REMARKABLY SELECTIVE COUPLING REACTIONS OF PHTHALIDES: SYNTHESIS OF BIOACTIVE NATURAL AND UNNATURAL BENZOFURANS AND BENZOPYRANS

THESIS

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IN

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BY

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Dedicated to my Parents….

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CERTIFICATE

This is to certify that the work incorporated in the thesis entitled "***Remarkably Selective Coupling Reactions of Phthalides: Synthesis of Bioactive Natural and Unnatural Benzofurans and Benzopyrans***" which is being submitted to the ***University of Pune*** for the award of ***Doctor of Philosophy*** in ***Chemistry*** by ***Mr. Mukulesh Mondal*** 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.

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Candidate's Declaration

I hereby declare that the thesis entitled "***Remarkably Selective Coupling Reactions of Phthalides: Synthesis of Bioactive Natural and Unnatural Benzofurans and Benzopyrans***" submitted by me for the degree of ***Doctor of Philosophy*** in ***Chemistry*** to the ***University of Pune*** is the record of work carried out by me during the period of August, 2001 to February, 2007 and has not been submitted by me for a degree to any other University or Institution. This work was carried out at the Division of Organic Chemistry (Synthesis), National Chemical Laboratory, Pune, India.

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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 and (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) and bromocresol green (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), MSL 300 and ACF 300 (300 MHz for ^{1}H NMR and 75 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 recorded on Finnigan-Mat 1020C mass spectrometer and were obtained at an ionization potential of 70 eV.
- Microanalytical data were obtained using a Carlo-Erba CHNS-O EA 1108 Elemental Analyser. Elemental analyses observed for all the newly synthesized compounds were within the limits of accuracy (± 0.3%).
- 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 their R_f values on TLC, 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.
- During the thermal condensation reactions with α,β-unsaturated aldehydes, always some polymeric material forms which also makes difficult the purification of products.
- **Independent referencing and numbering of compounds, schemes, tables & figures have been employed for each Section of Chapter II (Section A to E).**

ABBREVIATIONS

Aq.	Aqueous
Bn	Benzyl
Cat.	Catalytic
CCDC	Cambridge crystallographic data centre
CSA	10-Camphorsulfonic acid
DBP	Dibenzoyl peroxide
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DBN	1,5-Diazabicyclo[4.3.0]non-5-ene
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	Diethyl azodicarboxylate
DEPT	Distortionless Enhancement by Polarization Transfer
DIBAL-H	Diisobutylaluminium hydride
DMAP	4-(Dimethylamino)pyridine
DMF	Dimethylformamide
DMS	Dimethyl sulfide
DMSO	Dimethyl sulphoxide
EC	Effective concentration
ED	Effective dose
ee	Enantiomeric excess
equiv.	Equivalent(s)
h	Hour(s)
HIV	Human immunodeficiency virus
HPLC	High Performance Liquid Chromatography

Hz	Hertz
IC	Inhibitory concentration
IR	Infra Red
KHMDS	Potassium 1,1,1,3,3,3-hexamethydisilazane
LAH	Lithium aluminum hydride
LDA	Lithium diisopropylamide
m-CPBA	*m*-Chloroperbenzoic acid
min.	Minute(s)
mL	Millilitre(s)
mmol	Millimole(s)
Mp	Melting point
MS 4Å	Molecular sieves (4Å)
MS	Mass Spectrum
NBS	*N*-Bromosuccinimide
NMO	4-Methylmorpholine *N*-oxide
NMR	Nuclear Magnetic Resonance
ORTEP	Orthogonal Thermal Ellipsoid Plots
PCC	Pyridinium chlorochromate
PDC	Pyridinium dichromate
p-TSA	*p*-Toluenesulfonic acid
p-TsCl	*p*-Toluenesulfonyl chloride
Py	Pyridine
rt	Room temperature
TBAF	Tetrabutylammonium fluoride
TBAI	Tetrabutylammonium iodide

TBDMS / TBS	*t*-Butyldimethylsilyl
TEA	Triethylamine
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
Tlc/TLC	Thin layer chromatography
TMG	Tetramethyl guanidine
TMSCl	Trimethylchlorosilane
TMSOTf	Trimethylsilyl trifluoromethanesulfonate
TPAP	Tetrapropylammonium perruthenate
TPP	Triphenylphosphine

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Abstract

The present dissertation is divided into two chapters. The first chapter presents a short overview of the chemistry of the recently isolated important bioactive benzopyran

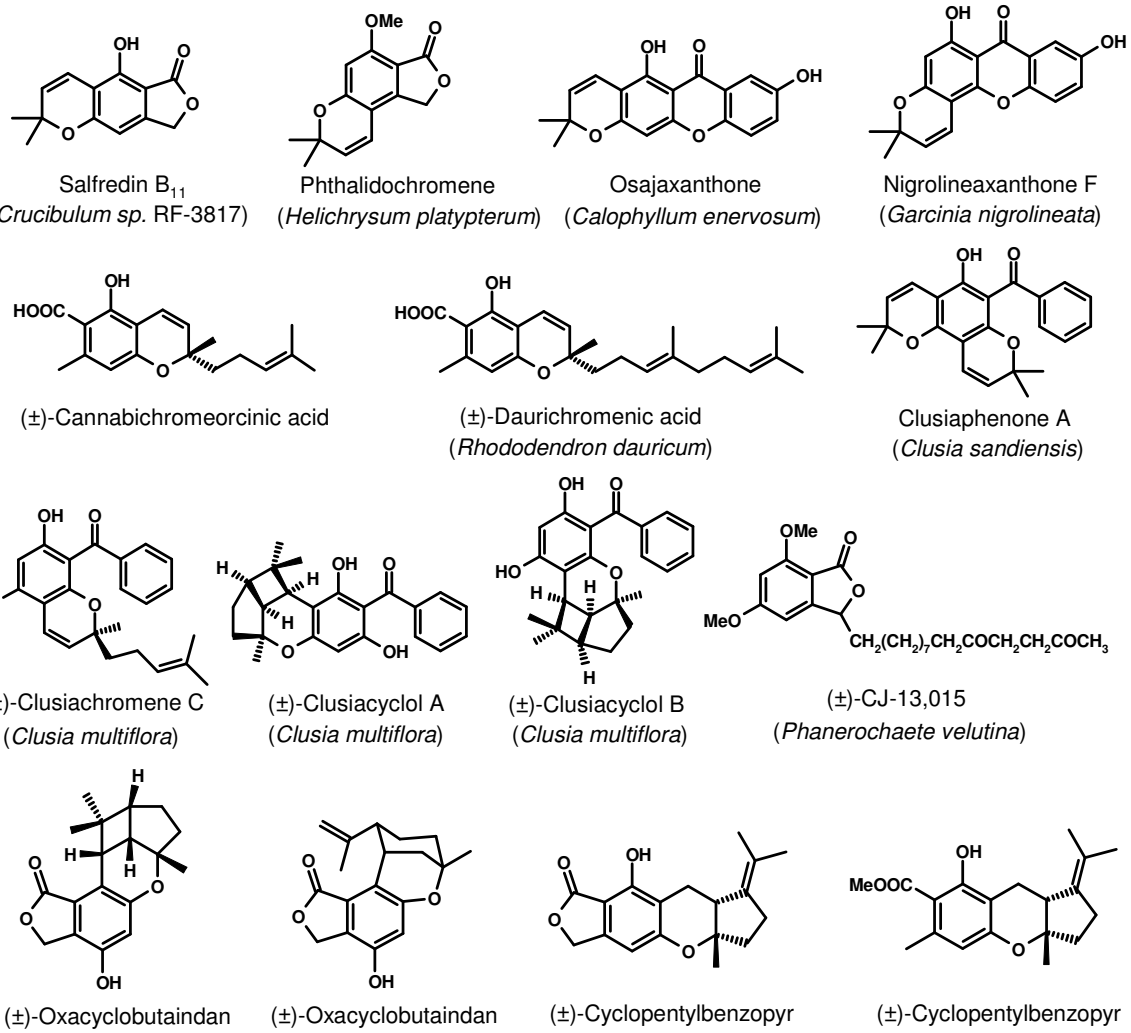


Figure 1. Natural and Unnatural Benzofurans and Benzopyrans Synthesized

containing natural products. In the second chapter, our contribution towards the total synthesis of bioactive natural products aldose reductase inhibitor salfredin B_{11}, phthalidochromine, xanthine oxidase inhibitor 1,3,7-trihydroxyxanthone, antimicrobial and anti-fish poison osajaxanthone, nigrolineaxanthone F, cannabichromeorcinic acid, potent anti-HIV agent daurichromenic acid, clusiaphenone A, clusiachromene C, clusiacyclol A, clusiacyclol B, novel anti-*Helicobacter pylori* CJ-13,015 and unnatural benzopyran hexahydrooxacyclobutaindane derivatives, oxabicyclononane derivative and isopropylidinecyclopentylbenzopyran derivatives (Figure 1) have been elaborated in details. This chapter also describes our ongoing studies towards the synthesis of mouse cell cycle progression inhibitor acetophthalidin.

Chapter One: A Concise Account on the Chemistry of Recently Isolated Bioactive Benzopyran Containing Natural Products

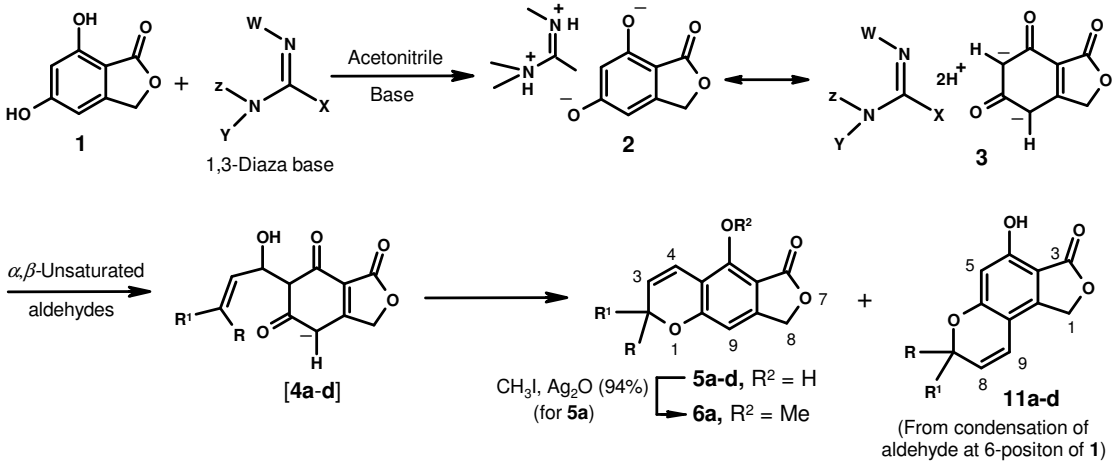
A large number of benzopyran containing natural products have been isolated from a variety of natural sources and synthesized in view of their promising activities. More than 4000 natural products with the common 2,2-dimethylbenzopyran template are known in the literature. This chapter portrays a short overview on isolation, bioactivity and synthesis of recently isolated important bioactive benzopyran containing natural products and also the recent developments in the area of complex benzopyran containing natural products with an emphasis on new synthetic routes and strategies.

Chapter Two: Facile Synthesis of Bioactive Natural and Unnatural Benzofurans and Benzopyrans

This chapter is divided into five sections. The first section presents a facile synthesis of salfredin B_{11} and phthalidochromine while the second section describes our studies towards the simple and efficient synthesis of 1,3,7-trihydroxyxanthone, osajaxanthone and nigrolineaxanthone F. The third section portrays an elegant access to cannabichromeorcinic acid, daurichromenic acid, clusiaphenone A, clusiachromene C, clusiacyclol A and clusiacyclol B. This section also describes three different thermal rearrangements and the synthesis of some structurally interesting benzopyran skeletons. The fourth section summarizes an efficient and short first total synthesis of natural benzofuran CJ-13,015, while the fifth section describes our ongoing studied towards the synthesis of acetophthalidin.

<u>Section A</u>: DBU-Induced Phenol-Keto Resonance in 3,5-Dihydroxyphthalide: Regioselectivities in Condensations with α,β-Unsaturated Aldehydes: Facile Synthesis of Bioactive Natural and Unnatural Benzopyrans

Salfredin B_{11} and phthalidochromine are two recently isolated natural products having benzopyran template. Only one synthesis of salfredin B_{11} is reported in the literature. This section reports an efficient DBU-induced regioselective coupling of α,β-unsaturated aldehydes with 3,5-dihydroxyphthalide (**1**) to obtain natural and several unnatural benzopyran derivatives (Scheme 1). The suitable condition for regioselective coupling of α,β-unsaturated aldehydes with 3,5-dihydroxyphthalide (**1**) to obtain linear benzopyran



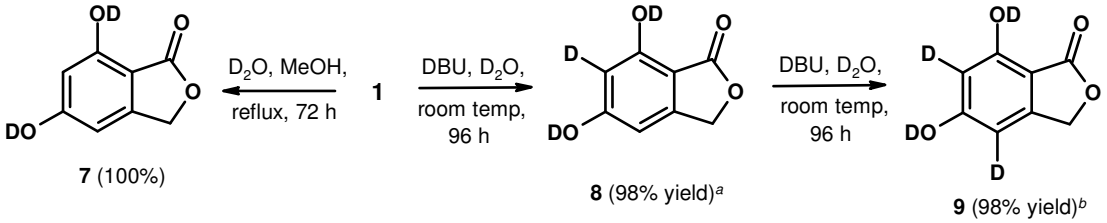
Scheme 1 **a**, R = R^1 = Me; **b**, R = H, R^1 = Me; **c**, R = Me, R^1 = CH_2-CH_2-CH=C(Me)$_2$; **d**, R = H, R^1 = Ph.
1,3-Diaza bases: DBU, DBN, Tetramethylguanidine, Guanidine.

was achieved by examining the reactions of phthalide **1** with 3-methyl-2-butenal in the presence of neutral, acidic and basic conditions using several bases and solvents at various temperatures and the results obtained are summarized in Table 1. To understand the observed 1,3-diaza base induced regioselectivity in the reactions of **1** with α,β-unsaturated aldehydes, we mixed 1.0 equivalent of phthalide **1** and 1.1 equivalents of DBU in acetonitrile at room temperature, where the TLC of the reaction mixture showed almost quantitative formation of a new material, presumed to be the DBU-**1** complex. The ^{1}H NMR and ^{13}C NMR spectra of the complex showed the absence of both aromatic protons and the two proton bearing aromatic ring carbons suggesting dianion structure **3**. In the dianionic species **3**, the relatively more reactive C-4 carbanion reacts with α,β-unsaturated

Table 1: Base catalyzed regioselective coupling of **1** with α,β-unsaturated aldehydes to obtain **5a-d**

Entry	Solvent	Aldehyde (equiv.)	Reagent	Condition	Product (Isolated yields, %)
1[a]	THF	3-Methyl-2-butanal (5)	Nil	Reflux, 48 h	**5a** (0) & **11a** (0)
2[a]	MeOH	3-Methyl-2-butanal (5)	Catalytic AcOH	Reflux, 48 h	**5a** (35) & **11a** (5)
3[a]	AcOH	3-Methyl-2-butanal (5)	AcOH	Reflux, 48 h	**5a** (21) & **11a** (7)
4[a]	EtOH	3-Methyl-2-butanal (excess)	DMAP (1.2 equiv)	70 °C, 48 h	**5a** (41) & **11a** (20)
5[a]	Nil	3-Methyl-2-butanal (excess)	Pyridine (1.5 equiv)	140 °C, 6 h	**5a** (50) & **11a** (25)
6[a]	Nil	3-Methyl-2-butanal (excess)	TEA (1.2 equiv)	70 °C, 48 h	**5a** (42) & **11a** (22)
7[a]	Nil	3-Methyl-2-butanal (5)	TEA (2.5 equiv)	70 °C, 48 h	**5a** (48) & **11a** (25)
8[a]	CH_3CN	3-Methyl-2-butanal (5)	TEA (2.5 equiv)	Reflux, 48 h	**5a** (37) & **11a** (18)
9[b]	Nil	3-Methyl-2-butanal (excess)	DBU (1.1 equiv)	50 °C, 24 h	**5a** (48) & **11a** (0)
10[b]	THF	3-Methyl-2-butanal (5)	DBU (1.1 equiv)	50 °C, 24 h	**5a** (61) & **11a** (0)
11[b]	MeOH	3-Methyl-2-butanal (5)	DBU (1.1 equiv)	50 °C, 24 h	**5a** (62) & **11a** (0)
12[b]	EtOH	3-Methyl-2-butanal (5)	DBU (1.1 equiv)	50 °C, 24 h	**5a** (67) & **11a** (0)
13[b]	CH_3CN	3-Methyl-2-butanal (5)	DBU (1.1 equiv)	50 °C, 24 h	**5a** (80) & **11a** (0)
14[b]	CH_3CN	3-Methyl-2-butanal (5)	DBU (0.1 equiv)	50 °C, 24 h	**5a** (11) & **11a** (0)
15[b]	CH_3CN	3-Methyl-2-butanal (5)	DBU (2.2 equiv)	50 °C, 24 h	**5a** (72) & **11a** (0)
16[b]	CH_3CN	3-Methyl-2-butanal (5)	DBN (1.1 equiv)	50 °C, 24 h	**5a** (75) & **11a** (0)
17[b]	CH_3CN	3-Methyl-2-butanal (5)	Guanidine (1.1 equiv)	50 °C, 24 h	**5a** (71) & **11a** (0)
18[b]	CH_3CN	3-Methyl-2-butanal (5)	TMG (1.1 equiv)	50 °C, 24 h	**5a** (74) & **11a** (0)
19[b]	CH_3CN	Crotonaldehyde (5)	DBU (1.1 equiv)	50 °C, 24 h	**5b** (72) & **11a** (0)
20[b]	CH_3CN	Citral (5)	DBU (1.1 equiv)	50 °C, 24 h	**5c** (65) & **11a** (0)
21[b]	CH_3CN	Cinnamaldehyde (5)	DBU (1.1 equiv)	50 °C, 24 h	**5d** (81) & **11a** (0)

[a] At 50 °C there was no reaction and we did not observe any formation of products **5a** and **11a** (by TLC). [b] TLC can easily detect the formation of **5a** and **11a**, even at very low concentrations. The TLC of these reaction mixtures revealed exclusive formation of **5a**.



7 (100%)

8 (98% yield)[a]

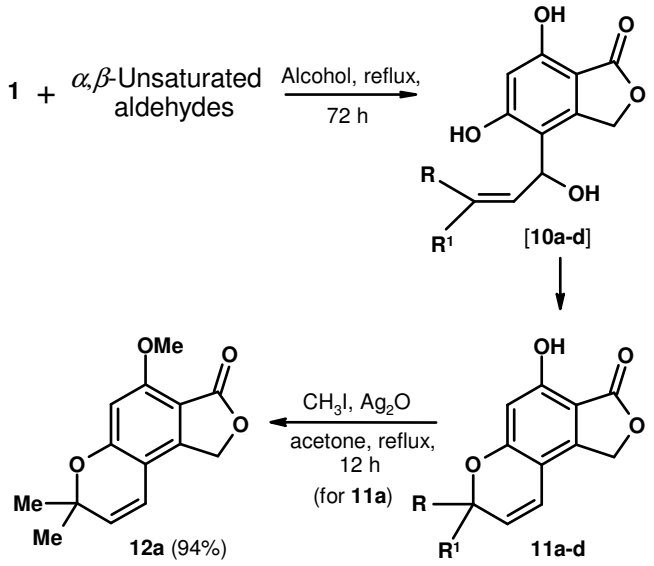
9 (98% yield)[b]

Scheme 2 [a] Nearly 100% deuterium incorporation at 4-position and 15% at 6-position. [b] Nearly 100% deuterium incorporation at 4-position and 85% at 6-position

aldehydes accounting for the present observed regioselectivity (Scheme 1). This double deprotanation and existence of dianion structure **3** was also supported by deuterium labeling experiment (Scheme 2).

The angular benzopyran **11a** appears to be the kinetically controlled product as the reaction of **1** and 3-methyl-2-butenal in refluxing methanol furnished exclusively **11a** in 60% yield (Table 2). The angular product **11a**, on methylation with methyl iodide in the

presence of Ag_2O, gave the desired natural product phthalidochromine (**12a**) in 96% yield (Scheme 3).



Scheme 3 **a**, R = R^1 = Me; **b**, R = H, R^1 = Me; **c**, R = Me, R^1 = CH_2-CH_2-CH=C(Me)$_2$; **d**, R = H, R^1 = Ph.

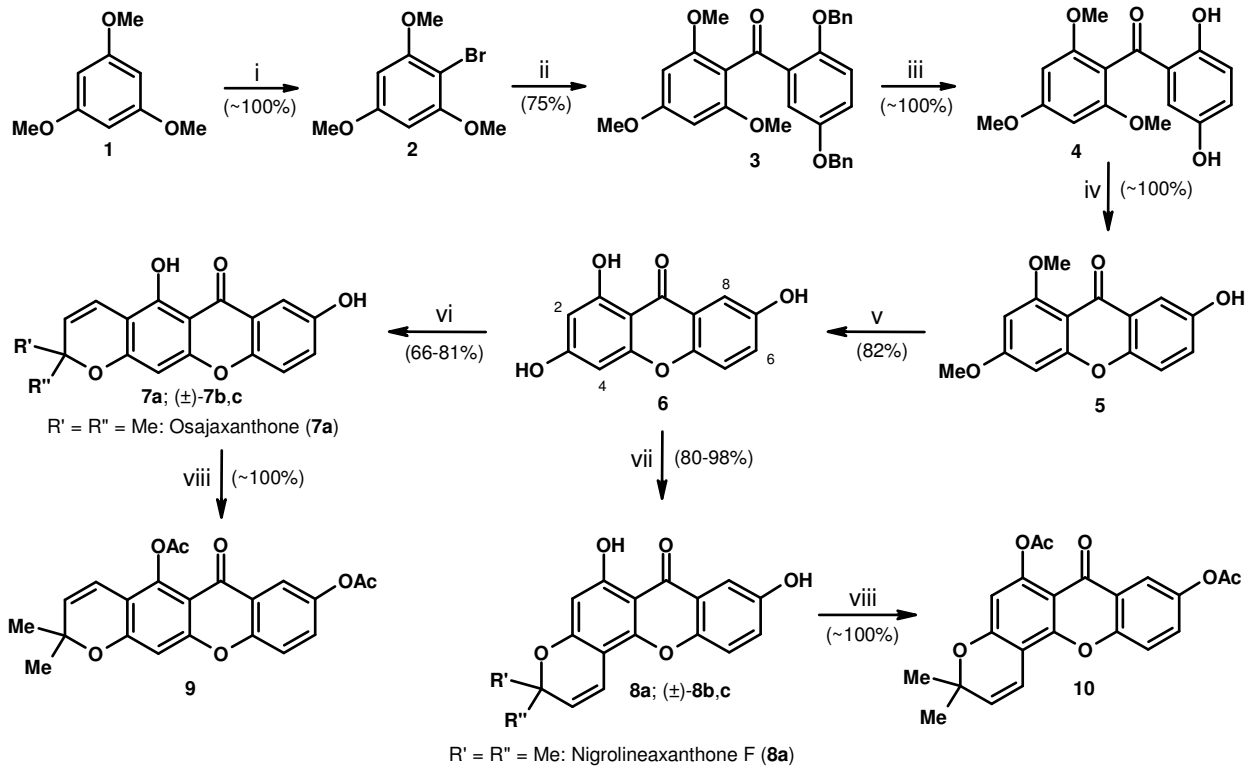
Table 2: Regioselective coupling of **1** with α,β-unsaturated aldehydes to obtain **11a**-**d**.

Entry	Solvent	Aldehyde (equiv.)	Condition	Product (Isolated yields, %)
1[a]	MeOH	3-Methyl-2-butanal (5)	Reflux, 60 h	**11a** (41)
2[a]	EtOH	3-Methyl-2-butanal (5)	65 °C, 48 h	**11a** (39)
3	EtOH	3-Methyl-2-butanal (5)	Reflux, 48 h	**11a** (42) & **5a** (7)
4[a]	MeOH	3-Methyl-2-butanal (15)	Reflux, 72 h	**11a** (60)
5[a]	MeOH	Crotonaldehyde (15)	Reflux, 72 h	**11b** (59)
6[a]	MeOH	Citral (15)	Reflux, 72 h	**11c** (51)
7[a]	EtOH	Cinnamaldehyde (15)	Reflux, 72 h	**11d** (51)

[a] The TLC of these reaction mixtures revealed exclusive formation of **11a**.

<u>Section B</u>: A Facile Synthesis of 1,3,7-Trihydroxyxanthone and its Regioselective Coupling Reactions with Prenal: Simple and Efficient Access to Osajaxanthone and Nigrolineaxanthone F

The natural and unnatural xanthones are an important class of compounds. Two multistep total syntheses of osajaxanthone (**7a**) have been reported using two different synthetic strategies while exclusive synthesis of Nigrolineaxanthone F is not known in the



a: R' = R'' = CH_3; **b**: R' = CH_3, R'' = H; **c**: R' = CH_3, R'' = $CH_2CH_2CH{=}C(CH_3)_2$.

Scheme 1 *Reagents, conditions and yields*: (i) CCl_4, NBS (1.0 equiv.), reflux, 6 h (~100%); (ii) THF, −78 °C, *n*-BuLi (1.0 equiv.), 45 min, methyl 2,5-dibenzyloxybenzoate, 30 min (75%); (iii) H_2, 10% Pd-C, methanol, rt, 6 h (~100%); (iv) (a) KOH (5.0 equiv.), MeOH, reflux, 12 h, (b) H^+/2 N HCl (~100%); (v) DCM, BBr_3 (6.0 equiv.), −78 °C to rt, 36 h (82%); (vi) Prenal/crotonaldehyde/citral (5 equiv.), $Ca(OH)_2$ (2.0 equiv.), methanol, rt, 36 h (**7a**: 75%; **7b**: 66%; **7c**: 81%); (vii) Prenal/crotonaldehyde/citral (10.0 equiv.), 140-150 °C 6 h (**8a**: 98%; **8b**: 86%; **8c**: 80%); (viii) Pyridine, Ac_2O, rt, 12 h (~100%).

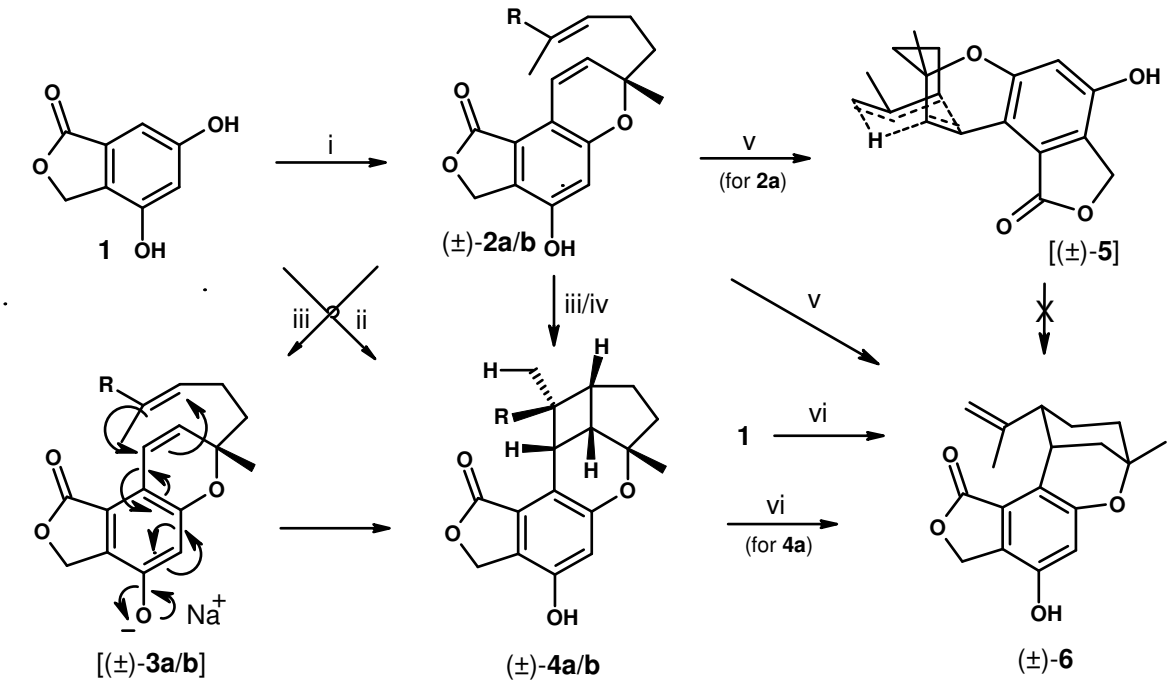
literature. In this section we report a short and efficient synthesis of xanthone **6** from 1,3,5-trimethoxybenzene (**1**) with 62% overall yield. The regioselective coupling reactions of 1,3,7-trihydroxyxanthone (**6**) with prenal in the presence of calcium hydroxide at room temperature and under thermal condition at 140-150 ^oC have been demonstrated to exclusively obtain the natural products osajaxanthone (**7a**) in 75% yield and nigrolineaxanthone F (**8a**) in 98% yield respectively (Scheme 1).

Section C: A Facile Phenol Driven Intramolecular Diastereoselective Thermal/Base Catalyzed Dipolar [2+2] Annulation Reactions: An Easy Access to Complex Bioactive Natural and Unnatural Benzopyran Congeners

Several structurally complex compounds with hexahydrooxacyclobutaindane moiety have been isolated as bioactive natural products. The natural products with

oxabicyclononane units are also known. This section illustrates a systematic study of the thermal/base catalyzed cycloaddition reactions of four different types of natural/unnatural phenolic substrates with citral and/or farnesal and also reports an easy thermal/base-catalyzed diastereoselective access to several structurally interesting bioactive natural and unnatural benzopyran congeners and a related novel thermal oxacyclobutaindane framework rearrangements (Schemes 1-4).

The reaction of 4,6-dihydroxyphthalide (**1**) with citral at 120-130 ^{o}C diastereoselectively furnished the corresponding oxacyclobutaindane derivative (±)-**4a** with 82% yield, where as the same reaction at 160-170 ^{o}C exclusively gave the oxabicyclononane (±)-**6** in 82% yield. The benzopyran **2a** underwent a facile phenol driven



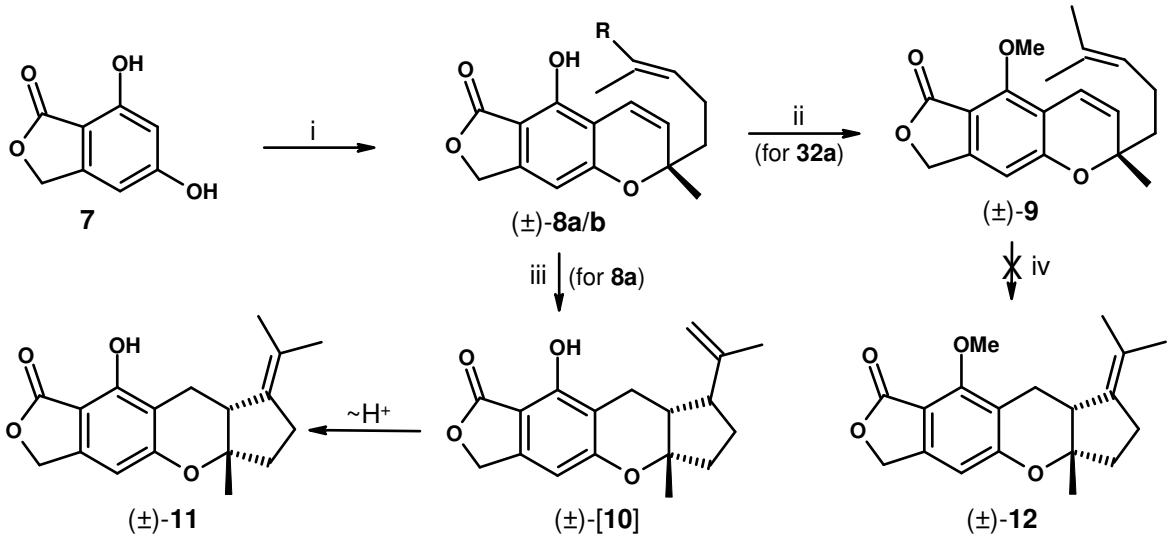
2a: R= $CH_2CH_2CH=C(CH_3)_2$; **2b**: R= $CH_2CH_2CH=C(CH_3)CH_2CH_2CH=C(CH_3)_2$;
4a: R = CH_3; **4b**: R= $CH_2CH_2CH=C(CH_3)_2$.

Scheme 1 *Reagents, conditions and yields*: (i) Citral/farnesal (5.00 equiv.), $Ca(OH)_2$ (1.50 equiv.), MeOH, 60 ^{o}C, 6 days (**2a**: 60%; **2b**: 63%); (ii) Citral (5.00 equiv.), 120-130 ^{o}C, 6 h (**4a**: 82%); (iii) (a) MeOH : 2 N NaOH (5 : 1), 0 ^{o}C to rt, 8-10 h, (b) H^{+}/2 N HCl (**4a**: 80%; **4b**: 78%); (iv) 120-130 ^{o}C, 6 h (**4a**: 76%); (v) 160-170 ^{o}C, 6 h (82%); (vi) Citral (5.00 equiv.), 160-170 ^{o}C, 6 h (82%).

thermal dipolar [2+2] cycloaddition reaction at 120-130 ^{o}C to yield **4a** in 76% yield. Similarly, both the benzopyrans **2a/b** on treatment with aqueous 2 N sodium hydroxide solution at room temperature followed by acidification also exclusively gave the

corresponding phenoxy anion driven dipolar [2+2] cycloaddition products **4a/b** in 80/78% yields. Both **2a** and **4a** on heating at 160-170 ^{o}C exclusively gave the rearranged product **6** in 80-82% yield, proving that oxabicyclononane **4** is formed via oxacyclobutaindane **3a** (Scheme 1). Finally, the formation of the compounds **4a** and **6** was confirmed from X-ray crystallographic data.

Due to the presence of a hydrogen bonded phenolic hydroxy group with an adjacent carbonyl group, the present phenol directed [2+2] cycloaddition of the linear benzopyrans **8a/b** was effective under thermal condition only. The linear benzopyran **8a** at 165-170 ^{o}C directly furnished the isopropylidinecyclopentylbenzopyran (±)-**11** in 90% yield via the phenol driven novel thermal framework rearrangement (Scheme 2). We were unable to arrest this reaction at the intermediate **10**. The methyl ether **9** failed to undergo any reaction on heating upto 200 ^{o}C indicating that the presence of free phenolic hydroxyl group is essential.

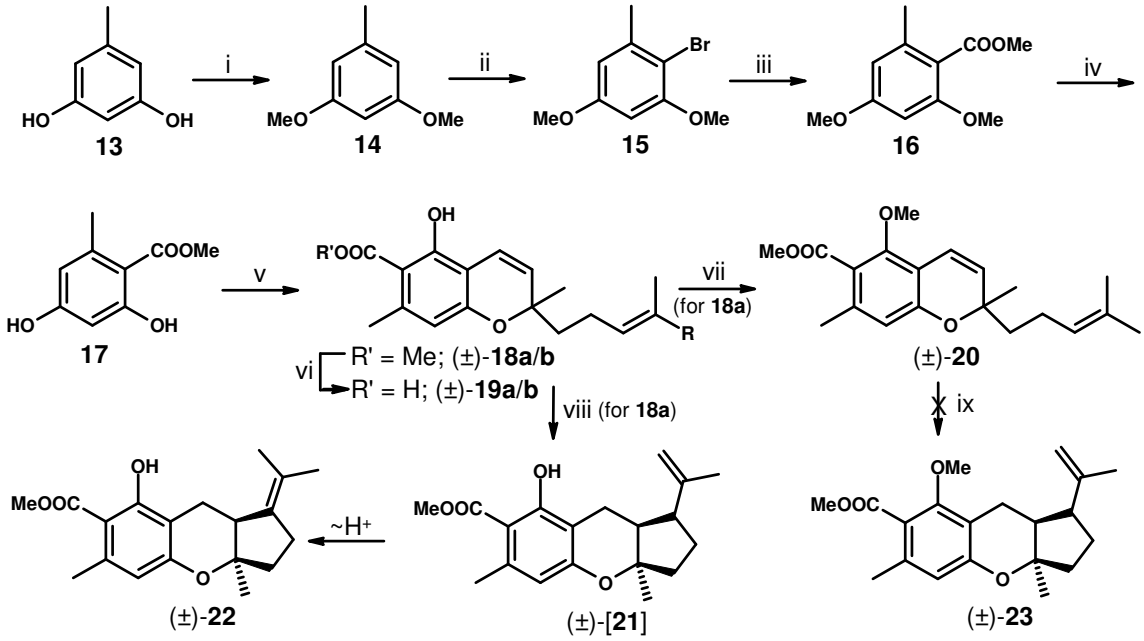


8a: R = CH_3; **8b**: R = $CH_2CH_2CH{=}C(CH_3)_2$.

Scheme 2 *Reagents, conditions and yields*: (i) Citral/farnesal (5.00 equiv.), DBU (1.10 equiv.), MeCN, 50 ^{o}C, 24 h (**8a**: 65%; **8b**: 68%); (ii) Acetone, K_2CO_3 (5.00 equiv.), MeI (5.00 equiv.), reflux, 6 h (99%); (iii) 165-170 ^{o}C, 6 h (**11**: 90%); (iv) Rt to 200 ^{o}C, 6 h (0%).

Four synthesis of daurichromenic acid and one synthesis of cannabichromeorcinic acid are known in the literature. This section describes synthesis of cannabichromeorcinic acid (**19a**) and daurichromenic acid (**19b**) from orcinol monohydrate (**13**) which on methylation, NBS-induced nuclear bromination, lithiation of the bromo compound followed by the treatment with methyl chloroformate and $AlCl_3$ induced demethylation

furnished the required phenolic ester **17** in 93% overall yield. The intermediate phenolic ester **17** on treatment with citral/farnesal in the presence of $Ca(OH)_2$ gave the desired benzopyrans **18a/b** in very good yields. Base induced hydrolysis of these esters **18a/b** provided the natural benzopyrans carboxylic acids **19a/b** in 82 and 80% yields respectively. On heating the benzopyran ester **18a** at 165-175 ^oC directly furnished the benzopyran (±)-**22** in 98% yield via the novel framework rearrangement (Scheme 3). Here also the methyl ether **20** failed to undergo any reaction on heating upto 200 ^oC.

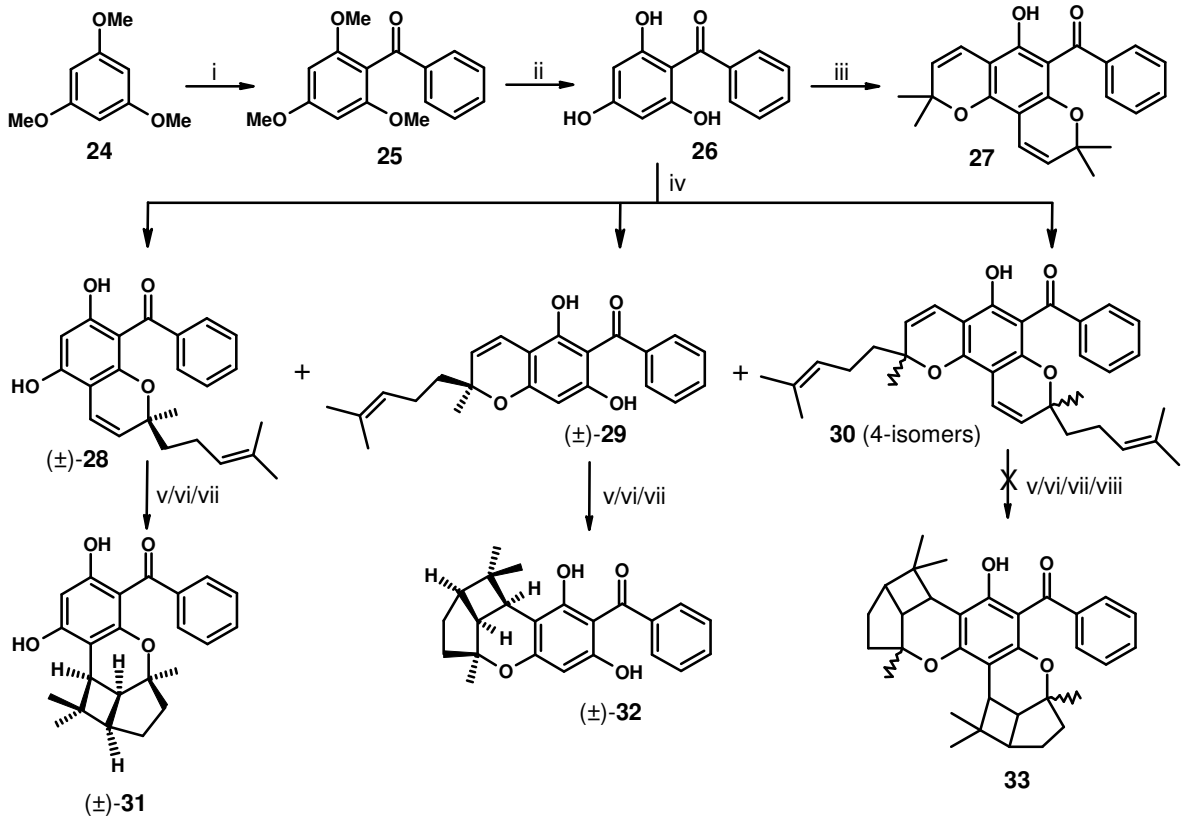


a: R = CH_3; **b**: R = $CH_2CH_2CH{=}C(CH_3)_2$.

Scheme 3 *Reagents, conditions and yields*: (i) Acetone, K_2CO_3 (5.00 equiv.), MeI (5.00 equiv.), reflux, 6 h (~100%); (ii) CCl_4, NBS (1.00 equiv.), reflux, 4 h (99%); (iii) (a) THF, −78 ^oC, *n*-BuLi (1.20 equiv.), 1 h, (b) $ClCO_2Me$ (excess), −78 ^oC to rt (96%); (iv) DCM, 0 ^oC, $AlCl_3$ (6.00 equiv.), rt, 12 h (98%); (v) MeOH, $Ca(OH)_2$ (2.00 equiv.), citral/farnesal (5.00 equiv.), rt, 72 h (**18a**: 72%; **18b**: 79%); (vi) MeOH : 3 N KOH (3:1), rt, 72 h (**19a**: 82%; **19b**: 80%); (vii) Acetone, K_2CO_3 (5.00 equiv.), MeI (5.00 equiv.), reflux, 6 h (98%); (viii) 175 ^oC, 6 h (98%); (ix) Rt to 200 ^oC, 6 h (0%).

The natural products clusiaphenone A (**27**), clusiachromene C (**28**), Clusiacyclol A (**32**) and B (**31**) are important class of compound originated from benzophenone derivative where as last two natural products bear complex oxacyclobutaindanes unit. This section reports the first efficient total synthesis of clusiaphenone A, clusiachromene C, Clusiacyclol A and B by using the phenol driven [2+2] dipolar cycloaddition strategy following the biogenetic type pathway (Scheme 4). The required intermediate trihydroxy

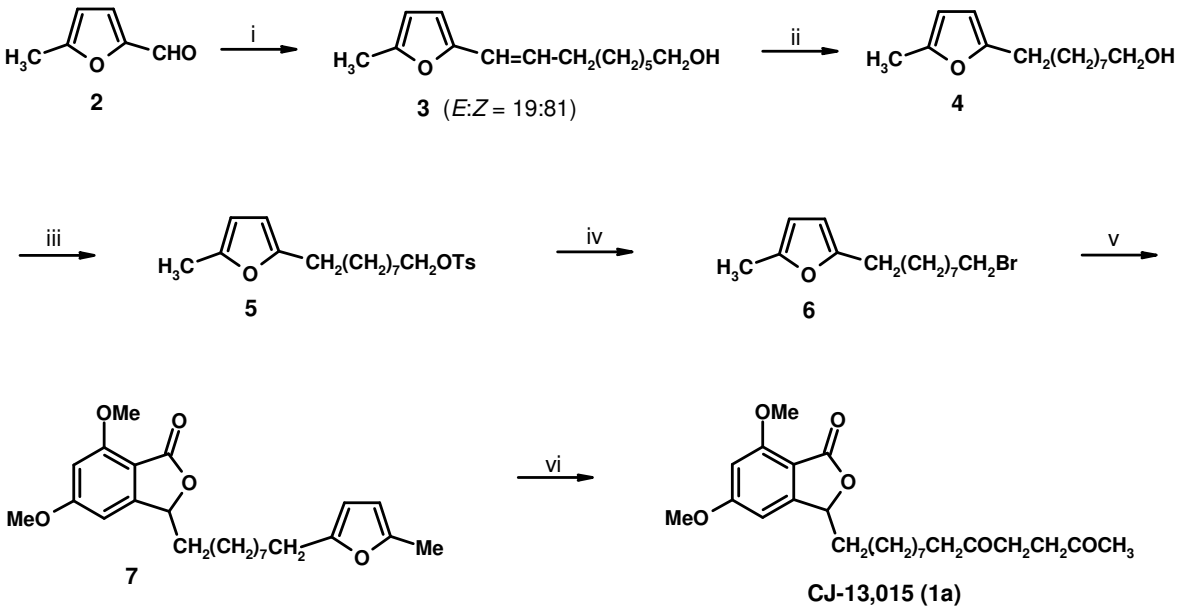
benzophenone **26** was synthesized from the symmetrical trimethoxy benzene **24** which on treatment with excess of prenal in the presence of DBU furnished the natural product **27** in 94% yield. We could stop the reaction of **26** with citral to obtain the column separable mixture of **28**, **29** and **30** by using less equivalents of DBU or to obtain the column separable mixture of **30**, **31** and **32** by using an excess amount of $Ca(OH)_2$, in very good yields. The naturally occurring pure (±)-clusiachromene C (**28**) on thermal/base catalyzed [2+2] cycloaddition gave the desired natural product (±)-clusiacyclol B (**31**) in very good yield. Similarly, **29** on thermal/base catalyzed reaction furnished the natural product (±)-clusiacyclol A (**32**) in very good yield.



Scheme 4 *Reagents, conditions and yields*: (i) $AlCl_3$ (1.50 equiv.), DCM, 0 °C, benzoyl chloride (1.00 equiv.), 0 °C to rt, 12 h (96%); (ii) DCM, BBr_3 (4.20 equiv.), −78 °C to rt, 48 h (92%); (iii) MeOH, DBU (2.20 equiv.), prenal (excess), rt, 36 h (94%); (iv) MeOH, DBU (0.80 equiv.), 0 °C, citral (1.00 equiv.), 6 h (**28**: 26%; **29**: 16%; **30**: 11%) or MeOH, $Ca(OH)_2$ (0.50 equiv.), rt, citral (1.00 equiv.), 96 h (**30**: 13%; **31**: 35%; **32**: 29%) or MeOH, DBU (2.20 equiv.), rt, citral (10.00 equiv.), 36 h (**30**: 95%); (v) MeOH, $Ca(OH)_2$ (0.20 equiv.), rt, 48 h (**4**: 79%; **3**: 76%); (vi) MeOH : 0.1 N KOH (3:1), rt, 24 h (**31**: 75%; **32**: 70%); (vii) 100-110 °C, 6 h (**31**: 82%; **32**: 80%); (viii) 170-180 °C, 6 h (0%).

<u>Section D</u>: Synthesis of a New Microbial Secondary Metabolite: Anti-*Helicobacter Pylori* CJ-13,015

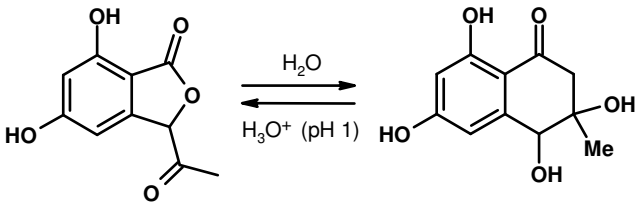
The root cause of gastric and duodenal ulcers is the presence of the microaerophilic Gram- negative bacterium *Helicobacter pylori*, which appear to live beneath the mucus layer of the stomach. Current therapy is not entirely successful in achieving long term eradication of *H. pylori* and relapse is a problem. However, long-term treatment with current therapies is not recommended and there is a need for a safe and effective treatment with a compound having an excellent anti-*H. pylori* activity. Recently, Dokker *et al* isolated new phthalide **1a** from the basidiomycete *Phanerochaerte velutina* with promising anti-*Helicobacter pylori* activity. This section reports the first total synthesis of CJ-13,015 (**1a**) (Scheme 1), starting from 5-methylfurfural (**2**) via the Wittig reaction of the ylide generated in situ from (8-hydroxyoctyl)triphenylphosphonium bromide, selective reduction of the newly formed carbon- carbon double bond, conversion of alcohol to halide, coupling with 3,5-dimethoxyphthalide carbanion and a chemoselective conversion of protective furan group to 1,4-dicarbonyl system as a key reaction.



Scheme 1 *Reagents, conditions and yields*: (i) $HOCH_2(CH_2)_6CH_2^+PPh_3Br^-$ (1.1 equiv.), $Na^+CH_2^-SOCH_3$ (2.2 equiv.), DMSO-THF (1:1), 0 ^oC, 1 h (82%); (ii) H_2, Pd-C, methanol, rt, 4 h (98%); (iii) *p*-TsCl (1.1 equiv.), TEA (2.2 equiv.), DMAP, DCM, rt, 6 h (96%); (iv) LiBr (8 equiv.), $NaHCO_3$ (10 equiv.), acetone, rt, 15 h (95%); (v) (a) 3,5-Dimethoxyphthalide (1.5 equiv.), LDA (1.5 equiv.), THF, 0 ^oC to rt, 30 min, (b) 6, rt to 50 ^oC, 1 h, aq. workup, (90%); (vi) H_2O-AcOH (1:1), cat. H^+/H_2SO_4 (dil.), reflux, 2 h, (98%).

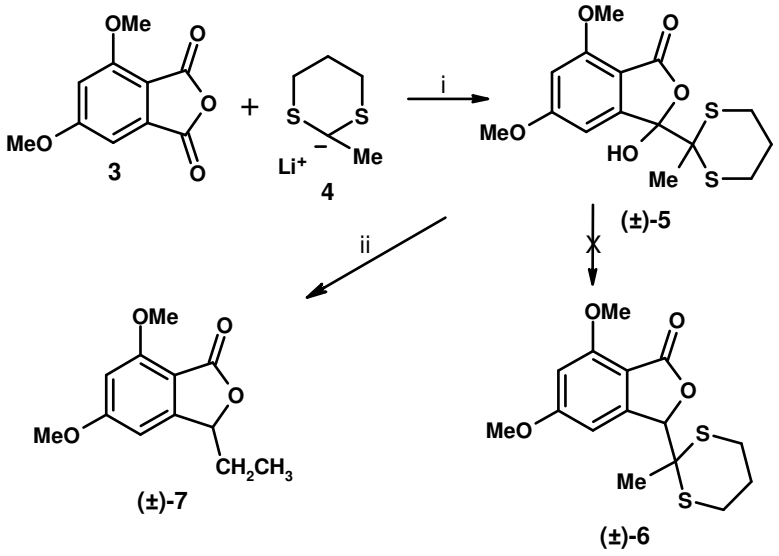
<u>Section E</u>: Studies Towards the Synthesis of Mammalian Cell Cycle Progression Inhibitor Acetophthalidin

Acetophthalidin, produced by fungal strain BM923 isolated from sea sediment. Two syntheses are reported in literature, development of new synthetic approach towards this natural product is a challenging task for the organic chemist. Acetophthalidin is very unstable, it undergoes isomerization to inactive trihydroxymellein during the isolation and was obtained only as a racemate.



Acetophthalidin (**1**) 3,4,6-Trihydroxymellein (**2**)

This section describes our ongoing efforts towards accomplishing the total synthesis of this bioactive natural product **1** starting from 3,5-dimethoxy phthalic anhydride (**3**). Regioselective nucleophilic addition of 2-lithio-2-methyl-1,3-dithiane (**4**) with **3** furnished

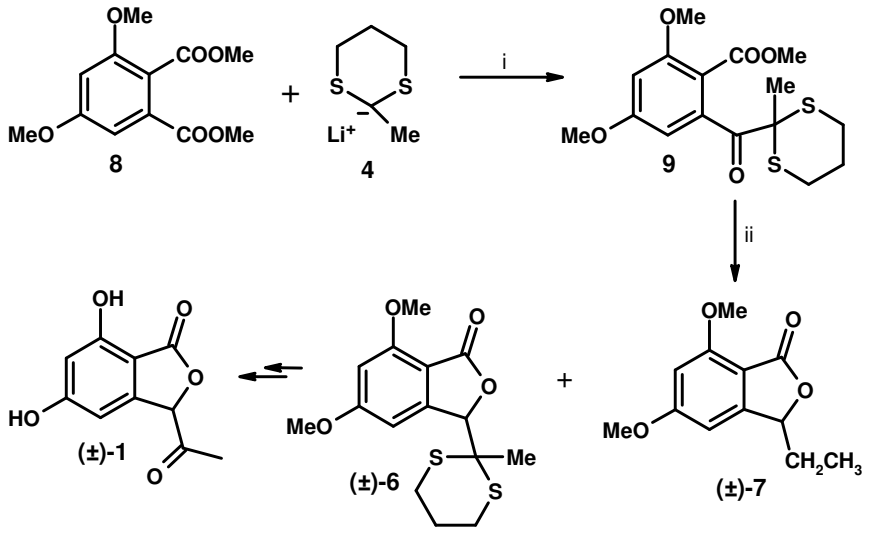


Scheme 1 *Reagents, conditions and yields*: (i) THF, −78 °C, 30 min (78%); (ii) 2 N NaOH, $NaBH_4$, 60 °C, 6 h (85%).

the substituted phthalaldehydic acid derivative **5**. Our all attempts to convert the phthalaldehydic acid derivative **5** to phtahlide **6** met with failure. Under the alkaline

conditions the reduction of phthalaldehydic acid derivative **5** furnished undesired alkyl substituted phthalide **7** via the reductive deprotection of the dithiane moiety (Scheme 1).

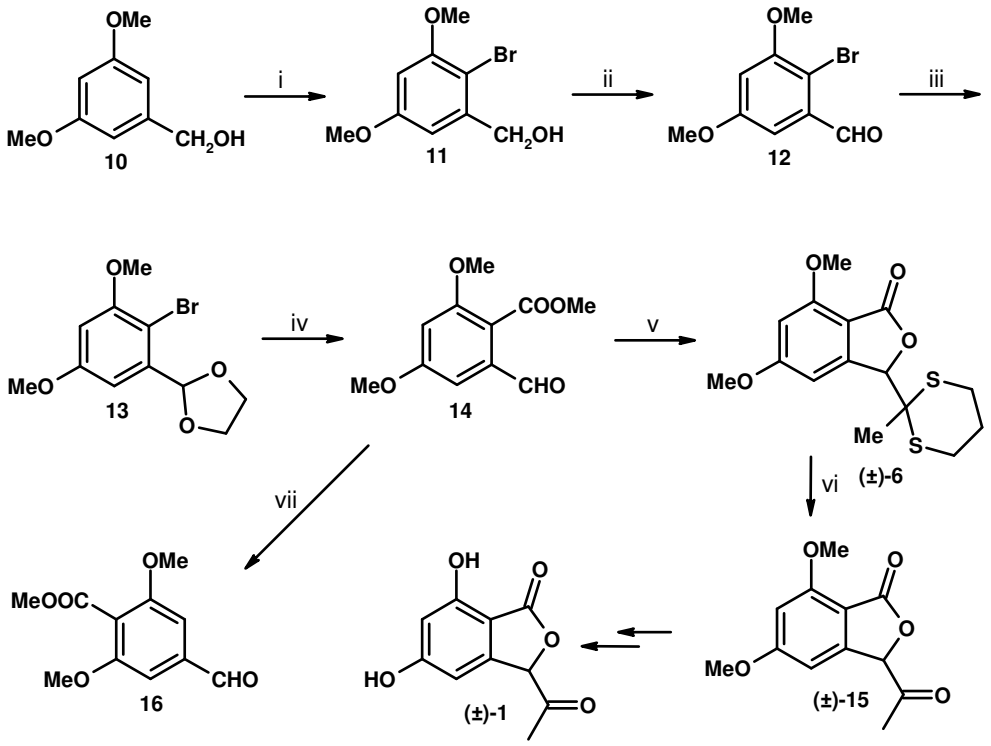
We changed our synthetic approach and our modified scheme involved the condensation reaction of lithio-2-methyl-1,3-dithiane (**4**) with diester **8**. The resulting keto-ester **9** was reluctant to undergo reduction at low temperature. The $NaBH_4$ reduction of keto-ester **9** at room temperature again furnished the undesired alkyl substituted phthalide **7** as a major product with very little amount of desired phthalide **6** (Scheme 2).



Scheme 2 *Reagents, conditions and yields*: (i) THF, −78 °C, 30 min (84%); (ii) $NaBH_4$ (2.00 equiv.), EtOH, rt, 24 h (**6**: 20%; **7**: 50%).

Next, an alternate strategy was planned to circumvent the above problem. We prepared the required substituted aldehyde ester **14** from 3,5-dimethoxybenzyl alcohol (**10**), which on NBS bromintation, followed by PCC oxidation, protection of the aldehyde, lithiation of the bromo compound and condensation of the lithiated species with methyl chloroformate directly furnished the aldehydes-ester **14**. Compound **14** underwent a smooth chemoselective condensation with lithio-2-methyl-1,3-dithiane to produce desired dithiane bearing phthalide **6** exclusively. Deprotection of the dithiane moiety using *p*-nitrobenzaldehyde in presence of TMSOTf furnished dimethyl ether of acetophthalidin (**15**). Demethylation of compound **15** to the natural product acetophthalidin (**1**) is in active progress. During this course of reaction, once we attempted the condensation of **14** with lithium acetylide (as an acyl precursor) with **14** but surprisingly, we got the ester migrated

rearranged symmetrical aldehyde-ester compound **16**, instead of the corresponding desired phthalide (Scheme 3).



Scheme 3 *Reagents, conditions and yields*: (i) CCl_4, NBS (1.00 equiv.), reflux, 6 h (98%); (ii) DCM, PCC, 6 h (79%); (iii) Toluene, ethylene glycol (2.50 equiv.), *p*-TSA (5 mol%), reflux, 9 h (88%); (iv) (a) THF, −78 ^{o}C, *n*-BuLi (1.10 equiv.), 1 h, (b) methyl chloroformate (4.00 equiv.), −78 ^{o}C to rt (87%); (v) THF, −78 ^{o}C, lithio-2-methyl-1,3-dithiane (84%); (vi) DCM, *p*-nitrobenzaldehyde (1.50 equiv.), 0 ^{o}C, TMSOTf (0.40 equiv.), 30 min (65%); (vii) DMSO, rt, lithium acetylide-ethylenediamine complex (1.20 equiv.), 1 h (72%).

Note: Compound numbers in the abstract are different from those in the thesis.

Chapter 1

A Concise Account on the Chemistry of Recently Isolated Bioactive Benzopyran Containing Natural Products

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This chapter features the following topics:

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1.3.1	*Monosubstituted 2H-1-Benzopyrans*	5
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1.3.3	*Synthesis of 2,2-Disubstituted 2H-1-Benzopyrans*	17
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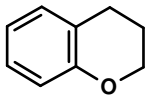
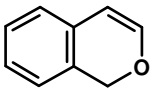
1.1 Introduction

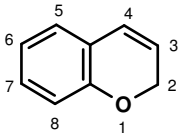
Compounds in which a benzene and a pyran ring are fused together are called benzopyrans (Figure 1). Depending on the position of oxygen atom, benzopyrans are classified into two classes, 1-benzopyran and 2-benzopyran. As per the position of double



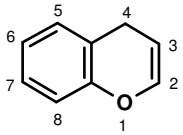
Dihydro-1-benzopyran (**1**)



2-Benzopyran (**2**)



2*H*-1-Benzopyran (**3**)

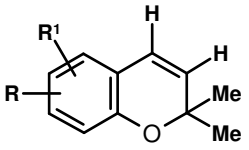


4*H*-1-Benzopyran (**4**)

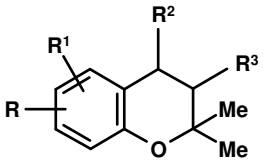
Figure 1. Benzopyran general structures

bond, 1-benzopyrans are further categorized as 2*H*-1-benzopyran and 4*H*-1-benzopyran. The common name chromene for 2*H*-1-benzopyrans was introduced by Houben[1] and then it was also called β-chromenone[2] and chrom-3-ene.[3]

Since the discovery of 1-benzopyran in the late nineteenth century[4] it has been found that almost every class of natural phenolic compound contains a 2,2-dialkylchromene ring,



2,2-Dimethyl-2*H*-benzopyran template
(~ 4000 Natural products)



Dihydro-2,2-dimethyl-
2*H*-benzopyran derivatives
(~ 8000 Natural products)

Figure 2. General structure of dimethyl-2*H*-1-benzopuran and analogues

and number of such discovered natural products increases every year. There are approximately 4,000 natural products[5] containing the 2,2-dimethyl-2*H*-benzopyran moiety, if the dihydro derivatives are also taken into account, then number increases up to 12,000 (Figure 2). Natural products play an important role in both drug discovery and chemical

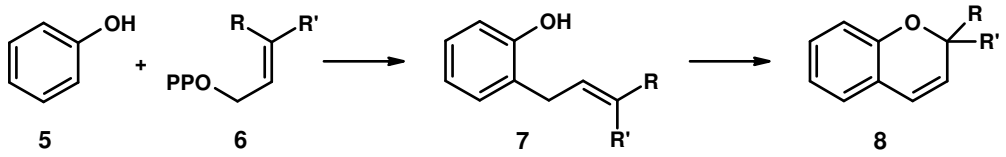
biology. Many natural products derived from several natural sources are well known as therapeutics agent as well as drug candidates.[6] 2,2-Dimethyl-2*H*-benzopyran moiety embedded in numerous natural products also have potential applications in medicine[7] as anti-cancer agent, [8] non-nucleoside, HIV-1-specific reverse transcriptase inhibitors currently in clinical development,[9] cancer chemopreventives,[10] insecticidal and anti-fungal agent[11] etc. Furthermore, pharmaceutical ligands that incorporate the 2,2-dimethyl-2*H*-benzopyran moiety into their structure have been also synthesized. Among these, some are the potassium-channel activators,[12] aldosterone biosynthesis inhibitor,[13] 5-hydroxytryptamine-3 receptor antagonist,[14] phosphodiesterase IV inhibiror[15] and ampicillin-derived anti-bacterial agent.[16]

Very large number of natural benzopyrans are known with diverse biological activities and in this chapter we have summarized a concise account on the isolation, bioactivity and the synthesis of the naturally occurring bioactive 2*H*-1-benzopyrans. In the present review chemistry of chrom-2-enes, or benzopyrylium salts, or fused pyrano-heterocycles has not been included. The chemistry of 2*H*-1-benzopyran is well documented[17-21] in a number of comprehensive books, monographs and continuously published in a broad range of scientific journals. This subject was possibly first time summarized by Wawzonek[17] in 1951. A brief but clear account of chrom-3-ene chemistry can be found in Dean's book[18] (1963), where a detail account is given for all the natural products known at that time. A section of the book[19] on the synthesis of natural products has also covered chromens. Katritzky and Boutlon have also elaborated the advances in the chemistry of chrom-3-ene in his book advances in heterocyclic chemistry.[20] The chemistry of several types of 1-benzopyrans has been summarized in a monograph[21] from Ellis. We have tried our best to summarize and present the information here, but no pretension of completeness is claimed. In order to simplify and understand the chemistry of the natural products with 2*H*-1-benzopyran templates, they have been divided according to their structures. Each group contains information about the natural products in tabular form, which shows the structure of natural product, name, bioactivity, the species from which it has been isolated and references pertaining to its isolation, activity and synthesis. The table is followed by the discussion and illustration of the synthesis of the important 2*H*-1-benzopyran containing natural products from the list. In the last part, biological activity and their clinical applications have been discussed which is followed by the summary and references.

1.2 Biosyntheses

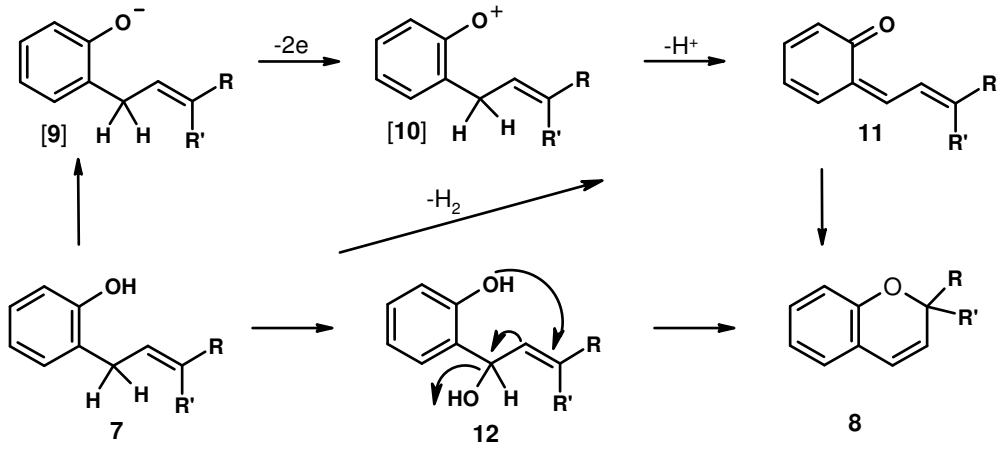
All natural 2,2-dialkyl-2*H*-1-benzopyrans are believed[22] to be originated *in vivo* from alkylation of a phenols or a substituted phenolic precursors with an allyl pyrophosphate. During the biosynthetic study of ubichromenol, it has been observed that

Scheme 1



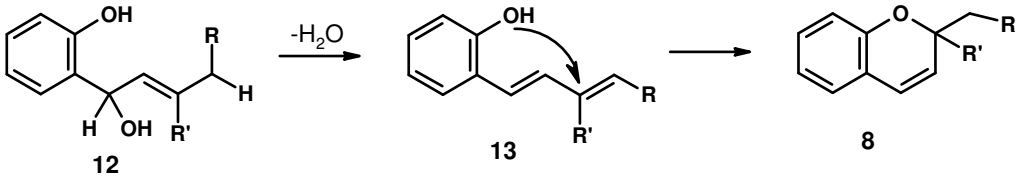
the incorporation of two molecules of ^{14}C-lebeled mevalonic acid takes place on an injection into rates.[23] Suzuki et al reported first time the biogenesis of a chromene from an isoprenoid precursor.[24] Various mechanisms have been postulated or suggested for the ring closure step on the basis of similar *in vitro* reactions (Scheme 1), although none of them is yet supported by *in vivo* experiments. According to the first proposed pathway[22] as shown in Scheme 1, an isoprenylated phenol may undergo a two electron oxidation to the cation

Scheme 2



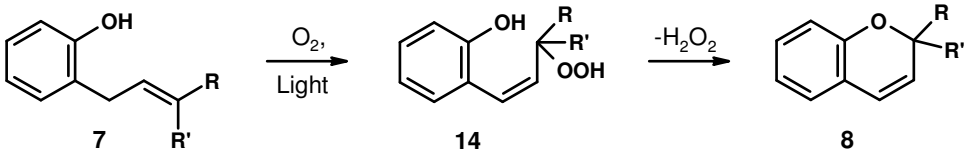
10, which can lose a proton to give the quinonemethide **11**. The further ring closure to the chromene occurs via an electrocyclic reaction. A more widely accepted variation of this hypothesis[25] requires the abstraction of a hydride ion from the benzylic position by a quinonelike coenzyme. Alternatively, oxidation of **7** at the benzylic position[26] could produce the alcohol **12**, which can produce compound **8** by concerted elimination of water

Scheme 3



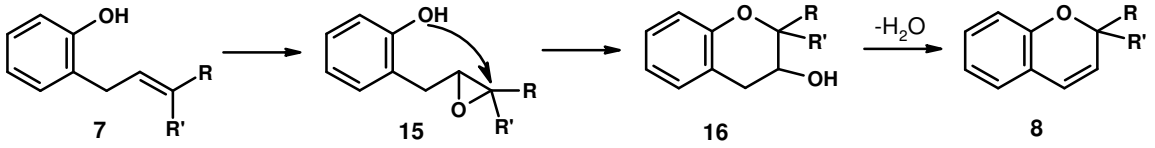
or through the intermediate benzylic cation (Scheme 2). It has also been suggested[27] that, this alcohol can be derived by condensation of citral or an equivalent unit with a phenol. Again the conversion of **12** into a diene **13** has been postulated[28] (Scheme 3). The photo oxidation of the allylic side chain of **7** has been also proposed[29] as the oxidative step in the

Scheme 4



ring closure sequence (Scheme 4). The epoxidation of the double bond of **7** has also been postulated[30] probably by analogy with the behavior of quinoline alkaloids (Scheme 5).

Scheme 5



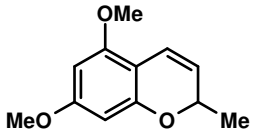
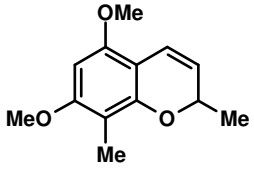
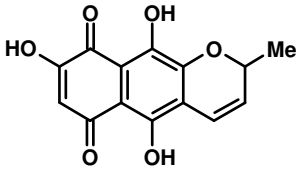
In summary, we feel that in nature the variety of oxidative ring closure of phenolic compounds constitute the biogenetic routes to benzopyrans and we strongly believe that the complex natural congeners of benzopyrans also originate via such oxidative ring closure pathways. Further studies to understand the clear biogenetic pathways will also certainly provide the fruitful solutions to chemists for the accomplishments of simple and efficient synthesis of variety of natural and unnatural benzopyrans.

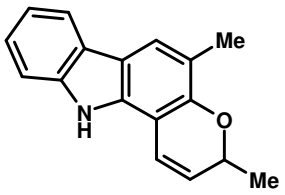
1.3 Classification of Benzopyrans

In present section the benzopyrans have been classified as mono-, di-, tri- and tetrasubstituted benzopyran compounds. The chemistry of these natural products has been summarized providing the details on source, activity and selected synthetic strategies and methodologies.

1.3.1 Monosubstituted 2*H*-1-Benzopyrans

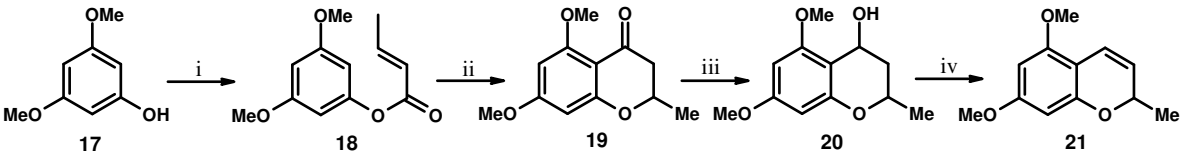
There are very few naturally occurring 2*H*-1-benzopyran which are mono substituted, this could be due to their relative instability.

No.	Mono-substituted 2*H*-1-Benzopyran Natural Products	Source	Activity	Ref.
1	 5,7-Dimethoxy-2-methyl-2*H*-chromene	Leaf oil of *Calyptranthes tricona*	Not known	31
2	 5,7-Dimethoxy-2,8-dimethyl-2*H*-chromene	Leaf oil of *Calyptranthes tricona*	Not known	31
3	 5,8,10-Trihydroxy-2-methyl-2*H*-benzo[*g*]chromene-6,9-dione	Not known	Not known	32

4	 Girinimbine	*M. koenigii*	Cyclo-oxygenase inhibitor	33

Isolation, activity and synthesis: 5,7-Dimethoxy-2-methyl-2*H*-chromene (**21**) and 5,7-Dimethoxy-2,8-dimethyl-2H-chromene are two recently isolated[31] natural products from the leaf oil of *Calyptranthes tricona* having α-monomethyl chromene skeleton. Natural product **21** was synthesized[31] from 3,5-dimethoxy phenol (**17**). Compound **17** on treatment with crotonyl chloride, followed by a Fries transposition to benzopyranone in presence of $AlCl_3$, reduction of the benzopyranone to alcohol and finally dehydration leads to the natural product **21** with 12% yield (Scheme 6). Girinimbine is another 2-oxygenated-3-methylcarbazole alkaloid with α-monomethyl chromene moiety. 5,8,10-Trihydroxy-2-methyl-2*H*-benzo[*g*]chromene-6,9-dione is another one of the rare α-monomethyl chromene natural product whose description has been given in a book[32] "Naturally Occurring Quinones" in 1970. Girinimbine was isolated[33] from stem bark of *M. koenigii* in Sri Lanka and exhibits cyclooxygenase inhibitory activity.

Scheme 6

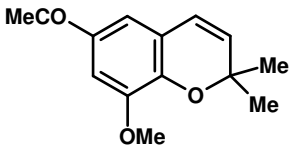
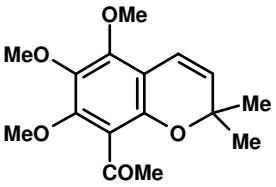
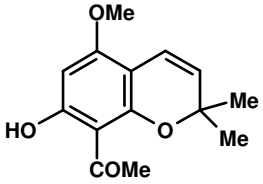
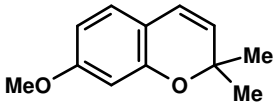
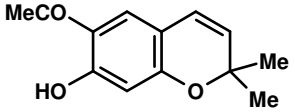


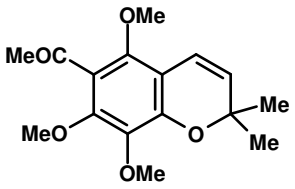
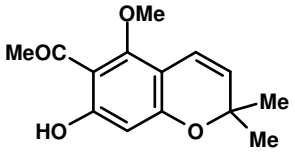
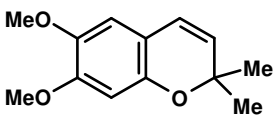
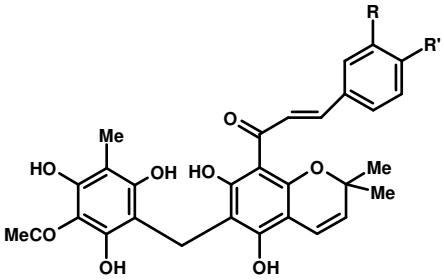
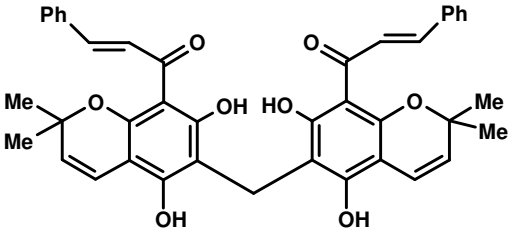
***Reagents, conditions and yields*:** (i) Crotonyl chloride, DMAP, Et_2O; (ii) $AlCl_3$, 150 ^oC; (iii) $LiAlH_4$; (iv) H_3O^+ (12% overall yield).

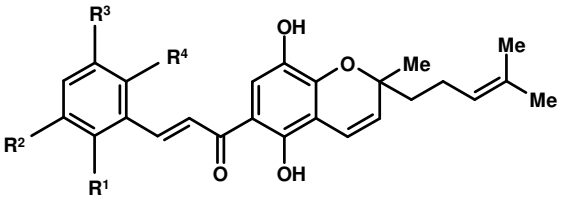
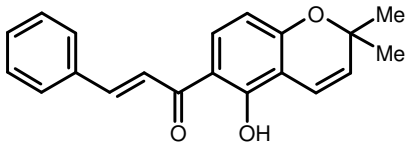
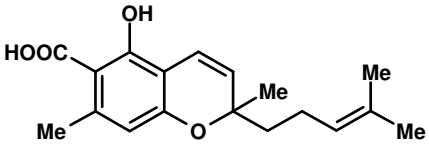
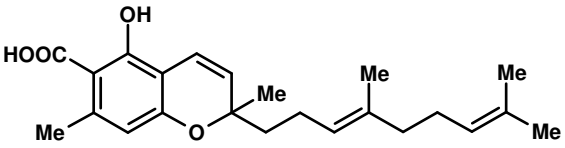
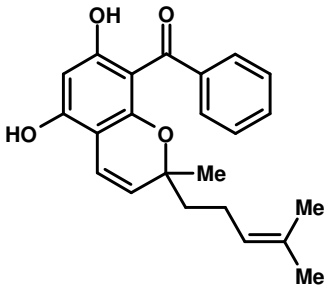
1.3.2 Natural Products with 2,2-Disubstituted 2*H*-1-Benzopyran Units

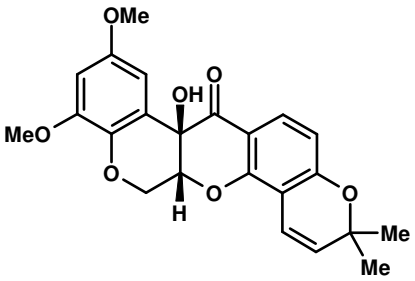
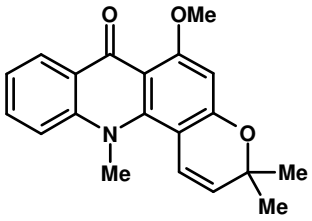
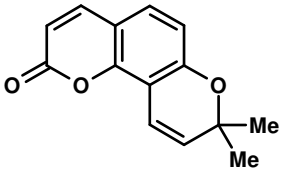
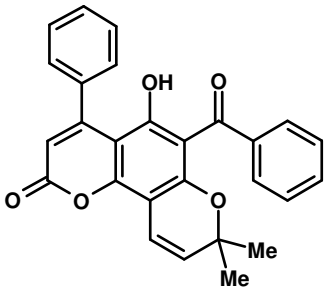
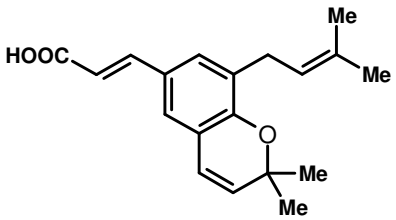
Many natural products containing various 2,2-disubstituted-2*H*-1-benzopyran moieties were known well before the year 1900, but characteristic tests were lacking, and their structures were not elucidated until the 1930. Also the growth of NMR technique and the detailed structural informations obtained from it provided the way to the identification of many natural products containing 2*H*-1-benzopyrans. Very large numbers of phenolic

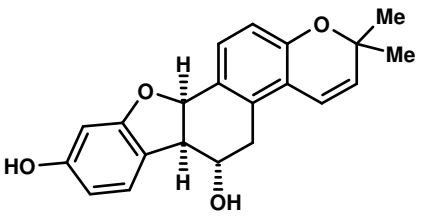
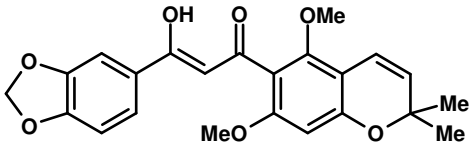
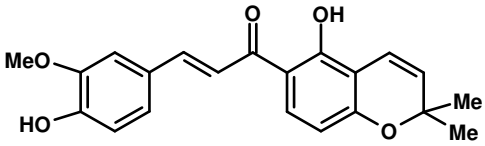
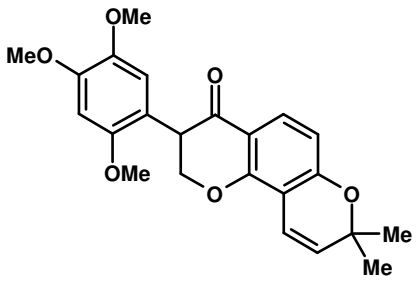
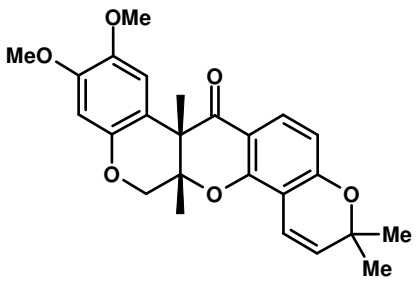
compounds with very diverse structural features exist in nature. These phenolic compounds undergo highly regioselective coupling reactions with naturally occurring prenal, citral and farnesal to provide an avenue of structurally interesting and biologically important benzopyrans. Some of the selected naturally occurring benzopyrans have been listed below with source, activity and synthesis details.

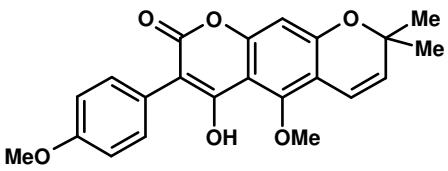
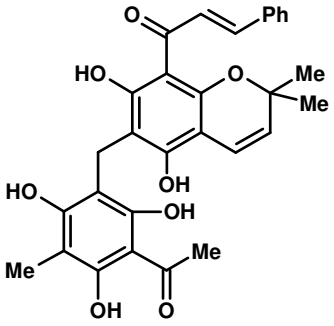
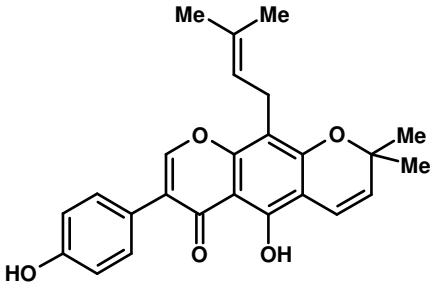
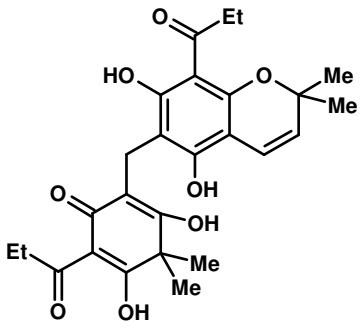
No.	2,2-Disubstituted 2*H*-1-Benzopyran Natural Products	Source	Activity	Ref.
1	 Acetovanillochromene	*Eupatorium riparium*	Not known	34, 35
2	 Alloevodione	*Evodia elleryana* F. Muell	Not known	34
3	 Alloevodionol	*Medicosma cunninghamii*	Not known	34, 36
4	 6-Demethoxyageratochromene	*Ageratum conyzoides*	Not known	37-40
5	 Eupatoriochromene	*Helianthella uniflora*	Not known	41

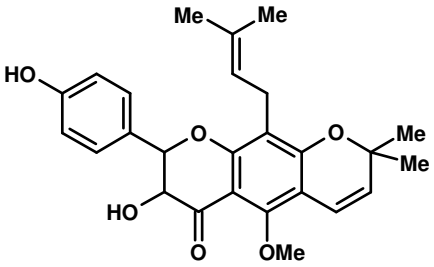
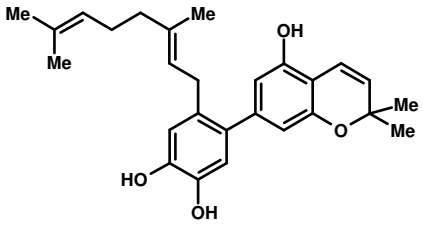
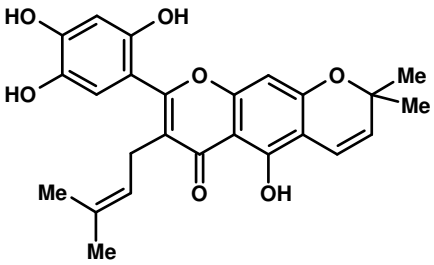
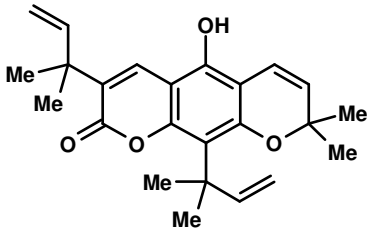
6	 Evodione	*Evodia elleryana*	Not known	18, 42-44
7	 Evodionol	*Melicope simplex*	Not known	18, 34, 41, 45-47
8	 Ageratochromene	*Ageratum conyzoides*	Not known	18, 37, 38, 48-50
9	 R = R' = H; Rottlerine R = H, R' = OH; 4-Hydroxyrottlerine R = R' = OH; 3,4-Dihydroxyrottlerine	*Malotus philippinensis*	Not known	18, 51-56
10	 Rottlerone	*Malotus philippinensis*	Not known	51-53

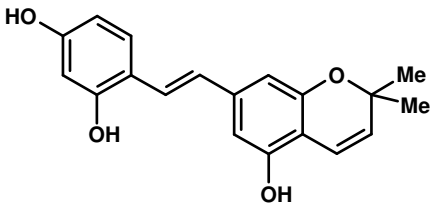
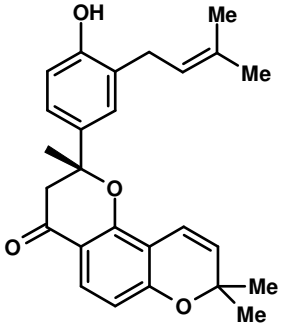
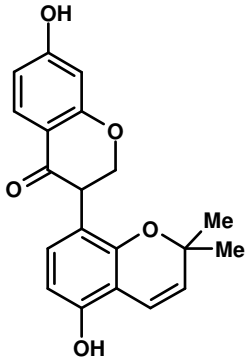
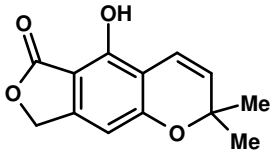
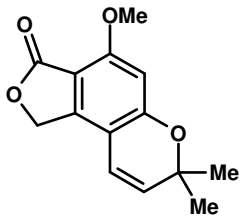
11	 R^1 = OH, R^2 = R^3 = R^4 = H; Flemingin A R^1 = R^4 = OH, R^2 = R^3 = H; Flemingin B R^1 = R^3 = OH, R^2 = R^4 = H; Flemingin C	*Flemingia rhodocarpa*	Not known, but used as cosmetic and dye	57
12	 Lonchocarpin	*Lonchocarpus scericeus*	Not known	18, 58, 59
13	 Cannabichromeorcinic acid	Not known	Not known	60
14	 Daurichromenic acid	*Rhododendron dauricum*	Anti-HIV	61
15	 Clusiachromene C	*Clusia multiflora*	Not known	62

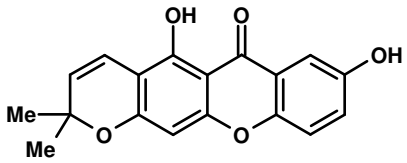
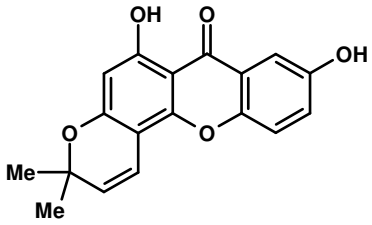
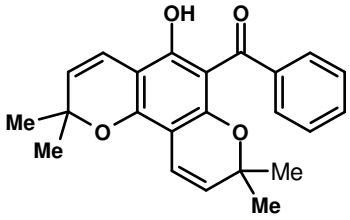
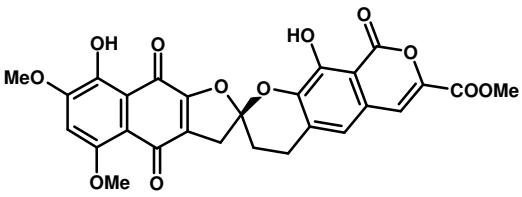
16	 Tephrosin	*Amorpha fruticosa*	Antitumor, [ED_{50} = 0.38 μg/mL (KB), ED_{50} = 0.06 μg/mL (P388)]	63
17	 Acronycine	*Glycosmis pentaphylla*	Antitumor, [IC_{50} = 2.0 μg/mL (L1210), IC_{50} = 0.06 μg/mL (8226 myeloma)]	64
18	 Seselin	*Pletospermium alatum*	Antitumor, [IC_{50} = 12.0 μg/mL (VCGIA)]	37, 65
19	 Calanone	*Calophyllum teysmannii var. inophylloide*	Antitumor, [ED_{50} = 21.0 μg/mL (P388)]	66
20	 2,2-Dimethyl-8-prenylchromene-6-propenoic acid	*Brazilian propolis*	Antitumor, [IC_{50} = 34 μM (HLC-2)]	67

21	 Daleformis	*Dalea filiciformis*	Metalloprotease inhibitor, inhibits endothelin converting enzyme [IC_{50} = 9.0 μM]	68
22	 Pongapinone A	*Pongamia pinnata*	Anti-inflammatory, inhibitor of interleukin-1 production [IC_{50} = 2.5 μg/mL]	69
23	 4-Hydroxy-3-methoxylonchocarpin	*Pongamia glabra*	NADH:ubiquinone oxidoreductase [IC_{50} = 4.8 μM]	10
24	 Lonchocarpusone	*Loncho-carpus nicoi*	NADH:ubiquinone oxidoreductase [IC_{50} = 4.4 μM]	10
25	 Deguelin	*Lonchocarpus utilis*	NADH:ubiquinone oxidoreductase [IC_{50} = 4.4 nM]	10, 70

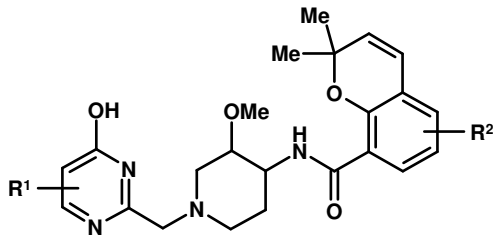
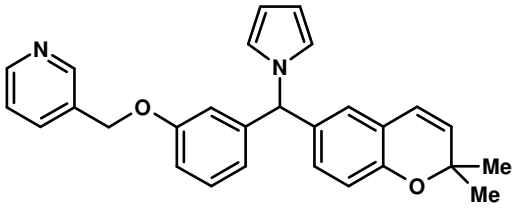
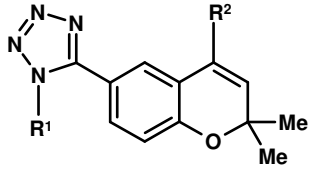
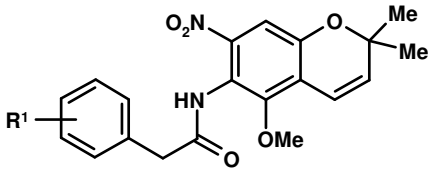
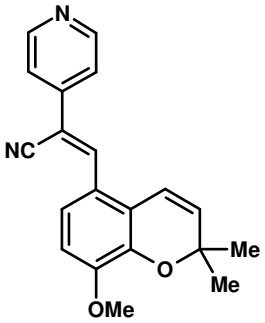
26	 Robustic acid	*D. scandens*	Inhibitor cAMP-dependent PK [IC_{50} = 10.0 μM]	71
27	 Rottlerin	*Mallotus philippinensis*	Inhibitor PKC_y [IC_{50} = 3 μM]	72
28	 Warangalone	*Derris scandens*	Inhibitor cAMP-dependent PK [IC_{50} = 3.5 μM]	73
29	 Drummondin A	*Hypericum drummondii*	Antibacterial [MIC = 0.01 μg/mL (*S. Aureus*)]	74, 75

30	 5-Methyllupinifolinol	*Mundulea suberosa*	Antibacterial [MIC = 0.01 μg/mL (*B. subtilis*)]	76
31	 (*E*)-3-(3,7-Dimethyl-2,6-dienyl)-5-(5-hydroxy-2,2-dimethyl-2*H*-chromene-7-yl)benzene-1,2-diol	*Clusia paralicola*	DNA cleaving agent [EC_{50} = 4.5 μg/mL (KB)]	77
32	 Artonin E	Not known	Inhibitor of arachidonate 5-lipoxygenase [IC_{50} = 0.36 μM]	78
33	 Clausenidin	*Clausena excavata*	Inhibitor of interferon-γ- induced nitric oxide generation	79

34	 Artocarbene	*Atrocurpus incisus*	Inhibitor of torosinanase	80
35	 Shinflavanone	*Glycyrrhiza glabra*	Inhibitor of OCL bone reabsorption [IC_{50} = 0.70 µg/mL]	81
36	 5-Deoxyglyasperin F	*Erythrina*	HIV-1 reverse transcriptase inhibitor [EC_{50} = 11.5 µg/mL (CEM-SS)]	82
37	 Salfredin B_{11}	*Crucibulum* sp. RF-3817	Aldose reductase inhibitor	83
38	 Phthalidochromine	*Helichrysum platypterum*	Not known	84

39	 Osajaxanthone	*Calophyllum enervosum*	Anti-fish poison	85
40	 Nigrolineaxanthone F	*Garcinia nigrolineata*	Not known	86
41	 Clusiaphenone A	*Clusia sandiensis*	Not known	87
42	 β-Rubromycin	*Streptomyces*	Inhibitor of human telomerase [IC_{50} = 3.0 µM]	88-91

Designed Pharmaceutical Ligands Containing 2,2-Dimethylbenzopyran Motifs

No.	Pharmaceutical Ligands Containing 2,2-Dimethylbenzopyran Motifs	Source	Activity	Ref.
1		Synthetic	5-HT3 receptor antagonist	92
2		Synthetic	Inhibitor of aldosterone biosynthesis [IC_{50} = 0.08 μM]	13
3		Synthetic	Potassium channel activator	93
4		Synthetic	Bradycardia activity	94
5		Synthetic	Inhibitor of phosphodiesterase IV	95

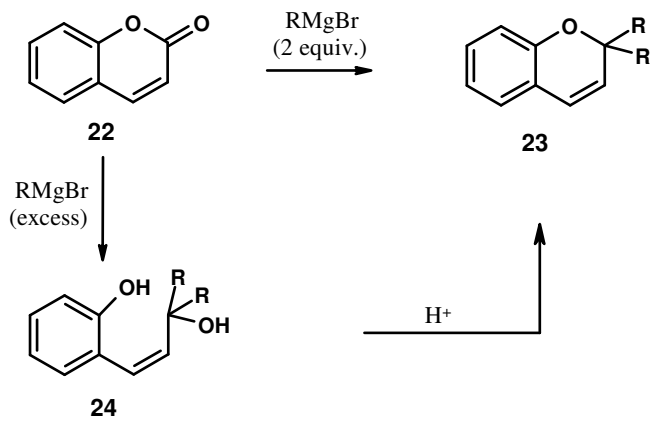
Isolation, activity and synthesis: Acetovanillochromene (entry 1) was isolated[34] from a Jamaican weed *Eupatorium riparium* Regel. The structure of acetovanillochromene has been confirmed by synthesis[35] from acetovanillone and 3-chloro-3-methyl-1-butyne. Both

the natural product 6-demethoxyageratochromene (entry 4) and ageratochromene (entry 8) have been isolated[37] from essential oil of the leaves of *Ageratum conyzoides* from India. Structures of both 6-demethoxyageratochromene and ageratochromene were confirmed by the synthesis[36] by using cyclization of the corresponding aryl propargyl ether. Evodionol (entry 7) was found[18,46] in the bark of New Zealand's *Melicope simplex*. The structure was finally verified when evodionol was synthesized by a DDQ cyclization of acronylin.[46] Rottlerine, 4-hydroxyrottlerine, 3,4-dihydroxyrottlerine and rottlerone (entry 9, 10) have been isolated[53,55] from the fruit glands of the plant *Malotus philippinensis*. From these fruit glands a drug is made which is the anthelmintic kamala. This drug candidate is also used as a pigment for orange silk. Rottlerine was first time isolated[56] in 1855, but at that time structure was not established with certainty. In 1938[53] the structure was elucidated using chemical degradation and spectral properties. 4-Hydroxyrottlerine, 3,4-dihydroxyrottlerine were isolated and identified in 1960s,[55] where as rottlerone was reported in 1937.[50] Flemingin A, flemingin B and flemingin C (entry 11) were found[57] in the seed pods of *Flemingia rhodocarpa* which has been used as cosmetic, dye and a drug called Wars (sold in East Africa). Lonchocarpin was first isolated as yellow-orange crystal from the seeds and roots of Lonchocarpus scericeus.[18] Lonchocarpin's structure was determined by degradation experiments[58] and synthesis[59] from benzaldehyde and β-tubaic acid. We have recently synthesized the natural products cannabichromeorcinic acid, caurichromenic acid and clusiachromene C and details about all these three natural products will be discussed in chapter 2, of the present dissertation as our contribution to the chemistry of benzopyrans.

1.3.3 General Synthetic Approaches to 2,2-Disubstituted 2*H*-1-Benzopyrans

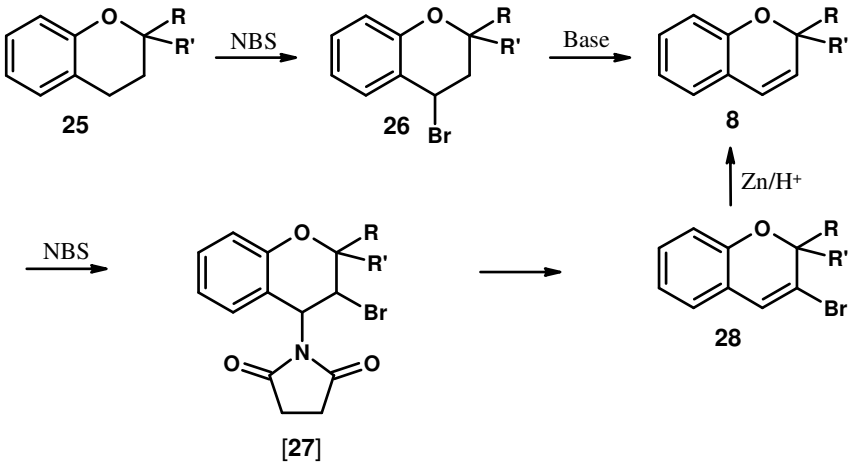
There are several general routes for the construction of 2,2-disubstituted 2*H*-1-benzopyran. Earlier results till 1973 have been summarized in Wawzonek's review[17] and Dean's monographs.[18,19] Synthesis of 2,2-disubstituted 2*H*-1-benzopyran from naturally occurring coumarines is well known method for a long time. The reactions of coumarin with Grignard reagent furnish 2,2-dialkylchromene **23**.[17,18] With the use of the excess of the Grignard reagent and more forcing conditions, the ring can open to give 2-(2-alkyl-2-hydroxy-)-but-3-enylphenols[96-100] from which the chromene can be obtained by an acid treatment[101-103] (Scheme 7). Another pathway that has attracted much more attention is the

Scheme 7



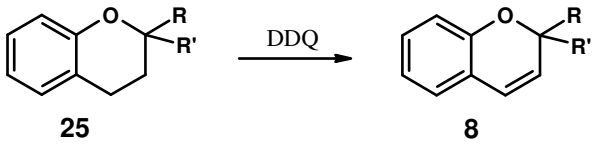
dehydrogenation of chromanes. NBS-bromination of chromanes **25** followed by dehydrobromination provides the desired chromene **8**[104-112] in fair yield (Scheme 8), but the formation of some amount of 3-bromochromene derivative **28** in the presence of excess NBS is a complication. The 3-bromo derivative can be transformed into the desired chromene by treatment with zinc and acid.[112] A more direct way to get the same dehydrogenation is to allow a chromane **25** to react with DDQ[113] (Scheme 9). The reaction

Scheme 8



is usually carried out in benzene or dioxane with nearly 40% yields and herein the improvement in yield is essential. This reaction was first reported by Schudel *et al*,[114] they dehydrogenated a dimer of tocopherol. The Claisen rearrangement of propargyl ethers of phenols is one of the widely used procedure for chromenes synthesis. This reaction was

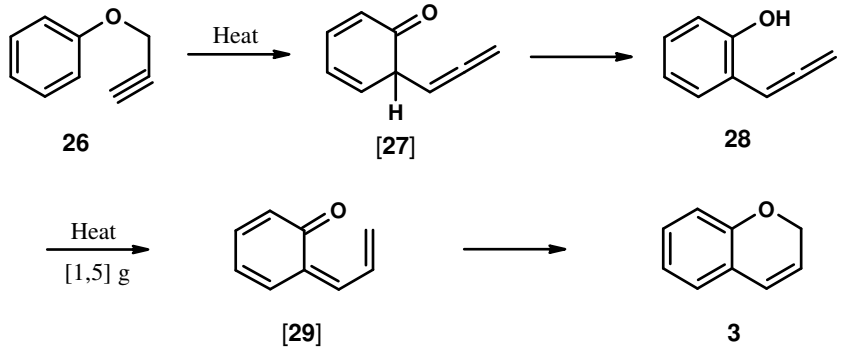
Scheme 9



25 **8**

introduced by Iwai and Ide in 1962,[115] but only in 1968 Schmid and co-workers[116] confirmed the mechanistic pathway as a Claisen rearrangement followed by a [1,5] sigmatropic shift (Scheme 10). This mechanism was also supported by thermal conversion of 2-allenylphenol (**28**) into chromene (**3**). Another reaction which requires *o*-quinoneallides as an intermediate is the synthesis of chromene by the reaction of benzyne intermediate with α,β-unsaturated aldehydes **31**[117] (Scheme 11). The formation of unstable benzoxete **33** was confirmed by isotope labeling experiment. The same *o*-quinoneallide intermediates are probably involved in the reaction of 3,3-dimethylallyltriphenylphosphorane **35** with *o*-benzoquinones **34**[118] which gives chromenes

Scheme 10

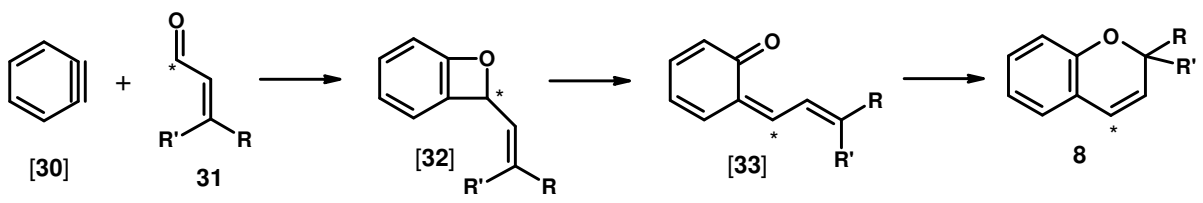


26 **[27]** **28**

[29] **3**

37, although in low yields (Scheme 12). In a series of papers, Schweizer's group has used another general procedure[119-121] for the synthesis of chromene in high yields by addition of

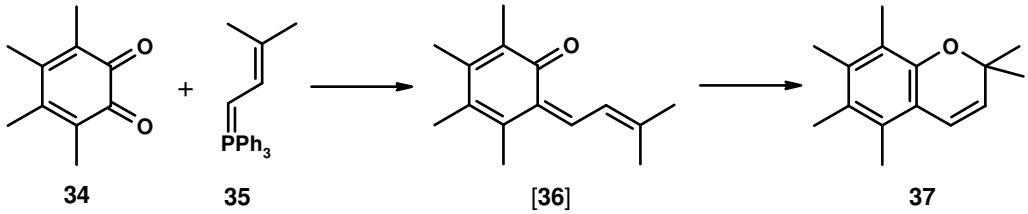
Scheme 11



[30] **31** **[32]** **[33]** **8**

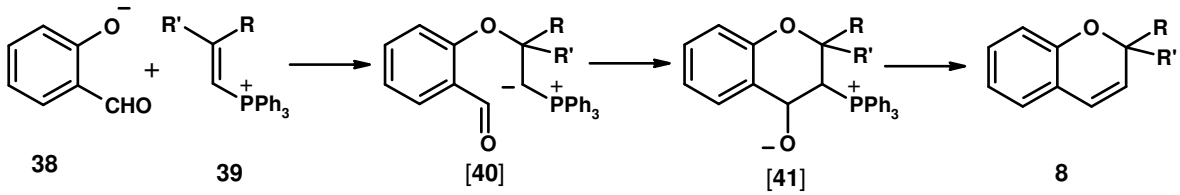
the phenolate anion of salicylaldehyde to a vinylphosphonium salt and subsequent Wittig reaction (Scheme 13). Another widely used procedure for the synthesis of chromene is the

Scheme 12



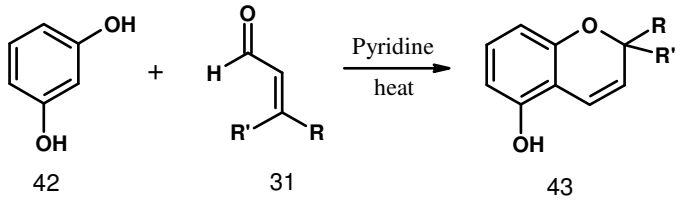
condensation of α,β-unsaturated aldehydes with the resorcinol derivatives in the presence of a base such as pyridine[122-125] (Scheme 14). Advantages of this procedure are the high

Scheme 13



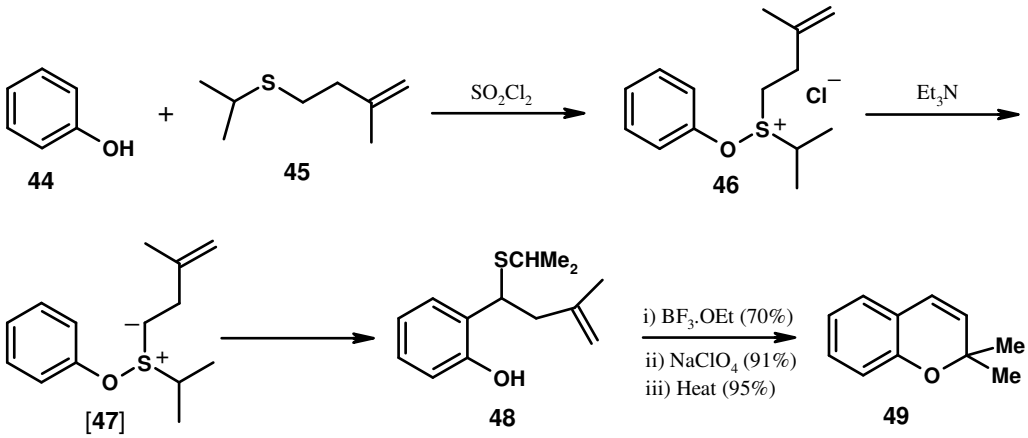
yields of the reactions and an easy accessibility of several natural α,β-unsaturated aldehydes. During this course of reaction, the cyclization may occur via ring closure with

Scheme 14



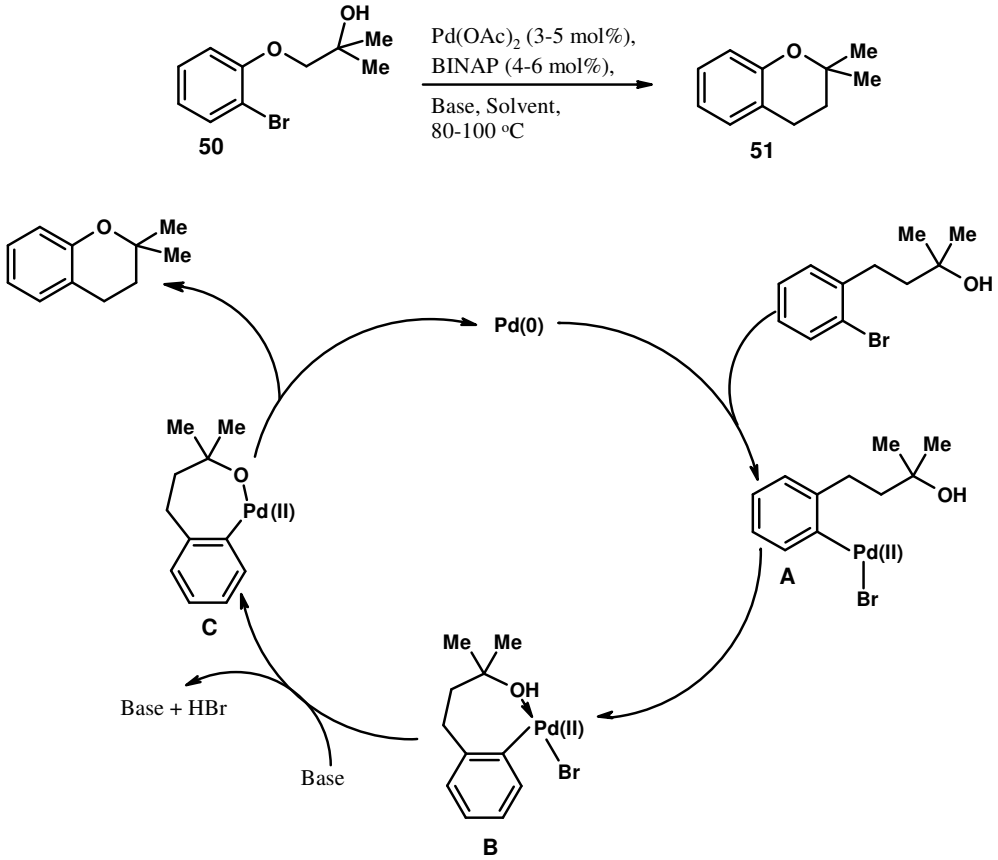
elimination of water molecule or through an *o*-quinoneallide intermediate.[123] Gassman and co-workers[126] have developed an efficient methodology for the regioselective *ortho* alkylation of phenols using [2,3] sigmatropic rearrangement of phenoxysulfonium ylides **47**. Sato and co-workers[127] extended this methodology for the synthesis of disubstituted benzopyrans. Phenol on reaction with isopropyl-(3-methyl-3-enyl)-sulfide (**45**) in presence

Scheme 15



of sulfuryl chloride followed by the treatment with triethyl amine furnished the corresponding phenoxysulfonium ylide **47**, which on heating undergoes [2,3] sigmatropic rearrangement to furnish 2-(1-(isopropylthio)-3-methylbut-3-enyl)phenol (**48**). Lewis acids

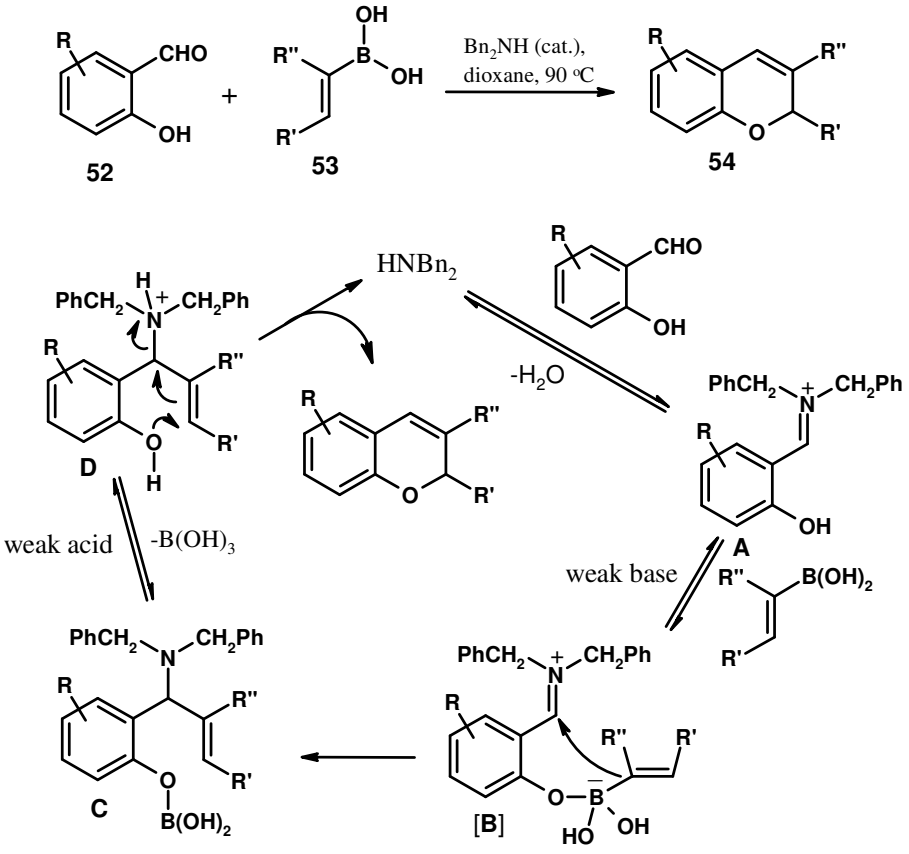
Scheme 16



(Ligands omitted in scheme)

catalyzed cyclization of **48** followed by sodium perchlorate mediated oxidation of the sulfide to the corresponding sulfoxide and finally thermal *syn*-elimination of the sulfoxide releases chromene **49** (Scheme 15). Buchwald and co-workers[128] reported an efficient intramolecular Pd-catalyzed ipso substitution of an aryl halide **50** with an alcohol to form 3,4-dihydro-2,2-disubstituted-2*H*-1-benzopyran (**51**) (Scheme 16). The mechanism of the Pd-catalyzed synthesis of chroman derivative most likely proceeds via a pathway through similar to that suggested for the Pd-catalyzed aryl amination reaction.[129] As shown in scheme 16, oxidative addition of the $Pd(0)L_n$ with the aryl halide affords the Pd(II) could afford the palladacycle **C**, which then undergoes reductive elimination to give the chroman derivative. Recently Wang *et al*[130] have reported that the Petasis condensation[131] of vinylic boronic acids, aromatic aldehydes and secondary amines is assisted by a hydroxyl group

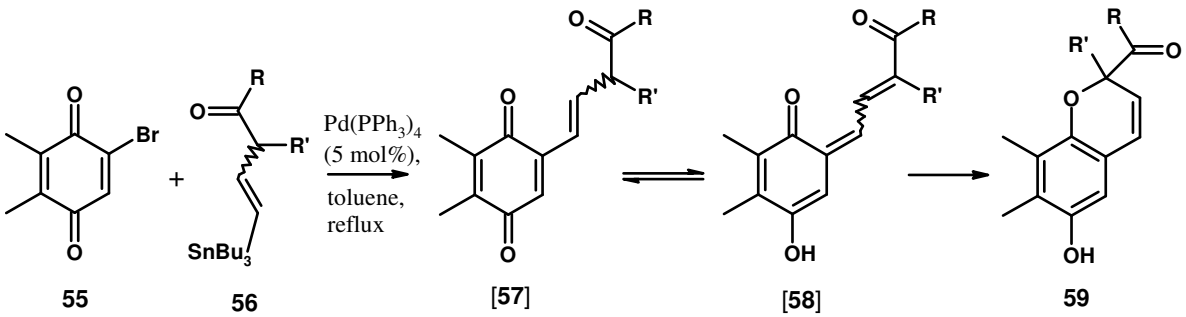
Scheme 17



adjacent to the aldehyde moiety. The products derived from salicylaldehydes and vinylboronic acids **53** undergo cyclization to 2*H*-chromene compounds with the

elimination of amine upon heating (Scheme 17). In the proposed catalytic cycle, the key intermediate **B** is assembled by iminium ion formation and coordination of the phenolate oxygen to the boronic acid. Intramolecular vinyl group transfer produces **C** which is the immediate precursor of the allylic amines. Cyclization to chromene **54** is likely promoted by protonation of the amine as shown, regenerating the catalyst. Primary amines are poor catalysts for the process, while the solid supported *N*-benzyl amine[132] is very effective. Parker *et al*[133] also serendipitously discovered a chromene preparation procedure while working on quinone under Stille coupling condition. Bromobenzoquinones **55** on coupling with vinyl stannanes **56** under Stille condition furnishes 2*H*-chromene **59** as major product

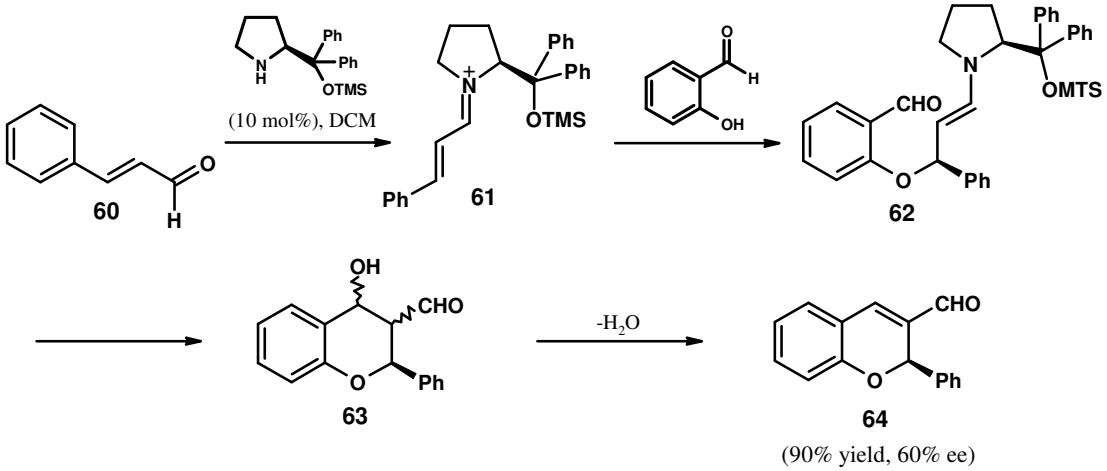
Scheme 18



55 **56** **[57]** **[58]** **59**

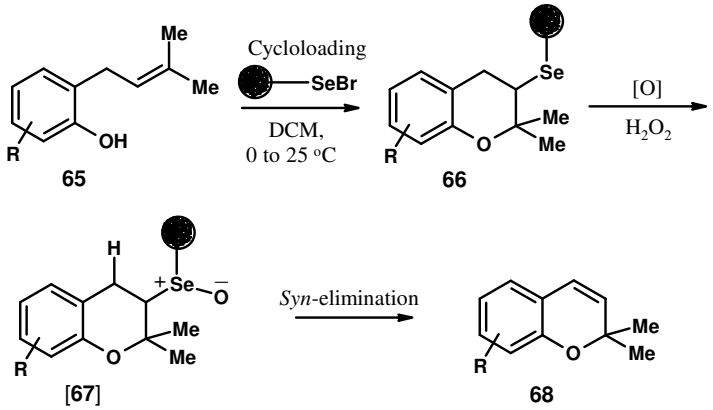
along with substituted hydroquinone derivatives. Experimental evidence supports a two step mechanism in which enolization is followed by a thermal 6π-electrocyclic reaction of an intermediate quinone methide **57** (Scheme 18). Polar and aprotic condition favors the reaction. There are few reports on unsymmetrical 2,2-disubstituted chiral benzopyran synthesis using kinetic resolution,[134] dehydrogenation of chiral chromane,[135] cyclization of α,β-unsaturated sulfoxide,[136] and Ru-catalyzed metathesis.[137,138] Recently, Arvidsson and co-workers[139] reported first, an organocatalyzed asymmetric synthesis of chiral benzopyrans. They have constructed the benzopyran unit through a domino reaction involving an oxa-Michael attack of salicylic aldehyde derivatives on the α,β-unsaturated aldehydes, activated through iminium-ion formation with the organo catalyst, followed by an intramolecular aldol reaction and subsequent elimination of water (Scheme 19). The overall reaction sequence provides benzopyrans **64** with aromatic C-2 substituents in up to 60% yields and 60% enantioselectivity, while C-2 aliphatic analogues were obtained in 90% enantiomeric excess, but with only 20% yield. They have also discussed the role of

Scheme 19



additives, as well as the possible process of racemization of the benzopyrans. In a recent series of publications by Nicolaou and co-workers described the design, chemical optimization, and eventual synthesis of natural product-like libaries centered around the 2,2-dimethyl-2*H*-1-benzopyran unit[5,140-144] using solid phase synthesis. 2,2-Dimethyl-2*H*-1-benzopyran is a structural motif, which has been labeled as a *privileged structure*. The concept of *privileged structure* is used to describe common structural motifs that are capable of interacting with a variety of unrelated biomolecular targets.[145] The key features

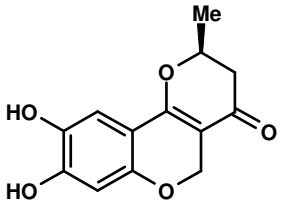
Scheme 20



in the synthesis of each class of benzopyran derivative is the initial cycloloading of various *ortho*-prenylated phenols **65** on a novel selenyl bromide polystyrene resin[146] to provide the supported benzopyran scaffold **66** (Scheme 20). Oxidative release from the support through the *syn*-elimination of the intermediate selenoxide provides the desired benzopyran

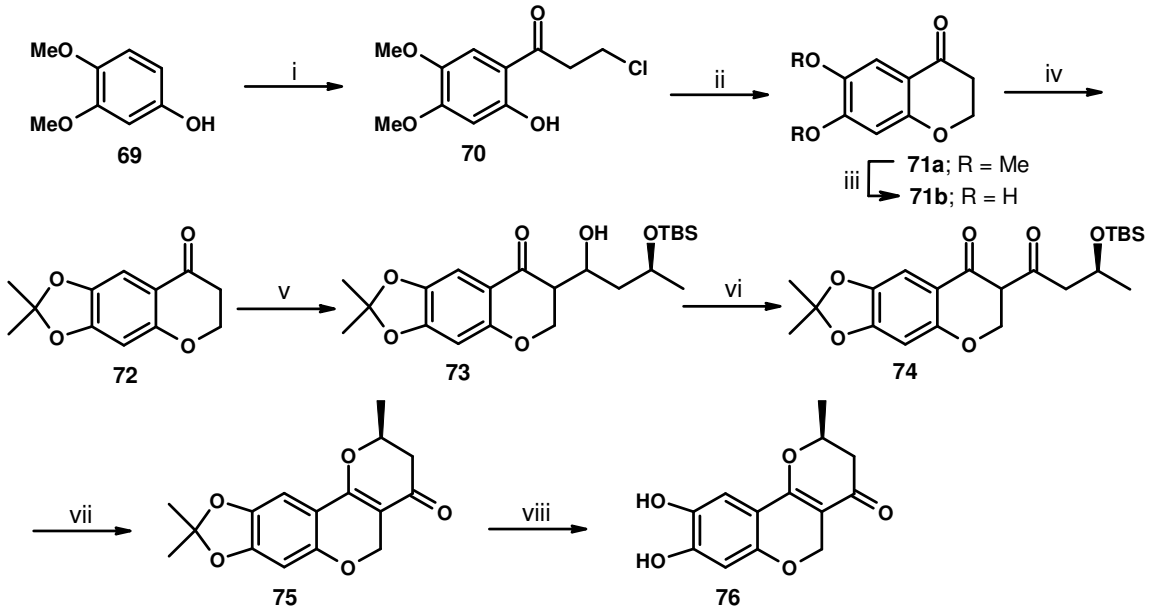
derivatives. In addition to its chemical stability, linkage of the scaffold via the pyran ring provides the advantages of allowing the derivatization of all the four remaining positions on the aromatic ring.

1.3.4 3,4-Disubstituted 2*H*-1-Benzopyran Containing Natural Product

No.	3,4-Disubstituted 2*H*-1-Benzopyran Natural Product	Source	Activity	Ref.
1	 Neuchromenin	*E. javanicum var. meloforme*	Inducer of neurite outgrowth [EC_{50} = 2.5-10 μg/mL (PC12)]	147

Synthesis: Hayakawa and co-workers isolated[147] a new 3,4-disubstituted-2*H*-benzopyran

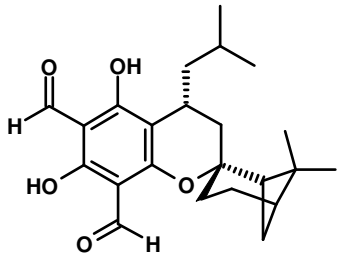
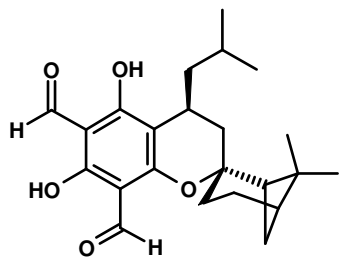
Scheme 21

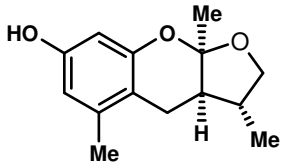
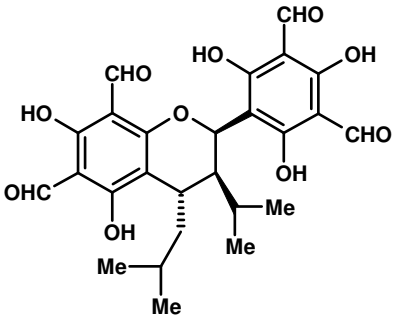


***Reagents, conditions and yields*:** (i) $Cl(CH_2)_2COCl$, $BF_3.OEt_2$, 65-85 °C, 3 h (25%); (ii) K_2CO_3, EtOH, rt, 14 h (76%); (iii) BBr_3, DCM, −10 °C to rt, 1 h, (88%); (iv) *p*-TsOH, $Me_2C(OMe)_2$, Me_2CO, benzene, MS 4 Å, reflux, 72 h, (84%); (v) LDA, (*S*)-3-(*tert*-butyldimethylsilyloxy)butanal, THF, below − 60 °C, 1 h; (vi) Dess-Martin periodinane, DCM, rt, 4 h; (vii) *p*-TsOH, benzene, 18 h (25% 3-steps); (vii) 10% HCl, THF, MeOH, reflux, 14 h (82%).

natural product 3,3'-bis(4-hydroxy-2*H*-benzopyran) (**76**) from the culture broth of *E. javanicum var. meloforme* PF1181 and found that the natural product is a very good inducer of neurite outgrowth of PC12 cells. Recently Mori and co-worker have synthesized[148] the natural product from 3,4-dimethoxyphenol (**69**) and determined the absolute configuration. 3,4-Dimethoxyphenol on Friedel-Crafts acylation with 3-chloropropanyl chloride followed by cyclization with potassium carbonate furnished the chromanone derivative **71**. Chromanone **71** on demethylation followed by acetonide protection gave the 1,3-benzodioxile derivative **72**. Compound **72** on cross aldol condensation with TBS-ether of (*S*)-3-hydroxybutanal,[149] Dess-Martin[150] oxidation of the secondary alcohol, removal of the TBS- protecting group, subsequent ring closure and finally hydrolysis of the acetonide group furnished the desired natural product **76** in 3.0% overall yield and 62% ee (Scheme 21). This synthesis also confirmed the (*S*)-configuration of the asymmetric centre in the natural product.

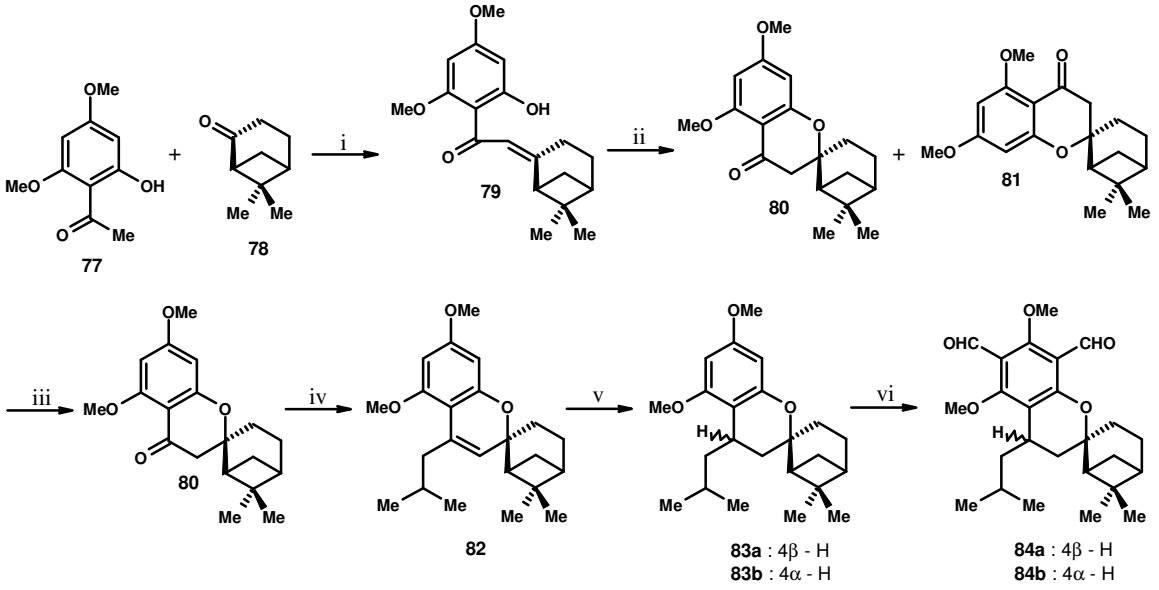
1.3.5 Trisubstituted 2*H*-1-Benzopyrans

No.	Trisubstituted 2*H*-1-Benzopyran Natural Products	Source	Activity	Ref.
1	 Robustadials A	*Eucalyptus robusta*	Antimalarial	151
2	 Robustadials B	*Eucalyptus robusta*	Antimalarial	151-153

3	 Alboatrin	*Verticillium alboatrum*	Phytotoxic	154-156
4	 Sideroxylonals	*Eucalyptus*	Antifouling	157

Isolation, activity and synthesis: All the naturally occurring trisubstituted-2*H*-benzopyrans are dihydro derivatives of 2*H*-benzopyrans. Two potent antimalarial natural products with dihydro-2*H*-benzopyran moiety, robustadials A and B have been isolated[151] from the leaves of *Eucalyptus robusta*. Salomon and co-workers have synthesized[152] the methyl ether of both robustadials A and B and hence established the correct structure of both the natural products. They have assembled the robustadials ring system in one step by a pyrrrolidine-catalyzed condendation[153] of (+)-nopinone (**78**) with 2,4-dimethoxy-6-hydroxyacetophenone (**77**). The formed α,β-unsaturated ketone **79** on cyclization furnished a 2:5 mixture of **80** and **81**. The required compound **80** on treatment with isobutylmagnasium bromide followed by dehydration of the resulting tertiary benzylic alcohol gave the chromene derivative **82**. Catalytic hydrogenation of alkene **82** produced the well separable epimers **83a** and **83b**. Both these epimers **83a** and **83b** on bromination, lithiation, quenching with carbon dioxide to form respective acids, esterification with diazomethane, DIBAL reduction of the ester to the corresponding alcohols and finally PDC oxidation to aldehydes provided the methyl ether of the corresponding natural products. From spectral analysis they have established the absolute stereochemistry of robustadials A and B corresponding to **84a** and **84b** (Scheme 22). Alboatrin (**88**) is a

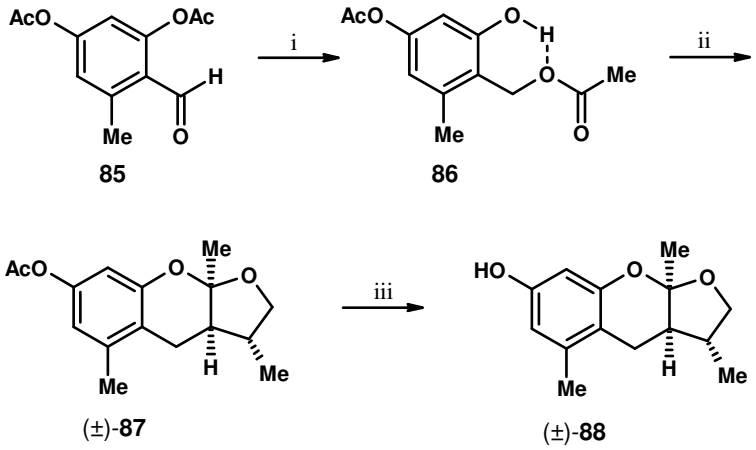
Scheme 22



***Reagents, conditions and yields*:** (i) Pyrrolidine, benzene; (ii) K_2CO_3, EtOH, reflux (90%); (iii) Silica gel column chromatographic separation (28%); (iv) Me_2CHCH_2MgBr, aq. HCl (75%); (v) H_2/Pd/C (**83a**: 11%; **83b**: 86%); (vi) (a) Pyridine, Br_2, DCM; (b) *n*-BuLi, THF, CO_2, aq. HCl, CH_2N_2, Et_2O; (c) DIBAL-H, toluene; (d) PDC, DCM (**84a**: 69%; **84b**: 51%).

phytotoxic natural product with trisubstitutedihydro-2*H*-benzopyran skeleton, isolated in 1988 by Ichiara *et al*[154] from *Verticillium alboatrum* and later on the structure was revised

Scheme 23

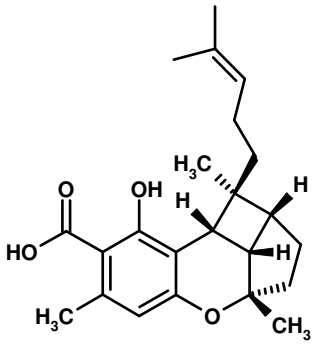
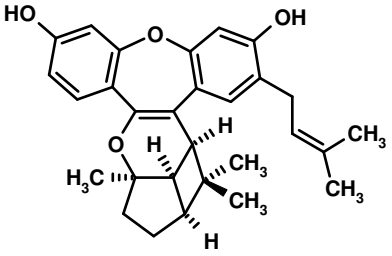


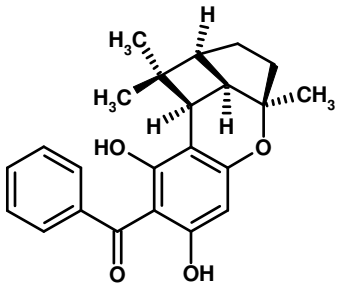
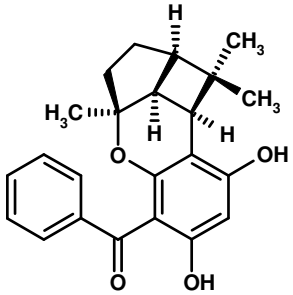
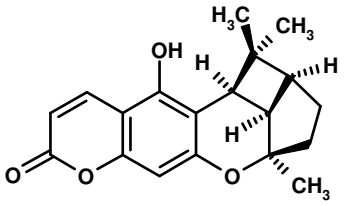
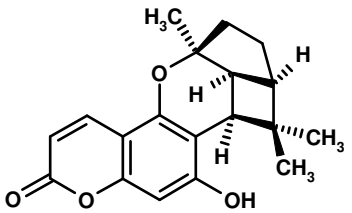
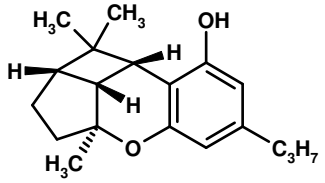
***Reagents, conditions and yields*:** (i) BH_3-DMS, THF, 0 ^oC to rt, 1 h (84%); (ii) (±)-4,5-Dihydro-2,4-dimethylfuran (1 equiv.), benzene, reflux, 36 h (93%); (iii) K_2CO_3 (3 equiv.), DCM/MeOH/H_2O (12:7:10), rt, 6 h (90%).

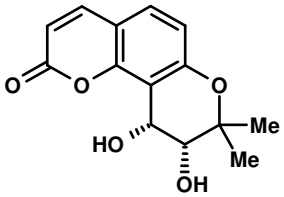
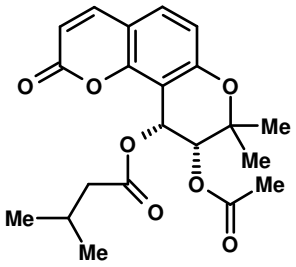
and established by Murphy *et al*.[155] Recently Baldwin and co-workers[156] have reported an efficient synthesis of Alboatrin starting from diacetete **85**. The diacetate **85** on BH_3-DMS reduction condition undergoes reduction and intramolecular transesterification to form **86**. This stable precursor **86** on simple heating in presence of (±)-4,5-dihydro-2,4-dimethylfuran afforded acetylalboatrin through *o*-quinone methide pathway. Finally deprotection of the acetyl group furnished the desired natural product (±)-alboatrin (**88**) (Scheme 23). Sideroxylonals is a 2,3,4-trisubstituted dihydro-2*H*-benzopyran containing natural product isolated[157] from the plant *Eucalyptus* and exhibits antifouling activity. The synthesis of target molecules containing two hexasubstituted benzene rings and a spiro carbon atom is a challenging task.

1.3.6 Tetrasubstituted 2*H*-1-Benzopyran Containing Natural Products

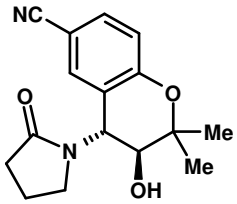
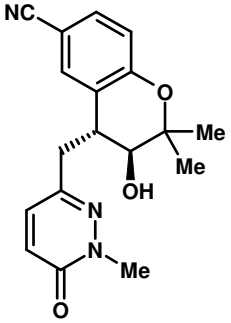
Like trisubstituted, all the naturally occurring tetrasubstituted-2*H*-benzopyrans are dihydro derivatives of 2*H*-benzopyrans.

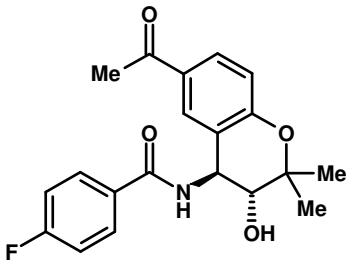
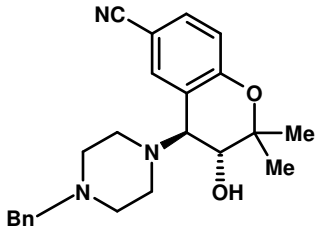
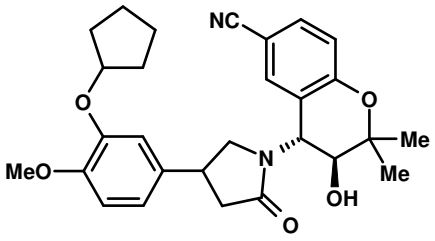
No.	Tetrasubstituted 2*H*-1-Benzopyran Natural Products	Source	Activity	Ref.
1	 Rhododaurichromanic acid A	*Rhododendron dauricum*	Potent anti-HIV agent	158-161
2	 Artocarpol A	*Artocarpus rigida*	Potent antiinflammatory	162-164

3	 Clusiacyclol A	*Clusia multiflora*	Not known	62
4	 Clusiacyclol B	*Clusia multiflora*	Not known	62
5	 Eriobrucinol	*Eriostemon brucei*	Not known	165, 166
6	 Isoeriobrucinol	*Eriostemon brucei*	Not known	166
7	 Cannabicyclovarin	*Meao strain*	Not known	167

8	 (+)-Khellactone	*Ammi vienaga*	Cytotoxic and antiviral	168, 169
9	 Suksdorfin	*Lomatium suksdorfi*	Potent anti-HIV	170

Important Designed Pharmaceutical Ligands with Tetrasubstituted 2*H*-1-Benzopyran Skeletons

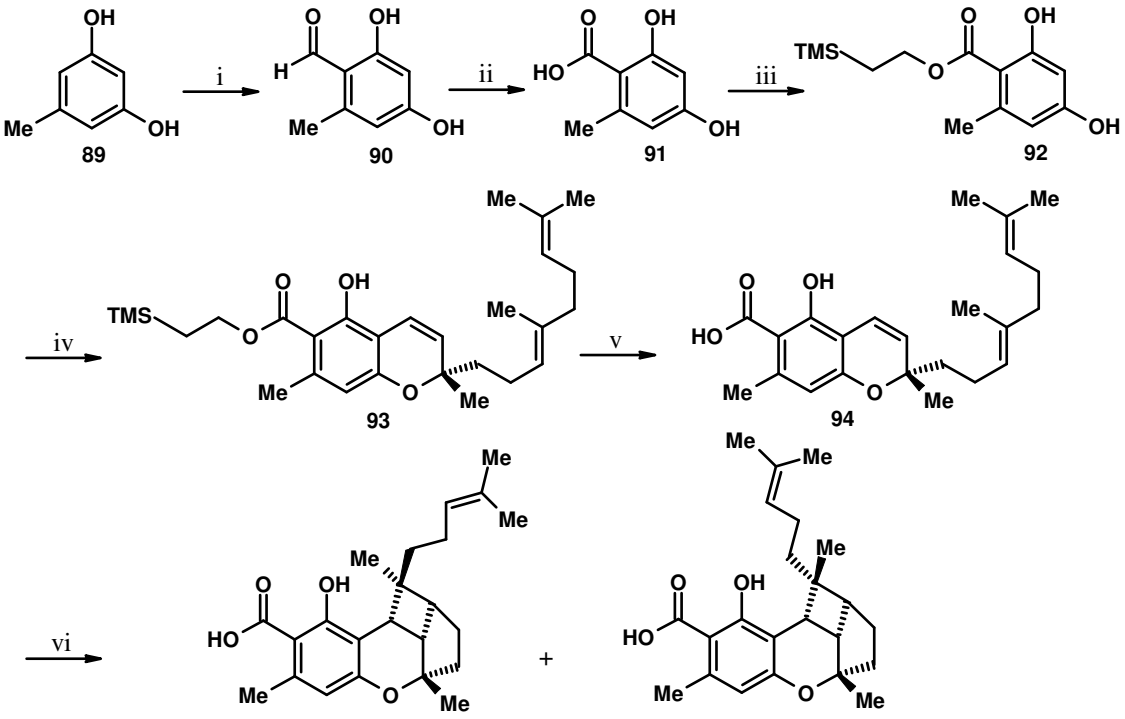
No.	Tetrasubstituted 2*H*-1-Benzopyran Containing Pharmaceutical Ligands	Source	Activity	Ref.
1	 Cromakalin	Synthetic	Activator of ATP-dependent potassium channels	171
2	 Symakalin	Synthetic	Activator of ATP-dependent potassium channels	172

3	 SB-204269	Synthetic	Antimigraine	173
4	 4-Benzylpiperazinobenzopyran	Synthetic	Modulate multidrug resistance	174, 175
5	 Benzopyran Ligand	Synthetic	Phosphodiesterase IV inhibitor	174, 175

Isolation, activity and synthesis: Among the tetrasubstituted dihydro-2*H*-benzopyran natural products rhododaurichromanic acid A (from *Rhododendron dauricum*)[158] and artocarpol A (from *Artocarpus rigida*)[162] are of current interest, as they possess potent anti-HIV and potent antiinflammatory activities respectively. Construction of these tetrasubstituted dihydro-2*H*-benzopyran skeleton, that is hexahydrooxacyclobutaindane moiety has been achieved by using the condensation reactions of phenolic compounds with citral and/or farnesal via [2+2] cycloaddition reactions. Jin and co-workers have completed[160] the short synthesis of rhododaurichromanic acid A starting from orcinol. Orcinol on formylation in presence of $POCl_3$ and DMF, followed by oxidation to the corresponding acid and finally on esterification with 2-(trimethylsilyl)ethanol furnished the β-trimethylsilylethyl ester **92**. The ester undergoes condensation with *trans*, *trans*-farnesal

in presence of $CaCl_2.H_2O$ and microwave irradiation to form desired benzopyran **93**. The compound **93** on TBAF mediated desilylation followed by irradiation with a low-pressure mercury lamp furnished the separable mixture of rhododaurichromanic acid A (**95**) and B (**96**) in 2:1 ratio with 60% yield (Scheme 24). Recently Hsung and co-workers[161] have also synthesized both rhododaurichromanic acid A and B using acid catalyzed cycloaddition reaction of the same benzopyran intermediate **94**. Wilson and co-workers[164] have

Scheme 24



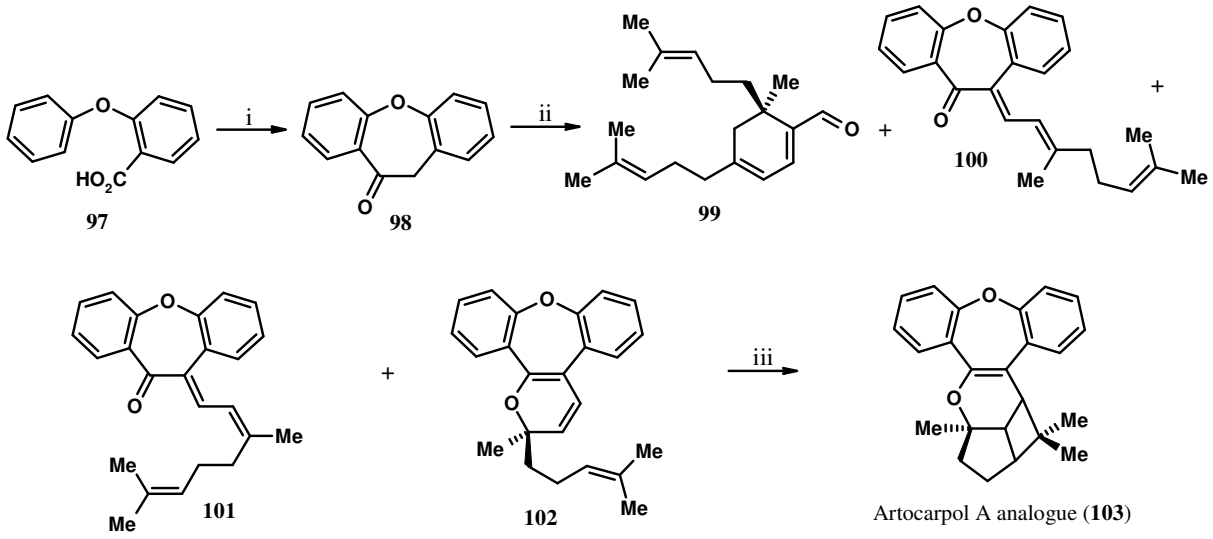
Rhododaurichromanic acid A (**95**) Rhododaurichromanic acid B (**96**)

***Reagents, conditions and yields*:** (i) $POCl_3$, DMF, 10% NaOH, 10% HCl (98%); (ii) NaH_2PO_4, $NaClO_2$, DMSO, H_2O (99%); (iii) $TMSCH_2CH_2OH$, DEAD, PPh_3, DCM, 25 ^oC (90%); (iv) *trans*, *trans*-farnesal, $CaCl_2.2H_2O$, NEt_3, EtOH, microwave, 20 min (60%); (v) TBAF, THF, 25 ^oC (94%); (vi) $h\nu$, hexane, 5 days (**95**: 40%; **96**: 20%).

accomplished the first total synthesis of artocarpol A analogue from commercially available 2-phenoxybenzoic acid (**97**). 2-Phenoxybenzoic acid was converted to known oxepinone **98** in five steps using the literature procedures. The oxepinone **98** on condensation with citral (*E*:*Z* = 2:1) in presence of allylamine and anhydrous magnesium sulfate in THF furnished the chromatographically separable mixture of the self-condensation product of citral **99**, the cross-condensation product (*E*,*E*)-**100**, (*E*,*Z*)-**101** and

the desired 2*H*-pyran **102** in 50% yield (Scheme 25). The cross-condensation products **100** and **101** were subsequently recycled to afford the desired 2*H*-pyran **102** in a combined overall yield of 70%. Irradiation of a dilute deoxygenated solution of the 2*H*-pyran **102** and benzophenone in benzene with a high pressure mercury lamp within a quartz reaction flask

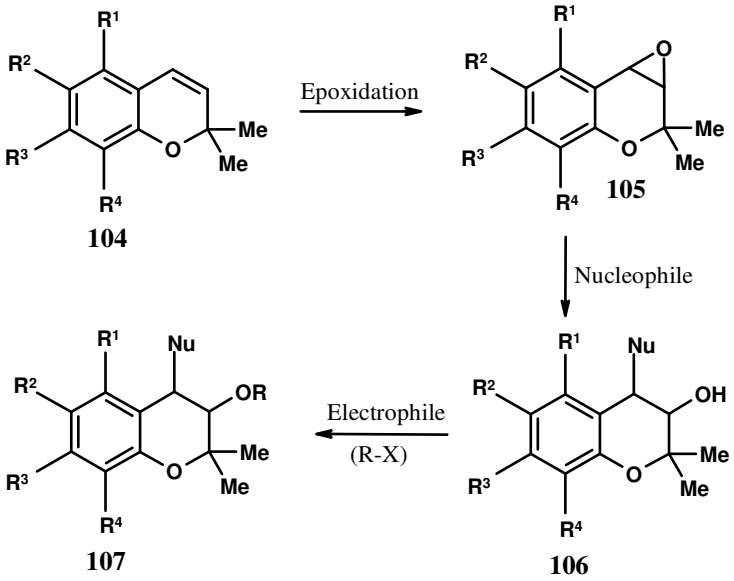
Scheme 25



***Reagents, conditions and yields*:** (i) (a) $LiAlH_4$, THF, reflux, 4 h (96%), (b) $SOCl_2$, pyridine, benzene, reflux, 24 h (98%), (c) NaCN, DMSO, rt, 24 h (90%), (d) KOH, EtOH, H_2O, reflux, 4 h (85%), (e) polyphosphoric acid, 100 ^oC, 4 h (84%); (ii) Citral, allylamine (6 eqiuiv.), $MgSO_4$, THF, reflux, 8 h [**99**: 20%; **100**:**101** = 1:1.6 (27%); **102**: 50%]; (iii) Benzophenone, benzene, $h\nu$, 24 h (45%).

afforded the artocarpol A analogue **103** in 45% yield. Another established routes for derivatizing the olefin site of benzopyran ring was through epoxidation.[176] The Nicolaou's group developed a "library-from-library" strategy[177] where an existing benzopyran library can be further derivatized at the pyran olefine site and there by increasing the structural diversity.[5] A defined benzopyran scaffold **104** (Scheme 26) was converted to the corresponding epoxide **105** which on regioselective nucleophilic ring opening furnished secondary alcohol **106**. This secondary alcohol on treatment with electrophiles produced derivatized tetrasubstituted dihydrobenzopyran **107**.

Scheme 26



In conclusion, we have provided a concise account of naturally occurring mono-, di-, tri-, tetra- and spirobenzopyrans with majorly used synthetic methods to design these useful and structurally interesting compounds. We feel that all these nice methods are general and the use of natural or unnatural α,β-unsaturated aldehydes and phenol derivatives will provide large numbers of pseudo natural products and natural products hybrids for structure activities relationship studies.

1.4 2*H*-Benzopyrans in Clinical Treatment

Several natural and synthetic 2*H*-benzopyrans are known to elicit a wide range of biological activities. This has spurred the preparation and pharmaceutical evaluation of a huge number of natural and synthetic 2*H*-benzopyran derivatives and intensive research in this area is in active progress.

One of the first uses perceived for the 2*H*-1-benzopyrans was due to their relationship to tetrahydrocannabinol.[178,179] Earlier, 2*H*-benzopyrans were considered to be analgesics,[96,180,181] antidepressants,[96,180,181] antianxietal,[96,180] antihypertensive,[96,180] and hypoglycemic agents.[182] In those days, people undoubtedly used the cultures containing 2*H*-1-benzopyran herbs, such as Tzotzil, which was widely used in Mexico for the treatment of diarrhea,[183,184] the Chinese drug Wu-Chu-Yu, used as a stimulant,

carminative, beobstrunet, stomachic astringent and anthelmintic remedy,[185] and the East African drug called Wars[57] (Wurrus or black Kamala) used as a cosmetic, dye and drug. 2*H*-1-Benzopyrans are also well known for their special photochemical properties.[186,187]

Recently many substituted-2*H*-benzopyrans containing natural products have found potential applications in medicine[7] as anti-cancer[8] agent, non-nucleoside, HIV-1-specific reverse transcriptase inhibitors currently in clinical development,[9] cancer chemopreventives,[10] insecticidal and anti-fungal[11] agent etc. Furthermore, a growing number of pharmaceutical designed synthetic ligands with substituted-2*H*-benzopyran moiety have shown promising bioactivity as potassium-channel activators,[12] aldosterone biosynthesis inhibitor,[13] 5-hydroxytryptamine-3 receptor antagonist,[14] phosphodiesterase IV inhibitor[15] and ampicillin-derived anti-bacterial agent.[16]

1.5 Summary

In this chapter we have presented a concise account of the natural 2*H*-1-benzopyrans along with some important pharmaceutical synthetic ligands with various substituted-2*H*-benzopyran moieties. All important natural and unnatural 2*H*-benzopyrans have been classified into four different classes according to the positions of substituents. The informations about the isolation, bioactivity and synthesis have been provided in a systematic manner. A part of this chapter has been used to discuss about biogenesis. Individual as well as general synthetic procedures have been explained and discussed. All together 26 schemes have been provided to discuss biogenesis/synthesis and various important synthetic approaches towards these natural products. The uses of natural and pharmaceutical designed synthetic 2*H*-benzopyrans for clinical purpose have been reviewed briefly in the last section. All the information collected and presented in this chapter has been well supported by providing more than 250 references from various books and international journals. The potential source of information also reveals the graph/histogram of the growth of benzopyran chemistry per decade. The investigations over the last few years have demonstrated that the natural 2*H*-benzopyrans and their synthetic derivatives exhibits a wide variety of pharmaceutical activities. Due to the vast fascinating structural diversity coupled with high biological importance, 2*H*-benzopyrans have spurred a lot of activity in the synthetic community towards their total synthesis that would pave the way for breakthrough in medicinal science. It is, therefore, imperative to

keep our efforts persistent in the synthesis of newer, more potent structurally more complex 2*H*-benzopyran natural products and analogues. Development of an efficient biogenetic type general route to benzopyrans skeleton is a real challenge. We strongly believe that from both basic and applied point of view the benzopyran field is of high importance and lot of new chemistry and practical applications are possible. In this context, as a part of this present dissertation, we have designed six naturally occurring 2,2-disubstituted-2*H*-benzopyrans and two tetrasubstituted-2*H*-benzopyrans. Our synthetic strategies towards the syntheses of all these natural 2*H*-benzopyrans will be discussed in details in the second chapter of present dissertation.

1.6 References

1. Houben, J. *Chem. Ber*. **1904**, *37*, 489.
2. Adams, R.; Rindfusz, R. E. *J. Am. Chem. Soc*. **1919**, *41*, 648.
3. Normant, H.; Maitte, P. *C. R. Acad. Sci., Paris*, **1952**, *234*, 1787.
4. (a) Bloch, M.; Kostanecki, S. v. *Ber*. **1900**, *33*, 471. (b) Bloch, M.; Kostanecki, S. v. *Ber*. **1900**, *33*, 1998.
5. Nicolaou, K. C.; Pfefferkorn, J. A.; Barluenga, S.; Mitchell, H. J.; Roecker, A. J.; Cao, G.-Q. *J. Am. Chem. Soc*. **2000**, *122*, 9968.
6. For reviews see: (a) Cragg, G. M.; Newman, D. J.; Snader, K. M. *J. Nat. Prod*. **1997**, *60*, 52. (b) Shu, Y.-Z. *J. Nat. Prod*. **1998**, *61*, 1053.
7. (a) Hepworth, J. D.; Gabbutt, C. D.; Heron, M. B. *Comprehensive Heterocyclic Chemistry II*, Pergamon, New York, 1996, 301. (b) Geen, G. R.; Evans, J. M.; Vong, A. K. *Comprehensive Heterocyclic Chemistry II*, Pergamon, New York, 1996, 469.
8. (a) Gunatilaka, A. A. L.; Kingston, D. G. I.; Wijeratne, E. M. K.; Bandara, B. M. R.; Hofmann, G. A.; Johnson, R. K. *J. Nat. Prod*. **1994**, *57*, 518. (b) Bandara, B. M. R.; Gunatilaka, A. A. L.; Wijeratne, E. M. K.; MacLeod, J. K. *Phytochemistry* **1990**, *29*, 297. (c) Magiatis, P.; Melliou, E.; Skaltsounis, A.-L.; Mitaku, S.; Leonce, S.; Renard, P.; Pierre, A.; Atassi, G. *J. Nat. Prod*. **1998**, *61*, 982. (d) Hughes, G. K.; Lakey, F. N.; Price, J. R.; Webb, L. J. *Nature* **1948**, *162*, 223. (e) Dorr, R. T.; Liddil, J. D.; Von Hoff, D. D.; Soble, M.; Osborne, C. K. *Cancer Res*. **1989**, *49*, 340 and references cited therein.
9. (a) Sorbera, L. A.; Leeson, P.; Castaner, J. *Drugs Future* **1999**, *24*, 235. (b) Kashman, Y.; Gustafson, K. R.; Fuller, R. W.; Cardellina II, J. H.; McMahon, J. B.; Currens, M. J.; Buckheit, Jr. R. W.; Hughes, S. H.; Cragg, G. M.; Boyd, M. R. *J. Med. Chem*. **1992**, *35*, 2735. (c) Xu, Z.-Q.; Hollingshead, M. G.; Borgel, S.; Elder, C.; Khilevich, A.; Flavin, M. T. *Bioorg. Med. Chem. Lett*. **1999**, *9*, 133 and references cited therein.
10. (a) Fang, N.; Casida, J. E.; *Proc. Natl. Acad. Sci. USA* **1998**, *95*, 3380. (b) Fang, N.; Casida, J. E.; *J. Nat. Prod*. **1999**, *62*, 205. (c) Kaouadji, M.; Agban, A.; Mariotte, A. M.; Tissut, M. *J. Nat. Prod*. **1986**, *49*, 281.
11. (a) Whyte, A. C.; Gloer, J. B.; Wicklow, D. T.; Dowd, P. F. *J. Nat. Prod*. **1996**, *59*, 1093. (b) Takasugi, M.; Nagao, S.; Ueno, S.; Masamune, T.; Shirata, A.; Takahashi, K. *Chem. Lett*. **1978**, 1239. (c) Shirata, A.; Takahashi, K.; Takasugi, M.; Nagao, S.;

Ishikawa, S.; Ueno, S.; Munoz, L.; Masamune, T. *Sanshi Shikenjo Hokoku* **1983**, *28*, 793.

12. Manley, P. W. (Sandoz Ltd., Switzerland), US-A 5574049 [*Chem. Abstr*. **1996**, *126*, 47104].
13. Soll, R. M.; Dollings, P. J.; Mitchell, R. D.; Hafner, D. A. *Eur. J. Med. Chem*. **1994**, *29*, 223.
14. Daele, V.; Paul, G. H.; Marie, J. P. R.; Laerhoven, V.; Carolus, W. J. WO-A 9412494 [*Chem. Abstr*. **1994**, *121*, 99834].
15. Gutterer, B.; Flockerzi, D.; Amschler, H.; Ulrich, W.-R.; Bar, T.; Martin, T.; Hatzelmann, A.; Boss, H.; Beume, R.; Hafner, D.; Kley, H.-P. (Byk Gulden Lomberg Chemische FabriK Gmbh, Germany), EP-B 819689 [*Chem. Abstr*. **1998**, *128*, 140610].
16. Eisai Co., Ltd., Japan, JP-A 78-146098 [*Chem. Abstr*. **1980**, *93*, 204640].
17. Wawzonek, S. "*Heterocyclic Compounds*" (R. C. Edlerfield, ed.), Vol. 2, p. 277, Wiley, New York, 1951.
18. Dean, F. M. "*Naturally Occurring Oxygen Ring Compounds*," Butterworth, London, 1963, 16.
19. Dean, F. M. "*The Total Synthesis of Natural Products*" (J. ApSimon, ed.), p. 467, Wiely (Interscience), New York, 1973.
20. Katritzky, A. R.; Boulton, A. J. "*Advances in Heterocyclic Chemistry*," Academic Press, New York, London, 1975, *18*, 159.
21. Ellis, G. P.; Ed., "*Chromenes, Chromanones, and Chromones*," John Wiley, New York, 1977, p. 2.
22. (a) Ollis, W. D.; Sutherland, I. O. "*Recent Developments in the Chemistry of Natural Phenolic Substances*," Pergamon, Oxford, 1961. (b) Ollis, W. D. *Experientia* **1966**, *22*, 777. (c) Ollis, W. D.; Gottlieb, O. R. *Chem. Commun*. **1968**, 1396.
23. (a) Ramasarma, T.; Joshi, V. C. *Bull. Nat. Inst. Sci. India* **1965**, *28*, 19 [*Chem. Abstr.* **1967**, *66*, 27120]. (b) Joshi, V. C.; Jayaraman, J.; Ramasarma, T. *Biochem. J*. **1964**, *92*, 9C. (c) Joshi, V. C.; Jayaraman, J.; Ramasarma, T. *Indian, J. Exp. Biol*. **1963**, *1*, 113 [*Chem. Abstr.* **1963**, *59*, 10575]. (d) Joshi, V. C.; Jayaraman, J.; Ramasarma, T. *Biochem. Biophys. Res. Commun*. **1963**, *12*, 247.
24. Suzuki, K. T.; Nozoe, S. *Chem. Commun*. **1972**, 1166.
25. Turner, A. B. *Quart. Rev*. **1964**, *18*, 347.

26. Mechoulam, R.; Gaoni, Y. *Fortschr. Chem. Org. Naturstoffe* **1967**, *25*, 201.
27. Crombie, L.; Ponsford, R. *Tetrahedron Lett*. **1968**, 4557.
28. Kane, V. V.; Razdan, R. K. *Tetrahedron Lett*. **1969**, 591.
29. Fourrey, J. C.; Rondest, J.; Polonsky, J. *Tetrahedron* **1970**, *26*, 3839.
30. Bohlmann, F.; Grenz, M. *Ber*. **1970**, *103*, 90.
31. Menut, C.; Bessiere, J. M.; Ntalani, H.; Verin, P.; Henriques, A. T.; Limberger, R. *Phytochemistry* **2000**, *53*, 975.
32. Thomson, R. H. "*Naturally Occurring Quinones*" Academic Press, New York, 1971.
33. Johannes, R.; Adeleke, A.; Kumar, V.; Aladesanmi, A. J. *Phytochemistry* **1994**, *36*, 1073.
34. Kirby, K. D.; Sutherland, M. D. *Aust. J. Chem*. **1956**, *9*, 411.
35. Taylor, D. R.; Wright, J. A. *Phytochemistry* **1971**, *10*, 1665.
36. Sutherand, M. D. *Univ. Queensl. Pap., Dept. Chem. 1*, No. 35 (**1949**) [*Chem. Abstr.* **1950**, *44*, 1230d].
37. Hlubucek, J. R.; Ritchie, E.; Taylor, W. C. *Aust. J. Chem*. **1971**, *24*, 2347.
38. Rudloff, E.; Sood, V. K. *Perfum. Essent. Oil Rec*., **1969**, *60*, 303 [*Chem. Abstr.* **1970**, *72*, 51815p].
39. Kasturi, T. R.; Manithomas, T. *Tetrahedron Lett*. **1967**, 2573.
40. Beck, J. R.; Kwok, R.; Booher, R. N.; Brown, A. C.; Patterson, L. E.; Pranc, P.; Rockey, B.; Pohland, A. *J. Am. Chem. Soc*. **1968**, *90*, 4706.
41. Anthonsen, T. *Acta Chem. Scand*. **1969**, *23*, 3605.
42. Wright, S. E. *J. Chem. Soc*. **1948**, 2005.
43. Jones, T. G. H.; Wright, S. E. *Univ. Queensl. Pap., Dept. Chem. 1*, No. 27 (**1946**) [*Chem. Abstr.* **1947**, *41*, 1391i].
44. Huls, R.; Brunelle, S. *Bull. Soc. Chim. Belg*. **1959**, *68*, 325 [*Chem. Abstr.* **1960**, *54*, 3397i].
45. Baldwin, M. E.; Bick, I. R. C.; Komzak, A. A.; Price, J. R. *Tetrahedron* **1961**, *16*, 206.
46. Jain, A. C.; Zutshi, M. K. *Tetrahedron Lett*. **1971**, 3179.
47. Lahey, F. N. *Univ. Queensl. Pap., Dept. Chem. 1*, No. 20, 2 (**1942**) [*Chem. Abstr.* **1943**, *37*, 34322].
48. Alertsen, A. R. *Acta Chem. Scand*. **1955**, *9*, 1725.
49. Huls, R. *Bull. Soc. Chim. Belg*. **1958**, *67*, 22 [*Chem. Abstr.* **1958**, *52*, 13717].

50. Alertsen, A. R. *Acta Polytech. Scand. Ser. 13*. **1961**, *10*, 1 [*Chem. Abstr.* **1962**, *57*, 16619b].
51. McGookin, A.; Robertson, A.; Whalley, W. B. *J. Chem. Soc*. **1940**, 787.
52. McGookin, A.; Robertson, A.; Tittensor, E. *J. Chem. Soc*. **1939**, 1579.
53. McGookin, A.; Percival, A. B.; Robertson, A. *J. Chem. Soc*. **1938**, 309.
54. Merlini, L. *Corsi Semin. Chim*. **1968**, *11*, 97 [*Chem. Abstr.* **1970**, *72*, 21564p].
55. Cardillo, G.; Merlini, L.; Mondelli, R.; Moreschini, L. *Gazz. Chim. Ital*. **1965**, *95*, 725 [*Chem. Abstr.* **1965**, *63*, 16294g].
56. Anderson, T. *Chem. Zentralbl*. **1855**, 372.
57. Cardillo, G.; Merlini, L.; Mondelli, R. *Tetrahedron* **1968**, *24*, 497.
58. Baudrenghien, J.; Jadot, J.; Huls, R. *Bull. Cl. Sci., Acad. Roy. Belg*. **1953**, *39*, 105 [*Chem. Abstr.* **1954**, *48*, 10744h].
59. Nickl, J. *Chem. Ber*. **1958**, *91*, 1372.
60. Shoyama, Y.; Hirano, H.; Nishioka, I. *Phytochemistry* **1984**, *23*, 1909.
61. (a) Jpn. Kokai Tokkyo Koho, JP 82-28,080,1982 [*Chem. Abstr*. **1982**, 97, 3777x]. (b) Hu, H.; Harrison, T. J.; Wilson, P. D. *J. Org. Chem.* **2004**, *69*, 3782.
62. Gonzalez, J. G.; Olivares, E. M.; Monache, F. D. *Phytochemistry* **1995**, *38*, 485.
63. Li, L.; Wang, H.-K.; Chang, J.-J.; McPhail, A. T.; McPhail, D. R.; Terada, H.; Konoshima, T.; Kokumai, M.; Kozuka, M.; Estes, J. R.; Lee, K.-H. *J. Nat. Prod*. **1993**, *56*, 690.
64. (a) Govindachari, T. R.; Pai, B. R.; Subramaniam, P. S. *Tetrahedron* **1966**, *22*, 3245. (b) Kawaii, S.; Tomono, Y.; Katase, E.; Ogawa, K.; Yano, M.; Takemura, Y.; Ju-ichi, M.; Ito, C.; Furukawa, H. *J. Nat. Prod*. **1999**, *62*, 587.
65. (a) Pillai, S. P.; Menon, S. R.; Mitscher, L. A.; Pillai, C. A.; Shankel, D. M. *J. Nat. Prod*. **1999**, *62*, 1358. (b) Bandara, B. M. R.; Gunatilaka, A. A. L.; Wijeratne, E. M. K.; MacLeod, J. K. *Phytochemistry* **1990**, *29*, 297.
66. Cao, S.-G.; Wu, X.-H.; Sim, K.-Y.; Tan, B. H. K.; Vittal, J. J.; Pereira, J. T.; Goh, S.-H. *Helv. Chim. Acta* **1998**, *81*, 1404.
67. Banskota, A. H.; Tezuka, Y.; Prasain, J. K.; Matsushige, K.; Saiki, I.; Kadota, S. *J. Nat. Prod*. **1998**, *61*, 896.
68. Patil, A. D.; Freyer, A. J.; Eggleston, D. S.; Haltiwanger, R. C.; Tomcowicz, B.; Breen, A.; Johnson, R. K. *J. Nat. Prod*. **1997**, *60*, 306.

69. Kitagawa, I.; Zhang, R.; Hori, K.; Tsuchiya, K.; Shibuya, H. *Chem. Pharm. Bull*. **1992**, *40*, 2041.
70. Gerhauser, C.; Lee, S. K.; Kosmeder, J. W.; Moriarty, R. M.; Hamel, E.; Mehta, R. G.; Moon, R. C.; Pezzuto, J. M. *Cancer Res*. **1997**, *57*, 3429 and references cited therein.
71. Wang, B. H.; Ternai, B.; Polya, G. *Phytochemistry* **1997**, *44*, 787.
72. Gschwendt, M.; Muller, H.-J.; Kielbassa, K.; Zang, R.; Kittstein, W.; Rincke, G.; Marks, F. *Biochem. Biophys. Res. Commun*. **1994**, *199*, 93.
73. Falshaw, C. P.; Harmer, R. A.; Ollis, W. D.; Wheeler, R. E.; Lalitha, V. R.; Rao, N. V. S. *J. Chem. Soc. C* **1969**, 374.
74. Jayasuriya, H.; McChesney, J. D.; Swanson, S. M.; Pezzuto. J. M. *J. Nat. Prod*. **1989**, *52*, 325.
75. Jayasuriya, H.; McChesney, J. D. *J. Chem. Soc., Chem. Commun*. **1988**, *24*, 1592.
76. Rao, E. V.; Sridhar, P.; Rao, B. V. L. N.; Ellaiah, P. *Phytochemistry* **1999**, *50*, 1417.
77. Seo, E.-K.; Huang, L.; Wall, M. E.; Wani, M. C.; Navarro, H.; Mukherjee, R.; Farnsworth, N. R.; Kinghorn, A. D. *J. Nat. Prod*. **1999**, *62*, 1484.
78. Reddy, G. R.; Ueda, N.; Hada, T.; Sackeyfio, A. C.; Yamamoto, S.; Hano, Y.; Aida, M.; Nomura, T. *Biochem. Pharmacol*. **1991**, *41*, 115.
79. Wu, T.-S.; Huang, S.-C.; Wu, P.-L.; Kuoh, C.-S.; *Phytochemistry* **1999**, *52*, 523.
80. Shimizu, K.; Kondo, R.; Sakai, K. *Phytochemistry* **1997**, *45*, 1297.
81. Kitagawa, I.; Chen, W.-Z.; Hori, K.; Harada, E.; Yasuda, N.; Yoshikawa, M.; Ren, J. *Chem. Pharm. Bull*. **1994**, *42*, 1056.
82. McKee, T. C.; Bokesch, H. R.; McCormick, J. L.; Rashid, M. A.; Spielvogel, D.; Gustafson, K. R.; Alavanja, M. M.; Cardellina, J. H.; Boyd, M. R. *J. Nat. Prod*. **1997**, *60*, 431.
83. Matsumoto, K.; Nagashima, K.; Kamigauchi, T.; Kawamura, Y.; Yasuda, Y.; Ishii, K.; Uotani, N.; Sato, T.; Nakai, H.; Terui, Y.; Kikuchi, J.; Ikenisi, Y.; Yoshida, T.; Kato, T.; Itazaki, H. *J. Antibiotics* **1995**, *48*, 439.
84. Jakupovic, J.; Schuster, A.; Sun, H.; Bolman, F.; Bhakuni, D. S. *Phytochemistry* **1987**, *26*, 580.
85. (a) Taher, M.; Idris, M. S.; Ahmad, F.; Arbain, D. *Phytochemistry* **2005**, *66*, 723. (b) Lopes, J. L. C.; Lopes, J. N. C.; Gilbert, B.; Bonini, S. E. *Phytochemistry* **1977**, *16*,

1101. (c) Wolfrom, M. L.; Dickey, E. E.; McWain, P.; Thompson, A.; Looker, J. H.; Windrath, O. M.; Komitsky, F. *J. Org. Chem*. **1964**, *29*, 689.

86. Rukachaisirikul, V.; Ritthiwigrom, T.; Pinsa, A.; Swangchote, P.; Taylor, W. C. *Phytochemistry* **2003**, *64*, 1149.
87. (a) Gonzalez, J. G.; Cuellar, V.; Betancourt, A.; Pinzon, M. I. *Phytochemistry* **1983**, *22*, 2088. (b) Monache, F. D.; Monache, G. D.; Baitz, E.-G. *Phytochemistry* **1991**, *30*, 2003. (c) Olivares, E. M.; Gonzalez, J. G.; Monache, F. D. *Phytochemistry* **1994**, *36*, 473.
88. (a) Brockmann, H.; Lenk, W.; Schwantje, G.; Zeeck, A.; *Tetrahedron Lett*. **1966**, 3525. (b) Brockmann, H.; Lenk, W.; Schwantje, G.; Zeeck, A. *Chem. Ber*. **1969**, *102*, 126.
89. Brockmann, H.; Zeeck, A. *Chem. Ber*. **1970**, *103*, 1709.
90. Ueno, T.; Takahashi, H.; Oda, M.; Mizunuma, M.; Yokoyama, A.; Goto, Y.; Mizushina, Y.; Sakaguchi, K.; Hayashi, H. *Biochemistry* **2000**, *39*, 5995.
91. Goldman, M. E.; Salituro, G. S.; Bowen, J. A.; Williamson, J. M.; Zink, L.; Schleif, W. A.; Emini, E. A. *Mol. Pharmacol*. **1990**, *38*, 20.
92. Daele, V.; Paul, G. H.; Marie, J. P. R.; Laerhoven, V.; Carolus, W. J. WO-A 9412494 [*Chem. Abstr.* **1994**, *121*, 99834].
93. Mackenzie, A. R.; Monaghan, S. M.; Pfizer, Research and Development Co., WO-A 9420491 [*Chem. Abstr.* **1994**, *123*, 55885].
94. Tanigawa, K.; Ikuyori, K.; Sato, M.; Yanagihara, K.; Yamashita, T. Japan Kokai Tokkyo Koho, Japanese Patent JP 11209366 [*Chem. Abstr.* **1999**, *131*, 129903].
95. Gutterer, B.; Flockerzi, D.; Amschler, H.; Ulrich, W.-R.; Bar, T.; Martin, T.; Hatzelmann, A.; Boss, H.; Beume, R.; Hafner, D.; Kley, H.-P. Byk Gulden Lomberg Chemische Fabrik Gmbh, Germany, European Patent Application EP 96-111557 19960718 [*Chem. Abstr.* **1998**, *128*, 140610].
96. Razdan, R. K.; Thompson, W. R.; Pars, H. G.; Granchelli, F. E. *Tetrahedron Lett*. **1967**, 3405.
97. Cook, C. E.; Corley, R. C.; Wall, M. E. *J. Org. Chem*. **1965**, *30*, 4114.
98. Cook, C. E.; Wall, M. E. *J. Org. Chem*. **1968**, *33*, 2998.
99. Cottam, J.; Livingstone, R. *J. Chem. Soc*. **1964**, 5228.
100. Cottam, J.; Livingstone, R. *J. Chem. Soc*. **1965**, 6646.
101. Ray, S.; Grover, P. K.; Anand, N. *Indian J. Chem*. **1970**, *8*, 961.
102. Cook, C. E.; Twine, C. E. *Chem. Commun*. **1968**, 791.

103. Cardillo, G.; Cricchio, R.; Merlini, L.; Nasini, G. *Gazz. Chim. Ital*. **1969**, *99*, 612.
104. Locksley, H. D.; Quillinan, A. J.; Scheinmann, F. *J. Chem. Soc. C* **1971**, 3804.
105. Fukami, H.; Nakayama, M.; Nakajima, M. *Agr. Biol. Chem*. **1961**, *25*, 243.
106. Fukami, H.; Oda, J.; Sakata, G.; Nakajima, M. *Agr. Biol. Chem*. **1961**, *25*, 252.
107. Jefferson, A.; Scheinmann, F. *J. Chem. Soc. C* **1966**, 175.
108. Hoffman-La, R. F. Belgian Patent 1964, 635999 [*Chem. Abstr.* **1964**, *61*, 13285].
109. Mercier, C. *Ann. Chim.* (*Paris*) **1970**, *5*, 373.
110. Piozzi, F.; Venturella, P.; Bellino, A. *Gazz. Chim. Ital*. **1969**, *99*, 711.
111. Grundon, M. F.; James, K. J. *Chem. Commun*. **1970**, 1427.
112. Jain, A. C.; Khanna, V. K.; Seshadri, T. R. *Tetrahedron* **1969**, 25, 2787.
113. Walker, D.; Hiebert, J. D. *Chem. Rev*. **1967**, *67*, 153.
114. Schudel, P.; Meyer, H.; Metzger, J.; Ruegg, R.; Isler, O. *Helv. Chim. Acta* **1963**, 46, 636.
115. (a) Iwai, I.; Ide, J. *Chem. Pharm. Bull*. **1962**, *10*, 926. (b) Iwai, I.; Ide, J. *Chem. Pharm. Bull*. **1963**, *11*, 1042.
116. Zsindely, J.; Schmid, H. *Helv. Chim. Acta* **1968**, *51*, 1510.
117. (a) Heaney, H.; Jablonski, J. M. *Chem. Commun*. **1968**, 1139. (b) Heaney, H.; Jablonski, J. M.; McCarty, C. T. *J. Chem. Soc., Perkin Trans. 1*, **1972**, 2903.
118. Cardillo, G.; Merlini, L.; Servi, S. *Ann. Chim*. (*Rome*) **1970**, *60*, 564.
119. (a) Schweizer, E. E. *J. Am. Chem. Soc*. **1964**, *86*, 2744. (b) Schweizer, E. E.; Liehr, J.; Monaco, D. J. *J. Org. Chem.* **1968**, *33*, 2416.
120. (a) Schweizer, E. E.; Minami, T.; Crouse, D. M. *J. Org. Chem.* **1971**, *36*, 4028. (b) Schweizer, E. E.; Wehman, A. T.; Nycz, D. M. *J. Org. Chem.* **1973**, *38*, 1583.
121. Schweizer, E. E.; Berninger, C. J.; Thompson, J. G. *J. Org. Chem.* **1968**, *33*, 336.
122. Crombie, L.; Ponsford, R. *J. Chem. Soc. C*, **1971**, 788.
123. Crombie, L.; Ponsford, R. *J. Chem. Soc. C*, **1971**, 796.
124. Crombie, L.; Bandaranayake, W. M.; Whiting, D. A. *J. Chem. Soc. C*, **1971**, 804.
125. Kane, V. V.; Razdan, R. K. *J. Am. Chem. Soc*. **1968**, *90*, 6551.
126. Gassman, P. G.; Amick, D. R. *J. Am. Chem. Soc*. **1978**, *100*, 7611.
127. Inoue, S.; Ikeda, H.; Sato, S.; Horie, K.; Ota, T.; Miyamoto, O.; Sato, K. *J. Org. Chem*. **1987**, *52*, 5495.
128. Palucki, M.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc*. **1996**, *118,* 10333.

129. (a) Guram, A. S.; Rennels, R. A.; Buchwald, S. L. *Angew. Chem. Int. Ed*. **1995**, *34*, 1348. (b) Hartwig, J. F.; Richards, S.; Baranano, D.; Paul, F. *J. Am. Chem. Soc*. **1996**, *118,* 3626. (c) Widenhoefer, R. A.; Zhong, H. A.; Buchwald, S. L. *Organometallics* **1996**, *15*, 2745. (d) Widenhoefer, R. A.; Buchwald, S. L. *Organometallics* **1996**, *15*, 2755. (e) Widenhoefer, R. A.; Buchwald, S. L. *Organometallics* **1996**, *15*, 3534.

130. Wang, Q.; Finn, M. G. *Org. Lett*. **2000**, *2*, 4063.

131. (a) Petasis, N. A.; Akritopoulou, I. *Tetrahedron Lett*. **1993**, *34*, 583. (b) Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc*. **1997**, *119*, 445. (c) Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc*. **1998**, *120*, 11798.

132. Brase, S.; Enders, D.; Kobberling, J.; Avemaria, F. *Angew. Chem. Int. Ed*. **1998**, *37*, 3413.

133. Parker, K. A.; Mindt, T. L. *Org. Lett*. **2001**, *3*, 3875.

134. Velde, S. L. V.; Jacobsen, E. N. *J. Org. Chem*. **1995**, *60*, 5830.

135. Stocker, A.; Netscher, T.; Ruttimann, A.; Muller, R. K.; Schneider, H.; Todaro, L. J.; Derung, G.; Woggon, W.-D. *Helv. Chim. Acta* **1994**, *77*, 1721.

136. Solladie, G.; Moine, G. *J. Am. Chem. Soc*. **1984**, *106*, 6097.

137. Harrity, J. P. A.; Visser, M. S.; Gleason, J. D.; Hoveyda, A. H. *J. Am. Chem. Soc*. **1997**, *119*, 1488.

138. Wipf, P.; Weiner, W. S. *J. Org. Chem*. **1999**, *64*, 5321.

139. Govender, T.; Hojabari, L.; Moghaddam, F. M.; Arvidsson, P. I. *Tetrahedron: Asymmetry* **2006**, *17*, 1763.

140. Nicolaou, K. C.; Pfefferkorn, J. A.; Roecker, A. J.; Cao, G.-Q.; Barluenga, S.; Mitchell, H. *J. Am. Chem. Soc*. **2000**, *122*, 9939.

141. Nicolaou, K. C.; Pfefferkorn, J. A.; Cao, G.-Q. *Angew. Chem. Int. Ed*. **2000**, *39*, 734.

142. Nicolaou, K. C.; Cao, G. -Q.; Pfefferkorn, J. A. *Angew. Chem. Int. Ed*. **2000**, *39*, 739.

143. Nicolaou, K. C.; Pfefferkorn, J. A.; Mitchell, H.; Roecker, A. J.; Barluenga, S.; Cao, G.-Q.; Affleck, R. L.; Lillig, J. E. *J. Am. Chem. Soc*. **2000**, *122*, 9954.

144. Nicolaou, K. C.; Evans, R. M.; Roecker, A. J.; Hughes, R.; Downes, M.; Pfefferkorn, J. A. *Org. Biomol. Chem.* **2003**, *1*, 908.

145. Evans, B. E.; Rittle, K. E.; Bock, M. G.; DiPardi, R. M.; Freidinger, R. M.; Whitter, W. L.; Lundell, G. F.; Veber, D. F.; Anderson, P. S.; Chang, R. S. L.; Lotti, V. J.; Cerino, D.

J.; Chen, T. B.; Kling, P. J.; Kundel, K. A.; Springer, J. P.; Harshfield. J. *J. Med. Chem*. **1998**, *31*, 2235.

146. Nicolaou, K. C.; Pastor, J.; Barluenga, S.; Winssinger, N. *Chem. Commun*. **1998**, 1947.
147. Hayakawa, Y.; Yamamoto, H.; Tsuge, N.; Seto, H. *Tetrahedron Lett*. **1996**, *37*, 6363.
148. Tanada, Y.; Mori, K. *Eur. J. Org. Chem*. **2001**, 1963.
149. Ohta, K.; Mitsunobu, O. *Tetrahedron Lett*. **1991**, *32*, 517.
150. Dess, D. B.; Martin, J. C. *J. Org. Chem*. **1983**, *48*, 4155.
151. Quin, G. W.; Chen, H. C.; Wang, H. C.; Qian, M. K. *Acta. Chim. Sin*. **1981**, *39*, 83.
152. Salomon, R. G.; Lal, K.; Samuel, M. M.; Zarate, E. A.; Youngs, W. J. *J. Am. Chem. Soc*. **1988**, *110*, 5213.
153. (a) Kabbe, H.-J. *Synthesis* **1978**, 886. (b) Bohlmann, F.; Vorwerk, E. *Chem. Ber*. **1981**, *114*, 147. (c) Kabbe, H.-J.; Widdig, A. *Angew. Chem. Int. Ed*. **1982**, *21*, 247.
154. Ichiara, A.; Nonaka, M.; Sakamura, S.; Sato, R.; Tajimi, A. *Chem. Lett*. **1988**, 27.
155. Graham, S. R.; Murphy, J. A.; Kennedy, A. R. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3071.
156. Rodriguez, R.; Adlington, R. M.; Moses, J. E.; Cowley, A.; Baldwin, J. E. *Org. Lett*. **2004**, *6*, 3617.
157. Bharate, S, B.; Bhutani, K. K.; Khan, S. I.; Tekwani, B. L.; Jacob, M. R.; Khan, I. A.; Singh, I. P. *Bioorg. Med. Chem*. **2006**, *14*, 1750.
158. Kashiwada, Y.; Yamazaki, K.; Ikeshiro, Y.; Yamagishi, T.; Fujioka, T.; Mihashi, K.; Mizuki, K.; Cosentino, L. M.; Fowke, K.; Natschke, S. L.-M.; Lee, K.-H. *Tetrahedron* **2001**, *57*, 1559.
159. Kurdyumov, A. V.; Hsung, R. P.; Ihlen, K.; Wang, J. *Org. Lett.* **2003**, *5*, 3935.
160. Kang, Y.; Mei, Y.; Du, Y.; Jin, Z. *Org. Lett.* **2003**, *5*, 4481.
161. Kurdyumov, A. V.; Hsung, R. P. *J. Am. Chem. Soc.* **2006**, *128*, 6272.
162. Lu, Y.-H.; Lin, C.-N.; Ko, H.-H.; Yang, S.-Z.; Tsao, L.-T.; Wang, J. P. *Helv. Chim. Acta* **2003**, *86*, 2566.
163. Hano, Y.; Inami, R.; Nomura, T. *Heterocycles* **1993**, *35*, 1341.
164. Paduraru, M. P.; Wilson, P. D. *Org. Lett.* **2003**, *5*, 4911.
165. Bukuru, J.; Van, T. N.; Puyvelde, L. V.; He, W.; Kimpe, N. D. *Tetrahedron* **2003**, *59*, 5905.

166. Crombie, L.; Redshaw, S. D.; Slack, D. A.; Whiting, D. A. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1411.

167. Shoyama, Y.; Morimoto, S.; Nishioka, I. *Chem. Pharm. Bull.* **1981**, *29*, 3720.

168. Lemmich, J.; Pedersen, P. A.; Nielsen, B. E. *Tetrahedron Lett*. **1969**, 3365.

169. Xie, L.; Takeuchi, Y.; Cosentino, M.; Lee, K.-H. *J. Med. Chem*. **1999**, *42*, 2662 and references cited therein.

170. Lee, T. T.-Y.; Kashiwada, Y.; Huang, L.; Snider, J.; Cosentino, M.; Lee, K.-H. *Bioorg. Med. Chem*. **1994**, *2*, 1051.

171. Ashwood, V. A.; Buckingham, R. E.; Cassidy, F.; Evans, J. M.; Faruk, E. A.; Hamilton, T. C.; Nash, D. J.; Stemp, G.; Willcocks, K. *J. Med. Chem*. **1986**, *29*, 2194.

172. Bergmann, R.; Eiermann, V.; Gericke, R. *J. Med. Chem*. **1990**, *33*, 2759.

173. Chan, W. N.; Evans, J. M.; Hadley, M. S.; Herdon, H. J.; Jerman, J. C.; Parsons, A. A.; Read, S. J.; Stean, T. O.; Thompson, M.; Upton, N. *Bioorg. Med. Chem. Lett*. **1999**, *9*, 285.

174. Hiessbock, R.; Wolf, C.; Richter, E.; Hitzler, M.; Chiba, P.; Kratzel, M.; Ecker, G. *J. Med. Chem*. **1999**, *42*, 1921.

175. Pinto, I. L.; Buckle, D. R.; Readshaw, S. A.; Smith, D. G. *Bioorg. Med. Chem. Lett*. **1993**, *3*, 1743.

176. Rovnyak, G. C.; Ahmed, S. Z.; Ding, C. Z.; Dzwonczyk, S.; Ferra, F. N.; Humphyreys, W. G.; Grover, G. J.; Santafianos, D.; Aywal, K. S.; Baird, A. J.; McLaughlin, L. G.; Normandin, D. E.; Sleph, P. G.; Traeger, S. C. *J. Med. Chem*. **1997**, *40*, 24 and references cited therein.

177. Ostresh, J. M.; Husar, G. M.; Blondelle, S. E.; Dorner, B.; Weber, P. A.; Houghten, R. A. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 11138.

178. Adams, R.; Cain, C. K.; Loewe, S. *J. Am. Chem. Soc*. **1941**, *63*, 1977.

179. Russel, P. B.; Todd, A. R.; Wilkinson, S.; McDonald, A. D.; Woolfe, G. *J. Chem. Soc*. **1941**, 169.

180. Thompson, W. R.; Razdan, R. K. *Afr. Patent* 6802269 (**1968**) [*Chem. Abstr.* **1969**, *70*, 68161d].

181. Razdan, R. K.; Thompson, W. R. *Ger. Patent* 2053405 (1971) [*Chem. Abstr.* **1971**, *75*, 35757c].

182. Anderson, W. *Ger. Patent* 2145559 (1972) [*Chem. Abstr.* **1972**, *77*, 114227z].

183. Meikle, T.; Stevens, R. *Tetrahedron Lett*. **1972**, 4787.
184. Parker, W. L.; Johnson, F. *J. Am. Chem. Soc*. **1968**, *90*, 4716.
185. Chu, J. H. *Sci. Rec*. (*China*), **1951**, *4*, 279 [*Chem. Abstr.* **1952**, *46*, 11589a].
186. Kolc, J.; Becker, R. S. *Phytochem. Photobiol*. **1970**, *12*, 383.
187. Davin, E.; Balmy, C.; Guglielmetti, R. *C. R. Acad. Sci., Paris, Ser. C*, **1972**, *79*, 275.

Chapter 2

Facile Synthesis of Bioactive Natural and Unnatural Benzofurans and Benzopyrans

This chapter features the following sections:

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2B	*Section B*	82
2C	*Section C*	112
2D	*Section D*	164
2E	*Section E*	186
2F	*Overall Conclusions and Perspectives*	209

This chapter is divided into five sections. The first section presents a facile synthesis of salfredin B_{11} and phthalidochromine while the second section describes our studies towards the simple and efficient synthesis of 1,3,7-trihydroxyxanthone, osajaxanthone and nigrolineaxanthone F. The third section portrays a facile access to cannabichromeorcinic acid, daurichromenic acid, clusiaphenone A, clusiachromene C, clusiacyclol A and clusiacyclol B. This section also describes two different thermal rearrangements and the synthesis of some structurally interesting unnatural benzopyran systems. The fourth section summarizes an efficient and short first total synthesis of natural benzofuran CJ-13,015 (anti-*Helicobacter pylori*), while the fifth section describes our ongoing studied towards the synthesis of acetophthalidin.

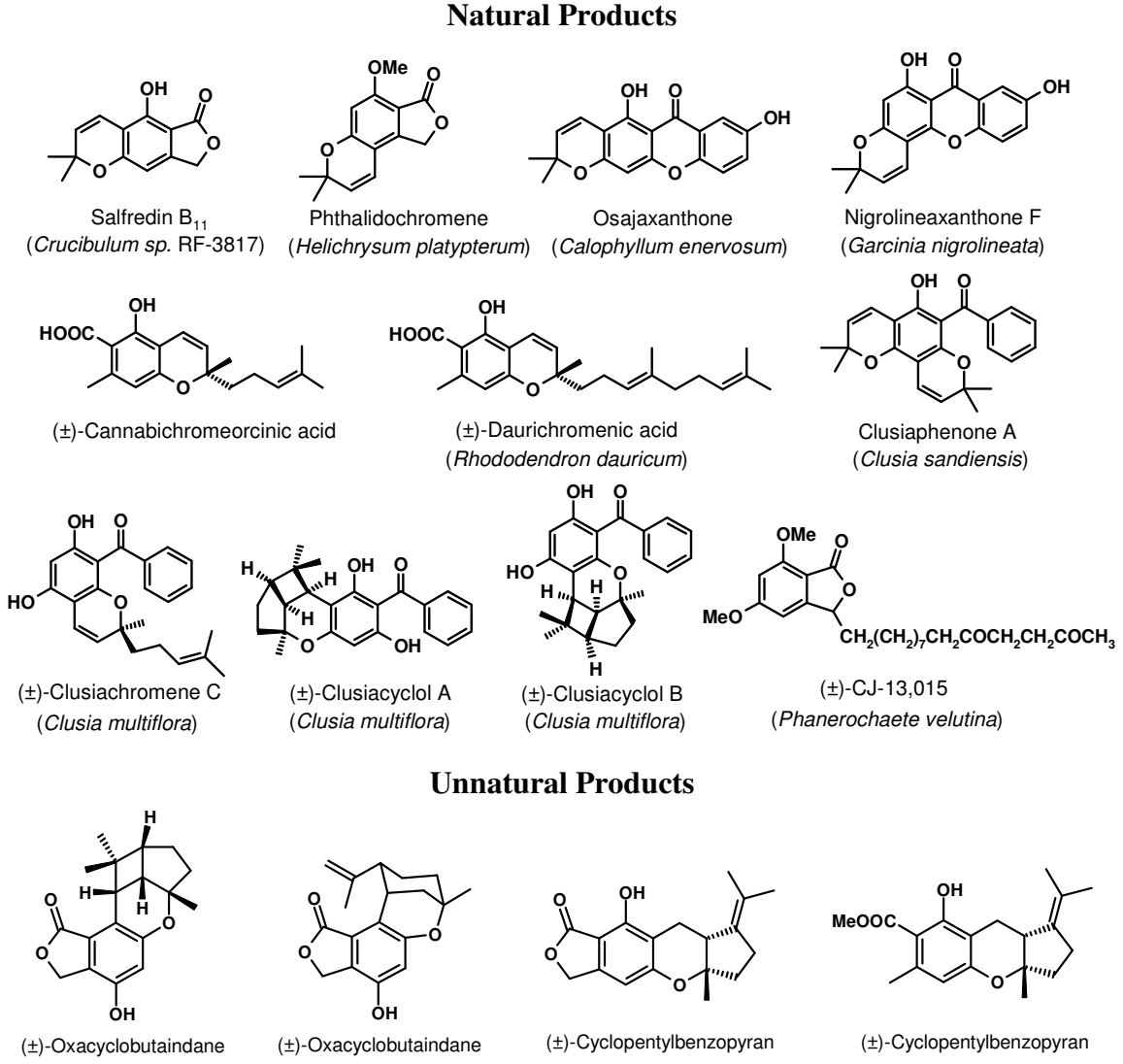

Figure 1. Natural and Unnatural Benzofurans and Benzopyrans Synthesized

2A. Section A

DBU-Induced Phenol-Keto Resonance in 3,5-Dihydroxyphthalide: Regioselectivities in Condensations with α,β-Unsaturated Aldehydes: Facile Synthesis of Bioactive Natural and Unnatural Benzopyrans

This section features the following topics:

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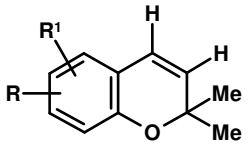
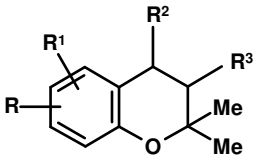
2A Section A: DBU-Induced Phenol-Keto Resonance in 3,5-Dihydroxyphthalide: Regioselectivities in Condensations with α,β-Unsaturated Aldehydes: Facile Synthesis of Bioactive Natural and Unnatural Benzopyrans

2A.1 Background

A large number of natural products with resorcinol nucleus/moiety has been isolated and synthesized in view of their promising bioactivities.[1] It has been also observed that almost every class of natural phenolic compounds contains 2,2-dimethyl-2*H*-1-benzopyran ring and number of such discovered natural product increases every year. There are approximately 4,000 natural products[2] containing the 2,2-dimethyl-2*H*-benzopyran moiety,



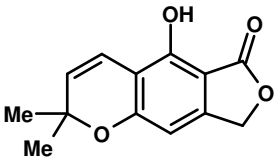
2,2-Dimethyl-2*H*-benzopyran template
(~ 4000 Natural products)



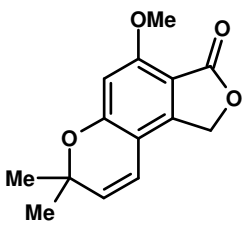
Dihydro-2,2-dimethyl-
2*H*-benzopyran derivatives
(~ 8000 Natural products)

Figure 1. Natural dimethyl-2*H*-1-benzopuran and derivatives

if the dihydro derivatives are also taken into account, then number increases up to 12,000 (Figure 1). Kamigauchi and co-workers[3] have recently isolated a 2,2-dimethylchromene containing natural product, salfredin B_{11} (**1a**) from *Crucibulum* sp. RF-3817. Salfredin B_{11} exhibits aldose reductase inhibitory activity. An aldose reductase is the enzyme that catalyzes the transformation of glucose to sorbitol in various tissues under conditions of hyperglycemia such as diabetes mellitus.[4] Elevated intracellular sorbitol levels led to the development of diabetic complications e. g. cataract,[5] neuropathy,[6] retinopathy[7] and nephropathy.[8] This enzyme is extensively present in mammalian organisms.[9] It has been expected therefore



Salfredin B_{11} (**1a**)



Phthalidochromine (**2a**)

Figure 2.

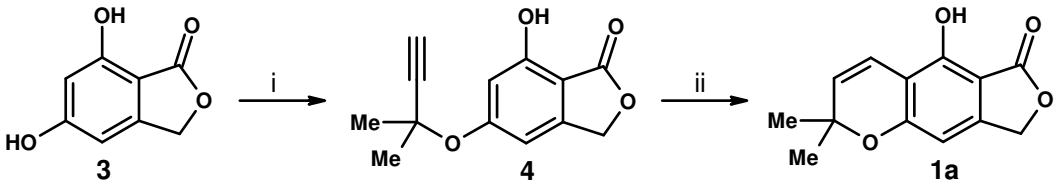
that inhibition of aldose reductase activity may provide a pharmacological approach to a treatment of these diabetic complications. Bhakuni and co-workers from India have also isolated a similar natural product phthalidochromine[10] (**2a**) from *Helichrysum platypterum* (Figure 2).

2A.1.1 Synthetic Approaches Towards Salfredin B_{11} and Phthalidochromine

The novel bioactivity of salfredin B_{11} and structural similarities between these two natural products have led to great interest in developing new synthetic strategy. There is only one report on the synthesis of Salfredin B_{11}. Till date, no synthesis of Phthalidochromine is reported. Before discussing our results, the reported synthetic approach towards Salfredin B_{11} is illustrated in brief in the following part.

[A] Mali's approach

Mali and co-workers[11] have reported a two steps synthesis of Salfredin B_{11} via the mono propargyl ether formation of the dihydroxyphthalide **3** using 3-chloro-3-methylbut-1-yne in DMF solution in the presence of potassium carbonate, potassium iodide and cuprous iodide at 60 ^{o}C. The propargyl ether **4** in *N*,*N*-dimethylaniline solution under thermal or microwave irradiation furnished Salfredin B_{11} (**1a**) in 82% yield (Scheme 1).



Scheme 1 *Reagents, conditions and yields*: (i) 3-Chloro-3-methyl-but-1-yne, K_2CO_3, KI, CuI, DMF, 60 ^{o}C, 4 h; (ii) $PhNMe_2$, reflux, 6 h (62%) or MWI, 3 min (82%).

2A.2 Rationale for Present Work

The benzopyran template of all the natural products with 2,2-disubstituted chromene moiety can be constructed by employing regioselective coupling reactions of naturally occurring resorcinol derivatives and α,β-unsaturated aldehydes.[3,10,12] A careful scrutiny of the structures of salfredin B_{11} (**1a**) and phthalidochromine (**2a**), led us to predict that, with the proper control of regioselectivity, the 3,5-dihydroxyphthalide (**3**) and 3-methyl-2-butenal would be potential starting materials for the concise biogenetic synthesis of these bioactive natural products. 3,5-Dihydroxyphthalide (**3**) is also a natural product and it was

isolated from the fresh leaves of plant *Anaphalis contorta* which is widely distributed in the temperate Himalayas.[13] So, the development of novel mild conditions for regioselective coupling of aldehydes with resorcinol derivatives at the 2- and 4-positions has been a challenging task in synthetic organic chemistry for the past several decades,[11,14,15] as it is delicately balanced on kinetic versus thermodynamic control. Earlier synthetic procedure for regioselective couplings of α,β-unsaturated aldehydes at the 2-position of resorcinol derivatives involve thermal intramolecular cyclizations[11,15] of the corresponding propargyl alcohols which may not be suitable for 3-butynes with unsaturated substituents, as this may result in intramolecular cyclization reactions. Recently, Shigemasa *et al* have reported an easy $Ca(OH)_2$ induced regioselective condensation of aldehydes at the 3-position of methyl 2,4-dihydroxybenzoate, but with α,β-unsaturated aldehydes, however reactions were not totally selective and along with desired product, they also isolated small amount of *bis*-condensed product.[14a] Moreover the conditions demand use of protic solvent and long reaction times (4 to 7 days).[14] We envisaged that the development of a mild suitable condition for the regioselective coupling of 3,5-dihydroxyphthalide (**3**) at both the 4- and 6-positions (Figure 3) with α,β-unsaturated aldehydes, particularly 3-methyl-2-butenal would provide an easy access to the natural products salfredin B_{11} and phthalidochromine.

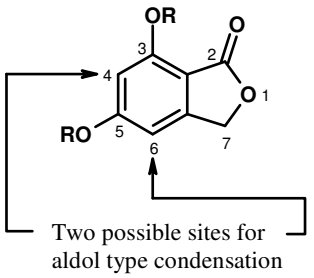
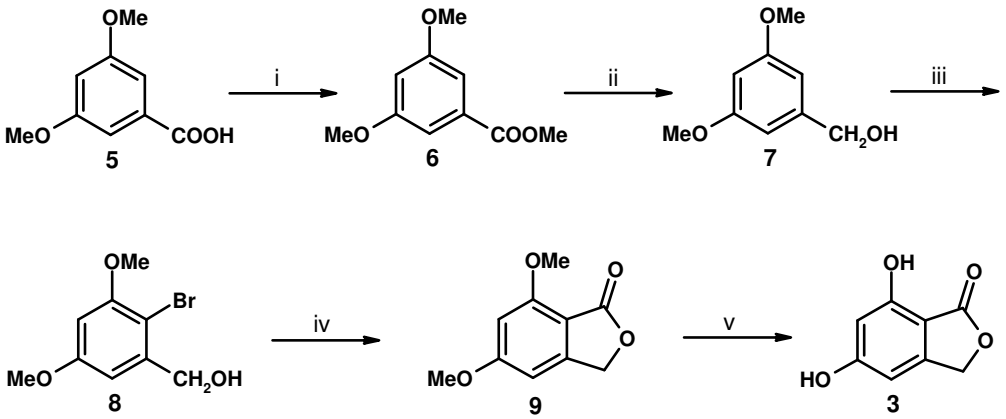


Figure 3.

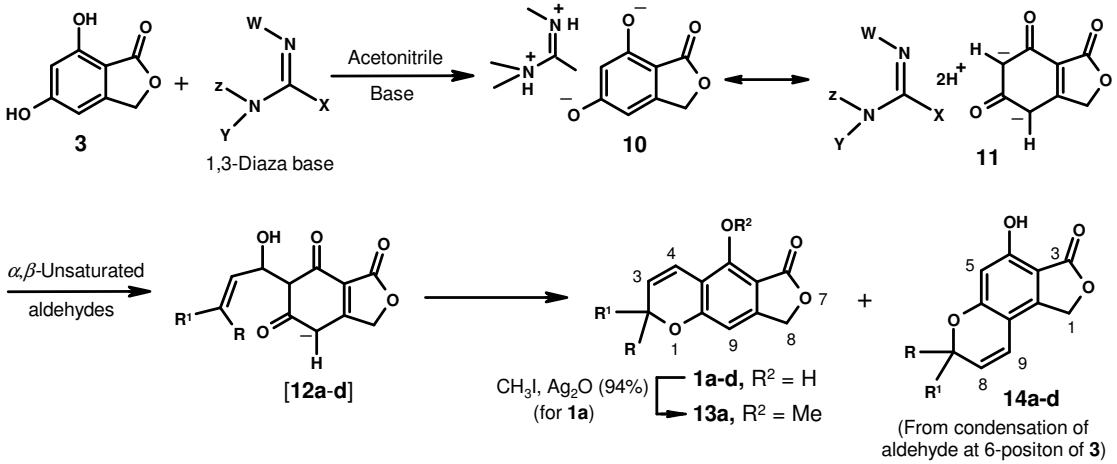
2A.3 Results and Discussion

The desired natural product 3,5-dihydroxyphthalide[13] (**3**) was prepared in five-steps starting from 3,5-dimethoxybenzoic acid (**5**). The acid **5** on esterification, reduction of the ester **6** to alcohol, NBS induced selective mono bromination of the benzyl alcohol **7**, lithiation of the bromocompound **8** followed by addition of carbon dioxide furnished the in situ lactonized dimethoxyphthalide **9**.[16] Finally $AlCl_3$ induced demethylation of **9** gave required dihydroxyphthalide **3** in 70% overall yield (Scheme 2). Then, we initially examined the reactions of phthalide **3** with 3-methyl-2-butenal in the presence of acetic acid, pyridine, triethylamine, DMAP in various solvents, but always observed formation of a mixture of **1a** (major) and **14a** (minor) (Table 1, entries 2-8). We assigned the structures for column purified **1a** and **14a** by comparison with the ^{1}H NMR data of natural products



Scheme 2 *Reagents, conditions and yields*: (i) MeOH, H^+/H_2SO_4 (cat.), reflux, 12 h (99%); (ii) THF, $LiAlH_4$ (1.20 equiv.), 0 °C to rt, 6 h (~100%); (iii) CCl_4, NBS (1.00 equiv.), gentle reflux, 6 h (98%); (iv) (a) THF, −78 °C, *n*-BuLi (2.20 equiv.), 45 min, CO_2, 1 h, (b) H^+/2 N HCl (79%); (v) DCM, $AlCl_3$ (6.00 equiv.), 0 °C to rt, 12 h (92%).

1a and **2a.** The C-3 proton signals for linear benzopyran **1a** and the corresponding C-8 proton signal in angular benzopyran **14a** appeared at δ 5.65 and 5.64 respectively. Due to the presence of a *peri*-interaction with C-5 hydroxyl group, the C-4 proton signal in **1a** appeared at δ 6.67, while the corresponding C-9 proton signal in **14a** appeared at δ 6.16, which helped us in clearly discriminating these linear and angular benzopyrans. Surprisingly, the DBU-catalyzed regioselective condensation of **3** with 3-methyl-2-butenal



Scheme 3 **a**, R = R^1 = Me; **b**, R = H, R^1 = Me; **c**, R = Me, R^1 = CH_2-CH_2-CH=C(Me)$_2$; **d**, R = H, R^1 = Ph.
1,3-Diaza bases: DBU, DBN, Tetramethylguanidine, Guanidine.

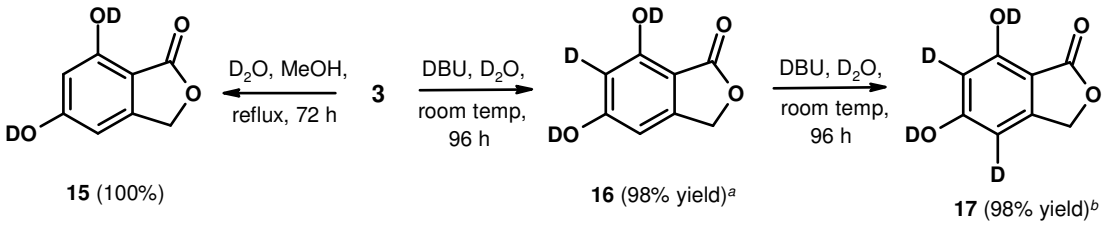
Table 1*:* Base catalyzed regioselective coupling of **3** with α,β-unsaturated aldehydes to obtain **1a-d**

Entry	Solvent	Aldehyde (equiv.)	Reagent	Condition	Product (Isolated % yields)
1[a]	THF	3-Methyl-2-butanal (5)	Nil	Reflux, 48 h	**1a** (0) & **14a** (0)
2[a]	MeOH	3-Methyl-2-butanal (5)	Catalytic AcOH	Reflux, 48 h	**1a** (35) & **14a** (5)
3[a]	AcOH	3-Methyl-2-butanal (5)	AcOH	Reflux, 48 h	**1a** (21) & **14a** (7)
4[a]	EtOH	3-Methyl-2-butanal (excess)	DMAP (1.2 equiv)	70 ^{o}C, 48 h	**1a** (41) & **14a** (20)
5[a]	Nil	3-Methyl-2-butanal (excess)	Pyridine (1.5 equiv)	140 ^{o}C, 6 h	**1a** (50) & **14a** (25)
6[a]	Nil	3-Methyl-2-butanal (excess)	TEA (1.2 equiv)	70 ^{o}C, 48 h	**1a** (42) & **14a** (22)
7[a]	Nil	3-Methyl-2-butanal (5)	TEA (2.5 equiv)	70 ^{o}C, 48 h	**1a** (48) & **14a** (25)
8[a]	CH_3CN	3-Methyl-2-butanal (5)	TEA (2.5 equiv)	Reflux, 48 h	**1a** (37) & **14a** (18)
9[b]	Nil	3-Methyl-2-butanal (excess)	DBU (1.1 equiv)	50 ^{o}C, 24 h	**1a** (48) & **14a** (0)
10[b]	THF	3-Methyl-2-butanal (5)	DBU (1.1 equiv)	50 ^{o}C, 24 h	**1a** (61) & **14a** (0)
11[b]	MeOH	3-Methyl-2-butanal (5)	DBU (1.1 equiv)	50 ^{o}C, 24 h	**1a** (62) & **14a** (0)
12[b]	EtOH	3-Methyl-2-butanal (5)	DBU (1.1 equiv)	50 ^{o}C, 24 h	**1a** (67) & **14a** (0)
13[b]	CH_3CN	3-Methyl-2-butanal (5)	DBU (1.1 equiv)	50 ^{o}C, 24 h	**1a** (80) & **14a** (0)
14[b]	CH_3CN	3-Methyl-2-butanal (5)	DBU (0.1 equiv)	50 ^{o}C, 24 h	**1a** (11) & **14a** (0)
15[b]	CH_3CN	3-Methyl-2-butanal (5)	DBU (2.2 equiv)	50 ^{o}C, 24 h	**1a** (72) & **14a** (0)
16[b]	CH_3CN	3-Methyl-2-butanal (5)	DBN (1.1 equiv)	50 ^{o}C, 24 h	**1a** (75) & **14a** (0)
17[b]	CH_3CN	3-Methyl-2-butanal (5)	Guanidine (1.1 equiv)	50 ^{o}C, 24 h	**1a** (71) & **14a** (0)
18[b]	CH_3CN	3-Methyl-2-butanal (5)	TMG (1.1 equiv)	50 ^{o}C, 24 h	**1a** (74) & **14a** (0)
19[b]	CH_3CN	Crotonaldehyde (5)	DBU (1.1 equiv)	50 ^{o}C, 24 h	**1b** (72) & **14b** (0)
20[b]	CH_3CN	Citral (5)	DBU (1.1 equiv)	50 ^{o}C, 24 h	**1c** (65) & **14c** (0)
21[b]	CH_3CN	Cinnamaldehyde (5)	DBU (1.1 equiv)	50 ^{o}C, 24 h	**1d** (81) & **14d** (0)

[a] At 50 ^{o}C there was no reaction and we did not observe any formation of product **1a** and **14a** (by TLC). [b] TLC can easily detect the formation of **1a** and **14a**, even at very low concentrations. The TLC of these reaction mixtures revealed exclusive formation of **1a**.

in acetonitrile at 50 ^{o}C exclusively furnished salfredin B_{11} (**1a**) in 80% yield via aldol type coupling of aldehyde with **3** at the 4-position followed by regioselective dehydrative ring closure with the more reactive C-5 hydroxyl group (Scheme 3). Analytical and spectral data obtained for **1a** were in complete agreement with the reported data,[3,11] and **1a** was further characterized as its methyl derivative **13a**. Similarly we observed the remarkable regioselectivity with DBN, tetramethylguanidine and guanidine, revealing that the 1,3-diaza system in the base is an important feature (Table 1, entries 9-21). This transformation is general and results obtained with 3-methyl-2-butenal and other α,β-unsaturated aldehydes are summarized in Table 1 (entries 9-21). In these experiments we found that use of 1.1 equivalents of 1,3-diaza base at 50 ^{o}C is required, as the use of 0.1 equivalent of DBU reduced the yield of **1a** to just 11%, while lower and higher temperatures using 1.1 equivalents of DBU also led to a decline in yield.

In an attempt to understand the observed 1,3-diaza base induced regioselectivity in the reaction of **3** with α,β-unsaturated aldehydes we mixed 1.0 equivalent of phthalide **3** and 1.1 equivalents of DBU in acetonitrile at room temperature, where the TLC of the reaction mixture showed almost quantitative formation of a new material, presumed to be the DBU-**3** complex. Unfortunately all our attempts to purify this postulated DBU-**3** complex met with failure.[17] The ^{1}H NMR and ^{13}C NMR spectra of the complex showed the absence of both aromatic protons and the two proton bearing aromatic ring carbons suggesting dianion structure **11**. Use of 0.5 equivalent of DBU indicated less than 50% formation of the same complex and none of any corresponding monoanionic species. To further confirm that this double deprotonation is DBU-dependent, we heated **3** with D_2O for more than 72 h under stirring and did not observe any incorporation of deuterium into the aromatic ring. However, on stirring the DBU-**3** complex with D_2O for 96 h at room temperature, we observed by ^{1}H NMR and ^{13}C NMR analysis selective incorporation of deuterium into the 4-position of the ring to the extent of 98% (with 15% deuterium incorporation at 6-position), and on stirring for a further 96 h we observed incorporation of a second deuterium atom into the 6-position of the ring to the extent of 85% (Scheme 4). We believe this to be strong evidence for DBU-enhanced generation of dianionic species **11**. In the condensation reaction with aldehydes, the relatively more reactive C-4 carbanion flanked between two carbonyls, reacts with α,β-unsaturated aldehydes accounting for the present observed regioselectivity. The C-6 carbanion thus formed is relatively more stable and less reactive as it is flanked between carbonyl and α,β-unsaturated lactone carbonyl.



15 (100%)

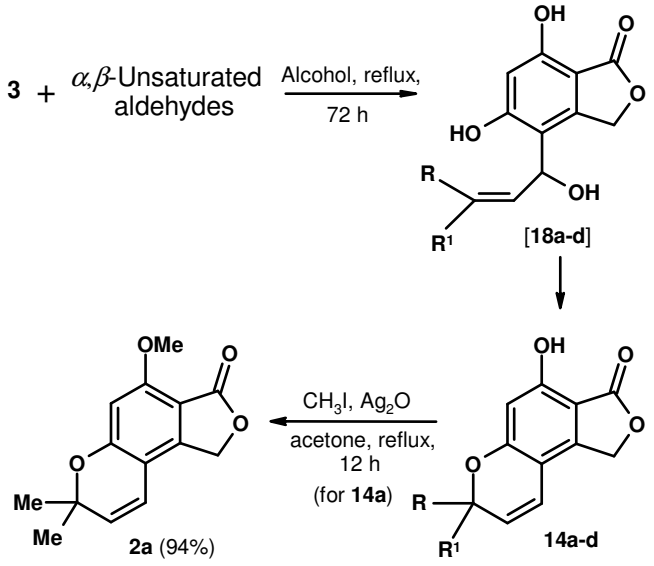
16 (98% yield)[a]

17 (98% yield)[b]

Scheme 4 [a] Nearly 100% deuterium incorporation at 4-position and 15% at 6-position.
[b] Nearly 100% deuterium incorporation at 4-position and 85% at 6-position.

Interestingly, the 3,5-dihydroxyphthalide (**3**) on reaction with 3-methyl-2-butenal in methanol under reflux for 60 h exclusively furnished the desired angular product **14a** in

41% yield via the expected natural mode of regioselective aldol type coupling of aldehyde at the 6-position of phthalide followed by dehydrative ring closure with the C-5 hydroxyl group, following a concerted mechanism (Scheme 5). In the present reaction **14a** would appear to be the kinetically controlled product as the same reaction in refluxing ethanol



Scheme 5 **a**, R = R^1 = Me; **b**, R = H, R^1 = Me; **c**, R = Me, R^1 = CH_2-CH_2-CH=C(Me)$_2$; **d**, R = H, R^1 = Ph.

Table 2: Regioselective coupling of **3** with α,β-unsaturated aldehydes to obtain **14a-d**

Entry	Solvent	Aldehyde (equiv.)	Condition	Product (Isolated % yields)
1[a]	MeOH	3-Methyl-2-butanal (5)	Reflux, 60 h	**14a** (41)
2[a]	EtOH	3-Methyl-2-butanal (5)	65 ^oC, 48 h	**14a** (39)
3	EtOH	3-Methyl-2-butanal (5)	Reflux, 48 h	**14a** (42) & **1a** (7)
4[a]	MeOH	3-Methyl-2-butanal (15)	Reflux, 72 h	**14a** (60)
5[a]	MeOH	Crotonaldehyde (15)	Reflux, 72 h	**14b** (59)
6[a]	MeOH	Citral (15)	Reflux, 72 h	**14c** (51)
7[a]	EtOH	Cinnamaldehyde (15)	Reflux, 72 h	**14d** (51)

[a] The TLC of these reaction mixtures revealed exclusive formation of **14a**.

again furnished the mixture of **1a** plus **14a** (Table 2, entry 3). However, we were unable to transform **14a** into **1a** by heating at 150 ^oC for 7 days. In the reaction of **3** and 3-methyl-2-butenal in methanol, addition of aldehyde in three portions at intervals of 24 h, exclusively furnished **14a** in 60% yield. The angular product **14a,** on methylation with methyl iodide in the presence of Ag_2O, gave the desired natural product phthalidochromine (**2a**) in 94%

yield. The analytical and spectral data obtained for **2a** were in complete agreement with reported data.[10] Similarly, the reaction of phthalide **3** with crotonaldehyde, citral and cinnamaldehyde furnished the angular products **14b-d** and the results obtained are summarized in Table 2 (entries 5-7). In all the above mentioned condensation reactions we could not exceed 60% yields of **14a-d** due to the labiality of the α,β-unsaturated aldehydes.

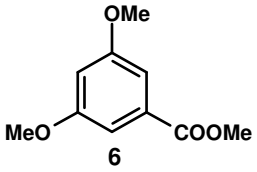
2A.4 Summary

For the first time we have demonstrated a dramatic DBU-induced double deprotonation of 3,5-dihydroxyphthalide and we have proved a bidentate base to be necessary for incorporating two deuterium labels onto the aromatic ring. We have been able to tune the regioselectivities in the condensation of 3,5-dihydroxyphthalide with several α,β-unsaturated aldehydes using DBU and neutral conditions to obtain exclusively the linear (65-81%) and angular (51-60%), bioactive natural and unnatural benzopyran derivatives in one step.[18] Further studies into this selectivity paradigm are in progress in our laboratory and the complete structural confirmation of the proposed dicarbanionic species is necessary. We feel this new approach to linear and angular benzopyrans to be advantageous and do have the ability to design libraries of natural product analogues for the structure activities relationship studies.

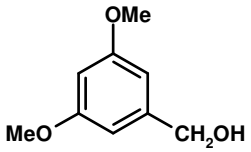
2A.5 Experimental Section

Commercially available 3,5-dimethoxybenzoic acid, $LiAlH_4$, NBS, *n*-BuLi (1.50 M), $AlCl_3$, DBU, DBN, tetramethylguanidine, guanidine, prenal, crotonaldehyde, citral, cinnamaldehyde and D_2O were used. Dichloromethane was distilled from phosphorous pentoxide under argon. Tetrahydrofuran was freshly distilled from benzophenone ketyl radical under argon prior to use. All yields given refer to as isolated yields.

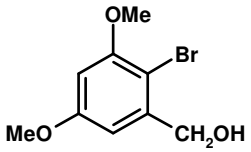
Methyl 3,5-dimethoxybenzoate (6). To a stirring solution of **5** (10.00 g, 54.95 mmol) in methanol (100 mL), 10 drops of conc. H_2SO_4 was added and the reaction mixture was refluxed for 12 h. After cooling, methanol was removed in vacuo. The residue was dissolved in ethyl acetate (200 mL) and the organic layer was washed with brine, saturated $NaHCO_3$ solution, brine and dried over Na_2SO_4. Removal of the solvent in vacuo followed by silica gel column chromatographic purification of the residue using 15% ethyl acetate in petroleum ether afforded **6** (10.66 g, 99%) as a colorless liquid.

 **6** $C_{10}H_{12}O_4$ (196)	Colorless liquid. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 3.83 (s, 6H), 3.91 (s, 3H), 6.65 (t, J = 4 Hz, 1H), 7.19 (d, J = 2 Hz, 2H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 51.5, 54.8, 105.0, 106.6, 131.5, 160.2, 166.1. **IR** ($CHCl_3$) 1722, 1599, 1462, 1431, 1350 cm^{-1}. **Anal. Calcd** for $C_{10}H_{12}O_4$: C, 61.22; H, 6.16. Found: C, 61.19; H, 6.20.

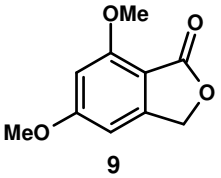
3,5-Dimethoxybenzyl alcohol (7). To a stirring mixture of $LiAlH_4$ (2.33 g, 61.22 mmol) in THF (75 mL) at 0 ^oC, a solution of **6** (10.00 g, 51.02 mmol) in THF (25 mL) was added dropwise and the reaction mixture was allowed to attain room temperature. After stirring for 6 h at room temperature, the reaction mixture was cooled to 0 ^oC and very slowly quenched with saturated aqueous solution of Na_2SO_4. The reaction mixture was filtered through celite and the filtrate was concentrated in vacuo. To the obtained residue was added ethyl acetate (150 mL) and the organic layer was washed with water, brine and dried over Na_2SO_4. Removal of the solvent in vacuo followed by silica gel column chromatographic purification of the residue using 40% ethyl acetate in petroleum ether afforded **7** (8.57 g, ~100%) as a colorless liquid.

 **7** **$C_9H_{12}O_3$ (168)**	Colorless liquid. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 2.86 (bs, 1H), 3.74 (s, 6H), 4.55 (s, 2H), 6.34 (t, J = 2 Hz, 1H), 6.48 (d, J = 2 Hz, 2H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 54.6, 64.0, 98.8, 104.0, 143.2, 160.3. **IR** (Neat) 3395, 1599 cm^{-1}. **Anal. Calcd** for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.31; H, 7.01.

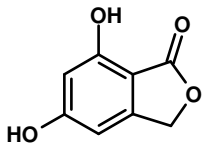
2-Bromo-3,5-dimethoxybenzyl alcohol (8). A mixture of **7** (8.00 g, 47.62 mmol) and NBS (8.48 g, 47.62 mmol) in CCl_4 (150 mL) was refluxed gently for 6 h. The reaction mixture was filtered under hot condition and concentration of the filtrate under vacuo followed by silica gel column chromatographic purification of the residue using 35% ethyl acetate in petroleum ether afforded **8** (11.53 g, 98%) as a white solid.

 **8** **$C_9H_{11}BrO_3$ (247)**	**Mp** 119-121 ^{o}C. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 2.16 (t, J = 6 Hz, 1H), 3.82 (s, 3H), 3.87 (s, 3H), 4.73 (d, J = 8 Hz, 2H), 6.44 (d, J = 2 Hz, 1H), 6.70 (d, J = 4 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 55.5, 56.3, 65.1, 98.8, 102.1, 104.7, 141.7, 156.5, 159.9. **IR** (Nujol) 3184, 1589 cm^{-1}. **Anal. Calcd** for $C_9H_{11}BrO_3$: C, 43.75; H, 4.49; Br, 32.34. Found: C, 43.69; H, 4.56; Br, 32.35.

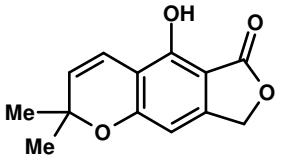
5,7-Dimethoxyisobenzofuran-3*H*-1-one (9). To a stirring solution of **8** (11.00 g, 44.53 mmol) in THF (100 mL) at −78 ^{o}C, *n*-BuLi (65 mL, 97.50 mmol) was added dropwise. After stirring at −78 ^{o}C for 45 min, dry CO_2 gas was passed in the reaction mixture for 1 h. Then the reaction mixture was allowed to attain room temperature, THF was removed in vacuo and the residue was acidified with 2N HCl. To the reaction mixture was added ethyl acetate (200 mL) and the organic layer was washed with water, brine and dried over Na_2SO_4. Removal of the solvent in vacuo followed by silica gel column chromatographic purification of the residue using 55% ethyl acetate in petroleum ether afforded **9** (6.83 g, 79%) as a colorless solid.

 **9** **$C_{10}H_{10}O_4$ (194)**	**Mp** 150-151 °C. **^{1}H NMR** (DMSO-d_6, 200 MHz) δ 3.89 (s, 6H), 5.23 (s, 2H), 6.60 (d, J = 2 Hz, 1H), 6.74 (d, J = 2 Hz, 1H). **^{13}C NMR** (DMSO-d_6, 50 MHz) δ 56.0, 56.2, 68.6, 98.7, 98.9, 105.5, 152.3, 159.3, 166.6, 168.1. **IR** (Nujol) 1747, 1614, 1601 cm^{-1}. **Anal. Calcd** for $C_{10}H_{10}O_4$: C, 61.85; H, 5.19. Found: C, 61.91; H, 5.09.

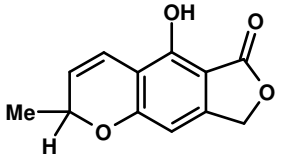
5,7-Dihydroxyisobenzofuran-3*H*-1-one (3). To a stirring mixture of $AlCl_3$ (26.74 g, 201.03 mmol) in DCM (150 mL) at 0 °C, a solution of **9** (6.50 g, 33.51 mmol) in DCM (50 mL) was added dropwise and the reaction mixture was allowed to attain room temperature slowly. After stirring for 12 h at room temperature, solvent was removed from the reaction mixture under vacuum and the solid residue was cooled to 0 °C. Water was added very slowly to this solid residue till the entire complex decomposed. The obtained solid compound was filtered, dried and recrystallization from ethyl acetate/methanol afforded **3** (5.12 g, 92%) as a colorless crystalline solid.

 **3** **$C_8H_6O_4$ (166)**	**Mp** 240-241 °C. **^{1}H NMR** (CD_3OD, 500 MHz) δ 5.17 (s, 2H), 6.29 (s, 1H), 6.39 (s, 1H). **^{13}C NMR** (CD_3OD, 125 MHz) δ 70.7, 101.6, 103.4, 104.4, 152.7, 159.7, 167.0, 172.8. **IR** (Nujol) 3348, 3211, 1722, 1611 cm^{-1}. **Anal. Calcd** for $C_8H_6O_4$: C, 57.84; H, 3.64. Found: C, 57.91; H, 3.58.

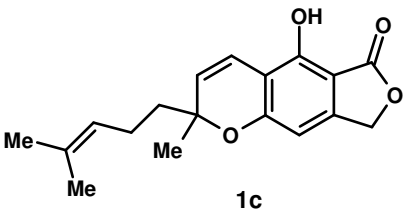
2,8-Dihydro-5-hydroxy-2,2-dimethyl-6*H*-furo[3,4-*g*]-1-benzopyran-6-one (Salfredin B_{11}, 1a). A mixture of dihydroxyphthalide **3** (500 mg, 3.00 mmol) and DBU (0.49 mL, 3.30 mmol) was dissolved in acetonitrile (15 mL) and stirred at room temperature for 10 minutes. 3-Methyl-2-butenal (1.40 mL, 15.00 mmol) was added to the reaction mixture and stirring was continued for 24 h at 50 °C. Evaporation of the solvent in vacuo and chromatography on silica gel (10% ethyl acetate in petroleum ether) afforded pure Salfredin B_{11} (**1a**) (558 mg, 80%) as a white crystalline solid.

 **1a** **$C_{13}H_{12}O_4$ (232)**	**Mp** 169-170 ^oC. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 1.46 (s, 6H), 5.22 (bs, 2H), 5.65 (d, J = 10 Hz, 1H), 6.39 (s, 1H), 6.67 (d, J = 10 Hz, 1H), 7.78 (s, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 28.1 (2-carbons), 70.4, 77.9, 102.2, 103.8, 108.8, 115.2, 129.0, 147.1, 152.1, 160.7, 172.5. **IR** (Nujol) 3398, 1742, 1462, 1377 cm^{-1}. **Anal. Calcd** for $C_{13}H_{12}O_4$: C, 67.23; H, 5.21. Found C, 67.37; H, 5.39.

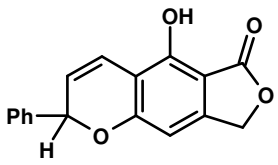
2,8-Dihydro-5-hydroxy-2-methyl-6*H*-furo[3,4-*g*]-1-benzopyran-6-one (1b). Compound **1b** was prepared from **3** and crotonaldehyde using the same procedure described for **1a**. **1b:** White crystalline solid.

 **1b** **$C_{12}H_{10}O_4$ (218)**	**Mp** 148-149 ^oC. **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 1.46 (d, J = 10 Hz, 3H), 5.07 (q, J = 5 Hz, 1H), 5.20 (s, 2H), 5.68 (d, J = 10 Hz, 1H), 6.38 (s, 1H), 6.71 (d, J = 10 Hz, 1H) 7.77 (bs, 1H). **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 21.4, 70.4, 72.5, 102.0, 104.1, 109.3, 116.7, 125.1, 147.2, 152.1, 161.1, 172.5. **IR** (Nujol) 3389, 1736, 1630, 1462 cm^{-1}. **Anal. Calcd** for $C_{12}H_{10}O_4$: C, 66.05; H, 4.62. Found: C, 65.88; H, 4.79.

2,8-Dihydro-5-hydroxy-2-methyl-2-(3'*E*-4'-methylpentenyl)-6*H*-furo[3,4-*g*]-1-benzopyran-6-one (1c). Compound **1c** was prepared from **3** and citral using the same procedure described for **1a**. **1c:** Thick oil.

 **1c** **$C_{18}H_{20}O_4$ (300)**	Thick oil. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 1.41 (s, 3H), 1.56 (s, 3H), 1.60-1.85 (m, 2H), 1.65 (s, 3H), 2.08 (q, J = 9 Hz, 2H), 5.07 (t, J = 6 Hz, 1H), 5.19 (s, 2H), 5.58 (d, J = 12 Hz, 1H), 6.36 (s, 1H), 6.69 (d, J = 12 Hz, 1H), 7.77 (bs, 1H). **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 17.6, 22.6, 25.5, 26.8, 41.5, 70.4, 80.4, 102.0, 103.7, 108.6, 115.7, 123.7, 127.9, 131.9, 147.1, 152.1, 161.1, 172.5. **IR** ($CHCl_3$) 3440, 1729, 1639, 1460, 1216, 1153, 757 cm^{-1}. **Anal. Calcd** for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 72.13; H, 6.99.

2,8-Dihydro-5-hydroxy-2-phenyl-6*H*-furo[3,4-*g*]-1-benzopyran-6-one (1d). Compound **1d** was prepared from **3** and cinnamaldehyde using the same procedure described for **1a**. **1d:** White crystalline solid.

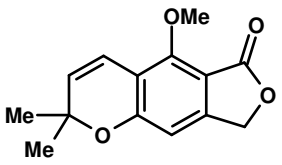


1d

$C_{17}H_{12}O_4$ (280)

Mp 155-156 °C.
^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.19 (s, 2H), 5.85 (dd, J = 8 & 2 Hz, 1H), 5.99 (bs, 1H), 6.39 (s, 1H), 6.93 (d, J = 8 Hz, 1H), 7.30-7.50 (m, 5H), 7.84 (bs, 1H).
^{13}C NMR ($CDCl_3$, 125 MHz) δ 70.4, 77.9, 102.0, 104.3, 108.9, 117.0, 122.9, 127.1 (2-carbons), 128.8 (3-carbons), 139.7, 147.4, 152.2, 160.5, 172.4.
IR (Nujol) 3402, 1736, 1632, 1462, 1377 cm^{-1}.
Anal. Calcd for $C_{17}H_{12}O_4$: C, 72.85; H, 4.32. Found: C, 72.69; H, 4.44.

2,8-Dihydro-5-methoxy-2,2-dimethyl-6*H*-furo[3,4-*g*]-1-benzopyran-6-one (13a). To a stirring mixture of **1a** (250 mg, 1.07 mmol) and Ag_2O (1.00 g, 4.31 mmol) in acetone (15 mL), methyliodide (0.70 mL, 10.77 mmol) was added and the reaction mixture was gently refluxed for 6 h. After cooling, reaction mixture was filtered through celite and concentration of the filtrate in vacuo followed by silica gel column chromatographic purification of the residue using 15% ethyl acetate in petroleum ether afforded **13a** (249 mg, 94%) as a white solid.

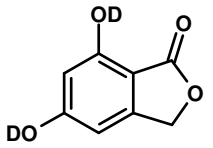


13a

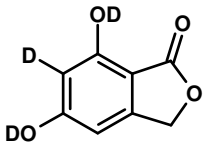
$C_{14}H_{14}O_4$ (246)

Mp 97-98 °C.
^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.45 (s, 6H), 4.11 (s, 3H), 5.15 (s, 2H), 5.68 (d, J = 10 Hz, 1H), 6.54 (s, 1H), 6.70 (d, J = 10 Hz, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz) δ 28.2 (2-carbons), 62.9, 68.7, 77.7, 104.8, 109.0, 114.5, 116.2, 130.2, 149.6, 155.2, 159.9, 168.6.
IR ($CHCl_3$) 1749, 1609, 1215, 758, 669 cm^{-1}.
Anal. Calcd for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73. Found: C, 68.42; H, 5.76.

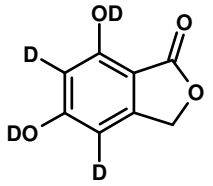
3,5-Dideuteroxyphthalide (15). To a stirring solution of **3** (200 mg, 1.20 mmol) in methanol (10 mL) was added D_2O (10 mL) and the reaction mixture was refluxed for 72 h. Methanol was removed in vacuo and the residue on silica gel column chromatographic purification using 90% ethyl acetate in petroleum ether afforded pure **15** (200 mg, 100%) as a colorless crystalline solid.

 **15** **$C_8H_4O_4D_2$ (168)**	**Mp** 230-231 ^oC. **^1H NMR** (CD_3OD, 500 MHz) δ 5.17 (s, 2H), 6.29 (s, 1H), 6.39 (s, 1H). **^{13}C NMR** (CD_3OD, 125 MHz) δ70.7, 101.6, 103.4, 104.4, 152.7, 159.7, 167.0, 172.8. **IR** (Nujol) 3348, 3211, 1722, 1611 cm^{-1}.

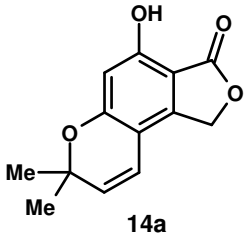
4-Deutero-3,5-dideuteroxyphthalide (16). To a stirring solution of **3** (200 mg, 1.20 mmol) in methanol (10 mL) was added a solution of DBU (0.18 mL, 1.20 mmol) and after stirring the reaction mixture for 1 h, methanol was removed in vacuo and the residue was dried. To this residue D_2O (10 mL) was added and the reaction mixture was stirred for 96 h at room temperature. D_2O was removed in vacuo and the residue on silica gel column chromatographic purification using 90% ethyl acetate in petroleum ether afforded pure **16** (199 mg, 98 %) as a colorless crystalline solid.

 **16** **$C_8H_3O_4D_3$ (169)**	**Mp** 225-226 ^oC. **^1H NMR** (CD_3OD, 500 MHz): δ 5.09 (s, 2H), 6.35 (s, 1H). **^{13}C NMR** (CD_3OD, 125 MHz) δ 70.6, 101.6, 103.4, 104.4, 152.5, 159.6, 166.9, 172.9. **IR** (Nujol) 3348, 3211, 1722, 1611 cm^{-1}. "Nearly 100% deuterium incorporation at 4-position and 15% at 6-position"

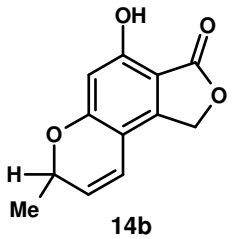
4,6-Dideutero-3,5-dideuteroxyphthalide (17). To a stirring solution of **3** (200 mg, 1.20 mmol) in methanol (10 mL) was added a solution of DBU (0.18 mL, 1.20 mmol) and after stirring the reaction mixture for 1 h, methanol was removed in vacuo and the residue was dried. To this residue D_2O (10 mL) was added and the reaction mixture was stirred for 192 h at room temperature. D_2O was removed in vacuo and the residue on silica gel column chromatographic purification using 90% ethyl acetate in petroleum ether afforded pure **17** (200 mg, 98 %) as a colorless crystalline solid.

 **17** **$C_8H_2O_4D_4$ (170)**	**Mp** 219-220 ^oC. **^1H NMR** (CD_3OD, 500 MHz) δ 5.15 (s, 2H). **^{13}C NMR** (CD_3OD, 125 MHz) δ 70.6, 101.8, 103.5, 104.5, 152.3, 159.1, 166.7, 172.9. **IR** (Nujol) 3344, 3209, 1723, 1607 cm^{-1}. "Nearly 100% deuterium incorporation at 4-position and 85% at 6-position"

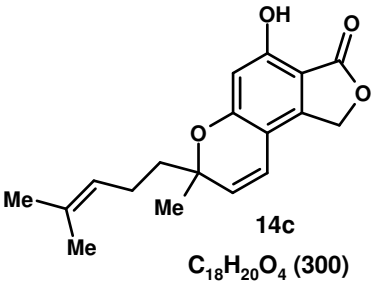
1,7-Dihydro-4-hydroxy-7,7-dimethyl-3*H*-furo[3,4-*f*]-1-benzopyran-3-one (Hydroxy phthalidochromine) 14a. Dihydroxyphthalide **3** (500 mg, 3.00 mmol) and 3-methyl-2-butenal (1.40 mL, 15.00 mmol) was dissolved in methanol (15 mL) and the reaction mixture was stirred under reflux for 72 h with another two additions of same amount of prenal after each 24 h. Evaporation of the solvent in vacuo and chromatography on silica gel (15% ethyl acetate in petroleum ether) afforded pure hydroxyphthalidochromine (**14a**) (418 mg, 60%) as a white crystalline solid.

 **14a** **$C_{13}H_{12}O_4$ (232)**	**Mp** 147-148 ^oC. **^1H NMR** ($CDCl_3$, 200 MHz) δ 1.47 (s, 6H), 5.26 (s, 2H), 5.64 (d, J = 10 Hz, 1H), 6.16 (d, J = 10 Hz, 1H), 6.35 (s, 1H), 7.66 (bs, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 28.1 (2-carbons), 69.1, 77.9, 103.6, 108.4, 116.3, 129.5, 142.8, 157.2, 159.6, 160.7, 172.1. **IR** (Nujol) 3441, 1724, 1460, 1153 cm^{-1}. **Anal. Calcd** for $C_{13}H_{12}O_4$: C, 67.23; H, 5.21. Found: C, 67.42; H, 5.11.

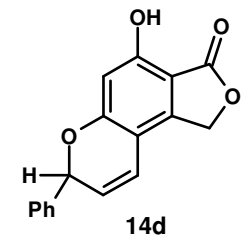
1,7-Dihydro-4-hydroxy-7-methyl-3*H*-furo[3,4-*f*]-1-benzopyran-3-one (14b). Compound **14b** was prepared from **3** and crotonaldehyde using the same procedure described for **14a**. **14b:** White crystalline solid.

 **14b** **$C_{12}H_{10}O_4$ (218)**	**Mp** 142-143 ^{o}C. **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 1.47 (d, J = 10 Hz, 3H), 5.08 (q, J = 8 Hz, 1H), 5.24 (s, 2H), 5.68 (dd, J = 10 Hz & 5 Hz, 1H), 6.21 (d, J = 10 Hz, 1H), 6.35 (s, 1H), 7.67 (bs, 1H). **^{1}H NMR** (Acetone-d_6, 500 MHz) δ 1.45 (d, J = 10 Hz, 3H), 5.12 (q, J = 8 Hz, 1H), 5.33 (s, 2H), 5.78 (d, J = 10 Hz, 1H), 6.32 (s, 1H), 6.43 (d, J = 10 Hz, 1H), 8.80 (bs, 1H). **^{13}C NMR** (Acetone-d_6, 125 MHz) δ 21.7, 69.1, 73.3, 103.8, 105.3, 109.4, 118.9, 126.1, 145.7, 158.2, 161.3, 170.9. **IR** (Nujol) 3382, 1726, 1632, 1462, 1377 cm^{-1}. **Anal. Calcd** for $C_{12}H_{10}O_4$: C, 66.05; H, 4.62. Found: C, 65.92; H, 4.51.

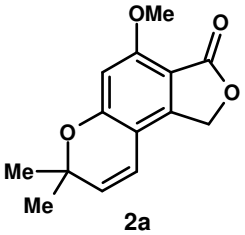
1,7-Dihydro-4-hydroxy-7-methyl-7-(3$'$*E*-4$'$-methylpentenyl)-3*H*-furo[3,4-*f*]-1-benzopyran-3-one (14c). Compound **14c** was prepared from **3** and citral using the same procedure described for **14a**. **14c:** Thick oil.

 **14c** **$C_{18}H_{20}O_4$ (300)**	Thick oil. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 1.43 (s, 3H), 1.57 (s, 3H), 1.66 (s, 3H), 1.40-1.65 (m, 2H), 2.00-2.20 (m, 2H), 5.00-5.15 (m, 1H), 5.25 (s, 2H), 5.58 (d, J = 9 Hz, 1H), 6.19 (d, J = 9 Hz, 1H), 6.34 (s, 1H), 7.65 (bs, 1H). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 17.6, 22.6, 25.6, 27.0, 41.5, 69.1, 80.4, 103.4, 103.6, 108.2, 116.9, 123.5, 128.4, 132.1, 142.8, 157.3, 161.2, 172.5. **IR** ($CHCl_3$) 3449, 1730, 1638, 1630, 1443, 1377 cm^{-1}. **Anal. Calcd** for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 71.77; H, 6.63.

1,7-Dihydro-4-hydroxy-7-phenyl-3*H*-furo[3,4-*f*]-1-benzopyran-3-one (14d). Compound **14d** was prepared from **3** and cinnamaldehyde using the same procedure described for **14a**. **14d:** White crystalline solid.

 **14d** **$C_{17}H_{12}O_4$ (280)**	**Mp** 179-180 ^{o}C. **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 5.29 (s, 2H), 5.85 (dd, J = 10 & 5 Hz, 1H), 6.00 (s, 1H), 6.37 (s, 1H), 6.39 (d, J = 10 Hz, 1H), 7.30-7.50 (m, 5H), 7.70 (bs, 1H). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 69.1, 77.9, 103.6, 104.3, 108.5, 118.0, 123.6, 126.9, 128.8 (2-carbons), 139.8, 143.1, 157.7, 160.7, 172.1. **IR** (Nujol) 3312, 1738, 1630, 1450, cm^{-1}. **Anal. Calcd** for $C_{17}H_{12}O_4$: C, 72.85; H, 4.32. Found: C, 72.99; H, 4.52.

1,7-Dihydro-4-methoxy-7,7-dimethyl-3*H*-furo[3,4-*f*]-1-benzopyran-3-one (Phthalidochromine, 2a). To a stirring mixture of **14a** (250 mg, 1.07 mmol) and Ag_2O (1.00 g, 4.31 mmol) in acetone (15 mL) was added methyl iodide (0.70 mL, 10.77 mmol) and the reaction mixture was gently refluxed for 6 h. After cooling, reaction mixture was filtered through cellite and concentration of the filtrate in vacuo followed by silica gel column chromatographic purification of the residue using 20% ethyl acetate in petroleum ether afforded **2a** (249 mg, 94%) as a white solid.

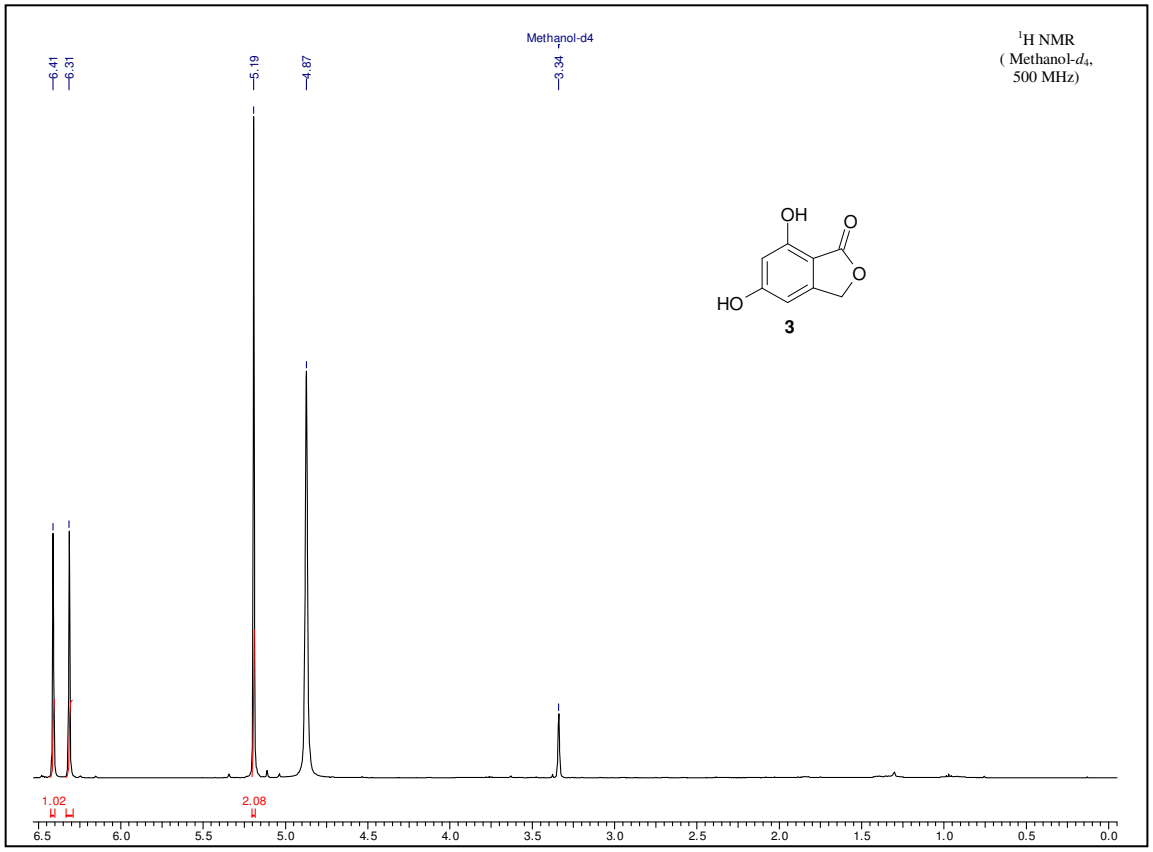


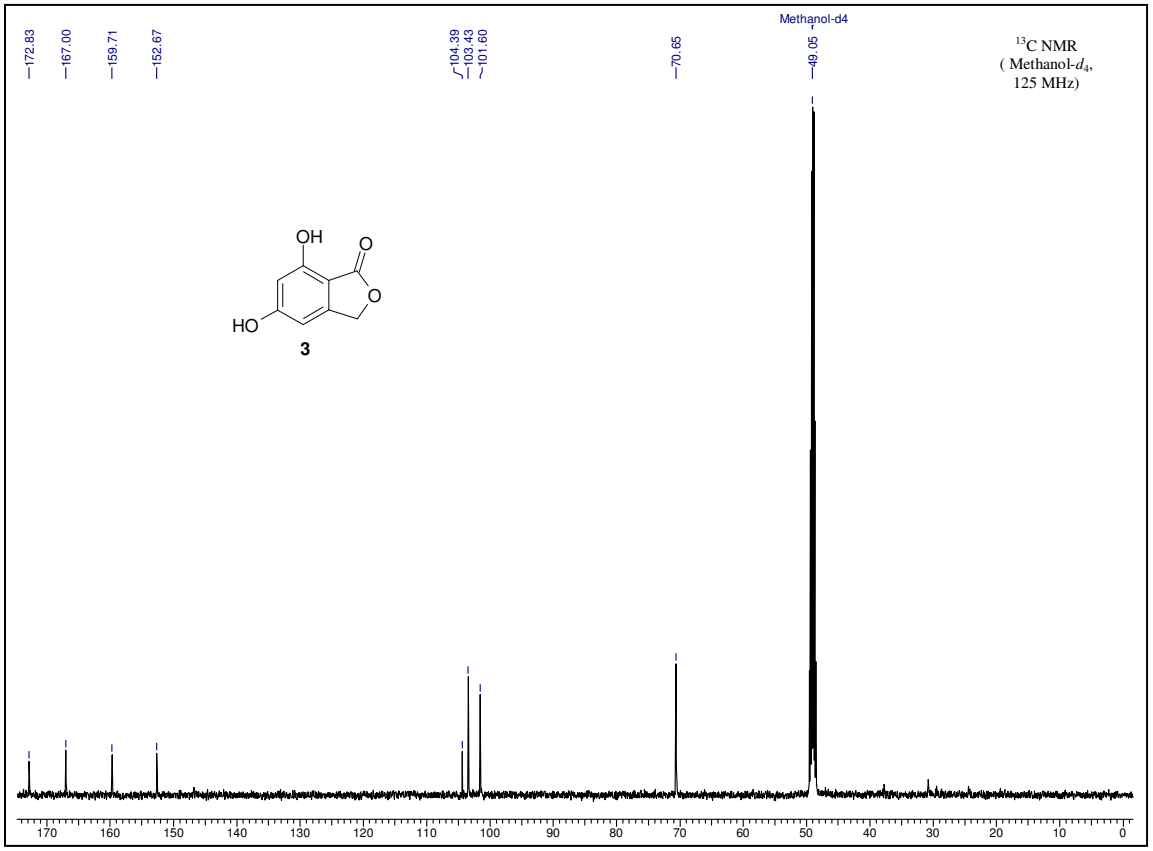
2a

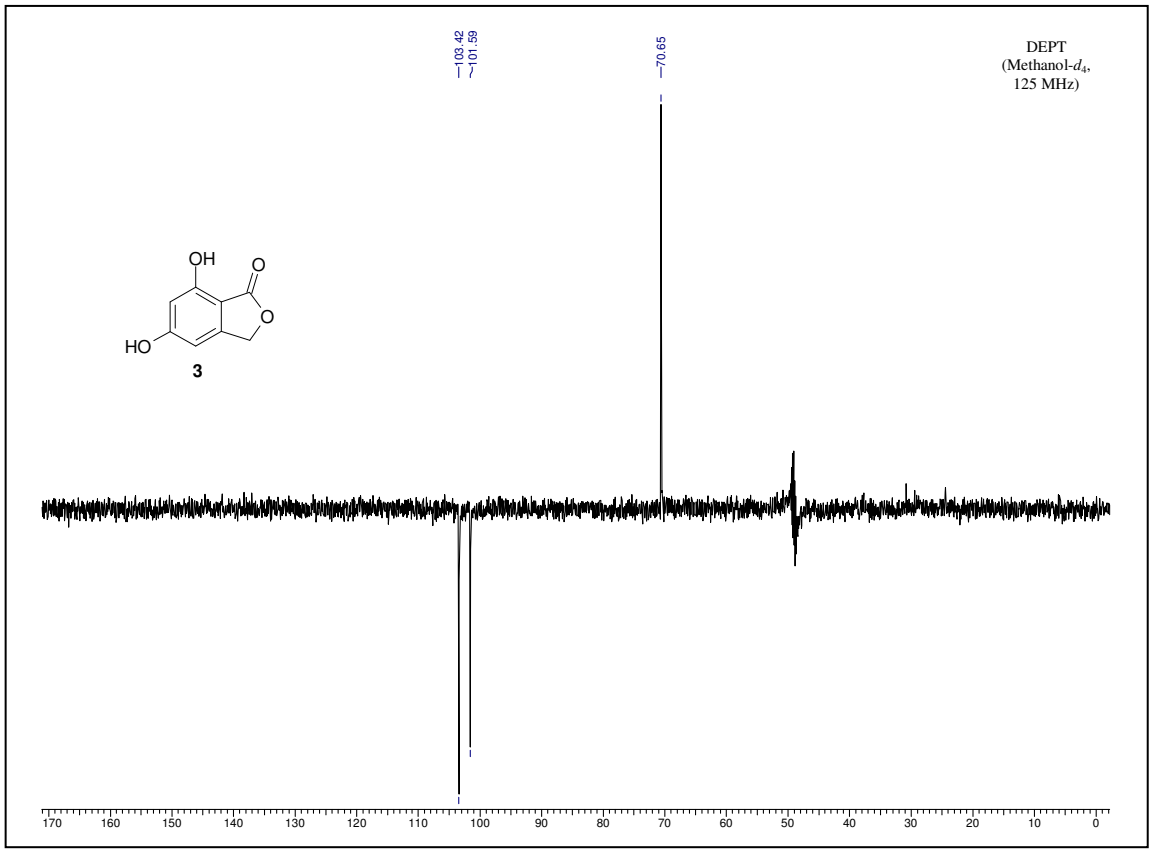
$C_{14}H_{14}O_4$ (246)

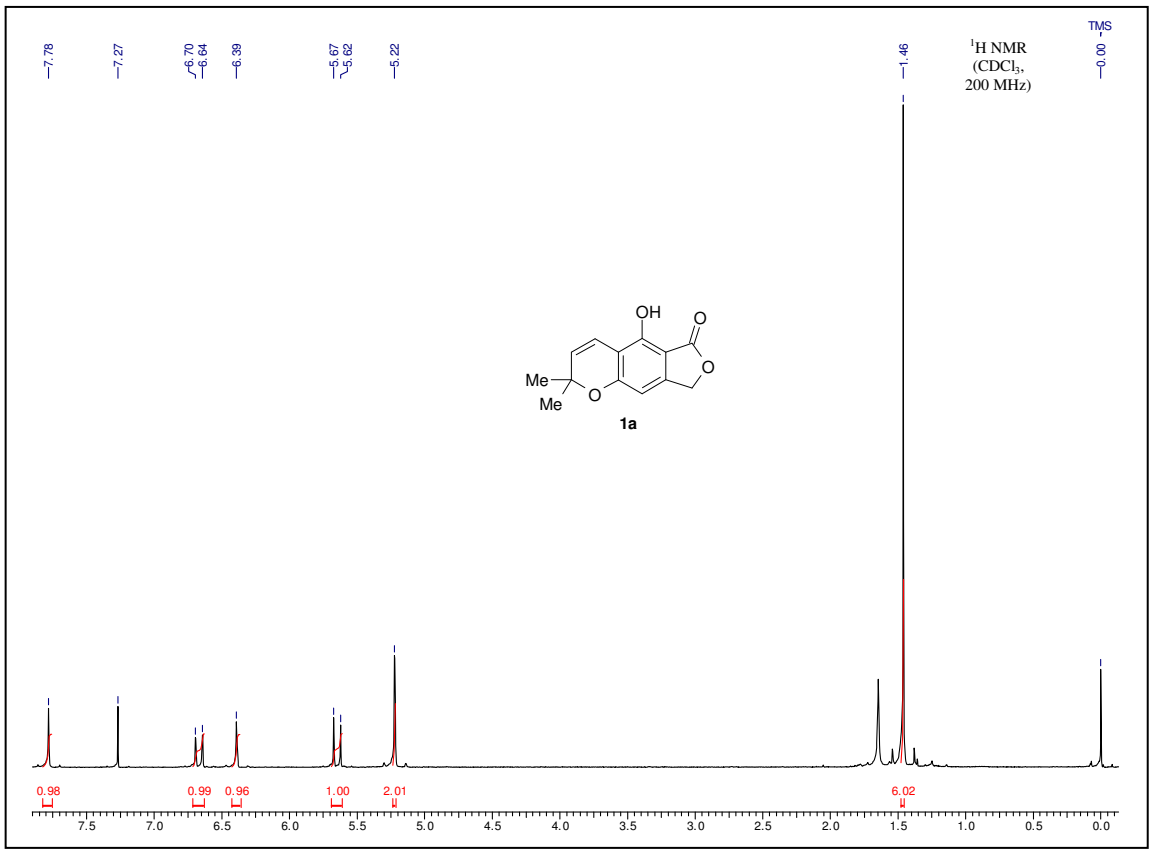
Mp 182-184 °C.
^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.47 (s, 6H), 3.92 (s, 3H), 5.16 (s, 2H), 5.62 (d, J = 10 Hz, 1H), 6.16 (d, J = 10 Hz, 1H), 6.35 (s, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz) δ 28.3 (2-carbons), 56.1, 67.2, 78.1, 100.0, 106.0, 107.7, 116.3, 129.1, 145.7, 159.6, 160.0, 168.7.
IR (Nujol) 1755, 1622, 1462, 1375, 1030 cm^{-1}.
Anal. Calcd for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73. Found: C, 68.49; H, 5.61.

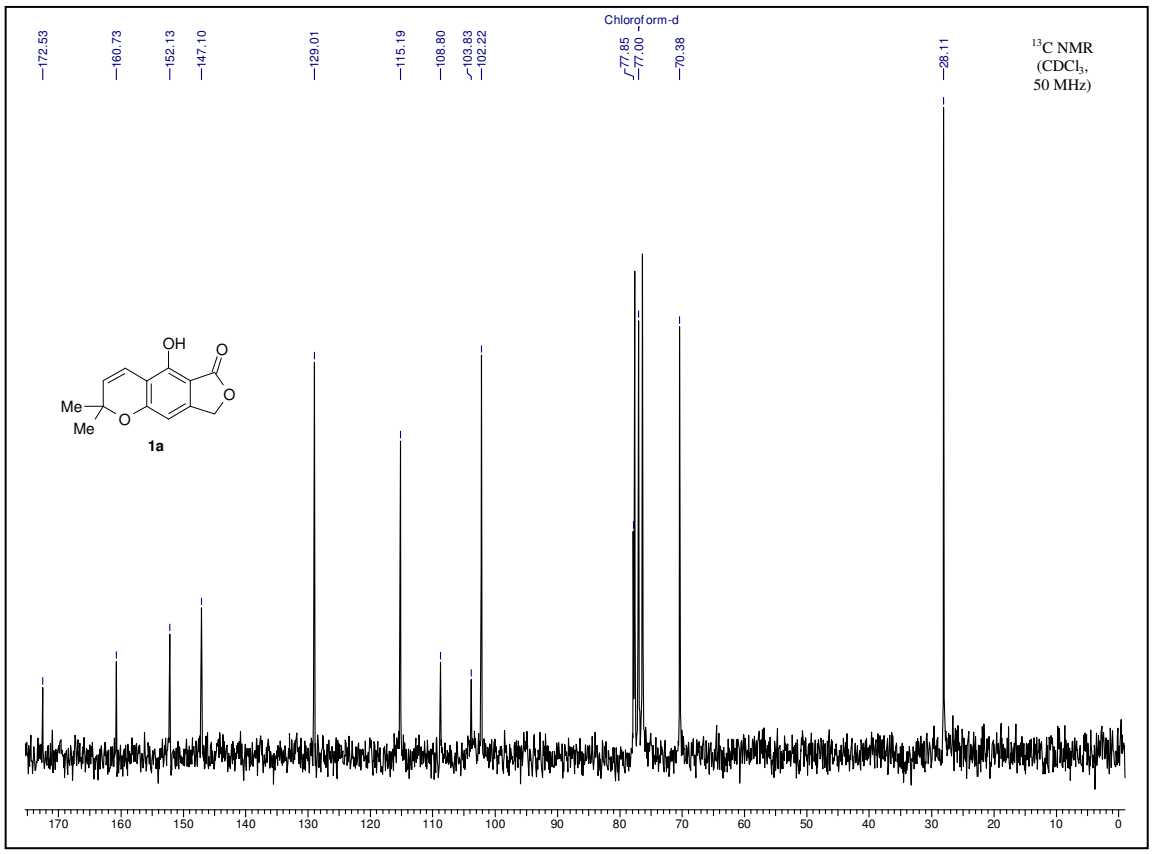
2A.6 Selected Spectra

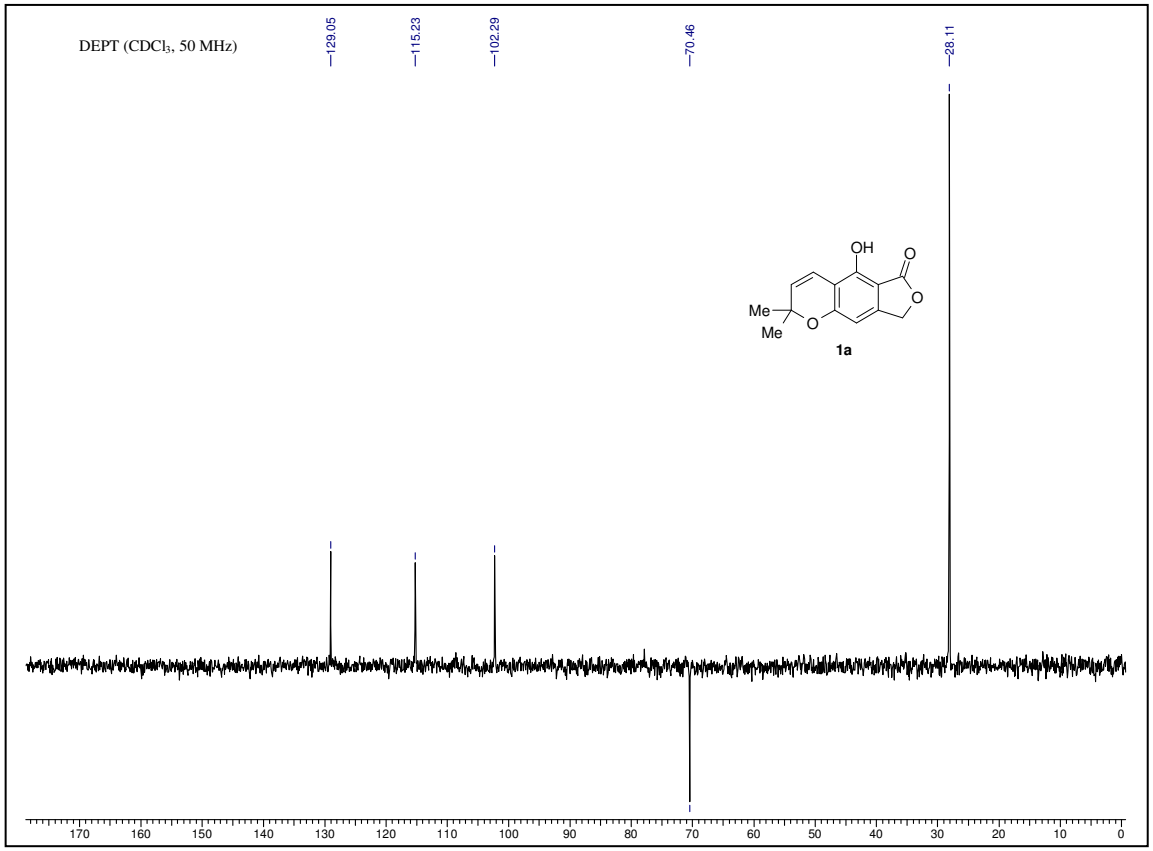

Methanol-d4
6.41
6.31
5.19
4.87
3.34
^{1}H NMR
(Methanol-d_4,
500 MHz)
OH
O
O
HO
3
1.02
2.08
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

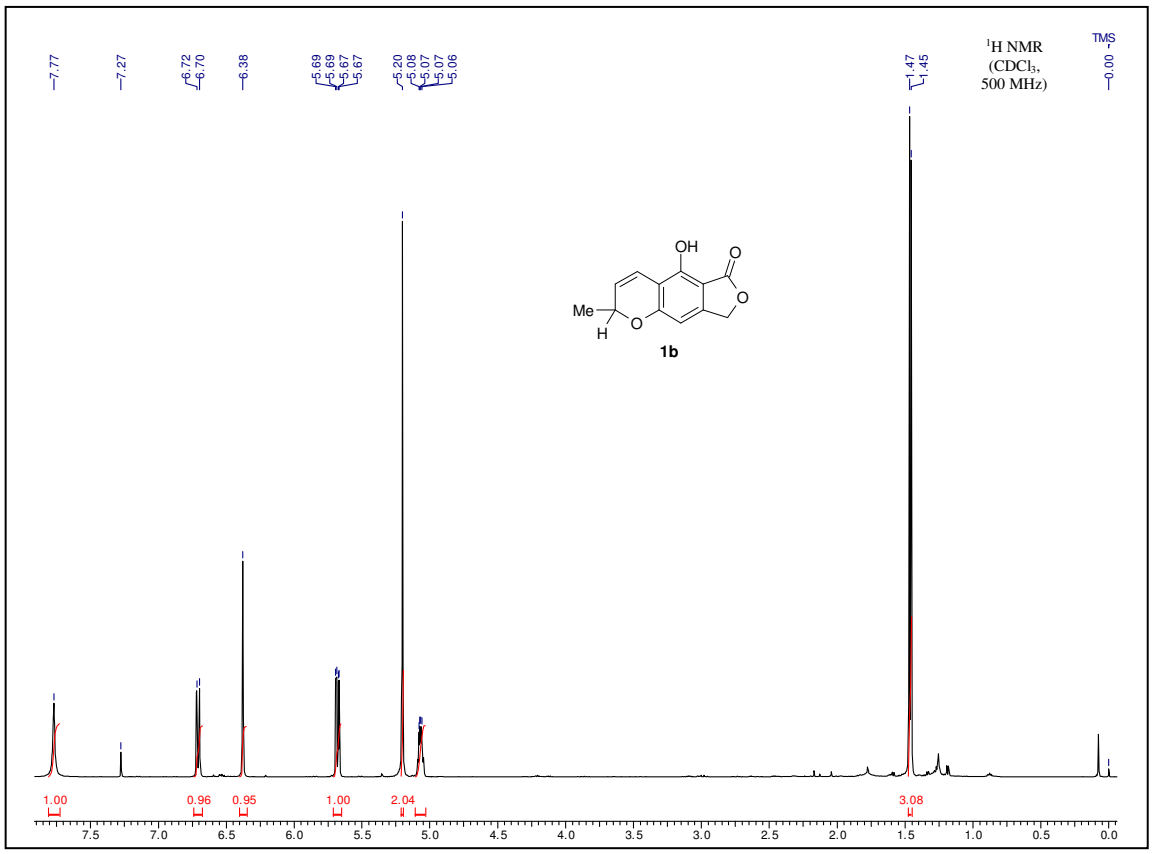

Methanol-d4
172.83
167.00
159.71
152.67
104.39
103.43
101.60
70.65
49.05
^{13}C NMR
(Methanol-d_4,
125 MHz)
OH
O
O
HO
3
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

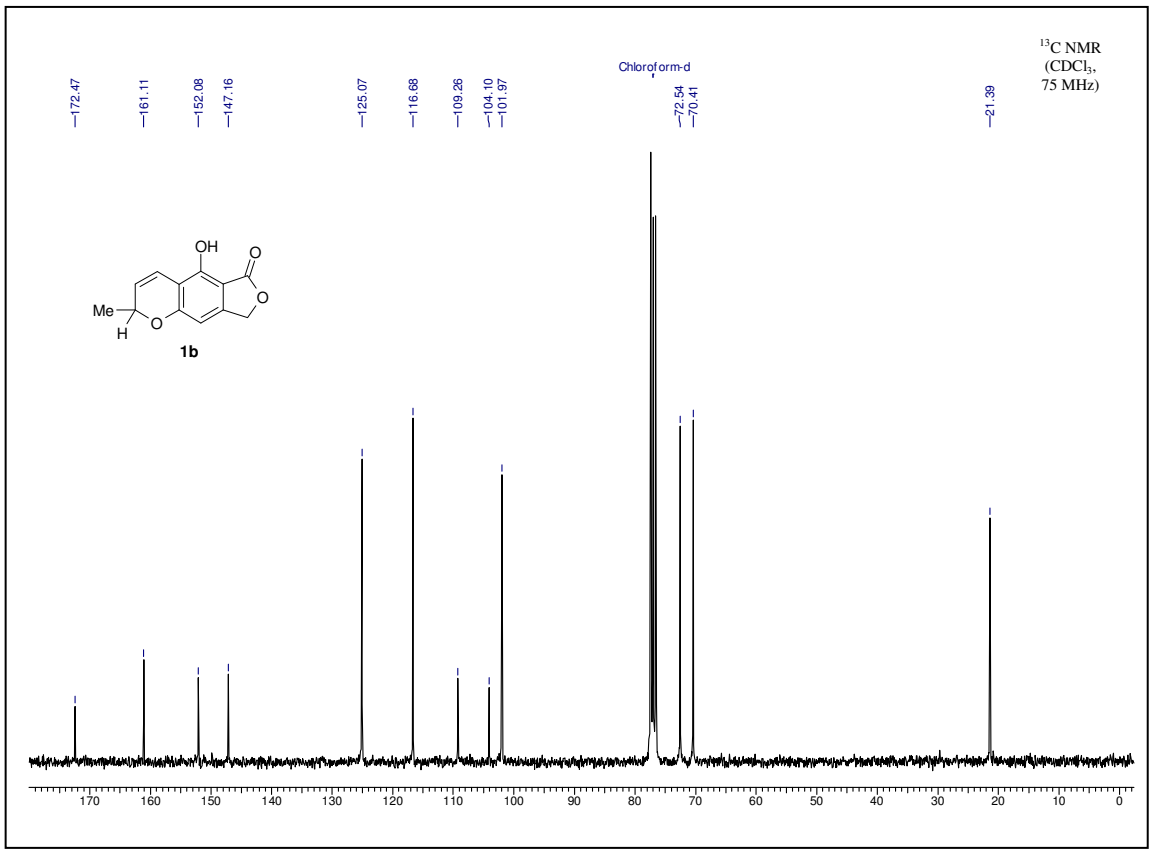

103.42
101.59
70.65
DEPT
(Methanol-d_4,
125 MHz)
OH
O
O
HO
3
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

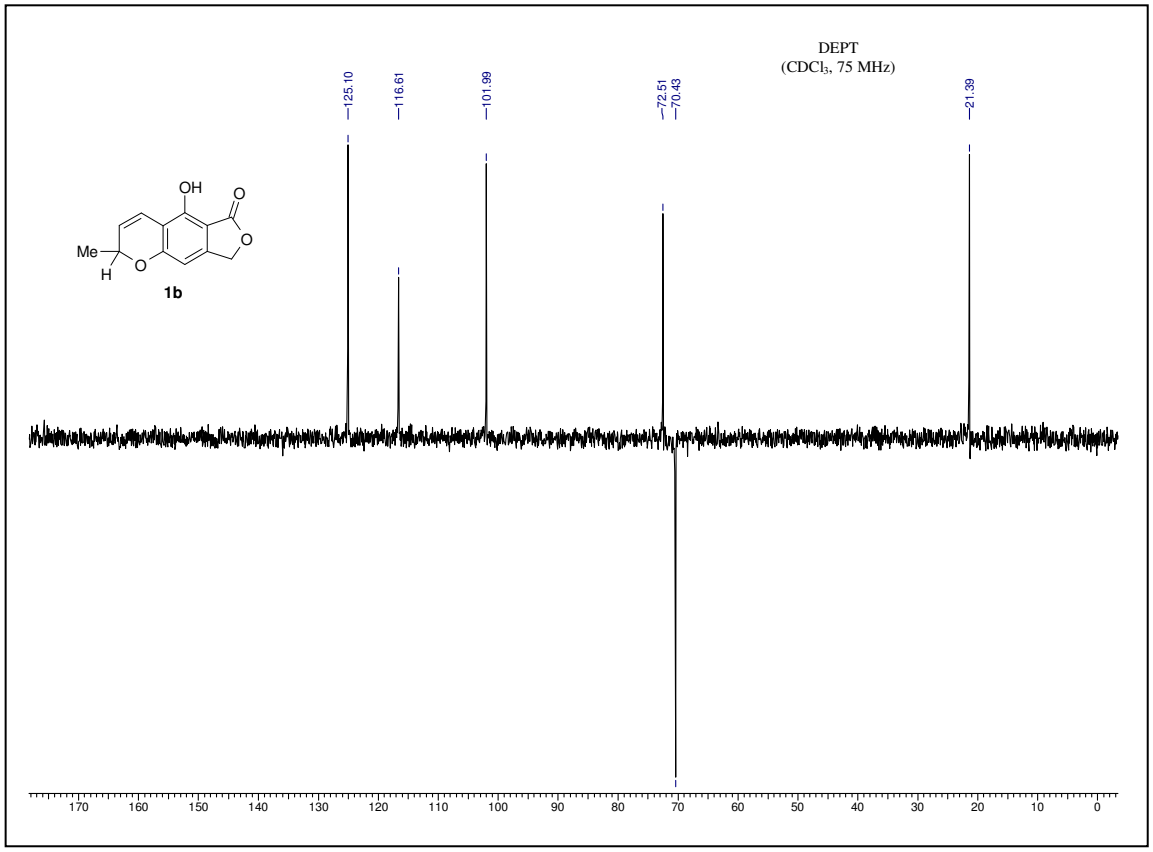

7.78
7.27
6.70
6.64
6.39
5.67
5.62
5.22
1.46
TMS
0.00
^{1}H NMR
($CDCl_3$,
200 MHz)
OH
O
O
Me
Me
O
1a
0.98
0.99
0.96
1.00
2.01
6.02
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

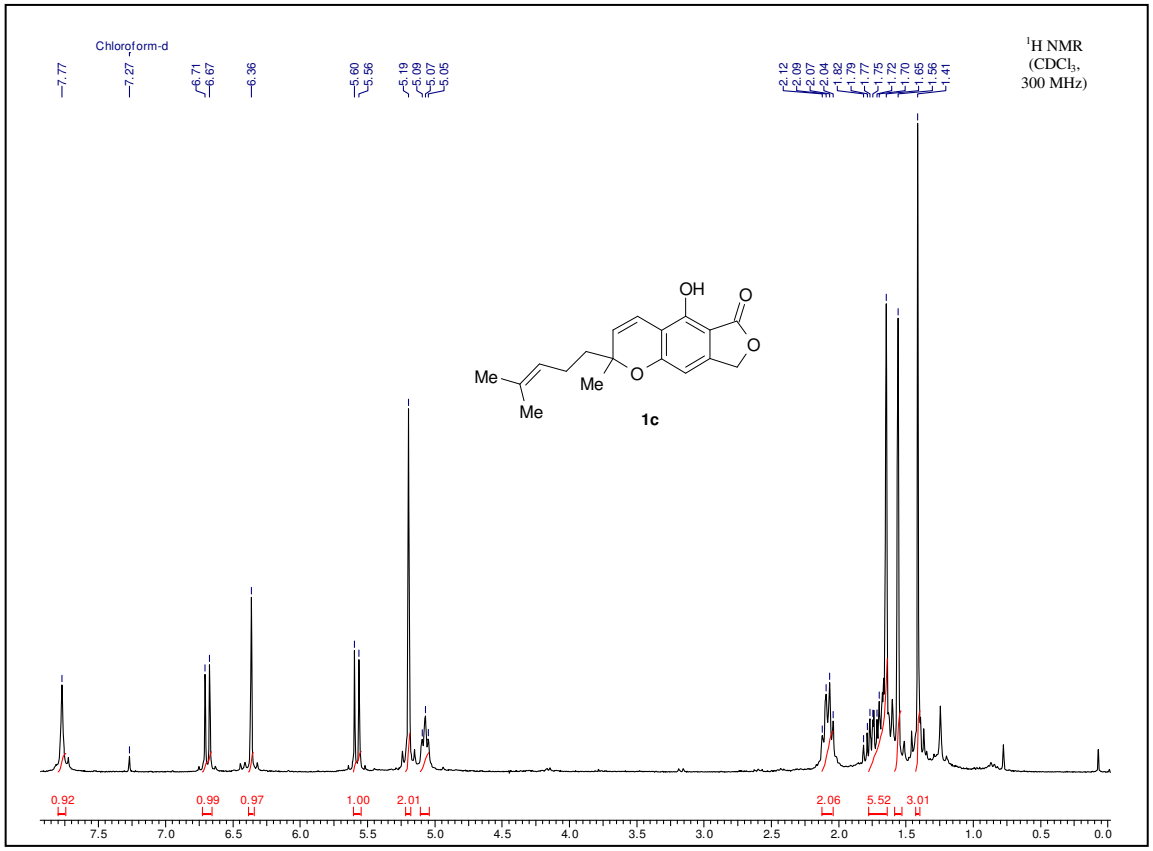

^{13}C NMR
(CDCl$_3$,
50 MHz)
Chloroform-d
172.53
160.73
152.13
147.10
129.01
115.19
108.80
103.83
102.22
77.85
77.00
70.38
28.11
OH
O
O
Me
Me
O
1a
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

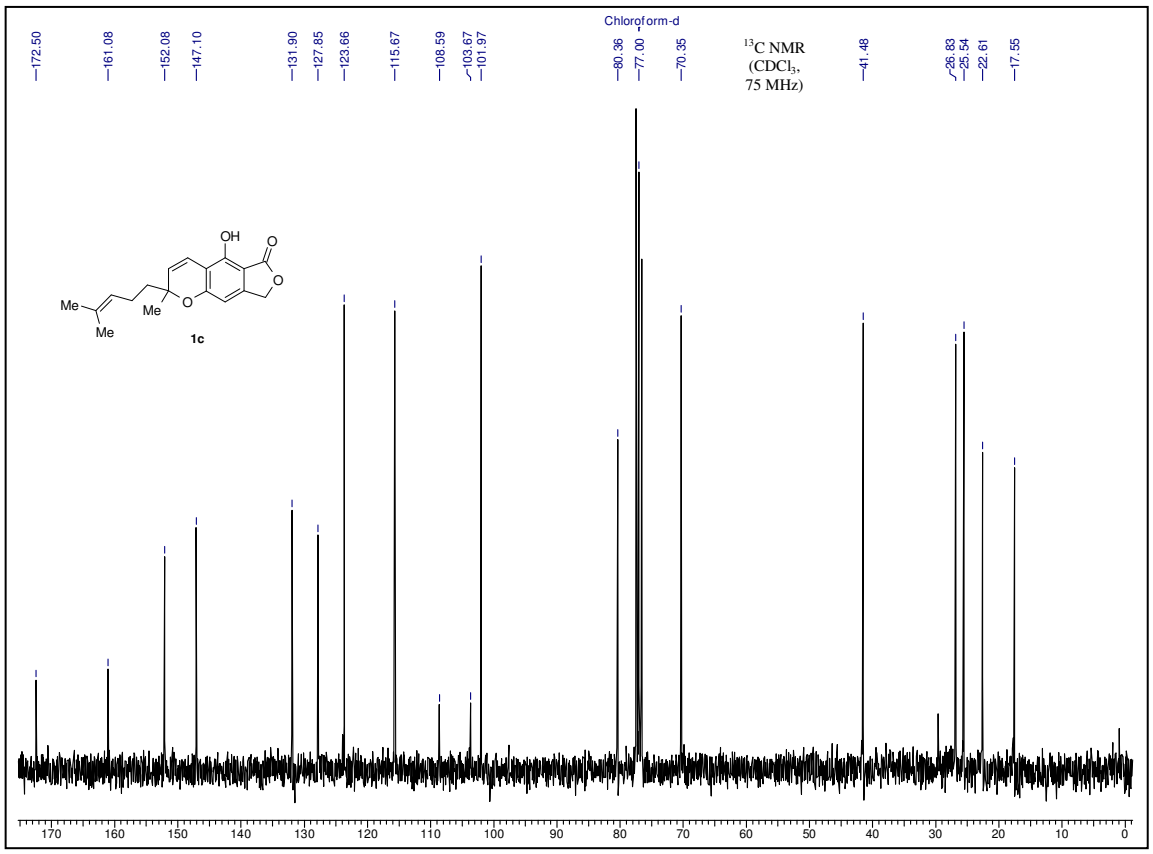

DEPT (CDCl$_3$, 50 MHz)
129.05
115.23
102.29
70.46
28.11
OH
O
O
Me
Me
O
1a
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

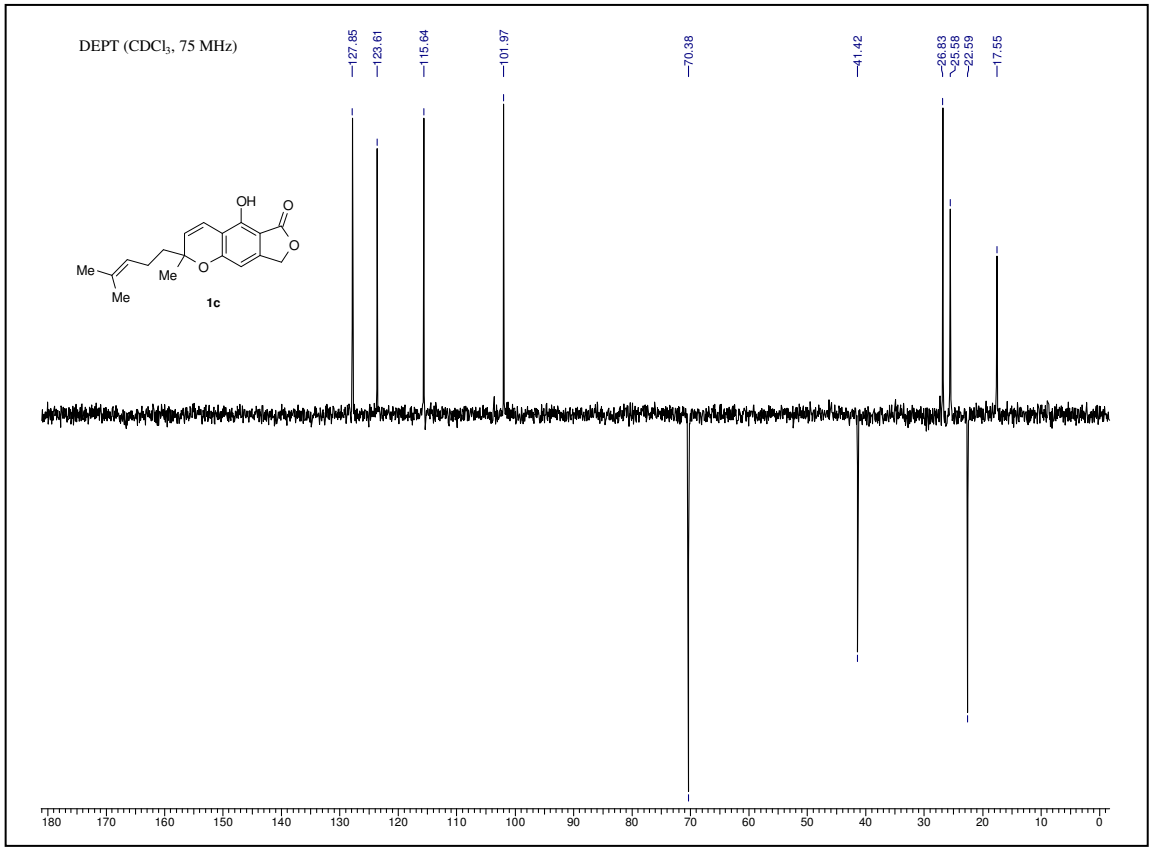

^{1}H NMR
($CDCl_3$,
500 MHz)
TMS
7.77
7.27
6.72
6.70
6.38
5.69
5.69
5.67
5.67
5.20
5.08
5.07
5.07
5.06
1.47
1.45
0.00
OH
O
Me
H
O
O
1b
1.00
0.96
0.95
1.00
2.04
3.08
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

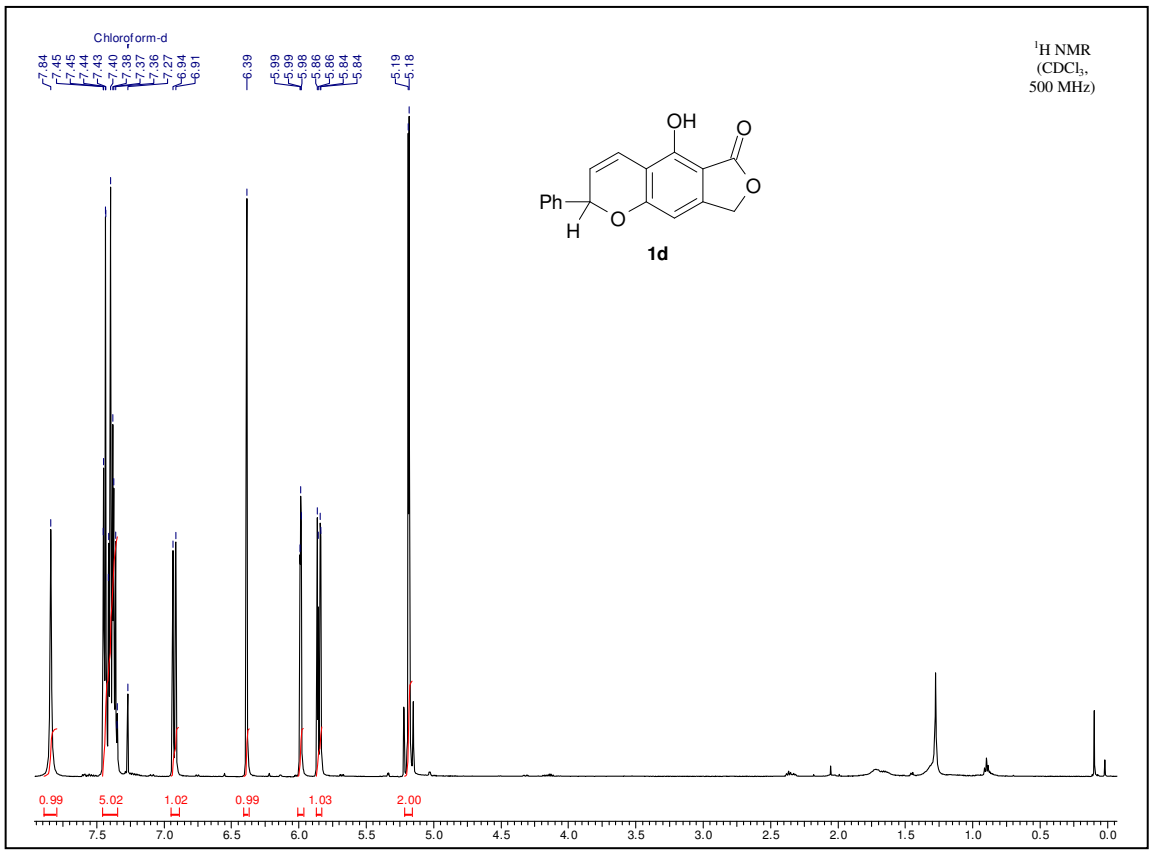

^{13}C NMR
($CDCl_3$,
75 MHz)
Chloroform-d
172.47
161.11
152.08
147.16
125.07
116.68
109.26
104.10
101.97
72.54
70.41
21.39
OH
O
Me
H
O
O
1b
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

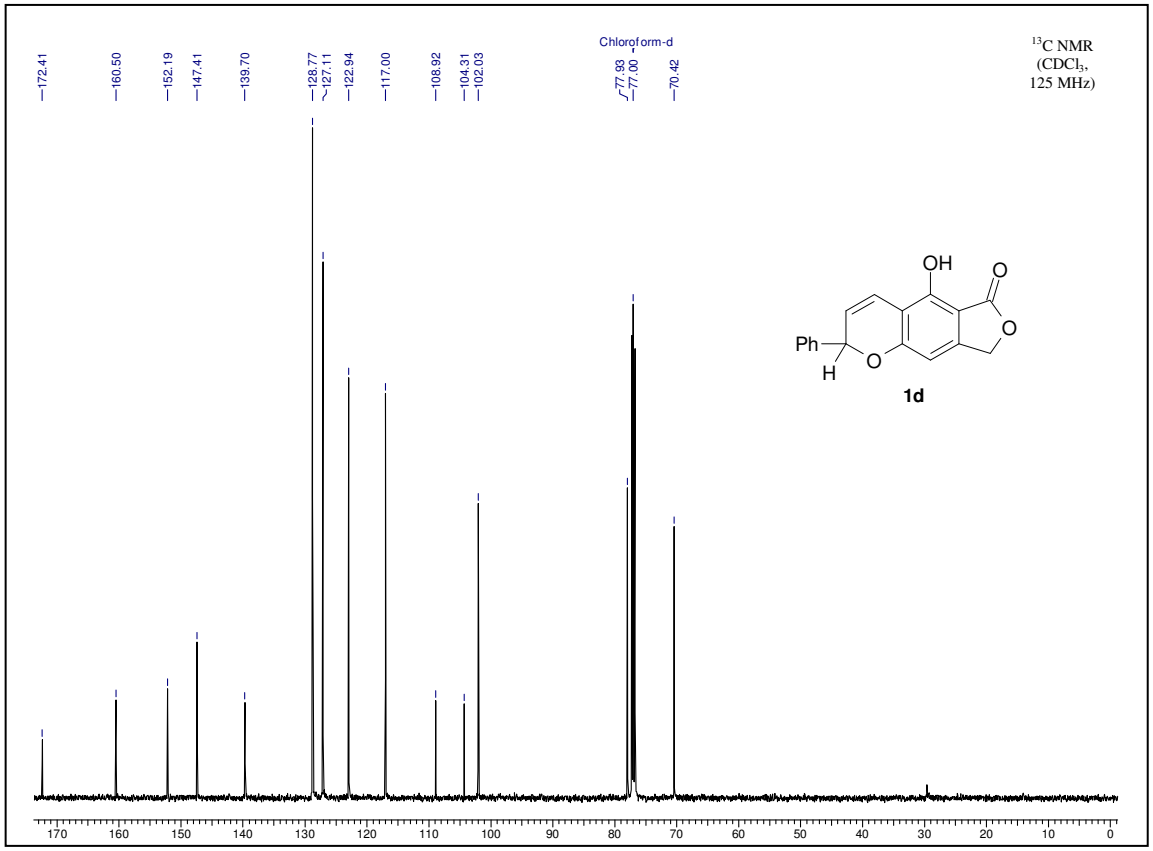

DEPT
(CDCl3, 75 MHz)
125.10
116.61
101.99
72.51
70.43
21.39
OH
O
Me
O
H
O
1b
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

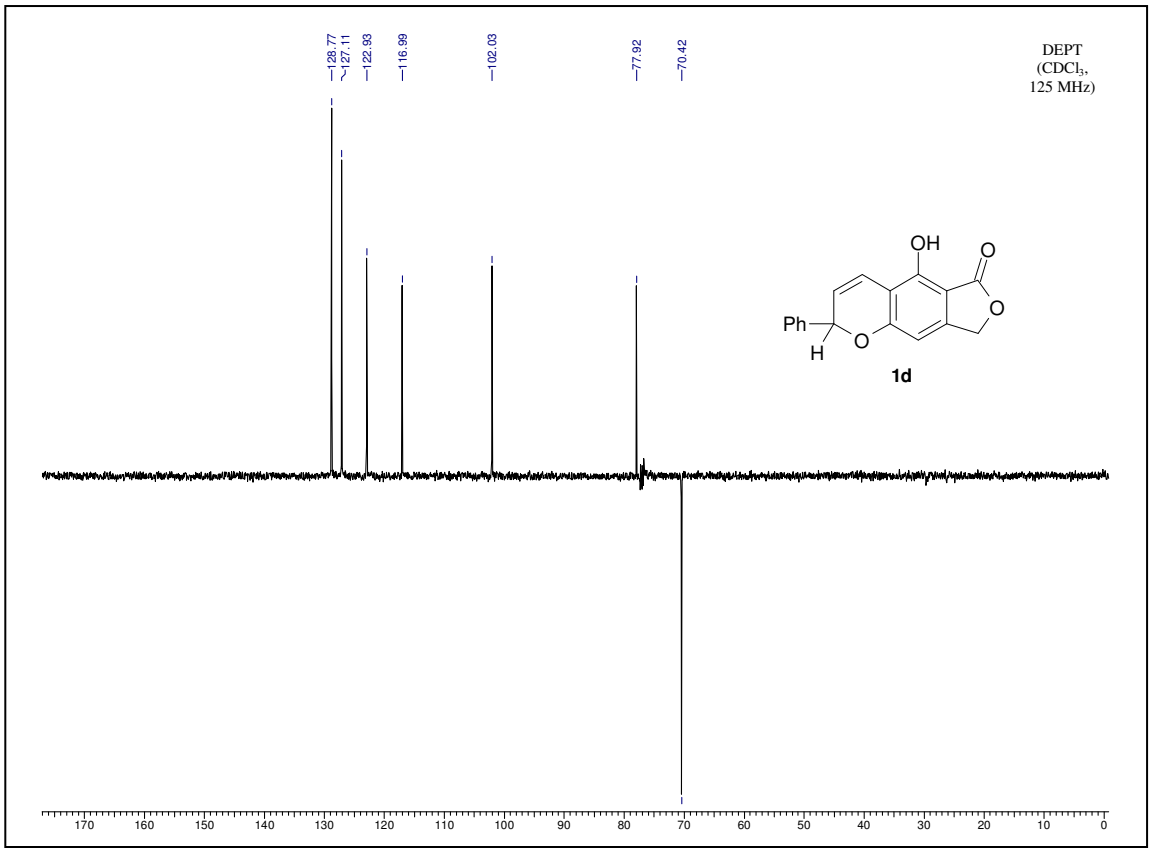

Chloroform-d
7.77
7.27
6.71
6.67
6.36
5.60
5.56
5.19
5.09
5.07
5.05
2.12
2.09
2.07
2.04
1.82
1.79
1.77
1.75
1.72
1.70
1.65
1.56
1.41
1H NMR
(CDCl3,
300 MHz)
OH
O
O
Me
Me
O
Me
1c
0.92
0.99
0.97
1.00
2.01
2.06
5.52
3.01
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

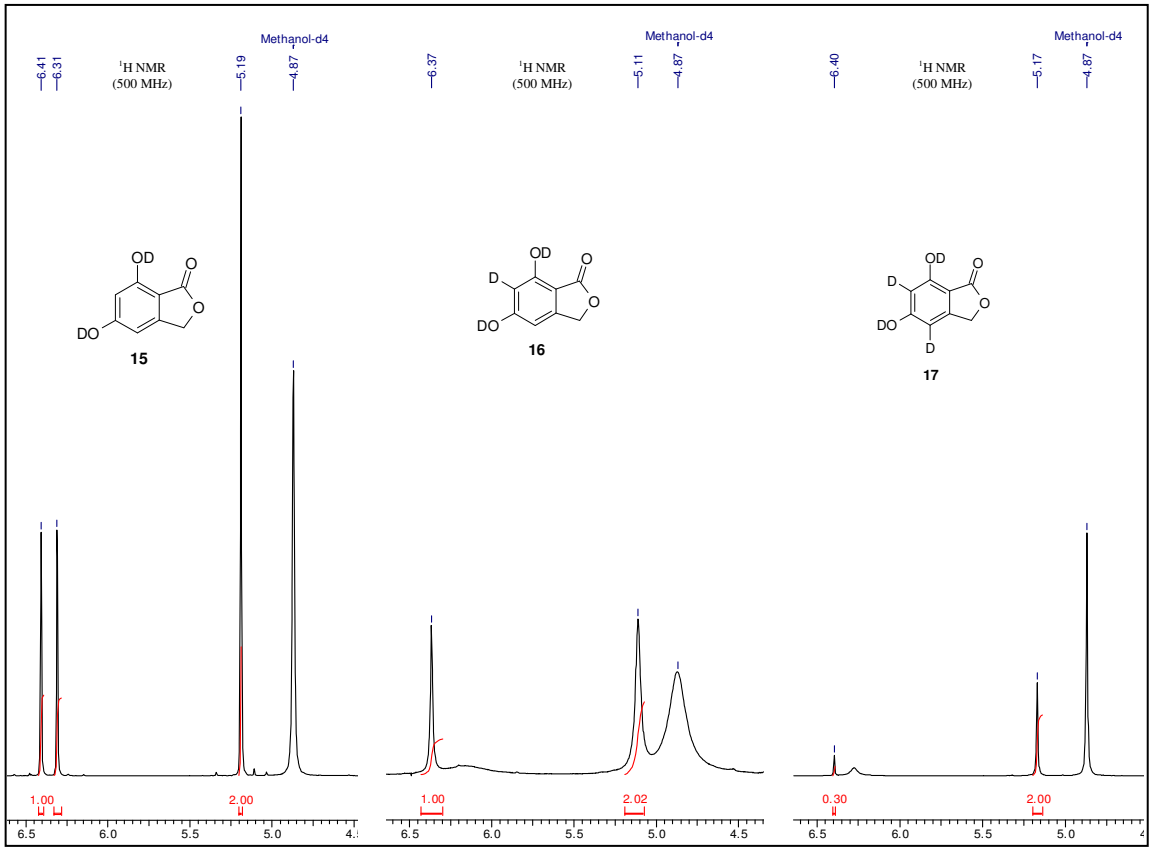

Chloroform-d
172.50
161.08
152.08
147.10
131.90
127.85
123.66
115.67
108.59
103.67
101.97
80.36
77.00
70.35
^{13}C NMR
($CDCl_3$,
75 MHz)
41.48
26.83
25.54
22.61
17.55
OH
O
O
Me
Me
Me
O
1c
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

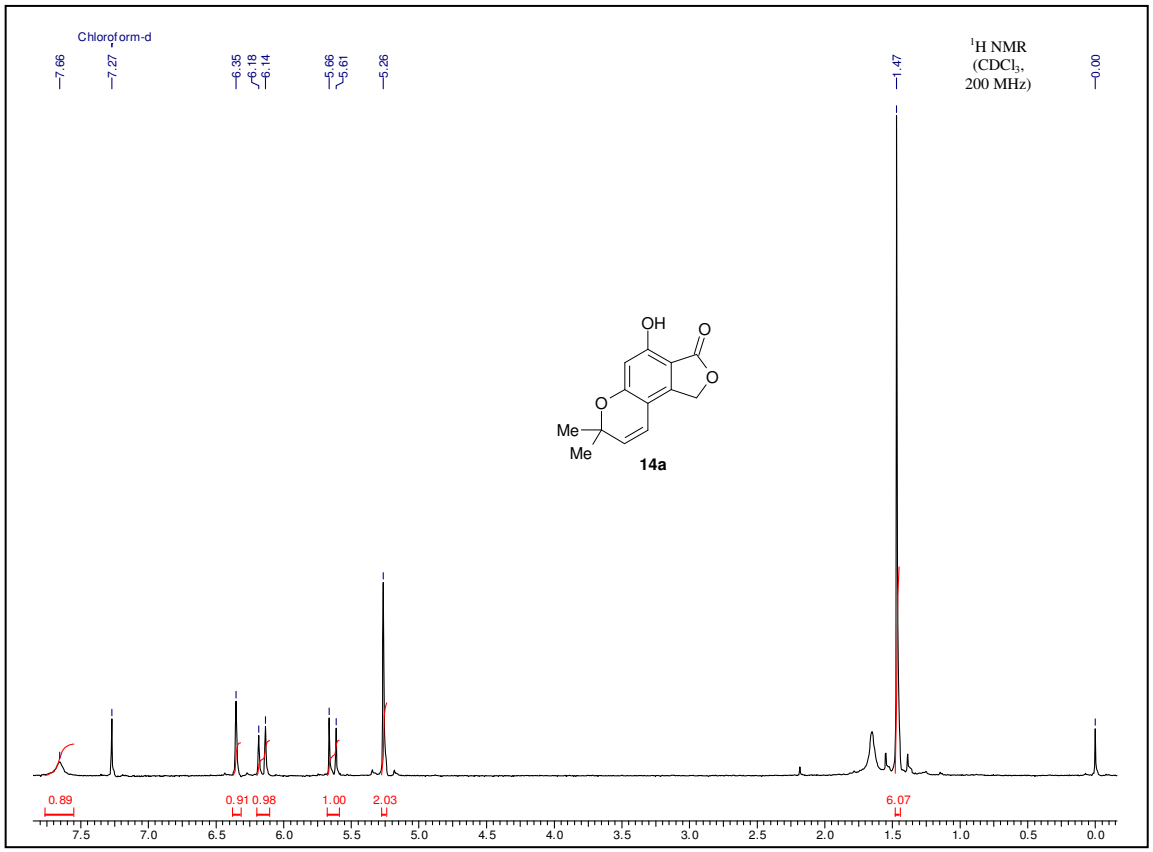

DEPT ($CDCl_3$, 75 MHz)
127.85
123.61
115.64
101.97
70.38
41.42
26.83
25.58
22.59
17.55
OH
O
O
Me
Me
Me
O
1c
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

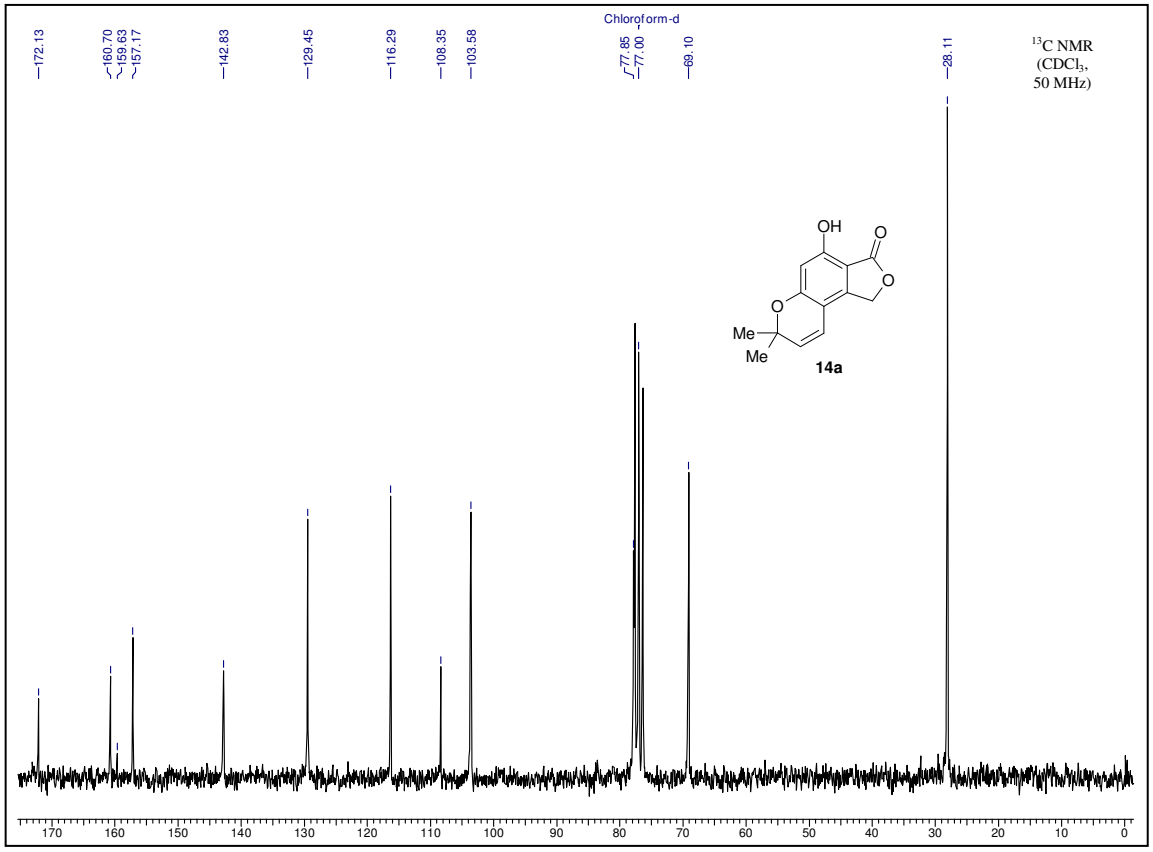

Chloroform-d
7.84
7.45
7.45
7.44
7.43
7.40
7.38
7.37
7.36
7.27
6.94
6.91
6.39
5.99
5.99
5.98
5.86
5.86
5.84
5.84
5.19
5.18
0.99
5.02
1.02
0.99
1.03
2.00
^{1}H NMR
($CDCl_3$,
500 MHz)
OH
O
O
Ph
O
H
1d

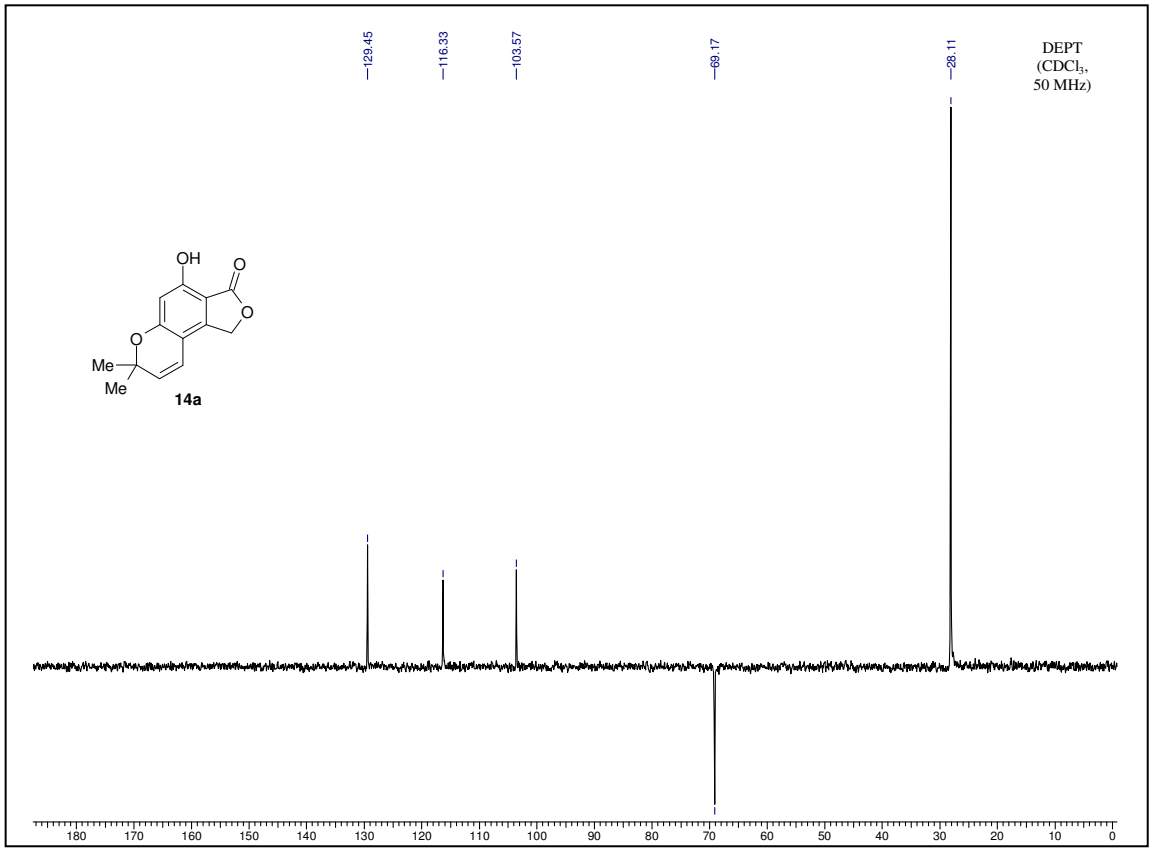

172.41
160.50
152.19
147.41
139.70
128.77
127.11
122.94
117.00
108.92
104.31
102.03
Chloroform-d
77.93
77.00
70.42
^{13}C NMR
($CDCl_3$,
125 MHz)
OH
O
O
Ph
O
H
1d

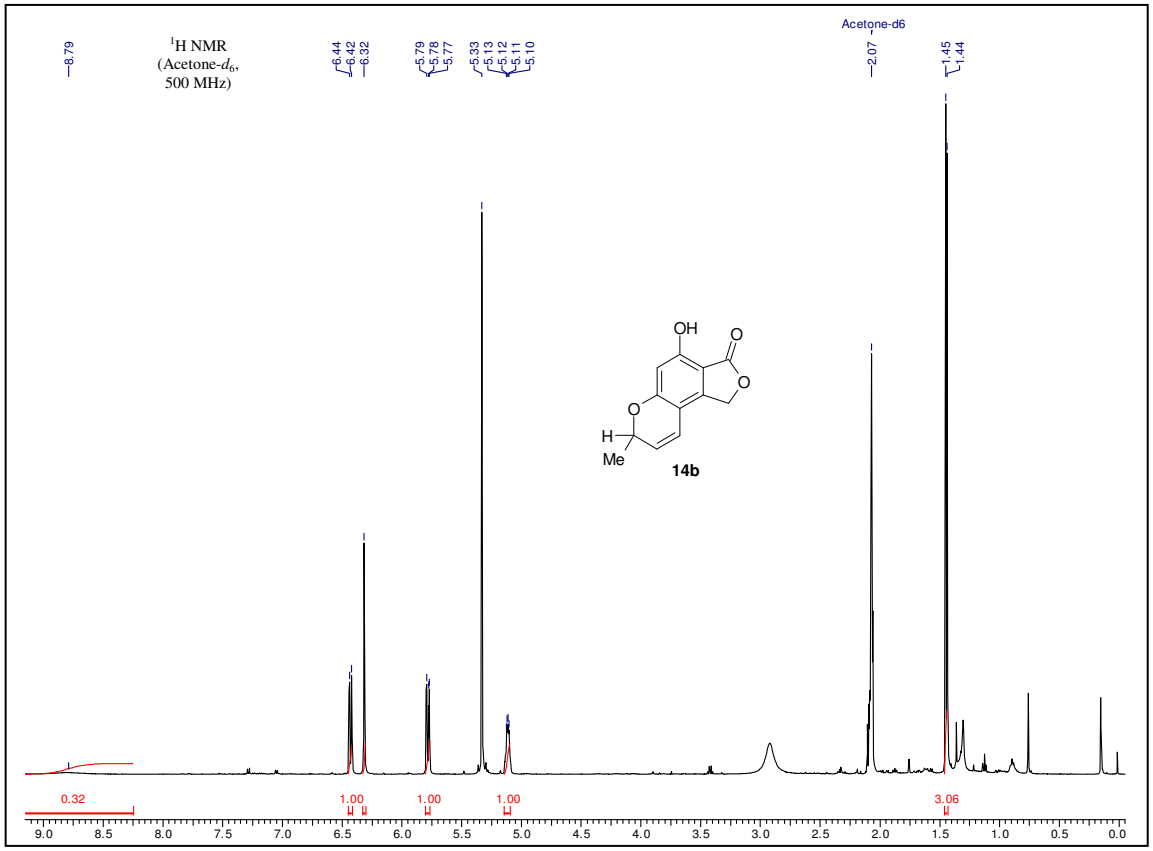

128.77
127.11
122.93
116.99
102.03
77.92
70.42
DEPT
(CDCl3,
125 MHz)
OH
O
O
Ph
H
O
1d

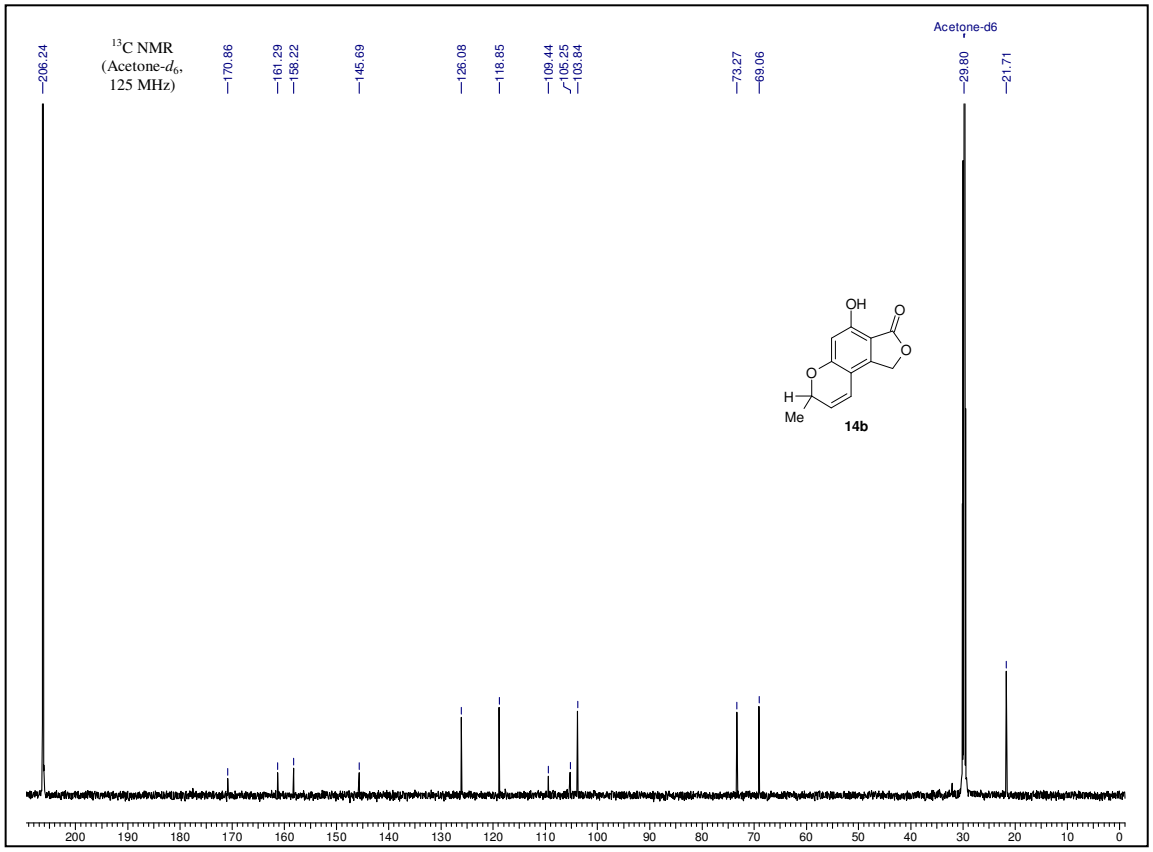

Methanol-d4
6.41
6.31
1H NMR
(500 MHz)
5.19
4.87
OD
O
O
DO
15
Methanol-d4
6.37
1H NMR
(500 MHz)
5.11
4.87
OD
O
D
O
DO
16
Methanol-d4
6.40
1H NMR
(500 MHz)
5.17
4.87
OD
O
D
O
DO
D
17
1.00
2.00
1.00
2.02
0.30
2.00


Chloroform-d
7.66
7.27
6.35
6.18
6.14
5.66
5.61
5.26
1.47
0.00
^{1}H NMR
($CDCl_3$,
200 MHz)
OH
O
O
O
Me
Me
14a
0.89
0.91
0.98
1.00
2.03
6.07
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


Chloroform-d
172.13
160.70
159.63
157.17
142.83
129.45
116.29
108.35
103.58
77.85
77.00
69.10
28.11
^{13}C NMR
($CDCl_3$,
50 MHz)
OH
O
O
O
Me
Me
14a
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


129.45
116.33
103.57
69.17
28.11
DEPT
(CDCl3,
50 MHz)
OH
O
O
O
Me
Me
14a
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0


8.79
1H NMR
(Acetone-d6,
500 MHz)
6.44
6.42
6.32
5.79
5.78
5.77
5.33
5.13
5.12
5.11
5.10
Acetone-d6
2.07
1.45
1.44
OH
O
O
O
H
Me
14b
0.32
1.00
1.00
1.00
3.06
9.0 8.5 8.0 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


^{13}C NMR
(Acetone-d_6,
125 MHz)
206.24
170.86
161.29
158.22
145.69
126.08
118.85
109.44
105.25
103.84
73.27
69.06
Acetone-d6
29.80
21.71
OH
O
O
O
H
Me
14b
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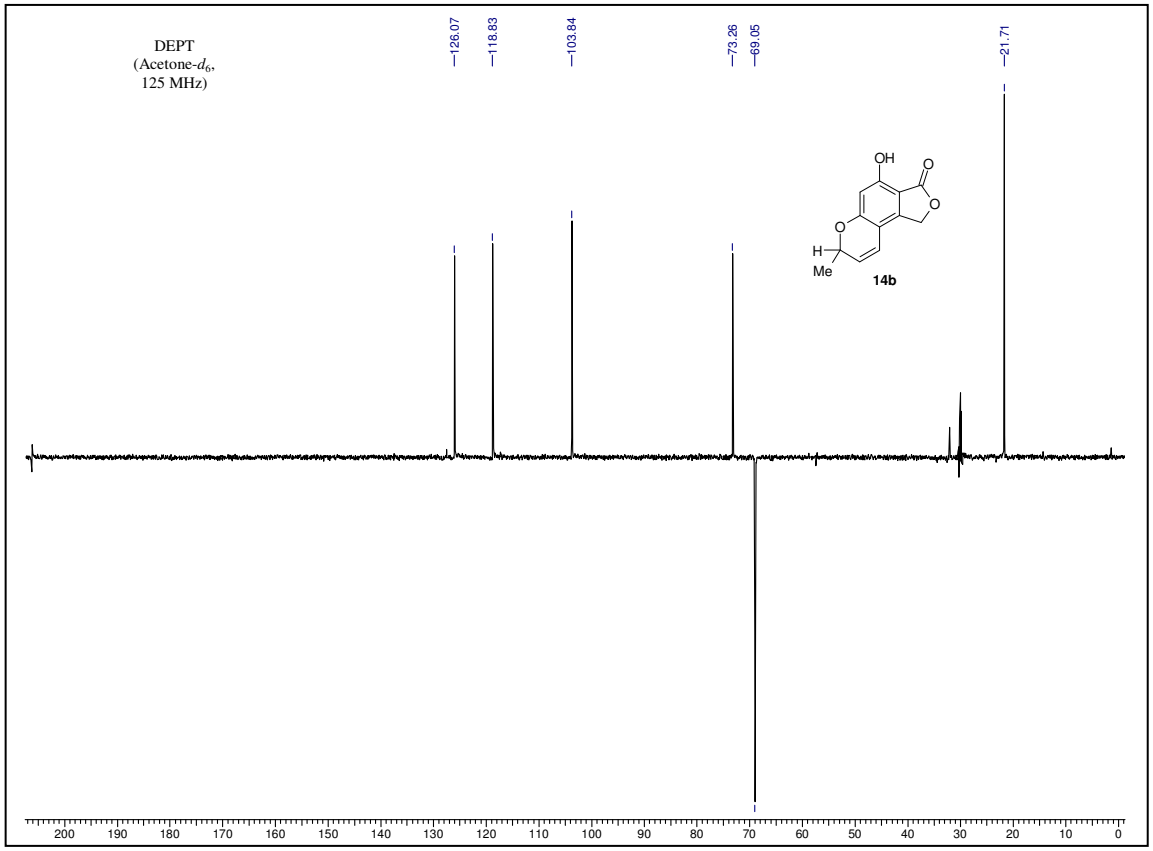
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125 MHz)
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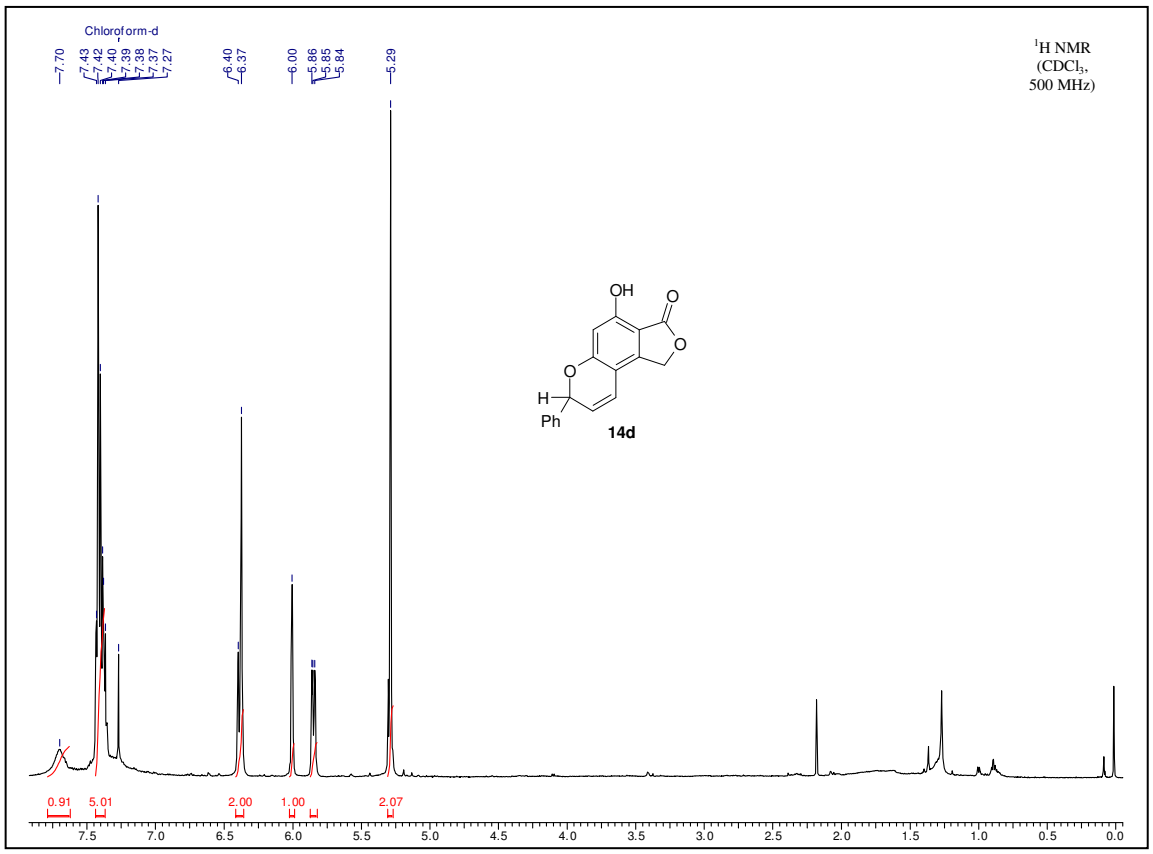
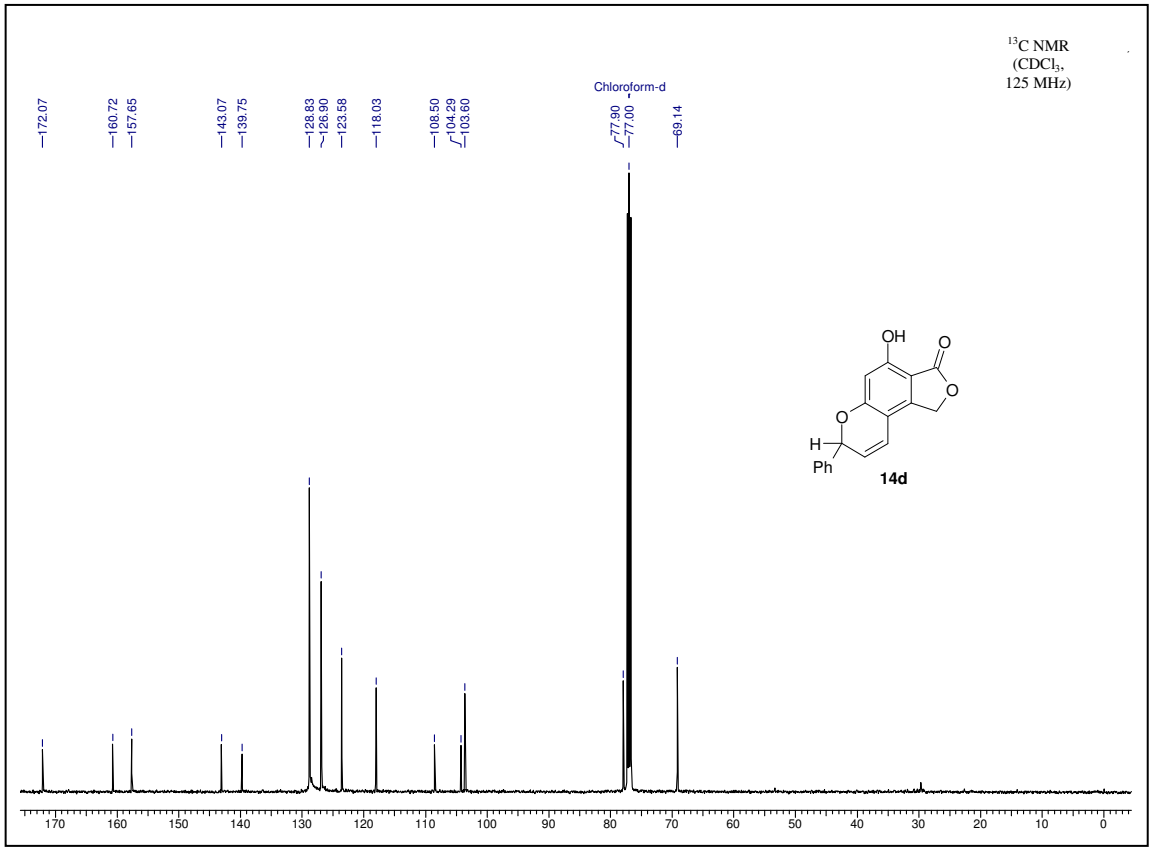
118.83
103.84
73.26
69.05
21.71
OH
O
O
O
H
Me
14b
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0


Chloroform-d
7.70
7.43
7.42
7.40
7.39
7.38
7.37
7.27
6.40
6.37
6.00
5.86
5.85
5.84
5.29
^{1}H NMR
($CDCl_3$,
500 MHz)
OH
O
O
O
H
Ph
14d
0.91
5.01
2.00
1.00
2.07
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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157.65
143.07
139.75
128.83
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123.58
118.03
108.50
104.29
103.60
77.90
77.00
69.14
OH
O
O
O
H
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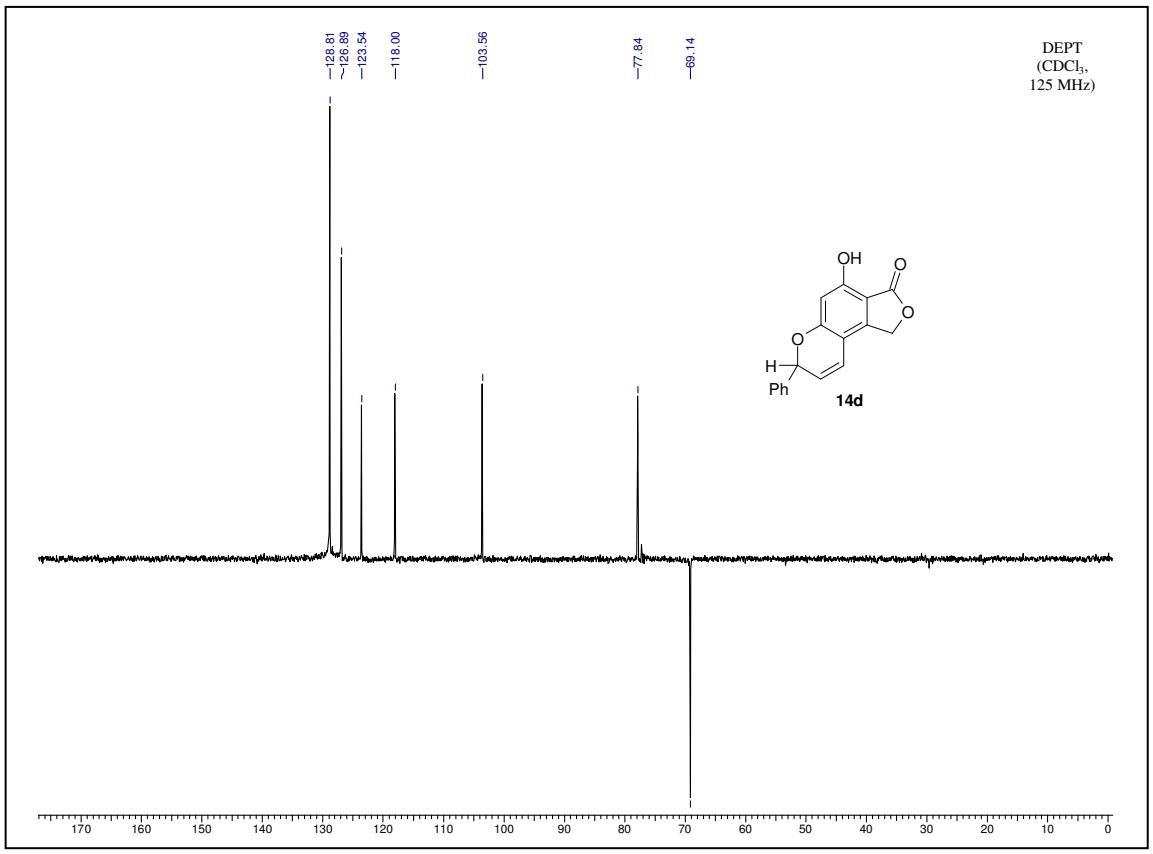
90
80
70
60
50
40
30
20
10
0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123.54
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77.84
69.14
DEPT
(CDCl3,
125 MHz)
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O
O
O
H
Ph
14d
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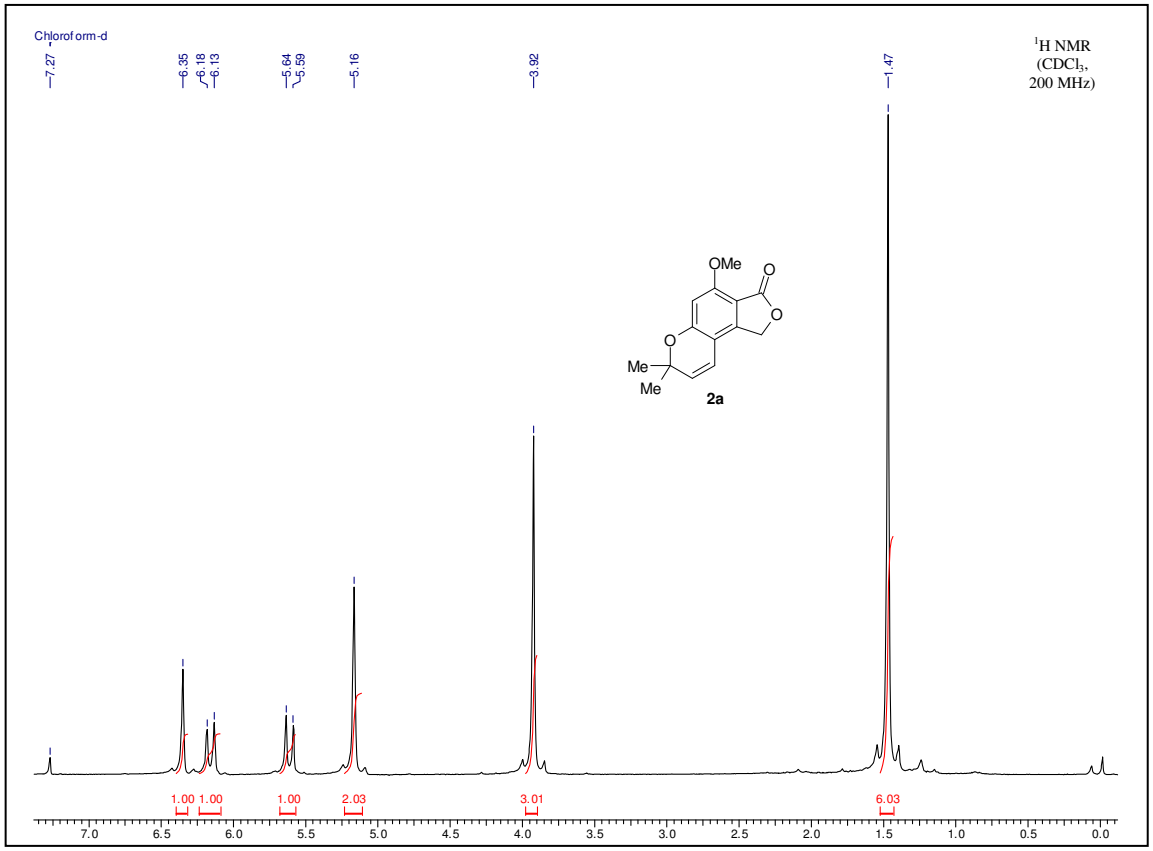
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0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7.27
6.35
6.18
6.13
5.64
5.59
5.16
3.92
1.47
1H NMR
(CDCl3,
200 MHz)
OMe
O
O
O
Me
Me
2a
1.00
1.00
1.00
2.03
3.01
6.03
7.0
6.5
6.0
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5.0
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4.0
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2.0
1.5
1.0
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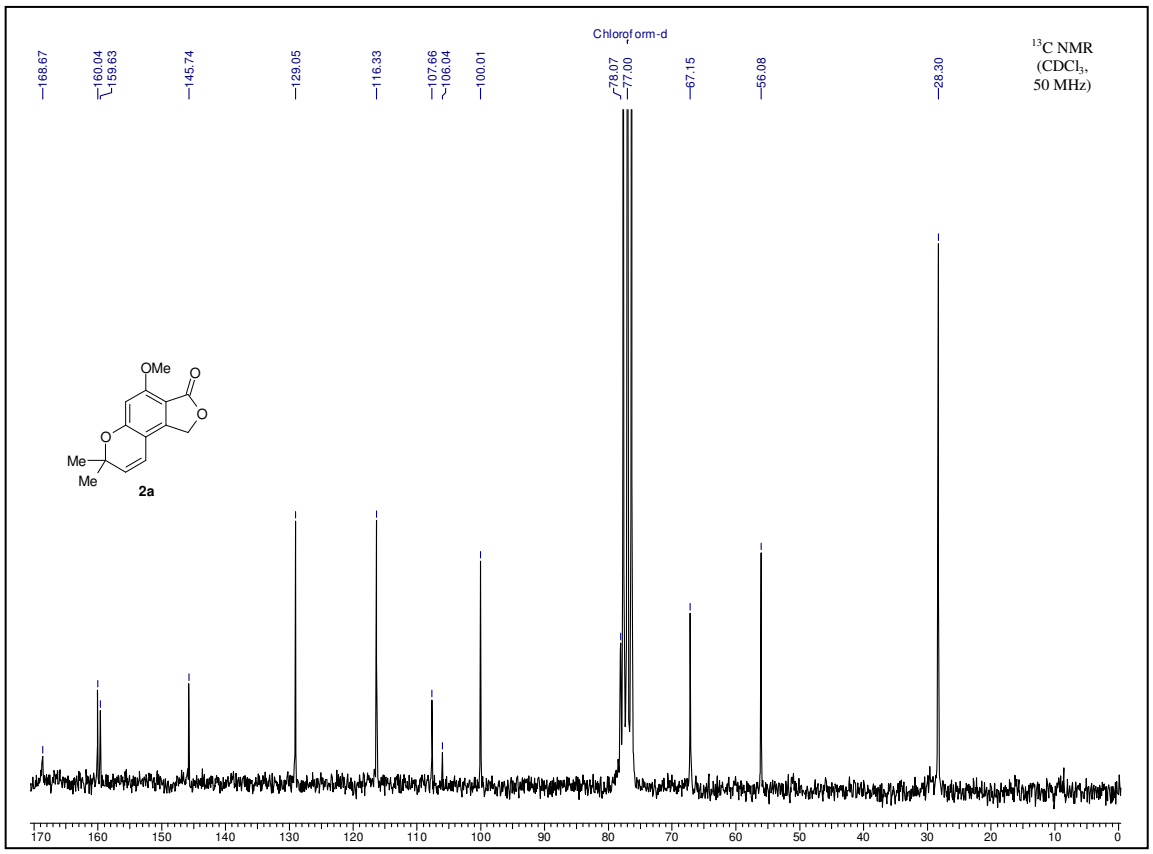
0.0


Chloroform-d
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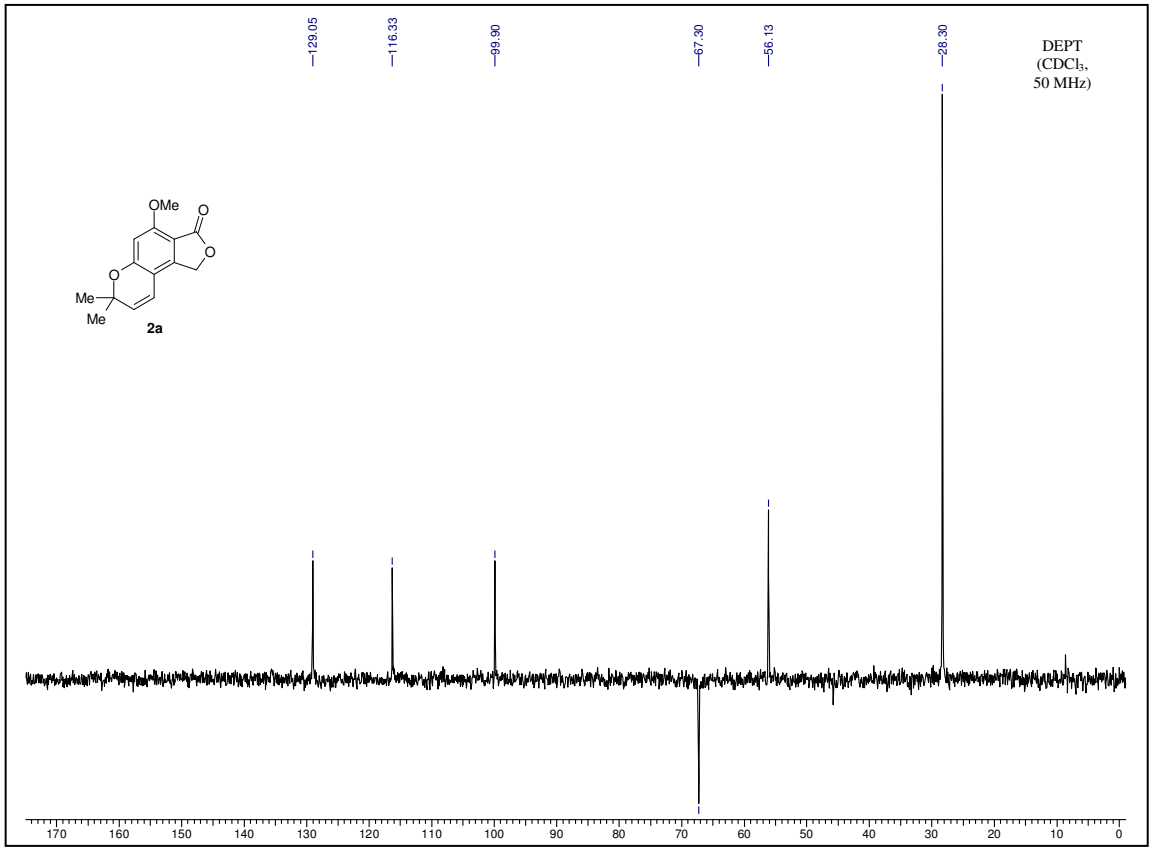
77.00
67.15
56.08
28.30
^{13}C NMR
($CDCl_3$,
50 MHz)
OMe
O
O
O
Me
Me
2a
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0


129.05
116.33
99.90
67.30
56.13
28.30
DEPT
($CDCl_3$,
50 MHz)
OMe
O
O
O
Me
Me
2a
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

2A.7 References and Footnote

1. (a) Cui, C.-B.; Ubukata, M.; Kekaya, H.; Onose, R.; Okada, G.; Takahasi, I.; Isono, K.; Osada, H. *J. Antibiotics* **1996**, *49*, 216. (b) Fukami, A.; Nakamura, T.; Kim, Y.-P.; Shiomi, K.; Hayashi, M.; Nagai, T.; Yomada, H.; Komiyama, K. *J. Antibiotics* **2000**, *53*, 1215. (c) Kinoshita, K.; Sasaki, T.; Awata, M.; Takada, M.; Yaginuma, S. *J. Antibiotics* **1997**, *50*, 961. (d) Dekker, K. A.; Inagaki, T.; Gootz, T. D.; Kaneda, K.; Nomura, E.; Sakakibara, T.; Sakemi, S.; Sugie, Y.; Yamauchi, Y.; Yoshikawa, N.; Kojima, N. *J. Antibiotics* **1997**, *50*, 833. (e) Furstner, A.; Thiel, O. R.; Kindler, N.; Bartkowska, B. *J. Org. Chem*. **2000**, *65*, 7990. (f) Nicolaou, K. C.; Winssinger, N.; Pastor, J.; Murphy, F. *Angew. Chem. Int. Ed*. **1998**, *37*, 2534 and references cited therein 1a-f.
2. (a) Nicolaou, K. C.; Evans, R. M.; Roecker, A. J.; Hughes, R.; Downes, M.; Pfefferkorn, J. A. *Org. Biomol. Chem.* **2003**, *1*, 908. (b) Nicolaou, K. C.; Pfefferkorn, J. A.; Cao, G.-Q. *Angew. Chem. Int. Ed*. **2000**, *39*, 734. (c) Nicolaou, K. C.; Cao, G.-Q.; Pfefferkorn, J. A. *Angew. Chem. Int. Ed*. **2000**, *39*, 739. (d) Nicolaou, K. C.; Pfefferkorn, J. A.; Barluenga, S.; Mitchell, H. J.; Roecker, A. J.; Cao, G.-Q. *J. Am. Chem. Soc*. **2000**, *122*, 9968.
3. Matsumoto, K.; Nagashima, K.; Kamigauchi, T.; Kawamura, Y.; Yasuda, Y.; Ishii, K.; Uotani, N.; Sato, T.; Nakai, H.; Terui, Y.; Kikuchi, J.; Ikenisi, Y.; Yoshida, T.; Kato, T.; Itazaki, H. *J. Antibiotics* **1995**, *48*, 439.
4. (a) Nishikawa, M.; Tsurumi, Y.; Murai, H.; Yoshida, K.; Okamoto, M.; Takase, S.; Tanaka, H.; Hirota, H.; Hashimoto, M.; Kohsaka, M. *J. Antibiotics* **1991**, *44*, 130. (b) Ozasa, T.; Yoneda, T.; Hirasawa, M.; Suzuki, K.; Tanaka, K.; Kadota, S.; Iwanami, M. *J. Antibiotics* **1991**, *44*, 768.
5. Kinoshita, J. H. Mechanism initiating cataract formation. *Proctor Lecture Invest. Ophthalmol*. **1974**, *13*, 713.
6. Gabbay, K. H. The sorbitol pathway and the complications of diabetes. *N. Engl. J. Med*. **1973**, *288*, 831.
7. Kuwabara, T.; Cogan, D. G. Retinal vascular patterns 4. Mural cells of the retinal capillaries. *Arch. Ophthalmol*. **1963**, *69*, 492.
8. Akagi, Y.; Kador, P. F.; Kuwabara, T.; Kinoshita, J. H. Aldose reductase in human retinal mural cells. *Invest. Ophthalmol. Visual Sci*. **1983**, *24*, 1516.

9. Gabbay, K. H. Hyperglycemia; polyol metabolism and complications of diabetes mellitus. *Annu. Rev. Med*. **1975**, *26*, 521.
10. Jakupovic, J.; Schuster, A.; Sun, H.; Bolman, F.; Bhakuni, D. S. *Phytochemistry* **1987**, *26*, 580.
11. Mali, R. S.; Babu, K. N. *J. Chem. Research (S)* **1998**, 292.
12. (a) Nozawa, Y.; Ito, M.; Sugawara, K.; Hanada, K.; Mizoue, K. *J. Antibiotics* **1997**, *50*, 641. (b) Kosin, J.; Ruangrungsi, N.; Ito, C.; Furukawa, H. *Phytochemistry* **1998**, *47*, 1167. (c) Paramana, D.; Lajis, N. H.; Mackeen, M. M.; Ali, A. M.; Aimi, A. N.; Kitajima, M.; Takayama, H. *J. Nat. Prod*. **2001**, *64*, 976. (d) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc*. **1998**, *120*, 9074. (e) Daikonya, A.; Katsuki, S.; Wu, J.-B.; Kitanaka, S. *Chem. Pharm. Bull*. **2002**, *50*, 1566. (f) Tahara, S.; Ibrahim, R. K. *Phytochemistry* **1995**, *38*, 1073 and references cited therein 12a-f.
13. Talapatra, B.; Roy, M. K.; Talaptra, S. K. *Indian J. Chem*. **1980**, *19B*, 927.
14. (a) Saimoto, H.; Yoshida, K.; Murakami, T.; Morimoto, M.; Sashiwa, H.; Shigemasa, Y. *J. Org. Chem*. **1996**, *61*, 6768. (b) Spyroudis, S.; Tarantill, P. *Tetrahedron* **1994**, *50*, 11541. (c) Kang, Y.; Mei, Y.; Du, Y.; Jin, Z. *Org. Lett*. **2003**, *5*, 4481.
15. (a) Tisdala, E. J.; Kochman, D. A.; Theodorakis, E. A. *Tetrahedron Lett*. **2003**, *44*, 3281. (b) Kalena, G. P.; Jain, A.; Banerji, A. *Molecules* **1997**, *2*, 100.
16. Paradkar, M. V.; Kulkarni, S. A.; Joseph, A. R.; Ranade, A. A. *J. Chem. Res. (S)*. **2000**, 364.
17. On silica gel column chromatographic purification of **10**, only **3** was eluted from the column while neutral alumina column purification gave only DBU.
18. Mondal, M.; Argade, N. P. *Synlett* **2004**, 1243.

2B. Section B

A Facile Synthesis of 1,3,7-Trihydroxyxanthone and its Regioselective Coupling Reactions with Prenal: Simple and Efficient Access to Osajaxanthone and Nigrolineaxanthone F

This section features the following topics:

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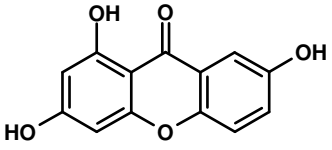
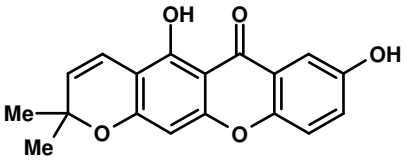
2B Section B: A Facile Synthesis of 1,3,7-Trihydroxyxanthone and its Regioselective Coupling Reactions with Prenal: Simple and Efficient Access to Osajaxanthone and Nigrolineaxanthone F

2B.1 Background

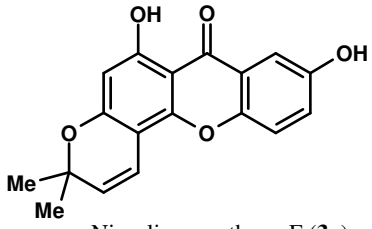
The natural and unnatural xanthones are an important class of compounds.[1] Several hydroxy and multiple hydroxy substituted xanthones exist in nature.[2] Nature very smartly explores all the available sites on these hydroxy substituted xanthones for remarkable regioselective coupling reactions with the naturally occurring prenal, citral and farnesal to design a vast array of corresponding pyranoxanthones and also to generate their complex structural architectures with the help of further intramolecular cyclizations.[1-4] The 1,3,7-trihydroxyxanthone (**1**) has been isolated from *Athyrium mesosorum* and it possesses xanthine oxidase inhibitor activity.[5] In nature xanthone **1** produces two structural analogs osajaxanthone (**2a**) and nigrolineaxanthone F (**3a**) via two different regioselective coupling reactions with prenal. Osajaxanthone (**2a**) has been isolated from *Calophyllum enervosum*, it possesses antimicrobial and anti-fish poison activities.[3] Nigrolineaxanthone F (**3a**) has been isolated from *Garcinia nigrolineata* species[4] (Figure 1).



1,3,7-Trihydroxyxanthone (**1**)



Osajaxanthone (**2a**)



Nigrolineaxanthone F (**3a**)

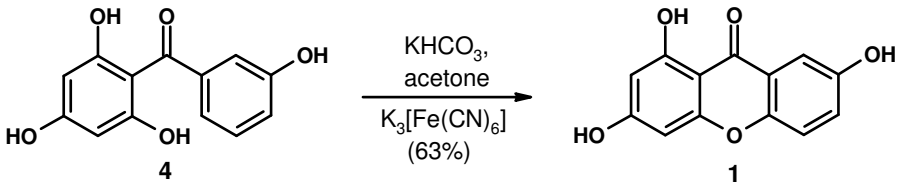
Figure 1

2B.1.1 Synthetic Approaches Towards 1,3,7-Trihydroxyxanthone, Osajaxanthone and Nigrolineaxanthone F

Before discussing our results, the reported synthetic approaches towards 1,3,7-trihydroxyxanthone, osajaxanthone and nigrolineaxanthone F are illustrated in brief in the following part.

[A] Ellis' Approach for 1,3,7-Trihydroxyxanthone

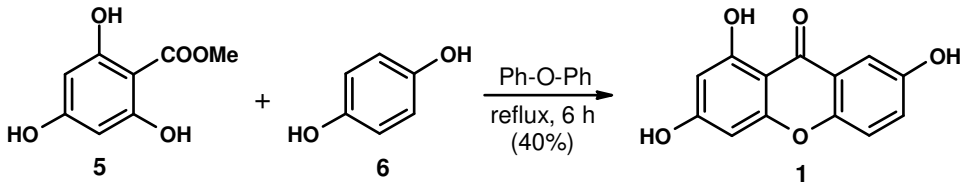
Ellis et al,[6b] reported an easy potassium hexacyanoferrate mediated oxidative *para*-coupling of 2,3',4,6-tetrahydroxybenzophenone (**4**) to form 1,3,7-trihydroxyxanthone (Scheme 1).



Scheme 1

[B] Trivedi's Approach for 1,3,7-Trihydroxyxanthone

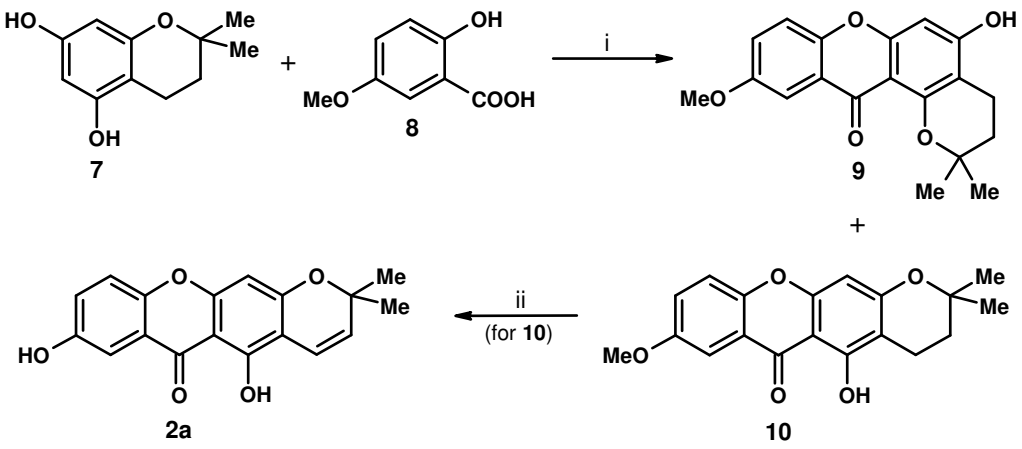
Trivedi and co-workers,[6a] completed synthesis of 1,3,7-trihydroxyxanthone in one step by using thermal condensation of hydroquinone with methyl 2,4,6-trihydroxybenzoate (**5**) in refluxing diphenylether (Scheme 2).



Scheme 2

[A] Wolform's Approach for Osajaxanthone

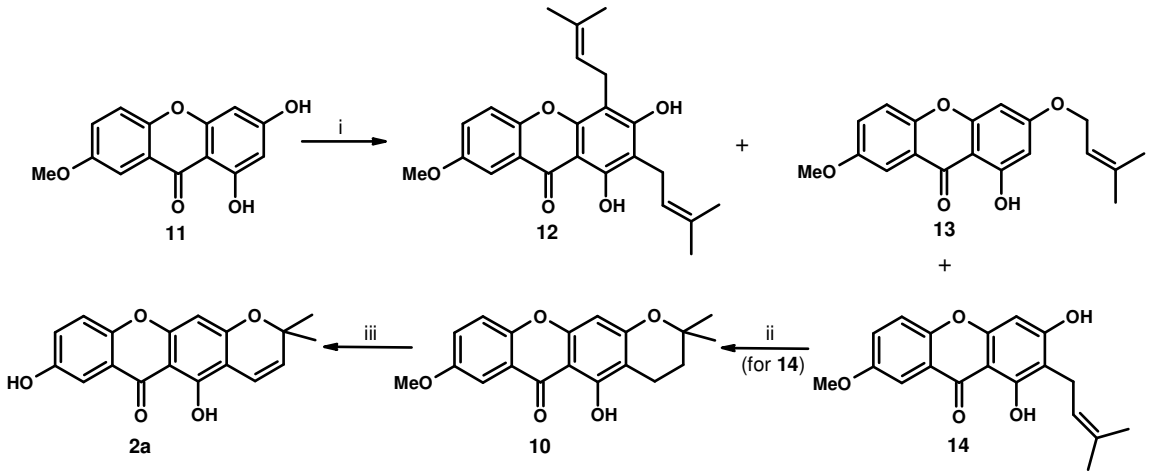
There are several synthetic approaches towards the synthesis of osajaxanthone. Wolfrom et al,[7a,b] first completed the synthesis of dihydroosajaxanthone monomethyl ether **10** by condensation of the dimethylchroman **7** with 2-hydroxy-5methoxybenzoic acid (**8**) in presence of phosphorous oxychloride and zinc chloride (Scheme 3). This condensation reaction furnished column separable mixture of dihydroosajaxanthone monomethyl ether **10**, along with an isomeric condensed compound **9**. The same group, later on completed the synthesis of osajaxanthone by utilizing the same intermediate dihydroosajaxanthone monomethyl ether. Monomethyl ether **10** on acetylation, NBS bromination, dehydrobromination, deacetylation and finally demethylation furnished the desired osajaxanthone.



Scheme 3 *Reagents, conditions and yields*: (i) $ZnCl_2$, $POCl_3$ (**9**: 10%; **10**: 10%); (ii) (a) Ac_2O, pyridine, (b) NBS, DBP, CCl_4, reflux, 8 h, (c) pyridine, 100 ^oC, 1 h, (d) EtOH, KOH (3%), 85 ^oC, 45 min, (e) benzene, $AlBr_3$ (15%).

[B] Seshadri's Approach for Osajaxanthone

Seshadri and co-workers[7c] reported a multi-step synthesis of osajaxanthone (Scheme 4). 1,3-Dihydroxy-7-methoxyxanthone (**11**) on treatment with prenyl bromide in presence of methanolic sodium methoxide gave a column separable mixture of 2,4-di-*C*-prenylated derivative **12**, 3-*O*-prenylated xanthone **13** and desired 2-*C*-prenylated xanthone **14**. The 2-prenylated compound **14** on cyclization furnished the linear dihydropyran derivatives **10** as



Scheme 4 *Reagents, conditions and yields*: (i) MeOH, NaOMe, prenyl bromide, reflux, 3 h (**12**: 30%; **13**: 5%; **14**: 20%); (ii) AcOH, HI, 120 ^oC, 3 h (70%); (iii) (a) Ac_2O, pyridine, (b) NBS, DBP, CCl_4, reflux, 8 h, (c) pyridine, 100 ^oC, 1 h, (d) EtOH, KOH (3%), 85 ^oC, 45 min, (e) benzene, $AlBr_3$, (f) Zn, AcOH (11%).

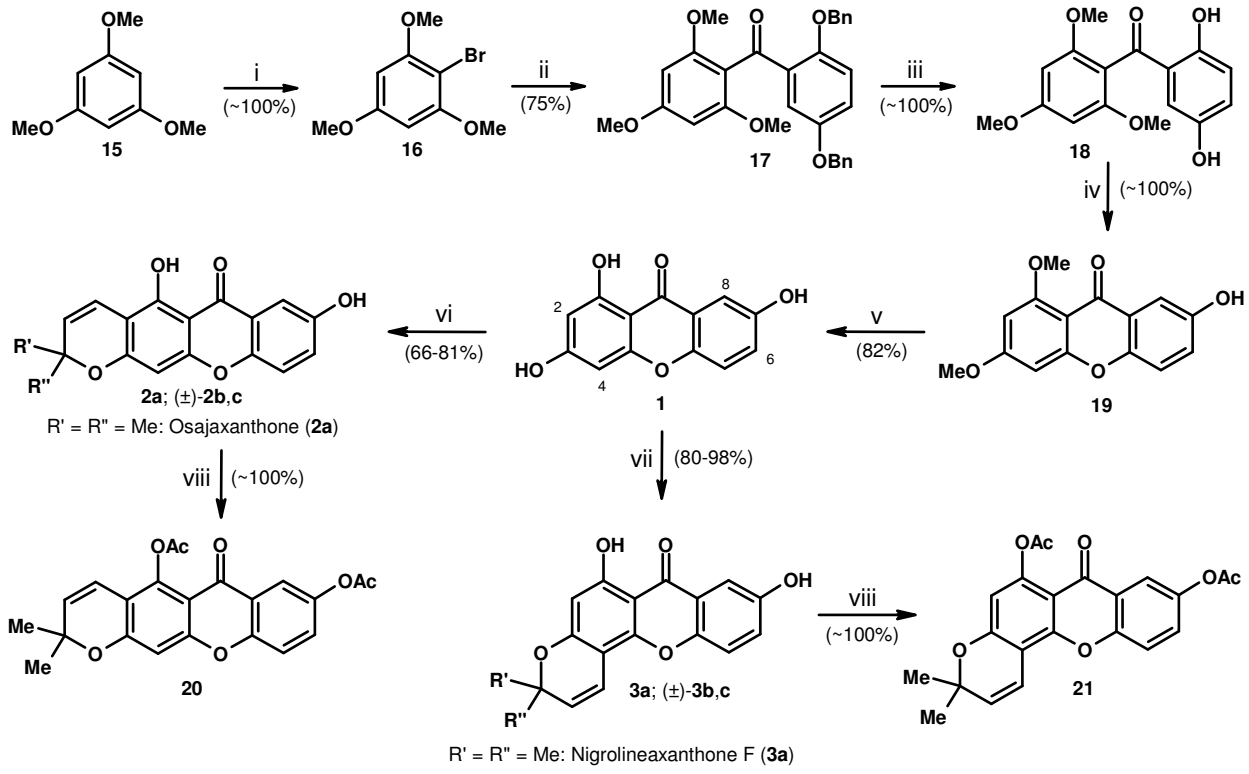
major product. The linear product which is dihydroosajaxanthone on acetylation, NBS bromination, dehydrobromination, deacetylation and finally debromination of some residual bromo compound with zinc and acetic acid furnished the desired natural product osajaxanthone.

2B.2 Rationale for Present Work

Till date, exclusive synthesis of Nigrolineaxanthone F is not known in the literature. All the reported attempts to condense 1,3,7-trihydroxyxanthone with prenal have resulted in formation of mixture of xanthones **2a** and **3a**.[7a,8] Hence, synthesis of both the linear and angular pyranoxanthones by using regioselective coupling reactions of xanthone **1** at the 2- and 4-positions with the *α*,*β*-unsaturated aldehydes under kinetic and thermodynamic conditions is a practical and challenging task of current interest. We envisaged a short and efficient route of xanthone **1** and development of suitable conditions for regioselective coupling reactions of **1** with prenal to exclusively design osajaxanthone (**2a**) and nigrolineaxanthone F (**3a**). Our studies on the synthesis of 1,3,7-trihydroxyxanthone, osajaxanthone and nigrolineaxanthone F are presented in the following part.

2B.3 Results and Discussion

1,3,5-Trimethoxybenzene (**15**) on treatment with NBS (1.00 equivalent) in refluxing CCl_4 furnished 2-bromo-1,3,5-trimethoxybenzene (**16**) in quantitative yield (Scheme 5). Bromobenzene **16** on *n*-BuLi (1.00 equivalent) induced lithiation followed by the benzoylation of the lithiated species with methyl 2,5-dibenzyloxybenzoate gave the corresponding dibenzyloxytrimethoxybenzophenone **17** in 75% yield. The benzophenone **17** when subjected to catalytic hydrogenation furnished the desired dihydroxytrimethoxybenzophenone **18** in nearly 100% yield. The benzophenone **18** on base-catalyzed intramolecular cyclization[9] via the oxa-Michael addition followed by elimination pathway furnished the dimethoxyhydroxyxanthone **19** in quantitative yield. The BBr_3 (6.00 equivalents) induced demethylations of xanthone **19** gave the naturally occurring 1,3,7-trihydroxyxanthone (**1**) in 82% yield. Starting from the symmetrical trimethoxybenzene **15**, the xanthone **1** was obtained in five steps with 62% overall yield. The analytical and spectral data obtained for xanthone **1** was in complete agreement with the reported data.[5,6] We feel that our present simple and efficient approach to xanthone **1**



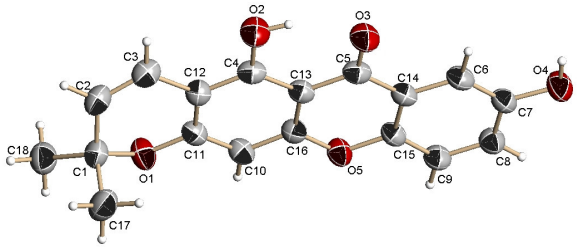
a: R' = R" = CH_3; **b**: R' = CH_3, R" = H; **c**: R' = CH_3, R" = $CH_2CH_2CH{=}C(CH_3)_2$.

Scheme 5 *Reagents, conditions and yields*: (i) CCl_4, NBS (1.00 equiv.), reflux, 6 h (~100%); (ii) THF, −78 °C, *n*-BuLi (1.00 equiv.), 45 min, methyl 2,5-dibenzyloxybenzoate, 30 min (75%); (iii) H_2, 10% Pd-C, methanol, rt, 6 h (~100%); (iv) (a) KOH (5.00 equiv.), MeOH, reflux, 12 h, (b) H^+/2 N HCl (~100%); (v) DCM, BBr_3 (6.00 equiv.), −78 °C to rt, 36 h (82%); (vi) Prenal/crotonaldehyde/citral (5.00 equiv.), $Ca(OH)_2$ (2.00 equiv.), methanol, rt, 36 h (**2a**: 75%; **2b**: 66%; **2c**: 81%); (vii) Prenal/crotonaldehyde/citral (10.00 equiv.), 140-150 °C 6 h (**3a**: 98%; **3b**: 86%; **3c**: 80%); (viii) Pyridine, Ac_2O, rt, 12 h (~100%).

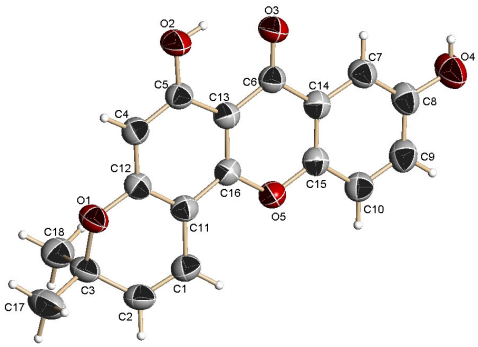
using two different protecting groups, selective deprotections and intramolecular cyclization is noteworthy.

Theoretically, the xanthone **1** can undergo coupling reactions with the *α,β*-unsaturated aldehydes at 2, 4, 6 and 8 positions to generate the corresponding benzopyrans via aldol type condensation followed by S_N2'-dehydrative ring closure reactions. The order of thermodynamic stability for these in situ generated carbanions will be 4 > 2 > 8 > 6 due to the flanking of the 4-position carbanion between carbonyl and *α,β*-unsaturated carbonyl, flanking of the 2-position carbanion between 1,3-dicarbonyl system (on conversion of enol to keto form), electron withdrawing inductive effect of xanthone carbonyl on the 8-position carbanion and formation of simple *α*-carbanion at the 6-position. Since, in xanthone **1**, the

ring A is doubly activated, the regioselective coupling reactions of xanthone **1** at the 2- and 4-positions with the *α*,*β*-unsaturated aldehydes to exclusively generate, respectively, the linear and angular pyranoxanthones under kinetic and thermodynamic conditions is a practical and challenging task of current interest. The DBU-induced generation of kinetic carbanion on 3,5-dihydroxyphthalide[10a] and $Ca(OH)_2$-induced generation of kinetic carbanion on methyl 2,4-dihydroxybenzoate[10b] and their condensation with *α*,*β*-unsaturated aldehydes are known in the literature.[10] The DBU-induced coupling of xanthone **1** with prenal in acetonitrile at room temperature was slow and gave **2a** in only 11% yield, after 72 hours reaction time. The same reaction on heating lost its selectivity and furnished a mixture of **2a** and **3a** in good yield. However, the $Ca(OH)_2$-induced regioselective generation of kinetic carbanion at the 2-position of xanthone **1** and its condensation with prenal at room temperature exclusively furnished the osajaxanthone (**2a**) in 75% yield. We surmise that the complexation of Ca^{2+} ion with xanthone could be responsible for the present observed selectivity. The reaction of xanthone **1** with prenal under thermodynamic condition (heat, 140-150 ^{o}C) with the generation of a stable carbanion at the 4-position, exclusively furnished the nigrolineaxanthone F (**3a**) in 98% yield. The osajaxanthone (**2a**) and nigrolineaxanthone F (**3a**) were further characterized as their respective diacetyl derivatives **20**[3b] and **21**. The analytical and spectral data obtained for xanthones **2a** and **3a** were in complete agreement with the reported data.[3,4,7,8] As expected, the linear product



Osajaxanthone (**2a**)



Nigrolineaxanthone F (**3a**)

Figure 2 ORTEP Diagram of **2a** and **3a** (Both the ellipsoids are drawn at 50% probability).

osajaxanthone (**2a**) was having the higher melting point than the corresponding angular nigrolineaxanthone F (**3a**), but the confirmatory structural discrimination of these two

natural products on the basis of ^{1}H and ^{13}C NMR data was a difficult task. Finally, the structures of these nice yellow crystalline linear and angular pyranoxanthones **2a** and **3a** were confirmed by using X-ray crystallographic data (Figure 2). The X- ray data revealed that the intramolecular O-H….O hydrogen bonding is seen for the compound **2a**, in addition to intermolecular O-H….O hydrogen bondings. The molecules of **2a** pack in a zig-zag manner when viewed down "a"-axis (Figure 3). Compound **3a** initially forms a dimer by intramolecular O-H…. O hydrogen bonding and intramolecular O-H….O hydrogen bondings in the packing of the molecules when viewed down "c"-axis (Figure 4).

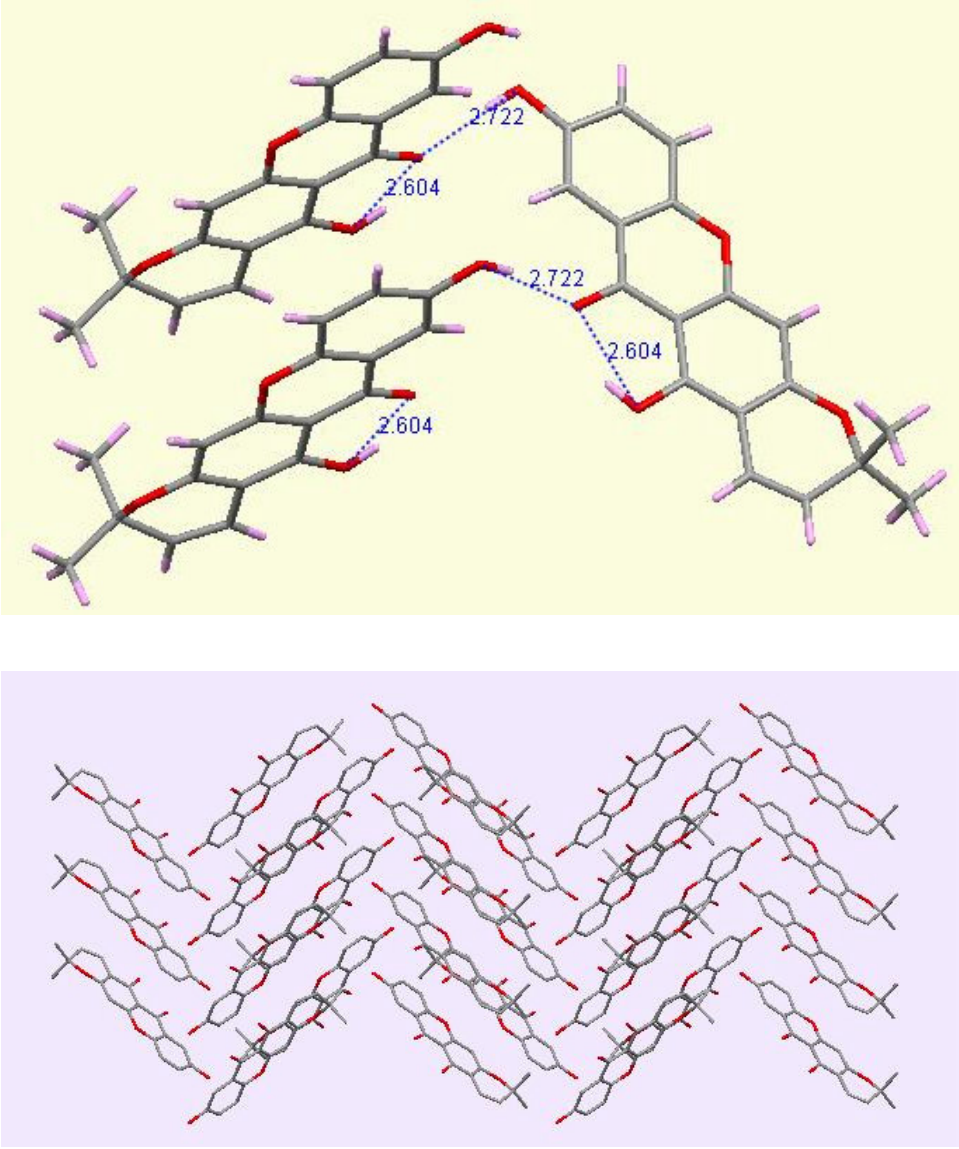


Figure 3 Intra and intermolecular hydrogen bonding in **2a** and packing of **2a**, in a zig-zag manner when viewed down "a"-axis.

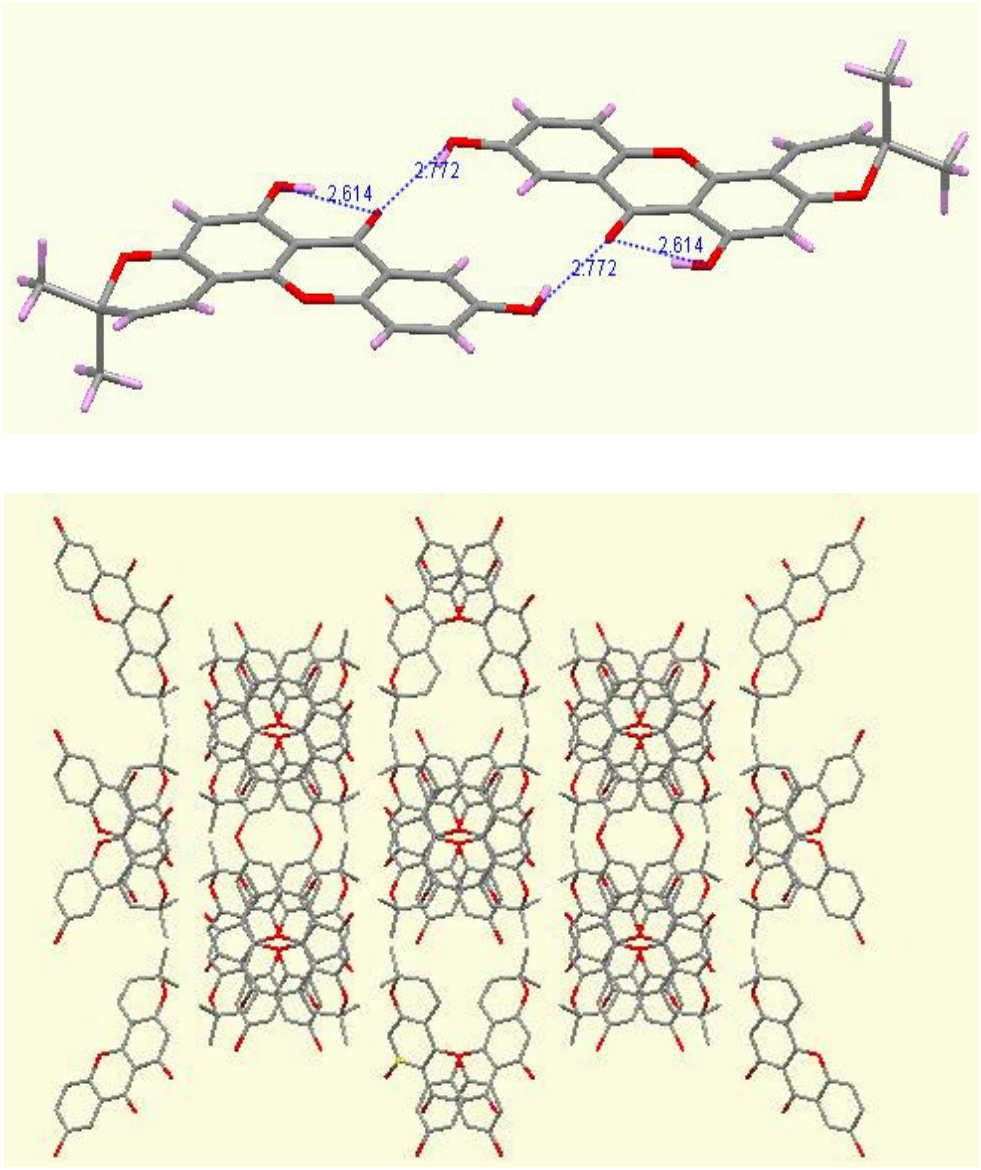


Figure 4 Dimeric **3a** with intra and intermolecular hydrogen bonding and packing of **3a** when viewed down "c"-axis.

The present approach to these xanthones is general in nature and we could also very selectively condense crotonaldehyde and citral with xanthone **1** to obtain the compounds **2b**,**c** and **3b**,**c** in very good yields.

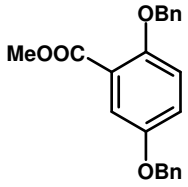
2B.4 Summary

In summary, we have demonstrated a facile five step synthesis of naturally occurring 1,3,7-trihydroxyxanthone starting from 1,3,5-trimethoxybenzene via NBS-induced nuclear bromination, lithiation followed by an in situ benzoylation with methyl 2,5-dibenzyloxybenzoate, selective deprotection of the two benzyl groups, base catalyzed intramolecular cyclization and demethylation pathway with 62% overall yield. The regioselective coupling reactions of 1,3,7-trihydroxyxanthone with prenal in the presence of calcium hydroxide at room temperature and under thermal condition at 140-150 ^{o}C have been demonstrated to exclusively obtain the natural products osajaxanthone in 75% yield and nigrolineaxanthone F in 98% yield respectively.[11] Our present approach to these three natural products has several advantages over other known approaches in the literature.

2B.5 Experimental Section

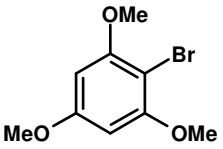
Commercially available 1,3,5-trimethoxybenzene, NBS, methyl 2,5-dihydroxybenzoate, benzylbromide, 10% Pd-C, BBr_3, 3-methyl-2-butenal, crotonaldehyde and citral were used. Melting points are uncorrected. Dichloromethane was distilled from CaH_2 under argon. Tetrahydrofuran was freshly distilled from benzophenone ketyl radical under argon prior to use. Column chromatographic separations were carried out on silica gel (60-120 mesh). All yields given refer to as isolated yields. IR spectra were recorded on FT-IR spectrometer. MS experiments were performed on a low resolution magnetic sector mass spectrometer.

Methyl 2,5-dibenzyloxybenzoate. To a stirring mixture of methyl 2,5-dihydroxybenzoate (10.00 g, 59.52 mmol) and anhydrous potassium carbonate (41.10 g, 297.62 mmol) in acetone (100 mL), benzylbromide (17.70 mL, 148.80 mmol) was added and the reaction mixture was refluxed for 6 h. After cooling, reaction mixture was filtered and concentration of the filtrate under vacuo followed by silica gel column chromatographic purification of the residue using 15% ethyl acetate in petroleum ether afforded methyl 2,5-dibenzyloxybenzoate (20.23 g, 98%).

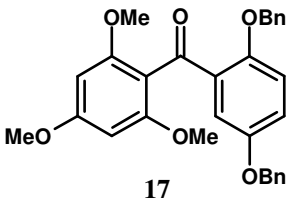
 Methyl 2,5-dibenzyloxybenzoate **$C_{22}H_{20}O_4$ (348)**	Colorless oil. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 3.90 (s, 3H), 5.03 (s, 2H), 5.12 (s, 2H), 6.94 (d, J = 9.1 Hz, 1H), 7.05 (dd, J = 9.1 & 3.2 Hz, 1H), 7.25-7.55 (m, 11H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 51.7, 70.2, 71.3, 115.9, 117.0, 119.9, 121.3, 126.7-128.2 (7 carbons) 136.5, 136.8, 152.3, 166.0. **MS** (*m/z*) 387, 371, 349, 317, 281, 257, 224, 181, 143. **IR** (Nujol) 1722, 1504 cm^{-1}. **Anal. Calcd** for $C_{22}H_{20}O_4$: C, 75.84; H, 5.79. Found: C, 76.02; H, 5.67.

2-Bromo-1,3,5-trimethoxybenzene (16). To a solution of **15** (10.00 g, 59.46 mmol) in CCl_4 (100 mL), NBS (10.58 g, 59.46 mmol) was added and the reaction mixture was refluxed gently for 3 h. After cooling, the reaction mixture was filtered and concentration of the filtrate under vacuo followed by silica gel column chromatographic purification of

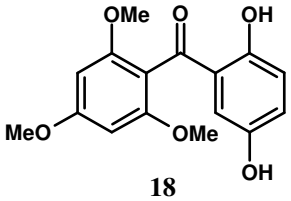
the residue using 25% ethyl acetate in petroleum ether gave **16**[12] (14.6 g, ~100%) as a white solid.

 **16** **$C_9H_{11}BrO_3$ (247)**	**Mp** 84-86 °C. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 3.79 (s, 3H), 3.85 (s, 6H), 6.14 (s, 2H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 55.3, 56.1, 91.4, 91.6, 157.2, 160.3. **MS** (*m/z*) 271, 269, 249, 247, 224, 119. **IR** (Nujol) 1589, 1574, 1462, 1377, 1346, 1229, 1207, 1155, 1128 cm^{-1}. **Anal. Calcd** for $C_9H_{11}BrO_3$: C, 43.75; H, 4.49; Br, 32.34. Found: C, 43.69; H, 4.53; Br, 32.59.

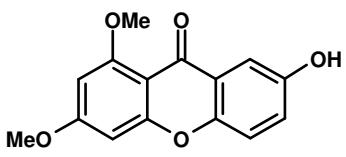
2,5-Dibenzyloxyphenyl 2',4',6'-trimethoxyphenyl methanone (17). To a stirring solution of **16** (10.00 g, 40.45 mmol) in THF (60 mL) at −78 °C was added *n*-BuLi (27.00 mL, 40.45 mmol) dropwise. After stirring at −78 °C for 45 min, this reaction mixture was added slowly to a stirring solution of methyl 2,5-dibenzyloxybenzoate (16.90 g, 48.55 mmol) in THF (80 mL) at −78 °C and stirred for a further 30 min. Saturated solution of NH_4Cl was then added to the reaction mixture at −78 °C and the reaction mixture was allowed to reach room temperature. THF was removed in vacuo. To the reaction mixture was added ethyl acetate (150 mL) and the separated organic layer was washed with water, brine and dried over Na_2SO_4. Removal of the solvent in vacuo followed by silica gel column chromatographic purification of the residue using 30% ethyl acetate in petroleum ether afforded **17** (14.6 g, 75%) as a white solid.

 **17** **$C_{30}H_{28}O_6$ (484)**	**Mp** 123-125 °C. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 3.57 (s, 6H), 3.77 (s, 3H), 4.86 (s, 2H), 5.04 (s, 2H), 5.97 (s, 2H), 6.88 (d, J = 9.0 Hz, 1H), 7.00-7.15 (m, 2H), 7.20-7.45 (m, 10H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 55.1, 55.7, 70.5, 71.3, 90.7, 114.5, 115.0, 116.3, 120.1, 127.2, 127.4, 127.5, 127.8, 128.0, 128.4, 130.8, 136.7, 136.9, 152.5, 152.6, 158.7, 162.0, 192.9. **MS** (*m/z*) 485, 391, 317, 261, 185. **IR** (Nujol) 1643, 1605, 1585, 1491, 1462, 1416, 1377 cm^{-1}. **Anal. Calcd** for $C_{30}H_{28}O_6$: C, 74.36; H, 5.82. Found: C, 74.29; H, 5.90.

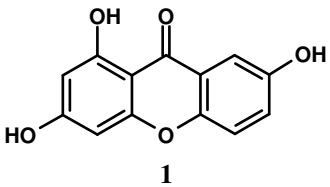
2,5-Dihydroxyphenyl 2',4',6'-trimethoxyphenyl methanone (18). To a stirring solution of **17** (10.00 g, 20.66 mmol) in methanol (100 mL) at room temperature, 10% Pd/C (500 mg) was added and the reaction mixture was subjected to hydrogenation at 65-psi hydrogen pressure for 24 h. The reaction mixture was filtered through celite and the filtrate was concentrated in vacuo. Silica gel column chromatographic purification of the residue using 40% ethyl acetate in petroleum ether furnished **18** (6.20 g, ~100%) as a yellow solid.

 **18** **$C_{16}H_{16}O_6$ (304)**	**Mp** 232-234 °C. **^{1}H NMR** (DMSO-d_6, 200 MHz) δ 3.69 (s, 6H), 3.85 (s, 3H), 6.34 (s, 2H), 6.66 (d, J = 2.9 Hz, 1H), 6.83 (d, J = 8.8 Hz, 1H), 7.00 (dd, J = 9.0 & 3.0 Hz, 1H), 9.10 (s, 1H), 11.45 (s, 1H). **^{13}C NMR** (DMSO-d_6, 100 MHz) δ 55.8, 56.1, 91.2, 109.1, 116.8, 118.4, 120.9, 125.4, 149.6, 154.8, 157.8, 162.6, 200.6. **MS** (*m/z*) 305, 279, 187, 155, 109. **IR** (Nujol) 3234, 1611, 1582, 1568, 1483, 1458 cm^{-1}. **Anal. Calcd** for $C_{16}H_{16}O_6$: C, 63.15; H, 5.30. Found: C, 63.19; H, 5.42.

7-Hydroxy-1,3-dimethoxy-xanthen-9-one (19). To an ice cooled stirring solution of **18** (5.00 g, 16.45 mmol) in methanol (30 mL), a solution of KOH (4.60 g, 82.24 mmol) in methanol (30 mL) was added slowly. The reaction mixture was refluxed gently for 12 h. After cooling to 0 ^{o}C, the reaction mixture was acidified with 2 N HCl and the solid compound obtained was filtered, washed with cold water and dried to provide **19** (4.40 g, ~100%) as a faint yellow solid.

 **19** **$C_{15}H_{12}O_5$ (272)**	**Mp** 290-292 °C. **^{1}H NMR** (DMSO-d_6, 200 MHz) δ 3.83 (s, 3H), 3.84 (s, 3H), 6.39 (d, J = 2.3 Hz, 1H), 6.54 (d, J = 2.3 Hz, 1H), 7.16 (dd, J = 9.0 & 2.9 Hz, 1H), 7.33 (d, J = 9.0 Hz, 1H), 7.38 (d, J = 2.9 Hz, 1H), 9.82 (s, 1H). **^{13}C NMR** (DMSO-d_6, 50 MHz) δ 56.1, 56.3, 93.0, 95.2, 106.1, 109.2, 118.5, 123.1, 123.3, 148.1, 153.9, 159.3, 161.6, 164.7, 173.7. **MS** (*m/z*) 273, 253, 205, 185, 155, 149, 125, 114, 109. **IR** (Nujol) 3391, 1638, 1632, 1593, 1460 cm^{-1}. **Anal. Calcd** for $C_{15}H_{12}O_5$: C, 66.17; H, 4.44. Found: C, 65.98; H, 4.58.

1,3,7-Trihydroxyxanthen-9-one (1). To a stirring suspension of **19** (4.00 g, 14.71 mmol) in dichloromethane (80 mL) at −78 °C, borontribromide (8.40 mL, 88.24 mmol) was added quickly and the reaction mixture was allowed to attain room temperature slowly. After stirring for 36 h at room temperature, the reaction mixture was cooled to 0 °C and very slowly quenched with water. Dichloromethane was removed in vacuo and ethyl acetate (100 mL) was added to the reaction mixture. The organic layer was washed with water, brine and dried over Na_2SO_4. Removal of the solvent under vacuo followed by silica gel column chromatographic purification of the residue using 30% ethyl acetate in petroleum ether afforded **1** (3.65 g, 82%) as a yellow solid.

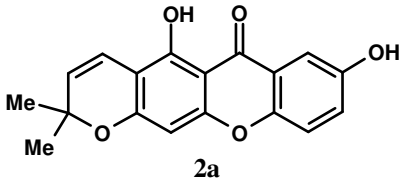


1

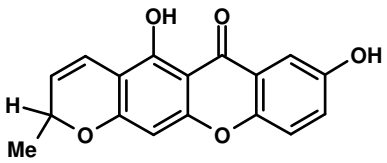
$C_{13}H_8O_5$ (244)

Mp 318-319 °C.
^{1}H NMR (DMSO-d_6, 200 MHz) δ 6.18 (d, J = 2.1 Hz, 1H), 6.35 (d, J = 1.9 Hz, 1H), 7.27 (dd, J = 9.0 & 3.0 Hz, 1H), 7.40 (d, J = 2.9 Hz, 1H), 7.45 (d, J = 9.1 Hz, 1H), 10.00 (s, 1H), 11.04 (s, 1H), 12.88 (s, 1H).
^{13}C NMR (DMSO-d_6, 50 MHz) δ 93.9, 98.0, 102.1, 108.2, 119.1, 120.6, 124.6, 149.2, 154.1, 157.7, 162.7, 163.0, 179.9.
MS (*m/z*) 291, 267, 259, 245, 224, 204, 191, 161, 127.
IR (Nujol) 3368, 3207, 1651, 1614, 1582, 1464 cm^{-1}.
Anal. Calcd for $C_{13}H_8O_5$: C, 63.94; H, 3.30. Found: C, 64.06; H, 3.35.

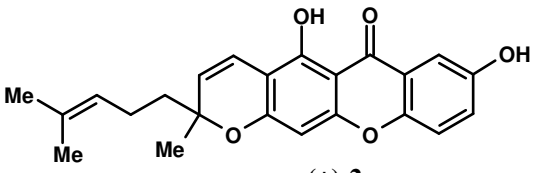
5,8-Dihydroxy-2,2-dimethyl-2*H*,6*H*-pyrano[3,2-*b*]xanthen-6-one (Osajaxanthone, 2a). To a stirring mixture of **1** (250 mg, 1.02 mmol) and $Ca(OH)_2$ (15 mg, 2.05 mmol) in methanol (10 mL) at room temperature, 3-methyl-2-butenal (prenal) (0.50 mL, 5.12 mmol) was added. After stirring for 36 h at room temperature, methanol was removed at room temperature under vacuo and the reaction mixture was diluted with ethyl acetate (30 mL). The organic layer was washed with 2 N HCl, water, brine and dried over Na_2SO_4. Removal of the solvent under vacuo followed by silica gel column chromatographic purification of the residue using 12% ethyl acetate in petroleum ether gave **2a** (235 mg, 75%) as a yellow solid.

 **2a** **$C_{18}H_{14}O_5$ (310)**	**Mp** 266-268 °C (MeOH:EtOH = 1:1). **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 1.43 (s, 6H), 5.77 (d, J = 10.1 Hz, 1H), 6.40 (s, 1H), 6.60 (d, J = 9.9 Hz, 1H), 7.29 (dd, J = 9.0 & 2.8 Hz, 1H), 7.40 (d, J = 2.6 Hz, 1H), 7.47 (d, J = 9.1 Hz, 1H), 10.07 (s, 1H), 13.26 (s, 1H). **^{13}C NMR** (DMSO-d_6, 100 MHz) δ 28.3, 78.8, 94.9, 103.1, 104.0, 108.2, 114.7, 119.5, 120.6, 125.2, 128.8, 149.4, 154.4, 157.0 (2 carbons), 160.4, 180.5. **MS** (*m/z*) 311, 301, 268, 239, 204, 188, 172, 126. **IR** (Nujol) 3227, 1651, 1632, 1609 cm^{-1}. **Anal. Calcd** for $C_{18}H_{14}O_5$: C, 69.67; H, 4.55. Found: C, 69.55; H, 4.73.

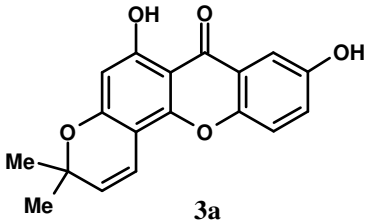
5,8-Dihydroxy-2-methyl-2*H*,6*H*-pyrano[3,2-*b*]xanthen-6-one (2b). It was prepared similarly using **1** (250 mg, 1.02 mmol) and crotonaldehyde (0.40 mL, 5.12 mmol). **2b**: Yellow solid (200 mg, 66%).

 **(±)-2b** **$C_{17}H_{12}O_5$ (296)**	**Mp** 263-265 °C. **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 1.40 (d, J = 6.6 Hz, 3H), 5.14 (m, 1H), 5.78 (dd, J = 10.0 & 2.4 Hz, 1H), 6.39 (s, 1H), 6.63 (d, J = 9.9 Hz, 1H), 7.29 (dd, J = 8.8 & 2.0 Hz, 1H), 7.39 (d, J = 2.2 Hz, 1H), 7.46 (d, J = 8.8 Hz, 1H), 10.06 (s, 1H), 13.23 (s, 1H). **^{13}C NMR** (DMSO-d_6, 100 MHz) δ 21.6, 72.8, 94.6, 103.1, 104.2, 108.1, 115.8, 119.3, 120.5, 124.9, 125.0, 149.2, 154.3, 156.8, 156.9, 160.7, 180.3. **MS** (*m/z*) 297, 279, 264, 239, 217, 180, 149, 117. **IR** (Nujol) 3279, 1653, 1611, 1585, 1464 cm^{-1}. **Anal. Calcd** for $C_{17}H_{12}O_5$: C, 68.92; H, 4.08. Found: C, 69.01; H, 3.96.

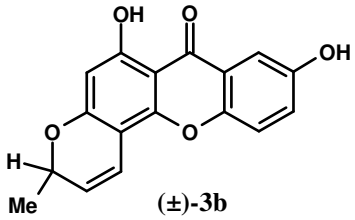
5,8-Dihydroxy-2-methyl-2-(4-methyl-pent-3-enyl)-2*H*,6*H*-pyrano[3,2-*b*]xanthen-6-one (2c). It was prepared similarly using **1** (250 mg, 1.02 mmol) and citral (0.90 mL, 5.12 mmol). **2c**: Faint yellow solid (310 mg, 81%).

 **(±)-2c** **$C_{23}H_{22}O_5$ (378)**	**Mp** 195-196 °C. **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 1.39 (s, 3H), 1.49 (s, 3H), 1.58 (s, 3H), 1.60-1.75 (m, 2H), 2.01 (q, J = 7.5 Hz, 2H), 5.04 (t, J = 7.1 Hz, 1H), 5.69 (d, J = 10.2 Hz, 1H), 6.34 (s, 1H), 6.62 (d, J = 10.1 Hz, 1H), 7.27 (d, J = 8.0 Hz, 1H), 7.38 (s, 1H), 7.43 (d, J = 9.1 Hz, 1H), 10.03 (s, 1H), 13.23 (s, 1H). **^{13}C NMR** (DMSO-d_6, 100 MHz) δ 17.6, 22.4, 25.6, 27.0, 41.2, 80.9, 94.5, 102.8, 103.6, 108.1, 115.2, 119.2, 120.5, 123.9, 124.9, 127.3, 131.3, 149.2, 154.3, 156.8, 156.9, 160.6, 180.2. **MS** (*m/z*) 379, 301, 267, 239, 217, 187, 154, 126. **IR** (Nujol) 3400, 1643, 1612, 1584, 1464 cm^{-1}. **Anal. Calcd** for $C_{23}H_{22}O_5$: C, 73.00; H, 5.86. Found: C, 73.11; H, 6.00.

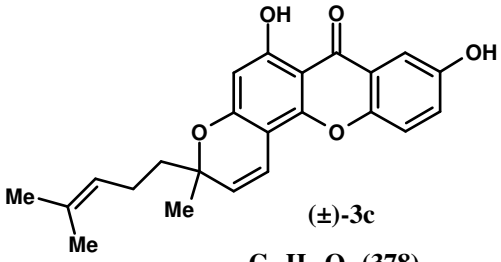
6,9-Dihydroxy-3,3-dimethyl-3*H*,7*H*-pyrano[2,3-*c*]xanthen-7-one (Nigrolineaxanthone F, 3a). A stirring mixture of **1** (250 mg, 1.02 mmol) and 3-methyl-2-butenal (prenal) (1.00 mL, 10.24 mmol) was heated at 140-150 ^{o}C for a period of 6 h. After cooling, the obtained residue on silica gel column chromatographic purification using 15% ethyl acetate in petroleum ether gave **3a** (310 mg, 98%) as a yellow solid.

 **3a** **$C_{18}H_{14}O_5$ (310)**	**Mp** 244-245 °C (EtOH). **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 1.43 (s, 6H), 5.77 (d, J = 10.2 Hz, 1H), 6.19 (s, 1H), 6.79 (d, J = 10.1 Hz, 1H), 7.31 (d, J = 9.0 Hz, 1H), 7.39 (s, 1H), 7.53 (d, J = 9.0 Hz, 1H), 10.06 (s, 1H), 12.98 (s, 1H). **^{13}C NMR** (DMSO-d_6, 100 MHz) δ 28.1, 78.6, 98.4, 100.7, 103.0, 108.1, 114.5, 119.4, 120.5, 125.0, 127.8, 149.2, 151.6, 154.4, 160.3, 162.4, 180.4. **MS** (*m/z*) 311, 229, 167. **IR** (Nujol) 3381, 1645, 1466 cm^{-1}. **Anal. Calcd** for $C_{18}H_{14}O_5$: C, 69.67; H, 4.55. Found: C, 69.58; H, 4.49.

6,9-Dihydroxy-3-methyl-3*H*,7*H*-pyrano[2,3-*c*]xanthen-7-one (3b). It was prepared similarly using **1** (250 mg, 1.02 mmol) and crotonaldehyde (0.80 mL, 10.24 mmol). **3b**: Yellow solid (260 mg, 86%).

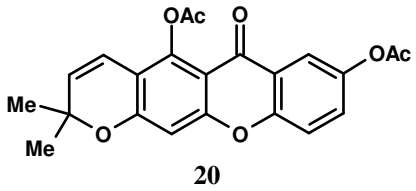
 **(±)-3b** **$C_{17}H_{12}O_5$ (296)**	**Mp** 139-141 °C. **^{1}H NMR** (DMSO-d_6, 200 MHz) δ 1.38 (d, J = 6.6 Hz, 3H), 5.08 (m, 1H), 5.70 (d, J = 10.1 Hz, 1H), 6.07 (s, 1H), 6.70 (d, J = 9.5 Hz, 1H), 7.25 (dd, J = 10.2 & 2.0 Hz, 1H), 7.33 (d, J = 1.4 Hz, 1H), 7.40 (d, J = 8.7 Hz, 1H), 10.01 (s, 1H). **^{13}C NMR** (DMSO-d_6, 50 MHz) δ 21.5, 72.8, 98.1, 101.0, 102.9, 108.1, 115.7, 119.2, 120.4, 123.8, 124.8, 149.1, 151.3, 154.3, 160.6, 162.4, 180.2. **MS** (*m/z*) 297, 283, 266, 239, 214, 206, 192, 154, 137, 126. **IR** (Nujol) 3335, 1653, 1578, 1464, 1377 cm^{-1}. **Anal. Calcd** for $C_{17}H_{12}O_5$: C, 68.92; H, 4.08. Found: C, 68.86; H, 4.13.

6,9-Dihydroxy-3-methyl-3-(4-methyl-pent-3-enyl)-3*H*,7*H*-pyrano[2,3-*c*]xanthen-7-one (3c). It was prepared similarly using **1** (250 mg, 1.02 mmol) and citral (1.75 mL, 10.24 mmol). **3c**: Yellow oil (309 mg, 80%).

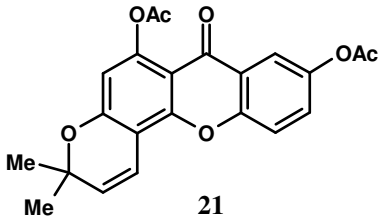
 **(±)-3c** **$C_{23}H_{22}O_5$ (378)**	Yellow oil. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.49 (s, 3H), 1.60 (s, 3H), 1.67 (s, 3H), 1.68-1.77 (m, 1H), 1.78-1.88 (m, 1H), 2.15 (q, J = 7.6 Hz, 2H), 5.12 (t, J = 6.5 Hz, 1H), 5.54 (d, J = 10.1 Hz, 1H), 6.21 (s, 1H), 6.74 (d, J = 10.0 Hz, 1H), 6.99 (d, J = 9.1 Hz, 1H), 7.17 (d, J = 8.0 Hz, 1H), 7.50 (s, 1H), 7.88 (bs, 1H), 12.54 (s, 1H). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 17.6, 22.6, 25.6, 27.1, 41.6, 80.8, 98.9, 100.6, 103.1, 108.3, 115.5, 118.7, 120.2, 123.6, 124.7, 125.7, 132.1, 149.8, 151.7, 153.2, 161.4, 162.8, 180.4. **MS** (*m/z*) 379, 344, 302, 265, 241, 220, 141. **IR** ($CHCl_3$) 3331, 1651, 1645 cm^{-1}. **Anal. Calcd** for $C_{23}H_{22}O_5$: C, 73.00; H, 5.86. Found: C, 73.20; H, 5.72.

5,8-Diacetoxy-2,2-dimethyl-2*H*,6*H*-pyrano[3,2-*b*]xanthen-6-one (20). To a stirring solution of **2a** (100 mg, 0.32 mmol) in pyridine (5 mL) was added acetic anhydride (5 mL) and the reaction mixture was kept in dark at room temperature for 24 h. The reaction mixture was poured into ice-cold water and extracted with ethyl acetate (15 mL x 5). The combined organic layer was washed with 10% aq. $CuSO_4$ solution, water, 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 25% ethyl acetate in petroleum ether gave **20** (125 mg, ~100%) as a white solid.

 **20** **$C_{22}H_{18}O_7$ (394)**	**Mp** 197-199 °C. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.49 (s, 6H), 2.31 (s, 3H), 2.50 (s, 3H), 5.75 (d, J = 10.1 Hz, 1H), 6.50 (d, J = 10.0 Hz, 1H), 6.73 (s, 1H), 7.35-7.45 (m, 2H), 7.89 (s, 1H). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 20.9, 21.0, 28.5, 78.4, 102.1, 108.7, 112.1, 115.0, 118.5, 118.6, 122.7, 128.2, 131.5, 145.5, 146.6, 152.7, 158.0, 159.0, 169.2 (2 carbons), 174.2. **MS** (*m/z*) 395, 375, 353, 300, 239. **IR** (Nujol) 1759, 1749, 1659, 1643, 1614, 1470 cm^{-1}. **Anal. Calcd** for $C_{22}H_{18}O_7$: C, 67.00; H, 4.60. Found: C, 67.15; H, 4.52.

6,9-Diacetoxy-3,3-dimethyl-3*H*,7*H*-pyrano[2,3-*c*]xanthen-7-one (21). Compound **21** was prepared from **3a** using the same procedure described for **20**. **21**: White solid (126 mg, ~100% yield).

 **21** **$C_{22}H_{18}O_7$ (394)**	**Mp** 185-187 °C. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.50 (s, 6H), 2.31 (s, 3H), 2.46 (s, 3H), 5.70 (d, J = 10.0 Hz, 1H), 6.47 (s, 1H), 6.88 (d, J = 10.3 Hz, 1H), 7.40 (dd, J = 8.8 & 2.7 Hz, 1H), 7.44 (d, J = 8.5 Hz, 1H), 7.90 (d, J = 2.7 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 20.9, 21.2, 28.4, 78.5, 107.3, 108.5, 108.6, 114.9, 118.5, 118.6, 122.6, 128.3, 129.4, 146.7, 150.7, 152.5, 152.9, 158.4, 169.2, 169.6, 174.2. **MS** (*m/z*) 395, 353, 301, 282, 260, 204, 149. **IR** (Nujol) 1763, 1751, 1653, 1464 cm^{-1}. **Anal. Calcd** for $C_{22}H_{18}O_7$: C, 67.00; H, 4.60. Found: C, 66.89; H, 4.66.

X-ray Crystal Structure Analysis

The X-ray data of Osajaxanthone (**2a**) and Nigrolineaxanthone F (**3a**) were collected on a SMART APEX CCD single crystal X-ray diffractometer with omega and phi scan mode and different number of scans and exposure times for different crystals using λ MoK_α = 0.71073 Å radiation, at T = 293(2) K with Oscillation / frame -0.3º, maximum detector swing angle = –30.0º, beam center = (260.2, 252.5), in plane spot width = 1.24. All the data were corrected for Lorentzian, polarization and absorption effects using SAINT and SADABS programs. The crystal structures were solved by direct method using SHELXS-97 and the refinement was performed[13] by full matrix least squares of F^2 using SHELXL-97.

X-ray Crystallographic Data for Osajaxanthone (2a)

Table 1 Crystal Data and Structure Refinement

Empirical formula	C_{18} H_{14} O_5
Formula weight	310.29
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system, space group	Monoclinic, $P2_1/c$
Unit cell dimensions	a = 11.8863(14) Å b = 5.3819(7) Å β = 101.436(2) º c = 22.632(3) Å
Volume	1419.0(3) $Å^3$
Z, Calculated density	1.452 Mg/m^3
Crystal size	0.27 x 0.18 x 0.06 mm
θ range for data collection	2.78 to 24.99 º
Reflections collected / unique	6315 / 2461 [R(int) = 0.0338]
Completeness to θ = 25.00	98.4%
Goodness-of-fit on F^2	0.842

Table 2 Bond lengths [Å] and angles [deg] for Osajaxanthone **2a**

O(1)-C(11)	1.3582(19)	C(2)-C(3)-H(3)	119.9
O(1)-C(1)	1.475(2)	C(12)-C(3)-H(3)	119.9
O(2)-C(4)	1.3524(17)	O(2)-C(4)-C(12)	117.62(17)
O(2)-H(2)	0.8200	O(2)-C(4)-C(13)	120.42(15)
O(3)-C(5)	1.2595(16)	C(12)-C(4)-C(13)	121.97(15)
O(4)-C(7)	1.3653(19)	O(3)-C(5)-C(13) 1	121.71(16)
O(4)-H(4)	0.8200	O(3)-C(5)-C(14)	121.71(15)
O(5)-C(16)	1.3659(19)	C(13)-C(5)-C(14)	116.58(14)
O(5)-C(15)	1.3797(18)	C(7)-C(6)-C(14)	120.42(15)
C(1)-C(2)	1.497(2)	C(7)-C(6)-H(6)	119.8
C(1)-C(17)	1.513(3)	C(14)-C(6)-H(6)	119.8
C(1)-C(18)	1.514(2)	O(4)-C(7)-C(6)	123.58(15)
C(2)-C(3)	1.327(2)	O(4)-C(7)-C(8)	116.92(16)
C(2)-H(2A)	0.9300	C(6)-C(7)-C(8)	119.50(16)
C(3)-C(12)	1.447(2)	C(9)-C(8)-C(7)	121.12(17)
C(3)-H(3)	0.9300	C(9)-C(8)-H(8)	119.4
C(4)-C(12)	1.388(2)	C(7)-C(8)-H(8)	119.4
C(4)-C(13)	1.414(2)	C(8)-C(9)-C(15)	119.26(15)
C(5)-C(13)	1.432(2)	C(8)-C(9)-H(9)	120.4
C(5)-C(14)	1.457(2)	C(15)-C(9)-H(9)	120.4
C(6)-C(7)	1.370(2)	C(16)-C(10)-C(11)	118.10(15)
C(6)-C(14)	1.404(2)	C(16)-C(10)-H(10)	120.9
C(6)-H(6)	0.9300	C(11)-C(10)-H(10)	120.9
C(7)-C(8)	1.394(2)	O(1)-C(11)-C(10)	117.10(14)
C(8)-C(9)	1.368(2)	O(1)-C(11)-C(12)	120.41(17)
C(8)-H(8)	0.9300	C(10)-C(11)-C(12)	122.42(16)
C(9)-C(15)	1.385(2)	C(4)-C(12)-C(11)	117.85(17)
C(9)-H(9)	0.9300	C(4)-C(12)-C(3)	123.97(15)
C(10)-C(16)	1.378(2)	C(11)-C(12)-C(3)	118.11(16)
C(10)-C(11)	1.385(2)	C(16)-C(13)-C(4)	116.86(15)
C(10)-H(10)	0.9300	C(16)-C(13)-C(5)	120.64(16)
C(11)-C(12)	1.403(2)	C(4)-C(13)-C(5)	122.49(14)
C(13)-C(16)	1.409(2)	C(15)-C(14)-C(6)	118.80(17)
C(14)-C(15)	1.388(2)	C(15)-C(14)-C(5)	119.30(15)
C(17)-H(17A)	0.9600	C(6)-C(14)-C(5)	121.89(14)
C(17)-H(17B)	0.9600	O(5)-C(15)-C(9)	116.53(14)
C(17)-H(17C)	0.9600	O(5)-C(15)-C(14)	122.57(16)
C(18)-H(18A)	0.9600	C(9)-C(15)-C(14)	120.90(16)
C(18)-H(18B)	0.9600	O(5)-C(16)-C(10)	116.15(14)
C(18)-H(18C)	0.9600	O(5)-C(16)-C(13)	121.16(14)
		C(10)-C(16)-C(13)	122.68(17)
C(11)-O(1)-C(1)	118.72(13)	C(1)-C(17)-H(17A)	109.5
C(4)-O(2)-H(2)	109.5	C(1)-C(17)-H(17B)	109.5
C(7)-O(4)-H(4)	109.5	H(17A)-C(17)-H(17B)	109.5
C(16)-O(5)-C(15)	119.70(12)	C(1)-C(17)-H(17C)	109.5
O(1)-C(1)-C(2)	110.07(14)	H(17A)-C(17)-H(17C)	109.5
O(1)-C(1)-C(17)	107.81(15)	H(17B)-C(17)-H(17C)	109.5
C(2)-C(1)-C(17)	110.57(15)	C(1)-C(18)-H(18A)	109.5
O(1)-C(1)-C(18)	104.23(14)	C(1)-C(18)-H(18B)	109.5
C(2)-C(1)-C(18)	112.53(16)	H(18A)-C(18)-H(18B)	109.5
C(17)-C(1)-C(18)	111.34(16)	C(1)-C(18)-H(18C)	109.5
C(3)-C(2)-C(1)	121.23(18)	H(18A)-C(18)-H(18C)	109.5
C(3)-C(2)-H(2A)	119.4	H(18B)-C(18)-H(18C)	109.5

X-ray Crystallographic Data for Nigrolineaxanthone F (3a)

Table 1 Crystal Data and Structure Refinement

Empirical formula	$C_{18}\ H_{14}\ O_5$
Formula weight	310.29
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system, space group	Monoclinic, C2/c
Unit cell dimensions	a = 18.5994 (9) Å b = 10.6620 (5) Å β = 102.537(1) º c = 14.7627(7) Å
Volume	2857.7(2) $Å^3$
Z, Calculated density	1.442 Mg/m^3
Crystal size	0.48 x 0.33 x 0.31 mm
θ range for data collection	2.22 to 25.00 º
Reflections collected / unique	9421 / 2515 [R(int) = 0.0424]
Completeness to θ = 25.00	99.8%
Goodness-of-fit on F^2	1.073

Table 2 Bond lengths [Å] and angles [deg] for Nigrolineaxanthone F **3a**

O(1)-C(12)	1.3532(16)	C(2)-C(3)	1.498(2)
O(1)-C(3)	1.4733(17)	C(2)-H(2A)	0.9300
O(2)-C(5)	1.3411(16)	C(3)-C(17)	1.509(2)
O(2)-H(2)	0.8200	C(3)-C(18)	1.514(2)
O(3)-C(6)	1.2477(17)	C(4)-C(5)	1.376(2)
O(4)-C(8)	1.3604(18)	C(4)-C(12)	1.3890(19)
O(4)-H(4)	0.8200	C(4)-H(4A)	0.9300
O(5)-C(16)	1.3663(16)	C(5)-C(13)	1.4258(19)
O(5)-C(15)	1.3707(17)	C(6)-C(13)	1.4400(19)
C(1)-C(2)	1.321(2)	C(6)-C(14)	1.463(2)
C(1)-C(11)	1.4485(19)	C(7)-C(8)	1.374(2)
C(7)-C(14)	1.401(2)	C(7)-H(7)	0.9300
C(1)-H(1)	0.9300	C(8)-C(9)	1.393(2)

C(9)-C(10)	1.368(2)	C(8)-C(7)-H(7)	119.7
C(9)-H(9)	0.9300	C(14)-C(7)-H(7)	119.7
C(10)-C(15)	1.387(2)	O(4)-C(8)-C(7)	123.90(14)
C(10)-H(10)	0.9300	O(4)-C(8)-C(9)	116.72(13)
C(11)-C(16)	1.392(2)	C(7)-C(8)-C(9)	119.38(14)
C(11)-C(12)	1.3999(19)	C(10)-C(9)-C(8)	121.08(14)
C(13)-C(16)	1.4029(19)	C(10)-C(9)-H(9)	119.5
C(14)-C(15)	1.387(2)	C(8)-C(9)-H(9)	119.5
C(17)-H(17A)	0.9600	C(9)-C(10)-C(15)	119.34(14)
C(17)-H(17B)	0.9600	C(9)-C(10)-H(10)	120.3
C(17)-H(17C)	0.9600	C(15)-C(10)-H(10)	120.3
C(18)-H(18A)	0.9600	C(16)-C(11)-C(12)	116.55(12)
C(18)-H(18B)	0.9600	C(16)-C(11)-C(1)	124.84(13)
C(18)-H(18C)	0.9600	C(12)-C(11)-C(1)	118.48(13)
		O(1)-C(12)-C(4)	116.86(12)
C(12)-O(1)-C(3)	118.17(10)	O(1)-C(12)-C(11)	120.28(12)
C(5)-O(2)-H(2)	109.5	C(4)-C(12)-C(11)	122.77(13)
C(8)-O(4)-H(4)	109.5	C(16)-C(13)-C(5)	117.57(12)
C(16)-O(5)-C(15)	119.54(11)	C(16)-C(13)-C(6)	120.70(12)
C(2)-C(1)-C(11)	119.40(13)	C(5)-C(13)-C(6)	121.73(12)
C(2)-C(1)-H(1)	120.3	C(15)-C(14)-C(7)	118.80(13)
C(11)-C(1)-H(1)	120.3	C(15)-C(14)-C(6)	119.85(13)
C(1)-C(2)-C(3)	121.01(13)	C(7)-C(14)-C(6)	121.34(13)
C(1)-C(2)-H(2A)	119.5	O(5)-C(15)-C(14)	122.53(12)
C(3)-C(2)-H(2A)	119.5	O(5)-C(15)-C(10)	116.62(13)
O(1)-C(3)-C(2)	109.90(12)	C(14)-C(15)-C(10)	120.85(13)
O(1)-C(3)-C(17)	104.06(12)	O(5)-C(16)-C(11)	115.39(12)
C(2)-C(3)-C(17)	112.75(14)	O(5)-C(16)-C(13)	121.59(12)
O(1)-C(3)-C(18)	107.87(12)	C(11)-C(16)-C(13)	123.01(12)
C(2)-C(3)-C(18)	110.23(13)	C(3)-C(17)-H(17A)	109.5
C(17)-C(3)-C(18)	111.74(15)	C(3)-C(17)-H(17B)	109.5
C(5)-C(4)-C(12)	119.39(13)	H(17A)-C(17)-H(17B)	109.5
C(5)-C(4)-H(4A)	120.3	C(3)-C(17)-H(17C)	109.5
C(12)-C(4)-H(4A)	120.3	H(17A)-C(17)-H(17C)	109.5
O(2)-C(5)-C(4)	118.72(12)	H(17B)-C(17)-H(17C)	109.5
O(2)-C(5)-C(13)	120.69(12)	C(3)-C(18)-H(18A)	109.5
C(4)-C(5)-C(13)	120.58(12)	C(3)-C(18)-H(18B)	109.5
O(3)-C(6)-C(13)	122.47(13)	H(18A)-C(18)-H(18B)	109.5
O(3)-C(6)-C(14)	121.97(13)	C(3)-C(18)-H(18C)	109.5
C(13)-C(6)-C(14)	115.56(12)	H(18A)-C(18)-H(18C)	109.5
C(8)-C(7)-C(14)	120.53(14)	H(18B)-C(18)-H(18C)	109.5

Crystal Packing Data for Osajaxanthone (2a)

Both intramolecular O-H….O hydrogen bonding and intermolecular O-H….O hydrogen bondings is seen for the compound **2a** (Figure 3). The molecules of **2a** pack in a zigzag manner when viewed down "a"-axis (Figure 3).

Analysis of Potential Hydrogen Bonds (**2a**)

Donor --- H....Acceptor	H...A	D...A	D - H...A
O(2) -- H(2) .. O(3) ^{Intra}	1.88	2.604(2)	147
O(4) -- H(4) .. O(3)^{i}	1.92	2.722 (2)	166

Equivalent Position Code

^{i} = -x,1/2+y,1/2-z

Crystal Packing Data for Nigrolineaxanthone F (3a)

Molecule **3a** exists as a dimer by intramolecular O-H….O hydrogen bonding and intermolecular O-H….O hydrogen bondings (Figure 4) in the packing of the molecules when viewed down "c"-axis (Figure 4).

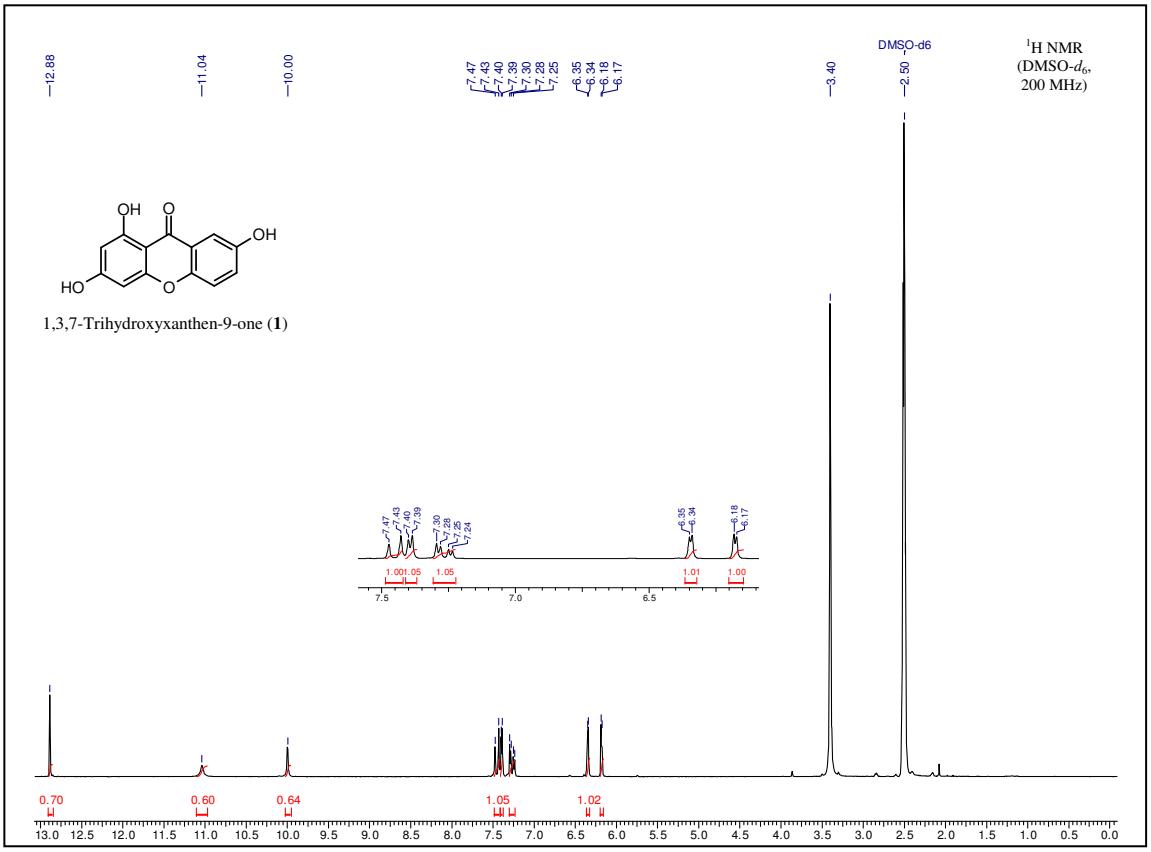
Analysis of Potential Hydrogen Bonds (**3a**)

Donor --- H....Acceptor	H...A	D...A	D - H...A
O(2) -- H(2) .. O(3)^{intra}	1.89	2.614(2)	147
O(4) -- H(4) .. O(3)^{i}	2.02	2.772(2)	152

Equivalent Position Code

^{i} = -x,3-y,-z

2B.6 Selected Spectra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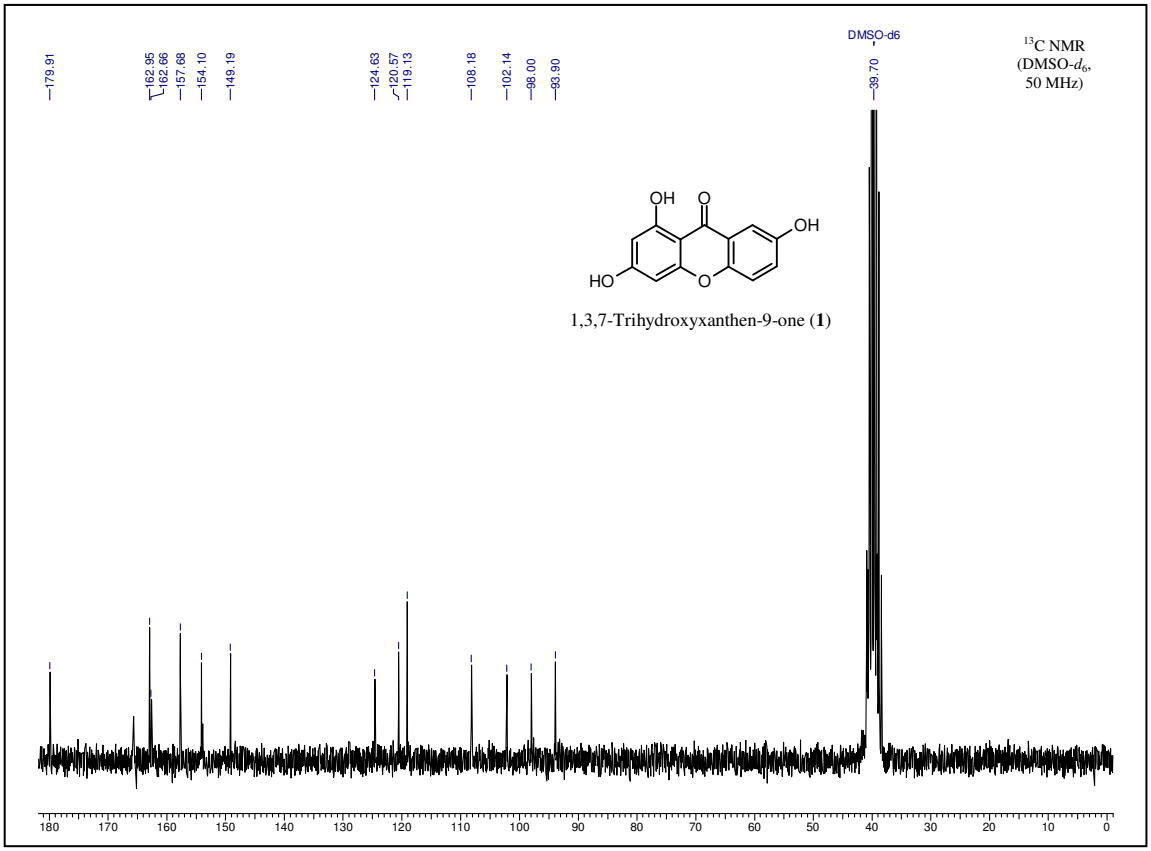
7.30
7.28
7.25
6.35
6.34
6.18
6.17
3.40
DMSO-d6
2.50
^{1}H NMR
(DMSO-d_6,
200 MHz)
OH
O
OH
HO
O
1,3,7-Trihydroxyxanthen-9-one (**1**)
0.70
0.60
0.64
1.05
1.02
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0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119.13
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102.14
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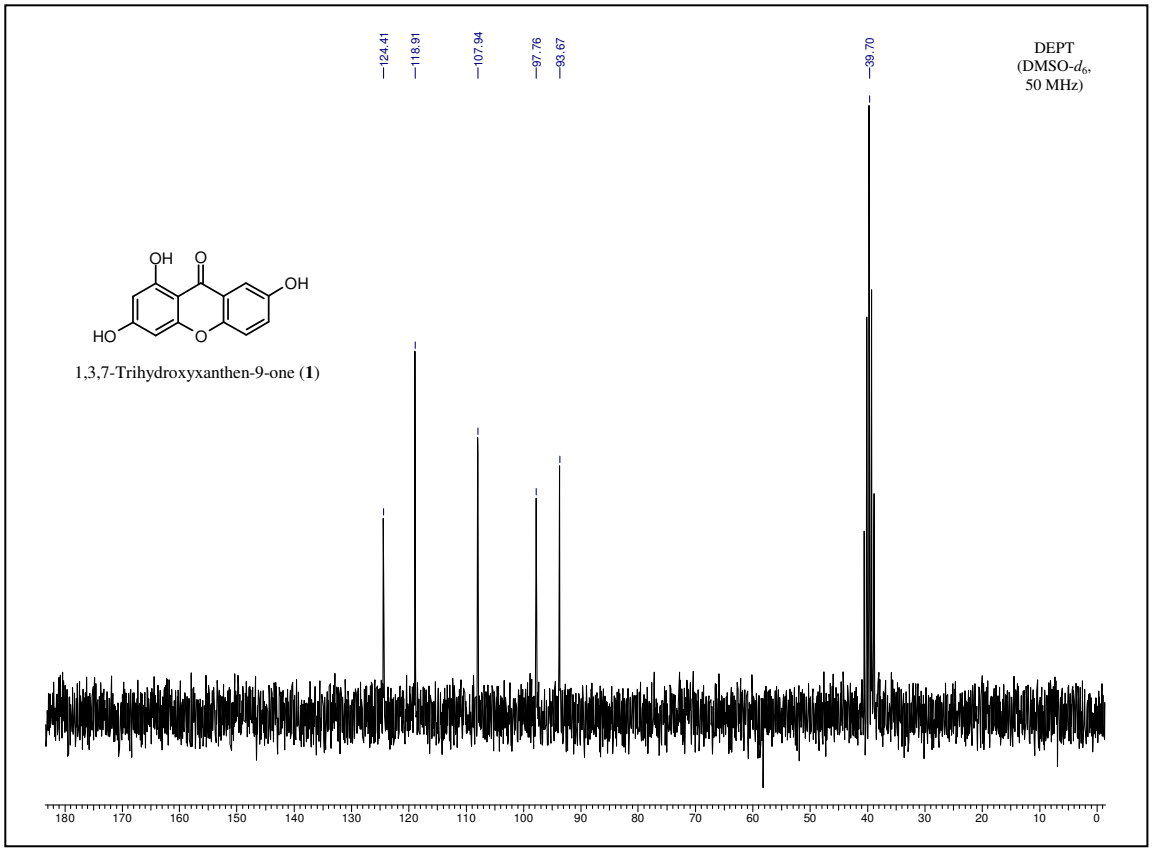
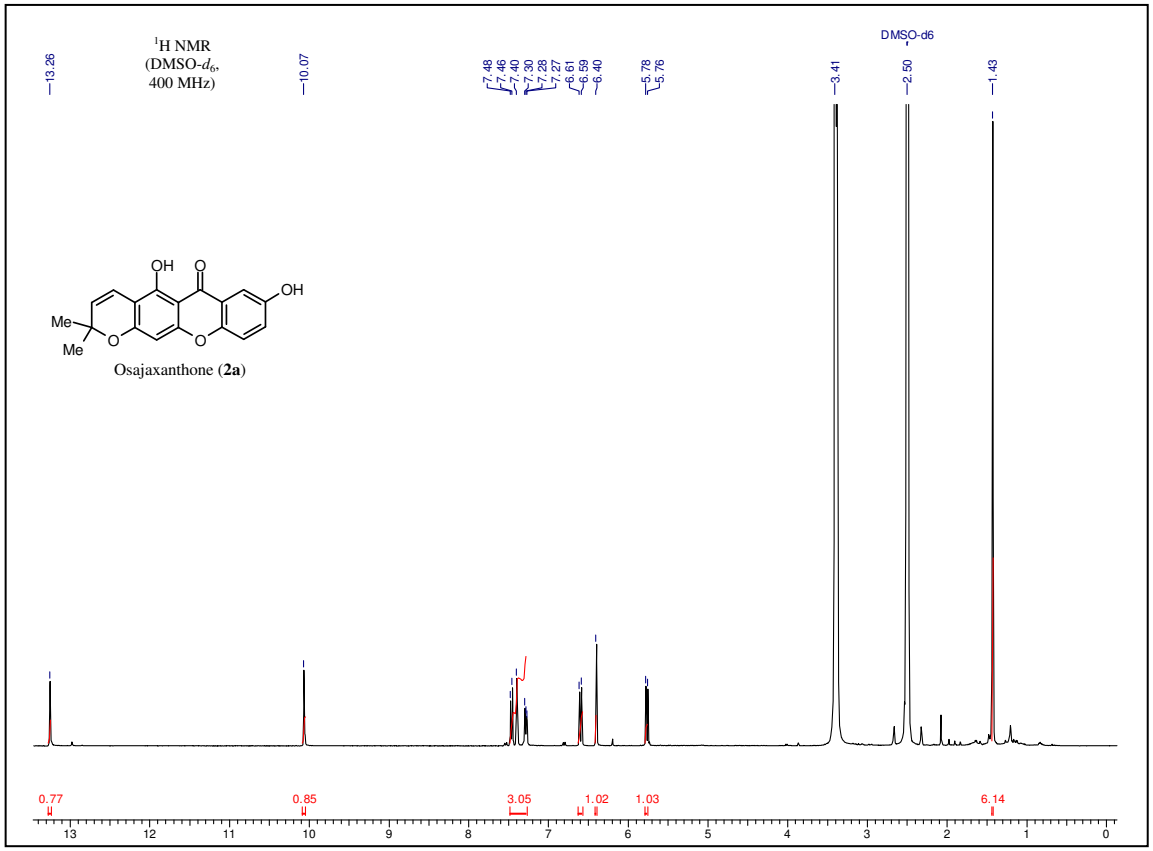
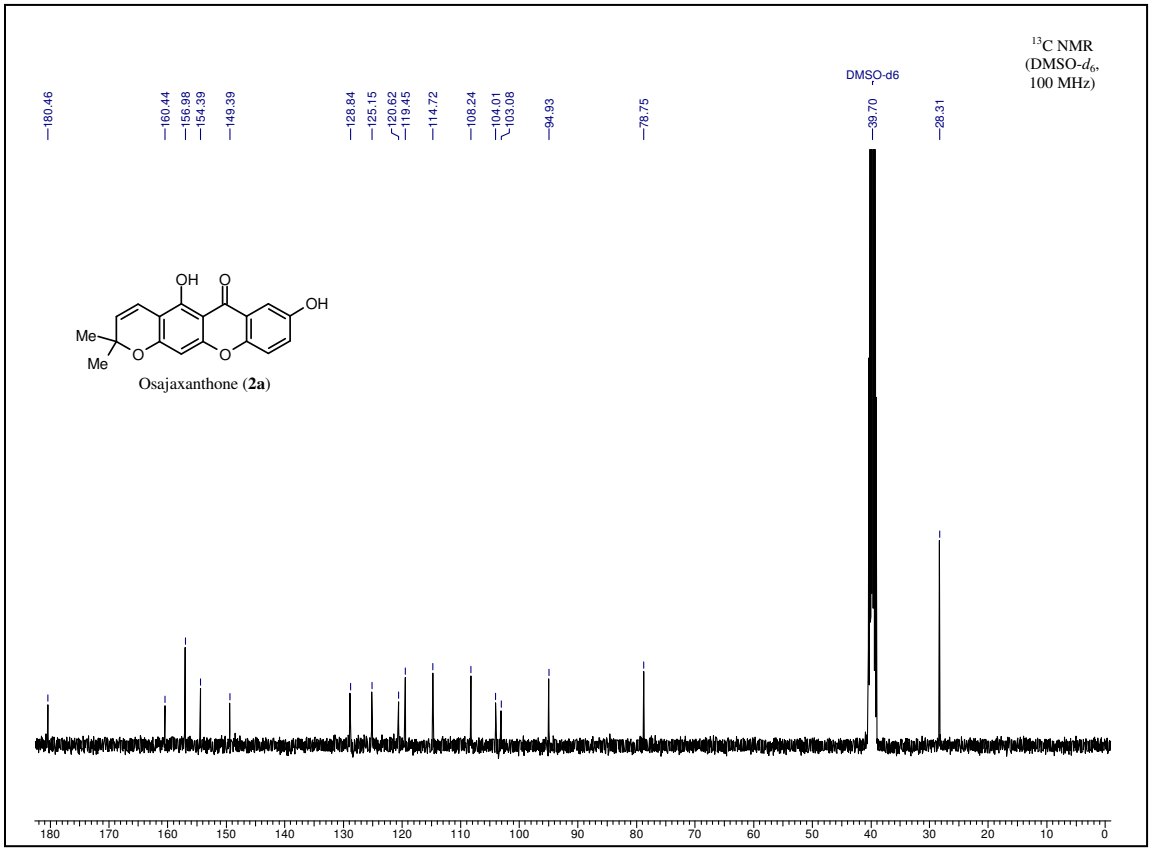
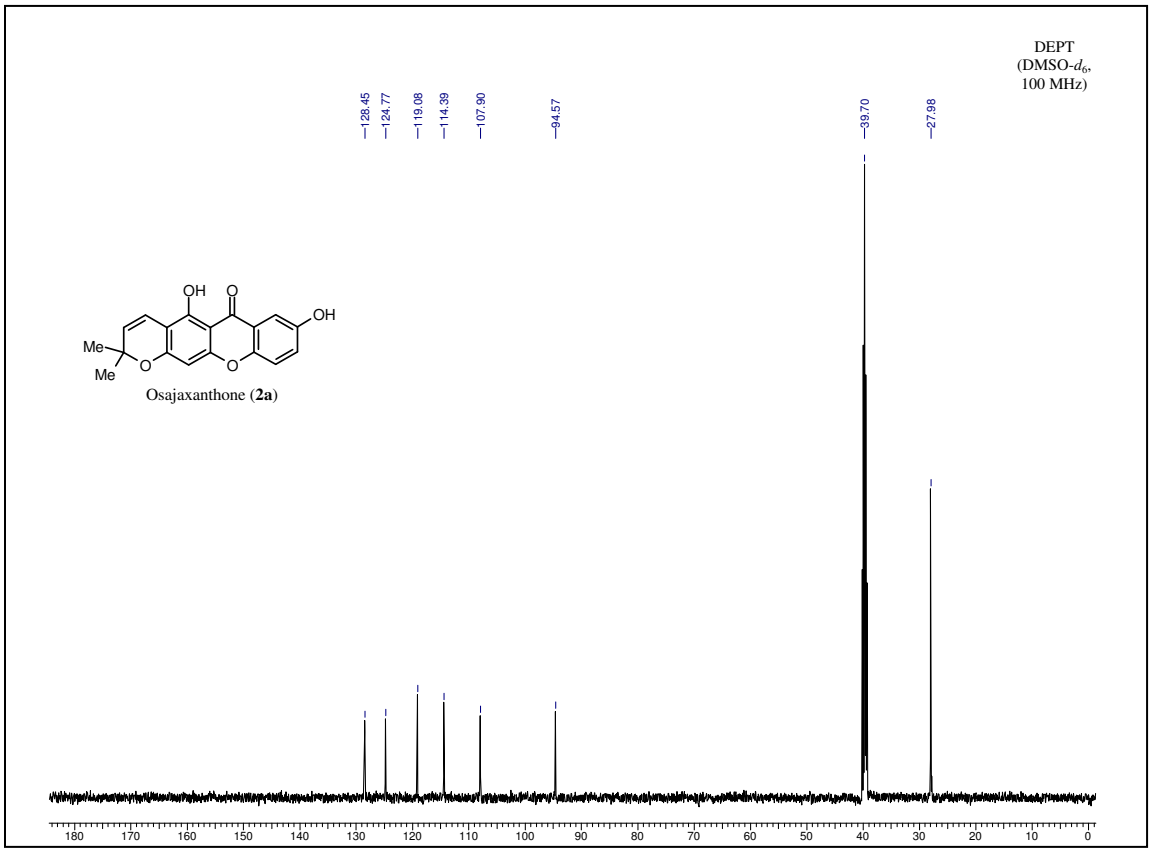
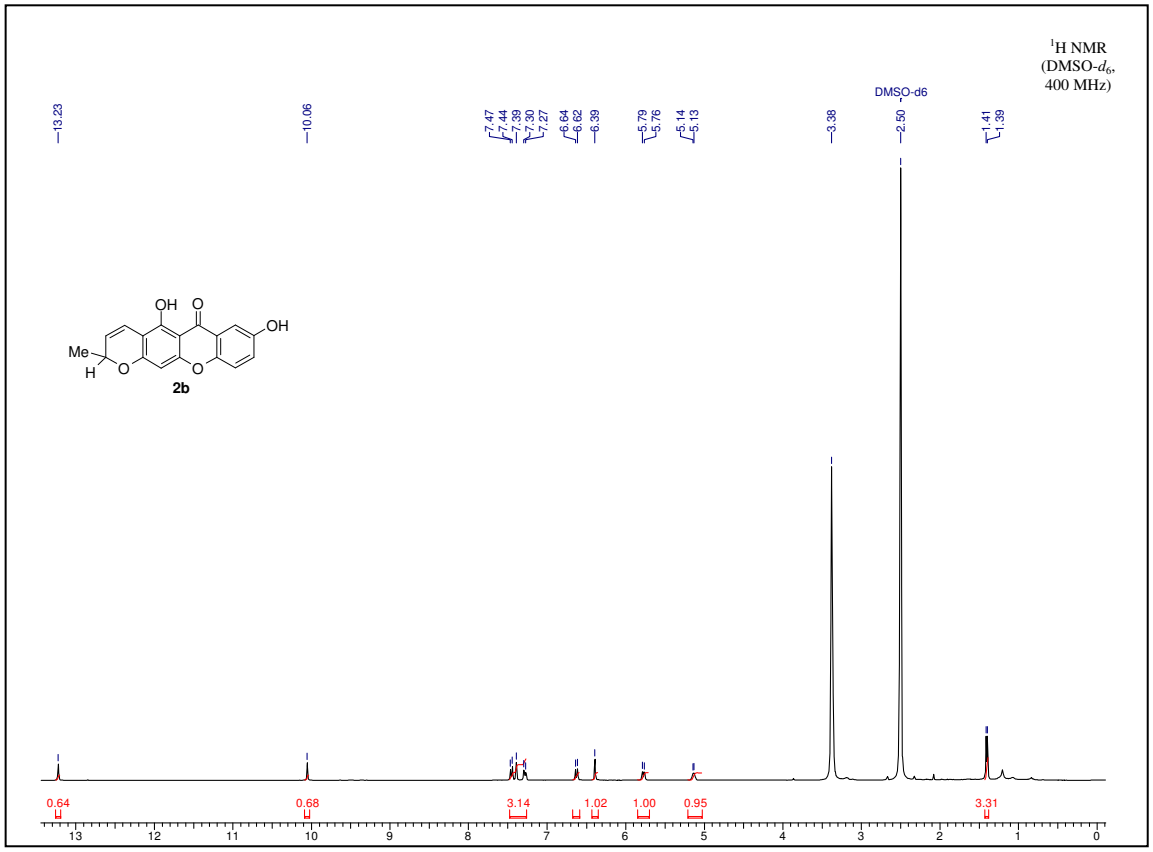
93.90
DMSO-d6
39.70
^{13}C NMR
(DMSO-d_6,
50 MHz)
OH
O
OH
HO
O
1,3,7-Trihydroxyxanthen-9-one (**1**)
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0


124.41
118.91
107.94
97.76
93.67
39.70
DEPT
(DMSO-d_6,
50 MHz)
OH
O
OH
HO
O
1,3,7-Trihydroxyxanthen-9-one (**1**)
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0


^{1}H NMR
(DMSO-d_6,
400 MHz)
13.26
10.07
7.48
7.46
7.40
7.30
7.28
7.27
6.61
6.59
6.40
5.78
5.76
3.41
DMSO-d6
2.50
1.43
OH
O
OH
Me
Me
O
O
Osajaxanthone (**2a**)
0.77
0.85
3.05
1.02
1.03
6.14
13 12 11 10 9 8 7 6 5 4 3 2 1 0


^{13}C NMR
(DMSO-d_6,
100 MHz)
DMSO-d6
180.46
160.44
156.98
154.39
149.39
128.84
125.15
120.62
119.45
114.72
108.24
104.01
103.08
94.93
78.75
39.70
28.31
OH
O
OH
Me
Me
O
O
Osajaxanthone (2a)
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0


DEPT
(DMSO-d_6,
100 MHz)
128.45
124.77
119.08
114.39
107.90
94.57
39.70
27.98
OH
O
OH
Me
Me
O
O
Osajaxanthone (2a)
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0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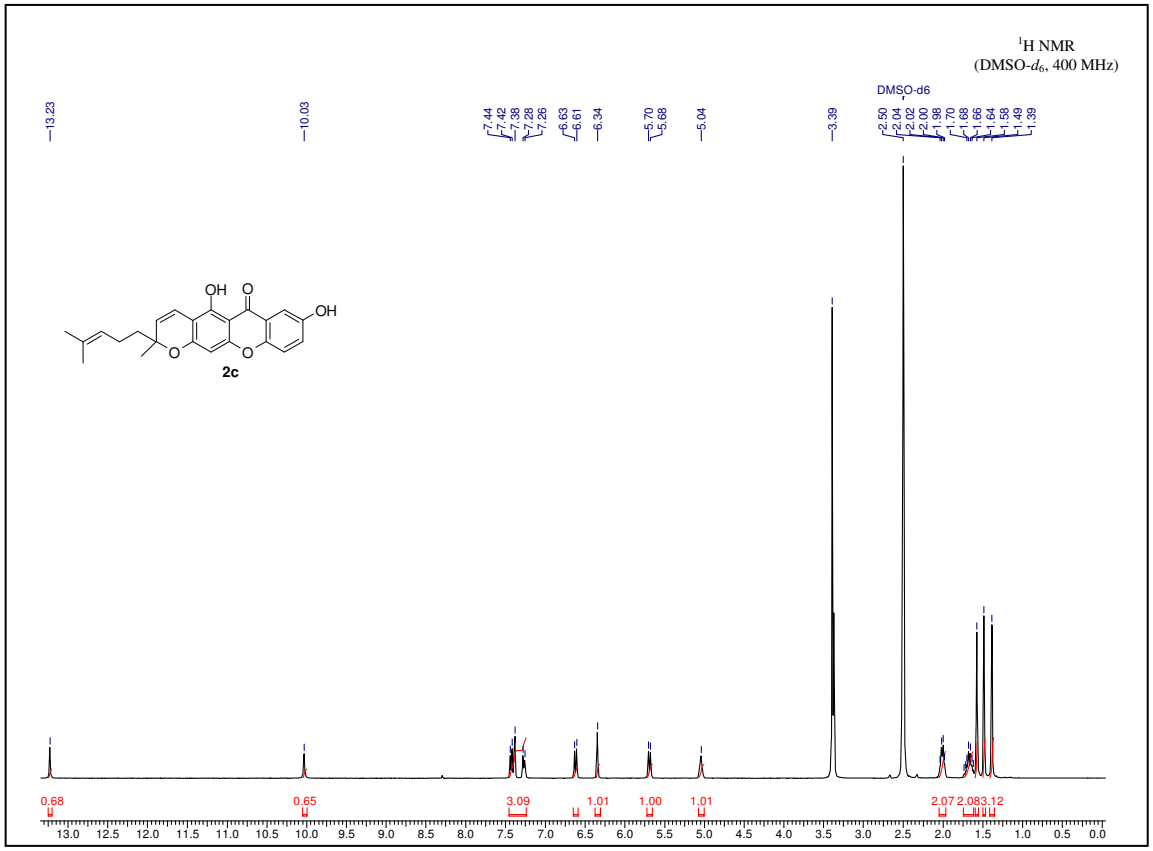
(DMSO-d_6,
400 MHz)
DMSO-d6
13.23
10.06
7.47
7.44
7.39
7.30
7.27
6.64
6.62
6.39
5.79
5.76
5.14
5.13
3.38
2.50
1.41
1.39
OH
O
OH
Me
H
O
O
2b
0.64
0.68
3.14
1.02
1.00
0.95
3.31


^{1}H NMR
(DMSO-d_6, 400 MHz)
DMSO-d6
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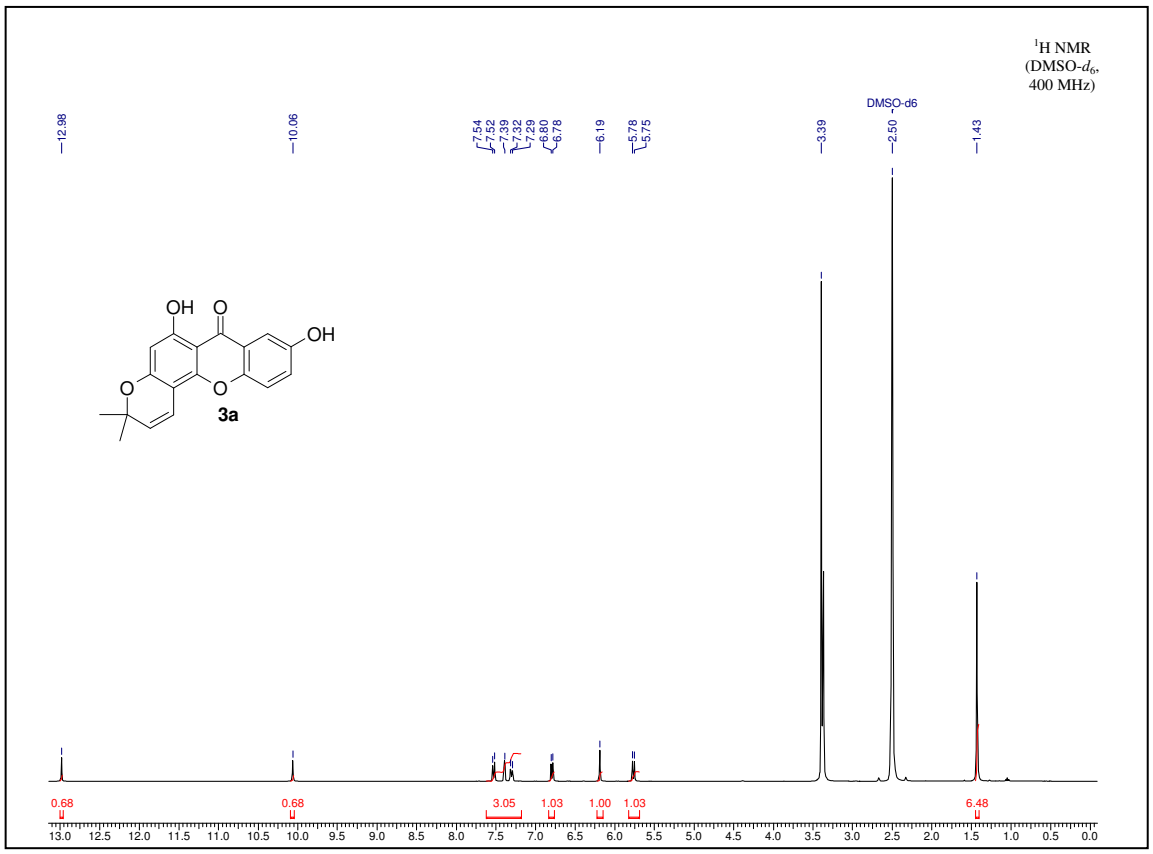
10.03
7.44
7.42
7.38
7.28
7.26
6.63
6.61
6.34
5.70
5.68
5.04
3.39
2.50
2.04
2.02
2.00
1.98
1.70
1.68
1.66
1.64
1.58
1.49
1.39
OH
O
OH
O
O
2c
0.68
0.65
3.09
1.01
1.00
1.01
2.07
2.08
3.12


^{1}H NMR
(DMSO-d_6,
400 MHz)
DMSO-d6
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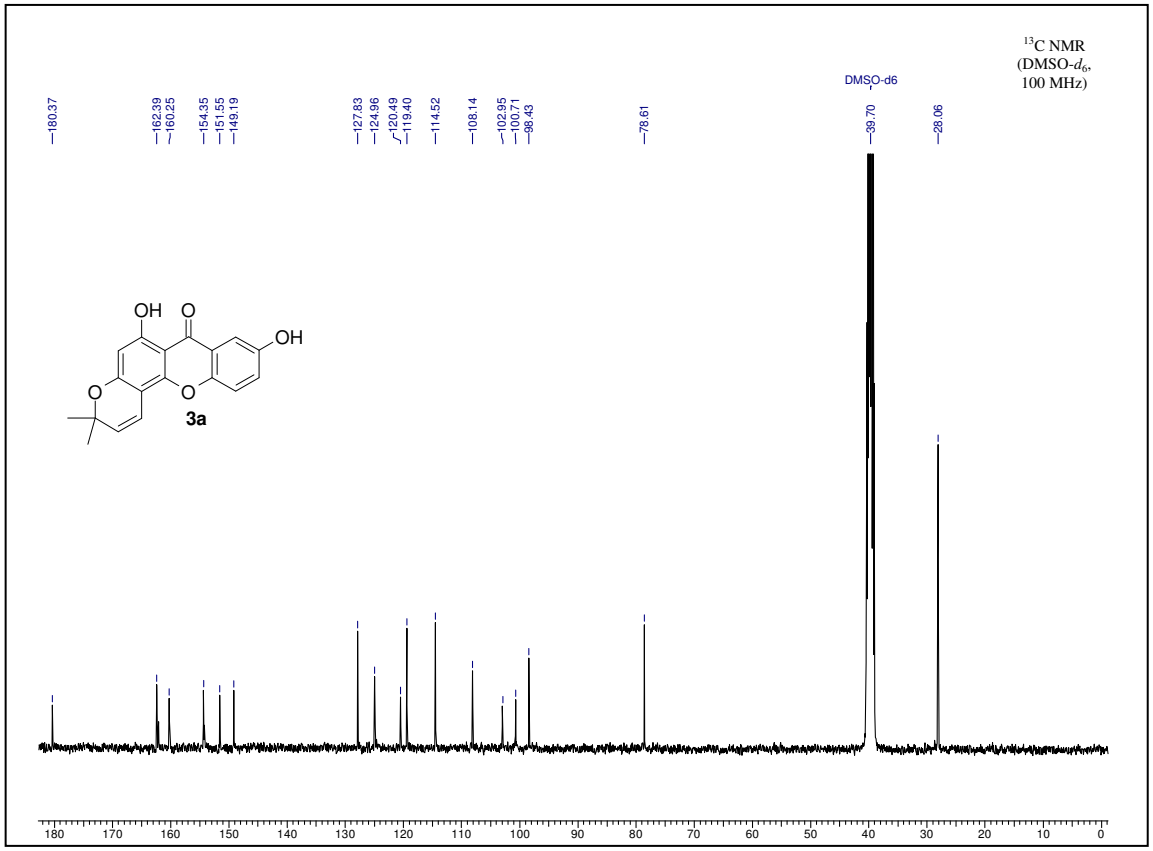
10.06
7.54
7.52
7.39
7.32
7.29
6.80
6.78
6.19
5.78
5.75
3.39
2.50
1.43
OH
O
OH
O
O
3a
0.68
0.68
3.05
1.03
1.00
1.03
6.48


^{13}C NMR
(DMSO-d_6,
100 MHz)
DMSO-d6
180.37
162.39
160.25
154.35
151.55
149.19
127.83
124.96
120.49
119.40
114.52
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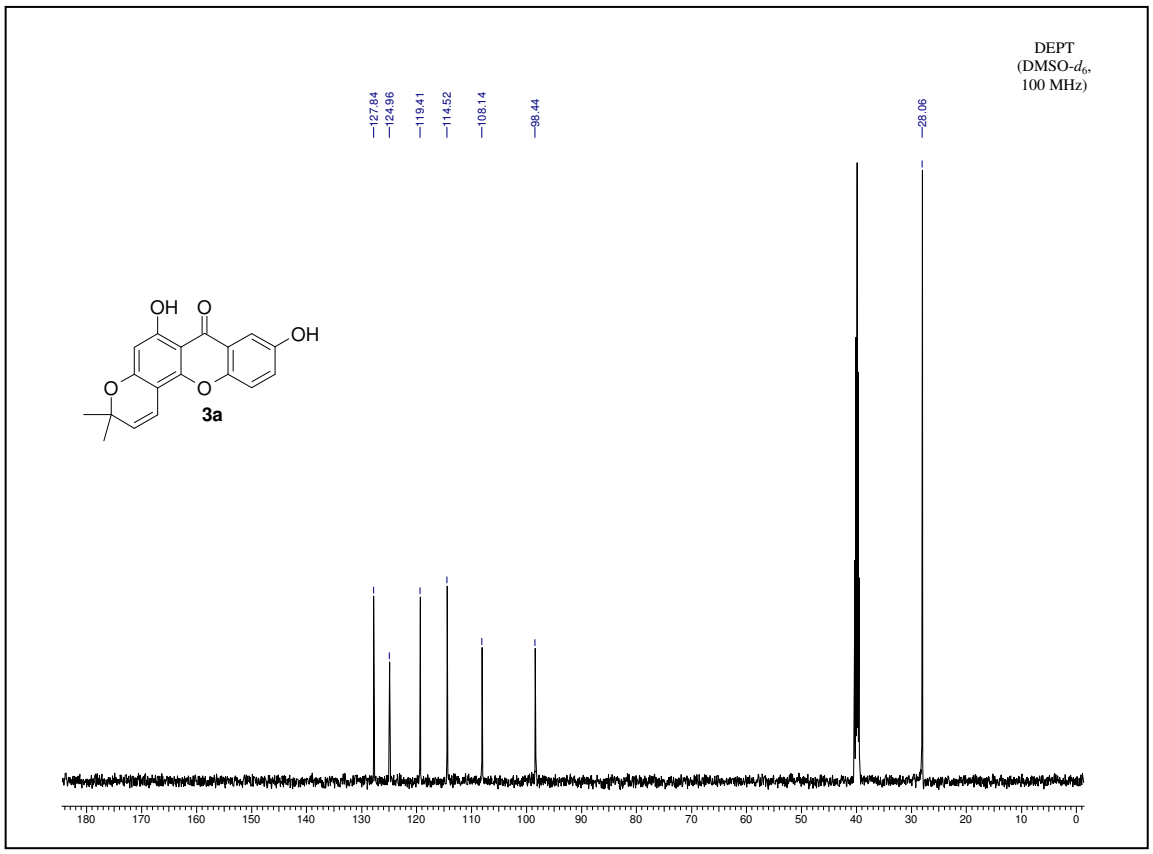
78.61
39.70
28.06
OH
O
OH
O
O
3a


DEPT
(DMSO-d_6,
100 MHz)
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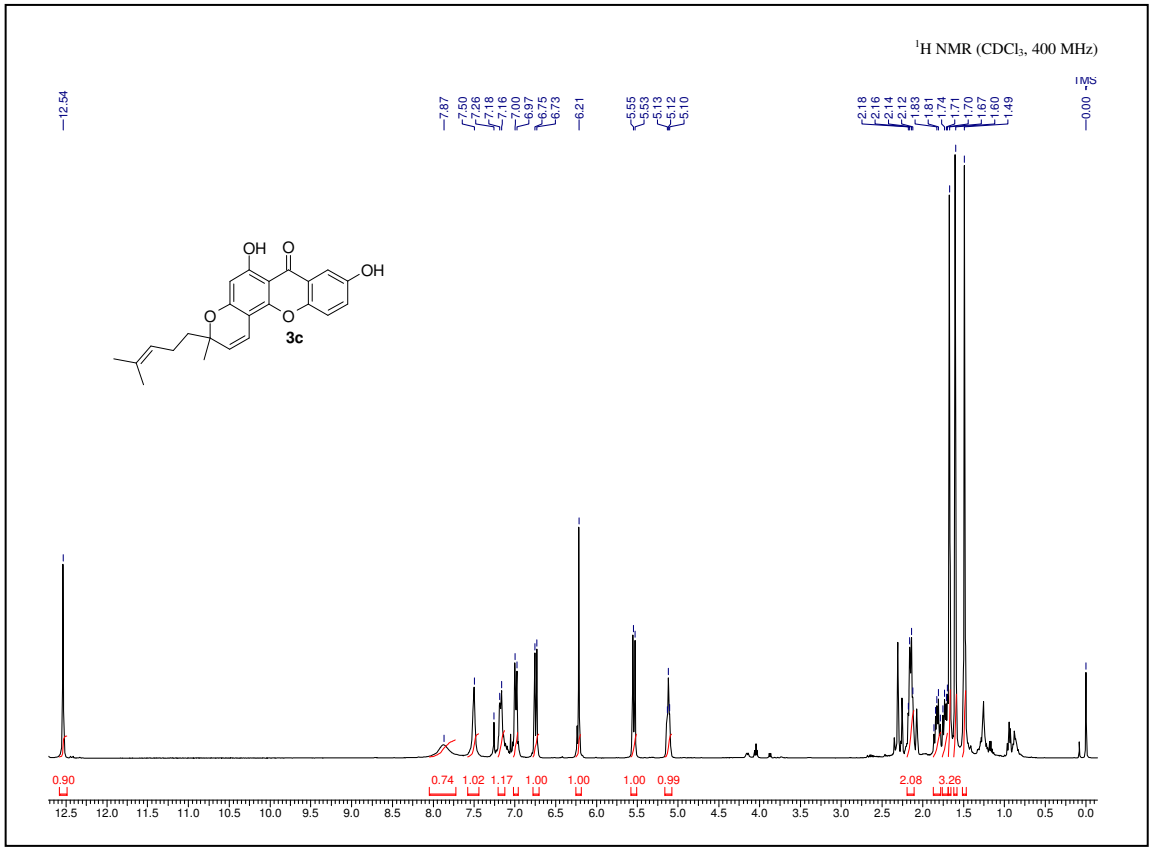
124.96
119.41
114.52
108.14
98.44
28.06
OH
O
OH
O
O
3a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12.54
7.87
7.50
7.26
7.18
7.16
7.00
6.97
6.75
6.73
6.21
5.55
5.53
5.13
5.12
5.10
2.18
2.16
2.14
2.12
1.83
1.81
1.74
1.71
1.70
1.67
1.60
1.49
TMS
0.00
OH
O
OH
O
O
3c
0.90
0.74
1.02
1.17
1.00
1.00
1.00
0.99
2.08
3.26

2B.7 References and Footnote

1. (a) Hay, A. E.; Aumond, M. C.; Mallet, S.; Dumontet, V.; Litaudon, M.; Rondeau, D.; Richomme, P. *J. Nat. Prod*. **2004**, *67*, 707. (b) Matsumoto, K.; Akao, Y.; Kobayashi, E.; Ohguchi, K.; Ito, T.; Tanaka, T.; Iinuma, M.; Nozawa, Y. *J. Nat. Prod*. **2003**, *66*, 1124. (c) Rukachaisirikul, V.; Kamkaew, M.; Sukavisit, D.; Phongpaichit, S.; Sawangchote, P.; Taylor, W. C. *J. Nat. Prod*. **2003**, *66*, 1531. (d) Gopalakrishnan, G.; Banumathi, B.; Suresh, G. *J. Nat. Prod*. **1997**, *60*, 519. (e) Marston, A.; Hamburger, M.; Sordat-Diserens, I.; Msonthi, J. D.; Hostettmann, K. *Phytochemistry* **1993**, *33*, 809. (f) Bo, T.; Liu, H. *J. Chromatography B* **2004**, *812*, 165 and references cited therein.
2. (a) Nicolaou, K. C.; Xu, H.; Wartmann, M. *Angew. Chem. Int. Ed*. **2005**, *44*, 756. (b) Dharmaratne, H. R.; Piyasena, K. G.; Tennakooan, S. B. *Nat. Prod. Res.* **2005**, *19*, 239. (c) Sukpondma, Y.; Rukachaisirikul, V.; Phongpaichit, S. *J. Nat. Prod*. **2005**, *68*, 1010 and references cited therein.
3. (a) Taher, M.; Idris, M. S.; Ahmad, F.; Arbain, D. *Phytochemistry* **2005**, *66*, 723. (b) Lopes, J. L. C.; Lopes, J. N. C.; Gilbert, B.; Bonini, S. E. *Phytochemistry* **1977**, *16*, 1101. (c) Wolfrom, M. L.; Dickey, E. E.; McWain, P.; Thompson, A.; Looker, J. H.; Windrath, O. M.; Komitsky, F. *J. Org. Chem*. **1964**, *29*, 689.
4. (a) Rukachaisirikul, V.; Ritthiwigrom, T.; Pinsa, A.; Swangchote, P.; Taylor, W. C. *Phytochemistry* **2003**, *64*, 1149. (b) For structures of other Nigrolineaxanthones, please see reference 4a.
5. Noro, T.; Ueno, A.; Mizutani, M.; Hashimoto, T.; Miyase, T.; Kuroyanagi, M.; Fukushima, S. *Chem. Pharm. Bull*. **1984**, *32*, 4455.
6. (a) Patel, G. N.; Trivedi, K. N. *Synth. Commun*. **1989**, *19*, 1641. (b) Ellis, R. C.; Whalley, B.; Ball, K. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1377. (c) Findlay, J. W. A.; Gupta, P.; Lewis, J. R. *J. Chem. Soc. (C)* **1969**, 2761 and references cited therein.
7. (a) Wolform, M. L.; Komitsky, Jr. F.; Looker, J. H. *J. Org. Chem*. **1965**, *30*, 144. (b) Wolfrom, M. L.; Koos, E. W.; Bhat, H. B. *J. Org. Chem*. **1967**, *32*, 1058. (c) Jain, A. C.; Khanna, V. K.; Seshadri, T. R. *Tetrahedron* **1969**, *25*, 2787. (d) Tisdale, E. J.; Kochman, D. A.; Theodorakis, E. A. *Tetrahedron Lett*. **2003**, *44*, 3281.
8. Lewis, J. R.; Reary, J. B. *J. Chem. Soc. (C)* **1970**, 1662.
9. Horne, S.; Rodrigo, R. *J. Org. Chem*. **1990**, *55*, 4520.

10. (a) Mondal, M.; Argade, N. P. *Synlett* **2004**, 1243. (b) Saimoto, H.; Yoshida, K.; Murakami, T.; Morimoto, M.; Sashiwa, H.; Shigemasa, Y. *J. Org. Chem.* **1996**, *61*, 6768.
11. Mondal, M.; Puranik, V. G.; Argade, N. P. *J. Org. Chem.* **2006**, *71*, 4992.
12. Higgs, D. E.; Nelen, M. I.; Detty, M. R. *Org. Lett.* **2001**, *3*, 349.
13. G. M. Sheldrick, SHELX-97 program for crystal structure solution and refinement, University of Göttingen, Germany, 1997.

2C. Section C

A Facile Phenol Driven Intramolecular Diastereoselective Thermal/Base Catalyzed Dipolar [2+2] Annulation Reactions: An Easy Access to Complex Bioactive Natural and Unnatural Benzopyran Congeners

This section features the following topics:

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2C Section C: A Facile Phenol Driven Intramolecular Diastereoselective Thermal/Base Catalyzed Dipolar [2+2] Annulation Reactions: An Easy Access to Complex Bioactive Natural and Unnatural Benzopyran Congeners

2C.1 Background

Several structurally complex compounds with hexahydrooxacyclobutaindane moiety have been isolated as bioactive natural products and the natural products with oxabicyclononane units are also known (Figure 1).[1-8] Among these, rhododaurichromanic

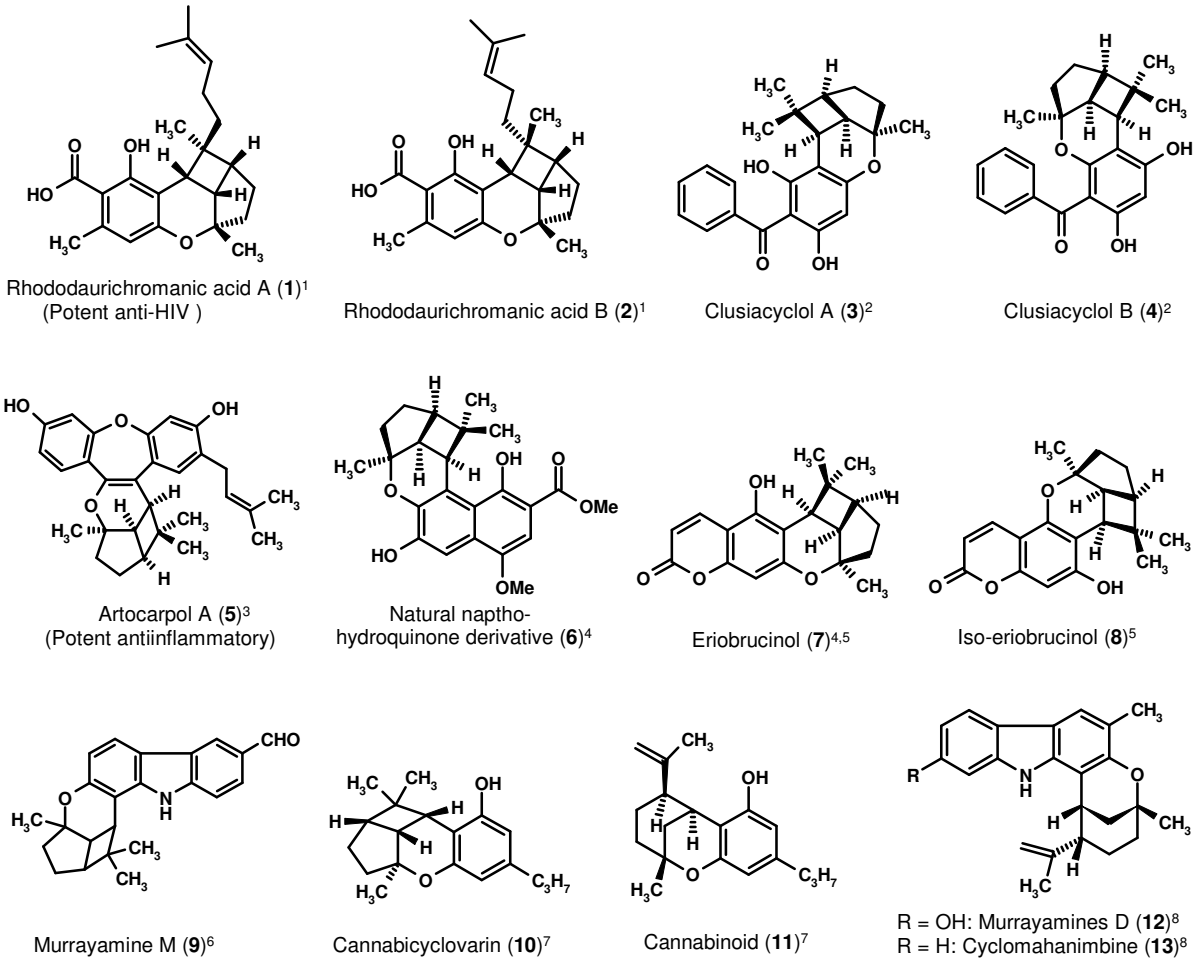


Figure 1. Naturally Occurring Hexahydrooxacyclobutaindanes and Oxabicyclononanes

acid A (**1**) (from *Rhododendron dauricum*)[1] and artocarpol A (**5**) (from *Artocarpus rigida*)[3] are of current interest, as they possess potent anti-HIV and potent antiinflammatory activities respectively.[1,3] Such type of natural and unnatural compounds with oxacyclobutaindane core units have been synthesized earlier by using intramolecular [2+2] photochemical[1b,c,3c,5,9,10] or acid catalyzed cationic[11] cycloaddition reactions of various suitably substituted benzopyrans. The construction of oxabicyclononane skeleton is known in the literature via intramolecular cyclization of phenolic groups with the correctly attached limonene moiety.[9]

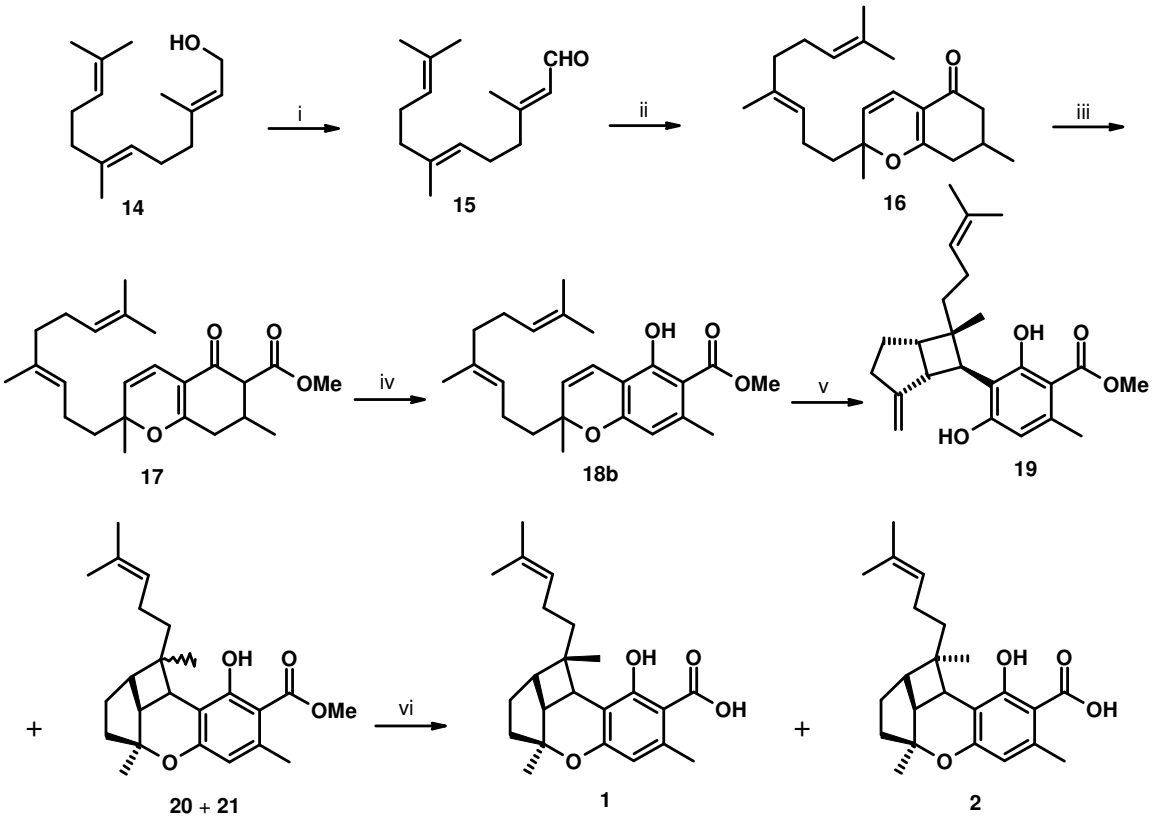
2C.1.1 Synthetic Approaches Towards Rhododaurichromanic Acid A, B and Artocarpol A

The clinical potential of these new complex bioactive natural products with oxacyclobutaindane unit have led to great interest in developing new synthetic strategies. Before discussing our results, the reported synthetic approaches towards rhododaurichromanic acid A, B and artocarpol A are illustrated in brief in the following part.

[A] Hsung's Approach Towards (±)-Rhododaurichromanic Acid A and B and Methyl Ester of (±)-Daurichromenic Acid

Hsung and co-workers[1b] have reported the first total synthesis of (±)-rhododaurichromanic Acid A (**1**) and B (**2**) using photochemical [2+2] cycloaddition of methyl ester of (±)-daurichromenic acid (**18b**) (Scheme 1). They have synthesized methyl ester of (±)-daurichromenic acid (**18b**), from (*E*,*E*)-farnesol (**14**) via oxidation to the corresponding α,β-unsaturated aldehydes **15**, followed by an in situ α,β-unsaturated iminium salt formation in presence of piperidine and acetic anhydride which on Knoevenagel condensation with 5-methyl-1,3-cyclohexanedione followed by a 6π-electron electrocyclic ring closure furnished the desired oxadecalin derivative **16** in 70% yield. The lithium enolate derived from (**16**) on treatment with Mander's reagent gave the β-ketoester **17** which on aromatization by DDQ oxidation furnished methyl ester of (±)-daurichromenic acid (**18b**) in 44% yield. The ester **18b** on irradiation in hexane using Pyrex as a cutoff filter afforded the desired inseparable mixture of cycloadducts **20** and **21** in 1:1 ratio with an overall 79% yield along with an undesired bicycloheptane derivative **19**. The cycloadduct mixture of **20** and **21** on saponification using 6 M aqueous NaOH in

THF/MeOH furnished the HPLC separable desired (±)-rhododaurichromanic Acid A (**1**) and B (**2**), in total six steps with a 15% overall yield.



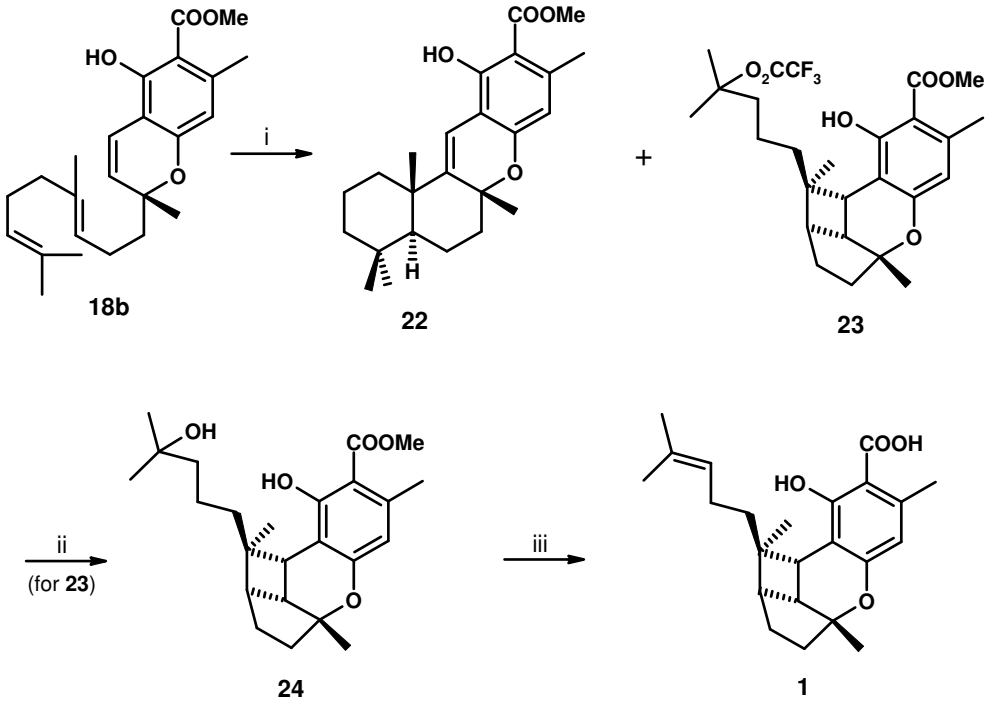
Scheme 1 *Reagents, conditions and yields*: (i) DMSO, DCM, SO_3-pyridine, Et_3N (94%); (ii) Piperidine, Ac_2O, 90 ^oC, EtOAc, 1 h, 5-methyl-1,3-cyclohexanedione, toluene, 90 ^oC, 12-18 h (70%); (iii) LDA, THF, −78 ^oC, $NCCO_2Me$ (71%); (iv) DDQ, toluene, reflux (44%); (v) Hexane, $h\nu$, pyrex, rt, 65 h [**20**+**21** (1:1), 79%]; (vi) Aq. 6 M NaOH, MeOH/THF, rt, 20 h (94%; **1**:**2** = 1:1).

[B] Kang's Approach Towards (±)-Rhododaurichromanic Acid A and B and Methyl Ester of (±)-Daurichromenic Acid

Kang *et al*[1c] reported a five steps synthesis of (±)-daurichromenic acid with 49% overall yield using microwave assisted tandem condensation and intramolecular S_N2'-type cyclization to form the 2*H*-benzopyran core structure. The (±)-daurichromenic acid in low pressure mercury lamp irradiation furnished (±)-rhododaurichromanic acid A (40%) and B (20%). The details have been discussed in First Chapter (Scheme 24) of present dissertation.

[C] Hsung's Approach Towards Rhododaurichromanic Acid A

Recently Hsung and co-workers[11] reported Bronsted acid such as trifluoroacetic acid (TFA) mediated unusual cationic [2+2] cycloaddition of daurichromenic ester **18b** to form natural didehydro hongoquercin A ester **22** and derivative of rhododaurichromanic acid A **23** as major product. Compound **23** was converted to the natural product rhododaurichromanic acid A (**1**) in three steps using K_2CO_3 mediated trifluoroacetate hydrolysis followed by elimination of tertiary hydroxyl group and finally ester hydrolysis sequence (Scheme 2).



Scheme 2 *Reagents, conditions and yields*: (i) TFA:DCM (1:20), 0 ^oC to rt, 0.5 h (**22**: 19%; **23**: 35%); (ii) K_2CO_3, MeOH/THF, rt (99%); (iii) (a) Burgess reagent, toluene, reflux, (b) Aq. 6 M NaOH, MeOH, rt, (c) H^+/HCl (91%).

[D] Wilson's Approach Towards Artocarpol A Analogue

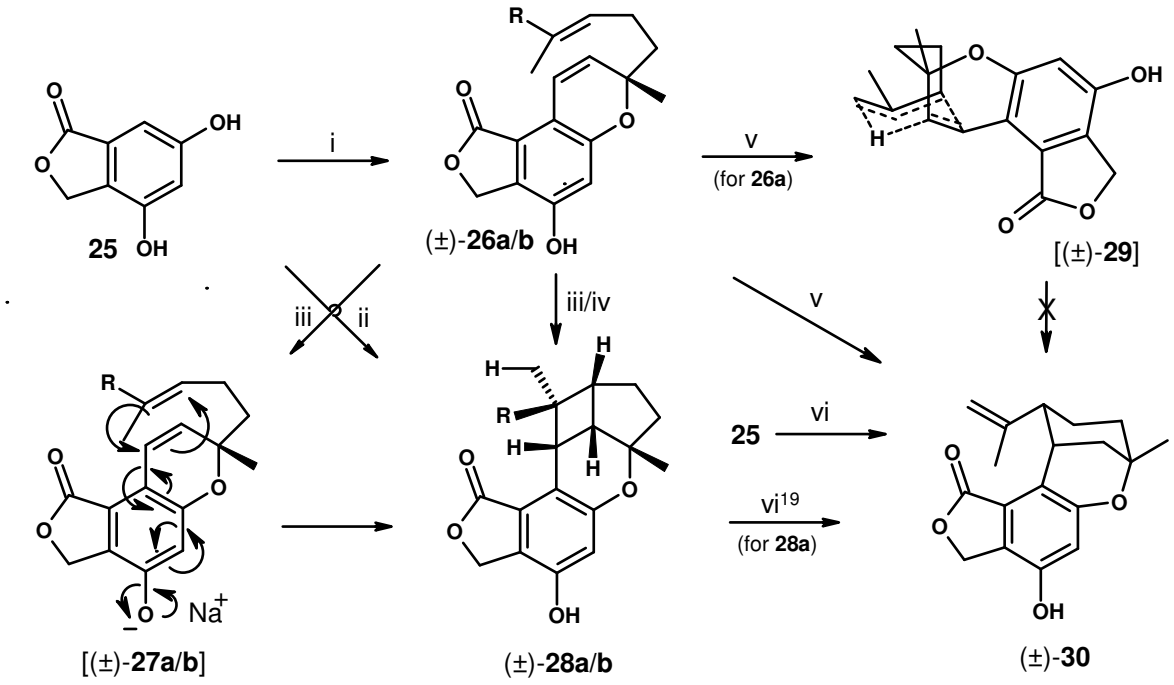
Wilson and co-workers[3c] have accomplished the first total synthesis of artocarpol A analogue from commercially available 2-phenoxybenzoic acid using photochemical [2+2] cycloaddition pathway. The details have been elaborated in First Chapter (Scheme 25) of present dissertation.

2C.2 Rationale for Present Work

All these natural products with oxacyclobutaindane moiety bear the free phenolic group/groups and one can easily make out that nature might be designing them by using the condensation reactions of phenolic compounds with α,β-unsaturated aldehydes to form corresponding benzopyran followed by intramolecular [2+2] cycloaddition reactions. It is also evident from the above reports that the construction of oxacyclobutaindane skeleton requires intramolecular photochemical cationic [2+2] cycloaddition reaction of the suitably substituted benzopyran. Hence the provision of a facile route to oxacyclobutaindane skeleton is a challenging task of current interest. We reasoned that all these molecules bear a free phenolic group and hence the intramolecular phenol driven thermal or base catalyzed [2+2] cycloaddition approach towards oxacyclobutaindane skeleton would be possible via the corresponding dipolar intermediates.[12] Hence, we envisaged an easy thermal or base catalyzed [2+2] cycloaddition approach towards these complex bioactive oxacyclobutaindanes and our studies on the synthesis of these bioactive natural products are presented in the following part.

2C.3 Result and Discussion

The reaction of 4,6-dihydroxyphthalide (**25**)[13] with citral (5.00 equiv.) at 120-130 ^{o}C exclusively furnished the corresponding oxacyclobutaindane derivative (±)-**28a** with 82% yield, via the benzopyran formation[14-16] **26a** followed by an in situ intramolecular [2+2] cycloaddition pathway tracing a highly diastereoselective route (Scheme 3). The structural assignment of **28a** was done on the basis of ^{1}H/^{13}C NMR and the X-ray crystallographic data (Figure 2). The reaction of phthalide **25** with citral at 160-170 ^{o}C exclusively gave the oxabicyclononane (±)-**30** in 82% yield. The two vinylic protons in the ^{1}H NMR spectrum of **30** appeared at 3.80 and 4.47 ppm and such an upfield shift could be due to the anisotropic effect of the lactone carbonyl group. The ^{13}C NMR and the corresponding DEPT spectra showed cleanly the presence of those two vinylic carbons and finally, the structure of **30** was confirmed from the X-ray crystallographic data (Figure 3). Both the structural skeletons, oxacyclobutaindane and oxabicyclononane, exist in nature. To study the mechanism of formation of both **28a** and **30**, we synthesized the intermediate benzopyran **26a/b**. The treatment of phthalide **25** with citral/farnesal in the presence of a



26a: R= CH_3; **26b**: R= $CH_2CH_2CH{=}C(CH_3)_2$; **28a**: R = CH_3; **28b**: R= $CH_2CH_2CH{=}C(CH_3)_2$.

Scheme 3 *Reagents, conditions and yields*: (i) Citral/farnesal (5.00 equiv.), $Ca(OH)_2$ (1.50 equiv.), MeOH, 60 °C, 6 days (**26a**: 60%; **26b**: 63%); (ii) Citral (5.00 equiv.), 120-130 °C, 6 h (**28a**: 82%); (iii) (a) MeOH : 2 N NaOH (5 : 1), 0 °C to rt, 8-10 h, (b) H^+/2 N HCl (**28a**: 80%; **28b**: 78%); (iv) 120-130 °C, 6 h (**28a**: 76%); (v) 160-170 °C, 6 h (82%); (vi) Citral (5.00 equiv.), 160-170 °C, 6 h (82%).

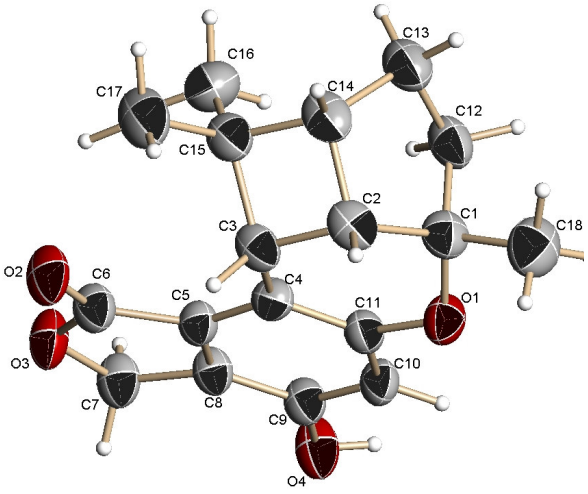


Figure 2. ORTEP diagram of **28a**
(ellipsoids are drawn at 40% probability)

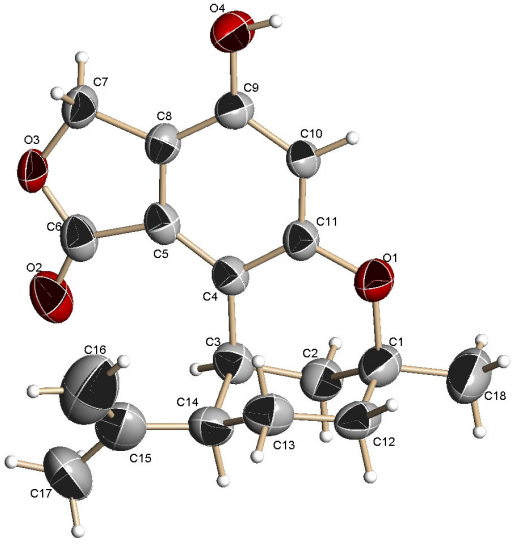
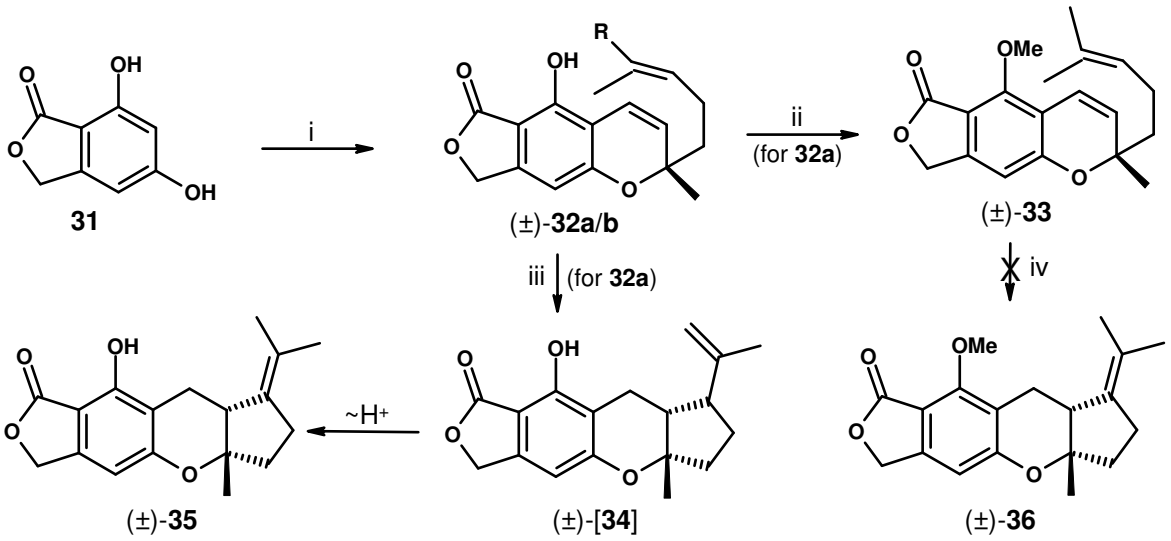


Figure 3. ORTEP diagram of **30**
(ellipsoids are drawn at 50% probability)

catalytic amount of $Ca(OH)_2$ in methanol gave the benzopyrans **26a/b** in 60/63% yields respectively.[14,15] Herein, the observed regioselectivity could be a result of selective formation of the relatively more stable carbanion at the 3-position of phthalide **25** in comparison with the formation at 5-position. The benzopyran **26a** underwent a facile phenol driven thermal dipolar [2+2] cycloaddition reaction at 120-130 ^{o}C to yield **28a** in 76% yield. Similarly, both the benzopyrans **26a/b** on treatment with aqueous 2 N sodium hydroxide solution at room temperature followed by acidification also exclusively gave the corresponding phenoxy anion driven dipolar [2+2] cycloaddition products **28a/b** in 80/78% yields via the corresponding intermediates **27a/b**. Both **26a** and **28a** on heating at 160-170 ^{o}C exclusively gave the rearranged product **30** in 80-82% yield. The possibility of the formation of oxabicyclononane **30** from the benzopyran **26a** at elevated temperature through a straight forward intramolecular ene reaction[17a,b] via the plausible intermediate **29** is excluded, as under the thermal ene-condition the symmetry allowed[17c] suprafacial-suprafacial [1,5]-H shift requires highly ordered cyclic transition state **29**, in which the isopropenyl group occupies the axial position, where as in product **30**, the isopropenyl group is in equatorial position. Hence, the formation of oxabicyclononane **30** from the benzopyran **26a** at elevated temperature could be a result of straight forward intramolecular cyclization to form **28a** at 120-130 ^{o}C followed by its thermal rearrangement at 160-170 ^{o}C. As a result of ring strain[18a] associated with the cyclobutane, the C-C bond is considerably weaker and thermolysis of cyclobutane leads to the further rearrangement.[18b] These observations revealed that in these reactions, the oxacyclobutaindane **28a** is a kinetically controlled product and it undergoes a framework rearrangement at 160-170 ^{o}C to exclusively furnish the rearranged thermodynamically controlled product **30**.

We planned to verify the generality of the present phenol directed [2+2] cycloaddition reaction and designed the linear benzopyrans **32a/b** in 65/68% yields using the conditions[14] developed by us earlier for the regioselective coupling of α,β-unsaturated aldehydes at the 4-position of phthalide **31**[13] (Scheme 4). The benzopyran **32b** is structurally very similar to the naturally occurring potent anti-HIV agent daurichromenic acid A.[1,20] In our hands, the base catalyzed intramolecular dipolar [2+2] cyclization of **32a** to the corresponding oxacyclobutaindane derivative met with failure and it could be a result of position of phenolic hydroxyl group which is intramolecularly

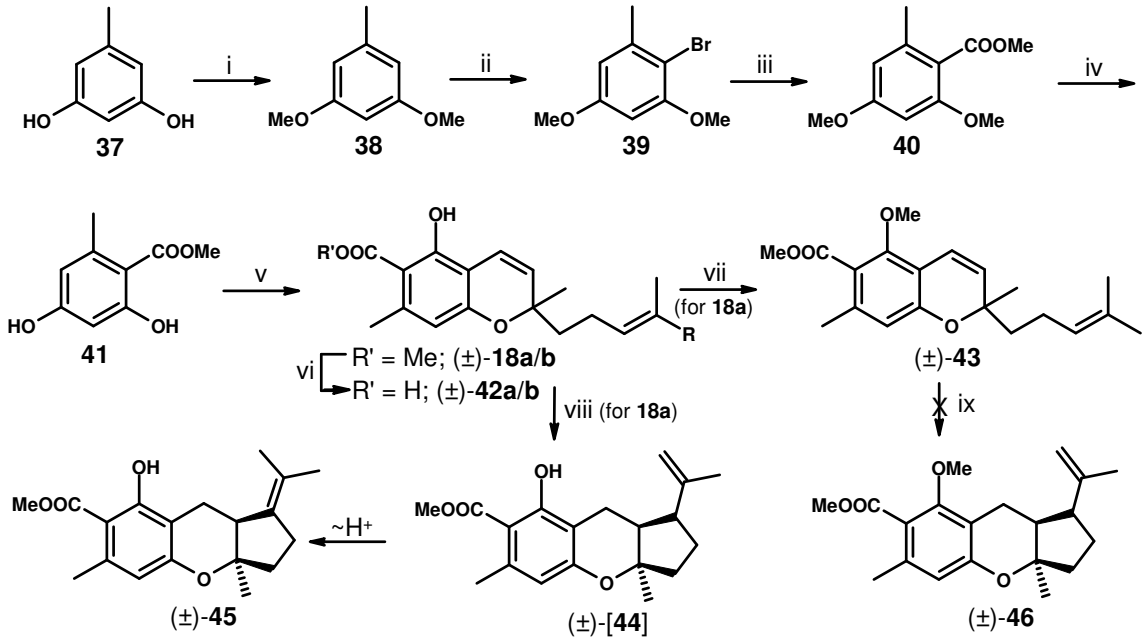


32a: R = CH_3; **32b**: R = $CH_2CH_2CH{=}C(CH_3)_2$.

Scheme 4 *Reagents, conditions and yields*: (i) Citral/farnesal (5.00 equiv.), DBU (1.10 equiv.), MeCN, 50 ^oC, 24 h (**32a**: 65%; **32b**: 68%); (ii) Acetone, K_2CO_3 (5.00 equiv.), MeI (5.00 equiv.), reflux, 6 h (99%); (iii) 165-170 ^oC, 6 h (**35**: 90%); (iv) Rt to 200 ^oC, 6 h (0%).

hydrogen bonded with the adjacent carbonyl group and the higher stability of the corresponding phenoxy anion due to the conjugation with the carbonyl group. We heated the benzopyran **32a** neat up to 160 ^oC with a gradual increase in temperature, but did not observe any thermal reaction. The heating of the above reaction mixture at 165-175 ^oC directly furnished the isopropylidinecyclopentylbenzopyran (±)-**35**[21] in 90% yield and we were unable to arrest this reaction at the intermediate **34**. The structure of this rearranged product was assigned on the basis of $^1H/^{13}C$ NMR data. The formation of **35** from **32a** at higher temperature could be a result of the possible intramolecular thermal symmetry allowed (suprafacial-suprafacial [1,5]-H shift) ene reaction[17] of **32a** to yield the intermediate **34**, followed by thermal isomerization to the more stable isopropylidinecyclopentylbenzopyran **35** with the tetrasubstituted carbon-carbon double bond. The methyl ether **33** failed to undergo any reaction[22] on heating upto 200 ^oC indicating that the presence of free phenolic hydroxyl group is essential to get the ene adduct. We surmise that the participation of phenolic hydroxyl group at elevated temperature can also lead to intramolecular dipolar [2+2] cycloaddition and hence the oxacyclobutaindane intermediate formation followed by rearrangement could be another possible pathway for the present reaction.

Similarly, we planed to synthesize the bioactive natural benzopyrans cannabichromeorcinic acid (**42a**)[23] and daurichromenic acid (**42b**)[1,20] (*Rhododendron dauricum*), and to employ the present dipolar [2+2] annulation approach for the synthesis of rhododaurichromanic acid A[1a] (Scheme 5). Our synthesis of **42a/b** started with orcinol monohydrate (**37**) as a suitable starting material. The compound **37** on methylation followed by NBS-induced nuclear bromination exclusively furnished the expected bromo compound **39**[24] in ~ 99% yield. The bromo compound **39** on lithiation followed by the treatment with methyl chloroformate gave the required ester **40**[25] in 96% yield, which on $AlCl_3$ induced demethylation provided the required phenolic ester **41** in 98% yield. The compound **41** is a natural product[26] and therefore our proposed route to **42a/b** appears to be biogenetic in nature. The treatment of the ester **41** with citral/farnesal in the presence of $Ca(OH)_2$ gave the desired benzopyrans **18a/b** in very good yields. The observed regioselectivity could be the result of a complexation of Ca^{2+} ion with both the phenolic groups, thus activating the 3-position of **41** for the condensation reaction.[14,15] Saponification of these esters **18a/b** provided the natural benzopyran carboxylic acids **42a/b** in 82 and 80% yields respectively. The analytical and spectral data obtained for **42a/b** were in complete agreement with the reported data for the natural cannabichromeorcinic acid (**42a**)[23] and daurichromenic acid (**42b**).[1a] Next we employed the phenol driven dipolar approach on daurichromenic ester **18a** for further cyclization. As earlier, we heated the benzopyran ester **18a** up to 160 ^{o}C and did not find any reaction, the increase in temperature to 165-175 ^{o}C directly furnished the benzopyran (±)-**45** in 98% yield. Herein also, as indicated in Scheme 4, the reaction followed a similar course to yield the unisolable ene reaction intermediate **44** and its in situ isomerization furnished (±)-**45**. In our hands an attempted base induced [2+2] cyclization provided only the corresponding acid **42a** and not the desired cyclized product. Both **18b/42b** on heating at 175 ^{o}C provided only polymeric gummy materials. Herein also a higher temperature was necessary to initiate the thermal reaction in **18a**, as the activating phenolic group is in conjugation and intramolecularlly hydrogen bonded with the adjacent carbonyl moiety. As earlier, here also we noticed that the present reaction is possible only in the presence of free phenolic hydroxyl group of **18a**, as the methyl ether **43** failed to undergo any reaction[22] on heating upto 200 ^{o}C. Hence the possibility of formation of the corresponding oxacyclobutaindane intermediate could be another possible pathway for the present reaction. Though we were



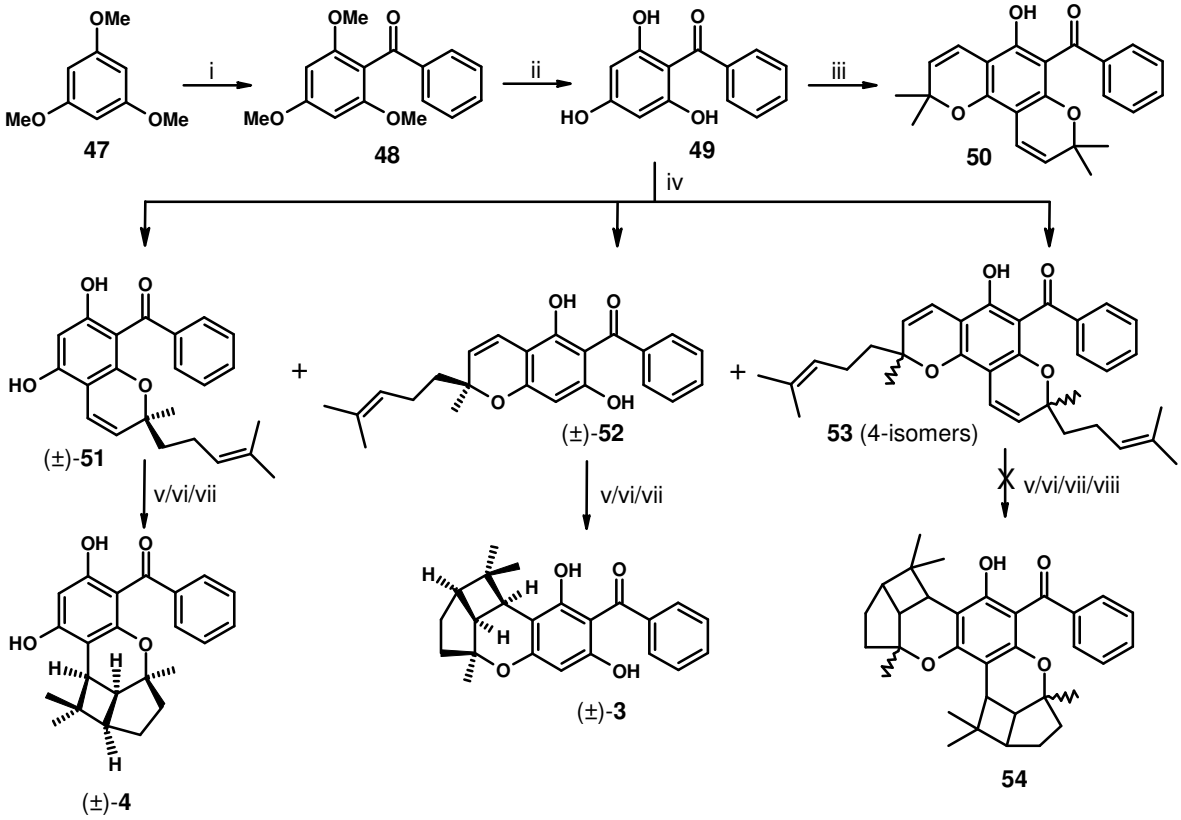
a: R = CH_3; **b**: R = $CH_2CH_2CH{=}C(CH_3)_2$.

Scheme 5 *Reagents, conditions and yields*: (i) Acetone, K_2CO_3 (5.00 equiv.), MeI (5.00 equiv.), reflux, 6 h (~100%); (ii) CCl_4, NBS (1.00 equiv.), reflux, 4 h (99%); (iii) (a) THF, –78 ^oC, *n*-BuLi (1.20 equiv.), 1 h, (b) $ClCO_2Me$ (excess), –78 ^oC to rt (96%); (iv) DCM, 0 ^oC, $AlCl_3$ (6.00 equiv.), rt, 12 h (98%); (v) MeOH, $Ca(OH)_2$ (2.00 equiv.), citral/farnesal (5.00 equiv.), rt, 72 h (**18a**: 72%; **18b**: 79%); (vi) MeOH : 3 N KOH (3:1), rt, 72 h (**42a**: 82%; **42b**: 80%); (vii) Acetone, K_2CO_3 (5.00 equiv.), MeI (5.00 equiv.), reflux, 6 h (98%); (viii) 175 ^oC, 6 h (98%); (ix) Rt to 200 ^oC, 6 h (0%).

unable to get the thermal [2+2] dipolar cycloaddition product from **18a**, a photochemical[1b,c] and cationic[11] conversion of **18b** to the rhododaurichromanic acid A and B is known.

Finally, we decided to synthesize the isomeric natural products Clusiacyclol A and B (*Clusia multiflora*)[2] using the present phenol driven [2+2] dipolar cycloaddition strategy following the biogenetic type pathway (Scheme 6). We synthesized the required natural product [27] trihydroxybenzophenone **49** from the symmetrical trimethoxybenzene **47** via Friedel-Crafts benzoylation, to obtain trimethoxybenzophenone **48**,[28] followed by its demethylation to obtain **49** in high yield. Initially, we planned for the synthesis of the relatively simple diprenylated natural product clusiaphenone A (**50**) (*Clusia sandiensis*).[29] The benzophenone derivative **49** in the presence of DBU underwent smooth condensation reactions with two molecules of the α,β-unsaturated aldehyde prenal to yield the natural product **50** in 94% yield. Later, we carried out systematic studies on condensation reaction

of citral with **49**. The benzophenone **49** on reaction with citral in the presence of $Ca(OH)_2$/DBU furnished a mixture of three products (by TLC). The silica gel column chromatographic separation of the above mixture followed by examination of ^1H NMR spectra revealed that mixture of products **51**+**4** (inseparable), **52**+**3** (inseparable) and a diastereomeric mixture of **53** (inseparable) were formed. In both **51** and **4** the methyl groups on the pyran ring were shielded due to the anisotropic effect of the adjacent phenyl group, which helped us to unambiguously discriminate them from the corresponding



Scheme 6 *Reagents, conditions and yields*: (i) $AlCl_3$ (1.50 equiv.), DCM, 0 ^oC, benzoyl chloride (1.00 equiv.), 0 ^oC to rt, 12 h (96%); (ii) DCM, BBr_3 (4.20 equiv.), −78 ^oC to rt, 48 h (92%); (iii) MeOH, DBU (2.20 equiv.), prenal (excess), rt, 36 h (94%); (iv) MeOH, DBU (0.80 equiv.), 0 ^oC, citral (1.00 equiv.), 6 h (**51**: 26%; **52**: 16%; **53**: 11%) or MeOH, $Ca(OH)_2$ (0.50 equiv.), rt, citral (1.00 equiv.), 96 h (**53**: 13%; **4**: 35%; **3**: 29%) or MeOH, DBU (2.20 equiv.), rt, citral (10.00 equiv.), 36 h (**53**: 95%); (v) MeOH, $Ca(OH)_2$ (0.20 equiv.), rt, 48 h (**4**: 79%; **3**: 76%); (vi) MeOH : 0.1 N KOH (3:1), rt, 24 h (**4**: 75%; **3**: 70%); (vii) 100-110 ^oC, 6 h (**4**: 82%; **3**: 80%); (viii) 170-180 ^oC, 6 h (0%).

isomeric products **52** and **3** respectively. Though both the positions in **49** are equivalent, one of the phenolic group is involved in intramolecular hydrogen bonding and the other

relatively free phenolic hydroxyl group participates in the intramolecular cyclization to yield mixture of **51**+**4**, always as a major product. However it was not possible to achieve complete regioselectivity in the coupling of **49** with citral to exclusively obtain either **51** or **52**. However, it was possible to stop the reaction of **49** with citral to obtain the column separable mixture of **51**+**52**+**53** by using less equivalents of DBU or to obtain the column separable mixture of **53**+**4**+**3** by using an excess amount of $Ca(OH)_2$, in very good yields. The naturally occurring pure (±)-clusiachromene C (**51**) (*Clusia multiflora*) on thermal/base catalyzed [2+2] cycloaddition gave the desired natural product (±)-clusiacyclol B (**4**) in very good yield. We expect (±)-**52** also to be a natural product from the sources containing **3**. Similarly, **52** on thermal/base catalyzed reaction furnished the natural product (±)-clusiacyclol A (**3**) in very good yield. Herein, we could stop the thermal reactions of **51** and **52** to obtain the kinetically controlled naturally occurring **4** and **3**, as the free non-hydrogen bonded phenolic group were available in both the compounds **51** and **52** respectively. The analytical and spectral data obtained for these natural products **50**, **51**, **4** and **3** were in complete agreement with the reported data.[2] In the reaction of **49** with citral, we could force the reaction to exclusively obtain the double condensed product **53** in excellent yield by using excess amount (5 equiv.) of citral, but as a diastereometic mixture in nearly 1:1 ratio. In our hands the compound **53** showed great reluctance to form the further cycloaddition product **54** under both thermal and base catalyzed conditions and only decomposed/polymeric materials were obtained.

2C.4 Summary

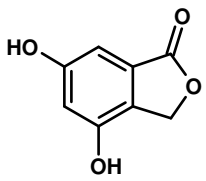
In summary, we have demonstrated a simple and efficient phenol directed intramolecular diastereoselective dipolar thermal/base catalyzed [2+2] cycloaddition approach to novel biologically important natural and unnatural benzopyran systems and the mechanistic aspects described in short are only the proposals.[30] The present approach to these complex oxacyclobutaindanes and the three different thermal framework rearrangements are noteworthy. These studies clearly reveal that in the present [2+2] cycloaddition approach, the presence of a free phenolic group is essential to design oxacyclobutaindanes either thermally or by using base catalysis. If the free hydroxyl group is involved in intramolecular hydrogen bonding with an adjacent carbonyl group, a higher temperature is necessary and in such cases it was not possible to stop the reactions at the

kinetically controlled products oxacyclobutaindanes, instead the rearranged thermodynamically controlled benzopyran derivatives were obtained. The control experiments with *O*-methyl ethers of starting phenols also clearly revealed that though the role is not clear, the free phenolic groups are essential for these thermal reactions. Such types of oxabicyclononanes units are also present in natural products and oxacyclobutaindanes can be the probable biogenetic intermediates. We feel that the present general approach to these important classes of compounds will be highly useful to design most of the natural products depicted in figure 1 and several other natural products and natural product analogs/congeners for structure-activity relationship studies. Synthesis of chiral chromans[31] and application of the present strategy would provide an easy access to enantiomerically pure benzopyran systems.

2C.5 Experimental Section

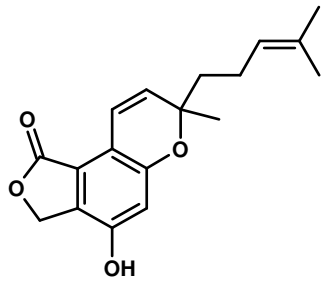
Commercially available methyl 3,5-dimethoxybenzoate, $Ca(OH)_2$, DBU, orcinol monohydrate, methyl iodide, NBS, *n*-BuLi (1.50 M), methyl chloroformate, anhydrous aluminum chloride, 1,3,5-trimethoxybenzene, BBr_3, 3-methyl-2-butenal, citral and farnesol were used. Melting points are uncorrected. Dichloromethane was distilled from phosphorous pentoxide under argon. Tetrahydrofuran was freshly distilled from benzophenone ketyl radical under argon prior to use. Column chromatographic separations were carried out on silica gel (60-120 mesh). All yields given refer to as isolated yields. IR spectra were recorded on FT-IR spectrometer. MS experiments were performed on a low resolution magnetic sector mass spectrometer.

4,6-Dihydroxyisobenzofuran-1(3*H*)-one (25). A stirring mixture of 4,6-dimethoxyphthalide[13a] (8.00 g, 41.24 mmol) and $AlCl_3$ (32.99 g, 247.42 mmol) in DCM (200.00 mL) was refluxed for 6 h. After cooling, solvent was removed from the reaction mixture and the solid residue was cooled to 0 ^oC. Water was added very slowly to this solid residue till the entire solid complex decomposed. Solid product obtained was filtered and recrystallization from ethyl acetate/methanol afforded **25** (5.88 g, 86%) as a colorless crystalline solid.

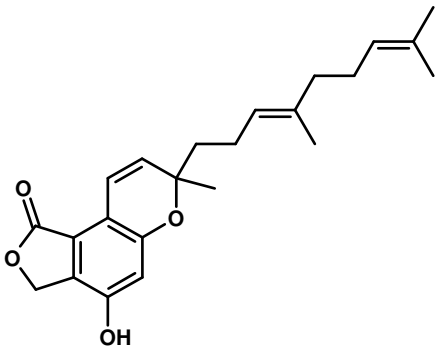
 **25** **$C_8H_6O_4$ (166)**	**Mp** 230-235 ^oC. **^{1}H NMR** (DMSO-d_6, 200 MHz) δ 4.50 (s, 2H), 5.93 (s, 2H), 9.40 (bs, 2H). **^{13}C NMR** (DMSO-d_6, 50 MHz) δ 67.9, 100.9, 108.1, 124.5, 127.2, 152.8, 159.6, 170.9. **IR** (Nujol) 3369, 3281, 1693, 1682, 1614 cm^{-1}. **Anal. Calcd** for $C_8H_6O_4$: C, 57.84; H, 3.64. Found: C, 57.93; H, 3.54.

4-Hydroxy-7-methyl-7-(4-methyl-pent-3-enyl)-3*H*,7*H*-2,6-dioxa-cyclopenta[*a*]napthylen-1-one (26a). To a stirring mixture of **25** (2.00 g, 12.05 mmol) and $Ca(OH)_2$ (1.33 g, 18.07 mmol) in methanol (50 mL) at room temperature, a solution of citral (10.42 mL, 60.24 mmol) in methanol (10 mL) was added. After stirring the reaction mixture for 6 days at 60 ^oC, methanol was removed in vacuo, and the reaction mixture was diluted with ethyl acetate (80 mL). The organic layer was washed with 2 N HCl, water,

brine and dried over Na_2SO_4. Removal of the solvent in vacuo followed by silica gel column chromatographic purification of the residue using a mixture of 15% ethyl acetate in petroleum ether gave **26a** (2.16 g, 60%) as a colorless thick oil.

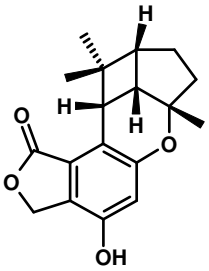
 **(±)-26a** **$C_{18}H_{20}O_4$ (300)**	Colorless thick oil. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 1.40 (s, 3H), 1.57 (s, 3H), 1.66 (s, 3H), 1.65-1.80 (m, 2H), 2.08 (t, J = 8 Hz, 2H), 5.09 (dt, J = 6 & 2 Hz, 1H), 5.21 (s, 2H), 5.61 (d, J = 10 Hz, 1H), 6.54 (s, 1H), 7.26 (d, J = 10 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 17.6, 22.6, 25.6, 26.4, 41.1, 68.3, 79.4, 109.2, 112.4, 117.2, 120.6, 123.7, 125.8, 129.3, 131.8, 151.1, 155.3, 172.9. **IR** ($CHCl_3$) 3238, 1713, 1622 cm^{-1}. **Anal. Calcd** for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 72.02; H, 6.63.

7-(4,8-Dimethyl-nona-3,7-dienyl)-4-hydroxy-7-methyl-3*H*,7*H*-2,6-dioxa-cyclopenta[*a*]napthylen-1-one (26b). It was prepared similarly using **25** (2.00 g, 12.05 mmol), $Ca(OH)_2$ (1.33 g, 18.07 mmol) and farnesal (13.27 g, 60.24 mmol). **26b**: (2.79 g, 63%) Colorless thick oil.

 **(±)-26b** **$C_{23}H_{28}O_4$ (368)**	Colorless thick oil. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 1.40 (s, 3H), 1.57 (s, 3H), 1.59 (s, 3H), 1.65-1.80 (m, 2H), 1.67 (s, 3H), 1.85-2.20 (m, 6H), 5.10 (t, J = 6 Hz, 2H), 5.20 (s, 2H), 5.61 (dd, J = 10 & 4 Hz, 1H), 6.51 (s, 1H), 7.27 (d, J = 10 Hz, 1H). **IR** ($CHCl_3$) 3383, 1751, 1734, 1626 cm^{-1}. **Anal. Calcd** for $C_{23}H_{28}O_4$: C, 74.97; H, 7.66. Found: C, 75.02; H, 7.52.

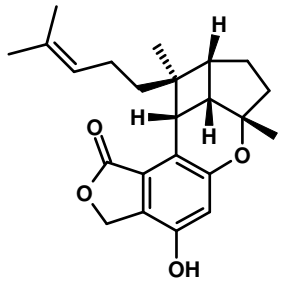
10,10,6*a*-Trimethyl-4-hydroxy-6*a*,7,8,9,11,13-hexahydro-3*H*-2,6-dioxacyclobuta[*cd*]indano[*b,g*]benzofuran-1-one (28a). ***Method A***: A stirring mixture of **25** (1.00 g, 6.02 mmol) and citral (5.21 mL, 30.12 mmol) was heated at 120-130 ^oC for a period of 6 h. After cooling, the obtained residue on silica gel column chromatographic purification using a mixture of 15% ethyl acetate in petroleum ether furnished **28a** (1.48 g,

82%) as a colorless crystalline solid. ***Method B***: Compound **26a** (500 mg, 1.66 mmol) was heated neat with stirring at 120-130 ^{o}C for a period of 6 h. After cooling, the obtained residue on silica gel column chromatographic purification using a mixture of 15% ethyl acetate in petroleum ether furnished **28a** (380 mg, 76%) as a colorless crystalline solid. ***Method C***: To a stirring solution of **26a** (500 mg, 1.66 mmol) in methanol (20 mL) at 0 ^{o}C, 2 N KOH (4 mL) was added dropwise. The reaction mixture was allowed to attain room temperature, after 8-10 h stirring at room temperature, methanol was removed in vacuo, and the reaction mixture was acidified slowly with 2 N HCl at 0 ^{o}C. The reaction mixture was extracted with ethyl acetate (30 mL × 2) and the combined organic layer was washed with water, brine and dried over Na_2SO_4. Removal of the solvent in vacuo followed by silica gel column chromatographic purification of the residue using a mixture of 15% ethyl acetate in petroleum ether gave **28a** (400 mg, 80%) as a colorless crystalline solid.

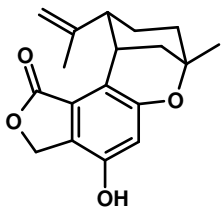
 (±)-**28a** **$C_{18}H_{20}O_4$ (300)**	**Mp** 256-258 ^{o}C (acetone). **^{1}H NMR** (DMSO-d_6, 200 MHz) δ 0.55 (s, 3H), 1.30 (s, 3H), 1.42 (s, 3H), 1.50-1.65 (m, 3H), 1.78 (t, J = 10 Hz, 1H), 2.25-2.40 (m, 1H), 2.57 (t, J = 10 Hz, 1H), 3.45 (d, J = 8 Hz, 1H), 5.15 (s, 2H), 6.56 (s, 1H), 10.22 (s, 1H). **^{13}C NMR** (DMSO-d_6, 50 MHz) δ 18.2, 25.2, 27.1, 33.4, 35.9, 37.8, 38.1, (one carbon signal below the DMSO-d_6 peaks), 46.5, 67.2, 83.9, 110.1, 113.9, 124.5, 127.8, 150.8, 154.8, 170.9. **^{1}H NMR** (Acetone-d_6, 500 MHz) δ 0.63 (s, 3H), 1.35 (s, 3H), 1.49 (s, 3H), 1.55-1.75 (m, 3H), 1.85-2.00 (m, 1H), 2.42 (t, J = 5 Hz, 1H), 2.64 (t, J = 10 Hz, 1H), 3.56 (d, J = 10 Hz, 1H), 5.16 (s, 2H), 6.64 (s, 1H). **^{13}C NMR** (Acetone-d_6, 125 MHz) δ 18.4, 25.9, 27.3, 33.8, 36.9, 39.0, 39.1, 40.9, 47.7, 67.5, 84.8, 110.8, 115.7, 125.9, 128.2, 151.3, 156.3, 171.4. **IR** (Nujol) 3236, 1717, 1622 cm^{-1}. **Anal. Calcd** for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 71.85; H, 6.86.

10,6*a*-Dimethyl-10-(4-methyl-pent-3-enyl)-4-hydroxy-6*a*,7,8,9,11,13-hexahydro-3*H*-2,6-dioxacyclobuta[*cd*]indano[*b,g*]benzofuran-1-one (28b). To a stirring solution of **26b** (500 mg, 1.35 mmol) in methanol (20 mL) at 0 ^{o}C, 2 N KOH (4 mL) was added dropwise. The reaction mixture was allowed to attain room temperature and after 10 h stirring at room temperature, methanol was removed under vacuo and the reaction mixture was acidified slowly with 2 N HCl at 0 ^{o}C. The reaction mixture was extracted with ethyl

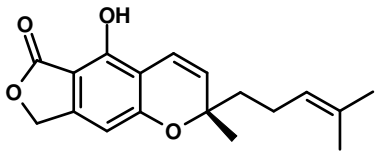
acetate (30 mL × 2) and the organic layer was washed with water, brine and dried over Na_2SO_4. Removal of the solvent in vacuo followed by silica gel column chromatographic purification of the residue using a mixture of 10% ethyl acetate in petroleum ether gave **28b** (390 mg, 78%) as a colorless thick oil.

 (±)-**28b** **$C_{23}H_{28}O_4$ (368)**	Colorless thick oil. **^{1}H NMR** (DMSO-d_6, 200 MHz) δ 0.55 (s, 3H), 1.31 (s, 3H), 1.34 (s, 3H), 1.42 (s, 3H), 1.53-1.67 (m, 5H), 1.79 (t, J = 10 Hz, 1H), 1.90-2.15 (m, 2H), 2.25-2.40 (m, 1H), 2.60 (t, J = 10 Hz, 1H), 3.45 (d, J = 8 Hz, 1H), 5.07 (t, J = 6 Hz, 1H), 5.15 (s, 2H), 6.56 (s, 1H), 10.22 (s, 1H). **IR** (Nujol) 3215, 1697, 1616 cm^{-1}. **Anal. Calcd** for $C_{23}H_{28}O_4$: C, 74.97; H, 7.66. Found: C, 75.11; H, 7.49.

9-Isopropenyl-6*a*-methyl-4-hydroxy-2,6-dioxabicyclo[3,3,1]nonyl[*b,g*]-3*H*-benzofuran-1-one (30). ***Method A***: A stirring mixture of **25** (500 mg, 3.01 mmol) and citral (2.60 mL, 15.06 mmol) was heated at 160-170 ^oC for a period of 6 h. After cooling, the obtained residue on silica gel column chromatographic purification using a mixture of 15% ethyl acetate in petroleum ether furnished **30** (741 mg, 82%) as a colorless crystalline solid. ***Method B***: A stirring mixture of **28a** (250 mg, 0.83 mmol) and citral (0.72 mL, 4.16 mmol) was heated at 160-170 ^oC for a period of 6 h. After cooling, the obtained residue on silica gel column chromatographic purification using a mixture of 15% ethyl acetate in petroleum ether furnished **30** (205 mg, 82%) as a colorless crystalline solid. ***Method C***: Compound **26a** (500 mg, 1.66 mmol) was heated neat with stirring at 160-170 ^oC for a period of 6 h. After cooling, the obtained residue on silica gel column chromatographic purification using a mixture of 15% ethyl acetate in petroleum ether furnished **30** (410 mg, 82%) as a colorless crystalline solid.

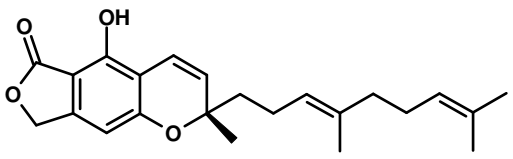
 **(±)-30** **$C_{18}H_{20}O_4$ (300)**	**Mp** 244-246 °C (acetone). **^{1}H NMR** (DMSO-d_6, 500 MHz) δ 1.26 (dt, J = 12.5 & 5 Hz, 2H), 1.30 (s, 3H), 1.57-1.66 (m, 1H), 1.75 (dt, J = 15 & 5 Hz, 1H), 1.80 (s, 3H), 1.88 (dd, J = 12.5 & 5 Hz, 1H), 1.99 (dd, J = 15 & 5 Hz, 1H), 2.25 (dt, J = 7.5 & 5 Hz, 1H), 3.80 (s, 1H, vinylic-H), 3.92 (s, 1H), 4.47 (s, 1H, vinylic-H), 5.04 (s, 2H), 6.47 (s, 1H), 10.13 (s, 1H). **^{13}C NMR** (DMSO-d_6, 125 MHz) δ 23.2, 24.5, 28.6, 29.0, 36.1, 39.5, 48.3, 66.7, 75.0, 106.8, 109.1, 112.7, 124.3, 124.9, 147.8, 150.8, 158.0, 170.6. **IR** (Nujol) 3238, 1711, 1622 cm^{-1}. **Anal. Calcd** for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 71.92; H, 6.79.

9-Hydroxy-6-methyl-6-(4-methyl-pent-3-enyl)-3*H*,6*H*-2,5-dioxacyclopenta[*b*]napthalen-1-one (32a). To a stirring solution of **31** (1.00 g, 6.02 mmol) and DBU (0.99 mL, 6.63 mmol) in acetonitrile (50 mL) at room temperature, citral (5.21 mL, 30.12 mmol) was added. After stirring for 24 h at 50 °C, acetonitrile was removed in vacuo and the reaction mixture was diluted with ethyl acetate (60 mL). The organic layer was washed with 2 N HCl, water, brine and dried over Na_2SO_4. Removal of the solvent in vacuo followed by silica gel column chromatographic purification of the residue using a mixture of 10% ethyl acetate in petroleum ether gave **32a** (1.17 g, 65%) as a colorless oil.

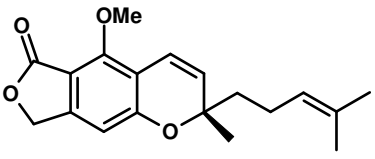
 **(±)-32a** **$C_{18}H_{20}O_4$ (300)**	Colorless thick oil. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 1.41 (s, 3H), 1.56 (s, 3H), 1.60-1.85 (m, 2H), 1.65 (s, 3H), 2.08 (q, J = 9 Hz, 2H), 5.07 (t, J = 6 Hz, 1H), 5.19 (s, 2H), 5.58 (d, J = 12 Hz, 1H), 6.36 (s, 1H), 6.69 (d, J = 12 Hz, 1H), 7.77 (bs, 1H). **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 17.6, 22.6, 25.5, 26.8, 41.5, 70.4, 80.4, 102.0, 103.7, 108.6, 115.7, 123.7, 127.9, 131.9, 147.1, 152.1, 161.1, 172.5. **IR** ($CHCl_3$) 3440, 1729, 1639, 1460, 1216, 1153, 757 cm^{-1}. **Anal. Calcd** for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 72.13; H, 6.99.

6-(4,8-Dimethyl-nona-3,7-dienyl)-9-hydroxy-6-methyl-3*H*,6*H*-2,5-dioxacyclopenta[*b*]napthalen-1-one (32b). It was prepared similarly using **31** (1.00 g,

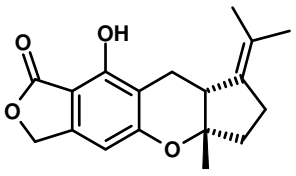
6.02 mmol), DBU (0.99 mL, 6.63 mmol) in acetonitrile (50 mL) and farnesal (6.64 g, 30.12 mmol). **32b**: (1.50 g, 68%) Thick oil.

 **(±)-32b** **$C_{23}H_{28}O_4$ (368)**	Colorless thick oil. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 1.43 (s, 3H), 1.57 (s, 3H), 1.59 (s, 3H), 1.65-1.85 (m, 2H), 1.67 (s, 3H), 1.90-2.20 (m, 6H), 5.08 (t, J = 6 Hz, 1H), 5.10 (t, J = 6 Hz, 1H), 5.21 (s, 2H), 5.60 (dd, J = 12 & 6 Hz, 1H), 6.38 (s, 1H), 6.71 (d, J = 12 Hz, 1H), 7.76 (s, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 15.8, 17.5, 22.4, 25.5, 26.4, 26.7, 39.5, 41.3, 70.2, 80.1, 101.8, 103.5, 108.4, 115.6, 123.3, 124.2, 127.7, 131.0, 135.4, 147.0, 151.9, 160.8, 172.3. **IR** (Neat) 3420, 1734, 1640 cm^{-1}. **Anal. Calcd** for $C_{23}H_{28}O_4$: C, 74.97; H, 7.66. Found: C, 75.09; H, 7.52.

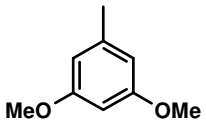
9-Methoxy-6-methyl-6-(4-methyl-pent-3-enyl)-3*H*,6*H*-2,5-dioxa-cyclopenta[*b*]napthalen-1-one (33). To a stirring mixture of **32a** (500 mg, 1.66 mmol) and anhydrous K_2CO_3 (1.15 g, 8.33 mmol) in acetone (30 mL), was added methyl iodide (1.03 mL, 16.66 mmol) and the reaction mixture was refluxed for 6 h. After cooling, the reaction mixture was filtered through celite. Removal of the solvent in vacuo followed by silica gel column chromatographic purification of the residue using a mixture of 10% ethyl acetate in petroleum ether afforded **33** (518 mg, 99%) as a colorless oil.

 **(±)-33** **$C_{19}H_{22}O_4$ (314)**	Colorless thick oil. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 1.42 (s, 3H), 1.56 (s, 3H), 1.66 (s, 3H), 1.68-1.79 (m, 2H), 2.01-2.17 (m, 2H), 4.12 (s, 3H), 5.03-5.13 (m, 1H), 5.15 (s, 2H), 5.63 (d, J = 10 Hz, 1H), 6.53 (s, 1H), 6.75 (d, J = 10 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 17.5, 22.6, 25.6, 26.9, 41.4, 62.8, 68.7, 80.1, 104.5, 108.8, 114.3, 116.6, 123.6, 129.1, 131.9, 149.6, 155.1, 160.2, 168.6. **IR** (Neat) 1755, 1643, 1609 cm^{-1}. **MS** (*m/z*) 315, 232, 131, 103. **Anal. Calcd** for $C_{19}H_{22}O_4$: C, 72.59; H, 7.05. Found: C, 72.41; H, 6.90.

10-Hydroxy-8-isopropyl-5*a*-methyl-5*a*,6,7,9-tetrahydro-3*H*-2,5-dioxa-dicyclopenta[*b*,*g*]napthalen-1-one (35). Compound **32a** (500 mg, 1.66 mmol) was heated neat with stirring at 165-170 ^{o}C for a period of 6 h. After cooling, the obtained residue on silica gel column chromatographic purification using a mixture of 10% ethyl acetate in petroleum ether furnished **35** (450 mg, 90%) as a colorless waxy solid.

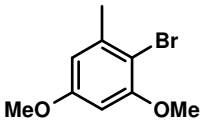
 **(±)-35** **$C_{18}H_{20}O_4$ (300)**	Colorless waxy solid. **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 1.39 (s, 3H), 1.50-1.59 (m, 1H), 1.67 (s, 3H), 1.73-1.83 (m, 2H), 1.87 (dd, J = 15 & 5 Hz, 1H), 1.94 (d, J = 5 Hz, 3H), 1.99-2.05 (m, 1H), 2.47 (dd, J = 15 & 5 Hz, 1H), 4.38 (s, 1H), 5.19 (s, 2H), 6.40 (s, 1H), 7.75 (s, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 20.0, 20.5, 22.4, 28.3, 29.2, 36.2, 40.0, 70.1, 76.4, 101.1, 102.1, 112.9, 123.2, 130.0, 145.2, 153.9, 163.8, 172.7. **IR** (Nujol) 3516, 3445, 1742, 1641, 1607 cm^{-1}. **MS** (*m/z*) 301, 131, 103. **Anal. Calcd** for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 72.10; H, 6.66.

1,3-Dimethoxy-5-methylbenzene (38). A stirring mixture of **37** (5.00 g, 35.17 mmol), anhydrous K_2CO_3 (24.30 g, 175.87 mmol) and methyl iodide (10.95 mL, 175.87 mmol) in acetone (100 mL) was refluxed for 6 h. After cooling, the reaction mixture was filtered through celite. Removal of the solvent in vacuo followed by silica gel column chromatographic purification of the residue using a mixture of 2% ethyl acetate in petroleum ether afforded **38** (5.35 g, ~100%) as a colorless oil.

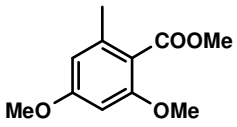
 **38** **$C_9H_{12}O_2$ (152)**	Colorless oil. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 2.30 (s, 3H), 3.76 (s, 6H), 6.29 (d, J = 2 Hz, 1H), 6.34 (d, J = 2 Hz, 2H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 21.6, 55.0, 97.4, 107.0, 140.0, 160.6. **IR** (Neat) 2999, 2947, 2837, 1607, 1597 cm^{-1}. **Anal. Calcd** for $C_9H_{12}O_2$: C, 71.03; H, 7.95. Found: C, 71.24; H, 7.88.

2-Bromo-1,5-dimethoxy-3-methylbenzene (39). To a solution of **38** (5.00 g, 32.85 mmol) in CCl_4 (60 mL) NBS (5.85 g, 32.85 mmol) was added and the reaction mixture was refluxed gently for 4 h. After cooling, the reaction mixture was filtered and

concentration of the filtrate in vacuo followed by silica gel column chromatographic purification of the residue using a mixture of 5% ethyl acetate in petroleum ether afforded **39** (7.51 g, 99%) as a low melting solid.

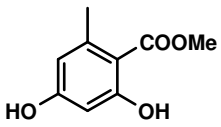
 **39** **$C_9H_{11}BrO_2$ (231)**	Low melting solid. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 2.38 (s, 3H), 3.78 (s, 3H), 3.85 (s, 3H), 6.34 (d, J = 2 Hz, 1H), 6.42 (d, J = 4 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 23.5, 55.4, 56.2, 97.2, 105.1, 107.2, 139.8, 156.6, 159.3. **IR** (Neat) 2939, 2839, 1612, 1591, 1574 cm^{-1}. **MS** (*m/z*) 233, 231, 205, 203, 195, 181, 166, 122, 102. **Anal. Calcd** for $C_9H_{11}BrO_2$: C, 46.78; H, 4.80; Br, 34.58. Found: C, 46.61; H, 4.92; Br, 34.69.

Methyl 2,4-dimethoxy-6-methylbenzoate (40). To a stirring solution of **39** (7.00 g, 30.30 mmol) in THF (60 mL) at -78 ^oC was added *n*-BuLi (1.50 M, 24.24 mL, 36.36 mmol) dropwise. After stirring at -78 ^oC for 1 h, freshly distilled methyl chloroformate (7.00 mL, 90.90 mmol) was added slowly to the above stirring reaction mixture. The reaction mixture was allowed to reach room temperature and the reaction was quenched with saturated solution of NH_4Cl. THF was removed in vacuo, ethyl acetate (150 mL) was added to the reaction mixture and the separated organic layer was washed with water, brine and dried over Na_2SO_4. Removal of the solvent in vacuo followed by silica gel column chromatographic purification of the residue using a mixture of 10% ethyl acetate in petroleum ether afforded **40** (6.10 g, 96%) as a colorless oil.

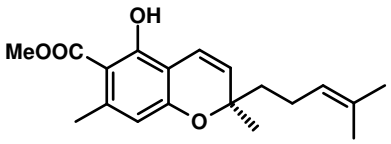
 **40** **$C_{11}H_{14}O_4$ (210)**	Colorless thick oil. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 2.28 (s, 3H), 3.79 (s, 3H), 3.80 (s, 3H), 3.88 (s, 3H), 6.31 (bs, 2H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 19.4, 51.5, 54.8, 55.4, 95.7, 106.3, 116.0, 137.8, 157.9, 161.1, 168.3. **IR** (Neat) 1728, 1607 cm^{-1}. **MS** (*m/z*) 211, 193, 179, 122, 102. **Anal. Calcd** for $C_{11}H_{14}O_4$: C, 62.85; H, 6.71. Found: C, 62.93; H, 6.56.

Methyl 2,4-dihydroxy-6-methylbenzoate (41). To a stirring mixture of $AlCl_3$ (20.95 g, 157.14 mmol) in DCM (100 mL) at 0 ^oC, a solution of **40** (5.50 g, 26.19 mmol) in DCM (40 mL) was added dropwise. The reaction mixture was allowed to reach room temperature and stirred for a further 12 h. After removal of the DCM in vacuo, the residue was cooled

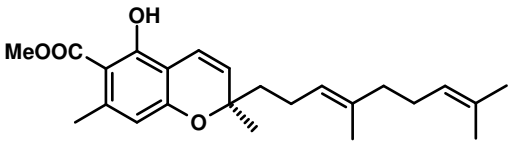
to 0 ^{o}C and water was added very slowly to decompose the formed complex. To this reaction mixture was added ethyl acetate (150 mL) and the separated organic layer was washed with water, brine and dried over Na_2SO_4. Removal of the solvent in vacuo followed by silica gel column chromatographic purification of the residue using a mixture of 15% ethyl acetate in petroleum ether furnished **41** (4.67 g, 98%) as a colorless crystalline solid.

 **41** **$C_9H_{10}O_4$ (182)**	**Mp** 136-138 ^{o}C. **^{1}H NMR** (DMSO-d_6, 200 MHz) δ 2.29 (s, 3H), 3.81 (s, 3H), 6.18 (bs, 2H), 10.01 (bs, 1H), 10.76 (bs, 1H). **^{13}C NMR** (DMSO-d_6, 50 MHz) δ 22.3, 51.9, 100.7, 107.5, 110.5, 141.1, 161.4, 161.5, 170.5. **IR** (Nujol) 3371, 3306, 1651, 1643 cm^{-1}. **Anal. Calcd** for $C_9H_{10}O_4$: C, 59.34; H, 5.53. Found: C, 59.23; H, 5.47.

Methyl-2,7-dimethyl-5-hydroxy-2-(4-methylpent-3-enyl)-2*H*-1-benzopyran-6-carboxylate (18a). To a stirring mixture of **41** (1.00 g, 5.49 mmol) and $Ca(OH)_2$ (814 mg, 10.99 mmol) in methanol (25 mL) at room temperature, citral (4.75 mL, 27.47 mmol) was added. After stirring for 72 h at room temperature, methanol was removed in vacuo and the reaction mixture was diluted with ethyl acetate (60 mL). The separated organic layer was washed with 2 N HCl, water, brine and dried over Na_2SO_4. Removal of the solvent in vacuo followed by silica gel column chromatographic purification of the residue using a mixture of 2% ethyl acetate in petroleum ether gave **18a** (1.25 g, 72%) as a colorless oil.

 **(±)-18a** **$C_{19}H_{24}O_4$ (316)**	Colorless oil. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 1.39 (s, 3H), 1.56 (s, 3H), 1.57-1.70 (m, 2H), 1.66 (s, 3H), 2.00-2.20 (m, 2H), 2.45 (s, 3H), 3.91 (s, 3H), 5.09 (t, J = 6 Hz, 1H), 5.47 (d, J = 10 Hz, 1H), 6.18 (s, 1H), 6.73 (d, J = 10 Hz, 1H), 11.99 (s, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 17.6, 22.6, 24.4, 25.6, 27.0, 41.6, 51.7, 79.6, 104.9, 107.0, 111.6, 116.8, 123.9, 126.2, 131.7, 142.7, 157.8, 159.7, 172.4. **IR** (Neat) 3017, 1726, 1659, 1651, 1645, 1620, 1614 cm^{-1}. **MS** (*m/z*) 317, 303, 301, 289, 285, 269, 233, 102. **Anal. Calcd** for $C_{19}H_{24}O_4$: C, 72.13; H, 7.65. Found: C, 72.02; H, 7.83.

Methyl-2,7-dimethyl-5-hydroxy-2-[(3*E*)-4,8-dimethyl-3,7-nonadienyl]-2*H*-1-benzopyran-6-carboxylate (18b). It was prepared similarly using **41** (1.00 g, 5.49 mmol), $Ca(OH)_2$ (814 mg, 10.99 mmol) and farnesal (6.05 g, 27.47 mmol). **18b**: (1.66 g, 79%) Colorless oil.

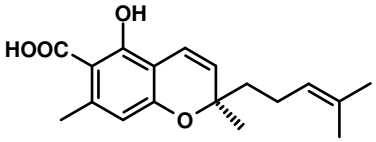


(±)-18b

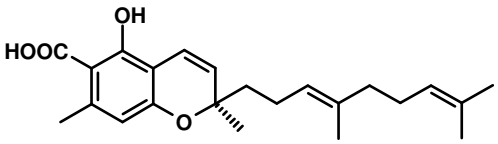
$C_{24}H_{32}O_4$ (384)

Colorless oil.
^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.39 (s, 3H), 1.57 (s, 3H), 1.60 (s, 3H), 1.68 (s, 3H), 1.85-2.25 (m, 8H), 2.46 (s, 3H), 3.91 (s, 3H), 5.10 (t, J = 6 Hz, 2H), 5.48 (d, J = 10 Hz, 1H), 6.19 (s, 1H), 6.74 (d, J = 10 Hz, 1H), 11.99 (s, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz) δ 15.9, 17.6, 22.5, 24.3, 25.6, 26.6, 26.9, 39.6, 41.5, 51.6, 79.6, 104.8, 107.0, 111.6, 116.8, 123.7, 124.3, 126.1, 131.2, 135.3, 142.6, 157.8, 159.7, 172.3.
IR (Neat) 2968, 2926, 1653, 1618 cm^{-1}.
MS (*m/z*) 385, 383, 369, 365, 353, 348, 317, 233, 209, 201, 125, 102.
Anal. Calcd for $C_{24}H_{32}O_4$: C, 74.97; H, 8.39. Found: C, 75.11; H, 8.45.

2,7-Dimethyl-5-hydroxy-2-(4-methylpent-3-enyl)-2*H*-1-benzopyran-6-carboxylic acid (42a). To a stirring solution of **18a** (500 mg, 1.58 mmol) in methanol (15 mL) at 0 ^oC, 3 N KOH (5 mL) was added slowly. The reaction mixture was allowed to attain room temperature and after 72 h stirring at room temperature methanol was removed in vacuo at room temperature. The reaction mixture was acidified with 2 N HCl at 0 ^oC and then extracted with ethyl acetate (50 mL × 2). The combined organic layer was washed with water, brine and dried over Na_2SO_4. Removal of the solvent in vacuo followed by silica gel column chromatographic purification of the residue using a mixture of 15% ethyl acetate in petroleum ether gave **42a** (392 mg, 82%) as a colorless oil.

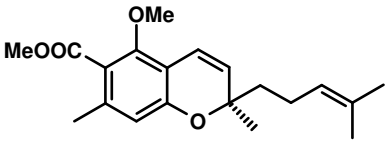
 **(±)-42a** **$C_{18}H_{22}O_4$ (302)**	Colorless thick oil. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.40 (s, 3H), 1.57 (s, 3H), 1.65-1.80 (m, 2H), 1.66 (s, 3H), 2.00-2.15 (m, 2H), 2.53 (s, 3H), 5.09 (t, J = 8 Hz, 1H), 5.48 (d, J = 8 Hz, 1H), 6.23 (s, 1H), 6.73 (d, J = 8 Hz, 1H), 11.71 (s, 1H). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 17.6, 22.7, 24.4, 25.6, 27.1, 41.7, 80.0, 103.6, 107.1, 112.1, 116.7, 123.9, 126.3, 131.9, 144.4, 158.9, 160.6, 176.0. **IR** (Nujol) 3061, 2700-2500, 1651, 1643, 1632, 1620, 1614 cm^{-1}. **MS** (*m/z*) 303, 301, 285, 279, 224, 219, 201, 199, 179, 157, 135, 102. **Anal. Calcd** for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33. Found: C, 71.39; H, 7.20.

2,7-Dimethyl-5-hydroxy-2-[(3*E*)-4,8-dimethyl-3,7-nonadienyl]-2*H*-1-benzopyran-6-carboxylic acid (42b). It was prepared similarly using **18b** (500 mg, 1.30 mmol), methanol (15 mL) and 3 N KOH (5 mL). **42b**: (385 mg, 80%) Colorless oil.

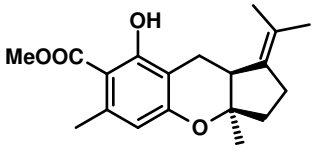
 **(±)-42b** **$C_{23}H_{30}O_4$ (370)**	Colorless thick oil. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.41 (s, 3H), 1.57 (s, 3H), 1.59 (s, 3H), 1.60-1.71 (m, 1H), 1.67 (s, 3H), 1.72-1.82 (m, 1H), 1.92-1.98 (m, 2H), 1.99-2.14 (m, 4H), 2.53 (s, 3H), 5.00-5.15 (m, 2H), 5.48 (d, J = 8 Hz, 1H), 6.23 (s, 1H), 6.73 (d, J = 8 Hz, 1H), 11.69 (s, 1H). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 16.0, 17.7, 22.6, 24.4, 25.7, 26.7, 27.2, 39.7, 41.7, 80.1, 103.6, 107.1, 112.2, 116.7, 123.7, 124.3, 126.3, 131.3, 135.5, 144.4, 159.0, 160.6, 176.1. **IR** ($CHCl_3$) 3057, 2700-2500, 1643, 1618 cm^{-1}. **MS** (*m/z*) 369, 353, 301, 279, 247, 233, 225, 219, 211, 205, 181, 157, 148, 135, 102. **Anal. Calcd** for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16. Found: C, 74.65; H, 8.04.

Methyl-2,7-dimethyl-5-methoxy-2-(4-methylpent-3-enyl)-2*H*-1-benzopyran-6-carboxylate (43). To a stirring mixture of **18a** (250 mg, 0.79 mmol), anhydrous K_2CO_3 (550 mg, 3.95 mmol) in acetone (25 mL) was added methyl iodide (0.49 mL, 7.91 mmol) and the reaction mixture was refluxed for 6 h. After cooling, the reaction mixture was

filtered through celite. Removal of the solvent in vacuo followed by silica gel column chromatographic purification of the residue using a mixture of 3% ethyl acetate in petroleum ether afforded **43** (255 mg, 98%) as a colorless oil.

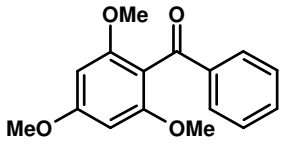
 **(±)-43** **$C_{20}H_{26}O_4$ (330)**	Colorless thick oil. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 1.38 (s, 3H), 1.57 (s, 3H), 1.66 (s, 3H), 1.89-2.20 (m, 4H), 2.25 (s, 3H), 3.79 (s, 3H), 3.90 (s, 3H), 5.08 (t, J = 8 Hz, 1H), 5.57 (d, J = 10 Hz, 1H), 6.43 (s, 1H), 6.57 (d, J = 10 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 17.6, 19.9, 22.6, 25.6, 26.4, 41.1, 51.9, 63.0, 78.7, 112.3, 113.8, 117.0, 120.0, 123.9, 128.8, 131.8, 137.7, 154.1, 155.2, 168.4. **IR** (Neat) 1730, 1634, 1609 cm^{-1}. **MS** (*m/z*) 331, 313, 299, 130. **Anal. Calcd** for $C_{20}H_{26}O_4$: C, 72.70; H, 7.93. Found: C, 72.59; H, 7.99.

Methyl 8-hydroxy-3*a*,6-dimethyl-1-(propan-2-ylidene)-1,2,3,3*a*,9,9*a*-hexahydrocyclopenta[*b*]chromene-7-carboxylate (45). Compound **18a** (250 mg, 0.79 mmol) was heated neat with stirring at 175 ^oC for a period of 6 h. After cooling, the obtained residue, on silica gel column chromatographic purification using a mixture of 2% ethyl acetate in petroleum ether, furnished **45** (245 mg, 98%) as a colorless oil.

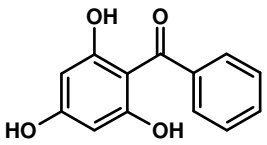
 **(±)-45** **$C_{19}H_{24}O_4$ (316)**	Colorless thick oil. **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 1.36 (s, 3H), 1.48-1.56 (m, 1H), 1.65 (s, 3H), 1.74-1.79 (m, 1H), 1.82 (dd, J = 10 & 5 Hz, 1H), 1.88-1.91 (m, 1H), 1.94 (d, J = 5 Hz, 3H), 1.96-2.20 (m, 1H), 2.43 (dd, J = 10 & 5 Hz, 1H), 2.44 (s, 3H), 3.88 (s, 3H), 4.33 (s, 1H), 6.23 (s, 1H), 11.93 (s, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 20.1, 20.7, 22.7, 24.1, 28.5, 29.6, 37.0, 40.3, 51.5, 75.8, 103.7, 110.9, 111.0, 122.7, 130.8, 140.2, 160.7, 161.7, 172.6. **IR** ($CHCl_3$) 3381, 1651, 1620, 1576 cm^{-1}. **Anal. Calcd** for $C_{19}H_{24}O_4$: C, 72.13; H, 7.65. Found: C, 72.05; H, 7.78.

Phenyl-(2,4,6-trimethoxyphenyl)-methanone (48). To an ice cooled stirring mixture of $AlCl_3$ (5.95 g, 44.59 mmol) in DCM (60 mL), benzoyl chloride (3.45 mL, 29.73 mmol)

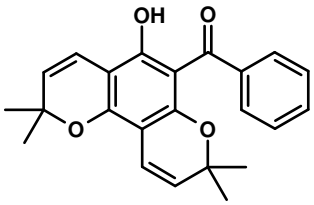
was added dropwise. After stirring at 0 ^{o}C for 1 h, the reaction mixture was added slowly to a stirring solution of 1,3,5-trimethoxybenzene (**47**) (5.00 g, 29.73 mmol) in DCM (50 mL) at 0 ^{o}C. The reaction mixture was allowed to attain room temperature and after further 12 h stirring the reaction mixture was poured slowly into ice cooled 50% HCl (60 mL). The organic layer was diluted with DCM (50 mL), and separated organic layer was washed with saturated $NaHCO_3$ solution, water, and brine and dried over Na_2SO_4. Removal of the solvent in vacuo followed by silica gel column chromatographic purification of the residue using a mixture of 20% ethyl acetate in petroleum ether gave **48** (7.76 g, 96%) as a white solid.

 **48** **$C_{16}H_{16}O_4$ (272)**	**MP** 113-115 ^{o}C. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 3.68 (s, 6H), 3.86 (s, 3H), 6.17 (s, 2H), 7.35-7.60 (m, 3H), 7.75-7.90 (m, 2H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 55.4, 55.7, 90.6, 110.8, 128.2, 129.3, 132.8, 138.1, 158.6, 162.3, 194.9. **IR** (Nujol) 1663, 1585 cm^{-1}. **Anal. Calcd** for $C_{16}H_{16}O_4$: C, 70.58; H, 5.92. Found: C, 70.69; H, 5.84.

Phenyl-(2,4,6-trihydroxyphenyl)-methanone (49). To a stirring solution of **48** (7.00 g, 25.73 mmol) in DCM (100 mL) at -78 ^{o}C, boron tribromide (10.21 mL, 108.09 mmol) was added quickly and the reaction mixture was allowed to reach the room temperature slowly. After stirring for 60 h at room temperature, the reaction mixture was cooled to 0 ^{o}C and very slowly quenched with water. DCM was removed in vacuo and ethyl acetate (300 mL) was added to the reaction mixture. The separated organic layer was washed with water, brine and dried over Na_2SO_4. Removal of the solvent in vacuo followed by silica gel column chromatographic purification of the residue using a mixture of 45% ethyl acetate in petroleum ether gave **49** (5.45 g, 92%) as a faint yellow crystalline solid.

 **49** **$C_{13}H_{10}O_4$ (230)**	**MP** 167-169 ^{o}C. **^{1}H NMR** (DMSO-d_6, 200 MHz) δ 5.87 (s, 2H), 7.35-7.60 (m, 3H), 7.64 (d, J = 8 Hz, 2H), 9.86 (s, 1H), 10.11 (s, 2H). **^{13}C NMR** (DMSO-d_6, 50 MHz) δ 94.7, 105.9, 128.2, 128.7, 132.0, 140.1, 159.7, 162.2, 196.8. **IR** (Nujol) 3192, 1626 cm^{-1}. **Anal. Calcd** for $C_{13}H_{10}O_4$: C, 67.82; H, 4.38. Found: C, 67.89; H, 4.44.

6-Benzoyl-5-hydroxy-2,2,8,8-tetramethyl-2*H*,8*H*-benzo-(1,2-*b*:3',4'-*b'*)-dipyran (50). To a stirring solution of **49** (500 mg, 2.17 mmol) and DBU (0.71 mL, 4.78 mmol) in methanol (15 mL) at room temperature, 3-methyl-2-butenal (prenal) (2.00 mL, 20.73 mmol) was added. After stirring the reaction mixture for 36 h at room temperature, methanol was removed in vacuo and the reaction mixture was diluted with ethyl acetate (50 mL). The separated organic layer was washed with 2 N HCl, water, brine and dried over Na_2SO_4. Removal of the solvent in vacuo followed by silica gel column chromatographic purification of the residue using a mixture of 5% ethyl acetate in petroleum ether gave **50** (740 mg, 94%) as a faint yellow crystalline solid.



50

$C_{23}H_{22}O_4$ (362)

MP 146-148 ^oC.

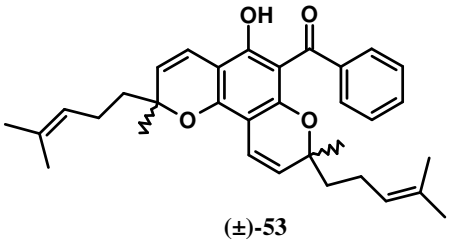
^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.97 (s, 6H), 1.47 (s, 6H), 5.29 (d, J = 10 Hz, 1H), 5.50 (d, J = 10 Hz, 1H), 6.52 (d, J = 10 Hz, 1H), 6.71 (d, J = 10 Hz, 1H), 7.30-7.55 (m, 5H), 12.73 (s, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.5, 28.4, 77.8, 78.3, 102.0, 102.2, 105.0, 115.9, 116.1, 125.0, 125.4, 127.1, 127.5, 129.9, 142.8, 155.5, 156.0, 159.7, 200.3.

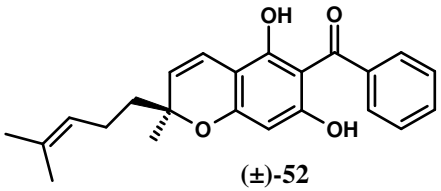
IR (Nujol) 3175, 1649, 1643, 1599 cm^{-1}.

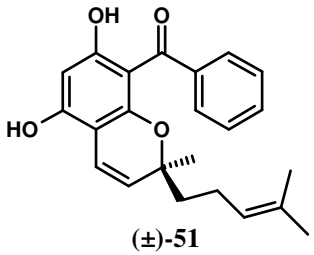
Anal. Calcd for $C_{23}H_{22}O_4$: C, 76.22; H, 6.12. Found: C, 76.15; H, 6.33.

6-Benzoyl-5-hydroxy-2,8-dimethyl-2,8-di-(4-methylpent-3-enyl)-2*H*,8*H*-benzo-(1,2-*b*:3',4'-*b'*)-dipyran (53). To a stirring solution of **49** (500 mg, 2.17 mmol) and DBU (0.71 mL, 4.78 mmol) in methanol (15 mL) at room temperature, citral (3.76 mL, 21.73 mmol) was added. After stirring for 36 h at room temperature, methanol was removed in vacuo and the reaction mixture was diluted with ethyl acetate (50 mL). The separated organic layer was washed with 2 N HCl, water, brine and dried over Na_2SO_4. Removal of the solvent in vacuo followed by silica gel column chromatographic purification of the residue using a mixture of 2% ethyl acetate in petroleum ether gave **53** (1.03 g, 95%) as a faint yellow gum **53** (diastereomeric mixture in nearly 1:1 ratio).

 **(±)-53** **$C_{33}H_{38}O_4$ (498)**	Faint yellow gum. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 0.98 (s, 3H), 1.00-1.35 (m, 4H), 1.44 (d, *J* = 2 Hz, 3H), 1.50 (s, 3H), 1.59 (s, 3H), 1.63 (s, 3H), 1.60-1.80 (m, 2H), 1.67 (s, 3H), 2.00-2.20 (m, 2H), 4.80-4.95 (m, 1H), 5.05-5.20 (m, 1H), 5.24 (d, *J* = 10 Hz, 1H), 5.44 (dd, *J* = 10 & 2 Hz, 1H), 6.55 (d, *J* = 10 Hz, 1H), 6.74 (d, *J* = 10 Hz, 1H), 7.30-7.52 (m, 5H), 12.71 (s, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 17.5, 22.4, 22.6, 25.5/25.6, 25.9, 26.9, 27.0, 40.8, 41.5/41.6, 80.3, 80.5/80.6, 101.5/101.6, 101.8/101.9, 104.7/104.8, 116.3, 116.5, 123.9, 124.1/124.2, 127.0, 127.5, 128.2, 129.5, 129.9, 131.4, 131.6, 132.8, 142.8, 155.6, 156.1, 159.6, 200.0 (on expansion seven carbons showed diastereomeric splitting). **IR** ($CHCl_3$) 3410, 1640, 1590 cm^{-1}. **MS** (*m/z*) 499, 405, 389, 373, 357, 341, 325, 309, 301, 279, 275, 245, 231, 205. **Anal. Calcd** for $C_{33}H_{38}O_4$: C, 79.49; H, 7.68. Found: C, 79.58; H, 7.53.

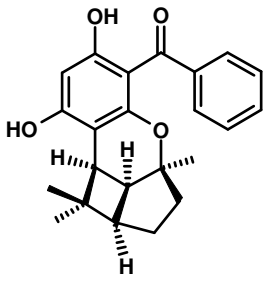
[5,7-Dihydroxy-2-methyl-2-(4-methylpent-3-enyl)-2*H*-1-benzopyran-8-yl]phenyl methanone (Clusiachromene C, 51) and **[5,7-Dihydroxy-2-methyl-2-(4-methylpent-3-enyl)-2*H*-1-benzopyran-6-yl]phenyl methanone (52).** To a stirring solution of **49** (2.00 g, 8.69 mmol) and DBU (1.04 mL, 6.96 mmol) in methanol (50 mL) at 0 ^oC, solution of citral (1.50 mL, 8.69 mmol) in methanol (10 mL) was added dropwise. After stirring for 6 h at 0 ^oC, methanol was removed in vacuo at 0 ^oC and the reaction mixture was diluted with ethyl acetate (75 mL). The separated organic layer was washed with 2 N HCl, water, brine and dried over Na_2SO_4. Immediately after removal of the solvent in vacuo, the residue was purified by silica gel column chromatographic purification. Elution with a mixture of 2% ethyl acetate in petroleum ether afforded **53** (476 mg, 11%) as a faint yellow gum. Elution with a mixture of 5% ethyl acetate in petroleum ether afforded **52** (506 mg, 16%) as a faint yellow oil. Further elution with a mixture of 10% ethyl acetate in petroleum ether gave **51** (822 mg, 26%) as a faint yellow oil.

 **(±)-52** **$C_{23}H_{24}O_4$ (364)**	Faint yellow oil. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 1.20-1.45 (m, 2H), 1.42 (s, 3H), 1.55-1.80 (m, 2H), 1.67 (s, 3H), 1.74 (s, 3H), 5.08 (t, *J* = 6 Hz, 1H), 5.42 (d, *J* = 10 Hz, 1H), 5.89 (s, 1H), 6.65 (d, *J* = 10 Hz, 1H), 7.30-7.70 (m, 5H), 7.78 (s, 1H), 10.15 (s, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 17.6, 22.6, 27.2, 27.5, 41.7, 80.5, 96.5, 102.4, 104.2, 116.3, 123.8, 124.6, 127.8, 128.8, 131.8, 131.9, 140.0, 158.1, 161.0, 161.4, 197.6. **IR** ($CHCl_3$) 3508, 3285, 1624, 1593 cm^{-1}. **MS** (*m/z*) 365, 327, 301, 210, 208, 192, 176, 103. **Anal. Calcd** for $C_{23}H_{24}O_4$: C, 75.80; H, 6.64. Found: C, 75.92; H, 6.65.

 **(±)-51** **$C_{23}H_{24}O_4$ (364)**	Faint yellow oil. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 0.99 (s, 3H), 1.10-1.35 (m, 2H), 1.50 (s, 3H), 1.57-1.72 (m, 2H), 1.64 (s, 3H), 4.88 (t, *J* = 6 Hz, 1H), 5.26 (d, *J* = 10 Hz, 1H), 5.96 (s, 1H), 6.53 (d, *J* = 10 Hz, 1H), 7.30-7.70 (m, 5+1H), 12.38 (s, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 17.6, 22.5, 25.6, 25.9, 40.8, 80.3, 95.8, 101.9, 105.4, 116.4, 123.8, 123.9, 127.1, 127.6, 130.1, 131.6, 142.6, 156.7, 158.9, 164.8, 200.3. **IR** ($CHCl_3$) 3522, 3504, 1632, 1620, 1594 cm^{-1}. **MS** (*m/z*) 365, 301, 279, 269, 253, 237, 231, 221, 207, 193, 191, 157, 135, 122, 102. **Anal. Calcd** for $C_{23}H_{24}O_4$: C, 75.80; H, 6.64. Found: C, 75.89; H, 6.81.

(1*a*,2,3,3*a*,8*b*,8*c*-Hexahydro-6,8-dihydroxy-1,1,3*a*-trimethyl-1*H*-4-oxanenzo [*f*]cyclobut[*cd*]inden-5-yl)phenyl methanone (Clusiacyclol B, 4). ***Method A***: To a stirring solution of **51** (500 mg, 1.37 mmol) in methanol (20 mL) at room temperature, $Ca(OH)_2$ (20 mg, 0.27 mmol) was added. After stirring for 48 h at room temperature, methanol was removed in vacuo and the reaction mixture was diluted with ethyl acetate (50 mL). The organic layer was washed with 2 N HCl, water, brine and dried over Na_2SO_4. Removal of the solvent in vacuo followed by silica gel column chromatographic purification of the residue using a mixture of 10% ethyl acetate in petroleum ether gave **4** (395 mg, 79%) as a white crystalline solid. ***Method B***: To a stirring solution of **51** (500 mg, 1.37 mmol) in methanol (15 mL) at 0 ^oC, 0.1 N KOH (5 mL) was added drop wise.

The reaction mixture was allowed to attain room temperature and after 24 h stirring at room temperature, methanol was removed in vacuo and the reaction mixture was acidified slowly with 2 N HCl at 0 ^{o}C. The reaction mixture was diluted with ethyl acetate (60 mL) and the separated organic layer was washed with water, brine and dried over Na_2SO_4. Removal of the solvent in vacuo followed by silica gel column chromatographic purification of the residue using a mixture of 10% ethyl acetate in petroleum ether gave **4** (375 mg, 75%) as a white crystalline solid. ***Method C***: Compound **51** (500 mg, 1.37 mmol) was heated neat at 100-110 ^{o}C for a period of 6 h with stirring. After cooling, the residue on silica gel column chromatographic purification using a mixture of 10% ethyl acetate in petroleum ether furnished **4** (410 mg, 82%) as a white crystalline solid.

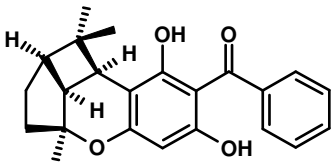


(±)-4

$C_{23}H_{24}O_4$ (364)

Mp 179-181 ^{o}C.
^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.68 (s, 3H), 0.81 (s, 3H), 1.32 (s, 3H), 1.36-1.50 (m, 2H), 1.59-1.71 (m, 1H), 1.78-1.88 (m, 1H), 2.29 (t, *J* = 8 Hz, 1H), 2.39 (dd, *J* = 12 & 8 Hz, 1H), 2.95 (d, *J* = 8 Hz, 1H), 5.96 (s, 1H), 6.02 (s, 1H), 7.30-7.50 (m, 5H), 12.43 (s, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz) δ 17.7, 25.8, 26.4, 33.6, 35.7, 37.2, 37.8, 39.0, 45.9, 84.1, 95.8, 103.4, 106.3, 126.8, 127.5, 129.6, 143.2, 156.3, 162.4, 164.3, 200.6.
IR ($CHCl_3$) 3327, 1624, 1603 cm^{-1}.
MS (*m/z*) 365, 285, 102.
Anal. Calcd for $C_{23}H_{24}O_4$: C, 75.80; H, 6.64. Found: C, 75.69; H, 6.52.

(1*a*,2,3,3*a*,8*b*,8*c*-Hexahydro-6,8-dihydroxy-1,1,3*a*-trimethyl-1*H*-4-oxanenzo [*f*]cyclobut[*cd*]inden-7-yl)phenyl methanone (Clusiacyclol A, 3). ***Method A***: It was prepared similarly by using **52** (250 mg, 0.68 mmol), methanol (20 mL) and $Ca(OH)_2$ (10 mg, 0.14 mmol). **3**: White solid (190 mg, 76%). ***Method B***: It was prepared similarly by using **52** (250 mg, 0.68 mmol), methanol (12 mL) and 0.1 N KOH (4 mL). **3**: (175 mg, 70%) White solid. ***Method C***: It was prepared similarly by heating **52** (250 mg, 0.68 mmol) neat. **3**: (200 mg, 80%) White solid.

 **(±)-3** **$C_{23}H_{24}O_4$ (364)**	**Mp** 137-139 ^oC. **^1H NMR** ($CDCl_3$, 500 MHz) δ 0.82 (s, 3H), 1.35 (s, 3H), 1.40 (s, 3H), 1.55-1.65 (m, 1H), 1.65-1.75 (m, 2H), 1.92-2.00 (m, 1H), 2.41 (t, *J* = 10 Hz, 1H), 2.58 (dd, *J* = 10 & 10 Hz, 1H), 3.06 (d, *J* = 10 Hz, 1H), 5.94 (s, 1H), 7.45 (s, 1H), 7.50 (t, *J* = 10 Hz, 2H), 7.57 (t, *J* = 10 Hz, 1H), 7.64 (d, *J* = 10 Hz, 2H), 10.20 (s, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 17.8, 25.6, 27.5, 33.6, 35.5, 37.3, 38.8, 39.0, 46.5, 84.8, 97.7, 104.3, 104.5, 127.9, 129.1, 132.1, 140.0, 158.8, 161.5, 161.6, 197.4. **IR** (Nujol) 3325, 1620, 1614, 1589 cm^{-1}. **MS** (*m/z*) 365, 301, 192, 131. **Anal. Calcd** for $C_{23}H_{24}O_4$: C, 75.80; H, 6.64. Found: C, 75.71; H, 6.75.

X-ray Crystal Structure Analysis Data for Oxacyclobutaindane 28a

A single crystal of the oxacyclobutaindane **28a** was grown by slow evaporation of the solution in acetone. Colorless rectangular crystal of approximate size 0.27 x 0.17 x 0.06 mm, was used for data collection on *Bruker SMART APEX* CCD diffractometer using MoK_α radiation with fine focus tube with 50kV and 30mA. Crystal to detector distance 6.05 cm, 512 x 512 pixels / frame, Quadrant data acquisition. Total scans = 4, total frames = 2424, Oscillation / frame -0.3º, exposure / frame = 20.0 sec / frame, maximum detector swing angle = –30.0º, beam center = (260.2, 252.5), in plane spot width = 1.24, SAINT integration, θ range = 1.53 to 25.0 º, completeness to θ of 25.0º is 99.9 %. SADABS correction applied. The crystal structures were solved by direct method using SHELXS-97 and the refinement was performed[32] by full matrix least squares of F^2 using SHELXL-97. Data collection and refinement parameters are listed in table 1. CCDC-280384 contains bond lengths, bond angles and other details supplementary crystallographic data[33] of oxacyclobutaindane **28a**.

Table 1 Crystal Data and Structure Refinement of Oxacyclobutaindane **28a**

Empirical formula	$C_{18}\ H_{14}\ O_5$
Formula weight	310.34

Temperature	297(2) K
Wavelength	0.71073 Å
Crystal system, space group	Monoclinic, $P2_1/c$
Unit cell dimensions	a = 13.3486(15) Å b = 5.3819(7) Å β = 93.676(2) ° c = 13.8757(15) Å
Volume	1471.9(3) $Å^3$
Z, Calculated density	1.355 Mg/m^3
Crystal size	0.27 x 0.17 x 0.06 mm
θ range for data collection	1.53 to 25.0 °
Reflections collected / unique	9215 / 2594 [R(int) = 0.0501]
Completeness to θ = 25.00	99.9%
Goodness-of-fit on F^2	1.010

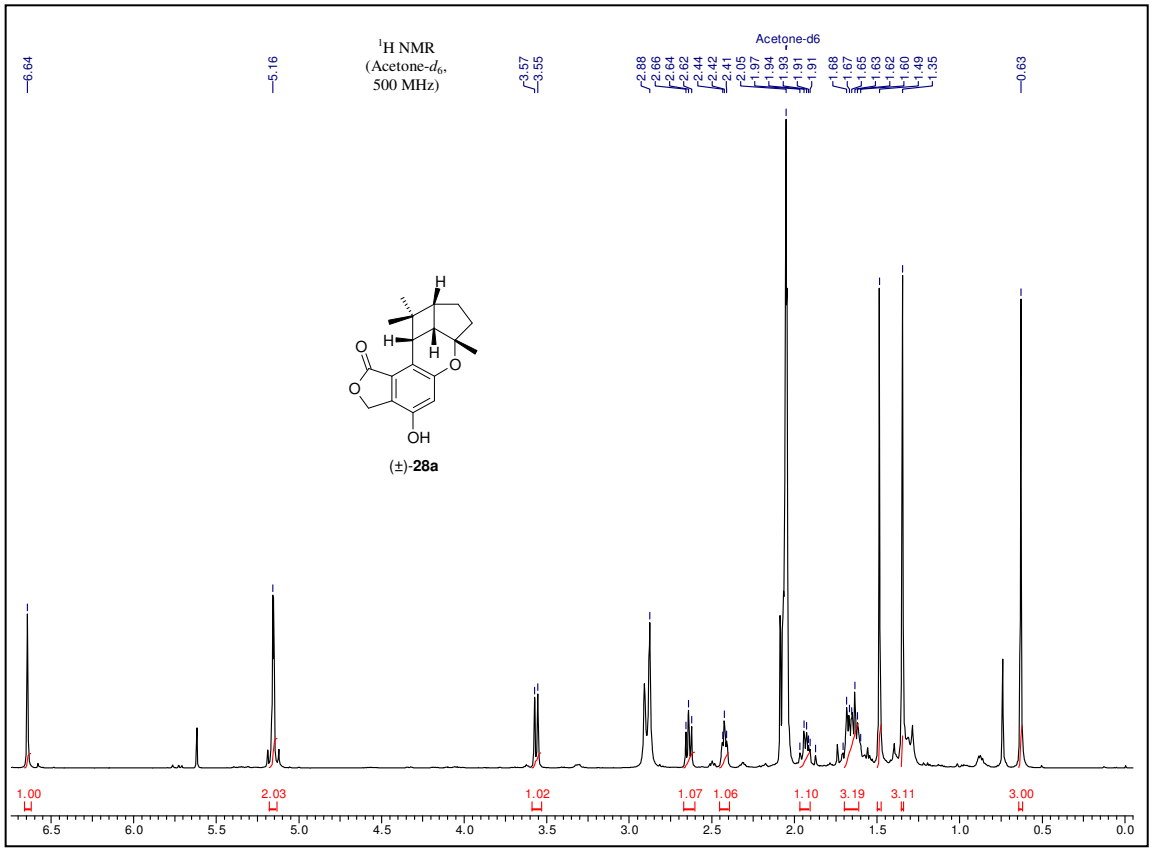
X-ray Crystal Structure Analysis Data for Oxabicyclononane 30

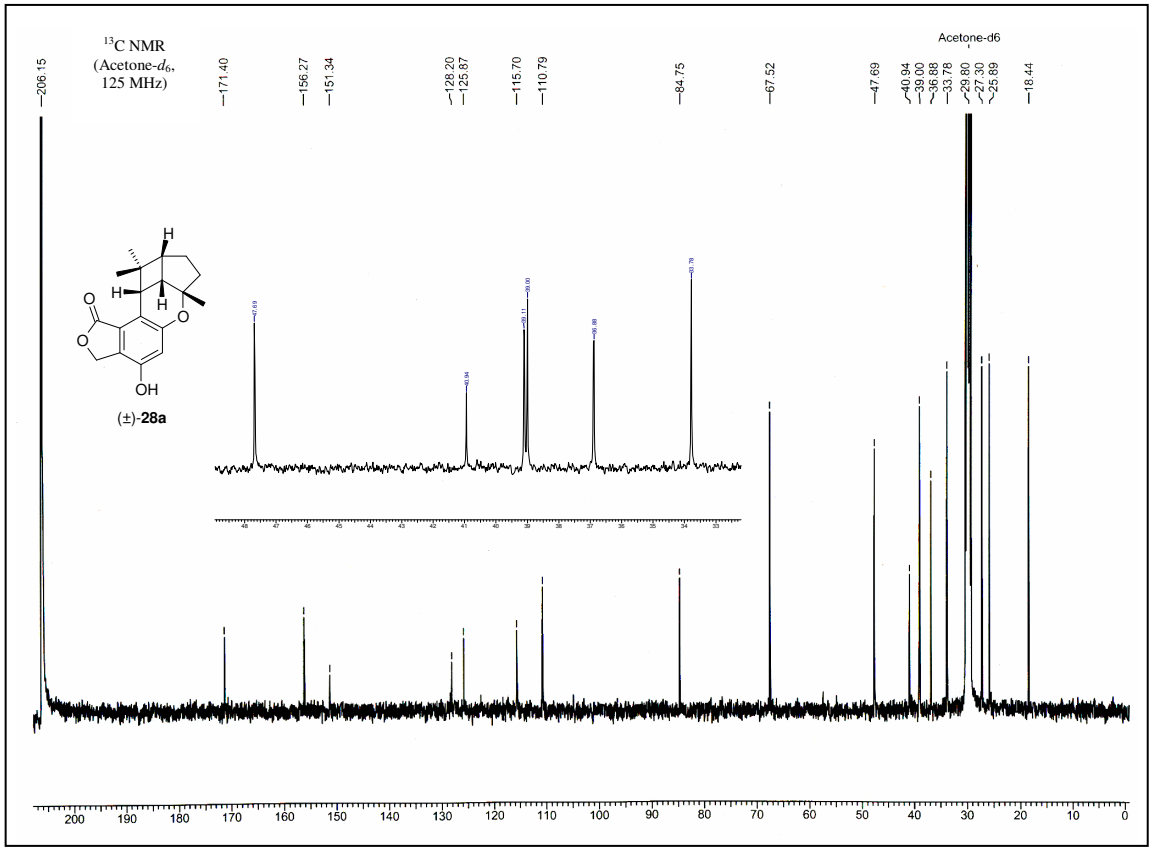
A single crystal of the oxabicyclononane **30** was grown by slow evaporation of the solution in acetone. Colorless rectangular crystal of approximate size 0.37 x 0.14 x 0.07 mm, was used for data collection on *Bruker SMART APEX* CCD diffractometer using MoK_α radiation with fine focus tube with 50kV and 30mA. Crystal to detector distance 6.05 cm, 512 x 512 pixels / frame, Quadrant data acquisition. Total scans = 3, total frames = 1818, Oscillation / frame -0.3º, exposure / frame = 15.0 sec / frame, maximum detector swing angle = –30.0º, beam center = (260.2, 252.5), in plane spot width = 1.24, SAINT integration, θ range = 2.32 to 24.99 °, completeness to θ of 24.99 ° is 100.0 %. SADABS correction applied. The crystal structures were solved by direct method using SHELXS-97 and the refinement was performed[32] by full matrix least squares of F^2 using SHELXL-97. Data collection and refinement parameters are listed in table 1. CCDC-280385 contains bond lengths, bond angles and other details supplementary crystallographic data[33] of oxabicyclononane **30**.

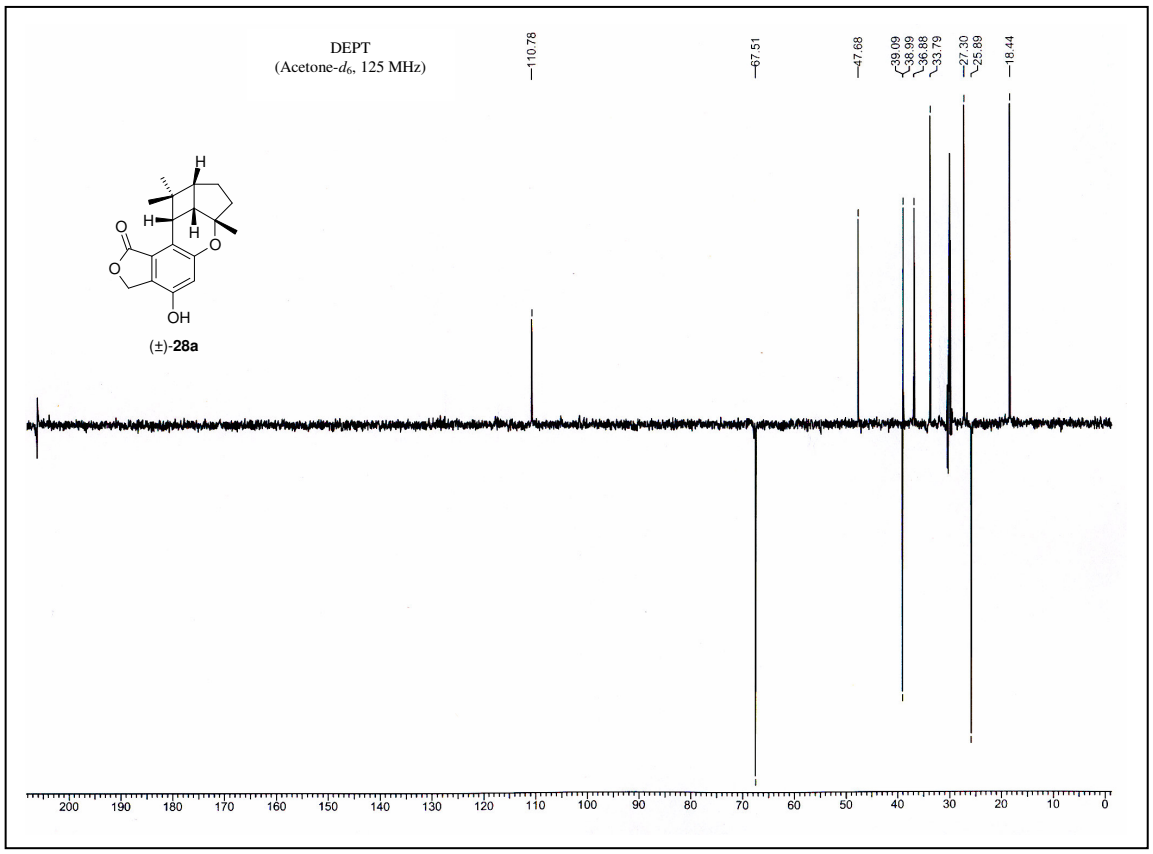
Table 1 Crystal Data and Structure Refinement of oxabicyclononane **30**

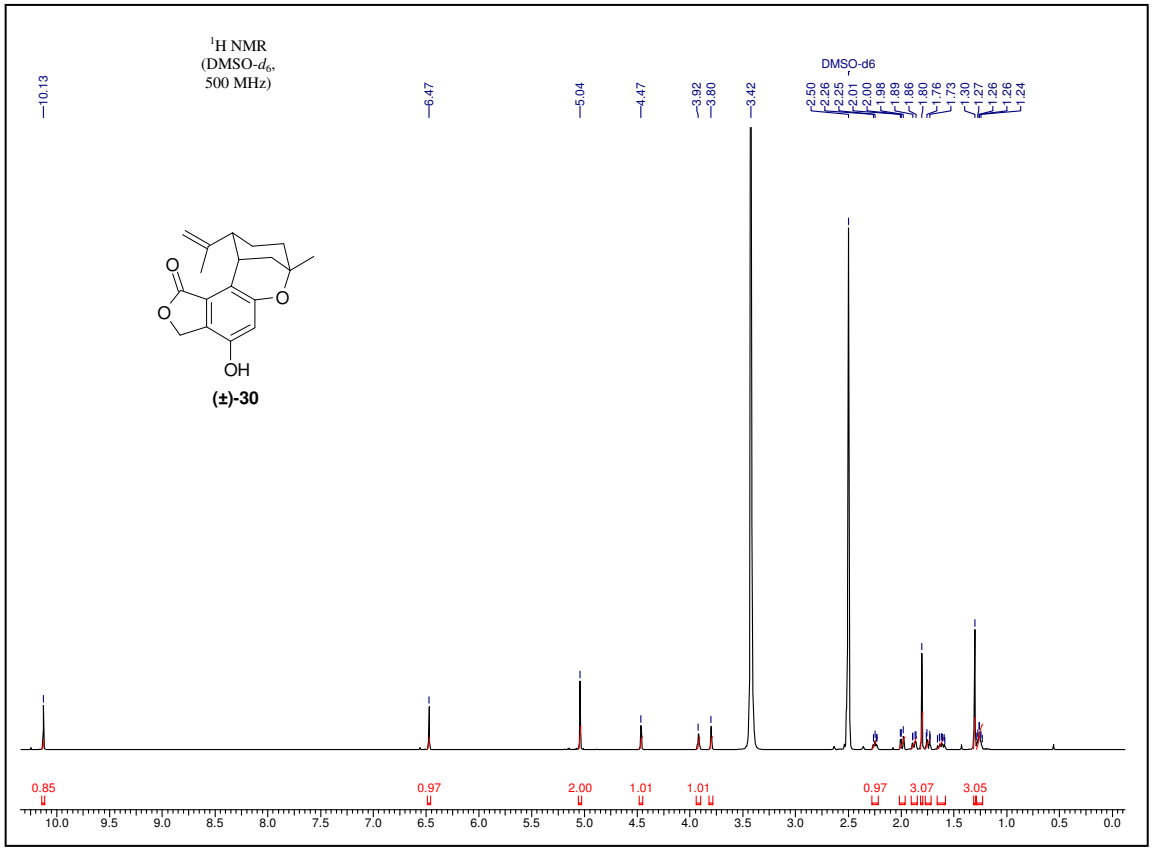
Empirical formula	$C_{18}\ H_{14}\ O_5$
Formula weight	310.34
Temperature	297(2) K
Wavelength	0.71073 Å
Crystal system, space group	Monoclinic, $P2_1/c$
Unit cell dimensions	a = 10.1385(7) Å b = 11.8567(8) Å β = 97.7790(10) º c = 13.1736(9) Å
Volume	1569.01(19) $Å^3$
Z, Calculated density	1.271 Mg/m^3
Crystal size	0.37 x 0.14 x 0.07 mm
θ range for data collection	2.32 to 24.99 º
Reflections collected / unique	9714 / 2758 [R(int) = 0.0398]
Completeness to θ = 25.00	100.0%
Goodness-of-fit on F^2	1.023

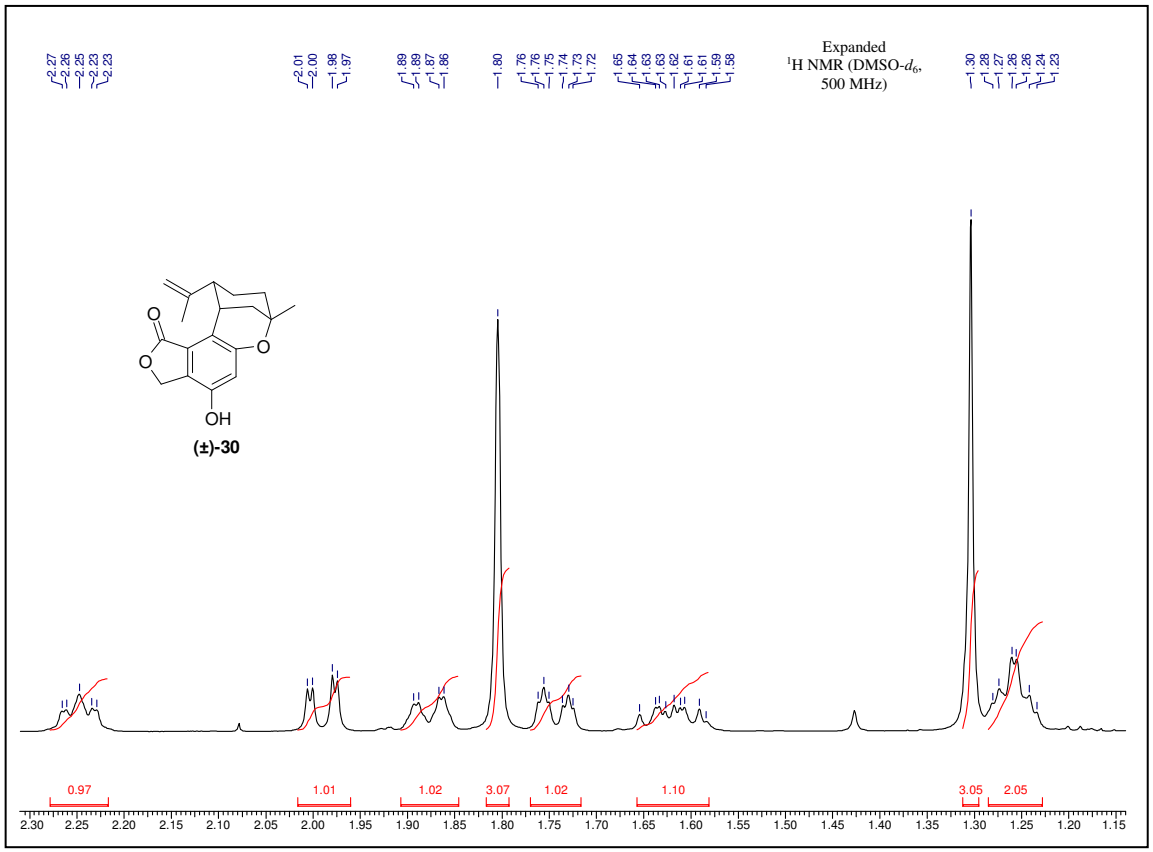
2C.6 Selected Spectra

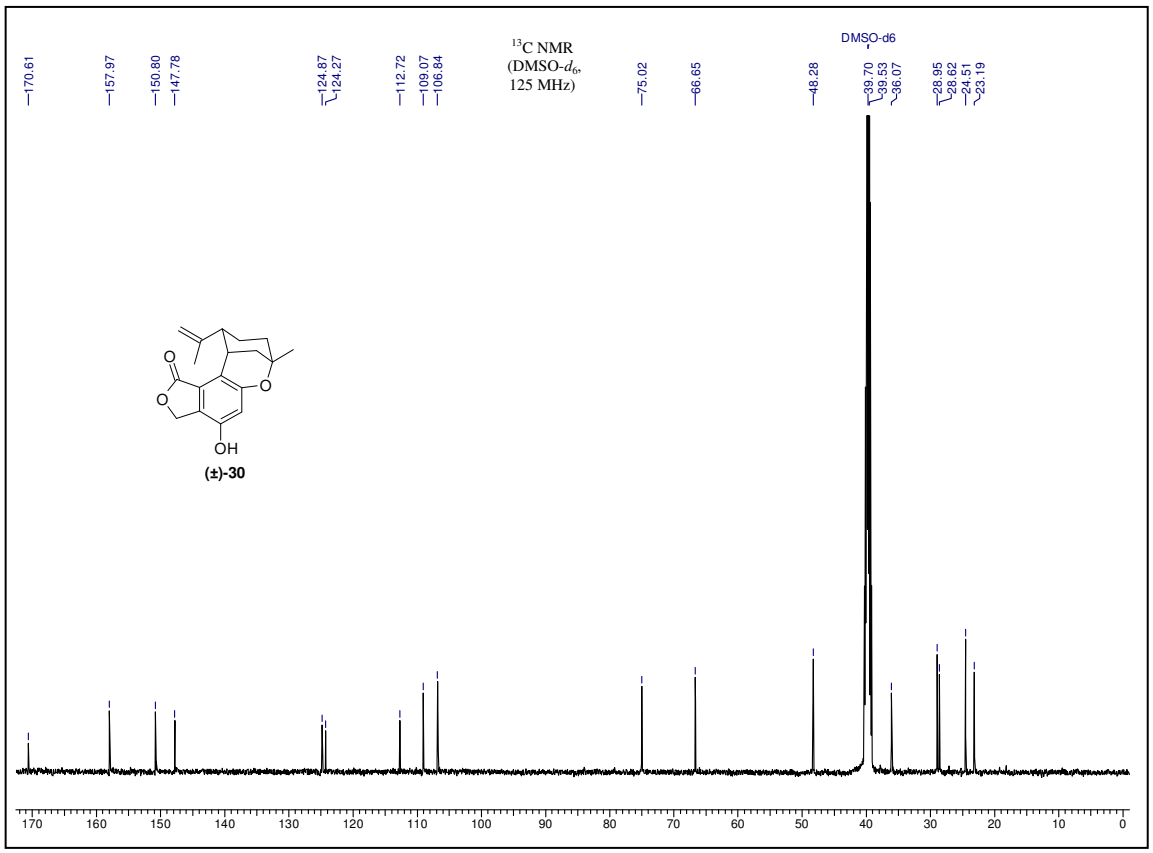

^{1}H NMR
(Acetone-d_6,
500 MHz)
Acetone-d6
6.64
5.16
3.57
3.55
2.88
2.66
2.64
2.62
2.44
2.42
2.41
2.05
1.97
1.94
1.93
1.91
1.91
1.68
1.67
1.65
1.63
1.62
1.60
1.49
1.35
0.63
(±)-28a
1.00
2.03
1.02
1.07
1.06
1.10
3.19
3.11
3.00

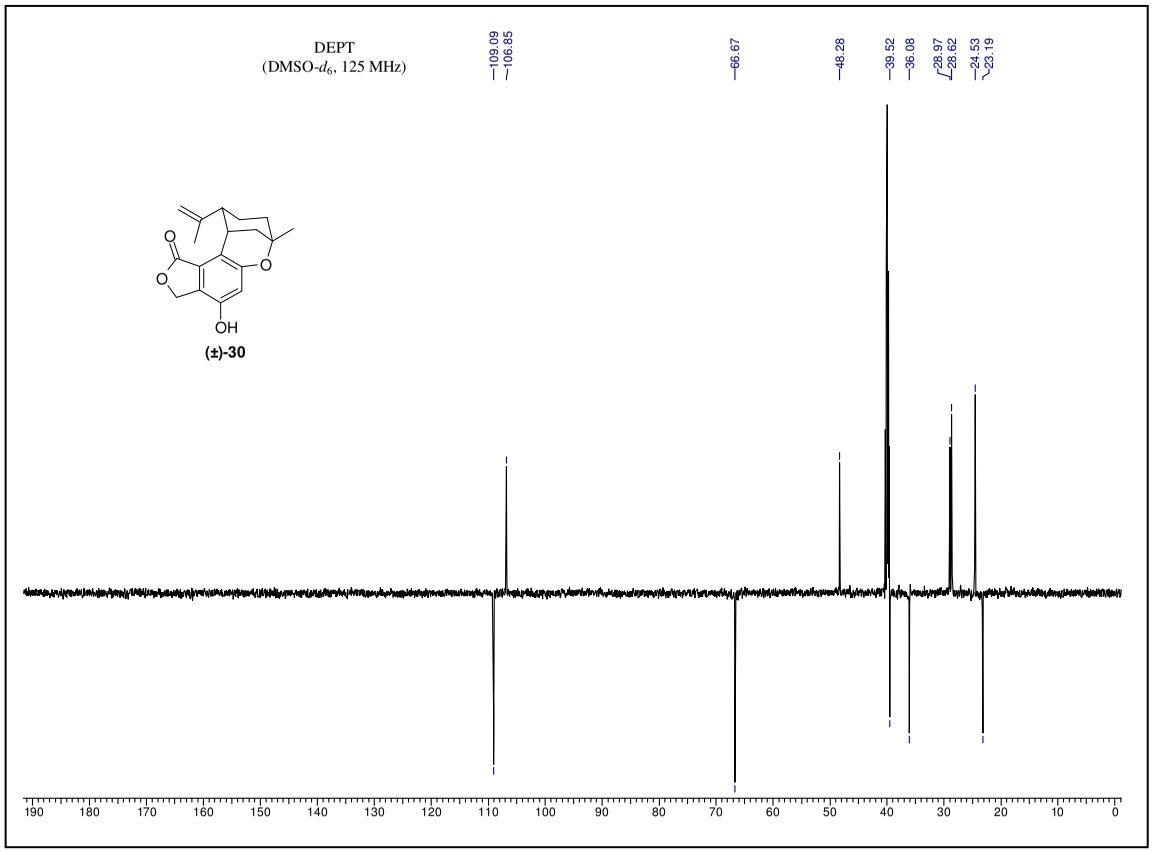

^{13}C NMR
(Acetone-d_6,
125 MHz)
Acetone-d6
206.15
171.40
156.27
151.34
128.20
125.87
115.70
110.79
84.75
67.52
47.69
40.94
39.00
36.88
33.78
29.80
27.30
25.89
18.44
(±)-28a

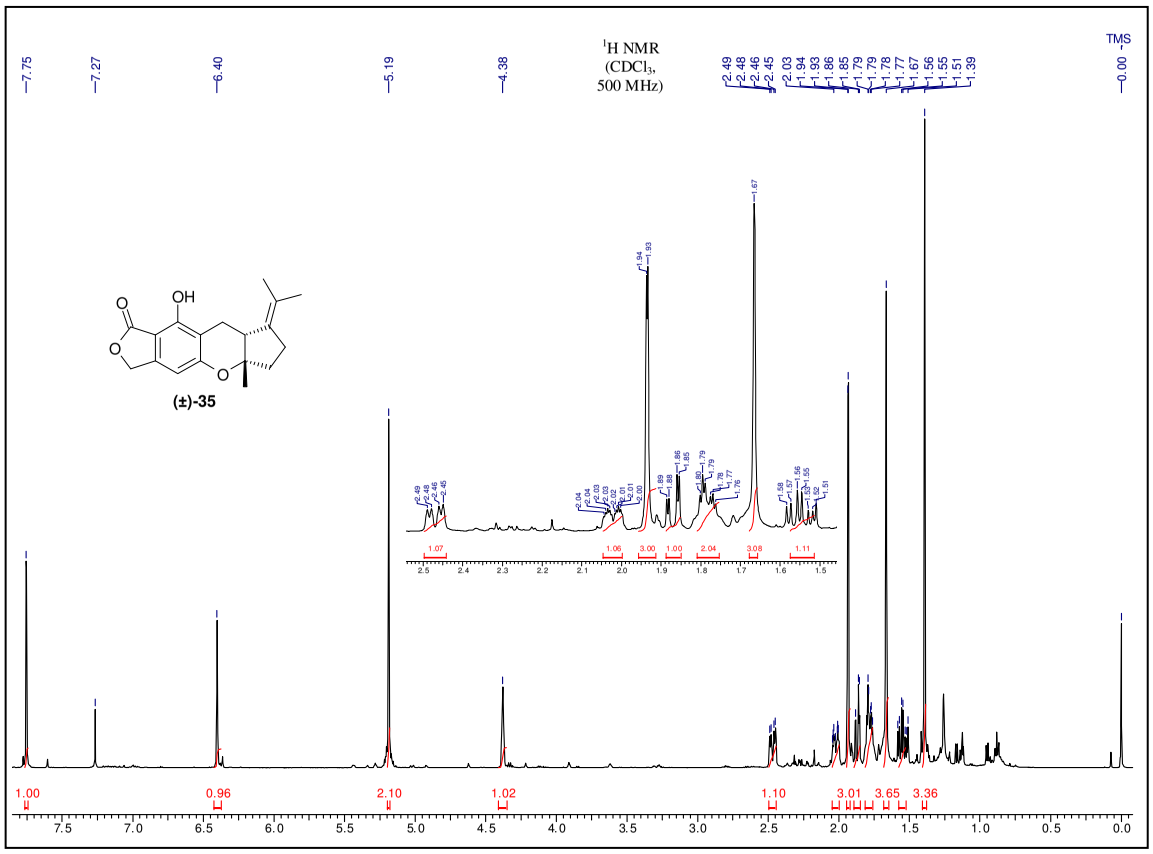

DEPT
(Acetone-d_6, 125 MHz)
110.78
67.51
47.68
39.09
38.99
36.88
33.79
27.30
25.89
18.44
(±)-28a

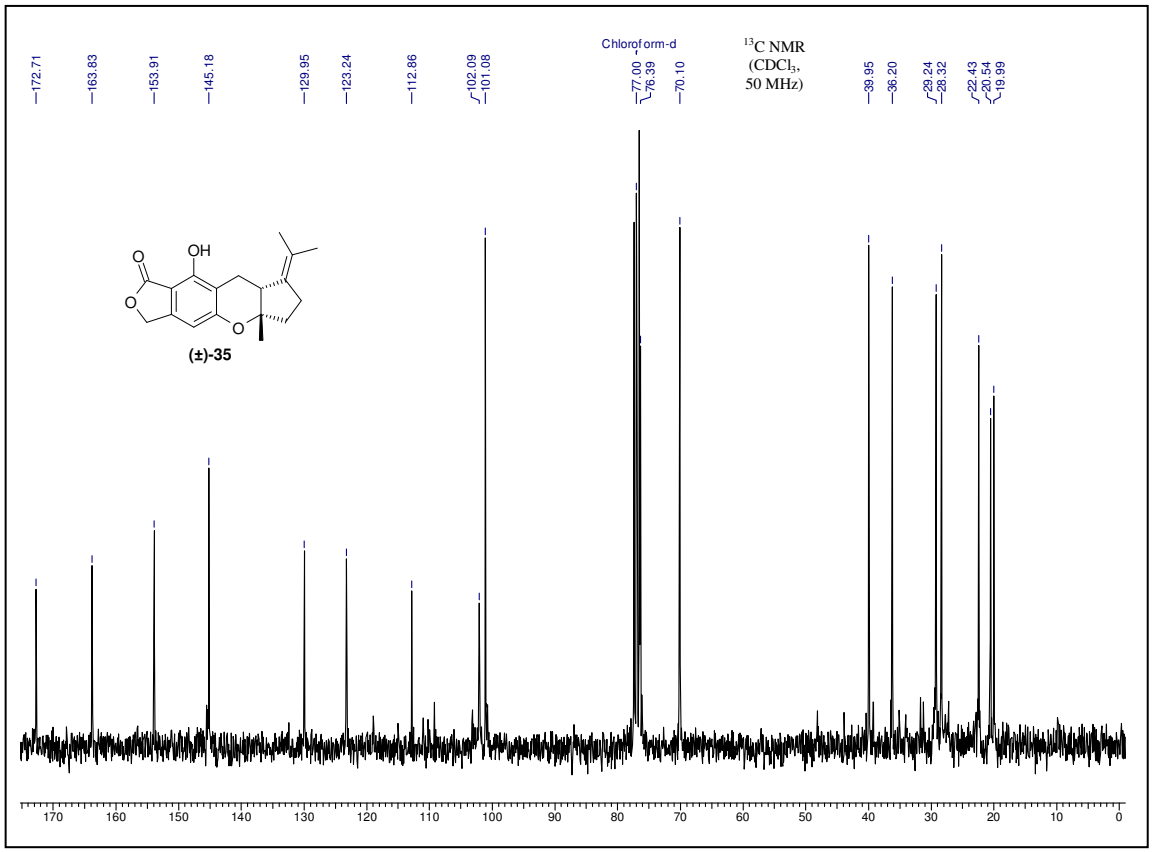

^{1}H NMR
(DMSO-d_6,
500 MHz)
DMSO-d6
10.13
6.47
5.04
4.47
3.92
3.80
3.42
(±)-30

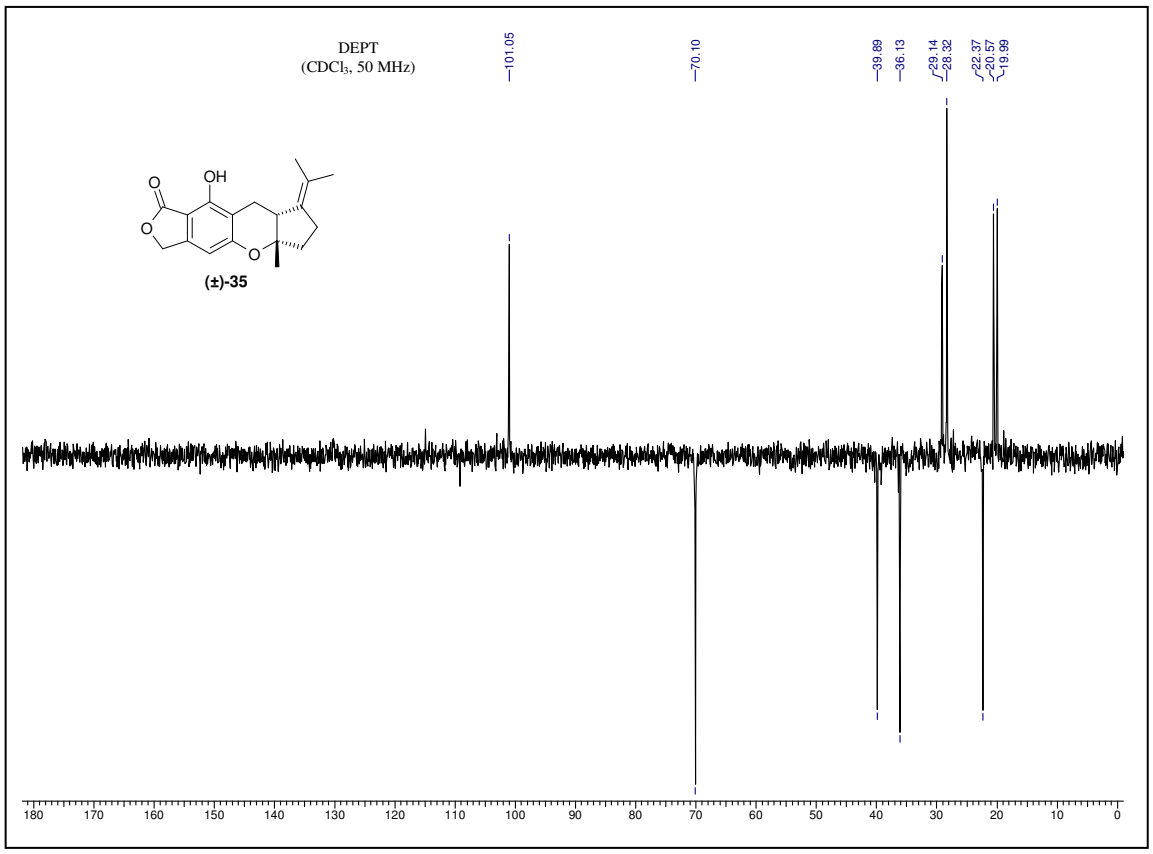

Expanded
^{1}H NMR (DMSO-d_6, 500 MHz)
2.27
2.26
2.25
2.23
2.23
2.01
2.00
1.98
1.97
1.89
1.89
1.87
1.86
1.80
1.76
1.76
1.75
1.74
1.73
1.72
1.65
1.64
1.63
1.63
1.62
1.61
1.61
1.59
1.58
1.30
1.28
1.27
1.26
1.26
1.24
1.23
O
O
O
OH
(±)-30
0.97
1.01
1.02
3.07
1.02
1.10
3.05
2.05
2.30 2.25 2.20 2.15 2.10 2.05 2.00 1.95 1.90 1.85 1.80 1.75 1.70 1.65 1.60 1.55 1.50 1.45 1.40 1.35 1.30 1.25 1.20 1.15

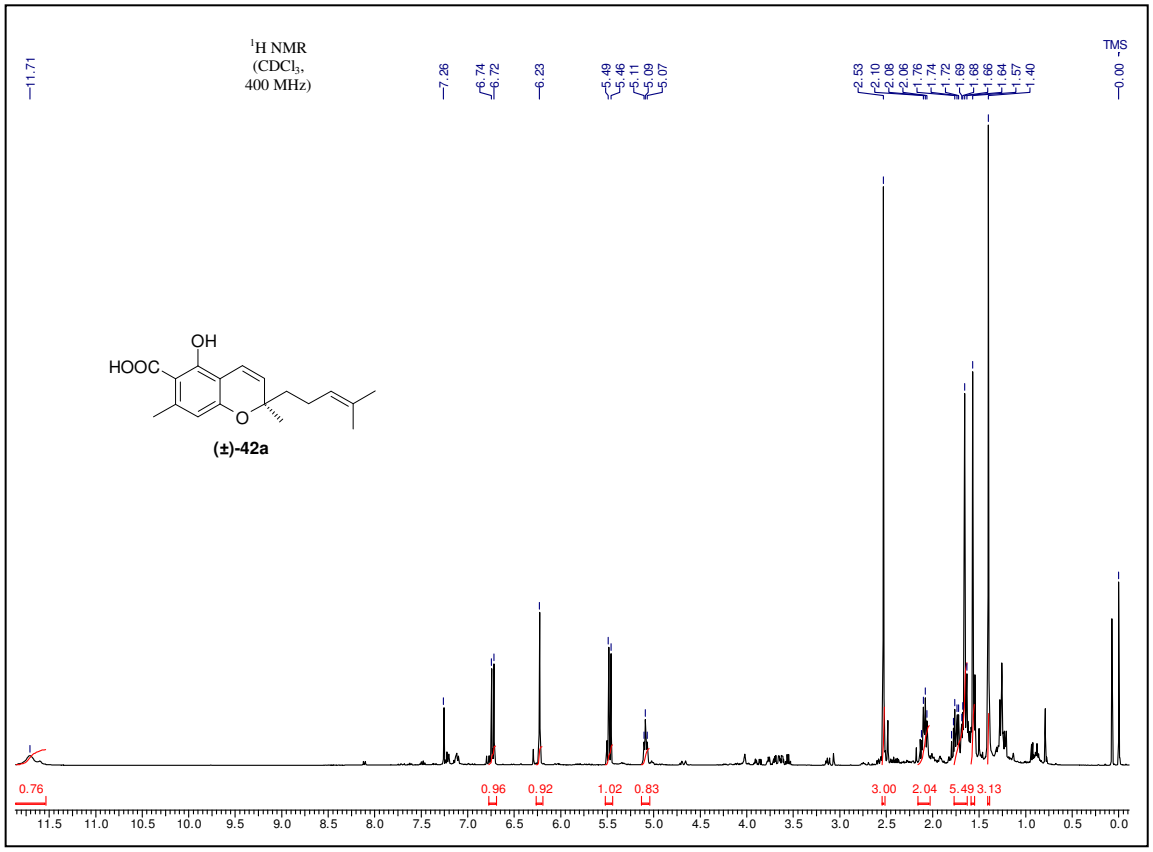

^{13}C NMR (DMSO-d_6, 125 MHz)
DMSO-d6
170.61
157.97
150.80
147.78
124.87
124.27
112.72
109.07
106.84
75.02
66.65
48.28
39.70
39.53
36.07
28.95
28.62
24.51
23.19
O
O
O
OH
(±)-30
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

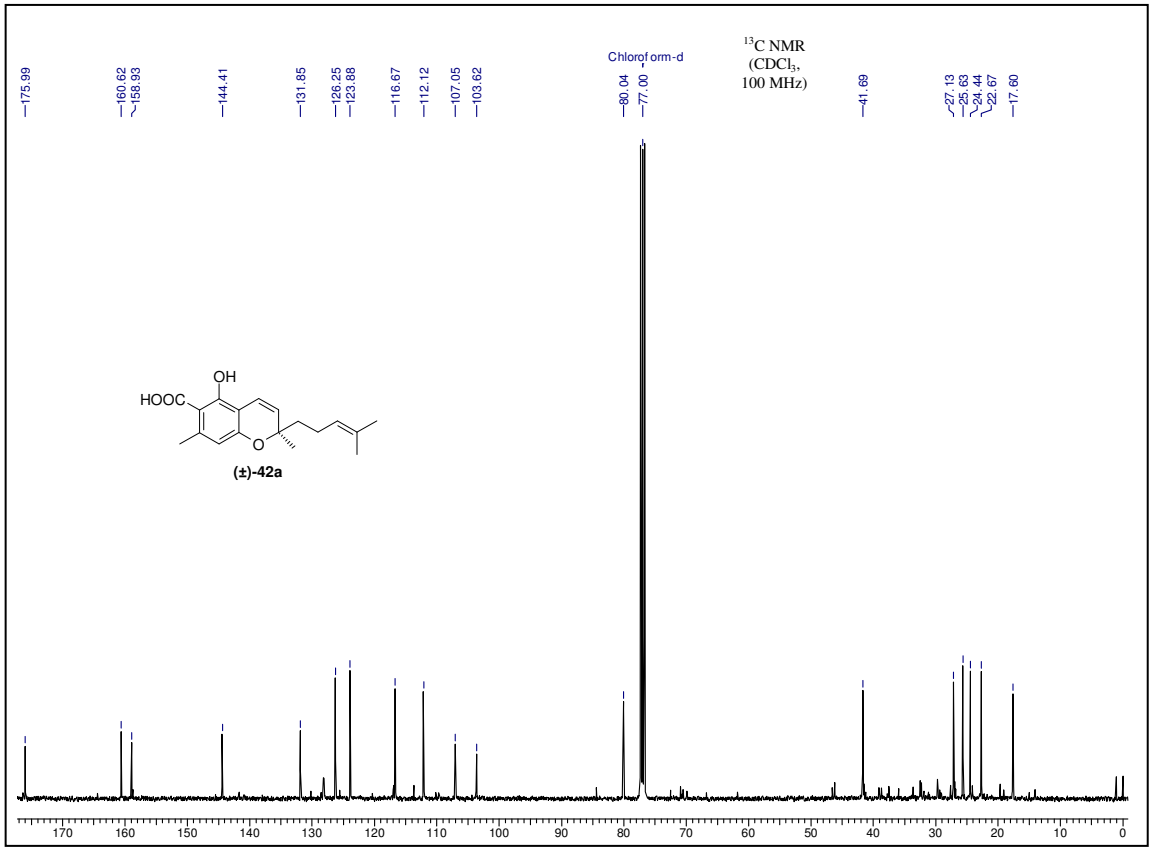

DEPT
(DMSO-d_6, 125 MHz)
109.09
106.85
66.67
48.28
39.52
36.08
28.97
28.62
24.53
23.19
OH
(±)-30

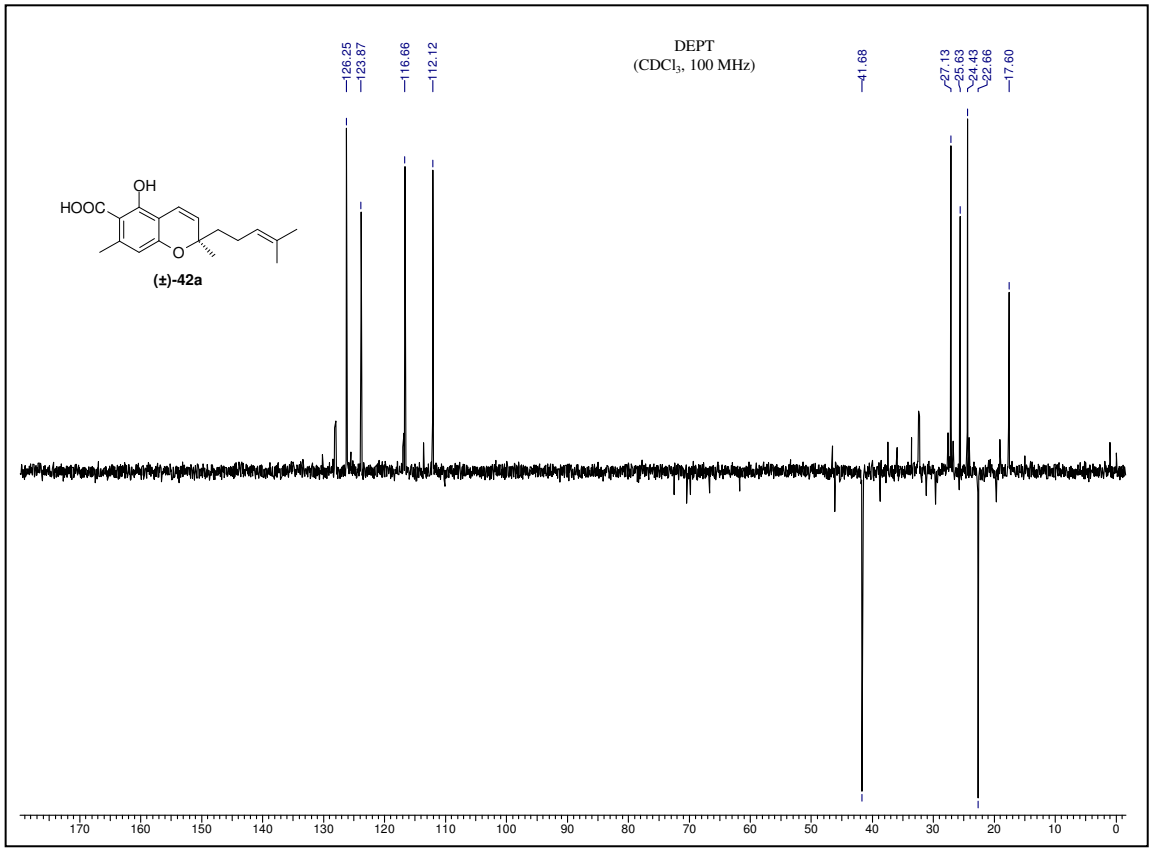

^{1}H NMR
($CDCl_3$,
500 MHz)
TMS
7.75
7.27
6.40
5.19
4.38
2.49
2.48
2.46
2.45
2.03
1.94
1.93
1.86
1.85
1.79
1.79
1.78
1.77
1.67
1.56
1.55
1.51
1.39
0.00
OH
(±)-35
1.00
0.96
2.10
1.02
1.10
3.01
3.65
3.36

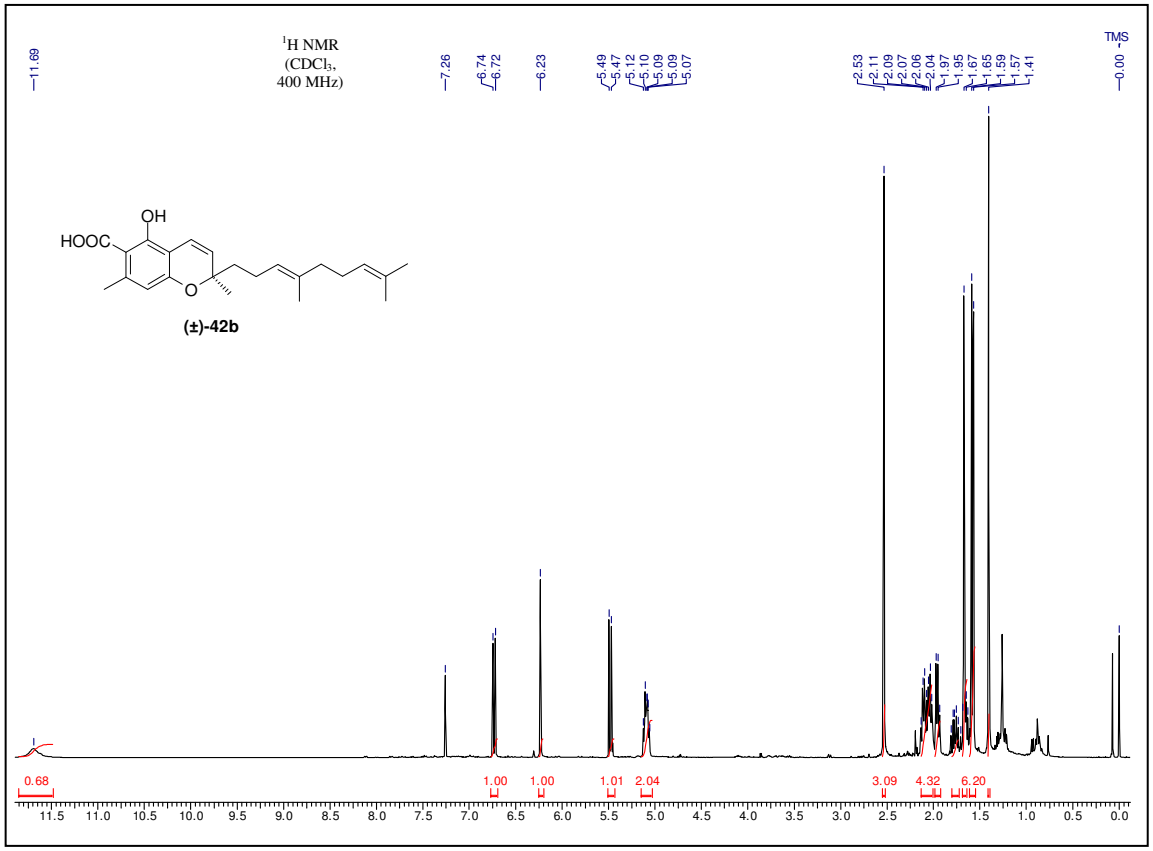

172.71
163.83
153.91
145.18
129.95
123.24
112.86
102.09
101.08
Chloroform-d
77.00
76.39
70.10
^{13}C NMR
($CDCl_3$,
50 MHz)
39.95
36.20
29.24
28.32
22.43
20.54
19.99
OH
O
O
O
(±)-35
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

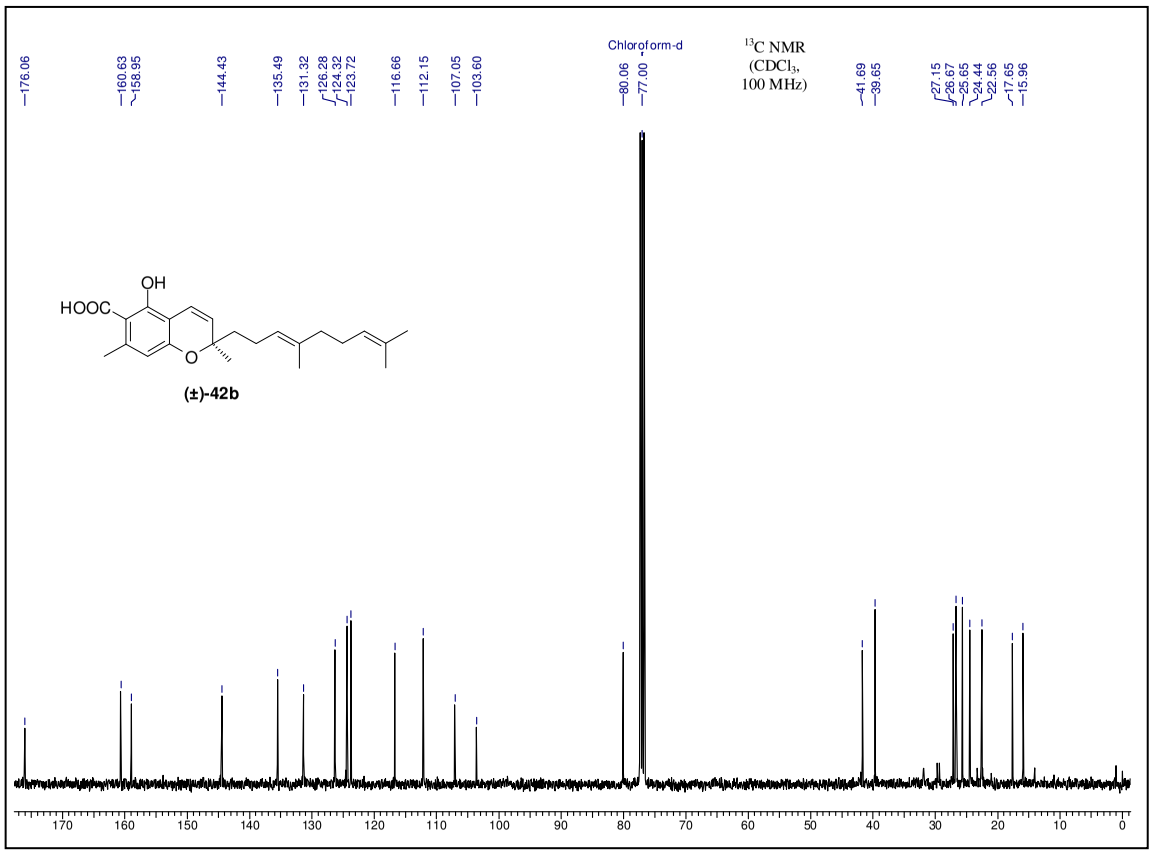

DEPT
($CDCl_3$, 50 MHz)
101.05
70.10
39.89
36.13
29.14
28.32
22.37
20.57
19.99
OH
O
O
O
(±)-35
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

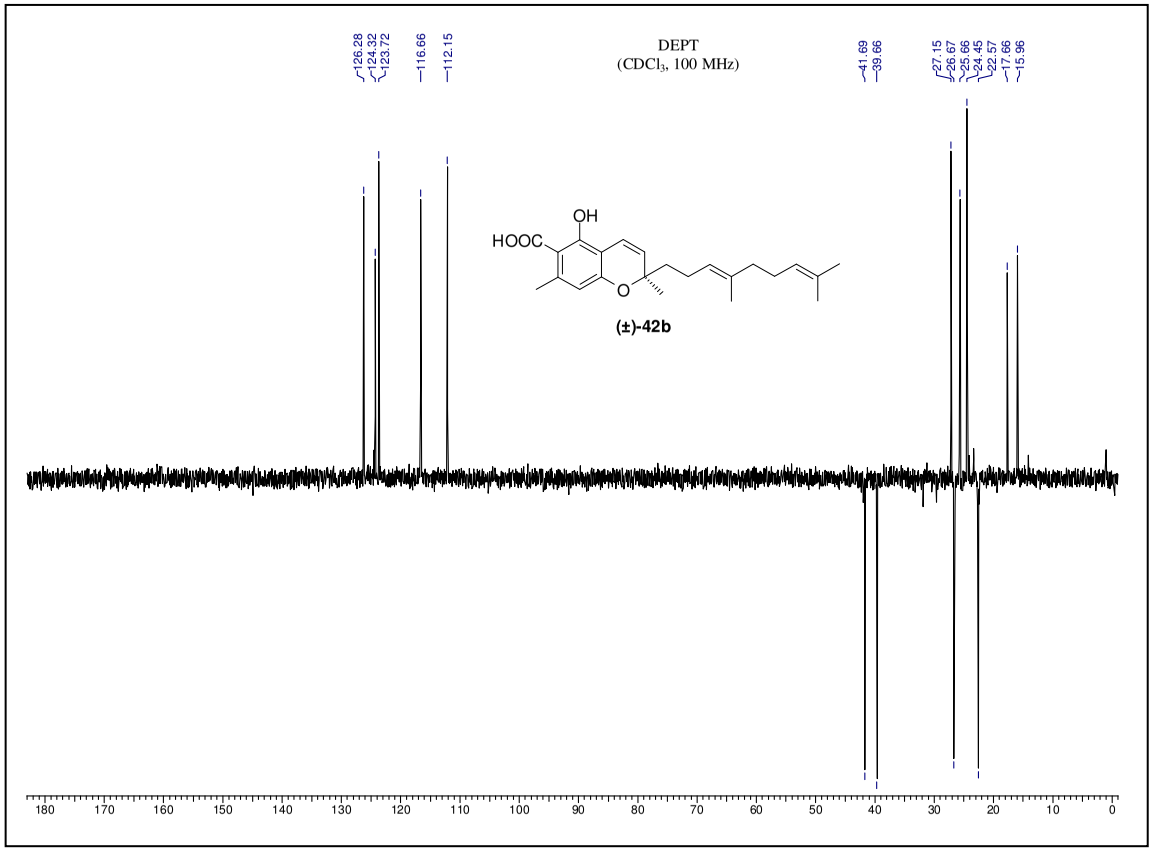

^{1}H NMR
(CDCl$_3$,
400 MHz)
TMS
OH
HOOC
O
(±)-42a

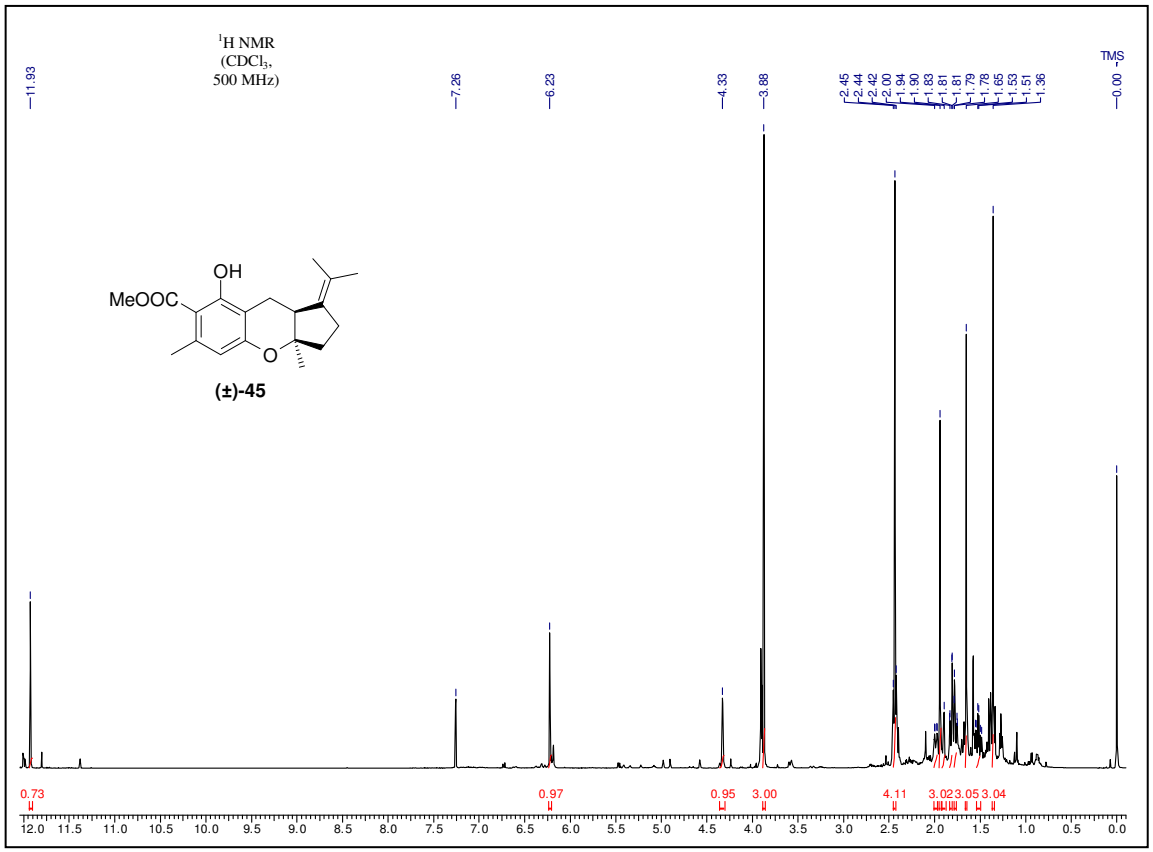

^{13}C NMR
(CDCl$_3$,
100 MHz)
Chloroform-d
OH
HOOC
O
(±)-42a

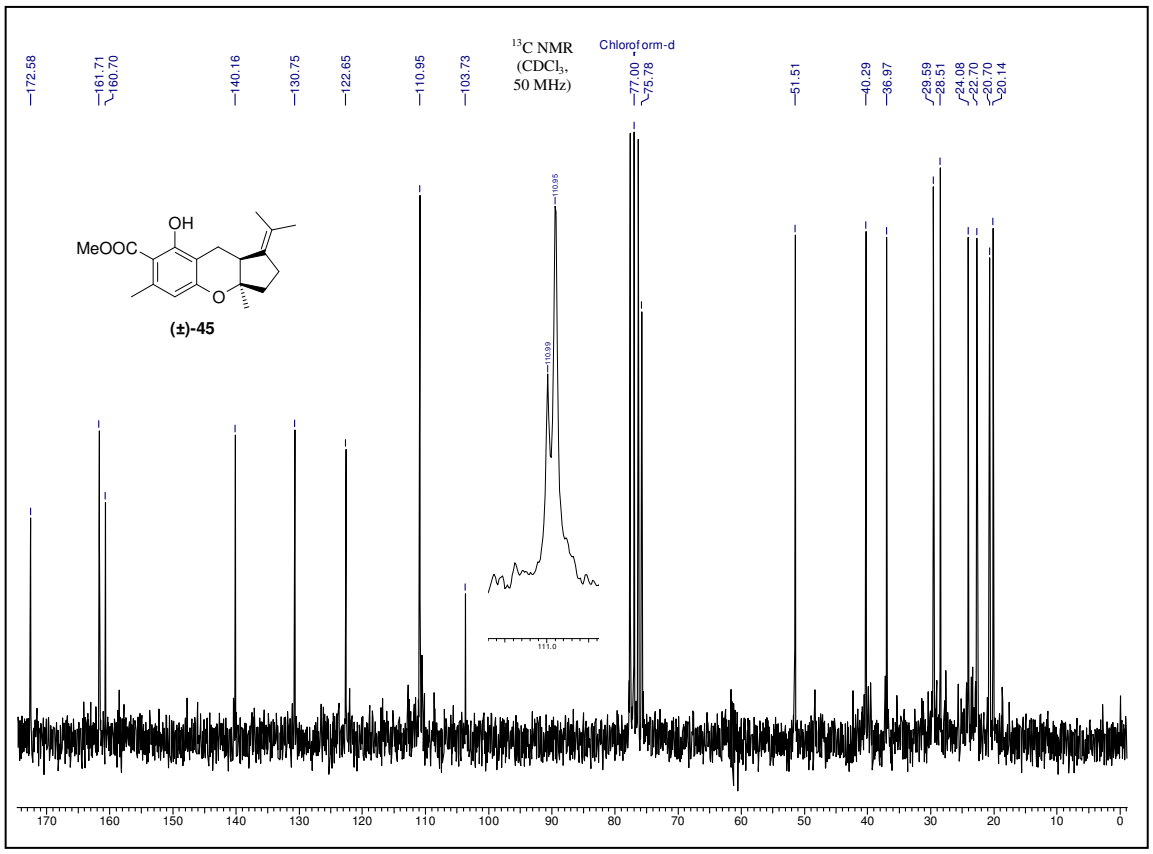

DEPT
(CDCl3, 100 MHz)
126.25
123.87
116.66
112.12
41.68
27.13
25.63
24.43
22.66
17.60
OH
HOOC
O
(±)-42a

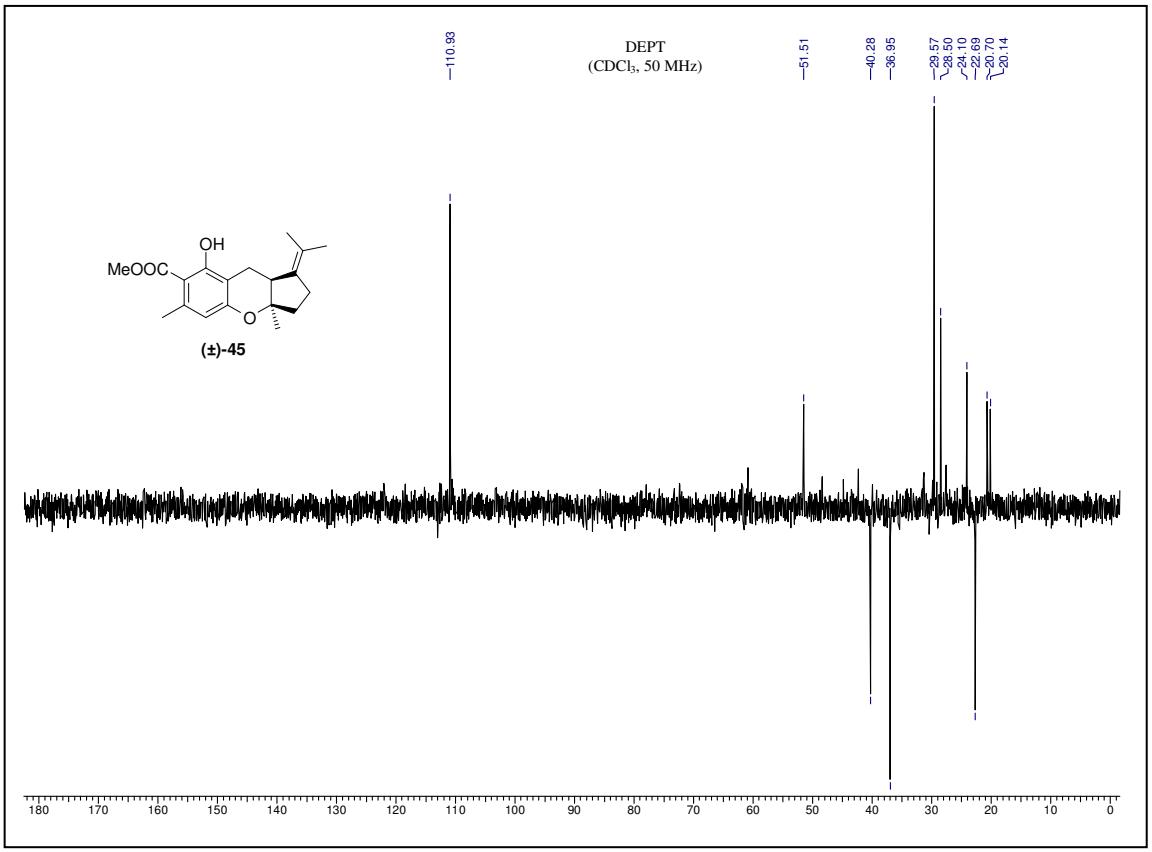

1H NMR
(CDCl3,
400 MHz)
11.69
7.26
6.74
6.72
6.23
5.49
5.47
5.12
5.10
5.09
5.09
5.07
2.53
2.11
2.09
2.07
2.06
2.04
1.97
1.95
1.67
1.65
1.59
1.57
1.41
TMS
0.00
OH
HOOC
O
(±)-42b
0.68
1.00
1.00
1.01
2.04
3.09
4.32
6.20

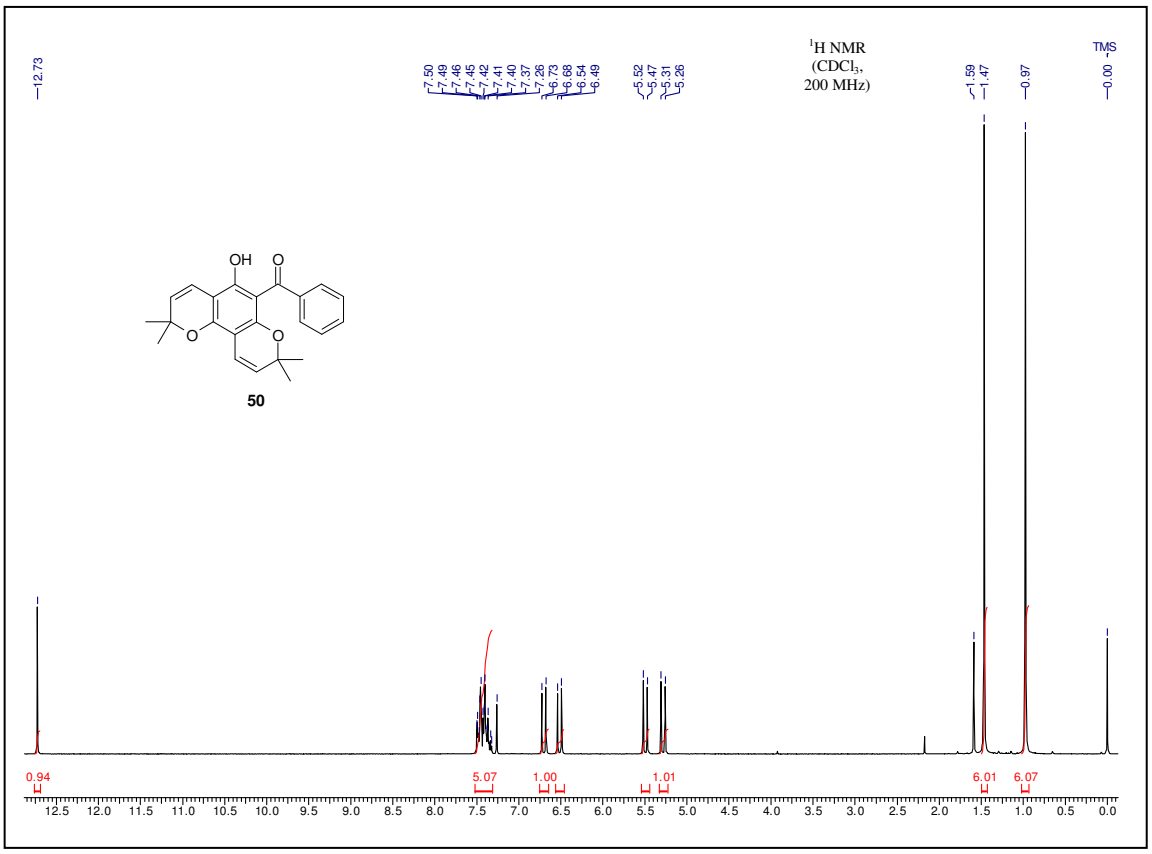

176.06
160.63
158.95
144.43
135.49
131.32
126.28
124.32
123.72
116.66
112.15
107.05
103.60
Chloroform-d
80.06
77.00
^{13}C NMR
($CDCl_3$,
100 MHz)
41.69
39.65
27.15
26.67
25.65
24.44
22.56
17.65
15.96
OH
HOOC
O
(±)-42b
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

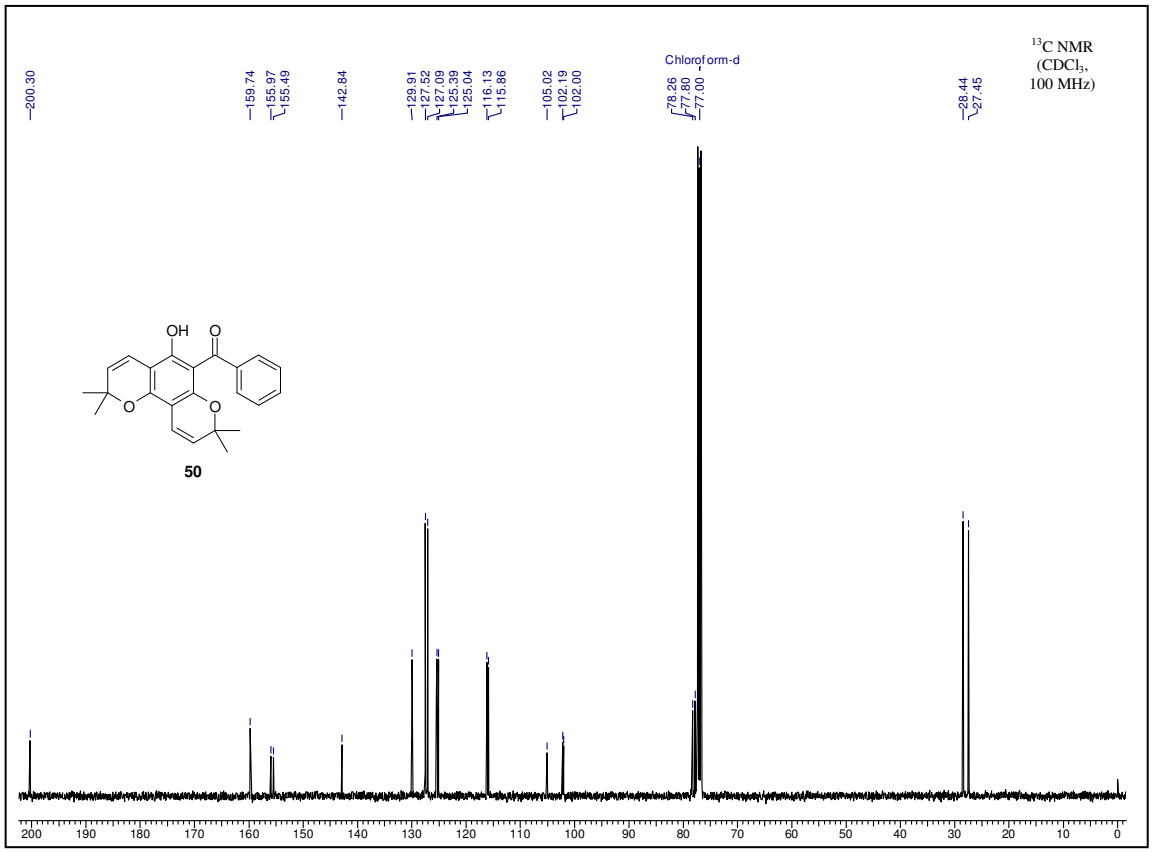

126.28
124.32
123.72
116.66
112.15
DEPT
($CDCl_3$, 100 MHz)
41.69
39.66
27.15
26.67
25.66
24.45
22.57
17.66
15.96
OH
HOOC
O
(±)-42b
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

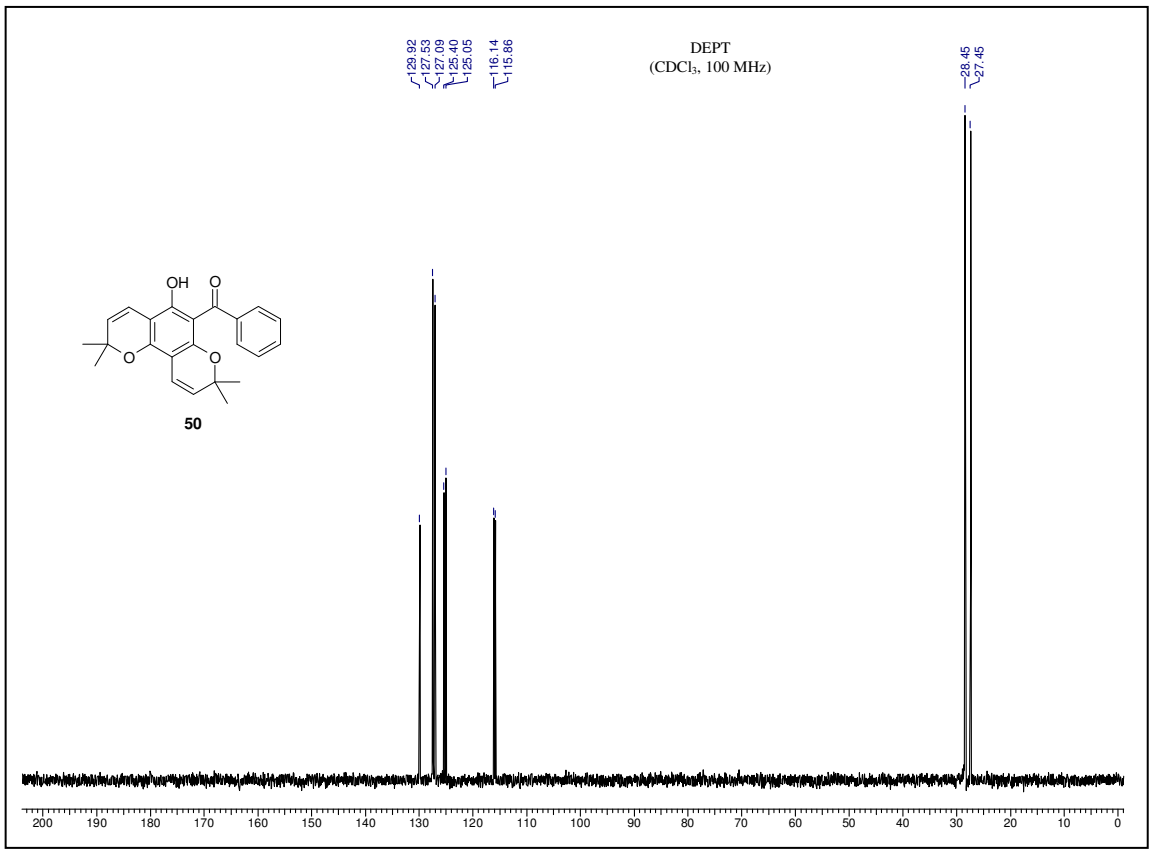

^{1}H NMR
($CDCl_3$,
500 MHz)
TMS
OH
MeOOC
O
(±)-45

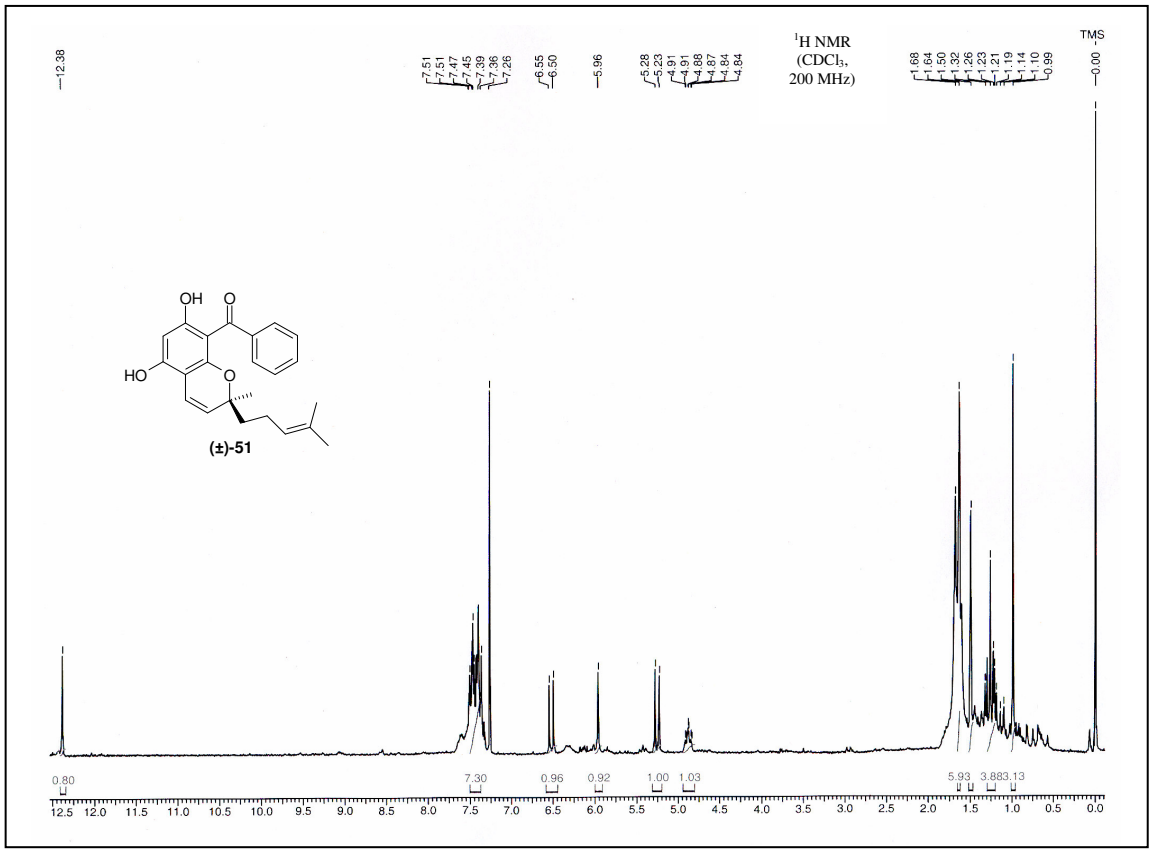

^{13}C NMR
($CDCl_3$,
50 MHz)
Chloroform-d
OH
MeOOC
O
(±)-45

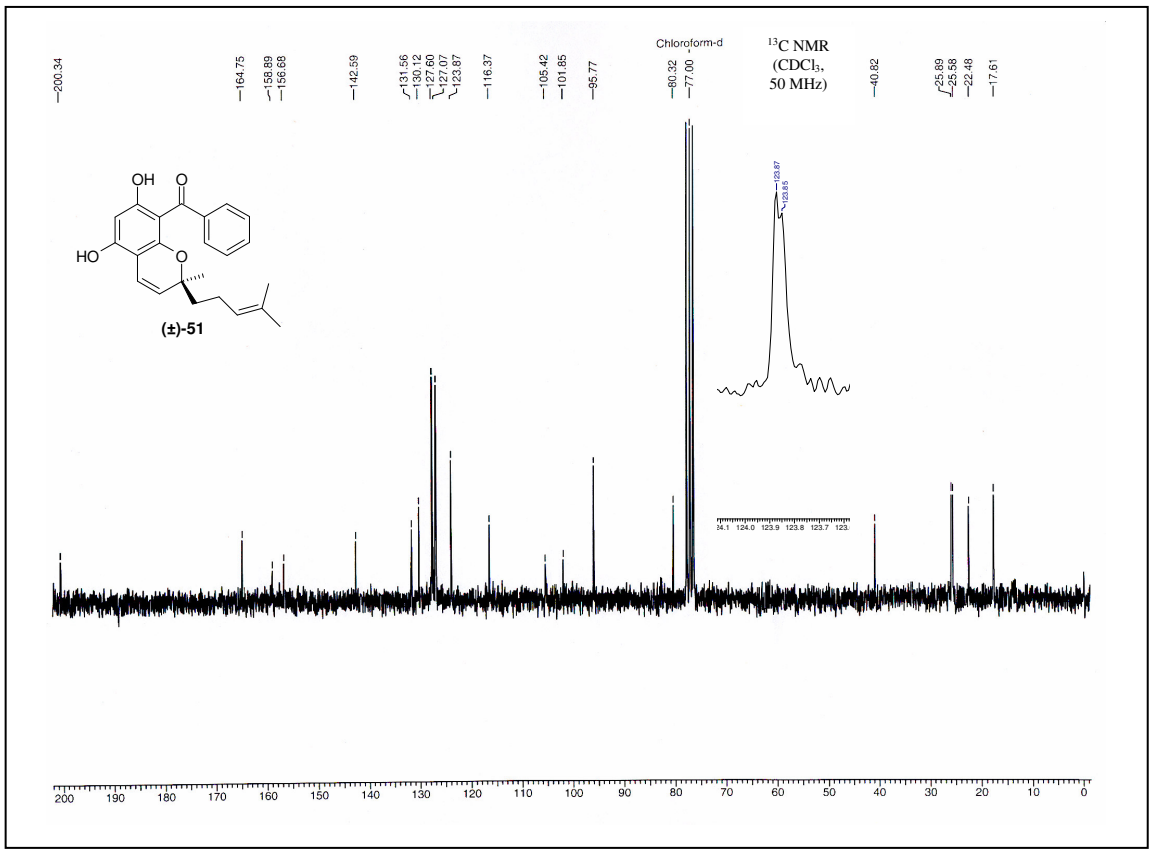

DEPT
(CDCl3, 50 MHz)
110.93
51.51
40.28
36.95
29.57
28.50
24.10
22.69
20.70
20.14
OH
MeOOC
O
(±)-45

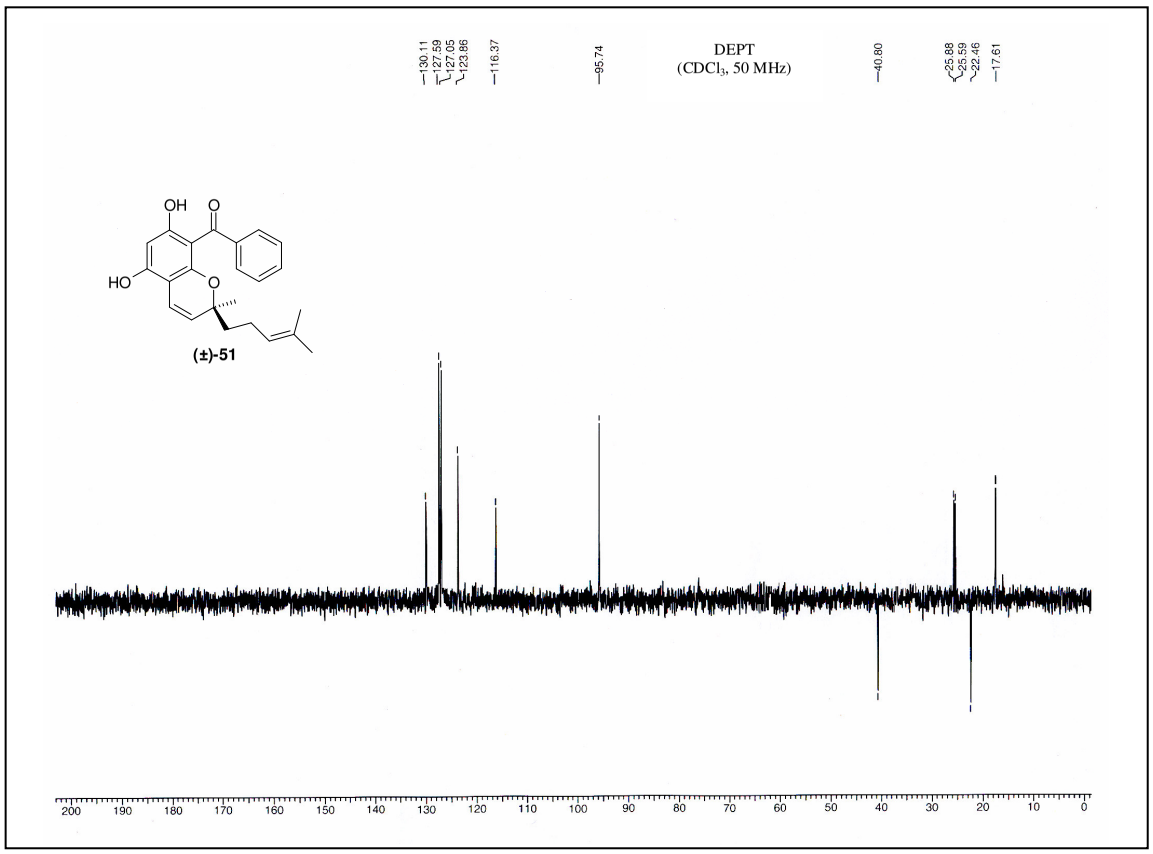

1H NMR
(CDCl3,
200 MHz)
TMS
12.73
7.50
7.49
7.46
7.45
7.42
7.41
7.40
7.37
7.26
6.73
6.68
6.54
6.49
5.52
5.47
5.31
5.26
1.59
1.47
0.97
0.00
OH
O
O
O
50
0.94
5.07
1.00
1.01
6.01
6.07


^{13}C NMR
(CDCl$_3$,
100 MHz)
Chloroform-d
200.30
159.74
155.97
155.49
142.84
129.91
127.52
127.09
125.39
125.04
116.13
115.86
105.02
102.19
102.00
78.26
77.80
77.00
28.44
27.45
OH
O
O
O
50


DEPT
(CDCl$_3$, 100 MHz)
129.92
127.53
127.09
125.40
125.05
116.14
115.86
28.45
27.45
OH
O
O
O
50


^{1}H NMR
(CDCl$_3$,
200 MHz)
TMS
OH
O
HO
O
(±)-51


Chloroform-d
^{13}C NMR
(CDCl$_3$,
50 MHz)
OH
O
HO
O
(±)-51


DEPT
(CDCl3, 50 MHz)
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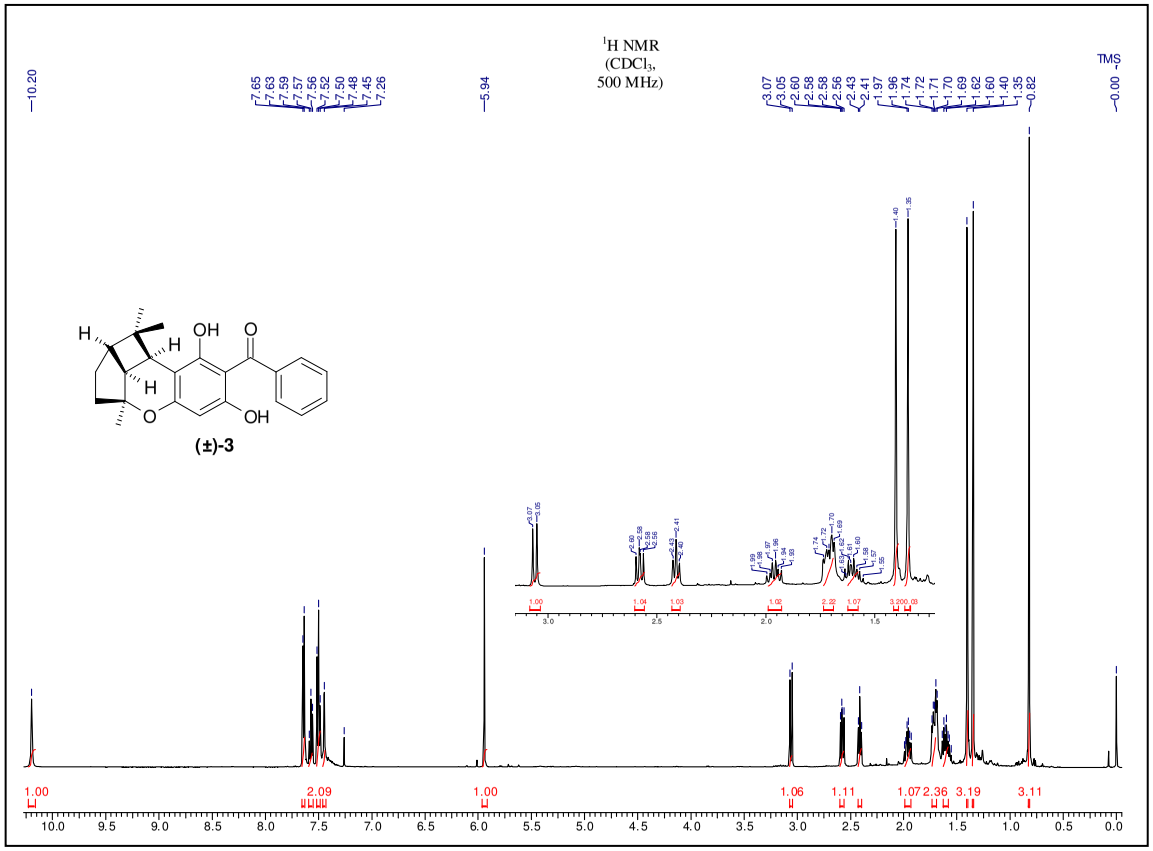
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3.05
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H
H
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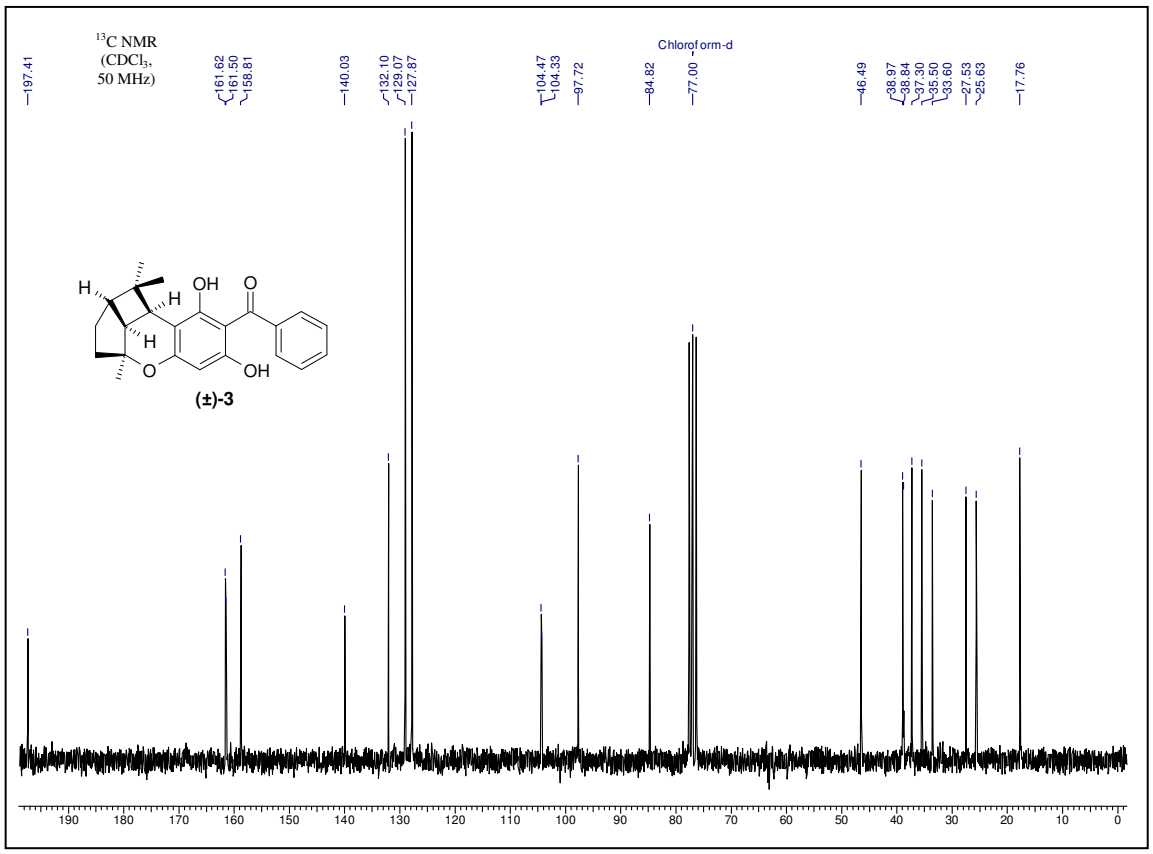
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161.50
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104.33
97.72
84.82
Chloroform-d
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33.60
27.53
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H
OH
O
O
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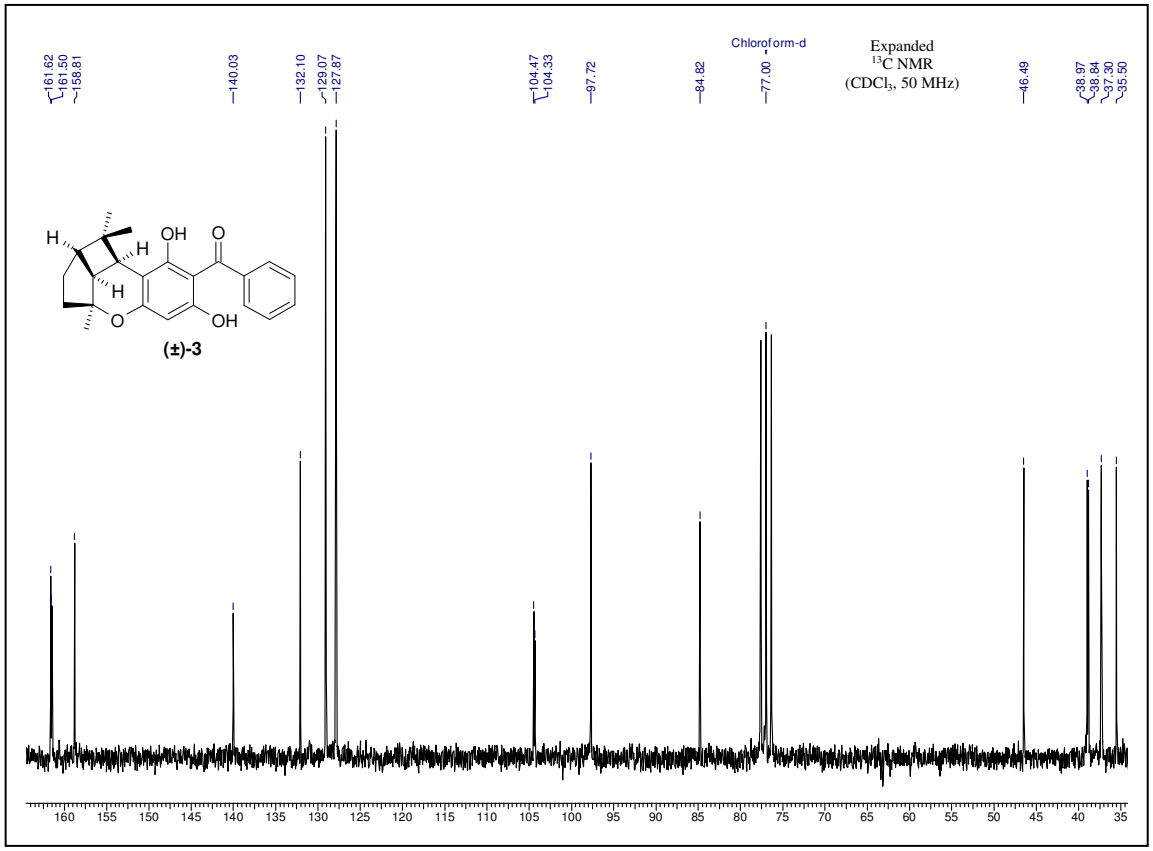
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161.50
158.81
140.03
132.10
129.07
127.87
104.47
104.33
97.72
84.82
Chloroform-d
77.00
Expanded
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($CDCl_3$, 50 MHz)
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38.84
37.30
35.50
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H
H
OH
O
O
OH
(±)-3
160
155
150
145
140
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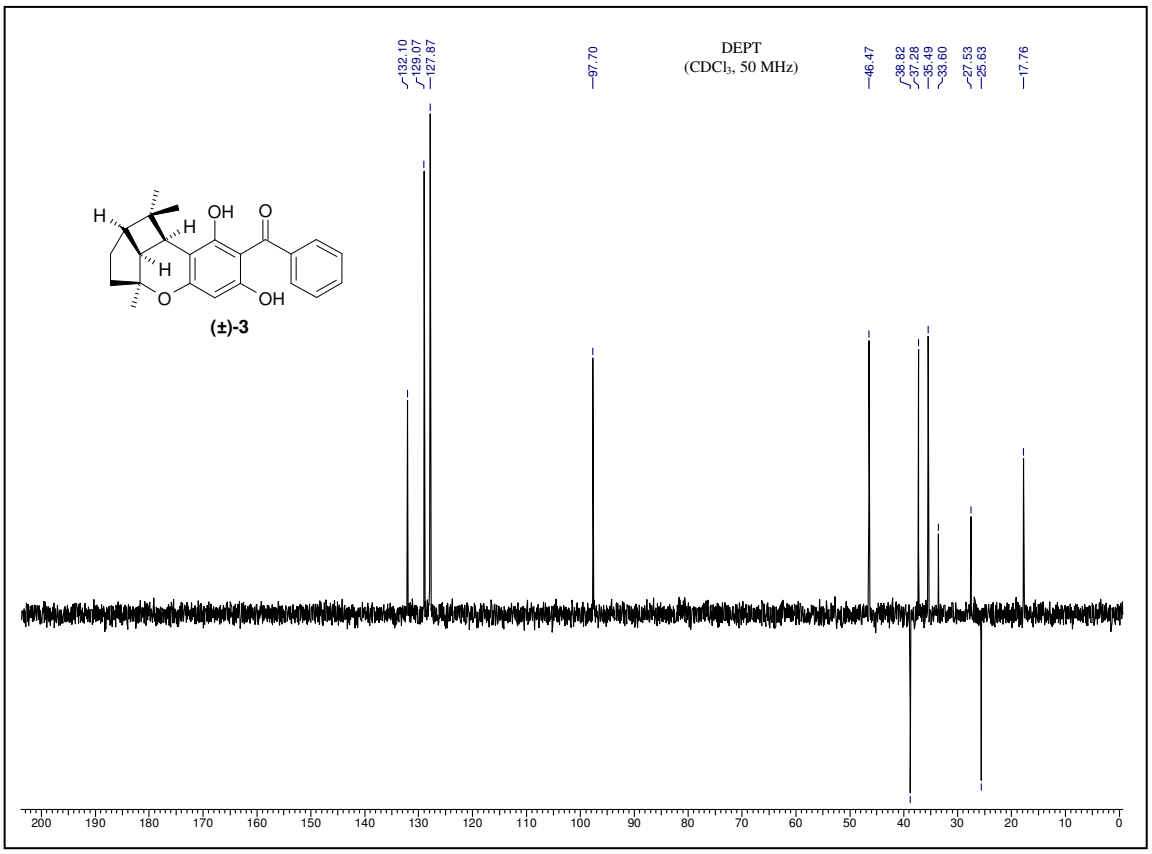
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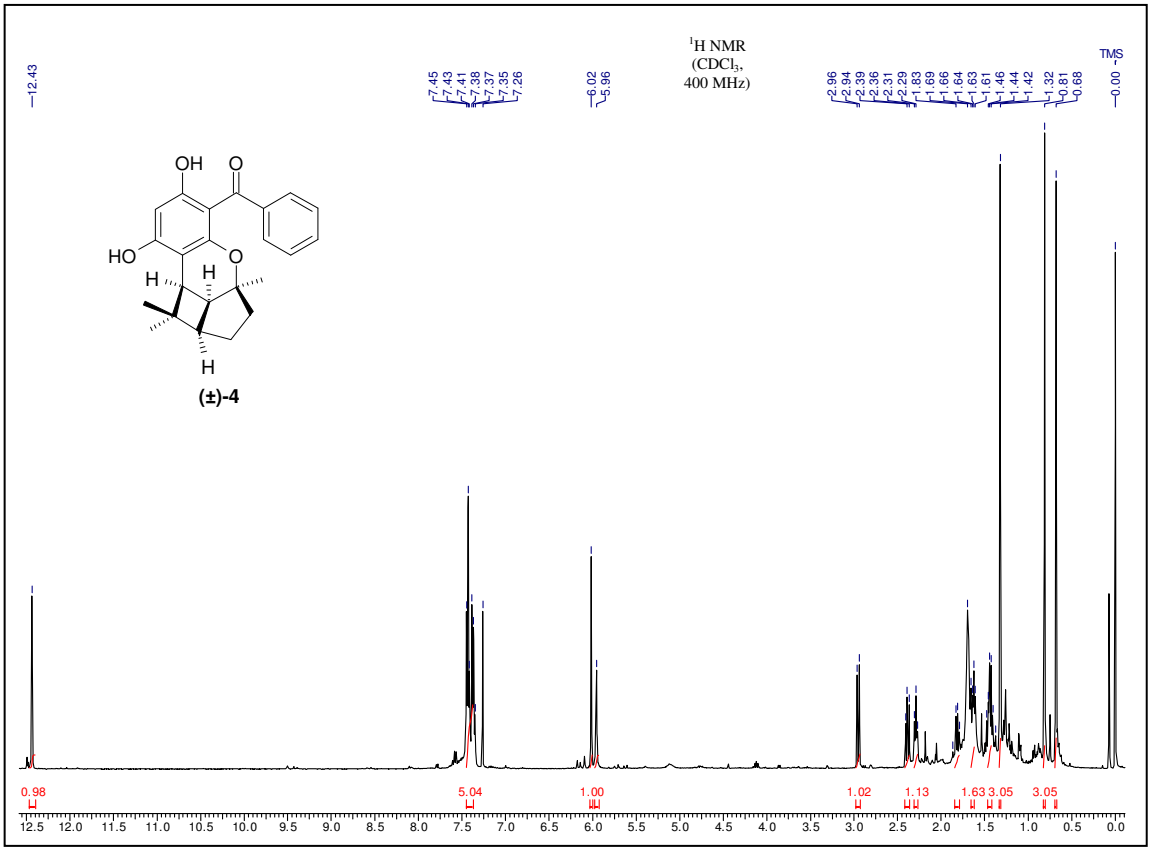
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2.36
2.31
2.29
1.83
1.69
1.66
1.64
1.63
1.61
1.46
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1.42
1.32
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0.68
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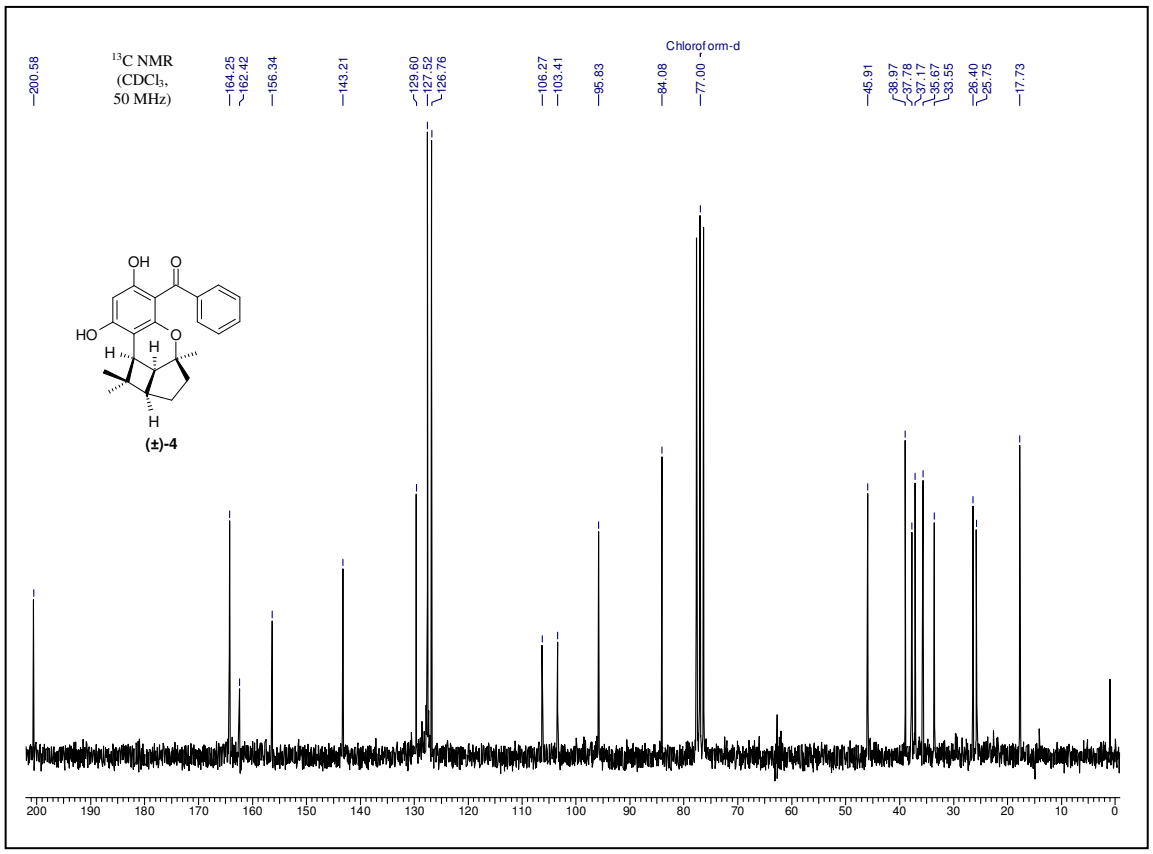
3.05
3.05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106.27
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84.08
77.00
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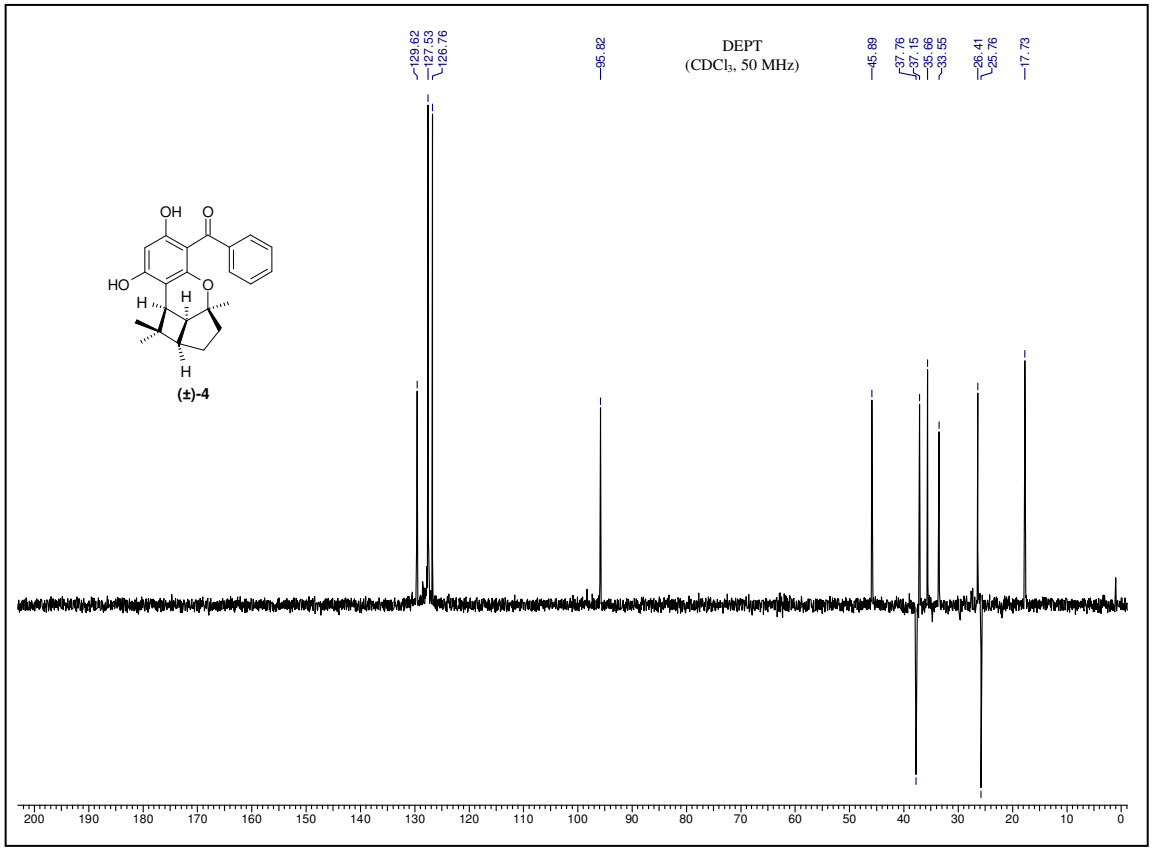
H
H
H
(±)-4


DEPT
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35.66
33.55
26.41
25.76
17.73
OH
O
HO
O
H
H
H
(±)-4

2C.7 References and Footnotes

1. (a) Kashiwada, Y.; Yamazaki, K.; Ikeshiro, Y.; Yamagishi, T.; Fujioka, T.; Mihashi, K.; Mizuki, K.; Cosentino, L. M.; Fowke, K.; Natschke, S. L.-M.; Lee, K.-H. *Tetrahedron* **2001**, *57*, 1559. (b) Kurdyumov, A. V.; Hsung, R. P.; Ihlen, K.; Wang, J. *Org. Lett.* **2003**, *5*, 3935. (c) Kang, Y.; Mei, Y.; Du, Y.; Jin, Z. *Org. Lett.* **2003**, *5*, 4481.
2. Gonzalez, J. G.; Olivares, E. M.; Monache, F. D. *Phytochemistry* **1995**, *38*, 485.
3. (a) Lu, Y.-H.; Lin, C.-N.; Ko, H.-H.; Yang, S.-Z.; Tsao, L.-T.; Wang, J. P. *Helv. Chim. Acta* **2003**, *86*, 2566. (b) Hano, Y.; Inami, R.; Nomura, T. *Heterocycles* **1993**, *35*, 1341. (c) Paduraru, M. P.; Wilson, P. D. *Org. Lett.* **2003**, *5*, 4911.
4. Bukuru, J.; Van, T. N.; Puyvelde, L. V.; He, W.; Kimpe, N. D. *Tetrahedron* **2003**, *59*, 5905.
5. Crombie, L.; Redshaw, S. D.; Slack, D. A.; Whiting, D. A. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1411.
6. Wu, T.-S.; Wang, M.-L.; Wu, P.-L.; Ito, C.; Furukawa, H. *Phytochemistry* **1996**, *41*, 1433.
7. Shoyama, Y.; Morimoto, S.; Nishioka, I. *Chem. Pharm. Bull.* **1981**, *29*, 3720.
8. (a) Wu, T.-S.; Wang, M.-L.; Wu, P.-L.; Jong, T.-T. *Phytochemistry* **1995**, *40*, 1817. (b) McPhail, A. T.; Wu, T.-S.; Ohta, T.; Fukukawa, H. *Tetrahedron Lett.* **1983**, *24*, 5377.
9. (a) Shani, A.; Mechoulam, R. *Tetrahedron* **1971**, *27*, 601. (b) Shani, A.; Mechoulam, R. *Tetrahedron* **1974**, *30*, 2437.
10. (a) Crombie, L.; Ponsford, R.; Shani, A.; Yagnitinsky, B.; Mechoulam, R. *Tetrahedron Lett.* **1968**, 5771. (b) Montero, J. L.; Winternitz, F. *Tetrahedron* **1973**, *29*, 1243.
11. Kurdyumov, A. V.; Hsung, R. P. *J. Am. Chem. Soc.* **2006**, *128*, 6272.
12. Graziano, M. L.; Iesce, M. R.; Cermola, F.; Cimminiello, G. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1269.
13. (a) Paradkar, M. V.; Kulkarni, S. A.; Joseph, A. R.; Ranade, A. A. *J. Chem. Res. (S).* **2000**, 364. (b) Talapatra, B.; Roy, M. K.; Talaptra, S. K. *Indian J. Chem.* **1980**, *19B*, 927. (c) For synthesis of 3,5-dihydroxyphthalide, see: Second Chapter, Section A, Scheme 2 of present dissertation.
14. Mondal, M.; Argade, N. P. *Synlett* **2004**, 1243.

15. Saimoto, H.; Yoshida, K.; Murakami, T.; Morimoto, M.; Sashiwa, H.; Shigemasa, Y. *J. Org. Chem*. **1996**, *61*, 6768.
16. (a) Shen, H. C.; Wang, J.; Cole, K. P.; McLaughlin, M. J.; Morgan, C. D.; Douglas, C. J.; Hsung, R. P.; Coverdale, H. A.; Gerasyuto, A. I.; Hahn, J. M.; Liu, J.; Sklenicka, H. M.; Wei, L.-L.; Zehnder, L. R.; Zificsak, C. A. *J. Org. Chem.* **2003**, *68*, 1729. (b) Hsung, R. P.; Kurdyumov, A. V.; Sydorenko, N. *Eur. J. Org. Chem.* **2005**, 23. (c) Lee, Y. R.; Choi, J. H.; Yoon, S. H. *Tetrahedron Lett.* **2005**, *46*, 7539.
17. (a) Tietze, L. F.; Beifuss, U.; Ruther, M. *J. Org. Chem.* **1989**, *54*, 3120. (b) Oppolzer, W.; Mahalanabis, K. K. *Tetrahedron Lett.* **1975**, *39*, 3411. (c) Paderes, G. D.; Jorgensen, W. L. *J. Org. Chem*. **1992**, *57*, 1904.
18. (a) Cox, J. D.; Pilcher, G. *Thermochemistry of Organic and Organometallic Compounds,* Academic Press, London, 1970. (b) Leber, P. A.; Baldwin J. E. *Acc. Chem. Res*. **2002**, *35*, 279.
19. Addition of 5 equivalents of citral is essential, as the melting point of **28a** is 256-258 ^{o}C.
20. (a) Jpn. Kokai Tokyo Koho, JP 82-28,080,1982; *Chem. Abstr*. **1982**, 97, 3777x. (b) Hu, H.; Harrison, T. J.; Wilson, P. D. *J. Org. Chem.* **2004**, *69*, 3782.
21. For isopropylidinecyclopentylbenzopyran derivative having *trans* ring junction, see: Yamada, Y.; Nakamura, S.; Iguchi, K.; Hosaka, K. *Tetrahedron Lett*. **1981**, *22*, 1355.
22. Malerich, J. P.; Trauner, D. *J. Am. Chem. Soc.* **2003**, *125*, 9554.
23. Shoyama, Y.; Hirano, H.; Nishioka, I. *Phytochemistry* **1984**, *23*, 1909.
24. Koch, K.; Podlech, J.; Pfeiffer, E.; Metzler, M. *J. Org. Chem*. **2005**, *70*, 3275.
25. Chevenier, E.; Lucatelli, C.; Pandya, U.; Wang, W.; Gimbert, Y.; Greene, A. E. *Synlett* **2004**, 2693.
26. (a) Mata, R.; Bye, R.; Linares, E.; Macias, M.; Cruz, I.-R.; Perez, O.; Timmermann, B. N. *Phytochemistry* **2003**, *64*, 285. (b) Nan, P.; Peng, S.; Zhang, Y.; Zhong, Y. *Nat. Prod. Lett*. **2002**, *16*, 249.
27. Lin, Y.-L.; Wu, Y.-S. *Helv. Chim. Acta* **2003**, *86*, 2156.
28. Zhou, C.; Larock, R. C. *J. Org. Chem*. **2006**, *71*, 3551.
29. (a) Gonzalez, J. G.; Cuellar, V.; Betancourt, A.; Pinzon, M. I. *Phytochemistry* **1983**, *22*, 2088. (b) Monache, F. D.; Monache, G. D.; Baitz, E.-G. *Phytochemistry* **1991**, *30*, 2003. (c) Olivares, E. M.; Gonzalez, J. G.; Monache, F. D. *Phytochemistry* **1994**, *36*, 473.
30. Mondal. M.; Argade, N. P.; Puranik, V. G. *J. Org. Chem*. **2007**, *72*, in press.

31. Trost, B. M.; Shen, H. C.; Dong, L.; Surivet, J.-P.; Sylvain, C. *J. Am. Chem. Soc*. **2004**, *126*, 11966.
32. G. M. Sheldrick, SHELX-97 program for crystal structure solution and refinement, University of Göttingen, Germany, 1997.
33. CCDC-280384 & 280385 contains the supplementary crystallographic data for oxacyclobutaindane **28a** and oxabicyclononane **30**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

2D. Section D

Synthesis of a New Microbial Secondary Metabolite: Anti-Helicobacter Pylori CJ-13,015

This section features the following topics:

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2D Section D: Synthesis of a New Microbial Secondary Metabolite: Anti-*Helicobacter Pylori* CJ-13,015

2D.1 Background

Gastric and duodenal ulcers affect a significant portion of the human population worldwide. The root cause of gastric and duodenal ulcers is the presence of the microaerophilic Gram-negative bacterium *Helicobacter pylori*, which appear to live beneath the mucus layer of the stomach (Figure 1).[1,2] Infection has been associated with chronic superficial gastritis, chronic active gastritis, peptic ulcer disease and gastric cancer in humans.[3] As a result, the International Agency for Research in Cancer classified *H. pylori* as a class I carcinogen in the year 1994.[4]

The current first-line triple-therapy for *H. pylori*-associated gastrointestinal diseases, using a combination of antibiotics with a proton-pump inhibitor, fails to fully eradicate *H. pylori* in approximately 10-23% of patients and relapse is a problem.[1,2] However, long-term treatment with current therapies is not recommended and accordingly, second-line or rescue treatments are often required.[5] Treatment failure is associated with the emergence of *H. pylori* strains that are resistant to the broad-spectrum antibiotics used.[4] Consequently, there is an urgent need for a safe and effective treatment with a compound having an excellent anti-*H. pylori* activity. Recently, in a screening program designed to discover such compounds, Dekker *et al*[6] isolated a new phthalide containing microbial secondary metabolite, CJ-13,015 (**1a**) along with other phthalide antibiotics **1b-g** from the basidiomycete *Phanerochaerte velutina* with promising anti-*Helicobacter pylori* activity (Figure 2). The secondary metabolites **1a**-**g** were isolated in very small amounts and a realistic supply of these natural products for further biological evaluation is necessary.

2D.1.1 Synthetic Approaches Towards anti-*Helicobacter pylori* Natural Products

The clinical potential of this new microbial secondary metabolite, CJ-13,015 has led to great interest in developing new syntheses and reported synthetic approaches are illustrated in brief in the following part.

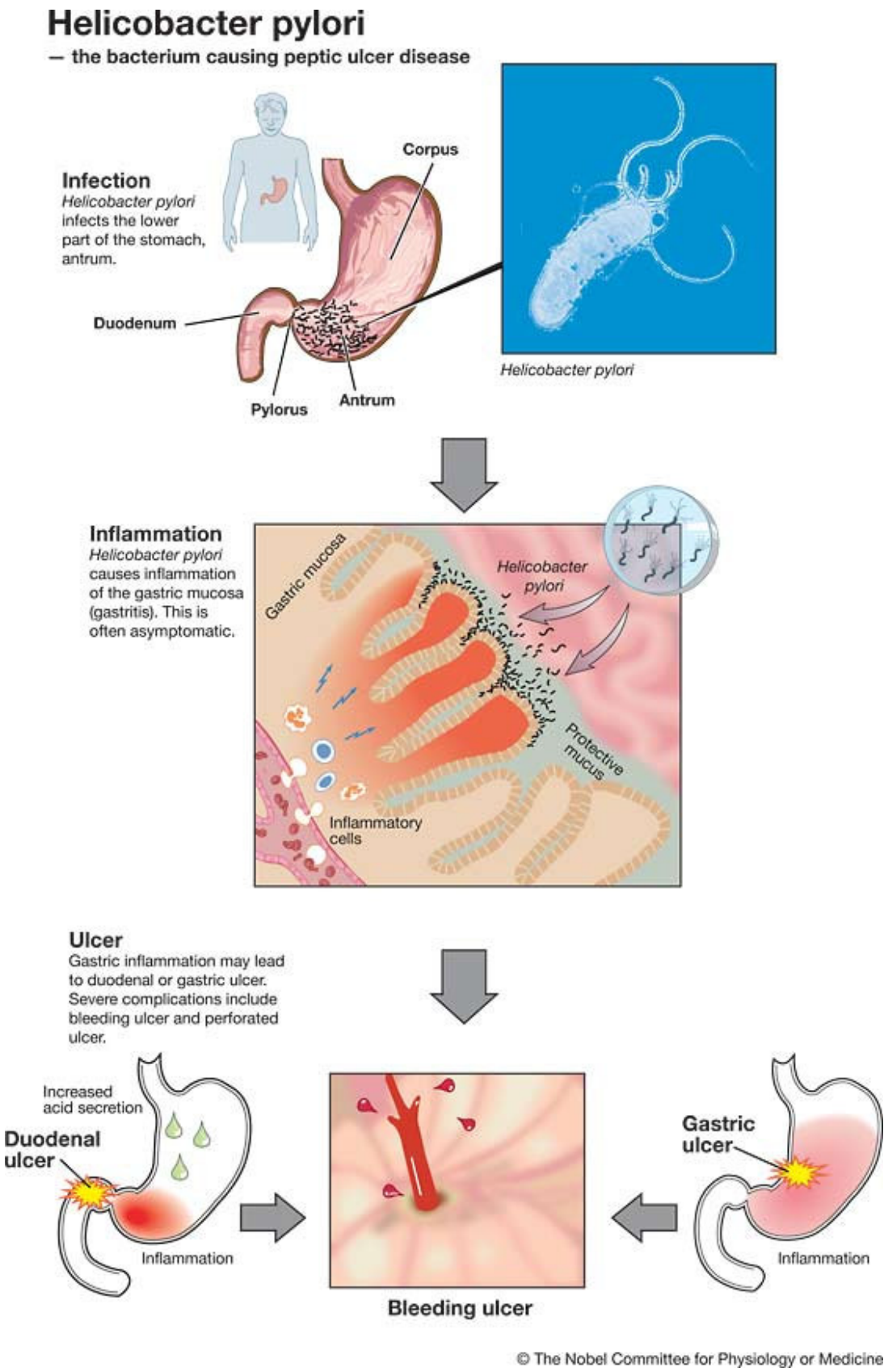
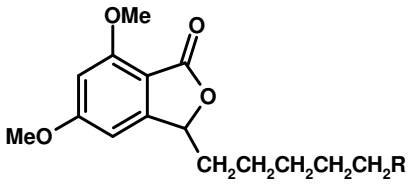


Figure 1. *Helicobacter pylori* Causing Peptic Ulcer (http://nobelprize.org/medicine/2005/press.html)



1a-g

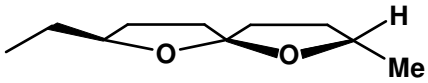
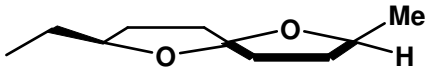
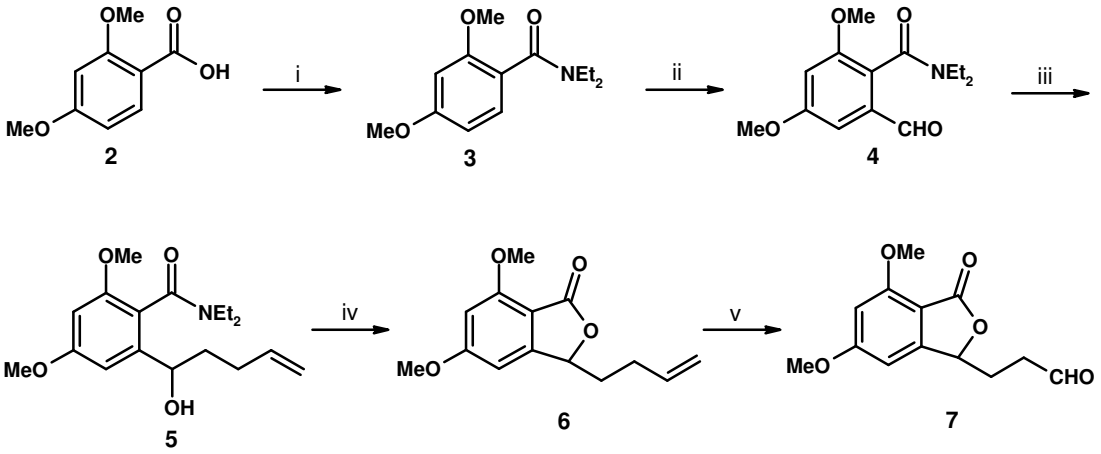
Compound	R	Activity (μg/disk that gives a 15 mm zone)
CJ-13,015 (**1a**)	$-CH_2CH_2CH_2CH_2COCH_2CH_2COCH_3$	2
CJ-13,102 (**1b**)	$-CH_2CH_2CH_2CH_2CH(OAc)CH_2CH_2COCH_3$	0.5
CJ-13,103 (**1c**)	$-CH_2CH_2CH_2CH_2CH_2CH_2COCH_2CH_2COCH_3$	50
CJ-13,104 (**1d**)	$-CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH(OH)CH_3$	500
CJ-13,108 (**1e**)	$-CH_2CH_2CH_2CH_2CH_2CH_2CH_2COCH_3$	10
CJ-12,954 (**1f**)		0.02
CJ-13,014 (**1g**)		0.02

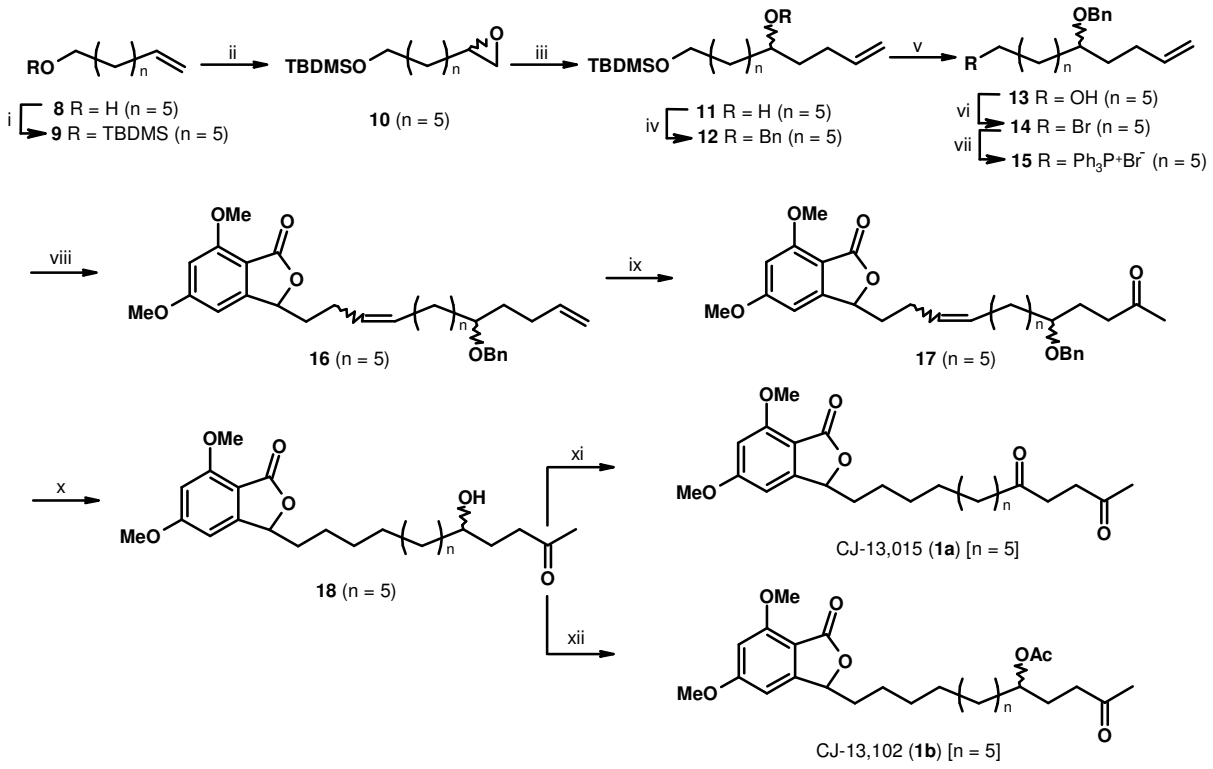
Figure 2. New Microbial Secondary Metabolites and Helicobactericidal Activities

[A] Brimble's Approach Towards CJ-13,015, CJ-13,102, CJ-13,103, CJ-13,104 and CJ-13,108

Brimble *et al*[7] reported a multistep synthesis of CJ-13,015 (**1a**) along with CJ-13,102 (**1b**), CJ-13,103 (**1c**), CJ-13,104 (**1d**) and CJ-13,108 (**1e**) using the Wittig reaction of a key phthalide-aldehyde **7** with the ylide generated from the appropriate phosphonium salts (Schemes 1 to 4). The building block phthalide-aldehydes **7** was prepared from 2,4-dimethoxybenzoic acid (**2**), firstly by conversion to the corresponding amide **3**. *ortho*-Lithiation followed by formylation provided aldehyde **4** which on treatment with but-3-en-1-ylmagnesium bromide furnished the alcohol derivative **5**. Acid-catalyzed cyclization



Scheme 1 *Reagents, conditions and yields*: (i) (a) $SOCl_2$, reflux, 2.5 h, (b) Et_2NH, DCM, rt, 12 h (96%); (ii) *t*-BuLi (1.10 equiv.), THF, –78 °C, 15 min, DMF, rt, 16 h (99%); (iii) But-3-en-1-1ylmagnesium bromide, Et_2O, rt, 30 min; (iv) *p*-TSA, reflux, 6 h, (87%); (v) O_3, MeOH, –50 °C. 10 min, Me_2S, rt, 1 h (79%).

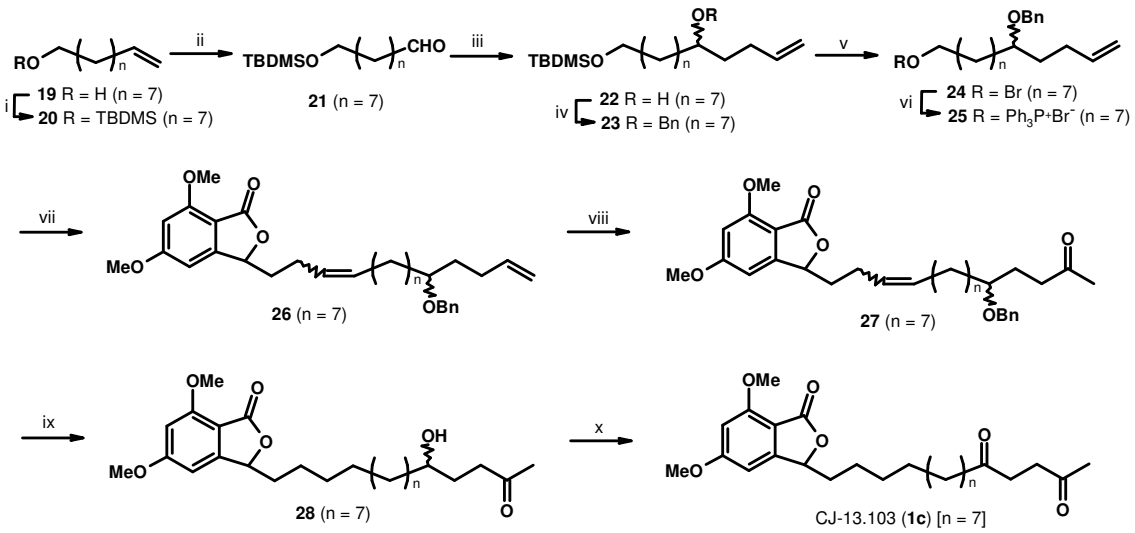


Scheme 2 *Reagents, conditions and yields*: (i) TBDMSCl, imidazole, DMAP, DCM, 0 °C, 3 h (99%); (ii) *m*-CPBA, NaOAc, DCM, rt, 18 h (99%); (iii) 5% CuCN, allylmagnesium bromide, Et_2O, –78 °C, 10 h (55%); (iv) NaH, TBAI, DMF, 0 °C, 75 min, BnBr, rt, 18 h (81%); (v) TBAF, THF, 0 °C, 2 h (97%); (vi) CBr_4, PPh_3, MeCN, 0 °C, 30 min (100%); (vii) PPh_3, MeCN, reflux, 26 h (80%); (viii) (a) *n*-BuLi, THF, –78 °C to rt, 30 min, (b) **7**, –78 °C to rt, 2 h (72%); (ix) $PdCl_2$, CuCl, DMF-H_2O (8:1), O_2, rt, 3 h (54%); (x) Pd/C, H_2, EtOAc, rt, 3 h; (xi) TPAP, NMO, DCM, rt, 30 min (37% from **17**); (xii) Ac_2O, DMAP, pyridine, rt, 8 h (83% from **17**).

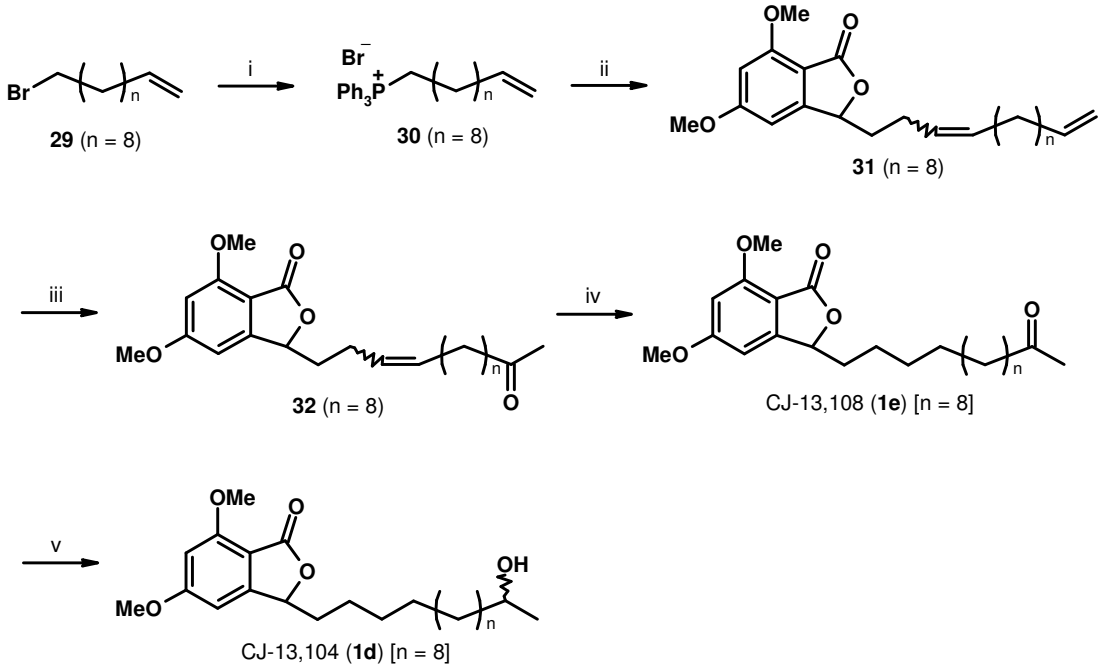
of **5** furnished phthalide **6** that upon ozonolysis of the terminal olefin gave the desired phthalide-aldehydes **7** in 65% overall yield (Scheme 1). The required side chain for CJ-13,015 (**1a**) and CJ-13,102 (**1b**) was synthesized from 7-octen-1-ol (**8**) (Scheme 2). Protection of the alcohol as TBDMS ether **9** followed by the epoxidation of the terminal olefin furnished the oxirane **10**. Ring opening of the epoxide using higher-order allyl-cuprate afforded alcohol **11**, which was protected as benzyl ether **12**. Desilylation of the TBDMS ether to alcohol **13** followed by conversion to bromocompound **14** and finally reaction with TPP furnished the desired phosphonium salt **15** in 34% overall yield (seven steps). Wittig reaction of the ylide generated from phosphonium salt **15** with phthalide aldehyde **7** gave compound **16** in 72% yields as a mixture of *E*- and *Z*- isomers. Selective Wacker oxidation of the terminal olefin to ketone **17** followed by hydrogenation of the internal olefin with the simultaneous removal of benzyl group furnished hydroxyketone **18** which on TPAP oxidation produced the natural product CJ-13,015 (**1a**). Direct acylation of the alcohol **18** provided another natural product CJ-13, 1002 (**1b**).

Using the same strategy, CJ-13,103 (**1c**) was synthesized from 9-decen-1-ol (**19**) (Scheme 3). Protection of the alcohol as TBDMS ether **20**, followed by ozonolysis of the terminal olefin furnished aldehyde **21**. Treatment of **21** with but-3-en-1-ylmagnesium bromide, protection of the secondary alcohol **22** as benzyl ether **23** followed by one pot desilylation-bromination to bromide **24**, and finally reaction with triphenylphosphine furnished the desired phosphonium salt **25**. The Wittig reaction of the ylide generated from **25** with **7** furnished olefin **26** as a mixture of *E*- and *Z*-isomers. Selective Wacker oxidation of the terminal olefin to ketone **27** followed by simultaneous hydrogenation of internal olefin and hydrogenation of benzyl ether to hydroxyketone **28** and finally oxidation of the alcohol furnished the natural product CJ-13,103 (**1c**).

Both the natural products CJ-13,104 (**1d**) and CJ-13-108 (**1e**) were synthesized from the phosphonium salt **30** of commercially available 10-undecen-1-ylbromide (**29**). Wittig reaction of the ylide generated from phosphonium salt **30**, with the aldehyde **7** gave the desired product **31** as a mixture of *E*- and *Z*-isomers. Selective Wacker oxidation of the terminal olefin to the methyl ketone **32** which upon hydrogenation of the internal olefin furnished the natural product CJ-13,108 (**1e**). Reduction of the ketone in **1e** with sodium borohydride gave another natural product CJ-13,104 (**1d**) (Scheme 4).



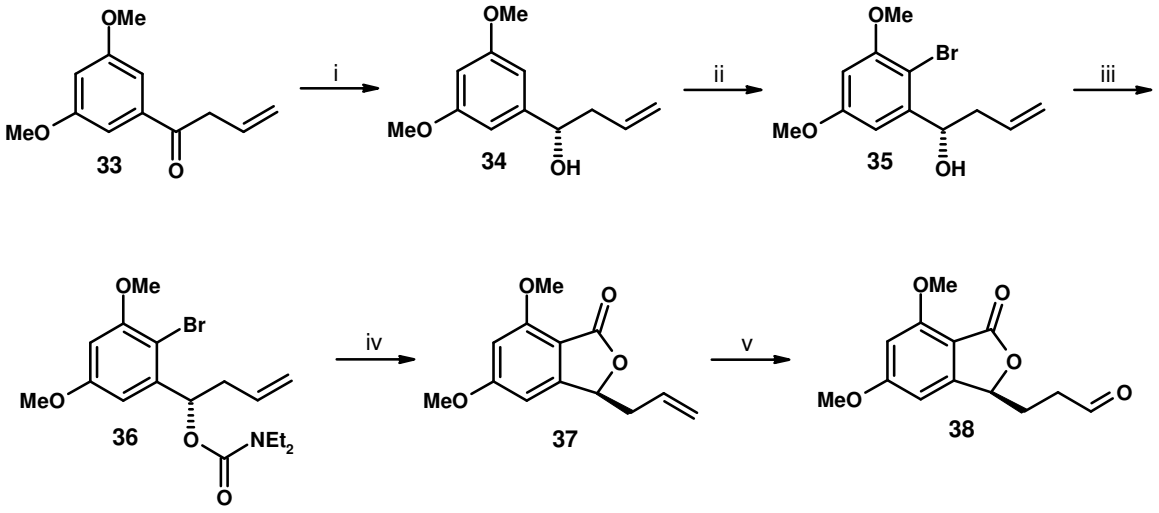
Scheme 3 *Reagents, conditions and yields*: (i) TBDMSCl, imidazole, DMAP, DCM, 0 ^{o}C, 3 h (96%); (ii) (a) O_3, MeOH, −50 ^{o}C, 10 min, (b) Me_2S, rt, 1 h (95%); (iii) But-3-en-1-ylmagnesium bromide, Et_2O, rt, 30 min (96%); (iv) (a) NaH, TBAI, DMF, 0 ^{o}C, 75 min, (b) BnBr, rt, 18 h (95%); (v) PPh_3Br_2, DCM, rt, 24 h (91%); (vi) PPh_3, MeCN, reflux, 24 h (80%); (vii) (a) *n*-BuLi, THF, −78 ^{o}C to rt, 30 min, (b) **7**, −78 ^{o}C to rt, 2 h (73%); (viii) $PdCl_2$, CuCl, DMF-H_2O (8:1), O_2, rt, 3 h (61%); (ix) 10% Pd/C, H_2, EtOAc, rt, 3 h; (x) TPAP, NMO, DCM, rt, 30 min (44% two steps).



Scheme 4 *Reagents, conditions and yields*: (i) PPh_3, MeCN, reflux, 24 h (96%); (ii) (a) *n*-BuLi, THF, −78 ^{o}C to rt, 30 min, (b) **7**, −78 ^{o}C to rt, 2 h (86%); (iii) $PdCl_2$, CuCl, DMF-H_2O (8:1), O_2, rt, 3 h (62%); (iv) 10% Pd/C, H_2, EtOAc, rt, 1 h (100%); (v) $NaBH_4$, MeOH, rt, 10 min (95%).

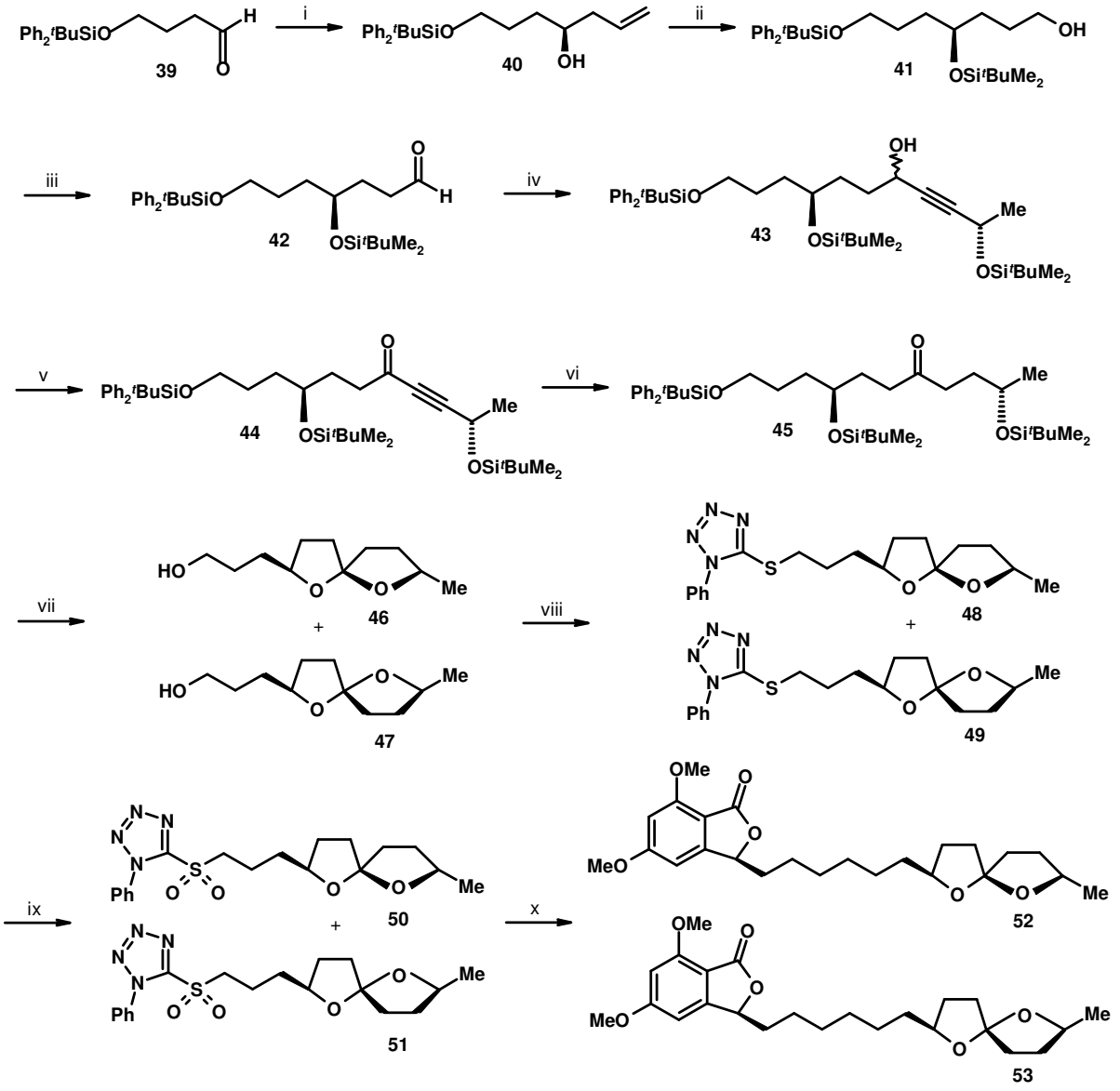
[B] Brimble's Approach Towards CJ-12,954 and CJ-13,014

Brimble *et al*[8] reported total synthesis of the enantiomers of the CJ-12,954 (**1f**) and CJ-13,014 (**1g**). They have synthesized the (*S*)-phthalide-aldehyde **38** by asymmetric reduction of the ketone **33**[9] using (*R*)-2-Me-CBS-oxazaborolidine and boran-dimethyl sulfide affording benzyl alcohol **34** (Scheme 5). The alcohol **34** on regioselective bromination and subsequent conversion to diethyl carbamate **36** followed by lithium-halogen exchange and intramolecular cyclization furnished the phthalide **37**. Hydroboration of the allyl group followed by oxidation furnished the desired (*S*)-phthalide-aldehyde **38**. They have



Scheme 5 *Reagents, conditions and yields*: (i) (a) (*R*)-MeCBS, BH_3-SMe_2, 15 min, (b) THF, **33**, 2 h (92% yield, 94% ee); (ii) NBS, NH_4OAc, Et_2O, 24 h (90%); (iii) NaH, THF, 0 ^oC, *N*,*N*-diethylcarbamoyl chloride (90%); (iv) *t*-BuLi, THF, −78 ^oC, 2 h, camphorsulfonic acid, 20 ^oC, 12 h (70%); (v) (a) 2-Methyl-2-butene, BH_3-SMe_2, THF, 0 ^oC, (b) MeOH, NaOH, 30% H_2O_2 (71%), (c) TPAP, NMO, DCM, 4Å mol. sieves, 6 h, 20 ^oC (72%).

synthesized the required side chain fragment from aldehyde **39** (Scheme 6). Addition of allylmagnesiun bromide to (+)-*β*-diisopinocamphenylmethoxyborane followed by addition of aldehyde **39** afforded (*S*)-homoallyl alcohol **40** in 82% yield and 94% ee. Silyl ether formation followed by hydroboration and oxidation of the resultant primary alcohol **41** gave aldehyde **42**. Addition of aldehyde **42** to lithium TBDMS ether of (*S*)-But-3-yn-2-ol at −78 ^oC provided alcohol **43** as a mixture of diastereoisomers which was oxidized to ketone **44** using TPAP and NMO. Reduction of the acetylene followed by spirocyclization furnished an inseparable 1:1 mixture of spiroacetals **46** and **47**. Mitsunobu displacement of



Scheme 6 *Reagents, conditions and yields*: (i) Allyl bromide, Mg, (+)-*β*-diisopinocampheylmethoxyborane, Et_2O, −78 °C to 20 °C (82% yield, 94% ee); (ii) (a) *t*-$BuMe_2SiCl$. imidazole, DMAP, DCM, 20 °C, 12 h (90%), (b) 2-Methyl-2-butene, BH_3-SMe_2, 0 °C (76%); (iii) Dess-Martin periodinane, pyridine, DCM, 20 °C (77%); (iv) (*S*)-But-3-yn-2-ol-TBDMS ether, *n*-BuLi, LiBr, THF, −78 °C (84%); (v) TPAP, NMO, DCM, 4Å mol. sieves, 20 °C (94%); (vi) H_2, PtO_2, K_2CO_3, THF-MeOH (1:1) (94%); (vii) (a) CSA, DCM, 20 °C, 4 h (93%), (b) TBAF, DCM, 20 °C , 3 h (77%); (viii) 1-Phenyl-1*H*-tetrazole-5-thiol, PPh_3, DEAD (78%); (ix) *m*-CPBA, $NaHCO_3$ (71%); (x) (a) KHMDS, THF, −78 °C, **38** (84%), (b) H_2, PtO_2, K2CO3, THF-MeOH (1:1) (85%).

hydroxyspiroacetals **46** and **47** with 1-phenyl-1*H*-tetrazole-5-thiol afforded sulfides **48** and **49**, which underwent oxidation to an inseparable mixture of sulfones **50** and **51**. Finally the modified Julia olefination of the mixture **50** and **51** with **38** followed by catalytic

hydrogenation furnished 1:1 mixture of phthalide-spiroacetals (3*S*,2"*S*,5"*S*,7"*S*)-**52** and (3*S*,2"*S*,5"*R*,7"*S*)-**53**. Comparison of the HPLC retention time and $[\alpha]_D$ value of the mixture **52** and **53** with the mixture of natural products **1f** and **1g**, established that **52** and **53** are enantiomer of **1f** and **1g** respectively and the absolute configuration of the natural product CJ-12,954 (**1f)** is (3*R*,2"*R*,5"*R*,7"*R*) and that of CJ-13,014 (**1g)** is (3*R*,2"*R*,5"*S*,7"*R*).

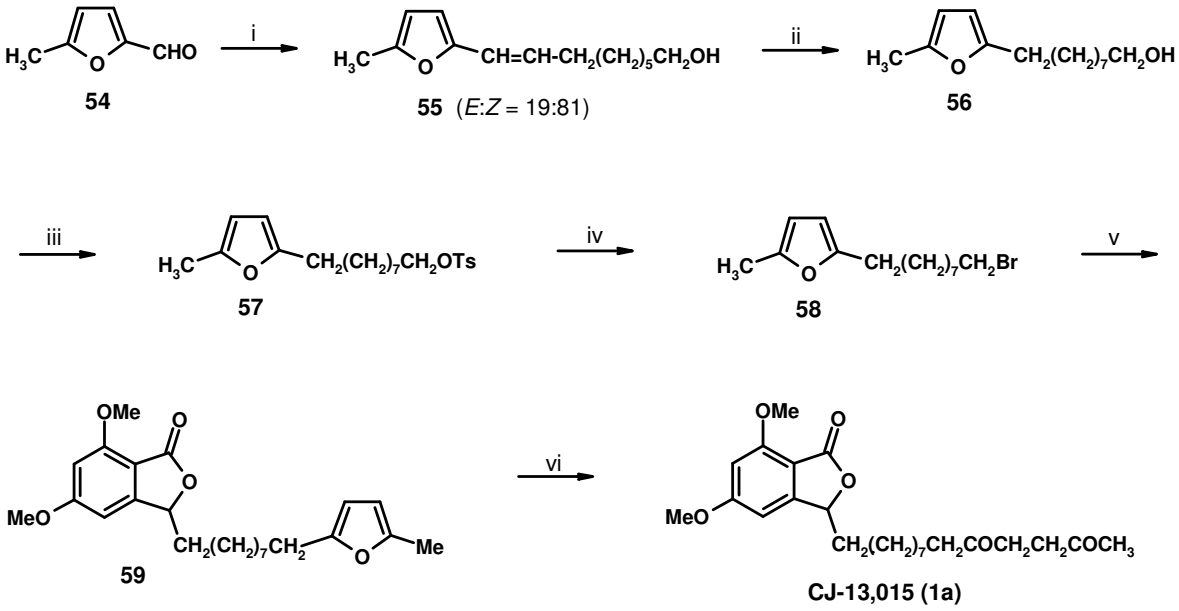
2D.2 Rationale for Present Work

It is evident from the above discussion that the novel microbial secondary metabolite, CJ-13,015 (**1a**) provides promising new lead for the treatment of *H. pylori*-related diseases. The high clinical potential of this natural product **1a** makes attractive synthetic target and the provision of a short and efficient synthetic route to this target molecule is an imperative task of current interest. In continuation of our on going work[10] of bioactive natural product synthesis, here we have designed an efficient synthetic route to this microbial secondary metabolite **1a** avoiding any protection deprotection chemistry. The retro synthetic analysis of microbial secondary metabolite CJ-13,015 revealed that 5-methylfurfural,[11] 8-bromo-1-octanol[12] and 3,5-dimethoxyphthalide[13] would be the suitable building blocks to design **1a**. We planned to construct the bond between phthalide and side chain using the nucleophilic substitution reaction of the appropriate side chain halide with the phthalide anion. 5-Methylfurfural would be the potential masked source for the remotely functionalized 1,4-diketone[8] part of the side chain.

2D.3 Results and Discussion

The Wittig reaction of 5-methylfurfural (**54**) with an ylide generated in situ from the reaction of (8-hydroxyoctyl)triphenylphosphonium bromide[11] and sodium methylsulfinylmethanide[14] in a mixture of DMSO-THF (1:1) mixture furnished the olefinic mixture of *Z*- and *E*-isomers **55** in 82% yield. Palladium on charcoal induced selective catalytic hydrogenation of the newly generated carbon-carbon double bond in **55** gave the disubstituted furan derivative **56** in quantitative yield. The primary alcohol **56** was treated with *p*-toluenesulfonyl chloride to form the corresponding tosylate **57** (96% yield), which on reaction with lithium bromide yielded the desired furan containing alkyl halide **58** in 95% yield. The halide **58** underwent a smooth S_N2 substitution reaction with the anion of

3,5-dimethoxyphthalide in THF at 50 ^{o}C to yield the desired coupled product **59** in 90% yield. The furan moiety in compound **59** underwent a clean chemoselective hydrolysis in refluxing acetic acid plus water mixture (1:1) in presence of catalytic amount of dilute sulfuric acid to exclusively furnish the desired bioactive natural product CJ-13,015 (**1a**) with 1,4-dicarbonyl system, in quantitative yield. Starting from 5-methylfurfural (**54**), 14-(1,3-dihydro-4,6-dimethoxy-3-oxo-1-isobenzofuranyl)-2,5-tetradecanedione (**1a**) was obtained in six-steps with 65% overall yield. The analytical and spectral data obtained for CJ-13,015 (**1a**)[10] was in complete agreement with reported data[6] (Scheme 7).



Scheme 7 *Reagents, conditions and yields*: (i) $HOCH_2(CH_2)_6CH_2^+PPh_3Br^-$ (1.10 equiv.), $Na^+CH_2^-SOCH_3$[14] (2.20 equiv.), DMSO-THF (1:1), 0 ^{o}C, 1 h (82%); (ii) H_2, Pd-C, methanol, rt, 4 h (98%); (iii) *p*-TsCl (1.10 equiv.), TEA (2.20 equiv.), DMAP, DCM, rt, 6 h (96%); (iv) LiBr (8.00 equiv.), $NaHCO_3$ (10.00 equiv.), acetone, rt, 15 h (95%); (v) (a) 3,5-Dimethoxyphthalide (1.50 equiv.), LDA (1.50 equiv.), THF, 0 ^{o}C to rt, 30 min, (b) **58**, rt to 50 ^{o}C, 1 h, aq. workup (90%); (vi) H_2O-AcOH (1:1), cat. H^+/H_2SO_4 (dil.), reflux, 2 h, (98%).

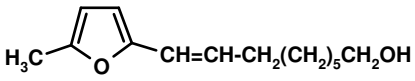
2D.4 Summary

In summary, we have demonstrated a simple and efficient first total synthesis of anti-*helicobacter pylori*, new microbial secondary metabolite, CJ-13,015 in six-steps with 65% overall yield starting from 5-methylfurfural via Wittig reaction of the ylide generated in situ from (8-hydroxyoctyl)triphenylphosphonium bromide, selective reduction of the newly formed carbon-carbon double bond, conversion of alcohol to halide, coupling with 3,5-dimethoxyphthalide carbanion and a chemoselective conversion of protective furan group to 1,4-dicarbonyl system as a key reaction.[15] In the present synthesis, use of furan as a protected source of 1,4-dicarbonyl system is noteworthy. We feel that the present approach is general in nature and can be employed to design several natural and unnatural analogues of this secondary metabolite. We feel that the use of suitable chiral base to generate the phthalide carbanion for the substitution of halide would provide a simple and efficient direct access to enantiomerically pure natural product CJ-13,015.

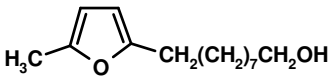
2D.5 Experimental Section

Commercially available 5-methylfurfural, 1,8-octanediol, sodium hydride, 10% Pd-C, *para*-toluenesulfonyl chloride, DMAP, lithium bromide, *n*-BuLi (1.50 M) were used. 3,5-Dimethoxyphthalide has been synthesized using known procedure.[16] Melting points are uncorrected. DMSO, triethylamine and diisopropylamine was distilled from CaH_2 under argon. Tetrahydrofuran was freshly distilled from benzophenone ketyl radical under argon prior to use. Column chromatographic separations were carried out on silica gel (60-120 mesh). All yields given refer to as isolated yields. IR spectra were recorded on FT-IR spectrometer.

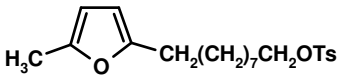
9-(5-Methylfuran-2-yl)non-8-en-1-ol (55). A stirring mixture of NaH (4.40 g, 110.00 mmol) in DMSO (10 mL) was heated at about 70 ^{o}C until the formation of a clear transparent solution. After cooling, the reaction mixture was diluted with THF (10 mL) and it was added drop wise to an ice cooled stirring solution of (8-hydroxyoctyl)triphenylphosphonium bromide (23.55 g, 50.00 mmol) in DMSO-THF (1:1) (100 mL) and the reaction mixture was allowed to stirr 1 h at 0 ^{o}C. 5-Methylfurfural (**54**, 5.00 g, 45.45 mmol) was added to this reaction mixture and after another 30 min stirring, the reaction was quenched with water (50 mL). THF was removed in vacuo, ethyl acetate (200 mL) was added to this reaction mixture and the separated organic layer was washed with brine (100 ml X 10) and dried over Na_2SO_4. Removal of the solvent in vacuo followed by silica gel column chromatographic purification of the residue using 10% ethyl acetate in petroleum ether afforded **55** (8.27 g, 82%) as a colorless liquid.

 **55** (*E*:*Z* = 19:81) **$C_{14}H_{22}O_2$ (222)**	Colorless thick oil. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 1.15-1.75 (bm, 10H), 2.31 (s, 3H), 2.42 (q, J = 6 Hz, 2H), 3.64 (t, J = 6 Hz, 2H), 5.35-5.60 (m, 1H), 5.80-6.05 (m, 1H), 6.05-6.25 (m, 2H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 13.45, 25.58, 29.07-29.18 (4 carbons), 32.52, 62.55, 106.96, 109.57, 117.25,* 118.54,** 128.20,** 129.60,* 150.74, 151.62 (* Vinylic carbons from *cis*-isomer, ** Vinylic carbons from *trans*-isomer). **IR** (Neat) 3371, 2926, 2856, 1595, 1020, 783 cm^{-1}. **Anal. Calcd** for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.52; H, 10.13.

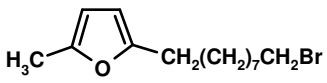
9-(5-Methylfuran-2-yl)nonan-1-ol (56). To a stirring solution of **55** (8.00 g, 36.04 mmol) in methanol (100 mL) at room temperature, 10% Pd/C (500 mg) was added and the reaction mixture was subjected to hydrogenation at 65-psi hydrogen pressure for 4 h. The reaction mixture was filtered through celite and the filtrate was concentrated in vacuo. Silica gel column chromatographic purification of the residue using 10% ethyl acetate in petroleum ether furnished **56** (7.91 g, 98%) as a colorless liquid.

 **56** **$C_{14}H_{24}O_2$ (224)**	Colourless thick oil. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 1.32 (bs, 10H), 1.40-1.70 (m, 4H), 2.26 (s, 3H), 2.56 (t, J = 8 Hz, 2H), 3.64 (t, J = 8 Hz, 2H), 5.84 (s, 2H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 13.34, 25.61, 27.89, 28.00, 29.03, 29.18 (2 carbons), 29.36, 32.56, 62.70, 104.96, 105.56, 149.82, 154.60. **IR** (Neat) 3381, 2926, 2855, 1020, 779 cm^{-1}. **Anal. Calcd** for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 74.81; H, 10.90.

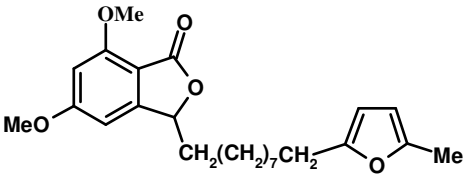
9-(5-Methylfuran-2-yl)-nonyl-4-methylbenzenesulfonate (57). To an ice cooled stirring mixture of *p*-toluenesulfonyl chloride (7.02 g, 36.83 mmol), triethylamine (10.25 mL, 73.66 mmol) and DMAP (100 mg) in DCM (50 mL), a solution of **56** (7.50 g, 33.48 mmol) in DCM (20 mL) was added drop wise and the reaction mixture was allowed to reach the room temperature. After stirring for 6 h at room temperature, the reaction mixture was poured into ice water (100 mL) and extracted with DCM (100 x 3). The combined organic layer was washed with water, brine and dried over Na_2SO_4. Removal of the solvent in vacuo followed by silica gel column chromatographic purification of the residue using 5% ethyl acetate in petroleum ether afforded **57** (12.15 g, 96%) as a colorless liquid.

 **57** **$C_{21}H_{30}O_4S$ (378)**	Colourless thick oil. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 1.24 (bs, 10H), 1.50-1.75 (m, 4H), 2.25 (s, 3H), 2.45 (s, 3H), 2.55 (t, J = 8 Hz, 2H), 4.02 (t, J = 6 Hz, 2H), 5.83 (s, 2H), 7.35 (d, J = 8 Hz, 2H), 7.80 (d, J = 8 Hz, 2H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 13.26, 21.39, 25.10, 27.82, 27.93, 28.59, 28.66, 28.88 (2 carbons), 29.03, 70.49, 104.97, 105.56, 127.65, 129.64, 133.02, 144.45, 149.74, 154.41. **IR** (Neat) 2927, 2856, 1599, 1360, 1177 cm^{-1}. **Anal. Calcd** for $C_{21}H_{30}O_4S$: C, 66.63; H, 7.99; S, 8.47. Found: C, 66.49; H, 8.15; S, 8.58.

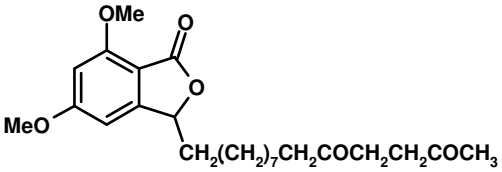
2-(9-Bromononyl)-5-methylfuran (58). To a stirring mixture of lithium bromide (18.41 g, 211.64 mmol), $NaHCO_3$ (22.22 g, 264.55 mmol) in acetone (100 mL), a solution of **57** (10.00 g, 26.45 mmol) in acetone (25 mL) was added and the reaction mixture was stirred for 15 h at room temperature. The reaction mixture was filtered through celite and the filtrate was concentrated in vacuo. The residue was dissolved in ethyl acetate (150 mL) and the organic layer was washed with water, brine and dried over Na_2SO_4. Removal of the solvent in vacuo followed by silica gel column chromatographic purification of the residue using 2% ethyl acetate in petroleum ether afforded **58** (7.21 g, 95%) as a colorless liquid.

 **58** **$C_{14}H_{23}BrO$ (287)**	Colorless thick oil. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 1.20-1.50 (m, 10H), 1.62 (quintet, J = 8 Hz, 2H), 1.87 (quintet, J = 8 Hz, 2H), 2.26 (s, 3H), 2.57 (t, J = 6 Hz, 2H), 3.42 (t, J = 8 Hz, 2H), 5.84 (s, 2H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 13.41, 27.97, 28.04, 28.63, 29.03-29.18 (4 carbons), 32.74, 33.77, 105.01, 105.63, 149.82, 154.52. **IR** (Neat) 2928, 2855, 1618, 1570, 1020, 779 cm^{-1}. **Anal. Calcd** for $C_{14}H_{23}BrO$: C, 58.54; H, 8.07. Found: C, 58.69; H, 8.16.

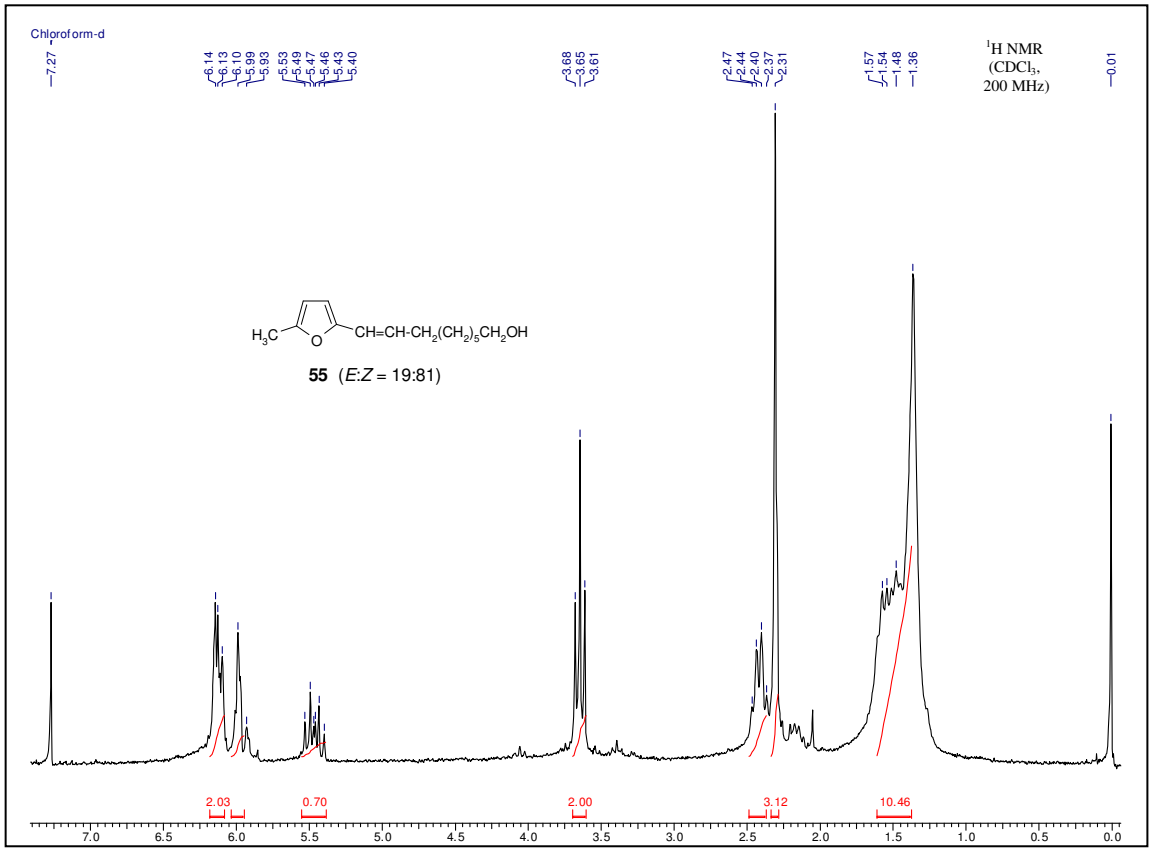
5,7-Dimethoxy-3-[9-(5-methylfuran-2-yl)nonyl]-3*H*-isobenzofuran-1-one (59). To an ice cooled stirring solution of diisopropylamine (2.92 mL, 20.90 mmol) in THF (10 mL) was added *n*-BuLi (13.94 mL, 20.90 mmol) dropwise. After stirring at 0 ^oC for 20 min, the reaction mixture was added slowly to a stirring solution of 3,5-dimethoxyphthalide (4.05 g, 20.90 mmol) in THF (50 mL) at 0 ^oC. The reaction mixture was allowed to attain room temperature. After stirring for 30 min at room temperature, to this reaction mixture a solution of **58** (4.00 g, 13.94 mmol) in THF (15 mL) was added and the reaction mixture was heated at 50 ^oC for 1 h. After cooling, saturated NH_4Cl solution (20 mL) was added to the reaction mixture and THF was removed in vacuo. To the reaction mixture was added ethyl acetate (200 mL) and the separated organic layer was washed with water, brine and dried over Na_2SO_4. Removal of the solvent in vacuo followed by silica gel column chromatographic purification of the residue using 25% ethyl acetate in petroleum ether afforded **59** (5.00 g, 90%) as a colorless thick liquid.

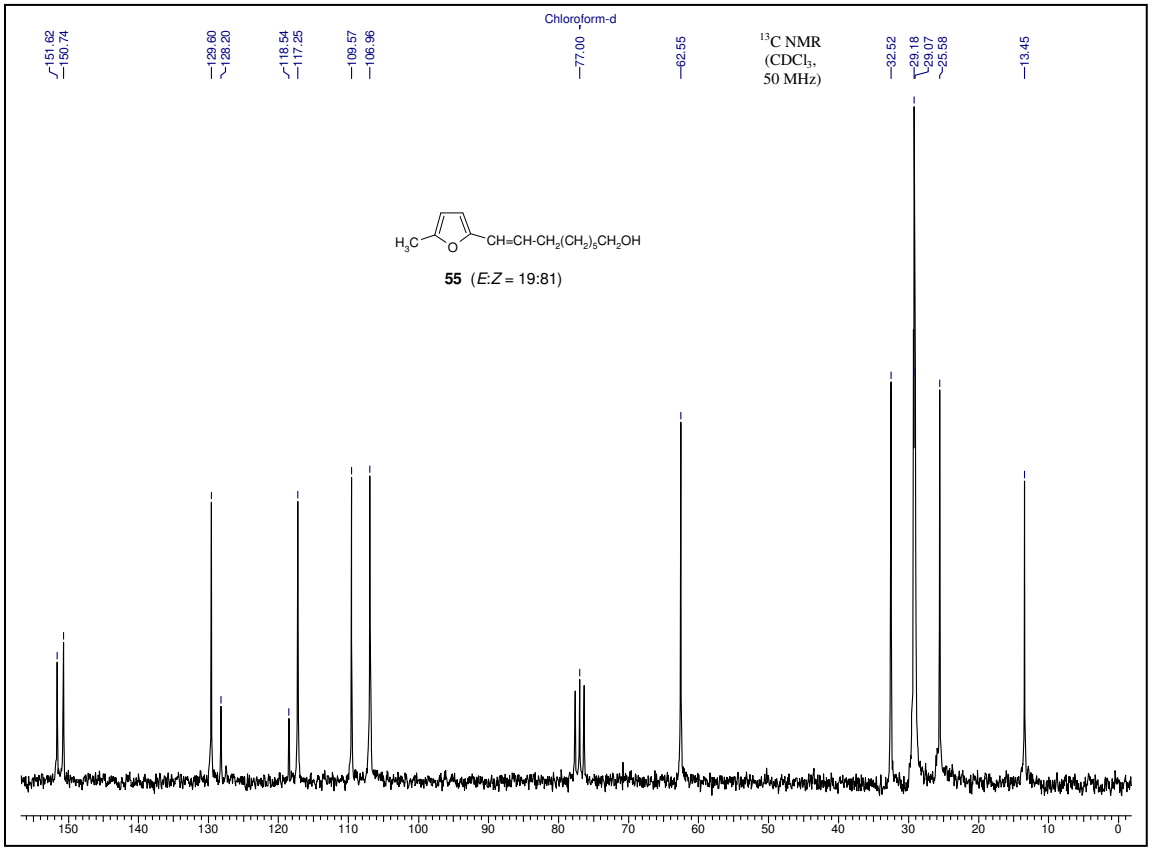
 **59** **$C_{24}H_{32}O_5$ (400)**	Colorless thick oil. **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 1.24-1.38 (m, 10H), 1.40-1.52 (m, 2H), 1.60 (quintet, J = 10 Hz, 2H), 1.65-1.75 (m, 1H), 1.93-2.20 (m, 1H), 2.25 (s, 3H), 2.55 (t, J = 10 Hz, 2H), 3.89 (s, 3H), 3.95 (s, 3H), 5.29 (m, 1H), 5.83 (s, 2H), 6.41 (s, 1H), 6.42 (s, 1H). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 13.41, 24.63, 28.04, 28.14, 29.13, 29.27, 29.30, 29.33, 29.36, 34.87, 55.88, 56.00, 79.87, 97.56, 98.70, 105.08, 105.71, 107.13, 149.97, 154.75, 155.22, 159.73, 166.70, 168.32. **IR** (Neat) 2928, 2855, 1747, 1607, 1030, 837 cm^{-1}. **Anal. Calcd** for $C_{24}H_{32}O_5$: C, 71.97; H, 8.05. Found: C, 72.08; H, 8.11.

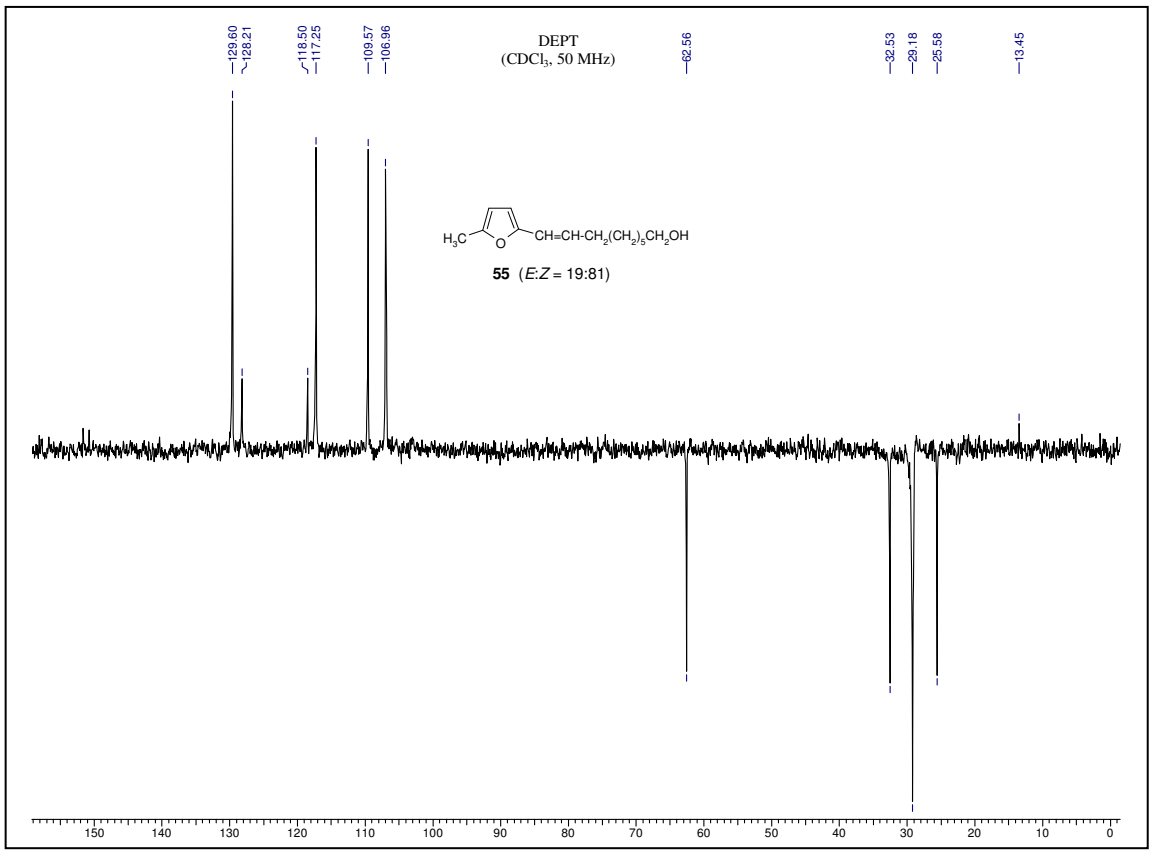
14-(1,3-Dihydro-4,6-dimethoxy-3-oxo-1-isobenzofuranyl)-2,5-tetradecanedione (CJ-13,015, 1a). A stirring solution of **59** (2.00 g, 5.00 mmol) in a mixture of acetic acid-water (1:1, 30 mL) containing six-drops of 6 N H_2SO_4 was refluxed gently for 2 h. After cooling, acetic acid was removed in vacuo, ethyl acetate (100 mL) was added to this reaction mixture and the separated organic layer was washed with saturated $NaHCO_3$ solution, water, brine and dried over Na_2SO_4. Removal of the solvent in vacuo followed by silica gel column chromatographic purification of the residue using 35% ethyl acetate in petroleum ether afforded **1a** (2.04 g, 98%) as a colorless crystalline solid.

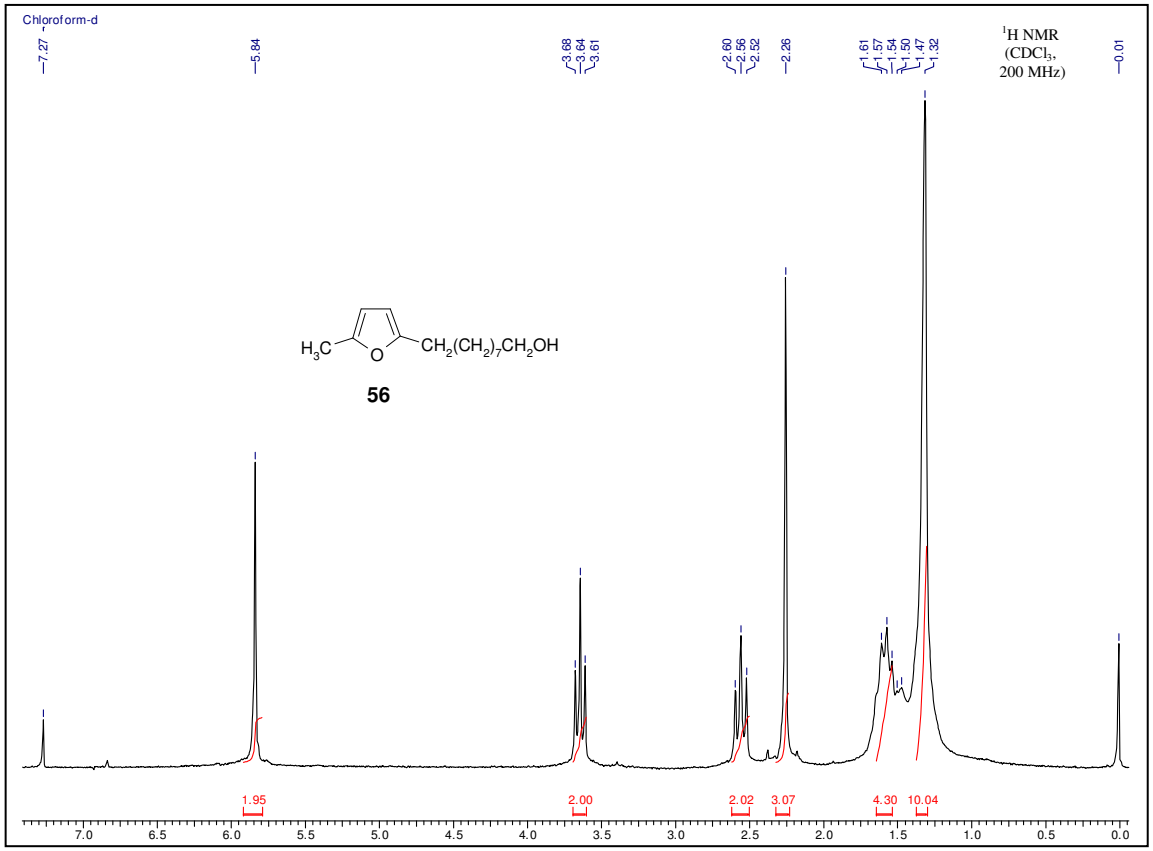
 **1a** **$C_{24}H_{34}O_6$ (418)**	**Mp** 104-106 ^{o}C. **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 1.25 (bs, 8H), 1.25-1.37 (m, 2H), 1.37-1.50 (m, 2H), 1.55 (quintet, J = 10 Hz, 2H), 1.63-1.73 (m, 1H), 1.92-2.01 (m, 1H), 2.17 (s, 3H), 2.43 (t, J = 10 Hz, 2H), 2.63-2.72 (m, 4H), 3.89 (s, 3H), 3.94 (s, 3H), 5.28 (m, 1H), 6.40 (s, 1H), 6.41 (s, 1H). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 23.79, 24.59, 29.09, 29.24 (4 carbons), 29.82, 34.81, 36.03, 36.89, 42.76, 55.86, 55.95, 79.84, 97.53, 98.67, 107.07, 155.19, 159.68, 166.69, 168.30, 207.04, 209.45. **IR** (Nujol) 1759, 1697, 1614, 1601, 1468, 837 cm^{-1}. **Anal. Calcd** for $C_{24}H_{34}O_6$: C, 68.88; H, 8.19. Found: C, 68.92; H, 8.07.

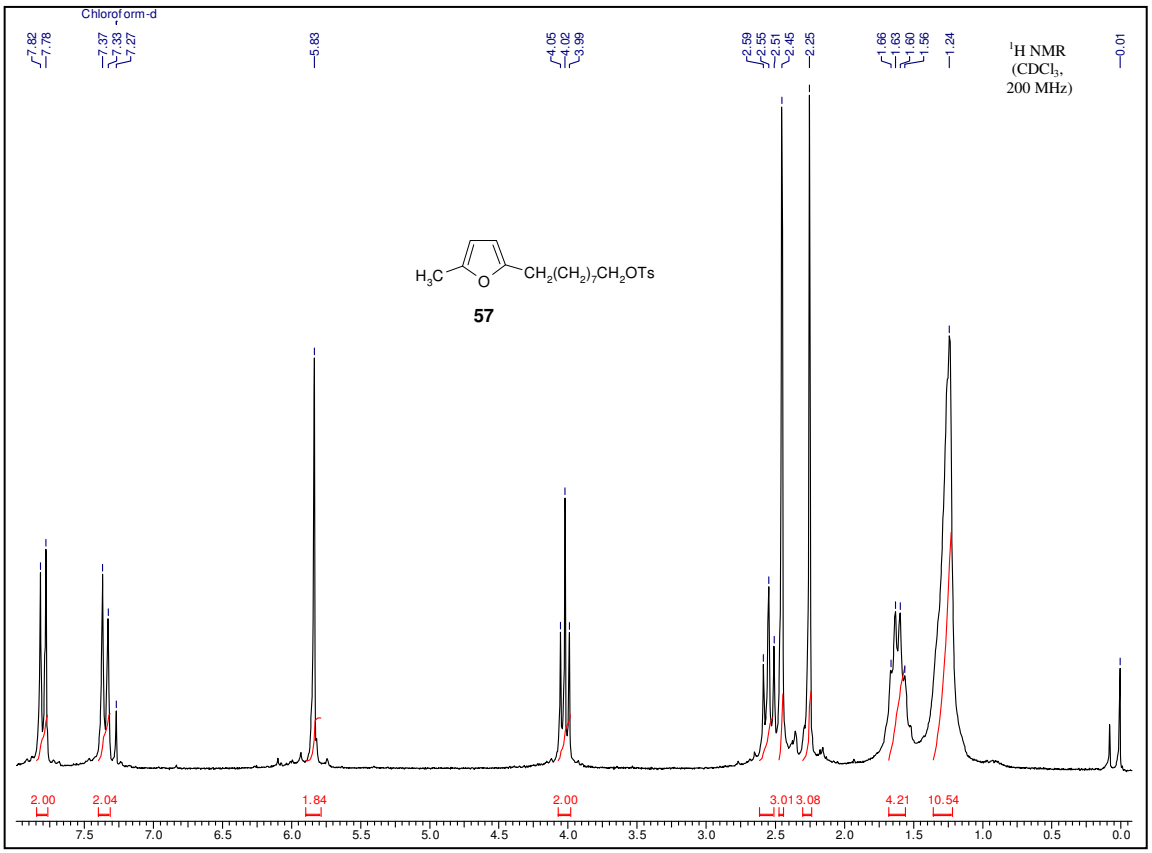
2D.6 Selected Spectra

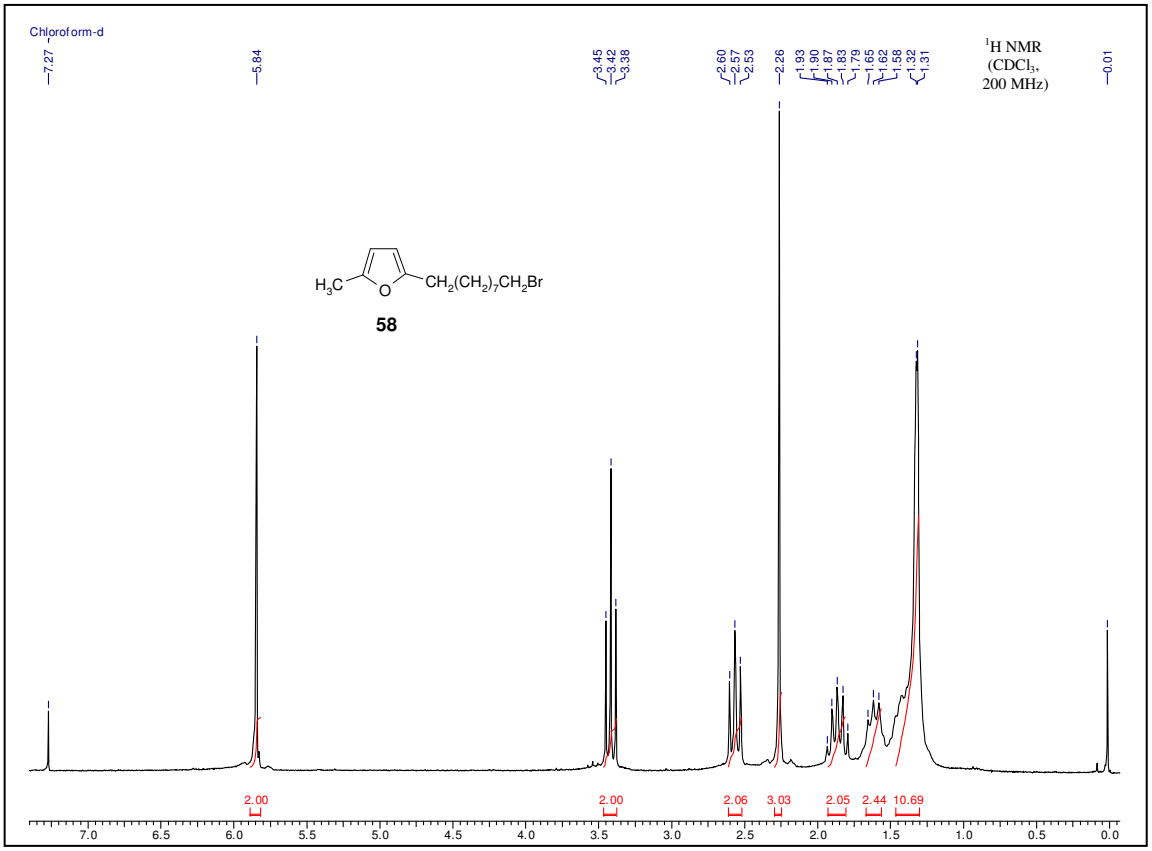

Chloroform-d
7.27
6.14
6.13
6.10
5.99
5.93
5.53
5.49
5.47
5.46
5.43
5.40
3.68
3.65
3.61
2.47
2.44
2.40
2.37
2.31
1.57
1.54
1.48
1.36
0.01
^{1}H NMR
($CDCl_3$,
200 MHz)
H_3C
O
CH=CH-CH_2-$(CH_2)_5$$CH_2$OH
55 (E:Z = 19:81)
2.03
0.70
2.00
3.12
10.46
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

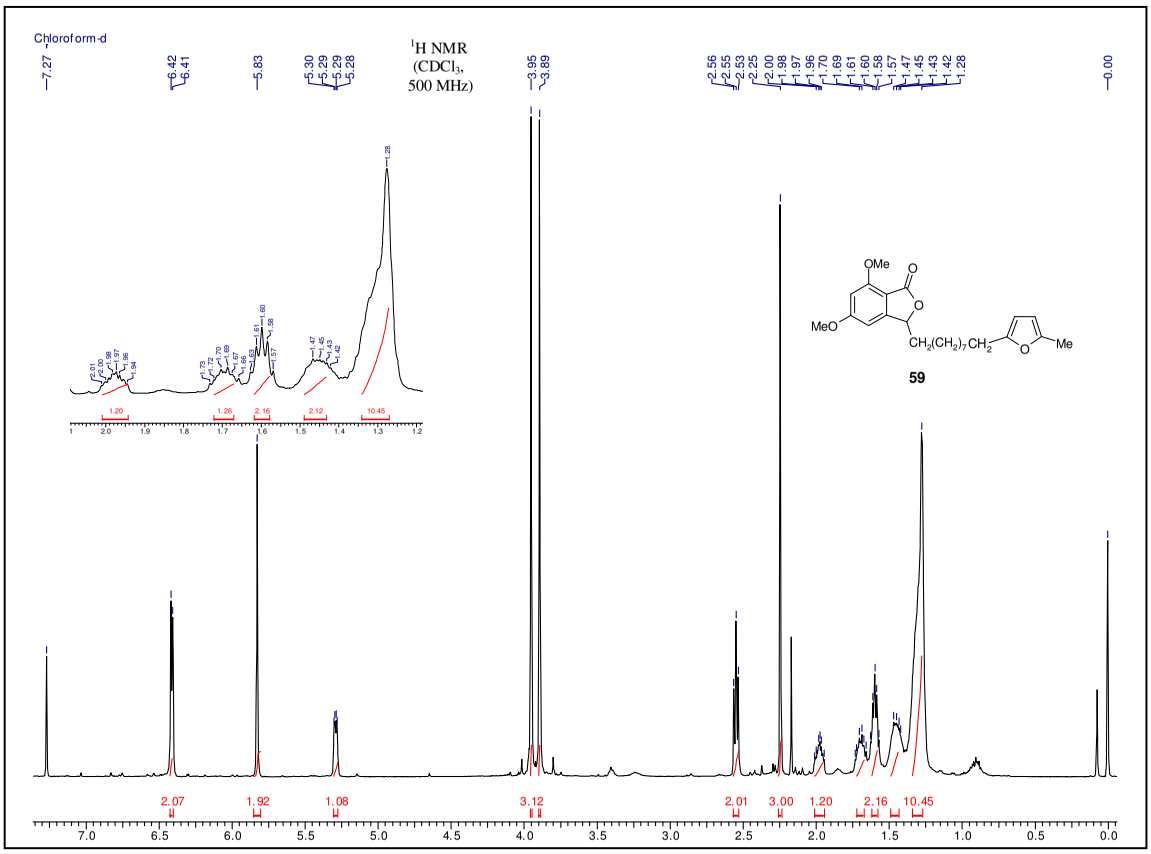

Chloroform-d
151.62
150.74
129.60
128.20
118.54
117.25
109.57
106.96
77.00
62.55
^{13}C NMR
($CDCl_3$,
50 MHz)
32.52
29.18
29.07
25.58
13.45
H_3C
O
CH=CH-CH_2-$(CH_2)_5$$CH_2$OH
55 (E:Z = 19:81)
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

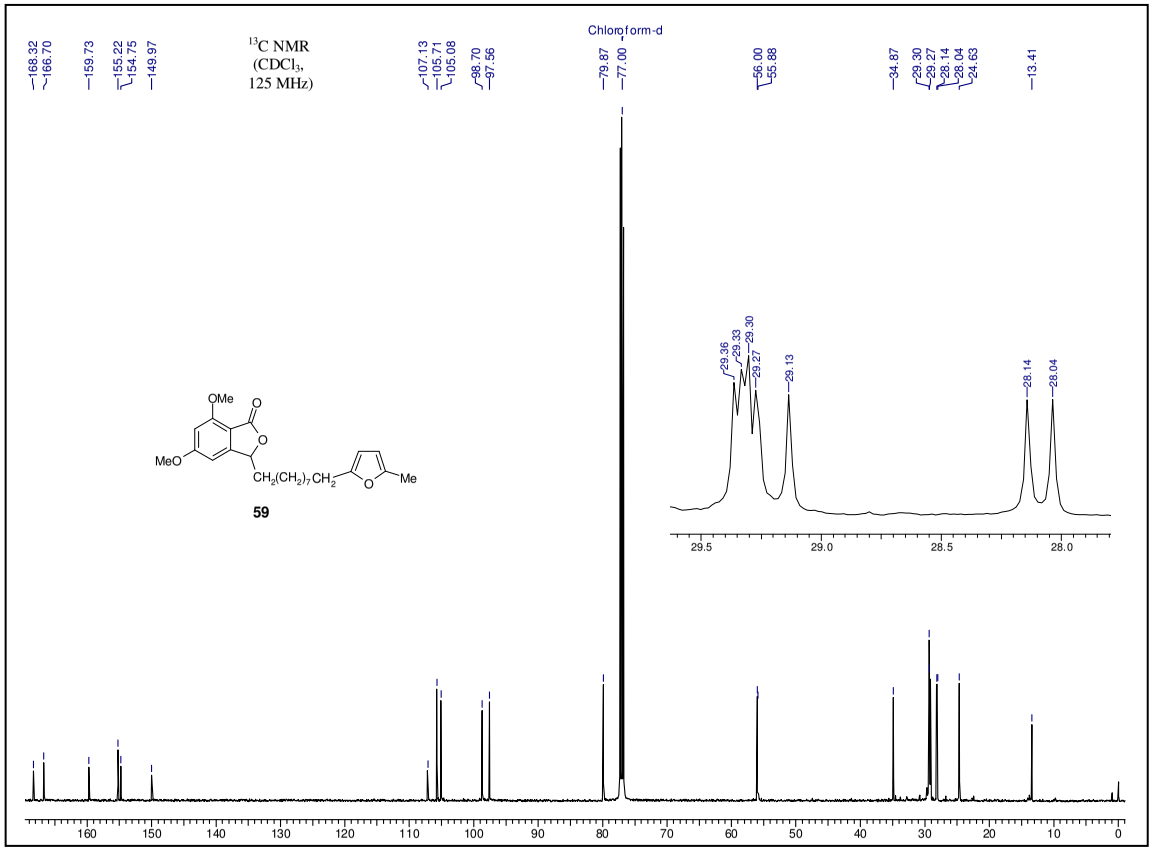

129.60
128.21
118.50
117.25
109.57
106.96
DEPT
(CDCl3, 50 MHz)
62.56
32.53
29.18
25.58
13.45
H3C
O
CH=CH-CH2(CH2)5CH2OH
55 (E:Z = 19:81)
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

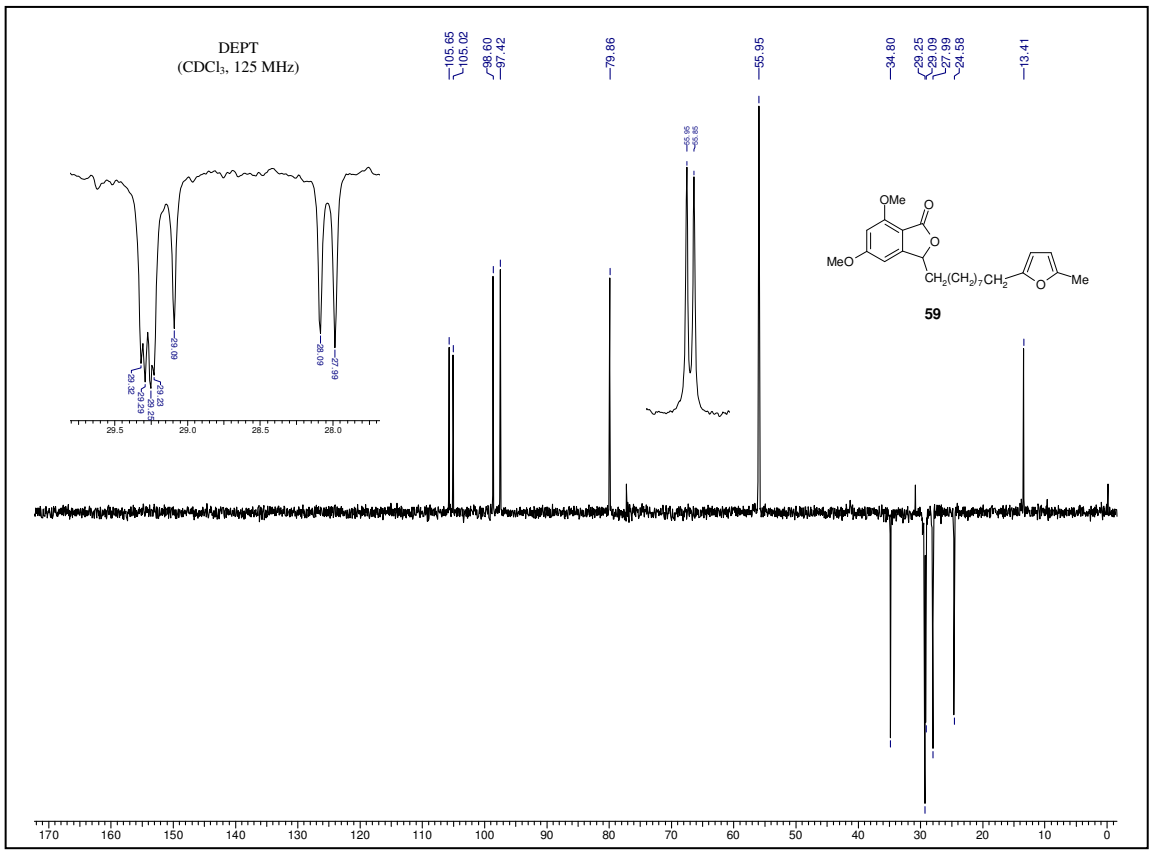

Chloroform-d
7.27
5.84
3.68
3.64
3.61
2.60
2.56
2.52
2.26
1.61
1.57
1.54
1.50
1.47
1.32
0.01
1H NMR
(CDCl3,
200 MHz)
H3C
O
CH2(CH2)7CH2OH
56
1.95
2.00
2.02
3.07
4.30
10.04
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

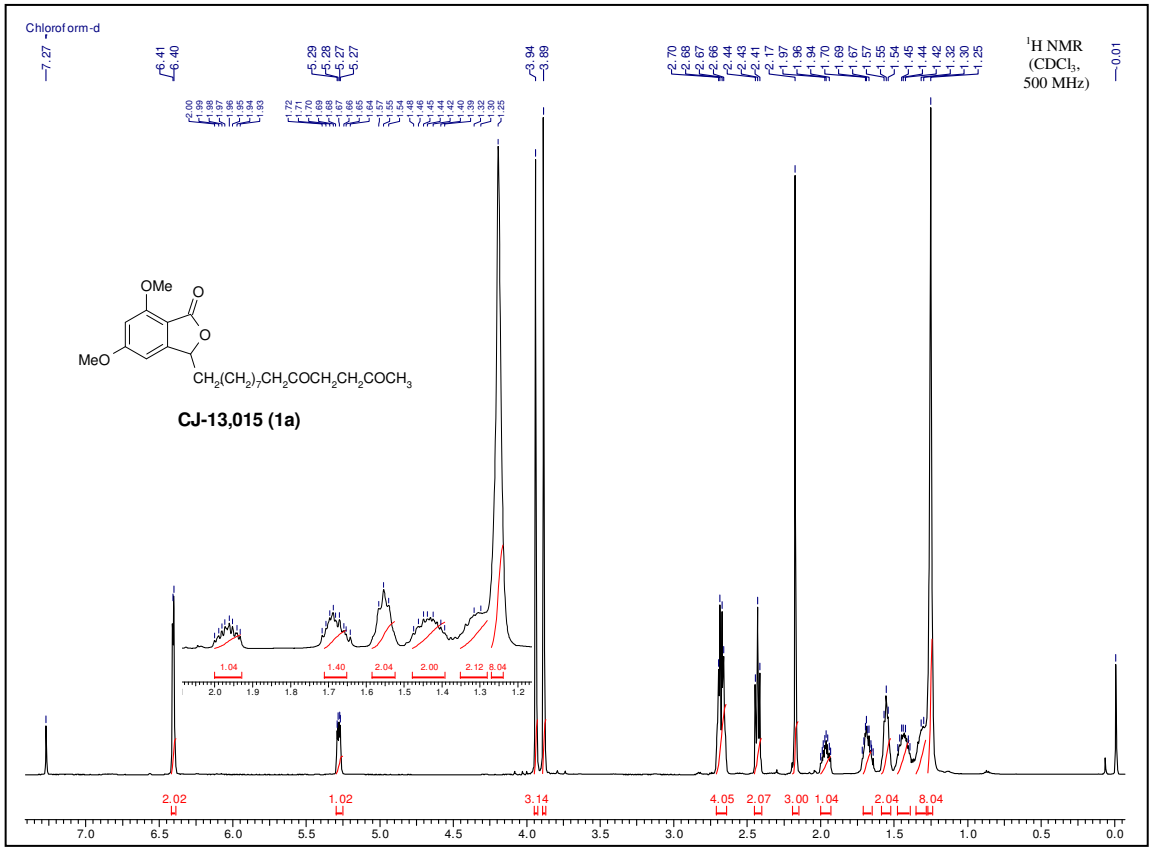

Chloroform-d
7.82
7.78
7.37
7.33
7.27
5.83
4.05
4.02
3.99
2.59
2.55
2.51
2.45
2.25
1.66
1.63
1.60
1.56
1.24
0.01
^{1}H NMR
($CDCl_3$,
200 MHz)
H_3C
$CH_2(CH_2)_7CH_2OTs$
57
2.00
2.04
1.84
2.00
3.01
3.08
4.21
10.54

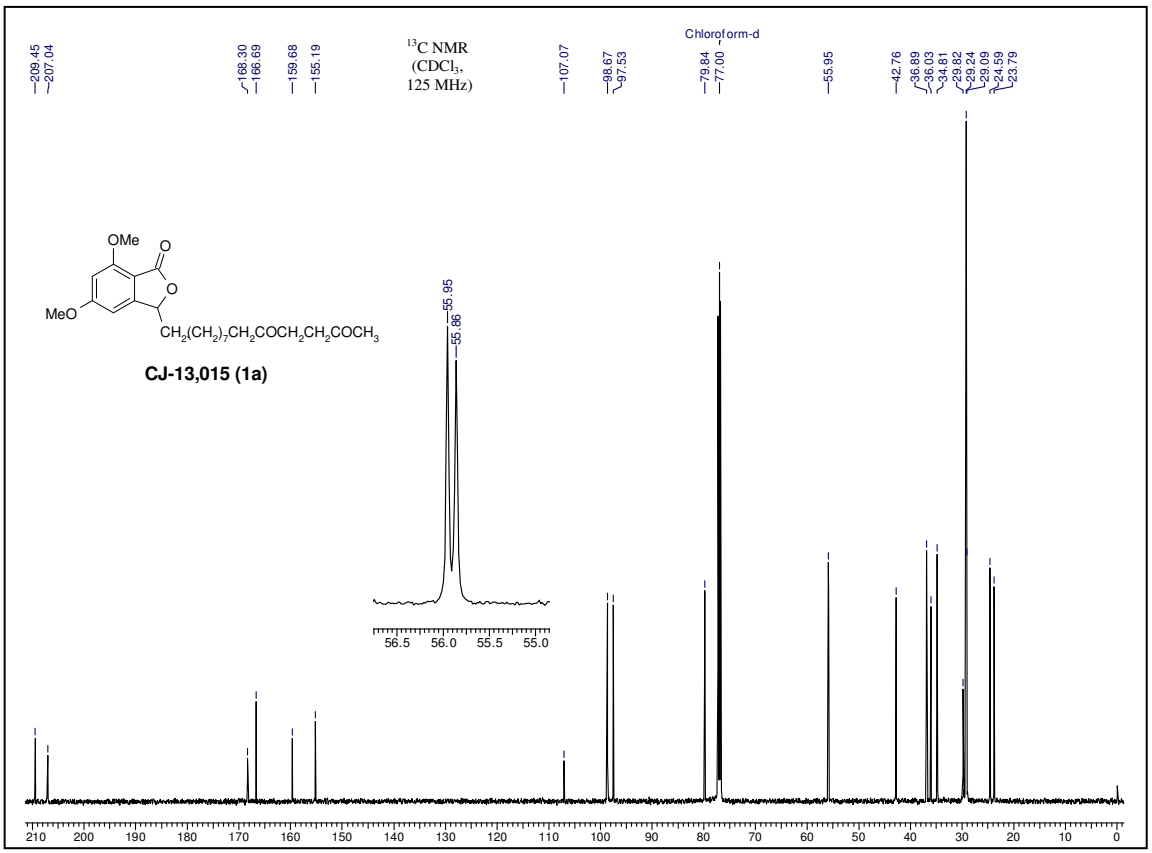

Chloroform-d
7.27
5.84
3.45
3.42
3.38
2.60
2.57
2.53
2.26
1.93
1.90
1.87
1.83
1.79
1.65
1.62
1.58
1.32
1.31
0.01
^{1}H NMR
($CDCl_3$,
200 MHz)
H_3C
$CH_2(CH_2)_7CH_2Br$
58
2.00
2.00
2.06
3.03
2.05
2.44
10.69

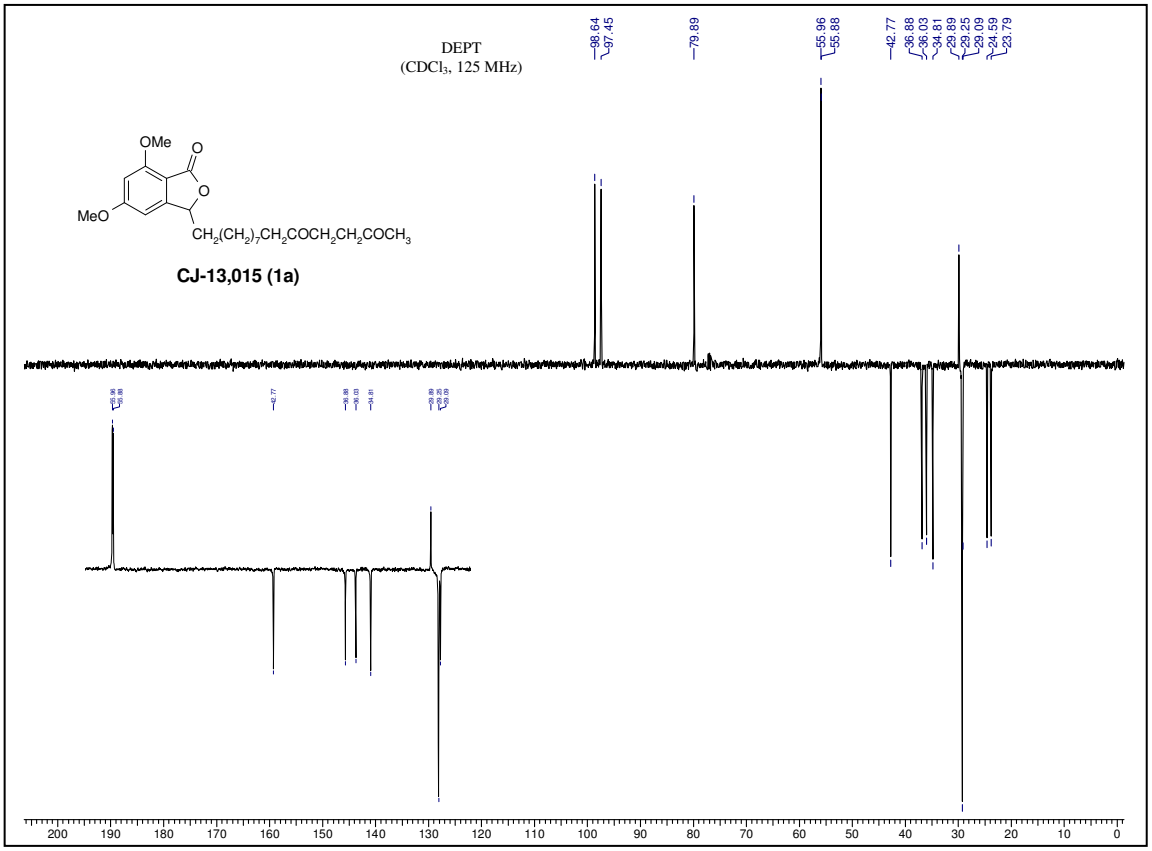

Chloroform-d
^{1}H NMR
(CDCl$_3$,
500 MHz)
OMe
MeO
CH$_2$(CH$_2$)$_7$CH$_2$
Me
59


Chloroform-d
^{13}C NMR
(CDCl$_3$,
125 MHz)
OMe
MeO
CH$_2$(CH$_2$)$_7$CH$_2$
Me
59


DEPT
(CDCl3, 125 MHz)
105.65
105.02
98.60
97.42
79.86
55.95
34.80
29.25
29.09
27.99
24.58
13.41
OMe
MeO
CH2(CH2)7CH2
Me
59


Chloroform-d
1H NMR
(CDCl3,
500 MHz)
OMe
MeO
CH2(CH2)7CH2COCH2CH2COCH3
CJ-13,015 (1a)


^{13}C NMR
($CDCl_3$,
125 MHz)
Chloroform-d
209.45
207.04
168.30
166.69
159.68
155.19
107.07
98.67
97.53
79.84
77.00
55.95
42.76
36.89
36.03
34.81
29.82
29.24
29.09
24.59
23.79
OMe
O
O
MeO
$CH_2(CH_2)_7CH_2COCH_2CH_2COCH_3$
CJ-13,015 (1a)
55.95
55.86
56.5
56.0
55.5
55.0
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


DEPT
($CDCl_3$, 125 MHz)
98.64
97.45
79.89
55.96
55.88
42.77
36.88
36.03
34.81
29.89
29.25
29.09
24.59
23.79
OMe
O
O
MeO
$CH_2(CH_2)_7CH_2COCH_2CH_2COCH_3$
CJ-13,015 (1a)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

2D.7 References and Footnotes

1. Blaser, M. J. *Clin. Infect. Dis*. **1992**, *15*, 386.
2. Rathbone, B. *Scrip Magazine* **1993**, 25.
3. Montecucco, C.; de Bernard, M. *Microbes Infect*. **2003**, *5*, 715.
4. Trust, T. J.; Alm, R. A.; Pappo, J. *Eur. J. Surg., Acta Chirurgica, Suppl*. **2001**, *586*, 82.
5. Parente, F.; Cucino, C.; Bianchi, P. G. *Digest. Liver Dis*. **2003**, *35*, 523.
6. Dekker, K. A.; Inagaki, T.; Gootz, T. D.; Kaneda, K.; Nomura, E.; Sakakibara, T.; Sakemi, S.; Sugie, Y.; Yamauchi, Y.; Yoshikawa, N.; Kojima, N. *J. Antibiot.* **1997**, *50*, 833.
7. Brimble, M. A.; Flowers, C. L.; Hutchinson, J. K.; Robinson, J. E.; Sidford, M. *Tetrahedron* **2005**, *61*, 10036.
8. Brimble, M. A.; Bryant, C. J. *Chem. Commun*. **2006**, 4506 and references cited therein.
9. They have prepared ketone **33** from 3,5-dimethoxybenzaldehyde and allylmagnesium bromide followed by the oxidation.
10. Mondal, M.; Argade, N. P. *Synlett* **2004**, 1243
11. For the synthesis of 1,4-dicarbonyl systems, see: (a) Piancatelli, G.; D'Auria, M.; D'Onofrio, F. *Synthesis* **1994**, 867. (b) Yuguchi, M.; Tokuda, M.; Orito, K. *J. Org. Chem*. **2004**, *69*, 908 and references cited therein.
12. Horiike, M.; Hirano, C. *Agric. Biol. Chem*. **1980**, *44*, 2229.
13. (a) Mali, R. S.; Babu, K. N. *J. Org. Chem*. **1998**, *63*, 2488. (b) Mali, R. S.; Jagtap, P. G.; Patil, S. R.; Pawar, P. N. *J. Chem. Soc., Chem. Commun*. **1992**, 883.
14. Mondal, M. *Synlett* Spotlight 139, **2005**, 2697.
15. Mondal, M.; Argade, N. P. *Tetrahedron Lett*. **2004**, *45*, 5693.
16. 3,5-Dimethoxyphthalide was synthesized from 3,5-dimethoxybenzoic acid in four-steps with 76% overall yield (Please see, Second Chapter, Section A, Scheme 1).

2E. Section E

Studies Towards the Synthesis of Mammalian Cell Cycle Progression Inhibitor Acetophthalidin

This section features the following topics:

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2E.2	*Rationale for Present Work*	188
2E.3	*Results and Discussion*	189
2E.4	*Summary*	191
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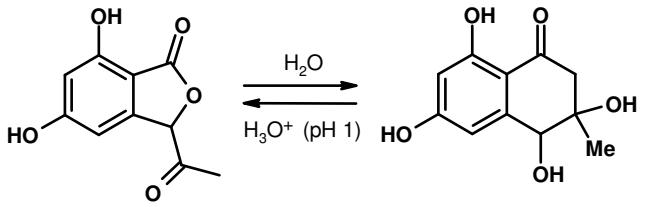
2E Section E: Studies Towards the Synthesis of Mammalian Cell Cycle Progression Inhibitor Acetophthalidin

2E.1 Background

Acetophthalidin (**1**) is an optically inactive metabolite, produced by fungal strain BM923 (the fungus belongs to the genus *Penicillium*) isolated from a sea sediment.[1] This simple phenolic lactone shows complete inhibition of the mammalian cell cycle[2] progression of mouse tsFT210 cells in the M phase even at a very low concentration (6.35 μg/mL).[1] However, it was hardly possible to isolate pure acetophthalidin from the culture broth of the producing strain, because **1** isomerizes readily to inactive 3,4,6,8-tetrahydroxy-3-methyl-3,4-dihydroisocoumarin (trihydroxymelleine, **2**) which can be converted into **1** by heating in water at pH 1 as a racemate (Scheme 1).[1] Trihydroxymelleine (**2**) was isolated[3] earlier as a metabolite of Ceratocystis minor, a



Acetophthalidin (**1**) 3,4,6-Trihydroxymellein (**2**)

Scheme 1

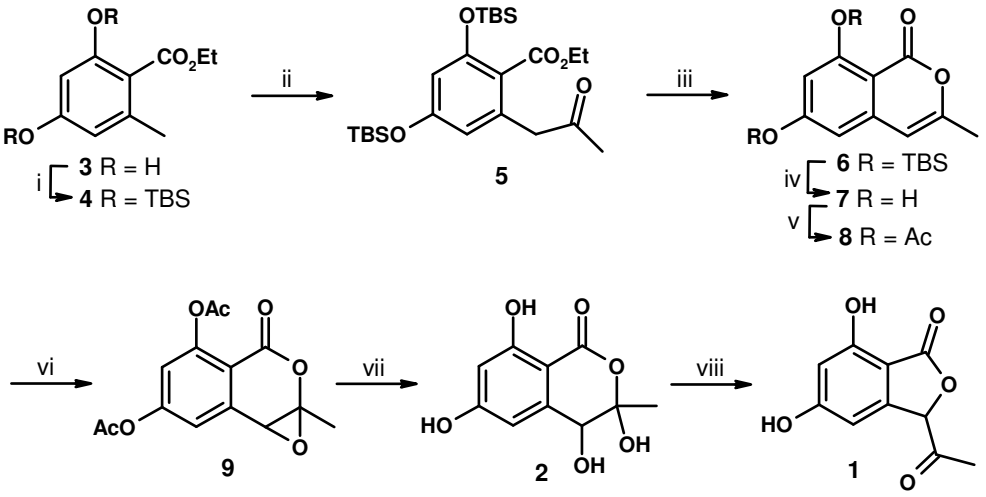
fungus associated with the blue stain disease of Canadian pine trees. Andersen later reported the production of **2** by *Penicillium brevicompactum*.[4] The unique structure and bioactivity of acetophthalidin attracted attention of synthetic organic chemists.

2E.1.1 Synthetic Approaches Towards Acetophthalidin

[A] Mori's Approach

Mori and co-workers have reported[5] the first synthesis of acetophthalidin (**1**) from ethyl 2,4-dihydroxy-6-methylbenzoate (**3**). Protection of the two phenolic hydroxyl group of compound **3** as the corresponding TBS ether **4** followed by treatment of the benzylic anion of **4** with *N*-methoxy-*N*-methylacetamide furnished the keto ester **5**. Compound **5** on

cyclization to isocoumarin **6** followed by removal of TBS protecting groups, again acyl protection of the both phenolic hydroxyl groups, finally epoxidation and ring opening of the unstable epoxide **9** with water and acyl deprotection furnished the pro-natural product **2**. Conversion of **2** into acetophthalidin (**1**) was executed by heating the acidic aqueous solution of **2** with 10% overall yield (Scheme 2).

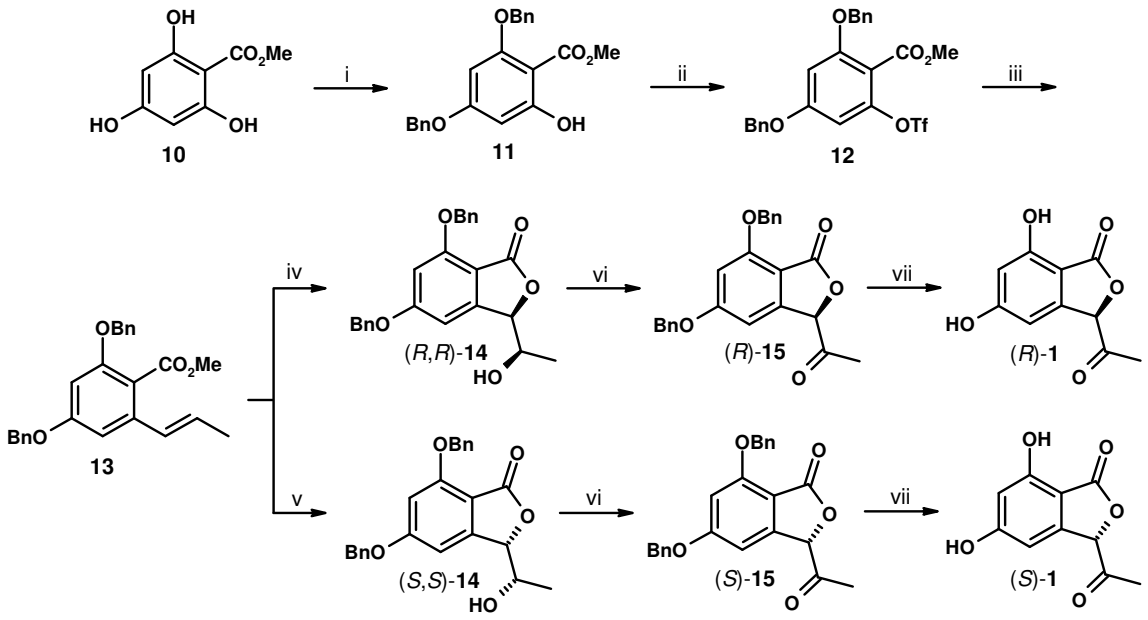


Scheme 2 *Reagents, conditions and yields*: (i) TBSCl, imidazole, DMF (quantitative); (ii) (a) −78 °C, THF, LDA, (b) AcN(OMe)Me (93% based on consumed **4**); (iii) NaH, *t*BuOH, toluene (75%); (iv) *n*-Bu_4NF, THF (92%); (v) Ac_2O, pyridine (94%); (vi) *m*-CPBA, $CHCl_3$; (vii) (a) 2 N HCl, THF, (b) K_2CO_3, MeOH (22% based on **8**); (viii) H_3O^+ (78%).

[B] Watanabe's Approach

Watanabe *et al*[6] have synthesized both the enantiomers of acetophthalidin (**1**) in order to find out the differences of their activities. They started with the selective dibenzylation of methyl phloroglucinolcarboxylate (**10**) to form the corresponding 2,4-dibenzyl ether **11** as a major product. The free hydroxyl group of **11** on trifluoromethanesulfonate conversion followed by coupling with tri-*n*-butyl-1-propenyltin under Stille's conditions furnished the mixture of *E*- and *Z*-olefin **13** (3:1) which on recrystallization from hexane/ethyl acetate gave pure *E*-isomer. Asymmetric dihydroxylation of **13** with AD-mix-β[7] gave optically active hydroxylactone (*R*, *R*)-**14**. Dess-Martin[8] oxidation of the *sec*-hydroxyl group in (*R*, *R*)-**14** furnished the dibenzyl acetophthalidin (*R*)-**15** with 89.7% ee, which on hydrogenolysis furnished the *R*-isomer of acetophthalidin (**1**) (Scheme 3). In the same manner, they have synthesized (*S*)-**1**, using asymmetric dihydroxylation of **13** with AD-mix-α[7] followed by the same sequence. In this case, the enantiomeric purity of (*S*)-**15** was

92.7% ee. After completion of six-steps synthesis of both the enantiomers of acetophthalidin with over all yield of 10.3% for (*R*)-**1** and 14.6% for (*S*)-**1**, they observed no differences in the activities of both the enantiomers and the enantiomerically pure synthetic **1** was very unstable with half life period of racemization ($T_{1/2}$ of $[\alpha]_D$) 33 min in methanol at 22 °C.



Scheme 3 *Reagents, conditions and yields*: (i) BnBr (2.10 equiv.), K_2CO_3, NaI, DMF, rt, 12 h (47%); (ii) Tf_2O, pyridine, DCM, –40 °C, 0.5 h, 0 °C, 3.5 h (77%); (iii) $MeCH{=}CHSnBu^n_3$, Pd(0)$[PPh_3]_4$, LiCl, THF, 90 °C, 7 d, recrystallization (59%); (iv) AD-mix-β, $MeSO_2NH_2$, *t*-BuOH, H_2O, 4 °C, 12 d, recrystallization (75%); (v) AD-mix-α, $MeSO_2NH_2$, *t*-BuOH, H_2O, 4 °C, 3 d, recrystallization (79%); (vi) Dess-Martin reagent, DCM, rt, 1 h [(*R*)-**15**: 91% yield, 89.7% ee; (*S*)-**15**: 99.5% yield, 92.7% ee]; (vii) H_2, 10% $Pd(OH)_2$-C, EtOAc, rt, 15 min [(*R*)-**1**: 71%; (*S*)-**1**: 87%].

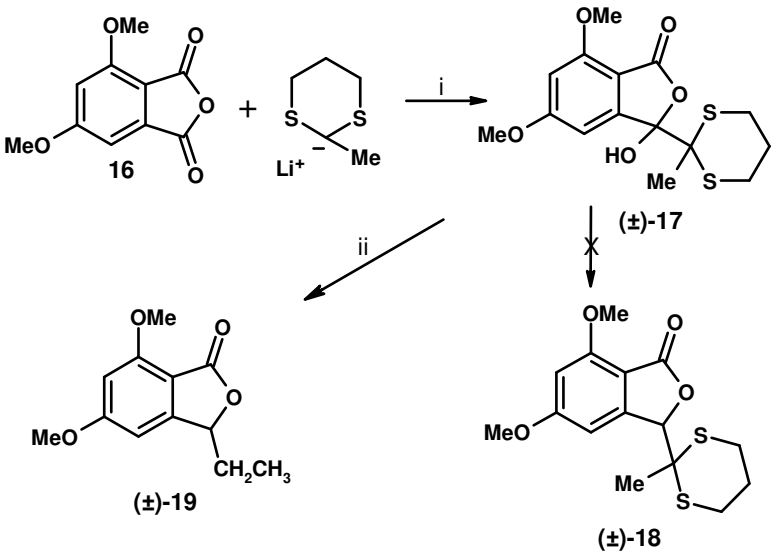
2E.2 Rationale for Present Work

It is evident from the above reports that acetophthalidin (**1**) is not very stable compound with a very low half life period of racemization. Activity wise, there is no difference in both the enantiomers. The unique structural features and bioactivity of acetophthalidin (**1**) promoted us to design new synthetic route to this natural product. In the past decade, we have in our group designed several structurally interesting bioactive natural and unnatural compounds using cyclic anhydrides as potential precursor.[9] Thus, in keeping with the trend, we launched a synthetic plan towards this natural product. Our ongoing efforts

towards the synthesis of the natural product acetophthalidin (**1**) using regioselective nucleophilic addition of an acyl equivalent to the required substituted phthalic anhydride as a key reaction are in progress. In the following part, our synthetic approaches towards the acetophthalidin (**1**) have been discussed in details.

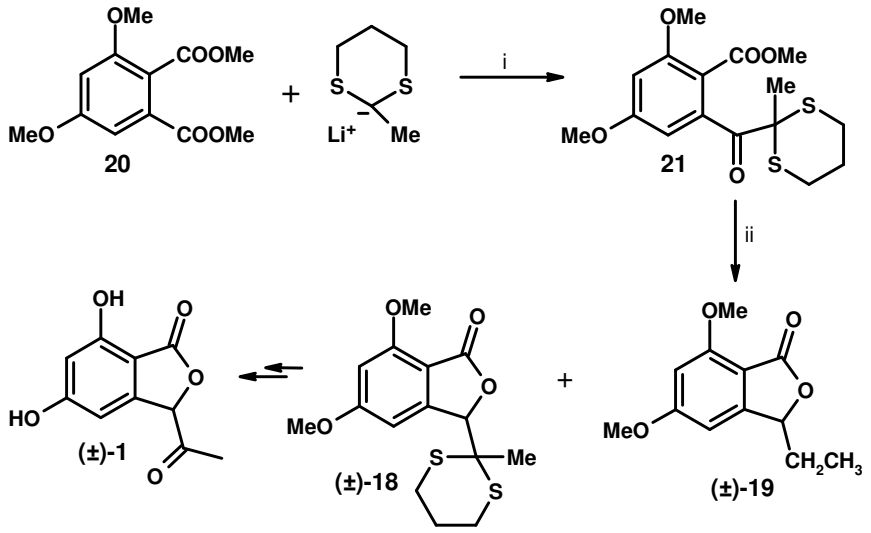
2E.3 Results and Discussion

We envisaged a regioselective nucleophilic addition of an acyl equivalent nucleophile with the required substituted phthalic anhydride as a key step in the total synthesis of acetophthalidin (**1**). The regioselective nucleophilic addition of 2-lithio-2-methyl-1,3-dithiane to 3,5-dimethoxyphthalic anhydride[10] (**16**) furnished the desired adduct **17**. Our all attempts to reduce the compound **17** to phtahlide **18** met with failure. Under the alkaline conditions the reduction of **17** furnished undesired ethyl substituted phthalide **19** via the reductive deprotection of the dithiane moiety (Scheme 4).



Scheme 4. *Reagents, conditions and yields*: (i) THF, −78 °C, 30 min (78%); (ii) 2 N NaOH, $NaBH_4$, 60 °C, 6 h (85%).

Accordingly, we changed our synthetic approach and our modified scheme involved the condensation reaction of lithio-2-methyl-1,3-dithiane with diester **20**.[11] The resulting keto-ester **21** was reluctant to undergo reduction at low temperature. The $NaBH_4$ reduction of

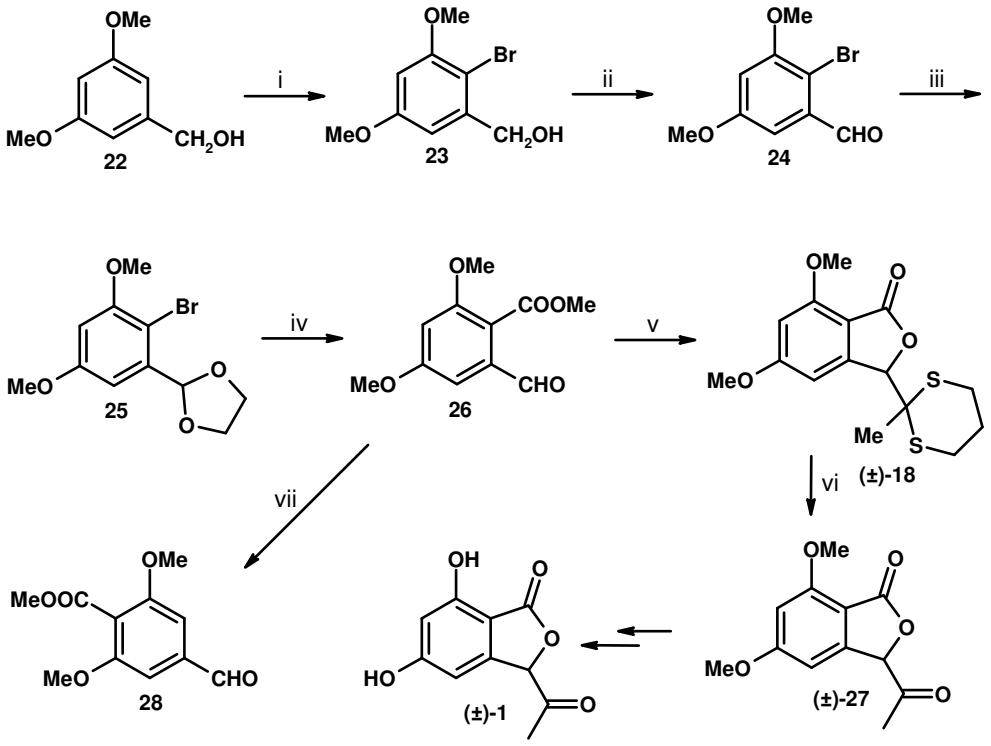


Scheme 5. *Reagents, conditions and yields*: (i) THF, −78 °C, 30 min (84%); (ii) $NaBH_4$ (2.00 equiv.), EtOH, rt, 24 h, (**18**: 20%; **19**: 50%).

keto-ester **21** at room temperature again furnished the undesired alkyl substituted phthalide **19** as a major product with little amount of desired phthalide **18** (Scheme 5).

Next, an alternate strategy was planned to circumvent the above problem. We prepared the required substituted aldehydes-ester **26** from 3,5-dimethoxybenzyl alcohol (**22**), which on NBS bromintation, followed by PCC oxidation, protection of the aldehyde, lithiation of the bromo compound and condensation of the lithiated species with methyl chloroformate directly furnished the aldehydes-ester **26**. Compound **26** underwent a smooth chemoselective condensation with lithio-2-methyl-1,3-dithiane to produce desired dithiane bearing phthalide **18** exclusively. Deprotection of the dithiane moiety via the exchange route using *p*-nitrobenzaldehyde in presence of TMSOTf furnished dimethyl ether of acetophthalidin (**27**). Demethylation of compound **27** to the natural product acetophthalidin (**1**) is in progress.

During this course of reaction, once we attempted the nucleophilic addition of lithium acetylide-ethylenediamine complex (as an acyl precursor) to **26** in DMSO at room temperature, but surprisingly, we got the ester migrated rearranged symmetrical aldehyde-ester compound **28**, instead of the corresponding desired phthalide (Scheme 6). It will be interesting and useful to study the mode of migration (intramolecular/intermolecular) of carbmethoxy group in the conversion of **26** to **28**. We surmise that the present rearrangement is favored entropically with the gain of symmetry.



Scheme 6. *Reagents, conditions and yields*: (i) CCl_4, NBS (1.00 equiv.), reflux, 6 h (98%); (ii) DCM, PCC, 6 h (79%); (iii) Toluene, ethylene glycol (2.50 equiv.), *p*-TSA (5 mol%), reflux, 9 h (88%); (iv) (a) THF, −78 ^{o}C, *n*-BuLi (1.10 equiv.), 1 h, (b) methyl chloroformate (4.00 equiv.), −78 ^{o}C to rt (87%); (v) THF, −78 ^{o}C, lithio-2-methyl-1,3-dithiane (84%); (vi) DCM, *p*-nitrobenzaldehyde (1.50 equiv.), 0 ^{o}C, TMSOTf (0.40 equiv.), 30 min (65%); (vii) DMSO, rt, lithium acetylide-ethylenediamine complex (1.20 equiv.), 1 h (72%).

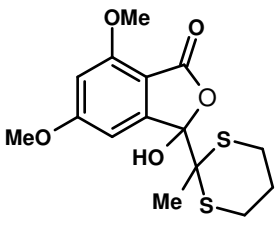
2E.4 Summary

In summary, we have completed the synthesis of acetophthalidindimethyl ether in six-steps with 32% overall yield. Demethylation of the dimethyl ether **27** to the natural product acetophthalidin (**1**) is in progress.

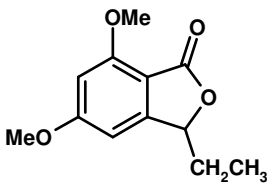
2E.5 Experimental Section

Commercially available 2-methyl-1,3-dithiane, *n*-BuLi (1.50 M), 3,5-dimethoxybenzyl alcohol, $NaBH_4$, NBS, ethylene glycol, *p*-TSA, methyl chloroformate, *p*-nitrobenzaldehyde, TMSOTf, lithium acetylide were used. Melting points are uncorrected. Dichloromethane was distilled from phosphorous pentoxide under argon. Tetrahydrofuran was freshly distilled from benzophenone ketyl radical under argon prior to use. Column chromatographic separations were carried out on silica gel (60-120 mesh). All yields given refer to as isolated yields. IR spectra were recorded on FT-IR spectrometer. MS experiments were performed on a low resolution magnetic sector mass spectrometer.

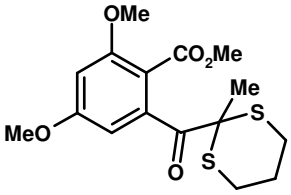
5,7-Dimethoxy-3-hydroxy-3-(2-methyl-1,3-dithian-2-yl)isobenzofuran-1(3*H*)-one (17). To a stirring solution of 2-methyl-1,3-dithiane (0.57 mL, 4.80 mmol) in THF (40 mL) at −78 °C was added *n*-BuLi (3.20 mL, 4.80 mmol) dropwise. After stirring at −78 °C for 45 min, this reaction mixture was added slowly to a stirring solution of 3,5-dimethoxyphthalic anhydride (**16**, 1.00 g, 4.80 mmol) in THF (50 mL) at −78 °C and stirred for a further 20 min. Saturated solution of NH_4Cl was then added to the reaction mixture at −78 °C and the reaction mixture was allowed to reach room temperature. THF was removed in vacuo. After acidification with 2 N HCl, to this reaction mixture was added ethyl acetate (150 mL) and the separated organic layer was washed with water, brine and dried over Na_2SO_4. Removal of the solvent in vacuo followed by silica gel column chromatographic purification of the residue using 40% ethyl acetate in petroleum ether afforded **17** (1.28 g, 78%) as a faint yellow gum.

 **(±)-17** **$C_{15}H_{18}O_5S_2$ (342)**	Faint yellow gum. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 1.69 (s, 3H), 1.75-1.95 (m, 1H), 2.15-2.35 (m, 1H), 2.53 (dt, *J* = 16 & 2 Hz, 2H), 3.32 (t, *J* = 14 Hz, 1H), 3.62 (t, *J* = 14 Hz, 1H), 3.89 (s, 3H), 3.98 (s, 3H), 5.51 (bs, 1H), 6.52 (s, 1H), 6.56 (s, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 23.7, 26.1, 27.7, 28.5, 53.9, 55.9, 56.1, 100.1, 101.0, 109.1, 109.4, 150.5, 159.3, 165.2, 166.2. **IR** (Nujol) 3383, 1759, 1614, 1597 cm^{-1}. **MS** (*m/z*) 343, 325, 209, 193, 166, 133, 106, 77, 59. **Anal. Calcd** for $C_{15}H_{18}O_5S_2$: C, 52.61; H, 5.30; S, 18.73. Found: C, 52.50; H, 5.42; S, 18.79.

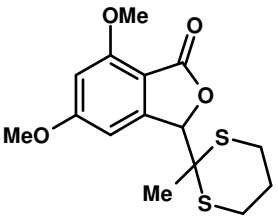
5,7-Dimethoxy-3-ethylisobenzofuran-1(3*H*)-one (19). A stirring mixture of **17** (500 mg, 1.46 mmol) in 2 N aqueous NaOH (10 mL) was heated at around 80 ^{o}C for few minutes until the formation of clear solution. After allowing to cool to room temperature, $NaBH_4$ (55 mg, 1.46 mmol) was added and the reaction mixture was heated at 60 ^{o}C for 6 h. After cooling to 0 ^{o}C, the reaction mixture was acidified with 2 N HCl, to this reaction mixture was added ethyl acetate (100 mL) and the organic layer was washed with water, brine and dried over Na_2SO_4. Removal of the solvent in vacuo followed by silica gel column chromatographic purification of the residue using 25% ethyl acetate in petroleum ether afforded **19** (276 mg, 85%) as a colorless thick oil.

 **(±)-19** **$C_{12}H_{14}O_4$ (222)**	Colorless thick oil. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 0.81 (t, J = 9 Hz, 3H),1.50-1.70 (m, 1H), 1.85-2.05 (m, 1H), 3.76 (s, 3H), 3.79 (s, 3H), 5.14 (dd, J = 6 & 3 Hz, 1H), 6.29 (s, 1H), 6.31 (s, 1H). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 8.1, 27.2, 55.4, 55.5, 80.3, 97.4, 98.2, 106.4, 154.3, 159.1, 166.4, 168.0. **IR** ($CHCl_3$) 1747, 1611 cm^{-1}. **MS** (*m/z*) 222, 193, 176, 161, 149, 135, 122, 106, 91, 77, 69, 63. **Anal. Calcd** for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.89; H, 6.21.

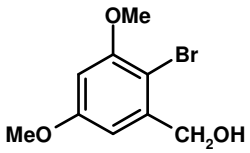
Methyl 2,4-dimethoxy-6-(2-methyl-1,3-dithiane-2-carbonyl)benzoate (21). To a stirring solution of 2-methyl-1,3-dithiane (0.47 mL, 3.94 mmol) in THF (40 mL) at −78 ^{o}C was added *n*-BuLi (2.62 mL, 3.94 mmol) dropwise. After stirring at −78 ^{o}C for 45 min, this reaction mixture was added slowly to a stirring solution of dimethyl 3,5-dimethoxyphthalate (**20**, 1.00 g, 3.94 mmol) in THF (50 mL) at −78 ^{o}C and stirred for a further 20 min. Saturated solution of NH_4Cl was then added to the reaction mixture at −78 ^{o}C and the reaction mixture was allowed to reach room temperature. THF was removed in vacuo. After acidification with 2 N HCl, to this reaction mixture was added ethyl acetate (150 mL) and the organic layer was washed with water, brine and dried over Na_2SO_4. Removal of the solvent in vacuo followed by silica gel column chromatographic purification of the residue using 30% ethyl acetate in petroleum ether afforded **21** (1.18 g, 84%) as a faint yellow gum.

 **21** **$C_{16}H_{20}O_5S_2$ (356)**	Faint yellow gum. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 1.45 (s, 3H), 1.75-2.25 (m, 2H), 2.55-2.75 (m, 2H), 3.13 (s, 3H), 3.20-3.40 (m, 2H), 3.93 (s, 3H), 3.97 (s, 3H), 6.53 (d, J = 2 Hz, 1H), 7.03 (d, J = 2 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 23.7, 25.0, 27.5, 27.8, 51.1, 52.7, 55.9 (2-carbons), 99.9, 101.9, 108.6, 112.8, 148.4, 159.0, 165.1, 166.1. **IR** ($CHCl_3$) 1765, 1611 cm^{-1}. **MS** (*m/z*) 356, 326, 296, 254, 223, 180, 165, 146, 133, 106, 90, 69, 59. **Anal. Calcd** for $C_{16}H_{20}O_5S_2$: C, 53.91; H, 5.66; S, 17.99. Found: C, 53.79; H, 5.59; S, 18.09.

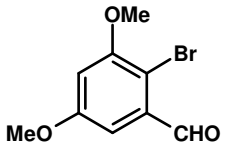
5,7-Dimethoxy-3-(2-methyl-1,3-dithian-2-yl)isobenzofuran-1(3*H*)-one (18). ***Method A***: To a stirring solution of **21** (1.00 g, 2.81 mmol) in ethanol (30 mL) at 0 ^{o}C was added $NaBH_4$ (213 mg, 5.61 mmol) and the reaction mixture was allowed to attain room temperature. After stirring for 24 h at room temperature, the reaction mixture was cooled to 0 ^{o}C and very slowly quenched with 2 N HCl. Ethanol was removed in vacuo and ethyl acetate (100 mL) was added to the reaction mixture. The organic layer was washed with water, brine and dried over Na_2SO_4. Removal of the solvent under vacuo followed by silica gel column chromatographic purification of the residue using 25% ethyl acetate in petroleum ether afforded **19** (312 mg, 50%) as a colorless thick oil and elusion using 30% ethyl acetate in petroleum ether afforded **18** (183 mg, 20%) as a faint yellow gum. ***Method B***: To a stirring solution of 2-methyl-1,3-dithiane (0.53 mL, 4.46 mmol) in THF (40 mL) at −78 ^{o}C was added *n*-BuLi (2.98 mL, 4.46 mmol) dropwise. After stirring at −78 ^{o}C for 45 min, this reaction mixture was added slowly to a stirring solution of **26** (1.00 g, 4.46 mmol) in THF (50 mL) at −78 ^{o}C and stirred for a further 20 min. Saturated solution of NH_4Cl was then added to the reaction mixture at −78 ^{o}C and the reaction mixture was allowed to reach room temperature. THF was removed in vacuo. After acidification with 2 N HCl, to this reaction mixture was added ethyl acetate (150 mL) and the separated organic layer was washed with water, brine and dried over Na_2SO_4. Removal of the solvent in vacuo followed by silica gel column chromatographic purification of the residue using 30% ethyl acetate in petroleum ether afforded **18** (1.22 g, 84%) as a faint yellow gum.

 **(±)-18** **$C_{15}H_{18}O_4S_2$ (326)**	Faint yellow gum. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 1.32 (s, 3H), 1.70-2.25 (m, 2H), 2.65-2.90 (m, 2H), 3.05-3.35 (m, 2H), 3.89 (s, 3H), 3.94 (s, 3H), 5.66 (s, 1H), 6.46 (d, J = 2 Hz, 1H), 6.97 (d, J = 2 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 23.0, 23.9, 26.6 (2-carbons), 50.0, 55.9 (2-carbons), 82.5, 99.0, 101.2, 107.6, 150.8, 159.3, 166.0, 167.3. **IR** (Nujol) 1755, 1601 cm^{-1}. **Anal. Calcd** for $C_{15}H_{18}O_4S_2$: C, 55.19; H, 5.56; S, 19.64. Found: C, 55.31; H, 5.39; S, 19.60.

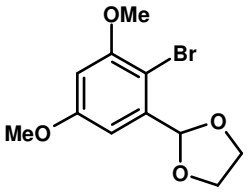
2-Bromo-3,5-dimethoxybenzyl alcohol (23). A mixture of **22** (8.00 g, 47.62 mmol) and NBS (8.48 g, 47.62 mmol) in CCl_4 was refluxed gently for 6 h. The reaction mixture was filtered under hot condition and concentration of the filtrate in vacuo followed by silica gel column chromatographic purification of the residue using 35% ethyl acetate in petroleum ether afforded **23** (11.53 g, 98%) as a white solid.

 **23** **$C_9H_{11}BrO_3$ (247)**	**Mp** 119-121 ^oC. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 2.16 (t, J = 6 Hz, 1H), 3.82 (s, 3H), 3.87 (s, 3H), 4.73 (d, J = 8 Hz, 2H), 6.44 (d, J = 2 Hz, 1H), 6.70 (d, J = 4 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 55.5, 56.3, 65.1, 98.8, 102.1, 104.7, 141.7, 156.5, 159.9. **IR** (Nujol) 3184, 1589 cm^{-1}. **Anal. Calcd** for $C_9H_{11}BrO_3$: C, 43.75; H, 4.49; Br, 32.34. Found: C, 43.69; H, 4.56; Br, 32.35.

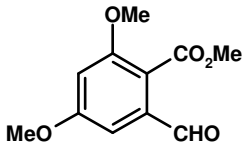
2-Bromo-3,5-dimethoxybenzaldehyde (24). To a stirring mixture of PCC (8.70 g, 40.48 mmol) and activated powdered molecular sieves (5.00 g) in DCM (80 mL) at 0 ^oC, a solution of **23** (10.00 g, 40.48 mmol) in DCM (50 mL) was added dropwise and the reaction mixture was allowed to attain room temperature. After stirring for 6 h at room temperature, diethyl ether (30 mL) was added and the reaction mixture was filtered through celite and the filtrate was concentrated in vacuo. Silica gel column chromatographic purification of the residue using 20% ethyl acetate in petroleum ether furnished **24** (7.84 g, 79%) as a colorless solid.

 **24** **$C_9H_9BrO_3$ (245)**	**Mp** 136-137 °C. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 3.85 (s, 3H), 3.92 (s, 3H), 6.72 (d, J = 2 Hz, 1H), 7.05 (d, J = 2 Hz, 1H), 10.42 (s, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 55.7, 56.5, 103.4, 105.7, 109.0, 134.6, 157.0, 159.8, 191.9. **IR** (Nujol) 1674, 1589 cm^{-1}. **Anal. Calcd** for $C_9H_9BrO_3$: C, 44.11; H, 3.70; Br, 32.60. Found: C, 44.17; H, 3.61; Br, 32.59.

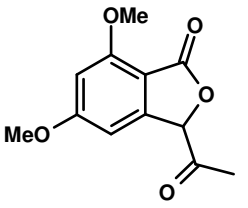
2-(2-Bromo-3,5-dimethoxyphenyl)-1,3-dioxolane (25). A stirring mixture of **24** (7.00 g, 28.57 mm0l), ethylene glycol (3.98 mL, 71.43 mmol) and *p*-TSA (245 mg, 1.43 mmol) in toluene (100 mL) was refluxed for 9 h using Dean-Stark apparatus. After cooling ethyl acetate (100 mL) was added to the reaction mixture. The combined organic layer was washed with water, saturated $NaHCO_3$ solution, brine and dried over Na_2SO_4. Removal of the solvent in vacuo followed by silica gel column chromatographic purification of the residue using 25% ethyl acetate in petroleum ether afforded **25** (7.26 g, 88%) as a colorless solid.

 **25** **$C_{11}H_{13}BrO_4$ (289)**	**Mp** 90-92 °C. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 3.82 (s, 3H), 3.87 (s, 3H), 4.00-4.23 (m, 4H), 6.12 (s, 1H), 6.51 (d, J = 2 Hz, 1H), 6.80 (d, J = 2 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 55.2, 56.0, 65.0, 100.2, 102.1, 103.1, 103.3, 138.1, 156.3, 159.5. **IR** (Nujol) 1591, 1462, 1454 cm^{-1}. **Anal. Calcd** for $C_{11}H_{13}BrO_4$: C, 45.70; H, 4.53; Br, 27.64. Found: C, 45.79; H, 4.42; Br, 27.70.

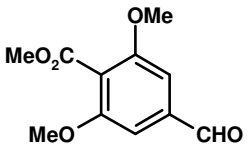
Methyl 2-formyl-4,6-dimethoxybenzoate (26). To a stirring solution of **25** (5.00 g, 17.30 mmol) in THF (80 mL) at −78 °C was added *n*-BuLi (12.69 mL, 19.03 mmol) dropwise. After stirring at −78 °C for 1 h, freshly distilled methyl chloroformate (5.35 mL, 69.20 mmol) was added slowly to the above stirring reaction mixture. The reaction mixture was allowed to reach room temperature and the reaction was quenched with saturated solution of NH_4Cl. THF was removed in vacuo, ethyl acetate (150 mL) was added to the reaction mixture and the separated organic layer was washed with water, brine and dried over Na_2SO_4. Removal of the solvent in vacuo followed by silica gel column chromatographic purification of the residue using a mixture of 30% ethyl acetate in petroleum ether afforded **26** (3.37 g, 87%) as a colorless crystalline solid.

 **26** **$C_{11}H_{12}O_5$ (224)**	**Mp** 102-103 ^oC. **^1H NMR** ($CDCl_3$, 200 MHz) δ 3.86 (s, 3H), 3.89 (s, 3H), 3.95 (s, 3H), 6.72 (d, J = 2 Hz, 1H), 6.98 (d, J = 2 Hz, 1H), 9.96 (s, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 52.5, 55.6, 56.2, 104.1, 105.0, 117.3, 135.7, 158.3, 161.8, 166.8, 190.0. **IR** (Nujol) 1724, 1697, 1605, 1582 cm^{-1}. **Anal. Calcd** for $C_{11}H_{12}O_5$: C, 58.93; H, 5.39. Found: C, 58.99; H, 5.28.

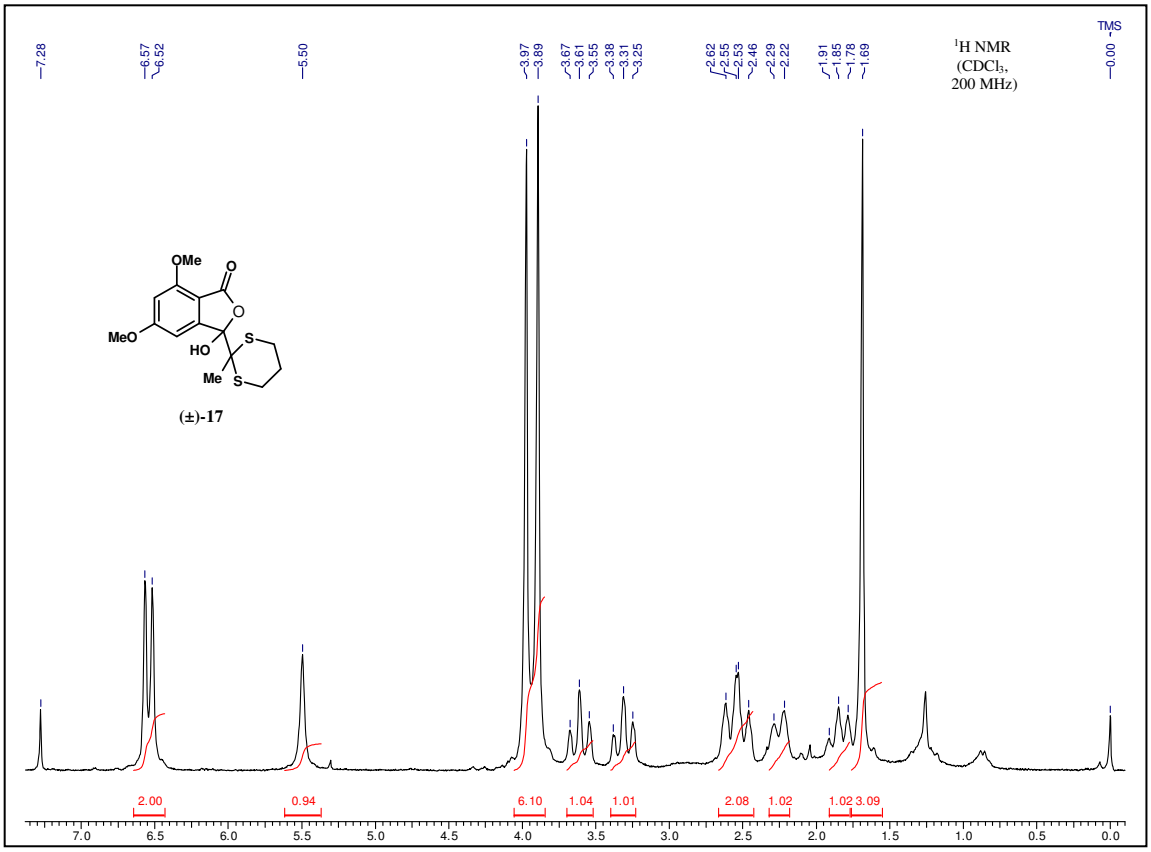
3-Acetyl-5,7-dimethoxyisobenzofuran-1(3*H*)-one (27). To a stirring solution of **18** (500 mg, 1.53 mmol) and *p*-nitrobenzaldehyde (347 mg, 2.30 mmol) in DCM (15 mL) at 0 ^oC, TMSOTf (0.11 mL, 0.61 mmol) was added very slowly and the reaction mixture was allowed to attain room temperature. After stirring for 30 min at room temperature, saturated aqueous $NaHCO_3$ solution was added to the reaction mixture. The reaction mixture was diluted with DCM (50 mL) and the combined organic layer was washed with water, brine and dried over Na_2SO_4. Removal of the solvent in vacuo followed by silica gel column chromatographic purification of the residue using 25% ethyl acetate in petroleum ether afforded **27** (235 mg, 65%) as a colorless thick liquid.

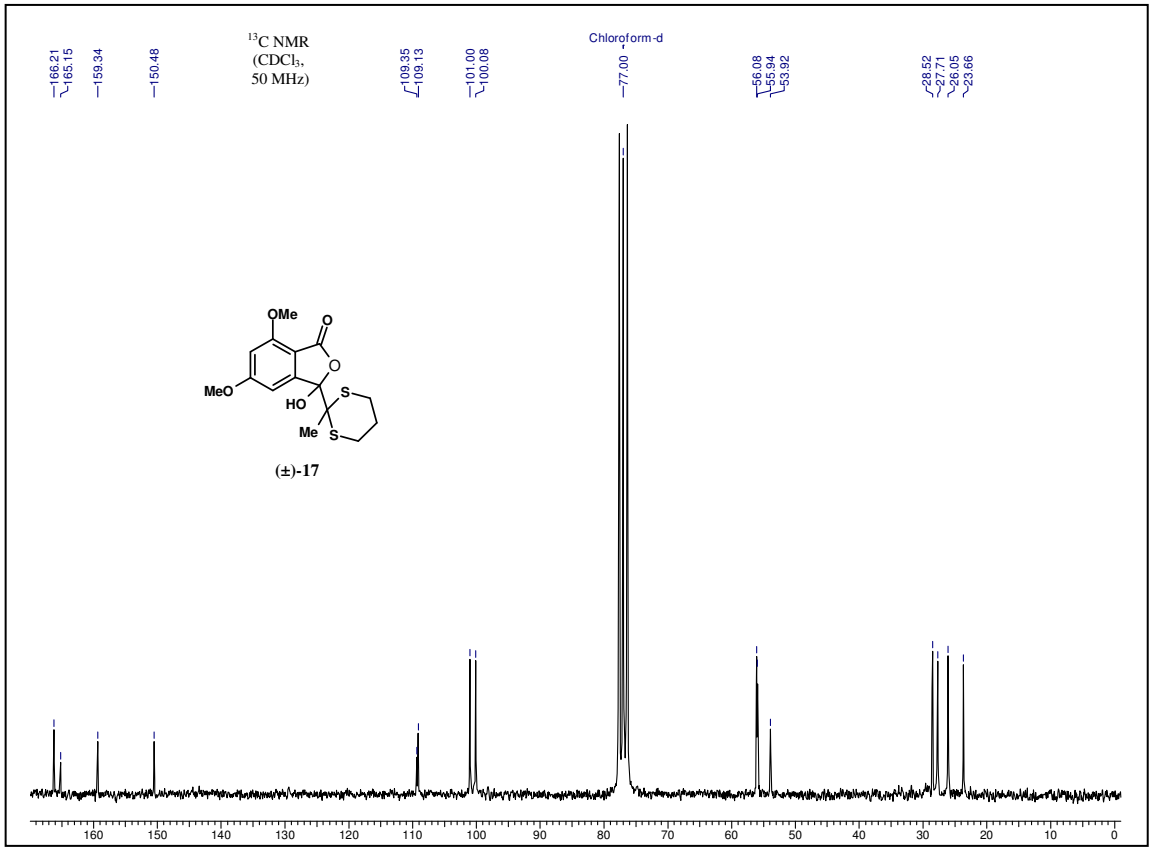
 **(±)-27** **$C_{12}H_{12}O_5$ (236)**	Colorless thick oil. **^1H NMR** ($CDCl_3$, 200 MHz) δ 2.20 (s, 3H), 3.89 (s, 3H), 3.97 (s, 3H), 5.52 (s, 1H), 6.49 (d, J = 2 Hz, 1H), 6.62 (t, J = 2 Hz, 1H). **Anal. Calcd** for $C_{12}H_{12}O_5$: C, 61.02; H, 5.12. Found: C, 61.11; H, 5.03.

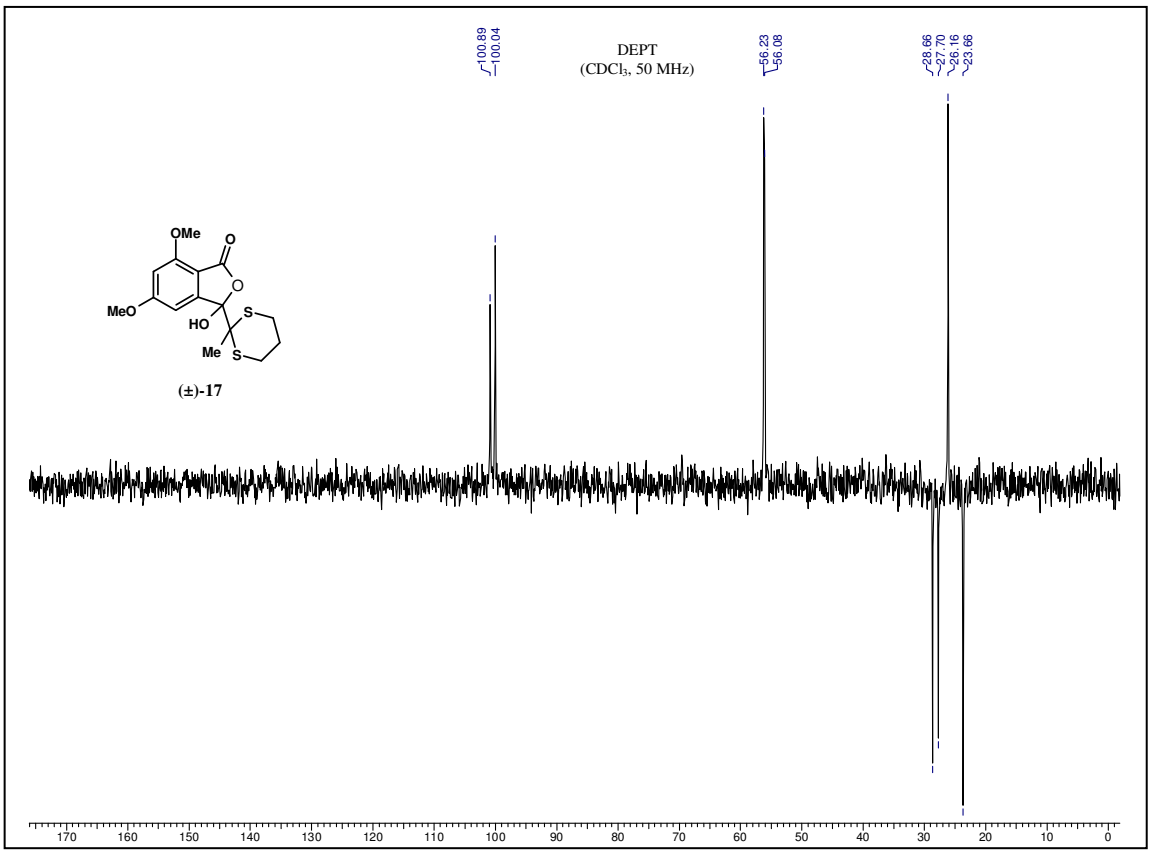
Methyl 4-formyl-2,6-dimethoxybenzoate (28). To a stirring solution of **26** (500 mg, 2.23 mmol) in DMSO (10 mL) at room temperature, lithium acetylide-ethylenediamine complex (246 mg, 2.68 mmol) was added. After stirring for 1 h at room temperature, water (2 mL) was added very slowly to the reaction mixture. Ethyl acetate (50 mL) was added to the reaction mixture and the separated organic layer was washed with brine thrice and dried over Na_2SO_4. Removal of the solvent in vacuo followed by silica gel column chromatographic purification of the residue using a mixture of 20% ethyl acetate in petroleum ether afforded **28** (360 mg, 72%) as a colorless thick oil.

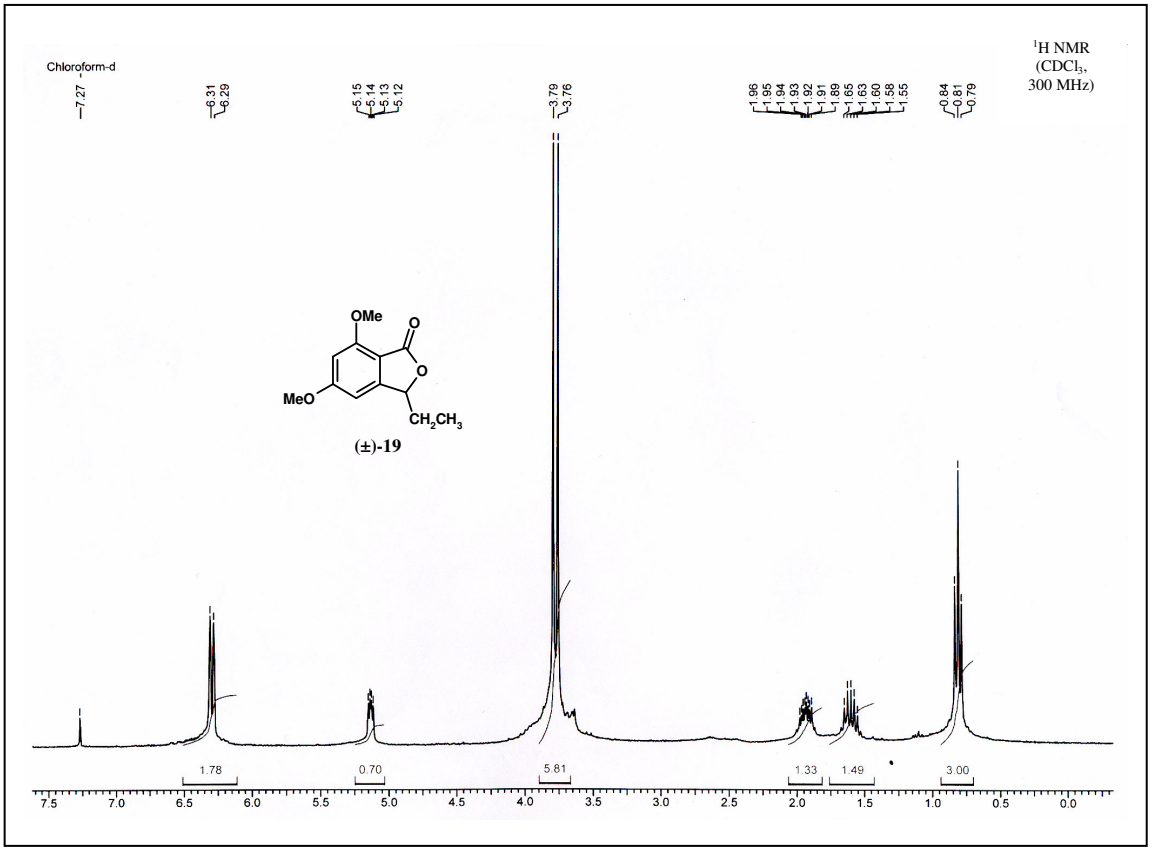
 **28** **$C_{11}H_{12}O_5$ (224)**	Colorless oil. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 3.90 (s, 6H), 3.94 (s, 3H), 7.08 (s, 2H), 9.95 (s, 1H). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 52.7, 56.3, 105.1, 118.3, 138.5, 157.8, 165.9, 191.3. **IR** ($CHCl_3$) 3422, 1732, 1705, 1587 cm^{-1}. **MS** (*m/z*) 225, 193. **Anal. Calcd** for $C_{11}H_{12}O_5$: C, 58.93; H, 5.39. Found: C, 59.01; H, 5.27.

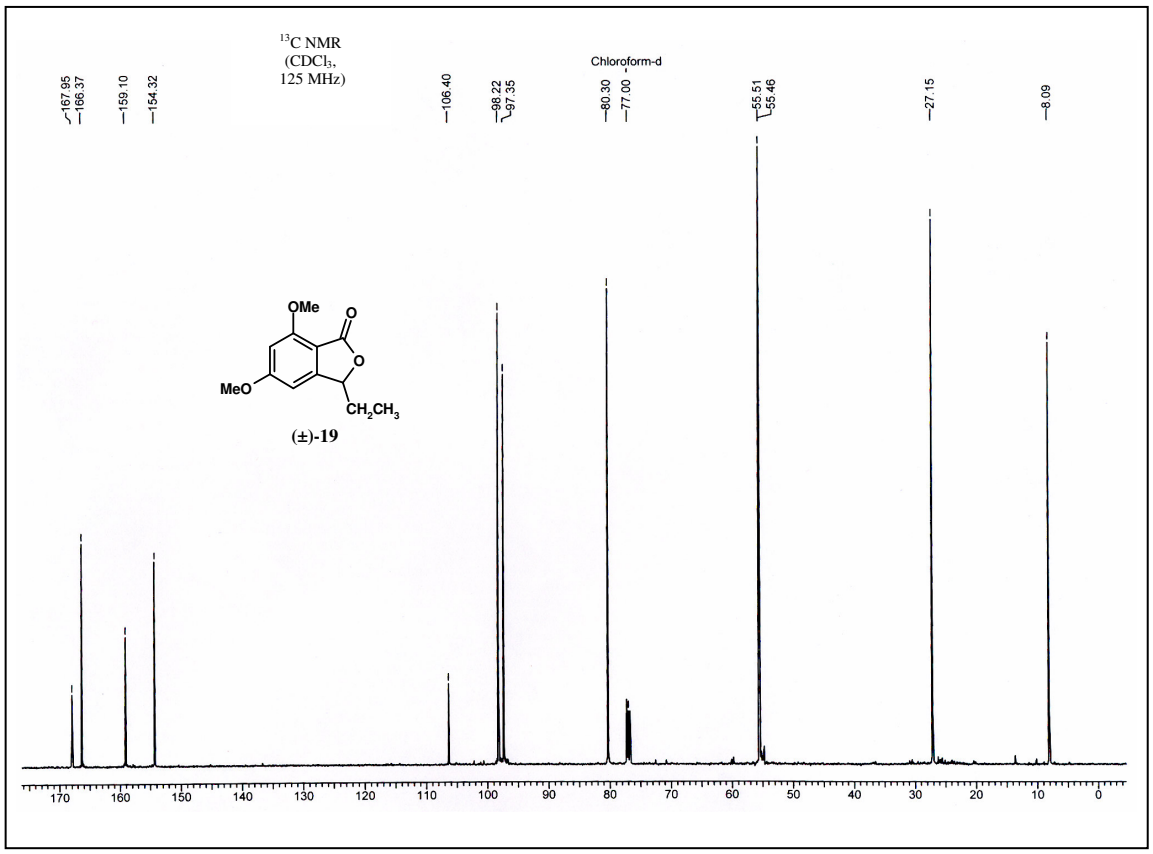
2E.6 Selected Spectra

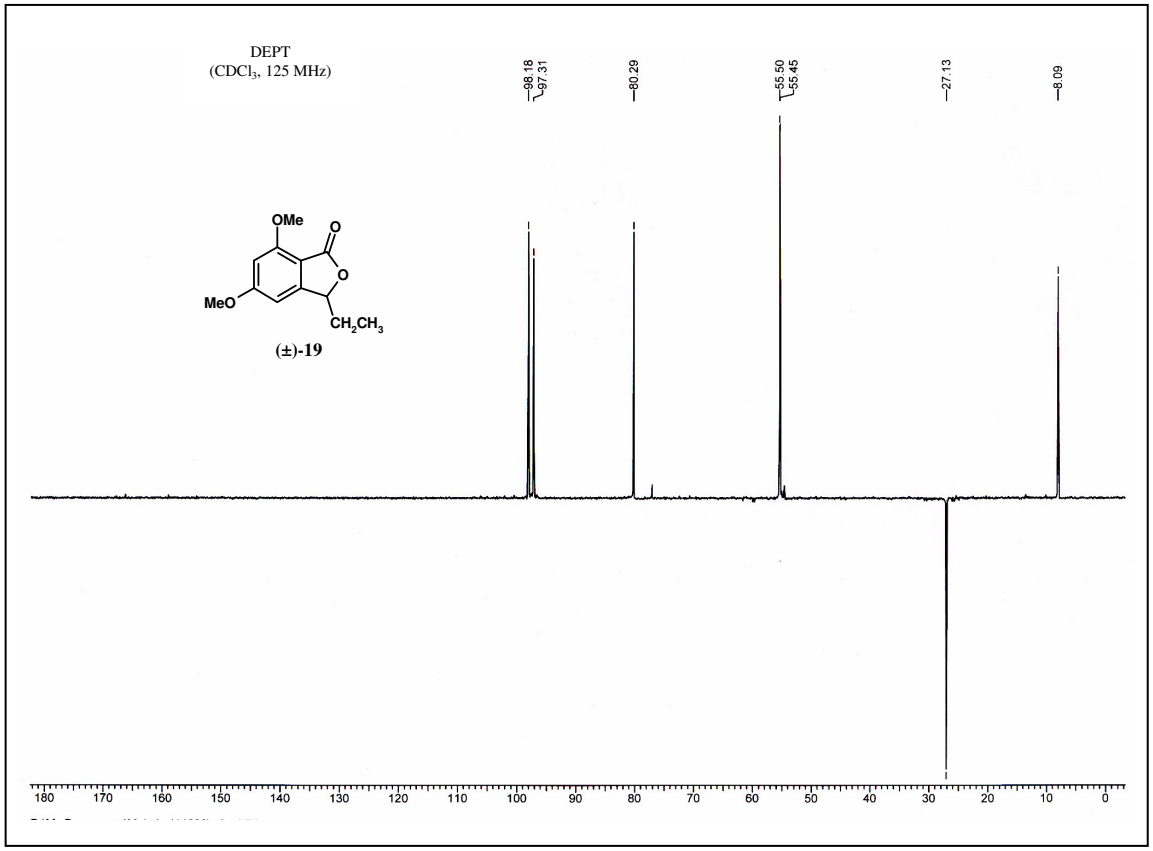

TMS
7.28
6.57
6.52
5.50
3.97
3.89
3.67
3.61
3.55
3.38
3.31
3.25
2.62
2.55
2.53
2.46
2.29
2.22
1.91
1.85
1.78
1.69
0.00
^{1}H NMR
($CDCl_3$,
200 MHz)
OMe
O
O
MeO
HO
S
Me
S
(±)-17
2.00
0.94
6.10
1.04
1.01
2.08
1.02
1.02
3.09
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

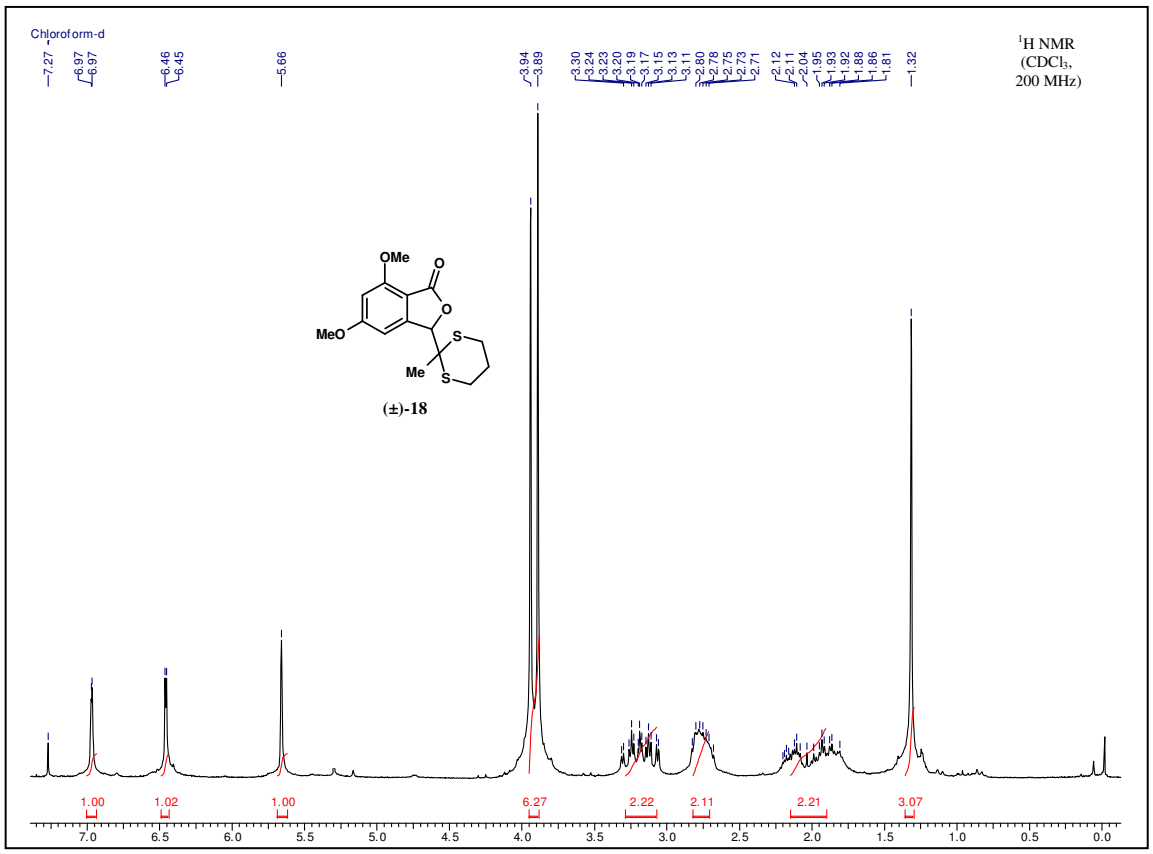

166.21
165.15
159.34
150.48
^{13}C NMR
($CDCl_3$,
50 MHz)
109.35
109.13
101.00
100.08
Chloroform-d
77.00
56.08
55.94
53.92
28.52
27.71
26.05
23.66
OMe
O
O
MeO
HO
S
Me
S
(±)-17
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

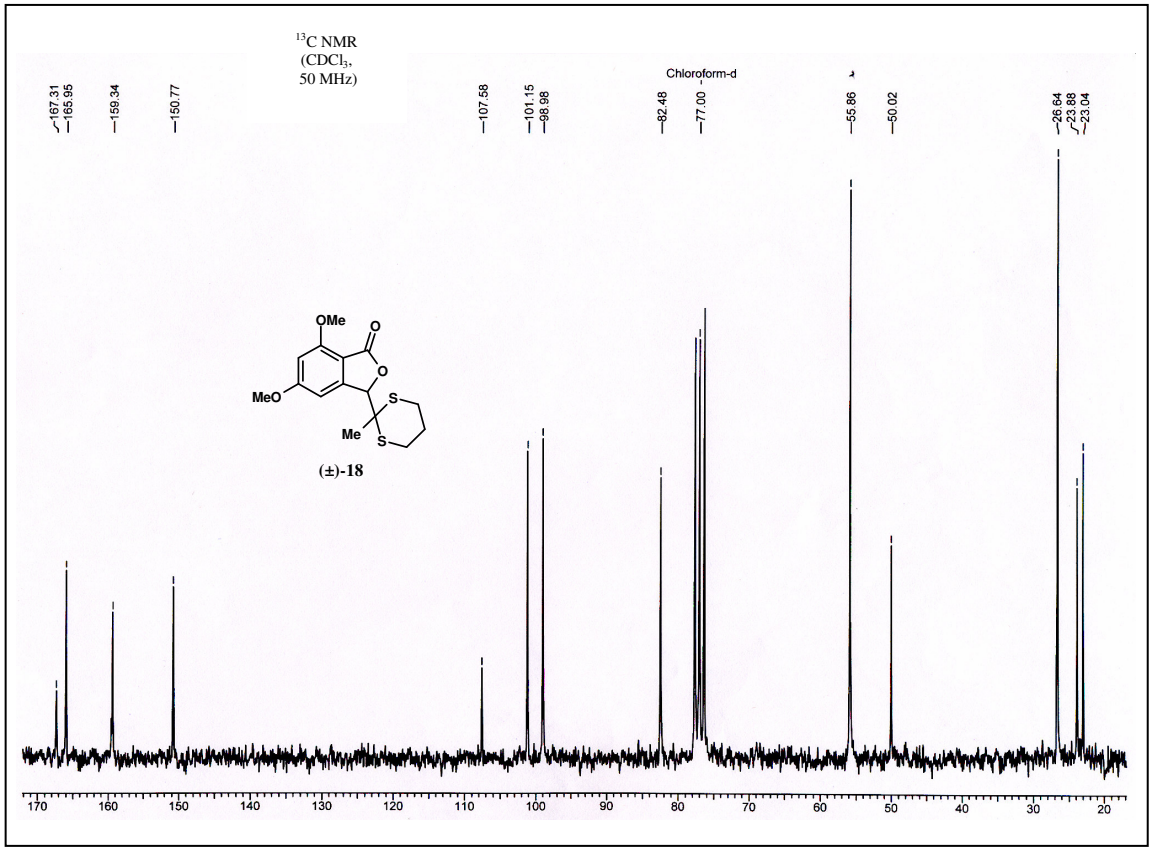

DEPT
(CDCl3, 50 MHz)
100.89
100.04
56.23
56.08
28.66
27.70
26.16
23.66
OMe
O
MeO
O
HO
S
Me
S
(±)-17

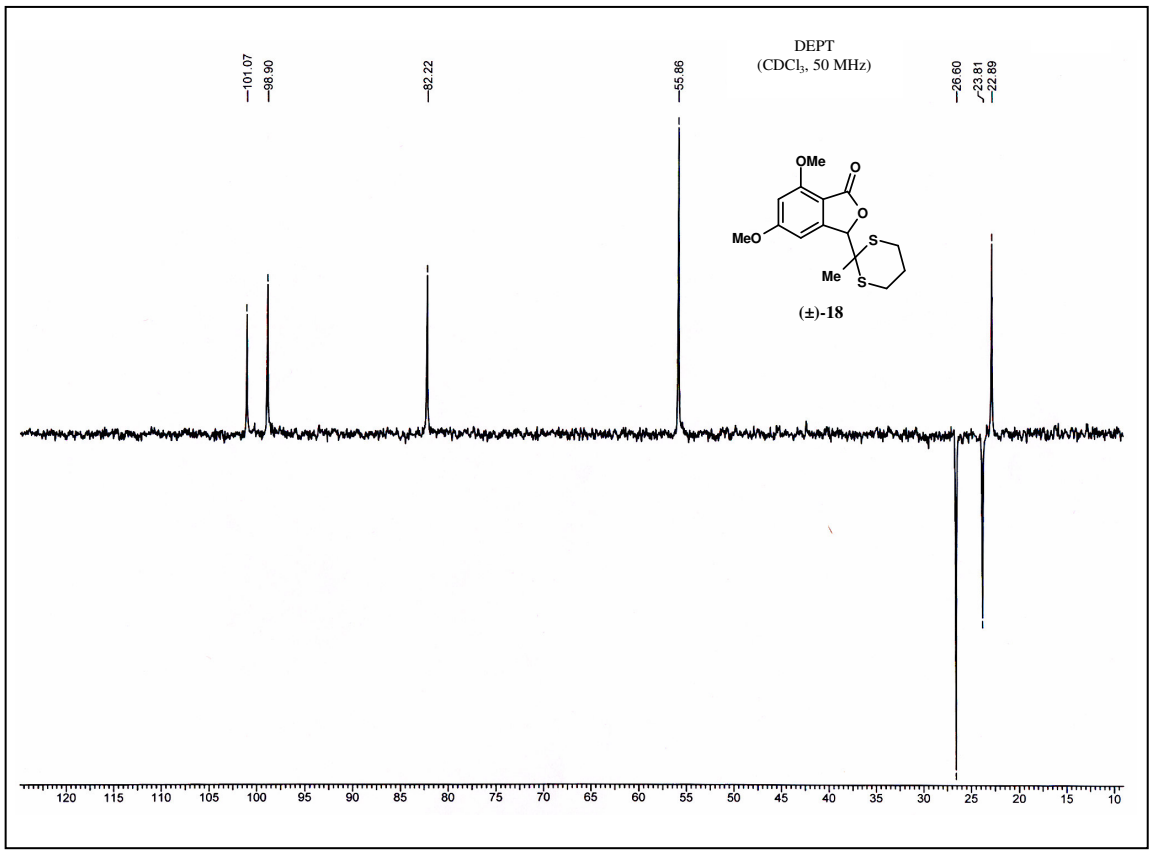

1H NMR
(CDCl3,
300 MHz)
Chloroform-d
7.27
6.31
6.29
5.15
5.14
5.13
5.12
3.79
3.76
1.96
1.95
1.94
1.93
1.92
1.91
1.89
1.65
1.63
1.60
1.58
1.55
0.84
0.81
0.79
OMe
O
O
MeO
CH2CH3
(±)-19
1.78
0.70
5.81
1.33
1.49
3.00

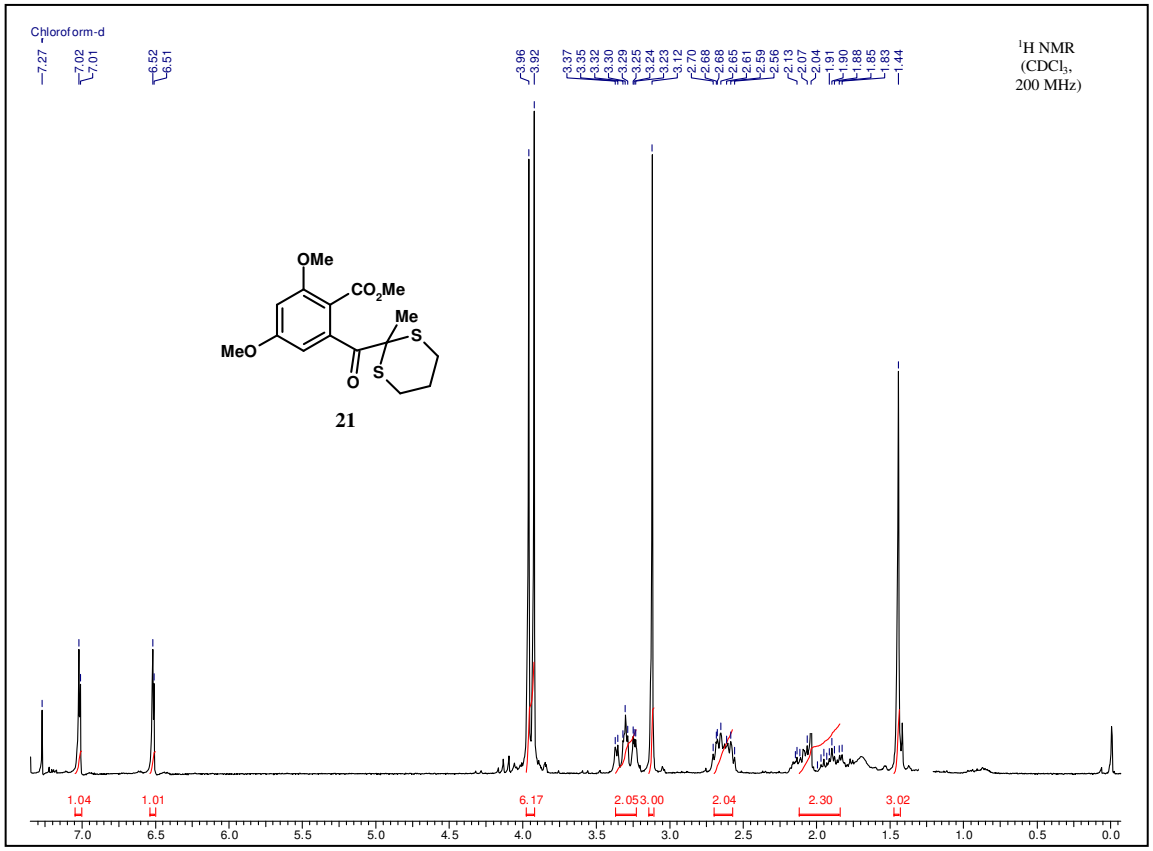

^{13}C NMR
(CDCl$_3$,
125 MHz)
Chloroform-d
167.95
166.37
159.10
154.32
106.40
98.22
97.35
80.30
77.00
55.51
55.46
27.15
8.09
OMe
O
O
MeO
CH$_2$CH$_3$
(±)-19

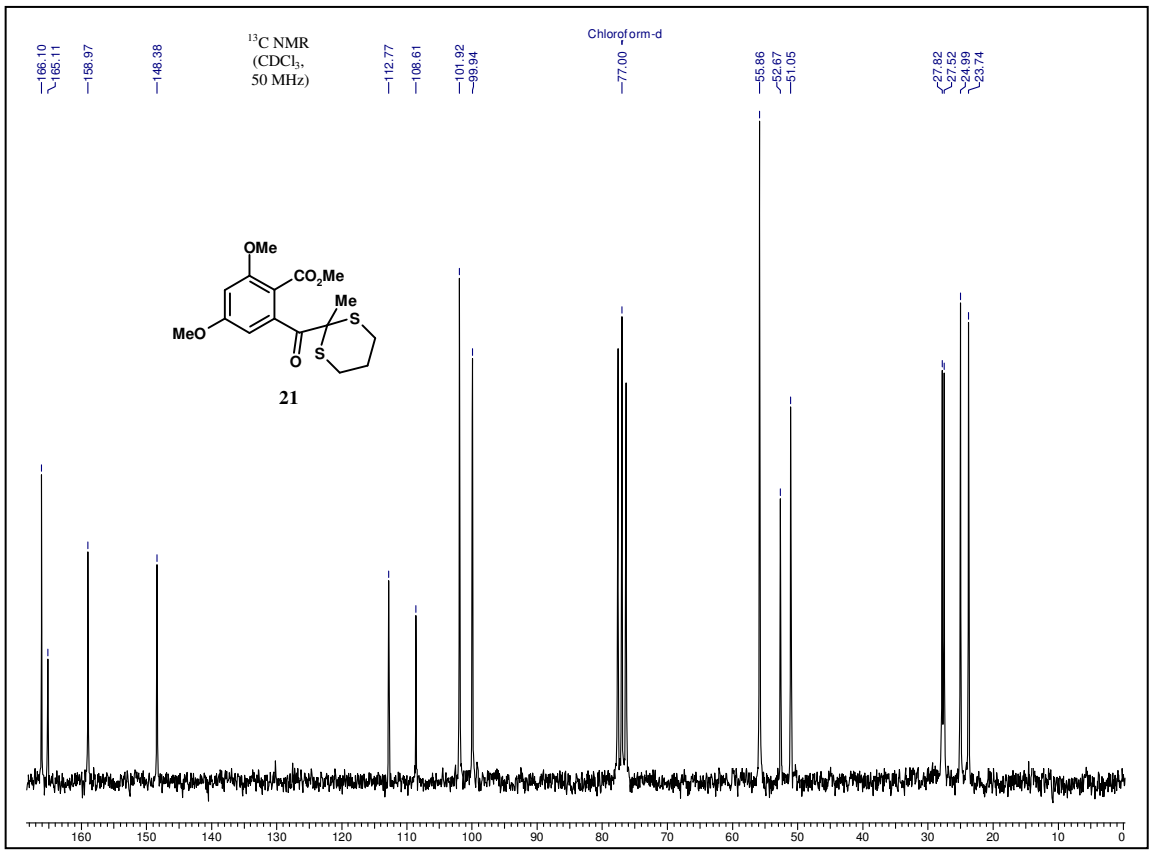

DEPT
(CDCl$_3$, 125 MHz)
98.18
97.31
80.29
55.50
55.45
27.13
8.09
OMe
O
O
MeO
CH$_2$CH$_3$
(±)-19

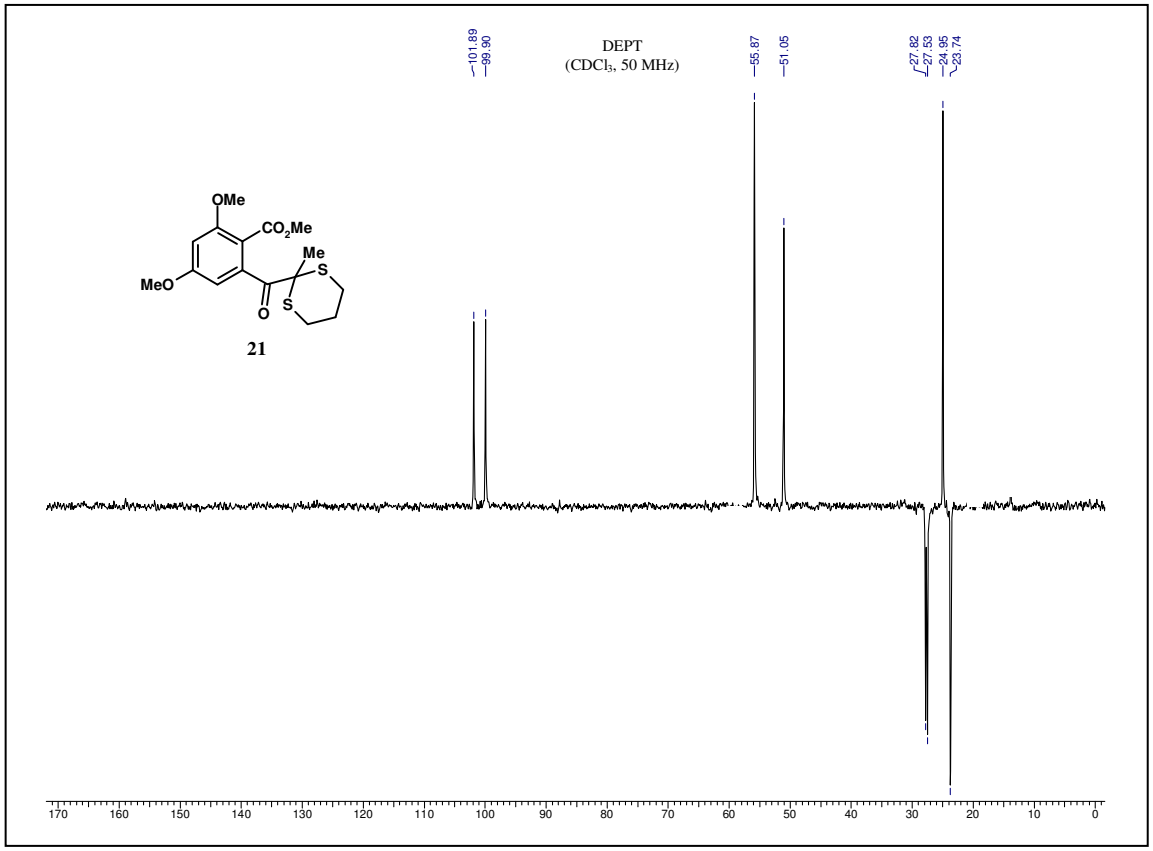

Chloroform-d
7.27
6.97
6.97
6.46
6.45
5.66
3.94
3.89
3.30
3.24
3.23
3.20
3.19
3.17
3.15
3.13
3.11
2.80
2.78
2.75
2.73
2.71
2.12
2.11
2.04
1.95
1.93
1.92
1.88
1.86
1.81
1.32
1H NMR
(CDCl3,
200 MHz)
OMe
O
O
MeO
S
Me
S
(±)-18
1.00
1.02
1.00
6.27
2.22
2.11
2.21
3.07
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

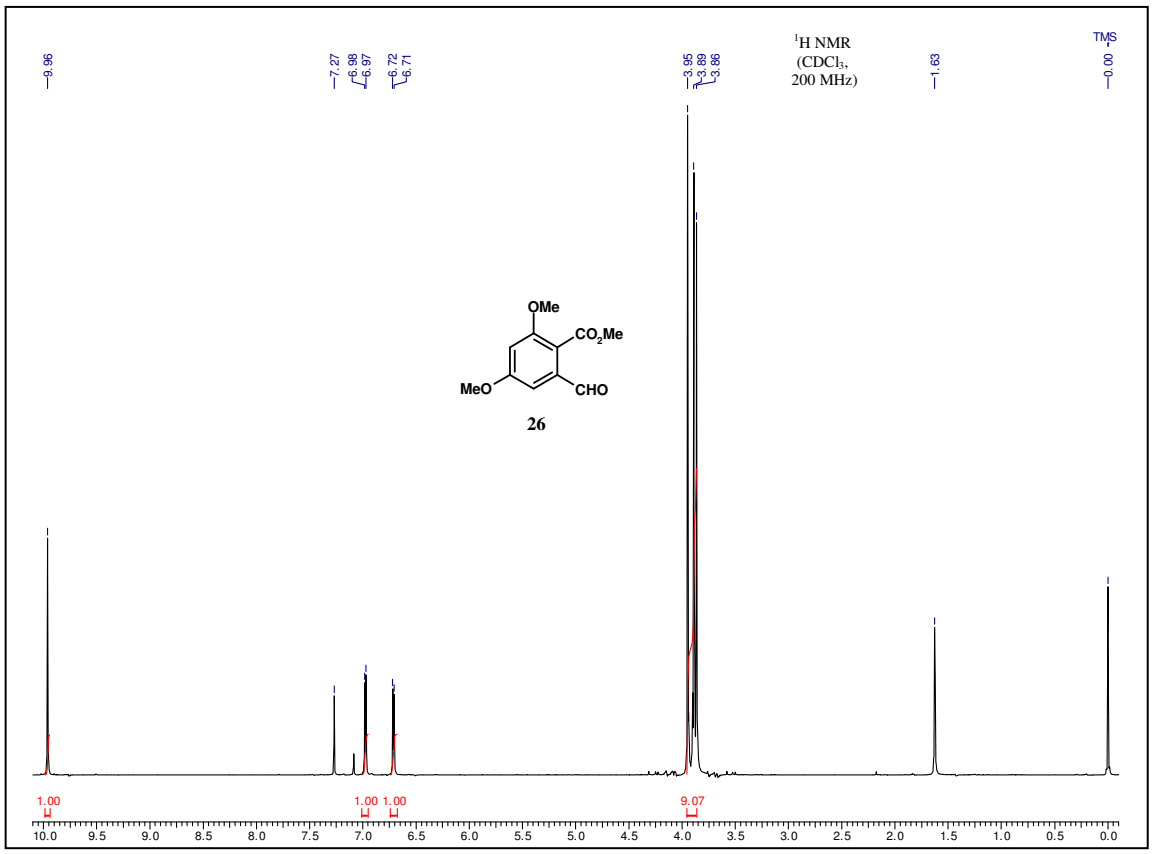

13C NMR
(CDCl3,
50 MHz)
Chloroform-d
167.31
165.95
159.34
150.77
107.58
101.15
98.98
82.48
77.00
55.86
50.02
26.64
23.88
23.04
OMe
O
O
MeO
S
Me
S
(±)-18
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20

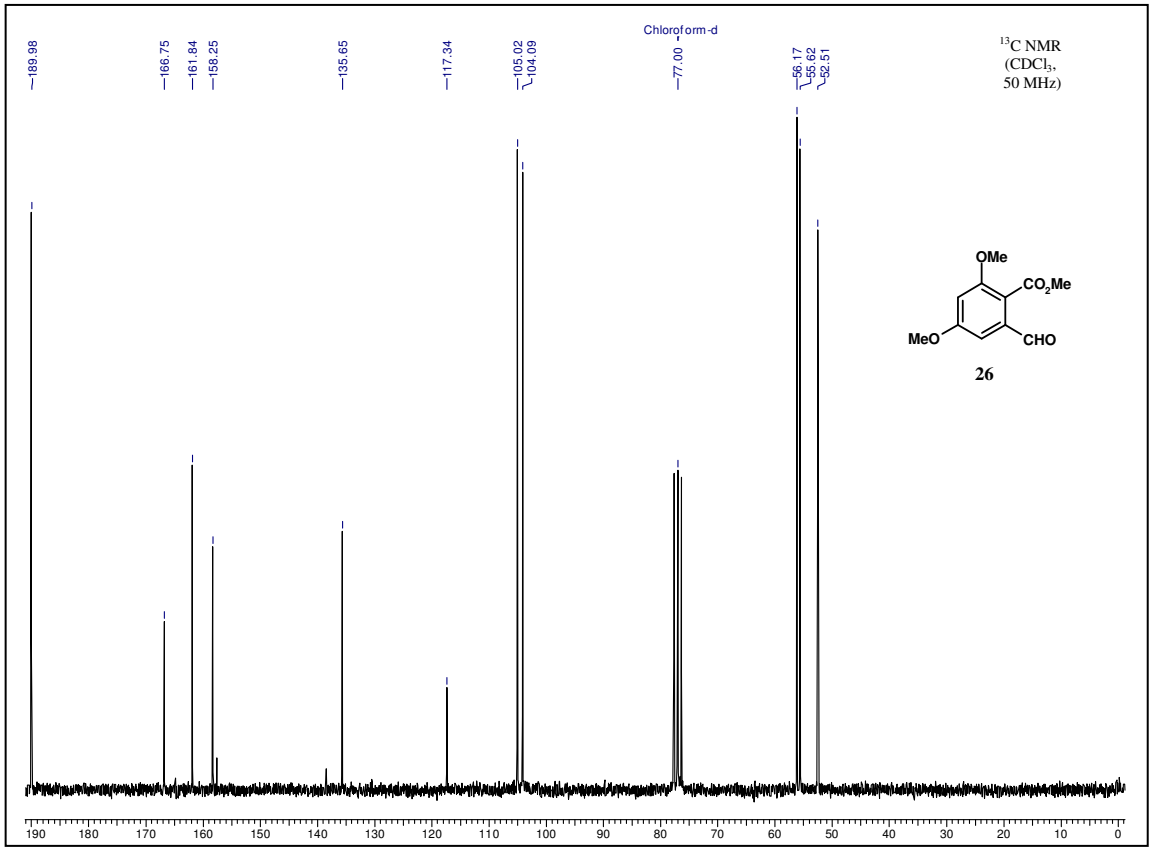

DEPT
(CDCl3, 50 MHz)
101.07
98.90
82.22
55.86
26.60
23.81
22.89
OMe
O
O
MeO
S
Me
S
(±)-18

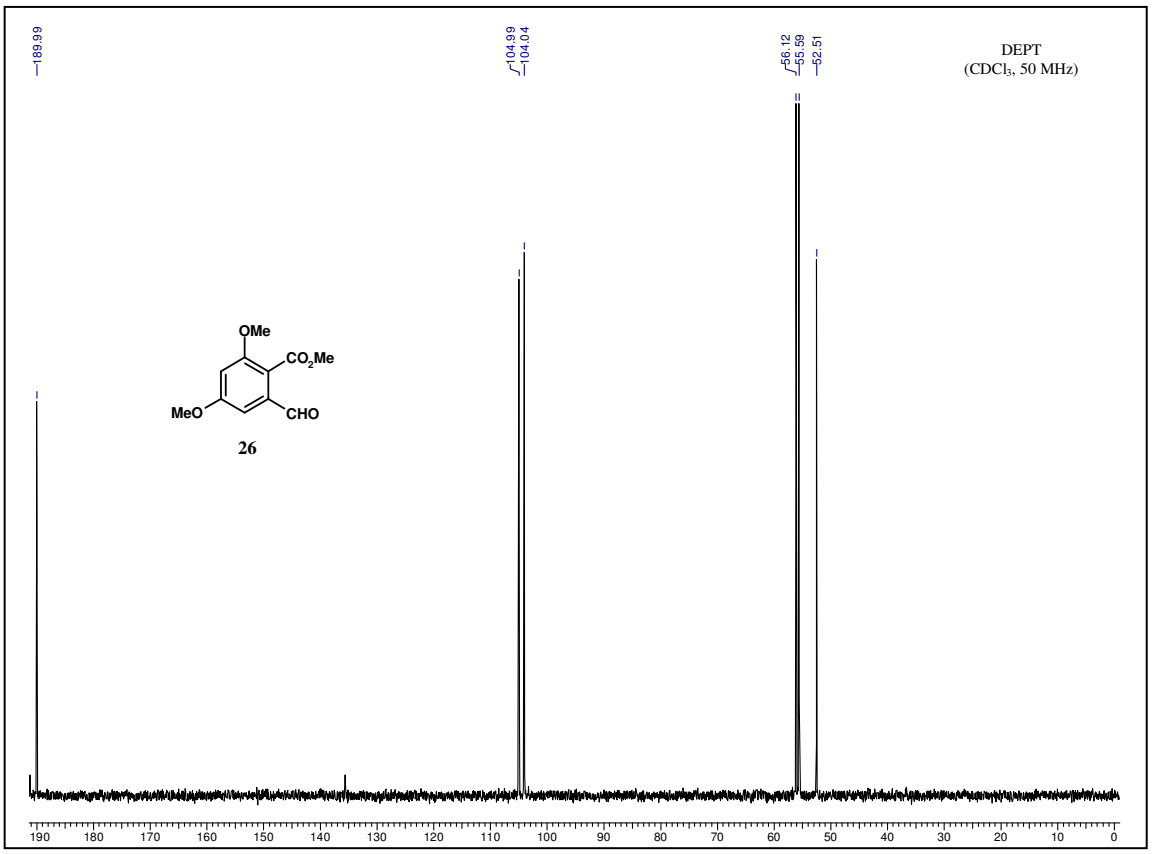

Chloroform-d
7.27
7.02
7.01
6.52
6.51
3.96
3.92
3.37
3.35
3.32
3.30
3.28
3.25
3.24
3.23
3.12
2.70
2.68
2.68
2.65
2.61
2.59
2.56
2.13
2.07
2.04
1.91
1.90
1.88
1.85
1.83
1.44
1H NMR
(CDCl3,
200 MHz)
OMe
CO2Me
Me
MeO
S
O
S
21
1.04
1.01
6.17
2.05
3.00
2.04
2.30
3.02

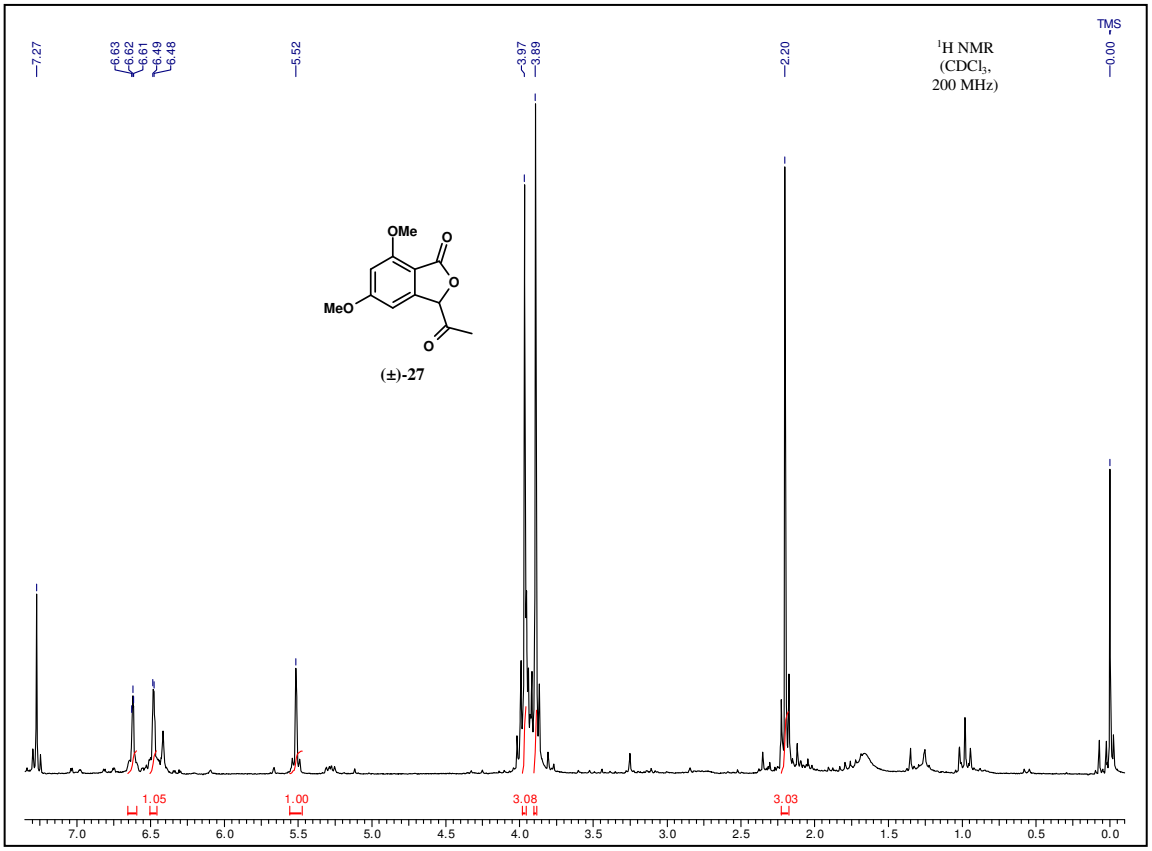

166.10
165.11
158.97
148.38
^{13}C NMR
($CDCl_3$,
50 MHz)
112.77
108.61
101.92
99.94
Chloroform-d
77.00
55.86
52.67
51.05
27.82
27.52
24.99
23.74
OMe
CO_2Me
Me
MeO
S
S
O
21
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

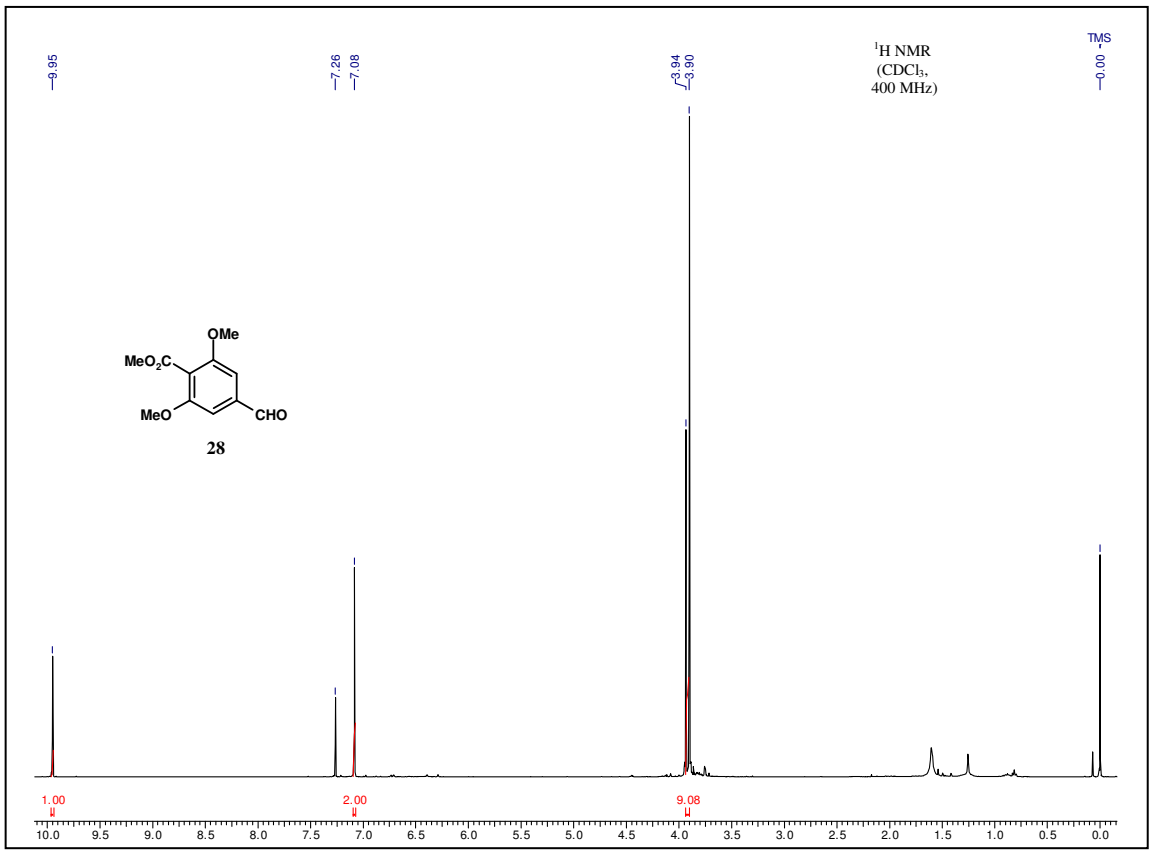

101.89
99.90
DEPT
($CDCl_3$, 50 MHz)
55.87
51.05
27.82
27.53
24.95
23.74
OMe
CO_2Me
Me
MeO
S
S
O
21
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

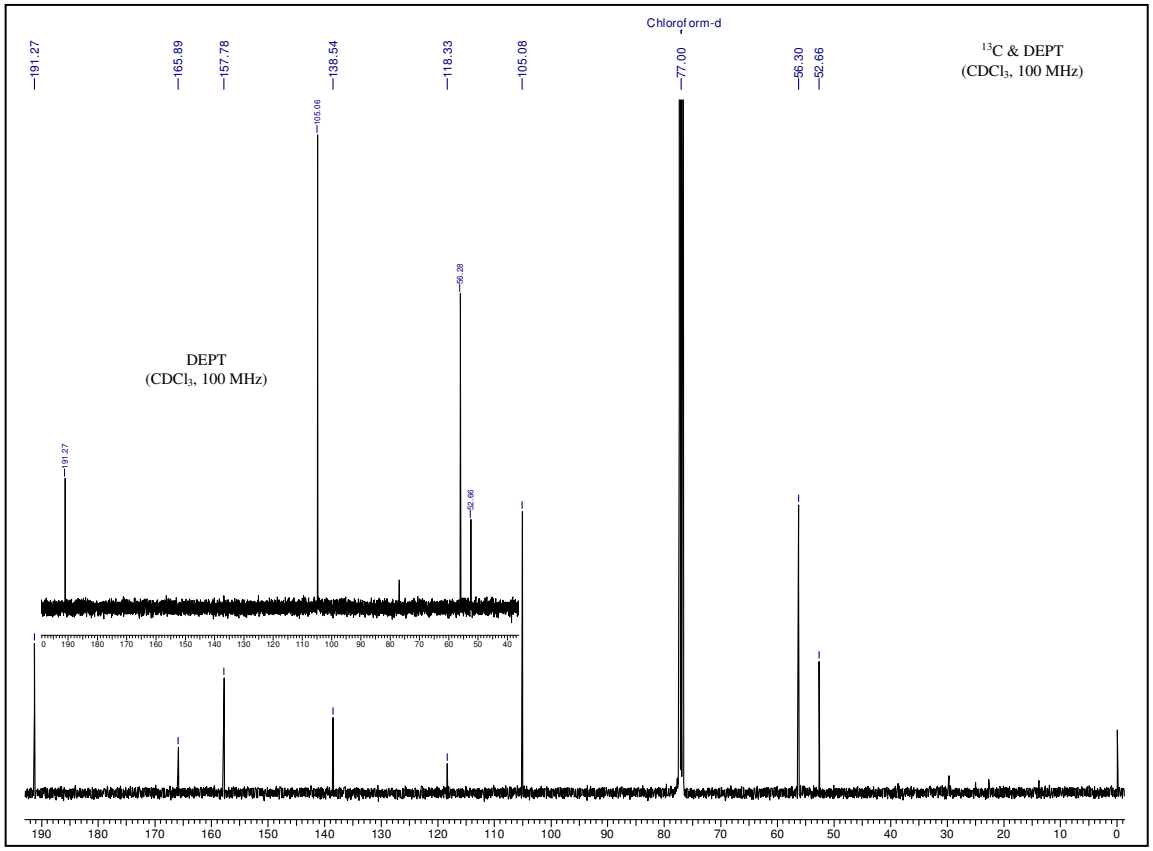

^{1}H NMR
(CDCl$_3$,
200 MHz)
TMS
9.96
7.27
6.98
6.97
6.72
6.71
3.95
3.89
3.86
1.63
0.00
OMe
CO$_2$Me
MeO
CHO
26
1.00
1.00
1.00
9.07


^{13}C NMR
(CDCl$_3$,
50 MHz)
Chloroform-d
189.98
166.75
161.84
158.25
135.65
117.34
105.02
104.09
77.00
56.17
55.62
52.51
OMe
CO$_2$Me
MeO
CHO
26


189.99
104.99
104.04
56.12
55.59
52.51
DEPT
(CDCl3, 50 MHz)
OMe
CO2Me
MeO
CHO
26


7.27
6.63
6.62
6.61
6.49
6.48
5.52
3.97
3.89
2.20
TMS
0.00
1H NMR
(CDCl3,
200 MHz)
OMe
MeO
(±)-27
1.05
1.00
3.08
3.03


^{1}H NMR
($CDCl_3$,
400 MHz)
TMS
9.95
7.26
7.08
3.94
3.90
0.00
OMe
MeO_2C
MeO
CHO
28
1.00
2.00
9.08


Chloroform-d
^{13}C & DEPT
($CDCl_3$, 100 MHz)
191.27
165.89
157.78
138.54
118.33
105.08
77.00
56.30
52.66
105.06
56.28
52.66
DEPT
($CDCl_3$, 100 MHz)
191.27

2E.7 References

1. Cui, C.-B.; Ubukata, M.; Kakeya, H.; Onose, R.; Okada, G.; Takahashi, I.; Isono, K.; Osada, H. *J. Antibiot*. **1996**, *46*, 216.
2. Osada, H.; Koshino, H.; Kudo, T.; Onose, R.; Isono, K. *J. Antibiot*. **1992**, *45*, 189.
3. Ayer, W. A.; Attah-Poku, S. K.; Browne, L. M.; Orszanska, H. *Can. J. Chem*. **1987**, *65*, 765.
4. Andersen, B. *Antonie van Leeuwenhook* **1991**, *60*, 115.
5. Nomoto, S.; Mori, K. *Liebigs Ann*. **1997**, 721.
6. (a) Watanabe, H.; Uchida, K.; Kitahara, T. *Heterocycles* **1997**, *46*, 45. (b) Uchida, K.; Watanabe, H.; Usui, T.; Osada, H.; Kitahara, T. *Heterocycles* **1998**, *48*, 2049.
7. Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhabg, X.-L. *J. Org. Chem*. **1992**, *57*, 2768.
8. Dess, D. B.; Martin, J. C. *J. Org. Chem*. **1983**, *48*, 4156.
9. (a) Gogoi, S.; Argade, N. P. *Tetrahedron* **2004**, *60*, 9093. (b) Mhaske, S. B.; Argade, N. P. *Tetrahedron* **2004**, *60*, 3417. (c) Mangaleswaran, S.; Argade, N. P. *Synthesis* **2004**, 1560. (d) Mhaske, S. B.; Argade, N. P. *J. Org. Chem*. **2001**, *66*, 9038. (e) Kar, A.; Argade, N. P. *J. Org. Chem*. **2002**, *67*, 7131. (f) Easwar, S.; Argade, N. P. *Synthesis* **2006**, 831. (g) Gogoi, S.; Argade, N. P. *Tetrahedron* **2006**, *62*, 2715. (h) Baag, M. M.; Argade, N. P. *Synthesis* **2006**, 1005. (i) Argade, N. P.; Balasubramaniyan, V. *Heterocycles* **2000**, *53*, 475 and references cited therein.
10. Franck, B.; Backhaus, H.; Rolf, M. *Tetrahedron Lett*. **1980**, *21*, 1185.
11. Parker, K. A.; Spero, D. M.; Koziski, K. A. *J. Org. Chem*. **1987**, *52*. 183.

2F Overall Conclusions and Perspectives

In the present chapter, we have described our studies towards the total synthesis of some biologically important and structurally interesting natural products and analogues. We have presented a remarkably tuned regioselectivities in the condensation of 3,5-dihydroxyphthalide with several α,β-unsaturated aldehydes using 1,3-diaza bases and neutral conditions to exclusively obtain the linear (65-81%) and angular (51-60%) bioactive natural and unnatural benzopyran derivatives in one step via phenol-keto resonance and facile biogenetic type synthesis of aldose reductase inhibitor salfredin B_{11} and the phthalidochromine. Herein, a concrete evidence for phenol-keto resonance involved during the process of condensation has also been provided by deuterium labeling experiments.

A facile five step synthesis of naturally occurring 1,3,7-trihydroxyxanthone from 1,3,5-trimethoxybenzene with 62% overall yield has been also portrayed employing a base-catalyzed intramolecular cyclization via the oxa-Michael addition elimination pathway. The regioselective coupling reactions of 1,3,7-trihydroxyxanthone with prenal in the presence of calcium hydroxide at room temperature and under thermal condition at 140-150 ^{o}C have been demonstrated to exclusively obtain the natural products, antimicrobial and anti-fish poison osajaxanthone in 75% yield and nigrolineaxanthone F in 98% yield respectively.

We have also utilized the regioselective condensation of several α,β-unsaturated aldehydes with dihydroxyphthalides, natural resorcyclic acid derivative and trihydroxy benzophenone towards the synthesis of some natural and unnatural 2,2-dialkylbenzopyrans and completed the synthesis of cannabichromeorcinic acid, potent anti-HIV agent daurichromenic acid, clusiaphenone A and clusiachromene C.

We have also designed a phenol driven intramolecular diastereoselective thermal/base catalyzed dipolar [2+2] annulation approach towards the construction of bioactive complex natural and unnatural hexahydrooxacyclobutaindanes and completed the first total synthesis of clusiacyclol A and clusiacyclol B. We feel that the present protocol would be instrumental in providing necessary diastereoselectivity and regiochemical control for the easy construction of several natural oxacyclobutaindanes. Another useful contribution in this present study resulted from three novel thermal framework rearrangements producing thermodynamically controlled natural oxabicyclononane skeleton and

isopropylidinecyclopentylbenzopyrans. The effects of the nature and the position of phenolic groups in the starting phenolic substances on the course of these cycloaddition reactions have been also well described.

An efficient six-steps first total synthesis of a novel microbial secondary metabolite, anti-*helicobacter pylori* CJ-13,015 has been demonstrated with 65% overall yield. Herein, an elegant means of remote 1,4-diketone functionalization by using chemoselective hydrolysis of 2,5-disubstituted furan avoiding any kind of protection-deprotection chemistry is noteworthy.

A six steps-synthesis of the dimethylacetophthalidin has been accomplished with 32% overall yield. The conversion of dimethylacetophthalidin to the naturally occurring mammalian cell cycle progression inhibitor acetophthalidin is in active progress.

All these studies also provided us a nice opportunity for learning a lot of new basic and applied chemistry not just from our work but also from the vast literature in this field. We also feel that the approaches which we have developed are quite general and biogenetic in nature and would be useful in designing several important complex natural products and analogues for structure activity relationship studies.

The benzopyran chemistry has enjoyed a glorious history with a nature gifted avenue. A look at the recent literature also revealed that the histogram of the benzopyran chemistry is in escalating slope and the increasing medicinal and pharmaceutical demands for natural and designed benzopyrans would maintain the high positive slope in the present day world of synthetic organic chemistry (& medicine). Vast array of compounds can be generated by permutations and combinations of natural and unnatural phenolic substances and α,β-unsaturated aldehydes for the structure activity relationship studies. Development of new biogenetic, cost effective and environment friendly approaches is real challenge. In our opinion, a combination of the natural and designed benzopyrans could serve as a launching pad to fight against present generation diseases. 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. DBU-Induced Phenol-Keto Resonance in 3,5-Dihydroxyphthalide: Regioselectivities in Condensations with α,β-Unsaturated Aldehydes: Facile Synthesis of Bioactive Natural and Unnatural Benzopyrans
   M. Mondal and N. P. Argade*
   Synlett **2004**, 1243.

2. Synthesis of a new microbial secondary metabolite: anti-*helicobacter pylori* CJ-13,015
   M. Mondal and N. P. Argade*
   Tetrahedron Lett. **2004**, *45*, 5693.

3. Sodium Methylsulfinylmethylide, A Versatile Reagent
   M. Mondal
   Synlett Spotlight 139, **2005**, 2697.

4. A Facile Synthesis of 1,3,7-Trihydroxyxanthone and its Regioselective Coupling Reactions with Prenal: Simple and Efficient Access to Osajaxanthone and Nigrolineaxanthone F
   M. Mondal, V. G. Puranik and N. P. Argade*
   J. Org. Chem. **2006**, *71*, 4992.

5. A Facile Phenol Driven Intramolecular Diastereoselective Thermal/Base Catalyzed Dipolar [2+2] Annulation Reactions: An Elegant Access to Complex Bioactive Natural and Unnatural Benzopyran Congeners
   M. Mondal, V. G. Puranik and N. P. Argade*
   J. Org. Chem. **2007**, *72*, 2068.

6. A Simple Approach Towards Mammalian Cell Cycle Progression Inhibitor Acetophthalidin
   M. Mondal and N. P. Argade*
   Unpublished result.

ERRATUM