ABSTRACT

Stereoselective Synthesis of *N*-Heterocycles Enabled by Tertiary Amine Catalysis and Synthetic Efforts Toward C-Ring Synthons of Rameswaralide

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Extensions of the nucleophile catalyzed aldol lactonization (NCAL) of keto acids, previously developed for the synthesis of carbocycle-fused β-lactones, are described to access a series of *N*-heterocycle-fused β-lactones. Pyrrolidine- and piperidine-fused tricyclic β-lactones were successfully prepared in moderate to good yields and with high diastereoselectivity. A catalytic, enantioselective process was developed for the synthesis of bicyclic *N*-heterocycle-fused β-lactones in high enantiomeric purity. The utility of these adducts was explored briefly through deprotection of the *N*-tosyl group and functionalization of the β-lactones.

The utility of chiral α,β unsaturated acylammonium salts, derived from carbonic anhydrides and chiral isothiourea catalysts, was extended to aza-Michael initiated organocascades, delivering pyrazolidinones and 1,5-benzodiazepinones.

Finally, efforts toward the synthesis of C ring synthons useful for the total synthesis of rameswaralide were pursued. Key strategies involved a C-H oxygenation and γ-alkylation of (*R*)-carvone leading to serviceable intermediates for a total synthesis of this natural product.

Stereoselective Synthesis of *N*-Heterocycles Enabled by Tertiary Amine Catalysis and Synthetic Efforts Toward C-Ring Synthons of Rameswaralide

by

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Approved by the Thesis Committee

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CHAPTER ONE

Introduction

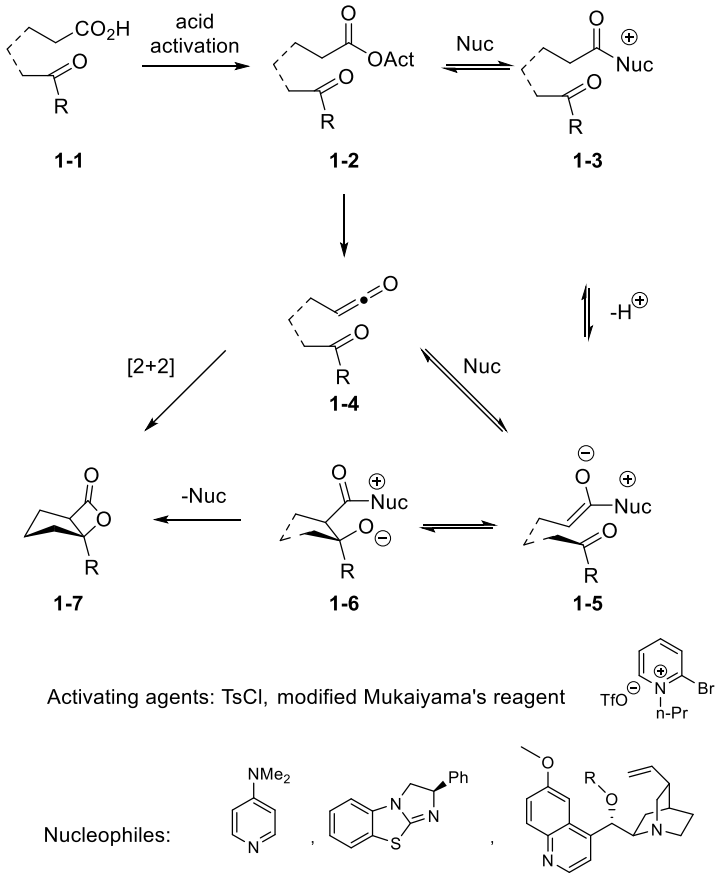
Organocatalysis

Organocatalysis is a widely studied and rapidly growing field over the past two decades. The advantages of organocatalysis such as mild conditions, simple operational requirements and recyclable catalysts are attractive to chemists. This has led to the development of numerous organocatalysts-enabled reaction modes that show excellent reactivity and selectivity.[1] This chapter will give an overview of the development of nucleophile catalyzed aldol lactonization (NCAL) organocascade reactions.

Nucleophile Catalyzed (Promoted) Aldol Lactonization (NCAL)

Nucleophile catalyzed aldol lactonization (NCAL) is an efficient method to deliver β-lactone moieties. The proposed mechanism of NCAL (Scheme 1-1) involves the activation of carboxylic acid **1-1** by an activating agent such as *p*-toluenesulfonyl chloride and modified Mukaiyama reagents, leading to the formation of a mixed anhydride or reactive ester **1-2**, which may either deliver an acylammonium intermediate **1-3** through acylation of an organonucleophile or a ketene **1-4** through elimination in the presence of the base. Ammonium enolate **1-5** is formed through the deprotonation of **1-3** which then undergoes an aldol-lactonization process to afford β-lactones, while ketene **1-4** can either deliver β-lactone **1-7** *via* [2+2] cycloaddition or acylammonium enolate **1-5** by organonucleophile attack onto the carbonyl carbon. The pathway involving ketene **1-4** is

less prevalent than the NCAL pathway due to the extremely low concentration of ketene at room temperature.[1a]

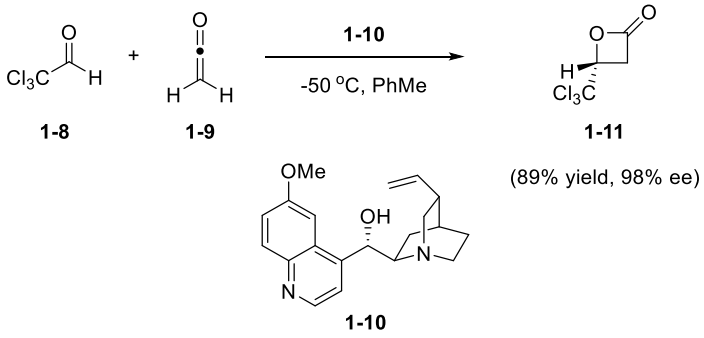


Scheme 1-1 Proposed mechanism for NCAL.

Intermolecular NCAL

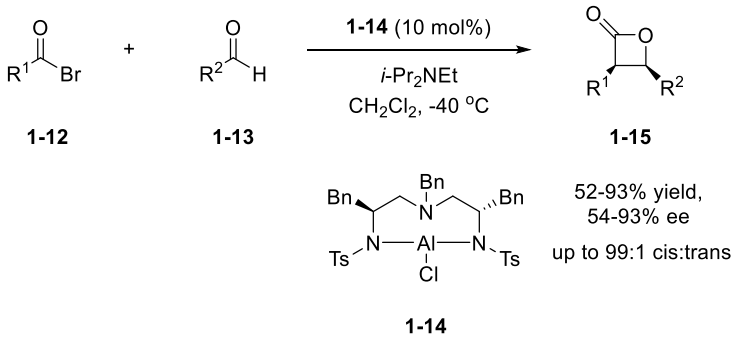
Dr. Wynberg and his co-workers explored a net [2+2] by reacting ketene **1-9** with aldehyde **1-8** which is catalyzed by **1-10** (Scheme 1-2).[2] An excellent yield of β-lactone **1-11** in enantiometric excess was produced. An ammonium enolate followed by an aldol-lactonization was thought to be involved in this transformation to give β-lactone.[3] Other carbonyl compounds were investigated for this methodology, however only moderate to good yields were obtained.[4] Later, his method was applied by many research groups for

the assembly of β-lactones.[5] Even though Wynberg's methodology required ketene generators such as a-halo acid chlorides and only a limited aldehyde and ketone substrate scope, it was the earliest example of an NCAL organocascade, which provided the basis for later, more comprehensive studies.



Scheme 1-2 Wynberg net [2+2] *via* nucleophilic catalysis.

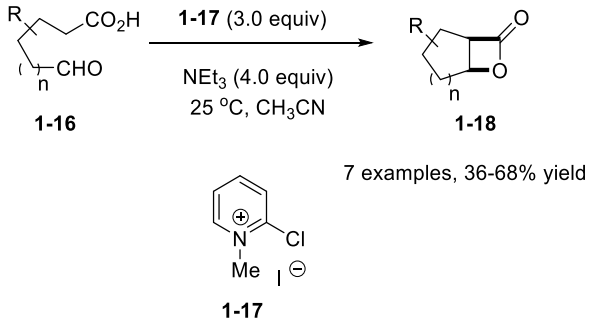
In 1999, Dr. Nelson developed a method involving *in situ* generated ketene from acyl halides. These, catalyzed by Lewis acid **1-14**, react with a variety of aldehydes to yield β-lactones (Scheme 1-3).[6] Both the substrate scope of the acyl halides and aldehydes were developed, and most of the examples provided excellent yield, ee, and de.[7] Dr. Nelson's work using acyl halides as the predominant generator of ketenes became the inspiration for later intramolecular NCAL work.



Scheme 1-3 Nelson acyl halide-aldehyde cyclocondensation.

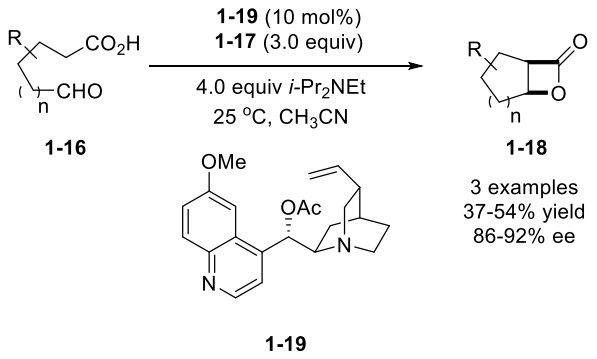
Intramolecular NCAL

Aldehyde-acid substrates for NCAL. Inspired by Dr. Wynberg and Dr. Nelson's work, the first intramolecular NCAL using aldehyde acid to form carbocycle-fused β-lactones was established by Dr. Romo and his co-workers (Scheme 1-4).[8] This racemic synthesis of bicyclic β-lactones was achieved by employing the Mukaiyama reagent as an activating agent and triethylamine as a nucleophile. The yields of bicyclic β-lactone were moderate to good with 7 examples. In this study, dropwise addition of aldehyde acid was found to be important to obtain high yields of NCAL product.



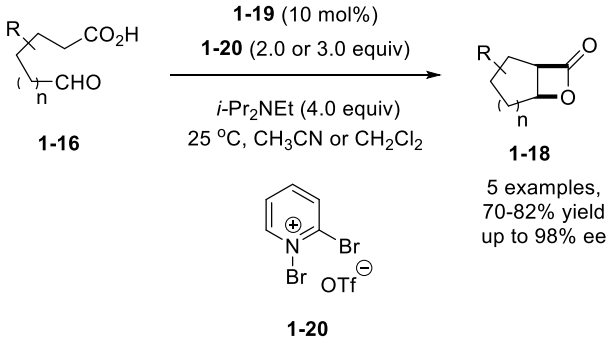
Scheme 1-4 Racemic NCAL of aldehyde acids.

In the same study, enantioselective NCAL, empolying a catalytic amount of *O*-Ac Quinidine as nucleophile, was also explored (Scheme 1-5). This initial study of only 3 examples, showed yields of 37% to 54% and 86% to 92% ee, which remained to be improved in their following work. The resultant high level of enantiocontrol suggests that β-lactone formation was being enabled by an NCAL process rather than a [2+2] mechanism.



Scheme 1-5 Enantioselective catalytic NCAL of aldehyde acids.

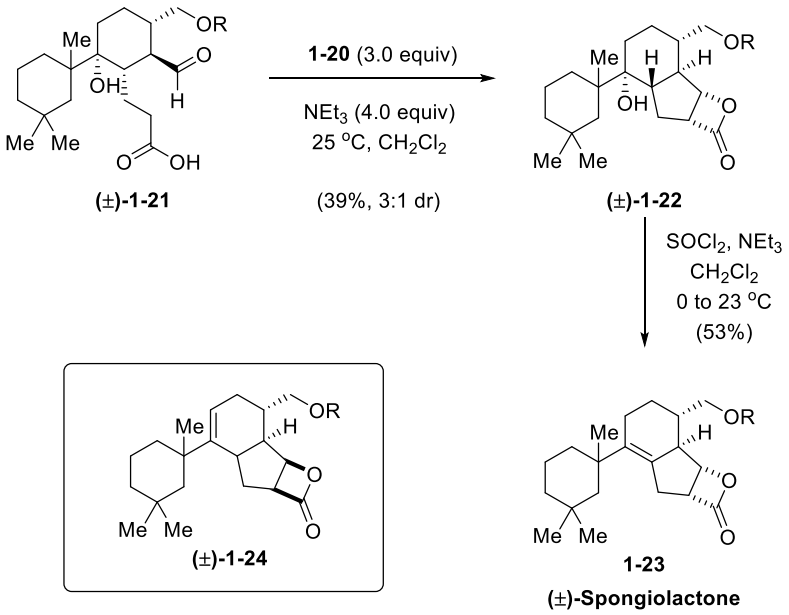
An improved protocol was then reported (Scheme 1-6), in which a modified Mukaiyama's agent **1-20** was applied as the activating reagent.[9] Carbocyclic β-lactones were synthesized in higher yields and even better enantioselectivity towards a broader substrate scope. The enhanced performance of **1-20** was attributed to greater solubility and a less nucleophilic counteranion, thus limiting β-lactones decomposition.



Scheme 1-6 Improved enantioselective catalytic NCAL of aldehyde acids.

NCAL organocascades of aldehyde acids have been applied to several total natural product syntheses, further proving the utility of this methodology. A recent example was reported by Dr. Romo and his co-workers, in which an NCAL of aldehyde acid was chosen as the key step in the construction of a (±)-Spongiolactone **1-23** (Scheme 1-7).[10] Aldehyde

acid **1-21** was synthesized after several steps and treated with the modified Mukaiyama's reagent **1-20** as the activating agent and triethylamine as the nucleophile to afford β-lactone **1-22** in moderate yield as the major diastereomer. The subsequent dehydration led to the formation of (±)-Spongiolactone **1-23** in 53% yield. The natural product and congeners were then applied to preliminary SAR studies, in which an analogue **1-24** was revealed to be more potent (IC_{50} = 29±10 μM) than the natural product (IC_{50} = 129±10 μM) against K562 cell line.

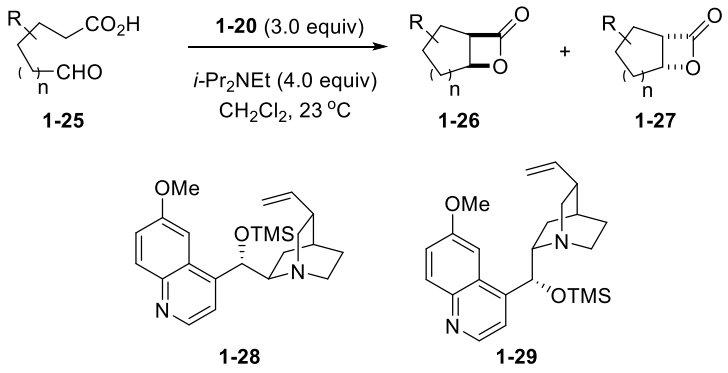


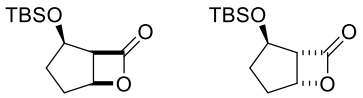
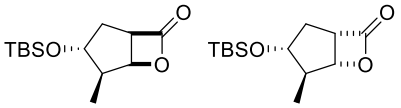
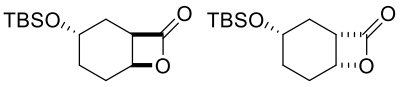
Scheme 1-7 Total synthesis of (±)-Spongiolactone

In 2010, Romo and co-worker published their work on the double diastereoselective NCAL to further expand this methodology further (Table 1-1).[11] Enantioenriched aldehyde acids were used to deliver carbocycle-fused-β-lactones, and no diastereoselectivity was observed when NEt_3 was used as the nucleophile. By using cinchona organocatalysts, the

yields decreased significantly for most cases, but diastereoselectivity was improved to >19:1 in a few cases.

Table 1-1 Double diastereoselective synthesis of carbocycle-fused β-lactones

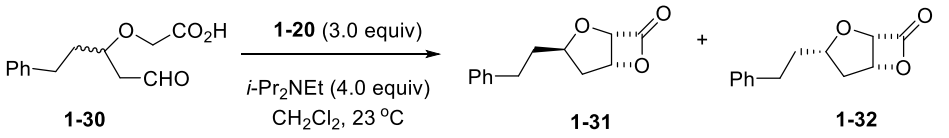


entry	β-lactone	NEt_3 % yield	**1-28** % yield	**1-29** % yield
1		55	82, 92% ee	42, 90% ee
2		84 (1:>19)	33 (1:>19)	23 (1:>19)
3		45 (2:1)	32 (1:3)	55 (10:1)
4		38 (2:1)	31 (1:>19)	10 (>19:1)

Besides assembly of carbocycles, NCAL was also chosen as a strategy for building heterocycles. An initial double diastereoselective tetrahydrofuran synthesis *via* an NCAL process was studied (Table 1-2). This was the first example of the synthesis of tetrahydrofuran-fused-β-lactones.[11] Racemic *O*-containing aldehyde acid **1-30** was used as the substrate for this NCAL study. With achiral NEt_3 as the nucleophile, β-lactones **1-31**

and **1-32** were generated in moderate yields and 1:1 dr. With **1-29** as the nucleophile, a decrease of yield from 47% to 39% and a slight increase of diastereoselectivity to 2:1 was observed, while the enantiocontrol was poor for both **1-31** and **1-32**.

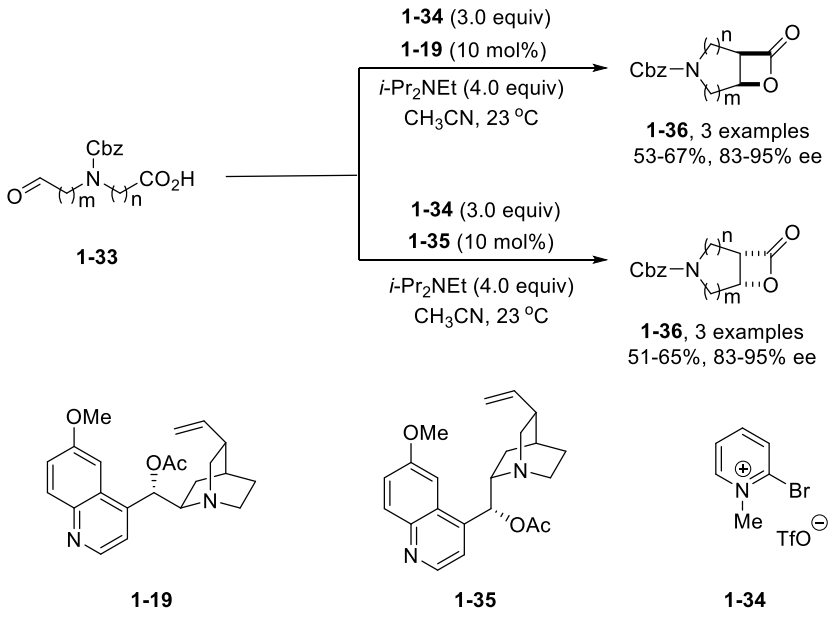
Table 1-2 Double diastereoselective synthesis of tetrahydrofuran-fused-β-lactones



1-30 **1-31** **1-32**

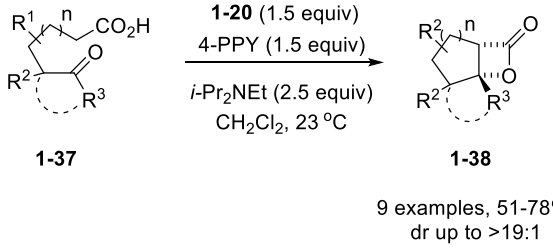
entry	nucleophile/base	(yield) dr (% ee)
1	NEt_3	47% dr 1:1
2	**1-28**	(39%), dr 2:1, 21% ee major, 12% ee minor

An Aza-variant NCAL was explored by Prof. Dikshit in order to develop a methodology for the construction of *N*-heterocycle-fused β-lactones (Scheme 1-8).[12] By using glycine derived aldehyde acids as substrates, optically active pyrrolidines and piperidines were synthesized in good yields and excellent ee with cinchona alkaloid catalysts (**1-19**, **1-35**) and the modified Mukaiyama reagent **1-34**. However, only three examples were included in their work, showing limited substrate scope.



Scheme 1-8 Aza variant NCAL

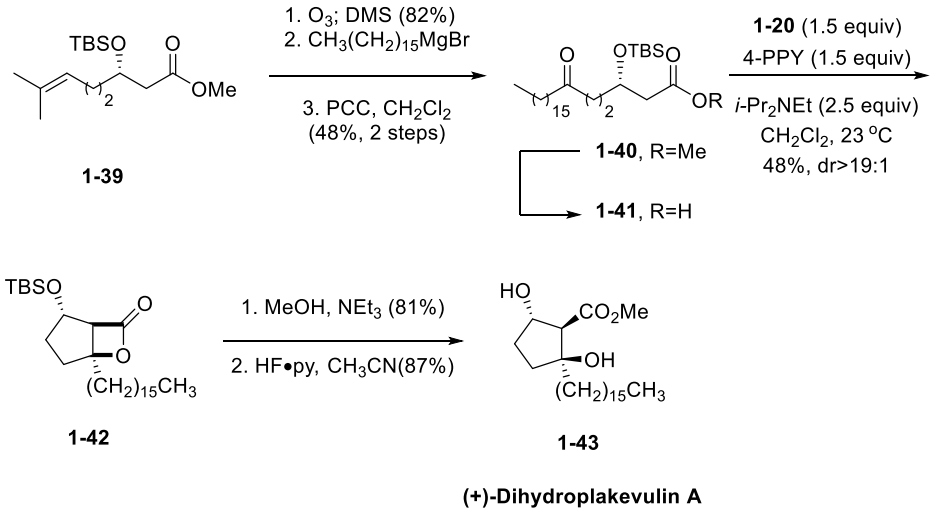
Keto acid substrates. The first organonucleophile-promoted bis-cyclization of comparatively less reactive substrates - keto acids, was developed by using superstoichiometric amounts of 4-PPY as nucleophile and **1-20** as the activating agent (Scheme 1-9).[13] Carbocycle-fused bi- and tricyclic β-lactones were synthesized in good yields and high diastereoselectivity.



Scheme 1-9 Organonucleophile-promoted *bis*-cyclization of keto acids

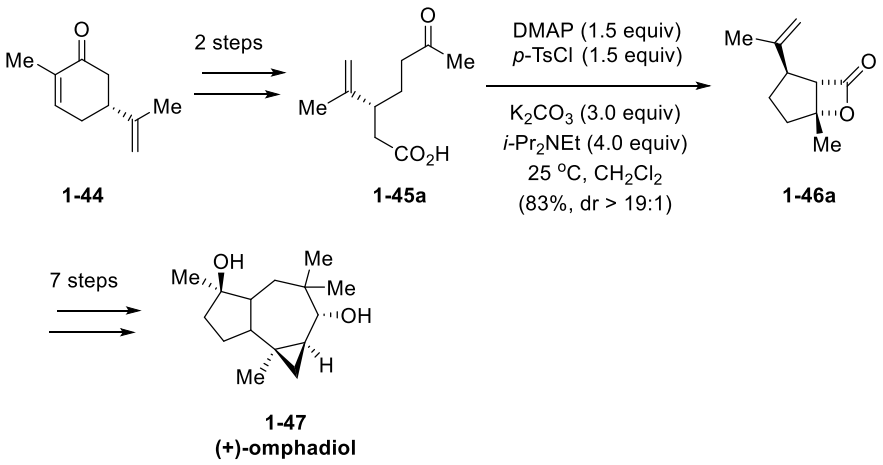
To demonstrate the utility of this methodology, a route towards (+)-Dihydroplakevulin A, a derivative of a DNA polymerase inhibitor, was developed (Scheme

1-10). With a known keto ester as the starting material, keto acid **1-41** was used in a sequencial synthesis using NCAL and other well-developped chemistry to produce β-lactone **1-42** in moderate yields and excellent dr. Opening of the β-lactone by MeOH and deprotection of the TBS group afforded (+)-Dihydroplakevulin A **1-43** in good yield.



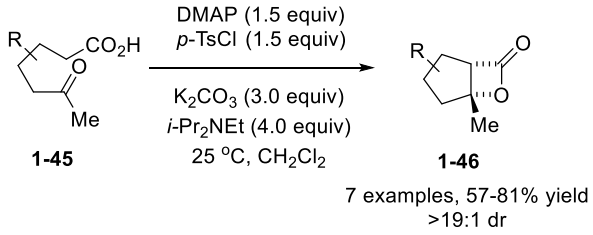
Scheme 1-10 Enantioselective synthesis of (+)-Dihydroplakevulin A

An enantioselective route towards (+)-omphadiol was developed, employing a key NCAL process of a keto acid which derived from a chiral pool substrate, (*R*)-Carvone (Scheme 1-11). [14] Instead of modified Mukaiyama's reagent, an inexpensive *p*-toluenesulfonyl chloride was used as the activating agent. By applying K_2CO_3 as a "shuttle base" in combination with *i*-Pr_2NEt, Dr. Romo and co-workers achieved a high yield and excellent dr for the bis-cyclization step. The reaction was carried out on a up to 10-gram scale, and the resulting β-lactone **1-46a** was applied as the key intermediate towards the synthesis of (+)-omphadiol.



Scheme 1-11 Total synthesis of (+)-omphadiol

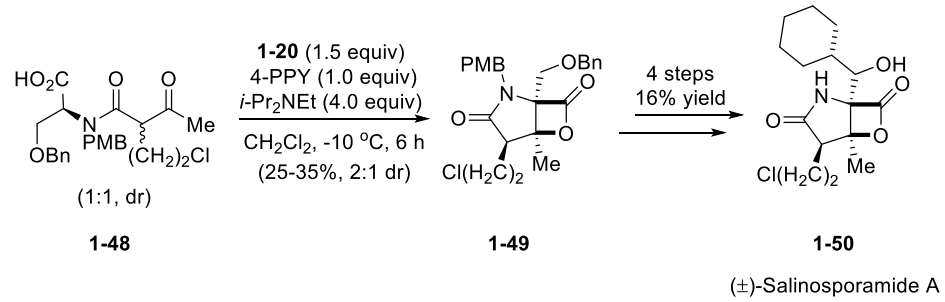
Based on the studies for the synthesis of (+)-omphadiol, an optimized diastereoselective NCAL methodology was developed with less expensive DMAP as the nucleophile, TsCl as the activating agent, and potassium carbonate as an additive, in which keto acids **1-45** bearing β or γ substituents were employed (Scheme 1-12).[15] β-lactones **1-46** with β substituents were all obtained with excellent substrate-controlled diastereoselectivity.



Scheme 1-12 Diastereoselective synthesis of bicyclic β-lactones.

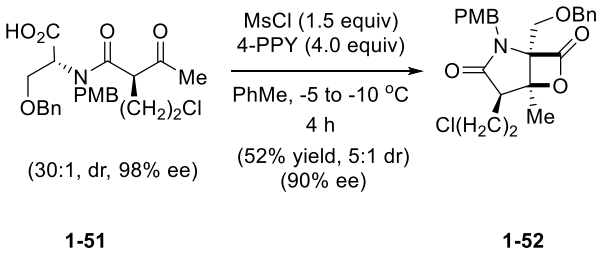
Besides the synthesis of carbocycle-fused-β-lactones, this *bis*-cyclization of keto acids enabled by stoichiometric nucleophiles was also applied to the synthesis *N*-heterocycle-fused-β-lactones.[16] Dr. Romo and co-worker first developed a concise route

towards racemic Salinosporamide A (Scheme 1-13), in which the *bis*-cyclization produced both γ-lactam and β-lactone moieties simultaneously in at 25-35% yields and 2:1 dr.



Scheme 1-13 Total synthesis of (±)-Salinosporamide A.

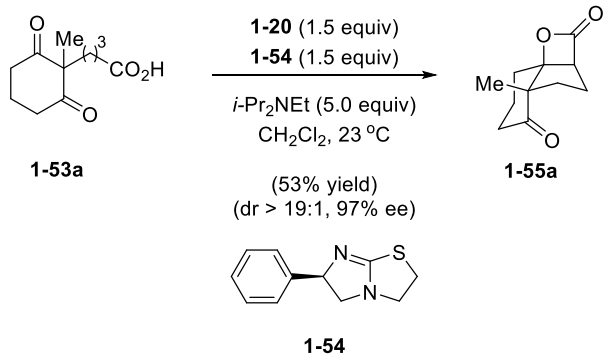
The *bis*-cyclization step was further optimized in later publications toward optically active (-)-Salinosporamide A, (-)-Homosalinosporamide A, and derivatives (Scheme 1-14).[17] Enantiomerically pure keto acid **1-51** was synthesized as the NCAL substrate. Furthermore, the use of mesyl chloride in toluene at low temperature minimized the decomposition of β-lactone **1-52**. A dramatic improvement of yield was thus observed. The diastereomeric ratio was also enhanced from 2:1 to 5:1.



Scheme 1-14 Modified *bis*-cyclization toward β-lactone **1-52**.

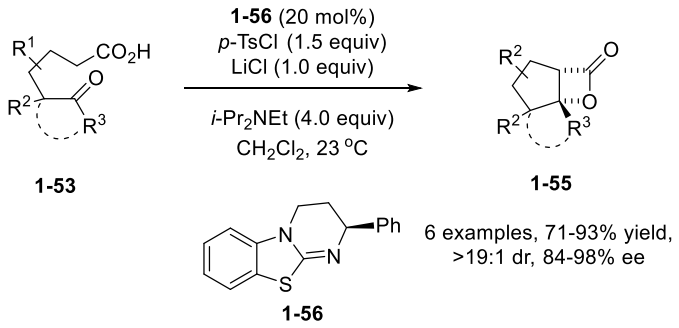
Enantioselective NCAL methodologies using keto acids as substrates were also studied by our group.[18] An Enantioselective desymmetrization with diketo acid **1-53** was explored by using superstoichiometric amounts of tetramisole **1-54**. This chiral lewis-base

promoted asymmetric synthesis β-lactone **1-55** in good yields and excellent ee as a single diastereomer.

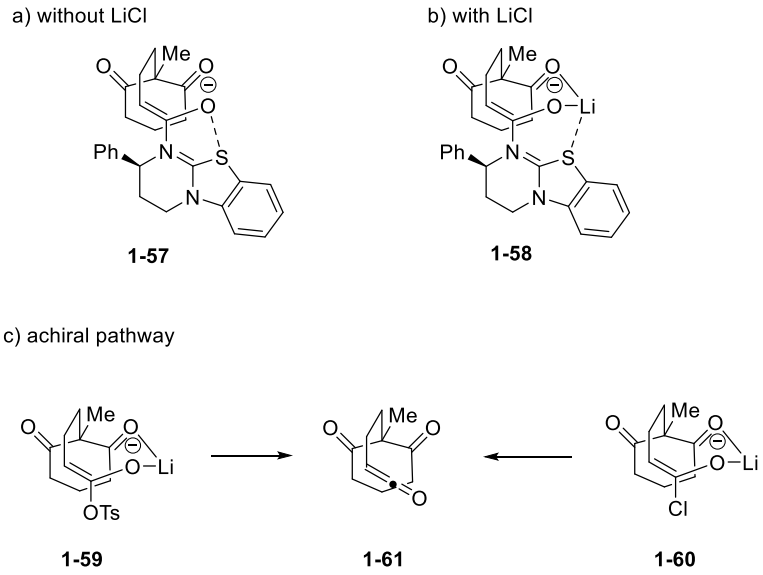


Scheme 1-15 Enantioselective desymmetrization of diketo acid **1-53**.

Dr. Leverett further improved the enantioselective desymmetrization by using a catalytic amount of isothiourea and a less expensive activating agent, TsCl, which exhibited equivalent performance to modified Mukaiyama reagent.[19] Meanwhile, LiCl was found to improve the yield dramatically but decrease the enantiocontrol slightly. Two plausible explanations are that 1) Li cation works as a Lewis acid, thus chelating the acid carbonyl group and the catalyst, leading to a chair-like transition state. However, greater freedom of rotation around C-N due to the replacement of n_O to $\sigma^*_{C\text{-}S}$ interaction resulted in a loss of enantiocontrol. (Scheme 1-17, a, b) 2) LiCl might also promote the generation of ketene, thus and leading to the achiral [2+2] pathway (Scheme 1-17, c). This optimized condition was further applied to a series of β-lactones synthesis with keto acids as substrates, all showing good to excellent yields and great ee.

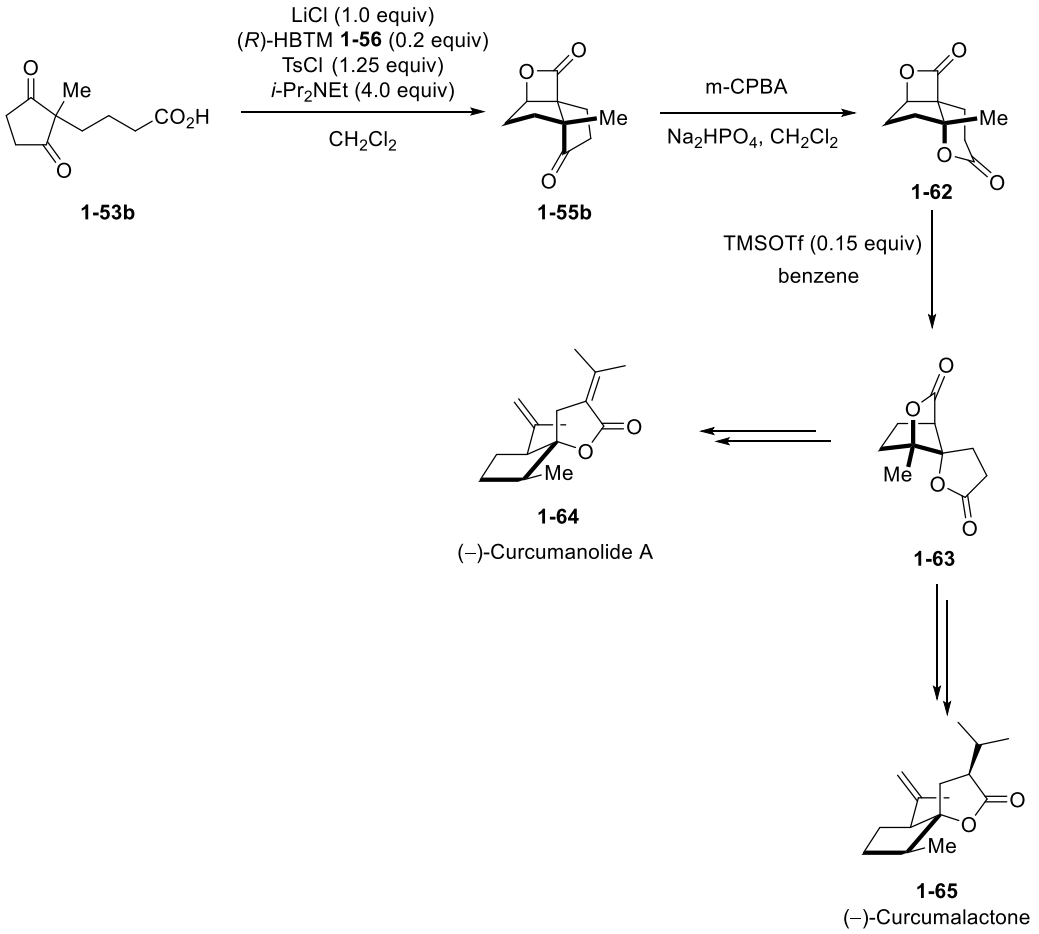


Scheme 1-16 Catalytic enantioselective NCAL of keto acids.



Scheme 1-17 Proposed transition states of NCAL with or without LiCl

The enantioselective desymmetrization NCAL cascade was applied as the key step in the synthesis of (−)-Curcumanolide A and (−)-Curcumalactone.[20] Tricylic-β-lactone **1-55b** was assembled through the enantioselective desymmetrization NCAL, and then exposed to Baeyer−Villiger oxidation to tricyclic β,δ-*bis*-lactone **1-62**. By using catalytic TMSOTf as the Lewis acid, a dyotropic rearrangement of **1-62** was achieved, yielding spiro-γ-lactone **1-63**, upon which further functionalization was carried out to give natural products (−)-Curcumanolide A and (−)-Curcumalactone.



Scheme 1-18 Synthesis of (−)-Curcumanolide A and (−)-Curcumalactone.

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CHAPTER TWO

Diastereo- and Enantioselective Synthesis of *N*-Heterocycle-Fused β-Lactones

Abstract

The utility of the nucleophile-catalyzed (Lewis base) aldol lactonization (NCAL) process for the diastereo- and enantioselective synthesis of *N*-heterocycle-fused-β-lactones from *N*-linked ketoacids is described. A series of bi- and tricyclic, *N*-heterocycle-fused, β-lactones were first synthesized in racemic fashion via the NCAL process with excellent diastereoselectivity (>19:1) utilizing 4-pyrrolidinopyridine as an effective achiral Lewis base. A catalytic, enantioselective version of this NCAL process using isothiourea catalysts provided access to bicyclic β-lactone-fused, *N*-heterocycles in moderate to good yields (up to 80%) with high enantiocontrol (up to >99:1 er). An unusual diastereodivergent NCAL process was discovered that leads to two different products; a tricyclic *N*-heterocycle-fused β-lactone and a bicyclic enamine derived from *in situ* decarboxylation of the diastereomeric tricyclic β-lactone. The reactivity of these adducts was briefly explored.

Introduction

As a class of unique oxygen-containing, strained heterocycles, β-lactones are not only versatile intermediates in synthetic chemistry[21] but are gaining increased use as tools for probing cellular function of enzymes and proteins with nucleophilic residues.[22] Our group first reported the catalytic, asymmetric intramolecular, nucleophile (Lewis base) catalyzed aldol lactonization (NCAL) process of aldehyde acids in 2001[8] building on the elegant work of Wynberg[2] which makes use of *in situ* generated ammonium enolate

intermediates[3, 23] to deliver carbocycle-fused, bicyclic β-lactones. The NCAL process was subsequently extended to keto acids leading to a variety of bi- and tricyclic carbocycle-fused β-lactones.[13, 19-20] and was applied to the synthesis of several natural products by our group[10, 13-14, 20] and others.[24] In addition, we also applied the NCAL reaction to the synthesis of oxygen heterocycle-fused β-lactones.[11] We returned to the original inspiration for development of the NCAL process, namely the structure of the proteasome inhibitors omuralide and salinosporamide, and considered application of the NCAL process to *N*-heterocycle-fused β-lactones. In 2007, we reported application of the NCAL process to a racemic synthesis of a γ-lactam-fused β-lactone as a key intermediate towards a synthesis of (±)-salinosporamide A.[16] We subsequently described a diastereoselective synthesis of this same γ-lactam-fused-β-lactone employing substrate control from a chiral keto acid precursor leading to a bioinspired, 9-step enantioselective, synthesis of (+)-salinosporamide A from *R*-(–)-*O*-Bn serine.[17b] The Dikshit group described application of the NCAL to *N*-linked aldehyde acids for the enantioselective synthesis of pyrrolidine- and piperidine-fused-β-lactones employing cinchona alkaloid Lewis bases.[12] Herein, we describe application of the NCAL process to *N*-linked keto acids for the diastereo- and enantioselective synthesis of bi- and tricyclic *N*-heterocycle-fused β-lactones including several that are substructures or potential precursors to substructures of natural products (Figure 2-1).

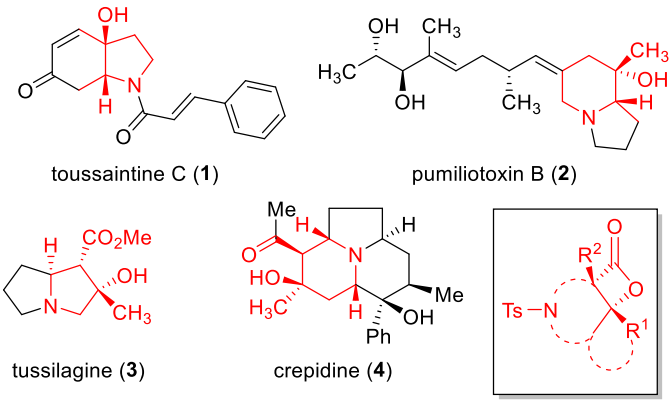
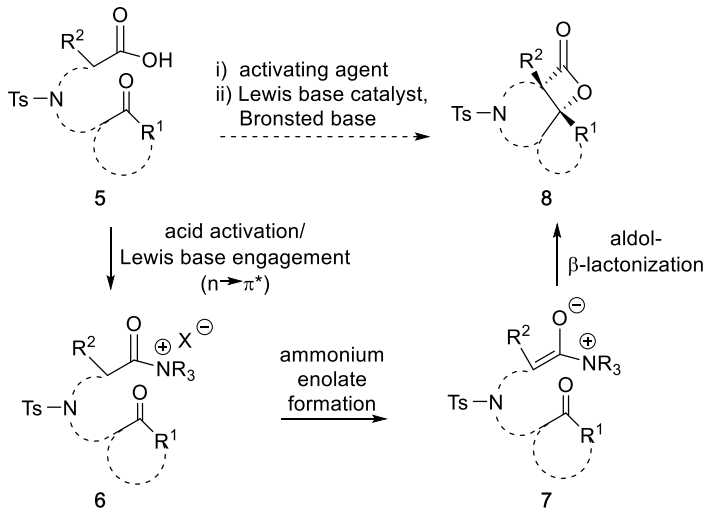


Figure 2-1 General structure of bi- and tricyclic N-heterocycle-fused β-lactones (inset) available through the described nucleophile (Lewis base)-catalyzed, aldol-lactonization (NCAL) process described herein and potentially useful for accessing various substructures (red) of natural products.

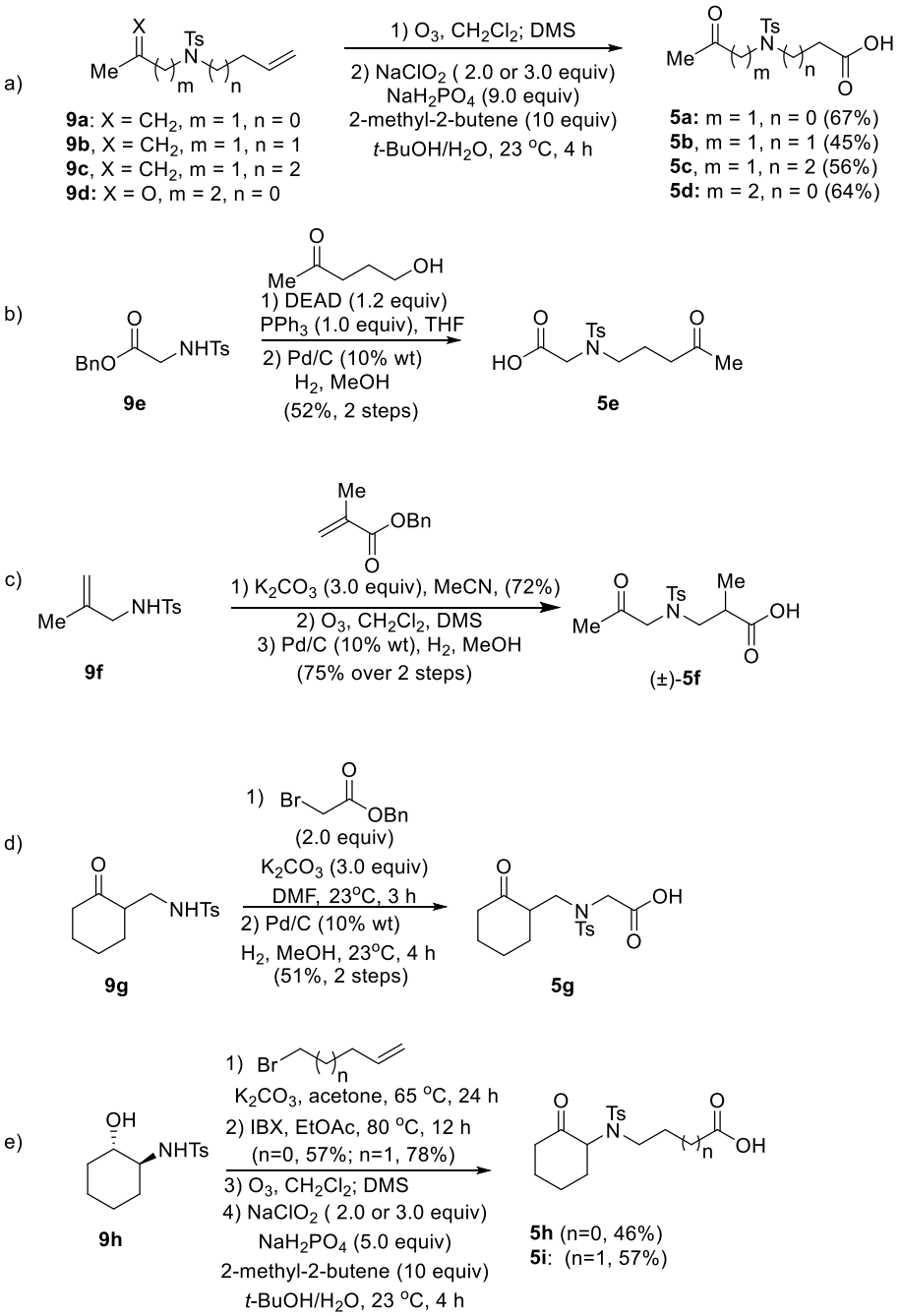
Mechanistically, the aldol-β-lactonization of *N*-linked keto acids towards *N*-heterocycle-fused-β-lactones were envisioned to be derived through carboxylic acid activation and a chiral Lewis base in the presence of a Brønsted base (Scheme 2-1). Activation of the carboxylic acid *via* an activated ester by use of various activating agents, such as *p*-toluenesulfonyl chloride[14-15, 19] and modified Mukaiyama's reagents, reagents[9, 12, 25], enables engagement by a chiral Lewis base through an initial $n \rightarrow \pi^*$ mode of interaction[26, 23b] to ultimately form an acylammonium intermediate **6**. Deprotonation by the Brønsted base leads to ammonium enolate **7** which then undergoes a thermodynamically controlled *syn*-aldol, since the *anti*-aldol cannot lactonize, followed by β-lactonization to afford β-lactone **8**. Although ketene formation is possible under these reaction conditions *via* elimination of acylammonium salt **7** enabling a possible racemic, [2+2] cycloaddition pathway to the β-lactone, the nucleophilicity of the Lewis base and low concentration of ketene at ambient temperature allows the NCAL pathway to be the most prevalent pathway.[1a]



Scheme 2-1 The catalytic, enantioselective, nucleophile (Lewis base)-catalyzed aldol-lactonization (NCAL) process to nitrogen-heterocycle-fused β-lactones **5** from *N*-linked keto acids **8**.

Results and Discussion

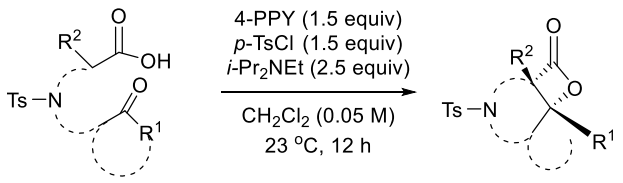
A series of *N*-linked keto acid substrates to be studied in the NCAL process were prepared through various synthetic routes (Scheme 2-2). A sequential ozonolysis/Pinnick oxidation of known terminal alkenes **9a-d**[27] led to keto acids **5a-d** in good yield (45-67%, 2 steps, Scheme 2-2 a). Keto acid **5e** was prepared *via* a Mitsunobu reaction/hydrogenolysis sequence from known *N*-Ts aminoester **9e**[28] and 1-hydroxy-4-pentanone in 52% yield (2 steps, Scheme 2-2 b). An aza-Michael reaction of *N*-Ts allylic amine **9f**[29] and benzyl methacrylate followed by ozonolysis and hydrogenolysis generated keto acid (±)-**5f** (Scheme 2-2 c). The synthesis of cyclic ketone acid substrates **5g-i** to access tricyclic β-lactones began with amino cyclohexanone **9g**[30] and amino alcohol **9h**[31] (Schemes 2-2 d, e). Keto acid **5g** was obtained from amino ketone **9g** in a 2-step sequence involving *N*-alkylation and hydrogenolysis while a 4-step sequence delivered keto acids **5h** and **5i** from β-amino alcohol **9h**.



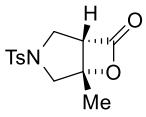
Scheme 2-2 Synthesis of keto acids **5a-i** as substrates for the NCAL process leading to bi- and tricyclic, N-heterocycle fused β-lactones

With scalable access to *N*-linked keto acids **5a-i**, we first explored the NCAL process towards racemic *N*-heterocycle-fused-β-lactones synthesis employing 4-pyrrolidinopyridine (4-PPY) as Lewis base (Table 2-1). Under typical NCAL conditions employed previously for carbocycle-fused β-lactones, with inexpensive *p*-toluenesulfonyl chloride as a carboxylic acid activating agent,[15] keto acids **5a-i** delivered the corresponding *N*-heterocycle-fused, β-lactones **8**. Pyrrolidine-fused β-lactones (**8a**, **8d**, **8h**, **8g**) were obtained in yields ranging from 72-82%. The sterically congested bis-quaternary center containing pyrrolidine **8f** could also be obtained but in only ~24% yield. Generally, piperidine-fused β-lactones (**8b**, **8e**, **8i**) were formed in lower yields (40-79%) compared to pyrrolidine-fused systems as previously observed in the carbocyclic series likely reflecting the kinetic differences in 5 vs 6-membered ring formation and lower stability of 6-membered ring-fused β-lactones.[9] An attempt was made to prepare the azepane-fused β-lactone **8c** however this did not provide detectable amounts of β-lactone. The tricyclic β-lactones **8g-h** were obtained in high diastereoselectivity (>19:1) and the relative stereochemistry shown for these adducts is supported by 2D NMR studies of pyrrolidine-fused, tricyclic β-lactone **8h** (see SI for details).

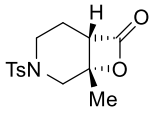
Table 2-1 Racemic synthesis of *N*-heterocycle-fused β-lactones through the organonucleophile (4-PPY) promoted bis-cyclization



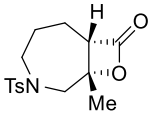
5 **8**



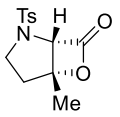
(±)-**8a** (72%)



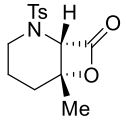
(±)-**8b** (40%)



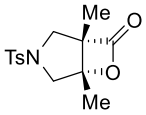
(±)-**8c** (0%)



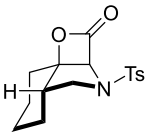
(±)-**8d** (78%)



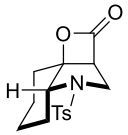
(±)-**8e** (48%)



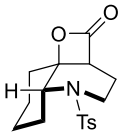
(±)-**8f** (24%)



(±)-**8g** (79%, dr > 19:1)



(±)-**8h** (82%, dr > 19:1)

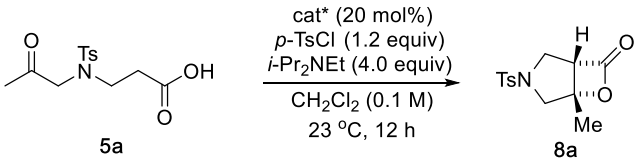


(±)-**8i** (69%, dr > 19:1)

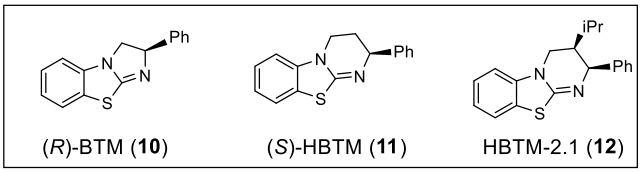
We next studied the enantioselective NCAL for the synthesis of *N*-heterocycle-fused β-lactones (NCAL) and keto acid **5a** was utilized for initial screening of catalysts and conditions. The chiral isothiourea catalysts benzotetramisole (BTM, **10**) and homobenzotetramisole (HBTM, **11)** developed by Birman[32] and HBTM 2.1 (**12**) developed by Smith[33] have served as excellent Lewis bases for the *in situ* preparation of chiral ammonium enolates[19-20, 23a, 34] and more recently unsaturated acylammonium enolates.[35] We therefore studied these Lewis bases initially and found that (*S*)- HBTM provided the best enantiomeric ratios among these catalysts (Table 2-2, entries 1-3) providing a 98:2 er albeit in low yield (34%). We studied the use of K_2CO_3 as stoichiometric insoluble base

with the use of Hünig's base as a shuttle base[36] (Table 2-2, entry 4), however this did not improve the yield dramatically. Crude ^{1}H NMR analysis of these initial reactions and considering mass recovery before and after chromatographic purification suggested that some loss of β-lactone product was likely occurring on silica gel through possible acylation. We considered that excess Hünig's base present in the crude reaction mixture could promote β-lactone acylation of silica gel, so excess amounts were removed from the crude reaction mixture (confirmed by crude ^{1}H NMR) by aqueous extraction prior to purification by automated flash chromatography. This led to an improvement in yield from 36 to 44% of β-lactone **8a** (Table 2-2, entry 5). Furthermore, use of normal flash chromatography instead of automated flash chromatography led to a further improvement to 52% likely due to the smaller particle size and increased surface area of the prepacked columns (Table 2-2, entry 5). We determined that use of the shuttle base was not responsible for major yield improvements but rather the method of purification was key and thus subsequent reactions only employed Hünig's base. The use of LiCl as additive was investigated next, given the utility in related reactions,[19,37] which led to a major improvement in yield to 78% with 99:1 er.

Table 2-2 Optimization of the enantioselective NCAL leading to pyrrolidine-fused β-lactone **8a**



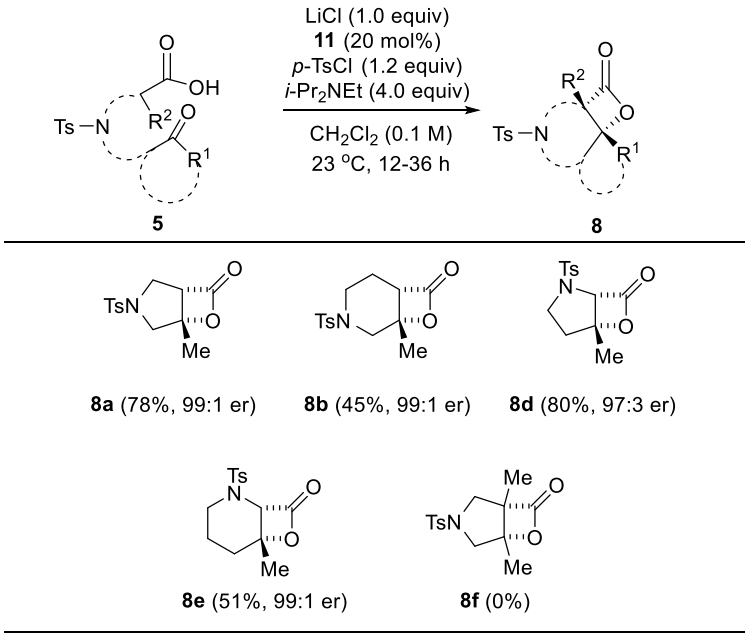
entry[a]	cat.	additive	% yield[b]	er[c]
1	10	-	12[d]	85:15
2	11	-	34[d]45[g]	98:2
3	12	-	trace[d]	ND
4	11	K_2CO_3 (3.0 equiv)	36[d], 44[e], 52[f]	99:1
5	11	LiCl (1.0 equiv)	78[f]	99:1



[a] The keto acid **5a** was added by syringe pump to the reaction mixture over 6 h. [b] Yields refer to isolated and purified β-lactone **8a.** [c] Determined by chiral HPLC analysis. [d] Purification involved concentration of the crude reaction mixture and direct loading on an automated flash chromatograph silica column. [e] An aqueous workup was performed to remove excess Hünig's base prior to loading on an automated flash chromatography silica column. [f] An aqueous workup was performed to remove excess Hünig's base prior to purification by normal flash chromatography. (er = enantiomeric ratio; ND = not determined)

With optimized conditions in hand, a brief survey of the scope of this NCAL process was explored with various *N*-linked keto acids (Table 2-3). For most bicyclic β-lactones (**8a**, **8b**, **8d**, **8e**), the yields were comparable to the corresponding racemic NCAL and the enantiomeric ratios were excellent (97:3 to 99:1). However, attempts to prepare β-lactone **8f** were unsuccessful likely due to the increased sterics of the Lewis base in forming vicinal quaternary centers. Absolute stereochemistry was assigned by comparison of the optical rotation of **8d** with literature values,[38] and was consistent with our previous transition state models of the NCAL toward bicyclic carbocycle fused β-lactones.[13]

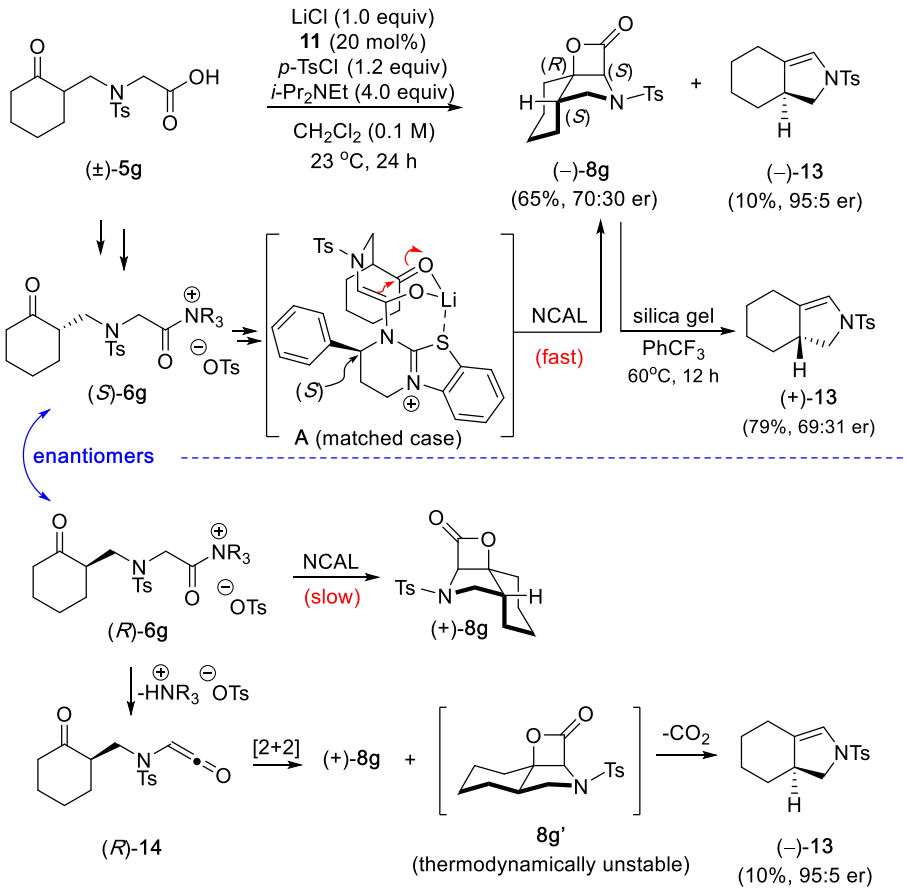
Table 2-3 Catalytic, asymmetric synthesis of N-heterocycle-fused bicyclic β-lactones **8** *via* the NCAL process



The more readily accessible, racemic keto acid **5g** (3 steps from commercially available material) was also investigated as a substrate for the enantioselective NCAL. This process could lead to high enantiopurity through a kinetic resolution since the substrate is racemic (Scheme 2-3). Under the optimized conditions, tricyclic β-lactone **8g** was obtained in 65% yield however with a 70:30 er. Enamine **13**, derived from presumed *in situ* decarboxylation of the β-lactone adduct, was isolated in 10% yield but surprisingly in high enantiopurity (95:5 er).

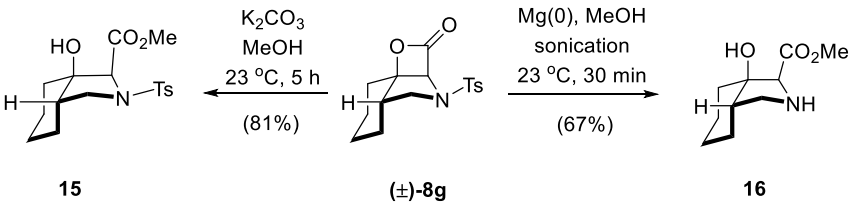
We propose that the observed enantioenriched enamine (–)-**13** is a result of a diastereodivergent process,[39] wherein one enantiomeric starting material proceeds through a NCAL pathway ((*S*)-**6g**) while the other ((*R*)-**6g**) proceeds through a [2+2] cycloaddition/decarboxylation pathway (Scheme 2-3). The NCAL pathway would be expected to lead to high diastereoselectivity and enantioselectivity in the matched case,

transition state arrangement **A**, *via* acylammonium salt (*S*)-**6g**, as observed in the bicyclic series herein and also previously in the carbocyclic series,[19] however an intervening [2+2] cycloaddition pathway with the presumed mismatched case (*i.e.* acylammonium salt (*R*)-**6g**) leads to a non-diastereoselective [2+2] cycloaddition pathway providing both diastereomeric β-lactones (+)-**8g** and **8g'**. The presence of the enantiomeric (+)-**8g** serves to lower the enantiopurity of the isolated tricyclic β-lactone (**–**)-**8g** (70:30 er). On the other hand, the strain associated with the diastereomeric β-lactone **8g'**, which could not be isolated likely due to its instability due to strain, leads to *in situ* decarboxylation under the reaction conditions providing enamine (–)-**13** with high enantiopurity since it is derived primarily from ketene (*R*)-**14**. Calculation of the total energy difference between diastereomeric β-lactones **8g** and **8g'** support the hypothesis that β-lactone **8g'** may undergo decarboxylation at ambient temperature ($\Delta E_{\mathbf{8g/8g'}}$, ~2.4-2.6 kcal/mol, from Chem3D and Avogrado using MMFF94 force fields). Heating in the presence of silica gel was required to induce decarboxylation of (+)-**8g**/(**–**)-**8g** and confirmed our prediction that the major product was the enantiomeric enamine (+)-**13** obtained in 79% yield (70:30 er). Overall, while a kinetic resolution is operative in this process, an intervening [2+2] cycloaddition pathway leads to lower enantiopurity of the tricyclic β-lactone (**–**)-**8g**.



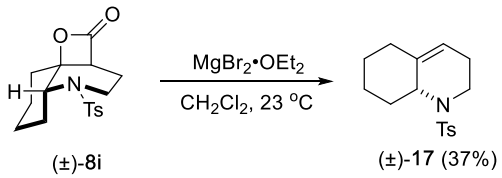
Scheme 2-3 Enantioselective NCAL leading to tricyclic β-lactone **8g** proceding through transition state arrangement **A** with alkene (–)-**13** as by-product and proposed mechanistic rationale for the high optical purity of alkene (–)-**13**.

A few transformations of the derived *N*-heterocycle-fused β-lactones were explored. Methanolysis of β-lactone (±)-**8i** under basic conditions afforded hydroxy ester (±)-**15** in 81% yield. As expected, treatment of β-lactone (±)-**8g** with Mg^0 in MeOH under sonication conditions led to cleavage of the tosyl group with concomitant opening of the β-lactone to provide amino ester (±)-**16**. Conditions were not found that enabled tosyl deprotection without β-lactone cleavage.



Scheme 2-4 Transformations of *N*-heterocycle-fused tricyclic β-lactone (±)-**8g**

A dyotropic rearrangement of β-lactone **8i** was attempted with stoichiometric amounts of $MgBr_2 \bullet OEt_2$[18-20], however this only led to low yields of the decarboxylation product, alkene (±)-**17** in low yield (37%) (Scheme 4).



Scheme 2-5 Attempted dyotropic rearrangement of fused tricyclic β-lactone **8i** leading to alkene **17** *via* decarboxylation

Summary

In summary, the intramolecular NCAL process has been extended to *N*-linked keto acid substrates leading to the synthesis of pyrrolidine and piperidine-fused β-lactones. Stoichiometric 4-PPY was identified as an optimal Lewis base for the racemic synthesis of several bi- and tricyclic *N*-heterocycle fused β-lactones in moderate to good yields (40-82%) with high diastereoselectivity in all cases (>19:1). Lower yields were obtained when synthesis of a pyrrolidine fused-β-lactone bearing adjacent quaternary carbons was attempted (24%). A catalytic, asymmetric version of these NCAL reactions was optimized and led to moderate to good yields (45-80%) of optically active bicyclic β-lactones (97:3-99:1 er), however lower enantioselectivity was obtained with a tricyclic-β-lactone **8g**

(70:30 er). A unique type of diastereodivergent process[39a] is proposed to account for an alkene by-product obtained in high enantiomeric purity (95:5 er) through a [2+2] cycloaddition/decarboxylation pathway from racemic starting material. This unique kinetic resolution which delivers two different products from racemic starting materials is under continued investigation. The described NCAL organocascade allows simultaneous assembly of a nitrogen heterocycle and a fused β-lactone readied for further transformations.

Experimental Procedures

General Information

All non-aqueous reactions were performed under a nitrogen atmosphere in oven-dried glassware. Dichloromethane (CH_2Cl_2) and Tetrahydrofuran (THF) were dried by passing through activated molecular sieves or alumina (solvent purification system). Diisopropylethylamine (DIPEA) 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. ^{1}H NMR spectra were measured at 600 MHz and 400 MHz and referenced relative to residual chloroform (7.26 ppm) and are reported in parts per million. Coupling constants (*J*) are reported in Hertz (Hz), with multiplicity reported following usual conventions: 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. ^{13}C NMR spectra were measured at 150 MHz and 101 MHz and referenced relative

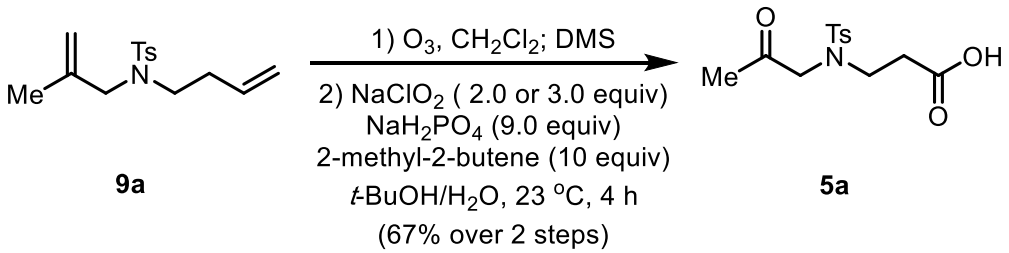
to residual chloroform (77.23 ppm) and are reported in parts per million (ppm). Flash column chromatography was performed with 60Å Silica Gel (230-400 mesh) as stationary phase using a gradient solvent system or on an automated flash chromatography system (EtOAc/hexanes as eluent unless indicated otherwise). High-resolution mass spectra (ESI) were obtained in the Mass Spectrometry Laboratory (Baylor University). 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. *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.

(*S*)-HTBM (**11**)[32b] and HBTM-2.1 (**12**)[23a] were synthesized according to literature procedures. (*R*)-BTM (**10**) was purchased from TCI chemicals. Alkenes **9a-c**[27], **9d**[38], **9g**[31] and **9h**[30] were prepared according to literature procedures.

Abbreviation List

DMS	=	Dimethylsulfide
DEAD	=	diethyl azodicarboxylate
IBX	=	2-iodoxybenzoic acid
4-PPY	=	4-pyrrolidinopyridine
p-TsCl	=	*p*-toluenesulfonyl chloride
i-Pr_2NEt	=	*N*,*N*-diisopropylethylamine
HBTM	=	homobenzotetramisole
$PhCF_3$	=	trifluorotoluene

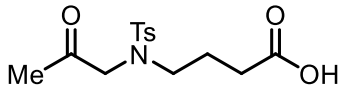
Representative Procedure for Synthesis of Keto Acid Substrates via Sequential Ozonolysis and Pinnick Oxidation as Described for Keto acid 5a:



(3-((4-Methyl-*N*-(2-oxopropyl)phenyl)sulfonamido)propanoic acid, 5a): To a solution of alkene **9a** (2.70 g, 9.70 mmol, 1.0 equiv) in CH_2Cl_2 was treated with ozone under -78 ºC *via* gas dispersion tube. After the solution turned pale blue, nitrogen gas was introduced until the blue color faded away. Then, dimethylsulfide (DMS) (14.5 mL, 193.7 mmol, 20.0 equiv) was added at -78 ºC. The reaction mixture was warmed up to 23 ºC and stirred for 18 h. The solution was concentrated *in vacuo,* and the mixture was used directly in the next step without further purification.

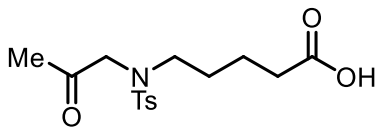
The crude aldehyde was dissolved in a mixture of tertbutyl alcohol (*t*-BuOH) (60 mL) and water H_2O (20 mL) at 23 ºC. Then, sodium phosphate mono basic (NaH_2PO_4) (10.40 g, 87.3 mmol, 9.0 equiv) and 2-methyl-2-butene (10.50 mL, 97.0 mmol, 10.0 equiv) was added and the reaction mixture was kept stirring until the inorganic salt was completely dissolved. Sodium chlorite (2.67 g, 12.7 mmol, 2.0 equiv), was then added in one portion. Upon completion (as judged by TLC), 1N HCl was added to adjust pH to 2-3. Additional water (100 mL) was added and the aqueous phase was extracted with ethyl acetate (100 mL×3). The combined organic phase was washed with brine (100 mL) and dried over sodium sulfate. The organic solvent was removed *in vacuo*. The crude product was purified by automated flash chromatography (0 → 100%, EtOAc/hexanes) to afford acid **5a** as a

white solid (1.95 g, 67%, over 2 steps). TLC (EtOAc, 100%): R_f = 0.35; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.3 Hz, 2H), 4.12 (s, 2H), 3.42 (t, *J* = 6.7 Hz, 2H), 2.72 (t, *J* = 6.7 Hz, 2H), 2.43 (s, 3H), 2.14 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 203.8, 177.2, 144.1, 136.0, 129.9 (2), 127.6 (2), 58.4, 45.0, 34.4, 27.0, 21.7. **IR** (thin film): 3200-3600 (br), 1731, 1714 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{13}H_{17}NNaO_5S$ $[M+Na]^+$: 322.0725, found: 322.0725.



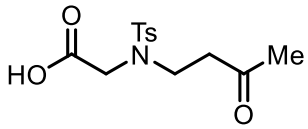
5b

4-((4-Methyl-*N*-(2-oxopropyl)phenyl)sulfonamido)butanoic acid (5b): Prepared according to the representative procedure for the sequential ozonolysis/Pinnick oxidation employing alkene **9b** (882 mg, 3.0 mmol, 1.0 equiv) and DMS (4.5 mL, 60.0 mmol, 20.0 equiv) for the ozonolysis and $NaClO_2$ (541 mg, 6.0 mmol, 2.0 equiv), NaH_2PO_4 (3.21 g, 9.0 equiv, 27.0 mmol), 2-methyl-1-butene (3.24 mL, 30.0 mmol, 10.0 equiv), *t*-BuOH (24 mL), H_2O (8 mL) for the Pinnick oxidation. The crude product was purified by automated flash chromatography (0 → 100%, EtOAc/hexanes) to afford keto acid **5b** as a while solid (423 mg, 45% yield over two steps). TLC (EtOAc, 100%): R_f = 0.45; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.70 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.3 Hz, 2H), 4.00 (s, 2H), 3.24 (t, *J* = 7.1 Hz, 2H), 2.50-2.34 (m, 5H), 2.20 (s, 3H), 4.13 (app p, *J* = 7.1 Hz, 2H); **^{13}C NMR** (101 MHz, CDCl3) δ 203.9, 178.0, 144.0, 136.2, 129.9 (2), 127.6 (2), 57.0, 48.4, 30.7, 27.2, 23.1, 21.8; **IR** (thin film): 2800-3600 (br), 1730, 1650 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{14}H_{19}NO_5SNa$ $[M+Na]^+$: 336.0882, found: 336.0878.



5c

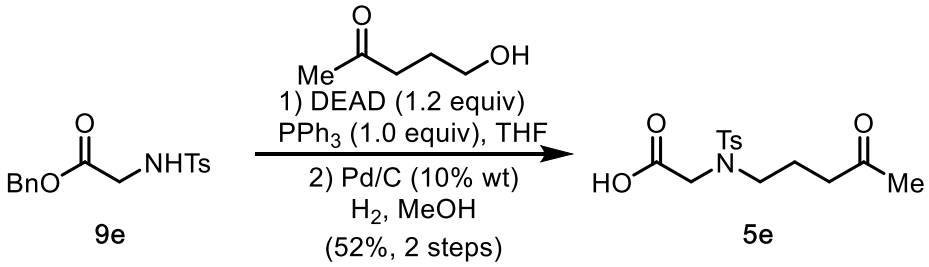
5-((4-Methyl-*N*-(2-oxopropyl)phenyl)sulfonamido)pentanoic acid (5c): Prepared according to the representative procedure for the sequential ozonolysis/Pinnick oxidation employing alkene **9c** (982 mg, 3.2 mmol, 1.0 equiv), DMS (4.8 mL, 20.0 equiv, 64.0 mmol) were used for ozonolysis. $NaClO_2$ (865 mg, 9.6 mmol, 3.0 equiv), NaH_2PO_4 (3.45 g, 29.0 mmol, 9.0 equiv), 2-methyl-1-butene (3.45 mL, 32.0 mmol, 10.0 equiv), ^{t}BuOH (24 mL), H_2O (8 mL) were used for Pinnick oxidation. Upon completion (as judged by TLC), the crude product was purified by automated flash chromatography (0 → 100%, EtOAc/hexanes) to afford keto acid **5c** as a colorless oil (579 mg, 56% yield over two steps). TLC (EtOAc, 100%): R_f = 0.50; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.68 (d, *J* = 8.3 Hz, 2H), 7.30 (d, *J* = 8.3 Hz, 2H), 3.93 (s, 2H), 3.15 (t, *J* = 7.0 Hz, 2H), 2.42 (s, 3H), 2.34 (t, *J* = 6.9 Hz, 2H), 2.19 (s, 3H), 1.74 – 1.33 (m, 4H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 204.4, 178.9, 143.9, 136.1, 129.9 (2), 127.6 (2), 57.0, 48.9, 33.4, 27.5, 27.2, 21.8, 21.7; **IR** (thin film): 1732 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{15}H_{21}NO_5SNa$ $[M+Na]^+$: 350.1038, found: 350.1028.



5d

***N*-(3-oxobutyl)-*N*-tosylglycine (5d)**: Prepared according to the representative procedure for the sequential ozonolysis/Pinnick oxidation employing alkene **9d** (1.20 g, 4.27 mmol, 1.0 equiv), DMS (3.2 mL, 42.7 mmol, 10.0 equiv) were used for ozonolysis. $NaClO_2$ (1.15 g, 12.7 mmol, 3.0 equiv), NaH_2PO_4 (4.60 g, 38.6 mmol, 9.0 equiv), 2-methyl-1-butene (4.60 mL, 42.7 mmol, 10.0 equiv), ^{t}BuOH (30 mL), H_2O (10 mL) were used for Pinnick oxidation. Upon completion (as judged by TLC), the crude product was purified by automated flash chromatography (0 → 100%, EtOAc/hexanes) to afford keto acid **5d**

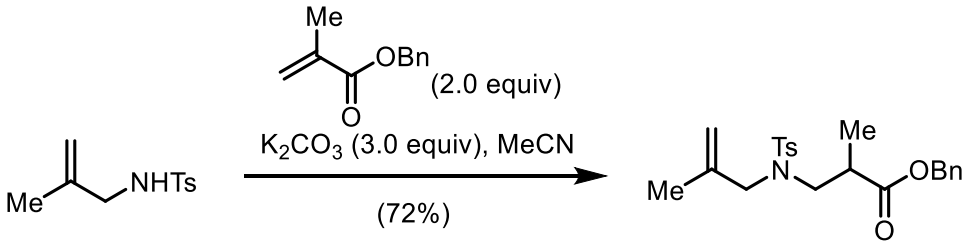
as a white solid (817 mg, 64% yield over two steps). TLC (EtOAc, 100%): R_f = 0.42; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.3 Hz, 2H), 4.10 (s, 2H), 3.42 (t, *J* = 6.4 Hz, 2H), 2.90 (t, *J* = 6.4 Hz, 2H), 2.43 (s, 3H), 2.15 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 207.8, 174.2, 144.1, 136.1, 130.0 (2), 127.5 (2), 50.5, 44.3, 43.9, 30.3, 21.8.; **IR** (thin film): 3000-3700, 1639; **HRMS** (ESI+) *m/z* calcd for $C_{13}H_{17}NNaO_5S$ $[M+Na]^+$: 322.0725, found: 322.0724.



***N*-(4-oxopentyl)-*N*-tosylglycine (5e)**: To a solution of amino ester **9e** (1.13g, 3.6 mmol, 1.2 equiv), 5-hydroxy-2-pentanone (306 mg, 3.0 mmol, 1.0 equiv) and triphenylphosphine (786 mg, 3.0 mmol, 1.0 equiv) in THF (30 mL) was added diethyl azodicarboxylate in toluene (1.56 mL, 3.6 mmol, 1.2 equiv) at 0 ºC dropwise over 5 min. Upon completion (as judged by TLC), the solvent was removed by rotary evaporation. The crude product was purified by automated flash chromatography (0 → 50%, EtOAc/hexanes) to afford keto ester inseparable from hydrazine derived from diethyl azodicarboxylate. The crude mixture (1.05 g) was taken directly into the next step without further purification.

To a solution of the crude keto ester in methanol was added Pd/C (105 mg). The suspension was charged with H_2 and stirred under H_2 atmosphere at 23 ºC. Upon completion (as judged by TLC), the suspension was filtered through a pad of Celite and the solvent was removed by rotary evaporation. The crude product was then purified by automated flash chromatography (0 → 100%, EtOAc/hexanes) to afford keto acid **5e** as a

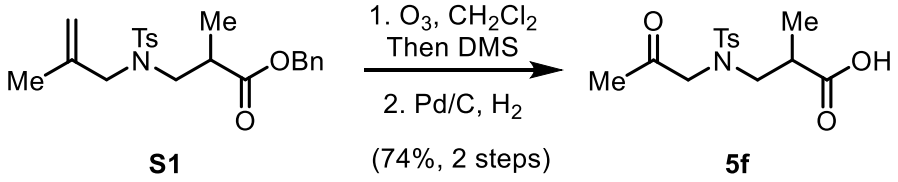
white solid (508 mg, 52% yield). TLC (EtOAc): R_f = 0.45; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.3 Hz, 2H), 5.69 (br, 1H), 3.98 (s, 2H), 3.20 (t, *J* = 6.7 Hz, 2H), 2.57 (t, *J* = 6.7 Hz, 2H), 2.41 (s, 3H), 2.14 (s, 3H), 1.76 (app p, *J* = 6.7, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 209.0, 173.5, 143.9, 136.3, 129.9(2), 127.5(2), 48.5, 48.3, 39.9, 30.3, 21.7, 21.6; **IR** (thin film): 2800-3600 (br), 1715 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{14}H_{19}NO_5SNa$ $[M+Na]^+$: 336.0882, found: 336.0873.



9f **S1**

Benzyl 2-methyl-3-((4-methyl-N-(2-methylallyl)phenyl)sulfonamido)propanoate (S1): To a solution of allylic amine **9f** (1.00 g, 1.0 equiv, 4.4 mmol) and K_2CO_3 (1.84 g, 3.0 equiv, 13.2 mmol) in acetonitrile at 23 ºC was added benzyl methacrylate (1.56 g, 2.0 equiv, 8.9 mmol). The reaction mixture was stirred at 23 ºC for 12 h. Upon completion (as judged by TLC), the solid was removed by filtration and the organic solvent was removed by rotary evaporation. The crude product was then purified by automated flash chromatography (0 - 50%, EtOAc/hexanes) to afford ester **S1** as a colorless oil (1.28 g, 72% yield). TLC (EtOAc/Hexanes, 1:1 v/v): R_f = 0.55; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.68 (d, *J* = 8.2 Hz, 2H), 7.44 – 7.29 (m, 5H), 7.27 (d, *J* = 8.2 Hz, 2H), 5.09 (d, *J* = 19.5 Hz, 1H), 5.07 (d, *J* = 19.5 Hz, 1H), 4.85 (d, *J* = 17.7 Hz, 1H), 3.67 (d, *J* = 24.2 Hz, 1H), 3.64 (d, *J* = 24.2 Hz, 1H), 3.33 (dd, *J* = 14.4, 7.1 Hz, 1H), 3.33 (dd, J = 56.0, 14.4, 7.1 Hz, 1H), 3.19 (dd, J = 56.0, 14.4, 7.1 Hz, 1H), 2.89 (td, 7.1, 7.1 Hz, 1H), 2.41 (s, 3H), 1.65 (s, 3H), 1.17 (d, *J* = 7.1 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 174.9, 143.5, 140.8, 136.6, 136.0,

129.8 (2), 128.7 (2), 128.4, 128.3 (2), 127.5 (2), 115.0, 66.6, 56.2, 51.3, 39.5, 21.7, 20.1, 15.6; **IR** (thin film): 1733, 1160 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{22}H_{27}NO_4SNa$ $[M+Na]^+$: 424.1558 found: 424.1578.

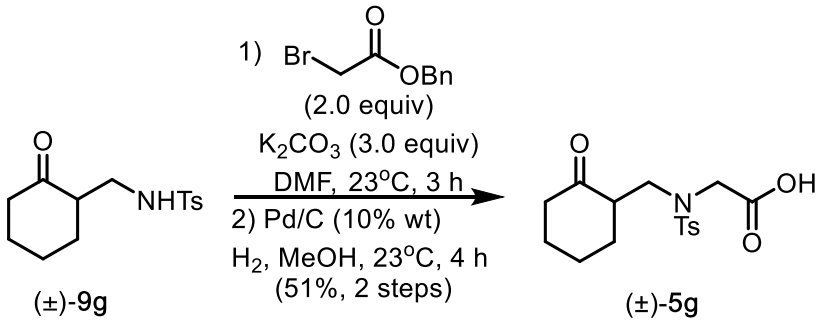


S1 **5f**

2-Methyl-3-((4-methyl-*N*-(2-oxopropyl)phenyl)sulfonamido) propanoic acid (5f): To a solution of alkene ester **S1** (1.20 g, 1.0 equiv, 3.0 mmol) in dichloromethane (60 mL) under -78 ºC was treated with ozone. After the solution turned pale blue, nitrogen gas was introduced until the blue color faded away. Then, DMS (2.3 mL, 30 mmol, 10.0 equiv) was added at -78 ºC. The reaction mixture was warmed up to 23 ºC and stirred overnight. The solvent was removed by rotary evaporation and the crude keto ester was directly used for the next step without further purifications.

To a solution of the crude keto ester in methanol (60 mL) was added Pd/C (122 mg, 10% wt). The suspension was charged with H_2 and stirred under H_2 atmosphere at 23 ºC. Upon completion (as judged by TLC), the suspension was filtered through a pad of Celite and the solvent was removed by rotary evaporation. The crude product was then purified by automated flash chromatography (0 → 100%, EtOAc/hexanes) to afford keto acid **5f** as a white solid (695 mg, 74% yield over two steps). TLC (EtOAc): R_f = 0.38; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.67 (d, *J* = 8.3 Hz, 2H), 7.30 (d, *J* = 8.3 Hz, 2H), 4.10 (d, *J* = 2.1Hz , 2H), 3.31 (d, *J* = 7.1 Hz, 2H), 2.87 (td, *J* = 7.1, 7.1 Hz, 1H), 2.42 (s, 3H), 2.12 (s, 3H), 1.20 (d, *J* = 7.1 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 203.8, 180.7, 144.0, 136.0, 129.9 (2),

127.7 (2), 58.6, 52.0, 40.1, 27.0, 21.8, 15.5; **IR** (thin film): 1732 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{14}H_{19}NO_5SNa$ $[M+Na]^+$: 336.0882, found: 336.0897.

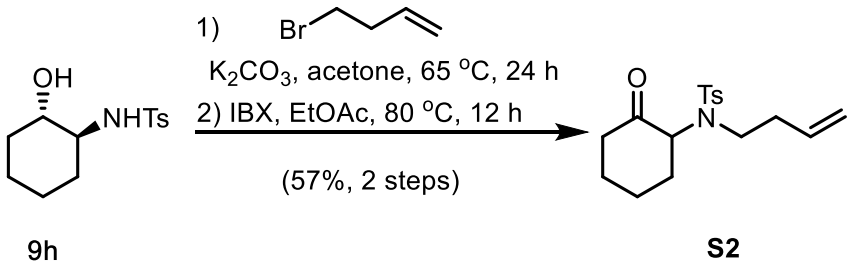


***N*-((2-oxocyclohexyl)methyl)-*N*-tosylglycine (5g)**: To a solution of amino ketone **9g**[31] (1.50 g, 5.0 mmol, 1.0 equiv) and K_2CO_3 (2.10 g, 15 mmol, 3.0 equiv) in DMF (25 mL) was added benzyl 2-bromoacetate (2.3 mL, 10.0 mmol, 2.0 equiv). The reaction was stirred for 3 h at ambient temperature (23 ºC). Upon completion (as judged by TLC), the inorganic salts were removed through filtration. Diethyl ether (100 mL) was added, and the organic phase was washed with water (100 mL x 2) and brine (100 mL). The organic phase was dried over $MgSO_4$. The solvent was removed by rotary evaporation. The crude mixture was filtered through a short pad of silica gel (100% hexane, then 100% EtOAc) to remove the excess benzyl 2-bromoacetate. The crude mixture was directly used in the next step without further purification.

To a solution of the crude keto ester (1.25 g) in methanol was added Pd/C (0.125 mg). The suspension was charged with H_2 and stirred under H_2 atmosphere at 23 ºC for 4 h. Upon completion (as judge by TLC), the suspension was filtered through a pad of Celite and the solvent was removed by rotary evaporation. The crude product was then purified by automated flash chromatography (0 → 100%, EtOAc/hexanes) to afford keto acid **5g** as a white solid (864 mg, 51% yield). (EtOAc, 100%): R_f = 0.60; **^{1}H NMR** (600 MHz, $CDCl_3$):

δ 7.67 (d, *J* = 8.3 Hz, 2H), 7.30 (d, *J* = 8.1 Hz, 2H), 4.23 (d, *J* = 18.5 Hz, 1H), 4.04 (d, *J* = 18.5 Hz, 1H), 3.40 (dd, *J* = 15.0, 7.1 Hz 1H), 3.23 (d, *J* = 15.0, 5.1 Hz, 1H), 2.82 (td, *J* = 12.5, 6.0 Hz, 1H), 2.43 (s, 3H), 2.37 (dddd, *J* = 13.4, 4.6, 3.1, 1.5 Hz, 1H), 2.31 (dt, *J* = 13.1, 6.1 Hz, 1H), 2.25 (ddd, *J* = 13.2, 5.7, 2.9 Hz, 1H), 2.09 (ddt, *J* = 12.5, 6.1, 2.9 Hz, 1H), 1.92 – 1.85 (m, 1H), 1.77 – 1.54 (m, 2H), 1.37 (dq, *J* = 12.8, 3.7 Hz, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 213.1, 174.4, 144.0, 136.2, 129.9 (2), 127.5 (2), 51.7, 50.5, 49.4, 42.3, 32.6, 28.2, 25.2, 21.7; **IR** (thin film): 1704 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{16}H_{21}NNaO_5S$ $[M+Na]^+$: 362.1038, found: 362.1034.

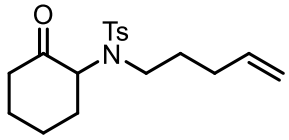
*Representative Procedure for the Sequential N-alkylation and IBX Oxidation as Described for **S2**:*



***N*-(but-3-en-1-yl)-4-methyl-*N*-(2-oxocyclohexyl)benzenesulfon-amide (S2)**: To a solution of amino alcohol **9h**[30] (3.23 g, 10.0 mmol 1.0 equiv) and K_2CO_3 (5.2 g, 30.0 mmol, 3.0 equiv) in acetone (50 mL) was added 4-bromo-1-butene (2.8 mL, 20.0 mmol, 2.0 equiv) at 23 ºC. The reaction mixture was heated up to 65 ºC for 24 h. Upon completion (as judged by TLC), the inorganic salts were removed by filtration and the solvent was removed by rotary evaporation. The remaining 4-bromo-1-butene was removed under high vacuum. The crude product was directly used in the next step without further purification.

To a solution of crude secondary alcohol in ethyl acetate (50 mL) was added 2-iodoxybenzoic acid (IBX). The reaction mixture was heated up to 80 ºC for 12 h. Upon

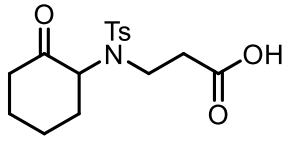
completion (as judged by TLC), the solid was removed by filtration and the solvent was removed by rotary evaporation. The crude product was purified by automated flash chromatography (0 → 50%, EtOAc/hexanes) to afford keto alkene **S2** (1.48 g, 46% yield over two steps). TLC (EtOAc:Hexanes, 1:3, v/v): R_f = 0.43; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.66 (d, *J* = 8.3 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 5.70 (ddt, *J* = 17.1, 10.3, 6.8 Hz, 1H), 5.09 – 4.85 (m, 2H), 4.57 (dd, *J* = 12.2, 5.7 Hz, 1H), 3.39 (ddd, *J* = 15.5, 11.0, 5.0 Hz, 1H), 2.92 (ddd, *J* = 15.5, 11.0, 5.5 Hz, 1H), 2.66 – 2.51 (m, 1H), 2.43 – 2.35 (m, 4H), 2.34 – 2.17 (m, 3H), 2.14 – 1.94 (m, 2H), 1.90 – 1.68 (m, 2H), 1.63 – 1.48 (m, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 206.0, 143.3, 137.4, 135.2, 129.6 (2), 127.5 (2), 116.8, 66.2, 46.3, 42.0, 36.2, 34.3, 26.8, 25.3, 21.8; **IR** (thin film): 1720 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{17}H_{23}NO_3SNa$ $[M+Na]^+$: 344.1296, found: 344.1291.



S3

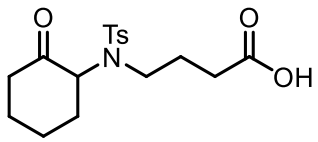
4-Methyl-*N*-(2-oxocyclohexyl)-*N*-(pent-4-en-1-yl)benzenesulfonamide (S3): Prepared according to the representative procedure for sequential *N*-alkylation and IBX oxidation. Amino alcohol **9h** (5.38 g, 20.0 mmol, 1.0 equiv), K_2CO_3 (10.3 g, 60.0 mmol), acetone (100 mL), and 5-bromo-1-pentene (6.0 mL, 40.0 mmol, 2.0 equiv) were used for *N*-alkylation. 2-iodoxybenzoic acid (IBX) (10.2 g, 40 mmol, 2.0 equiv) and ethyl acetate (100 mL) were used for IBX oxidation. Upon completion (as judged by TLC), the crude product was purified by automated flash chromatography (0 → 50%, EtOAc/hexanes) to afford keto alkene **S3** (3.87 g, 57% yield over two steps). TLC (EtOAc:Hexanes, 1:3, v/v): R_f = 0.45; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.66 (d, *J* = 8.3 Hz, 2H), 7.25 (d, *J* = 8.3 Hz, 2H), 5.75 (ddt, *J* = 16.8, 10.2, 6.4 Hz, 1H), 5.19 – 4.87 (m, 2H), 4.56 (dd, *J* = 12.2, 5.7 Hz, 1H), 3.32 (ddd, *J* = 15.4, 11.3, 4.4 Hz, 1H),

2.86 (ddd, *J* = 15.7, 10.8, 5.3 Hz, 1H), 2.49 – 2.34 (m, 4H), 2.34-2.18 (m, 2H) 2.09 – 1.88 (m, 5H), 1.86 – 1.67 (m, 2H), 1.67 – 1.46 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 206.0, 143.3, 137.8, 137.5, 129.6 (2), 127.5 (2), 115.4, 66.1, 46.4, 42.0, 34.3, 31.3, 30.9, 26.8, 25.4, 21.8; **IR** (thin film): 1715, 1641 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{18}H_{25}NO_3SNa$ $[M+Na]^+$: 362.1453, found: 362.1450.



5h

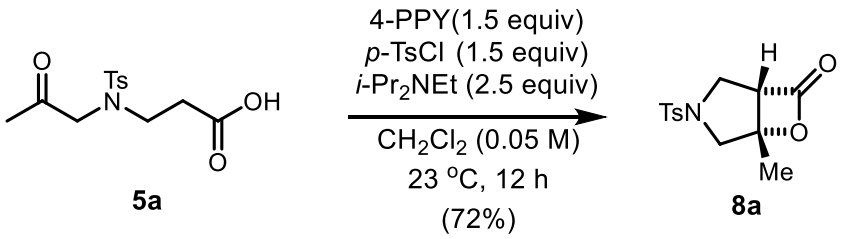
***N*-(3-oxobutyl)-*N*-tosylglycine (5h)**: Prepared according to the representative procedure for the sequential ozonolysis/Pinnick oxidation. Keto alkene **S2** (605 mg, 1.0 equiv, 1.8 mmol) and DMS (1.4 mL, 10.0 equiv, 18.0 mmol) was used for ozonolysis. $NaClO_2$ (0.38 g, 2.0 equiv, 3.6 mmol), NaH_2PO_4 (1.10 g, 5.0 equiv, 38.6 mmol), 2-methyl-2-butene (2.0 mL, 10.0 equiv, 18.0 mmol), *t*-BuOH (14 mL), H_2O (4.5 mL) were used for Pinnick oxidation. Upon completion (as judged by TLC), the crude product was purified by automated flash chromatography (0 → 100%, EtOAc/hexanes) to afford keto acid **5h** as a white solid (280 mg, 46% yield over two steps). TLC (EtOAc, 100%): R_f = 0.62; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.66 (d, *J* = 8.3 Hz, 2H), 7.28 (d, *J* = 8.3 Hz, 2H), 4.59 (dd, *J* = 12.4, 5.7 Hz, 1H), 3.54 (ddd, J = 15.5, 10.0, 5.5 1H), 3.26 (ddd, *J* = 15.5, 10.0, 5.5 Hz, 1H), 3.04 (ddd, *J* = 17.0, 9.9, 5.5 Hz, 1H), 2.70 (ddd, *J* = 17.0, 10.0, 5.5 Hz, 1H), 2.41 (m, 4H), 2.31 – 2.16 (m, 2H), 2.11 – 1.94 (m, 1H), 1.92 – 1.69 (m, 2H), 1.56 (qt, *J* = 12.9, 3.8 Hz, 1H), 1.23 (dt, *J* = 20.1, 7.1 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 206.0, 176.6, 143.7, 136.8, 129.8 (2), 127.5 (2), 66.5, 41.9, 41.6, 36.2, 33.6, 26.7, 25.2, 21.8; **IR** (thin film):1720 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{16}H_{21}NNaO_5S$ $[M+Na]^+$: 362.1038, found: 362.1034.



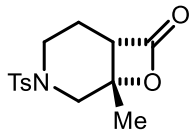
5i

***N*-(3-oxobutyl)-*N*-tosylglycine (5i)**: Prepared according to the representative procedure for the sequential ozonolysis/Pinnick oxidation. **S3** (1.20 g, 1.0 equiv, 3.60 mmol), DMS (2.7 mL, 10 equiv, 36.0 mmol) were used for ozonolysis. $NaClO_2$ (975 mg, 3.0 equiv, 10.8 mmol), NaH_2PO_4 (2.20 g, 5.0 equiv, 18.0 mmol), 2-methyl-2-butene (4.0 mL, 10.0 equiv, 36.0 mmol), *t*-BuOH (25 mL), H_2O (8 mL) were used for Pinnick oxidation. Upon completion (as judged by TLC), the crude product was purified by automated flash chromatography (0 → 100%, EtOAc/hexanes) to afford keto acid **5i** as a white solid (726 mg, 65% yield over two steps). TLC (EtOAc, 100%): R_f = 0.65; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.65 (d, *J* = 8.3 Hz, 2H), 7.25 (d, *J* = 8.3 Hz, 2H), 4.55 (dd, *J* = 12.7, 5.7 Hz, 1H), 3.34 (ddd, *J* = 15.5, 10.2, 5.4 Hz, 1H), 2.98 (ddd, *J* = 15.5, 10.2, 5.4 Hz, 1H), 2.45 – 2.33 (m, 6H), 2.31 – 2.18 (m, 2H), 2.14 – 1.95 (m, 3H), 1.95 – 1.68 (m, 3H), 1.55 (dddd, *J* = 17.7, 13.9, 8.9, 4.2 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 206.1, 178.8, 143.5, 137.1, 129.6 (2), 127.5 (2), 66.1, 45.8, 42.0, 34.0, 31.1, 26.8, 26.4, 25.3, 21.8; **IR** (thin film):1722 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{17}H_{23}NNaO_5S$ $[M+Na]^+$: 376.1195, found: 376.1189.

*Representative Procedure A for the Racemic Nucleophile-Catalyzed Aldol Lactonization (NCAL) Cascade as Described for β-Lactone **(±)-8a***

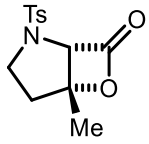


5-Methyl-3-tosyl-6-oxa-3-azabicyclo[3.2.0]heptan-7-one ((±)-8a): To an oven-dried, round-bottom flask equipped with a magnetic stir bar was added *p*-toluenesulfonyl chloride (28 mg, 0.15 mmol, 1.5 equiv), 4-PPY (22 mg, 0.15 mmol, 1.5 equiv), CH_2Cl_2 (1.5 mL) and *N*,*N*-diisopropylethylamine (37.5 μL, 0.25 mmol, 2.5 equiv) under nitrogen atmosphere at 23°C. The keto acid **5a** (30 mg, 0.10 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL) was added dropwise through syringe pump over 3 h. After the addition was complete, the reaction was allowed to stir for an additional 9 h. Upon completion (as judged by TLC), the solvent was concentrated by rotary evaporation and the crude mixture was purified by flash chromatography (0 → 40%, EtOAc/hexanes) to afford the β-lactone (±)-**8a** as a white solid (21 mg, 72% yield). TLC (EtOAc:hexanes, 3:7 *v/v*): R_f = 0.34. **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.71 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 3.94 (d, *J* = 10.7 Hz, 1H), 3.88 (d, *J* = 11.9 Hz, 1H), 3.59 (d, *J* = 6.2 Hz, 1H), 2.97 (dd, *J* = 10.7, 6.4 Hz, 1H), 2.75 (d, *J* = 11.9 Hz, 1H), 2.45 (s, 3H), 1.66 (s, 3H); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 167.2, 144.7, 132.6, 130.1 (2), 128.1 (2), 83.7, 58.8, 55.4, 48.1, 21.81, 19.4; **IR** (thin film): 1826 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{13}H_{15}NO_4SNa$ $[M+Na]^+$: 304.0619, found: 304.0622.



(±)-8b

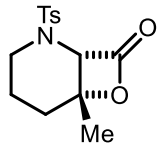
1-Methyl-3-tosyl-8-oxa-3-azabicyclo[4.2.0]octan-7-one ((±)-8b): Prepared according to representative procedure A for the racemic Nucleophile-catalyzed aldol lactonization (NCAL) cascade as described for β-lactone (±)-**8a** using *p*-toluenesulfonyl chloride (28 mg, 0.15 mmol, 1.5 equiv), 4-PPY (22 mg, 0.15 mmol, 1.5 equiv), CH_2Cl_2 (1.5 mL), *N*,*N*-diisopropylethylamine (37.5 μL, 0.25 mmol, 2.5 equiv) and keto acid **5b** (31 mg, 0.10 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL). The crude mixture was purified by flash chromatography (0 → 40%, EtOAc/hexanes) to afford β-lactone (±)-**8b** as a white solid (12 mg, 42% yield). TLC (EtOAc:hexanes, 3:7 *v/v*): R_f = 0.40. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.68 (d, *J* = 8.3 Hz, 1H), 7.33 (d, *J* = 8.3 Hz, 2H), 3.85 (d, *J* = 14.4 Hz, 1H), 3.43 – 3.34 (m, 1H), 3.27 (d, *J* = 14.4), 3.22 (td, *J* = 11.8, 6.0 Hz, 1H), 2.43 (s, 3H), 2.18 – 2.07 (m, 1H), 1.93 (ddt, *J* = 14.9, 10.6, 6.4 Hz, 1H), 1.59 (s, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 168.9, 144.2, 134.4, 130.0 (2), 127.7 (2), 76.5, 51.8, 49.8, 40.8, 23.2, 21.8, 19.7; **IR** (thin film): 1812 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{14}H_{17}NO_4SNa$ $[M+H]^+$: 318.0776, found: 318.0784.



(±)-8d

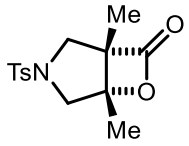
5-methyl-2-tosyl-6-oxa-2-azabicyclo[3.2.0]heptan-7-one ((±)-8d): Prepared according to representative procedure A for the racemic nucleophile-catalyzed aldol lactonization (NCAL) cascade as described for β-lactone (±)-**8a** using *p*-toluenesulfonyl chloride (28 mg, 0.15 mmol, 1.5 equiv), 4-PPY (22 mg, 0.15 mmol, 1.5 equiv), CH_2Cl_2 (1.5 mL) and *N*,*N*-diisopropylethylamine (37.5 μL, 0.25 mmol, 2.5 equiv) under nitrogen atmosphere at 23°C and keto acid **5d** (30 mg, 0.10 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL). The crude mixture was purified by flash chromatography (0→40%, EtOAc/hexanes) to afford β-

lactone (±)-**8d** as a white solid (22 mg, 78% yield). TLC (EtOAc:hexanes, 3:7 *v/v*): R_f = 0.37. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.78 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 2H), 5.07 (s, 1H), 3.99 (dd, J = 11.2, 8.2 Hz, 1H), 3.14 (td, *J* = 11.4, 5.8 Hz, 1H), 2.43 (s, 3H), 2.21 (dd, *J* = 14.3, 5.8 Hz, 1H), 1.80 (ddd, *J* = 14.3, 11.6, 8.2 Hz, 1H), 1.67 (s, 3H); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 164.7, 144.7, 135.0, 130.0 (2), 128.1 (2), 87.5, 73.7, 46.9, 35.4, 21.8, 20.9; **IR** (thin film): 1829 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{13}H_{15}NO_4SNa$ [M+Na]+: 304.0619, found: 304.0633.



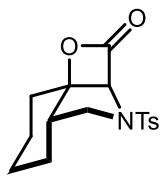
(±)-8e

6-methyl-2-tosyl-7-oxa-2-azabicyclo[4.2.0]octan-8-one ((±)-2-8e): Prepared according to representative procedure A for the racemic nucleophile-catalyzed aldol lactonization (NCAL) cascade as described for β- lactone (±)-**8a** using *p*-toluenesulfonyl chloride (28 mg, 0.15 mmol, 1.5 equiv), 4-PPY (22 mg, 0.15 mmol, 1.5 equiv), CH_2Cl_2 (1.5 mL), *N*,*N*-diisopropylethylamine (37.5 μL, 0.25 mmol, 2.5 equiv) and keto acid **5e** (31 mg, 0.10 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL). The crude mixture was purified by flash chromatography (0→40%, EtOAc/hexanes) to afford β-lactone (±)-**8e** as a white solid (14 mg, 48% yield). TLC (EtOAc:hexanes, 3:7 *v/v*): R_f = 0.45. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.77 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 8.3 Hz, 2H), 5.20 (s, 1H), 3.49 (dt, *J* = 11.1, 8.9 Hz, 1H), 3.28 – 3.07 (m, 1H), 2.43 (s, 3H), 2.19 – 2.09 (m, 1H), 1.78 (m, 3H), 1.63 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 168.5, 144.4, 135.2, 130.0 (2), 127.8 (2), 80.9, 65.1, 42.0, 31.1, 24.5, 21.8, 16.8; **IR** (thin film): 1828 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{14}H_{17}NO_4SNa$ $[M+Na]^+$: 318.0776, found: 318.0784.



(±)-8f

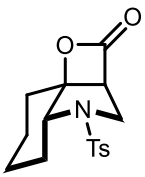
1,5-Dimethyl-3-tosyl-6-oxa-3-azabicyclo[3.2.0]heptan-7-one ((±)-8f): Prepared according to representative procedure A for the racemic nucleophile-catalyzed aldol lactonization (NCAL) cascade as described for (±)-**8a** using *p*-toluenesulfonyl chloride (56 mg, 0.30 mmol, 1.5 equiv), 4-PPY (44 mg, 0.30 mmol, 1.5 equiv), CH_2Cl_2 (3.0 mL), *N*,*N*-diisopropylethylamine (73.0 μL, 0.50 mmol, 2.5 equiv) and keto acid **5f** (62 mg, 0.20 mmol, 1.0 equiv) in CH_2Cl_2 (1.0 mL). The crude mixture was purified by flash chromatography (0→40%, EtOAc/hexanes) to afford β-lactone **(±)-8f** as a white solid (14 mg, 24% yield). TLC (EtOAc:hexanes, 3:7 *v/v*): R_f = 0.46; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.71 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 8.3 Hz, 2H), 3.95 (d, *J* = 10.6 Hz, 1H), 3.91 (d, *J* = 11.9 Hz, 1H), 2.78 (d, *J* = 11.9, 1H), 2.65 (d, *J* = 10.6, 1H), 2.45 (s, 3H), 1.50 (s, 3H), 1.25 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 170.9, 144.6, 132.9, 130.1 (2), 128.1 (2), 86.1, 62.8, 55.7, 54.2, 21.8, 16.4, 11.4; **IR** (thin film): 1826 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{14}H_{17}NO_4SNa$ $[M+Na]^+$: 318.0776, found: 318.0771.



(±)-8g

3-tosyloctahydro-2H-oxeto[3,2-c]isoindol-2-one ((±)-8g): Prepared according to the representative procedure A for the racemic nucleophile-catalyzed aldol lactonization (NCAL) cascade as described for (±)-**8a** using *p*-toluenesulfonyl chloride (85 mg, 0.45 mmol, 1.5 equiv), 4-PPY (66 mg, 0.45 mmol, 1.5 equiv), CH_2Cl_2 (5.5 mL), *N*,*N*-diisopropylethylamine (0.12 mL, 0.75 mmol, 2.5 equiv) and keto acid **5g** (101 mg, 0.30 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL). The crude mixture was purified by flash chromatography (0→40%, EtOAc/hexanes) to afford β-lactone **(±)-8g** as a white solid (76 mg, 79% yield). TLC (EtOAc:hexanes, 3:7 *v/v*): R_f = 0.52; **^{1}H NMR** (400 MHz, $CDCl_3$):

δ 7.78 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.3 Hz, 2H), 5.02 (s, 1H), 3.57 (d, *J* = 10.1 Hz, 1H), 3.24 (dd, *J* = 10.1, 5.0 Hz, 1H), 2.42 (s, 3H), 2.25 (ddd, *J* = 11.9, 6.4, 4.9 Hz, 1H), 2.21 – 2.14 (m, 1H), 2.02 – 1.84 (m, 3H), 1.72 (ddd, *J* = 17.4, 10.2, 6.6 Hz, 1H), 1.39 (app dq, *J* = 13.6, 3.7 Hz, 1H), 1.32 – 1.15 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 164.2, 144.3, 135.5, 129.8 (2), 128.0 (2), 89.0, 71.4, 52.0, 41.0, 30.3, 28.6, 23.7, 23.5, 21.8; **IR** (thin film): 1829 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{16}H_{19}NO_4SNa$ $[M+Na]^+$: 344.0932, found: 344.0938.

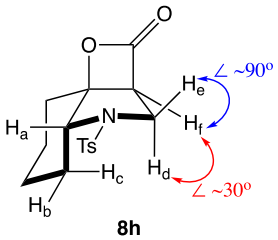


(±)-8h

4-tosyloctahydro-2H-oxeto[3,2-c]indol-2-one ((±)-8h): Prepared according to the representative procedure A for the racemic nucleophile-catalyzed aldol lactonization (NCAL) cascade as described for (±)-**8a** using *p*-toluenesulfonyl chloride (85 mg, 0.45 mmol, 1.5 equiv), 4-PPY (66 mg, 0.45 mmol, 1.5 equiv), CH_2Cl_2 (5.5 mL), *N*,*N*-diisopropylethylamine (0.12 mL, 0.75 mmol, 2.5 equiv) and keto acid **5h** (101 mg, 0.30 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL). The crude mixture was purified by flash chromatography (0→40%, EtOAc/hexanes) to afford β-lactone **(±)-8j** as a white solid (79 mg, 82% yield). TLC (EtOAc:hexanes, 3:7 *v/v*): R_f = 0.50; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.72 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.1 Hz, 2H), 4.07 (dd, *J* = 10.8, 7.0 Hz, 1H), 3.85 (d, *J* = 12.0 Hz, 1H), 3.58 (dd, *J* = 12.0, 6.5 Hz, 1H), 3.50 (d, *J* = 6.5 Hz, 1H), 2.42 (s, 3H), 2.32 (app qt, *J* = 7.1, 2.4 Hz, 1H), 2.28 – 2.14 (m, 1H), 1.97 (td, *J* = 13.7, 4.8 Hz, 1H), 1.88 (ddt, *J* = 13.5, 4.9, 2.6 Hz, 1H), 1.76 (dt, *J* = 8.9, 2.7 Hz, 1H), 1.33 – 1.24 (m, 2H), 1.24 – 1.10 (m, 1H); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 167.8, 144.1, 136.7, 129.9 (2), 127.4 (2), 86.3, 61.5, 57.6, 45.7, 31.1, 29.3, 23.6, 22.8, 21.8; **IR** (thin film): 1834 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{16}H_{19}NO_4SNa$ $[M+Na]^+$: 344.0932, found: 344.0929.

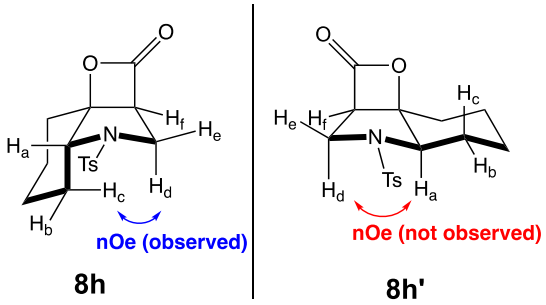
The relative stereochemistry of the major diastereomer obtained *via* the NCAL was assigned as **8h** based on strain considerations, analogy to tricyclic, carbocycle-fused β-lactones previously obtained *via* the NCAL, coupling constants and 2D NMR analysis (COSY and NOESY) as described below.

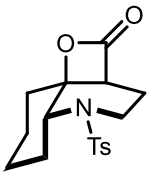
Analysis of chemical shift, coupling constants and COSY spectra indicates that signals in the δ 3.4 – 3.9 ppm range belong to one spin system (H_d, H_e, H_f), while the dd at δ 4.07 belongs to a different spin system assigned as Ha. The COSY spectra allowed assignment of H_b and H_c due to correlation between these protons and H_a. The signal at δ 1.24-1.33(m) is assigned as the axial proton (H_c) because it is significantly shielded relative to H_b assigned as the equatorial proton at δ 2.32 (apparent tq) notwithstanding shielding/deshielding effects of the tosyl group. Use of molecular models (and Chem3D) to analyze dihedral angles enabled assignment of H_d. This proton is assigned as the dd at δ 3.58 because the dihedral angle between H_f and H_d should be ~30˚. On the other hand, the dihedral angle between H_e and H_f is ~90˚so $^3J_{He,Hf}$ should be ~0, and indeed both H_e and H_f appear as doublets only coupled to H_d based on analysis of the COSY spectrum. Furthermore, vicinal coupling ($^3J_{Hd,Hf}$) should be smaller than germinal coupling ($^2J_{Hd,He}$) as observed He and Hf as shown in the spectra above.



8h

Following the assignment of H_d and H_c, we performed a NOESY experiment to reveal any nOe correlation between protons which would be expected for β-lactone **8h** and its diasteomer **8h'**. The nOe correlation observed between H_c (δ 1.24-1.33, m) and H_d (δ 3.58, dd) led to assignment of the relative stereochemistry of the major diastereomer obtained *via* the NCAL as **8h** (>19:1 dr) rather than **8h'**. Due to the high diastereoselectivity obtained in the NCAL, we could not isolate the diastereomer, pyrrolidine **8h'**, in order to confirm the anticipated nOe between H_a/H_d for this diastereomer.



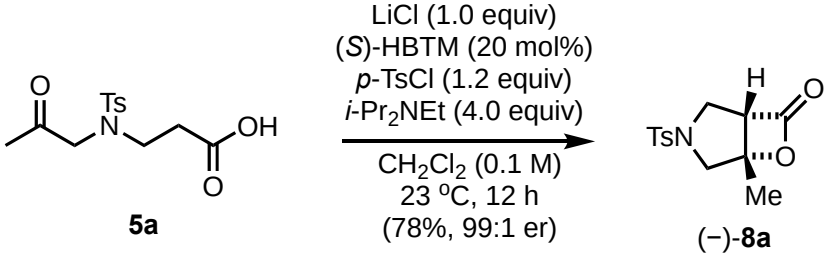


(±)-8i

5-tosyloctahydrooxeto[3,2-d]quinolin-2(2aH)-one ((±)-8i): Prepared according to the representative procedure A for the racemic nucleophile-catalyzed aldol lactonization (NCAL) cascade as described for (±)-**8a** using *p*-toluenesulfonyl chloride (85 mg, 0.45 mmol, 1.5 equiv), 4-PPY (66 mg, 0.45 mmol, 1.5 equiv), CH_2Cl_2 (5.5 mL), *N*,*N*-diisopropylethylamine (0.12 mL, 0.75 mmol, 2.5 equiv)and keto acid **5i** (106 mg, 0.30 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL) . The crude mixture was purified by flash chromatography (0→40%, EtOAc/hexanes) to afford β-lactone **(±)-8i** as a white solid (69 mg, 69% yield). TLC (EtOAc:hexanes, 3:7 *v/v*): R_f = 0.54; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.67 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 8.2 Hz, 2H), 4.02 (dd, *J* = 12.1, 5.4 Hz, 1H), 3.70 (ddd, *J* = 11.5, 6.1, 2.1 Hz, 1H), 3.28 (dd, *J* = 4.7, 2.8 Hz, 1H), 3.06 (td, *J* = 12.1, 5.9 Hz, 1H), 2.41 (s, 3H), 2.34 (ddd, *J* = 12.8, 5.3, 2.4 Hz, 1H), 2.27 – 2.16 (m, 1H), 2.16 – 2.06 (m, 1H), 1.97 (dd, *J* = 12.4, 3.1 Hz, 1H), 1.92 – 1.81 (m, 2H), 1.77 (dt, *J* = 13.1, 2.9 Hz,

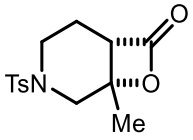
1H), 1.49 (ddd, *J* = 12.7, 12.2, 3.3 Hz, 1H), 1.45 – 1.30 (m, 1H), 1.23 – 1.05 (m, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 168.8, 143.8, 135.1, 129.7 (2), 127.6 (2), 78.9, 56.3, 50.5, 38.9, 36.8, 35.3, 24.4, 23.9, 21.8, 19.5; **IR** (thin film): 1823 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{17}H_{21}NO_4SNa$ $[M+Na]^+$: 358.1089, found: 358.1084.

Representative Procedure B for the Enantioselective Nucleophile-Catalyzed Aldol Lactonization (NCAL) Cascade as Described for (–)-8a:



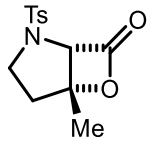
(1S,5S)-5-Methyl-3-tosyl-6-oxa-3-azabicyclo[3.2.0]heptan-7-one ((–)-**8a)**: To an oven-dried, 10 mL round-bottomed flask equipped with a magnetic stir bar was added *p*-toluenesulfonyl chloride (58 mg, 0.30 mmol, 1.2 equiv), lithium chloride (11 mg, 0.25 mmol, 1.0 equiv), (*S*)-HBTM (13 mg, 0.05 mmol, 0.2 equiv), CH_2Cl_2 (2.5 mL) and *N*,*N*-diisopropylethylamine (0.18 mL, 1.0 mmol, 4.0 equiv). To this mixture was added keto acid **5a** (0.25 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL) through syringe pump over 6 h. After the addition was complete, the reaction was allowed to stir for an additional 6 h. Upon completion (as judged by TLC), the reaction mixture was diluted with ether (20 mL), and the organic phase was then washed with water (2×20 mL) and brine (20 mL). The organic phase was dried over $MgSO_4$ and concentrated by rotary evaporation. The crude mixture was purified by flash chromatography (0 → 40%, EtOAc/hexanes) to afford the β-lactone (–)-**8a** as a white solid (55 mg, 78% yield). TLC (EtOAc:hexanes, 3:7 *v/v*): R_f = 0.34; $[\alpha]_D^{20}$ -6.00 (*c* = 1.0, $CHCl_3$). Enantiomeric ratio was determined by HPLC analysis in

comparison with authentic racemic material using a Chiralcel IA column: hexanes:*i*PrOH = 85:15, flow rate 1.0 mL/min, λ = 230 nm: t_{major} = 19.6 min, t_{minor} = 24.9 min; 99:1 er. Absolute stereochemistry was assigned by analogy to β-lactone (–)-**2-8d** given that (*S*)-HBTM was employed as Lewis base.



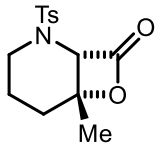
(–)-8b

(1S,6S)-1-Methyl-3-tosyl-8-oxa-3-azabicyclo[4.2.0]octan-7-one ((–)-**8b)**: Prepared according to representative procedure B for the enantioselective nucleophile-catalyzed aldol lactonization (NCAL) cascade as described for β-lactone (–)-**8a** using *p*-toluenesulfonyl chloride (58 mg, 0.30 mmol, 1.2 equiv), lithium chloride (11 mg, 0.25 mmol, 1.0 equiv), (*S*)-HBTM (13 mg, 0.05 mmol, 0.2 equiv), CH_2Cl_2 (2.5 mL), *N*,*N*-diisopropylethylamine (0.18 mL, 1.2 mmol, 4.0 equiv) and keto acid **5b** (79 mg, 0.25 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 ml). The crude mixture was purified by flash chromatography (0→40%, EtOAc/hexanes) to afford β-lactone (–)-**8b** as a white solid (33 mg, 45% yield). TLC (EtOAc:hexanes, 3:7 *v/v*): R_f = 0.40; $[\alpha]_D^{20}$ –78.40 (*c* = 0.5, $CHCl_3$). Enantiomeric ratio was determined by HPLC analysis in comparison with authentic racemic material using a Chiralcel IA column: hexanes:*i*PrOH = 85:15, flow rate 1.0 mL/min, λ = 230 nm: t_{minor} = 17.5min, t_{major} = 21.0 min; 99:1 er. Absolute stereochemistry was assigned by analogy to β-lactone (–)-**8d** given that (*S*)-HBTM was employed as Lewis base.



(–)-8d

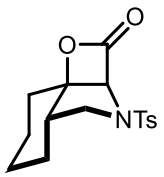
(1S,5R)-5-Methyl-2-tosyl-6-oxa-2-azabicyclo[3.2.0]heptan-7-one ((–)-8d): Prepared according to representative procedure B for the enantioselective nucleophile-catalyzed aldol lactonization (NCAL) cascade as described for β-lactone (–)-**8a** using *p*-toluenesulfonyl chloride (58 mg, 0.30 mmol, 1.2 equiv), lithium chloride (11 mg, 0.3 mmol, 1.0 equiv), (*S*)-HBTM (13 mg, 0.05 mmol, 0.2 equiv), CH_2Cl_2 (2.5 mL), *N*,*N*-diisopropylethylamine (0.18 mL, 1.2 mmol, 4.0 equiv) and keto acid **5d** (75 mg, 0.25 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL). The crude mixture was purified by flash chromatography (0→40%, EtOAc/hexanes) to afford β-lactone (–)-**8d** as a white solid (56 mg, 80% yield). TLC (EtOAc:hexanes, 3:7 *v/v*): R_f = 0.37; $[\alpha]_D^{20}$ = -119.20 (*c* = 1.0, $CHCl_3$). Enantiomeric ratio was determined by HPLC analysis in comparison with authentic racemic material using a Chiralcel IA column: hexanes:*i*PrOH = 85:15, flow rate 1.0 mL/min, λ = 230 nm: t_{major} = 16.1 min, t_{minor} = 20.6 min; 97:3 er. Absolute stereochemistry was assigned by comparison of the optical rotation to a literature value: $[\alpha]_D^{25}$ -127 (*c* = 1.08, $CHCl_3$).[38]



(+)-8e

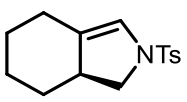
(1S,6R)-6-methyl-2-tosyl-7-oxa-2-azabicyclo[4.2.0]octan-8-one ((+)-8e): Prepared according to representative procedure B for the enantioselective nucleophile-catalyzed aldol lactonization (NCAL) cascade as described for (–)-**8a** using *p*-toluenesulfonyl chloride (58 mg, 0.30 mmol, 1.2 equiv), lithium chloride (11 mg, 0.3 mmol, 1.0 equiv), (*S*)-HBTM (13 mg, 0.05 mmol, 0.2 equiv), CH_2Cl_2 (2.5 mL), *N*,*N*-diisopropylethylamine (0.18 mL, 1.2 mmol, 4.0 equiv) and keto acid **5e** (79 mg, 0.25 mmol, 1.0 equiv) in CH_2Cl_2. The crude mixture was purified by flash chromatography (0→40%, EtOAc/hexanes) to afford β-lactone (+)-**8e** as a white solid (38 mg, 73% yield). TLC (EtOAc:hexanes, 1:1 *v/v*):

R_f = 0.45; $[\alpha]_D^{20}$ +45.60 (*c* = 1.0, $CHCl_3$). Enantiomeric ratio was determined by HPLC analysis in comparison with authentic racemic material using a Chiralcel IA column: hexanes:*i*PrOH = 85:15, flow rate 1.0 mL/min, λ = 230 nm: t_{minor} = 11.0 min, t_{major} = 13.3 min; 99:1 *e.r.*. Absolute stereochemistry was assigned by analogy to β-lactone (–)-**8d** given that (*S*)-HBTM was employed as Lewis base.



(–)-8g

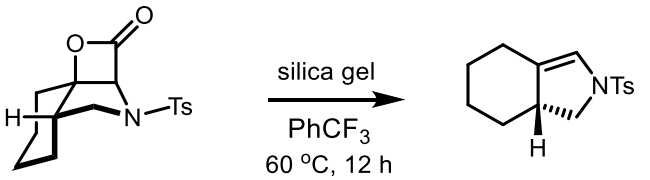
(2aS,4aS,8aR)-3-tosyloctahydro-2H-oxeto[3,2-c]isoindol-2-one ((–)-8g): Prepared according to representative procedure B for the enantioselective nucleophile-catalyzed aldol lactonization (NCAL) cascade as described for (–)-**8a** using *p*-toluenesulfonyl chloride (58 mg, 0.30 mmol, 1.2 equiv), lithium chloride (11 mg, 0.3 mmol, 1.0 equiv), (*S*)-HBTM (13 mg, 0.05 mmol, 0.2 equiv), CH_2Cl_2 (2.5 mL), *N*,*N*-diisopropylethylamine (0.18 mL, 1.2 mmol, 4.0 equiv) and keto acid **5g** (85 mg, 0.25 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL). The crude mixture was purified by flash chromatography (0→40%, EtOAc/hexanes) to afford β-lactone (–)-**8g** (55 mg, 68% yield) as a white solid. TLC (EtOAc:hexanes, 3:7 *v/v*): R_f = 0.52; $[\alpha]_D^{20}$ -51.20 (*c* = 1.0, $CHCl_3$). Enantiomeric ratio was determined by HPLC analysis in comparison with authentic racemic material using a Chiralcel IA column: hexanes:*i*PrOH = 90:10, flow rate 1.0 mL/min, λ = 230 nm: t_{major} = 21.2 min, t_{minor} = 25.0 min; 71:29 er. Absolute stereochemistry of the major enantiomer was assigned by analogy to β-lactone (–)-**8d** given that (*S*)-HBTM was employed as Lewis base.



(–)- 13

(*S*)-2-tosyl-2,4,5,6,7,7a-hexahydro-1H-isoindole (13): **13** was obtained as a side product from the synthesis of **(–)-8g** and was afforded as a white solid (7 mg, 10% yield). TLC (EtOAc:hexanes, 1:4 *v/v*): R*f* = 0.55; $[\alpha]_D^{20}$ -8.00 (*c* = 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.66 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 6.01 (t, *J* = 2.0 Hz, 1H), 3.68 (dd, *J* = 10.9, 10.0 Hz, 1H), 3.01 (dd, *J* = 10.9, 7.2 Hz, 1H), 2.58 – 2.47 (m, 1H), 2.43 (s, 3H), 2.41 – 2.26 (m, 2H), 1.90 – 1.70 (m, 1H), 1.71 – 1.61 (m, 1H), 1.31 – 1.02 (m, 3H), 0.77 (dq, *J* = 12.4, 3.3 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 143.7, 133.1, 129.8, 129.7 (2), 128.0 (2), 121.09, 53.8, 43.2, 34.4, 27.3, 25.7, 25.3, 21.8; **IR** (thin film): 1597 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{15}H_{19}NO_2SNa$ $[M+Na]^+$: 300.1034, found: 300.1030. Enantiomeric ratio was determined by HPLC analysis in comparison with authentic racemic material using a Chiralcel IA column: hexanes:*i*PrOH = 90:10, flow rate 1.0 mL/min, λ = 230 nm: t_{major} = 9.6 min, t_{minor} = 11.9 min; Enantiomeric ratio = 95:5.

Functionalization of tricyclic N-heterocycle-fused β-lactones

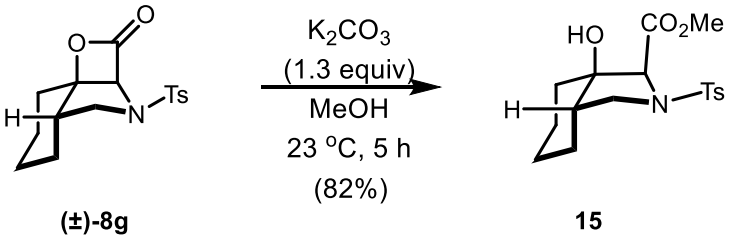


(–)-8g
(70:30 er)

(+)-13
(79%, 69:31 er)

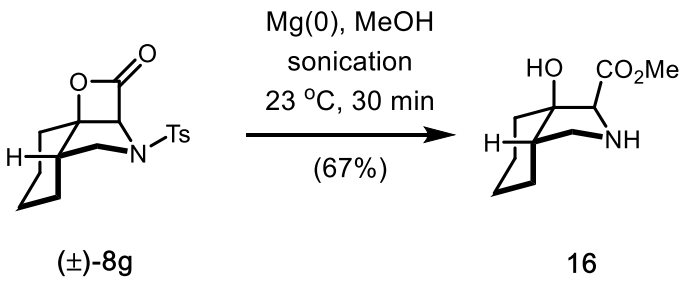
(*R*)-2-tosyl-2,4,5,6,7,7a-hexahydro-1H-isoindole ((+)-13): To a solution of **(–)-8g** (16 mg, 0.05 mmol, 1.0 equiv) in $PhCF_3$ (0.5 mL) was added silica gel (160 mg). The reaction mixture was heated to 60 ˚C for 12 h. Upon completion (as judged by TLC), the crude mixture was purified by flash chromatography (0→20%, EtOAc/hexanes) to afford **13** as

a white solid (11 mg, 79% yield). NMR data matched that obtained for (–)-**13** (*vide infra*). $[\alpha]_D^{20}$ +2.12 (*c* = 1.0, $CHCl_3$); Enantiomeric ratio was determined by HPLC analysis in comparison with authentic racemic material using a Chiralcel IA column: hexanes:*i*PrOH = 90:10, flow rate 1.0 mL/min, λ = 230 nm: t_{major} = 9.7 min, t_{minor} = 12.0 min; 69:31 er.



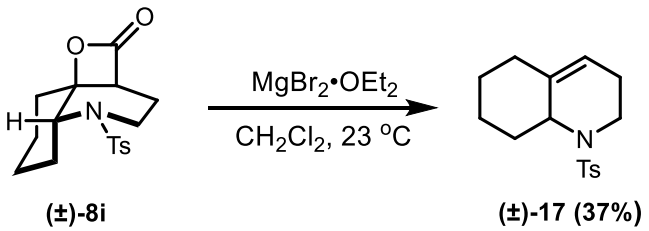
(±)-8g **15**

Methyl-7a-hydroxy-2-tosyloctahydro-1H-isoindole-1-carboxy-late (13): To a solution of **8g** (33 mg, 0.10 mmol, 1 equiv) in methanol (1.0 mL) was added p K_2CO_3 (18 mg, 0.13 mmol, 1.3 equiv). The reaction mixture was stirred at 23 ºC for 3 h. Upon completion (as judged by TLC), the inorganic salts were removed through filtration. The solvent was removed by rotary evaporation. The crude product was then purified by flash chromatography (0 → 30%, EtOAc/hexanes) to afford hydroxy ester **15** as a white solid (29 mg, 82% yield). TLC (EtOAc:hexanes, 1:3 *v/v*): R_f = 0.65; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.76 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 8.3 Hz, 2H), 4.17 (s, 1H), 3.73 (s, 3H), 3.59 (dd, *J* = 9.6, 6.9 Hz, 1H), 3.18 (dd, *J* = 9.6, 6.2 Hz, 1H), 2.43 (s, 3H), 2.31 (brs, 1H), 2.25 (td, *J* = 6.5, 6.5 Hz, 1H), 1.65 – 1.43 (m, 4H), 1.41 – 1.27 (m, 3H), 1.09 (ddd, *J* = 14.6, 11.7, 6.5 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 170.7, 143.9, 135.5, 129.8 (2), 127.7 (2), 79.3, 67.3, 52.6, 50.5, 43.6, 33.5, 24.6, 22.2, 22.2, 21.8; **IR** (thin film): 3491, 1742 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{17}H_{23}NNaO_5S$ $[M+Na]^+$: 376.1195, found: 376.1191.



(±)-8g 16

Methyl 7a-hydroxyoctahydro-1H-isoindole-1-carboxylate (16): To a solution of **8j** (33 mg, 0.10 mmol, 1 equiv) in methanol (2.0 mL) under nitrogen atmosphere was added magnesium powder (48 mg, 2.0 mmol, 20 equiv). The reaction mixture was sonicated at 23 ºC for 30 min. Upon completion (as judged by TLC), the crude product was directly purified by flash chromatography (9:90:1, MeOH: CH_2Cl_2: NEt_3) to afford amino hydroxy ester **16** as a white solid (13 mg, 67% yield). TLC (MeOH: CH_2Cl_2: NEt_3, 10:90:4 *v/v*): R_f = 0.55; **^{1}H NMR** (600 MHz, $CDCl_3$): δ 3.89 (s, 1H), 3.77 (s, 3H), 3.47 (dd, *J* = 10.3, 5.5 Hz, 1H), 2.71 (dd, *J* = 9.8, 2.1 Hz, 1H), 2.55 (brs, 1H), 2.24 (dt, *J* = 13.5, 3.7 Hz, 2H), 1.93 (dtd, *J* = 11.1, 5.9, 2.1 Hz, 1H), 1.79 – 1.70 (m, 2H), 1.69 – 1.63 (m, 1H), 1.56 (ddd, *J* = 13.5, 12.2, 4.4 Hz, 1H), 1.44 – 1.32 (m, 1H), 1.33 – 1.21 (m, 2H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 173.1, 81.4, 64.8, 52.4, 50.6, 47.5, 33.5, 29.2, 24.5, 23.4; **IR** (thin film): 3100-3700 (br), 1738 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{10}H_{18}NO_3$ $[M+H]^+$: 220.1287, found: 220.1289.



(±)-8i **(±)-17 (37%)**

1-tosyl-1,2,3,5,6,7,8,8a-octahydroquinoline ((±)-17): To a solution of tricyclic β-lactone **8j** (33 mg, 0.10 mmol, 1 equiv) in dichloromethane (1.0 mL) under nitrogen atmosphere was added magnesium bromide etherate (28 mg, 0.11 mmol, 1.1 equiv). The reaction mixture was sonicated at 23 ºC for 30 min. Upon completion (as judged by TLC), the crude product was directly purified by flash chromatography (0 - 25% EtOAc/Hexanes) to afford alkene **17** as a colorless liquid (13 mg, 37% yield). TLC (EtOAc:hexanes, 1:2 *v/v*): R_f = 0.80; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.69 (d, *J* = 8.3 Hz, 2H), 7.25 (d, *J* = 8.3 Hz, 2H), 5.37 – 5.31 (m, 1H), 4.10 (d, *J* = 6.9 Hz, 1H), 3.93 – 3.59 (m, 1H), 3.04 (ddd, *J* = 13.9, 11.5, 4.1 Hz, 1H), 2.40 (s, 3H), 2.22 (ddt, *J* = 13.0, 4.3, 2.3 Hz, 1H), 2.04 – 1.92 (m, 2H), 1.85 – 1.70 (m, 4H), 1.56 – 1.44 (m, 2H), 1.28 – 1.09 (m, 1H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 143.0, 139.0, 138.9, 129.8 (2), 127.0 (2), 116.8, 56.4, 39.1, 35.9, 34.5, 28.1, 25.7, 24.2, 21.7; **IR** (thin film): 1598 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{16}H_{22}NO_2S$ $[M+H]^+$: 292.1371, found: 292.1367.

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CHAPTER THREE

Aza-Michael-Initiated Organocascades by Employing α, β-Unsaturated acylammonium Intermediates

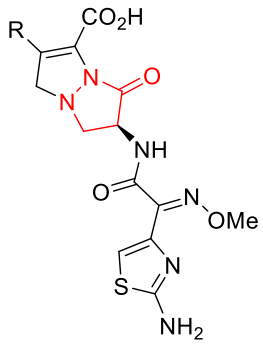
Abstract

The isothiourea-catalyzed enantioselective aza-Michael proton-transfer lactamization cascade reaction for the synthesis of *N*-heterocycles is described in this chapter. Optically active 1,5-benzodiazepinones and pyrazolidinones are synthesized in moderate yields and enantiomeric ratios.

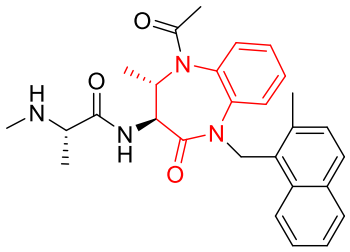
Introduction

The asymmetric aza-Michael reaction is an efficient method to form carbon-nitrogen bonds, thereby delivering numerous bioactive molecules such as β-amino acids.[40] Meanwhile, the enantioselective aza-Michael reaction can serve as an initial step in obtaining *N*-heterocycles through a series of cascade reactions *via* organocatalysis. Recently, iminium,[41] bifunctional,[42] and NHC[43] catalysis methods have been established by different research groups for the synthesis of *N*-heterocycles through the aza-Michael-initiated organocascade reactions. However, the use of α, β-unsaturated acylammonium catalysis in this area has not yet been reported. Herein, we present the first examples of an enantioselective, organocatalytic aza-Michael proton-transfer lactamization cascade reaction using α, β-unsaturated carbonic anhydride, which was activated *in situ* by a chiral isothiourea catalyst.

The α, β-unsaturated acylammonium salts, generated from the reaction of tertiary amine catalysts with acid derivatives, have already been proven as versatile intermediates for the synthesis of heterocycles. The aza-Michael reaction is the most common initial step of the transformations. In 2013, Smith's group reported a Michael enol-lactonization cascade reaction using symmetrical anhydrides as electrophiles to generate the α, β-unsaturated acylammonium salts.[33] Later, our group successively published two papers on the Michael-initiated organocascade reactions using commercially available acid chlorides as starting materials, wherein one article described a Michael aldol-lactonization process for the synthesis of bicyclic β-lactones,[44] while the other reported a Michael proton-transfer lactamization cascade reaction to form a series of *N*-heterocycles.[37] Matsubara and co-workers also reported their work in this area, in which a sulfa-Michael reaction served as the first step to initiate the cascade reaction.[45] Since many bioactive molecules have the potential to be generated from the aza-Michael-initiated organocascade reactions (Figure 3-1), we aimed to use α, β-unsaturated acylammonium salts as key intermediates and develop an enantioselective synthesis process for *N*-heterocycles, wherein the process would be initiated by the aza-Michael reaction.



antibacterial agents



Inhibitor of XIAP BIR2
(XIAP: inhibitor of apoptosis protein 3)
(IC_{50} = 0.046 μM)

Figure 3-1 Selected examples of small bioactive molecules that can be derived from the aza-Michael-initiated organocascade reactions.

Results and Discussion

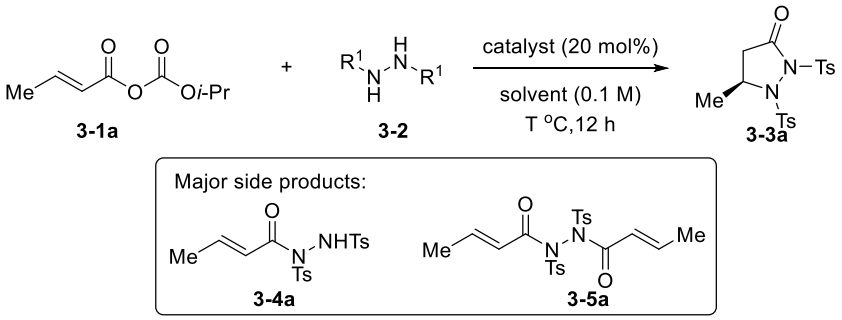
To investigate the aza-Michael-initiated organocascade reaction, we first used carbonic anhydride (**3-1**) and hydrazine (**3-2a**), which led to the synthesis of pyrazolidinone (**3-3a**). Catalyst screening revealed that HBTM-2.1 (**3-8**) exhibited the best performance among all the applied catalysts (Table 3-1, entries 1–5), providing the best enantioselectivity and a good yield. Further, low temperature (-30 °C) was found to be essential for this reaction (Table 3-1, entries 6–8), which suppressed the formation of *N*-acylation byproducts, **3-4a** and **3-5a**. The optimization of solvents showed that tetrahydrofuran (THF) provided the second best enantiomeric ratios (91:9 er) and an acceptable yield of 55% (Table 3-1, entries 10–12). On the other hand, acetonitrile provided an excellent yield (82%) for the reaction but with a poor er of 65:35 (Table 3-1, entry 10). The reaction in toluene demonstrated a slightly better enantiocontrol performance than the reaction in THF did; however, a dramatic decrease in yield was observed for the reaction in toluene (Table 3-1, entry 12). Furthermore, the replacement of protecting group Ts (**3-2a**) with Boc (**3-2b**) or Bz (**3-2c**) was also examined for the reaction

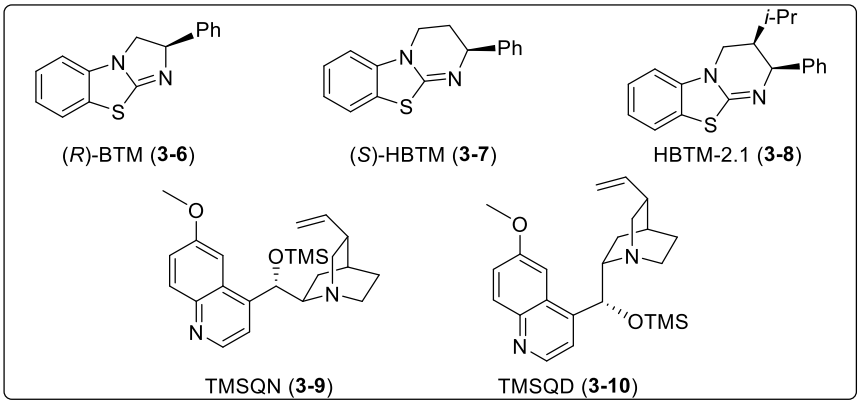
(Table 3-1, entries 13 and 14), which showed that neither of the two protecting groups resulted in the formation of **3-3a**; that is, only the starting materials remained. In most of the cases (except for Table 3-1, entries 13 and 14), side products **3-4a** and **3-5a** were formed, indicating that the *N*-acylation reaction of hydrazine is a competing pathway against the aza-Michael reaction.

After the optimization of conditions, the substrate scope of this method toward pyrazolidinones was explored for various carbonic anhydrides (Table 3-2). Carbonic anhydrides with primary aliphatic substituents such as methyl and ethyl groups were able to deliver the desired pyrazolidinones in moderate yields and good enantiomeric ratios. However, pyrazolidinones with isopropyl and phenyl substituents could not be synthesized possibly because the *i*-Pr substituent is more sterically hindered, and the Ph substituent delocalizes with the conjugated bond of the carbonic anhydride, both of which renders the aza-Michael acceptors less reactive and fail to favor the desired aza-Michael pathway.

Dimesyl phenylenediamine (**3-11**) was also studied as an aza-Michael donor, which led to the enantioselective synthesis of benzodiazepinones **3-12** (Scheme 3-1). The reactions were conducted using **3-6** as the catalyst and dichloromethane as the solvent at 23 °C. The optimized condition for the former cascade reaction did not work well for the formation of benzodiazepinone **3-12**. Ethyl benzodiazepinone **3-12a** was obtained in a yield of 70% and an er of 81:19. Interestingly, phenyl benzodiazepinone **3-12b** was also obtained with almost 46% yield and 91:9 er. A reasonable explanation is that phenylenediamine **3-11** is a relatively softer nucleophile, which allows the aza-Michael reaction to compete with the *N*-acylation reaction, whereas hydrazine **3-2a** is a harder aza- Michael donor because of which the *N*-acylation reaction completely outweighs the aza-Michael pathway.

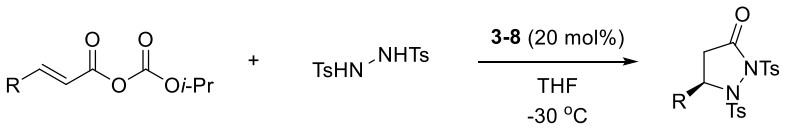
Table 3-1 Optimization of conditions toward enantioselective synthesis of pyrazolidinone **3-3a** through the aza-Michael initiated organocascade reaction.



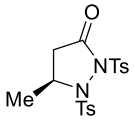
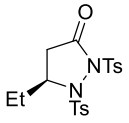
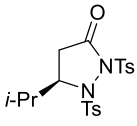
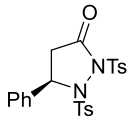


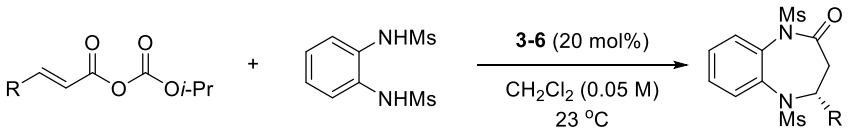
entry	catalyst	T/°C	solvent	R^1	Yield [%]	er
1	**3-6**	-30	CH_2Cl_2	Ts (**3-2a**)	85	77:23
2	**3-7**	-30	CH_2Cl_2	Ts (**3-2a**)	76	62:38
3	**3-8**	-30	CH_2Cl_2	Ts (**3-2a**)	77	84:16
4	**3-9**	-30	CH_2Cl_2	Ts (**3-2a**)	15	55:45
5	**3-10**	-30	CH_2Cl_2	Ts (**3-2a**)	23	57:43
6	**3-8**	-30	CH_2Cl_2	Ts (**3-2a**)	77	84:16
7	**3-8**	0	CH_2Cl_2	Ts (**3-2a**)	62	84:16
8	**3-8**	20	CH_2Cl_2	Ts (**3-2a**)	<40	84:16
10	**3-8**	-30	CH_3CN	Ts (**3-2a**)	82	65:35
11	**3-8**	-30	THF	Ts (**3-2a**)	55	91:9
12	**3-8**	-30	$PhCH_3$	Ts (**3-2a**)	26	94:6
13	**3-8**	-30	THF	Boc (**3-2b**)	-	-
14	**3-8**	-30	THF	Bz (**3-2c**)	-	-

Table 3-2 Substrate scope for enantioselective synthesis of pyrazolidinones.



3-1 **3-2a** **3-3**

			
55%, 91:9 er	46%, 94:6	0%	0%
3-3a	**3-3b**	**3-3c**	**3-3d**

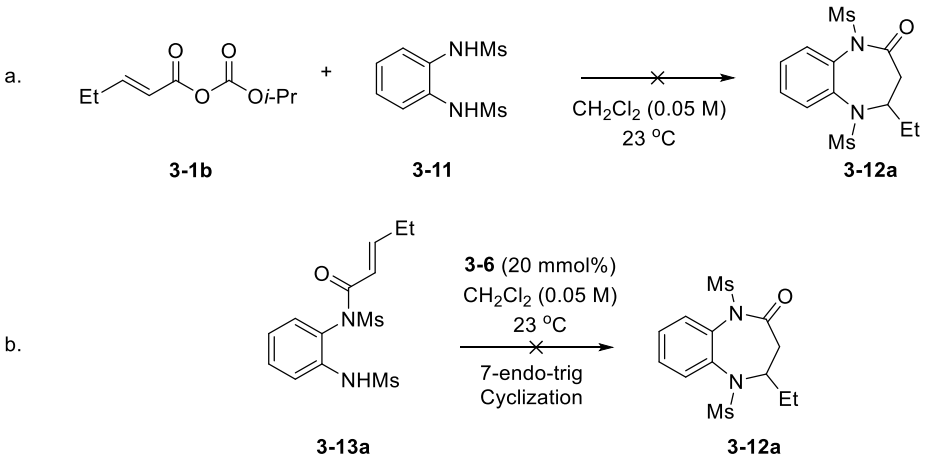


3-1 **3-11** **3-12**

3-12a, R = Et, 71%, 81:19 er
3-12b, R = Ph, 46%, 91:9 er

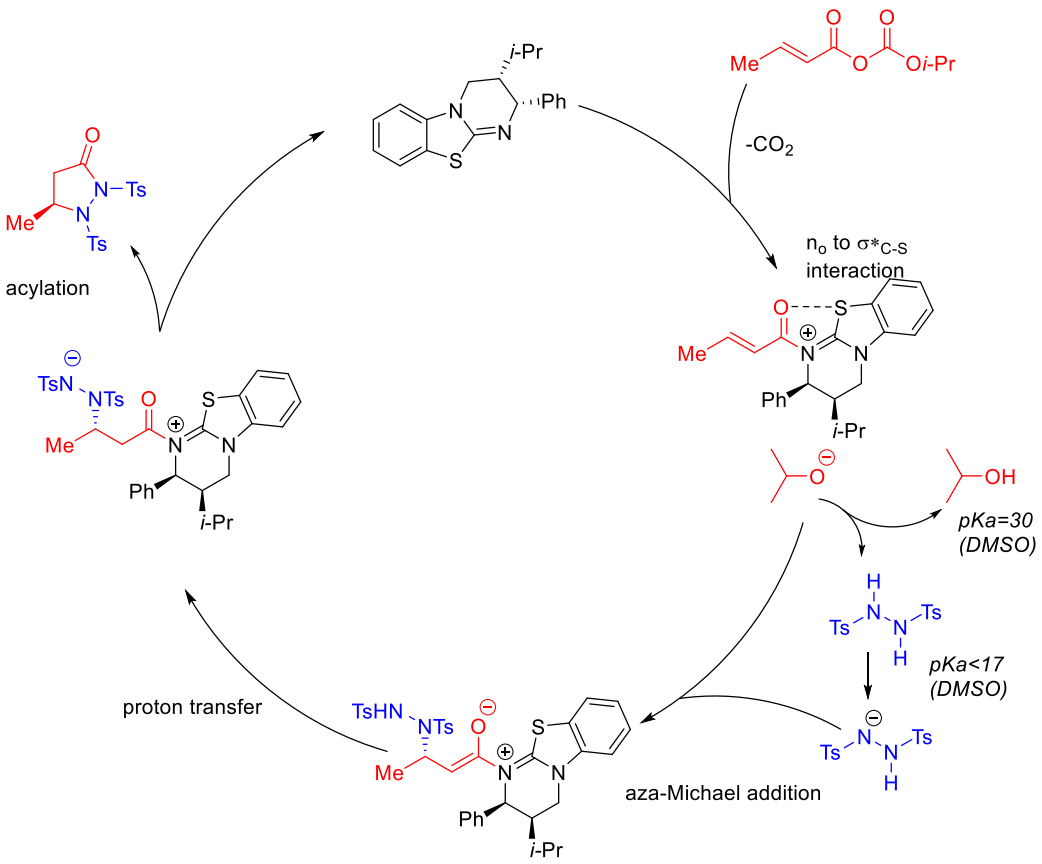
Scheme 3-1 Enantioselective synthesis of benzodiazepinones through aza-Michael initiated organocascade reaction employing α,β-unsaturated acylammonium intermediates.

Control experiments were also conducted to explain the formation of **3-12a** with unsatisfactory enantiocontrol performance. Without the catalyst, the aza-Michael-initiated organocascade reaction failed to yield the desired benzodiazepinone **3-12a** (Scheme 3-2). On the other hand, resubjecting the side product **3-13a** to the reaction condition shown in Scheme 3-1 did not lead to the formation of **3-12a** either, which excluded the possibility of the background reaction *via* 7-endo-trig cyclization. These preliminary results suggest that the enantiocontrol performance of the reaction is mainly because of the substrates and catalyst properties.



Scheme 3-2 Control experiments

The mechanism of aza-Michael-initiated organocascade reaction is proposed to be an aza-Michael proton-transfer acylation process (Scheme 3-3). The carbonic anhydride first reacts with the isothiourea catalyst to form an α,β-unsaturated acylammonium intermediate, whose conformation is partially enforced through a n_O to $\sigma^*_{C\text{-}S}$ interaction.[26, 33] Along the way, isopropoxide is generated through decarboxylation, serving as the base to deprotonate the aza-Michael donor,[45] which approached the α,β-unsaturated acylammonium intermediate from the opposite face of the phenyl and isopropyl groups on the catalyst. Sequentially, proton-transfer from the nitrogen atom to the ammonium enolate, followed by *N*-acylation, leads to the formation of the *N*-heterocycle and releases the catalyst.



Scheme 3-3 Proposed mechanism

Summary

In conclusion, we have developed some initial studies toward a methodology that highlights the utility of α,β-unsaturated acylammonium salts in the aza-Michael-initiated organocascade reactions. Ditosylhydrazine was first used as the aza-Michael donor and worked only with methyl and ethyl substituted carbonic anhydrides in the presence of the isothiourea catalyst, delivering pyrazolidinones in moderate yields and good enantiomeric ratios. Dimesyl phenylenediamine was also tested as the aza-Michael donor to afford 1,5-benzodiazepinone. When it reacted with the ethyl substituted carbonic anhydride, the yield was good (71%), but the enantiocontrol was moderate (81:19). On the other hand, this aza-Michael donor was found to react with the phenyl substituted unsaturated carbonic

anhydride. The resulting product was obtained in moderate yield (46%) and good enantioselectivity (91:9). The challenge of the aza-Michael-initiated organocascade reactions with α,β-unsaturated acylammonium salts is to modulate the reactivity of the nitrogen nucleophile for the desired pathway while achieving high enantioselectivity.

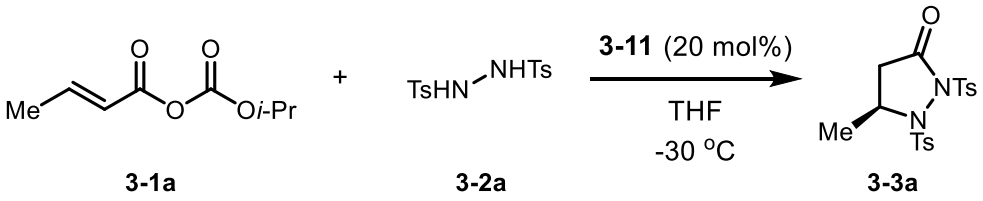
Experimental Procedures

Carbonic anhydrides **3-1a-d**,[45] ditosylhydrazine **3-2a**,[43b] and Dimesyl phenylenediamine **3-11** were prepared according to literature procedures.

Abbreviation List

HBTM-2.1 = (2*S*,3*R*)-3,4-Dihydro-3-isopropyl-2-phenyl-2H-pyrimido[2,1-b]benzothiazole

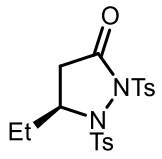
Representative procedure for the enantioselective aza-Michael initiated organocascade as described for 3-3a:



3-1a **3-2a** **3-3a**

(*S*)-5-Methyl-1,2-ditosylpyrazolidin-3-one (3-3a): To a solution of carbonic anhydride **3-1a** (26 mg, 0.15 mmol, 1.0 equiv) and ditosyl hydrazine **3-2a** (50 mg, 0.15 mol, 1.0 equiv) in THF (1.5 mL) was added HBTM-2.1 **3-11** (9.0 mg, 0.03 mmol, 0.2 equiv). The crude mixture was purified by flash chromatography (0→35%, EtOAc/hexanes) to **3-3a** (33 mg, 55% yield) as a white solid. TLC (EtOAc/Hexanes, 1:1 v/v): R_f = 0.67; $[\alpha]_D^{20}$ = -96.00 (*c* = 1.0, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.00 (d, *J* = 8.4 Hz, 2H), 7.65 (d, *J* = 8.3

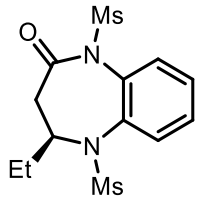
Hz, 2H), 7.37 (d, *J* = 8.6 Hz, 2H), 7.31 (d, *J* = 8.6 Hz, 2H), 4.70 – 3.83 (m, 1H), 2.47 (s, 3H), 2.43 (s, 3H), 2.02 (dd, *J* = 18.0, 7.4 Hz, 1H), 1.79 (d, *J* = 18.0 Hz, 1H), 1.15 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 174.3, 146.3, 146.1, 134.5, 131.4, 130.5 (2), 129.7 (2), 129.6 (2), 129.4 (2), 56.5, 38.0, 22.0, 22.0, 21.3; **IR** (thin film): 1766 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{18}H_{21}N_2O_5S_2$ $[M+H]^+$: 409.0892 found: 409.0904. Enantiomeric ratio was determined by HPLC analysis in comparison with authentic racemic material using a Chiralcel OD column: hexanes:*i*PrOH = 85:15, flow rate 1.0 mL/min, λ = 230 nm: t_{major} = 13.3 min, t_{minor} = 17.1 min; 91:9 er. Absolute stereochemistry was assigned by analogy to **3-3b**.



3-3b

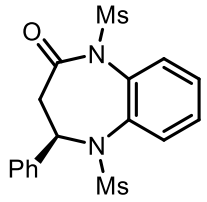
(*S*)-5-Ethyl-1,2-ditosylpyrazolidin-3-one (3-3b): Prepared according to the representative procedure for the aza-Michael initiated organocascade. Carbonic anhydride **3-2b** (28 mg, 0.15 mmol, 1.0 equiv), HBTM-2.1 **3-11** (9 mg, 0.03 mmol, 0.2 equiv), THF (1.5 mL), and ditosyl hydrazine **3-2a** (50 mg, 0.15 mmol, 1.0 equiv). The crude mixture was purified by flash chromatography (0→35%, EtOAc/hexanes) to **3-3b** (29 mg, 46% yield) as a white solid. TLC (EtOAc/Hexanes, 1:1 v/v): R_f = 0.72; $[\alpha]_D^{20}$ = -125.0 (*c* = 1.0, $CHCl_3$) **^{1}H NMR** (600 MHz, $CDCl_3$): δ 8.00 (d, *J* = 8.4 Hz, 2H), 7.65 (d, *J* = 8.3 Hz, 2H), 7.37 (d, *J* = 8.1 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 4.12 (dddd, *J* = 9.9, 8.0, 5.4, 1.0 Hz, 1H), 2.47 (s, 3H), 2.44 (s, 3H), 2.06 (dd, *J* = 17.7, 7.9 Hz, 1H), 1.85 (dd, *J* = 17.7, 1.0 Hz, 1H), 1.42-1.25 (m, 2H), 0.99 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 174.5, 146.2, 146.1, 134.7, 131.7, 130.4 (2), 129.7 (2), 129.6 (2), 129.5 (2), 62.2, 37.0, 27.9, 22.0, 22.0, 10.46; **IR** (thin film): 1766 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{19}H_{23}N_2O_5S_2$ $[M+H]^+$: 423.1048 found: 423.1062. Enantiomeric ratio was determined by HPLC analysis in comparison with

authentic racemic material using a Chiralcel OD column: hexanes:*i*PrOH = 70:30, flow rate 1.0 mL/min, λ = 230 nm: t_{major} = min, t_{minor} = min; 93:7 *e.r.* Absolute stereochemistry was assigned in comparison of the literature value (the opposite enantiomer of **3-3b**: $[\alpha]_D^{25}$ =+119.4 (c = 1.0, $CHCl_3$)).



3-12a

(*S*)-4-Ethyl-1,5-bis(methylsulfonyl)-1,3,4,5-tetrahydro-2H-benzo[b][1,4]-diazepin-2-one (3-12a): Prepared according to the representative procedure for the aza-Michael initiated organocascade. Dimesyl *o*-phenylenediamine (39 mg, 0.15 mmol, 1.0 equiv), (*R*)-BTM (11 mg, 0.25 mmol, 1.0 equiv), carbonic anhydride (28 mg, 0.30 mmol, 1.0 equiv) in CH_2Cl_2 (3.0 mL). Upon completion (as judged by TLC), the reaction mixture was concentrated by rotary evaporation and purified by flash chromatography (0 $\rightarrow$ 40%, EtOAc/hexanes) to afford a mixture of **3-12a** (37 mg, 71%). TLC (EtOAc:hexanes, 1:1 *v/v*): R_f =0.38; $[\alpha]_D^{20}$ = -2.70 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.70 – 7.38 (m, 4H), 4.74 (app dq, *J* = 12.9, 6.8 Hz, 1H), 3.57 (s, 3H), 3.07 (s, 3H), 2.65 (ddd, *J* = 13.1, 5.3, 1.8 Hz, 1H), 2.15 (app t, *J* = 12.5 Hz, 1H), 1.66-1.57 (m, 1H), 1.51 – 1.37 (m, 1H), 0.97 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.8, 136.1, 131.9, 131.2, 129.9, 129.8, 129.5, 62.7, 42.8, 42.0, 41.1, 28.7, 10.7; **IR** (thin film): 1712 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{13}H_{19}N_2O_5S_2$ $[M+H]^+$: 347.0735 found: 347.0736. Enantiomeric ratio was determined by HPLC analysis in comparison with authentic racemic material using a Chiralcel OD column: hexanes:*i*PrOH = 50:50, flow rate 1.0 mL/min, λ = 230 nm: t_{minor} = 15.9 min, t_{major} = 32.5 min; *e.r.* Absolute stereochemistry was assigned by analogy to **3-3b**.



3-12b

(*R*)-1,5-bis(methylsulfonyl)-4-phenyl-1,3,4,5-tetrahydro-2H-benzo[b]-[1,4]diazepin-2-one (3-12b): Prepared according to the representative procedure for the aza-Michael initiated organocascade. Dimesyl *o*-phenylenediamine (40 mg, 0.15 mmol, 1.0 equiv), (*R*)-BTM (7.6 mg, 0.02 mmol, 0.2 equiv), carbonic anhydride (35 mg, 0.15 mmol, 1.0 equiv) in CH_2Cl_2 (3.0 mL). Upon completion (as judged by TLC), the reaction mixture was concentrated by rotary evaporation and purified by flash chromatography (0 → 40%, EtOAc/hexanes) to afford an impure mixture**,** which was further purified by going through a short pipette column (100%, CH_2Cl_2) to afford **3-12b** as a white solid (27mg, 42%). TLC (EtOAc:hexanes, 1:1 *v/v*): R_f =0.46; $[\alpha]_D^{20}$ = -4.80 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.64 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.57 (td, *J* = 7.7, 1.5 Hz, 1H), 7.51 (td, *J* = 7.7, 1.6 Hz, 1H), 7.39 – 7.33 (m, 3H), 7.30 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.17 – 7.13 (m, 2H), 5.90 (dd, *J* = 13.0, 4.9 Hz, 1H), 3.58 (s, 3H), 2.92 – 2.85 (m, , 4H), 2.76 (dd, *J* = 13.0, 4.9 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.2, 138.5, 136.0, 131.7, 131.2, 130.2, 130.19, 129.8, 129.5 (2), 129.4, 126.6 (2), 63.9, 42.6, 42.1, 42.0; **IR** (thin film): 1711 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{17}H_{18}N_2O_5S_2Na$ $[M+Na]^+$: 417.0555 found: 417.0560. Enantiomeric ratio was determined by HPLC analysis in comparison with authentic racemic material using a Chiralcel OD column: hexanes:*i*PrOH = 50:50, flow rate 1.0 mL/min, λ = 230 nm: t_{minor} = 15.3 min, t_{minor} = 24.2 min; 91:9 er. Absolute stereochemistry was assigned by analogy to **3-3b**.

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CHAPTER FOUR

Synthetic Efforts Toward C-Ring Synthons of Rameswaralide

Abstract

Rameswaralide, a diterpene with novel structure and promising bioactivities, is highly desirable to be synthesized for biological investigation. Based on our retrosynthesis, Rameswaralide can be assembled through the incorporation of two simplified motifs—AD-ring and C-ring synthons, each of which has the potential to be readily synthesized from commercial available materials. Herein, we describe efforts toward C-ring synthons useful for the synthesis of rameswaralide involving γ-alkylation and C-H oxygenation of (*R*)- (-)-carvone.

Introduction

Many traditional and modern drugs are derived and inspired by natural products.[46] A novel diterpenoid, rameswaralide, was extracted from the soft coral *Sinularia dissecta* off the coast of Mandapam near Rameswaram in India. In 1998, Venkateswarlu's and Faulkner's groups elucidated its structure, which consists of six stereogenic centers with a 5,5,7,6-highly densely fused tetracyclic ABCD system.[47] The relative stereochemistry was first established by a series of 2D-NMR studies,[47] and the absolute stereochemistry was revealed by Venkateswarlu and co-workers through X-Ray crystallography in recent work.[48]

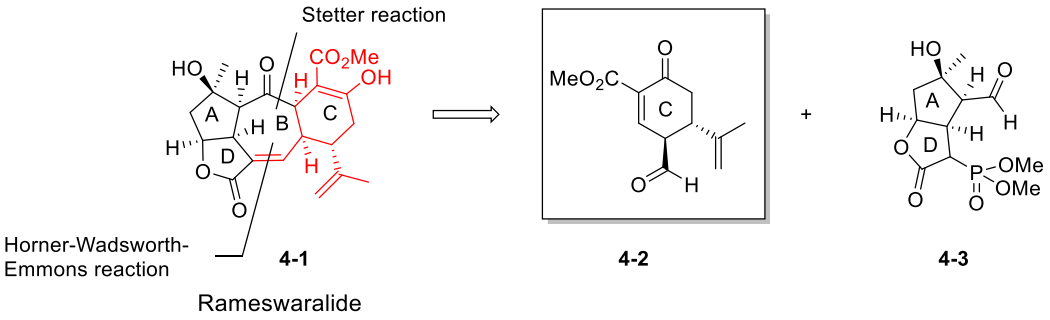
The uses of rameswaralide and its derivatives as therapeutic agents were patented two years after these compounds were isolated and characterized. Rameswaralide and its

derivatives exhibit numerous anti-inflammatory activities such as against arthritis, psoriasis, and inflammatory bowel diseases with a typical dosage of 0.5 mg/kg to 7 mg/kg, possibly by impeding the migration of inflammatory cells.[49] Recently, an in *vitro* study revealed the weak cytotoxic activity of rameswaralide toward four cancer cell lines.[48]

Many research groups have investigated rameswaralide *via* different synthetic routes.[50] However, the total synthesis of the natural product remains unaccomplished, which led to our interest in this synthetic challenge. Herein, we report some preliminary efforts toward the synthesis of C-ring synthons of rameswaralide, which have potential utility for a total synthesis of this natural product.

Method and Design

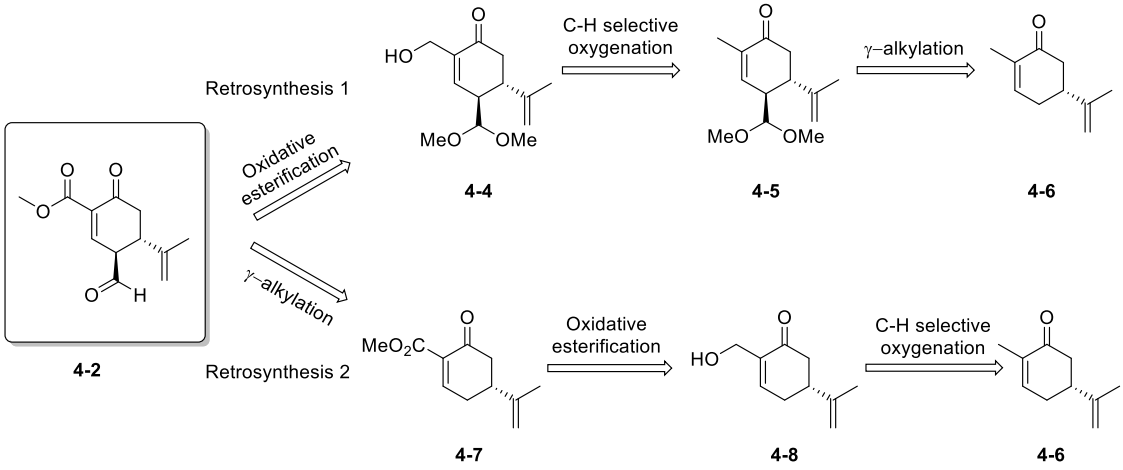
Retrosynthetically, rameswaralide is expected to be formed by the incorporation of C-ring synthon **4-2** with AD-ring synthon **4-3** *via* the Horner-Wadsworth-Emmons reaction and Strecker reaction (Scheme 4-1). Compound **4-2** is targeted in this chapter.



Scheme 4-1 Retrosynthesis of rameswaralide

As described in Scheme 4-2, Retrosynthesis 1, the ester group of **4-2** has the potential to be tracked back from the corresponding hydroxyl group of **4-4** through oxidative esterification and deprotection of the acetal group. C-H oxygenation is chosen as

the key strategy to install the primary alcohol on the β' methyl group of **4-5**. It is noticed that functionalization of the unactivated sp3 C-H bond is always challenging.[51] Fortunately, Sanford's[52] and Yu's group[53] have some achievements on the C-H oxygenation of α-methyl cyclohexane oxime,[52] which are promising starting points for us. The acetal group of **4-5** is expected to be introduced *via* a Mukaiyama-Claisen approach on the (*R*)-(-)-carvone, which has already been applied to some natural product syntheses.[54] Another retrosynthesis is similar to Retrosynthesis 1 (Scheme 4-2, Retrosynthesis 2) through rearrangement of the key steps. γ-Alkylation of **4-7** is chosen as the last step leading to the target **4-2**, while keto ester **4-7** is expected to be obtained from **4-8** through oxidative esterification. The hydroxyl carvone **4-8** can be tracked back from carvone **4-6** *via* a series of transformations including C-H oxygenation. Ideally, we seek to find a route toward target **4-2** within 5 steps from carvone.

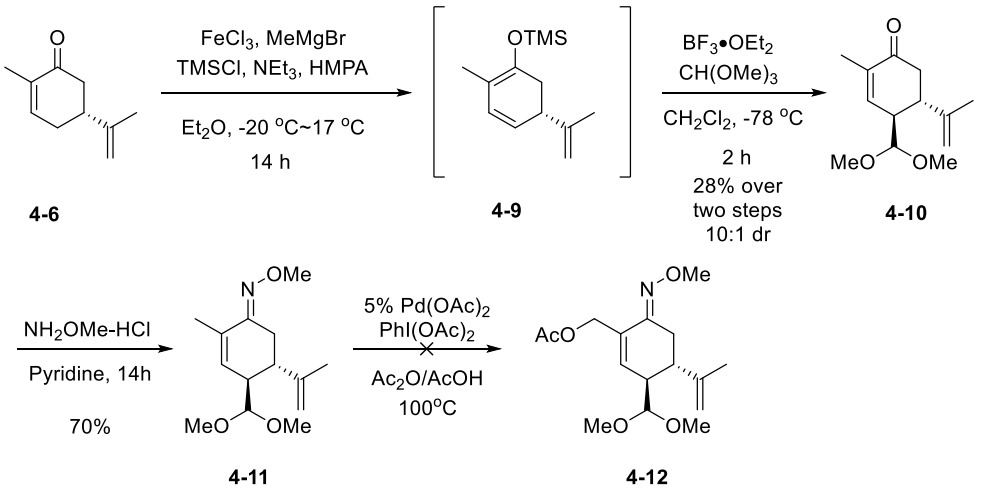


Scheme 4-2 Retrosynthesis of C-ring synthon **4-2**

Results and Discussion

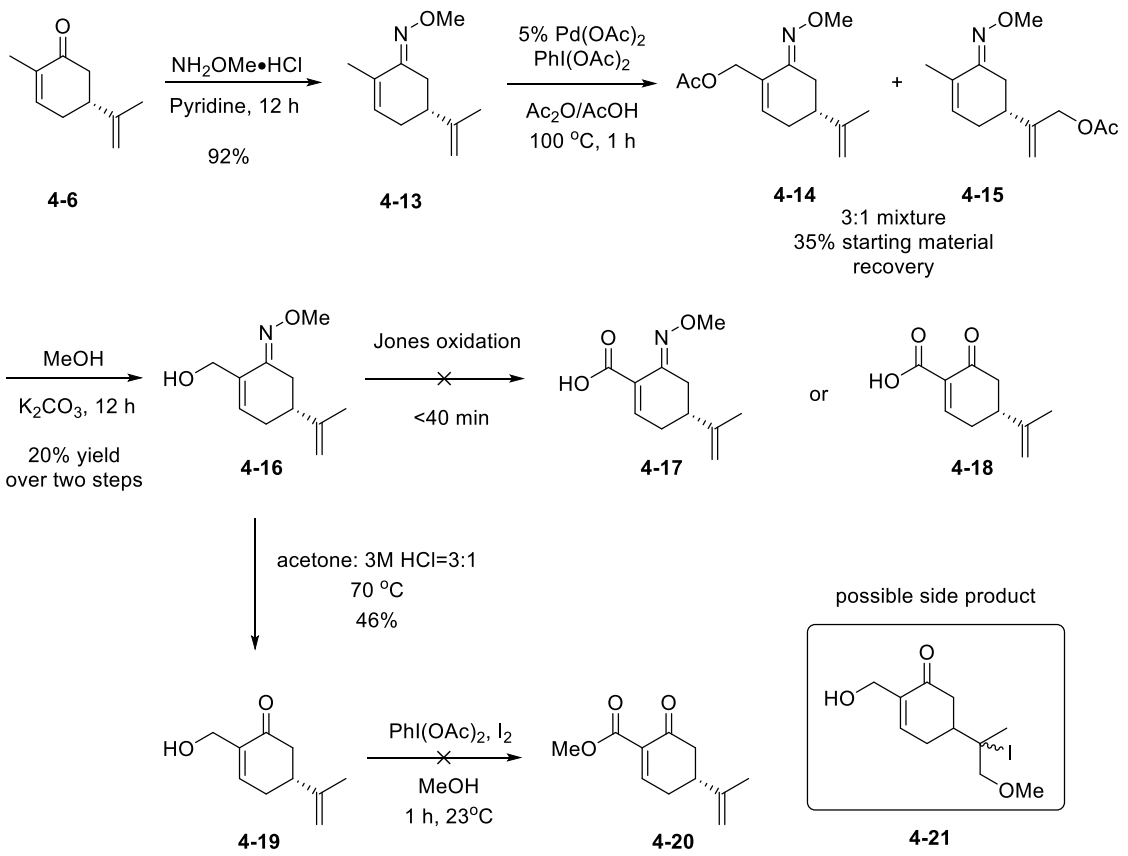
The initial attempt toward **4-2** commenced with γ-alkylation followed by C-H oxidation (Scheme 4-3). Exposure of carvone **4-6** to $FeCl_3$, MeMgBr, TMSCl, NEt_3, and HMPA could selectively form the thermodynamically stable diene **4-9**. These unique conditions were developed by Kraft and Holton[55] in 1986; however, the mechanism is still unclear. Further treatment of **4-9** with boron trifluoride diethyl etherate in the presence of orthoformate *via* a Mukaiyama-Claisen sequence afforded the γ-alkylation product **4-10** in 28% yield and 10:1 dr. Thereafter, *O*-methyl oxime, serving as a directing group for C-H oxidation at the β'-position, was obtained in 70% yield through the condensation of **4-10** and methoxyamine hydrochloride. Sanford's condition[52a] was then tested on **4-11**, which generated a complex mixture without the formation of the desired product **4-12**. Decomposition of the acetal group was observed under acidic condition. Since the performance of complex cyclohexene oxime substrates in Sanford's C-H oxygenation is unclear, we did not pursue this route further but studied the C-H oxygenation of a simpler system.

Another route was investigated wherein C-H functionalization of carvone **4-6** was carried out first, followed by the oxidation of primary alcohol and γ-alkylation (Scheme 4-4). Oxime **4-13** for C-H oxygenation was synthesized in excellent yield by treating carvone **4-6** with *O*-methyl hydroxylamine in pyridine. By applying Sanford's condition, an inseparable mixture of the desired product **4-14** and a regio isomer **4-15** were obtained in 3:1 ratio with 35% starting material recovery. Removal of the acetyl group under basic condition led to the separation of the regio isomers and gave the desired oxygenated product **4-16** in 20% yield in two steps. Direct oxidation of the primary alcohol of **4-16** to



Scheme 4-3 γ-Alkylation of carvone, and then C-H oxygenation towards the C-ring synthon

the corresponding carboxylic acid was then attempted *via* Jones oxidation, which was expected to remove the oxime group at the same time. Crude ^{1}H NMR suggested the decomposition of the conjugated enone, indicating that the condition was too harsh for the substrate. On the other hand, a sequence on **4-16** was conducted by the removal of oxime under acidic condition first, which provided the hydroxyl carvone **4-19** in 46% yield. Then, oxidative esterification of **4-19** was attempted through a known procedure, in which iodosobenzene diacetate and iodine were applied to oxidize the primary alcohol to the corresponding methyl ester in one step.[56] Though the condition worked well for the examples in the literature, it did not provide any desired product for us. However, it appeared to oxidize the terminal olefin, yielding **4-21** as a major product (suggested by crude ^{1}H NMR). This route was not explored further through stepwise oxidation because (1) too many steps were involved, deviating from the goal of a 5-step synthesis, and (2) the critical step—C-H oxygenation—provided a limited yield, which was not appropriate for the initial stage of total synthesis.



Scheme 4-4 C-H oxygenation of carvone, and then γ-alkylation towards the C-ring synthon

Summary

In summary, efforts have been made toward C-ring synthons of rameswaralide with carvone as the starting material. γ-Alkylation and C-H oxygenation were applied as key strategies, and two routes were were identified by rearranging these two steps. While γ-alkylation was successfully achieved through a Mukaiyama-Claisen approach, the following C-H oxygenation failed to give the desired product. On the other hand, C-H oxygenation of **4-13** only afforded the desired product in low yield. One-step oxidation of primary alcohol **4-16** to the corresponding carboxylic acid or methyl ester was not achieved, however this route was not pursued further since the number of steps to get to the desired

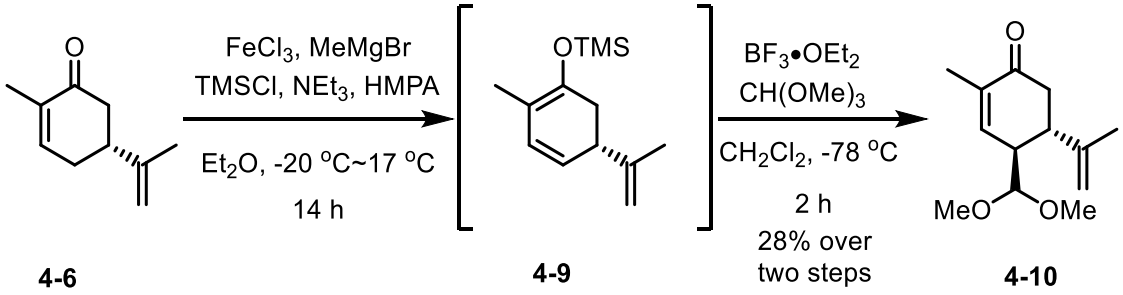
C-ring synthon exceeded our initial goal of only 5 steps. Therefore, we did not pursue this route further but rather we explore completely different retrosyntheses toward rameswaralide.

Experimental procedures

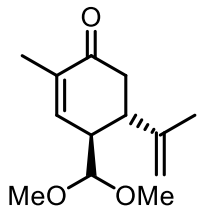
Abbreviation List

TMSCl	=	Trimethylsilyl chloride
HMPA	=	Hexamethylphosphoramide
BF_3-OEt_2	=	Boron trifluoride diethyl etherate
$Pd(OAc)_2$	=	Palladium(II) acetate
$PhI(OAc)_2$	=	Iodosobenzene diacetate

γ-Alkylation of (R)-carvone via a Mukaiyama-Claisen approach



4-6 **4-9** **4-10**



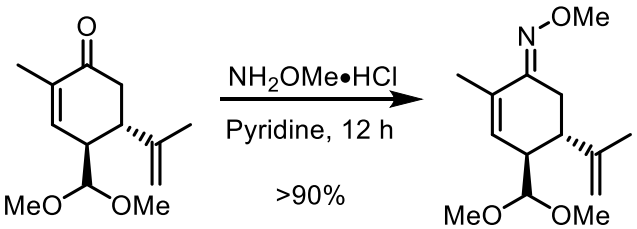
4-10

(4S,5S)-4-(dimethoxymethyl)-2-methyl-5-(prop-1-en-2-yl)cyclo-hex-2-en-1-one (4-10): To an oven-dried 50 mL 3-neck flask under nitrogen atmosphere was added $FeCl_3$ (75 mg, 0.48 mmol, 0.02 equiv) and dry ethyl ether (9 mL) at 23 °C. The reaction mixture was cooled down to -20 °C, and MeMgBr in Et_2O (2.80 M, 33.6 mmol, 1.4 equiv) was added dropwise over 15 min. (*R*)-cavone **4-6** (3.60 g, 24 mmol, 1.0 equiv,) was added

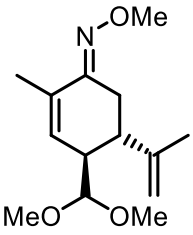
dropwise over 30 min. TMSCl (3.8 mL, 30.0 mmol, 1.25 equiv), NEt_3 (2.5 mL), HMPA (2.5 mL) was then added. The reaction mixture was then stirred at 23 ºC for 12 h. Upon completion (as judged by TLC), saturated $NaHCO_3$ (30 mL) was added. The mixture was filtered through a short pad of celite. The aqueous phase was washed with ethyl ether (2×30mL). The combined organic was dried over with magnesium sulfate. The organic solvent was removed by rotary evaporation. The crude product was directly used for the next step.

The crude diene was dissolved in dichloromethane (50 mL). Boron trifluoride diethyl etherate (3.0 mL, 24.0 mL, 1.0 equiv) was added to the solution dropwise over 1 h under -78 ºC. The reaction mixture was stirred at -78 for another 1 h. Upon completion (as judged by TLC), saturated NH_4Cl (20 mL) was added dropwise over 30 min. The organic phase was washed with brine (30 mL) and dried with sodium sulfate. The crude mixture was then purified by automated flash chromatography (0 - 20%, EtOAc/hexanes) to afford compound **4-10** as a colorless oil (1.52 g, 28% yield). TLC (EtOAc/Hexanes, 1:10 v/v): R_f = 0.32; $[\alpha]_D^{20}$ = +126.00 (*c* = 1.0, $CHCl_3$) **^{1}H NMR** (300 MHz, $CDCl_3$): δ 6.84 (dq, *J* = 2.7, 1.3 Hz, 1H), 4.98 – 4.69 (m, 2H), 4.26 (d, *J* = 3.0 Hz, 1H), 3.44 (s, 3H), 3.44 (s, 3H), 2.89 – 2.64 (m, 2H), 2.45 (s, 1H), 2.43(m, 1H), 1.79 (dd, *J* = 2.2, 1.4 Hz, 3H), 1.73 (dd, *J* = 1.5, 0.8 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 199.3, 144.9, 143.9, 136.2, 113.6, 105.9, 57.4, 56.1, 45.0, 43.5, 42.7, 19.7, 16.1; **IR** (thin film): 1733, 1160 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{13}H_{19}NO_3Na$ $[M+Na]^+$: 247.1310 found: 247.1322.

*Synthesis of oxime **4-11***



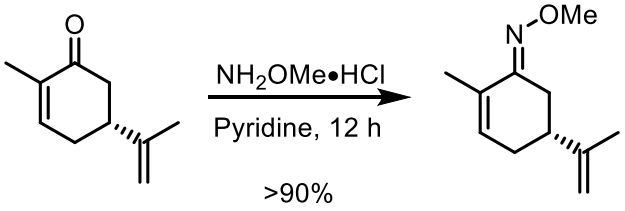
4-10 **4-11**



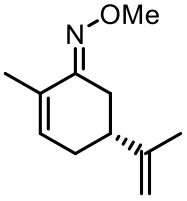
4-11

(4S,5S,E)-4-(dimethoxymethyl)-2-methyl-5-(prop-1-en-2-yl)cyclohex-2-en-1-one O-methyl oxime (4-11): To a solution of **4-10** (500 mg, 2.4 mmol, 1.0 equiv) in pyrdine (16 mL) was added methoxylamine hydrochloride (310 mg, 3.6 mmol, 1.5 equiv). The reaction mixture was stirred at 23 ºC for 18 h. Upon completion (as judged by TLC), 1N HCl (30 mL) and Et_2O was added. The organic phase was washed with water, saturated $CuSO_4$ solution and brine. The organic phase was dried over magenisum sulfate and concentrated by rotary evaporation. The crude mixture was purified by an automated flash chromatography to afford **4-13** as a colorless liquid (426 mg, 70% yield). TLC (EtOAc/Hexanes, 1:1 v/v): R_f = 0.55; $[\alpha]_D^{20}$ = +132.00 (*c* = 1.0, $CHCl_3$) **^{1}H NMR** (300 MHz, $CDCl_3$): δ 6.16 – 5.99 (m, 1H), 4.89 – 4.72 (m, 2H), 4.19 (d, *J* = 3.3 Hz, 1H), 3.88 (s, 3H), 3.42 (d, *J* = 1.5 Hz, 3H), 3.40 (d, *J* = 1.5 Hz, 3H), 2.92 (ddd, *J* = 16.6, 4.3, 1.4 Hz, 1H), 2.64 – 2.40 (m, 2H), 2.23 (ddd, *J* = 16.5, 11.2, 1.3 Hz, 1H), 1.90 – 1.82 (m, 3H), 1.75 – 1.70 (m, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 174.9, 143.5, 140.8, 136.6, 136.0, 129.8 (2), 128.7 (2), 128.4, 128.3 (2), 127.5 (2), 115.0, 66.6, 56.2, 51.3, 39.5, 21.7, 20.1, 15.6; **IR** (thin film): 1644, 1444 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{14}H_{24}NO_3$ $[M+H]^+$: 254.1756 found: 254.1740.

*Synthesis of oxime **4-13***



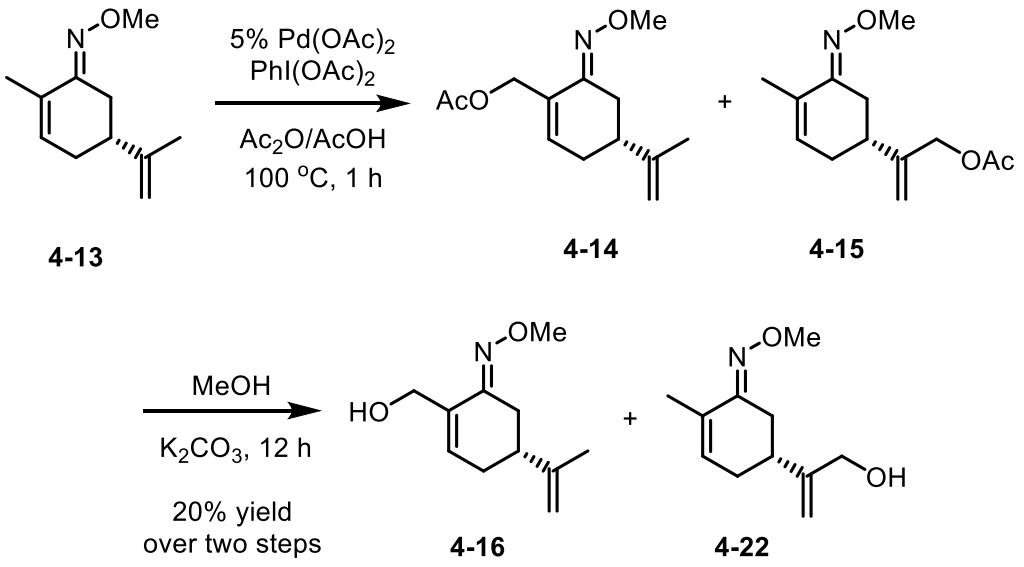
4-6 **4-13**

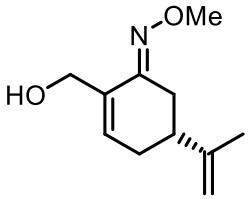


4-13

(4S,5S,E)-4-(dimethoxymethyl)-2-methyl-5-(prop-1-en-2-yl)cyclohex-2-en-1-one O-methyl oxime (4-13): To a solution of (*R*)-cavone **4-6** in pyrdine was added methoxylamine hydrochloride. The reaction mixture was stirred at 23 ºC for 18 h. Upon completion (as judged by TLC), 1N HCl (30 mL) and Et_2O was added. The organic phase was washed with water, saturated CuSO4 solution and brine. The organic phase was dried over magenisum sulfate and concentrated by rotary evaporation. The crude mixture was purified by an automated flash chromatography to afford **4-13** as a colorless liquid (1.28 g, 72% yield). TLC (EtOAc/Hexanes, 1:9 v/v): R_f = 0.65; $[\alpha]_D^{20}$ = +192.00 **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.99 (ddd, *J* = 5.8, 2.6, 1.2 Hz, 2H), 4.96 – 4.61 (m, 1H), 3.90 (s, 3H), 3.13 (ddd, *J* = 16.6, 4.1, 1.7 Hz, 1H), 2.39 – 2.19 (m, 2H), 2.12 – 1.94 (m, 2H), 1.84 (dt, *J* = 2.5, 1.2 Hz, 3H), 1.74 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 156.4, 148.2, 132.5, 130.7, 110.0, 61.9, 40.6, 30.5, 28.1, 20.9, 17.9 ; **IR** (thin film): 1650, 1467 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{11}H_{18}NO$ $[M+H]^+$: 180.1388 found: 180.1391.

*Synthesis of oxime alcohol **4-16** via a C-H oxygenation/acetyl deprotection sequence*



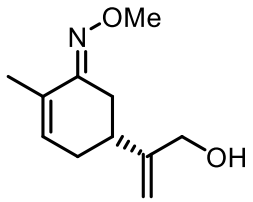


4-16

(4S,5S,E)-4-(dimethoxymethyl)-2-methyl-5-(prop-1-en-2-yl)cyclohex-2-en-1-one O-methyl oxime (4-16): To oven-dried a sealed tube was added **4-13** (1.01 g, 5.56 mmol, 1.0 equiv), $Pd(OAc)_2$ (70 mg, 0.27 mmol, 0.05 equiv,) and acetic acid and acetic anhydride at 23 ºC was added iodobenzene diacetate (2.26 g, 1.2 equiv, 6.67 mmol). The reaction mixture was heated to 100 ºC for 1 h. Upon completion (as judged by TLC), the organic solvent was removed by rotary evaporation. The crude product was then purified by automated flash chromatography (0 - 20%, EtOAc/hexanes) to afford compound a mixture of **4-14** and **4-15**. The crude mixture was directly used for the next step.

To a solution of the crude mixture (320 mg) in methanol was added potassium carbonate (40 mg). The reaction mixture was stirred at 23 ºC for 12 h. Upon completion (as judged by TLC), the solid was removed by filteration and the organic solvent was removed by rotary evaporation. The crude product was then purified by automated flash

chromatography (0 - 30%, EtOAc/hexanes) to afford as a brown oil (217 mg, 20%). TLC (EtOAc/Hexanes, 1:4 v/v): R_f = 0.35; $[\alpha]_D^{20}$ = +76.00 **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.20 (dd, *J* = 5.9, 2.6 Hz, 1H), 4.77 (app dt, *J* = 11.2, 1.1 Hz, 2H), 4.27 (s, 2H), 3.89 (s, 3H), 3.12 (ddd, *J* = 16.6, 4.0, 1.6 Hz, 2H), 2.39 – 2.24 (m, 2H), 2.18 – 1.93 (m, 2H), 1.74 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 155.5, 147.4, 133.6, 133.5, 110.2, 64.0, 62.1, 39.9, 30.0, 27.6, 20.6; **IR** (thin film): 3700-3000, 1642, 1439 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{11}H_{18}NO_2$ $[M+H]^+$: 196.1338 found: 196.1349.



4-22

(4S,5S,E)-4-(dimethoxymethyl)-2-methyl-5-(prop-1-en-2-yl)cyclohex-2-en-1-one O-methyl oxime (4-22): **4-22** was afford as a side product from the C-H oxygenation/acetyl deproection sequence. A brown oil (72 mg, 7% yield). TLC (EtOAc/Hexanes, 1:4 v/v): R_f = 0.20; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 5.97 (ddd, *J* = 5.8, 2.6, 1.3 Hz, 1H), 5.14 – 5.04 (m, 1H), 5.01 – 4.86 (m, 1H), 4.13 (s, 2H), 3.88 (s, 3H), 3.13 (ddd, *J* = 16.4, 4.0, 1.6 Hz, 1H), 2.52 – 2.20 (m, 2H), 2.19 – 1.99 (m, 2H), 1.83 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 156.0, 151.7, 132.2, 130.7, 109.7, 65.1, 61.9, 36.3, 30.9, 28.3, 17.8; **IR** (thin film): 3600-3100, 1643, 1439 cm^{-1}; **HRMS** (ESI+) *m/z* calcd for $C_{11}H_{18}NO_2$ $[M+H]^+$: 196.1338 found: 196.1382.

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CHAPTER FIVE

Conclusion

Extensions of the nucleophile-catalyzed (Lewis base) aldol lactonization (NCAL) process towards *N*-heterocycle-fused-β-lactones from keto acids were developed. Racemic NCAL process was first explored with 4-pyrrolidinopyridine as an effective nucleophile, delivering a variety of bi- and tricyclic *N*-heterocycle-fused β-lactones from moderate to good yield with excellent diastereoselectivity (>19:1). A catalytic, enantioselective version of this NCAL process using isothiourea and LiCl provided access to bicyclic *N*-heterocycles-fused β-lactone in moderate to good yields (up to 80%) with high enantiocontrol (up to >99:1 er). A preliminary investigation of kinetic resolution towards tricyclic-β-lactone **8g** was explored, but lower enantioselectivity of **8g** was obtained with a 70:30 er. Interestingly, an enamine **12** was afforded with an enantiomeric ratio of 95:5. We proposed a kinetic asymmetric transformation to account for an alkene by-product derived from a [2+2] cycloaddition/decarboxylation pathway from the racemic starting material. The utility of these β-lactone adducts was briefly demonstrated *via* a series of transformations including simple nucleophilic addition of β-lactone and tosyl deprotection. Dyotropic rearrangement of the 8i was also attempted with a treatment of Lewis acid. However, only decarboxylation of the β-lactone moiety was observed.

We also explored a methodology by employing α,β-unsaturated acylammonium salts as aza-Michael acceptors for the assembly of *N*-heterocycles. Ditosylhydrazine was used as an aza-Michael donor and was found to react with methyl and ethyl substituted

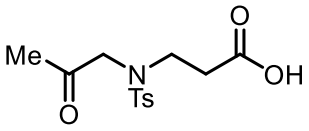
carbonic anhydrides, affording the corresponding pyrazolidinones (**3-3a**, **3-3b**) in moderate yields and good enantiomeric ratios. Dimesyl phenylenediamine could also be applied as an aza-Michael donor, which led to the formation of benzodiazepinones. As it reacted with ethyl substituted carbonic anhydride, a good yield of 71% was obtained but the enantiocontrol was just moderate (81:19 er). Unlike ditosyl hydrazine, this aza-Michael donor could react with phenyl substituted carbonic anhydride, delivering benzodiazepinone **3-12b** in moderate yield (46%) and good er (91:9).

Synthetic efforts towards Rameswaralide were made through a strategy involving γ-alkylation and C-H oxygenation as key steps. (*R*)-cavone was used as the starting material. To introduce the acetal group at the γ postion of carvone, a Mukaiyama-Claisen sequence was applied, providing the desired product **4-10** in a limited 28% yield. However, further C-H oxygenation was not successful due to the decomposition of acetal group under the acidic condition. On the other hand, C-H oxygenation of the oxime **4-13** was not as efficient as we proposed, which only gave 20% yield of the desired oxygenated product. The subsequent attempts for the oxidation of primary alcohol **4-16** was not promising either. Considering the practicality and efficiency, we decided not to explore this design but switch to an entirely different route for the total synthesis of rameswaralide.

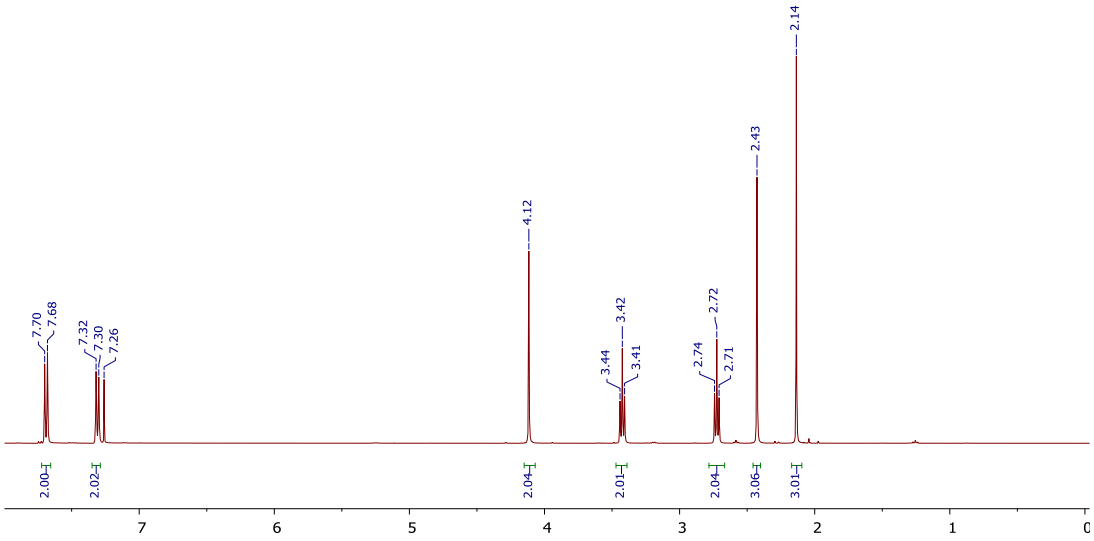
APPENDICES

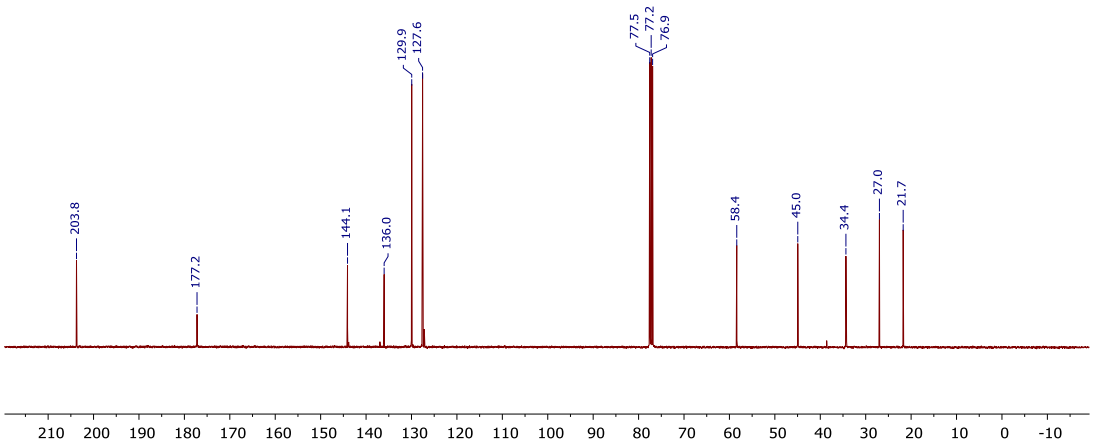
APPENDIX A

NMR Spectra

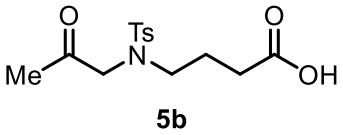


5a

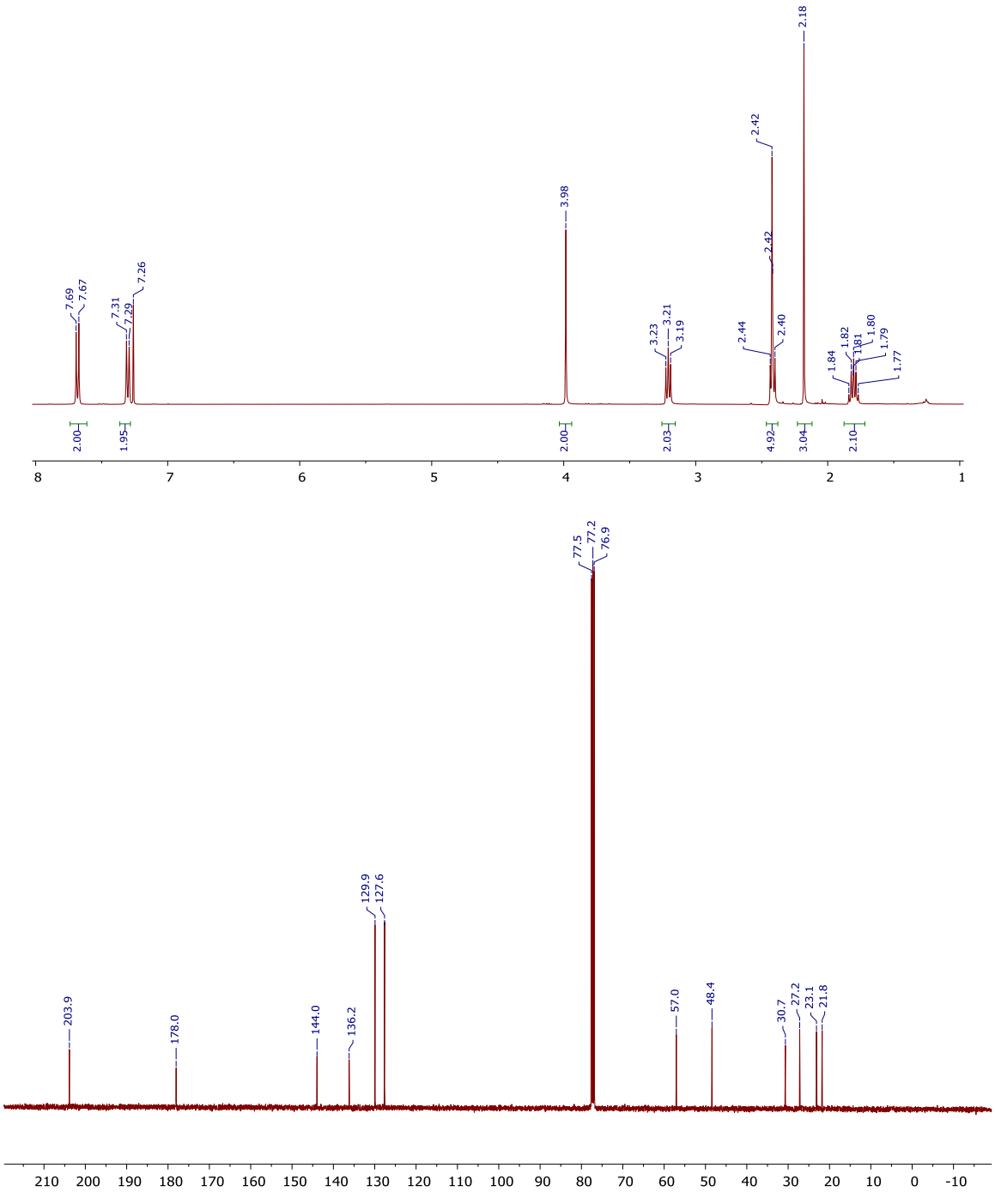




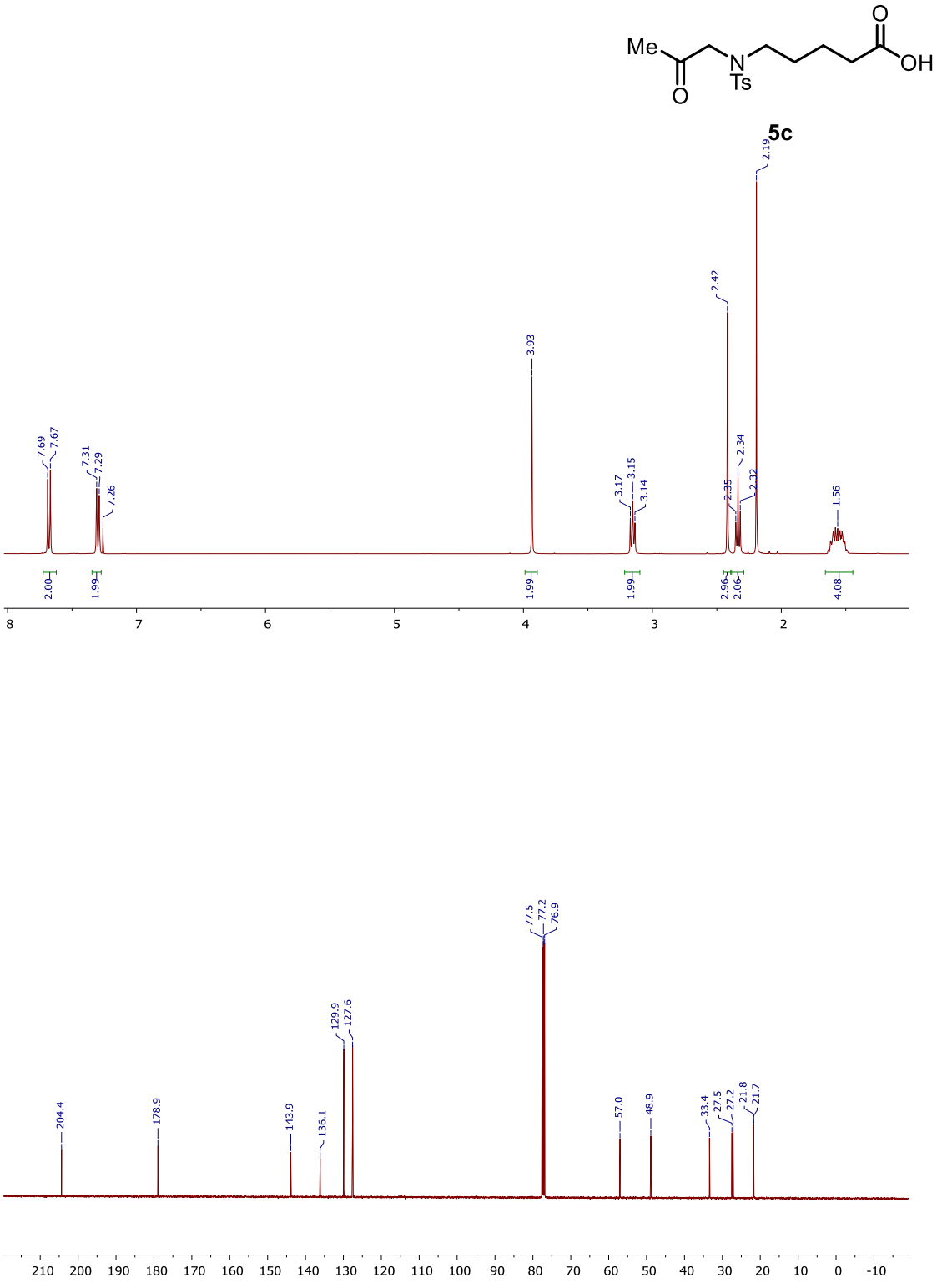
^{1}H (400 MHz) and ^{13}C NMR (101 MHz) spectra of keto acid **5a** in $CDCl_3$



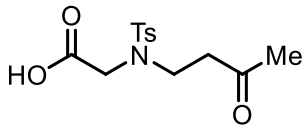
5b



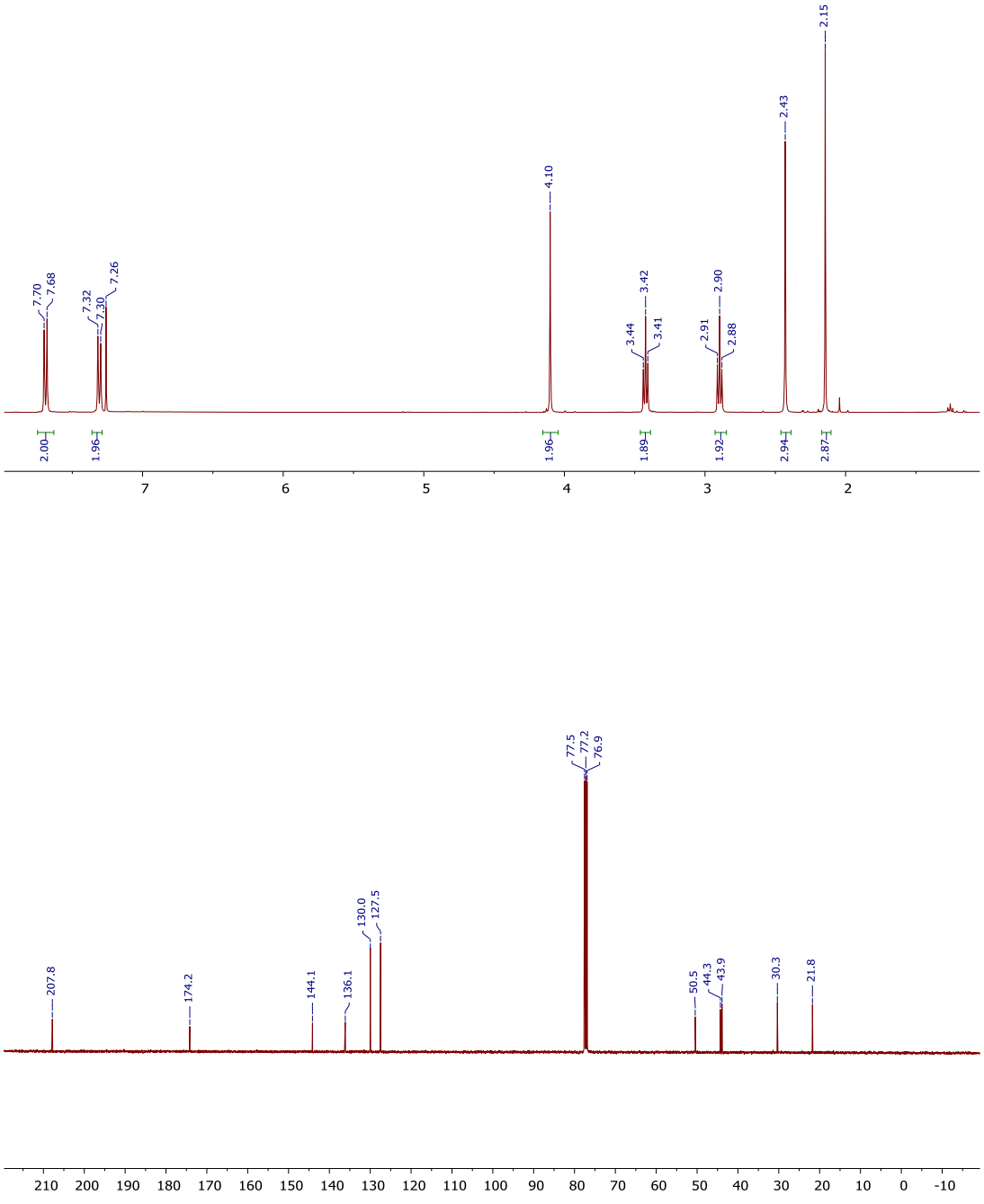
^{1}H (400 MHz) and ^{13}C NMR (101 MHz) spectra of keto acid **5b** in $CDCl_3$



^{1}H (400 MHz) and ^{13}C NMR (101 MHz) spectra of keto acid **5c** in $CDCl_3$



5d



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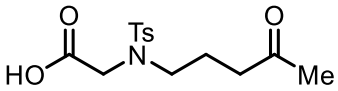

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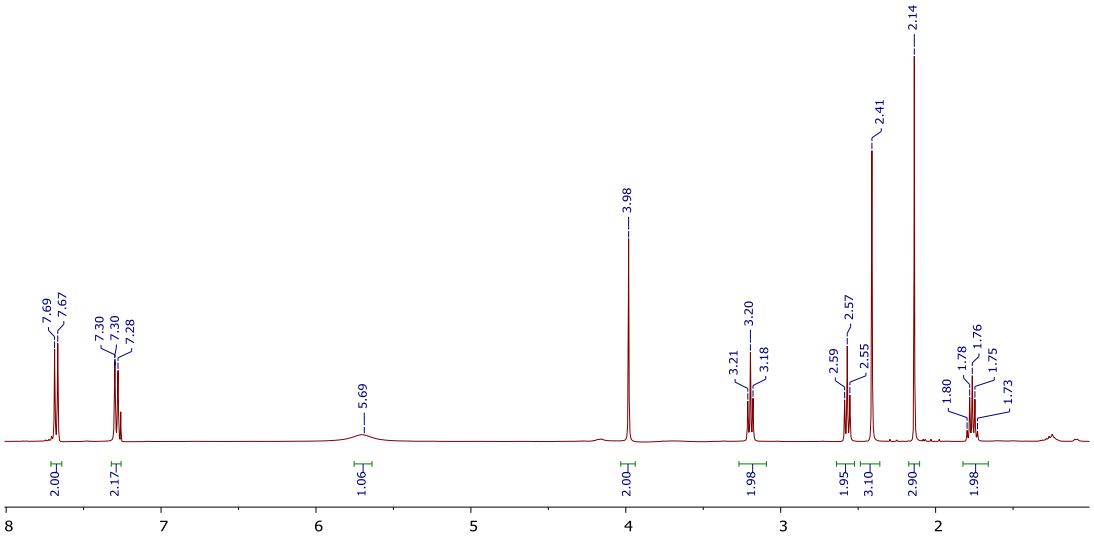
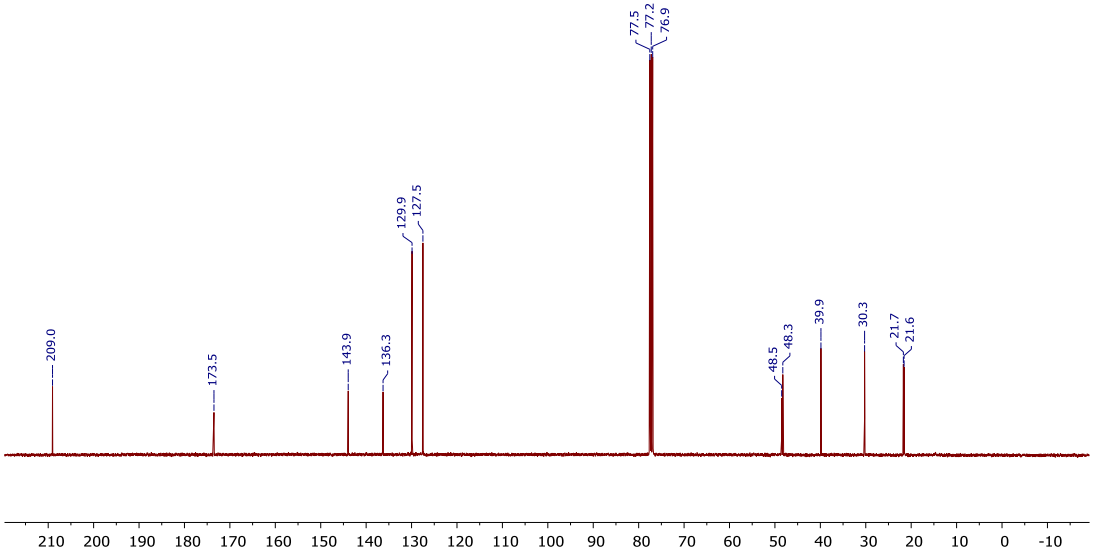
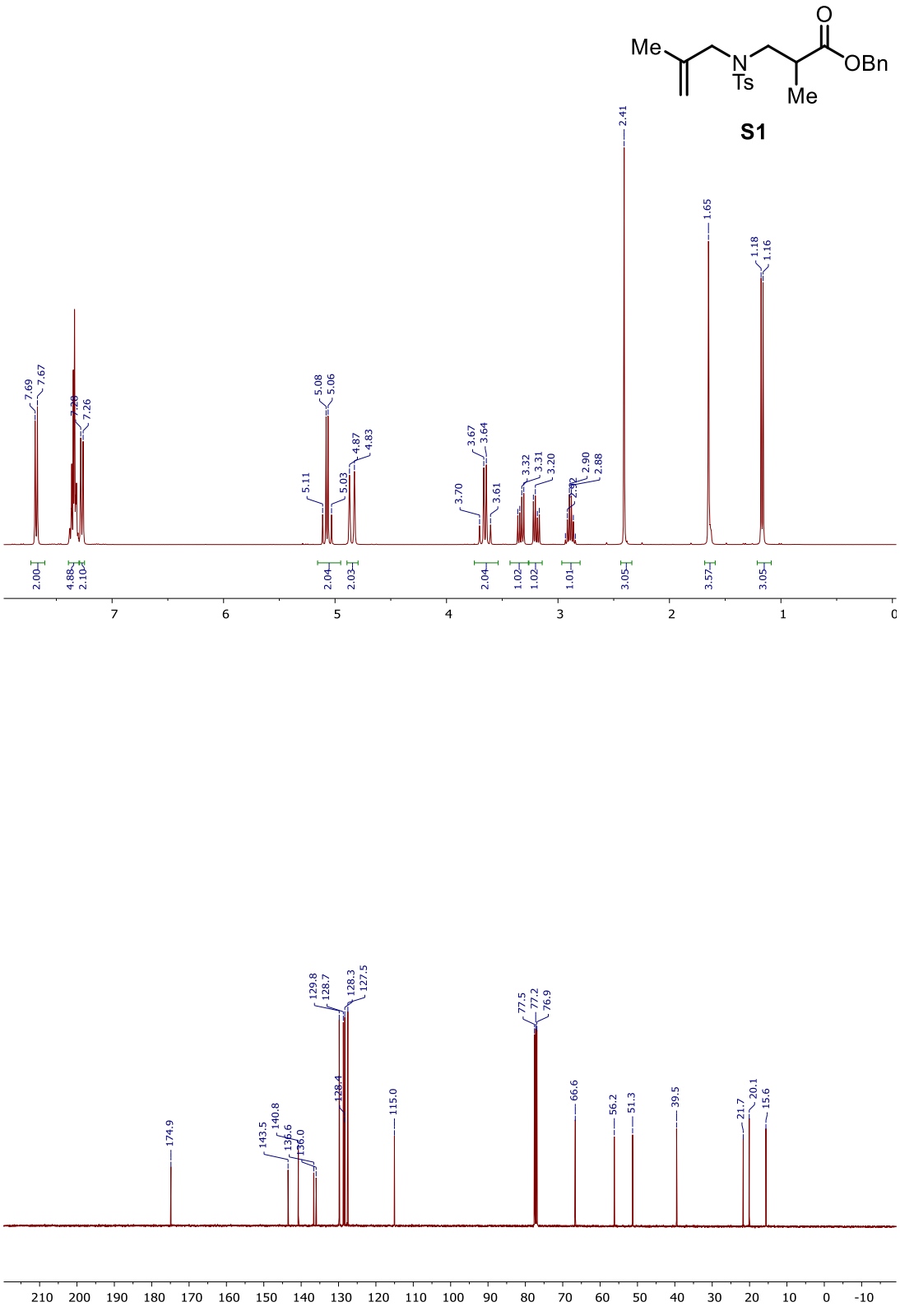
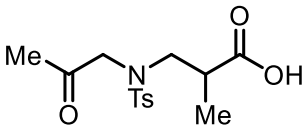




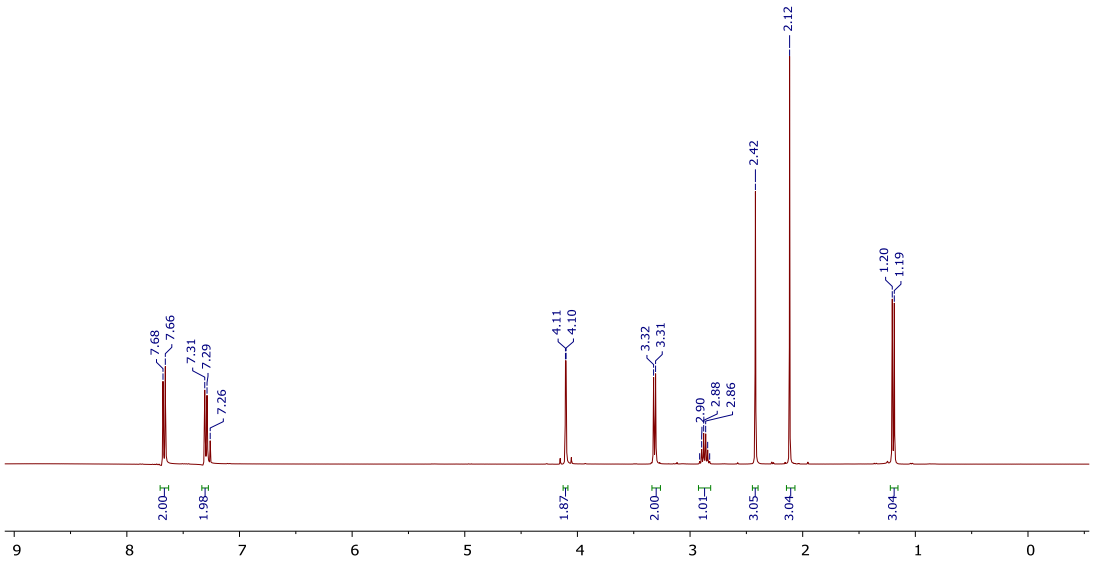
^{1}H (400 MHz) and ^{13}C NMR (101 MHz) spectra of keto acid **5e** in $CDCl_3$

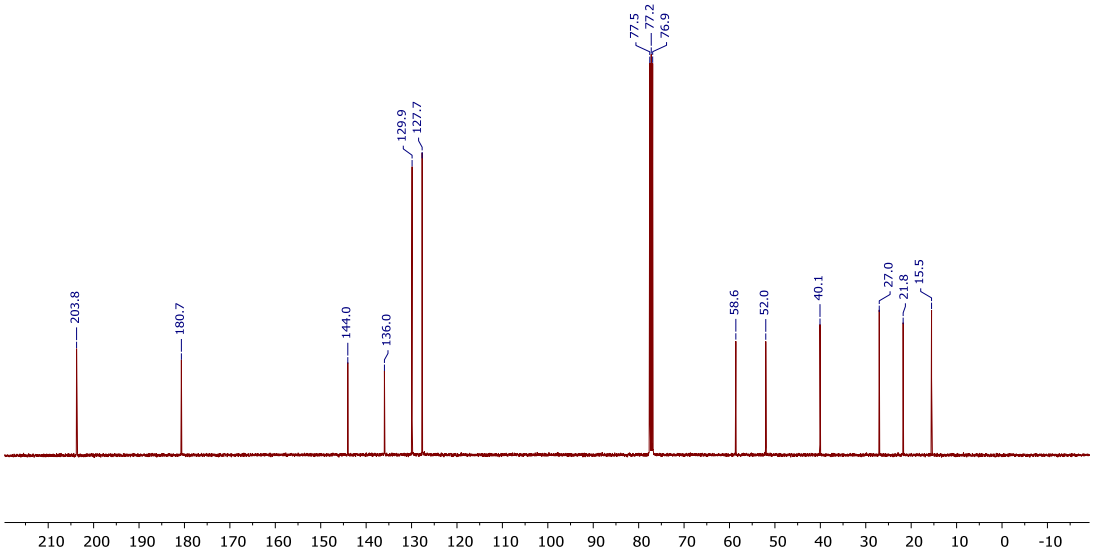


^{1}H (400 MHz) and ^{13}C NMR (101 MHz) spectra of **S1** in $CDCl_3$

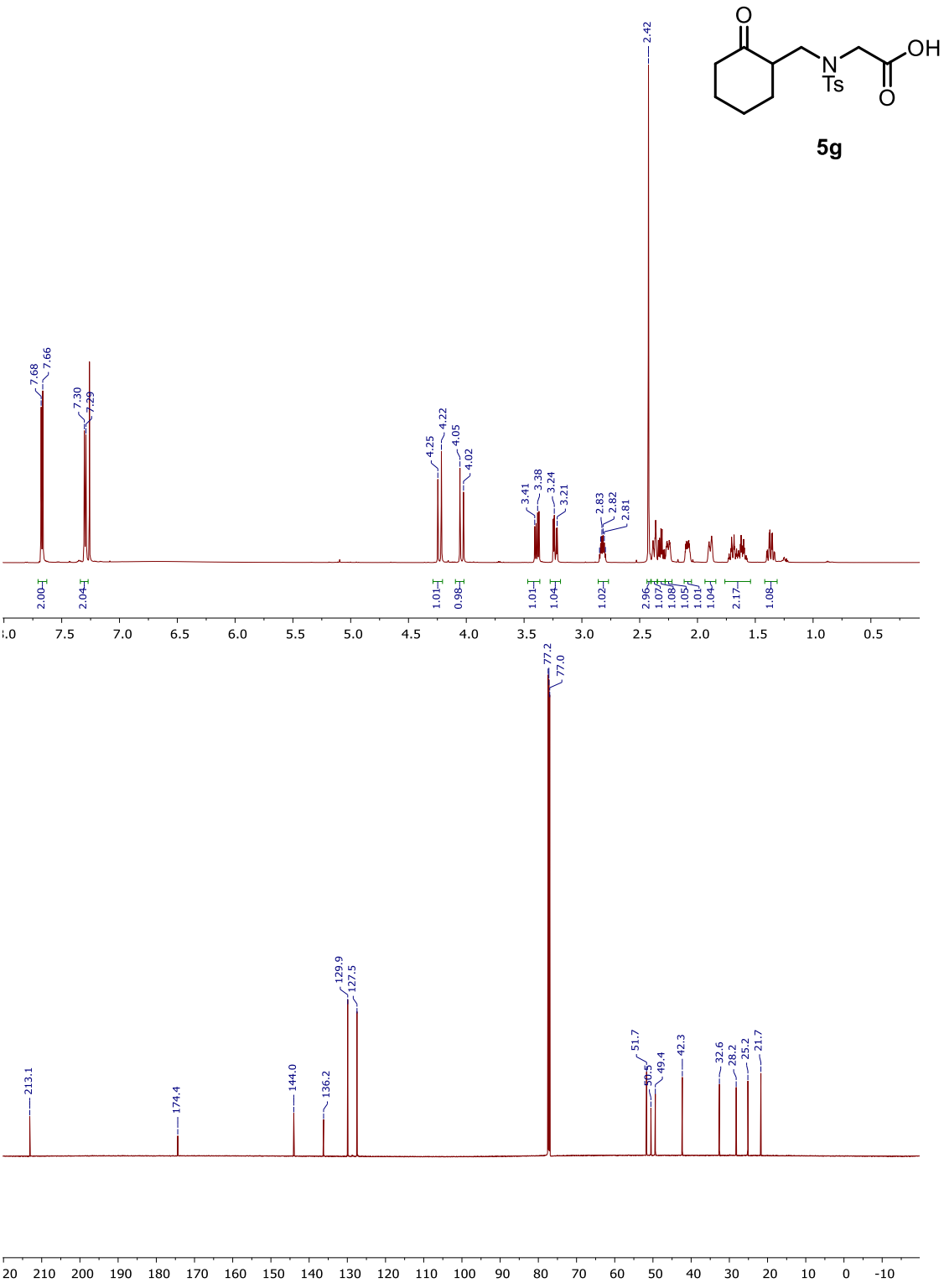


5f

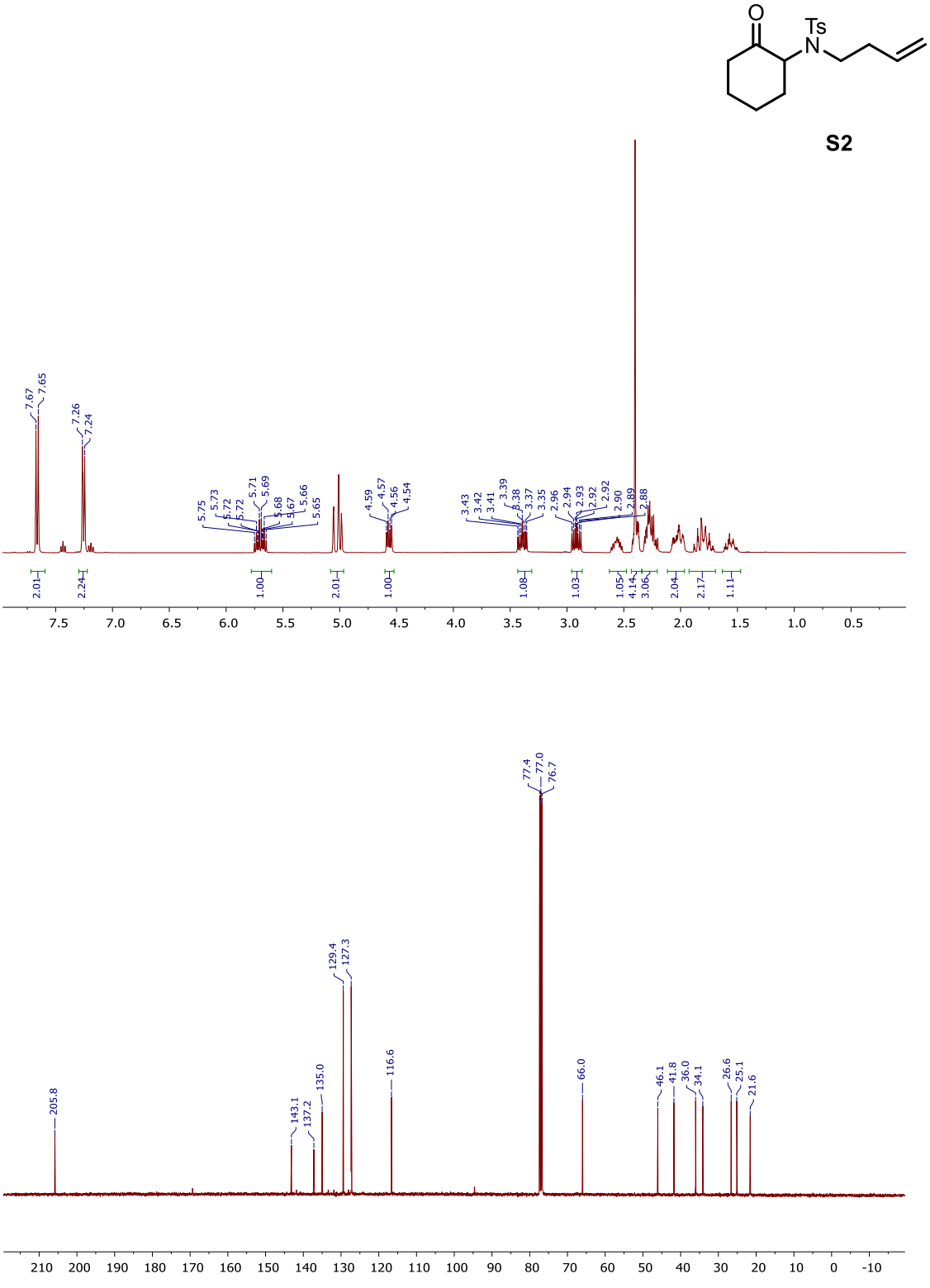




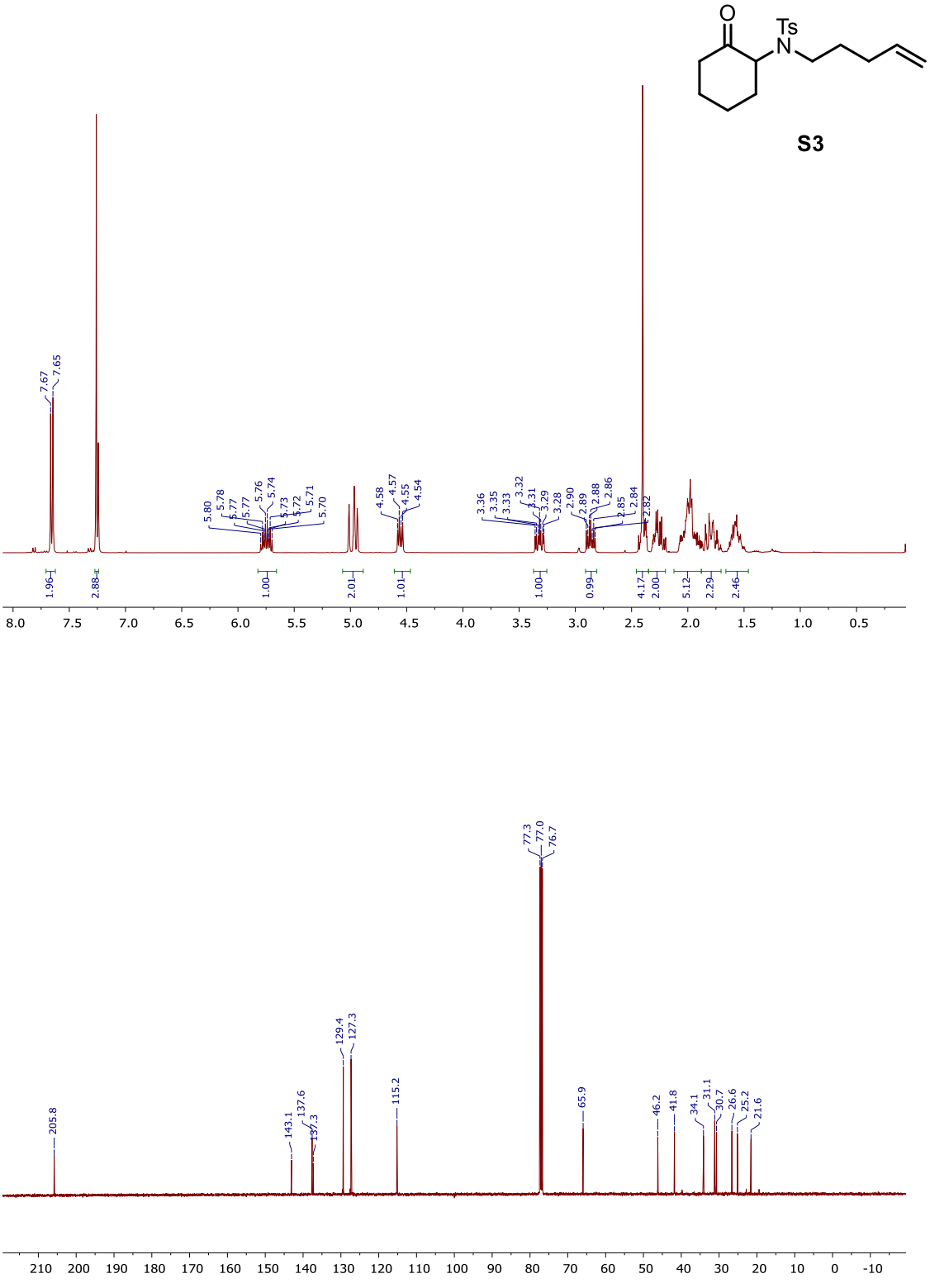
^{1}H (400 MHz) and ^{13}C NMR (101 MHz) spectra of keto acid **5f** in $CDCl_3$



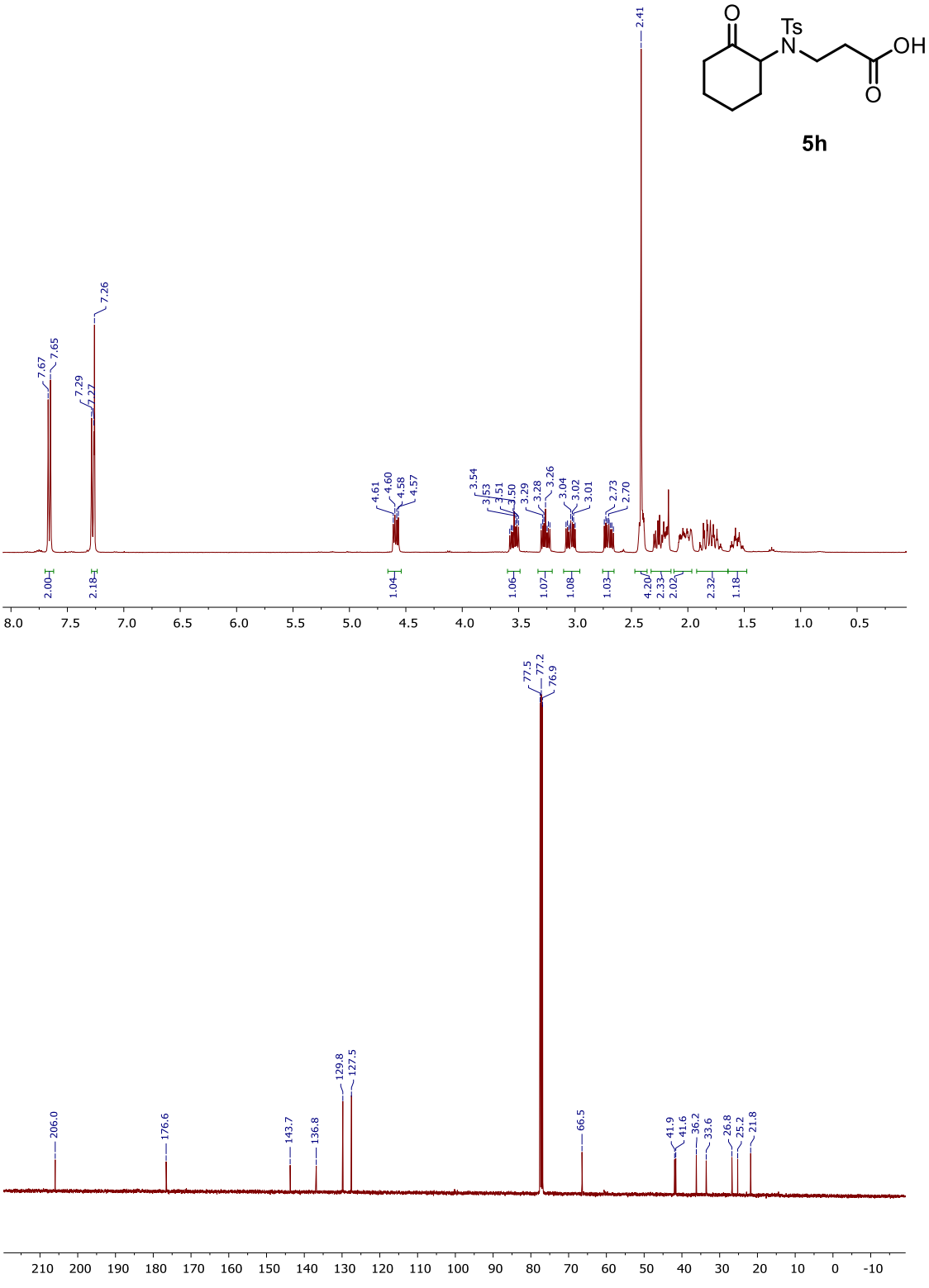
^{1}H (600 MHz) and ^{13}C NMR (150 MHz) spectra of keto acid **5g** in $CDCl_3$



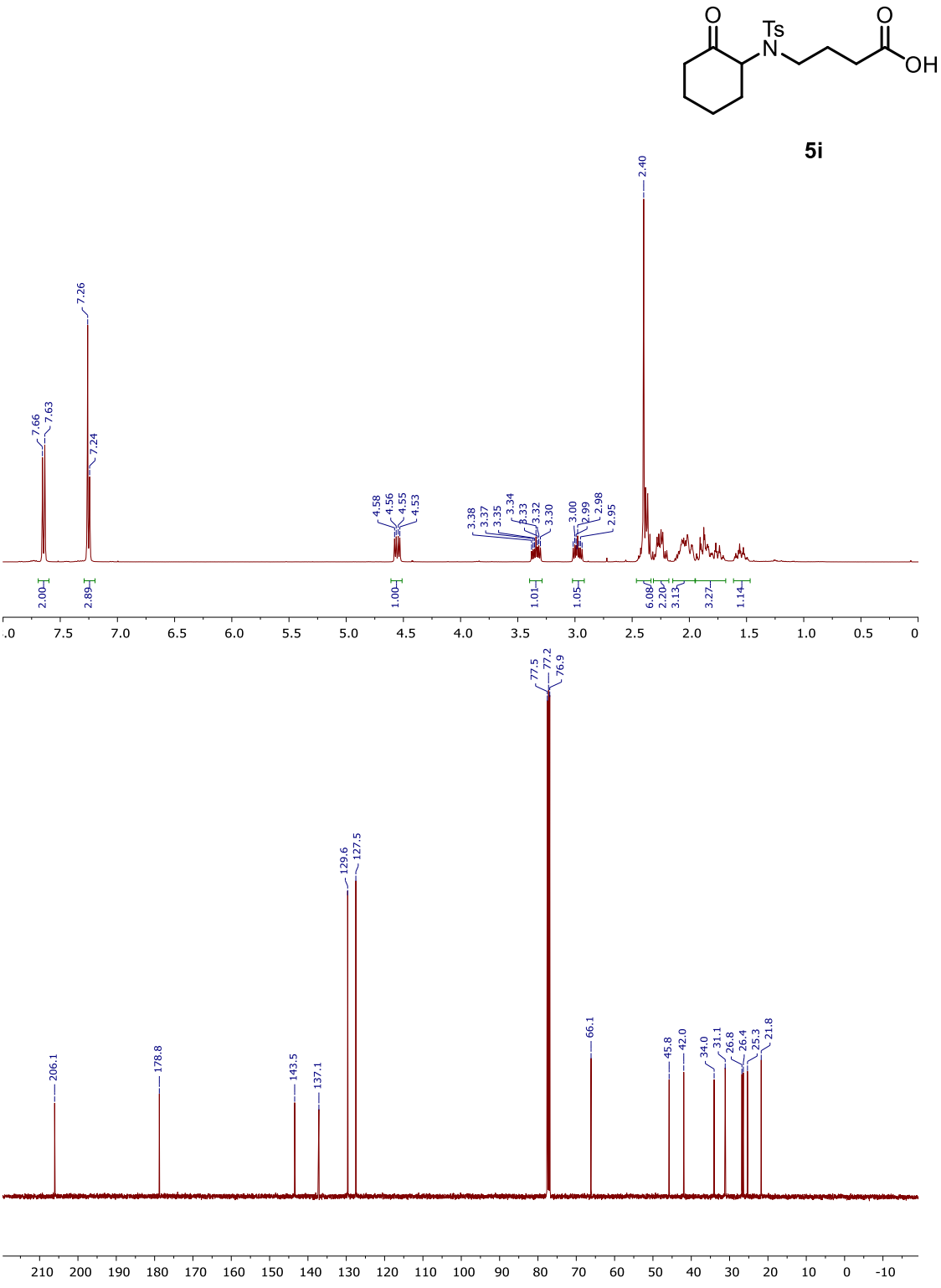
^{1}H (400 MHz) and ^{13}C NMR (101 MHz) spectra of **S2** in $CDCl_3$



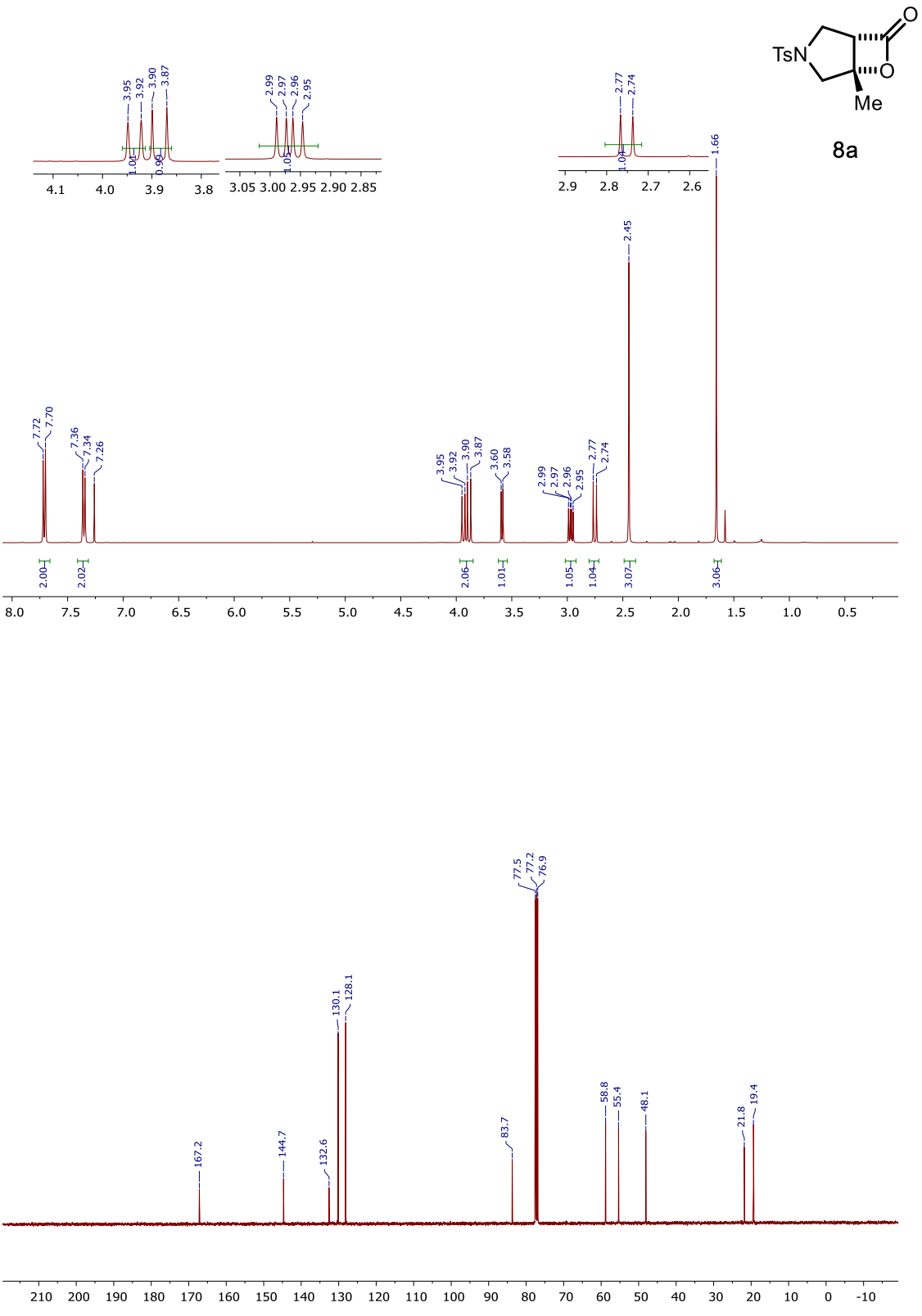
^{1}H (400 MHz) and ^{13}C NMR (101 MHz) spectra of **S3** in $CDCl_3$



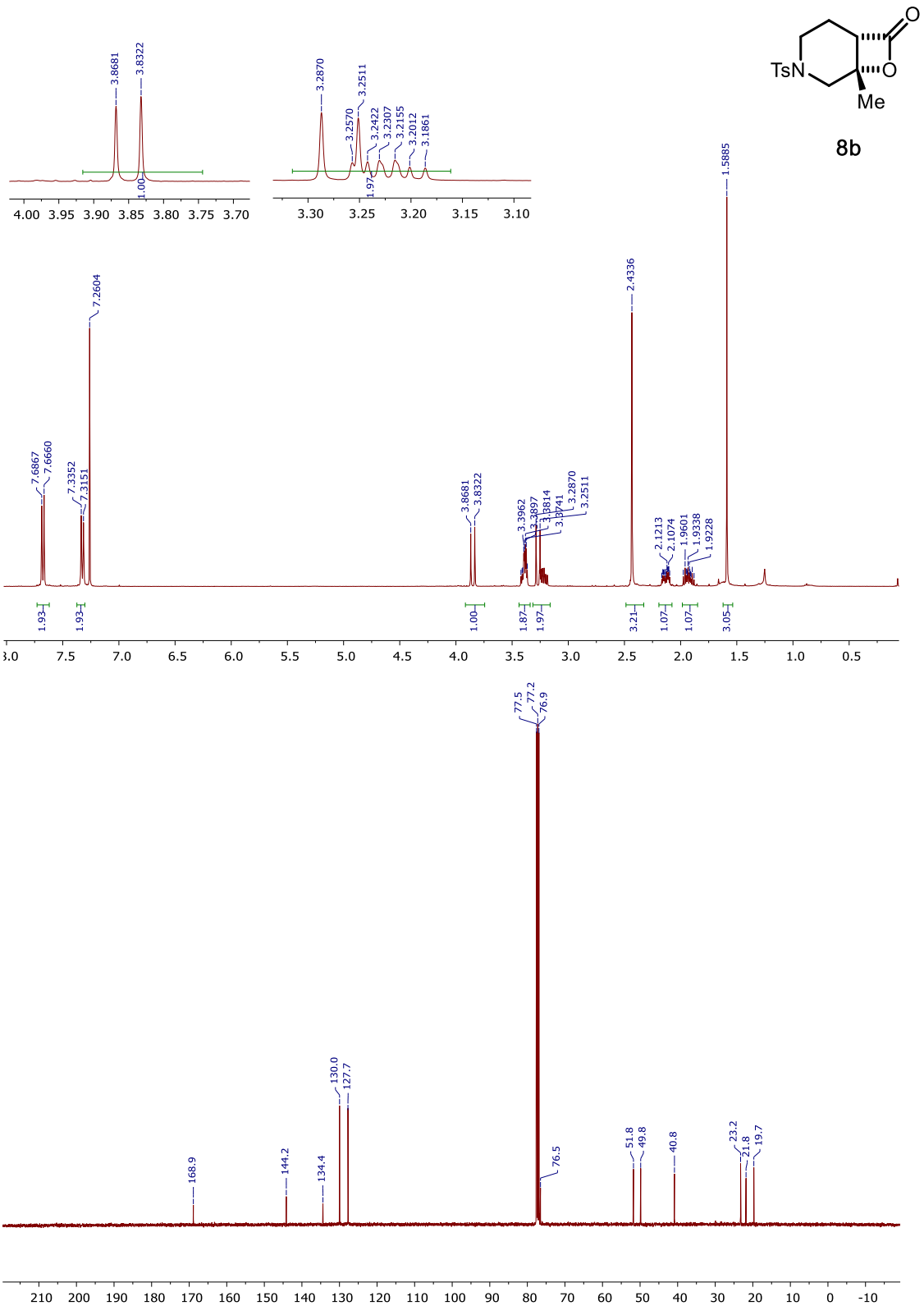
^{1}H (400 MHz) and ^{13}C NMR (101 MHz) spectra of keto acid **5h** in $CDCl_3$



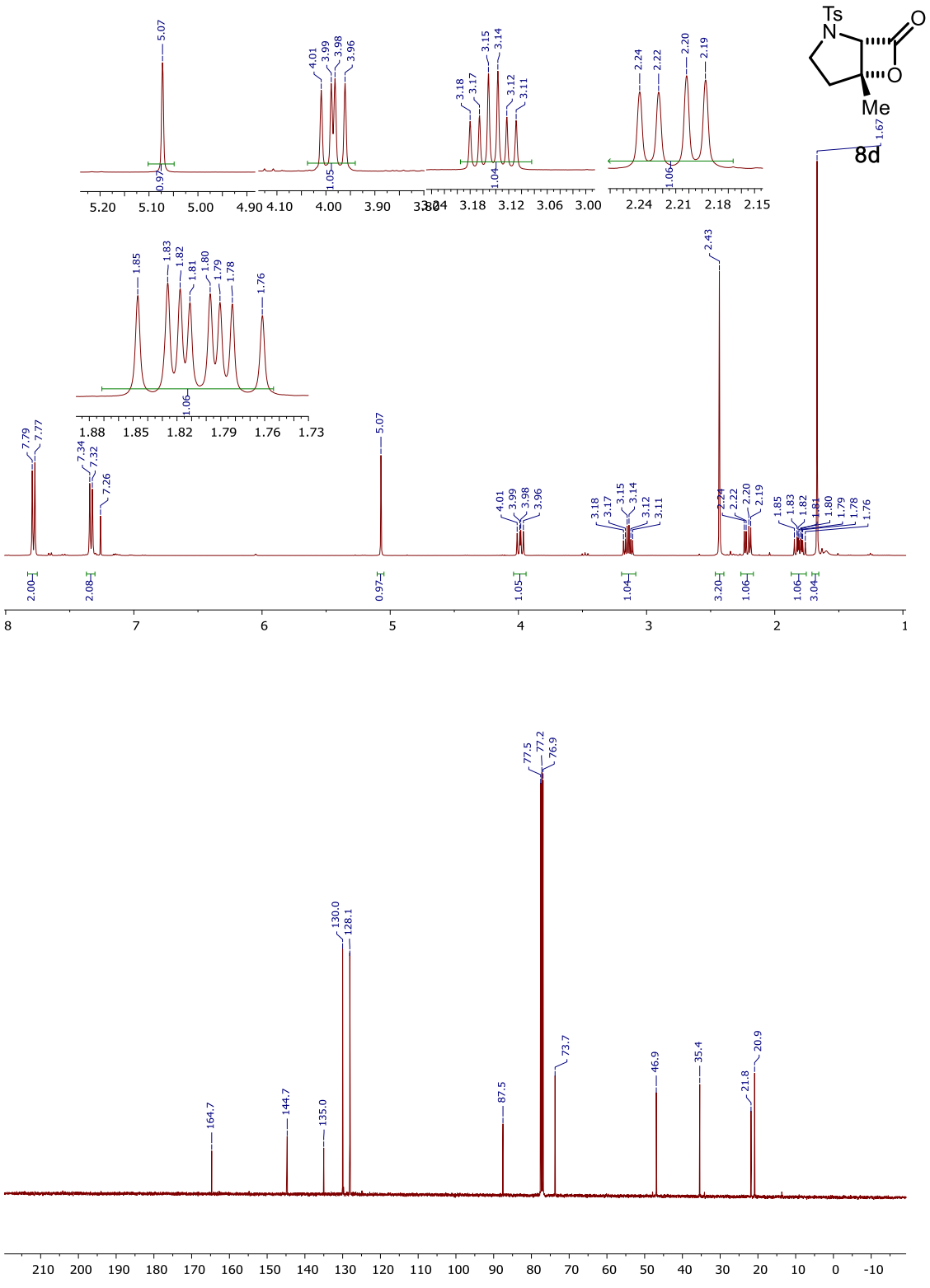
^{1}H (400 MHz) and ^{13}C NMR (101 MHz) spectra of keto acid **5i** in $CDCl_3$



^{1}H (400 MHz) and ^{13}C NMR (101 MHz) spectra of β-lactone **8a** in $CDCl_3$



^{1}H (400 MHz) and ^{13}C NMR (101 MHz) spectra of β-lactone **8b** in $CDCl_3$



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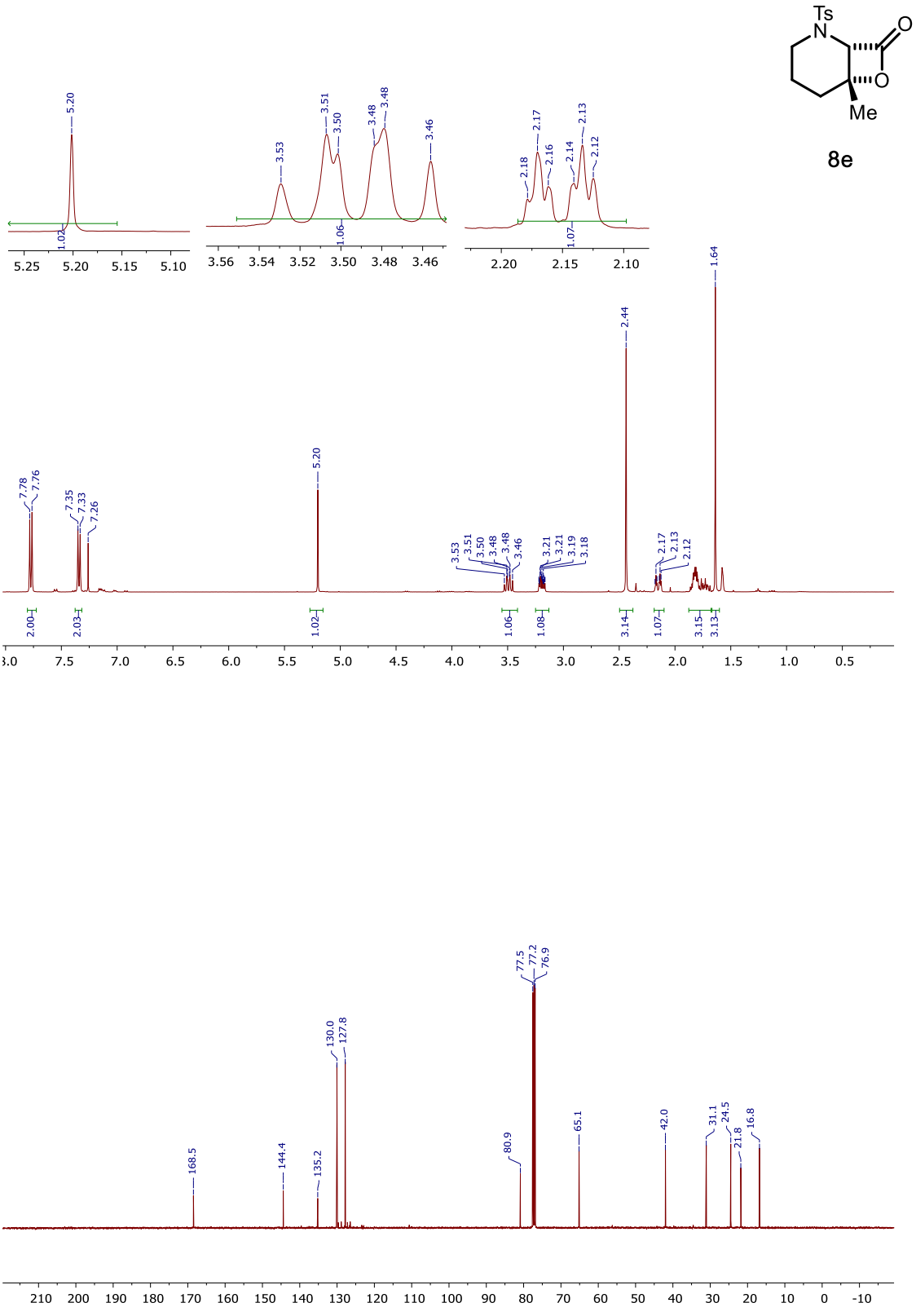

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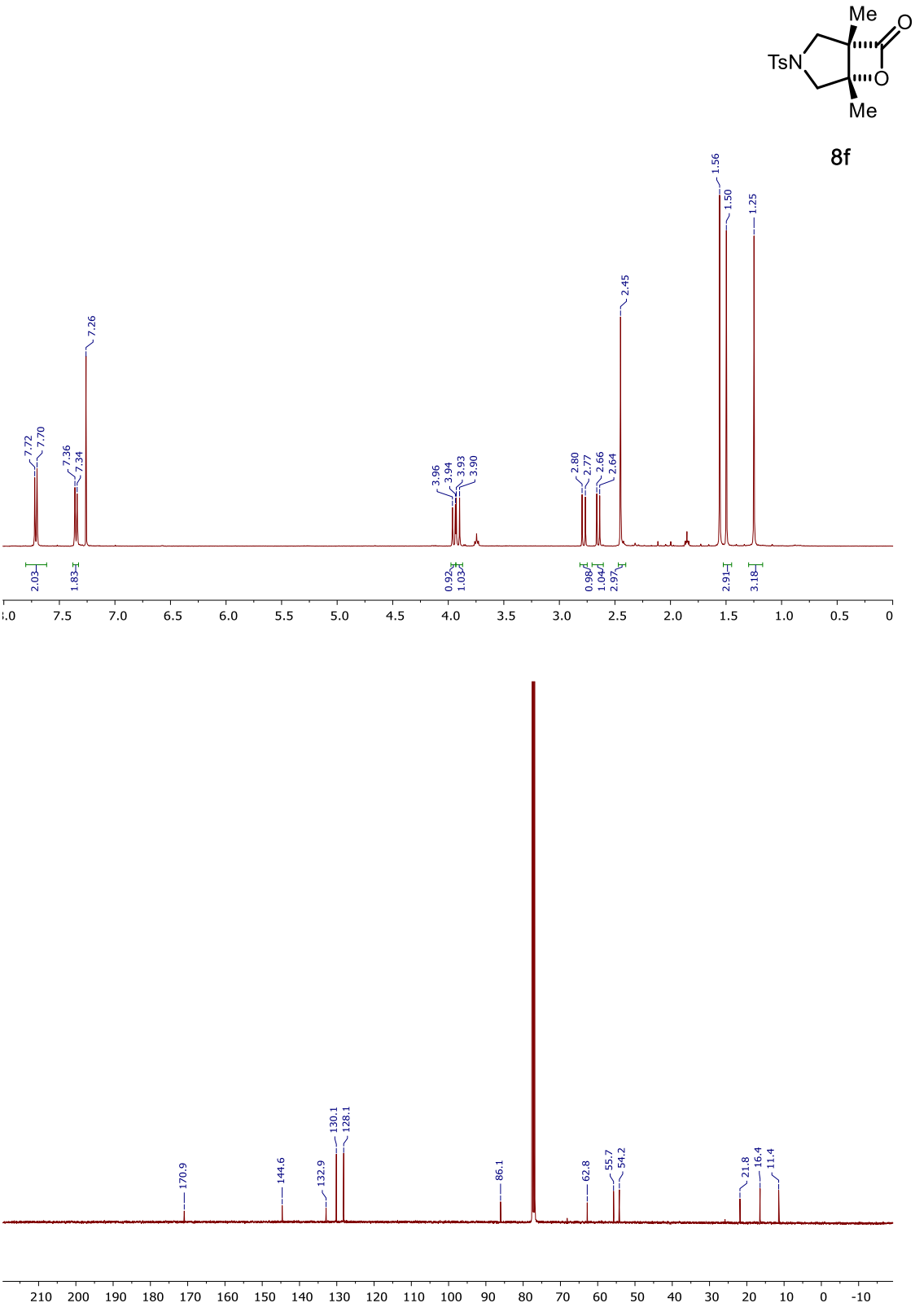

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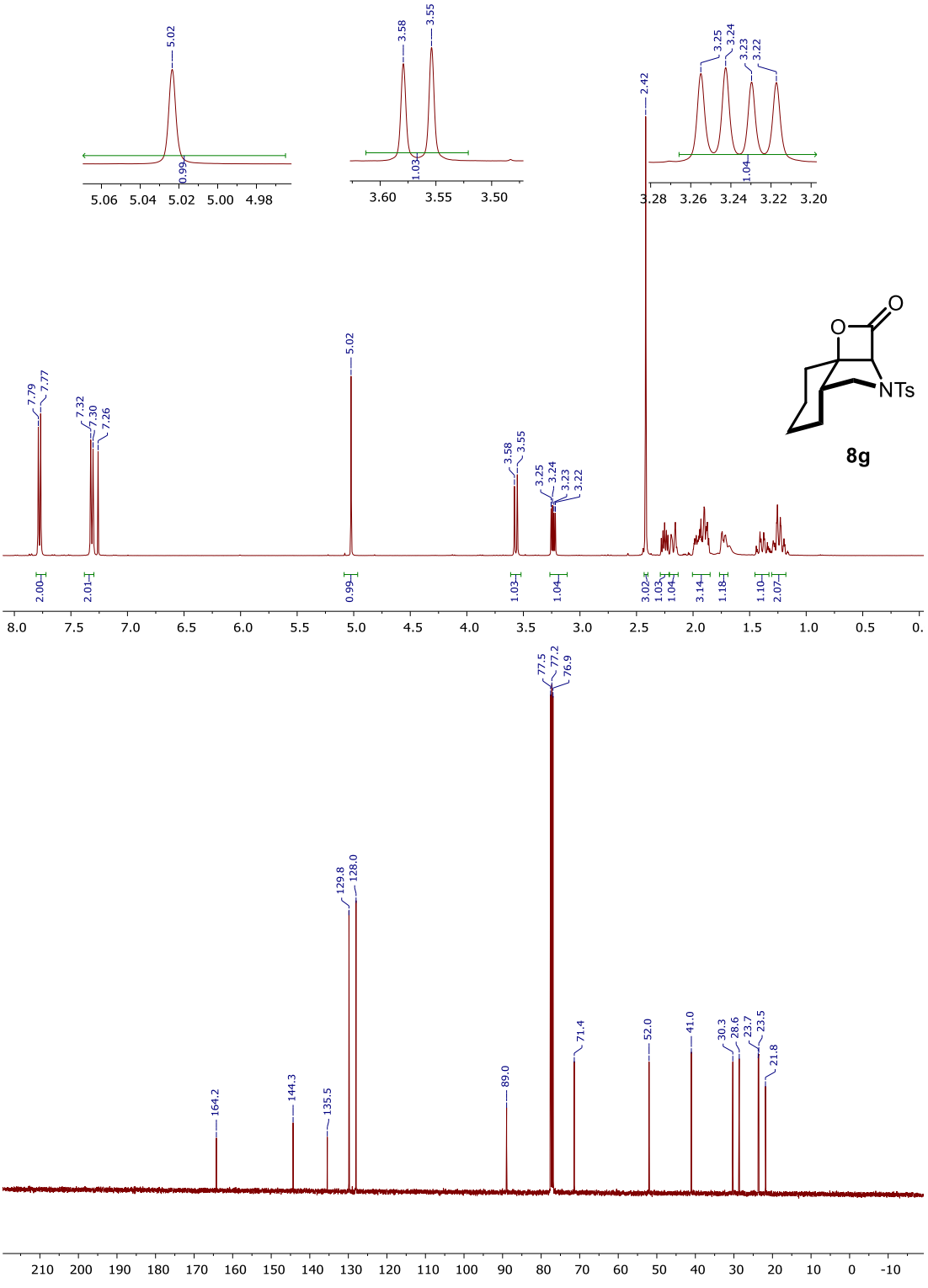
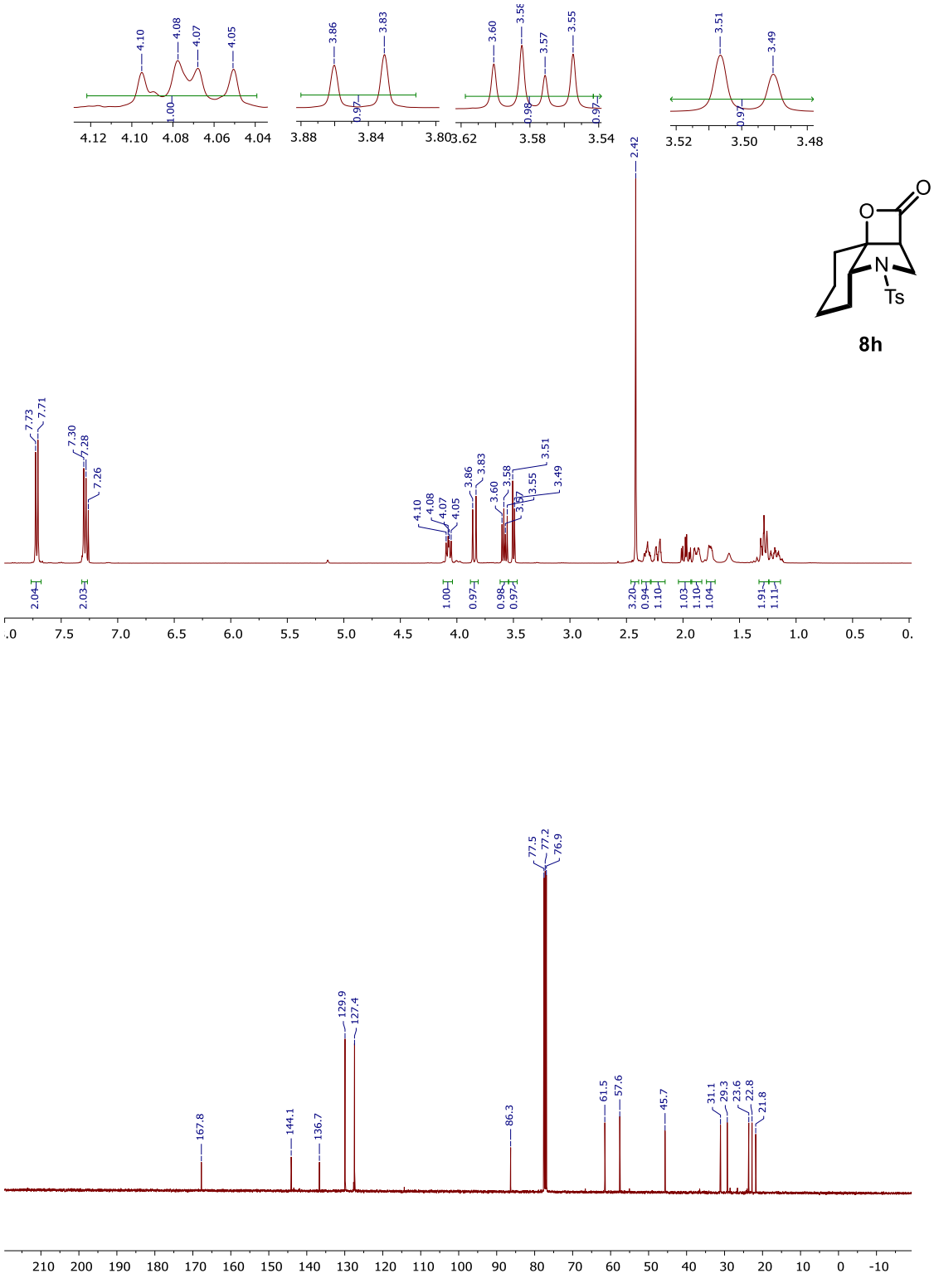
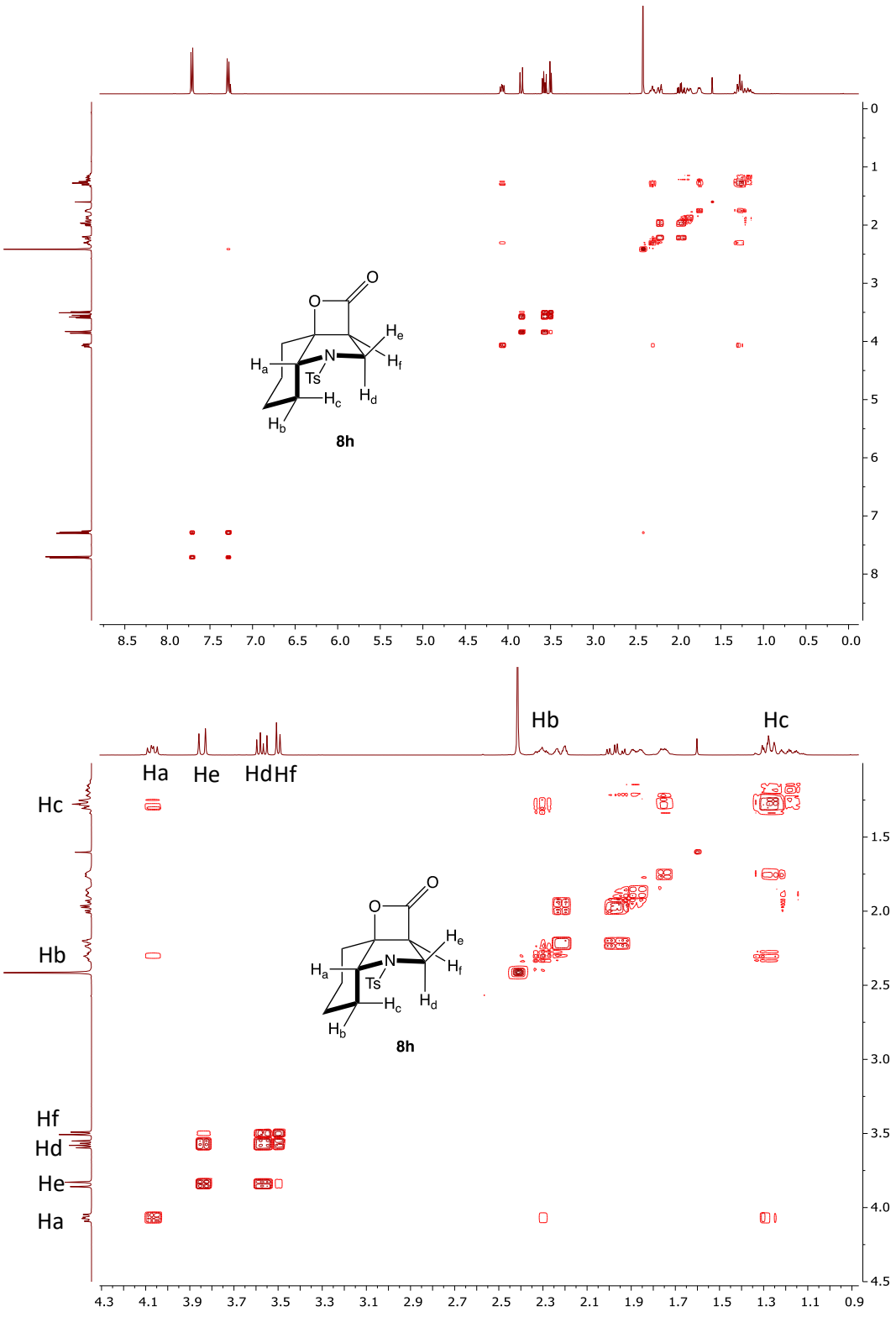


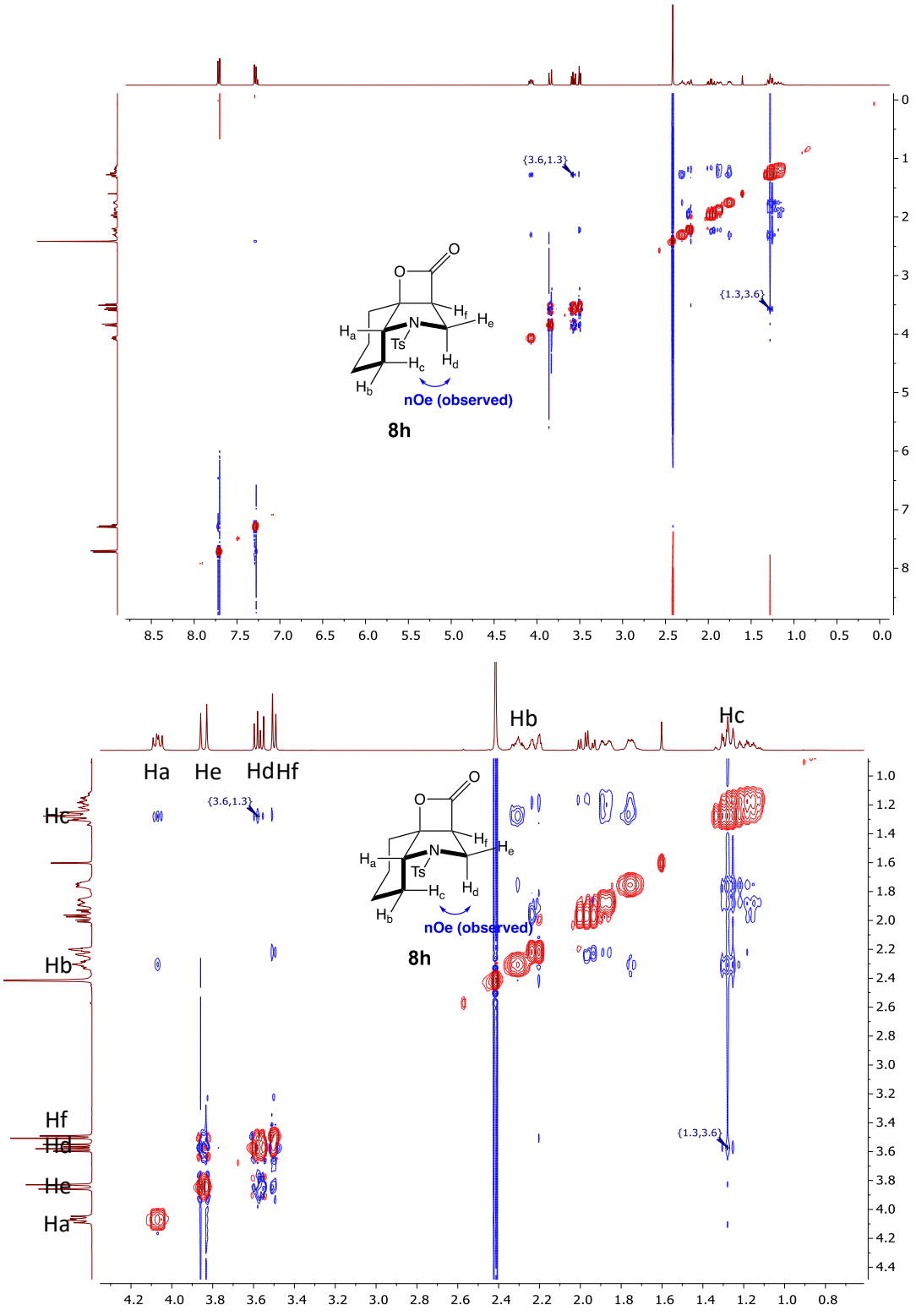
^{1}H (400 MHz) and ^{13}C NMR (101 MHz) spectra of β-lactone **8g** in $CDCl_3$



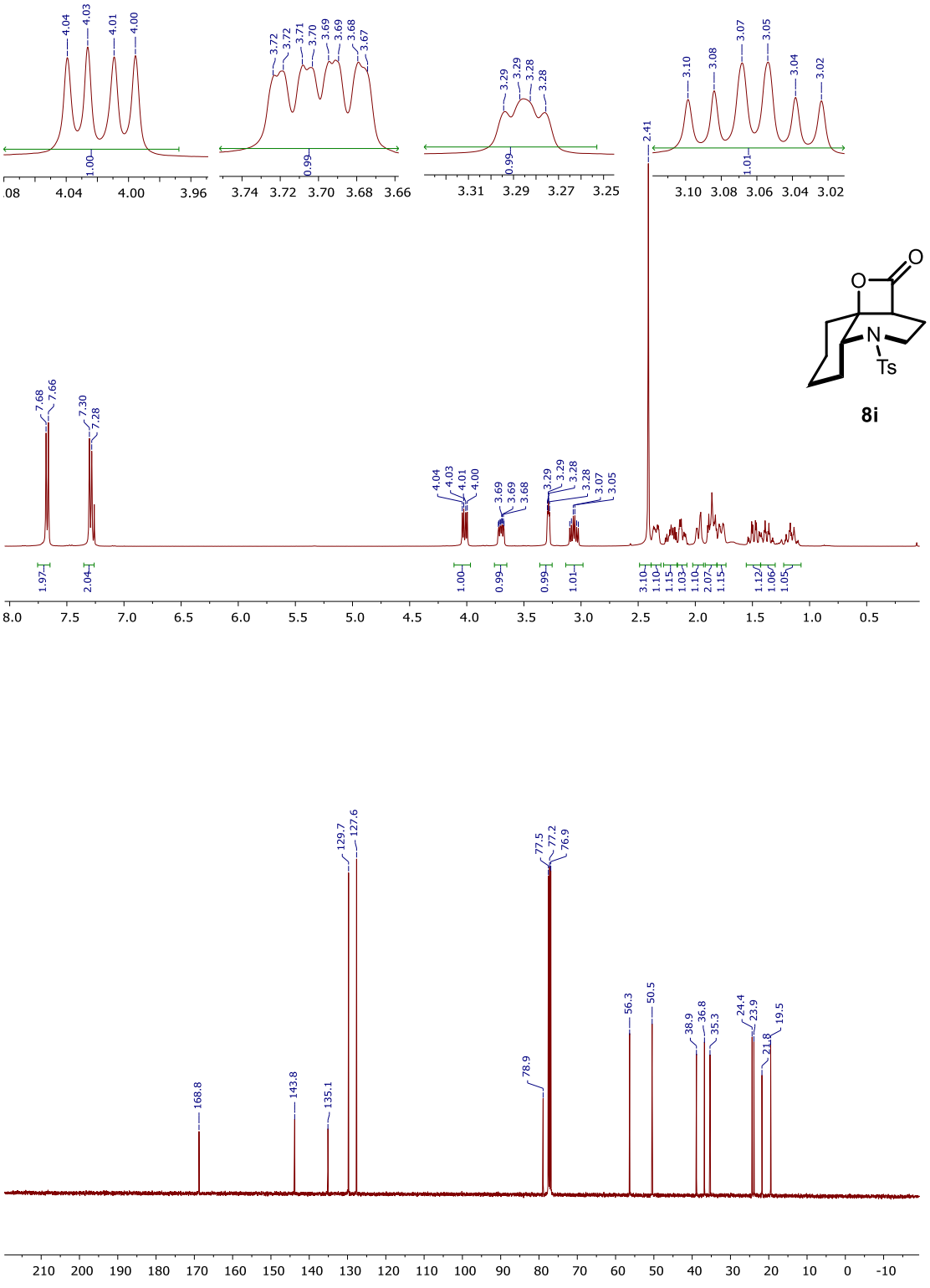
^{1}H (400 MHz) and ^{13}C NMR (101 MHz) spectra of β-lactone **8h** in $CDCl_3$



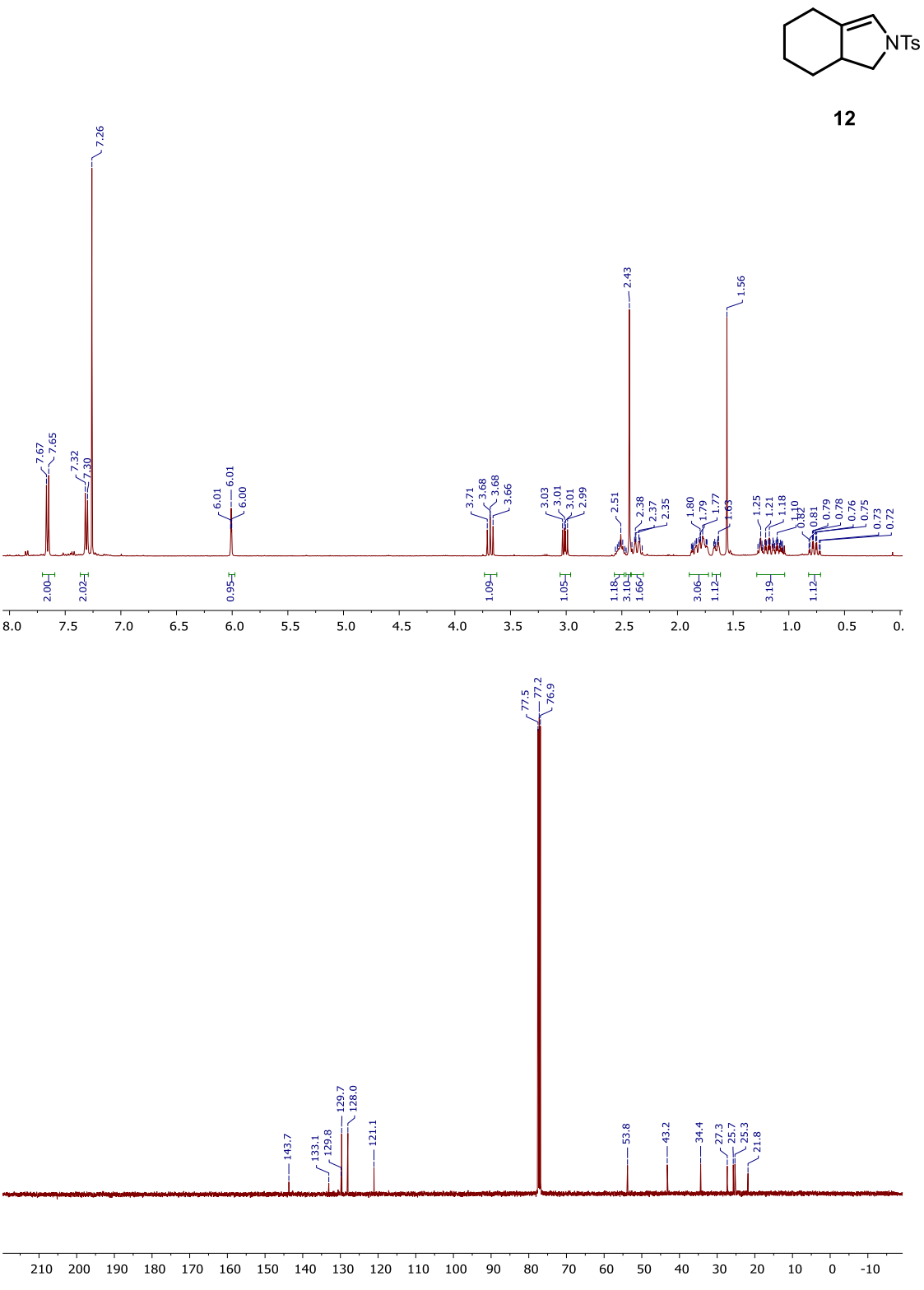
COSY (400 MHz) spectra of β-lactone **8h** in $CDCl_3$



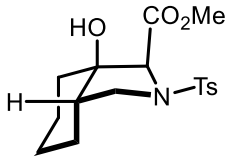
NOESY (400 MHz) spectra of β-lactone **8h** in $CDCl_3$



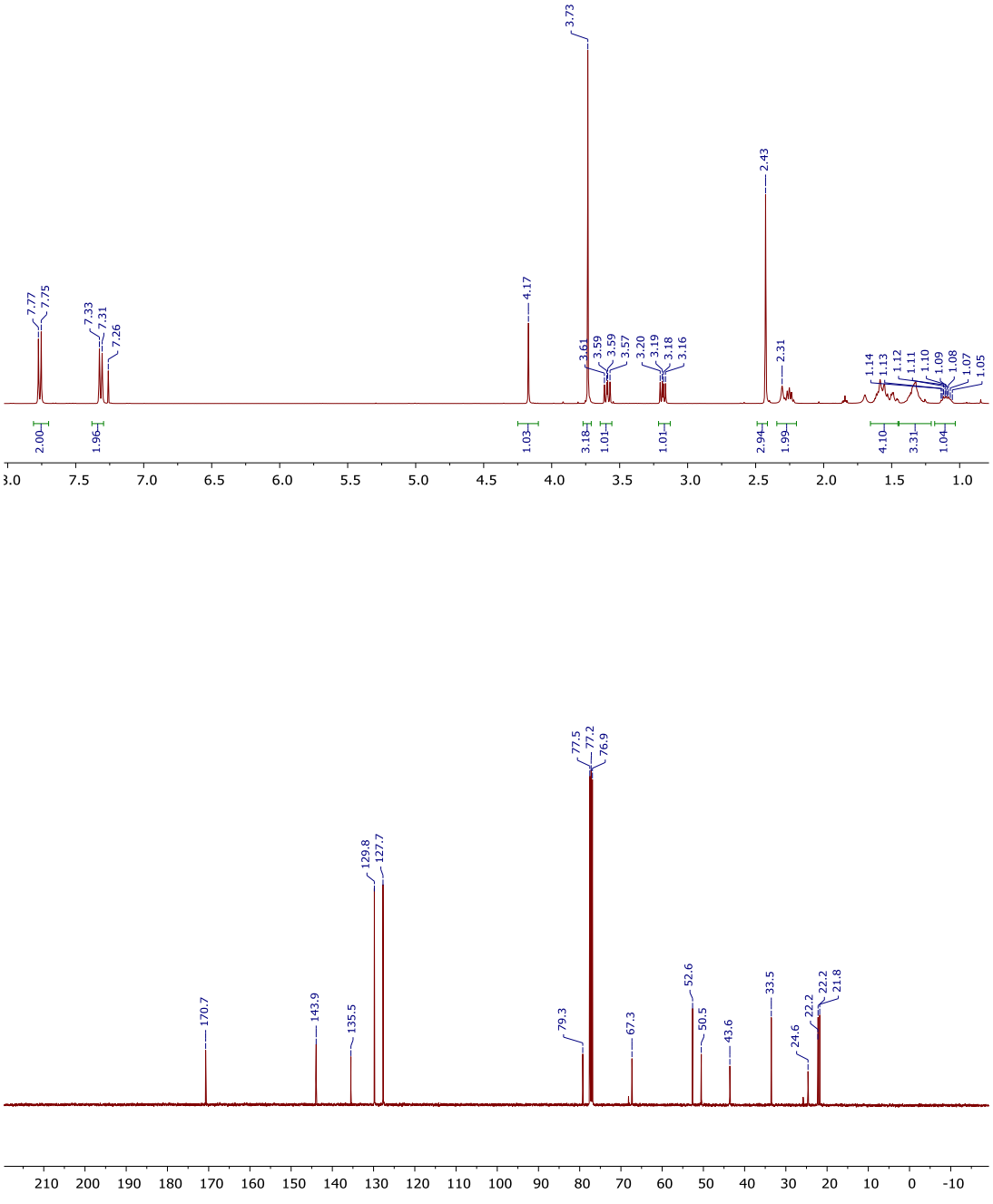
^{1}H (400 MHz) and ^{13}C NMR (101 MHz) spectra of β-lactone **8i** in $CDCl_3$



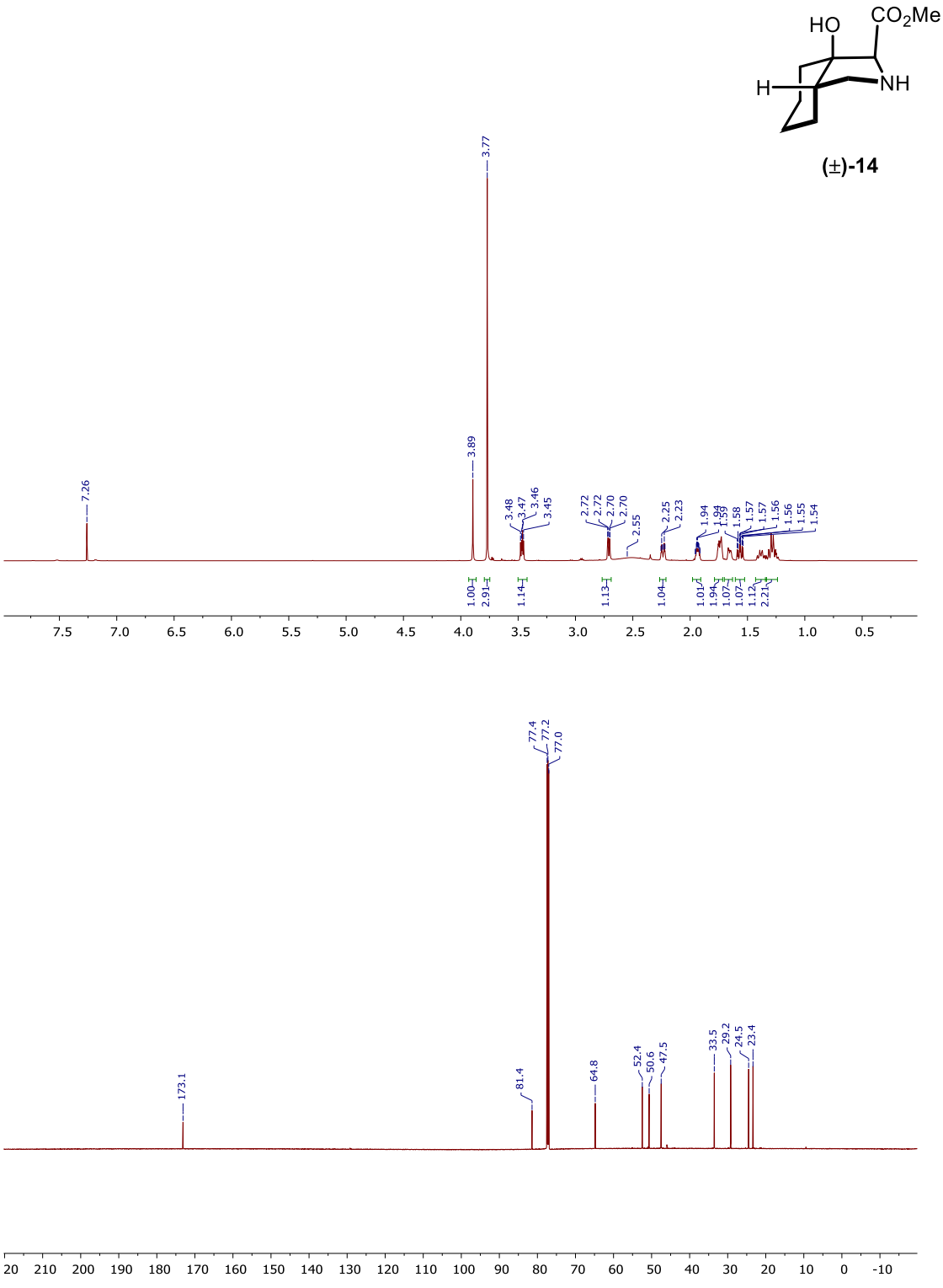
^{1}H (400 MHz) and ^{13}C NMR (101 MHz) spectra of **12** in $CDCl_3$



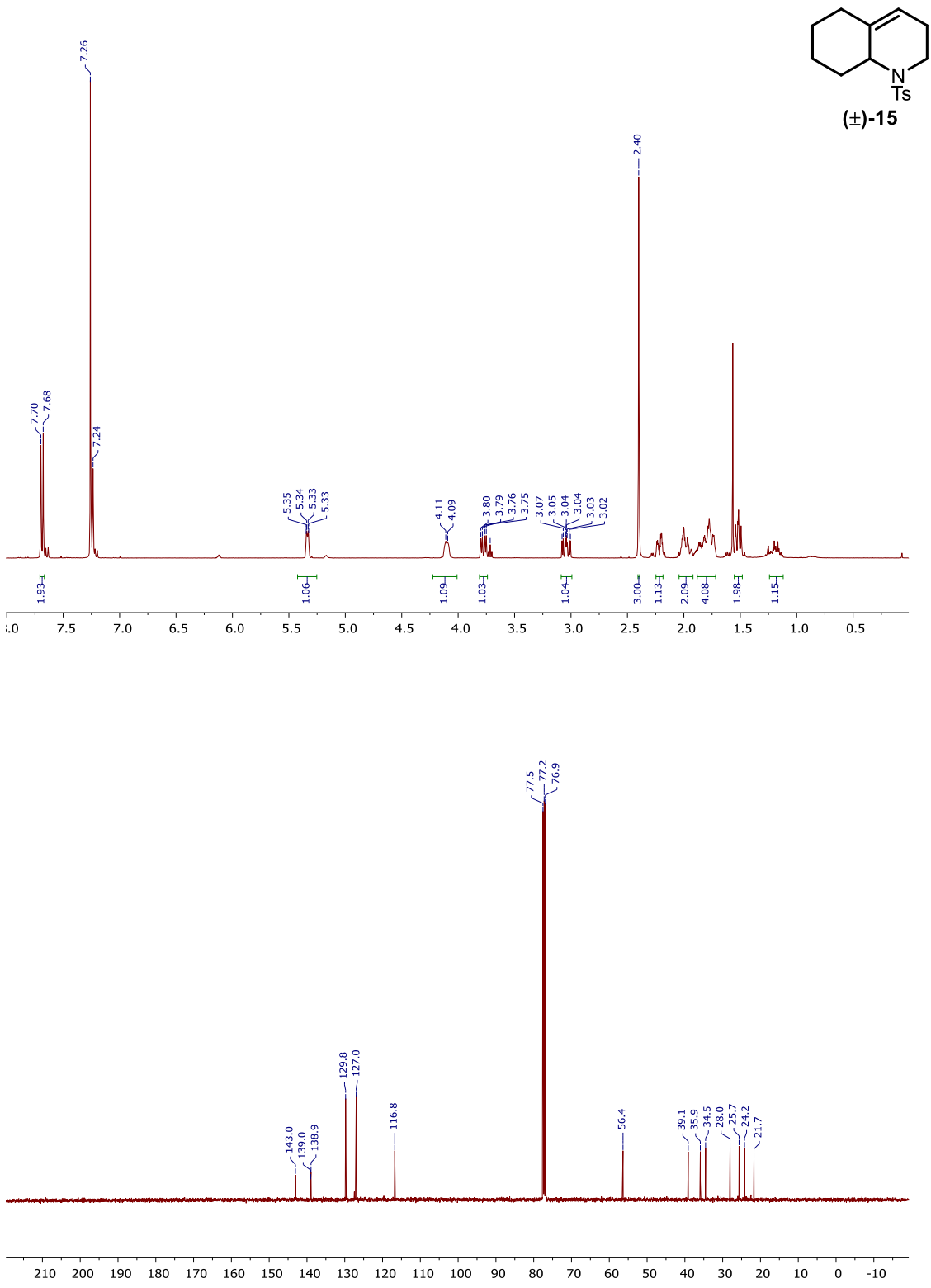
(±)-13



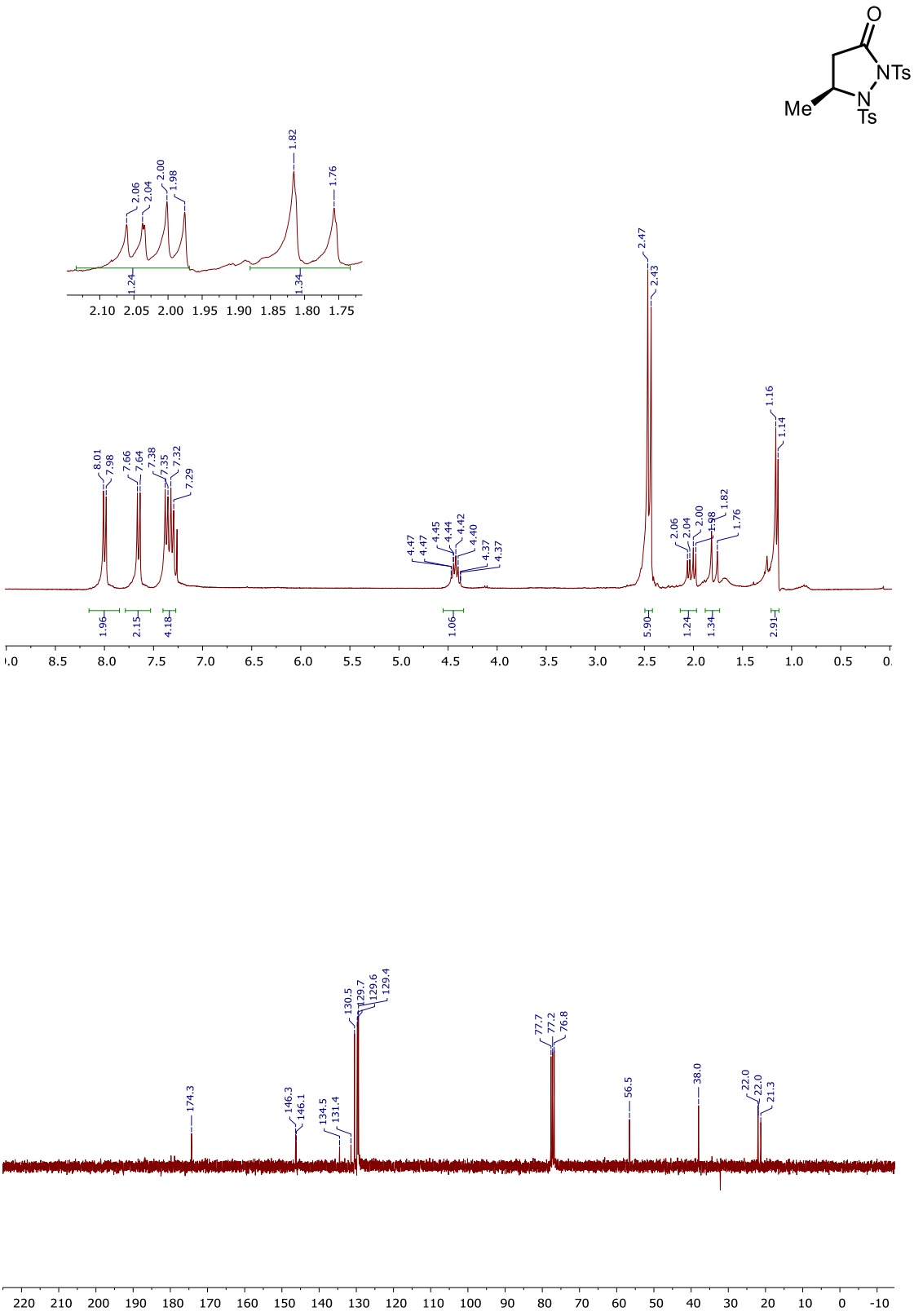
^{1}H (400 MHz) and ^{13}C NMR (101 MHz) spectra of **13** in $CDCl_3$



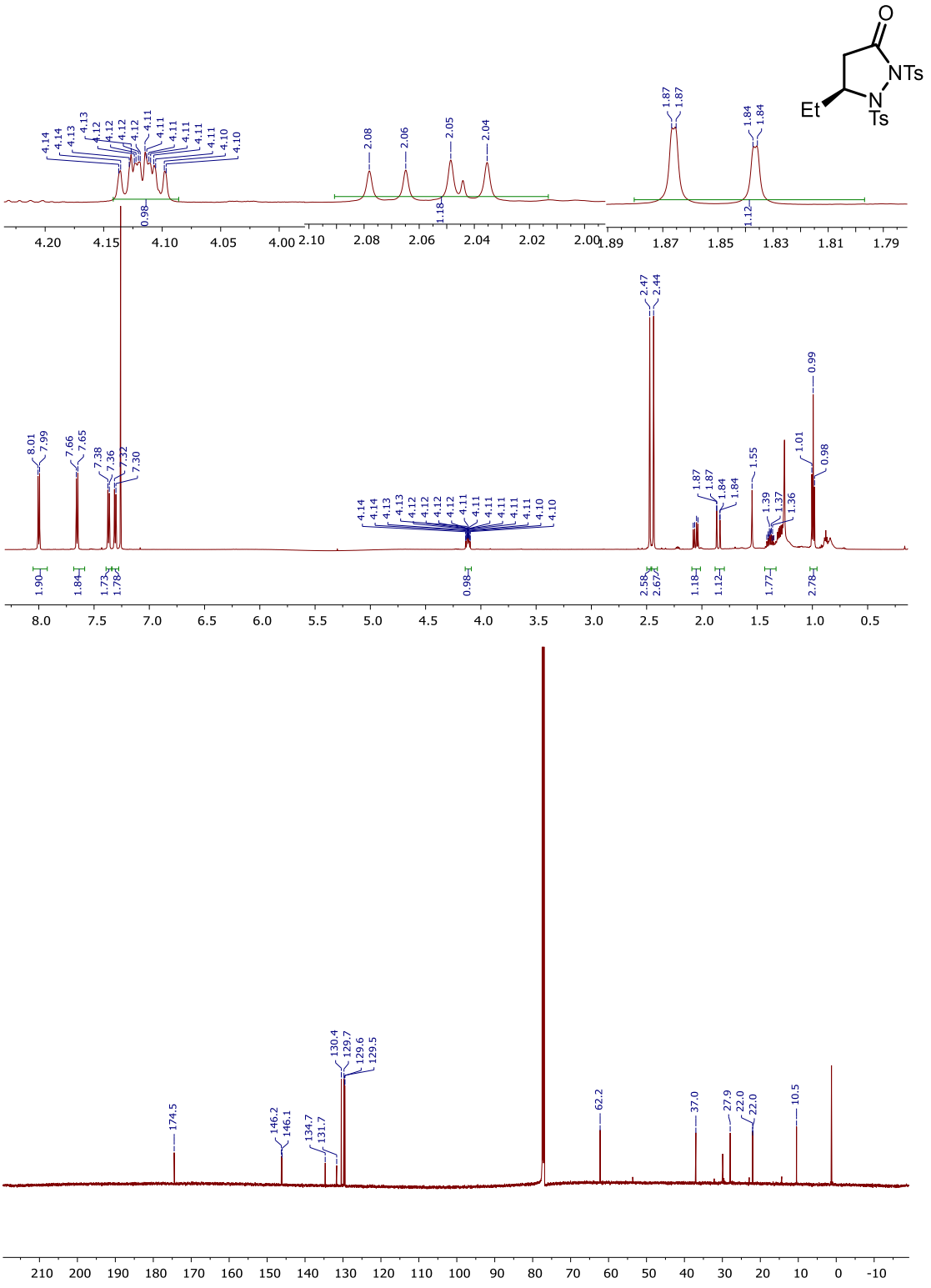
^{1}H (600 MHz) and ^{13}C NMR (151 MHz) spectra of **14** in $CDCl_3$



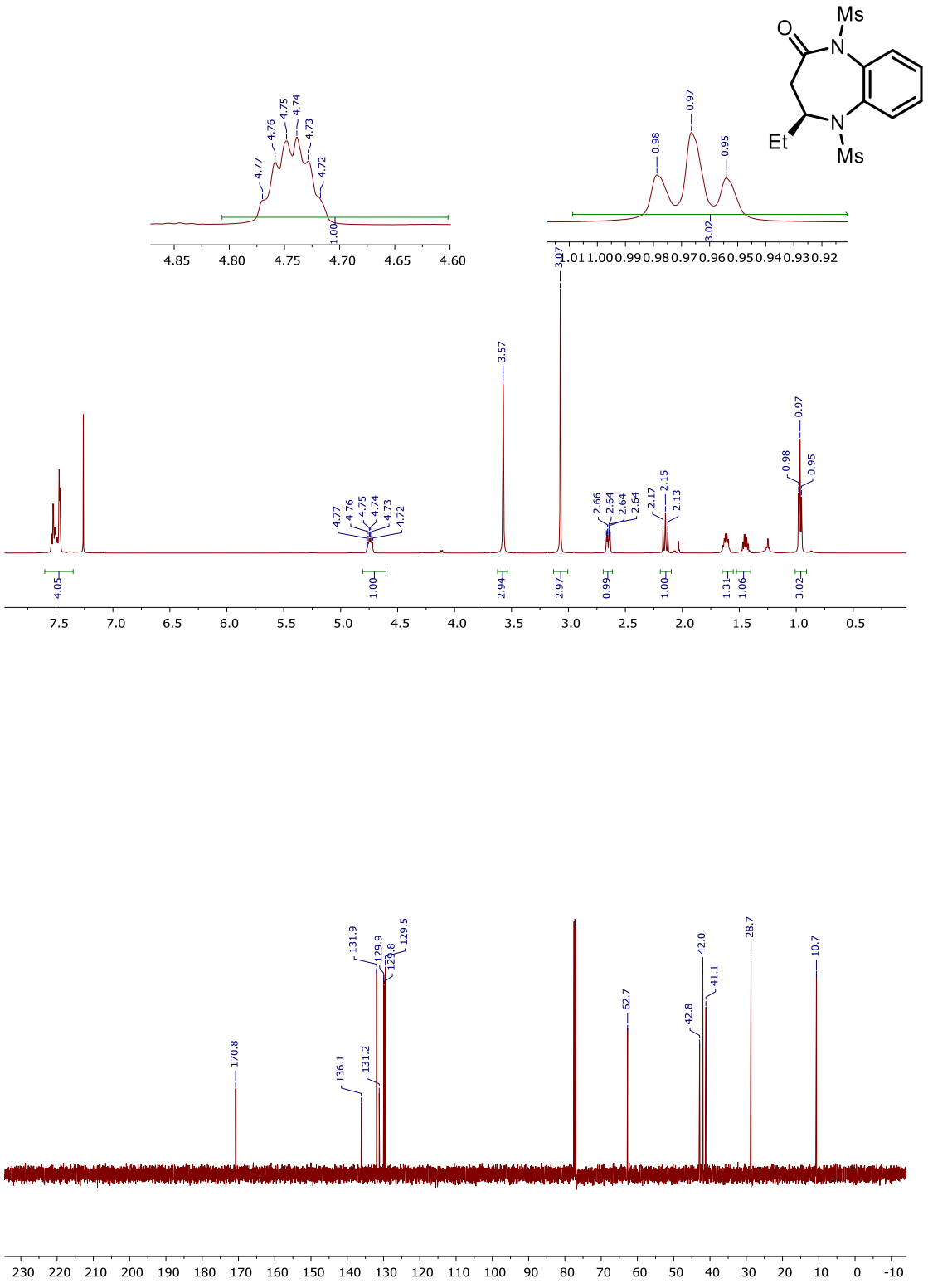
^{1}H (400 MHz) and ^{13}C NMR (101 MHz) spectra of **15** in $CDCl_3$



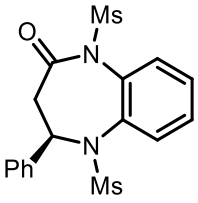
^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of **3-3a** in $CDCl_3$

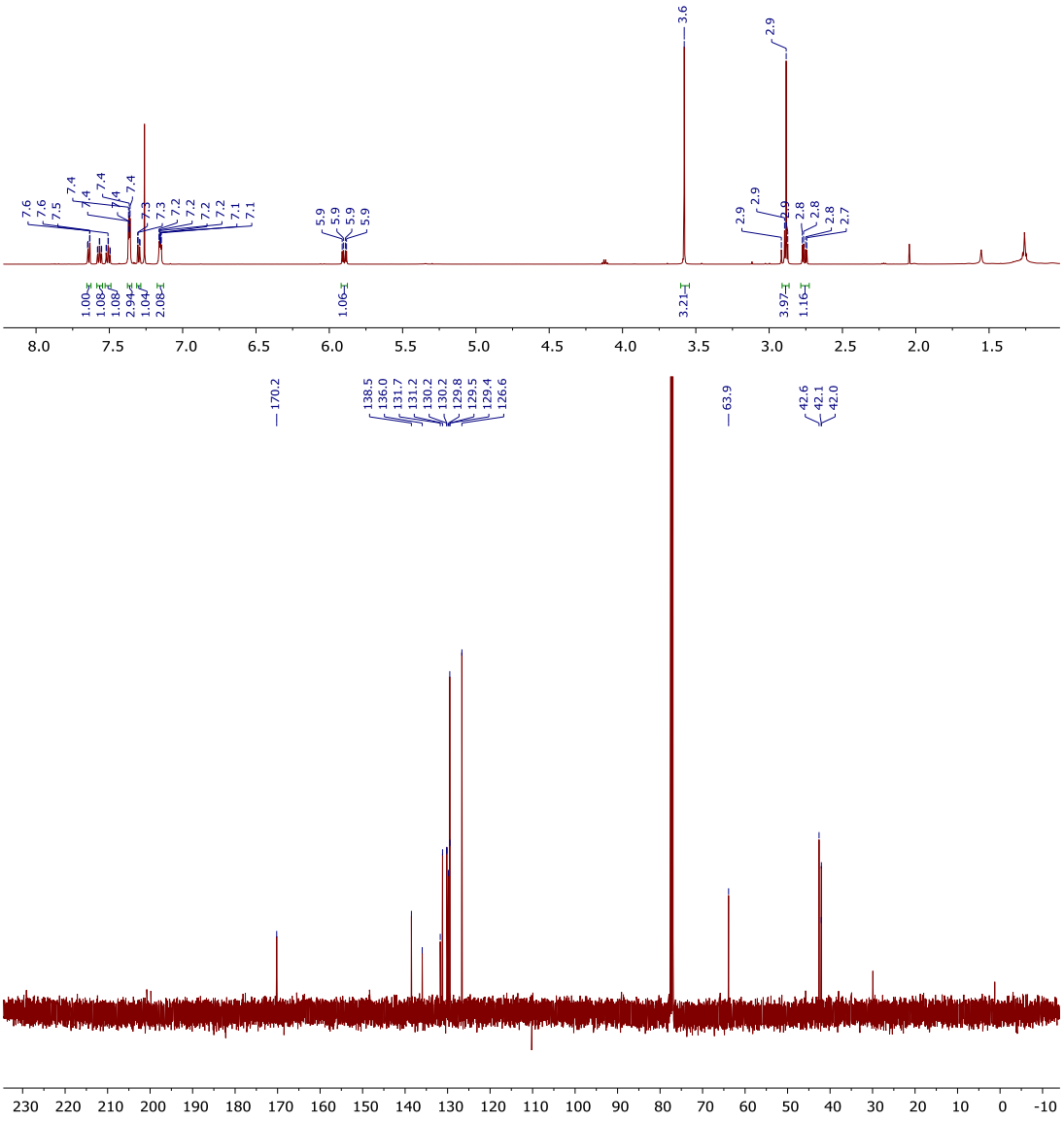


^{1}H (600 MHz) and ^{13}C NMR (151 MHz) spectra of **3-3b** in $CDCl_3$

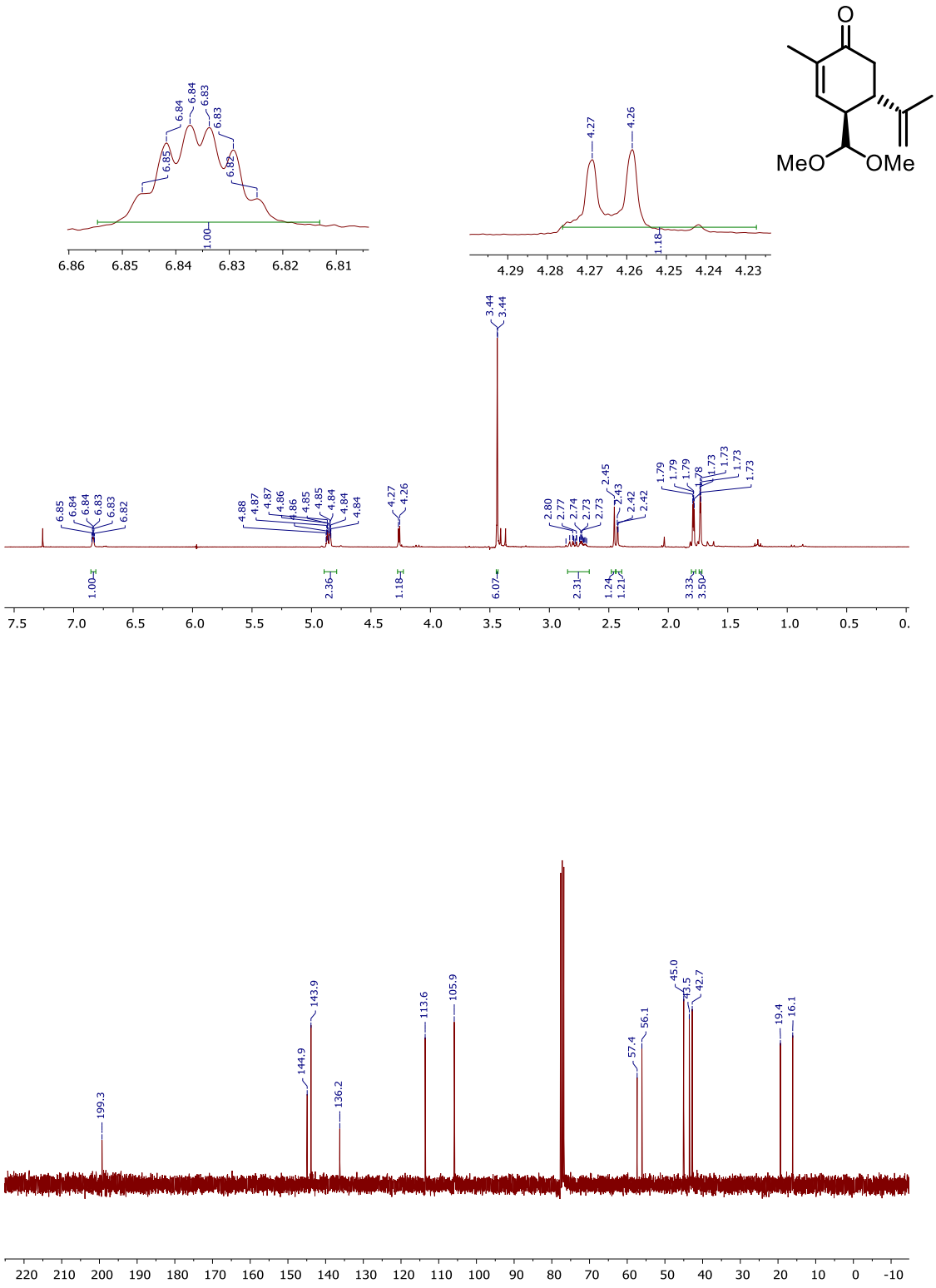


^{1}H (600 MHz) and ^{13}C NMR (151 MHz) spectra of **3-7b** in $CDCl_3$

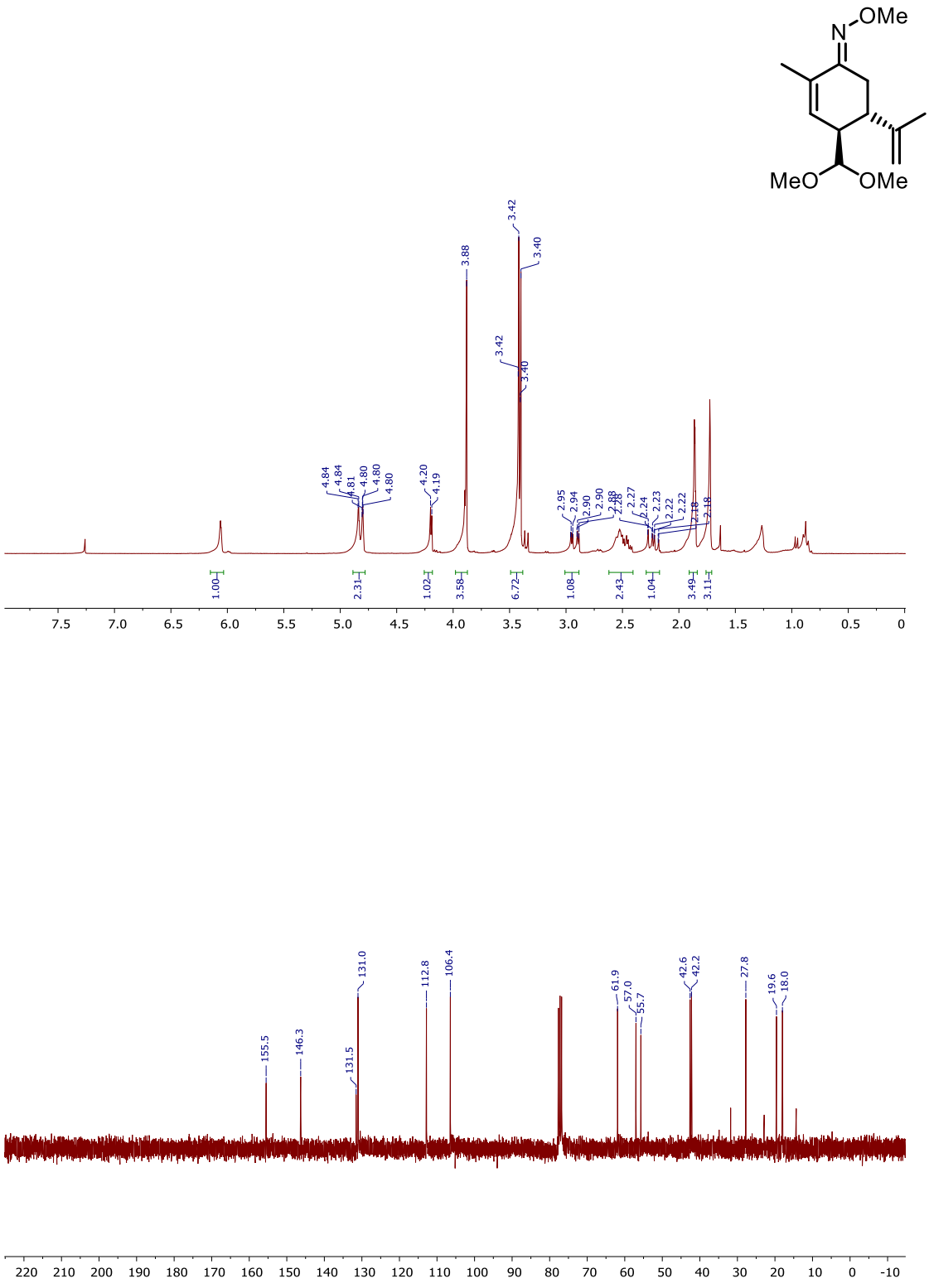




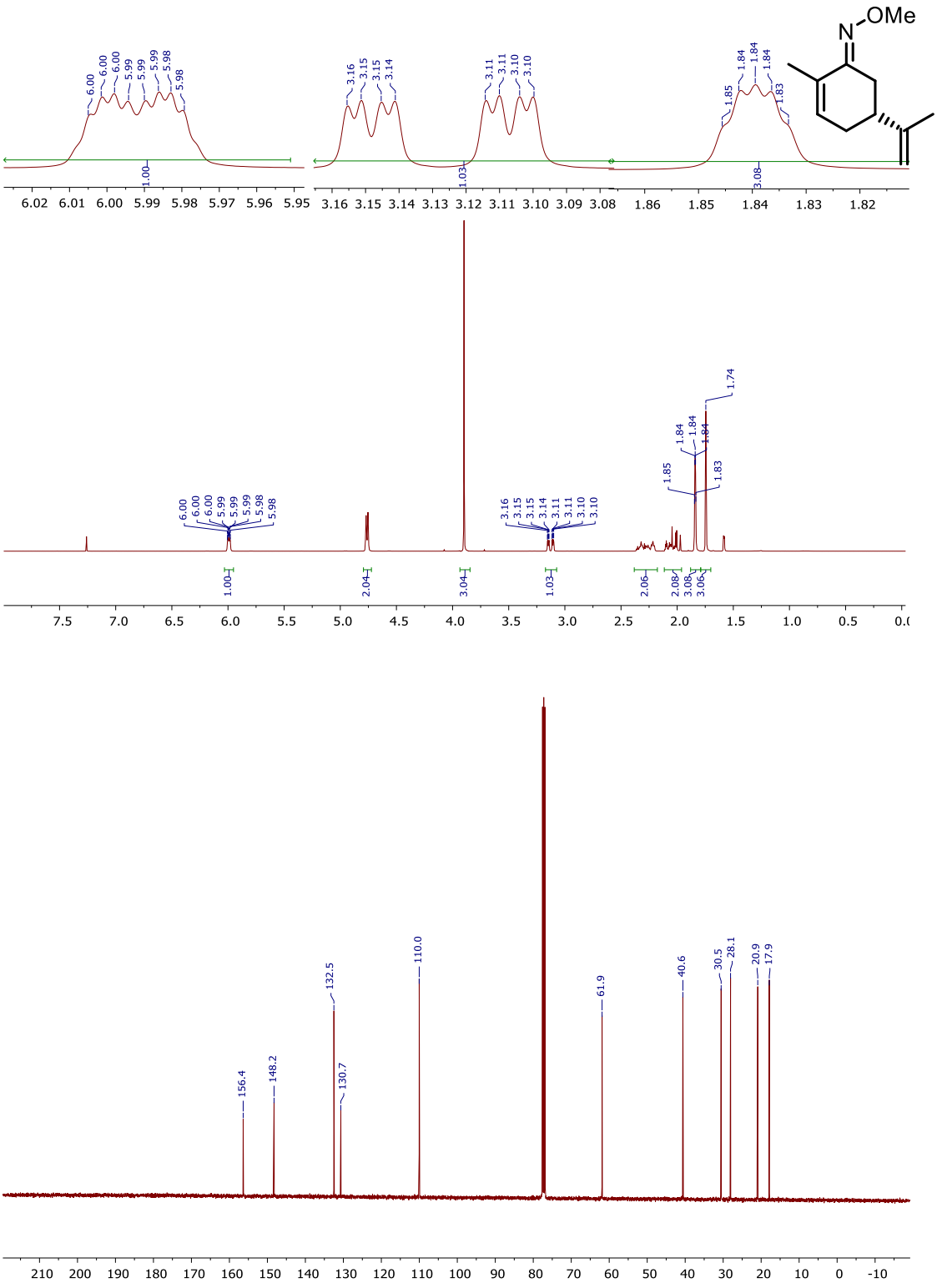
^{1}H (600 MHz) and ^{13}C NMR (151 MHz) spectra of **3-7d** in $CDCl_3$



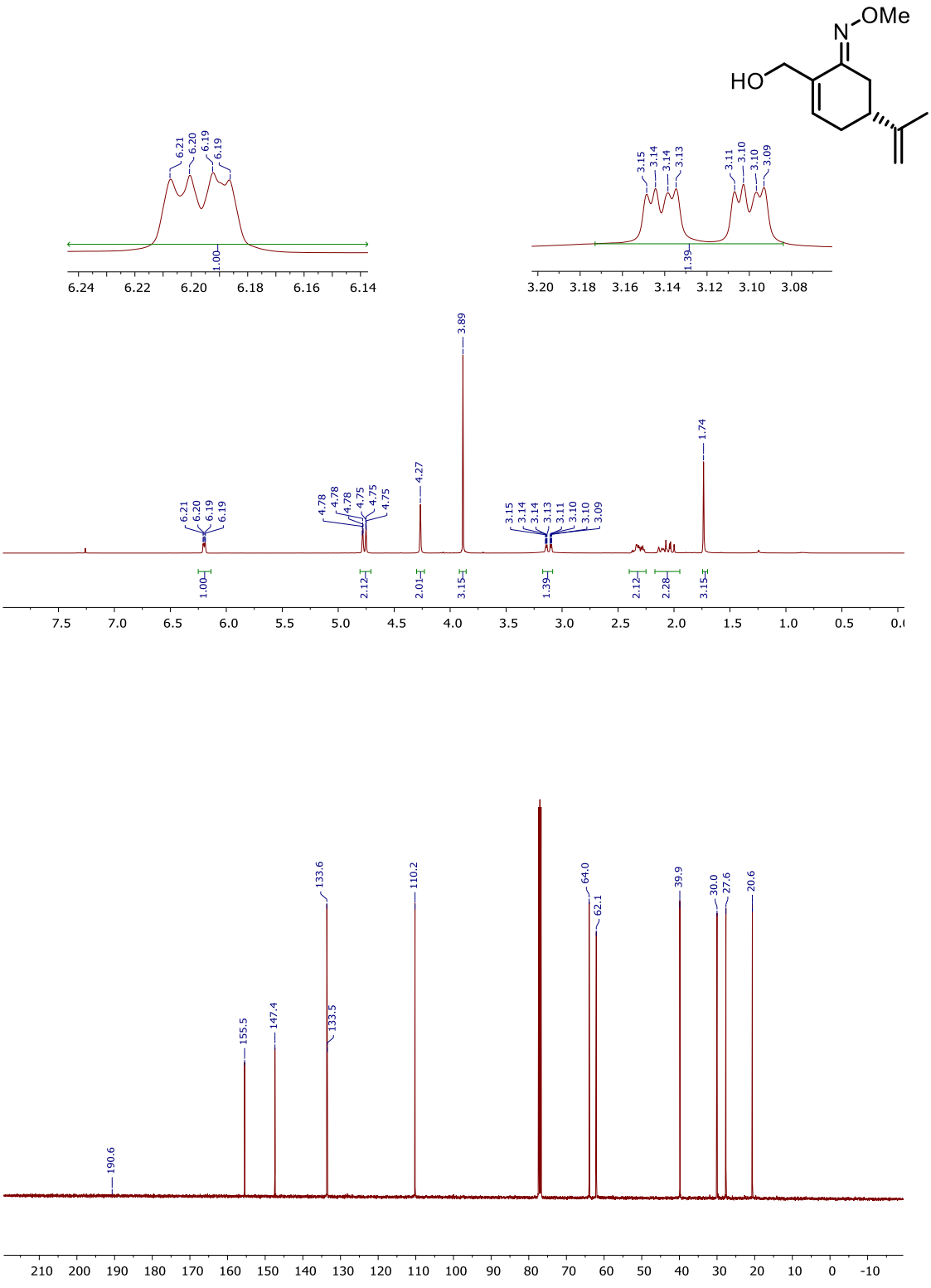
^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of **4-10** in $CDCl_3$



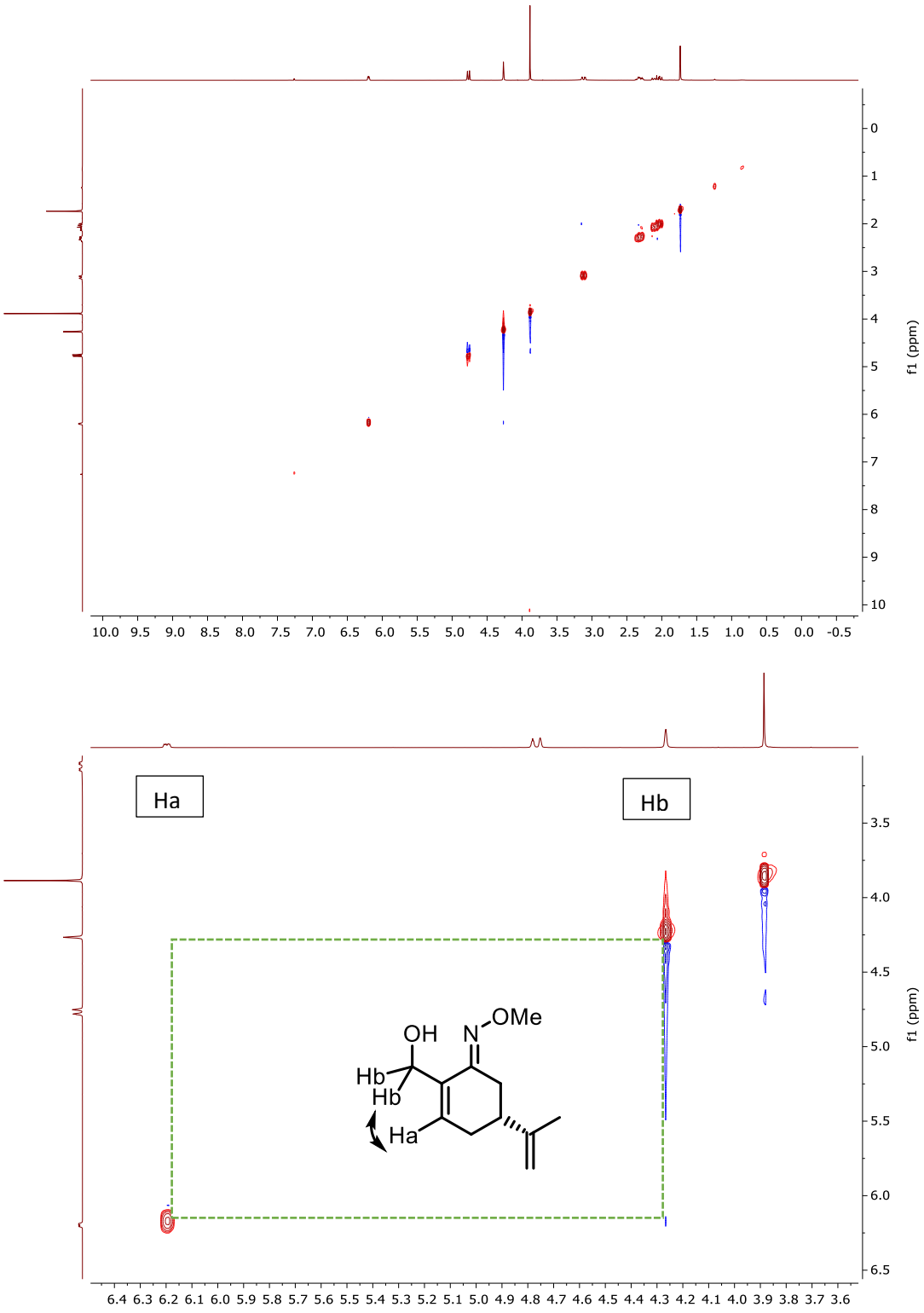
^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of **4-11** in $CDCl_3$



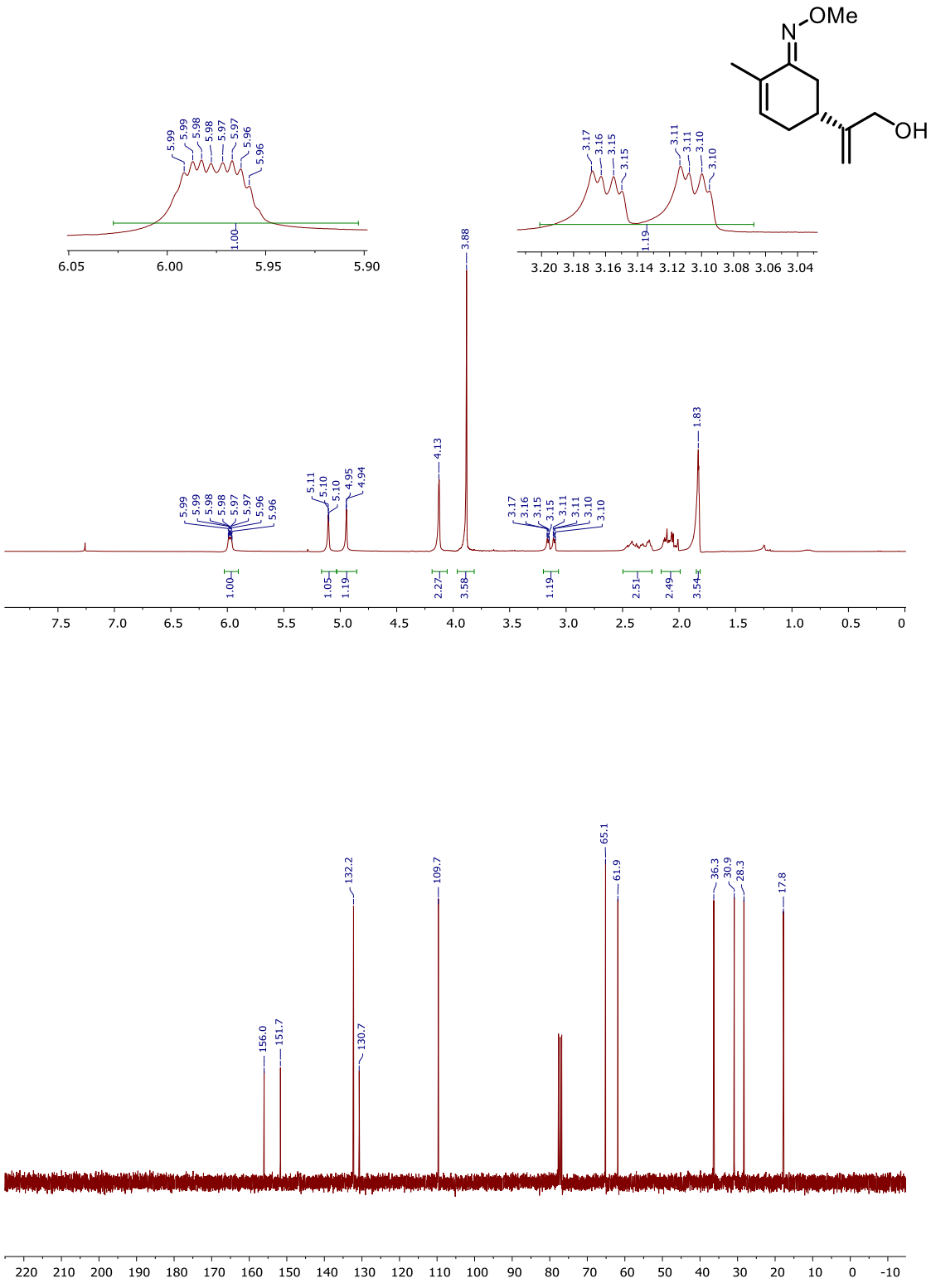
^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of **4-13** in $CDCl_3$



^{1}H (400 MHz) and ^{13}C NMR (101 MHz) spectra of **4-16** in $CDCl_3$



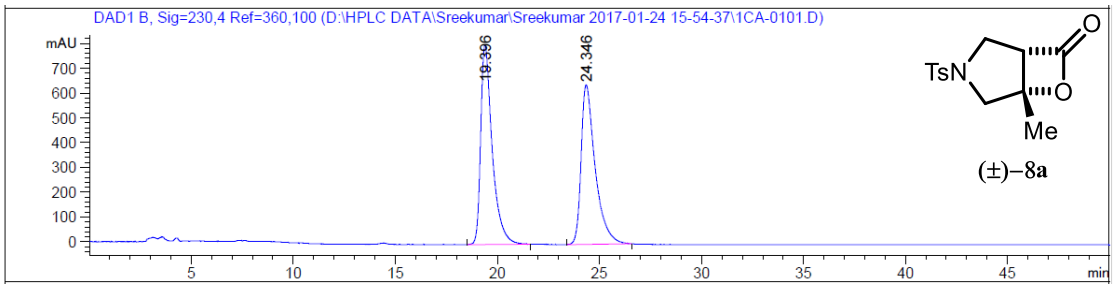
NOESY (400 MHz) spectra of **4-16** in $CDCl_3$



^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of **4-22** in $CDCl_3$

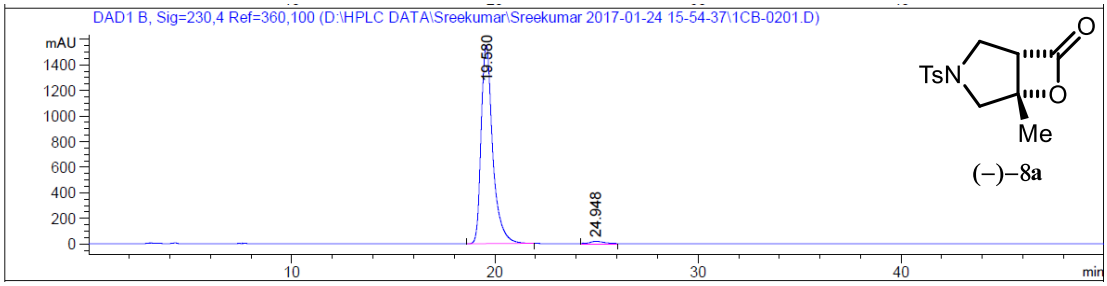
APPENDIX B

Chiral HPLC Chromatogram Profiles



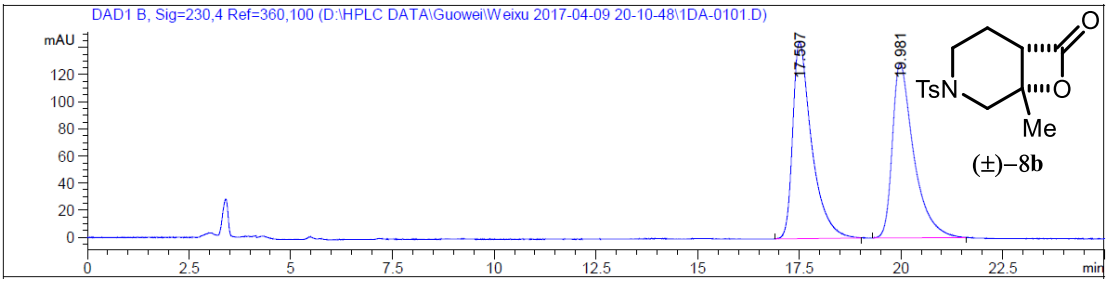
Signal 2: DAD1 B, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.396	BV R	0.4660	3.15721e4	805.17731	50.5042
2	24.346	VV R	0.5642	3.09418e4	643.76221	49.4958



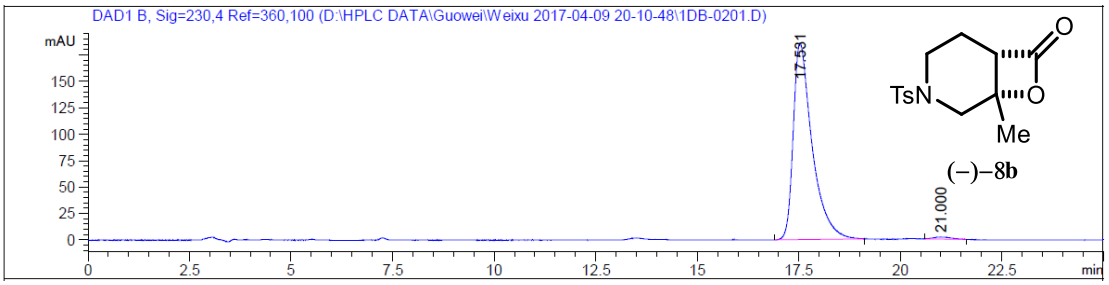
Signal 2: DAD1 B, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.580	VV R	0.4636	6.14282e4	1554.35254	98.7057
2	24.948	BV R	0.5257	805.50110	17.97745	1.2943



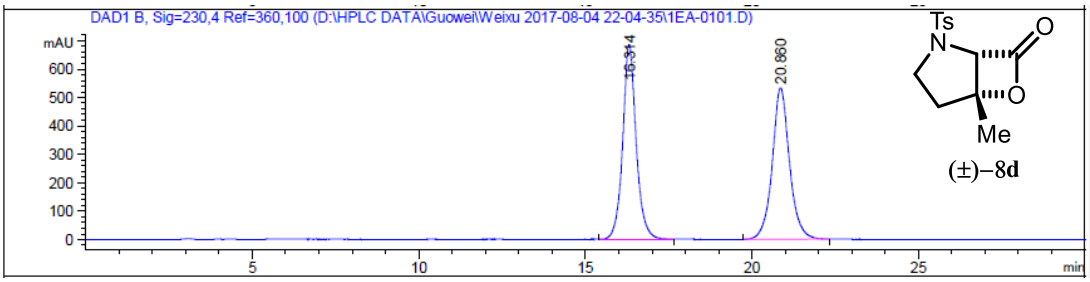
Signal 2: DAD1 B, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.507	BB	0.3854	4696.22119	144.97682	50.0448
2	19.981	BB	0.4279	4687.81787	128.85840	49.9552



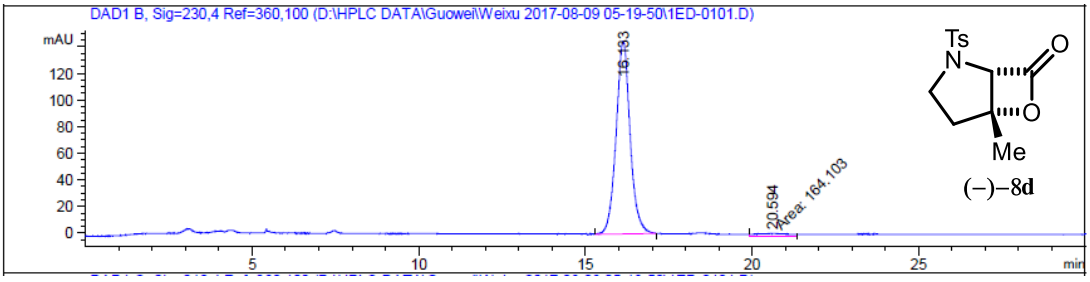
Signal 2: DAD1 B, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.531	BB	0.3829	6005.06641	185.87325	98.9798
2	21.000	BB	0.3610	61.89321	2.01392	1.0202



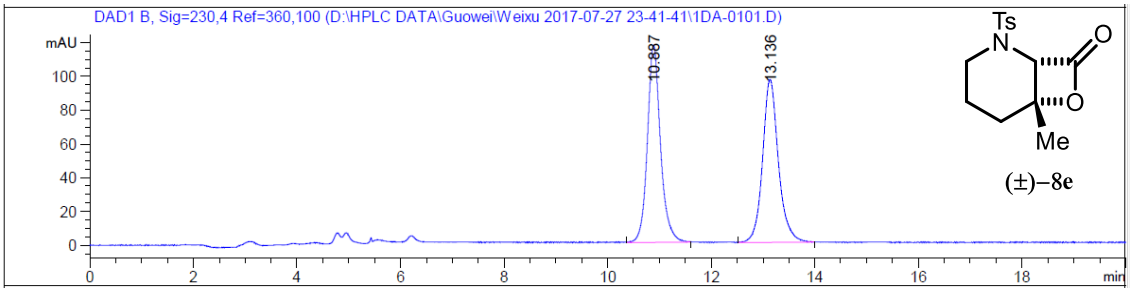
Signal 2: DAD1 B, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.314	BB	0.3372	1.92232e4	685.36444	49.9955
2	20.860	BB	0.4317	1.92267e4	533.17352	50.0045



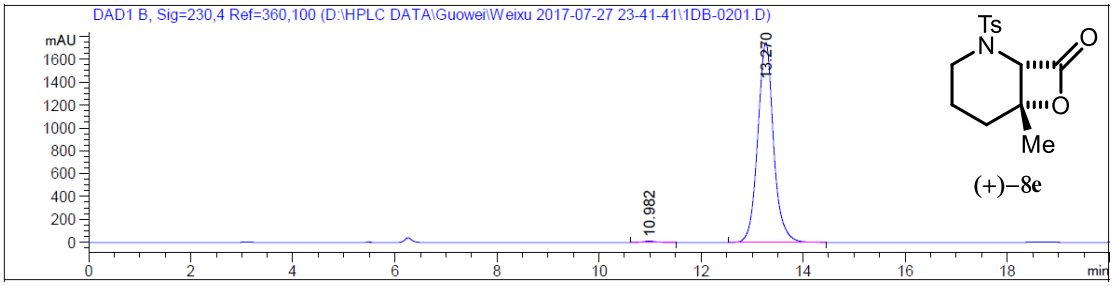
Signal 2: DAD1 B, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.133	BB	0.3441	4225.79102	144.73509	96.2618
2	20.594	MM	1.0249	164.10251	2.31470	3.7382



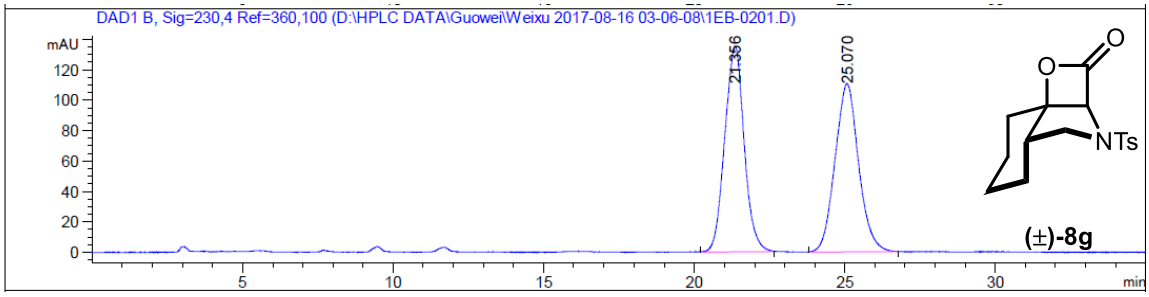
Signal 2: DAD1 B, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.887	BB	0.2337	2043.53784	116.75874	50.0112
2	13.136	BB	0.2504	2042.62366	96.33089	49.9888



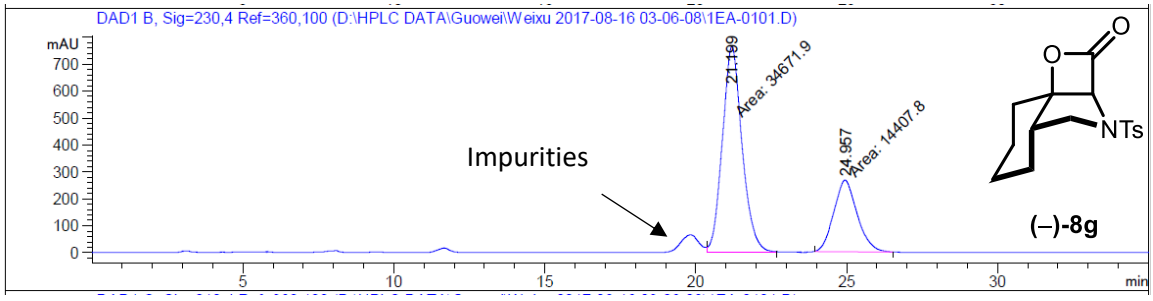
Signal 2: DAD1 B, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.982	BB	0.2042	220.05707	12.63368	0.5833
2	13.270	BB	0.2524	3.75037e4	1744.05200	99.4167



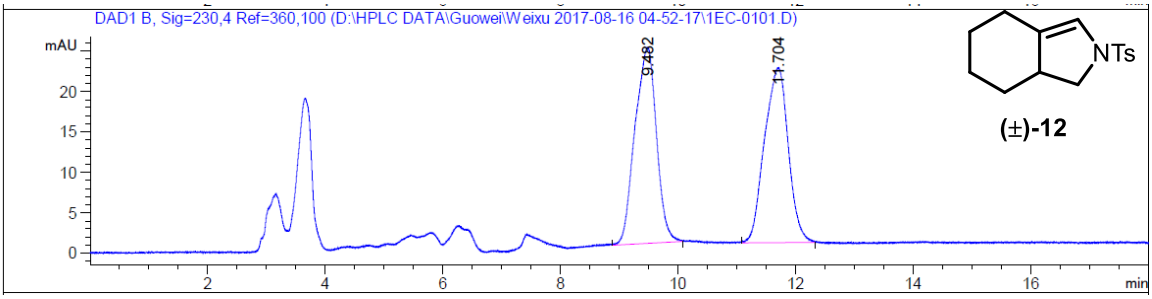
Signal 2: DAD1 B, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.356	BB	0.5232	6043.58691	135.14786	50.0863
2	25.070	BB	0.6360	6022.75537	110.64627	49.9137



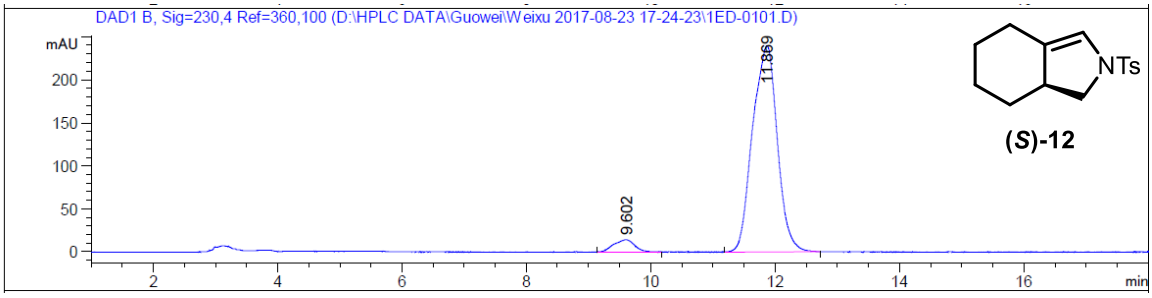
Signal 2: DAD1 B, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.199	MM	0.7543	3.46719e4	766.09528	70.6441
2	24.957	MM	0.8998	1.44078e4	266.86011	29.3559



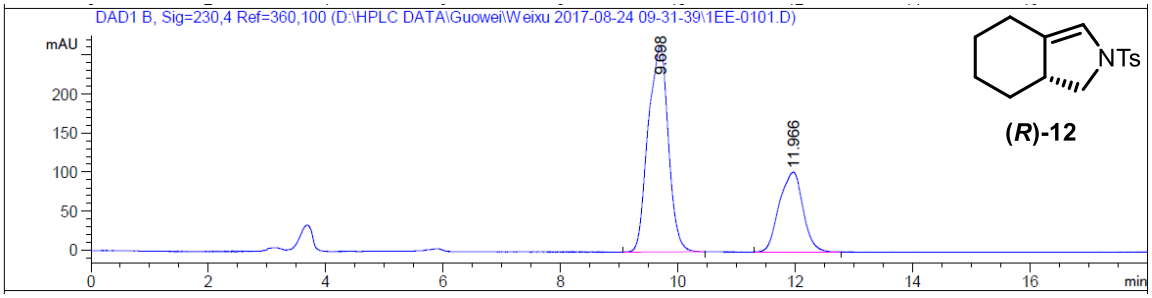
Signal 2: DAD1 B, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.482	BB	0.3015	617.19904	24.24791	50.3318
2	11.704	BB	0.3335	609.06274	21.66204	49.6682



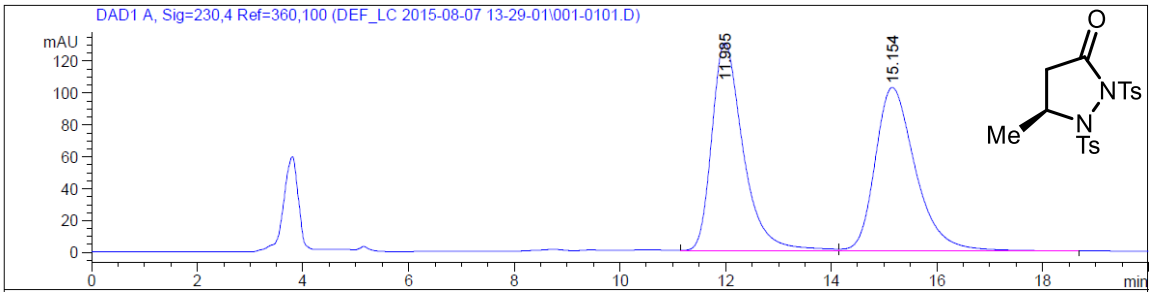
Signal 2: DAD1 B, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.602	BB	0.2763	336.69891	14.31820	4.8477
2	11.869	BB	0.3258	6608.82080	239.60852	95.1523



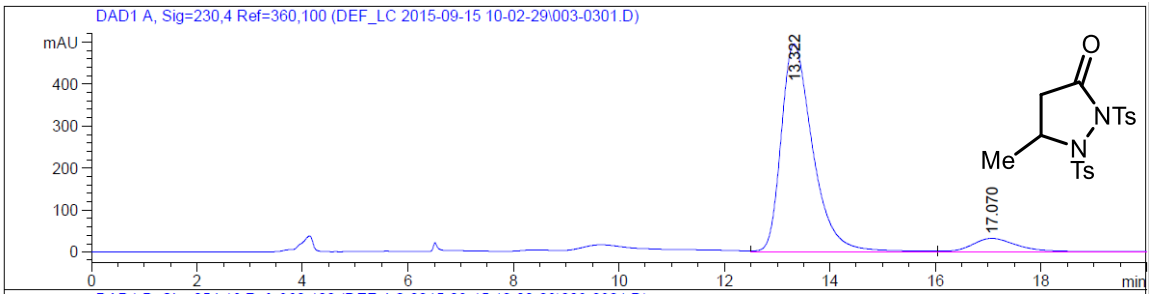
Signal 2: DAD1 B, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.698	BB	0.3165	6298.01563	264.25870	68.6735
2	11.966	BB	0.3300	2872.93726	102.34364	31.3265



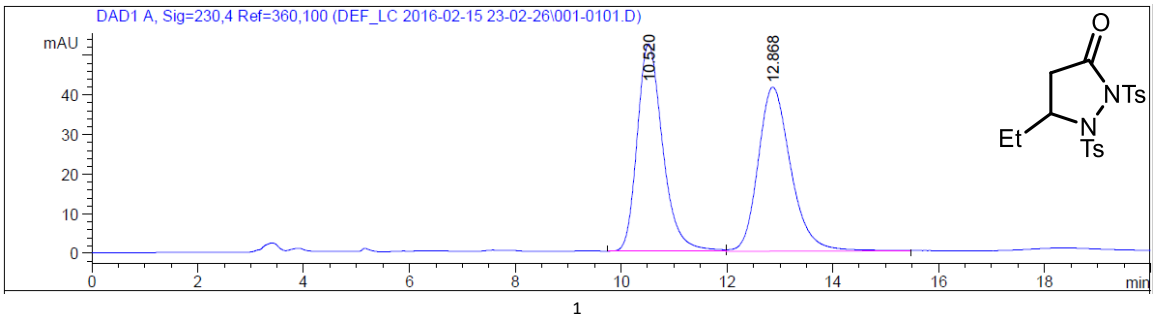
Signal 1: DAD1 A, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.985	VV	0.6300	5442.26709	130.63097	49.8223
2	15.154	VB	0.8147	5481.09912	102.69523	50.1777



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

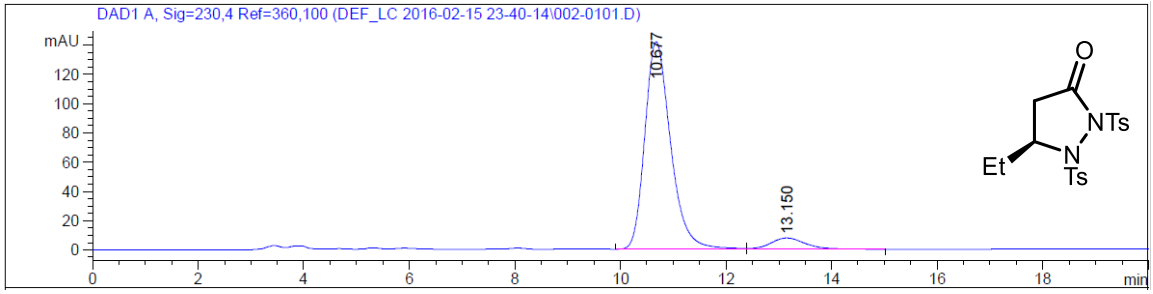
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.322	VV	0.6368	2.05798e4	495.29431	91.4535
2	17.070	VB	0.9124	1923.22559	31.85438	8.5465



1

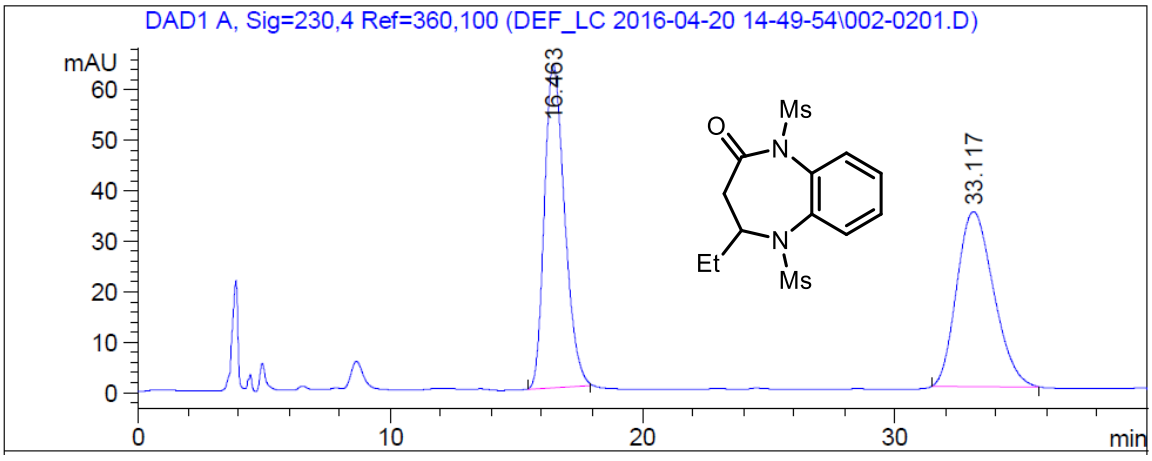
Signal 1: DAD1 A, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.520	VV	0.5112	1754.00159	52.30801	49.7036
2	12.868	VB	0.6602	1774.91895	41.39998	50.2964



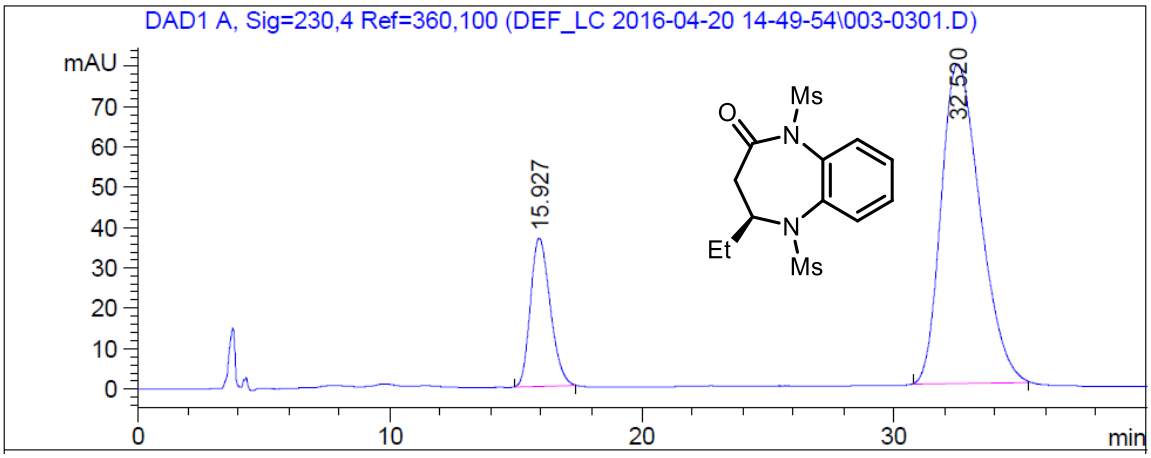
Signal 1: DAD1 A, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.677	VV	0.5258	4841.30469	141.97940	92.8407
2	13.150	VB	0.7256	373.33295	7.81172	7.1593



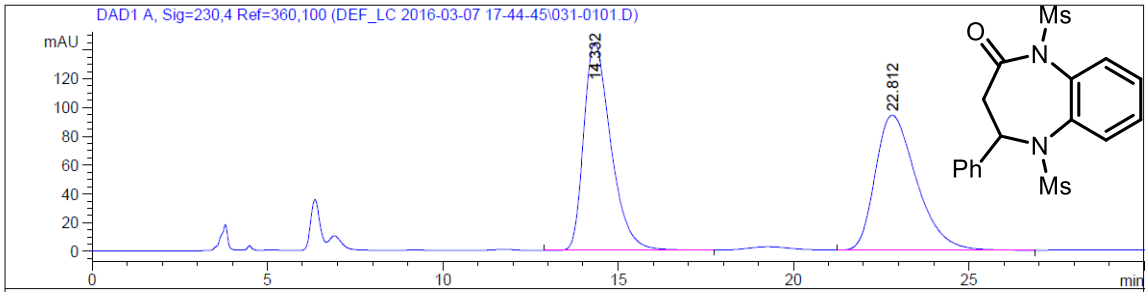
Signal 1: DAD1 A, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.463	BB	0.8498	3560.07666	64.11260	50.2882
2	33.117	BB	1.4931	3519.27197	34.64594	49.7118



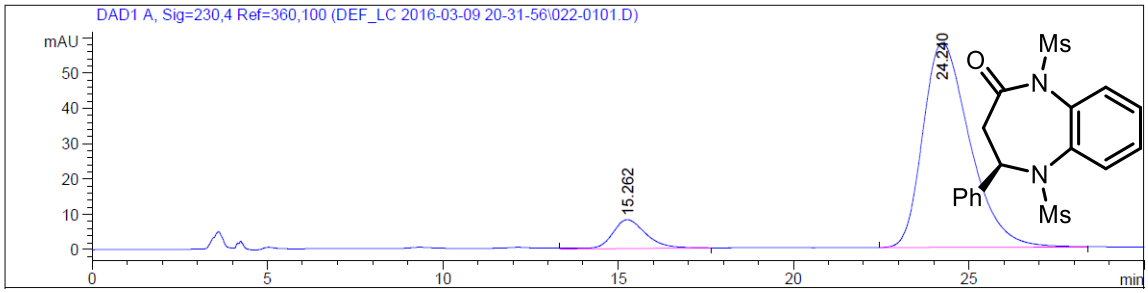
Signal 1: DAD1 A, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.927	BB	0.8336	2016.92957	36.90346	19.1656
2	32.520	BB	1.5919	8506.76074	79.27722	80.8344



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

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.332	VB	0.8238	7770.63379	144.41199	50.1738
2	22.812	VB	1.2610	7709.81738	93.99197	49.7811



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

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.262	VB	1.0302	546.80536	8.15619	9.2224
2	24.240	BB	1.4277	5382.26660	57.94378	90.7776

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