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The Rearrangement and Nucleophilic addition of Donor-Acceptor Cyclobutane: Novel Methodologies to Access δ-Lactones and Ring-Opened Products

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A thesis submitted in partial fulfillment of the requirements for the Master of Science degree in Chemistry

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Abstract

Donor-acceptor (D-A) cyclobutanes are a well recognized building block in synthetic organic chemistry thanks to their unique reactivity. A variety of synthetic methodologies such as cycloaddition, rearrangement, and ring-opening addition of D-A cyclobutanes have been reported. Among them, the rearrangement reactions of D-A cyclobutanes have attracted less interest compared with other methodologies as they too often require extreme reaction conditions. To further explore the rearrangement reactions of D-A cyclobutanes, in this work a ring expansion rearrangement reaction of D-A cyclobutanes analogous to the Cloke–Wilson reaction of cyclopropanes was examined. By exploiting the solvent effect in a Brønsted acid system, we successfully acquired the target lactone products in moderate yield (49–65%).

The current work also demonstrated that alkoxy-activated cyclobutanes could undergo a ring-opening and nucleophilic addition to generate nucleophilic substituted products under mild condition with good yield (58–98%). These products are good scaffolds to access cyclic compounds that are commonly found in natural products.

Keywords

Donor-acceptor cyclobutane, rearrangement reaction, solvent effect, Brønsted acid, nucleophilic addition, cyclic compound

Summary for Lay Audience

In modern society, the pharmaceutical and healthcare industries have improved the quality of public health and individual wellbeing. Organic synthesis is one basic area of chemistry that contributes to drug discovery and development. Many organic chemists work to find more efficient and cost-effective synthetic methods to make pharmacophores and drug related molecules.

In the cyclobutane molecule, the carbon bond angles are highly distorted from normal, and as a result cyclobutane becomes reactive. Putting electron-donating and electron-accepting (D-A) functional groups on adjacent carbons further increases reactivity, but in a controlled way that chemists can harness to make new molecules. Various strategies have been developed to transform D-A cyclobutanes into more valuable materials.

Biologically active molecules containing an oxygen atom within a cyclic structure, known as a heterocycle, are common in nature. My research focuses on accessing oxygen-containing heterocycles from D-A cyclobutane as starting materials. Lactone is one of the most common oxygen-containing heterocycles found in drugs and medicinal intermediates. In this thesis, we study the intramolecular oxygen transfer of D-A cyclobutane to access δ-lactone compounds.

Acknowledgments

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I thank my good friends, David, Jennifer, and Jay for the good times in school, giving me valuable advice and interesting research talks. These good friends make my school time more enjoyable filled with memories of funny jokes, chemistry stories and news.

Lastly, I thank my wife Jieun and my adorable children, David, Jason, Aiden and Katherine for their love and support. They motivate and encourage me every single moment of my life as I go to school and carry out research. I would not have finished school without Katherine's smile. They are the energy and inspiration of my life, and I am glad to dedicate this thesis to them.

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List of Abbreviations

Å	Angstrom
A	acceptor
Ac	acetyl
Ar	aryl
Bipy	2,2'-bipyridine
Box	bisoxazoline
Bn	benzyl
D	donor
D-A	donor-acceptor
DABCO	1,4-diazabicyclo[2.2.2]octane
DCE	1,2-dichloroethane
DCM	dichloromethane
DIC	diisopropylcarbodiimide
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
$E^{\oplus}$	electrophile
equiv	equivalent

ee	enantiomeric excess
h	hour(s)
HFIP	1,1,1,3,3,3-hexafluoro-2-propanol
HOTf	trifluoromethanesulfonic acid
Hz	Hertz
L	ligand
LA	Lewis acid
MAD	methylaluminum bis(2,6-di-*tert*-butyl-4-alkylphenoxide)
m-CPBA	*meta*-Chloroperoxybenzoic acid
Me	methyl
Mol	mole(s)
MS	molecular sieve
MTBE	methyl *tert*-butyl ether
NMR	nuclear magnetic resonance
NR	no reaction
NTf	trifluoromethylsulfonyl imide
$Nu^{\ominus}$	nucleophile
OTf	trifluoromethanesulfonate
Ph	phenyl
PBrP	*p*-Bromo phenyl

PMP	*p*-methoxy phenyl
PTSA	*p*-toluenesulfonic acid
rt	room temperature
*t*Bu	*tert*-butyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMSOTf	trimethylsilyl trifluoromethanesulfonate

Chapter 1

1 The Unique Reactivity of Donor-Acceptor Cyclobutane as a Versatile Building Block

1.1 Donor-Acceptor Cyclobutane

1.1.1 Ring Strain of Cyclobutane

Heterocyclic compounds prevail in natural products, biologically active molecules, and pharmaceuticals. As a result, many synthetic studies have been conducted to efficiently access heterocyclic compounds in novel way, ideally in fewer steps with higher yield. Strained cycloalkanes have proven to be highly useful building blocks in synthesis thanks to their unique reactivity.[1] Strained ring systems are remarkably reactive and may allow facile access to complex molecules with good yield. Specifically, highly strained rings can be cleaved under proper conditions, and with a suitable reaction partner the subsequent cyclization or addition reaction can then give the desired heterocyclic compound.

Figure 1. Strain energies of small carbocycles[2]

Cyclobutane is a four-membered carbon ring that adopts a puckered conformation. This conformation avoids the torsion strain from eclipsed hydrogens, although it also reduces the C–C–C bond angles further from ideal and increases the angle strain. Experimentally, cyclobutane has been determined to deviate from planarity by approximately 35° and has a C–C–C bond angle of 88° (Figure 2).[2] Thanks to the high ring strain, cyclobutane can readily cleave its C–C bond and subsequently undergo cyclization or addition reactions.

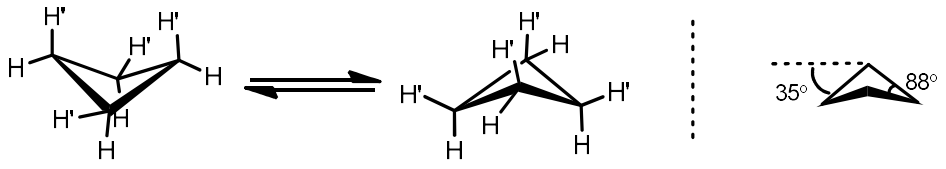


Figure 2. The geometry of the cyclobutane

1.1.2 Reactivity of Donor-Acceptor Cyclobutane with Dipolarophiles

The use of donor-acceptor cyclobutanes (D-A cyclobutanes), a subset of cyclobutanes, in organic synthesis was first reported in 1991.[3] D-A cyclobutanes have different properties compared to normal cyclobutanes in terms of ring cleavage and reactivity. The vicinally substituted electron-donating and electron-withdrawing groups in D-A cyclobutanes work cooperatively to give rise to an electron donating-accepting, or pushing-pulling effect, which facilitates the cleavage of C–C bond to break the ring[4] via heterolytic cleavage that either makes the intermediate molecule susceptible to nucleophilic attack or at the extreme generates a 1,4-zwitterionic intermediate.[5] D-A Cyclobutanes have been shown to undergo a variety of reactions with dipolarophiles (Figure 3). In addition, D-A cyclobutanes can be further activated with a Lewis acid, which likely coordinates with the electron-withdrawing groups.

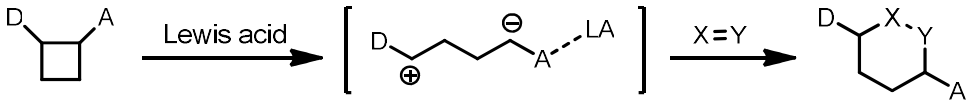
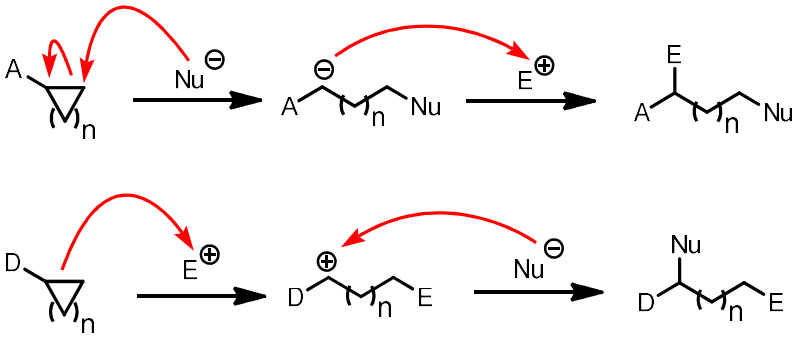


Figure 3. Lewis acid activated D-A cyclobutane and cycloaddition with a generic X=Y dipolarophile

1.1.3 Reactivity of Donor-Acceptor Cycloalkane with Nucleophiles

Alongside the cycloaddition reactions of D-A cycloalkane with dipolarophile, which are now vigorously studied by many organic chemists, the ring-opening reaction of D-A cycloalkane is also a focal point of cycloalkane chemistry.

D-A cycloalkanes can react with both nucleophiles and electrophiles based on their reactivity (Scheme 1). Cycloalkane with an electron-withdrawing group can be opened by a nucleophilic attack and give nucleophile adduct. In contrast, an electron-donating group on the cycloalkane increases the nucleophilicity of the cycloalkane and can attack an electrophile.



Scheme 1. Reactivity of donor- and acceptor-cycloalkane

The nucleophilic additions of D-A cycloalkane have particular synthetic utility because of the abundance of useful nucleophiles, such as indole, aryls, allyls, etc., to give useful products for further elaboration. Nucleophiles can attack D-A cycloalkanes via an S_N2-like pathway. In addition, a suitable catalyst, usually a Lewis acid, can increase the bond polarity in D-A cycloalkane to trigger the ring-opening reaction, in which the zwitterionic intermediate (**1-2**) are neutralized (**1-3**) by a proton transfer (Figure 4).

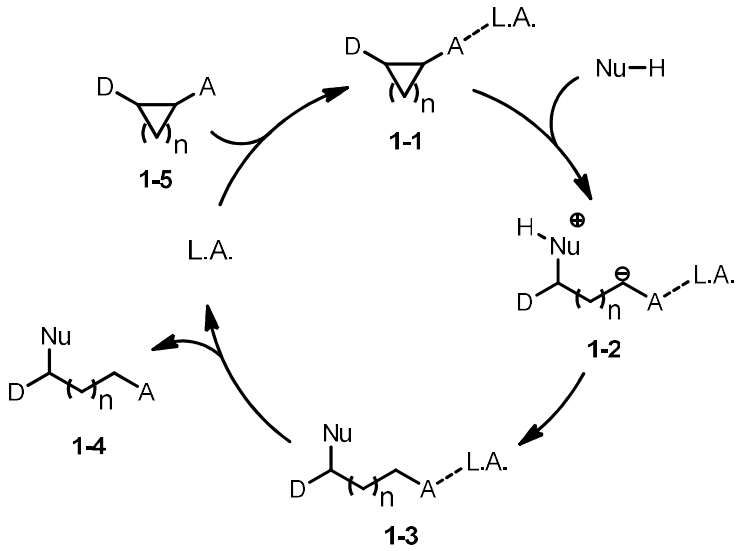


Figure 4. Lewis acid promoted nucleophilic ring-opening reaction of cyclopropane and proton transfer from porotic nucleophile

Chapter 2

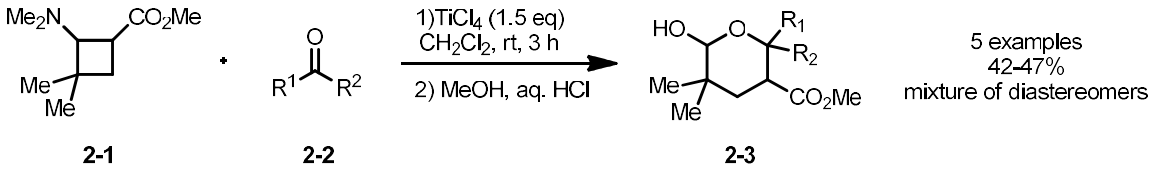
2 Facile Synthesis of δ-Lactone: Ring Expansion of Donor-Acceptor Cyclobutanes Analogously to the Cloke–Wilson Rearrangement

Oxygen-containing heterocycles prevail in natural products, medicinal intermediates, and bio-active molecules. Therefore, many synthetic methodologies have been developed to access *O*-heterocycles from a variety of starting materials. This chapter introduces a new methodology to access δ-lactone, a subset of *O*-heterocycles, from donor-acceptor (D-A) cyclobutanes via a reaction analogous to the Cloke–Wilson rearrangement.

2.1 Introduction

2.1.1 Previous Research on Formal Intermolecular Cycloaddition of D-A Cyclobutanes

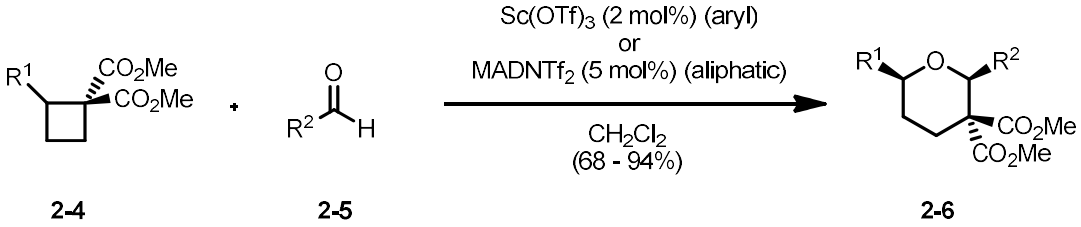
The first intermolecular cycloaddition of D-A cyclobutane was reported by Saigo in 1991.[3] They describe an annulation of D-A cyclobutane with aldehydes and ketone to produce tetrahydropyrans. In this reaction, stoichiometric titanium tetrachloride ($TiCl_4$) was used to afford a diastereomeric mixture of hemiacetal in modest yields after the hydrolysis of the intermediate aminal (**2-3**) (Scheme 2).



Scheme 2. [4+2] cycloaddition of amino-activated cyclobutane and carbonyl compounds

In 1997, Suzuki observed a [4+2] cycloaddition between D-A cyclobutane and 2-oxazoline without the need for a catalyst.[6] The application of D-A cyclobutanes in synthesis then remained dormant, until Johnson[7] and Christie and Pritchard[8] both independently reported the reaction of D-A cyclobutane with aldehydes in 2009. Johnson used scandium(III) trifluoromethanesulfonate, $Sc(OTf)_3$, to catalyze the reaction between D-A cyclobutane and aromatic aldehyde to form tetrahydropyrans (**2-6**) with high yield and high

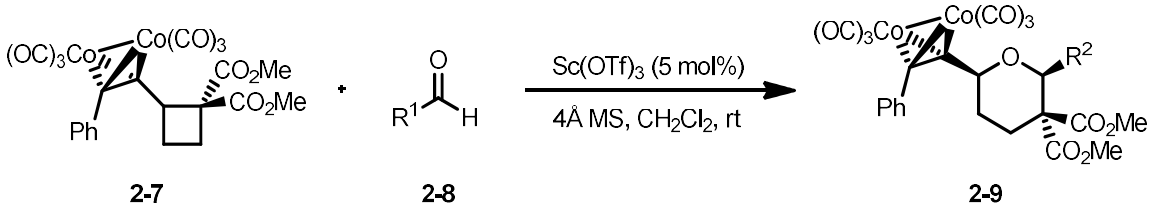
diastereoselectivity. The reaction scope could be extended to aliphatic aldehyde with the use of a more reactive and bulkier Lewis acid, $MADNTf_2$ (Scheme 3).



2-4 **2-5** **2-6**

Scheme 3. Johnson's formal [4+2] dipolar cycloaddition

Christie and Pritchard used a cobalt-alkyne complex as the electron-donating group in the D-A cyclobutane (**2-7**), and $Sc(OTf)_3$ as the Lewis acid to activate the cyclobutane in a Nicholas-type fashion (Scheme 4). The reaction gave good yields, but the scope was limited to electron-rich aromatic aldehydes. Electron-poor aromatic aldehydes gave low yields and aliphatic aldehydes were not reactive.

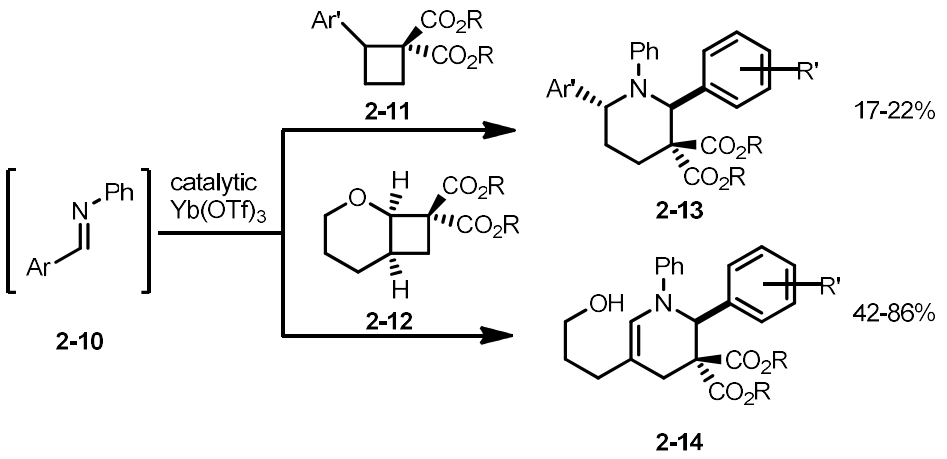


2-7 **2-8** **2-9**

Scheme 4. Christie and Pritchard's cobalt complex D-A cyclobutane and cycloaddition

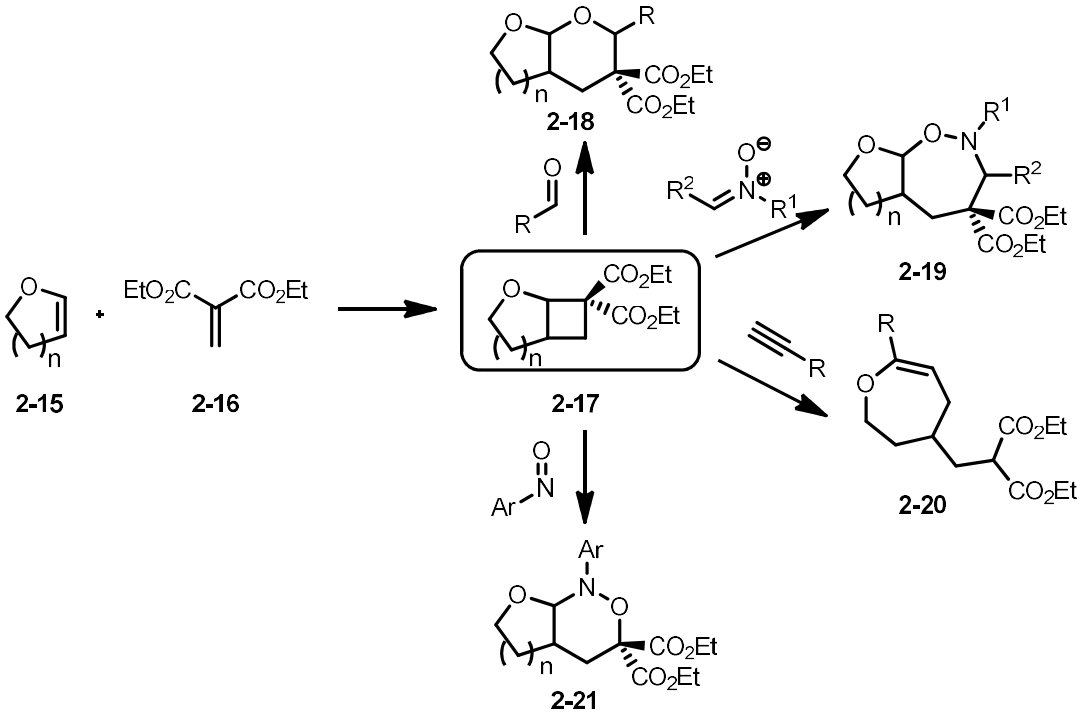
These early works showed that a formal [4+2] cycloadditions of D-A cyclobutane with suitable dipolarophile provide access to other heterocyclic molecules. Synthetic chemists then sought to explore other dipolarophiles and extend the scope of D-A cyclobutane substrates.

The Pagenkopf group developed many examples of D-A cyclobutane cyclization reactions, firstly in 2010 between imine and aryl-substituted D-A cyclobutanes to synthesize piperidines (**2-13, 2-14**)(Scheme 5).[9] Ytterbium(III) trifluoromethanesulfonate, $Yb(OTf)_3$, was used as a Lewis acid. The synthesis of alkoxy-substituted D-A cyclobutanes (e.g. **2-12**) were also developed in this research.



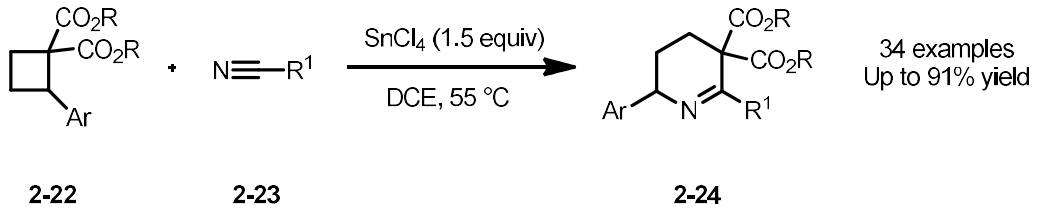
Scheme 5. Formal [4+2] cycloaddition with alkoxy D-A cyclobutanes and imines

The cycloaddition of alkoxy-substituted cyclobutanes was then systematically developed and shown to be highly versatile. Compatible dipolarophiles included aldehydes,[10] terminal alkynes,[11] nitrones,[12] and nitrosoarenes (Scheme 6).[13]



Scheme 6. Yb(OTf)3 catalyzed cycloadditions of alkoxy-substituted cyclobutanes

Most recently, the Pagenkopf group developed the cycloaddition of aryl-substituted cyclobutane with aromatic and aliphatic nitriles mediated by tin(IV) chloride (Scheme 7).[14] Generally speaking, the cyclization reactions between D-A cyclobutanes and dipolarophiles allow facile access to various heterocyclic motifs.



2-22 **2-23** **2-24**

Scheme 7. SnCl4 mediated [4+2] cycloaddition between D-A cyclobutane and nitriles

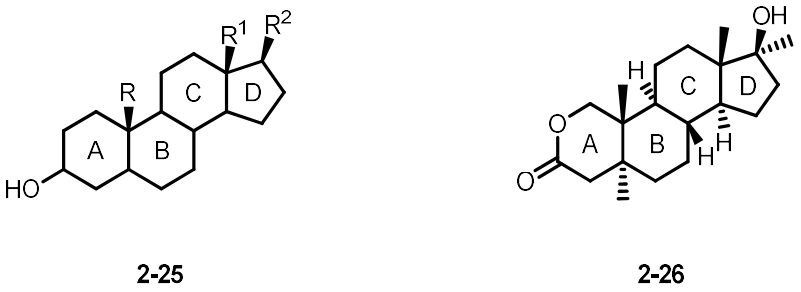
As such, many studies have been reported for cycloaddition of D-A cyclobutane with suitable dipolarophiles. In contrast, the ring-expansion of D-A cyclobutane via single-atom transfer has attracted less interest. The single-atom transfer to the D-A cyclobutane can readily access a variety of heterocycles and broaden the synthetic utility of D-A cyclobutane. Among the heterocycles, we focused on preparing oxygen-containing heterocycles due to their abundance in natural products and bioactive compounds.

2.1.2 Lactones

Lactone is an oxygen-containing heterocycle that contains a 1-oxacycloalkan-2-one structure (Figure 5 right). Naturally produced lactone has a variety of aromas and odors such as fruity, coconut, buttery, sweet, and so on.[15] In addition, lactone is widely used in food additives as a sequestrant, acidifier, and leavening agent because it can slowly hydrolyze to gluconic acid.[16]

Oxandrolone (**2-26**), a drug first made in 1962 and now sold under the brand names Oxandrin and Anavar, has anabolic and androgenic effect. Oxandrolone is structurally similar to steroids and contains a lactone moiety in place of the steroidal all carbon A ring (Figure 5).[17] It can promote muscle growth and accelerate weight gain, and is used to reduce weight loss due to surgery, trauma, or long term use of certain medication.[18] It can be used as a medication for treatment of severe burn injuries.[19] It was also previously used as a muscle booster or a performance enhancing drug in competitive athletics before it was

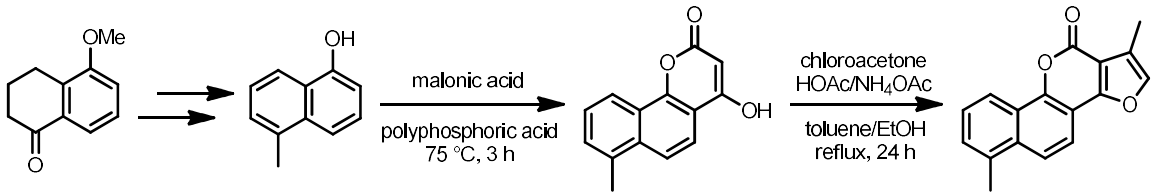
banned by the World Anti-Doping Agency.[20] Side effects of oxadrolone include virilization for females, loss of fertility for males, as well as other common anabolic and androgenic side effects.[21]



2-25 2-26

Figure 5. Structural similarity of general steroid skeleton (left) and oxandrolone (right)

Neo-tanshinlactone (**2-30**) is an antitumor agent[22] extracted from *Salvia miltiorrhiza*, a plant known as red sage, Chinese sage, or danshen.[23] In traditional Chinese medicine, danshen is used to treat coronary heart disease, angina pectoris, and myocardial infarction.[24] In 2004, the Lee group isolated, characterized and synthesized neo-tanshinlactone.[23] They synthesized neo-tanshinlactone by the lactonization of 5-methyl-1-naphthol (**2-28**)[25] followed by alkylation and intramolecular aldolization (Scheme 8).[26]



2-27 2-28 2-29 2-30

Scheme 8. Total synthesis of Neo-tanshinlactone

Camptothecin is a natural product extracted from the bark and stem of *Camptotheca acuminate* and first discovered in 1966 by Wall and Wani.[27] The plant extract containing camptothecin is used for cancer treatment in traditional Chinese medicine. The lactone ring in the compound plays a crucial role in the anti-cancer property of camptothecin because the lactone ring binds to the guanidinium component of arginine with both oxygen atoms serving simultaneously as a hydrogen bonding acceptor. In this way, camptothecin can bind

to topoisomerase and DNA complex (Figure 6).[28] Many analogues of camptothecin have been synthesized in the pursuit for enhanced anti-cancer properties.[29]

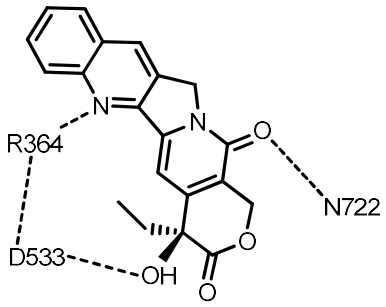


Figure 6. Hydrogen bonding between camptothecin and topoisomerase I

Other pharmaceutically active compounds containing a lactone moiety include artemisinin (anti-malarial),[30,31] lovastatin (a cholesterol lowering statin),[32, 33, 34] mevastatin (a statin), etc (Figure 7).

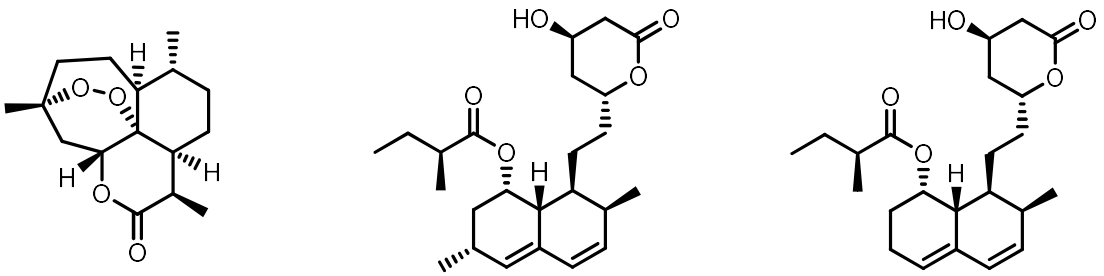


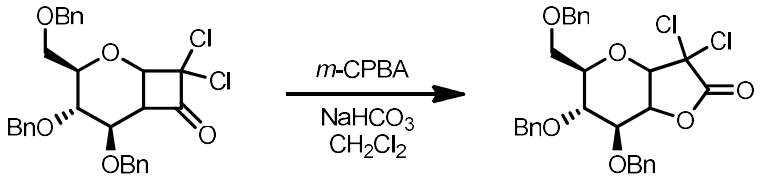
Figure 7. Chemical structures of artemisinin (left), lovastatin (middle), and mevastatin (right)

2.1.3 Access to Lactones via Baeyer–Villiger Oxidation

Baeyer–Villiger oxidation is a widely used reaction to access *O*-containing heterocycles. It uses peroxyacids or peroxides as an oxidant to convert ketones to esters or cyclic ketones to lactones.[35] The Baeyer–Villiger oxidation is widely used because it offers several advantages.[36] The reaction tolerates a number of functional groups in the substrate. Second, the regiochemistry and stereoselectivity can be readily predicted as the more electron rich group migrates with retention of stereochemistry. Third, a wide range of peroxyacid and peroxide can be used as the oxidants. Asymmetric Baeyer–Villiger oxidation is also

possible. However, the Baeyer-Villiger oxidation has a few limitations too. One of the biggest challenges of the oxidation is chemoselectivity. For example, electron-rich alkenes are epoxidized preferentially over ketone oxidation to the ester or lactone.

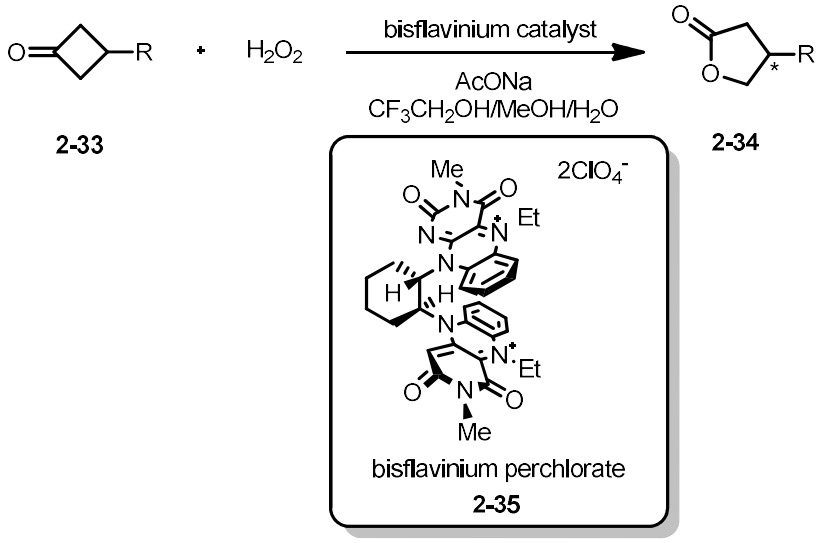
In 1997, Oh developed a method to access bicyclic lactone **2-32** via Baeyer–Villiger oxidation of a cyclobutanone **2-31** (Scheme 9).[37]



2-31 **2-32**

Scheme 9. Synthesis bicyclic lactone **2-32** from C-glucoside via Baeyer–Villiger oxidation

In 2002, Imada developed enantioselective access to lactone (**2-34**) from cyclobutanone via asymmetric Baeyer–Villiger reaction (Scheme 10).[38] Imada's reaction used the planar-chiral organocatalyst bisflavinium perchlorate (**2-35**) for the oxidation of cyclobutanone and gave optically active lactones with up to 74% enantiomeric excess (ee).



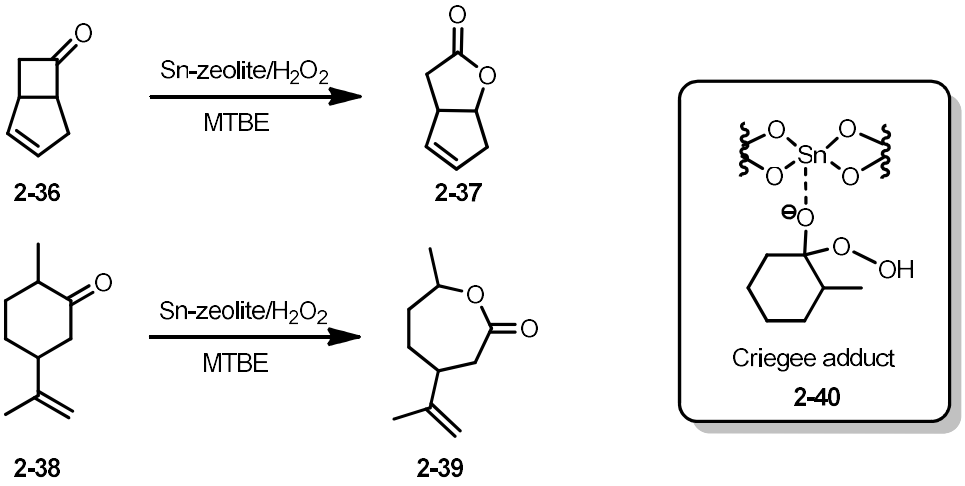
2-33 **2-34**

bisflavinium perchlorate

2-35

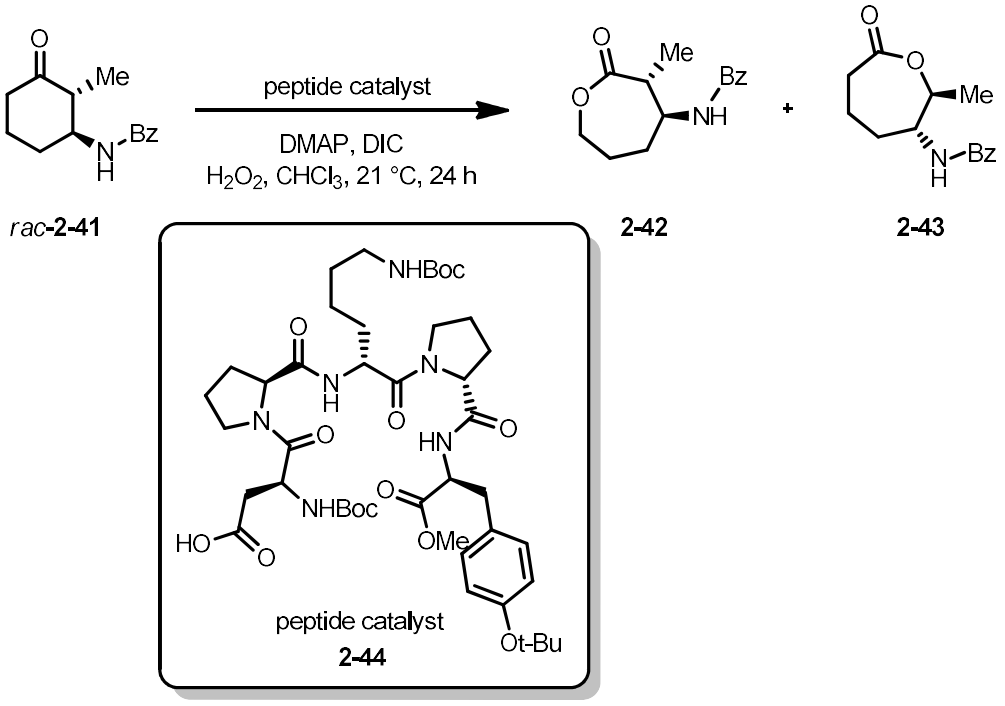
Scheme 10. Enantioselective lactone synthesis via asymmetric Baeyer–Villiger oxidation

In 2001, Corma reported Baeyer–Villiger oxidation reaction using Sn-zeolite beta as a heterogeneous chemoselective catalyst.[39] Interestingly, the zeolite catalyst is used in this work to control the chemoselectivity. The Sn atoms in the zeolite work as a Lewis acid to activate the carbonyl group of the ketone, the catalyst increases the electrophilicity of the carbonyl carbon atom. The hydroperoxide then attacks the more electrophilic carbonyl rather than reacting with the alkene (Scheme 11). Dioxiranes or carbonyl oxides known as 'Criegee adducts' (**2-40**) are generated as the intermediates.[40] Lactones are obtained after rearrangement.



Scheme 11. Chemoselective oxidations using Sn-zeolite and H_2O_2

Peptide-based catalysts have also been used for asymmetric Baeyer–Villiger oxidation. In 2016, the Miller group reported an asymmetric Baeyer–Villiger oxidation of a racemic cyclohexanone (*rac*-**2-41**) where regiochemistry is controlled by interactions between the substrate and the peptide-based catalyst (**2-44**) (Scheme 12).[41] Conformation changes of the peptide catalyst resulting from different hydrogen bonding interactions with the substrate lead to divergent products.

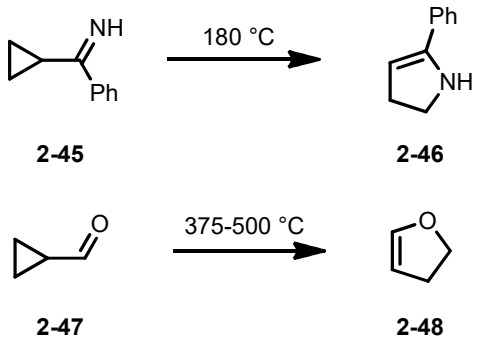


Scheme 12. Stereoselective Baeyer–Villiger oxidation by peptide-based catalyst

The Baeyer–Villiger oxidation has been accomplished for cyclobutanones, which are converted to γ-lactones, but not for other cyclobutanes. To date, the substrate scope of cyclobutane in Baeyer–Villiger oxidation still awaits further exploration.

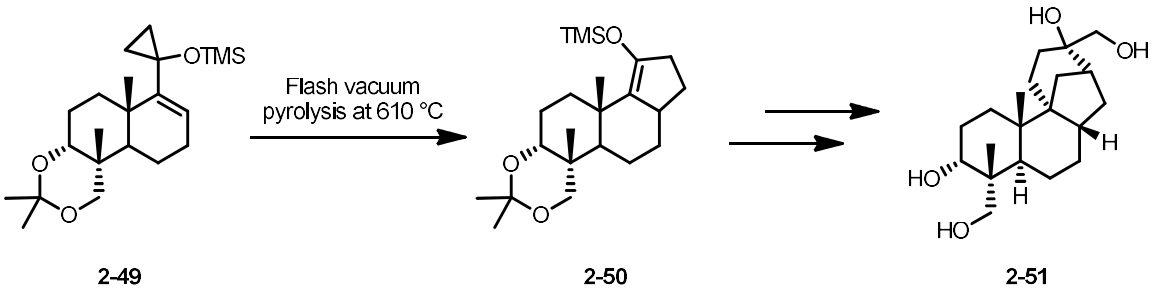
2.1.4 Cloke–Wilson Rearrangement

The Cloke–Wilson rearrangement is a ring expansion reaction that converts a cyclopropylmethanimine, cyclopropylcarbaldehyde, or vinylcyclopropane to a dihydrofuran, pyrroline or cyclopentene, respectively (Scheme 13).[42] Cyclopropane is reactive due to its ring strain, and readily undergoes ring-opening and radical cyclization to form more stable cyclic compounds.[43] The rearrangement was first discovered in 1929 when Cloke observed the transformation of cyclopropyl(phenyl)methanimine (**2-45**) to 5-phenyl-2,3-dihydro-1*H*-pyrrole (**2-46**) at 180 °C (Scheme 13).[44] Wilson extended the scope of the reaction in 1947 and made 2,3-dihydrofuran (**2-47**) from cyclopropanecarbaldehyde (**2-48**).[45] The Cloke-Wilson rearrangement is an effective reaction to form heterocycles that tolerate the high temperatures required.



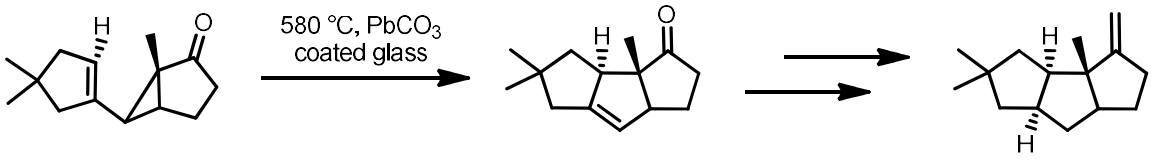
Scheme 13. The cyclopropylimine to pyrroline rearrangement by Cloke (top)
The cyclopropylcarbaldehyde to 2,3-dihydrofuran rearrangement by Wilson (bottom)

After the discoveries of Cloke and Wilson, the analogous vinylcyclopropane rearrangement was developed,[46] and has been used in the total synthesis of natural products. For example, the synthesis of aphidicolin (**2-51**) in 1979 by Trost features the rearrangement of a siloxyvinylcyclopropane to a cyclopentene with 97% yield (Scheme 14).[47]



Scheme 14. Application of vinylcyclopropane rearrangement for aphidicolin total synthesis

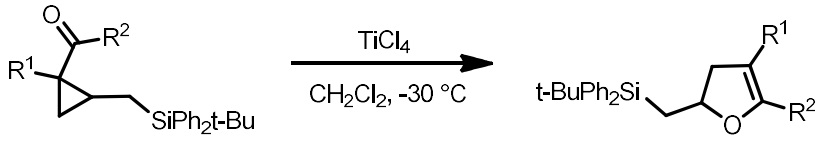
Another example is the total synthesis of hirsutene (**2-54**) by Hudicky in 1980 where a vinyl cyclopropane is converted to the corresponding cyclopentene (Scheme 15).[48] This conversion was also efficiently achieved at the remarkably high temperature of 580 °C.



2-52 2-53 2-54

Scheme 15. Application of vinylcyclopropane rearrangement for hirsutene total synthesis

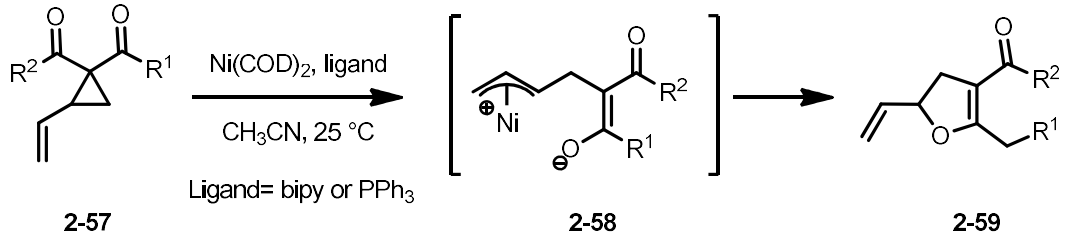
Much effort has been dedicated to obviating the high temperatures required in the Cloke–Wilson rearrangement. In 2001, Yadav reported a $TiCl_4$-mediated rearrangement reaction that proceeds at –30 °C (Scheme 16).[49] The silicon group stabilized an intermediate carbocation that is formed from ring opening then 5-*exo-trig* cyclization of the titanium enolate generates the dihydrofuran product (**2-56**).



2-55 2-56

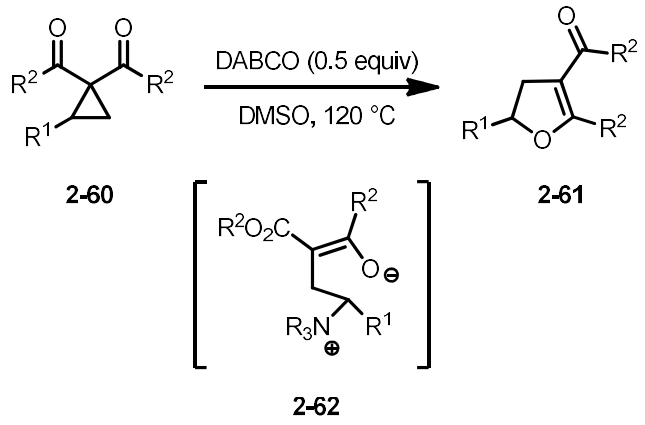
Scheme 16. TiCl4-mediated silicon assisted rearrangement

In 2006, the Johnson group reported a nickel-catalyzed Cloke–Wilson rearrangement of vinylcyclopropanes at ambient temperature under mild reaction conditions (Scheme 17).[50] Under transition metal catalysis, the cyclopropane ring is opened to form a π-allyl intermediate (**2-58**), which then undergoes the rearrangement to give the dihydrofuran product (**2-59**). Other Lewis acids and bases could also catalyze the reaction, but the nickel catalyst was the most efficient in terms of catalyst loading, reaction time, and functional group tolerance.



Scheme 17. Nickel-catalyzed rearrangement of cyclopropane

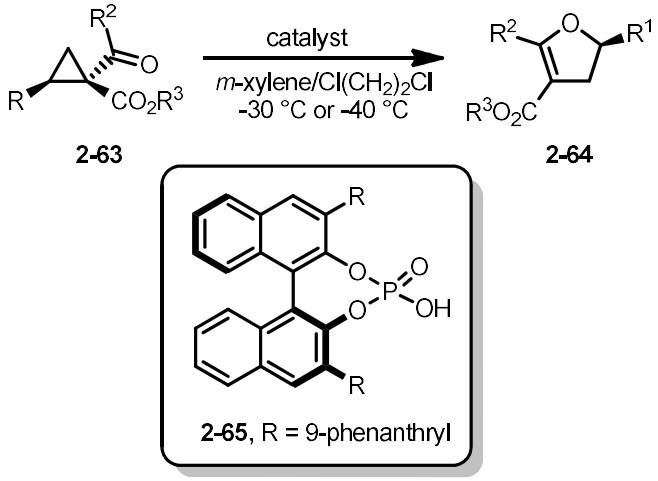
In 2017, Xu accomplished an organocatalytic Cloke–Wilson rearrangement of cyclopropyl ketones (**2-60**) to dihydrofuran (**2-61**) under mild conditions and with broad substrate scope in good yield (Scheme 18).[51] The authors propose initial nucleophilic attack of DABCO on the cyclopropane forms enolate **2-62**, which then undergoes a 5-*exo-tet* cyclization to generate the product and release the catalyst. Stereochemical analysis of reaction products from enantiomerically enriched cyclopropane **2-60** showed almost complete loss of stereochemical integrity. Therefore, a carbocation-like intermediate and S_N1-type ring closing mechanism is proposed for the rearrangement.



Scheme 18. DABCO-catalyzed Cloke–Wilson rearrangement of cyclopropane

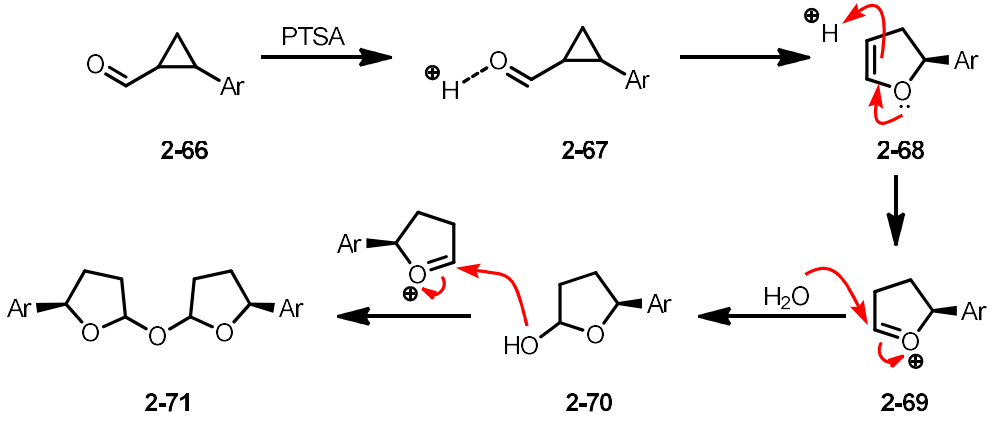
In 2018, the Vicario group reported an enantioselective Cloke–Wilson rearrangement mediated by a chiral phosphoric acid (**2-65**) (Scheme 19). [52] The corresponding dihydrofuran compounds (**2-64**) have been acquired from racemic cyclopropane starting materials (**2-63**) by the use of chiral catalyst **2-65** through a dynamic kinetic asymmetric transformation (DYKAT). The phosphoric acid triggers the D-A cyclopropane ring opening to generate an enol and benzylic cation intermediate. Hydrogen bonding between

the phosphate and the enol moiety and ionic bonding between the phosphate and the carbocation provide a well-organized environment to produce optically enriched products.



Scheme 19. Catalytic enantioselective Cloke–Wilson rearrangement

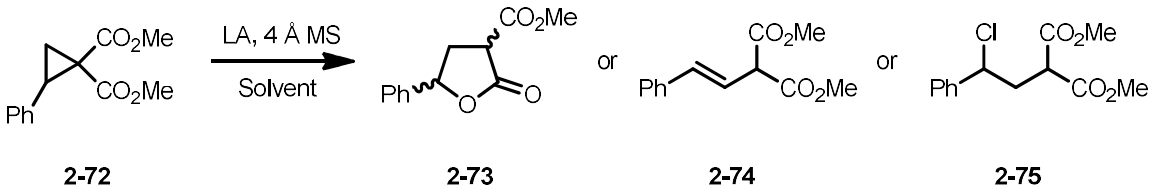
In 2020, the Banerjee group reported a metal-free transformation of cyclopropane carbaldehydes (**2-66**) to oxy-bis(2-aryltetrahydrofuran) derivatives (**2-71**) via a domino Cloke–Wilson rearrangement-hydration-dimerization (Scheme 20).[53] The reaction is catalyzed by *p*-toluenesulfonic acid and conducted in an open flask, which is cost-effective and user-friendly.



Scheme 20. Cloke–Wilson rearrangement-hydration-dimerization reaction of cyclopropane

2.1.5 Intramolecular Oxygen Transfer of Cyclopropanes to Prepare γ-Lactone

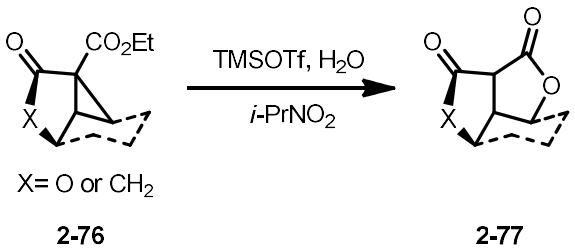
In 2010, the Melnikov group reported the Lewis acid-catalyzed isomerization of 2-arylcyclopropane-1,1-dicarboxylates.[54] In screening the reaction conditions, they found that three different compounds could be acquired (Scheme 21). The presence of a strong Lewis acid in the reaction produced γ-butyrolactone (**2-73**), isomeric propene (**2-74**), and chloride adduct ring-opened compounds (**2-75**). Lactone formation was dominant when $BF_3 \cdot Et_2O$ or $SnCl_4$ was used. The lactone is formed via the intramolecular attack of the ester carbonyl oxygen on the benzylic carbon atom followed by hydrolysis. The transformation of cyclopropane into the isomeric propene was the most efficient in the presence of TMSOTf. The ring-opened chloride adduct was dominant when $TiCl_4$ was used as the Lewis acid. This result showed that with the use of a suitable Lewis acid the reaction favors intramolecular rearrangement



2-72 **2-73** **2-74** **2-75**

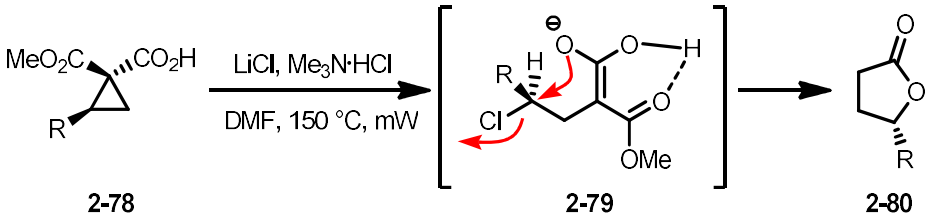
Scheme 21. Lewis acid-catalyzed reaction of D-A cyclopropane

In 2013, the Corey group reported an acid-catalyzed rearrangement of cyclopropane **2-76** to γ-lactone **2-77** (Scheme 22).[55] Treatment of cyclopropane with trimethylsilyl triflate (TMSOTf) and water (to generate some triflic acid) in *i*-$PrNO_2$ produced a γ-lactone compound at ambient temperature. The reaction tolerates fused functional groups on the cyclopropane and gives a good (60% – 86%) yield.



Scheme 22. Acid-catalyzed cyclopropyl ester to γ-lactone rearrangement

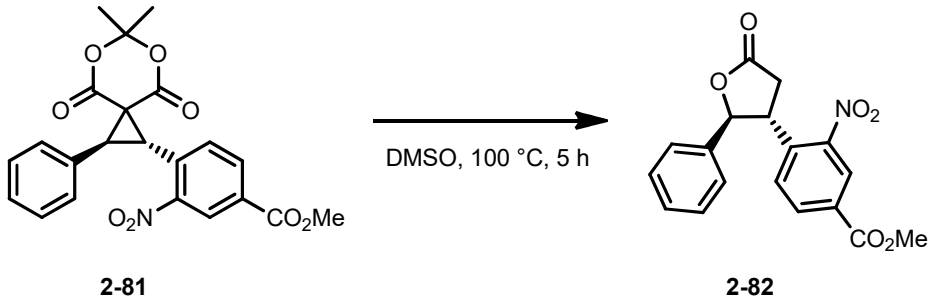
In 2013, the Kerr group reported an interesting rearrangement reaction of hemimalonate cyclopropane (**2-78**) (Scheme 23).[56] The hydrogen bonding of the hemimalonate moiety helps induce ring cleavage event and generates a zwitterionic intermediate. Then the zwitterionic intermediate easily undergoes a trivial conformational change that allows the enolate oxygen to attack thereby closing the ring to a lactone. Stereochemical retention of configuration is observed in this transformation because it is likely that the carbocation and enolate moieties remain in close proximity as a tight ion pair, and recombination to the product occurs faster than stereochemical scrambling of the carbocation. In the presence of nucleophilic halides, the same tight ion pair blocks one face of the carbocation, such that the halide attacks with inversion of stereochemistry at the benzylic carbon (Scheme 23, **2-80**). Subsequent displacement of the halide by the nucleophilic enolate again inverts the stereochemistry, and the overall double displacement sequence also results in retention of stereochemistry. Both reaction pathways produce a γ-lactone (**2-80**) as a mixture of diastereomers. Subsequent Krapcho dealkoxycarbonylation gives a butanolide product.



Scheme 23. Synthesis of butanolides with cyclopropane hemimalonate

In 2020, the Chang group described a thermal decarboxylative Cloke–Wilson rearrangement to afford γ-butyrolactones (**2-82**) (Scheme 24).[57] No catalyst or additive was

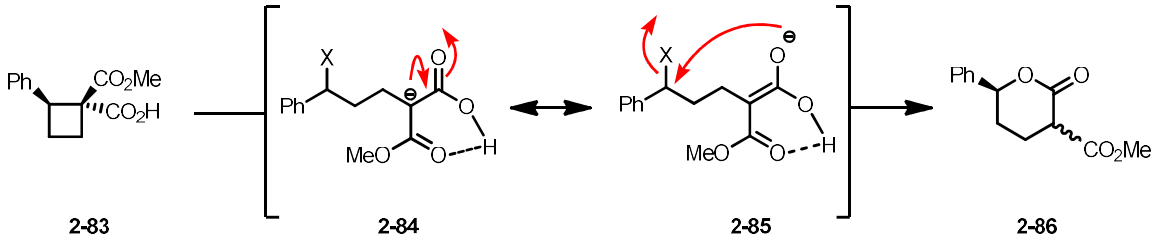
used and the rearrangement of cyclopropane was activated by heating in DMSO. The thermal rearrangement shows high efficiency and stereoselectivity.



Scheme 24. Thermal decarboxylative Cloke–Wilson rearrangement of cyclopropane to γ-butyrolactone

2.1.6 Research Plan

Cyclopropanes and cyclobutanes have shown similar reactivity thanks to their comparable ring strain.[1,2,4] Despite the successes in preparing γ-lactone via intramolecular oxygen transfer, similar transformations with cyclobutanes to give δ-lactones have not been reported. Therefore, in this work, we investigate the conversion of hemimalonate cyclobutanes (**2-83**) to δ-lactones (**2-86**) via an intramolecular oxygen transfer reaction that is homologous to the Cloke–Wilson rearrangement (Scheme 25).



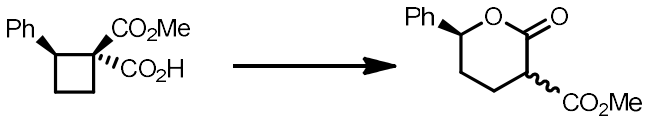
Scheme 25. Proposed reaction for intramolecular oxygen transfer of D-A cyclobutane

2.2 Result and Discussion

2.2.1 Initial Explorations

An initial attempt for the ring expansion of hemimalonate cyclobutane was conducted without any additives. We expected the hemimalonate cyclobutane can generate an internal hydrogen bond, however, the reaction didn't occur and only the starting material had been observed. Based on the result of the initial attempt, internal hydrogen bonding was not strong enough to activate the cyclobutane by S_N1-type pathway. However, the addition of a metal halide (in this case LiI) promotes the reaction through an S_N2-type pathway and successfully generated the desired product but in low yield (Table 1).

Table 1. Optimization of reaction condition of intramolecular rearrangement of hemimalonate cyclobutane

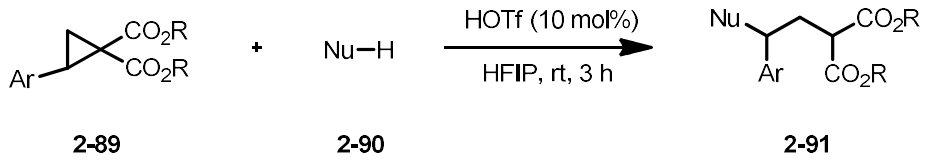


2-87 **2-88**

Reagent	Stoichiometry	Reaction temperature (°C)	Solvent	Result
None	n/a	65	HFIP	NR
LiI	2.0 equiv	rt	HFIP	NR
LiI	2.0 equiv	55	HFIP	12%
LiI	2.0 equiv	65	HFIP	16%
LiI	2.0 equiv	75	HFIP	16%
LiI	2.0 equiv	85	HFIP	19%
LiI	2.0 equiv	40	CH_2Cl_2	NR
LiI	1.5 equiv	65	HFIP	16%

NaI	2.0 equiv	55, 65, 75, 85	HFIP	trace
KI	2.0 equiv	65	HFIP	trace
Bu_4NI	2.0 equiv	65	HFIP	13%
Bu_4NBr	2.0 equiv	65	HFIP	trace
LiCl	2.0 equiv	65	HFIP	5%

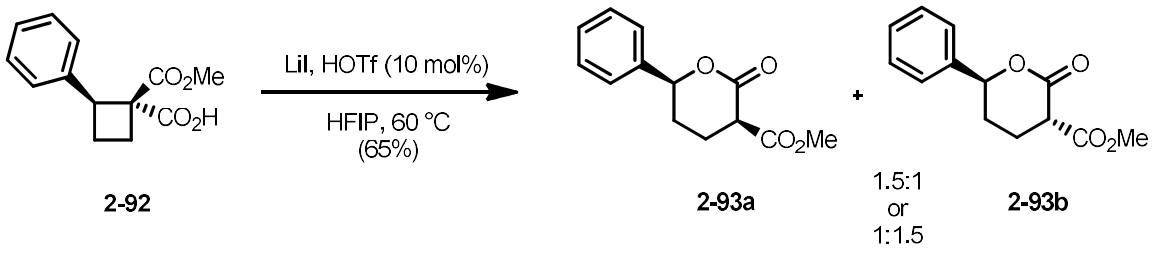
In 2018, the Moran group showed that the strong Brønsted acid in hexafluoroisopropanol HFIP enhances the efficiency of nucleophilic ring-opening reactions with D-A cyclopropanes (**2-89**). [58] The HOTf/HFIP system increases the polarization of the cyclopropane C–C bond, which makes the benzylic carbon more susceptible to nucleophilic attack (Scheme 26). These results inspired us to try the same conditions with our cyclobutanes.



2-89 **2-90** **2-91**

Scheme 26. Nucleophile ring opening reaction using HOTf/HFIP system

Gratifyingly, addition of 10 mol% HOTf to the ring opening reaction of the D-A cyclobutane increased the yield of the lactone product. The cyclobutane (**2-92**) was successfully transformed into the δ-lactone product **2-93** with a 65% yield as a 1.5:1 diastereomeric mixture (Scheme 27).



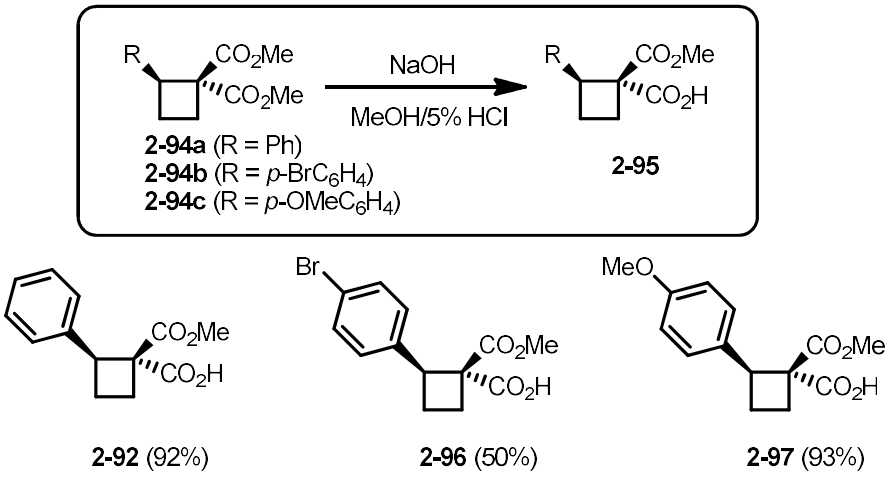
2-92 **2-93a** **2-93b**

Scheme 27. Transformation of hemimalonate D-A cyclobutane to δ-lactones

This optimized reaction condition has a few advantages. First, the reaction does not require the use of exogeneous Lewis acid or transition metal catalyst, but uses a Brønsted acid. This is a cost-effective because the transition metal catalyst is usually more expensive than Brønsted acid catalyst (ie, $Sc(OTf)_3$: \$67/g (\$32.97/mmol), HOTf: \$3.62/g (\$0.54/mmol)).[59] Also, the reaction can be conducted under a mild condition at 60 °C in 3 h.

2.2.2 Scope

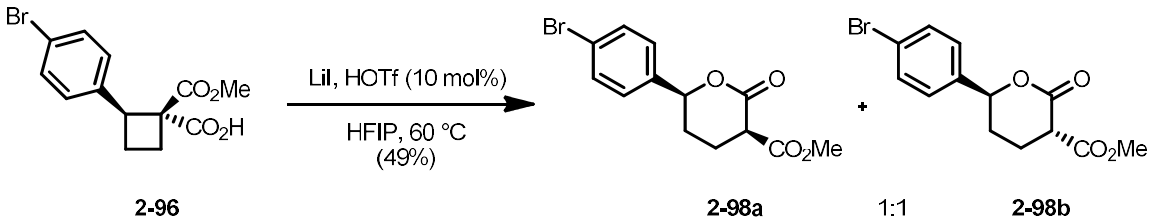
With our optimal conditions for the cyclobutane rearrangement, we then attempted to broaden the reaction scope with additional hemimalonate cyclobutanes. The hemimalonate was obtained by saponification with NaOH and acidifications with 5% HCl (Scheme 28). The ester *trans* to the donor group underwent saponification, which is the same selectivity observed with the analogous cyclopropane diester.[60] In particular, the phenyl-appended cyclobutane diester was hydrolyzed to the hemimalonate (**2-92**), and the spectra matched reported values.[7]



Scheme 28. Hydrolysis of cyclobutane diesters

We further investigated the rearrangement by exploring electron-poor aryl groups on the D-A cyclobutane. We firstly introduced a *p*-bromophenyl group in the D-A cyclobutane and under the standard conditions a 1:1 diastereomeric mixture of product (**2-98**) was

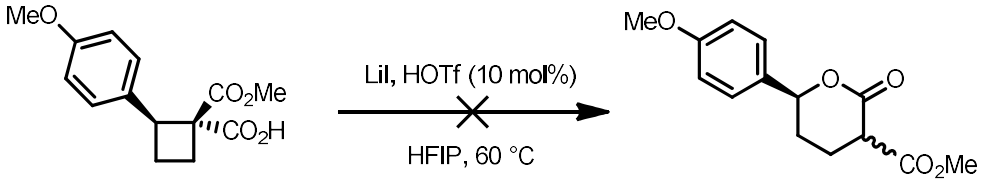
obtained with a 49% yield (Scheme 29), which is a lower yield than that obtained with phenyl cyclobutane (**2-93**) (65%).



2-96 **2-98a** 1:1 **2-98b**

Scheme 29. Rearrangement reaction of p-bromo phenyl appended cyclobutane

Next, the phenyl donor group was replaced with *p*-methoxy phenyl (**2-97**) to increase the electron donating ability of the phenyl group. However, the *p*-phenyl donor appears to be too electron rich as no product was obtained under the optimized reaction condition (Scheme 30).



2-97 **2-99**

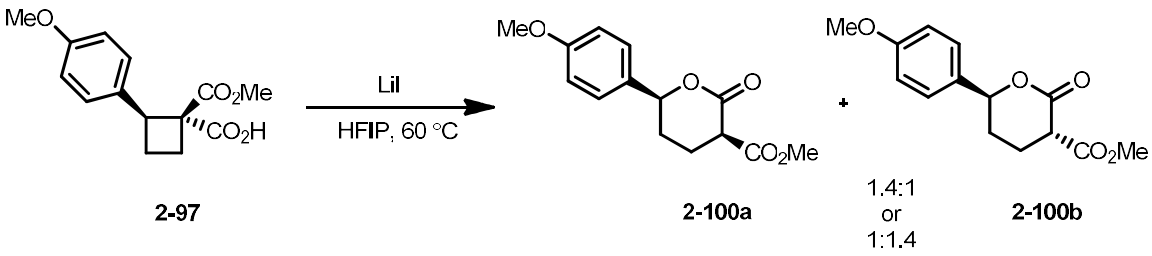
Scheme 30. Failure attempt of HOTf/HFIP system with methoxy appended cyclobutane

The *p*-methoxy phenyl substituent increases the electron density of the aromatic ring and enhances electron donation to the D-A cyclobutane. Therefore, cyclobutane is generally more reactive and ring cleavage can happen more easily. *p*-Methoxybenzyl alcohol is known to undergo rapid ionization and substitution,[61] and the desired lactone product, if formed, is going to be unstable and readily hydrolyzed.

Based on our preliminary Lewis acid screening, cyclobutane is easily decomposed with the use of strong Lewis acid. Similarly, through hydrogen bonding the HOTf/HFIP system increases the electron-withdrawing effect of the acceptor group on the cyclobutane, while simultaneously decreasing their nucleophilicity toward the intermediate carbocation. Alternatively, the Brønsted acid can deactivate the electron donating group by protonating

the methoxy group of the aryl donor. With both vicinal functional groups being electron deficient, the anticipated mode of reactivity with cooperative donating and accepting groups becomes inaccessible.

We then tested the reaction of *p*-methoxy phenyl substituted cyclobutane (**2-97**) at a lower temperature to decrease the cyclobutane decomposition, but the desired reaction outcome was still not observed. We then hypothesized that the methoxy group may be strong enough to activate the reactant without the HOTf catalyst that was necessary for the preceding examples. As a result, by skipping the addition of HOTf to the reaction system, the methoxy appended cyclobutane underwent the intended rearrangement in 43% yield as a 1.4:1 diastereomeric mixture (**2-100**).



Scheme 31. Rearrangement reaction of p-methoxy phenyl appended cyclobutane without HOTf

2.2.3 Mechanistic Discussion

The ring-opening step of the reaction is aided by iodide and intramolecular hydrogen bonding. A nucleophilic attack by iodide to the hemi-malonate gives the ring-opened intermediate. Simultaneously, intramolecular hydrogen bonding increases the electron-withdrawing effect of the acceptor group and accelerates the ring cleavage of cyclobutane. More interestingly, the electronegative fluorines in HFIP make it a good solvent for hydrogen bonding, which may increase the electron-withdrawing effect of the acceptor. Also, HFIP can coordinate with and stabilize the ring-opened intermediate (Figure 8).[62]

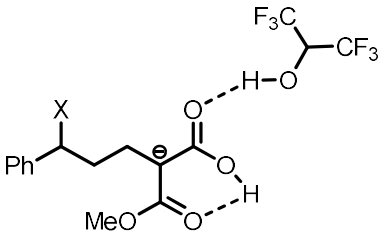


Figure 8. Hydrogen bond of HFIP with ring-opened intermediate

Specifically, it has been speculated that the HOTf activation by protonation is enhanced by stabilization of the triflate anion by the HFIP solvent (Figure 9).[63]

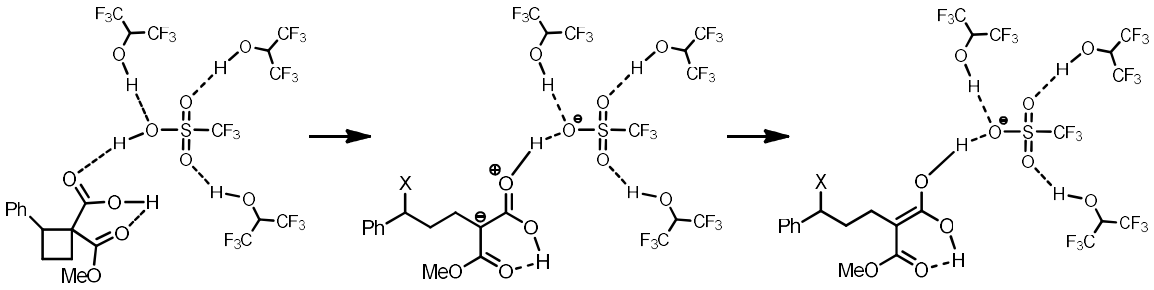


Figure 9. HOTf/HFIP system to enhance the pulling effect of acceptor group

In addition, the HOTf/HFIP system is believed to stabilize the ring-opened transition states (Figure 10). According to the DFT study by the Zhang group in 2020,[63] three HFIP molecules interact with HOTf through hydrogen bonding. The net effect of the three HFIP molecules significantly reduces the energy level of the transition state, thus a lower energy reaction pathway becomes available.

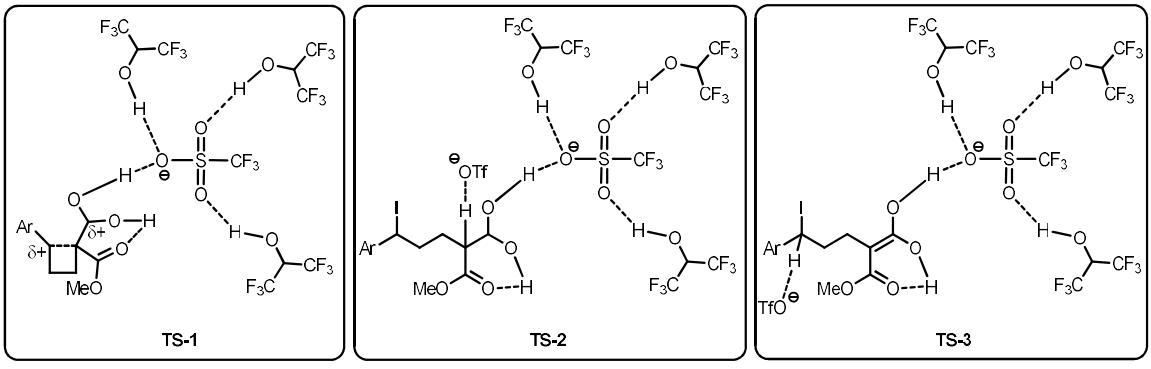
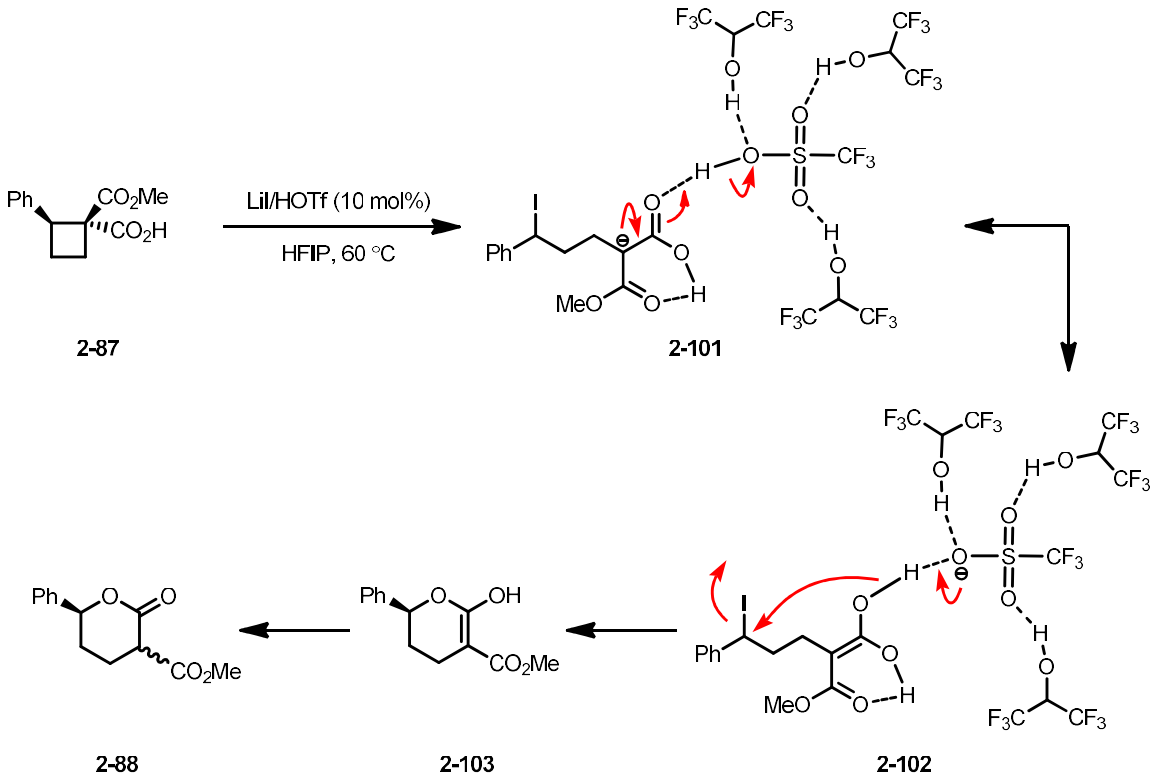


Figure 10. Three different transition states of the reaction

The HOTf/HFIP system catalyzes the transformation of hemimalonate cyclobutane to the δ-lactone product. HOTf/HFIP first coordinates with the hemimalonate to increase the electron withdrawing effect of the acceptor group in the D-A cyclobutane. Alternatively, the iodide ion cleaves the cyclobutane via S_N2 type attack. Once opened, an intramolecular oxygen attack gives enol **2-103** and the tautomer of δ-lactone **2-88** (Scheme 32). This mechanism predicts a mixture of stereoisomers where the initial stereochemistry is set during the tautomerization step. However, structures such as these undergo facile epimerization therefore the ratio of *cis* and *trans* diastereomers obtained is the thermodynamic ratio. Consistent with epimerization is that it proved impossible to separate these diastereomers by chromatography.



Scheme 32. Proposed mechanism of the rearrangement of hemi-malonate cyclobutane under HOTf/HFIP system

2.3 Conclusion and Future Work

We investigated a ring expansion reaction of D-A cyclobutane that was inspired by the Cloke–Wilson rearrangement. The developed reaction was performed in the HOTf/HFIP solvent system. HOTf coordinates with the hemimalonate D-A cyclobutane and increases the electron-withdrawing effect of the acceptor group to cleave a C–C bond. In addition, HFIP enhances reactivity by hydrogen bonding. The combined effect of HOTf/HFIP is very powerful to enhance the pulling effect of the acceptor group, so D-A cyclobutane with a strong donor can easily fragment and decompose. The HOTf/HFIP system likely protonates strong electron donating groups resulting in a reactivity umpolung. In the absence of HOTf the reaction proceeded in HFIP alone to give the desired product.

At this point in the research we were unable to broaden the reaction scope with more examples due to the lab shutdown during the COVID-19 pandemic period. To date we completed three examples covering a span of electron donating abilities, from the poorly electron donating *p*-bromophenyl, to an electronically neutral phenyl, to an electron rich *p*-methoxy phenyl, and developed optimized conditions for these reactions. This work will be suitable for publication once additional examples are optimized and compiled.

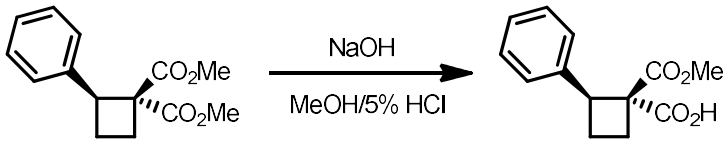
2.4 Experimental

2.4.1 General Synthetic Method

All reactions were run under an inert atmosphere (argon or nitrogen) and flasks were oven-dried and cooled in a desiccator prior to use. All chemicals used were of reagent grade and were obtained from commercial sources (Sigma Aldrich, Alfa Aesar or Oakwood chemical). HFIP was purified by the distillation and stored in a Schlenk flask. The progress of reaction was monitored by thin layer chromatography (TLC, SilicaPlate TLC Aluminum Backed TLC 200 μm) visualized under UV light (254 nm), and plates were also stained with ceric ammonium molybdate (CAM). [64] Standard column chromatography was performed using silica gel purchased from silicycle Chemical Division Inc. (Silicycle SiliaFlash P60, 40-63 μm, 60Å).

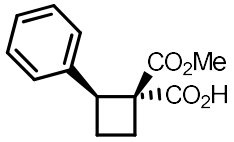
^{1}H NMR and ^{13}C NMR spectra were acquired on 400 and 600 MHz spectrometers (Bruker 400, Varian Inova 400 and Inova 600) in deuterated chloroform. ^{1}H NMR spectra were referenced to the residual proton signal in deuterated chloroform at δ 7.26 ppm. ^{13}C NMR spectra were referenced to deuterated chloroform at the center peak of the triplet at δ 77.16(t) ppm. Coupling constant '*J*' is in Hz. The peak multiplicities are described using the abbreviations as follows: s = singlet, d = doublet, t = triplet, dd = doublet of doublets, dt = doublet of triplet, m = multiplet, app = apparent. High resolution mass spectra (HRMS) were obtained on a Thermo Scientific DFS spectrometer at an ionizing voltage of 70 eV. Infrared Spectra (IR) were acquired using a Bruker FTIR spectrometer ALPHA II.

2.4.2 Procedure and Characterization Data for Hemimalonate Cyclobutanes



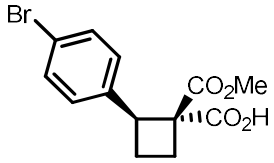
Hemimalonate D-A cyclobutanes were prepared using a literature procedure.[60, 65] To an oven-dried round-bottomed flask equipped with a magnetic stir bar were added sequentially the cyclobutane (1.0 equiv, 4.03 mmol, 1000 mg), MeOH (3 mL), and 10 N NaOH (1.2 equiv, 4.83 mmol, 0.48 mL). The reaction solution was stirred for 12 h at room temperature, and then diluted with ethyl acetate (20 mL) and water (20 mL). The aqueous layer was collected and extracted with ethyl acetate again to remove unreacted cyclobutane. The aqueous layer was acidified with 5% HCl to reach pH 2 and extracted with ethyl acetate (3 × 20 mL). The combined organic phases were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure to give the title product (872 mg, 92% yield) suitable for use without further purification.

(1S*,2S*)-1-(methoxycarbonyl)-2-phenylcyclobutanecarboxylic acid (2-92)



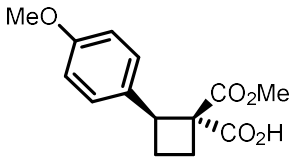
The title compound (**2-92)** was prepared through D-A cyclobutane hydrolysis to afford a white solid (873 mg, 92%). $\mathbf{R_f}$ = 0.41 (69% hexane, 30% ethyl acetate, and 1% acetic acid); **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.35-7.20 (m, 5H), 4.36 (dd, *J* = 9.1, 9.1 Hz, 1H), 3.33 (s, 3H), 2.74-2.64 (m, 2H), 2.53-2.44 (m, 1H), 2.26-2.19 (m, 1H); **^{13}C NMR (101 MHz, CDCl$_3$)** δ 176.0, 170.3, 138.6, 128.2, 127.4, 127.2, 59.3, 52.2, 46.1, 25.2, 20.6; **IR** (cm^{-1}) 2951, 1741, 1692, 1451, 1284, 768; **mp** 133-135 °C; **HRMS** (EI) m/z [M$^+$] 234.0893 (calculated for $C_{13}H_{14}O_4$ 234.0892).

(1S*,2S*)-2-(4-bromophenyl)-1-(methoxycarbonyl)cyclobutanecarboxylic acid (2-96)



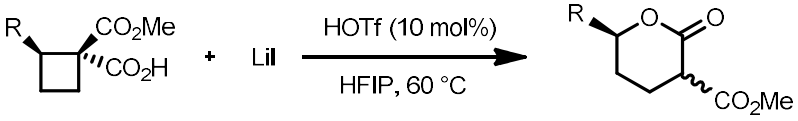
The title compound (**2-96**) was prepared from **2-94b** (0.96 mmol, 315 mg) according to the general hydrolysis procedure to afford a pale-orange solid (152 mg, 50%). $\mathbf{R_f}$ = 0.54 (69% hexane, 30% ethyl acetate, and 1% acetic acid); **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.41 (app d, *J* = 8.4 Hz, 2H), 7.16 (app d, *J* = 8.3 Hz, 2H), 4.29 (dd, *J* = 9.6, 9.6 Hz, 1H), 3.36 (s, 3H), 2.74-2.57 (m, 2H), 2.46-2.39 (m, 1H), 2.24-2.16 (m, 1H); **^{13}C NMR (101 MHz, CDCl$_3$)** δ 177.1, 169.5, 137.8, 131.2, 129.3, 121.1, 59.4, 52.3, 44.9, 25.6, 20.7; **IR** (cm^{-1}) 2953, 1740, 1700, 1242, 778; **mp** 99-101 °C.

(1S*,2S*)-1-(methoxycarbonyl)-2-(4-methoxyphenyl)cyclobutanecarboxylic acid (2-97)



The title compound (**2-97**) was prepared from **2-94c** (0.9 mmol, 250 mg) according to the general hydrolysis procedure to afford a white solid (222 mg, 93%). $\mathbf{R_f}$ = 0.48 (69% hexane, 30% ethyl acetate, and 1% acetic acid); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.18 (app d, *J* = 8.4 Hz, 2H), 6.83 (app d, *J* = 8.7 Hz, 2H), 4.28 (dd, *J* = 9.1, 9.1 Hz, 1H), 3.79 (s, 3H), 3.39 (d, *J* = 1.5 Hz, 3H), 2.69-2.62 (m, 2H), 2.57-2.46 (m, 1H), 2.25-2.17 (m, 1H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 175.2, 170.8, 158.8, 130.6, 128.6, 113.6, 59.3, 55.3, 52.4, 46.2, 24.8, 21.0; **IR** (cm^{-1}) 2949, 1746, 1694, 1410, 1175, 747; **mp** 115-117 °C; **HRMS** (EI) m/z [M^+] 264.0998 (calculated for $C_{14}H_{16}O_5$ 264.0998).

2.4.3 Procedure and Characterization Data for δ-Lactones



General reaction procedure A

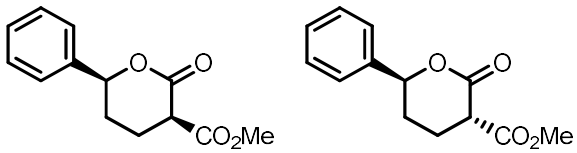
To an oven-dried tube equipped with a stir bar were added sequentially the hemimalonate D-A cyclobutane (1.0 equiv, 0.3 mmol, 70 mg) and lithium iodide (1.5 equiv, 0.45 mmol, 60 mg). The tube was sealed with a rubber septum and then flushed with argon. 1,1,3,3,3-hexafluoro-2-propanol (HFIP) (1 mL) was added by syringe to the sealed tube through the septum and the mixture was stirred at room temperature. A separate oven-dried round-bottomed flask equipped with a magnetic stir and rubber septum was flushed with argon, and then trifluoromethanesulfonic acid (10 mol%, 0.03 mmol, 2.6 μL) and HFIP (0.5 mL) were added. The prepared trifluoromethanesulfonic acid solution was slowly added to the sealed tube by cannula, and the resulting mixture was stirred at 60 °C for 3 h. Water was added and the resulting mixture was extracted with diethyl ether (3 × 15 mL). The

combined organic layer was washed with brine, dried over sodium sulfate and concentrated under reduced pressure. The residual material was purified by flash chromatography (69% hexane, 30% ethyl acetate, and 1% acetic acid) to give the product.

General reaction procedure B

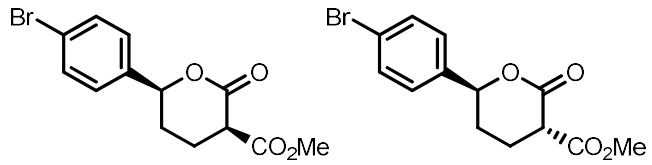
To an oven-dried tube equipped with a stir bar under argon atmosphere were added sequentially hemi-malonate cyclobutane (1.0 equiv, 0.3 mmol, 70 mg) and lithium iodide (1.5 equiv, 0.45 mmol, 60 mg). The tube was sealed, flushed with argon, and HFIP (1.5 mL) was added by syringe. The mixture was stirred at 60 °C for 3 h, water was added and the resulting mixture was extracted with diethyl ether (3 × 15 mL). The combined organic extracts were washed with brine, dried over sodium sulfate and concentrated under reduced pressure. The residual material was purified by flash chromatography (69% hexane, 30% ethyl acetate, and 1% acetic acid) to give the product.

Methyl 2-oxo-6-phenyltetrahydro-2*H*-pyran-3-carboxylate (2-93)



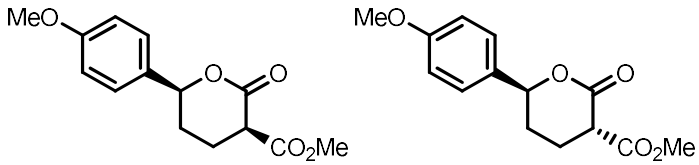
The title compounds (**2-93**) were prepared through general procedure A to afford a pale-yellow oil (45 mg, 65%). $\mathbf{R}_f$ = 0.36 (69% hexane, 30% ethyl acetate, and 1% acetic acid); The product is obtained as a 1.5:1 mixture of diastereomers based on integration of the benzylic methine ^{1}H NMR signal. **^{1}H NMR (600 MHz, CDCl$_3$)** major diastereomer δ 7.40-7.33 overlap (m, 5H), 5.38 (dd, *J* = 10.6, 3.6 Hz, 1H), 3.82 (s, 3H), 3.72 (dd, *J* = 7.4, 7.4 Hz, 1H), 2.40-2.33 overlap (m, 1H), 2.29-2.15 overlap (m, 2H), 2.10-1.91 overlap (m, 1H); minor diastereomer δ 7.40-7.33 overlap (m, 5H), 5.42 (dd, *J* = 10.9, 2.8 Hz, 1H), 3.83 (s, 3H), 3.63 (dd, *J* = 9.3, 7.3 Hz, 1H), 2.40-2.33 overlap (m, 1H), 2.29-2.15 overlap (m, 2H), 2.10-1.91 overlap (m, 1H); **^{13}C NMR (150 MHz, CDCl$_3$)** diastereomeric mixture δ 169.7, 169.5, 167.5, 166.7, 128.7, 128.5, 125.8, 125.7, 82.1, 81.8, 53.0, 52.9, 47.6, 46.2, 29.6, 28.5, 23.1, 21.9; **IR** (cm^{-1}) 2954, 1726, 1154, 961, 699; **HRMS** (EI) m/z [M$^+$] 233.0806 (calculated for $C_{13}H_{14}O_4$ 234.0892).

Methyl 6-(4-bromophenyl)-2-oxotetrahydro-2*H*-pyran-3-carboxylate (2-98)



The title compounds (**2-98**) were prepared through general procedure A to afford a pale-orange oil (15 mg, 49%). $\mathbf{R}_f$ = 0.51 (69% hexane, 30% ethyl acetate, and 1% acetic acid); The product is obtained as a 1:1 mixture of diastereomers based on integration of the benzylic methine ^{1}H NMR signal. **^{1}H NMR (600 MHz, CDCl$_3$)** diastereomer A δ 7.53-7.51 overlap (m, 2H), 7.25-7.22 overlap (m, 2H), 5.38 (dd, *J* = 11.0, 3.0 Hz, 1H), 3.83 (s, 3H), 3.63 (dd, *J* = 9.2, 7.2 Hz, 1H), 2.40-2.32 overlap (m, 1H), 2.29-2.14 overlap (m, 2H), 2.05-1.98 overlap (m, 1H); diastereomer B δ 7.53-7.51 overlap (m, 2H), 7.25-7.22 overlap (m, 2H), 5.33 (dd, *J* = 10.7, 3.6 Hz, 1H), 3.82 (s, 3H), 3.71 (dd, *J* = 7.5, 7.5 Hz, 1H), 2.40-2.32 overlap (m, 1H), 2.29-2.14 overlap (m, 2H), 2.05-1.98 overlap (m, 1H); **^{13}C NMR (101 MHz, CDCl$_3$)** diastereomeric mixture δ 169.8, 169.2, 143.2, 131.6, 127.6, 121.5, 73.3, 73.2, 61.6, 52.5, 51.5, 36.5, 29.7, 25.0, 14.1; **IR** (cm^{-1}) 2925, 1673, 1461, 1182, 830.

Methyl 6-(4-methoxyphenyl)-2-oxotetrahydro-2*H*-pyran-3-carboxylate (2-100)



The title compounds (**2-100**) were prepared through general procedure B to afford a pale-yellow oil (11 mg, 43 %). $\mathbf{R}_f$ = 0.38 (69% hexane, 30% ethyl acetate, and 1% acetic acid); The product is obtained as a 1.4:1 mixture of diastereomers based on integration of the benzylic methine ^{1}H NMR signal. **^{1}H NMR (400 MHz, CDCl$_3$)** major diastereomer δ 7.30-7.27 overlap (app dd, *J* = 8.8, 6.8 Hz, 2H), 6.92-6.89 overlap (app dd, *J* = 8.8, 1.6 Hz, 2H), 5.32 (dd, *J* = 10.0, 4.0 Hz, 1H), 3.82 overlap (s, 3H), 3.81 overlap (s, 3H), 3.71 (dd, *J* = 7.4, 7.4 Hz, 1H), 2.39-2.32 overlap (m, 1H), 2.26-2.19 overlap (m, 1H), 2.14-1.89 overlap (m, 2H); minor diastereomer δ 7.30-7.27 overlap (app dd, *J* = 8.8, 6.8 Hz, 2H), 6.92-6.89 overlap (app dd, *J* = 8.8, 1.6 Hz, 2H), 5.37 (dd, *J* = 11.0, 3.0 Hz, 1H), 3.82 overlap (s, 3H),

3.81 overlap (s, 3H), 3.61 (dd, J = 9.3, 7.4 Hz, 1H), 2.39-2.32 overlap (m, 1H), 2.26-2.19 overlap (m, 1H), 2.14-1.89 overlap (m, 2H); **^{13}C NMR (101 MHz, $CDCl_3$)** diastereomeric mixture δ 169.6, 167.7, 159.8, 127.4, 127.3, 114.1, 82.1, 81.7, 55.3, 53.0, 52.9, 47.7, 46.1, 29.5, 28.3, 23.1, 21.9; **IR** (cm^{-1}) 3378, 2926, 1705, 1370, 1181, 1040, 830.

2.5 References

[1] Namyslo, J. C.; Kaufmann, D. E. The Application of Cyclobutane Derivatives in Organic Synthesis. *Chem. Rev.* **2003**, *103*, 1485–1537.

[2] Wiberg, K. B. The Concept of Strain in Organic Chemistry. *Angew. Chem. Int. Ed.* **1986**, *25*, 312–322.

[3] Shimada, S.; Saigo, K.; Nakamura, H.; Hasegawa, M. Novel [4+2]-Type Reaction of 2-(Dimethylamino)Cyclobutanecarboxylic Esters with Carbonyl Compounds. *Chem. Lett.* **1991**, *20*, 1149–1152.

[4] De Nanteuil, F.; De Simone, F.; Frei, R.; Benfatti, F.; Serrano, E.; Waser, J. Cyclization and Annulation Reactions of Nitrogen-Substituted Cyclopropanes and Cyclobutanes. *Chem. Commun.* **2014**, *50*, 10912–10928.

[5] Matsuo, J. I. 1,4-Zwitterionic Intermediates Formed by Cleavage of a Cyclobutane Ring and Their Cycloaddition Reactions. *Tetrahedron Lett*. **2014**, *55*, 2589–2595.

[6] Yokozawa, T.; Tagami, M.; Takehana, T.; Suzuki, T. Synthesis of Terpolymers by Spontaneous Copolymerization of the Cyclobutane Adducts of Electron-Acceptor Olefins and Vinyl Ether with 2- Oxazolines. *Tetrahedron* **1997**, *53*, 15603–15616.

[7] Parsons, A. T.; Johnson, J. S. Formal [4 + 2] Cycloaddition of Donor-Acceptor Cyclobutanes and Aldehydes: Stereoselective Access to Substituted Tetrahydropyrans. *J. Am. Chem. Soc.* **2009**, *131*, 14202–14203.

[8] Allart, E. A.; Christie, S. D. R.; Pritchard, G. J.; Elsegood, M. R. J. Preparation of Highly Substituted Tetrahydropyrans via a Metal Assisted Dipolar Cycloaddition Reaction. *Chem. Commun.* **2009**, *47*, 7339–7341.

[9] Moustafa, M. M. A. R.; Pagenkopf, B. L. Ytterbium Triflate Catalyzed Synthesis of Alkoxy-Substituted Donor-Acceptor Cyclobutanes and Their Formal [4 + 2] Cycloaddition with Imines: Stereoselective Synthesis of Piperidines. *Org. Lett.* **2010**, *12*, 4732–4735.

[10] Moustafa, M. M. A. R.; Stevens, A. C.; Machin, B. P.; Pagenkopf, B. L. Formal [4 + 2] Cycloaddition of Alkoxy-Substituted Donor−Acceptor Cyclobutanes and Aldehydes Catalyzed by $Yb(OTf)_3$. *Org. Lett.* **2010**, *12*, 4736–4738.

[11] Machin, B. P.; Pagenkopf, B. L. $BF_3 \cdot OEt_2$-Catalyzed Reaction of Donor-Acceptor Cyclobutanes with Terminal Alkynes: Single-Step Access to 2,3-Dihydrooxepines. *Synlett* **2011**, 2799–2802.

[12] Stevens, A. C.; Palmer, C.; Pagenkopf, B. L. The Formal [4+3] Cycloaddition between Donor-Acceptor Cyclobutanes and Nitrones. *Org. Lett.* **2011**, *13*, 1528–1531.

[13] Vemula, N.; Stevens, A. C.; Schon, T. B.; Pagenkopf, B. L. The [4+2] Cycloaddition of Donor-Acceptor Cyclobutanes and Nitrosoarenes. *Chem. Commun.* **2014**, *50*, 1668–1670.

[14] Tong, D.; Wu, J.; Bazinski, N.; Koo, D.; Vemula, N.; Pagenkopf, B. L. Synthesis of Functionalized Tetrahydropyridines by $SnCl_4$-Mediated [4+2] Cycloaddition between Donor–Acceptor Cyclobutanes and Nitriles. *Chem. Eur. J.* **2019**, *25*, 15244–15247.

[15] Maga, J. A.; Katz, I. Lactones in foods. *Crit. Rev. Food. Sci. Nutr*. **1976**, *8*, 1–56.

[16] Guo, S.; Ono, T. The Role of Composition and Content of Protein Particles in Soymilk on Tofu Curding by Glucono-δ-lactone or Calcium Sulfate. *J. Food Sci*. **2005**, *70*, C258–C262.

[17] Pappo, R.; Jung, C. J. 2-Oxasteroids: A New Class of Biologically Active Compounds. *Tetrahedron Lett*. **1962**, *9*, 365–371.

[18] Orr, R.; Singh, M. F. The Anabolic Androgenic Steroid Oxandrolone in the Treatment of Wasting and Catabolic Disorders. *Drug* **2004**, *64*, 725–750.

[19] Demling, R. H.; Orgill, D. P. The Anticatabolic and Wound Healing Effects of the Testosterone Analog Oxandrolone After Severe Brun Injury. *J. Crit. Care*. **2000**, *15*, 12–17.

[20] Geyer, H.; Schanzer, W.; Thevis, M. Anabolic agents: recent strategies for their detection and protection from inadvertent doping. *Br J. Sports. Med*. **2014**, *48*, 820–826.

[21] Wit, J. M.; Oostdijk, W. Novel approaches to short stature therapy. *Best. Pract. Res. Cl. En.* **2015**, *29*, 353–366.

[22] Banerji, B.; Killi, S. K.; Katarkar, A.; Chatterje, S.; Tangella, Y.; Prodhan, C.; Chaudhuri, K. Neo-tanshinlactone D-ring modified novel analogues induce apoptosis in human breast cancer cell via DNA damage. *Bioorg. Med. Chem*. **2017**, *25*, 202–212.

[23] Wang, X.; Bastow, K. F.; Sun, C.; Lin, Y.; Yu, H.; Don, M.; Wu, T.; Nakamura, S.; Lee, K. Antitumore Agents. 239. Isolation, Structure Elucidation, Total Synthesis, and Anti-Breast Cancer Activity of Neo-tanshinlactone from *Salvia miltiorrhiza*. *J. Med. Chem*. **2004**, *47*, 5816–5819.

[24] Ryu, S. Y.; Lee, C. O.; Choi, S. U. In vitro cytotoxicity of tanshinones from *Salvia miltiorrhiza*. *Planta Med*. **1997**, *63*, 339–342.

[25] Kamijo, H.; Takido, T.; Nakazawa, T.; Itabashi, K.; Seno, M. Synthesis of 3-hydroxy-1H-phenalen-1-ones from methylthio-naphtalenes with malonic acids. *Nippon Kagaku Kaishi* **1993**, *11*, 1257–1262.

[26] Risitano, F.; Grassi, G.; Foti, F.; Bilardo, C. A convenient synthesis fo furo[3,2-c]coumarins by a tandem alkylation/intramolecular aldolization reaction. *Tetrahedron Lett*. **2001**, *42*, 3505–3505.

[27] Wall, M. E.; Wani, M. C.; Cook, C. E.; Palmer, K. H.; McPhail, A. T.; Sim, G. A. Plant Antitumor Agents. I. The Isolation and Structure of Camptothecin, a Novel Alkaloidal Leukemia and Tumore Inhibitor from Camptotheca acuminata. *J. Am. Chem. Soc*. **1966**, *88*, 3888–3890.

[28] Pommier, Y. Topoisomerase I inhibitors: camptothecins and beyond. *Nature Review Cancer* **2006**, *6*, 789–802.

[29] (a) Adams, D. J.; Dewhirst, M. W.; Flowers, J. L.; Gamcsik, M. P.; Colvin, O. M.; Manikumar, G.; Wani, M. C.; Wall, M. E. Camptothecin analogues with enhanced antitumor activity at acidic pH. *Cancer Chemother Pharmacol* **2000**, *46*, 263–271. (b) Fan, Y.; Shi, L. M.; Kohn, K. W.; Pommier, Y.; Weinstein, J. N. Quantitative Structure-Antitumor Activity Relationships of camptothecin Analogues: Cluster Analysis and Genetic Algorithm-Based Studies. *J. Med. Chem*. **2001**, *44*, 3254–3263.

[30] Klayman, D. L. Qunghaosu (Artemisinin): An Antimalarial Drug from China. *Science* **1985**, *228*, 1049–1055.

[31] Tu, Y. Artemisinin–A Gift from Traditional Chinese Medicine to the World (Nobel Lecture). *Angew. Chem. Int. Ed*. **2016**, *55*, 10210–10226.

[32] Henwood, J. M.; Heel, R. C. Lovastatin. A Preliminary Review of its Pharmacodynamic Properties and Therapeutic use in Hyperlipidaemia. *Drugs* **1988**, *36*, 429–454.

[33] Alberts, A. W. Discovery, biochemistry and biology of lovastatin. *American Journal of Cardiology* **1988**, *62*, J10–J15.

[34] (a) Hirama, M.; Uei, M. A chiral total synthesis of compactin. *J. Am. Chem. Soc*. **1982**, *104*, 4251–4253. (b) Hirama, M.; Iwashita, M. Total synthesis of (+)-monacoli K (mevinolin). *Tetrahedron Lett*. **1983**, *24*, 1811–1812.

[35] Kürti, L.; Czako, B. Strategic Applications of named reactions in Organic Synthesis. Elsevier Academic Press: Burlington, San Diego, London, 2005; pp 28.

[36] Brink, G. J.; Arends, I. W. C. E.; Sheldon, R. A. The Baeyer-Villiger Reaction: New Developments toward Greener Procedures. *Chem. Rev*. **2004**, *103*, 4105–4123.

[37] Oh, J. Synthesis of α-D-C-Glucoside Employing Dichloroketene Cycloaddition and Baeyer-Villiger Oxidation. *Tetrahedron Lett.* **1997**, *38*, 3249–3250.

[38] Murahashi, S.-I.; Ono, S.; Imada, Y. Asymmetric Baeyer-Villiger Reaction with Hydrogen Peroxide Catalyzed by a Novel Planar-Chiral Bisflavin. *Angew. Chem. Int. Ed.* **2002**, *41*, 2366–2368.

[39] Corma, A.; Nemeth, L. T.; Renz, M.; Valencia, S. Sn-zeolite beta as a heterogeneous chemoselective catalyst for Baeyer-Villiger oxidations. *Nature* **2001**, *412*, 423–425.

[40] Schweitzer-Chaput, B.; Kurten, T.; Klussmann, M. Acid-Mediated Formation of Radicals or Baeyer–Villiger Oxidation from Criegee Adducts. *Angew. Chem. Int. Ed*. **2015**, *54*, 11848–11851.

[41] Abascal, N. C.; Miller, S. J. Solution Structures and Molecular Associations of a Peptide-Based Catalyst for the Stereoselective Baeyer-Villiger Oxidation. *Org. Lett*. **2016**, *18*, 4646–4649.

[42] Hudlicky, T.; Reed, J. W. From Discovery to Application: 50 Years of the Vinylcyclopropane-Cyclopentene Rearrangement and Its Impact on the Synthesis of Natural Products. *Angew. Chem. Int. Ed*. **2010**, *49*, 4864–4876.

[43] Hudlicky, T.; Kutchan, T. M.; Naqvi, S. M. The vinylcyclopropane-cyclopentene rearrangement. *Org. React*. **1985**, *33*, 247–335.

[44] Cloke, J. B. The Formation of Pyrrolines From Gamma-Chloropropy and Cyclopropyl Ketimines. *J. Am. Chem. Soc*. **1929**, *51*, 1174–1187.

[45] Wilson, C. L. Reactions of Furan Compounds. VII. Thermal Interconversion of 2,3-Dihydrofuran and Cyclopropane Aldehyde. *J. Am. Chem. Soc*. **1947**, *69*, 3002–3004.

[46] Baldwin, J. E. Thermal Rearrangements of Vinylcyclopropanes to Cyclopentenes. *Chem. Rev*. **2003**, *103*, 1197–1212.

[47] Trost, B. M.; Nishimura, Y.; Yamamoto, K. A total synthesis of aphidicolin. *J. Am. Chem. Soc*. **1979**, *101*, 1328–1330.

[48] Hudlicky, T.; Kutchan, T. M.; Wilson, S. R.; Mao, D. T. Total Synthesis of (±)-Hirsutene. *J. Am. Chem. Soc*. **1980**, *102*, 6351–6353.

[49] Yadav, V. K.; Balamurugan, R. Silicon-Assisted Ring Opening of Donor-Acceptor substituted Cyclopropanes. An Expedient Entry to Substituted Dihydrofurans. *Org. Lett*. **2001**, *3*, 2717–2719.

[50] Bowman, R. K.; Johnson, J S. Nickel-Catalyzed rearrangement of 1-Acyl-2-vinylcyclopropanes. A Mild synthesis of Substituted Dihydrofurans. *Org. Lett*. **2006**, *8*, 573–576.

[51] Zhang, J.; Tang, Y.; Wei, W.; Wu, Y.; Li, Yang.; Zhang, J.; Zheng, Y.; Xu, S. Organocatalytic Cloke-Wilson Rearrangement: DABCO-Catalyzed Ring Expansion of Cyclopropyl Ketones to 2,3-Dihydrofurans. *Org. Lett*. **2017**, *19*, 3043–3046.

[52] Ortega, A.; Manzano, R.; Uria, U.; Carrillo, L.; Reyes, E.; Tejero, T.; Merino, P.; Vicario, J. L. Catalytic Enantioselective Cloke-Wilson Rearrangement. *Angew. Chem. Int. Ed*. **2018**, *57*, 8225–8229.

[53] Dey, R.; Rajput, S.; Banerjee, P. Metal-free domino Cloke-Wilson rearrangement-hydration-dimerization of cyclopropane carbaldehydes: A facile access to oxybis(2-aryltetrahydrofuran) derivatives. *Tetrahedron* **2020**, *76*, 131080.

[54] Chagarovskiy, A. O.; Ivanova, O. A.; Rakhmankulov, E. R.; Budynina, E. M.; Trushkov, I. V.; Melnikov, M. Y. Lewis Acid-Catalyzed Isomerization of 2-

Arylcyclopropane-1,1- Dicarboxylates: A New Efficient Route to 2-Styrylmalonates. *Adv. Synth. Catal.* **2010**, *352*, 3179–3184.

[55] Newhouse, T. R.; Kaib, P. S. J.; Gross, A. W.; Corey, E. J. Versatile Approaches for the Synthesis of Fused-Ring γ-Lactones Utilizing Cyclopropane Intermediates. *Org. Lett*. **2013**, *15*, 1591–1593.

[56] Grover, H. K.; Emmett, M. R.; Kerr, M. A. γ-Substituted Butanolides from Cyclopropane Hemimalonates: An Expedient Synthesis of Natural (*R*)-Dodecan-4-Olide. *Org. Lett.* **2013**, *15*, 4838–4841.

[57] Zhang, M.; Li, T.; Cui, C.; Song, X.; Chang, J. Stereoselective Sequential Spirocyclopropanation/Cloke–Wilson Rearrangement Reactions for Synthesis of *trans*-β, γ-Disubstituted γ-Butyrolactones Using Alkylidene Meldrum's Acid and Benzyl Halides. *J. Org. Chem*. **2020**, *85*, 2266–2276.

[58] Richmond, E.; Vukovic, V. D.; Moran, J. Nucleophilic Ring Opening of Donor-Acceptor Cyclopropanes Catalyzed by a Brønsted Acid in Hexafluoroisopropanol. *Org. Lett*. **2018**, *20*, 574–577.

[59] Sigma Aldrich Canada. Trifluoromethanesulfonic acid SKU-Pack Number: 347817-500G. Scandium(III) triflate SKU-Pack Number: 418218-5G. $Sc(OTf)_3$: \$67/g, HOTf: \$3.62/g. Each reaction required 10 mol% of catalyst, which is 14.76 mg of $Sc(OTf)_3$, and 4.5 mg of HOTf. Therefore, \$0.99 per reaction with $Sc(OTf)_3$, and \$0.016 per reaction with HOTf.

[60] Perreault, C.; Goudreau, S. R.; Zimmer, L. E.; Charette. A. B. Cycloadditions of Aromatic Azomethine Imines with 1,1-Cyclopropane Diesters. *Org. Lett.* **2008**, *10*, 689–692.

[61] Wuts, P. G. M.; Greene, T. W. Greene's protective groups in organic synthesis, 4th Edition. Ch 2 Protection for the Hydroxyl Group, Including 1,2- and 1,3-diols. John Wiley & Sons, Inc.: New York, 2006; pp 16–366.

[62] Irwin, L. C.; Renwick, C. R.; Kerr, M. A. Nucleophilic Opening of Donor–Acceptor Cyclopropanes with Indoles via Hydrogen Bond Activation with 1,1,1,3,3,3-Hexafluoroisopropanol. *J. Org. Chem.* **2018**, *83*, 6235–6242.

[63] Zhou, Y.; Xue, R.; Feng, Y.; Zhang, L. How does HOTf/HFIP Cooperative System Catalyze the Ring-Opening Reaction of Cyclopropanes? A DFT Study. *Asian J. Org. Chem*. **2020**, *9*, 311–316.

[64] Dissolve 0.5g of ceric ammonium sulfate and 12 g of ammonium molybdate in 235 mL of water. Add 15 mL of conc. sulfuric acid.

[65] Gutekunst, W. R.; Baran, P. S. Applications of C–H Functionalization Logic to Cyclobutane Synthesis. *J. Org. Chem*. **2014**, *79*, 2430–2452.

Chapter 3

3 Ring-Opening Reactions of Alkoxy-substituted Cyclobutanes with Indoles and Electron-rich Arenes

The nucleophilic addition reaction of D-A cyclobutane gives ring-opened products, which are good intermediates to access cyclic compounds commonly found in natural products and bioactive molecules. Alkoxy-substituted cyclobutanes have a strong electron donating group that facilitates cleavage of the ring, and therefore readily react with nucleophiles to give ring-opened products under suitable reaction conditions. In particular, indoles are effective nucleophiles to generate ring-opened products due to its electron-rich property. This chapter introduces a nucleophilic aryl addition to alkoxy-substituted cyclobutanes and discusses the opportunity to access cyclic compounds from such ring-opened products.

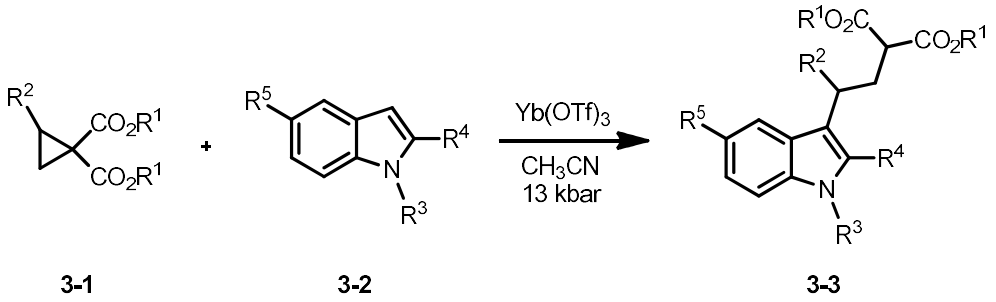
3.1 Introduction

3.1.1 Ring-opening Reactions of Donor-Acceptor Cyclopropane

D-A cyclopropane is a very useful building block as a 1,3-synthon. A number of interesting ring-opening reactions have been reported for D-A cyclopropane, with pioneering works from Wenkert (donor-cyclopropane), [66] Danishefsky (acceptor cyclopropane), [67] and Reissig (D-A cyclopropane).[68]

Under suitable conditions, D-A cyclopropane can undergo a nucleophilic addition reaction with a proper nucleophile to access ring-opened compounds. Therefore, the nucleophilic addition reactions of D-A cyclopropane have been vigorously researched with a variety of useful nucleophiles. In particular, indole is an efficient nucleophile because of its electron-rich property and many studies have been reported.[69]

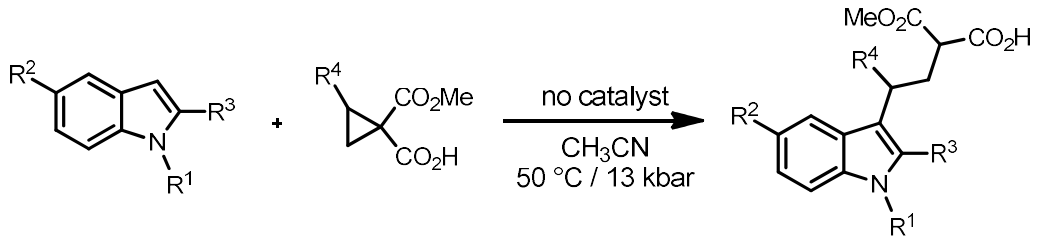
In 1997, the Kerr group reported the catalytic high pressure reaction of D-A cyclopropane with indole to access indolyl carbonyl compound **3-3** (Scheme 33).[70] The reaction proceeds at 13 kbar with $Yb(OTf)_3$ and affords homo-Michael addition products. After they reported the high pressure reaction of D-A cyclopropane with indole to access a indole adduct ring-opened compound, they developed the many different reaction conditions.



3-1 3-2 3-3

Scheme 33. The high pressure reaction of D-A cyclopropane with indole

In 2011, the Kerr group reported a nucleophilic addition of indole derivatives to hemimalonate cyclopropane (Scheme 34).[71] They converted one of the geminal esters on the cyclopropane **3-1** to the carboxylic acid to product the hemimalonate cyclopropane **3-5**. In this way, intramolecular hydrogen bonding of the hemimalonate can promote the ring cleavage event thereby facilitating nucleophilic attack by indole. The desired product was obtained under high pressure but without the use of Lewis acid catalyst. In 2018, they reported a similar work in which hexafluoroisopropanol was used as the solvent, and this change obviated the high pressure previously needed to activate the reaction.[56]

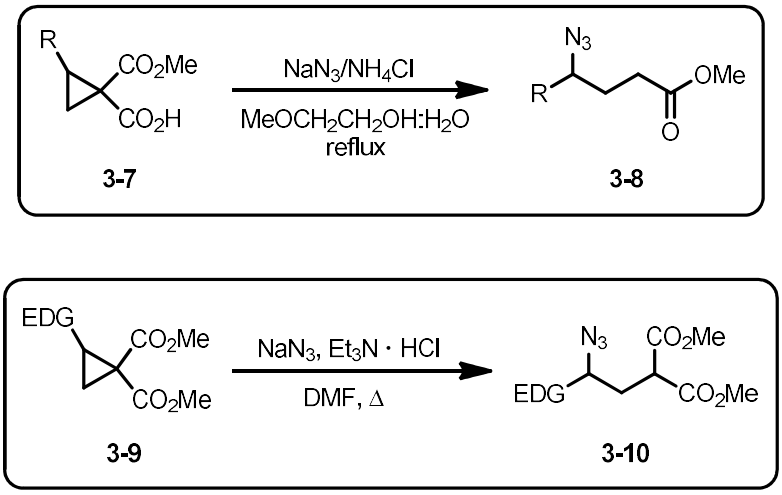


3-4 3-5 3-6

Scheme 34. Nucleophilic ring-opening of D-A cyclopropane with indoles

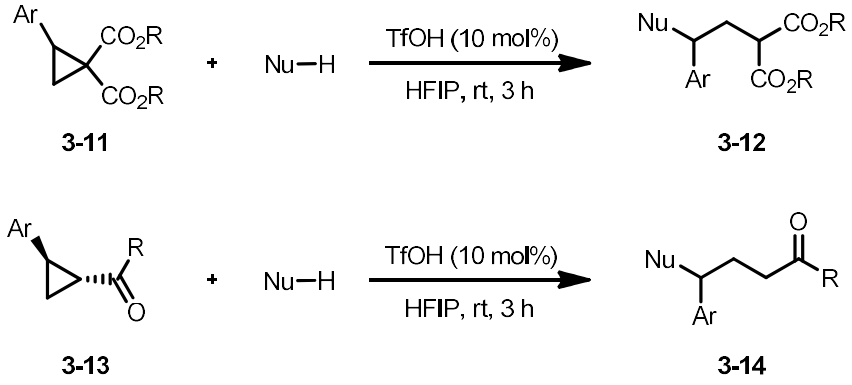
Azide is also a good nucleophile for the ring-opening reaction of D-A cyclopropane. In 2012, the Kerr group described a ring-opening reaction of D-A cyclopropane hemimalonate with sodium azide through an S_N2-like pathway (Scheme 35 top).[72] . The reaction of a hemimalonate cyclopropane with azide initially generates an acyl azide intermediate which then undergoes a [3,3]-sigmatropic rearrangement to make a ketene intermediate. The acid is regenerated by water and then decarboxylation gives ring-opened ester adducts **3-8**. In 2015, the Melnikove group described a similar process with an azide

ion (Scheme 35 bottom) and a cyclopropane diester.[73] The ring-opened adducts were further transformed into the five-, six-, and seven-membered *N*-heterocycles, as well as complex annulated compounds such as nicotine and atorvastatin.



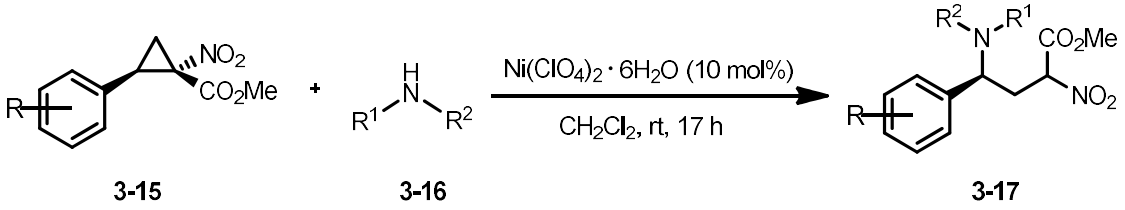
Scheme 35. Ring-opening of D-A cyclopropane with azide by Kerr (top) and Melnikov (bottom)

In 2018, the Moran group reported a Brønsted acid catalyzed nucleophilic ring-opening reaction of D-A cyclopropane with electron-rich arenes (Scheme 36).[58] Interestingly, the D-A cyclopropane could be activated by a Brønsted acid in hexafluoroisopropanol instead of a Lewis acid catalyst. The reaction was accomplished under mild conditions in good yield.



Scheme 36. Brønsted acid/HFIP catalyzed ring-opening of D-A cyclopropane

Amine is another nucleophile that proven to access a ring-opened cyclopropane compound. In 2008, the Charette group reported a Lewis acid-catalyzed ring-opening reaction of D-A cyclopropanes with amine (**3-16**) as nucleophile (Scheme 37).[74]

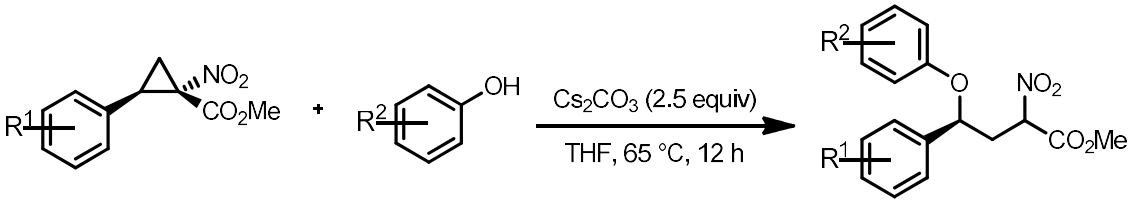


3-15 **3-16** **3-17**

Scheme 37. Nickel(II) perchlorate-catalyzed ring-opening of D-A cyclopropane with amine

The reaction tolerates a variety of amine nucleophiles and donor substituents on the cyclopropane ring with good yield. The use of weakly activating Lewis acids mostly prevents the loss of stereochemistry at the electrophilic carbon in the cyclopropane. The reaction undergoes an S_N2 pathway, which shows the absolute stereochemistry at the electrophilic carbon when enantioenriched cyclopropane is used as the starting material (**3-15**).

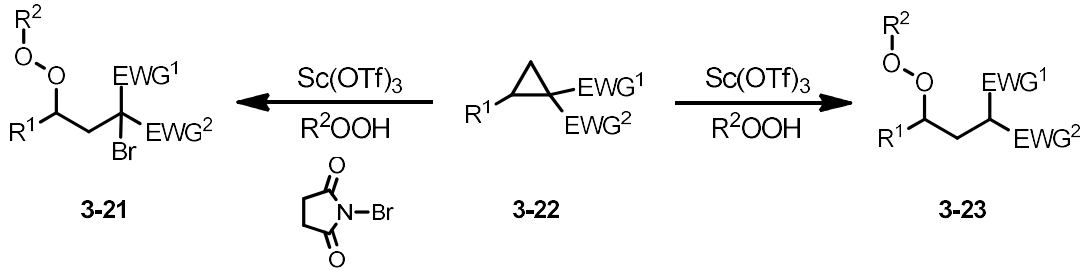
The Charette group subsequently reported a nucleophilic addition of phenols (**3-19**) to D-A cyclopropane (Scheme 38),[75] in which cesium carbonate is applied as a base. The reaction tolerates a variety of substituents on the phenol and the cyclopropane. The nucleophilic addition of the phenol derivative proceeds through an S_N2 pathway to give an optically active product.



3-18 **3-19** **3-20**

Scheme 38. Nucleophilic addition of phenol derivatives to D-A cyclopropane

Hydroperoxide has also been reported as a useful nucleophile for the ring-opening reaction of D-A cyclopropane. In 2019, the Saha group illustrated the $Sc(OTf)_3$-catalyzed nucleophilic ring-opening of D-A cyclopropane with hydroperoxide (Scheme 39).[76] In the presence of a suitable halogenating agent, a 1,3-bisfunctionalized product (**3-21**) can be obtained. For example, the use of *N*-bromosuccinimide and hydroperoxide with various D-A cyclopropane gives a wide range of 1,3-bifuncationalized products.

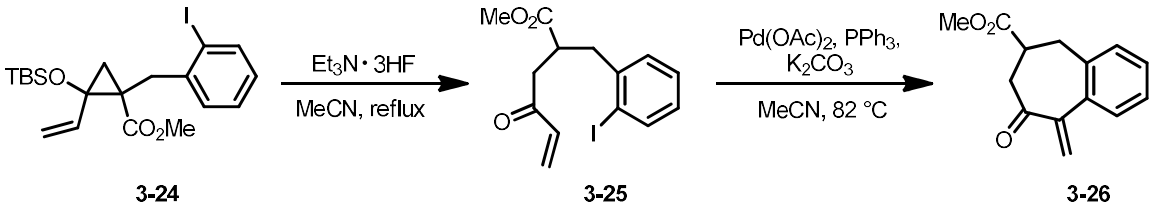


Scheme 39. Lewis acid catalyzed nucleophilic ring-opening and 1,3-bisfunctionalization of D-A cyclopropane

As such, the nucleophilic ring-opening reaction of D-A cyclopropane is actively studied with a wide range of nucleophiles. Many different reaction conditions have been explored as well, such as Lewis acid catalysis, high pressure activation, and Brønsted acid/solvent systems.

3.1.2 Annulation of Ring-opened Cycloalkane

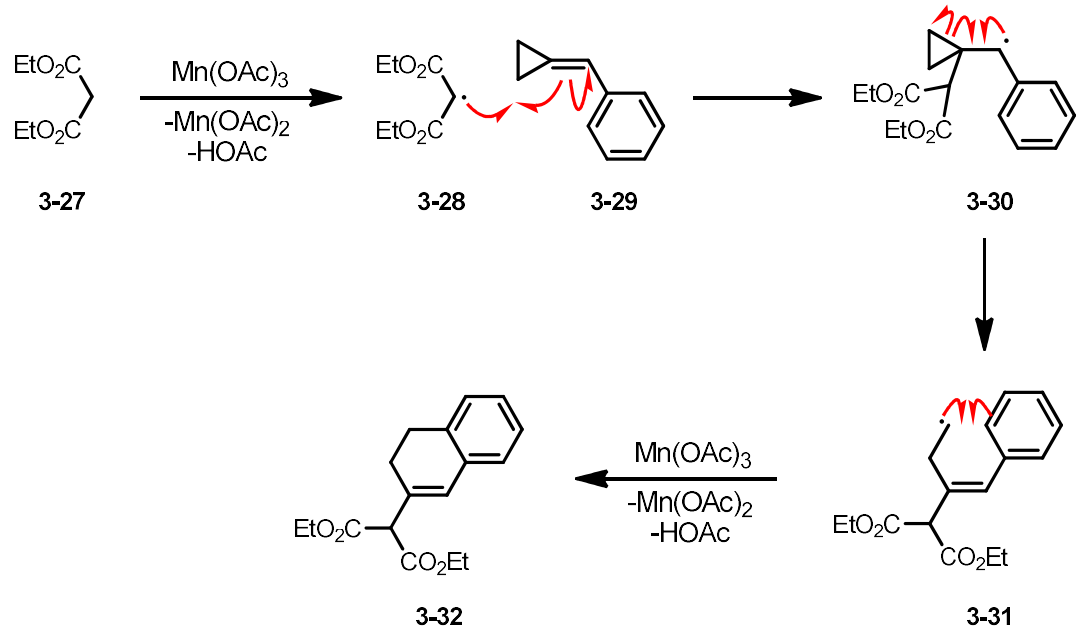
The nucleophile adduct ring-opened compounds are useful precursors to cyclic compounds, especially when the target product cannot be secured by intermolecular reactions. For example, the Reissig group in 2000 described a Pd-catalyzed cyclization of the ring-opened product of D-A cyclopropanes.[77] They first converted a D-A cyclopropane (**3-24**) into the oxo-ester intermediate (**3-25**) by desilylation, which was then cyclized to the tetrahydro benzo annulene product (**3-26**) by intramolecular Heck cyclization (Scheme 40).



3-24 3-25 3-26

Scheme 40. Ring-opening of D-A cyclopropane and Heck cyclization

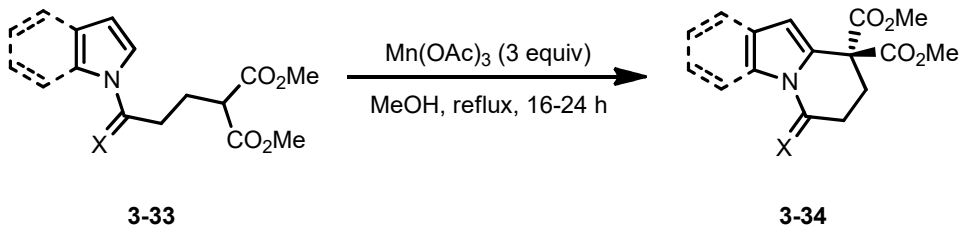
In 2004, the Chen group reported a tandem free-radical cyclization reaction of cyclopropanes.[78] Alkylidenecyclopropane (**3-29**) undergoes $Mn(OAc)_3$-mediated addition with malonate to produce a dihydronaphthalene skeleton (**3-32**) through radical cyclization. The reaction of malonate and $Mn(OAc)_3$ generates a stabilized radical intermediate that undergoes addition to an alkene functional group appended with cyclopropane. The cyclopropane (**3-30**) then undergoes a ring cleavage, and the somewhat unusual primary radical attacks the phenyl group intramolecularly to make a dihydronaphthalene product (Scheme 41).



3-27 3-28 3-29 3-30 3-31 3-32

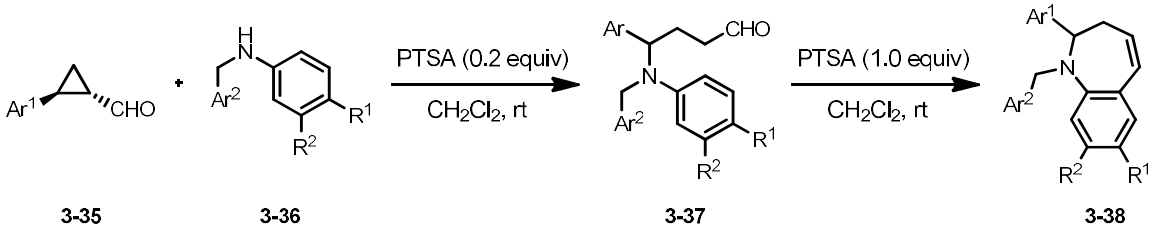
Scheme 41. Tandem radical cyclization of alkylidenecyclopropane with malonic acid diester

In 2006, the Kerr group reported the intramolecular oxidative cyclization reaction of malonyl radicals to indoles and pyrroles with stoichiometric manganese(III) triacetate (Scheme 42).[79]



Scheme 42. Cyclization of malonyl radicals to indoles and pyrroles

Most recently, the Banerjee group exploited a metal-free ring opening cyclization of D-A cyclopropanes (**3-35**) with *N*-benzyl anilines (**3-36**).[80] *p*-Toluenesulfonic acid (PTSA) was applied as a catalyst for the tandem ring-opening and cyclization reaction. Interestingly, the series of reactions are controlled by the amount of PTSA used. For example, substoichiometric use of PTSA (0.2 equivalents) only gave a ring-opened product (**3-37**) and an additional 1.0 equivalent of PTSA drove the cyclization to **3-38** (Scheme 43). The one-pot reaction operates under ambient conditions with yields ranging from 45% to 70%.

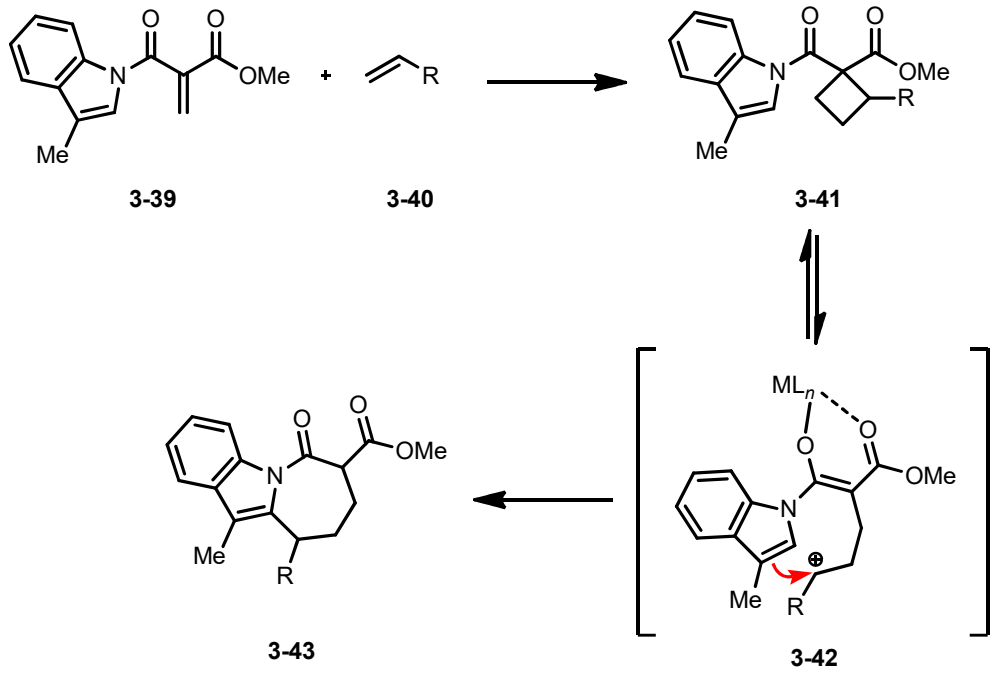


Scheme 43. Tandem ring-opening and cyclization reaction of D-A cyclopropane

3.1.3 Ring-opening Reaction of Donor-Acceptor Cyclobutane

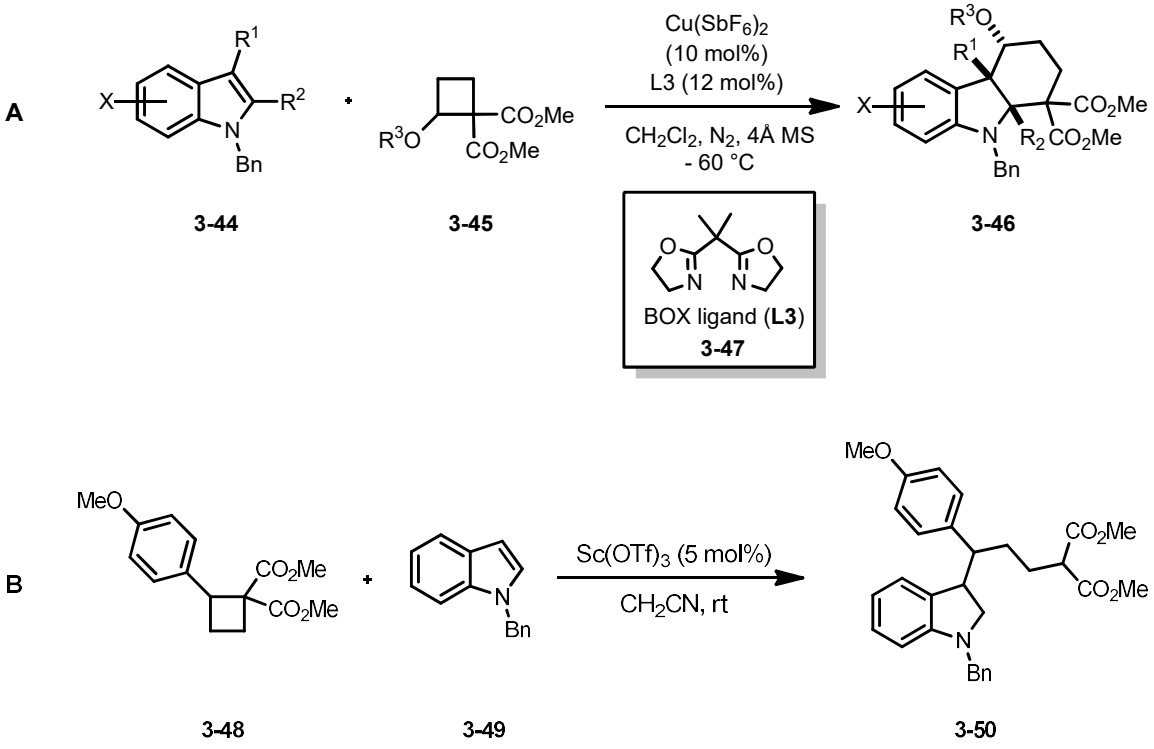
At the start of this project, the reaction of D-A cyclobutanes with simple nucleophiles to access a ring-opened adduct remained almost unreported in literature, as the preponderance of reactions with D-A cyclobutanes involved formal cycloaddition reactions. A first example was reported by France in 2014, where they synthesized the azepino indole skeleton (**3-43**).[81] They speculated that the cyclobutane **3-41** was in equilibrium with the

ring-opened form (**3-42**) that underwent intramolecular attack by the pendant indole (Scheme 44). The D-A cyclobutane was formed via [2+2] cycloaddition of alkylidene malonate **3-39** with alkenes **3-40**.



Scheme 44. Intramolecular ring-opening and cyclization of D-A cyclobutane

In 2017, the Tang group developed a methodology for the total synthesis of strychnine and akuammicine (Scheme 45A),[82] in which the Box ligand (**3-47**) promoted the reaction between a D-A cyclobutane and indole in a [4+2] annulation reaction. The fused product is analogous to Pagenkopf's work with D-A cyclopropanes.[83] In screening the reaction conditions and before the intended annulation was furnished, Tang found that the D-A cyclobutane gave a nucleophilic ring-opened product (**3-50**) under the catalysis of $Sc(OTf)_3$ (Scheme 45B).



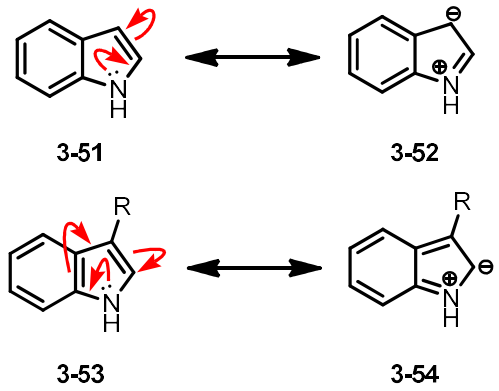
Scheme 45. Cu(II) catalyzed [4+2] cycloaddition of D-A cyclobutane with indole to form cyclohexane-fused indolines (A) and Sc(OTf)3-catalyzed ring-opening reaction of D-A cyclobutane with indole (B)

3.1.4 Research Plan

Although many studies have been reported for the addition of nucleophiles to D-A cyclopropanes, similar nucleophilic addition reactions of D-A cyclobutanes are scarce. Therefore, in this work, we decided to investigate the use of aromatics as nucleophiles in ring-opening reactions of alkoxy-substituted cyclobutanes. The reactive alkoxy-substituted D-A cyclobutanes are useful building blocks.[84] Furthermore, we aimed to explore the application of the ring-opened compounds in downstream annulation reactions to further increase molecular complexity.

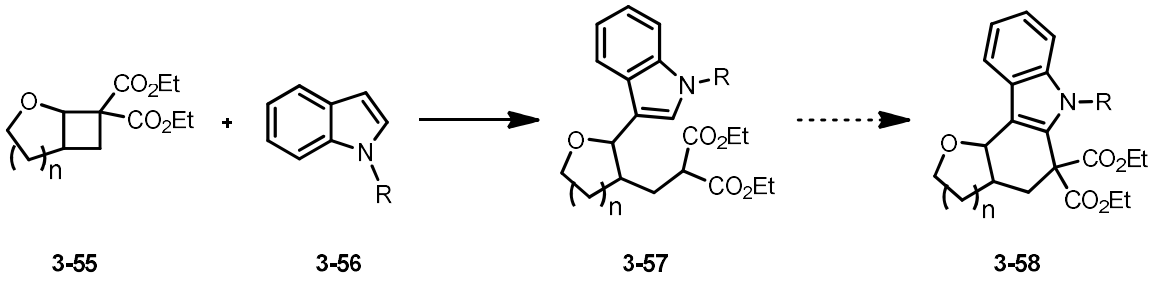
As we saw previously, indole is an effective nucleophile in ring opening reactions of cyclopropanes (Schemes 33 and 34) and cyclobutanes (Scheme 45). Generally, the most nucleophilic site of the indole is the 3-postion (**3-52**). When the indole 3-position is

substituted, electrophilic attack at the 2-position is observed, possibly due to initial C3 attack followed by a 1,2-migration. The nucleophilicity at either carbon can be rationalized by the resonance structures shown in Scheme 46.



Scheme 46. Resonance structures of indole

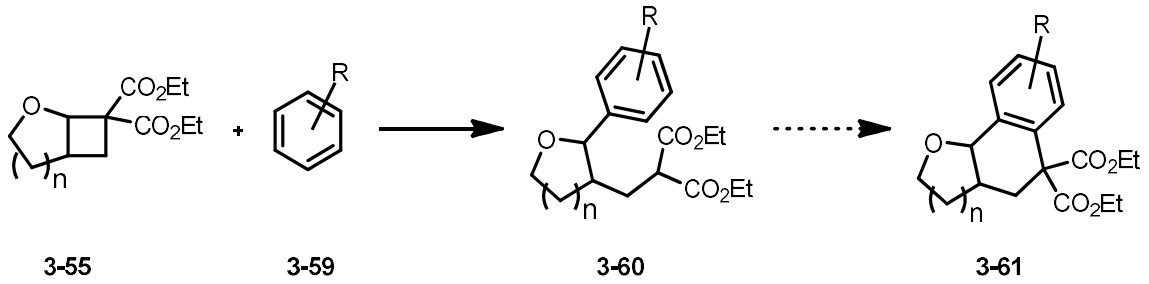
In view of the strong nucleophilicity of indole, it should be a viable partner in the ring opening reaction of alkoxy-substituted cyclobutane. Although Tang reported an indole addition to alkoxy-substituted cyclobutane, the proton transfer adduct was only observed as a byproduct. In addition, indole has not only high electron density but also a fused ring system, and the presumed adduct can be a good template for accessing tetrahydrocarbazole (**3-58**) via oxidative annulation (Scheme 47).



Scheme 47. Proposed nucleophilic ring-opening reaction and cyclization of alkoxy-substituted cyclobutanes with indoles

In addition, we also planned to test electron-rich arene species, which are highly nucleophilic, in the ring-opening reaction of alkoxy-substituted cyclobutanes. Likewise, the product **3-60** can likely be converted to the naphthofuran compound (**3-61**) via a radical

oxidative cyclization (Scheme 48).[85] Naphtofuran, a homolog of dihydrobenzofuran, is a notable core structure in natural products such as rubioncolin B,[86] nocardione,[87] and tanshinone.[88]

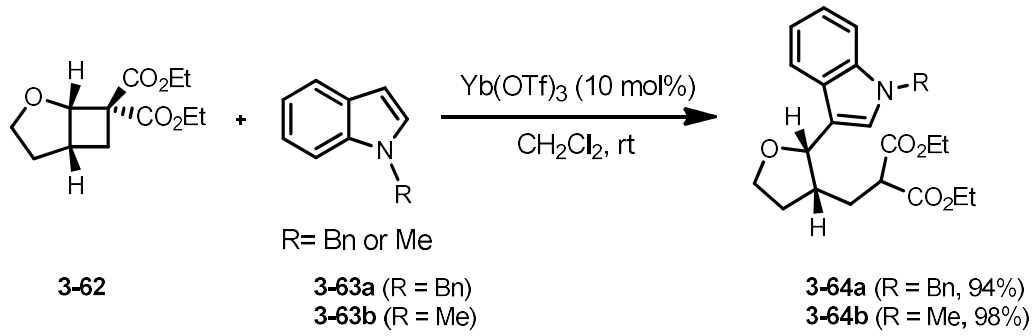


Scheme 48. Proposed nucleophilic ring-opening reaction of alkoxy-substituted cyclobutanes with electron-rich arenes

3.2 Result and Discussion

3.2.1 Reaction of Donor-Acceptor Cyclobutane with Indoles

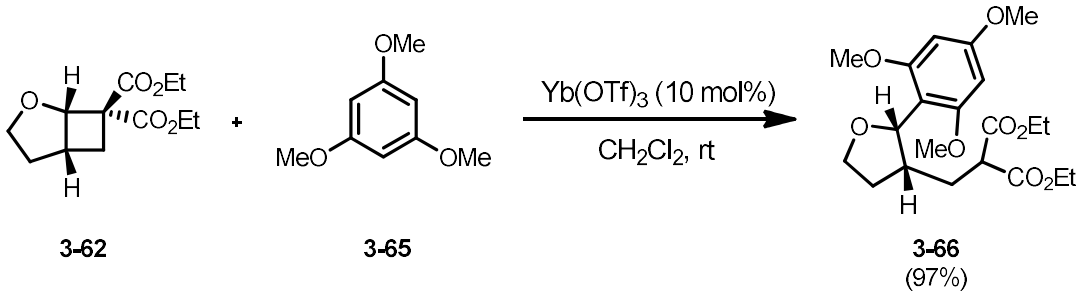
The C–C bond in the ring of alkoxy-substituted cyclobutanes is more easily cleaved than aryl activated cyclobutanes, therefore it is necessary to use a mild Lewis acid. We started the Lewis acid screening with $Yb(OTf)_3$, a Lewis acid proven to activate alkoxy-substituted cyclobutanes in our previous work,[9,10,12,13] and found that 10 mol% of $Yb(OTf)_3$ worked well with *N*-benzyl or *N*-methyl indole (Scheme 49), affording products **3-64** in 94% and 98%, respectively . In contrast, when 10 mol% of $Sc(OTf)_3$ was used, the alkoxy-substituted cyclobutane quickly decomposed and the desired product was not obtained.



Scheme 49. Ring-opening reaction of alkoxy-substituted cyclobutane with indoles

3.2.2 Reaction of Donor-Acceptor Cyclobutane with Electron-rich Arenes

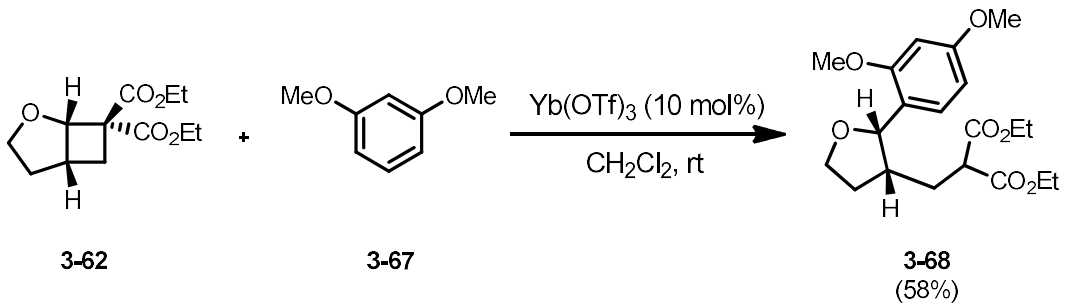
Electron-rich arenes are also good nucleophiles in the ring opening reaction of D-A cyclobutane **3-62**. Our preliminary result with electron rich 1,3,5-trimethoxybenzene (**3-65**), showed promise with an excellent 97% yield obtained from the reaction with cyclobutane (Scheme 50).



3-62 **3-65** **3-66** (97%)

Scheme 50. Ring-opening reaction of alkoxy-substituted cyclobutane with 1,3,5-trimethoxybenzene

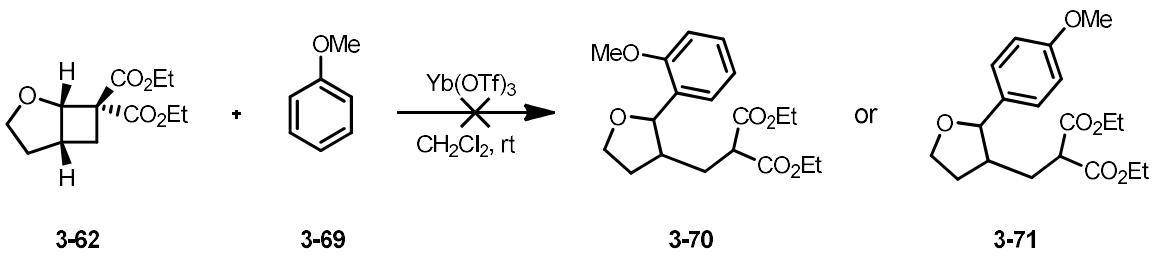
We next tested the arylation reaction with 1,3-dimethoxybenzene (**3-67**), but only a 58% yield was obtained (Scheme 51). Attempts to optimize the reaction with excess dimethoxybenzene, other catalysts and temperatures have yet to be undertaken



3-62 **3-67** **3-68** (58%)

Scheme 51. Ring-opening reaction of alkoxy-substituted cyclobutane with 1,3-dimethoxybenzene

Anisole (**3-69**) was also tested as a nucleophilic reactant for the aromatic addition reaction. However, anisole appears not to react under the initial reaction conditions, and no addition products were observed (Scheme 52).

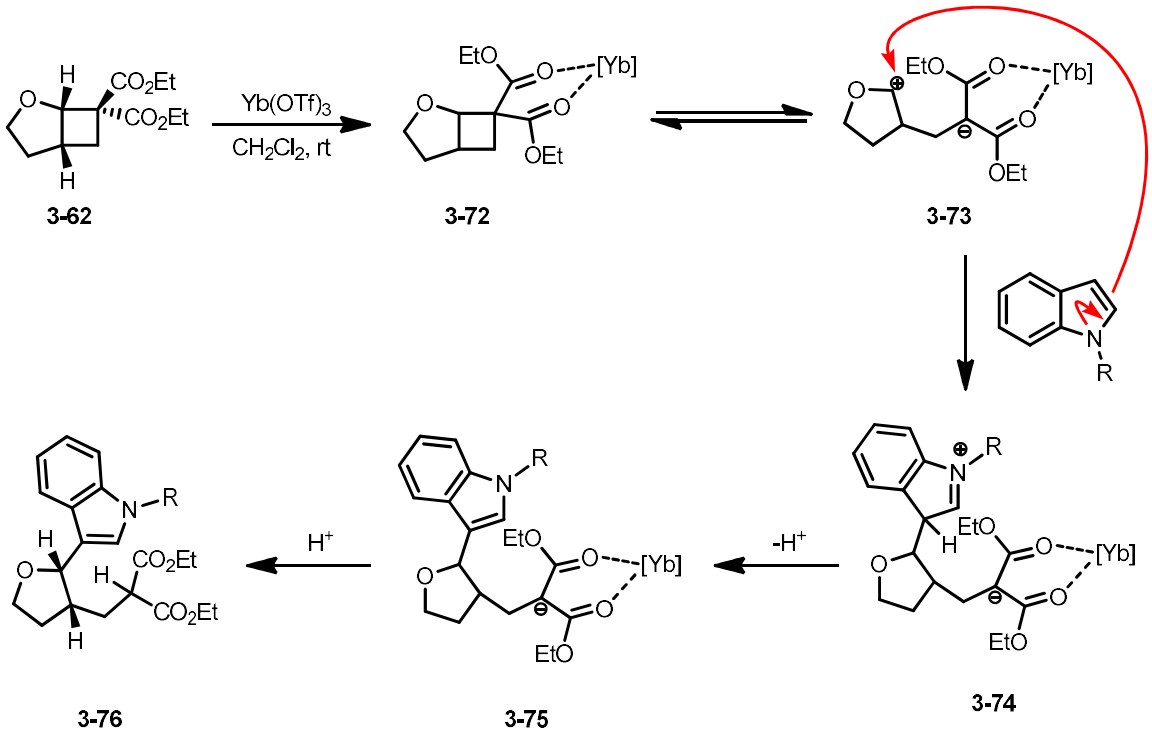


3-62 **3-69** **3-70** **3-71**

Scheme 52. Failed ring-opening reaction of alkoxy-substituted cyclobutane with anisole

3.2.3 Mechanistic Discussion

Alkoxy-substituted cyclobutane (**3-62**) is activated with $Yb(OTf)_3$ by coordination with esters, and the 3-postion of indole attacks the electrophilic site of cyclobutane to generate a zwitterionic intermediate (**3-73**) that gives the indole appended ring-opened product **3-76** after proton transfers (Scheme 53).

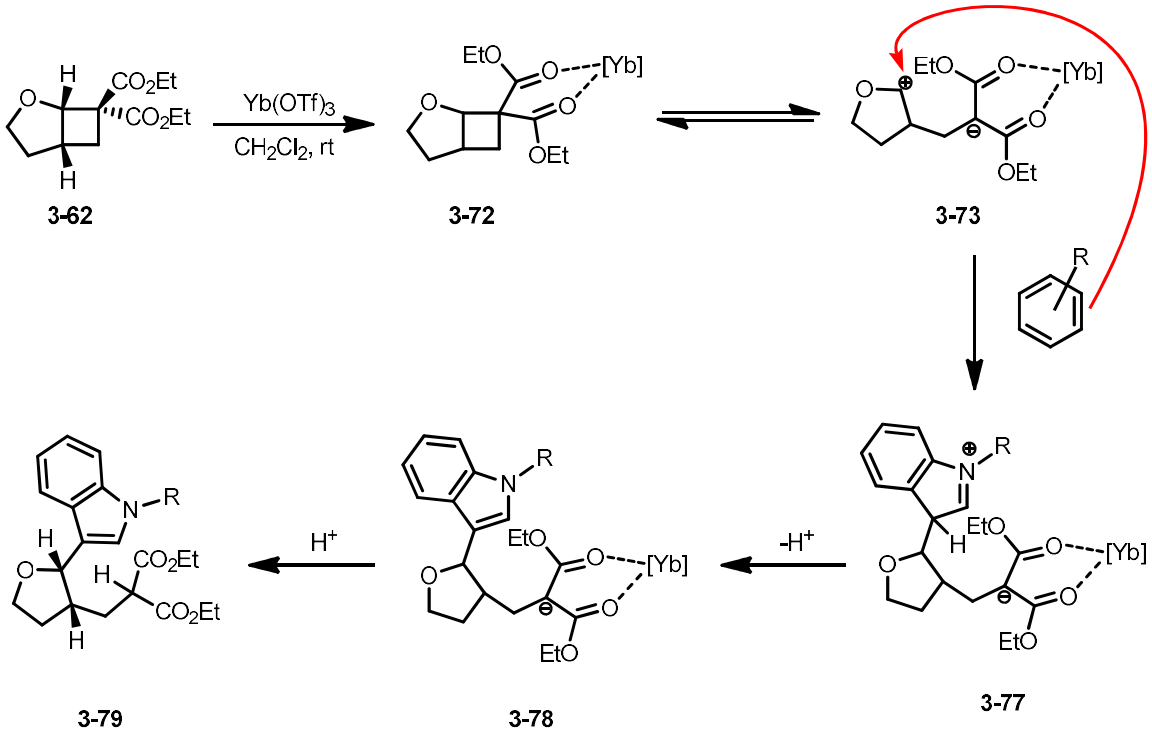


3-62 **3-72** **3-73** **3-74** **3-75** **3-76**

Scheme 53. Plausible mechanism of nucleophilic attack of indole to D-A cyclobutane

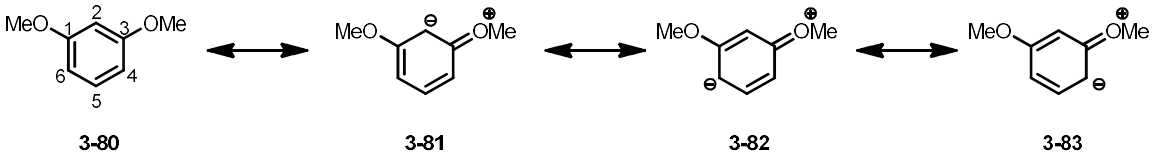
The reaction with electron-rich arenes has a similar pathway as indole addition. The alkoxy-substituted cyclobutane (**3-62**) is activated by $Yb(OTf)_3$, and the electron-rich arene

attacks the electrophilic site of cyclobutane. Subsequent proton shifts afford the desired product (**3-79**) (Scheme 54).



Scheme 54. Plausible mechanism of nucleophilic attack of electron-rich arene to D-A cyclobutane

1,3-Dimethoxybenzene has two possible nucleophilic sites (Scheme 55), but only the product with attached from C4 or C6 was acquired as a major product. C2 is sterically hindered by two adjacent methoxy groups and known no to participate in electrophilic aromatic substitution reactions. [89] Therefore, the product attached from C2 was not acquired.

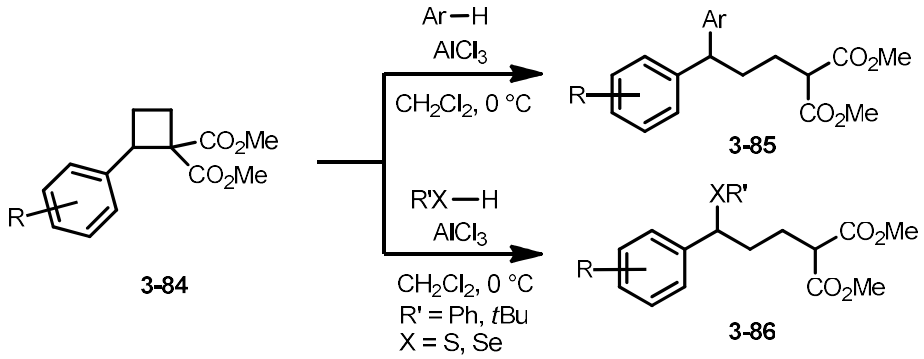


Scheme 55. Resonance structure of 1,3-dimethoxybenzene

3.3 Conclusion and Future Work

Nucleophilic ring-opening reactions are less well-studied for D-A cyclobutanes than for D-A cyclopropanes. In this work, we investigated the ring-opening reaction of alkoxy-cyclobutanes with electron rich aromatics and demonstrated some successful examples. The preliminarily reaction conditions with alkoxy-substituted cyclobutane **3-62** and electron rich aromatics show promise.

During our investigation of the nucleophilic ring-opening reaction of D-A cyclobutane with indoles and electron-rich arenes, the Werz group reported a similarly designed study with electron-rich arenes, thiols, and selenols with D-A cyclobutanes in2019 (Scheme 56).[90] This transformation, identical to what we intended in this chapter, was mediated by aluminum chloride ($AlCl_3$), and electron-rich arenes worked well as nucleophiles to produce ring-opened products in good yields.



Scheme 56. Ring-opening reaction of D-A cyclobutanes with electron-rich arenes

Because the work what we planned was essentially published by Werz in *Organic Letters,*[90] it was decided not to pursue this investigation further. It was ultimately gratifying though to learn that we were on the right track and our objective was realized.

3.4 Experimental

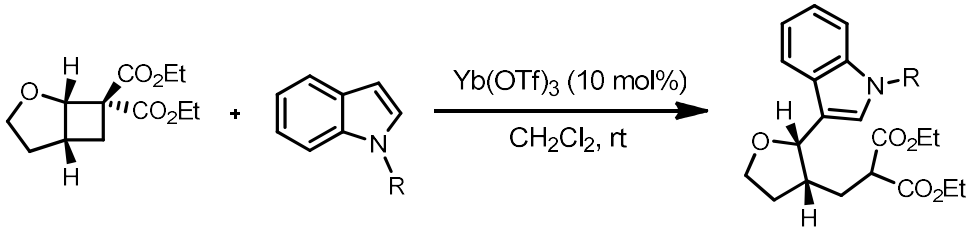
3.4.1 General Synthetic Method

All reactions were run under an inert atmosphere (argon or nitrogen) and flasks were oven-dried and cooled in a desiccator prior to use. All chemicals used were of reagent grade and

were obtained from commercial sources (Sigma Aldrich or Alfa Aesar). All solvents were purified by passing through an activated alumina column. The progress of reaction was monitored by thin layer chromatography (TLC, SilicaPlate TLC Aluminium Backed TLC 200 μm) visualized under UV light (254 nm), and plates were also stained with ceric ammonium molybdate (CAM). Standard column chromatography was performed using silica gel purchased from Silicycle Chemical Division Inc. (Silicycle SilicaFlash P60, 40-63 μm, 60Å).

^{1}H NMR and ^{13}C NMR spectra were acquired on 400 and 600 MHz spectrometers (Bruker 400, Varian Inova 400 and Inova 600) in deuterated chloroform. ^{1}H NMR spectra were referenced to the residual proton signal in deuterated chloroform at δ 7.26 ppm. ^{13}C NMR spectra were referenced to deuterated chloroform at the center peak of the triplet at δ 77.16(t) ppm. Coupling constant '*J*' is in Hz. The peak multiplicities are described using the abbreviations as follows: s = singlet, d = doublet, t = triplet, dd = doublet of doublets, dt = doublet of triplet, m = multiplet, app = apparent. High resolution mass spectra (HRMS) were obtained on a Thermo Scientific DFS spectrometer at an ionizing voltage of 70 eV. Infrared Spectra (IR) were acquired using a Bruker FTIR spectrometer ALPHA II.

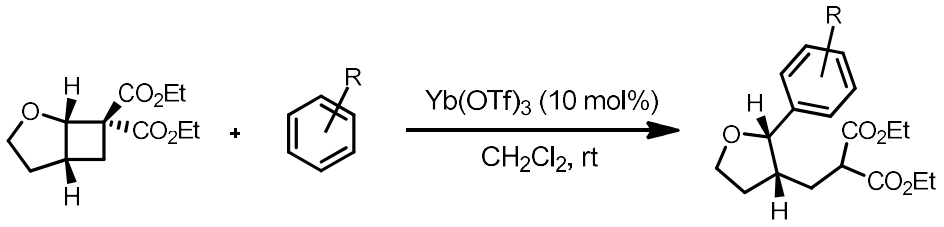
3.4.2 Procedures and Characterization Data



General reaction procedure A

To an oven-dried round bottom flask equipped with a stir bar under argon atmosphere were added the alkoxy-substituted cyclobutane (1.0 equiv, 0.2 mmol, 48 mg), the indole (2.0 equiv, 0.4 mmol), and CH_2Cl_2 (1 mL). A solution of $Yb(OTf)_3$ (10 mol%, 0.02 mmol, 12 mg) in CH_2Cl_2 (1 mL) was then added to the reaction mixture. The resulting solution was stirred for 1 h at room temperature. The mixture was then filtered through a celite pad and concentrated under reduced pressure. The residual material was purified by flash

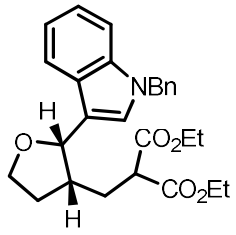
chromatography (70% hexane, 30% ethyl acetate) to isolate the product as a single diastereomer.



General reaction procedure B

To an oven-dried round bottom flask equipped with a stir bar under argon atmosphere were added the alkoxy-substituted cyclobutane (1.0 equiv, 0.2 mmol, 48 mg), the arene (3.0 equiv, 0.6 mmol), and CH_2Cl_2 (1 mL). A solution of $Yb(OTf)_3$ (10 mol%, 0.02 mmol, 12 mg) in CH_2Cl_2 (1 mL) was then added to the reaction mixture. The resulting solution was stirred for 1 h at room temperature. The mixture was then filtered through a celite pad and concentrated under reduced pressure. The residual material was purified by flash chromatography (70% hexane, 30% ethyl acetate) to isolate the product as a single diastereomer.

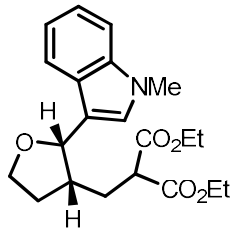
Diethyl 2-(((2S*,3R*)-2-(1-benzyl-1*H*-indol-3-yl)tetrahydrofuran-3-yl)methyl)malonate (3-64a)



The title compound (**3-64a**) was prepared through the general reaction procedure A to afford a pale-yellow oil (98 mg, 94%). $\mathbf{R_f}$ = 0.38 (70% hexane, and 30% ethyl acetate); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.69 (d, *J* = 7.8 Hz, 1H), 7.30-7.22 (m, 4H), 7.17-7.09 (m, 5H), 5.29 (s, 2H), 4.71 (d, *J* = 8.5Hz, 1H), 4.12-3.96 (m, 6H), 3.37 (dd, *J* = 7.7, 7.7 Hz, 1H), 2.52-2.46 (m, 1H), 2.35-2.27 (m, 1H), 2.17-2.10 (m, 1H), 2.05-1.97 (m, 1H), 1.80-1.74 (m, 1H), 1.14 (dd, *J* = 7.1, 7.1 Hz, 3H), 1.10 (dd, *J* = 7.1, 7.1 Hz, 3H); **^{13}C NMR (101**

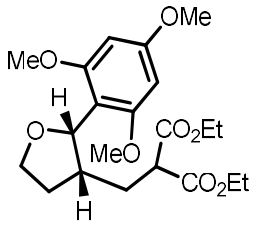
MHz, $CDCl_3$) δ 169.3, 169.1, 137.4, 137.3, 128.7, 127.6, 126.8, 126.5, 122.0, 120.0, 119.5, 114.8, 109.9, 80.7, 67.1, 61.4, 51.0, 50.1, 42.6, 32.8, 31.5, 14.0, 13.9; **IR** (cm^{-1}) 2929, 1727, 1466, 1172, 1017, 740

Diethyl 2-(((2S*,3R*)-2-(1-methyl-1*H*-indol-3-yl)tetrahydrofuran-3-yl)methyl)malonate (3-64b)



The title compound (**3-64b**) was prepared through the general reaction procedure A to afford a pale-yellow oil (73 mg, 98%). $\mathbf{R_f}$ = 0.31 (70% hexane, and 30% ethyl acetate); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.67 (app d, *J* = 7.9 Hz, 1H), 7.28 (app d, *J* = 8.2 Hz, 1H), 7.21 (app ddd, *J* = 6.0, 6.0, 1.0 Hz, 1H), 7.09 (app ddd, *J* = 7.5, 7.0, 1.0 Hz, 1H), 7.05 (app s, 1H), 4.71 (d, *J* = 8.5 Hz, 1H), 4.15-3.99 (m, 6H), 3.76 (s, 3H), 3.37 (dd, *J* = 8.3, 7.2 Hz, 1H), 2.52-2.42 (m, 1H), 2.34-2.26 (m, 1H), 2.18-2.11 (m, 1H), 2.00-1.92 (m, 1H), 1.81-1.72 (m, 1H), 1.18 (dd, *J* = 7.1, 7.1 Hz, 3H), 1.13 (dd, *J* = 7.1, 7.1 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.4, 169.2, 137.7, 127.2, 126.7, 121.8, 119.8, 119.3, 113.9, 109.3, 80.5, 67.1, 61.4, 51.1, 42.7, 32.8, 32.7, 31.5, 30.9, 14.0, 13.9; **IR** (cm^{-1}) 934, 1727, 1369, 1014, 739

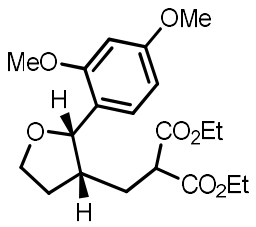
Diethyl 2-(((2S*,3R*)-2-(2,4,6-trimethoxyphenyl)tetrahydrofuran-3-yl)methyl)malonate (3-66)



The title compound (**3-66**) was prepared through the general reaction procedure B to afford a pale-yellow oil (80 mg, 97%). $\mathbf{R_f}$ = 0.23 (70% hexane, and 30% ethyl acetate); **^{1}H NMR**

(400 MHz, $CDCl_3$) δ 6.09 (s, 2H), 5.03 (d, *J* = 8.8 Hz, 1H), 4.13-3.96 (m, 6H), 3.77 (s, 3H), 3.76 (s, 6H), 3.30 (dd, *J* = 7.8, 7.8 Hz, 1H), 2.69-2.61 (m, 1H), 2.25-2.18 (m, 1H), 2.00-1.87 (m, 2H), 1.69-1.60 (m, 1H), 1.15 (app ddd, *J* = 13.7, 7.1, 7.1 Hz, 6H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.5, 169.4, 160.9, 159.8, 109.2, 91.1, 77.6, 67.8, 61.2, 61.1, 55.8, 55.2, 50.9, 40.5, 34.2, 32.2, 29.3, 14.0, 13.9; **IR** (cm^{-1}) 2938, 1728, 1606, 1464, 1122, 813 **HRMS** (EI) m/z [M+]; 410.1949 (calculated for $C_{21}H_{30}O_8$ 410.1941)

Diethyl 2-(((2S*,3R*)-2-(2,4-dimethoxyphenyl)tetrahydrofuran-3-yl)methyl)malonate (3-68)



The title compound (**3-68**) was prepared through the general reaction procedure B to afford a clear oil (80 mg, 58%). **R_f** = 0.35 (70% hexane, and 30% ethyl acetate); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.21 (app d, *J* = 8.3 Hz, 1H), 6.46 (app dd, *J* = 8.4, 2.4 Hz, 1H), 6.42 (app d, *J* = 2.3 Hz, 1H), 4.81 (d, *J* = 5.4 Hz, 1H), 4.20-4.06 (m, 6H), 4.00-3.96 (m, 1H), 3.79 (s, 3H), 3.79 (s, 3H), 3.43 (dd, *J* = 7.4, 7.4 Hz, 1H), 2.17-2.11 (m, 2H), 2.01-1.95 (m, 1H), 1.71-1.64 (m, 1H), 1.22 (app ddd, *J* = 7.1, 4.8, 4.8 Hz, 6H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.4, 169.4, 160.2, 157.7, 127.5, 122.7, 104.2, 98.4, 80.6, 67.6, 61.4, 61.3, 55.4, 55.3, 50.9, 44.1, 32.1, 31.7, 14.0; **IR** (cm^{-1}) 2979, 1728, 1446, 1151, 859

3.5 References

[66] Wenkert, E. Oxycyclopropanes in Organochemical Synthesis. *Acc. Chem. Res*. **1980**, *13*, 27–31.

[67] Danishefsky, S. Electrophilic Cyclopropanes in Organic Synthesis. *Acc. Chem. Res*. **1979**, *12*, 66–72.

[68] Reissig, H.-U. Lewis-acid-promoted Additions of Carbonyl Compounds to Donor-Acceptor Substituted Cyclopropanes: A New Synthesis of 2,3-Dihydrofurane Derivatives. *Tetrahedron Lett*. **1981**, *22*, 2981–2984.

[69] Lakhdar, S.; Westermaier, M.; Terrier, F.; Goumont, R.; Boubaker, T.; Ofial, A. R.; Mayr, H. Nucleophilic Reactivities of Indoles. *J. Org. Chem*. **2006**, *71*, 9088–9095.

[70] Harrington, P.; Kerr, M. A. The High Pressure Reaction of Cyclopropanes with Indoles Catalyzed by Ytterbium Triflate. *Tetrahedron Lett*. **1997**, *38*, 5949–5952.

[71] Emmett, M. R.; Kerr, M. A. Nucleophilic Ring Opening of Cyclopropane Hemimalonates Using Internal Brønsted Acid Activation. *Org. Lett*. **2011**, *13*, 4180–4183.

[72] Emmet, M. R.; Grover, H. K.; Kerr, M. A. Tandem Ring-Opening Decarboxylation of Cyclopropane hemimalonates with Sodium Azide: A short Route to γ-Aminobutyric Acid Esters. *J. Org. Chem*. **2012**, *77*, 6634–6637.

[73] Ivanov, K. L.; Villemson, E. V.; Budynina, E. M.; Ivanova, O. A.; Trushkov I. V.; Melnikov, M. Y. Ring Opening of Donor-Acceptor Cyclopropanes with the Azide ion: A Tool for Construction of N-Heterocycles. *Chem. Eur. J*. **2015**, *21*, 4975–4987.

[74] Lifchits, O.; Charette, A. B. A Mild Procedure for the Lewis Acid-catalyzed Ring-opening of Activated Cyclopropanes with Amine Nucleophiles. *Org. Lett*. **2008**, *10*, 2809–2812.

[75] Lifchits, O.; Alberico, D.; Zakharian, I.; Charette, A. B. Nucleophilic Addition of Phenol Drivatives to Methyl 1-Nitrocyclopropanecarboxylates. *J. Org. Chem*. **2008**, *73*, 6838–6840.

[76] Singh, K.; Bera, T.; Jaiswal, V.; Biswas, S.; Mondal, B.; Das, D.; Saha, J. Lewis Acid Catalyzed Nucleophilic Ring Opening and 1,3-Bisfunctionalization of Donor-Acceptor Cyclopropanes with Hydroperoxides: Access to Highly Funcitonalized Peroxy/(α-Heteroatome Substituted)Peroxy Compounds. *J. Org. Chem*. **2019**, *84*, 710–725.

[77] Khan, F. A.; Czerwonka, R.; Reissig, H. -U. Pd-Catalyzed Reactions of Donor-Acceptor-Substituted Cyclopropanes and Their Ring-Opened Derivatives: Attempted Heck Cyclization and Novel One-Pot Enolate Arylations. *Eur. J. Org. Chem*. **2000**, 3607–3617.

[78] Zhou, H.; Huang, X.; Chen, W. First tandem Free-Radical Cyclization Reaction of Alkylenecyclopropanes: A Novel and Efficient Method for the Preparation of 2-(3,4-Dihydronaphthalen-2-yl)malonic Acid Diethyl Esters. *J. Org. Chem*. **2004**, *69*, 5471–5472.

[79] Magolan, J.; Kerr, M. A. Expanding the Scope of $Mn(OAc)_3$-Mediated Cyclizations: Synthesis of the Tetracyclic Core of Tronocarpine. *Org. Lett*. **2006**, *8*, 4561–4564.

[80] Dey, R.; Banerjee, P. Metal-Free Ring Opening Cyclization of Cyclopropane Carbaldehydes and *N*-Benzyl Anilines: An Eco-Friendly Access to Functionalized Benzo[*b*]azepine Derivatives. *Adv. Synth. Catal*. **2019**, *361*, 2849–2854.

[81] Shenje, R.; Martin, M. C.; France, S. A Catalytic Diastereoselective Formal [5+2] Cycloaddition Approach to Azepino[1,2-*a*]indoles: Putative Donor-Acceptor Cyclobutanes as Reactive Intermediates. *Angew. Chem. Int. Ed*. **2014**, *53*, 13907–13911.

[82] Feng, L. W.; Ren, H.; Xiong, H.; Wang, P.; Wang, L.; Tang, Y. Reaction of Donor-Acceptor Cyclobutanes with Indoles: A General Protocol for the Formal Total Synthesis of (±)-Strychnine and the Total Synthesis of (±)-Akuammicine. *Angew. Chem. Int. Ed.* **2017**, *56*, 3055–3058.

[83] Bajtos, B.; Yu, M.; Zhao, H.; Pagenkopf, B. L. C-2/C-3 Annulation and C-2 Alkylation of Indoles with 2-Alkoxycyclopropanoate Esters. *J. Am. Chem. Soc*. **2007**, *129*, 9631–9634.

[84] Vemula, N.; Pagenkopf, B. L. Synthesis and Reactivity of Alkoxy-activated Cyclobutane-1,1-dicarboxylates. *Org. Chem. Front*. **2016**, *3*, 1205–1212.

[85] Snider, B. B. Manganese(III)-Based Oxidative Free-Radical Cyclizations. *Chem. Rev*. **1996**, *96*, 339–363.

[86] Lumb, J.-P.; Choong, K. C.; Trauner, D. *ortho*-Quinone Methides from *para*-Quinones: Total Synthesis of Rubioncolin B. *J. Am. Chem. Soc*. **2008**, *130*, 9230–9231.

[87] Tanada, Y.; Mori, K. Synthesis and Absolute Configuration of Nocardione A and B, Furano-*o*-naphthoquinone-Type Metabolites of *Nocardia* sp. With Antifungal, Cytotoxic, and Enzyme Inhibitory Activities. *Eur. J. Org. Chem*. **2001**, 4313–4319.

[88] Zhao, J.-L.; Zhou, L.-G.; Wu, J.-Y. Effects of Biotic and Abiotic Elicitors on Cell Growth and Tanshionone Accumulation in *Salvia miltiorrhiza* Cell Cultures. *Appl. Microbiol. Biotechnol*. **2010**, *87*, 137–144.

[89] Bolton, R. Sulphuryl Chloride as an Electrophile. Part IV, Steric Hindrance to Activation by the Methoxy-group. *J. Chem. Soc. B* **1970**, 1770–1772.

[90] Kreft, A.; Ehlers, S.; Jones, P. G.; Werz, D. B. Ring-Opening Reactions of Donor–Acceptor Cyclobutanes with Electron-Rich Arenes, Thiols, and Selenols. *Org. Lett.* **2019**, *21*, 6315–6319.

Chapter 4

4 Conclusion and Future Works

4.1 Conclusion

The ring expansion reaction of D-A cyclobutane has been developed to access δ-lactone compounds via intramolecular oxygen transfer. The reaction was inspired by the Cloke-Wilson rearrangement and conducted under ambient temperature with moderate yields. The synthesized δ-lactone compounds are obtained as a 1:1.5 to 1:1 ratio of diastereomers. This work offers some advantages compared with the classic Cloke-Wilson rearrangement that requires extreme reaction conditions such as high temperature. The reaction was promoted by a HOTf/HFIP system that increases the electron-withdrawing properties of the geminal esters on the D-A cyclobutane through hydrogen bonding. The solvent effect and a Brønsted acid system stabilize the transition states and lowers the activation energy of the reaction. D-A cyclobutane with a strong donor functional group can uncontrollably fragment under HOTf/HFIP conditions due to the powerful electron-withdrawing effect imparted to the protonated hemimalonate. To promote the reaction when strong donor groups are present on the D-A cyclobutane HOTf is not added and only the HFIP is exploited to apply a solvent effect.

The ring-opening reaction of D-A cyclobutanes with aromatic nucleophiles has been investigated as well. In this research, some reactions of alkoxy-substituted cyclobutanes with electron rich aromatic nucleophiles show excellent yields when catalyzed by $Yb(OTf)_3$ in dichloromethane. Alkoxy-substituted cyclobutane is very reactive because of the strong donor group, and a mild Lewis acid is sufficient to activate the cyclobutane with good nucleophiles.

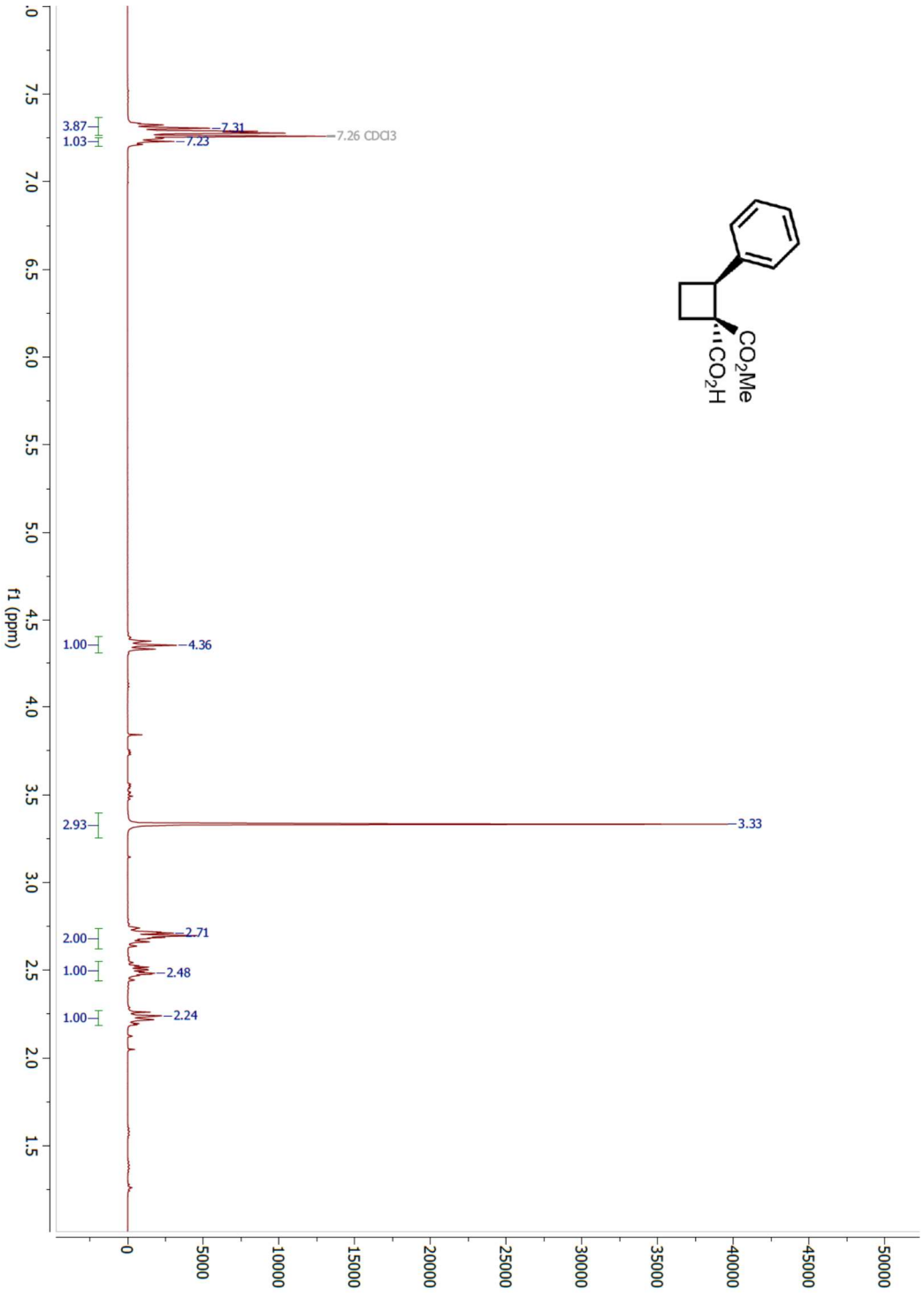
4.2 Future Works

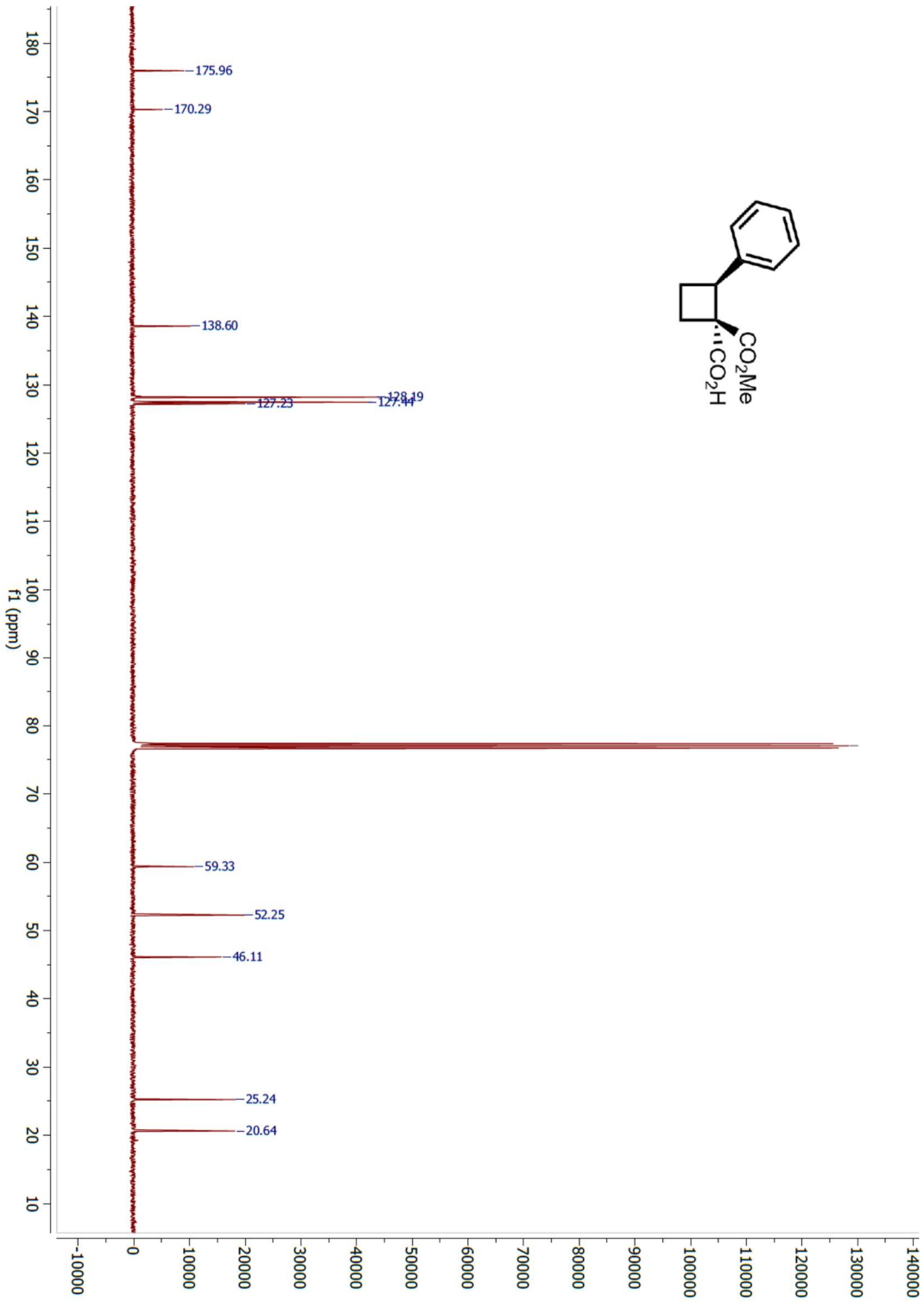
Due to the COVID-19 pandemic, the research lab was shutdown and we were unable to further explore the ring expansion reactions of D-A cyclobutanes and contribute more examples. Also, the reaction conditions necessary for the alkoxy-substituted cyclobutanes

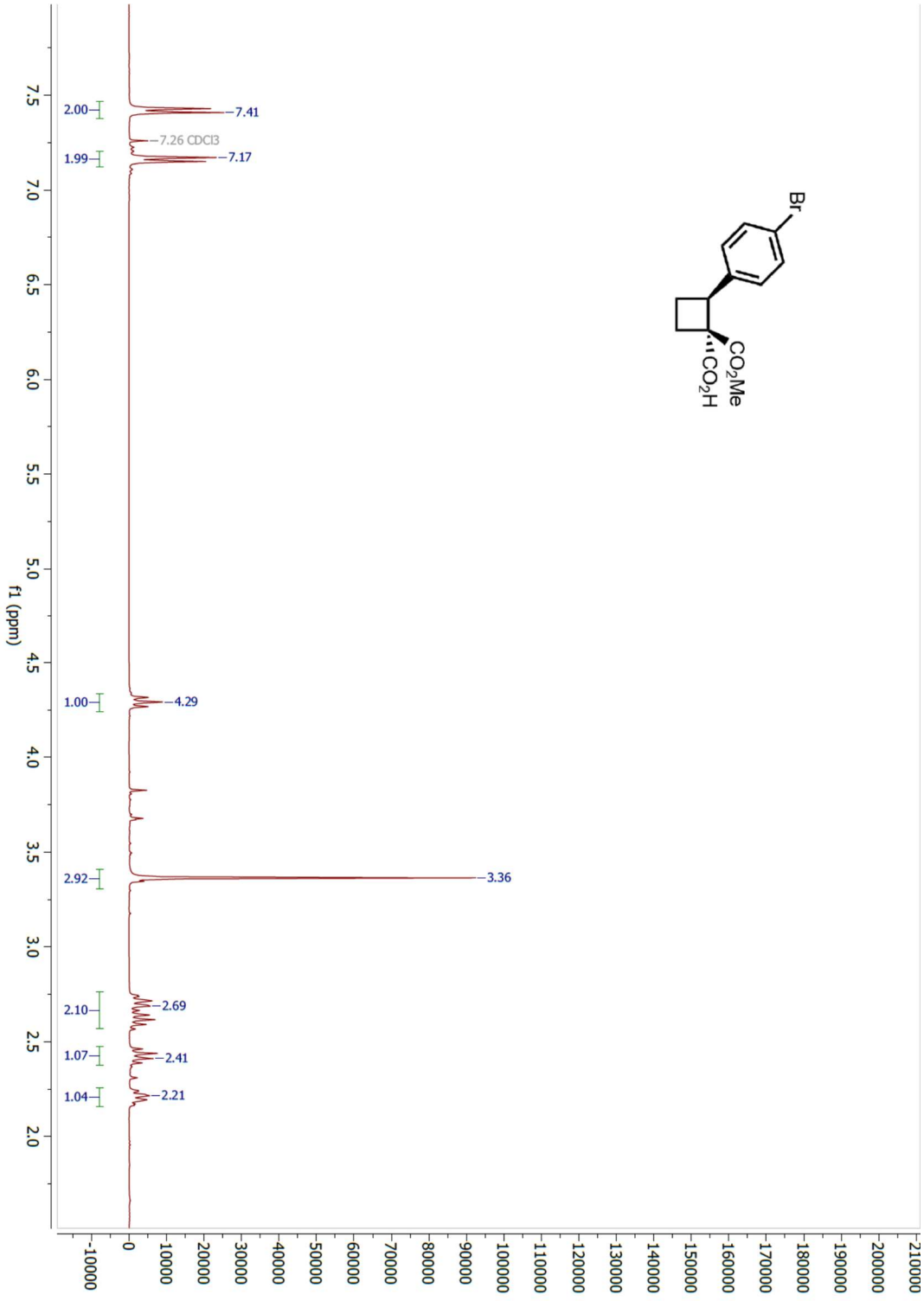
is not fully established. Therefore, to complete this research more examples are required, along with further optimization of the reaction conditions.

Work similar to our undertaking was reported by Werz, but the scope of aromatic nucleophilic additions to alkoxy-activated D-A cyclobutanes has only been reported with indoles, and there is value in further reaction discovery.

Appendix A – Supporting Information for Chapter 2




175.96
170.29
138.60
128.19
127.23
127.44
59.33
52.25
46.11
25.24
20.64
CO2Me
CO2H
f1 (ppm)


Br
CO2Me
CO2H
2.00
7.41
7.26 CDCl3
1.99
7.17
1.00
4.29
2.92
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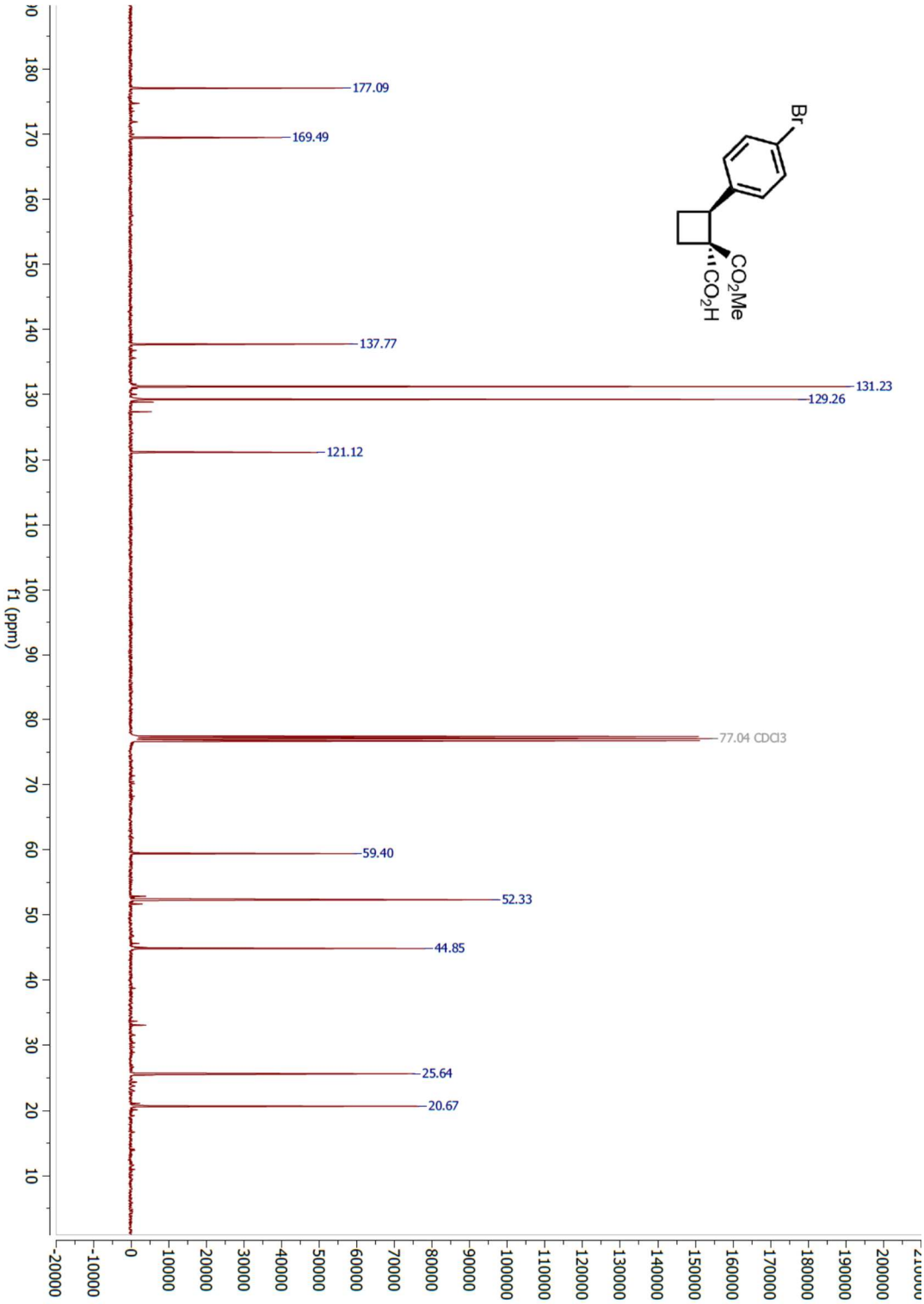
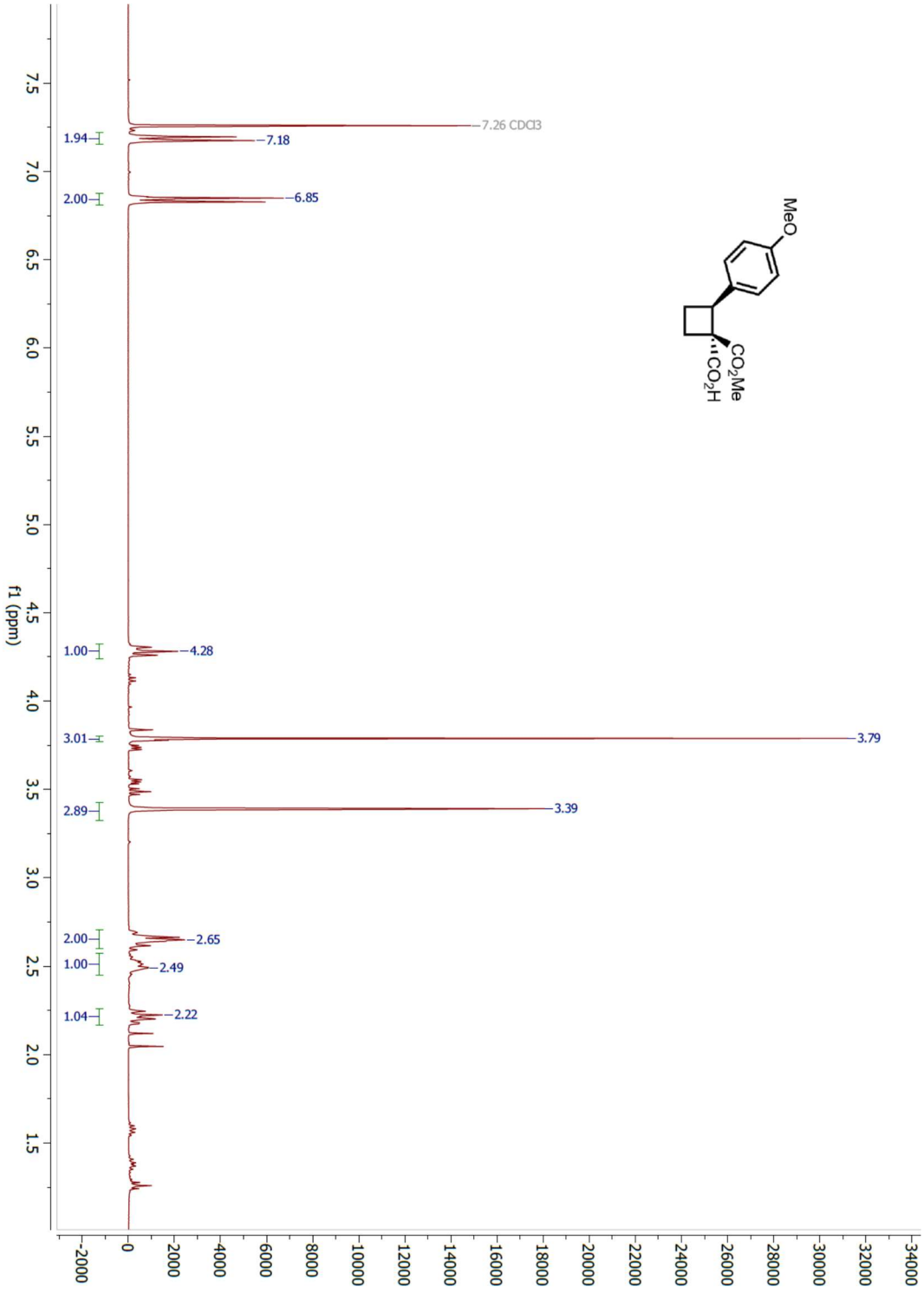
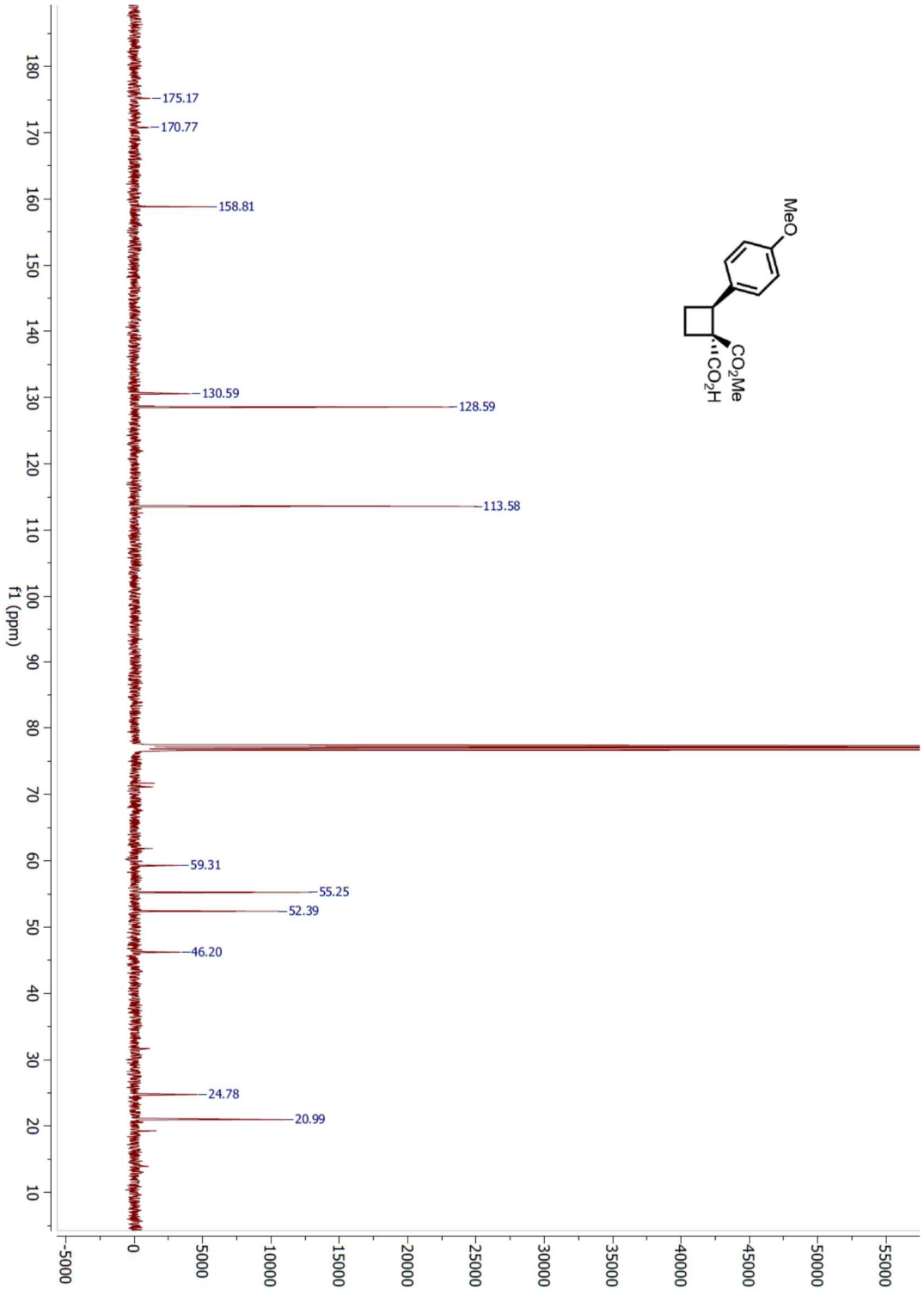
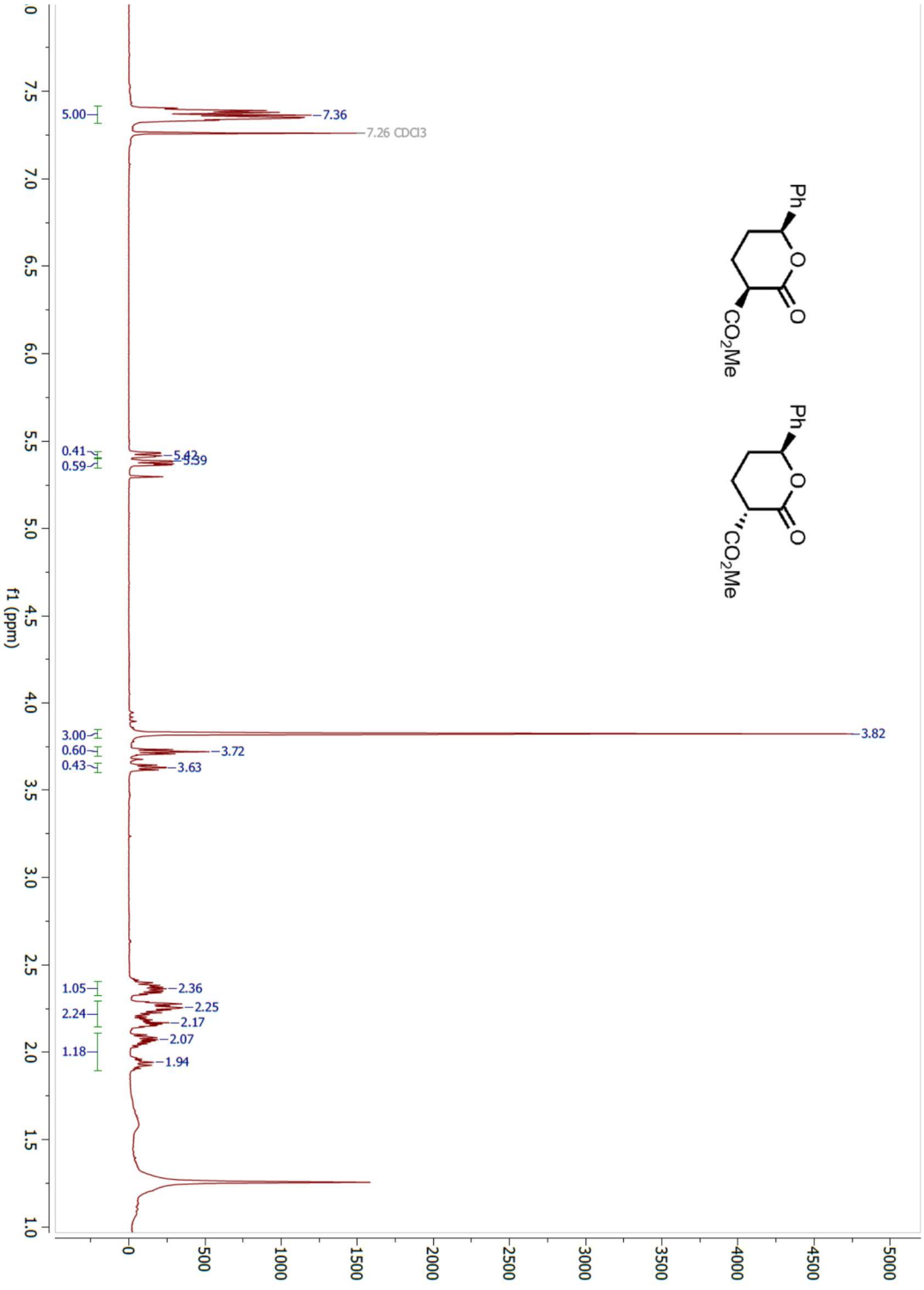
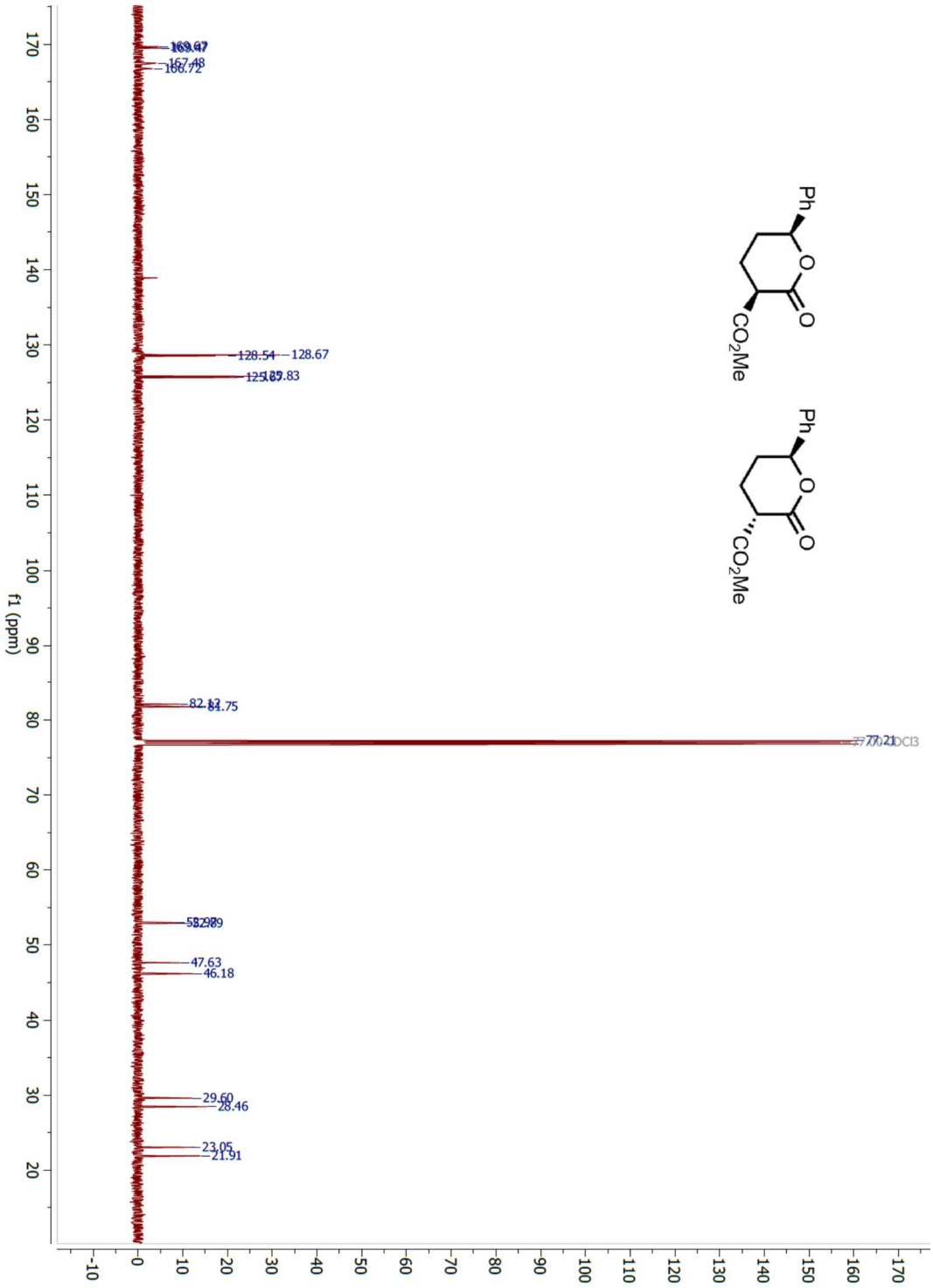
2.10
2.69
1.07
2.41
1.04
2.21
f1 (ppm)

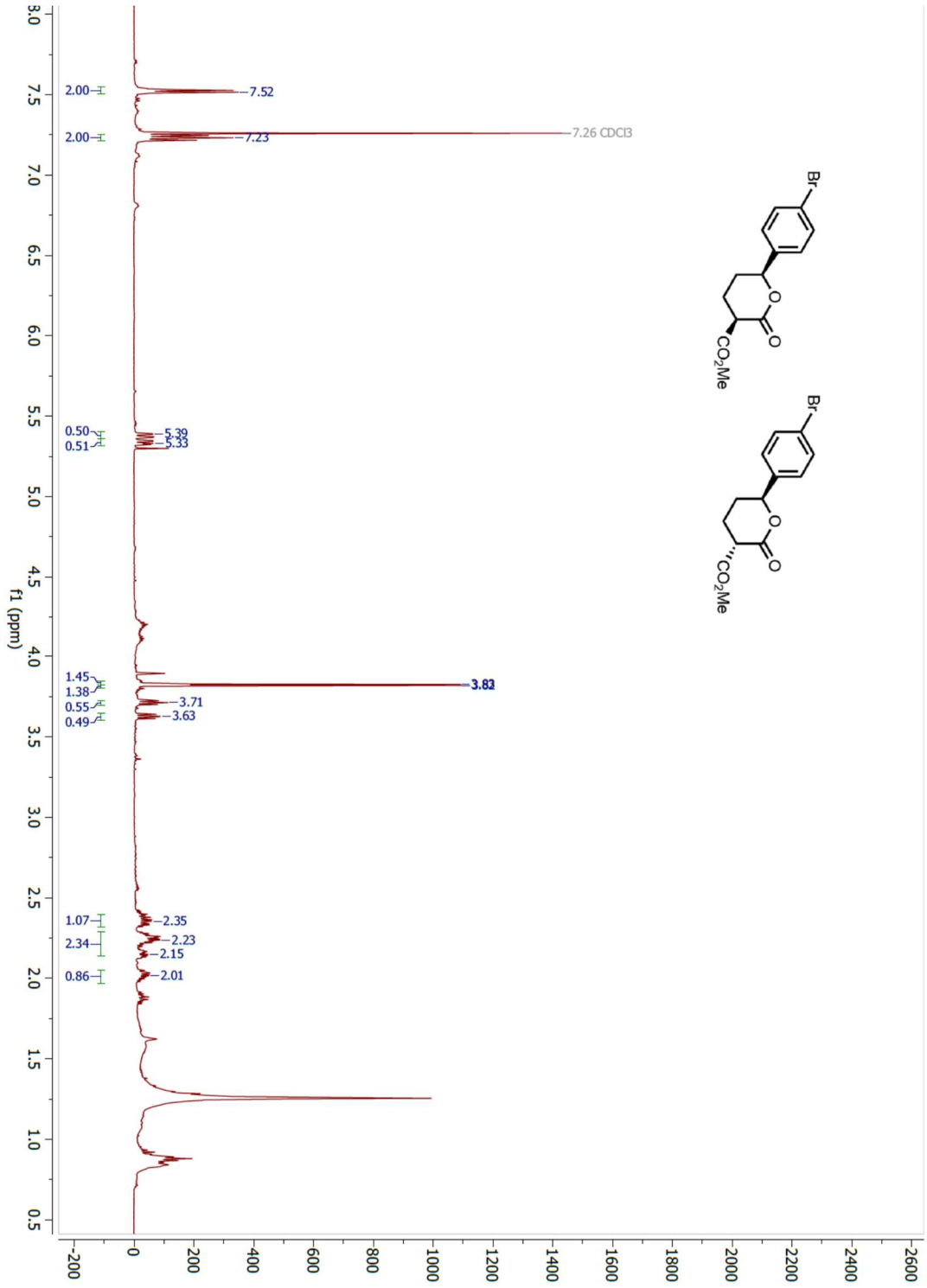

177.09
169.49
137.77
131.23
129.26
121.12
77.04 CDCl3
59.40
52.33
44.85
25.64
20.67
Br
CO2Me
CO2H
f1 (ppm)

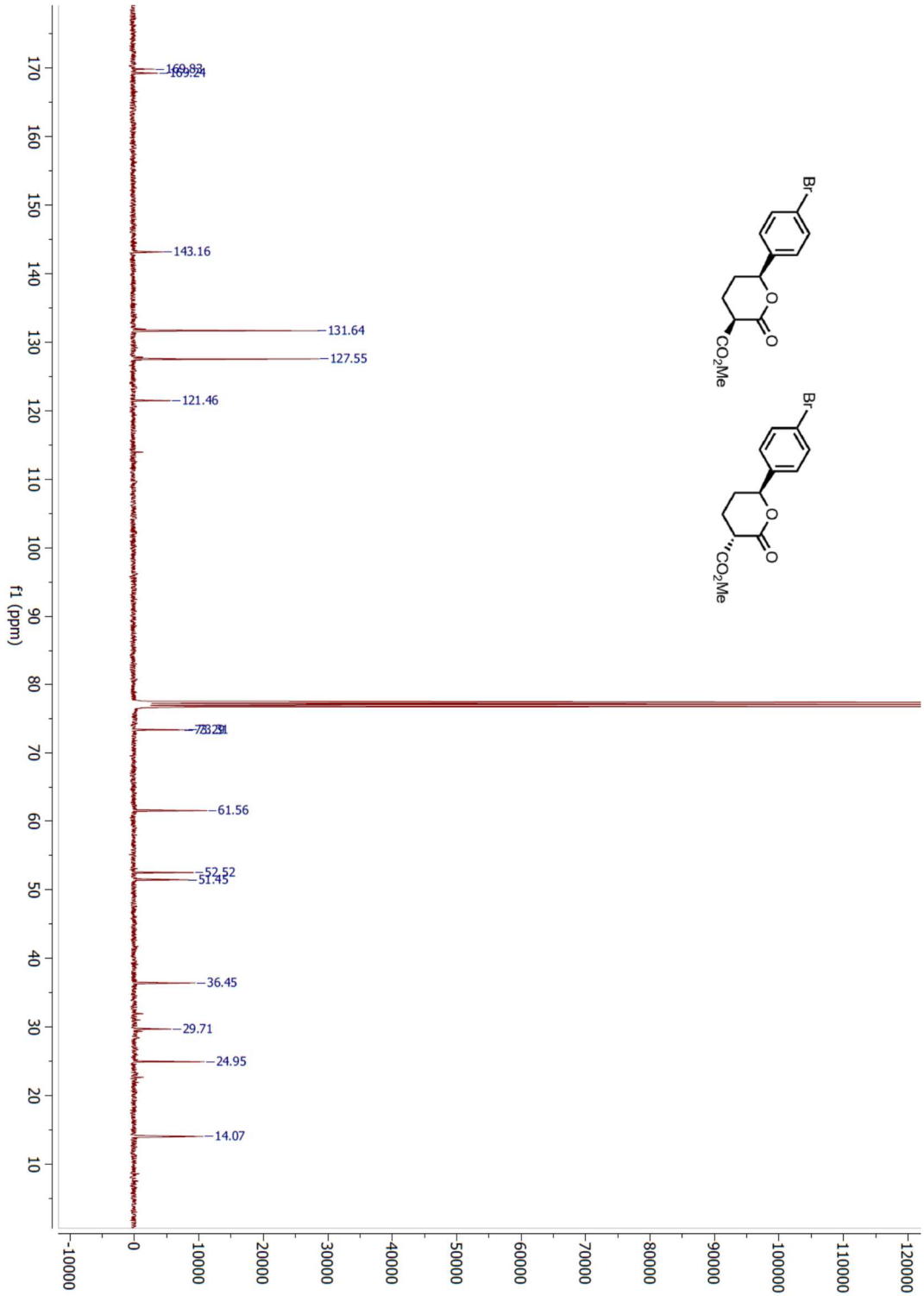

7.26 CDCl3
7.18
6.85
4.28
3.79
3.39
2.65
2.49
2.22
1.94
2.00
1.00
3.01
2.89
2.00
1.00
1.04
MeO
CO2Me
CO2H
f1 (ppm)

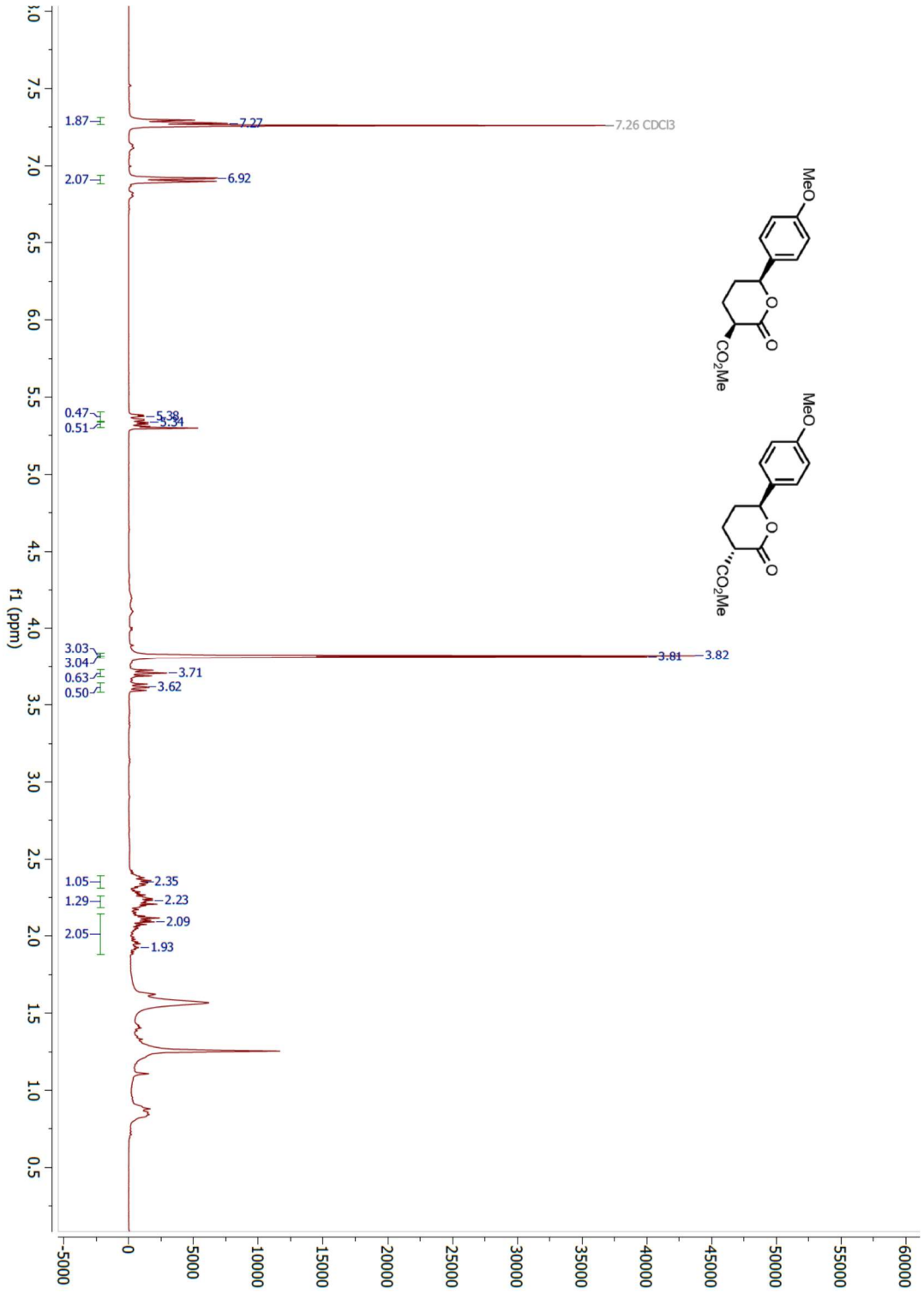

175.17
170.77
158.81
130.59
128.59
113.58
59.31
55.25
52.39
46.20
24.78
20.99
f1 (ppm)
MeO
CO2Me
CO2H

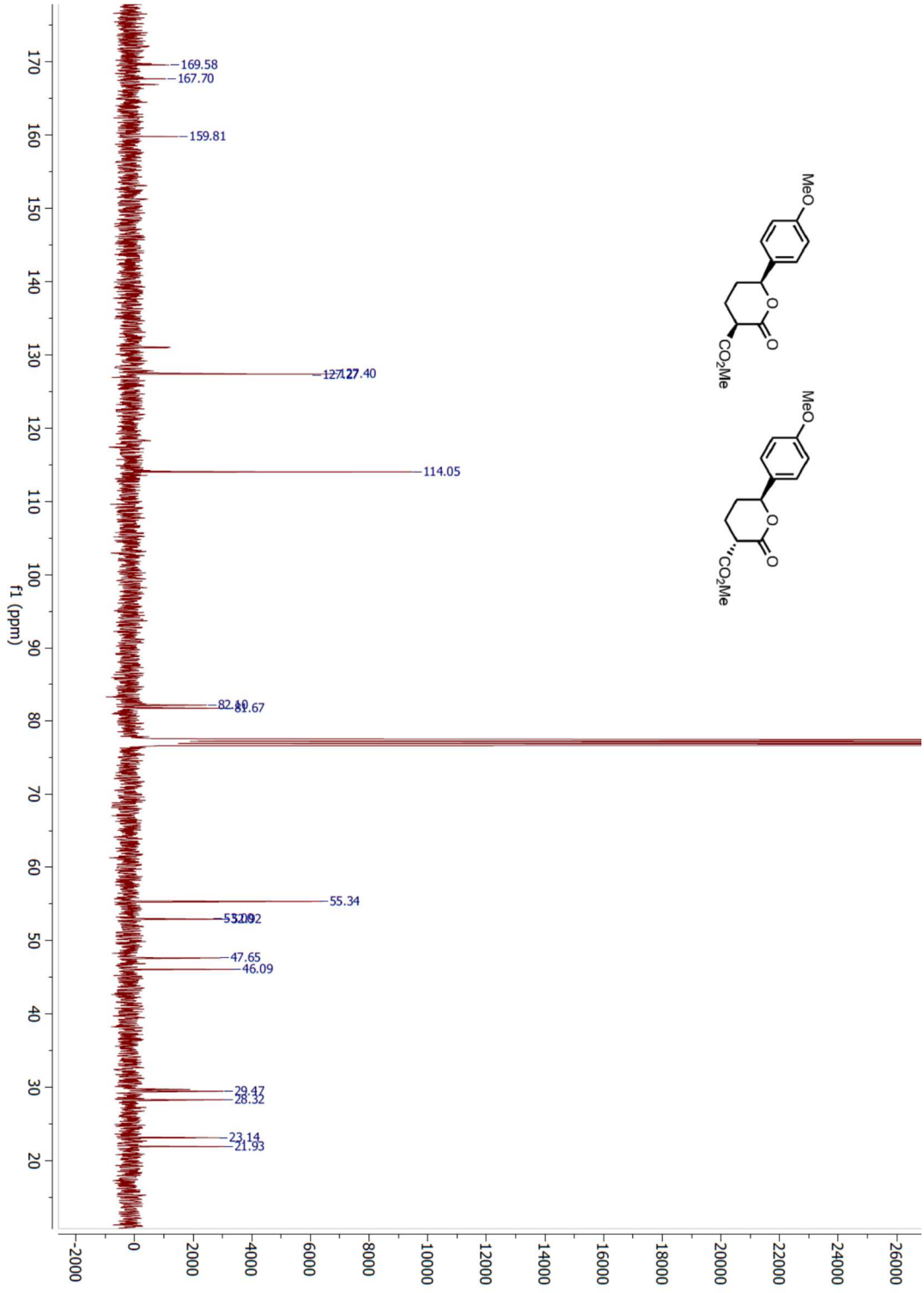

Ph
O
O
CO2Me
Ph
O
O
CO2Me
7.36
7.26 CDCl3
5.42
5.39
3.82
3.72
3.63
2.36
2.25
2.17
2.07
1.94
5.00
0.41
0.59
3.00
0.60
0.43
1.05
2.24
1.18
f1 (ppm)


Ph
O
O
CO2Me
Ph
O
O
CO2Me
f1 (ppm)
128.54
128.67
125.83
82.75
77.21
CDCl3
47.63
46.18
29.60
28.46
23.05
21.91

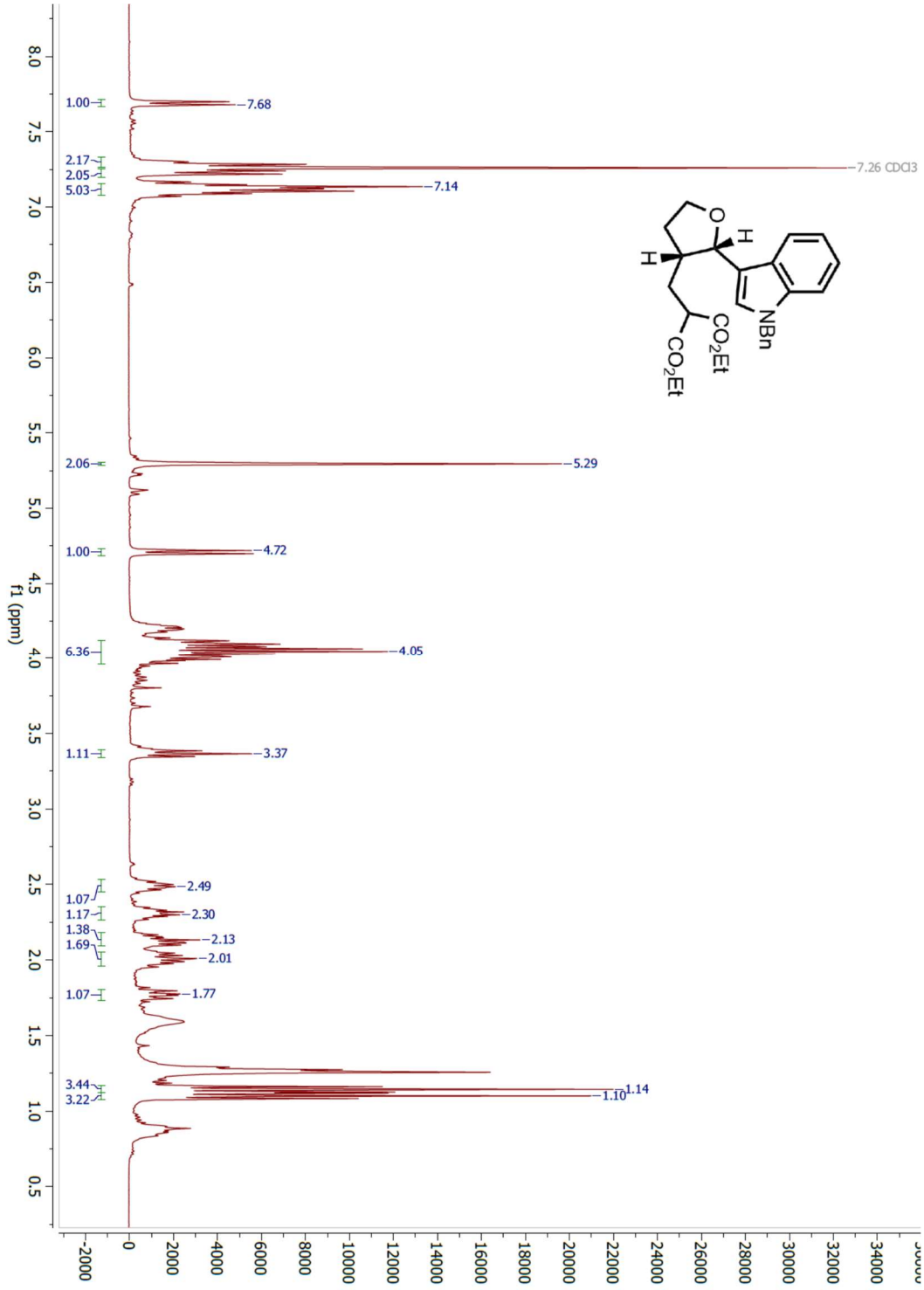

7.52
7.23
7.26 CDCl3
5.39
5.33
3.82
3.71
3.63
2.35
2.23
2.15
2.01
2.00
2.00
0.50
0.51
1.45
1.38
0.55
0.49
1.07
2.34
0.86
Br
CO2Me
Br
CO2Me
f1 (ppm)

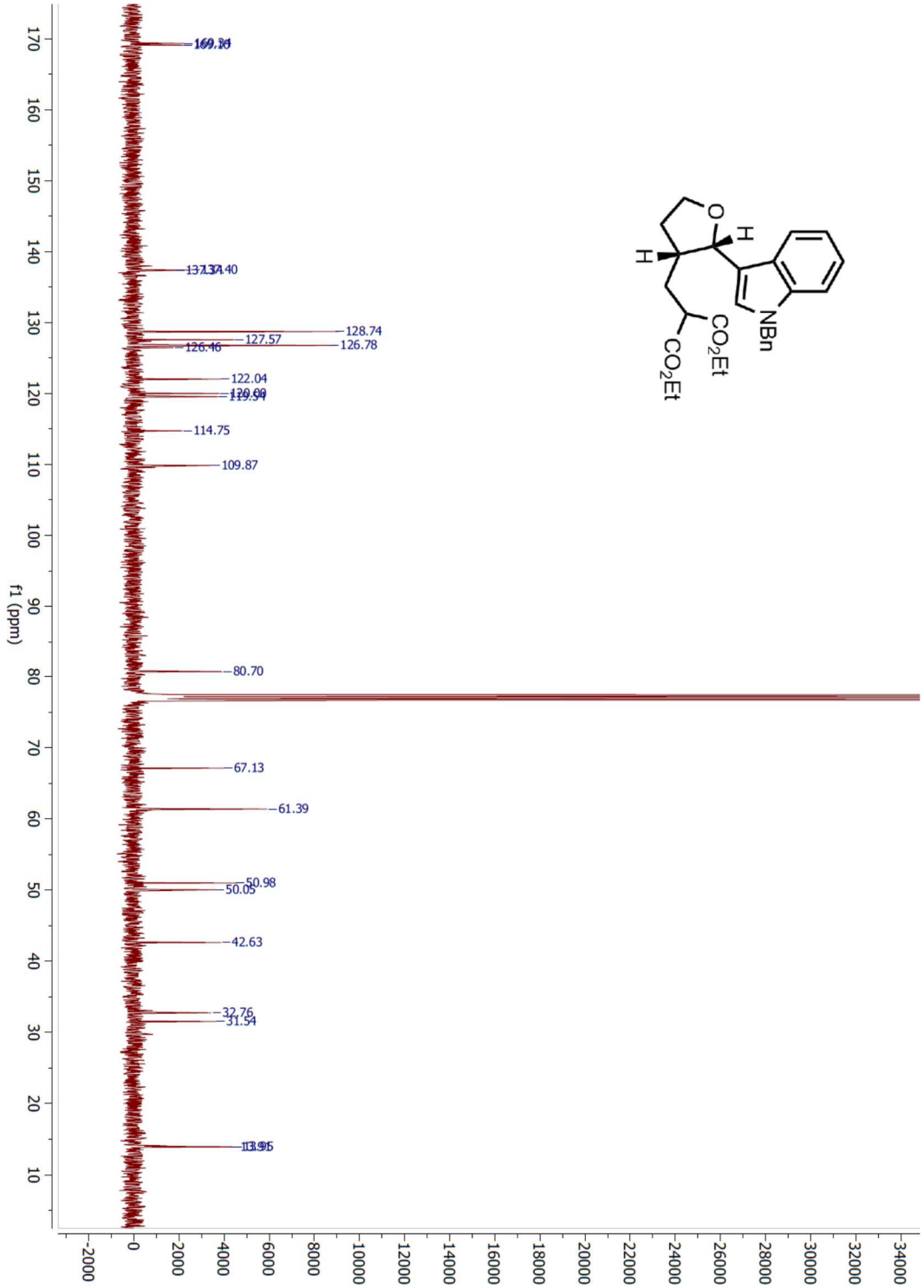

169.82
169.24
143.16
131.64
127.55
121.46
78.24
78.01
61.56
52.52
51.45
36.45
29.71
24.95
14.07
f1 (ppm)
Br
O
O
CO2Me
Br
O
O
CO2Me

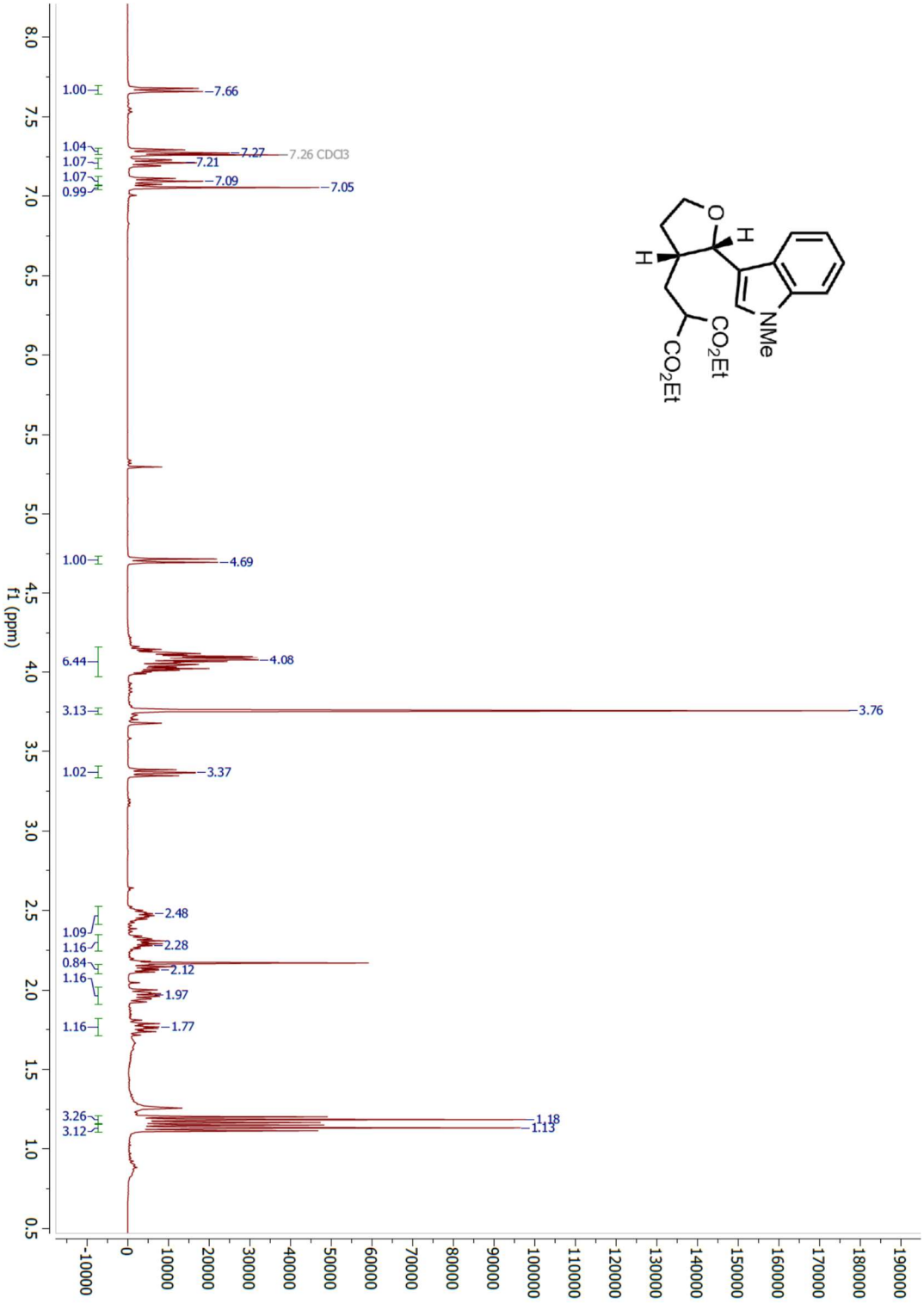

f1 (ppm)
1.87
7.27
7.26 CDCl3
2.07
6.92
0.47
0.51
5.38
5.34
3.03
3.04
0.63
0.50
3.81
3.82
3.71
3.62
1.05
1.29
2.05
2.35
2.23
2.09
1.93
MeO
CO2Me
MeO
CO2Me

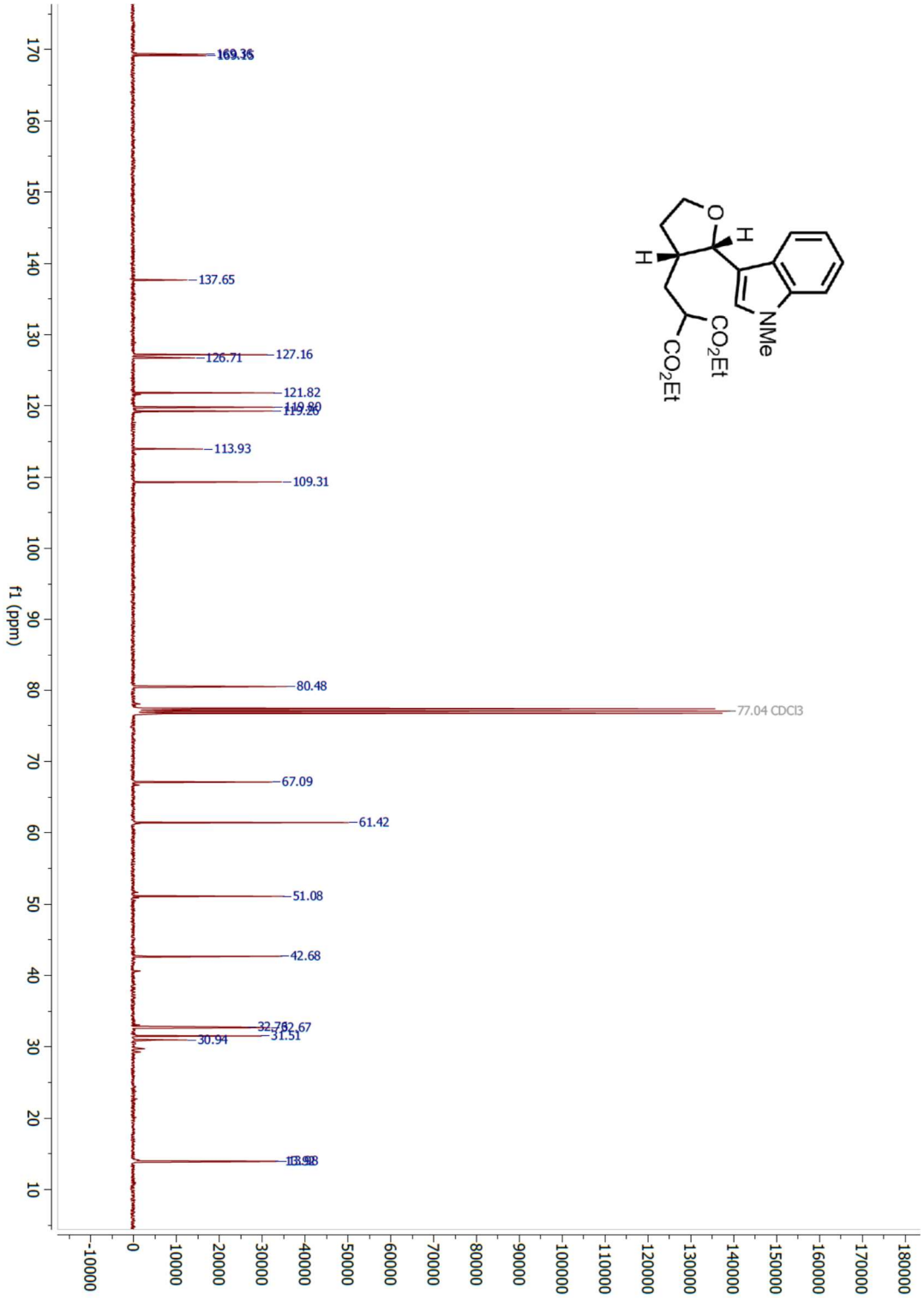

169.58
167.70
159.81
127.40
114.05
82.40
81.67
55.34
53.09
47.65
46.09
29.47
28.32
23.14
21.93
f1 (ppm)
MeO
CO2Me
MeO
CO2Me

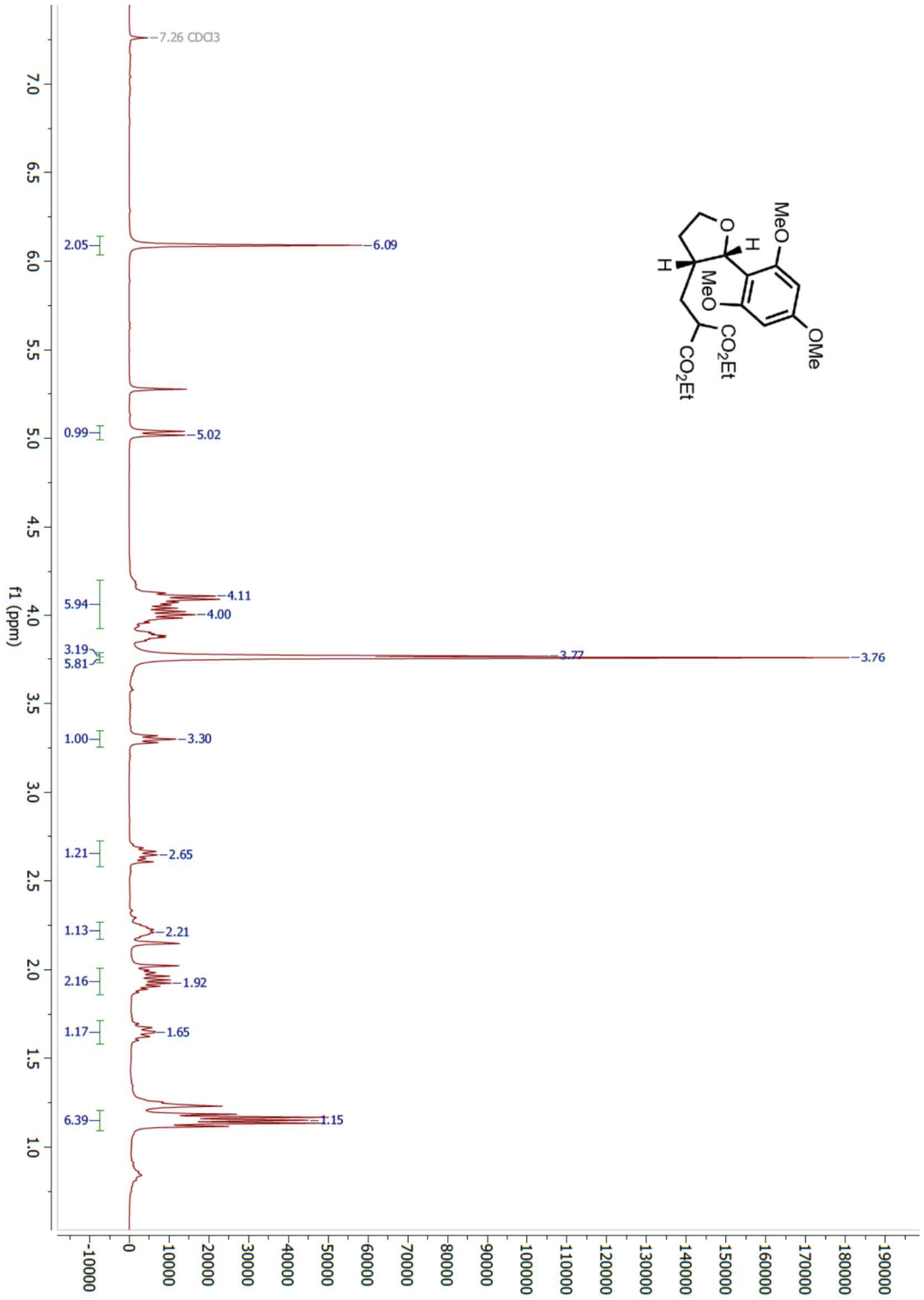
Appendix B – Supporting Information for Chapter 3

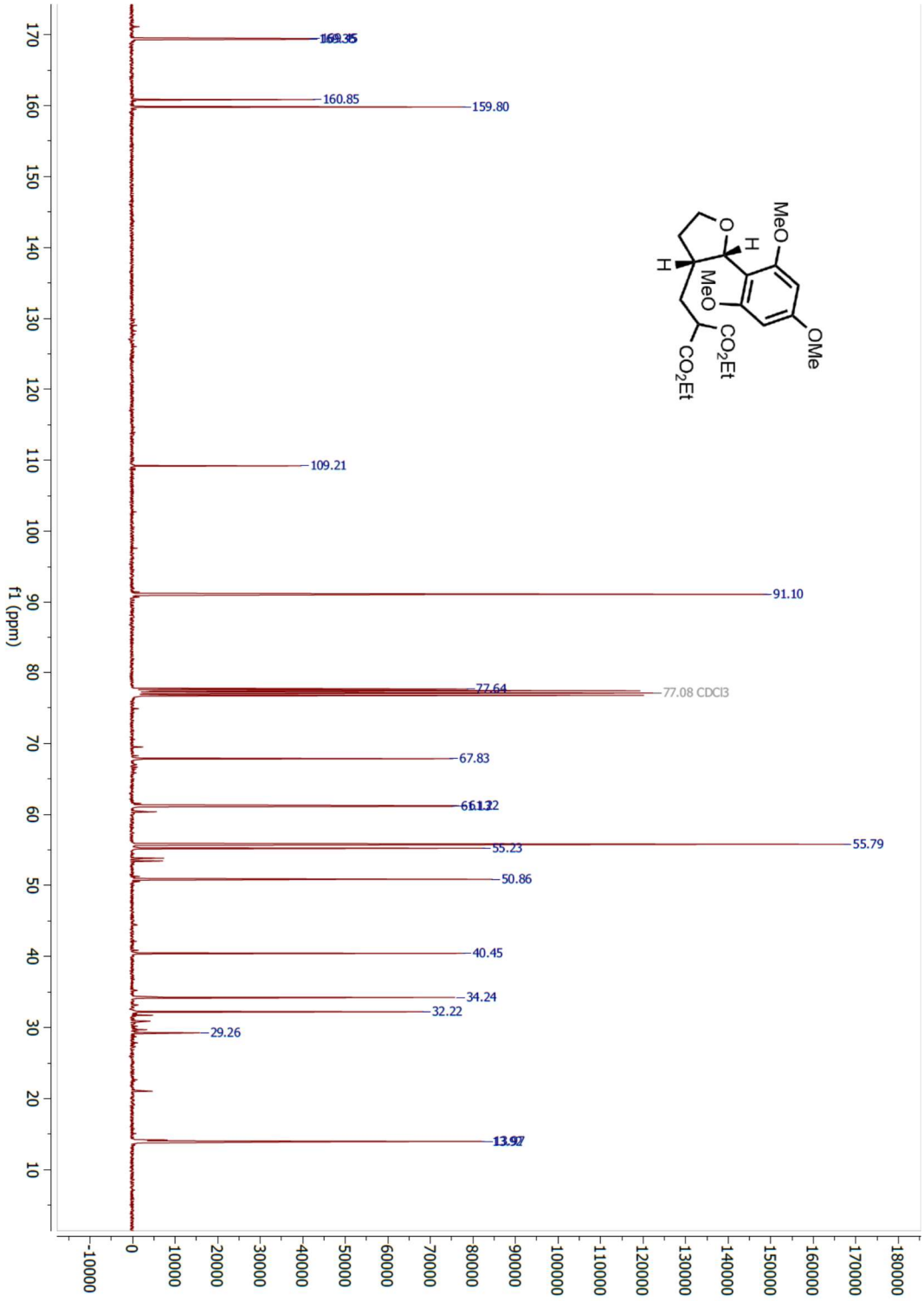


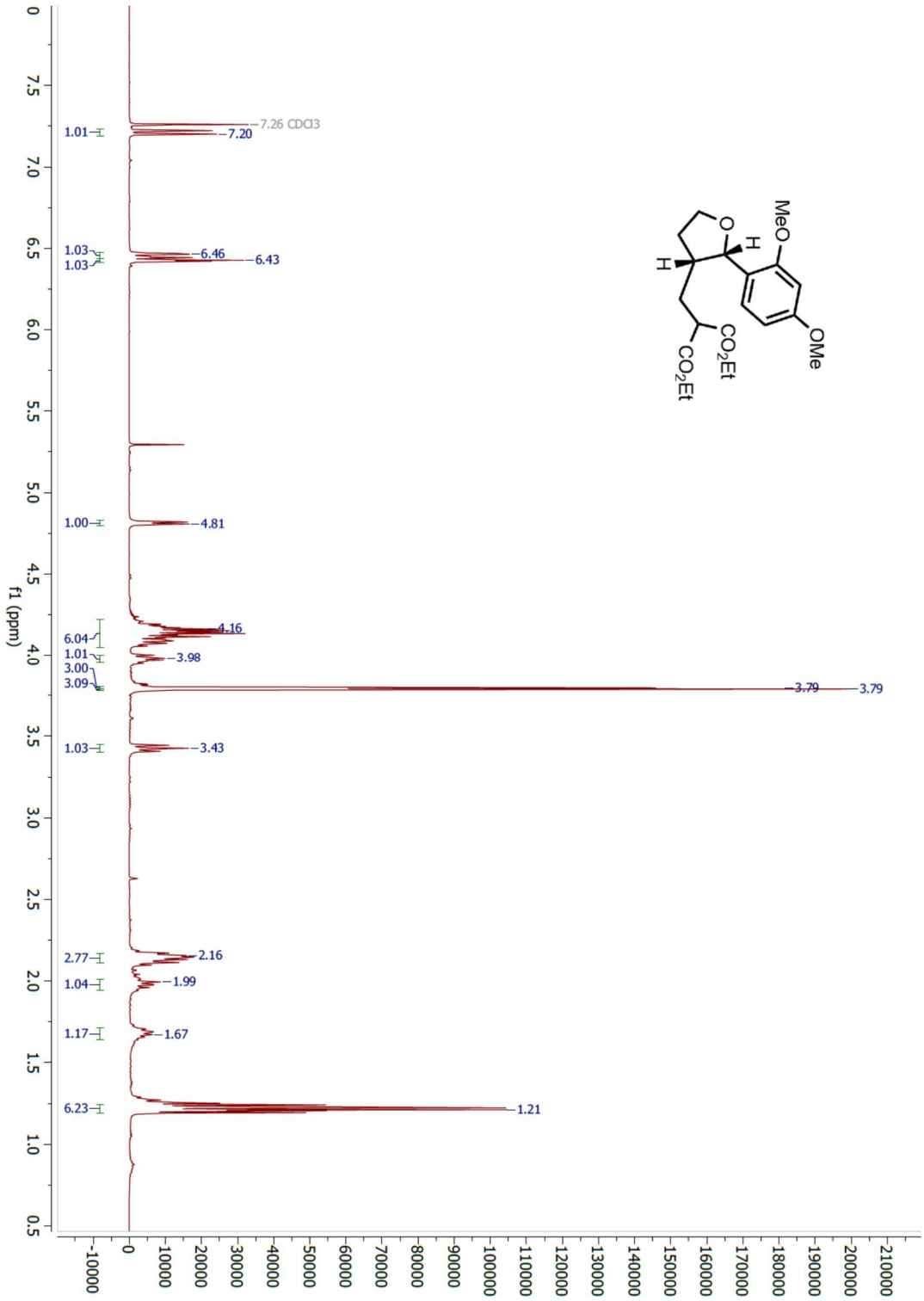

f1 (ppm)
128.74
127.57
126.78
126.46
122.04
114.75
109.87
80.70
67.13
61.39
50.98
50.05
42.63
32.76
31.54
O
H
H
CO2Et
CO2Et
NBn

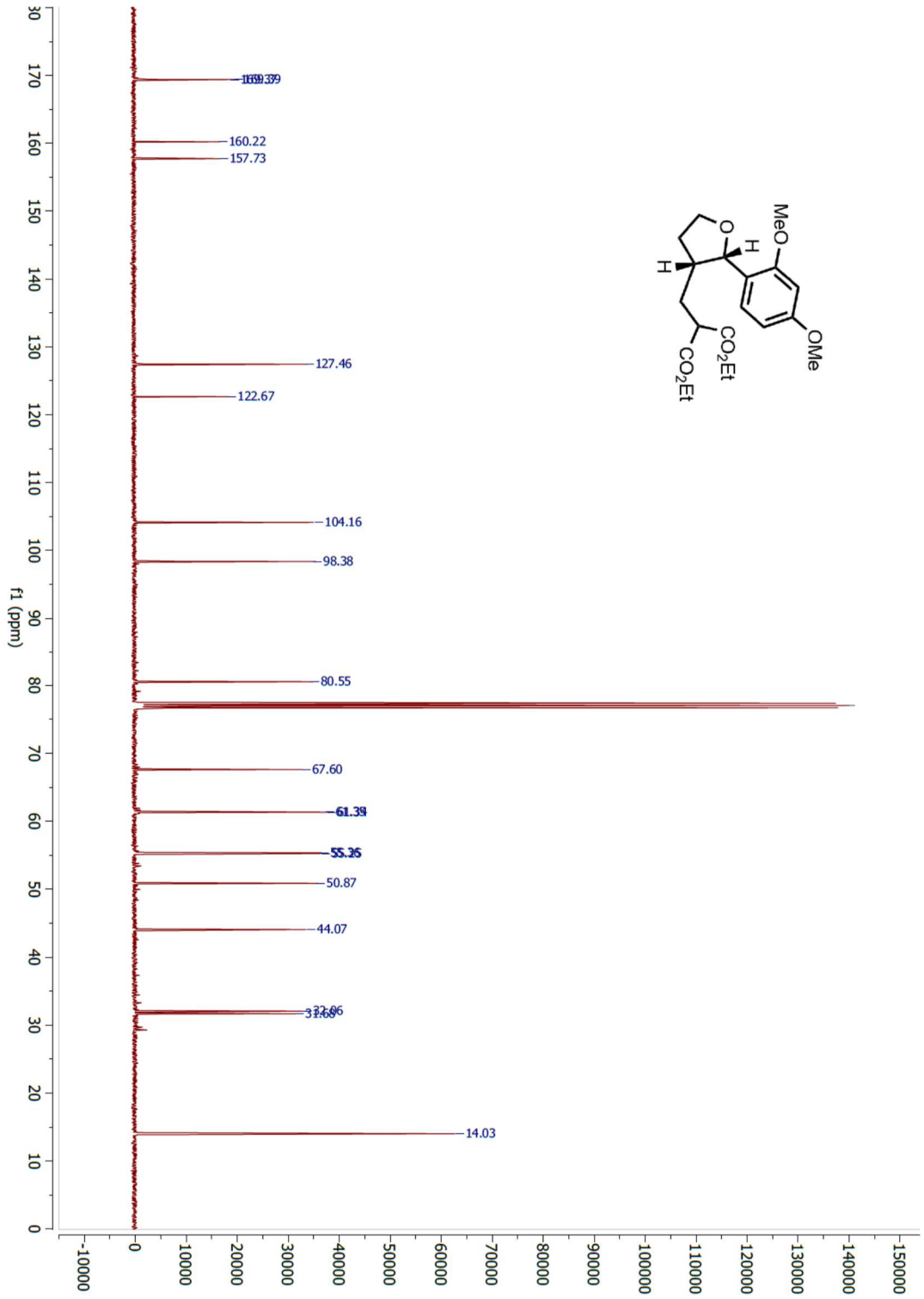

f1 (ppm)
1.00
7.66
1.04
7.27
7.26 CDCl3
1.07
7.21
1.07
7.09
0.99
7.05
1.00
4.69
6.44
4.08
3.13
3.76
1.02
3.37
2.48
1.09
1.16
2.28
0.84
2.12
1.16
1.97
1.16
1.77
3.26
1.18
3.12
1.13
O
H
H
NMe
CO2Et
CO2Et


169.36
137.65
127.16
126.71
121.82
113.93
109.31
80.48
77.04 CDCl3
67.09
61.42
51.08
42.68
32.78
31.51
30.94
f1 (ppm)
O
H
H
CO2Et
CO2Et
NMe


7.26 CDCl3
6.09
5.02
4.11
4.00
3.77
3.76
3.30
2.65
2.21
1.92
1.65
1.15
2.05
0.99
5.94
3.19
5.81
1.00
1.21
1.13
2.16
1.17
6.39
f1 (ppm)
MeO
H
O
H
MeO
CO2Et
CO2Et
OMe


160.85
159.80
109.21
91.10
77.64
77.08 CDCl3
67.83
55.79
55.23
50.86
40.45
34.24
32.22
29.26
MeO
MeO
OMe
CO2Et
CO2Et
H
H
O
f1 (ppm)


f1 (ppm)
7.26 CDCl3
7.20
6.46
6.43
4.81
4.16
3.98
3.79
3.79
3.43
2.16
1.99
1.67
1.21
1.01
1.03
1.03
1.00
6.04
1.01
3.00
3.09
1.03
2.77
1.04
1.17
6.23
MeO
OMe
CO2Et
CO2Et
O
H
H


f1 (ppm)
160.22
157.73
127.46
122.67
104.16
98.38
80.55
67.60
50.87
44.07
14.03
MeO
OMe
O
H
H
CO2Et
CO2Et

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Poster Presentation Award
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The University of Western Ontario

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2018-Present

Research Assistant Work Study Student
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Publications:

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Synthesis of Functionalized Tetrahydropyridines by SnCl4-mediated [4+2] Cycloaddition between Donor-Acceptor Cyclobutanes and Nitriles. David Tong, Jackie Wu, Nathan Bazinski, Donghyun Koo, Naresh Vemula and Brian L. Pagenkopf. *Chem. Eur. J.* **2019**, *25*, 15244–15247.

Conferences:

Crystallization-induced Emission Enhancement of Benzosilole Photoluminescence and Electrochemiluminescence. Donghyun Koo, Liuqing Yang, Jackie Wu, Zhifeng Ding and Brian L. Pagenkopf. Quebec-Ontario Mini-Symposium for Synthetic and Bioorganic Chemistry 2019 (QOMSBOC 2019), Ottawa, Canada, November 8-10, 2019.

Synthesis of Novel Benzosiloles as Electrochemiluminescence Chromophores. Donghyun Koo, Liuqing Yang, Tyler Day, Zhifeng Ding and Brian L. Pagenkopf. Quebec-Ontario Mini-Symposium for Synthetic and Bioorganic Chemistry 2018 (QOMSBOC 2018), Toronto, Canada, November 16-18, 2018.