NOVEL CARBON–CARBON AND CARBON–OXYGEN BOND FORMING REACTIONS WITH THE CYCLIC ANHYDRIDE DERIVATIVES: FACILE SYNTHESIS OF STRUCTURALLY INTERESTING BIOACTIVE NATURAL AND UNNATURAL PRODUCTS

THESIS

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By

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MARCH 2011

Dedicated to…

Rev. Dadaji

(Pandurangshashtri Athavale,

Founder,- Swadhyay Parivar)

&

My Family

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CERTIFICATE

This is to certify that the work incorporated in the thesis entitled "***Novel Carbon–Carbon and Carbon–Oxygen Bond Forming Reactions with the Cyclic Anhydride Derivatives: Facile Synthesis of Structurally Interesting Bioactive Natural and Unnatural Products***" which is being submitted to the ***University of Pune*** for the award of ***Doctor of Philosophy*** in ***Chemistry*** by ***Mr. Ramesh M. Patel*** was carried out by him under my supervision at the National Chemical Laboratory, Pune. Such material as has been obtained from other sources has been duly acknowledged in the thesis.

March 2011
Pune

Dr. N. P. Argade
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Candidate's Declaration

I hereby declare that the research work incorporated in the thesis entitled "***Novel Carbon–Carbon and Carbon–Oxygen Bond Forming Reactions with the Cyclic Anhydride Derivatives: Facile Synthesis of Structurally Interesting Bioactive Natural and Unnatural Products***" submitted for the degree of ***Doctor of Philosophy*** in ***Chemistry*** to the ***University of Pune***, has been carried out by me at the Division of Organic Chemistry, National Chemical Laboratory, Pune, India, from April 2005 to March 2011 under the supervision of Dr. Narshinha P. Argade. This work has not been submitted in part or full by me for a degree or diploma to this or any other University or Institution.

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A research thesis is an enriching experience, of knowledge enhancement, of bringing rigour in thinking, more importantly of realising that individual effort is actually an outcome of the support of many. That is probably why thesis writers feel the urge to write acknowledgements!

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I can't find the right words for my beloved wife Bhoomi, without her patience, love and sacrifice, this work would not have been possible. This Ph. D. thesis is the result of the extraordinary efforts, affection and sacrifices of my wife and family – they believed in me and allowed me to do what I wanted .

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Ramesh

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General Remarks

- All the solvents used were purified using the known literature procedures.
- Petroleum ether used in the experiments was of 60-80 °C boiling range.
- Silica gel column chromatographic separations were carried out by gradient elution with light petroleum ether-ethyl acetate mixture, unless otherwise mentioned (silica gel, 60-120 mesh/100-200 mesh/230-400 mesh).
- TLC was performed on E-Merck pre-coated 60 F_{254} plates and the spots were rendered visible by exposing to UV light, iodine, *p*-anisaldehyde (in ethanol), bromocresol green (in ethanol) and ninhydrin (in ethanol).
- IR spectra were recorded on Shimadzu FTIR instrument, for solid either as nujol mull or in chloroform solution (concentration 0.05 to 10%) and neat in case of liquid compounds.
- NMR spectra were recorded on Brucker ACF 200 (200 MHz for ^{1}H NMR and 50 MHz for ^{13}C NMR), ACF 400 (400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR) and DRX 500 (500 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR) spectrometers. Chemical shifts (δ) reported are referred to internal reference tetramethyl silane.
- Mass spectra were taken on MS-TOF mass spectrometer.
- HRMS were taken using EI method on MSI-UK AUTOCONCEPT DIP-EI and ESI method on MS-TOF mass spectrometer.
- Microanalysis data were obtained using Flash EA 1112 series and Elementar Vario EL analyser.
- All the melting points reported are uncorrected and were recorded using an electro-thermal melting point apparatus.
- All the compounds previously known in the literature were characterized by comparison of IR and NMR spectra as well as melting point with authentic samples.
- All the new experiments were repeated two or more times.
- Starting materials were obtained from commercial sources or prepared using known procedures.

Abbreviations

Å	Angstrom
Aq.	Aqueous
AIBN	2,2'-Azobisisobutyronitrile
CAN	Ceric ammonium nitrate
cat.	Catalytic
CCDC	Cambridge crystallographic data centre
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	Dicyclohexyldicarbodiimide
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEA	Diethylamine
DEPT	Distortionless enhancement by polarization transfer
DFT	Density Functional Theory
DIBAL-H	Diisobutylaluminium hydride
DMA	*N*,*N*-Dimethylacetamide
DMAP	4-(Dimethylamino)pyridine
DMF	Dimethylformamide
DMSO	Dimethyl sulphoxide
dppf	1,1'-Bis(diphenylphosphino)ferrocene
EDCI	*N*-Ethyl-*N*'-(3-dimethylaminopropyl)carbodimide hydrochloride
ee	Enantiomeric excess
ESI	Electro spray ionization
EI	Electron impact
eq.	Equation
equiv	Equivalent
h	Hour(s)
HRMS	High resolution mass spectra
HPLC	High performance liquid chromatography
Hz	Hertz
IC	Inhibitory concentration
IPA	Isopropyl alcohol
IR	Infra Red
HMDS	1,1,1,3,3,3-hexamethydisilazane
$HRh(PPh_3)_4$	Tetrakis triphenylphosphine rhodium hydride
LAH	Lithium aluminum hydride
LDA	Lithium diisopropylamine
MHz	Megahertz
min.	Minute(s)
mL	Millilitre(s)
mmol	Millimole(s)
Mp	Melting point
MS	Mass Spectrum
NBS	*N*-Bromosuccinimide
NMM	*N*-Methylmorpholine

NMO	4-Methylmorpholine *N*-oxide
NMR	Nuclear magnetic resonance
ORTEP	Orthogonal thermal ellipsoid plots
$Pd_2(dba)_3$	Tris(dibenzylideneacetone)dipalladium
PE	Petroleum ether
PPA	Polyphosphoric acid
p-TSOH	*p*-Toluenesulfonic acid
Py	Pyridine
rt	Room temperature
TBAF	Tetrabutylammonium floride
TBP	Tributylphosphine
TEA	Triethylamine
TES	Triethylsilyl
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMSOTf	Trimethylsilyl trifluoromethanesulfonate
TPP	Triphenylphosphine
UV	Ultraviolet

Abstract

The present dissertation entitled "***Novel Carbon–Carbon and Carbon–Oxygen Bond Forming Reactions with the Cyclic Anhydride Derivatives: Facile Synthesis of Structurally Interesting Bioactive Natural and Unnatural Products***" is divided into four chapters. The first chapter presents a concise literature account on the chemistry of dimethyl bromomethylfumarate and dialkyl alkylidenesuccinates obtained from the cyclic anhydrides. In the second chapter, we have demonstrated novel carbon–carbon bond forming S_N2' coupling reactions of Wittig reagents with the dimethyl bromomethylfumarate and their applications for the synthesis of lignan class of natural products gulbulin, prasanthaline, justicidin B and retrojusticidin B. In the third chapter, we have revealed two different type of novel carbon–oxygen bond forming reactions with the dialkyl alkylidenesuccinates and their applications for the synthesis of various natural and unnatural butenolides. In the fourth chapter, we have displayed racemic and chemoenzymatic total syntheses of the naturally occurring potent anti-HIV compound the (–)-1,3,4,5-tetragalloylapiitol (Figure 1).

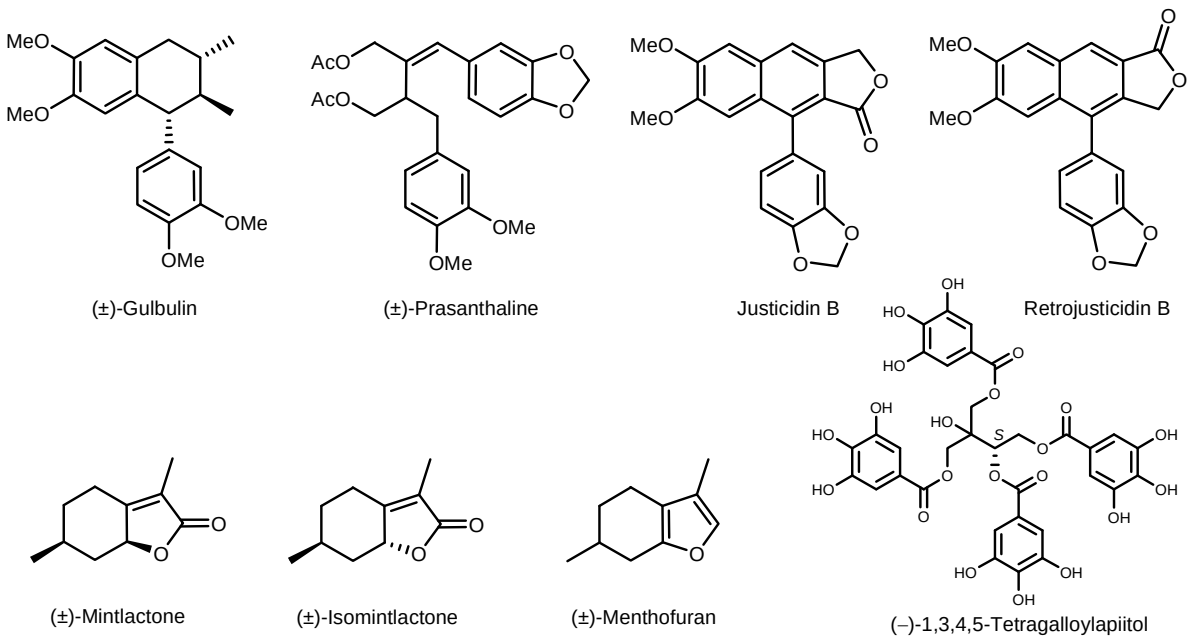
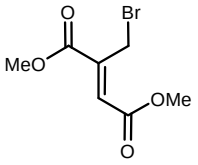


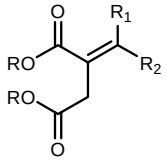
Figure 1. Structurally interesting bioactive natural products synthesized

Chapter 1: A Concise Account on the Chemistry of Dimethyl Bromomethylfumarate and Dialkyl Alkylidenesuccinates

Large number of natural and unnatural products has been synthesized by developing novel reactions with the cyclic anhydride derivatives, the dimethyl bromomethylfumarate and dialkyl alkylidenesuccinates. This chapter portrays a concise account on the methods of preparation of dimethyl bromomethylfumarate and dialkyl alkylidenesuccinates, their synthetic utilities for the

development of novel carbon–carbon and carbon–oxygen bond forming reactions and their applications for the total synthesis of various bioactive natural and unnatural products.





R = CH_3, C_2H_5; R_1 = H, alkyl; R_2 = alkyl

Figure 1. Cyclic anhydride derivatives, dimethyl bromomethylfumarate and dialkyl alkylidenesuccinates

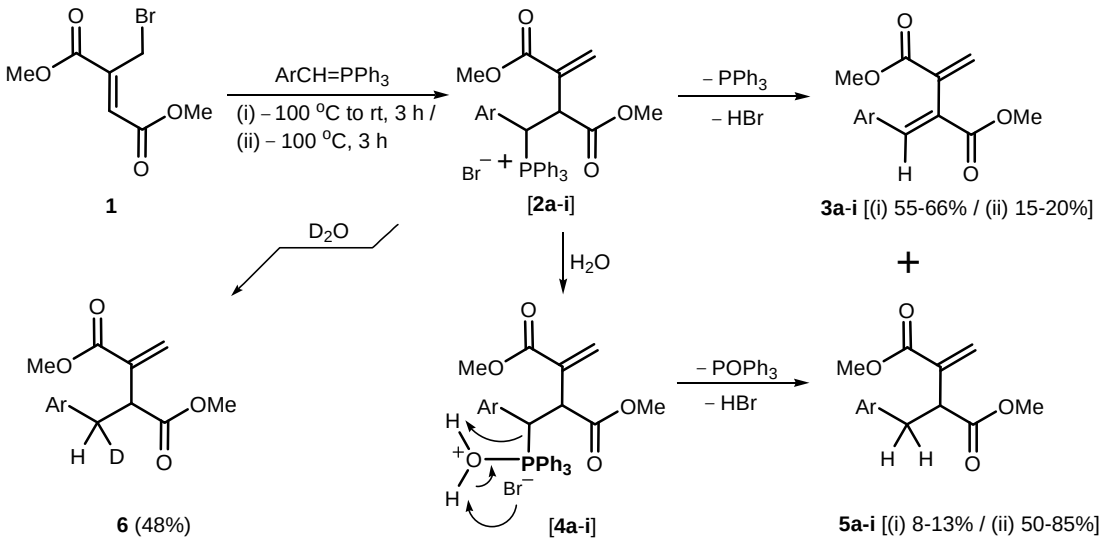
Chapter 2: Novel Carbon–Carbon Bond Forming Reactions with the Dimethyl Bromomethylfumarate: Synthesis of Bioactive Lignan Class of Natural Products

This chapter is divided into two sections. In the first section, we have demonstrated for the first time the pivotal S_N2' coupling reaction of Wittig reagents with dimethyl bromomethylfumarate to selectively obtain the corresponding enes and dienes. The present protocol has been used as a key step for the concise and efficient synthesis of lignan class of natural products (±)-gulbulin and (±)-prasanthaline. In the second section, a novel palladium catalyzed [2 + 2 + 2] cocyclization methodology to construct arylnapthalene framework with the formation of two new carbon–carbon bonds has been illustrated. The versatility of this method has been presented through the facile total synthesis of justicidin B and retrojusticidin B.

Section A: Facile S_N2' coupling reactions of Wittig reagents with dimethyl bromomethylfumarate: Synthesis of enes, dienes and related natural products

Enes and dienes are an important class of compounds and they find applications in the preparation of dyes, UV screens, drugs, in Diels-Alder reactions and also for the synthesis of complex natural products. Several elegant methods are known in the literature to design enes and dienes. The S_N2' coupling reaction is a very important tool to form new carbon–carbon bonds in synthetic organic chemistry and the propensity of Wittig reagents for the S_N2' coupling reaction was not studied. In this context, we have developed the S_N2' coupling reactions of Wittig reagents with dimethyl bromomethylfumarate (**1**) to obtain the variety of enes and dienes by taking the advantage of prestigious Wittig chemistry (Schemes 1 & 2).

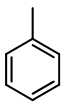
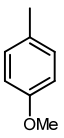
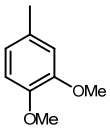
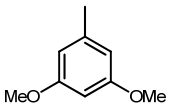
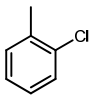
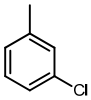
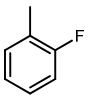
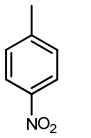
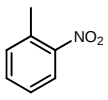
In the S_N2' coupling reaction of Wittig reagents with dimethyl bromomethylfumarate (**1**), the best result for diene was obtained by performing the reaction in THF at −100 ^oC and then quenching the reaction at room temperature at the end of 3 hours time (68% yield, **3**:**5** = 88:12). When the same reaction was quenched at −100 ^oC with water at the end of 3 hours time, we got the opposite selectivity, the ene **5a** was obtained as a major product and diene **3a** as a minor product (68% yield, **3**:**5** = 26:74) (Scheme 1).



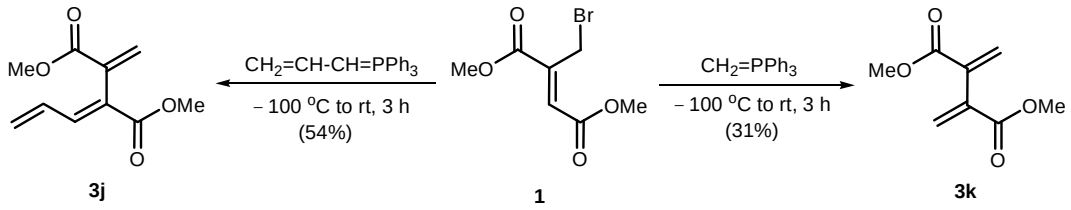
Scheme 1. S_N2' coupling reactions of Wittig reagents with dimethyl bromomethylfumarate

These experiments very clearly revealed the mechanistic aspects that (i) in the formation of diene the Wittig reagent couples with **1** in a S_N2' fashion, which is followed by an instantaneous abstraction of the acidic methine proton by the conjugate base, the bromide anion, with the elimination of PPh_3 to yield the diene with the exclusive *E*-geometry of the newly formed carbon–carbon double bond, (ii) the same reaction on quenching with water at –100 °C, the reductive elimination of Ph_3PO takes place with the formation of ene as a major product. To confirm the proposed mechanism of formation of enes, we quenched the reaction at –100 °C with D_2O and obtained the corresponding deutorated compound **6** in 48% yield. We have also studied the S_N2' coupling reactions of several other Wittig reagents generated from the phosphonium salts of corresponding benzyl bromides with **1** and obtained the corresponding enes and dienes, proving the generality of the present approach (Table 1).

Table 1. Synthesis of variety of enes **5** and dienes **3** from dimethyl bromomethylfumarate (**1**)

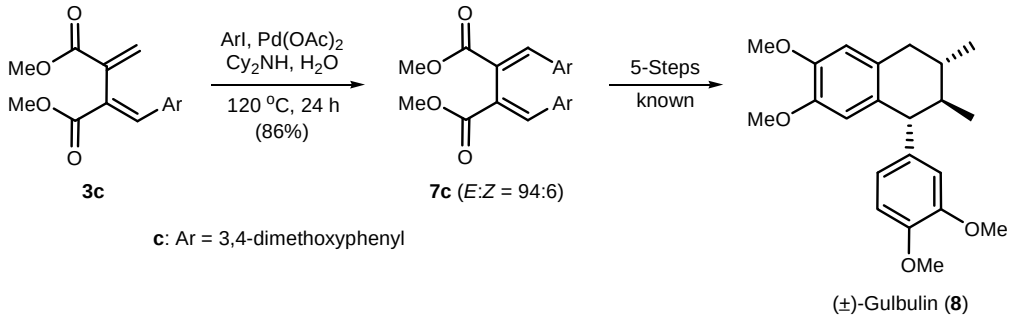
Entry		1	2	3	4	5	6	7	8	9
-Ar										
Products **3** & **5** – 100 °C to rt, 3 h	**3a-i** (yield)	**3a** (60%)	**3b** (64%)	**3c** (65%)	**3d** (64%)	**3e** (66%)	**3f** (62%)	**3g** (60%)	**3h** (00%)	**3i** (00%)
	5a-i (yield)	**5a** (8%)	**5b** (11%)	**5c** (10%)	**5d** (11%)	**5e** (12%)	**5f** (13%)	**5g** (10%)	**5h** (85%)	**5i** (85%)
Products **3** & **5** – 100 °C, 3 h	**3a-i** (yield)	**3a** (18%)	**3b** (20%)	**3c** (15%)	**3d** (17%)	**3e** (18%)	**3f** (20%)	**3g** (18%)	**3h** (00%)	**3i** (00%)
	5a-i (yield)	**5a** (50%)	**5b** (55%)	**5c** (60%)	**5d** (58%)	**5e** (60%)	**5f** (55%)	**5g** (52%)	**5h** (85%)	**5i** (85%)

We have also studied the S_N2' coupling reactions of relatively more reactive alkyl phosphoranes generated from phosphonium salts of allyl bromide and methyl iodide, with **1** and exclusively obtained the corresponding diene **3j** and dimethyl ester of fulgenic acid (**3k**) respectively but with lower yields (Scheme 2).



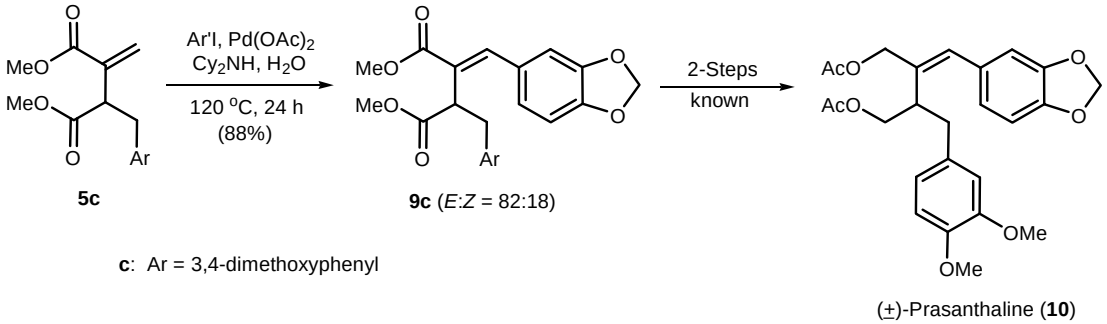
Scheme 2. Synthesis of symmetrical and unsymmetrical dienes

The ene and diene were utilized for the completion of formal synthesis of natural products (±)-gulbulin (from *Himantandra baccata* Bail) and (±)-prasanthaline (from *Jatropha gossypifolia* Linn). The diene **3c** on a Heck coupling reaction with an appropriate halide gave the (*E*,*E*)-diene **7c** as a major product in 86% yield (*E*:*Z* = 94:6, by ^{1}H NMR). The 5-step conversion of diene **7c** to (±)-gulbulin (**8**) is known in the literature (Scheme 3).



Scheme 3. Heck coupling reaction of diene, synthesis of (±)-gulbulin

Similarly, Heck coupling reaction of ene **5c** with appropriate halide gave the corresponding desired diester **9c** in 88% yield (*E*:*Z* = 82:18, by ^{1}H NMR). The two ester groups in compound **9c** on $LiAlH_4$ reduction followed by an in situ acylation of the formed intermediate 1,4-diol gave the natural product (±)-prasanthaline (**10**) is known in the literature (Scheme 4).



Scheme 4. Heck coupling reaction of ene, synthesis of (±)-prasanthaline

In summary, we have demonstrated for the first time the pivotal S_N2' coupling reactions of Wittig reagents to selectively obtain the corresponding enes and dienes. The versatility of this novel carbon–

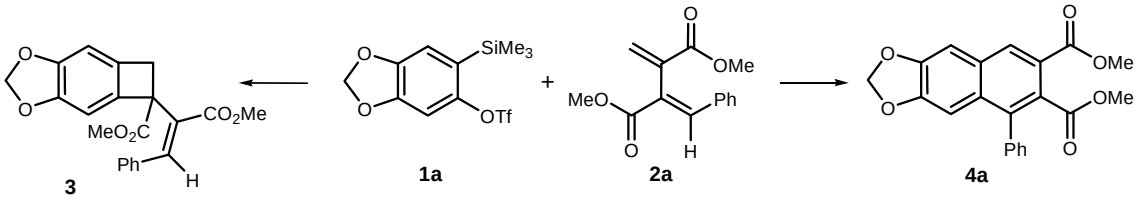
carbon bond forming method has been demonstrated through the facile synthesis of lignan class of natural products (±)-gulbulin and (±)-prasanthaline.

Section B: Pd catalyzed [2 + 2 + 2] cocyclization of arynes and dienes to arylnapthalene lignan Framework: Total synthesis of justicidin B and retrojusticidin B

A transition metal catalyzed [2 + 2 + 2] cocyclization of multiple bonds has been an atom economical and useful methodology for the synthesis of polycyclic compounds. However, to the best of our knowledge, only three example of transition metal catalyzed [2 + 2 + 2] cocyclization of dienes and arynes were reported. Arylnapthalene lactones are a subgroup of the lignan class of natural products that are characterized by a phenylpropanoid dimmer motif. Arylnapthalene lignans occur widely in nature and have received increasing attention over past several decades owing to their cytotoxic, antiviral, fungicidal, antiprotozoal and antiplatelet activities in cell based analysis. Pleasantly, many synthetic methodologies have been developed for the construction of arylnapthalene lignans. In this context, we have developed Pd catalyzed [2 + 2 + 2] cocyclization reaction of our synthesized dienes and arynes to arylnaphthalene skeletons (Tables 1 & 2).

The [2 + 2 + 2] cocyclization of dienes **2a**-**c** and aryne precursors **1a**/**b** directly furnished the corresponding in situ oxidized arylnapthalene frameworks **4a**-**f**, proving the generality of our present approach. On the basis of structural features of our dienes (linked double dienophile), we have

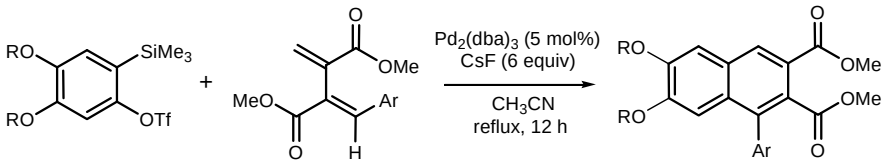
Table 1. Optimization of reaction conditions for [2 + 2 + 2] cocyclization of diene **2a** and aryne



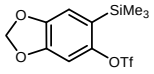
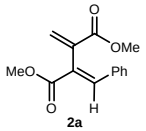
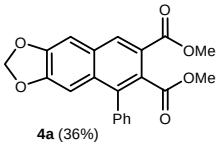
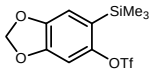
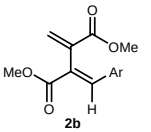
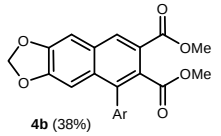
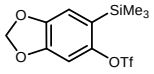
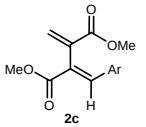
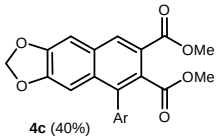
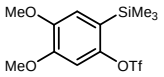
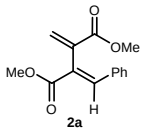
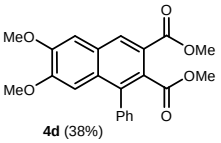
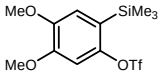
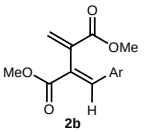
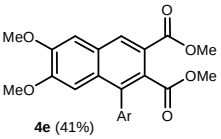
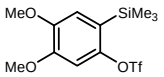
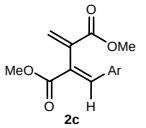
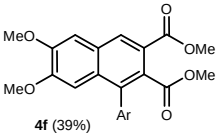
Entry	Reaction conditions [a]	**3**/**4a** (% yield)
1	CsF, CH_3CN, rt, 24 h	**3** (22)
2	CsF, CH_3CN, reflux, 12 h	**3** (11)
3	$Pd_2(dba)_3$, CsF, CH_3CN, rt, 24 h	NR [b]
4	$Pd_2(dba)_3$, CsF, CH_3CN, reflux, 12 h	**4a** (36)
5	$Pd_2(dba)_3$, P(*o*-tol)$_3$, CsF, CH_3CN, reflux, 24 h	**4a** (34)
6	$Pd_2(dba)_3$, dppf, CsF, CH_3CN, reflux, 24 h	**4a** (35)
7	$Pd_2(dba)_3$, TBP, CsF, CH_3CN, reflux, 24 h	**4a** (32)
8	$Pd(PPh_3)_4$, P(*o*-tol)$_3$, CsF, CH_3CN, reflux, 24 h	**4a** (12)
9	$Ni(cod)_2$, PPh_3, CsF, CH_3CN, reflux, 24 h	**4a** (08)
10	$Pd(OAc)_2$, PPh_3, CsF, CH_3CN, reflux, 24 h	NR [b]

[a] 5 mol% of catalyst; 20 mol% of ligand, and 6 equiv of CsF were used. [b] NR: no desired reaction.

Table 2. Generalization of Pd catalyzed [2 + 2 + 2] cocyclization of dienes **2a**-**c** and arynes

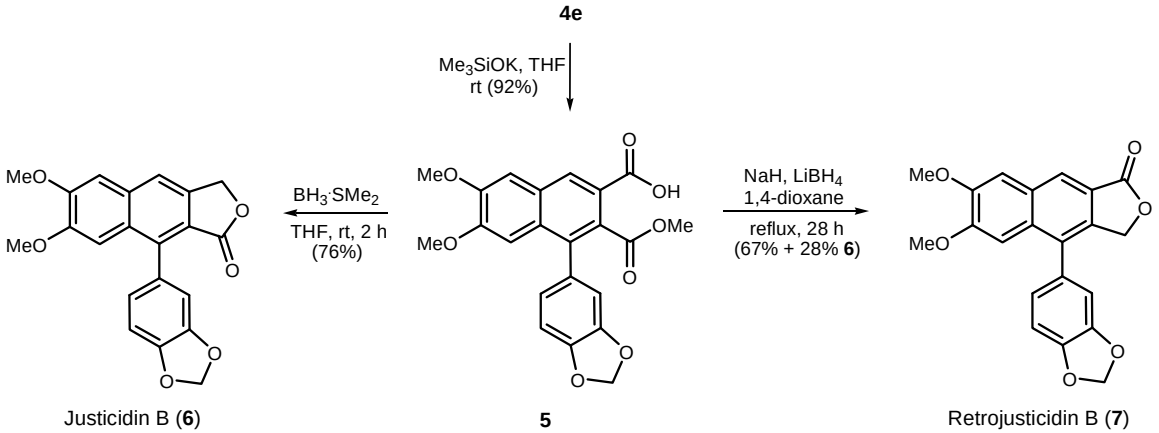


1a/b (1.50 equiv) **2a**-**c** (1.00 equiv) **4a**-**f**

Entry	Aryne precursor (**1**)	Diene (**2**)	Arylnaphthalene core (**4**)
1	 **1a**	 **2a**	 **4a** (36%)
2	 **1a**	 **2b** Ar = 3,4-methylenedioxyphenyl	 **4b** (38%) Ar = 3,4-methylenedioxyphenyl
3	 **1a**	 **2c** Ar = 3,4-dimethoxyphenyl	 **4c** (40%) Ar = 3,4-dimethoxyphenyl
4	 **1b**	 **2a**	 **4d** (38%)
5	 **1b**	 **2b** Ar = 3,4-methylenedioxyphenyl	 **4e** (41%) Ar = 3,4-methylenedioxyphenyl
6	 **1b**	 **2c** Ar = 3,4-dimethoxyphenyl	 **4f** (39%) Ar = 3,4-dimethoxyphenyl

proposed the [2 + 2 + 2] cocyclization mechanism, although we also keep open the possibility of involved direct [4 + 2] cycloaddition mechanism.

The usefulness of our methodology has been highlighted through the total synthesis of justicidin B and retrojusticidin B (Scheme 1). Thus, the sterically unhindered ester in compound **4e** was first regioselectively hydrolyzed to acid-ester **5** using potassium trimethylsilonate in THF at room temperature with 93% yield. The chemoselective reduction of an acid functionality in compound **5** with borane dimethyl sulfide complex followed by an acidic workup gave the justicidin B (**6**) in 76% yield. On the other hand, chemoselective ester reduction of sodium salt of compound **5** using lithium borohydride followed by the acidification gave column separable mixture of expected major product retrojusticidin B (**7**) in 67% yield with minor product justicidin B (28%), plausibly via the corresponding



Scheme 1. Concise synthesis of justicidin B and retrojustidin B

cyclic anhydride. Thus, we have completed a facile total synthesis of justicidin B and retrojusticidin B in just four steps with 18% and 16% overall yields respectively.

In conclusion, we have developed palladium catalyzed [2 + 2 + 2] cocyclization of dienes and arynes to arylnapthalene lignan framework with the formation of two new carbon–carbon bonds. The versatility of this method has been demonstrated through the facile total synthesis of justicidin B and retrojusticidin B. The present convergent strategy is general in nature and provides the way for the shorter and efficient synthesis of various arylnapthalene lignans. Further refinements of reaction conditions for the improvement of yields are in active progress.

Chapter 3. Novel Carbon–Oxygen Bond Forming Reactions with the Dialkyl Alkylidenesuccinates: Synthesis of Bioactive Natural and Unnatural Butenolides

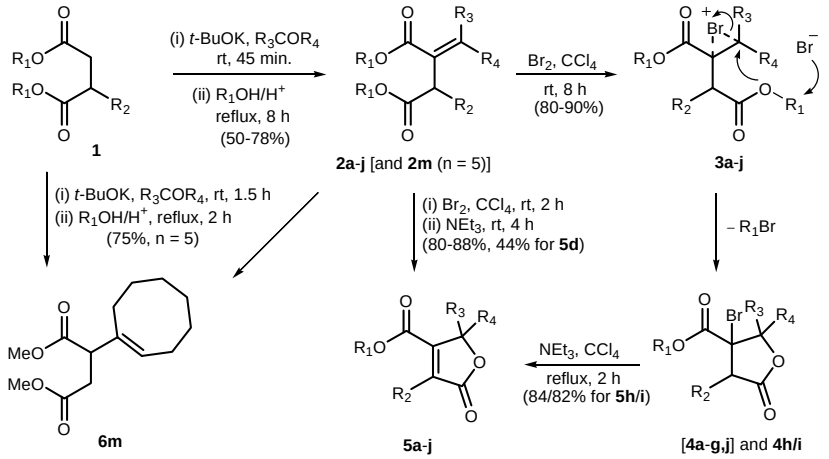
This chapter is divided into two sections. In the first section, we have demonstrated the bromine induced facile synthesis of butenolides and spirobutenolides from sterically congested tetrasubstituted dialkyl alkylidenesuccinates as a new carbon–oxygen bond forming reaction. In the second section, we have witnessed a novel regio- and stereoselective carbon–oxygen bond formation using selenium dioxide allylic oxidation reaction of (*E*)-dialkyl alkylidenesuccinates to natural and unnatural butenolides and fused butenolides, which provides the first example of (*Z*)-selective allylic alcohol formation via an exceptional *E*- to *Z*- carbon–carbon double bond isomerization. The versatility of this method has been displayed through the concise synthesis of mucocin precursor and facile total synthesis of (±)-mintlactone and (±)-isomintlactone.

Section A: Bromine induced facile synthesis of butenolides and spirobutenolides from sterically congested tetrasubstituted dialkyl alkylidenesuccinates

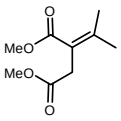
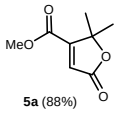
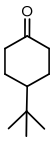
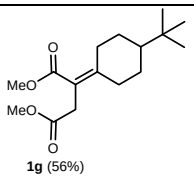
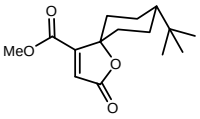
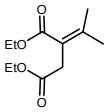
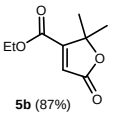
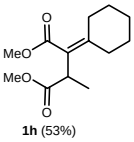
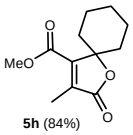
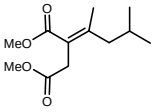
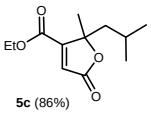
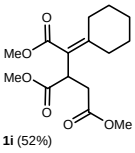
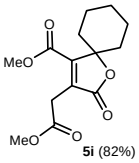
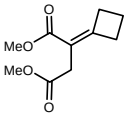
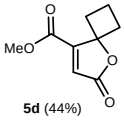
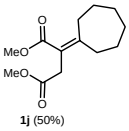
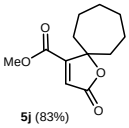
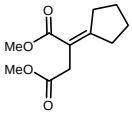
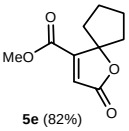
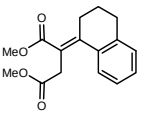
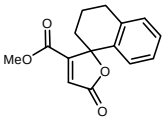
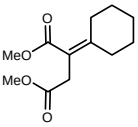
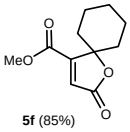
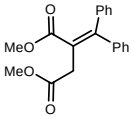
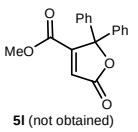
The natural and unnatural γ-butenolides are an important class of compounds that find major applications in organic, medicinal and polymer chemistry and a broad range of biological properties has

been conferred on them. Basically, the diverse range of γ-butenolide skeletons has been designed by employing new carbon–oxygen bond construction reactions and metal-catalyzed carbon–carbon bond

Table 1. Synthesis of butenolides and spirobutenolides via the bromination of tetrasubstituted C=C bonds



R_1 = Me/Et; R_2 = H, Me, CH_2CO_2Me; $R_3 = R_4$ = dialkyl, $CH_2(CH_2)_nCH_2$ (n =1-5)

No.	Ketones	Succinates (**1**)	Butenolides (**2**)	No.	Ketones	Succinates (**1**)	Butenolides (**2**)
1		 **1a** (69%)	 **5a** (88%)	**7**		 **1g** (56%)	 **5g** (84%)
2		 **1b** (69%)	 **5b** (87%)	**8**		 **1h** (53%)	 **5h** (84%)
3		 **1c** (62%)	 **5c** (86%)	**9**		 **1i** (52%)	 **5i** (82%)
4		 **1d** (74%)	 **5d** (44%)	**10**		 **1j** (50%)	 **5j** (83%)
5		 **1e** (52%)	 **5e** (82%)	**11**		 **1k** (72%)	 **5k** (not obtained)
6		 **1f** (60%)	 **5f** (85%)	**12**		 **1l** (78%)	 **5l** (not obtained)

formations. All these studies indicate that the development of new potential routes to γ-butenolides is still a challenging task of current interest. In this context, we have revealed the bromine induced facile synthesis of butenolides and spirobutenolides from sterically congested tetrasubstituted dialkyl alkylidenesuccinates as a new carbon–oxygen bond forming reaction (Table 1).

Based on the isolated intermediate **4h**, we surmise that during the course of the bromination reaction, the bromonium ion intermediates **3a**-**j**, as depicted in table 1 are formed. In the proposed intermediates **3a**-**j**, the bulkier bromide anion is unable to approach the quaternary carbons to form the expected dibromides. Hence the lone pair on the relatively smaller oxygen atom, intramolecularly and regioselectively, attacks the bromonium-bridge to form the γ-lactone. The simultaneous bromide anion induced dealkylation takes place to cancel the positive charge on an oxygen atom to form the intermediate products **4a**-**j**, which on dehydrobromination yield the target compounds **5a**-**j**.

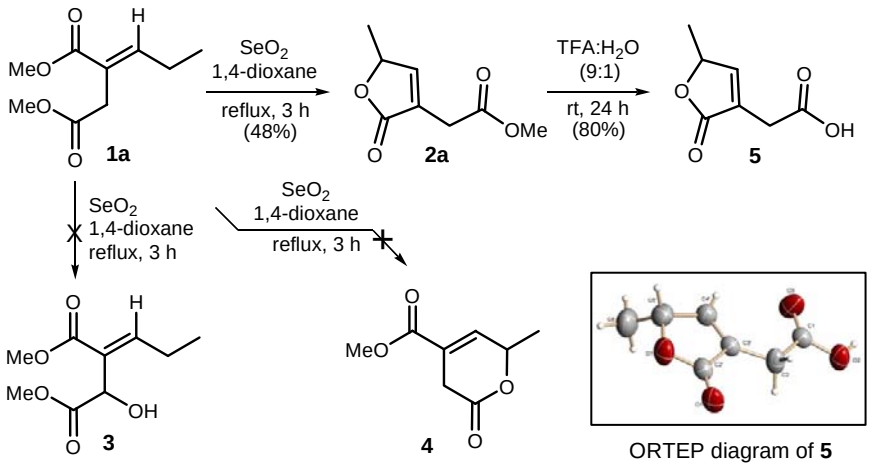
In summary, we have demonstrated a simple and efficient general approach to *gem*-dialkyl substituted quaternary butenolides by taking advantage of bromine stimulated structural rearrangement of sterically congested tetrasubstituted dialkyl alkylidenesuccinates.

Section B: Regio- and stereoselective selenium dioxide allylic oxidation of dialkyl alkylidenesuccinates to (Z)-allylic alcohols: Synthesis of natural and unnatural butenolides and fused butenolides

The selenium dioxide allylic oxidation of (*E*/*Z*)-alkenes to (*E*)-allylic alcohols via carbon−oxygen bond formation is an imperative well established reaction in synthetic organic chemistry. The natural and unnatural butenolides are an important class of compounds with a broad range of biological activities. A large number of such γ-butenolides has been synthesized during the past century using several elegant synthetic strategies. In continuation of our studies on cyclic anhydride derivatives to bioactive natural and unnatural products, we have demonstrated a novel regio- and stereoselective carbon–oxygen bond formation using selenium dioxide allylic oxidation of (*E*)-dialkyl alkylidenesuccinates to obtain butenolides and fused butenolides.

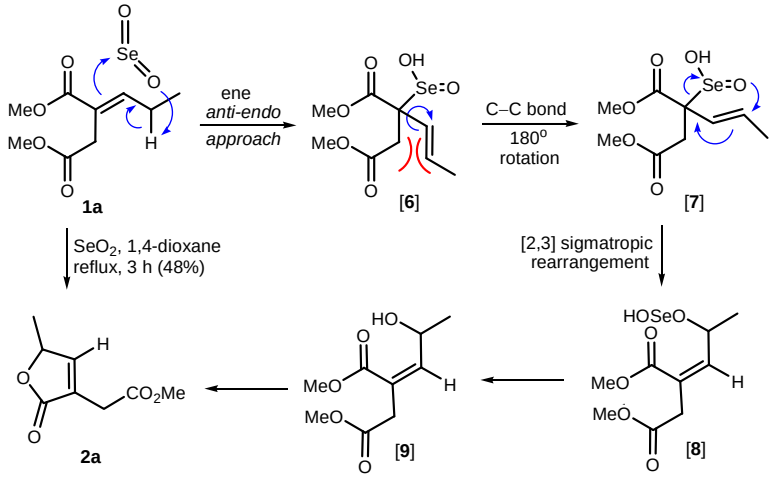
The allylic oxidation of compound **1a** with SeO_2 (1.60 equiv) in refluxing 1,4-dioxane regio- and stereoselectively furnished the butenolide **2a** in 48% yield. The corresponding crystalline acid **5** was obtained by acid catalyzed hydrolysis of ester **2a** and its structure was unequivocally confirmed by using the X-ray crystallographic data (Scheme 1).

We realized that our present example will be useful in highlighting the mechanistic aspects involved in the SeO_2 allylic oxidation reactions. As depicted in our scheme 2, the energetically favoured *anti*-approach of selenium dioxide towards **1a** in an ene reaction to form the intermediate **6** followed by an in situ 180° carbon–carbon bond rotation and then the [2,3] sigmatropic shift with concomitant resulting of butenolide **2a** could be the most promising pathway. We also rationalized that in the SeO_2



Scheme 1. Regio- and stereoselective SeO_2 oxidation of (*E*)-dimethyl propylidenesuccinate

allylic oxidation of **1a**, the expected axial orientation of the bulky $–CH_2CO_2Me$ group in the transition state could be responsible to preclude the formation of six membered compound **4**.

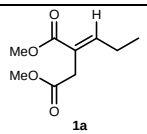
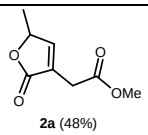
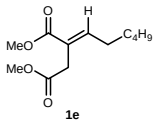
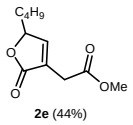
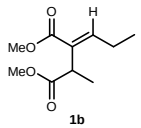
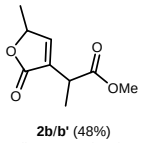
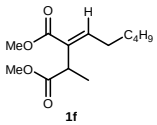
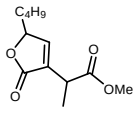
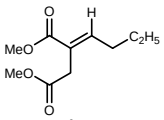
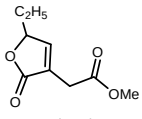
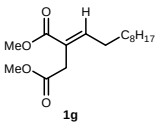
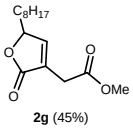
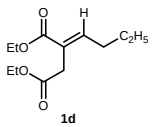
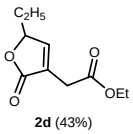
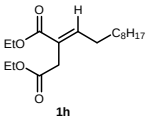
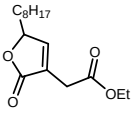


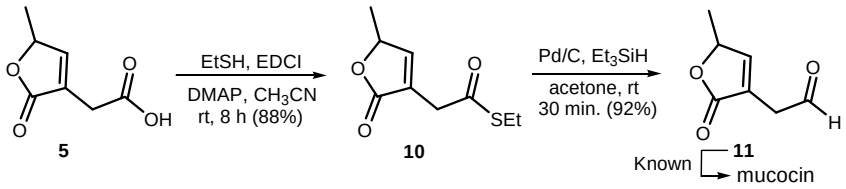
Scheme 2. Plausible mechanism for SeO_2 oxidation of (*E*)-dimethyl 2-propylidenesuccinate

We successfully proved the generality of our present approach by synthesizing various butenolides starting from diverse (*E*)-dialkyl alkylidenesuccinates (Table 1). The synthesized butenolide **5** was successfully transformed to the corresponding known wobbly mucocin precursor **11** in two steps via the thio-esterification followed by chemoselective reduction sequence (Scheme 3).

We have extended our SeO_2 allylic oxidation protocol for the synthesis of fused butenolides using symmetrically and unsymmetrically tetrasubstituted dialkyl alkylidenesuccinates (Table 2). We feel that in the stereoselective conversion of **12d** to **13d/d′**, the involvement of most acidic (*E*)-allylic axial proton-H_a in the ene reaction followed by the *E*- to *Z*- carbon–carbon bond isomerization, [2,3] sigmatropic shift and lactonization should be resulting in the diastereoselective formation of kinetically controlled major product **13d**.

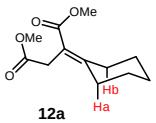
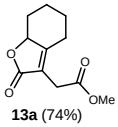
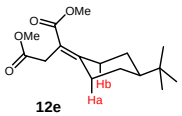
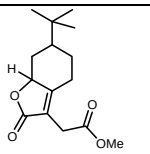
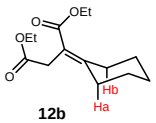
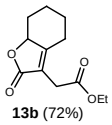
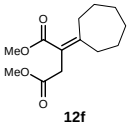
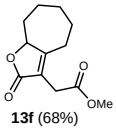
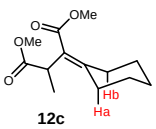
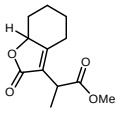
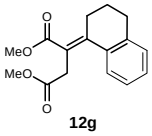
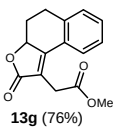
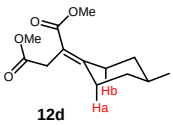
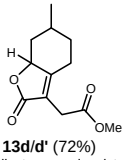
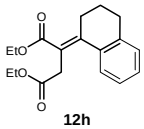
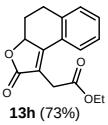
Table 1. Trisubstituted (*E*)-dialkyl alkylidenesuccinates to butenolides

Entry	SM	Product	Entry	SM	Product
1	 **1a**	 **2a** (48%)	5	 **1e**	 **2e** (44%)
2	 **1b**	 **2b/b'** (48%) (1:1 diastreomeric mixture)	6	 **1f**	 **2f/f'** (43%) (1:1 diastereomeric mixture)
3	 **1c**	 **2c** (45%)	7	 **1g**	 **2g** (45%)
4	 **1d**	 **2d** (43%)	8	 **1h**	 **2h** (42%)

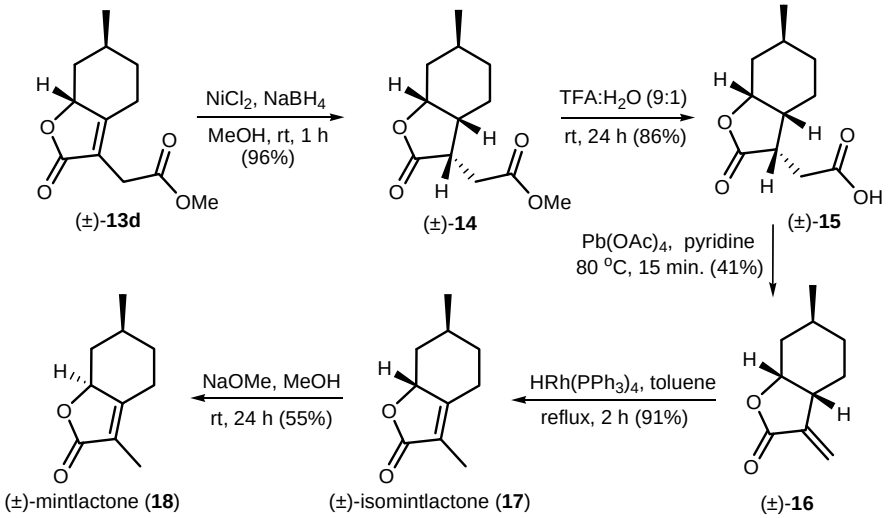


Scheme 3. Concise synthesis of mucocin precursor

Table 2. Tetrasubstituted dialkyl alkylidenesuccinates to fused butenolides

Entry	SM	Product	Entry	SM	Product
1	 **12a**	 **13a** (74%)	5	 **12e**	 **13e/e'** (66%) (7:3 diastereomeric mixture)
2	 **12b**	 **13b** (72%)	6	 **12f**	 **13f** (68%)
3	 **12c**	 **13c/c'** (70%) (2:1 diastereomeric mixture)	7	 **12g**	 **13g** (76%)
4	 **12d**	 **13d/d'** (72%) (3:1 diastereomeric mixture)	8	 **12h**	 **13h** (73%)

We have utilized our present approach to fused butenolides for the total synthesis of bioactive natural products isomintlactone and mintlactone (*Bursera graveolens*). One recrystallization of mixture of diastereomers **13d**/**d**′ with petroleum ether provided the diastereomerically pure (±)-**13d** in 66% yield (Scheme 4). The chemo- and diastereoselective reduction of **13d** with $NaBH_4$ in the presence of $NiCl_2$,



Scheme 4. Diastereoselective approach to mintlactone and isomintlactone

followed by acid catalyzed hydrolysis of **14** provided the corresponding carboxylic acid **15** in 86% yield. Oxidative decarboxylation of primary acid **15** with $Pb(OAc)_4$ followed by the rhodium catalyzed disubstituted exocylic to tetrasubstituted endocyclic carbon–carbon double bond isomerization in **16** provided the desired natural product (±)-isomintlactone (**17**) in 91% yield. The kinetically controlled natural product (±)-isomintlactone (**17**) on reaction with NaOMe in MeOH at room temperature smoothly got transformed to the thermodynamically more stable natural product, the (±)-mintlactone (**18**) in 55% yield via the inversion of configuration at an allylic center. Thus, starting from dimethyl 2-(4-methylcyclohexylidene)succinate (**12d**) the (±)-isomintlactone (**17**) and (±)-mintlactone (**18**) were respectively obtained in five/six steps with 14/8% overall yields.

In summary, we have witnessed the first example of (*Z*)-selective allylic alcohol formation in the SeO_2 oxidation of dialkyl alkylidenesuccinates to design a new general one-step approach to the diverse range of natural and unnatural butenolides and fused butenolides via an exceptional *E*- to *Z*- carbon–carbon double bond isomerization. The present protocol has been successfully extended for the synthesis of a mucocin precursor and the diastereoselective total synthesis of the natural product (±)-isomintlactone and its first time conversion to (±)-mintlactone. Our present protocol would also be useful for the synthesis of desired natural and unnatural α-methylene-γ-butyrolactones.

Chapter 4. Racemic and Chemoenzymatic Total Syntheses of the Naturally Occurring Potent Anti-HIV Compound (–)-1,3,4,5-Tetragalloylapiitol

Chapter 4A: Total synthesis of (±)-1,3,4,5-tetragalloylapiitol

The polygalloylated sugars have been recently isolated as bioactive natural products and they possess anti-HIV, antiviral, antitumor and anti-diabetic activities. HIV-1 RNase H is an attractive molecular target for the development of new anti-HIV agents as potential chemotherapeutics. Very recently, Gustafson et al. isolated a new potent HIV RNase H inhibitor (–)-1,3,4,5-tetragalloylapiitol (**1**) from an extract of the plant *Hylodendron gabunensis* (Figure 1).

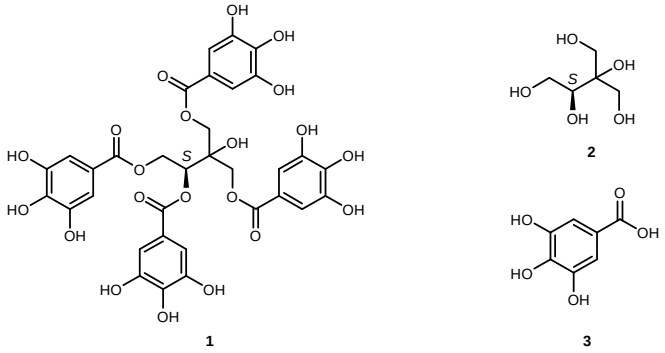
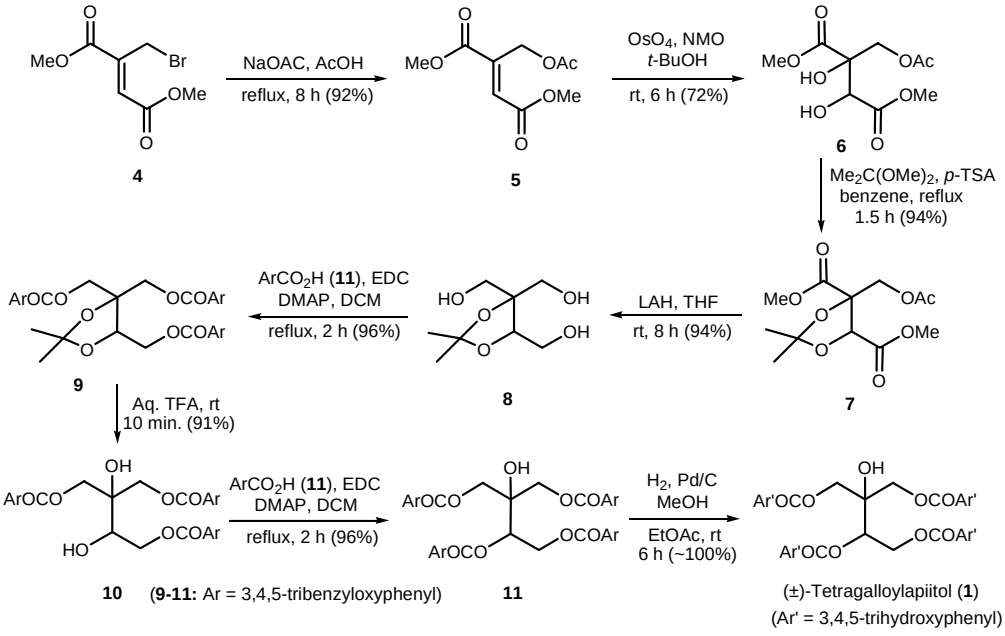


Figure 1. Natural products (–)-1,3,4,5-tetragalloylapiitol (**1**), (–)-apiitol (**2**) and gallic acid (**3**)



Scheme 1. Total synthesis of (±)-1,3,4,5-tetragalloylapiitol from dimethyl bromomethylfumarate

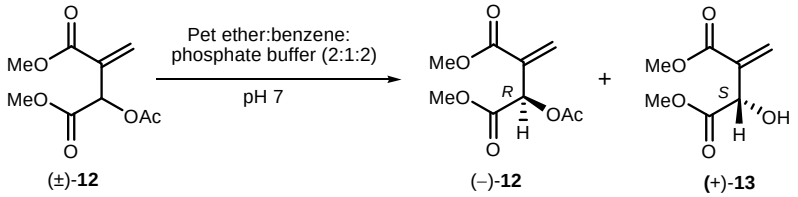
The structural features revealed that the natural products (–)-apiitol (**2**) and gallic acid (**3**) could be the biogenetic precursors of **1**. In continuation of our studies on cyclic anhydride derivatives to bioactive natural and unnatural products, starting from dimethyl bromomethylfumarate, facile total synthesis of (±)-1,3,4,5-tetragalloylapiitol has been demonstrated via allylic substitution, OsO_4 dihydroxylation, galloylation and reductive global *O*-benzyl deprotection pathway (Scheme 1).

In summary, starting from dimethyl bromomethylfumarate, we have achieved a straightforward first

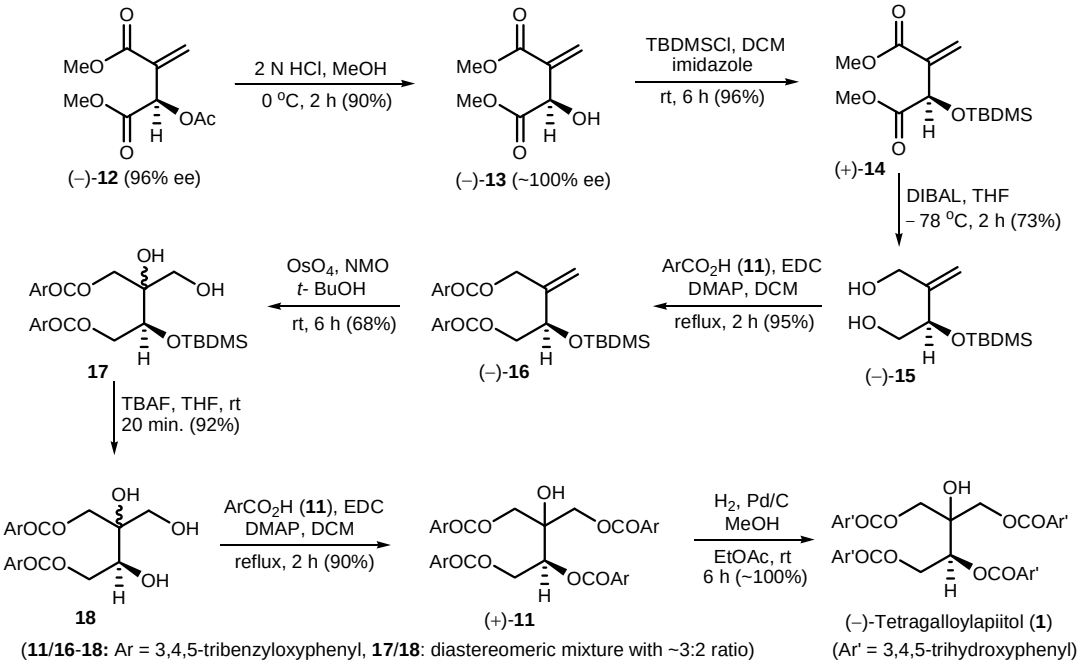
total synthesis of the naturally occurring potent anti-HIV compound (±)-1,3,4,5-tetragalloylapiitol in 8-steps with 49% overall yield.

4B: Chemoenzymatic total synthesis of potent HIV RNase H inhibitor (–)-1,3,4,5-tetragalloylapiitol

The chemoenzymatic synthesis provides a powerful approach and new opportunities for accessing chemical diversity. In continuance of our studies on (–)-1,3,4,5-tetragalloylapiitol, starting from racemic dimethyl 2-acetoxy-3-methylenesuccinate, chemoenzymatic facile total synthesis of (–)-1,3,4,5-tetragalloylapiitol has been demonstrated via an efficient lipase catalyzed resolution followed by the



Scheme 2. Lipase catalyzed resolution of (±)-dimethyl 2-acetoxy-3-methylenesuccinate



Scheme 3. Total synthesis of (–)-1,3,4,5-tetragalloylapiitol

chemoselective DIBAL reductions-double gallyolation, osmium tetroxide dihydroxylation-double gallyolation and reductive global *O*-benzyl deprotection pathway (Schemes 2 & 3).

In summary, starting from enantiomerically pure (–)-dimethyl 2-acetoxy-3-methylenesuccinate, total synthesis of the (–)-1,3,4,5-tetragalloylapiitol has been also demonstrated in 8-steps with 34% overall yield.

Note: Compound, scheme and figure numbers in the abstract are different from those in the thesis.

Chapter 1

A Concise Account on the Chemistry of Dimethyl Bromomethylfumarate and Dialkyl Alkylidenesuccinates

This chapter features the following topics:

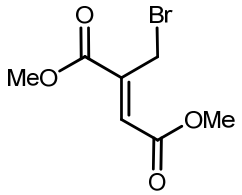
Chapter 1: Section A

A Concise Account on the Chemistry of Dimethyl Bromomethylfumarate

This section A of chapter 1 features the following topics:

1A.1: Introduction

Dimethyl bromomethylfumarate (**1**) was first prepared by Campbel et al.[1] in 1947 via bromination of the methyl group of dimethyl methylfumarate by using *N*-bromosuccinimide and dibenzoyl peroxide. Amri and co-workers[2] have synthesized dimethyl bromomethylfumarate by the bromination of dimethyl itaconate and dehydrobromination with triethylamine. Loh et al.[3] have synthesized dimethyl bromomethylfumarate by the Baylis-Hillman reaction involving the coupling of methyl glyoxylate with methyl acrylate in dioxane and subsequent bromination with PBr_3 in ether. Recently in 2004, dimethyl bromomethylfumarate has been prepared in our group[4] via allylic bromination and isomerization of the carbon–carbon double bond of dimethyl methylmaleate using *N*-bromosuccinimide and 2,2'-azobisisobutyronitrile.



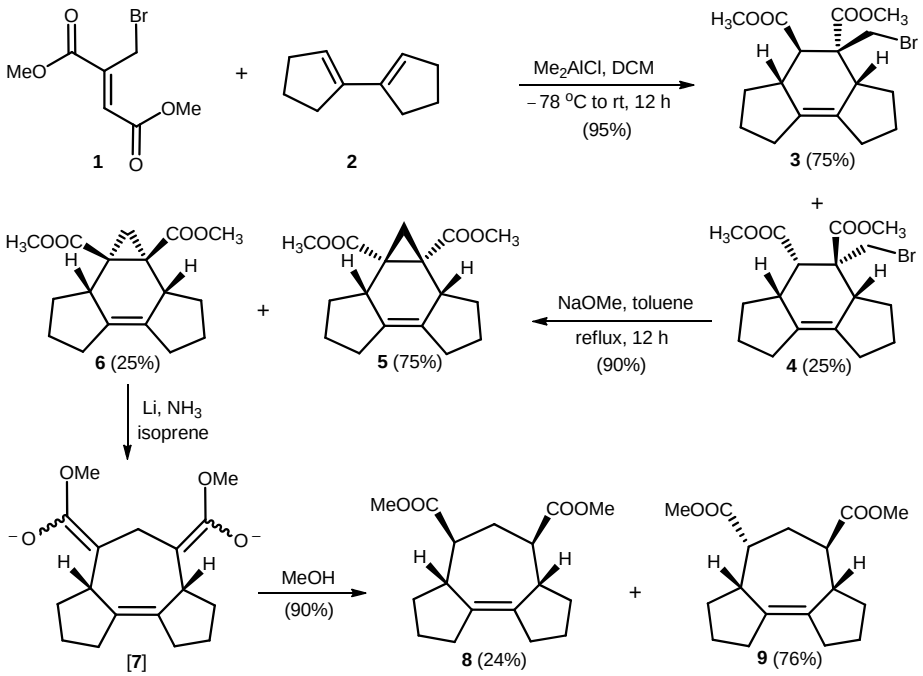
Dimethyl bromomethylfumarate (**1**)

1A.2: Synthetic utility of dimethyl bromomethylfumarate

The introduction of bromo-atom at the allylic position of dimethyl methylfumarate to form dimethyl bromomethylfumarate (**1**) opens more sites for nucleophilic reactions viz, allylic substitutions and S_N2' coupling reactions. Several natural and unnatural products have been synthesized using dimethyl bromomethylfumarate. This section portrays an application of dimethyl bromomethylfumarate to construct carbon–carbon bonds for the synthesis of natural and unnatural products. We have tried our best to summarize and concisely present the information here, but no pretension of completeness is claimed.

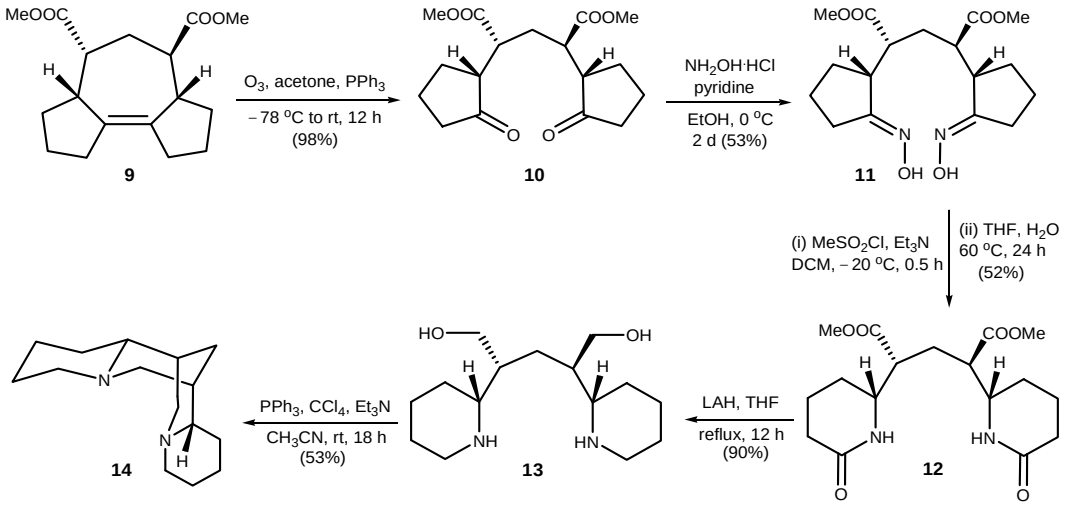
1A.2.1: Synthesis of (±)-sparteine

(–)-Sparteine (**14**) has been used to induce absolute stereocontrol in a number of lithiations.[5] Fleming and co-workers[6] have reported the racemic synthesis of sparteine by using Diels-Alder reaction between dimethyl bromomethylfumarate (**1**) and diene **2** to form the mixture of adducts **3** and **4** which on reaction with sodium methoxide gave the *meso* cyclopropane intermediates **5** and **6** (Scheme 1). Reductive cleavage of mixture of **5** and **6** using lithium in liquid ammonia followed by quenching with methanol gave ring expanded esters (**8**:**9** = 24:76), which were separated by crystallization and chromatographic purification of the mother liquor. The ozonolysis of ester **9** in acetone followed by reaction with hydroxylamine hydrochloride gave bisoxime **11** (Scheme 2). Beckmann rearrangement of bisoxime **11** to the bislactam **12**, followed by LAH reduction gave bispiperidine diol **13**. (±)-Sparteine



Scheme 1. Synthesis of (±)-sparteine precursor via Diels-Alder reaction of dimethyl bromomethylfumarate

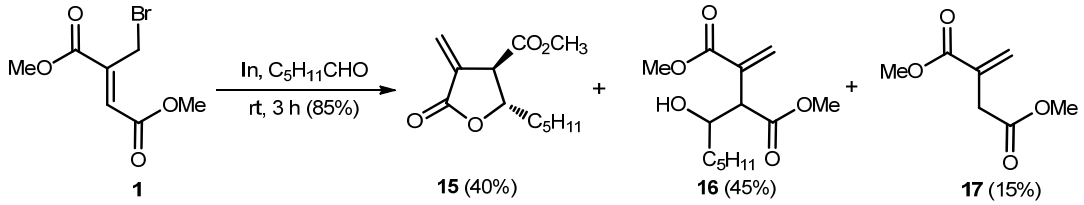
(**14**) was obtained by treating **13** with carbon tetrachloride and triphenylphosphine in 53% yield via two concomitant intramolecular cyclizations. Starting from **1**, the (±)-Sparteine (**14**) was obtained with 8% overall yield in 10-steps.



Scheme 2. Total synthesis of (±)-sparteine using Beckmann rearrangement

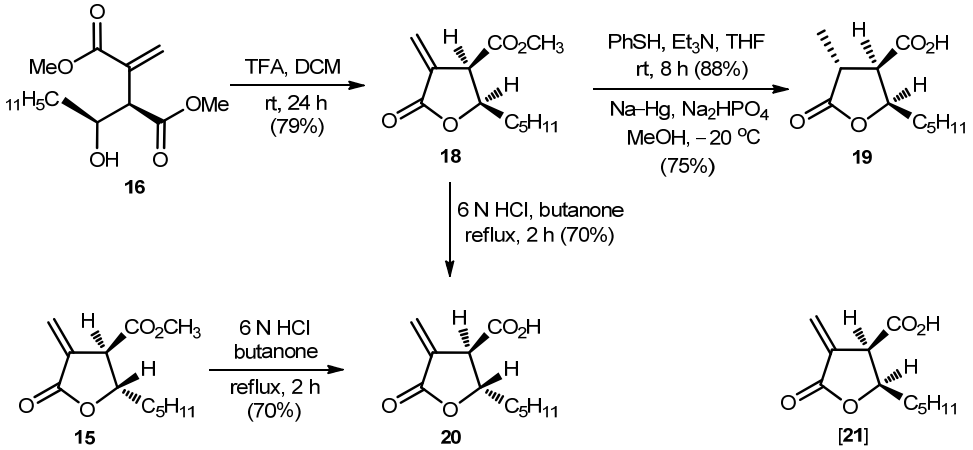
1A.2.2: Synthesis of (±)-methylenolactocin

α-Methylene-γ-butyrolactone is an integral building block of many bioactive natural products.[7] Among them, methylenolactocin (**20**) has attracted the major attention because of its promising anti-tumour activity and the unusual structure with high functionality and stereochemistry.[8] (±)-Methylenolactocin (**20**) and (±)-phaseolinic acid (**19**) have been isolated from the fungus *Macrophomina phaseolina*.[9] Loh



Scheme 3. Indium-mediated allylation reaction of dimethyl bromomethylfumarate with hexanal

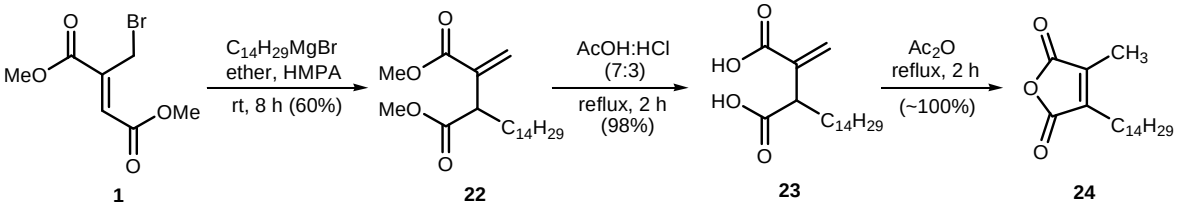
et al.[3] have reported the synthesis of (±)-methylenolactocin by developing an indium-mediated allylation reaction of dimethyl bromomethylfumarate (**1**) with hexanal as the key step (Scheme 3). Both the products, **15** and **16** were separated through the flash column chromatographic purification. In the presence of TFA, **16** was cyclized to the *cis*-β,γ-substituted lactone **18** in 79% yield (Scheme 4). Compound **18** was lead to a formal synthesis of (±)-phaseolinic acid (**19**) via a stereoselective hydrogenation using thiophenol, followed by removal of the sulfide group with Na–Hg.[10] Similarly, acidic hydrolysis of both **18** and **15** with 6 N HCl afforded (±)-methylenolactocin (**20**) in 70% yield. Herein plausibly for stability reasons, **18** undergoes epimerization via the intermediate acid **21** to furnish **20**.



Scheme 4. Synthesis of (±)-methylenolactocin and (±)-phaseolinic acid

1A.2.3: Synthesis of chaetomellic acid A

Chaetomellic acid A has been isolated from *Chaetomella acutiseta*[11] and its dianionic form is potent and highly specific inhibitor of rasfernesyl-protein transferase. Chaetomellic acid A (**24**) has been synthesized in our group[12] via selective S_N2' Grignard coupling reaction of tetradecylmagnesium

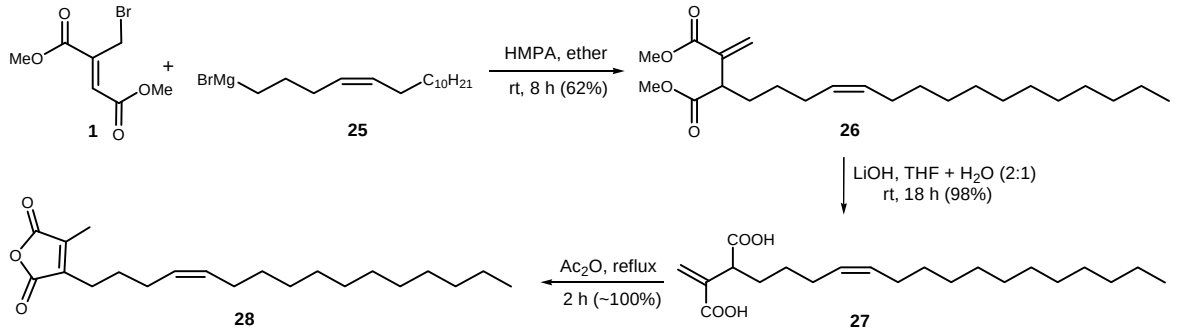


Scheme 5. Synthesis of chaetomellic acid A via chemoselective S_N2' Grignard coupling reaction

bromide with dimethyl bromomethylfumarate (**1**) followed by hydrolysis of the diester **22** to diacid **23** accompanied by ring closure and simultaneous exocyclic to endocyclic carbon–carbon double bond isomerization with 59% overall yield in 3-steps (Scheme 5).

1A.2.4: Synthesis of 1,7-(Z)-nonadecadiene-2,3-dicarboxylic acid

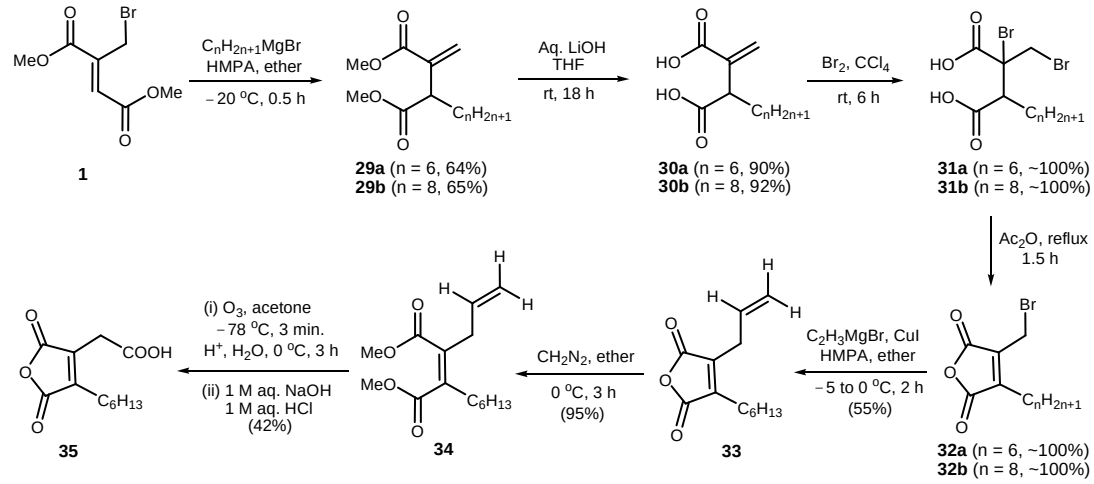
This novel dicarboxylic acid **27** was isolated from cultures of a white-rot fungus *Ceriporiopsis subvermispora*.[13] First synthesis of 1,7-(*Z*)-nonadecadiene-2,3-dicarboxylic acid has been reported from our group[12] by using the chemoselective S_N2' Grignard coupling reaction of (*Z*)-hexadeca-4-enylmagnesium bromide (**25**) with dimethyl bromomethylfumarate (**1**) (Scheme 6). (*Z*)-Hexadeca-4-enyl bromide was prepared from tetrahydrofurfuryl chloride by reaction with $C_{11}H_{23}Br$ in presence of $LiNH_2/NH_3$ followed by *cis*-hydrogenation of triple bond, tosylation of alcohol and substitution with LiBr. The S_N2' Grignard coupling reaction of **25** with **1** followed by hydrolysis of the diester **26** gave the natural product 1,7-(*Z*)-nonadecadiene-2,3-dicarboxylic acid (**27**) in 35% overall yields over 6-steps (starting from tetrahydrofurfuryl chloride). The diacid **27** in refluxing acetic anhydride furnished the isochaetomellic acid B (**28**) with an added advantage.



Scheme 6. Short and efficient synthesis of 1,7-(*Z*)-nonadecadiene-2,3-dicarboxylic acid

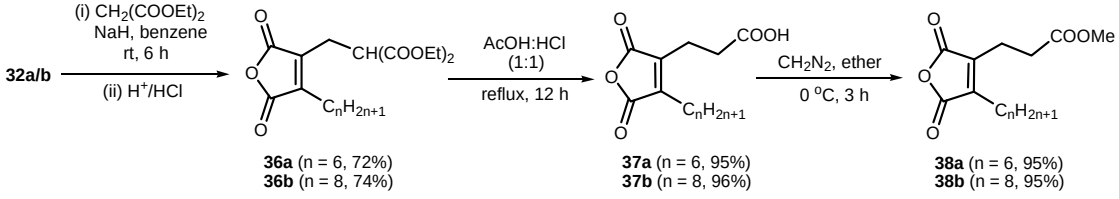
1A.2.5: Synthesis of natural and unnatural disubstituted maleic anhydrides

During the past decade, several structurally interesting compounds with dialkylsubstituted maleic anhydride moieties have been isolated as bioactive natural products and synthesized in view of their promising bioactivities.[14-16] The 2-carboxymethyl-3-hexylmaleic anhydride (**35**) has been isolated as a novel metabolite from the *Aspergillus* FH-X-213 from an apple.[17] In 1994, Soda et al.[18] reported the biotransformation of stearic acid with a microbial strain isolated from soil, *Pseudomonas cepacica* A-1419, to produce another two new maleic anhydride derivatives 2-(β-carboxyethyl)-3-hexylmaleic anhydride (**37a**) and 2-(β-carboxyethyl)-3-octylmaleic anhydride (**37b**). These natural products have been synthesized in our group[19] via the potential b uilding blocks 2-bromomethyl-3-alkylmaleic



Scheme 7. Synthesis of bioactive natural product 2-carboxymethyl-3-hexylmaleic anhydride

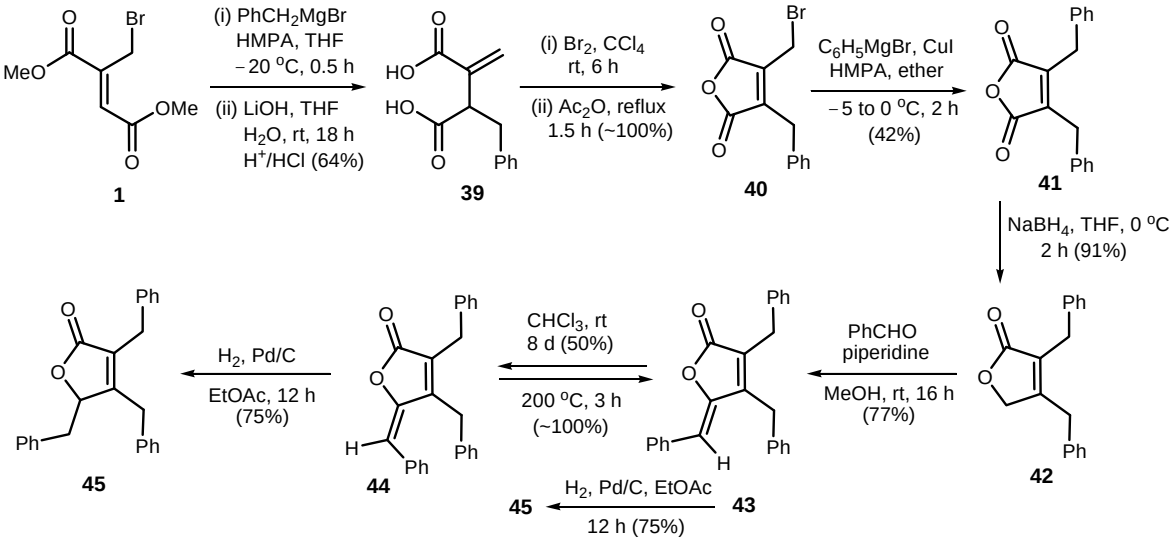
anhydrides **32a**/**b** (Scheme 7). These compounds **32a**/**b** were synthesized starting from dimethyl bromomethylfumarate via S_N2' Grignard coupling reaction, hydrolysis of formed diesters, molecular bromine addition and dehydrative ring closure reaction pathway with 49/51% overall yields in 4-steps. Chemoselective allylic substitution of bromo-atom in **32a** with Grignard reagent followed by esterification, ozonolysis and oxidation reaction sequence provided naturally occurring 2-carboxymethyl-3-hexylmaleic anhydride (**35**) in 13% overall yield over 7-steps. The synthesis of two naturally occurring 2-(β-carboxyethyl)-3-alkylmaleic anhydrides **37a**/**b** have been also completed via a chemoselective coupling reaction of diethylmalonate with **32a**/**b** followed by the decarboxylative acidic hydrolysis of *gem*-diesters **36a**/**b** (Scheme 8). The natural products were also further characterized as their methyl esters.



Scheme 8. Synthesis of 2-(β-carboxyethyl)-3-alkylmaleic anhydrides via diethyl malonate coupling

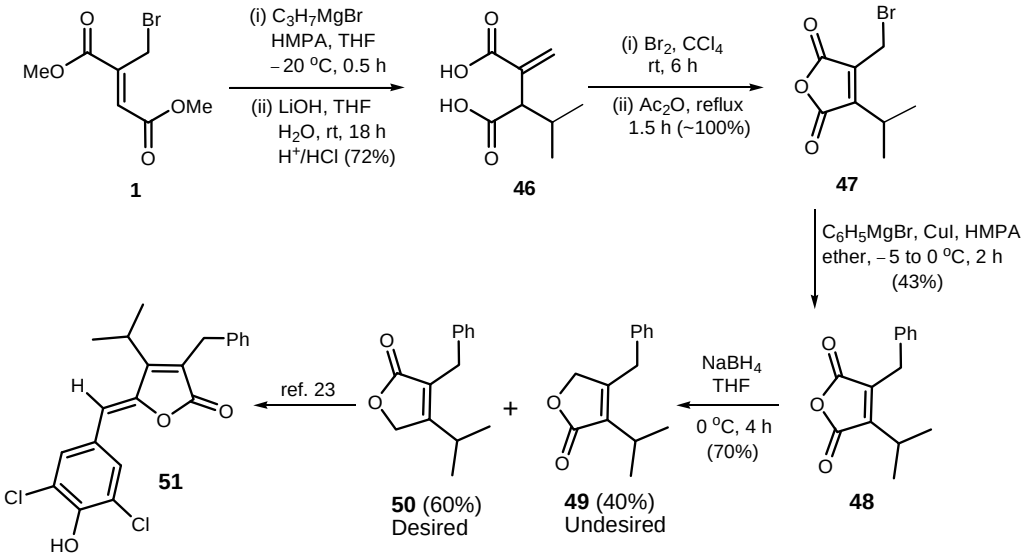
1A.2.6: Synthesis of maculalactones A-C and nostoclide I

Maculalactones A-C have been isolated from the epilithic-encrusting cyanobacterium *Kyrtuthrix maculans* from Hong Kong island and they possess marine anti-fouling activity.[20] Nostoclide I (**51**) has been isolated from the culture of a symbiotic blue-green alga, *Nostoc* sp., from the lichen *Peltigera canina* and possesses cytotoxic activity.[21] These naturally occurring maculalactone A (**45**), maculalactone B (**43**) maculalactone C (**44**) and nostoclide I (**51**) have been synthesized in our group[22] starting from dimethyl bromomethylfumarate (**1**) via the intermediates dibenzylmaleic anhydride (**41**)



Scheme 9. Synthesis of maculalactones A-C

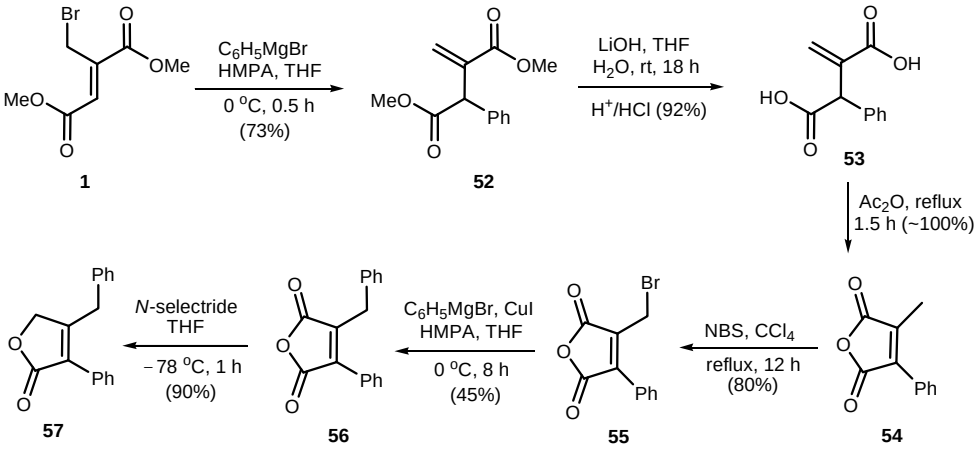
and benzylisopropylmaleic anhydride (**48**) (Schemes 9 & 10). The two anhydrides **41** and **48** were prepared by coupling reactions of appropriate Grignard reagents with dimethyl bromomethylfumarate (**1**) followed by LiOH-induced hydrolysis of esters to acids, bromination of carbon–carbon double bond, in situ dehydro-bromination and chemoselective allylic substitution of bromo-atom in disubstituted anhydrides **40** and **47** with appropriate Grignard reagents. The $NaBH_4$ reduction of these anhydrides **41** and **48** furnished the desired lactones **42** and **50** (desired) respectively. The lactone **42** on Knoevenagel condensation with benzaldehyde furnished maculalactone B (**43**), which on carbon–carbon double bond isomerization gave maculalactone C (**44**) for the associated π-stacking interactions between the two phenyl groups, while both **43** and **44** on selective catalytic hydrogenation gave maculalactone A (**45**), in 14% yield over 6-steps. The conversion of lactone **50** to nostoclide I (**51**) is known in the literature[23].



Scheme 10. Synthesis of nostoclide I via chemoselective allylic substitution with Grignard reagent

1A.2.7: Synthesis of gymnoascolide A

Gymnoascolides A-C were isolated from the Australian soil ascomycete *Gymnoascus reessii*[24] and *Malbranchea filamentosa* IFM41300.[25] Gymnoascolides A-C possess moderate activity against the pathogenic plant fungus *Septoria nodorum*.[24] Gymnoascolide A also possesses vasodilatory activity and it inhibits Ca^{2+} induced vasocintraction in aortic rings pretreated with high K^+ or norepinephrine.[25] Gymnoascolide A (**57**) has been synthesized in our group[26] via S_N2' Grignard coupling reaction of phenylmagnesium bromide with dimethyl bromomethylfumarate (**1**) followed by hydrolysis of the diester **52** to diacid **53** accompanied by ring closure and simultaneous exocyclic to endocyclic carbon–carbon double bond isomerization to form the anhydride **54** with 67% overall yield over 3-steps (Scheme 11). The allylic bromination of **54** using *N*-bromosuccinimide followed by the chemoselective allylic substitution of the bromo atom with phenylmagnesium bromide and regioselective carbonyl reduction using *N*-selectride exclusively furnished the natural product gymnoascolide A (**57**) in 22% overall yield over 6-steps. Herein, as expected the *N*-selectride regioselectively reduced the unhindered anhydride carbonyl group.

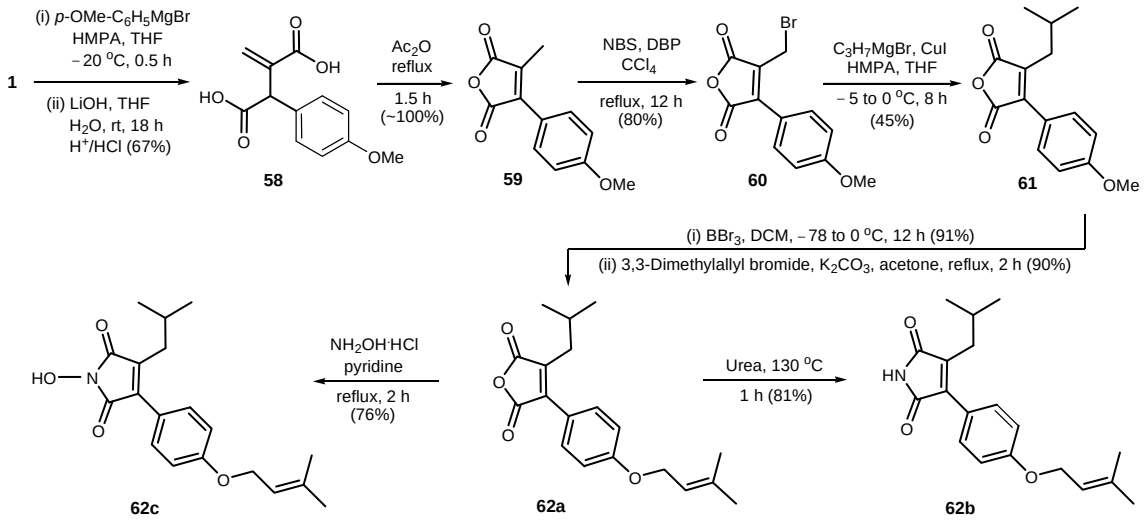


Scheme 11. Synthesis of gymnoascolide A via chemoselective S_N2' coupling and allylic substitution reactions

1A.2.8: Synthesis of cytotoxic camphorataanhydride A and camphorataimides B and C

Camphorataanhydride/imides were isolated from the mycelium of *Antrodia camphorata* and the imides **62b**/**c** showed appreciable cytotoxic effects on LLC tumor cells.[27] Camphorataanhydride A, Camphorataimides B and C have been synthesized in our group[28] via S_N2' Grignard coupling reaction of *p*-methoxyphenylmagnesium bromide with dimethyl bromomethylfumarate (**1**) followed by base catalyzed hydrolysis to diacid **58** which upon acetic anhydride induced ring closure gave the expected anhydride **59** in 67% yield over 3 steps (Scheme 12). The bromination of the allylic carbon using *N*-bromosuccinimide followed by the chemoselective allylic substitution of the bromo-atom with

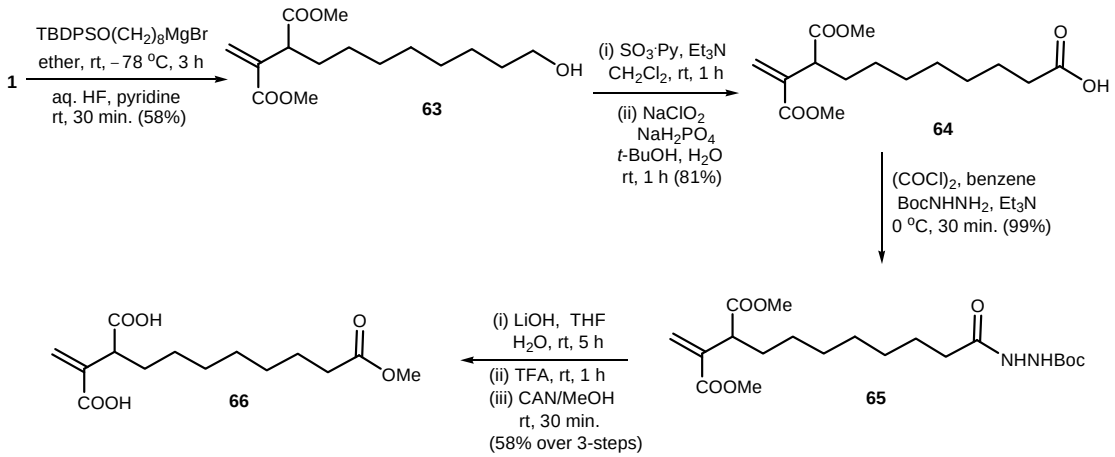
isopropylmagnesium bromide gave the desired product **61**. Boron tribromide induced demethylation followed by allylation furnished the naturally occurring camphorataanhydride A (**62a**) in 20% overall yield over 7-steps. The anhydride **62a** was heated with urea at 130 ^{o}C for one hour to obtain the natural bioactive camphorataimide B (**62b**) in 81% yield, while treatment of anhydride **62a** with hydroxylamine hydrochloride in refluxing pyridine gave camphorataimide C (**62c**) in 76% yield. Herein and also in the earlier examples, allylic substitutions of bromo-atom in anhydride to form the new carbon–carbon bond with intact preservation of an anhydride moiety is noteworthy.[28b]



Scheme 12. Synthesis of natural cytotoxic camphorataanhydride A and camphorataimides B and C

1A.2.9: Synthesis of tensyuic acid E

Tensyuic acids A-F were isolated from a culture broth of Aspergillus niger FKI-2342.[29] The structures of tensyuic acids A-F belong to the itaconic acid family and the tensyuic acid E exhibits antimicrobial and anticancer activities.[29] Omura and co-workers[30] have reported the first total synthesis of (±)-tensyuic

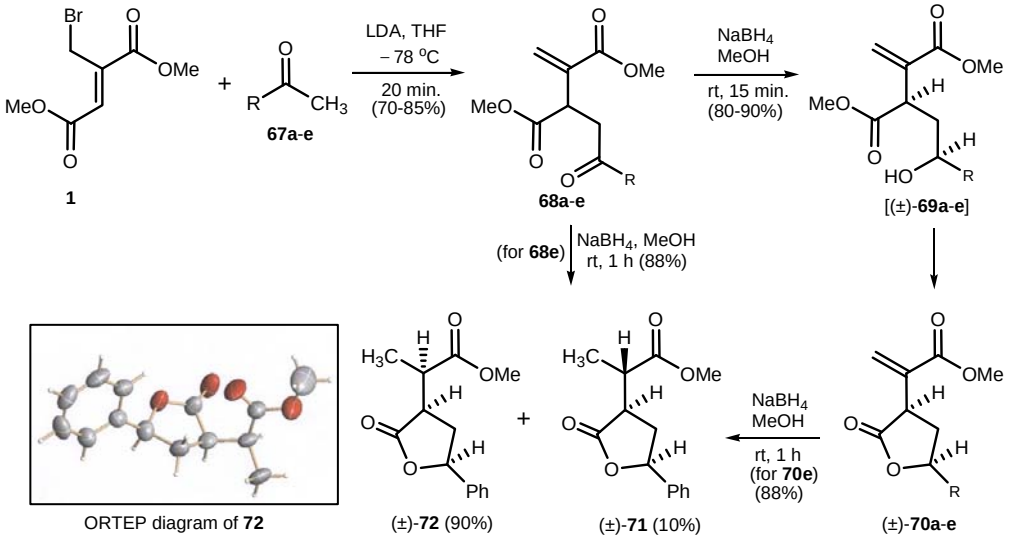


Scheme 13. Synthesis of (±)-tensyuic acid E via chemoselective S_N2' Grignard reaction and selective esterification

acid E (**66**) using chemoselective S_N2' Grignard reaction and selective esterification in 27% overall yield over 8-steps (Scheme 13). In the conversion of **65** to **66**, the formed intermediate hydrazide was treated with CAN as an oxidant in MeOH to achieve selective mono esterification.

1A.2.10: A facile chemo-, regio- and diastereoselective approach to cis-3,5-disubstituted γ-butyrolactones

The natural and unnatural γ-butyrolactones are important class of compounds that find major applications in organic, medicinal and polymer chemistry and a broad range of biological properties have been conferred on them.[31] A facile two-step approach for the synthesis of γ-butyrolactones has been developed in our group[32] via S_N2' coupling reaction of enolates of alkyl methyl ketones with dimethyl bromomethylfumarate (**1**) followed by diastereoselective $NaBH_4$ reduction of newly formed ketodiesters (±)-**68** to the *cis*-3,5-disubstituted lactones (±)-**70a**-**e** in excellent yields (Scheme 14). Treatment of the lactonylacrylate **70e** with $NaBH_4$ in methanol at room temperature for 1 h gave mixture of diastereomers (±)-**71** and (±)-**72** in a 1:9 ratio with 88% yield. Similarly, (±)-**68e** too, on treatment with an excess of $NaBH_4$, directly furnished the mixture of (±)-**71** and (±)-**72** in nearly the same ratio and yield. The mixture of **71** and **72** on recrystallization from dichloromethane provided analytically pure (±)-**72** with 69% recrystallization yield. Finally the structure of lactone **72** was established by them on the basis of X-ray crystallographic data.



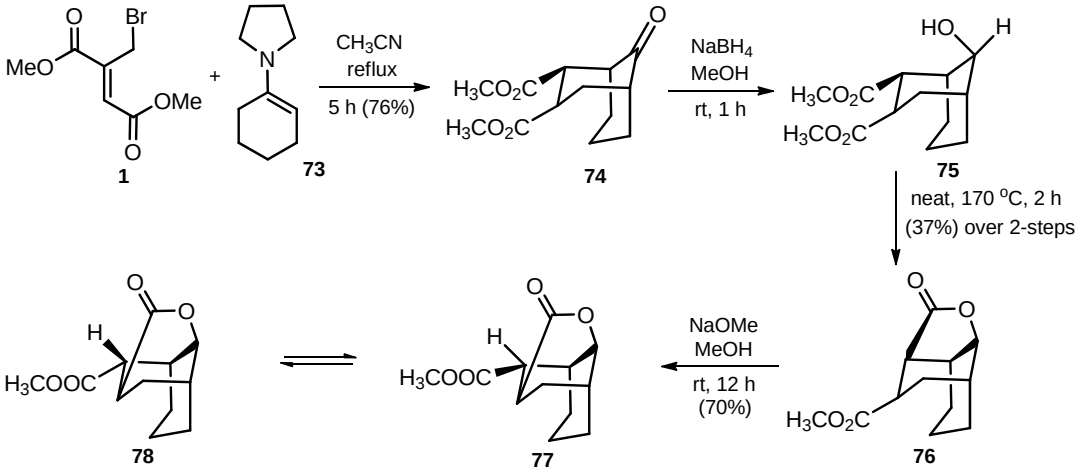
a, R = CH_2CH_3; **b**, R = $CH_2(CH_2)_2CH_3$; **c**, R = $CH_2(CH_2)_5CH_3$; **d**, R = $CH_2(CH_2)_8CH_3$; **e**, R = Ph.

Scheme 14. Synthesis of γ-butyrolactones

1A.2.11: Synthesis of bicyclo[3.3.1]nonanone architecture

Lawton and co-workers[33] have reported the synthesis of bicyclo[3.3.1]nonan-9-one derivative by the reaction of enamine of cyclohexanone with dimethyl bromomethylfumarate (**1**) followed by $NaBH_4$

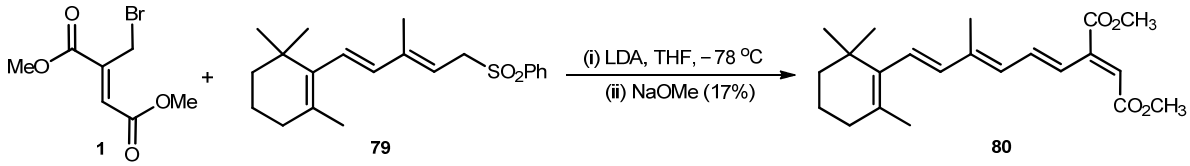
reduction to hydroxy diester **75**, which did not undergo complete γ-lactone formation until heated to 170 °C for 2 h (Scheme 15). The conversion of γ-lactone **76** into a 4:1 mixture of δ-lactone esters **77** and **78** was achieved using sodium methoxide via the C-3 ester epimerization, opening of the γ-lactone, conformational inversion to a boat form and condensation pathway to obtain **77**, which then an in situ epimerizes at the C-2 centre to an equilibrium mixture of **77** and **78**.



Scheme 15. Enamine coupling reactions with dimethyl bromomethylfumarate

1A.2.12: Synthesis of retinoic acid skeleton

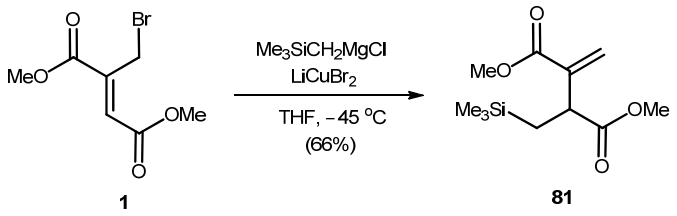
Retinoic acid (vitamin A acid) and its analogues have received considerable attention for their importance in controlling the normal growth, development, and differentiation of epithelial cells.[34] Welch et al.[35] have synthesized retinoic acid analogue by the deprotonation of sulfone **79**[36,37] with alkyl lithium reagent (*n*-BuLi or MeLi) or lithium diisopropylamide (LDA) followed by addition of bromide **1** effects alkylation. Elimination of benzenesulfonic acid to dimethyl ester **80** was conveniently accomplished by direct treatment with sodium methoxide (Scheme 16).



Scheme 16. Synthesis of retinoic acid framework via chemoselective allylic substitution

1A.2.13: Synthesis of functionalized homoallylsilane

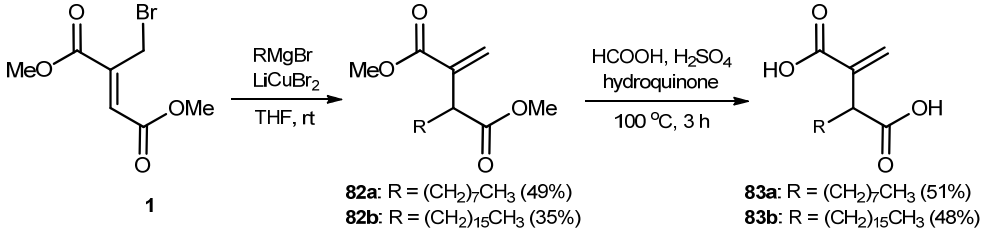
Amri and co-workers[38] have synthesized functionalized homoallylsilane **81** as a potential synthon via S_N2' coupling reaction of trimethylsilylmethylmagnesium chloride with dimethyl bromomethylfumarate (**1**) (Scheme 17).



Scheme 17. Synthesis of homoallylsilane

1A.2.14: Synthesis of alkylitaconic acids

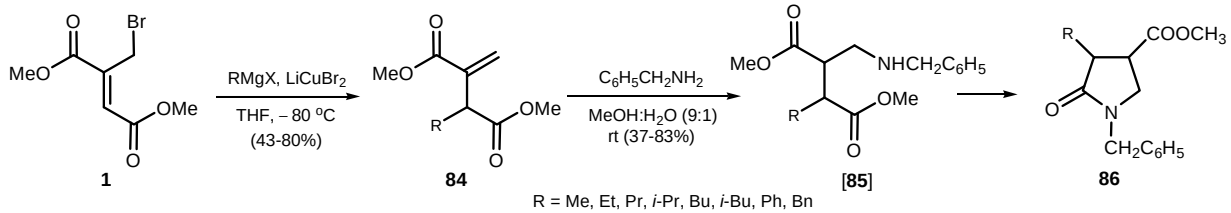
To analyze the physicochemical and redox properties of alkylitaconic acids, Watanabe and co-workers[39] have synthesized alkylitaconic acids **83a**/**b** using S_N2' Grignard coupling reaction of alkylmagnesium bromide with dimethyl bromomethylfumarate (**1**) followed by acidic hydrolysis using formic acid, sulfuric acid and hydroquinone as polymerization inhibitor in 25/17% overall yields (Scheme 18).



Scheme 18. Synthesis of alkylitaconic acids via S_N2' coupling reaction of alkylmagnesium bromide

1A.2.15: Synthesis of dimethyl 3-alkyl itaconates and 2-alkyl 3-carbomethoxy-γ-lactams

Amri and co-workers[40] have reported the synthesis of *β*-alkylated itaconates **84** and *α*-alkyl-*β*-carbomethoxy-*γ*-lactams **86** using S_N2' Grignard coupling reaction of alkylmagnesium bromide with dimethyl bromomethylfumarate (**1**) in the presence of catalytic amount of $LiCuBr_2$ followed by conjugate Michael addition/lactamization sequence using primary amine leading to the diastereoselective formation of *α*-alkyl-*β*-carbomethoxy-*γ*-lactams **86** with moderate to good yields (Scheme 19).

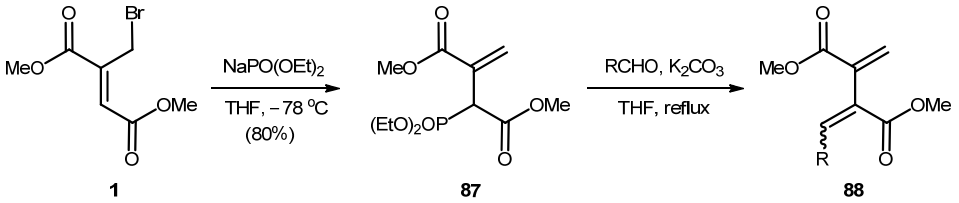


Scheme 19. Synthesis *β*-alkylated itaconates and *α*-alkyl-*β*-carbomethoxy-*γ*-lactams

1A.2.16: Synthesis of (E/Z)-1-alkyl-2,3-dimethoxycarbonyl-1,3-butadienes

2,3-Dimethoxycarbonylbutadienes are useful intermediates in organic synthesis.[41] Amri and co-

workers[42] have reported the synthesis of (*E*/*Z*)-1-alkyl-2,3-dimethoxycarbonyl-1,3-butadienes **88a**-**f** by using Wittig-Horner reaction of phosphonate **87**, prepared from dimethyl bromomethylfumarate (**1**) and sodium diethyl phosphite, and aldehydes using an aqueous potassium carbonate solution as a base (Scheme 20, Table 1).



Scheme 20. Synthesis of (*E*/*Z*)-1-alkyl-2,3-dimethoxycarbonyl-1,3-butadienes via Wittig-Horner reaction

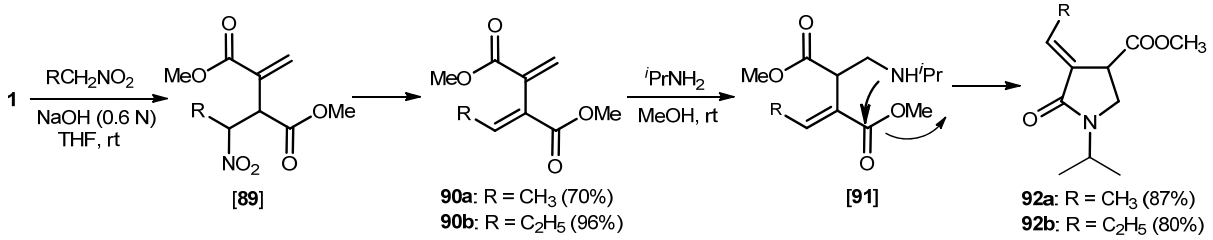
Table 1. Synthesis of (*E*/*Z*)-1-alkyl-2,3-dimethoxycarbonyl-1,3-butadienes **88a**-**f**

1,3-Dienes **88**	R	% *E*/*Z* [a]	Yield (%)
88a	H	-	71
88b	CH_3	78/22	66
88c	C_2H_5	82/18	62
88d	*n*-C_3H_7	80/20	67
88e	*i*-C_4H_9	70/30	67
88f	*n*-C_5H_{11}	75/25	68

[a] The *E* and *Z* configurations have been assigned on the basis of ^{1}H NMR chemical-shift data.

1A.2.17: Synthesis of α-alkylidene-γ-lactams

α-Alkylidene-*γ*-lactams show cytotoxicity, anti-tumor and anti-inflammation activities.[43] Amri and co-workers[44] have also reported the stereoselective synthesis of (*E*)-1-alkyl-2,3-dimethoxycarbonyl-1,3-butadienes **90a**/**b** using S_N2' coupling reaction of nitroalkanes with dimethyl bromomethylfumarate (**1**) and their reaction with primary amine furnished *α*-alkylidene-*γ*-lactams **92a**/**b** in good yields via selective conjugate addition followed by an intermolecular cyclization sequence (Scheme 21).

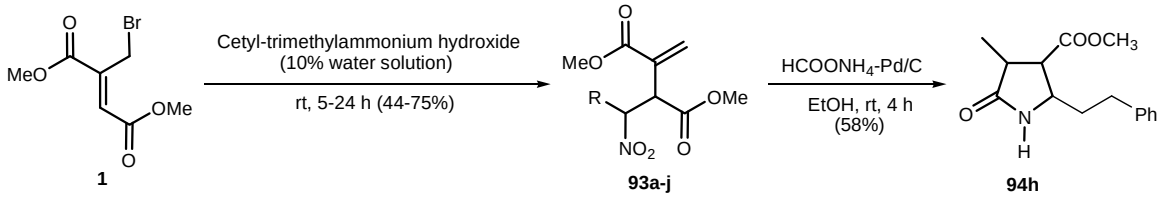


Scheme 21. Synthesis of *α*-alkylidene-*γ*-lactams via stereoselective S_N2' coupling reaction of nitroalkanes

1A.2.18: Chemoselective S_N2' coupling reaction of nitroalkanes: synthesis of γ-lactams

Ballini and coworkers[45] have reported chemoselective S_N2' coupling reaction of a variety of primary

nitroalkanes with dimethyl bromomethylfumarate (**1**) in the presence of cetyl-trimethylammonium hydroxide (CTAOH) catalyst to obtain α,β-unsaturated esters **93** in good yields with the retention of nitro group, which was then successfully converted to γ-lactams **94** using $HCOONH_4$–Pd/C induced reduction[46] of both the nitro group and the carbon–carbon double bond (Scheme 22).



R = CH_3, C_4H_9, C_7H_{15}, $C_{11}H_{23}$, $(CH_2)_2Me_2$, $(CH_2)_4OAc$, $(CH_2)_5OAc$, $(CH_2)_2Ph$, Ph, $-(CH_2)_5-$

Scheme 22. Synthesis of γ-lactams via S_N2' coupling reaction and double reduction

1A.3: Summary

In this section, we have presented a concise account on the chemistry of cyclic anhydride derivative, the dimethyl bromomethylfumarate. The dimethyl bromomethylfumarate has six alternate sites available for nucleophilic reactions, viz (i) two ester carbonyls for 1,2-additions (ii) two sites for Michael addition (iii) allylic bromo atom for nucleophilic substitution reaction (iv) one site for S_N2' coupling reaction. All the reactive sites have been appropriately used for the construction of variety of natural and unnatural products employing carbon–carbon bond formation reactions. The Diels-Alder reaction, indium-mediated allylation reaction, S_N2' Coupling reactions with Grignard reagents, nitroalkanes, enamines, alkyl enolates and nucleophilic allylic substitution of bromine with Grignard reagents and other nucleophiles clearly demonstrate impressive synthetic utilities of dimethyl bromomethylfumarate to construct carbon–carbon bonds. Overall the use of dimethyl bromomethylfumarate for the synthesis of a large numbers of bioactive natural and unnatural products has been briefly reviewed. All the information collected and presented here has been well supported by the provision of more than 60 references from various monographs and international journals.

Development of novel carbon–carbon bond forming reaction for the synthesis of bioactive natural and unnatural products has been foremost area of research in synthetic organic chemistry. In this context as a part of this dissertation, we have developed an unprecedented S_N2' coupling reaction of Wittig reagents with the dimethyl bromomethylfumarate to synthesize enes, dienes and related lignan class of natural products. Our synthetic strategies towards the development of novel carbon–carbon bonds and applications for the synthesis of bioactive natural products will be discussed in detail in the second chapter of this dissertation.

(±)-1,3,4,5-Tetragalloylapiitol, the polygalloylated sugar has been recently isolated as bioactive natural product and it possess HIV RNase H inhibitory activity. We have also reported first total synthesis of (±)-1,3,4,5-tetragalloylapiitol starting from dimethyl bromomethylfumarate. Our synthetic strategies towards the synthesis of bioactive natural product (±)-1,3,4,5-tetragalloylapiitol will be discussed in detail in the forth chapter of this dissertation.

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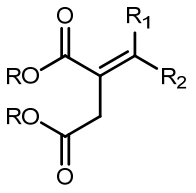
Chapter 1: Section B

A Concise Account on the Chemistry of Dialkyl 2-Alkylidenesuccinates

This section B of chapter 1 features the following topics:

1B.1: Introduction

Large numbers of natural and unnatural products have been synthesized by developing novel reactions with the cyclic anhydride derivatives, dialkyl 2-alkylidenesuccinates and dialkyl 2-arylidenesuccinates. This section portrays a concise account on the methods for preparation of dimethyl/diethyl 2-alkylidenesuccinates **1** and their utilities in the synthesis of natural and unnatural products. We have tried our best to summarize and concisely present the information here, but no pretension of completeness is claimed.



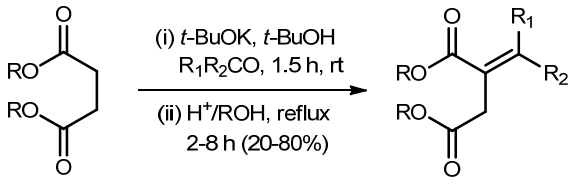
R = CH_3, C_2H_5; R_1 = H, alkyl; R_2 = alkyl

Dialkyl 2-alkylidenesuccinates **1**

1B.2: Methods of preparation of dialkyl 2-alkylidenesuccinates

Number of synthetic approaches for the synthesis of dialkyl 2-arylidenesuccinates have been developed[1] and further extended for the synthesis of dialkyl 2-alkylidenesuccinates **1** owing to their utilities for the synthesis of several commercially valuable materials and natural products. The various approaches for the synthesis of dimethyl/diethyl 2-alkylidenesuccinates **1** have been concisely presented below.

The first general and most widely used synthetic approach for the preparation of tri- and tetrasubstituted dialkyl (*E*)-alkylidenesuccinates **1** was reported by Stobbe et al.[2] in 1899 in moderate to good yields via base catalyzed condensation of dialkyl succinates **2** with aliphatic aldehydes and ketones followed by acid catalyzed esterification (Scheme 1).

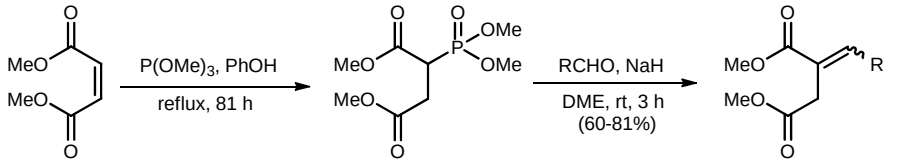


2 **1**

R = CH_3, C_2H_5; R_1 = H, alkyl; R_2 = alkyl

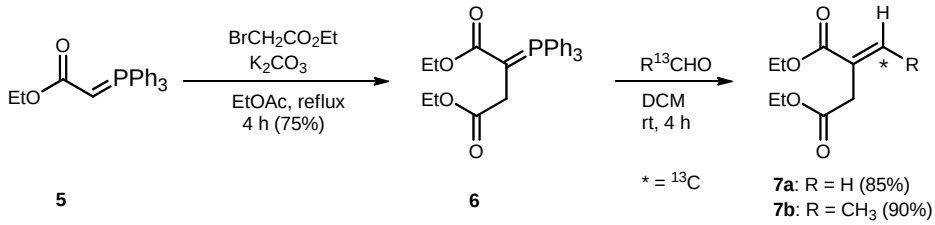
Scheme 1. Synthesis of tri- and tetra-substituted dialkyl 2-alkylidenesuccinates via Stobbe condensation

In 1975, Trost et al.[3] have reported new synthetic method for synthesis of tri-substituted dimethyl (*E*/*Z*)-alkylidenesuccinates **1** in 60-81% yields starting from trimethyl phosphite and dimethyl maleate (**3**) to form the alkyl phosphonate **4**, followed by Horrnor-Wittig-Emmons reaction with aliphatic aldehydes (Scheme 2).



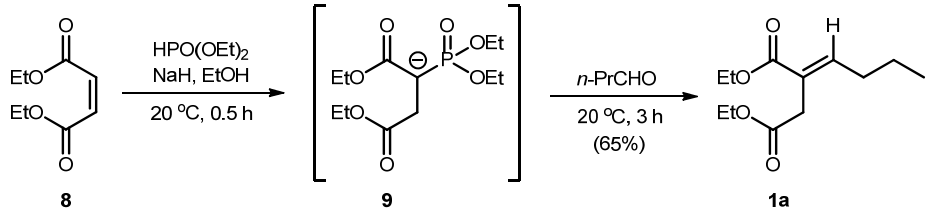
Scheme 2. Synthesis of dimethyl (*E*/*Z*)-alkylidenesuccinates via HWE reaction of alkyl phosponate

In 2003, Lugtenburg et al.[4] have reported the synthesis of ^{13}C isotope labeled tri-substituted diethyl (*E*)-alkylidenesuccinates **7a**/**b** in 85/90% yields starting from base catalyzed alkylation of phosphorane **5** with ethyl bromoacetate to form the stabilized Wittig ylide **6**, followed by Wittig reaction of phosphorane **6** with the corresponding ^{13}C isotope labeled aldehydes (Scheme 3).

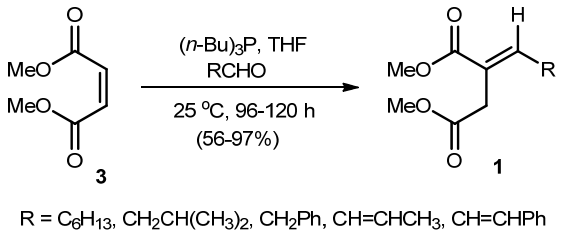


Scheme 3. Synthesis of diethyl 2-alkylidenesuccinates via Wittig reaction of stabilized ylide

Shen et al.[5] have reported sequential one-pot synthesis of diethyl (*E*)-butylidenesuccinate (**1a**) in 65% yield starting from Michael addition reaction of sodium diethyl phosphate, generated from diethyl phosphite and sodium hydride, to diethyl maleate (**8**) to furnish the phosphoryl-stabilized carbanion **9**, followed by HWE reaction with *n*-butanal (Scheme 4).



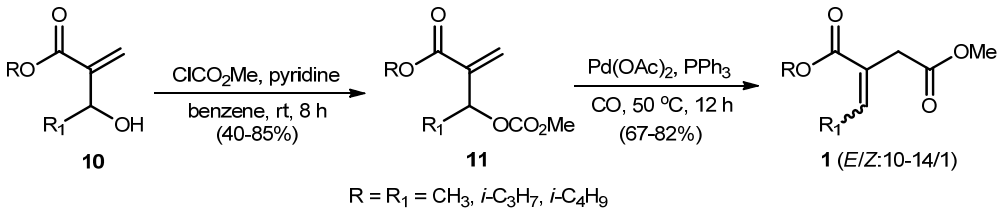
Scheme 4. Sequential one-pot synthesis of diethyl (*E*)-butylidenesuccinate



Scheme 5. One-step synthesis of tri-substituted dimethyl 2-alkylidenesuccinates

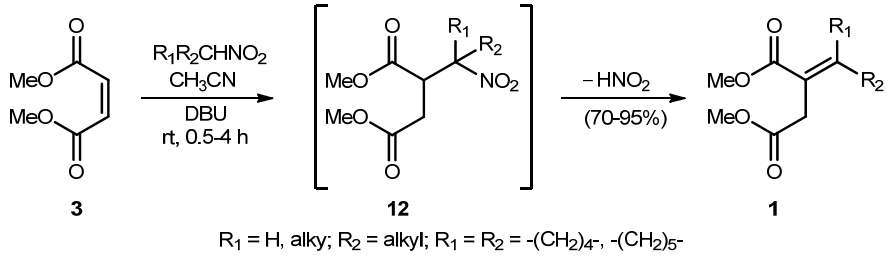
Mirand et al.[6] in 2003 and Bourguet et al.[7] in 2007 have reported one-step synthesis of tri-substituted dimethyl (*E*)-alkylidenesuccinates **1** in 56-97% yields via Michael type addition of reactive *n*-tributylphosphine to dimethyl maleate (**3**) followed by HWE reaction with aliphatic aldehydes in THF at 25 ^{o}C (Scheme 5).

Yamamoto et al.[8] have reported the synthesis of tri-substituted dimethyl (*E*/*Z*)-alkylidenesuccinates **1** starting from aliphatic allylic alcohols **10** via corresponding carbonate formation followed by palladium catalyzed carbonylation of the resulting aliphatic allylic carbonates **11** in 27-70% overall yields over 2-steps (Scheme 6).



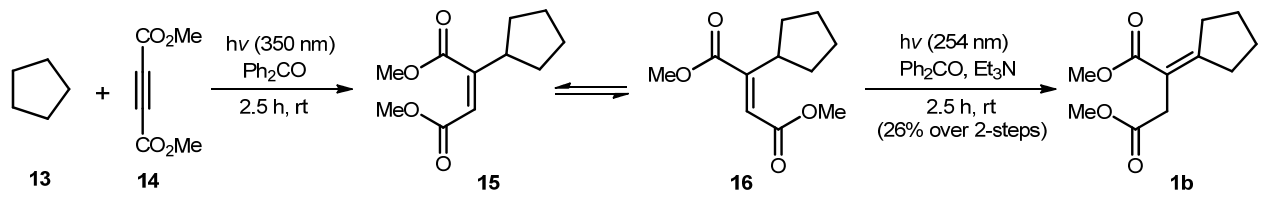
Scheme 6. Synthesis of tri-substituted dialkyl 2-alkylidenesuccinates via palladium catalyzed carbonylation

Ballini et al.[9] have reported a general stereoselective one-step synthesis of tri- and tetrasubstituted dimethyl (*E*)-alkylidenesuccinates **1** in excellent yields starting from dimethyl maleate (**3**) via Michael addition of several functionalized nitroalkanes in the presence of DBU as a base followed by elimination of nitrous acid (Scheme 7).



Scheme 7. Synthesis of tri- and tetrasubstituted dimethyl 2-alkylidenesuccinates

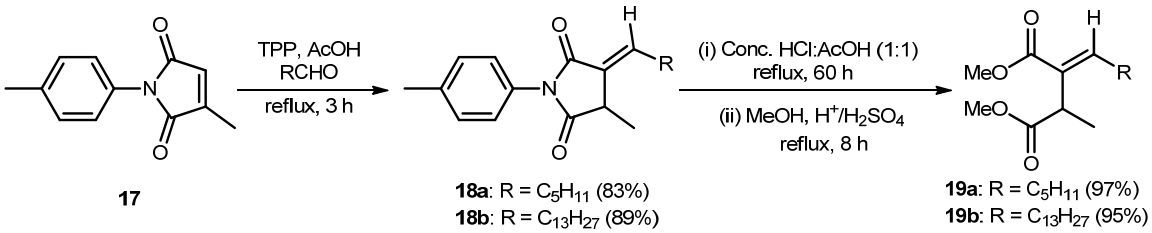
In 2009, Geragthy et al.[10] have reported benzophenone mediated photochemical reaction of cyclopentane (**13**) with dimethyl acetylenedicarboxylate (**14**) to form dimethyl 2-cyclopentylidenesuccinate (**1b**) in 26% yield over 2-steps via addition of a photochemically generated



Scheme 8. Synthesis of dimethyl 2-cyclopentylidenesuccinate via photochemical reaction

cyclopentyl radical to **14** followed by Et_3N induced photochemical isomerization of double bond (Scheme 8).

Recently in 2010, the dimethyl 2-alkylidene-3-methylsuccinates **19a/b** have been synthesized in our group[11] via acidic hydrolysis followed by esterification of 2-alkylidene-3-methylsuccinimides[12] **18a/b** in 97/95% overall yields (Scheme 9).



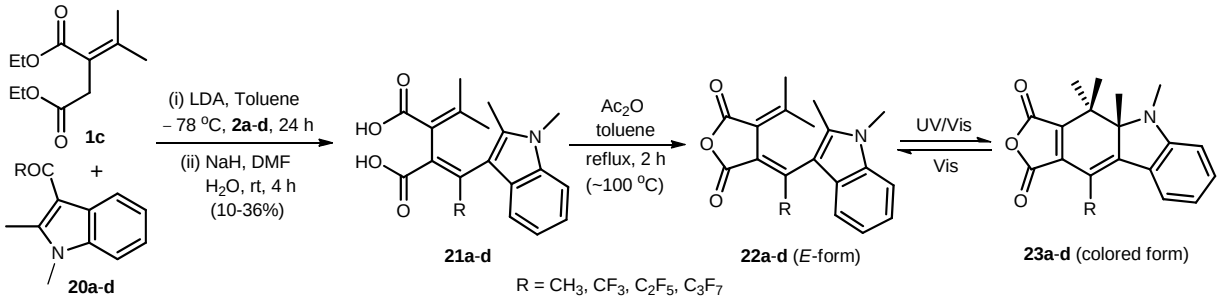
Scheme 9. Synthesis of dimethyl 2-alkylidene-3-methylsuccinates via acidic hydrolysis of imides

1B.3: Synthetic utility of dialkyl 2-alkylidenesuccinates

A large number of synthetic applications of dialkyl 2-arylidenesuccinates have been reported in the literature,[13] however the synthetic applications of dialkyl 2-alkylidenesuccinates **1** are relatively less explored. The diverse applications of dimethyl/diethyl 2-alkylidenesuccinates **1** for the synthesis of natural and unnatural products employing various carbon–carbon and carbon–oxygen bond forming reactions have been concisely presented in the following part.

1B.3.1: Synthesis of photochromic fulgides

Photochromic fulgides undergo reversible structural changes upon illumination and currently find commercial success as dyes and inks and in ophthalmic lenses due to the thermal stability of both forms of the molecules.[14] One important potential application is utility as the photoactive medium in an erasable rewriteable optical memory. A large numbers of useful fulgides have been synthesized by using Stobbe condensation,[15] out of which indolyl fulgides are of particular interest due to their enhanced photochemical and thermal stability and the shift of their *E*-form wavelength maxima into the near

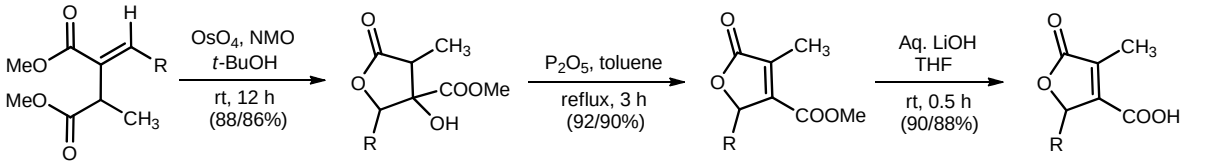


Scheme 10. Synthesis of indolyl fulgides via Stobbe condensation

visible region of the spectrum relative to other heteroaromatic fulgides.[16] Lee et al.[17] have reported the synthesis of the trifluoromethyl derivatives of an indolyl-based fulgides **22a**-**d**, starting from diethyl 2-isopropylidenesuccinate (**1c**) and acyl-indoles **20a**-**d** via Stobbe condensation using LDA as a base followed by basic hydrolysis and Ac_2O induced ring closure reaction (Scheme 10). The obtained fulgides possess the most promising combination of photochromic properties recorded till date.[16]

1B.3.2: Synthesis of (±)-striatisporolide A and (±)-lichesterinic acid

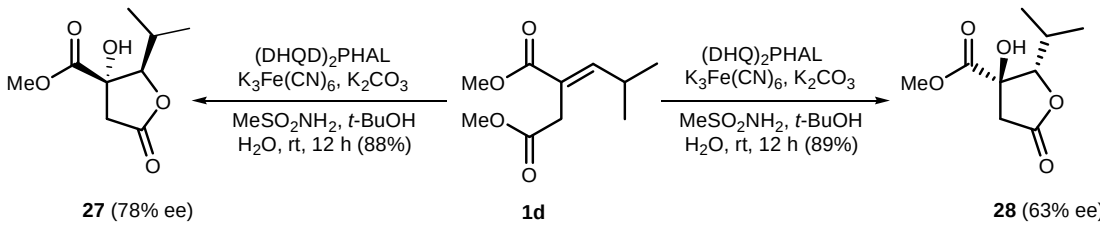
(±)-Striatisporolide A has been isolated from *Penicillum striatisporum* and it exhibits selective antifungal activity against *Candida albicans* versus *Saccharomyces cerevisiae*.[18] (±)-Lichesterinic acid has been isolated from icelandic moss *Cetraria islandica* and it shows antibacterial activity towards gram positive organisms.[19] (±)-Striatisporolide A (**26a**) and (±)-lichesterinic acid (**26b**) have been synthesized in our group[11] starting from dimethyl 2-alkylidene-3-methylsuccinates **19a**/**b** via OsO_4 induced dihydroxylation of carbon–carbon double bond followed by intramolecular dehydrative cyclization and basic hydrolysis in 73/68% overall yields over 3-steps (Scheme 11).



Scheme 11. Synthesis of (±)-striatisporolide A and (±)-lichesterinic acid

1B.3.3: Enantioselective synthesis of β-carbmethoxy-β-hydroxy-γ-lactones

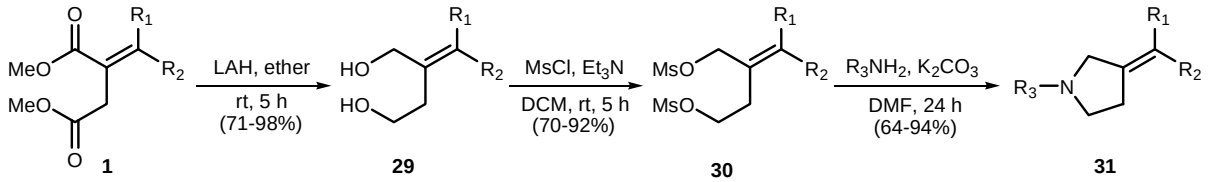
γ-Lactones are commonly encountered structural motif in nature and enantiomerically pure γ-lactones are of particular interest in the synthesis of natural and unnatural products.[20] Bruckner et al.[21] have reported Sharpless asymmetric dihydroxylation of dimethyl 2-isobutylidenesuccinate (**1d**) using $(DHQD)_2PHAL$ and $(DHQ)_2PHAL$ followed by spontaneous cyclization to selectively obtain β-carbmethoxy-β-hydroxy-γ-lactones **27**/**28** in 88/89% yields with 78/63% ee respectively (Scheme 12).



Scheme 12. Sharpless asymmetric dihydroxylation induced lactonization of dimethyl 2-isobutylidenesuccinate

1B.3.4: Synthesis of (E)-3-alkylidenepyrrolidines

Five membered nitrogen heterocycles constitute the essential core of many structural entities with enhanced biological activity.[22] Ballini et al.[23] reported the synthesis of *N*-protected (*E*)-3-alkylidenepyrrolidines **31**, starting from dimethyl 2-alkylidenesuccinates **1** via selective LAH reduction, mesytylation of formed diols **29** and step wise cyclization pathway in 32-85% overall yields over 3-steps (Scheme 13).

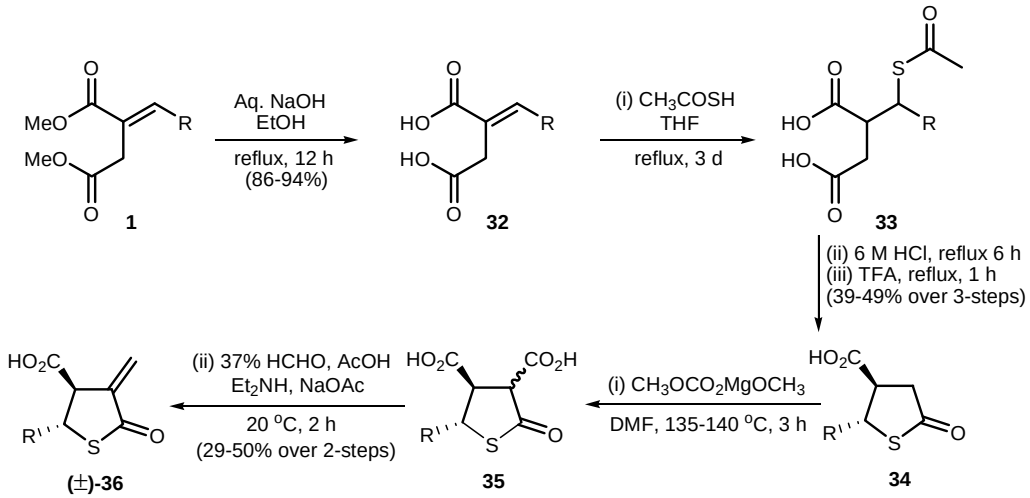


R_1 = H, CH_3; R_2 = CH_3, C_2H_5, C_3H_7, C_5H_{11}, -$(CH_2)_5$-; R_3 = benzyl, tosyl

Scheme 13. Synthesis of (*E*)-3-alkylidenepyrrolidines

1B.3.5: Synthesis of novel human fatty acid synthase inhibitor

Human fatty acid synthase (FAS) is a multi-enzyme complex containing seven functional proteins. Human FAS is a key enzyme in de novo biosynthesis of long chain fatty acids from acetyl-CoA, malonyl-CoA, and NADPH. It has been an attractive target for anti-obesity[24] and cancer treatments.[25] To obtain the advanced SAR and develop some novel inhibitors of FAS, Li et al.[26] have reported synthesis of some novel compounds **36** starting from dimethyl 2-alkylidenesuccinates **1** via basic hydrolysis to corresponding diacids **32**, followed by 1,4-addition of thioacetic acid to form thio-acids **33** (Scheme 14). The acidic hydrolysis of thioacetyl group followed by acid catalyzed cyclization furnished thiolactones **34**. The products **36** were obtained by the reaction of **34** with methyl methoxymagnesium carbonate



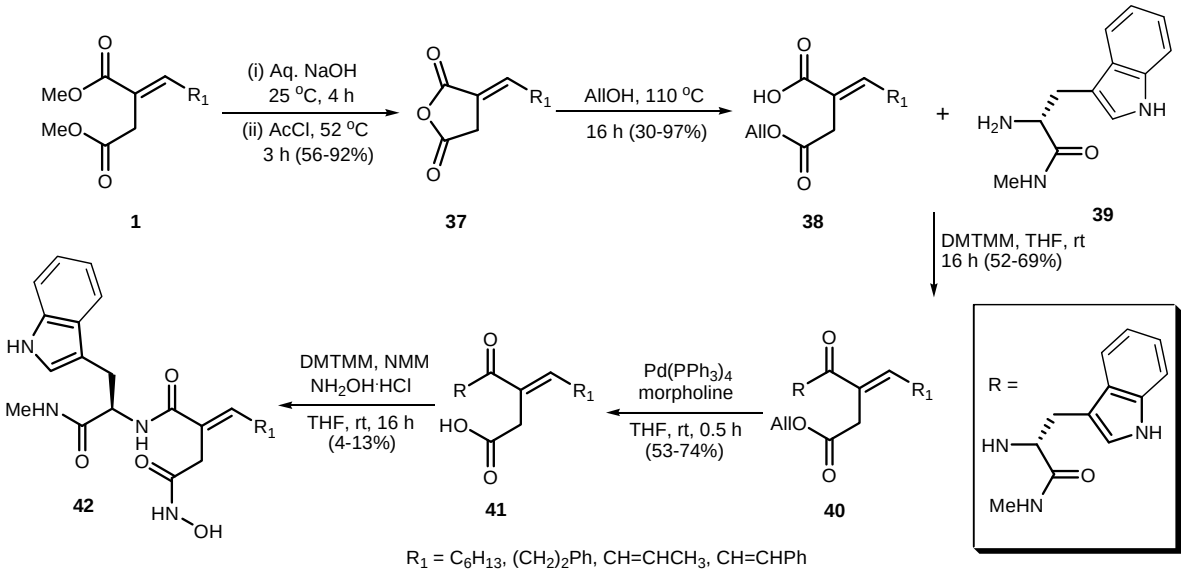
R_1 = C_7H_{15}, C_8H_{17}, C_9H_{19}, $C_{10}H_{21}$, $C_{11}H_{23}$

Scheme 14. Synthesis of novel human fatty acid synthase inhibitors

followed by reaction of diethylamine in formalin (Stock solution). Starting from dimethyl 2-alkylidenesuccinates **1**, novel compounds **36** were prepared in 10-23% overall yields over 6-steps.

1B.3.6: Synthesis of novel matrix metalloproteinases inhibitors

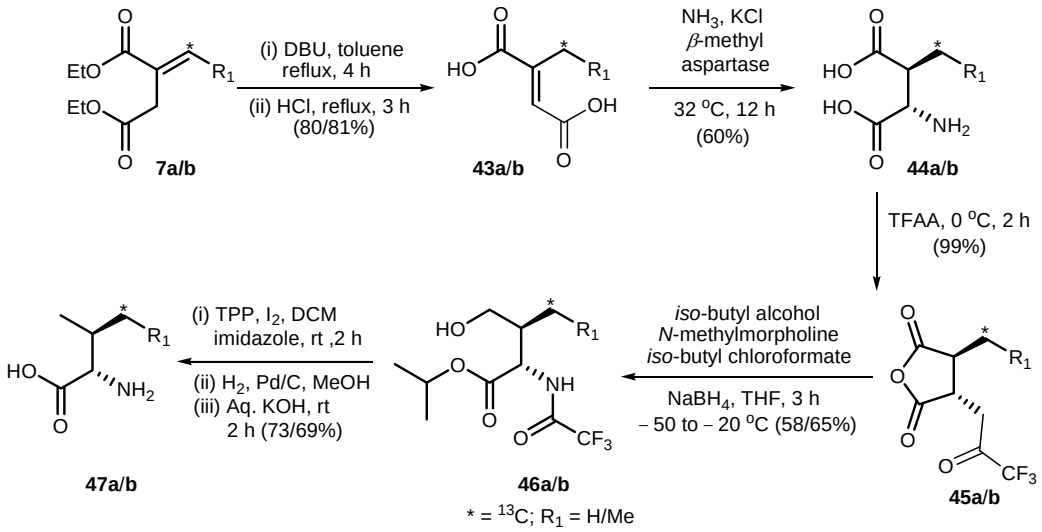
Matrix metalloproteinases (MMPs), a family of zinc endopeptidases, exhibit a wide spectrum of physiological and pathological activities.[27] Their involvement in all stages of cancer progression is now well documented and intensive efforts have been made to design MMP inhibitors as cancer therapeutical agents.[28] Bourguet et al.[7] have synthesized a myriad of MMP inhibitors **42** starting from dimethyl 2-alkylidenesuccinates **1** (Scheme 15) and then used as potential therapeutic agents to limit tumour progression. Basic hydrolysis of diesters **1** followed by dehydrative cyclization furnished the anhydrides **37** which on regioselective anhydride ring opening provided the monoallyl esters **38** as the single *E*-isomer. Coupling of L-tryptophan methylamide (**39**) with monoallylesters **38** gave the succinyltryptophanamides **40**. After deprotection of the allylesters **40** with tetrakis (triphenylphosphine)palladium (0), the obtained free acids **41** were reacted with hydroxylamine hydrochloride in the presence of 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMTMM) as coupling reagent to convert them directly into the pure *E*-hydroxamic acids **42**, but only in 4-13% yields. Starting from dimethyl alkylidenesuccinates **1**, novel compounds **42** were prepared in only 0.2-6% overall yields over 6-steps. Herein, we feel that further refinements in the reaction conditions to improve the yields are essential from the practical point of view.



Scheme 15. Synthesis of novel matrix metalloproteinases inhibitors

1B.3.7: Synthesis of (4-^{13}C)-(2S,3S)-valine and (4-^{13}C)-(2S,3S)-isoleucine

After successful completion of the human genome project, the total genomes of a plethora of other organisms are also becoming available, as are mutants that lead to malfunctioning or nonfunctioning proteins leading to genetic diseases. Furthermore, efficient biotechnological procedures are available to obtain membrane proteins using these genetic codes.[29] The fundamental challenge now is to study the chemical processes of these proteins involving bio-macromolecules without perturbation in the native states at the atomic level in time scales ranging from femtoseconds up to days. In order to study a system with site-directed isotope labeling of amino acids, Lugtenburg et al.[4] have reported the synthesis of (4-^{13}C)-(*2S*,*3S*)-valine (**47a**) and (4-^{13}C)-(*2S*,*3S*)-isoleucine (**47b**) starting from dimethy 2-alkylidenesuccinates via double bond isomerization followed by acidic hydrolysis to form diacids **43a**/**b**, which upon enantioselective Michael type addition using β-methyl aspatase furnished amino acids (*2S*,*3S*)-3-alkylaspartic acid **44a**/**b** (Scheme 16). TFAA induced amine protected cyclic anhydride formation followed by regioselective anhydride ring opening, mixed anhydride formation and $NaBH_4$ reduction of mixed anhydride furnished alcohols **46a**/**b**. The resulting alcohols were converted to iodides followed by hydrogen-iodine exchange using H_2 on Pd/C gave (4-^{13}C)-(*2S*,*3S*)-valine (**47a**) and (4-^{13}C)-(2S,3S)-isoleucine (**47b**) in 73/69% yields. Starting from dimethyl alkylidenesuccinates **7a**/**b**, novel compounds **47a**/**b** were prepared in 20-22% overall yields over 8-steps.

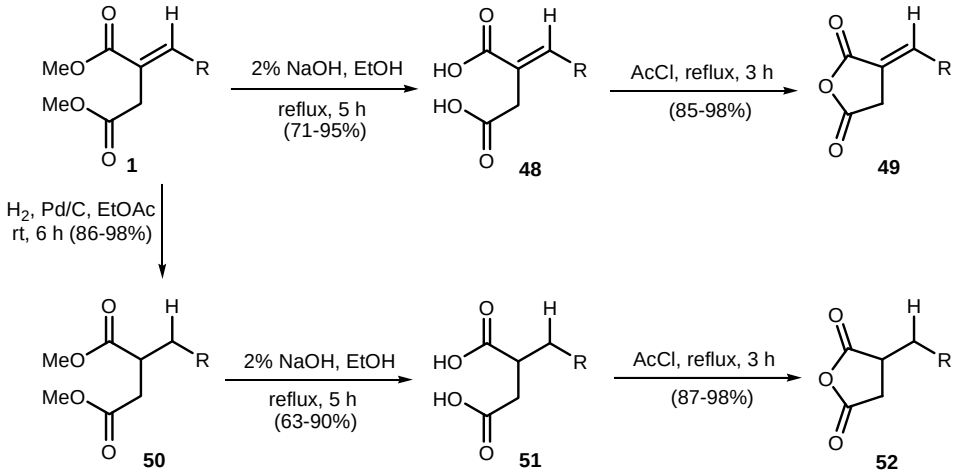


Scheme 16. Synthesis of of (4-^{13}C)-(*2S*,*3S*)-valine and (4-^{13}C)-(*2S*,*3S*)-isoleucine

1B.3.8: Synthesis of (E)-3-alkylidenesuccinic anhydrides and 3-alkylsuccinic anhydrides

(*E*)-3-Alkylidenesuccinic anhydrides and 3-alkylsuccinic anhydrides are important class of compounds due to their utilities as intermediates in the synthesis of important targets such as antibiotics, bioactive pyrrolidines, metalloproteinase inhibitors, inhibitors towards human leukocytes, and cephalotaxine.[30]

Ballini et al.[31] have reported the synthesis of (*E*)-3-alkylidenesuccinic anhydrides **49** starting from dimethyl (*E*)- alkylidenesuccinates **1** via basic hydrolysis followed by anhydride formation in 60-93% overall yields over 2-steps (Scheme 17). The reduction of double bond in dimethyl (*E*)-alkylidenesuccinates **1** followed by basic hydrolysis and anhydride formations furnished 3-alkylsuccinic anhydrides **52** in 47-86% overall yields over 3- steps.

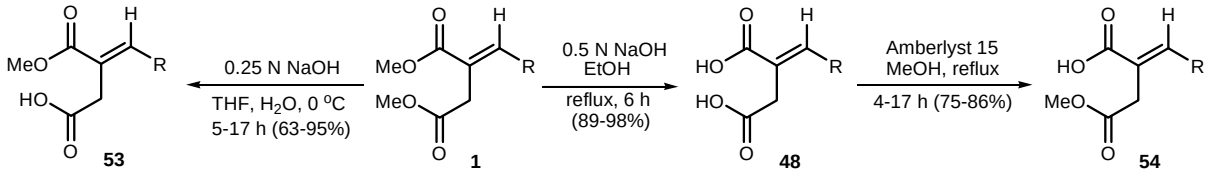


R = C_2H_5, C_4H_9, C_6H_{13}, $C_{10}H_{21}$, $CH(CH_3)_2$, $CH_2CH(CH_3)_2$, $CH_2CH_2COCH_3$, $(CH_2)_4CH_2OH$

Scheme 17. Synthesis of (*E*)-3-alkylidenesuccinic anhydrides and 3-alkylsuccinic anhydrides

1B.3.9: Regioselective synthesis of both monoesters of 2-alkylidenesuccinic acids

Monoesters of 2-alkylidenesuccinic acids are involved in a large number of synthetic processes leading to the preparation of biologically active substances.[32] Ballini et al.[33] have reported selective monohydrolyzation of diesters of 2-alkylidenesuccinic acids **1** at the more reactive ester group to the corresponding half-ester **53** in 63-95% yields (Scheme 18). Alternatively, complete hydrolysis of diesters **1** to the diacids **48** followed by subsequent selective methyl esterification of the alkanoic carboxyl group to furnish the other regioisomeric half-esters **54** in 67-84% overall yields over 2-steps.



R = C_2H_5, C_4H_9, C_6H_{13}, $C_{10}H_{21}$, $CH(CH_3)_2$, $CH_2CH(CH_3)_2$, $CH_2CH_2COCH_3$, $(CH_2)_4CH_2OH$

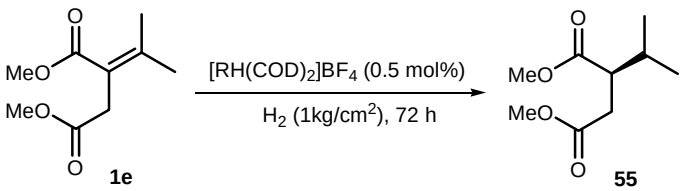
Scheme 18. Regioselective preparation of monoesters of 2-alkylidenesuccinic acids

1B.3.10: Asymmetric hydrogenation of dimethyl 2-propylidenesuccinate

The use of trans-chelating chiral diphosphine lingands in the asymmetric hydrogenation seems to be interesting not only from synthetic chemistry point of view but also for organometallic chemistry, although it has been scarcely studied.[34] Ito et al.[35] have reported catalytic asymmetric hydrogenation of

tetra-substituted dimethyl 2-isopropylidenesuccinate (**1e**) as a prochiral substrate using (*R*,*R*)-(*S*,*S*)-BuTRAP-rhodium complex in moderate enantioselectivity (78% ee) (Table 1).

Table 1. TRAP-rhodium complexes catalyzed asymmetric hydrogenation of dimethyl 2-propylidenesuccinate (**1e**)



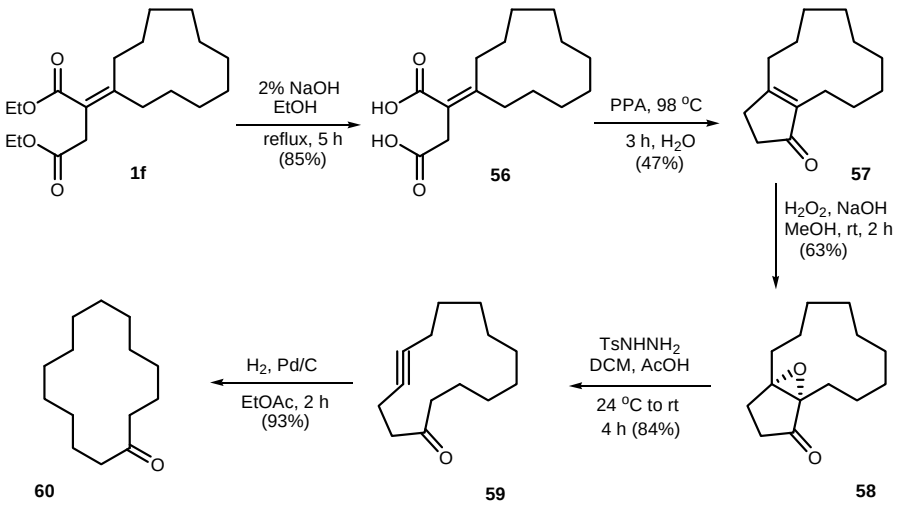
1e **55**

Entry	Ligand	Solvent	Temp. ^{o}C	% Yield	% Ee	Configuration [a]
1	EtTRAP	CH_2Cl_2	30	55	58	*S*
2	EtTRAP	*i*-PrOH	20	96	68	*S*
3	BuTRAP	*i*-PrOH	20	98	71	*S*
4	BuTRAP	*i*-PrOH	0	96	78	*S*
5	*i*-BuTRAP	*i*-PrOH	20	05	–	–
6	*i*-BuTRAP	*i*-PrOH	20	05	–	–
7	PhTRAP	*i*-PrOH	20	trace	–	–
8	FurTRAP	*i*-PrOH	20	13	06	*R*

[a] Configuration assignments were done on the basis of comparisons with the literature data.

1B.3.11: Synthesis of cyclotetradecanone via three carbon homologation

Natural products containing larger ring sizes are of particular interest in synthetic organic chemistry.[36] Eschenmoser et al.[37] in 1971 have reported three carbon homologation protocol to synthesize



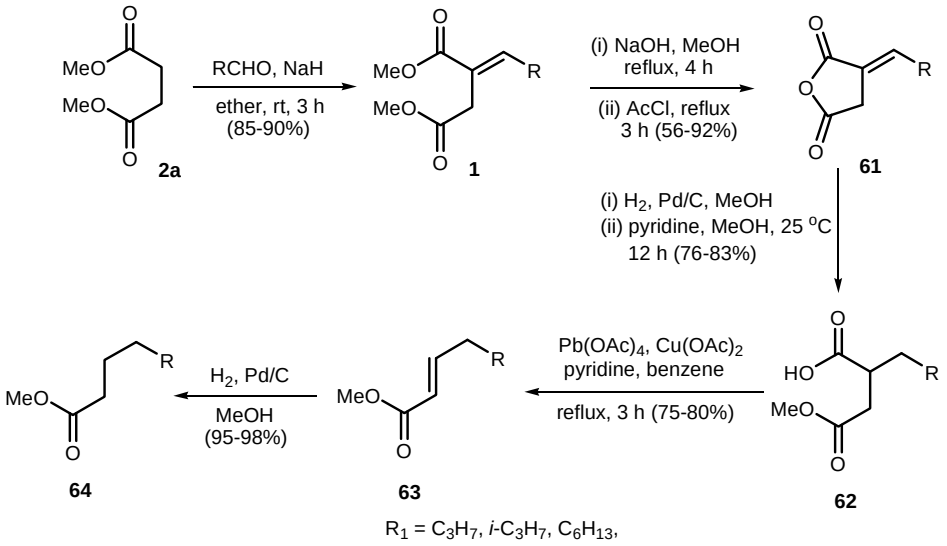
1f **56** **57** **58** **59** **60**

Scheme 19. Synthesis of cyclotetradecanone via three carbon homologation

cyclotetradecanone (**60**) starting from diethyl 2-undecylidenesuccinate (**1f**) via basic hydrolysis followed by acid catalyzed cyclization and decarboxylation furnished α,β-unsaturated ketone **57** (Scheme 19). Epoxidation of conjugated double bond in ketone **57** using H_2O_2/NaOH followed by ring expansion and alkyne formation using $TsNHNH_2$ gave γ-alkyne ketone **59**. Reduction of alkyne to alkane furnished cyclotetradecanone (**60**) in 93% yield. Starting from diethyl 2-undecylidenesuccinate (**1f**) cyclotetradecanone (**60**) was synthesized in 20% overall yield over 5-steps.

1B.3.12: Three carbon homologation of aldehyde

Rao et al.[38] have also reported three carbon homologation of aldehyde starting from dimethy 2-alkylidenesuccinates **1**, prepared by HWE reaction of dimethyl succinate (**2a**) and aliphatic aldehydes, via basic hydrolysis of **1** followed by dehydrative ring closure reaction to form the anhydrides **61** (Scheme 20). Regioselective anhydride ring opening followed by reduction of carbon–carbon double bond furnished the respective mono-esters **62**. Oxidative decarboxylation of acids using $Pb(OAc)_4$ followed by double bond reduction of formed olefins **63** furnished esters **64** with 3-carbon homologation of aldehydes in 26-54% overall yields over 7-steps.



Scheme 20. Three carbon homologation of aliphatic aldehydes to aliphatic esters

1B.4: Summary

In this section, we have presented a concise account on the chemistry of cyclic anhydride derivatives, the dimethyl/diethyl 2-alkylidenesuccinates. Number of methods of preparation of dimethyl/diethyl 2-alkylidenesuccinates utilizing Stobbe condensation of dialkyl succinates, HWE reaction of phosphorus ylides, addition-elimination reaction sequence of nitroalkanes, Pd catalyzed carbonylation reactions, photochemical reaction of cycloalkanes and hydrolysis of imides have been briefly described. The dialkyl 2-alkylidenesuccinates have five reactive sites available for reactions, viz (i) two ester carbonyls (ii) one conjugated double bond (iii) two allylic carbon atoms. All these reactive sites of tri- and tetra-substituted dimethyl/diethyl 2-alkylidenesuccinates have been used for the construction of variety of natural and unnatural products. The Stobbe condensation reaction of allylic carbon atom with different aldehydes to design photochromic fugides, Michael addition reaction of different nucleophiles on conjugated double bond to design bioactive inhibitors, asymmetric hydrogenation of conjugated double bond to synthesize natural and unnatural lactones, three carbon homologation of aldehydes and ketones and functionalization of different reactive sites to construct many structural entities with enhanced biological activities clearly demonstrate an impression about synthetic utilities of dimethyl/diethyl 2-alkylidenesuccinates. All the information collected and presented here has been well supported by the provision of more than 55 references from various international journals.

Development of novel carbon–oxygen bond forming reactions for the synthesis of bioactive natural and unnatural products has been premier area of research in synthetic organic chemistry. Although, a large number of synthetic applications of dimethyl/diethyl 2-alkylidenesuccinates via carbon–carbon bond formation have been reported in the literature, the synthetic applications of dimethyl/diethyl 2-alkylidenesuccinates via carbon–oxygen bond formation have been relatively less explored. In this context as a part of this dissertation, we have developed two novel carbon–oxygen bond forming reactions starting from tri- and tetra-substituted dimethyl/diethyl 2-alkylidenesuccinates and further extended for the synthesis of bioactive natural and unnatural γ-butenolides. Our synthetic strategies towards the development of novel carbon–oxygen bonds and further applications for the synthesis of γ-butenolides will be discussed in detail in the third chapter of this dissertation.

In the present chapter, we have summarized the methods of preparations of multifunctional building blocks the dimethyl bromomethylfumarate and dimethyl/diethyl 2-alkylidenesuccinates and their potential applications in the synthesis of structurally interesting bioactive molecules. In chapter 2 to 4, we will be presenting novel carbon–carbon and carbon–oxygen bond forming reactions developed and their applications for the total synthesis of γ-lactone containing bioactive natural products and (–)-1,3,4,5-tetragalloylapiitol utilizing these two above mentioned potential precursors.

1B.5: References

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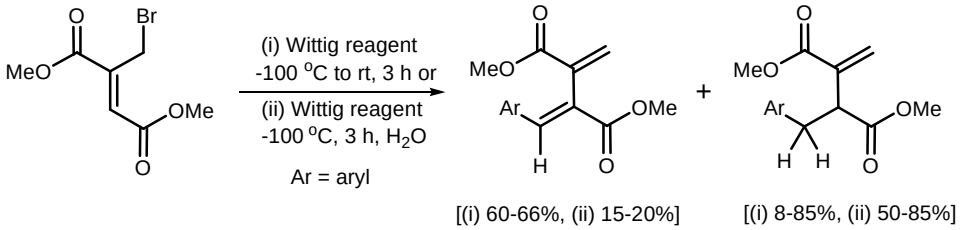
Chapter 2

Novel Carbon–Carbon Bond Forming Reaction with the Dimethyl Bromomethylfumarate: Synthesis of Bioactive Lignan Class of Natural Products

This chapter features the following topics:

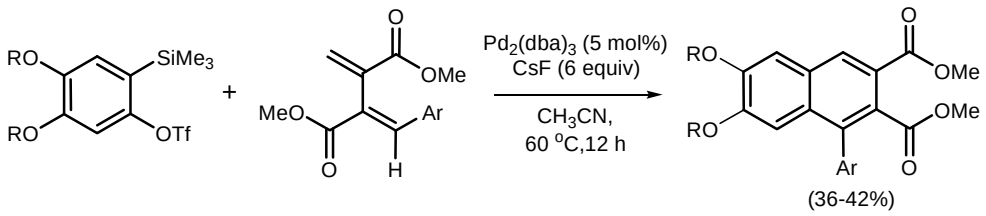
Note: *An independent figure, table, scheme, structure and reference numbers have been used for the each section.*

Section 2A: *Facile S_N2' coupling reactions of Wittig reagents with dimethyl bromomethylfumarate: Synthesis of enes, dienes and related natural products*



A new simple and efficient synthetic protocol with an ample scope has been demonstrated, by employing the S_N2' coupling reactions of the variety of Wittig reagents with dimethyl bromomethylfumarate to obtain the corresponding enes, dienes and related natural and unnatural products.

Section 2B: *Pd catalyzed [2 + 2 + 2] cocyclization of arynes and dienes to arylnapthalene lignan framework: Total synthesis of justicidin B and retrojusticidin B*



R = CH_3, -OCH_2O-; Ar = Phenyl, 3,4-dimethoxyphenyl, methylenedioxyphenyl

A novel palladium catalyzed [2 + 2 + 2] cocyclization of dienes and arynes to arylnapthalene frameworks with the formation of two new carbon–carbon bonds has been described. The versatility of this method is demonstrated through the facile total synthesis of justicidin B and retrojusticidin B in four steps, starting from dimethyl bromomethylfumarate. The present convergent strategy is general in nature and provides the way for the shorter and regioselective synthesis of various arylnapthalene lignans.

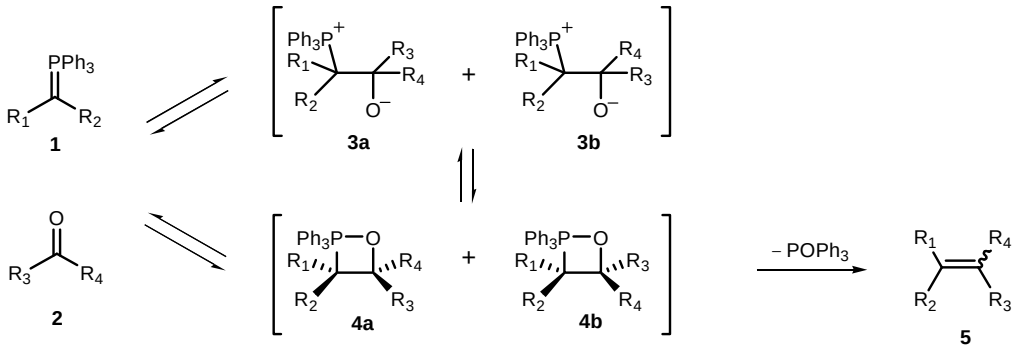
Chapter 2: Section A

Facile S_N2' Coupling Reactions of Wittig Reagents with Dimethyl Bromomethylfumarate: Synthesis of Enes, Dienes and Related Natural Products

This section A of chapter 2 features the following topics:

2A.1: Background

Geometrically defined enes and dienes are an important class of compounds and they find applications in the preparation of dyes, UV screens, drugs, in Diels-Alder reactions, and also for the synthesis of complex natural products.[1] A plethora of elegant chemical methods are known in the literature to design stereo-defined enes and dienes.[2] Recently, enes and dienes are synthesized by tandem homologation-allylboration,[2d] regioselective dienylation of aldehydes using dienylstannanes,[2e] metal mediated carbonylation,[2f] sequential Suzuki-Miyaura cross coupling reaction[2g] and dimethyl sulphonium methylide mediated olefination reaction.[2h-k] Among all, the Wittig olefination reaction[3] is regarded as one of the most strategic, widely applicable carbon–carbon double bond forming reaction available in organic synthesis[4] and the reaction has had an enormous impact on the sophistication of the total synthesis of organic molecules.[5] The Wittig reaction is a chemical reaction of nucleophilic triphenylphosponium ylide **1** (Wittig reagent) with an aldehyde or ketone **2** to give an olefin **5** with the elimination of triphenylphosphine oxide (Scheme 1).[6] The mechanism proposed is an addition of nucleophilic ylide carbon to the carbonyl group to yield a dipolar intermediate **3**, followed by formation of four-membered cyclic oxaphosphetane intermediate **4** which upon elimination of triphenylphosphine oxide furnishes an olefin **5**, where the formation of very strong phosphorus–oxygen bond (DH^o = 540 KJ mol^{-1}) in triphenylphosphine oxide is the driving force for olefin formation.[7] However, direct formation of four-membered cyclic oxaphosphetane intermediate **4** and reversible equilibrium has been also proposed for Wittig reaction mechanism.[8] The stereochemistry of the Wittig reaction depends strongly on both the steric bulk of ylide **1** and reaction conditions.[9] With nonstabilized triphenylphosphonium ylides **1** (R_2 = alkyl), the first step occurs easily with both aldehydes and ketones **2** and the decomposition of the oxaphosphetane **4** is the rate-determining step with the formation of preferentially *Z*-alkenes. However, with stabilised triphenylphosphonium ylides **1** (R_2 = alkoxycarbonyl, acyl, or cyano; where R_2 stabilises the negative charge) the first step is the slowest step, so the overall

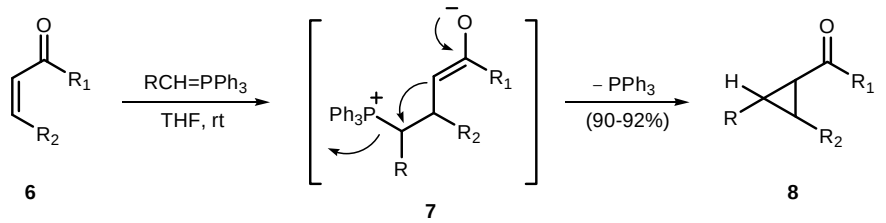


R_1, R_3 = alkyl, aryl; R_2 = H, alkyl, alkoxycarbonyl, acyl, cyano; R_4 = H, alkyl

Scheme 1. Wittig reaction of triphenylphosphine ylides with aldehydes and ketones

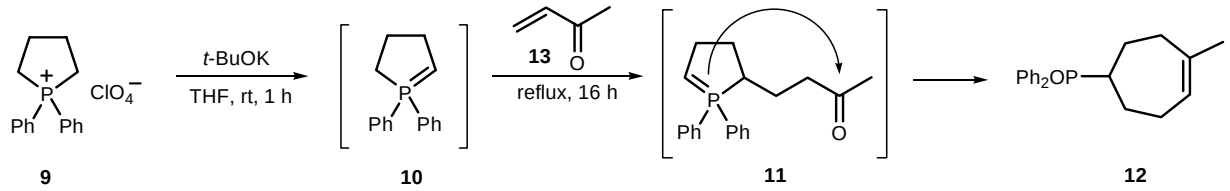
rate of alkene formation decreases with the formation of thermodynamically more stable *E*-isomer.[10] Wittig reaction is particularly effective with diverse range of aldehydes and ketones, however nucleophilic Michael-type addition of Wittig reagents on α,β-unsaturated carbonyl compounds are rare and to the best of our knowledge two examples are reported in the literature.[11,12]

Bestmann et al.[11] have reported cyclopropanation reaction with Wittig reagents via Michael-type addition reaction of alkylidenetriphenylphosporanes to α,β-unsaturated carbonyl compounds **6** followed by intramolecular cyclization to form cyclopropane products **8** with the elimination of triphenyl phosphine (Scheme 2).



Scheme 2. Synthesis of cyclopropanes via Michael-type addition of alkylidenetriphenylphosporanes

Yamamoto et al.[12] have reported synthesis of cycloheptenyldiphenylphosphine oxide **12** via a Michael-type addition reaction of five-membered cyclic wittig reagent **10** with methyl vinyl ketone to form intermediate **11**, followed by an intramolecular Wittig reaction (Scheme 3).



Scheme 3. Synthesis of cycloheptene via Michael-type addition of cyclic Wittig reagent

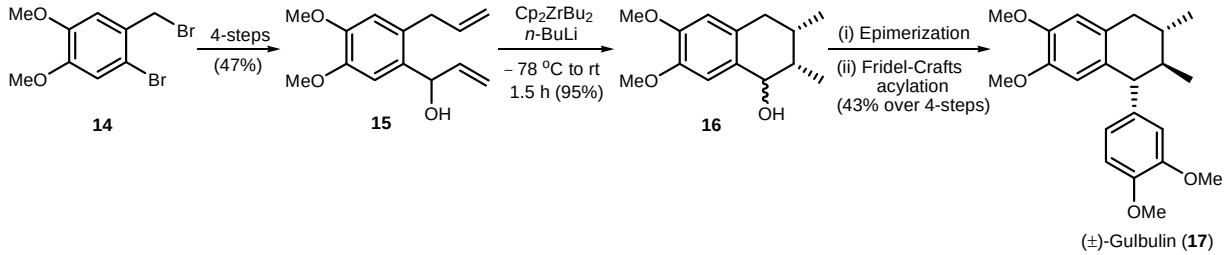
The S_N2' coupling reaction is a very important tool to form new carbon−carbon bonds in synthetic organic chemistry,[13] and the propensity of Wittig reagents for S_N2' coupling reactions was not studied. In chapter 1A, we have discussed in detail the S_N2' coupling reactions of different nucleophiles with dimethyl bromomethylfumarate. In this section, as a part of present dissertation, we have developed S_N2' coupling reaction of Wittig reagents with dimethyl bromomethylfumarate to synthesize enes, dienes and related lignan class of natural products (±)-gulbulin and (±)-prasanthaline.[14]

2A.2: Brief account on (±)-gulbulin and (±)-prasanthaline

Lignans are a class of secondary plant metabolites produced by oxidative dimerization of two phenylpropanoid units. The term *lignan* is applied to the optically active dimers of phenylpropanoids linked by the central carbon atoms of their side chains. Lignans are mostly present in nature in the free form, while their glycoside derivatives are only a minor form. They are widely distributed in the plant kingdom and have been found in species belonging to more than seventy families. Lignans are found in roots, rhizomes, stems, leaves, seeds and fruits. With some exceptions, wound resins of trees, heartwood, wood knots of *Picea abies*, flax,[15] do not provide commercially useful quantities. Lignans are found in most fibre-rich plants, including grains such as wheat, barley and oats; legumes such as beans, lentils and soybeans; and vegetables such as garlic, asparagus, broccoli and carrots.

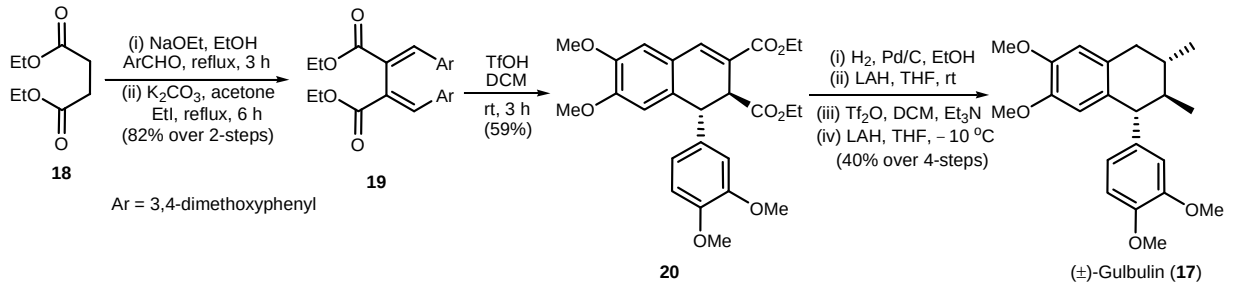
In spite of their extensive distribution, their biological functions in plants are as yet unclear.[16] Some lignans have potent antimicrobial, antifungal, antiviral, antioxidant, insecticidal and anti-feeding properties, and probably they play an important role in plant defense against various biological pathogens and pests. Furthermore, they may participate in plant growth and development. In addition to their purpose in nature, lignans also possess significant pharmacological activities, including antitumor, anti-inflammatory, immunosuppressive, cardiovascular, antioxidant and antiviral actions.[17] The significant bioactivities and structural diversity of lignans have triggered a vast amount of synthetic work.[18]

(±)-Galbulin (**17**) is a lignan class of natural product, first isolated from *Himantandra baccata* Bail in 1954.[19] In addition to the number synthesis of (±)-galbulin starting from other known lignans of similar structure,[20] two total synthesis of (±)-galbulin have been reported in the literature. Whitby et al.[21] described an interesting stereoselective synthesis of (±)-galbulin (**17**) via a zirconium-mediated cyclization of a 1,7-diene **15** as a key step followed by epimerization and Fridel-Crafts acylation with veratrole in 19% overall yield over 9-steps (Scheme 4).



Scheme 4. Synthesis of (±)-gulbulin via zirconium-mediated cyclization of 1,7-diene

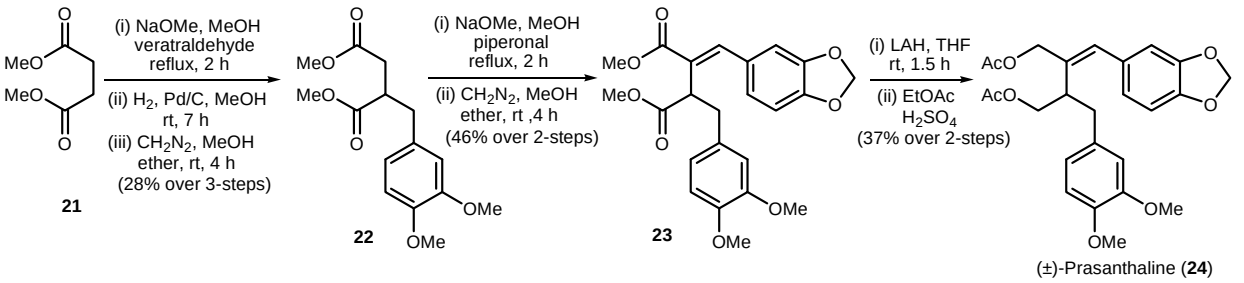
Charlton et al.[22] reported diastereoselective synthesis of (±)-galbulin (**17**) via triflic acid catalyzed cyclization of diethyl 2,3-diarylidenesuccinate **19** [prepared by Stobbe condensation of diethyl succinate



Scheme 5. Synthesis of (±)-gulbulin via TfOH catalyzed cyclization of diarylidenesuccinate

(**18**) with veratraldehyde in 82% yield over 2-steps] as a key step to furnish 1-aryl-1,2-dihydronapthalene **20**, followed by double bond reduction, LAH reduction of diesters, triflation of diols and substitution by hydrides gave (±)-galbulin (**17**) in 40% overall yield over 4-steps. Starting from diethyl succinate, the (±)-galbulin was synthesized in 19% overall yield over 7-steps (Scheme 5).

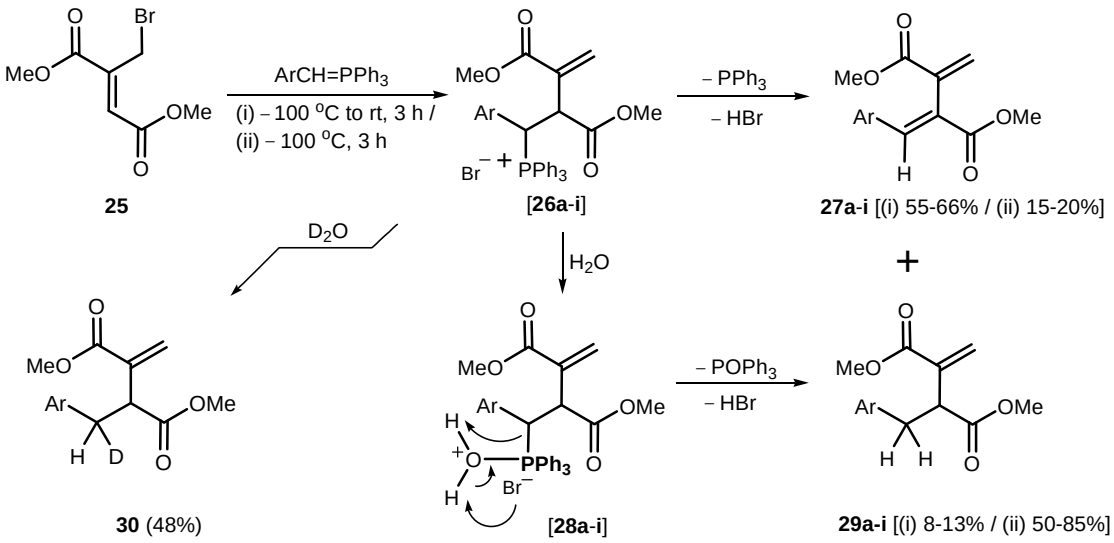
(±)-Prasanthaline (**24**) is a lignan class of natural product, first isolated from *Jatropha gossypifolia* Linn in 1988.[23] Banerji et al.[24] have reported first total synthesis of (±)-prasanthaline via Stobbe condensation of dimetyl succinate (**21**) with veratraldehyde followed by double bond reduction and esterification to obtain diester **22** in 28% yield over 3-steps (Scheme 6). The second Stobbe condensation of diesters **22** with piperonal, esterification, selective LAH reduction of formed diesters **23** and acylation path way gave (±)-prasanthaline (**24**) in 17% yield over 4-steps. Starting from dimethy succinate, the (±)-prasanthaline was synthesized in 5% yield over 7-steps.



Scheme 6. Synthesis of (±)-prasanthaline via stepwise double Stobbe condensation of dimethyl succinate

2A.3: Results and discussion

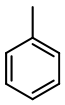
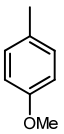
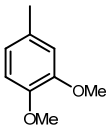
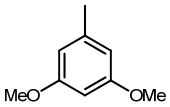
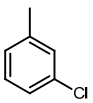
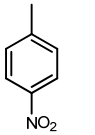
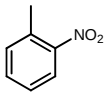
The dimethyl bromomethylfumarate (**25**) has been used for the synthesis of several natural and unnatural products employing the S_N2' coupling reactions with a variety of carbanionic species.[13,25] We envisaged that the S_N2' coupling reactions of Wittig reagents with dimethyl bromomethylfumarate having appropriately placed leaving group would be useful to provide a convenient approach to the variety of enes and dienes via the reductive removal of triphenylphosphine oxide and elimination of triphenylphosphine respectively. In this context, we decided to study the feasibility of S_N2' coupling



Scheme 7. S_N2' coupling reactions of Wittig reagents with dimethyl bromomethylfumarate

reactions of the Wittig reagents with the dimethyl bromomethylfumarate. Initially, we performed the reaction with equimolar amounts of dimethyl bromomethylfumarate (**25**) and the Wittig reagent benzylidenetriphenylphosphorane at 0 °C in THF and upon quenching with water at the same temperature, we obtained the column separable mixture of ene **29a** and diene **27a** in a 2:3 ratio with 30% yield (Scheme 7). On confirmation of feasibility of S_N2' coupling reactions of Wittig reagents with dimethyl bromomethylfumarate (**25**), we performed several experiments using different bases to generate the ylides (*n*-BuLi, NaH, $NaCH_2SOCH_3$, *t*-BuOK, DBU) and solvents (THF, ether, 1,4-dioxane, THF-dioxane, THF-HMPA) at different temperatures (–100, –78, –40, –20 and 0 °C and rt) to selectively obtain the ene **29a** and diene **27a** with high yields. In the S_N2' coupling reaction of dimethyl bromomethylfumarate (**25**) with Wittig reagents, the best result was obtained, when the *n*-BuLi was used as a base to generate the ylide and by performing the reaction in THF at –100 °C and then quenching the reaction at room temperature after 3 hours time (68% yield, **27a**:**29a** = 88:12). When the same reaction of dimethyl bromomethylfumarate (**25**) with Wittig reagent was quenched at –100 °C with water after 3 hours time, we obtained the opposite selectivity, and the ene **29a** was obtained as a major product and diene **27a** as a minor product (68% yield, **27a**:**29a** = 26:74). These experiments very clearly revealed that (i) in the formation of dienes, the Wittig reagent couples with **25** in a S_N2' fashion, which is followed by an instantaneous abstraction of the acidic methine proton by the conjugate base, the bromide anion, with the *anti*-elimination of PPh_3 to yield the diene **27a** with the exclusive *E*-geometry of the newly formed carbon–carbon double bond, and (ii) in the same reaction on quenching with water at –100 °C, the reductive removal of $POPh_3$ takes place with the formation of ene **29a** as a major product.[26] To confirm that in the formation of enes the hydrogen atom at benzylic position comes

Table 1. Synthesis of variety of enes **29** and dienes **27** from dimethyl bromomethylfumarate (**25**)

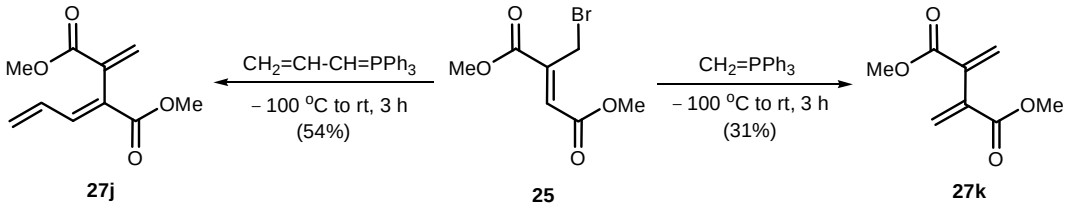
Entry		1	2	3	4	5	6	7	8	9
-Ar										
Products **27** & **29** – 100 °C to rt, 3 h	**27a-i** (yield)[a]	**27a** (60%)	**27b** (64%)	**27c** (65%)	**27d** (64%)	**27e** (66%)	**27f** (62%)	**27g** (60%)	**27h** (00%)	**27i** (00%)
	29a-i (yield)[a]	**29a** (8%)	**29b** (11%)	**29c** (10%)	**29d** (11%)	**29e** (12%)	**29f** (13%)	**29g** (10%)	**29h** (85%)	**29i** (85%)
Products **27** & **29** – 100 °C, 3 h	**27a-i** (yield)[a]	**27a** (18%)	**27b** (20%)	**27c** (15%)	**27d** (17%)	**27e** (18%)	**27f** (20%)	**27g** (18%)	**27h** (00%)	**27i** (00%)
	29a-i (yield)[a]	**29a** (50%)	**29b** (55%)	**29c** (60%)	**29d** (58%)	**29e** (60%)	**29f** (55%)	**29g** (52%)	**29h** (85%)	**29i** (85%)

[a] Obtained mixtures of enes and dienes were separated by silica gel column chromatography and the isolated yields are reported in parentheses.

from water, we quenched the reaction at –100 °C with D_2O and obtained the corresponding deuterium incorporated compound **30** in 48% yield. In the reactions of Wittig reagent with dimethyl bromomethylfumarate (**25**), we tried our best to exclusively obtain diene **27a** by using super dry THF and also by adding TEA as an external base for elimination of PPh_3, but all our attempts met with failure and we always ended up with isolation of ene **29a** as a minor product. We strongly believe that under the complete absence of moisture, the present reaction will provide the diene **27a** as an exclusive product. We also feel that the preparation of dimethyl bromomethylfumarate (**25**) using higher alcohols and the similar less activated substrates may not demand such a lower temperature for the effective S_N2' coupling reactions of the Wittig reagents.

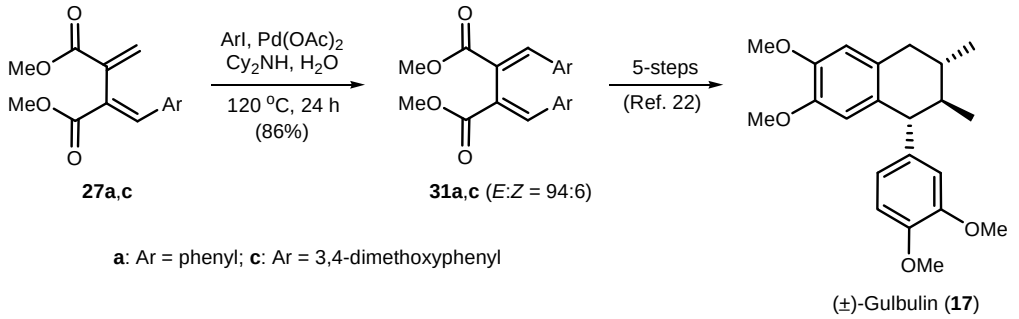
We studied the S_N2' coupling reactions of several other Wittig reagents generated from the phosphonium salts of corresponding benzyl bromides with dimethyl bromomethylfumarate (**25**) and obtained the corresponding enes **29a**-**g** and dienes **27a**-**g**, proving the generality of present approach (Table 1, entries 1-7). Surprisingly, the Wittig reagents generated from phosphonium salts of *ortho*- and *para*-nitrobenzyl bromides, on S_N2' condensations with dimethyl bromomethylfumarate (**25**), exclusively furnished corresponding enes **29h**,**i** in 85% yield under both the reaction conditions (entries 8 & 9). We feel that, this could be a result of higher stability of the unisolable intermediates **26h**,**i** and the non availability of bromide anion as a conjugate base due to the electron deficient nature of the phosphorus atom in those two cases.

Then, we studied the S_N2' coupling reactions of relatively more reactive phosphoranes generated from phosphonium salts of methyl iodide and allyl bromide, with dimethyl bromomethylfumarate (**25**) and exclusively obtained the corresponding diene **27j** and dimethyl ester of fulgenic acid (**27k**)[27] respectively, but in 54 and 31% yields (Scheme 8). Herein, as the ylides are relatively more reactive, the further refinements in reaction conditions for the improvement of yields of **27j** & **27k** are essential.



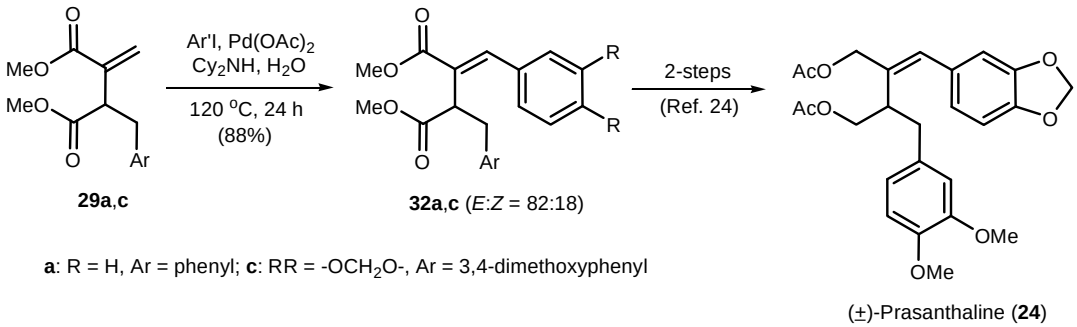
Scheme 8. Synthesis of symmetrical and unsymmetrical dienes

We decided to use both the enes and dienes for the short and efficient synthesis of natural products (±)-gulbulin (from *Himantandra baccata* Bail)[19] and (±)-prasanthaline (from *Jatropha gossypifolia* Linn).[23] The dienes **27a**,**c** on a Heck coupling reactions[28] with an appropriate halides gave the (*E*,*E*)-dienes **31a**,**c** as a major product in 86% yields (*E*:*Z* = 94:6, by ^{1}H NMR). The five-step conversion of diene **31c** to (±)-gulbulin (**17**) is known in the literature (Scheme 9).[22]



Scheme 9. Heck coupling reactions of dienes, synthesis of (±)-gulbulin

Similarly, Heck coupling reactions[28] of enes **29a**,**c** with appropriate halides gave the corresponding



Scheme 10. Heck coupling reactions of enes, synthesis of (±)-prasanthaline

desired diesters **32a**,**c** in 88% yields (*E*:*Z* = 82:18, by ^{1}H NMR). The known selective reduction of two ester groups in ene **32c** followed by an in situ acylation of the formed intermediate 1,4-diol, provided the natural product (±)-prasanthaline (**24**) (Scheme 10).[24]

2A.4: Summary

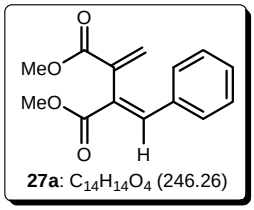
In the present section, we have demonstrated an unprecedented S_N2' coupling reactions of Wittig reagents to selectively obtain the corresponding enes and dienes, which is a pivotal new application of Wittig reagents. Herein, the enes have been obtained by using the Wittig reagents rather than the corresponding Grignard reagents, while dienes have been obtained with the recovery of triphenylphosphine. We feel that the use of Wittig reagents in the place of Grignard reagents in the synthesis of enes will positively widen the scope of S_N2' coupling reactions. The use of alkyl halides and benzyl halides instead of the corresponding aldehydes to obtain these products is an added advantage. We also feel that, our present protocol is general and the Wittig reagents will undergo the S_N2' coupling reactions with variety of other activated substrates to provide the corresponding enes, dienes, related natural (Lignan family) and unnatural products including several practically useful fulgides.[29] The present approach will also be useful for the intramolecular cyclizations in the construction of carbocycles and heterocycles.

2A.5: Experimental section

Commercially available citraconic anhydride, triphenyl phosphine, benzyl bromide, 2-nitrobenzyl bromide, 4-nitrobenzyl bromide, 4-methoxybenzyl bromide, 3,5-dimethoxybenzyl bromide, 3,4-dimethoxybenzyl bromide, 2-chlorobenzyl bromide, 3-chlorobenzyl bromide, 2-fluorobenzyl bromide, allyl bromide, 5-iodo-[1,3]dioxole, 4-iodo-1,2-dimethoxybenzene, methyl bromide, $Pd(OAc)_2$, Cy_2NH, iodobenzene, *n*-BuLi (1.50 M) and *N*-bromosuccinimide were used. The $LiAlH_4$ dried THF was used.

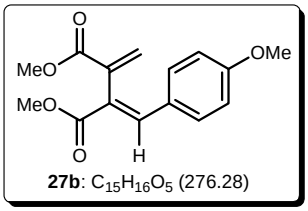
Preparation of triphenylphosphonium salts: To a stirring solution of triphenylphosphine (2.62 g, 10.00 mmol) in benzene (10 mL) at 0 °C was added benzyl bromide (1.67 mL, 14.00 mmol) in a drop wise fashion under argon atmosphere. Stirring was continued for 24 hours time at room temperature. The formed salt was filtered, washed with ether and petroleum ether respectively, dried under vacuum and stored in a desiccator over phosphorus pentoxide (4.30 g, 99%). All other triphenylphosphonium salts were prepared similarly.

(*E*)-Dimethyl 2-benzylidene-3-methylenesuccinate (27a). To a stirring solution of benzyltriphenylphosphonium bromide (866 mg, 2.00 mmol) in THF (25 mL) at –100 °C was added *n*-BuLi (1.34 mL, 2.00 mmol) in a drop wise fashion under argon atmosphere. The reaction mixture was allowed to reach to 0 °C temperature. Then, above reaction mixture was added to a stirring solution of **25** (569 mg, 2.40 mmol) in THF (20 mL) at –100 °C under argon atmosphere in a drop wise fashion. The reaction mixture was allowed to reach to room temperature and the reaction was then quenched with water. The reaction mixture was extracted with ethyl acetate (30 mL x 4) and the combined organic layer was washed with brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the residue using 10% ethyl acetate/petroleum ether as an eluent provided major product **27a** (296 mg, 60%) and minor product **29a** (39 mg, 8%) as thick oils. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.75 (s, 3H), 3.80 (s, 3H), 5.68 (d, *J* = 2 Hz, 1H), 6.49 (d, *J* = 2 Hz, 1H), 7.28−7.35 (m, 3H), 7.35−7.45 (m, 2H), 7.81 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 52.2, 52.3, 128.4, 128.5, 129.3, 130.0, 130.6, 134.3, 136.0, 141.8, 166.4, 167.2; IR ($CHCl_3$) ν_{max} 1717, 1630, 1618, 1497 cm^{-1}. Anal. Calcd for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73. Found: C, 68.13; H, 5.92.



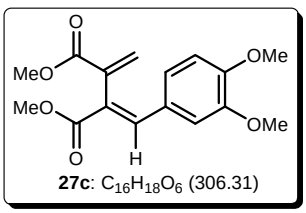
27a: $C_{14}H_{14}O_4$ (246.26)

(*E*)-Dimethyl 2-(4-methoxybenzylidene)-3-methylenesuccinate (27b). The similarly obtained crude product was purified by column chromatography using 25% ethyl acetate/petroleum ether as an eluent to obtain major product **27b** (64%) and minor product **29b** (11%) as thick oils. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.75 (s, 3H), 3.79 (s, 3H), 3.82 (s, 3H), 5.73 (d, *J* = 2 Hz, 1H), 6.53 (d, *J* = 2 Hz, 1H), 6.85 (d, *J* = 8 Hz, 2H), 7.42 (d, *J* = 10 Hz, 2H), 7.76 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 52.2, 52.3, 55.3, 114.0, 125.9, 126.9, 130.5, 132.0, 136.4, 141.4, 160.6, 166.6, 167.5; IR ($CHCl_3$) ν_{max} 1711, 1605, 1512 cm^{-1}. Anal. Calcd for $C_{15}H_{16}O_5$: C, 65.21; H, 5.84. Found: C, 65.17; H, 5.65.



27b: $C_{15}H_{16}O_5$ (276.28)

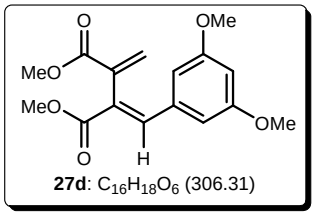
(*E*)-Dimethyl 2-(3,4-dimethoxybenzylidene)-3-methylenesuccinate (27c). The similarly obtained crude product was purified by column chromatography using 25% ethyl acetate/petroleum ether as an eluent to obtain major product **27c** (65%) and minor product **29c** (10%) as thick oils. ^{1}H NMR ($CDCl_3$, 200 MHz)) δ 3.73 (s, 3H), 3.79 (s, 3H), 3.81 (s, 3H), 3.88 (s, 3H), 5.76 (d, *J* = 2 Hz, 1H), 6.56 (d, *J* = 2 Hz, 1H), 6.82 (d, *J* = 8 Hz, 1H), 6.98−7.10 (m, 2H), 7.74 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 52.3 (2 carbons), 55.6, 55.8, 110.7, 112.5, 124.5, 125.7, 127.0, 130.5, 136.5, 141.6, 148.5, 150.2, 166.5, 167.4;



27c: $C_{16}H_{18}O_6$ (306.31)

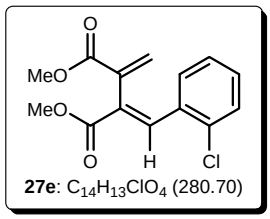
IR ($CHCl_3$) ν_{max} 1717, 1636, 1601, 1514 cm^{-1}. Anal. Calcd for $C_{16}H_{18}O_6$: C, 62.74; H, 5.92. Found: C, 62.83; H, 6.04.

(*E*)-Dimethyl 2-(3,5-dimethoxybenzylidene)-3-methylenesuccinate (27d). The similarly obtained crude product was purified by column chromatography using 25% ethyl acetate/petroleum ether as an eluent to obtain major product **27d** (64%) and minor product **29d** (11%) as thick oils. ^1H NMR ($CDCl_3$, 200 MHz) δ 3.74 (s, 3H), 3.75 (s, 6H), 3.80 (s, 3H), 5.72 (d, J = 2 Hz, 1H), 6.42 (t, J = 2 Hz, 1H), 6.51 (d, J = 2 Hz, 1H), 6.58 (d, J = 2 Hz, 2H), 7.73 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 52.2, 52.3, 55.2, 101.8, 107.9, 128.8, 130.5, 136.1, 136.2, 141.8, 160.6, 166.3, 167.0; IR ($CHCl_3$) ν_{max} 1717, 1593, 1437 cm^{-1}. Anal. Calcd for $C_{16}H_{18}O_6$: C, 62.74; H, 5.92. Found: C, 62.70; H, 5.89.



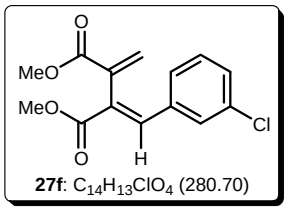
27d: $C_{16}H_{18}O_6$ (306.31)

(*E*)-Dimethyl 2-(2-chlorobenzylidene)-3-methylenesuccinate (27e). The similarly obtained crude product was purified by column chromatography using 10% ethyl acetate/petroleum ether as an eluent to obtain major product **27e** (66%) and minor product **29e** (12%) as thick oils. ^1H NMR ($CDCl_3$, 200 MHz) δ 3.76 (s, 3H), 3.83 (s, 3H), 5.54 (d, J = 2 Hz, 1H), 6.33 (d, J = 2 Hz, 1H), 7.10−7.30 (m, 3H), 7.35−7.43 (m, 1H), 7.94 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 52.2, 52.4, 126.6, 129.5, 130.0, 130.3, 130.7, 131.4, 133.7, 134.4, 135.6, 139.0, 166.3, 166.5; IR ($CHCl_3$) ν_{max} 1717, 1643, 1624, 1437 cm^{-1}. Anal. Calcd for $C_{14}H_{13}ClO_4$: C, 59.90; H, 4.67; Cl, 12.63. Found: C, 60.01; H, 4.88; Cl, 12.57.



27e: $C_{14}H_{13}ClO_4$ (280.70)

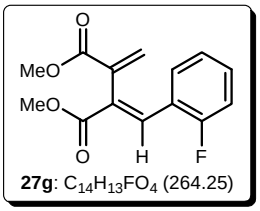
(*E*)-Dimethyl 2-(3-chlorobenzylidene)-3-methylenesuccinate (27f). The similarly obtained crude product was purified by column chromatography using 10% ethyl acetate/petroleum ether as an eluent to obtain major product **27f** (62%) and minor product **29f** (13%) as thick oils. ^1H NMR ($CDCl_3$, 200 MHz) δ 3.77 (s, 3H), 3.81 (s, 3H), 5.67 (d, J = 2 Hz, 1H), 6.49 (d, J = 2 Hz, 1H), 7.23−7.30 (m, 3H), 7.35−7.40 (m, 1H), 7.73 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 52.3, 52.4, 127.8, 129.2, 129.7 (2 carbons), 129.9, 130.9, 134.3, 135.6, 136.1, 140.1, 166.2, 166.8; IR ($CHCl_3$) ν_{max} 1728, 1630, 1599, 1574, 1437 cm^{-1}. Anal. Calcd for $C_{14}H_{13}ClO_4$: C, 59.90; H, 4.67; Cl, 12.63. Found: C, 59.67; H, 4.62; Cl, 12.78.



27f: $C_{14}H_{13}ClO_4$ (280.70)

(*E*)-Dimethyl 2-(2-fluorobenzylidene)-3-methylenesuccinate (27g). The similarly obtained crude product was purified by column chromatography using 10% ethyl acetate/petroleum ether as an eluent

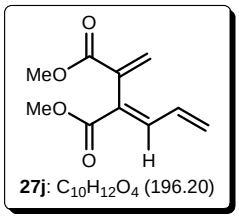
to obtain major product **27g** (60%) and minor product **29g** (10%) as thick oils. ^{1}H NMR ($CDCl_3$, 200 MHz)



27g: $C_{14}H_{13}FO_4$ (264.25)

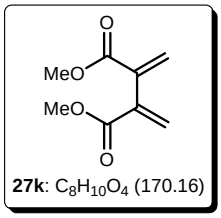
δ 3.77 (s, 3H), 3.81 (s, 3H), 5.60 (d, *J* = 2 Hz, 1H), 6.40 (d, *J* = 2 Hz, 1H), 6.95−7.10 (m, 2H), 7.20−7.40 (m, 2H), 7.89 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 52.3, 52.4, 115.8 (d, *J* = 22 Hz), 122.5 (d, *J* = 13 Hz), 123.9 (d, *J* = 3 Hz), 130.29 (d, *J* = 3 Hz), 130.34, 130.97 (d, *J* = 9 Hz), 131.01 (d, *J* = 2 Hz), 134.3 (d, *J* = 4 Hz), 135.9, 160.5 (d, *J* = 250 Hz), 166.3, 166.7; IR ($CHCl_3$) ν_{max} 1719, 1641, 1620, 1437 cm^{-1}. Anal. Calcd for $C_{14}H_{13}FO_4$: C, 63.63; H, 4.96. Found: C, 63.44; H, 4.89. (The C-F couplings observed in ^{13}C NMR spectrum have been reported in parenthesis).

(*E*)-Dimethyl 2-allylidene-3-methylenesuccinate (27j). The similarly obtained crude product was purified by column chromatography using 10% ethyl acetate/petroleum ether as an eluent to obtain **27j** (54%) as a thick oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.74 (s, 6H), 5.50 (dd, *J* = 10 and 2 Hz, 1H), 5.65 (d, *J* = 2 Hz, 1H), 5.68 (d, *J* = 16 Hz, 1H), 6.42−6.64 (m, 1H), 6.54 (d, *J* = 2 Hz, 1H), 7.34 (d, *J* = 12 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 52.0, 52.1, 126.6, 129.3, 130.3, 132.2, 135.0, 141.5, 166.2, 166.8; IR ($CHCl_3$) ν_{max} 1717, 1624, 1437 cm^{-1}. Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.22; H, 6.16. Found: C, 61.09; H, 6.24.



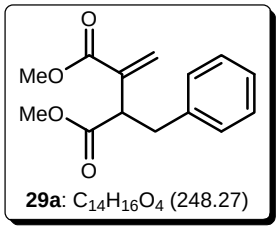
27j: $C_{10}H_{12}O_4$ (196.20)

Dimethyl 2,3-dimethylenesuccinate (27k). The similarly obtained crude product was purified by column chromatography using 10% ethyl acetate/petroleum ether as an eluent to obtain **27k** (31%) as a thick oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.77 (s, 6H), 5.82 (d, *J* = 2 Hz, 2H), 6.30 (d, *J* = 2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 52.1, 127.8, 138.4, 166.1; IR ($CHCl_3$) ν_{max} 1719, 1618, 1437 cm^{-1}. Anal. Calcd for $C_8H_{10}O_4$: C, 56.47; H, 5.92. Found: C, 56.34; H, 6.06.



27k: $C_8H_{10}O_4$ (170.16)

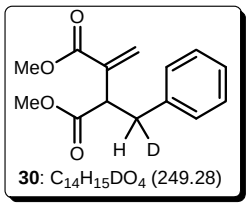
Dimethyl 2-benzyl-3-methylenesuccinate (29a).[2c] To a stirring solution of benzyltriphenylphosphonium bromide (866 mg, 2.00 mmol) in THF (25 mL) at –100 °C was added *n*-BuLi (1.34 mL, 2.00 mmol) in a drop wise fashion under argon atmosphere. The reaction mixture was allowed to reach to 0 °C temperature. Then, above reaction mixture was added to a stirring solution of **25** (521 mg, 2.00 mmol) in THF (20 mL) at –100 °C under argon atmosphere in a drop wise fashion. Stirring was continued for a further 3 hours time at the same temperature. The reaction was then quenched with water. The reaction mixture was extracted with ethyl acetate (30 mL x 4) and the combined organic layer was washed with brine and dried over Na_2SO_4. Concentration of the organic



29a: $C_{14}H_{16}O_4$ (248.27)

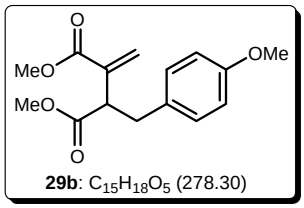
layer in vacuo followed by silica gel column chromatographic purification of the residue using 10% ethyl acetate/petroleum ether as an eluent provided major product **29a** (248 mg, 50%) and minor product **27a** (89 mg, 18%) as thick oils. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.96 (dd, *J* = 14 and 8 Hz, 1H), 3.25 (dd, *J* = 14 and 8 Hz, 1H), 3.63 (s, 3H), 3.75 (s, 3H), 3.83 (t, *J* = 8 Hz, 1H), 5.67 (s, 1H), 6.31 (s, 1H), 7.10−7.35 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 37.4, 48.8, 52.0, 52.1, 126.4, 127.5, 128.3, 128.9, 137.6, 138.7, 166.4, 173.0; IR ($CHCl_3$) ν_{max} 1740, 1721, 1632 cm^{-1}. Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.58; H, 6.41.

3-[Deutero(phenyl)methyl]-4-methylenehexane-2,5-dione (30). It was prepared by using the same procedure as described above and the reaction was quenched with D_2O. The crude product was purified by column chromatography using 10% of ethyl acetate/petroleum ether as an eluent to obtain major product **30** (48%) and minor product **27a** (21%) as thick oils. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.95 (d, *J* = 8 Hz, 0.8H), 3.18−3.25 (m, 0.2H), 3.63 (s, 3H), 3.75 (s, 3H), 3.79−3.90 (m, 1H), 5.67 (s, 1H), 6.31 (s, 1H), 7.10−7.35 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 37.1 (t, *J* = 10 Hz), 48.7, 52.0, 52.1, 126.4, 127.5, 128.3, 128.9, 137.6, 138.7, 166.4, 173.0; IR ($CHCl_3$) ν_{max} 1734, 1719, 1636, 1634 cm^{-1}. (The C–D coupling observed in ^{13}C NMR spectrum has been reported in parenthesis).



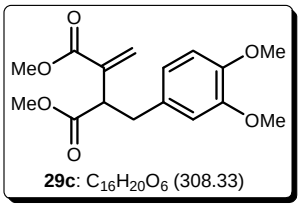
30: $C_{14}H_{15}DO_4$ (249.28)

Dimethyl 2-(4-methoxybenzyl)-3-methylenesuccinate (29b). The similarly obtained crude product was purified by column chromatography using 25% ethyl acetate/petroleum ether as an eluent to obtain major product **29b** (55%) and minor product **27b** (20%) as thick oils. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.91 (dd, *J* = 14 and 8 Hz, 1H), 3.18 (dd, *J* = 14 and 8 Hz, 1H), 3.63 (s, 3H), 3.76 (s, 3H), 3.77 (s, 3H), 3.70−3.83 (m, 1H), 5.68 (s, 1H), 6.31 (s, 1H), 6.81 (d, *J* = 8 Hz, 2H), 7.08 (d, *J* = 8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 36.6, 49.0, 52.0, 52.1, 55.1, 113.7, 127.4, 129.9, 130.8, 137.7, 158.2, 166.4, 173.1; IR ($CHCl_3$) ν_{max} 1732, 1715, 1630, 1612, 1514 cm^{-1}. Anal. Calcd for $C_{15}H_{18}O_5$: C, 64.74; H, 6.52. Found: C, 64.85; H, 6.68.



29b: $C_{15}H_{18}O_5$ (278.30)

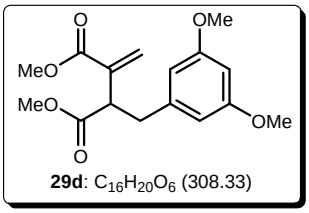
Dimethyl 2-(3,4-dimethoxybenzyl)-3-methylenesuccinate (29c). The similarly obtained crude product was purified by column chromatography using 25% ethyl acetate/petroleum ether as an eluent to obtain major product **29c** (60%) and minor product **27c** (15%) as thick oils. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.89 (dd, *J* = 14 and 6 Hz, 1H), 3.16 (dd, *J* = 14 and 8 Hz, 1H), 3.63 (s, 3H), 3.77 (s, 3H), 3.85 (s, 6H),



29c: $C_{16}H_{20}O_6$ (308.33)

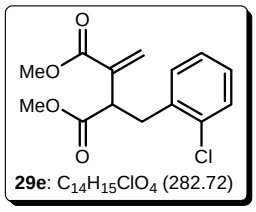
3.70−3.90 (m, 1H), 5.70 (s, 1H), 6.31 (s, 1H), 6.60−6.85 (m, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 37.3, 48.9, 52.0, 52.1, 55.8 (2 carbons), 111.2, 112.2, 121.0, 127.3, 131.3, 137.8, 147.7, 148.8, 166.3, 173.0; IR ($CHCl_3$) ν_{max} 1734, 1717, 1636 cm^{-1}. Anal. Calcd for $C_{16}H_{20}O_6$: C, 62.33; H, 6.54. Found: C, 62.47; H, 6.70.

Dimethyl 2-(3,5-dimethoxybenzyl)-3-methylenesuccinate (29d). The similarly obtained crude product was purified by column chromatography using 25% ethyl acetate/petroleum ether as an eluent to obtain major product **29d** (58%) and minor product **27d** (17%) as thick oils. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.90 (dd, *J* = 14 and 8 Hz, 1H), 3.20 (dd, *J* = 14 and 8 Hz, 1H), 3.65 (s, 3H), 3.76 (s, 9H), 3.80 (dd, *J* = 14 and 8 Hz, 1H), 5.69 (s, 1H), 6.31 (bs, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 37.6, 48.5, 52.1 (2 carbons), 55.2, 98.5, 106.9, 127.5, 137.6, 141.1, 160.7, 166.4, 172.9; IR ($CHCl_3$) ν_{max} 1732, 1717, 1597 cm^{-1}. Anal. Calcd for $C_{16}H_{20}O_6$: C, 62.33; H, 6.54. Found: C, 62.42; H, 6.61.



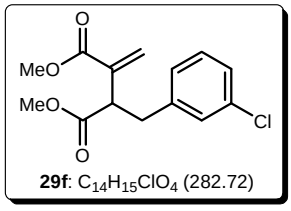
29d: $C_{16}H_{20}O_6$ (308.33)

Dimethyl 2-(2-chlorobenzyl)-3-methylenesuccinate (29e). The similarly obtained crude product was purified by column chromatography using 10% ethyl acetate/petroleum ether as an eluent to obtain major product **29e** (60%) and minor product **27e** (18%) as thick oils. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.11 (dd, *J* = 14 and 8 Hz, 1H), 3.39 (dd, *J* = 14 and 8 Hz, 1H), 3.64 (s, 3H), 3.74 (s, 3H), 3.90 (t, *J* = 8 Hz, 1H), 5.61 (s, 1H), 6.26 (s, 1H), 7.05−7.20 (m, 3H), 7.25−7.38 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 35.0, 47.0, 52.0 (2 carbons), 126.6, 127.9, 128.0, 129.5, 131.5, 134.2, 136.4, 137.6, 166.1, 172.6; IR ($CHCl_3$) ν_{max} 1734, 1717, 1636, 1630 cm^{-1}. Anal. Calcd for $C_{14}H_{15}ClO_4$: C, 59.48; H, 5.35; Cl, 12.54. Found: C, 59.38; H, 5.41; Cl, 12.47.



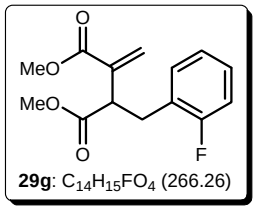
29e: $C_{14}H_{15}ClO_4$ (282.72)

Dimethyl 2-(3-chlorobenzyl)-3-methylenesuccinate (29f). The similarly obtained crude product was purified by column chromatography using 10% ethyl acetate/petroleum ether as an eluent to obtain major product **29f** (55%) and minor product **27f** (20%) as thick oils. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.93 (dd, *J* = 14 and 6 Hz, 1H), 3.22 (dd, *J* = 14 and 8 Hz, 1H), 3.64 (s, 3H), 3.77 (s, 3H), 3.70−3.85 (m, 1H), 5.67 (s, 1H), 6.32 (s, 1H), 7.00−7.10 (m, 1H), 7.10−7.30 (m, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 37.0, 48.6, 52.1, 52.2, 126.7, 127.2, 127.7, 129.0, 129.6, 134.0, 137.4, 140.8, 166.2, 172.6; IR ($CHCl_3$) ν_{max} 1736, 1719, 1636, 1618 cm^{-1}. Anal. Calcd for $C_{14}H_{15}ClO_4$: C, 59.48; H, 5.35; Cl, 12.54. Found: C, 59.55; H, 5.23; Cl, 12.67.



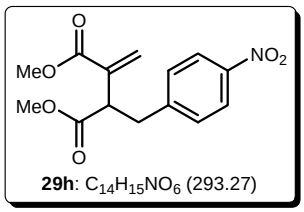
29f: $C_{14}H_{15}ClO_4$ (282.72)

Dimethyl 2-(2-fluorobenzyl)-3-methylenesuccinate (29g). The similarly obtained crude product was purified by column chromatography using 10% ethyl acetate/petroleum ether as an eluent to obtain major product **29g** (52%) and minor product **27g** (18%) as thick oils. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.06 (dd, *J* = 14 and 8 Hz, 1H), 3.29 (dd, *J* = 14 and 8 Hz, 1H), 3.65 (s, 3H), 3.75 (s, 3H), 3.60−3.85 (m, 1H), 5.62 (s, 1H), 6.28 (s, 1H), 6.90−7.25 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 30.7 (d, *J* = 2 Hz), 47.6 (d, *J* = 2 Hz), 52.07, 52.11, 115.2 (d, *J* = 22 Hz), 123.9 (d, *J* = 4 Hz), 125.6 (d, *J* = 16 Hz), 127.9, 128.3 (d, *J* = 9 Hz), 131.3 (d, *J* = 5 Hz), 137.4, 161.2 (d, *J* = 244 Hz), 166.2, 172.7; IR ($CHCl_3$) ν_{max} 1730, 1720, 1634 cm^{-1}. Anal. Calcd for $C_{14}H_{15}FO_4$: C, 63.15; H, 5.68. Found: C, 63.04; H, 5.79. (The C-F couplings observed in ^{13}C NMR spectrum have been reported in parenthesis).



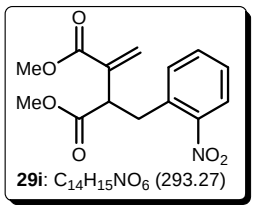
29g: $C_{14}H_{15}FO_4$ (266.26)

Dimethyl 2-methylene-3-(4-nitrobenzyl) succinate (29h). The similarly obtained crude product was purified by column chromatography using 10% ethyl acetate/petroleum ether as an eluent to obtain **29h** (85%) as a thick oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.07 (dd, *J* = 14 and 8 Hz, 1H), 3.34 (dd, *J* = 14 and 8 Hz, 1H), 3.64 (s, 3H), 3.77 (s, 3H), 3.70−3.90 (m, 1H), 5.66 (s, 1H), 6.32 (s, 1H), 7.34 (d, *J* = 8 Hz, 2H), 8.13 (d, *J* = 8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 37.2, 48.4, 52.2 (2 carbons), 123.5, 127.8, 129.8, 137.2, 146.6, 146.7, 166.1, 172.2; IR ($CHCl_3$) ν_{max} 1732, 1713, 1630, 1607 cm^{-1}. Anal. Calcd for $C_{14}H_{15}NO_6$: C, 57.33; H, 5.16; N, 4.78. Found: C, 57.38; H, 5.19; N, 4.69.



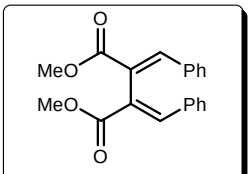
29h: $C_{14}H_{15}NO_6$ (293.27)

Dimethyl 2-methylene-3-(2-nitrobenzyl) succinate (29i). The similarly obtained crude product was purified by column chromatography using 10% ethyl acetate/petroleum ether as an eluent to obtain **29i** (85%) as a thick oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.27 (dd, *J* = 14 and 8 Hz, 1H), 3.63 (dd, *J* = 14 and 8 Hz, 1H), 3.64 (s, 3H), 3.74 (s, 3H), 3.89 (dd, *J* = 14 and 8 Hz, 1H), 5.62 (s, 1H), 6.29 (s, 1H), 7.29 (d, *J* = 8 Hz, 1H), 7.37 (t, *J* = 8 Hz, 1H), 7.50 (t, *J* = 8 Hz, 1H), 7.94 (d, *J* = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 34.4, 47.9, 52.2 (2 carbons), 124.9, 127.8, 128.3, 132.8, 133.0, 133.8, 137.5, 149.5, 166.1, 172.4; IR ($CHCl_3$) ν_{max} 1740, 1720, 1630, 1611 cm^{-1}. Anal. Calcd for $C_{14}H_{15}NO_6$: C, 57.33; H, 5.16; N, 4.78. Found: C, 57.24; H, 5.08; N, 4.85.



29i: $C_{14}H_{15}NO_6$ (293.27)

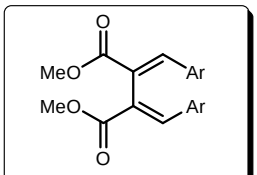
(2*E*,3*E*)-Dimethyl 2,3–dibenzylidenesuccinate (31a).[30] A mixture of **27a** (246 mg, 1.00 mmol), phenyl iodide (0.074 mL, 0.66 mmol), dicyclohexyl amine (0.20 mL, 1.00 mmol) and the catalyst $Pd(OAc)_2$ (6.7 mg, 3 mol %) in water (3 mL) was heated at 120 ^{o}C for 24 h. Then the reaction mixture was cooled and



31a: $C_{20}H_{18}O_4$ (322.35)

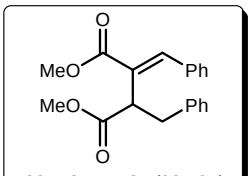
diluted with EtOAc (40 mL). The organic layer was washed with 2 N HCl (30 mL x 2), water (30 mL x 2) and dried over Na_2SO_4. Concentration of organic layer in vacuo followed by column chromatography purification using 10% ethyl acetate/petroleum ether to afford pure product **31a** (182 mg, *E*/*Z*:94/6, 86%) as a thick oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.70 (s, 6H), 7.15−7.30 (m, 6H), 7.30−7.45 (m, 4H), 7.88 (s, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 52.4, 126.6, 128.5, 129.4, 129.5, 134.5, 142.9, 167.3; IR ($CHCl_3$) ν_{max} 1709, 1638, 1605, 1435 cm^{-1}. Anal. Calcd for $C_{20}H_{18}O_4$: C, 74.52; H, 5.63; Found: C, 74.62; H, 5.55.

(2*E*,3*E*)-Dimethyl 2,3-*bis*(3,4-dimethoxydibenzylidene)succinate (31c). The similarly obtained crude product was purified by column chromatography using 30% ethyl acetate/petroleum ether as an eluent to obtain **31c** (*E*/*Z*:94/6, 86%) as a thick oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.71 (s, 6H), 3.75 (s, 6H), 3.86 (s, 6H), 6.80 (d, *J* = 8 Hz, 2H), 7.08−7.20 (m, 4H), 7.90 (s, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 52.1, 55.4, 55.6, 110.6, 111.6, 124.2, 124.4, 127.3, 142.0, 148.5, 150.3, 167.5; IR ($CHCl_3$) ν_{max} 1709, 1628 cm^{-1}. Anal. Calcd for $C_{24}H_{26}O_8$: C, 65.15; H, 5.92; Found: C, 65.23; H, 6.00.



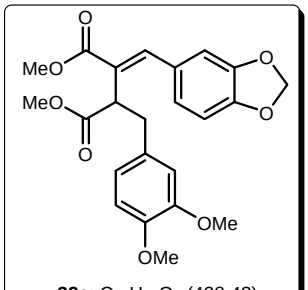
31c: $C_{24}H_{26}O_8$ (442.46)
(Ar = 3,4-dimethoxyphenyl)

(*E*)-Dimethyl 2-benzyl-3-benzylidenesuccinate (32a).[30] The similarly obtained crude product was purified by column chromatography using 10% ethyl acetate/petroleum ether as an eluent to obtain **32a** (*E*/*Z*:82/18, 88%) as a thick oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.98 (dd, *J* = 14 and 10 Hz, 1H), 3.42 (dd, *J* = 14 and 4 Hz, 1H), 3.73 (s, 3H), 3.84 (s, 3H), 4.00 (dd, *J* = 10 and 4 Hz, 1H), 6.81−6.92 (m, 3H), 7.06−7.16 (m, 3H), 7.18−7.31 (m, 4H), 7.76 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 35.9, 45.3, 52.0, 52.2, 126.1, 128.08, 128.12, 128.16, 128.20, 129.1, 130.4, 135.0, 138.9, 142.9, 167.0, 173.1; IR ($CHCl_3$) ν_{max} 1738, 1715, 1643, 1603 cm^{-1}. Anal. Calcd for $C_{20}H_{20}O_4$: C, 74.06; H, 6.22. Found: C, 73.89; H, 6.17.



32a: $C_{20}H_{20}O_4$ (324.37)

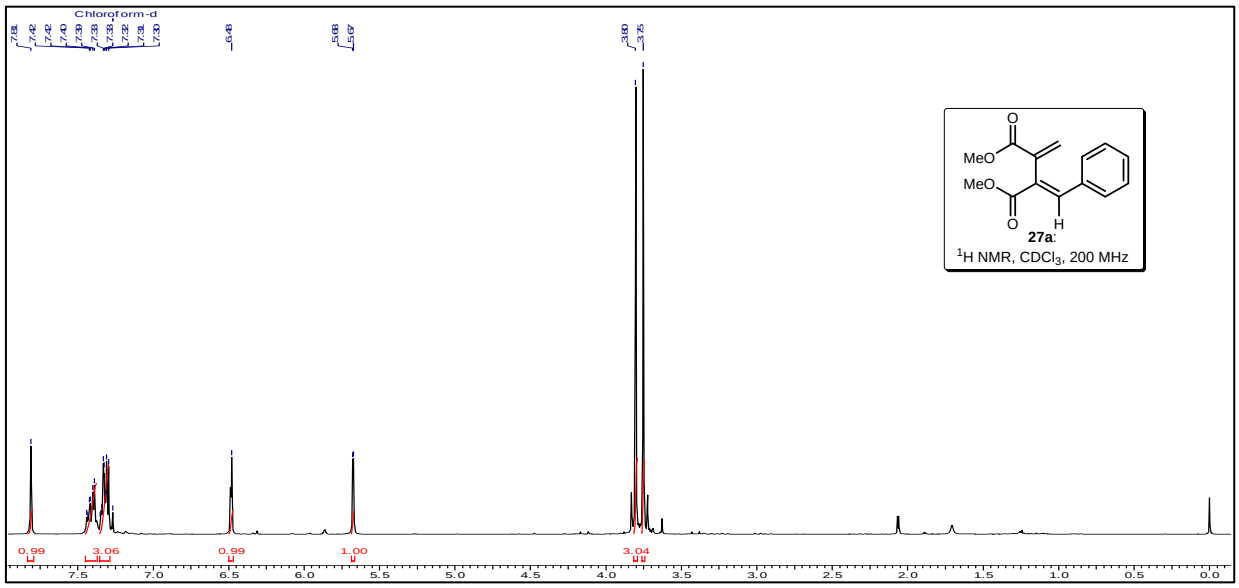
(*E*)-Dimethyl 2-(benzo [*d*][1,3] dioxal-5-ylmethyl)-3-(3,4-dimethoxybenzylidene) succinate (32c). The similarly obtained crude product was purified by column chromatography using 25% ethyl acetate/petroleum ether as an eluent to obtain **32c** (*E*/*Z*:82/18, 88%) as a thick oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.91 (dd, *J* = 14 and 10 Hz, 1H), 3.37 (dd, *J* = 14 and 4 Hz, 1H), 3.66 (s, 3H), 3.73 (s, 3H), 3.81 (s, 6H), 4.05 (dd, *J* = 10 and 4 Hz, 1H), 5.94 (s, 2H), 6.38 (dd, *J* = 6 and 2 Hz, 1H), 6.46 (dd, *J* = 8 and 2 Hz, 1H), 6.48 (d, *J* = 2 Hz, 1H), 6.66 (d, *J* = 6 Hz, 1H), 6.67 (s, 1H), 6.73 (d, *J* = 8 Hz, 1H), 7.63 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ

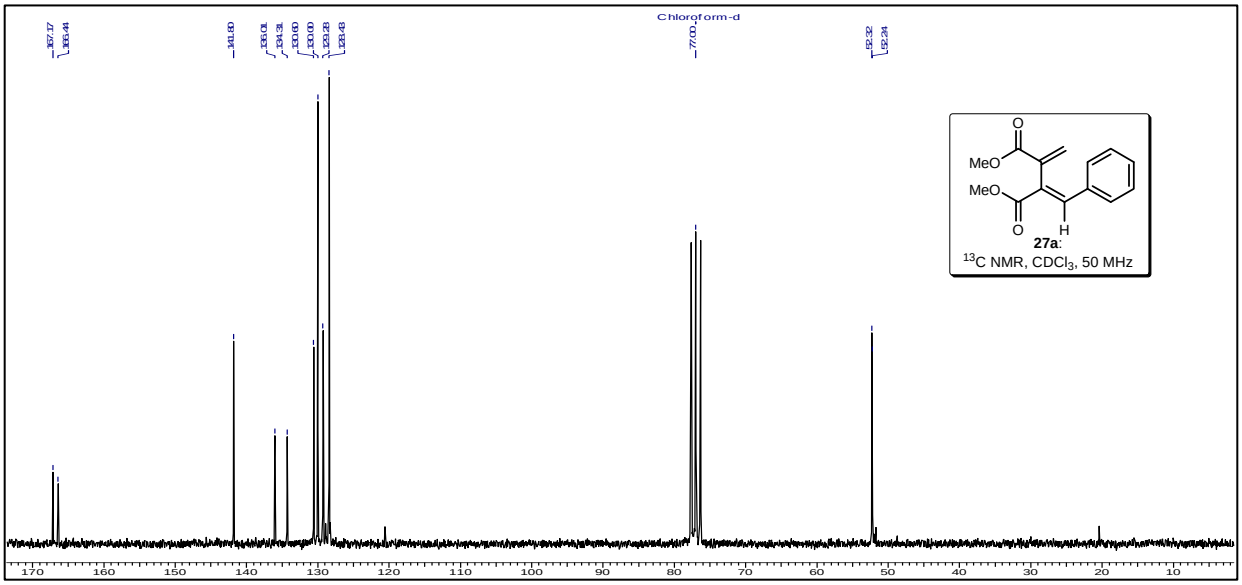


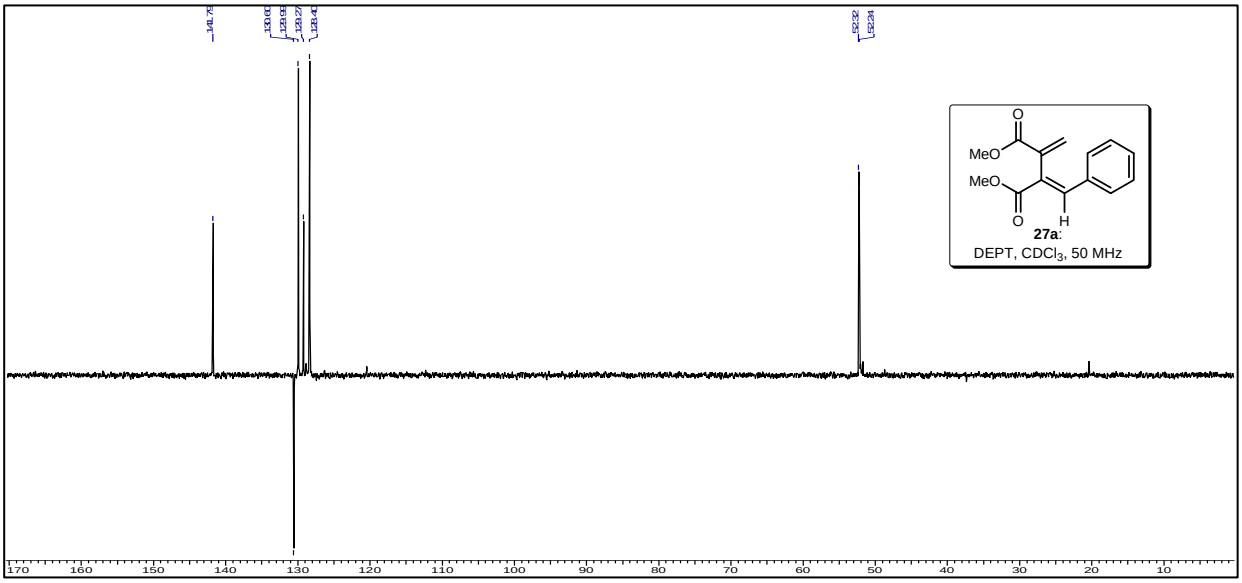
32c: $C_{23}H_{24}O_8$ (428.43)

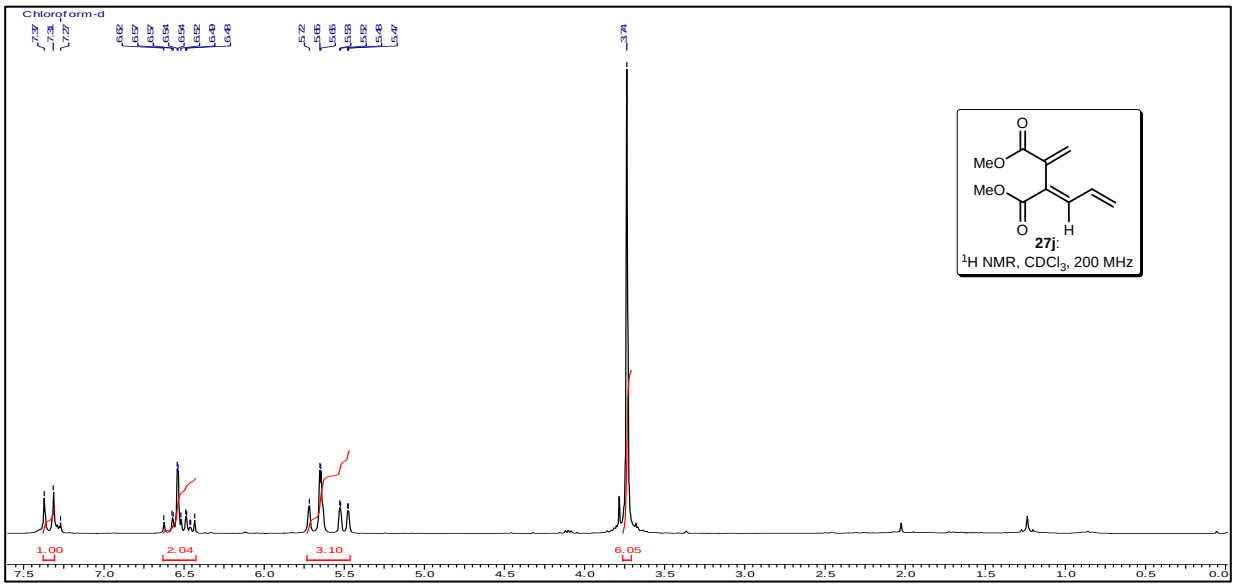
35.6, 45.4, 51.9, 52.2, 55.3, 55.8, 101.2, 108.1, 108.4, 110.8, 111.8, 121.1, 122.5, 128.8, 129.6, 131.4, 142.3, 147.3, 147.5, 147.6, 148.5, 167.0, 173.0; IR ($CHCl_3$) ν_{max} 1738, 1715, 1630, 1605 cm^{-1}. Anal. Calcd for $C_{23}H_{24}O_8$: C, 64.48; H, 5.65. Found: C, 64.53; H, 5.48.

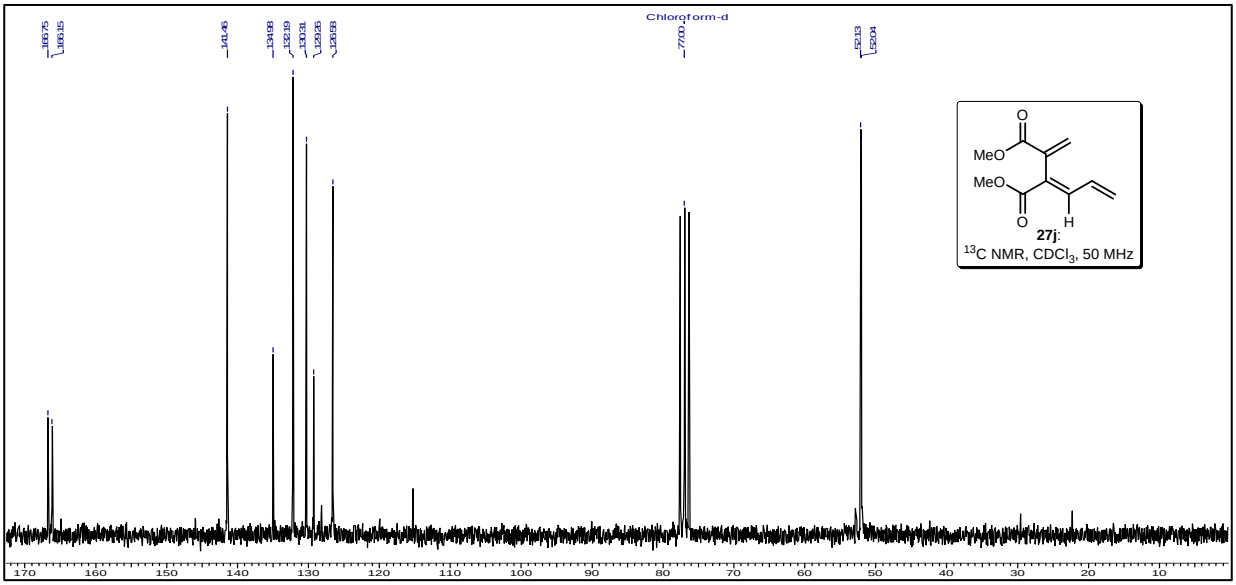
2A.6: Selected spectra

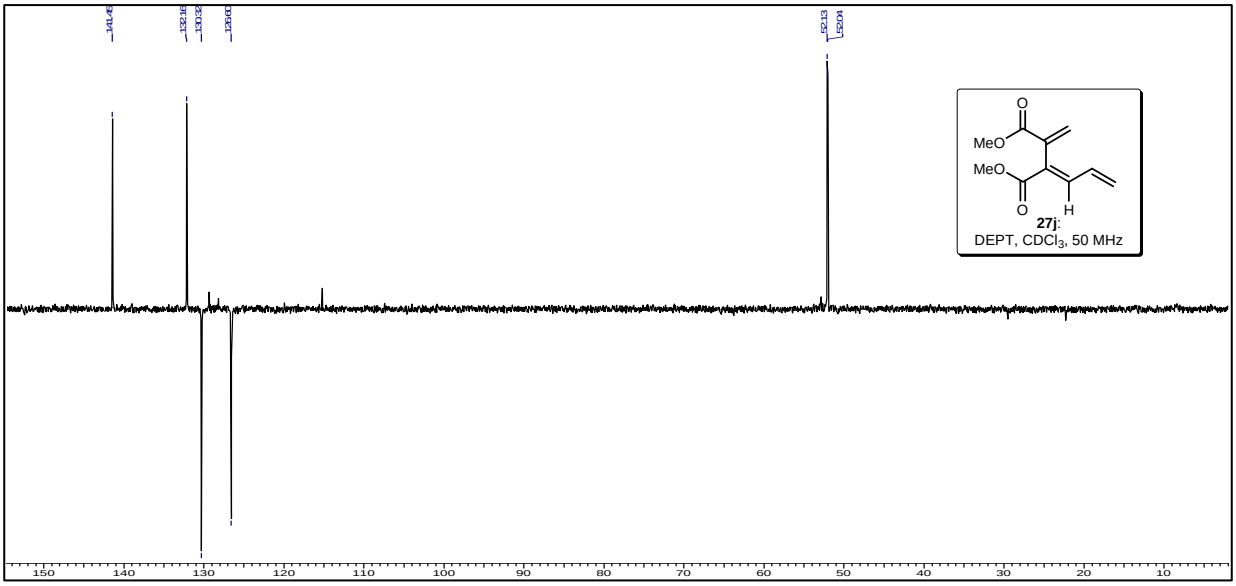

Chloroform-d
MeO
MeO
27a:
1H NMR, CDCl3, 200 MHz

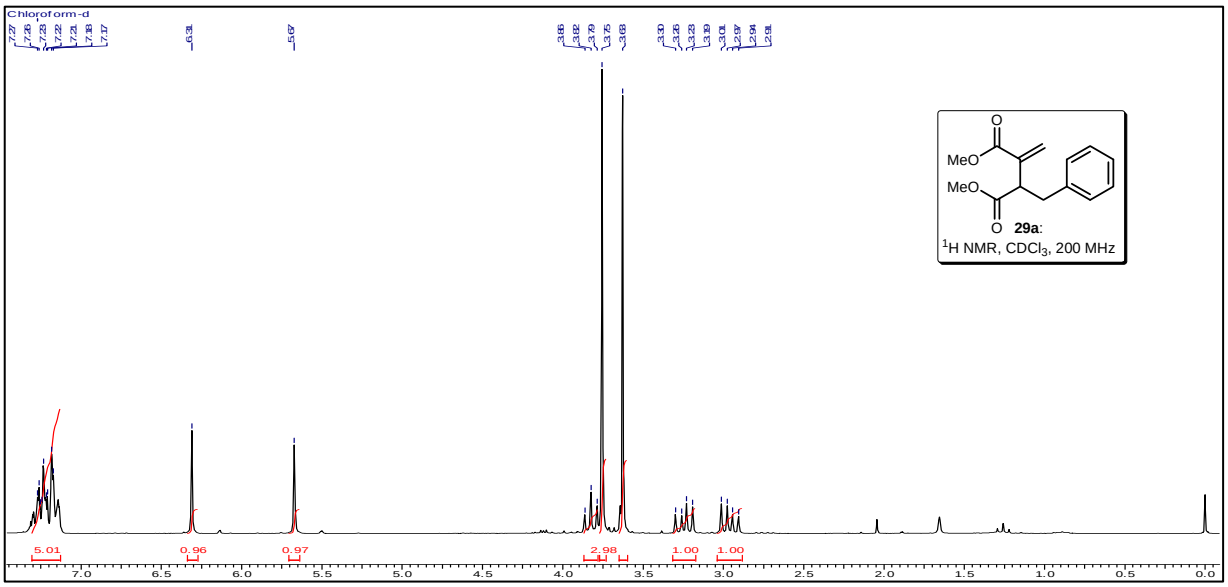

Chloroform-d
MeO
MeO
27a:
13C NMR, CDCl3, 50 MHz

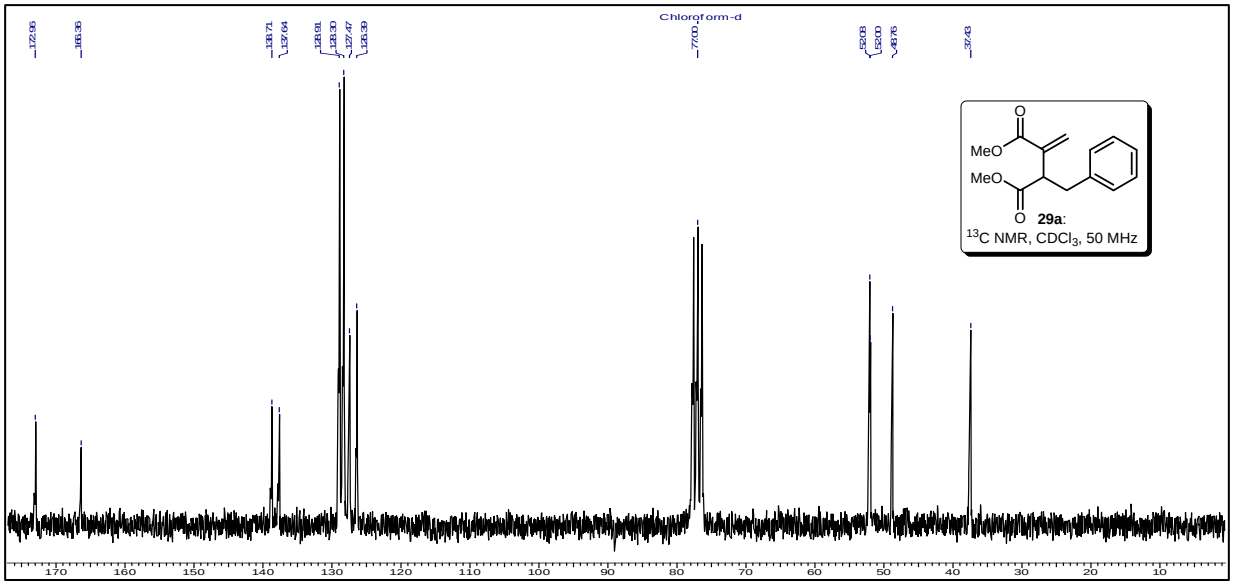

MeO
MeO
27a:
DEPT, CDCl3, 50 MHz

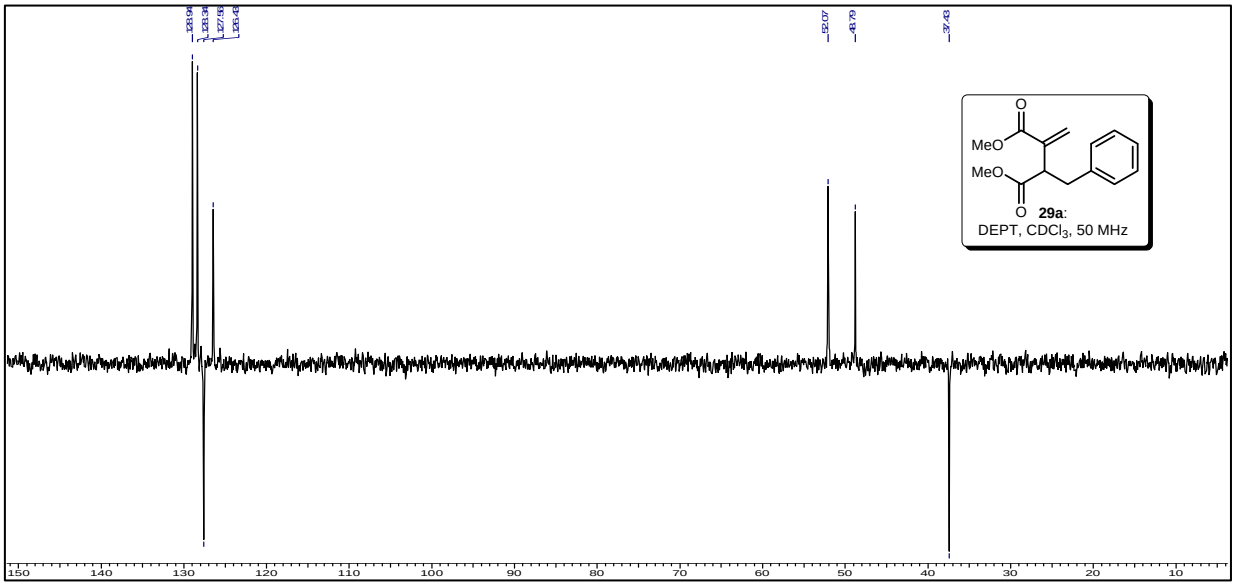

Chloroform-d
7.37
7.31
7.27
6.62
6.57
6.57
6.54
6.54
6.53
6.49
6.48
5.72
5.66
5.65
5.53
5.52
5.48
5.47
3.74
1.00
2.04
3.10
6.05
MeO
MeO
O
O
H
27j:
1H NMR, CDCl3, 200 MHz

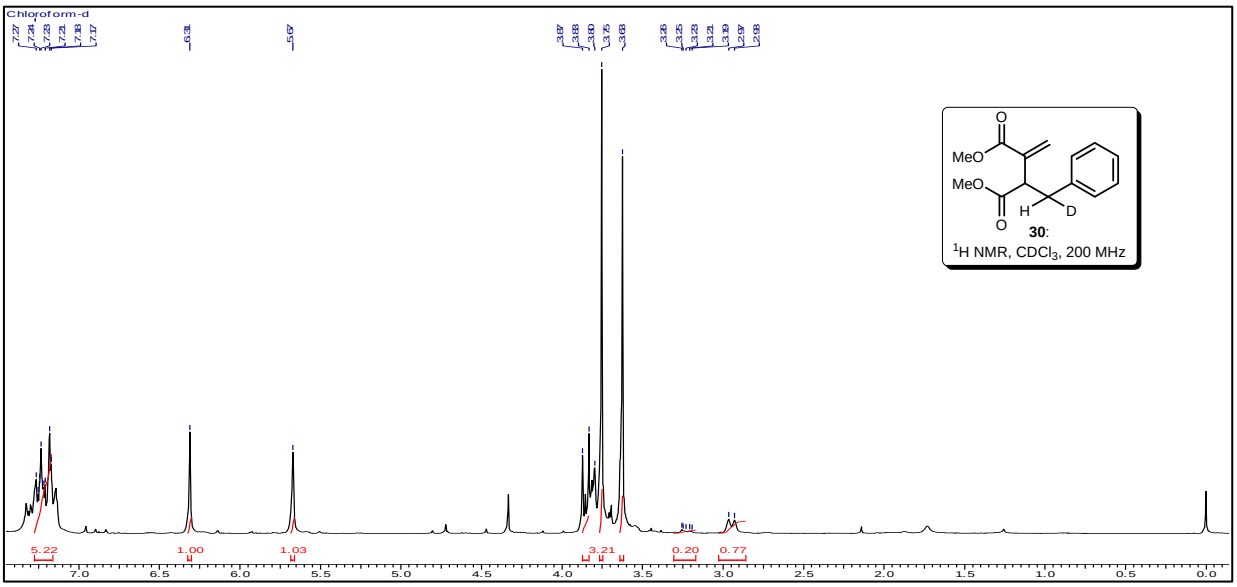

Chloroform-d
166.75
166.35
141.46
134.98
132.19
130.31
129.26
128.58
77.00
52.13
52.04
MeO
MeO
O
O
H
27j:
13C NMR, CDCl3, 50 MHz

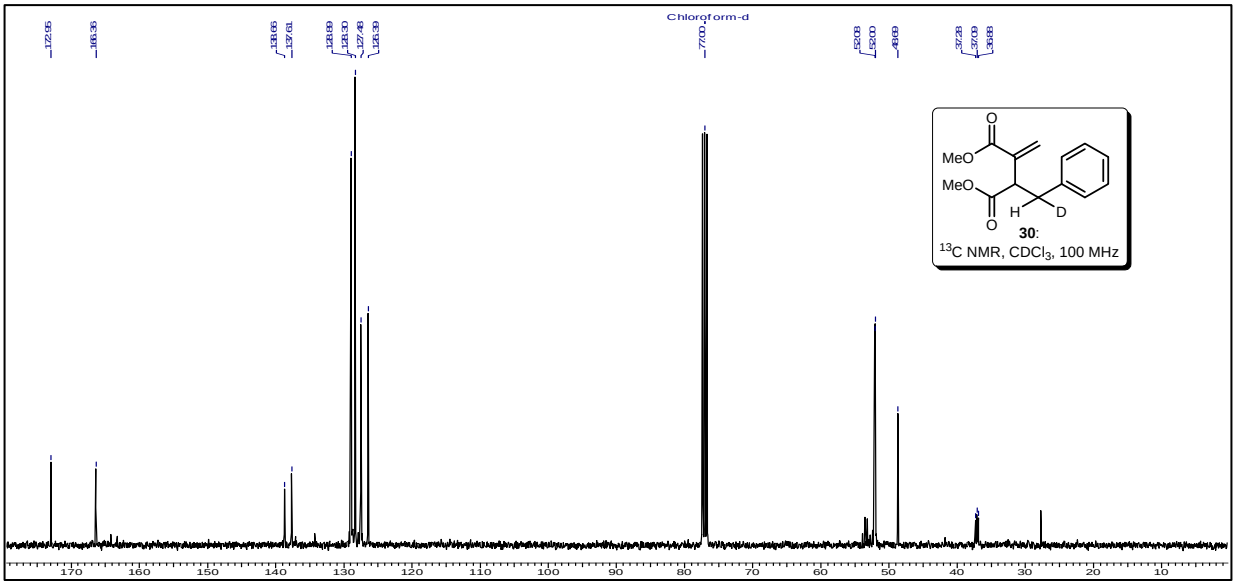

141.46
132.16
130.32
126.60
52.13
52.04
MeO
MeO
O
O
H
27j:
DEPT, CDCl3, 50 MHz

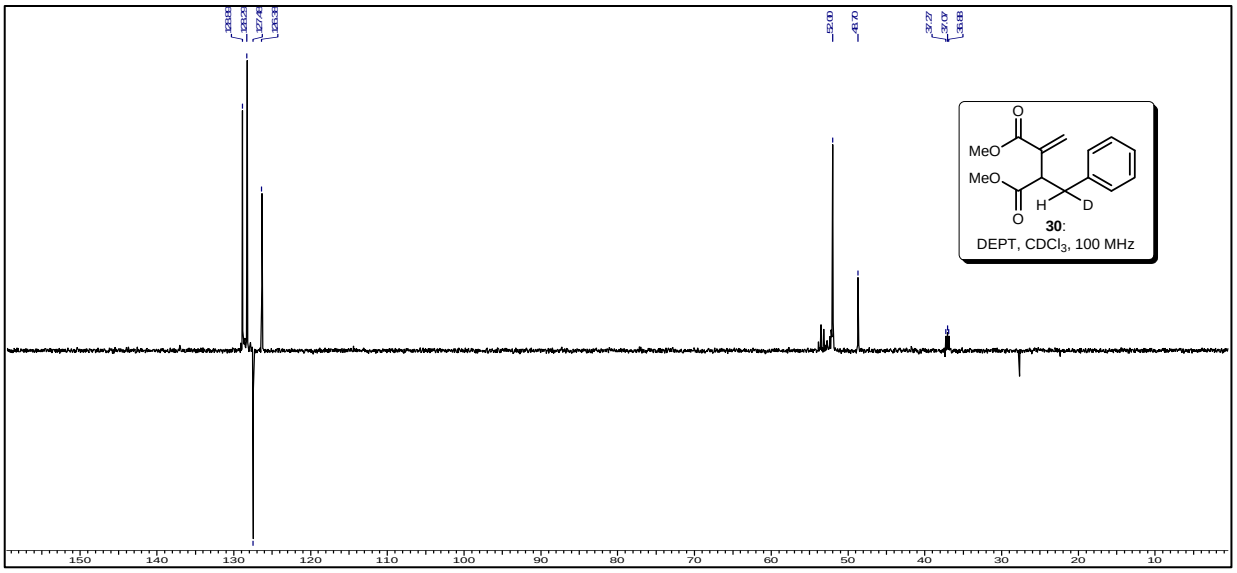

Chloroform-d
MeO
MeO
O
29a:
1H NMR, CDCl3, 200 MHz

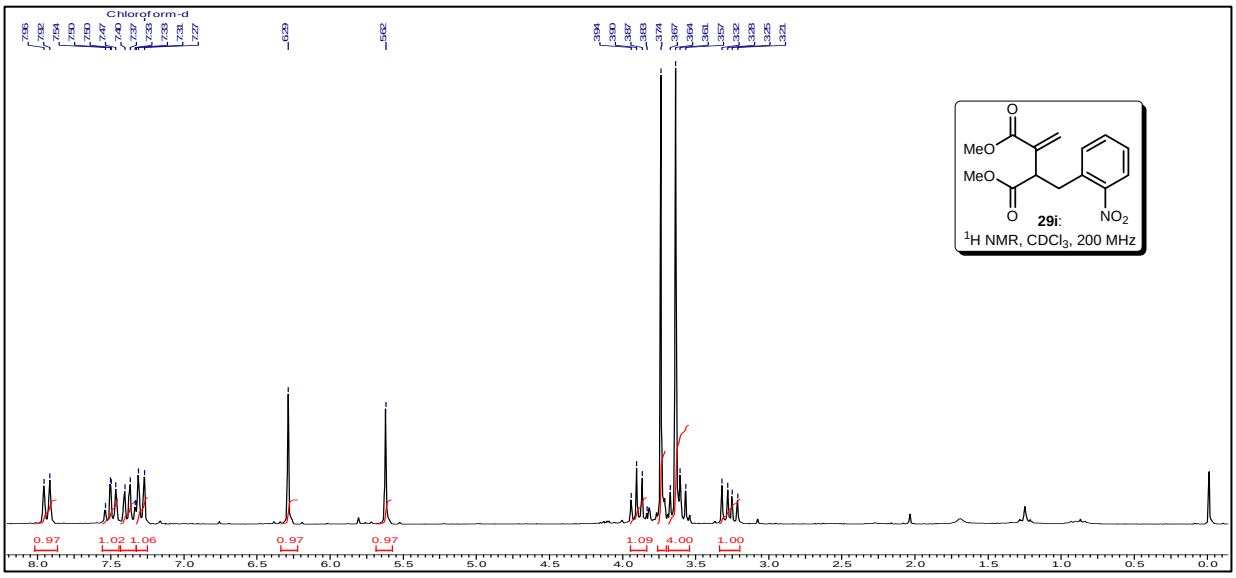

Chloroform-d
MeO
MeO
O
29a:
13C NMR, CDCl3, 50 MHz

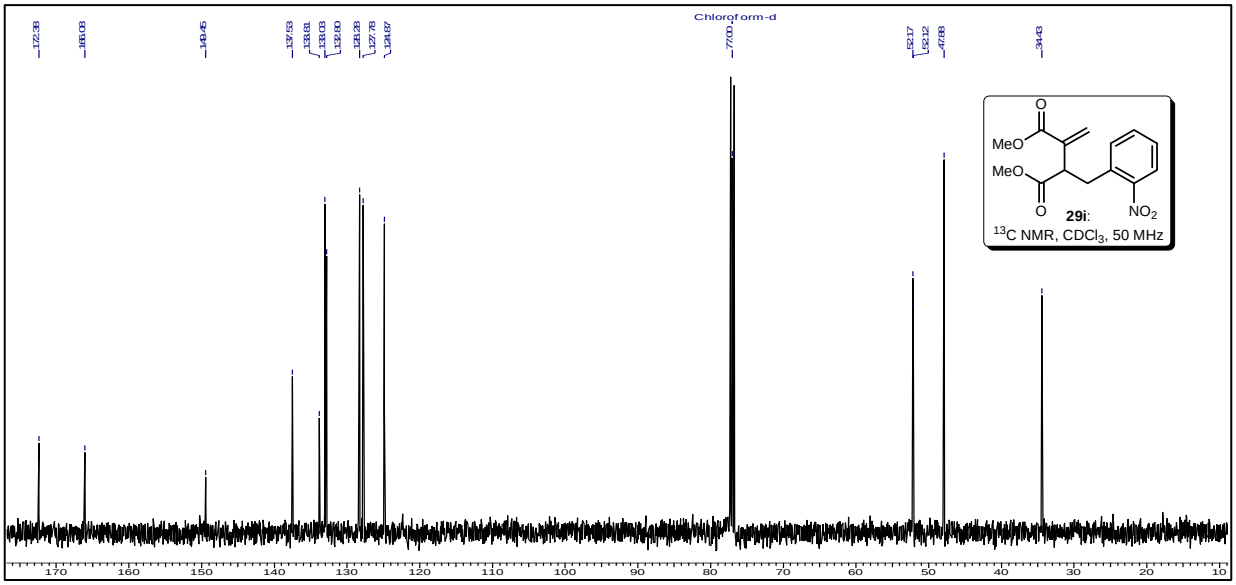

MeO
MeO
O
29a:
DEPT, CDCl3, 50 MHz

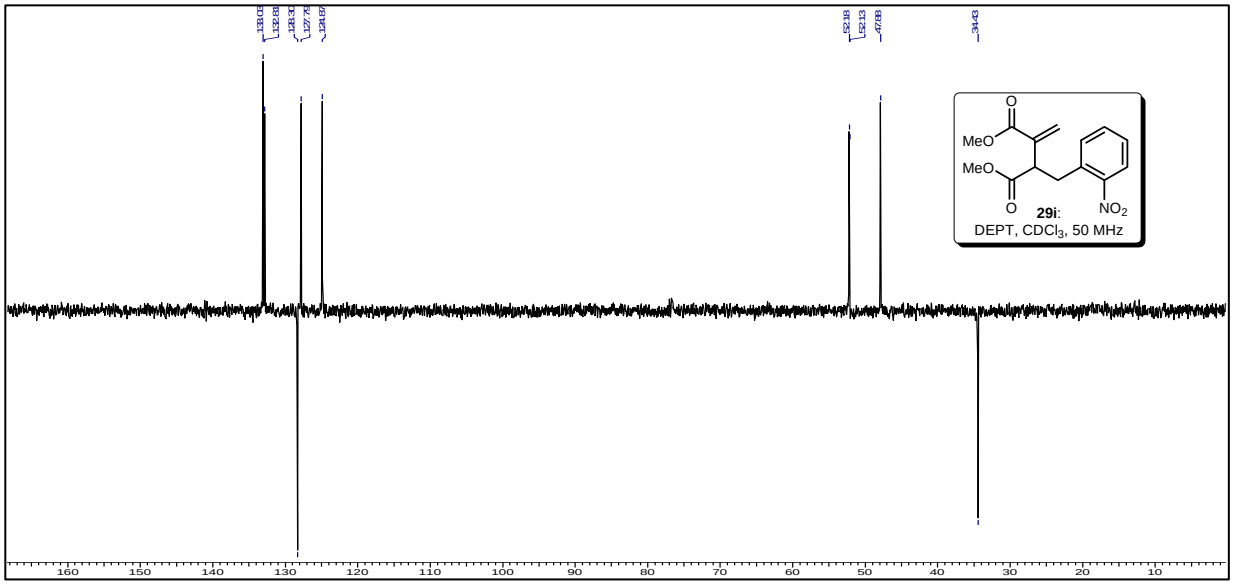

Chloroform-d
MeO
MeO
O
O
H
D
30:
1H NMR, CDCl3, 200 MHz
5.22
1.00
1.03
3.21
0.20
0.77

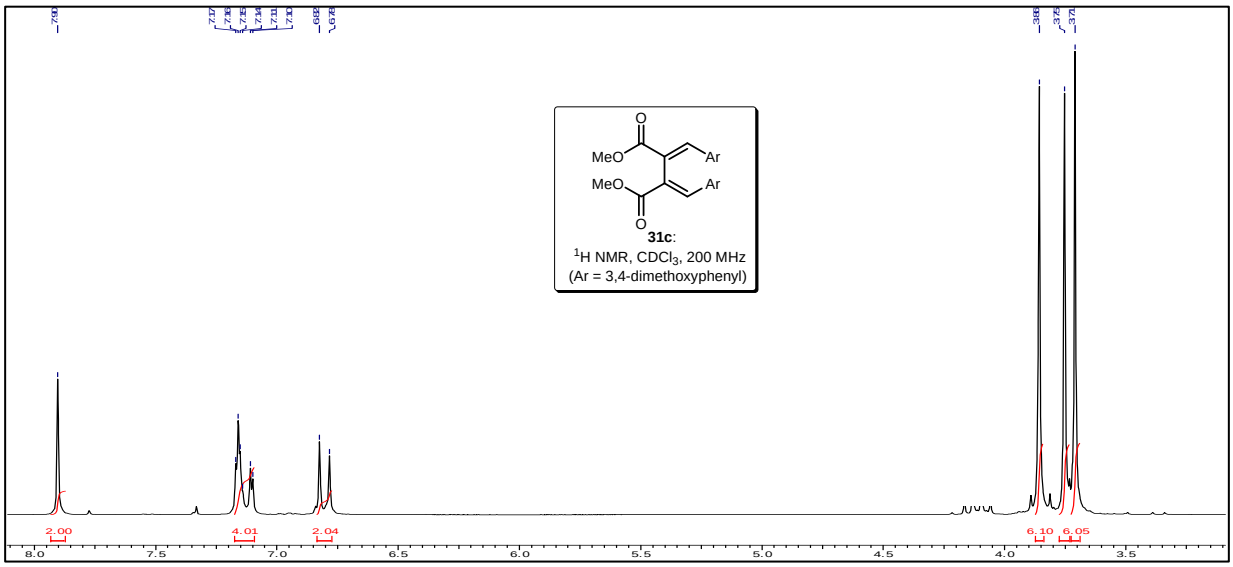

Chloroform-d
MeO
MeO
O
O
H
D
30:
13C NMR, CDCl3, 100 MHz

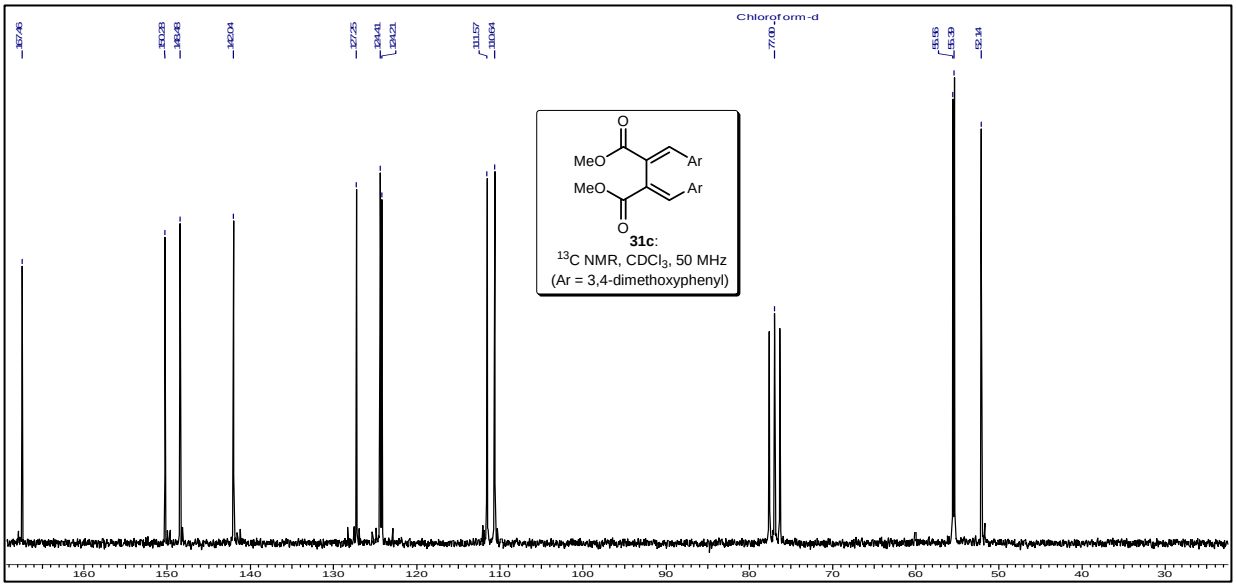

MeO
MeO
O
O
H
D
30:
DEPT, CDCl3, 100 MHz

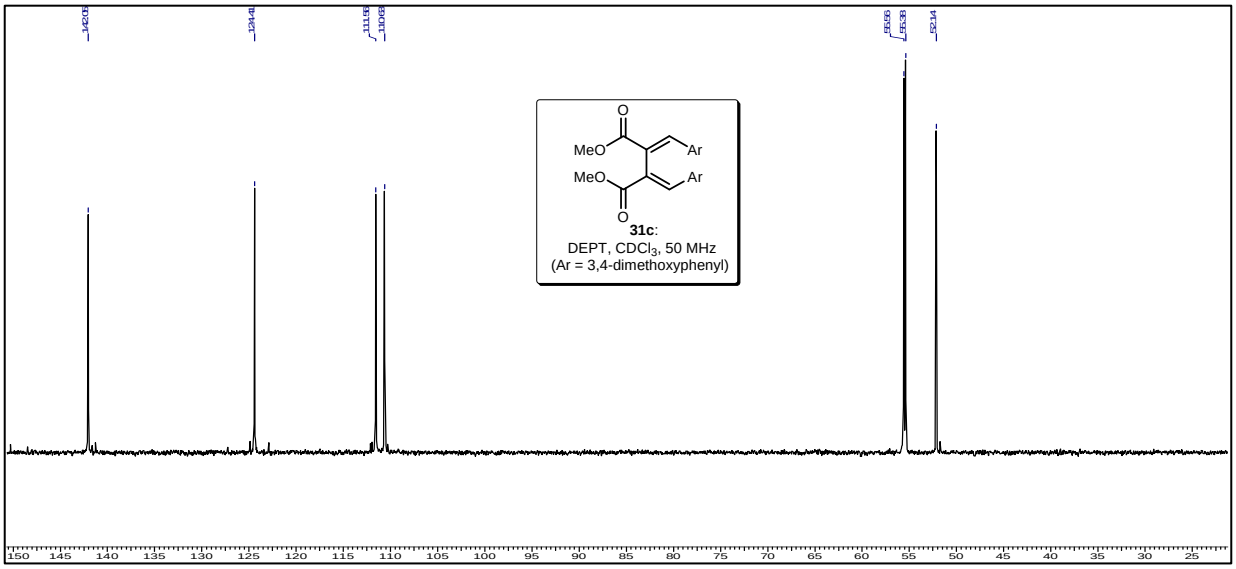

Chloroform-d
MeO
MeO
O
O
NO2
29i:
1H NMR, CDCl3, 200 MHz


Chloroform-d
MeO
MeO
O
O
NO2
29i:
13C NMR, CDCl3, 50 MHz


MeO
MeO
O
O
NO2
29i:
DEPT, CDCl3, 50 MHz


MeO
MeO
Ar
Ar
O
O
O
31c:
1H NMR, CDCl3, 200 MHz
(Ar = 3,4-dimethoxyphenyl)
2.00
4.01
2.04
6.10
6.05


Chloroform-d
MeO
MeO
Ar
Ar
O
O
O
31c:
13C NMR, CDCl3, 50 MHz
(Ar = 3,4-dimethoxyphenyl)


MeO
MeO
Ar
Ar
O
O
O
31c:
DEPT, CDCl3, 50 MHz
(Ar = 3,4-dimethoxyphenyl)

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(28) (a) Heck, R. F.; Nolly, J. P. *J. Org. Chem*. **1972**, *37*, 2320. (b) Heck, R. F. *Palladium Reagents in Organic Synthesis*, Academic Press, London, **1985**.

(29) Yokoyama, Y. *Chem. Rev*. **2000**, *100*, 1717.

(30) Andersson, J.; Eberson, L. *Nouveau J. de Chimie* **1977**, *1*, 413.

Chapter 2: Section B

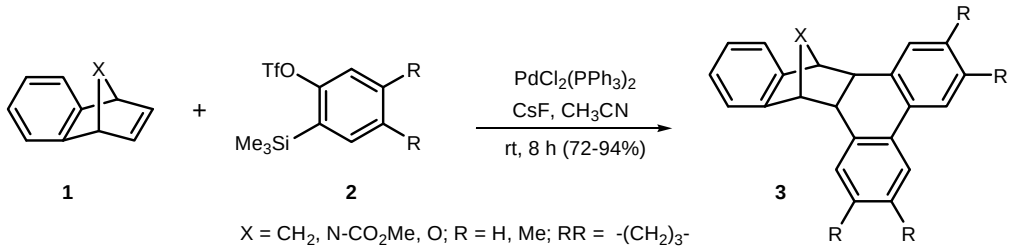
Pd Catalyzed [2 + 2 + 2] Cocyclization of Arynes and Dienes to Arylnapthalene Lignan Framework: Total Synthesis of Justicidin B and Retrojusticidin B

This section B of chapter 2 features the following topics:

2B.1: Background

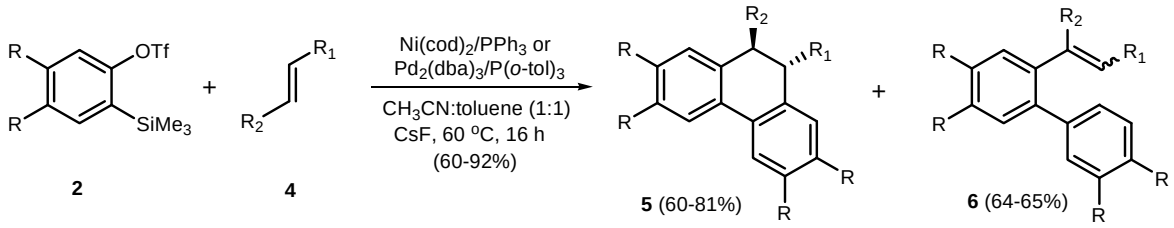
Transition metal catalyzed [2 + 2 + 2] cocyclization reactions have been an area of extensive investigation and have played a crucial role in the development of synthetic methodologies in organic synthesis.[1] Even though metal mediated cocyclization chemistry of arynes are well-known, their use has been restricted to only stoichiometric reactions.[2] However, the recent development of new methods for the generation of arynes under mild conditions[3] has led to the exploration of metal mediated cocyclization reactions of arynes. In 1998, Pena et al.[4] reported a palladium catalyzed trimerization of benzynes to give triphenylenes and extended this [2 + 2 + 2] cocyclization protocol for the synthesis of a number of structurally diverse polycyclic aromatic hydrocarbons.[5] Later, the same group showed that arynes underwent [2 + 2 + 2] cocyclization with alkynes (alkyne-aryne-aryne) to furnish the corresponding aromatic products chemoselectively.[6] Yamamoto and co-workers have also reported similar cocyclizations of arynes with alkynes[7] and with allyl chlorides[8] using palladium complexes as the catalysts. Recently, Cheng et al. have also developed nickel catalyzed highly chemoselective cocyclization of arynes with allenes,[9] allyl epoxides,[10] alkynyl stannanes[11] and boronic acids.[12] Although several type of copartners such as alkynes, allylic chlorides, allyl epoxides, boronic acids, alkynyl stannanes, allenes, aromatic halides[13] and carbon monoxide[14] have been used, however, to the best of our knowledge only three examples of metal mediated [2 + 2 + 2] cocyclization of arynes and alkenes have been reported in the literature to date.

Cheng et al.[15] have reported [2 + 2 + 2] cocyclization of bicyclic alkenes **1** and arynes (generated in situ from precursors **2** using CsF) catalyzed by $PdCl_2(PPh_3)_2$ in acetonitrile at room temperature to yield anellated 9,10-dihydrophenanthrene products **3** in moderate to excellent yields (Scheme 1).



Scheme 1. Pd catalyzed [2 + 2 + 2] cocyclization of bicyclic alkenes and arynes

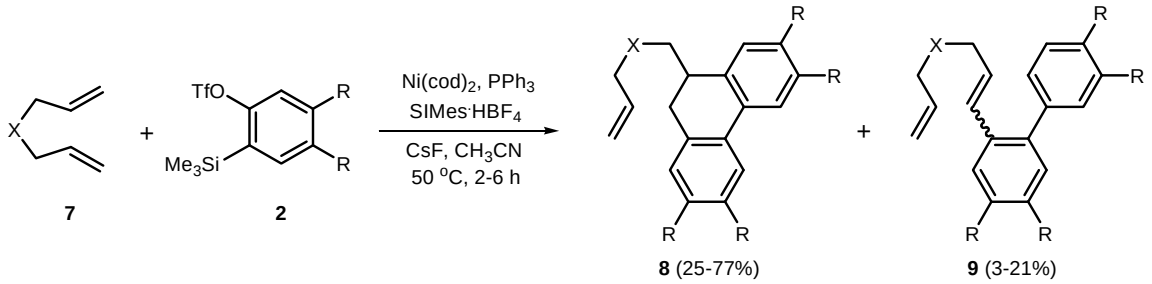
Pena et al.[16] have developed [2 + 2 + 2] cocyclization of electon-deficient alkenes **4** and arynes (generated in situ from precursors **2** using CsF) in CH_3CN:toluene (1:1) to selectively obtain 9,10-dihydrophenanthrenes **5** or *ortho*-olefinated biaryls **6**, depending on the catalytic system employed (Scheme 2). With $Ni(cod)_2/PPh_3$ catalytic system, the dihydrophenanthrenes **5** were obtained as the single products (60-81%), while $Pd_2(dba)_3/P(o\text{-tol})_3$ catalytic system furnished *ortho*-olefinated biaryls **6** as the major products (64-65%) with small amount of dihydrophenanthrenes **5** (6-28%).



R = H, Me; RR = -$(CH_2)_3$-, -OCH_2O-; R_1 = CO_2Me, CN, SO_2Me; R_2 = H, Me, CO_2Me

Scheme 2. [2 + 2 + 2] Cocyclization of electron-deficient alkenes and arynes

Sato et al.[17] have reported [2 + 2 + 2] cocyclization of unactivated alkenes **7** and arynes (generated in situ from precursors **2** using CsF) catalyzed by $Ni(cod)_2$/SIMes·HBF_4 in acetonitrile to yield 9,10-dihydrophenanthrene derivatives **8** in 25-77% yields (Scheme 3).



X = CH_2, $C(CO_2Me)_2$, N-Ts, O; R = H, OMe; RR = -OCH_2O-

Scheme 3. $Ni(cod)_2$/SIMes·HBF_4 catalyzed [2 + 2 + 2] cocyclization of unactivated alkenes and arynes

The metal catalyzed [2 + 2 + 2] cocyclization of arynes and alkenes to construct new carbon−carbon bonds has been challenging task of current interest and has not been explored for the synthesis of bioactive natural products. In section 2A, we have discussed in detail the S_N2' coupling reactions of Wittig reagents with dimethyl bromomethylfumarate to synthesize enes and dienes selectively.[18] In this section, as a part of present dissertation, we have developed novel Pd catalyzed [2 + 2 + 2] cocyclization of arynes and our synthesized dienes to regioselectively construct arylnapthalene lignan framework and further utilized it for the concise synthesis of justicidin B and retrojusticidin B.

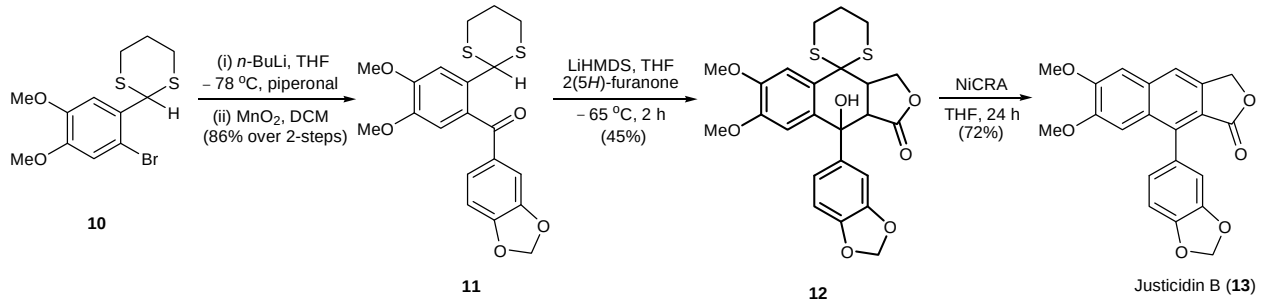
2B.2: Brief account of lignans justicidin B and retrojusticidin B

Arylnapthalene lactones are sub-group of the lignan class of natural products that are characterized by a phenylpropanoid dimmer motif. Arylnapthalene lignans occur widely in nature and have been frequently identified as constituents of tree bark and plants with folkloric medicinal usage.[19] Numerous biological assays have been conducted on arylnapthalene lignans and have received increasing attention over past several decades owing to their cytotoxic,[20] antiviral,[21] fungicidal,[22] hypolipidemic[23] and antiplatelet[24] activities in cell based analysis. Pleasantly, many synthetic methodologies have been developed for the synthesis of arylnapthalene lignans,[25] which includes (a) Michael addition of

cyanohydrins with α,*β*-unsaturated carboxylates followed by reaction with aldehyde, and intramolecular Friedel-Crafts cyclization,[26] (b) sequential Michael addition of 2-(*α*-lithio)benzonitriles with *α*,*β*-unsaturated carboxylates followed by intramolecular cyclization,[27] (c) Diels-Alder addition of benzoisofurans to the dienophile,[28] (d) Horner-Wadsworth-Emmons reaction followed by Claisen condensation,[29] (e) Pd-catalyzed benzannulation,[30] (f) transition metal mediated electrocyclization,[31] (g) Pd catalyzed intramolecular coupling of phenyl 2-bromonaphthoate followed by asymmetric reduction of lactones,[32] (h) transition metal catalyzed [2 + 2 + 2] cocyclization between *α*,*ω*-diynes and alkynes or arynes,[33] (i) DDQ induced cyclodehydrogenation of diarylidenesuccinic anhydride,[34] (j) silver catalyzed one-pot synthesis of alkynes[35] and (k) regio-controlled benzannulation of diaryl(gem-dichlorocyclopropyl)methanols.[36]

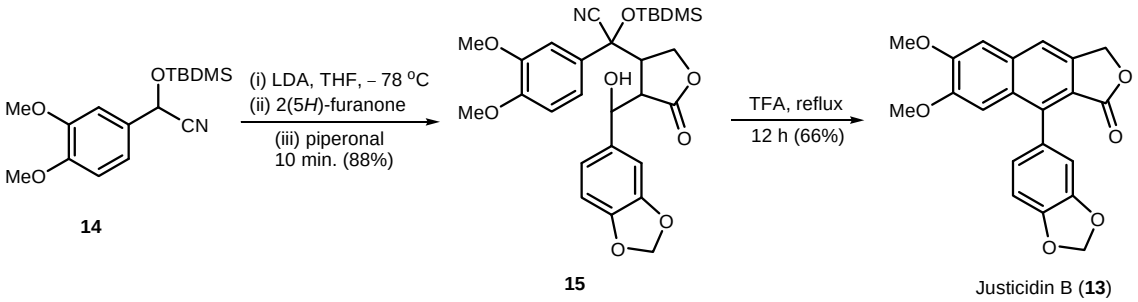
Justicidin B and retrojusticidin B are arynapthalene lignan class of natural products, found widely in nature[37] and they show inhibitory activity against HIV-1 reverse transcriptase.[38] Although, some total syntheses of justicidin B and retrojusticidin B have been reported in the literature,[34,39] we have discussed a few recent syntheses below.

Kamal et al.[40] have reported facile total synthesis of justicidin B by employing Michael Initiated Ring Closure (MIRC) reaction between benzophenone intermediate **11** and 2(5*H*)-furanone leading to the lignan precursors **12** in 45% yield (Scheme 4). The desulfurization of the dithiane from lignan **12** in presence of nickel-containing complex reducing agent (NiCRA), followed by an in situ aromatization furnished justicidin B (**13**) in 72% yield. Starting from dithiane of 6-bromoveratraldehyde **10**, the justicidin B (**13**) was synthesized in 28% overall yield over 4-steps.



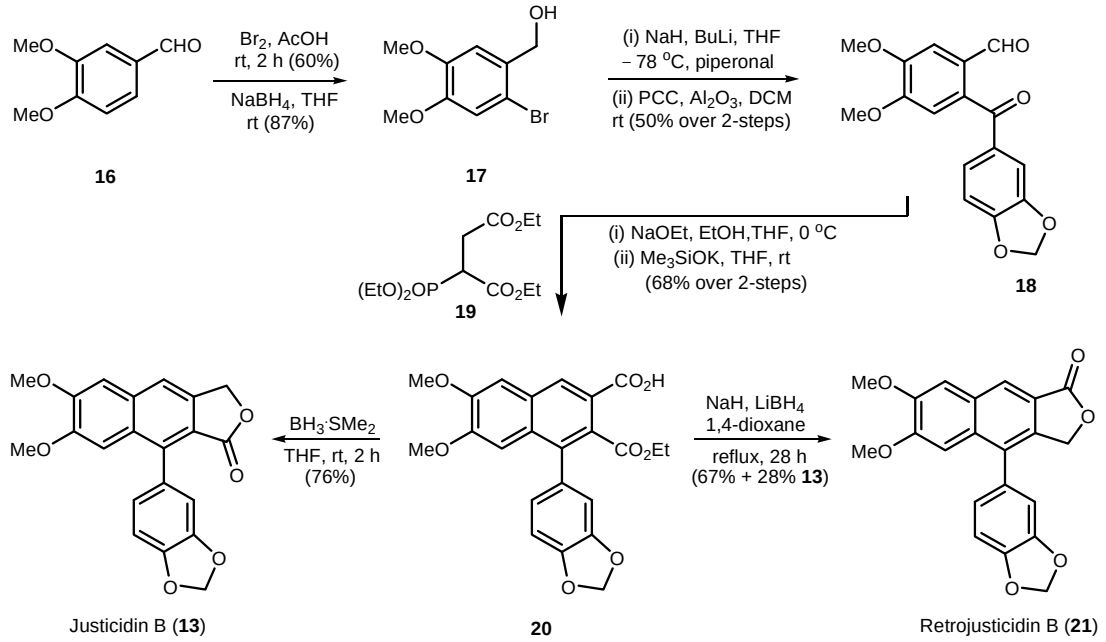
Scheme 4. Synthesis of justicidin B via Michael Initiated Ring Closure reaction

Iwasaki et al.[26] have reported total synthesis of justicidin B via conjugate Michael addition reaction of *O*-(*tert*-butyldimethylsilyl)-cyanohydrin compound **14** to 2(5*H*)-furanone followed by condensation with piperonal afforded compound **15** in 88% yield (Scheme 5). TFA-catalyzed ring closure reaction followed by aromatization furnished the justicidin B in 66% yield. Starting from *O*-(*tert*-butyldimethylsilyl)-cyanohydrin compound **14**, the justicidin B (**13**) was synthesized in 58% overall yield over 2-steps.



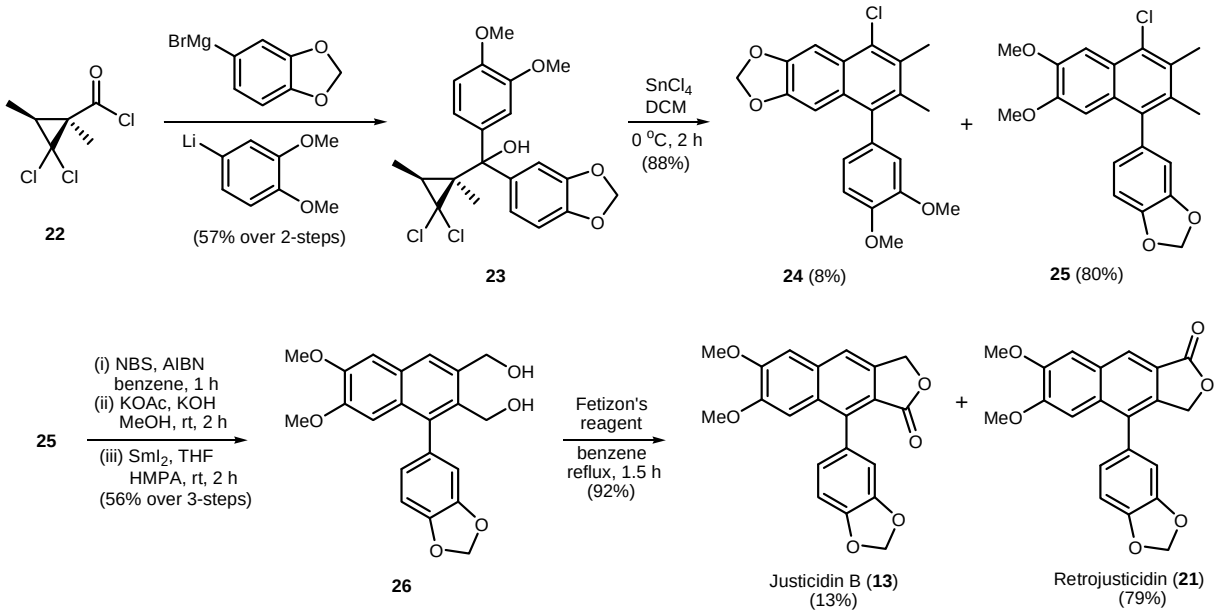
Scheme 5. Synthesis of justicidin B via conjugate Michael addition-condensation

Harrowven et al.[29] have reported total synthesis of justicidin B (**13**) and retrojusticidin B (**21**) via base induced tandem Horrner-Emmons-Claisen condensation of keto-aldehyde **18** and phosphonate **19** as a key step to construct highly substituted naphthalene diester followed by regioselective hydrolysis of less hindered ester unit furnished acid-ester **20** in 68% yield over 2-steps (Scheme 6). The chemoselective reduction of acid moiety furnished justicidin B (**13**) in 76% yield, while chemoselective reduction of ester afforded retrojusticidin B (**21**) in 67% yield along with justicidin B (**13**) in 28% yield. Starting from Veratraldehyde (**16**), the justicidin B (**13**) and retrojusticidin B (**21**) were respectively synthesized in 13% and 12% overall yields over 7-steps.



Scheme 6. Synthesis of justicidin B and retrojusticidin B via tandem Horrner-Emmons-Claisen condensation

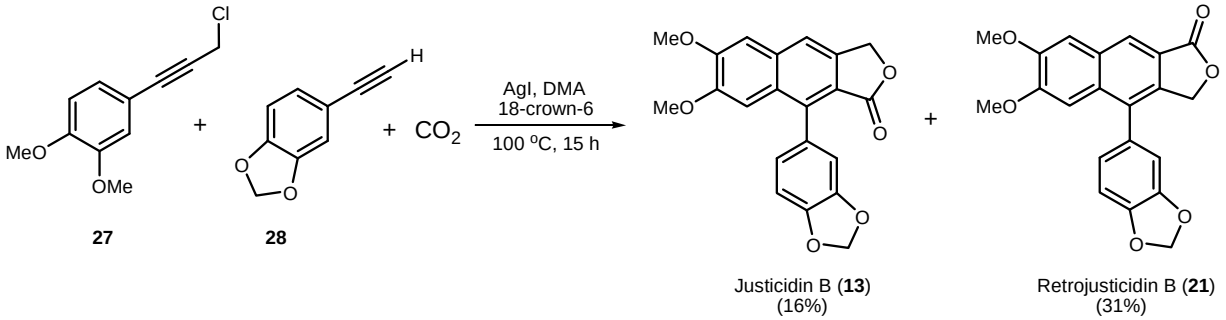
Tanabe et al.[35] have reported total synthesis of justicidin B (**13**) and retrojusticidin B (**21**) via Lewis acid catalyzed regiocontrolled benzannulation of diaryl(*gem*-dichlorocyclopropyl)methanols as a key step to synthesize Cl-substituted regioisomeric *α*-arylnaphthalenes **24**/**25** in 88% yield (Scheme 7). Benzylic



Scheme 7. Synthesis of justicidin B and retrojusticidin B via Lewis acid catalyzed regiocontrolled benzannulation

brominations of vicinal methyl groups of naphthalene **25**, followed by basic hydrolysis and dechlorination using SmI_2 gave the desired arylnapthalene diol **26** in 56% yield over 3-steps. Finally, oxidation of diol **26** using Fetizon's reagent (Ag_2CO_3-Celite),[41] followed by separation of the regioisomers gave justicidin B (**13**) and retrojusticidin B (**21**) respectively in 13% and 79% yields.[34] Starting from *gem*-dichlorocyclopropanecarbonyl chloride **22**, the justicidin B (**13**) and retrojusticidin B (**21**) were respectively synthesized in 3% and 20% overall yields over 7-steps.

Recently in 2010, Anastas et al.[36] have reported silver-catalyzed one-pot synthesis of justicidin B (**13**) and retrojusticidin B (**21**) along with other regio-isomers using carbon dioxide, arylpropargyl chloride **27** and arylacetylene **28** in 16% and 31% yield respectively (Scheme 8).



Scheme 8. One-pot synthesis of justicidin B and retrojusticidin B via silver-catalyzed benzannulation of alkynes

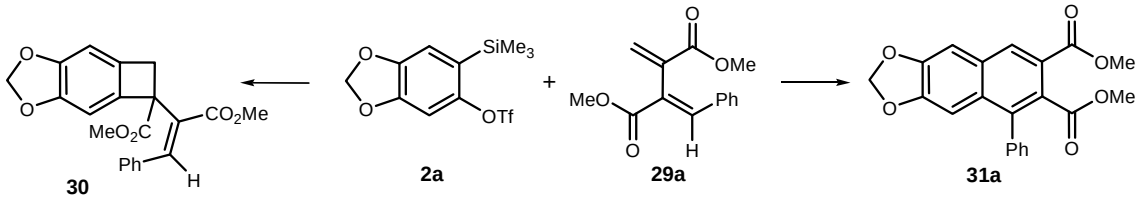
2B.3: Results and discussion

A transition metal catalyzed [2 + 2 + 2] cocyclization of multiple bonds has been an atom economical and useful methodology for the synthesis of polycyclic compounds.[42] However, the metal catalyzed [2 +

2 + 2] cocyclization of arynes and alkenes to construct new carbon−carbon bonds has been the challenging task of current interest and to the best of our knowledge, it has not been explored for the synthesis of bioactive natural products, till date. In section 2A, we have discussed in detail a novel S_N2'coupling reactions of Wittig reagents with dimethyl bromomethylfumarate to synthesize various enes and dienes and used for the synthesis of lignans class of natural products.[18] Although, a large number of synthetic strategies for the construction of arylnapthalene lignans have been reported in the literature, concise and general approaches for the regioselective synthesis of all these lignan class natural products are still in great demand. In this context, we envisaged that metal catalyzed [2 + 2 + 2] cocyclization reaction of our synthesized dienes and arynes would provide us one-step approach to construct arylnaphthalene lignan framework regioselectively, which can be further tailored to complete the total synthesis of arylnapthalene lignans. However, the major challenge we could foresee is the *E*,*E*-trans geometry of our synthesized diene (coupled double dienophile, ?). We assumed that we can overcome this difficulty by converting them to *E*,*E*-cis isomer either by (i) heat or (ii) by metal catalyzed coordination.

The reaction of diene **29a**, aryne precursor **2a** and CsF in CH_3CN at room temperature proved our foreseen difficulty correct and we isolated [2 + 2] cocyclization product **30** generated by the reaction between aryne and less substituted double bond of *E*, *E*-trans diene **29a** in 22% yield and 30% recovery

Table 1. Optimization of reaction conditions for [2 + 2 + 2] cocyclization of diene **29a** and arynes

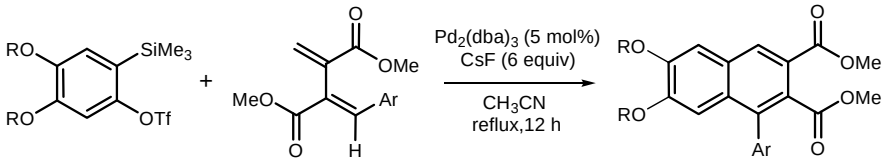


Entry	Reaction conditions [a]	**30**/**31a** (% yield)
1	CsF, CH_3CN, rt, 24 h	**30** (22)
2	CsF, CH_3CN, reflux, 12 h	**30** (11)
3	$Pd_2(dba)_3$, CsF, CH_3CN, rt, 24 h	NR [b]
4	$Pd_2(dba)_3$, CsF, CH_3CN, reflux, 12 h	**31a** (36)
5	$Pd_2(dba)_3$, P(*o*-tol)$_3$, CsF, CH_3CN, reflux, 24 h	**31a** (34)
6	$Pd_2(dba)_3$, dppf, CsF, CH_3CN, reflux, 24 h	**31a** (35)
7	$Pd_2(dba)_3$, TBP, CsF, CH_3CN, reflux, 24 h	**31a** (32)
8	$Pd(PPh_3)_4$, P(*o*-tol)$_3$, CsF, CH_3CN, reflux, 24 h	**31a** (12)
9	$Ni(cod)_2$, PPh_3, CsF, CH_3CN, reflux, 24 h	**31a** (08)
10	$Pd(OAc)_2$, PPh_3, CsF, CH_3CN, reflux, 24 h	NR [b]

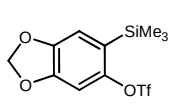
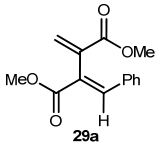
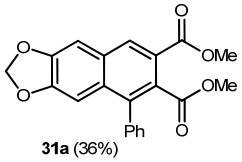
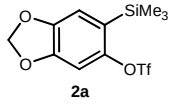
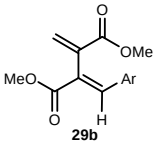
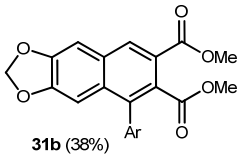
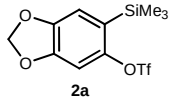
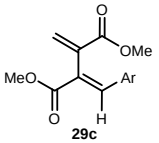
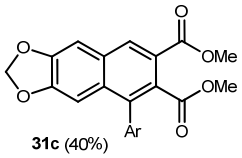
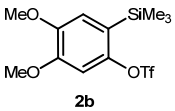
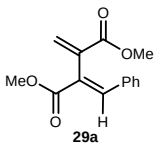
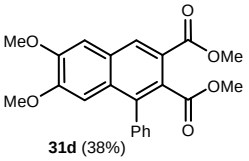
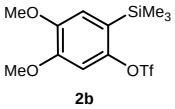
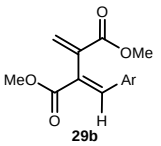
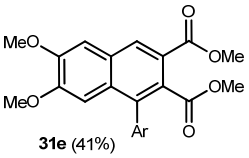
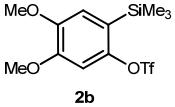
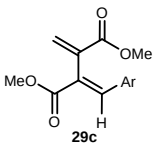
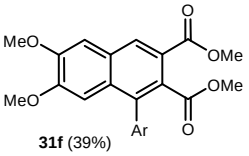
[a] 5 Mol % of catalyst; 20 mol % of ligand, and 6 equiv of CsF were used. [b] NR: No desired reaction.

of diene **29a** along with polymeric gums (Table 1). The same reaction mixture in refluxing CH_3CN gave less amount of [2 + 2] cocyclization product with more amount of polymeric gums precluding even traces of arynapthalene core **31a**. The $Pd_2(dba)_3$ catalyzed cocyclization reaction with diene and aryne precursor **2a** in CH_3CN at room temperature also met with failure with recovery of diene **29a** and remaining polymeric gums. However, to our delight when we refluxed the reaction mixture to 82 ^oC for 12 h, we could obtain arylnapthalene **31a** in lower yields without the formation of **30**. After extensive

Table 2. Generalization of Pd catalyzed [2 + 2 + 2] cocyclization of dienes **29a**-**c** and arynes



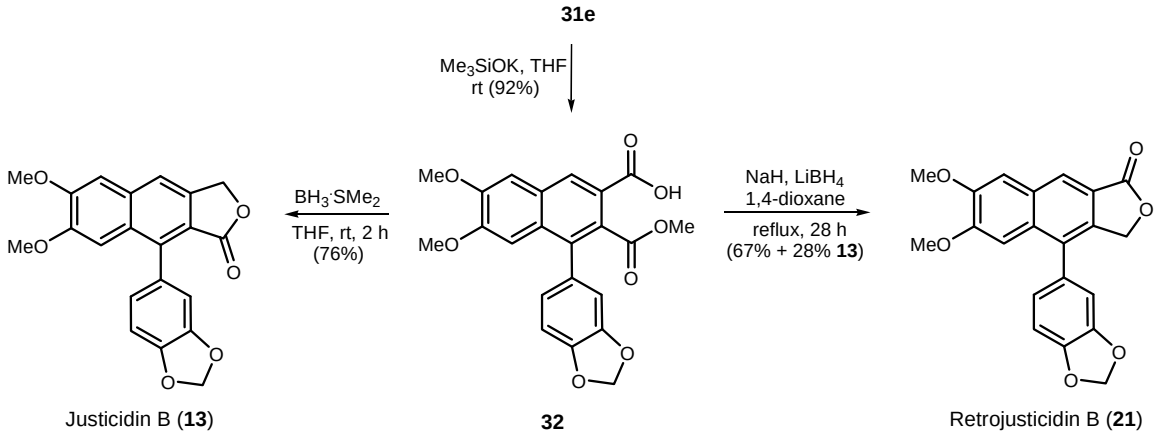
2a/b (1.50 equiv) **29a-c** (1.00 equiv) **31a-f**

Entry	Aryne precursor	Diene	Arylnaphthalene core
1	 **2a**	 **29a**	 **31a** (36%)
2	 **2a**	 **29b** Ar = 3,4-methylenedioxyphenyl	 **31b** (38%) Ar = 3,4-methylenedioxyphenyl
3	 **2a**	 **29c** Ar = 3,4-dimethoxyphenyl	 **31c** (40%) Ar = 3,4-dimethoxyphenyl
4	 **2b**	 **29a**	 **31d** (38%)
5	 **2b**	 **29b** Ar = 3,4-methylenedioxyphenyl	 **31e** (41%) Ar = 3,4-methylenedioxyphenyl
6	 **2b**	 **29c** Ar = 3,4-dimethoxyphenyl	 **31f** (39%) Ar = 3,4-dimethoxyphenyl

optimization of reaction conditions, when we performed the reaction using 1.00 equiv. of diene **29a**, 1.50 equiv. of aryne precursor **2a**, 5 mol% of $Pd_2(dba)_3{\cdot}CHCl_3$ catalyst, 6 equiv. of CsF under reflux in CH_3CN solvent in 12 h and we obtained arylnapthalene **31a** in 36% yield. All our efforts for further improve the yields using different ligands like PPh_3, P(*o*-tol)$_3$, dppf, various solvents like toluene, toluene/CH_3CN mixture, varying molar ratio of reactant and reagents and using different active catalyst like $Ni(COD)_2$, $Pd(PPh_3)_4$, $Pd(OAc)_2$ were not successful.

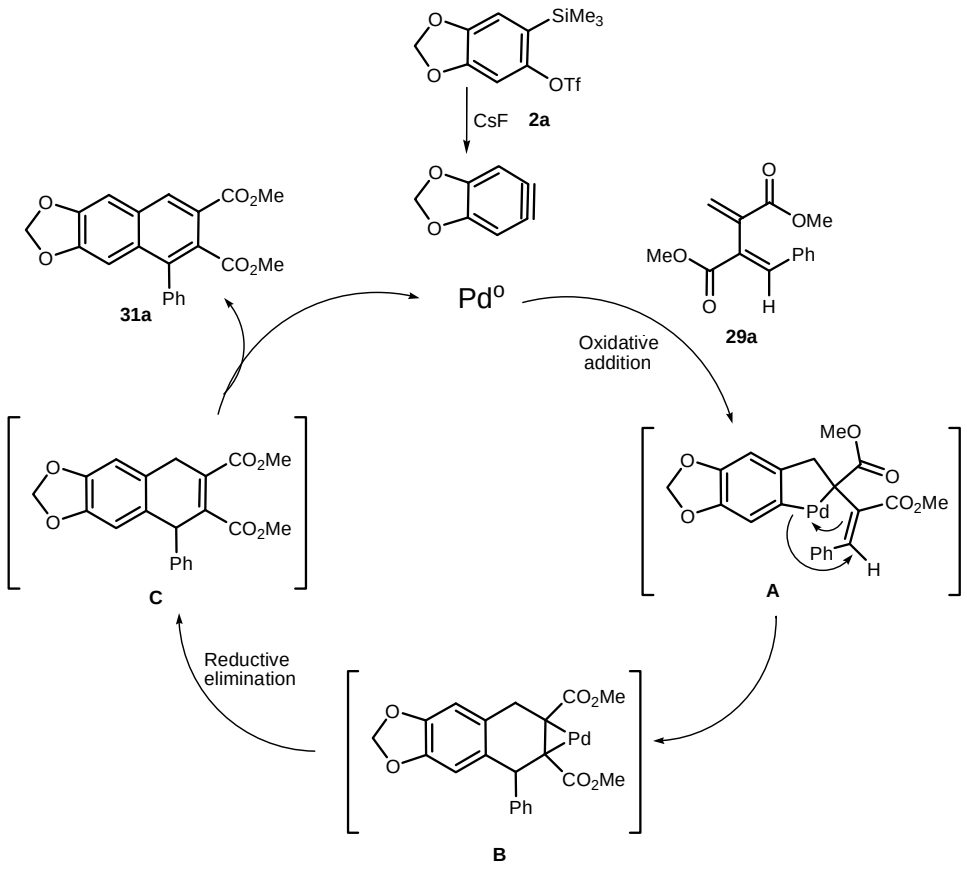
In order to prove the generality of our protocol, we performed reaction between different dienes **29a**-**c** and aryne precursors **2a**/**b** and obtained the products **31a**-**f** in 36-41% yields (Table 2). The arylnapthalenes **31b**, **31d** and **31e** are the key intermediates which can be regioselectively converted to arylnaphthalene lignan class of natural products using the elegant method developed by Padwa et al.[28]

The usefulness of our methodology has been demonstrated through the total synthesis of justicidin B and retrojusticidin B[29] (Scheme 9), found widely in nature[37] and show inhibitory activity of HIV-1 reverse transcriptase.[38] Thus, the sterically unhindered ester in compound **31e** was first regioselectively hydrolyzed to acid-ester **32** by using potassium trimethylsilonate in THF at room temperature with 92% yield. The chemoselective reduction of an acid functionality in compound **32** with borane dimethyl sulfide complex followed by an acidic workup gave the justicidin B (**13**) in 76% yield. On the other hand, chemoselective ester reduction of sodium salt of compound **32** using lithium borohydride followed by the acidification gave column chromatographic separable mixture of expected major product retrojusticidin B (**21**) (67% yield) with minor product justicidin B (**13**) (28%), plausibly via the corresponding cyclic anhydride. Thus starting from dimethyl bromomethylfumarate, we have completed facile total synthesis of justicidin B (**13**) and retrojusticidin B (**21**) in just four steps with 18% and 16% overall yields respectively.



Scheme 9. Concise synthesis of justicidin B and retrojustidin B

Based on the above results, a plausible mechanism for the Pd catalyzed [2 + 2 + 2] cocyclization of aryne and diene was proposed (Scheme 10). First, the catalysis was initiated by oxidative insertion of Pd^0 to aryne and less substituted double bond of diene to form a paladacycle A, which is probably stabilized by an intramolecular coordination of the oxygen atom from α,β-unsaturated moiety.[43] Subsequent insertion of more substituted double bond of the diene into the Pd−C (aryl) bond provides the intermediate B. Reductive elimination of Pd from intermediate B forms intermediate C with regeneration of the catalyst. The intermediate C, which is highly prone for aromatization, in situ oxidizes to arylnatphalene skeleton **31a**. On the basis of structural features of our dienes (linked double dienophile), we have proposed the [2 + 2 + 2] cocyclization mechanism. Although the [4 + 2] cycloaddition mechanism would involve unfavourable rotation of π-electrons in our substrates, we wish to keep open the possibility of [4 + 2] cycloaddition mechanism.



Scheme 10. Plausible Mechanism for [2 + 2 + 2] cocyclization of diene and aryne to arylnapthalene framework

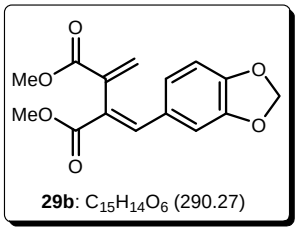
2B.4: Summary

In the present section, we have described a novel palladium catalyzed [2 + 2 + 2] cocyclization of dienes and arynes to arylnapthalene frameworks with the formation of two new carbon–carbon bonds. The versatility of this method is demonstrated through the facile total synthesis of justicidin B and retrojusticidin B in four steps, starting from dimethyl bromomethylfumarate. The present convergent strategy is general in nature and provides the way for the shorter and regioselective synthesis of various arylnapthalene lignans. However, further refinements of reaction conditions for the improvement of yields are in active progress. The direct generation of important biaryl systems without the aryl–aryl coupling strategy is also noteworthy.

2B.5: Experimental section

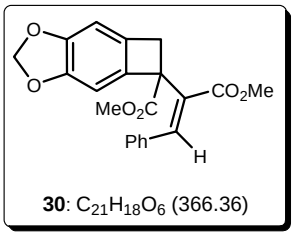
Commercially available CsF, $Pd_2(dba)_3.CHCl_3$, $Ni(cod)_2$, $Pd(PPh_3)_4$, $Pd(OAc)_2$, PPh_3, P(*o*-tol)$_3$, potassium trimethylsilonate, NaH, $LiBH_4$, borane dimethyl sulfide complex (10 M solution in dimethyl sulfide), 1,4-dioxane and acetonitrile were used. The aryne precursors **2a** and **2b** were prepared using the known procedures.[4a,5]

(*E*)-Dimethyl 2-(benzo[*d*][1,3]dioxol-5-ylmethylene)-3-methylenesuccinate (29b). To a stirring solution of 3,4- methylenedioxybenzyltriphenylphosphonium bromide (954 mg, 2.00 mmol) in THF (25 mL) at –100 °C was added *n*-BuLi (1.34 mL, 2.00 mmol) in a drop wise fashion under argon atmosphere. The reaction mixture was allowed to reach to 0 °C temperature. Then, above reaction mixture was added to a stirring solution of dimethyl bromomethylfumarate (569 mg, 2.40 mmol) in THF (20 mL) at –100 °C under argon atmosphere in a drop wise fashion. The reaction mixture was allowed to reach to room temperature and the reaction was then quenched with water. The reaction mixture was extracted with ethyl acetate (30 mL x 4) and the combined organic layer was washed with brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the residue using 10% ethyl acetate/petroleum ether as an eluent provided **29b** (365 mg, 63%) as thick oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.77 (s, 3H), 3.79 (s, 3H), 5.73 (d, *J* = 2 Hz, 1H), 5.98 (s, 2H), 6.53 (d, *J* = 2 Hz, 1H), 6.75−6.80 (m, 1H), 6.96 (dd, *J* = 6 and 2 Hz, 1H), 6.98 (s, 1H), 7.71 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 52.3 (2 carbons), 101.4, 108.4, 109.3, 126.2, 126.3, 128.3, 130.7, 136.2, 141.5, 147.7, 148.7, 166.5, 167.4; ESIMS (*m*/*z*) 259 $[M+H]^+$, 281 $[M+Na]^+$, 297 $[M+K]^+$; IR ($CHCl_3$) ν_{max} 1722, 1638, 1619 cm^{-1}.



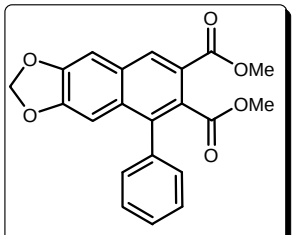
29b: $C_{15}H_{14}O_6$ (290.27)

(*E*)-Methyl 5-(3-methoxy-3-oxo-1-phenylprop-1-en-2-yl)-5,6-dihydrocyclobuta[4,5]benzo[1,2-*d*][1,3]dioxole- 5-carboxylate (30). To a stirring solution of aryne precursor **2a** (513 mg, 1.50 mmol) and diene **29a** (246 mg, 1.00 mmol) in CH_3CN (20 mL) at room temperature was added CsF (912 mg, 6.00 mmol) via solid addition funnel under argon atmosphere and the reaction mixture was further stirred at room temperature for 24 h. The reaction was quenched with saturated aq. NH_4Cl and concentrated in vacuo. To the obtained residue was added ethyl acetate (25 mL) and the organic layer was washed with brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using 10% ethyl acetate/petroleum ether as an eluent afforded product **30** as a colorless oil (80 mg, 22%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.94 (d, *J* = 14 Hz, 1H), 3.29 (d, *J* = 14 Hz, 1H), 3.77 (s, 3H), 3.86 (s, 3H), 5.84 (d, *J* = 2 Hz, 1H), 5.85 (d, *J* = 2 Hz, 1H), 6.49 (s, 1H), 6.55 (s, 1H), 7.34 (s, 5H), 7.90 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 41.1, 52.1, 52.8, 55.9, 100.1, 104.3, 105.9, 128.1, 128.6, 128.8, 131.8, 135.2, 135.9, 136.5, 140.2, 146.9, 147.9, 167.9, 173.9; ESIMS (*m*/*z*) 367 $[M+H]^+$, 389 $[M+Na]^+$, 405 $[M+K]^+$; HRMS (ESI) calcd for $C_{21}H_{18}O_6Na$ 389.1001, found 389.1006; IR ($CHCl_3$) ν_{max} 1728, 1712, 1630 cm^{-1}.



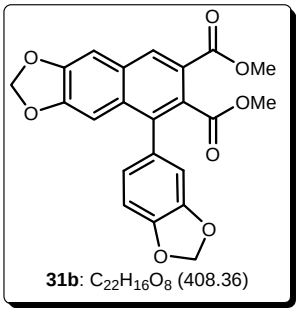
30: $C_{21}H_{18}O_6$ (366.36)

Dimethyl 5-phenylnaphtho[2,3-*d*][1,3]dioxole-6,7-dicarboxylate (31a). To a stirring solution of aryne precursor **2a** (513 mg, 1.50 mmol), diene **29a** (246 mg, 1.00 mmol) and $[Pd_2(dba)_3]\cdot CHCl_3$ (104 mg, 5 mol%) in CH_3CN (20 mL) at 60 ^{o}C was added CsF (912 mg, 6.00 mmol) via solid addition funnel under argon atmosphere and the reaction mixture was refluxed for 12 h with constant stirring. The reaction mixture was allowed to attain room temperature, quenched with saturated aq. NH_4Cl and concentrated in vacuo. To the obtained residue was added ethyl acetate (25 mL) and the organic layer was washed with brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using 10% ethyl acetate/petroleum ether as an eluent afforded product **31a** as a solid (131 mg, 36%). Mp 156–158 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.56 (s, 3H), 3.93 (s, 3H), 6.03 (s, 2H), 6.79 (s, 1H), 7.20 (s, 1H), 7.25−7.35 (m, 2H), 7.39−7.52 (m, 3H), 8.38 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 52.0, 52.4, 101.7, 103.3, 104.8, 122.8, 127.9, 128.1, 129.8, 129.9, 130.0, 130.2, 132.0, 136.9, 137.5, 148.7, 150.2, 166.3, 169.4; ESIMS (*m*/*z*) 365 $[M+H]^+$, 387 $[M+Na]^+$, 403 $[M+K]^+$; IR ($CHCl_3$) ν_{max} 1728, 1603 cm^{-1}. Anal. Calcd for $C_{21}H_{16}O_6$: C, 69.23; H, 4.43. Found: C, 68.87; H, 4.02.



31a: $C_{21}H_{16}O_6$ (364.35)

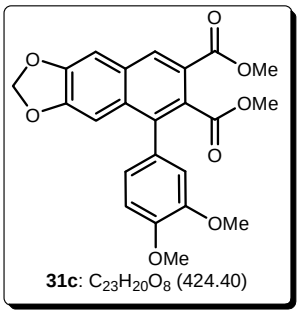
Dimethyl 5-(benzo[d][1,3]dioxol-5-yl)naphtho[2,3-*d*][1,3]dioxole-6,7-dicarboxylate (31b).[29] Compound



31b: $C_{22}H_{16}O_8$ (408.36)

31b was obtained from aryne precursor **2a** (513 mg, 1.50 mmol) and diene **29b** (290 mg, 1.00 mmol) using the same procedure described above for **31a**, as a solid (155 mg, 38%). Mp 217–219 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.67 (s, 3H), 3.94 (s, 3H), 6.04 (d, *J* = 2 Hz, 1H), 6.05 (d, *J* = 2 Hz, 1H), 6.06 (s, 2H), 6.77 (dd, *J* = 8 and 2 Hz, 1H), 6.80 (d, *J* = 2 Hz, 1H), 6.88 (s, 1H), 6.90 (dd, *J* = 8 and 2 Hz, 1H), 7.22 (s, 1H), 8.38 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 52.2, 52.5, 101.2, 101.7, 103.3, 104.8, 108.1, 110.7, 122.8, 123.7, 129.8, 129.9, 130.4 (2 carbons), 132.3, 137.0, 147.3 (2 carbons), 148.7, 150.3, 166.3, 169.5; ESIMS (*m*/*z*) 409 $[M+H]^+$, 431 $[M+Na]^+$, 447 $[M+K]^+$; IR ($CHCl_3$) ν_{max} 1723, 1619 cm^{-1}.

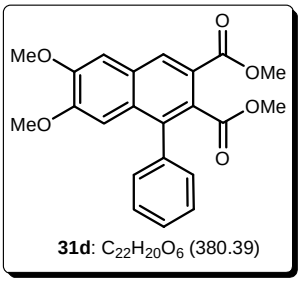
Dimethyl 5-(3,4-dimethoxyphenyl)naphtho[2,3-*d*][1,3]dioxole-6,7-dicarboxylate (31c).[29] Compound



31c: $C_{23}H_{20}O_8$ (424.40)

31c was obtained from aryne precursor **2a** (513 mg, 1.50 mmol) and diene **29c** (304 mg, 1.00 mmol) using the same procedure described above for **31a**, as a solid (170 mg, 40%). Mp 248–252 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.63 (s, 3H), 3.86 (s, 3H), 3.94 (s, 3H), 3.96 (s, 3H), 6.07 (s, 2H), 6.80–7.00 (m, 4H), 7.24 (s, 1H), 8.40 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 52.1, 52.4, 55.8, 55.9, 101.1, 105.2, 107.2, 108.1, 110.6, 122.5, 123.6, 128.4, 129.5, 130.1, 130.4, 130.6, 136.4, 147.2, 147.3, 150.4, 151.7, 166.4, 169.7; ESIMS (*m*/*z*) 425 $[M+H]^+$, 447 $[M+Na]^+$, 463 $[M+K]^+$; IR ($CHCl_3$) ν_{max} 1723, 1621 cm^{-1}.

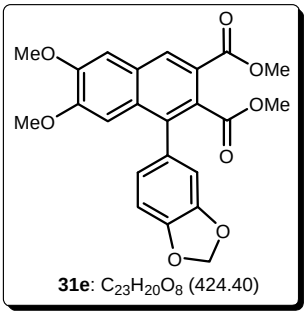
Dimethyl 6,7-dimethoxy-1-phenylnaphthalene-2,3-dicarboxylate (31d).[44] Compound **31d** was obtained



31d: $C_{22}H_{20}O_6$ (380.39)

from aryne precursor **2b** (537 mg, 1.50 mmol) and diene **29a** (246 mg, 1.00 mmol) using the same procedure described above for **31a**, as a solid (144 mg, 38%). Mp 128–130 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.58 (s, 3H), 3.73 (s, 3H), 3.94 (s, 3H), 4.03 (s, 3H), 6.80 (s, 1H), 7.25 (s, 1H), 7.31–7.41 (m, 2H), 7.41–7.53 (m, 3H), 8.46 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 52.0, 52.4, 55.7, 56.0, 105.4, 107.2, 122.6, 127.9, 128.1, 128.4, 129.5, 129.9, 130.0, 130.3, 136.95, 136.99, 150.5, 151.7, 161.5, 169.6; ESIMS (*m*/*z*) 381 $[M+H]^+$, 403 $[M+Na]^+$, 419 $[M+K]^+$; IR ($CHCl_3$) ν_{max} 1737, 1723, 1621 cm^{-1}.

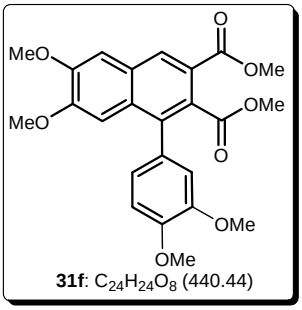
Dimethyl 1-(benzo[*d*][1,3]dioxol-5-yl)-6,7-dimethoxynaphthalene-2,3-dicarboxylate (31e).[28] Compound **31e** was obtained from aryne precursor **2b** (537 mg, 1.50 mmol) and diene **29b** (290 mg,



31e: $C_{23}H_{20}O_8$ (424.40)

1.00 mmol) using the same procedure described above for **31a**, as a solid (172 mg, 41%). Mp 168–171 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.67 (s, 3H), 3.79 (s, 3H), 3.93 (s, 3H), 4.01 (s, 3H), 6.03 (d, *J* = 2Hz, 1H), 6.05 (d, *J* = 2Hz, 1H), 6.77–6.95 (m, 4H), 7.23 (s, 1H), 8.43 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 52.1, 52.3, 55.7, 55.9, 101.1, 105.2, 107.2, 108.1, 110.5, 122.4, 123.6, 128.4, 129.5, 130.0, 130.4, 130.5, 136.3, 147.2, 147.3, 150.4, 151.7, 166.3, 169.6; ESIMS (*m*/*z*) 425 $[M+H]^+$, 447 $[M+Na]^+$; IR ($CHCl_3$) ν_{max} 1723, 1621 cm^{-1}. Anal. Calcd for $C_{23}H_{20}O_8$: C, 65.09; H, 4.75. Found: C, 65.31; H, 5.21.

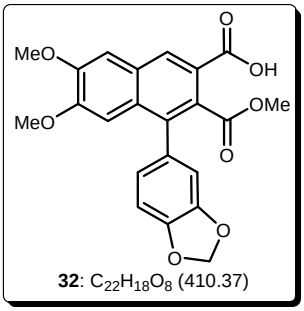
Dimethyl 1-(3,4-dimethoxyphenyl)-6,7-dimethoxynaphthalene-2,3-dicarboxylate (31f).[45] Compound



31f: $C_{24}H_{24}O_8$ (440.44)

31f was obtained from aryne precursor **2b** (537 mg, 1.50 mmol) and diene **29c** (304 mg, 1.00 mmol) using the same procedure described above for **31a**, as a solid (172 mg, 39%). Mp 129–131 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.56 (s, 3H), 3.77 (s, 3H), 3.87 (s, 3H), 3.95 (s, 3H), 3.97 (s, 3H), 4.04 (s, 3H), 6.88–7.00 (m, 4H), 7.25 (s, 1H), 8.46 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 52.3, 52.5, 55.8, 55.85, 55.91, 56.03, 105.4, 107.3, 110.7, 113.3, 122.5, 128.5, 129.3, 129.5, 130.1, 130.7, 136.7, 148.4, 148.5, 150.5, 151.7, 166.5, 169.9; ESIMS (*m*/*z*) 441 $[M+H]^+$, 463 $[M+Na]^+$, 479 $[M+K]^+$; IR ($CHCl_3$) ν_{max} 1722, 1621 cm^{-1}. Anal. Calcd for $C_{24}H_{24}O_8$: C, 65.45; H, 5.49. Found: C, 65.10; H, 5.73.

4-(Benzo[*d*][1,3]dioxol-5-yl)-6,7-dimethoxy-3-(methoxycarbonyl)-2-naphthoic acid (32).[29] To a stirring

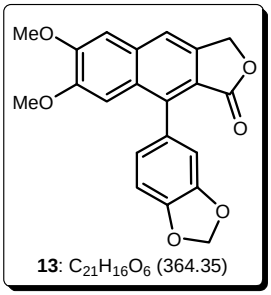


32: $C_{22}H_{18}O_8$ (410.37)

solution of diester **31e** (132 mg, 0.30 mmol) in THF (20 mL) at room temperature was added potassium trimethylsilonate (154 mg, 1.20 mmol) under argon atmosphere and the reaction mixture was stirred at room temperature for 5 h. The reaction was quenched with 2N HCl and concentrated in vacuo. The obtained residue was diluted with ethyl acetate (25 mL) and the organic layer was washed with brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using 40% ethyl acetate/petroleum ether with 0.5% acetic acid as an eluent afforded product **32** as a white solid (113 mg, 92%). Mp 251–253 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ3.67 (s, 3H), 3.81 (s, 3H), 4.04 (s, 3H), 6.05 (s, 1H), 6.09 (s, 1H), 6.80–6.94 (m, 4H), 7.26 (s, 1H), 8.53 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ52.3, 55.9, 56.1, 101.2, 105.4, 107.5, 108.2, 110.6, 122.6, 123.7, 128.4,

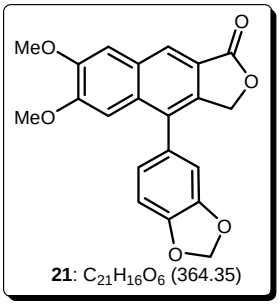
130.2, 130.3, 130.6, 131.1, 136.5, 147.3, 147.4, 150.6, 152.1, 169.6, 170.3; ESIMS (*m*/*z*) 411 $[M+H]^+$, 433 $[M+Na]^+$, 449 $[M+K]^+$; IR ($CHCl_3$) ν_{max} 1731, 1679, 1613 cm^{-1}.

9-(Benzo[*d*][1,3]dioxol-5-yl)-6,7-dimethoxynaphtho[2,3-*c*]furan-1(3*H*)-one (Justicidin B, 13).[29] To a stirring solution of acid-ester **32** (41 mg, 0.10 mmol) in THF (3 mL) at room temperature was added borane-dimethyl sulfide complex (10 M solution in dimethyl sulfide, 0.050 mL, 0.50 mmol) in a drop wise fashion under argon atmosphere and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was quenched with 3% ethanolic HCl (3 mL) and concentrated in vacuo. To the obtained residue was added ethyl acetate (25 mL) and the organic layer was washed with $NaHCO_3$, water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using 10% ethyl acetate/toluene as an eluent afforded justicidin B (**13**) as a yellow solid (28 mg, 76%). Mp 236–238 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.82 (s, 3H), 4.06 (s, 3H), 5.38 (s, 2H), 6.06 (d, *J* = 2 Hz, 1H), 6.11 (d, *J* = 2 Hz, 1H), 6.84 (dd, *J* = 8 and 2 Hz, 1H), 6.86 (d, *J* = 2 Hz, 1H), 6.98 (d, *J* = 8 Hz, 1H), 7.12 (s, 1H), 7.19 (s, 1H), 7.71 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 55.8, 56.0, 68.0, 101.2, 105.7, 106.0, 108.2, 110.5, 118.3, 118.4, 123.4, 128.2, 128.3, 128.8, 129.0, 133.1, 139.5, 139.6, 147.48, 147.51, 150.0, 151.7, 170.0; ESIMS (*m*/*z*) 365 $[M+H]^+$, 387 $[M+Na]^+$, 403 $[M+K]^+$; IR ($CHCl_3$) ν_{max} 1755, 1620 cm^{-1}.



13: $C_{21}H_{16}O_6$ (364.35)

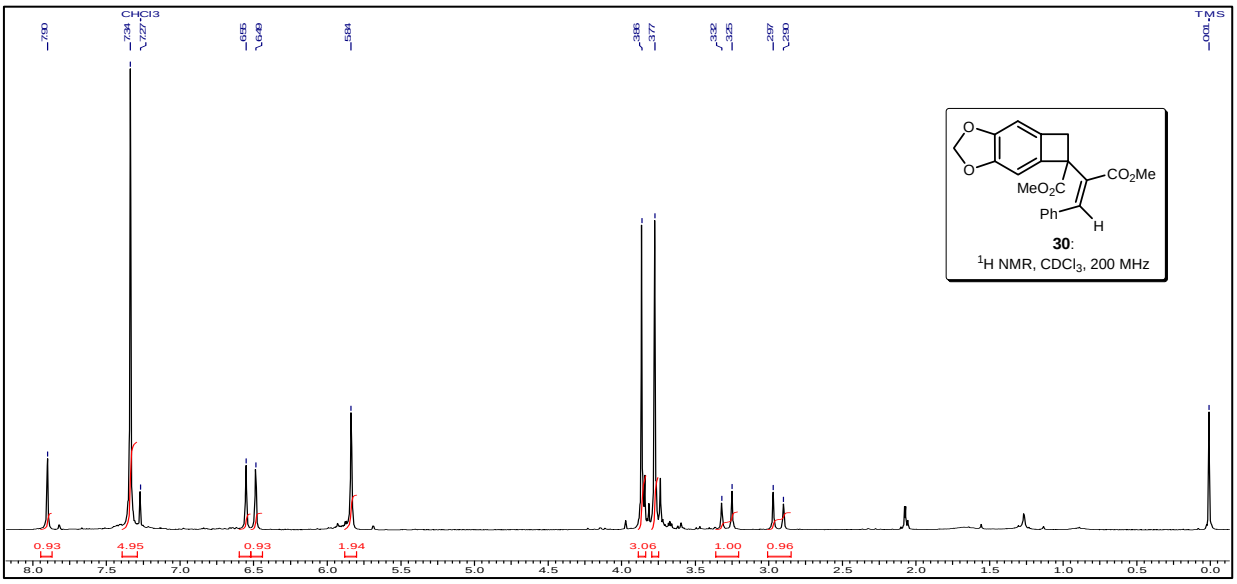
4-(Benzo[*d*][1,3]dioxol-5-yl)-6,7-dimethoxynaphtho[2,3-*c*]furan-1(3*H*)-one (Retrojusticidin B, 21).[29] To a stirring solution of acid-ester **32** (41 mg, 0.10 mmol) and NaH (32 mg, 0.80 mmol) in 1,4-dioxane (4 mL) at 0 °C was added lithium borohydride (2.0 M solution in THF, 0.30 mL, 0.60 mmol) in a drop wise fashion under argon atmosphere and the reaction mixture was refluxed with constant stirring for 28 h. The reaction mixture was allowed to attain room temperature, quenched with 2N HCl (5 mL) and concentrated in vacuo. To the obtained residue was added ethyl acetate (25 mL) and the organic layer was washed with $NaHCO_3$, water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using 10% ethyl acetate/toluene as an eluent afforded retrojusticidin B (**21**) as a white solid (24 mg, 67%) and justicidin B (**13**) as a yellow solid (10 mg, 28%). Mp 218–220 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.86 (s, 3H), 4.05 (s, 3H), 5.21 (s, 2H), 6.08 (d, *J* = 2 Hz, 1H), 6.12 (d, *J* = 2 Hz, 1H), 6.84 (dd, *J* = 8 and 2 Hz, 1H), 6.86 (d, *J* = 2 Hz, 1H), 7.00 (d, *J* = 10 Hz, 1H),



21: $C_{21}H_{16}O_6$ (364.35)

7.09 (s, 1H), 7.30 (s, 1H), 8.30 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 55.9, 56.0, 69.5, 101.4, 104.0, 107.6, 109.0, 109.5, 121.3, 122.7, 124.2, 129.7, 129.9, 131.6, 131.9, 137.9, 147.6, 148.3, 150.1, 152.0, 171.6; ESIMS (*m/z*) 365 $[M+H]^+$, 387 $[M+Na]^+$, 403 $[M+K]^+$; IR ($CHCl_3$) ν_{max} 1753, 1619 cm^{-1}.

2B.6: Selected spectra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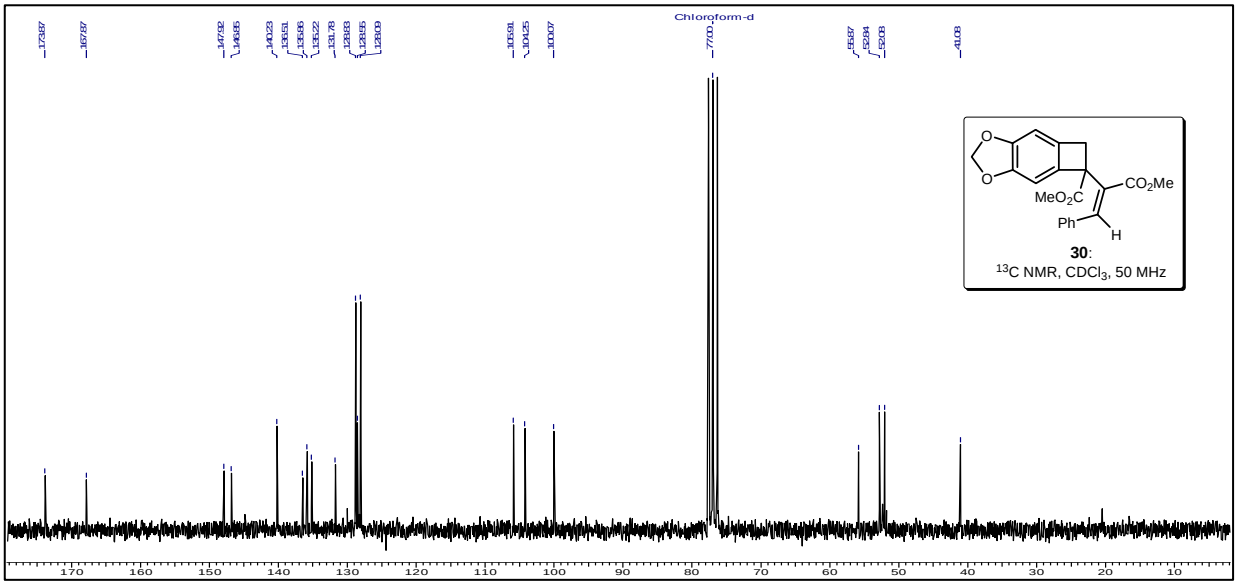
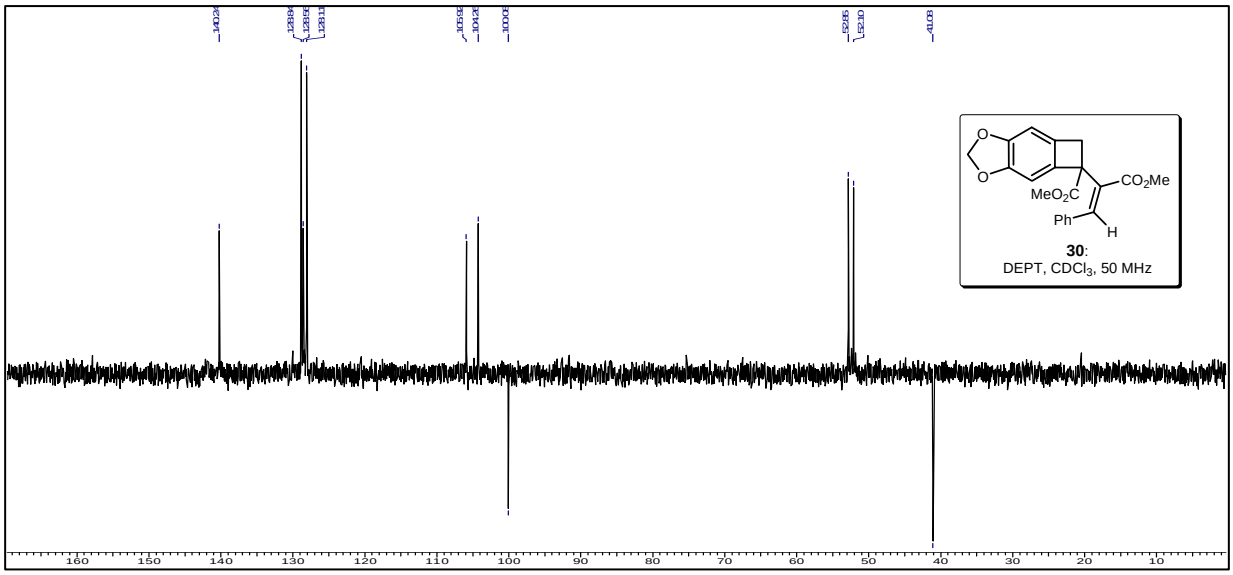
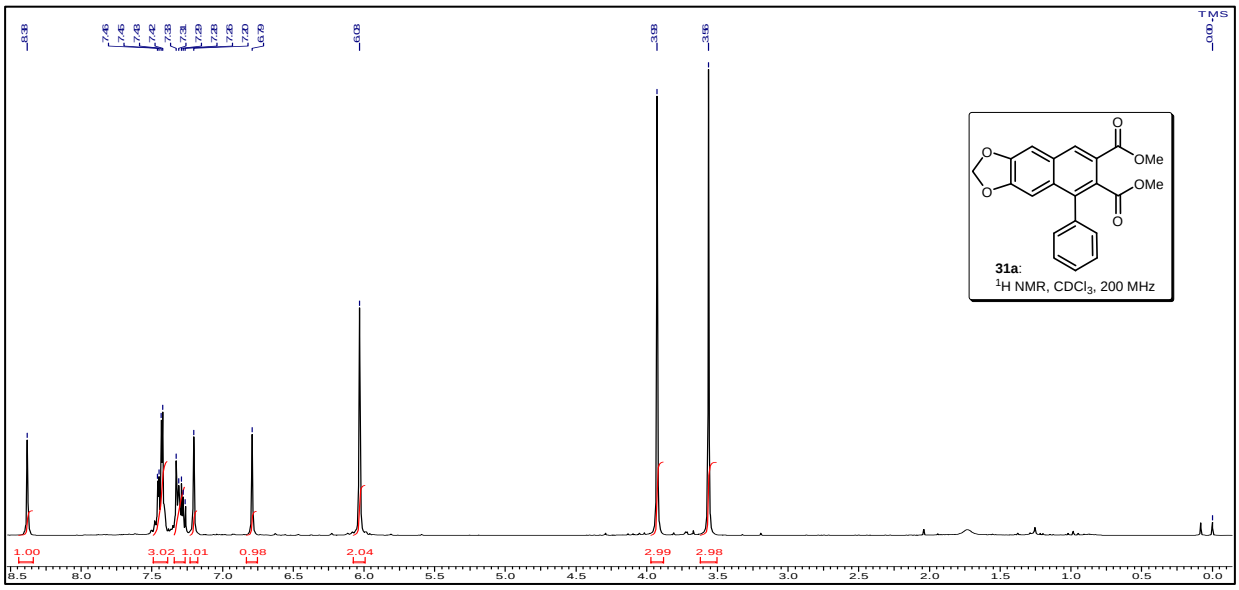
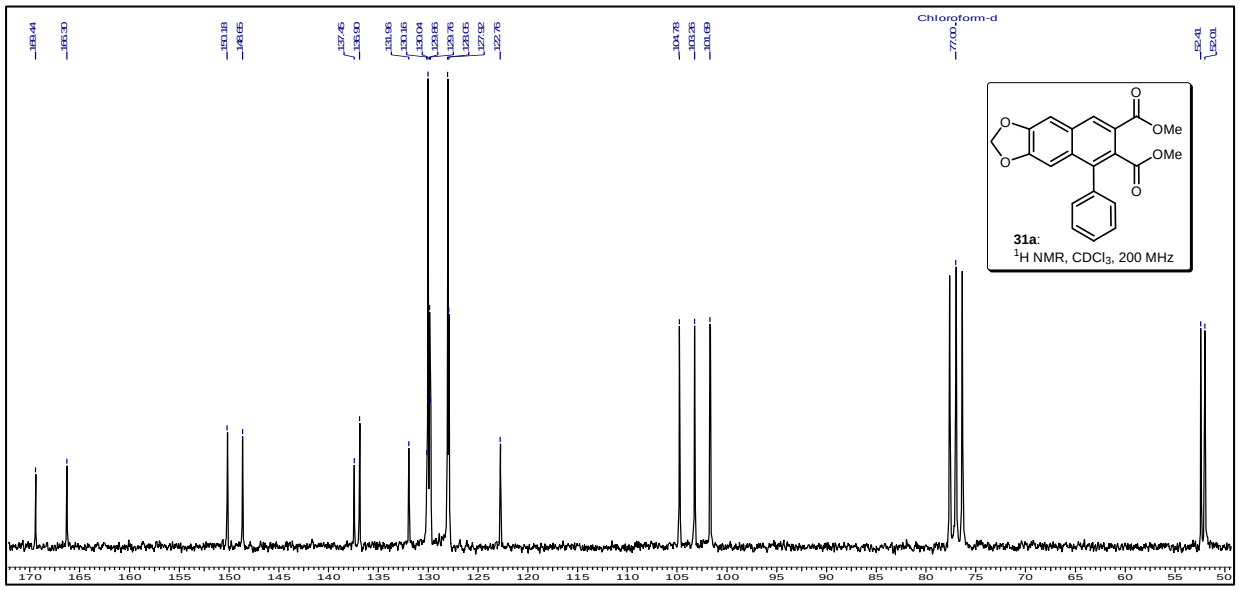
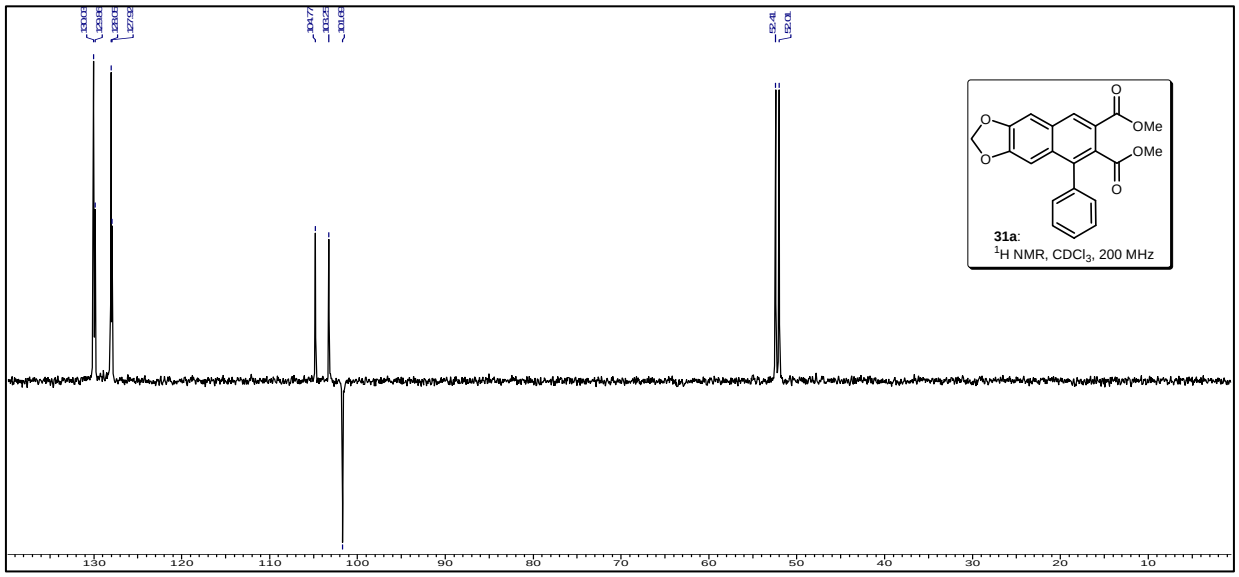
TMS
7.90
7.34
7.27
6.55
6.49
5.94
3.86
3.77
3.32
3.25
2.97
2.90
0.01
0.93
4.95
0.93
1.94
3.06
1.00
0.96
CO2Me
MeO2C
Ph
H
30:
1H NMR, CDCl3, 200 MHz

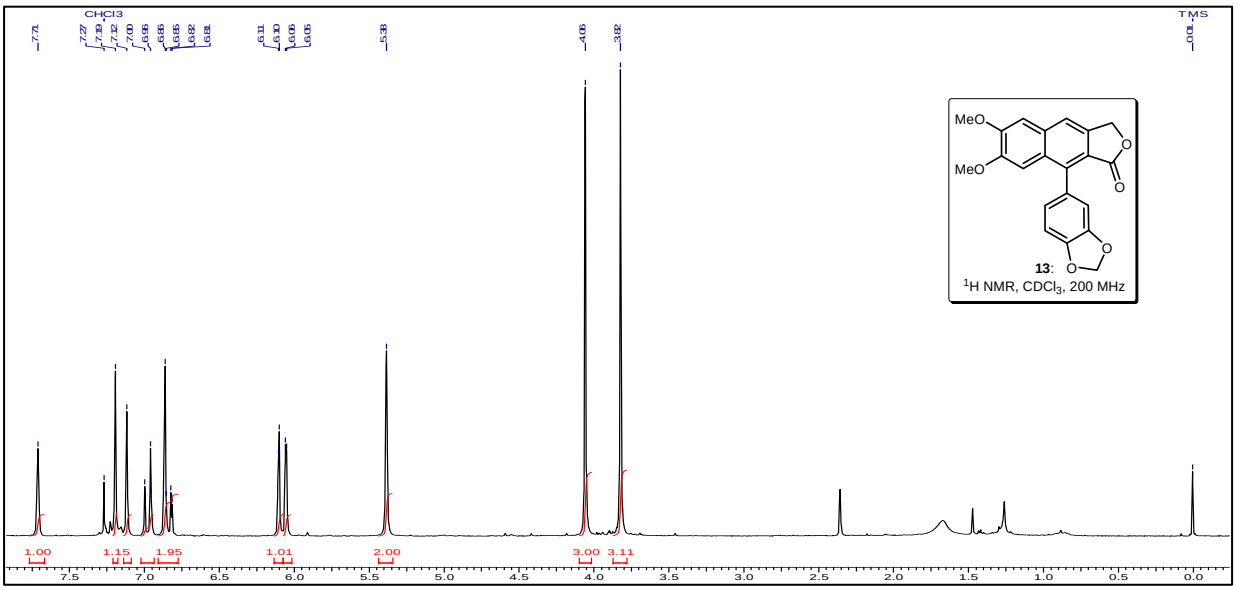

Chloroform-d
173.67
167.87
147.92
140.85
140.23
135.51
135.46
135.22
131.78
128.83
128.55
128.09
105.91
104.25
100.07
77.00
55.87
52.94
52.03
41.03
CO2Me
MeO2C
Ph
H
30:
13C NMR, CDCl3, 50 MHz

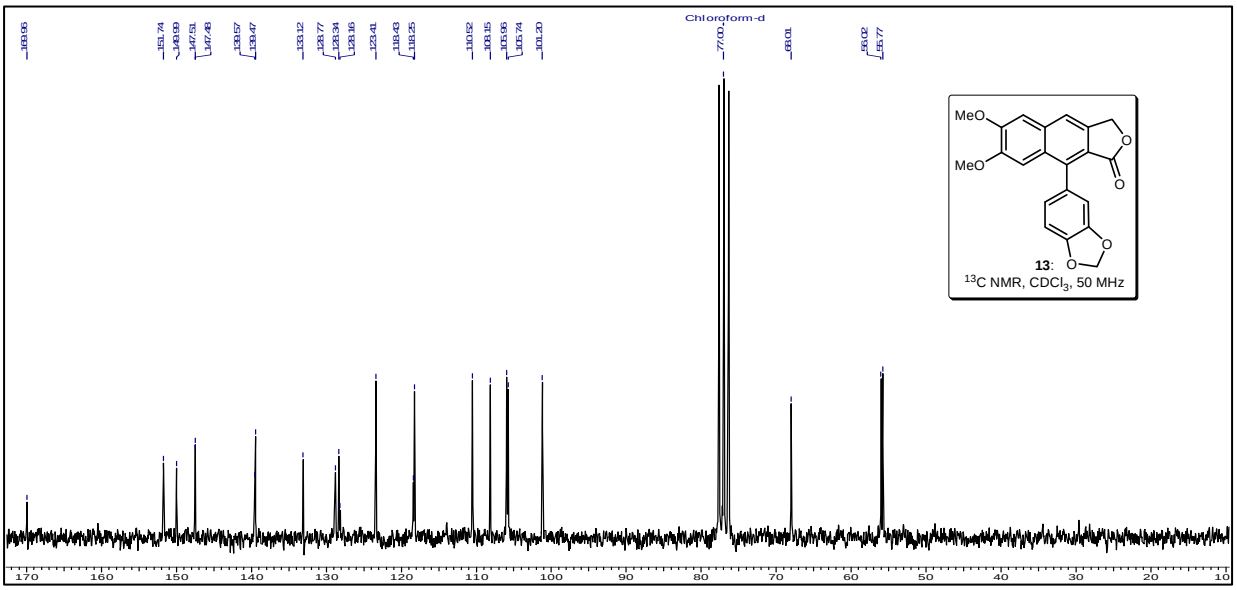

140.24
128.86
128.56
128.13
105.56
104.26
100.03
55.85
52.10
41.03
CO2Me
MeO2C
Ph
H
30:
DEPT, CDCl3, 50 MHz

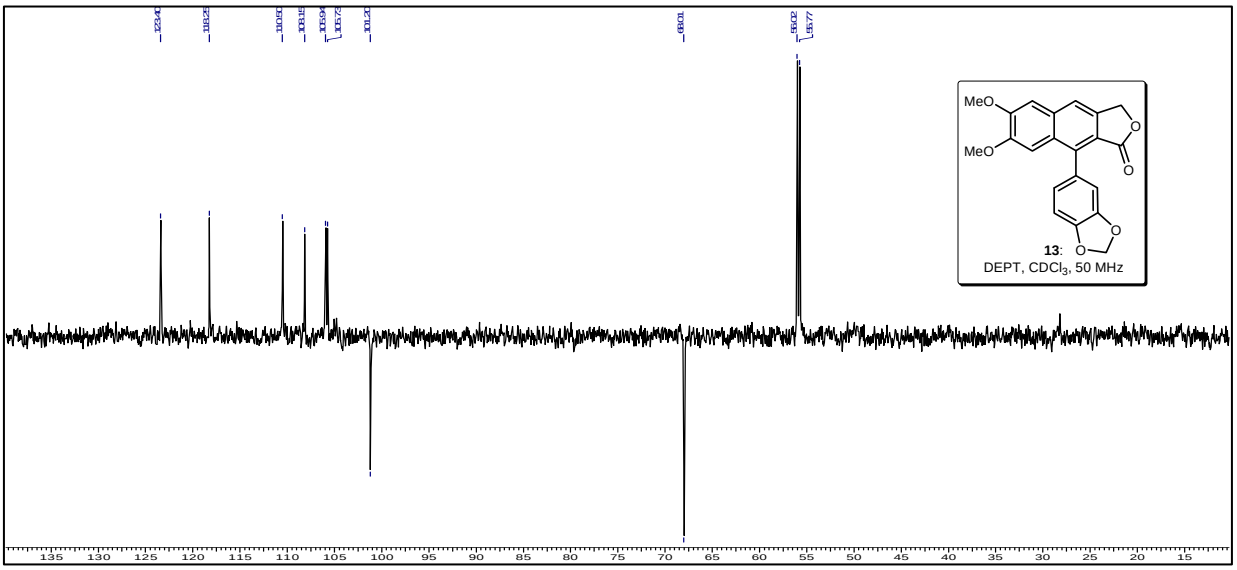

TMS
OMe
OMe
31a:
1H NMR, CDCl3, 200 MHz

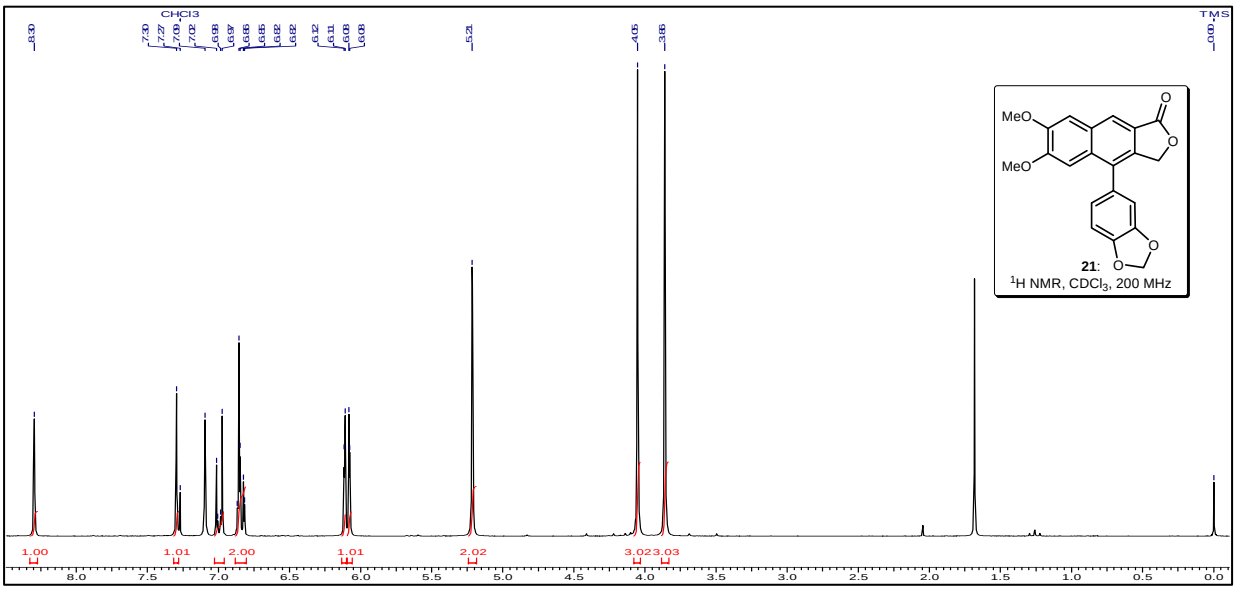

Chloroform-d
OMe
OMe
31a:
1H NMR, CDCl3, 200 MHz

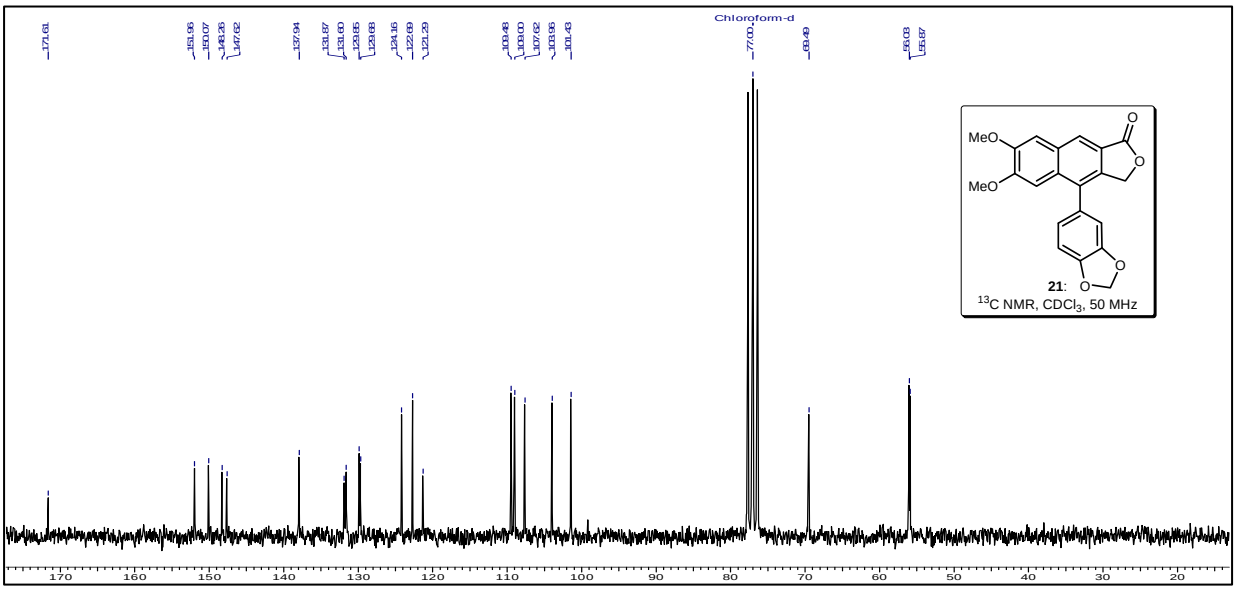

OMe
OMe
31a:
1H NMR, CDCl3, 200 MHz

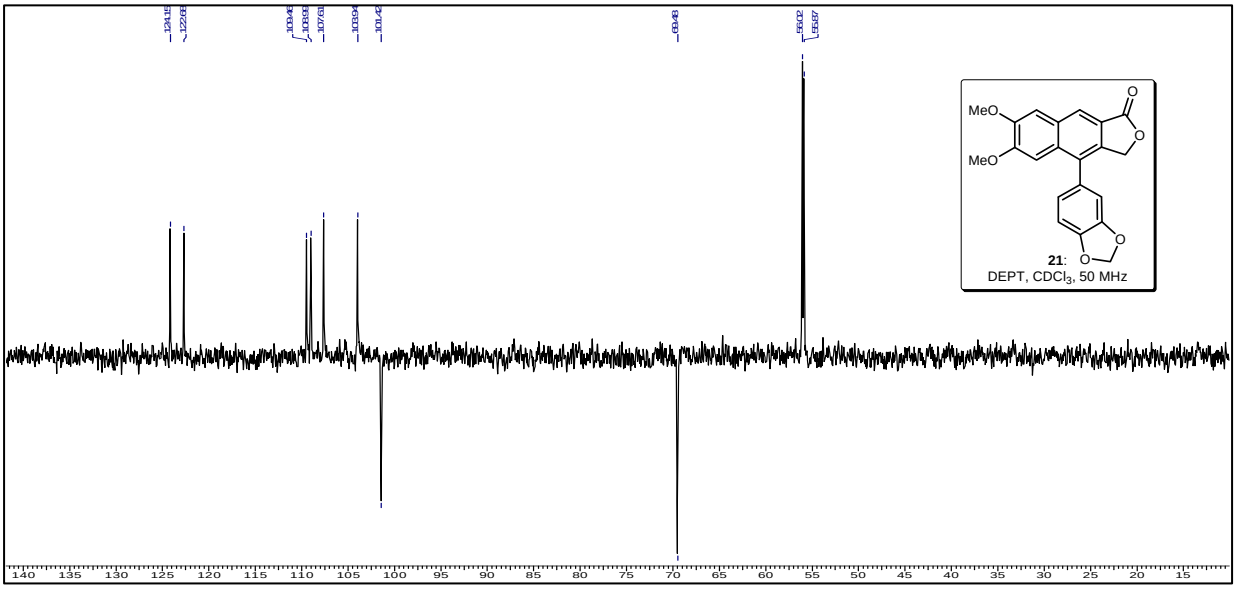

CHCl3
TMS
MeO
MeO
O
O
O
O
13:
1H NMR, CDCl3, 200 MHz


Chloroform-d
MeO
MeO
O
O
O
O
13:
13C NMR, CDCl3, 50 MHz


MeO
MeO
O
O
O
O
13:
DEPT, CDCl3, 50 MHz


CHCl3
TMS
MeO
MeO
O
21:
1H NMR, CDCl3, 200 MHz


Chloroform-d
MeO
MeO
O
21:
13C NMR, CDCl3, 50 MHz


MeO
MeO
O
21:
DEPT, CDCl3, 50 MHz

2B.7: References

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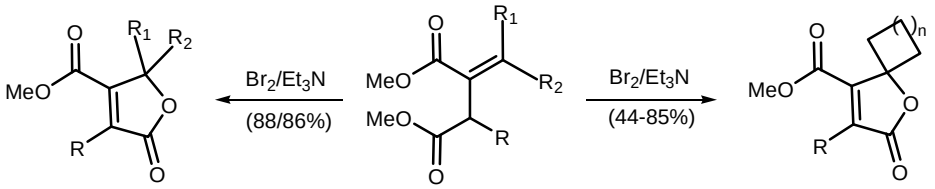
Chapter 3

Novel Carbon–Oxygen Bond Forming Reactions with the Dialkyl Alkylidenesuccinates: Synthesis of Bioactive Natural and Unnatural Butenolides

This chapter features the following topics:

Note: *An independent figure, table, scheme, structure and reference numbers have been used for the each section.*

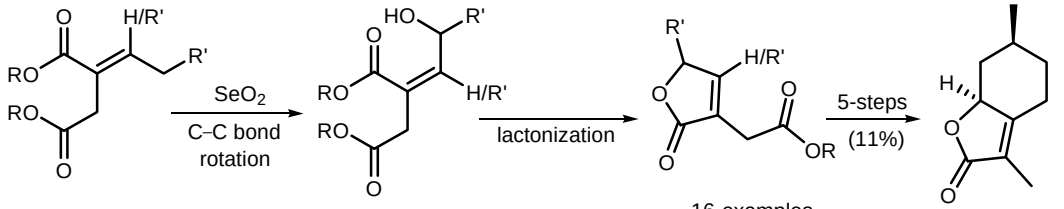
Section 3A: *Bromine induced facile synthesis of butenolides and spirobutenolides from sterically congested tetrasubstituted dialkyl alkylidenesuccinates*



R = H, Me, -CH_2CO_2Me; $R_1 = R_2$ =Me; R_1 = Me, R_2 = -$CH_2CH(Me)_2$; R_1/R_2 =-$CH_2(CH_2)_nCH_2$- (n = 1-4)

Starting from sterically congested tetrasubstituted dialkyl alkylidenesuccinates, facile general approach to several dialkyl substituted butenolides and spirobutenolides with the generation of quaternary carbon centre has been demonstrated via bromine induced dealkylative regioselective intramolecular cyclization and dehydrobromination pathway. The mechanistic aspects involved in the formation of butenolides have been also described in brief.

Section 3B. *Regio- and stereoselective selenium dioxide allylic oxidation of dialkyl alkylidenesuccinates to (Z)-allylic alcohols: Synthesis of natural and unnatural butenolides and fused butenolides*



R = Me/Et, R' = alkyl/-$(CH_2)_n$-

16-examples
(42-76%)

(±)-mintlactone

The first SeO_2 induced (*Z*)-selective allylic alcohol formation of dialkyl alkylidenesuccinates has been demonstrated to accomplish one-step syntheses of several essential butenolides and fused butenolides via an unusual *E*- to *Z*- carbon–carbon double bond isomerisation followed by the lactonization pathway. The present protocol has been successfully extended for the synthesis of a mucocin precursor and the diastereoselective total synthesis of the natural product (±)-isomintlactone and its first time conversion to (±)-mintlactone. We have also successfully altered the regioselectivity in lactonization with the ring expansion of γ-lactone to δ-lactone and provided the new approach to chromenone skeletons.

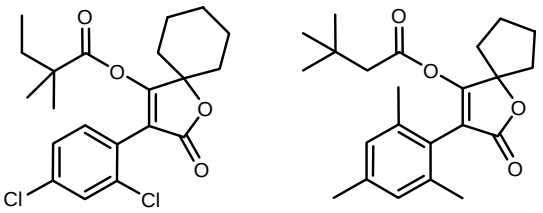
Chapter 3A

Bromine Induced Facile Synthesis of Butenolides and Spirobutenolides from Sterically Congested Tetrasubstituted Dialkyl Alkylidenesuccinates

This section A of chapter 3 features the following topics:

3A.1: Background

Butenolides and spirobutenolides, class of α,β-unsaturated lactones, are substances produced by organisms such as bacteria, fungi and gorgonians[1] and are prevalent structural motifs in more than 13000 natural products. Natural and unnatural butenolides and spirobutenolides are important class of compounds that find major applications in organic, medicinal and polymer chemistry. A broad range of biological properties has been conferred on them that include strong antibiotic, antihelmitic, antifungal, antitumor, antiviral, anti-inflammatory, cytostatic, antiallergenic and anti-HIV activities,[2] which make them interesting lead structures for new drugs. For examples, nonsteroidal anti-inflammatory drug Rofecoxib and promising cytostatic agent, the dimethylamino adduct of arglabin.[3] The spirobutenolides are of particular biological relevance and are present in a variety of pharmacologically relevant natural products, such as chlorotricolide,[4] hydnuferruginine,[5] andirolactone,[6] spirofragilide[7] and lambertellol A.[8] Moreover, the two important pesticides spirodiclofen (**1**) and spiromesifen (**2**) used to keep a control on severe crop damaging pests (*Tetranychus urticae*, *Panonychus ulmi* and *Bemisia tabaci*), also possess spirobutenolide skeletons (Figure 1).[9]

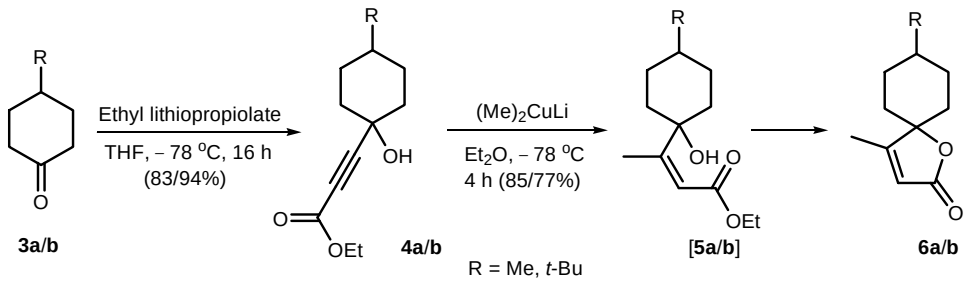


Spirodiclofen (**1**) Spiromesifen (**2**)

Figure 1. Pesticidal spirobutenolides of commercial interest

Basically, the diverse range of γ-butenolide skeletons has been designed by employing new carbon−oxygen bond construction reactions and metal-catalyzed carbon−carbon bond formations. A very large number of such butenolides and spirobutenolides have been synthesized during the past century using several elegant synthetic strategies.[10] Methods for the construction of such type of building blocks with a quaternary carbon centre are of special interest to organic chemists due to their presence in natural products.[4-8,11] They have been synthesized by using metal catalyzed carbonylation, metal catalyzed arylation, ring closing metathesis, oxidative cyclization and photocyclization methodologies.[11,12] Although, many synthetic strategies of spirobutenolides have been reported in the literature, we have summarized only some of the recent approaches below.

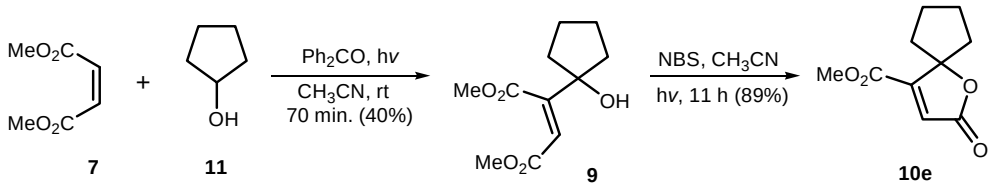
Caine et al.[13] have reported synthesis of spirobutenolides **6a**/**b** via addition of ethyl lithiopropiolate to cycloketones **3a**/**b** followed by Michael type stereoselective addition reaction of



Scheme 1. Synthesis of spirobutenolides via addition of ethyl lithiopropiolate

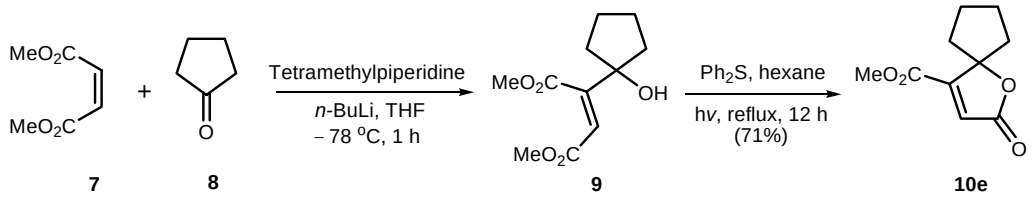
dimethyllithiumcuprate to alkynes **4a**/**b** and an in situ lactonization pathway in 71/72% yield over 2-steps (Scheme 1).

Harrowen et al.[12f,g] have reported a method of condensing dimethyl maleate (**7**) and cyclopentanone (**8**) using lithium amide as a base, followed by isomerization of maleate ester **9** to fumarate ester involving the radical-polar crossover sequence via addition and elimination of thiyl radical and an in situ lactonization pathway to synthesize spirobutenolide **10e** in 71% yield (Scheme 2).



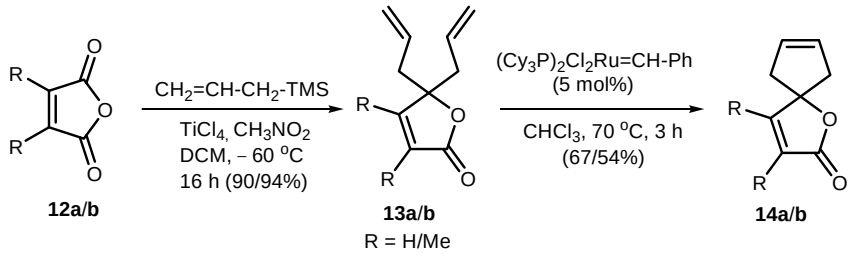
Scheme 2. Synthesis spirobutenolides via thiyl radical induced isomerization

Recently, Geraghty et al.[12q] have reported the photomediated generation of α-hydroxyalkyl radical from cyclopentanol (**11**) and its subsequent carbon–carbon bond forming reaction with dimethyl maleate (**7**) followed by NBS induced radical isomerization of maleate ester **9** to fumarate ester and an in situ lactonization, which furnished the spirobutenolide **10e** in 36% yield over 2-steps (Scheme 3).



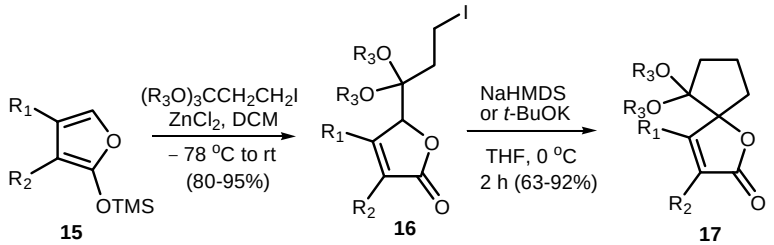
Scheme 3. Synthesis spirobutenolide via photomediated generation of α-hydroxyalkyl radical

Michaut et al.[14] have reported synthesis of spirobutenolides **14a**/**b** via $TiCl_4$ promoted double allylation reaction of cyclic anhydrides **12a**/**b** with allyltrimethylsilane followed by the ring closing metathesis in 60/51% yield over 2-steps (Scheme 4).



Scheme 4. Synthesis spirobutenolides via allylation-RCM sequence

Marko et al.[15] have reported synthesis of spirobutenolides **17** via $ZnCl_2$ catalyzed condensation of *ortho*-esters with 2-(trimethylsilyloxy)furan derivatives **15**, followed by base-mediated spiroannulation reaction with the 50-87% yields over 2-steps (Scheme 5).



Scheme 5. Synthesis spirobutenolides using 2-(trimethylsilyloxy)furan as a dianion equivalent

Natural and unnatural spirobutenolides are important class of compounds owing to their widespread biological activities and the development of new potential routes by employing novel carbon−oxygen bond construction reactions is still a challenging task of current interest. Earlier two Ph. D. dissertations from our group described details about the chemistry of butenolides,[16] hence to avoid repetition a concise introduction has been presented here. In chapter 1B, we have discussed in detail the diverse applications of dimethyl/diethyl 2-alkylidenesuccinates for the synthesis of natural and unnatural products. In this section, as a part of present dissertation, we have developed bromine induced facile synthesis of butenolides and spirobutenolides from sterically congested tetrasubstituted dimethyl/diethyl 2-alkylidenesuccinates.[17]

3A.2: Results and discussion

In continuation of our studies on cyclic anhydrides to bioactive natural and unnatural products,[18] we recently synthesized the tetrasubstituted dialkyl alkylidenesuccinates and systematically studied their bromination reactions. Our preliminary studies on halogenation of dimethyl 2-(propan-2-ylidene)succinate (**19a**) revealed the formation of methyl 2,2-dimethyl-5-oxo-2,5-dihydrofuran-3-carboxylate (**10a**) as the product, instead of the corresponding expected dihalo-compound. We

prepared a systematic plan to completely explore our observed fact with a perspective to develop a new general route to γ-butenolides (Table 1).

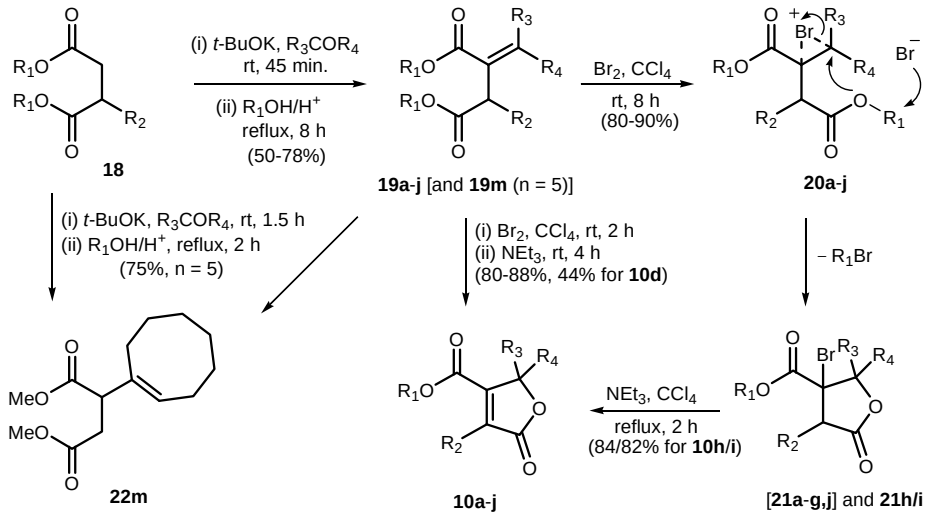
The base catalyzed Stobbe condensation of dimethyl succinate with acetone, isobutyl methyl ketone, cyclobutanone, cyclopentanone, cyclohexanone, 4-*tert*-butylcyclohexanone, cycloheptanone, α-tetralone and benzophenone, followed by esterification of the formed intermediate mono-esters,[19] respectively furnished the corresponding desired starting materials, the dimethyl alkylidenesuccinates **19a**, **19c**-**g** and **19j**-**l** in 50-78% yields.[20] Similarly, the condensation of diethyl succinate with acetone, condensation of dimethyl methylsuccinate with cyclohexanone and condensation of trimethyl propane-1,2,3-tricarboxylate with cyclohexanone, respectively furnished the required starting materials **19b**, **19h** and **19i** in 52-69% yields. In our hands, the Stobbe condensation of dimethyl succinate with cyclooctanone directly furnished the product **22m**[20c] via the expected intermediate **19m**. We feel that, herein the selective exocylic to endocyclic carbon−carbon double bond migration is notable, as the double bond in the intermediate **19m** does not get in conjugation with the two ester functionalities to form the corresponding dimethyl cyclooctylfumarate.

On having all these potential starting materials **19a**-**l** in hand, we studied their reactions with bromine to obtain the desired butenolides. The reactions of dialkyl alkylidenesuccinates **19a**-**c** with bromine in CCl_4 at room temperature directly furnished the corresponding butenolides **10a**-**c** in 82-84% yields. During our these studies, we noticed that the addition of triethylamine after 8 h reaction time provides the desired products with slight improvement in yields (86-88%).

As expected, the substrates **19d**-**j**, obtained by using cyclic ketones, on sequential treatment with bromine in CCl_4 and triethylamine gave the expected spirobutenolide products **10d**-**j** in 82-85% yields, except for **10d**. In the case of conversion of **19d** to **10d**, though we got the expected product, the yield was only 44% while the remaining was decomposed material, probably originated by an in situ cleavage of the cyclobutane ring during the course of reaction. As expected, in the bromination reaction of **19g**, we got an inseparable, nearly 1:1 mixture of diastereomers of **10g**. The substrates **19k** and **19l**, wherein the tetrasubstituted carbon−carbon double bonds are in conjugation with the aromatic ring, remained unreacted in our hands in the presence of bromine/triethylamine, under the standard reaction conditions and we were unable to obtain products **10k** and **10l**. The analytical and spectral data obtained for all the γ-butenolides were in complete agreement with the assigned structures. In the ^1H NMR spectra of **10a**-**g** and **10j**, the characteristic vinylic proton singlet appeared at δ 6.57 (ca).

In an attempt to study the mechanistic aspects involved in the conversion of compounds **19a**-**j** to **10a**-**j**, we noticed that the methine proton in the compound **21h** is not easily accessible to the base at room temperature for the last dehydrobromination process. Hence, we could successfully isolate the

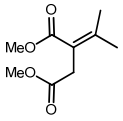
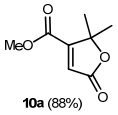
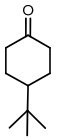
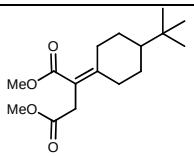
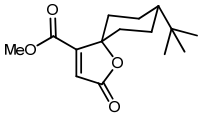
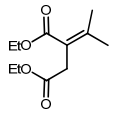
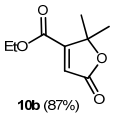
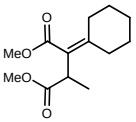
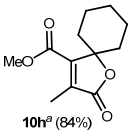
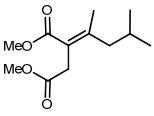
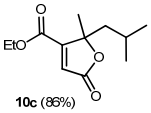
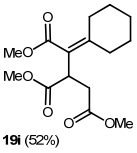
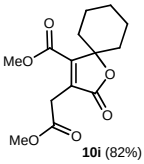
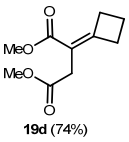
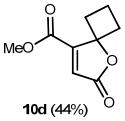
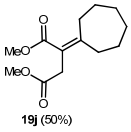
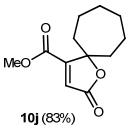
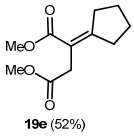
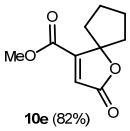
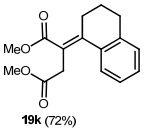
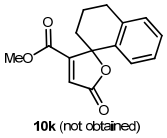
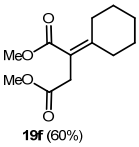
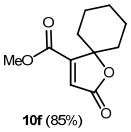
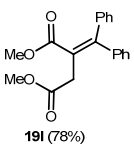
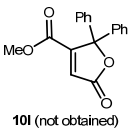
Table 1. Synthesis of butenolides and spirobutenolides via the bromination of tetrasubstituted C=C bonds



18 — 19a-j [and 19m (n = 5)] — 20a-j

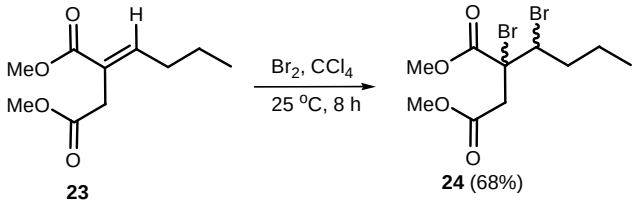
22m — 10a-j — [21a-g,j] and 21h/i

R_1 = Me/Et; R_2 = H, Me, CH_2CO_2Me; $R_3 = R_4$ = dialkyl, $CH_2(CH_2)_nCH_2$ (n =1-5)

No.	Ketones	Succinates	Butenolides	No.	Ketones	Succinates	Butenolides
1		 **19a** (69%)	 **10a** (88%)	7		 **19g** (56%)	 **10g** (84%)
2		 **19b** (69%)	 **10b** (87%)	8		 **19h** (53%)	 **10h**[a] (84%)
3		 **19c** (62%)	 **10c** (86%)	9		 **19i** (52%)	 **10i** (82%)
4		 **19d** (74%)	 **10d** (44%)	10		 **19j** (50%)	 **10j** (83%)
5		 **19e** (52%)	 **10e** (82%)	11		 **19k** (72%)	 **10k** (not obtained)
6		 **19f** (60%)	 **10f** (85%)	12		 **19l** (78%)	 **10l** (not obtained)

[a] Possesses antifungal and C1 esterase inhibitor activities.[21]

corresponding intermediate saturated bromolactone **21h** in 84% yield. The isolated intermediate **21h**, in the presence of triethylamine as the base, under reflux conditions gave the desired product **10h** in quantitative yield. Based on the isolated intermediate **21h**, we surmise that during the course of the bromination reaction, the bromonium ion intermediates **20a**-**j**, as depicted in table 1, are formed. In the proposed intermediates **20a**-**j**, the bulkier bromide anion is unable to approach the quaternary carbons to form the expected dibromides. Hence the lone pair on the relatively smaller oxygen atom, intramolecularly and regioselectively, attacks the bromonium-bridge to form the γ-lactone. The simultaneous bromide anion induced dealkylation takes place to cancel the positive charge on an oxygen atom to form the intermediate products **21a**-**j**, which on concomitant dehydrobromination yield the target compounds **10a**-**j**. The corresponding substrate **23**[22] with a trisubstituted carbon−carbon double bond, upon bromination, exclusively gave the corresponding dibromo compound **24** in 68% yield, while it remained unreacted with iodine (Scheme 6); these results directly support both our proposed strategy and described mechanistic pathway.



Scheme 6. Bromination of trisubstituted carbon−carbon double bond

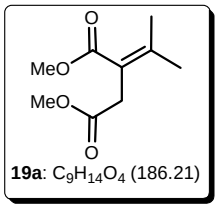
3A.3: Summary

In the present section, we have described a simple and efficient general approach to gem-dialkyl substituted quaternary butenolides by taking advantage of bromine stimulated structural rearrangement of sterically congested tetrasubstituted dimethyl/diethyl 2-alkylidenesuccinates*. The mechanistic aspects involved in the formation of butenolides and spirobutenolides via bromine induced dealkylative regioselective intramolecular cyclization and dehydrobromination pathway have been also studied. The present an in situ dealkylative intramolecular cyclization process involved in our approach along with the formation of novel carbon−oxygen bond, is noteworthy. We strongly believe that the present approach will be useful to design several desired bioactive natural and unnatural butenolides and spirobutenolides.*

3A.4: Experimental section

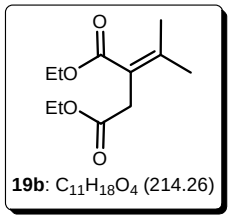
Commercially available dimethyl succinate, diethyl succinate, dimethyl methylsuccinate, trimethyl propane-1,2,3-tricaboxylate, isopropyl methyl ketone, cyclobutanone, cyclopentanone, cyclohexanone, *tert*-butylcyclohexanone, cycloheptanone, cyclooctanone, *α*-tetralone, benzophenone and potassium *tert*-butoxide were used.

Dimethyl 2-(propan-2-ylidene)succinate (19a). To a stirred solution of *t*-BuOK (1.22 g, 10.0 mmol) in *t*-BuOH (10 mL) was added a solution of dimethyl succinate (1.46 g, 10.0 mmol) in *t*-BuOH (5 mL) in a dropwise fashion under argon atmosphere with constant stirring. After stirring the reaction mixture for 10 min, a solution of acetone (696 mg, 12.0 mmol) in *t*-BuOH (5 mL) was added dropwise under argon atmosphere and the reaction mixture was stirred for 45 minutes at 25 ^{o}C. The reaction mixture was concentrated in vacuo. The obtained residue was dissolved in water (50 mL) and the aqueous layer was washed with ethyl acetate (20 mL x 2). The aqueous layer was acidified to pH 2 using 2 N HCl (20 mL). The acidified aqueous layer was extracted with ethyl acetate (20 mL x 3), washed with water, brine and dried over Na_2SO_4. The organic layer was concentrated in vacuo and the dried residue was dissolved in MeOH (30 mL). To the above solution was added concentrated H_2SO_4 (1 mL) and it was refluxed for 8 h with constant stirring. The reaction mixture was allowed to reach 25 ^{o}C and concentrated in vacuo. The obtained residue was dissolved in ethyl acetate (50 mL) and the organic layer was washed with 5% aqueous solution of $NaHCO_3$, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using 10% ethyl acetate/petroleum ether as an eluent afforded pure product **19a** as a thick oil[20] (1.28 g, 69%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.86 (s, 3H), 2.14 (s, 3H), 3.38 (s, 2H), 3.67 (s, 3H), 3.71 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 23.2 (2 carbons), 35.1, 51.4, 51.8, 120.2, 149.8, 168.2, 171.8. IR (neat) ν_{max} 1728, 1642 cm^{-1}. Anal. Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 58.16; H, 7.71.



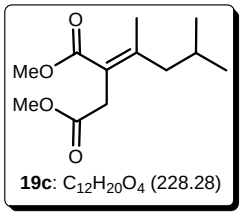
19a: $C_9H_{14}O_4$ (186.21)

Diethyl 2-(propan-2-ylidene)succinate (19b). It was obtained from diethyl succinate (1.74 g, 10.0 mmol) and acetone (696 mg, 12.0 mmol) using the same procedure described above for **19a**, as a thick oil[19] (1.48 g, 69%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.24 (t, *J* = 7 Hz, 3H), 1.27 (t, *J* = 7 Hz, 3H), 1.86 (s, 3H), 2.14 (s, 3H), 3.36 (s, 2H), 4.13 (q, *J* = 7 Hz, 2H), 4.18 (q, *J* = 7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.2, 23.2, 23.3, 35.5, 60.2, 60.7, 120.7, 148.9, 167.9, 171.5; IR (neat) ν_{max} 1738, 1719, 1642 cm^{-1}.



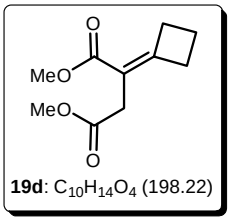
19b: $C_{11}H_{18}O_4$ (214.26)

(*E*)-Dimethyl 2-(4-methylpentan-2-ylidene)succinate (19c). It was obtained from dimethyl succinate (1.46 g, 10.0 mmol) and 4-methyl-2-pentanone (1.20 g, 12.0 mmol) using the same procedure described above for **19a**, as a thick oil (1.41 g, 62%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.90 (d, *J* = 6 Hz, 6H), 1.75−2.00 (m, 1H), 2.07 (d, *J* = 8 Hz, 2H), 2.10 (s, 3H), 3.41 (s, 2H), 3.67 (s, 3H), 3.72 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.7, 22.5, 27.2, 35.1, 45.6, 51.4, 51.9, 121.2, 152.0, 168.4, 172.0; IR ($CHCl_3$) ν_{max} 1743, 1720, 1630 cm^{-1}. Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.14; H, 8.83. Found: C, 62.81; H, 8.51.



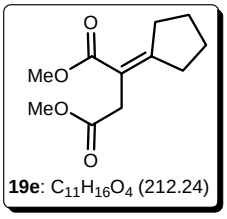
19c: $C_{12}H_{20}O_4$ (228.28)

Dimethyl 2-cyclobutylidenesuccinate (19d). It was obtained from dimethyl succinate (1.46 g, 10.0 mmol) and cyclobutanone (840 mg, 12.0 mmol) using the same procedure described above for **19a**, as a thick oil (1.47 g, 74%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.06 (quintet, *J* = 8 Hz, 2H), 2.82 (t, *J* = 8 Hz, 2H), 3.15 (s, 2H), 3.15 (t, *J* = 8 Hz, 2H), 3.69 (s, 3H), 3.71 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 16.4, 30.9, 32.9, 33.7, 51.3, 51.9, 117.3, 164.2, 167.0, 171.8; IR ($CHCl_3$) ν_{max} 1737, 1710, 1680 cm^{-1}. Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.40; H, 7.30.



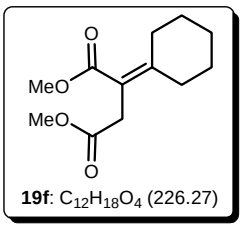
19d: $C_{10}H_{14}O_4$ (198.22)

Dimethyl 2-cyclopentylidenesuccinate (19e). It was prepared from dimethyl succinate (1.46 g, 10.0 mmol) and cyclopentanone (1.10 g, 12.0 mmol) using the same procedure described above for **19a**, as a thick oil[20] (1.10 g, 52%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.60-1.82 (m, 4H), 2.40 (t, *J* = 6 Hz, 2H), 2.82 (t, *J* = 6 Hz, 2H), 3.35 (s, 2H), 3.68 (s, 3H), 3.72 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 25.5, 26.9, 34.2, 34.5, 35.8, 51.3, 51.9, 116.6, 165.3, 167.5, 172.0; IR ($CHCl_3$) ν_{max} 1736, 1693, 1643 cm^{-1}. Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.35; H, 7.98.



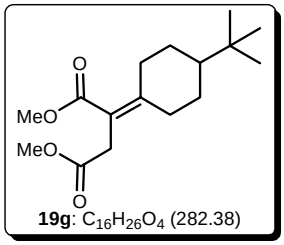
19e: $C_{11}H_{16}O_4$ (212.24)

Dimethyl 2-cyclohexylidenesuccinate (19f). It was obtained from dimethyl succinate (1.46 g, 10.0 mmol) and cyclohexanone (1.18 g, 12.0 mmol) using the same procedure described above for **19a**, as a thick oil[20] (1.36 g, 60%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.52−1.72 (m, 6H), 2.18−2.28 (m, 2H), 2.58−2.68 (m, 2H), 3.39 (s, 2H), 3.68 (s, 3H), 3.73 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 26.2, 27.9, 28.1, 32.3, 32.4, 34.6, 51.4, 51.8, 117.2, 155.2, 168.8, 171.8; IR ($CHCl_3$) ν_{max} 1742, 1710, 1635 cm^{-1}. Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.59; H, 7.72.



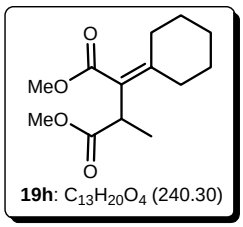
19f: $C_{12}H_{18}O_4$ (226.27)

Dimethyl 2-(4-*tert*-butylcyclohexylidene)succinate (19g). It was obtained from dimethyl succinate (1.46 g, 10.0 mmol) and 4-*tert*-butylcyclohexanone (1.85 g, 12.0 mmol) using the same procedure described above for **19a**, as a thick oil (1.58 g, 56%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.85 (s, 9H), 1.05−1.35 (m, 4H), 1.80−2.05 (m, 4H), 2.55−2.68 (m, 1H), 3.40 (s, 2H), 3.68 (s, 3H), 3.73 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 27.5, 28.4, 28.7, 32.0, 32.2, 32.4, 34.7, 47.7, 51.5, 51.9, 117.0, 155.4, 168.9, 171.9; IR ($CHCl_3$) ν_{max} 1741, 1705, 1652 cm^{-1}.



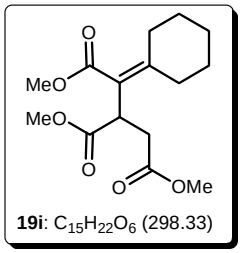
19g: $C_{16}H_{26}O_4$ (282.38)

Dimethyl 2-cyclohexylidene-3-methylsuccinate (19h). It was obtained from dimethyl 2-methylsuccinate (1.60 g, 10.0 mmol) and cyclohexanone (1.18 g, 12.0 mmol) using the same procedure described above for **19a**, as a thick oil (1.27 g, 53%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.32 (d, *J* = 8 Hz, 3H), 1.50−1.75 (m, 6H), 2.24 (t, *J* = 6 Hz, 2H), 2.30−2.60 (m, 2H), 3.64 (q, *J* = 8 Hz, 1H), 3.67 (s, 3H), 3.70 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 16.4, 26.4, 28.0, 28.2, 31.6, 32.9, 39.6, 51.3, 52.0, 124.7, 150.0, 169.0, 174.5; IR ($CHCl_3$) ν_{max} 1743, 1726, 1632 cm^{-1}. Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 64.64; H, 8.70.



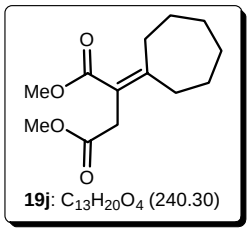
19h: $C_{13}H_{20}O_4$ (240.30)

Trimethyl 1-cyclohexylidenepropane-1,2,3-tricarboxylate (19i). It was obtained from trimethyl propane-1,2,3-tricaboxylate (2.18 g, 10.0 mmol) and cyclohexanone (1.18 g, 12.0 mmol) using the same procedure described above for **19a**, as a thick oil (1.55 g, 52%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.50−1.75 (m, 6H), 2.24−2.35 (m, 2H), 2.36 (dd, *J* = 17 and 6 Hz, 1H), 2.44−2.55 (m, 2H), 3.09 (dd, *J* = 17 and 8 Hz, 1H), 3.67 (s, 3H), 3.68 (s, 3H), 3.69 (s, 3H), 4.17 (dd, *J* = 9 and 6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 26.3, 28.0, 28.2, 31.9, 32.9, 35.8, 41.3, 51.4, 51.8, 52.2, 122.2, 152.8, 168.3, 172.3, 172.9; IR ($CHCl_3$) ν_{max} 1740, 1630 cm^{-1}. Anal. Calcd for $C_{15}H_{22}O_6$: C, 60.39; H, 7.43. Found: C, 60.25; H, 7.76.



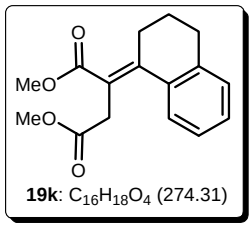
19i: $C_{15}H_{22}O_6$ (298.33)

Dimethyl 2-cycloheptylidenesuccinate (19j). It was obtained from dimethyl succinate (1.46 g, 10.0 mmol) and cycloheptanone (1.34 g, 12.0 mmol) using the same procedure described above for **19a**, as a thick oil (1.20 g, 50%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.40−1.80 (m, 8H), 2.36 (t, *J* = 6 Hz, 2H), 2.71 (t, *J* = 6 Hz, 2H), 3.38 (s, 2H), 3.67 (s, 3H), 3.71 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 26.2, 27.2, 28.5 (2 carbons), 33.7, 34.0, 34.8, 51.4, 51.9, 120.1, 158.2, 168.4, 172.0; IR ($CHCl_3$) ν_{max} 1741, 1717, 1652 cm^{-1}. Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 64.60; H, 7.90.



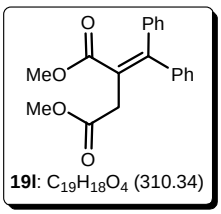
19j: $C_{13}H_{20}O_4$ (240.30)

(*E*)-Dimethyl 2-(3,4-dihydronapthalen-1(*2H*)-ylidene)succinate (19k). It was obtained from dimethyl succinate (1.46 g, 10.0 mmol) and α-tetralone (1.75 g, 12.0 mmol) using the same procedure described above for **19a**, as a thick oil (1.97 g, 72%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.85 (quintet, J = 6 Hz, 2H), 2.56 (t, J = 6 Hz, 2H), 2.75 (t, J = 6 Hz, 2H), 3.56 (s, 2H + 3H), 3.71 (s, 3H), 7.05−7.25 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 22.2, 28.7, 29.5, 36.2, 51.7, 52.1, 120.9, 125.1, 127.8, 128.0, 128.5, 135.4, 139.8, 145.2, 171.1, 171.3; IR ($CHCl_3$) ν_{max} 1740, 1707, 1619 cm^{-1}.



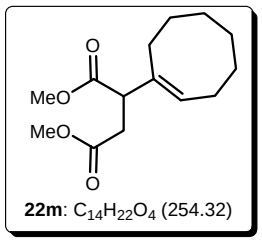
19k: $C_{16}H_{18}O_4$ (274.31)

Dimethyl 2-(diphenylmethylene)succinate (19l). It was obtained from dimethyl succinate (1.46 g, 10.0 mmol) and benzophenone (2.18 g, 12.0 mmol) using the same procedure described above for **19a**, as a solid (2.42 g, 78%). Mp 82−84 °C [lit.[20] 78−80 °C]; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.47 (s, 2H + 3H), 3.70 (s, 3H), 7.05−7.20 (m, 4H), 7.20−7.40 (m, 6H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 37.9, 51.5, 51.9, 124.5, 127.8 (2 carbons), 128.2, 128.3, 128.5, 128.9, 140.3, 141.7, 151.7, 169.8, 171.5; IR ($CHCl_3$) ν_{max} 1739, 1712, 1620 cm^{-1}. Anal. Calcd for $C_{19}H_{18}O_4$: C, 73.53; H, 5.85. Found: C, 73.70; H, 5.52.



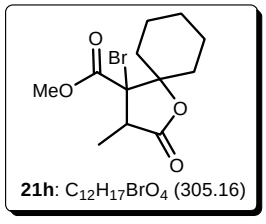
19l: $C_{19}H_{18}O_4$ (310.34)

(*E*)-Dimethyl 2-cyclooct-1-enylsuccinate (22m). It was obtained from dimethyl succinate (1.46 g, 10.0 mmol) and cyclooctanone (1.51 g, 12.0 mmol) using the same procedure described above for **19a**, as a thick oil[20] (1.91 g, 75%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.45 (br s, 8H), 2.00−2.30 (m, 4H), 2.49 (dd, J = 17 and 6 Hz, 1H), 2.96 (dd, J = 16 and 10 Hz, 1H), 3.51 (dd, J = 11 and 4 Hz, 1H), 3.67 (s, 3H), 3.69 (s, 3H), 5.58 (t, J = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 26.0, 26.2, 26.3, 27.8, 29.0, 29.4, 35.6, 48.7, 51.8, 52.0, 128.8, 136.5, 172.5, 173.8; IR ($CHCl_3$) ν_{max} 1739, 1654 cm^{-1}.



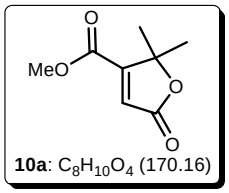
22m: $C_{14}H_{22}O_4$ (254.32)

Methyl 10-bromo-9-methyl-8-oxo-7-oxaspiro[5,4]decane-10-carboxylate (21h). It was obtained from **19h** (480 mg, 2.00 mmol) using the same procedure described below for **10a**, but in absence of triethylamine, as a thick oil (513 mg, 84%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.31 (d, J = 6 Hz, 3H), 1.50−1.80 (m, 8H), 1.80−1.95 (m, 1H), 2.04 (dd, J = 13 and 6 Hz, 1H), 3.25 (q, J = 6 Hz, 1H), 3.81 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 8.9, 22.0, 22.2, 24.7, 31.1, 34.9, 47.2, 53.6, 71.5, 86.8, 167.0, 173.4; IR ($CHCl_3$) ν_{max} 1790, 1756 cm^{-1}.



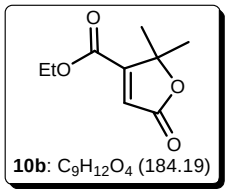
21h: $C_{12}H_{17}BrO_4$ (305.16)

Methyl 2,2-dimethyl-5-oxo-2,5-dihydrofuran-3-carboxylate (10a). To a stirred solution of **19a** (372 mg, 2.00 mmol) in CCl_4 (25 mL) was added a solution of Br_2 (480 mg, 3.00 mmol) in CCl_4 (5 mL) in a drop wise fashion and it was stirred for 8 h at 25 ^oC. Then, Et_3N (303 mg, 3.00 mmol) was added dropwise to the reaction mixture and it was further stirred for 2 h at 25 ^oC. The reaction mixture was concentrated in vacuo. The obtained residue was dissolved in ethyl acetate (50 mL), washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using 10% ethyl acetate/petroleum ether as an eluent afforded pure product **10a**, as a thick oil[12q] (299 mg, 88%). ^1H NMR ($CDCl_3$, 200 MHz) δ 1.63 (s, 6H), 3.88 (s, 3H), 6.58 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 25.1, 52.6, 87.2, 126.1, 160.9, 161.2, 169.8; IR ($CHCl_3$) ν_{max} 1764, 1730, 1633 cm^{-1}.



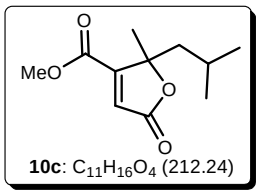
10a: $C_8H_{10}O_4$ (170.16)

Ethyl 2,2-dimethyl-5-oxo-2,5-dihydrofuran-3-carboxylate (10b). It was obtained from **19b** (428 mg, 2.00 mmol) using the same procedure described above for **10a**, as a thick oil (320 mg, 87%). ^1H NMR ($CDCl_3$, 200 MHz) δ 1.36 (t, J = 8 Hz, 3H), 1.62 (s, 6H), 4.33 (q, J = 8 Hz, 2H), 6.57 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.0, 25.1, 62.0, 87.2, 125.9, 160.8, 161.3, 169.9; IR ($CHCl_3$) ν_{max} 1770, 1725, 1633 cm^{-1}. Anal. Calcd for $C_9H_{12}O_4$: C, 58.69; H, 6.57. Found: C, 58.73; H, 6.49.



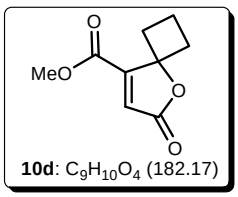
10b: $C_9H_{12}O_4$ (184.19)

Methyl 2-isobutyl-2-methyl-5-oxo-2,5-dihydrofuran-3-carboxylate (10c). It was obtained from **19c** (456 mg, 2.00 mmol) using the same procedure described above for **10a**, as a thick oil (365 mg, 86%). ^1H NMR ($CDCl_3$, 200 MHz) δ 0.87 (d, J = 10 Hz, 3H), 0.90 (d, J = 10 Hz, 3H), 1.55 (septet, J = 8 Hz, 1H), 1.61 (s, 3H), 1.84 (dd, J = 14 and 6 Hz, 1H), 1.98 (dd, J = 14 and 6 Hz, 1H), 3.89 (s, 3H), 6.62 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 23.7, 24.0, 24.1, 25.0, 45.5, 52.6, 89.7, 126.8, 160.3, 161.4, 170.1; IR (neat) ν_{max} 1767, 1731, 1633 cm^{-1}. Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.33; H, 7.40.



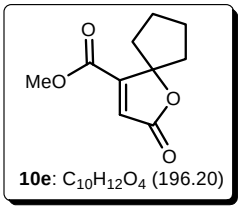
10c: $C_{11}H_{16}O_4$ (212.24)

Methyl 6-oxo-5-oxaspiro[3,4]oct-7-ene-8-carboxylate (10d). It was obtained from **19d** (198 mg, 1.00 mmol) using the same procedure described above for **10a**, as a thick oil[12q] (80 mg, 44%). ^1H NMR ($CDCl_3$, 500 MHz) δ 2.13 (quintet, J = 10 Hz, 2H), 2.55−2.65 (m, 2H), 2.77−2.85 (m, 2H), 3.94 (s, 3H), 6.55 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.3, 31.8 (2 carbons), 52.7, 89.0, 125.9, 157.5, 161.6, 169.8; IR ($CHCl_3$) ν_{max} 1761, 1726, 1630 cm^{-1}. Anal. Calcd for $C_9H_{10}O_4$: C, 59.34; H, 5.53. Found: C, 59.59; H, 5.70.



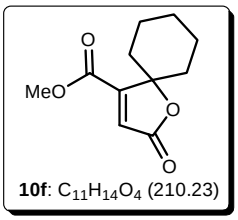
10d: $C_9H_{10}O_4$ (182.17)

Methyl 7-oxo-6-oxaspiro[4,4]non-8-ene-9-carboxylate (10e). It was obtained from **19e** (424 mg, 2.00 mmol) using the same procedure described above for **10a**, as a thick oil[12q] (322 mg, 82%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.75−2.10 (m, 6H), 2.20−2.45 (m, 2H), 3.88 (s, 3H), 6.62 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 25.2, 37.0, 52.6, 97.1, 126.8, 158.2, 161.4, 170.1; IR ($CHCl_3$) ν_{max} 1767, 1730, 1630 cm^{-1}. Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.22; H, 6.16. Found: C, 61.27; H, 6.04.



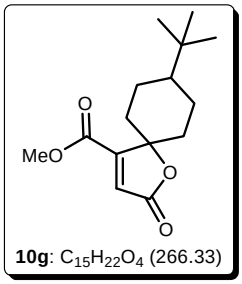
10e: $C_{10}H_{12}O_4$ (196.20)

Methyl 8-oxo-7-oxaspiro[5,4]dec-9-ene-10-carboxylate (10f). It was obtained from **19f** (452 mg, 2.00 mmol) using the same procedure described above for **10a**, as a white solid (357 mg, 85%). Mp 94−96 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.20−1.45 (m, 1H), 1.45−1.85 (m, 7H), 2.05−2.25 (m, 2H), 3.88 (s, 3H), 6.60 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.9, 24.2, 33.5, 52.6, 89.1, 126.3, 161.0, 161.4, 170.1; IR ($CHCl_3$) ν_{max} 1761, 1732, 1628 cm^{-1}. Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.85; H, 6.71. Found: C, 63.03; H, 6.88.



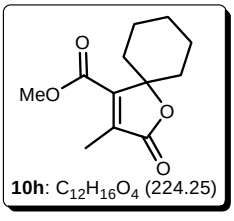
10f: $C_{11}H_{14}O_4$ (210.23)

Methyl 3-*tert*-butyl-8-oxo-7-oxaspiro[5,4]dec-9-ene-10-carboxylate (10g, 1:1-mixture of diastereomers). It was obtained from **19g** (564 mg, 2.00 mmol) using the same procedure described above for **10a**, as a yellow solid (447 mg, 84%). Mp 86−88 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.88 (s, 9H), 0.99 (s, 9H), 1.00−1.90 (m, 14H), 2.03−2.30 (m, 4H), 3.87 (s, 6H), 6.48 (s, 1H), 6.59 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.8, 23.0, 27.4, 27.7, 32.4, 32.8, 33.0, 34.1, 43.0, 46.2, 52.6, 52.7, 89.0, 89.8, 125.4, 126.5, 161.0, 161.4, 161.8, 162.5, 170.1, 170.3; IR ($CHCl_3$) ν_{max} 1767, 1731, 1629 cm^{-1}.



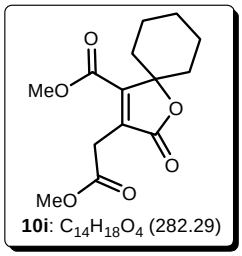
10g: $C_{15}H_{22}O_4$ (266.33)

Methyl 9-methyl-8-oxo-7-oxaspiro[5,4]dec-9-ene-10-carboxylate (10h). It was obtained from **19h** (480 mg, 2.00 mmol) using the same procedure described above for **10a**; herein, after addition of triethylamine, the reaction mixture was refluxed for two hours time to obtain **10h**, as a white solid (376 mg, 84%). Mp 92−94 °C [lit.[21] 94 °C]; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.15−1.37 (m, 1H), 1.38−1.55 (m, 2H), 1.60−1.85 (m, 5H), 2.05−2.25 (m, 2H), 2.16 (s, 3H), 3.88 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 11.3, 22.1, 24.3, 33.7, 52.2, 87.8, 136.5, 151.8, 162.9, 172.2; IR ($CHCl_3$) ν_{max} 1760, 1723, 1660 cm^{-1}. Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.33; H, 7.08.



10h: $C_{12}H_{16}O_4$ (224.25)

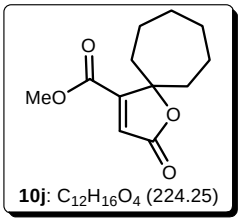
Dimethyl 8-oxo-7-oxaspiro[5,4]dec-9-ene-9-methylene-10-dicarboxylate (10i). It was obtained from



10i: $C_{14}H_{18}O_4$ (282.29)

19i (596 mg, 2.00 mmol) using the same procedure described above for **10a**; herein, after addition of triethylamine, the reaction mixture was refluxed for two hours time to obtain **10i**, as a white solid (463 mg, 82%). Mp 104−106 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.15−1.40 (m, 1H), 1.45−1.90 (m, 7H), 2.05−2.30 (m, 2H), 3.69 (s, 2H), 3.71 (s, 3H), 3.87 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 22.1, 24.3, 30.6, 33.6, 52.4, 52.5, 88.4, 132.9, 154.7, 162.1, 169.0, 171.0; IR ($CHCl_3$) ν_{max} 1762, 1748, 1728, 1664 cm^{-1}. Anal. Calcd for $C_{14}H_{18}O_6$: C, 59.57; H, 6.43. Found: C, 59.70; H, 6.35.

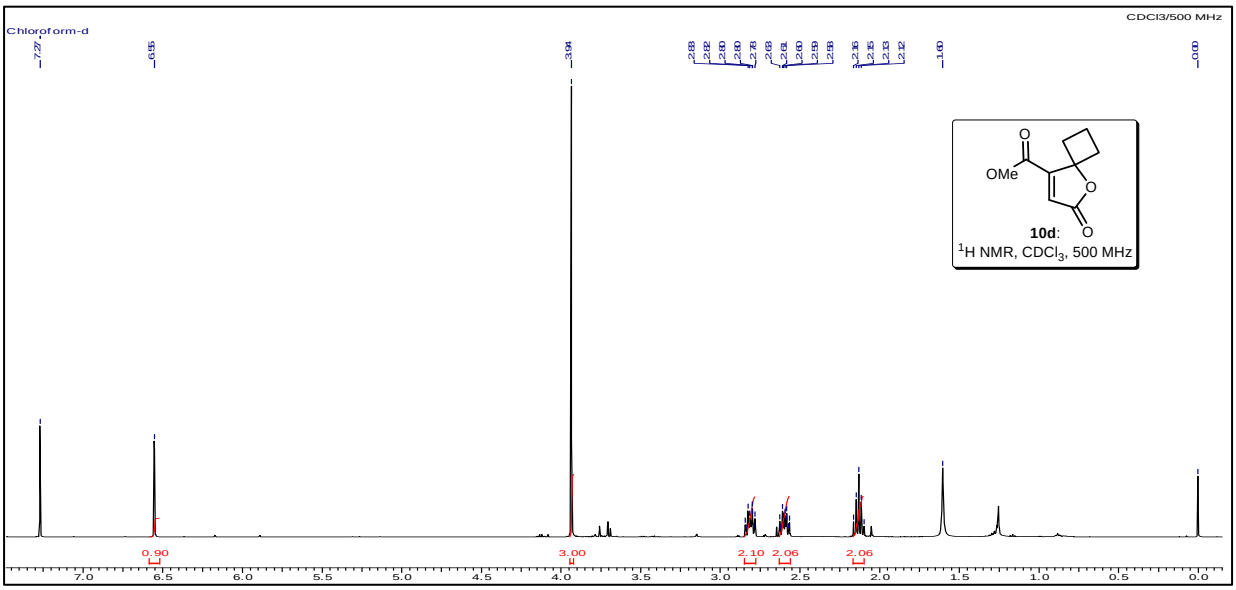
Methyl 9-oxo-8-oxaspiro[6,4]undec-10-ene-11-carboxylate (10j). It was obtained from **19j** (480 mg,

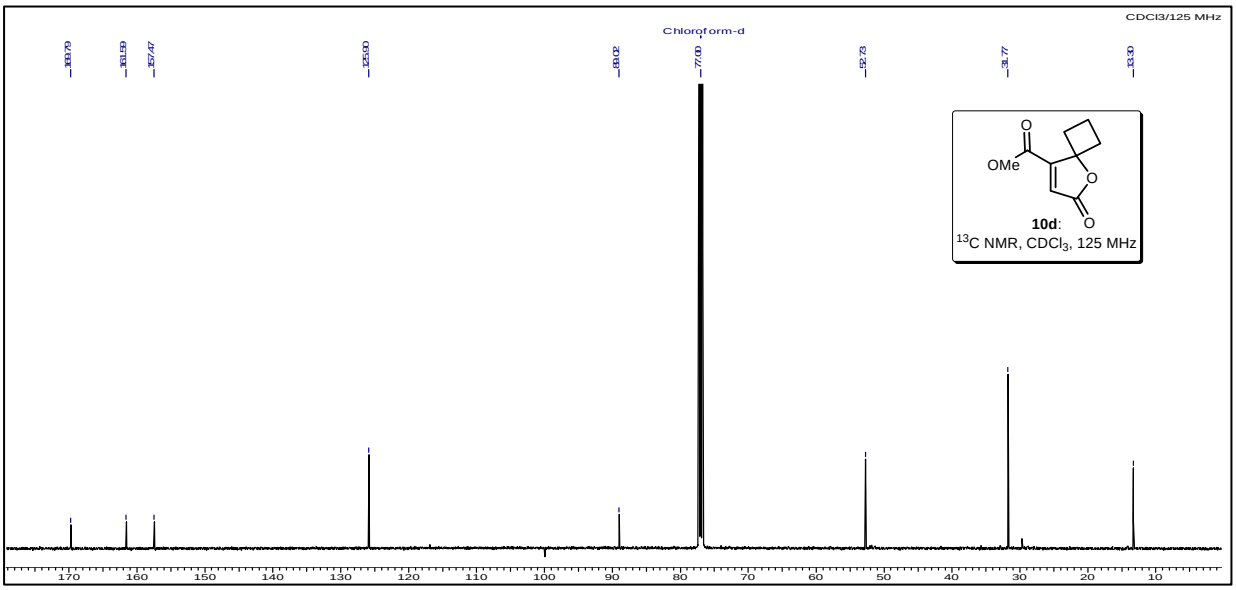


10j: $C_{12}H_{16}O_4$ (224.25)

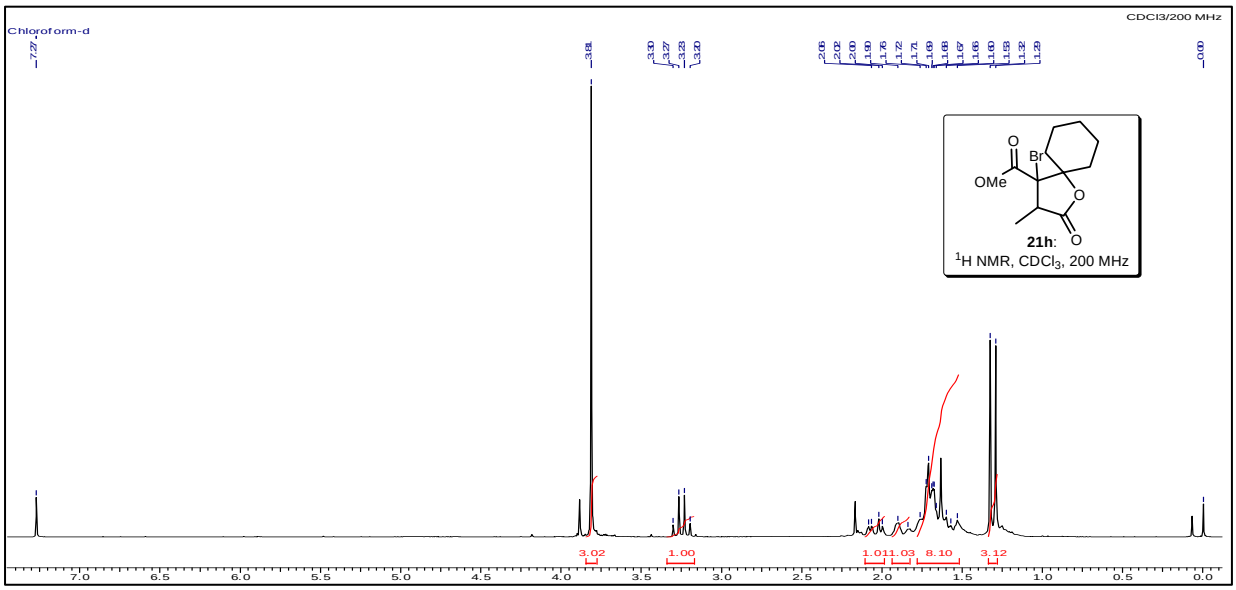
2.00 mmol) using the same procedure described above for **10a**, as a white solid (372 mg, 83%). Mp 70−72 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.50−2.00 (m, 10H), 2.10-2.33 (m, 2H), 3.87 (s, 3H), 6.51 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 22.9, 28.1, 37.3, 52.6, 92.4, 125.0, 161.6, 162.3, 170.5; IR ($CHCl_3$) ν_{max} 1767, 1732, 1634 cm^{-1}. Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.43; H, 7.28.

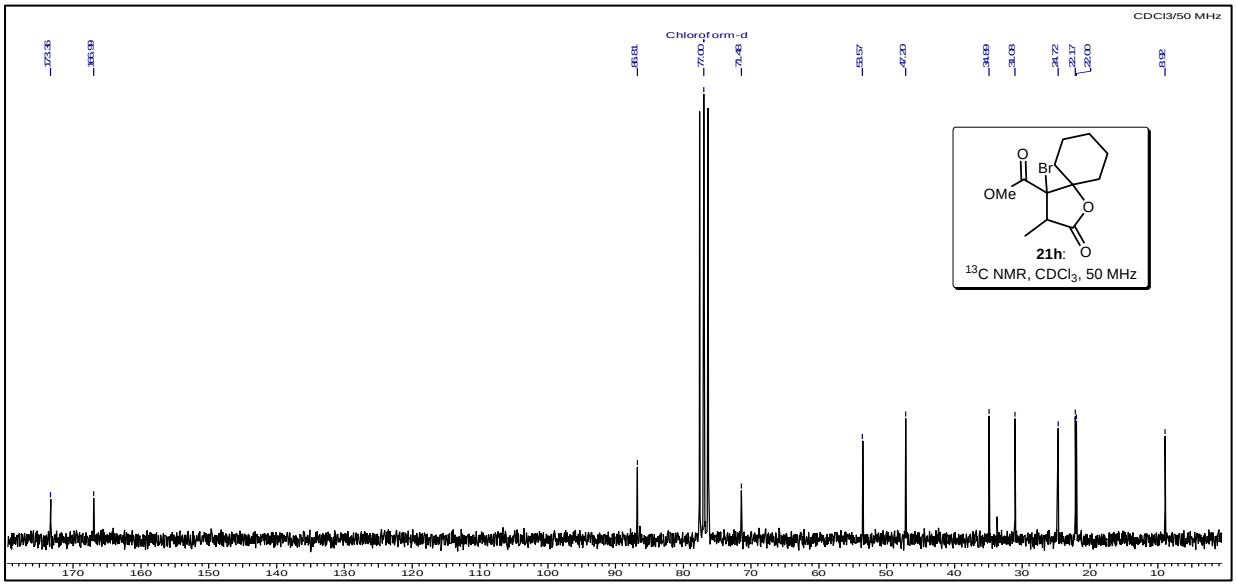
3A.5: Selected spectra

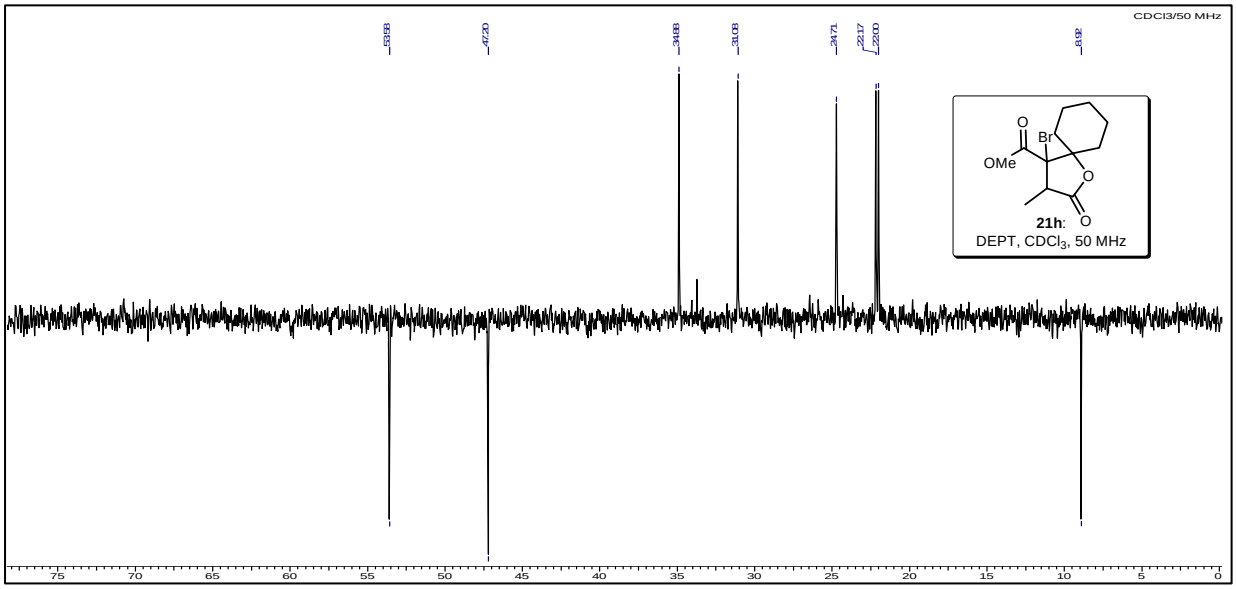

CDCl3/500 MHz
Chloroform-d
OMe
10d:
1H NMR, CDCl3, 500 MHz

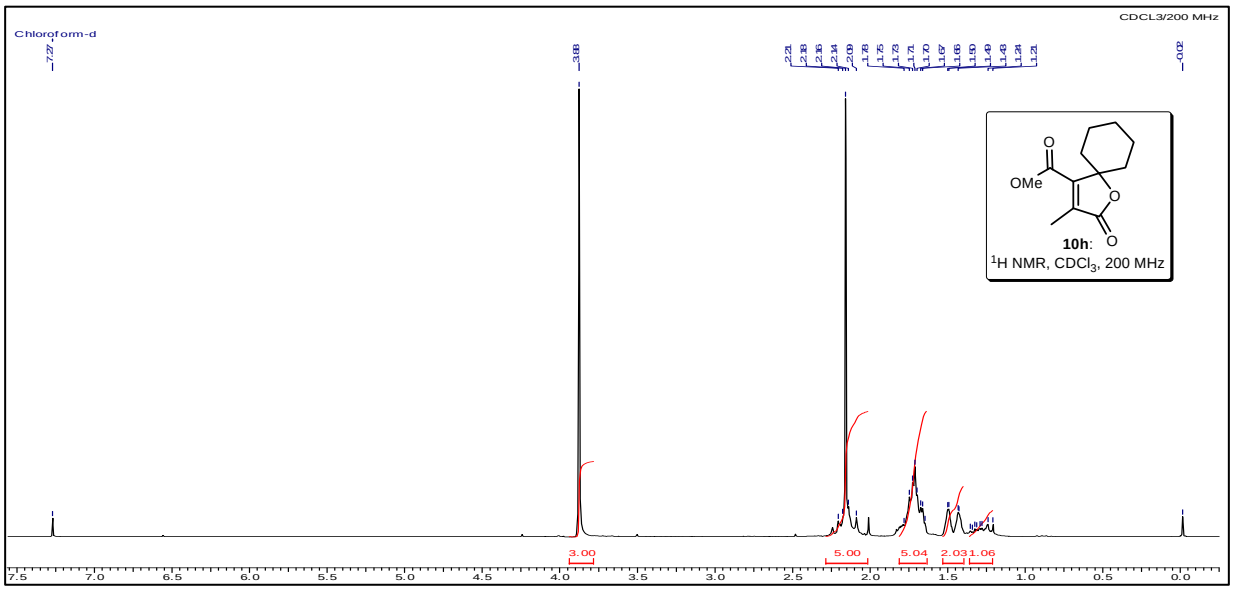

CDCl3/125 MHz
Chloroform-d
OMe
10d:
13C NMR, CDCl3, 125 MHz

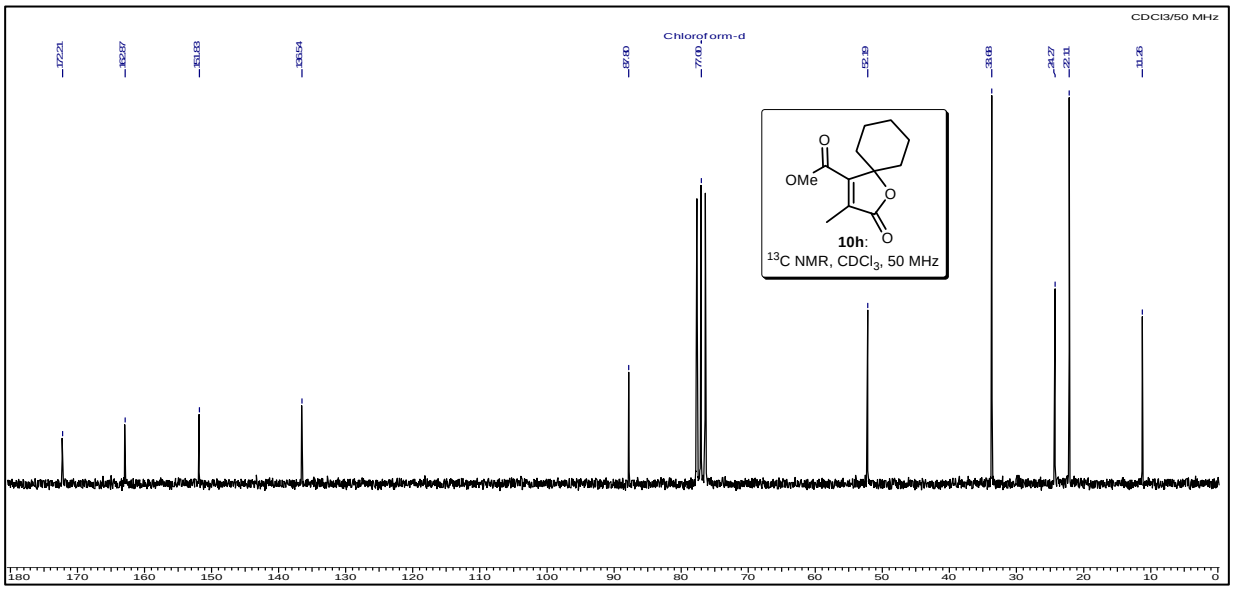

CDCl3/125 MHz
OMe
10d:
DEPT, CDCl3, 125 MHz

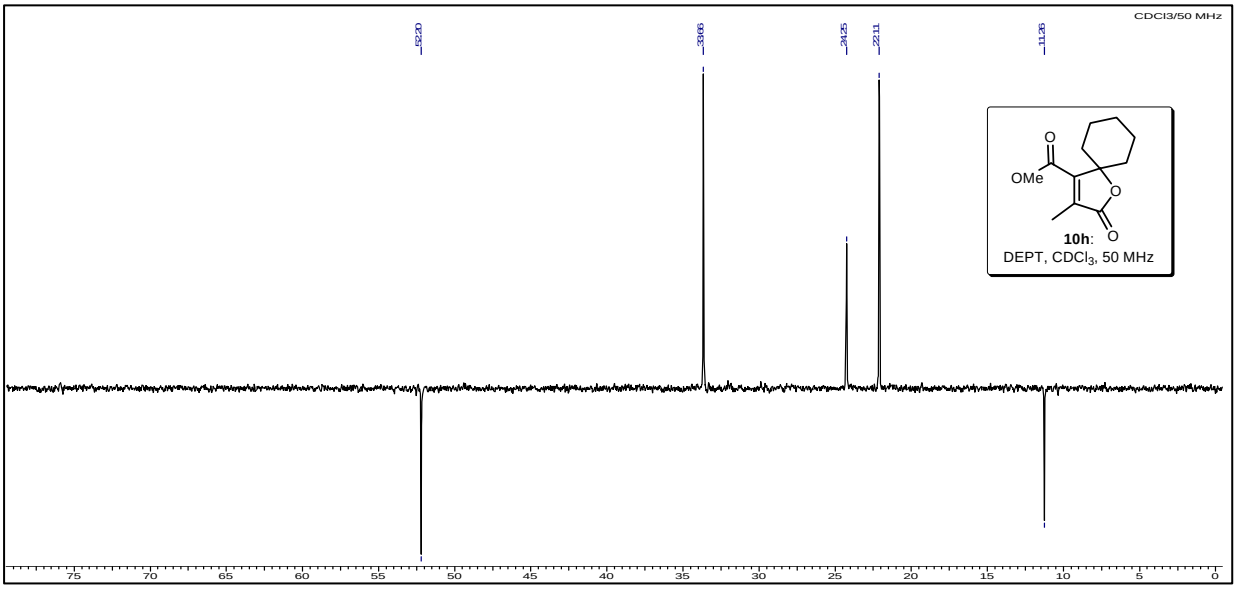

CDCl3/200 MHz
Chloroform-d
7.27
3.81
3.30
3.27
3.23
3.20
2.06
2.02
2.00
1.90
1.76
1.72
1.71
1.69
1.68
1.67
1.66
1.60
1.53
1.32
1.29
0.00
O
Br
OMe
O
O
O
21h:
1H NMR, CDCl3, 200 MHz
3.02
1.00
1.01
1.03
8.10
3.12
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


CDCl3/50 MHz
Chloroform-d
173.36
169.99
86.81
77.00
71.48
53.57
47.20
34.89
31.08
24.72
22.17
22.00
8.92
O
Br
OMe
O
O
21h:
13C NMR, CDCl3, 50 MHz
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10


CDCl3/50 MHz
53.58
47.20
34.88
31.08
24.71
22.17
22.00
8.92
O
Br
OMe
O
O
21h:
DEPT, CDCl3, 50 MHz
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0


CDCL3/200 MHz
Chloroform-d
OMe
O
O
O
10h:
1H NMR, CDCl3, 200 MHz


CDCl3/50 MHz
Chloroform-d
OMe
O
O
O
10h:
13C NMR, CDCl3, 50 MHz


CDCl3/50 MHz
OMe
O
O
O
10h:
DEPT, CDCl3, 50 MHz

3A.6: References

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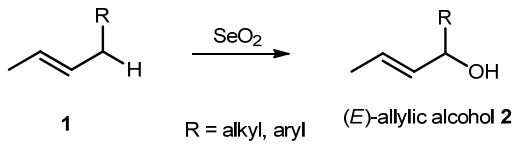
Chapter 3B

Regio- and Stereoselective Selenium Dioxide Allylic Oxidation of Dialkyl Alkylidenesuccinates to (Z)-Allylic Alcohols: Synthesis of Natural and Unnatural Butenolides and Fused Butenolides

This section B of chapter 3 features the following topics:

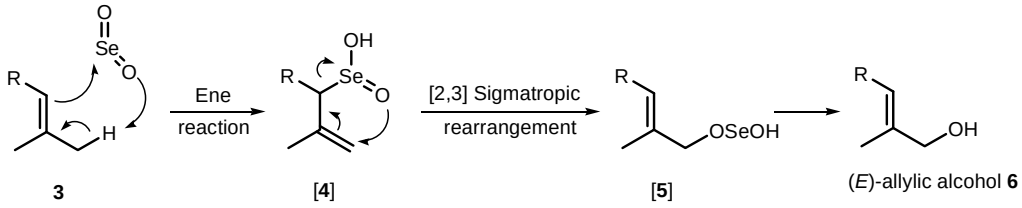
3B.1: Background

Selenium dioxide mediated allylic oxidation of an alkene is one of a limited number of chemical reaction which introduces hydroxyl group into a hydrocarbon molecule selectively with the formation of new carbon−oxygen bond.[1] The reaction reveals very useful regio- and stereoselectivity in the selenium dioxide allylic oxidation of (*E*/*Z*)-alkenes to furnish (*E*)-allylic alcohols exclusively/predominantly.[2] These unique mode of highly regio- and stereoselective interaction of selenium dioxide with olefins is well exemplified for the synthesis of several natural and unnatural products in synthetic organic chemistry.[3] Since Guillemonat has developed the SeO_2 mediated allylic oxidation of alkenes in 1939[4] (Scheme 1),



Scheme 1. Regioselective SeO_2 allylic oxidation

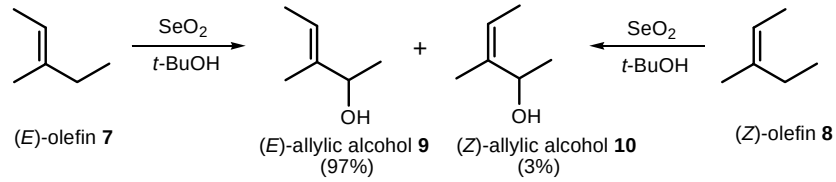
many proposals on mechanistic aspects of this important reaction were projected. However each of the early proposals had difficulty explaining the remarkable site selectivity of the reaction, hence they were ruled out on the basis of theoretical and practical evidences.[5] In 1972, a mechanistic proposal by Sharpless and co-workers[6] has been able to overcome most of these difficulties. Their mechanism consists of a three-step sequence commencing with an ene reaction followed by a [2,3] sigmatropic rearrangement which generates an easily solvolyzed Se" ester **5** (Scheme 2). In this mechanism the ene



Scheme 2. Widely accepted SeO_2 allylic oxidation mechanism proposed by Sharpless et al.

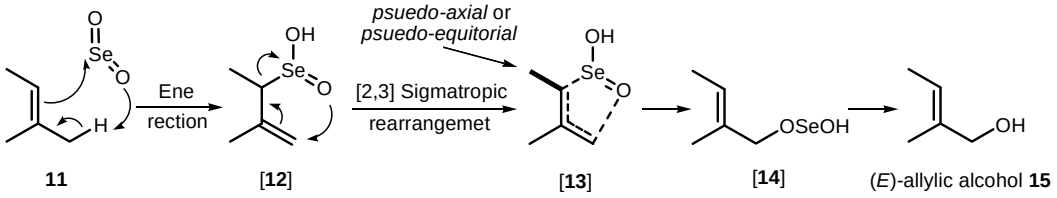
step can explain the site selectivity of the reaction, while the [2,3] sigmatropic shift explains the preference for (*E*)-allylic alcohol products. Both key steps of this sequence can be formulated as a thermally allowed six-electron pericyclic process under the Woodward-Hoffmann formalism. This transformation could then be expected to proceed with clearly defined stereochemical constraints. Their proposal conclusively explained the selective oxidation as a result of ene reaction followed by a [2,3] sigmatropic shift, that returns the double bond to its original position. Their mechanistic proposal has been further supported and accepted, by labeling experiments and DFT calculations.[7]

Synthetic applications of the SeO_2 allylic oxidation have revealed that the reaction proceeds to give predominantly (*E*)-allylic alcohols.[1-3] To examine the genesis of this geometric preference, Stephenson et al.[7a] focused on selenium dioxide allylic oxidation of (*E*/*Z*)-3-methyl-2-pentene (Scheme 3). In this case both the products (allylic alcohols) and the starting olefins are configurationally stable under the



Scheme 3. Regio- and stereoselective SeO_2 allylic oxidation of (*E*/*Z*)-3-methyl-2-pentene

reaction conditions. Interestingly, the product distribution was same from both the olefin isomers. Since neither starting material nor product isomerization was observed, this isomerization of the olefin geometry occurs in an intermediate stage along the oxidation pathway and leads to a strong preference for (*E*)-allylic alcohols. These results parallel the geometric preference shown by [3,3] sigmatropic rearrangements of the Cope and Claisen variety. The preference in the [3,3] cases apparently arises from the most favourable transition state geometry, generally a *pseudo*-chair cyclohexane with the largest groups in equatorial position[8]. Similar geometric selectivity is evident in the selenium dioxide rearrangement studied by Sharpless and Lauer,[6] indicating that an analogous steric effect might be operating in the *pseudo*-cyclopentane transition state. These results clearly clarify that in controlling olefin geometry, the ene step is nonselective, however the strong preference for trans allylic alcohol products in the reaction is due to steric preferences in the [2,3] sigmatropic rearrangement. In 2003, Ra et al.[7c] carried out DFT calculation on the selenium dioxide oxidation of 2-methyl-2-butene and show that the steric bulk of terminal methyl group in the [2,3]-sigmatropic rearrangement step would control



Scheme 4. DFT calculation on SeO_2 allylic oxidation of 2-methyl-2-butene

(*E*)-selectivity in the formation of the allylic alcohol (Scheme 4). In the transition state geometries of the [2,3]-sigmatropic rearrangement, the terminal methyl group may locate at a *pseudo-equatorial* or *pseudo-axial* position. The *pseudo-equatorial* conformation is calculated energetically more favored than the *pseudo-axial* conformation by 2.96 Kcal/mol, which contributes to high stereoselectivity observed in the overall reaction. The above results are in excellent agreement with the experimental observations of the allylic hydroxylation of 2-methyl-2-butene using selenium dioxide. Substitution of

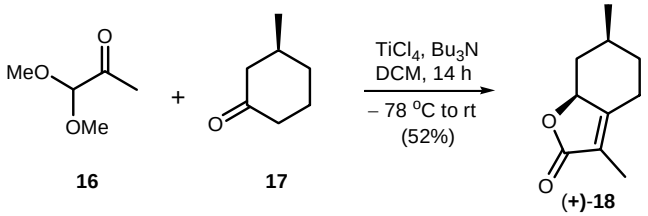
the terminal methyl group of 2-methyl-2-butene by the bulkier one like a *tert*-butyl group may increase the (*E*)/(*Z*)-ratio of the allylic alcohols.

The selenium dioxide allylic oxidation of (*E*/*Z*)-alkenes to (*E*)-allylic alcohols via carbon–oxygen bond formation is an imperative well established reaction in synthetic organic chemistry.[1-3] In chapter 1B, we have discussed in detail the diverse applications of dialkyl alkylidenesuccinates for the synthesis of natural and unnatural products. In this section, as a part of present dissertation, we have demonstrated the regio- and stereoselective SeO_2 allylic oxidation of dialkyl alkylidenesuccinates to constitute a new one-step approach to several significant butenolides and fused butenolides which to the best of our knowledge provides the first example of (*Z*)-selective allylic alcohol formation in the selenium dioxide allylic oxidation of olefins.[9]

3B.2: Brief account on mintlactone and isomintlactone

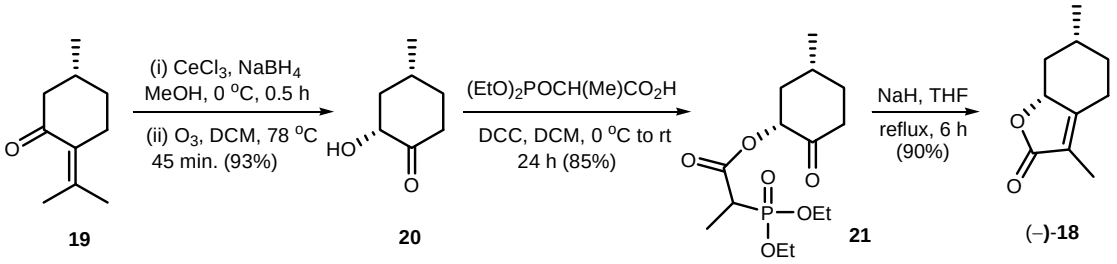
Among the plethora of heterocyclic subunits present in biologically active natural or synthetic products, butenolides and fused butenolides occupy a cardinal position. The natural and unnatural butenolides and fused butenolides are an important class of compounds that find major applications in organic, medicinal and polymer chemistry.[10] A broad range of biological properties has been conferred on them that include strong antibiotic, antihelmitic, antifungal, antitumor, antiviral, anti-inflammatory, cytostatic, antiallergenic and anti-HIV activities.[11] The number of synthetic strategies reported in the literature for their assembly is a clear testimony to their importance.[12] Basically, the diverse range of butenolide skeletons have been elegantly designed by employing new carbon–carbon and carbon–oxygen bond construction reactions. (−)-Mintlactone and (+)-isomintlactone are endo α,β-unsaturated monoterpene-γ-lactones, were isolated from the oil of the woods of *Bursera graveolens*.[13] Their enantiomers, (+)-Mintlactone and (−)-isomintlactone, isolated for the first time in 1968 from *Mentha cardiaca*.[14] These two diastereomeric *p*-menthanolides are also found in *Mentha arvensis*,[15] and as minor constituents of the commercially important essential oil (peppermint oil) of *Mentha piperita* L.[16] Their synthesis has attracted the attention of many organic chemists, as attested by the number of papers dealing with this subject.[17] Since in 2002, Ferraz et al.[18] have reviewed various approaches for the synthesis of mintlactone and isomintlactone in detail, we herein portray the recent synthetic approaches reported after 2002.

Tanabe et al.[19] have reported one-pot synthesis of (+)-mintlactone (**18**) via $TiCl_4$-Bu_3N mediated crossed aldol condensation of 1,1-dimetoxy-2-propanone (**16**) with 3-(*R*)-methylcyclohexanone (**17**) in 52% yield (Scheme 5).



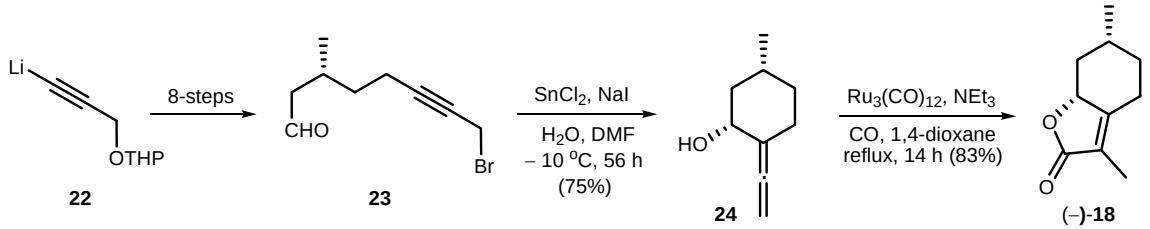
Scheme 5. Synthesis of (+)-mintlactone via $TiCl_4$-Bu_3N mediated crossed aldol condensation

Kumar et al.[20] have reported total synthesis of (−)-mintlactone (**18**) starting from (+)-pulegone (**19**) via stereoselective ketone reduction and ozonalysis followed by intramolecular Wittig-Horner reaction in 71% yield over 4-steps (Scheme 6).



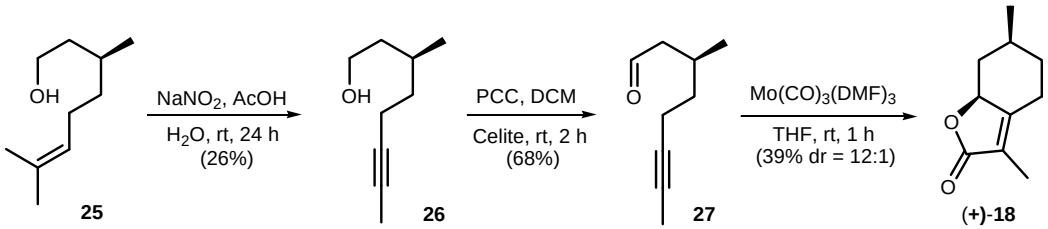
Scheme 6. Synthesis of (−)-mintlactone via intramolecular Wittig-Horner reaction

Bates et al.[21] have reported total synthesis of (−)-mintlactone (**18**) via $SnCl_2$ mediated highly diastereoselective intramolecular propargylic Barbier reaction to allenol (**24**) followed by ruthenium catalyzed cyclocarbonylation in 22% yield over 10-steps (Scheme 7).



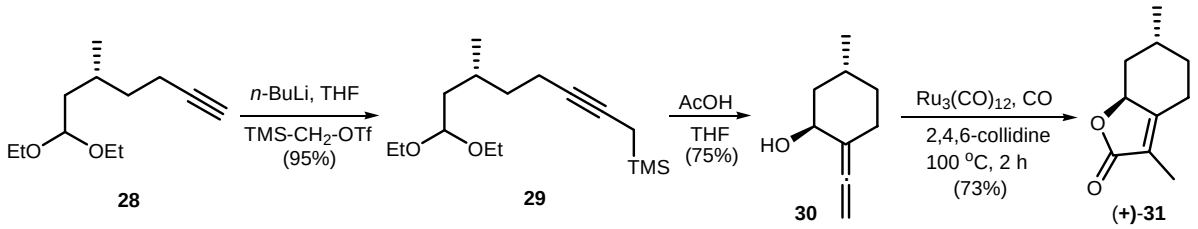
Scheme 7. Synthesis of (−)-mintlactone via ruthenium catalyzed cyclocarbonylation

Zhai et al.[22] have reported total synthesis of (+)-mintlactone (**18**) starting from (+)-citronellol (**25**) via nitrous acid induced formal isopropylidene dementhanation to alkyne **26** followed by oxidation and molybdenum catalyzed intramolecular hetero-Pauson-Khand reaction in 7% yield over 3-steps (Scheme 8).



Scheme 8. Synthesis of (+)-mintlactone via molybdenum catalyzed intramolecular hetero-Pauson-Khand reaction

Recently, Tsubuki et al.[23] have reported efficient total synthesis of (+)-isomintlactone (**31**) via ruthenium catalyzed cyclocarbonylation of allenyl alcohol **30** in 52% yield over 3-steps (Scheme 9).



Scheme 9. Synthesis of (+)-isomintlactone via ruthenium catalyzed cyclocarbonylation of allenyl alcohol

3B.3: Results and discussion

The butenolides and fused butenolides are prevalent structural motifs in large number of natural products and a broad range of biological properties has been conferred on them (Figure 1).[10-13,24] In continuance with our studies on synthesis of bioactive natural products,[25] we envisaged that selective SeO_2 induced allylic hydroxylation of dialkyl alkylidenesuccinates would constitute a new route to

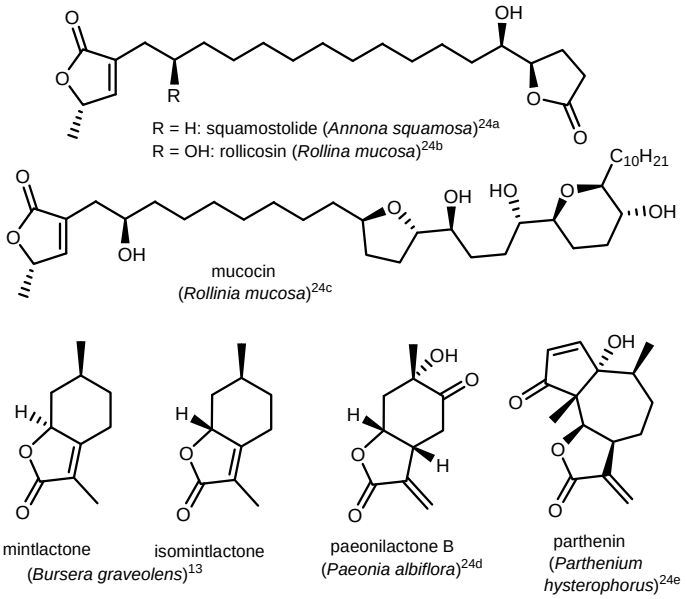
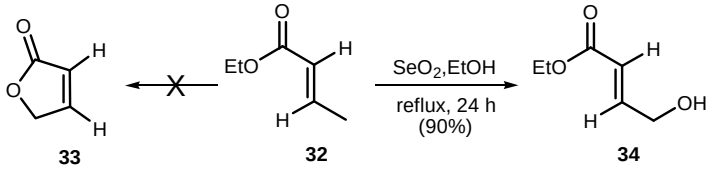


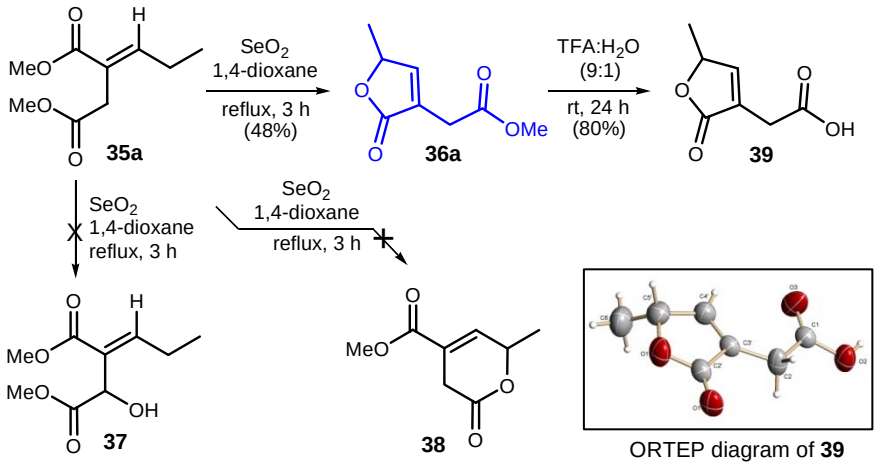
Figure 1. Naturally occurring bioactive butenolides and fused butenolides.[13,24]



Scheme 10. Stereoselective SeO_2 oxidation of ethyl 3-methyl-2-butenoate

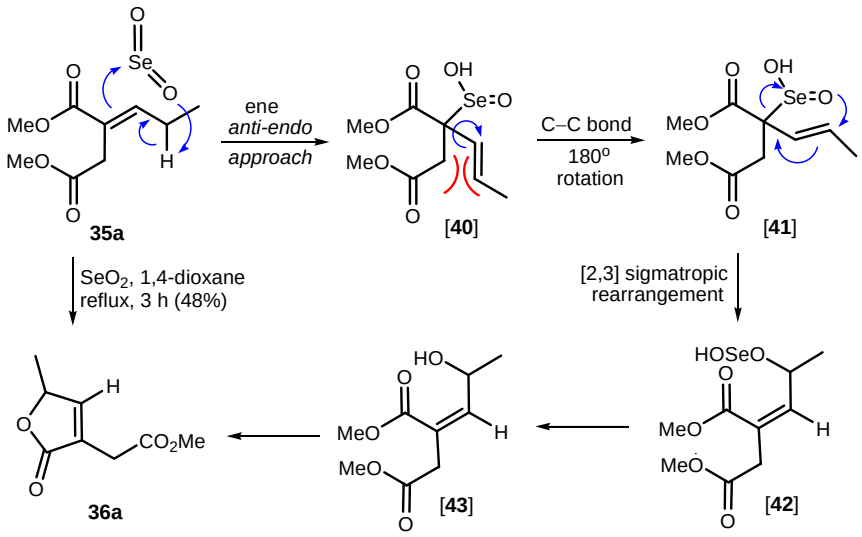
several pivotal furan/pyran frameworks via the intramolecular cyclization pathway. The stereoselective SeO_2 oxidation of ethyl 3-methyl-2-butenoate (**32**) is known to furnish the corresponding product ethyl

trans-3-(hydroxymethyl)-2-butenoate (**34**) in 90% yield (Scheme 10).[26] On the basis of above-mentioned reaction, a systematic study of the SeO_2 oxidation reactions of readily available starting materials (*E*)-dialkyl alkylidenesuccinates[27] was undertaken. As depicted in scheme 11, the initial expectation was that the regioselective SeO_2 allylic oxidation of (*E*)-dimethyl 2-propylidenesuccinate (**35a**) would provide the pyran skeleton **38**. In our hands, the allylic oxidation of compound **35a** in presence of catalytic amount of SeO_2 and *tert*-butyl hydroperoxide in *t*-butanol/1,4-dioxane solvents at room temperature was not successful[28] and the starting material remained unreacted even after 48 h. Fortunately, the reaction of compound **35a** with SeO_2 (1.60 equiv) in refluxing 1,4-dioxane was successful. To our surprise, the above-specified SeO_2 allylic oxidation reaction was completely regio- and stereoselective and exclusively provided the butenolide product **36a** but only in 48% yield. We were conscious about



Scheme 11. Regio- and stereoselective SeO_2 oxidation of (*E*)-dimethyl 2-propylidenesuccinate

the fact that the isomeric butenolide **36a** and the pyran **38** would display a very close resemblance in their NMR data. Hence the acid catalyzed ester hydrolysis of our product **36a** was performed and the

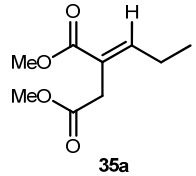
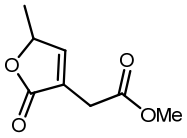
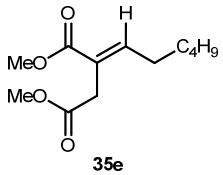
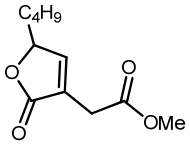
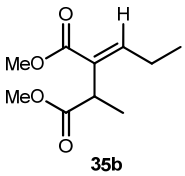
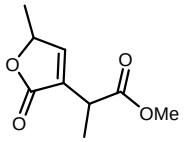
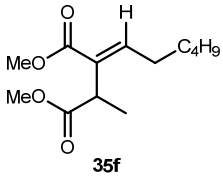
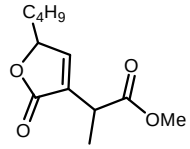
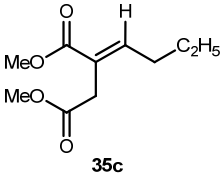
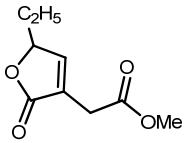
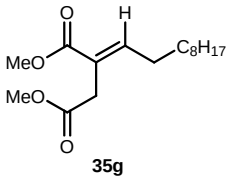
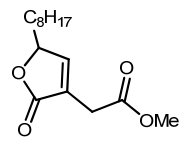
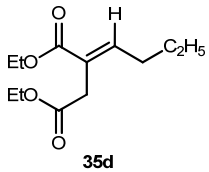
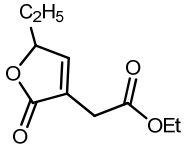
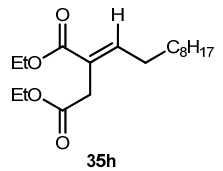
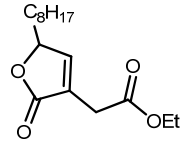


Scheme 12. Plausible mechanism for SeO_2 oxidation of (*E*)-dimethyl 2-propylidenesuccinate

structure of the obtained acid **39** was unequivocally confirmed by using X-ray crystallographic data. The authentication of butenolide structure **36a** revealed that in SeO_2 induced transformation of (*E*)-dimethyl 2-propylidenesuccinate (**35a**) to product **36a**, apart from allylic hydroxylation, the course of reaction involves contra thermodynamic *E*- to *Z*- carbon–carbon double bond isomerization and energetically favorable an in situ intramolecular cyclization step.

Rationalization of our present example indicated its usefulness in highlighting the mechanistic aspects involved in the SeO_2 allylic oxidation reactions. In the SeO_2-induced conversion of **35a** to **36a**, to the best of our knowledge, we witnessed the first example of SeO_2 allylic oxidation reaction to selectively form (*Z*)-allylic alcohol via an in situ contra thermodynamic *E*- to *Z*- carbon–carbon double bond isomerization step.[1-8] As reported earlier, in controlling the olefin geometry, the ene step is non selective.[6,7] However, the strong preference for contra thermodynamic *E*- to *Z*- carbon–carbon bond rotation in the conversion of compound **35a** to **36a** could be due to the unfavoured *pseudo*-axial orientation of the comparatively bulkier $–CH_2CO_2Me$ group in the formation of five membered cyclic

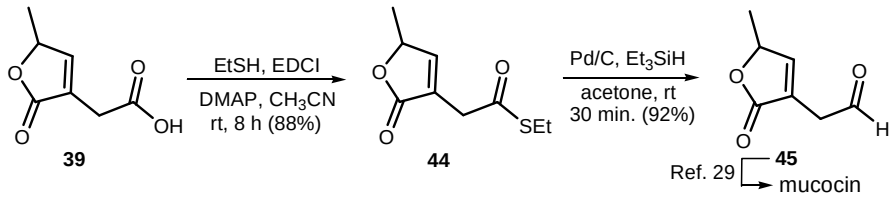
Table 1. Trisubstituted (*E*)-dialkyl alkylidenesuccinates to butenolides [a]

Entry	SM [b]	Product	Entry	SM [b]	Product
1	 **35a**	 **36a** (48%)	5	 **35e**	 **36e** (44%)
2	 **35b**	 **36b/b'** (48%) (1:1 diastreomeric mixture)	6	 **35f**	 **36f/f'** (43%) (1:1 diastereomeric mixture)
3	 **35c**	 **36c** (45%)	7	 **35g**	 **36g** (45%)
4	 **35d**	 **36d** (43%)	8	 **35h**	 **36h** (42%)

[a] Condition: SeO_2, 1,4-dioxane, reflux, 3 h. [b] SM: Starting material.

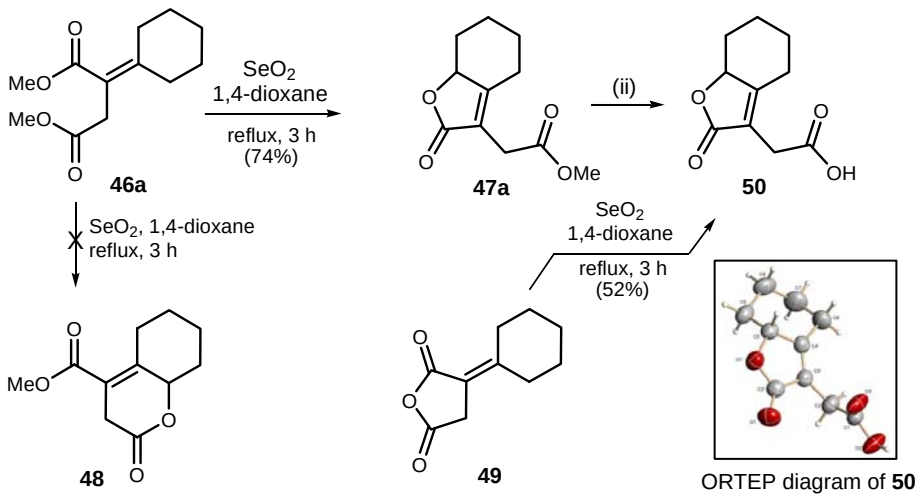
transition state involved in [2,3] sigmatropic rearrangement step. As depicted in scheme 12, the energetically favored anti approach of selenium dioxide towards **35a** in an ene reaction to form the intermediate **40**, followed by an in situ 180° C_α–C_β bond rotation and then the [2,3] sigmatropic shift with *pseudo*-equatorial orientation of the comparatively bulkier $–CH_2CO_2Me$ group and an in situ intramolecular cyclization to form butenolide **36a** could be the most promising pathway. Hence it also precludes the formation of six membered pyran **38**. Herein, we reason that due to the lack of steric effect of bulky α-substituent, the SeO_2 oxidation of compound **32** does not result in the corresponding γ-lactone **33** (Scheme 10).

To generalize our above specified protocol as indicated in table 1, the SeO_2 allylic oxidation reactions of (*E*)-dialkyl alkylidenesuccinates **35a**-**h** were respectively performed to deliver the corresponding desired products **36a**-**h** in one-step with 42-48% yields. As expected, the precursors **35b** and **35f** furnished the corresponding butenolides **36b/b'** and **36f/f'** as 1:1 diastereomeric mixtures. All our attempts to improve the yields by varying the reaction time, temperature, solvents (*t*-BuOH, C_2H_5OH, C_6H_6, CH_2Cl_2 and CH_3CO_2H) and molar amounts of SeO_2 were unsuccessful and always resulted in the formation of over oxidized decomposed residues. The utility of our present approach was illustrated by successfully transforming the butenolide **39** to the corresponding known wobbly mucocin precursor **45** in two steps via the thio-esterification followed by a chemoselective reduction sequence (Scheme 13).[29]



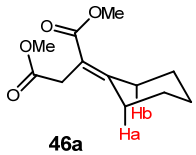
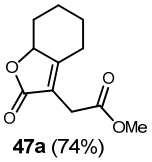
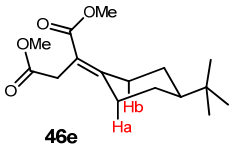
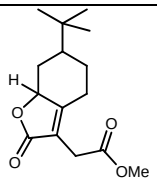
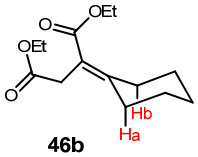
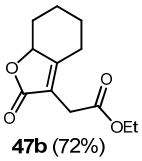
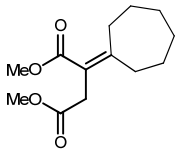
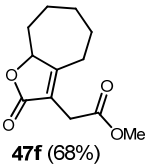
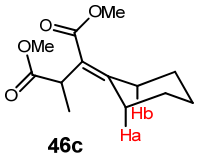
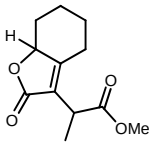
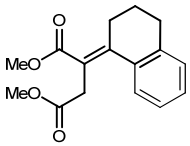
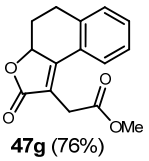
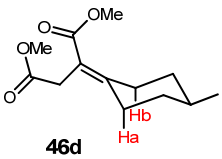
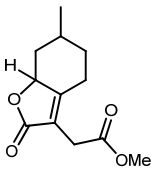
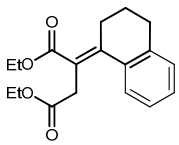
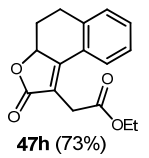
Scheme 13. Concise synthesis of mucocin precursor

In the second phase of studies, the SeO_2 oxidation protocol was extended to symmetrically and unsymmetrically tetrasubstituted dialkyl alkylidenesuccinates (Scheme 14, Table 2). As expected the regio- and stereoselective SeO_2 (1.60 equiv) oxidation of dimethyl 2-cyclohexylidenesuccinate (**46a**) in refluxing 1,4-dioxane also furnished the desired fused butenolide **47a** in one step with 74% yield. The SeO_2 oxidation of cyclohexylidenesuccinic anhydride (**49**)[30] and an acid catalyzed hydrolysis of ester **47a** furnished the same desired product, the acid **50** in very good yields. The structure of the acid **50** was also unambiguously established on the basis of X-ray crystallographic data. Similarly, the reactions of substrates **46b**-**h** with SeO_2 provided the desired fused butenolides **47b**-**h** in 66-76% yields. Herein the formed products **47a**-**h** could be more stable under our set of reaction conditions and hence were obtained in higher yields. As expected the products **47c/c'** were obtained as the corresponding diastereomeric mixture with 2:1 ratio. Similarly, stereoselective conversion of **46d/e** respectively



Scheme 14. Regio- and stereoselective SeO_2 oxidation of dimethyl 2-cyclohexylidenesuccinate

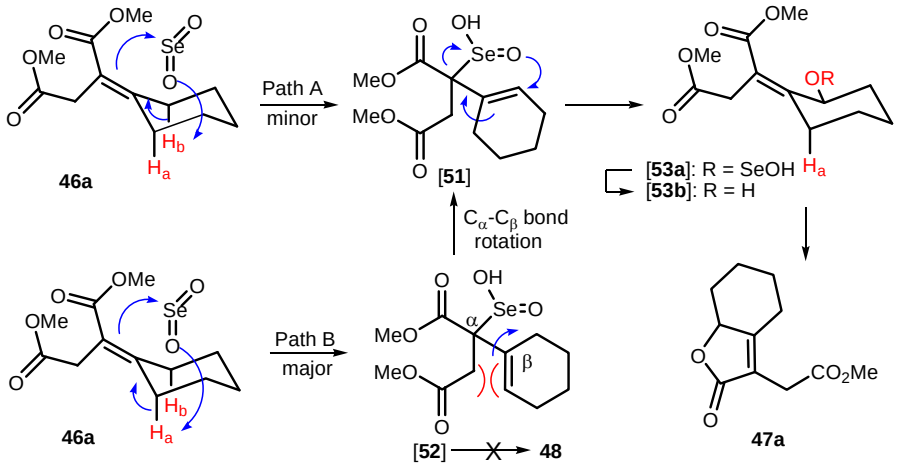
Table 2. Tetrasubstituted (*E*)-dialkyl alkylidenesuccinates to fused butenolides [a]

Entry	SM [b]	Product	Entry	SM [b]	Product
1	 **46a**	 **47a** (74%)	5	 **46e**	 **47e/e'** (66%) (7:3 diastereomeric mixture)
2	 **46b**	 **47b** (72%)	6	 **46f**	 **47f** (68%)
3	 **46c**	 **47c/c'** (70%) (2:1 diastereomeric mixture)	7	 **46g**	 **47g** (76%)
4	 **46d**	 **47d/d'** (72%) (3:1 diastereomeric mixture)	8	 **46h**	 **47h** (73%)

[a] Condition: SeO_2, 1,4-dioxane, reflux, 3 h. [b] SM: Starting material.

furnished the diastereomeric mixtures of **47d/d'** and **47e/e'** with 3:1 and 7:3 ratio. The present stereoselctive conversion can be clearly explained by ene followed by [2,3] sigmatropic shift

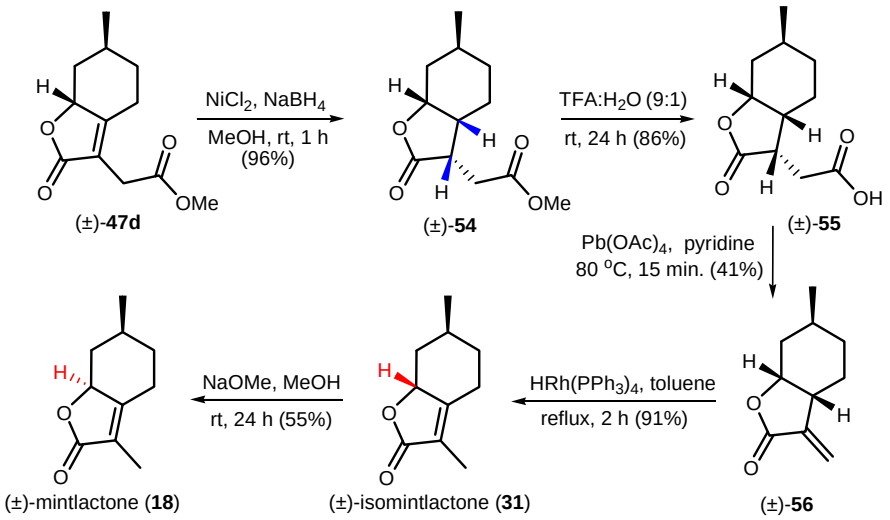
mechanistic pathway as proposed by Sharpless et al.[6,7] In the conversion of **46a-e** to **47a-e**, two independent stereoselective pathways might be operational (Scheme 15). In path B, the preference for C_α–C_β bond rotation could be due to the unfavoured *pseudo*-axial orientation of the comparatively bulkier –CH_2CO_2Me group in the formation of five membered cyclic transition state involved in [2,3] sigmatropic rearrangement step.[7] In the conversion of **46d**/**e** to the respective diastereomeric mixtures of **47d**/**d'** and **47e**/**e'**, the involvement of more acidic (*E*)-allylic axial proton-H_a in the ene reaction followed by the C_α–C_β bond rotation, [2,3] sigmatropic shift with the desired orientation of the comparatively bulkier –CH_2CO_2Me group and lactonization could be resulting in the diastereoselective formation of kinetically controlled major product **47d** following path B.



Scheme 15. Plausible mechanism for SeO_2 oxidation of dimethyl 2-cyclohexylidenesuccinate

The involvement of relatively less acidic (*Z*)-allylic axial proton-H_b in the ene reaction followed by [2,3] sigmatropic shift and lactonization should be directly resulting in the diastereoselective formation of thermodynamically controlled minor product **47d'** following path A, which supports our proposed mechanism.

As an extension of present approach to fused butenolides, the total synthesis of bioactive natural products isomintlactone and mintlactone (*Bursera graveolens*)[13] were planned. One recrystallization of mixture of diastereomers **47d**/**d**' with petroleum ether provided the diastereomerically pure (±)-**47d** in 66% yield (Scheme 16). The tentative stereochemical assignment of **47d** was made by comparison of reported ^{1}H NMR data of mintlactone and isomintlactone.[17-23] The chemo- and diastereoselective reduction of **47d** with $NaBH_4$ in the presence of $NiCl_2$ exclusively furnished the product **54** in 96% yield with the generation of two new asymmetric centers. In the reduction process of **47d**, the addition of hydride at β-carbon of α,β-unsaturated lactone from the less hindered side with the conversion of twist



Scheme 16. Synthesis of (±)-mintlactone and (±)-isomintlactone

boat to chair form followed by the pick-up of proton by thus formed stable axial carbanion from the same face, stereosectively results in the formation of product **54**. Acid catalyzed hydrolysis of ester **54** provided the corresponding carboxylic acid **55** in 86% yield. The stereochemical assignments of both (±)-**54**/**55** were finally established on the basis of X-ray crystallographic analysis data of the compound (±)-**55** (Figure 2). Oxidative decarboxylation[31] of primary acid **55** with $Pb(OAc)_4$ in the presence of $Cu(OAc)_2$

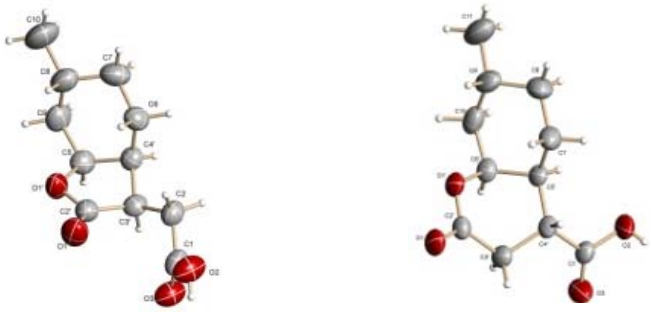
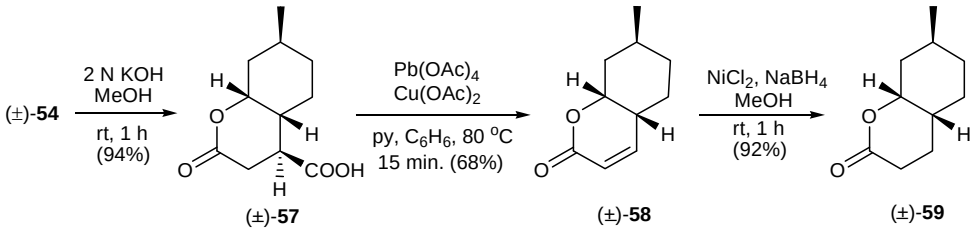


Figure 2. X-ray crystallographic data of γ/δ-lactones (±)-**55** and (±)-**57**

furnished the anticipated exocyclic α-methylene-γ-lactone product **56** with 41% yield. From the bioactivity point of view, among all types of butenolides, the α-methylene-γ-butyrolactones are of contemporary special interest as an alkylating agents via Michael-type acceptor of biological cellular nucleophiles or cysteine residues of functional proteins.[24,32] They possess wide range of important biological activities and the provision of new synthetic routes to such class of compounds is a challenging task of current interest.[32] Our present protocol also provides a concise and efficient new access to these exotic α-methylene-γ-butyrolactones. Finally, the rhodium catalyzed[33] disubstituted exocylic to tetrasubstituted endocyclic carbon–carbon double bond isomerization in **56** provided the desired natural product (±)-isomintlactone (**31**) in 91% yield. Number of independent synthesis of

mintlactone and isomintlactone have been well known in the literature, but the conversion of isomintlactone to the isomeric natural product mintlactone is not known till date.[17-23] On the basis of stereochemical features, we contemplated that the isomintlactone **31** could be a kinetically controlled product (twist boat form).[22] Hence we stirred (±)-isomintlactone (**31**) with NaOMe (1.20 equiv) in MeOH at room temperature and indeed obtained the thermodynamically more stable yet another natural product, the (±)-mintlactone (**18**) (chair form) in 55% yield via the inversion of configuration at an allylic center. Starting from dimethyl 2-(4-methylcyclohexylidene)succinate (**46d**) the (±)-isomintlactone (**31**) and (±)-mintlactone (**18**) were respectively obtained in five/six steps with 14/8% overall yields, and the obtained analytical and spectral data for both the natural products were in complete agreement with the reported data.[17-23] One step conversion of mintlactone/isomintlactone to the yet another natural product, (±)-menthofuran is well known in the literature.[34]

Finally, the regioselectivity in our formed lactone **47d** was altered to device a new approach to essential chromenones (Scheme 17).[35] Rewardingly, the base catalyzed hydrolysis of the reduced γ-lactone (±)-**54** followed by an acidification exclusively furnished the desired δ-lactone carboxylic acid (±)-**57** in 94% yield via the ring opening followed by 180^{o} carbon–carbon bond rotation and the ring closing pathway. The structure of acid (±)-**57** was also explicitly established by using the X-ray crystallographic analysis



Scheme 17. Ring expansion of γ-lactone to δ-lactone: synthesis of chromenone

data (Figure 2). Oxidative decarboxylation of secondary acid (±)-**57** with $Pb(OAc)_4$ in the presence of $Cu(OAc)_2$ furnished the anticipated oxidized hexahydrochromenone product (±)-**58** in 68% yield. Similarly, the nickel catalyzed $NaBH_4$ reduction of α,β-unsaturated carbon–carbon double bond provided the octahydrochromenone (±)-**59** in 92% yield.

3B.4: Summary

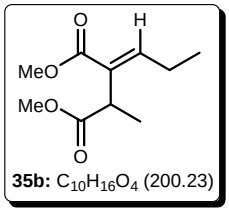
In the present section, we have demonstrated the first example of (Z)-selective allylic alcohol formation in the SeO_2 oxidation of dialkyl alkylidenesuccinates to design a new general one-step approach to the diverse range of natural and unnatural butenolides and fused butenolides via an exceptional E- to Z-carbon–carbon double bond isomerization. The present protocol has been successfully extended for the synthesis of a mucocin precursor and the diastereoselective total synthesis of the natural product (±)-

isomintlactone and its first time conversion to (±)-mintlactone. Our present protocol would also be useful for the synthesis of desired natural and unnatural α-methylene-γ-butyrolactones. We have also successfully altered the regioselectivity in lactonization with the ring expansion of γ-lactone to δ-lactone and provided the new approach to chromenone skeletons. We strongly believe that the present approach will be useful to design several desired bioactive complex natural products centralizing butenolide and fused butenolide moities.

3B.5: Experimental section

Commercially available dimethyl succinate, diethyl succinate, dimethyl methylsuccinate, propanal, butanal, hexanal, decanal, cyclohexanone, 4-methylcyclohexanone, *tert*-butylcyclohexanone, cycloheptanone, α-tetralone, selenium dioxide, sodium methoxide, trifloroacetic acid, ethanethiol, *N*-ethyl *N*'-(3-dimethylpropyl)carbodiimide (EDCI), triethylsilane, lead tetraacetate, cupric acetate, DMAP, 10% Pd/C, $NiCl_2.6H_2O$ and potassium *tert*-butoxide were used. $HRh(PPh_3)_4$ was prepared using the known procedure.[36] Starting materials **35a**, **35c**-**e**, **35g**,**h**, **46a**-**c**, **46e**-**h** were prepared using the known procedure.[27,37-40]

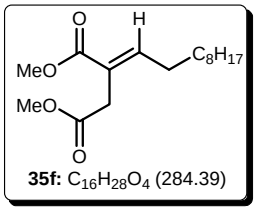
(*E*)-Dimethyl 2-decylidenesuccinate (35b). To a stirred solution of dimethyl citraconate (3.16 g, 20.00 mmol) and tributylphosphine (4.44 g, 22.00 mmol) in THF (30 mL) at room temperature was drop wise added a solution of propionaldehyde (1.74 g, 30.00 mmol) in THF (10 mL) and the reaction mixture was stirred for 4 h. The reaction mixture was concentrated in vacuo and the obtained residue was dissolved in ethyl acetate (50 mL). The organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using 10% ethyl acetate/petroleum ether as an eluent afforded pure product **35b** as a colorless oil (3.36 g, 84%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.07 (t, J = 8 Hz, 3H), 1.32 (d, J = 8 Hz, 3H), 2.20 (doublet of quintet, J = 8 and 4 Hz, 2H), 3.59 (q, J = 8 Hz, 1H), 3.65 (s, 3H), 3.71 (s, 3H), 6.83 (t, J = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.0, 15.8, 21.8, 37.5, 51.7, 51.9, 131.5, 145.5, 166.9, 174.1; ESIMS (*m*/*z*) 223 $[M+Na]^+$; IR ($CHCl_3$) ν_{max} 1746, 1715, 1643 cm^{-1}. Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 60.37; H, 7.69.



35b: $C_{10}H_{16}O_4$ (200.23)

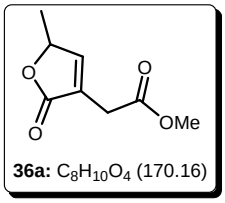
(*E*)-Dimethyl 2-methyl-3-propylidenesuccinate (35f). It was obtained from dimethyl maleate (2.88 g, 20.00 mmol), tributylphosphine (4.44 g, 22.00 mmol) and decanal (4.68 g, 30.00 mmol) using the same procedure described above for **35b**, as a thick oil (4.60 g, 81%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.88 (t, J = 8

Hz, 3H), 1.26 (br s, 12H), 1.45 (quintet, *J* = 8 Hz, 2H), 2.18 (q, *J* = 8 Hz, 2H), 3.36 (s, 2H), 3.68 (s, 3H), 3.75 (s, 3H), 6.98 (t, *J* = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.0, 22.6, 28.4, 28.9, 29.22, 29.25, 29.34, 29.41, 31.8, 32.0, 51.87, 51.91, 125.2, 146.2, 167.4, 171.3; ESIMS (*m*/*z*) 307 $[M+Na]^+$; IR ($CHCl_3$) ν_{max} 1736, 1716, 1652 cm^{-1}. Anal. Calcd for $C_{16}H_{28}O_4$: C, 67.57; H, 9.92. Found: C, 67.34; H, 9.78.



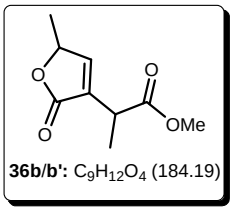
35f: $C_{16}H_{28}O_4$ (284.39)

Methyl 2-(5-methyl-2-oxo-2,5-dihydrofuran-3-yl)acetate (36a). To a stirred solution of alkylidenesuccinate **35a** (1.86 g, 10.00 mmol) in 1,4-dioxane (20 mL) was added SeO_2 (1.78 g, 16.00 mmol) and the reaction mixture was refluxed for 3 h. The reaction mixture was allowed to attain room temperature. The deposited selenium metal was filtered off and the residue was washed with 1,4-dioxane (5 mL). The filtrate was concentrated in vacuo and the obtained residue was dissolved in ethyl acetate (30 mL). The organic layer was washed with saturated $NaHCO_3$ solution, water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using 40% ethyl acetate/petroleum ether as an eluent afforded pure product **36a** as a colorless oil (816 mg, 48%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.44 (d, *J* = 6 Hz, 3H), 3.33 (t, *J* = 2 Hz, 2H), 3.72 (s, 3H), 5.08 (qq, *J* = 6 and 2 Hz, 1H), 7.40 (q, *J* = 2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 18.8, 30.1, 52.2, 78.0, 126.5, 152.6, 169.8, 172.9; ESIMS (*m*/*z*) 193 $[M+Na]^+$; IR ($CHCl_3$) ν_{max} 1756, 1748, 1662 cm^{-1}. Anal. Calcd for $C_8H_{10}O_4$: C, 56.47; H, 5.92. Found: C, 56.39; H, 6.00.



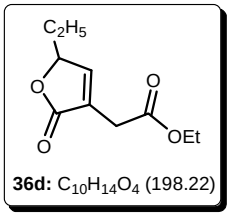
36a: $C_8H_{10}O_4$ (170.16)

Methyl 2-(5-methyl-2-oxo-2,5-dihydrofuran-3-yl)propanoate (36b/b', diastereomeric mixture, 1:1**).** It was obtained from alkylidenesuccinate **35b** (2.00 g, 10.00 mmol) and SeO_2 (1.78 g, 16.00 mmol) using the same procedure described above for **36a**, as a thick oil (846 mg, 46%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.45 (d, *J* = 6 Hz, 6H), 3.55 (tq, *J* = 8 and 2 Hz, 1H), 3.73 (s, 3H), 5.08 (qq, *J* = 8 and 2 Hz, 1H), 7.26 (q, *J* = 2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 16.6, 19.0, 36.2, 52.3, 77.76, 77.80, 133.1, 133.2, 150.4, 150.5, 172.33, 172.34, 173.2; ESIMS (*m*/*z*) 207 $[M+Na]^+$; IR ($CHCl_3$) ν_{max} 1758, 1746, 1667 cm^{-1}. Anal. Calcd for $C_9H_{12}O_4$: C, 58.69; H, 6.57. Found: C, 58.64; H, 6.43.



36b/b': $C_9H_{12}O_4$ (184.19)

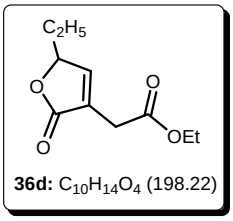
Methyl 2-(5-ethyl-2-oxo-2,5-dihydrofuran-3-yl)acetate (36c). It was obtained from alkylidenesuccinate **35c** (2.00 g, 10.00 mmol) and SeO_2 (1.78 g, 16.00 mmol) using the same procedure described above for **36a**, as a thick oil[41] (828 mg, 45%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.01 (t, *J* = 8 Hz, 3H), 1.60–1.95 (m, 2H), 3.36 (t, *J* = 2 Hz, 2H), 3.73 (s, 3H), 4.90–5.02 (m, 1H), 7.41 (q, *J* = 2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 9.0, 26.3, 30.2, 52.2,



36d: $C_{10}H_{14}O_4$ (198.22)

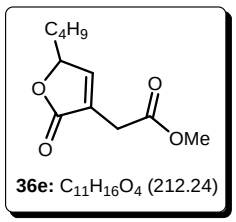
82.7, 127.0, 151.3, 169.9, 173.0; ESIMS (*m*/*z*) 207 $[M+Na]^+$; IR ($CHCl_3$) ν_{max} 1756, 1747, 1668 cm^{-1}. Anal. Calcd for $C_9H_{12}O_4$: C, 58.69; H, 6.57. Found: C, 58.52; H, 6.25.

Ethyl 2-(5-ethyl-2-oxo-2,5-dihydrofuran-3-yl)acetate (36d). It was obtained from alkylidenesuccinate **35d** (2.28 g, 10.00 mmol) and SeO_2 (1.78 g, 16.00 mmol) using the same procedure described above for **36a**, as a thick oil (851 mg, 43%). ^1H NMR ($CDCl_3$, 200 MHz) δ 0.98 (t, *J* = 8 Hz, 3H), 1.25 (t, *J* = 8 Hz, 3H), 1.55–1.93 (m, 2H), 3.32 (t, *J* = 2 Hz, 2H), 4.16 (q, *J* = 8 Hz, 2H), 4.87–5.00 (m, 1H), 7.38 (q, *J* = 2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 8.9, 14.0 26.3, 30.4, 61.2, 82.6, 127.0, 151.2, 169.4, 173.0; ESIMS (*m*/*z*) 221 $[M+Na]^+$; IR ($CHCl_3$) ν_{max} 1756, 1748, 1667 cm^{-1}. Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.87; H, 7.19.



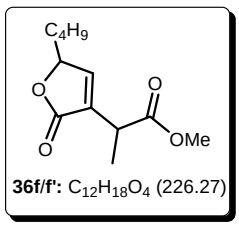
36d: $C_{10}H_{14}O_4$ (198.22)

Methyl 2-(5-butyl-2-oxo-2,5-dihydrofuran-3-yl)acetate (36e). It was obtained from alkylidenesuccinate **35e** (2.28 g, 10.00 mmol) and SeO_2 (1.78 g, 16.00 mmol) using the same procedure described above for **36a**, as a thick oil[42] (933 mg, 44%). ^1H NMR ($CDCl_3$, 200 MHz) δ 0.91 (t, *J* = 8 Hz, 3H), 1.20–1.55 (m, 4H), 1.55–1.85 (m, 2H), 3.36 (t, *J* = 2 Hz, 2H), 3.74 (s, 3H), 4.93–5.05 (m, 1H), 7.41 (q, *J* = 2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.8, 22.4, 27.0, 30.2, 32.9, 52.2, 81.8, 126.8, 151.6, 169.9, 173.0; ESIMS (*m*/*z*) 235 $[M+Na]^+$; IR ($CHCl_3$) ν_{max} 1756, 1748, 1666 cm^{-1}.



36e: $C_{11}H_{16}O_4$ (212.24)

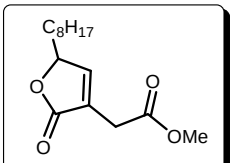
Methyl 2-(5-butyl-2-oxo-2,5-dihydrofuran-3-yl)propanoate (36f/f', diastereomeric mixture, 1:1**).** It was obtained from alkylidenesuccinate **35f** (2.42 g, 10.00 mmol) and SeO_2 (1.78 g, 16.00 mmol) using the same procedure described above for **36a**, as a thick oil (972 mg, 43%). ^1H NMR ($CDCl_3$, 200 MHz) δ 0.90 (t, *J* = 8 Hz, 3H), 1.25–1.50 (m, 4H), 1.43 (d, *J* = 8 Hz, 3H), 1.55–1.85 (m, 2H), 3.54 (tq, *J* = 8 and 2 Hz, 1H), 3.71 (s, 3H), 4.96 (t, *J* = 8 Hz, 1H), 7.25 (q, *J* = 2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.8, 16.5, 16.6, 22.4, 26.86, 26.91, 32.9, 36.19, 36.21, 52.3, 81.5, 81.6, 133.2, 133.3, 149.5, 172.41, 172.44, 173.2; ESIMS (*m*/*z*) 227 $[M+H]^+$, 249 $[M+Na]^+$, 265 $[M+K]^+$; IR ($CHCl_3$) ν_{max} 1757, 1747, 1668 cm^{-1}. Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.80; H, 7.77.



36f/f': $C_{12}H_{18}O_4$ (226.27)

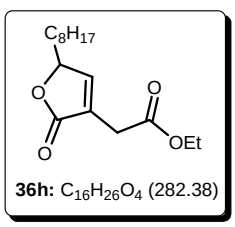
Methyl 2-(5-octyl-2-oxo-2,5-dihydrofuran-3-yl)acetate (36g). It was obtained from alkylidenesuccinate **35g** (2.84 g, 10.00 mmol) and SeO_2 (1.78 g, 16.00 mmol) using the same procedure described above for **36a**, as a thick oil (1.21 g, 45%). ^1H NMR ($CDCl_3$, 200 MHz) δ 0.88 (t, *J* = 6 Hz, 3H), 1.27 (br s, 10H), 1.35–

1.55 (m, 2H), 1.55–1.85 (m, 2H), 3.36 (t, *J* = 2 Hz, 2H), 3.74 (s, 3H), 4.93–5.05 (m, 1H), 7.42 (q, *J* = 2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.1, 22.6, 24.9, 29.1, 29.26, 29.31, 30.2, 31.8, 33.3, 52.3, 81.9, 126.7, 151.7, 169.9, 173.0; ESIMS (*m*/*z*) 269 $[M+H]^+$, 291 $[M+Na]^+$, 307 $[M+K]^+$; IR ($CHCl_3$) ν_{max} 1759, 1748, 1667 cm^{-1}. Anal. Calcd for $C_{15}H_{24}O_4$: C, 67.14; H, 9.01. Found: C, 66.79; H, 8.80.



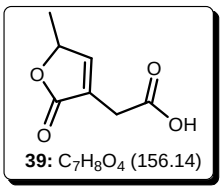
36g: $C_{15}H_{24}O_4$ (268.35)

Ethyl 2-(5-octyl-2-oxo-2,5-dihydrofuran-3-yl)acetate (36h). It was obtained from alkylidenesuccinate **35h** (3.12 g, 10.00 mmol) and SeO_2 (1.78 g, 16.00 mmol) using the same procedure described above for **36a**, as a thick oil (1.18 g, 42%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.87 (t, *J* = 6 Hz, 3H), 1.28 (br s, 10H), 1.31 (t, *J* = 6 Hz, 3H), 1.35–1.55 (m, 2H), 1.55–1.85 (m, 2H), 3.33 (t, *J* = 2 Hz, 2H), 4.19 (q, *J* = 6 Hz, 2H), 4.92–5.05 (m, 1H), 7.40 (q, *J* = 2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.05, 14.07, 22.6, 24.9, 29.1, 29.26, 29.29, 30.4, 31.8, 33.3, 61.2, 81.8, 126.8, 151.6, 169.5, 173.1; ESIMS (*m*/*z*) 283 $[M+H]^+$, 305 $[M+Na]^+$, 321 $[M+K]^+$; IR ($CHCl_3$) ν_{max} 1759, 1740, 1665 cm^{-1}. Anal. Calcd for $C_{16}H_{26}O_4$: C, 68.06; H, 9.28. Found: C, 68.16; H, 9.53.



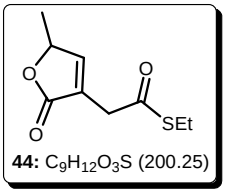
36h: $C_{16}H_{26}O_4$ (282.38)

2-(5-Methyl-2-oxo-2,5-dihydrofuran-3-yl)acetic acid (39). A solution of compound **36a** (680 mg, 4.00 mmol) in aqueous TFA (90%, 10 mL) was stirred for 24 h at room temperature. The concentration of reaction mixture in vacuo followed by silica gel column chromatographic purification of the resulting residue using 50% ethyl acetate/petroleum ether as an eluent furnished pure product **39** as a white solid (499 mg, 80%). Mp 130–132 °C; ^{1}H NMR (acetone-d_6, 200 MHz) δ 1.41 (d, *J* = 6 Hz, 3H), 3.34 (t, *J* = 2 Hz, 2H), 5.14 (qq, *J* = 8 and 2 Hz, 1H), 7.57 (q, *J* = 2 Hz, 1H); ^{13}C NMR (acetone-d_6, 50 MHz) δ 19.1, 30.6, 78.6, 127.5, 154.0, 170.9, 173.4; ESIMS (*m*/*z*) 179 $[M+Na]^+$; HRMS (ESI) calcd for $C_7H_8O_4Na$ 179.0320, found 179.0322; IR ($CHCl_3$) ν_{max} 2934, 2857, 1745, 1739, 1657 cm^{-1}.



39: $C_7H_8O_4$ (156.14)

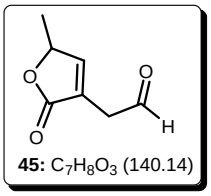
***S*-Ethyl 2-(5-methyl-2-oxo-2,5-dihydrofuran-3-yl)ethanethioate (44).** To a stirred solution of acid **39** (400 mg, 2.56 mmol), ethanethiol (239 mg, 3.85 mmol) and DMAP (31 mg, 0.26 mmol) in CH_3CN (15 mL) at room temperature was drop wise added a solution of EDCI (995 mg, 5.13 mmol) in CH_3CN (5 mL). The reaction mixture was further stirred for 8 h and then quenched with water (10 mL). The reaction mixture was concentrated in vacuo and the obtained residue was dissolved in ethyl acetate (30 mL). The organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo



44: $C_9H_{12}O_3S$ (200.25)

followed by silica gel column chromatographic purification of the resulting residue using 40% ethyl acetate/petroleum ether as an eluent afforded pure product **44** as a colorless oil (451 mg, 88%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.27 (t, J = 8 Hz, 3H), 1.46 (d, J = 6 Hz, 3H), 2.92 (q, J = 8 Hz, 2H), 3.55 (t, J = 2 Hz, 2H), 5.10 (qq, J = 8 and 2 Hz, 1H), 7.39 (q, J = 2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.5, 18.8, 23.7, 39.1, 78.1, 126.4, 153.0, 172.7, 194.9; ESIMS (m/z) 223 $[M+Na]^+$; HRMS (ESI) calcd for $C_9H_{12}O_3NaS$ 223.0404, found 223.0396; IR ($CHCl_3$) ν_{max} 1747, 1728, 1649 cm^{-1}.

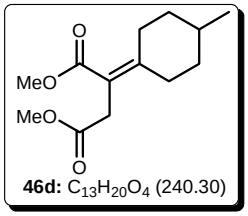
2-(5-Methyl-2-oxo-2,5-dihydrofuran-3-yl)acetaldehyde (45). To a stirred suspension of thioester **44**



45: $C_7H_8O_3$ (140.14)

(300 mg, 1.50 mmol) and 10% Pd/C (30 mg) in acetone (15 mL) at room temperature was drop wise added triethylsilane (Et_3SiH, 348 mg, 3.00 mmol) and the reaction mixture was stirred for 30 min. The reaction mixture was filtered through Celite and washed with acetone (5 mL). The concentration of the filtrate in vacuo followed by silica gel column chromatographic purification of the resulting residue using 5% ethyl acetate/petroleum ether as an eluent afforded product **45** as a colorless oil (193 mg, 92%).

Dimethyl 2-(4-methylcyclohexylidene)succinate (46d). To a stirred solution of *t*-BuOK (2.24 g, 20.00

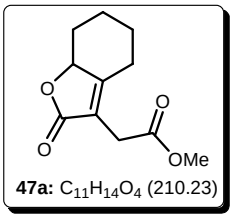


46d: $C_{13}H_{20}O_4$ (240.30)

mmol) in *t*-BuOH (20 mL) at room temperature was added a solution of dimethyl succinate (2.92 g, 20.00 mmol) in *t*-BuOH (10 mL) in a drop wise fashion under argon atmosphere with constant stirring. After stirring the reaction mixture for 10 min, a solution of 4-methyl cyclohexanone (2.69 g, 24.00 mmol) in *t*-BuOH (10 mL) was added drop wise under argon atmosphere and the reaction mixture was stirred for 45 minutes at room temperature. The reaction mixture was concentrated in vacuo. The obtained residue was dissolved in water (60 mL) and the aqueous layer was washed with ethyl acetate (30 mL x 2). The aqueous layer was acidified to pH 2 using 2 N HCl (30 mL). The acidified aqueous layer was extracted with ethyl acetate (20 mL x 3), washed with water, brine and dried over Na_2SO_4. The organic layer was concentrated in vacuo and the dried residue was dissolved in MeOH (40 mL). To the above solution was added concentrated H_2SO_4 (2 mL) and it was refluxed for 2 h with constant stirring. The reaction mixture was allowed to attain room temperature and concentrated in vacuo. The obtained residue was dissolved in ethyl acetate (60 mL) and the organic layer was washed with saturated $NaHCO_3$ solution, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using 10% ethyl acetate/petroleum ether as an eluent afforded pure product **46d** as a thick oil (3.26 g, 68%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.91 (d, J = 6 Hz, 3H), 0.95–1.30 (m, 2H), 1.50–1.75 (m, 1H), 1.75–2.10 (m, 4H), 2.45–2.65 (m, 1H), 3.22–3.38 (m,

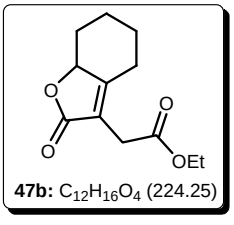
1H), 3.39 (s, 2H), 3.68 (s, 3H), 3.72 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.5, 31.6, 31.8, 32.3, 34.7, 35.9, 36.2, 51.5, 51.9, 117.4, 155.0, 168.9, 171.9; ESIMS (*m*/*z*) 263 $[M+Na]^+$; IR ($CHCl_3$) ν_{max} 1746, 1717, 1635 cm^{-1}. Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 64.64; H, 8.70.

Methyl 2-(2-oxo-2,4,5,6,7,7a-hexahydrobenzofuran-3-yl)acetate (47a). It was obtained from alkylidenesuccinate **46a** (2.26 g, 10.00 mmol) and SeO_2 (1.78 g, 16.00 mmol) using the same procedure described above for **36a**, as a thick oil[43] (1.55 g, 74%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.20–1.62 (m, 3H), 1.84–2.10 (m, 2H), 2.21 (dt, *J* = 14 and 6 Hz, 1H), 2.45–2.61 (m, 1H), 2.74–2.88 (m, 1H), 3.31 (s, 2H), 3.70 (s, 3H), 4.67 (dd, *J* = 10 and 6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 22.6, 26.2, 26.7, 28.4, 34.3, 52.3, 80.4, 117.0, 166.5, 170.0, 173.4; ESIMS (*m*/*z*) 211 $[M+H]^+$, 233 $[M+Na]^+$; IR ($CHCl_3$) ν_{max} 1759, 1747, 1690 cm^{-1}. Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.85; H, 6.71. Found: C, 62.47; H, 6.85.



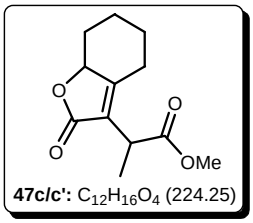
47a: $C_{11}H_{14}O_4$ (210.23)

Ethyl 2-(2-oxo-2,4,5,6,7,7a-hexahydrobenzofuran-3-yl)acetate (47b). It was obtained from alkylidenesuccinate **46b** (2.54 g, 10.00 mmol) and SeO_2 (1.78 g, 16.00 mmol) using the same procedure described above for **36a**, as a thick oil (1.61 g, 72%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.24 (dt, *J* = 8 and 2 Hz, 3H), 1.20–1.60 (m, 3H), 1.80–2.07 (m, 2H), 2.19 (dt, *J* = 14 and 6 Hz, 1H), 2.40–2.60 (m, 1H), 2.79 (dd, *J* = 14 and 2 Hz, 1H), 3.27 (s, 2H), 4.13 (dq, *J* = 8 and 2 Hz, 2H), 4.65 (dd, *J* = 12 and 6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.0, 22.5, 26.1, 26.7, 28.5, 34.2, 61.1, 80.3, 117.0, 166.4, 169.5, 173.4; ESIMS (*m*/*z*) 225 $[M+H]^+$, 247 $[M+Na]^+$, 263 $[M+K]^+$; IR ($CHCl_3$) ν_{max} 1752, 1734, 1687 cm^{-1}. Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.38; H, 7.50.



47b: $C_{12}H_{16}O_4$ (224.25)

Methyl 2-(2-oxo-2,4,5,6,7,7a-hexahydrobenzofuran-3-yl)propanoate (47c/c', diastereomeric mixture, 2:1**).** It was obtained from alkylidenesuccinate **46c** (2.40 g, 10.00 mmol) and SeO_2 (1.78 g, 16.00 mmol) using the same procedure described above for **36a**, as a thick oil (1.57 g, 70%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.10–1.60 (m, 3H), 1.40 (d, *J* = 8 Hz, 1H), 1.41 (d, *J* = 8 Hz, 2H), 1.83–2.25 (m, 3H), 2.45–2.60 (m, 1H), 2.80–2.95 (m, 1H), 3.60 (q, *J* = 6 Hz, 1H), 3.69 (s, 3H), 4.60 (dd, *J* = 10 and 6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 15.7, 16.1, 22.5, 26.2, 26.3, 26.4, 26.5, 34.3, 34.4, 34.6, 34.8, 52.19, 52.24, 80.0, 122.8, 164.5, 172.9, 173.2; ESIMS (*m*/*z*) 225 $[M+H]^+$, 247 $[M+Na]^+$; IR ($CHCl_3$) ν_{max} 1759, 1747, 1681 cm^{-1}. Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.17; H, 6.83.



47c/c': $C_{12}H_{16}O_4$ (224.25)

Methyl 2-((±)-6-methyl-2-oxo-2,4,5,6,7,7a-hexahydrobenzofuran-3-yl)acetate (47d/d', diastereomeric mixture, 3:1**).** It was obtained from alkylidenesuccinate **46d** (2.40 g, 10.00 mmol) and SeO_2 (1.78 g, 16.00 mmol) using the same procedure described above for **36a**, as a white solid (1.61 g, 72%). Recrystalization of **47d**/**d'** with petroleum ether provided analytically pure **47d** as a white solid. Mp 86–88 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.15 (d, J = 6 Hz, 3H), 1.43 (dt, J = 12 and 4 Hz, 1H), 1.52–1.72 (m, 1H), 1.75–1.90 (m, 1H), 2.18–2.55 (m, 3H), 2.61–2.75 (m, 1H), 3.31 (s, 2H), 3.70 (s, 3H), 4.90 (dd, J = 12 and 6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 17.1, 22.2, 27.1, 28.3, 31.6, 39.6, 52.2, 77.7, 116.7, 167.0, 170.0, 173.5; ESIMS (m/z) 247 $[M+Na]^+$, 263 $[M+K]^+$; IR ($CHCl_3$) ν_{max} 1754, 1737, 1691 cm^{-1}. Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.13; H, 6.84.

47d/d': $C_{12}H_{16}O_4$ (224.25)

Methyl 2-(6-(*tert*-butyl)-2-oxo-2,4,5,6,7,7a-hexahydrobenzofuran-3-yl)acetate (47e/e', diastereomeric mixture, 7:3**).** It was obtained from alkylidenesuccinate **46e** (2.82 g, 10.00 mmol) and SeO_2 (1.78 g, 16.00 mmol) using the same procedure described above for **36a**, as a white solid (1.76 g, 66%). Mp 70–73 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.87 (s, 9H), 0.90–2.35 (m, 5H), 2.45–2.87 (m, 2H), 3.25 (s, 0.60H), 3.27 (s, 1.40H), 3.67 (s, 3H), 4.67 (dd, J = 12 and 6 Hz, 0.30H), 4.97 (t, J = 8 Hz, 0.70H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 22.2, 24.3, 25.9, 27.2, 27.4, 27.5, 28.2, 28.6, 30.6, 32.3, 32.8, 35.3, 43.0, 44.6, 52.0, 78.5, 80.9, 116.5, 117.9, 166.6, 167.2, 169.7, 169.9, 173.3, 173.8; ESIMS (m/z) 267 $[M+H]^+$, 289 $[M+Na]^+$, 305 $[M+K]^+$; IR ($CHCl_3$) ν_{max} 1759, 1755, 1748, 1732, 1688 cm^{-1}. Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.65; H, 8.33. Found: C, 67.71; H, 8.60.

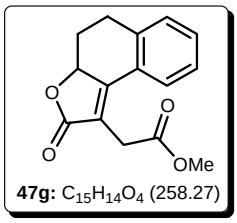
47e/e': $C_{15}H_{22}O_4$ (266.33)

Methyl 2-(2-oxo-4,5,6,7,8,8a-hexahydro-2*H*-cyclohepta[*b*]furan-3-yl)acetate (47f). It was obtained from alkylidenesuccinate **46f** (2.40 g, 10.00 mmol) and SeO_2 (1.78 g, 16.00 mmol) using the same procedure described above for **36a**, as a thick oil (1.52 g, 68%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.15–1.70 (m, 4H), 1.70–2.05 (m, 3H), 2.25–2.45 (m, 1H), 2.45–2.83 (m, 2H), 3.27 (s, 2H), 3.70 (s, 3H), 4.88–5.00 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 25.4, 26.1, 27.6, 28.7, 29.7, 33.6, 52.2, 83.8, 119.9, 169.3, 169.7, 173.3; ESIMS (m/z) 225 $[M+H]^+$, 247 $[M+Na]^+$, 263 $[M+K]^+$; IR ($CHCl_3$) ν_{max} 1756, 1747, 1669 cm^{-1}. Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.07; H, 7.27.

47f: $C_{12}H_{16}O_4$ (224.25)

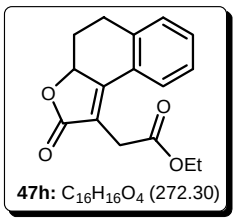
Methyl 2-(2-oxo-2,3a,4,5-tetrahydronaptho[2,1-*b*]furan-1-yl)acetate (47g). It was obtained from alkylidenesuccinate **46g** (2.74 g, 10.00 mmol) and SeO_2 (1.78 g, 16.00 mmol) using the same procedure

described above for **36a**, as a thick oil (1.96 g, 76%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.70–1.95 (m, 1H), 2.62–2.76 (m, 1H), 3.06–3.17 (m, 2H), 3.53 (dd, J = 16 and 2 Hz, 1H), 3.73 (d, J = 16 Hz, 1H), 3.75 (s, 3H), 5.10 (dd, J = 14 and 6 Hz, 1H), 7.29–7.46 (m, 3H), 7.63 (dd, J = 6 and 2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 27.6, 30.1 (2 carbons), 52.5, 79.0, 116.1, 127.1, 127.67, 127.73, 129.4, 131.1, 138.1, 159.5, 170.0, 173.9; ESIMS (m/z) 259 $[M+H]^+$, 281 $[M+Na]^+$; IR ($CHCl_3$) ν_{max} 1749, 1659 cm^{-1}. Anal. Calcd for $C_{15}H_{14}O_4$: C, 69.76; H, 5.46. Found: C, 69.68; H, 5.72.



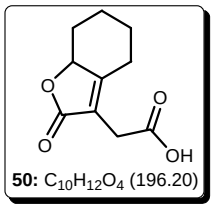
47g: $C_{15}H_{14}O_4$ (258.27)

Ethyl 2-(2-oxo-2,3a,4,5-tetrahydronaptho[2,1-*b*]furan-1-yl)acetate (47h). It was obtained from alkylidenesuccinate **46h** (3.02 g, 10.00 mmol) and SeO_2 (1.78 g, 16.00 mmol) using the same procedure described above for **36a**, as a thick oil (1.99 g, 73%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.25 (t, J = 8 Hz, 3H), 1.70–1.95 (m, 1H), 2.60–2.75 (m, 1H), 3.05–3.20 (m, 2H), 3.52 (dd, J = 16 and 2 Hz, 1H), 3.70 (d, J = 16 Hz, 1H), 4.19 (q, J = 8 Hz, 2H), 5.09 (dd, J = 12 and 6 Hz, 1H), 7.25–7.45 (m, 3H), 7.63 (dd, J = 6 and 2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.1, 27.6, 30.2, 30.3, 61.4, 79.0, 116.3, 127.0, 127.6, 127.8, 129.3, 131.0, 138.1, 159.4, 169.5, 173.9; ESIMS (m/z) 295 $[M+Na]^+$; IR ($CHCl_3$) ν_{max} 1754, 1731, 1657 cm^{-1}. Anal. Calcd for $C_{16}H_{16}O_4$: C, 70.58; H, 5.92. Found: C, 70.84; H, 5.77.



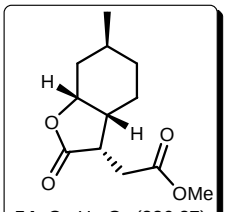
47h: $C_{16}H_{16}O_4$ (272.30)

2-(2-Oxo-2,4,5,6,7,7a-hexahydrobenzofuran-3-yl)acetic acid (50). It was obtained from butenolide **47a** (1.05 g, 5.00 mmol) and TFA (90%, 15 mL) using the same procedure described above for **39**, as a white solid (804 mg, 82%). It was also obtained from cyclohexylidenesuccinic anhydride (**49**) (1.80 g, 10.00 mmol) and SeO_2 (1.78 g, 16.00 mmol) using the same procedure described above for **36a**, as a white solid[44] (1.02 g, 52%). Mp 122–124 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.15–1.63 (m, 3H), 1.85–2.11 (m, 2H), 2.23 (dt, J = 12 and 6 Hz, 1H), 2.45–2.64 (m, 1H), 2.75–2.90 (m, 1H), 3.36 (s, 2H), 4.69 (dd, J = 12 and 8 Hz, 1H), 8.28 (br s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 22.6, 26.2, 26.7, 28.5, 34.2, 80.7, 116.5, 167.1, 173.7, 174.7; ESIMS (m/z) 197 $[M+H]^+$, 219 $[M+Na]^+$, 235 $[M+K]^+$; IR ($CHCl_3$) ν_{max} 2929, 2852, 1748, 1712, 1674 cm^{-1}. Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.22; H, 6.16. Found: C, 60.92; H, 6.59.



50: $C_{10}H_{12}O_4$ (196.20)

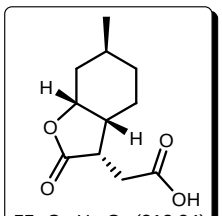
Methyl 2-((±)-6-methyl-2-oxo-octahydrobenzofuran-3-yl)acetate (54). To a stirred solution of butenolide **47d** (1.00 g, 4.50 mmol) and $NiCl_2{\cdot}6H_2O$ (213 mg, 0.89 mmol) in MeOH (20 mL) at room temperature was portion wise added $NaBH_4$ (848 mg, 22.30 mmol) and the reaction mixture was stirred for 1 h. The reaction mixture was concentrated in vacuo and the obtained residue was dissolved in ethyl



54: $C_{12}H_{18}O_4$ (226.27)

acetate (30 mL). The organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using 30% ethyl acetate/petroleum ether as an eluent afforded pure product **54** as a colorless oil (969 mg, 96%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.82–1.31 (m, 3H), 0.92 (d, J = 8 Hz, 3H), 1.43–1.74 (m, 3H), 2.24 (qd, J = 15 and 4 Hz, 1H), 2.36–2.56 (m, 1H), 2.45 (dd, J = 18 and 10 Hz, 1H), 2.85 (dd, J = 18 and 4 Hz, 1H), 3.21 (ddd, J = 10, 6 and 6 Hz, 1H), 3.72 (s, 3H), 4.53 (dd, J = 6 and 2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.8, 23.0, 26.1, 29.3, 31.7, 35.9, 37.6, 44.2, 52.0, 78.6, 172.1, 177.6; ESIMS (m/z) 249 $[M+Na]^+$, 265 $[M+K]^+$; IR ($CHCl_3$) ν_{max} 1775, 1740 cm^{-1}. Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.91; H, 7.93.

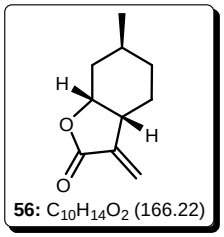
2-((±)-6-Methyl-2-oxo-octahydrobenzofuran-3-yl)acetic acid (55). It was obtained from butenolide **54**



55: $C_{11}H_{16}O_4$ (212.24)

(900 mg, 10.00 mmol) and aqueous TFA (90%, 10 mL) using the same procedure described above for **39**, as a white solid (726 mg, 86%). Mp 128–130 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.80–1.32 (m, 3H), 0.93 (d, J = 6 Hz, 3H), 1.42–1.75 (m, 3H), 2.24 (qd, J = 15 and 4 Hz, 1H), 2.35–2.55 (m, 1H), 2.50 (dd, J = 18 and 10 Hz, 1H), 2.89 (dd, J = 18 and 4 Hz, 1H), 3.21 (ddd, J = 10, 5 and 5 Hz, 1H), 4.54 (dd, J = 6 and 2 Hz, 1H), 8.50 (br s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.8, 23.0, 26.0, 29.4, 31.6, 35.8, 37.5, 44.0, 78.8, 177.3, 177.8; ESIMS (m/z) 235 $[M+Na]^+$, 263 $[M+K]^+$; IR ($CHCl_3$) ν_{max} 1766, 1727, 1638 cm^{-1}. Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.38; H, 7.46.

(±)-6-Methyl-3-methylene-hexahydrobenzofuran-2(3*H*)-one (56). To a stirred suspension of acid **55**

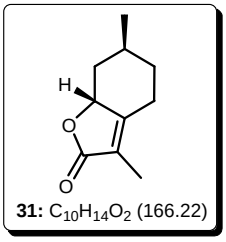


56: $C_{10}H_{14}O_2$ (166.22)

(700 mg, 3.30 mmol), $Pb(OAc)_4$ (1.90 g, 4.29 mmol) and $Cu(OAc)_2$ (60 mg, 0.33 mmol) in dry benzene (20 mL) at 80 °C was drop wise added pyridine (783 mg, 9.91 mmol) and the reaction mixture was further refluxed for 15 min. until the reaction mixture became blue in color. The reaction mixture was allowed to attain room temperature. The reaction mixture was concentrated in vacuo and the obtained residue was dissolved in ethyl acetate (30 mL). The organic layer was washed with saturated $NaHCO_3$ solution, saturated $CuSO_4$ solution, water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using 40% ethyl acetate/petroleum ether as an eluent afforded pure product **56** as a colorless oil[18] (225 mg, 41%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.80–1.05 (m, 1H), 0.94 (d, J = 6 Hz, 3H), 1.20–1.45 (m, 2H), 1.55–1.75 (m, 2H), 1.75–1.90 (m, 1H), 2.20 (qd, J = 15 and 4 Hz, 1H), 2.84 (ddd, J = 11, 6 and 4 Hz,

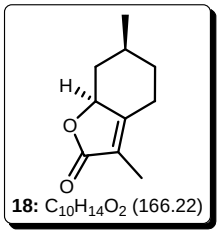
1H), 4.52 (dd, *J* = 6 and 4 Hz, 1H), 5.53 (d, *J* = 1 Hz, 1H), 6.10 (d, *J* = 1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.7, 25.6, 28.3, 31.2, 35.7, 39.4, 77.2, 119.6, 142.2, 171.0; ESIMS (*m*/*z*) 167 $[M+H]^+$, 189 $[M+Na]^+$, 205 $[M+K]^+$; IR ($CHCl_3$) ν_{max} 1771, 1668, 1641 cm^{-1}. Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.44; H, 8.16.

(±)-3,6-Dimethyl-5,6,7,7a-tetrahydrobenzofuran-2(4*H*)-one (Isomintlactone, 31). To a stirred solution of butenolide **56** (200 mg, 1.21 mmol) in dry toluene (10 mL) was added catalyst $[RhH(Ph_3P)_4]$ (139 mg, 0.12 mmol) and the reaction mixture was refluxed for 2 h until all **56** was consumed (monitored by GC). The reaction mixture was allowed to attain room temperature. The reaction mixture was filtered off and the residue was washed with toluene (5 mL). The filtrate was concentrated in vacuo and the silica gel column chromatographic purification of the resulting residue using 20% ethyl acetate/petroleum ether as an eluent afforded pure product **31** as a white solid[18] (182 mg, 91%). Mp 78–80 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.15 (d, *J* = 4 Hz, 3H), 1.37 (dt, *J* = 12 and 4 Hz, 1H), 1.50–1.62 (m, 1H), 1.73–1.85 (m, 1H), 1.81 (s, 3H), 2.22–2.31 (m, 1H), 2.31–2.43 (m, 2H), 2.69 (dd, *J* = 14 and 4 Hz, 1H), 4.82 (dd, *J* = 10 and 4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 8.2, 17.2, 21.7, 27.3, 31.6, 39.5, 77.5, 119.3, 163.0, 175.0; ESIMS (*m*/*z*) 167 $[M+H]^+$ 189 $[M+Na]^+$; IR ($CHCl_3$) ν_{max} 1756, 1641 cm^{-1}. Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.15; H, 8.12.



31: $C_{10}H_{14}O_2$ (166.22)

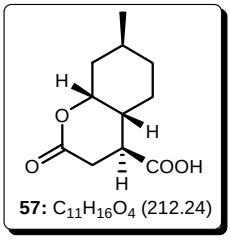
(±)-3,6-Dimethyl-5,6,7,7a-tetrahydrobenzofuran-2(4*H*)-one (Mintlactone, 18). To a stirred solution of isomintlactone, (**31**) (200 mg, 1.21 mmol) in dry MeOH (10 mL) was added NaOMe (78 mg, 1.45 mmol) and the reaction mixture was stirred at room temperature for 24 h. The reaction mixture was then concentrated in vacuo. The obtained residue was dissolved in ethyl acetate (15 mL) and acidified to pH 2 using 2 N HCl (5 mL). The organic layer was separated and the aqueous layer was further extracted with ethyl acetate (10 mL x 2). The combined organic layer was washed with water, brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using 20% ethyl acetate/petroleum ether as an eluent furnished pure product **18** as a colorless oil[18] (110 mg, 55%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.90–1.20 (m, 2H), 1.01 (d, *J* = 8 Hz, 3H), 1.60–1.80 (m, 1H), 1.81 (t, *J* = 2 Hz, 3H), 1.87–2.02 (m, 1H), 2.19 (dt, *J* = 14 and 4 Hz, 1H), 2.36–2.49 (m, 1H), 2.80 (ddd, *J* = 14, 6 and 2 Hz, 1H), 4.63 (dd, *J* = 11 and 6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 8.2, 21.2, 25.4, 29.8, 34.5, 42.0, 79.9, 119.6, 162.3, 174.9; ESIMS (*m*/*z*) 167 $[M+H]^+$, 189



18: $C_{10}H_{14}O_2$ (166.22)

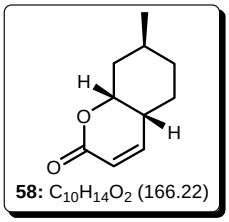
[M+Na]$^+$; IR ($CHCl_3$) ν_{max} 1756, 1645, 1715, 1688 cm^{-1}. Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.16; H, 8.07.

(±)-7-Methyl-2-oxo-octahydro-2*H*-chromene-4-carboxylic acid (57). An aqueous solution of 2 N KOH (5 mL) was added to a stirring solution of **54** (678 mg, 3.00 mmol) in MeOH (20 mL) at room temperature and the reaction mixture was stirred for 1 h. The reaction mixture was then concentrated in vacuo. The obtained residue was dissolved in ethyl acetate (15 mL) and acidified to pH 2 using 2 N HCl (5 mL). The organic layer was separated and the aqueous layer was further extracted with ethyl acetate (10 mL x 2). The combined organic layer was washed with water, brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using 50% ethyl acetate/petroleum ether as an eluent furnished pure product **57** as a white solid (598 mg, 94%). Mp 141–143 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.92 (d, J = 6 Hz, 3H), 0.98–1.32 (m, 2H), 1.51 (dq, J = 14 and 4 Hz, 1H), 1.64–1.92 (m, 3H), 2.02–2.24 (m, 2H), 2.58–2.96 (m, 3H), 4.55 (d, J = 4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.8, 25.6, 27.9, 29.0, 33.7, 36.4, 38.2, 41.9, 75.5, 171.2, 178.6; ESIMS (m/z) 213 [M+H]$^+$, 230 [M+NH$_3$]$^+$, 235 [M+Na]$^+$, 251 [M+K]$^+$; IR ($CHCl_3$) ν_{max} 2923, 1732, 1602 cm^{-1}. Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.11; H, 7.19.



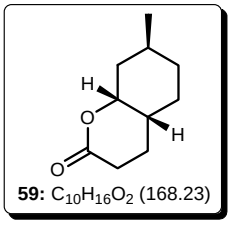
57: $C_{11}H_{16}O_4$ (212.24)

(±)-7-Methyl-4a,5,6,7,8,8a-hexahydrochromen-2-one (58). To a stirred suspension of acid **57** (530 mg, 2.50 mmol), $Pb(OAc)_4$ (1.44 g, 3.25 mmol) and $Cu(OAc)_2$ (46 mg, 0.25 mmol) in dry benzene (20 mL) at 80 ^{o}C was drop wise added pyridine (593 mg, 7.50 mmol). The reaction mixture was further refluxed for 15 min. until the reaction mixture became blue in color. The reaction mixture was allowed to attain room temperature. The reaction mixture was concentrated in vacuo and the obtained residue was dissolved in ethyl acetate (30 mL). The organic layer was washed with saturated $NaHCO_3$ solution, saturated $CuSO_4$ solution, water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using 20% ethyl acetate/petroleum ether as an eluent afforded pure product **58** as a colorless oil (282 mg, 68%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.83–1.10 (m, 1H), 0.93 (d, J = 8 Hz, 3H), 1.13–1.43 (m, 2H), 1.62–1.93 (m, 3H), 2.04–2.22 (m, 2H), 4.56 (dd, J = 6 and 2 Hz, 1H), 5.97 (dd, J = 10 and 2 Hz, 1H), 6.97 (dd, J = 10 and 6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.8, 25.9, 26.8, 32.9, 35.2, 38.2, 76.4, 120.1, 150.8, 165.1; ESIMS (m/z) 167 [M+H]$^+$, 189 [M+Na]$^+$; IR ($CHCl_3$) ν_{max} 1729 cm^{-1}. Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.66; H, 8.36.



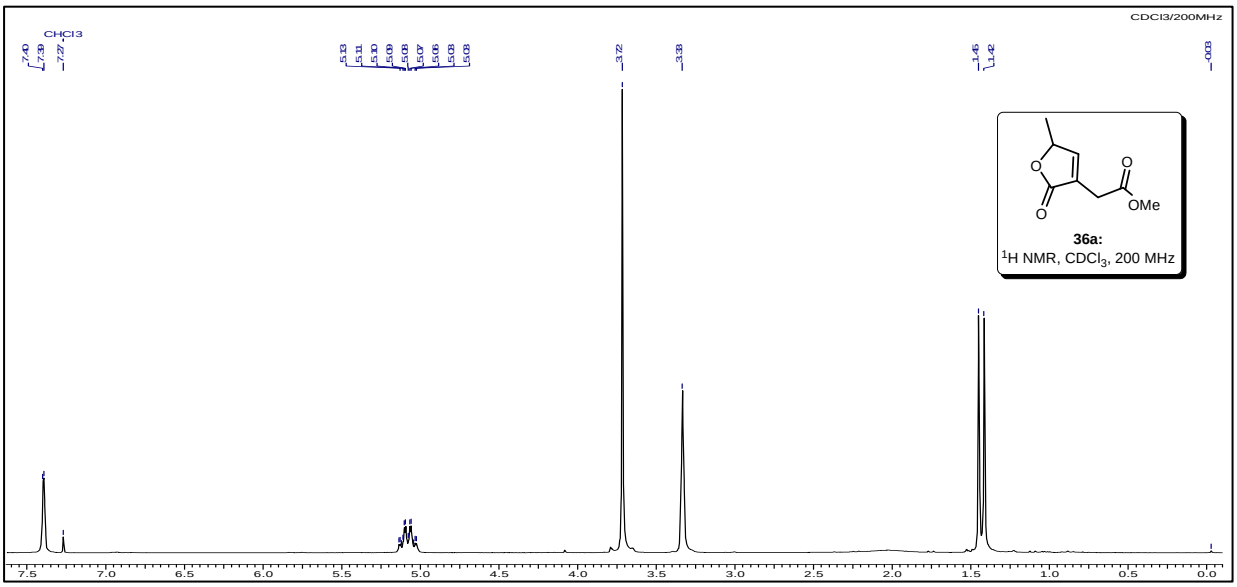
58: $C_{10}H_{14}O_2$ (166.22)

(±)-7-Methyl-octahydrochromen-2-one (59). To a stirred solution of butenolide **58** (200 mg, 1.21 mmol) and $NiCl_2{\cdot}6H_2O$ (57 mg, 0.24 mmol) in MeOH (20 mL) at room temperature was portion wise added $NaBH_4$ (229 mg, 6.02 mmol) and the reaction mixture was stirred for 1 h. The reaction mixture was concentrated in vacuo and the obtained residue was dissolved in ethyl acetate (30 mL). The organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using 20% ethyl acetate/petroleum ether as an eluent afforded pure product **59** as a colorless oil (186 g, 92%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.90 (d, J = 6 Hz, 3H), 0.90–1.30 (m, 2H), 1.40–1.90 (m, 6H), 1.95–2.20 (m, 2H), 2.48 (d, J = 8 Hz, 1H), 2.52 (d, J = 8 Hz, 1H), 4.51 (dd, J = 6 and 4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.8, 24.6, 25.6, 26.1, 26.4, 32.2, 33.7, 38.9, 78.4, 172.7; ESIMS (m/z) 169 $[M+H]^+$, 191 $[M+Na]^+$; IR ($CHCl_3$) ν_{max} 1732 cm^{-1}. Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.47; H, 9.06.



59: $C_{10}H_{16}O_2$ (168.23)

3B.6: Selected spectra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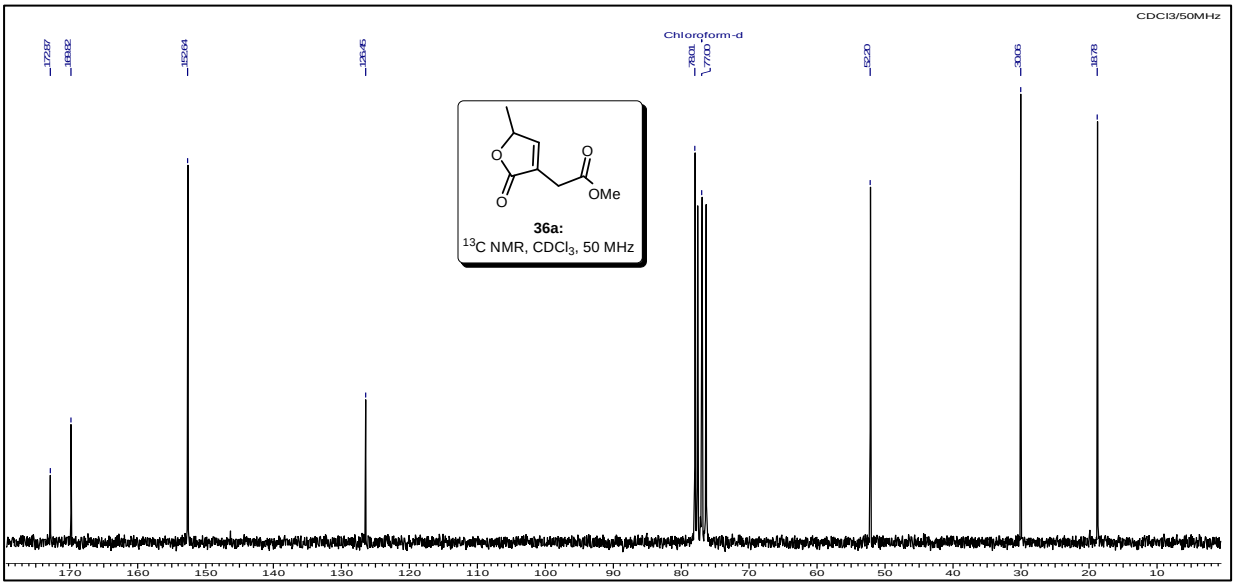
7.40
7.39
7.27
5.13
5.11
5.10
5.09
5.08
5.07
5.06
5.03
5.03
3.72
3.38
1.46
1.42
0.00
O
O
O
OMe
36a:
1H NMR, CDCl3, 200 MHz
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


CDCl3/50MHz
Chloroform-d
172.87
169.82
135.64
126.46
78.01
77.00
52.20
30.06
18.78
O
O
O
OMe
36a:
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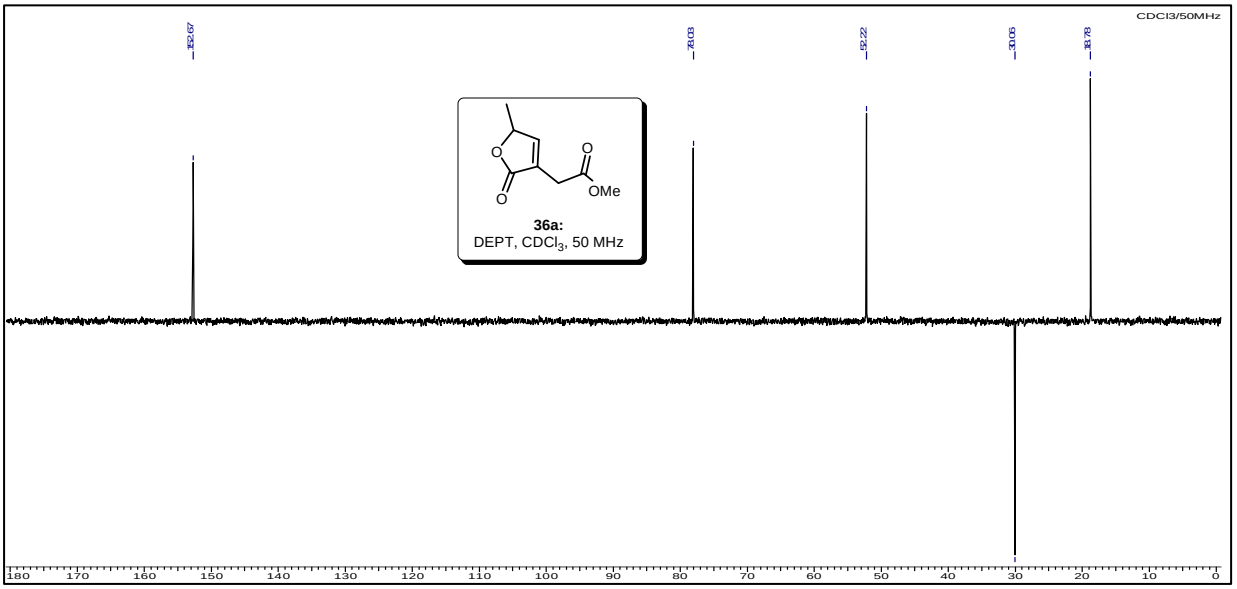
100
90
80
70
60
50
40
30
20
10


CDCl3/50MHz
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78.03
52.22
30.06
18.78
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O
O
OMe
36a:
DEPT, CDCl3, 50 MHz
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160
150
140
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70
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50
40
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20
10
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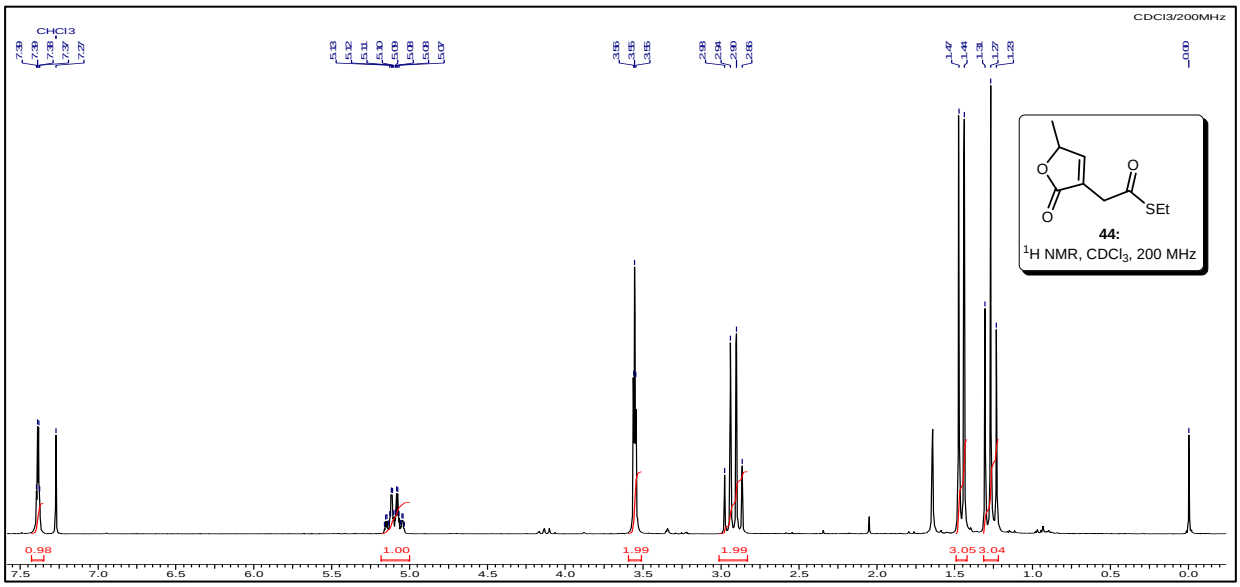
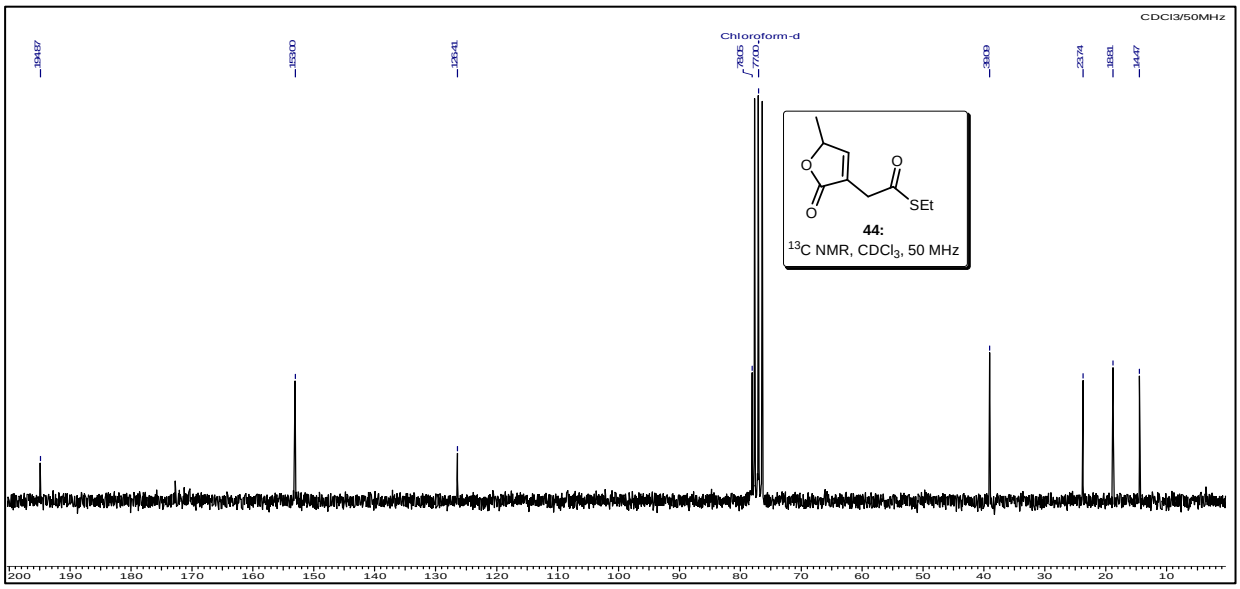
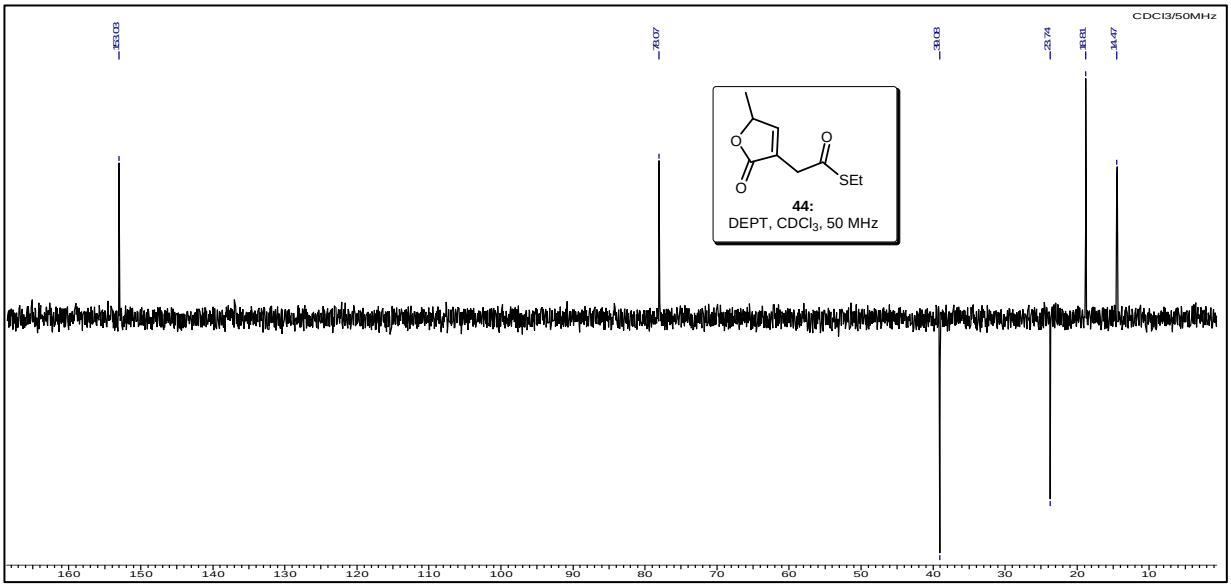

CDCl3/200MHz
CHCl3
44:
1H NMR, CDCl3, 200 MHz


CDCl3/50MHz
Chloroform-d
44:
13C NMR, CDCl3, 50 MHz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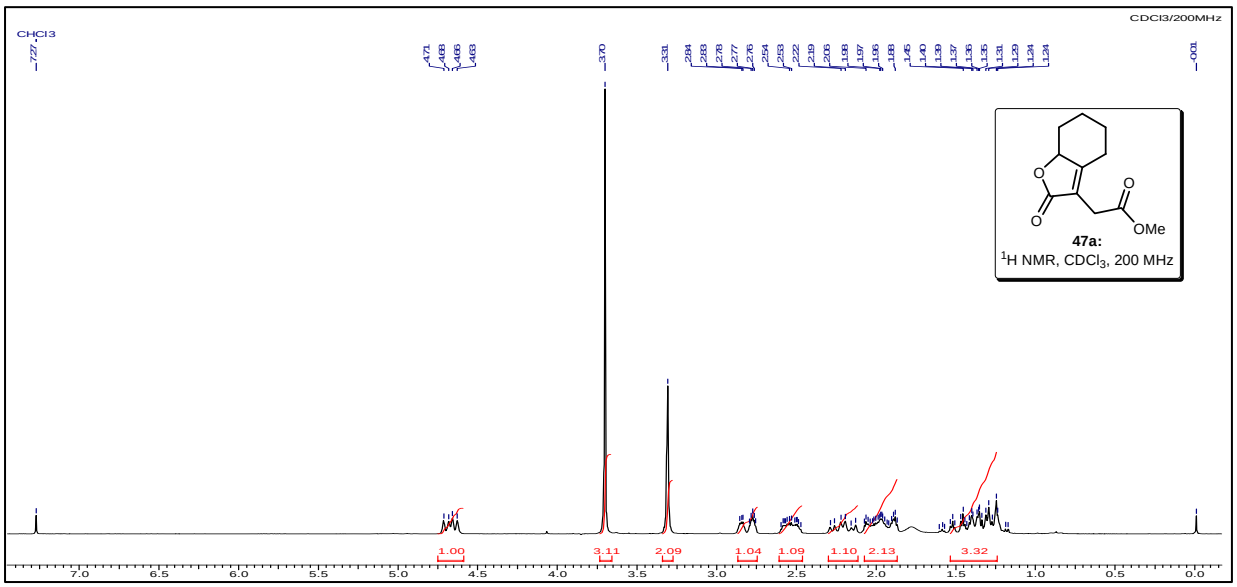
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2.78
2.77
2.76
2.54
2.53
2.22
2.19
2.05
1.98
1.97
1.96
1.88
1.45
1.40
1.39
1.37
1.36
1.35
1.31
1.29
1.24
1.24
0.01
1.00
3.11
2.09
1.04
1.09
1.10
2.13
3.32
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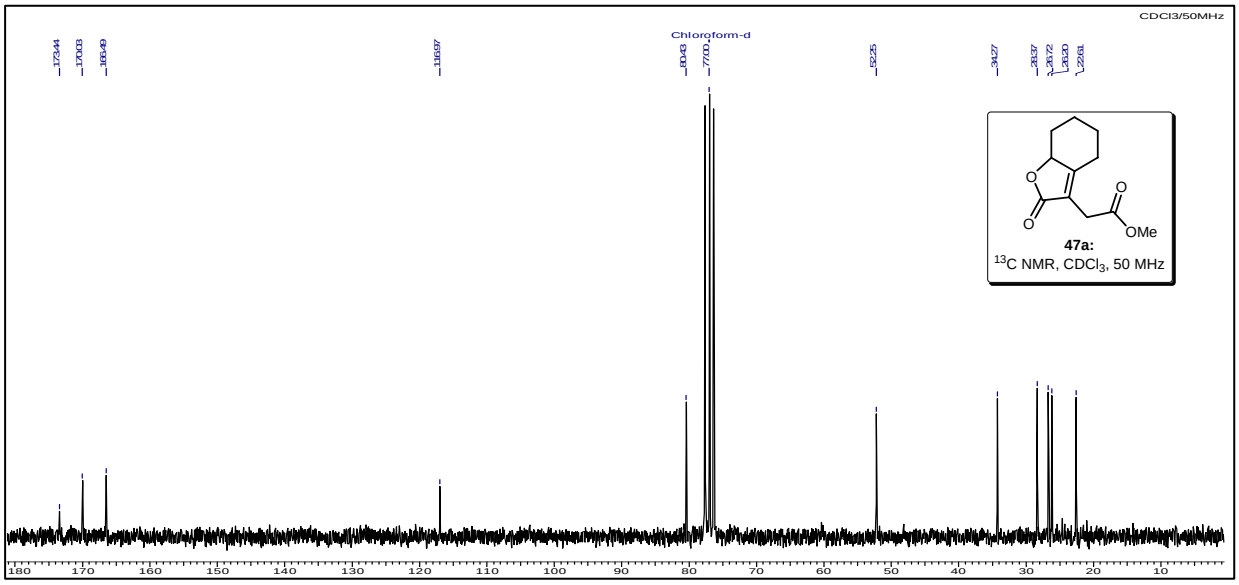
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116.97
80.43
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26.72
26.20
22.61
47a:
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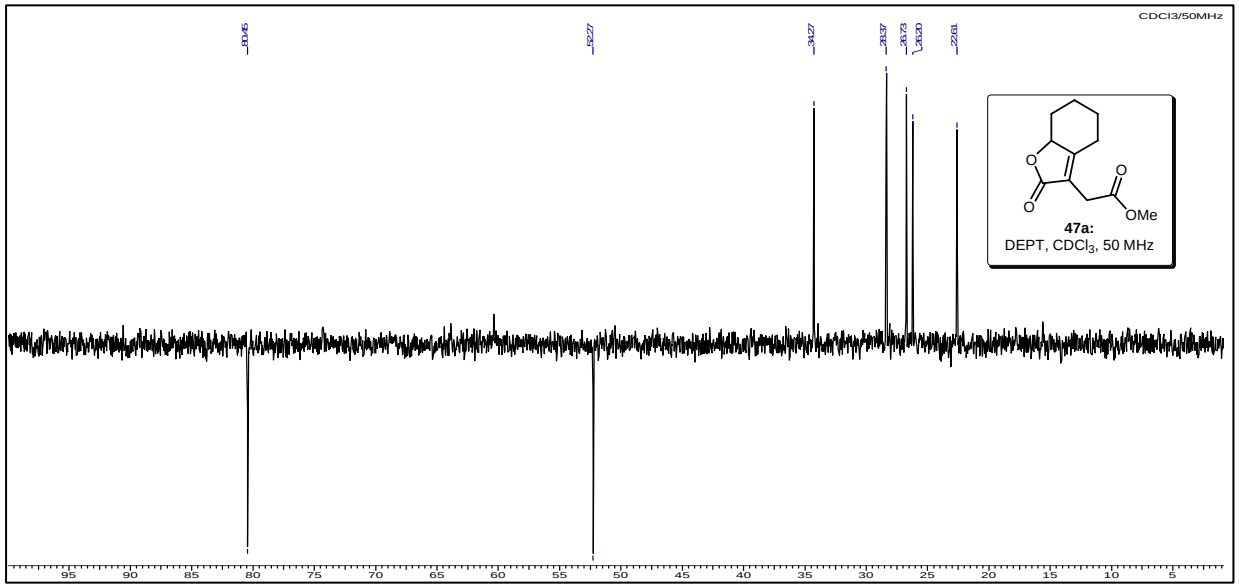
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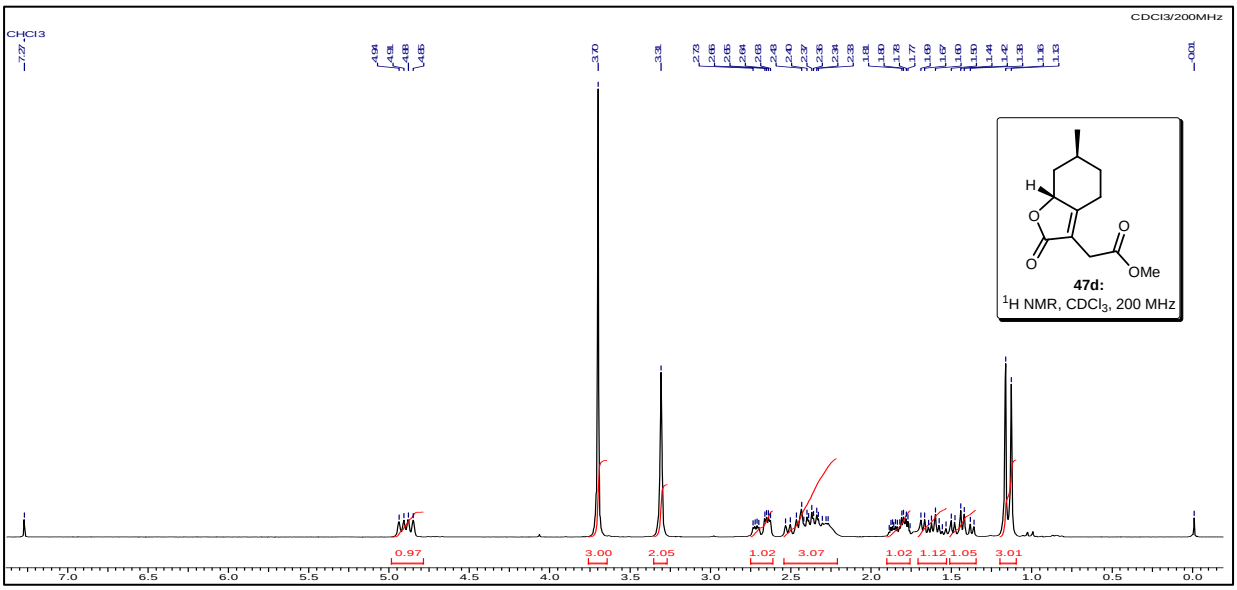
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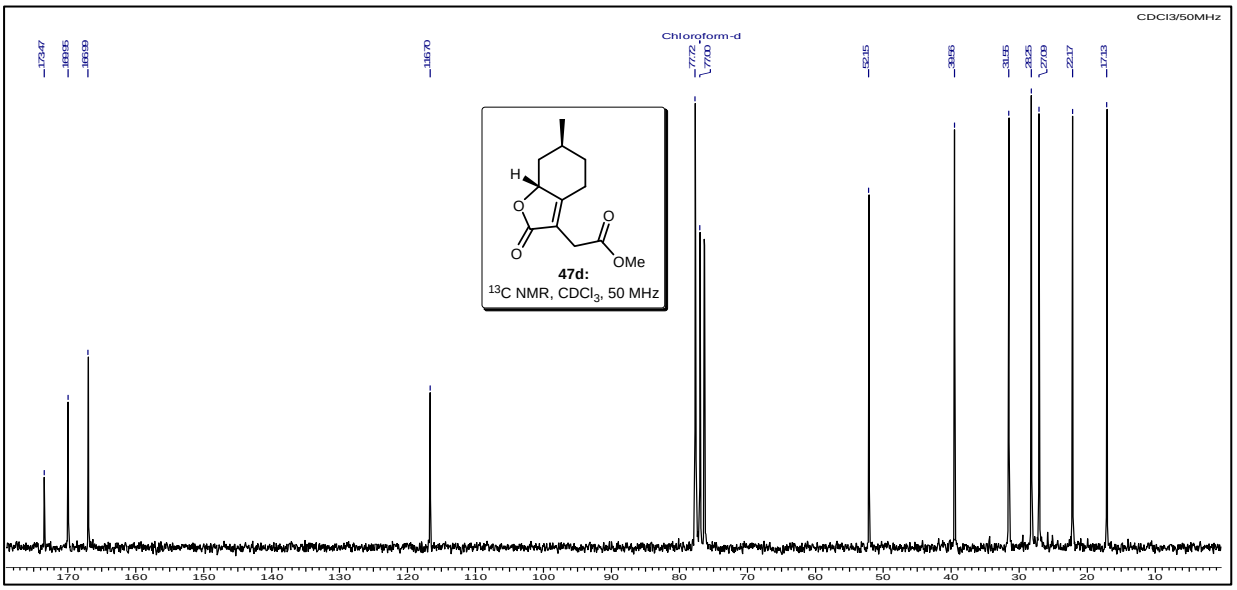
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Chloroform-d
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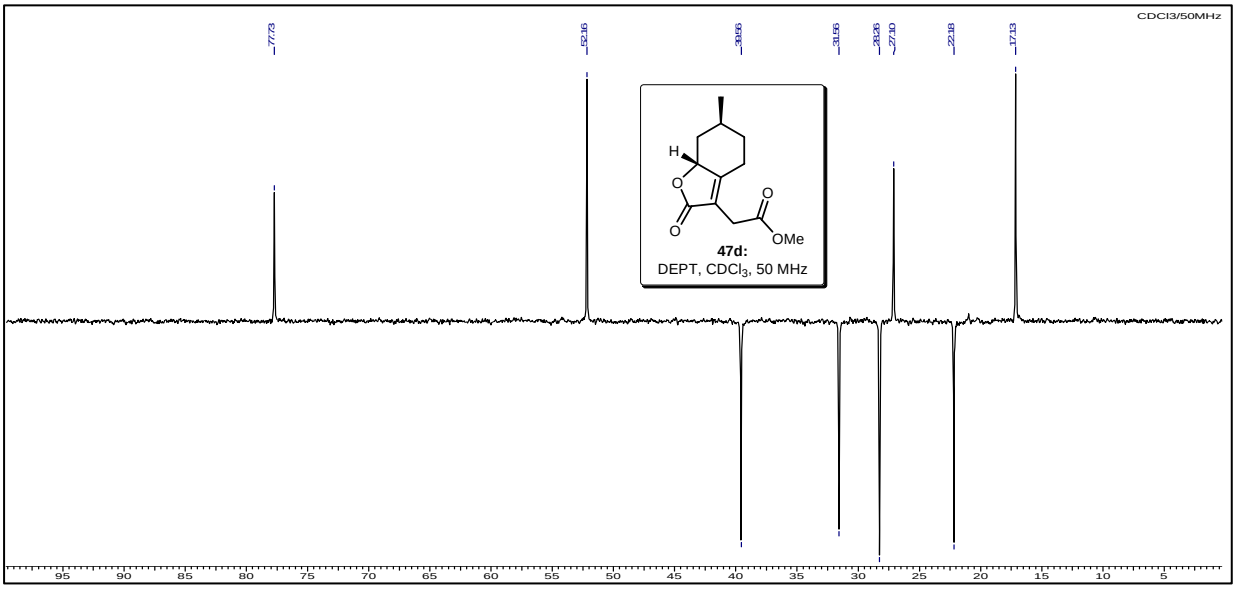
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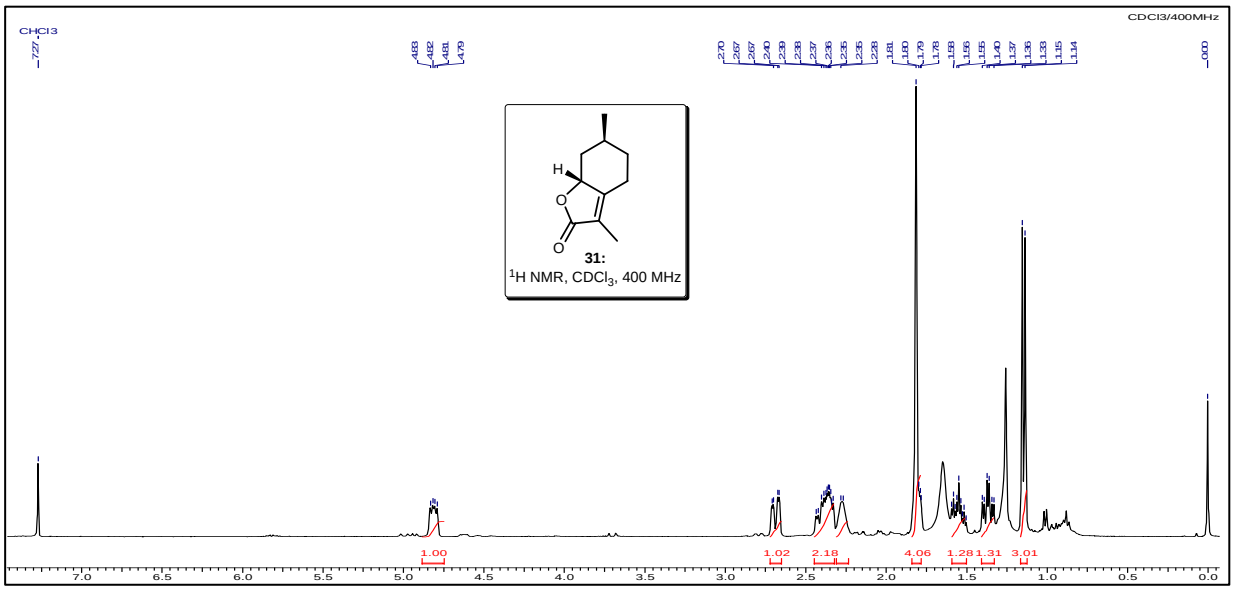
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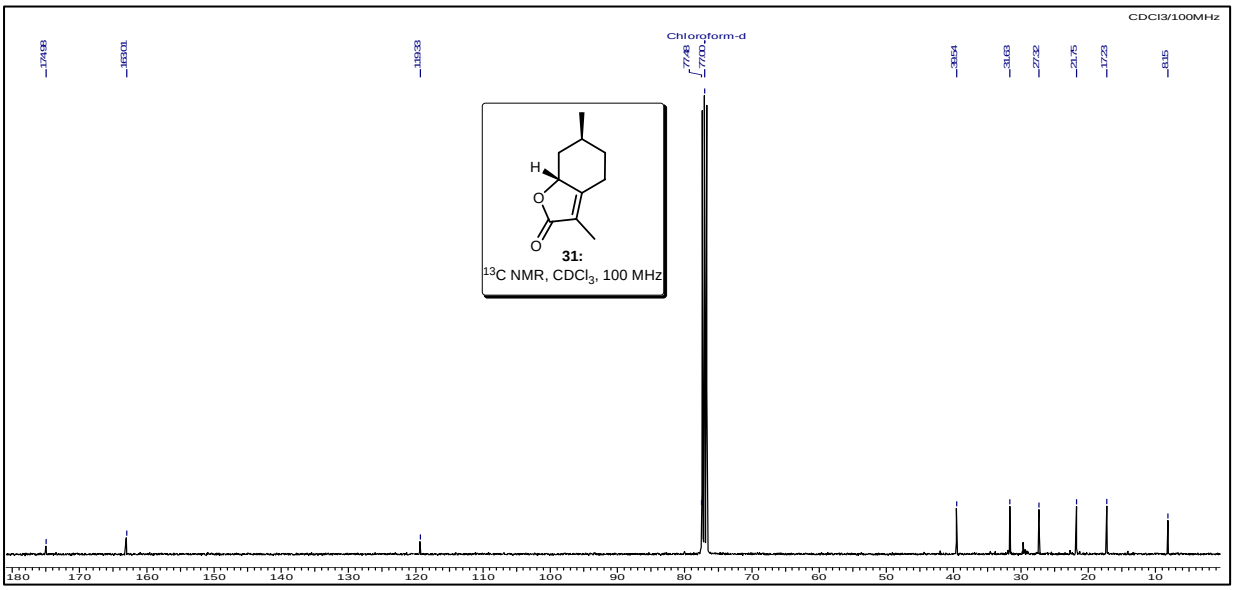
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Chloroform-d
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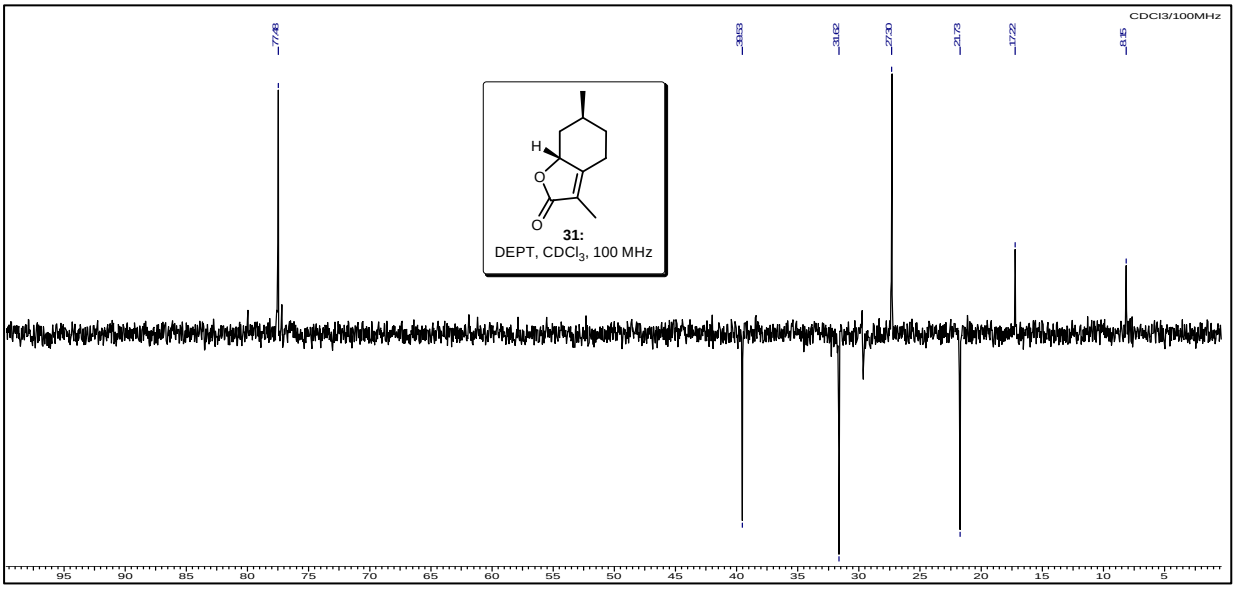
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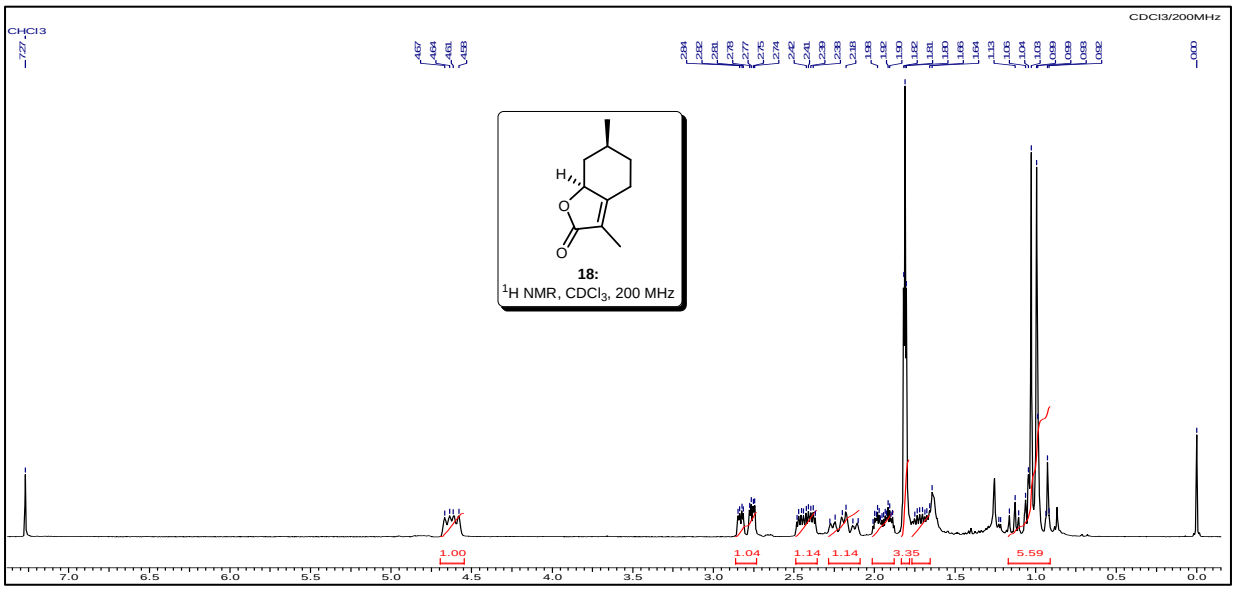
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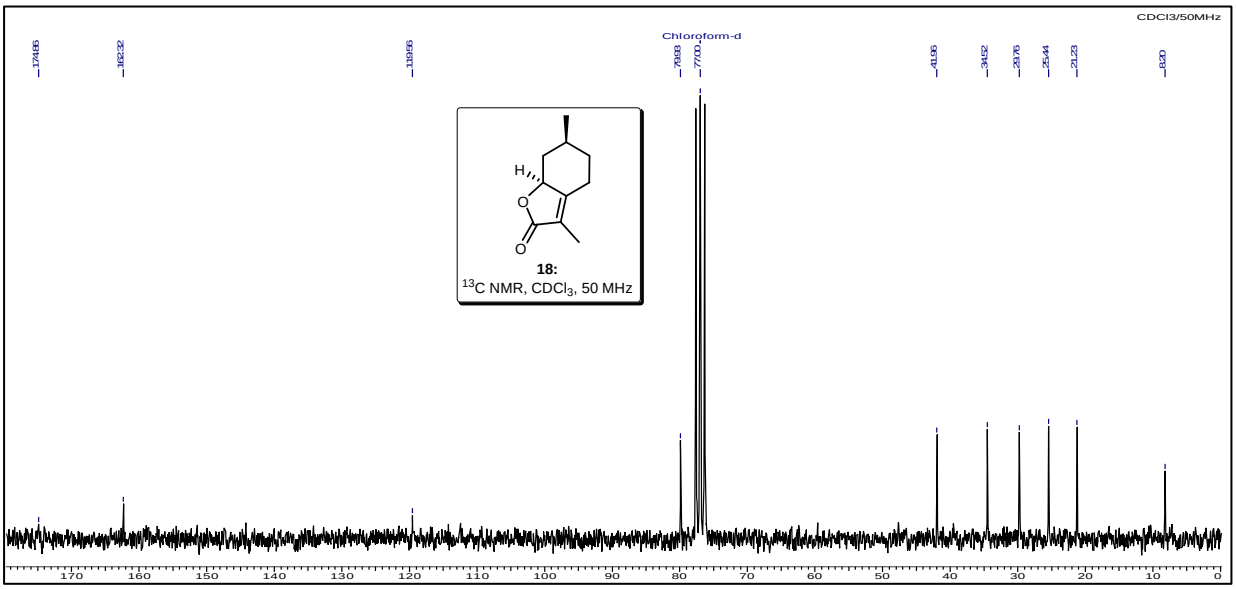
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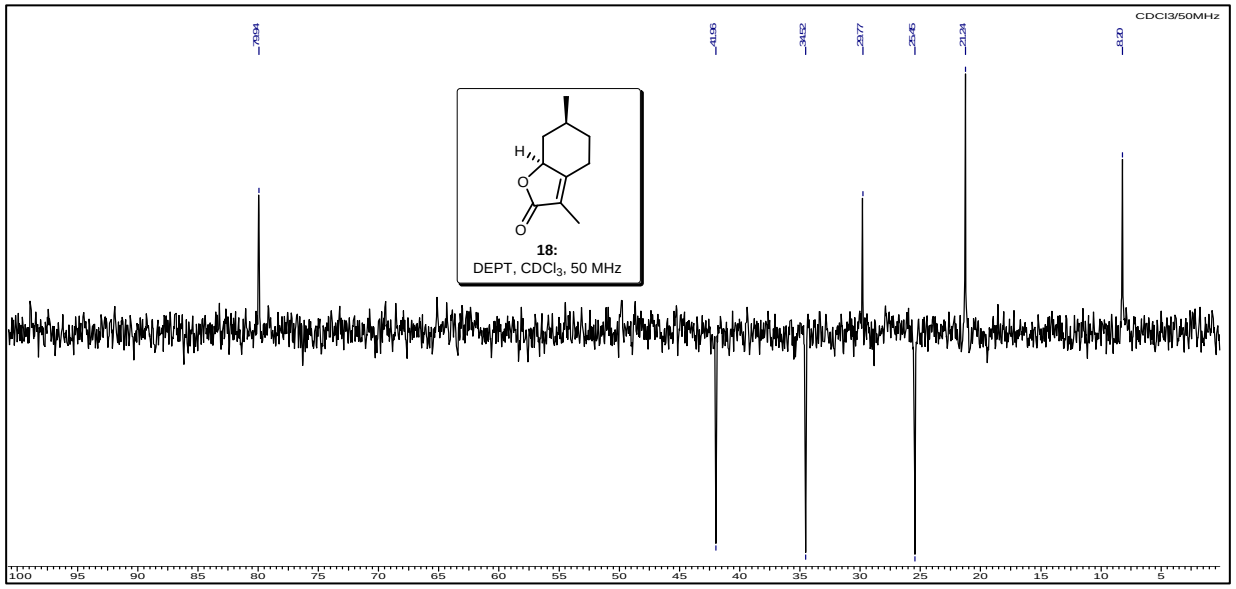
Chloroform-d
18:
13C NMR, CDCl3, 50 MHz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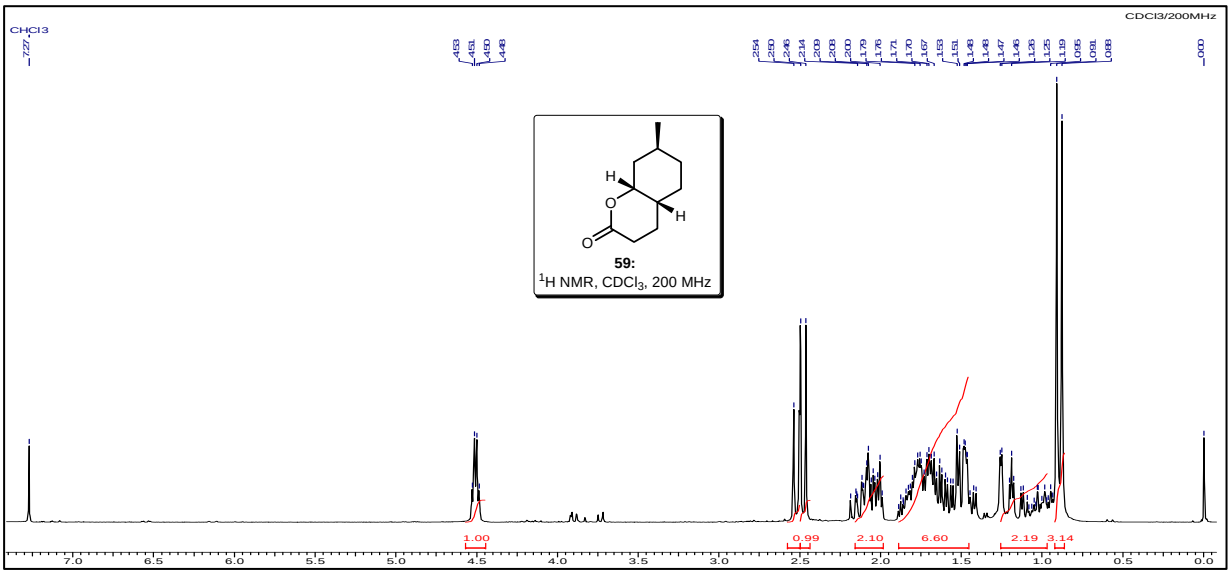
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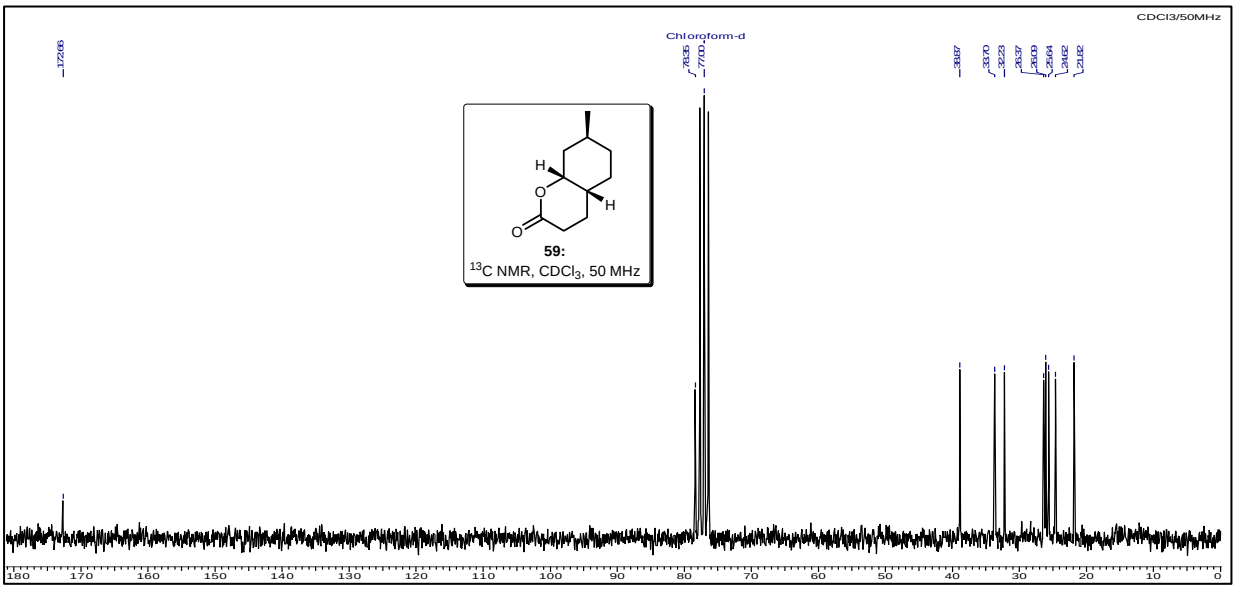
0.99
2.10
6.60
2.19
3.14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Chloroform-d
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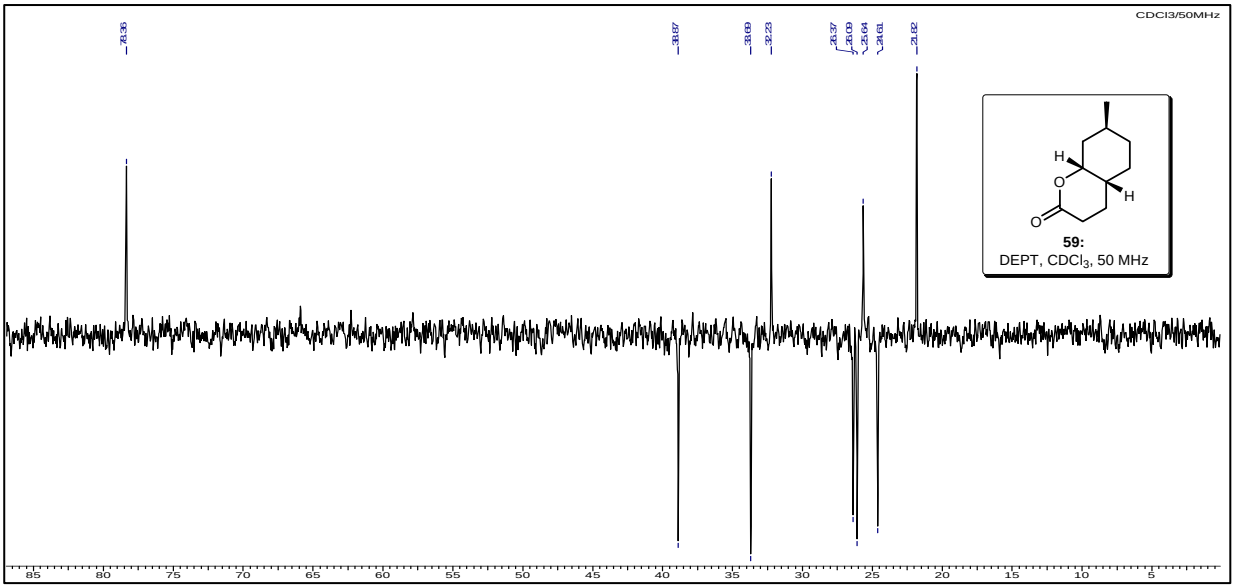
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59:
DEPT, CDCl3, 50 MHz

3B.7: References

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Chapter 4

Racemic and Chemoenzymatic Total Syntheses of Naturally Occurring HIV RNase H Inhibitor 1,3,4,5-Tetragalloylapiitol

This chapter features the following topics:

4.1: Introduction

Human immunodeficiency virus-type 1 (HIV-1) reverse transcriptase (RT) has two distinct enzymatic domains, and these domains separately carry out a RNA-dependent/DNA-dependent DNA polymerization reaction and ribonuclease H (RNase H) hydrolytic activity. RNase H specifically hydrolyzes the RNA strand of a RNA/DNA heteroduplex.[1] The RNase H function of HIV RT is required to effectively incorporate viral genetic information into the host cell genome.[2] While both of the RT activities are critical for viral infectivity, only the polymerase activity has been successfully explored as a target for commercial drugs.[3] Therefore, HIV-1 RNase H remains an attractive molecular target for developing new anti-HIV agents for potential chemotherapeutic applications.[4] Recently in 2007, Gustafson et al.[5] have isolated (–)-1,3,4,5-tetragalloylapiitol (**1**) from the aqueous extract of the plant *Hylodendron gabunensis* and was found to be a potent inhibitor of RNase H enzymatic activity. The structure of **1** was elucidated by NMR analyses and found to be an apiitol (**2**)[6] sugar moiety coupled with four gallic acid (**3**) residues (Figure 1). Optical rotation measurements of the free sugar obtained by basic hydrolysis of 1,3,4,5-tetragalloylapiitol (**1**) indicated that the 3*S*-absolute configuration was the same as that of D-apiitol (**2**). Compound **1** inhibits HIV-1, HIV-2, and human RNase H with IC_{50} values of 0.24, 0.13, and 1.5 μM, respectively, but it does not show inhibition of *E. coli* RNase H at 10 μM.[5]

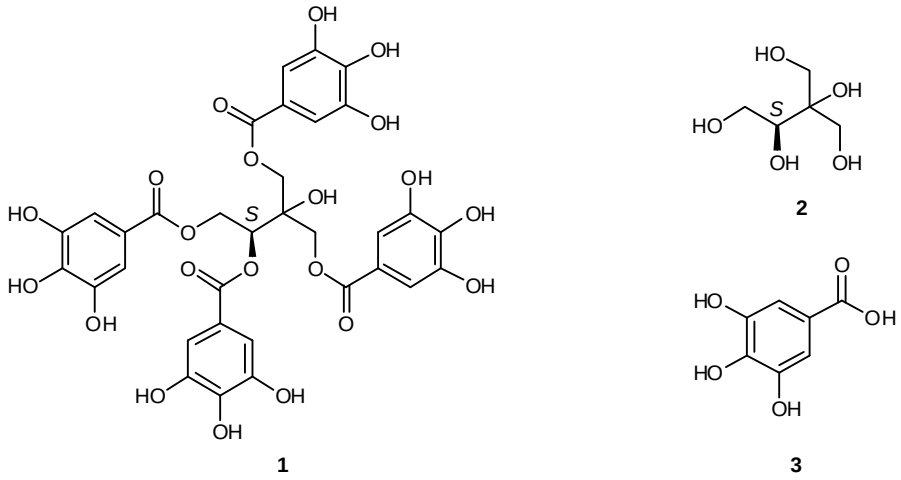


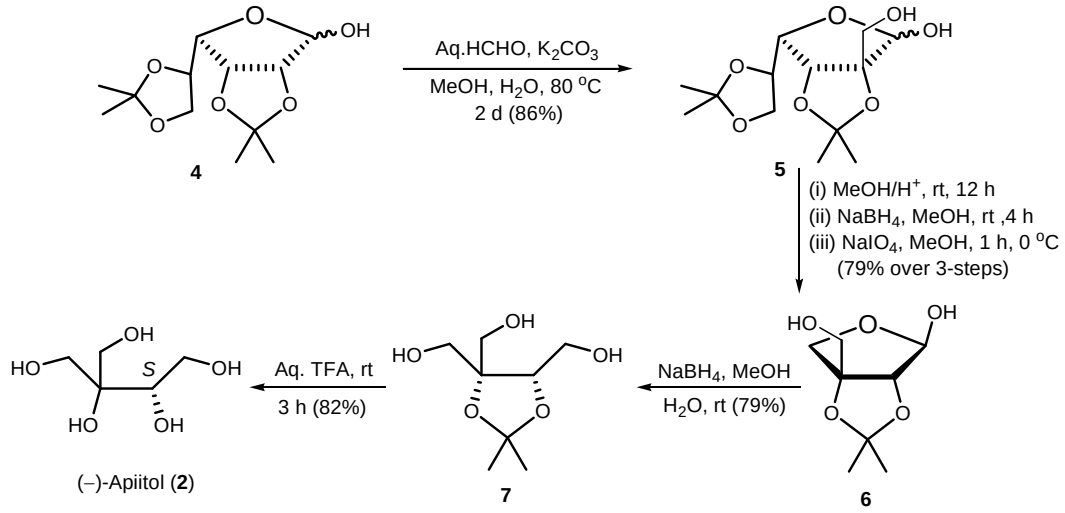
Figure 1. Natural products (–)-1,3,4,5-tetragalloylapiitol (**1**), (–)-apiitol (**2**) and gallic acid (**3**)

4.2: Total synthesis of (±)-1,3,4,5-tetragalloylapiitol

4.2.1: Background

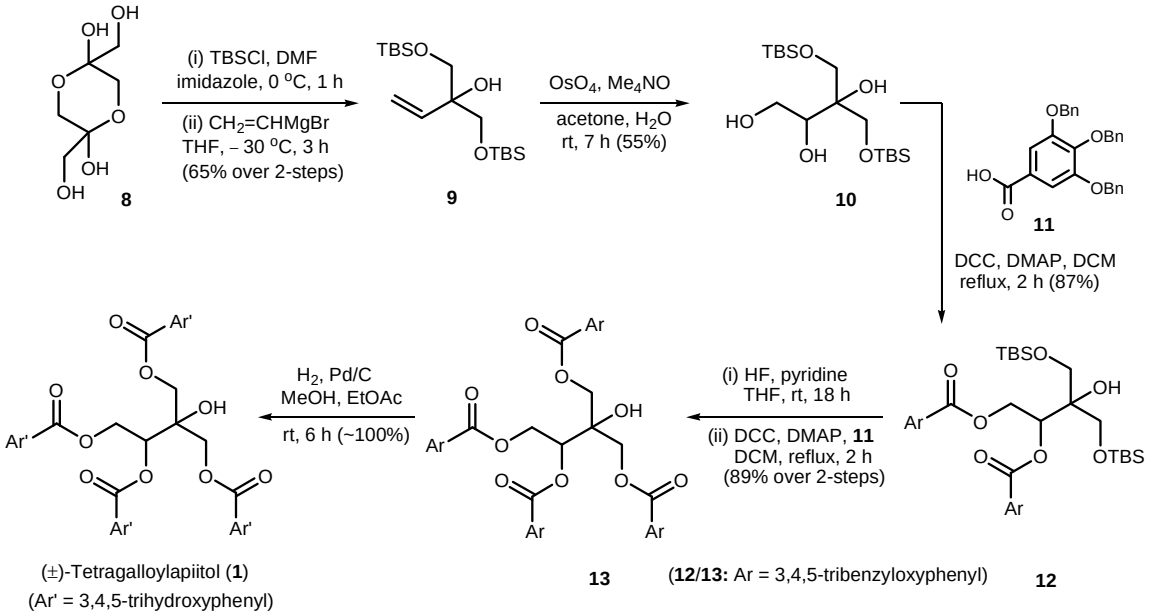
One synthesis of (–)-apiitol (**2**) has been reported by Witczak et al.[7] in 1984. Treatment of 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose[8] (**4**) with aqueous 37% formaldehyde and K_2CO_3 in MeOH at 80 ^oC exclusively furnished the 2-*C*-hydroxymethyl derivative **5** in 86% yield (Scheme 1). The removal of 5,6-*O*-isopropylidene group via selective acidic hydrolysis followed by $NaBH_4$ reduction and $NaIO_4$-oxidation

reaction sequence in one-pot afforded 2-*C*-(hydroxymethy)-2,3-*O*-isopropylidene-D-mannofuranose (**6**) in 79% yield over 3-steps. $NaBH_4$ reduction of **6** gave crystalline 3-*C*-(hydroxymethyl)-2,3-*O*-isopropylideneerythritol (**7**) in 79% yield. Deprotection of ketal **7** with 90% aqueous trifluoroacetic acid provided the desired (–)-apiitol (**2**) in 82% yield. Starting from 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose (**4**), the (–)-apiitol (**2**) was synthesized in 44% overall yield over 6-steps.



Scheme 1. Synthesis of (–)-apiitol from D-mannofuranose

After the successful completion of first total synthesis of (±)-1,3,4,5-tetragalloylapiitol (**1**) from our group,[9] Kraus et al.[10] in 2010, have reported the nice synthesis of (±)-1,3,4,5-tetragalloylapiitol (**1**) starting from 1,3-dihydroxyacetone dimer (**8**) via TBS-ether protection of primary alcohols in DMF using

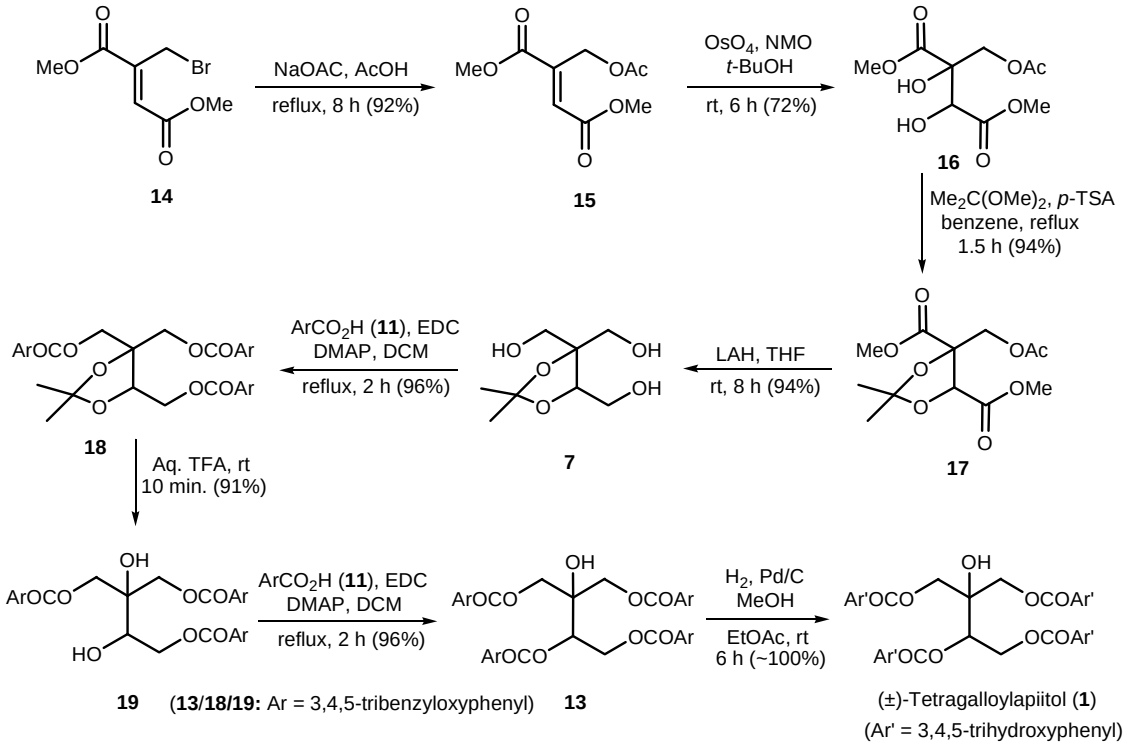


Scheme 2. Synthesis of (±)-1,3,4,5-tetragalloylapiitol from 1,3-dihydroxyacetone dimer

imidazole as a base followed by addition of vinylmagnesium bromide in THF to furnish allyl alcohol **9** in 65% yield over 2-steps (Scheme 2). Dihydroxylation of olefin **9** using catalytic amount of OsO_4 and tetramethylammonium *N*-oxide in aqueous acetone gave required triol **10** in 55% yield, which upon double galloylation using tri-*O*-benzylgallic acid (**11**)[11] and DCC as a coupling reagent furnished the galloylated product **12** in 87% yield. Removal of the TBS-ether protecting groups with HF·pyridine[12] followed by second double galloylation gave the tetraester **13** in 89% yield over 2-steps. Global deprotection[10] of twelve benzyl groups afforded (±)-1,3,4,5-tetragalloylapiitol (**1**) in quantitative yield which was purified by recrystallization from toluene-ethylacetate. Starting from 1,3-dihydroxyacetone dimer (**8**), the (±)-1,3,4,5-tetragalloylapiitol (**1**) was synthesized in 28% overall yields over 7-steps.

4.2.2: Results and discussion

The structural features revealed that the natural products (–)-apiitol (**2**)[6] and gallic acid (**3**) could be the biogenetic precursors of (–)-1,3,4,5-tetragalloylapiitol **1** (Figure 1). We reasoned that cyclic anhydride derivative, the dimethyl bromomethylfumarate (**14**) would be the suitable precursors to design the pentahydroxy sugar, the (±)-apiitol (**2**). One of the hydroxyl group can be generated by allylic nucleophilic substitution reaction of bromine, two hydroxyl units can be introduced by osmium tetroxide dihydroxylation of carbon–carbon double bond and finally, last two hydroxyl units can be originated from the reduction of the two carbonyl groups (Scheme 3).



Scheme 3. First total synthesis of (±)-1,3,4,5-tetragalloylapiitol

The dimethyl bromomethylfumarate (**14**)[13] on refluxing with sodium acetate in acetic acid underwent a smooth chemoselective allylic nucleophilic substitution reaction with the weak nucleophile, the carboxylate anion to yield dimethyl acetoxymethylfumarate (**15**) in 92% yield. The osmium tetroxide induced dihydroxylation of carbon=carbon double bond in **15**, in the presence of *N*-methylmorpholine *N*-oxide (NMO) as the oxidizing agent furnished the diol **16** in 72% yield. The protection of *cis*-diol **16** as ketal **17** (94%), followed by $LiAlH_4$-reduction gave the crystalline triol **7** in 94% yield. The conversion of triol **7** to the sugar, apiitol (**2**) is known in the literature.[7] We envisaged the higher propensity of apiitol for intramolecular dehydrative cyclizations. Therefore, we first transformed the all primary alcohols in triol **7** to the required triester **18** using the triple benzyl protected gallic acid[11] and *N*-ethyl *N*'-(3-dimethylpropyl)carbodiimide (EDC) as the dehydrating agent, in 96% yield. The aqueous TFA-induced chemoselective deprotection of ketal **18** gave the desired diol **19** in 91% yield. Again the EDC induced regioselective dehydrative coupling of secondary alcohol with tribenzyl protected gallic acid[11] yielded dodecabenzyl protected tetraester **13** in 96% yield. Finally, the catalytic hydrogenation using the palladium on charcoal was used for very clean removal of all the twelve benzyl groups to obtain the desired natural product (±)-**1** in ~100% yield. The analytical and spectral data obtained for (±)-1,3,4,5-tetragalloylapiitol (**1**) were in complete agreement with the reported data.[5] Starting from dimethyl bromomethylfumarate (**14**), first total synthesis of potent HIV RNase H inhibitor (±)-1,3,4,5-tetragalloylapiitol (**1**) was demonstrated in 49% overall yield over 8-steps.

4.3: Chemoenzymatic total synthesis of potent HIV RNase H inhibitor (–)-1,3,4,5-tetragalloylapiitol

4.3.1: Background

Enzymes are proteins that are built up in nature from twenty different amino acids. The term enzyme was coined by Kanne in 1876 and experimentation on enzymes began in 1897. Active sites of enzymes evolved to allow the enzymes to mediate biological reactions under ambient conditions and thus they serve as excellent biological "catalysts", forming a bridge between chemistry and biology. Almost all processes in a biological cell need enzymes in order to occur at significant rates. Since enzymes are extremely selective for their substrates and speed up only a selective reactions from among many possibilities, the set of enzymes made in a cell determines which metabolic pathways occur in that cell. Like all catalysts, enzymes work by lowering the activation energy (E_a or $\Delta G^{\ddagger}$) for a reaction, thus dramatically accelerating the rate of the reaction. As with all catalysts, enzymes are not consumed by the reactions they catalyze. The catalytic ability of enzymes depends upon their three-dimensional architectures, which are basically determined by the L-amino acid sequence. The 3-D structure of an enzyme often reveals that it possesses an active site, where the reaction takes place. In a racemic

substrate, only one isomer would possess a complementary structure, that is, the groups are correctly aligned and fit into the active site pockets, while the opposite isomer turns out to be a misfit and does not react. There are six main classes of enzymes as shown:

1. ***Oxidoreductases:*** These enzymes mediate oxidation and reduction, including the insertion of oxygen to alkenes. This group also includes enzymes that are responsible for the addition or removal of hydrogen.
2. ***Transferases:*** These enzymes are involved in the transfer of one group, such as an acyl or a sugar unit from one substrate to another.
3. ***Hydrolases:*** This group includes the enzymes that mediate the hydrolysis or formation of amides, epoxides, esters and nitriles.
4. ***Lyases:*** These are group of enzymes that fragment larger molecules with the elimination of smaller units.
5. ***Isomerases:*** These enzymes are involved in epimerization, racemization and other isomerization reactions.
6. ***Ligases:*** This group includes the enzymes responsible for the formation of C−C, C−N, C−O and C−S bonds.

In recent years, all these enzymes have emerged as powerful tools in organic synthesis for bringing about kinetic resolution of racemates as they are extremely specific in their action and offer a high degree of chemo-, regio- and stereoselectivity, which is of high importance in organic synthesis.

Hydrolases form the most important class of enzymes[14] and among them, the lipases have been the most popular and widely used. Lipases are ubiquitous enzymes that are found in bacteria/fungi,[15] plants[16] and animals.[17] In general, cells produce lipases to hydrolyze the extracellular fats and lipases are specially structured to act at water/organic interface (they undergo an interfacial activation leading to a large increase in hydrolytic activity).[18] For this reason, lipases appear to have optimum property among the enzymes to operate in organic solvents, in this case the interface is between the insoluble enzyme with its essential water of hydration and the organic solvent containing the acylating agent. Taking advantage of this property, chemists have discovered lipases to be one of the most versatile classes of biocatalysts in organic synthesis. The versatility and popularity of lipases could be attributed to their high catalytic efficiency on a broad range of substrates (they can accommodate substrates other than triglycerides such as aliphatic, aromatic, alicyclic and bicyclic esters including the esters based on organometallic sandwich compounds), combined with high regioselectivity and chiral recognition,[18] their high stability in organic solvents and at elevated temperatures,[19] the reversibility of their mode of action,[20] their non-toxic and environment friendly nature[21] and finally their low cost.

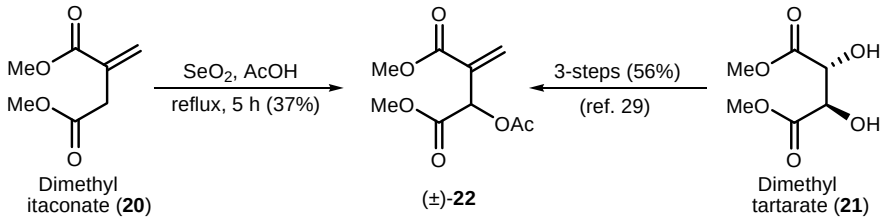
The use of organic solvents for lipase-catalyzed reactions has added a new perspective (in neat organic solvents enzymes retain the minimum amount of water which is necessary for their catalytic activity). This is because of the obvious advantages such as (i) increased substrate solubility and wider range of reactants, (ii) transformations of water-sensitive substrates, (iii) ease of operation and (iv) modified enzyme specificity. Moreover, the use of organic solvents is seen to enhance the enantioselectivity[22] and thermostability[23] of the enzymes, probably due to restricted conformational flexibility. The free energy of fat hydrolysis is close to 0 kJ mol^{-1}.[24] As a result, thermodynamic equilibria are largely governed by the reactant concentrations and lipase catalyzed ester hydrolysis in water can easily be reversed, in non-aqueous media, into ester synthesis or transesterification. The acyl lipase formed in the first step of the enzymatic reaction can formally be considered as an acylating agent. The wide substrate specificity of this enzyme class allows acylation of nucleophiles other than those with hydroxyl groups, for example hydroperoxides, thiols and amines. Hydrolysis is usually performed in a biphasic system consisting of an aqueous buffer and an organic solvent while esterification is effected in an organic solvent with an irreversible acyl donor[20] such as the enol ester vinyl acetate. The enzyme is conveniently removed by filtration during work-up and can be reused.

Secondary alcohols are by far the most widely explored substrates in lipase-catalyzed resolutions. This is not only due to the importance of chiral secondary alcohols in organic synthesis but also that lipases usually show much higher enantioselectivity in the case of secondary alcohols as against primary and tertiary ones. In our group, over the past few years, we have been successfully using the enzymes in preparation of chiral secondary alcohols,[25] other important chiral intermediates and have also carried out studies relating to their selectivity pattern.[26] Earlier three Ph. D. dissertations from our group described details about the use of lipases,[26] so as to avoid repetition a concise introduction has been presented here. In this chapter, as a part of present dissertation, we have accomplished a straightforward chemoenzymatic total synthesis of the naturally occurring potent anti-HIV compound (–)-1,3,4,5-tetragalloylapiitol in very good overall yield via an efficient lipase catalyzed resolution for the preparation of enantiomerically pure building block dimethyl acetoxyitaconate.[27]

4.3.2: Results and discussion

The chemoenzymatic synthesis provides a powerful approach and new opportunities for accessing chemical diversity.[28] We reasoned that (±)-dimethyl 2-acetoxy-3-methylenesuccinate (**22**) would be the potential precursor for the chemoenzymatic total synthesis of (–)-1,3,4,5- tetragalloylapiitol (**1**) via the lipase catalyzed resolution followed by reduction of two ester units and the consequent carbon–carbon double bond dihydroxylation route.

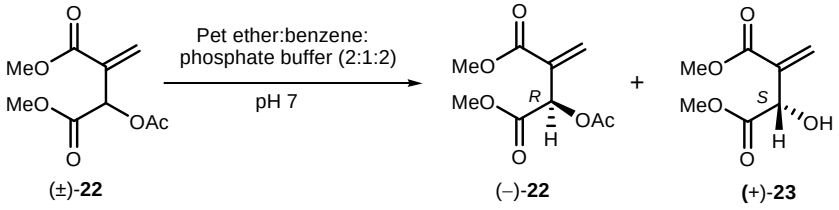
We started our synthesis with selenium dioxide allylic oxidation of dimethyl itaconate (**20**) and obtained the desired product (±)-**22**, but only in 37% yield (Scheme 4). All our attempts to further improve the yield were ineffective and under the forced reaction conditions we always ended up with the formation of decomposed materials and polymeric gums. Even the use of catalytic amount of SeO_2 and *t*-BuOOH at room temperature for the conversion of **20** to (±)-**22** was not effective and the starting material remained unreacted. Finally starting from dimethyl tartarate (**21**), the required precursor (±)-**22** was synthesized in three steps with very good overall yield by using the known Baylis-Hillman reaction between the methyl 2-oxoacetate and methyl acrylate, followed by the *O*-acylation step.[29]



Scheme 4. Synthesis of (±)-dimethyl 2-acetoxy-3-methylenesuccinate

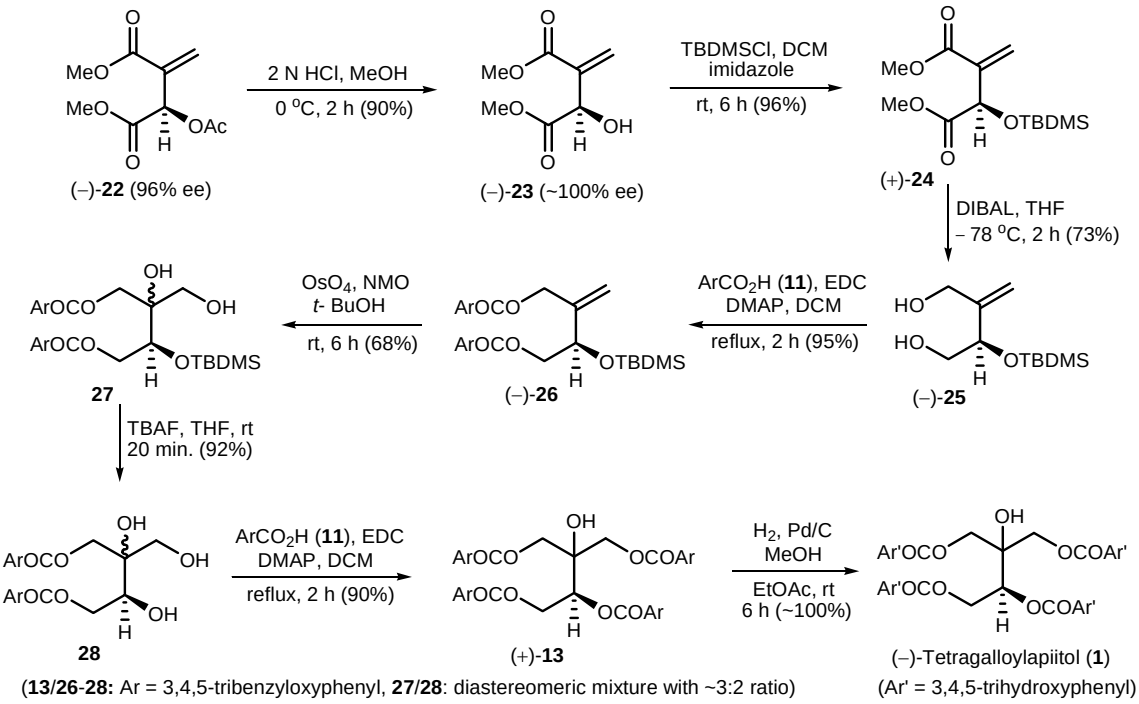
On the basis of higher acidity of a methine proton in (–)-**22** and the anticipated propensity for racemization, an enzymatic resolution of (±)-**22** appeared more appropriate. Hence the systematic studies on biphasic hydrolytic enzymatic resolution of (±)-**22** using the promising enzymes *Pig pancreas* lipase (PPL), *Candida cylindracea* lipase (CCL) and *Pseudomonas cepacia* lipase (Amano PS) for the

Table 1. Lipase catalyzed resolution of (±)-dimethyl 2-acetoxy-3-methylenesuccinate



Entry	Enzyme	Temp/Time[a]	(–)-**22**: % Yield/Ee
1	PPL	25 °C, 48 h	NR[b]
2	PPL	35 °C, 48 h	NR
3	CCL	25 °C, 48 h	NR
4	CCL	35 °C, 48 h	57/25
5	Amano PS	25 °C, 96 h	83/ND[c]
6	Amano PS	35 °C, 8 days	44/95
7	Amano PS	50 °C, 84 h	42/97

[a] Reactions were monitored by HPLC. [b] NR: no reaction. [c] ND: not determined.



Scheme 5. Total synthesis of (–)-1,3,4,5-tetragalloylapiitol from (*R*)-dimethyl 2-hydroxy-3-methylenesuccinate

preparation of enantiomerically pure (–)-**22** were planned.[25,29,30] The enzyme PPL was ineffective in recognizing our racemic substrate **22**, while we obtained very low enantiomeric excess upon exercise of enzyme CCL (Table 1, entry 4). Fortunately, the readily available and relatively cheaper enzyme Amano PS, which is specific for the secondary alcohols, better recognized our starting material (±)-**22**. The Amano PS catalyzed resolutions of (±)-**22** at 25 °C and 35 °C were found to be slow (Table 1, entries 5 and 6). The same Amano PS catalyzed biphasic resolution of (±)-**22** at 50 °Cfurnished the desired unhydrolyzed enantiomerically pure (–)-**22** in 42% yield with 97% ee (by chiral HPLC) in 84 hours (Table 1, entry 7). In the above mentioned enzymatic resolution the hydrolyzed alcohol (+)-**23** was obtained in 58% yield, but with only 53% ee. The same reaction at about 40% conversion also provided the product (+)-**23** in very good yield with 87% ee (by chiral HPLC).[31] We infer that both the multifunctional enantiomerically pure products (–)-**22** and (+)-**23** would serve as an important building blocks for the total synthesis of several desired bioactive natural and unnatural products.

The enantiomerically pure (–)-dimethyl 2-acetoxy-3-methylenesuccinate (**22**) on acid catalyzed methanolysis delivered the desired alcohol (–)-**23** in 90% yield with ~100% ee (by chiral HPLC), which on treatment with TBDMSCl gave the corresponding silyl ether (+)-**24** in 96% yield (Scheme 5). To avoid the foreseen difficulty of possible intramolecular cyclization upon dihydroxylation to form the γ-lactone, we first considered for the reduction of both the ester moieties in (+)-**24** to the corresponding primary alcohols. The DIBAL (6.00 equiv) reduction of diester (+)-**24** at –78 °C exclusively provided the expected

diol (–)-**25** in 73% yield. At this stage we decided for the double gallyolation of diol (–)-**25** rather than the immediate dihydroxylation of the carbon−carbon double bond to form the corresponding tetrol for two obvious reasons viz. (i) to keep the polarity of our intermediate compounds under control for the convenient column chromatographic purifications and (ii) to avoid any plausible intramolecular shuffling of our protecting TBDMS group.[32] The *N*-ethyl *N*'-(3-dimethylpropyl)carbodiimide (EDC) induced dehydrative double coupling of diol (–)-**25** with the triple benzyl protected gallic acid (**11**)[11] furnished the required diester (–)-**26** in 95% yield. The osmium tetroxide induced dihydroxylation of carbon–carbon double bond in compound (–)-**26** in the presence of *N*-methylmorpholine *N*-oxide (NMO) as the oxidizing agent yielded the diastereomeric mixture of desired diol **27** in 68% yield with ~3:2 ratio (by NMR). The TBAF-deprotection of silyl ether **27** provided the expected diastereomeric mixture of triol **28** in 92% yield. It is notable that the triol **28** contains free 1°, 2° and 3° alcohol units, but providentially we did not noticed any intramolecular acyl migration under our reaction conditions.[32a] The second EDC induced selective dehydrative double coupling of 1° and 2° alcohol units in triol **28** with the tri-benzyl protected gallic acid yielded the required enantiomerically pure dodecabenzyl protected tetraester (+)-**13** in 90% yield. The final product **1** is very polar in nature as it contains the free 12-phenolic and an alcoholic hydroxyl groups. Hence we decided to check the enatiomeric purity of the penultimate step product (+)-**13**, alas all attempts to resolve the sample of (±)-**13** from our earlier racemic synthesis[9] on suitable chiral columns were futile. Finally, the hydrogenolysis using the palladium on charcoal was used for the global deprotection of benzyl groups in (+)-**13** to obtain the desired natural product (–)-**1** in ~100% yield. The analytical and spectral data obtained for (–)-1,3,4,5-tetragalloylapiitol (**1**) were in complete agreement with the reported data.[5,9] Starting from enantiomerically pure (–)-dimethyl 2-acetoxy-3-methylenesuccinate (**22**), total synthesis of potent HIV RNase H inhibitor (–)-1,3,4,5-tetragalloylapiitol has been demonstrated in 8-steps with 34% overall yield.

4.4: Summary

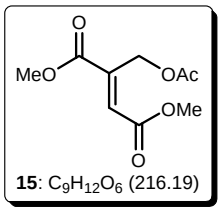
Racemic and chemoenzymatic total syntheses of potent HIV RNase H inhibitor (−)-1,3,4,5-tetragalloylapiitol have been demonstrated using dimethyl bromomethylfumarate and (–)-dimethyl 2-acetoxy-3-methylenesuccinate respectively. In the racemic approach, chemoselective allylic nucleophilic substitution of bromine with the weak nucleophile, the carboxylate anion, osmium tetroxide induced dihydroxylation, chemoselective deprotection of ketal, regioselective dehydrative coupling of secondary alcohol and global deprotection of twelve benzyl groups were the key steps. In the chemoenzymatic synthesis, an efficient enzymatic resolution for the preparation of enantiomerically pure dimethyl acetoxyitaconate and DIBAL reduction of two different ester functions were the involved key steps. We feel that the use of anhydride derivatives for the syntheses of a sugar moiety is noteworthy. We strongly

feel that the present flexible approaches will be useful to design several bioactive tetragalloylapiitol analogs in racemic and enantiomerically pure form for SAR studies, hence HIV-1 RNase H will also become an attractive molecular target for developing new anti-HIV agents for potential chemotherapeutic applications.

4.5: Experimental Section

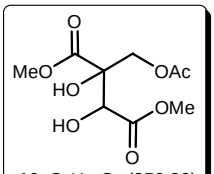
Commercially available osmium tetroxide, *N*-methylmorpholine-*N*-oxide (NMO), 2,2-dimethoxypropane, trifluoroacetic acid, *N*-ethyl *N*'-(3-dimethylpropyl)carbodiimide (EDC), $LiAlH_4$, *N*,*N*-(dimethylamino)pyridine, TBDMCl, DIBAL and TBAF solution in THF (1.0 M) were used. 3,4,5-Tribenzyloxybenzoic acid was prepared using a known procedure.[11]

Dimethyl 2-(acetoxymethyl)fumarate (15). A stirred solution of **14** (7.11 g, 30 mmol) and NaOAc (4.92 g, 60.00 mmol) in AcOH (80 mL) was refluxed for 8 h. The reaction mixture was allowed to reach 25 °C and was concentrated in vacuo. The residue was dissolved in ethyl acetate (50 mL) and the organic layer was washed with 5% aqueous solution of $NaHCO_3$, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using 10% ethyl acetate/petroleum ether as an eluent afforded pure product **15** as a thick oil (5.97 g, 92%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.05 (s, 3H), 3.82 (s, 3H), 3.85 (s, 3H), 5.22 (s, 2H), 6.94 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 20.5, 52.1, 52.7, 57.7, 130.9, 139.8, 164.9, 165.6, 170.2; IR ($CHCl_3$) ν_{max} 1735, 1732, 1729, 1653 cm^{-1}. Anal. Calcd for $C_9H_{12}O_6$: C, 50.00; H, 5.59. Found: C, 50.08; H, 5.47.



15: $C_9H_{12}O_6$ (216.19)

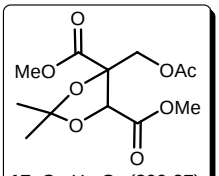
Dimethyl 2-(acetoxymethyl)-2,3-dihydroxysuccinate (16). To a stirred solution of olefin **15** (5.41 g, 25.00 mmol) in *t*-BuOH (30 mL) was added NMO solution in water (60%, 15 mL) with constant stirring at 25 °C. The reaction mixture was cooled to 10 °C and was added solution of OsO_4 in *t*-BuOH (0.1 M, 0.63 mL, 0.13 mmol) with constant stirring. The reaction mixture was stirred at 10 °C for 6 h and then quenched with addition of solid Na_2SO_3 (2.00 g). The stirring was continued for 45 min. and the reaction mixture was extracted with ethyl acetate (25 mL x 3). The combined organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using 40% ethyl acetate/petroleum ether as an eluent furnished pure product **16** as a thick oil (4.51 g, 72%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.06 (s, 3H),



16: $C_9H_{14}O_8$ (250.20)

3.62 (bd, *J* = 8 Hz, 1H), 3.87 (s, 6H), 4.00 (bs, 1H), 4.36–4.49 (m, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 20.5, 53.1, 53.5, 65.5, 72.6, 79.0, 170.3, 170.8, 171.5; IR ($CHCl_3$) ν_{max} 3499, 3481, 1801, 1747, 1643 cm^{-1}. Anal. Calcd for $C_9H_{14}O_8$: C, 43.21; H, 5.64. Found: C, 43.30; H, 5.69.

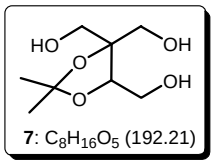
Dimethyl 4-(acetoxymethyl)-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate (17). To a solution of diol **16**



17: $C_{12}H_{18}O_8$ (290.27)

(4.00 g, 16.00 mmol) in benzene (50 mL) was added 2,2-dimethoxypropane (3.33 g, 32.00 mmol) and *p*-toluenesulphonic acid monohydrate (4 mg, 0.02 mmol) and the stirred reaction mixture was refluxed for 1 h using Dean and Stark apparatus containing freshly conditioned 4Å molecular sieves (5 g). The reaction mixture was concentrated in vacuo and silica gel column chromatographic purification of the resulting residue using 30% ethyl acetate/petroleum ether as an eluent afforded pure product **17** as a thick oil (4.36 g, 94%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.45 (s, 3H), 1.58 (s, 3H), 2.03 (s, 3H), 3.79 (s, 3H), 3.83 (s, 3H), 4.34 (s, 2H), 5.07 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 20.5, 25.6, 27.1, 52.5, 53.2, 63.5, 77.9, 83.7, 113.1, 167.9, 169.9, 170.0; IR ($CHCl_3$) ν_{max} 1751, 1749, 1735, 1215 cm^{-1}. Anal. Calcd for $C_{12}H_{18}O_8$: C, 49.65; H, 6.25. Found: C, 49.52; H, 6.33.

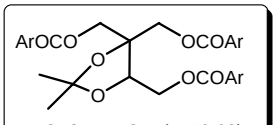
(2,2-Dimethyl-1,3-dioxolane-4,4,5-triyl)trimethanol (7). To a stirring slurry of $LiAlH_4$ (1.38 g, 36.00



7: $C_8H_{16}O_5$ (192.21)

mmol) in THF (60 mL) at 0 °C, a solution of **17** (3.50 g, 12.00 mmol) in THF (40 mL) was added dropwise and the reaction mixture was allowed to reach at room temperature. After stirring for 6 h at 25 °C, the reaction mixture was cooled to 0 °C and very slowly quenched with few drops of saturated aqueous solution of Na_2SO_4. The reaction mixture was filtered through celite. The concentration of the filtrate in vacuo afforded pure product **7** as a white solid (2.32 g, 94%). M.p. 86-88 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.41 (s, 3H), 1.46 (s, 3H), 1.76 (bs, 1H), 2.54 (bs, 1H), 2.95 (bs, 1H), 3.70 (q, *J* = 12 Hz, 2H), 3.78 (s, 2H), 3.93 (d, *J* = 6 Hz, 2H), 4.14 (t, *J* = 6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 26.5, 28.3, 60.0, 62.1, 64.8, 78.8, 83.3, 108.5; IR ($CHCl_3$) ν_{max} 3400–3300 cm^{-1}. Anal. Calcd for $C_8H_{16}O_5$: C, 49.99; H, 8.39. Found: C, 50.07; H, 8.41.

(2,2-Dimethyl-1,3-dioxolane-4,4,5-triyl)tris(methylene)tris(3,4,5-tris(benzyloxy)benzoate) (18). A

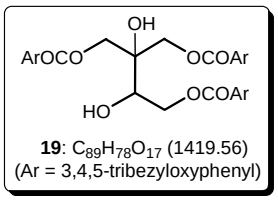


18: $C_{92}H_{82}O_{17}$ (1459.63)
(Ar = 3,4,5-tribezyloxyphenyl)

suspension of triol **7** (482 mg, 2.50 mmol), 3,4,5-tribenzyloxybenzoic acid (4.95 g, 11.25 mmol), EDC (2.87 g, 11.25 mmol) and *N*,*N*-(dimethylamino)pyridine (1.01 g, 8.25 mmol) in CH_2Cl_2 (40 mL) was refluxed for 2 h. The reaction mixture was concentrated in vacuo. The residue was treated with water (50 mL) and extracted with ethyl acetate (25 mL x 3). The combined organic layer was washed with water,

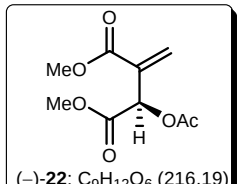
brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using 30% ethyl acetate/petroleum ether (3:7) as an eluent afforded pure product **18** as a white solid (3.51 g, 96%). M.p. 75−76 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.48 (s, 3H), 1.55 (s, 3H), 4.40−4.66 (m, 6H), 4.77 (dd, *J* = 10 and 4 Hz, 1H), 4.96−5.07 (m, 16H), 5.09 (s, 2H), 7.10−7.45 (m, 51H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 26.28, 28.10, 70.87, 70.94, 75.03, 77.07, 81.04, 108.68, 108.75, 108.84, 109.87, 124.11, 124.24, 127.41, 127.46, 127.52, 127.89, 128.06, 128.09, 128.12, 128.35, 128.41, 128.45, 136.45, 136.51, 137.29, 137.34, 137.38, 142.42, 142.56, 142.60, 152.44, 152.49, 152.52, 165.23, 165.48, 165.57; IR ($CHCl_3$) ν_{max} 1719, 1653, 1215 cm^{-1}. Anal. Calcd for $C_{92}H_{82}O_{17}$: C, 75.70; H, 5.66. Found: C, 75.66; H, 5.48.

2,3-Dihydroxy-2-((3,4,5-tris(benzyloxy)benzoyloxy)methyl)butane-1,4-diyl bis(3,4,5-tris(benzyloxy)benzoate) (19). Compound **18** (2.00 g, 1.37 mmol) was dissolved in aqueous TFA (90%, 8 mL) and the mixture was stirred for 10 minutes at 10 °C. The reaction mixture was concentrated in vacuo and to the residue was added toluene and again it was concentrated in vacuo. Silica gel column chromatographic purification of the resulting residue using 20% ethyl acetate/petroleum ether (1:4) as an eluent furnished pure product **19** as a white solid (1.77 g, 91%). M.p. 96−98 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.80−4.10 (m, 2H), 4.30−4.70 (m, 5H), 4.80−5.10 (m, 18H), 7.00−7.40 (m, 51H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 65.09, 65.18, 65.29, 71.02, 74.37, 75.07, 77.15, 108.93, 108.98, 109.02, 124.07, 124.30, 127.43, 127.49, 127.72, 127.88, 127.95, 128.11, 128.27, 128.37, 128.45, 128.61, 136.49, 137.27, 142.58, 142.68, 142.72, 152.47, 152.50, 166.03, 166.35, 166.43; IR ($CHCl_3$) ν_{max} 3506, 3423, 1734, 1719, 1703 cm^{-1}. Anal. Calcd for $C_{89}H_{78}O_{17}$: C, 75.30; H, 5.54. Found: C, 75.41; H, 5.63.



19: $C_{89}H_{78}O_{17}$ (1419.56)
(Ar = 3,4,5-tribezyloxyphenyl)

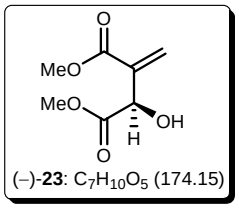
(*R*)-Dimethyl 2-acetoxy-3-methylenesuccinate (22). To a stirred solution of acetate (±)-**22** (1.00 g, 4.63 mmol) in a mixture of petroleum ether and benzene (15 mL, 1:2) were successively added the phosphate buffer (pH 7, 10 mL) and enzyme Amano PS (100 mg). The resulting reaction mixture was stirred at 50 °C for 84 h, with monitoring the reaction progress by chiral HPLC. The reaction mixture was filtered through Celite bed and washed with ethyl acetate (50 mL). The organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using 15% ethyl acetate/petroleum ether as an eluent afforded pure product (**–**)-**22** as a colorless oil (421 mg, 42% yield, 97% ee). $[\alpha]^{25}_D$ = – 49.9 (*c* 0.50, EtOH); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.18 (s, 3H), 3.77 (s, 3H), 3.82 (s, 3H), 6.00 (s, 1H), 6.02 (s, 1H),



(–)-**22**: $C_9H_{12}O_6$ (216.19)

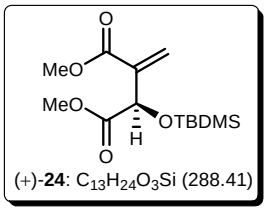
6.51 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 20.6, 52.3, 52.7, 70.2, 130.7, 134.6, 164.8, 168.3, 169.6; ESIMS (*m*/*z*) 217 $[M+H]^+$, 239 $[M+Na]^+$, 255 $[M+K]^+$; IR ($CHCl_3$) ν_{max} 1755, 1747, 1732, 1638 cm^{-1}. In the above mentioned enzymatic resolution the hydrolyzed opposite isomer (+)-**23** was obtained in 58% yield with only 53% ee. *HPLC conditions:* column: Kromasil 5-CelluCoat (250 x 4.6 mm), wavelength: 220 nm, flow rate: 0.5 mL/min, retention time: 19.8 min (+)-isomer, 25.2 min (–)-isomer.

(*R*)-Dimethyl 2-hydroxy-3-methylenesuccinate (23). To a stirred solution of acetate (–)-**22** (400 mg, 1.85 mmol) in methanol (10 mL) at 0 °C was added 2 N HCl (10 mL) and the reaction mixture was further stirred for 2 h. The reaction mixture was concentrated in vacuo and the obtained residue was diluted with ethyl acetate (20 mL). The organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using 25% ethyl acetate/petroleum ether as an eluent afforded pure product (–)-**23** as a colorless oil (290 mg, 90%). $[\alpha]^{25}_D$ = –19.7 (*c* 0.68, EtOH); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.58 (br s, 1H), 3.79 (s, 6H), 4.88 (br s, 1H), 5.97 (s, 1H), 6.39 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 52.1, 53.0, 71.2, 129.2, 137.8, 165.6, 172.7; ESIMS (*m*/*z*) 175 $[M+H]^+$, 197 $[M+Na]^+$; IR ($CHCl_3$) ν_{max} 3503, 1746, 1726, 1636 cm^{-1}.



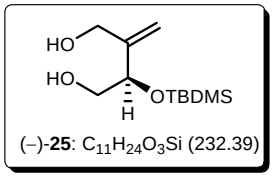
(–)-**23**: $C_7H_{10}O_5$ (174.15)

(*R*)-Dimethyl 2-((*tert*-butyldimethylsilyl)oxy)-3-methylenesuccinate (24). To a stirred solution of alcohol (–)-**23** (250 mg, 1.44 mmol) in dichloromethane (10 mL) at 0 °C were added imidazole (108 mg, 1.58 mmol) and TBDMSCl (239 mg, 1.58 mmol). The reaction mixture was allowed to attain room temperature and further stirred for 6 h. The reaction mixture was concentrated in vacuo and the obtained residue was diluted with ethyl acetate (20 mL). The organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using 5% ethyl acetate/petroleum ether as an eluent afforded pure product (+)-**24** as a colorless oil (397 mg, 96%). $[\alpha]^{25}_D$ = + 23.9 (*c* 0.60, EtOH); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.10 (s, 3H), 0.13 (s, 3H), 0.91 (s, 9H), 3.72 (s, 3H), 3.78 (s, 3H), 5.08 (dd, *J* = 2 and 2 Hz, 1H), 6.07 (dd, *J* = 2 and 2 Hz, 1H), 6.38 (dd, *J* = 2 and 2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ –5.4, –5.2, 18.3, 25.6, 52.0, 52.3, 70.9, 126.4, 138.7, 165.9, 171.2; ESIMS (*m*/*z*) 289 $[M+H]^+$, 311 $[M+Na]^+$; IR ($CHCl_3$) ν_{max} 1759, 1736, 1686 cm^{-1}.



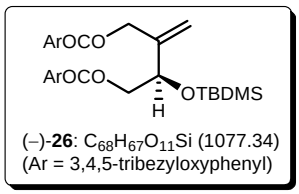
(+)-**24**: $C_{13}H_{24}O_3Si$ (288.41)

(*R*)-2-((*tert*-Butyldimethylsilyl)oxy)-3-methylenebutane-1,4-diol (25). To a stirred solution of diester (+)-**24** (350 mg, 1.22 mmol) in THF (10 mL) at ⁻78 °C was dropwise added DIBAL solution in toluene (1 M, 7.30 mL, 7.30 mmol) and the reaction mixture was stirred for 2 h at the same temperature. The reaction was quenched with saturated NH_4Cl solution and then concentrated in vacuo. The obtained residue was diluted with ethyl acetate (20 mL) and washed with brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using 40% ethyl acetate/petroleum ether as an eluent afforded pure product (–)-**25** as a colorless oil (206 mg, 73%). $[\alpha]^{25}_D$ = –7.0 (*c* 0.16, EtOH); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.07 (s, 3H), 0.10 (s, 3H), 0.91 (s, 9H), 2.46 (br s, 2H), 3.54–3.70 (m, 2H), 4.10 (d, *J* = 12 Hz, 1H), 4.21 (d, *J* = 12 Hz, 1H), 4.34 (t, *J* = 6 Hz, 1H), 5.18 (br s, 1H), 5.20 (br s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ –5.1, –4.8, 18.1, 25.7, 63.1, 66.5, 75.2, 114.2, 148.1; ESIMS (*m*/*z*) 255 $[M+Na]^+$; HRMS (ESI) calcd for $C_{11}H_{24}O_3NaSi$ 255.1392, found 255.1383; IR ($CHCl_3$) ν_{max} 3456, 1652 cm^{-1}.



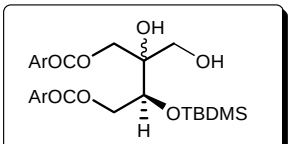
(–)-**25**: $C_{11}H_{24}O_3Si$ (232.39)

(*R*)-2-((*tert*-Butyldimethylsilyl)oxy)-3-methylenebutane-1,4-diyl bis(3,4,5-tris(benzyloxy)benzoate) (26). To a stirred solution of mixture of diol (–)-**25** (150 mg, 0.65 mmol), 3,4,5-tris(benzyloxy)benzoic acid (tribenzylgallic acid) (626 mg, 1.42 mmol) and catalytic amount of DMAP in dichloromethane (10 mL) at room temperature was dropwise added a solution of EDCI (371 mg, 1.94 mmol) in dichloromethane (3 mL). The reaction mixture was further stirred for 3 h and then quenched with water (10 mL). The reaction mixture was extracted with dichloromethane (2 X 25 mL) and the combined organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using 15% ethyl acetate/petroleum ether as an eluent afforded pure product (–)-**26** as a white solid (662 mg, 95%). Mp 59–61 °C; $[\alpha]^{25}_D$ = –4.2 (*c* 0.34, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.08 (s, 3H), 0.10 (s, 3H), 0.91 (s, 9H), 4.38 (d, *J* = 6 Hz, 2H), 4.62 (t, *J* = 6 Hz, 1H), 4.80–5.00 (m, 2H), 5.05 (s, 4H), 5.09 (s, 8H), 5.34 (s, 1H), 5.40 (s, 1H), 7.15–7.45 (m, 34H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ –4.9, –4.8, 18.1, 25.7, 64.4, 68.2, 71.04, 71.06, 72.3, 75.1, 108.9, 117.1, 125.0, 127.46, 127.49, 127.86, 127.94, 128.1, 128.4, 128.5, 136.56, 136.62, 137.4, 142.36, 142.41, 143.4, 152.49, 152.53, 165.7, 165.9; ESIMS (*m*/*z*) 1100 $[M+Na]^+$; IR ($CHCl_3$) ν_{max} 1716, 1590 cm^{-1}. Anal. Calcd for $C_{67}H_{68}O_{11}Si$: C, 74.70; H, 6.36. Found: C, 74.37; H, 5.84.



(–)-**26**: $C_{68}H_{67}O_{11}Si$ (1077.34)
(Ar = 3,4,5-tribezyloxyphenyl)

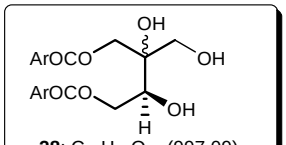
3-((*tert*-Butyldimethylsilyl)oxy)-2-hydroxy-2-(hydroxymethyl)butane-1,4-diyl bis(3,4,5-tris(benzyloxy)benzoate) [diastereomeric mixture (3:2), **27].** To a stirred solution of diester (–)-**26** (600



27: $C_{67}H_{70}O_{13}Si$ (1111.35)
(Ar = 3,4,5-tribezyloxyphenyl)

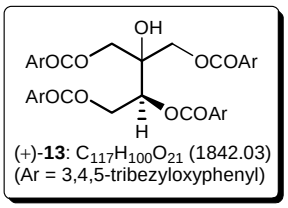
mg, 0.56 mmol) and aqueous solution of NMO (60%, 3 mL) in *t*-butanol (10 mL) at room temperature was added OsO_4 solution in *t*-butanol (0.22 mL, 1 M, 0.22 mmol) and the reaction mixture was further stirred for 6 h. The reaction was quenched with saturated solution of sodium sulfite and concentrated in vacuo. The obtained residue was diluted with ethyl acetate (25 mL) and washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using 35% ethyl acetate/petroleum ether as an eluent afforded product **27** as a colorless oil (421 mg, 68%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.07–0.13 (m, 12H), 0.92 (s, 18H), 2.42 (br s, 4H), 3.65–3.83 (m, 4H), 4.05–4.10 (m, 2H), 4.35–4.70 (m, 8H), 5.02–5.15 (m, 24H), 7.20–7.45 (m, 68H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ –5.6, 18.2, 25.8, 64.1, 64.3, 64.9, 65.0, 65.4, 65.9, 71.06, 71.12, 72.5, 74.0, 74.3, 75.1, 108.96, 109.01, 109.07, 109.10, 124.3, 124.6, 124.68, 124.71, 127.4, 127.5, 127.9, 127.96, 127.98, 128.2, 128.5, 136.6, 137.32, 137.34, 142.4, 142.57, 142.62, 152.5, 152.6, 166.1, 166.25, 166.31, 166.6; ESIMS (*m*/*z*) 1134 $[M+Na]^+$; IR ($CHCl_3$) ν_{max} 3463, 1716, 1590 cm^{-1}. Anal. Calcd for $C_{67}H_{70}O_{13}Si$: C, 72.41; H, 6.35. Found: C, 72.11; H, 6.78.

2,3-Dihydroxy-2-(hydroxymethyl)butane-1,4-diyl bis(3,4,5-tris(benzyloxy)benzoate) [diastereomeric mixture (3:2), **28].** To a stirred solution of diol **27** (400 mg, 0.36 mmol) in THF (10 mL) at 0 °C was added TBAF solution in THF (1 M, 0.43 mL, 0.43 mmol) and the reaction mixture was further stirred at the same temperature for 20 min. The reaction was then quenched with saturated solution of NH_4Cl and concentrated in vacuo. The obtained residue was diluted with ethyl acetate (25 mL) and the organic layer was washed with brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using 65% ethyl acetate/petroleum ether as an eluent afforded product **28** as a colorless oil (330 mg, 92%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.22 (br s, 4H), 3.56–3.90 (m, 4H), 4.00–4.12 (m, 2H), 4.35–4.70 (m, 8H), 4.92–5.00 (m, 2H), 5.00–5.15 (m, 24H), 7.15–7.45 (m, 68H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 63.6, 64.1, 65.1, 65.3, 65.65, 65.69, 71.20, 71.24, 72.1, 72.2, 74.3, 74.8, 75.12, 75.14, 109.2, 109.25, 109.33, 109.4, 127.46, 127.48, 127.5, 127.6, 127.95, 127.97, 128.0, 128.1, 128.2, 128.3, 128.4, 128.46, 128.48, 128.50, 128.53, 136.56, 136.59, 137.31, 137.33, 152.58, 152.61, 166.5, 166.56, 166.58, 166.7; ESIMS (*m*/*z*) 1020 $[M+Na]^+$; IR ($CHCl_3$) ν_{max} 3462, 1716, 1590 cm^{-1}. Anal. Calcd for $C_{61}H_{56}O_{13}$: C, 73.48; H, 5.66. Found: C, 73.08; H, 5.33.



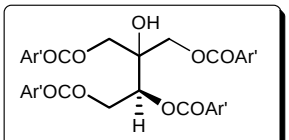
28: $C_{61}H_{56}O_{13}$ (997.09)
(Ar = 3,4,5-tribezyloxyphenyl)

(*S*)-3-Hydroxy-3-(((3,4,5-tris(benzyloxy)benzoyl)oxy)methyl)butane-1,2,4-triyl tris(3,4,5-tris(benzyloxy)benzoate) (13). To a stirred solution of mixture of triol **28** (300 mg, 0.30 mmol), 3,4,5-tris(benzyloxy)benzoic acid (tribenzylgallic acid) (291 mg, 0.66 mmol) and DMAP (4 mg, 0.03 mmol) in dichloromethane (15 mL) was dropwise added a solution of EDCI (172 mg, 0.90 mmol) in dichloromethane (5 mL) at room temperature. The reaction mixture was stirred for 5 h and then quenched with water (15 mL). The reaction mixture was extracted with dichloromethane (2 X 30 mL). The combined organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using 40% ethyl acetate/petroleum ether as an eluent afforded pure product (+)-**13** as a white solid (499 mg, 90%). Mp 130–131 °C; $[\alpha]^{25}_{D}$ = +26.5 (*c* 0.11, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.42 (br s, 1H), 4.46 (dd, *J* = 25 and 15 Hz, 2H), 4.58 (d, *J* = 10 Hz, 1H), 4.62–4.68 (m, 1H), 4.70 (d, *J* = 10 Hz,1H), 4.87–5.15 (m, 25H), 5.87–5.93 (m, 1H), 7.15–7.45 (m, 68H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 62.7, 65.4, 65.5, 70.9, 71.0, 71.1, 72.3, 74.3, 75.0, 75.1, 108.8, 109.1, 109.3, 123.9, 123.95, 124.03, 124.4, 127.4, 127.46, 127.52, 127.6, 127.8, 127.9, 127.96, 127.98, 128.09, 128.14, 128.3, 128.39, 128.40, 128.45, 128.47, 128.5, 136.3, 136.4, 136.5, 136.6, 137.3, 137.37, 137.38, 142.5, 142.8, 142.9, 143.1, 152.5, 152.56, 152.58, 152.61, 165.1, 165.7, 166.1, 166.2; ESIMS (*m*/*z*) 1859 $[M+NH_3]^+$, 1865 $[M+Na]^+$, 1881 $[M+K]^+$; IR ($CHCl_3$) ν_{max} 3447, 1724, 1589, 1215 cm^{-1}. [Similarly, the compound **19** was transformed to (±)-**13**].



(+)-**13**: $C_{117}H_{100}O_{21}$ (1842.03)
(Ar = 3,4,5-tribezyloxyphenyl)

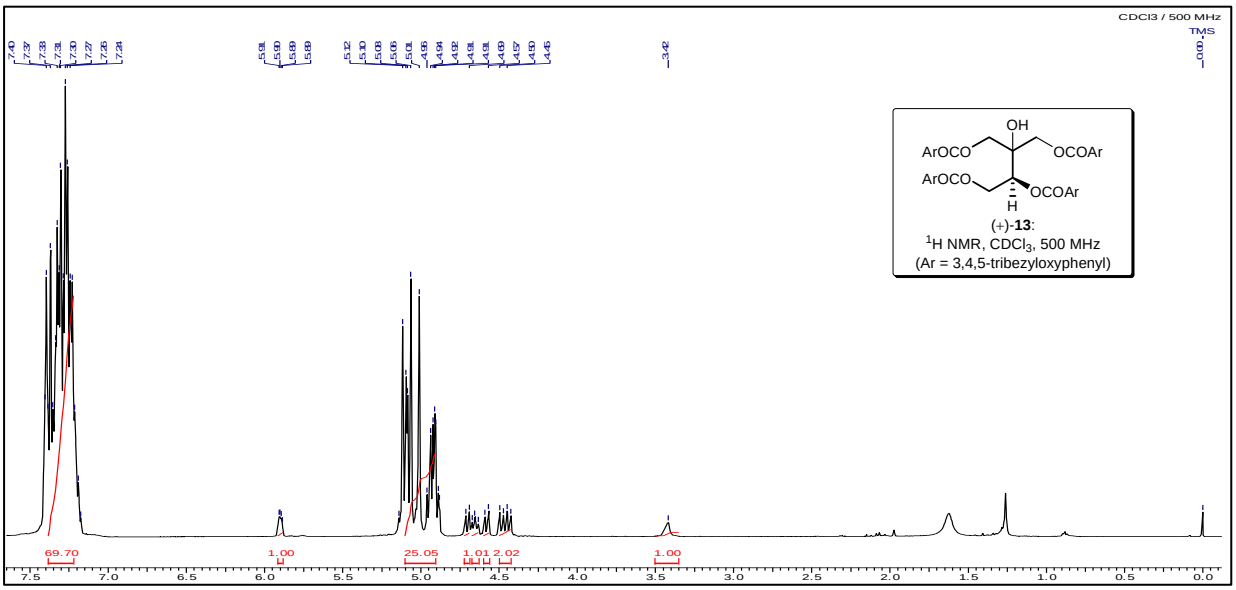
(*S*)-3-Hydroxy-3-(((3,4,5-trihydroxybenzoyl)oxy)methyl)-butane-1,2,4-triyl tris(3,4,5-trihydroxybenzoate) [(–)-tetragalloylapiitol, 1a]. To a stirred solution of (+)-**13** (450 mg, 0.24 mmol) in a mixture of ethyl acetate and methanol (20 mL, 1:1) at room temperature was added 10% Pd/C (50 mg) and the reaction mixture was subjected to hydrogenation at 65-psi hydrogen pressure for 8 h. The reaction mixture was filtered through Celite bed and washed with methanol. The concentration of the filtrate in vacuo followed by silica gel column chromatographic purification of the resulting residue using methanol/chloroform (3:1) as an eluent furnished pure product (–)-**1** as pale purple solid (185 mg, ~100%). The analytically pure sample was obtained by reversed-phase C_{18} HPLC (Grace Denali i.d. 4 x 250 mm) with a isocratic elution from 30% aqueous MeOH. Mp > 300 °C; $[\alpha]^{25}_{D}$ = –23.6 (*c* 0.03, MeOH); ^{1}H NMR (C_5D_5N, 400 MHz) δ 4.88 (d, *J* = 12 Hz, 1H), 4.92 (d, *J* = 12 Hz, 1H), 4.98 (d, *J* = 12 Hz, 1H), 5.06 (dd, *J* = 12 and 8 Hz, 1H), 5.12 (d, *J* = 12 Hz, 1H), 5.31 (br d, *J* = 12 Hz, 1H), 6.45 (dd, *J* = 8 and 4 Hz, 1H), 7.80 (s, 2H), 7.82 (s, 2H), 7.84 (s, 2H), 7.87 (s, 2H); ^{13}C NMR (C_5D_5N, 100 MHz) δ 63.8, 65.5, 72.7, 74.3, 110.3, 120.5, 120.66, 120.71, 141.1, 141.2, 147.4, 147.5, 166.4, 166.8, 166.9, 167.1; ESIMS (*m*/*z*) 759

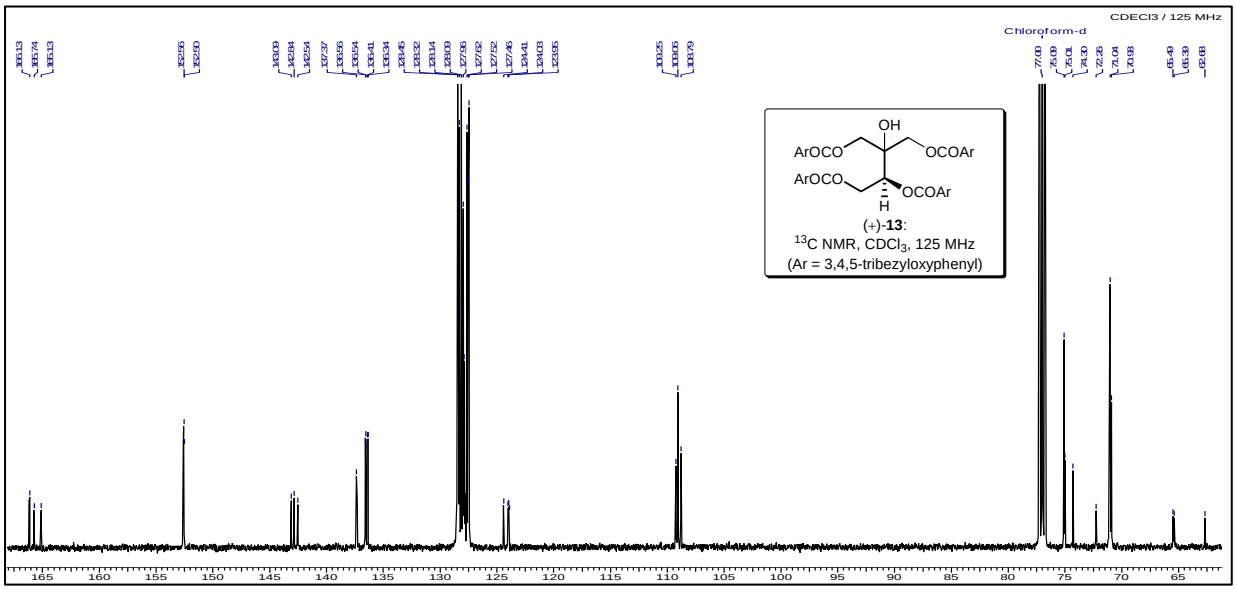


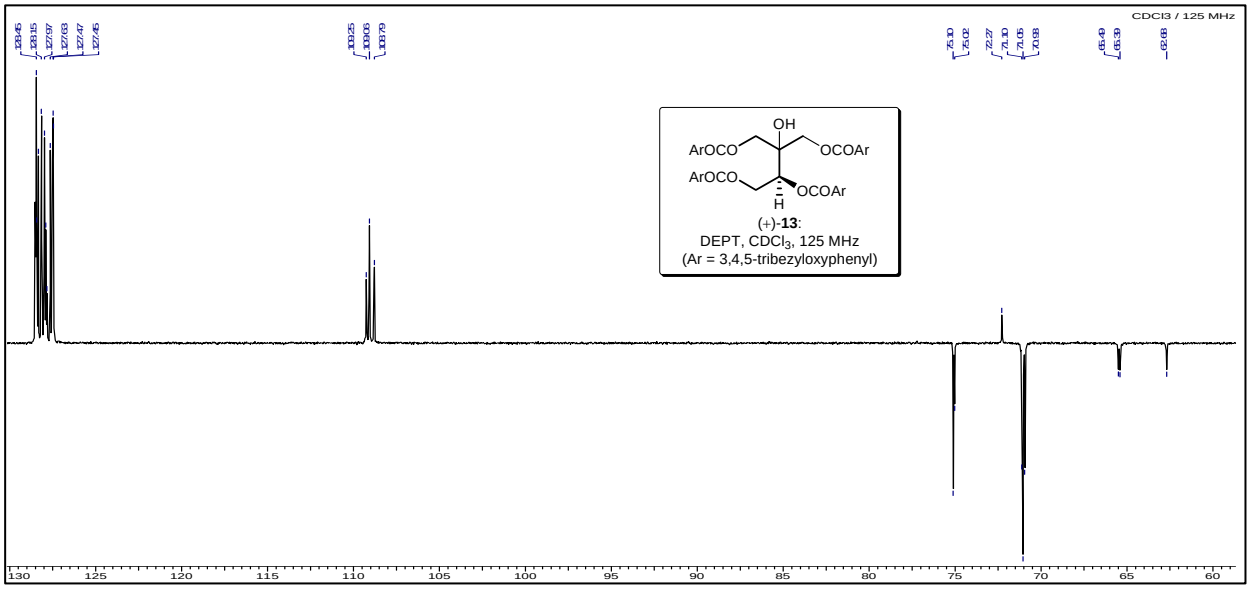
(–)-1: $C_{33}H_{28}O_{21}$ (760.56)
(Ar' = 3,4,5-trihydroxyphenyl)

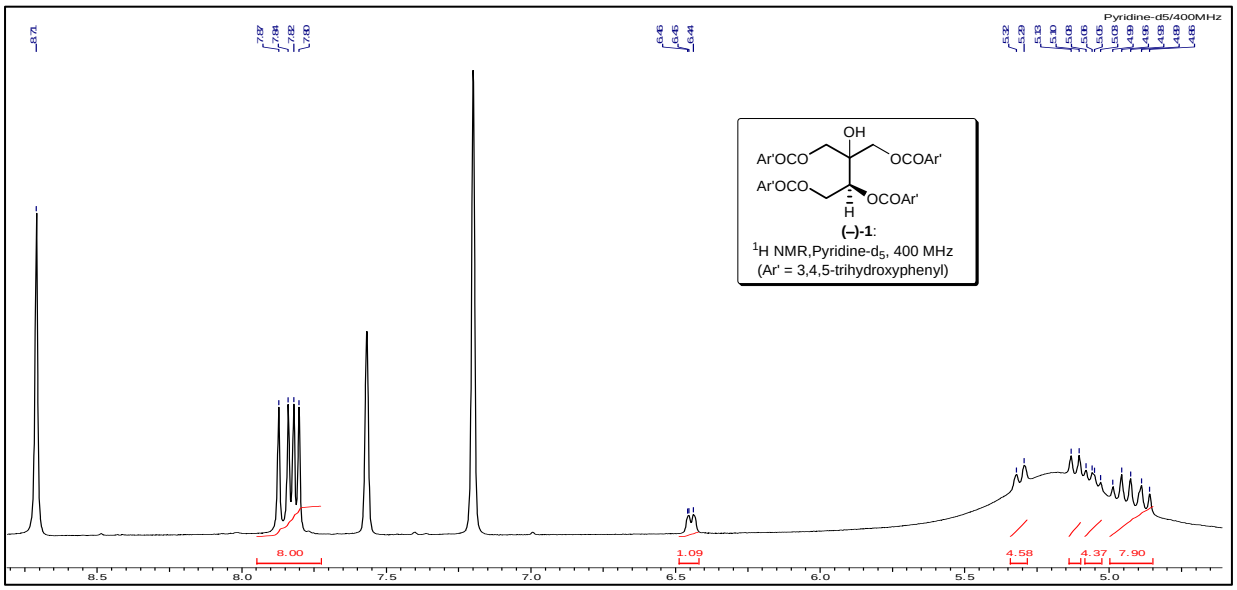
$[M–H]^-$ (calcd for $C_{33}H_{27}O_{21}$); IR (Nujol) ν_{max} 3432, 1742, 1682 cm^{-1}. [Similarly, the compound (±)-**13** was transformed to (±)-**1**].

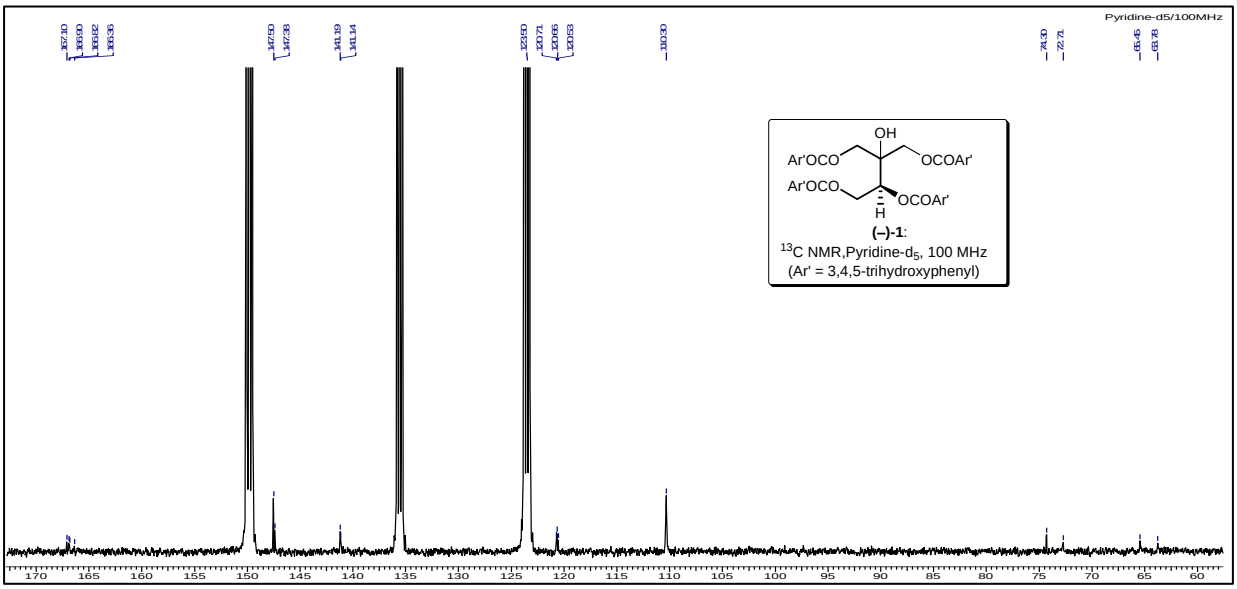
4.6: Selected spectra

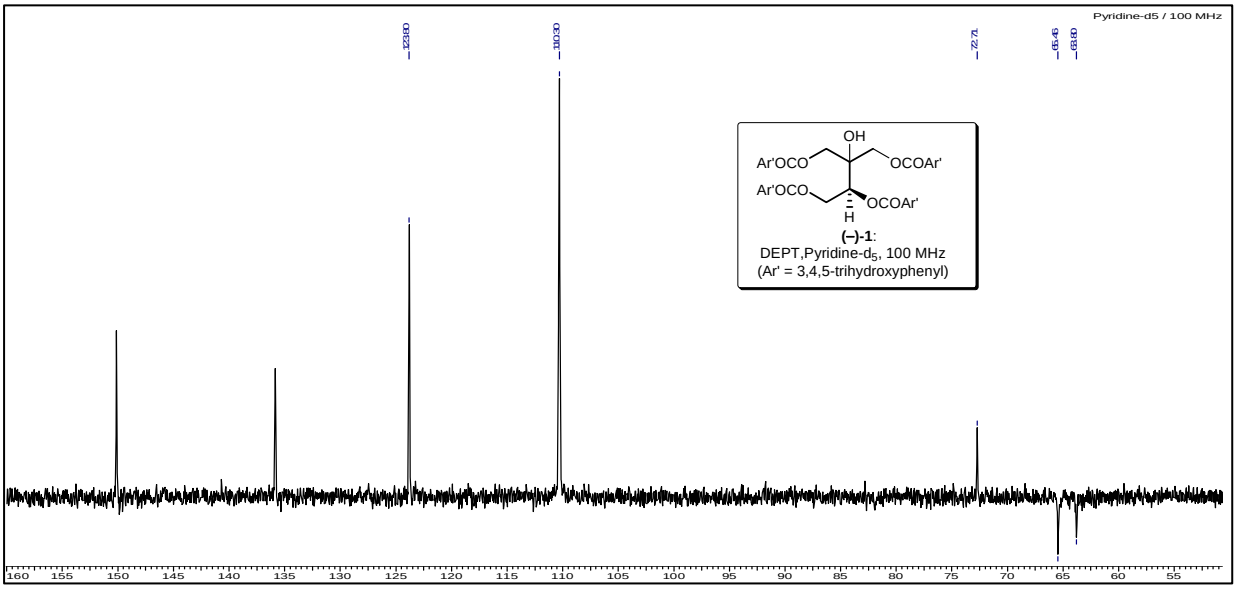

CDCl3 / 500 MHz
TMS
OH
ArOCO
OCOAr
ArOCO
OCOAr
H
(+)-13:
1H NMR, CDCl3, 500 MHz
(Ar = 3,4,5-tribezyloxyphenyl)


CDECl3 / 125 MHz
Chloroform-d
OH
ArOCO
OCOAr
ArOCO
OCOAr
H
(+)-13:
13C NMR, CDCl3, 125 MHz
(Ar = 3,4,5-tribezyloxyphenyl)


CDCl3 / 125 MHz
OH
ArOCO
OCOAr
ArOCO
OCOAr
H
(+)-13:
DEPT, CDCl3, 125 MHz
(Ar = 3,4,5-tribezyloxyphenyl)


Pyridine-d5/400MHz
8.71
7.87
7.84
7.82
7.80
6.46
6.45
6.44
5.32
5.29
5.13
5.10
5.08
5.06
5.05
5.03
4.99
4.96
4.93
4.89
4.88
OH
Ar'OCO
OCOAr'
Ar'OCO
OCOAr'
H
(–)-1:
1H NMR,Pyridine-d5, 400 MHz
(Ar' = 3,4,5-trihydroxyphenyl)
8.00
1.09
4.58
4.37
7.90
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0


Pyridine-d5/100MHz
157.40
156.90
156.82
156.35
147.50
147.38
141.19
141.14
123.90
120.71
120.66
120.53
110.30
74.30
72.71
65.46
63.78
OH
Ar'OCO
OCOAr'
Ar'OCO
OCOAr'
H
(–)-1:
13C NMR,Pyridine-d5, 100 MHz
(Ar' = 3,4,5-trihydroxyphenyl)
170
165
160
155
150
145
140
135
130
125
120
115
110
105
100
95
90
85
80
75
70
65
60


Pyridine-d5 / 100 MHz
123.90
110.30
72.71
65.46
63.80
OH
Ar'OCO
OCOAr'
Ar'OCO
OCOAr'
H
(–)-1:
DEPT,Pyridine-d5, 100 MHz
(Ar' = 3,4,5-trihydroxyphenyl)
160
155
150
145
140
135
130
125
120
115
110
105
100
95
90
85
80
75
70
65
60
55

4.7: References

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Overall Conclusion and Perspective

Development of novel carbon–carbon and carbon–oxygen bond forming reaction for the synthesis of complex bioactive natural products has been foremost area of research in synthetic organic chemistry. Present dissertation describes our studies towards the development of novel carbon–carbon and carbon–oxygen bond forming reactions with the cyclic anhydride derivatives, the dimethyl bromomethylfumarate and dialkyl alkylidenesuccinates and their applications for the facile synthesis of structurally interesting bioactive natural and unnatural products along with the concise account of the chemistry of dimethyl bromomethylfumarate and dialkyl alkylidenesuccinates. The dimethyl bromomethylfumarate and dialkyl alkylidenesuccinates have six/five alternate sites available for various nucleophilic reactions respectively. Various carbon–carbon and carbon–oxygen bond forming methodologies by exploring these reactive sites to synthesize several natural and unnatural products have also been summarized.

We have demonstrated an unprecedented S_N2' coupling reactions of Wittig reagents to selectively obtain the corresponding enes and dienes, which is a pivotal new application of Wittig reagents. Herein, the enes have been obtained by using the Wittig reagents rather than the corresponding Grignard reagents, while dienes have been obtained with the recovery of triphenylphosphine. We feel that the use of Wittig reagents in the place of Grignard reagents in the synthesis of enes will positively widen the scope of S_N2' coupling reactions. Synthesis of lignan class of natural products, the (±)-gulbulin and (±)-prasanthaline has been described using the present protocol as a key step. We have also utilized our synthesized dienes for the development of a novel palladium catalyzed [2 + 2 + 2] cocyclization protocol to construct arylnapthalene frameworks with the formation of two new carbon–carbon bonds. The versatility of this method is demonstrated through the facile total synthesis of justicidin B and retrojusticidin B. The present convergent strategy is general in nature and provides the way for the shorter and regioselective synthesis of various arylnapthalene lignans. However, further refinements of reaction conditions for the improvement of yields are necessary.

We have described a simple and efficient general approach to gem-dialkyl substituted quaternary butenolides with the formation of novel carbon−oxygen bond, by taking advantage of bromine stimulated structural rearrangement of sterically congested tetrasubstituted dimethyl/diethyl 2-alkylidenesuccinates. The mechanistic aspects involved in the formation of butenolides and spirobutenolides via bromine induced dealkylative regioselective intramolecular cyclization and dehydrobromination pathway have been also studied. We have also witnessed the first example of (Z)-

selective allylic alcohol formation in the selenium dioxide oxidation of dialkyl alkylidenesuccinates to design a new general one-step approach to the diverse range of natural and unnatural butenolides and fused butenolides via an exceptional E- to Z- carbon–carbon double bond isomerization. The present protocol has been successfully extended for the synthesis of a mucocin precursor and the diastereoselective total synthesis of the natural product (±)-isomintlactone and its first time conversion to (±)-mintlactone. Our present protocol would also be useful for the synthesis of desired natural and unnatural α-methylene-γ-butyrolactones. We have also successfully altered the regioselectivity in lactonization with the ring expansion of γ-lactone to δ-lactone and provided the new approach to chromenone skeletons. We strongly believe that the present carbon−oxygen bond construction approaches will be useful to design several desired bioactive complex butenolides, spirobutenolides and fused butenolides natural products.

We have also completed racemic and chemoenzymatic total syntheses of potent HIV RNase H inhibitor (−)-1,3,4,5-tetragalloylapiitol using cyclic anhydride derivatives, the dimethyl bromomethylfumarate and (–)-dimethyl 2-acetoxy-3-methylenesuccinate respectively. In our opinion, the use of anhydride derivatives for the syntheses of a sugar moiety is noteworthy. We feel that the present flexible approaches will be useful to design several bioactive tetragalloylapiitol analogs in racemic and enantiomerically pure form for SAR studies, hence HIV-1 RNase H will also become an attractive molecular target for developing new anti-HIV agents for potential chemotherapeutic applications.

All these studies provided us a nice opportunity for learning a lot of new basic and applied chemistry not only from our work but also from the vast literature. We also feel that the novel carbon–carbon and carbon–oxygen bond forming approaches which we have developed are quite general in nature and would be useful in designing several important complex lignan and butenolide natural products and natural product hybrids for structure activity relationship studies. A look at the recent literature of carbon–carbon and carbon–oxygen bond forming approaches revealed that both discipline have enjoyed a glorious past and still area of current interest in the present day world of medicinal and synthetic chemistry. In our opinion, the histogram of chemistry of lignans and butenolides are in escalating slope and their increasing medicinal and pharmaceutical demands would maintain the high positive slope. Finally, on the basis of literature and our contribution to the field of novel carbon–carbon and carbon–oxygen bond forming approaches for the synthesis of structurally interesting bioactive natural and unnatural products, it can be said with assurance that this interesting discipline will spread the wings still wider in the field of organic and pharmaceutical chemistry in future.

List of Publications

(1) Facile S_N2' coupling reactions of Wittig reagents with dimethyl bromomethylfumarate: Synthesis of enes, dienes, and related natural products
Ramesh M. Patel and Narshinha P. Argade*
J. Org. Chem. **2007**, *72*, 4900.

(2) Total synthesis of (±)-1,3,4,5-tetragalloylapiitol
Ramesh M. Patel and Narshinha P. Argade*
Synthesis **2009**, 372.

(3) Bromine-induced facile synthesis of butenolides and spirobutenolides from sterically congested tetrasubstituted dialkyl alkylidenesuccinates
Ramesh M. Patel and Narshinha P. Argade*
Synthesis **2010**, 1188.

(4) General approach to 2,4-dialkyl-3-carboxybutyrolactones: An efficient synthesis of (±)-striatisporolide A and (±)-lichesterinic acid
Ramesh M. Patel and Narshinha P. Argade*
Indian J. Chem. **2010**, *49B*, 1071.

(5) Chemoenzymatic total synthesis of potent HIV RNase H inhibitor (–)-1,3,4,5 tetragalloylapiitol
Ramesh U. Batwal, **Ramesh M. Patel** and Narshinha P. Argade*
Tetrahedron: Asymmetry **2011**, *22*, In press.

(6) Regio- and stereoselective selenium dioxide allylic oxidation of dialkyl alkylidenesuccinates to (*Z*)-allylic alcohols: Synthesis of natural and unnatural fused butenolides
Ramesh M. Patel, Vedavati G. Puranik and Narshinha P. Argade*
Manuscript under preparation

Erratum