β-LACTONES AS KEY BUILDING BLOCKS: SYNTHETIC APPLICATIONS TO DIVERSE NATURAL PRODUCTS

A Dissertation

by

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ABSTRACT

A history and detailed account of the applications of β-lactones towards natural products and bioactive compounds in the last ten years is discussed as these small heterocycles are becoming more widely recognized for their reactivity, numerous methods of construct, and high degree of functionalization.

An improvement to the nucleophile catalyzed aldol-β-lactonization of keto-acids is reported employing commodity reagents delivering gram quantities of bicyclic β-lactone.

The first total synthesis of caulolactone A is reported employing a highly diastereoselective biscyclization to a key carvone–derived β-lactone. The natural product was completed from chiral pool (*R*)-carvone in 10 total steps.

Towards rapidly generating complex cyclopentanes an organocatalyzed tandem Michael aldol-lactonization process is reported. Subsequently revealing conditions for an enantioselective variant generating two C-C bonds, one C-O bond, two rings, and up to three contiguous stereocenters from simple starting materials.

From the end is where we begin….

ACKNOWLEDGEMENTS

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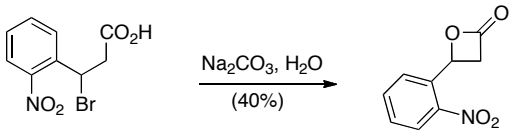
CHAPTER I

INTRODUCTION: β-LACTONES IN NATURAL PRODUCT SYNTHESIS

1.1. Introduction

1.1.1. Brief History of β-Lactones

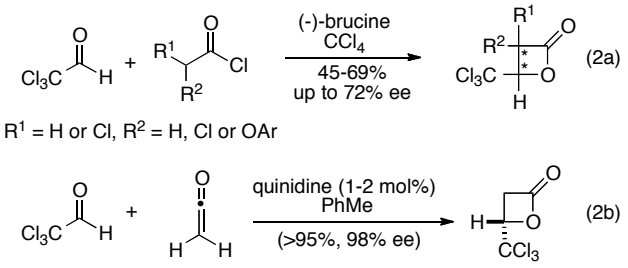
Since the account of the 1st isolated β-lactone by Einhorn in 1883[1] (Eq. 1) these small-oxygenated heterocycles largely remain underutilized intermediates in the synthesis of natural products and bioactive compounds. In the last 20 years, the field of synthetic organic chemistry has seen an exponential growth in the development of methodology for synthesizing β-lactones and their application as advantageous intermediates in natural product synthesis. They are being increasingly targeted due



(1)

to their presence in natural products, potential as enzyme inhibitors, and versatility as synthetic intermediates. It was almost 85 years after Einhorn's reported isolation that Borrman and Wegler disclosed the first enantioenriched β-lactone synthesis from the reaction of an acid chloride with chloral in the presence of (-)-brucine (Eq. 2a).[2] Wynberg continued this work and reported the first catalytic, asymmetric synthesis of β-lactones using 1-2 mol% of the cinchona alkaloid quinidine (Eq. 2b).[3] This discovery opened the door for the propagation of the use and exploration of β-lactones in synthesis. While Wynberg's work has also had a profound impact on modern organocatalysis, it

serves as the foundation for enantioselective β-lactone synthesis.



The present review will focus on the use of β-lactones as intermediates in total synthesis and the synthesis of β-lactone containing natural products. Providing detailed information for evaluating the broad synthetic utility of this motif as well as the reaction tolerance of β-lactones. Emphasis will be placed on highlighting the robust nature of β-lactones in the realm of natural product synthesis. Focus will be on the application to natural products and bioactive compounds since 2003. Examples prior to 2003 can be seen in the 2004 Heterocycles review by Romo *et al.*[4] This review is not meant to convey every use of β-lactones in synthesis since 2003 alternatively it serves to depict the applications in recent years and serve as admission to the literature for those interested.

1.1.2. Four-Membered Oxygenated Heterocycles

β-Lactones, as they are more commonly referred to, are 3 carbon 2 oxygen containing cyclic esters. Formally referred to as oxetan-2-ones, or 2-oxetanones, with the simplest of them being β-propiolactone (Figure 1). As a functional group, β-lactones have often been thought of as unstable, highly reactive, and difficult to handle stemming from their potential votality[5] and tendency towards decarboxylation.[6] They are a

functional derivative of oxetane, the core of the 4-membered oxygenated heterocyclic family (Figure 1). In 1995, it was reported that "the importance of four-membered heterocycles for organic synthesis is limited."[7] While the 'importance' has been explored in the realm of medicinal chemistry being highlighted by Carreira. Oxetane and 3-oxetanone have been referred to as *neglected synthetic intermediates* for synthesis and drug discovery with several citations of the prevalence of these small heterocycles on the rise.[8,9]

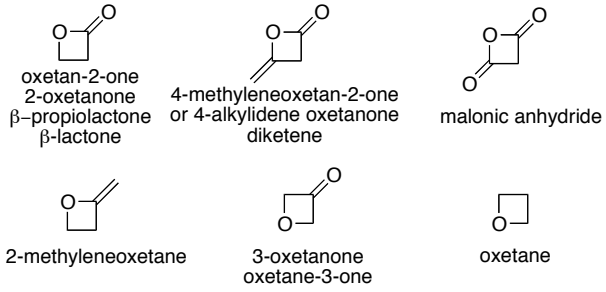
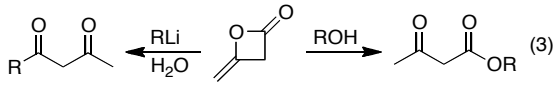


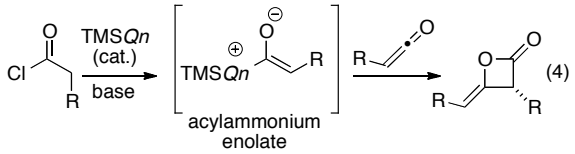
Figure 1. Four-Membered Oxygenated Heterocycles

Another functional derivative of oxetane, 4-alkylidene oxetanone, or commonly called diketene, has found widespread synthetic and industrial use as a highly reactive acylating agent,[7,10] being extensively utilized for generating 1,3-diketones[11] or β-ketoesters (Eq. 3).[12] Calter's homo ketene dimerization was the first report of a catalytic, asymmetric



route to this oxetane functional derivative. Drawing from Wynberg's work of using cinchona alkaloids to generate an optically active ammonium enolate, variously

substituted ketene dimers can be readily accessed with high levels of enantioinduction (Eq. 4).[13]

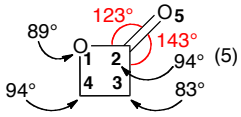


Malonic anhydride, the most obscure of this class of heterocycles has been synthesized by ozonolysis of diketene, however upon warming quickly decomposes to carbon dioxide and ethenone.[14] Other structures that have garnered interest in the class include 2-methyleneoxetane which can be accessed by methylenation of the corresponding β-lactone.[15] Howell and co-workers have extensively studied further functionalization[16] and applications of 2-methyleneoxetanes in the synthesis of bioactive compounds with examples shown herein.[17]

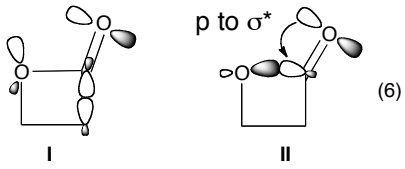
1.1.3. Structure and Physical Organic Properties

Often referred to as the smallest lactone rings that are synthetically viable,[18] the structural and spectroscopic properties of β-lactones have been extensively reviewed by Searles.[19] Mulzer[20] established vicinal coupling constants from ^{1}H NMR for differentiating *cis* and *trans* β-lactones[21] (J = 4-4.5 and 6.5 Hz respectively) and ^{17}O NMR has been used to distinguish the two oxygen atoms.[22] Numerous computational and experimental studies have been conducted on β-lactones including β-propiolactone, herein only applicable data will be addressed.[23,24] The most diagnostic feature that has aided in the characterization of β-lactones is the intense IR absorption at ν = 1840-1810 cm^{-1}, attributed to the carbonyl stretching.[25] Both bond lengths[26] and angles[23a,24c,27] have

been experimentally and computationally[28] determined for β-propiolactone (Eq. 5)



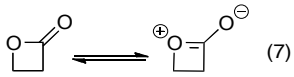
which attest to the angle strain. The deviation from standard bond angles reveal the sp^2-hydridized C_2 atom has an endocyclic bond angle of 94°, determined by electron diffraction,[24c] diverging from the more typical 120° at sp^2 centers. It should be noted when assessing the *exocyclic* bond angles ($O_1C_2O_5$ and $C_3C_2O_5$) they are enhanced to compensate for the $O_1C_2O_3$ angle of 94°. Interestingly, there is a difference of ~20° between the $O_1C_2O_5$ and $C_3C_2O_5$ angles indicating the carbonyl group is tilted towards the ether-like oxygen in the ring. The deformed bond angle investigated by Bürgi, was determined to be in agreement with an anomeric effect through analysis of the relevant molecular orbitals (MO).[23a] Given that the p-type lone pair of the carbonyl oxygen governs the highest occupied molecular orbital (HOMO), and the C-C bonding orbital is higher in energy than the C-O bonding orbital the tilt minimizes the interaction of the HOMO with the C-C bonding orbital, a destabilizing interaction (**I**, Eq. 6).



Deformation in bond angle too enhances the stabilizing interaction of the HOMO by maximizing the overlap with the empty antibonding σ*(C-O) orbital (**II**, Eq. 6).[23a,29] In small rings, such is the case of β-lactones, the σ(C-C) bonding orbital is higher in energy

than the σ*(C-O) and in accordance with 'Walsh Rules' this geometry leads to the greatest stabilization of the HOMO.[30] The negative hyperconjugation[23a,31] stemming from the tilted carbonyl serves as a two electron stabilizing interaction. Though most prominent in β-lactones it is observed to lesser degree in γ-lactones.[29,31]

As opposed to the oxetane ring which can adopt a puckered conformation to eliminate Pitzer strain from eclipsing interactions of the C-H bonds,[7] β-lactones assume a strictly planar conformation which has been corroborated by X-ray and MM2 calculations of several structures.[23a,25] The ester type resonance stabilization is cited as the primary attribute resulting in planarity according to Allinger (Eq. 7).[24a] To adopt a puckered conformation, would cause the ester linkage to twist out of plane, a barrier of 10 kcal/mol. The presumed resonance coupled with the stabilizing interactions attribute to the planar conformation.[24a]


(7)

Analysis of the reported 102 solved β-lactone crystal structures from the Cambridge Structural Database (CSD, update May 2013, 658,047 structures) reveals the average $O_1C_2O_5$ angle to be 126.12°±1.61°, while monocyclic β-lactones have an angle of 126.52° ± 0.75° in accordance with that of β-propiolactone (Table 1). In light of this the $C_3C_2O_5$ has a bond angle of 138.89°± 1.58 and 138.27°± 0.81° for all β-lactone structures and monocyclic ones respectively confirming the significant angle deformation.

Table 1. Average bond and dihedral angles of β-lactones from CSD.

Angle	Mean	Min.	Max
A-$O_1C_2O_5$	126.12°± 1.61°	116.18°	129.83°
B-$O_1C_2O_5$	126.52°± 0.87°	124.51°	128.56°
A-$C_3C_2O_5$	138.89°± 1.58°	134.97°	148.51°
B-$C_3C_2O_5$	138.27°± 0.81°	136.79°	140.41°
ϕ A*	3.15°± 2.38°	0.06°	9.29°
ϕ B*	2.90°± 4.87°	0.22°	9.12°

A refers to values from all reported -lactone X-rays from CSD, B refers monocyclic -lactones from CSD. *Values were obtained from averaging all four dihedral angles in the lactone ring. [32] Scrutiny of the structures shows an average absolute dihedral angle (ϕ) of 3.15°± 2.38°, statistically 0° from further analysis of the CSD.[32]

The dihedral angle of 0.22°, determined by X-ray of monocyclic tri-aryl β-lactone (**I**, Figure 2) places the O_1, C_2, C_3, C_4, and O_5, atoms in the same place. However, the β-lactone fused γ-lactam (**II**, Figure 2) deviates from planarity by 9.29° stemming from stereoelectronic effects for structural stabilization. Despite the fact that β-lactones are cyclic esters they behave quite differently than larger cyclic and acyclic esters, in that they are significantly more reactive,[33] attributing to the *cis*-conformation of the ester.

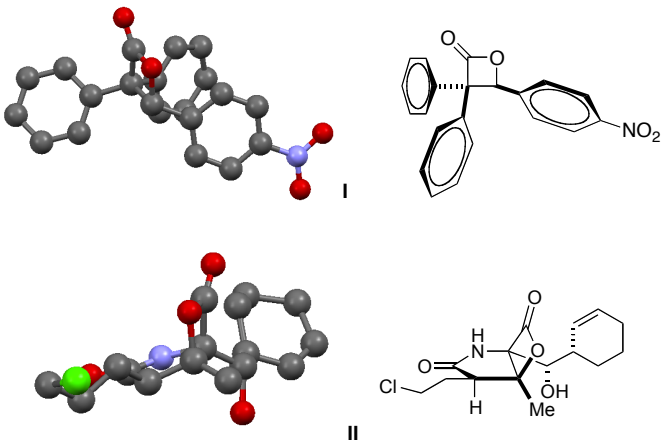
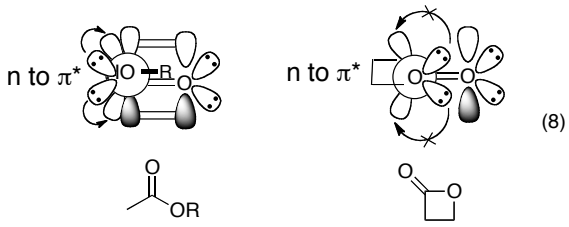


Figure 2. Crystal structures of mono- and bicyclic β-lactones.

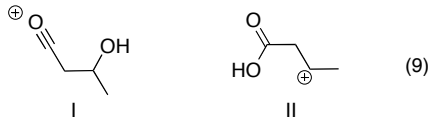
The compulsory restriction of bond angles inhibits the stabilizing interaction of the n to π* (Eq. 8) that is present in the *S-trans*-conformation of the corresponding ester. The overall ring stain of 22.8 kcal/mol[34] is a testament to the inherent reactivity of β-lactones, reminiscent of epoxides (27.2 kcal/mol)[35] in that they elicit more electrophillic character than corresponding acyclic esters or larger lactones.[36]



(8)

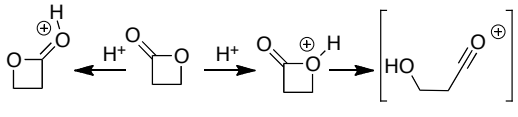
Prompted by the work that protonated β-lactones in solution lead to alkyl bond scission[37] LeBlanc and cowokers preformed *ab initio* molecular orbital calculations disclosing protonation in the gas phase delivers two stable structures (Eq. 9).[29] Unlike higher lactones (i.e. γ-,δ-lactones, etc.), β-lactones are known to undergo acyl (**I**) or alkyl

bond cleavage (**II**).[25,38] That these two carbocations are relatively similar in energy, attests to the fact that the mode of bond fission cannot be predicted solely on the reactive intermediate as is true with higher lactones.



(9)

Abbound and coworkers, elaborated *ab initio* calculations, posing protonation at the ether-like oxygen preferentially cleaved the C-O_{acyl} bond, a peculiarity exclusively observed in β-lactones (Eq. 10). [39] Stabilized by the C=O and C-O_{alkyl} bonds shortening, the acylium ion was documented as the preferred intermediate for acyl bond cleavage under mildly acidic conditions.[39] Whereas protonation of γ-butyrolactone revealed stable cyclic oxonium ion, devoid of cleavage in the absence of a nucleophile (Eq. 11).[39] Protonation at the carbonyl oxygen of both lactones produces stable *cis* intermediates, stabilized by the ether-like oxygen (*vida supra*).[29] Striking is that protonation at the carbonyl oxygen of β-butyrolactone consequently leads to C-O_{alkyl} bond fission observed by NMR studies, indicative of intermediate **II** (Eq. 9).[37]



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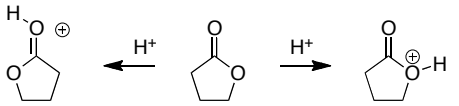
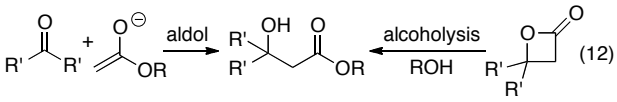


(11)

1.1.4. Reactivity

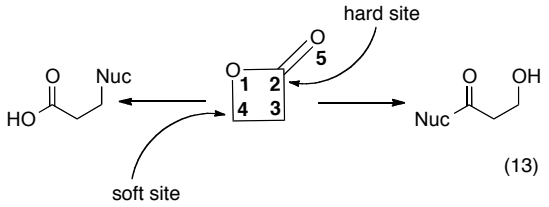
The paucity of crossed aldol reactions employing asymmetric catalysis devoid of pre-enolization[40] or functionalization has elicited considerable interest for methodology

development in recent years.[41] While elegant examples have been reported, the scarcity sparked interest in viewing β-lactones as 'activated aldol products',[42] permitting an alternative approach to classical examples of asymmetric cross aldol reactions (Eq. 12).[13a,43] Alcoholysis of a β-lactone reveals a β-hydroxy ester, the equivalent of an ester enolate cross aldol reaction (Eq. 12). This motif has been realized as an appropriate aldol surrogate.



(12)

Another testament to the strain present in β-lactones is the bifunctional electrophillic character that permits C-O_{alkyl} or C-O_{acyl} bond fission, with the former only being exhibited by β-lactones.[37,44] Two different pathways, whose selectivity has been explained thus far through Hard Soft Acid Base (HSAB) theory,[45] operate to open the β-lactone ring.[45a,46] The two sites of reactivity for nucleophiles have been categorized as the 'soft' sp^3 carbon (C_4) and the 'hard' sp^2 carbon (C_2)(Eq. 13).[47,48] Addition to the C_4 atom follows a nucleophilic substitution mechanism (S_N2) with scission of the C_{alkyl}-O bond, and is precedented to proceed with complete inversion of configuration, to a β-substituted carboxylic acid (Eq. 13).[49] Whereas nucleophilic attack at the C_2 carbon

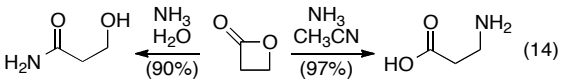


(13)

follows an addition/elimination pathway to β-hydroxy ketones, esters, or amides with retention of configuration. The Hard Soft Acid Base theory (HSAB)[45a,46] has been

applicable to an extent at predicting the reactive site for various nucleophiles. Hard nucleophiles (alkoxides,[50] alkyllithiums, thiolates, Grignards,[51] etc.) and hydride reducing agents (DIBAlH (diisobutylaluminium hydride), $LiAlH_4$, and BH_3•DMS) predominately result in cleavage of the C-O_{acyl} bond to carbonyls or 1,3-diols respectively. [25,51-52] The C_2 has a higher degree of s-character and the larger HOMO-LUMO (lowest unoccupied molecular orbital) gap is amenable for hard nucleophiles, dictated principally by electrostatic interactions.[53] Soft nucleophiles (halides,[52f] benzethiol,[54] thiourea,[52c] azide,[55] organocuprates,[49a,56] etc.),[36,57] classified as larger and relatively polarizable, react at the C_4 position as can be expected due to achieving better electronic matching with the electrophilic β-carbon.[47b,45b]

The product distribution while sensitive to the nucleophile is often times dictated by the solvent and reaction conditions. Selectivity of alcohols,[58] phenols,[52b] ammonia, 1° and 2° amines,[59] along with nitrates and cyanides,[60] are dominated by solvent and pH as was described in an early series of publications by Gresham et al.[48,50] Polar protic solvents have tended to favor C_2-O_1 bond cleavage, yielding the amide with ammonia, while aprotic solvents lend themselves to C_4-O_1 cleavage delivering amino acids (Eq. 14).[59] One assumption for this regioselectivity is the stabilization garnered by charge separation in polar aprotic solvents, desirable for S_N2 type reactions.[61] Early rate studies



(14)

to discern nucleophilic preferences by Gresham revealed chloride, bromide, iodide, acetate, thiocyanate, thiosulfate, and hydroxyl groups to exhibit second order kinetics as nucleophiles both strong and weak (hard or soft) have the potential for a S_N2 type reaction.[48,50,62]

In addition to the aforementioned dual modes of reactivity for nucleophilic addition *via* acyl or alkyl bond scission (**a** and **b**, Figure 3), β-lactones have been reported to undergo a plethora of transformations to a wide array of functional groups.[26a] Reactions of β-lactones have been divided into four main categories: 1) ring opening *via* nucleophilic attack 2) Lewis acid catalyzed rearrangements 3) decarboxylation and 4) addition to an electrophile through an enolate intermediate.

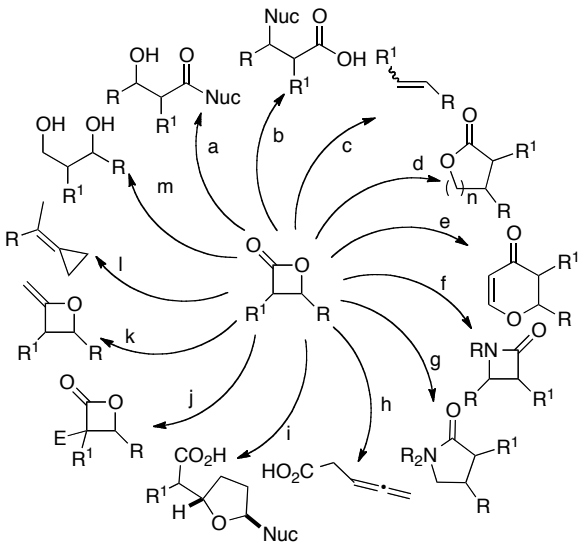


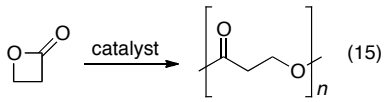
Figure 3. General transformations of the β-lactone motif.

Stereoselective decarboxylation to E or Z olefins (c) is carried out through thermal,

photolytic or radical cleavage mechanisms, while some have been reported to undergo spontaneous decarboxylation. Thermal decarboxylation of β-lactones is unique mechanistically acting as a rare example of a reverse [2+2] cyclization process.[63] β-Lactones are amenable to a variety of rearrangements to generate ring expansion products,[64] dyotropic rearrangements to γ-lactones (**d**, n = 1),[65] intramolecular allysilane addition to δ-lactones (**d**, n = 2),[66] or reaction with hydrazone anions to form 2,3-dihydro-4*H*-pyrones (**e**).[67] Direct conversion to a β-lactam (**f**) can be accomplished by a one-pot Miller-Mitsunobu reaction as Romo showed.[68] While Namy and Machrouhi showed that β-lactones could be coupled with aldimines or Schiff bases via a dual catalyst system to provide facile access to γ-lactams (**g**).[69] The Nelson group has worked at exploiting the usefulness of this motif as building blocks for creating enantioenriched β-amino acids (**b**),[70] allenes (**h**),[71] and β-β-disubstituted carboxylic acids.[36] As a gateway to another class of heterocycles Romo *et al* showed facile conversion to tetrahydrofurans (**i**) employing a Mead reductive cyclization.[72] Electrophilic addition through enolate formation has been recognized to further substitute the β-lactone core, subsequently the enolate proceeds to react with aldehydes in a highly diastereoselective aldol reaction (**j**).[73] Howell pioneered conversion of the carbonyl to a methylene moiety (**k**),[16,17] while Danheiser exhibited thermal decomposition of spirocyclic cyclopropane-β-lactones to generate alkylidenecyclopropanes (**l**).[74] While reduction with $LiAlH_4$ has been extensively reported to give rise to stereodefined 1,3-diols for further manipulations.

Aside from the aforementioned synthetic transformations these small heterocycles have found use in industrial settings for polymer synthesis and chain

polymerization reactions.[75] The polymerization of β-propiolactone forming polyester acids[76] applied in plastics and clothing (Eq. 15).[77]



(15)

β-propiolactone was previously responsible for more than 85% of the production of manufactured acrylic acid and esters in the United States.[78]

1.1.5 Biological Relevance

Often coined as 'privileged' structures, β-lactones biological importance should not be understated as many exhibit a high degree of binding specificity, for varied enzyme classes, eliciting various modes of biological activity. β-Propiolactone long functioned as a key toxoiding agent inactivating polio and rabies viruses[79] for the preparation of human and animal vaccines.[78,80] Sterilization of blood plasma, tissue grafts, surgical equipment, enzymes, etc attest to the disinfectant properties of this simple β-lactone,[81] while it has also taken on the role as a sporicide, providing protection from vegetative bacteria and pathogenic fungi.[82] The more functionalized disubstituted *trans*-β-lactones including the belactosins[83] ebelactones,[84] panclicin,[85] and tetrahydrolipstatin,[86] have often been considered pivotal structural motifs functioning as pancreatic lipase inhibitors (Figure 4).[87] By means of irreversible acylation by the serine protease[88] the aforementioned natural products permit the absorption of fat. A

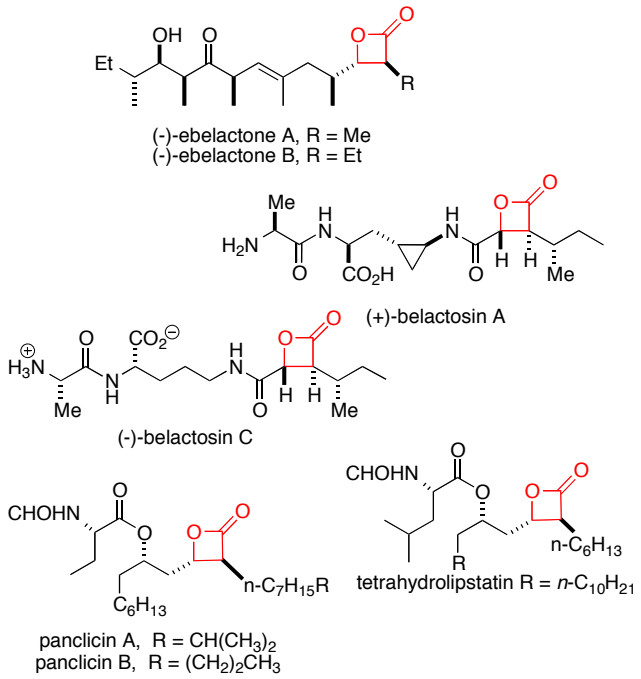


Figure 4. Trans-disubstituted β-lactone natural products.

simplified schematic, figure 5, illustrates acylation by the hydroxyl or thiol group of cysteine, serine or threonine amino acids in enzyme active sites facilitating selective and irreversible inhibition under mildly acidic media.[89] Covalent reactions with active sites

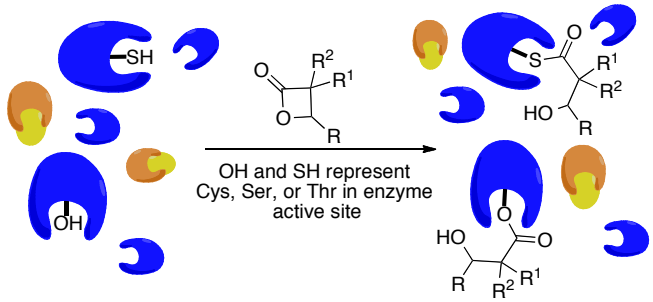
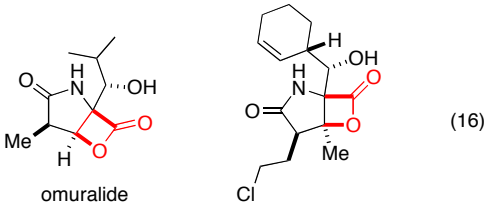


Figure 5. β-Lactones as bioactive acylating agents.

of enzymes, permit β-lactone containing natural products to have promising and varied biological activity.[90] A number of β-lactone containing natural products have been studied as anti-obesity treatments,[87] with tetrahydrolipstatin being the first FDA approved anti-obesity drug (Figure 4). Ebelectone A, has become an attractive antimicrobial agent by way of irreversible acylation of the β-lactone with Ser143 in the active site of homoserine transacetylase (HTA). Modifications of the natural product's scaffold stemming from structure activity relationships (SAR) has permitted the design of new antimicrobial agents which is a never-ending need for due to the evolving antibiotic resistance of pathogens.[91] Similarly, the β-lactone moieties of omuralide and salinosporamide A have shown to be an essential feature in retaining bioactivity for selective inhibition of the 20S proteasome (Eq. 16).[86b,92]



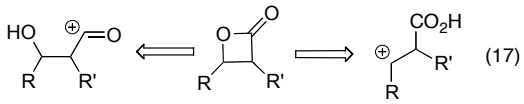
(16)

As a result of their covalent interactions with enzymes, β-lactones have proven to be advantageous for developing activity-based protein profiling (ABPP) for the identification of dedicated target enzymes[93] and developing activity-based probes.[94,95] Sieber recently reported the use of β-lactone containing natural product, vibralactone, as a tool to further study biological activity.[96]

1.1.6. Synthetic Design

The β-lactone motif can be thought of as a synthon for adding two oxygen's and

three carbons rapidly. As mentioned in the reactivity section it is a precursor to all the functional groups in figure 3. Often times β-lactones are employed as a protecting group, for masking oxygen functionality, or to differentiate oxygen substutients.[97] They can be selectively cleaved in the presence of acyclic esters, and chemoselectively reacted with regards to nucleophilic additions or reductions compared to other carbonyls. β-Lactones have found widespread use as synthon for acylation or β-functionalization (Eq. 17).



(17)

They have garnered interest in the realm of total synthesis due to the varied ways in which they can be constructed (Figure 6). Diverse intramolecular and intermolecular methods providing convenient templates to β-lactones have been disclosed, here only reviewing those falling within the bounds of the review. Intramolecular halolactonization of α,β- or β-γ-unsaturated acids (**a**), β-hydroxy acid cyclization (**b**), intramolecular nucleophile-catalyzed aldol-lactonization from keto- or aldehyde-acid substrates (**c**), and NHC (*N*-heterocyclic carbene) promoted aldol-lactonization of α,β-unsaturated aldehydes (**d**) have been well studied and applied to natural product synthesis. Of the intermolecular methods formal [2+2] cycloadditions have been the most prevalent, employing *in situ* generated ketenes from an acyl halide reacting with a ketone or aldehyde (**e**), or reaction of a ketene directly (**f**). The Mukaiyama-aldol-lactonization serves as a robust method for delivering β-lactones from thiopyridal acetals and aldehydes or ketones (**g**) an intermolecular variant of the aldol process for C-C bond construction. Carbonylation of epoxides with CO is distinctive in that it is the only

method used herein that does not require a preexisting carbonyl for β-lactone formation.

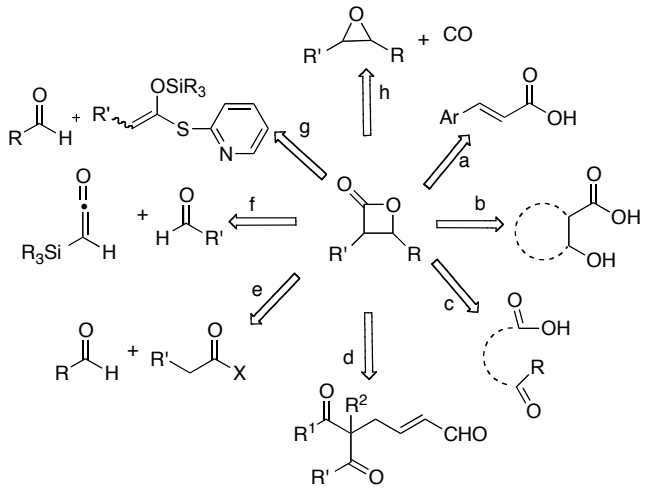


Figure 6. Templates to β-lactones.

A plethora of reviews exist on numerous topics relating to β-lactones, dealing with their general synthesis,[98] specifically from ketenes[98] or ammonium enolates,[99] as well as asymmetric design.[100] Transformations of β-lactones have been documented[4,25] and advancements in functionalization was reviewed by Romo *et al* in 2008.[101] Specialized reviews, as in the applications and stability of spiro-epoxy β-lactones too have been reported.[102] Structural features and reactivity of β-lactones[103] as well as biological aspects including use of activity based probes[94] have been addressed in the literature. The bioactivity of β-lactone containing natural products[104] and the synthesis of natural 2-oxetanones[57] specifically lactacystin/omuralide[105], and salinosporamide[106] and derivates[107] have appeared in the literature. However, the exponential growth in

methodology and applications in recent years as a synthetic intermediate has warranted a review on the role this small heterocyclic has had in the realm of natural product and bioactive compound construction. The following sections of the review will highlight the use of β-lactones in the synthesis of natural products and bioactive compounds, being arranged by the method in which the β-lactone was constructed. Figure 5 stands to highlight the methods for construction of β-lactones that have been applied in the synthesis of natural products and bioactive compounds in the last ten years, thus each method will be the heading of the remaining sections. In each section various applications in addition to the construction methods of the β-lactone will be assessed. While some use β-lactones as synthetic intermediates or protecting groups others are towards accessing a core of a natural product or class or natural products, or in a formal synthesis. Shown highlighted in red of each natural product or bioactive compound are the carbon's and oxygen's stemming from β-lactone chemistry. Each containing varying degrees of β-lactone incorporation in the final target, for some the β-lactone is fully incorporated in the final structure, whereas others maintain the hydroxy or carboxylic acid moiety (or both), or no trace whatsoever.

1.2. β-Hydroxy Acid Cyclization

1.2.1. Introduction and Mechanism

One of the oldest and most precedent methods for the formation of β-lactones has been the cyclization of β-hydroxy acids. Lactonization from β-hydroxy acids is

documented to occur through either carboxylic group activation (CGA) or hydroxy group activation (HGA) (Figure 7).[108]

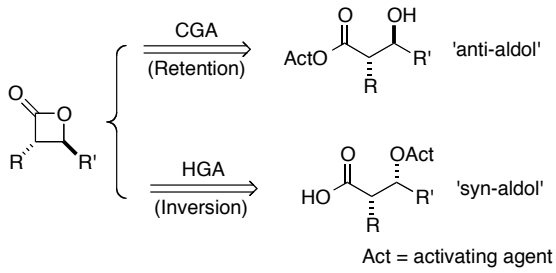


Figure 7. General approaches for β-hydroxy acid cyclization.

The CGA method occurs by way of an intramolecular 4-*exo*-tet cyclization, and the HGA method employs a 4-*exo*-trig cyclization, both favorable according to Baldwin's rules.[109] The mechanism of the complementary modes of activation are shown in figure 8, in subsequent schemes the carbon and oxygen functionality resulting from the β-lactone motif of natural products synthesized by both methods is highlighted in red.

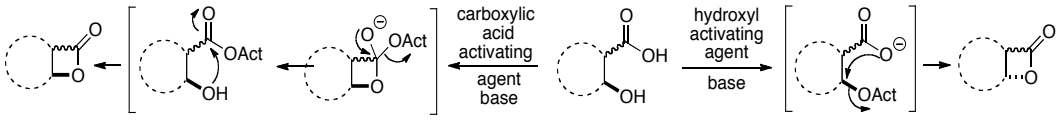


Figure 8. Cyclization of β-hydroxy acids and applications.

1.2.2. Carboxylic Group Activation (CGA)

During carboxylic group activation the β-hydroxy group *syn* to the carboxylic acid moiety attacks the activated acid delivering a *cis*-β-lactone (Figure 8). The relative configuration of the carboxylic acid and hydroxy group dictate the resulting configuration of the β-lactone formed. Conversely if the acid and hydroxy is initially *anti* after cyclization it will yield a *trans*-β-lactone. A surfeit of methods and reagents have been employed for carboxylic acid activation including but not limited to the following: Adams cyclization ($PhSO_2Cl$ and py (pyridine)),[110] Yamaguchi conditions (2,4,6-trichlorobenzoyl chloride and DMAP),[111] Mukaiyama's reagent,[112] Staab's reagent (CDI), PyBOP,[113] BOP, BOPCl, HATU, MNBA,[114] Vederas method,[115,116] DCC, CIP[117] EDC, DEAD, and DIAD (Figure 9). A plethora of other reagents historically used for macrolactonizations or peptide couplings have frequently been employed for carboxylic acid activation. Traditionally preference has been for carboxylic group activation (CGA) methods of lactonization as the resulting ring closure proceeds with retention of configuration. The vast range of conditions for establishing the *syn* stereochemistry required for the β-hydroxy acid has also promoted the CGA method as most favorable for β-lactone formation.

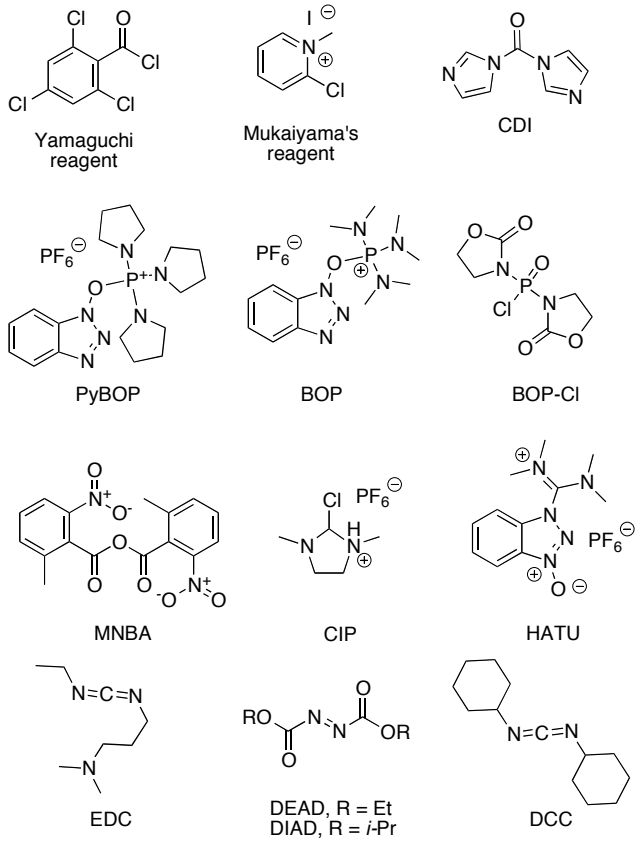


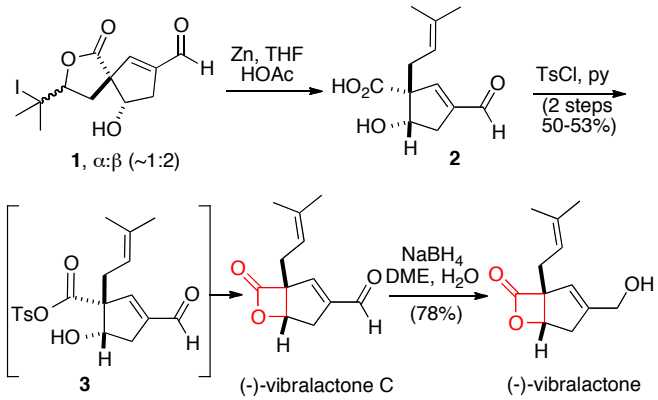
Figure 9. Activating Agents.

1.2.2.1. Vibralactone and Vibralactone C

The pancreatic lipase inhibitors, vibralactone and vibralactone C, both β-lactone containing natural products[87,118] were synthesized by way of carboxylic group activation of a the appropriate β-hydroxy carboxylic acid. Vibralactone recently elucidated in 2006 by Liu and co-workers[119] was synthesized racemically[120] and enantioselectively by Snider,[121] with the latter employing Schultz's asymmetric Birch reductive alkylation[122] to establish absolute stereochemistry. Zinc mediated retro-iodolactonization of the diastereomeric mixture of iodo-γ-lactones **1** converged to a single diastereomer of β-

hydroxy acid **2** (proceeding in 27% yield for the α-substituted diastereomer and 56% for the β-diastereomer) (Scheme 1.1). Lactonization was accomplished using conditions developed by Adam *et al.*,[110] TsCl activation of the acid (**3**), in the presence of py (pyridine), with concomitant cyclization by the hydroxyl group delivered (-)-vibralactone C. Subsequent chemoselective reduction of the aldehyde in the presence of the β-lactone delivered (-)-vibralactone.

Scheme 1. 1

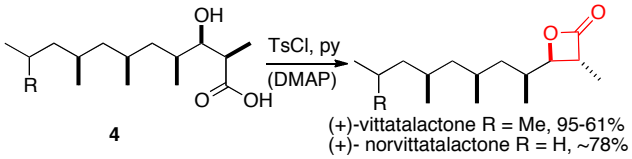


1.2.2.2. Vittatalactone and Norvittatalactone

The polydeoxypropionate vittatalactone (R = Me) also a β-lactone containing natural product has been synthesized enantioselectively[123] several times along with one known synthesis of the analogue, norvittatalactone (R = H, Scheme 1.2).[124] These molecules have attracted attention due to their potential applications for developing an environmentally benign plant protection strategy.[125] The absolute configuration was first

determined by Breit and Schmidt as they synthesized the enantiomer of vittatalactone, confirming the relative stereochemistry as possessing a *trans*–configured β-lactone with an all *syn*-tetramethyl side chain.[123b] Each synthesis has relied on various strategies for installing the polyproprionate fragments while all reported syntheses have employed a late stage lactonization to install the β-lactone using Adam's conditions[110] and in cases the assistance of DMAP aided in improving cyclization yields.[124,126] All reported syntheses of vittatalactone (*supra vide*) constructed the β-lactone as one of or the final synthetic steps, retrosynthetically implying that it was a labile functional group.

Scheme 1.2

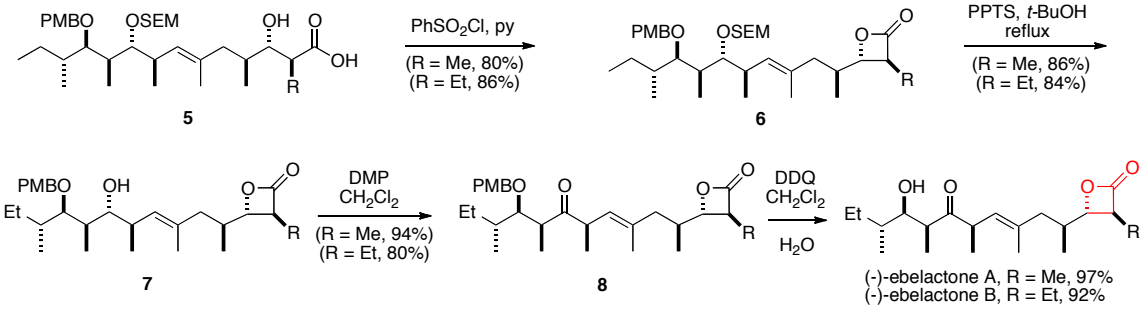


1.2.2.3. Ebelactones A and B

Since the first synthesis of the ebelactones A and B in 1995 by Paterson and Hulme[127] two additional syntheses have emerged in 2002 by Mandal[128] and 2012 by Pons and co-workers[129] all using a modified procedure of Adam *et al* (*vide supra*),[110] opting for benzenesulfonyl chloride vs. TsCl, to install the β-lactone from a β-hydroxy acid (Scheme 1.3). The Pons synthesis highlighted the robustness of β-lactone (**6**), while experimenting with the protecting group strategy, concluding SEM (2-

trimethylsilylethyoxymethyl) could be removed under refluxing conditions with the buffered acid, PPTS (pyridinium *p*-toluenesulfonate) and alcohol, in good yields. With such buffered conditions there was no reported nucleophilic opening of the β-lactones. All attempts at using a fluorine source ($Bu_4NF•3H_2O$ or TASF $[(Me_2N)_3S^+Me_3SiF_2]$[130] refluxing in THF, HF or HF•py) for deprotection however perturbed the β-lactone. The resulting secondary alcohol (**7**) was oxidized using Dess-Martin periodinane (DMP), and PMB (*p*-methoxybenzyl) deprotection with DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) gave both ebelactone A and B in 2.9% and 3.7% overall yields respectively, displaying compatibility with oxidizing conditions.

Scheme 1.3

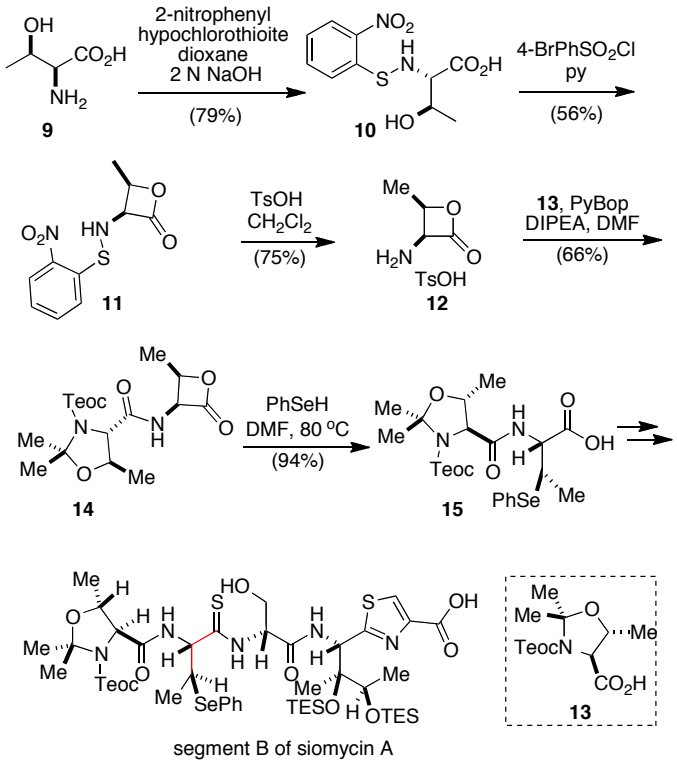


1.2.2.4. Siomycin A and Largamide H

While planning the synthesis of the complex antibiotic siomycin A Hashimoto and Nakata[131] dissected the molecule into five 'practical' segments, three of which relied on β-lactone chemistry to complete. Segment B began with chemistry developed by

Vederas for obtaining optically pure β-lactone salts of *L*-threonine (**12**, Scheme 1.4).[115,116] *N*-Acylation of *L*-threonine with 2-nitrobenzenesulfenyl chloride, followed by carboxylate activation with 4-bromobenzenesulfonyl chloride revealed α-amino-β-lactone in 56% yield (**11**). Acid catalyzed cleavage of the S-N bond to the amine salt was accomplished without disrupting the optical purity of the β-lactone. The amine salt **12** was then coupled to carboxylic acid (**13**) using PyBOP under basic conditions to activate the acid.[113] A critical step for the synthesis was the opening of β-lactone **14** by phenylselenylation stemming from attack at the β-position. Exploration of a variety of conditions meet with failure (Shirahama's conditions,[132] PhSeNa, etc.), however benzeneselenol (PhSeH) in DMF provided nearly quantitative conversion to β-selenide **15**. This was the first reported example using PhSeH to open a β-substituted β-lactone.[133] In this instance the β-lactone motif served as both a protecting group for the carboxylic acid during the amide coupling and as a hydroxy activating group assisting in phenylselenation. Highlighted in red of segment B are the carbons stemming from β-lactone **12**.

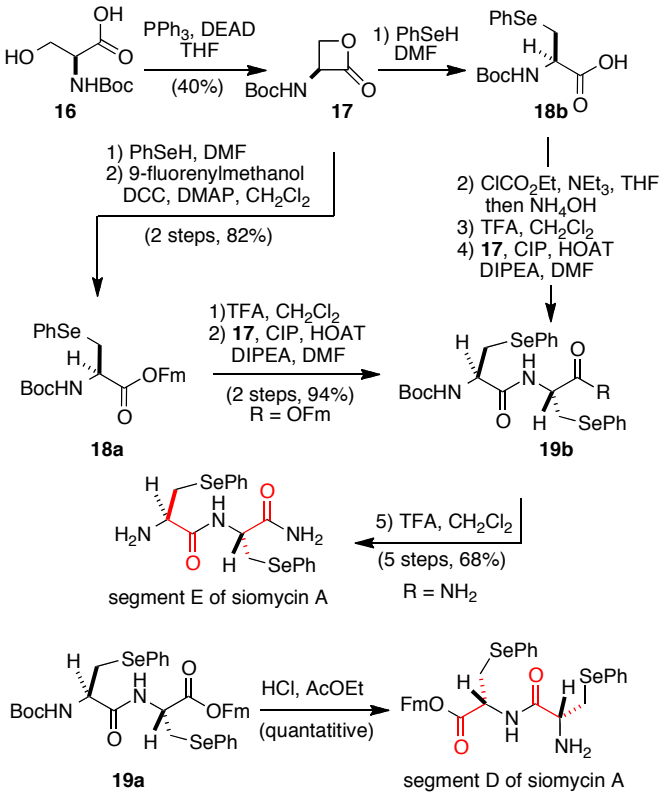
Scheme 1.4



Segments D and E began with optically active α-amino β-hydroxy acid **16** that lactonized under standard Mitsunobu conditions (DEAD/PPh_3) *via* hydroxyl group activation yielding known Boc-*L*-serine β-lactone (**17**, Scheme 1.5).[134] Using the previously discussed ring-opening tactic with PhSeH[133] the authors then diverged to make segments D and E. Towards segment D the resultant carboxylic acid was converted to Fm-ester **18a** by treatment with 9-flourenylmethanol[135] and DCC. Deprotection of the Boc (di-*tert*-butyl dicarbonate) group and condensation, with the aforementioned Boc-*L*-serine β-lactone (**17**), assisted by CPI [117] delivered amide **19a** (R = OFm). Dipeptide segment D was completed by hydrolysis of the Fm ester for late

stage coupling (not pictured). β-phenylselenide **18b** was transformed to an amide by way of an anhydride intermediate and treatment with aqueous ammonia, similarly Boc deprotection and CIP assisted condensation with β-lactone **17**, generated amide **19b** (R = NH_2). Subsequent treatment with TFA (trifluoroacetic acid) completed segment E from **17** in 68% yield over five steps. Hashimoto and Nakata's experimentally efficient design and synthesis of siomycin A is evident by the incorporation of intermediate **17** on four separate occasions installing differential functionalities of fragments D and E while transferring chirality from the same β-lactone.

Scheme 1.5



Siomycin A, shown in figure 10 tracks segments B, D, and E with inclusion of the carbon and oxygen's stemming from the corresponding β-lactones highlighted in red.

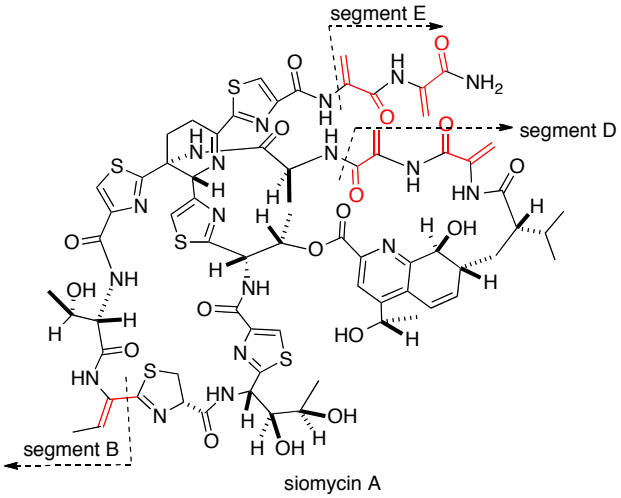


Figure 10. Siomycin A and β-lactone incorporation.

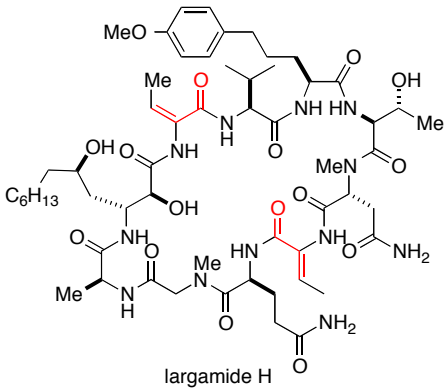


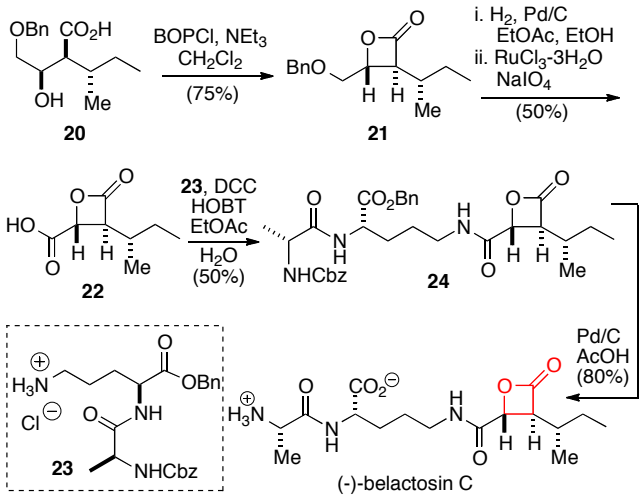
Figure 11. β-Lactone applications to largamide H.

Correspondingly, the synthesis of largamide H (Figure 11) employed the same β-lactone from the segment D and E constructs of siomycin A (Scheme 1.5) for accessing the enone systems in red, functionalizing intermediate **19b** through a selenium promoted *syn* elimination (Figure 11).[136]

1.2.2.5. Belactosin's A and C

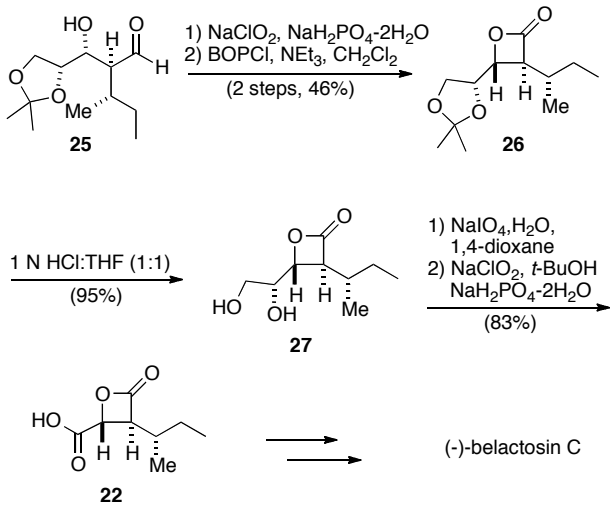
Belactosin C, as with the aforementioned β-lactone containing natural products has also garnered the interest of synthetic groups as an inhibitor of the 20S proteasome, a target for controlling auto-immune diseases and cancer.[137] Of the reported syntheses there have only been two different modes of cyclization for installing the β-lactone, here reviewing the hydroxy acid method for lactonization[89,138] a subsequent section will address the alternative approach.[139] The first synthesis by Kumaraswamy and coworkers[89] cited lactonization as only being achievable by BOBCl activation, in the process confirming the *trans*-configuration of (-)-belactosin C (Scheme 1.6). After installing β-lactone hydrogenolysis and oxidation to carboxylic acid **22** was completed. Subsequent coupling of β-lactone **22** with Cbz (carboxybenzyl)-protected amine salt **23** and deprotection gave rise to the natural product.

Scheme 1.6



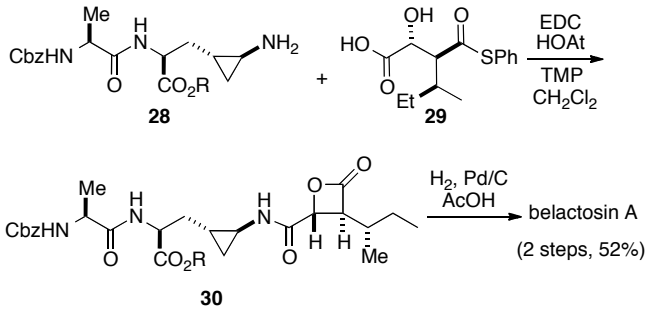
A late report by Kumaraswamy and co-workers established the appropriate *trans* stereochemistry of the β-lactone motif at a earlier stage of the synthesis.[138a] Commencing from β-hydroxy aldehyde **25** Pinnick oxidation and BOPCl mediated β-lactonization produced the acetonide-protected β-lactone **26** (Scheme 1.7). Deprotection with HCl and concomitant oxidative cleavage provided access to **22,** a common intermediate in the aforementioned synthesis (Scheme 1.6).[89] In this later synthesis the authors were able to generate the *trans*-configured β-lactone in an efficient manner showing reaction tolerance to both acidic and highly oxidizing conditions.

Scheme 1.7



Meijer and Larionov[138b] serendipitously discovered a tandem acylation-β-lactonization sequence as an alternative to the belactosin core. Amine **28** and acid-thioester **29** underwent direct coupling using EDC, TMP (2,2,6,6-tetramethylpiperidine), and HOAt (1-hydroxy-7-azabenzotriazole) (Scheme 1.8). The hydroxyl group cyclized with the thioester to β-lactone **30** and subsequent hydrogenolysis delivered belactosin A in 52% yield over two steps. Thioester **29** too was coupled with amine salt **23** and deprotection outlined in scheme 6 provided access to belactosin C (2 steps, 80%). This was the first reported literature example of a domino-type acylation-β-lactonization process, permitting a general approach to belactosin derivatives.

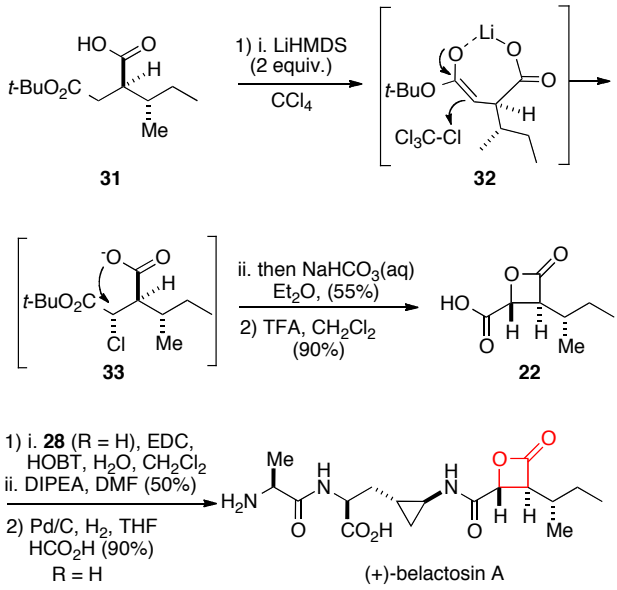
Scheme 1.8



The bioactivity of the belactosin's prompted Armstrong and coworkers[140] to expanded the scope of the precedented stereoselective chlorination of a monosubstituted succinate[141] employing a chlorination-β-lactonization sequence to belactosin A. Monosubstituted succinate **31**, prepared from *L*-isoleucine, was deprotonated with LiHMDS (lithium bis(trimethylsilyl)amide) participating in a stereoselective chlorination with carbon tetrachloride (CCl_4) *in situ* forming chloro-carboxylate **32** (Scheme 9). Lactonization occurred upon exposure to the biphasic mixture of ether/$NaHCO_3$ (aq), as previously reported by Barlaam.[141b] Care was taken to avoid reported S_N2 ring opening at the C_2 position[142] by removing chloride from the ether phase. Conventionally not a HGA method, as chloride serves as an analogous 'activated hydroxyl group', nevertheless resulting in inversion of intermediate **33**. Transformation to the known carboxylic acid **22** (*vide supra*) was facile under acidic conditions, while the natural product was achieved by EDC coupling with amine **28** (R = H, Scheme 1.9) proceeding in moderate yield.[143] This was the first report of a biphasic strategy for peptide coupling in the presence of a β-lactone; additionally the chlorination-

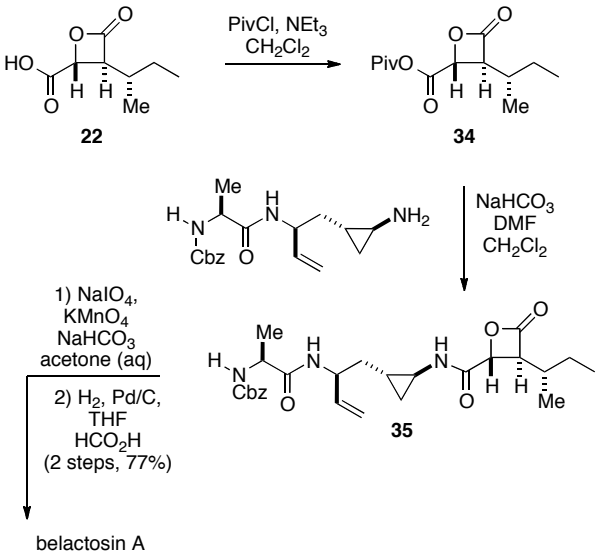
lactonization sequence negated a formal activation step for cyclization minimizing use of protecting groups through selective activation of carboxylic acid **22**.

Scheme 1.9



Shuto and co-workers[144] followed a strategy similar to Armstrongs[140] approach for forming β-lactone **22** (Scheme 1.10). Activation of carboxylic acid in **22** with pivaloyl chloride (PivCl) to the mixed anhydride **34** followed by amine acylation delivered tripeptide **35** in excellent yield. Here opting to install the carboxylic acid of the natural product at the final stage of the synthesis avoiding a protection/deprotection sequence or selective activation for β-hydroxy cyclization. Surprisingly, the β-lactone moiety was unaffected during oxidative cleavage of the terminal olefin in **35** with $NaIO_4$ and $KMnO_4$. Lastly deprotection of the Cbz group, in which all syntheses to date employ as the final step, delivered belactosin A.

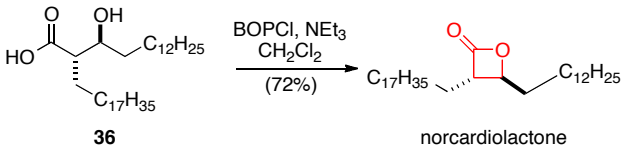
Scheme 1.10



1.2.2.6. Nocardiolactone

Kumaraswamy and coworkers in continuing their interests of making *trans*-substituted β-lactones[89,138a,145] completed the synthesis of nocardiolactone,[146] a simplified structural motif of the ebelactone's, belactosin's, and tetrahydrolipstatin. BOPCl-Mediated cyclization of hydroxy acid **36**, which in turn was obtained from a (*S*)-proline-catalyzed cross-aldol, gave way to the natural product in good yield as the final step (Scheme 1.11).

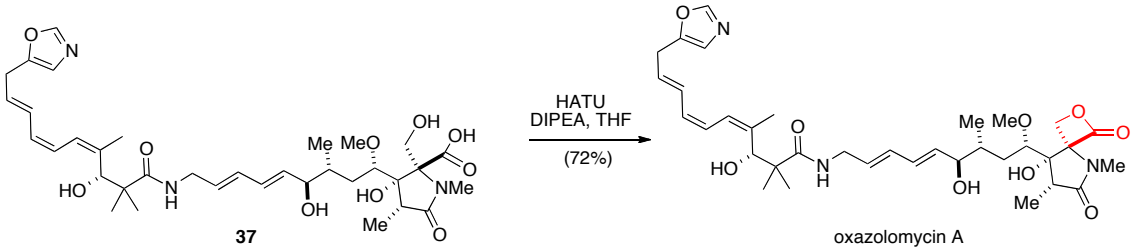
Scheme 1.11



1.2.2.7. Oxazolomycin A

Oxazolomycin A has drawn considerable attention because of its unique spirocyclic-β-lactone-γ-lactam core and structural similarities to known 20S proteasome inhibitors salinosporamide and omuralide. It has a wide array of biological activities including *in vivo* antitumor activity[147] with Hatakeyama and coworkers reporting the first synthesis of oxazolomycin A in 2011.[148] Donohoe and coworkers subsequently disclosed the only reported asymmetric route to the pyrrolidinone core.[149] Both tactics made use of HATU activation of the carboxylic acid moiety for generating the spirocyclic β-lactone-γ-lactam core of the natural product (Scheme 1.12). Hatakeyama's synthesis reported installation of the spirocyclic core as the final step delivering the natural product in 72% yield.

Scheme 1.12

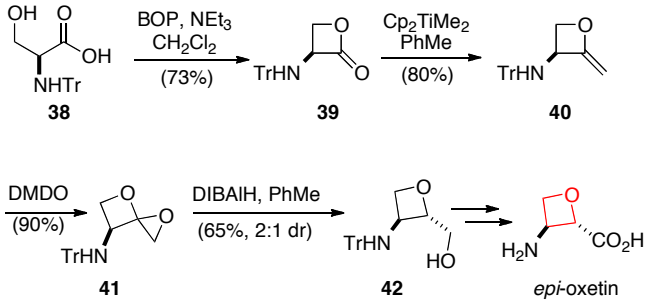


1.2.2.8. *Epi*-Oxetin

The Howell group has pioneered the synthetic utility of 2-methyleneoxetanes (*vide supra)*[16] in 2008 reporting a methenylation-epoxidation sequence while completing *epi*-oxetin (Scheme 1.13).[150] Access to optically active β-lactone **39** was achieved with Liskamp's procedure,[151] by treatment of *N*-tritylserine (obtained from *L*-serine) with

BOP and NEt_3. Methylenation with the Petasis reagent (Cp_2TiMe_2) delivered substituted 2-methyleneoxetane **40** in 80% yield[15] which was transformed to dioxaspirohexane **41** with DMDO (dimethyldioxirane).[152] When treated with DIBAlH, the epoxide could be selectively cleaved to a primary alcohol[153] yielding the *anti* bis-substituted oxetane **42**. Stereoselectivity from the reduction favored the undesired diastereomer, presumably from complexation of the nitrogen lone pair with DIBAlH. Howell and Blauvelt used the β-lactone **39** as a as a gateway to various 4-membered oxygen containing heterocycles as is evident in this synthesis from the transformation of the β-lactone to 2-methyleneoxetane and then to a substituted oxetane ring.

Scheme 1.13

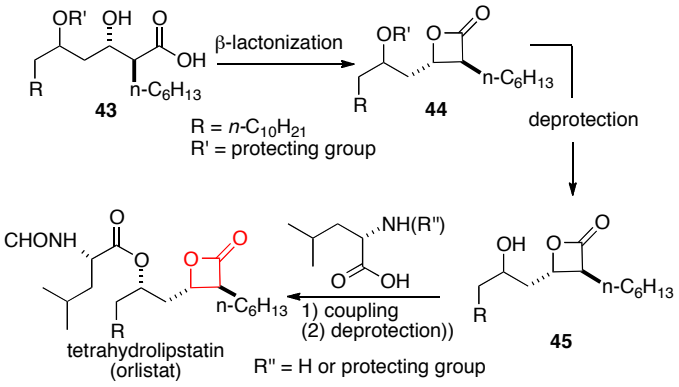


1.2.2.9. Tetrahydrolipstatin

Due to the potent and irreversible inhibition of pancreatic lipase[86] tetrahydrolipstatin, currently marketed as the anti-obesity drug Xenical®/Alli®, has been targeted by numerous groups in the last 17 years.[73c,154,155] Of the syntheses since 2003 (Yadav[156] Kumaraswamy[145,157] Raghavan[158] Ghosh,[159] Hanson,[160] and Shiina[161]) that involve hydroxy-acid cyclization all have followed the general sequence outlined in scheme 1.14. By protecting the δ-hydroxy group in **43** (as a silyl group, benzyl ether,

methyl ether, etc.) the β-alcohol has been cyclized under a variety of conditions (Yamaguchi cyclization, BOPCl, Adams *et al*[110] cyclization and modifications thereof, MNBA, etc.). Following cyclization, deprotection of the secondary alcohol and coupling with either (*S*)-*N*-formyl leucine or a protected analogue thereof has established the ester side-chain. Coupling has employed both carboxyl group activation (CGA) and hydroxy group activation (HGA) methods. Beginning with *syn*-β,δ-alcohols, CGA strategies used DCC and DMAP for installing the ester side chain whereas HGA methods utilized *anti*-β,δ-alcohols with Mitsunobu conditions (DEAD/PPh_3 or DIAD/ PPh_3). The increase of methodology and activation methods for forming β-lactones has lead to a variety of methods to access tetrahydrolipstatin, allowing greater synthetic versatility for constructing β-hydroxy acid **43**.

Scheme 1.14

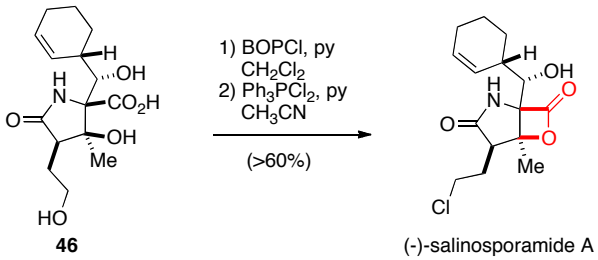


1.2.2.10 Salinosporamide A and Analogues

The potent inhibitor of the 20S proteasome, salinsporamide A, which is currently in testing as a drug candidate for multiple myeloma[106] has been synthesized by several synthetic groups[106,162] focusing largely on the route to hydroxy acid **46** (Scheme 1.15).[163]

Corey[163a] first reported the enantioselective synthesis and final two steps, which several other syntheses utilized as their end game strategy.[163a-c] Reporting a β-lactonization chlorination sequence to salinsporamide A with BOPCl in py and triphenylphosphine dichloride proceeding in good yield (>60%) over two steps, similar yields were seen with others following this strategy.[163a-c]

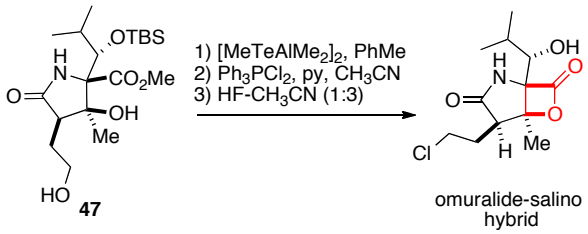
Scheme 1.15



Corey reported an improved end strategy in the *clasto*-lactacystin-salinosporamide hybrid synthesis utilizing $(MeTeAlMe_2)_2$, a demethylating reagent developed to specifically hydrolyze the 'unusually' difficult methyl ester of **47** (Scheme 1.16).[164] The propensity for retro-aldol, and susceptibility to decomposition under various conditions, complicated the seemingly simple transformation however the tellurium derived reagent prompted efficient demethylation. While ensuing lactonization with phosphine derived chlorinating agent, presumably through *in situ* acid chloride formation both cyclized the tertiary alcohol, and chlorinated the primary alcohol. Lastly acid-mediated silyl deprotection furnished the natural product analogue. Pattenden[163e]

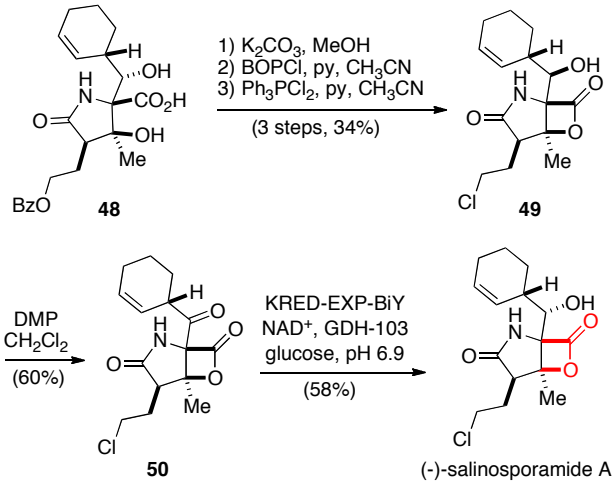
and Omura[165] also employed this tellurium-mediated transformation, chlorination-β-lactonization sequence to racemic and optically active salinosporamide A, respectively.

Scheme 1.16. Salino-omuralide hybrid synthesis.



Potts *et al.* of Nereus Pharmaceuticals[166] after following the β-lactonization chlorination sequence with BOPCl and Ph_3PCl_2 (*vide supra*)[163a] took a biological approach, relying on an enantioselective enzymatic reduction to establish the secondary alcohol's stereochemistry (Scheme 1.17). Benzyl deprotection, β-lactonization, and chlorination preceded in moderate yield over three steps affording the hydroxy epimer of salinsporamide (**49**). Dess-Martin oxidation produced keto-salinosporamide (**50**) permitting excellent stereocontrol in the ketoreductase enzyme-mediated reduction to (-)-salinosporamide.[166] To the best of our knowledge this is the first time an enzymatic reduction was used in the end game approach for a β-lactone containing compound, eluding to the highly specific nature of enzymes.

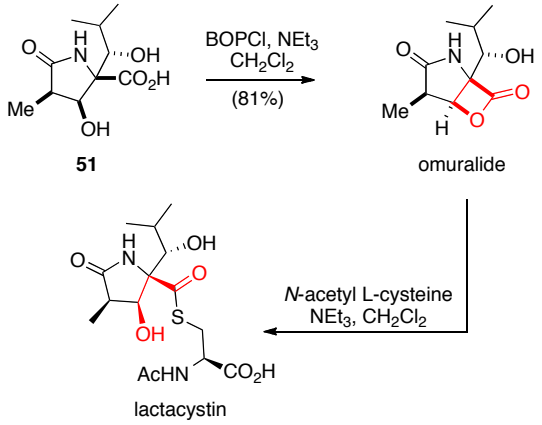
Scheme 1.17



1.2.2.11. Omuralide and Lactacystin

As with salinosporamide A, the structurally related natural products lactacystin and omuralide (also referred to as *clasto*-lactacystin) are known to be selective and potent inhibitors of the 20S proteasome and too have elicited attention[105,162b] (synthesis since 2007 review)[167] from the synthetic community. Omuralide and salinosporamide A bear structural similarities in that the cyclohexene of salinosporamide A is replaced with a *sec*-butyl group and the ethyl chloride by a methyl, while lactacystin is the cysteine thioester derivative of omuralide. As with the majority of the salinosporamide A syntheses (*vide supra*) β-lactonization of β-hydroxy acid **51** to omuralide was accomplished by carboxylic acid activation with BOPCl (Scheme 1.18). Direct introduction of the cysteine moiety to lactacystin, followed the initial procedure by Corey with *N*-acetyl L-cysteine mediated ring opening.[168]

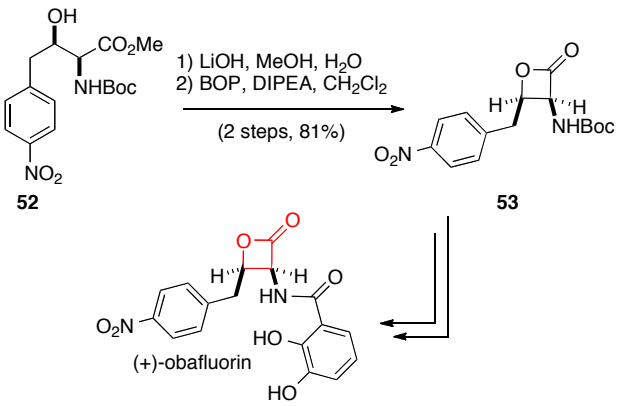
Scheme 1.18



1.2.2.12. Obafluorin

Demonstrating the utility for functionalizing unactivated C(sp^3)-H bonds He and Chen completed a formal synthesis of the antibiotic (+)-obafluorin. [169,170] Aryl threonine derived hydroxy ester **52** was hydrolyzed and cyclized with BOP to β-lactone **53**, a known intermediate from a synthesis previously reported by Vederas (Scheme 1.19).[116,171]

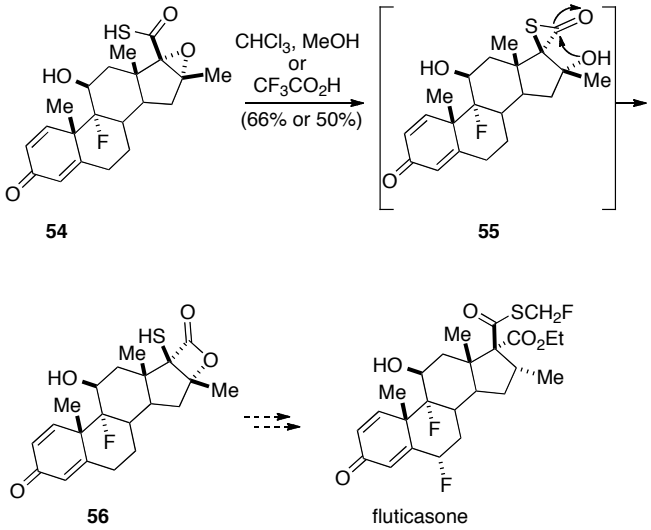
Scheme 1.19



1.2.2.13. Fluticasone Propionate

In the pursuit of readily accessible intermediates for synthesizing glucocorticoid antedrugs, specifically fluticasone propionate which is currently marketed as Flovent/Flonase by GlaxoSmithKline as a potent anti-inflammatory asthma treatment,[172] Bain and Procopiou *et al*[173] came across an unprecedented rearrangement to β-lactone **56** (Scheme 1.20). Exposure of epoxy-thioester **54** to a chloroform/methanol mixture or triflic acid, invoked epoxide opening and intramolecular cyclization to spirocyclic α-thiolactone intermediate **55**. Opening of the α-thiolactone by the liberated hydroxyl group provided the thermodynamically favored thiol-substituted β-lactone **56**. Subsequent applications involved late stage intermediates of synthetic trifluorinated glucocorticoid fluticasone propionate and derivatives thereof.[174]

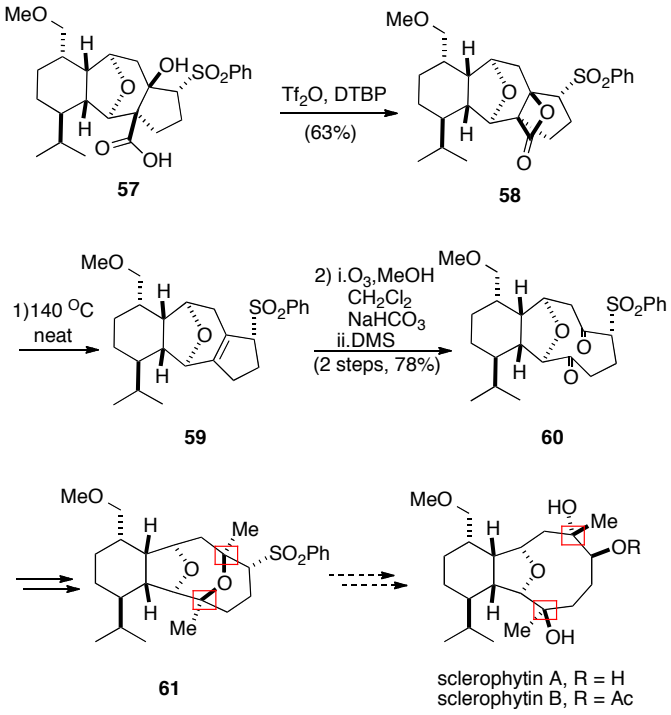
Scheme 1.20



1.2.2.14. Sclerophytin A and B

Molander and Jeffrey took a unique approach employing β-lactone chemistry for synthesizing macrocyclic intermediate **60** (Scheme 1.21).[175] Carboxylic group activated lactone formation with Tf_2O (trifluoromethanesulfonic anhydride) in the presence of DTBP (2,6-di-*tert*-butylpyridine) and direct thermolysis to tetrasubstituted olefin **59** created a platform for ring-expansion of the cyclopentene. Oxidative cleavage with ozone to cyclodecane diketone **60** was carried on to late stage intermediate **61**, which is the core structure towards the synthesis of sclerophytin A and B.

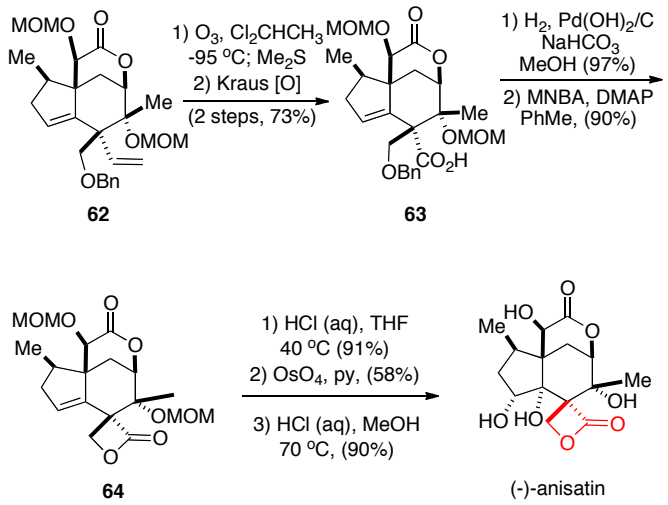
Scheme 1.21



1.2.2.15. Anisatin

One of the most densely congested and compact β-lactone containing natural products (-)-anisatin, has proven to be a challenging structure synthetically bearing 8 contiguous stereogenic centers, and four rings, one of which is a spirocyclic β-lactone moiety (Scheme 1.22). The structural complexity and biological activity as a strong $GABA_A$ antagonist[176] has elicited attention from the synthetic community[177] however there are only two total syntheses to date. Originally completed by Niwa[178] and co-workers in 1990, forming the β-lactone as the second to last step *via* Adam's cyclization conditions,[110] Fukuyama and co-workers[179] recently disclosed a different approach of increasing the oxidation state of anisatin through the synthesis with minimal protecting groups. Ozonolysis of olefin **62** with ensuing Kraus oxidation[180] ($NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, t-BuOH-H_2O), followed by Pearlman's catalyst aided hydrogenolysis provided hydroxy acid **63**. The crucial spiro-lactonization, proceeded in 90% yield with MNBA[181] and DMAP as a nucleophilic promoter. Selective deprotection of the tertiary methyl ether with HCl, Os-mediated dihydroxylation of the tri-substituted olefin, and deprotection of the secondary methyl ether finalized the second (-)-anisatin synthesis. Noteworthy is the necessity to protect the tertiary alcohol prior to β-lactonization; ozonolysis of **64** in the presence of the unprotected tertiary alcohol gave a complex mixture presumably due to retro-aldol of the resulting β-hydroxy aldehyde. Additionally the free-tertiary alcohol of **64** was reported to preferentially cyclize to *cis*-fused β-lactone-cyclohexane system (not shown). The spiro-cylcic β-lactone proved to be rather robust surviving HCl/MeOH at elevated temperatures.

Scheme 1.22

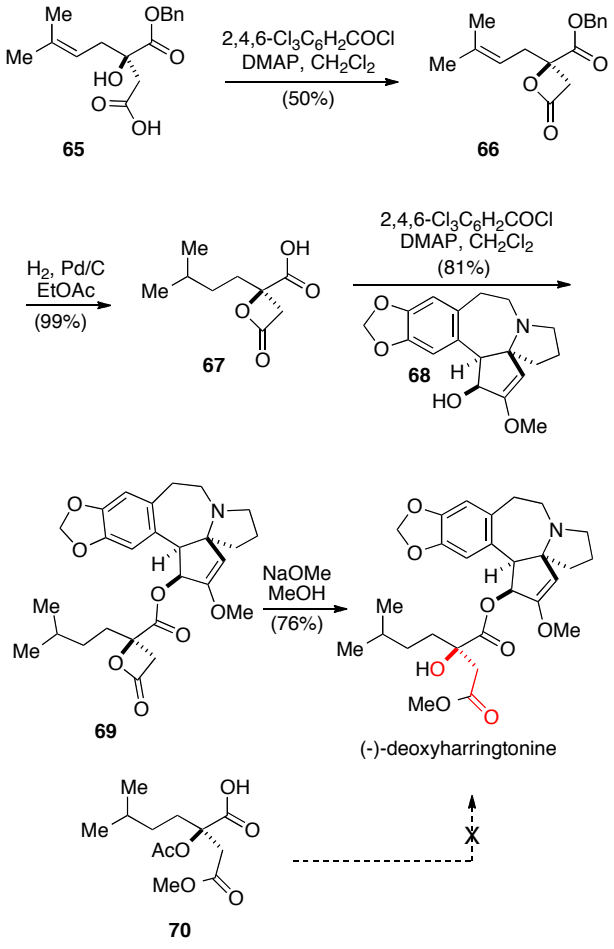


1.2.2.16. Cephalotaxus Esters

Capitalizing on the strained bond angles and acylating potential of β-lactones, Djaballah and Gin were able to successfully append the hindered side chain of several cephalotaxus esters through a common late stage intermediate as an efficient and convergent tactic to these bioactive compounds (Scheme 1.23 and 1.24).[182] The most challenging part of synthesizing cephalotaxus esters, a treatment component for chronic myeloid leukemia,[183] is the installation of acyl side chain, which is often inefficient or prohibited.[184,185] This challenge arises from the secondary alcohol of cephalotaxine (**68**) being 'buried' within the concave face, as well the α-quaternary carbon of the acyl side chain in (-)-deoxyharringtonine further inhibits the coupling of these two fragments (Scheme 1.23). Not to mention the lack of direct routes to the optically active acyl fragments. To hurdle through this challenge of coupling the two 'handicapped' pieces

Djaballah and Gin synthesized β-lactone **66** from lactonization of (*R*)-malic acid derived hydroxy acid **65** with Yamaguchi conditions.[111,182] A second treatment of Yamaguchi condition's was employed for acylating cephalotaxine (**68**) with β-lactone **67** following a Pd-catalyzed hydrogenolysis of **66**. The coupling of fragments **67** and **68** was achieved in 81% yield, which is impressive considering the difficulties of previous syntheses for installing the acyl side chain end game approach.[185] Lastly ring opening with methanol gave way to (-)-deoxyharringtonine.

Scheme 1.23

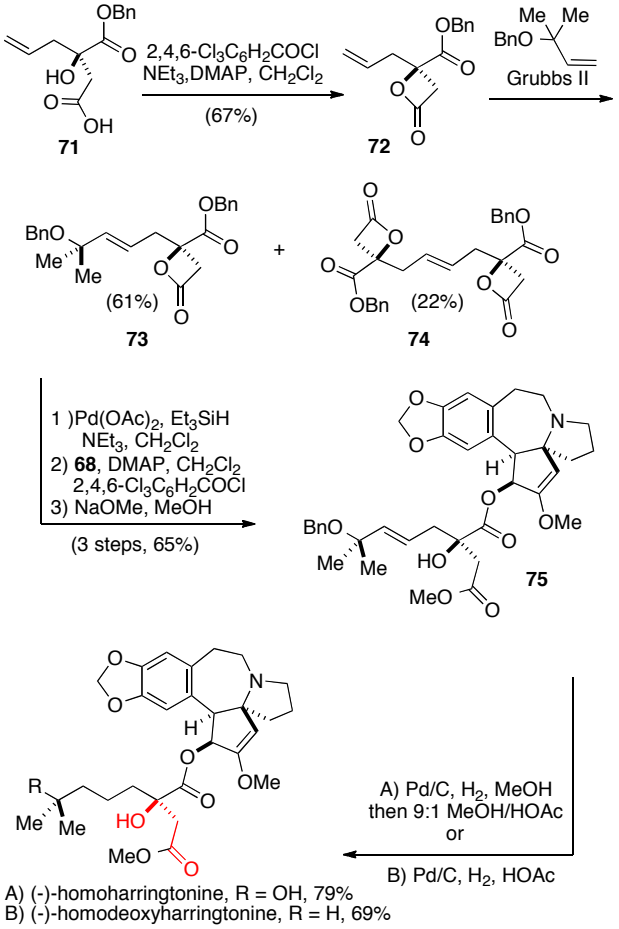


In efforts to explore a more direct route and understand the necessity of the β-lactone, coupling was attempted with identical conditions employing linear derivative **70** finding that only traces of protected (-)-deoxyharringtonine were observed. The authors were attracted to the β-lactone moiety as a useful intermediate for several of the reasons that most shy from using them in synthesis, the strain energy from bond angle compression, and enhanced electrophillicity. Rationalizing the carbonyl (C_2) of **67** would be more electrophilic as a result of increased s-character of the *exocyclic* bonds *via* induction thereby enhancing p-character for the *endocyclic* bonds (those contained in the β-lactone) an 'C_2'-acylium like intermediate' once the free acid is activated to ester derivatives of (**69**) from vicinal π-delocalization.

The development of a successful late stage acylation tactic facilitated the synthesis of (-)-homoharringtonine and (-)-homodeoxyharringtonine (Scheme 1.24). β-Hydroxy acid **71**, derived from (R)-malic acid, followed the previously utilized lactonization conditions (scheme 1.23) and direct cross metathesis to deliver disubstituted alkenyl-β-lactone **73** and the dimeric bis-β-lactone **74**. Re-subjecting dimeric lactone **74** to Grubbs II, provided enhanced quantities of the desired cross metastasis product **73**. Selective benzyl ester cleavage, esterification with cephalotaine (**68**, *vide supra*), and ring-opening proceeded in 65% yield over three steps to methyl ester **75**. The β-lactone moiety was unperturbed by this sequence of events involving metathesis, hydrosilylation, and coupling, to a degree surprising as β-lactones themselves are rather electrophilic and prone to solvolysis. This could be attributed to the sterically congested environment of the secondary alcohol of cephalotaine preventing

β-lactone ring opening. Following lactone opening, Pd-mediated hydrogenolysis and hydrogenation in methanol afforded (-)-homoharringtonine (conditions A), while the absence of methanol gave way to (-)-homodeoxyharringtonine (conditions B). Djaballah and Gin highlighted the use of β-lactones for difficult acylation reactions of sterically encumbered alcohols.

Scheme 1.24

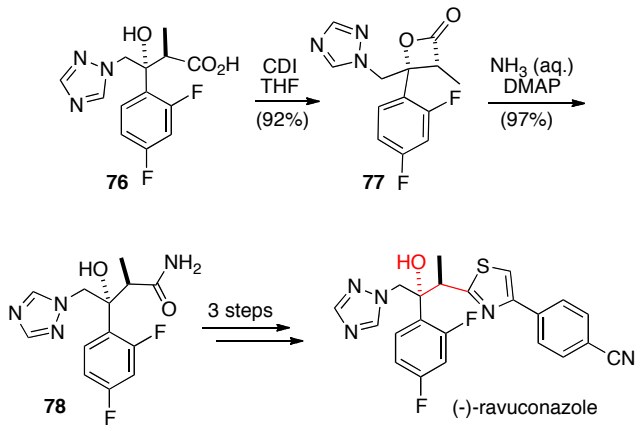


1.2.2.17. Ravuconazole

Zhu and coworkers[186] published an *improved* synthesis of the antifungal triazole,[187] ravuconazole, currently in phase II clinical trials[188] with kilogram processes

being developed for phase III clinical trials[189] employing an enzymatic lipase AK for establishing absolute stereochemistry. β-Hydroxy acid **76** activated by CDI lactonization proceeding in 92% yield; ensuing ring opening with aqueous ammonia resulted in hydroxy amide **78** (Scheme 1.25). Benzylic β-lactone **77** was unexpectedly stable, considering benzylic β-lactones are prone to spontaneous decarboxylation.[190] Is this instance the β-lactone was employed for facile conversion of the carboxylic acid to amide **78** devoid of formally protecting the secondary alcohol.

Scheme 1.25



1.2.3. Hydroxyl Group Activation (HGA)

The latter method for cyclization of β-hydroxy esters, hydroxyl group activation (HGA), proceeds with inversion of configuration at the hydroxy position (Figure 8). Activation of the β-hydroxyl group followed by an intramolecular nucleophilic displacement by the carboxylate anion provides the β-lactone motif.[191] The overall transformation follows an S_N2 pathway resulting in net inversion at the alcohol stereocenter. If the β-hydroxyl and carboxylic acid groups are initially in a *syn*–

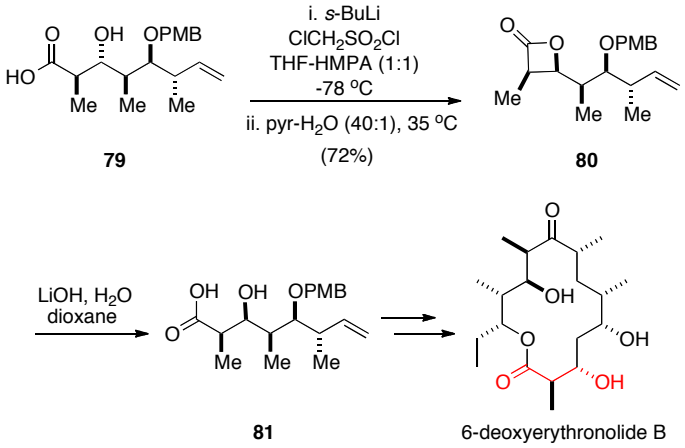
configuration the resultant β-lactone will bear a *trans*-configuration. Mitsunobu type conditions are typically employed for this type of cyclization (DEAD/PPh_3 or DIAD/ PPh_3),[192] activation of the alcohol with MsCl (methanesulfonyl chloride),[56a,] TsCl (*p*-toluenesulfonyl chloride),[108a,193] etc. have also proven fruitful. The HGA method is less common for the synthesis of β-lactones for several reasons; it is often necessary to mask the carboxylic acid in order to selectively activate the β-hydroxy group, which can require additional protection/deprotection steps, or intricate planning of the synthesis. Secondly, after the β-hydroxyl is converted into a good leaving group it makes the selective deprotection of the carboxylic acid rather difficult, as the activated alcohol is vulnerable under basic/nucleophilic conditions. Although methods have been developed to compensate for the shortcomings of this strategy (Lenz[194] and Giannessi[191,195] having reported esterification of the acid and mesylation of the alcohol followed by hydrogenolysis or hydrolysis, respectively to provide the carboxylic acid and activated alcohol) it has nevertheless been employed less frequently for lactonizing β-hydroxy acids.

1.2.3.1.6-Deoxyerythronolide B

In hopes of employing β-lactone chemistry for effective acylation, Krische and coworkers reported the most concise route to any erythromycin in their synthesis of 6-deoxyerythronolide B (Scheme 1.26).[196] The approach for synthesizing *cis*-β-lactone **79** relied on a hydroxy acid activation strategy for inverting the stereochemistry β to the carboxylic acid during lactone formation. Initial attempts with Mitsunobu conditions lead to decarboxylative-Grob-type elimination forming an analogous *cis*-olefin in >70%

yield (not pictured).[197] Successful β-lactonization resulted from treating the dianion of **79** with methanesulfonyl chloride (MsCl),[193] albeit in low yields, 15-20%, along with recovered starting material. The recovery of starting material indicated the need for a more electrophilic reagent to selectively and completely acylate the β-hydroxy group. Certainly, using chloromethanesulfonyl chloride delivered β-lactone **80** in 72% yield. Though the goal was to exploit the β-lactone in hopes of directly acylating another fragment of the natural product this approach was meet with failure. Finding in the course of their studies that *cis*-disubstituted β-lactones are obstinate acylating agents,[198] therefore hydrolysis with LiOH to the carboxylic acid **81** permitting coupling providing access to the natural product. To this end the β-lactone essentially functions to invert the β-hydroxy group of acid **79**, acting as an alternative method to a Mitsunobu reaction and ether hydrolysis.

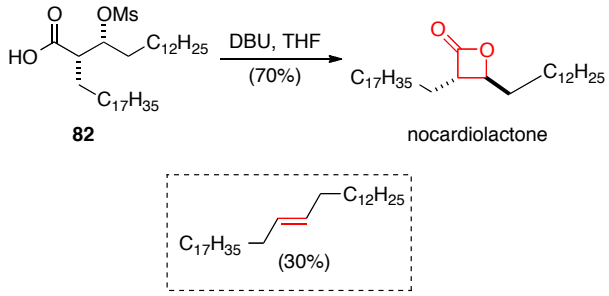
Scheme 1.26



1.2.3.2. Nocardiolactone and Valilactone

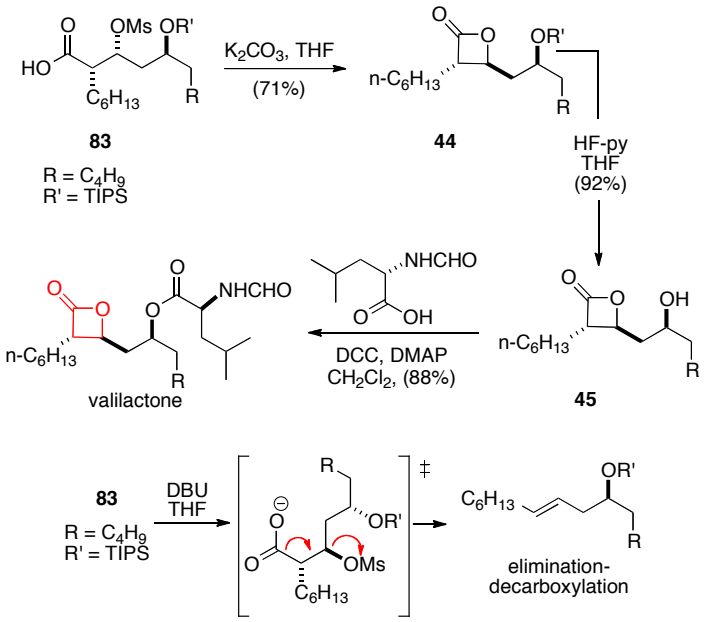
Synthesizing the *trans* α,β-disubstituted β-lactone, nocardiolactone Wu and Sun developed a DBU (1,8-diazabicyclo[5.4.0]undec-7-ene)-mediated lactonization procedure carried out in a homogenous media (Scheme 1.27).[108a] At the time of initial publication this was the first alternative to the biphasic protocols for hydroxyl group activation (HGA) in the presence of the carboxylic acid.[108b] Prior attempts at lactonizing **82** with Na_2CO_3 in H_2O-Et_2O,[193] or a dianion derivative thereof (proved successful in scheme 28), delivered no desired β-lactone product. The long hydrophobic substutients and relatively unfunctionalized nature of substrate **82** lead to solubility issues with typical biphasic conditions (H_2O-Et_2O or H_2O-CH_3Cl).[199] Discovering cyclization of the β-mesylate with DBU delivered nocardiolactone in 70% yield, while 30% *trans*-olefin was isolated (boxed in scheme 2). The authors reported this HGA method, 'more convenient' than standard Mitsunobu conditions; though the necessity for differentiating the hydroxy and carboxylic acid moieties was not completely negated with this procedure. It was however strategically planned into their route as the carboxylic acid underwent hydrogenolysis to give the 'unmasked' carboxylic acid **82** prior to the lactonization event. Regardless, offering alternative conditions for cyclizing β-hydroxy acids with such non-polar substrates.

Scheme 1.27



Sun and Wu used the same approach to synthesize valilactone, structurally similar to tetrahydrolipstatin (R= $C_{10}H_{21}$) which is another potent lipase inhibitor.[200] In this instance their previously developed conditions of DBU in THF for cyclizing **83**, however delivered predominately the elimination-decarboxylation pathway product observed as in nocardiolactone and traces of starting material (Scheme 1.28). Finding that K_2CO_3 was sufficient for permitting β-lactonization, with subsequent steps following those similarly noted for tetrahydrolipstatin (Scheme 1.14), deprotection, and esterification with (*S*)-*N*-formylvaline.[201]

Scheme 1.28



1.3. Intermolecular Lewis Acid Catalyzed [2+2] Cycloaddition

1.3.1. Introduction and Mechanism

Convergent access to β-lactones in the last 100 years has been realized from the [2+2] cycloaddition of ketenes and carbonyl compounds first reported by Staudinger.[202,203] Since this report the use of ketenes or *in situ* generated ketenes[204] with aldehydes has been the forefront for synthesizing enantiomerically pure β-lactones.[98,203] These thermally allowed[205] [2+2] cycloadditions have involved Lewis acid, Lewis base, or a combination of both for catalysis. The generally accepted Lewis acid catalyzed mechanism involves carbonyl activation, invoking asynchronous bond formation with the C_3-C_4 bond advancing to zwitterionic transition states with concomitant lactonization *via* C_2-O_1 bond formation (Figure 12).[206]

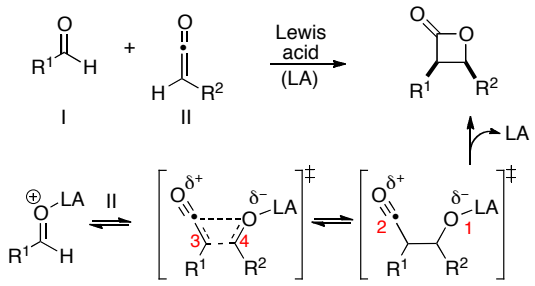


Figure 12. Lewis acid mediated net [2+2] cycloaddition. [206]

The Lewis acid promoted cycloaddition proceeds by effectively lowering the LUMO (lowest unoccupied molecular orbital) of the aldehyde, which reacts with the ketene HOMO (highest occupied molecular orbital)[207] In many cases Lewis acid catalysis is necessary for the cycloaddition to occur and unless the carbonyl coupling partner is activated by having electron-withdrawing substutients.[208] In 1975 Zaitseva brought new life to this transformation employing silylketenes[209] though selectivity was an issue, in that various Lewis acids including BF_3•Et_2O, as reported by Brady, delivered mixtures of *cis* and *trans* β-lactones.[210] Yamamoto developed conditions for the stereoselective formation of *cis*-β-lactones by employing the bulky aluminum based Lewis acid MABR (methylaluminum bis(4-bromo-2,6-di-*t*-butylphenoxide)).[207b] This Lewis acid mediated mechanism[211] was determined to favor the arrangement of intermediate **I** having a smaller steric interaction with R^2 than R^3 solely delivering the *cis*-β-lactone **A** (Figure 13). Whereas significantly smaller Lewis acids, *e.g.* BF_3•Et_2O, have minimal interactions with the R groups of the ketene thus selectivity is dictated by interactions of

the approaching aldehyde with the ketene, **II** and **IV**. If R^2 and R^3 are relatively similar a mixture of *cis* and *trans* will be observed from **II** and **IV,** respectively. However when R^2 = H and R^3 = *t*-butylMe_2Si arrangement **IV** is favored over **II** delivering only the *trans*-β-lactone **B**.[207b]

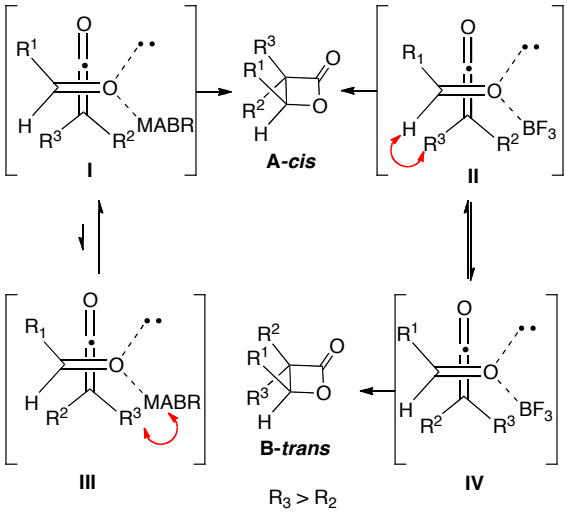


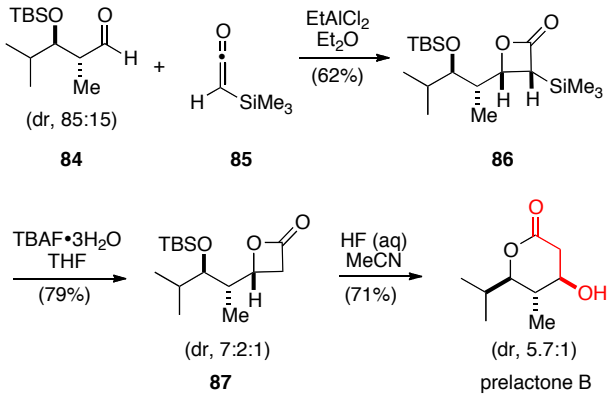
Figure 13. Selectivity for Lewis acid catalyzed cycloadditions.

1.3.1.1.(±)-Prelactone B, (±)-Goniothalaminm, and (-)-Massoialactone

Pons and coworkers have showed the synthetic potential of β-siloxy-β-lactones transforming them to δ-lactones trough an intramolecular HF-mediated transacylation reaction, providing access to (±)-prelactone B, goniothalamin, and massoialactone.[212,213] The key β-lactone intermediates were formed using an Al-mediated [2+2] cycloaddition with the appropriately substituted aldehydes and trimethylsilyl ketene[214] (Scheme 1.29). Commencing with *trans*-α-methyl-β-siloxy aldehyde **84**, as a 85:15 mixture of

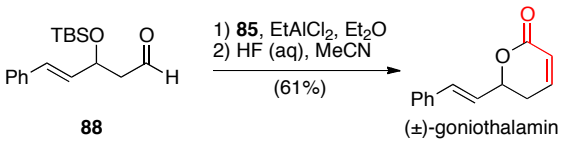
diastereomers, delivered cycloadduct bis-silyl-*cis*-β-lactone **86** that was carried on to a two-step approach mediated by fluorine. Firstly, C-Si cleavage then a second fluorine source (HF) revealed an alkoxide intermediate with concomitant transacylation to the δ-lactone, prelactone B as a 5.7:1 mixture of diastereomers.

Scheme 1.29



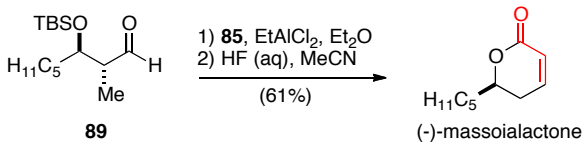
The tandem deprotection-lactonization approach was also applied to the α,β-unsaturated dihydropyrone, (±)-goniothalamin (Scheme 1.30).[213,215] The $EtAlCl_2$ promoted [2+2] cycloaddition provided a mixture of four diastereomers (81:10:7:2 *cis*/*cis*/*trans*/*trans*) of the resultant β-lactone (not pictured), presumably due to the lack of significant steric interactions, the diastereoselectivity was inconsequential and the mixture was directly subjected to excess HF. At this juncture, HF facilitated a one-pot bis-desilylation domino transacylation, β-hydroxy elimination to deliver the dihydropyranone natural product in 61% yield over two steps.

Scheme 1.30



A third application of the lactone ring expansion made use of optically active β-siloxy aldehyde **89**, readily available from (-)-dimethyl malonate[212] for the enantioselective synthesis of (-)-massoialactone (Scheme 1.31).[212,213,215] Using the same reaction conditions (*supra vida)* delivered the lactone in 61% yield from the corresponding aldehyde (**89**) devoid of stereochemical erosion. The six-step total synthesis proceeded in 34% overall yield and >99% ee, as Pons very elegantly highlighted the creativity for developing reactions with β-lactones as a robust method providing rapid access to δ-lactones.

Scheme 1.31

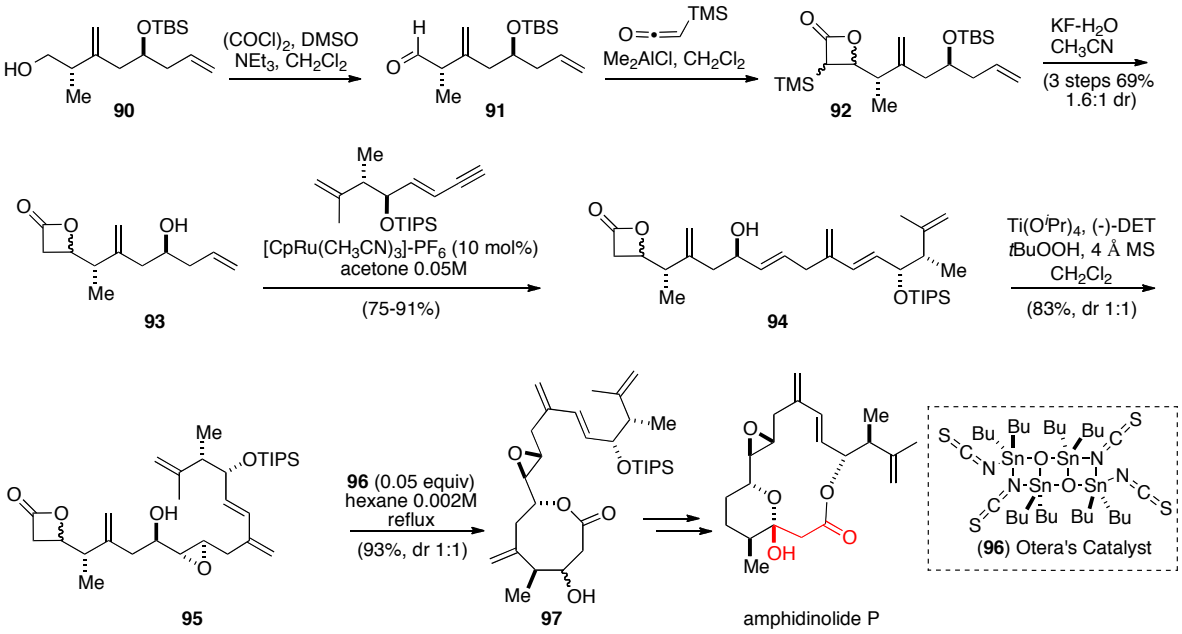


1.3.1.2. Amphidinolide P

Whilst revising the route to amphidinolide P, Trost and co-workers turned to β-lactone intermediate **92** as a gateway to the eight-membered lactone **97** (Scheme 1.32).[97] Seeking to exploit the β-lactone as both an activated acyl group for translactonization, concurrently functioning as a protecting group for minimizing chemoselectivity issues in the end-game, [2+2] Me_2AlCl-mediated cycloaddition[205,209a] of enantioenriched aldehyde **91** and trimethylsilylketene[216] provided a 1.6:1 mixture of diastereomers. This mixture, though separable was carried on due to the inconsequential nature of the resultant stereocenter (being oxidized at a later stage of the synthesis). Cleavage of both the C-Si and O-Si bonds without perturbing the lactone proved fruitful employing

conditions reported by Romo and Zemibro.[217] Mono-substituted terminal olefin **93** underwent selective Ru-catalyzed alkene-alkyne coupling developed in the Trost laboratory[218] followed by Katsuki-Sharpless asymmetric epoxidation furnishing a 1:1 mixture of diastereomers **95** (again resulting from the mixture at the β-lactone stereocenter). Finally, the β-lactone was functionalized using Otera's catalyst[219] to prompt formation of the eight-membered lactone **97** in 93% yield. Subsequent oxidation, deprotection, and lactonization yielded amphidinolide P. This synthesis demonstrated usefulness of a β-lactone intermediate in the formation of a medium-sized ring and its efficacy in minimizing unnecessary protection/deprotection sequences for differentiating the two secondary alcohols. Additionally, highlighting the chemo- and regioselectivity of the Ru-catalyzed alkene-alkyne coupling and capability with an array of functional groups (β-lactone, silyl ethers, and free alcohols).

Scheme 1.32.



1.3.2. Chiral Lewis Acid [2+2] Overview

Moving away from substrate control Miyano,[220] building on Yamamato's approach, reported the first chiral aluminum-BINOL (1,1′-bi-2-naphthol) Lewis acid complex to deliver β-lactones of moderate optical purity, with iterations by Pons,[221] Romo,[222] Nelson,[223] Evans,[205] and Corey[204] following suit.[203,224] Herein discussing Nelson's recently developed chiral Al-based Lewis acid's as the applications fall within the bounds of this review being utilized in natural product synthesis. The chiral Lewis acid catalyzed [2+2] cycloaddition follows the aforementioned mechanistic pathway however this transformation has shown itself to be a more practical procedure employing acid halides (X = Cl or Br), transformed to ketenes by a hindered tertiary base (DIPEA) *in situ,* negating the need for silyl- or preformed ketenes (Figure 14).[225] Elimination of

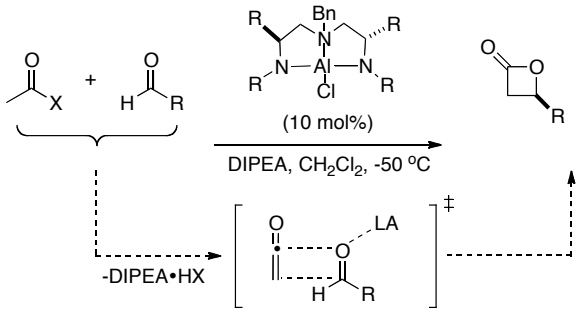


Figure 14. Catalytic enantioselective Lewis acid catalyzed [2+2].

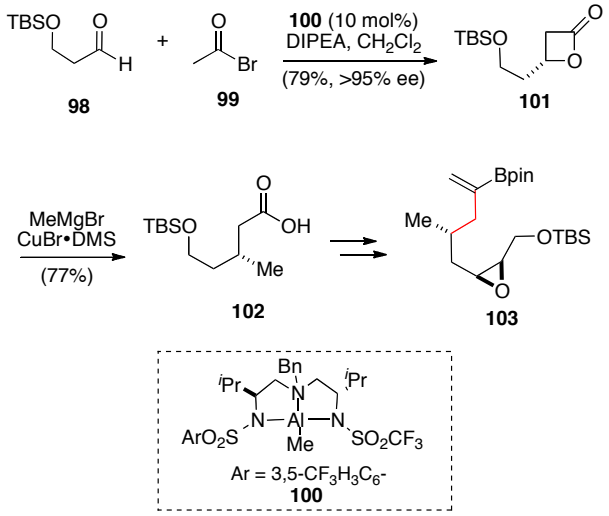
HX, promoted by the amine base provides the ketene intermediate, with the aldehyde component serving as the appropriate electrophile permitting C-C bond formation, catalyzed by the Lewis acid as lactone formation was retarded in the absence of Lewis acid.[211,226] Moreover, the combination of Al(III) with amine ligands enhanced the Lewis acidity permitting effective cross coupling on non-activated aldehydes, expanding the synthetic utility of amenable coupling partners.[226] The Nelson group has coined the acronym AAC referring to this transformation as an acyl halide-aldehyde cyclocondensation reaction.

1.3.2.1. Amphidinolide B

The Nelson laboratory utilized their developed methodology for dictating several stereocenters of the polyketide amphidinolide B by way of a chiral Lewis acid catalyzed [2+2] cycloaddition (Scheme 1.33 and 1.34).[227] The synthetic route instigated by β-siloxy aldehyde **98** and acetyl bromide catalyzed by the chiral Al(III) complex **100** furnished the TBS-protected β-lactone in good yield and enantioselectivity[223a] The

methylketene intermediate (not pictured) formed *in situ* highlights the progression of this chemistry diverging from silyl or unsubstituted ketene substrates. Transformation of the lactone was accomplished using a stereoselective Cu-mediated S_N2 reaction with MeMgBr[36] cleaving the C-O acyl bond to β-methyl carboxylic acid **102**. This fragment was eventually converted to the boronic ester **103**, preserving the methyl stereocenter for incorporation into the natural product.

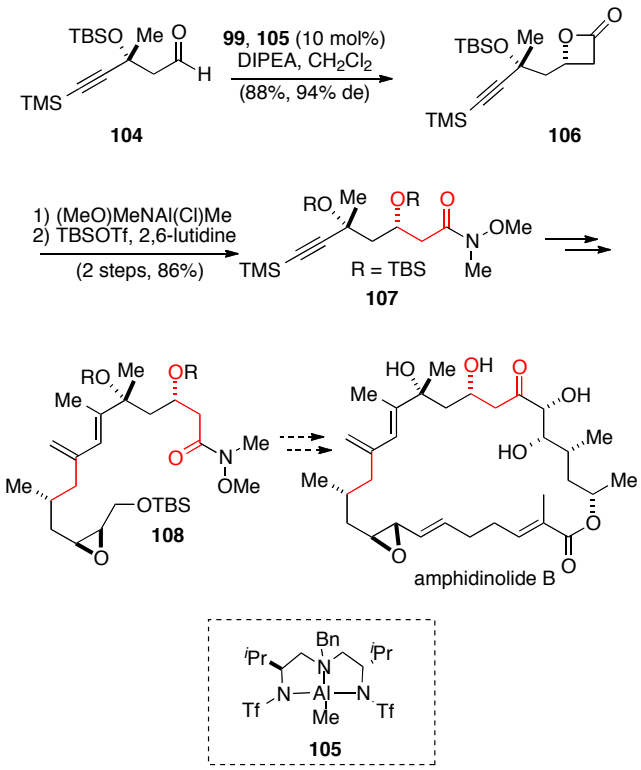
Scheme 1.33



As part of a convergent approach a second β-lactone intermediate was recruited, exhibiting the participation of a significantly more complex aldehyde **104**, bearing a β-quaternary carbon and alkynal substutient (Scheme 1.34). Acetyl bromide coupled with chiral aldehyde **104** through the Al-mediated [2+2] cycloaddition delivered the 1,3 *syn*-β-lactone in both excellent yield and diastereoselectivity.[223a] *N*-Methoxylmethyl ring opening and silyl protection of the resultant secondary alcohol perturbed the lactone ring to linear Weinreb amide **107**. The remnants of the two β-lactones can be seen in **108**

highlighted in red, with incorporation of the β-hydroxy carbonyl and establishment of the methyl-bearing stereocenter from **107** and **103** respectively in hopes of this late stage intermediate giving access to amphidinolide B.

Scheme 1.34

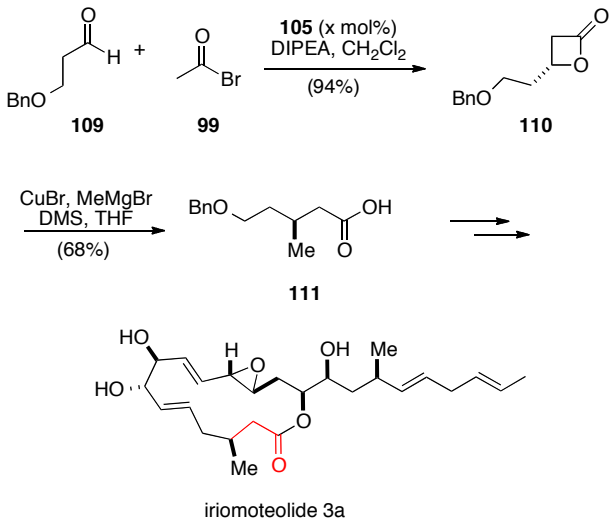


1.3.2.2. Iromoteolide 3a

In efforts to evaluate the biological activity of iriomoteolide 3a and analogues thereof Nevado and co workers split the natural product into four fragments utilizing a catalytic, asymmetric cyclocondensation reaction to engender enantioenriched β-methyl hydroxy acid **111** (Scheme 1.35).[228] Modifications of the AAC conditions developed by Nelson,[223a] with Al(II) catalyst **105** (formed *in situ*),[229] produced the cross aldol-lactonization of aldehyde **109** and acetyl bromide **99** in excellent yield. (The authors

make no note of the enantioselectivity in their SI or original manuscript). Dimethylcuprate addition facilitated C-O_{alkyl} bond cleavage providing rapid access to the optically active building block **111** for completion of the synthesis, establishing the β-methyl stereocenter of the macrolactone further exhibiting the usefulness of methylketene equivalents.

Scheme 1.35

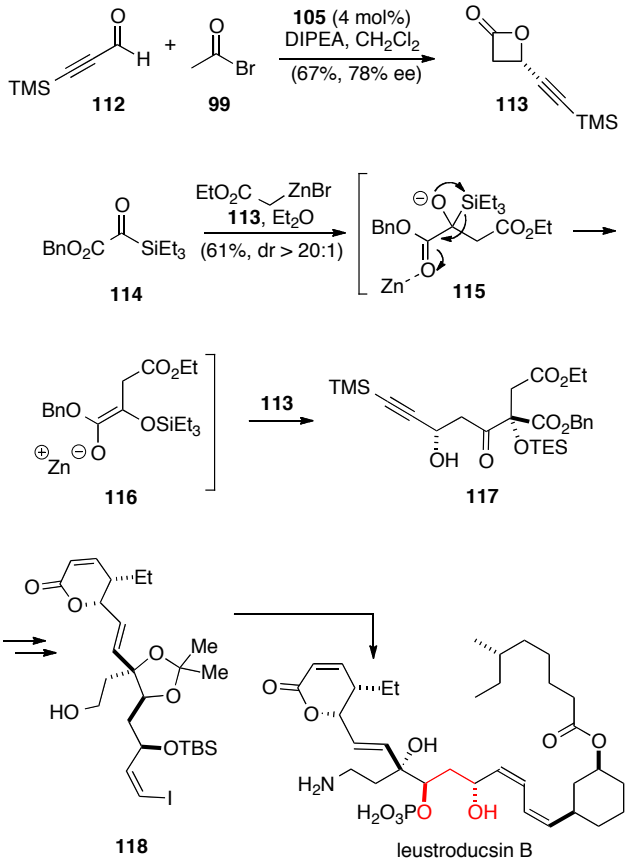


1.3.2.3. Leustroducsin B

A novel application of enantioenriched β-lactones from the AAC reaction was reported by Johnson and coworkers in the formal synthesis of leustroducsin B instituting a tandem multi-component reaction sequence (Scheme 1.36).[230,231] Reformatsky reaction of (2-ethoxy-2-oxoethyl)zinc(II) bromide and silyl glyoxylate **114** followed by a [1,2]-Brook rearrangement delivered intermediate enolate **116**. Ensuing Claisen reaction with β-lactone **113** serving as an electrophilic trap and incipient C-O acyl bond cleavage generated the complex linear fragment **117** as a single diastereomer through 1,4-

induction from the optically active β-lactone. Subsequent transformations delivered known intermediate **118** previously reported in the completed synthesis the Imanishi group.[232] The disparate nature of the β-lactone annulled the requirement for sequential addition of reagents as with previous endeavors employing ketones[233] due to the indiscriminate nature of the Reformatsky reagent. Additionally, the strain associated with the β-lactone ring elicited reactivity similar to an aldehyde serving as a suitable carbonyl motif, diminishing competitive reaction with the Reformatsky reagent.[230]

Scheme 1.36.



Diastereoselectivity is premised on a closed transition state, with the *in situ* formed zinc-enolate adopting the appropriate geometry through 7-membered ring chelate **I** and **II**

(Figure 15). Approach of the enolate is postulated to be from the less hindered diastereotopic face of the β-lactone through 1,4-stereoinduction exclusively delivering **117**. The multicomponent sequence stands as a testament to the utility of β-lactones for transferring chirality to the newly generated quaternary center, as all carbon quaternary centers in the realm of asymmetric synthesis are difficult to construct especially in acyclic settings.[234,223a,235]

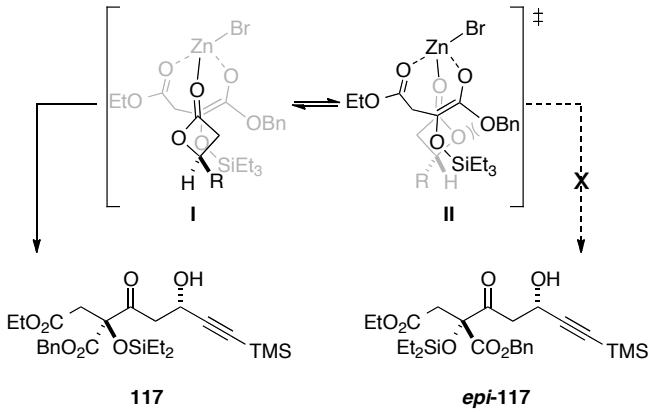


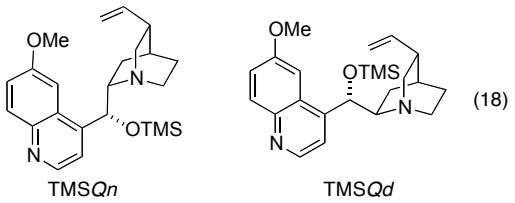
Figure 15. Johnson's proposed transition states for diastereoselectivity.[230]

1.4. Intermolecular Lewis Base Nucleophile Catalyzed Aldol-Lactonization

1.4.1. Introduction and Mechanism

Lewis base catalyzed net [2+2] cycloadditions have also been well documented in the literature as reliable methods for the synthesis of versatile optically active β-

lactones. Wynberg's pioneering research developing a catalytic asymmetric β-lactone synthesis with cinchona alkaloid catalysts TMS*Qd* or TMS*Qn* (Eq. 18) served as the standard for preparing optically active β-lactones under Lewis base catalysis.[3,236]



(18)

The generally accepted mechanism for the Wynberg Lewis base catalyzed net [2+2] employs a chiral tertiary amine nucleophile ($^{*}NR_3$, historically TMS*Qd* or TMS*Qn*) adding to the electrophilic ketene creating an ammonium enolate intermediate (Figure 16). Intermolecular aldol with an activated, non-enolizable aldehyde (here chloral) and ensuing β-lactonization regenerates the catalyst and delivers the optically active β-lactone. The Lewis base catalyzed variant involves a stepwise mechanism and can generally be coined as a nucleophile catalyzed aldol-lactonization (NCAL) process.

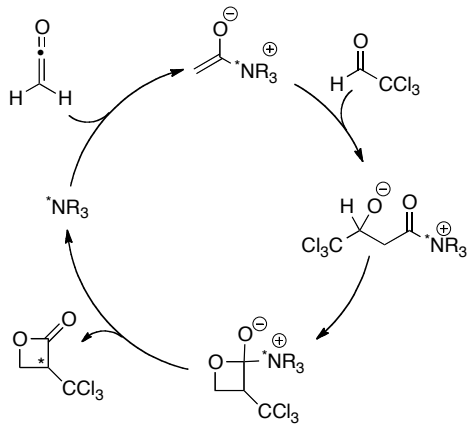
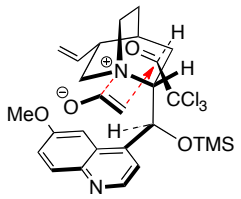


Figure 16. Lewis base catalyzed net [2+2] cycloaddition. [237]

Cinchona alkaloids have proven to be predictable and robust catalysts for the synthesis of optically active β-lactones with Wynberg proposing ketene activation.[3] Chiral ammonium enolates, obtained by nucleophilic attack of cinchona alkaloids have been suggested to explain asymmetric induction by Wynberg,[236b,238] Romo,[239] Nelson,[235a] and Armstrong.[240] Preferential nucleophilic attack by the N_{sp3} quinuclidine nitrogen permits catalytic asymmetric induction from the more stable quinculidinium ion than corresponding attack of the N_{sp2} delivering the quinolinium ion. Enantioselectivity arises from approach of the aldehyde from the β-face of TMS*Qd*-ammoninium enolate (Eq. 19). [236b,241]

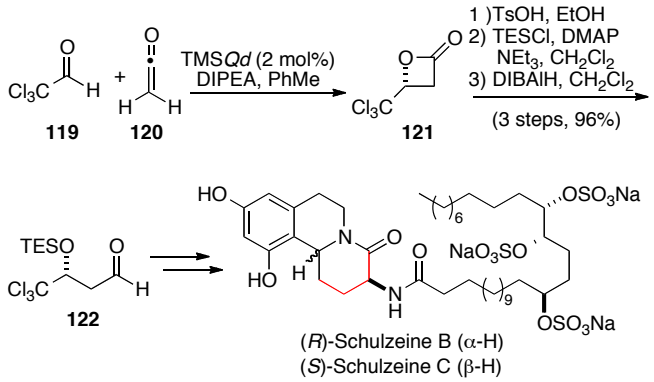


(19)

1.4.1.1. Schulzeine B and C

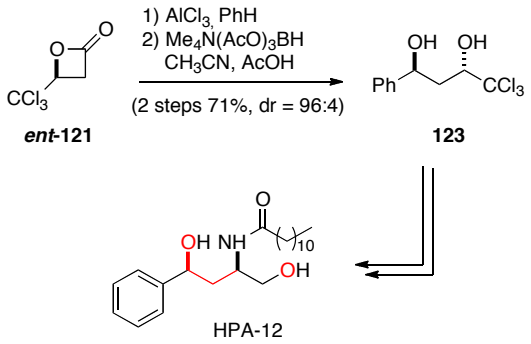
Romo and Liu employed Wynberg's (*R*)-trichloromethyl-β-lactone (**121**),[3] which is now commercially available, as a versatile and readily accessible chiral starting material to in the first reported synthesis of schulzeine B and C (Scheme 1.37).[242] Silyl protection following alcoholysis, and DIBAlH reduction delivered enantioenriched aldehyde **122**[243] serving to effectively install three carbons and one stereocenter into the nanomolar α-glucosidase inhibitors[244] schulzeine B and C. [242]

Scheme 1.37



Wynberg's (*S*)-β-lactone prepared using the pseudoenantiomeric catalyst TMS*Qd*,[3] provided expedient delivery to the nanomolar ceramide transfer protein inhibitor HPA-12 in five steps (Scheme 1.38).[245] Friedel-Crafts acylation followed by tetramethylammonium triacetoxyborohydride reduction[246] furnished the *anti*-diol **123** *via* 1,3-direction in 71% and high diastereoselectivity. Wynberg's β-lactone (both *R* and *S* enantiomers) have found widespread application as commercially available chiral pool, being increasingly utilized as commodity chemicals for various synthetic endeavors.

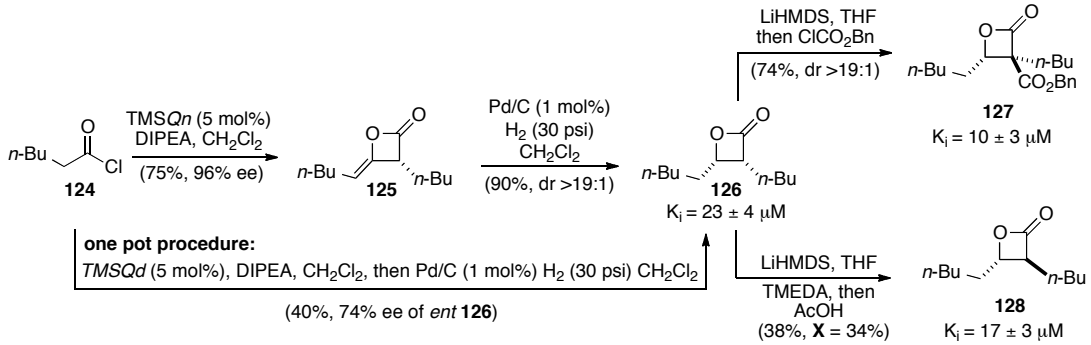
Scheme 1.38



1.4.1.2. Fatty Acid Synthase Inhibitors

Calter's Lewis base catalyzed procedure for the synthesis of enantiomerically pure ketene dimers proved fruitful while developing a one-pot ketene dimerization-hydrogenation sequence to fatty acid synthase (FAS) inhibitors (Scheme 1.39).[13c,203] Employing chiral Lewis base TMS*Qd* for dimerization of acid halide **124**, direct filtration after cyclization for removal of quaternary ammonium salts and immediate hydrogenation delivered *cis*-β-lactone **126**. When employing a one-pot procedure the fatty acid synthase inhibitor **126** (K_i = 23 ± 4 μM, apparent inhibition constant against FAS thioesterase domain) suffered from diminished yield (75% to 40 %) and enantioselectivity (ee 96% to 74%) compared to purification of the dimmer prior to hydrogenation.[247] Nevertheless offering a facile procedure to accessing optically active *cis*-β-lactone derivatives of **126**.The resulting product from the one-pot or two-step procedure was functionalized to the more potent inhibitor **127** through enolate acylation generating a new quaternary center. *Trans*-substituted β-lactone core **128** too employed LiHMDS for epimerization of the α-stereocenter. A plethora of derivatives employing the sequences outlined in scheme 1.39 were synthesized for biological screening comparing efficacy to known FAS inhibitor tetrahydrolipstatin.

Scheme 1.39[247]

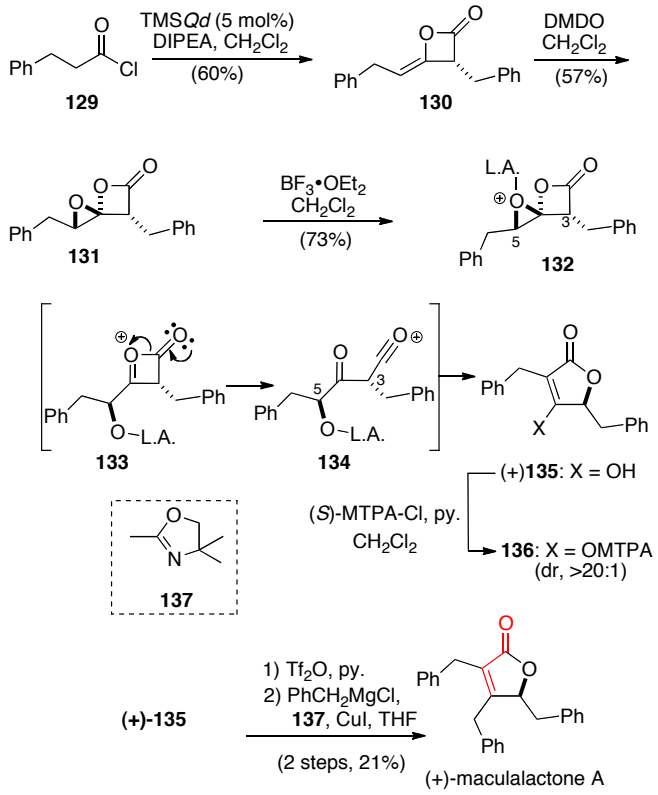


1.4.1.3. (+) Maculalactone A

Expanding the applications of Wynberg's β-lactone synthesis and Calter's ketene dimerization, Romo described a novel and concise route to the γ-lactone derived natural product (+)-maculalactone employing an unusually stable spiroepoxy-β-lactone as the key intermediate (Scheme 1.40).[248] Optically active β-lactone **130** was easily accessed implementing Calter's organocatalytic ketene dimerization[13c] of 3-phenylpropanoyl chloride with TMS*Qd* in 60% yield, with *z*-olefin geometry.[247] Epoxidation mediated by DMDO (dimethyldioxirane) generated the dibenzyl spiroepoxy-β-lactone **131**, in 57% yield, which was isolated and purified by chromatography with silica gel. Romo reported this and derivatives of 1,4-dioxaspiro[2.3]-hexan-5-ones[249] as a new class of heterocycles whose prior existence was unknown, and revealed their relative stability, ~7 days when stored purified at -20°. Lewis acid mediated rearrangement established the γ-lactone core presumably through coordination of the epoxide facilitating the cleavage to oxocarbenium **133**. Acyllium intermediate **129,** fostered by lactone ring-opening, followed corollary cyclization with the Lewis acid stabilized alkoxide delivering to the

γ-lactone core. Recrystallization afforded tetronic acid **135** in 86% yield. To confirm the enantiopurity at this stage, Mosher ester **136** revealed no stereochemical erosion during cyclization. The final feat to the natural product involved triflate formation and Negishi cross coupling with benzyl cuprate facilitated by oxazoline ligand (**137**).[250] The β-lactone **130** not only served to establish absolute stereochemistry and incorporate three carbons and one oxygen directly but also expanded the confines of β-lactones exuding a new heterocycle in the process.

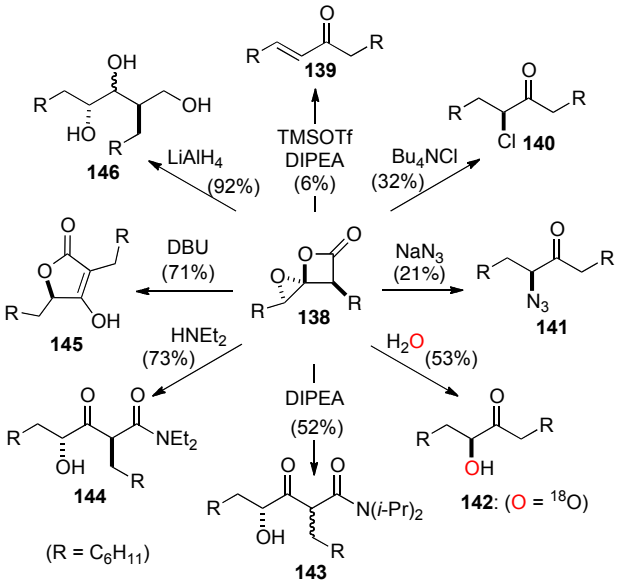
Scheme 1.40



In addition to the aforementioned Lewis acid/Lewis base mediated cyclization, preliminary studies by the Romo group revealed the unique reactivity of spiroepoxy β-

lactones.[249] One can envision four major modes of functionalization stemming from the three reactive centers in the highly strained spirocycle **138**. Functionalization to enone **139**, albeit in low yield, was accomplished with TMSOTf (Trimethylsilyl trifluoromethanesulfonate) and DIPEA (Scheme 1.41). Tetrabutylammonium chloride (Bu_4NCl) and sodium azide delivered α-substituted ketones **140** and **141**, respectively presumably *via* invertive epoxide cleavage followed by lactone ring opening and decarboxylation. This pathway was confirmed by the incorporation of ^{18}O, through the addition of neutral water (**142**). As an alternative method to generate a tertiary amide restricting the α-center from epimerization, N,N-diisopropylethylamine was added to the spiroepoxy-β-lactone **138** delivering the 1,3-dicarbonyl as a 1:1 mixture of diastereomers, while diethylamine provided a single diastereomer of **144**. Interestingly, the non-nucleophilic base DBU produced butenolide **145**, similarly to butenolide **135** (Scheme 40). Triol **146** was obtained by reduction with $LiAlH_4$ as expected in good yield.

Scheme 1.41[249]



1.5. Intermolecular Lewis Acid Lewis Base Nucleophile Catalyzed Aldol-Lactonization

1.5.1. Introduction and Mechanism

The synergistic combination of Lewis acid and base catalysis has found widespread success in the synthesis of complex optically active β-lactones (Figure 17). Cinchona alkaloid-Lewis acid catalyst systems are marked by the exceptional enantio- and diastereoselectivity observed bestowing more flexible and general routes to highly substituted β-lactone motifs.[223b] Advantages of this cooperative catalyst combination, TMS*Qd*/TMS*Qn* and $LiClO_4$ include participation of sterically hindered aldehydes, notably the addition of α-branching, having previously been inert with Al(III) Lewis acid variant and extensions to substituted *in situ* ketenes previously not permitted.[223b]

While Calter's cinchona alkaloid and scandium triflate catalyst system is prominent for accessing disubstituted β-lactones.[251] In 2008 the first report of cooperative catalysis, employing dual activation through Lewis acid and ammonium salt (Lewis base) catalysis, was shown by Peters for generating selective *trans*-β-lactones. [252]

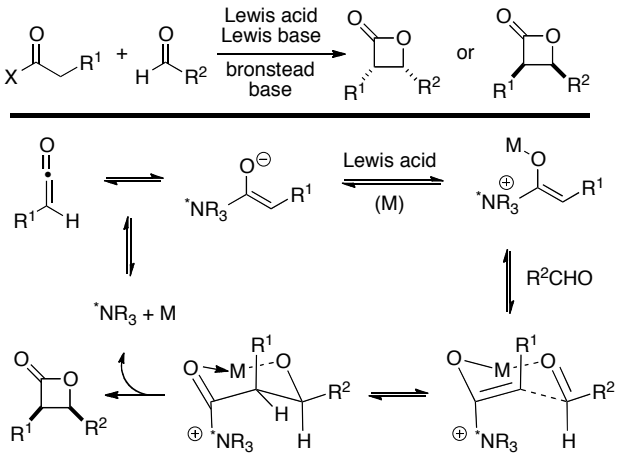


Figure 17. Proposed mechanism by Nelson of cooperative catalysis.[235a]

Whereas Lewis acid activation permits more electrophilic aldehydes compensating for the weakly nucleophilic ketene, Lewis base promoted ammonium enolate formation augments nucleophilicity to the ketene eliciting a mode of dual activation for both reaction partners (Figure 17). The co-catalyst system is a hybrid of each individual catalyst, ketene generation aided by Bronstead base sanctions ammonium enolate formation while Lewis acid activation of the aldehyde is postulated to invoke a closed transition state serving also to stabilize the enolate from a bidendate metal. A significant draw of employing Nelson's acyl halide-aldehyde

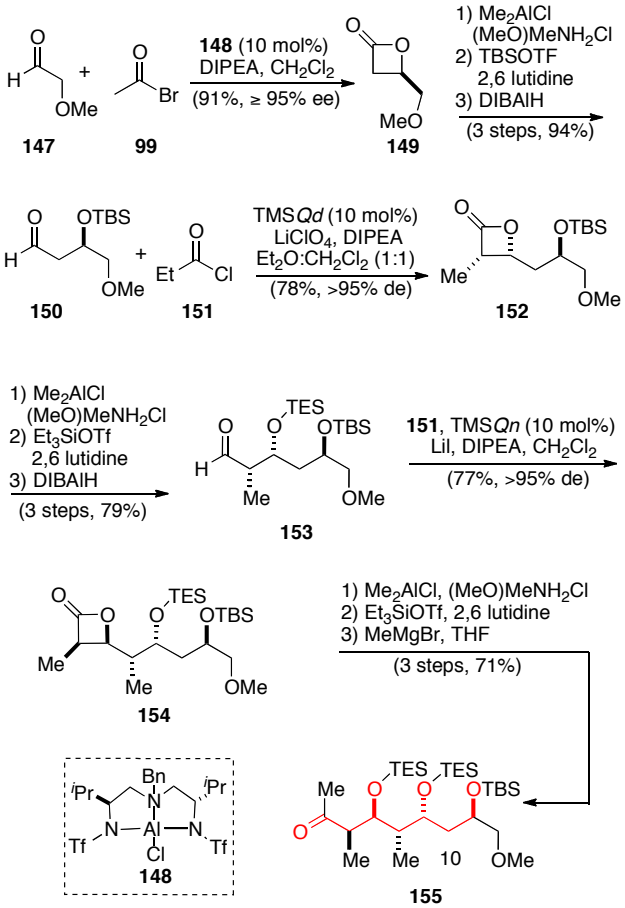
cyclocondensation (AAC) reaction is it is a catalytic, asymmetric aldol addition reaction. This in of itself eliminates the necessity for stochiometric chiral auxiliaries and improving synthetic efficiency, as there are no additional steps required for installing and destroying/recycling/or removing the auxiliary after the reaction. Exhibiting the magnitude of asymmetric aldol-based reactions for synthesizing repeating propionates in an *iterative* fashion.

1.5.1.1. Apoptolidin C Aglycon

Nelson and coworkers exploited the utility of the AAC reaction as a catalytic asymmetric aldol equivalent for assembling propionate linkages in the synthesis of apoptolidin C aglycon.[253] An approach of iterative assembly was employed whereby stereodefined polyketide units could be repetitively created using the AAC methodology (Scheme 1.42).[223a,235d,254] Commencing with β-lactone formation from acetyl bromide (**99**) and methoxyacetaldehyde (**147**), catalyzed by the chiral Al(III) complex **148** β-lactone **149** was provided in excellent yield and enantioselectivity.[223a,235d,254] To elongate the chain and allow for a second application of the AAC, the resulting β-lactone was converted to the Weinreb amide, followed by silyl protection, and DIBAlH-mediated reduction to chiral aldehyde **150**. The cinchona alkaloid *O*-trimethylsilylquinidine (TMS*Qd*) catalyzed the second cyclocondensation of **150** with propionyl chloride set the *syn* relationship of the propionate aldol β-lactone. Conversion of the β-lactone to another aldehyde equivalent (**152**) followed the same tactic, ring opening, protection, and reduction while the third AAC iteration employed *O*-trimethylsilylquinine (TMS*Qn*) to established the *syn,anti,syn* relationship of the alcohol functionality in β-lactone **154** in

77% as a single diastereomer. Completion of this fragment involved refunctionalization to methyl ketone **155** through amide formation, protection of the emergent alcohol, and addition of MeMgBr.

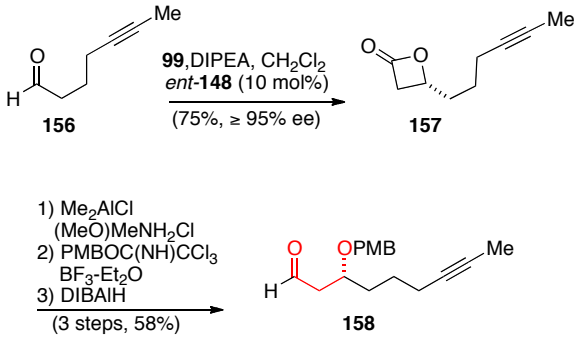
Scheme 1.42



Repetition of the aforementioned sequence yielded enantioenriched β-lactone **157** from cyclocondensation of 5-heptynal[255] and acetyl bromide (**99**) catalyzed by the enantiomer of **148** (Scheme 1.43). Recurring transformation to an aldehyde was prompted by amine

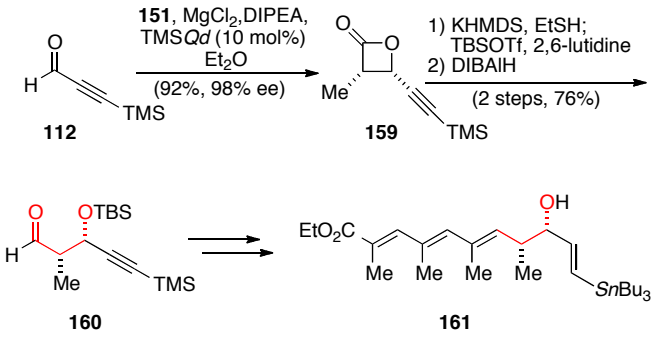
opening of the lactone, PMP protection of the incipient alcohol and DIBAlH reduction in 58% yield over the three steps.

Scheme 1.43



Assembly of the tetraene fragment **161** commenced with TMS*Qd* catalyzed AAC of 3-trimethylsilylpropynal (**112**) and propionyl chloride, producing β-lactone **159** with high levels of absolute and relative stereocontrol (Scheme 1.44). Here, Nelson and coworkers employed a condensed refunctionalization of the β-lactone moiety to an aldehyde with a two-step approach. A one-pot thioester formation and silyl protection of the incipient alcohol allowed for DIBAlH reduction directly to the aldehyde. The *syn* propionate aldol equivalent was then carried on to generate tetraene **161**.

Scheme 1.44



The end-game strategy to apoptolidin C aglycone stitched together all three fragments using classical transformations while highlighting utility of the AAC approach for generating aldol equivalents. Of the ten asymmetric centers, 8 were instituted from catalytic asymmetric Lewis acid or base catalyzed net [2+2] reactions using a diverse array of functionalized aldehydes for coupling with acid halides (Figure 18).[223a,235d,254]

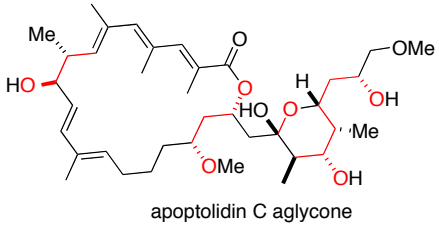


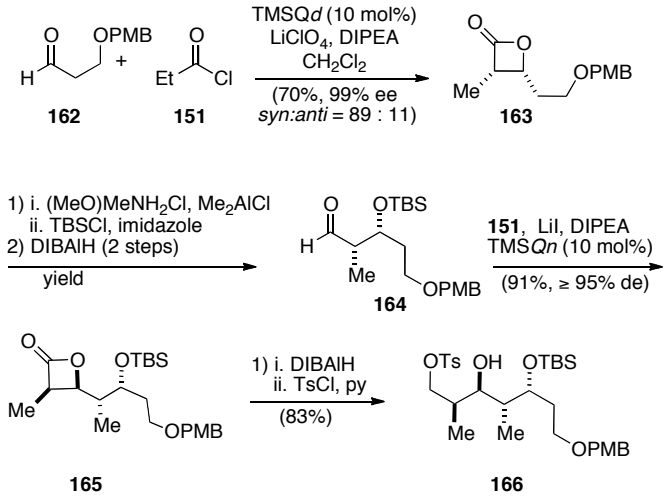
Figure 18. β-Lactone incorporation of apoptolidin C aglycone.

1.5.1.2. (-)-Pironetin

To test whether the catalyst would be able to override the stereochemical bias stemming from the alpha stereocenter of the aldehyde-coupling partner was explored in the synthesis of (-)-pironetin (Scheme 1.45 and 1.46). This was the first example of a matched/mismatched situation; during model studies for the iterative AAC reaction it was experimentally determined that there was a degree of double diastereoselection. These model studies uncovered the conditions for matched/mismatched between the substrate's and the catalyst's chirality. Synthesis of the polyketide commenced with AAC catalyzed by TMS*Qd* delivering syn β-lactone **163** from reaction of propionyl chloride and the PMB-protected aldehyde **162** with excellent enantioselectivity (99% ee)

and high diastereoselectivity (89:11, *cis*:*trans*)(Scheme 1.45). It was next carried onto a two-step procedure, ring opening to the Weinreb amide, protection of the resultant secondary alcohol as a silyl ether, and reduction to aldehyde **164** setting the stage for a second AAC reaction. This time being catalyzed by the pseudoenantiomeric catalyst TMS*Qn* to deliver the *syn*:*anti*:*syn* β-lactone **165** as a single diastereomer presumably through a matched catalyst/substrate system. Both AAC reactions established all four contiguous stereogenic centers in a catalytic asymmetric fashion. Reduction of **165** to the 1,3-diol and tosylation of the primary alcohol provided access to the highly oxygenated fragment **166**.

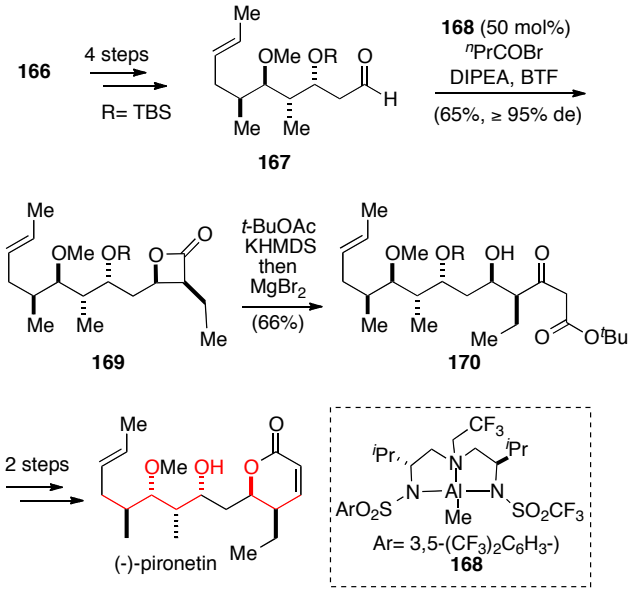
Scheme 1.45



The synthesis of (-)-pironetin was complete by caring on fragment **166** to aldehyde **167** for a four carbon homologation with butyryl chloride (Scheme 46).[230] The third AAC reaction could not be catalyzed by a cinchona alkaloid therefore Nelson and coworkers moved to Al(III) based Lewis acid **168**. While substantial increase in catalyst loading (50 mol%) produced a diminished yield, 65%, it exhibited flexibility in the

methodology that the Lewis acid mediated AAC is an alternative approach to the Lewis base or cinchona alkaloid catalyzed variant. The selectivity and predictably should exemplify the usefulness of this as an alternative to traditional aldol reactions employing chiral auxiliaries as six stereocenters were established with the AAC methodology serving as a potential solution to asymmetric aldol addition reactions, delivering *syn* propionate aldol equivalents.[235d] Subsequently β-lactone **169** was converted to β-keto ester **170** by the enolate of *t*-BuOAC mediated by $MgBr_2$ permitting selective ring opening and C-O acyl bond scission.

Scheme 1.46.

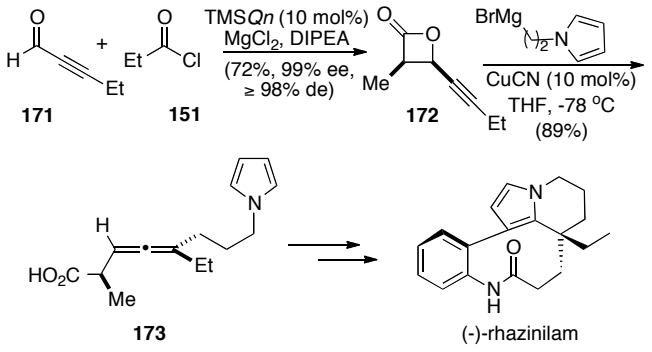


1.5.1.3. (-)-Rhazinilam

One of the most direct routes to optically active allenes for subsequent functionalization is realized through the appropriate opening of chiral β-lactones (Scheme 1.47). 2-Pentynal (**171**) and propionyl chloride (**151**) provided the allene

precursor in excellent yield as well as enantio- and diastereoselectivity, performing the net [2+2] catalyzed by TMS*Qd*.[223,235a] Cu-Mediated S_N2' ring opening of the optically active β-lactone **172** by the pyrrole based Gringard gave way to the chiral β-allenic acid **173**. The remote alkyne of **172** was predicted to be the site of addition due to the stereoelectronic effects of both reactant and reagent (*supra vida*), serving to dictate the selectivity and deliver a single diastereomer of the optically active allene. This transfer of chirality between the β-lactone and allene was further propagated by serving to establish the absolute stereochemistry of the resulting quaternary carbon in (-)-rhazinilam after metal-catalyzed cyclization (not shown). Although none of the oxygen functionality resulting from the β-lactone was incorporated into the final natural product structure, the necessary quaternary carbon center could not have been established without the chiral allene intermediate. Synthetically the β-lactone moiety served as a means to replace chiral ligands for the metal–catalyzed cyclization that ensued. In this regard the alkyne substutient of β-lactone **172** functioned as an activated propargylic ether.[71]

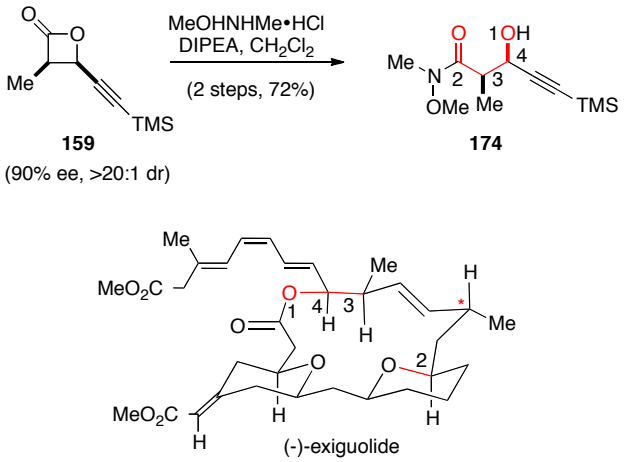
Scheme 1.47



1.5.1.4. (-)-Exiguolide

Scheidt and co workers reported an extraordinary example of repurposing the β-lactone skeleton for completing the 3rd reported synthesis of the structurally intriguing 16-membered macrolactone (-)-exiguolide (Scheme 1.48).[256] Enlisting the efficient and well-established methods for catalytic asymmetric formation of β-lactone's, **159** (reported in Scheme 1.44) was directly converted to Weinreb amide **174**. Though using aforementioned methodology for forming the β-lactone and functionalizing it, the synthesis highlighted the β-lactone for establishing the absolute stereochemistry of the methyl and the hydroxy group of **174**, which were pivotal in key steps of the synthesis. The hydroxy group later underwent an Eschenmoser-Claisen rearrangement diastereoselectively, establishing the stereocenter in exiguolide denoted with a red asterisk. While the C_2 position of the β-lactone is incorporated in the tetrahydropyran ring from a stereoselective dioxinone-directed Prins cyclization. In this elegant synthetic design Scheidt showed the incorporate of the β-lactone in a novel way, cleaving first the C_2-O_1 bond by amide formation and subsequently the C_2-C_3 bond while maintaining the stereochemical integrity at both asymmetric centers. This exemplified the notion that the carbons and oxygen incorporated form β-lactone intermediates don't necessarily have to remain as a consecutive 3-carbon chain or as a 1,3-oxgyen functionality.[223]

Scheme 1.48

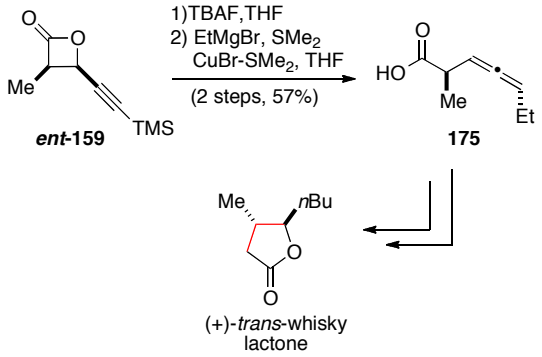


1.5.1.5. (+)-*Trans*-Whisky Lactone

A drastically different approach for repurposing intermediate **159** was through allene **175** to a chiral γ-butyrolactone core (Scheme 1.49). Attention has been paid to chiral γ-butyrolactones due to both their bioactivity[257] and application as building blocks in the synthesis of more complex molecules.[258] Ma and coworkers made use of Nelson's[71] two step route to chiral allenes from aldehyde and acyl halide precursors in their synthesis of (+) and (-)-*trans*-whisky lactones.[259] *Cis*-alkynl β-lactone **159**, generated using the AAC[235a,260] reaction (*vida supra*) between 3-(trimethylsilyl)propynal[261] and propionyl chloride with the appropriately selected chiral catalyst, TMS*Qn* proceeded in both high yield and enantioselectivity. Subsequent TBAF (tetra-*n*-butylammonium fluoride) removal of the silyl group and S_N2'-type ring opening with EtMgBr, mediated by CuBr-DMS, delivered chiral 3,4-allenoic acid **175**. Ma and coworkers took advantage of the chiral allene to perform a diastereoselective

halolactonization to deliver (+)-*trans*-whisky lactone. The (-) enantiomer was synthesized similarly employing TMS*Qn* to catalyze the AAC reaction.

Scheme 1.49

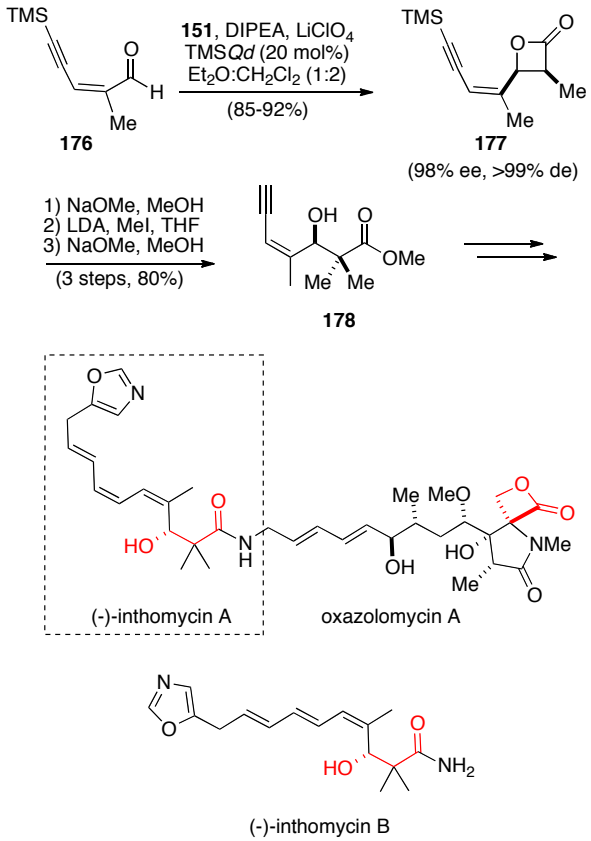


1.5.1.6. (-)-Inthomycins A-C and Oxazolomycin A

In order to provide convenient templates to various members of oxazolo-triene antibiotics Hatakeyama reported a convergent tactic to the olefin isomers, inthomycins of A-C (Scheme 1.50 and 1.51), with inthomycin A (Scheme 1.50, boxed, amide = NH_2) being the left handed segment of oxazolomycin A (*vida supra*).[148] The potent and varied biological activities include but are not limited to antitumor, antibacterial, and antiviral,[147] with inthomycin A acting as a strong inhibitor of prostate cancer cell growth and has prompted alternative approaches for their rapid assembly.[262] [148] [263] The general route to the triene fragment was reported with Nelson's catalytic enantioselective acyl-halide aldehyde cyclocondensation reaction building on the work from their previously reported synthesis of neooxazolomycin.[264] Though many ynal's have been used with this cinchona alkaloid-catalyzed reaction (*supra vida*) conjugated ones as **176** and **179** have been infrequently employed.[235d,265] Previously attempting the net [2+2] of aldehyde **176**

with TMS*Qd* and isobutyryl chloride, or dimethylketene with Fu's catalyst[266] delivered no desired β-lactone. Thus showing some limitations of the methodology in that the all carbon quaternary center α- to the lactone is now amenable with conjugated aldehydes such as **176**.

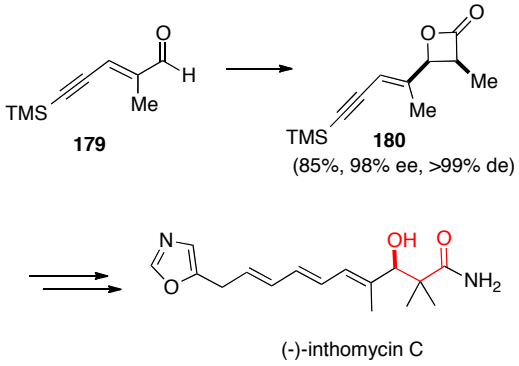
Scheme 1.50



Commencing the synthesis with known *Z*-eneyne aldehyde **176**[267] and *E*-eneyne (**179**) organocatalytic asymmetric [2+2] cycloaddition developed by Nelson delivered β-lactones **177** and **180** respectively in 85-92% yield with excellent enantio- and diastereoselectivity (Scheme 1.51). The β-lactone **177** was opened to the methyl ester with sodium methoxide, methylated and desilylated giving β-hydroxy esters **178**, with β-

lactone **180** following suit. To distinguish between oxazolomycin A/inthomycin A and inthomycin B later transformations involved stereoselective iodination diimide reduction or hydrozirconation iodination. While inthomycin C's *E,E* olefin geometry was established from a stanyl-cuprate addition. The success of these investigations put forth the growing applications and power of cyclocondensation methods for generating increasingly complex optically active β-lactone intermediates.

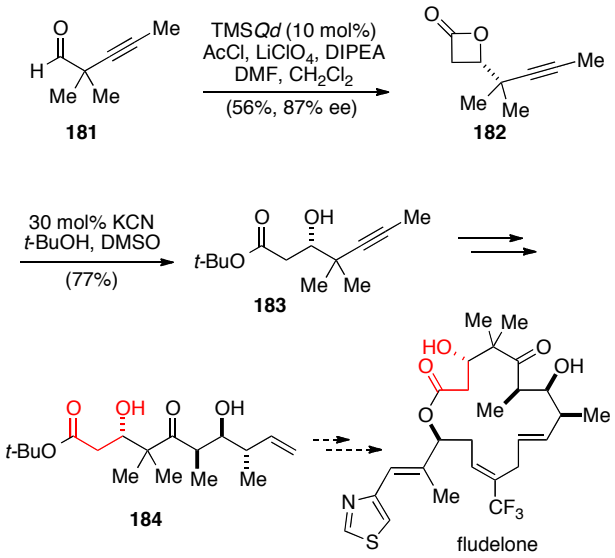
Scheme 1.51



1.5.1.7. Fludelone

Nelson's AAC methodology has proven to be powerful in its application to total synthesis, as Leighton and coworkers made use of it for a fragment towards the synthesis of fludelone (Scheme 1.52).[268] Alkynl-aldehyde **181** and propionyl chloride revealed β-lactone **182** in 56%, and insipient alcoholysis delivered the *t*-butylester **183**. Extraordinarily, the alkynyl-α-quaternary substituted aldehyde did not hamper the transformation under the generally utilized reaction conditions.

Scheme 1.52

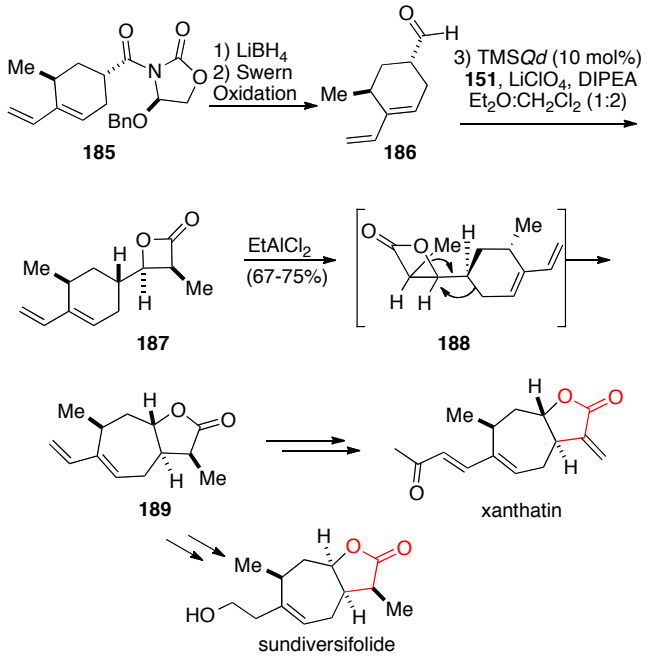


1.5.1.8. Xanthane-Type Sesquiterpenoids

Expanding on the first reported rearrangement of β-lactones to γ-butryloactones by Mulzer and Bruntrup[65,269] Tang and coworkers developed a controllable Wanger-Meerwein-type dyotropic rearrangement of *cis*-β-lactones to γ-butryloactones.[270] The necessary enantioenriched β-lactones were synthesized using the organocatalyzed reaction pioneered by Nelson[235a] propionyl chloride and aldehyde **186** with cinchona alkaloid catalysis (Scheme 1.53). Oxazolidinone **185** went through a consecutive reduction, oxidation, and organocatalytic asymmetric [2+2] cycloaddition to *cis*-substituted β-lactone **187** in 55% yield over the three steps on a 2 g scale. Aimed at expanding the scope a $EtAlCl_2$-mediated dyotropic rearrangement of the *cis*-β-lactone delivered *trans*-fused γ-butryloactone-cycloheptene **189**, in 67-75% yield (100-500mg respectively), a known intermediate. Having a robust scaleable route to the *trans*-5-7

ring system permitted a formal synthesis of xanthatin[271] along with various xanthane-type sesquiterpenoids, and the first completed synthesis of sundiversifolide.

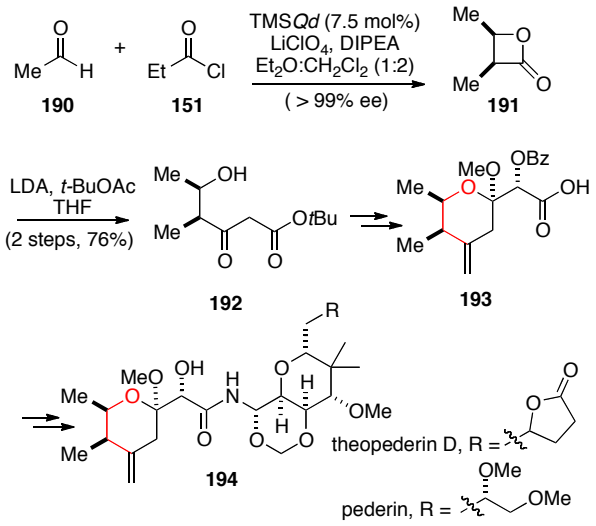
Scheme 1.53



1.5.1.9. Pederin and Theopederin. Exploiting the use of β-lactones as effective acylating agents Floreancig[272] and coworkers set out to develop a catalytic asymmetric method for construct of the acyl subunit **192**, a common intermediate toward synthesizing pederin and theopederin (Scheme 1.54). Asymmetric induction in previous syntheses arose from chiral pool, stochiometric chiral auxiliaries or reagents, therefore in developing a more practical protocol Floreancig turned to a catalytic asymmetric synthesis of β-lactone **191**. Here the volatile β-lactone **191**, serving an effective aldol surrogate, was synthesized enantio- and diastereoselectively *via* TMS*Qn*-catalyzed cyclocondensation of acetaldehyde with propionyl chloride.[235a] This was immediately reacted with the lithium enolate of *t*-BuOAc to afford the β-hydroxy-1,3-dicarbonyl **192**.

Subsequent transformations were in accordance with Nakata's route[273] to des-methylene pederic acid derivative **193**. Late stage synthesis of pederin and theopederin involved amide coupling of the des-methylene pederic acid derivative **194.**

Scheme 1.54

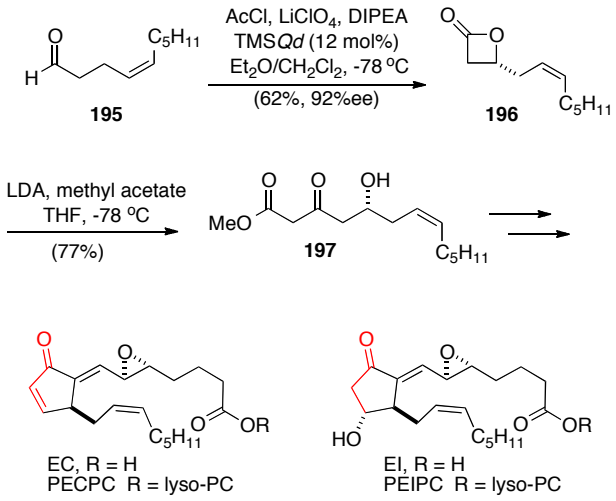


1.5.1.9. Epoxyisoprostaines

Understanding or testing of biological function(s) of natural products for their potential as therapeutic agents is often the driving force for developing more efficient and practical synthetic routes, as is the case with the epoxyisoprostanes. Carriera and coworkers chose commercially available (*Z*)-decenal **195** and acetyl chloride, commencing the synthesis with a cinchona alkaloid catalyzed AAC reaction to deliver β-lactone **196** (Scheme 1.55).[274] Following lactonization, ring opening mediated by the lithium enolate of methyl acetate generated the acyclic (*Z*)-alkenyl-dicarbonyl **197**, with the β-lactonization event serving to establish the absolute stereochemistry of the β-

hydroxy group whose chirality was transferred to the alkenyl substituted carbon in later transformations to EI and PEIPC, as well as the dihydro derivatives EC and PECPC.

Scheme 1.55



1.5.1.10. Erythronolide B

To truly exemplify the power of iterative acyl-halide aldehyde cyclocondensation reactions for generating stereodefined polypropionate fragments,[254] and the ease with which they can be employed in complex natural product synthesis Nelson and coworkers completed erythronolide B (Figure 19 and Schemes 1.56 and 1.56).[275] Since β-lactones are well known to be aldol surrogates the natural product can be retrosynthetically dissected to several fragments for stereoselectively installing 5 of the 7 oxygens (Figure 19). Disconnection to propionate triene fragments A and B permits subsequent breakdown to several readily accessible ketene and aldehyde precursors. This highly convergent approach allows for simple iterations as each fragment can be employed with different catalyst systems for defining absolute configuration when retrosynthetically

dissecting molecule Nelson synthesized erythronolide B.[275] The retrosynthetic design employs a methyl ketene on three separate occasions times, which is readily accessed from *in situ* reaction with propionyl chloride and base for defining the C_2, C_3, C_8, C_{10}, and C_{11} centers of erythronolide B.

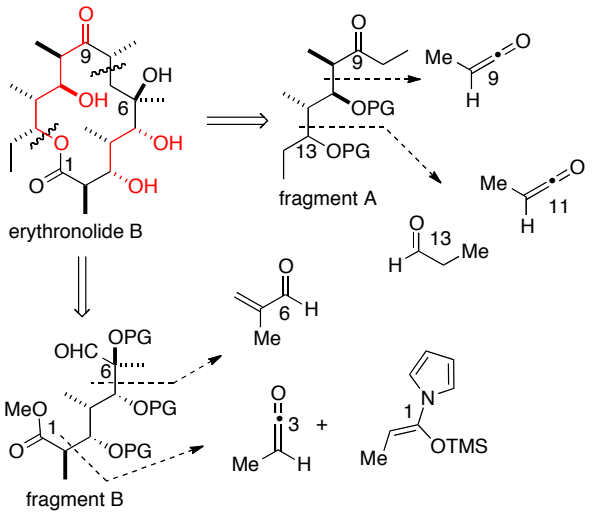
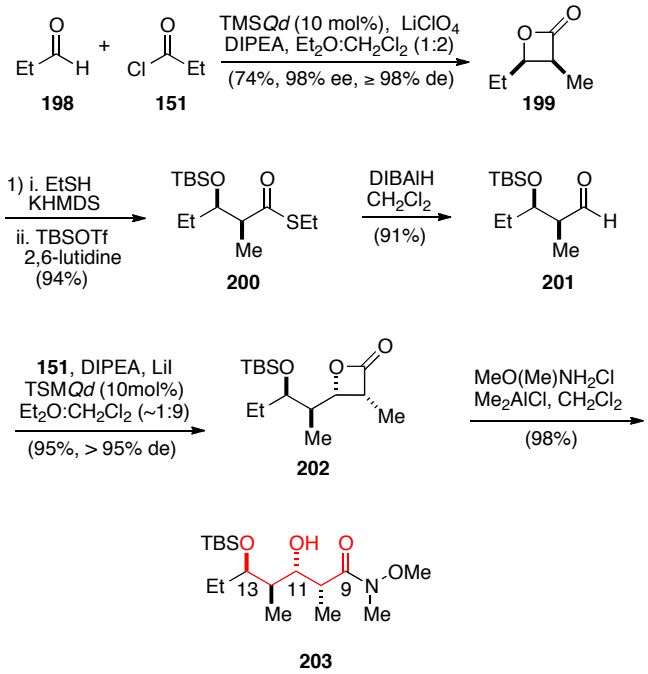


Figure 19. Deconstruction of erythronolide B.

The C_9-C_{13} portion initiated by a propionate homologation cycloaddtion sequence of propionaldehyde and propionyl chloride with TMS*Qd* rendered *cis*-β-lactone **199**, whose direct conversion to the aldehyde for an iteration of the AAC reaction was achieved by addition of ethylthiolate (Scheme 1.56). Pre-generation of the anion with KHMDS (potassium bis(trimethylsilyl)amide) ensured C-O acyl bond scission, and quenching with TBSOTf (*tert*-Butyldimethylsilyl trifluoromethanesulfonate) delivered the β-siloxy thioester **200**. DIBAlH- mediated

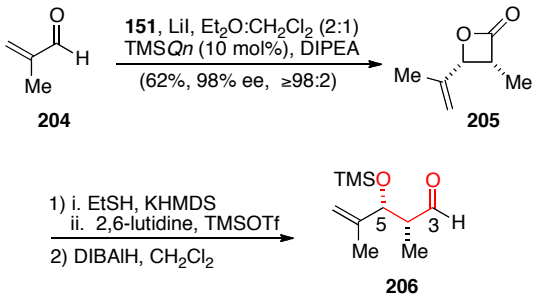
reduction to aldehyde **201** permitted a second AAC employing the same conditions as the first iteration providing the *syn*, *anti, syn* β-lactone trimer **202** with high diastereoselectivity (>95% de). Functionalization of the second lactone with *N,O*-dimethylhydroxylamine to the Weinreb amide fostered subsequent carbon homologation to **203**.

Scheme 1.56



Introduction of the C_3-C_5 centers by the cinchona-alkaloid-catalyzed cyclocondensation engaging methacrolein **204** and propionyl chloride with TMS*Qd* to *syn*-β-lactone intermediate **205** (Scheme 1.57). This lactone was then transformed to the β-siloxy aldehyde **206** by way of ethylthiolate ring opening and TBS protection of the liberated alcohol and reduction by DIBAlH.

Scheme 1.57



The power of this Lewis base catalyzed net [2+2] is assessed in the direct formation of six of the ten stereocenters in erythronolide B, with the remaining instituted from diastereoselective transformations of the AAC established centers (Figure 19).

1.6. Intramolecular Nucleophile Catalyzed Aldol-Lactonization

1.6.1. Introduction and Mechanism

While investigating an intramolecular variant of the Wynberg synthesis Romo and coworkers developed a method for generating novel β-lactone scaffolds from unactivated carbonyl's through a tandem nucleophile catalyzed aldol-lactonization (NCAL).[239a,239b,239c,276,277] The pioneering NCAL process of carboxylic acids tethered to carbonyl electrophiles (aldehydes or ketones) serves as a general method for accessing optically active substituted β-lactones rapidly.[204,278,279,280] The Lewis base or nucleophilic catalysts makes use of acylammonium and ammonium enolate intermediates that Wynberg so classically forged with cinchona alkaloids for his enantioselective process.[3] Employing an intramolecular aldol-lactonization permits the use of 'unactivated' ketones or aldehydes as it minimizes entropic barriers that can be

problematic intermolecularly.[281] Therefore it is not necessary to have a highly electrophilic coupling partner, moving away from the requirement for a ketene generator or activated aldehyde (*i.e.* α-dihalogenated aldehydes or Lewis acid activation) as is the drawback of the Wynberg procedure (Figure 20).[282] The intramolecular NCAL has been proposed once[283] and documented[284] however, Romo and coworkers reported the first catalytic, enantioselective, aldol-lactonization involving non-activated aldehydes providing absolute regio- and stereochemical control of the resultant bicyclic-β-lactone.[239c]

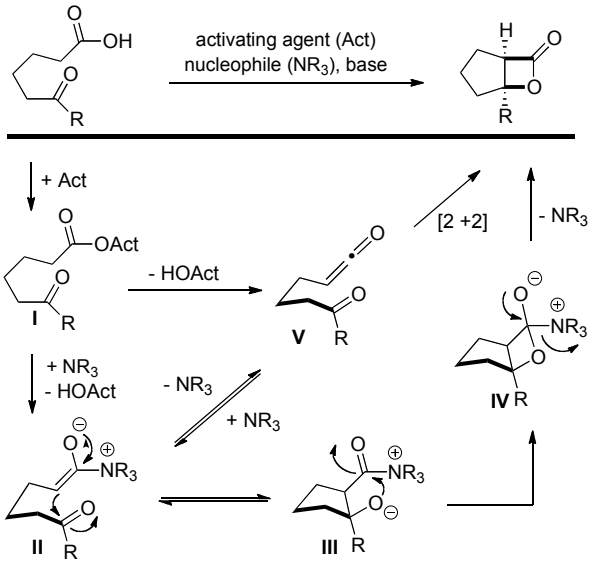


Figure 20. Proposed mechanism for NCAL process.

The generally accepted mechanism involves deprotonated of the carboxylic acid with a tertiary amine base, typically DIPEA, followed by carboxylic acid activation (Act,

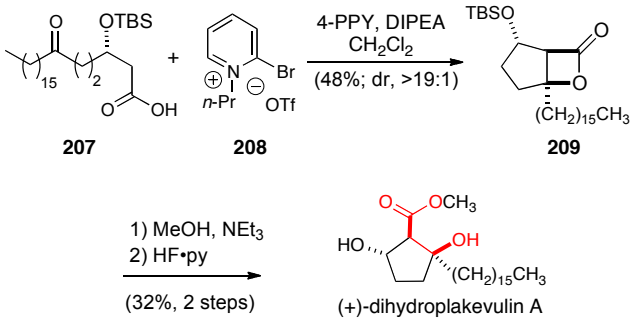
as seen in the CGA and HGA modes of cyclization) to activated acid **I** (Figure 20). Transacylation by an highly nucleophilic tertiary amine,[285,286] (DMAP, 4-PPY, *cinchona* alkaloids, etc.,) with ensuing deprotonation generates ammonium enolate **II**. Intramolecular aldol, and β-lactonization by an 'S_N2' process[287] (**II** to **III**) facilitates catalyst turnover delivering the bicyclic β-lactone.[235c,239c,247,278,288] While an intramolecular thermal [2+2] cycloaddtion,[284b,289] via ketene **V** has not been ruled out, high levels of enantioinduction from chiral tertiary amine nucleophiles suggest involvement of the nucleophile. [239c,288b,290] Early studies employing activating agent Mukaiyama's reagent,[291] and DMAP/4-PPy revealed no product was observed in the absence of base, serving as indirect evident for the transient ammonium enolate intermediate **II**.[288b] Thus far only *cis*-cyclopentyl fused β-lactones have been accessed presumably due to the ring constraints imposed by the pendant cyclopentane preventing the *trans*-β-lactone. The robust nature of the methodology is exemplified by the various natural products accessed and the ease of the protocol for gram scale preparation of bicyclic β-lactones. [290,280,277]

1.6.1.1 (+)-Dihydroplakevulin

Romo and coworkers circumvented the necessity of a highly electrophilic carbonyl for β-lactone formation in their synthesis of the DNA polymerase inhibitor dihydroplakevulin A (Scheme 1.58).[288b] Optically active keto-acid **207**, nucleophilic promoter 4-PPY, and the carboxylic acid activating agent, modified Mukaiyama's reagent **208** (2-bromo-*N*-propylpyridinium triflate)[292] with DIPEA lead to bis-cyclization providing bicyclic β-lactone **209** in moderate yield as a single diastereomer (dr > 19:1).

Methanolysis and silyl deprotection delivered (+)-dihydroplakevulin A. The nucleophile-catalyzed aldol lactonization effectively served to construction the cyclopentane core with the β-siloxy group relaying stereochemical bias for the aldol-lactonization in turn establishing the β-hydroxy ester's relative and absolute stereochemistry.

Scheme 1.58



1.6.1.2. (±)-Cinnabaramide A, (-)-Salinosporamide A, and (-)-Homo-salinosporamide

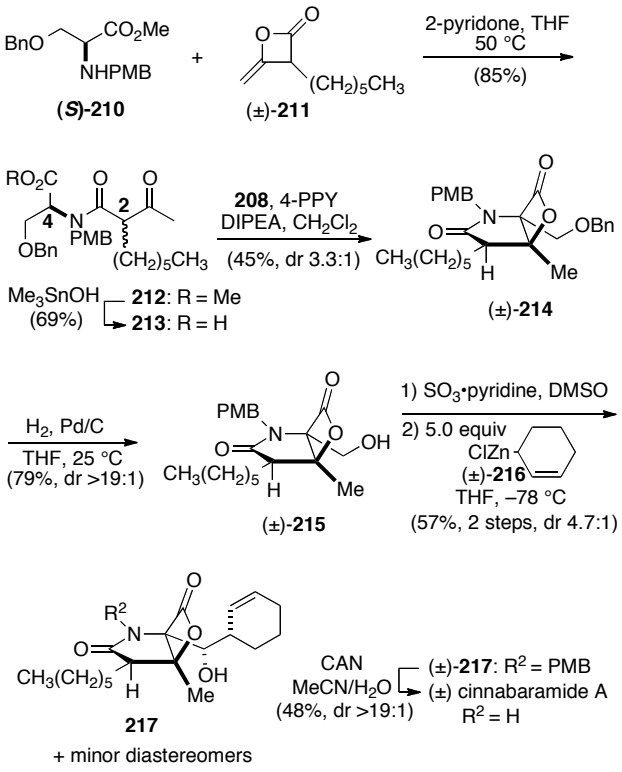
The Romo group also has shown significant interest in the γ-lactam fused β-lactone-containing proteasome inhibitors salinosporamide A, homosalinosporamide, and cinnabaramide A putting forth racemic and enantioselective syntheses using the NCAL for the key cyclization of the bicyclic core (Schemes 1.59-61).[276,293] Inspired by the NCAL process and applications to keto-acid substrates[288b] and expanding the work from carbocycle-fused β-lactones, a strategy to the core of these proteasome inhibitors was realized by simultaneous C-C and C-O bond formation from keto-acid precursor **213**.[276] The racemic synthesis of cinnabaramide A involved acylation of PMB-glycine benzyl ester **210** following Calter's procedure[13c] with unsymmetrical ketene dimer **211**[294] providing a 1:1 mixture of diastereomers of linear NCAL precursor **212** (Scheme 1.59).

Cleavage of the methyl ester with trimethyltin hydroxide[295] delivered keto-acid **213** which was subjected to the NCAL conditions similar to those reported for carbocycles[288b] with Mukaiyama's reagent (**208**) and 4-PPY delivering β-lactone **214** as a 3.3:1 mixture of diastereomers. During the course of the bis-cycliztion the ammonium enolate of **213** destroyed the C_4 stereocenter delivering a racemate of diastereomers in modest yield with the desired diastereomer being favored. The diastereoselectivity after hydrogenolysis, was enhanced (dr >19:1) owing to separation at this stage. Subsequent Parikh-Doering oxidation,[296] addition of zincate **216** following Corey's procedure[163a] (zincate was prepared immediately prior to addition using *n*-butyllithium, cyclohexenyl tributyltin, and $ZnCl_2$) and oxidative cleavage of the PMP group delivered cinnabaramide A as a single diastereomer. The onset studies demonstrated the tolerance of the labile β-lactone during zincate addition and oxidative deprotection, as being unaffected.

With the goal of ultimately developing an enantioselective synthesis it was essential to develop reaction conditions for the NCAL that minimized by-products and inhibited epimerization of the C2 stereocenter in **213** and correspondingly **218.** After carboxylic acid activation and nucleophilic displacement acy1 ammonium **220** could be deprotonated to reveal three conformations of the ammonium enolate **221** (Scheme 60). Having realized that **221** and **221'** were unproductive intermediates for the biscyclization as the ketone and ammonium enolate were not proximal to permit cyclization, they would ultimately equilibrate to the reactive conformation **221''** permitting preservation

of enantiopurity as the α-proton is in plane with the carbonyl of the amide stemming from $A^{1,3}$-strain.[297] Interestingly was the effect that the absolute stereochemistry of the

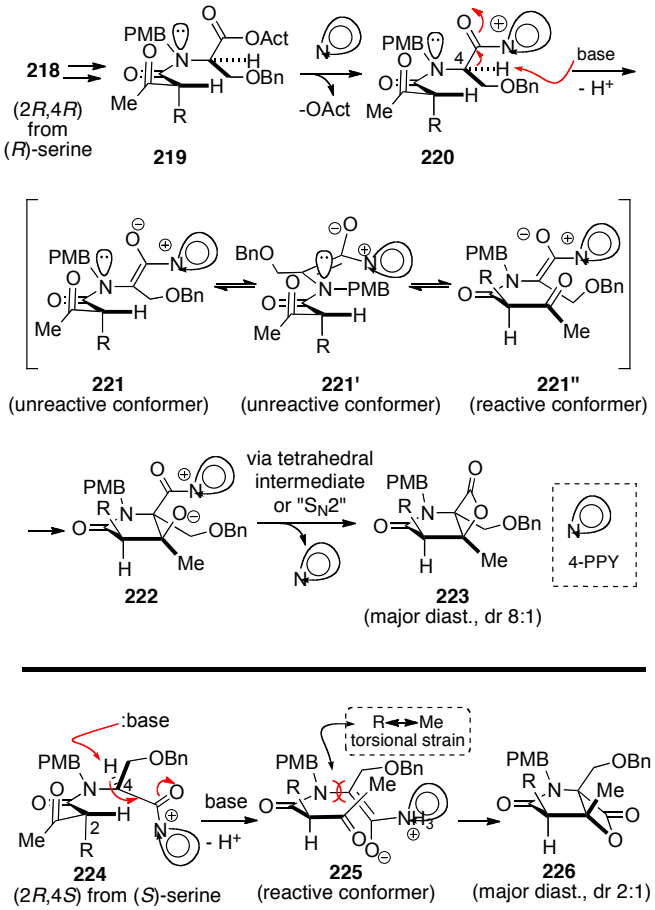
Scheme 1.59[293b]



C4 position, derived from (*S*) or (*R*)-serine, had on the diastereoselectivity. Discovering that (*R*)-serine derived keto-acid **221''** favored an 8:1 mixture with β-lactone **223** being the major diastereomer (Scheme 1.60), whereas (*S*)-serine keto-acid **224** provided a 1:2 mixture of diastereomers with β-lactone **226** favored. The diastereoselectivity arises from steric interactions in the initial aldol reaction, presumably the torsional strain that occurs with the methyl ketone and the substutient at C2 in **225** is void in **221** while the modestly favored intermediate dictates the relative stereochemistry for the ensuing

lactonization.[298] Romo and coworkers reported the possibility of a chiral memory effect whereby the absolute stereochemistry of C4 presumably from the required conformation for deprotonation stemming from the N-C4 rotamer of acyl ammoniums **220** and the diastereomeric **224** lead to ammonium enolates **221** and **225** respectively. In this case the (*R*)-serine derived acyl ammonium **220** delivers the N-C4 rotamer **221''** ultimately providing β-lactone **223** as the major diastereomer conversely (*S*)-serine derived acyl ammonium **224** provides access to **226** as the major diastereomer.

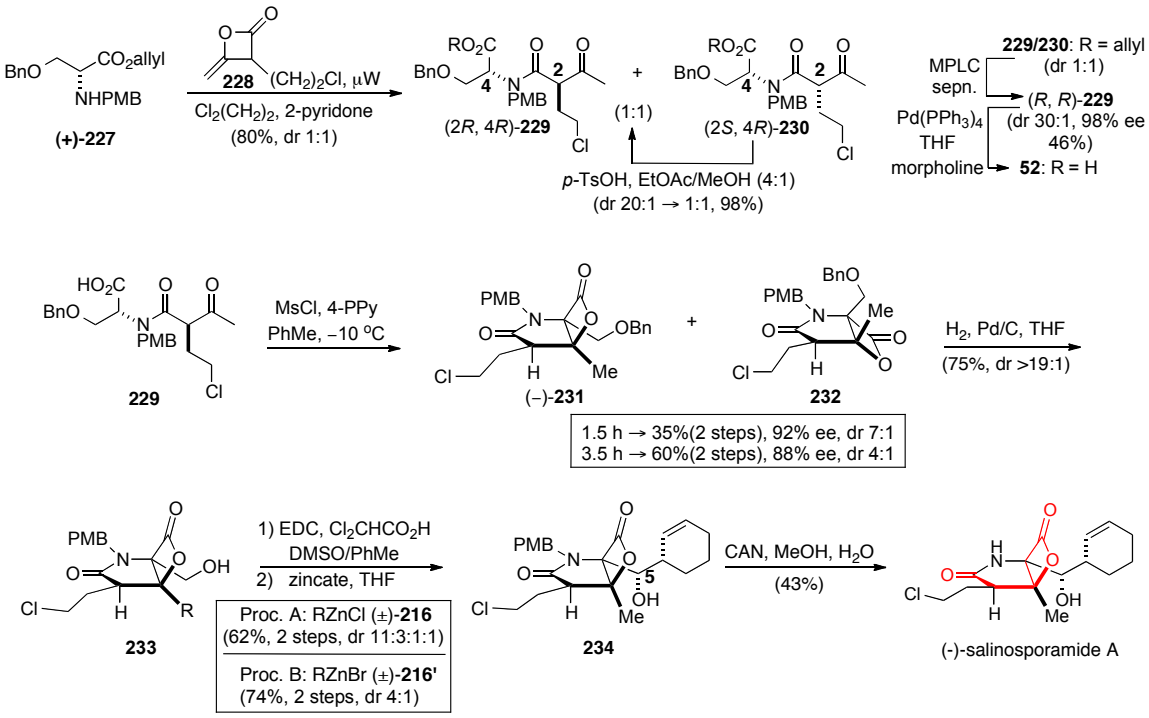
Scheme 1.60[293b]



Having worked out conditions for the key cyclization Romo and coworkers completed the synthesis of (-)-salinosporamide A. Microwave-assisted acylation of PMB-protected amine **227,** derived from (*R*)-serine, and ketene dimer **228** delivered a 1:1 mixture of diastereomers **229A** and **229B** (Scheme 1.61). The diastereomers were separated by MPLC on gram scale (dr 30:1, 98% ee, 46% yield isolated for desired diastereomer) while the undesired diastereomer **229B** was epimerized at the C2 center (devoid of the C4) with *p*-TsOH permitting an effective resolution of ketene dimer **228**. The C4 carboxylic acid was then revealed by Pd(0)-mediated deprotection, which proved to be the best conditions for minimizing epimerization at C2, providing keto-acid **230** as a single diastereomer for biscyclization. Optimization of the NCAL conditions revealed MsCl and 4-PPy in less polar solvents produced the highest dr of 7:1 with ~3% epimerization being observed. Longer reaction time (1.5 to 3.5 hours) enhanced the yield from 35% to 60% (over two steps) albeit at the cost of diminished diastereoselectivity (7:1 to 4:1) and enantioselectivity (92% ee to 88% ee). Subsequent hydrogenolysis and separation of the minor diastereomer followed by a modified Pfitzner-Moffatt oxidation provided the necessary aldehyde.[299] Zincate addition with activated zinc following Knochel's procedure,[300] significantly improved the reaction output with minimal byproducts and improved the yield and diastereoselectivity[293b]. Lastly, PMP-deprotection delivered the natural product as a 15:1 mixture of diastereomers. Romo and coworkers made effective use of the ketene dimer strategy for accessing the keto-acid **231** in what still stands as the shortest total synthesis of (-)-salinosporamide A. (-)-Homosalinosporamide A was achieved following similar reaction conditions with the

one carbon homologue of ketene dimer of **228** while the NCAL proceeded in 60% yield (dr 3.5:1) subsequent transformations to (-)-homosalinosporamide A were carried out using identical conditions.

Scheme 1.61[293b]

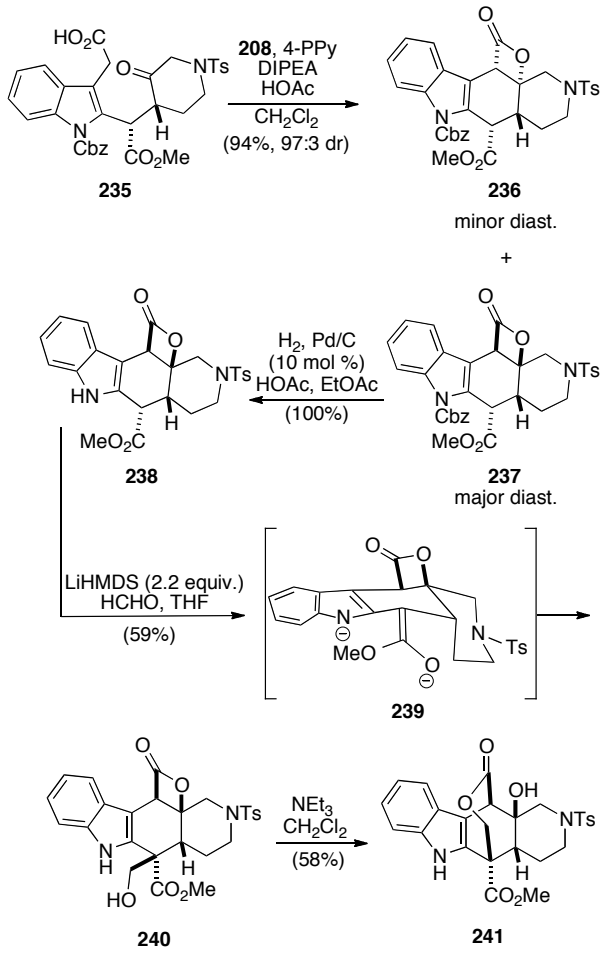


1.6.1.3. (±)-Alstilobanine A and E, (±)-Angustilodine

Syntheses of alkaloid natural products have typically shied from β-lactone intermediates, potentially due to the possibility of the *N*-heteroatom intercepting β-lactone formation. Nevertheless, Weinreb employed intramolecular cyclization conditions by Romo *et al*[235c,278,288b,290,293] as a key step for constructing the requisite *cis*-2-azadecal in his synthesis of the indole alkaloids, (±)-alstilobanine A and E as well as (±)-angustilodine (Scheme 1.62-64).[301, 302] Cyclization of the cyclohexane-fused β-

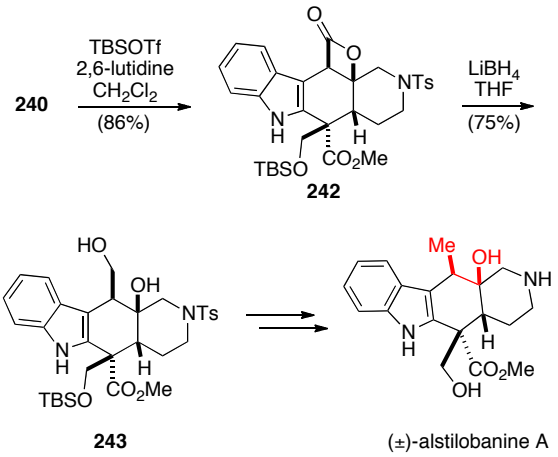
lactone was accomplished in excellent yield using NCAL conditions (*vide supra*), with the addition of acetic acid to avoid epimerization of the methyl ester of **235**, delivering the desired *cis*-fused ring system **237** along with *trans*-fused **236** (*cis*:*trans* 97:3) in 94% yield (Scheme 1.62). The mixture of β-lactone diastereomers were carried on to hydrogenolysis, after which the N-H indole diastereomers were separated using chromatography, the *cis*-fused ring system **238** was isolated in 94% over the two steps along with 3% of the Cbz-free intermediate of **235**.[302] Previous work proved it was necessary to remove the Cbz, due to conformational constraints, to successfully generate enolate **239**. Stereoselective hydroxymethylation of **239** on the α-face with monomeric formaldehyde[303] delivered a single diastereomer at the newly formed quaternary carbon center. However the free hydroxy group of **240** proved to be problematic under basic conditions causing acyl migration to **241**, in addition to retro-aldol process.

Scheme 1.62



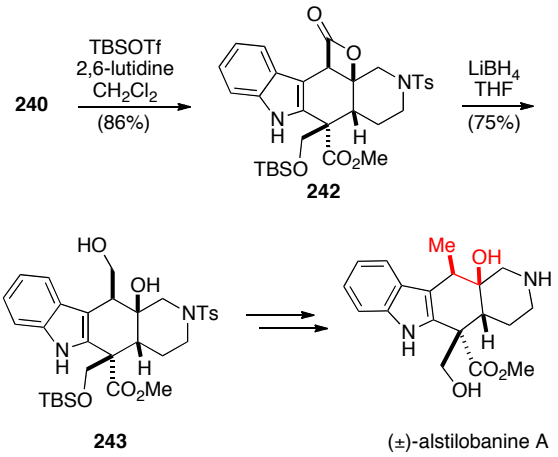
To circumvent the tranesterification event, and prevent retro-aldol processes, the hydroxymethyl was protected as silyl ether **242**, with concomitant reduction of the β-lactone to 1,3-diol **243** by $LiBH_4$ (Scheme 1.63). The β-lactone served to stereoselectively install the *cis*-2-azadecalin moiety, establishing two new stereocenters, one being a quaternary center en route to alstilobanine.

Scheme 1.63



It was realized that monoterpene indole alkaloids, alstilobanine E and angustilodine, could be derived from a common β-lactone intermediate **242** (Scheme 1.64). Protection of the indole proved necessary to attenuate reactivity at the C3 indole position (observing cyclopropane formation while attempting to cyclized the ether ring of the natural products when the indole was unprotected) and reduction proceeded in good yield to diol **245** which was used to complete the first total synthesis of (±)-alstilobanine E and (±)-angustilodine. The stereoselective NCAL to delivered the requisite *cis*-2-azadecalin. Weinreb elegantly employed a common β-lactone intermediate for the *cis*-2-azadecalin and establishing the relative stereochemistry of three centers which directed stereoselective hydroxymethylation for the three natural products.

Scheme 1.64

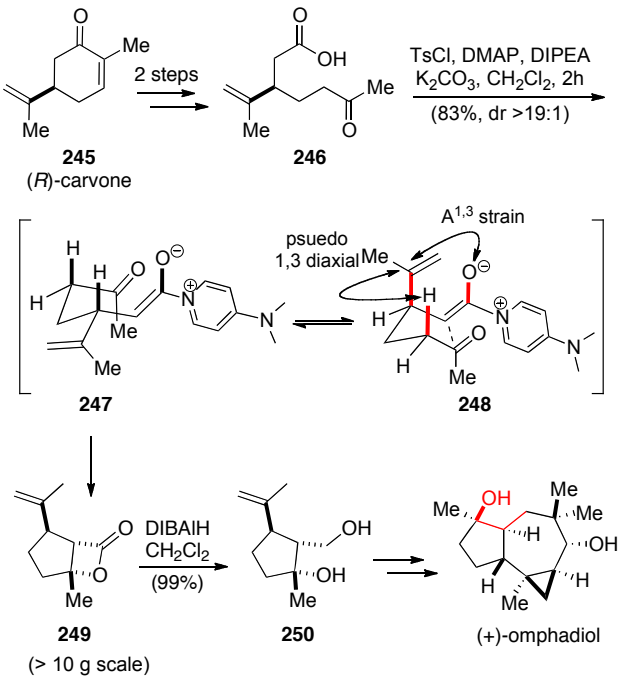


1.6.1.4. (+)-Omphadiol

Demonstrating the synthetic utility of β-lactones Romo and Liu took an interesting approach to the sesquiterpene omphadiol, developing a robust and practical route to carvone-derived bicyclic β-lactone **249** as a general intermediate to several bioactive natural products (Scheme 1.65).[304] (*R*)-Carvone was used as chiral pool providing rapid access to optically active keto-acid **246** by way of a formal hydration and oxidative cleavage (not shown). Facile aldol-β-lactonization delivered carvone-derived bicyclic β-lactone **249**.[247] Optimization of NCAL reaction conditions[277] employed K_2CO_3 as a shuttle base[305] for diminishing the reaction time (from 24 to 2 h) along with commercially available TsCl (as the acid activating agent) delivering a practical and reliable procedure proceeding in excellent yield and diastereoselectivity (83%, >19:1 dr) on larger than a 10 g scale. The diastereoselectivity is rationalized from the chair-like transition states of the two possible ammonium enolates **247** and **248**, wherein the latter the isopropenyl moiety adopts a pseudo-axial position thereby causing

a pseudo 1,3-diaxial interactions as well as 1,3-allylic strain. These unfavorable interactions are devoid in **247**, which is believed to undergo a facile aldol and subsequent lactonization to **249**. Quantitative reduction with DIBAlH generated 1,3-diol **250** which was taken on to the natural product. A highlight of this approach is the use of (*R*)-carvone, which severed to establish the absolute stereochemistry generating two additional stereocenters, with each additional center was established from highly diastereoselective transformations from (*R*)-carvone. Absolute stereochemistry with all remaining 5 being established through highly diastereoselective transformations.[304]

Scheme 1.65

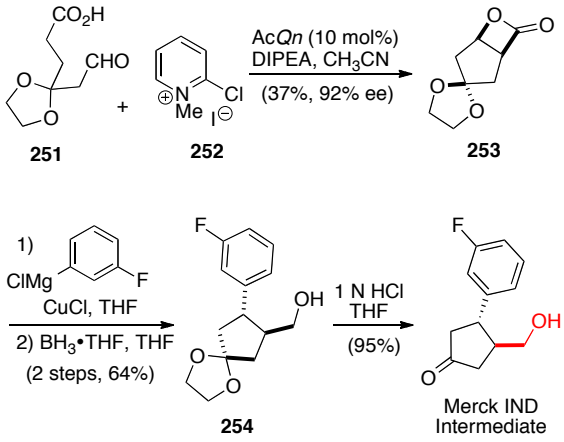


1.6.1.5. Merck Investigational New Drug

Capitalizing on the selective and inherent reactivity of β-lactones Romo and coworkers reported an expedient synthesis to the Merck investigational new drug (IND)

intermediate (Scheme 1.66).[306] Catalytic enantioselective nucleophile-catalyzed aldol-lactonization (NCAL), of aldehyde acid **251** with Ac*Qn* rendered optically active tricyclic β-lactone **253**.[235c,239b,c] Functionalization by way of 1,4-cuprate addition, proceeding in an S_N2 fashion for invertive ring opening exclusively delivering stereodefined cyclohexyl carboxylic acid. Succeeding boron-mediated reduction and cleavage of the dioxolane delivered the Merck IND in 3 steps from the known β-lactone **253**.[235c,239c]

Scheme 1.66.



Stereochemical rational of the catalytic asymmetric NCAL drew from previous models with cinchona alkaloids (*supra vida*). Approach of the aldehyde from the si face of the (*Z*)-(O)-ammonium enolate, minimizes interactions with the quinoline ring, delivering the *cis*-aldolate (Figure 21).

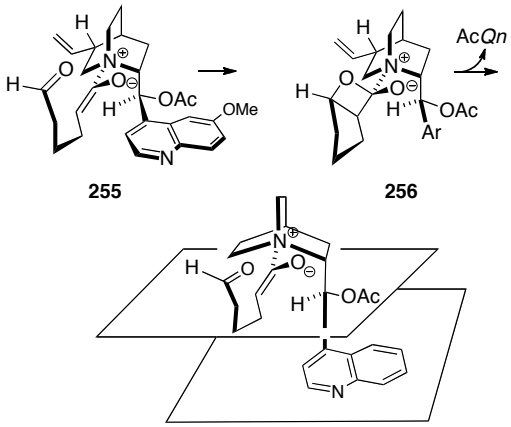
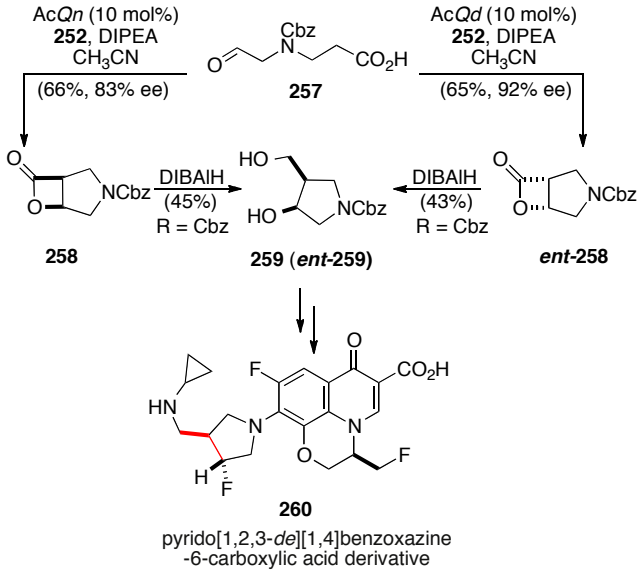


Figure 21. Proposed transition states for AcQn-catalyzed NCAL.[239c]

1.6.1.6. Fluoroquinolone Antibiotic Derivatives

Dikshit and Sikriwal pursued a catalytic intramolecular NCAL variant using nearly identical conditions to those reported by Romo[239c] for piperidine and pyrrolidine cores (Scheme 1.67).[307] The pseudoenantiomeric catalysts Ac*Qn* and Ac*Qd* paralleled in efficiency delivering 66% yield and 83% ee to β-lactone **258** and 65% yield and 92% ee for the enantiomer, ***ent*-258** to pyrrolidine-fused β-lactones. The formal synthesis of several fluoroquinolone antibiotic derivatives[308] have been reported using known aza-sugars **259**, specifically pyrido[1,2,3-*de*][1,4]benzoxazine-6-carboxylic acid (**260**) currently under investigations for clinical trials due to the potent antibacterial activity rivaling current treatments clinafloxacin and levofloxacin (levaquin ®).[308]

Scheme 1.67

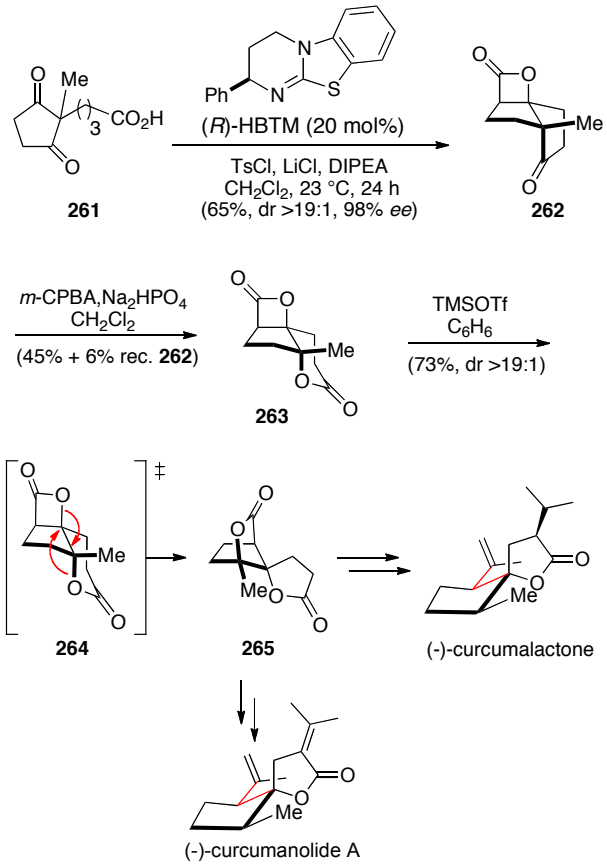


1.6.1.7. (-)-Curcumanolide A and (-)-Curcumalactone

Having developed an efficient catalytic desymmetrization of dione keto-acids[278] it was applied to the synthesis of (-)-curcumanolide A and (-)-curcumalactone (Scheme 1.68).[309] Starting with dione keto-acid **261** optimization revealed that the isothiourea catalyst HBTM (homobenzotetranisole), developed by the Birman group,[310] in conjunction with Lewis acid LiCl, gave tricyclic β-lactone **262** in 65% yield on a gram scale with excellent levels of diastereo- and enantioselectivity (Scheme 1.68).[290] Showing what could be done in the presence of a β-lactone, Baeyer-Villiger oxidation was conducted, converting the β-lactone **262** to δ-lactone **263** in 45% yield under buffered conditions, while starting material ~6% of starting material was recovered and resubjected to the reaction conditions. An unprecedented dyotropic rearrangement via

1,2-acyl migration to spirocyclic bis-γ-lactone **265** provided a rapid route to the core of (-)-curcumalactone and (-)-curcumanolide A.

Scheme 1. 68



The model for enantioinduction, in agreement with that initially proposed by Birmann[311] supports an S-O nonbonding interaction ($\eta_O \rightarrow \sigma^*_{C\text{-}S}$) of the isothiourea catalyst and ammonium enolate (A, Figure 22). The omission of LiCl delivered β-lactone **262** with diminished yield (59%) and identical enantiomeric excess. In the presence of LiCl this interaction is replaced by a Li-S both activating the ketone and enhancing the chair-like transition state (**267**).[251] The cooperative catalysis of LiCl[267] and HBTM was provoked to involve a chelation of lithium stabilizing the ammonium enolate and coordination to

the chiral nucleophile tightening the transitions state. (B, Figure 22). Investigation of the potential achiral pathways (B, Figure 22) revealed 18% yield of β-lactone **262** when the reaction was run devoid of (*S*)-HBTM revealing the achiral pathway is operational to deliver racemic product. Whereby ketene intermediate **270** is possible from **268** or **269**.[284b,289]

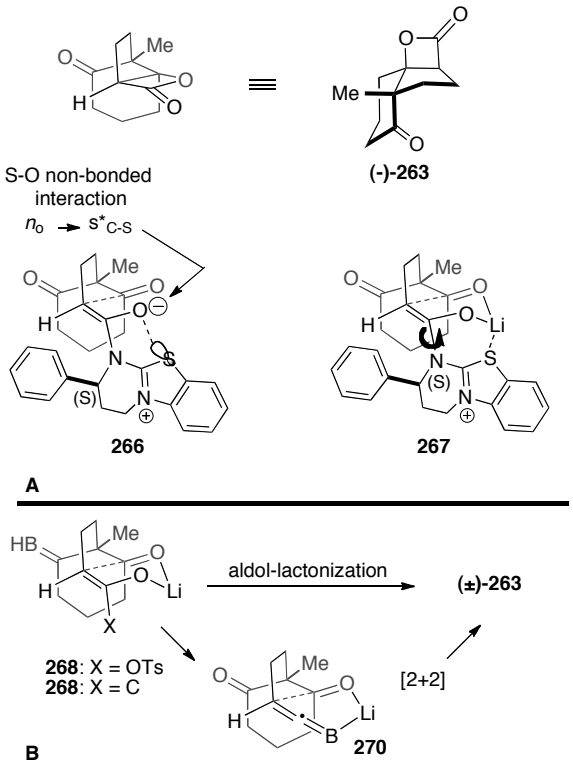
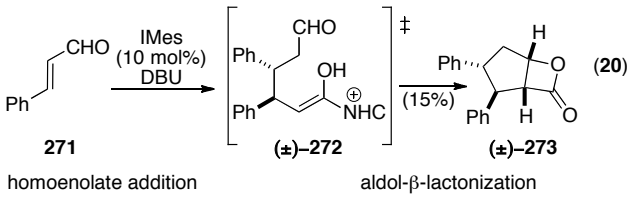


Figure 22. Desymmetrization NCAL proposed transition states.

1.6.1.7.1. NHC-Catalyzed Introduction and Overview

Leaps and bounds have been made in the realm of *N*-heterocyclic carbene (NHC) chemistry in the last 9 years[312,313,314] with its applications to natural product synthesis

standing as an emerging area, however it has been largely untapped for the use of β-lactone synthesized by NHC methodology. In 2006 Nair reported the first cyclopentene from NHC catalysis of unsaturated aldehydes and chalcones denoting a transient β-lactone intermediate.[315,316] Scheidt and coworkers early work aimed to develop new NHC-catalyzed reactions perusing homoenolate and enol/enolate reactivity stemming from the same substrates. Discovering NHC-catalysis employing achiral IMes (bis(1,3-(2,4,6-trimethylphenyl)imidazol-2-ylidene)) lead to dimerization of cinnamaldehyde proceeding through a Michael aldol-lactonization delivering the bicyclic β-lactone, as was confirmed by X-ray analysis (Eq. 20).[190]



Expanding the breadth to chiral carbene catalysts, Scheidt and others had developed a new variant for catalytic, enantioselective aldol reactions. Further development of the reaction permitted the desymmetrization of achiral substrates providing rapid access to quaternary carbon centers and complex scaffolds. The proposed mechanism involves conjugate addition of the NHC catalyst to the enal substrate delivering homoenol/homoenolate **I** while ensuing protonation (HNR_3^+) generates enol **II** (Figure 23). Intramolecular aldol of enol **II** with either ketone (R^1) provides the stereodefined cyclopentane core, delivering chiral acyl azolium intermediate **III**. The activated acyl group, analogous to acyl ammoniums seen with Lewis base catalysis is poised for an intramolecular β-lactonization with the tertiary alcohol providing the optically active

cyclopentane fused β-lactone **IV**. When R^1 is aliphatic β-lactone **IV** is stable and isolable, however when R^1 is an aryl moiety spontaneous liberation of carbon dioxide (-CO_2) is observed providing optically active cyclopentene **V**.[190,315]

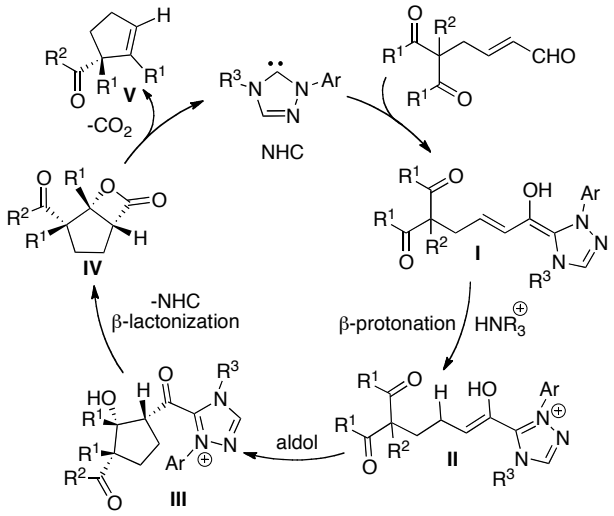


Figure 23. Proposed mechanism of NHC-catalyzed β-lactone formation.[190]

Triazolium salt **274** was identified as the optimal carbene catalyst for desymmetrization of 1,3-diketone substrates tethered to an α,β-unsaturated aldehyde (**273**) (Figure 24). Formation of *Z*(O)-enol intermediate **276** involves hydrogen bonding through a six-membered transition state dictating the absolute stereochemistry of the ensuing aldol reaction. As depicted this array minimizes the non-bonding interactions among the phenyl's of the catalyst and the R group from the ketone electrophile. While the relative stereochemistry between R^1 and the lactone ring is dictated by the flexibility of the diketone moiety, either being linear or in a locked cyclic array.[190]

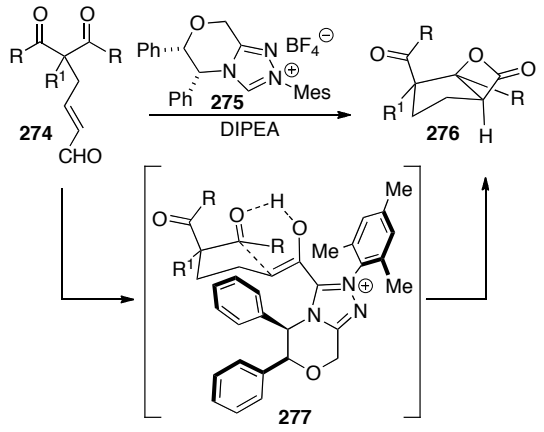
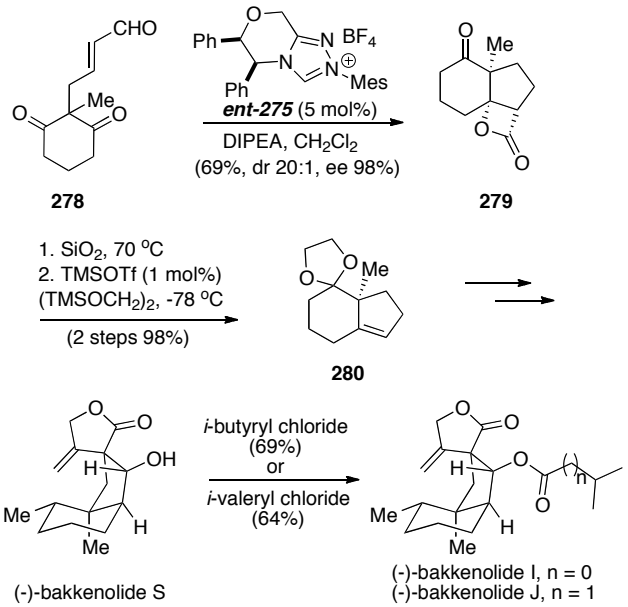


Figure 24. Desymmetrization by NHC catalysis

1.6.1.7.1.1. (-)-Bakkenolides I, J, and S

This desymmetrization approach was utilized for the synthesis of the bakkenolides I, J and S as a powerful strategy for constructing the angular quaternary methyl group present in these challenging natural products (Scheme 1.69).[317,318] The authors foresaw employing methodology they previously disclosed to access the 6-5-bicyclic ring system through a desymmetrization of 1,3-diketone **278** with chiral triazolium salt ***ent*-275**.[190] During cyclization the achiral aldehyde underwent a tandem homoenolate protonation, intramolecular aldol acylcation delivering the tricyclic β-lactone **279** in 69% yield. This robust method was applied on a 5g scale with excellent enantio- and diastereocontrol (98% ee, >20:1 dr). With tricyclic β-lactone tricycle in hand, it was functionalized by a silica gel-mediated decarboxylation,[43a,319] and ketal formation in 98% over the two steps. The desymmetrization to β-lactones highlights a unique alternative for the synthesis of optically active quaternary carbons centers, a challenge in organic chemistry.

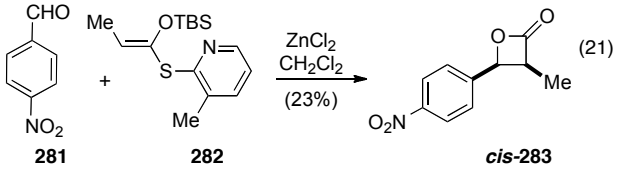
Scheme 1.69



1.7. Intermolecular Tandem Mukaiyama Aldol-Lactonization

1.7.1. Introduction and Mechanism

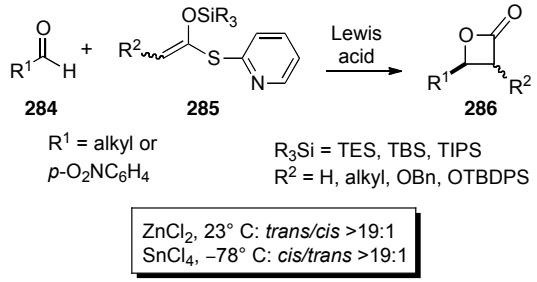
In 1994, Hirai and co-workers reported a single example of a *cis*-β-lactone **283** produced in low yield from *p*-nitrobenzaldehyde **281** and thiopyridyl ketene acetal **282** (Eq. 21).[320] Although the yield was not optimal, this constituted the first example of β-lactone formation via the Mukaiyama aldol lactonization reaction.[321]



Building on the work of Hirai, Romo and coworkers extensively developed the tandem Mukaiyama aldol- lactonization (TMAL) providing access to both cis- and trans-β-

lactones 286 from aldehydes 284 and thiopyridyl ketene acetals 285 (Scheme 1.70).[322] Employing $ZnCl_2$ trans-β-lactone could be synthesized in good to moderate yields with high diastereoselectivity (dr >19:1).[43b,323]Conversely, complete reversal in selectivity can be achieved with Lewis acid $SnCl_4$ at low temperatures (dr > 19:1) favoring the cis-β-lactone.[322] Based upon initial experimental results and corroborated by calculations (B3LYP/BSI), asynchronous, concerted transition states between aldehydes and thiopyridyl ketene acetals were proposed[324] that account for several unique features of this reaction including the superior reactivity of alphatic aldehydes, and the stereoconvergence of (*E*) and (*Z*).

Scheme 1.70



Both computational and experimental evidence proposed an initial pre-coordination of the thiopyridyl ketene acetal **285** with $ZnCl_2$ forming chelate complexes (*E*)- or (*Z*)-**287**·$ZnCl_2$ (Figure 25).[324] Upon addition of the aldehyde **285**, coordination to $ZnCl_2$ affords the precursors (*E*)- or (*Z*)-**288** to asynchronous, concerted transition states (*E*)- or (*Z*)-**289**. The newly formed 4-6 ring systems (*E*)- or (*Z*)-**290** subsequently collapse into silylated-β-lactones (*E*)- or (*Z*)-**291**. Capture of this intermediate with chloride from complex **293** delivers *trans*-β-lactone **286**.

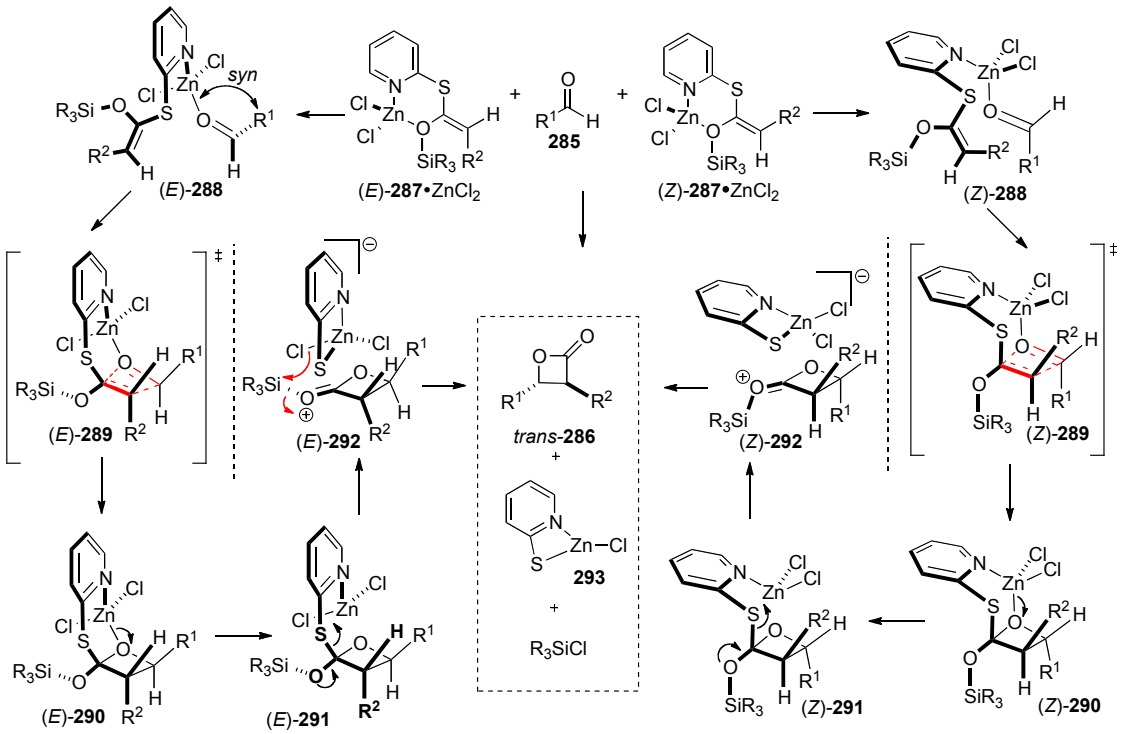
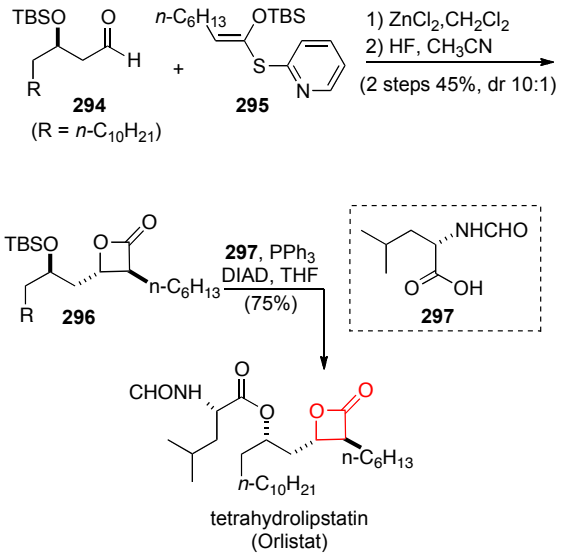


Figure 25. Transition states and mechanism of the TMAL reaction.[324]

1.7.1.1.Tetrahydrolipstatin. This method was applied to fatty acid synthase (FAS) inhibitor, (-)-panclicin D, in the first reported example of a substrate controlled diastereoselective TMAL.[323] Subsequently Zhang and coworkers exhibited the utility of the TMAL reaction to **296** in their total synthesis of tetrahydrolipstatin, while the end game approach followed aforementioned conditions (Scheme 1.71).[325]

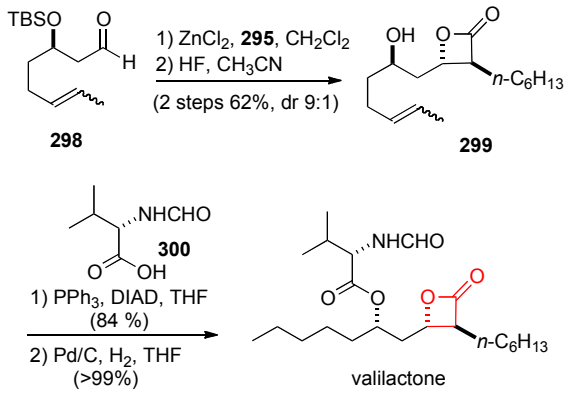
Scheme 1.71



1.7.1.1. Valilactone

Romo and coworkers extended this diastereoselective TMAL process toward a "second generation" strategy providing divergent access to tetrahydrolipstatin, valilactone, and several other derivatives (Scheme 1.72).[326] Several β-lactone containing derivatives were subjected to inhibition studies of the thioesterase domain of FAS which demonstrated the viability of particular congeners of tetrahydrolipstatin with increased potency as potential preclinical drug candidates.[327]

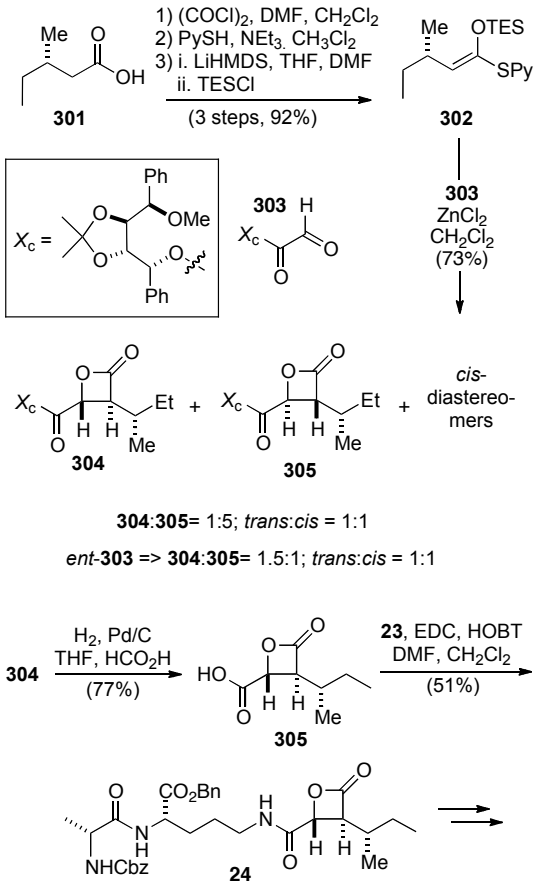
Scheme 1.72



1.7.1.2. (-)-Belactosin C

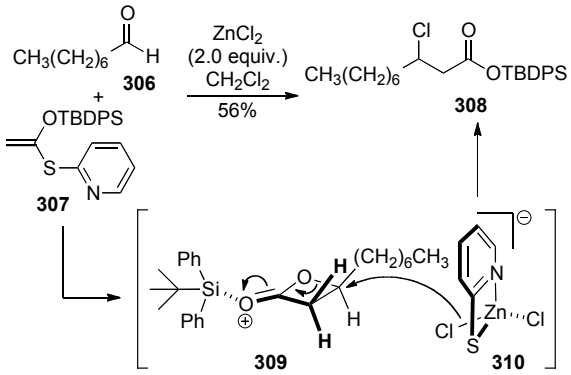
Whereas substituted aldehydes provided good diastereoselectivity, substituted ketene acetals were less effective. However, a unique application of the TMAL in the total synthesis of (-)-belactosin C was demonstrated by two related strategies toward this bioactive natural product. Synthesis of the substituted thiopyridyl ketene acetal **302** and a chiral auxiliary-based aldehyde **303** gave the substrates necessary for a proximal double diastereoselective TMAL, which proved to afford the best results (Scheme 1.73).[139] This advanced β-lactone intermediate **304** was hydrogenated to remove the chiral auxiliary and the resulting acid **305** was subjected to peptide coupling en route to (-)-belactosin C.[139]

Scheme 1.73



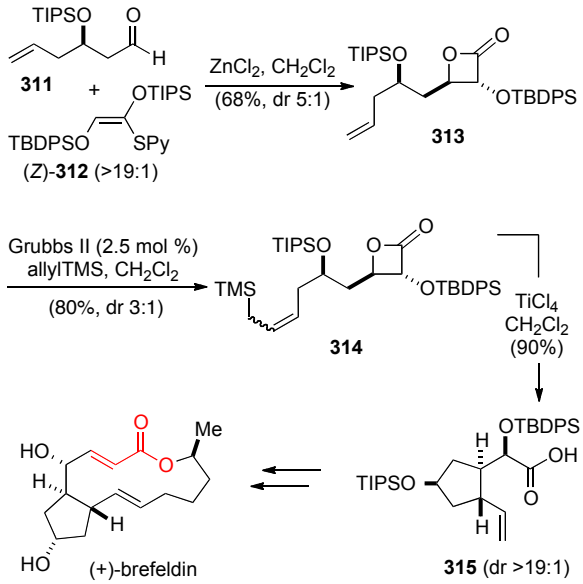
In the course of studying the TMAL, several intriguing by-products were observed that were dependent on the silyl group of the thiopyridyl ketene acetal. One such by-product was β-chlorosilyl ester **308**, which is derived from intermolecular chloride attack of the silylated β-lactone **309** (Scheme 1.74). As opposed to cases with less bulky silyl groups in which mixtures of products were observed, no β-lactone was detected due to the very bulky TBDPS (*tert*-butyldiphenylsilyl) protecting group on the thiopyridyl ketene acetal.

Scheme 1.74



These results and others led Romo and coworkers to explore the utility of the β-lactone as either an isolable or transient intermediate toward more complex ring systems. Toward the total synthesis of (+)-brefeldin A, the TMAL reaction was utilized with β-silyloxy aldehyde **311** and thiopyridyl ketene acetal (*Z*)-**312** (Scheme 1.75).[328] Although longer reaction time was required, *syn*-β-lactone **313** was isolated in good yield and moderate diastereoselectivity. After Grubbs cross metathesis[329] with allyltrimethylsilane, $TiCl_4$-promoted cyclization proceeded smoothly to deliver the crucial cyclopentane acid **315** as a single diastereomer (>19:1) for completing the synthesis of (+)-brefeldin A.

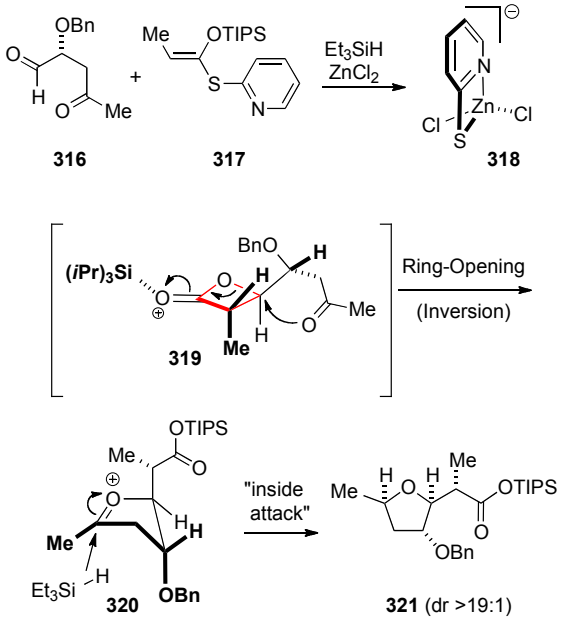
Scheme 1.75



1.7.1.3. Colopsinol B

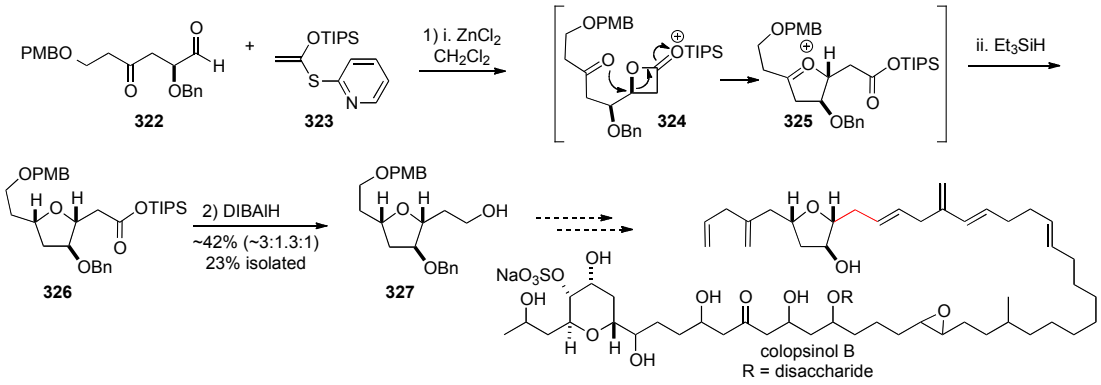
In an effort to combine the TMAL with the reductive cyclization of keto-β-lactones developed by Mead and coworkers,[330] Romo and coworkers envisioned the capture of a transient silylated-β-lactone with a pendant ketone in a single reaction (Scheme 1.76).[72,331] Upon treatment α-benzyloxy aldehyde **316** with thiopyridyl ketene acetal **317**, Et_3SiH, and $ZnCl_2$ in THF **321** was obtained as a single diastereomer. Chelation-controlled TMAL likely gives rise to silylated β-lactone **319**, which undergoes ring-opening via the pendant ketone to deliver oxocarbenium **320**. This oxocarbenium adopts the favored envelope with the benzyloxy substutient oriented in the pseudoaxial position and Et_3SiH approaches through the preferred "inside attack" model as set forth by Woerpel.[332]

Scheme 1.76



The THF fragment of colopsinol B[333] was deemed an adequate target to demonstrate application of this three-component TMAL-based process in which two new stereocenters and two new bonds (one C-C and one C-O) are constructed (Scheme 1.77).[331] Treatment of α-benzyloxy-γ-ketoaldehyde **322** with ketene acetal **333** followed by reduction of the silyl ester with DIBAlH delivered the substituted tetrahydrofuran portion (**327**) of colopsinol B in moderate yield.

Scheme 1.77



1.8. Epoxide Carbonylation

1.8.1. Introduction and Mechanism

The last ten years has seen an expansion in the development of methodology for carbonylation of epoxides to β-lactones however few examples have been applied to the synthesis of natural products (**A**, Figure 26).[334,335,336,337] The proposed mechanism invokes metal-activation of the epoxide and subsequent oxidative addition of CO followed by CO insertion and lactonization to reductively eliminate the metal catalyst (**B**, Figure 26). With the substutients of the epoxide dictating the relative stereochemistry or absolute (in the case of employing a chiral ligand)[338] of the resulting β-lactone. Preferential epoxide opening and C-O bond formation occurs on the side with the smallest R group, as a result of minimizing steric interactions.

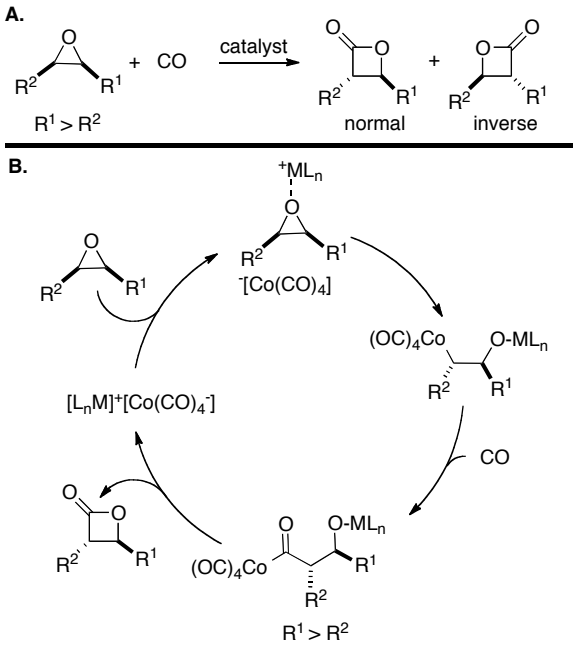


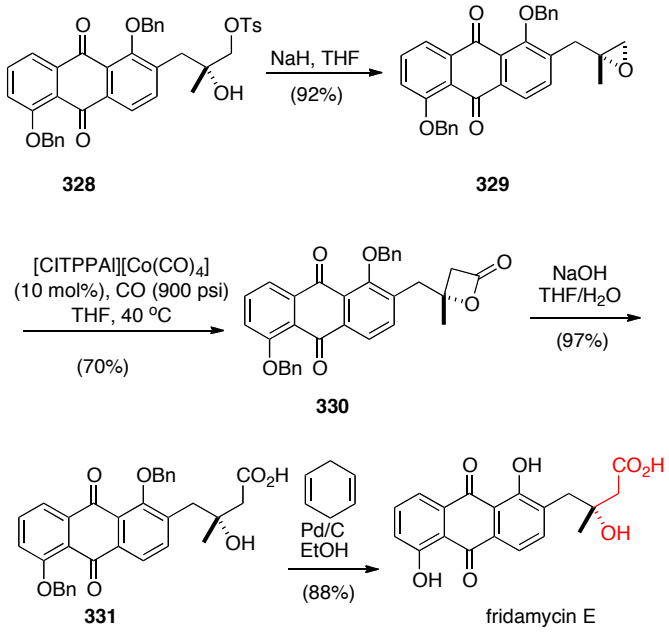
Figure 26. Carbonylation of epoxides to β-lactones.

1.8.1.1. Fridamycin E

Coates and O'Doherty reported in 2011 one of the first applications for the insertion of CO to optically active epoxides delivering substituted β-lactones with a Al-Co bimetallic catalyst.[339] Carbonylation of epoxide **329** was utilized to deliver the active tertiary β-hydroxyl carboxylic acid, highlighted in red, of the natural fridamycin E by way of β-lactone intermediate **330** (Scheme 1.78).[339] Sharpless asymmetric dihydroxylation established the absolute stereochemistry of the tosylated anthraquinone alcohol (**328**) while base induced cyclization smoothly delivered the anthraquinone epoxide. Using methodology developed in their laboratory 10 mol% of the [CITPPAl][$Co(CO)_4$] (CITTP = *meso*-tetra(4-Clphenyl)porphyrinato) catalyst system

facilitated CO insertion generating β-lactone **330** in 70%. Despite concerns of the catalyst being oxidized by the anthraquinone, or Lewis acid promoted conversion of the epoxide to the allylic alcohol, the insertion of CO proved to be the dominant pathway under the reaction conditions. No signs of decarboxylation were observed using the relatively low temperature of 40 °C, however at temperatures of up to 60 °C decarboxylation of the β-lactone occurred yielding a disubstituted-olefin derivative of **330** in ~20% yield. The synthesis was complete by aqueous hydrolysis of the lactone ring and Pd-mediated hydrogenolysis, providing a 9 step 16% overall yield *de novo* synthesis to both enantiomers of fridamycin E. The unprecedented end game carbonylation and lactone functionalization exhibit a unique platform for generating optically active β-hydroxy acids.

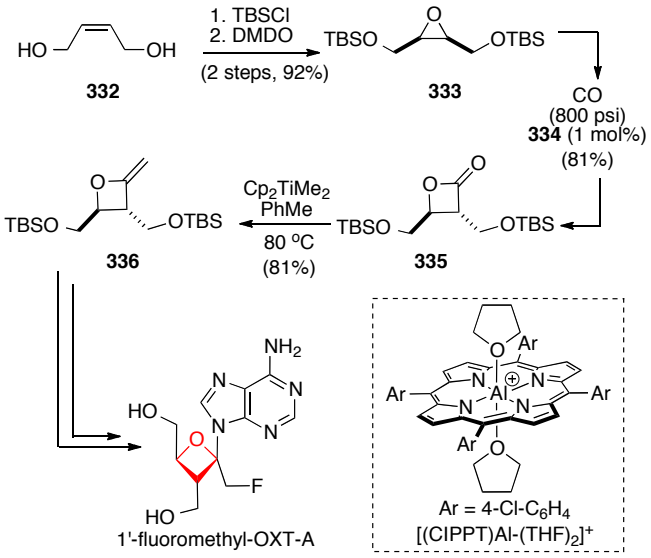
Scheme 1.78



1.8.1.2. 1'-Fluoromethyl-OXT-A. I

A collaborative between Howell and Coates was reported a concise route to the HIV-1 inhibitor, 1'-fluoromethyl-OXT-A through CO insertion methodology.[340] Silyl protection of (*Z*)-but-2-ene-1,4-diol with concomitant epoxidation by DMDO provided the carbonylation precursor **333** in high yield (Scheme 1.79). Catalyst **334** proved to be both active and selective delivering β-lactone **335** in 81% yield as a single diastereomer.[341] Subsequently methylenation with Petasis reagent[16a](*vide supra*) functionalized the β-lactone to **336**. Further manipulations inevitability transformed the β-lactone to the oxetane core of 1'-fluoromethyl-OXT-A.[342]

Scheme 1.79



1.9. Halolactonization

1.9.1. α,β-Unsaturated Halolactonization Mechanism and Overview

Halolactonization of α,β-unsaturated carboxylic acids to form β-lactones was first confirmed in 1937 by Bartlet and Tarbell has since been slow to progress the applications in synthesis.[343] Deprotonation of α,β-unsaturated carboxylic acid permits cyclization opening the bromonium intermediate to the more stable β-lactone (**B**, Figure 27).

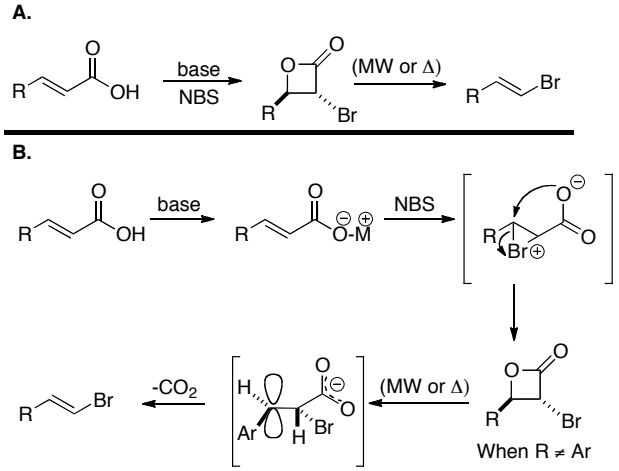


Figure 27. Mechanism of α,β-unsaturated halolactonization.

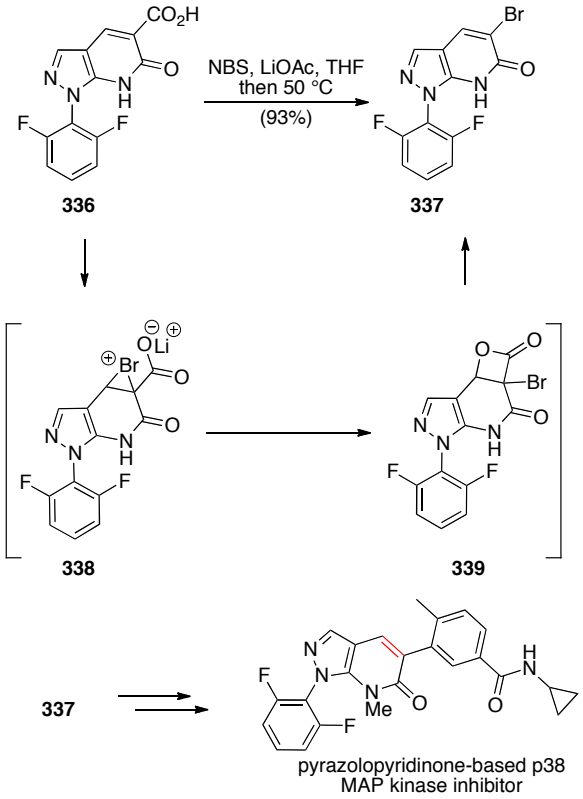
The labile nature of the resultant *cis*-β-lactone often makes purification difficult by chromatography, and when an aryl group occupies the β position spontaneous decarboxylation predominately occurs inhibiting isolation of the β-lactone intermediate. Owing to the elimination of an eclipsing interaction, the decarboxylative rates of *trans*-β-lactones is higher than that of *cis*-products.[344] Therefore most applications of the

methodology propose or allude to a transient β-lactone intermediate. While coupling the halolactonization to decarboxylation conditions (heat, microwave, acid-catalysis, etc.) has been frequently employed in the literature for synthesizing alkyl-substituted bromo-styrenes,[345] often relying on Kuang's 'halodecarboxylation' procedure[345a] to access bromo-styrene products for Suzuki or Heck cross couplings.[346]

1.9.1.1. P38 MAP Kinase Inhibitor

While developing an industrial scale, *practical*, synthesis of the pyrazolopyridinone-based p38 MAP kinsase inhibitor at Amgen, Milburn and co-workers performed a kilogram scale decarboxylative-bromination.[347] In order to install the necessary vinylic bromide for future Suzuki cross coupling, an NBS (*N*-bromosuccinimide)-mediated Hunsdiecker-type reaction[348,349] was carried out, presumably with the unsaturated carboxylic acid **336** undergoing bromination to form brominium intermediate **338** with insipid β-lactonization of the carboxylate (Scheme 1.80). Subsequent decarboxylation ensued upon heating at 50 °C. While the authors speculated the mechanism proceeded as shown, they were unable to confirm (*via* react-IR or LC/MS) evidence of the β-lactone intermediate. However, Kuang and coworkers previously confirmed (by NMR) such an intermediate during mechanistic studies on the decarboxylative-bromination of cinnamic acid.[350]

Scheme 1.80



1.9.2. β-γ-Unsaturated Halolactonization Mechanism and Overview

In the 1970's Barnett and McKenna, broadened the applications and the range of amenable substrates disclosing the first halolactonization of β-γ-unsaturated carboxylic acids to γ-bromo-β-lactones.[351] Amazing is the observed selectivity of the transformation with β-lactones being exclusively achieved under kinetic control, while prolonged exposure to the reaction conditions provided the thermodynamically more stable γ-lactone (Figure 28).[9b,352,353] Subsequent methodology revealed 4-*exo*-trig cyclization was favored with strong electron with-drawing groups at the γ-position, whereas hydrogen substitution favored the γ-lactone.[354]

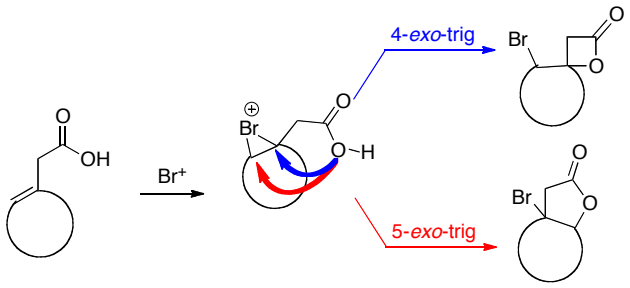
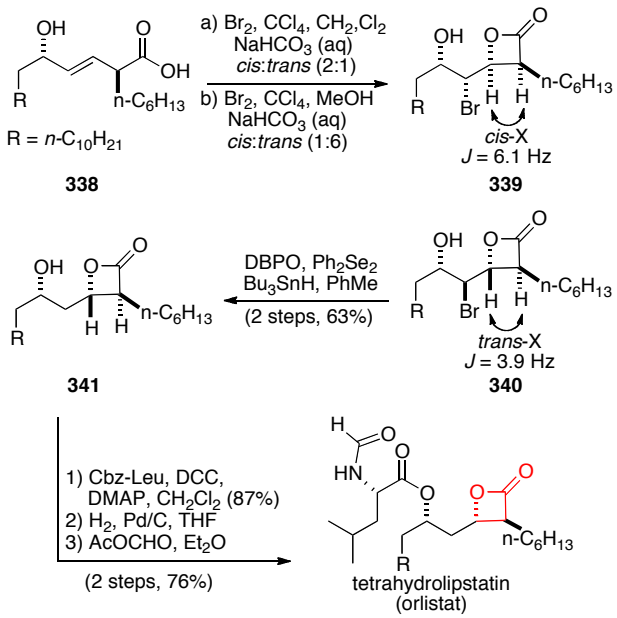


Figure 28. Modes of cyclization for β-γ-unsaturated carboxylic acids.

1.9.2.1 Tetrahydrolipstatin. McLeod and co-workers employed this kinetic cyclization in a distinct and efficient approach to the frequently synthesized *tran*-β-lactone tetrahydrolipstatin.[355] The β,γ-unsaturated acid was synthesized in 7 steps with Sharpless asymmetric dihydroxylation establishing the absolute stereochemistry of the secondary alcohol **338** (Scheme 1.81). The key step, bromolactonization, was originally carried out using conditions established by Barnett (conditions a),[351] surprisingly delivering a 2:1 mixture of *cis*:*trans* β-lactones respectively, with no detection of γ-lactone formation. This diastereomeric β-lactones **339** and **340** were confirmed by their characteristic coupling constants, which is in agreement with reported literature values.[356] The high level of regio-control during lactonization, i.e. exclusive β-lactone formation, is believed to stem from the inductively withdrawing effect of the secondary alcohol, thus favoring opening of the brominum ion intermediate at the position β to the carboxylic acid. The secondary alcohol additionally seemed to dictate the diastereoselectivity, with the preferred *trans*-β-lactone being the minor diastereomer.[357] The diastereoselectivity however was reversed employing the polor protic co-solvent methanol (conditions b), by

reducing the stereochemical influence of the secondary alcohol's inductive properties, allowing the α-alkyl chain to dominate facial selectivity. The diastereomeric mixture could be obtained as a 1:6 mixture of *cis*:*trans*, and was carried on as a mixture to radical debromination as **339** and **340** were prone to decomposition during purification with silica gel (purification afforded 13% of the *tran*-β-lactone exclusively). Crich and Mo's (REF) conditions of tributyltin hydride, diphenyldiselenide, with di-*tert*-butylperoxyoxalate (DBPO) as the radical initiator delivered the debrominated β-lactone

Scheme 1.81



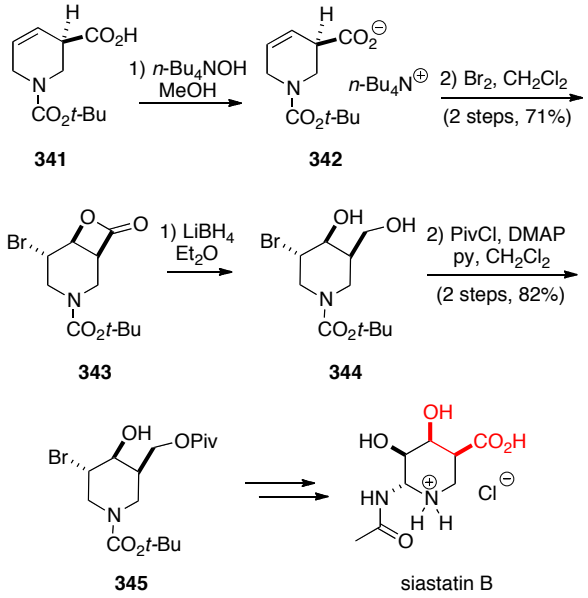
341 in 76% yield over the two steps. The debromination strategy beneficially funneled out the undesired *cis*-β-lactone, presumably from 'rapid radical β-scission' of the increased strain in the *cis*-β-lactone, or enhanced instability of it to the reaction conditions (previously observing only the *trans* product after purification). Nevertheless the remaining steps to tetrahydrolipstatin involved those similarly reported (*supra vida*),

esterification with Cbz-leucine, followed by hydrogenolysis and formylation all proceeding in good yields.

1.9.2.1. Siastatin B and 3-C-Benzylsiastatin.

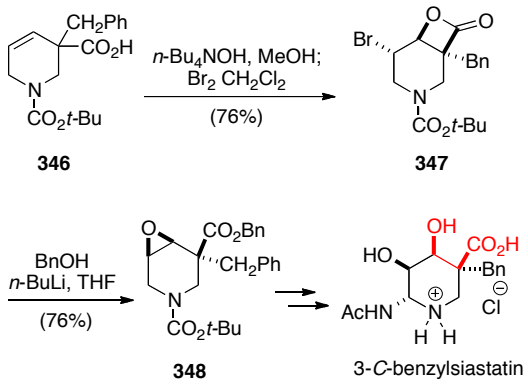
Although the zwitterionic natural product siastain B, known for its sialidase inhibitory activity,[358] was synthesized in 2000 by Knapp and Zhao we bear it worth mentioning as it was overlooked in previous reviews.[359] Using tetra-*n*-butylammonium hydroxide to generate the carboxylate salt followed by treatment with bromine in dichloromethane, delivered the *cis*-β-lactone **342** in 71% yield over the two steps, devoid of any γ-lactone products (Scheme 1.82). The β-lactone ring was then immediately reduced to the 1,3-diol with protection of the primary alcohol and en route to siastatin B. Bromolactonization offered an alternative to traditional olefin oxidation methods for stereospecifically incorporating the necessary oxygen functionality.[359]

Scheme 1.82



While making analogues of siastatin B Knapp and Zhao modified their approach to a one-pot carboxylate formation-bromolactonization procedure to give the benzyl substituted *cis*-β-lactone **347** (Scheme 1.83). Addition of the lithium salt of benzyl alcohol permitted esterification of the β-lactone with concomitant epoxide formation by displacement of the bromine with the generated secondary alkoxide. With the authors denoting no evidence of decarboxylation of the homobenzylic β-lactone, exemplifying direct conversion of the lactone to an epoxide, in a streamlined synthesis of 3-*C*-benzylsiastatin.[359]

Scheme 1.83

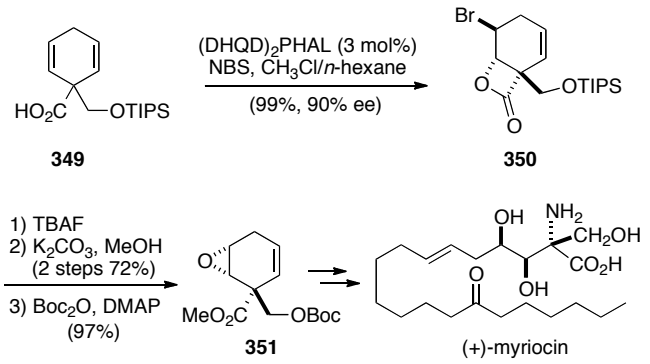


1.9.2.2. (+)-Myriocin

A significant advancement for the bromolactonization of unsaturated-carboxylic acids reported by Hasahima and Kan en route to natural products was the organocatalyzed desymmetrization of cyclohexadiene **349** (Scheme 1.84).[360] Previously reporting racemic intermediate **351**, in completing myriocin,[361] 3mol% of $(DHQD)_2PHAL$ was the optimal catalyst delivering gram scale quantities of tricyclic β-lactone **350** as a single diastereomer in quantitative yield with high ee. Preliminary

reports by Whiteside postulate a tight ion pair of the monobromo anion with brominated -$(DHQD)_2PHAL$, or associated hydrogen bonding of the protonated catalyst and brominium intermediate.[362] This method was general to other substrates and experimentally facile devoid of air or moisture precautions and chromatography for purification. Key intermediate **351** was readily achieved following a 3-step procedure. The simultaneous construct of three contagious stereocenters, one of which is a chiral quaternary center with quantitative levels of conversion on gram scale has permitted additional application notably to the synthesis of sphingofungin E (not shown).[363]

Scheme 1.84



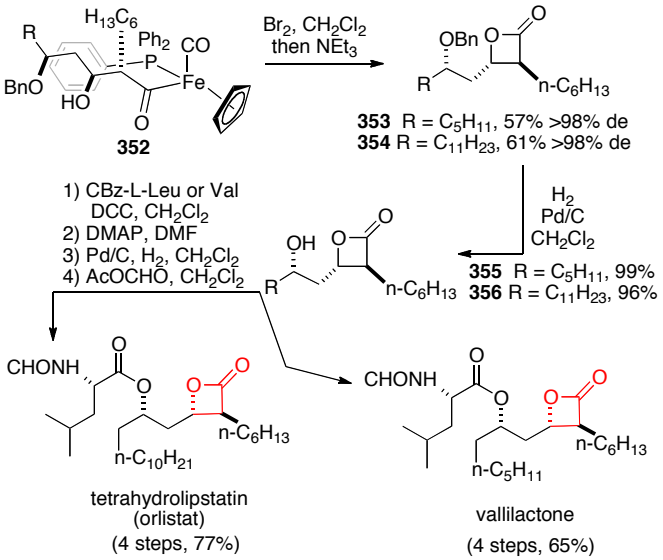
1.10. Miscellaneous β-Lactone Construction Methods

1.10.1. Fe-Mediated β-lactone Formation to Tetrahydrolipstatin and Valilactone

The Davies group previously disclosed a powerful stereodirecting effect of chiral iron auxiliary $[(\eta^5\text{-}C_5H_5)Fe(CO)(PPh_3)]$[364] for synthesizing intermediate **352** via a highly diastereoselective aldol reaction.[365] Subsequently a tandem oxidative-decomplexation-cyclization reaction of the aldol adduct **352** provided a new method for synthesizing the

β-lactone containing natural products tetrahydrolipstatin and valilactone.[364,365] Single electron transfer by Br_2 activated the Fe-acyl complex facilitating decomplexation with concomitant β-lactonization providing *trans*-β-lactones **353** and **354** (Scheme 1.85). The resultant β-lactones followed aforementioned reactions to provide the bioactive natural products. While iron-carbonyl complexes has been extensively documented in the literature for the synthesis of β-lactones[366] and employed for the synthesis of other β-lactone containing natural products[104,367] we briefly present this method due to the limited use in synthesis during the bounds of this review.

Scheme 1.85

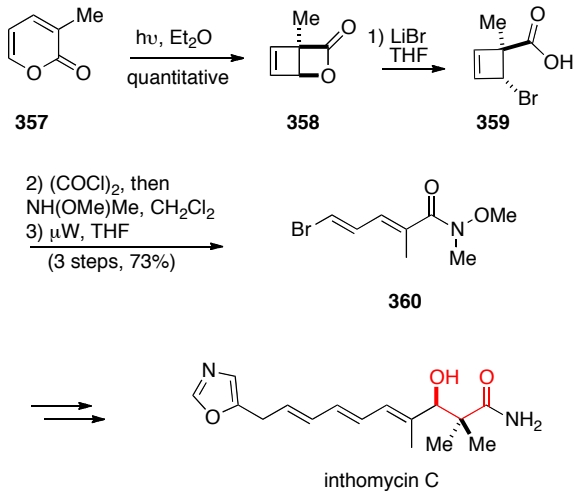


1.10.2. Photoisomerization β-Lactone Formation to Inthomycin C

The photoisomerization reaction of 2-pyrone derivatives to β-lactones has been reported in the literature however scarcely utilized stemming from instability, sensitivity, and virtually undocumented functionalization of the resultant β-lactone.[368] Enticed by

the potential as a versatile synthetic building block Maulide and coworkers pursued various transformations of cyclobutene fused β-lactones initially reporting a Pd-mediated ring opening to *cis*-substituted cyclobutenes.[369] Subsequently they disclosed the serendipitous discovery of *trans*-halocyclobutenes via alkali halide ring opening en route to inthomycin C (Scheme 1.86).[370] Photochemical isomerization of **357** to β-lactone **358** proceeded in quantitative yield. Following ring-opening with LiBr, amide formation and 4π-electrocyclization known intermediate **360** was obtained as a single isomer.[369a]

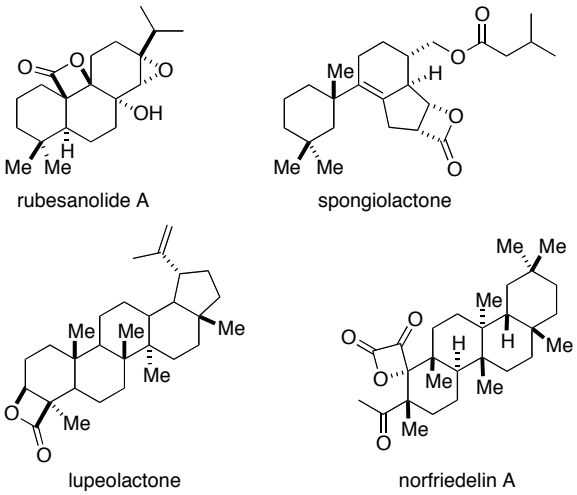
Scheme 1.86



1.11 Concluding Remark

The continued isolation of natural products bearing complex scaffolds with embedded β-lactone moieties and potent bioactivity has prompted the application and exploration of β-lactones (Scheme 1.87).[371,372,373,374]

Scheme 1.87



In addition, their use as specific enzyme inhibitors for a variety of biological activities has attracted the attention of many synthetic groups for exploiting the full potential of the β-lactone construct. The high degree of flexibility and plethora of documented transformations for direct functionalization employing this motif exhibits the emerging role as a valuable precursor or intermediate in natural product synthesis.

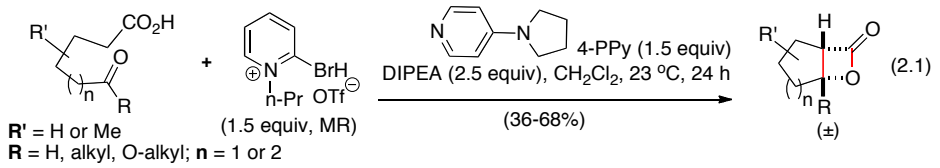
CHAPTER II

A PRACTICAL, DIASTEREOSELECTIVE NUCLEOPHILE CATALYZED ALDOL-LACTONIZATION (NCAL) PROCESS*

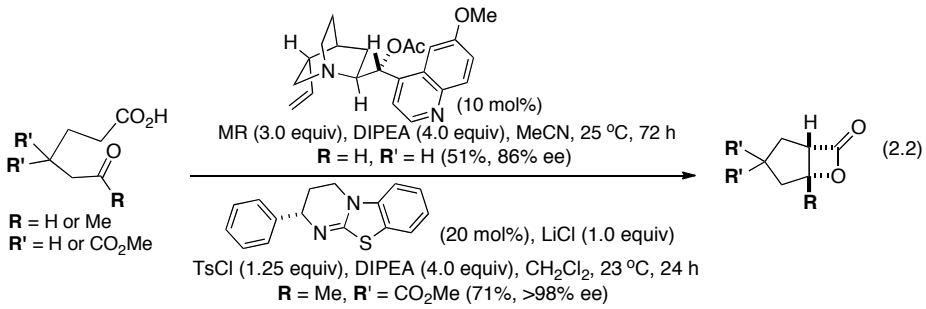
2.1. Nucleophile Catalyzed Aldol-Lactonization

Our interest in β-lactone chemistry has focused on the construction of polycyclic fused β-lactones in the assembly of complex natural products. Employing a nucleophile-catalyzed aldol lactonization (NCAL) process keto- or aldehyde-acids undergo biscyclization forming a new C-C and C-O bond. The methodology has been utilized as a key cyclization step for the synthesis of several natural products including dihyrdroplakevulin A, salinosporamide A, omphadiol, curcumanolide A and curcumalactone (Chapter I). Exploration of the NCAL reaction and substrate scope has been underway in the Romo group since the seminal publication in 2001.[239c] Preliminary reaction conditions employed Mukaiyama's reagent and derivatives thereof along with nucleophilic promoter 4-PPy to form bicyclic and tricyclic β-lactones from aldehyde acids, keto-acids, and dione keto-acid substrates in good yields. (Eq 2.1).[235c,239b,288b]

*Reprinted with permission from "A Diastereoselective, Nucleophile-Promoted Aldol-Lactonization of Ketoacids leading to Bicyclic-β-Lactone" by Gang Liu, Morgan E. Shirley, and Daniel Romo, 2012. *J. Org. Chem.* 77, 2496-2500, Copyright 2012 by ACS Publications.



Subsequent organocatalyzed reaction conditions, found cinchona alkaloid nucleophiles to be optimal in the biscyclization of aldehyde-acids for the construction of fused carbocyclic β-lactones and β-lactone fused tetrahydrofurans (Eq 2.2).[279] While homobenzotetramisole (HBTM), developed by the Birman group was determined to be the most advantageous catalyst for desymmetrization of keto-acids.[290]

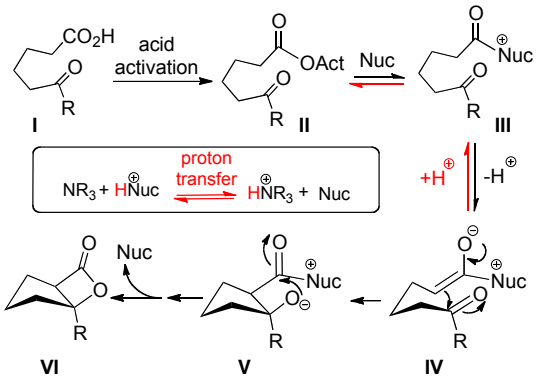


The extended reaction times (up to 72 h), slow addition of the substrate (via syringe pump over 1-2 h), necessity to prepare Mukiayama's reagent, required excess of the nucleophilic promoter (4-PPy), along with diminished yield and selectivity upon scaling up promoted the exploration of a more practical protocol for the NCAL. As a program aimed at providing rapid access to complex scaffolds en route to bioactive natural products, we explored ways to add greater practicality to our established NCAL process.

The aldol-lactonization process is proposed to involve acylammonium intermediate **III**, following transacylation of the activated acid **II** (Scheme 2.1). Ensuing deprotonation, and intramolecular aldol-lactonization provides the β-lactone. While ketene intermediates can be invoked for this process, the high diastereoselectivity

observed with β-substituted acid substrates serves as indirect evidence for the transient ammonium enolate leading to $A^{1,3}$-strain in transition states (vide infra).

Scheme 2.1



Analysis of our working mechanistic pathway for the NCAL process to rationalize the slow reaction rate revealed a possible deleterious equilibrium between the tertiary amine acting as a Bronsted base, and the amine employed as a Lewis base (Scheme 2.1). This is related to Lectka's observations rendering the Lewis base non-nucleophilic due to its protonation state.[98,305,375] Furthermore, reversible deprotonation (**III** to **IV**) and possibly to a lesser extent formation of the acyl ammonium species (**II** to **III**) could both significantly retard the reaction rate.

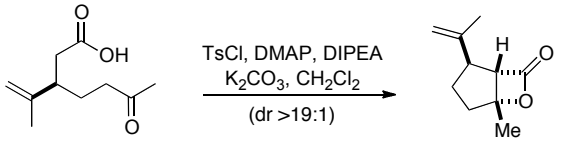
2.2. Optimization of NCAL Conditions for Keto-Acids

When keto-acid **2.1**, derived from (*R*)-carvone, was subjected to previously reported bis-cyclization conditions (Mukaiyama's reagent and 4-PPy) β-lactone **2.2** was obtained in 52% yield during a 48 h reaction time (entry 1, Table 2). Initial optimization aimed to use commercially available reagents; as such 4-nitrobenzenesulfonyl chloride and tosyl chloride were screened as alternative activating agents showing increased

yields (entries 2-3). With tosyl chloride proving to be superior attention was directed to the nucleophilic promoter. Another salient reaction parameter is the nucleophilicity of the Lewis base, which plays a crucial role in the kinetics of the NCAL process. Previously, we noted that the NCAL process with aldehyde-acids could be mediated by cinchona alkaloids bearing a quiniculidine-type tertiary amine In contrast, a stronger and more planar nucleophile, 4-pyrrolidinopyridine (4-PPy), was most effective for the bis-cyclization of keto-acids.[288b] The cost of 4-PPy relative to other potential nucleophilic amines and the hygroscopic nature of this reagent led us to explore alternatives. The commodity chemical DMAP initially resulted in low yield, however the reaction was slow to progress as evidence by the significant amounts of recovered keto-acid after 48 hours (entry 4). In efforts to ensure all acid was being neutralized, potassium carbonate was used in combination with DIPEA as a "shuttle" base.[98,305,375] The increased yield and dramatic reduction in reaction time (entry 5-6), built off Leckta's previously reported inclusion of potassium carbonate use as a phase transfer base to neutralize organic acid byproducts. The addition of potassium carbonate made it no longer necessary to use slow addition of keto-acid *via* syringe pump addition and promoted the bis-cyclization in yields comparable to those obtained with 4-PPy (entries 5 and 6).

The NCAL of keto-acid **2.1a** yielded a single diastereomer whose absolute stereochemistry was confirmed by X-ray analysis. This showed a *trans* relationship

Table 2. Optimization of NCAL conditions for keto-acid 2.1.



2.1a **2.2a**

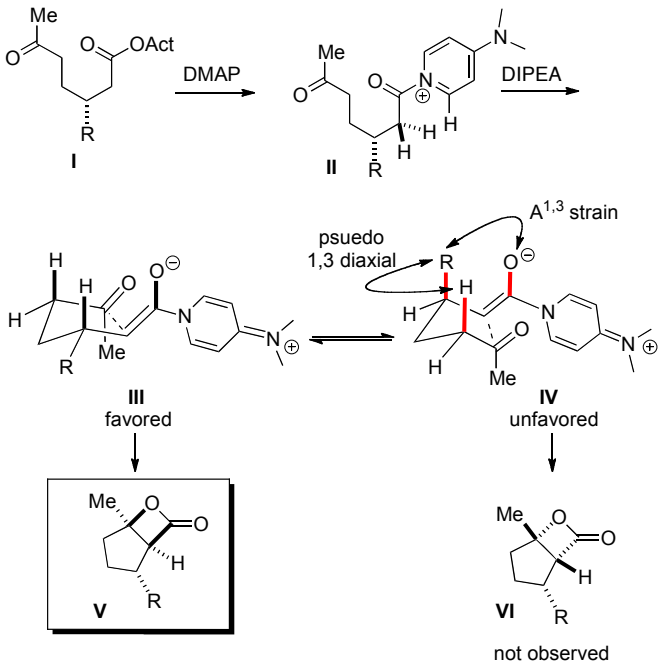
entry	activating reagent	nucleophile	additive	time	% yield [a]
1	M.R.	4-PPy	--	48 h	52
2	*p*-$NO_2C_6H_4SO_2Cl$	4-PPy	--	48 h	57
3	TsCl	4-PPy	--	48 h	68
4	TsCl	$DMAPH_2$	--	48 h	37 [b]
5	TsCl	4-PPy	K_2CO_3	3 h	73
6	TsCl	DMAP	K_2CO_3	3 h	76 [c]

[a] Isolated yield after chromatography. [b] Yield 77% based on recovered starting material. [c] Performed on 8 g scale, range 8 g to 14 g scale 71-83%

between the isopropylidene moiety and the β-lactone. The high diastereoselectivity can be rationalized on the basis of the proposed transition-state arrangements for the aldol-lactonization process (Scheme 2.2) Deprotonation of acylammonium **II** leads to an ammonium enolate, which can exist in two reactive conformations, **III** and **IV.** Note that the olefin geometry of the enolate has not been assigned but is expected to be the *Z*(O)-ammonium enolate, which minimizes developing torsional strain with the ortho-hydrogens of the pyridine ring during the deprotonation step (see structure **II**). In the two possible transition-state arrangements, the ammonium enolate can adopt **III** and **IV**. In the latter, which is a higher energy arrangement **IV**, the β-substituent (R) adopts a pseudoaxial position furthermore causing an unfavorable 1,3-allylic interaction. The absence of these unfavorable steric interactions as viewed in transition-state arrangement

of **III** leads to this conformation being the lower energy pathway and the formation of the anti- substituted cyclopentane **V**.

Scheme 2.2



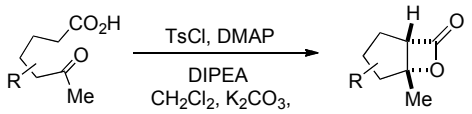
2.3. Substrate Scope

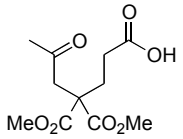
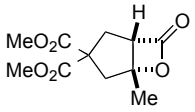
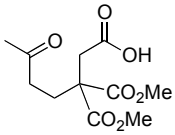
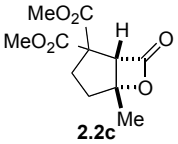
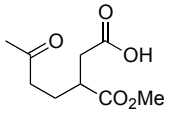
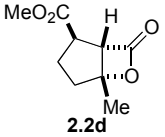
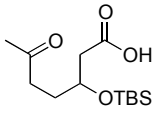
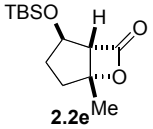
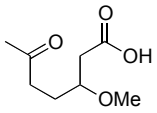
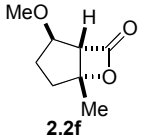
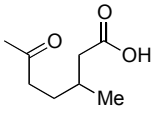
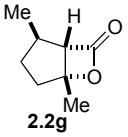
This improved procedure renders a range of keto-acids suitable substrates for the bis-cyclization leading to a series of bicyclic β-lactones in useful yields (Table 3).

To fully explore the applicability of the diastersoselctivey and generality of these practical conditions the corresponding β-substituted keto-acids were synthesized and subjected them to the NCAL process utilizing TsCl and DMAP with K_2CO_3 (entry 6, Table 3). Keto-acids bearing β- and γ-diester substutients, with respect to the carboxylic

acid functionality, gave moderate to good yields in short reaction times (0.5 to 2 h), presumably assisted by the *gem*-disubstituent effect. Among the monosubstituted substrates, β-substituted acids were found to be unique in providing high diastereoselectivity as previously observed.[288b] Keto-acid substrates with various substituents at this position ranging from methyl ester, siloxy, and methyl ether all gave the corresponding bicyclic β-lactones with high diastereoselectivity (>19:1 dr, judged by 500 MHz ^{1}H NMR) delivering the *anti*-diastereomers. With the ultimate goal of employing intermediate β-lactone **2.2** for natural product synthesis explored its compatibility with synthetically useful transformations. Os-mediated dihydroxylation, and cross metathesis both proved to be unfruitful for selective functionalization of the olefin. Oxidation of the pendant olefin with *m*-CPBA afforded the corresponding epoxide **2.8** with excellent yield (98%) and moderate diastereoselectivity (dr 4:1). In addition, ozonolysis of the olefin under standard conditions delivered the methyl ketone **2.9** in 65% yield (Scheme 2.4).

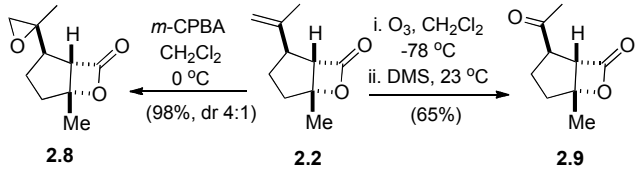
Table 3. Practical nucleophile promoted aldol-lactonization of keto-acids mediated by DMAP.



entry [a]	keto acid	β-lactone	reaction time (h)	yield [b]
1	 **2.1b**	 **2.2b**	0.5	81
2	 **2.1c**	 **2.2c**	0.5	67
3	 **2.1d**	 **2.2d**	1	75
4	 **2.1e**	 **2.2e**	2	68
5	 **2.1f**	 **2.2f**	2	64
6	 **2.1g**	 **2.2g**	6	57

[a]General reaction conditions: DMAP (1.5 equiv). *p*-TsCl (1.1 equiv), DIPEA (4.0 equiv), K_2CO_3 (3.0 equiv), CH_2Cl_2, 23 °C. Diastereoselectivity of entries 3-6 is >19:1 as judged by 500 mHz ^{1}H NMR. [b] Values refer to isolated yields after column chromatography.

Scheme 2.4



In summary, a practical nucleophile-promoted, aldol lactonization of keto-acids is described that renders this process much more amenable to scale-up as demonstrated by the 8 to 14 g synthesis of β-lactone **2.2**. The improved procedure utilizes potassium carbonate as a stoichiometric, insoluble base to accelerate the reaction and further improvements using commercially available, inexpensive reagents provided rapid access to a series of bicyclic β-lactones. The high diastereoselectivity observed for β-substituted keto-acid substrates renders this procedure a very reliable method for the rapid construction of complex, substituted five-membered carbocycles.

CHAPTER III

β-LACTONE-BASED TOTAL SYNTHESIS OF (+)-CAULOLACTONE A

3.1 Introduction

Caulolactone A (**3.3**) a sesquiterpenoid from the stalk of the plant Asarum caulescens, a species native to Mt. Khotsu, Japan, was isolated by Iwata and co-workers.[376] There is no reported biological data for caulolactone A due to insufficient quantities obtained upon isolation. However, many natural products isolated from the same species as caulolactone A are known to display a wide array of biological activities, including anti-hepatotoxic activity (clearing the liver of toxins), potent vasorelaxant activity (widening of the blood vessels), anti-ulcer effects, anti-inflammatory, anti-emetic, and antipyretic activity.[377]

The structure of caulolactone A was determined by NMR analysis and features a *cis*-fused bicyclic core containing an α,β-unsaturated δ-lactone fused to a tetrasubstituted cyclopentane (Figure 29) The cyclopentane ring has three contiguous stereogenic centers, one of them being a quaternary carbon center. As part of a unified strategy to rapidly access bioactive natural products, we identified a common tetrasubstituted cyclopentane. This common core (as shown in blue, Figure 29) could be applied to a wide array of natural products including zedoarondiol,[378] omphadiol,[304] chinesin I,[379] cyclic lycopene deriveratives, tomoenone F, pyxidatol,[380] aromadendrane, pycnanthquinone C,[381] and (+)-4-epi-alismoxide.[382]

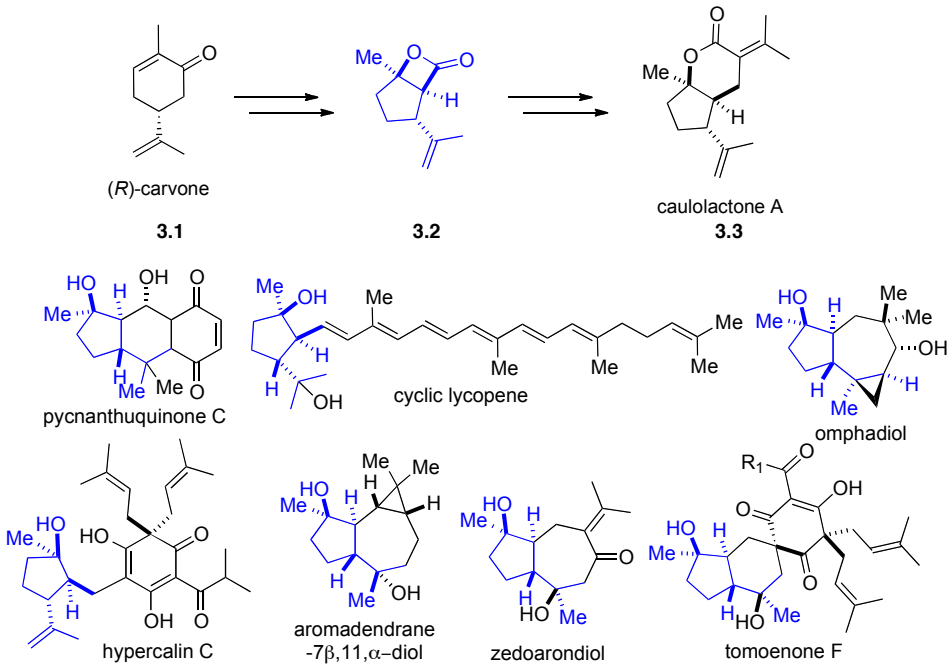


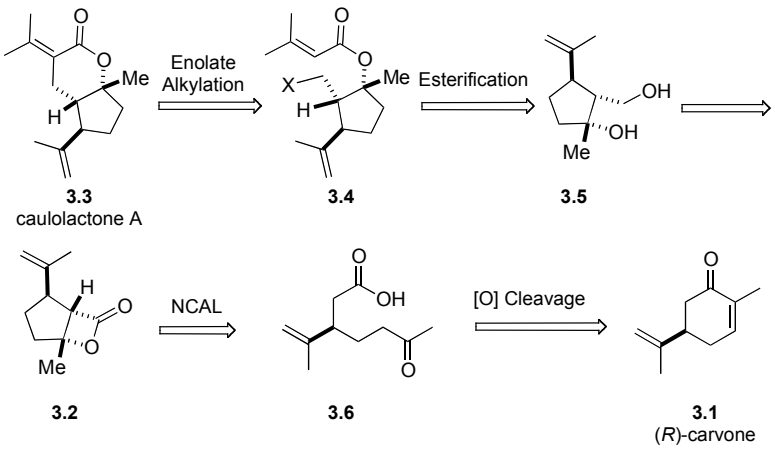
Figure 29. Unified approach to cyclopentane natural products.

Our approach to caulolactone A was premised on employing β-lactone **3.2** (this structure was first mentioned in Chapter II and is fully characterized as structure **2.2a** see Appendix B), accessible via a practical multi-gram (>13 g scale) NCAL process of keto-acids, as a key intermediate to the substituted cyclopentane core. The bicyclic β-lactone moiety served as a versatile starting point for the synthesis of several terpenoids demonstrating its utility by the concise syntheses of caulolactone A and omphadiol.[304] Reporting herein the first synthesis of caulolactone A as part of a unified strategy to bioactive terpene and sequiterpenoids natural products.

3.2 Retrosynthetic Plan

From a retrosynthetic standpoint we envisioned the final C-C bond formed *via* α-alkylation of an extended enolate (**3.4**, Scheme 3.1), which in turn would be derived from esterification of 1,3-diol **3.5** with 3,3-dimethylacrylate. Subsequently intermediate **3.5** is a reduced form of the key intermediate β-lactone **3.2**. As mentioned previously the β-lactone was synthesized from a highly diastereoselective NCAL of keto-acid **3.6** on gram scale (Chapter I) with (*R*)-carvone serving as chiral pool to establish absolute and relative stereochemistry.

Scheme 3.1

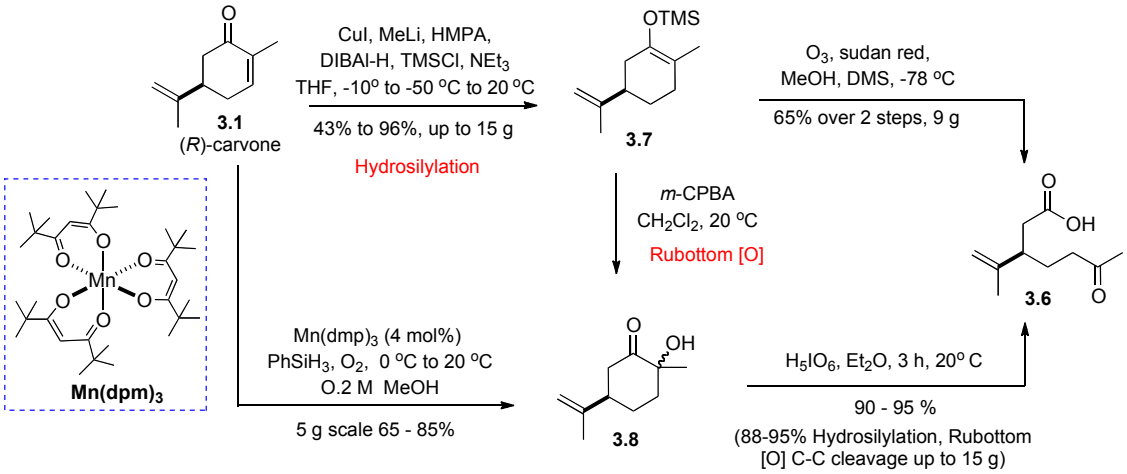


3.3 Route to (*R*)-Carvone β-Lactone

Requiring large quantities of β-lactone **3.2** warranted exploration of robust economical methods for accessing known keto-acid **3.6** on gram scale,[383] initial conditions employed Me-Cu catalyzed conjugate reduction and silylation to deliver silyl enol ether **3.7** as reported by Saegusa[384] (Scheme 3.2). Ensuing ozonolysis in the presence of diazo indicator sudan red provided the desired intermediate **3.6** in relatively

good yields however both the sensitivity of the silyl enol ether and selectivity of oxidative cleavage providing highly variable yields. While an intermediate Rubottom oxidation and periodic acid oxidative cleavage circumvented problems with ozonolysis formation of the silyl enol ether was still problematic. Conjugate reduction and enolate trapping with TMSCl proved to be unfruitful to intermediate **3.7**, delivering a mixture of 1,2- and 1,4-reduction.[385] The stability of α-hydroxy ketone **3.8** and ease of conversion to the desired keto-acid lead us to a Mn(II)-mediated oxidation of carvone reported by Magnus.[386] Even though the procedure was limited to ~5 gram scale (after which diminished yields were observed) it was experimentally facile and negated the very tedious conditions to silyl enol ether **3.7**.

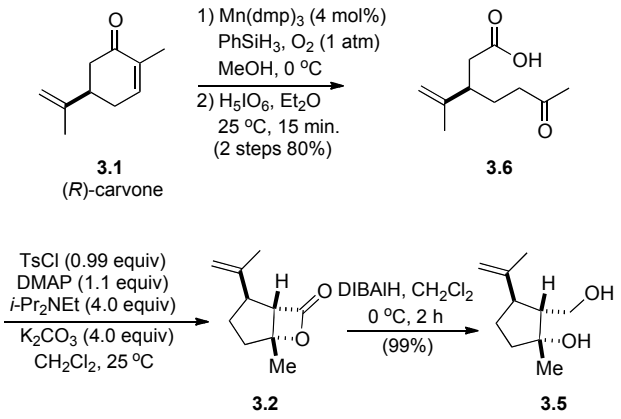
Scheme 3.2



The Mn(III)-mediated oxidation and oxidative cleavage with periodic acid provided keto-acid **3.6** in reliable yields. Using sub stoichiometric amounts of TsCl for the NCAL reaction permitted isolation of intermediate **3.2** without formal purification simply a short passage through a silica gel plug removed the solids and polar byproducts (Scheme

3.3). Subsequent reduction with DIBAlH proceeded in nearly quantitative yield to 1,3-diol **3.5**.

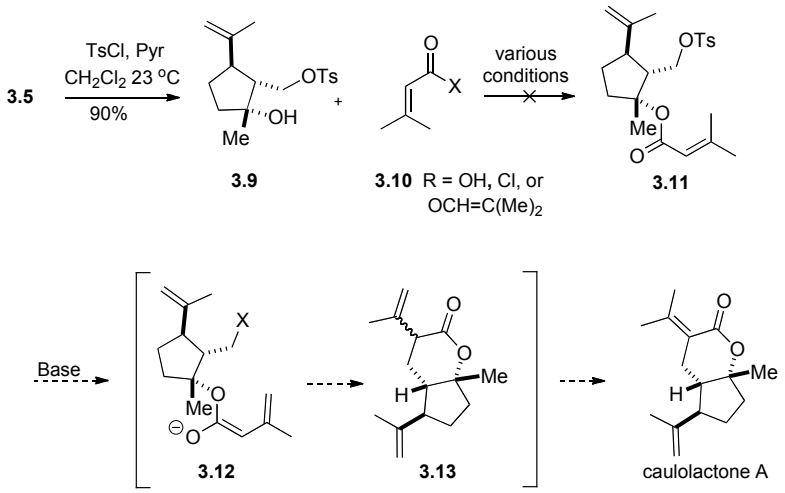
Scheme 3.3



3.4. Studies to Bicyclic Core

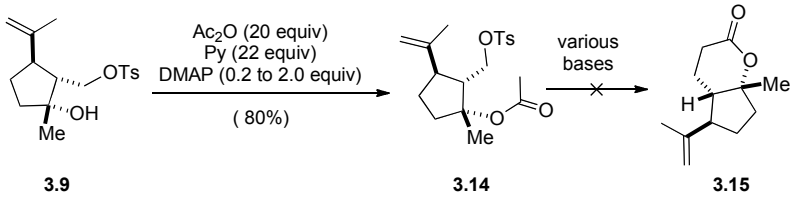
Tosylation of the primary alcohol **3.5** proceeded well en route to intramolecular alkylation via dienolate **3.12** and subsequent base-induced olefin isomerization to the natural product (Scheme 3.4). While efforts directed towards installing the remaining carbons by acylation with β-dimethylacroyl chloride (**3.10**, R = Cl) proved challenging. All attempts to acylate utilizing standard coupling conditions with the acid derivative of **3.10** (R = OH) met only failure. Extensive efforts to acylate the tertiary alcohol with the chloride[387] or anhydride[388] derivative **3.10** resulted in various elimination products or decomposition.

Scheme 3.4



Owing to steric factors and the electronics of the 3,3-disubstituted acrylate acylation with acetic anhydride only provided possible when utilizing acetic anhydride as a solvent (Scheme 3.5). After obtaining the acylated tertiary alcohol **3.14** it was necessary to cyclize to the desired ring system. All attempts to then cyclize *via* tosylate displacement with an acetate enolate (LiHMDS, LDA, *t*-BuOK, etc.) resulted in recovery of starting material or decomposition.

Scheme 3.5.

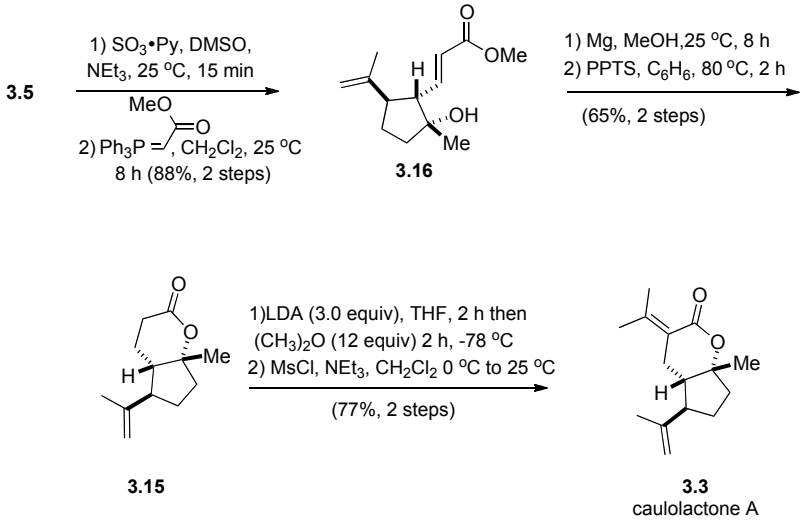


3.5. Completion of (+)-Caulolactone A

Alternatively Parihk-Doering oxidation[296] of **3.5** and immediate Wittig olefination proved successful for installing the necessary carbons to form the γ-lactone

3.16 (Scheme 3.6). Reduction to the saturated ester was then carried out using magnesium, in which case some of the resulting alcohol cyclized to **3.15**. Cyclization to the biscyclic δ-lactone could be pushed to higher conversion under reflux with PPTS. The final steps involved a two-step aldol condensation with acetone to yield caulolactone A in 10 steps and 26% overall yield.

Scheme 3.6



This concise synthesis made use of natural product (R)-carvone for readily available starting material and served to establish the absolute stereochemistry of the molecule.

CHAPTER IV

DEVELOPMENT AND APPLICATION OF A NUCLEOPHILE-CATALYZED MICHAEL ALDOL-β-LACTONIZATION (NCMAL) PROCESS FOR PRACTICAL CYCLOPENTANE SYNTHESIS*

4.1. Introduction

Synthetic transformations that rapidly assemble complexity are actively being pursued given the importance of these processes for improvements in synthetic efficiency. As such organocascade reactions have emerged as some of the most powerful strategies to rapidly construct structural complexity[389] Numerous are the conventional methods for constructing cyclohexanes including Robinson annulation,[390] cationic polyene olefin cyclization,[391] and the venerable Diels-Alder.[392] Whereas the Pauson-Khand reaction,[393] trimethylenemethane [3+2] cycloaddition,[394] photochemical olefin-arene cycloaddition,[395] and the Nazarov cyclization,[396] used for cyclopentane synthesis suffer from the requirement for specialized substrates or have limited enantioselective modifications. Owing to the structural diversity and complexity of substituted cyclopentanes in pharmaceutical agents and bioactive natural products[397] (A, Figure 30)

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*Reprinted with permission from "Rapid Assembly of Complex Cyclopentanes Employing Chiral, α,β-Unsaturated Acylammonium Intermediates" by Gang Liu, Morgan E. Shirley, Khoi N. Van, Rae Lynn McFarlin, and Daniel Romo, 2013. *Nature Chem.* 5, 1049-1057, Copyright 2013 by Macmillan Publishers Limited.

we aimed to develop a more direct and general way for forming this motif. We recently disclosed a nucleophile-catalyzed Michael aldol β-lactonization (NCMAL) delivering a diverse array of β-lactone-fused cyclopentane scaffolds (B, Figure 30) a structural motif found in the natural products spongiolactone, vibralactone A, and chinensin II.

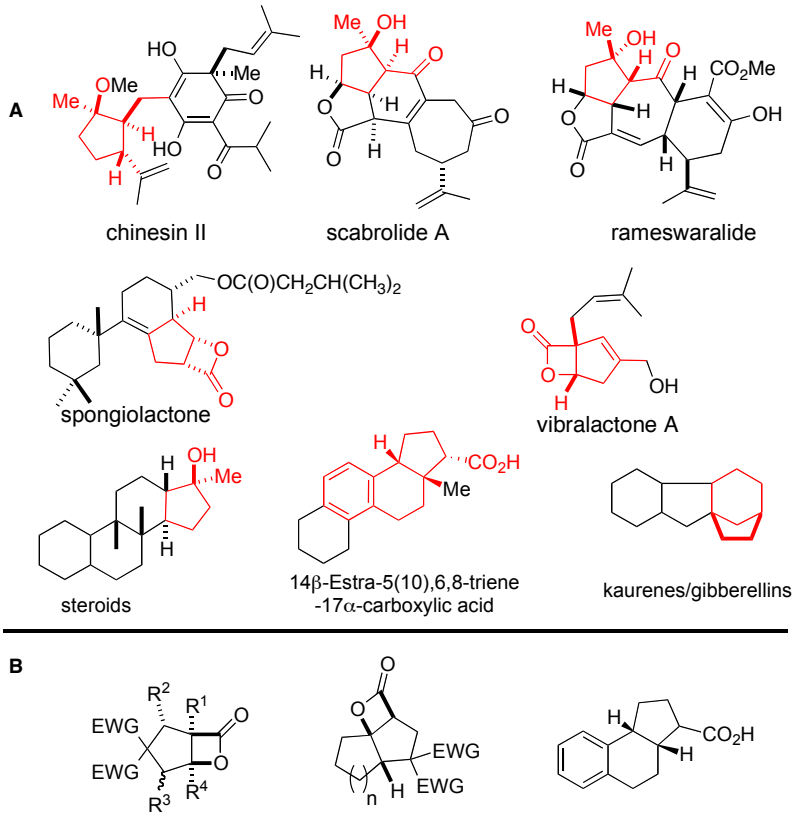


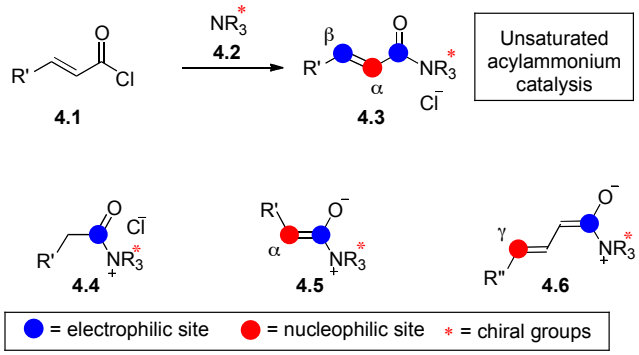
Figure 30. Natural products accessible via NCMAL methodology.

While our work with the NCAL has proved robust for generating cyclopentane fused β-lactones, the requirement for tethered keto-acids often hampers the utility, as the NCAL precursors require several steps and can be difficult themselves to synthesize (Chapter

II). Prompted by our continued interest in ammonium enolate we sought to improve the synthetic efficiency of complex cyclopentanes by developing a tandem organocascade process from readily or commercially available reagents.

In the context of nucleophilic chiral amine catalysis **4.4-4.6** are the reported reactive intermediates for asymmetric bond-forming events (Scheme 4.1).[285] Chiral acylammonium intermediate **4.4**, possessing an electrophilic site has been used for kinetic resolution of alcohols.[398] The versatile chiral ammonium enolate, **4.5** has found

Scheme 4.1

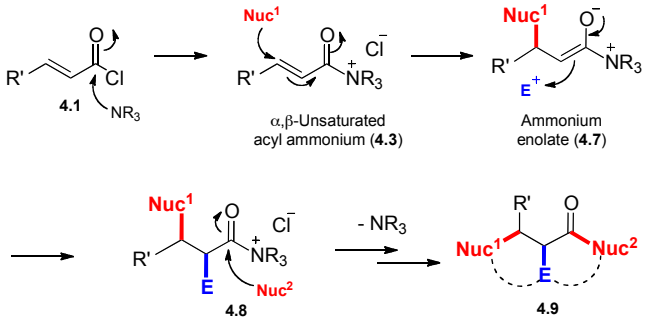


widespread applications, notably building on Wynberg's aldol-β-lactonization.[99] While the most recently reported intermediate, ammonium dienolate **4.6**, has been reported in [4+2] cycloadditions.[399] Building on our previously described aldol-β-lactonization process (Chapter I and II) and interests in ammonium enolate chemistry we sought to exploit the full reaction potential of chiral α,β,-unsaturated acylammonium intermediate **4.3** envisioning that the three disparate reactive sites could be sequentially revealed to induce tandem bond-forming events (Scheme 4.1) Fu reported the seminal application of chiral acylammonium 4.3, in a single example providing a net [3+2] cycloaddition of a silylated indene and acyl unsaturated acyl fluoride.[400] The only other report of this

intermediate was by the Smith group (while we were in manuscript preparation), employing unsaturated, mixed anhydrides and 1,3-dicarbonyl compounds to enol lactones by way of a tandem Michael-enol-lactonization process.[401] With only two reports of unsaturated chiral acylammonium **4.3** both of which overlooked the full potential of the latent, triple reactivity for multiple bond forming events we developed a novel organocascade process involving a nucleophile-catalyzed, Michael-aldol-β-lactonization (NCMAL) sequence that rapidly generates stereochemically complex cyclopentanes from commodity unsaturated acid chlorides including both fused and bridged cyclopentyl systems (B, Figure 30).

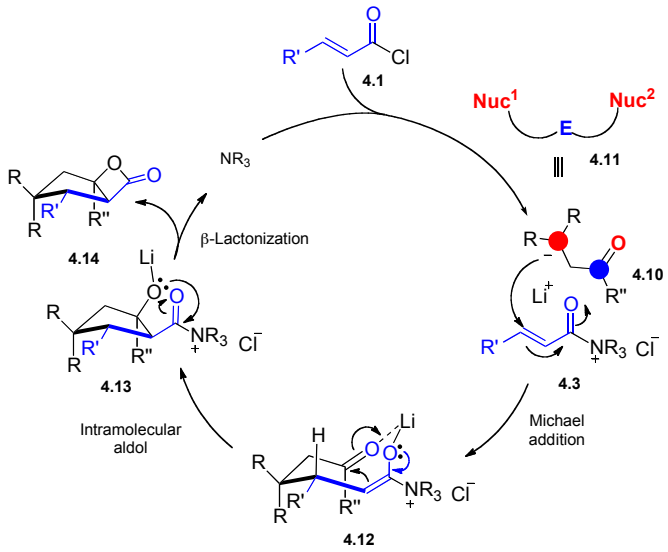
Building on our previously described aldol-β-lactonization process (Chapter I and II) we pioneered a catalytic, asymmetric activation of acid chlorides through use of a a chiral amine nucleophile (NR_3^*). Seeking to exploit the full reaction potential of chiral α,β,-unsaturated acylammonium intermediate **4.3** we envisioned three disparate reactive sites that could be sequentially revealed to induce tandem bond-forming events (Scheme 4.2). Following Michael addition by an appropriate nucleophile (Nuc^1), a chiral ammonium enolate **4.7** is revealed enabling α-substitution with a tethered electrophile (E) to deliver the acylammonium **4.8**. While a second nucleophilic addition to the resulting acyl ammonium (**4.8**) regenerates the amine catalyst effectively stitching three bonds together in a tandem process.

Scheme 4.2



The envisioned catalytic cycle for the organocascade process would be initiated by an intermolecular Michael of a tethered, triply-reactive reagent **4.11**, such as anionic ketone **4.10**, to the α,β-unsaturated acyl ammonium intermediate **4.3**. The key, chiral intermediate **4.3** would be derived from simple substitution of a chiral amine catalyst (NR_3) 4.**2** with an unsaturated acid chloride **4.1** (Scheme 4.3). Generation of the versatile ammonium enolate **12** engages with the pendant ketone in an intramolecular aldol-β-lactonization templated by a Li(I) cation to deliver a stereoselective aldol reaction leading to formation of cyclopentane **4.13**. Based on our previous studies, high *anti* diastereoselectivity was anticipated for β-substituted acid chlorides since this alleviates developing $A^{1,3}$-strain during the aldol-lactonization step.

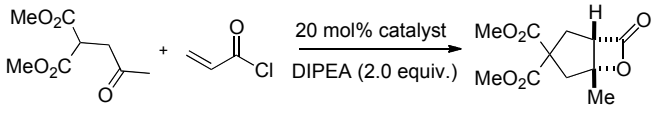
Scheme 4.3



4.2 Condition Optimization

Our initial reaction conditions involved generation of the malonate anion with various Brønsted bases in the presence of a nucleophilic catalyst followed by slow addition of the acid chloride to the mixture. Use of the nucleophile alone or the strong Brønsted base, DBU (1,8- diazabicyclo[5.4.0]undec-7-ene) did not provide the desired bicyclic-β-lactone **4.14a** (Table 4, entries 1, 2). While combined Lewis acid Lewis base conditions (DBU and LiClO4, entry 3) afforded the desired product in 68% yield, this was not general for all substrates, notably cyano-esters (provided less than 40% conversion albeit optimization). Employing LDA or LiHMDS or the 'troublesome' substrates (compounds **4.10f-i**) drastically enhanced the yield. The stronger lithium bases lead to further improvement in yields (entries 4-6) up to 75% yield, with weakly coordinating counter ions (Na^+ or K^+) having an adverse effect (entries 7, 8).

Table 4. Optimization of the NCMAL process.



4.10a (1.0 equiv.) **4.1a** (2.0 equiv.) **(±)-4.14a**

entry	base	catalyst	solvent	% yield*
1	--	DMAP	CH_2Cl_2	<5
2	DBU	DMAP	CH_2Cl_2	<5
3	$LiClO_4$ + DBU	DMAP	CH_2Cl_2	68
4	LDA	DMAP	THF/CH_2Cl_2	73
5	^{t}BuLi	DMAP	THF/CH_2Cl_2	75
6	LiHMDS	DMAP	THF/CH_2Cl_2	75
7	NaHMDS	DMAP	THF/CH_2Cl_2	23
8	KHMDS	DMAP	THF/CH_2Cl_2	<5
9	^{i}PrMgCl	DMAP	THF/CH_2Cl_2	75
10	LiHMDS	4-PPY	THF/CH_2Cl_2	84
11	LiHMDS	9-AJ†	THF/CH_2Cl_2	77
12	LiHMDS	--	THF/CH_2Cl_2	<5

*Refers to isolated yields. <5% yield indicates that β-lactone was not detected by TLC, ^{1}H NMR (500 MHz), or FT-IR. † 9-azajulolidine (9-AJ). Initial reaction design and inception by Dr. Gang Liu, originally employing entry 3. Due to issues with these conditions for mixed EWD I moved to LDA/LiHMDsS With the goal of a general approach subsequentconditio were screeed, ultimately revealing finding LiHMDS to be most general for ensuing substrate variety.

After a brief screening of nucleophiles, including 9-azajulolidine, revealed 4-PPy and LiHMDS was an optimal combination for the NCMAL process (entries 10-11). As evidence for the requirement of the nucleophile, a control reaction without 4-PPY did not afford any β-lactone (entry 12).

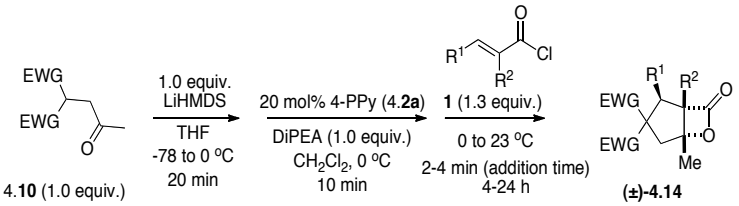
4.3 Substrate Scope

Exploring the generality an investigation of the Michael donors, bearing two electron with-drawing groups (Table 5, entries 1-9) with acryloyl chloride was

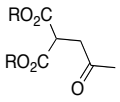
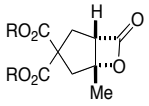
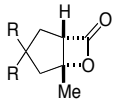
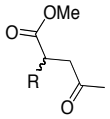
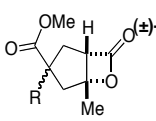
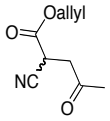
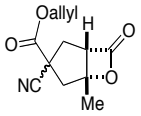
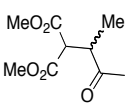
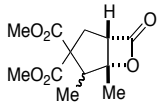
undertaken. The substrates were obtained in a single step by alkylation of the corresponding malonates with chloroacetone (Appendix A). As depicted in Table 5, a variety of keto diesters, diketones, and dinitriles (entries 1-5) participate in the NCMAL process to provide the desired cyclopentanes **4**.**14b-f** 53-83% yields. When a β-keto ester or α-cyano esters were used as Michael donors (Table 5, entries 6-8), cyclopentanes **4.14g,h** were obtained in 65-72% yields with poor diastereoselectivity (dr 1-1.7:1) as expected, however inconsequential given that these diastereomers would ultimately converge to a single diastereomer following decarboxylation (*vide infra*). Introduction of an α-keto stereocenter, as in ketomalonate **4.10j**, also led to a mixture of diastereomers **4.14j** (dr 2:1) in 81% yield.

Variation of the Michael acceptors through the study of a diverse array of commercially available α,β-unsaturated acid chlorides was undertaken next. Under the optimized NCMAL conditions, cyclopentanes were readily accessed bearing up to three contiguous stereocenters with excellent relative stereochemical control (Table 5, entries 10-17) Aryl-substituted acid chlorides with varied electronic properties (entries 12-14) proceeded in 83-90% yields. Use of sorbic chloride (**4.1g**) provided a 64% yield of

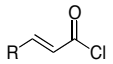
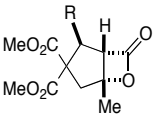
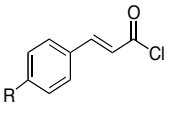
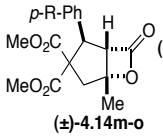
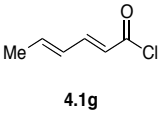
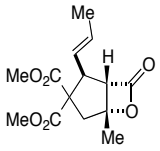
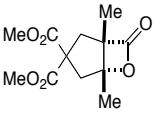
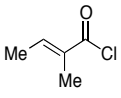
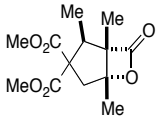
Table 5. Scope of a racemic NCMAL process.



Varying the Michael donor with acryloyl chloride **1a**

entry	Michael donor	bicyclic-b-lactone	% yield (dr)*
1 2 3	 **4.10b-d**		(**±)-4.14b:** R = tBu, 73 (**±)-4.14c**: R = allyl, 83 (**±)-4.14d**: R = Bn, 53
4δ 5δ	 **4.10e-f**		(**±)-4.14e**: R = C(O)Me, 64 (**±)-4.14f**: R = CN, 60
6 7	 (±)-**4.10g-h**		(**±)-4.14g**: R = C(O)Me 72 (1:1) (**±)-4.14h**: R = CN 65 (1.7:1)
8	 **(±)-4.10i**	 (±)-4.**14i**	55 (1.16:1)
9	 **(±)-4.10j**	 (±)-4.**14j**	84 (2:1)†

Varying the Michael acceptor with acetodimethyl malonate **10a***,†

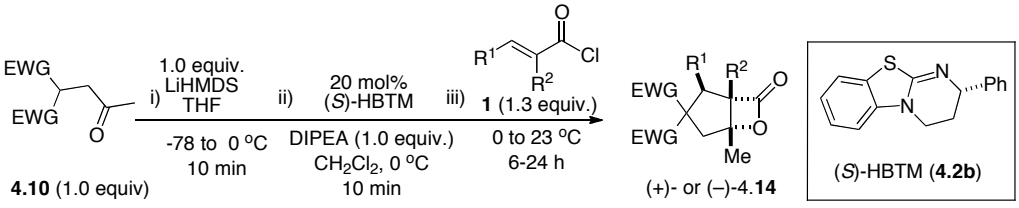
entry	Michael acceptor	bicyclic-b-lactone	% yield (dr)*,†,ω
10 11	 **4.1b-c**		(**±)-4.14k**: R = Me 94 (>19:1)‡ (**±)-4.14l**: R = CO_2Et 91 (>19:1)
12 13 14	 **4.1d-f**	 **(±)-4.14m-o**	(**±)-4.14m**: R = H, 90 (>19:1)‡ (**±)-4.14n**: R = NO_2, 83 (>19:1) (**±)-4.14o**: R = OMe 87 (>19:1)
15	 **4.1g**	 **(±)-4.14p**	64 (>19:1)
16	 **4.1h**	 **(±)-4.14q**	78
17	 **4.1i**	 **(±)-4.14r**	60 (>19:1)‡

*All yields refer to isolated yields. † Diasteromeric ratio determined by ^{1}H NMR. ‡ Relative stereochemistry verified by X-ray analysis.
δ Reaction performed by Rae Lynn McFarlin. ωReaction performed by Dr Gang Liu.

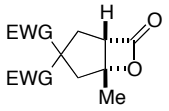
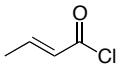
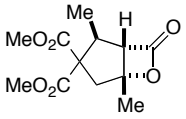
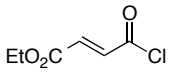
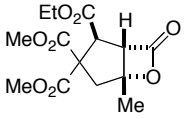
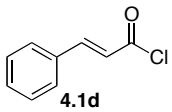
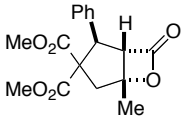
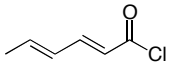
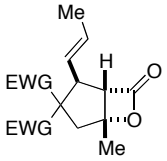
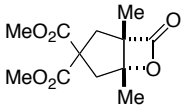
cyclopentane **4.14p** with the installation of an alkene moiety on the bicyclic providing a robust functional handle for subsequent manipulations and diversification (**4.1g**, entry 15). An α-substituted acid chloride **4.1h** (entry 16) was also reactive under standard conditions and afforded cyclopentane **4.14q** in 78% yield bearing two contiguous quaternary stereocenters, one of which is an all carbon quaternary center. Finally, a highly congested cyclopentane **4.14r** was accessible with α,β-dimethyl acryloyl chloride **4.1i** (entry 17) in 60% yield as a single diastereomer.

In line with our previous findings of chiral isothiourea, homobenzotetramisole (HBTM) developed by Birman, proved to be the optimal catalyst to promote an enantioselective NCMAL (Table 6). Employing the aforementioned optimized conditions for the racemic NCMAL, HBTM uniformly delivered the cyclopentanes (+)-**4.14a,** (+)-**4**.**14c,** and (+)-**4.14d** in 59-74% yields and 93-96% ee (Table 4, entries 1-4). The bis-allyl malonate ester 4.**10d** was of particular interest for enabling further functionalization or removal of an electron-withdrawing group from the cyclopentane adducts (+)-**4**.**14c** and (+)-**4.14d** through mild Pd(0)-catalyzed decarboxylative transformations (entry 3). The absolute configuration of β-lactone (+)-**4.14a** was confirmed by X-ray analysis of a derivative following ring opening with *p*-bromobenzylamine (Appendix A). The diketone substrate **4.10e** was also well tolerated in the asymmetric process, leading to diketo cyclopentanes (+)-**4.14e** in 61% yield and 95% ee (Table 6, entry 5). The practicality of the NCMAL process was demonstrated by a gram-scale reaction using dimethyl keto malonate **10a** as Michael donor delivering (+)-**4.14a** with comparable results (74% yield, 93% ee, Table 6, entry 2).

Table 6. Catalytic, enantioselective, nucleophile catalyzed, Michael aldol-β-lactonization.



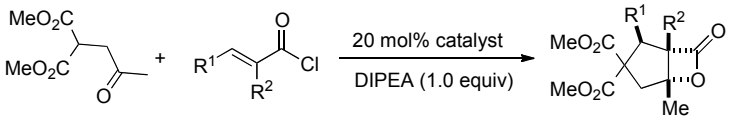
4.10 (1.0 equiv) (+)- or (–)-4.**14**

entry	Michael donor (EWG)	acid chloride	bicyclic-β-lactone		% yield (dr)*	% ee
1†,∞	**4.10a** (CO_2Me)			**(+)-4.14a**§	72(>19:1)	97
2†,‡,ω	**4.10a**	 **4.1a**		**(+)-4.14a**	74(>19:1)	93
3†	**4.10c** (CO_2allyl)			**(+)-4.14c**	74(>19:1)	95
4†	**4.10d** (CO_2Bn)			**(+)-4.14d**	59(>19:1)	98
5†	**4.10e** (C(O)Me)			**(+)-4.14e**	61(>19:1)	95
6	**4.10a**	 **4.1b**		**(+)-4.14k**	80 (>19:1)	94
7†,ω	**4.10a**	 **4.1c**		**(+)-4.14l**	95 (>19:1)	90
8†,ω	**4.10a**			**(-)-14.4l**ò	90 (>19:1)	89
9	**4.10a**	 **4.1d**		**(+)-4.14m**	80 (>19:1)	99
10ϒ	**4.10a**			**(+)-4.14m**	78 (>19:1)	90
11	**4.10a**	 **4.1g**		**(+)-4.14p**§	62 (>19:1)	99
12	**4.10a**			**(-)-4.14p**ò	60 (>19:1)	99
13	**4.10c**			**(+)-4.14s**	54 (>19:1)	94
14	**4.10a**	 **4.1h**		**(+)-4.14q**	80 (>19:1)	99

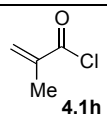
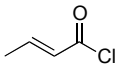
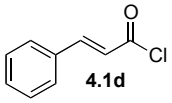
*All yields refer to isolated yields, enantiomeric excess was determined by chiral GC or HPLC (See Appendix), diastereomeric ratios were determined by ^{1}H NMR (500 MHz), and addition of acid chloride was over a 2 h period. Reaction times varied from 6 to 24 h (see Supplementary for reaction details). †Acid chlorides were added over 4 min. §Absolute stereochemistry was confirmed by X-ray analysis of (+)-**14p** and a derivative of (+)-**14a** and others assigned by analogy. ‡Reaction was performed on gram scale. ϒ5 mol% (*S*)-HBTM was employed. ò (*R*)-HBTM was employed as catalyst.∞Reaction initially run by Dr. Gang Liu, and replicatied by Rae Lynn McFarlin and Morgan E. Shirley. ωReaction by Rae Lynn Mcfarlin.

To probe whether the initial Michael addition could proceed in an enantioselective manner, we next studied β-substituted acid chlorides. Indeed, use of (*S*)-HBTM with acid chlorides **4.1b-c** and **4.1d,g** gave cyclopentanes (+)-**4.14k-l** and (+)-**4.14m,p** in 89-99% ee as single diastereomers in 62-95% yields (Table 6, entries 6-12) including those bearing ethyl ester and alkenyl substituents suitable for further functionalization. The relative and absolute stereochemistry of the alkenyl substituted cyclopentane (+)-**4.14p** was confirmed by X-ray analysis (Appendix A). When α-substituted acid chlorides were studied, an important difference in reaction outcomes noted under standard conditions. Optimization studies revealed that extending the addition time of the acid chloride once again led to higher conversion and enantioselectivity. A competitive, racemic background pathway with several acid chlorides revealed a racemic background reaction with varying rates owing to the unique reactivity behavior of the Michael accepters with the enantioselective NCMAL (Table 7).

Table 7. Competitive NCMAL reactions.



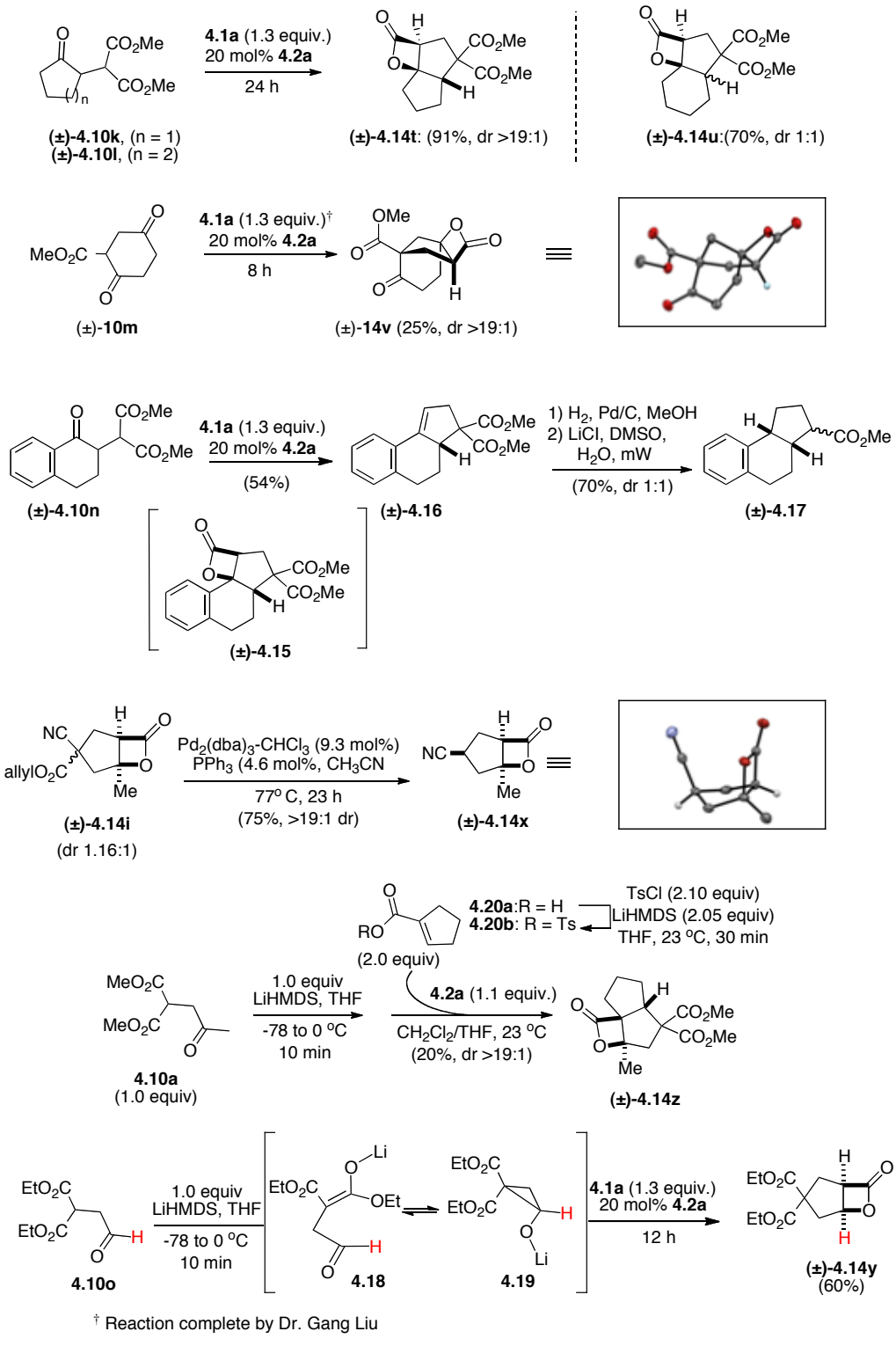
4.10a (1.0 equiv.) **4.1** (2.0 equiv.) **4.14**

entry	catalyst	acid chloride (**4.1**)	add. time	yield %	ee
1	---	 **4.1h**	---	80	0
2	(S)-HBTM		4 min	78	30
3	(S)-HBTM		2 h	80	99
4	(S)-HBTM	 **4.1b**	4 min	60	80
5	(S)-HBTM		2 h	80	93
6	---		---	43	0
7	(S)-HBTM	 **4.1d**	4 min	72	80
8	(S)-HBTM		2 h	80	99
9	(S)-HBTM		10 h	81	95

4.4. Applications and Derivatization

To demonstrate the utility of the described organocascade process for ring annulation leading to more complex molecular architectures, a collection of polycyclic carbocycles with fused or bridged topology were targeted using monocyclic Michael donors. Cyclopentanone **4.10k** was readily combined with acryloyl chloride (**4.1a**) to give the tricyclic 5,5,4-bicyclic system **4.14t** as a single diastereomer in 91% yield (Figure 30). In contrast, cyclohexanone **4.10l** afforded the corresponding tricyclic products **4.14u** in 70% yield as a 1:1 mixture of diastereomers likely owing to the lower energy difference between *cis*- and *trans*-fused 5,6-bicyclic systems. Cyclohexanedione

4.10m also participated as a Michael donor with acryloyl chloride (**4.1a**) to give the tricyclic cyclopentane **4.14v** possessing a bridged topology, albeit in 25% yield (Figure 30). The relative stereochemistry was confirmed by single crystal X-ray analysis and the bridged cyclopentane in **4.14v** is reminiscent of one substructure of the gibberellin family of terpenoids. The tetralone-derived malonate **4.10n** also participated in the NCMAL, however the presumed intermediate β-lactone **4.15**, possessing a benzylic C-O bond, underwent facile decarboxylation to deliver the cyclopentene **4.16**. Following hydrogenation and Krapcho decarboxylation, the monoester **4.17** was obtained, demonstrating removal of an activating group in the Michael donor. Furthermore, the monoester **4.17** resembles a previously described steroidal intermediate (Figure 30). The Pd(0)-mediated decarboxylation of the allyl ester substituted cyclopentane **14i** was explored. Mild conditions were identified that led to reductive decarboxylation of the mixture of diastereomeric cyclopentanes **4.14i** at 77 ^{o}C which importantly left the β-lactone intact and converged to a single diastereomer of the cyano-substituted cyclopentane **4.14x**. The relative stereochemistry of **4.14x** was verified by X-ray analysis (inset, Figure 31; Appendix A). To the best of our knowledge, this is the first example of ester decarboxylation in the presence of a β-lactone. Extension of the NCMAL from ketone substrates to the corresponding aldehyde malonates too proved fruitful.



† Reaction complete by Dr. Gang Liu

Figure 31. Extensions of the NCMAL process.

We built our enantioselective model stemming from a report by the Smith group of an X-ray crystal structure of an HBTM-derived, unsaturated acylammonium salt supporting an interaction between the acylammonium oxygen and the sulfur atom of the isothiourea first proposed by Birman for these catalysts (Figure 32) The observed facial selectivity during the Michael addition this interaction and the half-chair conformation of the pyrimidine ring enforced by the planarity of the C-N-C moiety. These factors place the phenyl ring in a pseudoaxial orientation effectively blocking the *re* face of the unsaturated acylammonium with (*S*)-HBTM. The high diastereoselectivity observed during the aldo step derives from minimization of $A^{1,3}$-strain described previously.

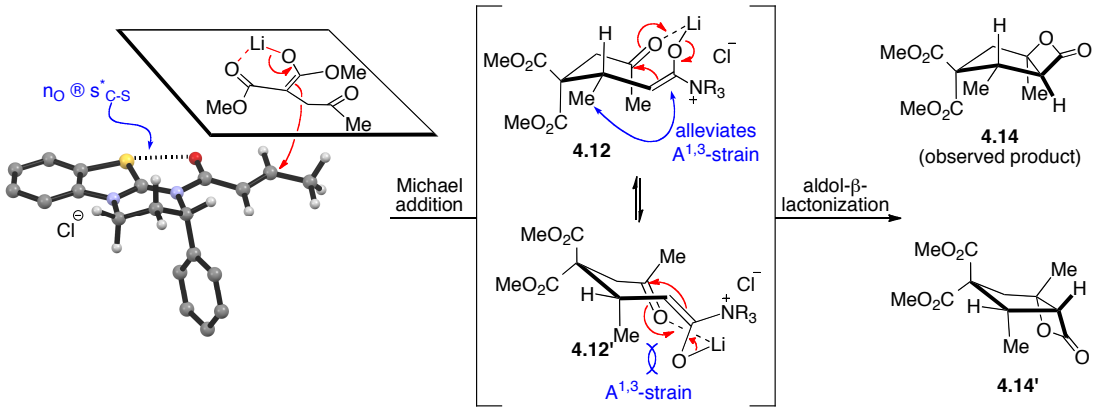


Figure 32. Proposed transition state arrangements for enantioselective NCMAL.

The complexity-generating, nucleophile-catalyzed, Michael-aldol-β-lactonization process described herein delivers high synthetic efficiency for complex cyclopentane synthesis by formation of three new bonds, up to three stereogenic centers, and two rings in a single operation from simple starting materials. Furthermore, the

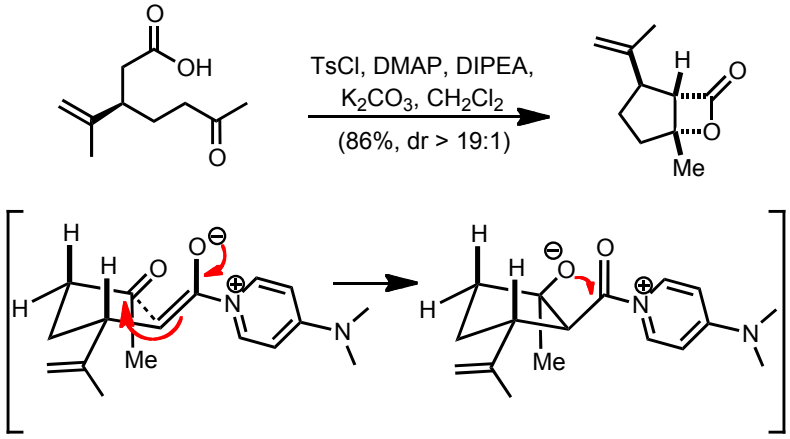
simple yet powerful asymmetric activation mode of commercially available, unsaturated acid chlorides utilized to its full potential for the first time by reaction at all three positions, provides a new paradigm for the design of additional organocascade processes. Further explorations are currently underway discerning g the unique and selective nature of chiral α,β-unsaturated acyl ammoniums for multiple bond forming events.

CHAPTER V

CONCLUSION

A practical, diastereoselective nucleophile catalyzed aldol-lactonization (NCAL) process has been developed for accessing bicyclic β-lactones from keto-acid substrates as a C-C and C-O bond forming strategy for the assembly of complex natural products. Reaction rates were increased and yields improved by addition of K_2CO_3 as a shuttle base. This new and improved protocol allows for facile construction of substituted bicyclic β-lactones from commercially available and inexpensive acid-activating agent TsCl and nucleophilic promoter DMAP (Scheme 5.1), with β-substituted acids afforded products as a single diastereomer.

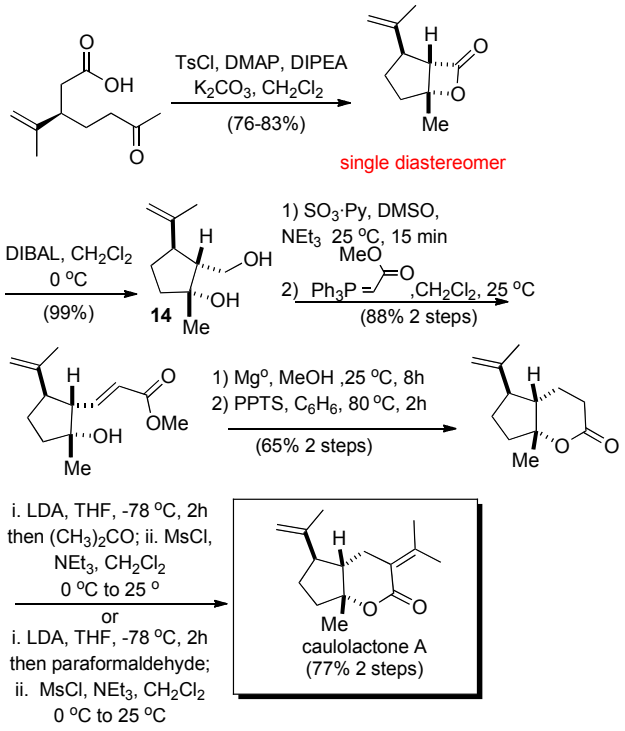
Scheme 5.1



A concise synthesis of caulolactone A was reported that employs the aforementioned NCAL conditions for the generation of a versatile bicyclic β-lactone. The synthesis of caulolactone A was completed in 10 steps with a 26% overall yield void of protecting groups relying on a highly diastereoselective bis-cyclization with a carvone

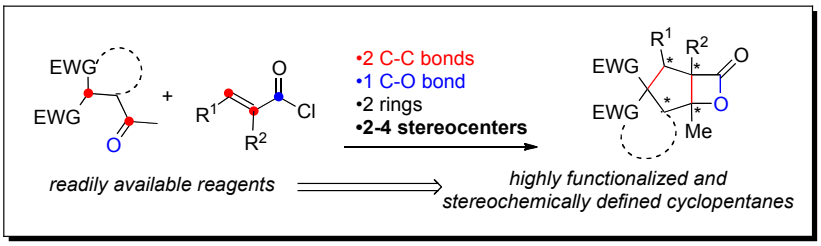
derived keto-acid (Scheme 5.2). The key aldol lactonization provides a tetrasubstituted cyclopentane core that is present in a diverse array of bioactive natural products.

Scheme 5.2



As our interest in β-lactones and more recently our desire for developing efficient methods to complex cyclopentane scaffolds, the nucleophile-catalyzed Michael-aldol β-lactonization was disclosed. This highly efficient bonding forming process was used to construct two C-C bonds, one C-O bond, and two rings via an ammonium enolate species chemoselectively formed from chiral a-,β-unsaturated acyl ammoniums (Scheme 5.3). Subsequent explorations revealed the potential to make polycyclic bridged and fused scaffolds in a single step from commodity chemicals with high levels of enantio- and diastereocontrol.

Scheme 5.3



Applications of this methodology and extensions to accessing natural products warrants itself for further explorations.

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APPENDIX A: ABBREVIATIONS

4-PPY	4-pyrrolidinopyridine
AAC	acyl halide-aldehyde cyclocondensation
AcCl	acetyl chloride
AcOH	acetic acid
Ac*Qd*	*O*-acetyl quinidine
Ac*Qn*	*O*-acetyl quinine
Boc	di-*tert*-butyl dicarbonate
BTF	trifluoromethylbenzene
CAN	ceric ammonium nitrate
Cbz	carboxybenzyl
CDI	*N*,*N*'-carbonyldiimidazole
CGA	carboxyl group activation
CIP	2-chloro-1,3-dimethylimidazolidium hexafluorophosphate
CITPP	*meso*-tetra(4-Clphenyl)porphyrinato
CSD	Cambridge Structural Database
DBPO	di-*tert*-butylperoxyoxalate
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	1,3-dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DET	diethyl tartrate
$(DHQD)_2PHAL$	hydroquinidine 1,4-phthalazinediyl diether
DIAD	diisopropyl azodicarboxylate
DIBAlH	diisobutylaluminium hydride
DIPEA	*N,N*-diisopropylethylamine
DMAP	4-(dimethylamino)pyridine
DMDO	dimethyldioxirane
DME	dimethyl ether
DMP	Dess-Martin periodinane
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
DTBP	2,6-di-*tert*-butylpyridine
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
EDCI	see EDC
ee	enantiomeric excess
Et	ethyl
EtOAc	ethyl acetate

FDA	Food and Drug Adminstration
Fm	fluorenylmethyl
GDH-103	glucose dehydrogenase 103
Grubbs II	2nd generation Hoveyda-Grubbs catalyst
HATU	1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b] pyridinium 3-oxid hexafluorophosphate
HBTM	homobenzotetranisole
HGA	hydroxy group activation
HMPA	hexamethylphosphoramide
HOAc	acetic acid
HOAT	1-hydroxy-7-azabenzotriazole
HOBT	hydroxybenzotriazole
HOMO	highest occupied molecular orbital
HSAB	Hard Soft Acid Base
IMes	bis(1,3-(2,4,6-trimethylphenyl)imidazol-2-ylidene)
IND	investigational new drug
KHMDS	potassium bis(trimethylsilyl)amide
LDA	lithium diisopropylamide
leu	leucine
LiHMDS	lithium bis(trimethylsilyl)amide
LUMO	lowest unoccupied molecular orbital
Lyso-PC	1-palmitoyl-sn-glycero-3-phosphatidylcholine
MABR	methylaluminum bis(4-bromo-2,6-di-*t*-butylphenoxide)
mcPBA	*m*-chloroperoxybenzoic Acid
Me	methyl
Mes	mesitylene
MNBA	2-methyl-6-nitrobenzoic anhydride
MO	molecular orbitals
MPLC	medium pressure liquid chromatography
MsCl	methanesulfonyl chloride
(-)-MTPACl	Mosher's acid chloride or (2R)-3,3,3-Trifluoro-2-methoxy-2-phenylpropanoyl chloride
Mukaiyama's reagent	2-chloro-1-methylpyridinium iodide
NAD+	nicotinamide adenine dinucleotide
NBS	*N*-bromosuccinimide
NCAL	nucleophile catalyzed aldol-lactonization
NHC	*N*-heterocyclic carbene
o-Ns	*o*-nitrobenzenesulfonyl
PyBOP	benzo-triazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate

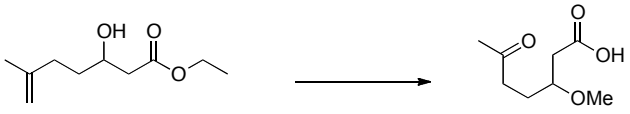
SEM	2-trimethylsilylethyoxymethyl
TBAF	tetra-n-butylammonium fluoride
TBDPS	(*tert*-butyldiphenylsilyl)
TBSCl	*tert*-butyldimethylsilyl chloride
TBSOTf	*tert*-butyldimethylsilyl trifluoromethanesulfonate
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxy
Teoc	2-(trimethylsilyl)ethyl carbonate
TESCl	chlorotriethylsilane
Tf	triflate or trifluoromethanesulfonate
Tf_2O	trifluoromethanesulfonic anhydride
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TMP	2,2,6,6-tetramethylpiperidine
TMSOTf	trimethylsilyl trifluoromethanesulfonate
TMS*Qd*	trimethylsilyl quinidine
TMS*Qn*	trimethylsilyl quinine
Tr	trityl or triphenylmethyl
Ts	tosyl or toluenesulfonyl
TsCl	*p*-toluenesulfonyl chloride
TsOH	*p*-toluenesulfonic acid

APPENDIX B: EXPERIMENTAL AND SPECTRAL DATA

General Procedures:

All non-aqueous reactions were performed under a nitrogen atmosphere in oven-dried glassware. Dichloromethane (CH_2Cl_2) was dried by passing through activated molecular sieves or alumina (solvent purification system). Tetrahydrofuran (THF) was distilled over sodium and benzophenone. *N'N'*-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 500 MHz and 300 MHz and referenced relative to residual chloroform (7.26 ppm) or benzene (7.16 ppm) and were reported in parts per million. Coupling constants (*J*) were reported in Hertz (Hz), with multiplicity reported following usual convention: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; ddd, doublet of doublet of doublets; dddd, doublet of doublet of doublet of doublets; dt, doublet of triplets; dq, doublet of quartets; ddq, doublet of doublet of quartets; ABq, AB quartet; m, multiplet; bs, broad singlet (prefix app indicates 'apparent'). ^{13}C NMR spectra were measured at 125 MHz and 75 MHz and referenced relative to residual chloroform (77.23 ppm) or benzene (128.06 ppm) and were reported in parts per million (ppm). Flash column chromatography was performed with 60Å Silica Gel (230-400 mesh) as stationary phase using a gradient solvent system or on an automated flash chromatography system (EtOAc/hexanes as eluent unless indicated otherwise). High resolution mass spectra (ESI) were obtained through the Laboratory for Biological Mass Spectrometry (Texas

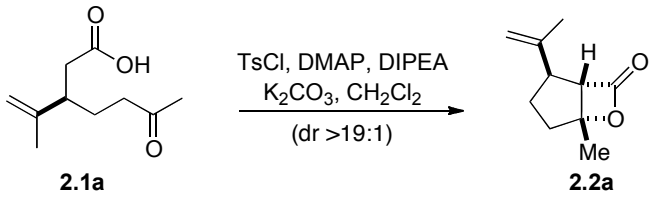
A&M University). Thin Layer Chromatography (TLC) was performed using glass-backed silica gel F254 (Silicycle, 250-μm thickness). Visualization of developed plates was performed by fluorescence quenching or by staining with phosphomolybdic acid (PMA), potassium permanganate ($KMnO_4$), *p*-anisaldehyde or cerium sulfate. *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 using a chromatographic system using various chiral columns (25 cm) as noted. Gas Chromatography (GC) was performed on a gas chromatographic system using a chiral column as noted. X-ray diffraction was obtained by the X-ray Diffraction Laboratory at Texas A&M University. Hazard Warning. Ozonides produced from the oxidative cleavage were reduced using excess dimethyl sulfide. Stirring for at least 9 h at 23 °C prior to workup ensured complete ozonide reduction; however, an ozonide test is recommended. **(***S***)**-(+)-HBTM was synthesized according to the literature procedure.[310b] (*S*)-BTM was purchased from TCI chemicals and used as received. All unsaturated acid chlorides were purchased from Sigma-Aldrich and used as received without further purification.



2.S1 **2.1f**

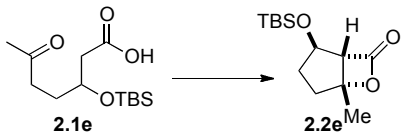
3-Methoxy-6-oxoheptanoic Acid (2.S1). Ethyl 3-hydroxy-6-methylhept-6-enoate (0.90 g, 4.8 mmol, 2.8 equiv.) was added to a round dissolved in 8 mL of CH_2Cl_2 along with 0.1 g of 4 Å powdered molecular sieves and Proton Sponge (0.37 g, 1.7 mmol, 1.0

equiv.). The flask was then wrapped in foil, trimethyloxonium tetrafluoroborate (0.25 g, 1.7 mmol, 1.0 equiv.) was added, the resulting mixture was stirred overnight (~8 h). After completion of the reaction, 1 mL of 2-propanol was added, and the reaction mixture was extracted with $NaHCO_3$ (3 × 5 mL) and brine (1 × 5 mL), dried over Na_2SO_4, and concentrated by rotary evaporation. The product was of sufficient purity to carry on. It was redissolved in 5 mL of methanol and 1 ml of 2 M NaOH and heated to 65 °C for 3 h. After 3 h, it was cooled to 23 °C, acidified with 1 M HCl, and diluted with 8 mL of ethyl acetate. The organic layer was washed with brine (1 × 5 mL), dried over Na_2SO_4, and concentrated by rotary evaporation. The resulting compound, 3-methoxy-6-methylhept-6-enoic acid, was dissolved in 9 mL of CH_2Cl_2 and cooled to -78 °C, at which point ozone was bubbled through the solution until it turned a deep blue color. Then oxygen was bubbled through until the color dissipated, at which time dimethyl sulfide (0.3 mL, 4.0 mmol, 2.5 equiv.) was added and the reaction was allowed to stir overnight (10 h) while warming to 23 °C. The solution was then concentrated by rotary evaporation and purified by flash column chromatography (SiO_2, eluting with 20 to 50% EtOAc/hexanes) to afford keto-acid **2.1f** as a pale yellow liquid (0.15 g, 43% over three steps): IR (thin film) 3128, 2936, 2373, 2334, 1708 cm^{-1}; ^1H NMR (500 MHz; $CDCl_3$): δ 3.68-3.63 (m, 1H), 3.34 (s, 3H), 2.60-2.51 (m, 3H), 2.44 (ddd, J = 15.5, 5.6, 0.9 Hz, 1H), 2.14 (s, 3H), 1.90 (m, 1H), 1.79 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 208.5, 176.3, 76.4, 57.0, 38.9, 38.8, 30.0, 27.4; HRMS (ESI+) calcd. for $C_8H_{14}O_4Li$ (M + Li) 181.1052, found 181.1049.

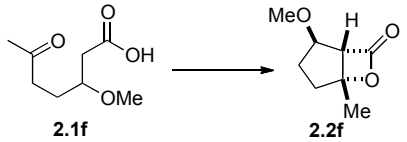


2.1a **2.2a**

(1S,2R,5R)-5-Methyl-2-(prop-1-en-2-yl)-6-oxabicyclo[3.2.0]heptan-7-one (2.2a). (Table 2, entry 6): To a mixture of TsCl (210 mg, 1.1 mmol. 1.1 equiv.), DMAP (183 mg, 1.5 mmol, 1.5 equiv.), and *N*,*N*-diisopropylethylamine (0.7 mL, 4 mmol, 4.0 equiv.) in CH_2Cl_2 (2.8 mL) was added dropwise a solution of keto-acid **2.1a** (184 mg, 1 mmol, 1.0 equiv.) in CH_2Cl_2 (0.5 mL). The reaction mixture was stirred at ambient temperature (23 °C) for 10 min and then powdered anhydrous K_2CO_3 (414 mg, 3 mmol, 3.0 equiv.) was added in one portion. The reaction was stirred at room temperature for 2 h and then diluted with hexanes and passed through a pad of silica gel to remove solids. The volatiles were removed by rotavap and the residue was purified by flash column chromatography (SiO_2, eluting with 20 to 50% EtOAc/hexanes) to afford β-lactone **2.2a** as a colorless liquid (117 mg, 71%). $[\alpha]_D^{23} = +33.8$ (*c* = 1.4, $CHCl_3$); IR (thin film) 2975, 2937, 1818, 1643 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.76 (s, 1H), 4.41 (s, 1H), 3.47 (s, 1H), 2.84 (d, *J* = 7.0 Hz, 1H), 1.99-2.12 (m, 2H), 1.84-1.92 (m, 1H), 1.73 (s, 3H), 1.68 (s, 3H); 1.62-1.67 (m, 1H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.1, 145.1, 109.8, 87.9, 63.0, 45.7, 33.7, 28.3, 22.5, 21.6; LRMS (ESI+) calcd. for $C_{10}H_{15}O_2$ (M+H) 167.1072. Found 167.1079.

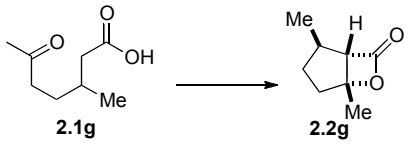


2-((tert-Butyldimethylsilyl)oxy)-5-methyl-6-oxabicyclo-[3.2.0]heptan-7-one (2.2e). β-Lactone **2.2e** was prepared according to the representative procedure from keto-acid **2.1e** (75 mg, 0.27 mmol, 1.0 equiv.), p-TsCl (59 mg, 0.31 mmol, 1.1 equiv.), DMAP (49 mg, 0.41 mmol, 1.5 equiv.), *N,N*-diisopropylethylamine (0.19 mL, 1.1 mmol, 4.0 equiv.) and K_2CO_3 (111 mg, 0.81 mmol, 3.0 equiv.) in CH_2Cl_2 (0.9 mL) after a reaction time of 2 h. Purification by flash column chromatography (SiO_2, eluting with 20 to 50% EtOAc/hexanes) afforded β-lactone **2.2e** as a colorless liquid (47 mg, 68%). All spectral data were in accordance with those previously reported.[288b]

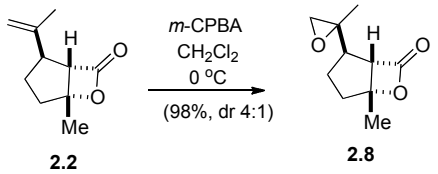


2-Methoxy-5-methyl-6-oxabicyclo[3.2.0]heptan-7-one (2.2.f). β-Lactone **2.2f** was prepared according to the representative procedure from keto-acid **2.1f** (61 mg, 0.35 mmol, 1.0 equiv.), TsCl (74 g, 0.39 mmol, 1.1 equiv.), DMAP (64 mg, 0.53 mmol, 1.5 equiv.), *N,N*-diisopropylethylamine (0.24 mL, 1.4 mmol, 4.0 equiv.), and K_2CO_3 (144 mg, 1.1 mmol, 3.1 equiv.) in CH_2Cl_2 (1.2 mL) after a reaction time of 2 h. Purification by flash column chromatography (SiO_2, eluting with 20 to 50% EtOAc/hexanes) afforded β-lactone **2.7f** as a colorless liquid (35 mg, 64 %). IR (thin film) 2998, 2945, 1828, 1552 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.01 (d, J = 3.5 Hz, 1H), 3.59 (s, 1H), 3.30 (s, 3H), 2.11-2.21 (m, 2H), 1.86-2.06 (m, 2H), 1.75 (s, 3H), ^{13}C NMR (125 MHz,

$CDCl_3$) δ 168.6, 87.8, 81.7, 64.0, 56.5, 33.7, 30.0, 21.9; LRMS (ESI+) calcd. for $C_8H_{13}O_3$ (M+H) 157.0865. Found 157.0881.

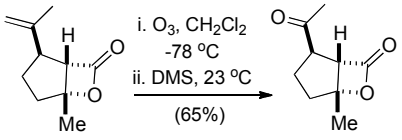


2,5-Dimethyl-6-oxabicyclo[3.2.0]heptan-7-one (2.2.g). β-Lactone **2.2g** was prepared according to the representative procedure from keto-acid **2.6g** (84 mg, 0.53 mmol, 1.0 equiv.), p-TsCl (112 g, 0.58 mmol, 1.1 equiv.), 4-DMAP (97 mg, 0.8 mmol, 1.5 equiv.), *N,N*-diisopropylethylamine (0.37 mL, 2.1 mmol, 3.9 equiv.), and K_2CO_3 (220 mg, 1.59 mmol, 3.0 equiv.) in CH_2Cl_2 (1.7 mL) after a reaction time of 6 h. Purification by flash column chromatography (SiO_2, eluting with 20 to 50% EtOAc/hexanes) afforded β-lactone **2.2g** as a colorless liquid (42.3 g, 57%): IR (thin film) 2996, 2943, 1823 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 3.14 (s, 1H), 2.50-2.58 (m, 1H), 2.01-2.13 (m, 2H), 1.75-1.85 (m, 1H), 1.72 (s, 3H), 1.62-1.68 (m, 1H), 0.97 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.7, 87.4, 65.5, 34.2, 33.0, 30.5, 22.1, 18.6; HRMS (ESI+) calcd. for $C_8H_{13}O_2$ (M + H) 141.0916, found 141.0934.



(1S,2R,5R)-5-Methyl-2-(2-methyloxiran-2-yl)-6-oxabicyclo-[3.2.0]heptan-7-one (2.8). β-Lactone **2.2** was dissolved in CH_2Cl_2 (5 mL) and taken to 0 °C, Na_2HPO_4 (24 mg, 1.7 mmol, 2.0 equiv.) and *m*-CPBA (15 mg, 0.85 mmol, 1.0 equiv.) were added, and the reaction was allowed to warm to 23 °C overnight (~8 h). The reaction mixture was

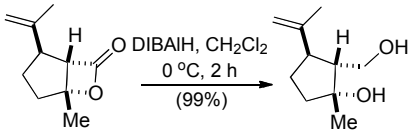
then filtered to remove excess solids and washed with an aqueous solution of saturated K_2CO_3 (2 × 5 mL) and brine (5 mL). It was then dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, eluting with 10 to 40% EtOAc/hexanes) afforded an inseparable, diastereomeric mixture of epoxy β-lactones **2.8** (dr 4:1) as a colorless liquid (16 mg, 98%): IR (thin film) 2976, 2925, 1818 cm^{-1}. Data for major diastereomer: ^1H NMR (500 MHz, $CDCl_3$): δ 3.43 (s, 1H), 2.66-2.60 (m, 2H), 2.51 (d, J = 4.5, 1H), 2.18-2.08 (m, 3H), 2.00-1.96 (m, 1H), 1.72 (s, 3H), 1.71-1.65 (m, 2 H), 1.36 (s, 3H); 13C NMR (125 MHz, $CDCl_3$): δ 170.8, 88.3, 66.1, 57.2, 51.8, 44.7, 35.0, 27.2, 21.7, 15.5; HRMS (ESI+) calcd for $C_{10}H_{14}O_3Li$ (M + Li) 189.1103, found 189.1111.



2.2 **2.9**

(1S,2R,5R)-2-Acetyl-5-methyl-6-oxabicyclo[3.2.0]heptan-7-one (2.9). β-Lactone **2.2** (83 mg, 0.50 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (9 mL) and taken to -78 °C, at which point ozone was bubbled through the solution until it turned a deep blue color. Then oxygen was bubbled through until the color dissipated, at which time dimethyl sulfide was added (2.0 mL, 2.66 mmol, XX equiv) and the reaction was allowed to stir overnight (~10 h) while warming to ambient temperature (23 ºC). The solution was concentrated by rotary evaporation and purified by flash column chromatography (SiO_2, eluting with 10 to 30% EtOAc/hexanes) to afford β-lactone **2.9** as a colorless liquid (55 mg, 65%): $[\alpha]_D^{19}$ = +50 (*c* = 1.5, $CHCl_3$); IR (thin film) 2984, 2937, 1815, 1702 cm^{-1}; ^1H

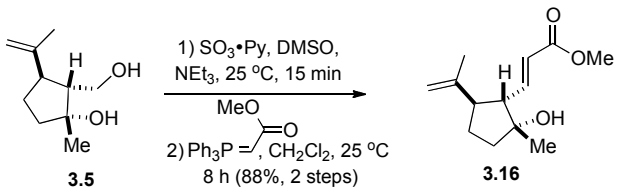
NMR (500 MHz; $CDCl_3$): 3.66 (s, 1H), 3.30 (d, J = 8.0 Hz, 1H), 2.24-2.20 (m, 1H), 2.20 (s, 3H), 2.12-2.03 (m, 2H), 1.67 (s, 3H), 1.55-1.48 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 207.3, 170.5, 88.2, 60.4, 52.0, 33.9, 28.2, 27.6, 21.4; HRMS (ESI+) calcd for $C_9H_{12}O_3Li$ (M + Li) 175.0946, found 175.0950.



3.2 3.5

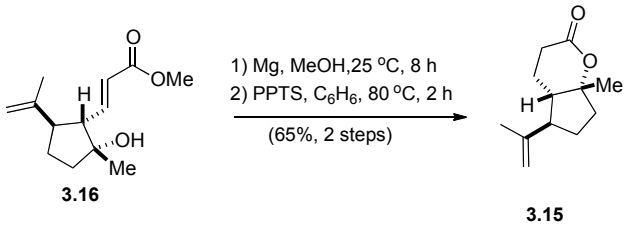
(1*R*,2*R*,3*R*)-2-(Hydroxymethyl)-1-methyl-3-(prop-1-en-2-yl)cyclopentanol (**3.5**). To a solution of **3.2** (2.01 g, 12.09 mmol, 1.00 equiv.) in 121 mL of dry CH_2Cl_2 at 0 °C was added neat DIBAlH (8.62 mL, 48.37 mmol, 4.00 equiv.) dropwise. The reaction remained at 0 °C for 5 h at which time 12 mL of EtOAc was added dropwise followed by 30 mL of a saturated aqueous solution of Rochelle's salt. The reaction was allowed to stir ~8 h to quench excess DIBAL. It was then diluted with 50 mL EtOAc and the organic extract was then washed with brine (2 x 20 mL), dried anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by flash column chromatography eluting 10 to 30% EtOAc/Hexanes afforded **3.5** (2.03 g, 99%) as a white crystalline solid. $[\alpha]_D^{19}$ = -28.0 (*c* = 1.0, $CHCl_3$); IR (thin film): 3347 (br s), 2988, 1643 cm^{-1}; ^1H NMR (500 MHz; $CDCl_3$): δ 4.78-4.75 (m, 2H), 3.91 (dd, *J* = 11.3, 3.2 Hz, 1H), 3.71 (dd, *J* = 11.3, 5.0 Hz, 1H), 2.87 (dt, *J* = 10.8, 8.8 Hz, 1H), 2.75 (br s, 1H), 2.57 (br s, 1H), 1.98-1.90 (m, 1H), 1.78-1.72 (m, 2H), 1.70 (s, 3H), 1.59 (ddd, *J* = 10.9, 5.0, 3.2 Hz, 1H), 1.54-1.49 (m, 1H), 1.40 (s, 3H); ^{13}C (500 MHz; $CDCl_3$): δ 147.1, 110.9, 81.8, 61.2,

52.8, 47.2, 41.9, 28.7, 28.2, 19.5 HRMS (ESI+) calcd. for $C_{10}H_{18}O_2$ (M+Li) 177.1467. Found 177.1571.



(*E*)-Methyl 3-((1*S*,2*R*,5*R*)-2-hydroxy-2-methyl-5-(prop-1-en-2-yl)cyclopentyl)acrylate (**3.16**)**:** To a solution round-bottomed flask with diol **3.5** (1.13 g, 6.66 mmol, 1.00 equiv.) was added NEt_3 (7.42 mL, 52.24 mmol, 7.84 equiv.) and DMSO (16.54 mL, 232.94 mmol, 34.98 equiv.). Then SO_3-pyridine (4.24 g, 26.62 mmol, 4.00) dissolved in DMSO (16.54 mL, 232.94 mmol, 34.98 equiv.) was added. The reaction was stirred at room temperature for 15 min and then saturated aqueous $NaHCO_3$ (35 mL) was added and allowed to stir for 5 min. The mixture was then extracted with EtOAc (3 x 35 mL) the combined organic layer was then dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting solution was then dissolved in CH_2Cl_2 (64 mL) and methyl 2-(triphenylphosphoranylidene)-acetate (2.67 g, 7.99 mmol, 1.20 equiv.) was added and the reaction was allowed to stir overnight (~8 h) then concentrated under reduced pressure and purified by flash column chromatography eluting 20 to 30 % EtOAc/hexanes afforded **3.16** (1.31 g, 88% over two steps) as a colorless oil. $[\alpha]_D^{19}$ = -68.57 (*c* = 1.05, $CHCl_3$); IR (thin film): 3467 (br s), 2963, 2360, 1723, 1650 cm^{-1}; ^1H NMR (500 MHz; $CDCl_3$): δ 6.92 (dd, *J* = 15.8, 8.88 Hz, 1H), 5.84 (d, *J* = 15.8 Hz, 1H) 4.70-4.68 (m, 2H), 3.72 (s, 3H), 2.88 (q, *J* = 10.0 Hz, 1H), 2.26 (dd, *J* = 10.9, 9.1 Hz, 2H), 1.65 (s, 3h), 2.13-2.0 (m, 1H), 1.82 (dd, *J* = 8.2, 7.0 Hz, 2H), 1.65 (s, 3H), 1.61-

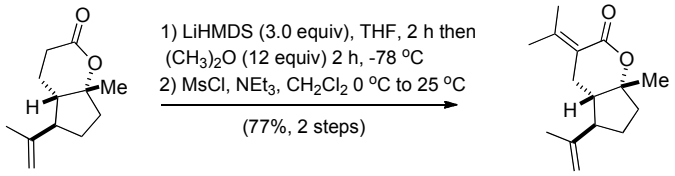
1.48 (m, 2H), 1.30 (s, 3H); ^{13}C (500 MHz; $CDCl_3$): δ 166.8, 147.7, 146.0, 123.8, 111.0, 81.9, 56.9, 51.7, 50.6, 40.5, 28.7, 27.3, 20.0; HRMS (ESI+) calcd. for $C_{13}H_{20}O_3$ (M+Li) 231.1572. Found 231.1660.



3.16 **3.15**

(4a*S*,5*R*,7a*R*)-7a-Methyl-5-(prop-1-en-2-yl)hexahydrocyclopenta[*b*]pyran-2(3*H*)-one-(3.15). To a solution of methyl ester **3.16** (0.45 g, 2.0 mmol, 1.0 equiv.) in a round-bottomed flask was added MeOH (20 mL) and Mg turnings (0.97g, 40.08 mmol, 20.0 equiv.), which were activated by washing with a 10% aqueous solution of HCl for 2 min followed by through rinsing with MeOH prior to addition. The reaction was monitored by TLC, and after 8 h the crude reaction mixture was concentrated to remove all MeOH, then dissolved in EtOAc (200 mL) and filtered through a coarse fritted funnel. After which the mixture was concentrated under reduced pressure. To the crude mixture in benzene (20 mL) was added PPTS (1.01 g, 2.0 mmol, 1.0 equiv.) and allowed to stir under reflux conditions for 4 h. Saturated aqueous NH_4Cl solution (8 mL) was added and the mixture was extracted with EtOAc (3 x 10 mL), and washed with brine (10 mL). The organic extract was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 1: 1: 1.5: 2 (dichloromethane: pentane: hexane: diethyl ether)) to furnish **3.15** (0.25 g, 65% over two steps) as a colorless oil**.** = -24.6^o (*c* = 1.22, $CHCl_3$); IR (thin film): 2967, 1732, 1640 cm^1; ^{1}H NMR (500 MHz; $CDCl_3$): δ 4.77 (dt, *J* = 19.7, 1.2 Hz, 2H), 2.54-2.49 (m, 1H),

2.45-2.42 (m, 2H), 2.07-1.97 (m, 2H), 1.95-1.87 (m, 2H), 1.84 (dt, *J* = 10.5, 5.2 Hz, 1H), 1.75-1.67 (m, 4H), 1.55-1.51 (m, 1H), 1.47 (s, 3H); ^{13}C NMR (500 MHz; $CDCl_3$): δ 172.2, 145.6, 111.3, 91.4, 50.4, 44.6, 40.4, 28.2, 27.9, 26.3, 20.3, 19.7; HRMS (ESI+) calcd. for $C_{12}H_{18}O_2$ (M+Li) 195.1385. Found 195.1393.



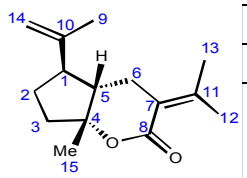
3.15 **3.3** caulolactone A

(4a*S*,5*R*,7a*R*)-7a-Methyl-5-(prop-1-en-2-yl)-3-(propan-2ylidene)hexahydro-cyclopenta[*b*]pyran-2(3*H*)-one-(5).To a round-bottomed flask was added a solution of lactone of **3.15** (143 mg g, 0.74 mmol, 1.0 equiv.) in THF (14.70 mL). The reaction was taken to -78 °C with a dry ice/acetone bath and allowed to react for 3 h, followed by addition of freshly distilled acetone stored under nitrogen over molecular sieves (0.65 mL, 8.83 mmol, 12.0 equiv.). After an additional 3 h the reaction was quenched with a saturated aqueous NH_4Cl solution (5 mL) and extracted with EtOAc (3 x 10 mL), then washed with brine (10 mL). The organic extract was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was then dissolved in CH_2Cl_2 (7.4 mL) and taken to 0 °C at which time NEt_3 (0.82 mL, 5.88 mmol, 8.0 equiv.) was added followed by dropwise addition of MsCl (0.17 mL, 2.19 mmol, 3.0 equiv.). After addition the ice bath was removed and the reaction was warmed to reflux for 3 h. The resulting solution was then concentrated under reduced pressure and purified by flash column chromatography to afford **3.3** (132 mg, 77% over two steps) as a colorless oil. $[\alpha]_D^{19}$ =

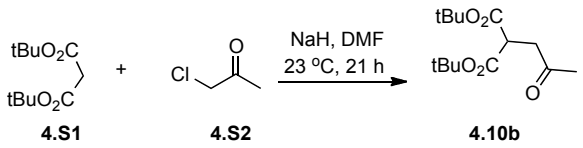
+48.5° (*c* = 0.3, MeOH); IR (thin film): 2951, 1708, 1083 cm[1]; ^{1}H NMR (500 MHz; $CDCl_3$): δ 4.76 (s, 1H), 4.69 (s, 1H), 2.58-2.35 (m, 3H), 2.20 (t, *J* = 1.51 Hz, 3H), 2.02-1.88 (m, 3H), 1.85 (s, 3H), 1.82-1.77 (m, 1H), 1.54-1.45 (m, 1H), 1.40 (s, 3H); ^{13}C NMR (500 MHz; $CDCl_3$): δ 167.5, 151.0, 146.0, 118.4, 111.3, 89.4, 51.0, 45.7, 40.1, 27.8, 26.0, 25.9, 23.9, 23.3, 19.7; HRMS (ESI+) calcd. for $C_{15}H_{22}O_2$ (M+H) 235.1698. Found 235.1725.

The following except is characterization data listed from the isolation paper: "Colorless needles, mp 97-98 °C, $C_{15}H_{22}O_2$ $[\alpha]_D^{19}$ = +170 ° (*c* = 0.3, MeOH), IR ν_{max} CCl_4 1715 cm^{-1}, UV λ_{max} MeOH 234 nm (ε, 16000). These data showed the presence of α,β-unsaturated lactone group in the molecule, and aldo CD ($[\theta]_{225}$ + 700, $[\theta]_{210}$ + 840) supported the presence of this group. ^{1}H-NMR (δ CCl_4 + TMS) 1.18 (*tert*. Methyl on a carbon atom bounded with the oxygenic function), 1.72, 1.81, 2.13 (three olefinic methyls), 4.74 (2H, s, terminal methylene)."

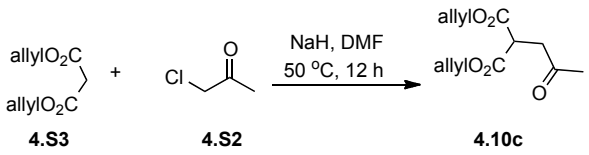
Comparison of ^{1}H NMR δ with isolation paper: As such the 5 singlets (4 methyls and the terminal methylene's) were compared.



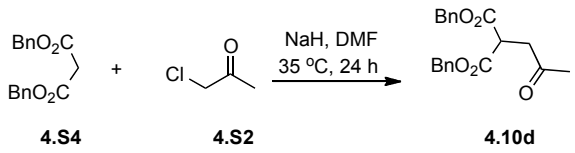
Comparison of Proton Natural and Synthetic						
all (s) H	**H-14**	**H-12**	**H-13**	**H-9**	**H-15**	**solvent**
Natural:	4.74	2.13	1.81	1.72	1.18	CCl_4 + TMS
Isolation:	4.76, 4.69	2.20	1.85	1.69	1.40	$CDCl_3$
Δδ	0.00	0.07	0.04	0.03	0.22	



Di-*tert*-butyl 2-(2-oxopropyl)malonate (4.10b). To an oven dried, round-bottomed flask was added NaH 60% in mineral oil (0.49 g, 9.83 mmol, 1.25 equiv.) and 20 mL anhydrous DMF. The flask was then cooled to 0 °C with an ice bath and di-*tert*-butyl malonate (**4.S1**, 2.0 mL, 8.93 mmol, 1.00 equiv.) was added dropwise. After 25 min, chloroacetone (**4.S2**, 1.08 mL, 13.40 mmol, 1.50 equiv.) was added dropwise and the ice bath removed and allowed to warm up to ambient temperature (23 °C). After 21 h the reaction mixture was cooled to 0 °C with an ice bath and 10 mL of sat. NH_4Cl was added slowly. The mixture was warmed to ambient temperature (23 °C), extracted with EtOAc (4 x 15 mL), and the combined organic extracts were then washed with water (15 mL) and brine (15 mL). The organic layer was collected and dried over $MgSO_4$, filtered, concentrated by rotary evaporation, and purified by flash column chromatography (gradient SiO_2, 20 → 60% EtOAc/hexanes) to afford keto diester **4.10b** (1.46 g, 60%) as a colorless oil: TLC (EtOAc:hexanes, 5:5 *v/v)*: $R_f = 0.80$; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.68 (t, J = 7.2 Hz, 1H), 2.95 (d, J = 7.2 H, 2H), 2.20 (s, 3H), 1.45 (s, 18H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 205.1, 168.1(2), 81.7(2), 49.0, 42.0, 29.8, 27.8(6); IR (thin film): 2982, 2928, 1726 cm^{-1}; HRMS (ESI+) *m/z* calcd. for $C_{14}H_{24}LiO_5$ $[M+Li]^+$: 279.1784; found 279.1781.

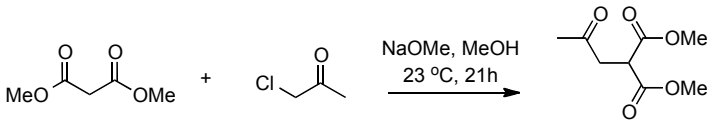


Diallyl 2-(2-oxopropyl)malonate (4.10c). To an oven dried, round-bottomed flask was added NaH 60% in mineral oil (1.16 g, 28.97 mmol, 1.06 equiv.) and then 50 mL anhydrous DMF followed by dropwise addition of diallyl malonate[415] (**4.S3**, 5.00 g, 27.14 mmol, 1.00 equiv.) at ambient temperature (23 °C). After 25 min, chloroacetone (**4.S2**, 6.55 mL, 81.41 mmol, 3.00 equiv.) was added dropwise and the reaction mixture was heated to 50 °C for 12 h, after which time it was allowed to cool to ambient temperature (23 °C) and 15 mL of sat. NH_4Cl was added. The mixture was extracted with EtOAc (4 x 20 mL) and then washed with water (20 mL) and brine (20 mL). The organic layers were combined and dried over $MgSO_4$, filtered, concentrated by rotary evaporation, and purified by flash column chromatography (gradient SiO_2, 20 → 60% EtOAc/hexanes) to afford keto diester **4.10c** (4.24 g, 65%) as a colorless oil: TLC (EtOAc:hexanes, 1:9 *v/v)*: R_f = 0.75; ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.93-5.86 (m, 2H), 5.35 (q, *J* = 1.5 Hz, 1H), 5.31 (q, *J* = 1.5 Hz, 1H), 5.26 (q, *J* = 1.3 Hz, 1H), 5.24 (q, *J* = 1.3 Hz, 1H), 4.65 (m, 2H), 4.63 (m, 2H), 3.94 (t, *J* = 7.1 Hz, 1H), 3.09 (d, *J* = 7.2 Hz, 2H), 2.21 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 205.0, 168.7(2), 131.6(2), 119.0(2), 66.5(2), 47.1, 42.3, 30.0; IR (thin film): 3081, 2951, 1741 cm^{-1}; HRMS (ESI+) *m/z* calcd. for $C_{12}H_{16}LiO_5$ $[M+Li]^+$: 247.1158; found 247.1149.



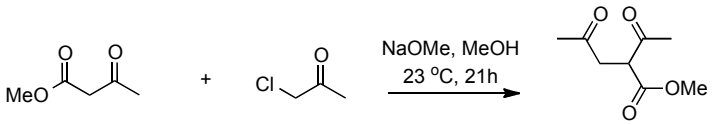
4.S4 **4.S2** **4.10d**

Dibenzyl 2-(2-oxopropyl)malonate (4.10d). To an oven dried, round-bottomed flask containing dibenzyl malonate (**4.S4**, 2.50 mL, 12.0 mmol, 1.00 equiv.) in 24 mL of anhydrous DMF at 0 °C was slowly added NaH 60% in mineral oil (0.51 g, 12.8 mmol, 1.07 equiv.). After 5 min at 0 °C chloroacetone (**4.S2**, 2.88 mL, 35.8 mmol, 3.00 equiv.) was added dropwise and the reaction mixture was heated at 35 °C for 24 h, after which time it was allowed to cool to ambient temperature (23 °C) and 15 mL of sat. NH_4Cl was added. The mixture was extracted with EtOAc (4 x 20 mL) and then washed with water (20 mL) and brine (20 mL). The organic layers were combined and dried over $MgSO_4$, filtered, concentrated by rotary evaporation, and purified by flash column chromatography (SiO_2, 10 → 60% EtOAc/hexanes) to afford keto diester **4.10d** (1.90 g, 47%) as a colorless oil: TLC (EtOAc:hexanes, 3:7 *v/v)*: R_f = 0.45; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31-7.27 (m, 5H), 7.26-7.24 (m, 5H), 5.17 (s, 2H), 5.11 (s, 2H), 3.96 (t, *J* = 7.1 Hz, 1H), 3.06 (d, *J* = 7.1 Hz, 2H), 2.13 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 204.9, 168.7, 135.3, 128.7, 128.5, 128.3, 67.6, 47.1, 42.1, 29.8; IR (thin film): 1753, 1726, 1270, 1226, 1152 cm^{-1}; HRMS (ESI+) *m/z* calcd. for $C_{20}H_{20}LiO_5$ $[M+Li]^+$: 347.1471; found 347.1476.



4.S5 **4.S2** **4.10e**

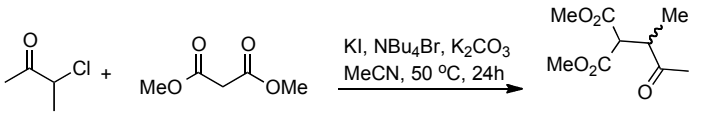
3-Acetylhexane-2,5-dione (4.10e). In an oven dried, 250 mL round-bottomed flask was added acetylacetone (**4.S5**, 5.0 g, 49.9 mmol, 1.00 equiv.) dissolved in 100 mL of spectra grade benzene. DBU (7.5 mL, 50 mmol, 1.00 equiv.) was slowly added to the solution. Upon completion of the addition, chloroacetone (**4.S2**, 5.23 mL, 65.0 mmol, 1.30 equiv.) was added dropwise and the reaction mixture was stirred for 24 h at ambient temperature (23 ºC). The reaction mixture was then diluted with CH_2Cl_2 (40 mL), washed with brine (50 mL), dried over Na_2SO_4, and concentrated by rotary evaporation. Flash column chromatography (SiO_2, 10 → 40% EtOAc/hexanes) afforded triketone **4.10e** (2.34 g, 30%) as a yellow oil. All characterization data was in accordance with previously reported data for this compound.[416]



4.S7 **4.S2** **(±)-4.10g**

Methyl 2-acetyl-4-oxopentanoate ((±)-4.10g). An oven dried, 500 mL round-bottomed flask was charged with 225 mL of MeOH under a nitrogen atmosphere and then cooled to 0 °C with an ice bath prior to the addition of methylacetoacetone (**4.S7**, 10.0 mL, 92.7 mmol, 1.0 equiv.) followed by NaOMe (5.51 g, 102 mmol, 1.10 equiv.). After 25 min at 0 °C, chloroacetone (**4.S2**, 10.4 mL, 130 mmol, 1.40 equiv.) was added dropwise. After

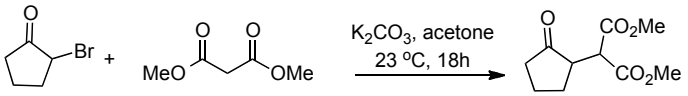
the addition, the ice bath was removed and the reaction was stirred at ambient temperature (23 °C) for 21 h. The reaction was again cooled to 0 °C and 100 mL of sat. NH_4Cl was added. The reaction mixture was then extracted with EtOAc (4 x 100 mL), then washed with water (2 x 25 mL) and brine (1 x 50 mL). The organic layer was collected and dried over $MgSO_4$, filtered, concentrated by rotary evaporation, and purified by flash column chromatography (SiO_2, 20 → 60% EtOAc/hexanes) to afford diketo ester **(±)-**4.**10g** (6.86 g, 43%) as a pale yellow oil: TLC (EtOAc:hexanes, 5:5 *v/v)*: R_f = 0.50; ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.02 (dd, *J* = 8.3, 5.7 Hz, 1H), 3.73 (s, 3H), 3.15 (dd, *J* = 18.5, 8.3 Hz, 1H), 2.95 (dd, *J* = 18.5, 5.6 Hz, 1H), 2.35 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 205.8, 202.3, 169.5, 53.6, 52.9, 41.8, 30.3, 29.9; IR (thin film): 3002, 2955, 2928, 1759.



4.S8 **4.S9** **(±)-4.10j**

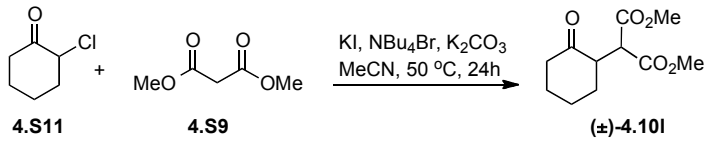
Dimethyl 2-(3-oxobutan-2-yl)malonate ((±)-4.10j). To a 250 mL, round-bottomed flask were added dimethyl malonate (**4.S9**, 1.81 mL, 15.84 mmol, 1.0 equiv.), 3-chlorobutan-2-one (**4.S8**, 2.0 mL, 20 mmol, 1.25 equiv.), KI (0.13 g, 0.79 mmol, 0.05 equiv.), K_2CO_3 (2.63 g, 19.0 mmol, 1.20 equiv.), *n*-Bu_4NBr (0.10 g, 0.32 mmol, 0.02 equiv.) and MeCN (25 mL). The reaction was heated to 50 °C for 12 h. Stirring was continued for another 12 h at ambient temperature (23 °C). After which time, the reaction was concentrated under reduced pressure by rotary evaporation, diluted with 20 mL of CH_2Cl_2, and filtered to remove solids. The filtrate was then concentrated by rotary

evaporation and purified by flash column chromatography (SiO_2, 20 → 60% EtOAc/hexanes) to afford keto diester **(±)-4.10j** (3.17 g, 99%) as a colorless oil. ^{13}C NMR (125 MHz, $CDCl_3$): δ 209.6, 169.1, 169.0, 54.1, 52.9, 52.8 45.9, 28.8, 14.6. All other characterization data was in accordance with previously reported data for this compound.

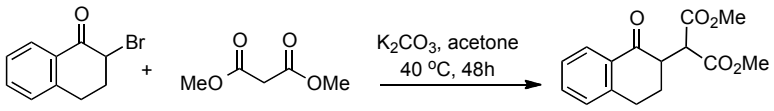


4.S10 **4.S9** **(±)-4.10k**

2-(2-Oxocyclopentyl)malonate ((±)-4.10k). To 2-bromocyclopentanone (**4.S10**, prepared and purified immediately prior to use,[417] 3.42 g, 21.0 mmol, 1.50 equiv.) was added dimethyl malonate (**4.S9**, 1.60 mL, 14.0 mmol, 1.00 equiv.), K_2CO_3 (2.50 g, 18.1 mmol, 1.30 equiv.) and acetone (30 mL), which was allowed to react for 18 h at ambient temperature (23 °C). After which time, the reaction was concentrated under reduced pressure by rotary evaporation, diluted with 20 mL of CH_2Cl_2 and then filtered to remove the solids. The filtrate was then concentrated by rotary evaporation and purified by flash column chromatography (SiO_2, 20 → 60% EtOAc/hexanes) to afford cyclopentanone diester **(±)-4.10k** as a colorless oil (720 mg, 24%)[418]: TLC (EtOAc:hexanes, 1:1 *v/v)*: R_f = 0.53; ^1H NMR (500 MHz, $CDCl_3$): δ 3.83 (d, *J* = 5.7 Hz, 1H), 3.77 (s, 3H), 3.72 (s, 3H), 2.73-2.69 (m, 1H), 2.36 (dd, *J* = 18.8, 8.4 Hz, 1H), 2.28-2.20 (m, 2H), 2.12-2.08 (m, 1H), 1.90-1.78 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 217.1, 169.0, 168.4, 52.7, 52.6, 51.0, 48.6, 37.4, 26.6, 20.6; IR (thin film): 2956, 2880, 1738 cm^{-1}; HRMS (ESI+) *m/z* calcd. for $C_{10}H_{14}LiO_5$ $[M+Li]^+$: 221.1001; found 221.1002.

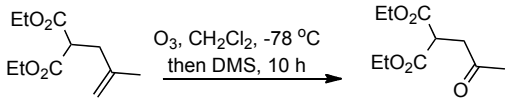


Dimethyl 2-(2-oxocyclohexyl)malonate ((±)-4.10l). To a 250 mL round-bottomed flask were added 2-chlorocyclohexanone (**4.S11**, 5.0 mL, 44 mmol, 1.25 equiv.), dimethyl malonate (**4.S9**, 4.0 mL, 35 mmol, 1.0 equiv.), KI (0.30 g, 1.81 mmol), K_2CO_3 (5.87 g, 42.5 mmol, 1.22 equiv.), *n*-Bu_4NBr (0.23 g, 0.71 mmol, 0.02 equiv.) and MeCN (50 mL). The reaction mixture was heated to 50 °C for 12 h and then stirred at ambient temperature (23 °C) for an additional 12 h. The reaction was then concentrated under reduced pressure by rotary evaporation, diluted with 50 mL of CH_2Cl_2 and filtered to remove the solids. The filtrate was then concentrated by rotary evaporation and purified by flash column chromatography (SiO_2, 20 → 60% EtOAc/hexanes) to afford cyclohexanone diester **(±)-4.10l** (967 mg, 12%) as a pale yellow oil: TLC (EtOAc:hexanes, 5:5 *v/v)*:R_f = 0.65; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.58 (s, 3H), 3.57 (s, 3H), 3.51 (d, *J* = 9.5 Hz, 1H), 3.07-3.01 (m, 1H), 2.29-2.26 (m, 2H), 2.00-1.96 (m, 1H), 1.90-1.85 (m, 1H), 1.79-1.75 (m, 1H), 1.63-1.45 (m, 2H), 1.44-1.35 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 209.9, 169.1, 169.0, 52.9, 52.8, 52.1, 50.6, 42.1, 31.4, 27.9, 25.2; IR (thin film): 2955, 2863, 1738, 1706 cm^{-1}; HRMS (ESI+) *m/z* calcd. for $C_{11}H_{16}LiO_5$ $[M+Li]^+$: 235.1158; found 235.1154.



4.S12 **4.S9** **(±)-4.10n**

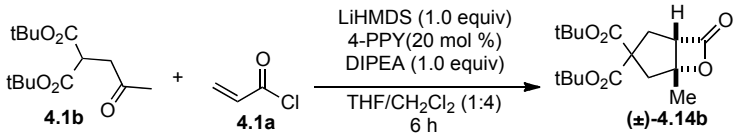
Dimethyl 2-(1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)malonate ((±)-4.10n). To a 50 mL, round-bottomed flask were added dimethyl malonate (**4.S9**, 1.45 mL, 12.7 mmol, 1.00 equiv.), K_2CO_3 (4.39 g, 31.7 mmol, 2.51 equiv.) and acetone (8 mL). The reaction was heated to 40 °C, then **4.S12** (4.0 g, 17.77 mmol, 1.40 equiv.) which was freshly prepared and used immediately without purification, was added dropwise over ~4 min and the reaction was maintained at 40 °C for 48 h. After 48 h, the reaction was allowed to cool to ambient temperature (23 °C) and EtOAc (20 mL) and water (20 mL) were added and the reaction was stirred for an additional 10 min. The organic layer was collected, washed with brine 2 x 10 mL, dried over $MgSO_4$, filtered, concentrated by rotary evaporation, and purified by flash column chromatography (SiO_2, 5 → 30% EtOAc/hexanes) to afford aromatic keto diester **(±)-4.10n** (1.97 g, 56%) as a yellow/orange solid: TLC (EtOAc:hexanes, 2:8 *v/v)*: R_f = 0.48; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.00 (d, *J* = 7.9 Hz, 1H), 7.48 (td, *J* = 7.5, 1.3 Hz, 1H), 7.31-7.28 (m, 1H), 7.26-7.23 (m, 1H), 4.02 (d, *J* = 7.1 Hz, 1H), 3.80 (s, 3H), 3.76 (s, 3H), 3.38-3.33 (m, 1H), 3.12 (dt, *J* = 16.4, 8.5 Hz, 1H), 3.00 (dt, *J* = 16.7, 3.4 Hz, 1H), 2.20-2.15 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 196.9, 169.3, 169.0, 143.9, 133.9, 132.2, 128.9, 127.8, 127.0, 52.9, 52.8, 52.2, 48.5, 29.6, 26.8; IR (thin film): 2952, 1735, 1676, 1270, 1217, 1155, 764, 749 cm^{-1}; HRMS (ESI+) *m/z* calcd. for $C_{15}H_{16}LiO_5$ $[M+Li]^+$: 283.1158; found 283.1172.



4.S13 **4.10o**

Diethyl 2-(2-oxoethyl)malonate (4.10o). Ozone was bubbled through a 100 mL round-bottomed flask with diethyl 2-(2-methylallyl)malonate (**4.S13**, 1.04 mL, 4.93 mmol, 1.00 equiv.) and CH_2Cl_2 (29 mL) at -78°C until it turned a deep blue color. Then oxygen was bubbled through until the color dissipated at which time dimethyl sulfide (1.00 mL, 13.4 mmol, 2.72 equiv.) was added and the reaction was allowed to stir overnight (10 h) while warming to ambient temperature (23 °C). The reaction mixture was concentrated under reduced pressure by rotary evaporation, and purified by flash column chromatography (SiO_2, 20 → 60% EtOAc/hexanes) to afford aldehyde diester **4.10o** (718 mg, 67%) as a colorless oil. All characterization data was in accordance with previously reported data for this compound.

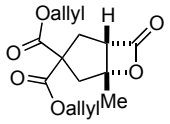
Representative procedure for the racemic the nucleophile-catalyzed Michael-aldol-β-lactonization (NMCAL) process as described for β-lactone (±)-4.14b.



Di-*tert*-butyl 5-methyl-7-oxo-6-oxabicyclo[3.2.0]heptane-3,3-dicarboxylate ((±)-4.14b). To an oven-dried, 25 mL round-bottomed flask equipped with a magnetic stir bar were added Michael donor **4.10b** (88 mg, 0.32 mmol, 1.00 equiv.) and THF (1 mL). The mixture was cooled to -78 °C with vigorous stirring and LiHMDS (320 μL of a 1.0 M solution in THF, 0.32 mmol, 1.00 equiv.) was added dropwise via microliter syringe

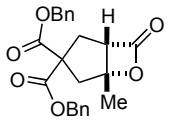
over ~ 4 min. After the addition, the reaction was stirred for 10 min at -78 °C and then warmed to 0 °C by switching the dry ice/acetone bath to an ice/water bath. Stirring was continued for an additional 10 min at this temperature, and then CH_2Cl_2 (4 mL), 4-PPY (80 μL of a 0.82 M solution in CH_2Cl_2, 0.064 mmol, 0.20 equiv.) and $EtN(^iPr)_2$ (60 μL, 0.32 mmol, 1.00 equiv.) were added via microliter syringe, sequentially. The reaction was allowed to stir for an additional 10 min at 0 °C before acryloyl chloride (**4.1a**, 261 μL of a 1.612 M solution in CH_2Cl_2, 0.42 mmol, 1.30 equiv.) was added via microliter syringe dropwise over ~ 2 min. After the addition, the ice bath was removed and the reaction was stirred for 6 h at ambient temperature (23 °C). At this time, the reaction was cooled to 0 °C and silica gel (2 mL) was added and the reaction was stirred at 0 °C for 10 min. The ice/water bath was removed and the reaction stirred at ambient temperature (23 °C) for 20 min. The mixture was then diluted with hexanes (4.0 mL), filtered through a short silica gel pad (~2 mL of silica gel), and rinsed with EtOAc (3 x 4 mL). The filtrate was then concentrated by rotary evaporation and following ^{1}H NMR analysis of the crude reaction mixture, it was purified by flash column chromatography (SiO_2, 10 → 30% EtOAc/hexanes) to afford bicyclic-β-lactone **(±)-4.14b** (77 mg, 73%) as colorless needles: m.p. 73.2 – 75.2 °C (recrystallized from hexanes: CH_2Cl_2 (1:1)); TLC (EtOAc:hexanes, 3:7 *v/v)*: R_f = 0.66; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.46 (d, J = 9.0 Hz, 1H), 2.99 (d, J = 14.1 Hz, 1H), 2.34, 2.87 (ABq, J_{AB} = 15.4 Hz, 2H), 2.07 (dd, J = 14.1, 9.1 Hz, 1H), 1.63 (s, 3H), 1.46 (s, 9H), 1.43 (s, 9H); ^{13}C NMR(125 MHz, $CDCl_3$): δ 169.6, 169.2, 168.9, 87.0, 82.7, 82.6, 62.2, 58.8, 43.3, 34.3, 27.8(3), 27.5(3), 21.6; IR

(thin film): 2981, 2928, 1833, 1732 cm^{-1}; HRMS (ESI+) *m/z* calcd. for $C_{17}H_{26}LiO_6$ $[M + Li]^+$: 333.1889; found 333.1902.



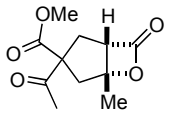
(±)-4.14c

Diallyl 5-methyl-7-oxo-6-oxabicyclo[3.2.0]heptane-3,3-dicarboxylate ((±)-4.14c). Prepared according to the representative procedure using Michael donor **4.10c** (77 mg, 0.32 mmol, 1.00 equiv.), THF (1 mL), LiHMDS (320 μL of a 1.0 M solution in THF, 0.32 mmol, 1.00 equiv.), CH_2Cl_2 (4 mL), 4-PPY (80 μL of a 0.82 M solution in CH_2Cl_2, 0.064 mmol, 0.20 equiv.) and *N'N'*-diisopropylethylamine (60 μL, 0.32 mmol, 1.00 equiv.), and acryloyl chloride (**4.1a**, 261 μL of a 1.612 M solution in CH_2Cl_2, 0.42 mmol, 1.30 equiv.). After addition of acryloyl chloride, the reaction was allowed to react for 6 h at ambient temperature (23 ^oC). Purification by flash column chromatography (SiO_2, 10 → 30% EtOAc/hexanes) afforded bicyclic-β-lactone **(±)-4.14c** (78 mg, 83%) as a colorless oil: TLC (EtOAc:hexanes, 3:7 *v/v)*: R_f = 0.45; ^1H NMR (500 MHz, $CDCl_3$): δ 5.92-5.80 (m, 2H), 5.34-5.22 (m, 4H), 4.69-4.57 (m, 4H), 3.54 (dd, *J* = 8.8, 0.9 Hz, 1H), 3.12 (app d, *J* = 14.2 Hz, 1H), 3.01 (dd, *J* = 15.3, 0.9 Hz, 1H), 2.44 (d, *J* = 15.3 Hz, 1H), 2.21 (dd, *J* = 14.2, 9.0 Hz, 1H) 1.7 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ170.1, 169.6, 169.0, 131.6, 131.2, 119.24, 119.22, 87.0, 77.2, 67.1, 66.8, 59.0, 43.8, 34.7, 21.6; IR (thin film): 2362, 2339, 1824, 1729 cm^{-1}; HRMS (ESI+) *m/z* calcd. for $C_{15}H_{19}O_6$ $[M + H]^+$ 295.1182; found 295.1177.



(±)-4.14d

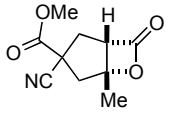
Dibenzyl 5-methyl-7-oxo-6-oxabicyclo[3.2.0]heptane-3,3-dicarboxylate ((±)-4.14d). Prepared according to the representative procedure using Michael donor **4.10d** (77 mg, 0.23 mmol, 1.00 equiv.), THF (1 mL), LiHMDS (320 μL of a 1.0 M solution in THF, 0.32 mmol, 1.4 equiv.), CH_2Cl_2 (4 mL), 4-PPY (80 μL of a 0.82 M solution in CH_2Cl_2, 0.064 mmol, 0.23 equiv.) and $EtN(^iPr)_2$ (60 μL, 0.32 mmol, 1.4 equiv.), and acryloyl chloride (**4.1a**, 261 μL of a 1.612 M solution in CH_2Cl_2, 0.42 mmol, 1.8 equiv.). After addition of acryloyl chloride, the reaction was allowed to react for 6 h at ambient temperature (23 ^oC). Purification by flash column chromatography (SiO_2, 10 → 50% EtOAc/hexanes) afforded bicyclic-β-lactone **(±)-4.14d** (47 mg, 53%) as a white solid: TLC (EtOAc:hexanes, 3:7 *v/v)*: R_f = 0.32; ^1H NMR (500 MHz, $CDCl_3$): δ 7.23 (dt, *J* = 7.3, 3.4 Hz, 6H), 7.18 (dd, *J* = 6.1, 3.4 Hz, 2H), 7.13 (dd, *J* = 6.5, 2.7 Hz, 2H), 5.12 (d, *J* = 12.2 Hz, 1H), 5.05-4.99 (m, 3H), 3.45 (d, *J* = 8.9 Hz, 1H), 3.07 (d, *J* = 14.1 Hz, 1H), 2.36, 2.96 (ABq, J_{AB} = 15.3 Hz, 2H), 2.12 (dd, *J* = 14.2, 9.0 Hz, 1H), 1.62 (s, 3H).; ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.1, 169.7, 169.0, 135.2, 135.0, 128.8(2), 128.7(2), 128.65, 128.63(2), 128.5, 128.1(2), 86.9, 68.2, 67.9, 60.9, 59.0, 43.7, 34.6, 21.6; IR (thin film): 1829, 1735, 1264 cm^{-1}; HRMS (ESI+) *m/z* calcd. for $C_{23}H_{22}LiO_6$ $[M + Li]^+$: 401.1576; found 401.1560.



(±)-4.14g

Methyl 3-acetyl-5-methyl-7-oxo-6-oxabicyclo[3.2.0]heptane-3-carboxylate ((±)-4.14g). Prepared according to the representative procedure using Michael donor **4.10g** (55 mg, 0.32 mmol, 1.00 equiv.), THF (1 mL), LiHMDS (320 μL of a 1.0 M solution in THF, 0.32 mmol, 1.00 equiv.), CH_2Cl_2 (4 mL), 4-PPY (80 μL of a 0.82 M solution in CH_2Cl_2, 0.064 mmol, 0.20 equiv.), $EtN(^iPr)_2$ (60 μL, 0.32 mmol, 1.00 equiv.), and acryloyl chloride (**4.1a**, 261 μL of a 1.612 M solution in CH_2Cl_2, 0.42 mmol, 1.30 equiv.). After addition of acryloyl chloride, the reaction was allowed to react for 8 h at ambient temperature (23 ^oC) as opposed to the standard 6 h. Purification by flash column chromatography (SiO_2, 25 → 55% EtOAc/hexanes) afforded a mixture of diastereomers (~1:1) of bicyclic-β-lactone (±)-**4.14g** (52 mg, 72%) as a pale yellow oil: TLC (EtOAc:hexanes, 5:5 *v/v)*, R_f = 0.31 and 0.28; (Note: Sufficient amounts of each diastereomer were isolated by flash chromatography to obtain ^1H but not ^{13}C NMR of each diastereomer), Diast. with R_f = 0.31: ^1H NMR (500 MHz, $CDCl_3$): δ 3.76 (s, 3H), 3.51 (app d, J = 8.5 Hz, 1H), 3.04 (app d, J = 14.0 Hz, 1H), 2.33, 2.87 (ABq, J_{AB} = 15.3 Hz, 2H), 2.18 (s, 3H), 2.04 (dd, J = 14.0, 8.9 Hz, 1H), 1.67 (s, 3H); Diast. with R_f = 0.31: ^1H NMR (500 MHz, $CDCl_3$): δ 3.72 (s, 3H), 3.48 (app d, J = 8.5 Hz, 1H), 3.14 (app d, J = 14.2 Hz, 1H), 2.44, 2.93 (ABq, J_{AB} = 15.6 Hz, 2H), 2.25 (s, 3H), 2.15 (dd, J = 14.2, 9.1, 1H), 1.68 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 201.6, 201.5, 171.6, 171.2, 169.2, 168.9, 87.0, 86.7, 67.8, 67.1, 59.0, 58.8, 53.5 (2), 43.0, 42.5, 33.6, 33.2, 26.9 26.5, 21.8,

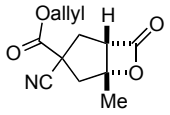
21.7; IR (thin film):1827, 1711 cm^{-1}; HRMS (ESI+) *m/z* calcd. for $C_{11}H_{15}O_5$ $[M+H]^+$: 227.0919; found 227.0923.



(±)-4.14h

Methyl 3-cyano-5-methyl-7-oxo-6-oxabicyclo[3.2.0]heptane-3-carboxylate ((±)-4.14h). Prepared according to the representative procedure using known Michael donor **4.10h**[419] (50 mg, 0.32 mmol, 1.00 equiv.), THF (1 mL), LiHMDS (320 μL of a 1.0 M solution in THF, 0.32 mmol, 1.00 equiv.), CH_2Cl_2 (4 mL), 4-PPY (80 μL of a 0.82 M solution in CH_2Cl_2, 0.064 mmol, 0.20 equiv.), $EtN(^iPr)_2$ (92 μL, 0.48 mmol, 1.50 equiv.), acryloyl chloride (**4.1a**, 261 μL of a 1.612 M solution in CH_2Cl_2, 0.42 mmol, 1.30 equiv.). After the addition of acryloyl chloride, the reaction was allowed to react at ambient temperature (23 ^oC) for 6 h. Purification by flash column chromatography (SiO_2, 10 → 40% EtOAc/hexanes) afforded a mixture of diastereomers (1.7:1) of bicyclic-β-lactone (±)-**4.14h** (44 mg, 65%) as a yellow oil: TLC (EtOAc:hexanes, 3.5:6.5 *v/v)*: R_f = 0.38 and 0.12; (Note: Sufficient amounts of each diastereomer were separated by flash chromatography to obtain ^1H and ^{13}C NMR for each diastereomer) Diast. with R_f = 0.38: ^1H NMR (500 MHz, $CDCl_3$): δ 3.89 (s, 3H), 3.74 (app d, *J* = 8.6 Hz, 1H), 2.91, 2.36 (ABq, J_{AB} = 15.2 Hz, 2H), 2.53 (dd, *J* = 14.4, 8.5 Hz, 1H), 2.82 (app d, *J* = 14.4 Hz, 1H), 1.77 (s, 3H); ^{13}C NMR (125 MHz; $CDCl_3$): δ168.1, 167.7, 118.3, 86.3, 59.4, 54.7, 47.2, 45.4, 37.0, 21.6; Diast. with R_f = 0.12: ^1H NMR (500 MHz, $CDCl_3$): δ 3.86 (s, 3H), 3.65 (app d, *J* = 9.0 Hz, 1H), 3.25 (app d, *J* = 14.3 Hz, 1H),

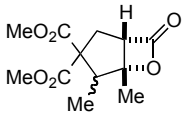
3.24, 2.39 (ABq, J_{AB} = 15.1, 2H), 2.42 (dd, J = 9.1, 14.5 Hz, 1H), 1.73 (s, 3H); ^{13}C NMR (125 MHz; $CDCl_3$): δ167.6, 166.9, 118.2, 86.0, 59.2, 54.6, 46.9, 46.1, 35.5, 21.6; IR (thin film): 2357, 1824, 1747 cm^{-1}; HRMS (ESI+) *m/z* calcd. for $C_{10}H_{11}LiNO_4$ $[M+Li]^+$: 216.0848; found 216.0839.



(±)-4.14i

Allyl 3-cyano-5-methyl-7-oxo-6-oxabicyclo[3.2.0]heptane-3-carboxylate ((±)-4.14i). Prepared according to the representative procedure using known Michael donor **4.10i** (58 mg, 0.32 mmol, 1.00 equiv.), THF (1 mL), LiHMDS (320 μL of a 1.0 M solution in THF, 0.32 mmol, 1.00 equiv.), CH_2Cl_2 (4 mL), 4-PPY (80 μL of a 0.82 M solution in CH_2Cl_2, 0.064 mmol, 0.20 equiv.), $EtN(^iPr)_2$ (60 μL, 0.32 mmol, 1.00 equiv.), acryloyl chloride (**4.1a**, 261 μL of a 1.612 M solution in CH_2Cl_2, 0.42 mmol, 1.30 equiv.). After addition of acryloyl chloride, the reaction was allowed to react at ambient temperature (23 ºC) for 24 h. Purification by flash column chromatography (SiO_2, 10 → 50% EtOAc/hexanes) afforded a mixture of diastereomers (1.16:1) of bicyclic-β-lactone **(±)-4.14i** (41 mg, 55%) as a yellow oil: TLC (EtOAc:hexanes, 3.5:6.5 *v/v)*: R_f = 0.39; (NMR data is provided for the ~1.2:1 mixture of diastereomers which were inseparable) ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.97-5.89 (m, 2H), 5.44-5.38 (m, 2H), 5.35-5.32 (m, 2H), 4.75-4.71 (m, 4H), 3.74 (d, J = 8.0 Hz, 1H), 3.63 (dd, J = 9.0, 1 Hz, 1H), 3.25 (dd, J = 14.5, 7.5 Hz, 2H), 2.92 (dd, J = 15.0, 1.0 Hz, 1H), 2.82 (d, J = 14.5 Hz, 1H), 2.53 (dd, J = 14.5, 8.5 Hz, 1H), 2.45-2.40 (m, 2H), 2.38 (d, J = 2.5 Hz, 1H), 1.77 (s, 3H), 1.74 (s,

3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.75, 167.53, 167.28, 166.08, 130.58, 130.47, 120.50, 120.39, 118.23, 118.20, 86.34, 86.04, 68.48, 68.23, 59.35, 59.19, 47.37, 47.12, 46.05, 45.33, 36.92, 35.52, 21.57 (2); IR (thin film): 2937, 2246, 1822, 1745 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{12}H_{14}NO_4$ $[M+H]^+$: 236.0923; found 236.1220.

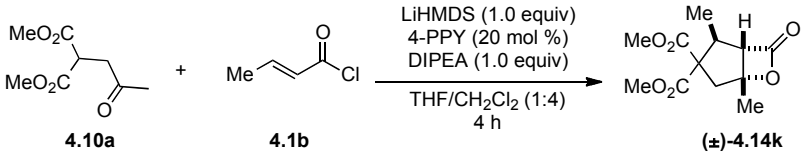


(±)-4.14j

Dimethyl 4,5-dimethyl-7-oxo-6-oxabicyclo[3.2.0]heptane-3,3-dicarboxylate ((±)-4.14j). Prepared according to the representative procedure using Michael donor **4.10j** (65 mg, 0.32 mmol, 1.00 equiv.), THF (1 mL), LiHMDS (320 μL of a 1.0 M solution in THF, 0.32 mmol, 1.00 equiv.), CH_2Cl_2 (4 mL), 4-PPY (80 μL of a 0.82 M solution in CH_2Cl_2, 0.064 mmol, 0.20 equiv.), $EtN(^iPr)_2$ (60 μL, 0.32 mmol, 1.00 equiv.), and acryloyl chloride (**4.1a**, 261 μL of a 1.612 M solution in CH_2Cl_2, 0.42 mmol, 1.30 equiv.). After the addition of acryloyl chloride, the reaction was allowed to react for 12 h at ambient temperature (23 ^oC) as opposed to the standard 6 h. Purification by flash column chromatography (SiO_2, 15 → 50% EtOAc/hexanes) afforded a mixture of diastereomers (2:1) of bicyclic-β-lactone **(±)-4.14j** (69 mg, 84%) as a pale yellow oil: TLC (EtOAc:hexanes, 4:6 *v/v)*: R_f = 0.33 and 0.42; (Note: Sufficient amounts of each diastereomer were isolated by flash chromatography to obtain ^{1}H but not ^{13}C NMR of each diastereomer), Diast. with R_f = 0.42: ^{1}H NMR (500 MHz; $CDCl_3$): δ 3.72 (s, 3H), 3.71 (s, 3H), 3.51 (dd, *J* = 9.1, 1.5 Hz, 1H), 3.39 (q, *J* = 7.6 Hz, 1H), 2.81 (dd, *J* = 14.7, 1.4 Hz, 1H), 2.66 (dd, *J* = 14.7, 9.0 Hz, 1H), 1.59 (s, 3H), 0.90 (d, *J* = 7.6 Hz, 3H);

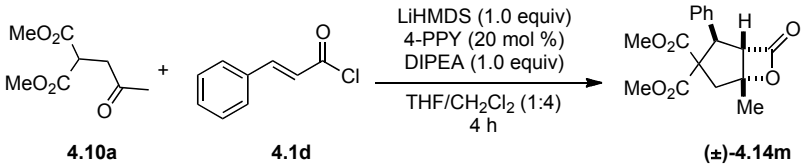
Diast. with R_f = 0.33: ^{1}H NMR (500 MHz; $CDCl_3$): δ 3.72 (s, 3H), 3.71 (s, 3H), 3.52 (dd, *J* = 9.1, 0.7 Hz, 1H), 2.95 (app d, *J* = 14.3 Hz, 1H), 2.71 (q, *J* = 7.1 Hz, 1H), 2.00 (dd, *J* = 14.3, 9.1 Hz, 1H), 1.60 (s, 3H), 1.19 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz; $CDCl_3$): δ 171.1, 170.0, 169.9, 169.8, 169.31, 169.27, 89.12, 87.9, 65.5, 63.1, 58.4, 57.9, 53.4, 53.23, 53.20, 52.6, 47.7, 45.8, 33.6, 31.0, 20.5, 19.6, 13.0, 9.8; IR (thin film): 2961, 1824, 1735 cm^{-1}; HRMS (ESI+) *m/z* calcd. for $C_{12}H_{16}OLiO_6$ $[M+Li]^+$: 263.1107; found 263.1115.

Representative procedure for the racemic nucleophile-catalyzed Michael-aldol-β-lactonization (NMCAL) process when varying the Michael acceptors as described for β-lactone (±)-4.14k.



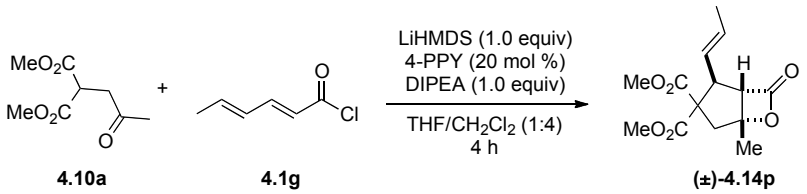
Dimethyl 2,5-dimethyl-7-oxo-6-oxabicyclo[3.2.0]heptane-3,3-dicarboxylate ((±)-4.14k). To an oven-dried, 25 mL round-bottomed flask equipped with a magnetic stir bar was added dimethyl 2-(2-oxopropyl) malonate (**4.10a**, 61.0 mg, 0.32 mmol, 1.00 equiv.) along with THF (1 mL) and the mixture was cooled to -78 ^{o}C. With vigorous stirring, LiHMDS (320 μL of a 1.0 M solution in THF, 0.32 mmol, 1.00 equiv.) was added dropwise via microliter syringe. After complete addition, the reaction was stirred for 10 min at -78 ^{o}C and then warmed to 0 ^{o}C by switching the dry ice/acetone bath to an ice/water bath. Stirring was continued for an additional 10 min at this temperature, and then CH_2Cl_2 (4 mL), 4-PPY (80 μL of a 0.82 M solution in CH_2Cl_2, 0.064 mmol, 0.20

equiv.) and EtN(^{i}Pr)$_2$ (60 μL, 0.32 mmol, 1.00 equiv.) were added via microliter syringe, sequentially. The reaction was allowed to stir for an additional 10 min at 0 ^{o}C before (*E*)-but-2-enoyl chloride (**4.1b**, 260 μL of a 1.6 M solution in CH_2Cl_2, 0.42 mmol, 1.30 equiv.) was added via microliter syringe dropwise over ~2 min. After complete addition, the ice bath was removed and the reaction was stirred for 4 h at ambient temperature (23 ^{o}C). The reaction was then cooled to 0 ^{o}C and silica gel (2 g) was added and stirred at 0 ^{o}C for 10 min. Then the ice/water bath was removed and the reaction stirred at ambient temperature (23 ^{o}C) for 20 min. The mixture was then diluted with hexanes (4.0 mL), filtered through a short silica gel pad (~2 g of silica gel), and rinsed with EtOAc (3 x 4 mL). The filtrate was then concentrated by rotary evaporation, analyzed by ^{1}H NMR. Purification by flash column chromatography (SiO_2, 10 → 40% EtOAc/hexanes) afforded a single diastereomer of bicyclic-β-lactone **(±)-4.14k** (77.1 mg, 94%) as a white solid: TLC (EtOAc:hexanes, 3:7 *v/v)*: R_f = 0.25; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.71 (s, 3H), 3.70 (s, 3H), 3.42 (app q, J = 7.5 Hz, 1H), 3.17 (app s, 1H), 2.63, 2.82 (ABq, J_{AB} = 16.5 Hz, 1H), 1.66 (s, 3H), 0.86 (d, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.6, 168.8, 168.3, 86.0, 65.9, 64.5, 53.2, 53.0, 40.9, 39.6, 22.2, 17.0; IR (thin film): 2996, 2927, 1835, 1735, 1730 cm^{-1}; HRMS (ESI+) *m/z* calcd. for $C_{12}H_{17}O_6$ $[M+H]^+$: 257.1025; found 257.1038.



Dimethyl 5-methyl-7-oxo-2-phenyl-6-oxabicyclo[3.2.0]heptane-3,3-dicarboxylate

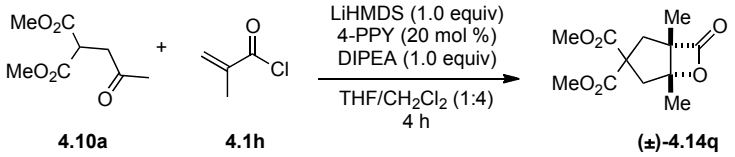
((±)-4.14m). Prepared according to the representative procedure for **(±)-4.14k**, except that cinnamoyl chloride (**4.1d**, 70 mg, 0.42 mmol, 1.30 equiv.) was added as the Michael acceptor to afford a single diastereomer of bicyclic-β-lactone **(±)-4.14m** (91.6 mg, 90%) as a white solid: TLC (EtOAc:hexanes, 2:8 *v/v)*: R_f = 0.15; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27 (m, 3H), 6.95 (d, *J* = 7.0 Hz, 2H), 4.62 (s, 1H), 3.78 (s, 3H), 3.68 (s, 1H), 3.30 (s, 3H), 2.90 (app s, 2H), 1.89 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.6, 167.9, 167.6, 138.2, 128.7 (2), 128.0, 127.9(2), 87.3, 66.8, 65.4, 53.5, 52.63, 51.0, 41.9, 21.4; IR (thin film): 2967, 2935, 1829, 1732, 1728 cm^{-1}; HRMS (ESI+) *m/z* calcd. for $C_{17}H_{19}O_6$ $[M+H]^+$: 319.1182; found 319.1149.



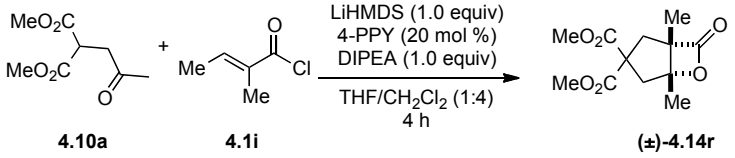
4.10a **4.1g** **(±)-4.14p**

Dimethyl 5-methyl-7-oxo-2-((E)-prop-1-en-1-yl)-6-oxabicyclo [3.2.0]heptane-3,3-dicarboxylate ((±)-4.14p). Prepared according to the representative procedure for **(±)-4.14k**, except that sorbic chloride (**4.4.1g**, 51.4 *u*L, 0.42 mmol, 1.3 equiv) was added as the Michael acceptor to afford a single diastereomer of bicyclic-β-lactone **(±)-4.14p** (58.0 mg, 64%) as a white solid: TLC (EtOAc:hexanes, 3:7 *v/v)*: R_f = 0.50; ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.59 (m, 1H), 5.09 (m, 1H), 3.90 (app d, *J* = 10.0 Hz, 1H), 3.75 (s, 3H), 3.63 (s, 3H), 3.33 (s, 1H), 2.65, 2.82 (ABq, J_{AB} = 16.0 Hz, 2H), 1.71 (s, 3H), 1.64 (dd, *J* = 6.5, 1.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): 170.5, 168.4, 168.0, 130.0, 126.4, 86.4, 65.3, 64.5, 53.3, 53.0, 48.6, 41.5, 22.0, 18.0; IR (thin film): 2977, 2963, 1829, 1732, 1729 cm^{-1}; HRMS (ESI+) *m/z* calcd. for $C_{14}H_{19}O_6$ $[M+H]^+$: 283.1182; found

283.1203.



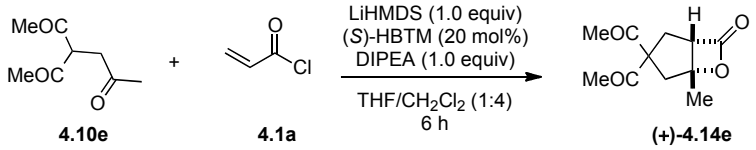
Dimethyl 1,5-dimethyl-7-oxo-6-oxabicyclo[3.2.0]heptane-3,3-dicarboxylate ((±)-4.14q). Prepared according to the representative procedure for **(±)-4.14k**, except that methacryloyl chloride (**4.1h**, 41 μL, 0.42 mmol, 1.30 equiv.) was added as the Michael acceptor to afford a single diastereomer of bicyclic-β-lactone **(±)-14.4q** (64.1 mg, 78%) as a white solid: TLC (EtOAc:hexanes, 2.5:7.5 *v/v)*: R_f = 0.45; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.73 (s, 3H), 3.71 (s, 3H), 1.85, 3.15 (ABq, J_{AB} = 14 Hz, 2H), 2.40, 2.98 (ABq, J_{AB} = 15 Hz, 2H), 1.52 (s, 3H), 1.27 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): 172.4, 170.9, 170.3, 89.3, 62.3, 58.4, 53.4, 53.2, 44.1, 42.1, 18.7, 14.1; IR (thin film): 2986, 2937, 1829, 1739, 1725 cm^{-1}; HRMS (ESI+) *m/z* calcd. for $C_{12}H_{17}O_6$ $[M+H]^+$: 257.1025; found 257.1058.



Dimethyl 1,2,5-trimethyl-7-oxo-6-oxabicyclo [3.2.0]heptane-3,3-dicarboxylate ((±)-4.14r). Prepared according to the representative procedure for **(±)-4.14k**, except that (*E*)-2-methylbut-2-enoyl chloride (**4.1i**, 50 mg, 0.42 mmol, 1.30 equiv.) was added as the Michael acceptor, to afford a single diastereomer of bicyclic-β-lactone **(±)-4.14r** (52 mg, 60%) as a white solid: TLC (EtOAc:hexanes, 3:7 *v/v)*: R_f = 0.20; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.75 (s, 3H), 3.74 (s, 3H), 3.38 (q, *J* = 8.0 Hz, 1H), 2.58, 2.86 (ABq, J_{AB} =

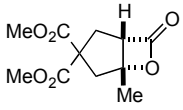
15.5 Hz, 2H), 1.52 (s, 3H), 1.21 (s, 3H), 0.78 (d, J = 8.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.0, 170.7, 169.2, 88.8, 64.5, 63.3, 53.3, 53.1, 42.1, 41.7, 19.2, 12.3, 11.4; IR (thin film): 2995, 2928, 1832, 1732, 1728 cm^{-1}; HRMS (ESI+) *m/z* calcd. for $C_{13}H_{19}O_6$ $[M+H]^+$: 271.1182; found 271.1159.

Representative procedure for the enantioselective nucleophile-catalyzed Michael-aldol-β-lactonization (NMCAL) process as described for β-lactone (+)-4.14e.



Methyl-7-oxo-6-oxabicyclo[3.2.0]heptane-3,3-diyldiethanone ((+)-4.14e). To an oven-dried, 25 mL round-bottomed flask equipped with a magnetic stir bar was added Michael donor **4.10e** (49.8 mg, 0.32 mmol, 1.00 equiv.) along with THF (1 mL) and cooled to -78 °C. With vigorous stirring, LiHMDS (320 μL of a 1.0 M solution in THF, 0.32 mmol, 1.00 equiv.) was added dropwise via microliter syringe over ~4 min. After the addition the reaction was stirred for 10 min at -78 °C and then warmed to 0 °C by switching the dry ice/acetone bath to an ice/water bath. Stirring was continued for an additional 10 min at this temperature, and then CH_2Cl_2 (3 mL), (*S*)-HBTM (17 mg, 0.064 mmol, dissolved in 1.1 mL CH_2Cl_2, 0.20 equiv.) and $EtN(^iPr)_2$ (60 μL, 0.32 mmol, 1.00 equiv.) were added via microliter syringe sequentially. The reaction was allowed to stir for an additional 10 min at 0 °C before acryloyl chloride (**4.1a**, 261 μL of a 1.612 M solution in CH_2Cl_2, 0.42 mmol, 1.30 equiv.) was added via microliter syringe dropwise

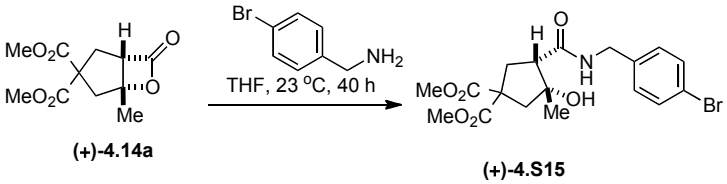
over 4 min (addition time varied from 4 min- 2h dependent on acid chloride employed) at 0 °C. After complete addition, the ice bath was removed and the reaction stirred for 6 h (reaction time varied from 6-24 h dependent on acid chloride employed) at ambient temperature (23 °C). When the reaction was judged complete by TLC, the reaction was cooled to 0 °C and silica gel (2 g) was added and stirred at 0 °C for 10 min. Then the ice/water bath was removed and the reaction stirred at ambient temperature (23 °C) for 20 min. The mixture was then diluted with hexanes (4.0 mL), filtered through a short silica gel pad (~2 g of silica gel), and rinsed with EtOAc (3 x 4 mL). This process removes polar impurities including (*S*)-HBTM. The filtrate was concentrated by rotary evaporation, and following ^{1}H NMR analysis of the reaction mixture, it was purified by flash column chromatography (SiO_2, 10 → 50% EtOAc/hexanes) to afford bicyclic-β-lactone **(+)-4.14e** (41.2 mg, 61%) as a white solid: $[\alpha]_D^{21}$ = +167.34 (*c* = 1.00, $CHCl_3$). Enantiomeric excess was determined by HPLC analysis in comparison with authentic racemic material using a Chiralcel AD-H column: hexanes:*i*PrOH = 95:05, flow rate 0.5 mL/min, λ = 210 nm: t_{minor} = 52.0 min, t_{major} = 67.4 min; 95% *ee*. Spectral data matched that reported above for the racemic compound.



(+)-4.14a

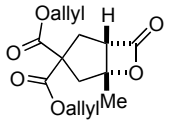
(1*S*,5*R*)-Dimethyl 5-methyl-7-oxo-6-oxabicyclo[3.2.0]heptane-3,3-dicarboxylate ((+)-4.14a). Prepared according to the representative procedure using Michael donor **4.10a** (60.0 mg, 0.32 mmol, 1.00 equiv.), THF (1 mL), LiHMDS (320 μL of a 1.0 M solution in THF, 0.32 mmol, 1.00 equiv.), CH_2Cl_2 (3 mL), (*S*)-HBTM (17 mg, 0.064

mmol, dissolved in 1.1 mL CH_2Cl_2, 0.20 equiv.), *N',N'*-diisorpopylethylamine 60 μL, 0.32 mmol, 1.00 equiv.), and acryloyl chloride (**4.1a**, 34 μL, 0.42 mmol, dissolved in 260 μL CH_2Cl_2, 1.30 equiv.). After the addition of acryloyl chloride at 0°C (over ~ 4 min), the reaction was allowed to react for 6 h at ambient temperature (23 ºC). After ^{1}H NMR analysis of the reaction mixture, it was purified by flash column chromatography (SiO_2, 20 → 50% EtOAc/hexanes) to afford bicyclic-β-lactone **(+)-4.14a** (55.8 mg, 72% yield) as a colorless oil: $[\alpha]_D^{21}$ = +67.25 (*c* = 1.00, $CHCl_3$). Enantiomeric excess was determined by chiral GC analysis in comparison with authentic racemic material; t_{minor} = 253.1 min, t_{major} = 263.4 min; 97% *ee*. Spectral data matched that previously reported[1] and absolute stereochemistry was assigned by derivatization as described below.



(3*R*,4*S*)-Dimethyl4-((4-bromobenzyl)carbamoyl)-3-hydroxy-3-methylcyclo-pentane 1,1-dicarboxylate ((+)-4.S15). To an oven-dried, 5 mL round-bottomed flask was added β-lactone **(+)-4.14a** (49 mg, 0.20 mmol, 1.00 equiv) and *p*-bromobenzylamine (0.10 mL, 0.80 mmol, 4.00 equiv), in THF (2 mL). The reaction was allowed to stir at ambient temperature (23 °C) for 40 h. Upon completion (as judged by TLC), the reaction was concentrated by rotary evaporation and purified by flash column chromatography (SiO_2, 20 → 60% EtOAc/hexanes) to afford amide **(+)-4.S15** (56 mg, 65%) as a colorless

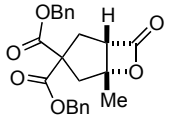
crystalline solid: m.p. 118–121 °C (recrystallized from $CDCl_3$); TLC (EtOAc:hexanes, 5:5 *v/v*): R_f = 0.35; $[\alpha]_D^{19}$ = +8.00 (*c* = 1.00, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.46 (d, *J* = 8.3 Hz, 2H), 7.14 (d, *J* = 8.3 Hz, 2H), 6.38 (brs, 1H), 4.45 (dd, *J* = 14.9, 5.9, 1H), 4.41 (dd, *J* = 15.0, 5.9 Hz, 1H), 3.76 (s, 3H), 3.72 (s, 3H), 2.80 (app t, *J* = 12.7 Hz, 1H), 2.66, 2.13 (ABq, J_{AB} = 14.0, 2H), 2.61 (dd, *J* = 13.3, 7.9 Hz, 1H), 2.52 (dd, *J* = 12.1, 7.9 Hz, 1H), 1.37 (s, 3H) (OH not observed); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.3, 173.1, 172.7, 137.1, 132.1(2), 129.6(2), 121.8, 80.0, 58.0, 53.8, 53.4, 53.3, 48.5, 43.0, 37.5, 25.7; IR (thin film): 3336, 2960, 2922, 1732, 1637 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{18}H_{23}BrNO_6$ $[M+H]^+$: 428.0709; found 428.0692.



(+)-4.14c

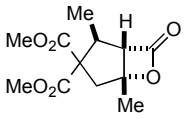
(1*R*,5*S*)-Diallyl 5-methyl-7-oxo-6-oxabicyclo[3.2.0]heptane-3,3-dicarboxylate ((+)-4.14c). Prepared according to the representative procedure using Michael donor **4.10c** (76 mg, 0.32 mmol), THF (1 mL), LiHMDS (320 μL of a 1.0 M solution in THF, 0.32 mmol, 1.00 equiv.), CH_2Cl_2 (3 mL), (*S*)-HBTM (17 mg, 0.064 mmol, dissolved in 80 μL CH_2Cl_2, 0.20 equiv.), $EtN(^iPr)_2$ (60 μL, 0.32 mmol, 1.00 equiv.), and acryloyl chloride (**4.1a**, 34 μL, 0.42 mmol, dissolved in 260 μL CH_2Cl_2, 1.30 equiv.). After the addition of acryloyl chloride at 0 °C (over ~4 min), the reaction was allowed to stir for 6 h at ambient temperature (23 ºC). Purification by flash column chromatography afforded bicyclic-β-lactone **(+)-4.14c** (69 mg, 74%) as a colorless oil: $[\alpha]_D^{19}$ = +39.8 (*c* = 0.200, $CHCl_3$). Enantiomeric excess was determined by HPLC analysis in comparison with

authentic racemic material using a Chiralcel IA column: hexanes:*i*PrOH = 92:08, flow rate 0.5 mL/min, λ = 210 nm: t_{major} = 17.3 min, t_{minor} = 21.3 min; 95% *ee*. Spectral data matched that reported above for the racemic compound that reported above for the racemic compound.



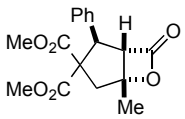
(+)-4.14d

(1*S*,5*R*)-Dibenzyl 5-methyl-7-oxo-6-oxabicyclo[3.2.0]heptane-3,3-dicarboxylate ((+)-4.14d). Prepared according to the representative procedure using Michael donor **4.10d** (95 mg, 0.28 mmol, 1.0 equiv.), THF (1 mL), LiHMDS (256 μL of a 1.0 M solution in THF, 0.26 mmol, 0.93 equiv.), CH_2Cl_2 (3 mL), (*S*)-HBTM (10.4 mg, 0.033 mmol, dissolved in 104 μL CH_2Cl_2, 0.12 equiv.), $EtN(^iPr)_2$ (48 μL, 0.28 mmol, 1.0 equiv.), and acryloyl chloride (**4.1a**, 34 μL, 0.42 mmol, dissolved in 227 μL CH_2Cl_2, 1.5 equiv.). After the addition of acryloyl chloride at 0 °C (over ~4 min), the reaction was allowed to react for 6 h at ambient temperature (23 ºC). Purification by flash column chromatography afforded bicyclic-β-lactone **(+)-4.14d** (59 mg, 59%) as a colorless oil: $[\alpha]_D^{19}$ = +41.3 (*c* = 0.36, $CHCl_3$). Enantiomeric excess was determined by HPLC analysis in comparison with authentic racemic material using a Chiralcel OD-H column: hexanes:*i*PrOH = 95:05, flow rate 1.0 mL/min, λ = 210 nm: t_{major} = 36.6 min, t_{minor} = 45.6 min; 98% *ee*. Spectral data matched that reported above for the racemic compound.



(+)-4.14k

(1*S*,2*S*,5*R*)-Dimethyl 2,5-dimethyl-7-oxo-6-oxabicyclo[3.2.0]heptane-3,3-dicarboxylate ((+)-4.14k). Prepared according to the representative procedure using Michael donor **4.10a** (60 mg, 0.32 mmol, 1.00 equiv.), THF (1 mL), LiHMDS (320 μL of a 1.0 M solution in THF, 0.32 mmol, 1.00 equiv.), CH_2Cl_2 (4 mL), (*S*)-HBTM (17 mg, 0.064 mmol, dissolved in 1.1 mL CH_2Cl_2, 0.20 equiv.), $EtN(^iPr)_2$ (60 μL, 0.32 mmol, 1.00 equiv.), and (*E*)-but-2-enoyl chloride (**4.1b**, 40 μL, 0.42 mmol, dissolved in 2 mL CH_2Cl_2, 1.30 equiv.). The solution of (*E*)-but-2-enoyl chloride was added by syringe pump over 2 h at 0 °C, the reaction was allowed to stir for 16 h at ambient temperature (23 °C). Purification by flash column chromatography afforded a single diastereomer of bicyclic-β-lactone **(+)-4.14k** (65 mg, 80%) a colorless solid: $[\alpha]_D^{21}$ = +116.51 (*c* = 1.00, $CHCl_3$). Enantiomeric excess was determined by HPLC analysis in comparison with authentic racemic material using a Chiralcel OD-H column: hexanes:*i*PrOH = 90:10, flow rate 0.5 mL/min, λ = 210 nm: t_{major} = 22.4 min, t_{minor} = 29.1 min 94% *ee*. Spectral data matched that reported above for the racemic compound.



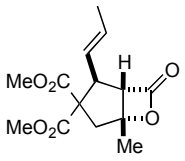
(+)-4.14m

(1*S*,2*R*,5*R*)-Dimethyl 5-methyl-7-oxo-2-phenyl-6-oxabicyclo[3.2.0]heptane-3,3-

dicarboxylate ((+)-4.14m). Prepared according to the representative procedure using Michael donor **4.10a** (61 mg, 0.32 mmol, 1.00 equiv.), THF (1 mL), LiHMDS (320 μL of a 1.0 M solution in THF, 0.32 mmol, 1.00 equiv.), CH_2Cl_2 (3 mL), (*S*)-HBTM (17 mg, 0.064 mmol, dissolved in 400 μL CH_2Cl_2, 0.20 equiv.), $EtN(^iPr)_2$ (60 μL, 0.32 mmol, 1.00 equiv.), and cinnamoyl chloride (**4.1d**, 67.7 mg, 0.35 mmol, dissolved in 2.6 mL CH_2Cl_2, 1.10 equiv.). The solution of cinnamoyl chloride was added by syringe pump over 2 h at 0 ^oC, and then the reaction was allowed to stir for 18 h at ambient temperature (23 ^oC). Purification by flash column chromatography afforded a single diastereomer of bicyclic-β-lactone **(+)-4.14m** (82 mg, 80%) as a white solid: $[\alpha]_D^{21}$ = +188.23 (*c* = 0.17, $CHCl_3$). Enantiomeric excess was determined by HPLC analysis in comparison with authentic racemic material using a Chiralcel AD-H column: hexanes:*i*PrOH = 70:30, flow rate 0.5 mL/min, λ = 210 nm: t_{major} = 12.0 min, t_{minor} = 13.1 min; 99% *ee*. Spectral data matched that reported above for the racemic compound.

Use of a lower catalyst loading for the NCMAL (5 mol%) as described for bicyclic-β-lactone (+)-4.14m. This reaction was run according to the procedure described above for (+)-**4.14m** with the exception that a lower catalyst loading (5 vs 20 mol%) and a longer total reaction time (26 h vs 20 h) were employed. Michael donor **4.10a** (72 mg, 0.38 mmol, 1.00 equiv.), THF (1 mL), LiHMDS (380 μL of a 1.0 M solution in THF, 0.38 mmol, 1.00 equiv.), CH_2Cl_2 (3.6 mL), (*S*)-HBTM (5.1 mg, 0.019 mmol, dissolved in 500 μL CH_2Cl_2, 0.05 equiv.), $EtN(^iPr)_2$ (71 μL, 0.38 mmol, 1.00 equiv.), and cinnamoyl chloride (**4.1d**, 82 mg, 0.49 mmol, dissolved in 2.7 mL CH_2Cl_2, 1.30 equiv.).

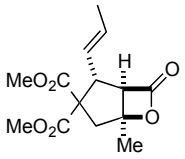
The solution of cinnamoyl chloride was added by syringe pump over 8 h at 0 °C, and the reaction was allowed to stir for 18 h at ambient temperature (23 °C). Purification by flash column chromatography afforded a single diastereomer of bicyclic-β-lactone (+)-**4.14m** (94 mg, 78%) as a white solid. Enantiomeric excess was determined by chiral HPLC analysis in comparison with racemic material (Chiralcel AD-H column: hexanes:*i*PrOH = 70:30, flow rate 0.5 mL/min, λ = 210 nm): t_{major} = 12.0 min, t_{minor} = 13.1 min; 90% *ee*.



(+)-4.14p

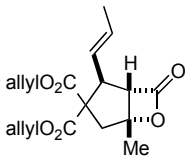
(1*S*,2*S*,5*R*)-Dimethyl-5-methyl-7-oxo-2-((*E*)-prop-1-en-1-yl)-6-oxabicyclo[3.2.0] heptane-3,3-dicarboxylate ((+)-4.14p). Prepared according to the representative procedure using Michael donor **4.10a** (60.0 mg, 0.32 mmol, 1.00 equiv.), THF (1 mL), LiHMDS (320 μL of a 1.0 M solution in THF, 0.32 mmol, 1.00 equiv.), CH_2Cl_2 (4 mL), (*S*)-HBTM (17 mg, 0.064 mmol, dissolved in 1 mL CH_2Cl_2, 0.20 equiv.), $EtN(^iPr)_2$ (60 μL, 0.32 mmol, 1.00 equiv.), and sorbic chloride (**4.1g**, 51.4 μL, 0.42 mmol, dissolved in 2 mL CH_2Cl_2, 1.3 equiv.). The solution of sorbic chloride was added by syringe pump over 2 h at 0 °C, and then the reaction was allowed to stir for 16 h at ambient temperature (23 °C). Purification by flash column chromatography afforded a single diastereomer of bicyclic-β-lactone **(+)-4.14p** (56.0 mg, 62%) a white crystalline solid: m.p. 98–102 °C (recrystallized from $CDCl_3$); $[\alpha]_D^{23}$ = +140.00 (*c* = 1.00, $CHCl_3$). Enantiomeric excess was determined by HPLC analysis in comparison with authentic

racemic material using a Chiralcel AD-H column: hexanes:*i*PrOH = 70:30, flow rate 0.5 mL/min, λ = 210 nm: t_{major} = 22.2 min, t_{minor} = 27.1 min; 99% *ee*. Spectral data matched that reported above for the racemic compound.



(–)-4.14p

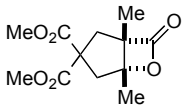
(1*R*,2*R*,5*S*)-Dimethyl5-methyl-7-oxo-2-((*E*)-prop-1-en-1-yl)-6-oxabicyclo[3.2.0] heptane-3,3-dicarboxylate ((-)-4.14p). Prepared according to the representative procedure using Michael donor **4.10a** (60.0 mg, 0.32 mmol, 1.00 equiv.), THF (1 mL), LiHMDS (320 μL of a 1.0 M solution in THF, 0.32 mmol, 1.00 equiv.), CH_2Cl_2 (3 mL), (*R*)-HBTM (17 mg, 0.064 mmol, dissolved in 1 mL CH_2Cl_2, 0.20 equiv.), $EtN(^iPr)_2$ (60 μL, 0.32 mmol, 1.00 equiv.), and sorbic chloride (**4.1g**, 51.4 μL, 0.42 mmol, dissolved in 2 mL CH_2Cl_2, 1.30 equiv.). The solution of sorbic chloride was added by syringe pump over 2 h at 0 °C, and then the reaction was allowed to react for 21 h at room temperature (23 °C). Purification by flash column chromatography afforded a single diastereomer of bicyclic-β-lactone **(-)-4.14p** (54.2 mg, 60%) a colorless solid: $[\alpha]_D^{21}$ = -138.00 (*c* = 1.00, $CHCl_3$). Enantiomeric excess was determined by HPLC analysis in comparison with authentic racemic material using a Chiralcel AD-H column: hexanes:*i*PrOH = 70:30, flow rate 0.5 mL/min, λ = 210 nm: t_{minor} = 22.2 min, t_{major} = 27.2 min; 99% *ee*. Spectral data matched that reported above for the racemic compound.



(+)-4.14s

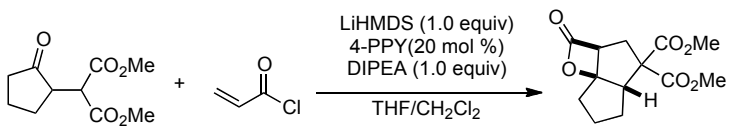
(1*S*,2*S*,5*R*)-Diallyl1,5-dimethyl-7-oxo-2-((*E*)-prop-1-en-1-yl)-6-oxabicyclo[3.2.0] heptane-3,3-dicarboxylate ((+)-4.14s). Prepared according to the representative procedure using Michael donor **4.10c** (76 mg, 0.32 mmol, 1.00 equiv.), THF (1 mL), LiHMDS (320 μL of a 1.0 M solution in THF, 0.32 mmol, 1.00 equiv.), CH_2Cl_2 (3 mL), (*S*)-HBTM (17 mg, 0.064 mmol, dissolved in 1 mL CH_2Cl_2, 0.20 equiv.), $EtN(^iPr)_2$ (60 μL, 0.32 mmol, 1.00 equiv.), and sorbic chloride (**4.1g**, 51.4 μL, 0.42 mmol, dissolved in 2 mL CH_2Cl_2, 1.30 equiv.). The solution of sorbic chloride was added by syringe pump over 2 h at 0 °C, and then the reaction was allowed to stir for 21 h at ambient temperature (23 °C). Purification by flash column chromatography afforded a single diastereomer of bicyclic-β-lactone **(+)-4.14s** (59 mg, 54%) a colorless oil: TLC (EtOAc:hexanes, 2:8 *v/v)*: R_f = 0.64; $[\alpha]_D^{23}$ = +76.8 (*c* = 0.53, $CHCl_3$). Enantiomeric excess was determined by HPLC analysis in comparison with authentic racemic material using a Chiralcel AD-H column: hexanes:*i*PrOH = 95:05, flow rate 0.5 mL/min, λ = 210 nm: t_{major} = 17.7 min, t_{minor} = 25.5 min; 94% *ee*. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.91-5.77 (m, 2H), 5.62-5.57 (m, 1H), 5.34-5.21 (m, 4H), 5.14-5.08 (m, 1H), 4.69-4.61 (m, 2H), 4.58-4.50 (m, 2H), 3.95 (app d, *J* = 10.0 Hz, 1H), 3.35 (s, 1H), 2.69, 2.87 (ABq, J_{AB} = 15.7 Hz, 2H), 1.73 (s, 3H), 1.63 (dd, *J* = 6.5, 1.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.7, 168.1, 167.7, 131.5, 131.4, 130.3, 126.5, 119.3, 119.1, 86.5, 67.1, 66.7, 65.5, 64.7, 48.7, 41.7, 22.2, 18.0; IR (thin film): 2940, 2857, 1835, 1741, 1270, 1149 cm$^-$

[1]; HRMS (ESI+) *m/z* calcd. for $C_{18}H_{22}LiO_6$ $[M+Li]^+$: 341.1576; found 341.1562.



(+)-4.14q

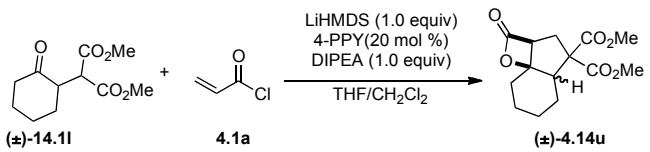
(1*S*,5*R*)-Dimethyl 1,5-dimethyl-7-oxo-6-oxabicyclo[3.2.0]heptane-3,3-dicarboxylate ((+)-4.14q). Prepared according to the representative procedure using Michael donor **4.10a** (60.0 mg, 0.32 mmol, 1.00 equiv.), THF (1 mL), LiHMDS (320 μL of a 1.0 M solution in THF, 0.32 mmol, 1.00 equiv.), CH_2Cl_2 (3 mL), (*S*)-HBTM (17 mg, 0.064 mmol, dissolved in 1 mL CH_2Cl_2, 0.20 equiv.), $EtN(^iPr)_2$ (60 μL, 0.32 mmol, 1.00 equiv.), and methacryloyl chloride (**4.1h**, 41.0 μL, 0.42 mmol, dissolved in 2 mL CH_2Cl_2, 1.30 equiv.). The solution of methacryloyl chloride was added by syringe pump over 2 h at 0 °C, and then the reaction was stirred for 18 h at ambient temperature (23 °C). Purification by flash column chromatography afforded a single diastereomer of bicyclic-β-lactone **(+)-4.14q** (65.4 mg, 80%) as colorless solid: $[\alpha]_D^{21}$ = +83.3 (*c* = 0.24, $CHCl_3$). Enantiomeric excess was determined by HPLC analysis in comparison with authentic racemic material using a Chiralcel OD-H column: hexanes:*i*PrOH = 92:08, flow rate 1.0 mL/min, λ = 210 nm: t_{minor} = 12.3 min, t_{major} = 15.2 min; 99% *ee*. Spectral data matched that reported above for the racemic compound.



(±)-14.10k **4.1a** **(±)-4.14t**

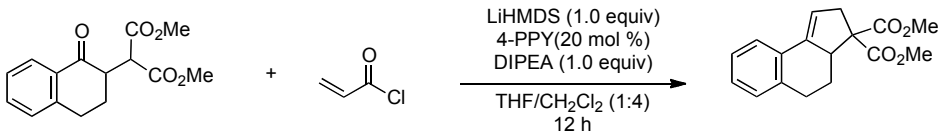
Dimethyl 2-oxohexahydropentaleno[6a,1-*b*]oxete-4,4(2*H*)-dicarboxylate ((±)-4.14t). Prepared according to the representative procedure for **(±)-14a**, except that Michael

donor **(±)-4.10k** (68 mg, 0.32 mmol, 1.00 equiv.) was used, along with THF (1 mL), LiHMDS (320 μL of a 1.0 M solution in THF, 0.32 mmol, 1.00 equiv.), CH_2Cl_2 (4 mL), 4-PPY (80 μL of a 0.82 M solution in CH_2Cl_2, 0.064 mmol, 0.20 equiv.), $EtN(^iPr)_2$ (60 μL, 0.32 mmol, 1.00 equiv.), and acryloyl chloride (**4.1a**, 261 μL of a 1.612 M solution in CH_2Cl_2, 0.42 mmol, 1.30 equiv.). After addition of acryloyl chloride at 0°C (over ~4 min), the reaction was allowed to stir for 24 h at ambient temperature (23 °C). The mixture was then diluted with hexanes (4.0 mL), filtered through a short silica gel pad (~2 g of silica gel), and rinsed with EtOAc (3 x 4 mL). The filtrate was then concentrated by rotary evaporation the resulting oil was of sufficient purity to warrant no further purification affording a single diastereomer of tricyclic-β-lactone **(±)-4.14t** (78 mg, 91%): as a colorless oil: TLC (EtOAc:hexanes, 3:7 *v/v)*: R_f = 0.43; ^{1}H NMR (500 MHz, $CDCl_3$): 3.74 (s, 3H), 3.71 (s, 3H), 3.59 (dd, *J* = 9.0, 1.0 Hz, 1H), 3.50 (dd, *J* = 11.0, 8.0 Hz, 1H), 2.83 (app d, *J* = 15.0, 1H), 2.65 (dd, *J* = 15.0, 9.0 Hz, 1H), 2.34-2.28 (m, 1H), 2.18-2.14 (m, 1H), 1.94-1.81 (m, 2H), 1.80-1.71 (m, 1H), 1.30-1.23 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4, 169.5(2), 95.7, 63.4, 59.4, 53.5, 53.2, 52.0, 31.7, 31.5, 27.3, 23.3; IR (thin film): 2363, 2340, 1824, 1732 cm^{-1}; HRMS (ESI+) *m/z* calcd. for $C_{13}H_{16}O_6Li$ $[M+Li]^+$: 275.1107; found 275.1106.



Dimethyl 2-oxohexahydro-2H-indeno[7a,1-b]oxete-4,4(4aH)-dicarboxylate ((±)-4.14u). Prepared according to the representative procedure for **(±)-4.14a**, except that

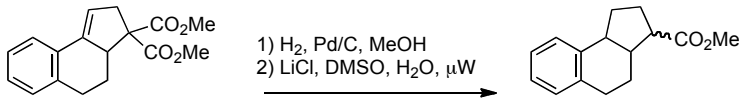
Michael donor **(±)-4.10l** (73 mg, 0.32 mmol, 1.00 equiv.), THF (1 mL), LiHMDS (320 μL of a 1.0 M solution in THF, 0.32 mmol, 1.00 equiv.), CH_2Cl_2 (4 mL), 4-PPY (80 μL of a 0.82 M solution in CH_2Cl_2, 0.064 mmol, 0.20 equiv.), $EtN(^iPr)_2$ (60 μL, 0.32 mmol), and acryloyl chloride (**4.1a**, 261 μL of a 1.612 M solution in CH_2Cl_2, 0.42 mmol, 1.30 equiv.). After addition of acryloyl chloride at 0°C (over ~4 min), the reaction was allowed to stir for 24 h at ambient temperature (23 °C). Purification by flash column chromatography (SiO_2, 10 → 30% EtOAc/hexanes) afforded a mixture of diastereomers (1:1) of bicyclic-β-lactone **(±)-4.14u** (60 mg, 70%) as a colorless oil: TLC (EtOAc:hexanes, 3:7 *v/v)*: R_f = 0.41; (NMR data is provided for the 1:1 mixture of diastereomers); ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.77-3.69 (m, 12H), 3.44 (dd, *J* = 11.3, 8.9 Hz, 2H), 3.17 (dd, *J* = 12.9, 5.8 Hz, 1H), 3.04 (d, *J* = 14.0 Hz, 1H), 2.96 (d, *J* = 14.8 Hz, 1H), 2.70 (dd, *J* = 14.8, 9.1 Hz, 1H), 2.42 (dd, *J* = 12.5, 3.7 Hz, 1H), 2.13-2.09 (m, 2H), 2.05-1.87 (m, 5H), 1.79-1.72 (m, 4H), 1.67-1.51 (m, 2H), 1.40-1.11 (m, 3H), 0.92 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.0, 169.91, 169.86, 169.5, 169.2, 168.7, 88.9, 88.6, 64.7, 61.1, 55.6, 55.2, 53.4, 53.3, 53.2, 52.6, 51.9, 47.6, 34.1, 32.8, 31.7, 31.0, 26.6, 25.5, 24.4, 24.1, 23.7, 22.1; IR (thin film): 2958, 2863, 1830, 1735 cm^{-1}; HRMS (ESI+) *m/z* calcd. for $C_{14}H_{18}O_6Li$ $[M+Li]^+$: 289.1263; found 289.1277.



(±)-14.1n **4.1a** **(±)-4.16**

Dimethyl 4,5-dihydro-2*H*-cyclopenta[*a*]naphthalene-3,3(3a*H*)-dicarboxylate ((±)-4.16). Prepared according to the representative procedure using Michael donor **(±)-4.10n**

(88 mg, 0.32 mmol, 1.00 equiv.), THF (1 mL), LiHMDS (320 μL of a 1.0 M solution in THF, 0.32 mmol, 1.00 equiv.), CH_2Cl_2 (4 mL), 4-PPY (80 μL of a 0.82 M solution in CH_2Cl_2, 0.064 mmol, 0.20 equiv.), $EtN(^iPr)_2$ (60 μL, 0.32 mmol, 1.00 equiv.), and acryloyl chloride (**4.1a**, 261 μL of a 1.612 M solution in CH_2Cl_2, 0.42 mmol, 1.30 equiv.). After addition of acryloyl chloride at 0°C (over ~4 min), the reaction was allowed to stir for 12 h at ambient temperature (23 °C). Purification by flash column chromatography (SiO_2, 5 → 30% EtOAc/hexanes) afforded tricyclic compound **(±)-4.16** as a white solid (49 mg, 54%): TLC (EtOAc:hexanes, 3:7 *v/v)*: R_f = 0.69; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.54 (t, *J* = 4.5 Hz, 1H), 7.12-7.07 (m, 3H), 6.00 (dd, *J* = 2.6, 5.1 Hz, 1H), 3.76 (s, 3H), 3.69-3.67 (m, 1H), 3.67 (s, 3H), 3.28 (app dt, *J* = 2.5, 17.4, 1H), 2.95 (ddd, *J* = 4.4, 12.6, 16.8 Hz, 1H), 2.85 (ddd, *J* = 2.4, 4.4, 16.6 Hz, 1H), 2.78 (app dt, *J* = 2.4, 17.4 Hz, 1H), 2.21-2.17 (m, 1H), 1.33 (ddd, *J* = 4.5, 12.7, 25.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.6, 171.2, 139.1, 136.6, 131.3, 129.1, 127.7, 126.3, 124.9, 118.2, 63.2, 52.9, 52.4, 50.1, 40.7, 30.8, 26.1; IR (thin film): 1735, 1270, 1243 cm^{-1}; HRMS (ESI+) *m/z* calcd. for $C_{17}H_{18}LiO_4$ $[M+Li]^+$: 293.1365; found 293.1375.

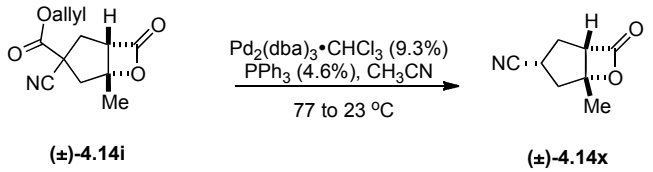


(±)-4.16 (±)-4.17

Methyl 2,3,3a,4,5,9b-hexahydro-1*H*-cyclopenta[*a*]naphthalene-3-carboxylate ((±)-4.17). To an oven dried, round-bottomed flask containing (±)-**4.16** (39 mg, 0.14 mmol, 1.0 equiv.) and 20% Pd/C (12.0 mg, 0.2 equiv.) was added MeOH (15 mL). The reaction was then purged with H_2 gas, and stirred at ambient temperature (23 °C) under a H_2

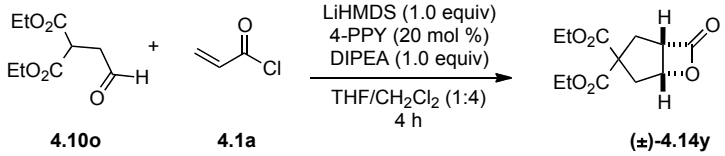
atmosphere (1 atm, balloon) for 2 h. The H_2 balloon was removed and the reaction was filtered through celite to remove the Pd to provide a single diastereomer (~ 41 mg) and was of sufficient purity to carry on directly to the subsequent decarboxylation.

To a portion of the crude diester (2.7 mg, .0094 mmol) from the hydrogenation above was added DMSO (0.60 mL) and H_2O (60 μL) in a microwave reaction tube. To this mixture was added LiCl (3.9 mg, 0.094 mmol, 10.0 equiv.) and the reaction was placed in a microwave reactor and heated to 180 ^oC for 20 min. Then $NaHCO_3$ (4 mL) was added to the reaction mixture and it was extracted with Et_2O (3 x 4 mL). The organic layer was washed with brine (2 x 4 mL), collected and dried over $MgSO_4$, filtered, concentrated by rotary evaporation, and purified by flash column chromatography (gradient SiO_2, 0 → 15% EtOAc/hexanes) afforded a mixture of diastereomers (1:1) of monoester (±)-**4.17** (1.5 mg, 70%) as a colorless oil: TLC (EtOAc:hexanes, 1:9 *v/v)*: R_f = 0.67; (NMR data is provided for the inseparable 1:1 mixture of diastereomers) ^1H NMR (500 MHz; $CDCl_3$): δ 7.15-7.08 (m, 8H), 3.72 (s, 3H), 3.71 (s, 3H), 3.27 (dd, *J* = 18.5, 8.4 Hz, 1H), 3.22-3.12 (m, 2H), 2.80-2.52 (m, 7H), 2.33-2.15 (m, 4H), 2.05-1.99 (m, 1H), 1.95-1.84 (m, 4H), 1.78-1.70 (m, 1H), 1.64-1.42 (m, 2H);^{13}C NMR (125 MHz, $CDCl_3$): δ 177.0, 174.8, 139.9(2), 137.1, 136.0, 129.2, 129.1, 128.9, 128.7, 126.2, 126.1, 125.8, 125.6, 52.0, 51.7, 50.2, 49.0, 43.4, 42.2, 41.93, 41.89, 35.2, 33.1, 29.9, 29.3, 28.9, 27.5, 24.9, 21.4; IR (thin film): 2919, 2854, 1741, 1459, 1430, 1205, 906, 737 cm^{-1}; HRMS (ESI+) *m/z* calcd. for $C_{15}H_{18}LiO_2$ $[M+Li]^+$: 237.1467; found 237.1471.



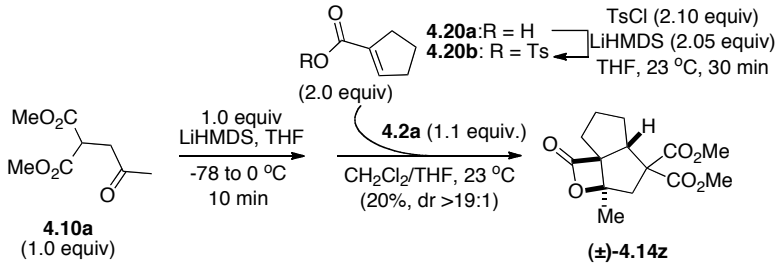
(±)-4.14i **(±)-4.14x**

5-Methyl-7-oxo-6-oxabicyclo[3.2.0]heptane-3-carbonitrile ((±)-4.14x). To an oven-dried, 10 mL round-bottomed flask equipped with a magnetic stir bar was added $Pd_2(dba)_3$-$CHCl_3$ (47 mg, 0.045 mmol, 0.092 equiv.), triphenylphosphine (6 mg, 0.023 mmol, 0.047 equiv.), bicyclic-β-lactone **(±)-4.14i** (115 mg, 0.489 mmol, 1.00 equiv., as a 1.16:1 mixture of diastereomers) along with CH_3CN (6 mL). After addition, the flask was equipped with a reflux condenser and the reaction mixture was heated to 77 °C using an oil bath. With vigorous stirring the reaction remained at 77 °C for 6 h. After which the oil bath was removed and the reaction stirred at ambient temperature (23 °C) for 17 h. The mixture was then diluted with hexanes (4.0 mL), filtered through a short silica gel pad (~2 mL of silica gel), and rinsed with EtOAc (3 x 4 mL). The filtrate was concentrated by rotary evaporation and purified by flash column chromatography (gradient SiO_2, 20 → 100% EtOAc/hexanes) afforded a single diastereomer of bicyclic-β-lactone **(±)-4.14x** (55.6 mg, 75% yield) a colorless solid: m.p. 101-103 °C (recrystallized from $CDCl_3$); TLC (EtOAc:hexanes, 5:5 v/v): R_f = 0.25; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.64 (app d, *J* = 8.3 Hz, 1H), 3.35 (app t, *J* = 8.0 Hz, 1H), 2.66 (app d, *J* = 15.1 Hz, 1H), 2.58 (app d, *J* = 14.4 Hz, 1H), 2.20 (app dt, *J* = 14.4, 8.1 Hz, 1H), 2.00 (dd, *J* = 15.1, 8.2 Hz, 1H), 1.73 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): 168.8, 120.9, 86.9, 59.2, 40.0, 31.5, 28.2, 21.5; IR (thin film): 2360, 2339, 2235, 1807 cm^{-1}; HRMS (ESI-) *m/z* calcd for $C_8H_8NO_2$ $[M - H]^-$: 150.0555; found 150.0562.



Diethyl 7-oxo-6-oxabicyclo[3.2.0]heptane-3,3-dicarboxylate ((±)-4.14y).

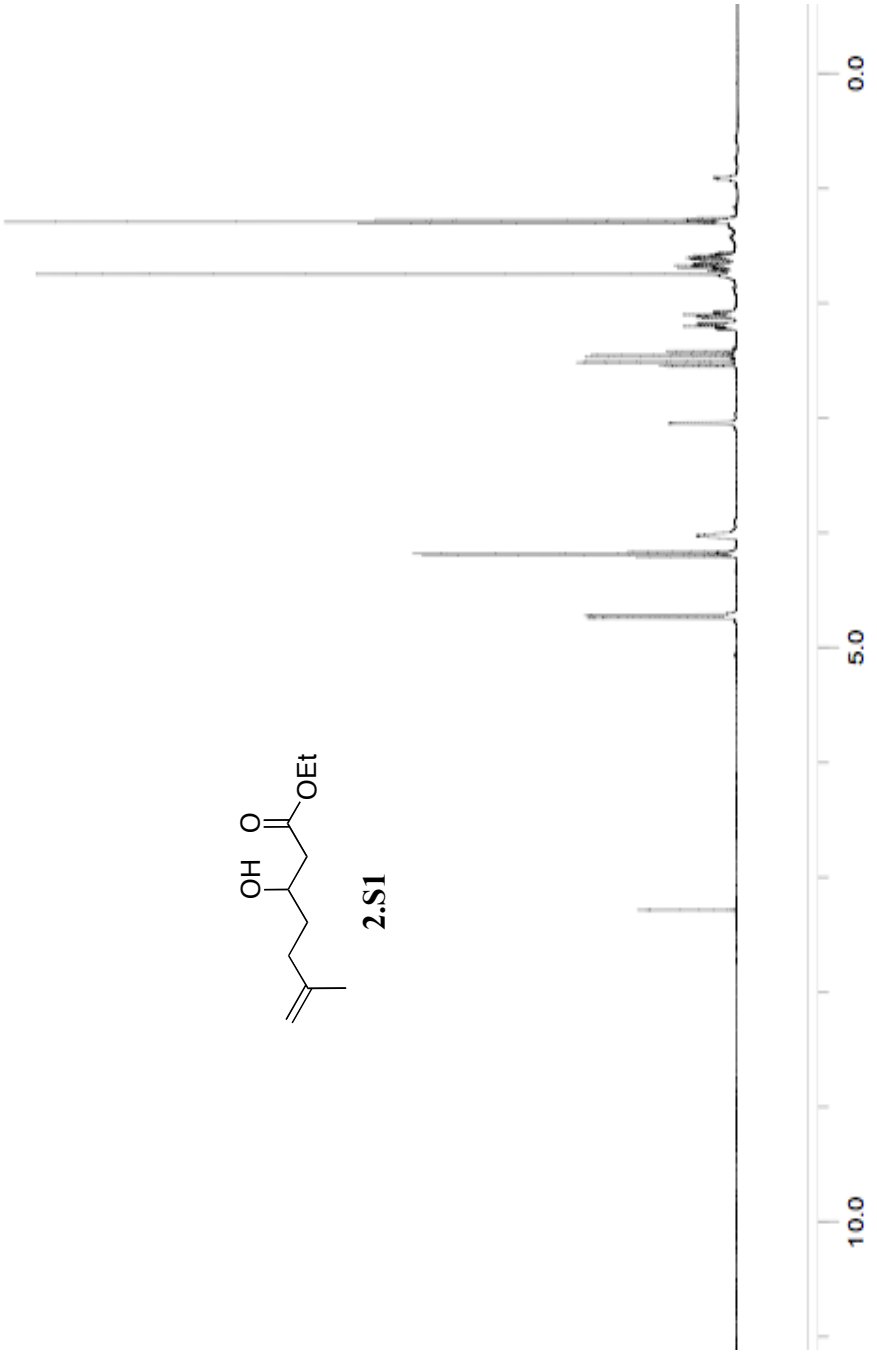
Prepared according to the representative procedure using Michael donor **4.10o** (64.7 mg, 0.32 mmol, 1.00 equiv.), THF (1 mL), LiHMDS (320 μL of a 1.0 M solution in THF, 0.32 mmol, 1.00 equiv.), CH_2Cl_2 (4 mL), 4-PPY (80 μL, 0.064 mmol of a 0.82 M solution in CH_2Cl_2, 0.20 equiv.), $EtN(^iPr)_2$ (60 μL, 0.32 mmol, 1.00 equiv.), and acryloyl chloride (**4.1a**, 261 μL of a 1.612 M solution in CH_2Cl_2, 0.42 mmol, 1.30 equiv.). After addition of acryloyl chloride at 0°C (over ~4 min), the reaction was allowed to stir for 12 h at ambient temperature (23 °C). Purification by flash column chromatography (SiO_2, 5 → 30% EtOAc/hexanes) afforded bicyclic β-lactone **(±)-4.14y** as a colorless oil (49 mg, 60%): TLC (EtOAc:hexanes, 3:9 *v/v)*: R_f = 0.38; ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.10 (m, 1H), 4.33-4.23 (m, 4H), 4.04 (app dd, *J* = 9.1, 3.9 Hz, 1H), 3.23 (app d, *J* = 14.2 Hz, 1H), 3.08 (app d, *J* = 15.6 Hz, 1H), 2.52 (dd, *J* = 15.6, 3.6 Hz, 1H), 2.15 (dd, *J* = 14.2, 9.2 Hz, 1H), 1.35-1.30 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.5, 170.1, 169.2, 62.5, 60.1, 56.1, 45.1, 39.1, 34.1, 29.8, 14.1, 14.0; IR (thin film): 2925, 2854, 1838, 1735 cm^{-1}; HRMS (ESI+) *m/z* calcd. for $C_{12}H_{17}O_6$ $[M+H]^+$: 257.1025; found 257.1034.



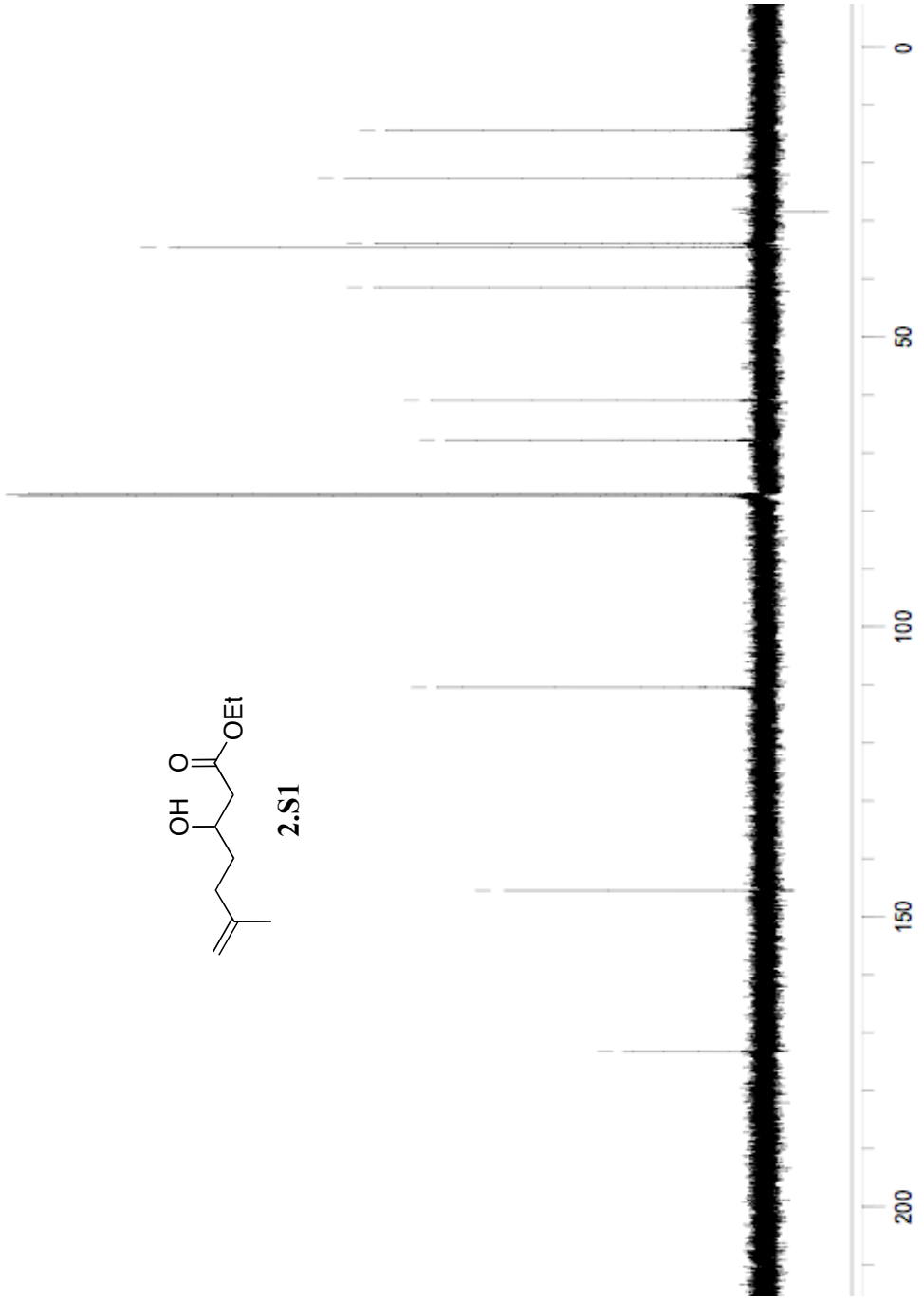
Dimethyl 2a-methyl-1-oxohexahydropentaleno[1,6a-*b*]oxete-4,4(1*H*)-dicarboxylate ((±)-4.14z). To an oven-dried, 10 mL round-bottomed flask equipped with a magnetic stir bar were added cyclopent-1-enecarboxylic acid (**4.20a**, 38.6 mg, 0.344 mmol, 2.00 equiv.) TsCl (66.1 mg, 0.347 mmol, 2.02 equiv.) and THF (1.1 mL) and the mixture was cooled to -78 ^{o}C. With vigorous stirring, LiHMDS (353 μL of a 1.0 M solution in THF, 0.353 mmol, 2.05 equiv.) was added dropwise via microliter syringe. After the addition was complete, the reaction was allowed to react at ambient temperature (23 ^{o}C) for ~1 h. To an oven-dried, 25 mL round-bottomed flask equipped with a magnetic stir bar was added Michael donor **4.10a** (32.4 mg, 0.172 mmol, 1.00 equiv.) and THF (0.55 mL) and the mixture was cooled to -78 ^{o}C. With vigorous stirring, LiHMDS (181 μL of a 1.0 M solution in THF, 0.181 mmol, 1.05 equiv.) was added dropwise via microliter syringe. After complete addition, the reaction was stirred for 10 min at -78 ^{o}C and then warmed to 0 ^{o}C by switching the dry ice/acetone bath to an ice/water bath. Stirring was continued for an additional 10 min at 0 ^{o}C, and then 4-PPY (**4.2a**, 28.0 mg, 0.189 mmol, dissolved in 1.7 mL CH_2Cl_2, 1.1 equiv) was added. The reaction was allowed to stir for an additional 10 min at 0 ^{o}C and then the previously prepared tosyl anhydride from **4.20a** was added over ~4 min at 0 ^{o}C. After the addition was complete, the reaction was stirred for 12 h at room temperature (23 ^{o}C). The reaction was then cooled to 0 ^{o}C and silica gel (2 g) was added and stirred at 0 ^{o}C for 10 min. The ice/water bath was removed and the reaction stirred at ambient temperature (23 ^{o}C) for 20 min. The mixture was then diluted with hexanes (4.0 mL), filtered through a short silica gel pad (~2 mL of silica gel), and the flask was rinsed with EtOAc (3 x 4 mL) with each portion passed through silica plug.

The filtrate was then concentrated by rotary evaporation and analyzed by ^{1}H NMR which showed ~3:2 ratio of **4.10a**/**4.14z**.

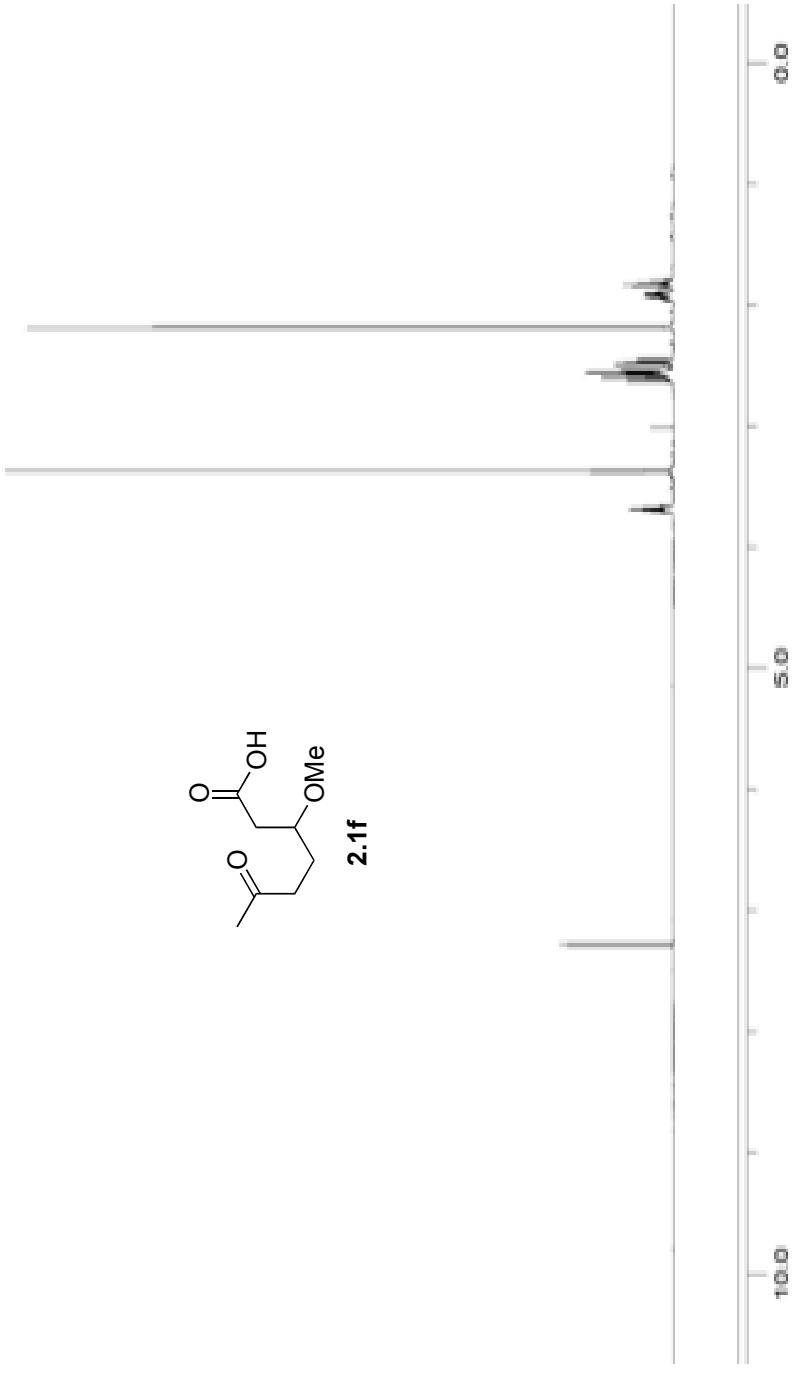
The crude material was directly subject to $NaBH_4$ to chemoselectively reduce unreacted **14.0a** (which co-eluted with product). The crude reaction mixture was dissolved in MeOH (2.0 mL) and cooled to 0 ^{o}C, then $NaBH_4$ (15.5 mg, 0.41 mmol, 2.38 equiv.). After 1.5 h, the reaction was quenched with sat. NH_4Cl (4 mL), and extracted with EtOAc (4 x 4 mL) and then washed with brine (5 mL). The organic layers were combined and dried over $MgSO_4$, filtered, concentrated by rotary evaporation, and purified by flash column chromatography (gradient SiO_2, 5 → 35% EtOAc/hexanes) to afford a single diastereomer (>19:1 as judged by 500 MHz NMR) of bicyclic-β-lactone **(±)-4.14z** (9.8 mg, 20%) as a white solid: TLC (EtOAc:hexanes, 3:7 *v/v)*: R_f = 0.14; ^{1}H NMR (500 MHz; $CDCl_3$): δ 3.78 (s, 3H), 3.74 (s, 3H), 3.62 (dd, *J* = 11.6, 7.1 Hz, 1H), 2.87 (d, *J* = 15.8 Hz, 1H), 2.64 (d, *J* = 15.8 Hz, 1H), 2.22 (m, 1H), 1.88-1.68 (m, 4H), 1.53 (s, 3H), 1.14 (m, *J* = 7.4 Hz, 1H); ^{13}C NMR (125 MHz; $CDCl_3$): δ 172.7, 171.1, 169.5, 89.7, 72.9, 61.5, 53.8, 53.4, 53.2, 41.8, 28.9, 26.3, 25.8, 20.1; IR (thin film): 2958, 2928, 2857, 1833, 1738 cm^{-1}; HRMS (ESI+) *m/z* calcd. for $C_{14}H_{19}O_6$ $[M+H]^+$: 283.1182; found 283.1168.



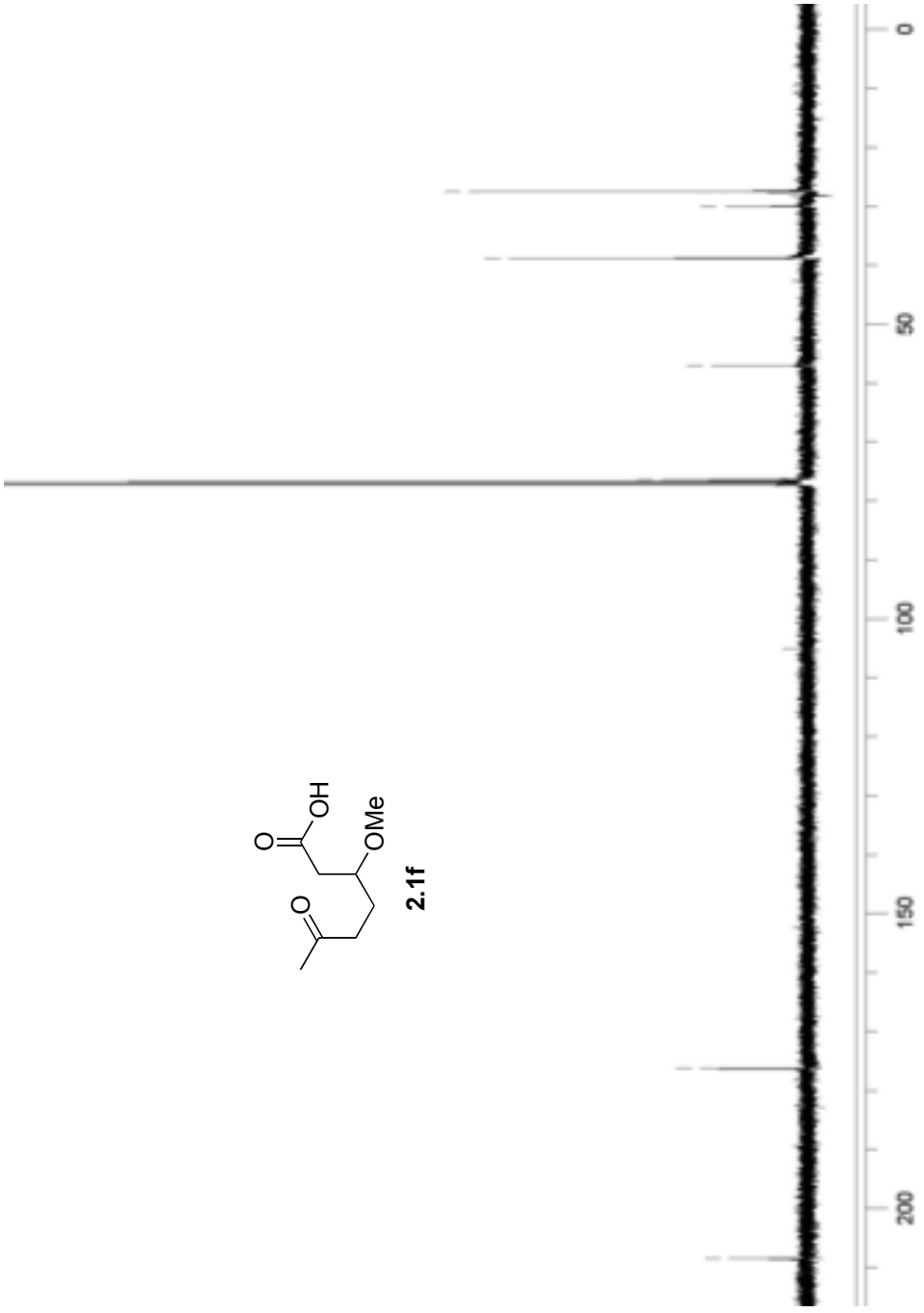
^{1}H (500 MHz) spectra of substrate **2.S1** in $CDCl_3$



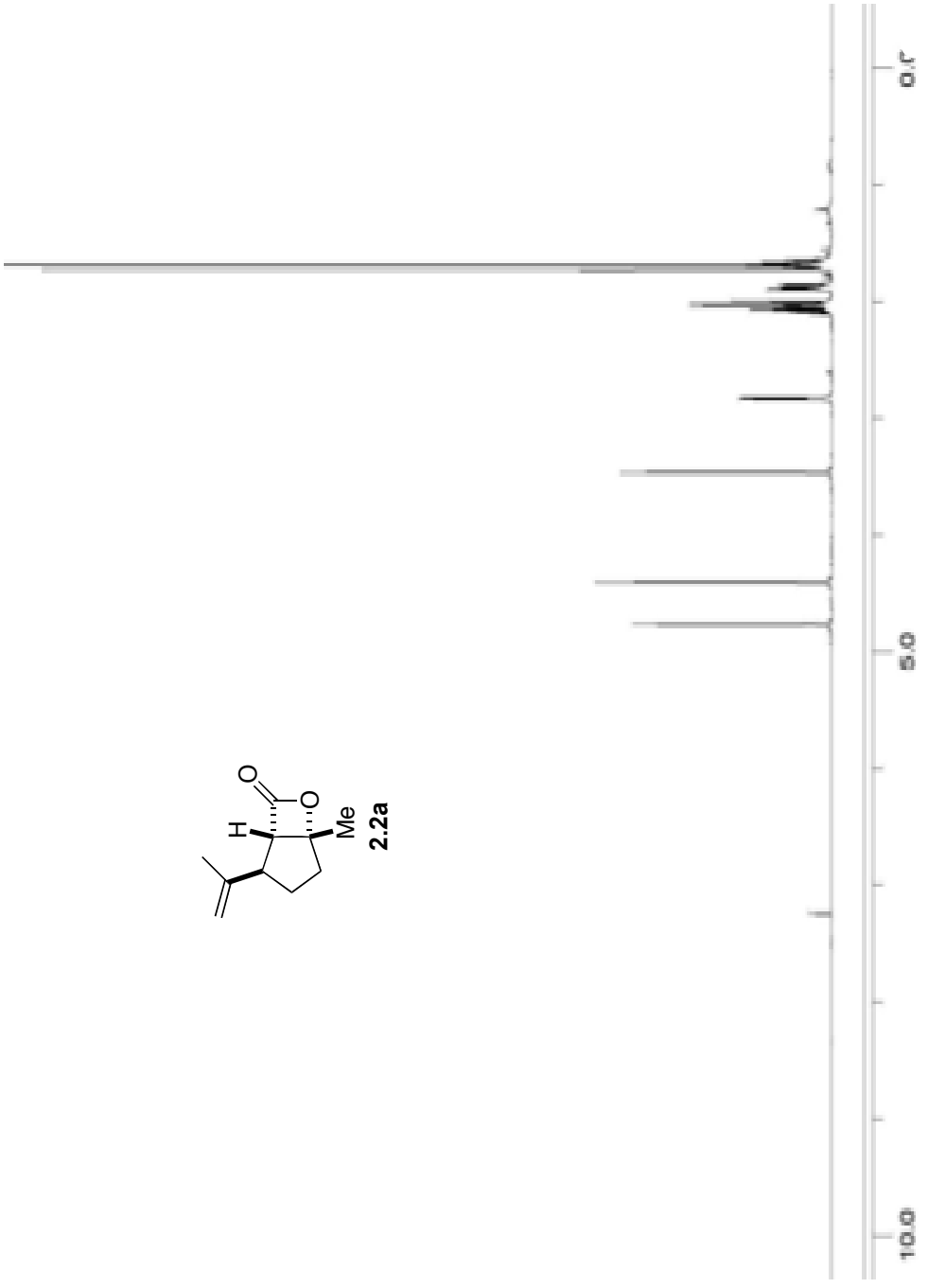
^{13}C NMR (125 MHz) spectra of substrate **2.S1** in $CDCl_3$



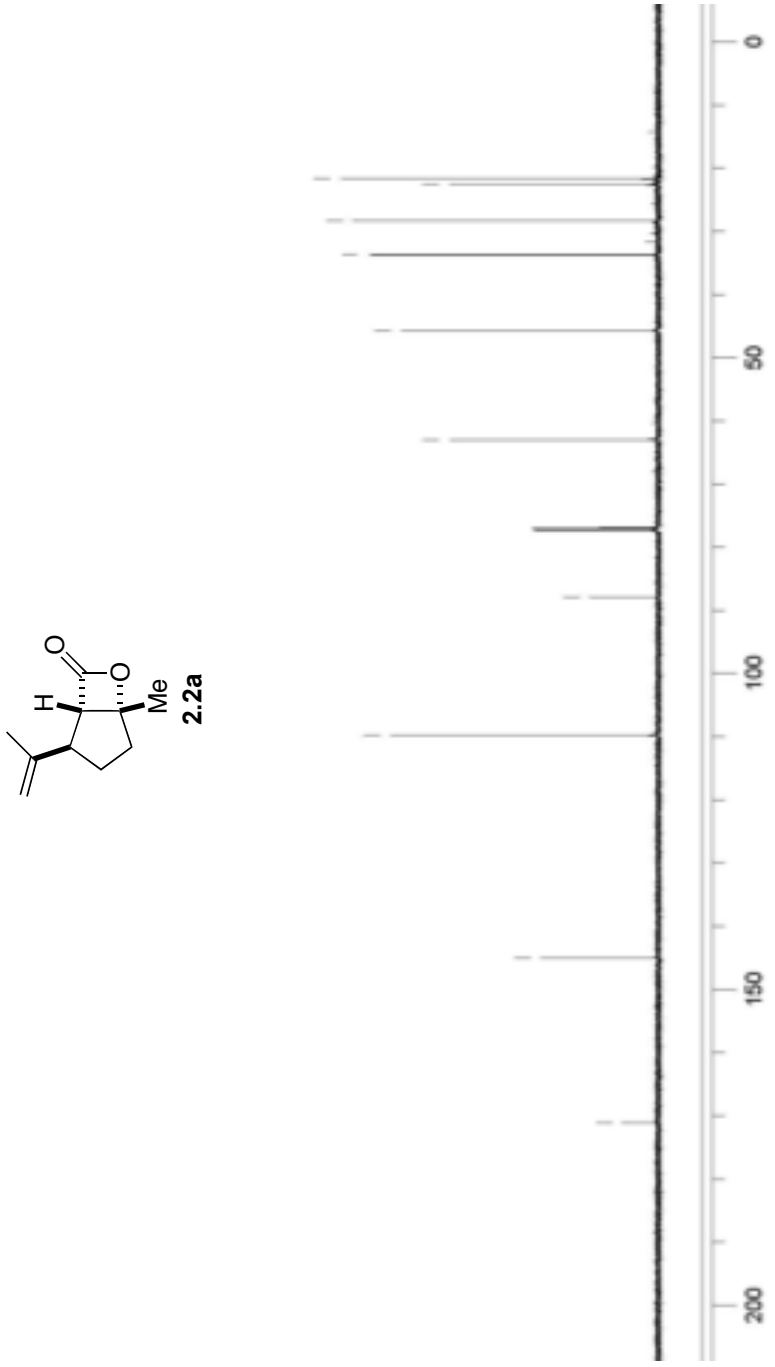
^{1}H (500 MHz) spectra of substrate **2.1f** in $CDCl_3$



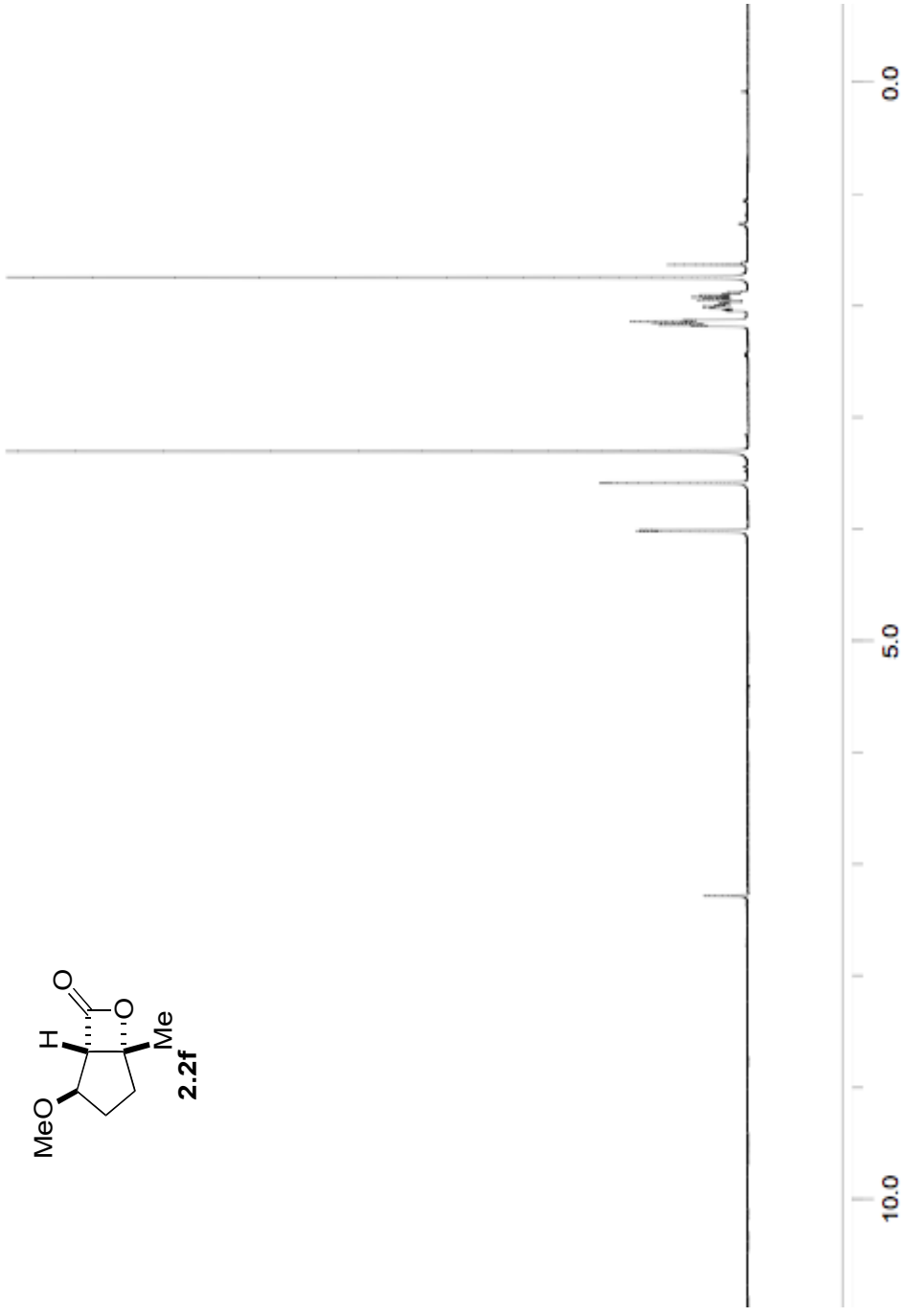
^{13}C NMR (125 MHz) spectra of substrate **2.S1** in $CDCl_3$



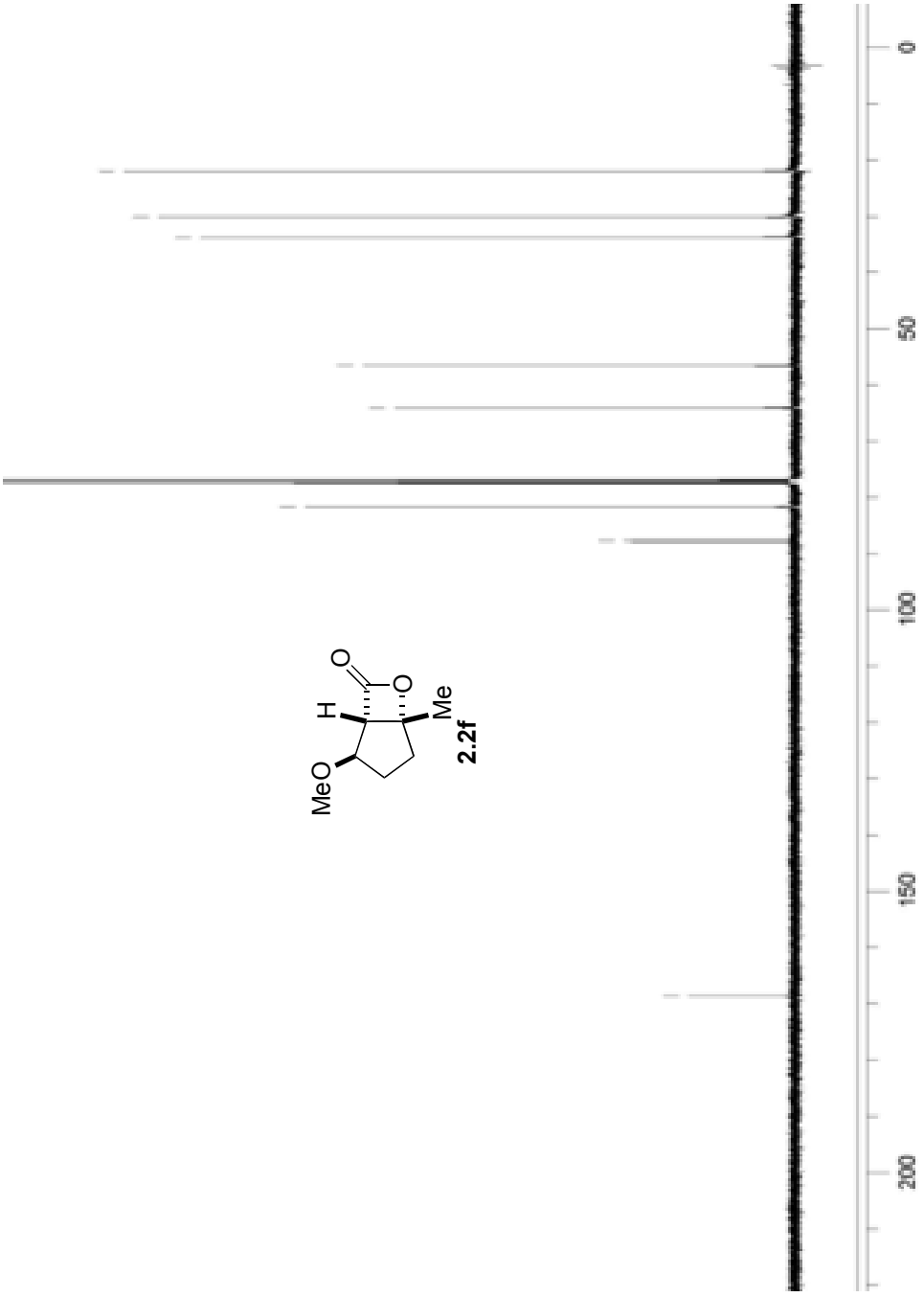
^{1}H (500 MHz) spectra of β-lactone **2.2a** in $CDCl_3$



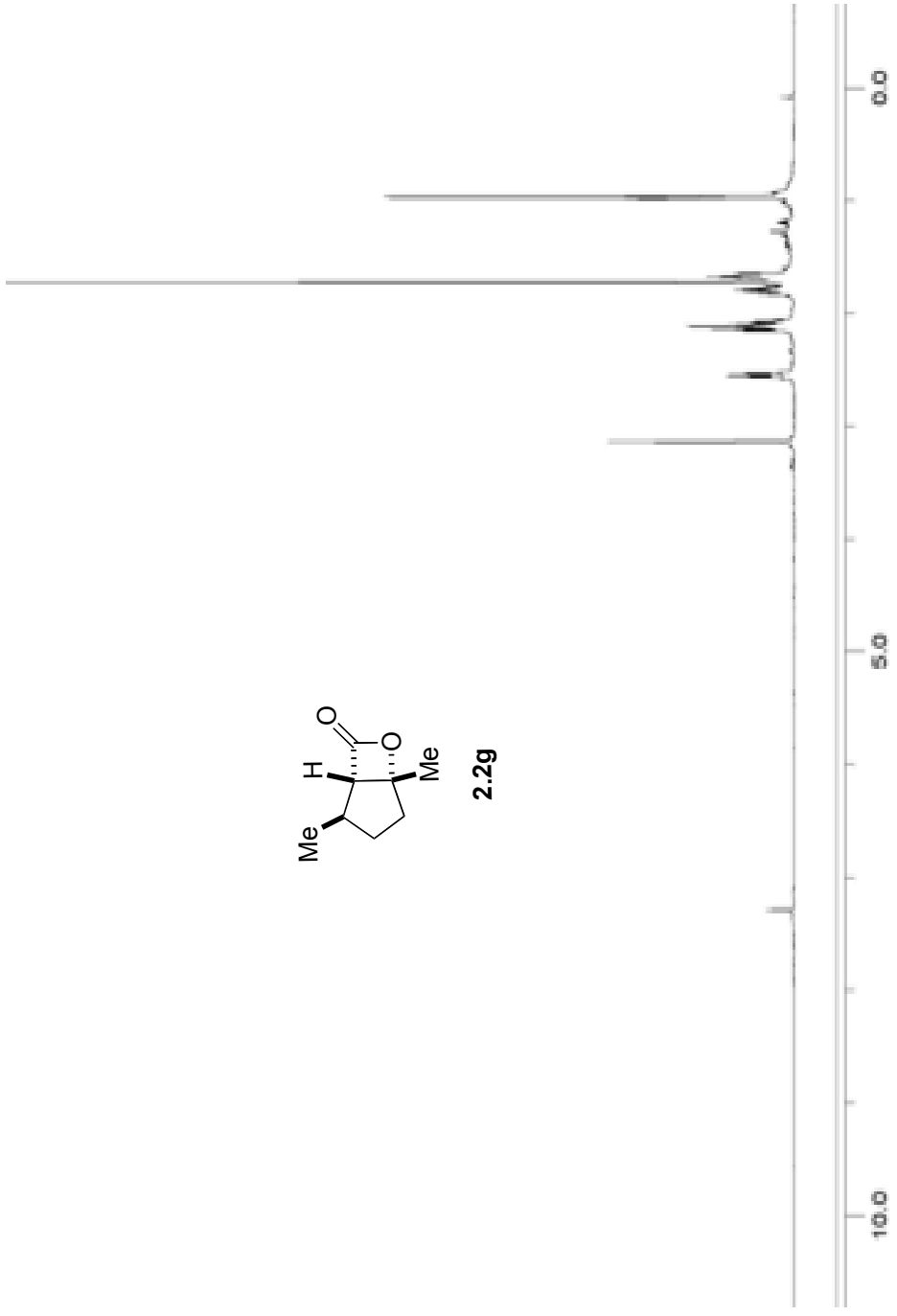
^{13}C NMR (125 MHz) spectra of β-lactone **2.2a** in $CDCl_3$



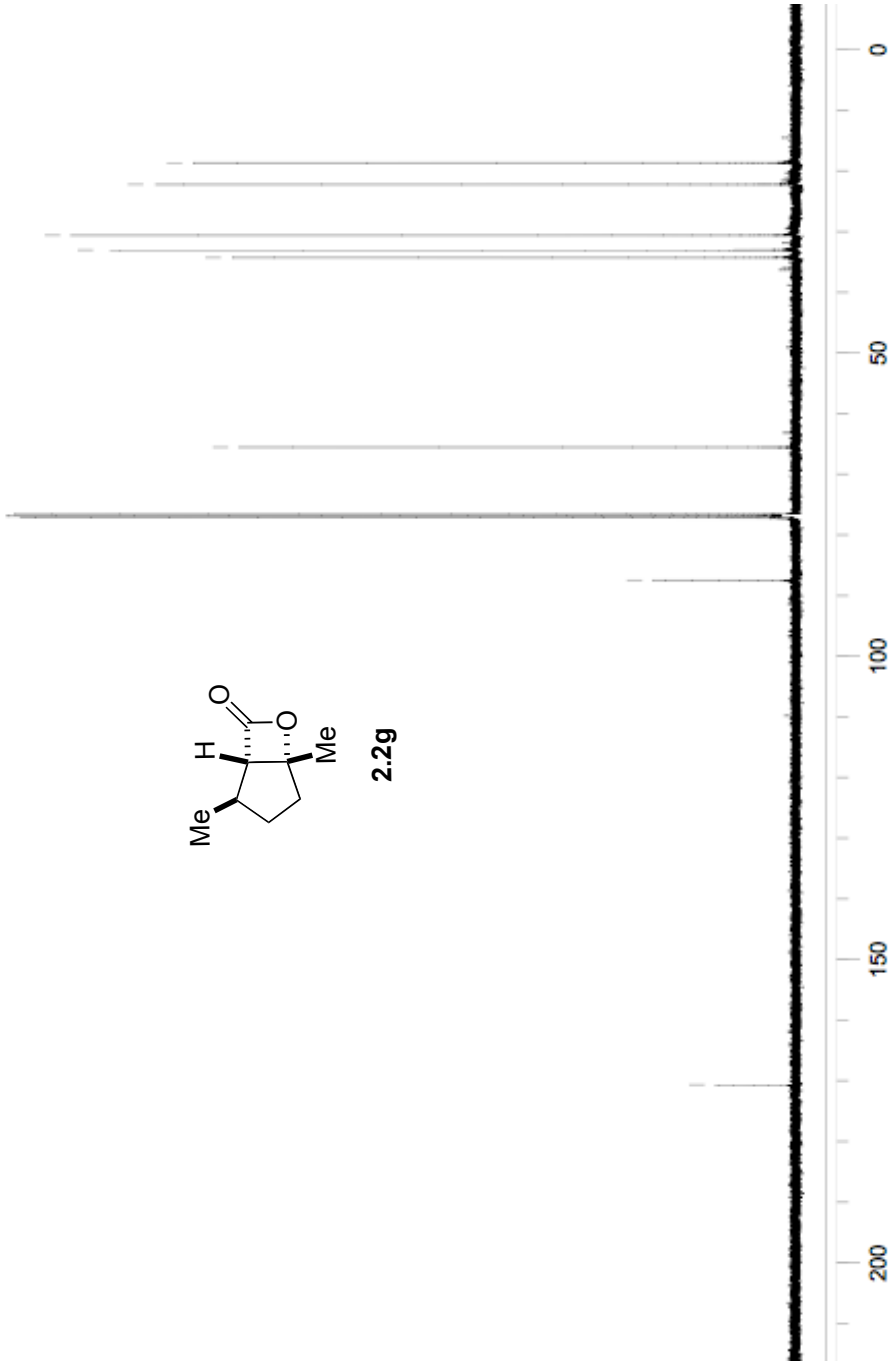
^{1}H (500 MHz) spectra of β-lactone **2.2f** in $CDCl_3$



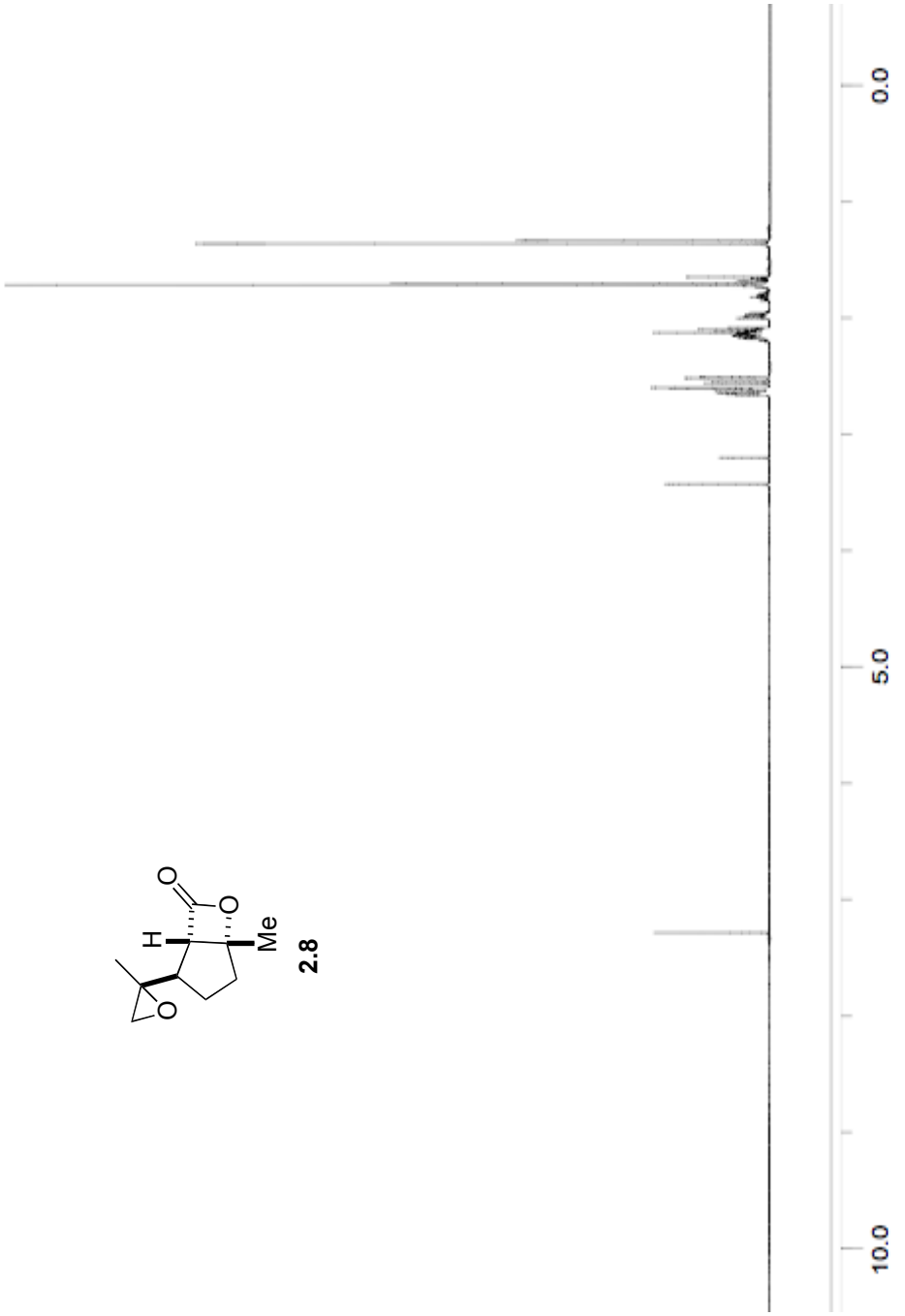
^{13}C NMR (125 MHz) spectra of β-lactone **2.2f** in $CDCl_3$



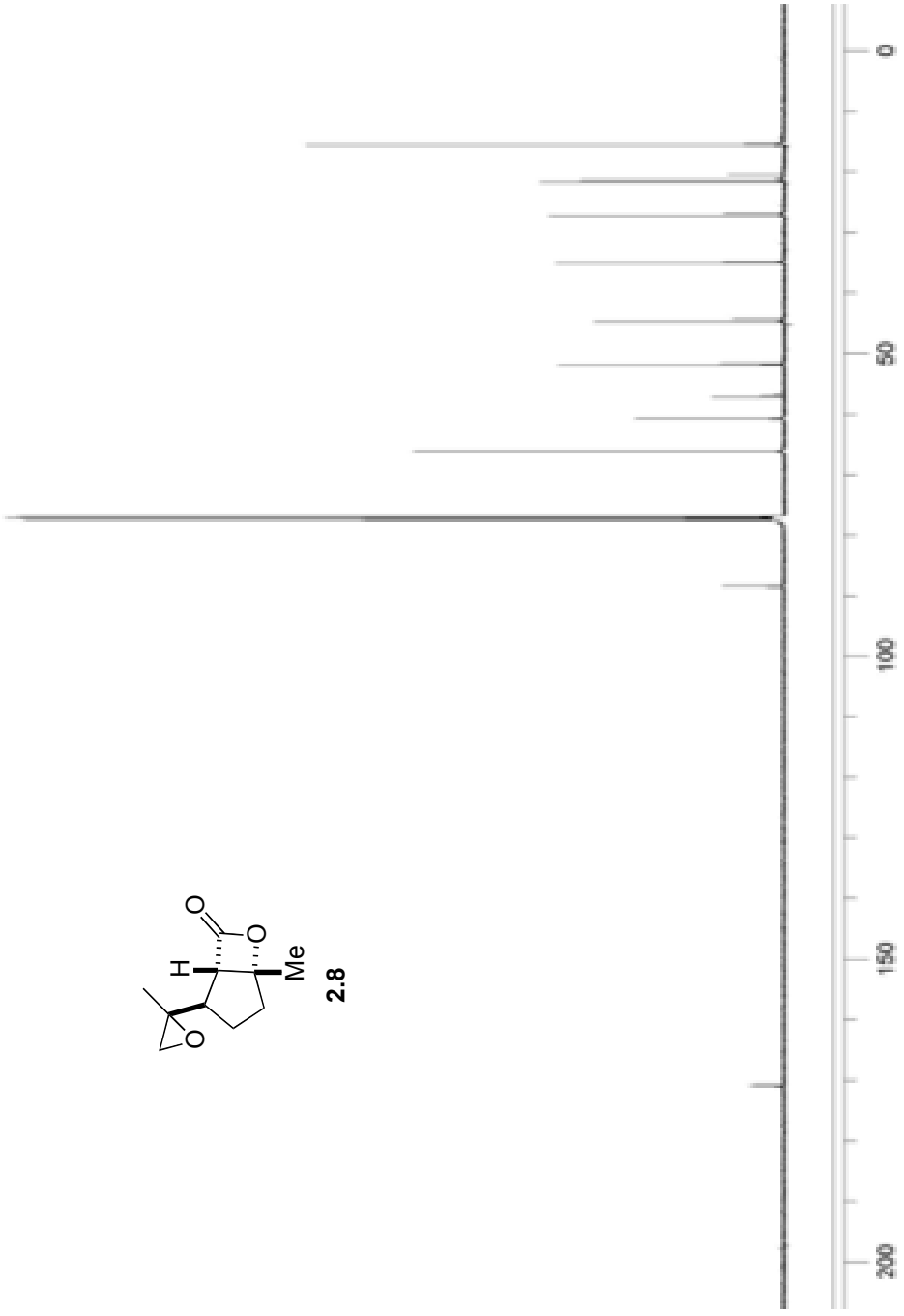
^{1}H (500 MHz) spectra of β-lactone **2.2g** in $CDCl_3$



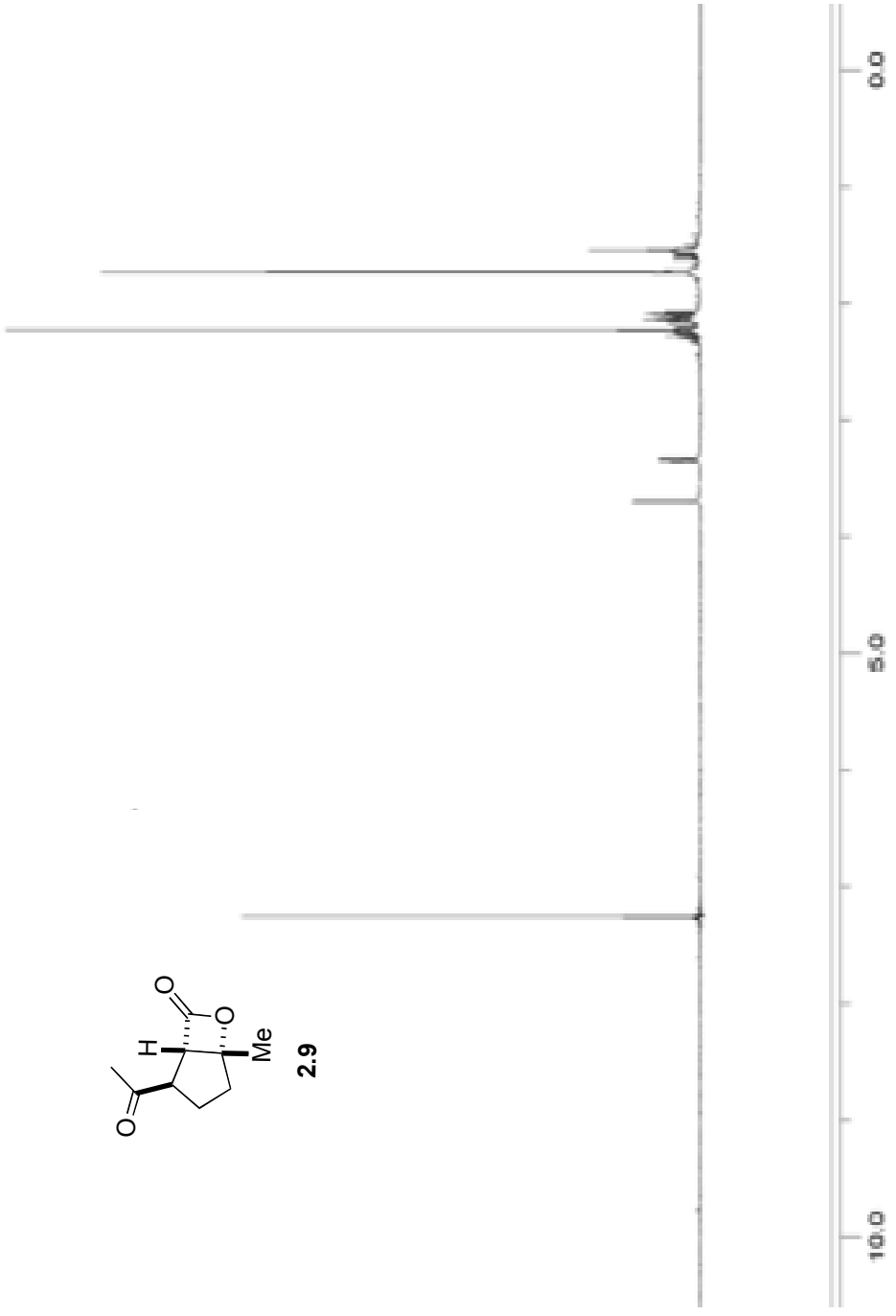
^{13}C NMR (125 MHz) spectra of β-lactone **2.2g** in $CDCl_3$



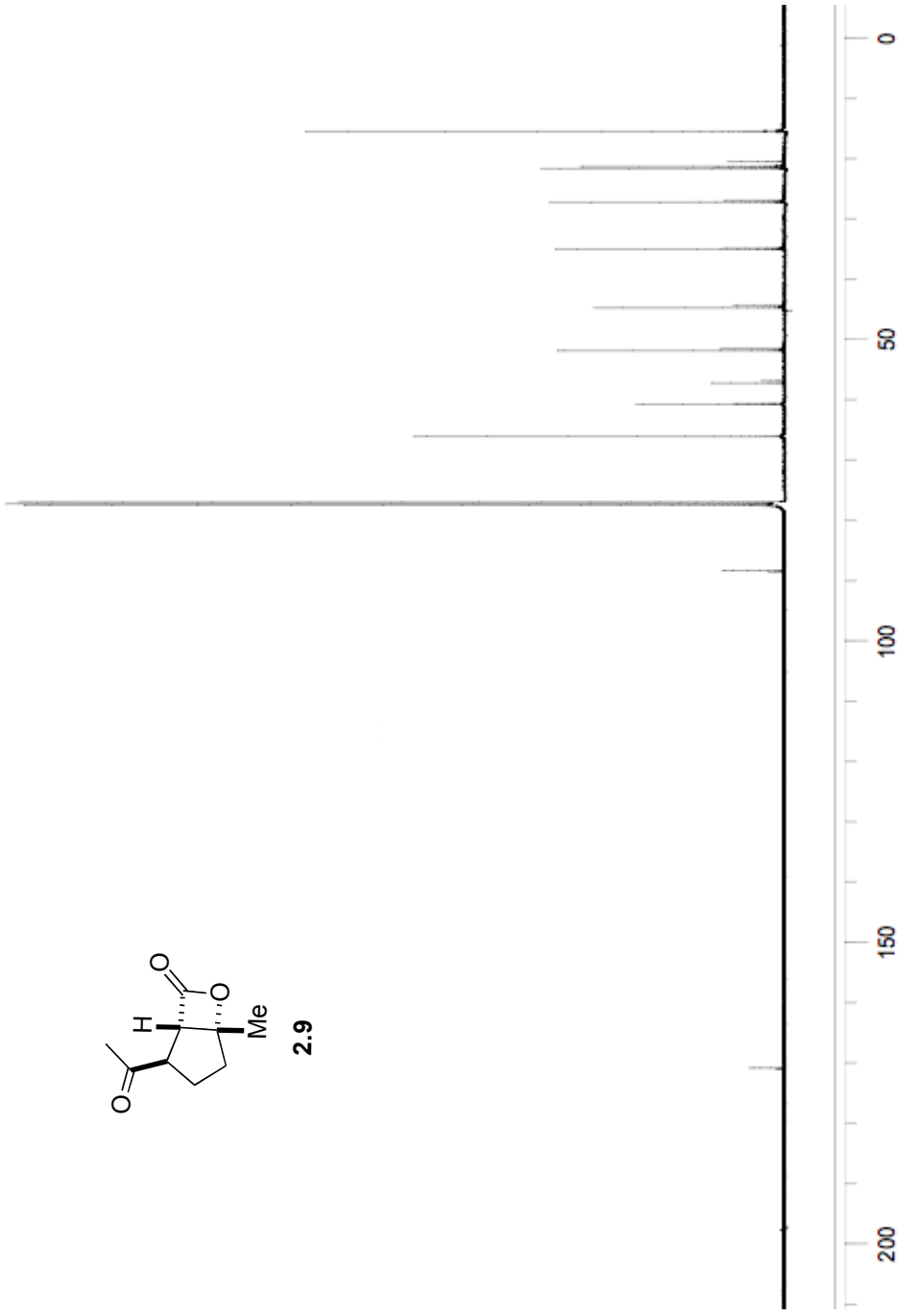
^{1}H (500 MHz) spectra of diastereomers of β-lactone **2.8** in $CDCl_3$



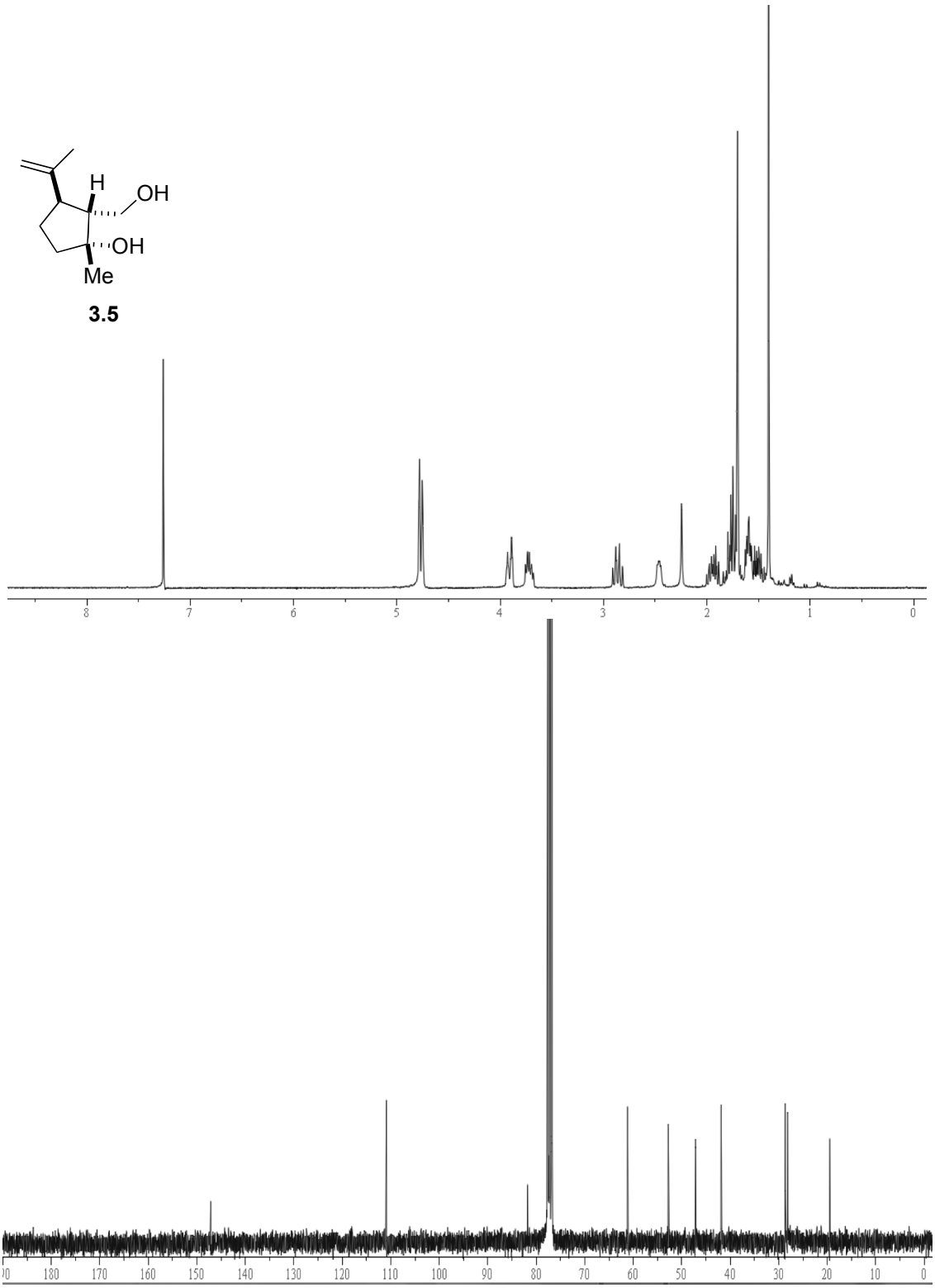
^{13}C NMR (125 MHz) spectra of diastereomers of β-lactone **2.8** in $CDCl_3$



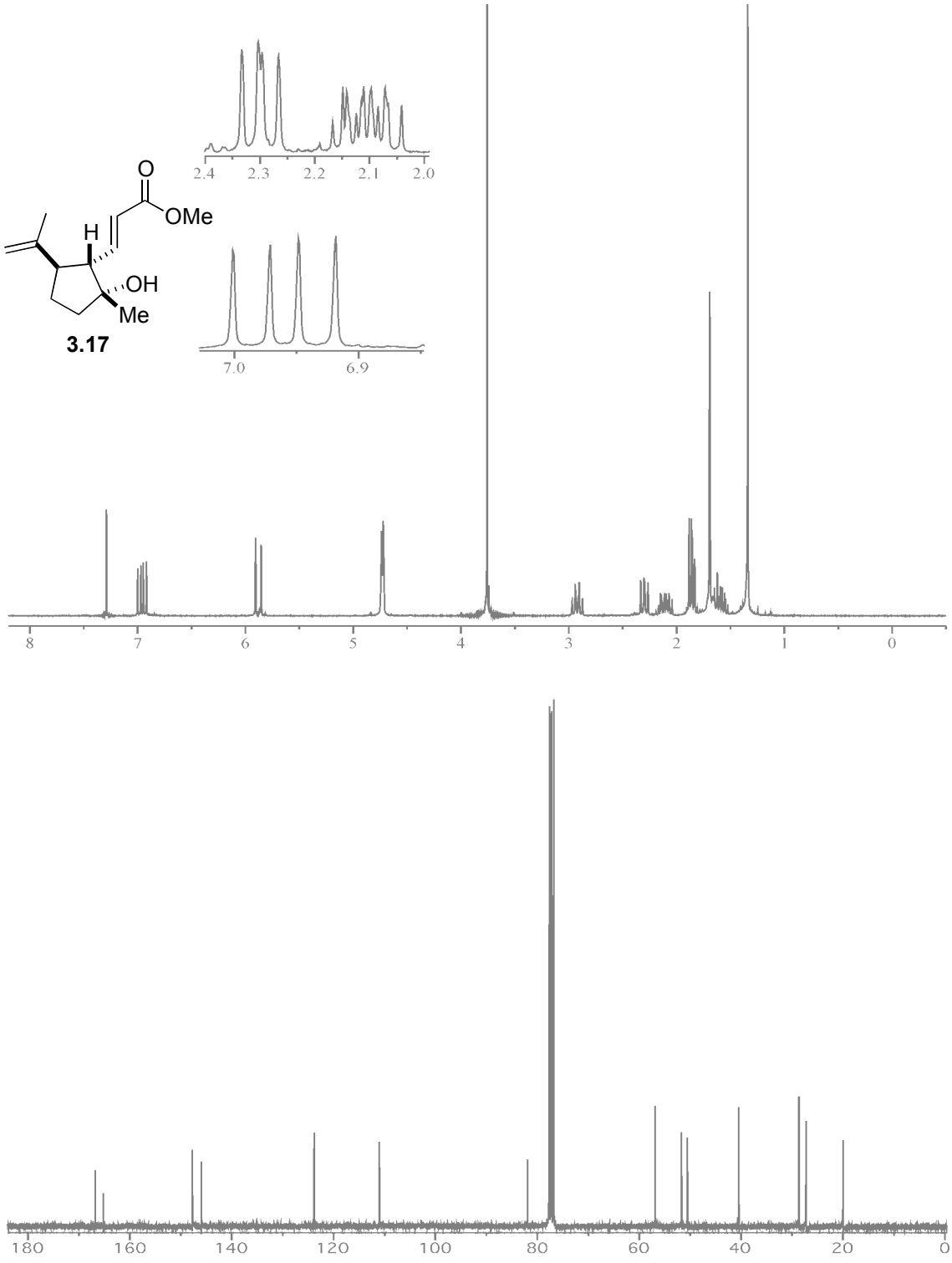
^{1}H (500 MHz) spectra of β-lactone **2.9** in $CDCl_3$



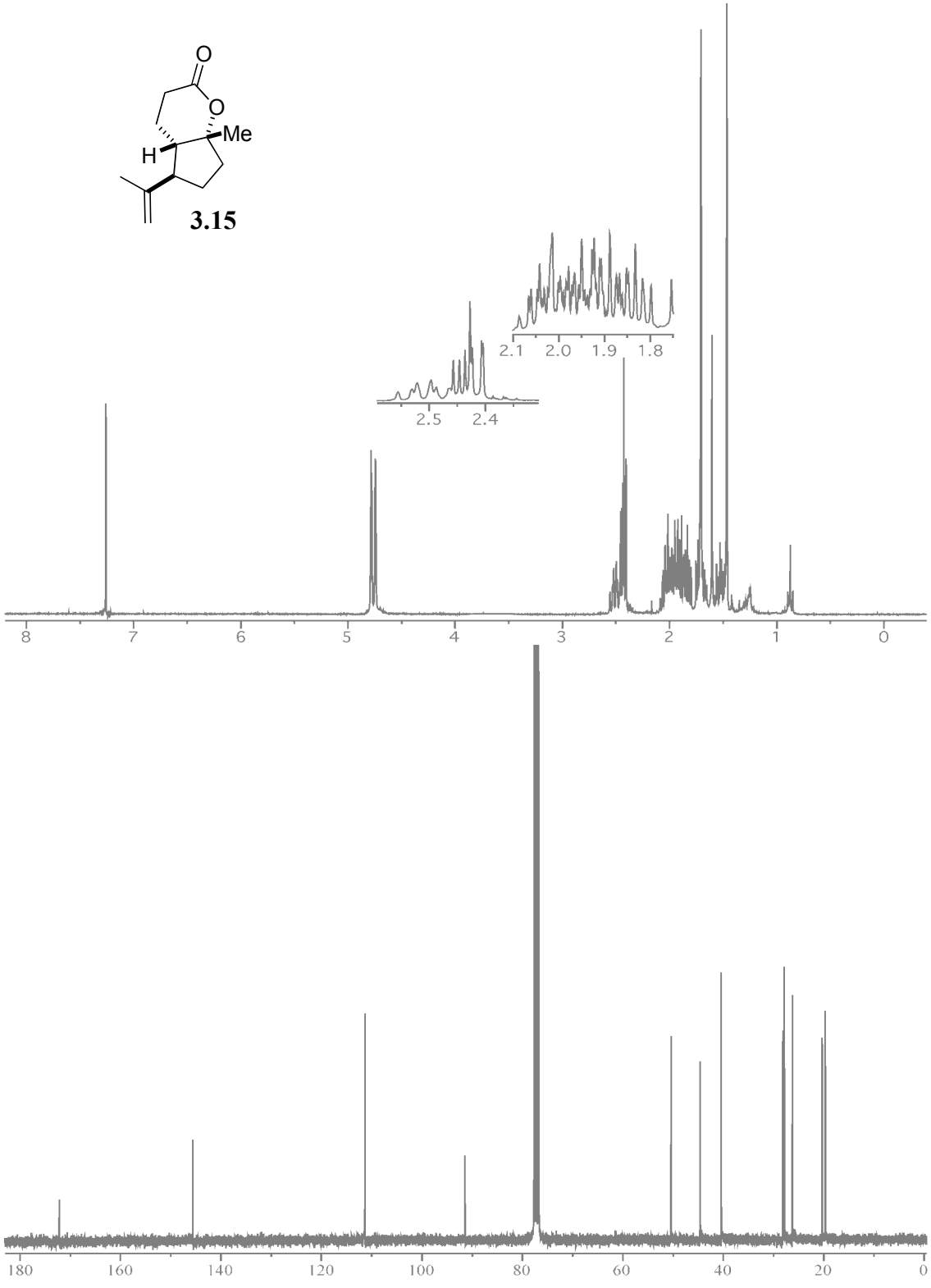
^{13}C NMR (125 MHz) spectra of β-lactone **2.9** in $CDCl_3$



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

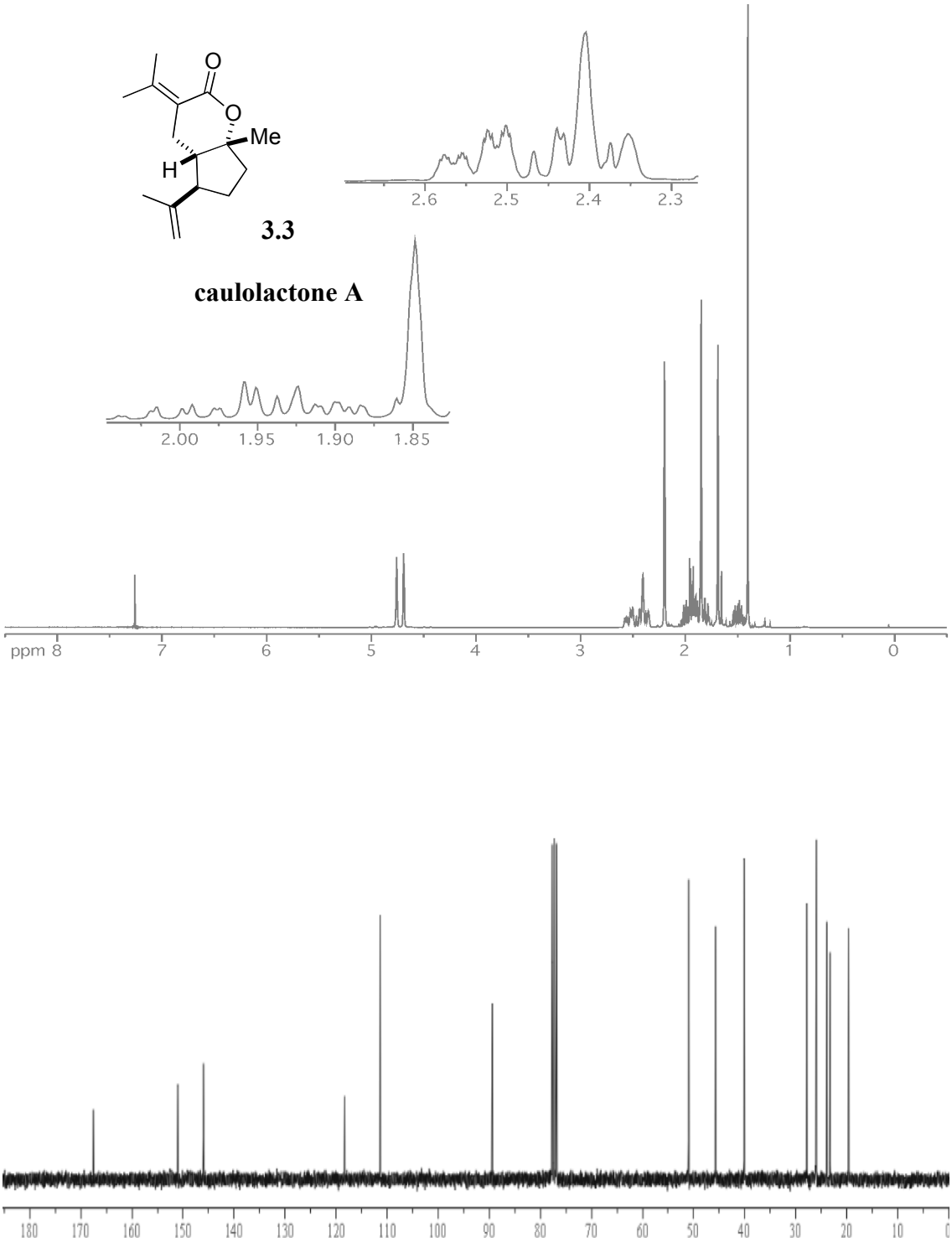


^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of substrate **3.17** in $CDCl_3$

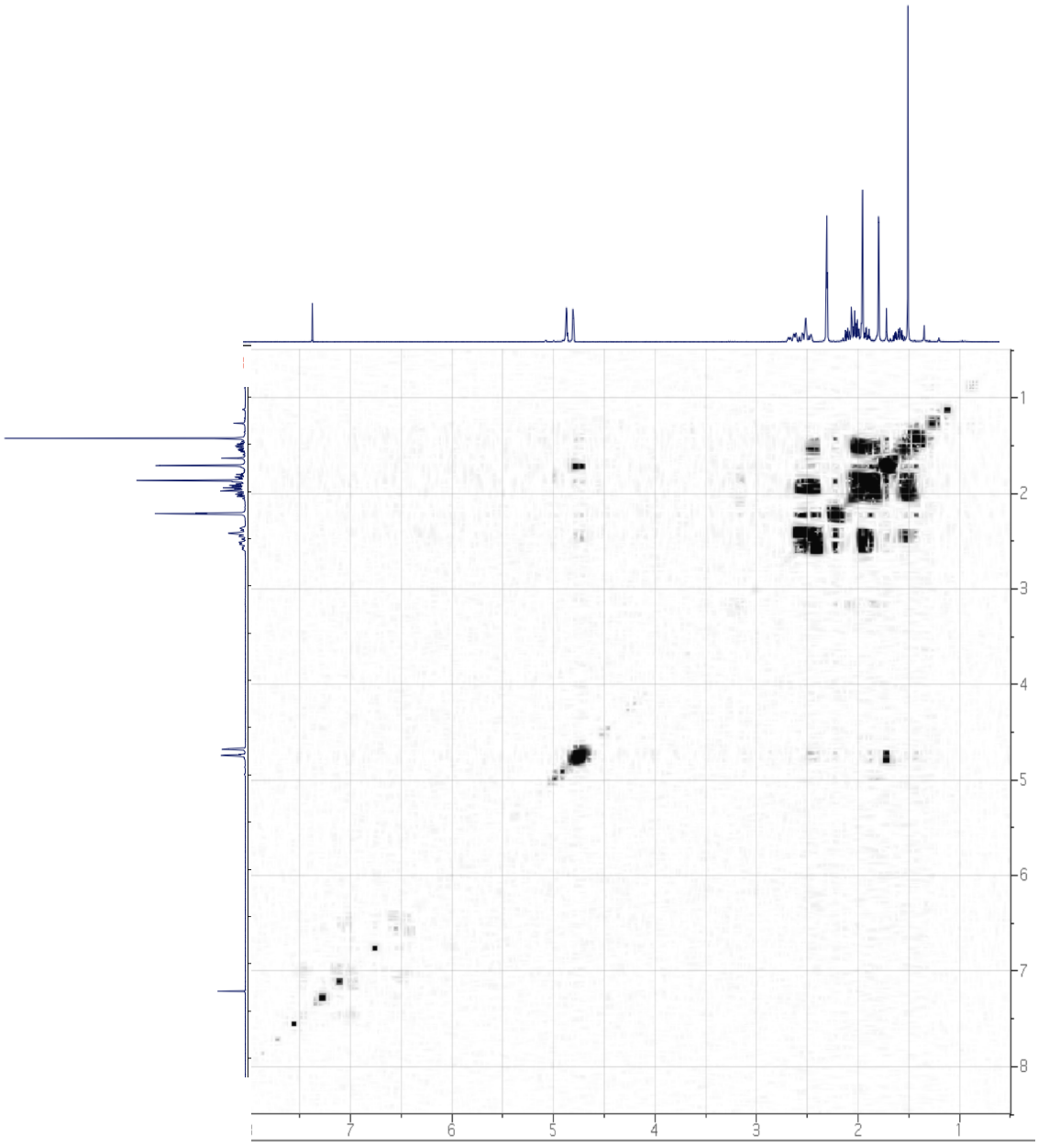


3.15

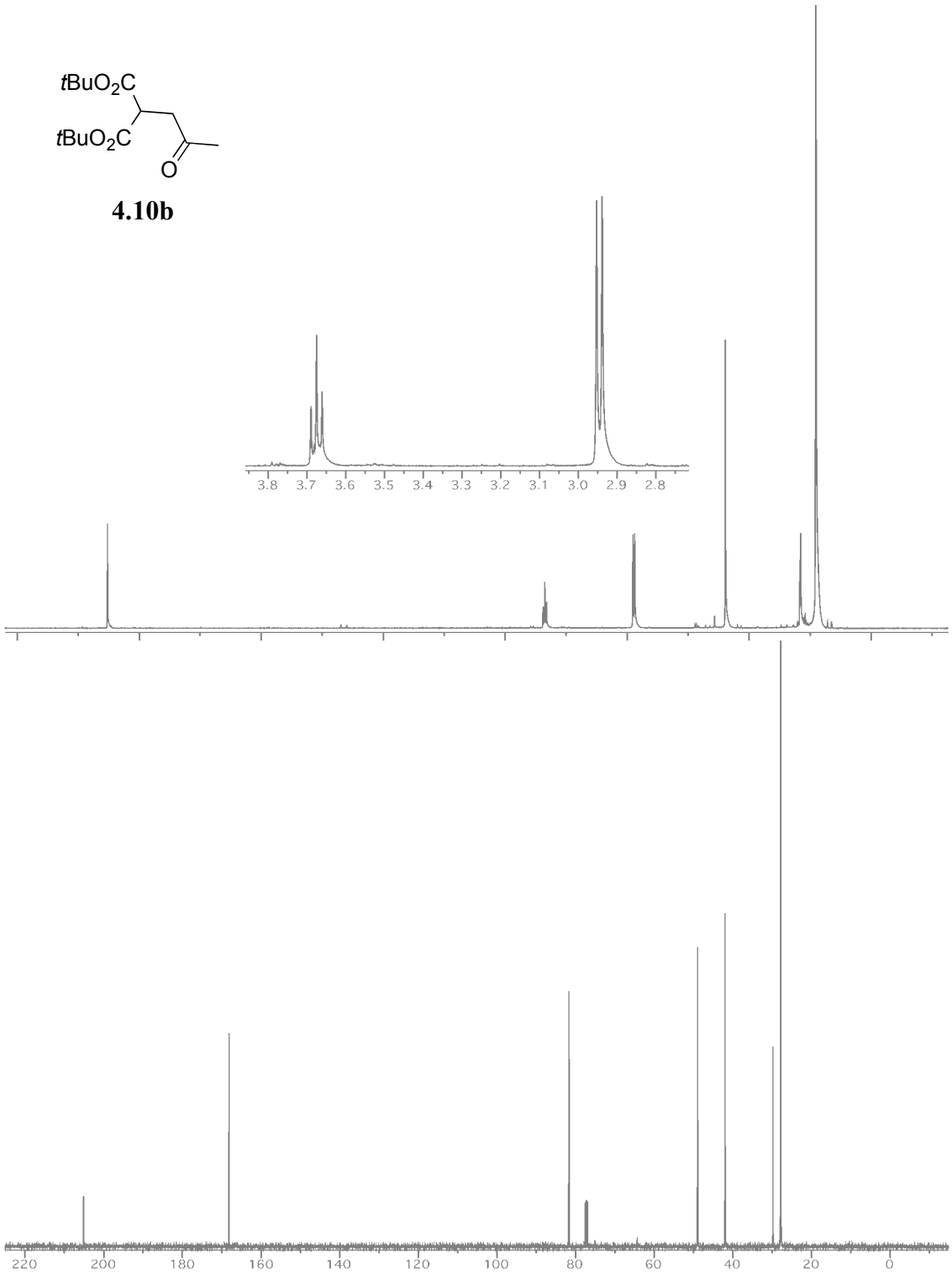
^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of substrate **3.15** in $CDCl_3$



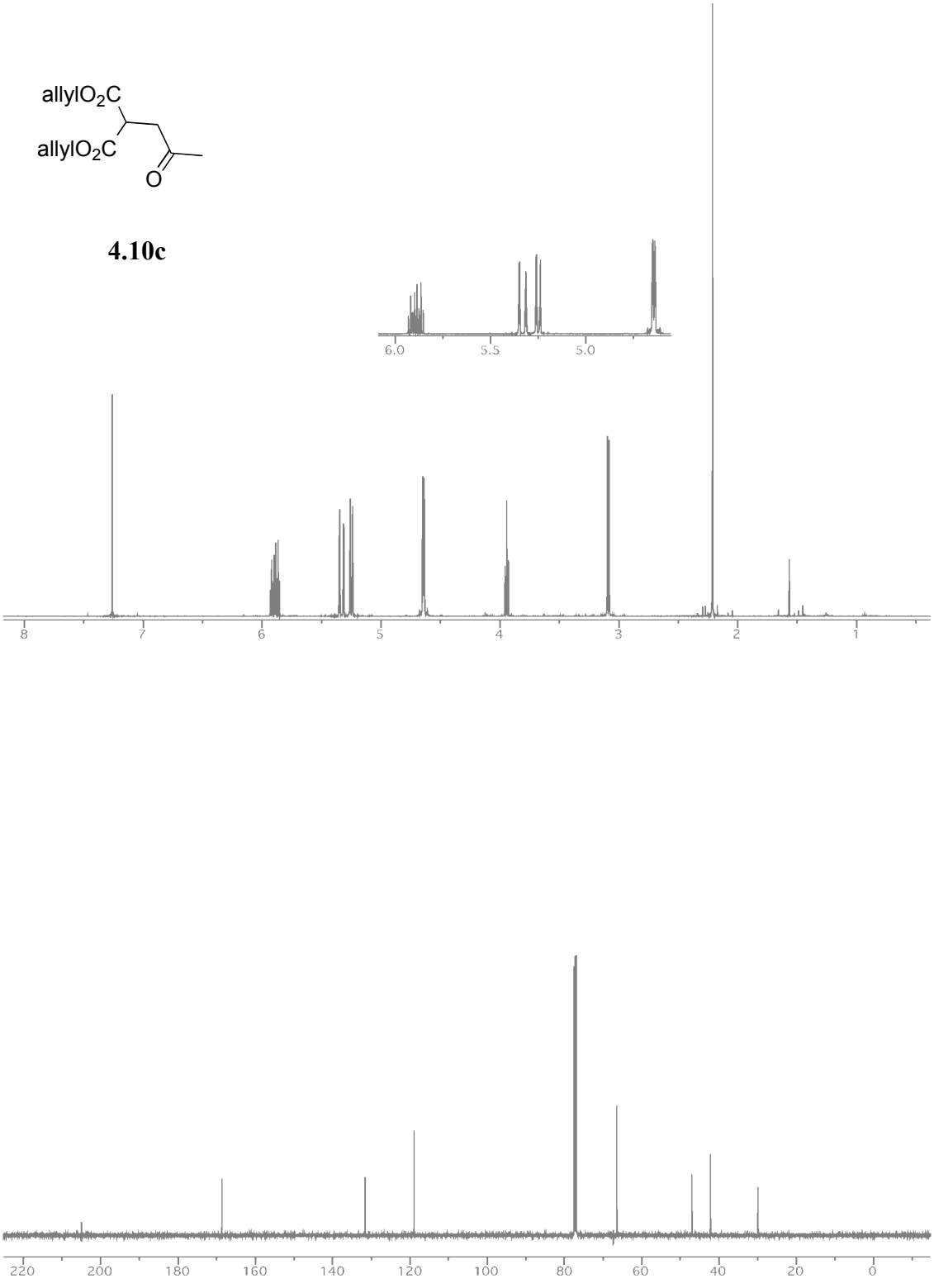
^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of substrate **3.3** in $CDCl_3$



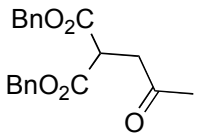
^{1}H (500 MHz) COSY of **3.3** in $CDCl_3$



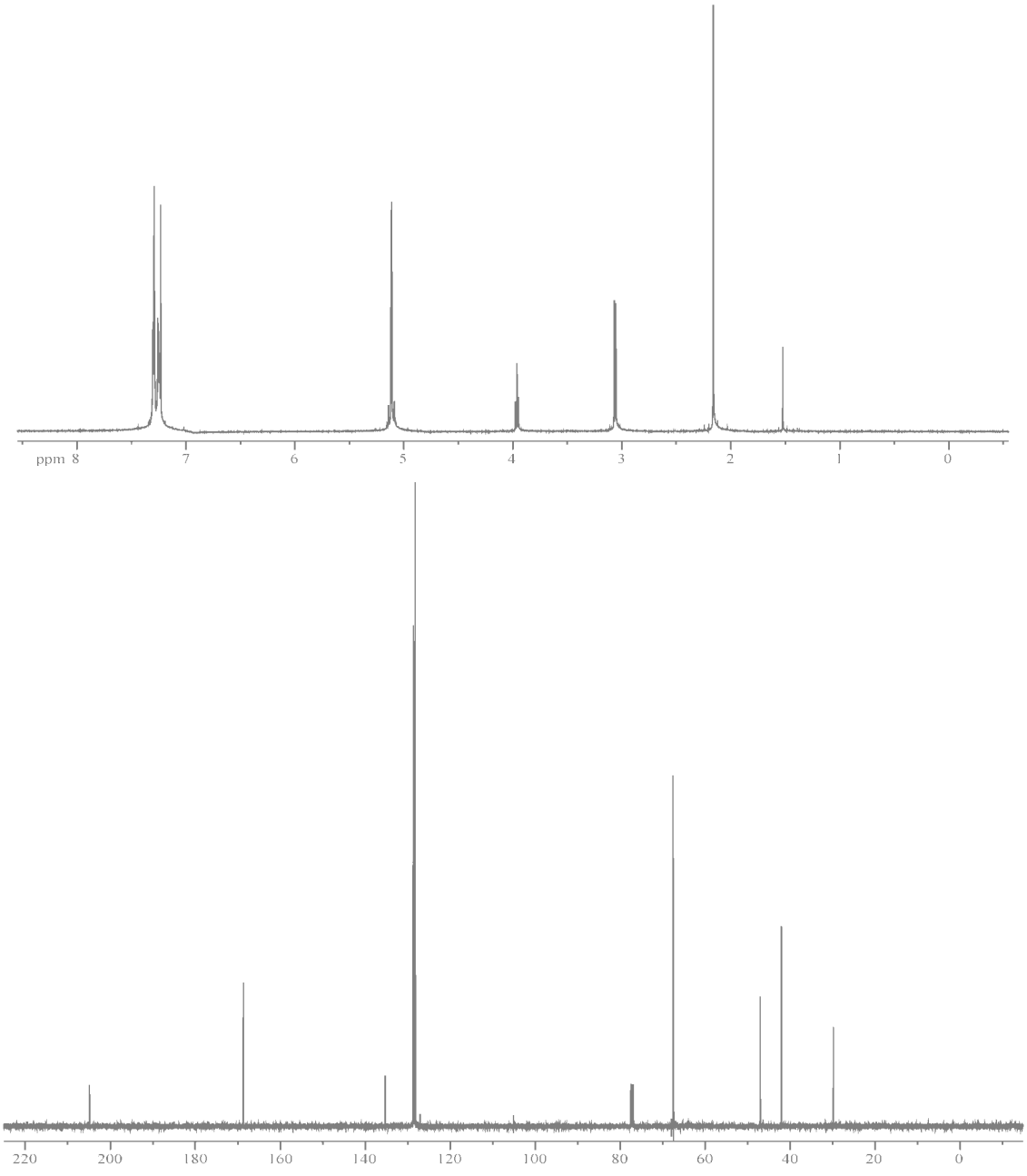
^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of substrate **4.10b** in $CDCl_3$



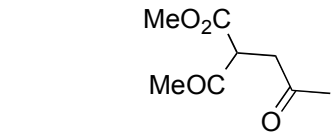
^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of substrate **4.10c** in $CDCl_3$



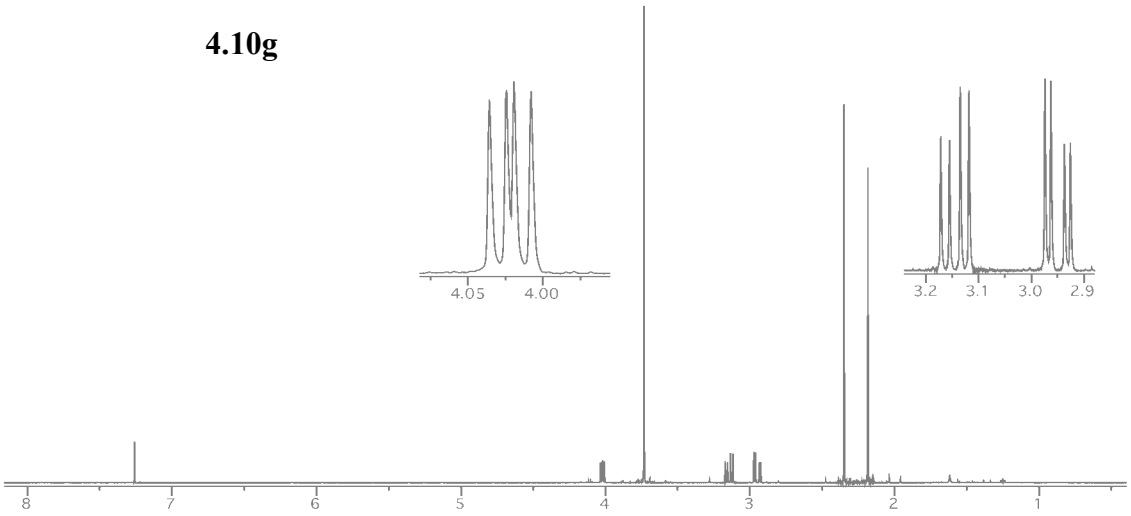
4.10d

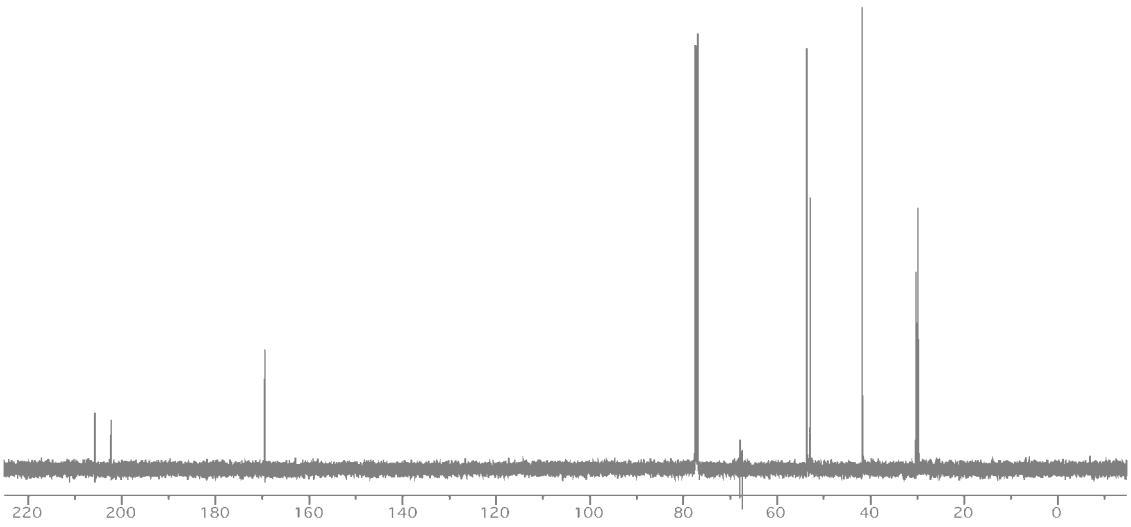


^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of substrate **4.10d** in $CDCl_3$

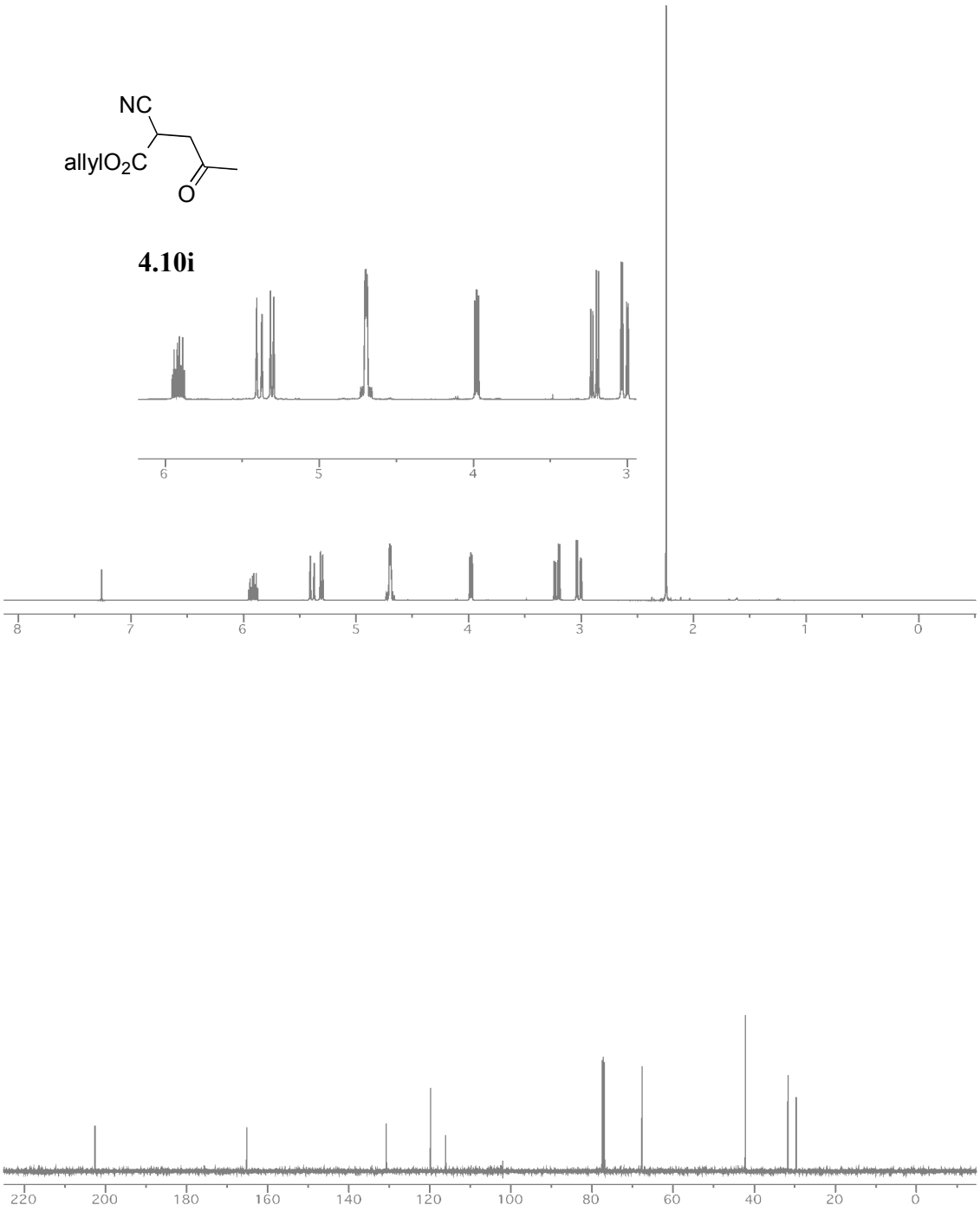


4.10g

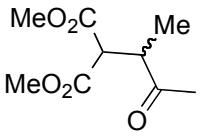




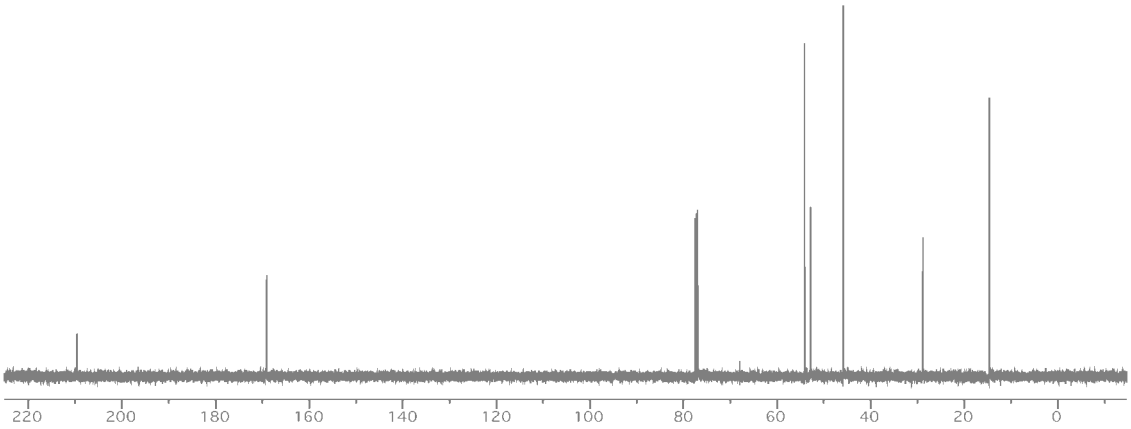
^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of substrate **4.10g** in $CDCl_3$



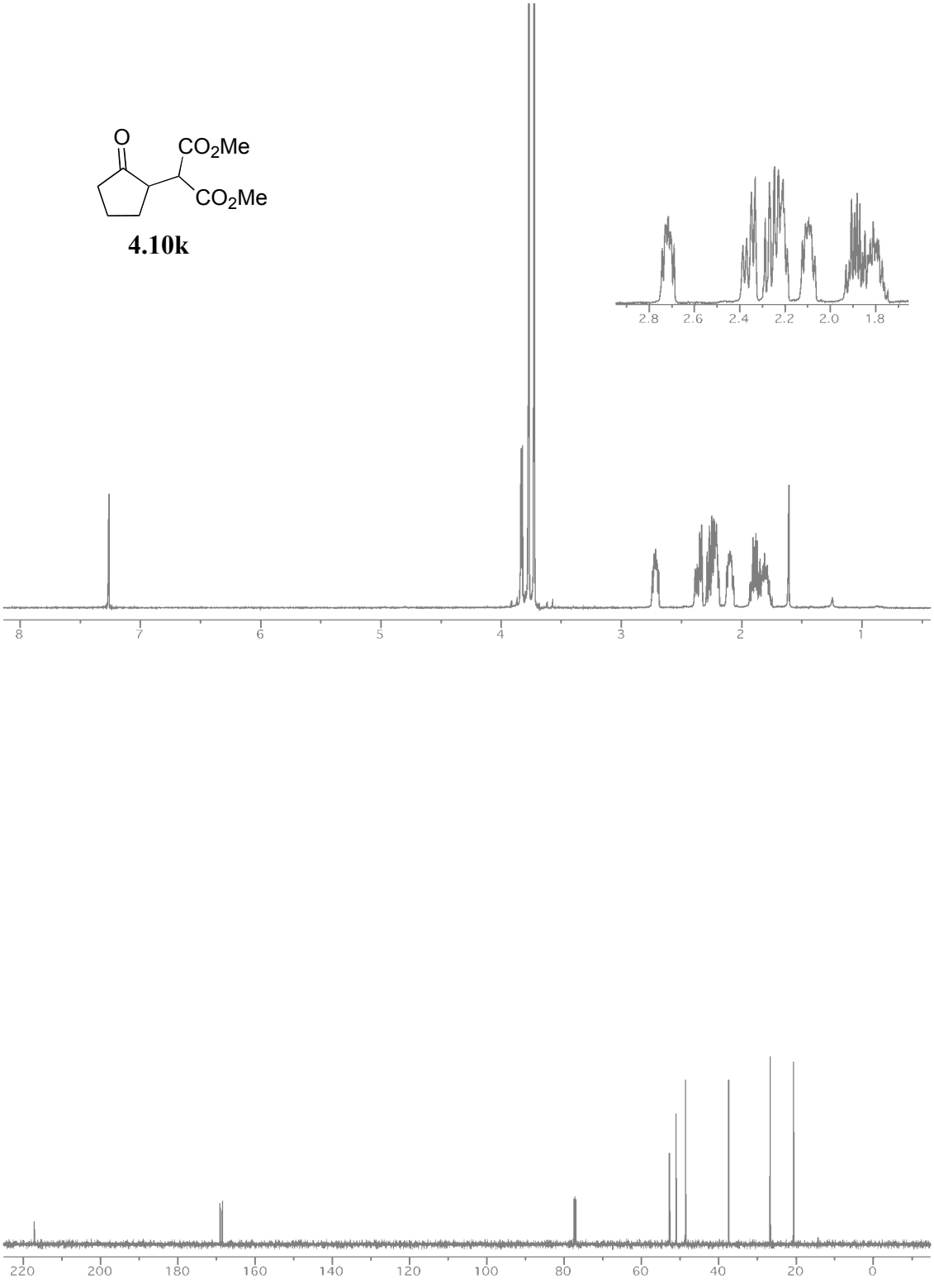
^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of substrate **4.10i** in $CDCl_3$.



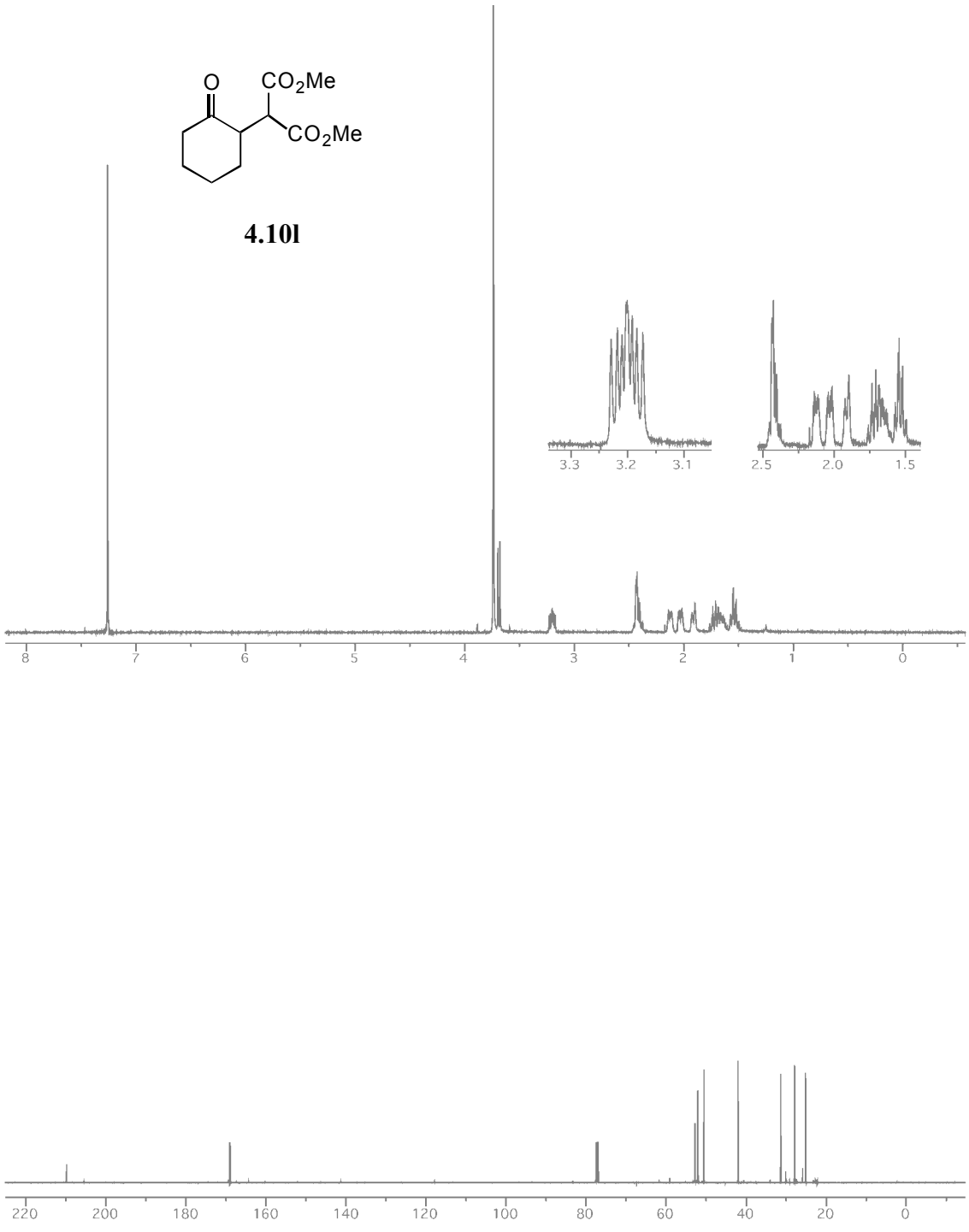
4.10j



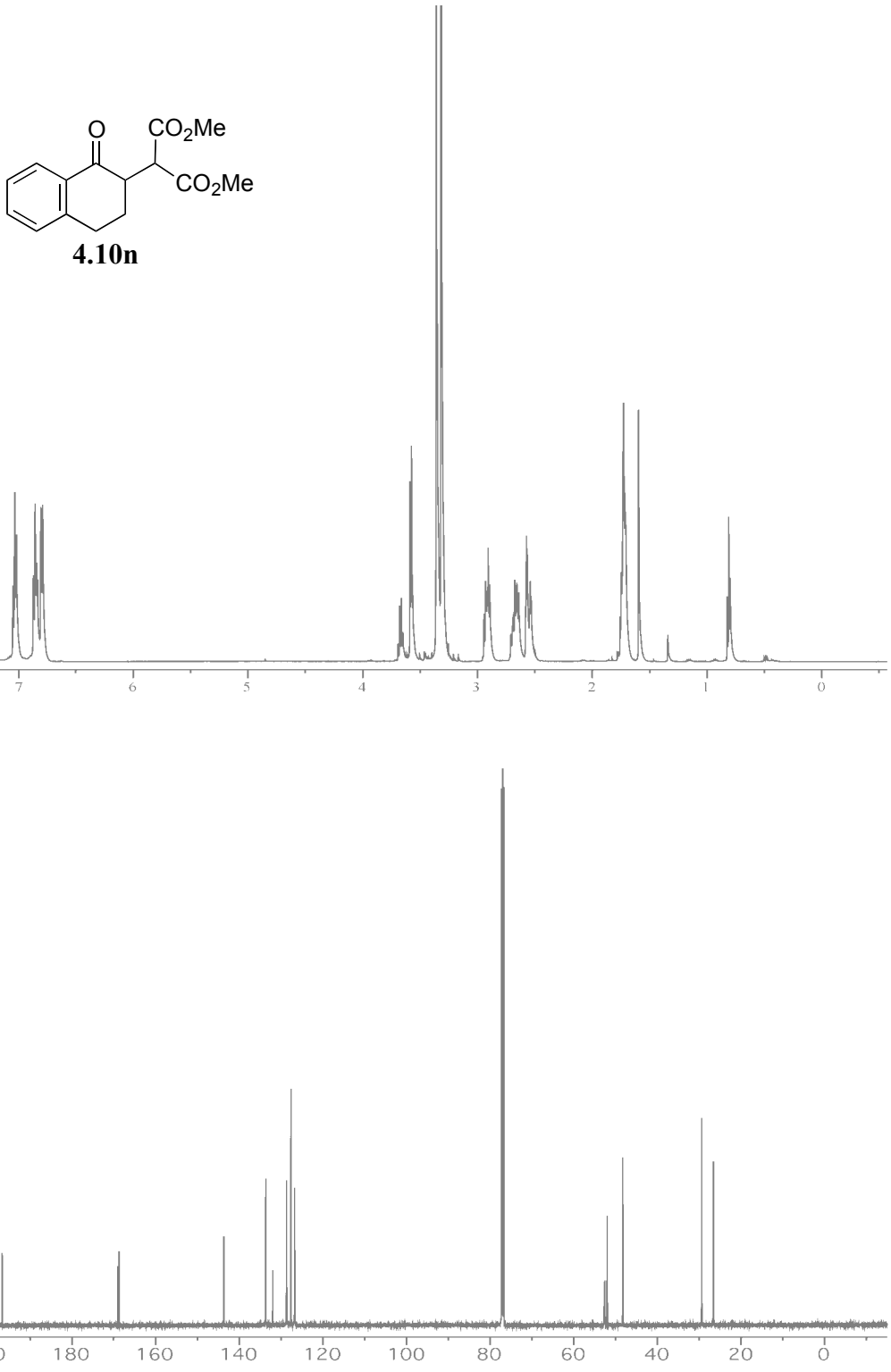
^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of substrate **4.10j** in $CDCl_3$



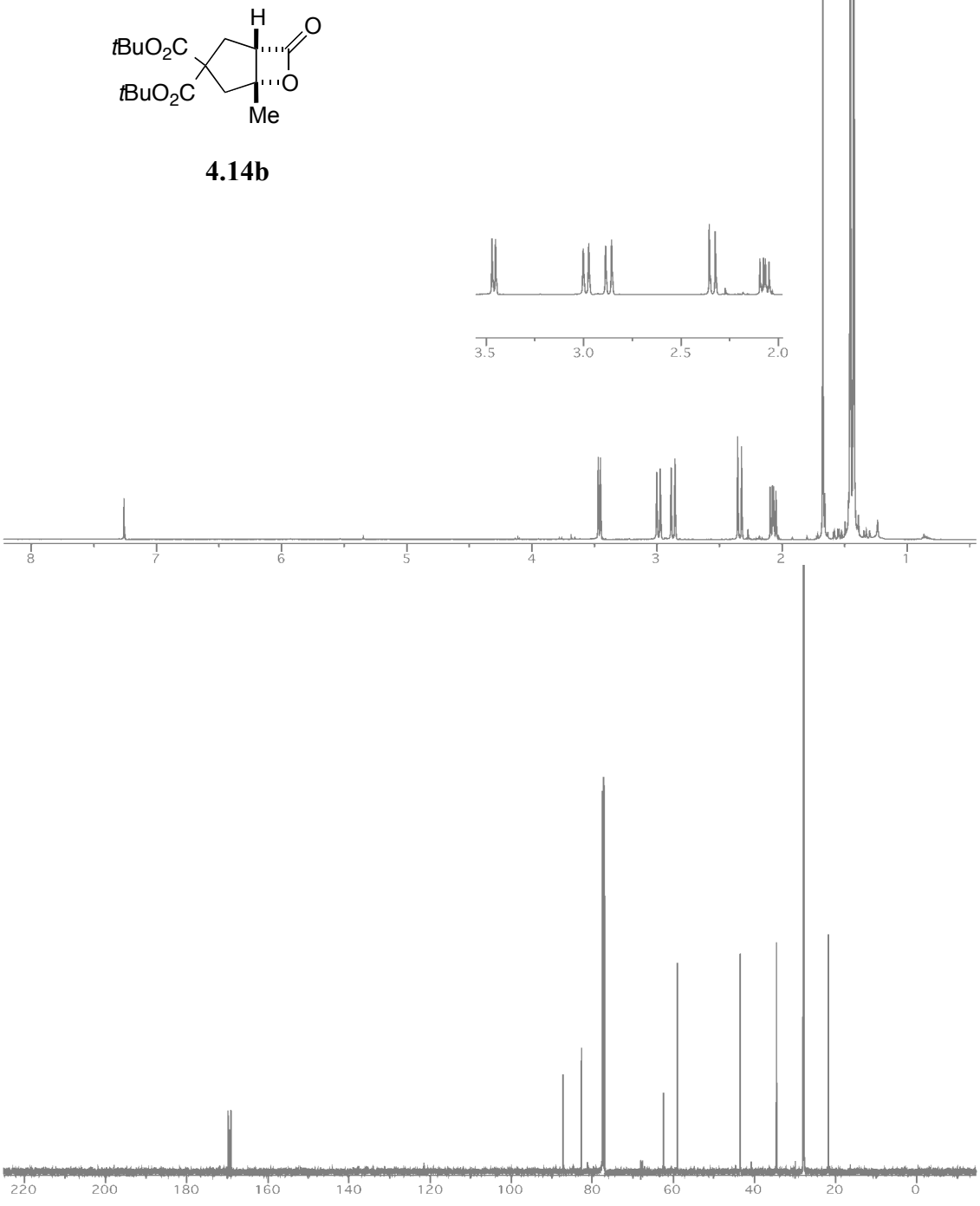
^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of substrate **4.10k** in $CDCl_3$



^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of substrate **4.10l** in $CDCl_3$

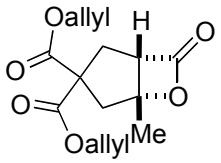


^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of substrate **4.10n** in $CDCl_3$



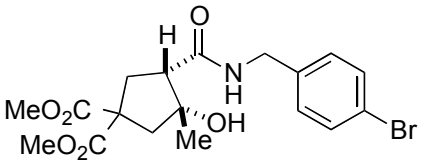
4.14b

^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of β-lactone **4.14b** in $CDCl_3$

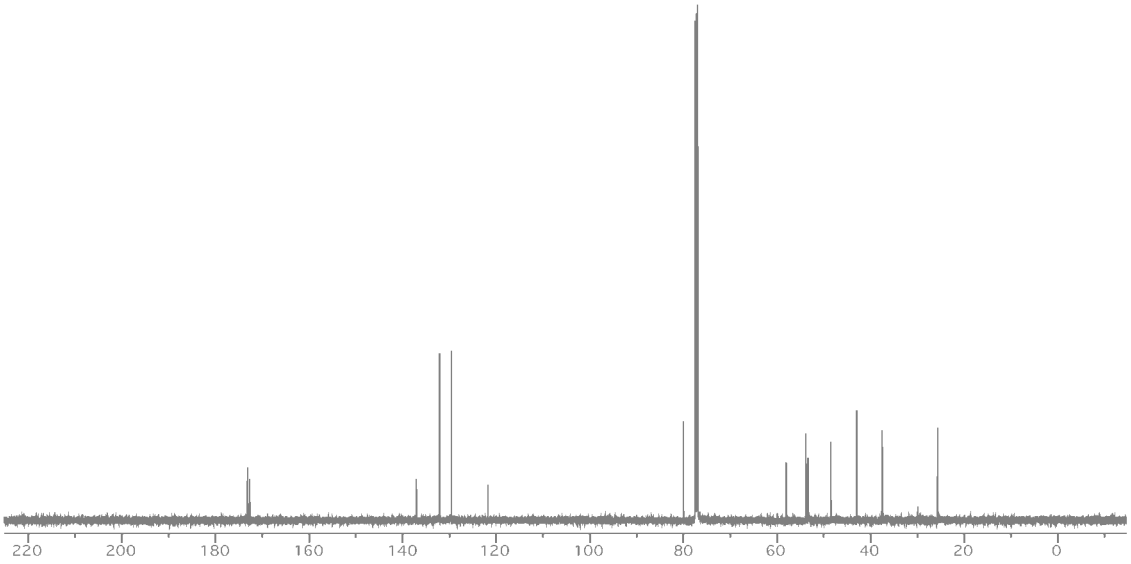


4.14c

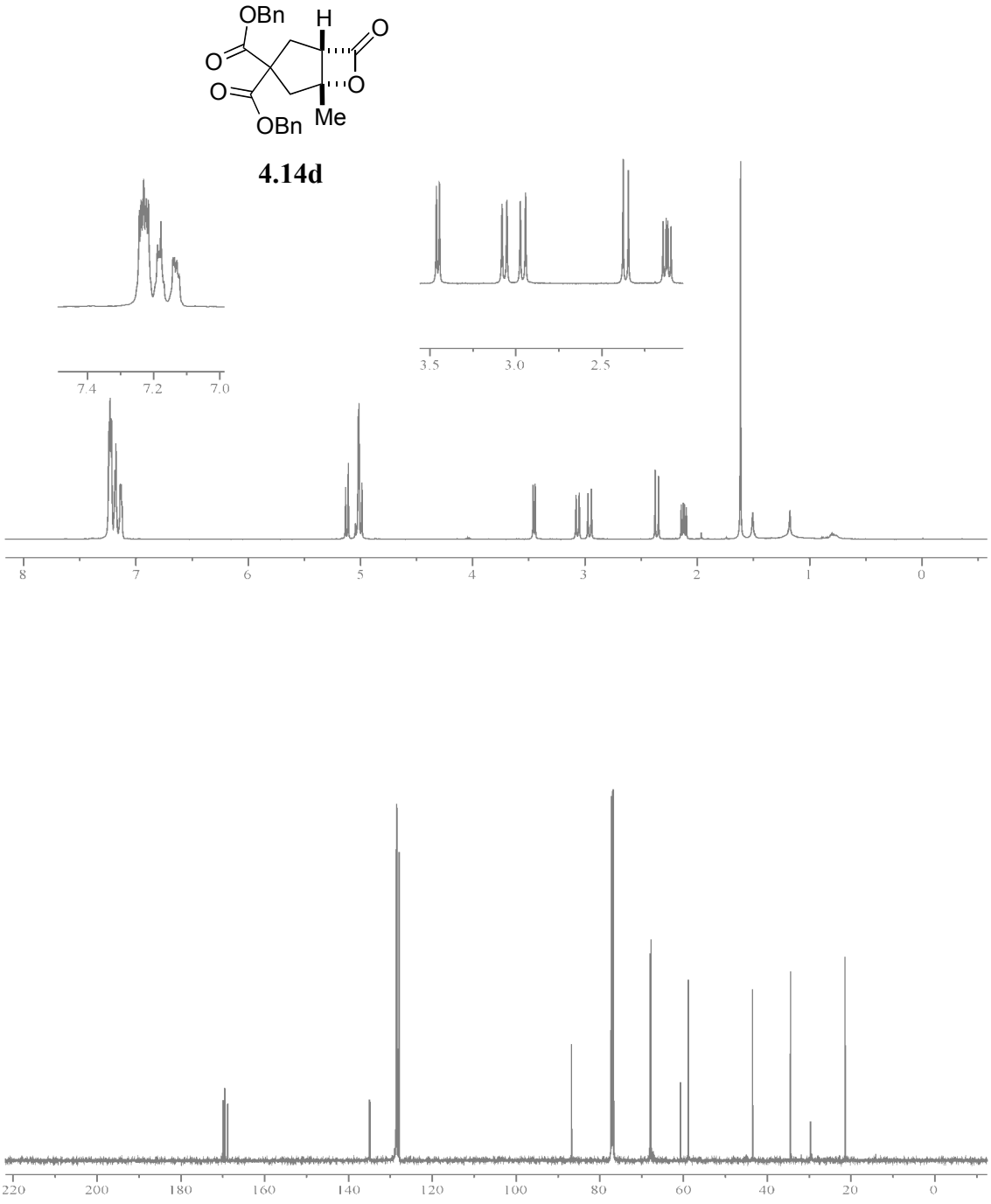
^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of β-lactone **4.14c** in $CDCl_3$



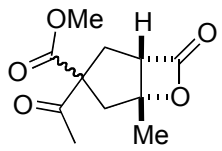
4.S15



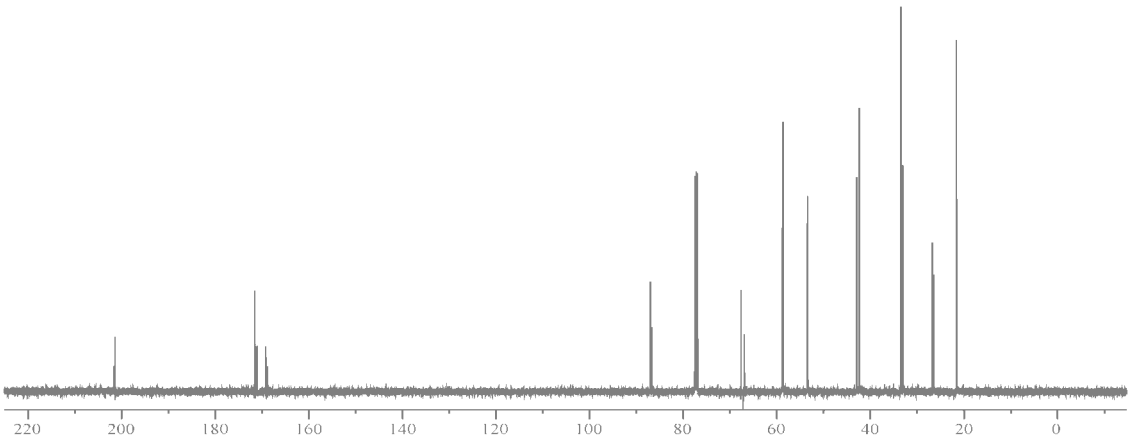
^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of amide **4.S15** in $CDCl_3$



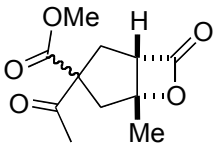
^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of β-lactone **4.14d** in $CDCl_3$



4.14g



^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of diastereomers of **4.14g** in $CDCl_3$

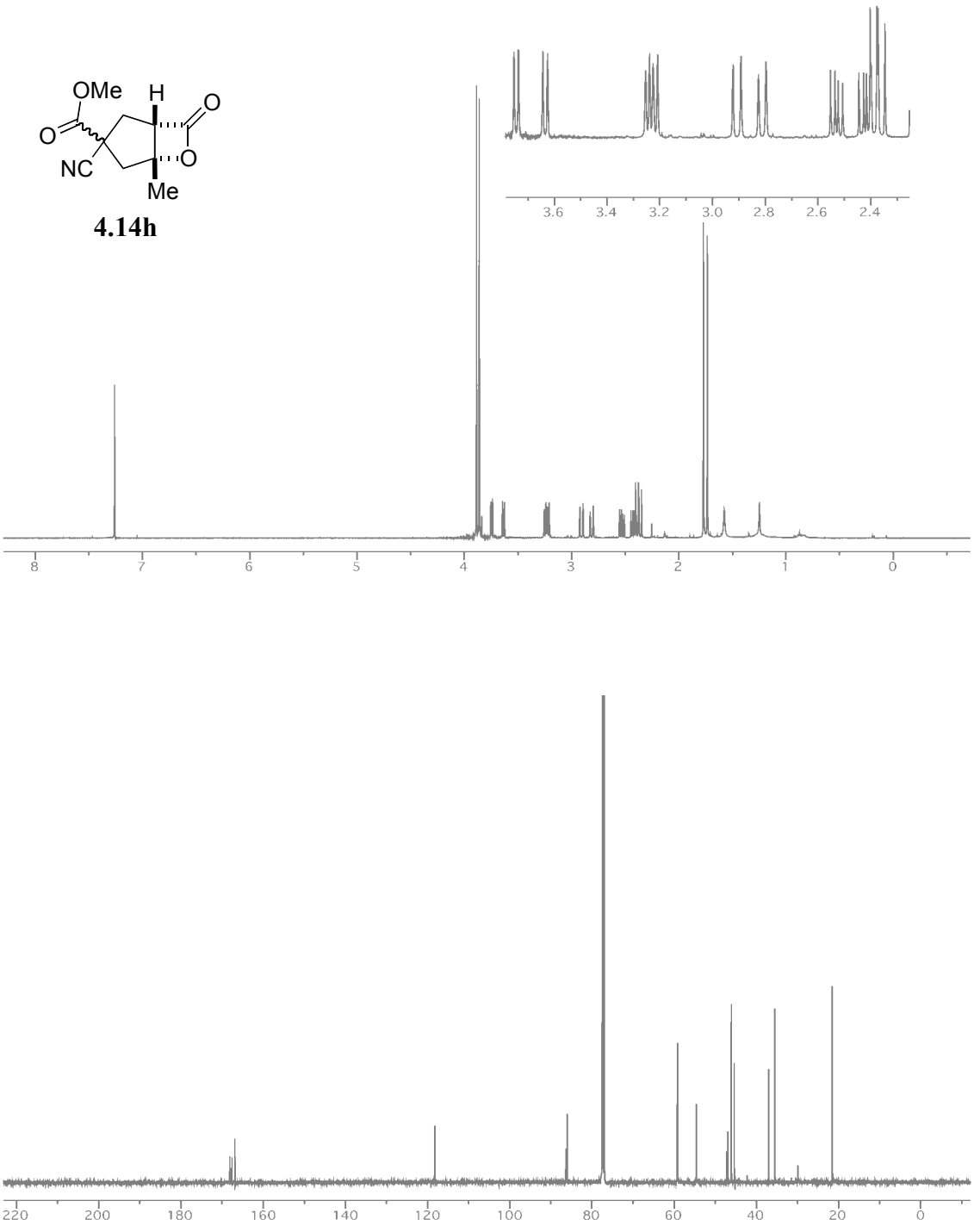


4.14g

higher R_f diastereomer

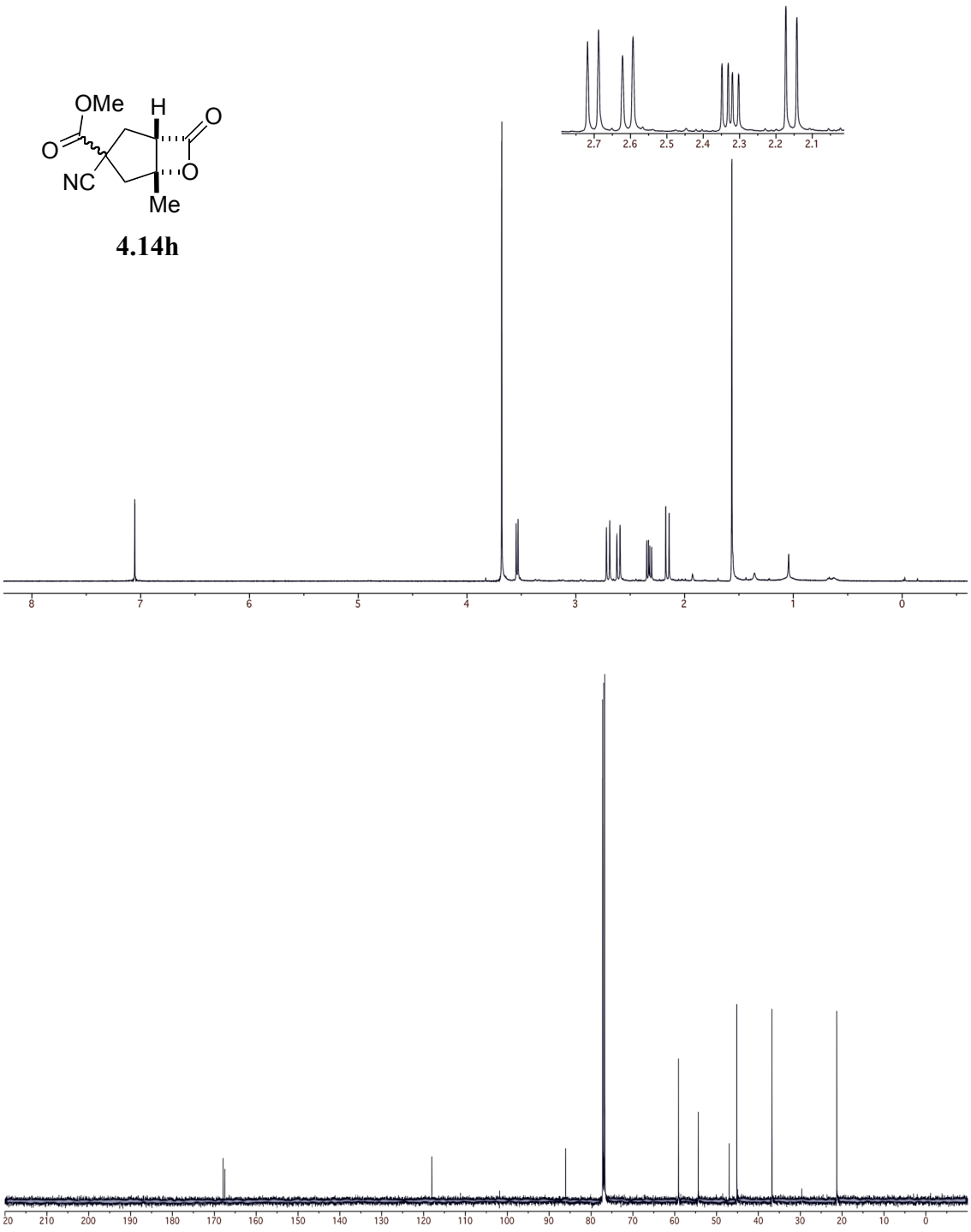
lower R_f diastereomer

^{1}H (500 MHz) spectra of each diastereomer of **4.14g** in $CDCl_3$



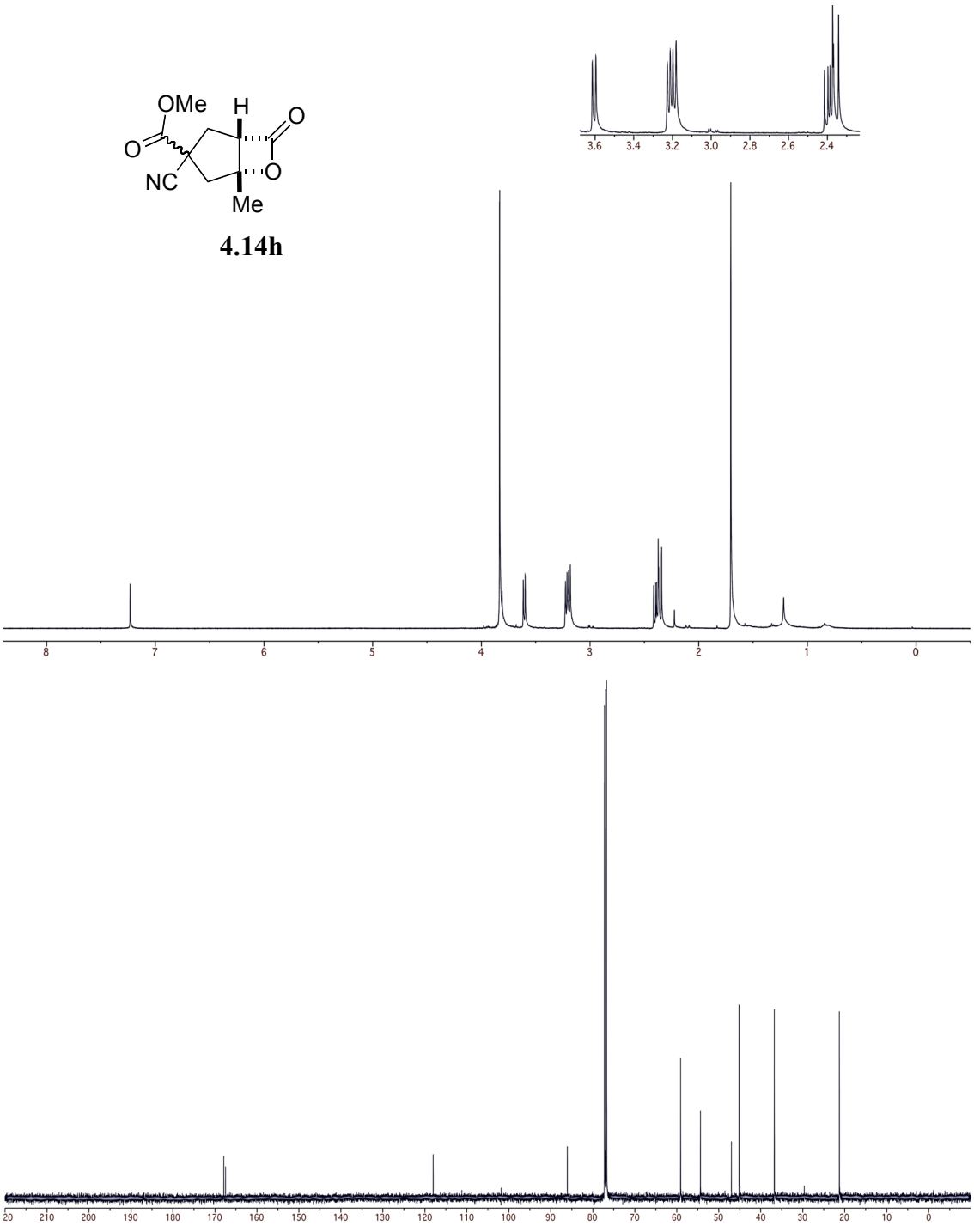
4.14h

^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of diastereomers of **4.14h** in $CDCl_3$



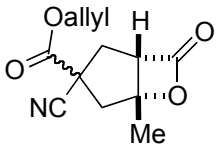
4.14h

^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of single diastereomer (higher R_f) of **4.14h** in $CDCl_3$

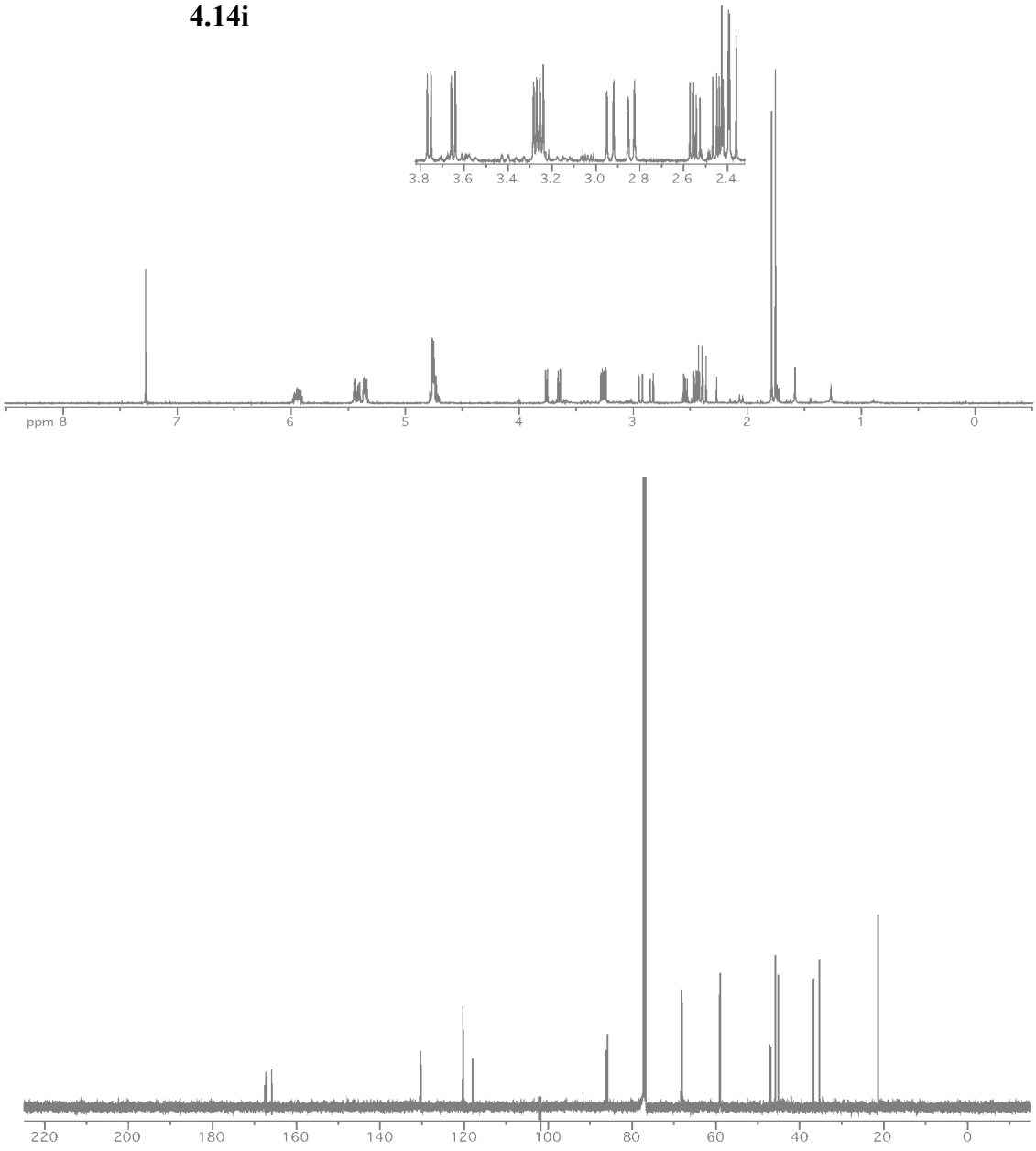


4.14h

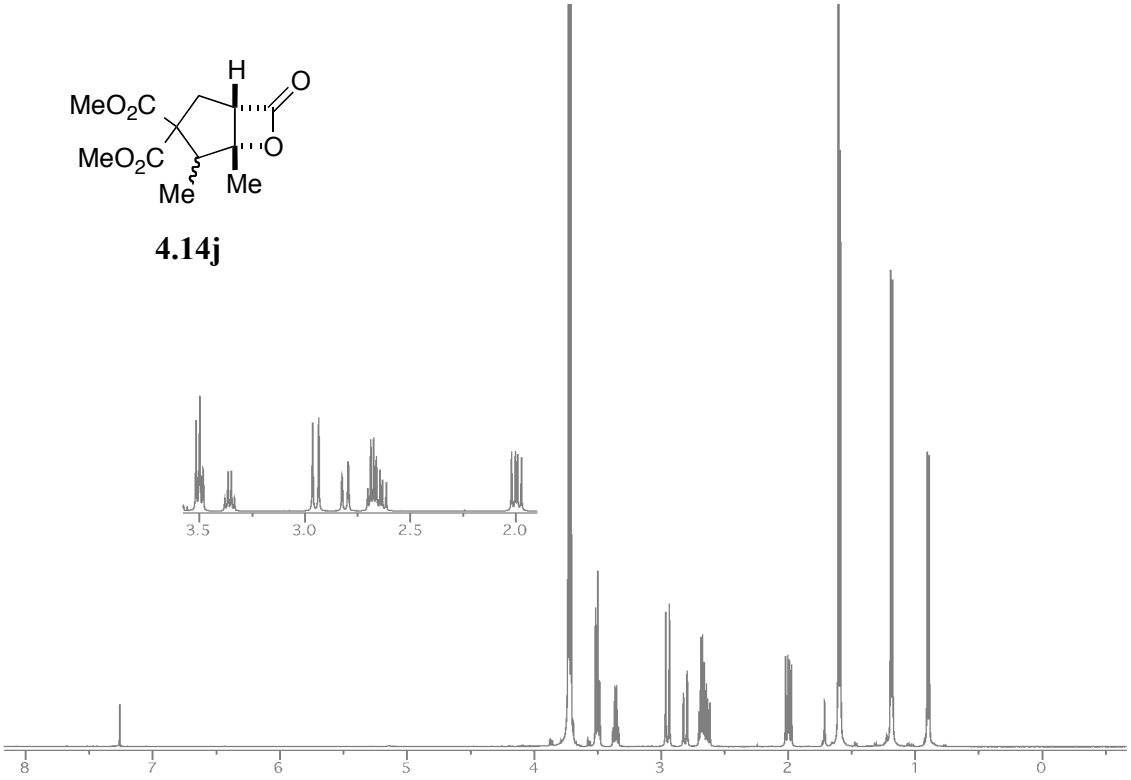
^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of single diastereomer (lower R_f) of **4.14h** in $CDCl_3$

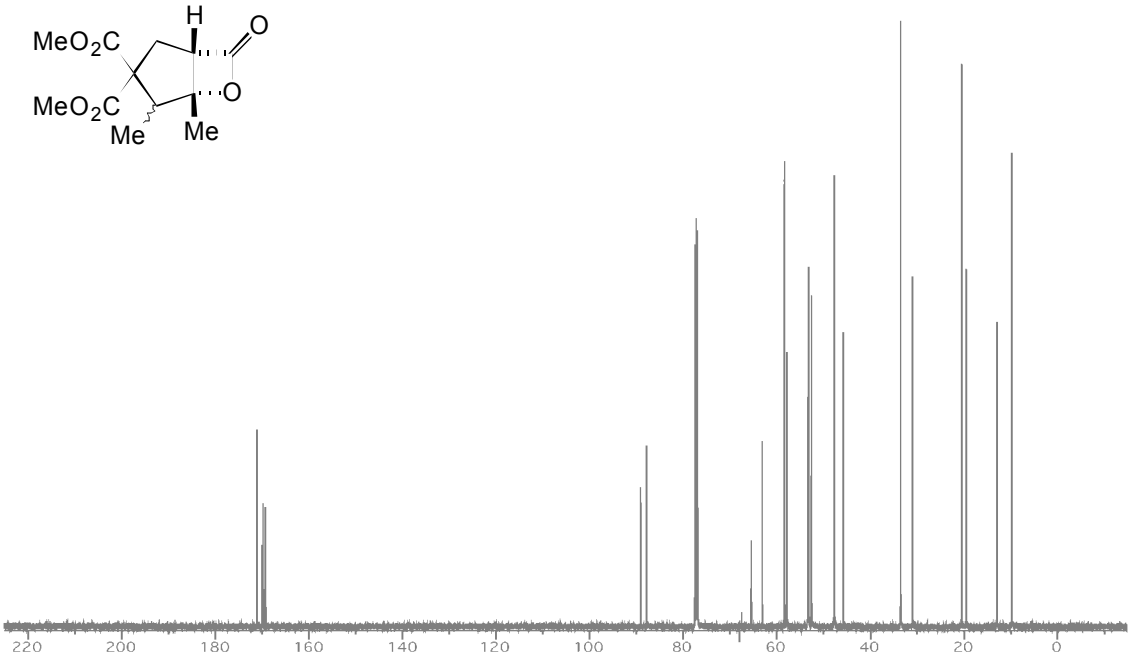


4.14i

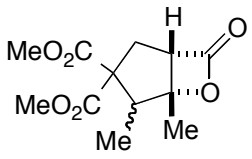


^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of β-lactones **4.14i** (dr, 1.2:1) in $CDCl_3$

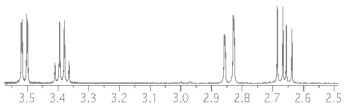




^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of β-lactones **4.14j** (dr 2:1) in $CDCl_3$

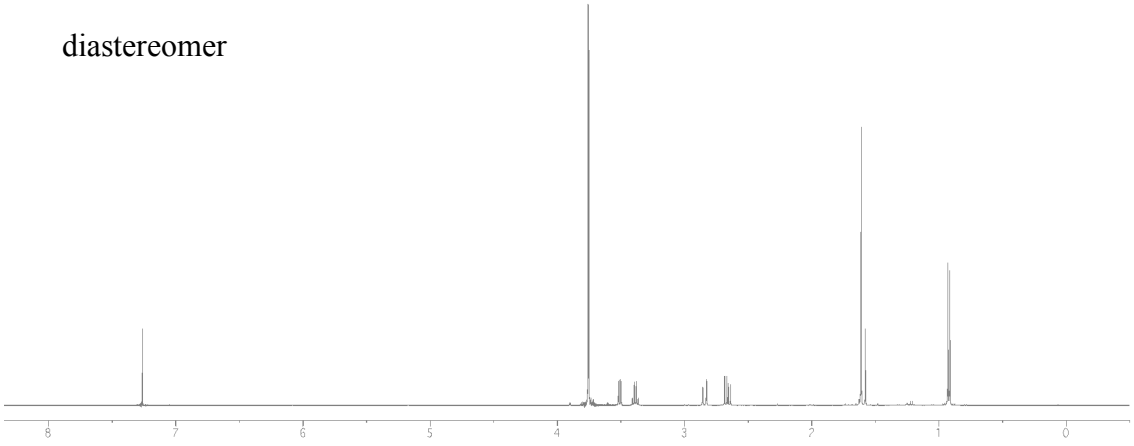


4.14j



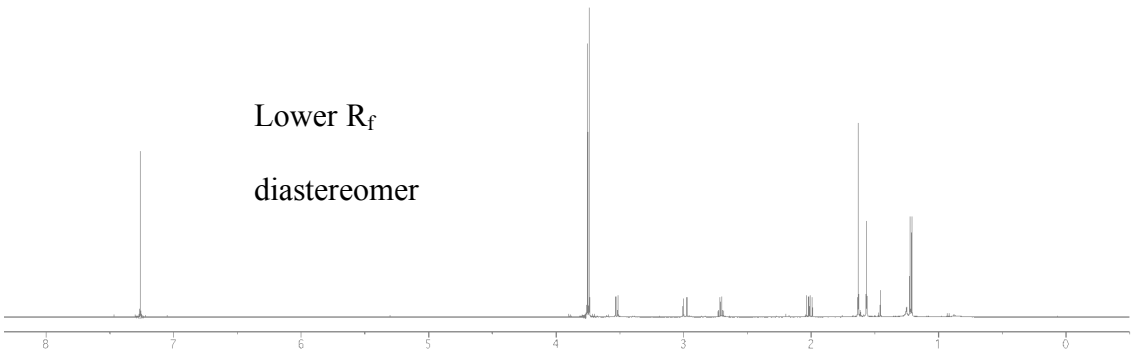
Higher R_f

diastereomer

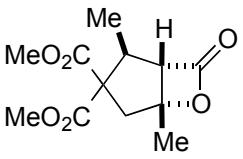


Lower R_f

diastereomer

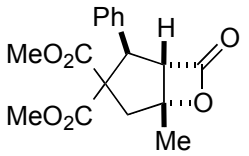


^{1}H (500 MHz) spectra of the separated diastereomers of β-lactone **4.14j** in $CDCl_3$

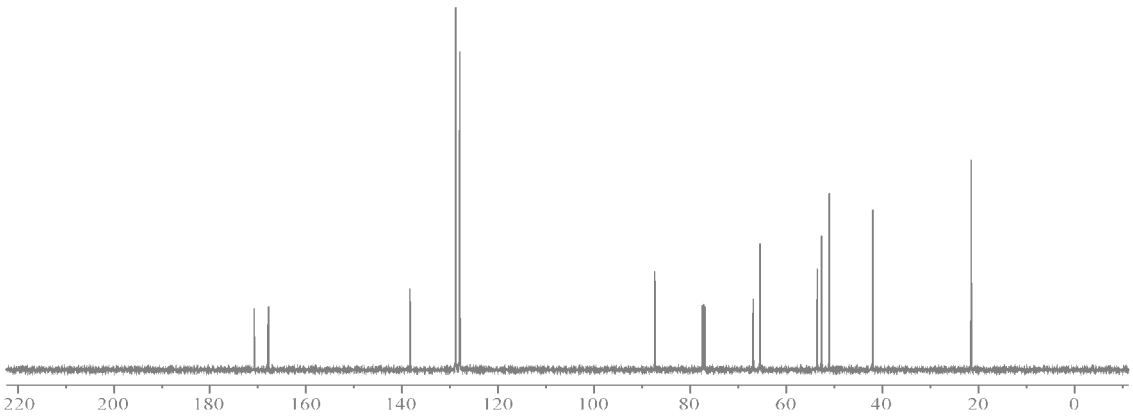


4.14k

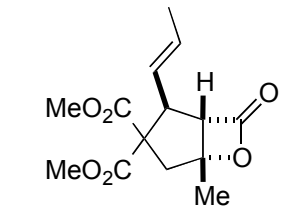
^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of β-lactone **14k** in $CDCl_3$



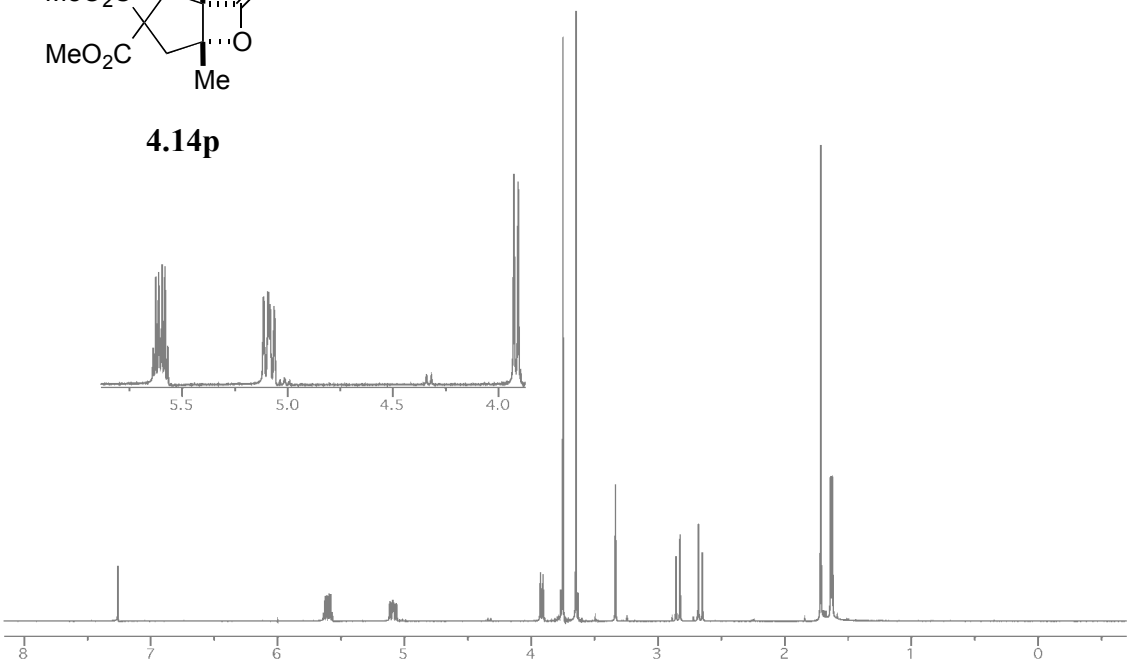
14m

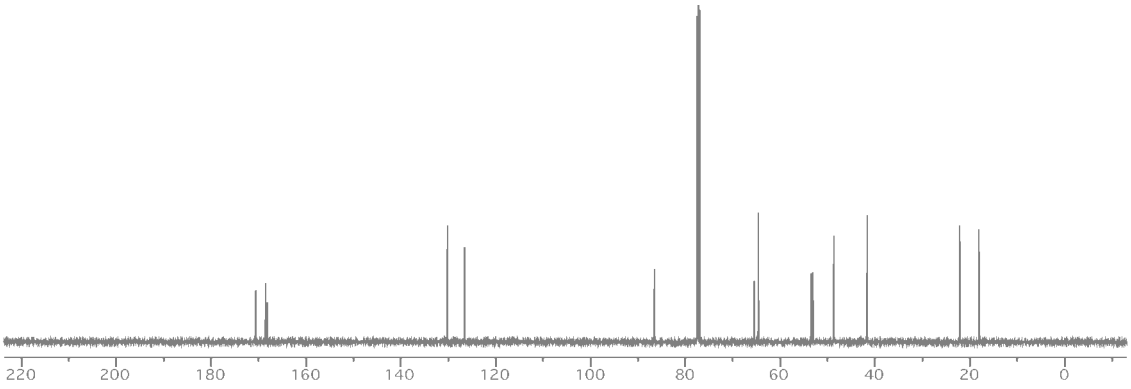


^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of β-lactone **14m** in $CDCl_3$

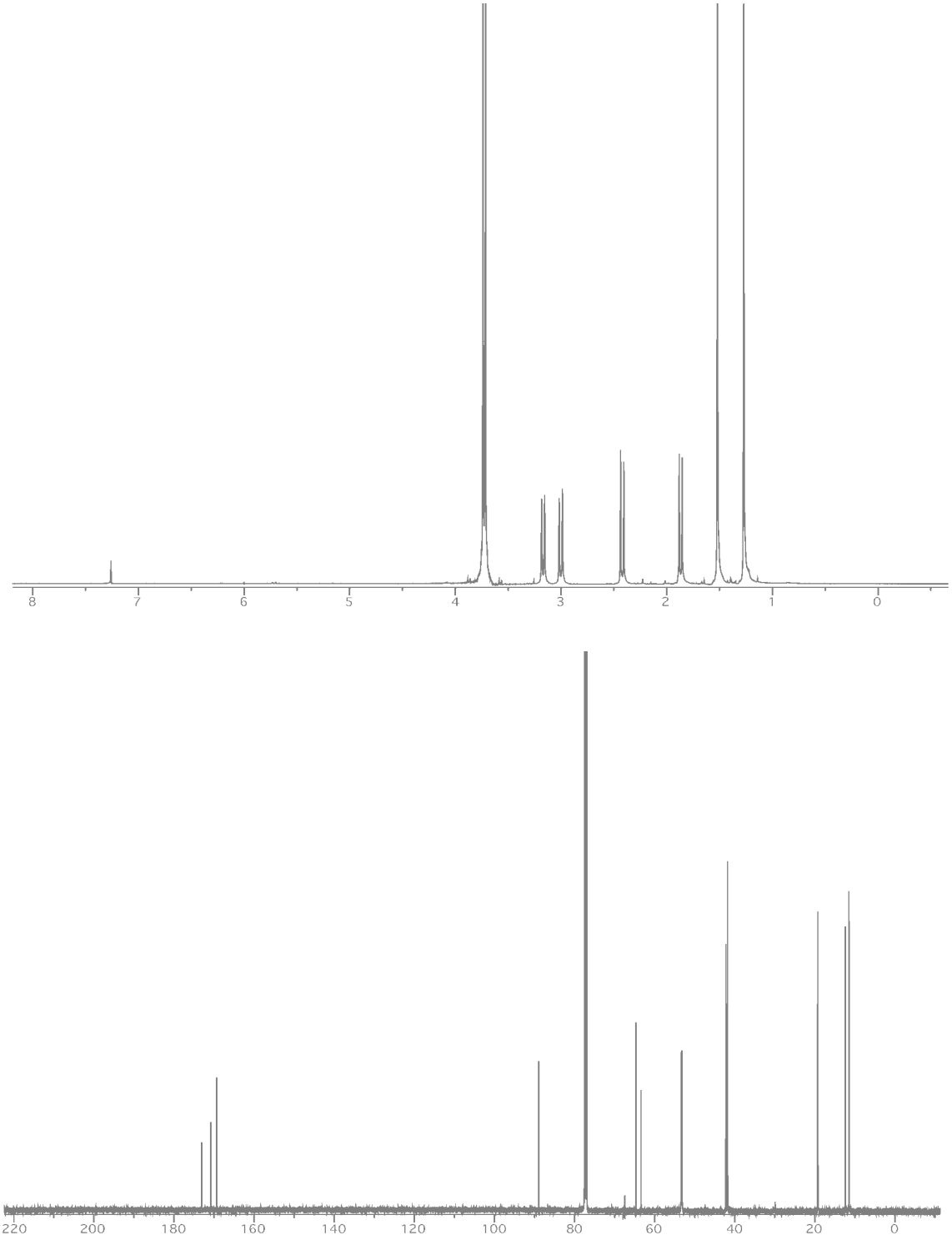


4.14p

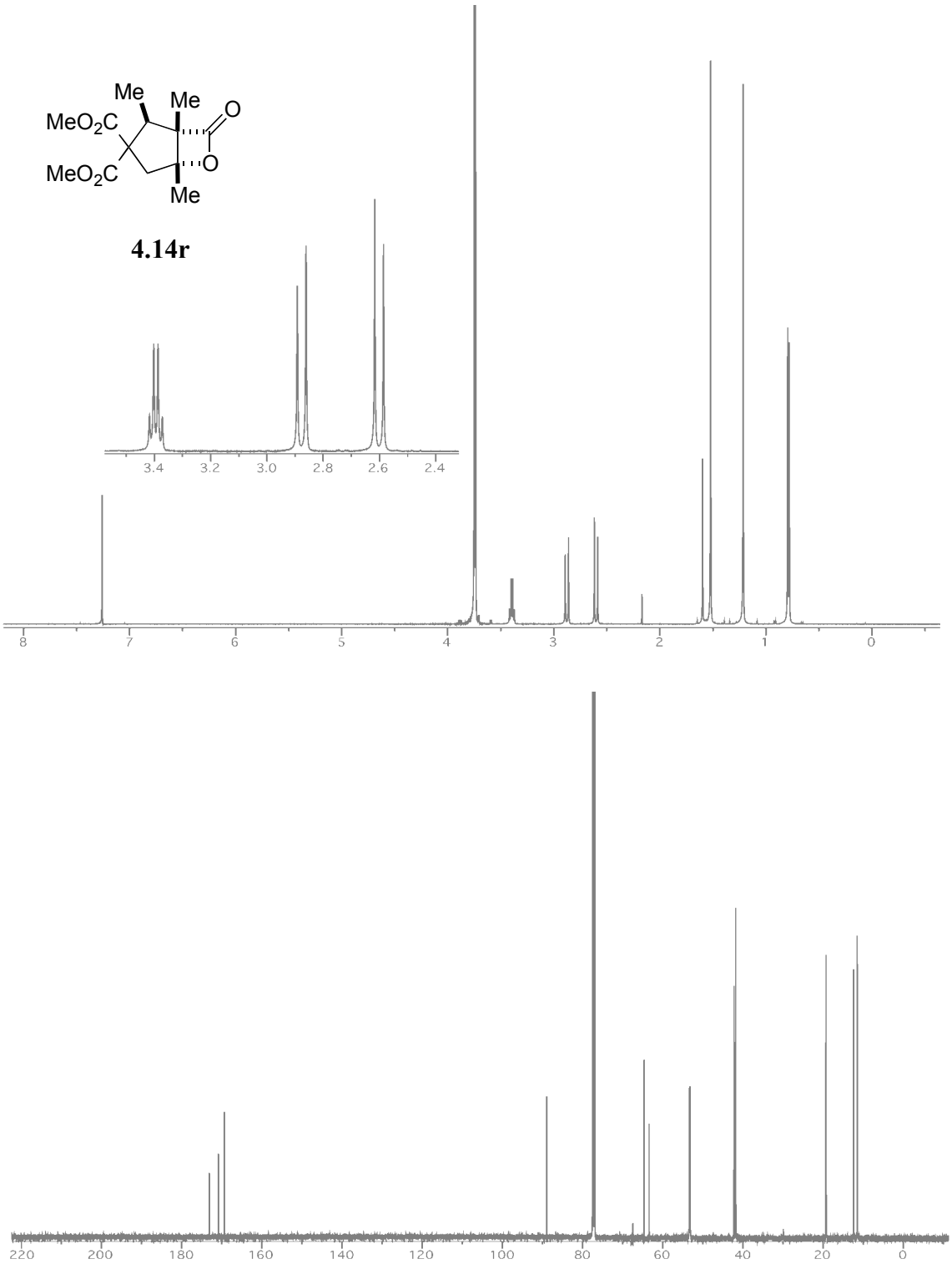




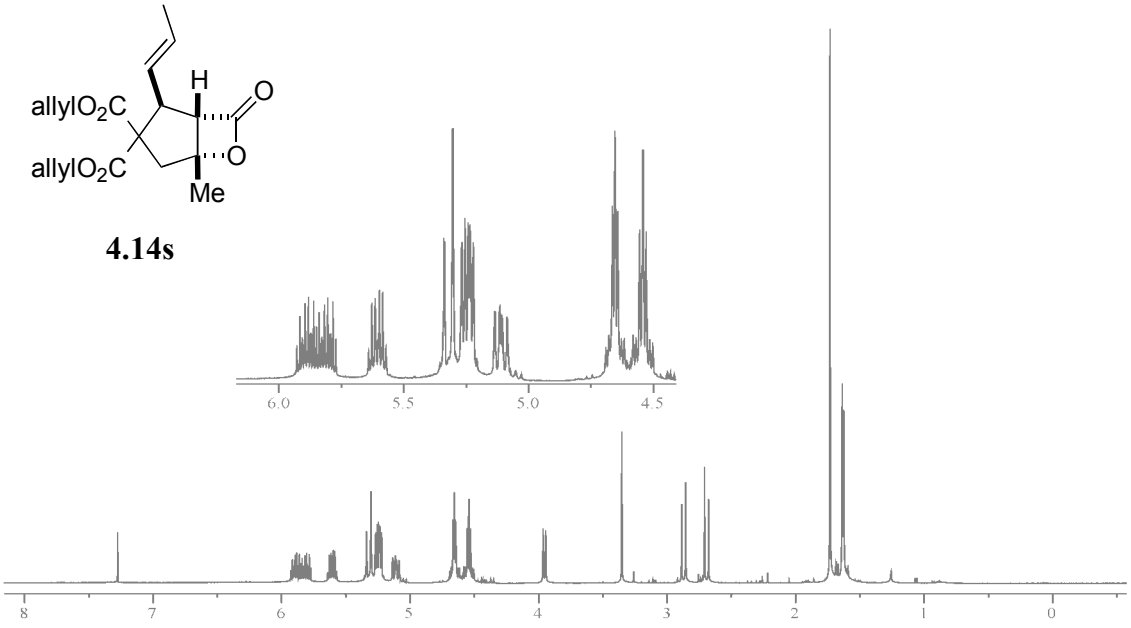
^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of β-lactone **4.14p** in $CDCl_3$



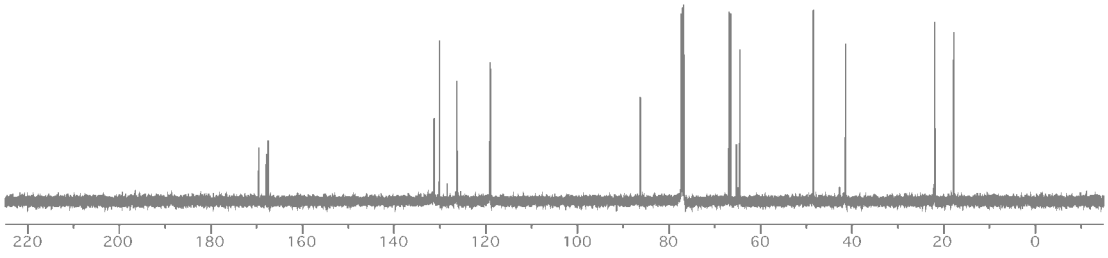
^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of β-lactone **4.14q** in $CDCl_3$



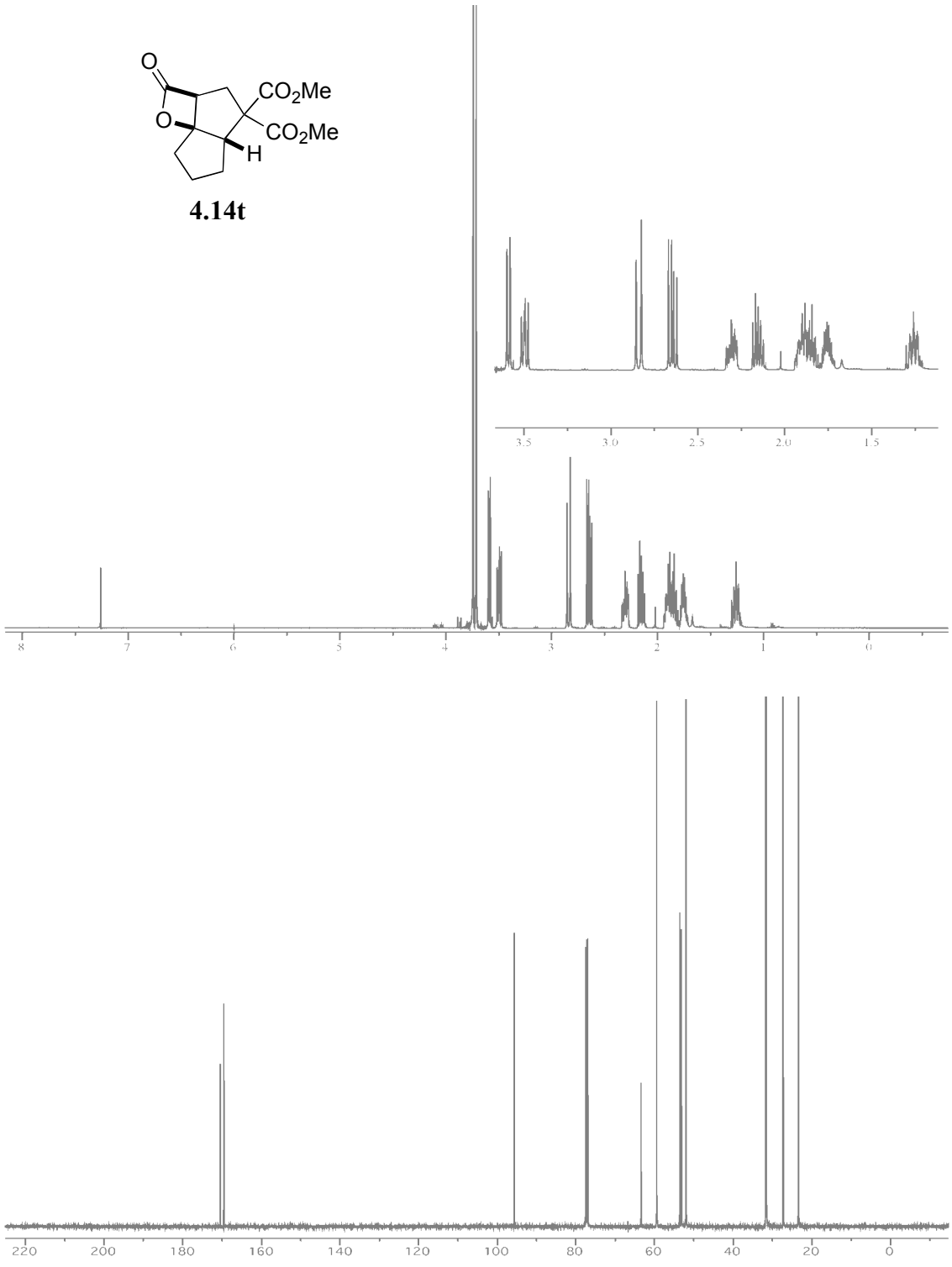
^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of β-lactone **4.14r** in $CDCl_3$



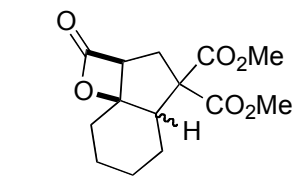
4.14s



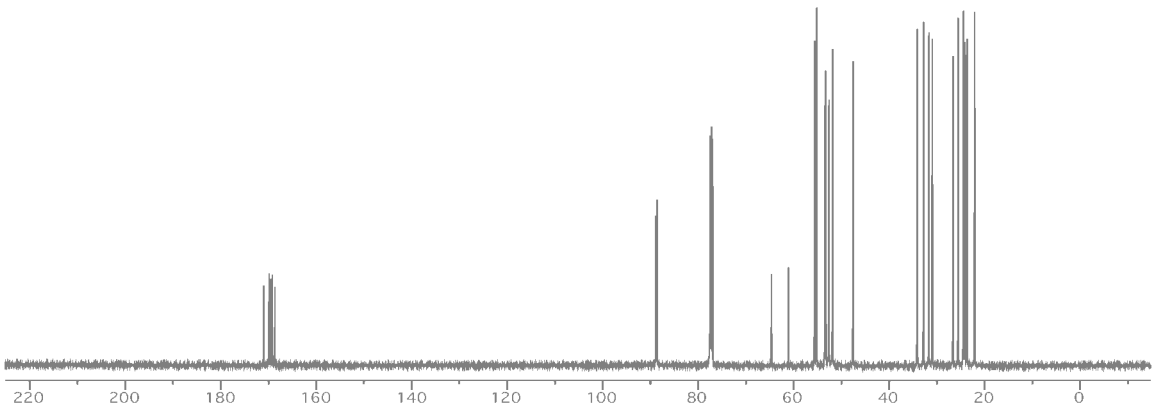
^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of β-lactone **4.14s** in $CDCl_3$



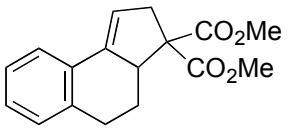
^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of tricyclic β-lactone **4.14t** in $CDCl_3$



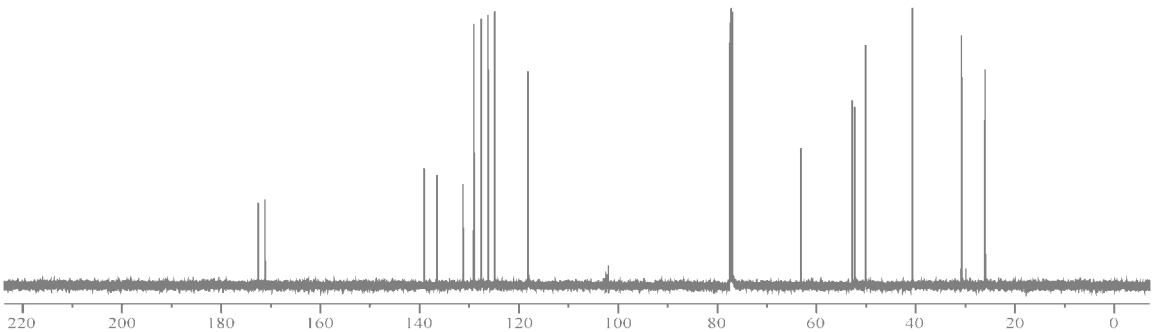
4.14u



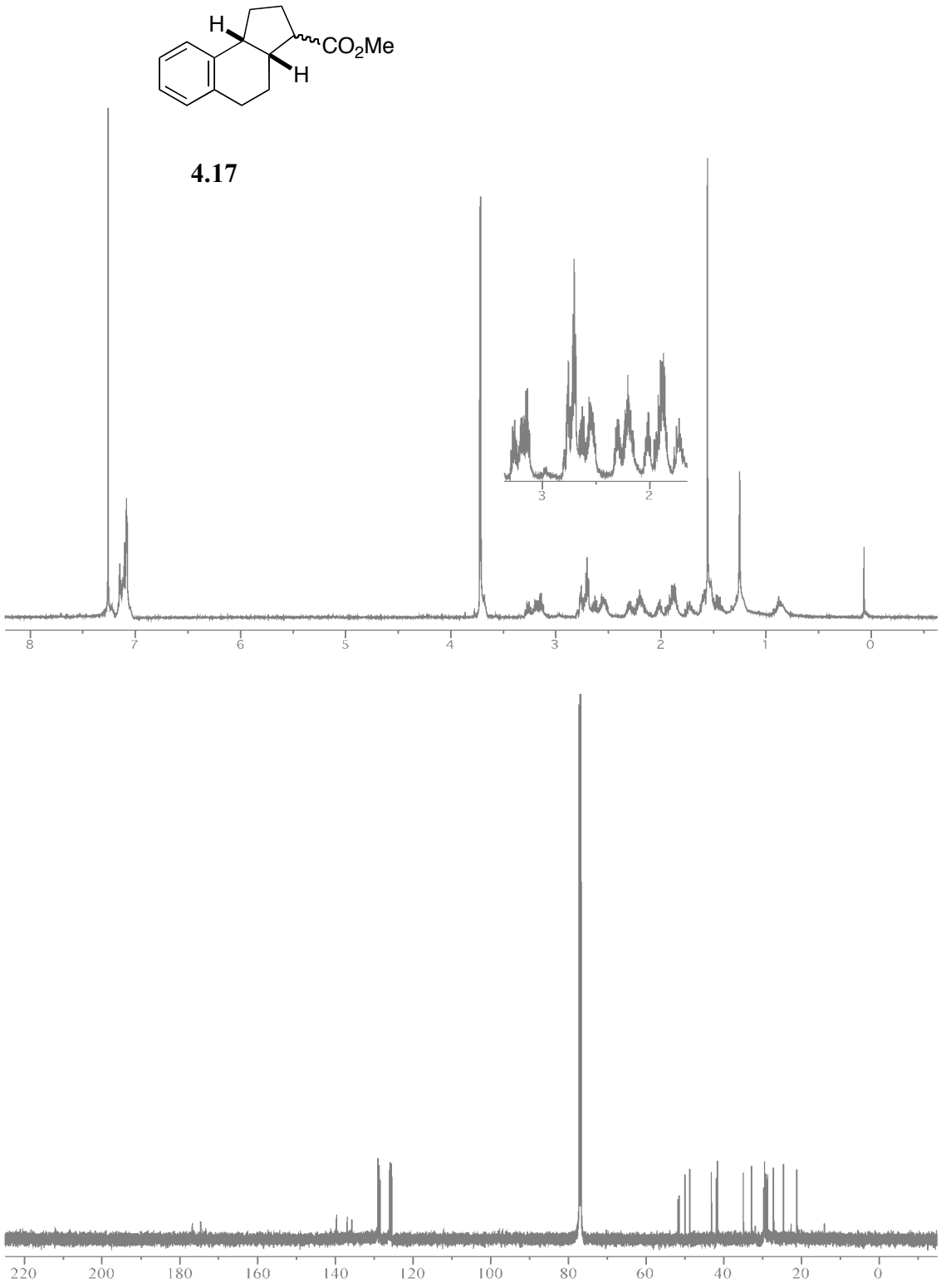
^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of tricyclic β-lactone **4.14u** in $CDCl_3$



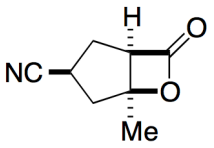
4.16



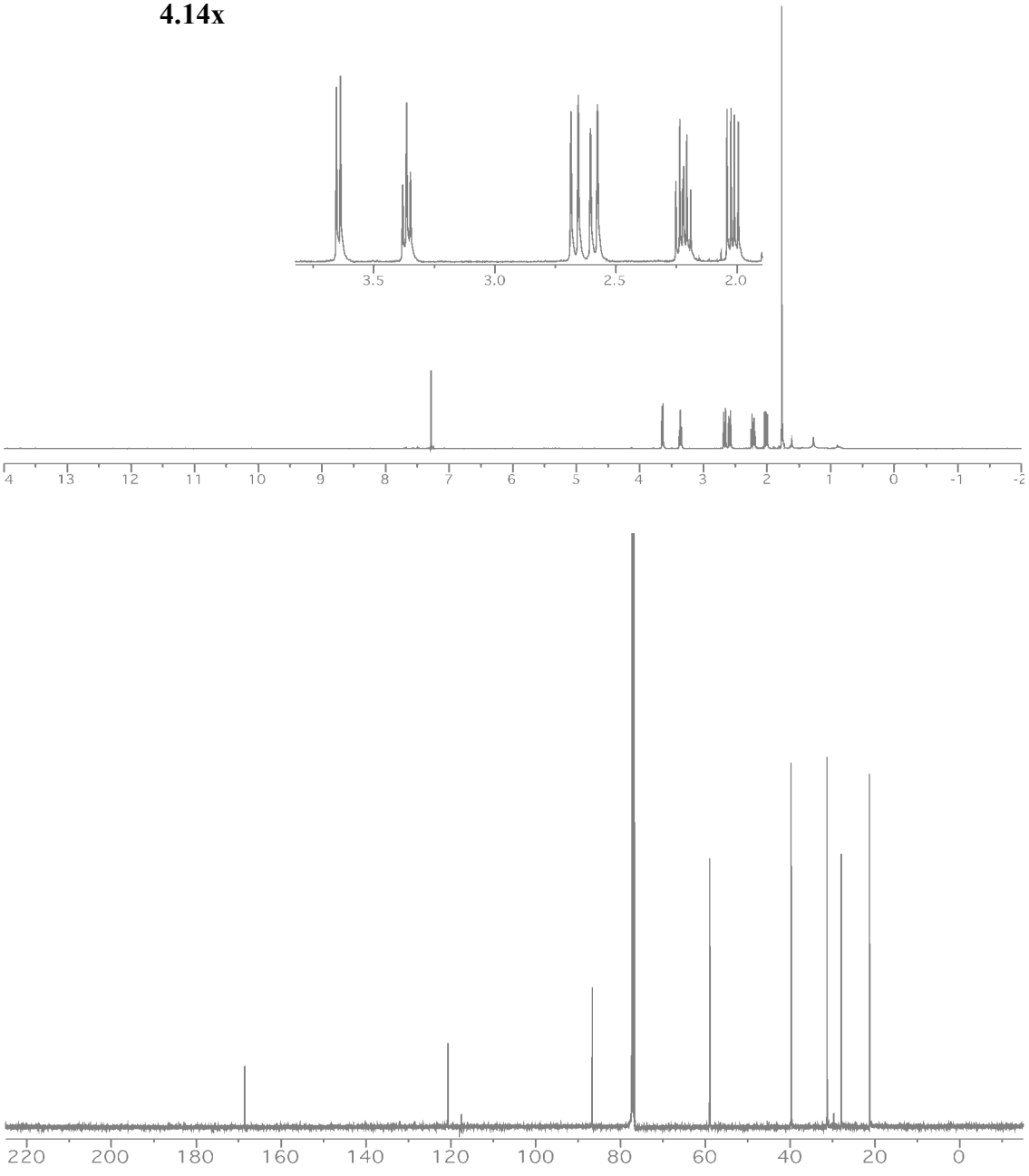
^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of cyclopentene **4.16** in $CDCl_3$



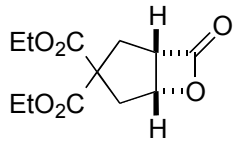
^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of cyclopentane **4.17** in $CDCl_3$



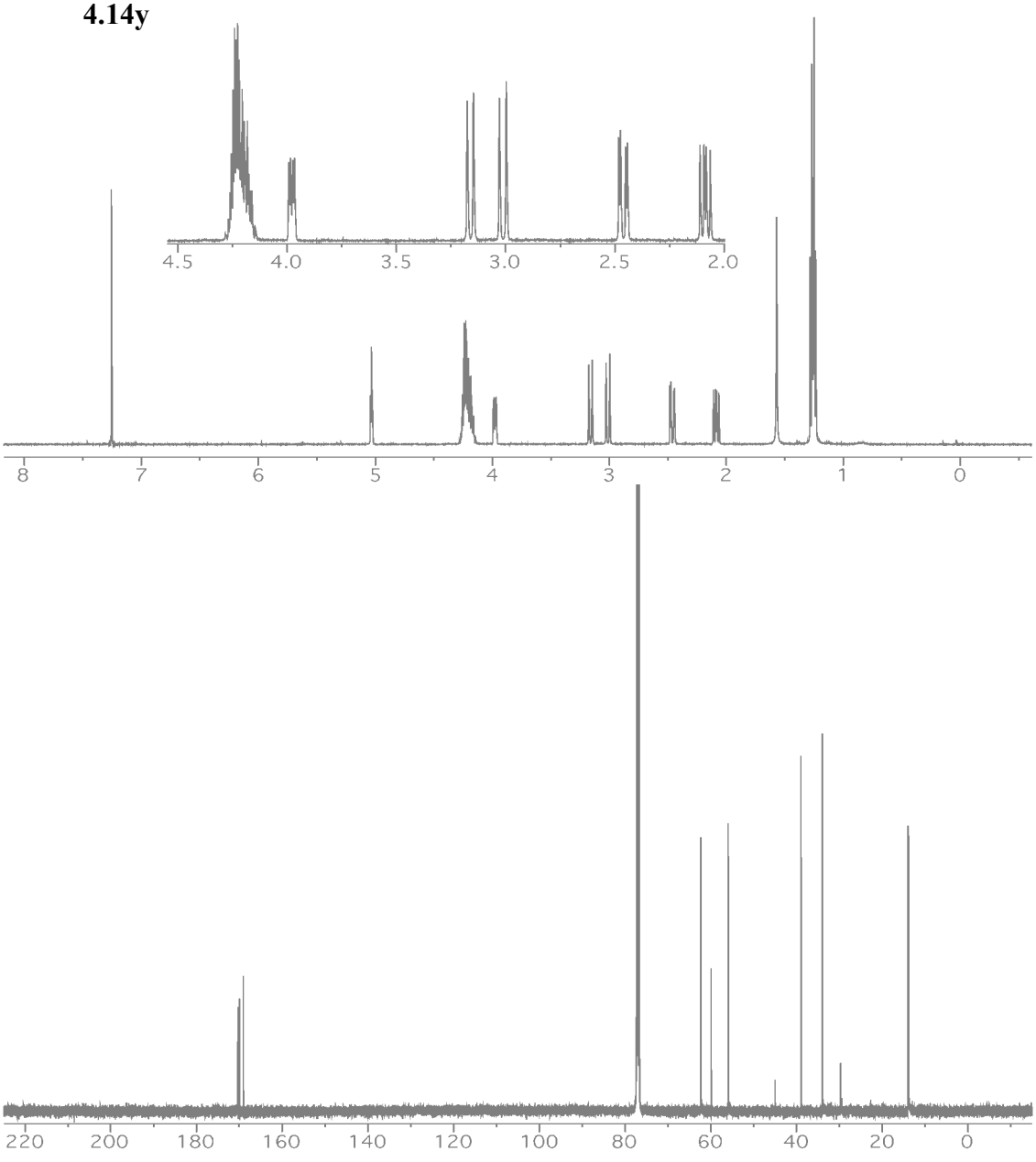
4.14x



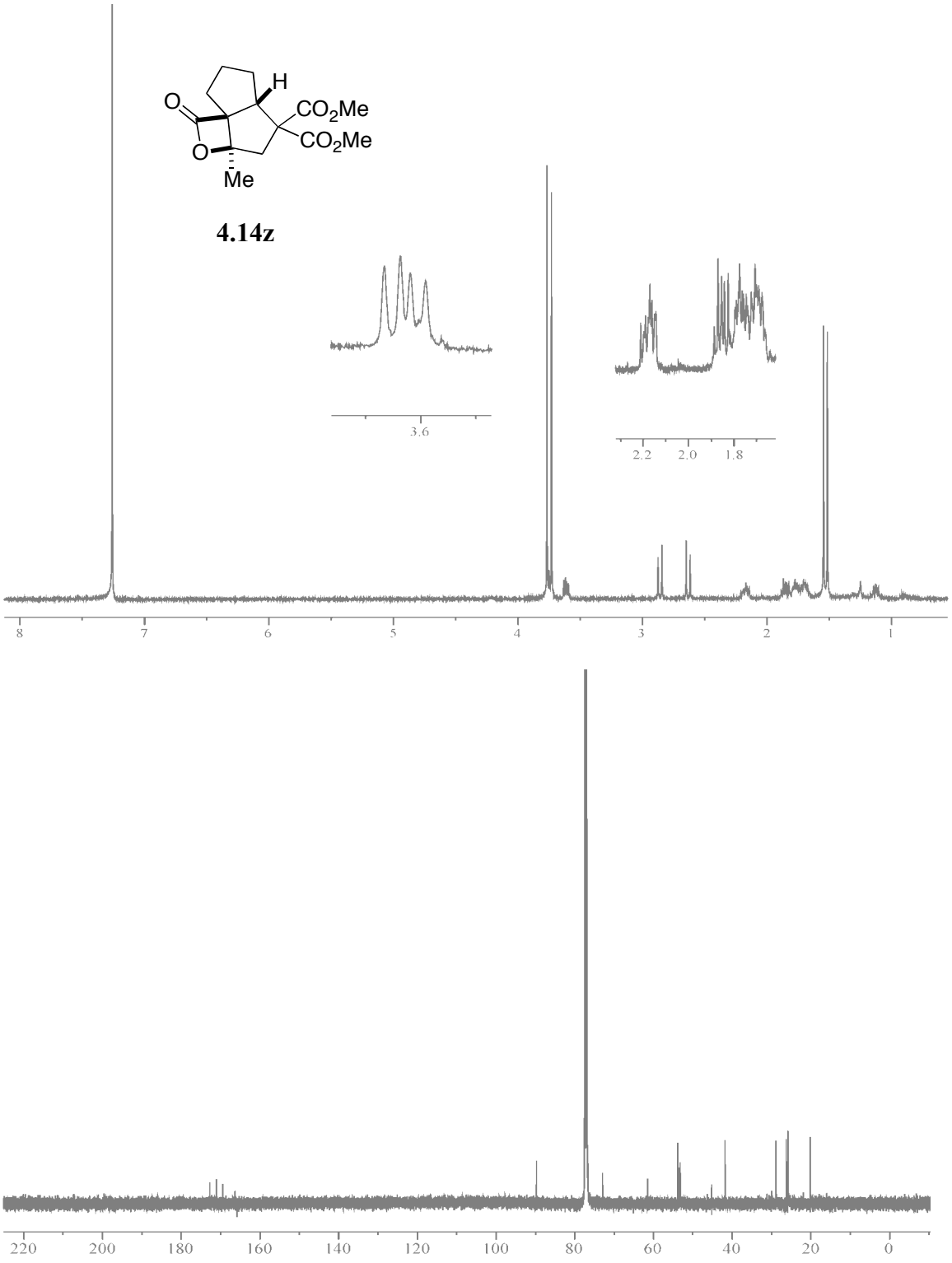
^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of β-lactone **4.14x** in $CDCl_3$



4.14y



^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of β-lactone **4.14y** in $CDCl_3$



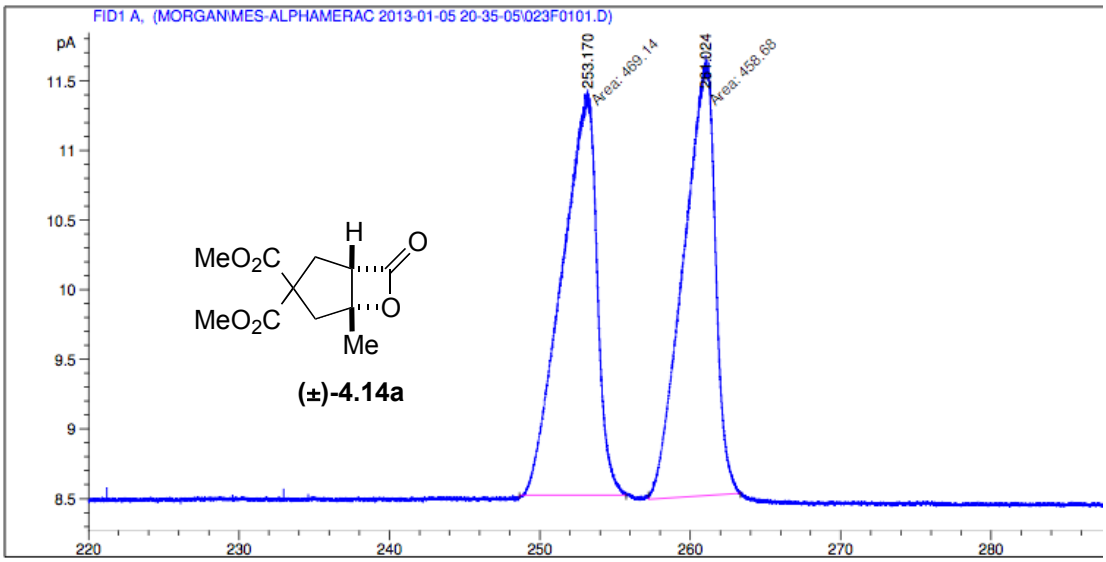
^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of tricyclic β-lactone **4.14z** in $CDCl_3$

Figure S1. Chiral GC determination of enantiomeric excess.

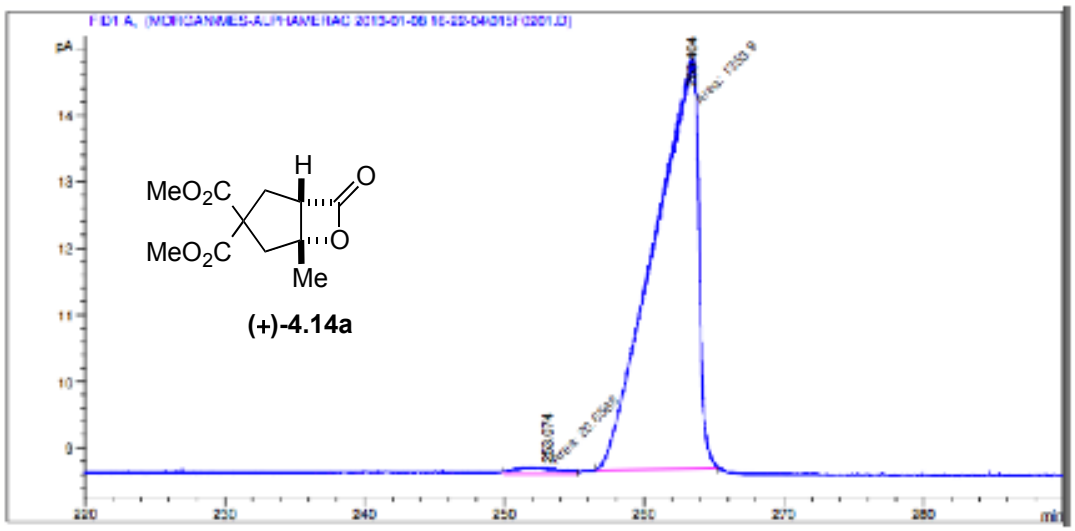
Determination of enantiomeric excess of β-lactone (+)-14a:

Analysis of β-lactone (+)-14a: Method: CHIRALDEX-BDM GC column, 13.85 psi, 70-160 °C oven temperature

Temp (°C)	Rate (°C/min)	Hold time (min)	Total time (min)
70	0.00	2.00	2.00
80	6.00	5.00	8.67
94	0.05	3.00	291.67
160	40.0	1.00	294.32

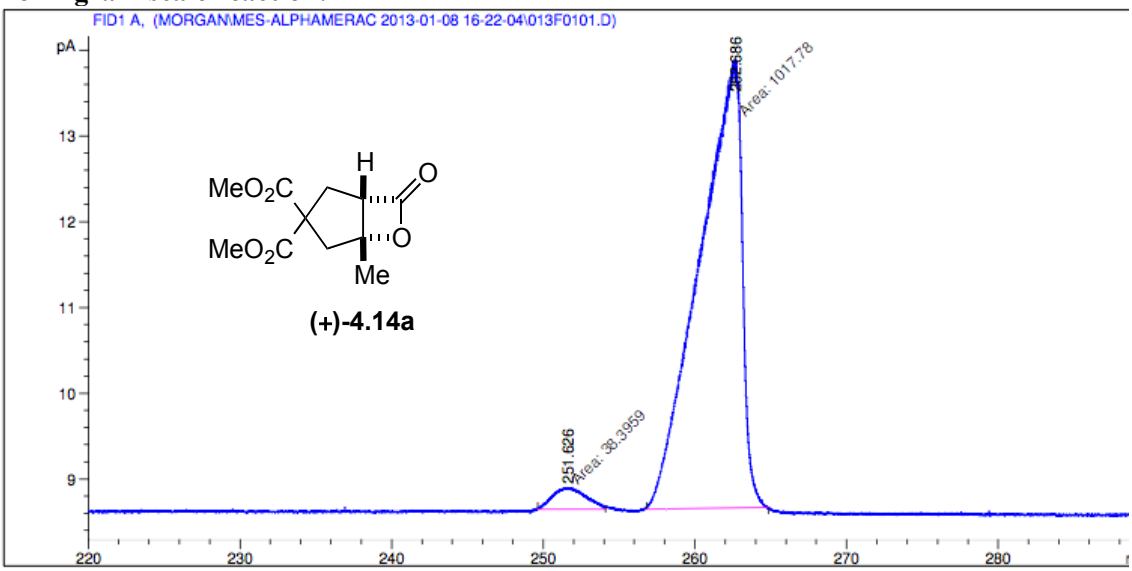


Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	253.170	MM	2.6883	469.14023	2.90851	50.56371
2	261.024	MM	2.4268	458.67972	3.15007	49.43629
Totals :				927.81995	6.05858	



Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	253.074	MM	3.0844	20.65680	1.11619e-1	1.50280
2	263.404	MM	3.6433	1353.90149	6.19348	98.49720
Totals :				1374.55829	6.30510	

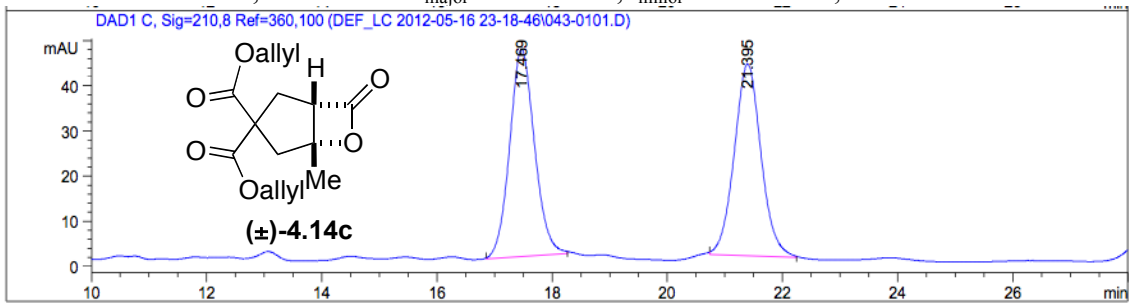
For 1 gram scale reaction:



Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	251.626	MM	2.4909	38.39586	2.56910e-1	3.63537
2	262.686	MM	3.2436	1017.77905	5.22972	96.36463
Totals :				1056.17491	5.48663	

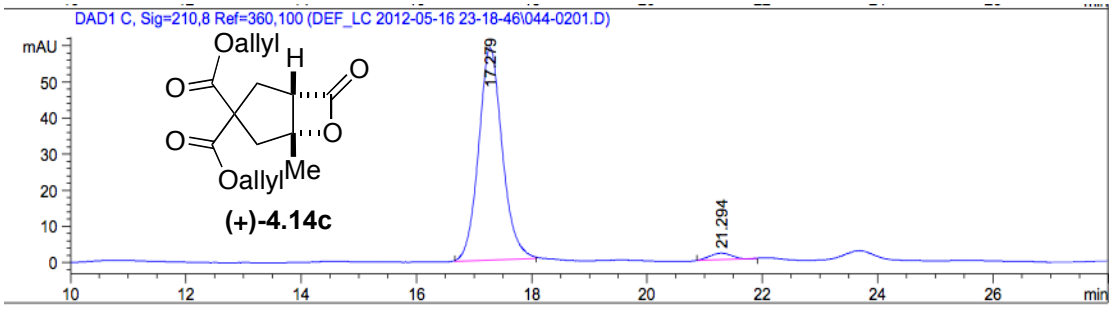
Figure S2. Chiral HPLC determination of enantiomeric excess.
Determination of enantiomeric excess of β-lactone (+)-4.14c:

Chiral HPLC Analysis of β-lactone (+)-4.14c: Chiralcel IA column: hexanes:*i*PrOH = 92:08, flow rate 0.5 mL/min, λ = 210 nm: t_{major} = 17.28 min, t_{minor} = 21.29 min; 95% *ee*.



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

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.469	BB	0.4584	1380.03906	45.94238	50.0339
2	21.395	BB	0.4922	1378.16772	42.51847	49.9661
Totals :				2758.20679	88.46085	

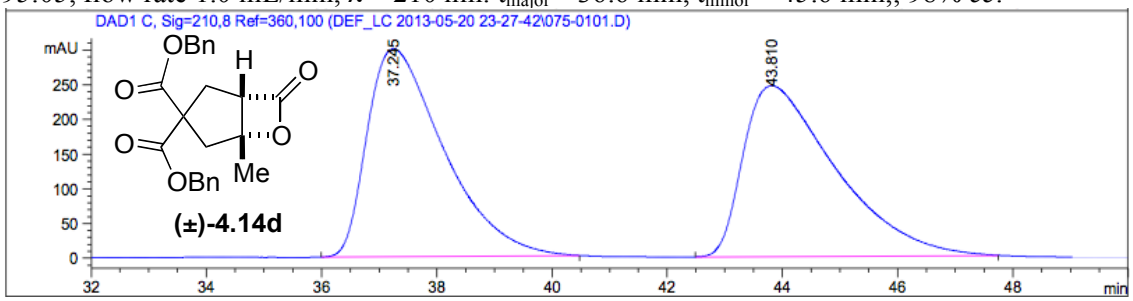


Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.279	BB	0.4330	1679.59167	58.83675	97.3688
2	21.294	BB	0.3267	45.38679	1.80935	2.6312
Totals :				1724.97847	60.64610	

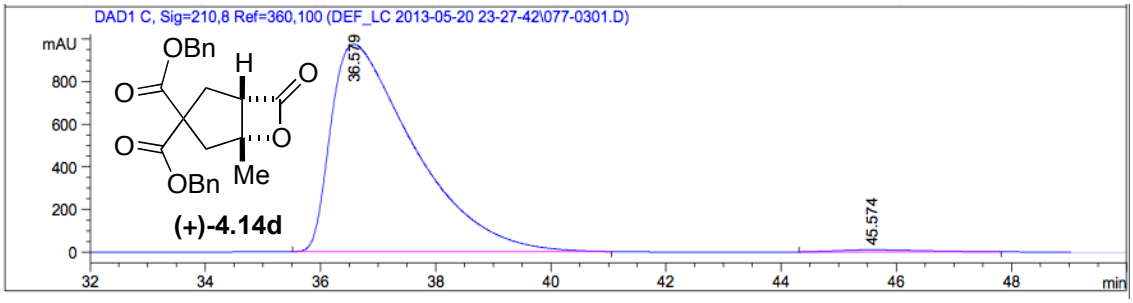
Determination of enantiomeric excess of β-lactone (+)-4.14d:

Chiral HPLC Analysis of β-lactone (+)-4.14d: Chiralcel OD-H column: hexanes: *i*PrOH = 95:05, flow rate 1.0 mL/min, λ = 210 nm: t_{major} = 36.6 min, t_{minor} = 45.6 min,; 98% *ee*.



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

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	37.245	BB	1.3899	2.77147e4	299.96042	50.2328
2	43.810	BB	1.6070	2.74579e4	246.23305	49.7672
Totals :				5.51726e4	546.19347	

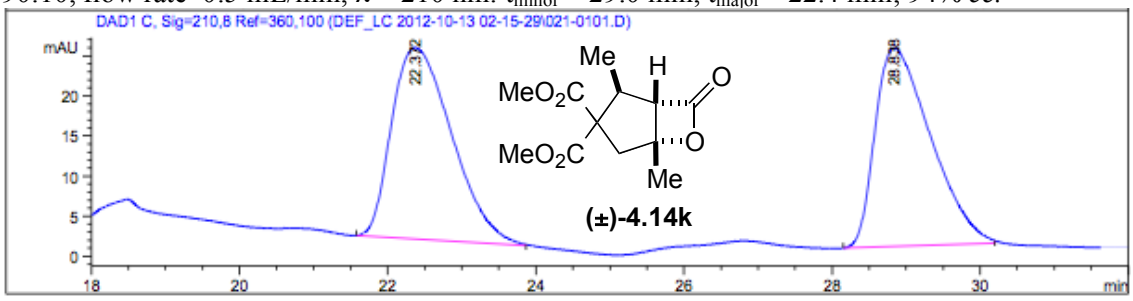


Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	36.579	BB	1.4738	9.74570e4	971.97943	98.9620
2	45.574	BB	1.2386	1022.21277	9.75475	1.0380
Totals :				9.84792e4	981.73418	

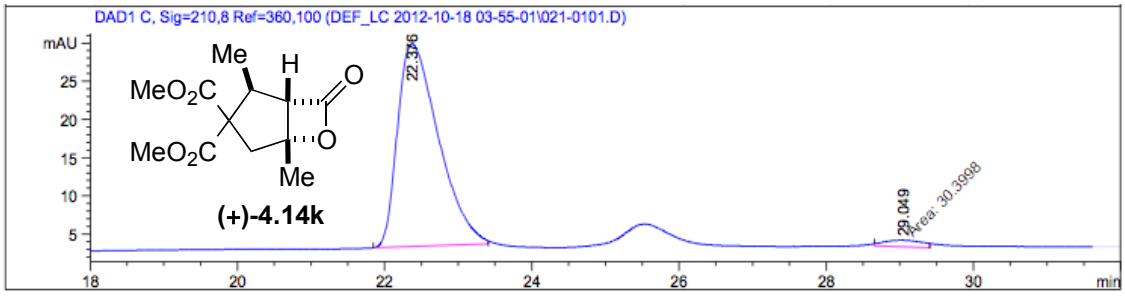
Determination of enantiomeric excess of β-lactone 4.14k:

Chirla HPLC Analysis of (+)-β-lactone 4.14k: Chiralcel OD-H column: hexanes:*i*PrOH = 90:10, flow rate 0.5 mL/min, λ = 210 nm: t_{minor} = 29.0 min, t_{major} = 22.4 min; 94% *ee*.



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

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	22.372	BB	0.8831	1347.21545	23.84849	51.0730
2	28.838	BB	0.7853	1290.60730	24.71064	48.9270
Totals :				2637.82275	48.55913	

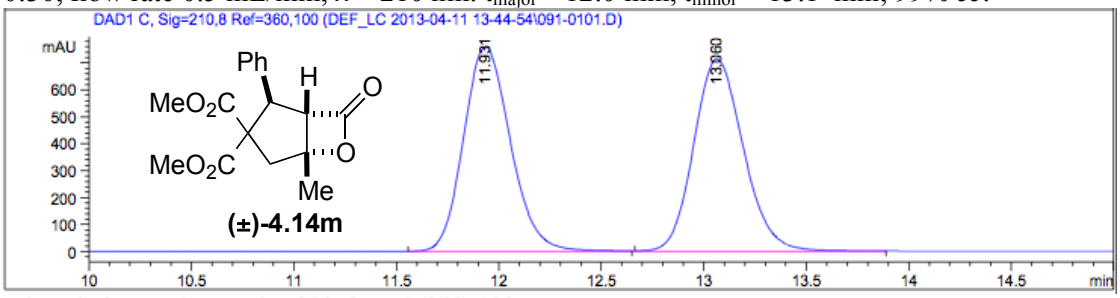


Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	22.376	BB	0.5900	1023.85535	26.54196	97.1165
2	29.049	MM	0.5977	30.39977	8.47750e-1	2.8835
Totals :				1054.25512	27.38971	

Determination of enantiomeric excess of β-lactone (+)-4.14m:

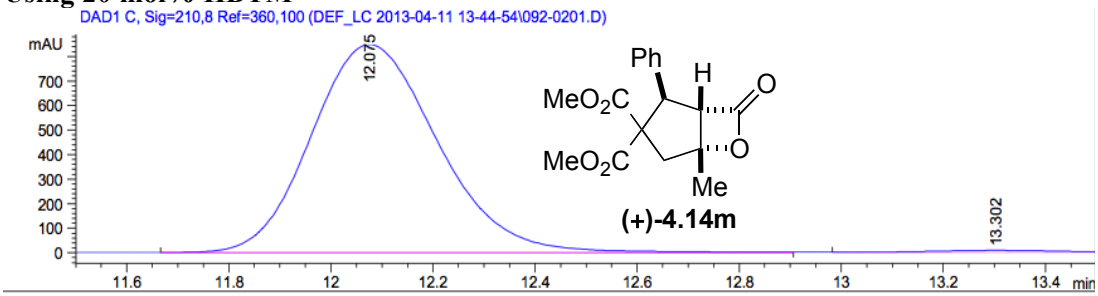
Chiral HPLC Analysis of (+)-β-lactone (+)-4.14m: Chiralcel AD-H column: hexanes:*i*PrOH = 70:30, flow rate 0.5 mL/min, λ = 210 nm: t_{major} = 12.0 min, t_{minor} = 13.1 min; 99% *ee*.



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

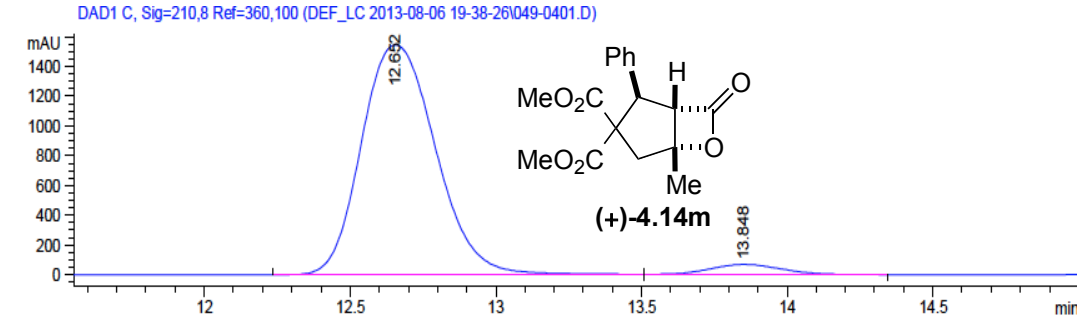
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.931	BB	0.2474	1.20770e4	760.01733	50.0964
2	13.060	BB	0.2606	1.20305e4	713.89355	49.9036
Totals :				2.41075e4	1473.91089	

Using 20 mol% HBTM



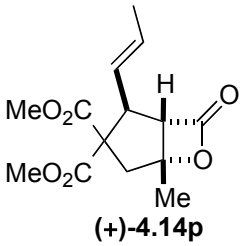
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.075	BB	0.2685	1.45686e4	847.91510	98.9681
2	13.302	BB	0.2827	151.90509	8.10490	1.0319

Using 5 mol% HBTM



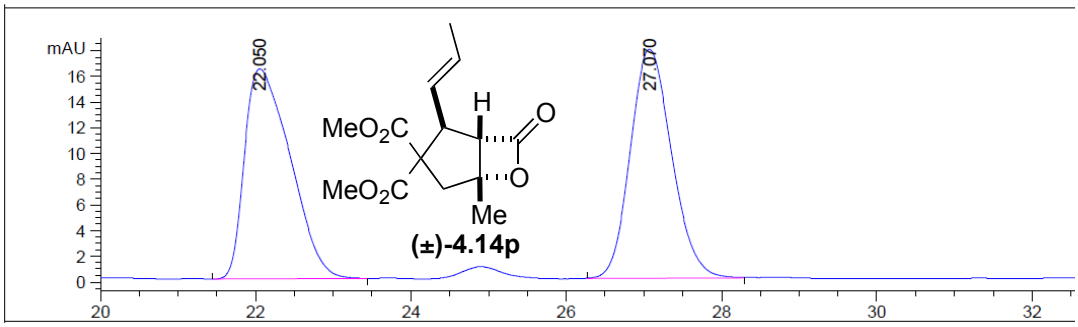
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.652	BV	0.2808	2.73653e4	1544.16235	95.7366
2	13.848	VB	0.2717	1218.64624	69.13052	4.2634

Determination of enantiomeric excess of β-lactone (+)-4.14p:



(+)-4.14p

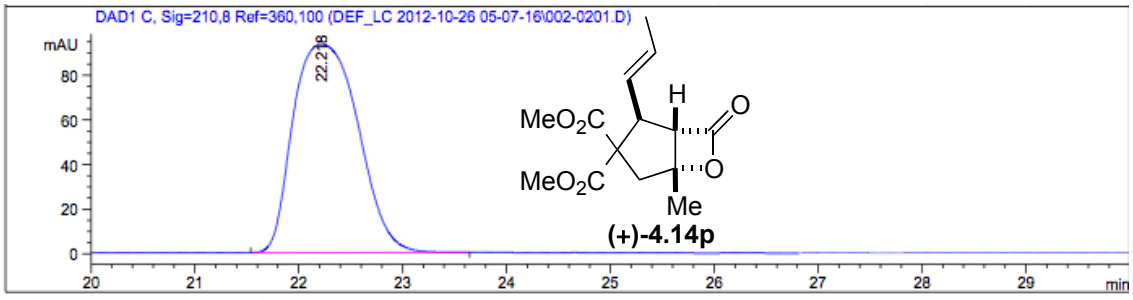
Chiral HPLC Analysis of β-lactone (+)-4.14p: Chiralcel AD-H column: hexanes:*i*PrOH = 70:30, flow rate 0.5 mL/min, λ = 210 nm: t_{major} = 22.2 min, t_{minor} = 27.0 min; 99% *ee*.



(±)-4.14p

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

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	22.050	BB	0.6828	2204.23926	53.93431	50.5226
2	27.070	BB	0.5737	2158.63965	58.60735	49.4774
Totals :				4362.87891	112.54166	



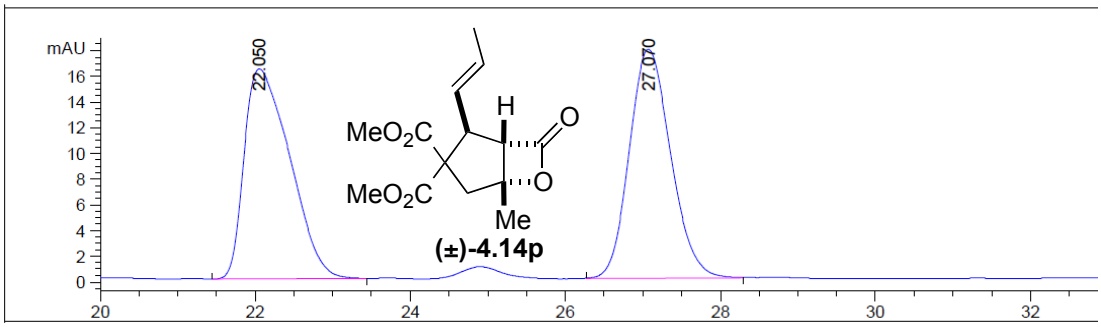
(+)-4.14p

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

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	22.218	BB	0.7221	4071.58838	93.48624	100.0000
Totals :				4071.58838	93.48624	

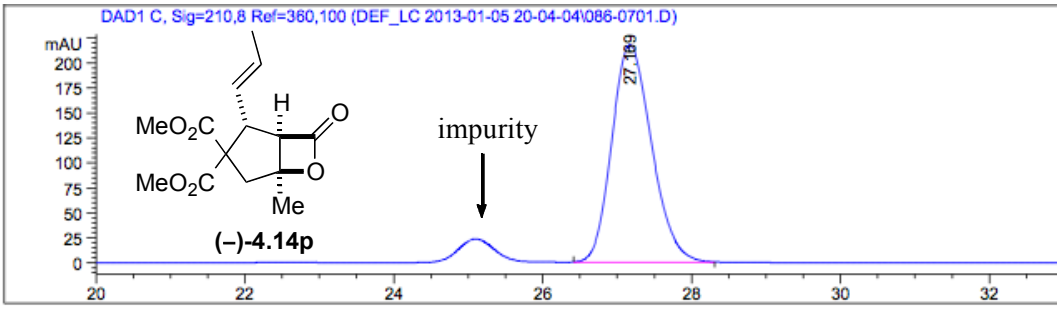
Determination of enantiomeric excess of β-lactone (-)-4.14p:

Chiral HPLC Analysis of β-lactone (-)-4.14p derived from use of (*R*)-HBTM: Chiralcel AD-H column: hexanes:*i*PrOH = 70:30, flow rate 0.5 mL/min, λ = 210 nm: t_{minor} = 22.2 min, t_{major} = 27.2 min; 99% *ee*.



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

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	22.050	BB	0.6828	2204.23926	53.93431	50.5226
2	27.070	BB	0.5737	2158.63965	58.60735	49.4774
Totals :				4362.87891	112.54166	

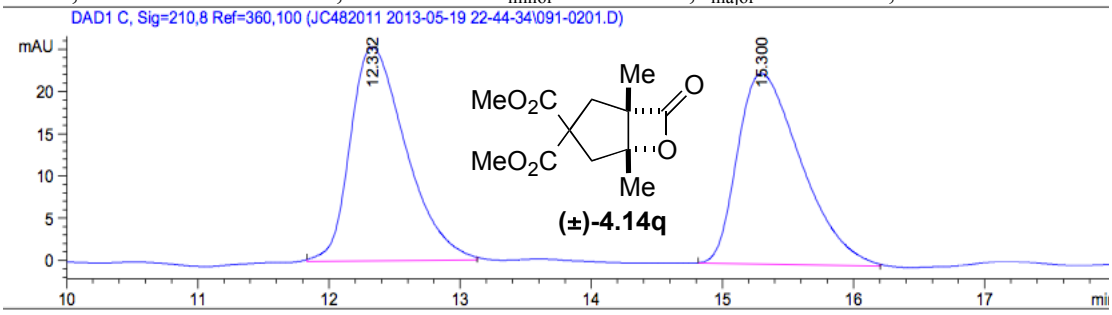


Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	27.169	BB	0.5773	8080.22998	217.58018	100.0000
Totals :				8080.22998	217.58018	

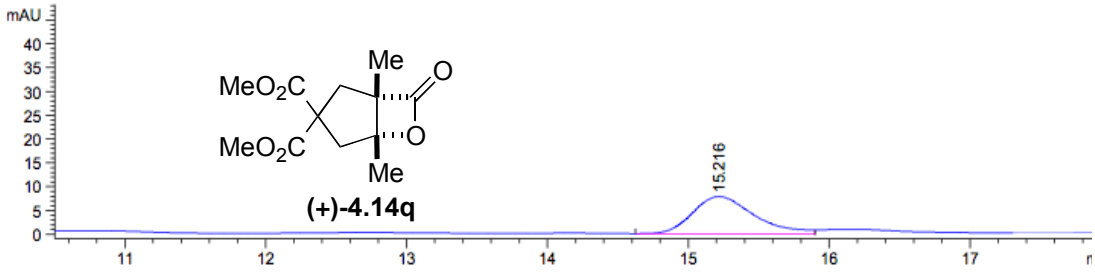
Determination of enantiomeric excess of β-lactone (+)-4.14q:

Chiral HPLC Analysis of β-lactone (+)-4.14q: Chiralcel OD-H column: hexanes:*i*PrOH = 92:08, flow rate 1.0 mL/min, λ = 210 nm: t_{minor} = 12.3 min, t_{major} = 15.3 min; 99% *ee*.



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

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.332	BB	0.4513	745.72705	25.34275	49.4180
2	15.300	BB	0.5243	763.29059	22.58295	50.5820
Totals :				1509.01764	47.92570	

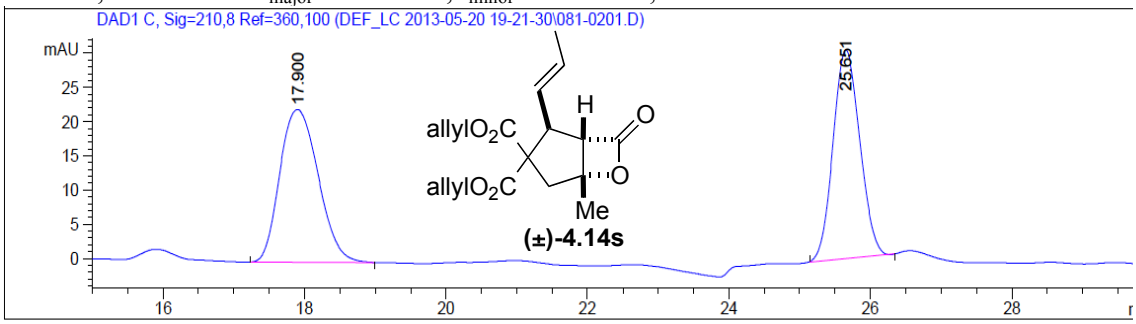


Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.214	BB	0.4135	218.03964	7.91135	100.0000
Totals :				218.03964	7.91135	

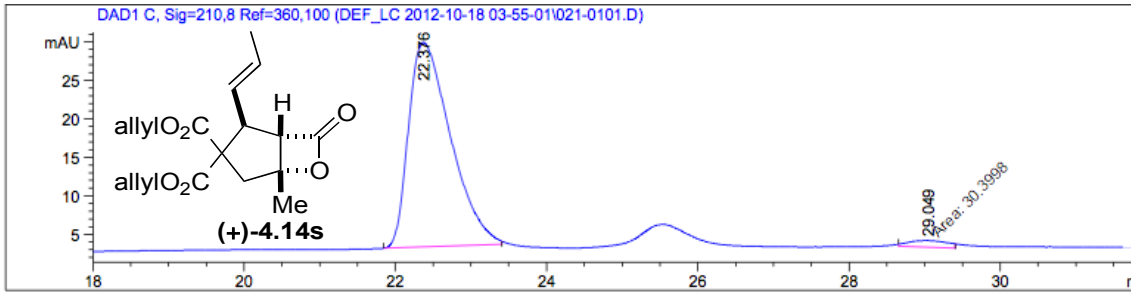
Determination of enantiomeric excess of β-lactone (+)-4.14s:

Analysis of β-lactone (+)-4.14s: Chiralcel AD-H column: hexanes:*i*PrOH = 92:08, flow rate 1.0 mL/min, λ = 210 nm: t_{major} = 12.3 min, t_{minor} = 15.3 min; 94% *ee*.



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

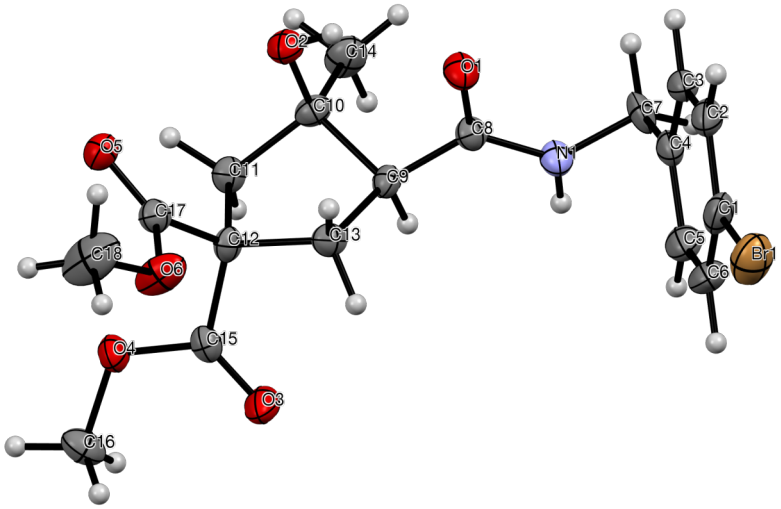
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.900	BB	0.6046	842.74713	22.31680	51.3632
2	25.651	BB	0.4075	798.01489	30.47148	48.6368
Totals :				1640.76202	52.78828	



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

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	22.376	BB	0.5900	1023.85535	26.54196	97.1165
2	29.049	MM	0.5977	30.39977	8.47750e-1	2.8835
Totals :				1054.25512	27.38971	

Single crystal X-ray structure (ORTEP) of amide (+)-**4.S15**. The crystals were grown from a concentrated solution of amide (+)-**4.S15** in $CDCl_3$, using a slow evaporation method (probability ellipsoids are shown at the 50% level). X-ray crystallographic data have been deposited in the Cambridge Crystallographic Data Centre database (http://www.ccdc.cam.ac.uk/) under accession code CCDC 927699.



Crystal data and structure refinement for DRB_MS_121026_A1_306.

Identification code	drb	
Empirical formula	C18 H22 Br N O6	
Formula weight	428.28	
Temperature	110(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	C2	
Unit cell dimensions	a = 25.835(5) Å	□= 90°.
	b = 10.3517(19) Å	□= 102.657(2)°.
	c = 7.2252(13) Å	□ = 90°.
Volume	1885.3(6) $Å^3$	
Z	4	
Density (calculated)	1.509 Mg/m^3	
Absorption coefficient	2.214 mm^{-1}	
F(000)	880	
Crystal size	0.14 x 0.09 x 0.02 mm^3	
Theta range for data collection	2.13 to 24.99°.	
Index ranges	-30<=h<=30, -12<=k<=12, -8<=l<=8	
Reflections collected	8634	
Independent reflections	3250 [R(int) = 0.0389]	
Completeness to theta = 24.99°	99.5 %	

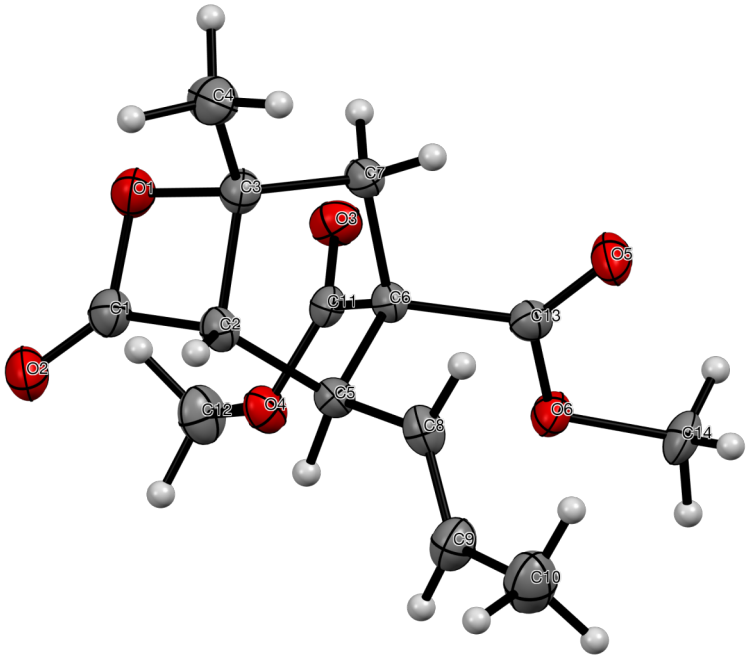
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9571 and 0.7469
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3250 / 1 / 239
Goodness-of-fit on F^2	1.043
Final R indices [I>2sigma(I)]	R1 = 0.0332, wR2 = 0.0734
R indices (all data)	R1 = 0.0412, wR2 = 0.0760
Absolute structure parameter	0.024(8)
Largest diff. peak and hole	0.338 and -0.217 e.Å^{-3}

Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for DRB_MS_121026_A1_306. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Br(1)	685(1)	-33(1)	9099(1)	48(1)
O(1)	713(1)	5887(2)	4818(3)	29(1)
O(2)	1086(1)	7405(2)	2361(3)	27(1)
O(3)	2953(1)	7004(3)	6603(3)	44(1)
O(4)	3083(1)	7706(2)	3812(3)	28(1)
O(5)	2044(1)	6847(2)	442(3)	27(1)
O(6)	2447(1)	5245(2)	2257(3)	40(1)
N(1)	956(1)	6502(3)	7883(4)	26(1)
C(1)	619(1)	1805(4)	8885(5)	33(1)
C(2)	183(1)	2324(3)	7673(5)	30(1)
C(3)	142(1)	3657(3)	7526(4)	27(1)
C(4)	531(1)	4459(4)	8572(5)	26(1)
C(5)	956(1)	3896(4)	9789(5)	34(1)
C(6)	1008(2)	2576(4)	9959(5)	36(1)
C(7)	489(1)	5917(4)	8371(6)	29(1)
C(8)	1032(1)	6437(3)	6107(4)	23(1)
C(9)	1515(1)	7101(3)	5697(5)	21(1)
C(10)	1376(1)	8053(3)	4015(4)	24(1)
C(11)	1923(1)	8349(3)	3638(5)	24(1)
C(12)	2217(1)	7037(3)	3886(4)	21(1)
C(13)	1908(1)	6180(3)	5063(5)	24(1)
C(14)	1079(2)	9251(3)	4446(5)	37(1)
C(15)	2787(1)	7219(3)	4968(5)	24(1)
C(16)	3644(1)	7911(4)	4675(6)	34(1)

C(17)	2219(1)	6402(3)	1974(5)	25(1)
C(18)	2506(2)	4556(4)	551(5)	58(1)

Single crystal X-ray structure (ORTEP) of bicyclic-β-lactone (+)-**4.14p**. The crystals were grown from a concentrated solution of amide β-lactone (+)-**4.14p** in $CDCl_3$, using a slow evaporation method (probability ellipsoids are shown at the 50% level). X-ray crystallographic data have been deposited in the Cambridge Crystallographic Data Centre database (http://www.ccdc.cam.ac.uk/) under accession code CCDC 927698.



Alert level B:THETM01_ALERT_3_B The value of sine(theta_max)/wavelength is less than 0.575. Calculated sin(theta_max)/wavelength = 0.5617

Author Response: Data was collected on a Bruker GADDS instrument with Cu-source and MWPC (multiwire proportional counter) detector. Under these experimental conditions the maximum angle that can be collected is 120 degrees two-theta.

Crystal data and structure refinement for DRB_MS_121001_G_290A.

Identification code	drb	
Empirical formula	C14 H18 O6	
Formula weight	282.28	
Temperature	110(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 8.9133(3) Å	α= 90°.

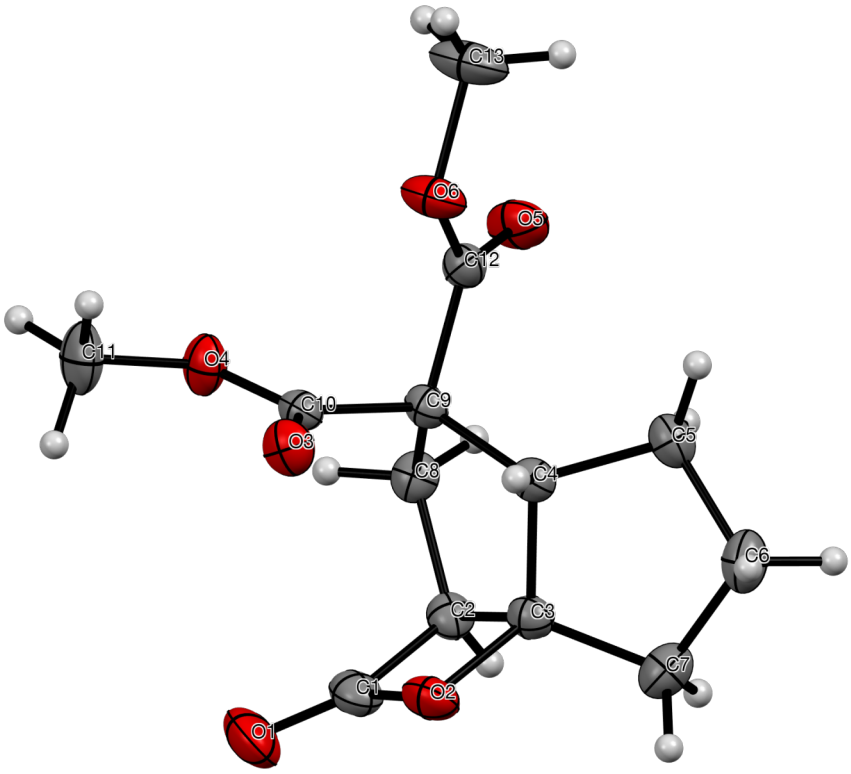
	b = 12.1780(5) Å β= 90°.
	c = 12.9803(5) Å γ = 90°.
Volume	1408.96(9) $Å^3$
Z	4
Density (calculated)	1.331 Mg/m^3
Absorption coefficient	0.878 mm^{-1}
F(000)	600
Crystal size	0.22 x 0.09 x 0.02 mm^3
Theta range for data collection	4.98 to 60.00°.
Index ranges	-10<=h<=10, -13<=k<=12, -14<=l<=14
Reflections collected	28220
Independent reflections	2069 [R(int) = 0.0521]
Completeness to theta = 60.00°	99.3 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9826 and 0.8302
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2069 / 0 / 185
Goodness-of-fit on F^2	1.082
Final R indices [I>2sigma(I)]	R1 = 0.0309, wR2 = 0.0823
R indices (all data)	R1 = 0.0335, wR2 = 0.0833
Absolute structure parameter [Hooft]	-0.2(2) [-0.17(8)]
Largest diff. peak and hole	0.354 and -0.198 $e.Å^{-3}$

Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for DRB_MS_121001_G_290A. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	9124(2)	-236(2)	3096(2)	28(1)
C(2)	9367(2)	773(2)	2425(2)	22(1)
C(3)	10333(2)	1184(2)	3330(2)	24(1)
C(4)	12006(3)	1254(2)	3248(2)	34(1)
C(5)	7993(2)	1542(2)	2327(1)	21(1)
C(6)	7898(2)	2068(1)	3429(1)	20(1)
C(7)	9541(2)	2173(2)	3776(2)	22(1)
C(8)	8260(2)	2364(2)	1486(2)	25(1)
C(9)	7444(3)	2434(2)	634(2)	31(1)
C(10)	7747(3)	3153(2)	-266(2)	44(1)
C(11)	7020(2)	1369(2)	4210(2)	21(1)

C(12)	5329(3)	-75(2)	4489(2)	32(1)
C(13)	7142(2)	3197(2)	3406(1)	22(1)
C(14)	4819(2)	4115(2)	3334(2)	28(1)
O(1)	9897(2)	159(1)	3923(1)	30(1)
O(2)	8513(2)	-1106(1)	3034(1)	34(1)
O(3)	7127(2)	1509(1)	5125(1)	28(1)
O(4)	6140(2)	622(1)	3771(1)	24(1)
O(5)	7794(2)	4054(1)	3458(1)	33(1)
O(6)	5661(1)	3095(1)	3329(1)	25(1)

Single crystal X-ray structure (ORTEP) of tricyclic-β-lactone (±)-**4.14t**. The crystals were grown from a concentrated solution of β-lactone (±)-**4.14t** in $CDCl_3$, using a slow evaporation method (probability ellipsoids are shown at the 50% level). X-ray crystallographic data have been deposited in the Cambridge Crystallographic Data Centre database (http://www.ccdc.cam.ac.uk/) under accession code CCDC 940571.



Crystal data and structure refinement for DRB_MS_120913_A3_SS4BL.

Identification code	drb
Empirical formula	C13 H16 O6

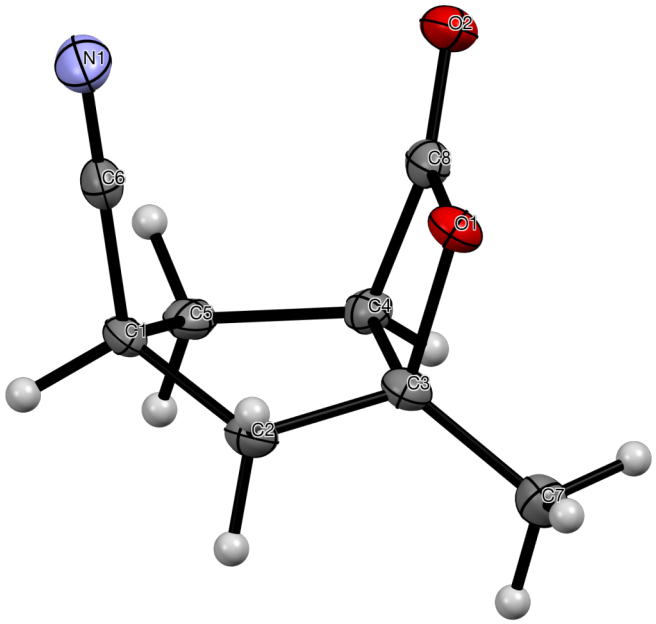
Formula weight	268.26
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2(1)/n
Unit cell dimensions	a = 7.7457(16) Å □= 90°.
	b = 12.057(3) Å □= 98.045(2)°.
	c = 14.063(3) Å □ = 90°.
Volume	1300.4(5) $Å^3$
Z	4
Density (calculated)	1.370 Mg/m^3
Absorption coefficient	0.109 mm^{-1}
F(000)	568
Crystal size	0.18 x 0.17 x 0.11 mm^3
Theta range for data collection	2.23 to 27.49°.
Index ranges	-9<=h<=9, -15<=k<=15, -18<=l<=18
Reflections collected	13565
Independent reflections	2950 [R(int) = 0.0252]
Completeness to theta = 27.49°	99.3 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9881 and 0.9806
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2950 / 0 / 174
Goodness-of-fit on F^2	1.050
Final R indices [I>2sigma(I)]	R1 = 0.0360, wR2 = 0.0952
R indices (all data)	R1 = 0.0420, wR2 = 0.1003
Largest diff. peak and hole	0.329 and -0.174 $e.Å^{-3}$

Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for DRB_MS_120913_A3_SS4BL. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	2877(2)	4445(1)	1736(1)	32(1)
C(2)	3301(2)	4346(1)	2819(1)	25(1)
C(3)	1821(2)	5195(1)	2823(1)	24(1)
C(4)	2657(1)	6276(1)	3221(1)	21(1)
C(5)	2043(2)	6336(1)	4208(1)	27(1)
C(6)	131(2)	5990(1)	3970(1)	32(1)
C(7)	210(2)	4989(1)	3305(1)	33(1)
C(8)	4981(2)	4892(1)	3286(1)	24(1)

C(9)	4642(1)	6153(1)	3192(1)	21(1)
C(10)	5127(2)	6620(1)	2250(1)	22(1)
C(11)	7411(2)	6797(1)	1318(1)	41(1)
C(12)	5673(2)	6792(1)	4024(1)	24(1)
C(13)	6744(2)	8558(1)	4535(1)	47(1)
O(1)	3415(2)	4100(1)	1042(1)	48(1)
O(2)	1518(1)	5163(1)	1754(1)	32(1)
O(3)	4187(1)	7150(1)	1671(1)	30(1)
O(4)	6772(1)	6359(1)	2161(1)	31(1)
O(5)	6208(1)	6396(1)	4790(1)	37(1)
O(6)	5840(1)	7850(1)	3791(1)	34(1)

Single crystal X-ray structure (ORTEP) of bicyclic-β-lactone (±)-**4.14x**. The crystals were grown from a concentrated solution of β-lactone (±)-**4.14x** in $CDCl_3$, using a slow evaporation method (probability ellipsoids are shown at the 50% level). X-ray crystallographic data have been deposited in the Cambridge Crystallographic Data Centre database (http://www.ccdc.cam.ac.uk/) under accession code CCDC 940570.



Alert level B: THETM01_ALERT_3_B The value of sine(theta_max)/wavelength is less than 0.575. Calculated sin(theta_max)/wavelength = 0.5617

Author Response: Data was collected on a Bruker GADDS instrument with Cu-source and MWPC (multiwire proportional counter) detector. Under these experimental conditions the maximum angle that can be collected is 120 degrees two-theta.

Crystal data and structure refinement for DRB_MS_130218_G_RB1.

Identification code	drb
Empirical formula	C8 H9 N O2
Formula weight	151.16
Temperature	110(2) K
Wavelength	1.54178 Å
Crystal system	Monoclinic
Space group	P2(1)/c
Unit cell dimensions	a = 5.6893(5) Å □= 90°. b = 10.7024(11) Å □= 95.454(6)°. c = 12.4002(12) Å □ = 90°.
Volume	751.62(12) $Å^3$
Z	4
Density (calculated)	1.336 Mg/m^3
Absorption coefficient	0.802 mm^{-1}
F(000)	320
Crystal size	0.06 x 0.05 x 0.03 mm^3
Theta range for data collection	5.47 to 60.00°.
Index ranges	-6<=h<=6, 0<=k<=12, 0<=l<=13
Reflections collected	1110
Independent reflections	1110 [R(int) = 0.0000]
Completeness to theta = 60.00°	99.6 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9764 and 0.9535
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1110 / 0 / 101
Goodness-of-fit on F^2	1.013
Final R indices [I>2sigma(I)]	R1 = 0.0460, wR2 = 0.1087
R indices (all data)	R1 = 0.0600, wR2 = 0.1126
Largest diff. peak and hole	0.226 and -0.279 $e.Å^{-3}$

Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for DRB_MS_130218_G_RB1. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	26(3)	3346(1)	3528(1)	20(1)
O(2)	-1888(3)	5167(2)	3834(1)	25(1)
N(1)	-2187(4)	4260(2)	910(2)	29(1)
C(1)	2299(4)	4353(2)	1607(2)	17(1)
C(2)	3130(4)	3186(2)	2264(2)	19(1)
C(3)	2655(4)	3448(2)	3422(2)	18(1)

C(4)	2415(4)	4876(2)	3522(2)	17(1)
C(5)	2834(4)	5426(2)	2420(2)	20(1)
C(6)	-227(4)	4286(2)	1214(2)	20(1)
C(7)	3996(4)	2697(2)	4296(2)	24(1)
C(8)	-138(4)	4594(2)	3664(2)	19(1)

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