ray crystallography of amide derived from amidation of β-lactone **2.11b** with 4-bromobenzyl amine (Scheme 2.4a).[16] Recognizing the potential of this methodology toward preparation of highly substituted cyclohexane, we decided to generate a fifth stereo center *via* a Pd(0)-mediated deallyl decarboxylation method.[46] β-lactone **2.11k** was

prepared from the non-symmetrical methylene malonate **2.5c** and upon β-lactone ring opening, the resultant amide **2.19** was subjected to a deallyl decarboxylation process to deliver bicyclic **2.20** in good yield (Scheme 2.4). It is worth noting that the ethyl ester adjacent to the new stereocenter was epimerized in the reaction condition.



Scheme 2.4 Applications of the MMAL adducts

Further development of this methodology included the expansion of the scope of the olefin component. Thus far, these studies are limited to alkenes **2.5** as the Michael acceptors where the electron withdrawing groups are esters. Other electrophiles could be included such as **2.22**, **2.25**, and **2.28** to delivered β-lactones **2.24**, **2.27**, and **2.30**, respectively. Preliminary results showed the potential for these substrates by the successful formation of their corresponding Michael adducts of these substrates with β-ketoester **2.4c** (Scheme 2.5).

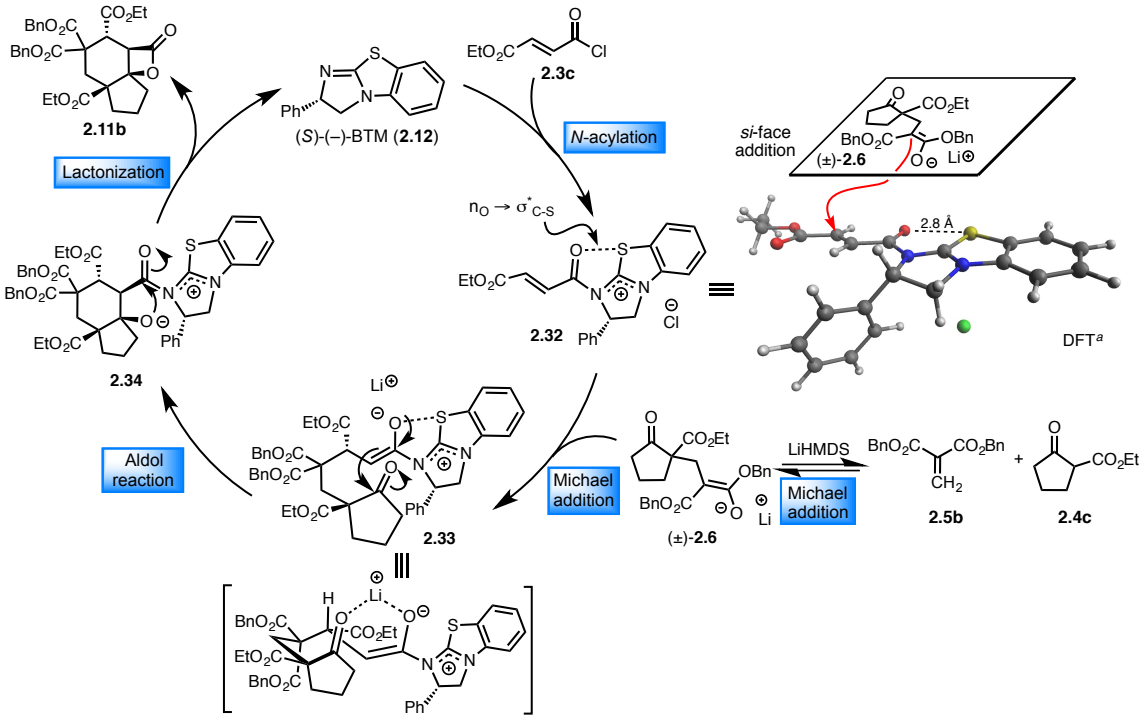


Scheme 2.5 Expanding the scope of Michael acceptors as a direction in MMAL's future development

2.2.5 Proposed mechanism and rationalization for observed enantio- and diastereo- selectivity

During this MMAL process, an *in situ* generated Michael adduct (±)-**2.6** from either cyclic or acyclic β-ketoesters (*e.g*. **2.4c**) and 2-methylenemalonate **2.5b** underwent another Michael reaction with α,β-unsaturated acylammonium **2.32**. In the case of chiral isothiourea catalysts (BTM (**2.12**), HBTM 2.1 (**2.16**)), the α,β-unsaturated acylammonium salt adopts a lower-energy conformation that alleviates non-bonded interactions enforced to some extent by a proposed $n_o \rightarrow \sigma^*_{C\text{-}S}$ interaction[13-14,19,22] and that adopts the extended *s-cis*-conformation of the unsaturated amide. Initial nucleophilic addition of the malonate anion in a Michael fashion thus occurs from the least hindered face, opposite the phenyl group of the catalyst. The subsequent ammonium enolate **2.33**,

with a pendant ketone, is set up for an aldol β-lactonization cascade to form β-lactones **2.11b**. We have previously described that the diastereoselectivity of this aldol process is substrate-controlled due to $A^{1,3}$-strain[18m] and in this case also the high ring strain associated with the fused *trans*-bicyclic system, delivering **2.11b** as the most thermodynamically stable adduct (Scheme 2.6).



Scheme 2.6 Proposed catalytic cycle for the MMAL reaction and DFT-derived conformational model of the HBTM acylammonium salt[22]

2.3 Conclusion

In conclusion, the underexplored α,β-unsaturated acylammonium salts was used to develop a catalytic, enantioselective one-pot, three-component reaction to gain access to [4.2.0] bicyclic β-lactones. In one single operation, this organocascade forms four bonds,

two rings and up to five contiguous stereocenters with excellent enantio- and diastereo-control. By exploiting this multicomponent process, complex structural motifs can be accessed more readily and efficiently than classical stepwise approach. Further studies are underway to investigate the potential for dynamic kinetic resolution involving this MMAL process.

CHAPTER III

TANDEM MICHAEL PROTON-TRANSFER LACTAMIZATION VIA α,β-UNSATURATED ACYLAMMONIUM SALTS*

3.1 Introduction

Discovery of reactive intermediates through generic modes of substrate activation is central to the field of asymmetric organocatalysis. Methods for generating such intermediates in a catalytic asymmetric fashion have fueled the design of a variety of new and, in some cases, practical asymmetric transformations.[47] Recently, there has been a significant expansion of the reactions that are catalyzed by chiral tertiary amines.[2] Based on our interest in developing expedient routes to pyrrolidinone subunits,[48] we envisioned that a suitable Michael donor bearing a pendant amine, for example, α- or β-aminomalonates, could serve as a twofold nucleophile to undergo an enantioselective nucleophile-catalyzed Michael proton-transfer lactamization (NCMPL) cascade with the α,β-unsaturated acylammonium.

Pyrrolidinones or γ-lactams are frequently encountered structural subunits in numerous bioactive natural products and pharmaceuticals (Scheme 3.1). Examples of bioactive agents include the nanomolar inhibitor of the proteasome, salinosporamide A,[49] and the antibacterial and antitumor agent neooxazolomycin.[50] While clausenamide

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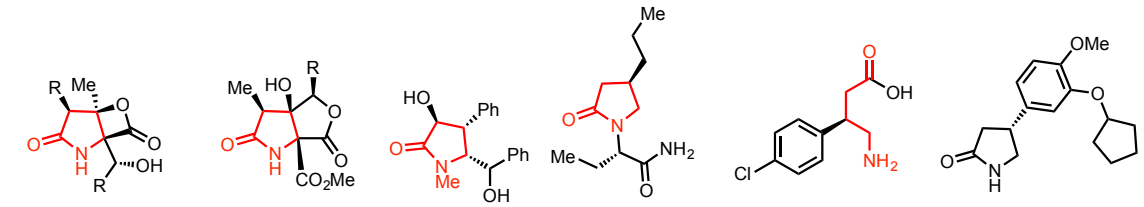
is used for the treatment of chronic viral hepatitis,[51] brivaracetam[52] and rolipram[53] have utility for the treatment of depression and epileptic seizures, respectively. Additionally, baclofen is an inhibitory neurotransmitter and an antispastic agent.[54] β-Substituted pyrrolidinone derivatives have been utilized for the synthesis of pyroglutamic acids[55] and proline derivatives,[56] with the latter used widely in organocatalysis.[47b]



Scheme 3.1 Examples of pyrrolidinone-containing and pyrrolidinone derived natural products and drugs

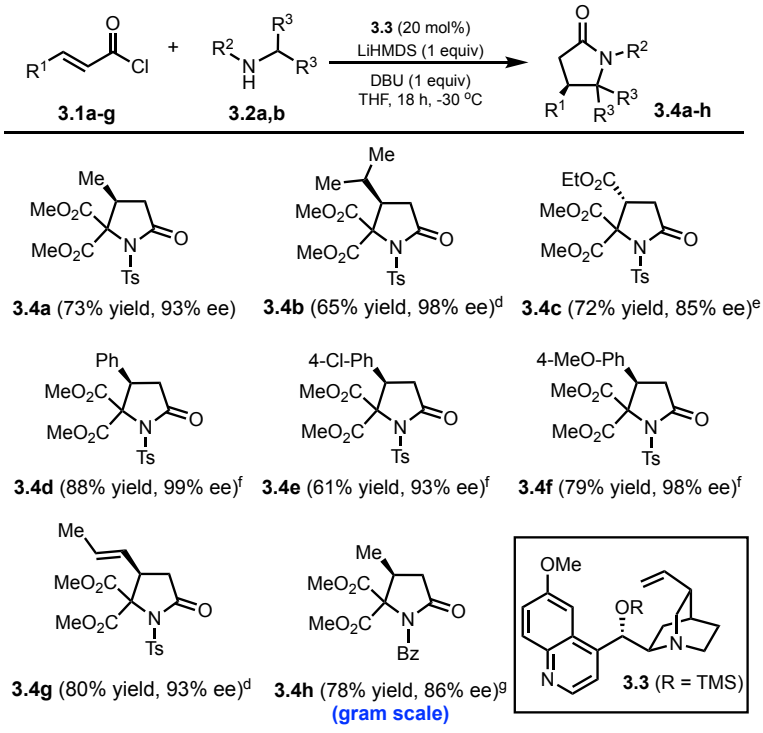
Arguably, a Michael lactamization process involving α,β-unsaturated acid chlorides with α-aminomalonates is one of the most direct methods for the synthesis of pyrrolidinones. However, to date, only achiral promoters for this reaction have been utilized resulting in racemic adducts.[57] Until recently, most methods for the enantioselective synthesis of β-substituted pyrrolidinones were based on chiral starting materials or stoichiometric reagents.[58] An important advancement in this area was described by Taylor and Jacobsen wherein an enantioselective Michael reaction of an unsaturated acyclic imide was catalyzed by a chiral Lewis acid.[59] *N*-heterocyclic carbene (NHC) homoenolates[60] have also been utilized for the synthesis of pyrrolidinones. Recently, Scheidt and co-workers reported the coupling of *N*-benzoyl hydrazones and

unsaturated aldehydes, mediated by NHC/Lewis acid cooperative catalysis, thus leading to cis-γ-lactams.[61] Rovis and co-workers reported a similar process, but using a NHC/Brønsted acid combination, for the synthesis of *trans*-γ-lactams.[62] Given the importance of pyrrolidinone-containing compounds and catalytic asymmetric routes to these intermediates,[63] we sought to develop a highly practical and scalable method for their synthesis from commodity acid chlorides employing a NCMPL process.

Initial exploration of reaction conditions revealed the importance of DBU as an acid scavenger and under these reaction conditions, use of TMSQD (**3.3**) delivered the pyrrolidinone **3.4** in good yield and enantioselectivity. The absence of DBU or substitution of DBU with Hünig's base returned only trace amounts of the desired product. The use of the *N*-tosyl aminomalonate **3.2a** was also found to be important to deliver good results in this reaction. With the optimized reaction conditions in hand for this process, we studied several β-substituted acid chlorides and found that β-aryl, β-alkyl, β-alkenyl, and β-carbonyl unsaturated acid chlorides are well tolerated in the reaction and lead to pyrrolidinone derivatives in 61-88% yield and 85-99% *ee* (Table 3.1). In the case of ethyl fumaroyl chloride ($R^1 = CO_2Et$) delivering the pyrrolidinone **3.4c**, the combination of $(DHQ)_2PHAL$ and Hünig's base provided superior results to those obtained with DBU, which presumably leads to product racemization. In the case of the β-aryl acid chlorides **3.1d-f**, the electronic properties of the arene substituents had little influence on the enantioselectivity, thus leading to the pyrrolidinones **3.4d-f** with 93-99% *ee*. β-Propenyl acid chloride (**3.1g**) led to **3.4g** in 80% yield and 93% *ee*. To demonstrate the practicality of the process, a gram-scale reaction was performed with

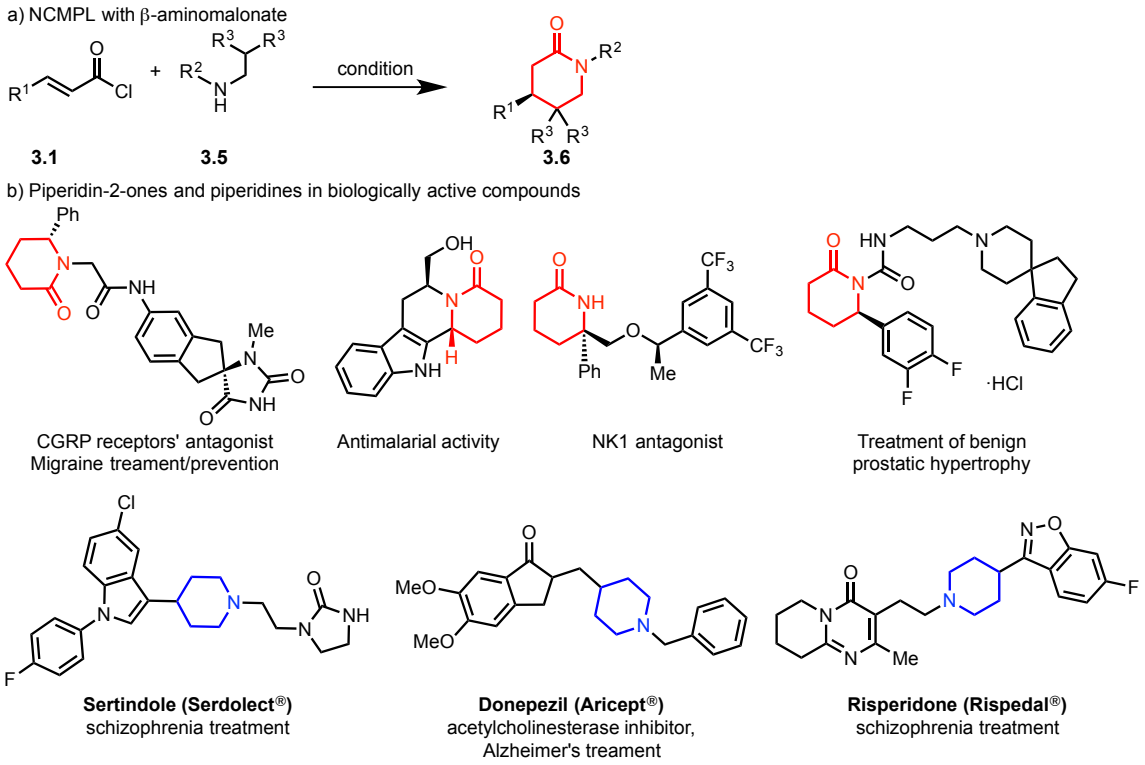
3.1a and **3.2a** to afford crystalline **3.4h** in 78% yield and 86% *ee*. (See section 1.1.4 for a detailed discussion of the reaction mechanism)

Table 3.1 NCMPL of acid chlorides with α-aminomalonates.[a–c]



[a] Reactions were performed with 1 equiv of **3.2** and 1.5 equiv of **3.1** with the latter added over 5 h (syringe pump). [b] Yields refer to purified, isolated product. [c] Enantiomeric excess was determined by HPLC analysis using a chiral stationary phase. [d] This reaction was performed with 2.0 equiv of **3.1** and conducted at -10 °C. [e] $(DHQ)_2PHAL$ and *i*-Pr_2NEt were used for this substrate. [f] This reaction was performed with 2.0 equiv of **3.1** and conducted at -15 °C.

Toward expanding the breadth of this strategy for heterocycle synthesis, we wanted to explore the use of β-aminomalonates such as **3.5** to access chiral piperidin-2-ones **3.6** (Scheme 3.2a). Piperidin-2-ones or δ-lactams are not only encountered as structural subunits in bioactive molecules but also piperidine precursors which are found in numerous natural products and pharmaceuticals (Scheme 3.2b).



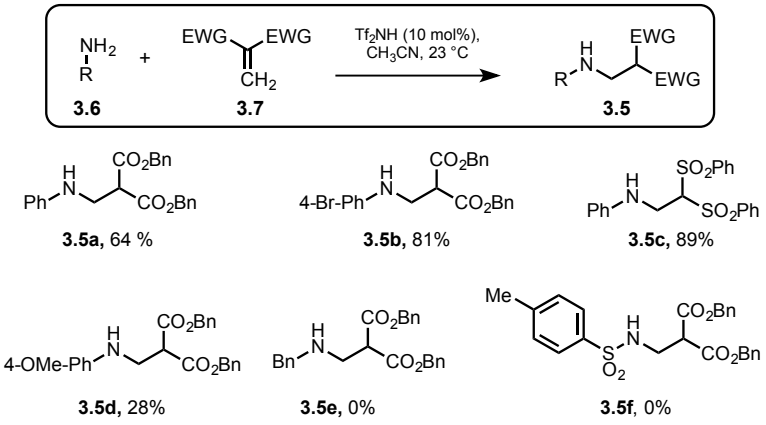
Scheme 3.2 a) Expanding NCMPL toward synthesis of piperidinones; and b) piperidinone and piperidine-containing biologically active compounds

3.2 Results and Discussion

3.2.1 Synthesis of chiral piperidinones

Our efforts toward piperidinone started with the preparation of β-aminomalonate **3.5**. Unlike the α-aminomalonates **3.2**, which were easily prepared, we encountered difficulty in the preparation of amine **3.5** under basic conditions, namely, retro-conjugate addition. Ultimately, it was found that several β-aminomalonates **3.5** could be successfully prepared under acidic conditions (Scheme 3.3). Amine **3.5a** could be obtained in good yield from aniline and olefin **3.7** with catalytic amount of Tf_2NH. A

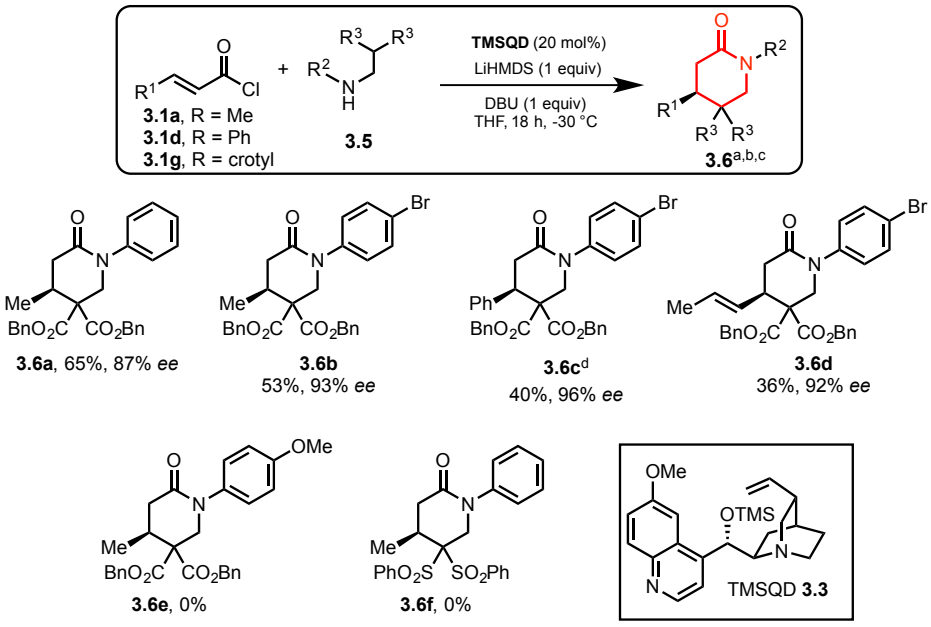
sulfone as the electron withdrawing group on **3.7** was also a good substrate to give amine **3.5c** in good yield. Additionally, 4-bromoaniline efficiently delivered product **3.5b** while electron rich aniline (*p*-OMe) was not a good substrate giving a 28% yield of **3.5d**. Benzyl amine and $TsNH_2$ did not provide the desired adducts **3.5e** and **3.5f**, respectively, under the indicated conditions.



Scheme 3.3 Preparation of β-aminomalonates

Having β-aminomalonates **3.5** in hand, we started to explore these bis nucleophiles in the NCMPL method to access chiral piperidin-2-ones **3.6** (Scheme 3.4). Following a brief screening of reaction conditions, *N*-phenyl-β-aminomalonate **3.5a** participated in a NCMPL with crotonoyl chloride **3.1a** to deliver the piperidinone **3.6a** in 65% yield and 87% *ee*. The electron-deficient *N*-aryl substituent (R^2 = 4-Br-C_6H_4) led to improved enantioselectivity (93% *ee*) but reduced yield (53%) for piperidinone **3.6b** from **3.1a**, whereas cinnamoyl chloride (**3.1d**) gave 40% yield of piperidinone **3.6c** in 96% *ee*. Sorbic chloride **3.1g** delivered lactam **3.6d** in similar results. Disappointingly, neither **3.5c** nor **3.5d** led to the desired δ-lactams **3.6e** or **3.6f**, respectively. A common

problem leading to reduced yields when employing β-aminomalonates as bis nucleophiles was their degradation through a retro-aza Michael reaction. However, the simplicity of the procedure and utility of piperidin-2-ones with β-stereogenic centers, which exhibit stimulant or depressant action on the central nervous system,[64] make this an attractive and practical strategy to chiral β-substituted piperidin-2-ones.



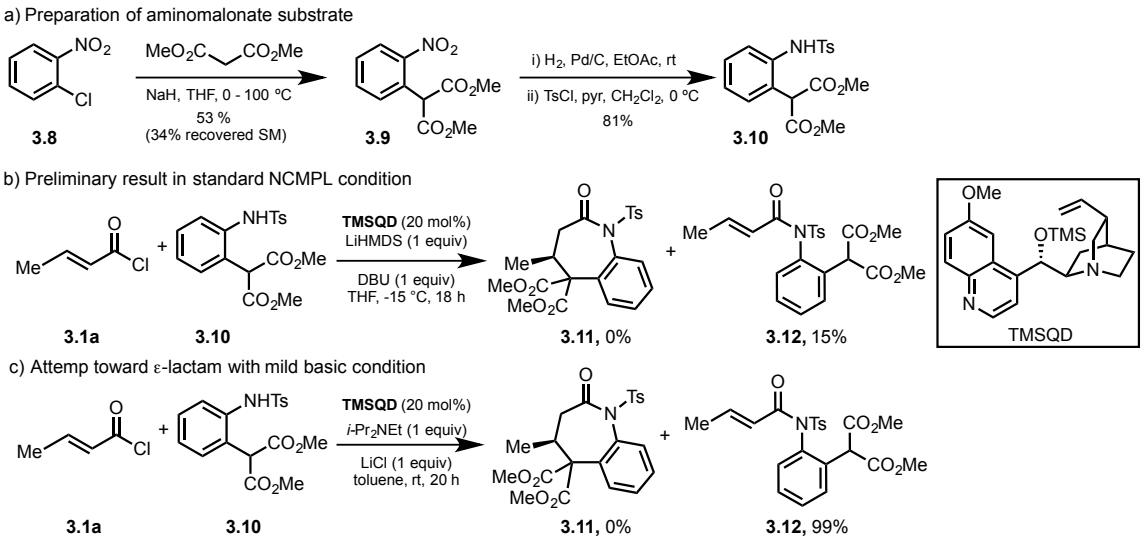
[a] Reactions were performed with 1 equiv of **3.2** and 1.5 equiv of **3.1** with the latter added over 5 h (syringe pump). [b] Yields refer to purified, isolated product. [c] Enantiomeric excess was determined by HPLC analysis using a chiral stationary phase. [d] This reaction was performed with 2.0 equiv of **3.1** and conducted at -15 °C.

Scheme 3.4 Exploring NCMPL toward chiral piperidinones

3.2.2 Efforts toward synthesis of ε-lactams

Having some success with the preparation of δ-lactams (piperidiones), we steered our focus toward medium-sized rings, specifically, ε-lactam. The most common issues with forming medium-sized rings (7- and 8-membered rings) include: 1) their inherent higher ring strain, and 2) the deceasing probability of the end-to-end reaction with the

increased chain length of the substrate.[65] The latter could be mitigated by a more rigid substrate thereby minimizing the entropic cost of the medium-sized ring formation process. Therefore, it was decided that aniline **3.10** would be the first substrate to test in this procedure. The desired aminomalonate **3.10** was prepared with ease from chloronitrobenzene **3.8** (Scheme 3.5a). Unfortunately, the initial test of this substrate under the standard conditions for the NCMPL led to a small amount of undesired, unsaturated amide **3.12** and none of the desired lactam **3.11** (Scheme 3.5b). Switching to a milder base, by replacing LiHMDS with Hünig's base, exclusively yielded the undesired amide **3.12** (Scheme 3.5c). These preliminary results suggested that there were competing rates between the *N*-acylation resulting in the formation of amide **3.12** versus the initial Michael reaction in the desired NCMPL process.

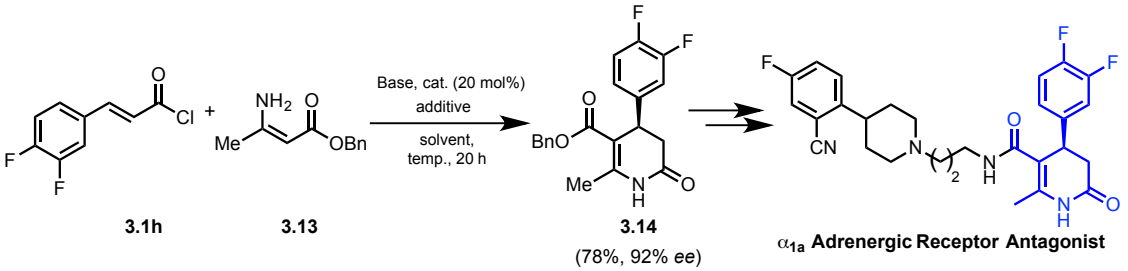


Scheme 3.5 Preparation of the aminomalonate substrate and preliminary results toward the synthesis of ε-lactam

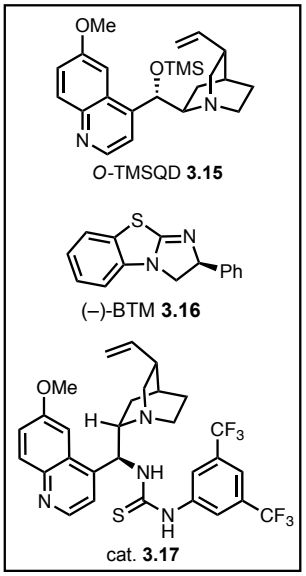
3.2.3 Synthesis of a chiral dihydropyridinone

Another class of nitrogen heterocycles that could be accessed by this cascade process is dihydropyridinones, and their presence in several drug candidates encouraged us to apply the NCMPL to these targets. Initial reaction with standard NCMPL conditions did not deliver product **3.14** in good yield or enantioselectivity (Table 3.2, entry 1). Switching to a combination of LiHMDS and Hünig's base along with higher temperature (but not exceeding 5 °C) resulted in a better enantioselectivity (Table 3.2, entries 2-4). A brief survey of catalysts confirmed that *O*-TMSQD **3.15** offered the best enantioselectivity for this reaction (Table 3.2, entries 2, 5-7). Benzyl acetoacetate was observed as a result of the hydrolysis of enamine **3.13**, hence, molecular sieves were added to circumvent this issue, in combination with switching the solvent to toluene (Table 3.2, entry 8). It was later found that merely using Hünig's base offered the best result for this reaction (Table 3.2, entries 9-10). The key to success of this reaction was the use of a nonpolar solvent and LiCl as an additive, which had a profound effect on enantioselectivity (Table 3.2, entry 11). This mild process delivered the dihydropyridinone **3.14** in 78% yield and 92% *ee*. This particular dihydropyridinone was targeted since it has recently been used in the synthesis of the α_{1a} adrenergic receptor antagonist.[17]

Table 3.2 Optimization of NCMPL toward a dihydropyridinone



Entry	Bases	Cat.	Additive	Solvent, temp.	Result
1	LiHMDS (1.3 equiv), DBU (1.0 equiv)	*O*-TMSQD **3.15**	-	THF, -10 ºC	30%, 10% *ee*
2	LiHMDS (1.3 equiv), *i*Pr$_2$NEt (1.0 equiv)	*O*-TMSQD **3.15**	-	THF, -15 ºC	ND, 60% *ee*
3	LiHMDS (1.3 equiv), *i*Pr$_2$NEt (1.0 equiv)	*O*-TMSQD **3.15**	-	THF, 5 ºC	ND, 75% *ee*
4	LiHMDS (1.3 equiv), *i*Pr$_2$NEt (1.0 equiv)	*O*-TMSQD[a] **3.15**	-	THF, 40 ºC	ND, 65% *ee*
5	LiHMDS (1.3 equiv), *i*Pr$_2$NEt (1.0 equiv)	(DHQ)$_2$PHAL[a]	-	THF, 0 ºC	ND, 40% *ee*
6	LiHMDS (1.3 equiv), *i*Pr$_2$NEt (1.0 equiv)	(–)-BTM **3.16**	-	THF, -15 ºC	ND, 10% *ee*
7	LiHMDS (1.3 equiv), *i*Pr$_2$NEt (1.0 equiv)	cat. **3.17**	-	THF, -15 ºC	ND, 10% *ee*
8	LiHMDS (1.3 equiv), *i*Pr$_2$NEt (1.0 equiv)	*O*-TMSQD **3.15**	MS (4 Å)	PhMe, 0 - 23 ºC	ND, 76% *ee*
9	*i*Pr$_2$NEt (3 equiv)	*O*-TMSQD **3.15**	MS (4 Å)	PhMe, 23 ºC	66%, 90% *ee*
10	*i*Pr$_2$NEt (3 equiv)	*O*-TMSQD **3.15**	MS (4 Å)	THF, 23 ºC	40%, 89% *ee*
11	***i*Pr$_2$NEt (3 equiv)**	***O*-TMSQD 3.15**	**LiCl, MS (4 Å)**	**PhMe, 23 ºC**	**78%, 92% *ee***



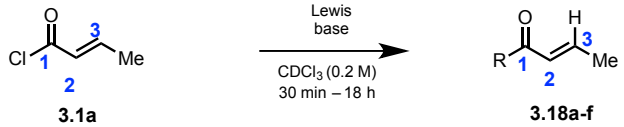
[a]2 h addition of acid chloride
ND = not determined

3.2.4 NMR study of α,β-unsaturated acylammonium salts

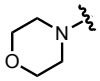
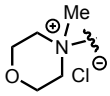
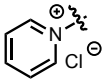
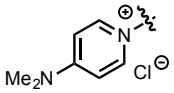
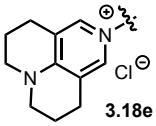
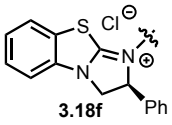
To gain insights into the degree of activation of acid chlorides upon formation of their α,β-unsaturated acylammonium salts adducts,[66,15-16] which were revealed during our previous studies of various organocascade processes, the ^{13}C NMR chemical shift of the β-carbon (C3) was determined for various acylammonium salts. In analogy to a method previously used to measure the Lewis acidity of various Lewis acids upon complexation to α,β-unsaturated carbonyl compounds,[21] we measured the chemical shift

differences of the β-carbon upon reaction of crotonoyl chloride **3.1a** with several Lewis bases in comparison to the starting acid chloride and a related tertiary amide **3.18a**. However, in the aforementioned study, Lewis acid activation presumably occurs through inductive π-system activation upon Lewis acid complexation to the carbonyl oxygen lone pair leading to reduced electron density at the β-carbon and a greater downfield chemical shift for stronger Lewis acids. In the case of acylammonium salt formation from acid chlorides, activation, if any, would presumably result from inductive effects propagated through the σ-framework, which may also be revealed through reduced electron density at the β-carbon. Giving this, we measured the ^{13}C chemical shifts in $CDCl_3$ at 23 °C for various acylammonium salts formed through the reaction of an acid chloride with various tertiary amines (Table 3.3).

Table 3.3 NMR study of acylammonium salts



3.1a **3.18a-f**

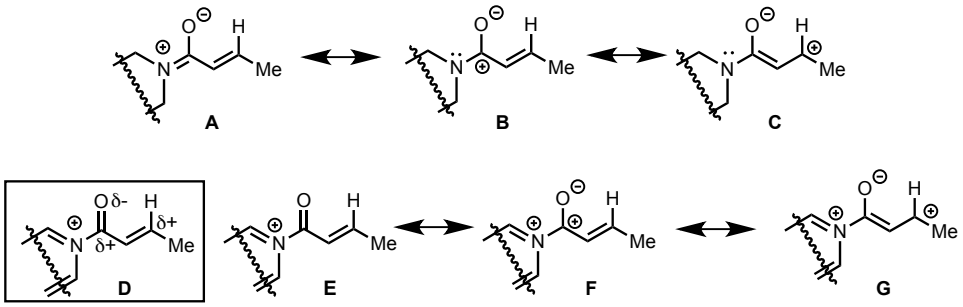
Entry	Lewis base	R	^{13}C NMR δ (ppm)				^{1}H NMR δ (ppm)	
			C1	C3	Δδ C3[a]	C2	H3	Δδ H3[a]
1	-	Cl	165.7	152.9	-	127.6	7.22	-
2	morpholine	 **3.18a**	165.5	142.0	+10.9	ND[c]	6.80	+0.42
3	*N*-methyl morpholine[b]	 **3.18b**	161.9	149.6	+3.3	ND[c]	7.09	+0.13
4	pyridine[b]	 **3.18c**	162.0	149.6	+3.3	ND[c]	7.10	+0.12
5	DMAP	 **3.18d**	162.8	156.8	-3.9	118.2	7.48	-0.26
6	9-azajulolidine	 **3.18e**	163.4	155.6	-2.7	ND[c]	7.39	-0.17
7	(–)-BTM	 **3.18f**	163.4	152.4	+0.5	119.3	7.07	+0.15

[a]Change in chemical shift for ^{13}C and ^{1}H of C3 and H3 in acylammonium salt relative to C3 and H3 of acid chloride.
[b]In these cases, complete conversion to the corresponding acylammonium salts was never observed as judged by NMR
[c]ND = not determined

The ^{13}C chemical shifts of crotonyl chloride **3.1a** (δ 152.9) and the derived morpholino amide **3.18a** (δ 142.0) were measured and used as comparators (Table 3.3, entries 1 and 2). As expected, the acid chloride **3.1a** had a significant downfield chemical shift for the β-carbon ($\Delta\delta$ −10.9) compared to the amide **3.18a**. The use of the

tertiary amine, *N*-methyl morpholine, led to acylammonium salt **3.18b** with a significant downfield chemical shift for the β-carbon ($\Delta\delta$ −7.6) compared to amide **3.18a**, but not to the extent of crotonyl chloride ($\Delta\delta$ −10.9). The use of pyridine led to acylpyridinium salt **3.18c** that had a nearly identical chemical shift for the β-carbon (entry 4) as the *N*-methyl morpholine derived salt **3.18b**. It should be noted that in the case of *N*-methylmorpholine and pyridine, unreacted Lewis base and acid chloride remained, suggesting an equilibrium between the acid chlorides and the derived acylpyridinium salts. On the other hand, the use of DMAP and 9-azajulolidine led to complete conversion and significant downfield shifts of the β-carbon compared to the acid chloride ($\Delta\delta$ −3.9, −2.7, respectively), suggesting a decrease in reversibility and overall, deshielding effect of the positive charge in these intermediates, respectively. The observed chemical shifts could also suggest that the ability to delocalize the positive charge on nitrogen to a greater extent through substituted pyridinium intermediates may lead to lower electron density at the β-carbon, which is further shown by consideration of contributing resonance structures (Scheme 3.6). In the case of the chiral Lewis base benzotetramisole (BTM), a significant change in the chemical shift of the β-carbon compared to the acid chloride was not observed (Table 3.3, entry 7). However, it is also important to note that formation of isothiourea-based acylammonium salts is expected to lead to steric impediment at the carbonyl carbon, which slows 1,2-addition enabling 1,4-addition to become the predominant pathway. Thus, the formation of chiral acylammonium salts with isothioureas and cinchona alkaloids may not lead to dramatic activation of the β-carbon, but rather a significant decrease in 1,2-reactivity enabling these Michael-

initiated organocascades. Of the acylammonium salts studied, two groups of these intermediates appear to emerge. One group possesses a more localized positive charge on nitrogen and are formed reversibly[22] (Table 3.3, highlighted in blue) while a second group possesses a delocalized positive charge and are formed irreversibly (Table 3.3, highlighted in red) reflected in the observed chemical shift differences of the β-carbons.



Scheme 3.6 Resonance structure comparisons of tertiary amides and acylammonium salts.

3.3 Conclusion

Herein, we described the first highly enantioselective version of the nucleophile-catalyzed Michael proton-transfer lactamization cascade with commodity acid chlorides using readily available *O*-trimethylsilylquinidine (TMSQD), leading to various nitrogen heterocycles, specifically, the syntheses of chiral piperidinones and a dihydropyridone. NMR studies of the acylammonium salts provided valuable information regarding the extent of β-carbon activation upon reaction of acid chlorides with tertiary amines.

CHAPTER IV

PROGRESS TOWARD SYNTHESIS OF RAMESWARALIDE

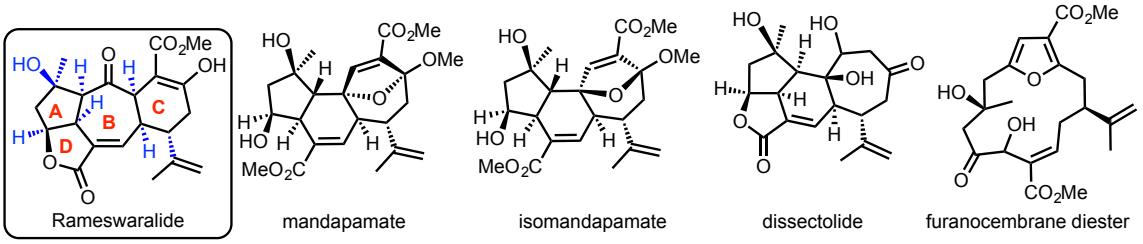
4.1 Introduction

Though combinatorial chemistry and biosynthesis have gained some attention in the pharmaceutical industry, a large percentage of pharmaceutical drugs are comprised of natural products and natural product derivatives.[67] Moreover, natural products have been continuously serving as lead compounds in drug discovery and design.[68] Countless useful therapeutic agents have been developed from bioactive products isolated from plant species, marine organisms and microorganisms. The number of discovered natural products is growing every day, arguably making natural products an unlimited source of potential pharmaceutical agents.

4.1.1 Rameswaralide: isolation, structure and proposed biosynthesis

The structure of rameswaralide was elucidated in 1998 by a joint effort of Venkateswarlu and Faulkner groups.[69] This diterpene natural product was extracted as a white solid from soft coral *sinularia dissecta* that was collected from the coast of India in 1996. Recently, rameswaralide was isolated from another species of this soft coral, *sinularia inelegans*.[70] Consisting of seven stereogenic centers with a highly dense fused tetracyclic ABCD system, this diterpenoid has been a challenging synthetic target. Key highlights of this natural products include an *exo*-methylene-γ-lactone ring D, a fully substituted cycloheptenone ring B, a tertiary alcohol on ring A, a propylene moiety on

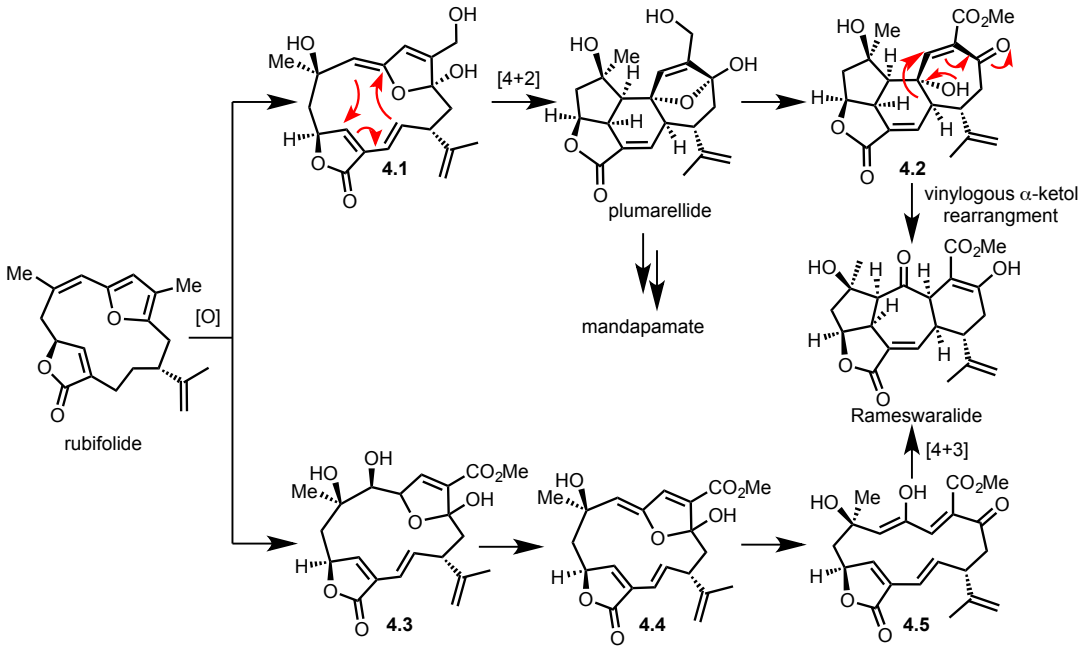
ring C as well as the *cis*-fused AB-, BC-, and AD- ring junctions (Scheme 4.1). The relative stereochemistry was first established through a series of 2D-NMR experiments[69] and later was confirmed, along with the absolute stereochemistry, by X-ray crystallography.[70]



Scheme 4.1 Rameswaralide and other natural products from *sanularia dissecta*

Other natural products isolated from the same species, *sinularia dissecta*, include mandapamate, isomandapamate, dissectolide, and furanocembrane diester,[69,71] which are likely interrelated biosynthetically. To date, the biosynthetic pathway of rameswaralide remains unknown, but it was proposed that the natural product could be derived from rubifolide, a ubiquitous structure in corals and marine environments (Scheme 4.2).[72] The oxidation adduct of rubifolide, such as **4.1**, can proceed through a [4+2] cycloaddition to form plumarellide, another natural product found in corals. Subsequent cleavage of adduct **4.2** can then undergo a vinylogous α-ketol rearrangement to deliver rameswaralide.[72-73] It is noted that the natural product plumarellide is structurally related to mandapamate which was isolated from the same species as rameswaralide. Another possible biosynthetic pathway involves the oxidative adduct **4.3** which forms

monohydrofuran **4.4** upon dehydration. Upon ring opening at the cyclic hemiketal, the macrolide **4.5** can deliver rameswaralide *via* a [4+3] cycloaddition.[71-72]



Scheme 4.2 Speculated biosyntheses of rameswaralide

4.1.2 Rameswaralide: biological activity

Two years after the isolation and characterization work was published, rameswaralide and several of its derivatives were patented toward their use as therapeutic agents.[74] Once administered, with a typical dosage of 0.5 mg/kg to 7 mg/kg, rameswaralide and its derivatives have been found to exhibit anti-inflammatory activity against arthritis, psoriasis and inflammatory bowel disease in both mammal and human subjects. The proposed mode of action includes impeding migration of inflammatory cells, such as monocytes, macrophages, and neutrophils. It was also proposed that these

agents could potentially inhibit the synthesis of inflammatory mediators including products of arachidonic acid metabolism such as leukotrienes and prostaglandins.

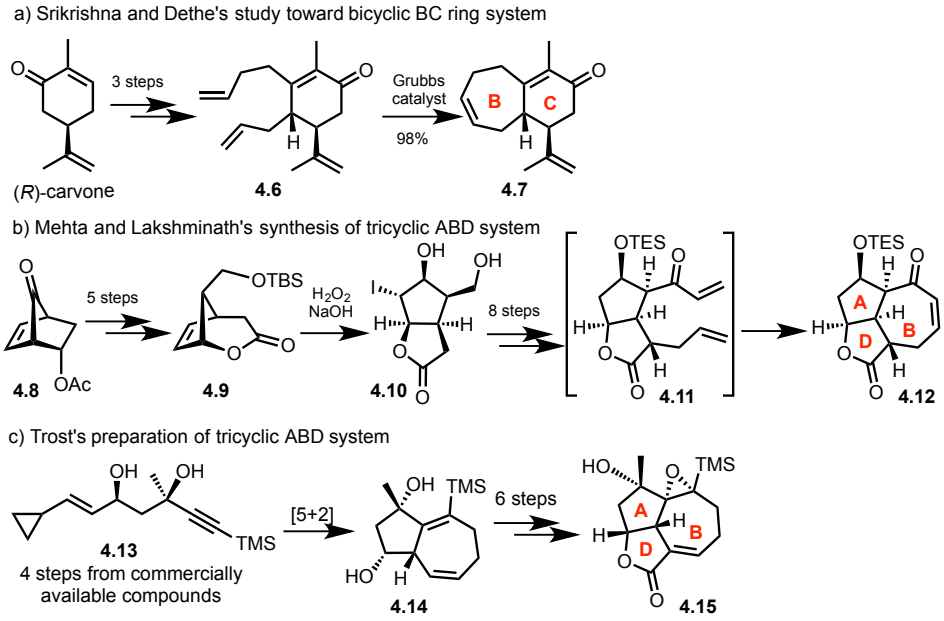
In a recent *in vitro* study, rameswaralide was shown to exhibit weak cytotoxic activity toward four cancer cell lines, with IC_{50} values of 137 μM, 67 μM, 145 μM, and 93 μM against DU145 (human prostate carcinoma epithelial), A549 (human lung carcinoma epithelial), HeLa (human epithelial cervical cancer), and MCF-7 (human breast adenocarcinoma), respectively.[70]

4.1.3 Previous synthetic studies toward rameswaralide

In 2004, Srikrishna and Dethe targeted the bicyclic BC ring that is present in rameswaralide as well as guanacastepenes (Scheme 4.3a).[75] In a short sequence involving alkylations and oxidative transposition, diene **4.6** was prepared from (*R*)-carvone. In the subsequent key transformation, ring closing metathesis (RCM) was employed using Grubbs I catalyst delivering the desired bicyclic BC rings in excellent yield. In spite of its short and efficient route toward the bicyclic system of rameswaralide, there were no further advancements toward the natural product with this bicyclic intermediate.

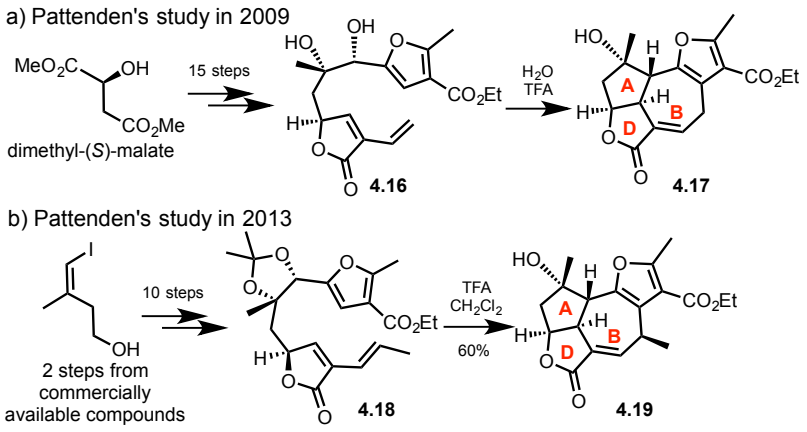
Later, tricycle ABD system of rameswaralide, was prepared by Mehta and Lakshminath (Scheme 4.3b).[76] Starting with a known ketone **4.8**, the Corey-lactone derivative **4.10** was prepared in six steps. Upon further manipulation, tricycle ABD **4.12** was constructed *via* RCM of diene intermediate **4.11**.

Trost and coworkers also developed a route toward a similar tricyclic ABD system by utilizing their own methodology (Scheme 4.3c).[77] Under ruthenium catalysis, enyne **4.13** underwent an intramolecular [5+2] cycloaddition to deliver bicycle **4.14**, which was elaborated to lactone **4.15** in six steps.



Scheme 4.3 Previous attempts toward the core structure of rameswaralide

Taking a different approach, Pattenden and coworkers investigated the proposed biosynthesis of rameswaralide, specifically, the intramolecular [4+3] cycloaddition (see scheme 4.2).[71-72] The feasibility of this intramolecular cycloaddition was probed by using advanced intermediates **4.16** and **4.18** as cyclization precursors (Scheme 4.4). Under an acidic conditions, these intermediates likely underwent a step-wise cycloaddition to deliver tricyclic adducts **4.17** and **4.19**, respectively. This study supported the proposed intramolecular [4+3] cyclization in the biosynthetic pathway.



Scheme 4.4 Pattenden's studies toward rameswaralide based on proposed biosynthetic pathway

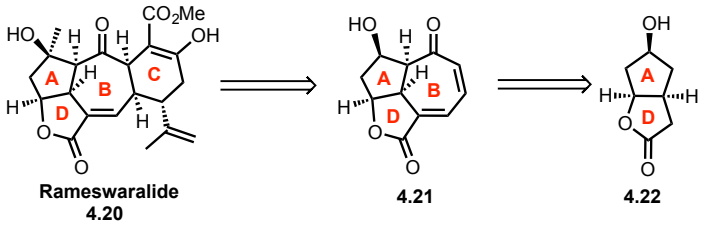
Interests in rameswaralide and its derivatives led to several attempted total syntheses.[71-72,75-77] Despite these efforts, the total synthesis of rameswaralide has not been reported. With the goal to further investigate rameswaralide's biological activity, and better understand its unknown biosynthesis as well as modes of action, the total synthesis of rameswaralide is proposed with a focus on the tricyclic ABD ring.

4.2 Results and Discussion

4.2.1 General approach towards the synthesis of rameswaralide

Recently, the Romo group has described an approach to total synthesis termed *bioactivity-guided retrosynthesis*, in which incremental increases in complexity through systematic modifications of the postulated pharmacophore of a natural product guides the synthesis. While it is difficult to determine the pharmacophore of rameswaralide, following this guideline of increasing complexity, we focused on the preparation of the

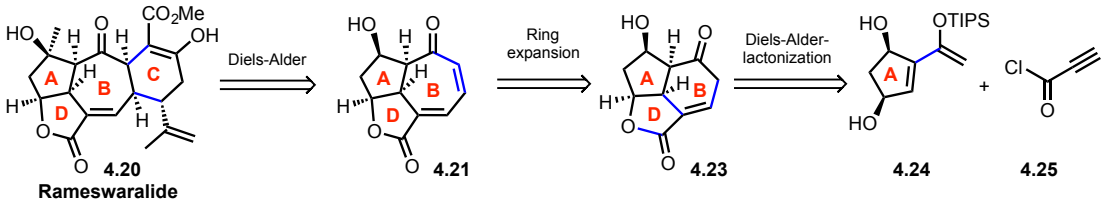
bicycle **4.22**, which can be elaborated toward tricycle ABD **4.21**, enabling us to study the structure activity relationship along the way (Scheme 4.5).



Scheme 4.5 General retrosynthetic approach toward the synthesis of rameswaralide

4.2.2 First generation synthesis: alkynyl acylammonium salts as a key intermediate toward the tricyclic core

The initial studies toward the synthesis of rameswaralide exploited α,β-unsaturated acylammonium salts' chemistry developed in our laboratory. Retrosynthetically, we proposed that the C ring of **4.20** could be formed from a Diels-Alder reaction (Scheme 4.6). In turn, the cycloheptadienone ring B of **4.21** could be achieved from the ring expansion of a 6-membered ring of the tricycle **4.23**. Herein, it is envisioned that the fused BD-ring could be constructed simultaneously from a Diels-Alder-γ-lactonization sequence of an acid chloride **4.25** and cyclopentene **4.24**.

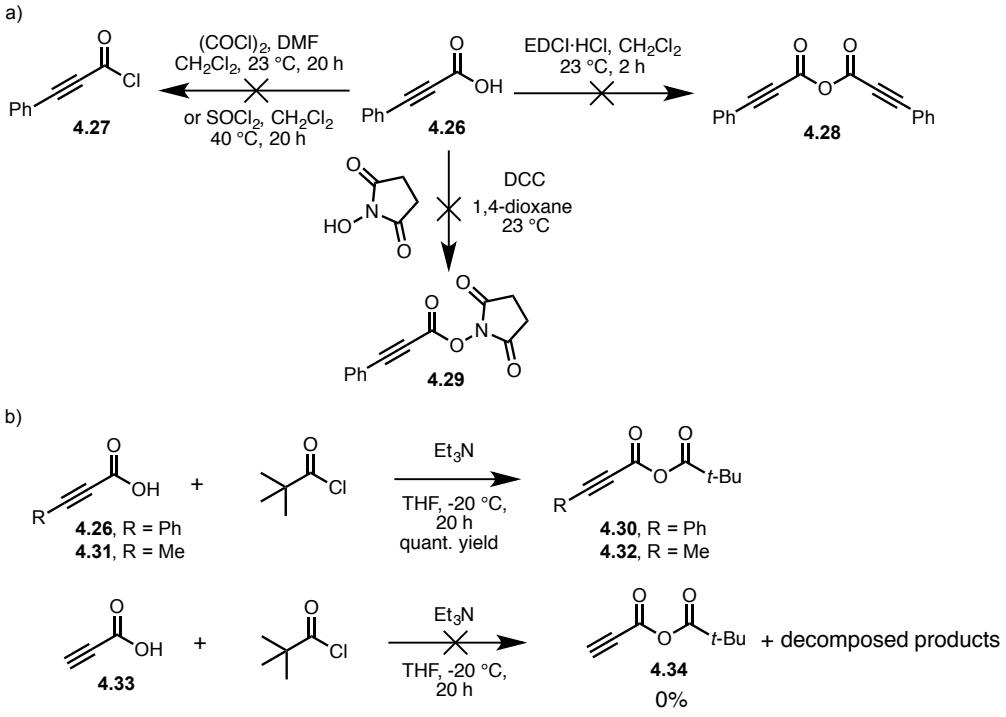


Scheme 4.6 Alkynyl acylammonium salt approach toward synthesis of rameswaralide

While the nucleophile-catalyzed Diels-Alder γ-lactonization (DAL) with α,β-unsaturated acid chlorides *via* an alkenyl acylammonium salt intermediate has been studied extensively in the Romo group[22-23] (also see section 1.1.7), a more efficient approach toward tricycle **4.23** would arguably be the use of an alkynyl acylammonium salt. Therefore, we were prompted to examine the Diels-Alder γ-lactonization using acetylene acid chloride for the first time. We decided to systematically investigate the reactivity of alkynyl acylammonium salts.

4.2.2.1 Generation of reactive starting material alkynyl acid derivatives

From our previous studies of α,β-unsaturated acylammonium salts (see section 1.1.4 – 1.1.7), we know that a reactive starting material is required, such as an acid chloride, to enable the sufficient formation of the critical unsaturated acylammonium salt. While the alkenyl acid chlorides are generally commercially available, the same is not true for alkynyl acid chlorides. In the case of non-commercially available acid chlorides, either the use of *in situ* activation of the corresponding acid through conversion to more reactive carboxylic acid derivative, such as anhydrides, or acid chlorides is employed. Attempts to convert phenyl propiolic acid **4.26** to the corresponding acid chloride **4.27**, symmetrical anhydride **4.28** and activated ester **4.29** were unsuccessful (Scheme 4.7a). Fortunately, pivaloyl anhydrides **4.30** and **4.32** could be prepared readily from phenyl propiolic acid **4.26** and methyl propiolic acid **4.31**, respectively. Interestingly, the same conditions did not lead to the desired pivaloyl anhydride adduct of propiolic acid **4.33**, presumably due to the high reactivity at the β-carbon (Scheme 4.7b).

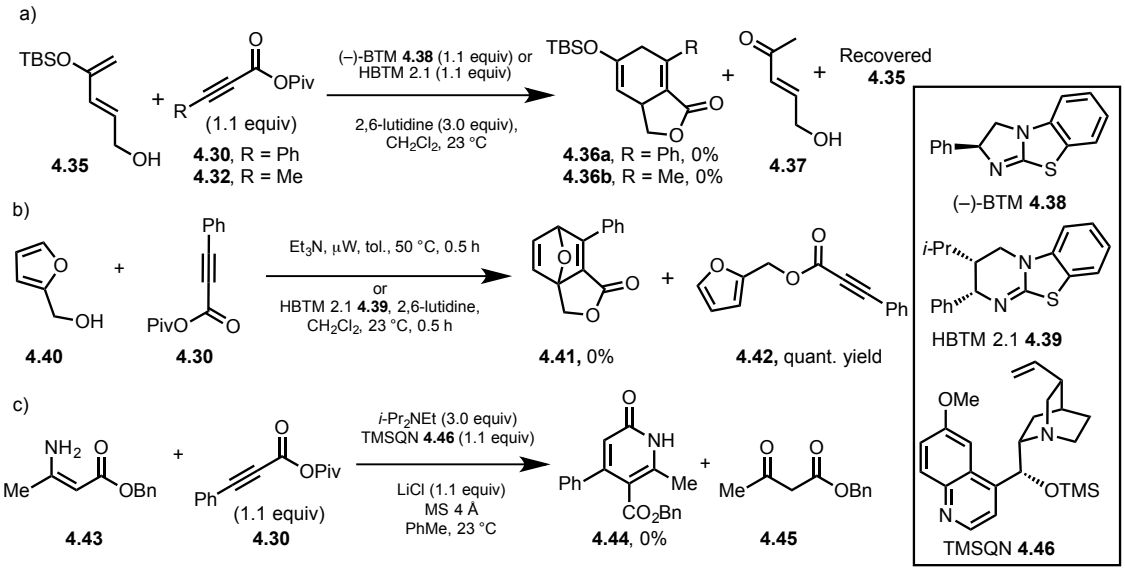


Scheme 4.7 Preparation of activated alkynyl carboxylic derivatives

4.2.2.2 Reactivity of alkynyl acid anhydrides

Having the alkynyl acid anhydride in hands, we decided to test this starting material in various reaction cascades. The Diels-Alder lactonization (DAL) cascade was first chosen as it would be the direct model study for the synthesis of rameswaralide. Using the established conditions with alkenyl acylammonium salts, diene **4.35** did not react with alkynyl anhydride **4.30** or **4.32** to deliver the corresponding desired lactones **4.36a** or **4.36b**, respectively. Instead, unreacted starting materials **4.35** and its desilylated adduct **4.37** were isolated (Scheme 4.8a). When more stable furfuryl alcohol **4.40** was used in place of diene **4.35**, only the undesired *O*-acylation adduct **4.42** was isolated, and the desired lactone **4.41** was not observed (Scheme 4.8b). Mimicking the nucleophile-

catalyzed Michael proton-transfer lactamization (NCMPL) process that was previously developed earlier in the Romo group (see section 3.2.3), anhydride **4.30** was exposed to enamine **4.43**. The desired pyridinone **4.44** was not obtained, however, the hydrolyzed product **4.45** of the starting material **4.43** was isolated (Scheme 4.8c).

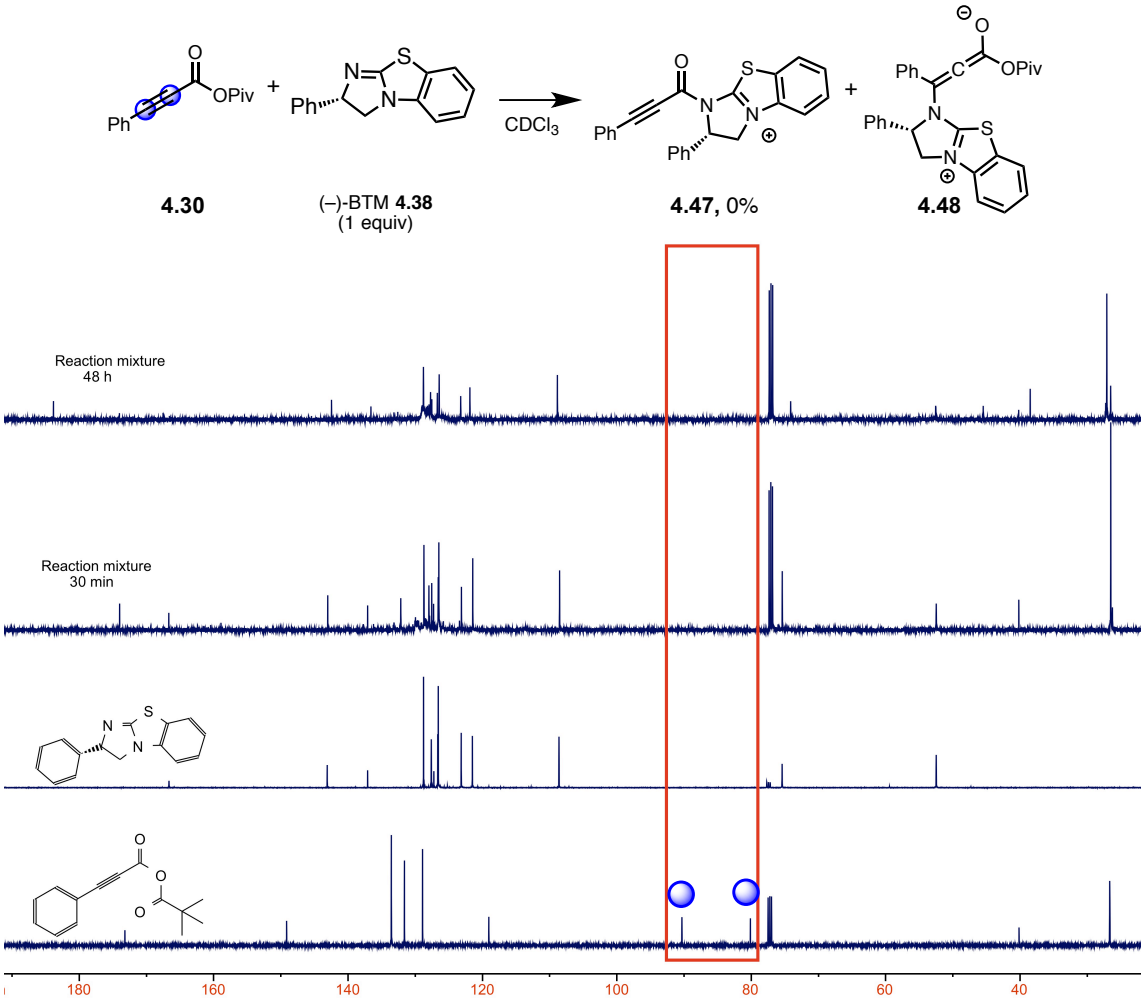


Scheme 4.8 Attempts in using alkynyl reagents in DAL and NCMPL reactions

4.2.2.3 Preliminary NMR study of alkynyl acid anhydrides and tertiary amine catalysts

To better understand the reactivity of the alkynyl anhydrides in the presence of different catalysts employed in the previous reactions, an NMR study was performed. By observing the reactions between anhydride **4.30** and amines (–)-BTM **4.38** and TMSQN **4.46**, we hoped to gain further insights into the formation of the undesired products observed in the previous reactions. In the case of (–)-BTM **4.38**, the alkyne signals at 80.0 and 90.2 ppm in ^{13}C NMR disappeared upon mixing **4.38** with anhydride **4.30**

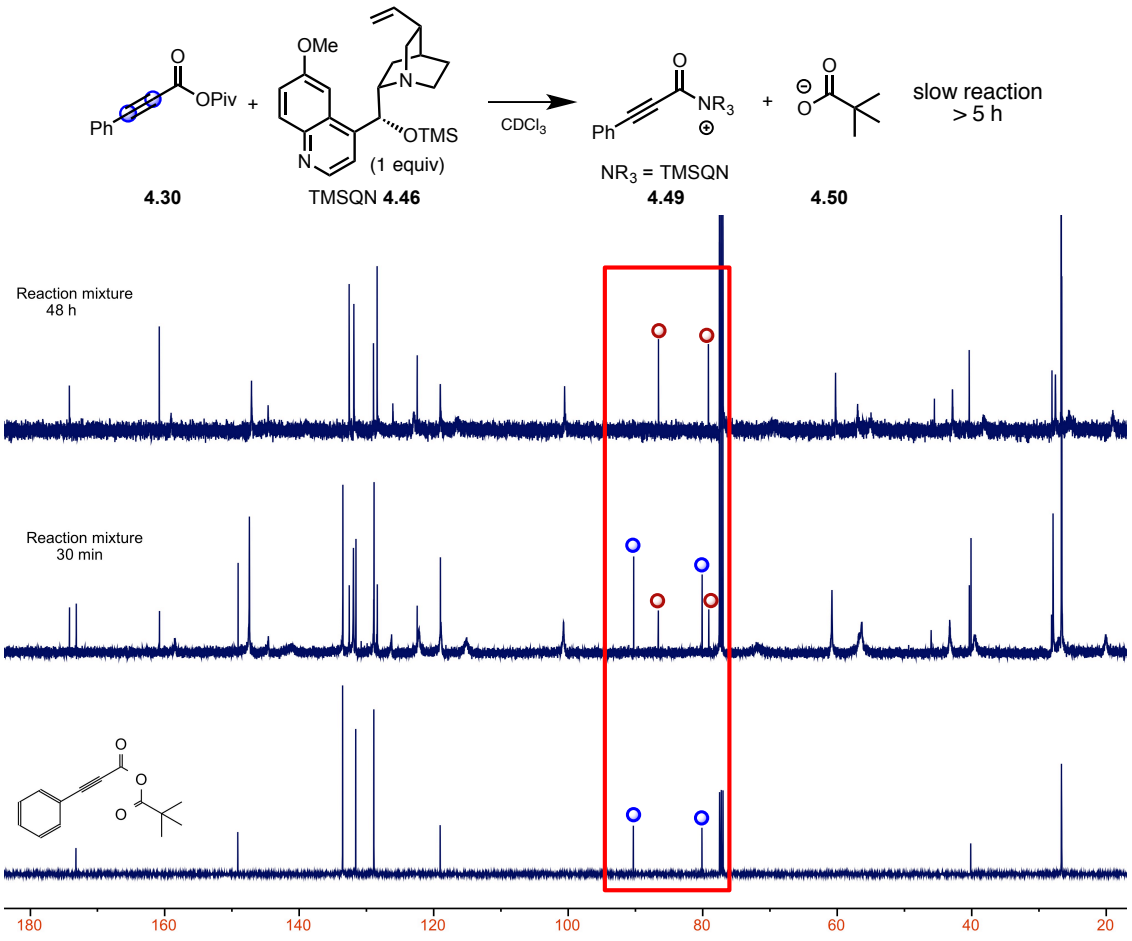
(Scheme 4.9), suggesting no formation of the desired alkynyl acylammonium **4.47**. It was speculated that the nucleophilic BTM **4.38** could undergo a conjugate addition onto the β-carbon leading to ketene **4.48**.



Scheme 4.9 ^{13}C NMR observation of the reaction between alkynyl anhydride and BTM

Interestingly, in a similar experiment with TMSQN **4.46** as the amine catalyst, the alkyne signals in ^{13}C NMR slightly shifted upfield, suggesting the presence of an alkynyl species (Scheme 4.10). While further study and evidence are required to confirm

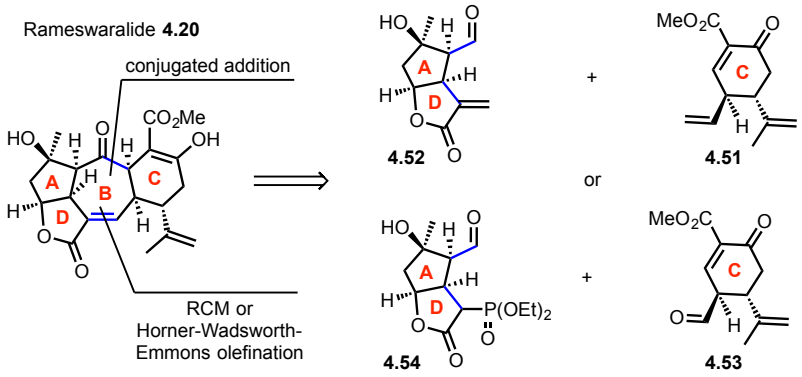
this observation, this preliminary study suggested the subtle differences of the amine catalysts in the generation of alkynyl acylammonium species. Specifically, cinchona alkaloid amines appear to be more suitable, as the more nucleophilic isothiourea catalysts (such as BTM **4.38**) tend to undergo undesired conjugate addition. However, considering the significant amount of work required for the development of this alkynyl acylammonium methodology, we decided to pursue other synthetic routes toward rameswaralide.



Scheme 4.10 ^{13}C NMR observation of the reaction between alkynyl anhydride and TMSQN

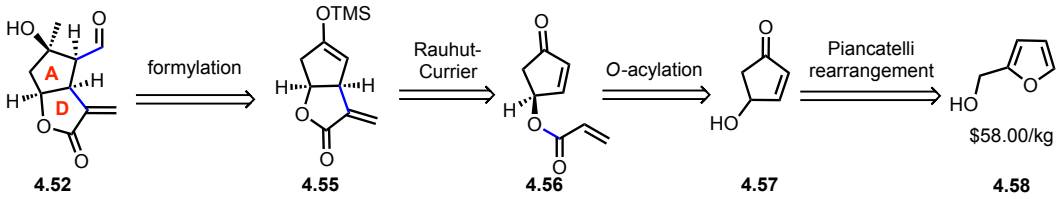
4.2.3 Second generation synthesis: studies toward the formation of bicyclic γ-lactone *via* $C_\alpha - C_\beta$ bond formation

Our current attempt toward the synthesis of rameswaralide consists of a late-stage formation of ring B. Retrosynthetically, ring B could be formed by way of two key reactions: conjugate addition and Horner-Wadsworth-Emmons (HWE) olefination of aldehyde **4.53** and phosphonate lactone **4.54** (Scheme 4.11). Alternatively, a ring closing metathesis (RCM) could also be employed for the formation of ring B. Together with the goals of increasing complexity, we focused our initial attention towards the construction of the bicyclic AD ring system.



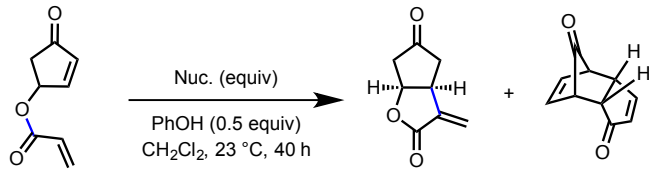
Scheme 4.11 Synthetic strategies toward construction of ring B

In the first generation synthetic analysis toward the bicyclic AD system, aldehyde **4.52** was envisioned to be accessed from a formylation of silyl enol ether **4.55** (Scheme 4.12). A key transformation, the Rauhut-Currier reaction, could be utilized to generate a lactone ring from the starting acylated alcohol **4.56**. Cyclopentenone **4.57** could be prepared *via* a Piancatelli rearrangement of commercially available furfuryl alcohol **4.58**.

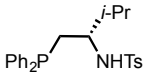
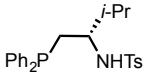


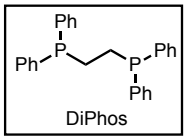
Scheme 4.12 Proposed retrosynthetic analysis of bicyclic AD *via* a key Rauhut-Currier reaction

Table 4.1 Investigation of the Rauhut-Currier reaction toward bicyclic lactone



4.56 **4.59** **4.60**

Entry	Nuc. (equiv)	Additive	Result
1	PPh_3 (1)	-	Recovered **4.56**
2	DABCO (1)	-	Recovered **4.56**
3	DiPhos (1)	-	Recovered **4.56**
4	$P(cyclohexyl)_3$ (1)	-	Recovered **4.56** and 8% of **4.60**
5[a]	$P(cyclohexyl)_3$ (1)	-	messy rxn
6	$P(n\text{-}Bu)_3$ (1)	-	Recovered **4.56**
7		-	Recovered **4.56**
8[b]	$P(n\text{-}Bu)_3$ (1)	TMSOTf	Recovered **4.56**
9[b]		TMSOTf	Recovered **4.56**
10	$TiCl_4$ (1)	-	Recovered **4.56**
11	$SnCl_4$ (1)	-	Recovered **4.56**

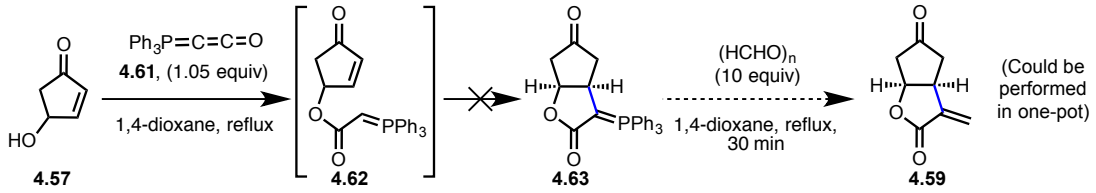


[a]The reaction was performed in a microwave reactor at 50 °C in 1 h
[b]TMSOTf was added to target lactone **4.55** instead of **4.59**

The possibility of the Rauhut-Currier reaction[78] was studied by screening a variety of nucleophiles. Both phosphine and amine nucleophiles, typically used for

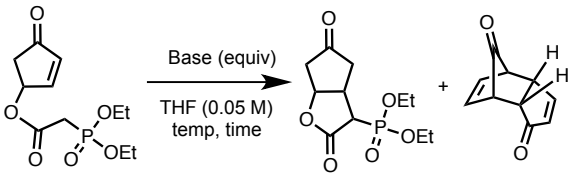
Rauhut-Currier reaction, did not lead to the desired adduct, but instead, starting material **4.56** was recovered (Table 4.1, entries 1-7). In the case of P(cyclohexyl)$_3$ as a nucleophile, β-elimination followed by Diels-Alder reaction led to a low yield of bicyclic **4.60** (entry 4). An attempt to capture the alkoxide adduct with TMSOTf delivering silyl enol ether **4.55** was not successful (entries 8-9). Lewis acids such as $TiCl_4$ and $SnCl_4$ were also found to be ineffective in this reaction (entries 10-11).

In 2009, Taylor and Wood established a one-pot annulation approach to α-alkylidene-γ-lactones using Bestmann ylide **4.61**.[79] Applying this method to cyclopentenone **4.57**, the desired γ-lactone **4.63** was not observed, presumably due to the instability of the intermediate **4.62**, such as decomposing *via* β-elimination (Scheme 4.13).



Scheme 4.13 An attempted one-pot reaction toward α-alkylidene-γ-lactone **4.59**

As we attempted to redesign the aforementioned approach, we envisioned that the bicyclic AD system could be formed *via* an intramolecular conjugated addition[80] of the α-phosphonate ester **4.64** (Scheme 4.14). To this end, multiple conditions including various bases, temperatures, and concentration did not lead to the desired γ-lactone **4.65**. Instead, the bicyclic ketone **4.60** was observed in conjunction with unreacted starting material **4.64**.



4.64 **4.65** **4.60**

Selected examples of tested conditions:

Entry	Base (equiv)	Temp./ Time	Yield (**4.65**)	Yield (**4.60**)	Recovered **4.64**
1	LiHMDS (1.2 equiv)	-78 °C / 1 h	0%	16%	24%
2	NaOMe (1.2 equiv)	-78 °C / 1 h	0%	16%	56%
3	DBU (1.2 equiv)	-78 °C / 1 h	0%	9%	67%
4	NaOMe (1.2 equiv)	-78 °C / 5 h	0%	14%	< 5%
5	DBU (1.2 equiv)	-78 °C / 5 h	0%	16%	21%
6	DBU (2 equiv)	-78 °C / 5 h	0%	22%	9%

Tested conditions:

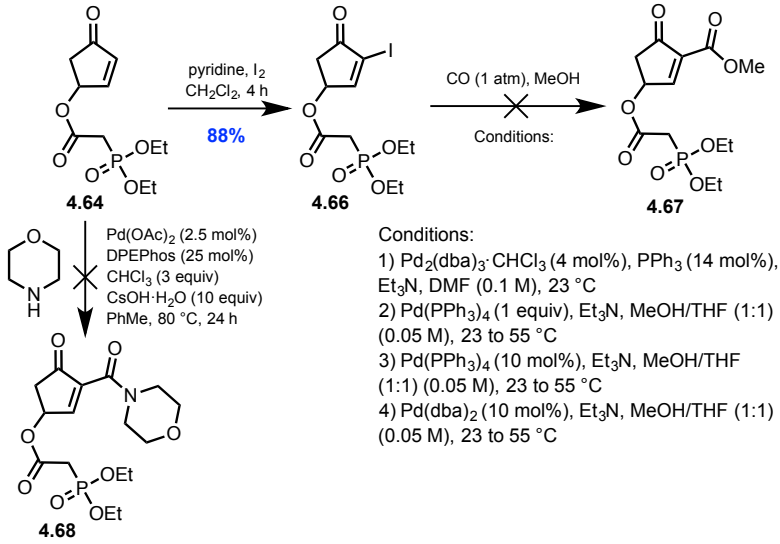
Base (equiv)
LiHMDS, NaHMDS, KHMDS, KO*t*-Bu, NaOMe, DBU (0.9, 1.2, 2 equiv)

Solvent (conc.) + Additive
THF (0.01, 0.05, 0.1 M) TMSCl additive

Temperature
-100, -78, 0, 23 °C

Duration
1–20 h

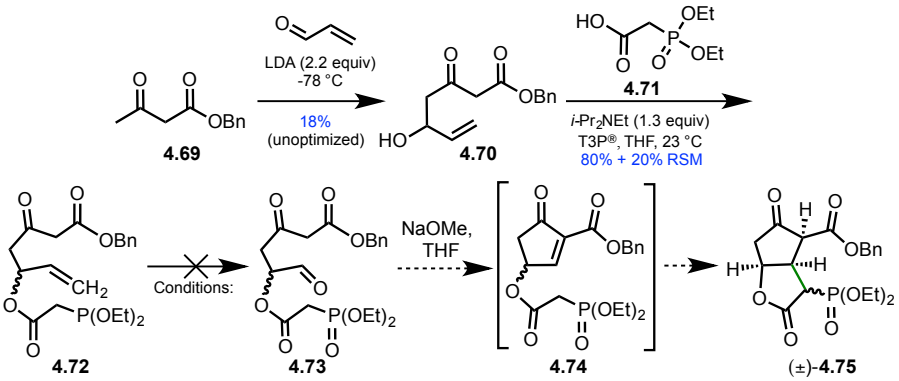
Scheme 4.14 Selected examples of tested conjugate addition toward bicyclic lactone



Scheme 4.15 Attempted syntheses of better Michael acceptors for the intramolecular Michael addition toward bicyclic lactone AD system

Based on our observation of the lack of desired reactivity of **4.64**, we hypothesized that an electron withdrawing group at the α-position of the cyclopentenone would increase the feasibility of a Michael addition. Hence, we sought to prepare a cyclopentenone functionalized with α-electron withdrawing group such as **4.67** and **4.68** (Scheme 4.15). However, a variety of Pd-catalyzed carbonylative esterification of iodocyclopentenone **4.66** did not give the desired adduct under 1 atm pressure (balloon) of CO. A direct acylation using *in situ* CO generation[81] was applied to the conjugated cyclic ketone **4.64** but desired product **4.68** was not observed.

In an alternative approach to the bicyclic lactone system, aldehyde **4.73** was proposed to undergo Knoevanagel condensation and conjugated addition to deliver bicyclic lactone **4.75** (Scheme 4.16). Secondary alcohol **4.70** was prepared by reaction of the bis-enolate of benzyl acetoacetate **4.69** and acrolein. This unoptimized condition gave limited yield but enough material to attempt the next step. Acylation of alcohol **4.70** with diethylphosphonoacetic acid **4.71** delivered the desired ester product **4.72** with 20% recovered alcohol **4.70**. The amount of Hünig's base was proven to be important because any increase of this base's amount reduced the amount of product. Our original plan of oxidizing the terminal alkene **4.72** to aldehyde **4.73** followed by Knoevanagel condensation to deliver cyclopentenone **4.74** was not successful. All of our attempts to oxidize the terminal alkene in **4.72** did not lead to the desired aldehyde **4.73**.

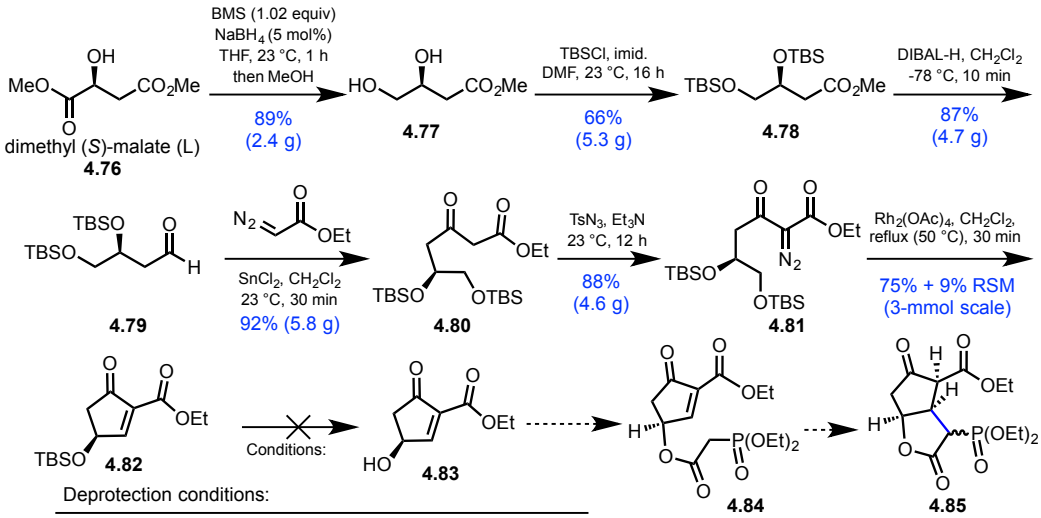


Selected oxidation conditions:

Entry	Conditions	Results
1	i) O_3, CH_2Cl_2, -78 °C; ii) DMS; 0.04M, 48 h	<5% desired product
2	i) O_3, CH_2Cl_2, -78 °C; ii) DMS; 0.06M, 24 h	<5% desired product
3	i) O_3, CH_2Cl_2, -78 °C; ii) DMS; 0.01M, 24 h	<5% desired product
4	i) O_3, CH_2Cl_2, -78 °C; ii) DMS; 0.01M, 3 h	<5% desired product
5	OsO_4 (1 equiv), H_2O:DMF, $NaIO_4$	no product, decomposed SM
6	OsO_4 (10 mol%), H_2O:DMF, $NaIO_4$	no product, decomposed SM

Scheme 4.16 A failed attempt to prepare bicyclic lactone **4.75**

In another route employing the Michael addition to construct the bicyclic lactone AD system, chiral dimethyl (*S*)-malate **4.76** was selectively reduced, followed by silyl protection to deliver ester **4.78** (Scheme 4.17). Upon DIBAL-H reduction, aldehyde **4.79** was converted to β-ketoester **4.80** which subsequently formed the α-diazo adduct **4.81** *via* a diazo transfer reaction. The Rh-catalyzed cyclization went smoothly to deliver cyclopentenone **4.82**.[82] Unfortunately, all of our attempts to remove the TBS- protecting group were not successful. Subsequently, we attempted to remove the silyl group *in situ* and carry the reaction mixture through the subsequent acylation. However, desired cyclopentenone **4.84** was also not observed.

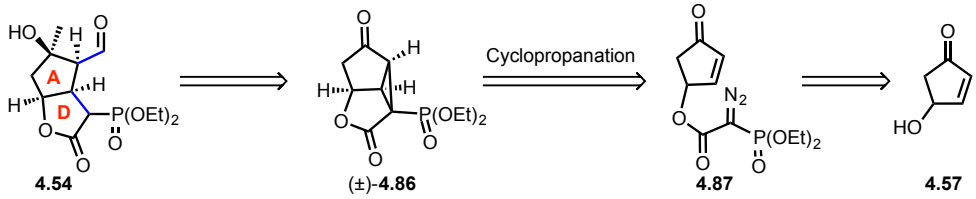


Deprotection conditions:

Entry	Conditions	Results
1	TBAF, THF, 23 °C	decomposed
2	AcCl (5 equiv), MeOH, 23 °C	decomposed
3	TBAF, AcOH, THF, 23 °C	decomposed
4	TASF, DMF or CH_2Cl_2, 23 °C	decomposed
5	PPTS, EtOH:H_2O (9:1), 23 °C	Recovered SM **4.82**
6	DDQ, CH_2Cl_2, 23 °C	Recovered SM **4.82**

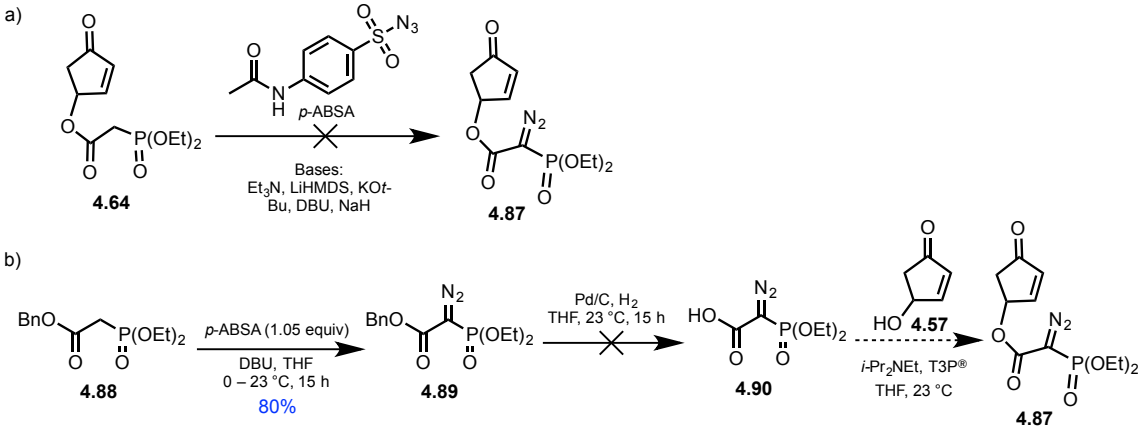
Scheme 4.17 An alternative route toward the bicyclic lactone using a chiral starting material

Exhausting the Michael addition method, we decided to explore a ring-opening approach[83] by utilizing a cyclopropane moiety on lactone **4.86** towards the desired bicyclic lactone **4.54** (Scheme 4.18). We proposed that cyclopropane **4.86** could be constructed from α-diazoester **4.87** *via* a Rh-catalyzed cyclopropanation reaction.



Scheme 4.18 Cyclopropanation approach en route to bicyclic AD system

α-Diazoester **4.87** was envisioned to be accessed by way of diazo transfer using previously prepared phosphonate ester **4.64** (Scheme 4.19). However, under various basic conditions, the diazo transfer reaction did not occur. Alternatively, an acylation of alcohol **4.57** and the α-diazoacid **4.90** was proposed to be a viable route toward the diazoester **4.87**. However, hydrogenolysis[84] of the benzyl ester **4.89** failed to deliver the desired acid **4.90**.

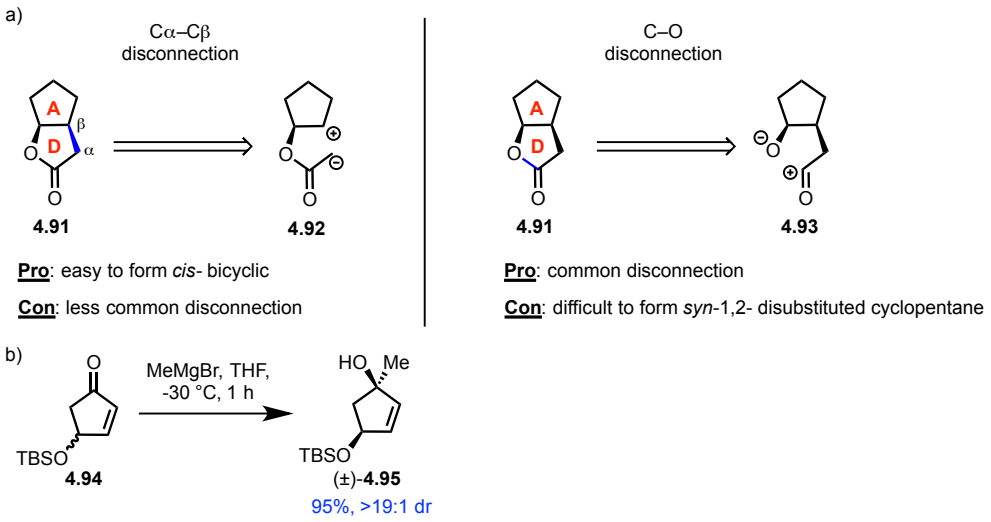


Scheme 4.19 Failed attempts toward construction of diazoester **4.87**

4.2.4 Current route toward bicyclic γ-lactone core

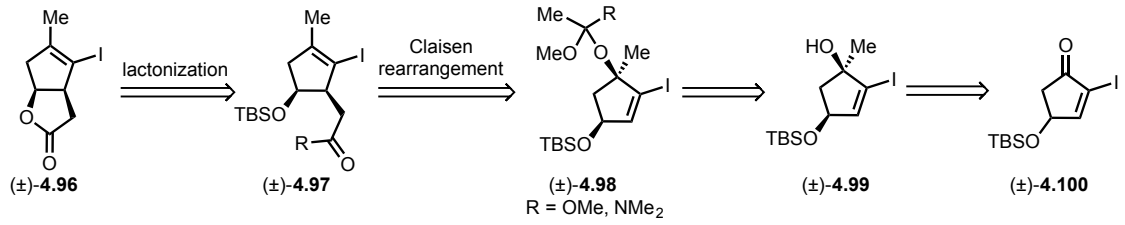
In our earlier retrosynthetic analyses, we attempted a Cα–Cβ bond disconnection on the γ-lactone moiety. In comparison to the C–O bond disconnection, this approach is less common. However, if one wants to form the lactone *via* the C-O bond, it is required to have the *syn*-1,2-disubstituted cyclopentane, which could be difficult due to the small ring size. On the other hand, our proposed Cα–Cβ bond disconnection approach would offer an advantage for the construction of the *cis*-fused bicyclic γ-lactone due to the inherent thermodynamically unstable *trans*-fused 5,5-bicyclic system (Scheme 4.20a).

Indeed, up to this point, all of our approaches toward the bicyclic γ-lactone involve the Cα–Cβ bond disconnection. However, one observation in these early studies urged us to reconsider the C–O bond disconnection approach (Scheme 4.20b). Specifically, methylation of racemic **4.94** gave good yield of the tertiary alcohol **4.95**, and, more importantly, exclusively as one diastereomer with *cis*-1,4-diol configuration. This high diastereoselectivity is likely due to the steric interactions of the TBS protected alcohol. In consequence, if the *cis*- configuration could be transferred from the C1 to C3 position, we could potentially form the precursor **4.93**, enabling us to build the γ-lactone ring *via* the C-O bond.



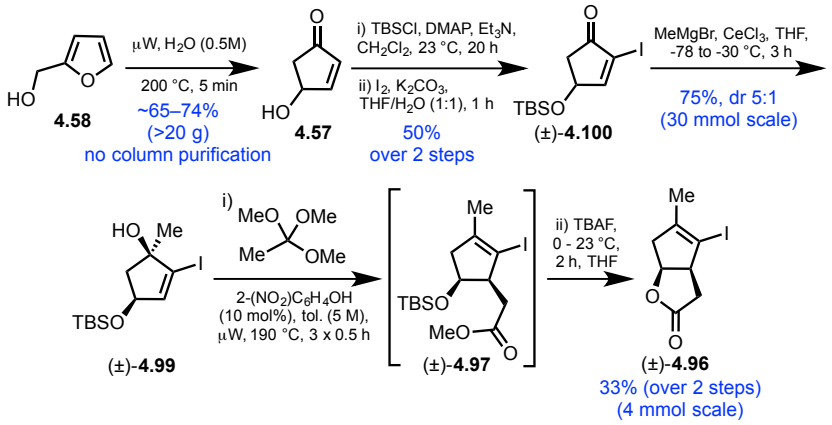
Scheme 4.20 Comparison of different approaches toward the *cis*-bicyclic γ-lactone

Retrosynthetically, the γ-lactone **4.96** could be constructed *via* an intramolecular lactonization of *cis*-3,4-disubstituted cyclopentene **4.97**. We envisioned that this cyclopentene is the product of Claisen rearrangement[85] of allylic ether **4.98** which could be prepared from functionalization of cyclopentenone **4.100** (Scheme 4.21).



Scheme 4.21 Retrosynthetic analysis toward bicyclic lactone *via* lactonization

In a forward sense, commercially available furfuryl alcohol **4.58** was subjected into a Piancatelli rearrangement to deliver cyclopentenone **4.57**. The microwave condition circumvented the low yielding and harsh condition (*e.g* heating at reflux in acidic medium for multiple hours) found in conventional Piancatelli reaction.[86-87] The concentration of the reaction was crucial as high reaction concentrations led to more build-up of polymerized side adducts. It is also worth noting that the product alcohol **4.57** is extracted with water and, hence, free of organic side-products, avoiding column chromatography purification. Upon the TBS protection and α-iodination,[85,88] cyclopentenone **4.100** was isolated in good yield. The tertiary alcohol **4.99** was effectively prepared *via* methylation of ketone **4.100**. The presence of anhydrous $CeCl_3$ tremendously improved the yield of the desired alcohol from 45 to 75%. Tertiary alcohol **4.99** then underwent Johnson-Claisen rearrangement in the presence of trimethyl orthoacetate. Upon silyl deprotection with TBAF, the crude TBS-protected alcohol **4.97** readily cyclized to deliver lactone **4.96**. While the yield was moderate over two steps, it was acceptable considering that five consecutive transformations happened: addition to the orthoacetate, elimination to form enol ether, Johnson-Claisen rearrangement, silyl deprotection, and lactonization.



Scheme 4.22 Current synthetic route toward bicyclic γ-lactone moiety of rameswaralide

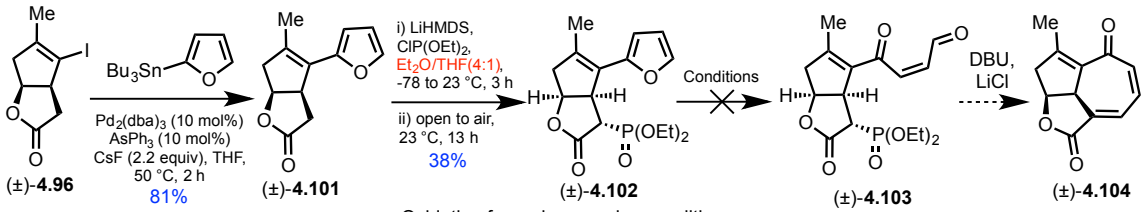
4.2.5 Synthetic efforts toward tricyclic and tetracyclic core of rameswaralide

4.2.5.1 Tricyclic core of rameswaralide

Considering the potential for structure activity relationship studies (SAR) of the tricyclic core of rameswaralide, and as a good model substrate for the construction of the ultimate tetracyclic skeleton, we began our investigations for the formation of the tricyclic core ABD system.

Vinyl iodide **4.96** was coupled with a furan *via* Stille coupling to deliver vinyl furan **4.101** in good yield (Scheme 4.23). The phosphonate group was attached to the Cα of the γ-lactone to prepare for the Horner-Wadsworth-Emmons (HWE) reaction. It was found that the direct reaction of **4.101** with diethyl chlorophosphate did not give the desired **4.102**. Instead, the described procedure involved a one-pot reaction of **4.101** and diethyl chlorophosphite, and was subsequently oxidized in air to deliver α-phosphonate-γ-lactone **4.102**.[89] In this reaction, the diethyl ether as solvent was found to be critical for the construction of the desired adduct. A small amount of THF as co-solvent was also

required to solubilize the starting lactone **4.101**. Subsequent oxidative ring-opening of furan leading to *Z*-enal **4.103**,[90] followed by HWE reaction would result in formation of our desired tricycle **4.104**. Unfortunately, various oxidative ring-opening conditions did not provide the *Z*-enal required for the tricycle formation. Thus, the preparation of thetricycle system needed revision.



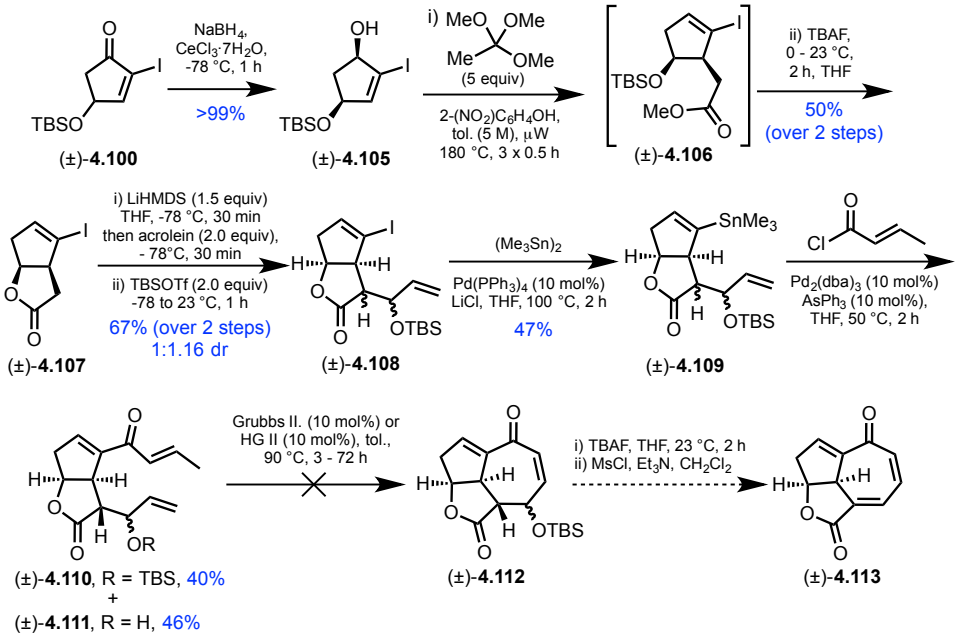
Oxidative furan ring-opening conditions:

Entry	Conditions	Yield (**4.103**)
1	KBr, $NaHCO_3$, Oxone, THF/H_2O (4:1), 0 °C, 2 h	0%
2	NBS, $NaHCO_3$, $Acetone/H_2O$ (10:1), -15 °C, 1 h	0%
3	NBS, pyr, THF/H_2O (4:1), -20 °C, 1 h	0%
4	KBr, $NaHCO_3$, Oxone, $THF/acetone/H_2O$ (5:4:1), 0 °C, 2 h	0%
5	NBS, $NaHCO_3$, $THF/acetone/H_2O$ (5:4:1), 0 °C, 1 h	0%
6	NBS, pyr, $THF/acetone/H_2O$ (5:4:1), -20 °C, 1 h	trace of the *E*-isomer

Scheme 4.23 First design for the construction of a tricyclic core of rameswaralide

In this current route, we decided to generate the secondary alcohol **4.105** instead of using the tertiary alcohol **4.99**. It was reasoned that the methyl group on the A ring locates on the convex side of rameswaralide, thus, kinetically favored to be installed in a later stage. Luche reduction of cyclopentenone **4.100** delivered secondary alcohol **4.105**, which followed the Johnson-Claisen rearrangement to produce bicyclic γ-lactone **4.107** in good yield over two steps. Subsequent aldol reaction with acrolein, followed by a TBS protection provided the protected allylic alcohol **4.108**, which was readily

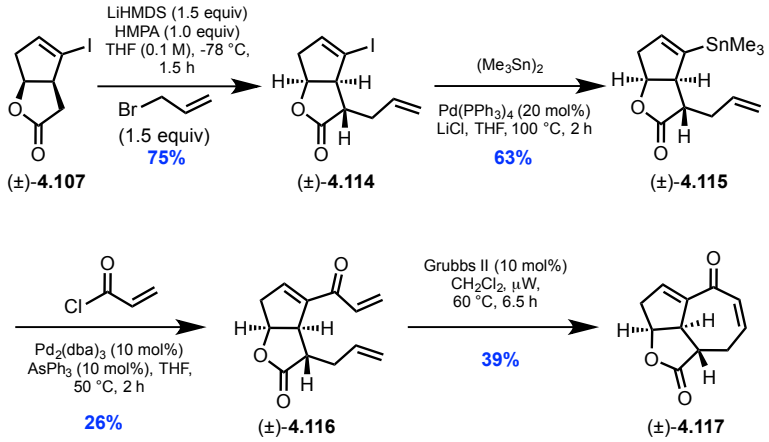
converted to vinyl tin **4.109**. When **4.109** was subjected to Stille cross-coupling condition, a mixture of the coupling product **4.110** and the corresponding desilylated adduct **4.111** were obtained. Upon the successful RCM reaction of **4.110**, cycloheptenone **4.112** could undergo TBS deprotection and β-elimination of the alcohol moiety to deliver the desired tricycle **4.113**. Unfortunately, all of our attempts of RCM reaction on substrate **4.110** did not lead to the desired product **4.112**, with complete recover of starting material **4.110** as the result.



Scheme 4.24 RCM toward tricyclic core of rameswaralide employing allylic alcohol **4.110**

With observed inactivity of **4.110** under various RCM conditions, we converted lactone **4.107** to vinyl iodide **4.114** and subsequent vinyl tin **4.115,** hypothesizing that the bulky OTBS moiety hindered the RCM reaction.[91] To our delight, the Stille adduct

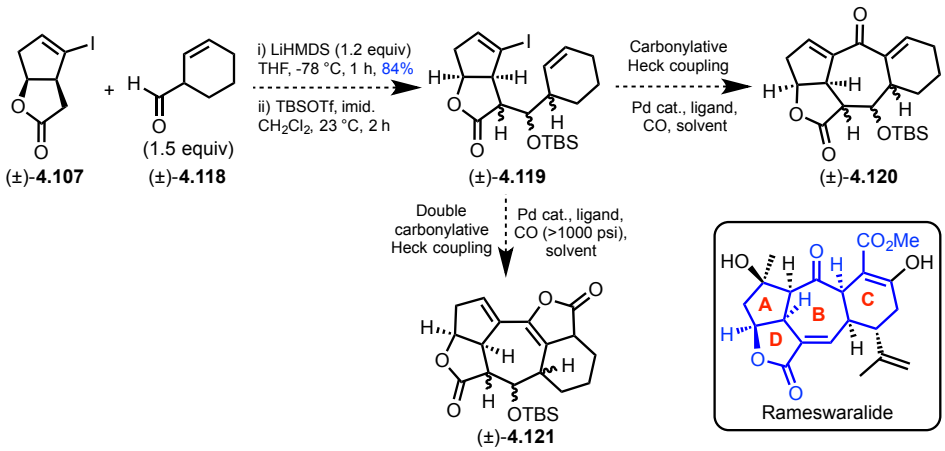
4.116 underwent RCM reaction in the presence of Grubbs II catalyst to deliver the desired cycloheptenone **4.117**, suggesting the detrimental effect of steric hindrance on substrates of RCM reaction.



Scheme 4.25 Synthesis of cycloheptenone 4.117 employing RCM

4.2.5.2 Proposal toward tetracyclic core of rameswaralide

To access the tetracyclic core of rameswaralide, we proposed an intramolecular carbonylative Heck coupling to form the B ring. Vinyl iodide **4.107**, employed in our previous tricycle synthesis, could serve as a common intermediate leading to the Heck coupling precursor **4.119**. Vinyl iodide **4.119** could then undergo intramolecular Heck coupling under a mild pressure of CO, to deliver cycloheptanone **4.120**, whose structure resembles the tetracyclic core of rameswaralide. Interestingly, a recent study by Beller and coworkers has shown that high pressure of CO (>1000 psi) could result in a double carbonylative Heck coupling.[92] Appling this method on vinyl idodide **4.119** would provide us the lactone **4.121** with the carbonyl group installed on ring C in one transformation.



Scheme 4.26 Proposed synthetic route toward the tetracyclic core of rameswaralide

4.3 Conclusion

With our interests in the synthesis and structure activity relationships, a synthetic route, with an increasing complexity of each fragment, was proposed towards the core structure of rameswaralide. The bicyclic AD core of rameswaralide was achieved in six efficient steps. The tricyclic ABD and tetracyclic ABCD core structures are currently pursued.

CHAPTER V

CONCLUSION

5.1 Multicomponent, Catalytic, Enantioselective Michael Michael Aldol β-lactonization (MMAL)

With a vision to combine the efficiency of the described organocascade with a multicomponent reaction, we have developed a catalytic enantioselective multicomponent reaction toward the syntheses of [4.2.0]-bicyclic systems which are present in many natural products. We designed an initial Michael reaction to obtain a competent Michael donor for the subsequent Michael–aldol-lactonization to rapidly achieve molecular complexity in a highly atom-economic manner. In a single operation, we generate four contiguous stereocenters, four new bonds and two new rings in a highly stereoselective manner with isothiourea catalysts as nucleophilic promoters. This three-component reaction highlights the potential of incorporating α,β-unsaturated acylammonium salts into the design of multicomponent, organocascade processes.

5.2 Tandem Michael Proton-transfer Lactamization (NCMPL) toward Chiral Piperidinones and a Dihydropyridinone

We have developed the first direct catalytic asymmetric synthesis of pyrrolidinones from commodity acid chlorides utilizing α,β-unsaturated acylammoniums. Importantly, the formation of these intermediates clearly imparts high facial selectivity and modulates the reactivity of acid chlorides, thus biasing them toward Michael (1,4) addition versus acyl (1,2) substitution. The described methodology is

operationally simple, scalable, and can be carried out using inexpensive and readily available catalysts under mild reaction conditions. We demonstrated the utility of this strategy by applications to biologically relevant *N*-heterocycles including piperidin-2-ones, and a dihydropyridone. Piperidin-2-ones or δ-lactams are not only encountered as structural subunits in bioactive molecules but also precursors of piperidines which are found in numerous natural products and pharmaceuticals. Using β-aminomalonates as two-fold nucleophiles, several chiral piperidin-2-ones have been synthesized with excellent enantioselectivity. With an analogous methodology, a dihydropyridone was also accessed by this reactive intermediate. Furthermore, NMR studies of the reactive intermediate α,β-unsaturated acylammonium salts provided insights into the 1,4 reactivity (versus 1,2 reactivity) by mainly deactivating the acyl carbon (thus reducing 1,2 addition) through electronic and steric effects.

5.3 Progress toward Synthesis of Rameswaralide

Rameswaralide has been a long time interest in our research group due to its complex chemical structure and incomplete biological activity study. With the aim of studying the structure activity relationship during the synthesis, a route toward the rameswaralide core with increasing complexity was designed. The bicyclic core AD was achieved in six steps *via* a key Johnson-Claisen rearrangement. The tricyclic core of rameswaralide was then achieved in an additional four steps employing RCM as a key transformation to construct the seven-membered ring. The tetracyclic core of rameswralide is proposed to be constructed *via* an intramolecular carbonylative Heck coupling.

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APPENDIX A

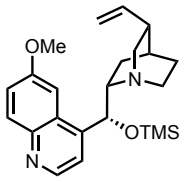
EXPERIMENTAL DATA

General Information

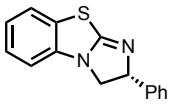
All non-aqueous reactions were performed under a nitrogen or argon atmosphere in oven-dried glassware. Dichloromethane (CH_2Cl_2), tetrahydrofuran (THF) were dried by passing through activated molecular sieves or alumina (solvent purification system). Diisopropylethylamine (*i*-Pr_2NEt) was distilled from potassium hydroxide prior to use. Other solvents and reagents were used as received from commercially available sources. Deuterated solvents were purchased from either Aldrich or Cambridge Isotopes and used as received. ^1H NMR spectra were measured at 600, 500, 400 and 300 MHz and referenced relative to residual chloroform (7.26 ppm) and was reported in parts per million. Coupling constants (*J*) were reported in Hertz (Hz), with multiplicity reported following usual convention: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; ddd, doublet of doublet of doublets; dddd, doublet of doublet of doublet of doublets; dt, doublet of triplets; dq, doublet of quartets; ddq, doublet of doublet of quartets; m, multiplet; bs, broad singlet; app, apparent. ^{13}C NMR spectra were measured at 150, 125, 100, and 75 MHz and referenced relative to residual chloroform (77.2 ppm) and was reported in parts per million (ppm). Flash column chromatography was performed with 60Å Silica Gel (230-400 mesh) as stationary phase using a gradient solvent system or on an automated flash chromatography system (EtOAc/hexanes as eluent unless indicated otherwise). High resolution mass spectra (ESI) were obtained through Texas A&M University Laboratory for Biological Mass Spectrometry and Baylor University Mass Spectrometry Center. Thin Layer Chromatography (TLC) was performed using glass-backed silica gel F254 (Silicycle, 250 μm thickness).

Visualization of developed plates was performed by fluorescence quenching unless indicated otherwise. *Fourier* Transform Infrared (FTIR) spectra were recorded as thin films on NaCl plates. Optical rotations were recorded on a polarimeter at 589 nm employing a 25 mm cell. High Performance Liquid Chromatography (HPLC) was performed on a chromatographic system using various chiral columns (25 cm) as noted.

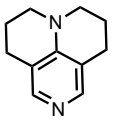
O-TMS quinine[1] (TMSQN) was synthesized according to literature procedures. (+)-BTM and (–)-BTM were purchased from TCI chemicals**.** Acid chlorides **2.3a-c** were purchased from Sigma-Aldrich and **3.1h** was prepared from the corresponding acids according to literature procedures.[2]



TMSQN



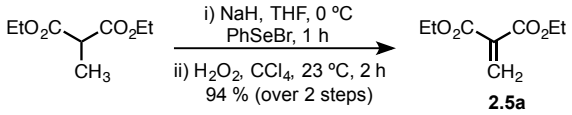
(+)-BTM



9-Azajulolidine

Abbreviation list

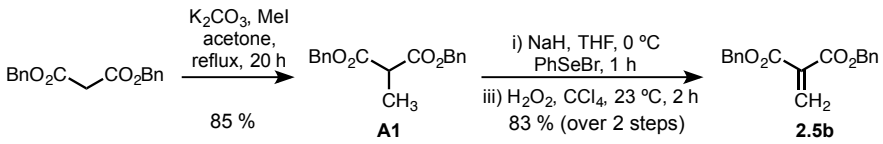
4-PPY	=	4-Pyrrolidinopyridine
9-AJ	=	9-azajulolidine
(*R*)-(+)-BTM	=	benzotetramisole
DBU	=	1,8-diazabicyclo[5.4.0]undec-7-ene
DIPEA	=	*N*,*N*-diisopropylethylamine
DMAP	=	4-(Dimethylamino)pyridine
LiHMDS	=	lithium bis(trimethylsilyl)amide
TBSCl	=	*tert*-butyldimethylsilyl chloride
TMSQN	=	*O*-trimethylsilyl quinine



Diethyl 2-methylenemalonate (2.5a): prepared by a modified published procedure.[3] Into an oven-dried, 500-mL round-bottomed flask containing NaH (60% suspension in mineral oil, 1.50 g, 37.5 mmol, 1.5 equiv) in THF (90 mL) cooled to 0 °C was added slowly diethyl 2-methylmalonate (purchased from Sigma-Aldrich and used as is) (4.27 mL, 25.0 mmol, 1.0 equiv). After gas evolution had ceased, a solution of PhSeBr (7.08 g, 30.0 mmol, 1.2 equiv) in THF (30 mL) was quickly added at 0 °C, resulting in a bright yellow solution. After 30 min, the reaction mixture was diluted with Et_2O (20 mL) and quenched with saturated $NaHCO_3$ (50 mL). The organic layer was separated and washed with 10% $NaHSO_3$ (2 × 50 mL), H_2O (3 × 50 mL) and dried over anhydrous Na_2SO_4. The filtrate was concentrated by rotary evaporation, and purified by an automated flash chromatography system (0 → 50% EtOAc/hexanes) to afford diethyl 2-methyl-2-(phenylselanyl)malonate which was carried on directly to the next step.

An oven-dried, 250-mL round-bottomed flask was charged with a solution of diethyl 2-methyl-2-(phenylselanyl)malonate in anhydrous CCl_4 (34 mL), followed by addition of H_2O_2 (35% in H_2O, 21.4 mL, 250 mmol, 10.0 equiv). The reaction temperature was maintained at ambient temperature (23 °C) using a water bath. After 2 h, H_2O (10 mL) was added to dissolve the white precipitate. The organic layer was then separated and the aqueous phase was extracted with anhydrous CCl_4 (3 × 10 mL), and the combined organics were dried over anhydrous Na_2SO_4. The filtrate was concentrated by rotary evaporation (without heating) to afford pure diethyl 2-methylenemalonate **2.5a**

(4.1 g, 94% yield, light yellow liquid) of sufficient purity to be used directly in the next step (Note: purification of this compound led to extensive loss of material on silica). The compound **2.5a** was stored as a solution in anhydrous benzene (1.0 M) at –20 °C to prevent decomposition. TLC (EtOAc:hexanes, 1:9 *v/v)*: R_f = 0.50; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 6.46 (s, 2H), 4.24 (q, *J* = 7.2 Hz, 4H), 1.28 (t, *J* = 7.1 Hz, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 164.0, 135.2, 134.0, 61.5, 14.1. Spectral data match what was previously synthesized.[4]



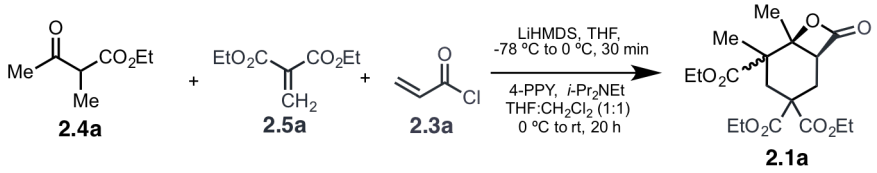
Dibenzyl 2-methylenemalonate (2.5b). Dibenzyl 2-methylmalonate **A1** was prepared by a modified reported procedure.[5] In an oven-dried, 250-mL round-bottomed flask, dibenzyl malonate (14.2 g, 50.0 mmol, 1.0 equiv) and anhydrous K_2CO_3 (8.3 g, 60.0 mmol, 1.2 equiv) were dissolved in anhydrous acetone (50 mL) and stirred at ambient temperature (23 °C) for 5 minutes, then iodomethane (3.73 mL, 60.0 mmol, 1.2 equiv) was added dropwise. The reaction mixture was refluxed (60-65 °C) for 20 h. Upon completion (as judged by TLC), the reaction mixture was diluted with Et_2O (50 mL) and filtered through a pad of celite (Et_2O wash). The filtrate was concentrated by rotary evaporation, and purified by an automated flash chromatography system (0 → 10% EtOAc/hexanes) to obtain dibenzyl 2-methylmalonate **A1** (12.6 g, 85% yield) as clear liquid. Spectral data matched that previously reported.[6]

Dibenzyl 2-methylenemalonate **2.5b** was prepared by a modified published procedure.[3] Into an oven-dried, 250-mL round-bottomed flask containing NaH (60% suspension in mineral oil, 1.40 g, 35.0 mmol, 1.5 equiv) in THF (80 mL) cooled to 0 °C was added slowly a solution of dibenzyl 2-methylmalonate **A1** (6.90 g, 23.3 mmol, 1.0 equiv) in THF (10 mL). After gas evolution had ceased, a solution of PhSeBr (6.61 g, 28.0 mmol, 1.2 equiv) in THF (20 mL) was quickly added at 0 °C, resulting in a bright yellow solution. After 30 min, the reaction mixture was diluted with Et_2O (20 mL) and quenched with saturated $NaHCO_3$ (50 mL). The organic layer was separated and washed with 10% $NaHSO_3$ (2 × 50 mL), H_2O (3 × 50 mL) and dried over anhydrous Na_2SO_4. The filtrate was concentrated by rotary evaporation, and purified by an automated flash chromatography system (0 → 10% EtOAc/hexanes) to afford dibenzyl 2-methyl-2-(phenylselanyl)malonate which was carried on directly to the next step.

An oven-dried, 100-mL round-bottomed flask was charged with a solution of dibenzyl 2-methyl-2-(phenylselanyl)malonate in anhydrous CCl_4 (30 mL), followed by addition of H_2O_2 (35% in H_2O, 20.0 mL, 233 mmol, 10.0 equiv). The reaction temperature was maintained at ambient temperature (23 °C) using a water bath. After 2 h, H_2O (10 mL) was added to dissolve the white precipitate. The organic layer was then separated and the aqueous phase was extracted with anhydrous CCl_4 (3 × 10 mL), and the combined organics were dried over anhydrous Na_2SO_4. The filtrate was concentrated by rotary evaporation to afford pure dibenzyl 2-methylenemalonate **2.5b** (5.67 g, 83% yield, light yellow liquid) of sufficient purity to be used directly in the next step (Note: purification of this compound led to extensive loss of material on silica). The compound

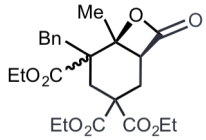
2.5b was stored as a solution in anhydrous benzene (1.0 M) at –20 °C to prevent decomposition. TLC (EtOAc:hexanes, 2:8 *v/v)*: R_f = 0.80; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.42-7.35 (m, 10H), 6.65 (s, 2H), 5.31 (s, 4H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 163.7 (2), 135.6 (2), 135.4, 134.5, 128.6 (4), 128.4 (2), 128.3 (4), 67.3 (2); **IR** (thin film): 3066, 3034, 2956, 1735, 1498, 1456, 1385, 1324, 1223, 1123 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{18}H_{16}O_4Na$ $[M+Na]^+$: 319.0941; found 319.0929.

Representative procedure for racemic Michael Michael aldol lactonization:



Triethyl (1*S*,6*S*)-5,6-dimethyl-8-oxo-7-oxabicyclo[4.2.0]octane-3,3,5-tricarboxylate ((±)-2.1a). An oven-dried, 10-mL round-bottomed flask was charged with a solution of LiHMDS (0.33 mL of 1.0 M solution in THF, 0.33 mmol, 1.1 equiv) in THF (0.5 mL) at -78 °C, followed by slow, dropwise addition of a solution of β-ketoester **2.4a** (43 mg, 0.30 mmol, 1.0 equiv) in THF (0.5 mL) by syringe over ~ 2 min. The resulting mixture was warmed to 0 °C and stirred for 30 min, then a solution of diester **2.5a** (0.33 mL of 1.0 M solution in benzene, 0.33 mmol, 1.1 equiv), diluted to 1.0 mL with THF, was added dropwise via a syringe over ~ 3 min. After 30 min at 0 °C, a solution of 4-PPY (9 mg, 0.06 mmol, 20 mol%) and *i*-Pr_2NEt (78 μL, 0.30 mmol, 1.0 equiv), weighed out in a vial and diluted with CH_2Cl_2 (1.0 mL), was added via a syringe. A solution of acid chloride **2.3a** (41 mg, 1.5 mmol, 1.5 equiv) in CH_2Cl_2 (1.0 mL) was then added at 0 °C over 30 min by a syringe pump. The reaction temperature was maintained at 0 °C

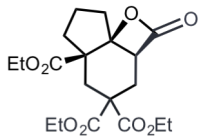
throughout the addition of **2.3a** and then the reaction was stirred at room temperature (23 °C) for an additional 3 h. Upon completion (as judged by TLC), the reaction was concentrated by rotary evaporation and the product was purified by an automated flash chromatography system (gradient of 0 to 40% EtOAc/hexanes) to afford two separable 2 diastereomers of bicyclic-β-lactone **2.1a** (diastereomer A: 30 mg, 27% yield; diastereomer B: 30 mg, 27% yield;) as a yellow, viscous liquid. Diastereomer A: TLC (EtOAc:hexanes, 2:8 *v/v,* Hanessian's stain): R_f = 0.38. **^{1}H NMR** (500 MHz, benzene-d_6): δ 4.07 – 3.80 (m, 7H), 2.94 (t, *J* = 4.2 Hz, 1H), 2.88 – 2.82 (m, 2H), 2.74 (d, *J* = 15.6 Hz, 1H), 1.36 (s, 3H), 1.18 (s, 3H), 0.98 – 0.85 (m, 9H); **IR** (thin film): 2983, 2940, 1828, 1731, 1449, 1387, 1367, 1245, 1111, 1057, 856, 825 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{18}H_{26}O_8Na$ $[M+Na]^+$: 393.1520, found: 393.1506. Diastereomer B: TLC (EtOAc:hexanes, 2:8 *v/v,* Hanessian's stain): R_f = 0.32. **^{1}H NMR** (500 MHz, benzene-d_6): δ 4.00 – 3.81 (m, 6H), 3.52 (d, *J* = 16.0 Hz, 1H), 2.80 (d, *J* = 16.0 Hz, 1H), 2.70 (dd, *J* = 6.3, 2.6 Hz, 1H), 2.61 (dd, *J* = 16.6, 2.6 Hz, 1H), 2.52 (dd, *J* = 16.6, 6.3 Hz, 1H), 1.37 (s, 3H), 1.13 (s, 3H), 0.91 (t, *J* = 7.1 Hz, 3H), 0.85 (app q, *J* = 7.1 Hz, 6H); **^{13}C NMR** (125 MHz, benzene-d_6): δ 172.6, 172.2, 171.2, 168.9, 78.7, 62.4, 62.0, 61.5, 54.3, 51.3, 47.9, 31.6, 23.5, 21.3, 20.2, 14.0, 13.8, 13.8; **IR** (thin film): 2983, 2940, 1828, 1731, 1449, 1387, 1367, 1245, 1111, 1057, 856, 825 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{18}H_{26}O_8Na$ $[M+Na]^+$: 393.1520, found: 393.1506.



(±)-**2.1b**

Triethyl (1*S*,6*S*)-5-benzyl-6-methyl-8-oxo-7-oxabicyclo[4.2.0]octane-3,3,5-tricarboxylate ((±)-**2.1b**): Prepared according to the procedure for compound **2.1a** using LiHMDS (0.33 mL of 1.0 M solution in THF, 0.33 mmol, 1.1 equiv) in THF (0.5 mL), ethyl 2-benzylacetoacetate **2.4b** (66 mg, 0.30 mmol, 1.0 equiv) in THF (0.5 mL), a solution of diester **2.5a** (0.33 mL of 1.0 M solution in benzene, 0.33 mmol, 1.1 equiv) in THF (0.5 mL), a solution of 4-PPY (9 mg, 0.06 mmol, 20 mol%) and *i*-Pr_2NEt (78 μL, 0.30 mmol, 1.0 equiv) in CH_2Cl_2 (1.0 mL), and a solution of acid chloride **2.3a** (41 mg, 1.5 mmol, 1.5 equiv) in CH_2Cl_2 (1.0 mL). Upon completion (as judged by TLC), the crude product was purified by an automated flash chromatography system (gradient of 0 to 40% EtOAc/hexanes) to afford a 1:1 diastereomeric mixture of bicyclic-β-lactone **2.1b** (117 mg, 75% yield) as a yellow, viscous liquid: TLC (EtOAc:hexanes, 2:8 *v/v,* Hanessian's stain): R_f = 0.37. NMR data is reported as a 1:1 diastereomeric mixture: **^{1}H NMR** (500 MHz, benzene-d_6): δ 7.18 – 6.95 (m, 10H), 4.09 – 3.72 (m, 12H), 3.45 – 3.36 (m, 2H), 3.22 (d, *J* = 15.9 Hz, 1H), 3.11 (d, *J* = 13.5 Hz, 1H), 2.95 (d, *J* = 13.5 Hz, 1H), 2.84 – 2.81 (m, 1H), 2.81 – 2.76 (m, 1H), 2.71 – 2.52 (m, 5H), 2.31 (d, *J* = 14.7 Hz, 1H), 2.13 – 2.06 (m, 1H), 1.52 (s, 3H), 1.50 (s, 3H), 0.95 (dt, *J* = 20.8, 7.1 Hz, 6H), 0.84 (t, *J* = 7.2 Hz, 3H), 0.79 (td, *J* = 7.1, 0.9 Hz, 6H), 0.68 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (125 MHz, benzene-d_6): δ 172.10, 171.80, 171.39, 170.78, 170.78, 170.53, 168.59, 168.22, 136.32, 136.30, 130.56, 129.62, 128.12, 127.96, 126.70, 126.55, 79.14, 79.04, 62.15, 62.07, 61.47, 61.37, 61.07, 60.69, 54.25, 52.30, 51.80, 51.70, 50.82, 39.87, 38.29, 31.41, 25.85, 23.89, 23.32, 22.23, 21.55, 13.52, 13.49, 13.41, 13.27, 13.15; **IR** (thin film):

2980, 2956, 2918, 2849, 1829, 1733, 1455, 1251, 1096 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{24}H_{30}O_8Na$ $[M+Na]^+$: 469.1833, found: 469.1818.

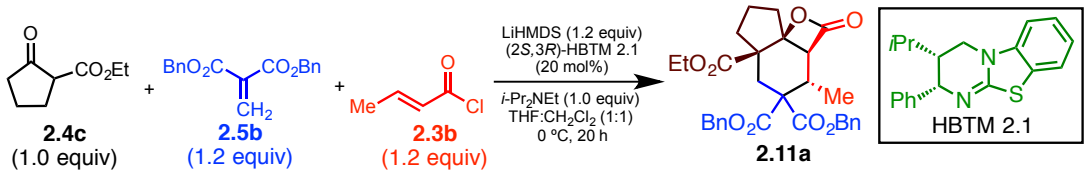


(±)-2.1c

Triethyl (2a*S*,5a*R*,8a*S*)-2-oxotetrahydro-2*H*-indeno[3a,4-*b*]oxete-4,4,5a(5*H*,6*H*)-tricarboxylate ((±)-**2.1c**): Prepared according to the procedure for compound **2.1a** using LiHMDS (0.33 mL of 1.0 M solution in THF, 0.33 mmol, 1.1 equiv) in THF (0.5 mL), ethyl 2-oxocyclopentanecarboxylate **2.4c** (47 mg, 0.30 mmol, 1.0 equiv) in THF (0.5 mL), a solution of diester **2.5a** (0.33 mL of 1.0 M solution in benzene, 0.33 mmol, 1.1 equiv) in THF (0.5 mL), a solution of 4-PPY (9 mg, 0.06 mmol, 20 mol%) and *i*-Pr_2NEt (78 μL, 0.30 mmol, 1.0 equiv) in CH_2Cl_2 (1.0 mL), and a solution of acid chloride **2.3a** (41 mg, 1.5 mmol, 1.5 equiv) in CH_2Cl_2 (1.0 mL). Upon completion (as judged by TLC), the crude product was purified by an automated flash chromatography system (gradient of 0 to 45% EtOAc/hexanes) to afford a single diasteremer of tricyclic-β-lactone **2.1c** (66.4 mg, 58% yield) as a yellow, viscous liquid: TLC (EtOAc:hexanes, 2:8 *v/v,* Hanessian's stain): R_f = 0.47. **^{1}H NMR** (500 MHz, benzene-d_6): δ 3.99 – 3.90 (m, 4H), 3.82 (q, *J* = 7.1 Hz, 2H), 3.32 (dd, *J* = 10.2, 9.3 Hz, 1H), 3.04 (d, *J* = 15.2 Hz, 1H), 2.76 (dd, *J* = 14.2, 10.2 Hz, 1H), 2.63 – 2.47 (m, 2H), 2.25 (dd, *J* = 15.2, 1.3 Hz, 1H), 2.07 – 1.94 (m, 1H), 1.77 – 1.63 (m, 2H), 1.58 – 1.36 (m, 2H), 0.97 (t, *J* = 7.1 Hz, 3H), 0.89 (t, *J* = 7.1 Hz, 3H), 0.83 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (125 MHz, benzene-d_6): δ 172.9, 171.6, 170.7, 169.4, 85.3, 61.8, 61.8, 61.7, 52.7, 52.5, 51.2, 39.4, 39.0, 37.1, 27.0, 23.3, 13.9, 13.9, 13.9; **IR** (thin film): 2979, 2959, 2933, 2873, 2852, 1834, 1733, 1465, 1367, 1250,

1100, 1024, 860 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{19}H_{26}O_8Na$ $[M+Na]^+$: 405.1520, found: 405.1508.

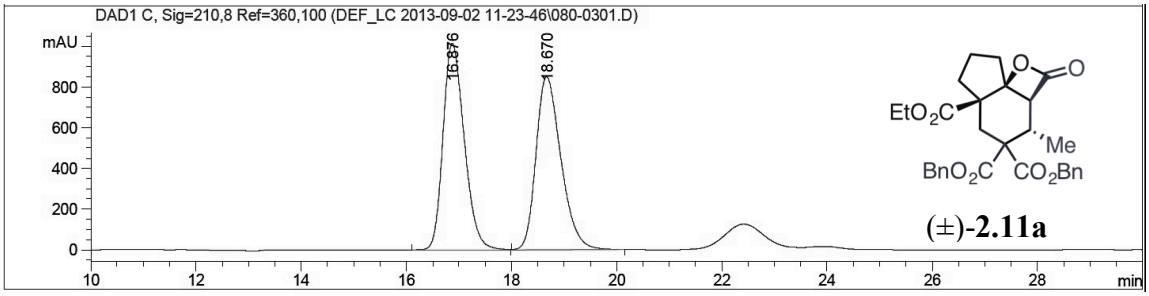
Representative procedure for the enantioselective Michael Michael aldol lactonization:



4,4-Dibenzyl 5a-ethyl (2a*S*,3*S*,5a*R*,8a*S*)-3-methyl-2-oxotetrahydro-2*H*-indeno[3a,4-*b*]oxete-4,4,5a(5*H*,6*H*)-tricarboxylate ((+)-2.11a). Into an oven-dried, 10-mL round-bottomed flask containing a solution of LiHMDS (0.36 mL of 1.0 M solution in THF, 0.36 mmol, 1.2 equiv) in THF (0.5 mL) at 0 °C, was added dropwise a solution of ethyl 2-oxocyclopentanecarboxylate **2.4c** (47 mg, 0.30 mmol, 1.0 equiv) in THF (0.5 mL) over ~ 2 min. The resulting mixture was stirred for 15 min at 0 °C, followed by a dropwise addition of a solution of diester **2.5b** (0.36 mL of 1.0 M solution in benzene, 0.36 mmol, 1.2 equiv) in THF (0.5 mL) over ~ 2 min. After 15 min at 0 °C, a solution of (2*S*,3*R*)-HBTM 2.1 (19 mg, 0.060 mmol, 20 mol%) and *i*-Pr_2NEt (78 µL, 0.30 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL) was added. A solution of acid chloride **2.3b** (38 mg, 0.36 mmol, 1.2 equiv) in CH_2Cl_2 (1.0 mL) was then added at 0 °C over 5 h using a syringe pump. The reaction temperature was maintained at 0 °C throughout the addition of **2.3b** and then the reaction was stirred at this temperature for 15 h. Upon completion (as judged by TLC), the reaction was concentrated by rotary evaporation and the product

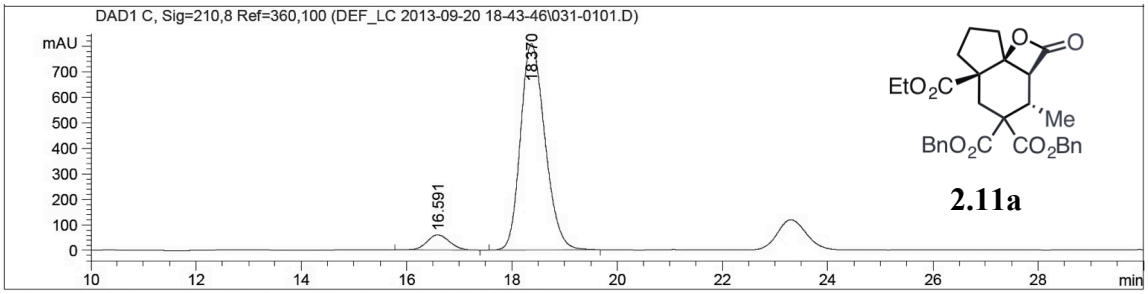
was purified by an automated flash chromatography system (0 to 30% gradient of EtOAc/hexanes) to afford a single diastereomer of tricyclic-β-lactone **2.11a** (67 mg, 43% yield) as a yellow, viscous liquid: TLC (EtOAc:hexanes, 2:8 *v/v,* Hanessian's stain): $R_f = 0.50$. $[\alpha]_D^{23.3} = +1.60$ (c = 1.0, $CHCl_3$). Enantiomeric ratio was determined by HPLC analysis in comparison with authentic racemic material using a Chiracel AD-H column: hexanes:*i*PrOH = 95:5, flow rate 1.0 mL/min, λ = 210 nm: t_{minor} = 16.6 min, t_{major} = 18.4 min; 93.5:6.5 *er*. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.43 – 7.23 (m, 10H), 5.21 (s, 2H), 5.13 (app d, J = 4.3 Hz, 2H), 4.16 (q, J = 7.1 Hz, 2H), 3.26 (d, J = 11.6 Hz, 1H), 2.98 (d, J = 15.2 Hz, 1H), 2.88 – 2.76 (m, 1H), 2.60 (ddd, J = 13.0, 7.4, 5.1 Hz, 1H), 2.31 – 2.16 (m, 2H), 2.10 – 1.85 (m, 2H), 1.72 – 1.57 (m, 2H), 1.25 (t, J = 7.1 Hz, 3H), 1.21 (d, J = 6.6 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 173.1, 171.0, 170.8, 170.2, 135.3, 134.7, 128.8, 128.8, 128.6, 128.5, 128.4, 87.3, 67.7, 67.6, 61.8, 57.5, 57.0, 52.5, 39.7, 39.0, 38.7, 33.7, 23.7, 16.8, 14.1; **IR** (thin film): 3065, 3034, 2963, 1828, 1729, 1498, 1455, 1370, 1251, 750, 698 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{30}H_{33}O_8$ $[M+H]^+$: 521.2175, found: 521.2159.

Determination of enantiomeric ratio of β-lactone 2.11a:



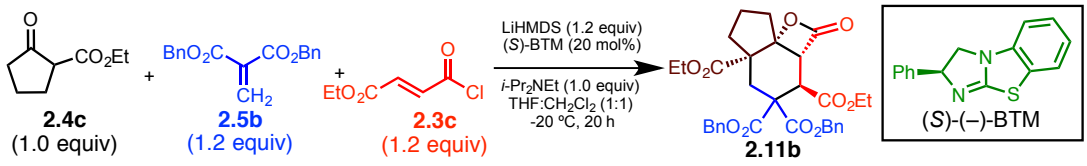
Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.876	BB	0.4350	2.84231e4	1014.05951	50.3565
2	18.670	BB	0.5025	2.80206e4	850.11774	49.6435



Signal 3: DAD1 C, Sig=210,8 Ref=360,100

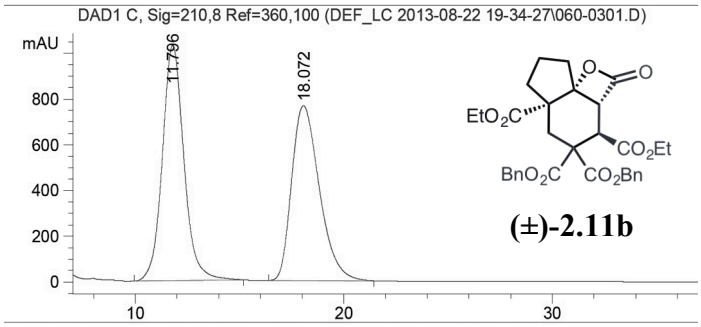
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.591	BB	0.4725	1789.42395	59.21666	6.4220
2	18.370	BB	0.5026	2.60748e4	807.71515	93.5780



(2a*R*,3*R*,5a*S*,8a*R*)-4,4-Dibenzyl 3,5a-diethyl 2-oxohexahydro-2*H*-indeno[3a,4-*b*]oxete-3,4,4,5a(5*H*)-tetracarboxylate ((+)-2.11b). Into an oven-dried, 10-mL round-bottomed flask containing a solution of LiHMDS (0.36 mL of 1.0 M solution in THF, 0.36 mmol, 1.2 equiv) in THF (0.5 mL) at -20 °C, was added dropwise a solution of ethyl 2-oxocyclopentanecarboxylate **2.4c** (47 mg, 0.30 mmol, 1.0 equiv) in THF (0.5 mL) over ~ 2 min. The resulting mixture was stirred for 15 min at -20 °C, followed by a dropwise addition of a solution of diester **2.5b** (0.36 mL of 1.0 M solution in benzene, 0.36 mmol, 1.2 equiv) in THF (0.5 mL) over ~ 2 min. After 15 min at -20 °C, a solution

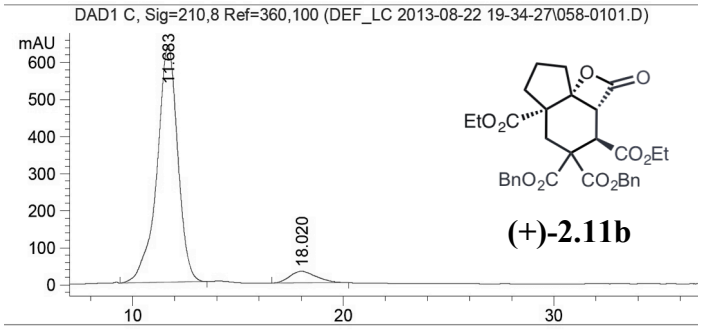
of (*S*)-BTM (15 mg, 0.060 mmol, 20 mol%) and *i*-Pr_2NEt (78 μL, 0.30 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL) was added. A solution of acid chloride **2.3c** (59 mg, 0.36 mmol, 1.2 equiv) in CH_2Cl_2 (1.0 mL) was then added at -20 °C over 5 h using a syringe pump. The reaction temperature was maintained at -20 °C throughout the addition of **2.3c** and then the reaction was stirred at this temperature for 15 h. Upon completion (as judged by TLC), the reaction was concentrated by rotary evaporation and the product was purified by an automated flash chromatography system (0 to 30% gradient of EtOAc/hexanes) to afford a single diastereomer of tricyclic-β-lactone **2.11b** (107 mg, 61% yield) as a yellow, viscous liquid: TLC (EtOAc:hexanes, 2:8 *v/v,* Hanessian's stain): R_f = 0.42; $\left[\alpha\right]_D^{17}$ = +3.49 (*c* = 1.0, $CHCl_3$). Enantiomeric ratio was determined by HPLC analysis in comparison with authentic racemic material using a Chiracel AS-H column: hexanes:*i*PrOH = 90:10, flow rate 1.0 mL/min, λ = 210 nm: t_{major} = 11.7 min, t_{minor} = 18.0 min; 94:6 *er*. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.36-7.28 (m, 10H), 5.19 (app s, 2H), 5.16, 5.12 (ABq, J_{AB} = 11.9 Hz, 2H), 4.15-4.04 (m, 4H), 4.02, 3.81 (ABq, J_{AB} = 9.6 Hz, 2H), 3.06 (d, *J* = 15.1 Hz, 1H), 2.67-2.62 (m, 1H), 2.41 (d, *J* = 15.1 Hz, 1H), 2.18-2.14 (m, 1H), 1.80-1.70 (m, 1H), 1.67-1.54 (m, 3H), 1.20 (t, *J* = 7.1 Hz, 3H), 1.17 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 172.5, 170.3, 170.2, 169.3, 168.1, 135.0, 134.3, 129.1 (2), 128.9, 128.7 (2), 128.6 (2), 128.4, 128.2 (2), 85.7, 68.3, 68.1, 61.91, 61.90, 55.9, 52.7, 52.2, 43.3, 39.7, 39.3, 39.2, 23.3, 13.9, 13.8; **IR** (thin film): 2978, 1836, 1737, 1453, 1370, 1269, 1027 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{32}H_{35}O_{10}$ $[M+H]^+$: 579.2230, found: 579.2251. Absolute stereochemistry was assigned by derivatization as described below.

Determination of enantiomeric ratio of β-lactone (+)-2.11b:



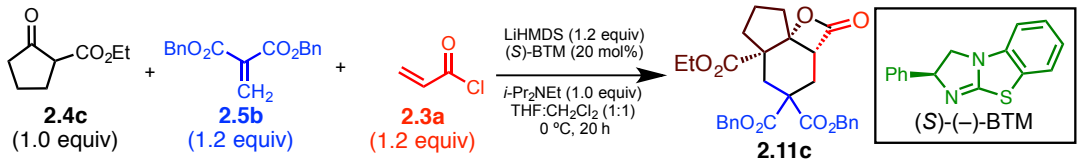
Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.796	BB	1.1004	7.41597e4	1029.46375	51.1980
2	18.072	BB	1.4385	7.06891e4	764.67401	48.8020



Signal 3: DAD1 C, Sig=210,8 Ref=360,100

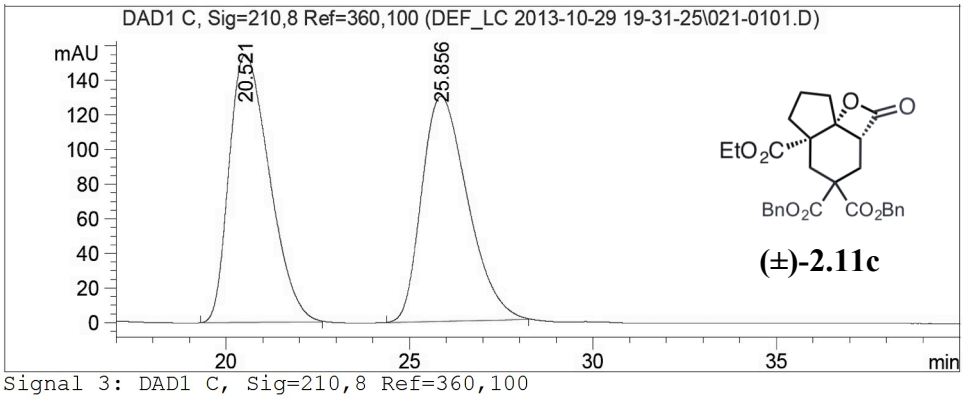
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.683	VB	1.0269	4.38763e4	639.15222	94.1020
2	18.020	BB	1.2085	2750.03003	31.01342	5.8980



4,4-Dibenzyl 5a-ethyl (2a*R*,5a*S*,8a*R*)-2-oxotetrahydro-2*H*-indeno[3a,4-*b*]oxete-4,4,5a(5*H*,6*H*)-tricarboxylate ((–)-2.11c). Prepared according to the procedure for compound **2.11b** using a solution of LiHMDS (0.36 mL of 1.0 M solution in THF, 0.36 mmol, 1.2 equiv) in THF (0.5 mL), a solution of ethyl 2-oxocyclopentanecarboxylate **2.4c** (47 mg, 0.30 mmol, 1.0 equiv) in THF (0.5 mL), a solution of diester **2.5b** (0.36 mL of 1.0 M solution in benzene, 0.36 mmol, 1.2 equiv) in THF (0.5 mL), (*S*)-BTM (15 mg, 0.060 mmol, 20 mol%) and *i*-Pr_2NEt (78 μL, 0.30 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL), and a solution of acid chloride **2.3a** (41 mg, 0.45 mmol, 1.5 equiv) in CH_2Cl_2 (1.0 mL). The reaction was stirred at 0 °C for 15 h. Upon completion (as judged by TLC), the reaction was concentrated by rotary evaporation and the product was purified by an automated flash chromatography system (0 to 30% gradient of EtOAc/hexanes) to afford a single diastereomer of tricyclic-β-lactone **2.11c** (29 mg, 19% yield) as a yellow, viscous liquid: TLC (EtOAc:hexanes, 2:8 *v/v,* Hanessian's stain): R_f = 0.47. $[\alpha]_D^{24.0}$ = -52.00 (*c* = 1.0, $CHCl_3$). Enantiomeric ratio was determined by HPLC analysis in comparison with authentic racemic material using a Chiracel AS-H column: hexanes:*i*PrOH = 90:10, flow rate 1.0 mL/min, λ = 210 nm: t_{minor} = 21.7 min, t_{major} = 27.5 min; 72:28 *er*. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.36 – 7.23 (m, 10H), 5.17 – 5.03 (m, 4H), 4.13 (q, *J* = 7.2 Hz, 2H), 3.52 (t, *J* = 10.0 Hz, 1H), 2.88 (d, *J* = 15.4 Hz, 1H), 2.65 – 2.43 (m, 3H), 2.27 – 2.15 (m, 2H), 1.94 – 1.77 (m, 2H), 1.68 – 1.57 (m, 2H), 1.22 (t, *J* =

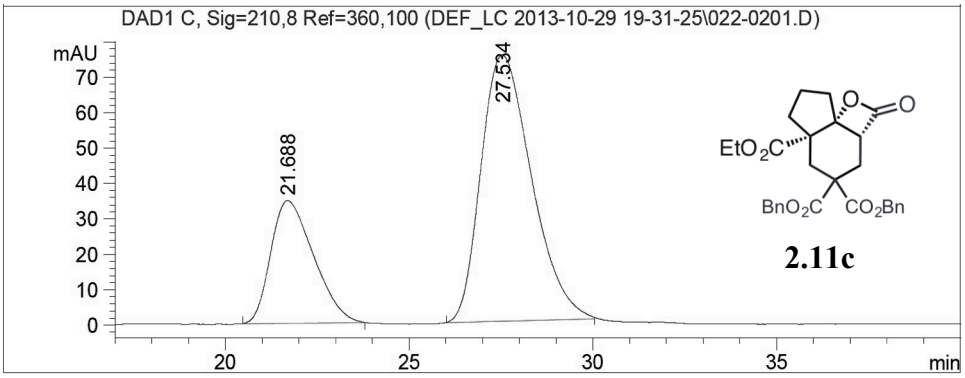
7.1 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 173.0, 171.2, 170.5, 170.0, 135.2, 134.8, 128.9, 128.8, 128.7, 128.7, 128.6, 128.3, 85.7, 68.0, 67.8, 61.8, 52.4, 52.3, 50.6, 39.3, 38.8, 36.6, 26.7, 23.1, 14.1. **IR** (thin film): 3064, 3034, 2927, 2871, 1832, 1732, 1498, 1455, 1374, 1327, 1216, 1160 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{29}H_{30}O_8Na$ $[M+Na]^+$: 529.1833, found: 529.1819.

Determination of enantiomeric ratio of β-lactone 2.11c:



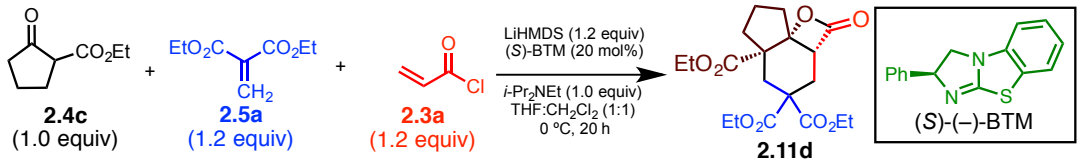
Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.521	BB	1.1982	1.18090e4	154.75983	51.0343
2	25.856	BB	1.3207	1.13303e4	130.01407	48.9657



Signal 3: DAD1 C, Sig=210,8 Ref=360,100

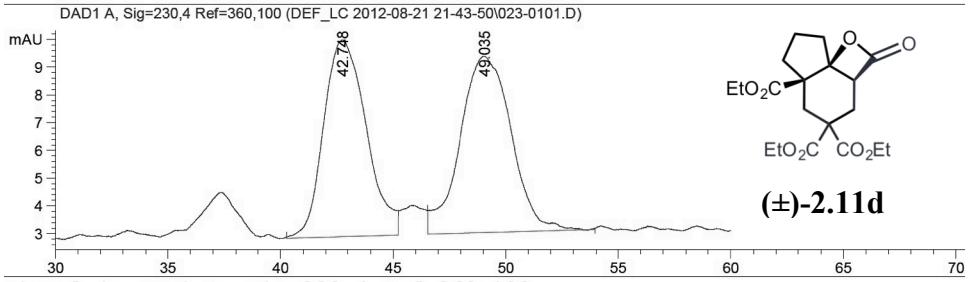
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.688	BB	1.1265	2808.02905	34.68701	28.0649
2	27.534	BB	1.4119	7197.45850	75.25040	71.9351



Triethyl (2a*R*,5a*S*,8a*R*)-2-oxotetrahydro-2*H*-indeno[3a,4-*b*]oxete-4,4,5a(5*H*,6*H*)-tricarboxylate ((–)-2.11d). Prepared according to the procedure for compound **2.11b** using a solution of LiHMDS (0.36 mL of 1.0 M solution in THF, 0.36 mmol, 1.2 equiv) in THF (0.5 mL), a solution of ethyl 2-oxocyclopentanecarboxylate **2.4c** (47 mg, 0.30 mmol, 1.0 equiv) in THF (0.5 mL), a solution of diester **2.5a** (0.36 mL of 1.0 M solution in benzene, 0.36 mmol, 1.2 equiv) in THF (0.5 mL), (*S*)-BTM (15 mg, 0.060 mmol, 20 mol%) and *i*-Pr_2NEt (78 μL, 0.30 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL), and a solution of acid chloride **2.3a** (41 mg, 0.45 mmol, 1.5 equiv) in CH_2Cl_2 (1.0 mL). The reaction was then stirred at 23 °C for 15 h. Upon completion (as judged by TLC), the reaction was concentrated by rotary evaporation and the product was purified by an automated flash chromatography system (0 to 30% gradient of EtOAc/hexanes) to afford a single diastereomer of tricyclic-β-lactone **2.11d** (44 mg, 39% yield) as a yellow, viscous liquid: Spectral data match with previously synthesized lactone **2.1c**. $[\alpha]_D^{22.5}$ = -12.13 (*c* = 1.0, $CHCl_3$). Enantiomeric ratio was determined by HPLC analysis in comparison with

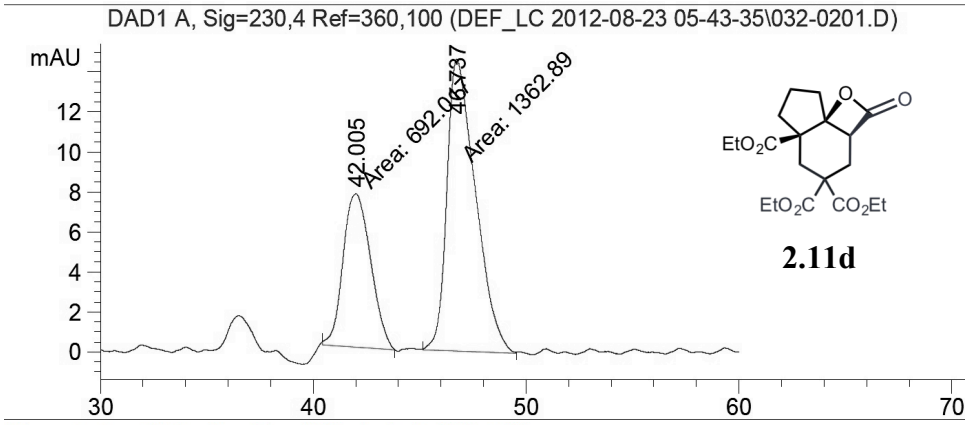
authentic racemic material using a Chiracel AD-H column: hexanes:*i*PrOH = 99:1, flow rate 1.0 mL/min, λ = 230 nm: t_{minor} = 42.0 min, t_{major} = 46.7 min; 66.5:33.5 *er*.

Determination of enantiomeric ratio of β-lactone 2.11d:



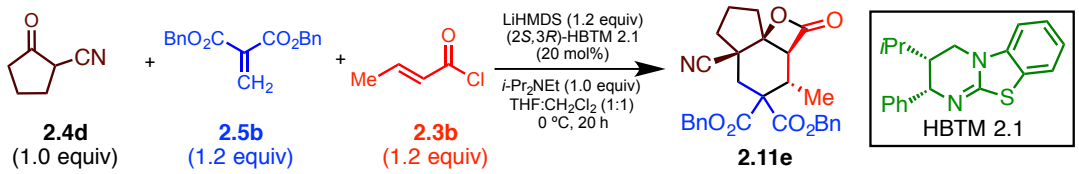
Signal 1: DAD1 A, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	42.748	BV	1.7150	927.40405	7.06713	48.1330
2	49.035	VB	1.9010	999.34894	6.34666	51.8670



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

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	42.005	MM	1.5044	692.01721	7.66658	33.6764
2	46.737	MM	1.5568	1362.88806	14.59060	66.3236

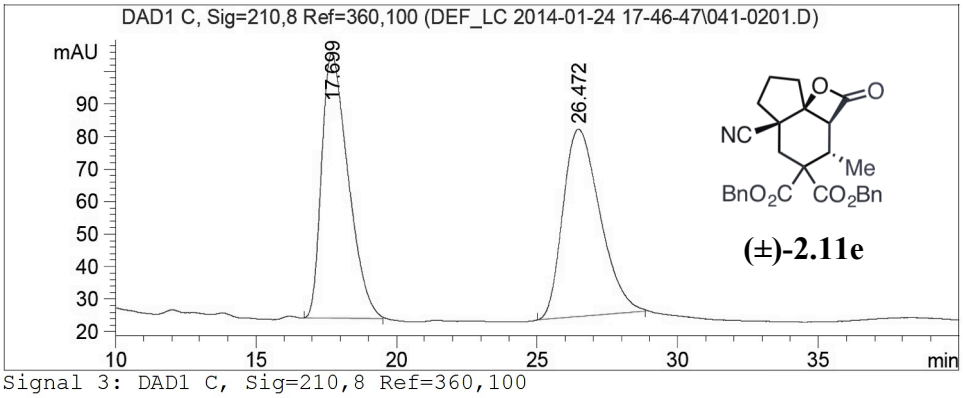


2.4d (1.0 equiv) + **2.5b** (1.2 equiv) + **2.3b** (1.2 equiv) → **2.11e**

Dibenzyl (2a*S*,3*S*,5a*S*,8a*S*)-5a-cyano-3-methyl-2-oxohexahydro-2*H*-indeno[3a,4-*b*]oxete-4,4(5*H*)-dicarboxylate ((+)-2.11e): Prepared according to the procedure for compound **2.11a** using a solution of LiHMDS (0.36 mL of 1.0 M solution in THF, 0.36 mmol, 1.2 equiv) in THF (0.5 mL), a solution of cyclopentanone-2-carbonitrile **2.4d** (33 mg, 0.30 mmol, 1.0 equiv) in THF (0.5 mL), a solution of diester **2.5b** (0.36 mL of 1.0 M solution in benzene, 0.36 mmol, 1.2 equiv) in THF (0.5 mL), (2*S*,3*R*)-HBTM 2.1 (19 mg, 0.060 mmol, 20 mol%) and *i*-Pr_2NEt (78 µL, 0.30 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL), and a solution of acid chloride **2.3b** (38 mg, 0.36 mmol, 1.2 equiv) in CH_2Cl_2 (1.0 mL). The reaction was stirred at 0 °C for 15 h. Upon completion (as judged by TLC), the reaction was concentrated by rotary evaporation and the product was purified by an automated flash chromatography system (gradient of EtOAc/hexanes) to afford a single diastereomer of tricyclic-β-lactone **2.11e** (35 mg, 25% yield) as a yellow, viscous liquid: TLC (EtOAc:hexanes, 4:6 *v/v,* Hanessian's stain): $R_f = 0.53$. $[\alpha]_D^{24.6} = +13.33$ ($c = 0.68$, $CHCl_3$). Enantiomeric ratio was determined by HPLC analysis in comparison with authentic racemic material using a Chiracel AS-H column: hexanes:*i*PrOH = 80:20, flow rate 1.0 mL/min, λ = 210 nm: $t_{major} = 17.8$ min, $t_{minor} = 26.7$min; 60.5:39.5 *er*. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.42 – 7.18 (m, 10H), 5.25 – 5.18 (m, 2H), 5.13 – 5.04 (m, 2H), 3.31 (d, $J = 8.3$ Hz, 1H), 3.18 (dq, $J = 8.4$, 6.9 Hz, 1H), 2.80 (d, $J = 15.3$ Hz, 1H), 2.57 – 2.48 (m, 1H), 2.39 – 2.28 (m, 1H), 2.22 – 2.10 (m, 2H), 2.05 – 1.88 (m, 2H), 1.86 – 1.75

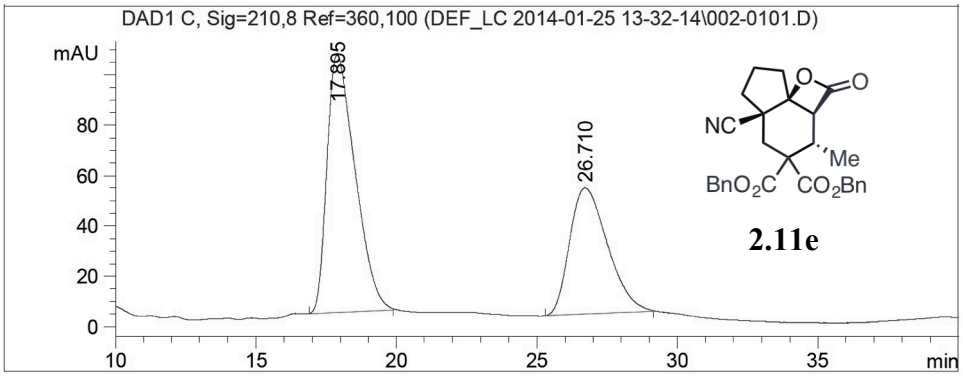
(m, 1H), 1.07 (d, J = 6.8 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 169.82, 169.64, 167.91, 134.89, 134.43, 128.92, 128.82, 128.78, 128.67, 128.63, 128.60, 119.77, 84.33, 68.33, 68.07, 58.11, 56.33, 41.87, 39.80, 37.09, 36.83, 32.14, 22.79, 17.38. **IR** (thin film): 3034, 2968, 1838, 1735, 1455, 1217, 1150, 1077 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{28}H_{27}NO_6Na$ $[M+Na]^+$: 496.1736, found: 496.1753.

Determination of enantiomeric ratio of β-lactone 2.11e:



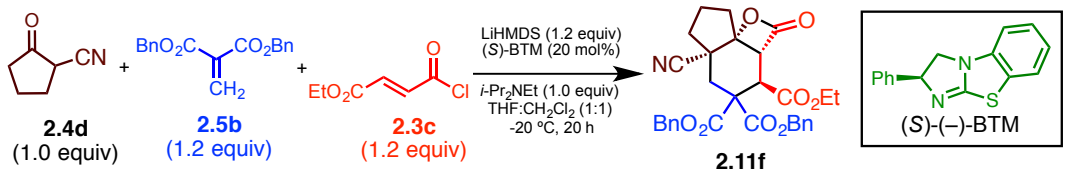
Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.699	BB	0.9683	5332.97363	81.40694	50.2158
2	26.472	BB	1.2417	5287.12842	57.66631	49.7842



Signal 3: DAD1 C, Sig=210,8 Ref=360,100

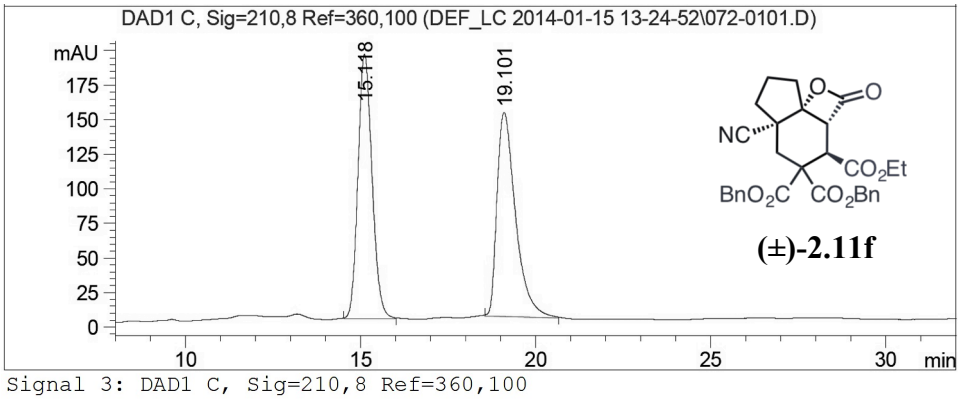
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.895	BB	1.0104	7143.37158	102.58030	60.2539
2	26.710	BB	1.2799	4712.07666	50.25450	39.7461



4,4-Dibenzyl 3-ethyl (2a*R*,3*R*,5a*R*,8a*R*)-5a-cyano-2-oxohexahydro-2*H*-indeno[3a,4-*b*]oxete-3,4,4(5*H*)-tricarboxylate ((–)-2.11f): Prepared according to the procedure for compound **2.11b** using a solution of LiHMDS (0.36 mL of 1.0 M solution in THF, 0.36 mmol, 1.2 equiv) in THF (0.5 mL), a solution of cyclopentanone-2-carbonitrile **2.4d** (33 mg, 0.30 mmol, 1.0 equiv) in THF (0.5 mL), a solution of diester **2.5b** (0.36 mL of 1.0 M solution in benzene, 0.36 mmol, 1.2 equiv) in THF (0.5 mL), (*S*)-BTM (15 mg, 0.060 mmol, 20 mol%) and *i*-Pr_2NEt (78 µL, 0.30 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL), and a solution of acid chloride **2.3c** (59 mg, 0.36 mmol, 1.2 equiv) in CH_2Cl_2 (1.0 mL). The reaction was stirred at -20 °C for 15 h. Upon completion (as judged by TLC), the reaction was concentrated by rotary evaporation and the product was purified by an automated flash chromatography system (gradient of EtOAc/hexanes) to afford a single diastereomer of tricyclic-β-lactone **2.11f** (41 mg, 26% yield) as a yellow, viscous liquid: TLC (EtOAc:hexanes, 4:6 *v/v,* Hanessian's stain): R_f = 0.43. $[\alpha]_D^{25.2}$ = -13.87 (*c* = 1.0, $CHCl_3$). Enantiomeric ratio was determined by HPLC analysis in comparison with authentic racemic material using a Chiracel AD-H column: hexanes:*i*PrOH = 80:20, flow

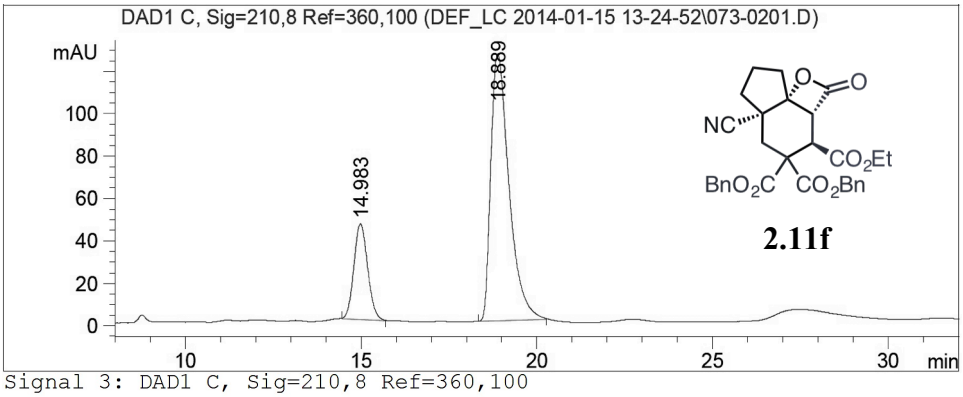
rate 1.0 mL/min, λ = 210 nm: t_{minor} = 14.98 min, t_{major} = 18.88 min; 79:21 *er*. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.41 – 7.16 (m, 10H), 5.22 (dd, *J* = 71.1, 12.1 Hz, 2H), 5.04 (d, *J* = 3.3 Hz, 2H), 4.09 – 3.91 (m, 4H), 2.92 (dd, *J* = 15.2, 1.2 Hz, 1H), 2.66 – 2.56 (m, 1H), 2.46 – 2.34 (m, 1H), 2.29 (d, *J* = 15.2 Hz, 1H), 2.25 – 2.17 (m, 1H), 2.02 – 1.91 (m, 2H), 1.90 – 1.81 (m, 1H), 1.21 (dt, *J* = 46.0, 7.2 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 171.28, 168.27, 168.01, 165.98, 134.57, 134.34, 128.98, 128.78, 128.75, 128.63, 128.59, 128.41, 119.77, 82.07, 68.80, 68.26, 62.50, 54.83, 54.25, 42.74, 42.59, 42.39, 39.03, 35.54, 23.02, 14.01. **IR** (thin film): 2964, 1844, 1737, 1454, 1372, 1227 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{30}H_{30}NO_8$ $[M+H]^+$: 532.1971, found: 532.1992.

Determination of enantiomeric ratio of β-lactone 2.11f:



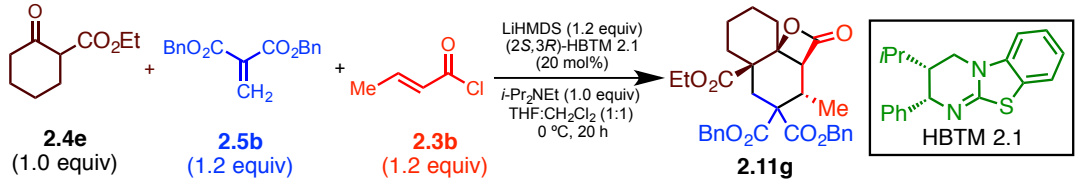
Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.118	BB	0.4362	5346.36084	191.20993	49.6200
2	19.101	BB	0.5670	5428.24268	147.62009	50.3800



Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.983	BB	0.4233	1226.70898	45.10589	21.2857
2	18.889	BB	0.5500	4536.35303	126.01450	78.7143

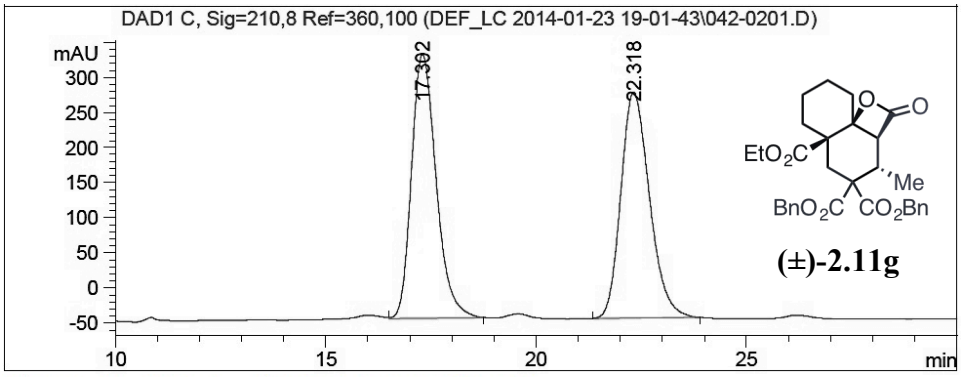


2.4e (1.0 equiv) + **2.5b** (1.2 equiv) + **2.3b** (1.2 equiv) → **2.11g**

4,4-Dibenzyl 5a-ethyl (2a*S*,3*S*,5a*R*,9a*S*)-3-methyl-2-oxohexahydronaphtho[8a,1-*b*]oxete-4,4,5a(2*H*,5*H*)-tricarboxylate ((+)-2.11g): Prepared according to the procedure for compound **2.11a** using a solution of LiHMDS (0.36 mL of 1.0 M solution in THF, 0.36 mmol, 1.2 equiv) in THF (0.5 mL), a solution of ethyl 2-oxocyclohexane-1-carboxylate **2.4e** (51 mg, 0.30 mmol, 1.0 equiv) in THF (0.5 mL), a solution of diester **2.5b** (0.36 mL of 1.0 M solution in benzene, 0.36 mmol, 1.2 equiv) in THF (0.5 mL), (2*S*,3*R*)-HBTM 2.1 (19 mg, 0.060 mmol, 20 mol%) and *i*-Pr_2NEt (78 µL, 0.30 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL), and a solution of acid chloride **2.3b** (38 mg, 0.36 mmol, 1.2 equiv) in CH_2Cl_2 (1.0 mL). The reaction was stirred at 0 °C for 15 h. Upon completion (as judged by TLC), the reaction was concentrated by rotary evaporation and the product

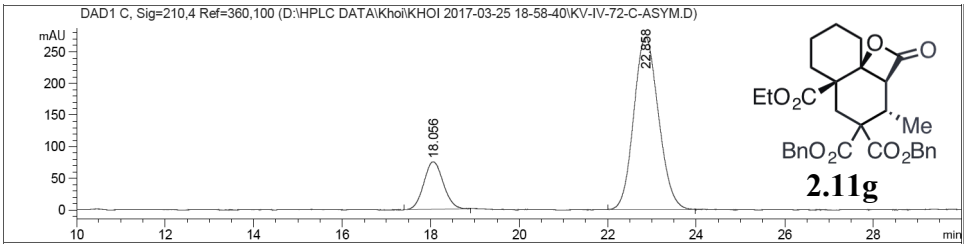
was purified by an automated flash chromatography system (gradient of EtOAc/hexanes) to afford a single diastereomer of tricyclic-β-lactone **2.11g** (44 mg, 27% yield) as a yellow, viscous liquid: TLC (EtOAc:hexanes, 2:8 *v/v,* Hanessian's stain): R_f = 0.35. $[\alpha]_D^{25.0}$ = +8.13 (*c* = 1.0, $CHCl_3$). Enantiomeric ratio was determined by HPLC analysis in comparison with authentic racemic material using a Chiracel AD-H column: hexanes:*i*PrOH = 95:5, flow rate 1.0 mL/min, λ = 210 nm: t_{minor} = 18.0 min, t_{major} = 23.1 min; 81:19 *er*. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.37 – 7.17 (m, 10H), 5.16 (d, *J* = 1.5 Hz, 2H), 5.15 – 5.03 (m, 2H), 4.21 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.99 (dq, *J* = 10.8, 7.1 Hz, 1H), 2.86 (d, *J* = 12.2 Hz, 1H), 2.76 – 2.68 (m, 2H), 2.59 (d, *J* = 15.4 Hz, 1H), 2.26 (ddd, *J* = 15.1, 13.5, 4.3 Hz, 1H), 2.08 – 2.00 (m, 1H), 1.89 (dtd, *J* = 15.0, 3.5, 1.6 Hz, 1H), 1.75 – 1.62 (m, 3H), 1.60 – 1.35 (m, 2H), 1.21 (t, *J* = 7.1 Hz, 3H), 1.10 (d, *J* = 6.5 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 174.27, 171.62, 170.86, 170.13, 135.43, 134.74, 128.77, 128.62, 128.59, 128.54, 128.51, 128.45, 77.35, 67.76, 67.62, 61.70, 59.97, 57.21, 46.60, 36.37, 33.95, 32.89, 30.94, 21.17, 20.42, 17.56, 14.01. **IR** (thin film): 3034, 2939, 2866, 1823, 1727, 1455, 1265, 1234 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{31}H_{34}O_8Na$ $[M+Na]^+$: 557.2151, found: 557.2176.

Determination of enantiomeric ratio of β-lactone 2.11g:



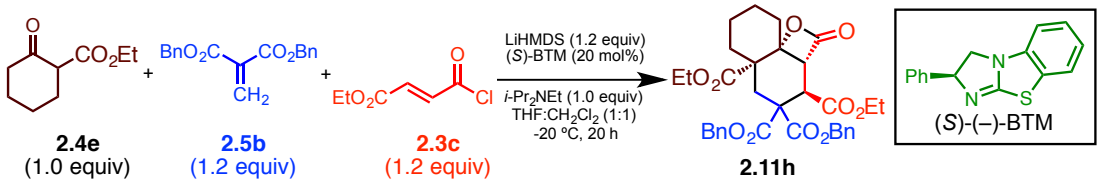
Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.302	VB	0.6348	1.53190e4	376.41660	50.0538
2	22.318	BB	0.7355	1.52861e4	322.19159	49.9462



Signal 3: DAD1 C, Sig=210,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.056	BB	0.4381	2303.95044	75.27995	17.8802
2	22.858	BB	0.5740	1.05816e4	272.51196	82.1198



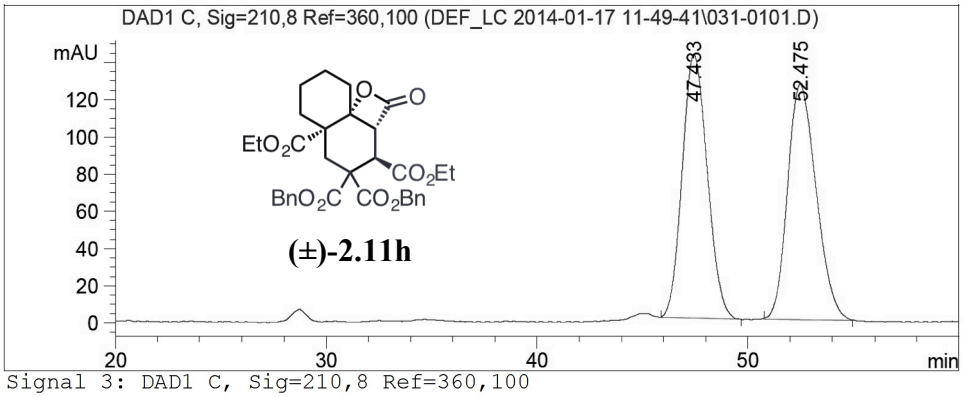
2.4e (1.0 equiv) **2.5b** (1.2 equiv) **2.3c** (1.2 equiv) **2.11h**

4,4-Dibenzyl 3,5a-diethyl (2a*R*,3*R*,5a*S*,9a*R*)-2-oxohexahydronaphtho[8a,1-*b*]oxete-3,4,4,5a(2*H*,5*H*)-tetracarboxylate ((–)-2.11h): Prepared according to the procedure for

compound **2.11b** using a solution of LiHMDS (0.36 mL of 1.0 M solution in THF, 0.36 mmol, 1.2 equiv) in THF (0.5 mL), a solution of ethyl 2-oxocyclohexane-1-carboxylate **2.4e** (51 mg, 0.30 mmol, 1.0 equiv) in THF (0.5 mL), a solution of diester **2.5b** (0.36 mL of 1.0 M solution in benzene, 0.36 mmol, 1.2 equiv) in THF (0.5 mL), (*S*)-BTM (15 mg, 0.060 mmol, 20 mol%) and *i*-Pr_2NEt (78 μL, 0.30 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL), and a solution of acid chloride **2.3c** (59 mg, 0.36 mmol, 1.2 equiv) in CH_2Cl_2 (1.0 mL). The reaction was stirred at -20 °C for 15 h. Upon completion (as judged by TLC), the reaction was concentrated by rotary evaporation and the product was purified by an automated flash chromatography system (gradient of EtOAc/hexanes) to afford a single diastereomer of tricyclic-β-lactone **2.11h** (40 mg, 23% yield) as a yellow, viscous liquid: TLC (EtOAc:hexanes, 2:8 *v/v,* Hanessian's stain): R_f = 0.38. $[\alpha]_D^{25.0}$ = -41.47 (*c* = 1.0, $CHCl_3$). Enantiomeric ratio was determined by HPLC analysis in comparison with authentic racemic material using a Chiracel AD-H column: hexanes:*i*PrOH = 95:5, flow rate 1.0 mL/min, λ = 210 nm: t_{minor} = 47.7 min, t_{major} = 52.6 min; 94:6 *er*. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.35 – 7.24 (m, 10H), 5.19 – 5.12 (m, 3H), 5.06 (d, *J* = 12.0 Hz, 1H), 4.18 – 4.09 (m, 1H), 4.08 – 3.92 (m, 4H), 3.59 (dd, *J* = 9.1, 0.9 Hz, 1H), 2.76 (dd, *J* = 15.7, 0.9 Hz, 1H), 2.60 (d, *J* = 15.6 Hz, 1H), 2.00 (ddd, *J* = 14.3, 9.8, 3.7 Hz, 2H), 1.89 – 1.80 (m, 1H), 1.67 (ddd, *J* = 14.6, 10.5, 4.3 Hz, 1H), 1.61 – 1.48 (m, 2H), 1.47 – 1.20 (m, 2H), 1.16 (dtd, *J* = 16.8, 7.1, 0.9 Hz, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 173.64, 170.98, 170.48, 170.32, 168.16, 135.01, 134.73, 128.88, 128.78, 128.71, 128.67, 128.60, 128.52, 77.19, 68.39, 68.37, 61.88, 61.76, 55.88, 55.07, 46.61, 42.01, 35.07, 34.43, 31.74, 21.54, 20.56, 14.03, 14.00. **IR** (thin film): 3065, 3034, 2939, 2867, 1834, 1731,

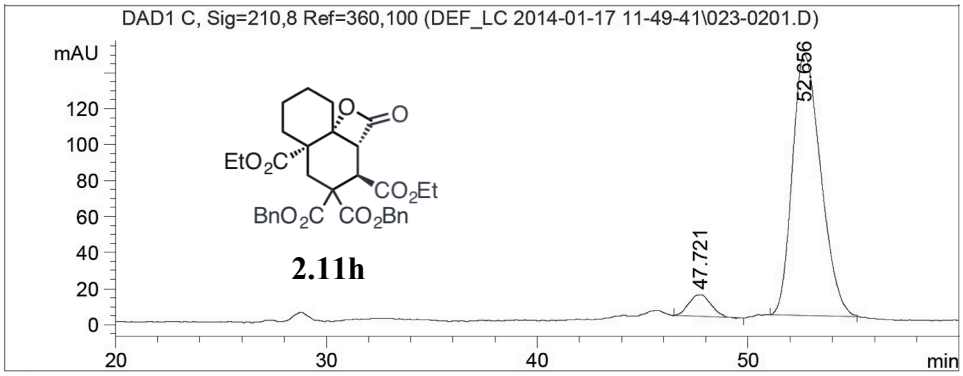
1498, 1455, 1372, 1236 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{33}H_{36}O_{10}Na$ $[M+Na]^+$: 615.2201, found: 615.2181.

Determination of enantiomeric ratio of β-lactone 2.11h:



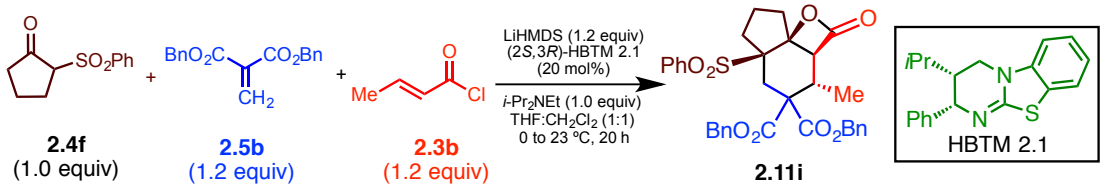
Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	47.433	BB	1.2473	1.17156e4	141.89255	49.5783
2	52.475	BB	1.3216	1.19149e4	126.64445	50.4217



Signal 3: DAD1 C, Sig=210,8 Ref=360,100

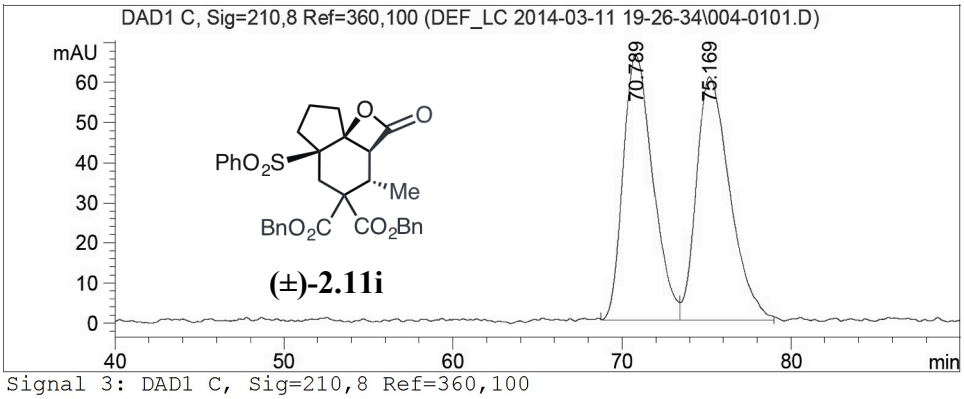
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	47.721	BB	0.8817	896.45911	12.05278	6.1726
2	52.656	BB	1.3951	1.36266e4	145.44211	93.8274



Dibenzyl (2a*S*,3*S*,5a*R*,8a*S*)-3-methyl-2-oxo-5a-(phenylsulfonyl)hexahydro-2*H*-indeno[3a,4-*b*]oxete-4,4(5*H*)-dicarboxylate ((+)-2.11i): Prepared according to the procedure for compound **2.11a** using a solution of LiHMDS (0.36 mL of 1.0 M solution in THF, 0.36 mmol, 1.2 equiv) in THF (0.5 mL), a solution of 2-(phenylsulfonyl)cyclopentan-1-one[7] **2.4f** (67 mg, 0.30 mmol, 1.0 equiv) in THF (0.5 mL), a solution of diester **2.5b** (0.36 mL of 1.0 M solution in benzene, 0.36 mmol, 1.2 equiv) in THF (0.5 mL), (2*S*,3*R*)-HBTM 2.1 (19 mg, 0.060 mmol, 20 mol%) and *i*-Pr_2NEt (78 μL, 0.30 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL), and a solution of acid chloride **2.3b** (47 mg, 0.45 mmol, 1.5 equiv) in CH_2Cl_2 (1.0 mL). The reaction was warmed to 23 °C and stirred for 15 h. Upon completion (as judged by TLC), the reaction was concentrated by rotary evaporation and the product was purified by an automated flash chromatography system (gradient of EtOAc/hexanes) to afford a single diastereomer of tricyclic-β-lactone **2.11i** (69 mg, 41% yield) as a light yellow solid: m.p. = 74 – 75 °C. TLC (Et_2O:hexanes, 8:2 *v/v,* Hanessian's stain): R_f = 0.59; $[\alpha]_D^{22.6}$ = +15.60 (*c* = 1.0, $CHCl_3$). Enantiomeric ratio was determined by HPLC analysis in comparison with authentic racemic material using a Chiracel AD-H column: hexanes:*i*PrOH = 95:5, flow rate 1.0 mL/min, λ = 210 nm: t_{minor} = 71.8 min, t_{major} = 75.5 min; 85.5:14.5 *er*. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 8.00 – 7.94 (m, 2H), 7.62 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.8 Hz, 2H), 7.39 – 7.15 (m, 10H), 5.20 – 5.02 (m, 4H), 3.40 (d, *J* =

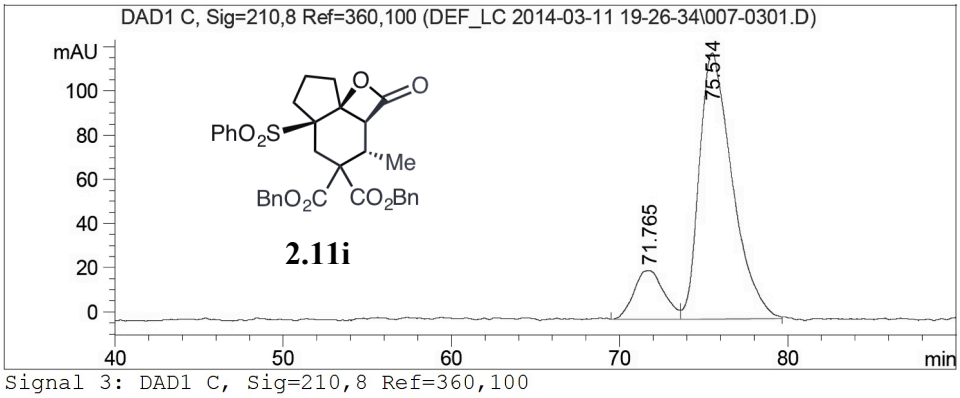
11.4 Hz, 1H), 3.11 (d, *J* = 15.3 Hz, 1H), 2.80 (dt, *J* = 14.4, 7.2 Hz, 1H), 2.49 (d, *J* = 15.4 Hz, 1H), 2.41 – 2.26 (m, 2H), 1.80 (dt, *J* = 13.7, 6.9 Hz, 1H), 1.68 (dt, *J* = 14.4, 6.9 Hz, 1H), 1.58 (dp, *J* = 14.1, 7.1 Hz, 1H), 1.35 – 1.24 (m, 1H), 1.18 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 169.68, 169.39, 168.72, 136.73, 134.66, 134.24, 134.17, 131.58, 129.12, 128.99, 128.80, 128.78, 128.77, 128.75, 128.58, 83.89, 70.50, 68.08, 67.86, 59.97, 56.50, 40.19, 39.10, 38.61, 35.09, 21.68, 15.98. **IR** (thin film): 3065, 3034, 2966, 2885, 1833, 1730, 1650, 1498, 1455, 1381, 1306, 1248, 1137, 1079, 910, 734, 696 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{33}H_{32}O_8SNa$ $[M+Na]^+$: 611.1710, found: 611.1705.

Determination of enantiomeric ratio of β-lactone 2.11i:



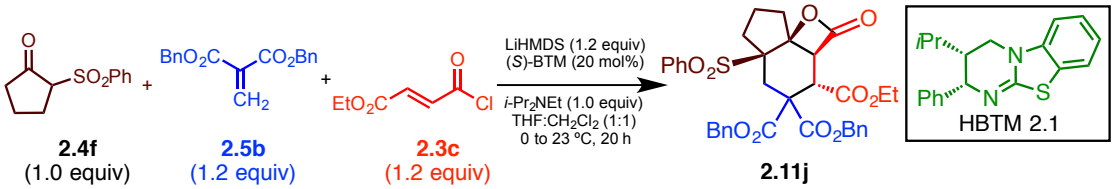
Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	70.789	BV	1.8134	8115.40771	66.42419	49.2328
2	75.169	VB	1.9391	8368.32520	60.75117	50.7672



Signal 3: DAD1 C, Sig=210,8 Ref=360,100

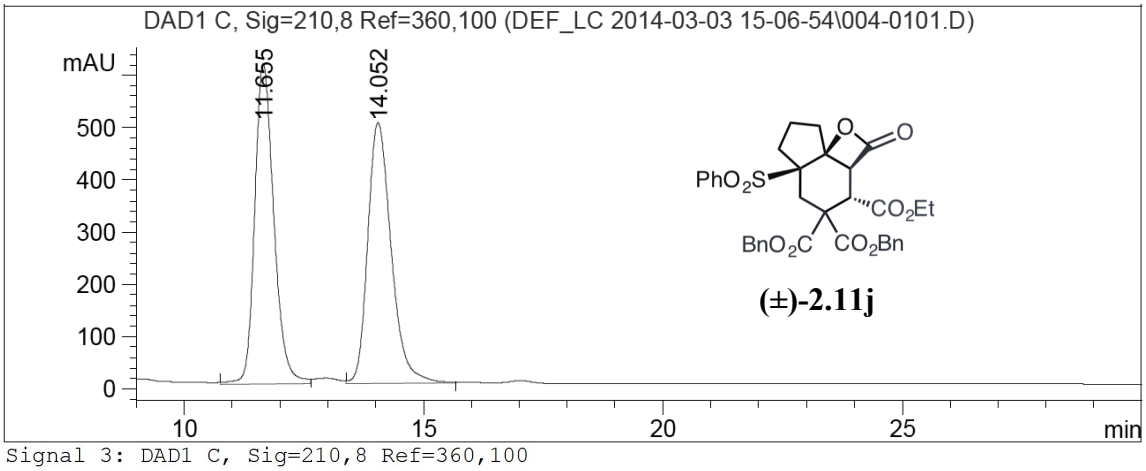
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	71.765	BV	1.6312	2746.07642	22.13802	14.3265
2	75.514	VB	1.9400	1.64217e4	120.34490	85.6735



4,4-Dibenzyl 3-ethyl (2a*S*,3*S*,5a*R*,8a*S*)-2-oxo-5a-(phenylsulfonyl)hexahydro-2*H*-indeno[3a,4-*b*]oxete-3,4,4(5*H*)-tricarboxylate ((+)-2.11j): Prepared according to the procedure for compound **2.11a** using a solution of LiHMDS (0.36 mL of 1.0 M solution in THF, 0.36 mmol, 1.2 equiv) in THF (0.5 mL), a solution of 2-(phenylsulfonyl)cyclopentan-1-one[7] **2.4f** (67 mg, 0.30 mmol, 1.0 equiv) in THF (0.5 mL), a solution of diester **2.5b** (0.36 mL of 1.0 M solution in benzene, 0.36 mmol, 1.2 equiv) in THF (0.5 mL), (2*S*,3*R*)-HBTM 2.1 (19 mg, 0.060 mmol, 20 mol%) and *i*-Pr_2NEt (78 μL, 0.30 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL), and a solution of acid chloride **2.3c** (73 mg, 0.45 mmol, 1.5 equiv) in CH_2Cl_2 (1.0 mL). The reaction was warmed to 23 °C and stirred for 15 h. Upon completion (as judged by TLC), the reaction

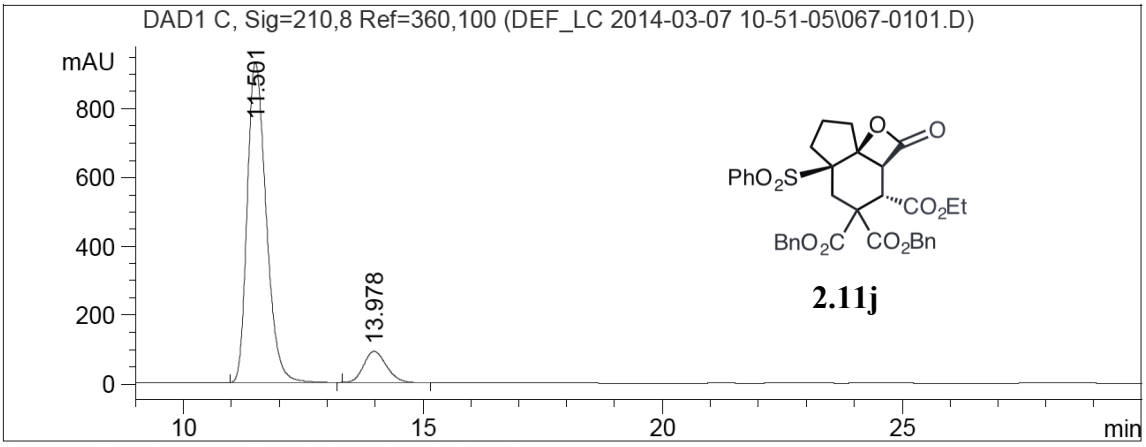
was concentrated by rotary evaporation and the product was purified by an automated flash chromatography system (gradient of EtOAc/hexanes) to afford a single diastereomer of tricyclic-β-lactone **2.11j** (101 mg, 52% yield) as a light yellow solid: m.p = 81 – 82 °C; TLC (EtOAc:hexanes, 4:6 *v/v,* Hanessian's stain): R_f = 0.47. $[\alpha]_D^{25.0}$ = +33.87 (*c* = 1.0, $CHCl_3$). Enantiomeric ratio was determined by HPLC analysis in comparison with authentic racemic material using a Chiracel AD-H column: hexanes:*i*PrOH = 60:40, flow rate 1.0 mL/min, λ = 210 nm: t_{major} = 11.5 min, t_{minor} = 13.98 min; 89:11 *er*. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.93 – 7.90 (m, 2H), 7.59 (td, *J* = 7.4, 1.3 Hz, 1H), 7.43 – 7.27 (m, 12H), 5.26 – 5.06 (m, 4H), 4.05 – 4.02 (m, 2H), 3.56 (d, *J* = 10.1 Hz, 1H), 3.24 – 3.15 (m, 1H), 2.79 (dt, *J* = 13.7, 6.8 Hz, 1H), 2.66 – 2.56 (m, 1H), 2.24 (dd, *J* = 13.9, 6.6 Hz, 1H), 1.85 (dt, *J* = 13.5, 6.6 Hz, 1H), 1.65 – 1.58 (m, 3H), 1.40 – 1.24 (m, 1H), 1.16 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 169.54, 169.30, 168.48, 166.70, 136.80, 134.82, 134.23, 134.03, 131.58, 129.34, 129.14, 128.84, 128.82, 128.79, 128.74, 128.53, 83.49, 70.33, 68.72, 68.52, 62.16, 56.23, 54.81, 43.25, 40.30, 39.45, 37.86, 21.88, 13.95. **IR** (thin film): 2977, 1842, 1737, 1447, 1372, 1267 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{35}H_{34}O_{10}SLi$ $[M+Li]^+$: 653.2033, found: 653.2025.

Determination of enantiomeric ratio of β-lactone 2.11j:



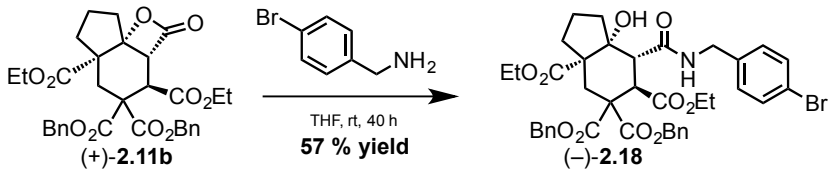
Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.655	VV	0.4370	1.76190e4	617.22937	49.5183
2	14.052	VV	0.5441	1.79618e4	503.61926	50.4817



Signal 3: DAD1 C, Sig=210,8 Ref=360,100

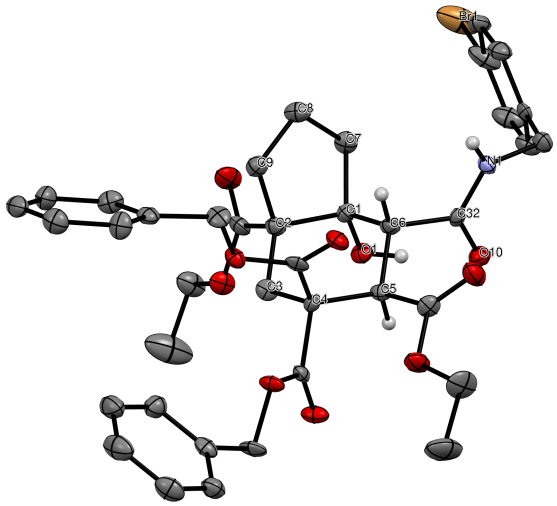
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.501	BV	0.4301	2.56943e4	930.56653	89.1211
2	13.978	VB	0.5257	3136.46313	92.01909	10.8789



(3a*S*,6*R*,7*R*,7a*R*)-5,5-Dibenzyl 3a,6-diethyl 7-(benzylcarbamoyl)-7a-hydroxyhexahydro-1*H*-indene-3a,5,5,6(6*H*)-tetracarboxylate ((–)-**2.18**). Into an oven-dried, 25-mL round-bottomed flask containing a solution of β-lactone (+)-**2.11b** (400 mg, 0.69 mmol, 1.0 equiv) in THF (7 mL), was added dropwise *p*-bromobenzylamine (0.35 mL, 2.8 mmol, 4.0 equiv). The reaction was allowed to stir at ambient temperature (23 °C) for 40 h. Upon completion (as judged by TLC), the reaction was concentrated by rotary evaporation and purified by an automated flash chromatography system (gradient of EtOAc/hexanes) to afford bicyclic amide (–)-**2.18** (300 mg, 57% yield) as a colorless solid: TLC (EtOAc:hexanes, 2:8 *v/v*): R_f = 0.35; $[\alpha]_D^{20}$ = -24.15 (*c* = 1.00, $CHCl_3$); **^{1}H NMR** (500 MHz, C_6D_6): δ 7.21 (d, *J* = 8.3 Hz, 2H), 7.16-7.08 (m, 5H), 7.08-6.96 (m, 5H), 6.93 (d, *J* = 8.3 Hz, 2H), 6.61 (t, *J* = 6.0 Hz, 1H), 5.74 (s, 1H), 5.07-5.01 (m, 4H), 4.36 (d, *J* = 11.8 Hz, 1H), 4.22 (dd, *J* = 15.0, 6.0 Hz, 1H), 4.08 (dd, *J* = 15.0, 6.0 Hz, 1H), 3.98-3.88 (m, 2H), 3.84-3.71 (m, 2H), 2.68, 3.45 (ABq, J_{AB} = 14.9 Hz, 2H), 2.91 (d, *J* = 11.8 Hz, 1H), 2.17-2.08 (m, 2H), 1.94-1.84 (m, 2H), 1.49-1.39 (m, 2H), 0.92 (t, *J* = 7.1 Hz, 3H), 0.83 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (125 MHz; C_6D_6): δ 174.9, 172.9, 172.2, 170.7, 170.6, 137.8, 135.6, 135.1, 131.4 (2), 129.6 (2), 128.35 (2), 128.28 (2), 128.23 (2), 128.13, 128.07 (2), 127.95, 120.9, 80.8, 67.55, 67.46, 60.85, 60.83, 57.1, 54.7, 48.7, 44.9, 42.6, 36.9, 34.1, 33.6, 20.7, 13.7, 13.5;

IR (thin film): 3357, 2959, 1741, 1645, 1547, 1489, 1261 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{39}H_{43}BrNO_{10}$ $[M+H]^+$: 764.2065; found 764.2055.

Figure A1. Single crystal X-ray structure (ORTEP) of amide (–)-**2.18**. The crystals were grown from a concentrated solution of amide (–)-**2.18** in Et_2O/pentane (1:1 *v/v*, 0.5 mL), using a slow evaporation method (probability ellipsoids are shown at the 50% level). X-ray crystallographic data have been deposited in the Cambridge Crystallographic Data Centre database (http://www.ccdc.cam.ac.uk/) under accession code CCDC 927697.



Alert level B:
THETM01_ALERT_3_B The value of sine(theta_max)/wavelength is less than 0.575
Calculated sin(theta_max)/wavelength = 0.5616
Author Response: Data was collected on a Bruker GADDS instrument with Cu-source and MWPC (multiwire proportional counter) detector. Under these experimental conditions the maximum angle that can be collected is 120 degrees two-theta.

PLAT029_ALERT_3_B _diffrn_measured_fraction_theta_full Low 0.944
Author Response: The compound crystallizes in triclinic P1. Extended data collection (12 sets of data) was carried out. No efforts were made to remount the crystal and collect the data and merge them to increase the completeness.

PLAT089_ALERT_3_B Poor Data / Parameter Ratio (Zmax < 18) 5.82

Author Response: The data to parameter ratio reported is (4623 data for 464 parameters) 9.96

PLAT220_ALERT_2_B Large Non-Solvent C Ueq(max)/Ueq(min) ... 4.3 Ratio
Author Response: The thermal parameters of the terminal O-Et group showed elongated thermal ellipsoids, possibly indicating a disorder. No efforts were made to model this disorder.

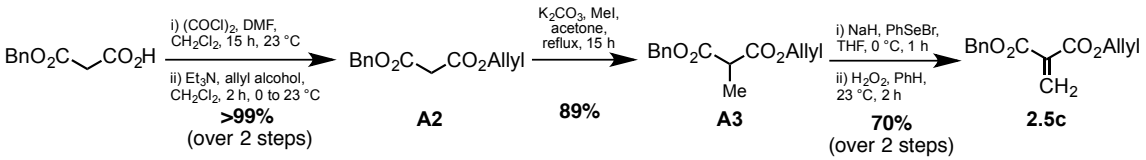
Table A1. Crystal data and structure refinement for DRB_KV_130207_G_94.

Identification code	drb	
Empirical formula	C39 H42 Br N O10	
Formula weight	764.65	
Temperature	110(2) K	
Wavelength	1.54178 Å	
Crystal system	Triclinic	
Space group	P1	
Unit cell dimensions	a = 8.0123(4) Å	α= 76.698(4)°.
	b = 9.5367(5) Å	β= 83.324(4)°.
	c = 12.5723(7) Å	γ = 77.616(4)°.
Volume	910.87(8) $Å^3$	
Z	1	
Density (calculated)	1.394 Mg/m^3	
Absorption coefficient	2.036 mm^{-1}	
F(000)	398	
Crystal size	0.36 x 0.06 x 0.04 mm^3	
Theta range for data collection	3.62 to 59.99°.	
Index ranges	-8<=h<=8, -10<=k<=10, -14<=l<=14	
Reflections collected	10251	
Independent reflections	4623 [R(int) = 0.0470]	
Completeness to theta = 59.99°	94.4 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9230 and 0.5277	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4623 / 3 / 464	
Goodness-of-fit on F^2	1.072	
Final R indices [I>2sigma(I)]	R1 = 0.0401, wR2 = 0.0962	
R indices (all data)	R1 = 0.0465, wR2 = 0.1031	
Absolute structure parameter [Flack / Hooft]		[0.03(2) / 0.04(1)]
Extinction coefficient	0.0281(12)	
Largest diff. peak and hole	0.342 and -0.611 $e.Å^{-3}$	

Table A2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for DRB_KV_130207_G_94. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	1413(4)	1827(3)	11000(2)	20(1)
O(2)	-138(4)	5371(4)	10656(3)	32(1)
O(3)	2720(4)	4695(3)	10515(3)	25(1)
O(4)	1481(4)	2017(3)	6731(2)	22(1)
O(5)	2309(4)	4176(3)	6591(2)	19(1)
O(6)	6103(3)	1405(3)	8573(2)	23(1)
O(7)	5556(3)	2419(3)	6822(2)	19(1)
O(8)	1823(4)	-1155(4)	8247(3)	31(1)
O(9)	4431(4)	-591(3)	7747(3)	27(1)
O(10)	1120(4)	-871(3)	10821(3)	22(1)
N(1)	-1298(5)	-441(4)	9920(3)	18(1)
C(1)	458(5)	2384(5)	10047(3)	18(1)
C(2)	1102(5)	3801(5)	9400(4)	19(1)
C(3)	2888(5)	3451(5)	8826(4)	18(1)
C(4)	3154(5)	2265(4)	8130(4)	16(1)
C(5)	2582(5)	874(5)	8823(3)	16(1)
C(6)	734(5)	1216(5)	9324(4)	18(1)
C(7)	-1458(6)	2946(5)	10309(4)	22(1)
C(8)	-2038(6)	4156(6)	9302(4)	28(1)
C(9)	-398(6)	4595(5)	8682(4)	22(1)
C(10)	1136(6)	4706(5)	10255(4)	24(1)
C(11)	2788(6)	5484(6)	11376(5)	33(1)
C(12)	4597(8)	5506(9)	11477(6)	64(2)
C(13)	2222(5)	2789(5)	7082(4)	17(1)
C(14)	1334(6)	4749(5)	5615(4)	22(1)
C(15)	1567(5)	6296(5)	5169(4)	20(1)
C(16)	1276(6)	7320(5)	5816(4)	25(1)
C(17)	1415(6)	8756(6)	5368(5)	29(1)
C(18)	1826(6)	9214(6)	4246(4)	27(1)
C(19)	2148(6)	8174(6)	3597(4)	29(1)
C(20)	2013(6)	6726(6)	4056(4)	27(1)
C(21)	5104(5)	1944(5)	7871(4)	16(1)
C(22)	7392(5)	2319(6)	6527(4)	24(1)
C(23)	7597(5)	3272(5)	5399(4)	21(1)
C(24)	6689(6)	4689(5)	5150(4)	25(1)
C(25)	6921(6)	5554(6)	4125(4)	34(1)
C(26)	8055(7)	5017(7)	3354(5)	39(2)

C(27)	8978(6)	3582(6)	3582(4)	32(1)
C(28)	8729(6)	2720(5)	4615(4)	26(1)
C(29)	2834(6)	-374(5)	8246(4)	21(1)
C(30)	4920(7)	-1819(6)	7213(5)	37(1)
C(31)	6754(6)	-1940(7)	6845(6)	48(2)
C(32)	203(5)	-153(5)	10070(4)	15(1)
C(33)	-2153(6)	-1436(5)	10754(4)	22(1)
Br(1)	-5455(1)	1769(1)	14453(1)	55(1)
C(34)	-2984(5)	-700(5)	11682(4)	18(1)
C(35)	-2182(6)	-935(6)	12653(4)	26(1)
C(36)	-2913(6)	-193(6)	13465(4)	32(1)
C(37)	-4435(6)	786(6)	13320(4)	34(1)
C(38)	-5253(6)	1058(5)	12357(4)	23(1)
C(39)	-4535(5)	302(5)	11565(4)	25(1)



Allyl benzyl malonate (A2). In an oven dried, 100-mL round-bottomed flash, monobenzyl malonate (6.0 g, 31 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (30 mL) and cooled to 0 °C. Oxalyl chloride (10.5 mL, 124 mmol, 4.0 equiv) was added dropwise followed by one drop of DMF. After 1 h, the ice bath was removed and the reaction mixture was stirred for 15 h. Excess oxalyl chloride was removed by azeotroping with benzene (3 x 10 mL). The crude product was concentrated by rotary evaporation and carried on directly to the next step.

In an oven dried, 250-mL round-bottomed flask, the crude product in the previous step (30.9 mmol, 1.0 equiv) and allyl alcohol (2.52 mL, 37.1 mmol, 1.2 equiv) were dissolved in CH_2Cl_2 (100 mL) and cooled to 0 °C. Et_3N (6.5 mL, 46 mmol, 1.5 equiv) was added dropwise over 30 min. The ice bath was removed and solution was stirred for

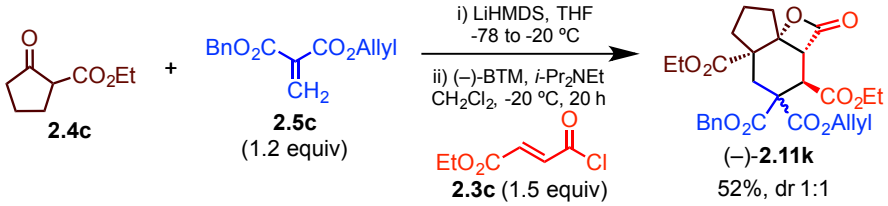
1 h. The reaction was quenched with water (30 mL). The organic layer was isolated and washed with saturated $NaHCO_3$ (3 x 45 mL) and dried over anhydrous Na_2SO_4. The filtrate was concentrated by rotary evaporation to afford 4.6 g (>99% yield) of **A2**. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.40 – 7.34 (m, 5H), 6.00 – 5.84 (m, 1H), 5.34 (dd, *J* = 17.2, 1.5 Hz, 1H), 5.25 (dd, *J* = 10.4, 1.3 Hz, 1H), 5.20 (s, 2H), 4.65 (dt, *J* = 5.7, 1.4 Hz, 2H), 3.47 (s, 2H); **^{13}C NMR** (125 MHz; $CDCl_3$): δ 166.24, 166.03, 135.23, 131.45, 128.56, 128.40, 128.29, 118.74, 67.19, 66.04, 41.46.

1-Allyl 3-benzyl 2-methylmalonate (A3): An oven-dried round-bottomed flask was charged with allyl benzyl malonate (2.24 g, 9.59 mmol, 1.0 equiv), anhydrous K_2CO_3 (2.65 g, 19.2 mmol, 2.0 equiv), and anhydrous acetone (56 mL). The reaction mixture was stirred at room temperature (23 °C) for 10 min before iodomethane was added dropwise to the reaction mixture. The reaction was refluxed for 40 h. Upon completion, the reaction was filtered and concentrated to give **A3** (2.1 g, 89% yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.38 – 7.29 (m, 5H), 5.92 – 5.80 (m, 1H), 5.35 – 5.27 (m, 1H), 5.22 (dd, *J* = 10.4, 1.3 Hz, 1H), 5.18 (dd, *J* = 16.4, 2.1 Hz, 3H), 4.62 (ddt, *J* = 6.0, 3.2, 1.4 Hz, 1H), 3.56 (dtd, *J* = 9.7, 7.6, 7.0 Hz, 1H), 1.48 (dd, *J* = 7.3, 1.8 Hz, 3H); **^{13}C NMR** (125 MHz; $CDCl_3$): δ 169.77, 169.58, 135.40, 131.57, 128.53, 128.29, 128.10, 118.50, 67.06, 65.91, 46.12, 13.59.

1-Allyl 3-benzyl 2-methylenemalonate (2.5c): Prepared according to the procedure for compound **2.5b** using NaH (0.48 g, 12 mmol, 1.5 equiv), a solution of **A3** (2.0 g, 8.1 mmol, 1.0 equiv) in THF (5 mL), a solution of PhSeBr (2.3 g, 9.7 mmol, 1.2 equiv) in THF (10 mL). The reaction was concentrated and the crude mixture was purified by

automated flash chromatography (0 to 5% EtOAc:hexane) to deliver 1-allyl 3-benzyl 2-methyl-2-(phenylselanyl)malonate which was carried on directly to the next step.

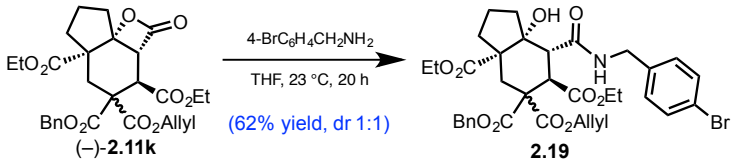
An oven-dried, 100-mL round-bottomed flask was charged with a solution of 1-allyl 3-benzyl 2-methyl-2-(phenylselanyl)malonate in anhydrous benzene (8 mL), followed by addition of H_2O_2 (35% in H_2O, 14.0 mL, 162 mmol, 20.0 equiv). The reaction temperature was maintained at ambient temperature (23 °C) using a water bath. After 2 h, H_2O (10 mL) was added to dissolve the white precipitate. The organic layer was then separated, washed with H_2O, and dried over anhydrous Na_2SO_4. The filtrate was concentrated by rotary evaporation to afford pure **2.5c** (1.4 g, 70% yield over 2 steps, light yellow liquid) of sufficient purity to be used directly in the next step (Note: purification of this compound led to extensive loss of material on silica). The compound **2.5c** was stored as a solution in anhydrous benzene (1.0 M) at –20 °C to prevent decomposition. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.42 – 7.28 (m, 5H), 6.58 (s, 2H), 5.93 (ddt, J = 17.2, 10.5, 5.7 Hz, 1H), 5.42 – 5.14 (m, 4H), 4.71 (dt, J = 5.7, 1.5 Hz, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 163.51, 163.32, 135.32, 135.19, 134.42, 131.47, 128.50, 128.29, 128.10, 118.60, 67.08, 65.94.



4-Allyl 4-benzyl 3,5a-diethyl (2a*R*,3*R*,5a*S*,8a*R*)-2-oxotetrahydro-2*H*-indeno[3a,4-*b*]oxete-3,4,4,5a(5*H*,6*H*)-tetracarboxylate ((–)-2.11k). Prepared according to the

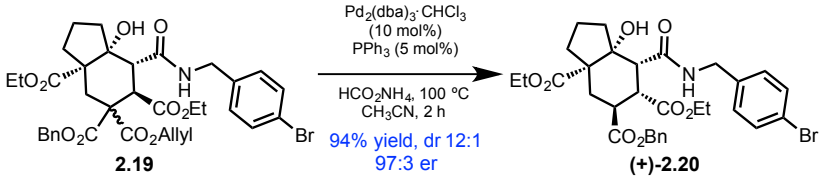
procedure for compound **2.11b** using a solution of LiHMDS (0.36 mL of 1.0 M solution in THF, 0.36 mmol, 1.2 equiv) in THF (0.5 mL), a solution of ethyl 2-oxocyclopentanecarboxylate **2.4c** (47 mg, 0.30 mmol, 1.0 equiv) in THF (0.5 mL), a solution of diester **2.5c** (0.36 mL of 1.0 M solution in benzene, 0.36 mmol, 1.2 equiv) in THF (0.5 mL), (*S*)-BTM (15 mg, 0.060 mmol, 20 mol%) and *i*-Pr_2NEt (78 μL, 0.30 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL), and a solution of acid chloride **2.3c** (73 mg, 0.45 mmol, 1.5 equiv) in CH_2Cl_2 (1.0 mL). The reaction was stirred at -20 °C for 15 h. Upon completion (as judged by TLC), the reaction was concentrated by rotary evaporation and the product was purified by an automated flash chromatography system (gradient of EtOAc/hexanes) to afford a 1:1 mixture of diastereomers of tricyclic-β-lactone **2.11k** (83 mg, 52% yield) as a yellow, viscous liquid: TLC (EtOAc:hexanes, 3:7 *v/v,* Hanessian's stain): R_f = 0.44. $[\alpha]_D^{24.7}$ = -40.40 (*c* = 1.0, $CHCl_3$). NMR data is reported as a 1:1 mixture of diastereomers. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.40 – 7.26 (m, 10H), 5.92 – 5.75 (m, 2H), 5.35 – 5.07 (m, 8H), 4.64 (d, *J* = 5.8 Hz, 2H), 4.60 (d, *J* = 5.9 Hz, 2H), 4.22 – 3.96 (m, 10H), 3.79 (dd, *J* = 9.5, 0.6 Hz, 1H), 3.76 (dd, *J* = 9.6, 0.6 Hz, 1H), 3.07 (d, *J* = 15.1 Hz, 1H), 3.04 (d, *J* = 15.1 Hz, 1H), 2.74 – 2.58 (m, 2H), 2.40 (d, *J* = 15.0 Hz, 1H), 2.39 (d, *J* = 15.1 Hz, 1H), 2.37 – 2.09 (m, 2H), 1.95 – 1.79 (m, 2H), 1.80 – 1.49 (m, 6H), 1.30 – 1.16 (m, 12H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 172.64, 172.62, 170.41, 170.39, 170.30, 169.38, 169.31, 168.18, 168.16, 135.09, 134.48, 131.38, 130.90, 129.22, 128.97, 128.78, 128.64, 128.53, 128.35, 120.08, 118.88, 85.81, 85.79, 68.37, 68.18, 67.09, 66.99, 62.02, 61.99, 55.94, 55.86, 53.04, 52.76, 52.36, 52.32, 43.35, 39.84, 39.83, 39.69, 39.47, 39.34, 39.10, 23.46, 23.41, 14.05, 14.01, 13.98, 13.96. **IR** (thin film):

2981, 1836, 1738, 1453, 1370, 1270, 1026 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{28}H_{32}O_{10}Na$ $[M+Na]^+$: 551.1888, found: 551.1843.



5-Allyl 5-benzyl 3a,6-diethyl (3a*S*,6*R*,7*R*,7a*R*)-7-((4-bromobenzyl)carbamoyl)-7a-hydroxyhexahydro-5*H*-indene-3a,5,5,6(4*H*)-tetracarboxylate (**2.19**). Into an oven-dried, 1-dram vial containing a solution of β-lactone (–)-**2.11k** (30 mg, 0.057 mmol, 1.0 equiv) in THF (1 mL), was added dropwise *p*-bromobenzylamine (29 μL, 0.23 mmol, 4.0 equiv). The reaction was allowed to stir at ambient temperature (23 °C) for 20 h. Upon completion (as judged by TLC), the reaction was concentrated by rotary evaporation and purified by an automated flash chromatography system (gradient of Et_2O/hexanes) to afford a 1:1 diastereomeric mixture of bicyclic amide **2.19** (26 mg, 62% yield) as a white solid: TLC (Et_2O:hexanes, 6:4 *v/v,* Hanessian's stain): R_f = 0.38; NMR data is reported as a 1:1 diastereomeric mixture of bicyclic amide **2.19:** **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.47 – 7.43 (m, 4H), 7.35 – 7.28 (m, 10H), 7.20 (t, *J* = 8.2 Hz, 4H), 6.57 (t, *J* = 5.9 Hz, 1H), 6.43 (t, *J* = 5.8 Hz, 1H), 5.81 (dddt, *J* = 17.3, 14.9, 10.4, 5.9 Hz, 2H), 5.29 (ddq, *J* = 17.2, 4.6, 1.5 Hz, 2H), 5.26 – 5.08 (m, 8H), 4.63 – 4.52 (m, 4H), 4.48 (app dt, *J* = 14.9, 5.7 Hz, 2H), 4.34 (app ddd, *J* = 15.4, 10.3, 5.5 Hz, 2H), 4.23 – 4.06 (m, 4H), 4.03 – 3.89 (m, 4H), 3.89 – 3.81 (m, 2H), 2.99 (d, *J* = 14.9 Hz, 1H), 2.93 (d, *J* = 14.8 Hz, 1H), 2.62 (d, *J* = 11.9 Hz, 1H), 2.55 (d, *J* = 12.0 Hz, 1H), 2.44 (d, *J* = 11.5 Hz, 1H), 2.42 (d, *J* = 11.6 Hz, 1H), 2.14 – 1.29 (m, 12H), 1.26 (t, *J* = 7.1 Hz, 6H),

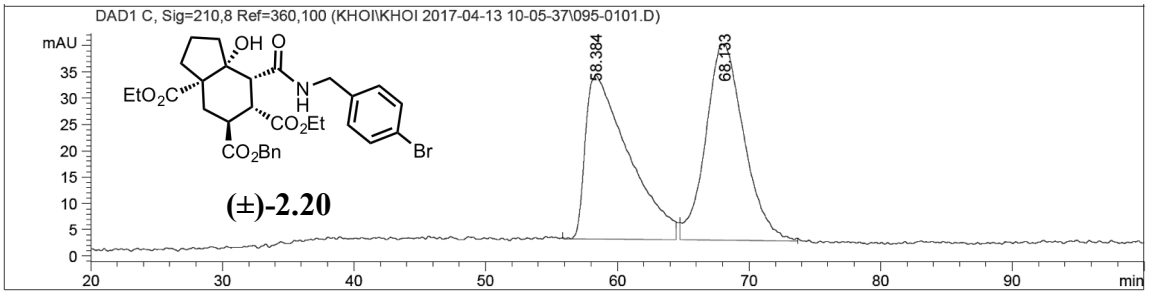
1.11 (app dt, J = 20.1, 7.1 Hz, 6H); **^{13}C NMR** (150 MHz; $CDCl_3$): δ 175.66, 175.43, 173.11, 172.92, 172.15, 171.97, 170.60, 170.54, 170.26, 170.16, 137.15, 137.09, 135.18, 134.82, 131.81, 131.80, 131.49, 131.14, 129.80, 129.71, 128.82, 128.67, 128.64, 128.62, 128.49, 128.35, 121.46, 121.41, 119.34, 118.90, 80.38, 80.24, 67.95, 67.93, 67.88, 67.83, 66.85, 66.76, 61.48, 61.43, 56.81, 56.75, 54.38, 54.29, 48.85, 48.34, 44.79, 44.55, 43.33, 43.23, 35.89, 35.58, 33.22, 33.04, 32.70, 31.68, 29.84, 20.03, 19.81, 14.17, 13.93; **IR** (ATR): 3364, 3068, 3035, 2981, 2959, 2931, 2856, 1725, 1647, 1543, 1249, 1190, 1107, 1013, 734, 699 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{35}H_{40}BrNO_{10}$ $[M+H]^+$: 714.1910; found 714.1908.



5-Benzyl 3a,6-diethyl (3a*S*,5*S*,6*S*,7*R*,7a*R*)-7-((4-bromobenzyl)carbamoyl)-7a-hydroxyoctahydro-3a*H*-indene-3a,5,6-tricarboxylate ((+)-2.20). An oven-dried, 10-mL microwave vial containing a solution of amide **2.19** (21.4 mg, 0.0300 mmol, 1.0 equiv), $Pd_2(dba)_3{\cdot}CHCl_3$ (3.0 mg, 0.0030 mmol, 10 mol%), PPh_3 (0.4 mg, 0.0015 mmol, 5.0 mol%), and HCO_2NH_4 (7.6 mg, 0.12 mmol, 4.0 equiv) in CH_3CN (0.6 mL) was degassed with Ar (3 times) and then heated in a microwave reactor at 100 °C for 2 h. Upon completion (as judged by TLC), the reaction was concentrated by rotary evaporation and purified by flash chromatography (gradient of Et_2O/hexanes) to afford a 12:1 diastereomeric mixture of bicyclic amide (+)-**2.20** (17.8 mg, 94% yield) as a clear

yellow liquid: TLC (Et_2O:hexanes, 8:2 *v/v,* Hanessian's stain): R_f = 0.44; $[\alpha]_D^{22.5}$ = +4.27 (*c* = 0.5, $CHCl_3$). Enantiomeric ratio was determined by HPLC analysis in comparison with authentic racemic material using a Chiracel AD-H column: hexanes:*i*PrOH = 95:5, flow rate 1.0 mL/min, λ = 210 nm: t_{minor} = 60.8 min, t_{major} = 66.7 min; 97:3 *er*. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.37 – 7.24 (m, 9H), 6.21 (t, *J* = 5.6 Hz, 1H), 5.57 (s, 1H), 5.18 (d, *J* = 12.3 Hz, 1H), 5.05 (d, *J* = 12.3 Hz, 1H), 4.55 (dd, *J* = 14.7, 6.3 Hz, 0H), 4.48 (dd, *J* = 14.6, 5.8 Hz, 1H), 4.35 (dd, *J* = 14.6, 5.3 Hz, 1H), 4.21 (qd, *J* = 7.1, 1.8 Hz, 2H), 4.01 (q, *J* = 7.1 Hz, 2H), 3.65 (ddd, *J* = 11.8, 5.6, 3.8 Hz, 1H), 3.47 (ddd, *J* = 5.4, 3.9, 1.1 Hz, 1H), 3.08 (d, *J* = 3.9 Hz, 1H), 2.70 (ddd, *J* = 14.7, 3.9, 1.3 Hz, 1H), 2.28 – 2.16 (m, 1H), 2.02 – 1.57 (m, 6H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.14 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (125 MHz; $CDCl_3$): δ 177.07, 173.45, 173.08, 172.55, 137.98, 136.05, 128.81, 128.55, 128.34, 128.22, 128.06, 127.64, 81.90, 66.43, 61.63, 61.26, 53.26, 49.79, 43.96, 43.16, 37.92, 37.57, 37.15, 29.28, 19.71, 14.12, 14.10; **IR** (ATR): 3362, 3064, 3032, 2977, 2958, 2928, 1724, 1649, 1539, 1454, 1368, 1190, 1028, 909, 730, 696 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{31}H_{37}BrNO_8$ $[M+H]^+$: 630.1697; found 630.1655.

Determination of enantiomeric ratio of amide 2.20:



Signal 3: DAD1 C, Sig=210,8 Ref=360,100

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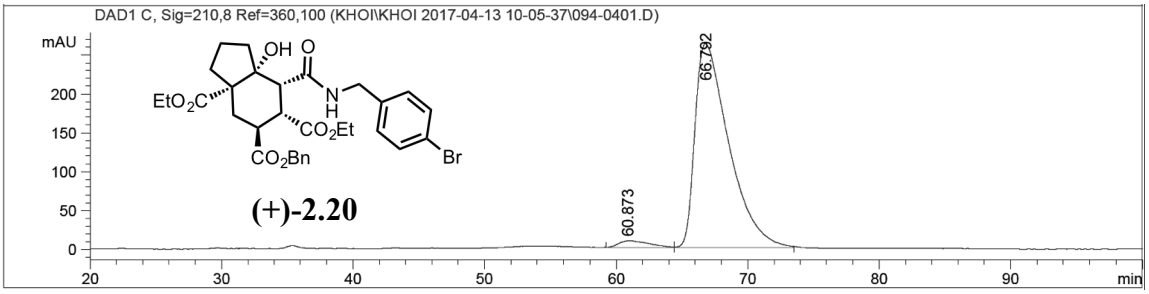
2	68.133	BB	2.4272	7543.01514	37.36546	51.5017



Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
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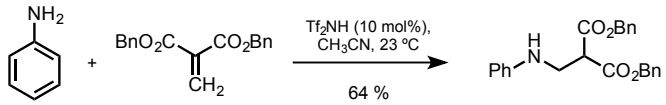
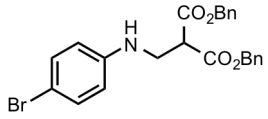
2	66.792	VB	2.5061	4.67009e4	262.68811	97.2566



Dibenzyl 2-(phenylamino)methyl)malonate (3.5a). Prepared according to the literature procedure[8] using aniline (186 mg, 2.0 mmol, 2.0 equiv), bis(trifluoromethanesulfon)imide (28.0 mg, 0.1 mmol, 10 mol%), and **2.5b** (296 mg in 1

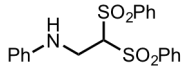
mL benzene, 1.0 mmol, 1.0 equiv) in CH_3CN (2 mL). Upon completion (as judged by TLC), the crude product was purified by an automated flash chromatography system (0 → 30% EtOAc/hexanes) to afford aniline derivative **3.5a** (250 mg, 64% yield) as a yellow liquid: TLC (EtOAc:hexanes, 1:9 *v/v)*: R_f = 0.50; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.36-7.27 (m, 10H), 7.21-7.18 (m, 2H), 6.78-6.75 (m, 1H), 6.63-6.61 (m, 2H), 5.19 (s, 4H), 3.89 (dd, *J* = 7.0, 6.2 Hz, 1H), 3.78 (d, *J* = 6.6 Hz, 2H); **^{13}C NMR** (125 MHz; $CDCl_3$): δ 168.1 (2), 146.7, 135.1 (2), 129.4 (2), 128.6 (4), 128.5 (2), 128.2 (4), 118.2, 113.2 (2), 67.4 (2), 51.2, 42.8; **IR** (thin film): 2958, 1732, 1603, 1508, 1455, 1380, 1155, 1028 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{24}H_{24}NO_4$ $[M+H]^+$: 390.1700, found: 390.1695.



3.5b

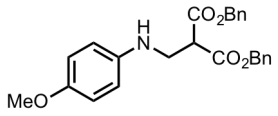
Dibenzyl 2-(((4-bromophenyl)amino)methyl)malonate (**3.5b**): Prepared according to the procedure for compound **3.5a** using 4-bromoaniline (1.72 g, 10.0 mmol, 2.0 equiv), bis(trifluoromethanesulfon)imide (141 mg, 0.50 mmol, 10 mol%), and **2.5b** (5.00 mL of 1.0 M solution in benzene, 5.00 mmol, 1.0 equiv) in CH_3CN (5 mL). Upon completion (as judged by TLC), the crude product was crystallized from a solution of Et_2O/hexanes (1:1 *v/v*) to afford aniline derivative **3.5b** (1.90 g, 81% yield) as a light orange solid: TLC (EtOAc:hexanes, 2:8 *v/v)*: R_f = 0.33; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.37-7.33 (m, 6H), 7.31-7.24 (m, 6H), 6.49-6.45 (m, 2H), 5.21 (s, 4H), 4.17 (bs, 1H), 3.84 (t, *J* = 6.5 Hz, 1H), 3.73 (t, *J* = 5.9 Hz, 2H); **^{13}C NMR** (125 MHz; $CDCl_3$): δ 168.0 (2), 145.9, 135.1 (2), 132.1 (2), 128.69 (4), 128.56 (2), 128.3 (4), 114.7 (2), 109.8, 67.5 (2), 51.1,

42.7; **IR** (thin film): 3416, 3033, 2954, 1731, 1594, 1499, 1455, 1380 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{24}H_{23}BrNO_4$ $[M+H]^+$: 468.0805, found: 468.0801.



3.5c

***N*-(2,2-bis(phenylsulfonyl)ethyl)aniline** (**3.5c**): Prepared according to the procedure for compound **3.5a** using aniline (186 mg, 2.00 mmol, 2.0 equiv), bis(trifluoromethanesulfon)imide (28 mg, 0.10 mmol, 10 mol%), and 1,1-bis(phenylsulfonyl)ethylene (purchased from Sigma-Aldrich) (308 mg, 1.00 mmol, 1.0 equiv) in CH_3CN (1 mL). Upon completion (as judged by TLC), the crude product was purified by an automated flash chromatography system to afford aniline derivative **3.5c** (356 mg, 89% yield); Spectra data matched that previously reported.[9]

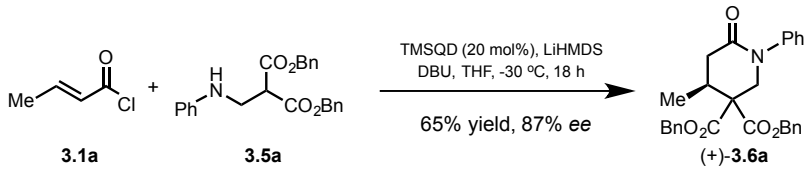


3.5d

Dibenzyl 2-(((4-methoxyphenyl)amino)methyl)malonate (**3.5d**): Prepared according to the procedure for compound **3.5a** using 4-methoxyaniline (246 mg, 2.00 mmol, 2.0 equiv), bis(trifluoromethanesulfon)imide (28 mg, 0.10 mmol, 10 mol%), and **2.5b** (1.00 mL of 1.0 M solution in benzene, 1.00 mmol, 1.0 equiv) in CH_3CN (2 mL). Upon completion (as judged by TLC), the crude product was purified by an automated flash chromatography system (0 → 30% EtOAc/hexanes) to afford aniline derivative **3.5d** (117 mg, 28% yield): TLC (EtOAc:hexanes, 2:8 *v/v)*: R_f = 0.49; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.39 – 7.28 (m, 10H), 6.80 (d, J = 8.9 Hz, 2H), 6.59 (d, J = 8.8 Hz, 2H), 5.19 (s, 4H), 3.88 (t, J = 6.6 Hz, 1H), 3.76 (s, 3H), 3.74 (d, J = 6.6 Hz, 2H); **^{13}C NMR** (125

MHz; $CDCl_3$): δ 168.2, 152.7, 140.9, 135.2, 128.6, 128.2, 115.0, 114.8, 67.4, 55.8, 51.3, 43.9; **HRMS** (ESI+) *m/z* calcd for $C_{25}H_{26}NO_5$ $[M+H]^+$: 420.1811, found: 420.1832.

Representative Procedure for Nucleophile Catalyzed Michael Proton-Transfer δ-Lactamization Cascade with β-Aminomalonates and Acid Chlorides as Described for Pyrrolidinone (+)-3.6a

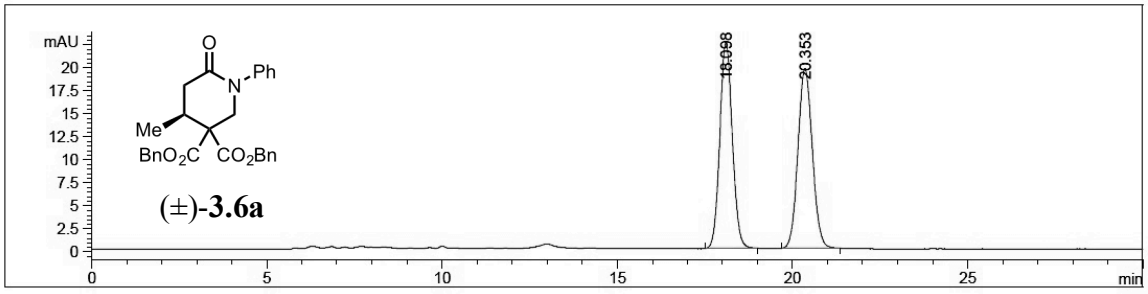


3.1a **3.5a** (+)-**3.6a**

(*S*)-dibenzyl 4-methyl-6-oxo-1-phenylpiperidine-3,3-dicarboxylate (3.6a). To an oven-dried, 25-mL round-bottomed flask equipped with a magnetic stir bar was added aminomalonate **3.5a** (149.0 mg, 0.38 mmol, 1.0 equiv) along with THF (2.0 mL) and cooled to –30 °C. With vigorous stirring, LiHMDS (0.4 mL of a 1.0 M solution in THF, 0.4 mmol, 1.05 equiv) was added dropwise over 5 min. After the addition was complete, the reaction was stirred for 15 min at –30 °C. After which time, TMSQD (30 mg, 0.076 mmol in 0.5 mL THF, 20 mol%) and DBU (58 mg, 0.38 mmol in 0.5 mL THF, 1.0 equiv) were added sequentially, followed by **3.1a** (60 mg, 0.576 mmol, 1.5 equiv) in 1 mL THF over 5 h using a syringe pump and allowed to react for additional 13 h at –30 °C. Upon completion (as judged by TLC), 1N HCl (0.3 mL) was added, and the reaction was concentrated by rotary evaporation and purified by an automated flash chromatography system (0 → 40%, EtOAc/hexanes) to afford δ-lactam (+)-**3.6a** (115.0 mg, 65% yield) as a viscous liquid: TLC (EtOAc:hexanes, 5:5 *v/v*): R_f = 0.33; $[\alpha]_D^{16.6}$ =

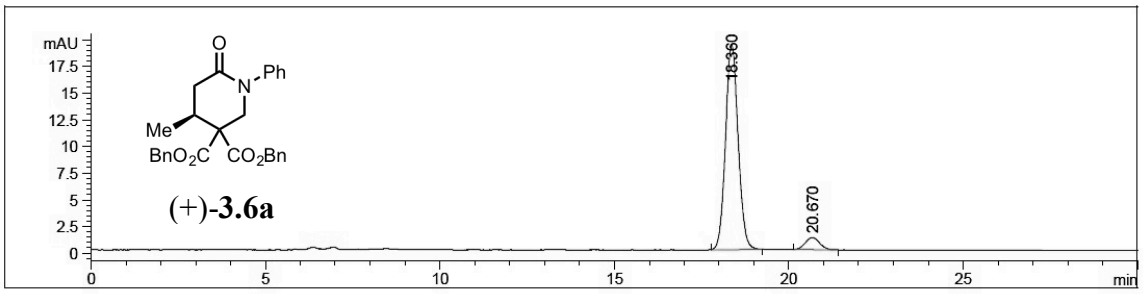
+25.61 (*c* = 1.0, $CHCl_3$). Enantiomeric ratio was determined by HPLC analysis in comparison with authentic racemic material using a Chiracel AD-H column: hexanes:*i*PrOH = 70:30, flow rate 0.5 mL/min, λ = 254 nm: t_{major} = 18.3 min, t_{minor} = 20.6 min; 87% *ee*. Absolute stereochemistry was assigned by analogy to compound **3h** in this publication.[10] **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.37-7.24 (m, 13H), 7.14-7.12 (m, 2H), 5.25-5.12 (m, 4H), 4.16-4.13 (m, 2H), 2.99 (qdd, *J* = 7.0, 6.3, 5.6 Hz, 1H), 2.89 (dd, *J* = 17.9, 6.3 Hz, 1H), 2.44 (dd, *J* = 17.9, 5.6 Hz, 1H), 1.16 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 168.7, 168.5, 167.8, 142.3, 134.8, 134.7, 129.3 (2), 128.71 (3), 128.68 (3), 128.45 (2), 128.44 (2), 127.2, 126.3 (2), 68.0, 67.7, 57.6, 52.2, 37.5, 31.9, 17.1; **IR** (thin film): 2965, 1733, 1662, 1596, 1496, 1350, 1265, 1111, 752 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{28}H_{27}LiNO_5$ $[M+Li]^+$: 464.2044, found: 464.2067.

Chiral HPLC analysis of (+)-3.6a:



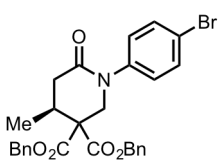
Signal 2: DAD1 B, Sig=254,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.098	BB	0.3864	556.79230	22.36686	49.8439
2	20.353	BB	0.4419	560.28033	19.57645	50.1561



Signal 2: DAD1 B, Sig=254,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.360	BB	0.3894	483.12387	19.21100	93.6190
2	20.670	BB	0.4350	32.92952	1.15363	6.3810

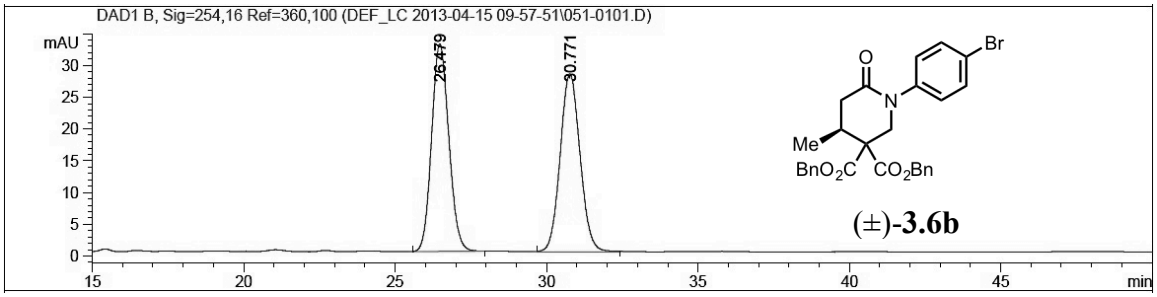


3.6b

Dibenzyl (*S*)-1-(4-bromophenyl)-4-methyl-6-oxopiperidine-3,3-dicarboxylate (3.6b): Prepared according to the representative procedure using β-aminomalonate **3.5a** (70.2 mg, 0.15 mmol, 1.00 equiv), LiHMDS (0.16 mL, 1.0 M solution in THF, 0.16 mmol, 1.05 equiv), TMSQD (11.9 mg, 0.03 mmol in 0.20 mL THF, 20 mol%), DBU (22.8 mg, 0.15 mmol in 0.20 mL THF, 1.0 equiv) and crotonoyl chloride (**3.1a**) (24.0 mg, 0.23 mmol, 1.50 equiv) in THF (1.0 mL) at –30 ºC. Purification of crude product by an automated flash chromatography system (0 → 40%, EtOAc/hexanes) to afford δ-lactam (+)-**3.6b** (44.0 mg, 53% yield) as a viscous liquid. TLC (EtOAc:hexanes, 3:7 *v/v*): R_f = 0.30; $[\alpha]_D^{20.2}$ = +17.80 (*c* = 1.0, $CHCl_3$). Enantiomeric ratio was determined by HPLC analysis in comparison with authentic racemic material using a Chiralcel AD-H column: hexanes:*i*PrOH = 70:30, flow rate 0.5 mL/min, λ = 254 nm: t_{major} = 25.9 min, t_{minor} = 30.3 min; 93% *ee*. Absolute stereochemistry was assigned by analogy to compound **3h** in this publication.[10] **^{1}H NMR** (500 MHz; $CDCl_3$): δ 7.29-7.26 (m, 2H), 7.21-7.06 (m, 10H),

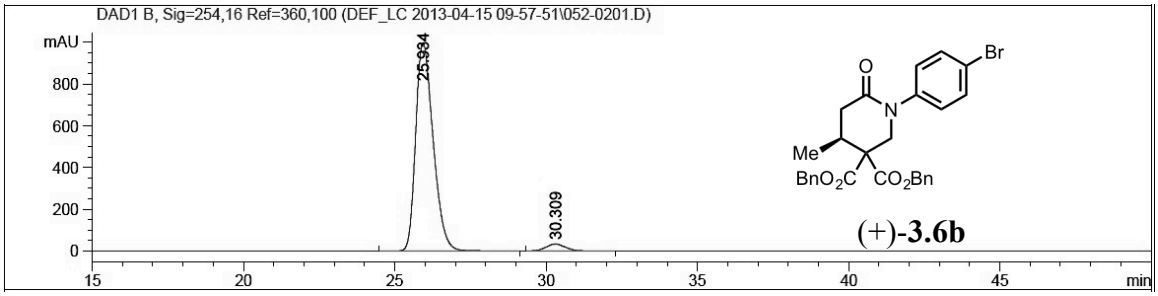
6.82-6.79 (m, 2H), 5.06 (d, J = 12.1 Hz, 1H), 5.01 (s, 2H), 4.94 (d, J = 12.1 Hz, 1H), 3.97-3.91 (m, 2H), 2.80 (qdd, J = 7.0, 6.4, 5.7 Hz, 1H), 2.69 (dd, J = 18.0, 6.4 Hz, 1H), 2.25 (dd, J = 18.0, 5.7 Hz, 1H), 0.97 (d, J = 7.0 Hz, 3H); **^{13}C NMR** (125 MHz; $CDCl_3$): δ 168.57, 168.48, 167.7, 141.2, 134.67, 134.64, 132.3 (2), 128.76, 128.72(2), 128.69, 128.5 (4), 127.9 (4), 120.6, 68.0, 67.7, 57.5, 51.9, 37.5, 31.8, 17.1; **IR** (thin film): 3064, 3033, 2963, 2928, 1733, 1655, 1489, 1265, 1215 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{28}H_{27}BrNO_5$ $[M+H]^+$: 536.0994, found: 536.1129.

Chiral HPLC analysis of (+)-3.6b:



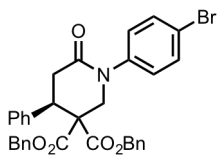
Signal 2: DAD1 B, Sig=254,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	26.479	BB	0.6124	1289.42993	32.67210	50.3473
2	30.771	BB	0.7057	1271.63867	28.00774	49.6527



Signal 2: DAD1 B, Sig=254,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	25.934	VB	0.6204	3.99975e4	996.33337	96.3490
2	30.309	BB	0.6970	1515.64539	33.68023	3.6510

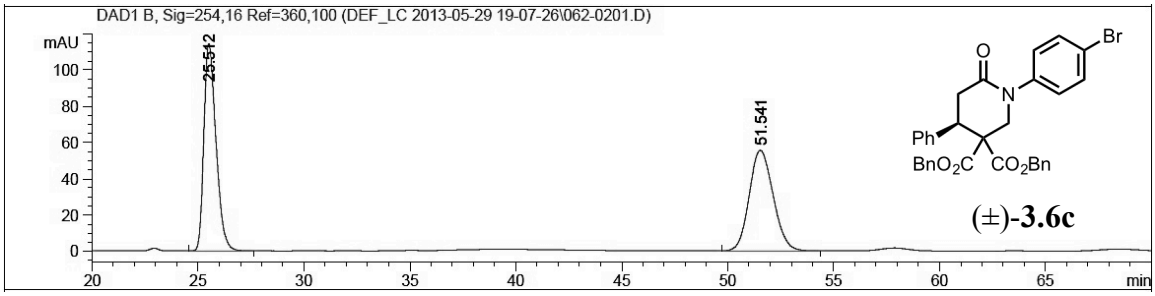


3.6c

Dibenzyl (*R*)-1-(4-bromophenyl)-6-oxo-4-phenylpiperidine-3,3-dicarboxylate (3.6c): Prepared according to the representative procedure using β-aminomalonate **3.5b** (180 mg, 0.38 mmol, 1.00 equiv), LiHMDS (0.50 mL, 1.0 M solution in THF, 0.50 mmol, 1.30 equiv), TMSQD (30.1 mg, 0.076 mmol in 0.50 mL THF, 20 mol%), DBU (58.4 mg, 0.38 mmol in 0.50 mL THF, 1.0 equiv) and *trans*-cinnamoyl chloride (**3.1d**) (128 mg, 0.77 mmol, 2.00 equiv) in THF (1.0 mL) at –10 ºC. Purification of crude product by an automated flash chromatography system (0 → 40%, EtOAc/hexanes) to afford δ-lactam (+)-**3.6c** (92.0 mg, 40% yield) as a viscous liquid. TLC (EtOAc:hexanes, 2:8 *v/v*): R_f = 0.38; $[\alpha]_D^{21.5}$ = +50.17 (*c* = 1.0, $CHCl_3$). Enantiomeric ratio was determined by HPLC analysis in comparison with authentic racemic material using a Chiralcel AD-H column: hexanes:*i*PrOH = 70:30, flow rate 0.5 mL/min, λ = 254 nm: t_{minor} = 25.8 min, t_{major} = 50.7 min; 96% *ee*. Absolute stereochemistry was assigned by analogy to compound **3h** in this publication.[10] **^{1}H NMR** (500 MHz; $CDCl_3$): δ 7.48-7.45 (m, 2H), 7.40-7.28 (m, 9H), 7.24-7.14 (m, 6H), 7.01-6.98 (m, 2H), 5.33 (d, *J* = 11.9 Hz, 1H), 5.07 (d, *J* = 11.9 Hz, 1H), 4.96 (d, *J* = 12.1 Hz, 1H), 4.89 (d, *J* = 12.1 Hz, 1H), 4.27-4.24 (m, 2H), 4.11 (dd, *J* = 13.3, 1.3 Hz, 1H), 3.35 (dd, *J* = 18.2, 7.4 Hz, 1H), 2.91 (dd, *J* = 18.2,

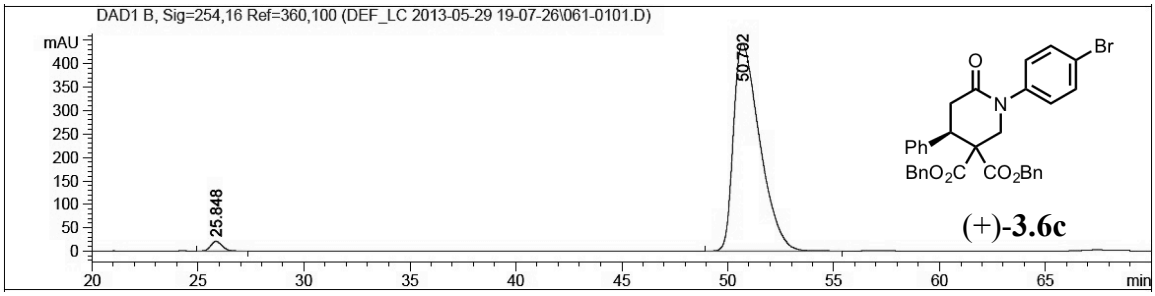
3.7 Hz, 1H); **^{13}C NMR** (125 MHz; $CDCl_3$): δ 168.8, 168.5, 167.0, 141.2, 139.2, 134.59, 134.40, 132.3 (2), 128.88, 128.86 (2), 128.78 (2), 128.74 (2), 128.70, 128.66 (2), 128.53 (2), 128.33 (2), 128.0, 127.6 (2), 120.6, 68.3, 67.7, 58.5, 51.0, 42.1, 36.1; **IR** (thin film): 3089, 3063, 3032, 2926, 2855, 1735, 1664, 1489, 1265 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{33}H_{28}BrNO_5Li$ $[M+Li]^+$: 604.1311, found: 604.1343.

Chiral HPLC analysis of (+)-3.6c:



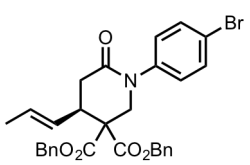
Signal 2: DAD1 B, Sig=254,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	25.512	VB	0.6024	4527.85059	114.23516	50.9397
2	51.541	BB	1.2293	4360.79883	55.46533	49.0603



Signal 2: DAD1 B, Sig=254,16 Ref=360,100

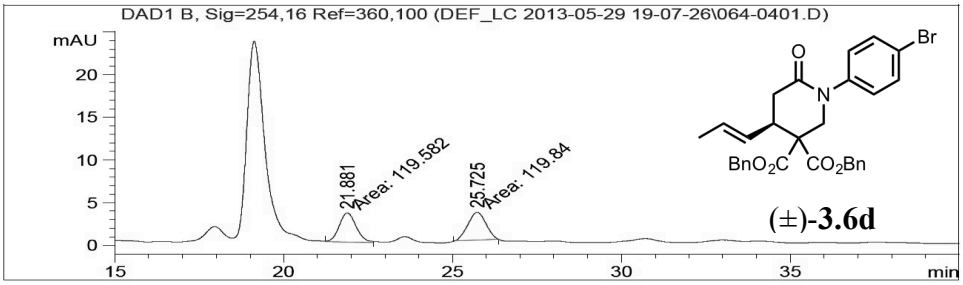
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	25.848	VB	0.5866	785.39832	20.88906	2.0108
2	50.702	VB	1.3293	3.82735e4	442.40445	97.9892



3.6d

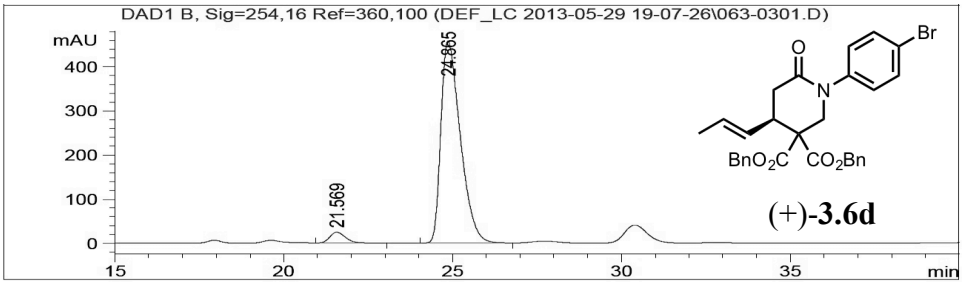
Dibenzyl (*R*,*E*)-1-(4-bromophenyl)-6-oxo-4-(prop-1-en-1-yl)piperidine-3,3-dicarboxylate (3.6d): Prepared according to the representative procedure using β-aminomalonate **3.5b** (180 mg, 0.38 mmol, 1.00 equiv), LiHMDS (0.50 mL, 1.0 M solution in THF, 0.50 mmol, 1.30 equiv), TMSQD (30.1 mg, 0.076 mmol in 0.50 mL THF, 20 mol%), DBU (58.4 mg, 0.38 mmol in 0.50 mL THF, 1.0 equiv) and sorbic chloride (**3.1g**) (100 mg, 0.77 mmol, 2.00 equiv) in THF (1.0 mL) at –10 ºC. Purification of crude product by an automated flash chromatography system (0 → 40%, EtOAc/hexanes) to afford δ-lactam (+)-**3.6d** (77.8 mg, 36% yield) as a viscous liquid. TLC (EtOAc:hexanes, 2:8 *v/v*): R_f = 0.34; $[\alpha]_D^{21.7}$ = +29.13 (*c* = 1.0, $CHCl_3$). Enantiomeric ratio was determined by HPLC analysis in comparison with authentic racemic material using a Chiralcel AD-H column: hexanes:*i*PrOH = 70:30, flow rate 0.5 mL/min, λ = 254 nm: t_{minor} = 21.5 min, t_{major} = 24.8 min; 92% *ee*. Absolute stereochemistry was assigned by analogy to compound **3h** in this publication.[10] **^{1}H NMR** (500 MHz; $CDCl_3$): δ 7.44 – 7.41 (m, 2H), 7.36 – 7.32 (m, 6H), 7.25 (ddt, *J* = 15.4, 7.8, 2.9 Hz, 4H), 6.95 – 6.92 (m, 2H), 5.62 – 5.43 (m, 2H), 5.26 – 5.01 (m, 4H), 4.09 (d, *J* = 3.7 Hz, 2H), 3.44 – 3.40 (m, 1H), 2.90 (dd, *J* = 18.2, 6.6 Hz, 1H), 2.60 (dd, *J* = 18.2, 5.3 Hz, 1H), 1.58 (d, *J* = 5.4 Hz, 3H); **^{13}C NMR** (125 MHz; $CDCl_3$): δ 168.4, 168.3, 167.4, 141.3, 134.8, 134.7, 132.3, 130.0, 128.8, 128.8, 128.8, 128.7, 128.7, 128.6, 128.0, 127.9, 120.6, 68.1, 67.8, 57.8, 52.2, 40.6, 35.5, 18.1; **IR** (thin film): 3064, 3033, 2959, 2853, 1734, 1664, 1489, 1455, 1264, 1227, 1067 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{30}H_{29}BrNO_5$ $[M+H]^+$: 562.1229, found: 562.1215.

Chiral HPLC analysis of (+)-3.6d:



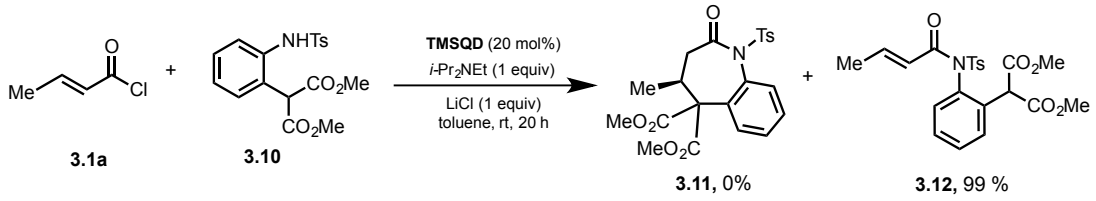
Signal 2: DAD1 B, Sig=254,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.881	MM	0.5818	119.58243	3.42547	49.9463
2	25.725	MM	0.6156	119.83981	3.24470	50.0537



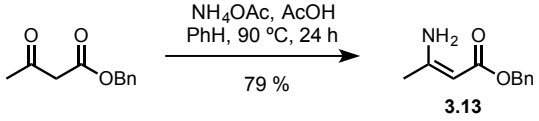
Signal 2: DAD1 B, Sig=254,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.569	VB	0.5145	818.51575	24.70920	4.2831
2	24.865	BV	0.6141	1.82920e4	457.81378	95.7169



Dimethyl (*E*)-2-(2-(*N*-tosylbut-2-enamido)phenyl)malonate (3.12): Into a mixture of amine **3.10**[11] (145 mg, 0.384 mmol, 1.0 equiv), TMSQD (30 mg, 0.077 mmol, 20 mol%), LiCl (16.3 mg, 0.384 mmol, 1.0 equiv) in dry toluene (3.0 mL) was added a

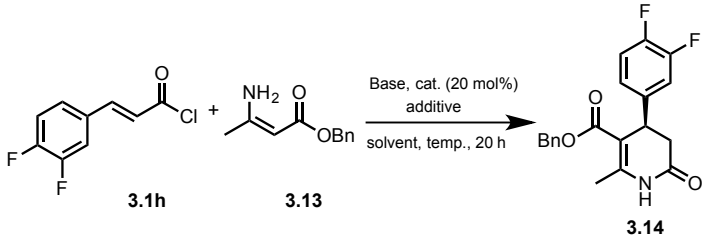
solution of *i*-Pr_2NEt (0.20 mL, 1.2 mmol, 3 equiv) in dry toluene (1.0 mL) dropwise (over 2 min). The solution of crotonoyl chloride **3.1a** (80 mg, 0.77 mmol, 2.0 equiv) in dry toluene (4.0 mL) was then added dropwise over 5 h using a syringe pump. The reaction mixture was stirred at room temp (23 °C) for 20 h. Upon completion (judged by TLC), the reaction mixture was concentrated and purified by an automated flash chromatography system to afford amide **3.12** (169 mg, 99% yield); **^{1}H NMR** (500 MHz; $CDCl_3$): δ 7.95 (d, *J* = 8.4 Hz, 2H), 7.80 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.56 (td, *J* = 7.7, 1.3 Hz, 1H), 7.39 (td, *J* = 7.7, 1.5 Hz, 1H), 7.34 (d, *J* = 8.7 Hz, 1H), 7.04 – 6.91 (m, 2H), 5.41 (dd, *J* = 14.9, 1.8 Hz, 1H), 5.22 (s, 1H), 3.83 (s, 3H), 3.69 (s, 3H), 2.45 (s, 3H), 1.68 (dd, *J* = 7.0, 1.7 Hz, 3H); **^{13}C NMR** (125 MHz; $CDCl_3$): δ 168.5, 167.9, 165.4, 146.8, 145.3, 135.7, 135.3, 134.5, 131.6, 130.6, 129.9, 129.8, 129.6, 129.5, 122.6, 53.2, 53.0, 52.4, 21.9, 18.4.



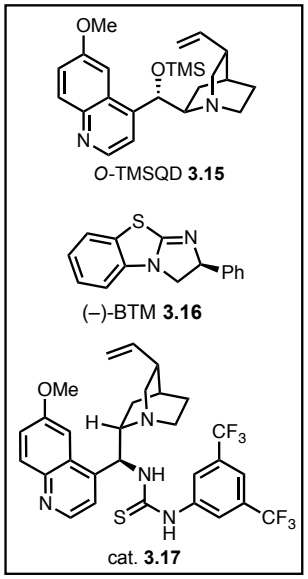
3.13

Benzyl (*Z*)-3-aminobut-2-enoate (3.13). An oven-dried, 100-mL round-bottomed flask containing benzyl acetoacetate (3.45 mL, 20.0 mmol, 1.0 equiv), ammonium acetate (3.08 g, 40.0 mmol, 2.0 equiv), acetic acid (1.14 mL, 20.0 mmol, 1.0 equiv) and THF (50 mL) was equipped with a Dean Stark trap and refluxed at 90 ºC for 24 h. The reaction mixture was then cooled down to room temperature, followed by washing with sat. $NaHCO_3$ (2 × 50 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated on *vacuo*. The crude product was recrystallized from a solution of

Et_2O:hexanes (1:1 *v/v*) to afford pure desired enamine **3.13** (3.00 g, 79 % yield) as a white solid. TLC (EtOAc:hexanes, 1:9 *v/v*): R_f = 0.22; **^{1}H NMR** (500 MHz; $CDCl_3$): δ 7.95 (bs, 1H), 7.41-7.31 (m, 5H), 5.15 (s, 2H), 4.63 (s, 1H), 1.92 (s, 3H); **^{13}C NMR** (125 MHz; $CDCl_3$): δ 169.9, 160.3, 137.3, 128.5 (2), 127.85 (2), 127.77, 83.8, 64.5, 22.4; **IR** (thin film): 3476, 3446, 3337, 3032, 2950, 1666, 1620, 1562, 1283, 1157 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{11}H_{13}NO_2$ $[M+H]^+$: 192.1025, found: 192.1035.



Entry	Bases	Cat.	Additive	Solvent, temp.	Result
1	LiHMDS (1.3 equiv), DBU (1.0 equiv)	*O*-TMSQD **3.15**	-	THF, -10 ºC	30%, 10% *ee*
2	LiHMDS (1.3 equiv), *i*Pr_2NEt (1.0 equiv)	*O*-TMSQD **3.15**	-	THF, -15 ºC	ND, 60% *ee*
3	LiHMDS (1.3 equiv), *i*Pr_2NEt (1.0 equiv)	*O*-TMSQD **3.15**	-	THF, 5 ºC	ND, 75% *ee*
4	LiHMDS (1.3 equiv), *i*Pr_2NEt (1.0 equiv)	*O*-TMSQD[a] **3.15**	-	THF, 40 ºC	ND, 65% *ee*
5	LiHMDS (1.3 equiv), *i*Pr_2NEt (1.0 equiv)	$(DHQ)_2PHAL$[a]	-	THF, 0 ºC	ND, 40% *ee*
6	LiHMDS (1.3 equiv), *i*Pr_2NEt (1.0 equiv)	(–)-BTM **3.16**	-	THF, -15 ºC	ND, 10% *ee*
7	LiHMDS (1.3 equiv), *i*Pr_2NEt (1.0 equiv)	cat. **3.17**	-	THF, -15 ºC	ND, 10% *ee*
8	LiHMDS (1.3 equiv), *i*Pr_2NEt (1.0 equiv)	*O*-TMSQD **3.15**	MS (4 Å)	PhMe, 0 - 23 ºC	ND, 76% *ee*
9	*i*Pr_2NEt (3 equiv)	*O*-TMSQD **3.15**	MS (4 Å)	PhMe, 23 ºC	66%, 90% *ee*
10	*i*Pr_2NEt (3 equiv)	*O*-TMSQD **3.15**	MS (4 Å)	THF, 23 ºC	40%, 89% *ee*
11	***i*Pr_2NEt (3 equiv)**	***O*-TMSQD 3.15**	**LiCl, MS (4 Å)**	**PhMe, 23 ºC**	**78%, 92% *ee***



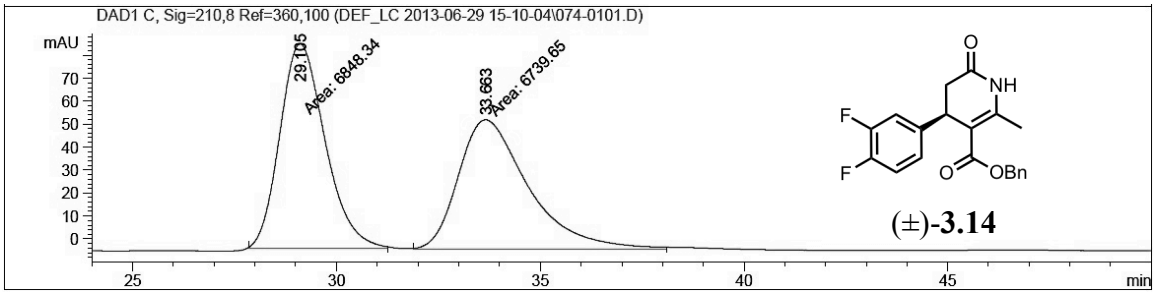
ND = not determined; [a]the acid chloride was added over a 2-h period (instead of 5 h); [b]the reaction was performed in 0.198 mmol scale of compound **3.13**

Method A (entries 1-7): To an oven-dried, 25 mL round-bottomed flask equipped with a magnetic stir bar was added enamine **3.13** (73.4 mg, 0.38 mmol, 1.00 equiv) along with THF (2.0 mL) and cooled to indicated temperature. With vigorous stirring, LiHMDS (0.5 mL of a 1.0 M solution in THF, 0.4 mmol, 1.30 equiv) was added dropwise over 5 min. After the addition was complete, the reaction was stirred for 15 min at the same temperature. After this time, the catalyst (0.076 mmol in 0.5 mL THF, 20 mol%) and base (0.38 mmol in 0.5 mL THF, 1.00 equiv) were added sequentially, followed by 3,4-difluorocinnamoyl chloride **3.1h** (157 mg, 0.768 mmol, 2.00 equiv) in 1 mL THF over 5 h using a syringe pump and allowed to react for additional 15 h at the indicated temperature. Preparatory TLC was then performed on an aliquot of the reaction mixture to determine enantiomeric ratio of the product. Entries 2-7 were not purified further due to low enantiomeric ratio.

Method B (entries 8-11): entry 9 is used to describe this method. Into a mixture of enamine **3.13** (191 mg, 1.00 mmol, 1.00 equiv), TMSQD (79.3 mg, 0.20 mmol, 20 mol%), *i*-Pr_2NEt (0.52 mL, 3.00 mmol, 3.00 equiv), LiCl (42.4 mg, 1.00 mmol, 1.00 equiv) and molecular sieves (4Å) (500 mg) in anhydrous toluene (10 mL) was added a solution of 3,4-difluorocinnamoyl chloride **3.1h** (405 mg, 2.00 mmol, 2.00 equiv) in anhydrous toluene (10 mL) at room temperature (23 ºC) over 5 h using a syringe pump. The reaction was then stirred for another 15 h. Upon completion (as judged by TLC), the reaction was concentrated by rotary evaporation and purified by an automated flash chromatography system (0 → 70%, EtOAc/hexanes) to afford δ-lactam (–)-**3.14** (279

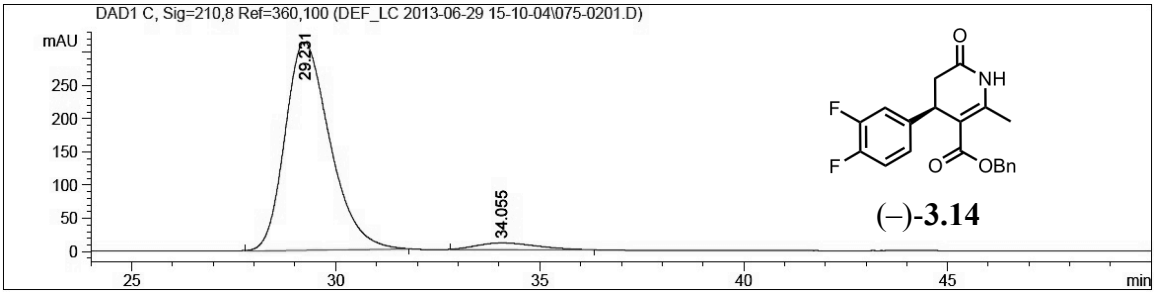
mg, 78% yield) as a viscous yellow liquid: TLC (EtOAc:hexanes, 3:7 *v/v*): R_f = 0.38; $[\alpha]_D^{21}$ = –41.15 (*c* = 1.0, $CHCl_3$). Enantiomeric ratio was determined by HPLC analysis in comparison with authentic racemic material using a Chiracel OJ-H column: hexanes:*i*PrOH = 70:30, flow rate 0.5 mL/min, λ = 210 nm: t_{major} = 29.2 min, t_{minor} = 34.0 min; 92% *ee*. Absolute stereochemistry was assigned by comparison to previously reported (*R*)-*tert*-butyl 4-(3,4-difluorophenyl)-2-methyl-6-oxo-1,4,5,6-tetrahydropyridine-3-carboxylate; $[\alpha]_D^{27}$ = –71.7 (*c* = 2.0, $CHCl_3$).[12] **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.94 (s, 1H), 7.32-6.88 (m, 8H), 5.15 (d, *J* = 12.5 Hz, 1H), 5.10 (d, *J* = 12.5 Hz, 1H), 4.25 (d, *J* = 8.1 Hz, 1H), 2.94 (dd, *J* = 16.6, 8.1 Hz, 1H), 2.65 (d, *J* = 16.6 Hz, 1H), 2.45 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 170.6, 166.2, 150.83 (dd, $J_{C\text{-}F}$ = 122.7, 12.7 Hz, 1C), 148.86 (dd, $J_{C\text{-}F}$ = 121.8, 12.7 Hz, 1C), 147.35, 139.04 (dd, $J_{C\text{-}F}$ = 4.7, 3.9 Hz, 1C), 135.9, 128.5 (2), 128.17, 127.92 (2), 122.68 (dd, *J* = 6.2, 3.5 Hz, 1C), 117.56 (d, *J* = 17.2 Hz, 1C), 115.83 (d, *J* = 17.5 Hz, 1C), 106.3, 66.2, 37.96, 37.3, 19.2; **IR** (thin film): 3238, 3133, 2956, 1700, 1632, 1517, 1284, 1208, 1186, 1087 cm^{-1}; **HRMS** (ESI–) *m/z* calcd for $C_{20}H_{16}F_2NO_3$ $[M\text{-}H]^-$: 356.1098, found: 356.0874.

Chiral HPLC analysis of (–)-3.14:



Signal 3: DAD1 C, Sig=210,8 Ref=360,100

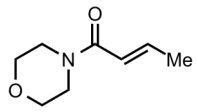
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	29.105	MM	1.2819	6848.34375	89.03769	50.4000
2	33.663	MM	1.9928	6739.65332	56.36643	49.6000



Signal 3: DAD1 C, Sig=210,8 Ref=360,100

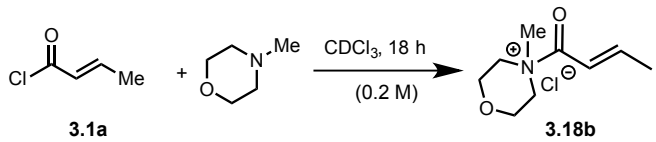
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	29.231	BB	1.1741	2.39208e4	312.84778	95.9208
2	34.055	BB	1.2153	1017.27838	9.87937	4.0792

NMR study of acylammonium salts

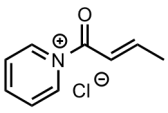


3.18a

(E)-1-morpholinobut-2-en-1-one (3.18a): this compound was prepared according to a literature report.[13] **^{1}H NMR** (500 MHz, $CDCl_3$):δ 6.80 (dq, *J* = 14.7, 7.0 Hz, 1H), 6.15 (dd, *J* = 14.7, 1.6 Hz, 1H), 3.59 (bs, 6H), 3.47 (bs, 2H), 1.80 (dd, *J* = 7.0, 1.6 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$):δ 165.6, 142.0, 121.0, 66.8 (2), 46.0, 42.1, 18.2.

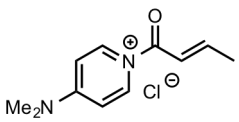


(E)-4-(but-2-enoyl)-4-methylmorpholin-4-ium chloride (3.18b): A solution of *N*-methylmorpholine (22.0 μL, 0.2 mmol, 1.0 equiv) in $CDCl_3$ (0.5 mL) was added into a solution of crotonoyl chloride **3.1a** (20.8 mg, 0.2 mmol, 1.0 equiv) in $CDCl_3$ (0.5 mL). The resulting mixture was stirred at room temperature (23 °C) for 18 h, followed by immediate NMR analysis. The product was observed as 4:1 mixture of acylammonium **3.18b** and crotonoyl chloride (**3.1a**); the reported NMR signals are for compound **3.18b** only. **^{1}H NMR** (500 MHz, $CDCl_3$):δ 7.09 (dq, *J* = 15.5, 6.9 Hz, 1H), 5.85 (dq, *J* = 15.5, 1.7 Hz, 1H), 3.95 (bs), 2.94 (bs), 2.66 (bs), 1.90 (dt, *J* = 6.9, 1.7 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 161.9, 149.6, 122.0, 64.5, 54.0, 44.5, 18.5.



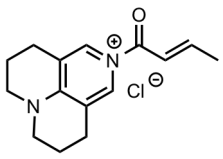
3.18c

(*E*)-1-(but-2-enoyl)pyridin-1-ium chloride (3.18c): Prepared according to the representative procedure for compound **3.18b** using pyridine (16.1 μL, 0.2 mmol, 1.0 equiv), crotonoyl chloride **3.1a** (20.8 mg, 0.2 mmol, 1.0 equiv) and $CDCl_3$ (1.0 mL) over 18 h at room temperature (23 °C). The product was observed as 1:2.5 mixture of acylammonium **3.18c** and crotonoyl chloride (**3.1a**); the reported NMR signals are for compound **3.18c** only. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.71 (d, *J* = 4.7 Hz, 2H), 8.04 (t, *J* = 7.7 Hz, 1H), 7.61 (t, *J* = 6.4 Hz, 2H), 7.10 (dq, *J* = 15.3, 7.2 Hz, 1H), 5.86 (dq, *J* = 15.3, 1.7 Hz, 1H), 1.91 (dd, *J* = 7.2, 1.7 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): 162.0, 149.6, 145.8, 140.7, 125.5, 122.0, 18.5.



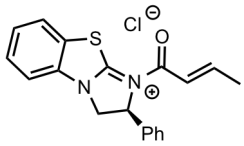
3.18d

(*E*)-1-(but-2-enoyl)-4-(dimethylamino)pyridin-1-ium chloride (3.18d): Prepared according to the representative procedure for compound **3.18b** using DMAP (24.4 mg, 0.2 mmol, 1.0 equiv), crotonoyl chloride **3.1a** (20.8 mg, 0.2 mmol, 1.0 equiv) and $CDCl_3$ (1.0 mL) over 30 min at room temperature (23 °C). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 9.14 (d, *J* = 8.2 Hz, 2H), 7.48 (dq, *J* = 14.8, 6.6 Hz, 1H), 7.41 (dq, *J* = 14.8, 1.0 Hz, 1H), 7.31 (d, *J* = 8.2 Hz, 2H), 3.44 (s, 6H), 2.12 (dd, *J* = 6.6, 1.0 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 162.8, 158.5, 156.8, 137.7, 118.3, 108.5, 41.7, 19.7.



3.18e

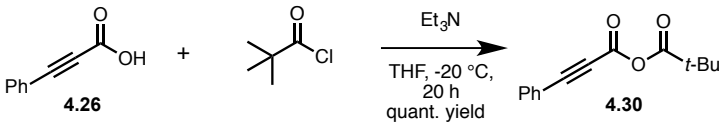
(*E*)-2-(but-2-enoyl)-5,6,9,10-tetrahydro-4*H*,8*H*-pyrido[3,2,1-*ij*][1,6]naphthyridin-2-ium chloride (3.18e): Prepared according to the representative procedure for compound **3.18b** using 9-azajulolidine (34.4 mg, 0.2 mmol, 1.0 equiv), crotonoyl chloride **3.1a** (20.8 mg, 0.2 mmol, 1.0 equiv) and $CDCl_3$ (1.0 mL) over 30 min at room temperature (23 °C). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.85 (s, 2H), 7.76 (dq, *J* = 14.6, 1.6 Hz, 1H), 7.39 (dt, *J* = 14.6, 7.1 Hz, 1H), 3.61 (t, *J* = 5.8 Hz, 4H), 2.90 (t, *J* = 6.2 Hz, 4H), 2.09 (dd, *J* = 7.1, 1.6 Hz, 3H), 1.98 (tt, *J* = 6.2, 5.8 Hz, 4H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 163.4, 155.6, 154.5, 132.9, 119.1, 117.2, 51.1, 23.8, 19.4 (2).



3.18f

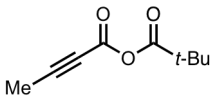
(*S*,*E*)-1-(but-2-enoyl)-2-phenyl-2,3-dihydrobenzo[*d*]imidazo[2,1-*b*]thiazol-1-ium chloride (3.18f): Prepared according to the representative procedure for compound **3.18b** using (+)-BTM (50.5

mg, 0.2 mmol, 1.0 equiv), crotonoyl chloride **3.1a** (20.8 mg, 0.2 mmol, 1.0 equiv) and $CDCl_3$ (1.0 mL) over 30 min at room temperature (23 °C). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.23 (d, *J* = 8.2 Hz, 1H), 7.69 (d, *J* = 8.2 Hz, 1H), 7.55 (ddd, *J* = 8.2, 7.4, 1.0 Hz, 1H), 7.46 (ddd, *J* = 8.2, 7.4, 1.0 Hz, 1H), 7.41-7.37 (m, 3H), 7.36-7.32 (m, 3H), 7.07 (dq, *J* = 14.9, 7.1 Hz, 1H), 7.11-7.04 (m, 1H), 6.19 (app t, *J* = 11.0 Hz, 1H), 6.06 (dq, *J* = 14.9, 1.6 Hz, 1H), 4.60 (dd, *J* = 11.4, 5.1 Hz, 1H), 1.74 (dd, *J* = 7.1, 1.6 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 166.1, 163.4, 152.4, 137.5, 132.9, 129.96, 129.88, 129.75, 129.66, 127.2, 126.0, 125.5, 119.4, 114.5, 66.8, 57.4, 19.0.



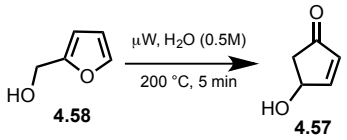
3-Phenylpropiolic pivalic anhydride (4.30). Into a solution of phenylpropiolic acid (73 mg, 0.50 mmol, 1.0 equiv) in THF (0.5 mL) at -20 °C was added a solution of pivaloyl chloride (68 μL, 0.55 mmol, 1.1 equiv) in THF (0.5 mL), followed by an addition of Et_3N (77 μL, 0.55 mmol, 1.1 equiv) in THF (0.5 mL). The resulting mixture was stirred at -20 °C for 20 h. The reaction was then diluted with Et_2O (0.75 mL), filtered through a pad of Celite (eluted with Et_2O, 10 mL) to yield pure desired pivaloyl anhydride **4.30** (115 mg, >99% yield) as a clear, light yellow liquid. TLC (EtOAc:hexanes, 2:8 *v/v*): R_f = 0.69. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.64 – 7.58 (m, 2H), 7.54 – 7.46 (m, 1H), 7.44 – 7.36 (m, 2H), 1.32 (s, 9H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 173.13, 149.07, 133.48, 131.53, 128.83, 118.97, 90.24, 80.04, 40.08, 26.58; **IR** (thin film): 2977, 2935, 2876,

2223, 1802, 1720, 1490, 1285, 1132, 1044, 1011, 997 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{14}H_{14}O_3Na$ $[M+Na]^+$: 253.0841, found: 253.0843.



4.31

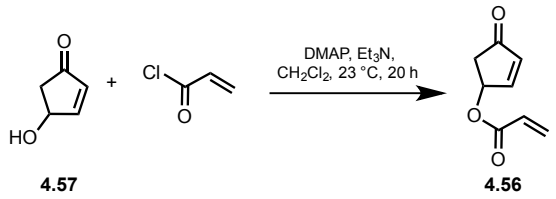
But-2-ynoic pivalic anhydride (4.31): Prepared according to the representative procedure for compound **4.30** using a solution of 2-butynoic acid (42 mg, 0.50 mmol, 1.0 equiv) in THF (0.5 mL), a solution of pivaloyl chloride (68 μL, 0.55 mmol, 1.1 equiv) in THF (0.5 mL), Et_3N (77 μL, 0.55 mmol, 1.1 equiv) in THF (0.5 mL). After work-up, the pure anhydride (84 mg, >99 yield) was obtained as a clear liquid. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 2.02 (s, 3H), 1.24 (s, 9H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 173.11, 148.55, 90.04, 71.92, 39.89, 26.44, 4.12. **IR** (thin film): 2979, 2939, 2877, 2242, 1803, 1772, 1749, 1727, 1480, 1462, 1399, 1370, 1215, 1054, 998 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_9H_{12}O_3Li$ $[M+Li]^+$: 175.0946, found: 175.0961.



4.58 **4.57**

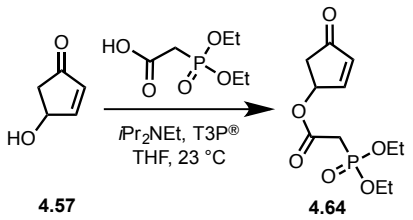
4-hydroxycyclopent-2-en-1-one ((±)-4.57). To a 35-mL microwave vial was added furfuryl alcohol **4.58** (0.80 mL, 10 mmol) and de-ionized water (20 mL). The solution was heated to 200 °C using a microwave reactor (set temperature: 200 °C, hold time: 5 min). The content of 12 vials was combined into a 500-mL separatory funnel. Each microwave vial was washed with EtOAc (3 x 4 mL) (heating using heat gun might be required for complete dissolution of remaining organics in the vials for quantitative

transfer). The layers were separated and the organic layer (~150 mL) was extracted with de-ionized water (3 x 50 mL). The combined aqueous layers were extracted again with EtOAc (1 x 100 mL). The aqueous layers were combined and concentrated *in vacuo* by rotary evaporation (water bath temp was increased from 20 → 40 → 55 °C, vacuum pressure was reduced slowly from 1,000 mbar to 20 mbar). The crude product was further dried on high vacuum to deliver the desired 4-hydroxycyclopentenone **4.57** (7.6 g, 65% yield) as a viscous, dark red liquid. This was used in the next step without further purification. Spectral data matched that previously reported.[14]



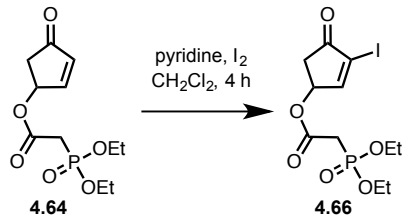
4-Oxocyclopent-2-en-1-yl acrylate (4.56). Into a solution of hydroxycyclopentenone **4.57** (0.98 g, 10 mmol, 1.0 equiv), Et_3N (2.8 mL, 20 mmol, 2.0 equiv), DMAP (0.24 g, 2.0 mmol, 20 mol%) in CH_2Cl_2 (50 mL) at 23 °C was added acryloyl chloride (1.6 mL, 20 mmol, 2.0 equiv) dropwise over 3 min. The resulting mixture was stirred at 23 °C for 20 h. Upon completion (as judged by TLC), the reaction was concentrated by rotary evaporation and purified by an automated flash chromatography system (gradient of EtOAc/hexanes) to afford acrylate **4.56** (684 mg, 45% yield) as a viscous yellow liquid: TLC (Et_2O:hexanes, 3:7 *v/v*): R_f = 0.23. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.57 (dd, *J* = 5.7, 2.4 Hz, 1H), 6.41 (dd, *J* = 17.3, 1.3 Hz, 1H), 6.32 (dd, *J* = 5.7, 1.3 Hz, 1H), 6.09 (dd, *J* = 17.3, 10.5 Hz, 1H), 5.90 (dtd, *J* = 6.0, 2.3, 1.3 Hz, 1H), 5.87 (dd, *J* = 10.5, 1.3 Hz,

1H), 2.83 (dd, J = 18.7, 6.4 Hz, 1H), 2.33 (dd, J = 18.7, 2.2 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 204.90, 165.52, 158.96, 137.14, 132.07, 127.69, 72.08, 41.05; **IR** (thin film): 3080, 2938, 1725, 1633, 1591, 1408, 1352, 1294, 1266, 1183, 1101, 1050, 985, 810 cm^{-1}; **HRMS** (ESI-) *m/z* calcd for $C_8H_7O_3$ $[M-H]^-$: 151.0390, found: 151.0400.



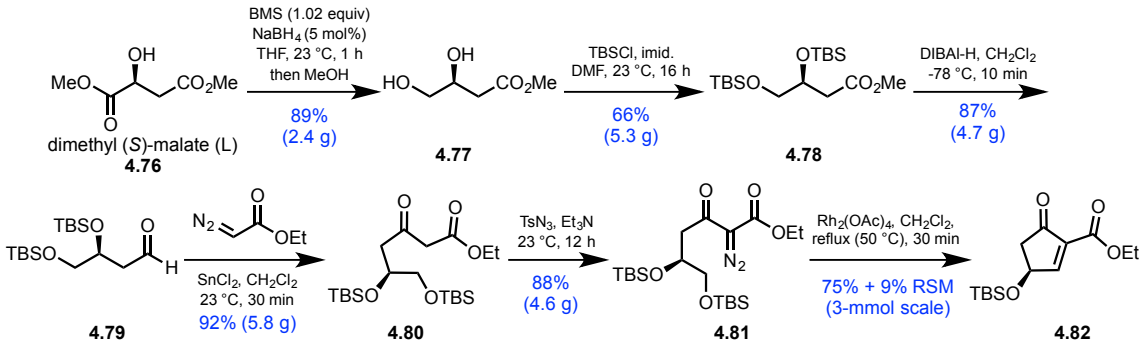
4.57 **4.64**

4-Oxocyclopent-2-en-1-yl 2-(diethoxyphosphoryl)acetate (4.64). Into a solution of hydroxycyclopentenone **4.57** (0.98 g, 10 mmol, 1.0 equiv), diethylphosphonoacetic acid (1.77 mL, 11.0 mmol, 1.05 equiv), *i*-Pr_2NEt (7.10 mL, 27.3 mmol, 2.60 equiv) in THF (20 mL) was added a solution of propylphosphonic anhydride solution (T3P®, 50% in EtOAc, 8.10 mL, 13.6 mmol, 1.3 equiv) slowly over 30 min at 23 °C. The resulting mixture was stirred at 23 °C for 48 h. Upon completion (as judged by TLC), the reaction was added H_2O (20 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with 1M HCl (20 mL), saturated solution of $NaHCO_3$ (20 mL), brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated to deliver pure **4.64** (1.79 g, 62% yield) as a viscous, clear, yellow liquid. Spectral data matched that previously reported.[15]

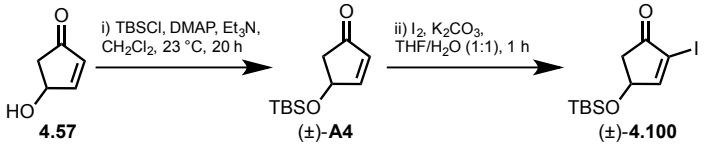


4.64 **4.66**

3-Iodo-4-oxocyclopent-2-en-1-yl 2-(diethoxyphosphoryl)acetate (4.66). Into a solution of cyclopentenone **4.64** (0.83 g, 3.0 mmol, 1.0 equiv) in CH_2Cl_2 (6 mL) was added a solution of I_2 (1.14 g, 4.50 mmol, 1.50 equiv) and anhydrous pyridine (0.49 mL, 6.0 mmol, 2 equiv) in CH_2Cl_2 (24 mL) slowly over 5 min. The resulting mixture was stirred at 23 °C for 4 h. Upon completion (as judged by TLC), the reaction was quenched with saturated solution of $Na_2S_2O_3$ until the dark red color disappeared (~ 60 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were washed with brine (60 mL), dried over anhydrous Na_2SO_4 and concentrated to afford pure iodocyclopentenone **4.66** (1.06 g, 88% yield). TLC (EtOAc:hexanes, 7:3 *v/v*): R_f = 0.24. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.89 (d, *J* = 2.7 Hz, 1H), 5.81 (dt, *J* = 6.5, 2.3 Hz, 1H), 4.13 (dqd, *J* = 8.2, 7.1, 1.1 Hz, 4H), 3.01 – 2.89 (m, 3H), 2.47 (dd, *J* = 18.8, 2.0 Hz, 1H), 1.31 (td, *J* = 7.1, 1.3 Hz, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 198.73, 165.33 (d, *J* = 6.4 Hz), 163.35, 108.42, 73.91, 62.97 (d, *J* = 6.3 Hz), 62.96 (d, *J* = 6.3 Hz), 38.24, 34.29 (d, *J* = 133.6 Hz), 16.45, 16.40; **IR** (thin film): 2982, 2931, 1722, 1585, 1372, 1345, 1271, 1116, 1052, 1025, 976 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{11}H_{17}IO_6P$ $[M+H]^+$: 402.9802, found: 402.9824.



Ethyl (*S*)-3-((*tert*-butyldimethylsilyl)oxy)-5-oxocyclopent-1-ene-1-carboxylate (4.82). Prepared according to a similar literature procedure[16] to obtain pure cyclopentenone **4.82** (0.64 g, 75% yield) and recovered **4.81** (0.12 g, 9%). The following characterization data are described for **4.82**. TLC (EtOAc:hexanes, 2:8 *v/v*, $KMnO_4$ stain): R_f = 0.66. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.94 (d, *J* = 2.3 Hz, 1H), 4.92 (dt, *J* = 6.1, 2.4 Hz, 1H), 4.27 – 4.19 (m, 2H), 2.81 (dd, *J* = 18.1, 6.1 Hz, 1H), 2.35 (ddd, *J* = 18.2, 2.6, 0.9 Hz, 1H), 1.27 (t, *J* = 7.1 Hz, 3H), 0.84 (s, 9H), 0.08 (app pd, *J* = 8.5 Hz, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 199.20, 168.71, 161.49, 136.93, 68.01, 61.19, 46.43, 25.67, 18.02, 14.14, -4.80, -4.80; **IR** (thin film): 2956, 2931, 2887, 2858, 1731, 1628, 1472, 1391, 1259, 1093, 1031, 906, 836, 779, 669 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{14}H_{25}O_4Si$ $[M+H]^+$: 285.1522, found: 285.1535.

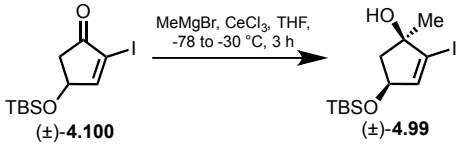


4-((*tert*-butyldimethylsilyl)oxy)cyclopent-2-en-1-one ((±)-A4). To an oven-dried, 500-mL round-bottomed flask equipped with a magnetic stir bar was added

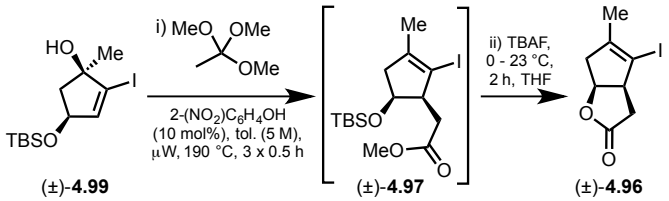
hydrocyclopentenone **4.57** (9.81 g, 100 mmol, 1.00 equiv), Et_3N (20.9 mL, 150 mmol, 1.50 equiv) and DMAP (1.22 g, 10.0 mmol, 10.0 mol%) in CH_2Cl_2 (200 mL). The resulting mixture was cooled to 0 °C, followed by addition of a solution of TBSCl (16.6 g, 110 mmol, 1.10 equiv) in CH_2Cl_2 (50 mL) using an addition funnel, rapidly dropwise, over 30 min. After the complete addition, the reaction mixture was allow to warm up to room temperature (23 °C) and stirred overnight. Upon reaction completion (as judged by TLC, usually *ca*. 20 h), the reaction mixture was diluted with CH_2Cl_2 (100 mL), washed with H_2O (100 mL), 1 M HCl (100 mL), saturated aqueous $NaHCO_3$ (100 mL), brine (100 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo.* The crude product was a dark red liquid, (18.1 g, 85% yield) and was used in the next step without further purification. Spectral data matched that previously reported.[14]

4-((*tert*-butyldimethylsilyl)oxy)-2-iodocyclopent-2-en-1-one ((±)-4.100). Prepared according to a literature procedure.[17] To a mixture of crude **A4** (18 g, 85 mmol, 1.0 equiv) in THF/H_2O (400 mL, 1:1) was added K_2CO_3 (17.6 g, 127 mmol, 1.50 equiv), I_2 (26.0 g, 102 mmol, 1.20 equiv), and DMAP (3.1 g, 26 mmol, 0.30 mmol) at 23 °C. The resulting mixture was stirred at 23 °C for 1 h before it was quenched with a sat. solution of $NaHSO_3$ (250 mL), and extracted with Et_2O (3 x 100 mL). The combined organic layers were washed with sat. aqueous $NaHCO_3$ (300 mL), brine (300 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo.* The crude product was purified by an automated flash chromatography system (0 → 20%, EtOAc/hexanes) to afford cyclopentenone **4.100** (16.9 g, 50% yield from **4.57**) as a clear, light yellow liquid, which solidified upon storage at –20 °C. TLC (EtOAc:hexanes, 1:9 *v/v*): R_f = 0.40.

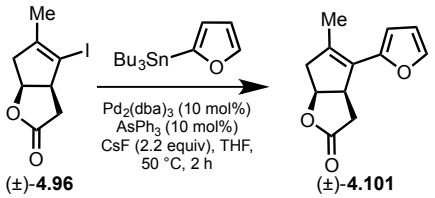
Spectral data matched that previously reported.[14]



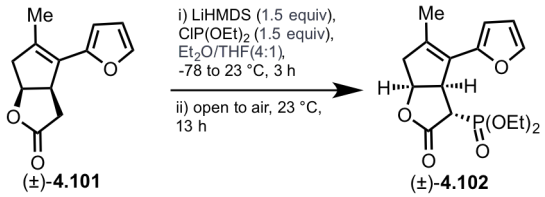
(1*R*,4*S*)-4-((*tert*-butyldimethylsilyl)oxy)-2-iodo-1-methylcyclopent-2-en-1-ol ((±)-4.99). Prepared according to a literature procedure[14] with modification. THF (60 mL) was added to the powder of anhydrous $CeCl_3$ (dried according to the literature procedure[18]) (8.87 g, 36.0 mmol, 1.20 equiv) in one-portion at 0 °C with vigorous stirring and then sonicated for 1 h at 23 °C. The resulting milky suspension was cooled to -78 °C, followed by a dropwise addition of MeMgBr (3.0 M in Et_2O, 12.0 mL, 36.0 mmol, 1.20 equiv) over 15 min. The resulting mixture was stirred at -78 °C for an additional 30 min, followed by an addition of a solution of **4.100** (10.1 g, 30.0 mmol, 1.00 equiv) in THF (200 mL) over 30 min using an addition funnel. After an additional 30 min at -78 °C, the resulting mixture was warmed to -30 °C and stirred for 1 h. Upon completion (as judged by TLC, usually *ca*. 1 h), the reaction mixture was slowly and carefully quenched with sat. NH_4Cl (100 mL) and extracted with Et_2O (3 x 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated *in vacuo* and purified by an automated flash chromatography system (0 → 30%, EtOAc/hexanes) to afford a 5:1 mixture of diastereomers of cyclopentene **4.99** (7.97 g, 75% yield) as a clear, yellow liquid. Spectral data matched that previously reported.[14]



(3a*S*,6a*S*)-4-Iodo-5-methyl-3,3a,6,6a-tetrahydro-2*H*-cyclopenta[*b*]furan-2-one ((±)-4.96). Prepared according to a literature procedure[17] with modification. Into a 35-mL microwave vessel equipped a magnetic stir bar were added cyclopentene **4.99** (1.4 g, 4.0 mmol, 1.0 equiv), trimethyl orthoacetate (2.6 mL, 20 mmol, 5.0 equiv), 2-nitrophenol (56 mg, 0.40 mmol, 10 mol%), and toluene (0.8 mL). The resulting mixture was heated to 190 °C (set temperature: 190 °C, hold time: 30 min) using a microwave reactor for 30 min, following by cooling down to 50 °C for 5 min. The heating-cooling cycle was repeated for 2 more times. The solvent was removed *in vacuo*, followed by an addition of THF (20 mL). After cooling to 0 °C, a solution of TBAF (1.0 M in THF, 12 mL, 12 mmol, 3.0 equiv) was added in one-portion. The resulting mixture was warmed to 23 °C and stirred for 2 h. Upon completion (as judged by TLC, usually *ca*. 2 h), the reaction mixture was concentrated *in vacuo* and purified by an automated flash chromatography system (0 → 30%, EtOAc/hexanes) to afford γ-lactone **4.96** (0.35 g, 33% yield over 2 steps) as a clear, yellow liquid. Spectral data matched that previously reported.[14]

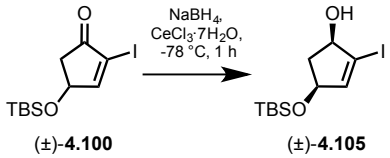


(3a*R*,6a*S*)-4-(Furan-2-yl)-5-methyl-3,3a,6,6a-tetrahydro-2*H*-cyclopenta[*b*]furan-2-one (±)-4.101. Into a 35-mL microwave vessel were added vinyl iodine **4.96** (0.26 g, 1.0 mmol, 1.0 equiv), 2-(tributylstannyl)furan (0.47 mL, 1.5 mmol, 1.5 equiv), $Pd_2(dba)_3$ (92 mg, 0.10 mmol, 10 mol%), $AsPh_3$ (31 mg, 0.10 mmol, 10 mol%), CsF (0.33 g, 2.2 mmol, 2.2 equiv) and THF (10 mL). The resulting mixture was heated to 50 °C in a microwave for 2 h. Upon completion (as judged by TLC, usually *ca*. 2 h), the reaction mixture was concentrated *in vacuo* and purified by an automated flash chromatography system (0 → 30%, EtOAc/hexanes) to afford γ-lactone **4.101** (165 mg, 81% yield) as a clear liquid. TLC (EtOAc:hexanes, 2:8 *v/v*): R_f = 0.41. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.36 (d, *J* = 1.7 Hz, 1H), 6.38 (dd, *J* = 3.3, 1.8 Hz, 1H), 6.18 (d, *J* = 3.4 Hz, 1H), 5.07 (td, *J* = 6.4, 1.1 Hz, 1H), 3.83 (ddt, *J* = 10.1, 6.3, 1.9 Hz, 1H), 2.94 – 2.68 (m, 3H), 2.59 (dd, *J* = 18.3, 2.3 Hz, 1H), 1.97 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 176.81, 150.78, 141.55, 133.81, 125.00, 110.95, 107.91, 81.54, 47.16, 45.84, 33.35, 15.36; **IR** (thin film): 3120, 2956, 2932, 2855, 1772, 1494, 1416, 1295, 1175, 1021, 737 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{12}H_{13}O_3$ $[M+H]^+$: 205.0865, found: 205.0859.



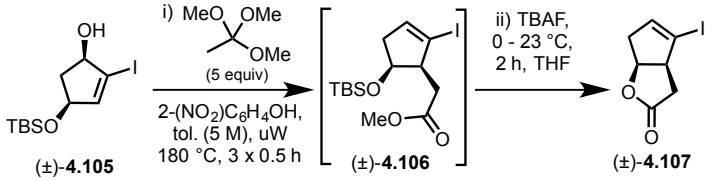
Diethyl ((3*R*,3a*R*,6a*S*)-4-(furan-2-yl)-5-methyl-2-oxo-3,3a,6,6a-tetrahydro-2*H*-cyclopenta[*b*]furan-3-yl)phosphonate (±)-4.102. Into a cooled (-78 °C) solution of LiHMDS (1.0 M in THF, 0.90 mL, 0.90 mmol, 1.5 equiv) under Ar atmosphere was added a solution of γ-lactone **4.101** (0.12 g, 0.60 mmol, 1.0 equiv) in THF (1.2 mL) dropwise over 5 min. The reaction was stirred at -78 °C for 1 h, followed by addition of a solution of diethyl chlorophosphite (95%, 0.14 mL, 0.90 mmol, 1.5 equiv) in Et_2O (4.8 mL), dropwise over 5 min. The reaction mixture was then warmed to 23 °C and stirred for 2 h. After this time, a 12-mL syringe filled with air was injected into the reaction. The reaction mixture was open to air by equipping the flask with a septum and a 16-G needle inserted (completely open the reaction flask to air led to complete evaporation of the solvent overnight). Upon completion (as judged by TLC), the reaction mixture was quenched with sat. solution of NH_4Cl (1.0 mL), concentrated *in vacuo* and purified by an automated flash chromatography system (0 → 80%, EtOAc/hexanes) to afford γ-lactone **4.102** (78 mg, 38% yield) as a clear liquid. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.42 (s, 1H), 6.46 – 6.39 (m, 2H), 5.19 (t, *J* = 5.9 Hz, 1H), 4.29 – 4.19 (m, 4H), 4.18 – 4.10 (m, 1H), 3.26 (dd, *J* = 23.8, 1.5 Hz, 1H), 2.91 (dd, *J* = 19.0, 5.9 Hz, 1H), 2.80 (d, *J* = 18.8 Hz, 1H), 2.06 (sf, 3H), 1.41 (t, *J* = 7.1 Hz, 3H), 1.38 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 171.49 (d, *J* = 4.9 Hz), 150.49, 142.16, 134.45, 123.65 (d, *J* = 13.3 Hz), 111.20, 108.45, 81.49, 63.73 (d, *J* = 7.1 Hz), 63.34 (d, *J* = 6.6 Hz), 50.41 (d, *J* = 3.0 Hz),

45.58, 44.79 (d, J = 133.1 Hz), 16.49 (app t, J = 5.6 Hz), 15.56; **^{31}P NMR** (243 MHz, $CDCl_3$) δ 19.9; **IR** (thin film): 2920, 2360, 2341, 1774, 1654, 1442, 1253, 1161, 1054 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{16}H_{22}O_6P$ $[M+H]^+$: 341.1154, found: 341.1180.



(±)-**4.100** (±)-**4.105**

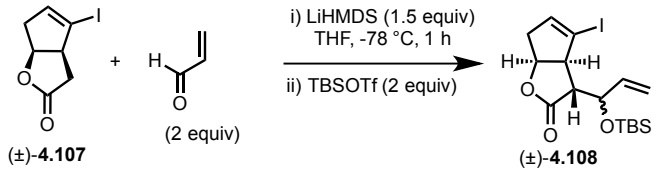
(1*R*,4*S*)-4-((*Tert*-butyldimethylsilyl)oxy)-2-iodocyclopent-2-en-1-ol ((±)-4.105). Prepared according to the literature procedure[17] using iodocyclopentenone **4.100** (1.0 g, 3.0 mmol, 1.0 equiv), $NaBH_4$ (0.14 g, 3.6 mmol, 1.2 equiv), $CeCl_3 \cdot H_2O$ (1.3 g, 3.6 mmol, 1.2 equiv) and MeOH (9.0 mL) to give pure alcohol **4.105** (1.0 g, 99% yield) after work-up. Spectral data matched that previously reported.[17]



(±)-**4.105** (±)-**4.106** (±)-**4.107**

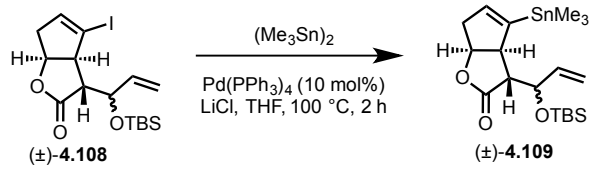
(3a*S*,6a*S*)-4-Iodo-3,3a,6,6a-tetrahydro-2*H*-cyclopenta[*b*]furan-2-one ((±)-4.107). Prepared according to the procedure for compound **4.96** using: step i) cyclopentene **4.105** (1.36 g, 4.00 mmol, 1.00 equiv), trimethyl orthoacetate (2.60 mL, 20.0 mmol, 5.00 equiv), 2-nitrophenol (56 mg, 0.40 mmol, 10 mol%), and toluene (0.8 mL) at 180 °C; step ii) THF (20 mL), a solution of TBAF (1.0 M in THF, 12 mL, 12 mmol, 3.0 equiv). Upon completion (as judged by TLC, usually *ca*. 2 h), the reaction mixture was concentrated *in vacuo* and purified by an automated flash chromatography system (0 →

30%, EtOAc/hexanes) to afford γ-lactone **4.107** (0.50 g, 50% yield over 2 steps) as a clear liquid. Spectral data matched that previously reported.[17]



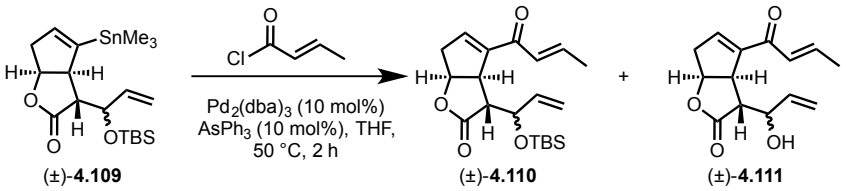
(3*R*,3a*S*,6a*S*)-3-(1-((*Tert*-butyldimethylsilyl)oxy)allyl)-4-iodo-3,3a,6,6a-tetrahydro-2*H*-cyclopenta[*b*]furan-2-one ((±)-4.108). Into a cooled (-78 °C) solution of γ-lactone **4.107** (0.25 g, 1.0 mmol, 1.0 equiv) in THF (8.5 mL) was added dropwise LiHMDS (1.0 M in THF, 1.5 mL, 1.5 mmol, 1.5 equiv). The resulting mixture was stirred at -78 °C for 30 min, followed by a dropwise addition of acrolein (90%, 0.15 mL, 2.0 mmol, 2.0 equiv). After 30 min at -78 °C, TBSOTf (0.34 mL, 1.5 mmol, 1.5 equiv) was added quickly and the reaction mixture was warmed to 23 °C and stirred for 1 h. The reaction was quenched with sat. aq. NH_4Cl (1.5 mL), concentrated *on vacuo* and purified by an automated flash chromatography system (0 → 20%, Et_2O/hexanes) to afford γ-lactone **4.108** as 2 diasteremers: diastereomer A (130 mg, 31% yield over 2 steps) as a clear liquid and diastereomer B (151 mg, 36% yield over 2 steps) as a clear liquid. Diastereomer A: TLC (Et_2O:hexanes, 2:8 *v/v*, $KMnO_4$ stain): R_f = 0.66. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.13 – 6.04 (m, 1H), 5.94 – 5.81 (m, 1H), 5.41 – 5.23 (m, 2H), 4.92 – 4.84 (m, 1H), 4.79 (dq, *J* = 3.8, 1.8 Hz, 1H), 3.50 (dp, *J* = 5.9, 1.9 Hz, 1H), 2.69 – 2.62 (m, 2H), 2.59 (t, *J* = 1.9 Hz, 1H), 0.93 – 0.81 (m, 6H), 0.16 – -0.00 (m, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 176.78, 137.83, 137.71, 116.17, 96.77, 81.92, 72.63, 54.44, 51.52,

41.03, 26.00, 18.29, -0.02; **IR** (thin film): 3092, 2956, 2929, 2856, 1774, 1602, 1471, 1403, 1350, 1253, 1177, 1030, 843 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{16}H_{26}IO_3Si$ $[M+H]^+$: 421.0690, found: 421.0667. Diastereomer B: TLC (Et_2O:hexanes, 2:8 *v/v*): R_f = 0.59. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.13 – 6.04 (m, 1H), 5.90 (ddt, *J* = 17.0, 10.3, 5.6 Hz, 1H), 5.39 – 5.16 (m, 2H), 4.88 – 4.79 (m, 1H), 4.60 – 4.48 (m, 1H), 3.55 – 3.41 (m, 1H), 2.77 (ddd, *J* = 20.2, 4.1, 1.8 Hz, 1H), 2.69 – 2.60 (m, 2H), 0.93 – 0.80 (m, 6H), 0.18 – -0.01 (m, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 174.89, 137.70, 136.55, 117.21, 96.72, 81.16, 73.09, 56.40, 52.07, 41.13, 25.97, 18.25, 0.20; **IR** (thin film): 3092, 2956, 2929, 2856, 1774, 1602, 1471, 1403, 1350, 1253, 1177, 1030, 843 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{16}H_{26}IO_3Si$ $[M+H]^+$: 421.0690, found: 421.0673.



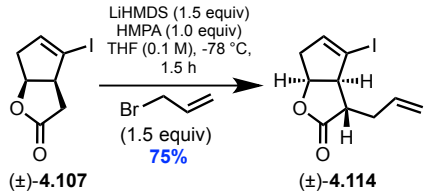
(3*R*,3a*S*,6a*S*)-3-(1-((*tert*-butyldimethylsilyl)oxy)allyl)-4-(trimethylstannyl)-3,3a,6,6a-tetrahydro-2*H*-cyclopenta[*b*]furan-2-one ((±)-4.109). A 10-mL microwave vessel containing vinyl iodide **4.108** (126 mg, 0.300 mmol, 1.00 equiv), $(Me_3Sn)_2$ (77.8 µL, 0.375 mmol, 1.25 equiv), $Pd(PPh_3)_4$ (35 mg, 0.030 µmol, 10 mol%) and anhydrous LiCl (dried by heating with heat gun under vacuum for 3 min, 67.4 mg, 1.59 mmol, 5.3 equiv) in THF (3.0 mL) was heated to 100 °C in a microwave reactor for 2 h. The reaction was then concentrated and purified by an automated flash chromatography system (0 → 20%, Et_2O/hexanes) to afford vinyl stannane **4.109** (64 mg, 47% yield) as a clear liquid.

TLC (Et_2O:hexanes, 1:9 *v/v*, $KMnO_4$ stain): R_f = 0.45. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 5.91 – 5.80 (m, 2H), 5.38 (dt, *J* = 17.1, 1.7 Hz, 1H), 5.25 (dt, *J* = 10.5, 1.6 Hz, 1H), 5.08 – 5.01 (m, 1H), 4.74 (dq, *J* = 3.7, 1.8 Hz, 1H), 3.58 – 3.52 (m, 1H), 2.71 (s, 2H), 2.44 (t, *J* = 2.0 Hz, 1H), 0.96 – 0.81 (m, 3H), 0.25 – -0.02 (m, 21H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 178.53, 145.55, 139.14, 138.71, 116.07, 84.79, 73.26, 53.04, 52.88, 41.36, 26.06, 18.31, 0.05, -9.29; **IR** (thin film): 2959, 2928, 2857, 1769, 1580, 1351, 1253, 1179, 1133, 1028, 843, 776 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{19}H_{35}O_3SiSn$ $[M+H]^+$: 459.1372, found: 459.1346.

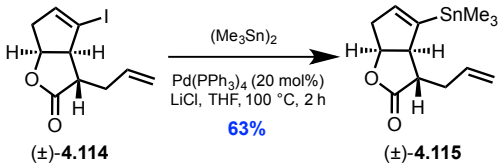


(3*R*,3a*R*,6a*S*)-4-((*E*)-But-2-enoyl)-3-(1-((*tert*-butyldimethylsilyl)oxy)allyl)-3,3a,6,6a-tetrahydro-2*H*-cyclopenta[*b*]furan-2-one ((±)-4.110). A 10-mL microwave vessel containing vinyl stannane **4.109** (59 mg, 0.13 mmol, 1.0 equiv), crotonoyl chloride (90%, 21 μL, 0.20 mmol, 1.5 equiv), $Pd_2(dba)_3$ (12 mg, 0.013 mmol, 10 mol%), $AsPh_3$ (4.0 mg, 0.013 mmol, 10 mol%) in THF (1.3 mL) was heated to 50 °C in a microwave reactor for 2 h. The reaction was then concentrated and purified by an automated flash chromatography system (0 → 100%, Et_2O/hexanes) to afford the desired γ-lactone **4.110** (19 mg, 40% yield) as a clear liquid and alcohol **4.111** (15 mg, 46% yield) as a clear liquid. Characterization data for γ-lactone **4.110:** TLC (Et_2O:hexanes, 5:5 *v/v*, $KMnO_4$ stain): R_f = 0.50. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 6.87 – 6.77 (m, 1H), 6.58 (d, *J* = 2.4

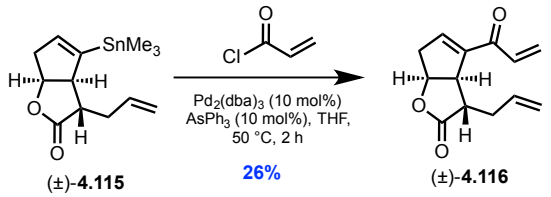
Hz, 1H), 6.51 (dd, *J* = 15.3, 1.7 Hz, 1H), 6.02 (ddd, *J* = 17.6, 10.3, 7.5 Hz, 1H), 5.20 (dt, *J* = 17.2, 1.3 Hz, 1H), 5.07 (dt, *J* = 10.4, 1.2 Hz, 1H), 4.97 (tdd, *J* = 5.4, 2.3, 1.2 Hz, 1H), 4.52 (dd, *J* = 7.6, 2.6 Hz, 1H), 3.56 (dt, *J* = 6.5, 1.8 Hz, 1H), 2.85 – 2.78 (m, 2H), 2.60 (t, *J* = 2.4 Hz, 1H), 1.81 (dd, *J* = 6.9, 1.7 Hz, 3H), 0.79 (s, 9H), 0.00 (s, 3H), -0.05 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 187.02, 176.31, 144.83, 143.71, 140.49, 138.57, 127.31, 116.55, 81.22, 76.30, 52.13, 50.82, 40.79, 25.95, 18.48, 18.22, -3.95, -4.58; **IR** (thin film): 2956, 2919, 2851, 1771, 1665, 1618, 1577, 1540, 1470, 1369, 1253, 1169, 1085, 837 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{20}H_{31}O_4Si$ $[M+H]^+$: 363.1986, found: 363.1976. Characterization data for γ-lactone **4.111:** TLC (Et_2O:hexanes, 5:5 *v/v*, $KMnO_4$ stain): R_f = 0.09. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 6.91 (dq, *J* = 15.5, 6.9 Hz, 1H), 6.72 (q, *J* = 2.5 Hz, 1H), 6.61 (dq, *J* = 15.2, 1.6 Hz, 1H), 6.14 (ddd, *J* = 17.2, 10.5, 4.8 Hz, 1H), 5.43 (dt, *J* = 17.2, 1.6 Hz, 1H), 5.32 (dt, *J* = 10.5, 1.5 Hz, 1H), 5.15 – 5.09 (m, 1H), 4.70 (ddt, *J* = 5.1, 3.5, 1.7 Hz, 1H), 3.70 (dt, *J* = 6.4, 1.9 Hz, 1H), 2.95 – 2.87 (m, 2H), 2.80 (dd, *J* = 3.5, 2.0 Hz, 1H), 1.90 (dd, *J* = 6.9, 1.7 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 187.02, 178.25, 144.37, 143.93, 141.11, 137.89, 127.14, 116.16, 82.37, 72.59, 50.42, 47.02, 40.33, 18.45; **IR** (thin film): 3450 (br), 2917, 2849, 1763, 1661, 1612, 1442, 1371, 1303, 1195, 1129 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{14}H_{16}O_4Na$ $[M+Na]^+$: 271.0941, found: 271.0935.



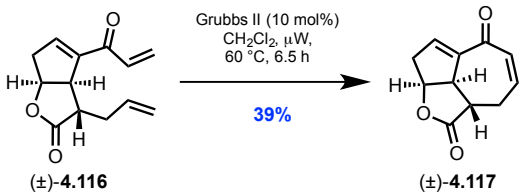
(3*S*,3a*S*,6a*S*)-3-allyl-4-iodo-3,3a,6,6a-tetrahydro-2*H*-cyclopenta[*b*]furan-2-one ((±)-4.114). Into a cooled (-78 °C) solution of γ-lactone **4.107** (0.25 g, 1.0 mmol, 1.0 equiv) in THF (8.5 mL) was added dropwise LiHMDS (1.0 M in THF, 1.5 mL, 1.5 mmol, 1.5 equiv). The resulting mixture was stirred at -78 °C for 30 min, followed by addition of HMPA (174 μL, 1.0 mmol, 1.0 equiv) and a dropwise addition of allyl bromide (130 μL, 1.5 mmol, 1.5 equiv). After 1 h at -78 °C, the reaction was quenched with sat. aq. NH_4Cl (1.5 mL), concentrated *on vacuo* and purified by an automated flash chromatography system (0 → 50%, Et_2O/hexanes) to afford γ-lactone **4.114** as a single diastereomer (217 mg, 75% yield) as a clear liquid. TLC (Et_2O:hexanes, 4:6 *v/v*, $KMnO_4$ stain): R_f = 0.47. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 6.08 (tt, *J* = 3.1, 1.6 Hz, 1H), 5.78 (ddt, *J* = 17.1, 10.1, 7.1 Hz, 1H), 5.20 – 5.13 (m, 2H), 4.91 (tt, *J* = 6.0, 1.1 Hz, 1H), 3.28 (dp, *J* = 5.9, 1.9 Hz, 1H), 2.72 – 2.61 (m, 3H), 2.52 (dddt, *J* = 14.2, 6.3, 4.8, 1.3 Hz, 1H), 2.39 (dtt, *J* = 14.0, 8.5, 1.2 Hz, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 177.11, 137.73, 133.38, 119.10, 96.00, 80.17, 58.00, 44.23, 41.07, 35.67; **IR** (thin film): 3078, 2917, 2847, 1769, 1640, 1602, 1439, 1351, 1170, 1022, 925 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{10}H_{12}IO_2$ $[M+H]^+$: 290.9876, found: 290.9883.



(3*S*,3a*S*,6a*S*)-3-allyl-4-(trimethylstannyl)-3,3a,6,6a-tetrahydro-2*H*-cyclopenta[*b*]furan-2-one ((±)-4.115). A 10-mL microwave vessel containing vinyl iodide **4.114** (145 mg, 0.500 mmol, 1.00 equiv), $(Me_3Sn)_2$ (130 μL, 0.625 mmol, 1.25 equiv), $Pd(PPh_3)_4$ (58 mg, 0.050 μmol, 10 mol%) and anhydrous LiCl (dried by heating with heat gun under vacuum for 3 min, 112 mg, 2.65 mmol, 5.3 equiv) in THF (5.0 mL) was heated to 100 °C in a microwave reactor for 2 h. The reaction was then concentrated and purified by an automated flash chromatography system (0 → 40%, Et_2O/hexanes) to afford vinyl stannane **4.115** (100 mg, 63% yield) as a clear liquid. TLC (Et_2O:hexanes, 2:8 *v/v*, $KMnO_4$ stain): R_f = 0.48. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 5.86 – 5.78 (m, 2H), 5.23 – 5.16 (m, 2H), 5.10 (ddd, *J* = 6.5, 4.6, 2.4 Hz, 1H), 3.34 (dh, *J* = 5.3, 1.7 Hz, 1H), 2.74 (ddt, *J* = 4.9, 3.6, 1.7 Hz, 2H), 2.56 (dddt, *J* = 13.7, 6.8, 4.7, 1.3 Hz, 1H), 2.49 (ddd, *J* = 8.8, 4.6, 1.9 Hz, 1H), 2.43 – 2.35 (m, 1H), 0.18 (s, 9H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 178.99, 145.66, 139.13, 134.28, 118.85, 82.80, 57.03, 45.84, 41.50, 36.43, -9.33; **IR** (thin film): 2979, 2916, 2849, 1768, 1640, 1578, 1231, 1170, 1044, 1016, 925, 770 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{13}H_{21}O_2Sn$ $[M+H]^+$: 329.0558, found: 329.0571.



(3*S*,3a*R*,6a*S*)-4-acryloyl-3-allyl-3,3a,6,6a-tetrahydro-2*H*-cyclopenta[*b*]furan-2-one ((±)-4.116). A 10-mL microwave vessel containing vinyl stannane **4.115** (65 mg, 0.20 mmol, 1.0 equiv), acryloyl chloride (24 μL, 0.30 mmol, 1.5 equiv), $Pd_2(dba)_3$ (18 mg, 0.02 mmol, 10 mol%), $AsPh_3$ (6.0 mg, 0.02 mmol, 10 mol%) in THF (2.0 mL) was heated to 50 °C in a microwave reactor for 2 h. The reaction was then concentrated and purified by an automated flash chromatography system (0 → 100%, Et_2O/hexanes) to afford the desired γ-lactone **4.116** (11.3 mg, 26% yield) as a clear liquid. TLC (Et_2O:hexanes, 6:4 *v/v*, $KMnO_4$ stain): R_f = 0.26. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 6.88 (dd, *J* = 17.1, 10.5 Hz, 1H), 6.77 (q, *J* = 2.4 Hz, 1H), 6.31 (dd, *J* = 17.1, 1.6 Hz, 1H), 5.89 (ddt, *J* = 17.2, 10.1, 7.2 Hz, 1H), 5.77 (dd, *J* = 10.5, 1.6 Hz, 1H), 5.24 (dq, *J* = 17.0, 1.5 Hz, 1H), 5.18 (ddt, *J* = 10.1, 1.9, 1.0 Hz, 1H), 5.06 (dddd, *J* = 5.9, 5.1, 2.2, 0.8 Hz, 1H), 3.57 (dp, *J* = 5.5, 1.7 Hz, 1H), 2.95 (dtd, *J* = 5.1, 2.5, 1.6 Hz, 2H), 2.78 (ddd, *J* = 7.3, 5.3, 2.1 Hz, 1H), 2.64 (dddt, *J* = 13.9, 7.5, 5.3, 1.2 Hz, 1H), 2.53 (dtt, *J* = 14.1, 7.1, 1.3 Hz, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 187.12, 178.68, 144.68, 141.76, 133.77, 131.90, 129.10, 119.01, 80.60, 50.32, 44.13, 40.69, 36.08; **IR** (thin film): 3078, 2919, 2849, 1769, 1660, 1609, 1439, 1411, 1352, 1298, 1210, 1171, 1044, 1017, 978 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{13}H_{15}O_3$ $[M+H]^+$: 219.1016, found: 219.1028.



(2a*S*,2a^1*R*,8a*S*)-2a^1,3,8,8a-tetrahydro-1*H*-azuleno[1,8-*bc*]furan-1,5(2a*H*)-dione ((±)-4.117). A 10-mL microwave vessel containing enone **4.116** (4.3 mg, 0.020 mmol, 1.0 equiv), Grubbs II catalyst (2 mg, 0.002 mmol, 10 mol%) in CH_2Cl_2 (2.0 mL) was heated to 60 °C in a microwave reactor for 6.5 h. The reaction was then concentrated and purified by an automated flash chromatography system (0 → 100%, Et_2O/hexanes) to afford the desired cycloheptenone **4.117** (1.5 mg, 39% yield) as a clear liquid. TLC (100% Et_2O, $KMnO_4$ stain): R_f = 0.54. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.51 (td, *J* = 2.6, 1.0 Hz, 1H), 6.47 (ddd, *J* = 13.3, 5.1, 3.2 Hz, 1H), 6.18 (ddd, *J* = 13.3, 2.9, 1.6 Hz, 1H), 5.33 (td, *J* = 8.7, 5.1 Hz, 1H), 3.50 (dddd, *J* = 10.9, 8.6, 2.3, 1.1 Hz, 1H), 3.19 (ddd, *J* = 20.4, 8.8, 2.5 Hz, 1H), 2.94 (dddd, *J* = 19.8, 5.2, 4.1, 1.7 Hz, 1H), 2.84 – 2.74 (m, 2H), 2.52 (ddt, *J* = 19.8, 12.0, 3.0 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 187.01, 175.86, 143.80, 142.19, 136.12, 133.25, 80.01, 50.68, 45.42, 39.70, 31.34; **IR** (ATR): 2960, 2924, 2854, 1776, 1640, 1609, 1259, 1189, 1021, 959, 918, 797 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{11}H_{10}O_3Li$ $[M+Li]^+$: 197.0790, found: 197.0782.

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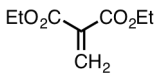
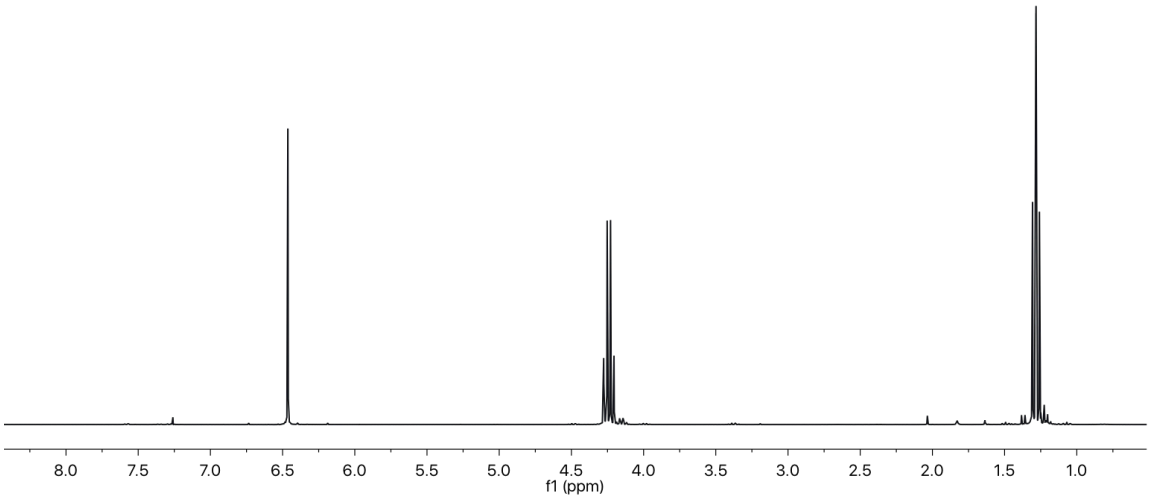
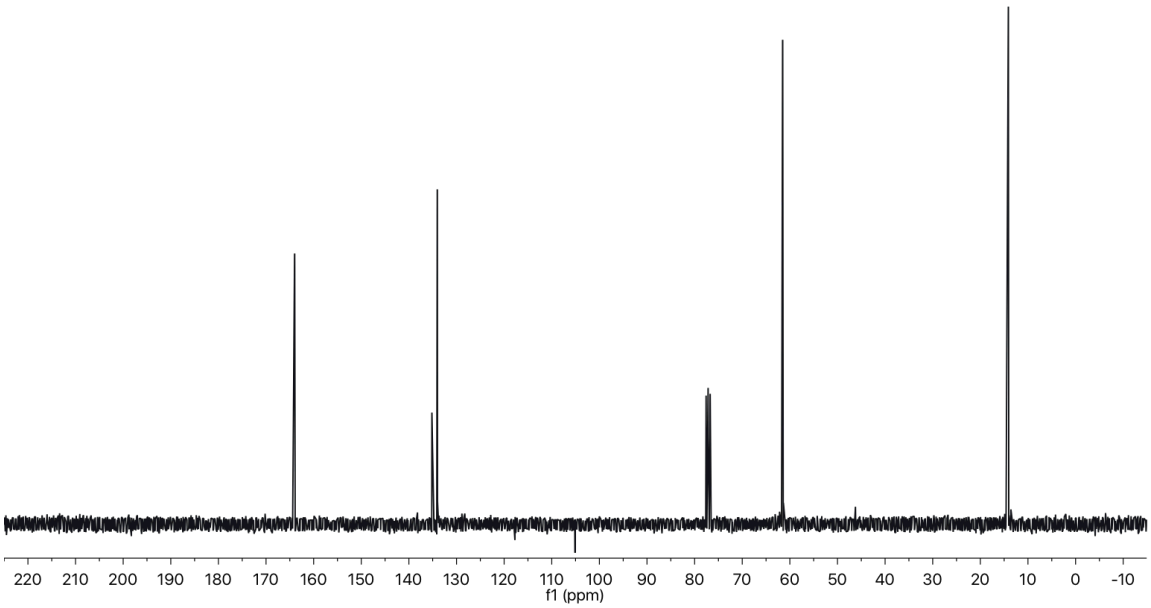
APPENDIX B

SELECTED SPECTRAL DATA

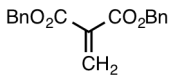


2.5a

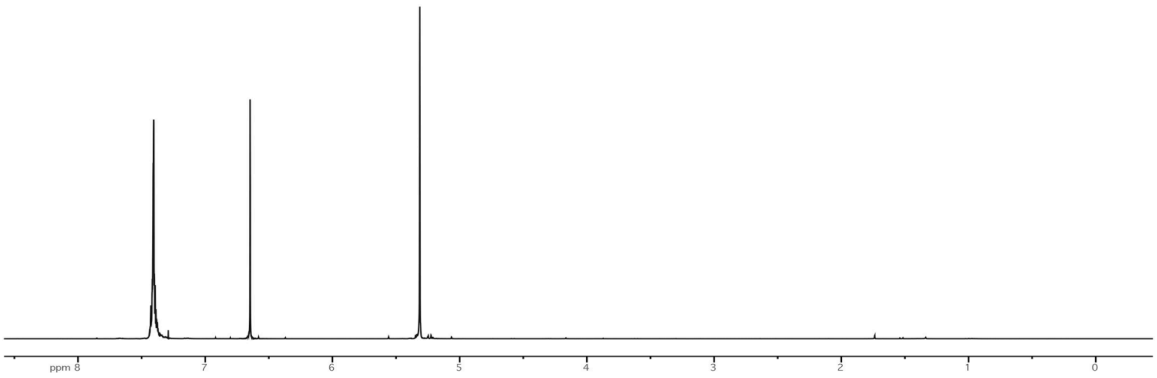


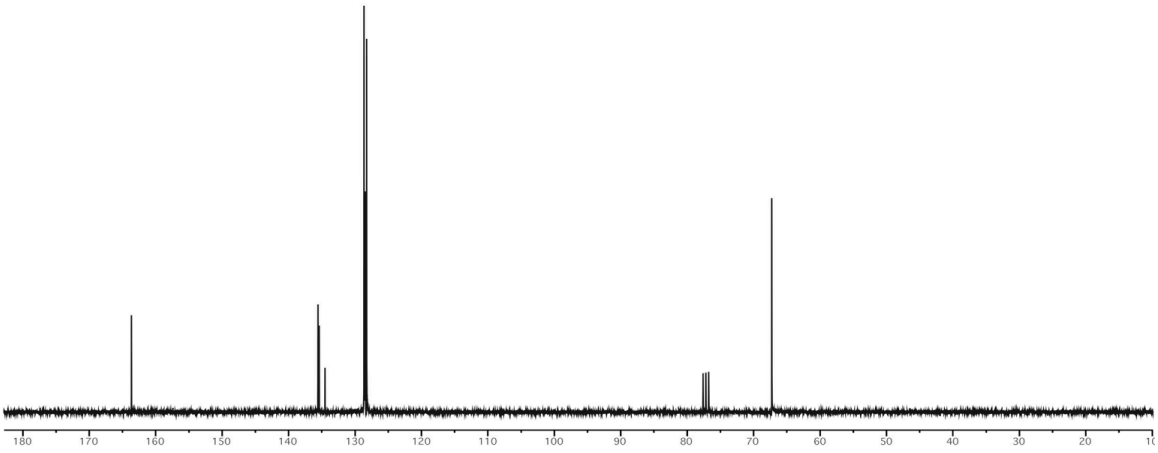


^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of enone **2.5a** in $CDCl_3$

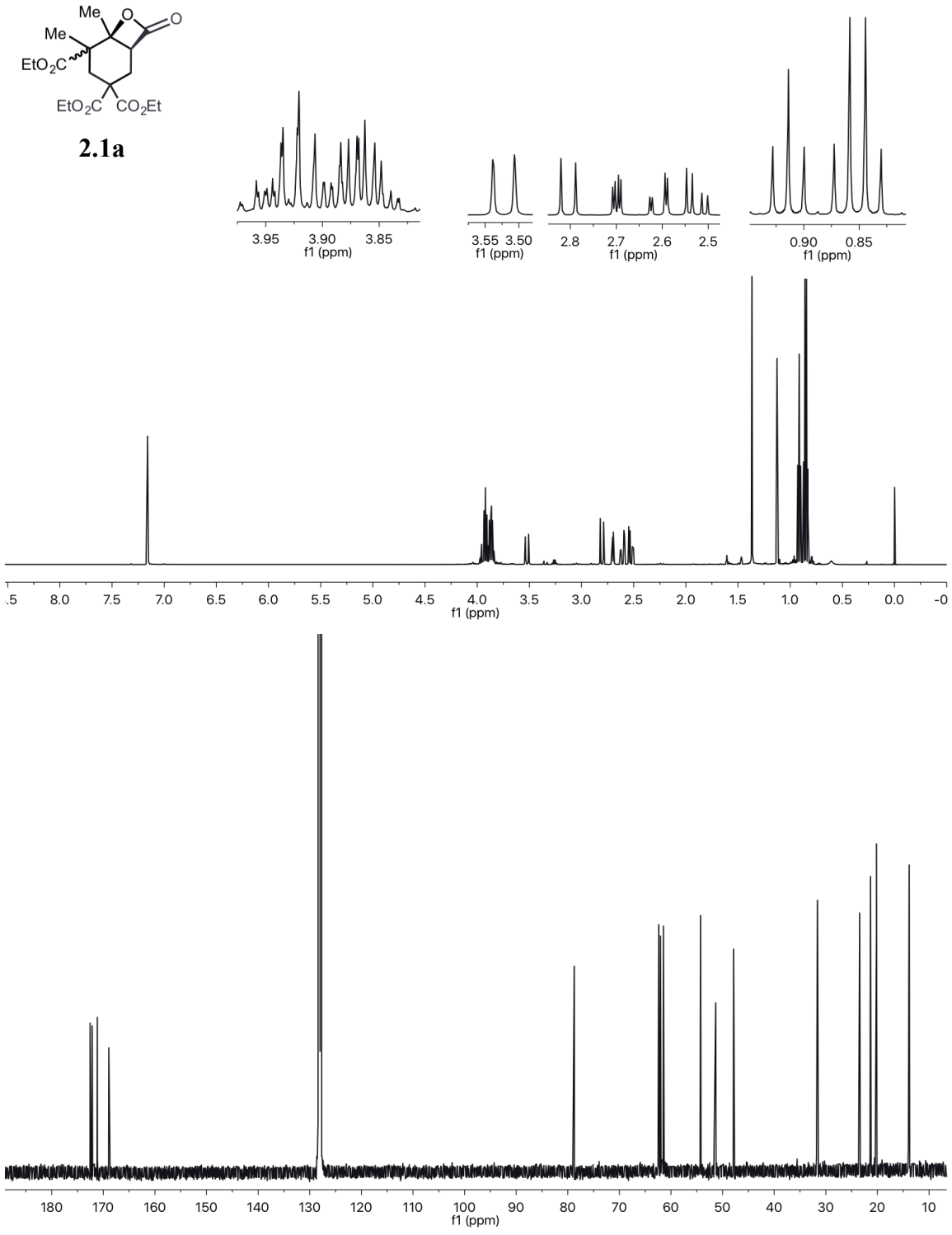


2.5b



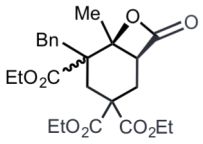


^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of enone **2.5b** in $CDCl_3$

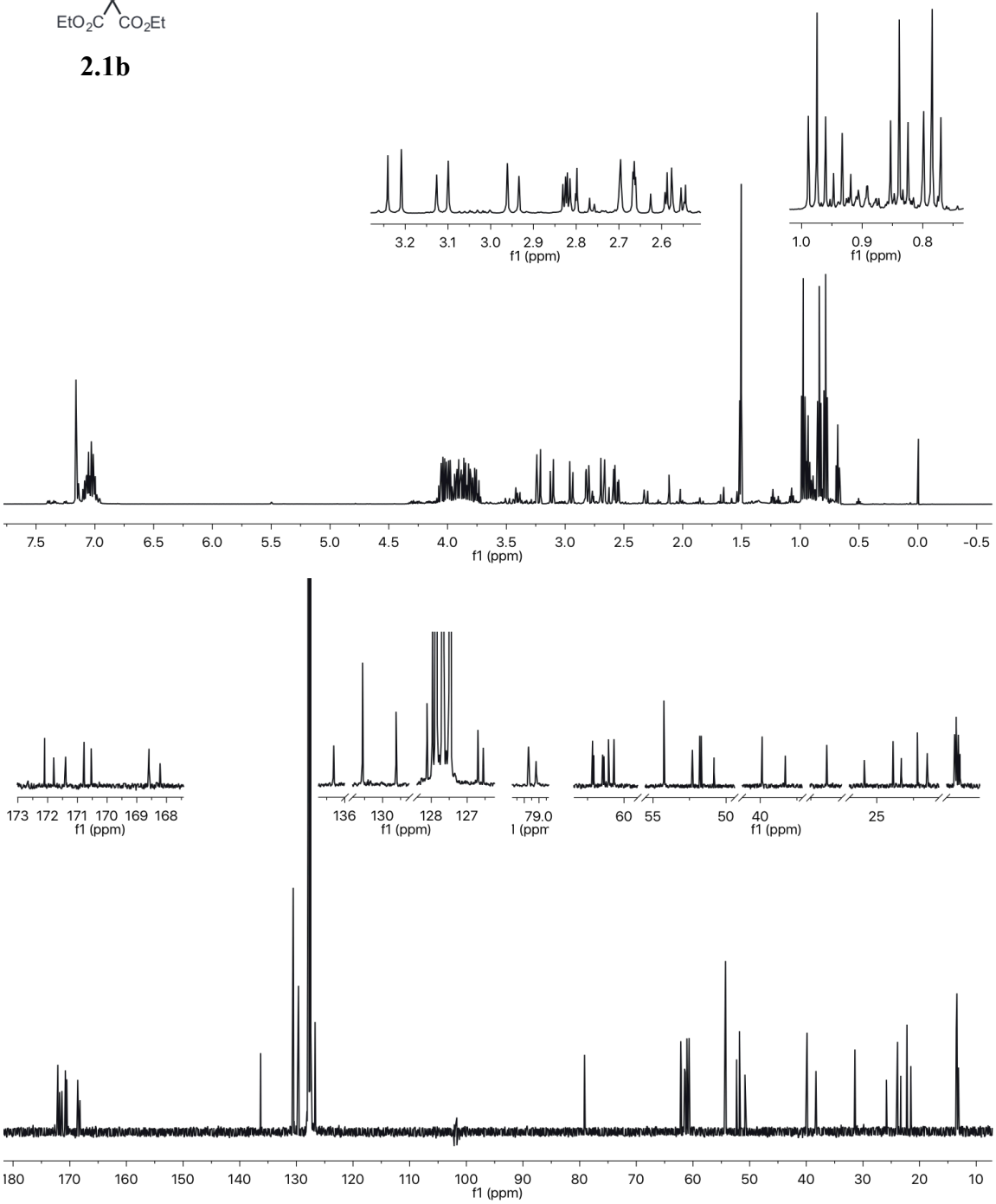


2.1a

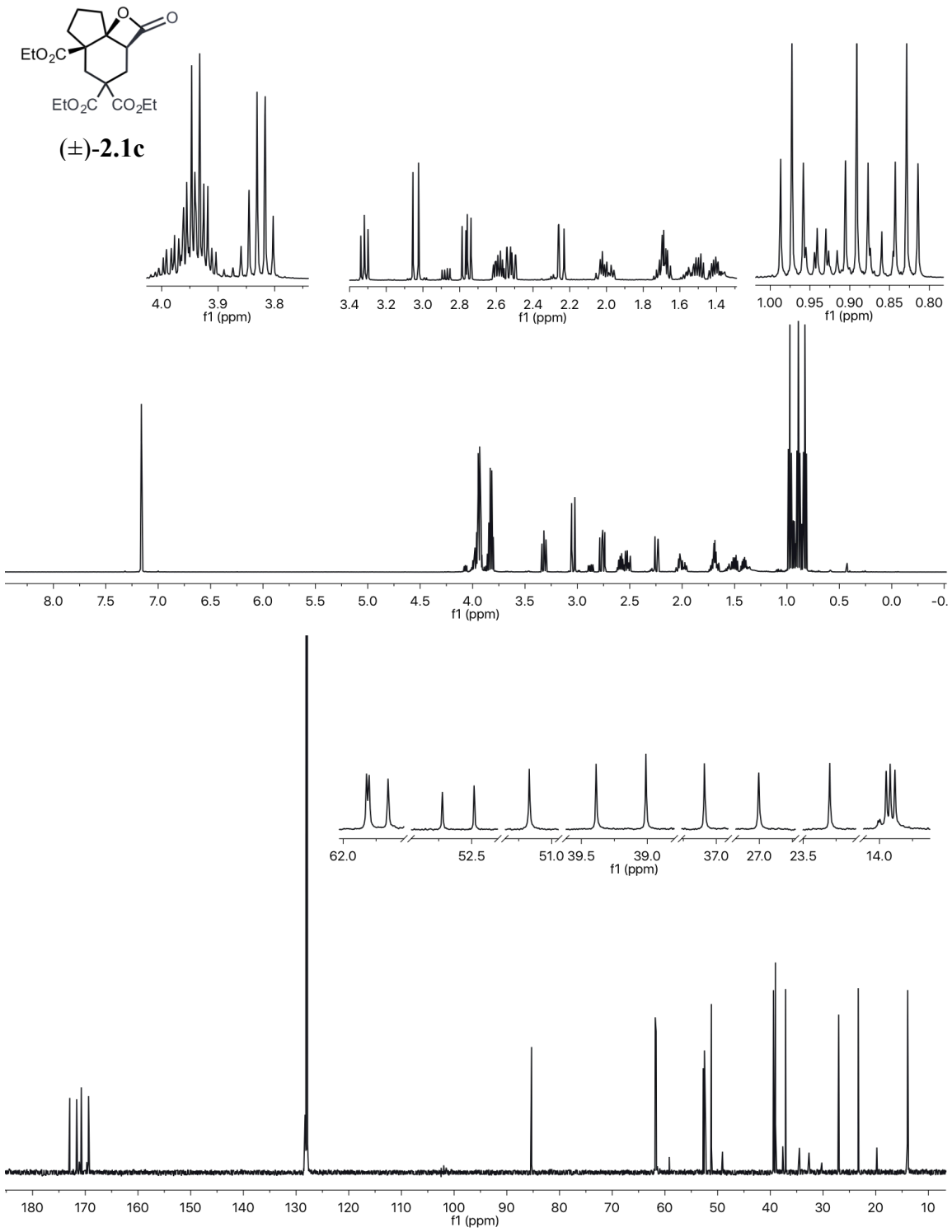
^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of β-lactone **2.1a** in C_6D_6



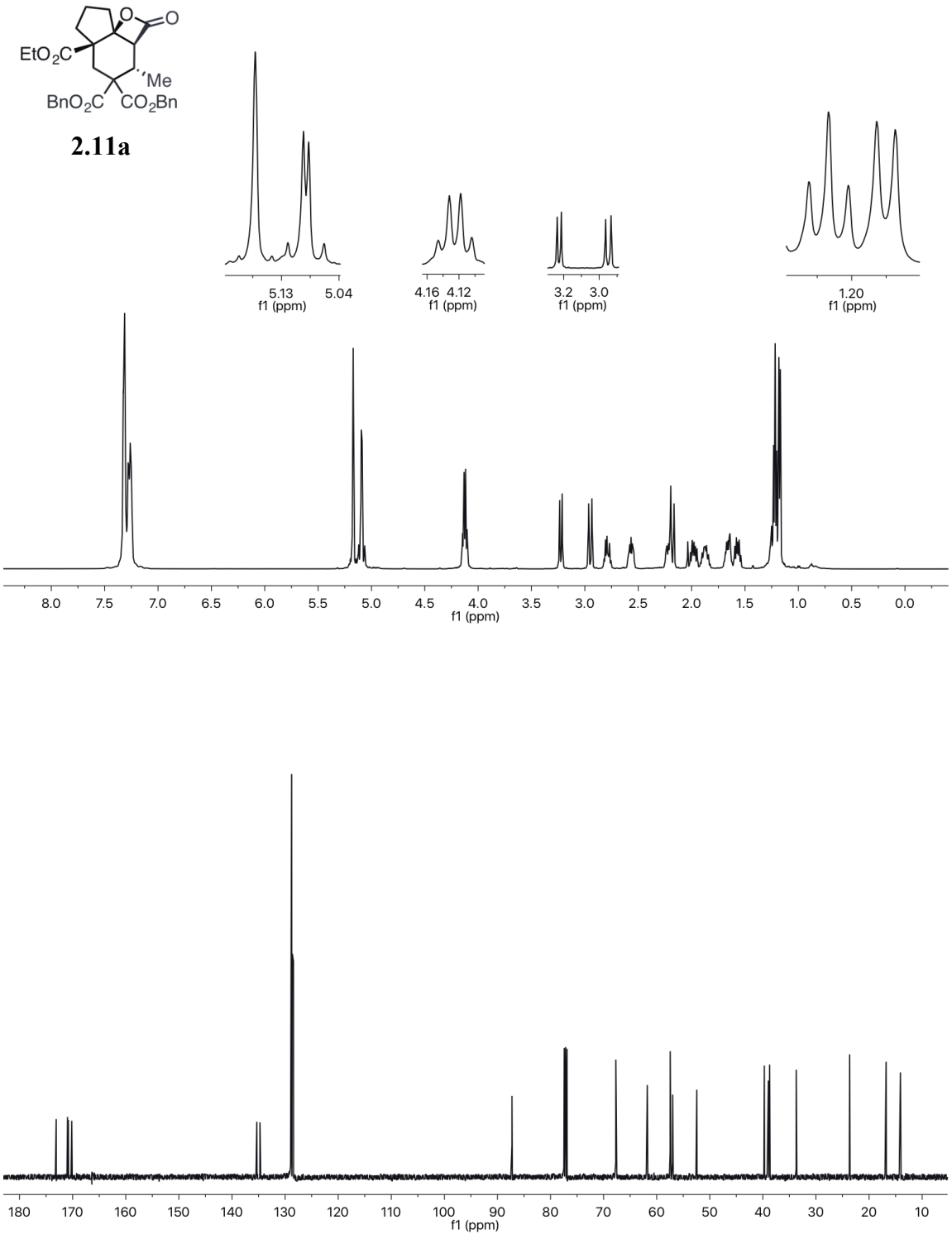
2.1b



^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of β-lactone **2.1b** in C_6D_6

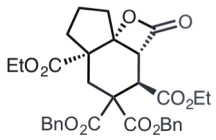


^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of β-lactone **2.1c** in C_6D_6

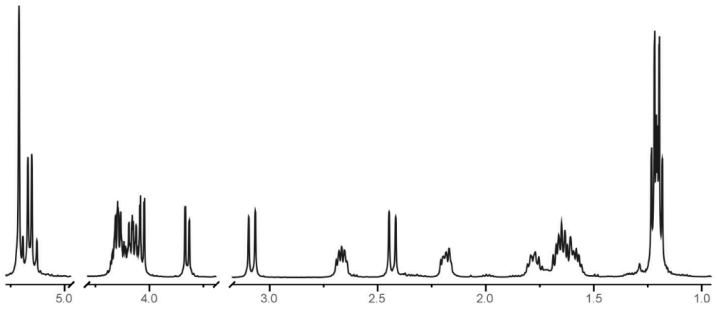


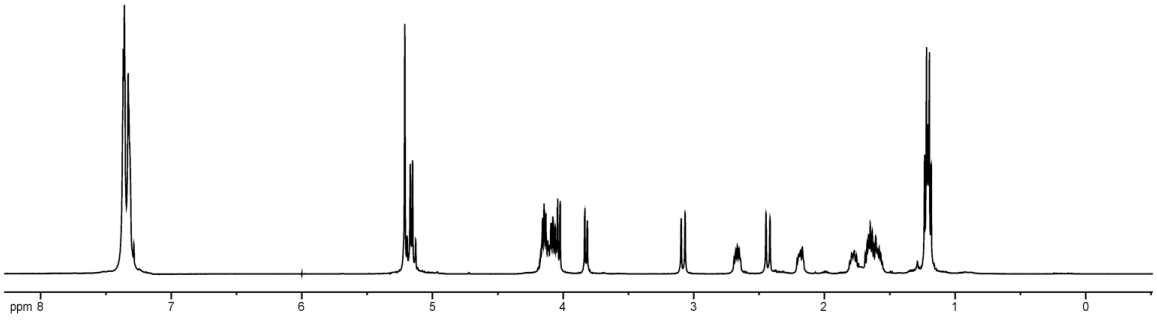
2.11a

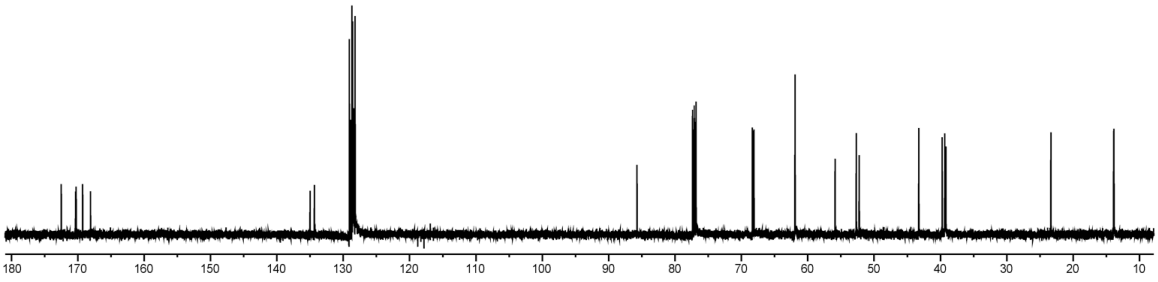
^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of β-lactone **2.11a** in $CDCl_3$



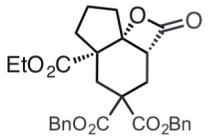
(+)-2.11b



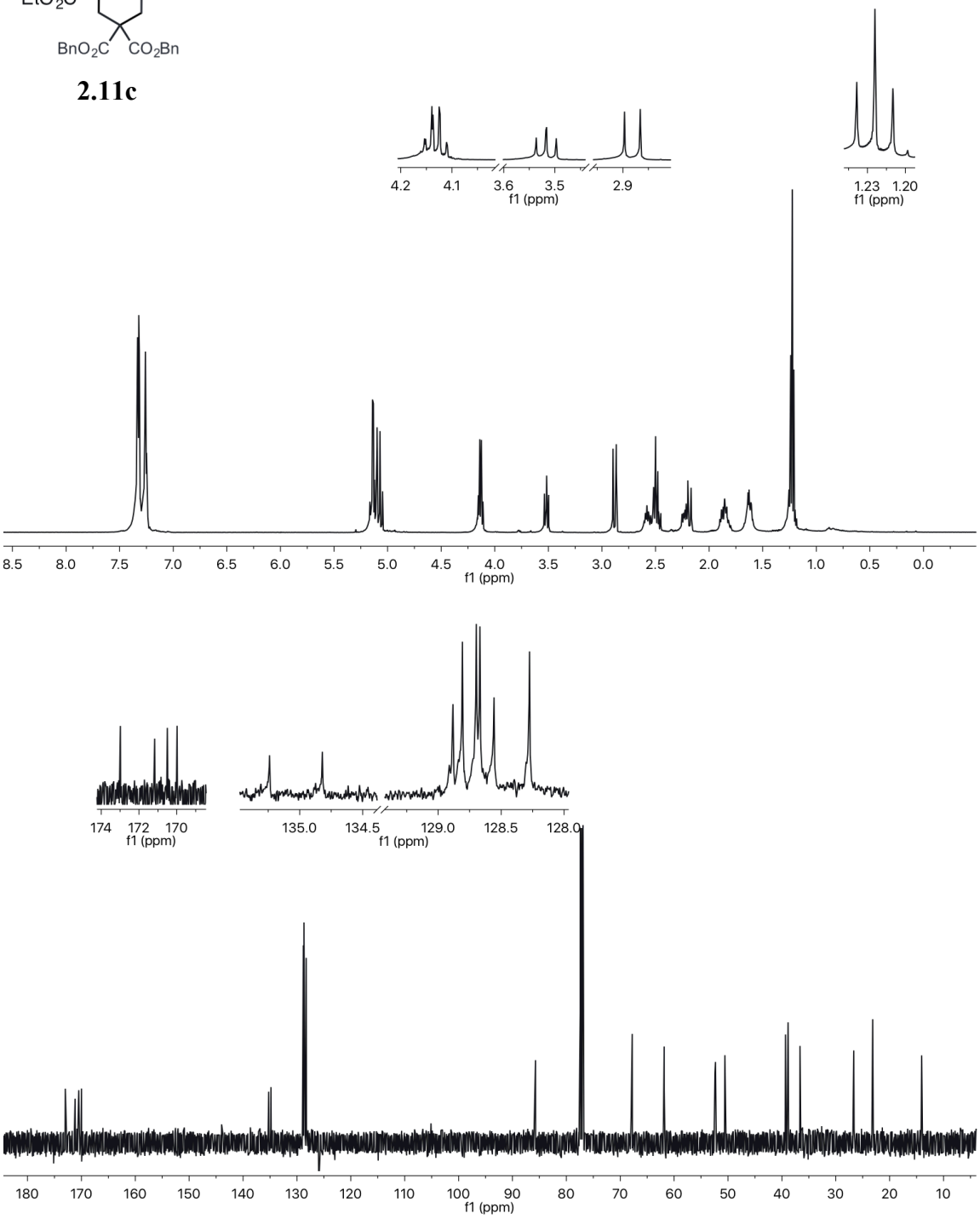




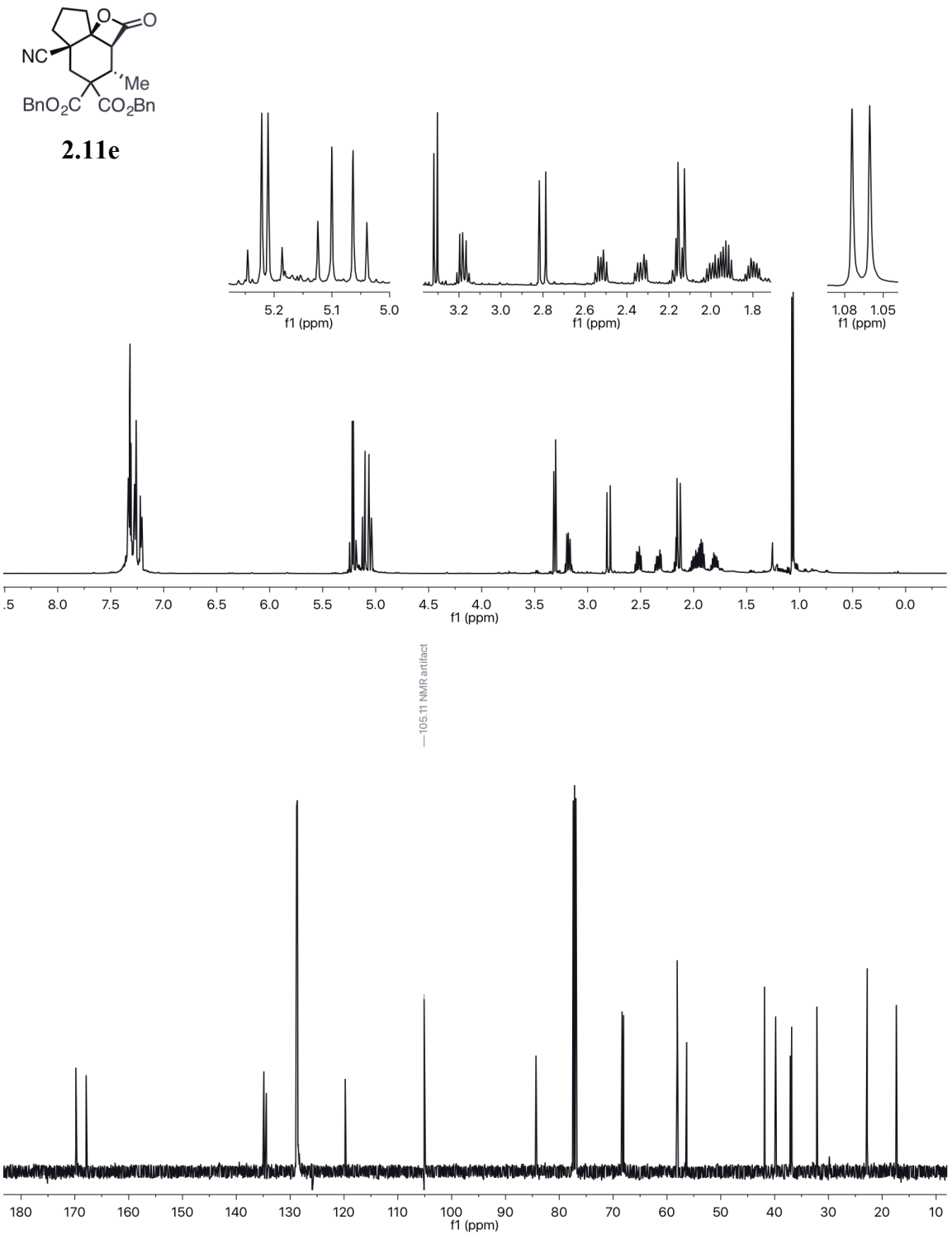
^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of β-lactone (+)-**2.11b** in $CDCl_3$



2.11c

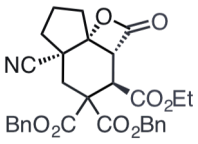


^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of β-lactone (+)-**2.11c** in $CDCl_3$

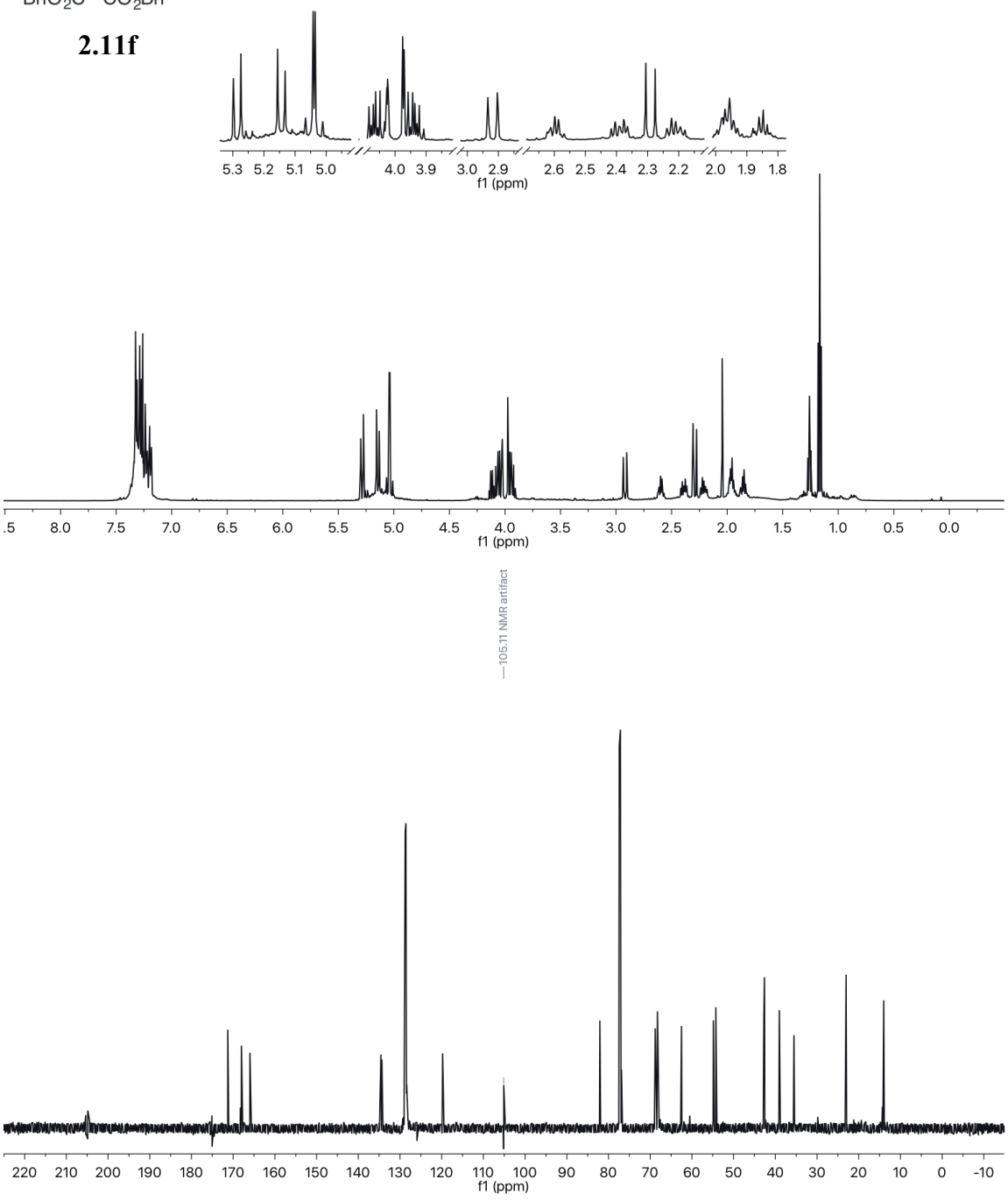


2.11e

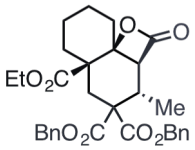
^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of β-lactone **2.11e** in $CDCl_3$



2.11f

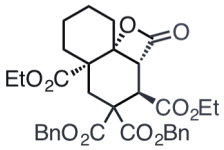


^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of β-lactone **2.11f** in $CDCl_3$

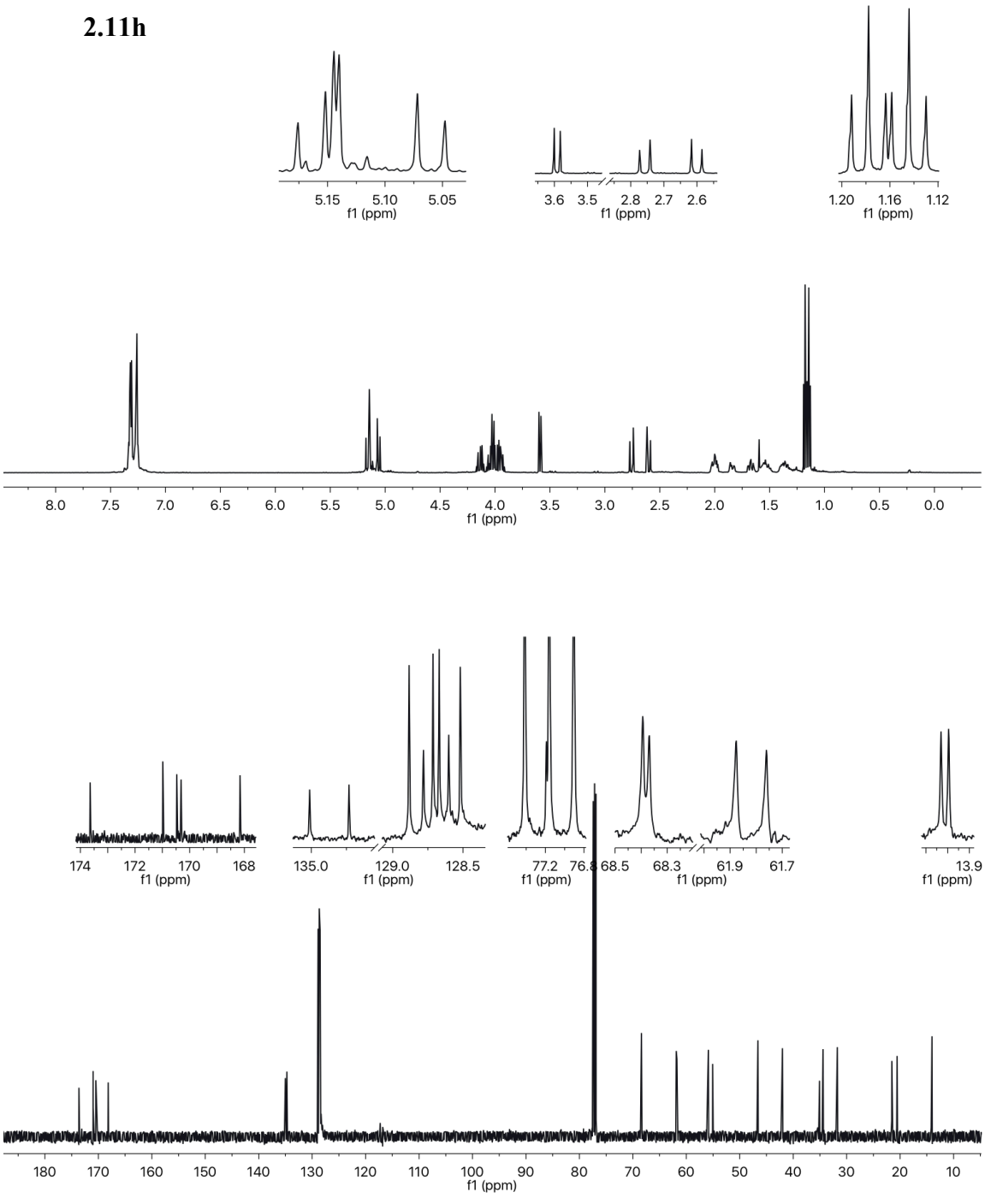


2.11g

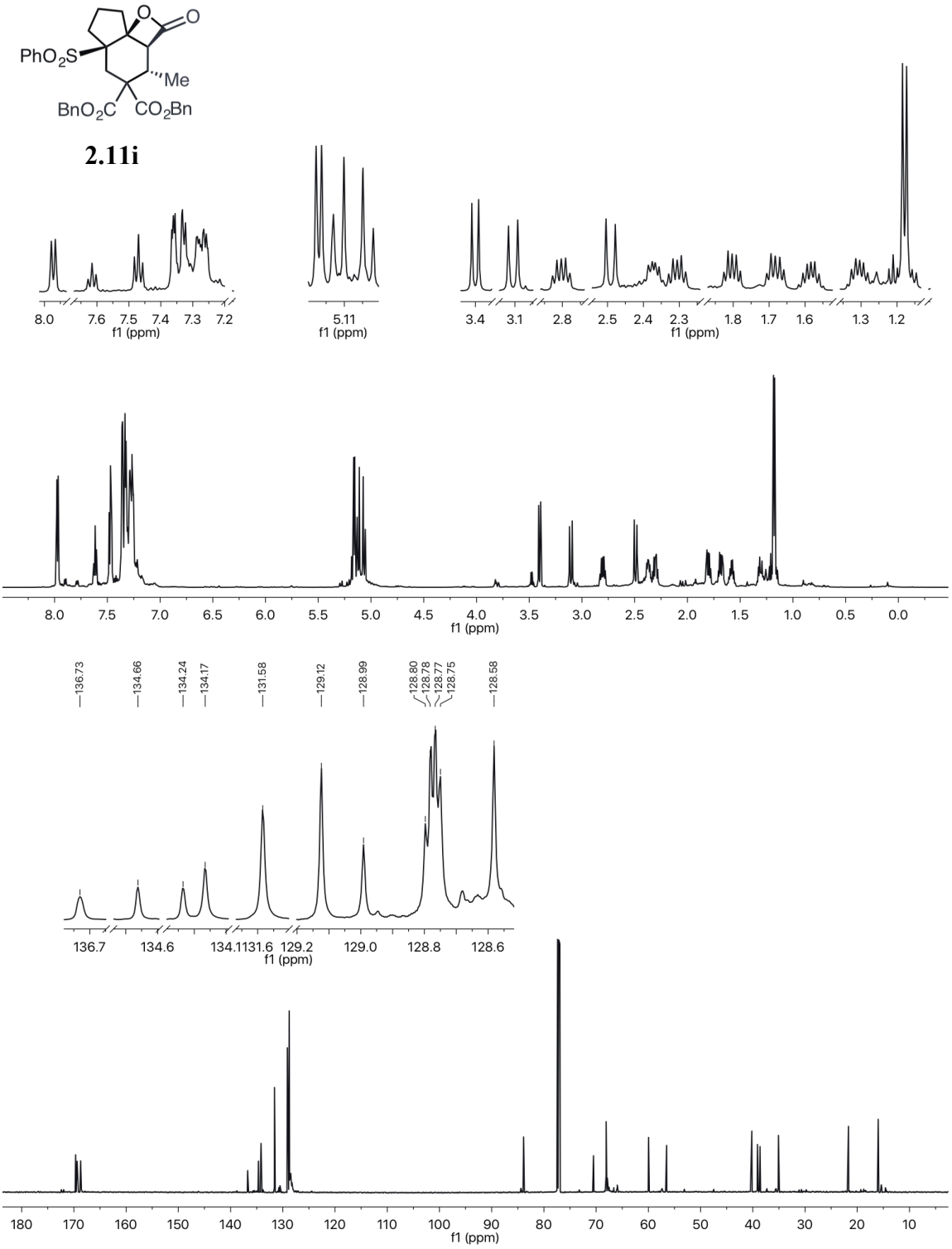
^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of β-lactone **2.11g** in $CDCl_3$



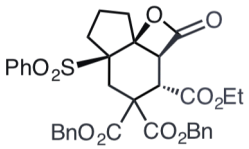
2.11h



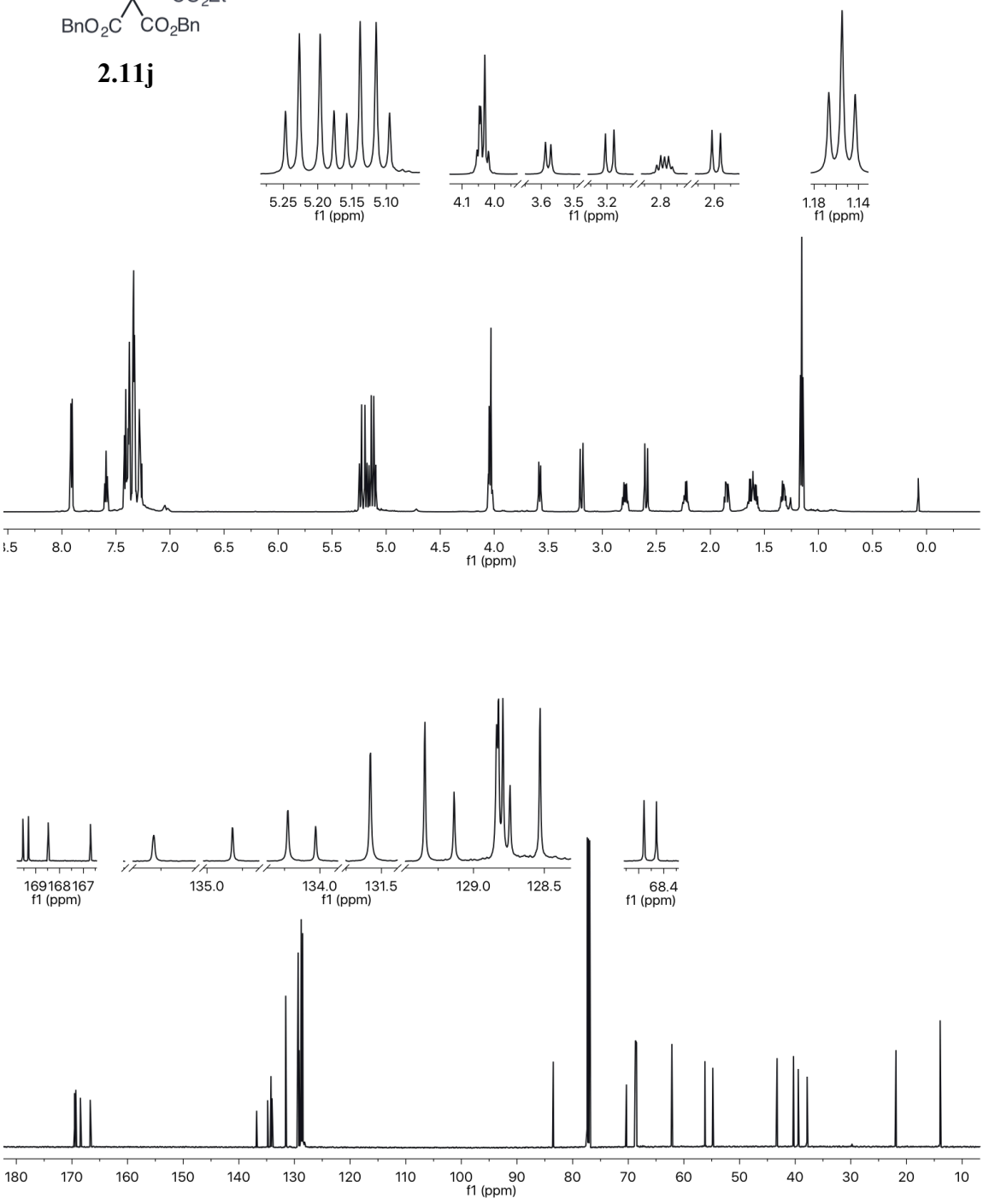
^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of β-lactone **2.11h** in $CDCl_3$



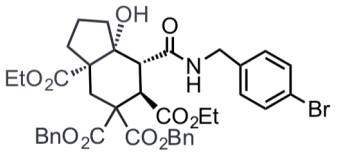
^{1}H NMR (600 MHz) and ^{13}C NMR (150 MHz) spectra of β-lactone **2.11i** in $CDCl_3$



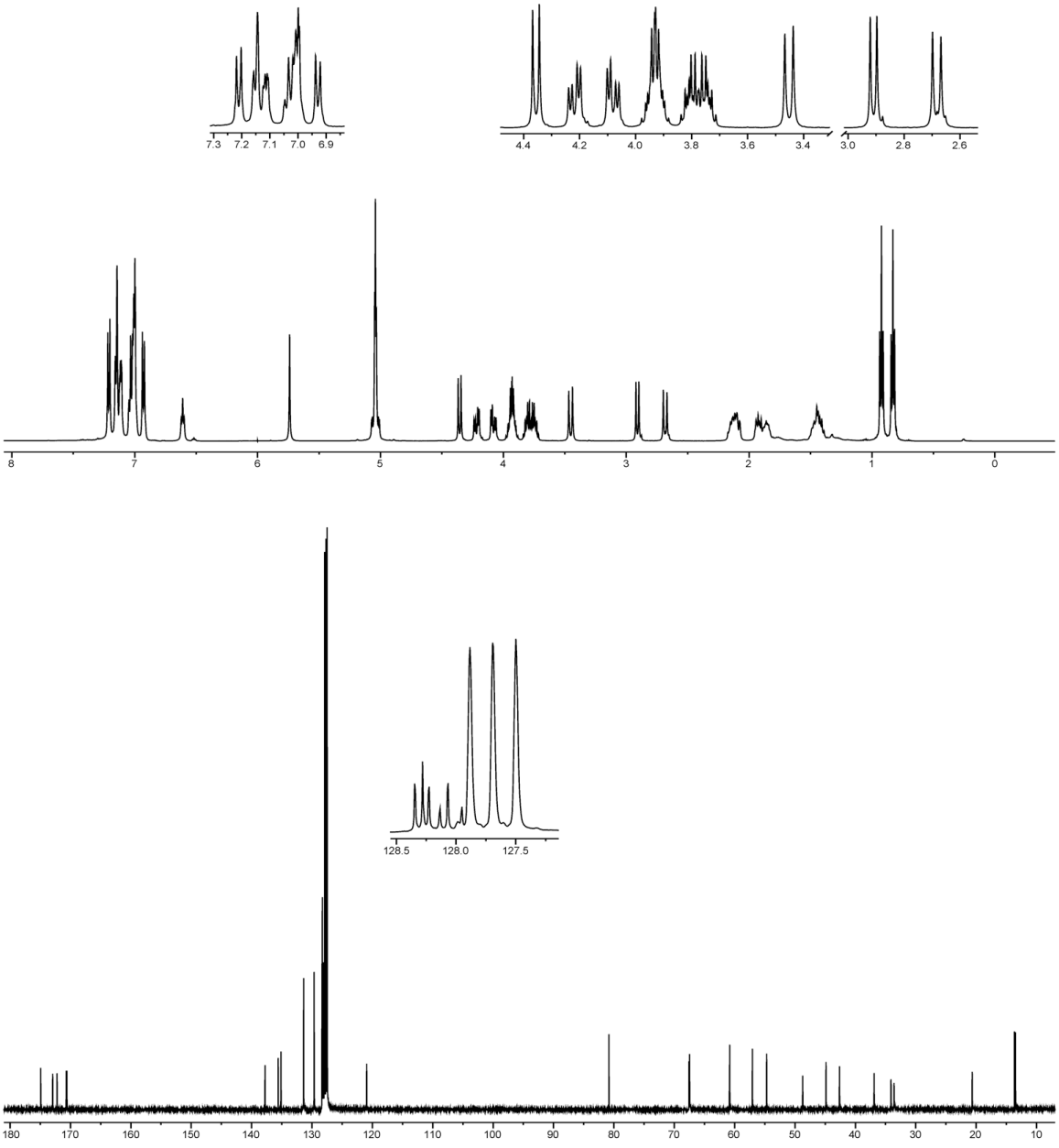
2.11j



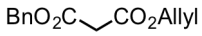
^{1}H (600 MHz) and ^{13}C NMR (150 MHz) spectra of β-lactone **2.11j** in $CDCl_3$



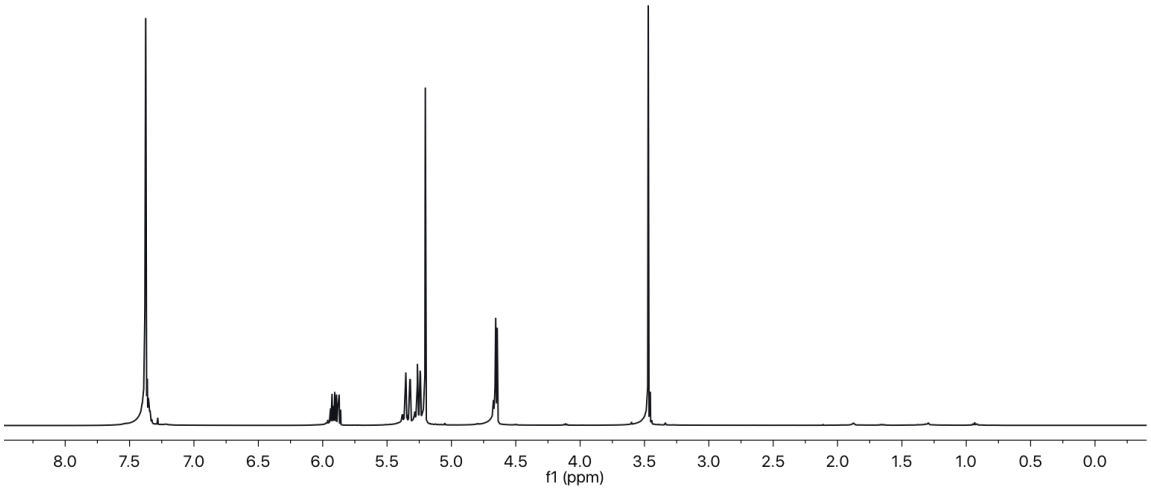
(–)-**2.18**

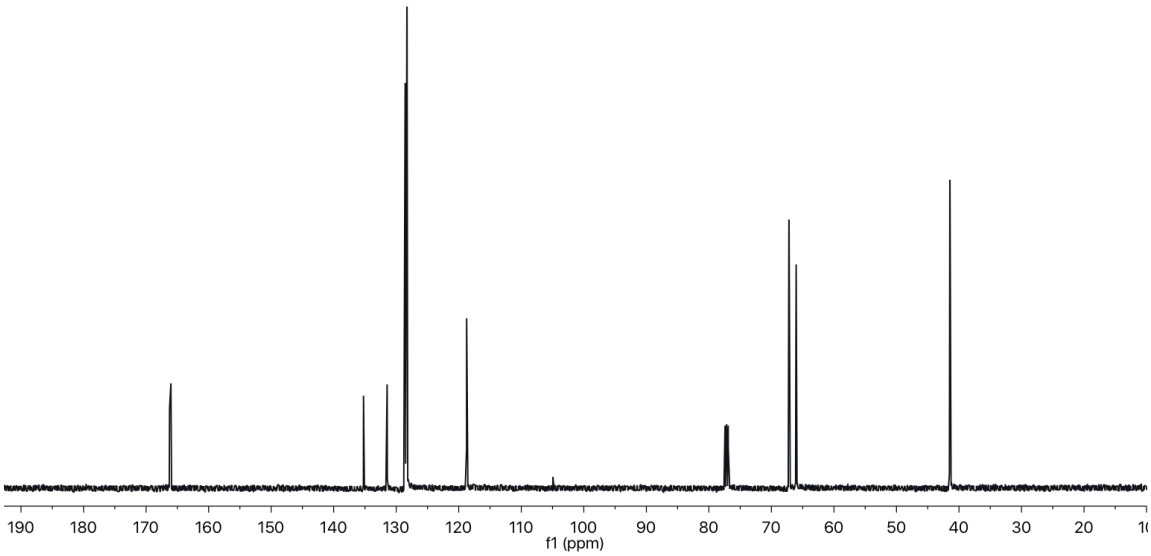


^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of amide (–)-**2.18** in C_6D_6

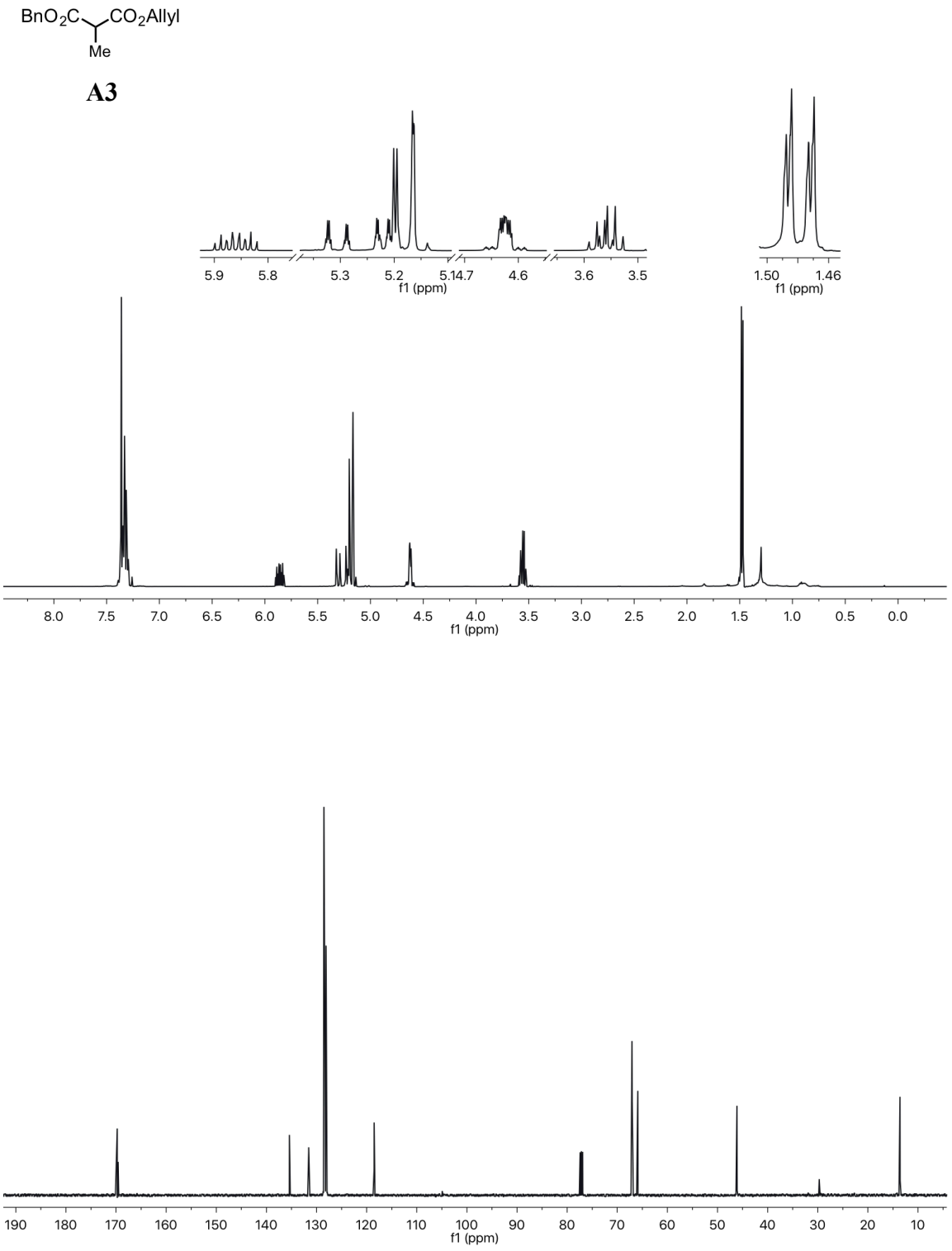


A2

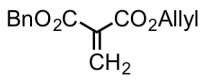




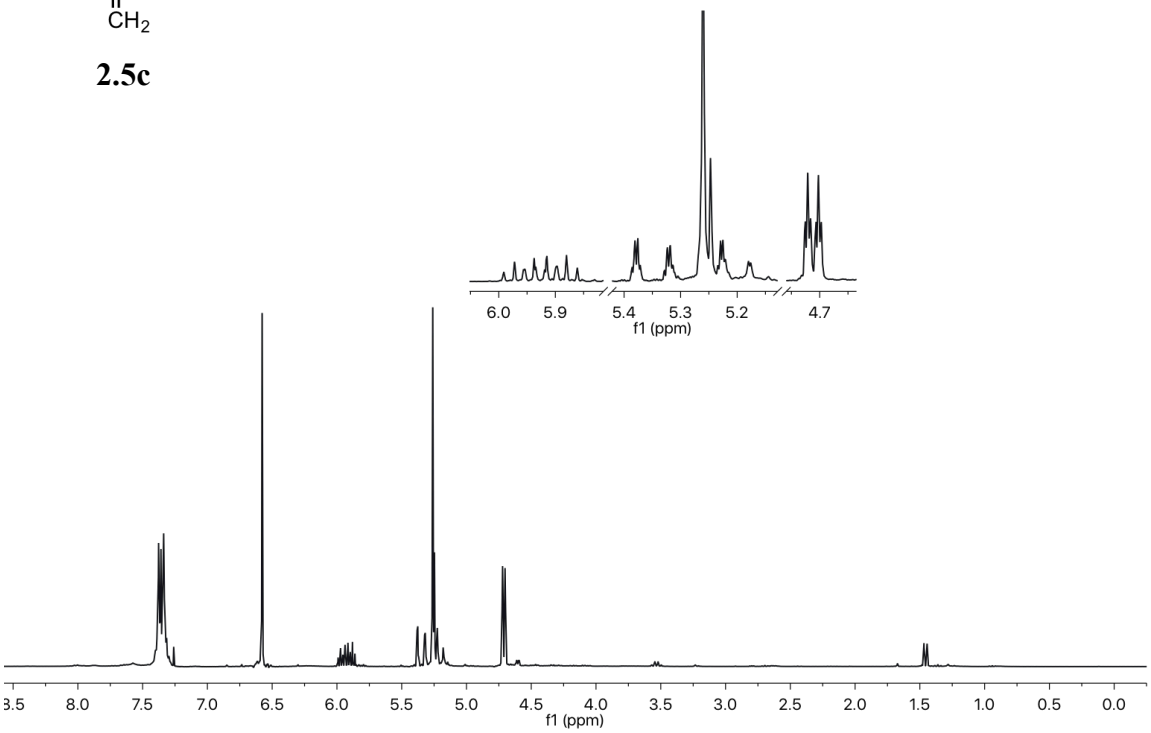
^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of **A2** in $CDCl_3$

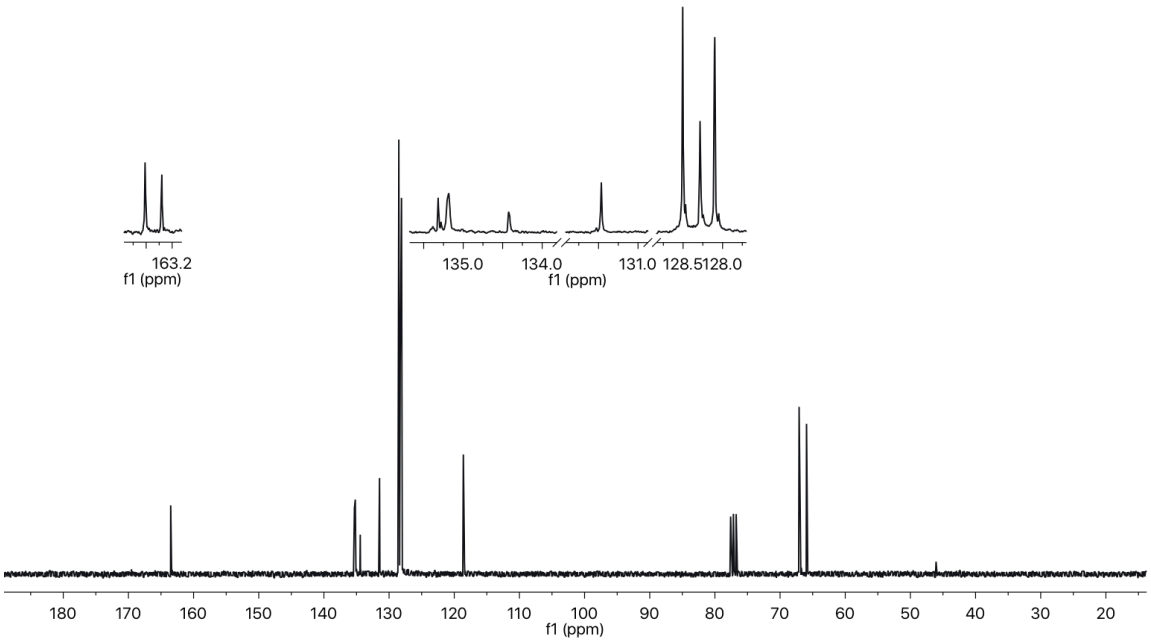


^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of **A3** in $CDCl_3$

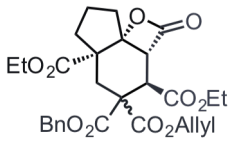


2.5c

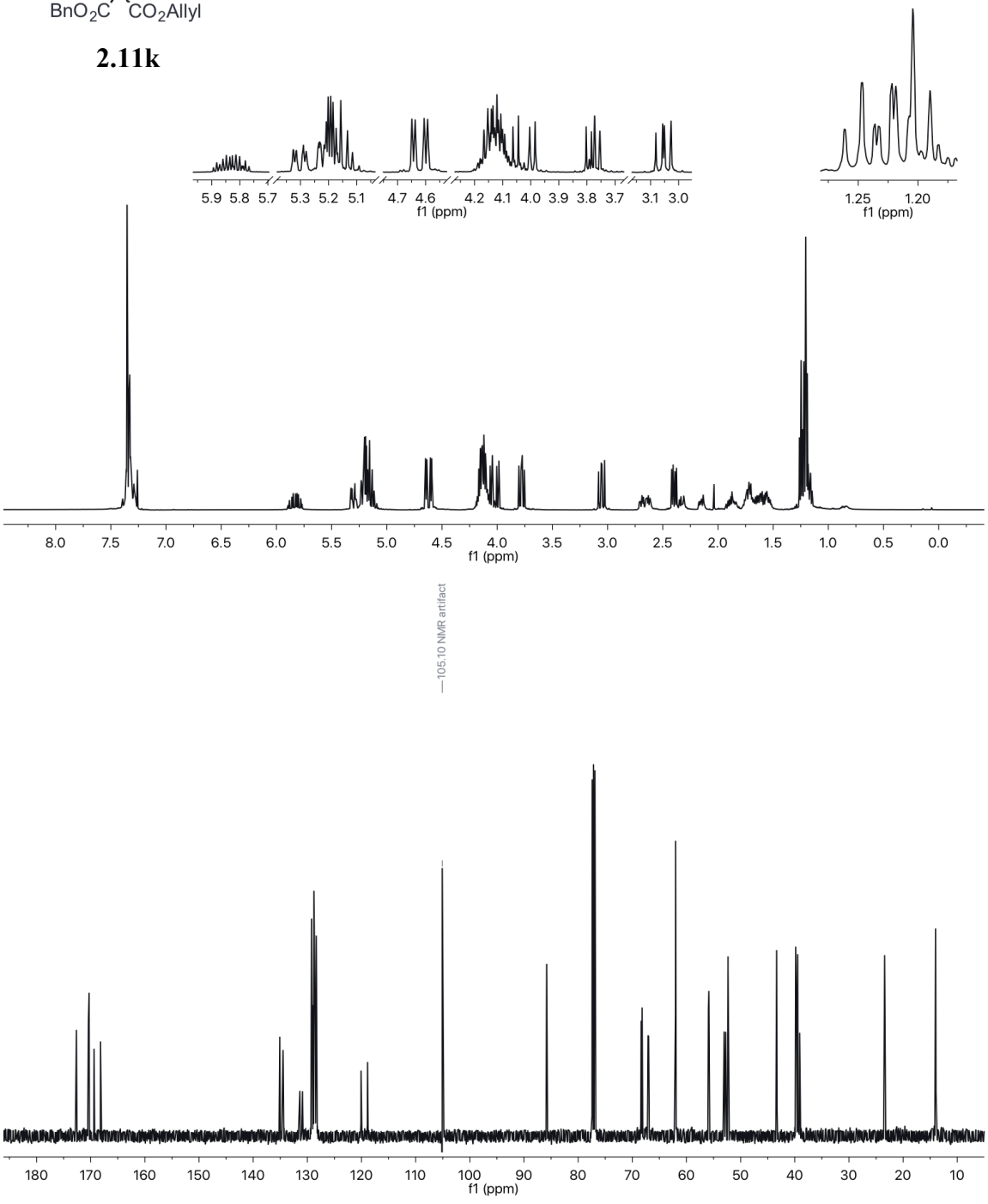




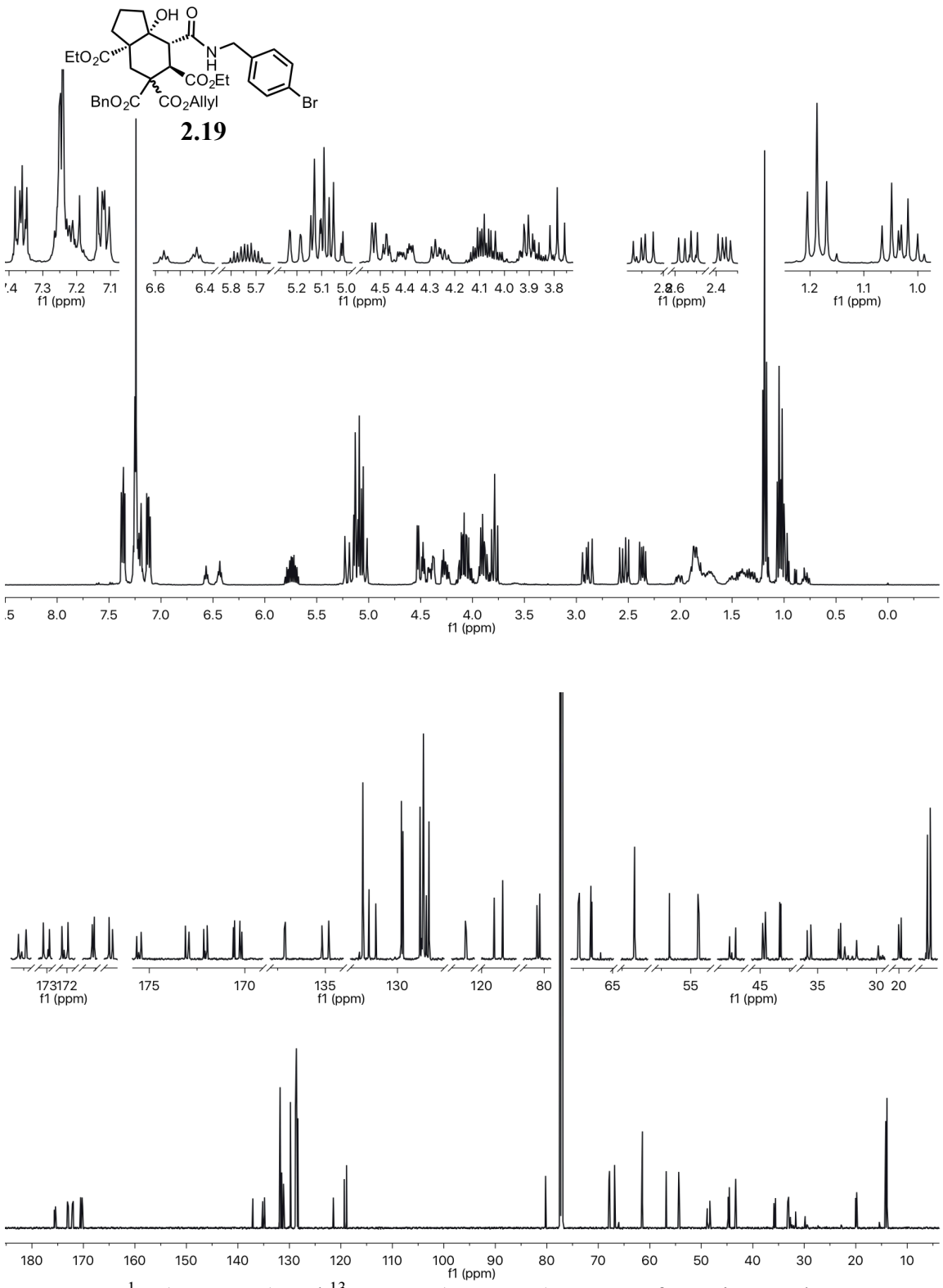
^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of **2.5c** in $CDCl_3$



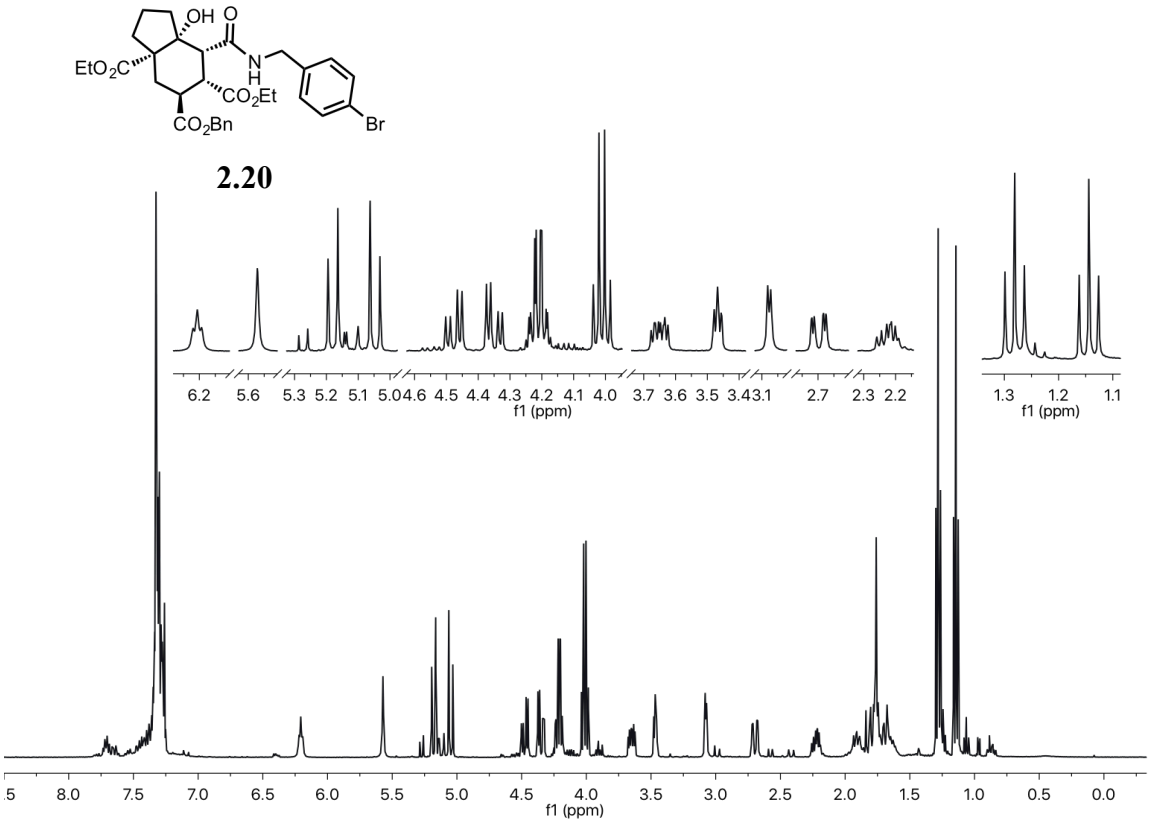
2.11k

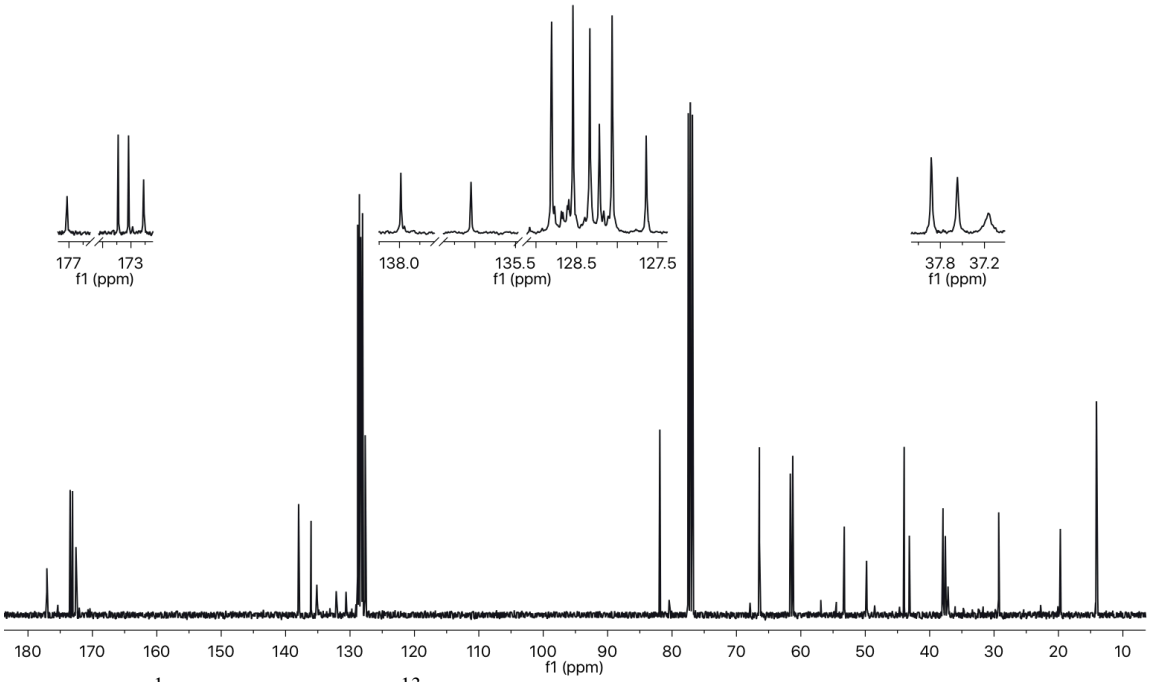


^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of **2.11k** in $CDCl_3$



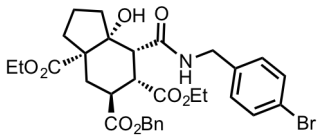
^{1}H (400 MHz) and ^{13}C NMR (150 MHz) spectra of **2.19** in $CDCl_3$



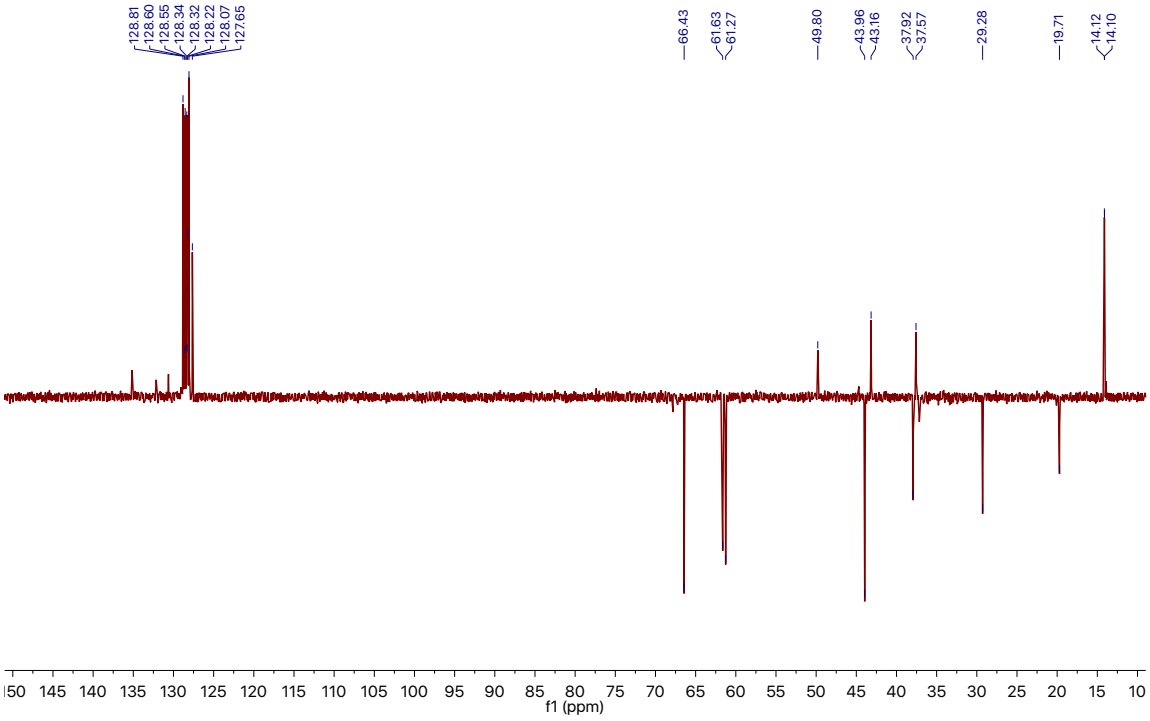


^{1}H (400 MHz) and ^{13}C NMR (125 MHz) spectra of **2.20** in $CDCl_3$

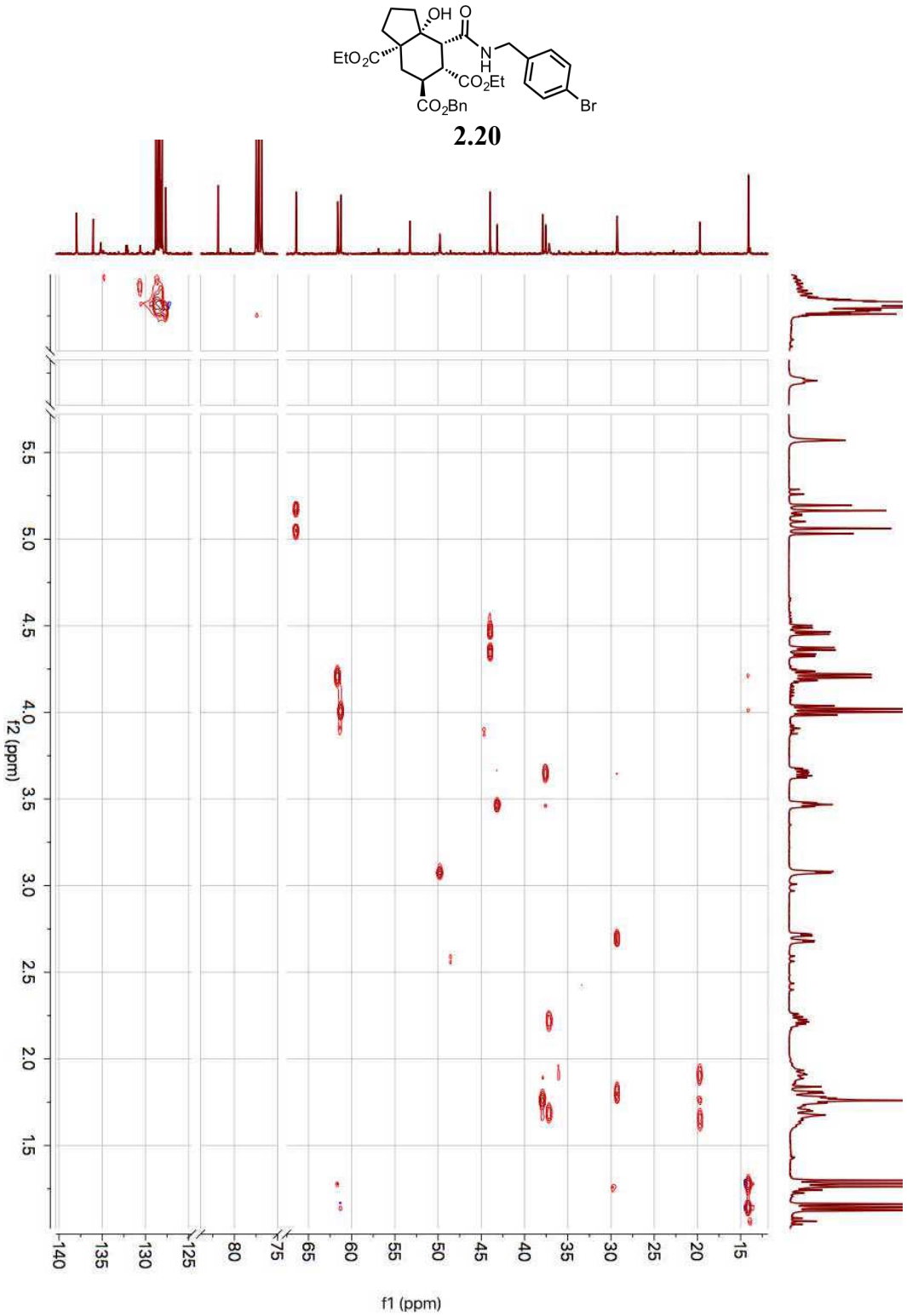
Determination of relative stereochemistry of amide 2.20



2.20

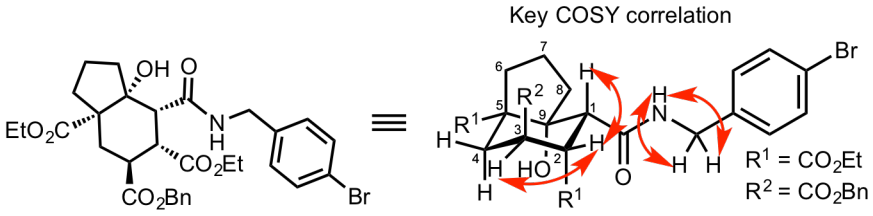


DEPT135 (400 MHz, $CDCl_3$) spectrum of **2.20** in $CDCl_3$

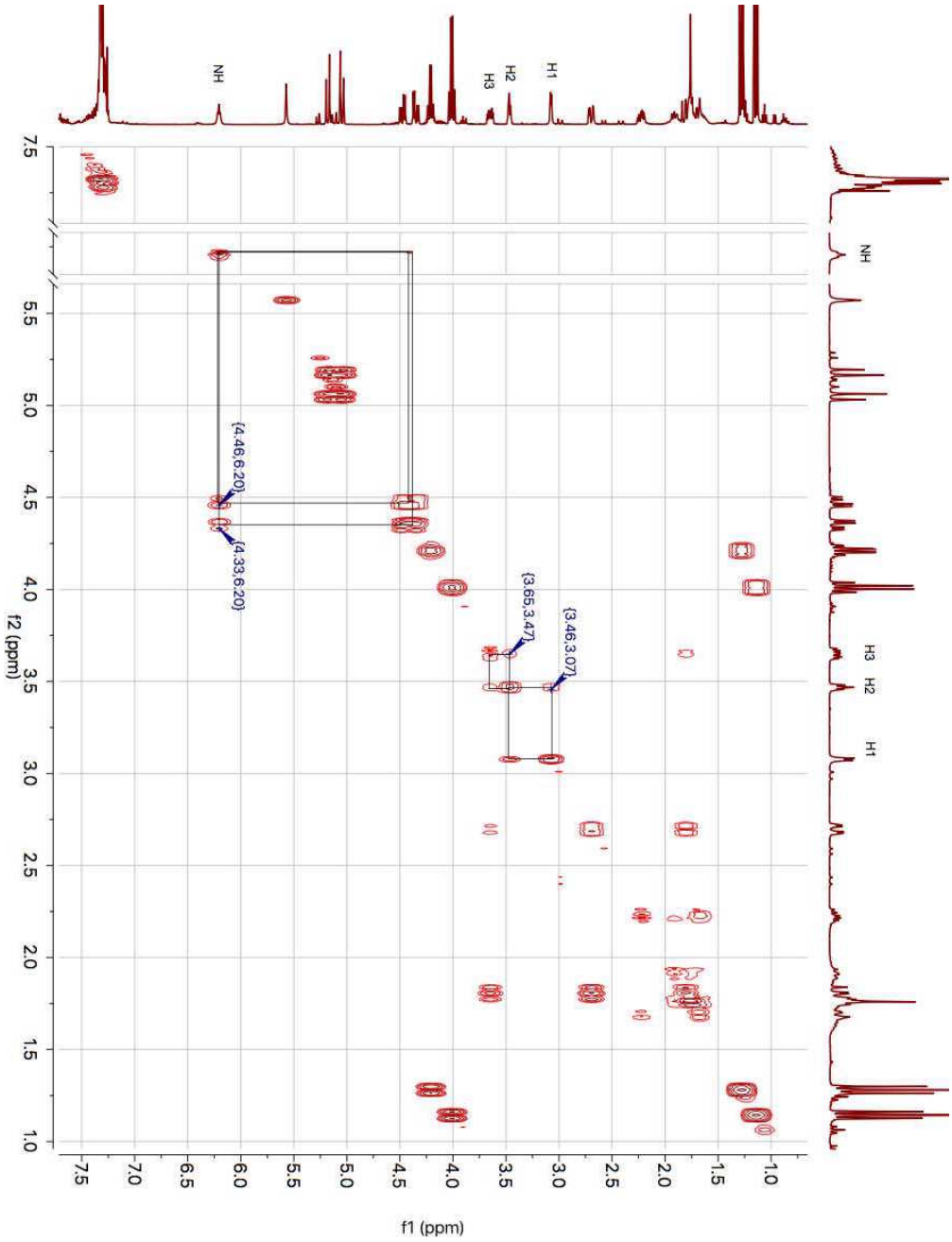


2.20

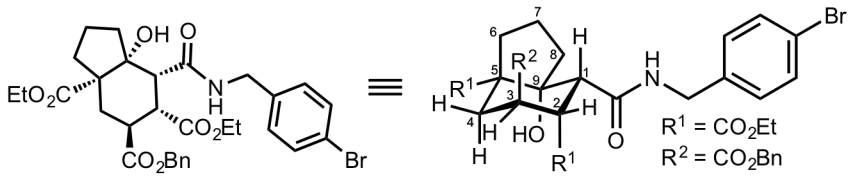
^{1}H-^{13}C HSQC (400 MHz, $CDCl_3$) spectrum of compounds **2.20**



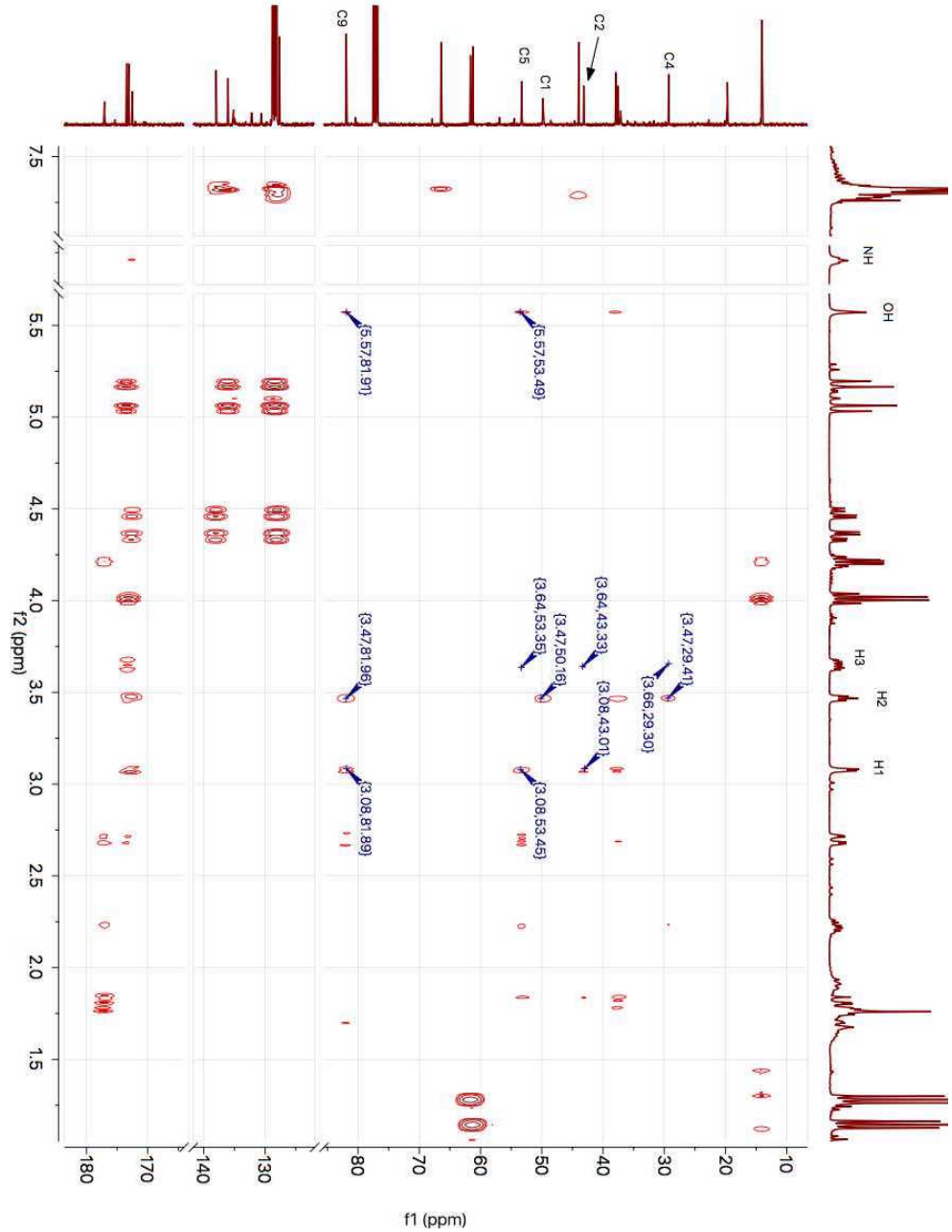
2.20



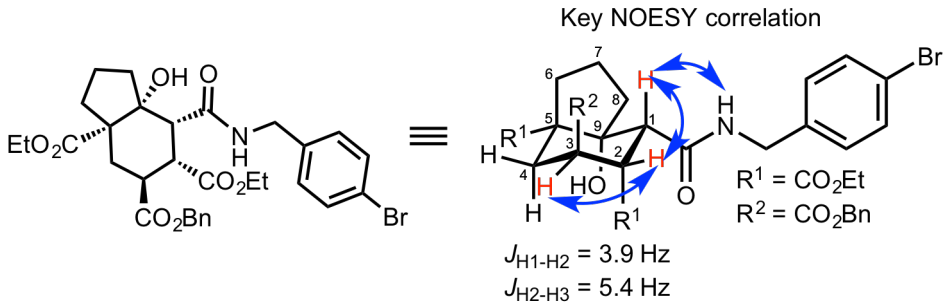
^{1}H-^{1}H COSY (400 MHz, $CDCl_3$) spectrum of compounds **2.20**



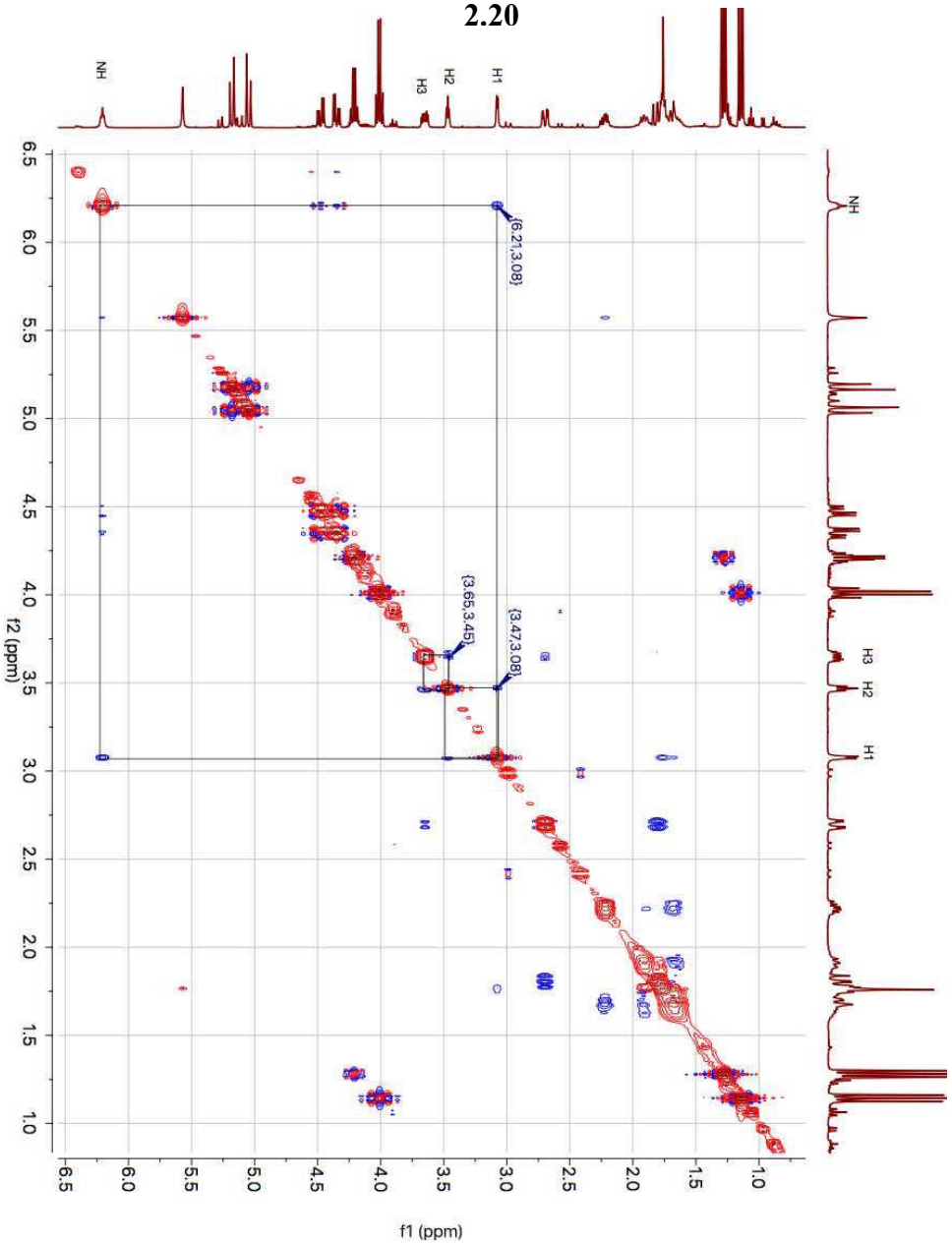
2.20



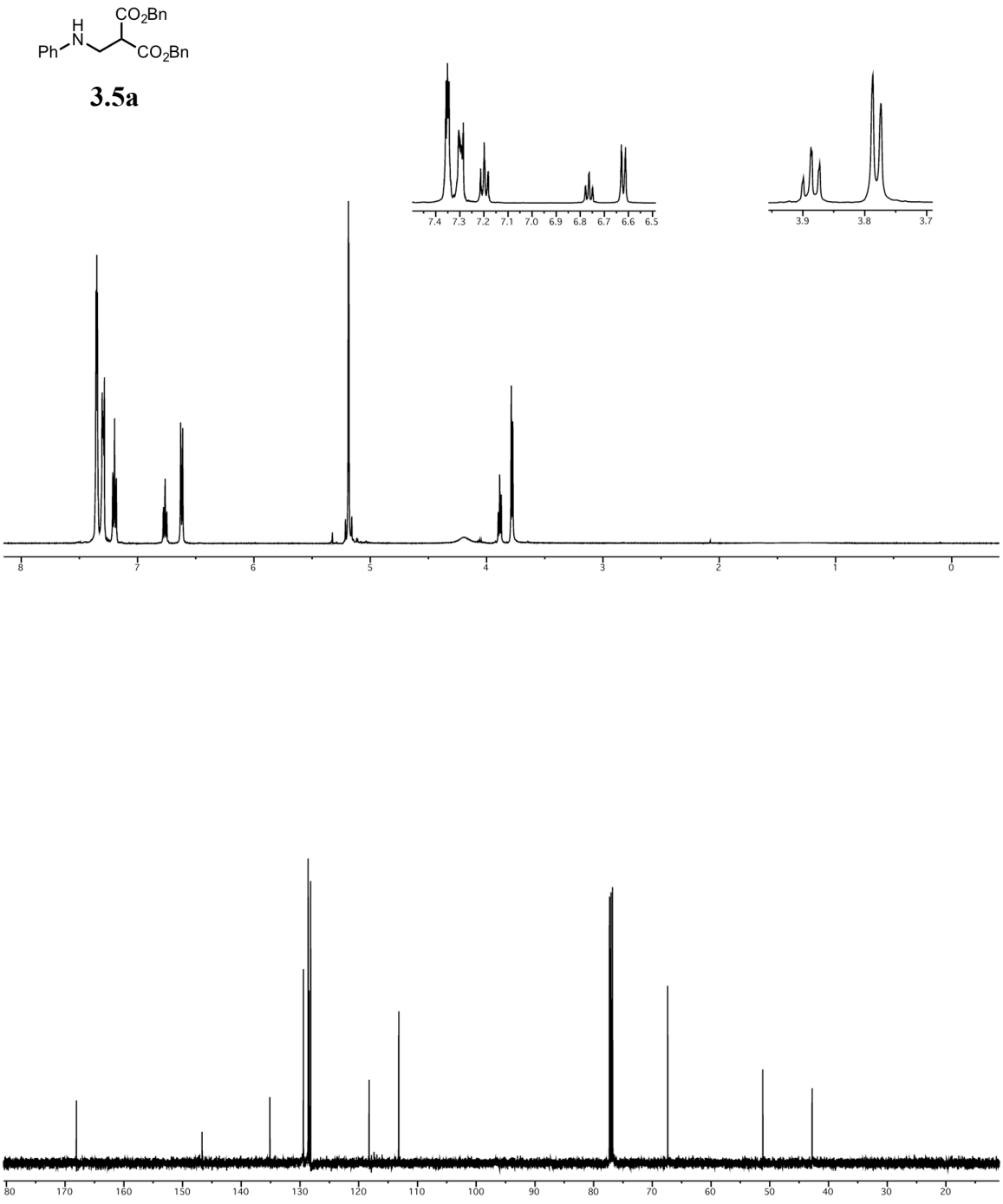
^{1}H-^{13}C HMBC (400 MHz, $CDCl_3$) spectrum of compounds **2.20**



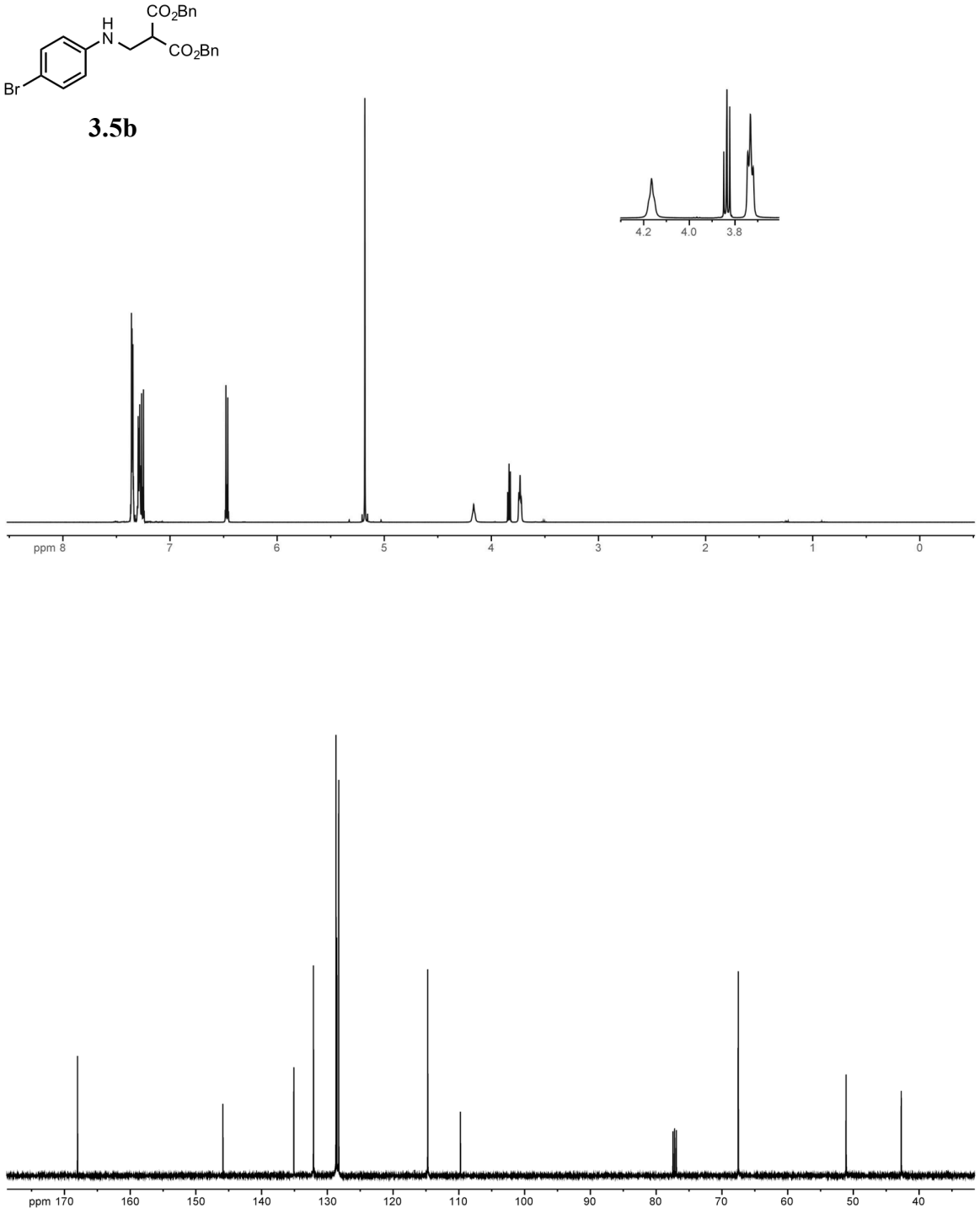
2.20



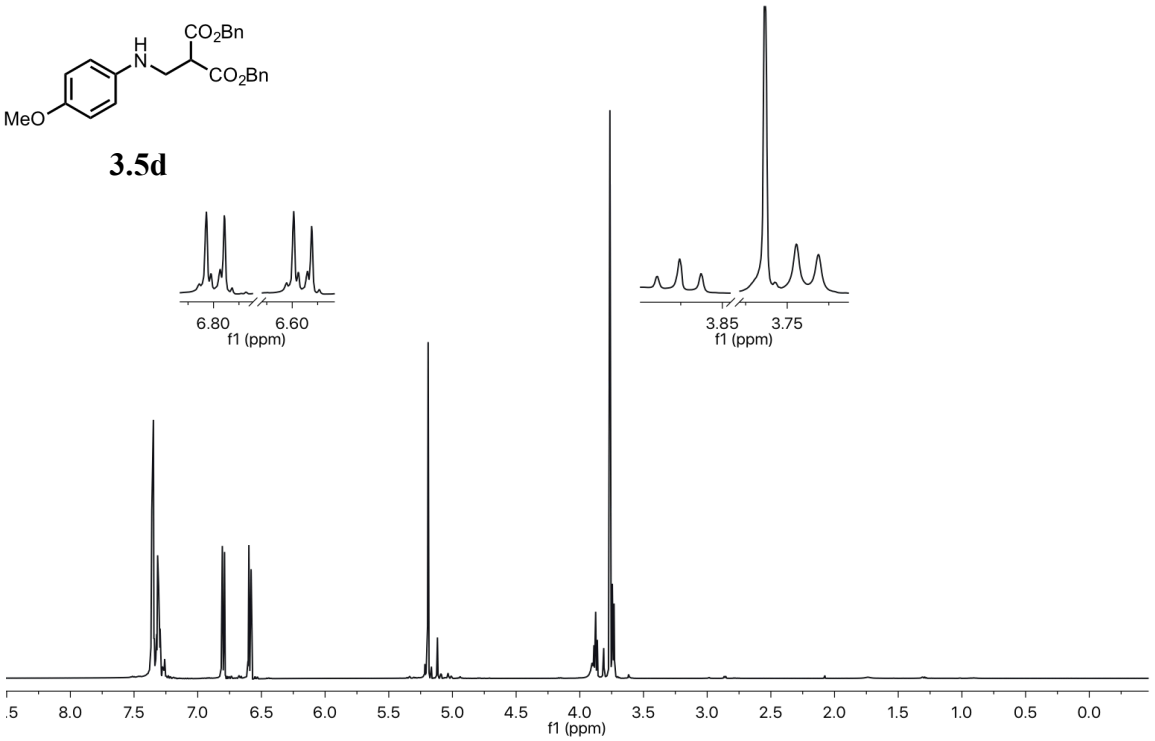
^{1}H-^{1}H NOESY (400 MHz, $CDCl_3$) spectrum of compounds **2.20**



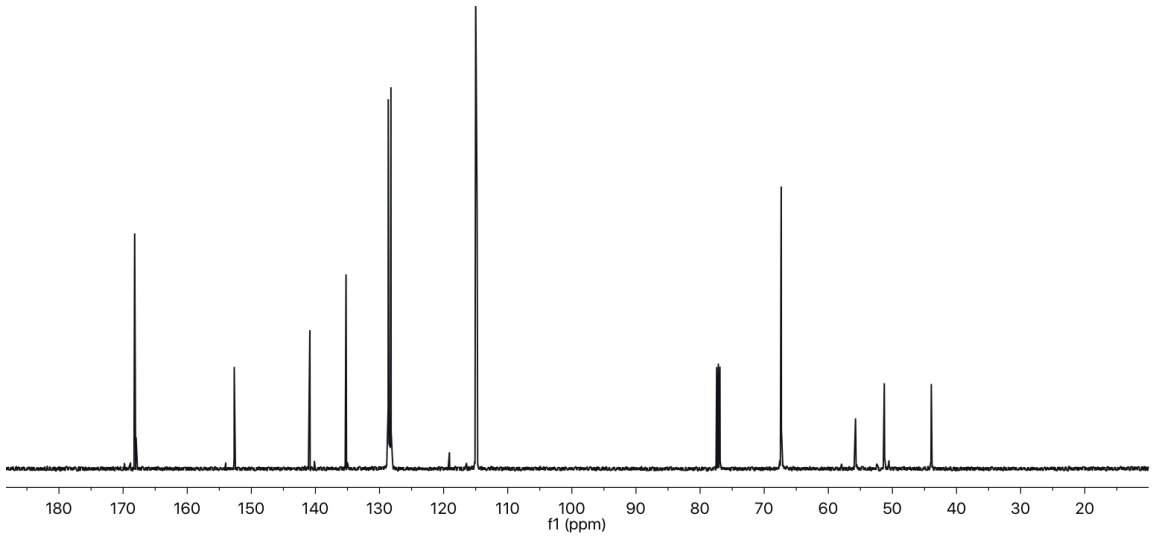
^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of aminoester **3.5a** in $CDCl_3$



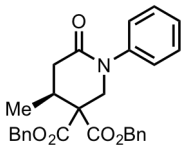
^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of aminoester **3.5b** in $CDCl_3$



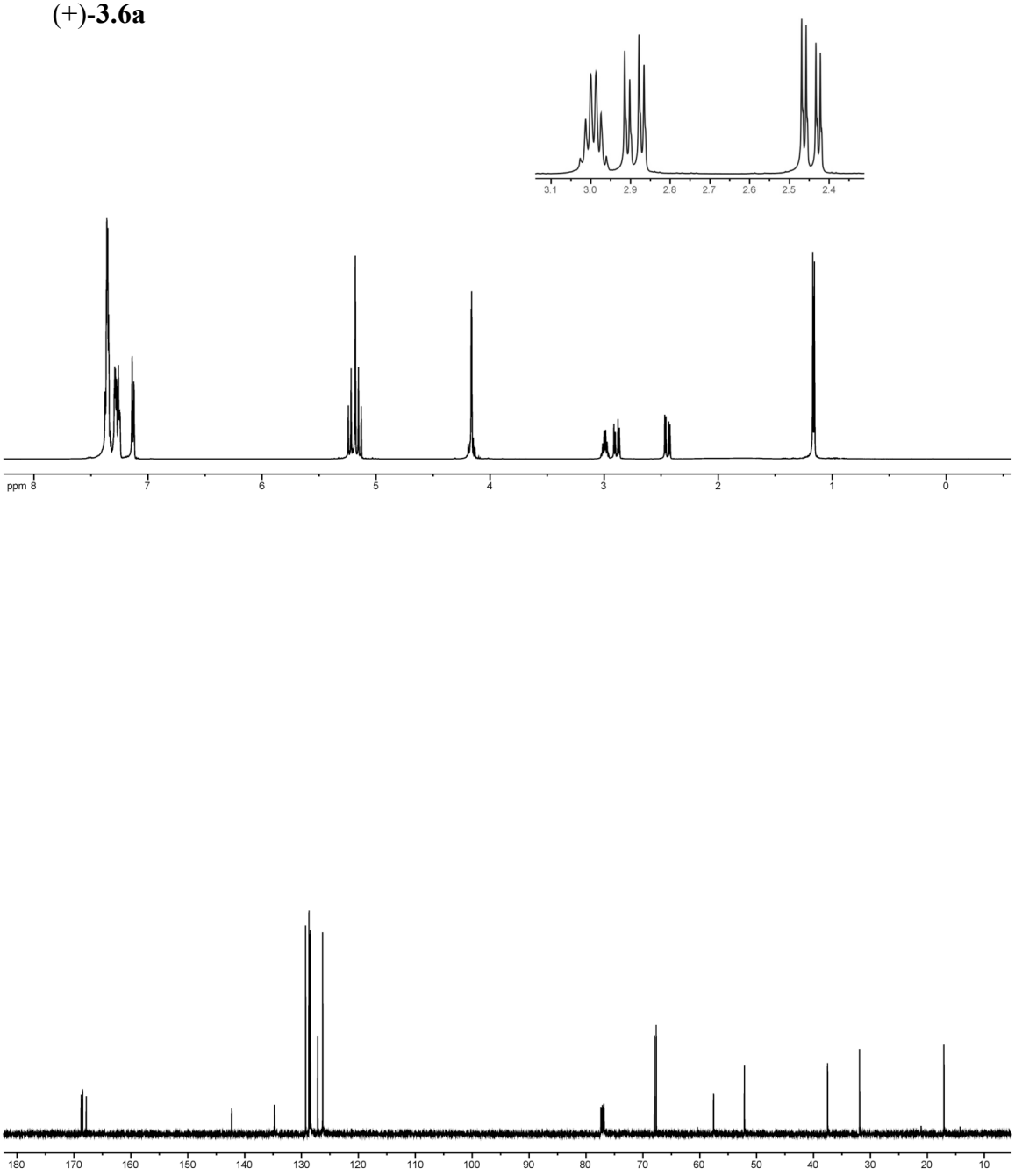
3.5d



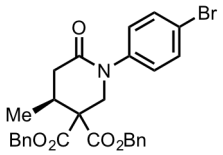
^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of amine **3.5d** in $CDCl_3$



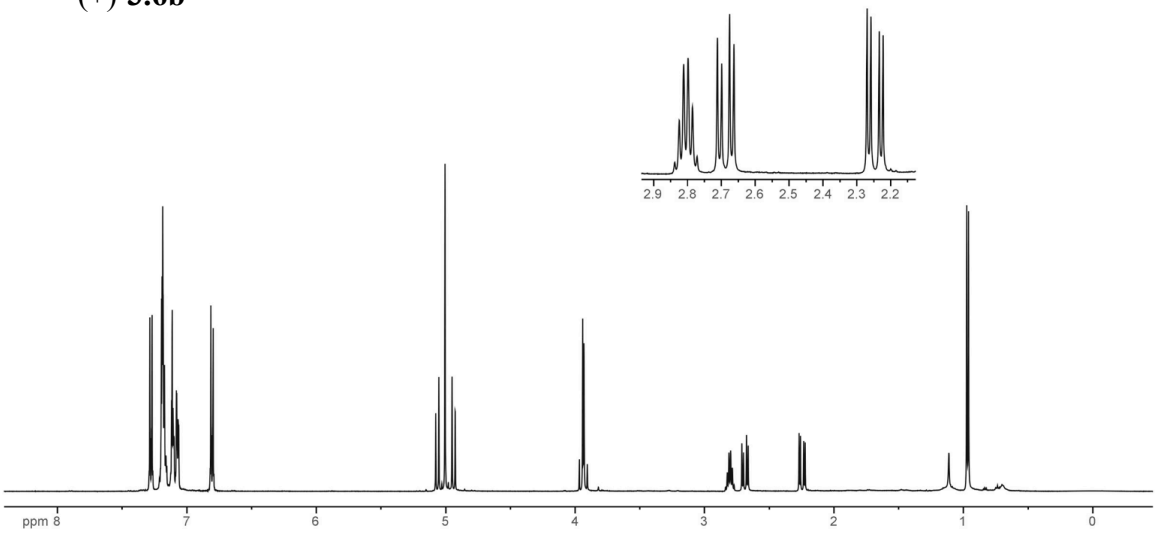
(+)-**3.6a**

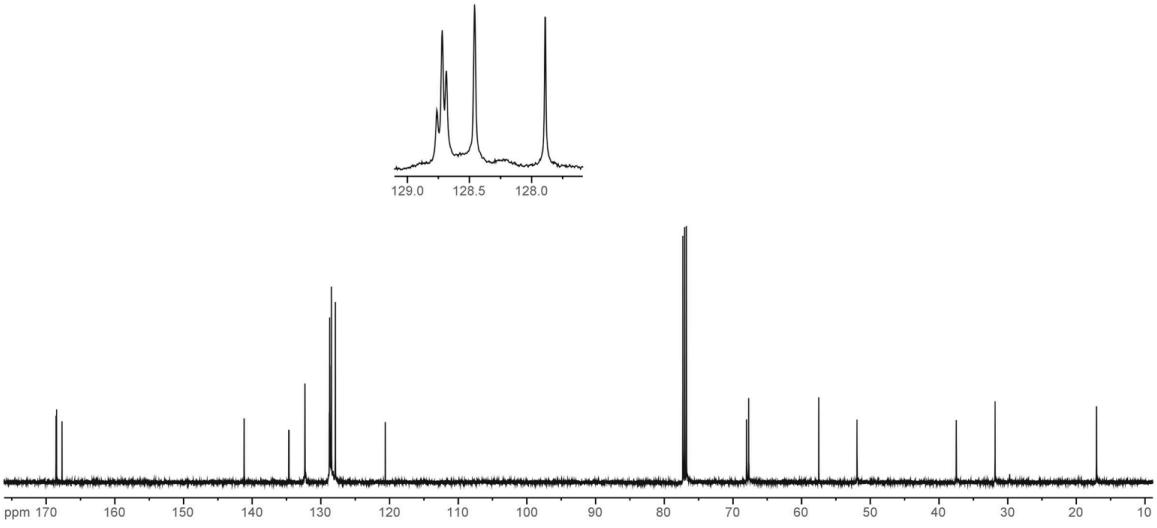


^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of δ-lactam (+)-**3.6a** in $CDCl_3$

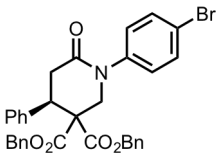


(+)-**3.6b**

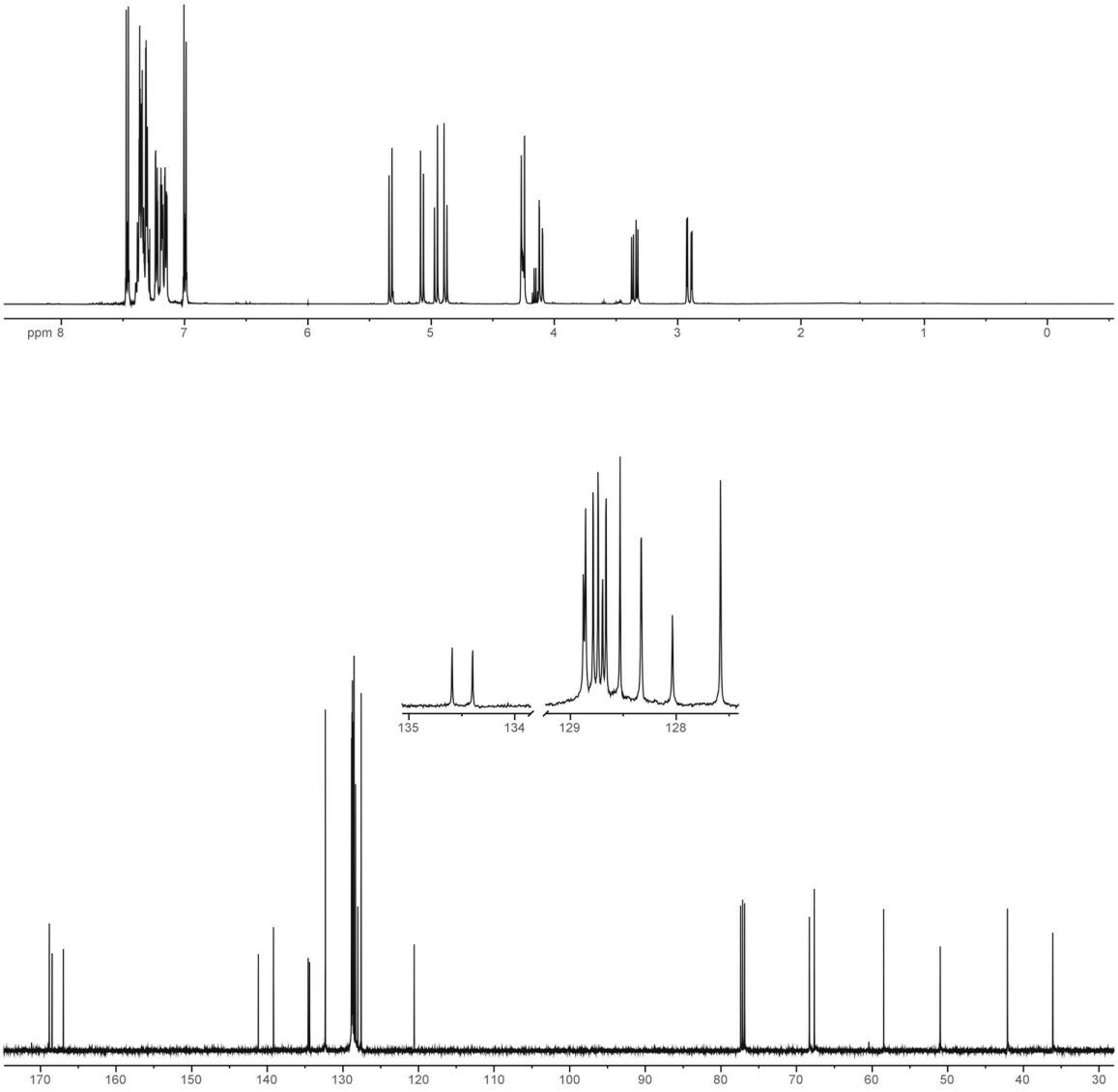




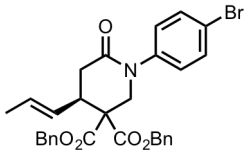
^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of δ-lactam (+)-**3.6b** in $CDCl_3$



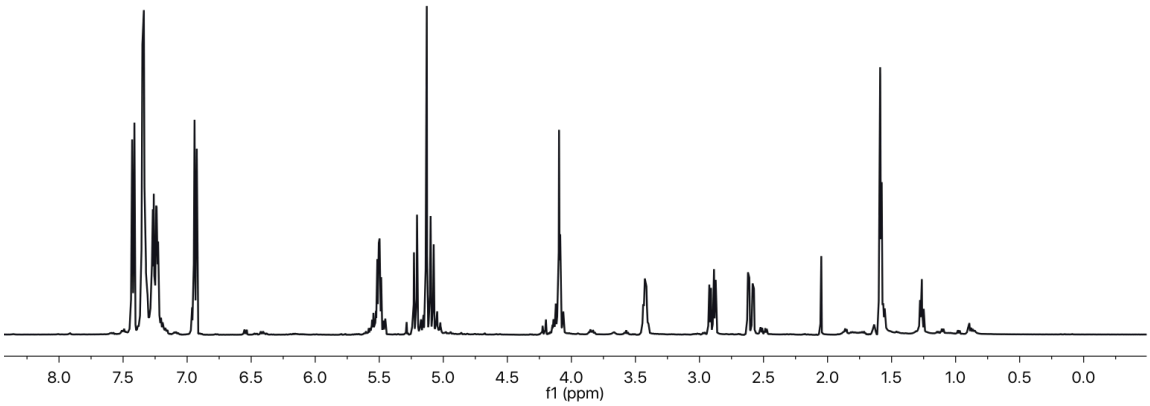
(+)-**3.6c**

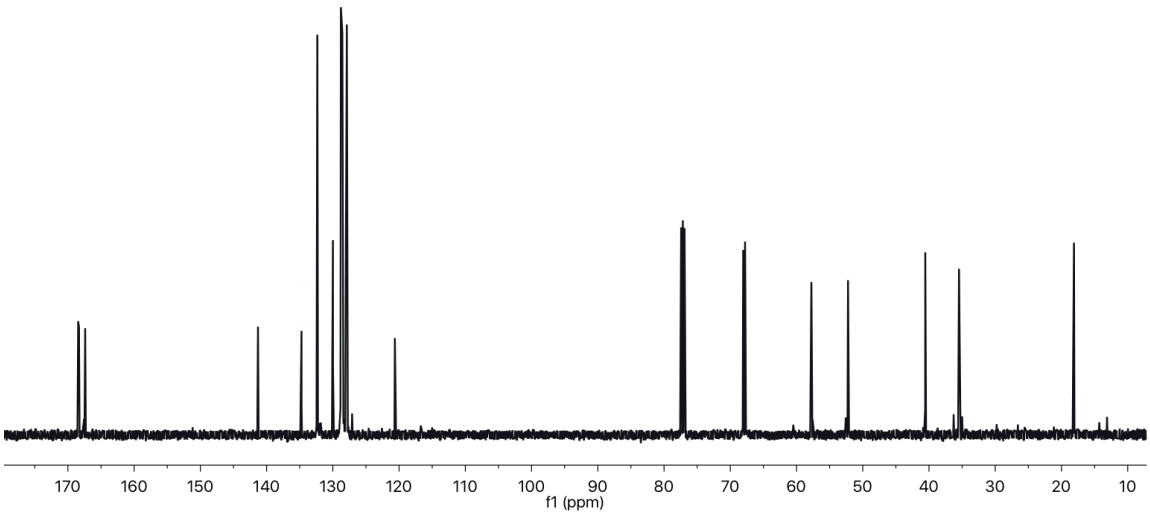


^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of δ-lactam (+)-**3.6c** in $CDCl_3$

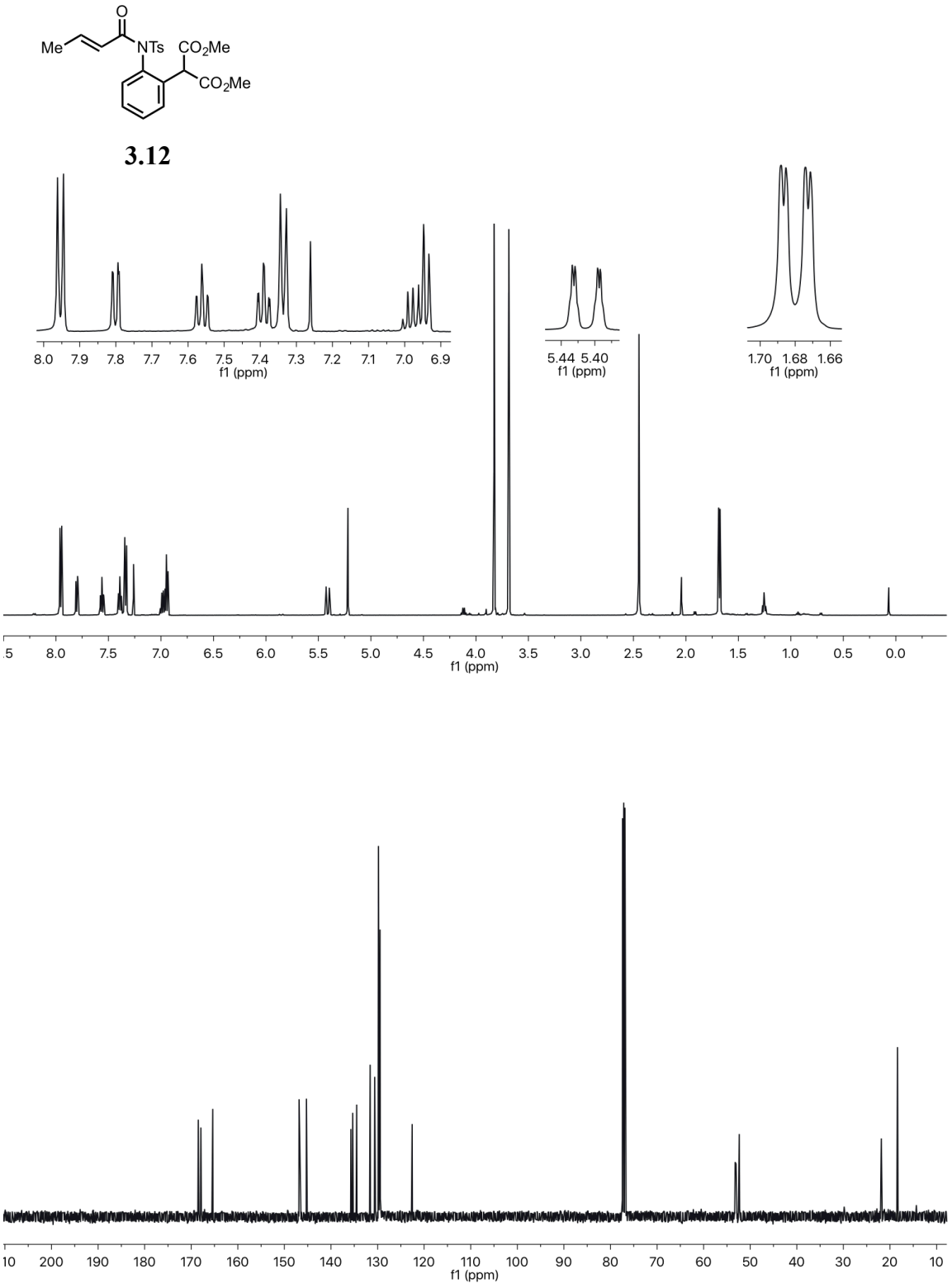


3.6d

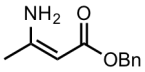




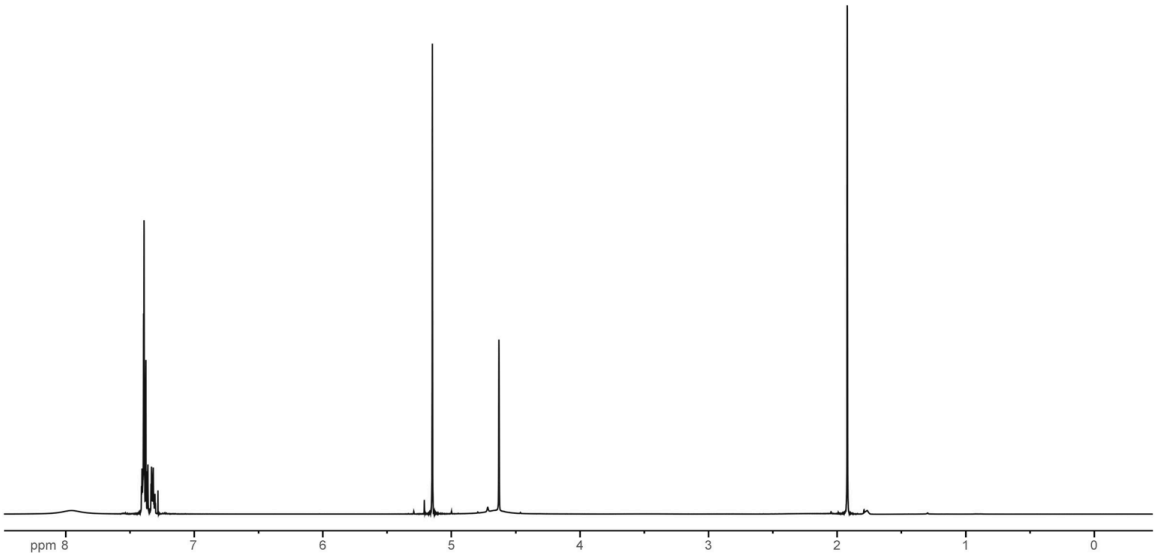
^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of δ-lactam **3.6d** in $CDCl_3$

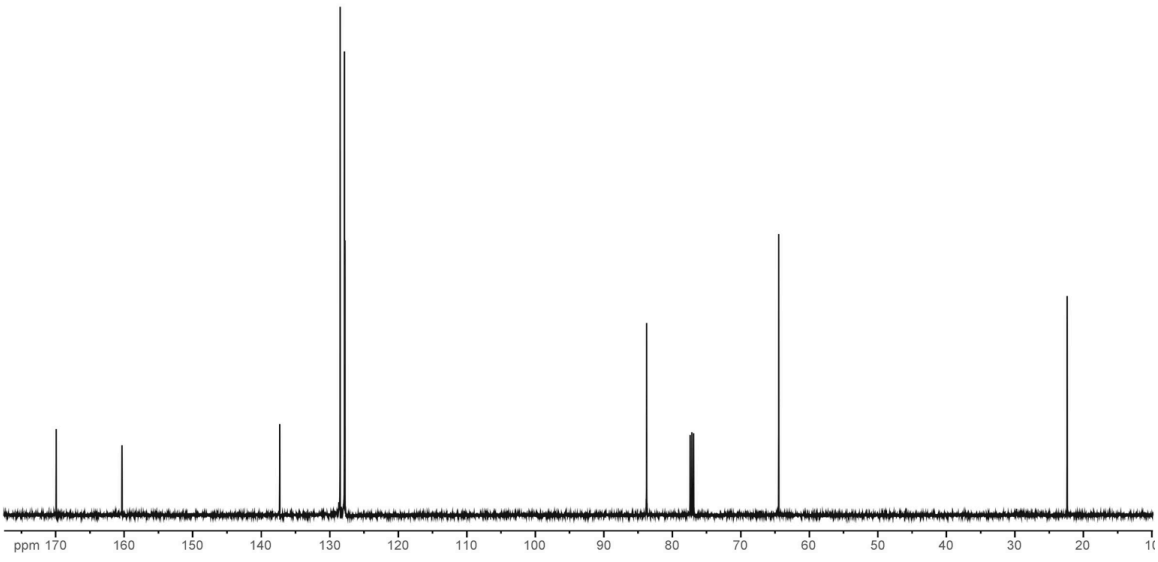


^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of amide **3.12** in $CDCl_3$

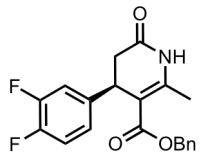


3.13



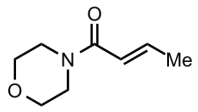


^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of enamine **3.13** in $CDCl_3$

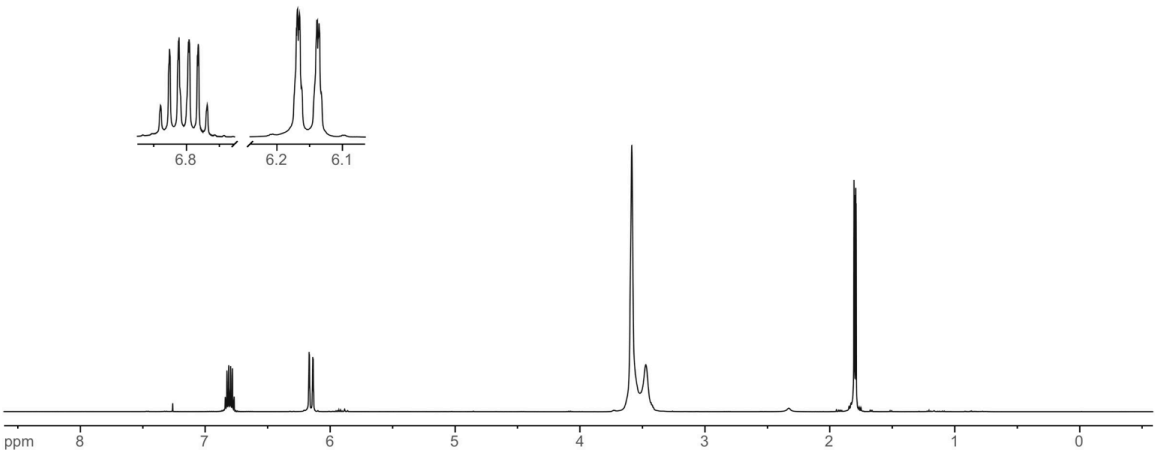


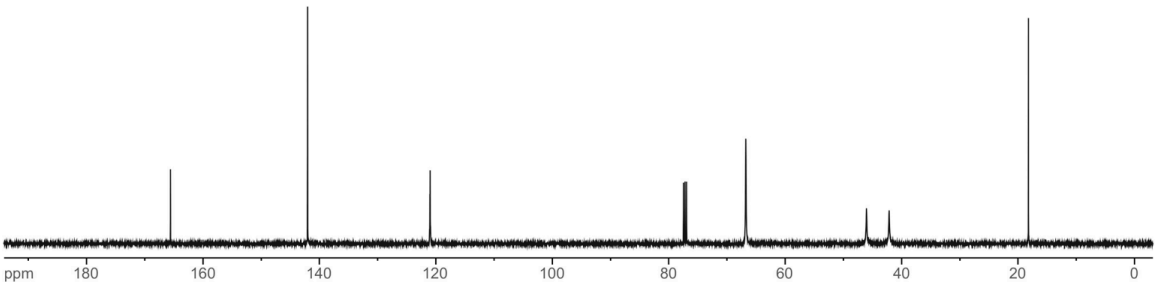
(–)-**3.14**

^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of δ-lactam (–)-**3.14** in $CDCl_3$

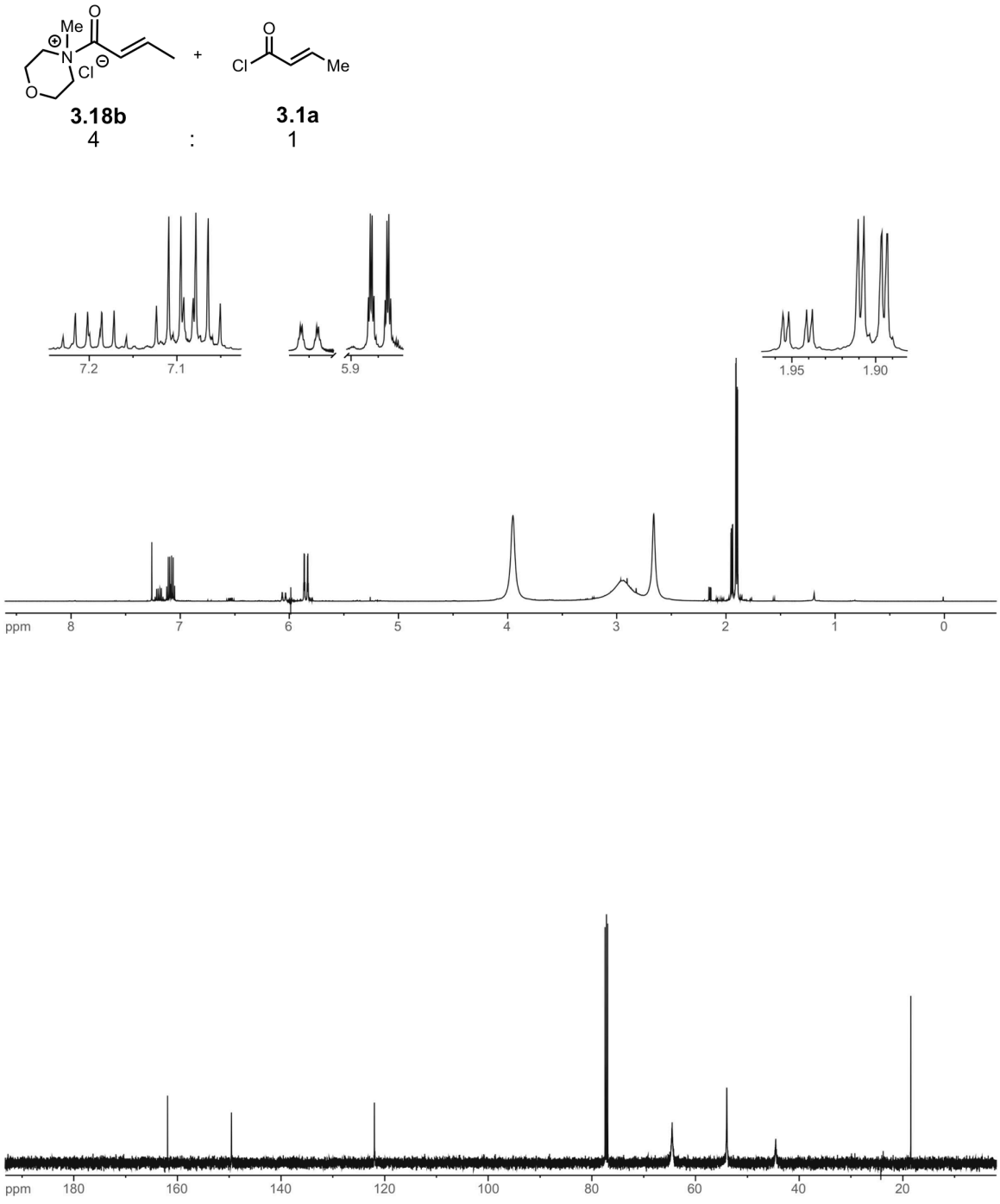


3.18a

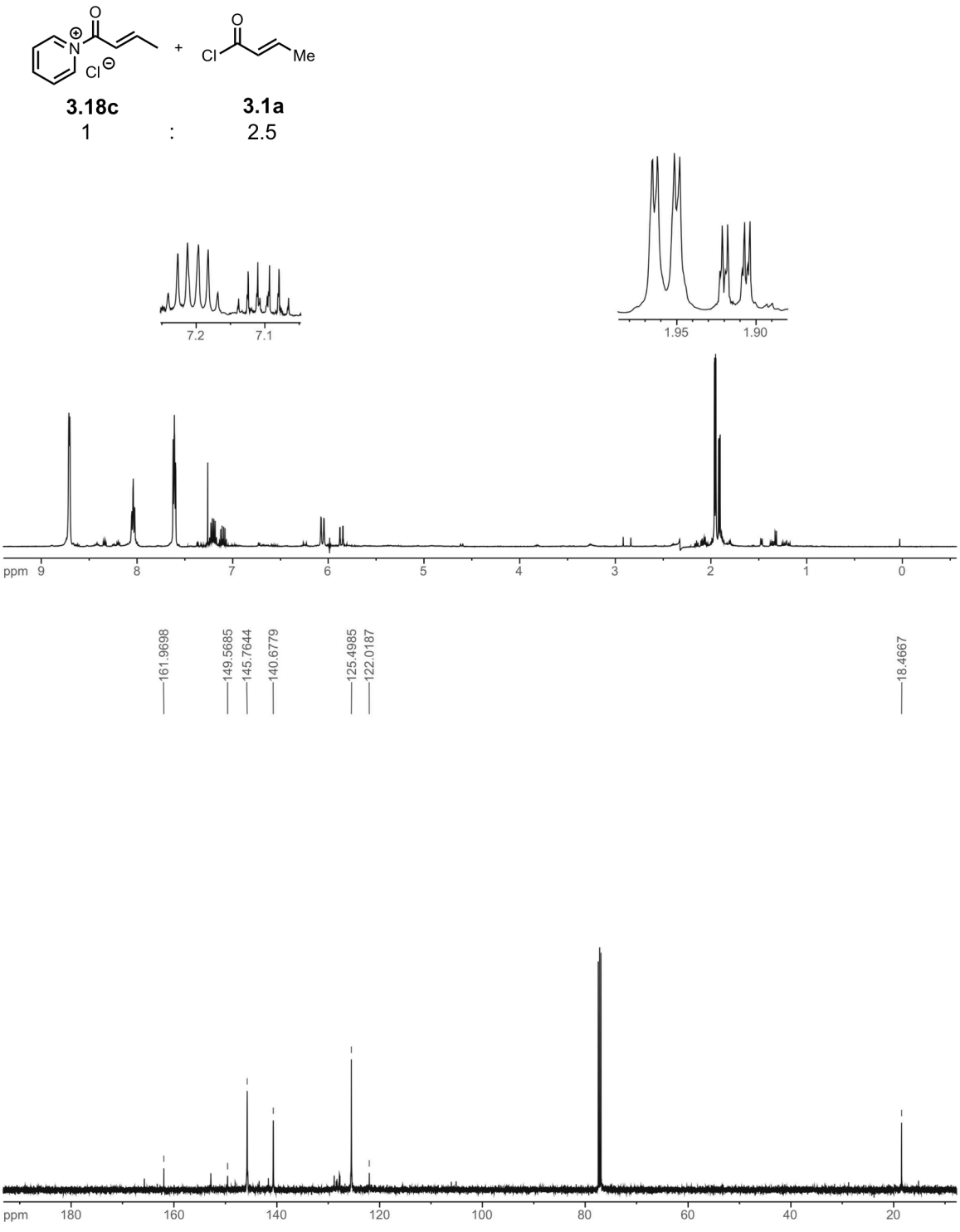




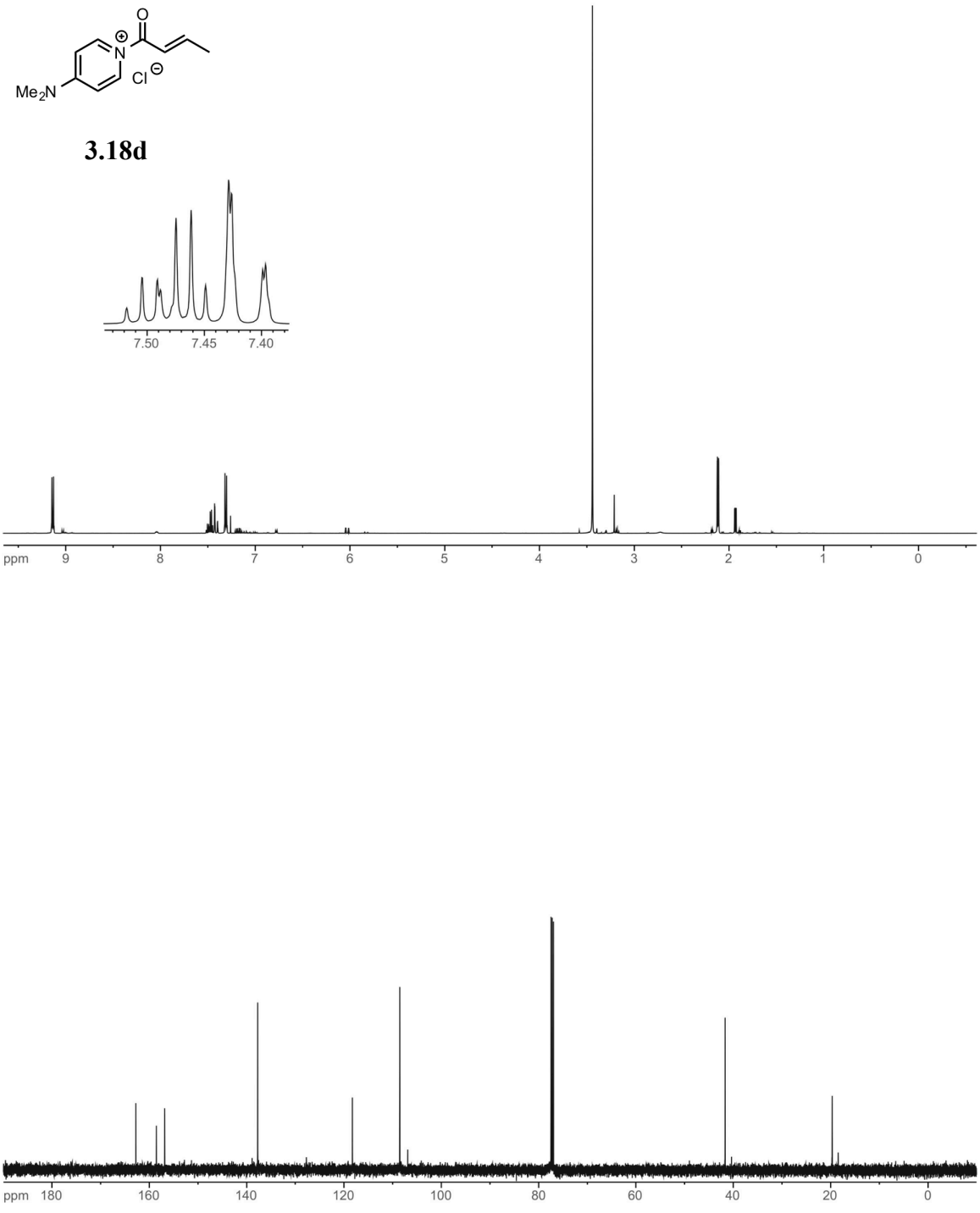
^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of amide **3.18a** in $CDCl_3$



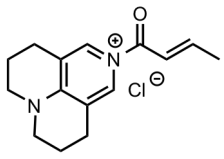
^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of acylammonium salt **3.18b** in $CDCl_3$



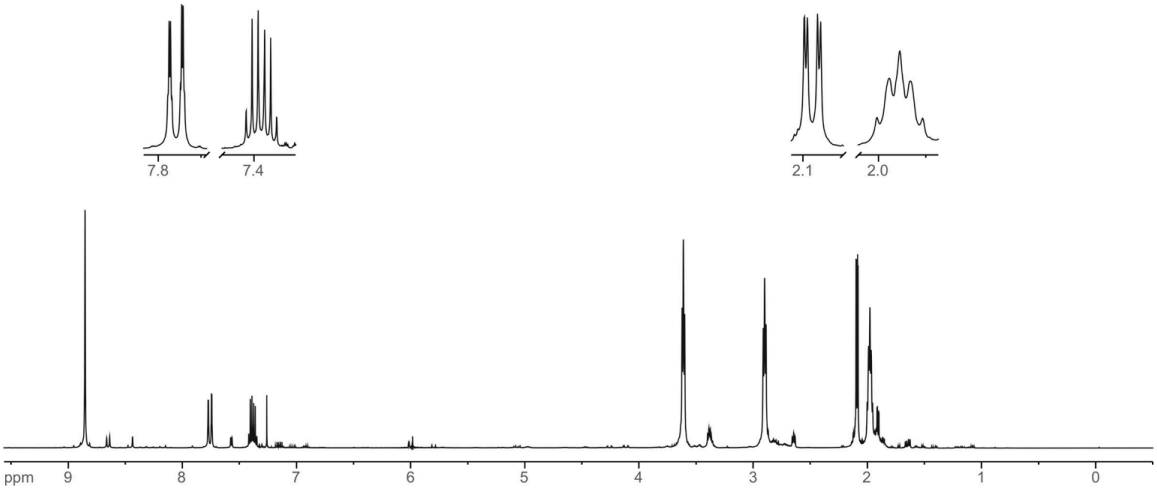
^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of acylammonium salt **3.18c** in $CDCl_3$

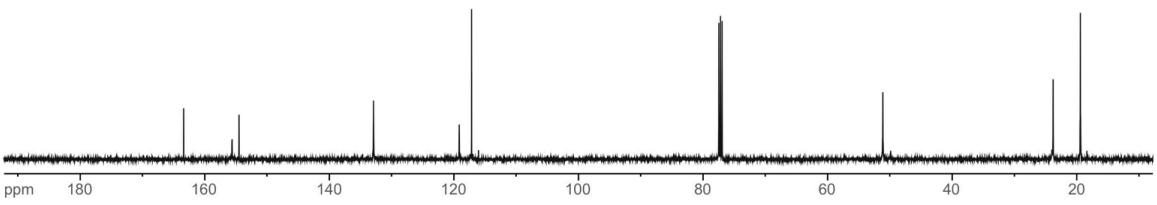


^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of acylammonium salt **3.18d** in $CDCl_3$

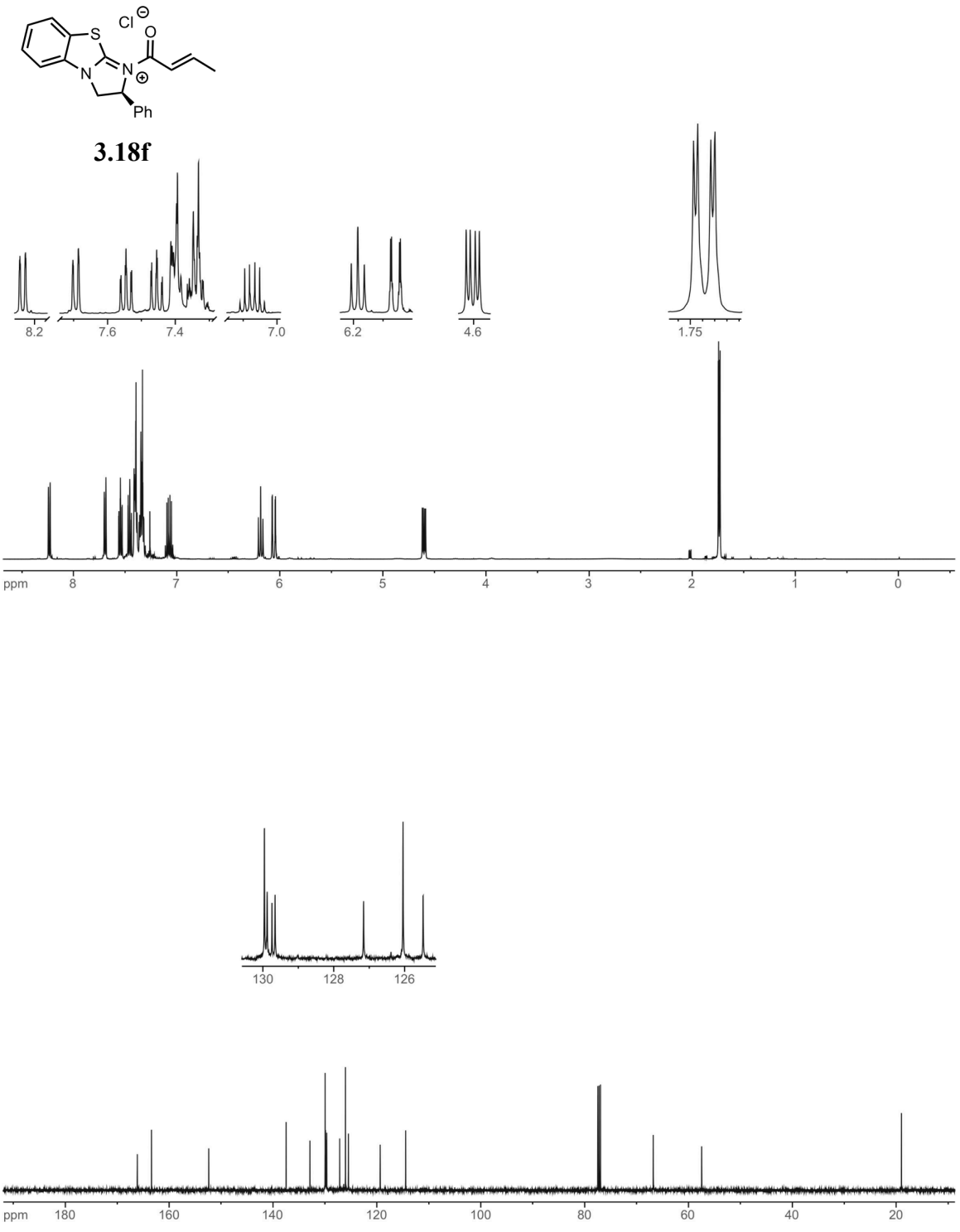


3.18e



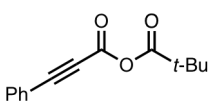


^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of acylammonium salt **3.18e** in $CDCl_3$

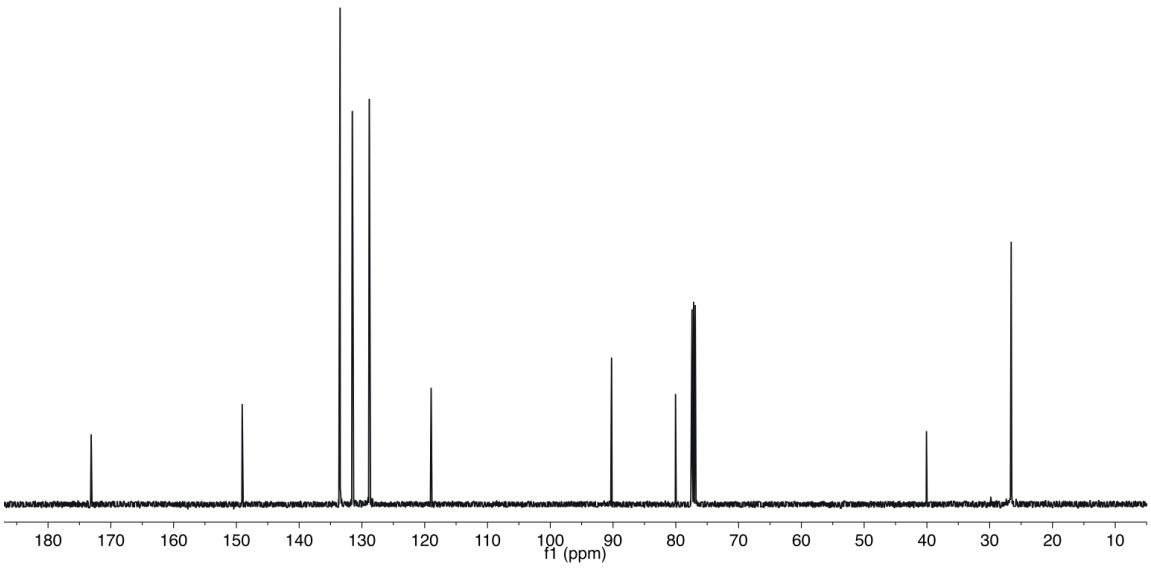


3.18f

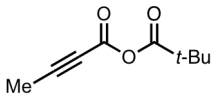
^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of acylammonium salt **3.18f** in $CDCl_3$



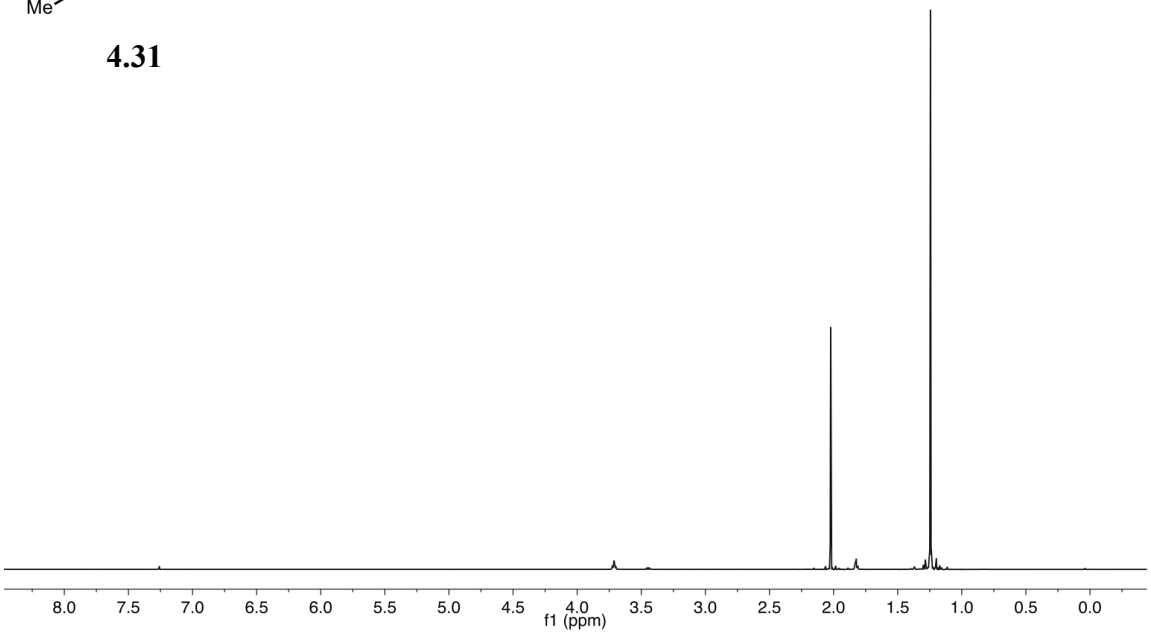
4.30

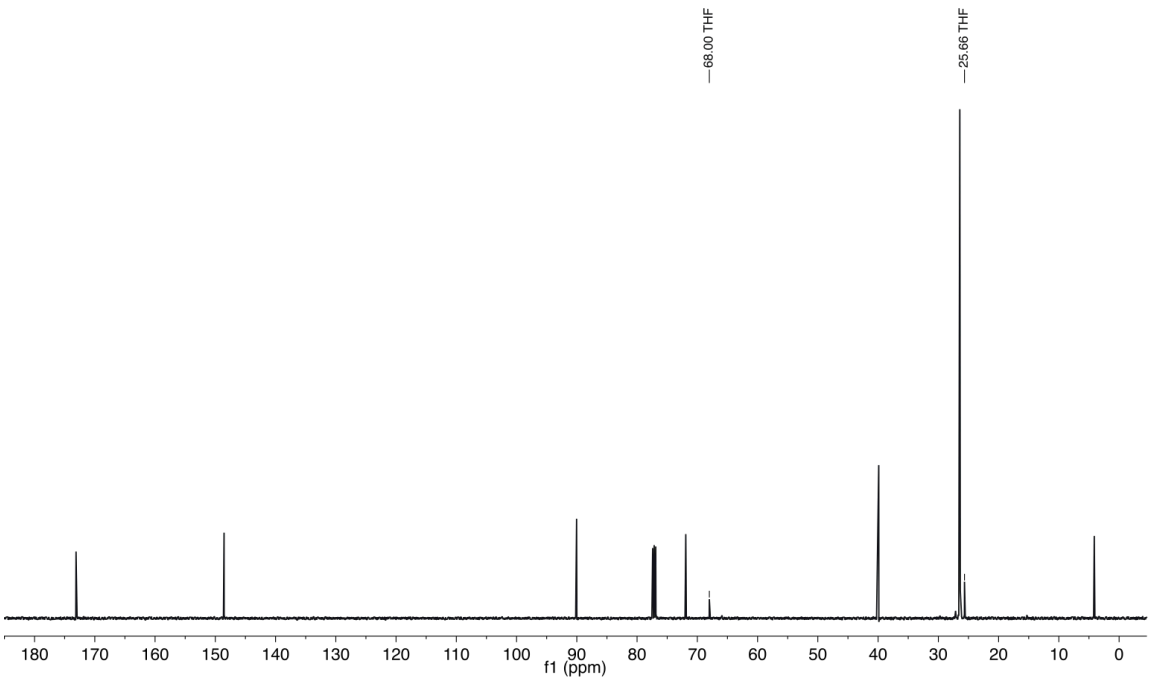


^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of anhydride **4.30** in $CDCl_3$

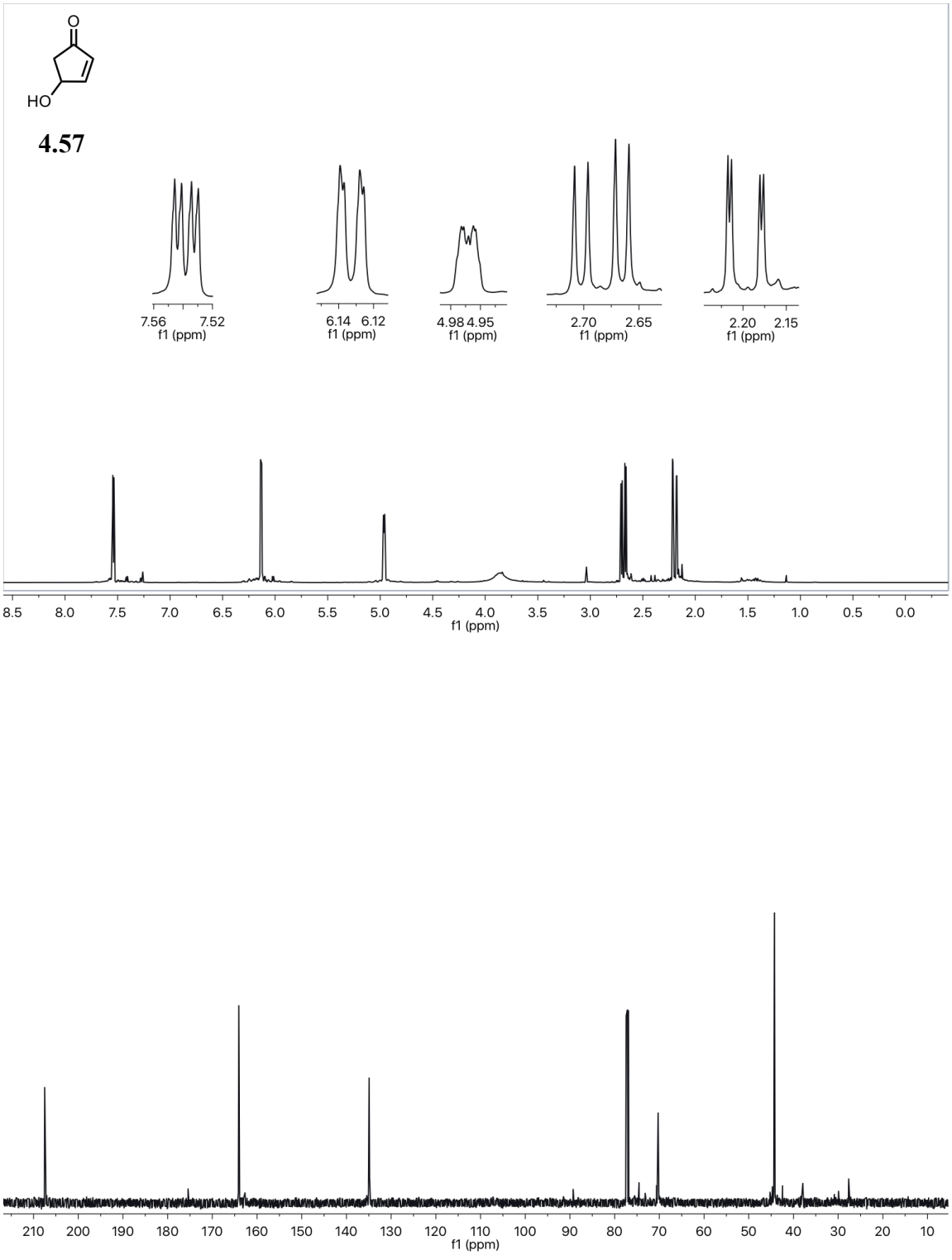


4.31

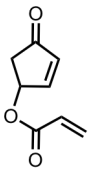




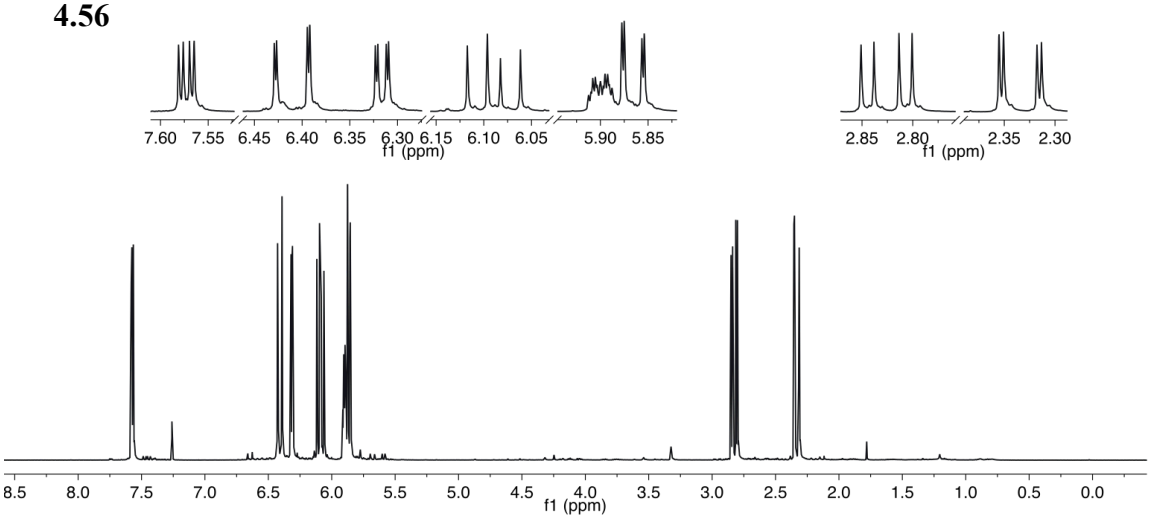
^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of anhydride **4.31** in $CDCl_3$

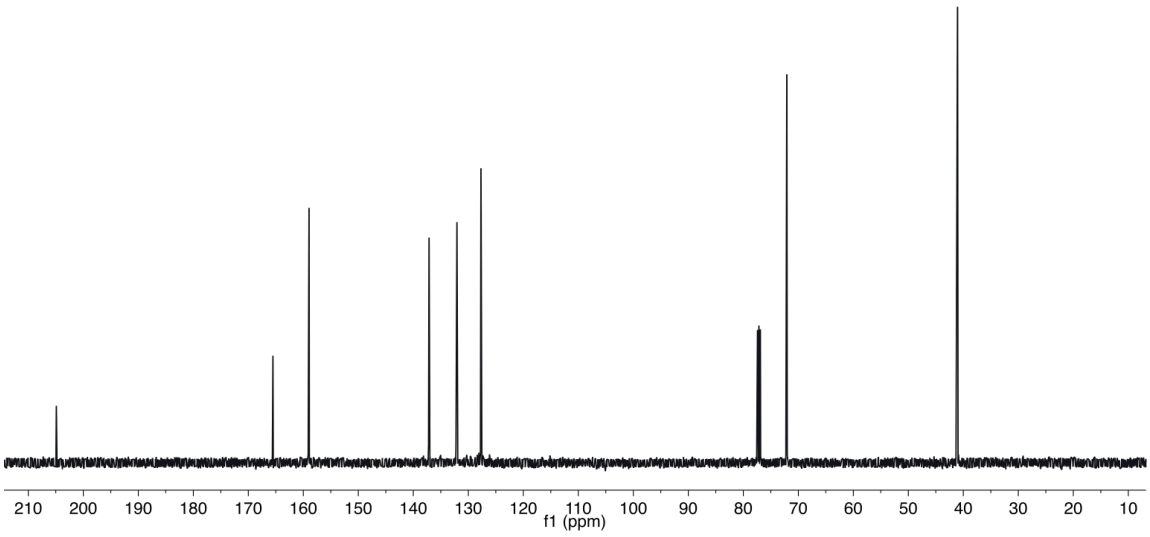


^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of **4.57** in $CDCl_3$

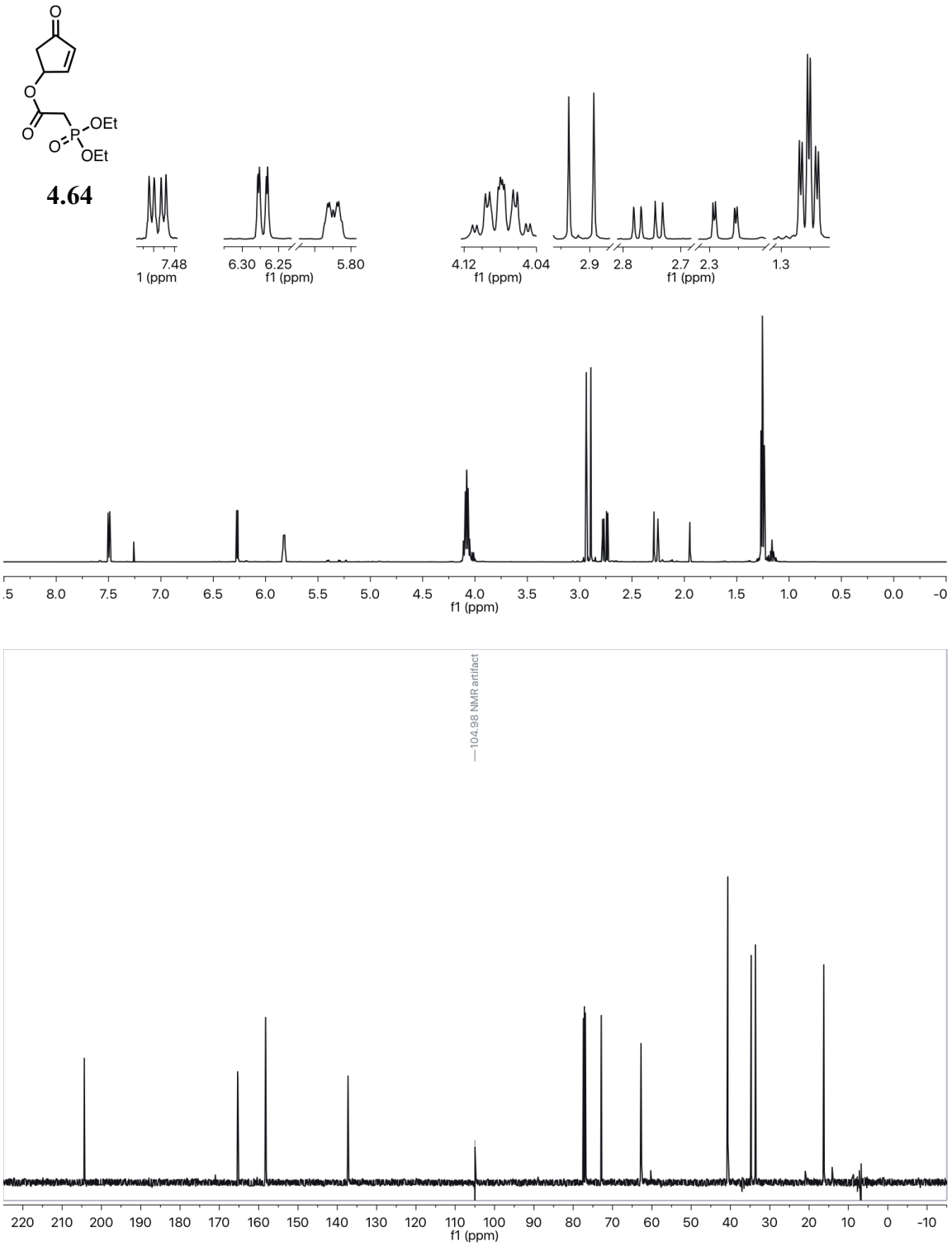


4.56

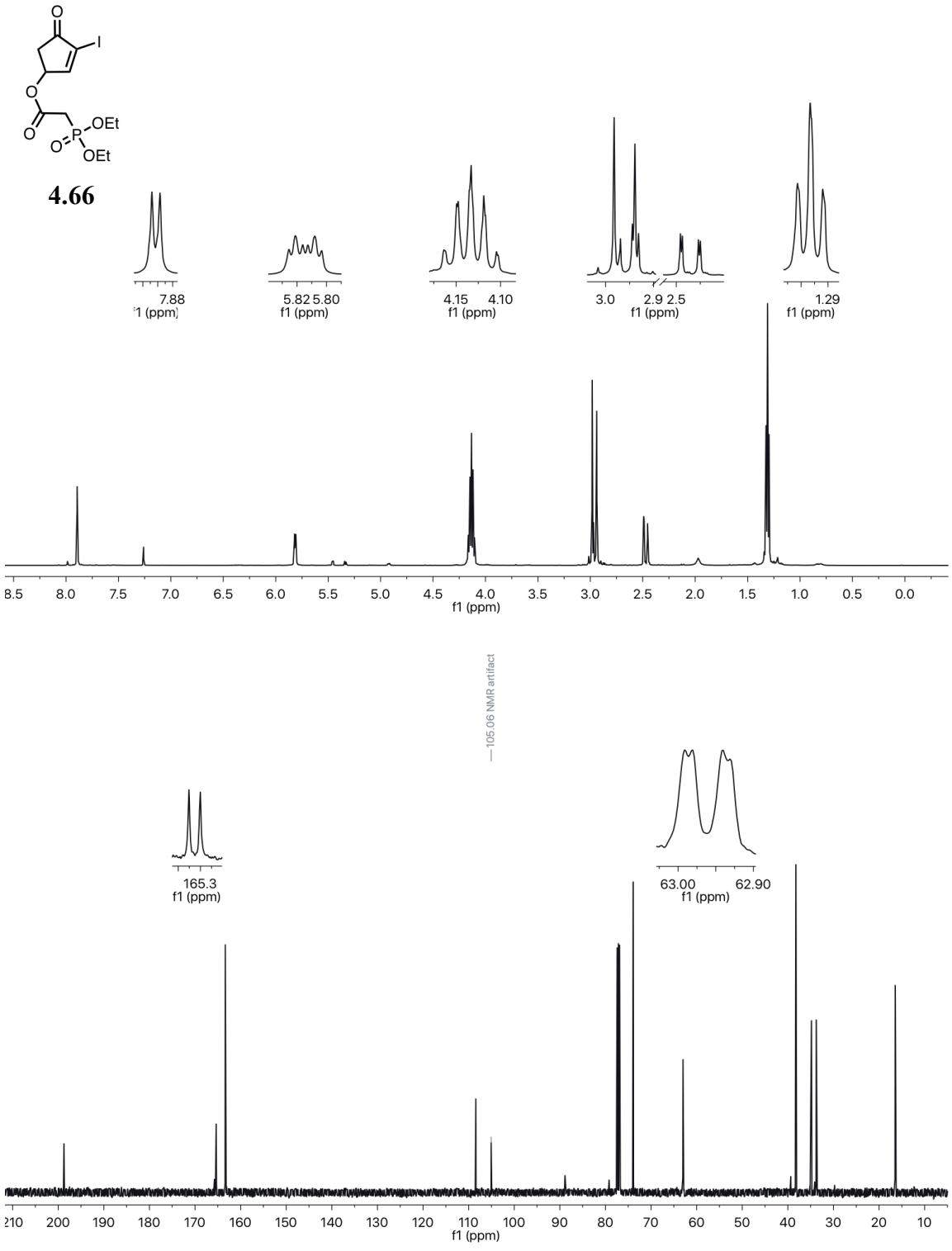




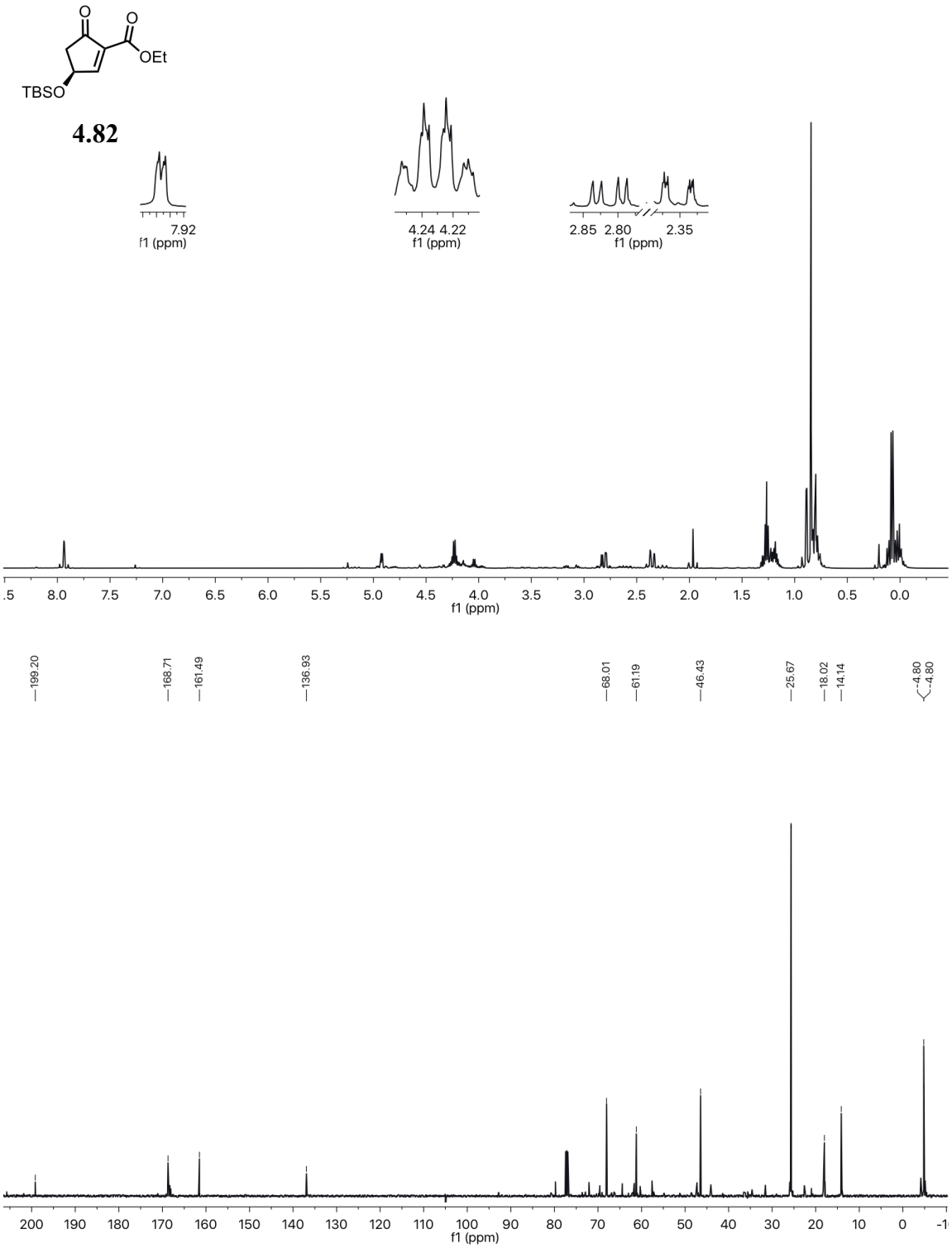
^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of **4.56** in $CDCl_3$



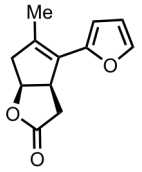
^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of **4.64** in $CDCl_3$



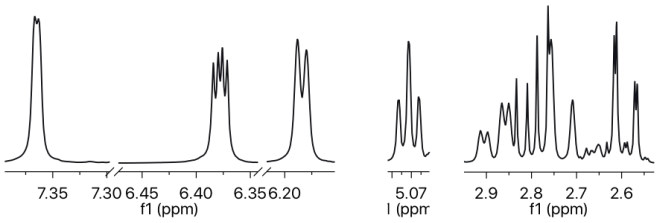
^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of **4.66** in $CDCl_3$

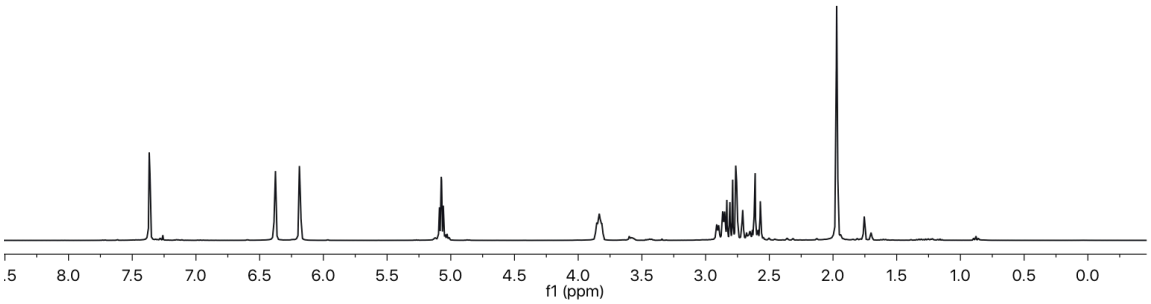


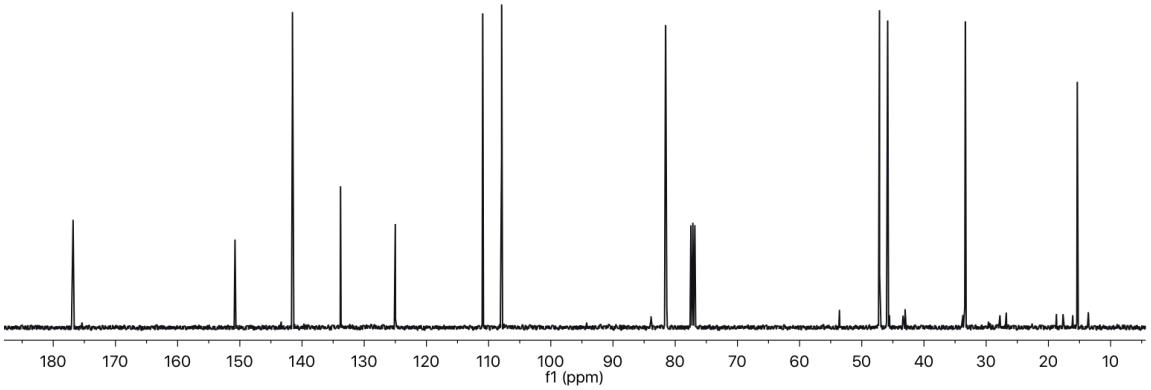
^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of **4.82** in $CDCl_3$



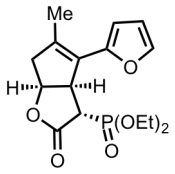
(±)-**4.101**



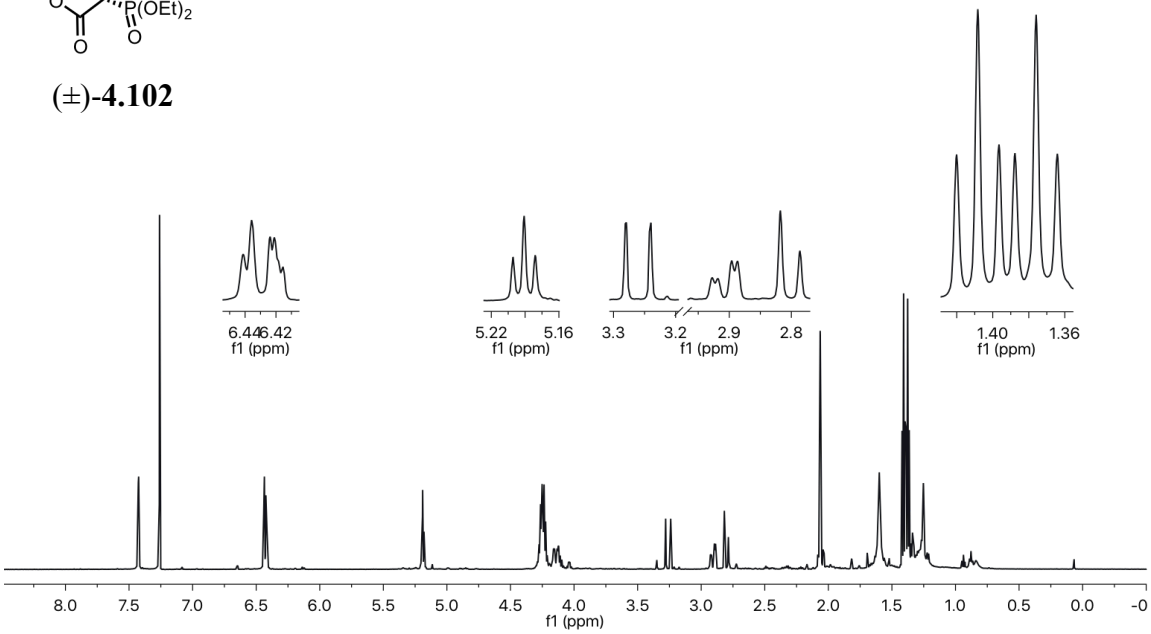


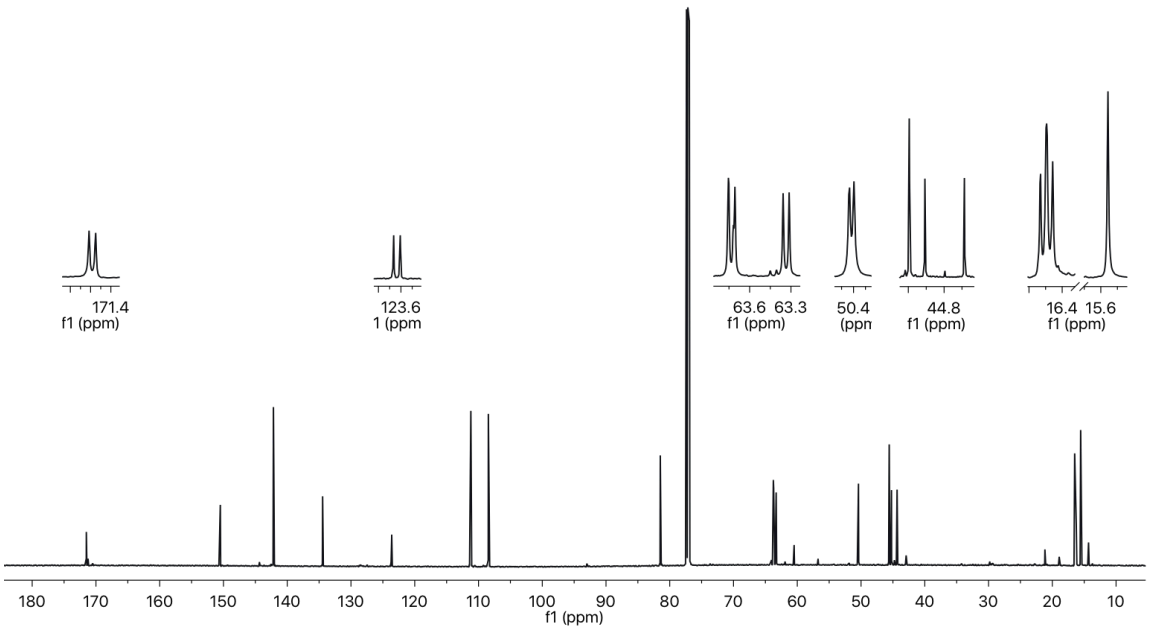


^{1}H (400 MHz) and ^{13}C NMR (100 MHz) spectra of **4.101** in $CDCl_3$

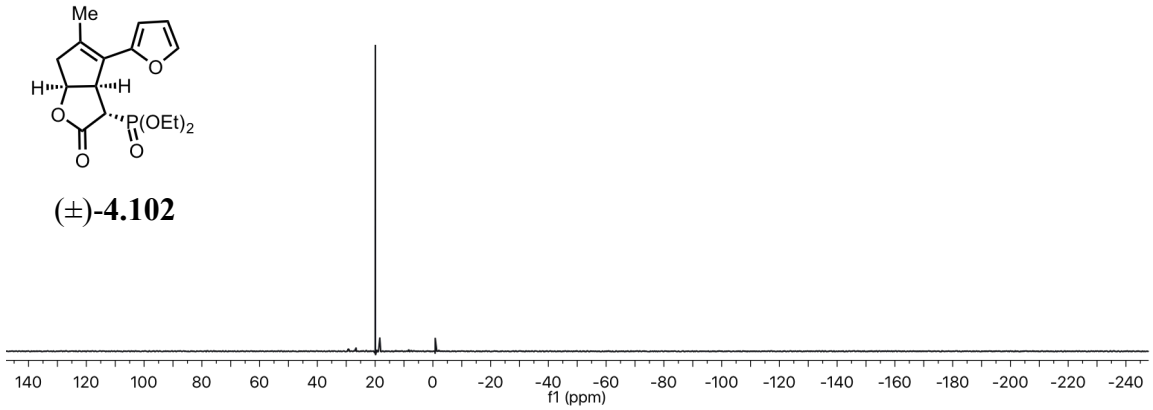


(±)-**4.102**

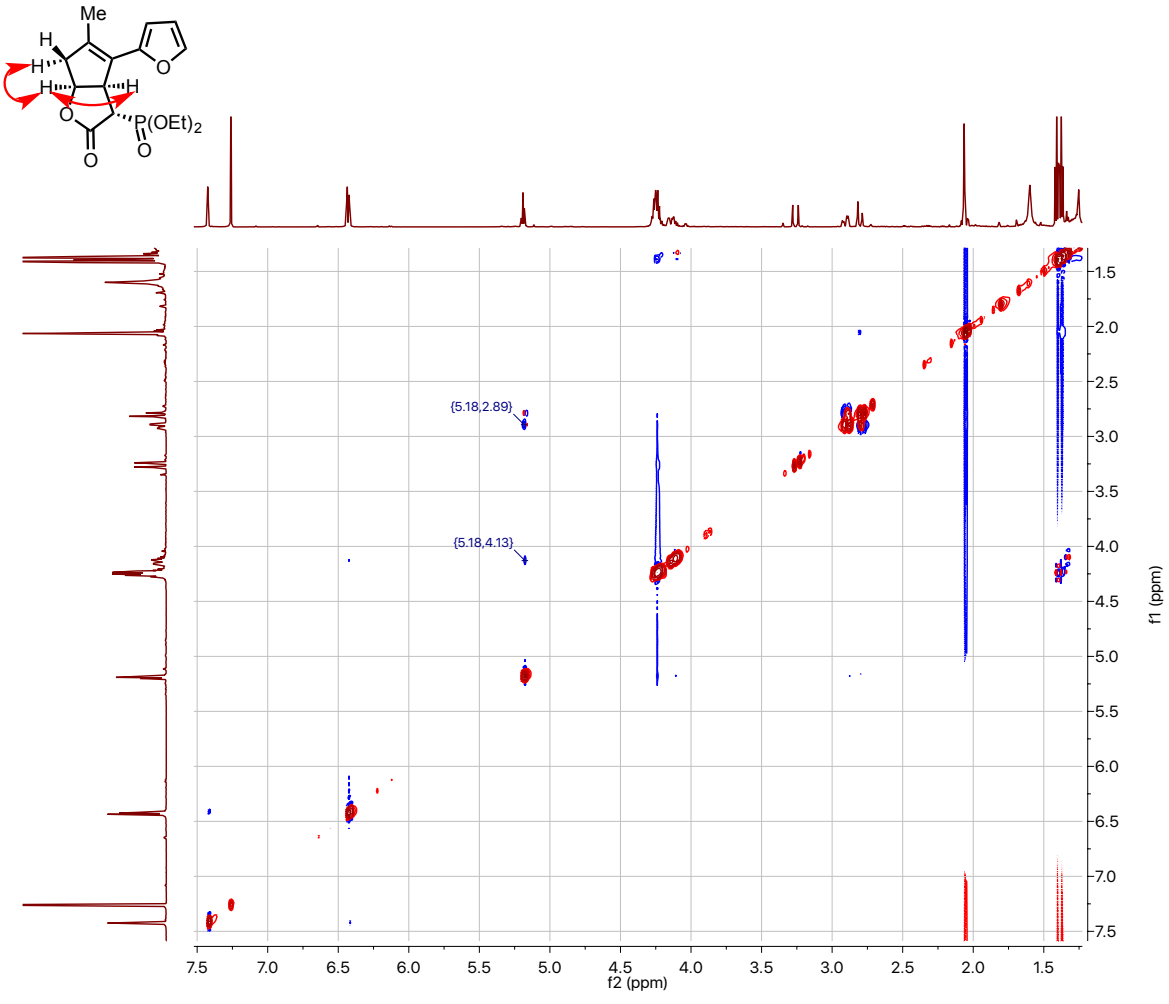




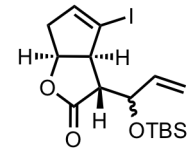
^{1}H (600 MHz) and ^{13}C NMR (150 MHz) spectra of **4.102** in $CDCl_3$



(±)-**4.102**

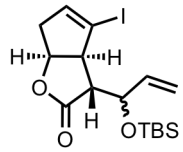


^{31}P (243 MHz) and NOESY NMR (600 MHz) spectra of **4.102** in $CDCl_3$



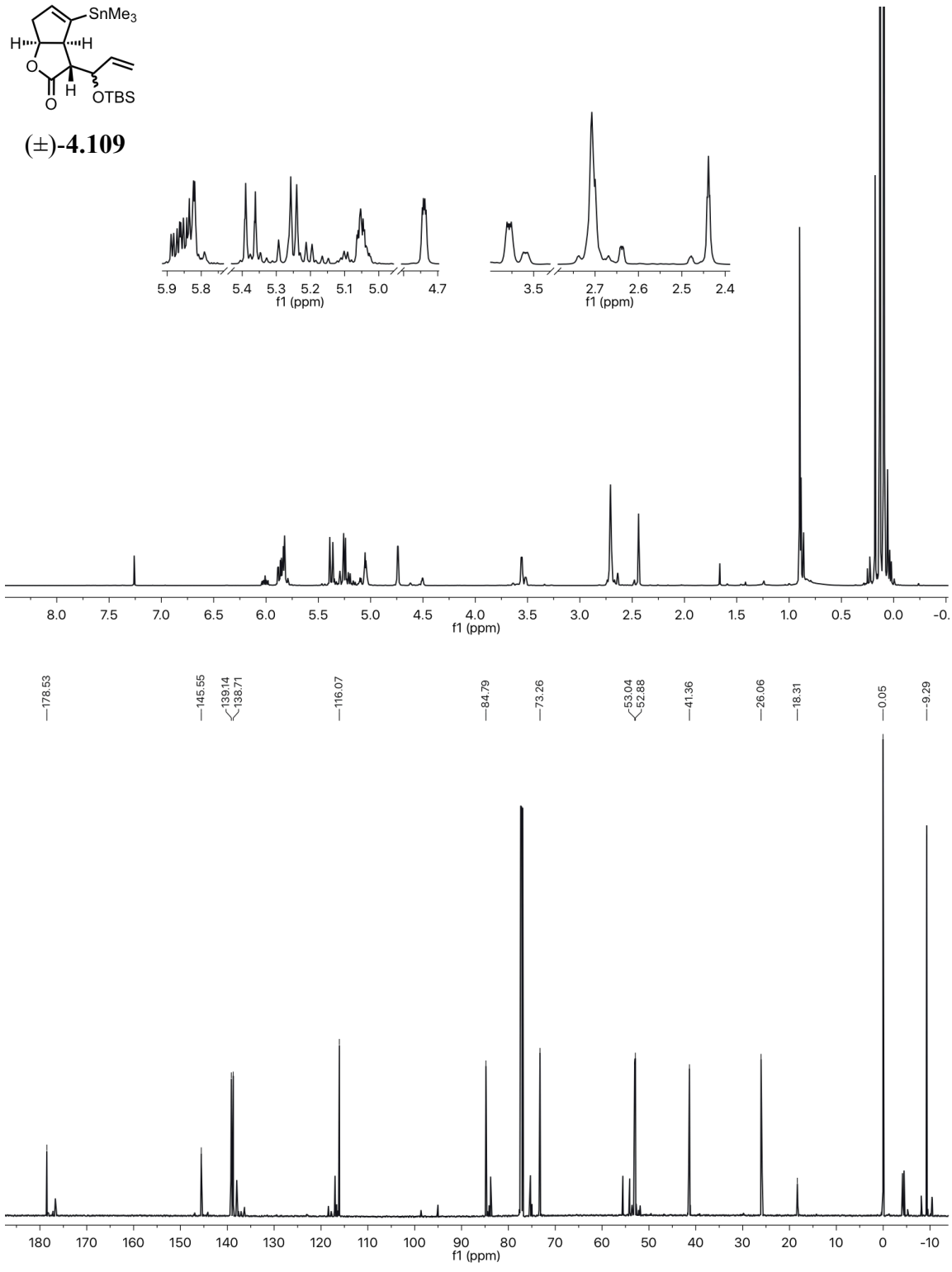
(±)-**4.108**
Diastereomer A

^{1}H (400 MHz) and ^{13}C NMR (100 MHz) spectra of **4.108**, diastereomer A in $CDCl_3$



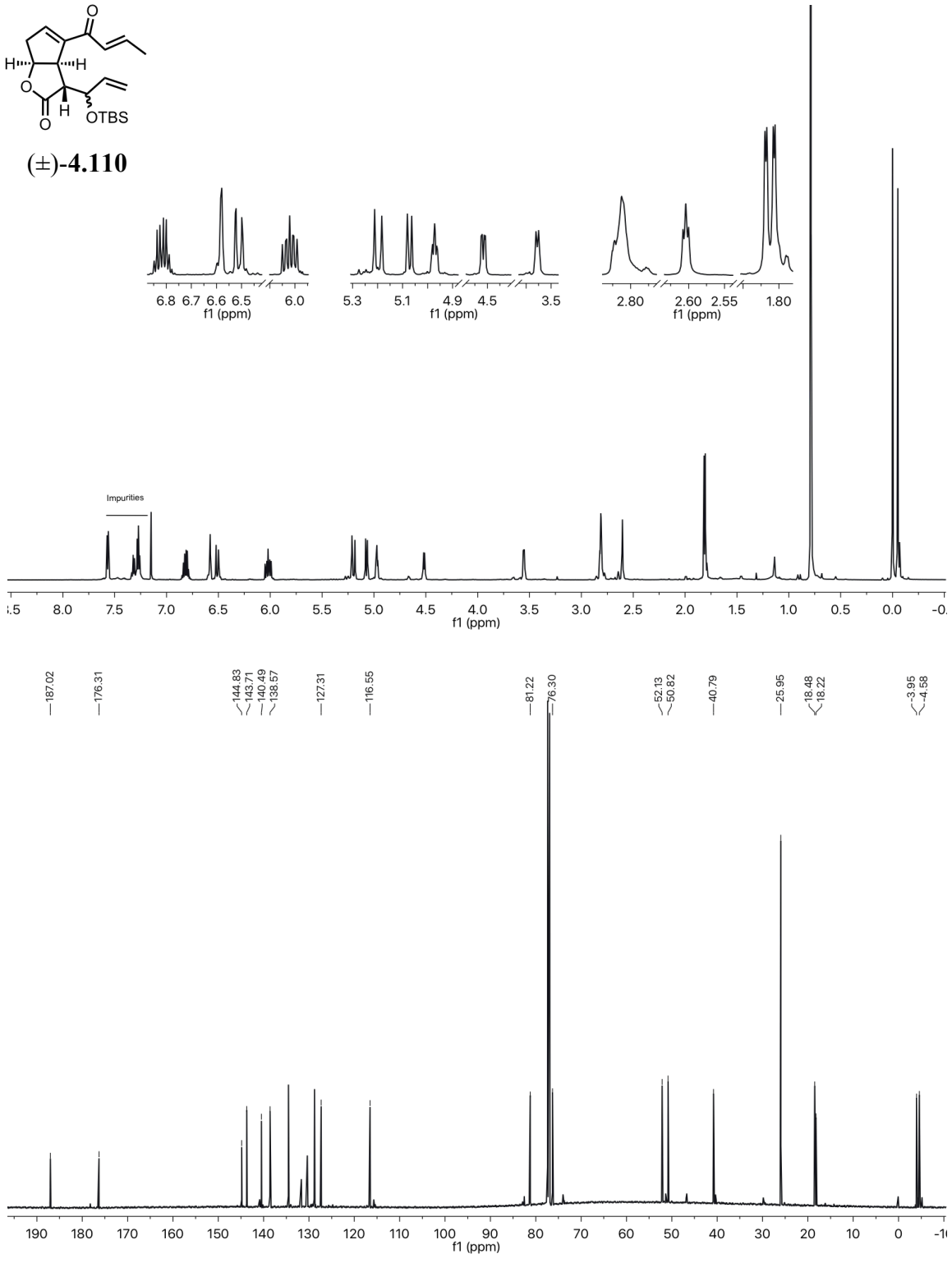
(±)-**4.108**
Diastereomer B

^{1}H (400 MHz) and ^{13}C NMR (100 MHz) spectra of **4.108**, diastereomer B in $CDCl_3$



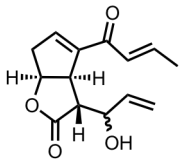
(±)-**4.109**

^{1}H (600 MHz) and ^{13}C NMR (150 MHz) spectra of **4.109** in $CDCl_3$

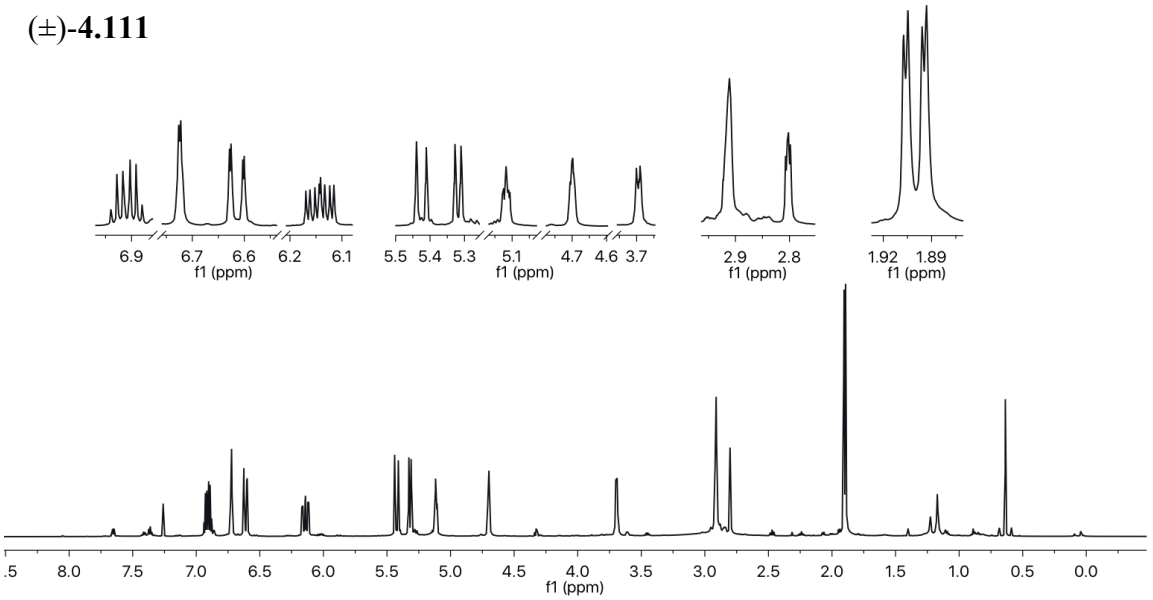


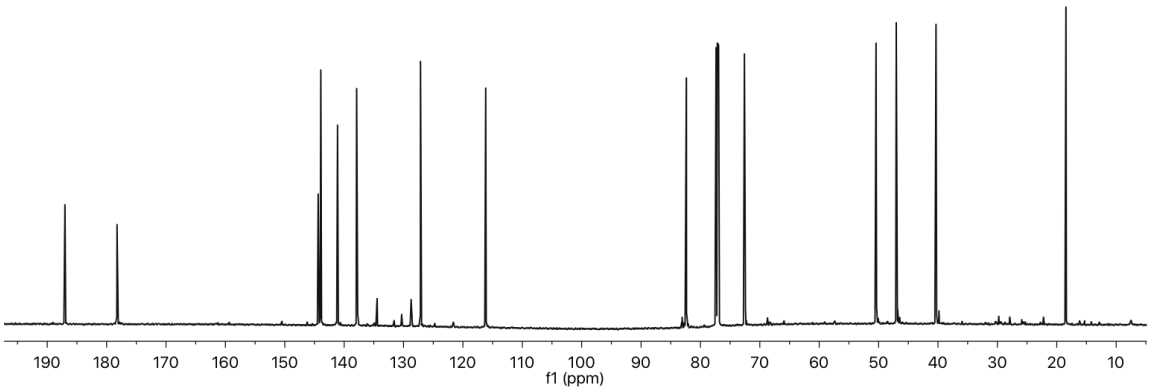
(±)-**4.110**

^{1}H (600 MHz) and ^{13}C NMR (150 MHz) spectra of **4.110** in $CDCl_3$

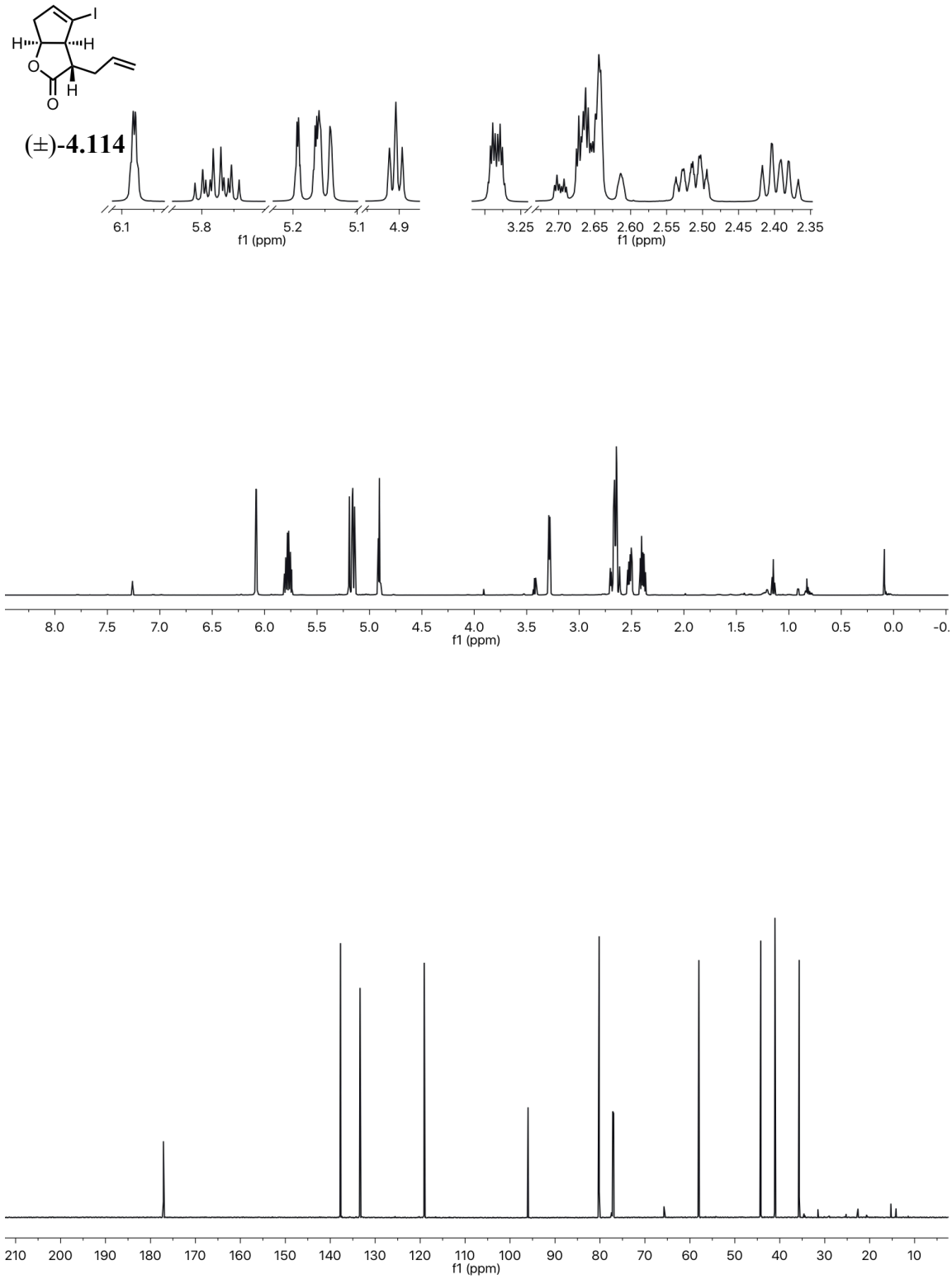


(±)-**4.111**

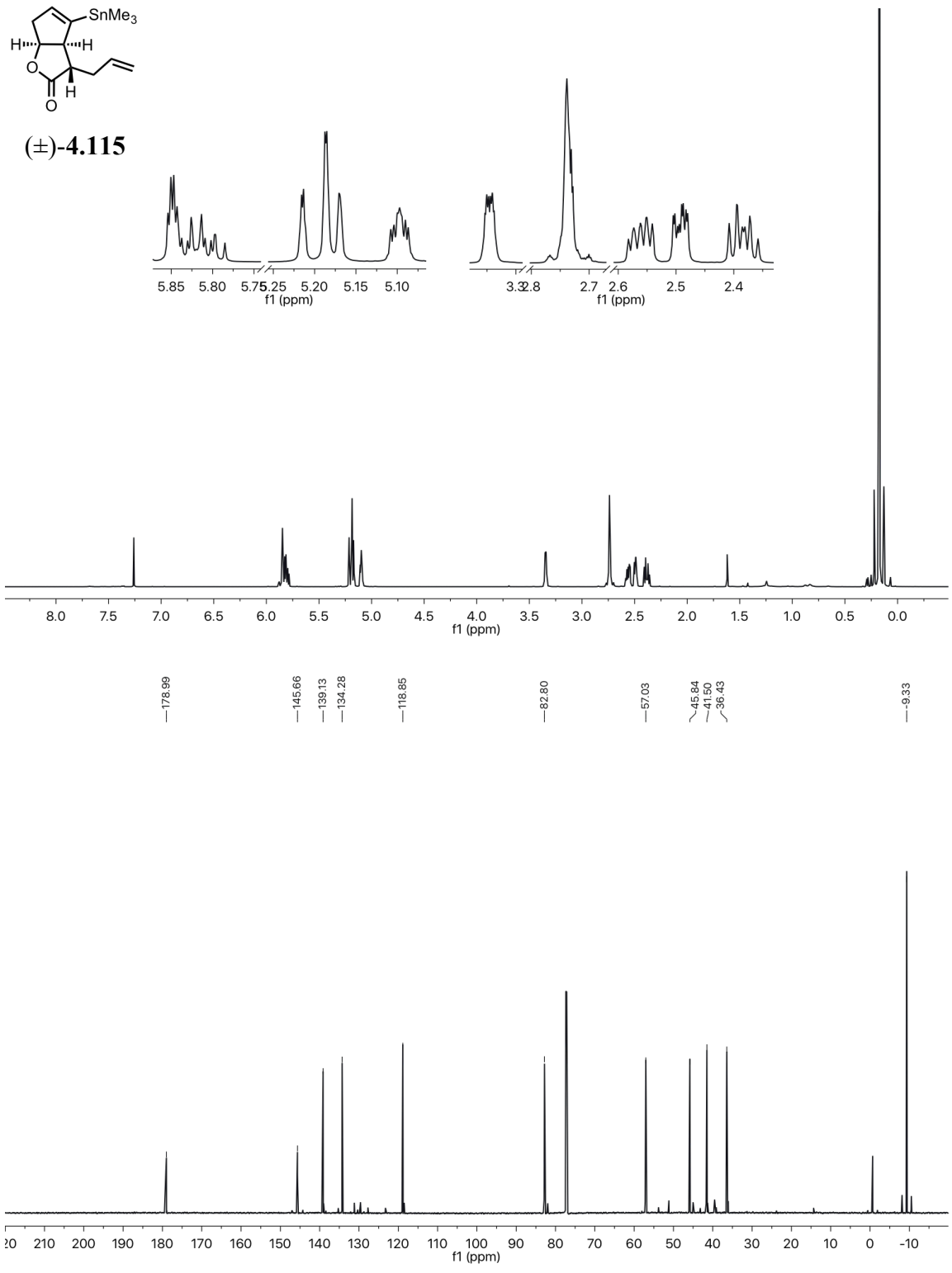




^{1}H (600 MHz) and ^{13}C NMR (150 MHz) spectra of **4.111** in $CDCl_3$



^{1}H (600 MHz) and ^{13}C NMR (150 MHz) spectra of **4.114** in $CDCl_3$



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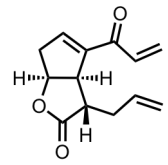
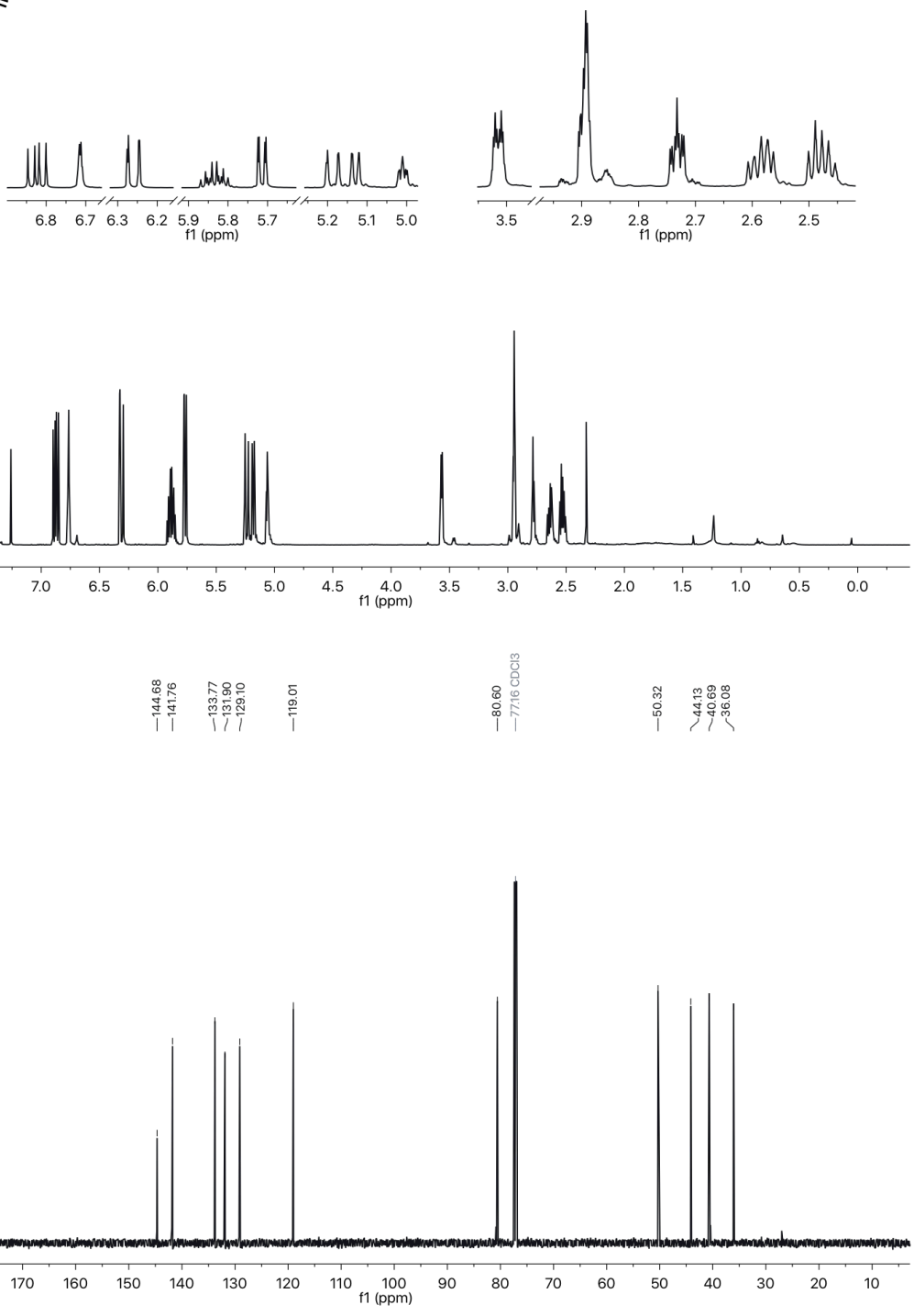


(±)-**4.116**



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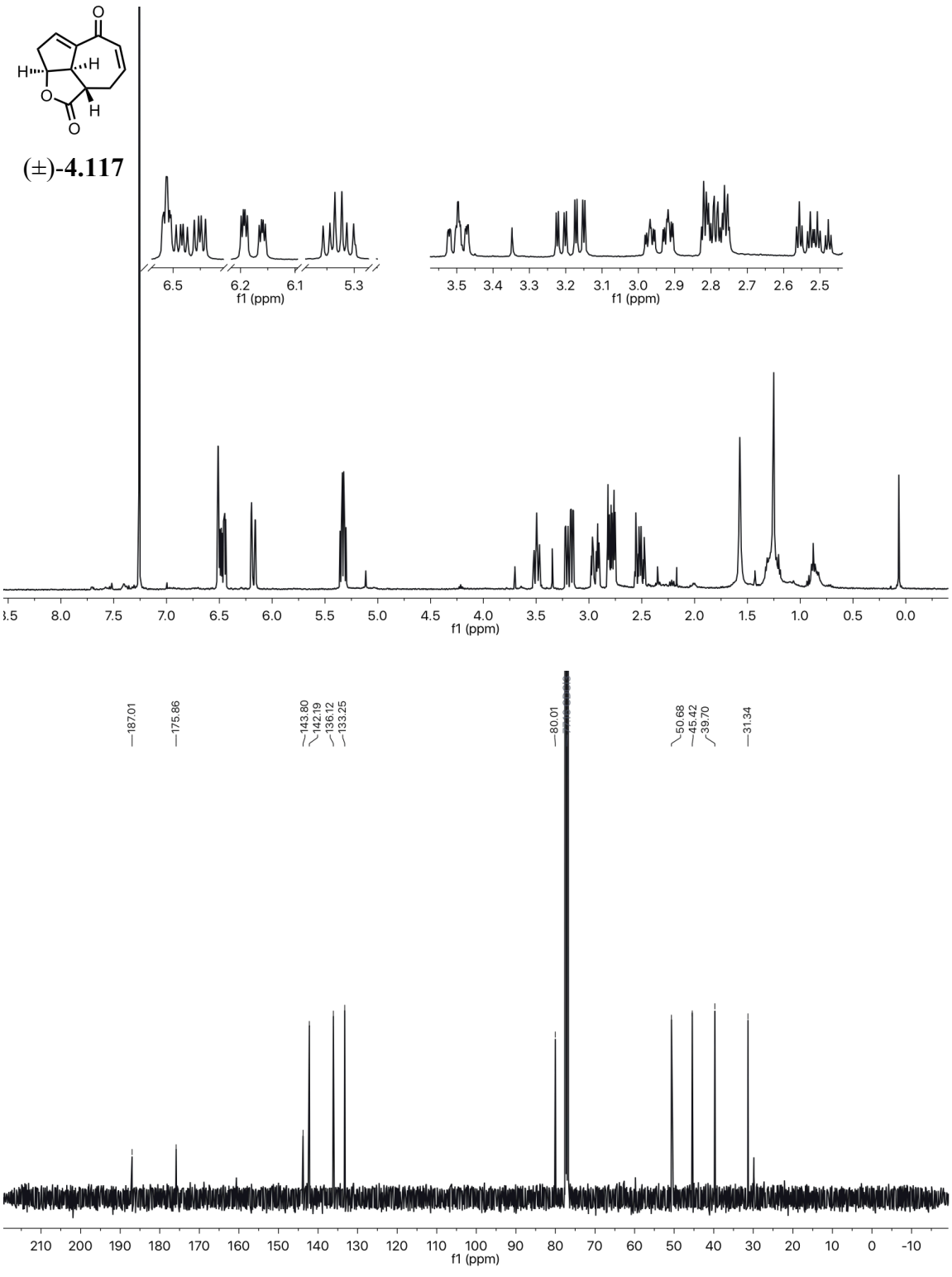

^{1}H (400 MHz) and ^{13}C NMR (100 MHz) spectra of **4.117** in $CDCl_3$

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