INVERSE ELECTRON DEMAND DIELS-ALDER BASED APPROACH TO 6H-DIBENZO [b,d] PYRAN-6-ONES AND ITS APPLICATION IN TARGET-ORIENTED SYNTHESIS

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Inverse Electron Demand Diels–Alder Based Approach to *6H*-Dibenzo[*b*,*d*]pyran-6-ones and Its Application in Target-Oriented Synthesis

by

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A thesis submitted to the

School of Graduate Studies

in partial fulfillment of the

requirements for the degree of

Doctor of Philosophy

Memorial University of Newfoundland

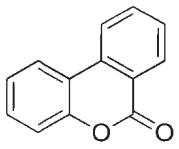
St. John's, Newfoundland and Labrador, Canada

2012

(Defended on 29th October, 2012)

Abstract

This thesis deals with the exploration and the development of Inverse Electron-Demand Diels–Alder (IEDDA)-based methodologies to access 6*H*-dibenzo[*b,d*]pyran-6-ones (DBPs) and their application in target-oriented synthesis. Due to its importance throughout this dissertation, the Diels-Alder reaction is discussed in some detail in Chapter 1. This is followed by a discussion of the evolution of research on the IEDDA reaction in the Bodwell group. A detailed investigation of the methods that were developed to produce DBPs is described in Chapter 2 and Chapter 3. Furthermore, the scope of these methodologies was demonstrated by applying these approaches to the synthesis of natural and non-natural products. In this regard, their use in the synthesis of elaborated chiral pyrenophanes (non-natural products) is presented in Chapter 4, and their application in the synthesis of natural products such as Cannabinol and Defucogilvocarcin V is displayed in Chapter 2 and Chapter 5.



6*H*-dibenzo[*b,d*]pyran-6-one

Acknowledgements

First and foremost, I would like to thank my supervisor, Prof. Graham J. Bodwell, for giving me the opportunity to join his research group. Over the past five years, as a graduate student, it has been a great pleasure being associated with him and watching his passion for chemistry. His ability to bring meaningful and insightful discussion on any aspect of organic chemistry is very inspiring. As a teacher, he makes sure that he is communicating from the understanding levels of students. As a supervisor, the amount of effort he puts in moulding the students to next levels is amazing, starting from how to use the chemical terminology accurately to reporting one's results in articles. He insists on "paying attention to details," as it will make students look good and gain confidence as they progress in their programme.

Personally, I have lots of memories with Graham at both personal and professional level during my programme and they are going to stay for a long time. To begin with, I still remember the day I met Graham on my first day in the department. Amit Kudale, a former graduate student of the Bodwell group, took me to Graham's office and introduced me to him. The chat was very casual and brief and at the end of it he said, "you are not working for me but for youself, remember this always." It took a while, probably a year, for me to realize it means the motivation to work hard should come from within myself. As a supervisor, he never pushed or forced me to do what he wanted or the way he wanted things to be done. I must thank Graham for giving me the freedom to work on the projects I wanted, yet watching critically and giving valuable suggestions whenever needed. I never hesitated to knock on his office door when I had a

problem or some exciting result to share. Despite his hectic work schedule, he always found time for me instantly in most cases, and in exceptions he would provide the next possible time. His enthusiasm to discuss the issues associated with the projects and encouragement when things are not falling in place is unforgettable. To say precisely, as a supervisor he has always been available to me on a daily basis. On a personal level, I like his simplicity and friendly nature as he enjoys nonchemistry-related conversations as well with the group members. Another important quality I noticed in him is generosity, as he often takes the group to lunch or dinner.

One of the best things that had happened while I was graduate student was the International Conference on Heterocyclic Chemistry (ICHC-2009) in St. John's, one of the best conferences in the field of organic chemistry. Many eminent scientists from around the globe attended this event. It was my first conference as a graduate student, and it was a delight to listen to the exciting chemistry going on in their laboratories in their own words. The most important thing that happened to me at this conference was the inspiration I derived by listening to the talks of fellow graduate students from other universities. In the years to come, this really helped me to work with a lot more focus on the completion of projects. I would like to thank the chair of this conference, Dr. Mohsen Daneshtalab, for his efforts to bring this conference to St. John's.

I would like to convey my heartful thanks to the Bodwell group members during my time for keeping the lab environment a peaceful and joyful place to work. Baozhong Zhang, Amit Kudale, Bradley Merner, Tieguang Yao, Anh Thu Dang, Salah Al-Dukhi and Jennifer Swyers were the students in the group when I joined. I am thankful to all of

them for welcoming me to the group and helping me to find things in the lab and answering to my queries. Particularly, Amit had helped me in finding an accommodation by the time I reached St. John's and took me around to complete the registration formalities. Yixi Yang, who joined the group a semester later to me, was a good friend to me. Since we were working on the same side of the lab, we used to talk a lot while working. Soon after Yixi, Venkataramana Gandikota joined the group as a postdoc. We used to debate on many issues, mostly on chemistry, and it was a learning experience with him. His interest and follow up on the ongoing research in material-related chemistry was very inspiring and he often used to share news and views with me. Kiran Unikela joined the group in the summer of 2009, and was lucky not to be welcomed by St. John's bitter weather. He has such a unique personality, expresses his feelings freely and is always joyful. It has been a nice experience working with him. Mark MacKinnon, though he joined the group much later than me, has been great in taking care of the group responsibilities, especially ordering chemicals. He is very cool tempered and it has been a good experience working with him too. The last one of my long-term associates in the group is Kerry-Lynn Williams. She is one the most active people I have ever seen in my life. With her graceful smile and energetic manner, she always keeps the group lively. More recently, Joseph and Jill joined the group and it has been wonderful to interact with them as well. I would like to wish Kiran, Mark, Kerry and Joseph every success in their research endeavours. Two other visiting graduate students I spent good time with were Michal Buchta of the Czech Republic and Haruka Omachi of Japan. They were very friendly and it was really a great experience spending time with students from different

countries. I would also like to mention Honours students that I have met at Memorial during my time in the group, Simon Brake and Wilson Humphries, with whom I used to spend good times chatting to. Jay Duffett and Melissa O'Brien are two other undergraduates who I enjoyed talking to and they were really nice. I would also thank Bod group former graduate student and a current professor at Mount Saint Vincent University, Ian R. Pottie, whose thesis has served as a reference and base for my projects.

Beyond the Bodwell group, other organic groups have also been so friendly that I never had the answer of "NO", when I needed something from them. The Georghiou group, especially Ahmed Zein, Tayel Al-hujran and Gopikishore Valluru has been very helpful and friendly to me. From the Pansare group, Vikrant Adsool was one of the biggest inspirations for me with his productivity in research. Rajnikant Lingampally was very helpful for me in the department at the early part of my programme and I thank him for that. Though Rajender Dyapa, Eldho Paul, Kaivalya Kulkarni and Rakesh Thorat joined the programme much later than me, they mingled well with me and have been very friendly. The Zhao group, especially Karimulla Mulla, Yousuf Pourghaz, Kathleen Woolridge and Stephen Bouzan have been very helpful. Another guy I should mention here is Prateek Dongare of the Thompson group, who has worked on a collaborative project and he has been a good friend as well.

The department's general office staff is gratefully thanked for their help during my programme. My special thanks goes to the late Viola Martin, who had helped me a lot answering all my queries, since the starting of submission of my application for admission to the time she stopped working in the department. She was such a patient and

wonderful person and her ever-smiling greetings have always been missing in the department since then. I would also like to thank other general office staff Rosalind Collins, Mary Flinn and Ebony Penney for their help regarding conference travel reimbursement, departmental seminars and teaching assistantship scheduling etc. Another person I would like to acknowledge here is senior demonstrator Patrick Hannon, with whom I co-demonstrated CHEM 3410 and CHEM 3411 laboratory courses for three years. His liveliness, wit, interest and enthusiasm in demonstration to students have been unchanged, even after so many years of doing it. His commitment to work and enjoying the work he does is very inspiring.

The technical support provided by C-CART is greatly acknowledged for the characterization of compounds reported in this thesis. I would like to thank Julie Collins and Dr. Brent Myron for IR, and Dr. Celine Schneider for NMR training. I would like to convey my special thanks to Ms. Linda Winsor, not only for training me for LCMS but also for running HRMS spectra for most of the compounds in this thesis.

I would also like to thank my supervisory committee, Dr. Sunil Pansare and Dr. Christopher Kozak, for their discussion during committee meetings. I am especially grateful for their critical reading and suggestions during the writing of this thesis.

Last but not the least, generous financial support from the School of Graduate Studies is gratefully acknowledged.

Penchal R. Nandaluru

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List of Abbreviations and Symbols

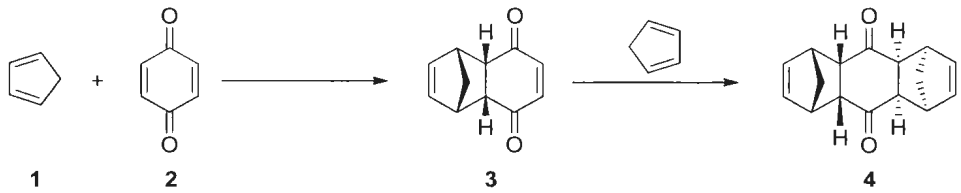
Ac	acetyl
APCI	atmospheric pressure chemical ionization
Bu	butyl
d	day(s)
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
Et	ethyl
ESI	electrospray ionization
g	gram(s)
h	hour(s)
HRMS	high resolution mass spectrometry
Hz	hertz
iPr	isopropyl
IR	infrared (spectroscopy)
J	coupling constant

mg	milligram
Me	methyl
MHz	megahertz
ml	milliliter
mmol	millimole
MOM	methoxymethyl
mp	melting point
NMR	nuclear magnetic resonance (spectroscopy)
PCC	pyridinium chlorochromate
Ph	phenyl
o-tolyl	2-methylphenyl
ppm	parts per million
PTSA	*para*-toluenesulfonic acid
rt	room temperature
tlc	thin layer chromatography
TMEDA	*N*,*N*,*N*',*N*'-tetramethylethylenediamine
TMS	tetramethylsilane
°C	degree Celsius
δ	chemical shift

Chapter 1

Introduction

The German chemist, Prof. Otto Diels and his student, Kurt Alder published a landmark article in 1928,[1] which ushered in a new era in the field of organic chemistry. This article describes the [4+2] cycloaddition reaction between cyclopentadiene (**1**) and 1,4-benzoquinone (**2**) to give adducts **3** and **4** (Scheme 1.1). Although there were some reports of [4+2] cycloadditions prior to this work,[2] it was Diels and Alder who properly identified the products that were produced from the above reaction. This discovery provided the synthetic community with the spectacular "Diels-Alder reaction," and for their contributions, these two eminent chemists were awarded the Nobel Prize in 1950. Over the years, the Diels-Alder reaction has progressed enormously to equip the synthetic organic chemistry community with an invaluable tool. Its ability to rapidly access complex products with a high degree of regio- and stereoselectivity make this reaction one of the most useful organic transformations to the practitioners of organic synthesis.

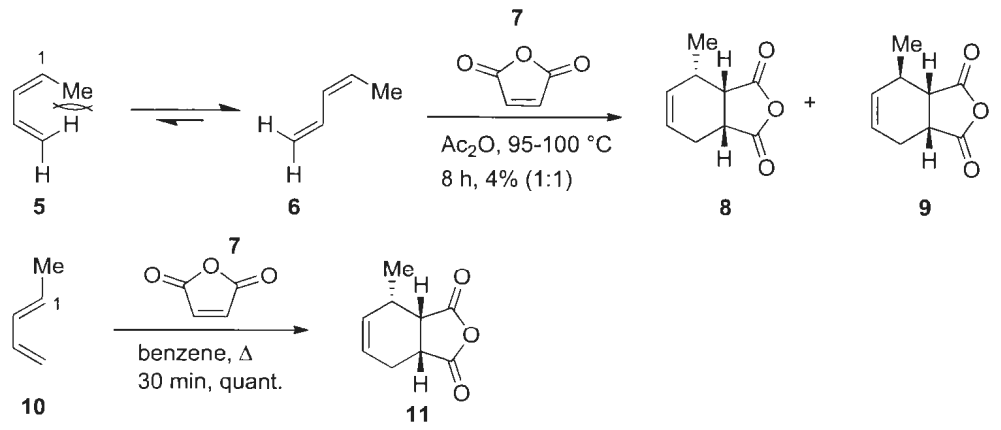


Scheme 1.1. First report of the [4+2] cycloaddition by Otto Diels and Kurt Alder.

1.1 Concepts of the Diels-Alder reaction

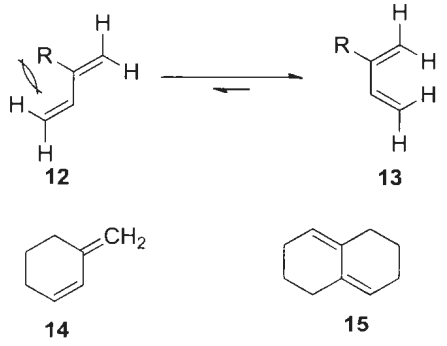
1.1.1 Effect of the conformation of the diene

In general, the Diels-Alder reaction involves a cyclic or acyclic 1,3-butadiene system (the diene or 4π component) and an alkene or alkyne (the dienophile or 2π component). The conformation of the diene is absolutely critical for the success of the Diels-Alder reaction. The most favourable conformation of the diene for Diels-Alder reaction is the *s-cis* comformation. Therefore, any substituent(s) or structural feature that favours *s-cis* conformation facilitates the reaction. On the other hand, substituent(s) or structural features that disfavor the *s-cis* conformation have the effect of retarding the reaction significantly. For example, *cis*-piperylene (**5**), an acyclic diene substituted at C1 position, is known to react with maleic anhydride (**7**) to give a mixture of adducts **8** and **9** (1:1) in very poor yield (4%),[3] whereas the corresponding *trans*-piperylene (**10**) afforded the Diels-Alder adduct **11** as a single diastereomer in quantitative yield (Scheme 1.2).[4] In the case of C2-substituted butadienes, the conformational equilibrium typically favours the *s-cis* isomer, thereby promoting the Diels-Alder reaction (Scheme 1.3). For both C1- and C2-substituted dienes, steric effects are responsible for the conformational preferences.



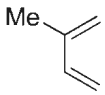
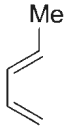
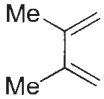
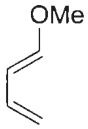
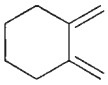
Scheme 1.2. Diels-Alder reactions of *cis*- and *trans*-piperylene with maleic anhydride.

The conformational requirement is more emphatically exemplified when the diene has a fixed conformation. Dienes **14** and **15** have a fixed *transoid* geometry (Scheme 1.3), and thus no cycloadditions are observed. In contrast, dienes with an enforced *s-cis* conformation, such as cyclopentadiene (**23**), 9,10-dimethylanthracene (**22**) and 1,2-dimethylenecyclohexadiene (**21**) are especially reactive.



Scheme 1.3. Conformations of some dienes

The difference in reactivity of a variety of dienes with maleic anhydride and tetracyanoethylene in comparison to butadiene is given in Table 1.1.[4] Rate increases of 2-6 orders of magnitude are achieved upon fixing the conformation of the diene.

Entry	Diene	Relative rate of reactivity with maleic anhydride (at 30 °C)	Relative rate of reactivity with tetracyanoethylene (TCNE) [at 20 °C]
1	 **16**	1.0	1.0
2	 **17**	2.3	2.2
3	 **18**	3.3	4.0
4	 **19**	4.9	46.8
5	 **20**	12.3	1150
6	 **21**	110	2370

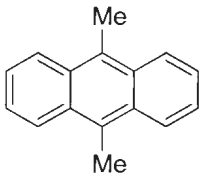
7	 **22**	234	2,500,000
8	 **23**	1350	82900

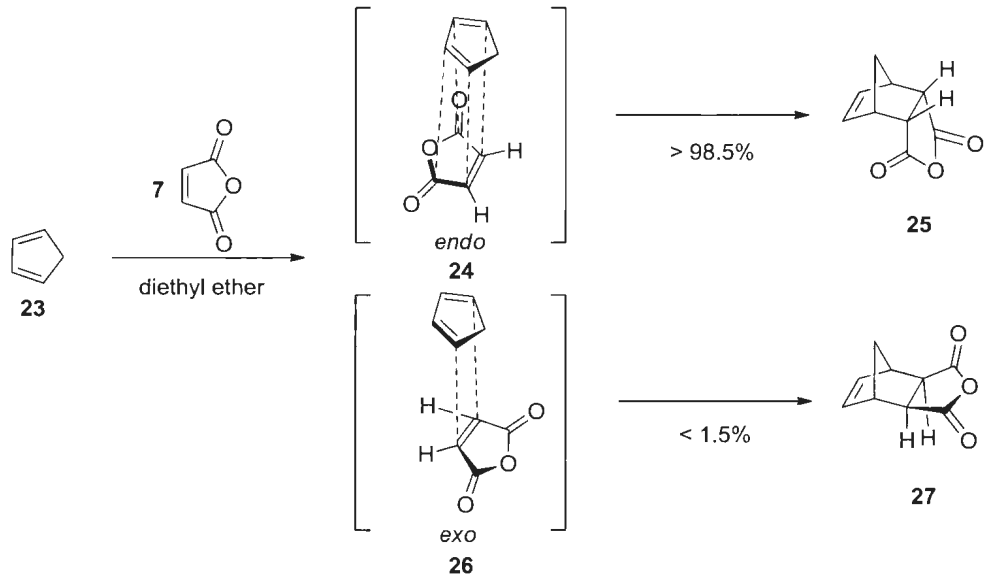
Table 1.1. Relative rates of reactivity of several dienes with maleic anhydride and TCNE (adapted from reference 4).

1.2 Stereochemistry of the Diels-Alder reaction

1.2.1 Diastereoselectivity

The Diels-Alder reaction, in general, follows Alder's rule.[5] According to Alder and Stein, the major product of the cycloaddition results from maximum accumulation of double bonds participating in the reaction, as well as secondary interactions of substituents present on the dienophile. Woodward and Hoffmann attributed *endo* preference of the Diels-Alder reaction to the secondary orbital interactions of *p*-orbitals that are not involved in the formation of new sigma bonds.[6] For example, cyclopentadiene reacts with maleic anhydride to afford the product **25**, which arises from the *endo* transition state, almost exclusively (> 98.5%). The thermodynamically favoured product **27**, which is produced from the *exo* transition state **26** is obtained only in negligible quantities (< 1.5%) [Scheme 1.4].[7] While there can be no doubt that *endo* transition states are typically lower in energy than the corresponding *exo* transition states, there has been a long-lasting debate on whether secondary orbital interactions are

responsible for this or whether they even exist. Though there is some computational support for the notion of secondary orbital interactions favoring *endo* products,[8] other factors such as solvent effects, steric interactions, electrostatic forces, etc.,[9] have been more convincingly linked to the general preference for the *endo* transition state.

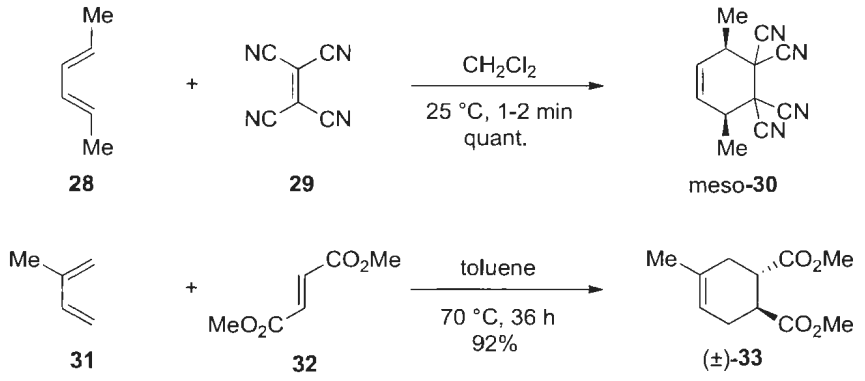


Scheme 1.4. *Exo*- and *endo*- transition states leading to adducts **25** and **27**.

1.2.2 Stereospecificity

Using the language of Frontier Molecular Orbital (FMO) theory, the Diels-Alder reaction is a suprafacial addition with respect to both the diene and the dienophile components and thus more precisely termed as a $[4\pi_s+2\pi_s]$ cycloaddition. Being a concerted reaction, it is necessarily stereospecific with respect to both the diene and the dienophile. In this regard, the existing relative stereochemical relationships in the starting materials is reflected in the cycloadduct.

For example, the reaction between (*E*,*E*)-2,4-hexadiene (**28**) and TCNE (**29**) at ambient temperature afforded the adduct **30** in quantitative yield (Scheme 1.5).[10] The *cis*-relation of the methyl substituents on the diene is completely transferred to the product. In another, more recent example, *trans*-dimethyl fumarate (**32**) reacted with isoprene (**31**) to generate the corresponding cycloadduct **33**, where by the *trans* geometry of the dienophile is reflected in the product.[11]

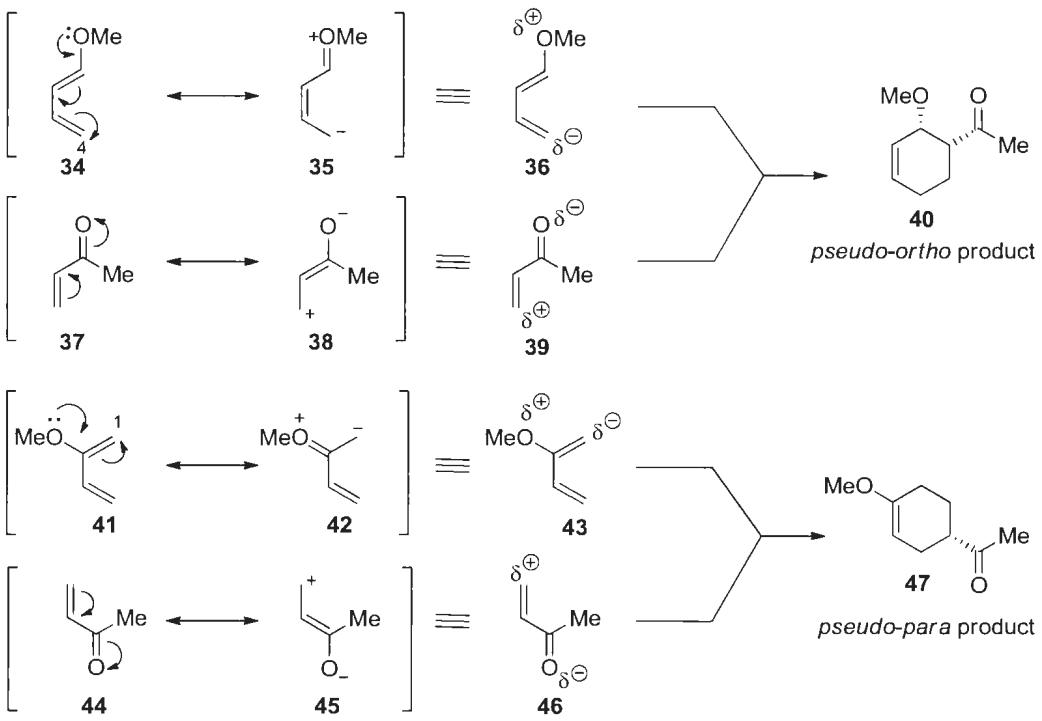


Scheme 1.5. Preservation of relative stereochemistry in the Diels-Alder reaction.

1.2.3 Regioselectivity

The regiochemical outcome of the Diels-Alder reaction can be predicted with a reasonable degree of confidence by the position of the substituent(s) on the diene and the dienophile components. This is commonly illustrated using resonance structures and matching the partially charged ends of the two components with the more pronounced partial charges.

For an example, the Diels-Alder reaction between 1-methoxybutadiene (**34**) and methyl vinyl ketone (**37**) is known to afford *ortho*-substituted product **40** (Scheme 1.6).[12] The non-bonding pair of electrons on the C1 methoxy group of the diene allows a charge-separated resonance structure (**35**) to be drawn and this contributes to its resonance hybrid **36**, thereby leaving a partial negative charge at C4 of the diene. Similarly, the electron-withdrawing acetyl group at one end of the dienophile **37** imparts a partial positive charge at the opposite end in its resonance hybrid (**39**). The initial contact of the carbon with partial negative charge in **36** and the carbon with partial positive charge in **39** leads to the 3,4-disubstituted cyclohexene product **40**. In the case of 2-methoxybutadiene (**41**), the methoxy group generates a negative charge at the C1 position of the diene (in its resonance structure **42**) and its Diels-Alder reaction with methyl vinyl ketone provides the 1,4-disubstituted cyclohexene product **47**.[13]



Scheme 1.6. Examples of regioselectivity in the Diels-Alder reaction.

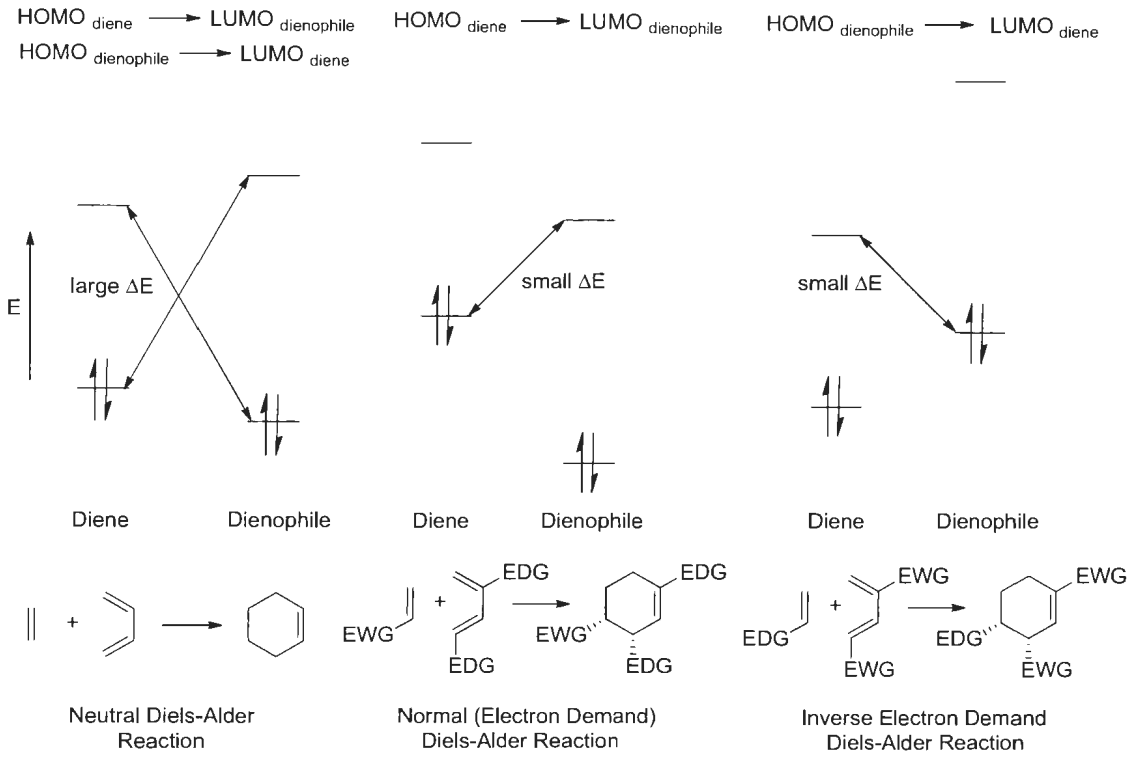
1.3 Classification of the Diels-Alder reactions

The Diels-Alder reaction can be classified into three types, according to the electronic nature of the diene and the dienophile: 1) the neutral Diels-Alder reaction, 2) the normal (electron demand) Diels-Alder reaction, and 3) the inverse electron demand Diels-Alder (IEDDA) reaction. FMO theory is commonly used to explain the reactivity of the Diels-Alder reaction. By this approach, decreasing the energy gap between frontier orbitals of the two reaction partners is predicted to lower the electronic component (but not the steric component) of the activation barrier to reaction.[14] Indeed, the energy gap between the Highest Occupied Molecular Orbital of the diene (HOMO)

and the Lowest Unoccupied Molecular Orbital (LUMO) of the dienophile has been correlated with the rate of reaction.

In the case of a neutral Diels-Alder reaction, the energy gap between the HOMO of the diene and LUMO of the dienophile is large and so is the energy gap between the HOMO of the dienophile and LUMO of the diene (Scheme 1.7). Thus, elevated temperature is required to cause the reaction partners to react. In the second category, *i.e.* the normal Diels-Alder reaction, the diene is substituted with one or more electron-donating groups (EDG). This has the effect of raising the energy level of the HOMO. Similarly, the LUMO of the dienophile can be lowered by placing electron-withdrawing groups (EWG) on it. The net result is that the energy gap between the HOMO of the diene and LUMO of the dienophile is significantly reduced, thereby facilitating the reaction. This category is by far the most extensively explored category and, consequently, a broad range of stable dienes is readily available. Danishefsky's diene[15] and Rawal's diene[16] are two especially useful ones (Scheme 1.8). These dienes owe their usefulness to the 1,3-relationship between the two substituents. This arrangement of donor groups allows them to electronically bias the diene system in a cooperative fashion, which leads to high reactivity and high levels of regioselectivity. Furthermore, the functional groups provide opportunities for further synthetic manipulation following Diels-Alder reaction. The third category is the IEDDA reaction, which involves the use of an electron deficient diene and an electron rich dienophile. In this case, the dominant orbital interaction is between the HOMO of the dienophile and the LUMO of the diene. Although this version of the Diels-Alder reaction has received considerable attention over

the past few decades, it is still heavily overshadowed by the normal Diels-Alder reaction. A major reason for this is that few generally useful electron deficient dienes are commercially available or easily synthesized (see following section).



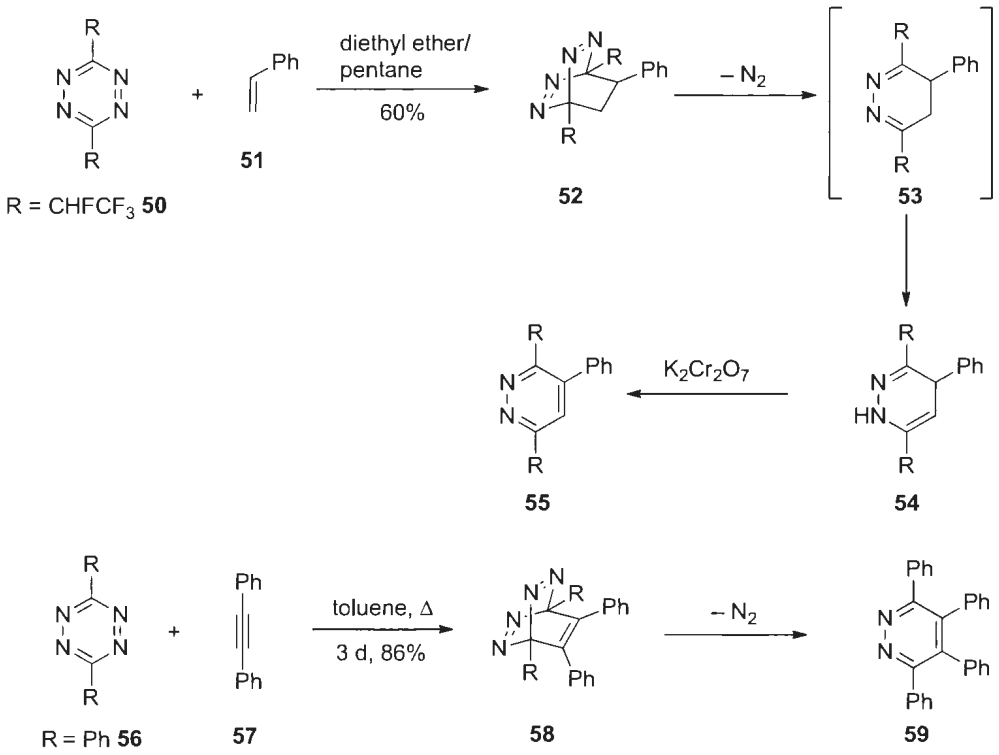
Scheme 1.7. Types of Diels-Alder reactions.

Scheme 1.8. Notable dienes for the normal Diels-Alder reaction.

1.4 The inverse electron demand Diels-Alder (IEDDA) reaction

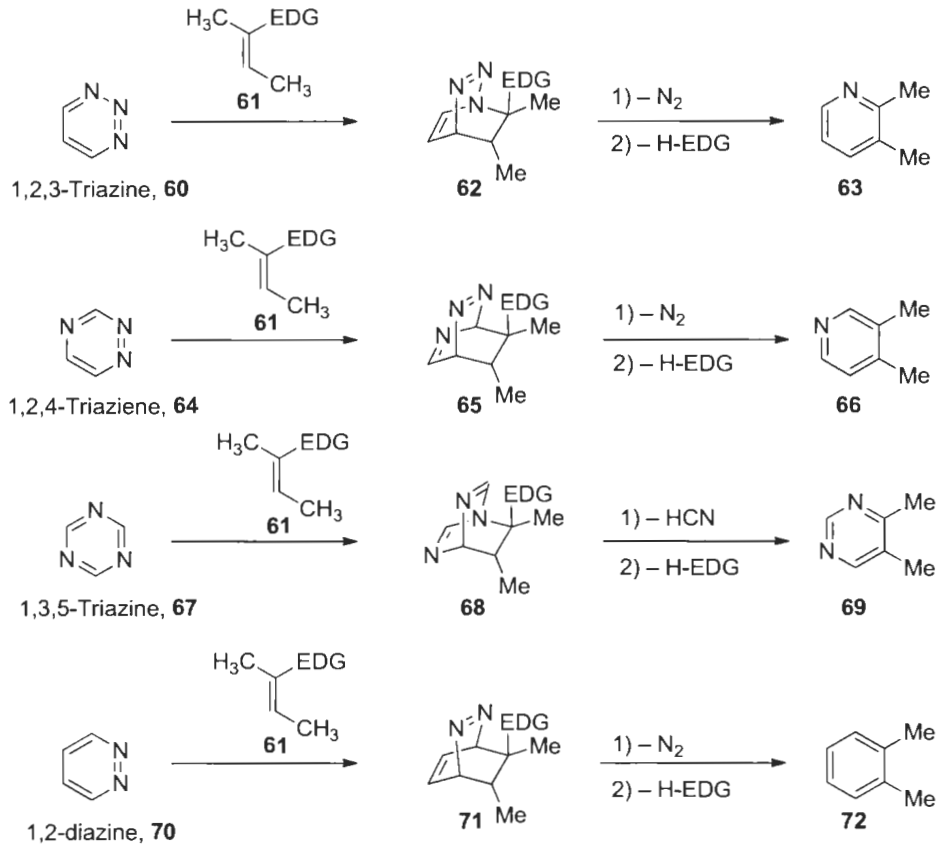
Among the three types of Diels-Alder reactions, the normal (electron demand) Diels-Alder is by far the most highly developed and widely used reaction. This is not to say that its counterpart, the IEDDA reaction has been ignored. In fact, it has been receiving attention for over half a century.

The first examples of the IEDDA reaction were reported by Carboni *et al.* in 1957 (Scheme 1.9).[17] 1,2,4,5-Tetrazines **50** and **56** served as heteroaromatic electron-deficient dienes. In this regard, the LUMO of the diene is lowered by virtue of the presence of the electronegative nitrogen atoms in the diene unit housed by the 1,2,4,5-tetrazine system. When olefins were used as dienophiles, *e.g.* styrene (**51**), dihydropyridazines such as **54** were obtained as products, which were subsequently oxidized to pyridazines such as **55**. Dihydropyridazine **54** presumably arises from an initial [4+2] cycloaddition to give **52**, followed by a retro-[4+2] cycloaddition (to expel nitrogen gas) and a double bond migration. Alternatively, pyridazines were obtained directly when alkynes were used as dienophiles. For example, diene **56** reacted with diphenylacetylene (**57**), presumably via cycloadduct **58**, to afford pyradazine **59** in good yield (86%).



Scheme 1.9. IEDDA reactions of 1,2,4,5-tetrazines **50** and **56**.

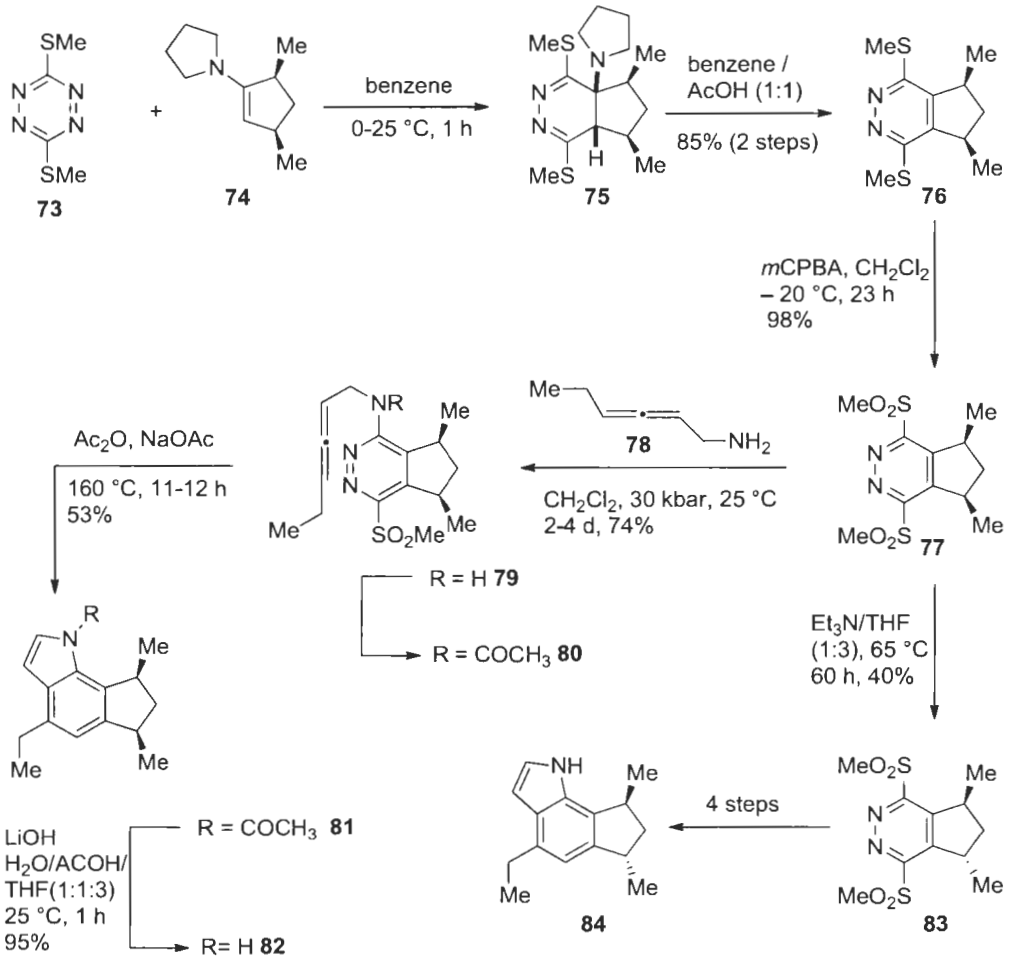
In the following years, numerous investigations employing heteroaromatic systems, including tetrazines,[18] triazines,[19] and diazines,[20] as electron-deficient dienes were reported. As illustrated in Scheme 1.10, these reactions generate various heteroaromatic and aromatic (in the case of diazines) compounds upon reaction with electron-rich dienophiles such as **61**. All but one of these types of heterocyclic compounds involves the expulsion of N_2 from the initial cycloadduct. The exception is 1,3,5-triazines (**67**), which undergo the elimination of HCN following cycloaddition. Aromatization typically occurs after the loss of N_2 or HCN by elimination of H–EDG (*e.g.* an alcohol if EDG is an alkoxy group).



Scheme 1.10. General representation of IEDDA reactions of some heterocycles (adapted from reference 18 b).

The IEDDA reaction has been shown to be very useful in the field of natural products synthesis. For example, Boger *et al.*'s very short total syntheses of (±)-*cis*- and (±)-*trans*-trikentrin A[21] magnificently demonstrate the use of sequential IEDDA reactions of hetero-aromatic azadienes (Scheme 1.11). In this work, 3,6-bis(methylthio)-1,2,4,5-tetrazine (**73**) reacted with enamine **74** in an IEDDA fashion to afford **75**, which was aromatized to **76** by an acid-catalyzed elimination of pyrrolidine in high yield (85%, 2 steps). Oxidation of **76** with *m*CPBA afforded disulfone **77**, which underwent

nucleophilic aromatic substitution with allene amine **78** to provide **79**. The acylation of the secondary amine gave **80**, which set the stage for the next (intramolecular) IEDDA reaction between one of the double bonds of the allene moiety and the 1,2-diazine.

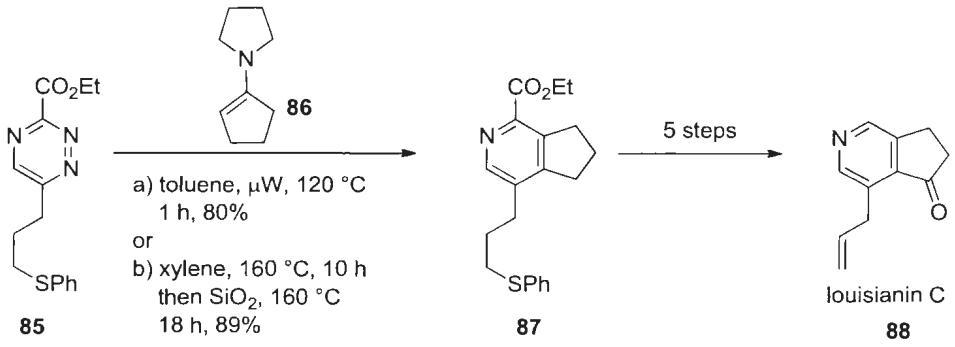


Scheme 1.11. Total syntheses of (±)-*cis*- and (±)-*trans*-trikentrin A by Boger *et al.*

Thermolysis of **80** furnished *N*-acyl-*cis*-trikentrin A **81** (via a cycloaddition, expulsion of N_2 and a dehydrogenation). The acetyl group in **81** was smoothly removed to *cis*-

trikentrin A (**83**). The epimerization of intermediate **77** using trimethylamine to give *trans*-**78**, followed by the same set of reactions employed for the synthesis *cis*-trikentrin A (**77** to **82**) furnished *trans*-trikentrin A (**84**), thereby completing the total synthesis of these two indole alkaloids.

More recently, the use of a 1,2,4-triazine as the electron-rich diene was reported in the total synthesis of louisianin family of natural products.[22] The key and common intermediate for these pyridine-containing alkaloids was accomplished by a regioselective IEDDA reaction of 1,2,4-triazine **85** with cyclopentanone-derived enamine **86** (Scheme 1.12). In this event, both microwave and thermal conditions were employed and the product **87** was obtained as the sole regioisomer. This compound was further elaborated to all four members of this family (one of which is shown in the Scheme 1.12).

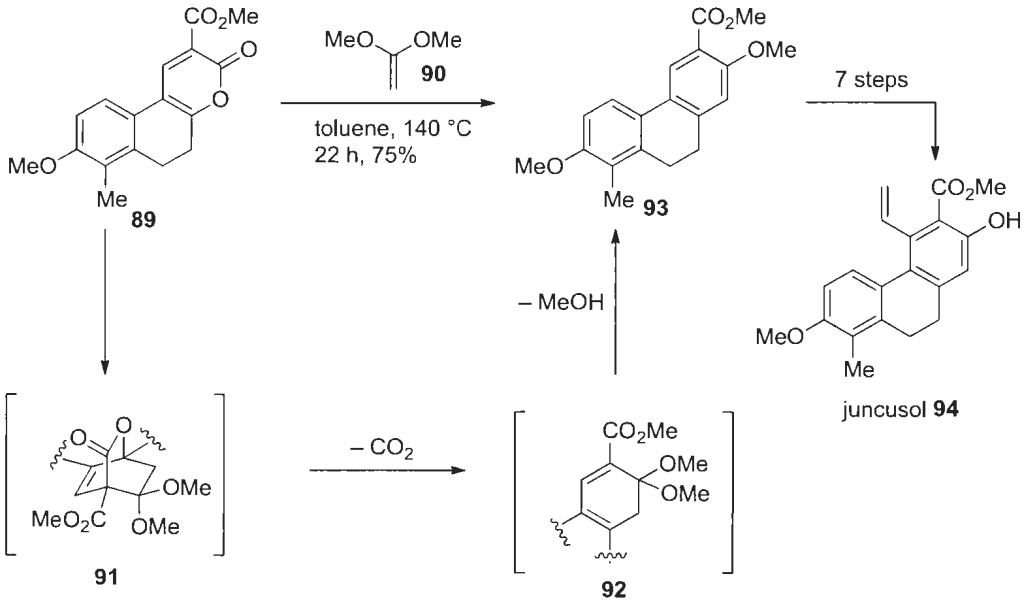


Scheme 1.12. The IEDDA reaction of 1,2,4-triazine **85** in the synthesis of louisianin C.

1.4.1 All-carbon IEDDA dienes

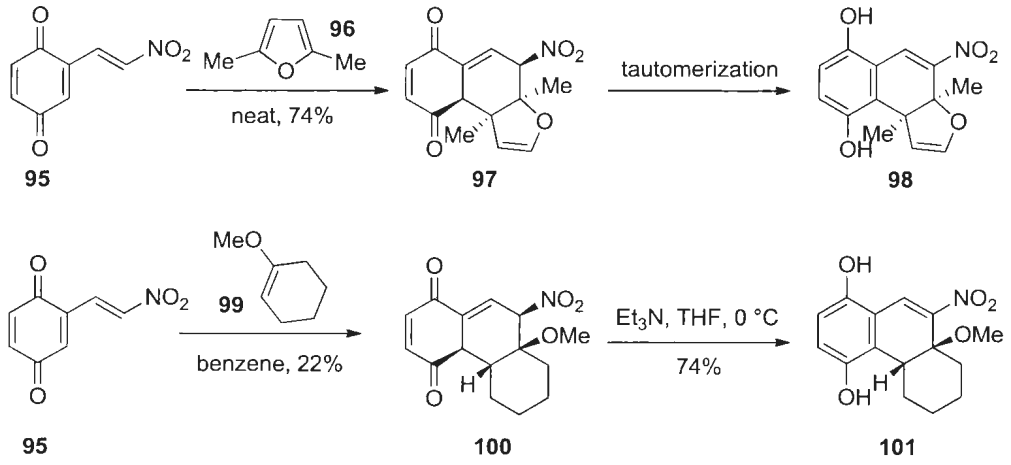
Although heteroaromatic azadienes are the most commonly used electron-deficient dienes, a variety of other diene systems with no heteroatoms in the diene unit have also been employed.

One such system is 2-pyranone. It is known to undergo IEDDA reactions, following a similar order of events as in the case of azadienes. However, instead of N_2 or HCN, CO_2 is extruded from the initial cycloadduct. Boger and co-workers reported the use of 3-carbomethoxy-2-pyranone (**89**) as the electron-deficient diene in the synthesis of juncusol (**94**),[23] a 9,10-dihydrophenanthrene-containing compound (Scheme 1.13). Diene **89** was subjected to the IEDDA reaction with ketene acetal **90** (an electron-rich dienophile) to afford **93** (75%), generating the C ring of the natural product. As alluded to above, this process goes through the intermediacy of an adduct such as **91**, followed by the elimination of CO_2 and methanol. From the exclusive placement of the remaining OMe group at the site *ortho* to the ester, it can be inferred that the IEDDA reaction occurred in a highly regioselective manner. Here and in most other examples, the sense of the regioselectivity is exactly what would be predicted using the considerations presented in Section 1.2.3.



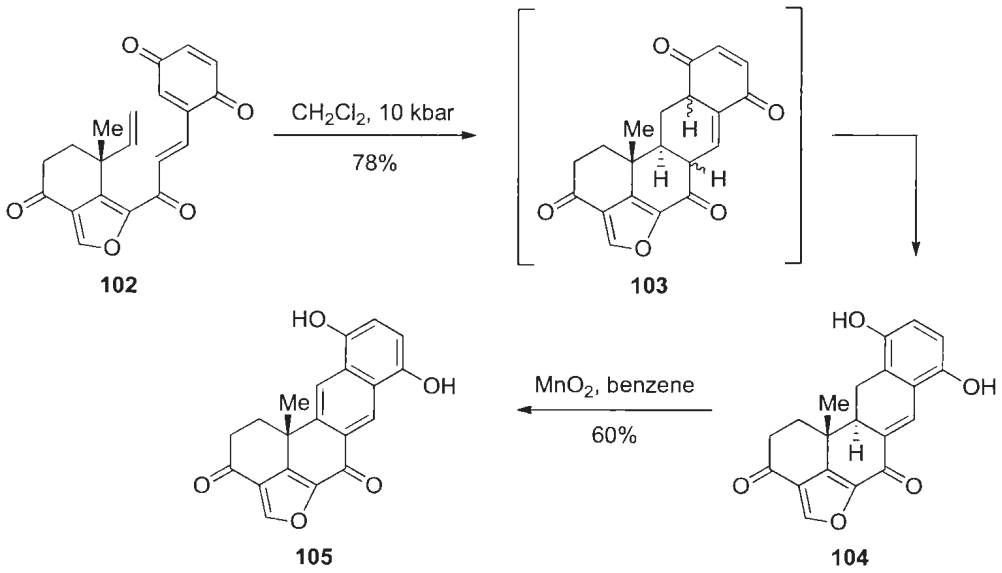
Scheme 1.13. The IEDDA reaction of **89** in the synthesis of juncusol.

Noland and Kedrowski reported IEDDA reactions of nitrovinyl quinones with furans and indoles,[24] as well as enol ethers (Scheme 1.14).[25] Along with complete regioselectivity, the diene underwent *endo*-selective cycloaddition with dienophiles having endocyclic heteroatom-based substituents (furans and indoles). Interestingly, in the case of dienophiles with exocyclic heteroatom-based substitutents, *e.g.* **99**, the reaction proceeded with *exo* diastereoselectivity. The authors reasoned that the heterocyclic dienophiles had the opportunity for secondary interactions that stabilized the *endo* transition state, whereas dienophiles without a heteroatom-based substituent could not participate in such interactions. Whatever the reasons for the change in *endo*/*exo* selectivity, the adducts were found to tautomerize to the corresponding hydroquinones in polar solvents or upon subsequent treatment with Et_3N.



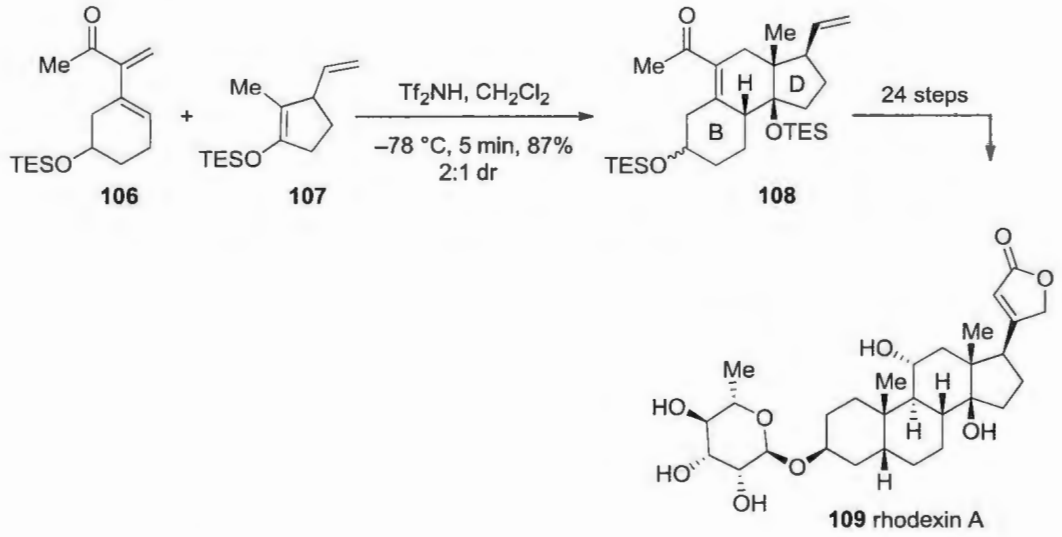
Scheme 1.14. IEDDA reactions of vinylquinone **95**.

Based on the IEDDA behavior of the vinyl quinone motif in the previous examples, Dirk Trauner's group applied an intramolecular version of this reaction to the total synthesis of (−)-helenaquinone (**105**), a pentacyclic natural product.[26] In this regard, an intermediate **102** was subjected to a key intramolecular IEDDA reaction leading to the pentacyclic product **104**, which was subsequently oxidized to **105**, thereby completing the synthesis of the natural product (Scheme 1.15). Unlike in the previous two examples of nitrovinyl quinones, the mode of cycloaddition (*exo* or *endo*) cannot be determined in this event, because the initially formed adduct **103** could not be isolated.



Scheme 1.15. The IEDDA-reaction in the synthesis of (−)-helenaquinone.

In a recent report on the first total synthesis of rhodexin A,[27] Jung and co-workers used a Tf_2NH-catalyzed IEDDA reaction as a key reaction to construct the BCD ring system of the natural product (Scheme 1.16). This reaction set four contiguous stereocenters via an *exo* transition state to afford **108** as a mixture of epimers (isomers at the *O*-silyl-containing carbon in the B ring). Both diastereomers were useful for further synthetic work, as the offending stereocenter was destroyed later by converting the *O*-silyl group to a ketone. The diene and the dienophile were designed in such a way that the A ring could be easily fused onto the B ring and the butenolide moiety could be attached to the D ring.



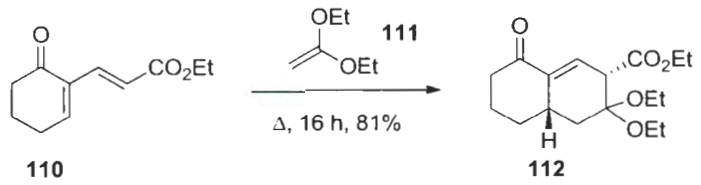
Scheme 1.16. The IEDDA reaction in the total synthesis of rhodexin A.

1.4.2 IEDDA reactions in the Bodwell Group

Over the past 15 years, efforts in the Bodwell group have led to the synthesis of a variety of electron-deficient all-carbon dienes. The common feature of these dienes is the presence of electron-withdrawing groups on the diene unit with a 1,3-relationship. As in the cases of Danishefsky's diene and Rawal's diene, this arrangement allows the EWGs to co-operatively bias the diene system and this causes the dienes to undergo completely regioselective cycloaddition upon IEDDA reaction with electron-rich dienophiles. These dienes have been used in the synthesis of several different classes of compounds.

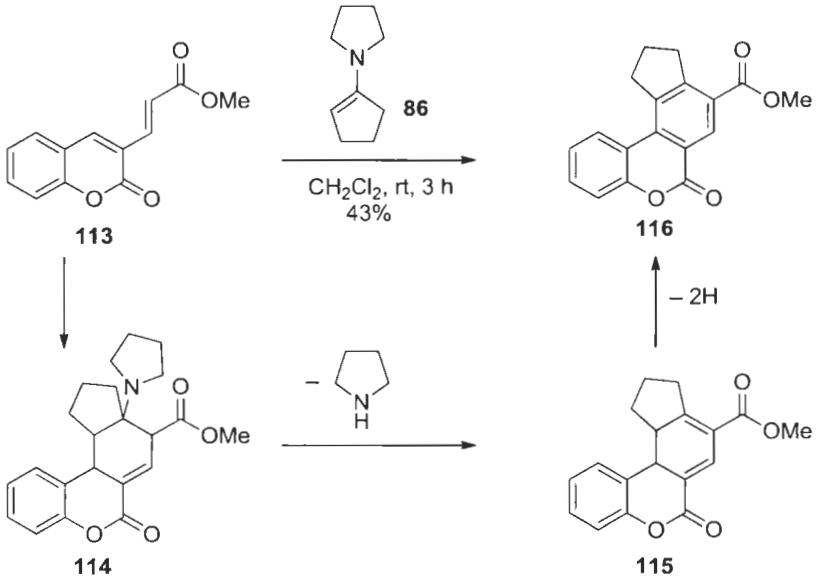
The first report from the Bodwell group on the IEDDA reaction came in 1997. In this work, cyclohexenone-derived diene **110** underwent IEDDA reactions with a variety of electron-rich dienophiles in a completely regioselective fashion. For example, diene **110** reacted with ketene acetal **111** to afford the adduct **112** (Scheme 1.17).[28] This diene

also reacted with vinyl ethers and styrenes to give richly-functionalized [6,6] ring systems.



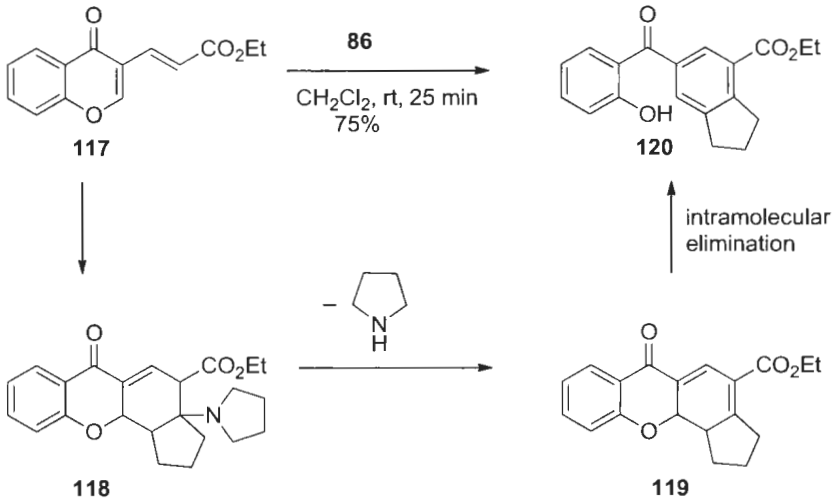
Scheme 1.17. The IEDDA reaction of **110** with ketene acetal **111**.

Following this report, IEDDA reactions of the coumarin-fused diene **113** with enamines (eletron-rich dienophiles), *e.g.* **86**, were reported.[29] In this regard, the initially formed cycloadduct **114**, underwent elimination of pyrrolidine and dehydrogenation (presumably, a transfer hydrogentation to enamine **86**) to afford 6*H*-dibenzo[*b,d*]pyran-6-ones (**116**) (Scheme 1.18).



Scheme 1.18. The IEDDA reaction of coumarin-fused diene **113** with enamine **86**.

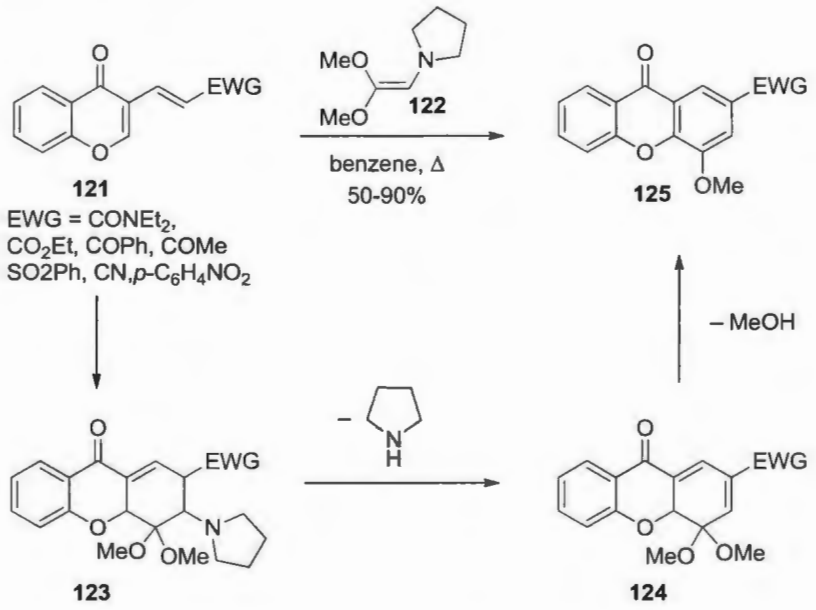
In a later report, chromone-based diene **117**, which was synthesized from the corresponding 3-formylchromene using a Horner-Wadsworth-Emmons reaction, underwent an IEDDA-initiated domino sequence with a series of enamines (*e.g.* **86**) to produce a variety of 2-hydroxybenzophenones (*e.g.* **120**).[30] Interestingly, the second elimination was intramolecular (with respect to the leaving group) (**119** to **120**), thereby generating 2-hydroxybenzophenones instead of the expected xanthones (Scheme 1.19).



Scheme 1.19. The IEDDA reaction of diene **117** leading to 2-hydroxybenzophenone **120**.

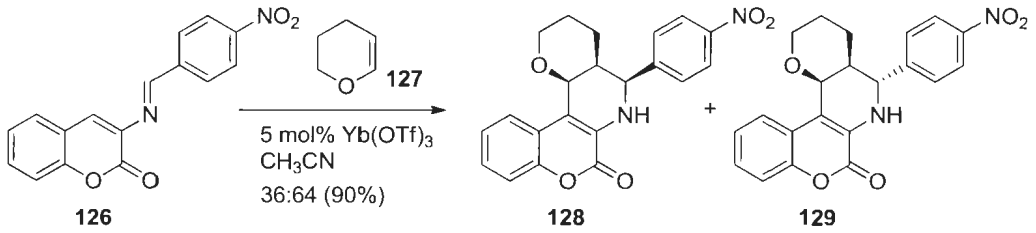
In order to synthesize xanthones, the intramolecular elimination needed to be blocked. Accordingly, the dienophiles (*e.g.* **122**) were modified such that there is no hydrogen atom present for this elimination to occur, as it is in intermediate **124** (Scheme 1.20). Thus, presumed intermediate diene **124**, formed by the initial elimination of pyrrolidine from adduct **123**, underwent a subsequent elimination of methanol to generate

a new aromatic ring (**125**). Using this strategy, a variety of C-ring-substituted xanthones was synthesized from chromone diene **121**, which vary in the nature of their electron-withdrawing groups.[31] A notable feature of the reactions involving dienophile **122** was that the regioselectivity of the cycloaddition was dictated by the pyrrolidinyl group and not the two methoxy groups.



Scheme 1.20. IEDDA reactions of diene **121** leading to xanthones.

To further demonstrate the value of the IEDDA reaction and to develop an efficient entry into functionalized nitrogen-containing polycyclic systems, 2-azadienes (*e.g.* **126)** were prepared.[32] These dienes reacted with a variety of dienophiles (*e.g.* **127**), followed by tautomerization of the initial adduct (not shown) to afford pentacyclic systems as a mixture of diastereomers (**128** and **129**), which are the products of *endo* and *exo* transition states (Scheme 1.21).



Scheme 1.21. The $Yb(OTf)_3$-catalyzed IEDDA reaction of azadiene **126** with dihydropyran (**127**).

Although the IEDDA methodology developed in the Bodwell group has shown significant promise to access different classes of compounds, its application to target molecules was at a very primitive stage at the outset of the work described herein. Thus the work described in this thesis had the overarching goal of more fully developing the synthesis of 6*H*-dibenzo[*b*,*d*]pyran-6-ones (DBPs) (Scheme 1.18) and applying it to the synthesis of specific targets.

The starting point of this work was the stepwise method for the synthesis of DBPs, which was developed previously in the Bodwell group (Scheme 1.18). Subsequently, it was found that enamines could be generated *in situ* and react with these dienes to afford DBPs. Chapter 2 contains a part of the work associated with the development these methods.

In Chapter 3, the details of the development of a multicomponent reaction leading to a variety of A- and C-ring substituted DBPs are presented. This highly productive reaction was then employed in a total synthesis of a natural product, cannabinol.

The DBPs also offered a new entry into the synthesis of novel chiral pyrenophanes, which are non-natural products. One of the dibenzopyranones generated by the multicomponent methodology was used as the starting material to the concise synthesis of a set of C_2-symmetric pyrenophanes. The results of this work are described in Chapter 4.

In related work, a stepwise (non-multicomponent) approach to DBPs was used in the synthesis of defucogilvocarcin V, an antitumor compound. This strategy offered the potential to synthesize some new C-8 analogs along with the targeted defucogilvocarcin V. These findings are presented in Chapter 5.

This is a publication-based dissertation. As such, each subsequent Chapter is a slightly modified version of the publication given at the beginning of each Chapter. The contributions of all authors are explained at the beginning of each Chapter.

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Chapter 2

Synthesis of 6*H*-Dibenzo[*b*,*d*]pyran-6-ones Using the Inverse Electron Demand Diels–Alder Reaction

This chapter is based upon the following publication:

Pottie, I. R.; Nandaluru, P. R.; Benoit, W. L.; Miller, D. O.; Dawe, L. N. Bodwell, G. J. *J. Org. Chem.* **2011**, *76*, 9015–9030.

Contributions of authors

G. J. Bodwell: research supervisor, manuscript preparation.

I. R. Pottie: synthetic experimental work for a major portion of the publication.

P. R. Nandaluru: some synthetic experimental work (The contributions of P. R. Nandaluru are presented in this chapter and those of I. R. Pottie have been omitted except where they are related to the discussion), manuscript preparation.

W. L. Benoit: undergraduate student who assisted I. R. Pottie with a small portion of the synthetic work.

D. O. Miller, L. N. Dawe: X-ray crystal structure determinations.

2.1 Introduction

A variety of natural products feature a 6*H*-dibenzo[*b,d*]pyran-6-one (**1**) core, including fasciculiferol (**2**),[1] alternariol (**3**),[2] autumnariol (**4**),[3] autumnariniol (**5**),[3] altenuisol (**6**)[4] and ellagic acid (**7**)[5] (Figure 2.1). Furthermore, dibenzopyranones have served as intermediates in the synthesis of cannabinoids[6] and other pharmaceutically interesting compounds, *e.g.* progesterone, androgen and glucocorticoid receptor agonists,[7] endothelial proliferation inhibitors[8] and antidyslipidemic agents.[9]

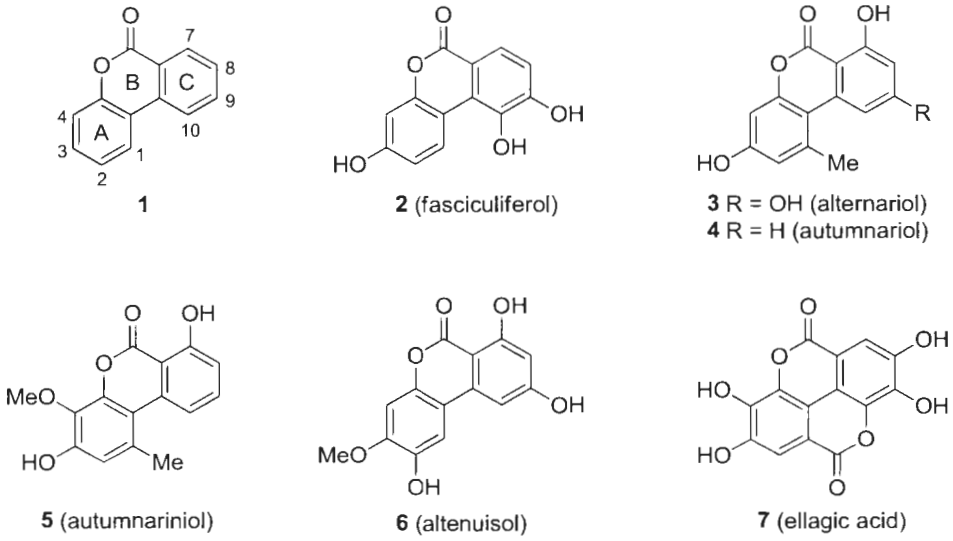
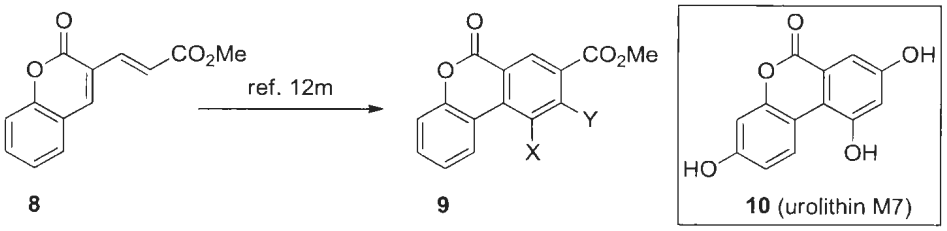


Figure 2.1. Structures of 6*H*-dibenzo[*b,d*]pyran-6-one (**1**) and some natural products containing this motif.

Numerous approaches to the synthesis of 6*H*-dibenzo[*b,d*]pyran-6-ones have been reported. These can be broadly classified according to the bonds formed during the key step(s) as follows: approaches that involve (1) biaryl bond formation followed by lactonization,[10] (2) construction of an ester or ether followed by intramolecular biaryl

bond formation,[11] (3) a cyclization to form the C ring (or B and C rings), with or without a subsequent aromatization,[6d,12] (4) rearrangement of spirocyclic compounds,[13] (5) biomimetic syntheses of alternarial derivatives[14] and (6) miscellaneous methods.[15] In the third category, enediyne cycloaromatization,[12a–c] ruthenium-catalyzed [2+2+2] cycloaromatization,[6d] 6π electrocyclic ring closure,[12d] condensations involving chromones[12e] and coumarins[12f–h] bearing electron-withdrawing groups, and the Diels-Alder reaction[12i–n] have been exploited. Of these methods, the Diels-Alder reaction arguably offers the greatest potential for diversity-oriented synthesis. An existing coumarin system can be designed to function as either a diene or a dienophile in either the normal or inverse electron demand version of the reaction. For the normal Diels-Alder reaction, coumarin-based dienophiles[12j–l] and a diene[12i] have been reported. The Bodwell has group communicated the only example of a coumarin-based diene (**8**) to be used as a substrate in an inverse electron demand Diels-Alder (IEDDA)-based synthesis of C-ring functionalized 6*H*-dibenzo[*b,d*]pyran-6-ones[12m] **9** (Scheme 2.1) and, more recently, an application of this methodology in the total synthesis of urolithin M7 (**10**).[16]

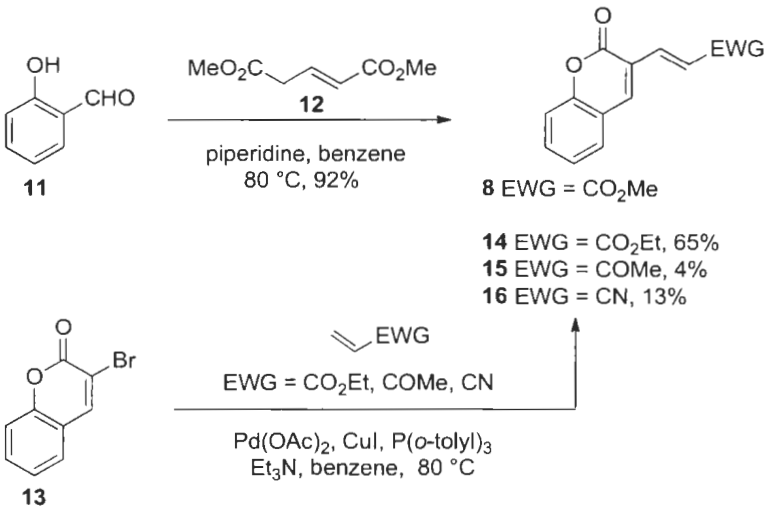


8 **9** **10** (urolithin M7)

Scheme 2.1. First report on 6*H*-dibenzo[*b,d*]pyran-6-ones from the Bodwell group, and urolithin M7.

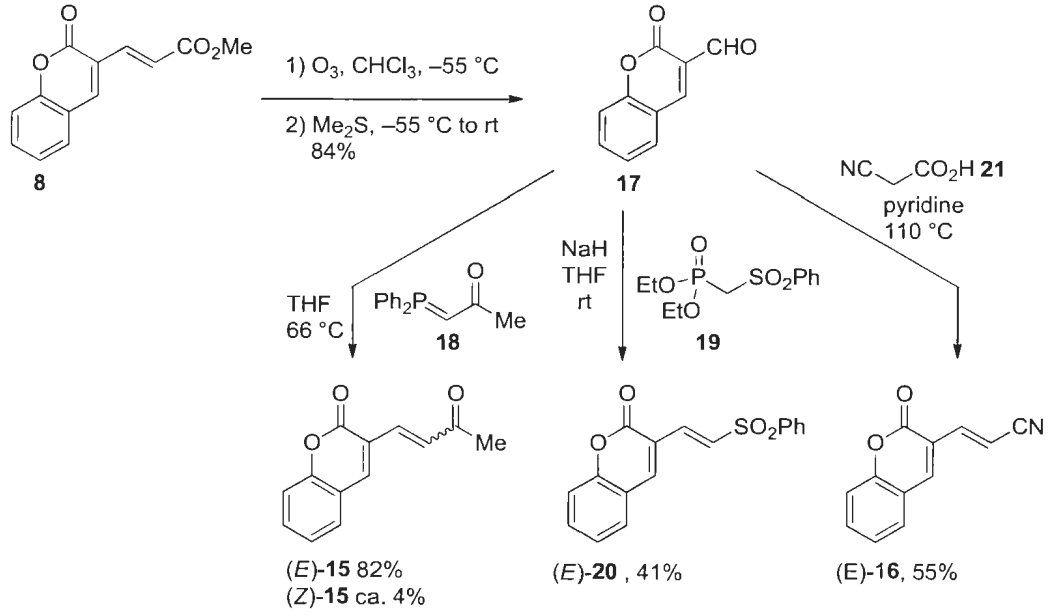
2.2 Results and Discussion

As reported earlier,[12m] coumarin-fused diene **8** was synthesized in a single step from salicylaldehyde (**11**) and dimethyl glutaconate (**12**) (Scheme 2.2). This involves a transesterification and a vinylogous Knoevenagel condensation, although the order of events is unclear. An important feature of diene **8** is that the electron-withdrawing groups on the diene unit have a 1,3 relationship, as do the electron-donating groups on Danishefsky's diene.[17] However, the synthesis of diene **8** is not easily modified to allow for the incorporation of a variety of other electron-withdrawing groups at the terminus of the diene system. Accordingly, an alternative and more general approach to the synthesis of a family of electron deficient, coumarin-fused dienes was sought.



Scheme 2.2. Synthetic approach to coumarin-fused dienes **8**, and **14**–**16**.

The use of 3-bromocoumarin (**13**)[18] as a common starting material in the Heck reaction with various electron-deficient alkenes was identified as a promising route (Scheme 2.2). After some optimization, good results were obtained using ethyl acrylate. Diene **14** was obtained in 65% yield. However, the use of these conditions with methyl vinyl ketone or acrylonitrile afforded dienes **15** and **16** in very poor yield. Faced with the prospect of reoptimizing the Heck reaction for each electron-deficient alkene, another approach was investigated. This involved the use of the Horner-Wadsworth-Emmons reaction to generate the electron-deficient diene system, which had been used successfully for other electron deficient dienes (Scheme 2.3).[19] Thus, access to multigram quantities of 3-formylcoumarin (**17**) was required and this was achieved by ozonolysis of diene **8**. At 84%, the yield of this reaction is somewhat better than that reported by Triggle *et al.* for the oxidative cleavage of **14** using $OsO_4/NaIO_4$ (70%).[20]



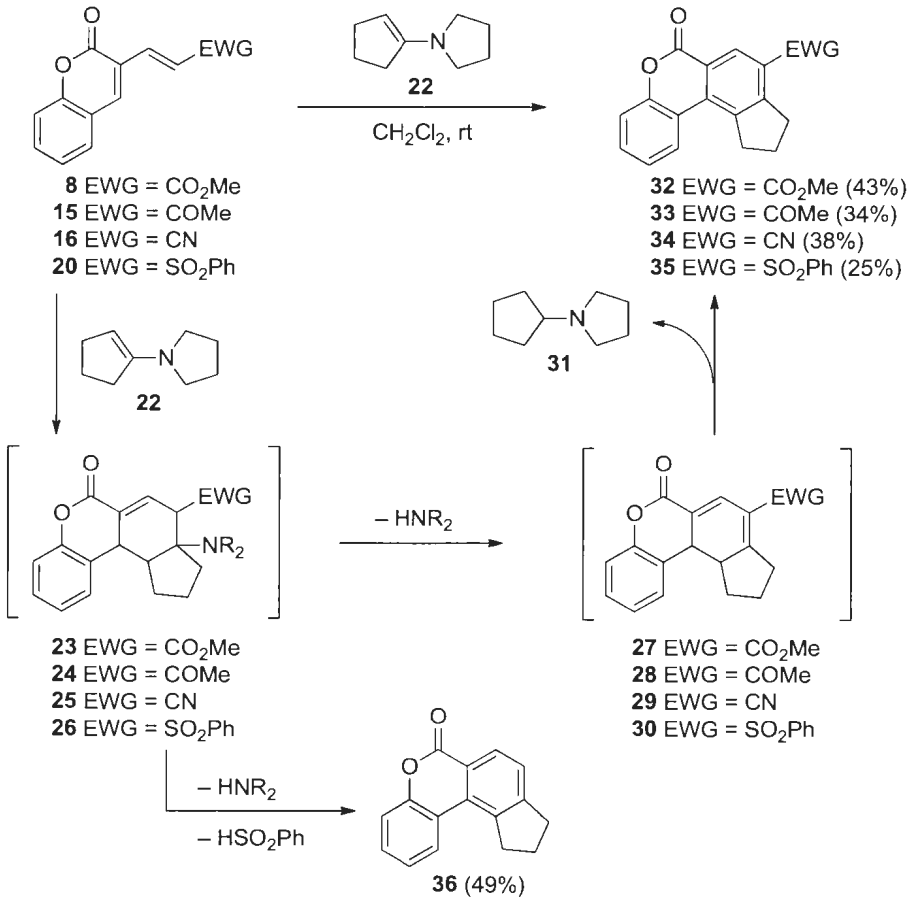
Scheme 2.3. Synthesis of coumarin-fused dienes **15**, **16** and **20**.

Aldehyde **17** was reacted with phosphonate **19**[21] to afford diene **20** in modest yield (work done by I. R. Pottie). In this regard, only the *E* isomer of sulfone **20** was isolated. Methyl ketone **15** was synthesized using a Wittig reaction between **17** and ylide **18** (work done by I. R. Pottie).[22] Both geometric isomers were produced, but they could be separated using flash chromatography to afford (*E*)-**15** (82%). A 9:1 mixture of (*Z*)-**15** / (*E*)-**15** (4%) was also isolated. Finally, isomerically pure cyanodiene (*E*)-**16** was synthesized using decarboxylative Knoevenagel condensation of **17** with cyanoacetic acid (**21**).[23] Attempts to generate the corresponding nitrodiene using a Henry reaction of **17** with nitromethane were unsuccessful (work done by I. R. Pottie).

The investigation of the IEDDA chemistry of dienes **8**, **15**, **16** and **20** commenced with the reaction of **8** with ethyl vinyl ether. Although ethyl vinyl ether is a relatively weak dienophile, it had been found to react with a related electron-deficient dienophile at 80 °C.[19a] However, **8** was unreactive towards ethyl vinyl ether (by tlc analysis) after heating for 4d at 120 °C. Partial aromatic character (even a small amount) in the pyranone ring would be expected to decrease the Diels-Alder reactivity. In view of the lower reactivity of **8**, a more reactive dienophile was employed. Indeed, the enamine (**22**) derived from cyclopentenone and pyrrolidine reacted smoothly with diene **8** in dichloromethane at ambient temperature to afford dibenzopyranone **32** in 43% yield (Scheme 2.4).[12m] Under the same conditions, dienes **15**, **16** and **20** provided the corresponding dibenzopyranones **33-35** (25-38%).

The products presumably arise from a formal IEDDA reaction[24] to afford adducts **23-26**, followed by 1,2-elimination to give cyclohexadienes **27-30** and a dehydrogenation

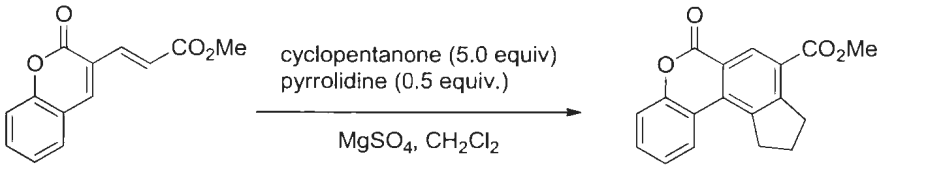
(Scheme 2.4). Transfer hydrogenation[25] to enamine **22** (giving amine **31**) is a pathway for the dehydrogenation of **27-30** to afford **32-35**. For dienes **8**, **15** and **16**, no intermediates or byproducts were isolated or observed (by tlc analysis) during the course of these reactions. However, the use of diene **20** gave rise to the formation of dibenzopyranone **36** (49%), which lacks the sulfonyl group, in addition to **35**. Allylic sulfones are known to undergo 1,4-elimination of benzenesulfinic acid,[26] so it seems likely that **36** is formed by a 1,4-elimination of benzenesulfinic acid from **26** followed by a 1,2-elimination of pyrrolidine.



Scheme 2.4. IEDDA reactions of dienes **8**, **15**, **16** and **20** with preformed enamine **22**.

Using this preformed enamine strategy, diene **8** was reacted with a variety of enamines to afford the corresponding C-ring substituted dibenzopyranones (work done by I. R. Pottie and it is omitted from the publication on which this chapter is based). In considering the further extension of the methodology, the synthesis of the required enamines in reasonably pure form was identified as a potential problem.[27] As such, attention was turned to the possibility of generating the enamines *in situ*. Moreover, the proposed mechanism for dibenzopyranone formation involves the elimination of the secondary amine used to generate the enamine, so the opportunity to perform these reactions organocatalytically also presented itself.

Using the optimized *in situ* enamine generation conditions developed by I. R. Pottie, dienes **8**, **15, 16** and **20** were converted into the corresponding dibenzopyranones **32-35** in yields that matched or exceeded those obtained using preformed enamine **22** (Scheme 2.5). In the case of sulfone-bearing diene **20**, the byproduct **36** (45%) was again produced along with **35** (14%). The product distribution was similar to that obtained using preformed enamine **22**.



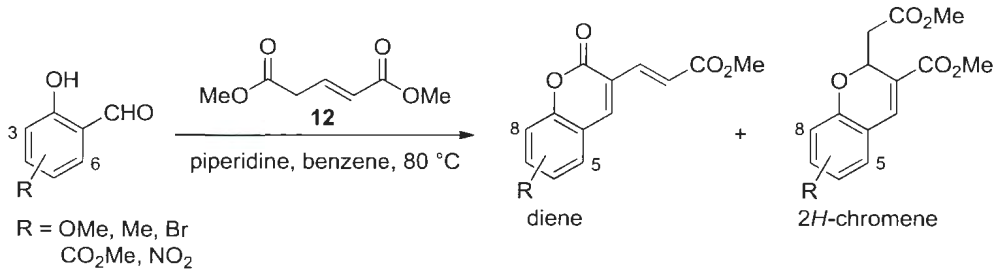
8 EWG = CO_2Me
15 EWG = COMe
16 EWG = CN
20 EWG = SO_2Ph

32 EWG = CO_2Me (74%)
33 EWG = COMe (46%)
34 EWG = CN (38%)
35 EWG = SO_2Ph (14%)
36 EWG = H (45%)

Scheme 2.5. IEDDA reactions of dienes **8**, **15**, **16** and **20** under *in situ* conditions.

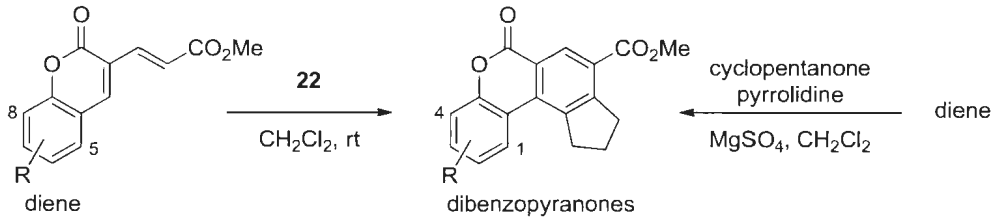
By employing these *in situ* conditions, a wide range of ketones were reacted with diene **8** to produce a variety of C-ring substituted dibenzopyranones (work done by I. R. Pottie and it is omitted from the publication on which this chapter is based). This method allowed the use of ketones that would otherwise be difficult or not possible to isolate as their enamines.

To demonstrate that A-ring substituted dibenzopyranones are also accessible using the IEDDA-based approach, a series of salicylaldehydes was reacted with dimethyl glutaconate (**12**) to afford the corresponding coumarin-fused dienes (Scheme 2.6) (work done by I. R. Pottie and it is omitted from the publication on which this chapter is based on). With the exception of some cases (R = 5-Me, 4-Me, 3-Me), 2*H*-chromenes were also obtained along with the required dienes. In contrast to the diene products, which arise from a combination of vinylogous Knoevenagel condensation and transesterification, the 2*H*-chromene products arise from a combination of vinylogous Knoevenagel condensation and conjugate addition.



Scheme 2.6. Synthesis of substituted coumarin-fused dienes.

The dienes were reacted with **22** using both the preformed enamine (work done by I. R. Pottie) and the method involving its generation *in situ* (Table 2.1). In the case of the parent diene **8**, it had already been found that the *in situ* method gave a much better yield of dibenzopyranone **32** (Table 2.1, Entry 1). This was also the case for dienes **38**, **39**, **40** and **41**, but the superiority of the *in situ* method was less pronounced (Table 2.1, Entries 2–5). For dienes **42**, **43** and **44**, better yields were obtained using preformed **22** (Table 2.1, Entries 6–8). Overall, the yields using preformed **22** were more consistent than when using the *in situ* method. In both instances, nitro-substituted diene **44** stood out as the poorest-yielding example.[28]

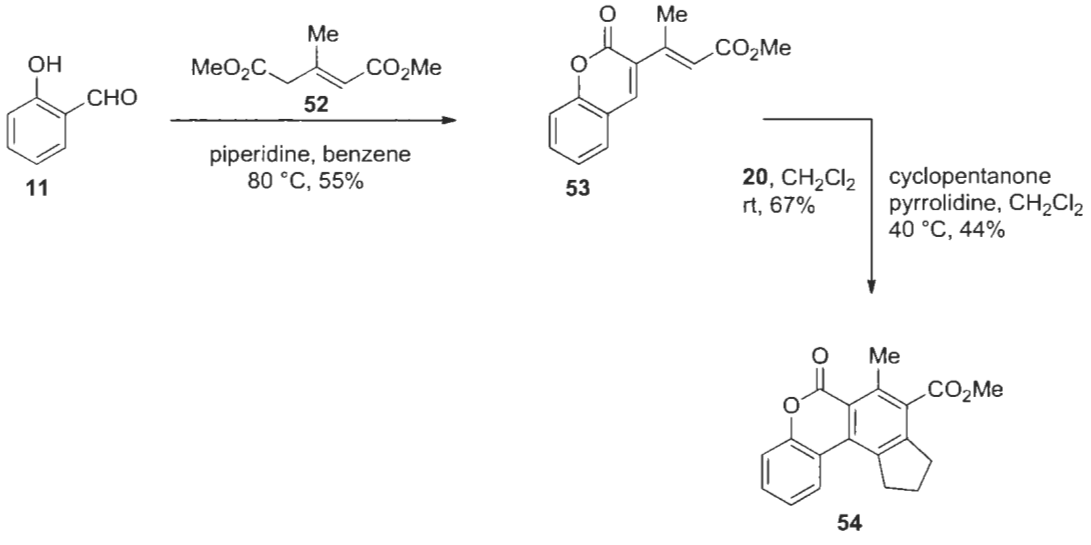


			Pottie's work	Nandaluru's work
Entry	Diene	Dibenzopyranone	% yield (preformed **22**)	% yield (*in situ* **22**)
1	**8** R = H	**32** R = H	43	74
2	**38** R = 6-Me	**45** R = 2-Me	47	50
3	**39** R = 7-Me	**46** R = 3-Me	51	57
4	**40** R = 8-Me	**47** R = 4-Me	48	54
5	**41** R = 6-OMe	**48** R = 2-OMe	51	64
6	**42** R = 6-Br	**49** R = 2-Br	51	35
7	**43** R = 6-CO_2Me	**50** R = 2-CO_2Me	41	34
8	**44** R = 6-NO_2	**51** R = 2-NO_2	24	22

Table 2.1: Results of reactions of enamine **22** with coumarin-fused dienes.

As a further example of the scope of the methodology, salicylaldehyde (**11**) was reacted with dimethyl 3-methylglutaconate (**52**) to afford diene **53** (55%), which bears a methyl group on the diene unit. Reaction of **53** with preformed enamine **20** gave dibenzopyranone **54** (67%) (Work done by I. R. Pottie), in which the newly-formed

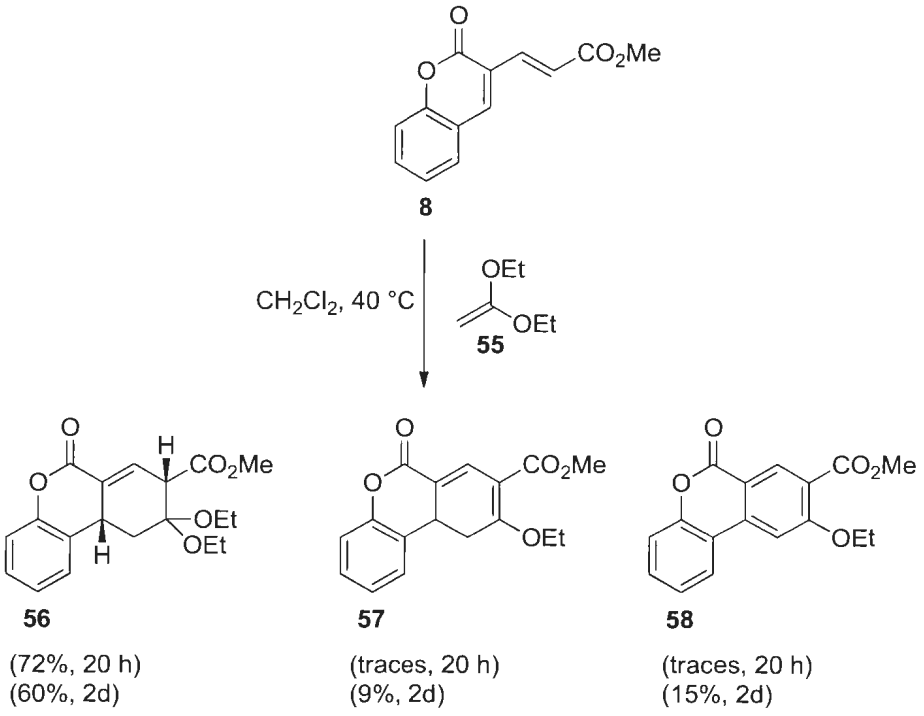
aromatic ring is hexasubstituted. Generation of the enamine *in situ* gave a 44% yield of **54** (Scheme 2.7).



Scheme 2.7. Synthesis of dibenzopyranone **54** having hexasubstituted C-ring.

Whereas ethyl vinyl ether was found to be unreactive towards diene **8**, ketene acetal **55**[29] reacted slowly at reflux in dichloromethane (Scheme 2.8). The IEDDA adduct **56** was isolated in 72% yield after 20 h of reaction. Upon extending the reaction time to 48 h, **56** (60%) was still the major product, but cyclohexadiene **57** (9%) and dibenzopyranone **58** (15%) were also isolated. As for most of the reactions with enamines described above, the formation of dibenzopyranone **58** can be explained by a sequential IEDDA / elimination / transfer hydrogenation process. Diene **57** appears simply to be the result of a sequential IEDDA / elimination sequence. The relative

configuration in **56** was established using an X-ray crystal structure determination (experimental section), and it is fully consistent with a concerted cycloaddition. The much slower rate of elimination in adduct **56** than that in the corresponding enamine adducts (*e.g.* **23**, Scheme 4) is likely due to the absence of an organic base. In the reactions involving enamines, pyrrolidine (a 2° amine), adducts such as **23** (a 3° amine) and the enamines themselves (3° amines) are present.



Scheme 2.8. IEDDA reaction of diene **8** with ketene acetal.

2.3 Conclusions

A set of coumarin-fused electron deficient 1,3-dienes was synthesized, which differ in the nature of the electron withdrawing group (EWG) at the terminus of the diene unit and (when EWG = CO_2Me) the nature and position of substituents. These dienes reacted with the enamine derived from cyclopentanone and pyrrolidine to afford the corresponding cyclopenteno-fused 6*H*-dibenzo[*b,d*]pyran-6-ones, most likely via a domino inverse electron demand Diels-Alder (IEDDA) / elimination / transfer hydrogenation sequence.

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2.5 Experimental procedures and characterization data

General: Reactions were performed using anhydrous solvents under a balloon containing N_2 unless otherwise indicated. All reactions were performed with oven-dried (120 °C) glassware. THF was distilled immediately prior to use from sodium / benzophenone. All other chemicals and solvents were used as received. Solvents were removed under reduced pressure using a rotary evaporator. Chromatographic separations were achieved using Silicycle silica gel 60, particle size 40-63 mm. Thin-layer chromatography (tlc) was performed using commercially precoated plastic-backed POLYGRAM® SIL G/UV254 silica gel plates, layer thickness 200 mm. Compounds on tlc plates were visualized using a UV lamp (254 and 365 nm). Melting points were obtained using Fisher-Johns apparatus or OptiMelt automated melting point system and are uncorrected. Infrared (IR) spectra were recorded using solid samples on a Bruker TENSOR 27 instrument. ^1H and ^{13}C spectra were obtained from $CDCl_3$ or DMSO-d_6 solutions using Bruker Advance (500 or 300 MHz) instruments. Chemical shifts are relative to internal standards: TMS (δ_H = 0.00 ppm) and $CDCl_3$ (δ_C = 77.23 ppm), respectively. Low-resolution and high-resolution mass spectrometric (MS) data were obtained using an Agilent 1100 series LC/MSD instrument and a Waters Micromass® GCT premierTM instrument.

Note: Procedures and characterization are provided only for compounds not reported in I. R. Pottie's dissertation.

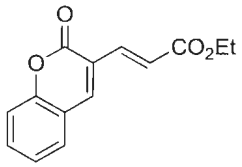
Standard procedure A (for IEDDA reactions using preformed enamines)

To a magnetically stirred, room temperature solution of the diene (1.0 equiv.) in dichloromethane was added neat enamine (1.5 equiv.) dropwise and the resulting solution was stirred at room temperature for the amount of time indicated. The disappearance of the starting material was monitored by tlc. The solvent was then removed under reduced pressure and the residue was subjected to flash chromatography on silica gel to afford the product(s).

Standard procedure B (for IEDDA reactions using in situ-generated enamines)

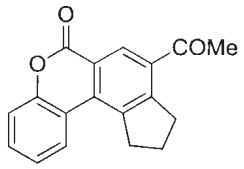
To a magnetically stirred, room temperature solution of the diene (1.0 equiv.), the ketone (5.0 equiv.) and $MgSO_4$ (2.0 equiv) in dichloromethane was added pyrrolidine (0.5 equiv.). The mixture was stirred at room temperature and the disappearance of the diene was monitored by tlc. When the diene had been consumed, the $MgSO_4$ was removed by gravity filtration. The filtrate was washed with aqueous 1 M HCl solution, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was subjected to flash chromatography on silica gel to afford the product(s).

Ethyl (*E*)-3-(2-oxo-2*H*-chromen-3-yl)acrylate (14)



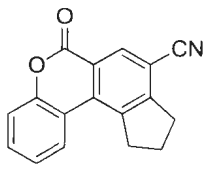
A mixture of 3-bromocoumarin (1.00 g, 5.18 mmol), ethyl acrylate (0.84 mL, 7.70 mmol), $Pd(OAc)_2$ (46 mg, 0.20 mmol), P(*o*-tolyl)$_3$ (94 mg, 0.31 mmol), CuI (35 mg, 0.18 mmol), triethylamine (3.58 mL, 25.8 mmol) in benzene (10 mL) was heated at reflux for 4 h. The reaction mixture was cooled to room temperature and aqueous 1 M HCl solution (20 mL) was added. The resulting mixture was extracted with chloroform and the combined organic extracts were dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was subjected to flash chromatography on silica gel (chloroform). The product was triturated with ether (2 × 5 mL) to afford **14** as a cream colored solid (0.82 g, 65%): mp 120–121 °C; IR (powder) ν = 2978 (w), 1708 (s), 1604 (m), 1165 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ = 7.88 (s, 1 H), 7.60–7.54 (m, 2 H), 7.57 (d, J = 16.1 Hz, 1 H), 7.36 (d, J = 8.3 Hz, 1 H), 7.33–7.30 (m, 1 H), 7.10 (d, J = 15.9 Hz, 1 H), 4.27 (q, J = 7.1 Hz, 2 H), 1.34 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (500 MHz) δ 166.9, 159.1, 153.5, 143.4, 137.8, 132.9, 128.5, 124.8, 123.8, 122.4, 119.0, 116.7, 60.8, 14.3; APCI-(–)-MS *m/z* (%) 244 (M^+,100), 212 (40), 245 (20); HRMS (APCI-(+)) calcd for $C_{14}H_{13}O_4$: 245.0814, found 245.0815.

8-Acetylbenzo[*b*]-2,3-dihydro-1*H*-indeno[5,4-*d*]-6*H*-pyran-6-one (33)



Using standard procedure A (12 h, 0.30 g scale, chloroform used for chromatography), **33** (0.13 g, 34%) was obtained as a white solid: mp 220–223 °C; IR (powder) ν = 1720 (s), 1603 (m), 1184 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ = 8.83 (s, 1 H), 8.26 (d, J = 8.1 Hz, 1 H), 7.56 (t, J = 7.7 Hz, 1 H), 7.44 (d, J = 8.2 Hz, 1 H), 7.39 (t, J = 7.7 Hz, 1 H), 3.49 (t, J = 7.5 Hz, 2 H), 3.44 (t, J = 7.8 Hz, 2 H), 2.73 (s, 3 H), 2.28 (quint, J = 7.7 Hz, 2 H); ^{13}C NMR (125 MHz) δ = 198.6, 161.2, 154.4, 152.0, 142.3, 134.6, 133.5, 131.3, 130.9, 126.9, 124.5, 120.3, 118.9, 118.0, 35.1, 33.9, 28.3, 25.2; EI-(+)-MS *m/z* (%) 279 ($[M + 1]^+$, 100), 171 (15); HRMS (EI) calcd for $C_{18}H_{14}O_3$: 278.0943, found 278.0947. Using standard procedure B (5 h, 0.30 g scale, chloroform used for chromatography), **33** (0.18 g, 46%) was obtained as a white solid.

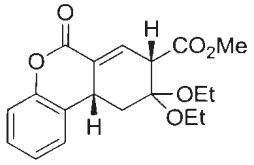
8-Cyanobenzo[*b*]-2,3-dihydro-1*H*-indeno[5,4-*d*]-6*H*-pyran-6-one (34)

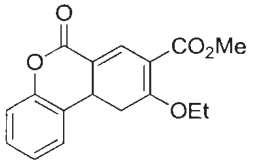


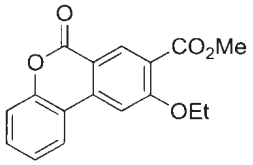
Using standard procedure A (3 h, 0.30 g scale, chloroform used for chromatography), **34** (0.15 g, 38%) was obtained as a white solid: mp 301–304 °C; IR (powder) ν = 2220 (w), 1724 (s), 1594 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ = 8.62 (s, 1 H), 8.21 (d, J = 8.0

Hz, 1 H), 7.60 (t, J = 7.6 Hz, 1 H), 7.45 (d, J = 8.2 Hz, 1 H), 7.41 (t, J = 7.6 Hz, 1 H), 3.59 (t, J = 7.3 Hz, 2 H), 3.31 (t, J = 7.6 Hz, 2 H), 2.40 (quint, J = 7.5 Hz, 2 H); ^{13}C NMR (125 MHz) δ = 160.0, 155.9, 152.0, 141.4, 135.3, 133.7, 131.6, 126.8, 124.7, 121.2, 118.3, 118.2, 116.7, 109.3, 36.0, 32.8, 24.7; EI-(+)-MS *m/z* (%) 262 ([M + 1]$^+$, 100), 263 (15), 284 (20); HRMS (EI) calcd for $C_{17}H_{11}NO_2$: 261.0790, found 261.0793. Using standard procedure B (3 h, 0.30 g scale, chloroform used for chromatography), **34** (0.15 g, 38%) was obtained as a white solid.

9,9-Diethoxy-8,9,10,10a-tetrahydro-6*H*-dibenzo[*b*,*d*]pyran-6-one-8-carboxylic acid methyl ester (56), 9-ethoxy-10,10a-dihydro-6*H*-dibenzo[*b*,*d*]pyran-6-one-8-carboxylic acid methyl ester (57), and 9-ethoxy-6*H*-dibenzo[*b*,*d*]pyran-6-one-8-carboxylic acid methyl ester (58).



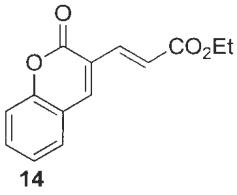




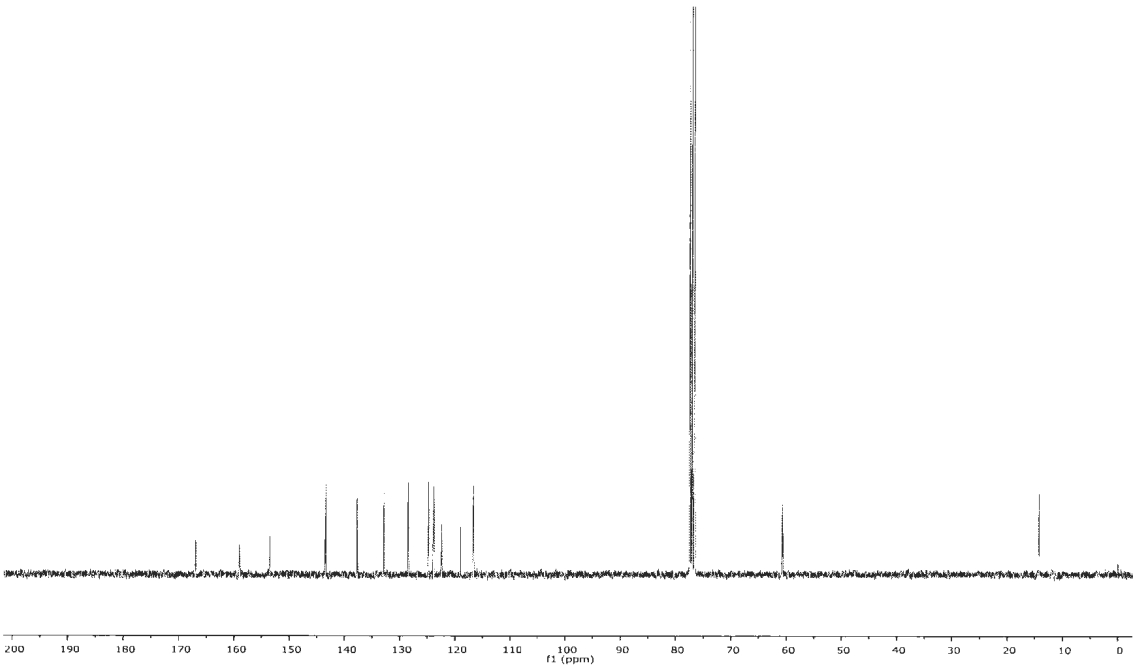
To a solution of diene **8** (0.40 g, 1.74 mmol) in dichloromethane (8 mL) was added 1,1-diethoxyethene (1.15 g, 9.91 mmol) and the resulting mixture was heated at reflux 20 h. The reaction mixture was cooled to room temperature, the solvent was removed under reduced pressure and the residue was subjected to flash chromatography on silica gel (dichloromethane) to give **56** (0.43 g, 72%) as a pale yellow solid: mp 151–154 °C; IR (powder) ν = 1738 (s), 1649 (w), 1201 (s) cm^{-1}; ^{1}H NMR (CD_2Cl_2, 500 MHz) δ = 7.32–7.27 (m, 2H), 7.20–7.17 (m, 1H), 7.01–7.05 (m, 1H), 6.89 (dd, J = 5.3, 3.2 Hz, 1H), 3.89

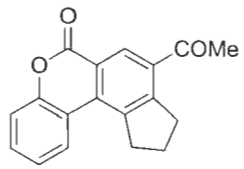
(m, 1H), 3.80–3.78 (m, 1H), 3.67–3.61 (m, 2H), 3.66 (s, 3H), 3.59–3.53 (m, 2H), 2.77 (ddd, J = 13.0, 5.7, 1.8 Hz, 1H), 2.34 (dd, J = 13.0, 11.1 Hz, 1H), 1.18 (t, J = 7.0 Hz, 3H), 1.17 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ = 169.5, 163.0, 150.7, 136.3, 130.0, 128.6, 125.4, 125.0, 124.4, 117.3, 99.2, 56.6, 56.1, 52.7, 50.2, 33.2, 30.7, 15.4, 15.3; APCI-(–)-MS *m/z* (%) 346 (M^+, 5), 345 (40), 300 (15), 299 (100); HRMS (APCI-(+)) calcd for $C_{19}H_{23}O_6$: 347.1495, found 347.1497. Upon extending the reaction time to 2 d, compounds **56** (0.36 g, 60%) **57** (0.047 g, 9%) and **58** (0.078 g, 15%) were obtained. **57**: mp 177–180 °C; IR (powder) ν = 1703 (s), 1618 (m), 1520 (s) cm^{-1}; ^{1}H NMR (CD_2Cl_2, 500 MHz) δ = 7.91 (d, J = 3.4 Hz, 1H), 7.32–7.26 (m, 2H), 7.18–7.15 (m, 1H), 7.07–7.05 (m, 1H), 4.41–4.35 (m, 1H), 4.27–4.21 (m, 1H), 4.16 (ddd, J = 18.8, 7.6, 3.3 Hz, 1H), 3.75 (s, 3H), 3.35 (dd, J = 17.2, 7.6 Hz, 1H), 2.63 (dd, J = 18.8, 16.9 Hz, 1H), 1.44 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ = 171.4, 164.0, 161.3, 150.8, 141.1, 129.0, 125.9, 124.5, 121.8, 117.7, 111.8, 106.7, 63.3, 51.5, 32.2, 31.2, 15.1; EI-MS *m/z* (%) 301 ([M + 1]$^+$, 100), 241 (55), 323, (50), 269 (40); HRMS (EI) calcd for $C_{17}H_{16}O_5$: 300.0998, found 300.1006. **58**: mp 218–220 °C; IR (powder) ν = 1711 (s), 1608 (m) cm^{-1}; ^{1}H NMR (CD_2Cl_2, 500 MHz) δ = 8.70 (s, 1H), 8.06 (dd, J = 7.9, 1.6 Hz, 1H), 7.57–7.54 (m, 2H), 7.39–7.33 (m, 2H), 4.34 (q, J = 7.0 Hz, 2H), 3.91 (s, 3H), 1.55 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz) δ 165.3, 163.3, 160.4, 152.6, 139.7, 135.1, 131.9, 124.9, 123.6, 122.6, 118.2, 117.8, 113.9, 104.7, 65.7, 52.5, 14.7; EI-MS *m/z* (%) 299 ([M + 1]$^+$, 100), 267 (60); HRMS (APCI-(+)) calcd for $C_{17}H_{15}O_5$: 299.0919, found 299.0917.

1.6 Selected ^{1}H and ^{13}C NMR spectra for Chapter 2



14

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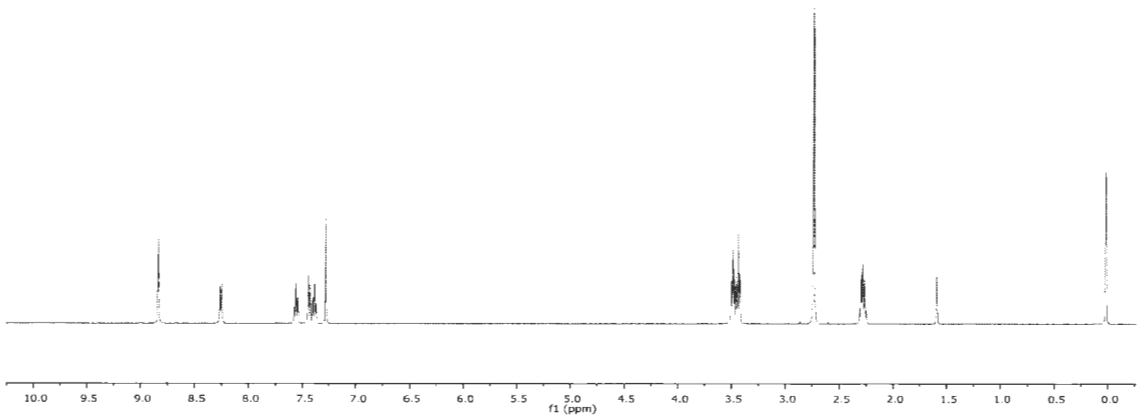
33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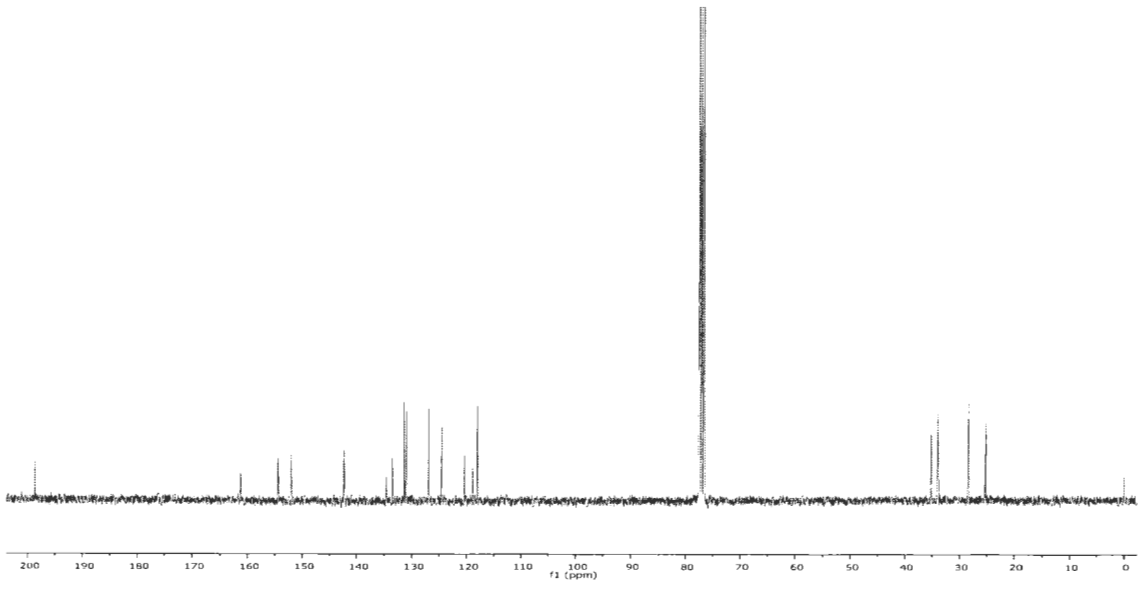
f1 (ppm)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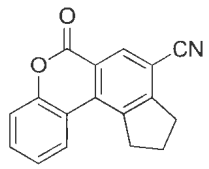
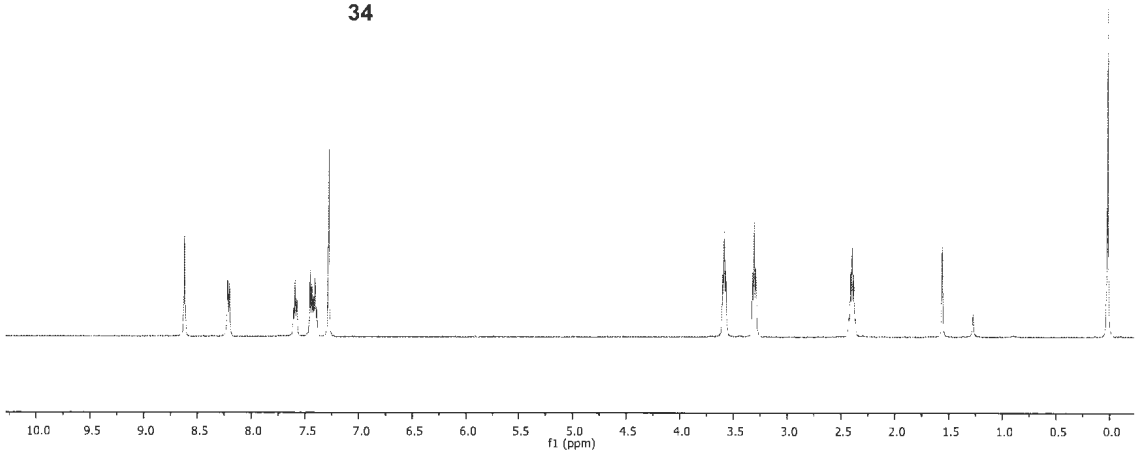
f1 (ppm)


O
O
CN

34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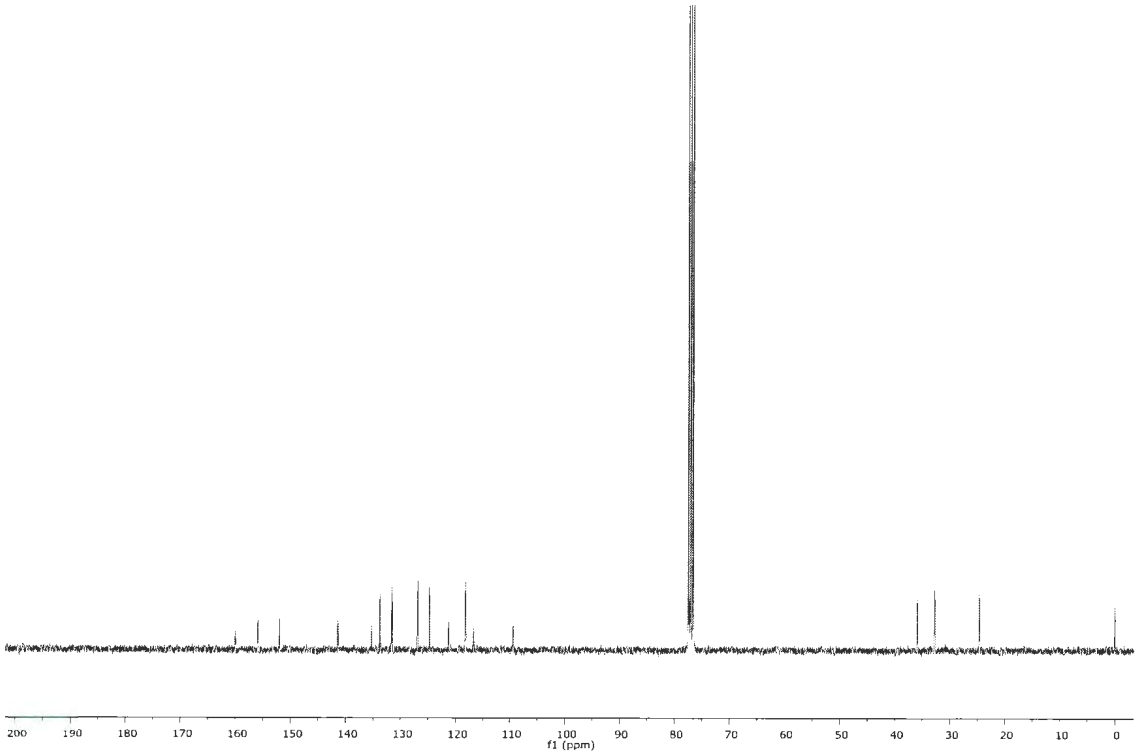
f1 (ppm)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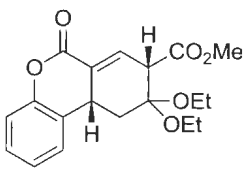
f1 (ppm)


O
H
CO_2Me
O
OEt
OEt
H

56

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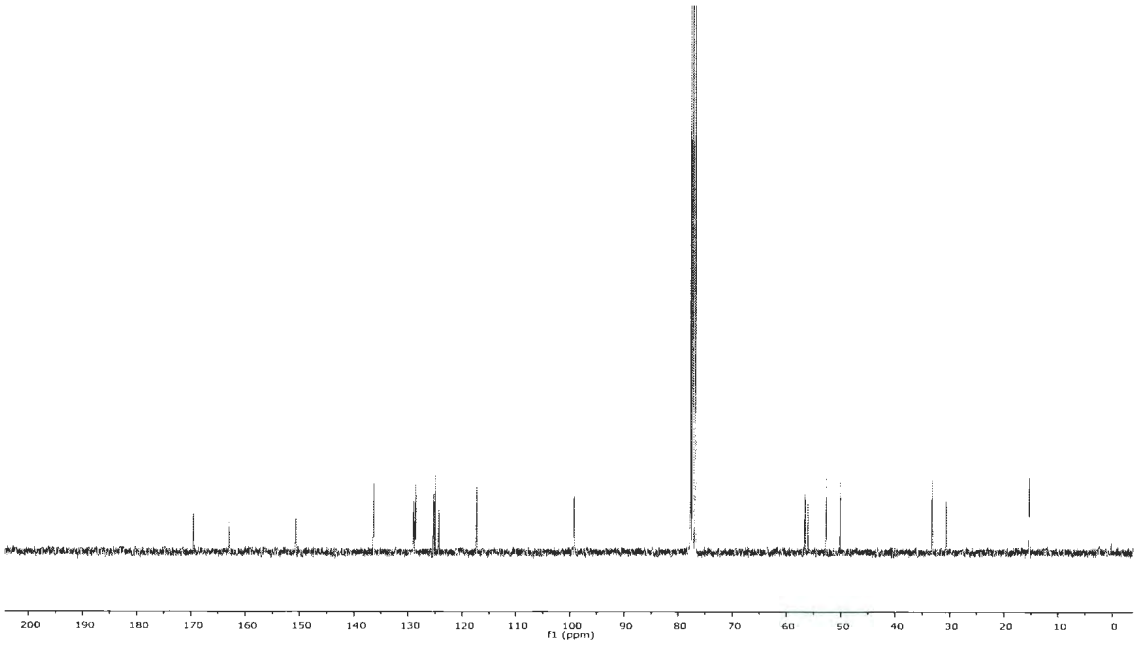
f1 (ppm)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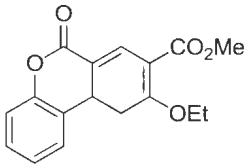
f1 (ppm)


O
O
CO2Me
OEt

57

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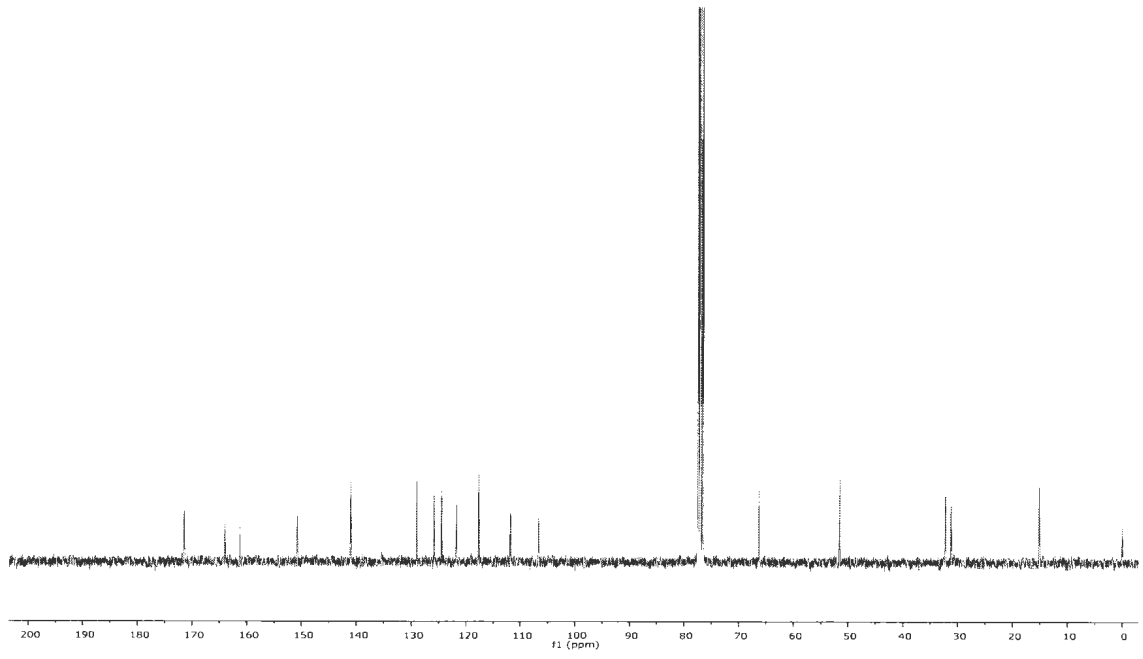
f1 (ppm)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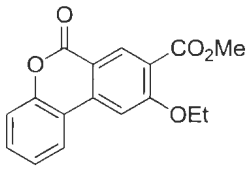
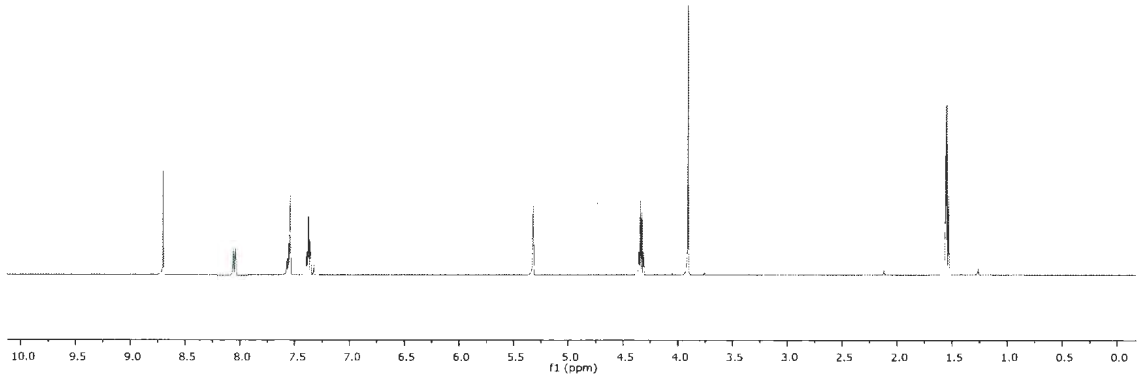
f1 (ppm)


O
O
CO2Me
OEt

58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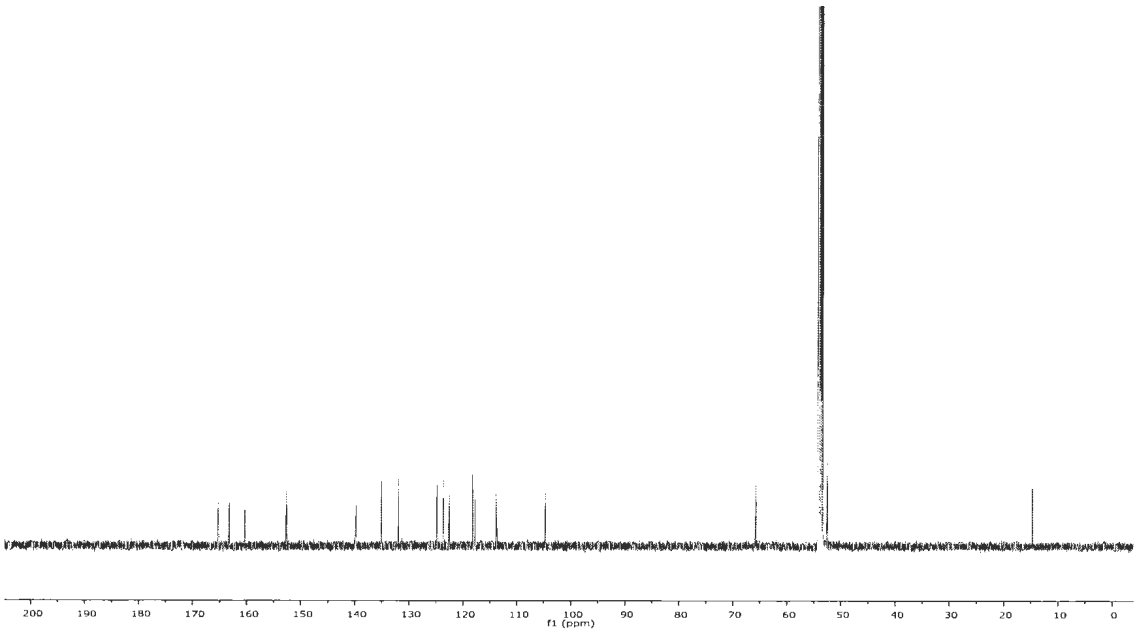
f1 (ppm)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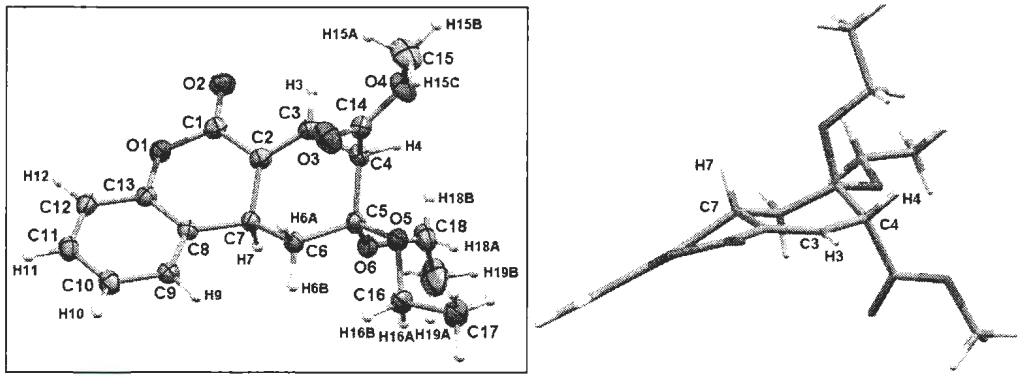
f1 (ppm)

2.7 X- ray crystallographic information for compound 56

56 (Figure 1a and 1b) also crystallized as a racemic twin in $P2_12_12_1$ with four formula units per unit cell (Figure 2). Absolute configuration at C4 is R, and at C7 is S.



(a) **(b)**

Figure 1: (a) Asymmetric unit of **56**, with 50% probability ellipsoids and (b) side-view represented with capped-sticks.

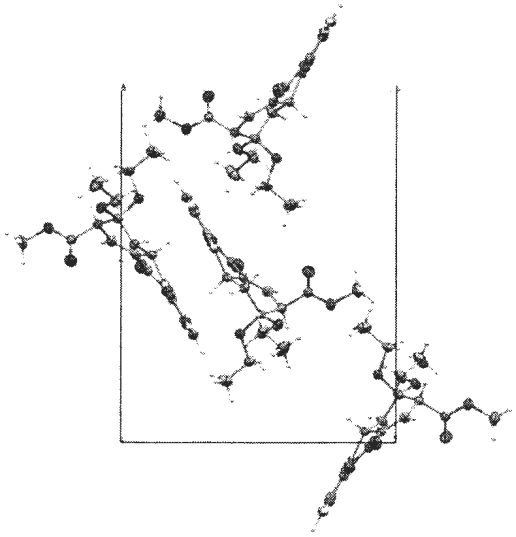


Figure 2: Packed unit cell of **56**, viewed along the a-axis.

Table 1 Summary of Crystallographic Data

Compound reference	**56**
Chemical formula	$C_{19}H_{22}O_6$
Formula Mass	346.38
Crystal system	Orthorhombic
a/Å	7.939(2)
b/Å	13.091(3)
c/Å	16.816(4)
α/°	90.00
β/°	90.00
γ/°	90.00
Unit cell volume/Å^3	1747.7(7)
Temperature/K	163(2)
Space group	$P2_12_12_1$
No. of formula units per unit cell, *Z*	4
Radiation type	MoKα
Absorption coefficient, μ/mm^{-1}	0.098
No. of reflections measured	23193
No. of independent reflections	3611
R_{int}	0.0331
Final R_1 values ($I > 2\sigma(I)$)	0.0323
Final $wR(F^2)$ values (all data)	0.0831
Goodness of fit on F^2	1.061

References

a) Altomare, A., Cascarano, G., Giacovazzo, C., Guagliardi, A., Burla, M., Polidori, G., and Camalli, M., *J. Appl. Cryst.*, **1994**, *27*, 435. b) Sheldrick, G.M. *Acta Cryst.* **2008**, *A64*, 112-122. c) Cromer, D. T. & Waber, J. T.; "International Tables for X-ray Crystallography", Vol. IV, The Kynoch Press, Birmingham, England, Table 2.2 A (1974). d) Ibers, J. A. & Hamilton, W. C., *Acta Crystallogr.*, **1964**, *17*, 781. e) Creagh, D. C. & McAuley, W.J .; "International Tables for Crystallography", Vol C, (A.J.C. Wilson, ed.), Kluwer Academic Publishers, Boston, Table 4.2.6.8, pages 219-222 (1992). f) Creagh, D. C. & Hubbell, J.H..; "International Tables for Crystallography", Vol C, (A.J.C. Wilson, ed.), Kluwer Academic Publishers, Boston, Table 4.2.4.3, pages 200-206 (1992). g) Hooft, R.W.W., Straver, L.H., Spek, A.L. *J. Appl. Crystallogr.* **2008**, *41*, 96-103. h) Dolomanov, O.V., Bourhis, L.J., Gildea, R.J., Howard, J.A.K., Puschmann, H. *J. Appl. Cryst.* **2009**, *42*, 339-341.

Chapter 3

Multicomponent Synthesis of 6*H*-Dibenzo[*b*,*d*]pyran-6-ones and a Total Synthesis of Cannabinol

This chapter is based upon the following publication:

Nandaluru, P. R.; Bodwell, G. J. *Org. Lett.* **2012**, *14*, 310–313.

Contributions of authors

G. J. Bodwell: research supervisor, manuscript preparation.

P. R. Nandaluru: experimental work, manuscript preparation.

3.1 Introduction

Multicomponent reactions (MCR) are highly valuable transformations due to their ability to incorporate three or more substrates into a single target in one operation.[1] MCRs typically achieve a substantial increase in molecular complexity and offer opportunities for diversity-oriented synthesis. They have proven to be valuable in drug discovery,[2] as well as in the total synthesis of natural products.[3]

Cannabinoids form a class of about 70 natural products that have been isolated from the plant *Cannabis sativa*.[4] Cannabinol (**1**), Δ^9-tetrahydrocannabinol (THC) (**2**), and cannabinodiol (**3**) are prominent members of this family (Figure 3.1). G-protein coupled cellular receptors, CB_1 and CB_2, are the targets of the cannabinoids.[5] While the CB_1 receptor is widely present in the central nervous system (CNS), especially the brain, the CB_2 receptor is less widely distributed. The CB_2 receptor is present in organs and tissues of immune-related systems, such as the spleen, thymus, bone marrow and B lymphocytes. Hence, cannabinoid agonists that selectively bind to one of the receptors are desirable in that side effects associated with the expression of the other receptor would be minimized.[6]

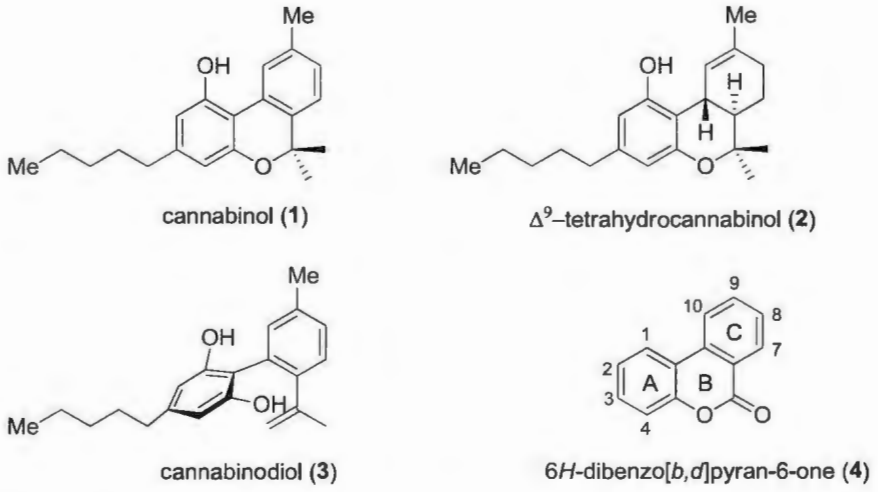


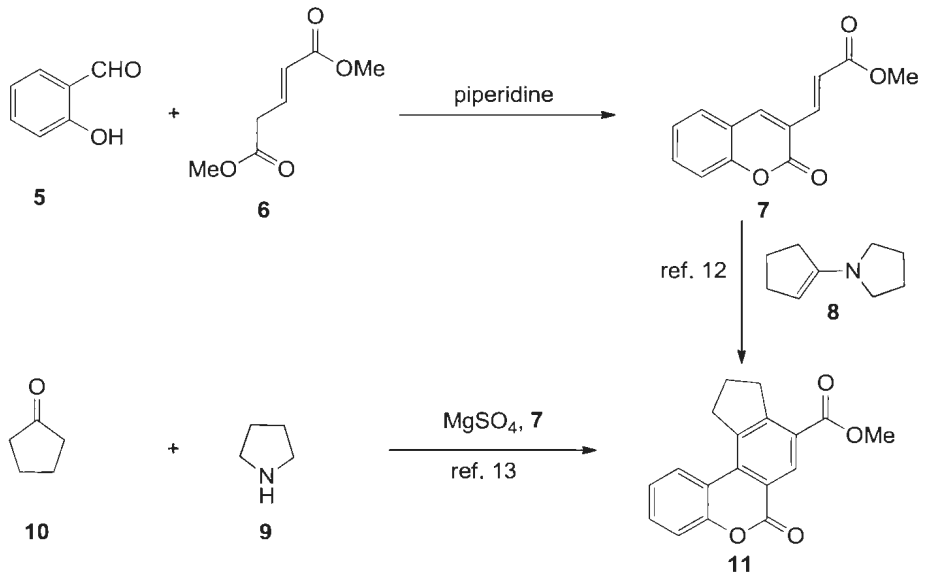
Figure 3.1. Prominent cannabinoids **1-3** and 6*H*-dibenzopyranone (**4**)

Several strategies for the synthesis of cannabinol (**1**) and its derivatives have been reported. These can be classified according to the key steps involved: 1) aromatization of tetrahydrocannabinols,[7] 2) a nucleophilic aromatic substitution / lactonization / Grignard reaction sequence,[8] 3) a Suzuki coupling / lactonization / Grignard reaction sequence,[9] 4) Ru-catalyzed cyclotrimerization followed by a Grignard reaction.[10] The latter three categories all involve the intermediacy of a derivative of 6*H*-dibenzo[*b,d*]pyranone (DBP) (**4**).

3.2 Results and Discussion

In connection with ongoing studies of the inverse electron demand Diels-Alder (IEDDA) reaction,[11] an IEDDA-based route to DBPs was developed by the Bodwell group. In its original form, an electron-deficient diene such as **7** (the product of a reaction between salicylaldehyde (**5**) and dimethyl glutaconate (**6**)) was reacted with an enamine, *e.g.* **8**, to afford the corresponding DBP, e.g. **11** (Scheme 3.1).[12] Subsequently,

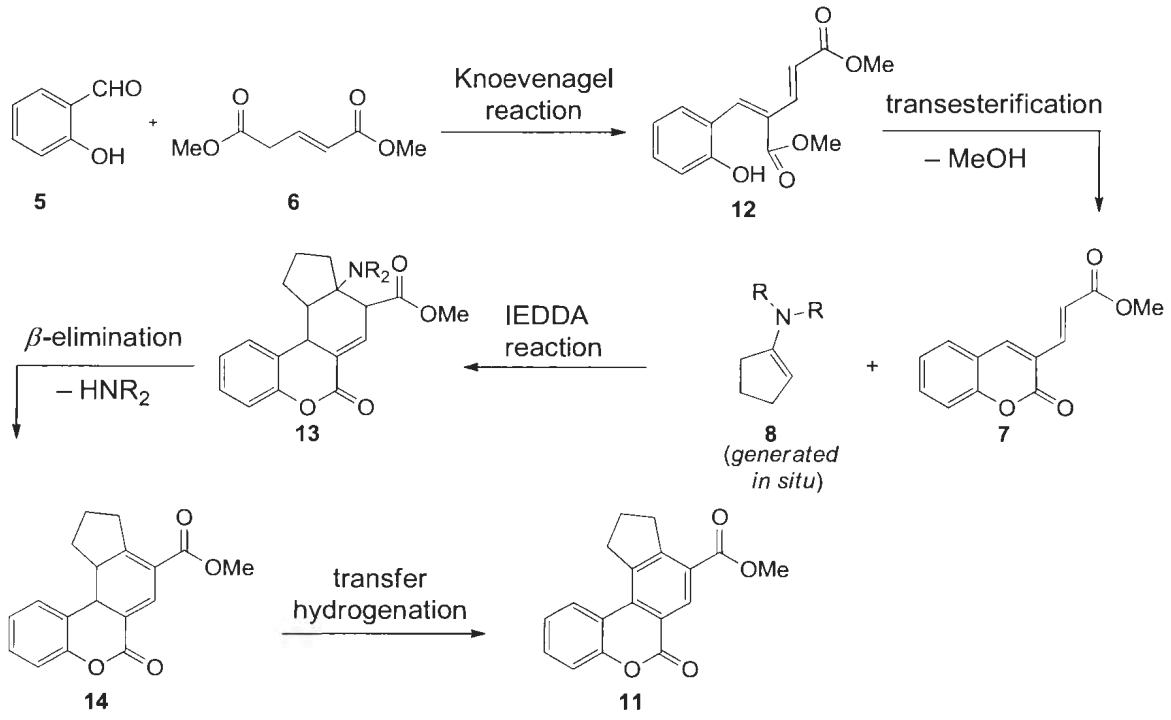
it was found that an electron-rich dienophile (the enamine) could be generated *in situ* from a secondary amine and a ketone, e.g. **9** and **10**.[13] The formation of DBP **11** was explained by a domino sequence consisting of an IEDDA reaction, a 1,2-elimination of the secondary amine and a dehydrogenation (most likely a transfer hydrogenation to a hydrogen acceptor, e.g. the enamine). This methodology was applied to the synthesis of a metabolite of ellagic acid, urolithin M7.[14]



Scheme 3.1. Stepwise IEDDA-based approaches to DBPs.

The observation that a 2° amine plays a catalytic role in both the formation of the electron-deficient diene (Knoevenagel condensation) and the electron-rich dienophile (enamine formation and subsequent elimination) prompted us to investigate the possibility of generating both IEDDA partners *in situ*. If successful, this would be a multicomponent domino reaction consisting of six steps: Knoevenagel reaction, transesterification, enamine formation, IEDDA reaction, 1,2-elimination and transfer

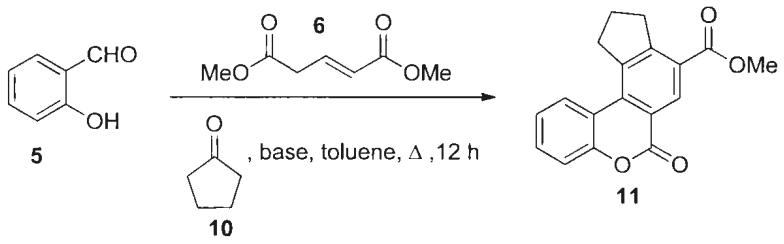
hydrogenation (Scheme 3.2). The anticipated dual catalytic function of the 2° amine presented an opportunity to perform auto-tandem organocatalysis.[15] The existence of precedents for the simultaneous *in situ* generation of both the diene and dienophile in the normal Diels-Alder reaction,[16] and the application of the IEDDA reaction in MCRs[17] augured well for the success of the proposed MCR.



Scheme 3.2. Six reactions in the formation of DBPs.

A mixture of salicylaldehyde (**5**), dimethyl glutaconate (**6**), and cyclopentanone (**10**) with morpholine as the base and toluene as the solvent was chosen for initial experiments. DBP **11** was obtained from the outset and, through variation of the relative amounts of the reactants and base, it was found that a maximum yield of 50% was

obtained when 1:2:2:2.5 ratio of 5:6:10:morpholine was used (entry 8, Table 3.1). While holding this ratio constant, the solvent and base were varied, and it was found that a maximum yield of 69% was obtained using pyrrolidine as the base and 1,4-dioxane as the solvent (entry 9, Table 3.2). Only with pyrrolidine as the base was any reaction at room temperature observed (tlc analysis). Although progress at room temperature was minimal, it was found that slightly better yields were obtained when reactions were first stirred at room temperature for 2 h before heating at reflux. Reactions conducted in 1,4-dioxane were somewhat slower than those in other solvents, so they were heated for 24 h instead of 12 h. Conditions have not yet been identified, under which sub-stoichiometric amounts of base afford competitive yields of **11**.



Entry	Salicylaldehyde (equiv.)	Dimethyl gluta-conate (equiv.)	Cyclopentanone (equiv.)	Morpholine (equiv.)	Isolated yield (%)
1	1	1	1	1	21
2	1	2	1	1	28
3	1	2	2	1	28
4	1	2	2	2	32
5	1	2	3	2	46
6	1	2	5	2	49
7	1	2	8	2	50
8	1	2	5	2.5	50
9	2	2	5	3	45

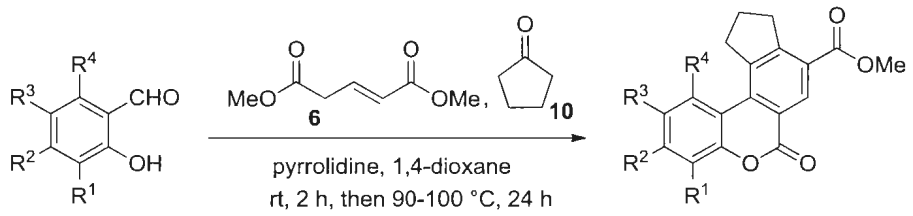
Table 3.1. Optimization of stoichiometry for the MCR.

Entry	Base (2.5 equiv.)	Solvent	Isolated yield (%)
1	piperidine	toluene	53
2	pyrrolidine	toluene	60
3	morpholine	ethanol	54
4	L-proline	ethanol	43
5	piperidine	ethanol	57
6	pyrrolidine[a]	ethanol	56
7	morpholine	1,4-dioxane[b]	49
8	piperidine	1,4-dioxane[b]	52
9	pyrrolidine	1,4-dioxane[b]	69
10	pyrrolidine[a]	chloroform	50
11	pyrrolidine[a]	THF	45
12	pyrrolidine[a]	acetonitrile	58

[a]The reaction mixture was stirred at room temperature for 2 h prior to heating at reflux.
[b]The reaction mixture was heated at reflux for 24 h

Table 3.2. Optimization of the base and the solvent for the MCR.

Using the best conditions for the synthesis of **11**, a series of salicylaldehydes[18] was reacted with dimethyl glutaconate (**6**) and cyclopentanone (**10**) to afford a set of A-ring substituted DBPs, most of which had been previously synthesized using a stepwise approach (Table 3.3).[12,13] The yields ranged from 0% to 79% and, where comparisons could be made, were superior (by 1–44%, Table S1) to those obtained using stepwise syntheses.



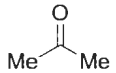
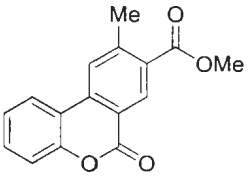
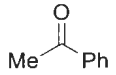
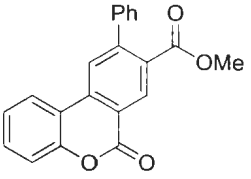
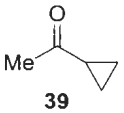
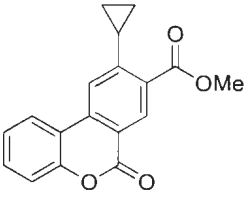
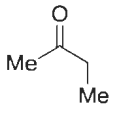
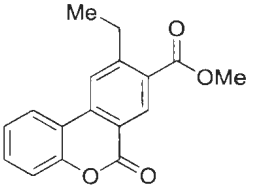
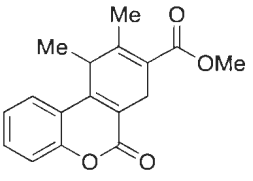
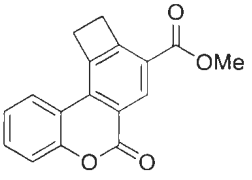
Entry	Salicylaldehdye	Substituent	6*H*-dibenzo[*b*,*d*] pyran-6-one	Isolated yield (%)
1	**5**	none	**11**	69
2	**15**	R^1 = OMe	**16**	57
3	**17**	R^2 = OMe	**18**	64
4	**19**	R^3 = OMe	**20**	79
5	**21**	R^4 = OMe	**22**	no product
6	**23**	R^1 = Me	**24**	48
7	**25**	R^2 = Me	**26**	62
8	**27**	R^3 = Me	**28**	68
9	**29**	R^3 = Br	**30**	67
10	**31**	$R^3 = CO_2Me$	**32**	51
11	**33**	$R^3 = NO_2$	**34**	10

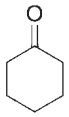
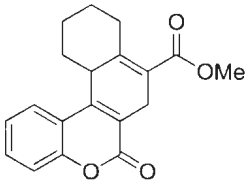
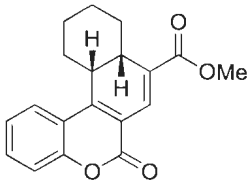
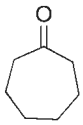
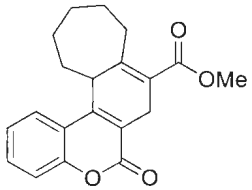
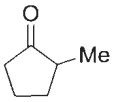
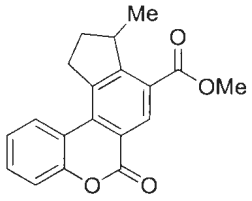
Table 3.3. Synthesis of A-ring substituted DBPs.

Only 6-methoxysalicylaldehyde (**21**) failed to afford any of the desired DBP (Table 3.3, Entry 5). Excluding cyclopentanone (**10**) from the reaction mixture led to the formation of the corresponding methoxydiene (*cf.* **7**),[19] and it was unreactive towards *in*

situ-generated enamine **8**. Presumably, steric hindrance at the transition state of the cycloaddition inhibits the reaction (TS-I, Figure 3.2). The other methoxy-substituted salicylaldehydes (**15**, **17**, **19**) and the corresponding methyl-substituted salicylaldehydes (**23**, **25**, **27**) reacted smoothly to afford the respective DHPs (48–79%). In both series, the yield for the 5-substituted system was the best, followed by the 4- and 3-isomers (Table 3.3, Entries 2–4 and 6–8). For the various 5-substituted salicylaldehydes (**19**, **27**, **29**, **31**, **33**), the yields were good until the substituent became strongly electron withdrawing (Table 3.3, Entries 4 and 8–11). However, the drop in yield only became drastic when a nitro group was present. This is presumably due to the preferential formation of an isomeric 2*H*-chromene over the desired nitrodiene.[13]

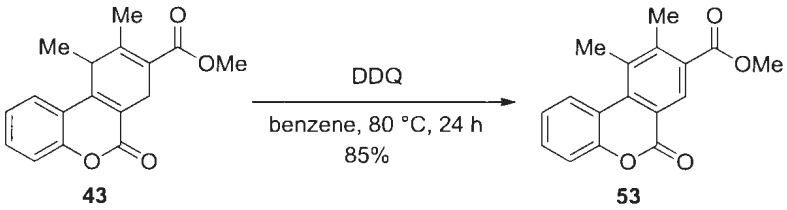
The ability of the MCR to generate C-ring-substituted DBPs was then probed by conducting it with a series of ketones, several of which had previously been used in stepwise DBP syntheses (Table 3.4).[12,13] Methyl ketones (**35**, **37**, **39**, **41**) reacted to afford the corresponding 9-substituted DBPs **36** (71%), **38** (36%), **40** (45%) and **42** (39%), respectively (Table 3.4, Entries 1–4). In the case of butanone (**41**), nonaromatized byproduct **43** was obtained in 12% yield. This compound arises from IEDDA reaction of diene **7** with the more highly substituted enamine derived from **41**. As previously observed for systems bearing a substituent (*i.e.* one that is not part of a ≤5-membered fused ring) at the 10 position of the DBP skeleton, dehydrogenation did not occur.[13] However, reaction of **43** with DDQ afforded the corresponding DBP **53** in 85% yield (Scheme 3.3).

Entry	Ketone	DBP	Isolated yield (%)
1	 **35**	 **36**	71
2[a]	 **37**	 **38**	36
3[a]	 **39**	 **40**	45
4	 **41**	 **42**  **43**	39, 12
5[a]	 **44**	 **45**	35

6[a]	 **46**	 **47**  **48**	60 (57:4)
7[a]	 **49**	 **50**	48
8[a]	 **51**	 **52**	36

[a] 3.0 equiv. of ketone was used instead of 5.0.

Table 3.4. Synthesis of C-ring substituted DBPs using the MCR.



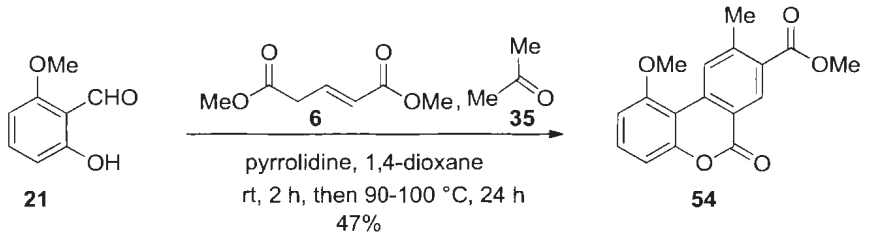
43 **53**

Scheme 3.3. Synthesis of DBP **53**.

In line with the stepwise DBP syntheses,[12,13] small cyclic ketones (≤5-membered) **44** and **10** reacted to afford DBPs **45** (35%) and **11** (69%), whereas larger cyclic ketones

(≥6-membered) **46** and **49** afforded nonaromatized products (Table 3.4, Entries 5–7). Cyclohexanone (**46**) gave a mixture of cyclohexadienes **47** and **48** (60% combined yield, 57:3 by ^{1}H NMR analysis), and cycloheptanone (**49**) gave only 1,4-cyclohexadiene **50** (48%). The aromatization of **47**/**48** and **49** using DDQ was reported earlier.[13] 2-Methylcyclopentanone (**51**) afforded only DBP **52**, which arises from reaction of the less substituted enamine (Table 3.4, Entry 8). Where comparisons are available, the yields of the MCR are mostly better than those of the corresponding stepwise syntheses (Table S2). Exceptions are acetophenone (**37**), cyclohexanone (**46**) and cycloheptanone (**49**).

6-Methoxysalicylaldehyde (**21**), which had failed to afford DBP **22** in a MCR with cyclopentanone (**10**), reacted with **6** and acetone (**35**) to provide DBP **54** (47%) (Scheme 3.4). The MCR clearly tolerates one, but not two substituents in the bay region of the DBP framework. When compared to the failed reaction of salicylaldehyde **21** with cyclopentanone (**10**), the enamine derived from acetone does not encounter significant steric repulsions with the methoxy group of the diene derived from **21** during IEDDA reaction (Figure 3.2, TS-II). Thus the DBP was obtained in the latter case and not the former case.



Scheme 3.4. MCR leading to DBP **54**.

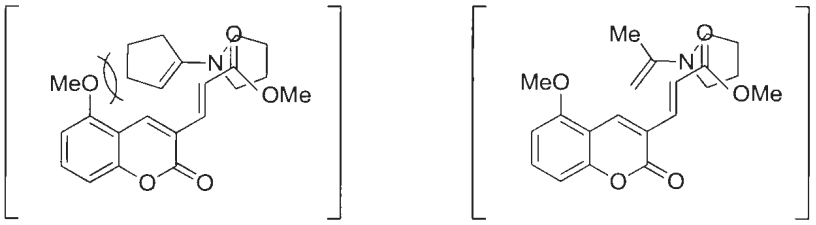
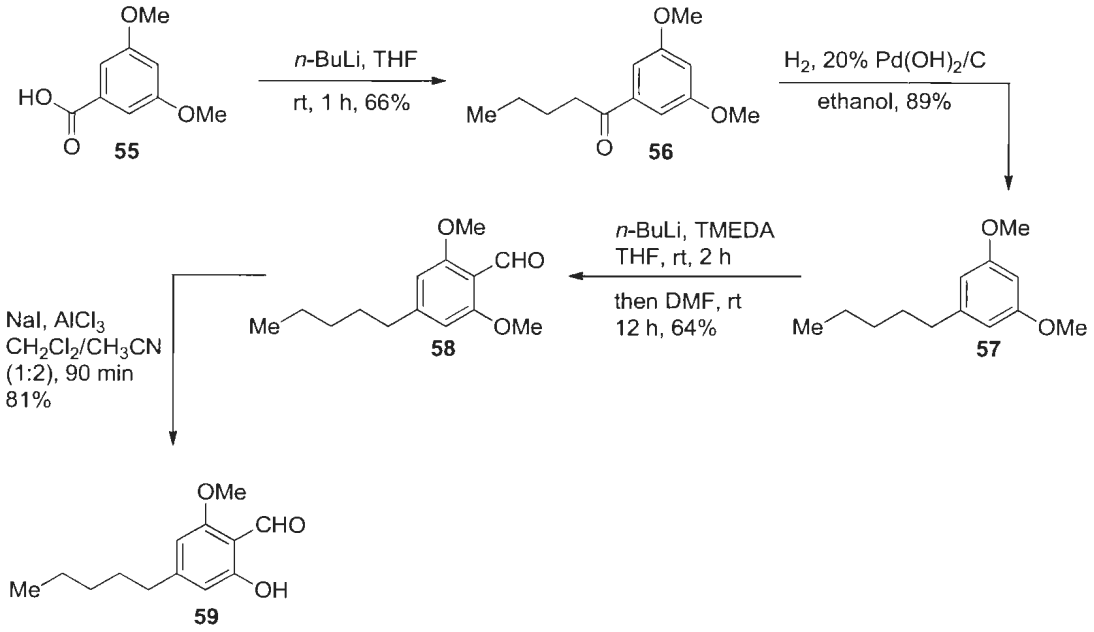


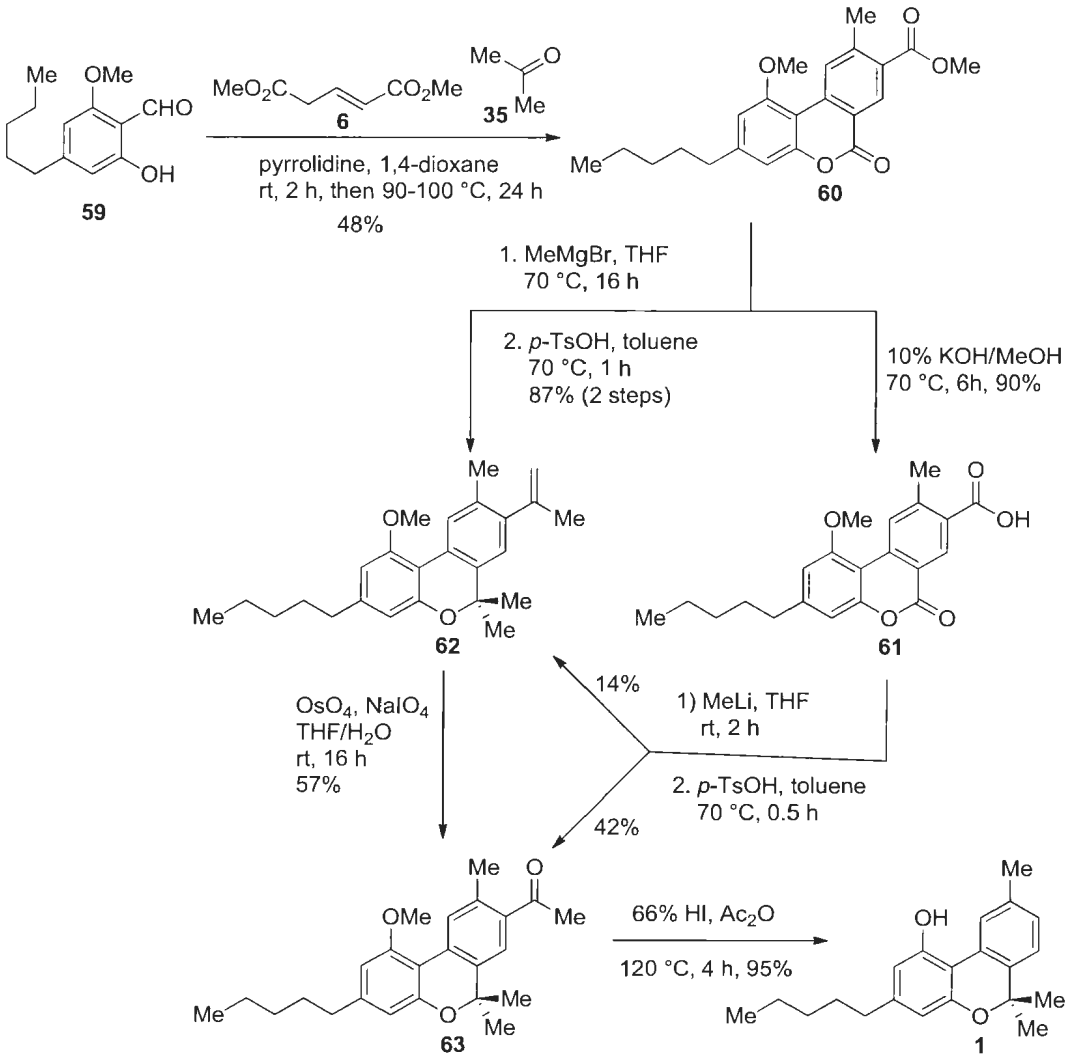
Figure 3.2. Transition states during cycloaddtions for diene derived from **21** with enamines derived from cyclopentanone and acetone.



Scheme 3.5. Synthesis of salicylaldehyde **58** using reported procedures.

Salicylaldehyde **59**, which was prepared from 3,5-dimethoxybenzoic acid (**55**) using known literature procedures (Scheme 3.5),[20] also reacted well with **6** and **35**, affording DBP **60** (48%) on a 1.2 g scale. This product was converted into cannabinol

(**1**) by two different four-step pathways (Scheme 3.6). Hydrolysis of **60** afforded acid **61** (90%). Treatment of **61** with MeLi (8 equiv.), followed by reaction of the crude product with *p*-TsOH, brought about simultaneous conversion of the acid group to a methyl ketone and the pyranone system to a dimethylpyran unit. Alkene **62** (14%) was consistently obtained along with the intended product **63** (42%). Alternatively, alkene **62** could be accessed by Grignard reaction of **60** with MeMgBr, followed by treatment of the crude product with *p*-TsOH (87%, 2 steps). Oxidative cleavage of the terminal alkene then afforded methyl ketone **63** (57%). The synthesis of cannabinol (**1**) was then completed by reacting **63** with HI/Ac_2O, which effected both demethylation and deacylation in high yield (95%). This seldom-used retro-Friedel-Crafts acylation relies upon the presence of an adjacent methyl group.[21]



Scheme 3.6. Synthesis of cannabinol (**1**)

3.3 Conclusions

In conclusion, previously reported stepwise syntheses of DBPs have been combined to afford a multicomponent domino reaction that performs substantially better than the stepwise approaches in most cases. Six reactions (Knoevenagel reaction, transesterification, enamine formation, IEDDA reaction, 1,2-elimination, transfer

hydrogenation) occur during the MCR, in which both IEDDA components are generaterd *in situ* and pyrrolidine mediates two separate processes (Knoevenagel reaction and enamine formation). This chemistry has been applied in the total synthesis of cannabinol (**1**).

3.4 References

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16) Ramachary, D. B.; Barbas III, C. F. *Chem. Eur. J.* **2004**, *10*, 5323.

17) (a) Kudale, A. A.; Kendall, J.; Miller, D. O.; Collins, J. L.; Bodwell, G. J. *J. Org. Chem.* **2008**, *73*, 8437. (b) Kudale, A. A.; Miller, D. O.; Dawe, L. N.; Bodwell, G. J. *Org. Biomol. Chem.* **2011**, *9*, 7196.

18) Salicylaldehydes **23**, **25** and **27** were synthesized using Skattebøl formylation: (a) Hofsløkken, N. U.; Skattebøl, L. *Acta Chem. Scand.* **1999**, *53*, 258. Salicylaldehyde **31** was synthesized using Duff formylation: Duff, C. J. *J. Chem. Soc.* **1941**, 547. (c) Lindoy, L. F.; Meehan, G. V.; Svenstrup, N. *Synthesis*, **1998**, 1029. The remaining salicylaldehydes were purchased.

19) This diene was obtained as a *ca.* 1:1 mixture with an unidentified byproduct.

20) Baeckström, P.; Sundström, G. *Acta Chem. Scand.* **1970**, 716. (b) Toräng, J.; Nieger, M.; Bräse, S. *Synthesis* **2005**, 1888.

21) Olah, G. A.; Laali, K.; Mehrotra, A. K. *J. Org. Chem.* **1983**, *48*, 3360.

3.5 Experimental procedures and characterization data

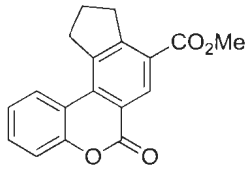
General I: The general experimental can be found in page 47.

General II: Acetone was distilled from K_2CO_3. Anhydrous 1,4-dioxane was obtained commercially.

General procedure for synthesis of 6*H*-dibenzo[*b*,*d*]pyran-6-ones (DBPs)

To a solution of the salicylaldehyde (1.0 equiv.), dimethyl glutaconate (**6**) (2.0 equiv.) and ketone (5.0 equiv.) in 1,4-dioxane (10 mL) was added pyrrolidine (2.5 equiv.) and the resulting mixture was stirred at room temperature for 2 h and then heated at 90–100 °C for 24 h. The reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure. The residue was dissolved in $CHCl_3$ (50 mL), washed with 1 M HCl solution (20 mL), dried over Na_2SO_4, gravity filtered and the solvent was removed under reduced pressure. The residue was subjected to column chromatography (1% MeOH / $CHCl_3$) and the product obtained was triturated with diethyl ether (2 × 5 mL) to give the DBP.

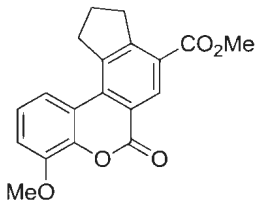
Benzo[*b*]-2,3-dihydro-1*H*-indeno[5,4-*d*]-6*H*-pyran-6-one-8-carboxylic acid methyl ester (11)[1]



Salicylaldehyde (**5**) (0.50 g, 4.09 mmol), dimethyl glutaconate (**6**) (1.29 g, 8.18 mmol), cyclopentanone (**10**) (1.72 g, 20.5 mmol) and pyrrolidine (0.72 g, 10 mmol) in 1,4-dioxane (10 mL) afforded DBP **11** (0.83 g, 69%) as a colorless solid. R_f = 0.60 (30% ethyl acetate / hexanes); mp 231–232 °C; IR (neat) ν = 1717 (s), 1601 (m), 1201 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 8.90 (s, 1H), 8.19 (d, J = 7.9 Hz, 1H), 7.51–7.48 (m, 1H), 7.36–7.32 (m, 2H), 3.94 (s, 3H), 3.47–3.42 (m, 4H), 2.27 (quint, J = 7.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 166.00, 160.95, 155.29, 151.91, 141.78, 134.43, 132.02, 130.72, 126.86, 126.62, 124.34, 120.37, 118.81, 117.90, 52.11, 35.31, 33.59, 24.96; EI-MS *m/z* (%) 294 (M^+, 100%), 279 (22), 263 (40), 262 (30), 191 (23), 178 (21), 152 (11); HRMS [EI-(+)] calcd for $C_{18}H_{14}O_4$ 294.0892, found 294.0888.

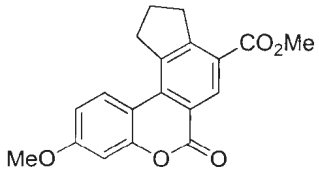
[1] Characterization data for this compound were originally reported in: Pottie, I. R.; Nandaluru, P. R.; Benoit, W. L.; Miller, D. O.; Dawe, L. N.; Bodwell, G. J. *J. Org. Chem.* **2011**, *76*, 9015. The data presented here are (in whole, or in part) new, but virtually identical to the previously reported data.

4-Methoxybenzo[*b*]-2,3-dihydro-1*H*-indeno[5,4-*d*]-6*H*-pyran-6-one-8-carboxylic acid methyl ester (16)



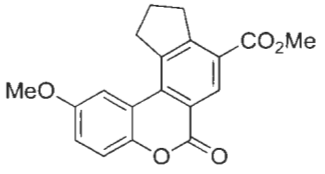
Salicylaldehyde **15** (0.50 g, 3.3 mmol), dimethyl glutaconate (**6**) (1.03 g, 6.52 mmol), cyclopentanone (**10**) (1.38 g, 16.4 mmol) and pyrrolidine (0.58 g, 8.2 mmol) in 1,4-dioxane (10 mL) afforded DBP **16** (0.60 g, 57%) as a colorless solid. R_f = 0.50 (30% ethyl acetate / hexanes); mp 224–227 °C; IR (neat) ν = 1714 (s), 1584 (m), 1275 (m), 1232 (m), 1206 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ = 8.94 (s, 1H), 7.78 (d, J = 8.3 Hz, 1H), 7.26 (t, J = 8.2 Hz, 1H), 7.09–7.07 (m, 1H), 3.98 (s, 3H), 3.94 (s, 3H), 3.46–3.42 (m, 4H), 2.26 (quint, J = 7.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 165.99, 160.41, 155.25, 147.94, 142.05, 141.70, 134.63, 132.01, 126.60, 123.79, 120.32, 119.44, 118.23, 112.66, 56.22, 52.07, 35.35, 33.58, 24.94; APCI-(+)-MS *m/z* (%) 326 (24), 325 ($[M + 1]^+$, 100); HRMS [EI-(+)] calcd for $C_{19}H_{16}O_5$ 324.0998, found 324.0996.

3-Methoxybenzo[*b*]-2,3-dihydro-1*H*-indeno[5,4-*d*]-6*H*-pyran-6-one-8-carboxylic acid methyl ester (18)



Salicylaldehyde **17** (0.50 g, 3.3 mmol), dimethyl glutaconate (**6**) (1.03 g, 6.52 mmol), cyclopentanone (**10**) (1.38 g, 16.4 mmol) and pyrrolidine (0.58 g, 8.2 mmol) in 1,4-dioxane (10 mL) afforded DBP **18** (0.68 g, 64%) as a colorless solid. R_f = 0.50 (30% ethyl acetate / hexanes); mp 260–261 °C; IR (neat) ν = 1713 (s), 1616 (m), 1241 (m), 1201 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ = 8.94 (s, 1H), 8.14 (d, J = 8.8 Hz, 1H), 6.93–6.90 (m, 2H), 3.94 (s, 3H), 3.90 (s, 3H), 3.46–3.42 (m, 4H), 2.28 (quint, J = 7.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 166.48, 161.86, 161.58, 155.50, 153.89, 140.93, 135.24, 132.55, 128.27, 125.97, 119.43, 112.32, 112.24, 102.30, 56.00, 52.35, 35.46, 33.94, 25.24; APCI-(+)-MS *m/z* (%) 326 (23), 325 ([M + 1]$^+$, 100); HRMS [EI-(+)] calcd for $C_{19}H_{16}O_5$ 324.0998, found 324.1005.

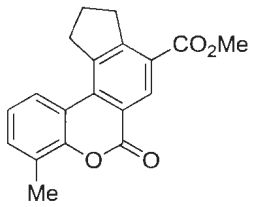
2-Methoxybenzo[*b*]-2,3-dihydro-1*H*-indeno[5,4-*d*]-6*H*-pyran-6-one-8-carboxylic acid methyl ester (20)[1]



Salicylaldehyde **19** (0.50 g, 3.3 mmol), dimethyl glutaconate (**6**) (1.03 g, 6.52 mmol), cyclopentanone (**10**) (1.38 g, 16.4 mmol) and pyrrolidine (0.58 g, 8.2 mmol) in 1,4-dioxane (10 mL) afforded DBP **20** (0.84 g, 79%) as a colorless solid. R_f = 0.50 (30% ethyl acetate / hexanes); mp 244–245 °C; IR (neat) ν = 1717 (s), 1598 (m), 1280 (m), 1244 (s), 1204 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ = 8.96 (s, 1H), 7.71 (d, J = 2.7 Hz, 1H), 7.33 (d, J = 9.0 Hz, 1H), 7.09 (dd, J = 9.0, 2.8 Hz, 1H), 3.95 (s, 3H), 3.90 (s,

3H), 3.50 (t, J = 7.5 Hz, 2H), 3.46 (t, J = 7.8 Hz, 2H), 2.29 (quint, J = 7.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 166.07, 161.17, 155.94, 155.21, 146.24, 141.74, 134.46, 132.17, 126.77, 120.59, 119.34, 118.59, 116.77, 111.34, 55.85, 52.14, 35.19, 33.58, 25.01; APCI-(+)-MS *m/z* (%) 327 (4), 326 (23), 325 ([M + 1]$^+$, 100); HRMS [EI-(+)] calcd for $C_{19}H_{16}O_5$ 324.0998, found 324.1000.

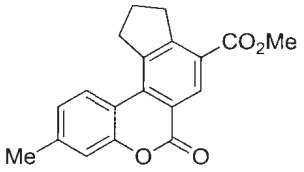
4-Methylbenzo[*b*]-2,3-dihydro-1*H*-indeno[5,4-*d*]-6*H*-pyran-6-one-8-carboxylic acid methyl ester (24)[1]



Salicylaldehyde **23** (0.50 g, 3.7 mmol), dimethyl glutaconate (**6**) (1.16 g, 7.33 mmol), cyclopentanone (**10**) (1.54 g, 18.3 mmol) and pyrrolidine (0.65 g, 9.1 mmol) in 1,4-dioxane (10 mL) afforded DBP **24** (0.55 g, 48%) as a colorless solid. R_f = 0.60 (30% ethyl acetate / hexanes); mp 228–229 °C; lR (neat) ν = 1714 (s), 1588 (w), 1236 (s), 1225 (s), 1195 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 8.89 (s, 1H), 8.02 (d, J = 8.1 Hz, 1H), 7.35 (d, J = 7.2 Hz, 1H), 7.22 (t, J = 7.8 Hz, 1H), 3.94 (s, 3H), 3.45–3.41 (m, 4H), 2.47 (s, 3H), 2.26 (quint, J = 7.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 166.05, 160.96, 155.13, 150.16, 141.79, 134.85, 132.17, 131.93, 127.02, 126.42, 124.56, 123.65, 120.23, 118.47, 52.07, 35.46, 33.60, 24.98, 16.30; GC-MS *m/z* (%) 308 (M$^+$, 100), 293 (16), 277

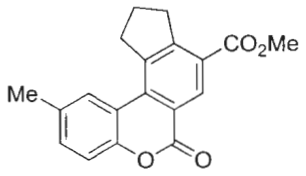
(34), 248 (15), 205 (17), 189 (25), 165 (13); HRMS [EI-(+)] calcd for $C_{19}H_{16}O_4$ 308.1049, found 308.1045.

3-Methylbenzo[*b*]-2,3-dihydro-1*H*-indeno[5,4-*d*]-6*H*-pyran-6-one-8-carboxylic acid methyl ester (26)[1]



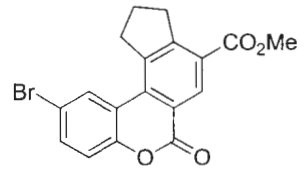
Salicylaldehyde **25** (0.50 g, 3.7 mmol), dimethyl glutaconate (**6**) (1.16 g, 7.33 mmol), cyclopentanone (**10**) (1.54 g, 18.3 mmol) and pyrrolidine (0.65 g, 9.1 mmol) in 1,4-dioxane (10 mL) afforded DBP **26** (0.70 g, 62%) as a colorless solid. R_f = 0.60 (30% ethyl acetate / hexanes); mp 268–269 °C; IR (neat) ν = 1710 (s), 1623 (w), 1597 (w), 1282 (w), 1236 (s), 1206 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ = 8.88 (s, 1H), 8.04 (d, J = 8.6 Hz, 1H), 7.14–7.12 (m, 2H), 3.94 (s, 3H), 3.42 (t, J = 7.7 Hz, 4H), 2.44 (s, 3H), 2.27 (quint, J = 7.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 166.07, 161.17, 155.13, 151.91, 141.73, 141.33, 134.62, 132.03, 126.61, 126.12, 125.42, 119.98, 118.03, 116.17, 52.06, 35.21, 33.59, 24.89, 21.34; GC-MS *m/z* (%) 308 (M^+, 100), 293 (14), 277 (37), 249 (15), 205 (16), 189 (25), 165 (12); HRMS [EI-(+)] calcd for $C_{19}H_{16}O_4$ 308.1049, found 308.1044.

2-Methylbenzo[*b*]-2,3-dihydro-1*H*-indeno[5,4-*d*]-6*H*-pyran-6-one-8-carboxylic acid methyl ester (28)[1]



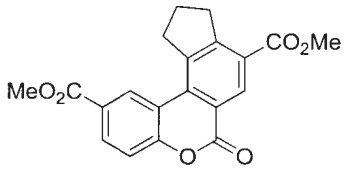
Salicylaldehyde **27** (0.50 g, 3.7 mmol), dimethyl glutaconate (**6**) (1.16 g, 7.33 mmol), cyclopentanone (**10**) (1.54 g, 18.3 mmol) and pyrrolidine (0.65 g, 9.1 mmol) in 1,4-dioxane (10 mL) afforded DBP **28** (0.77 g, 68%) as a colorless solid. R_f = 0.60 (30% ethyl acetate / hexanes); mp 258–260 °C; IR (neat) ν = 1714 (s), 1597 (w), 1281 (w), 1234 (m), 1206 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ = 8.92 (s, 1H), 7.97 (s, 1H), 7.31–7.26 (m, 2H), 3.94 (s, 3H), 3.47–3.43 (m, 4H), 2.47 (s, 3H), 2.29–2.26 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 166.09, 161.19, 155.17, 150.01, 141.69, 134.57, 133.82, 132.08, 131.57, 126.94, 126.49, 120.46, 118.52, 117.61, 52.10, 35.39, 33.58, 25.00, 21.40; EI-MS *m/z* (%) 308 (M^+, 100), 277 (29), 249 (14), 205 (14), 189 (11), 109 (5); HRMS [EI-(+)] calcd for $C_{19}H_{16}O_4$ 308.1049, found 308.1046.

2-Bromobenzo[*b*]-2,3-dihydro-1*H*-indeno[5,4-*d*]-6*H*-pyran-6-one-8-carboxylic acid methyl ester (30)[1]



Salicylaldehyde **29** (0.50 g, 2.5 mmol), dimethyl glutaconate (**6**) (0.79 g, 5.0 mmol), cyclopentanone (**10**) (1.04 g, 12.4 mmol) and pyrrolidine (0.44 g, 6.2 mmol) in 1,4-dioxane (10 mL) afforded DBP **30** (0.62 g, 67%) as a colorless solid. R_f = 0.70 (30% ethyl acetate / hexanes): mp 262–263 °C; IR (neat) ν = 1717 (s), 1594 (w), 1274 (m), 1232 (m), 1202 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ = 8.94 (s, 1H), 8.33 (s, 1H), 7.61 (d, J = 8.4 Hz, 1H), 7.29–7.26 (m, 1H), 3.96 (s, 3H), 3.47 (t, J = 7.1 Hz, 4H), 2.32–2.29 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 165.87, 160.39, 155.68, 150.86, 142.02, 133.50, 133.16, 132.17, 129.48, 127.35, 120.55, 120.41, 119.60, 117.14, 52.24, 35.13, 33.61, 25.01; EI-MS *m/z* (%) 374 (M^+ ^{81}Br, 97), 372 ($M^{+79}Br$, 100), 343 (29), 341 (33), 178 (14), 176 (20); HRMS [EI-(+)] calcd for $C_{18}H_{13}O_4{}^{79}Br$ 371.9997, found 371.9999.

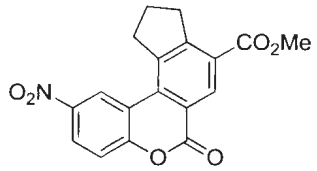
Benzo[*b*]-2,3-dihydro-1*H*-indeno[5,4-*d*]-6*H*-pyran-6-one-2,8-dicarboxylic acid dimethyl ester (32)[1]



Salicylaldehyde **31** (0.50 g, 2.8 mmol), dimethyl glutaconate (**6**) (0.88 g, 5.6 mmol), cyclopentanone (**10**) (1.17 g, 13.9 mmol) and pyrrolidine (0.49 g, 6.9 mmol) in 1,4-dioxane (10 mL) afforded DBP **32** (0.50 g, 51%) as a colorless solid. R_f = 0.60 (30% ethyl acetate / hexanes): mp > 300 °C; IR (neat) ν = 1738 (m), 1717 (s), 1611 (w), 1256 (s), 1236 (m), 1203 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ = 8.96 (d, J = 1.3 Hz, 1H), 8.94 (s, 1H), 8.17 (dd, J = 8.6, 1.7 Hz, 1H), 7.43 (d, J = 8.6 Hz, 1H), 3.99 (s, 3H), 3.96

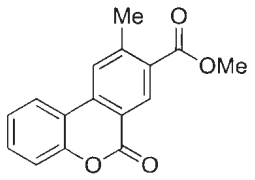
(s, 3H), 3.56 (t, J = 7.5 Hz, 2H), 3.47 (t, J = 7.8 Hz, 2H), 2.32 (quint, J = 7.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 166.05, 165.91, 160.35, 155.84, 154.90, 142.23, 133.66, 132.15, 131.71, 129.05, 127.28, 126.36, 120.29, 118.76, 118.11, 52.55, 52.24, 35.19, 33.66, 25.01; GC-MS *m/z* (%) 352 (M^+, 100), 321 (57), 293 (22), 189 (21), 176 (30); HRMS [EI-(+)] calcd for $C_{20}H_{16}O_6$ 352.0947, found 352.0946.

2-Nitrobenzo[*b*]-2,3-dihydro-1*H*-indeno[5,4-*d*]-6*H*-pyran-6-one-8-carboxylic acid methyl ester (34)[1]



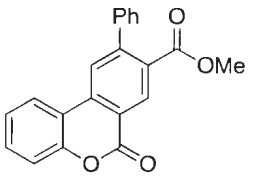
Salicylaldehyde **33** (0.50 g, 3.0 mmol), dimethyl glutaconate (**6**) (0.94 g, 6.0 mmol), cyclopentanone (**10**) (1.25 g, 14.9 mmol) and pyrrolidine (0.53 g, 7.5 mmol) in 1,4-dioxane (10 mL) afforded DBP **34** (0.10 g, 10%) as a colorless solid. R_f = 0.70 (30% ethyl acetate / hexanes); mp 272–273 °C; IR (neat) ν = 1752 (m), 1726 (s), 1599 (w), 1529 (m), 1350 (m), 1272 (w), 1205 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 9.21 (s, 1H), 8.98 (s, 1H), 8.40 (d, J = 8.1, 1H), 7.54 (d, J = 8.7 Hz, 1H), 3.98 (s, 3H), 3.59 (m, 2H), 3.51 (t, J = 7.4 Hz, 2H), 2.38–2.35 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 165.68, 159.57, 156.38, 155.72, 144.08, 142.57, 132.53, 132.34, 128.15, 125.59, 122.96, 120.24, 119.33, 119.00, 52.40, 35.10, 33.70, 25.02; EI-MS *m/z* (%) 339 (M^+, 100), 307 (48), 280 (22), 234 (13), 176 (16); HRMS [EI-(+)] calcd for $C_{18}H_{13}NO_6$ 339.0743, found 339.0746.

9-Methyl-6*H*-dibenzo[*b*,*d*]pyran-6-one-8-carboxylic acid methyl ester (36)[1]



Salicylaldehyde (**5**) (0.50 g, 4.1 mmol), dimethyl glutaconate (**6**) (1.29 g, 8.16 mmol), anhydrous acetone (**35**) (1.18 g, 20.3 mmol) and pyrrolidine (0.72 g, 10 mmol) in 1,4-dioxane (10 mL) afforded DBP **36** (0.78 g, 71%) as a colorless solid. R_f = 0.60 (30% ethyl acetate / hexanes); mp 216–217 °C; IR (neat) ν= 1715 (s), 1608 (m), 1311 (m), 1240 (m), 1186 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ = 8.92 (s, 1H), 8.07–8.05 (m, 1H), 7.94 (s, 1H), 7.53–7.50 (m, 1H), 7.36–7.34 (m, 2H), 3.95 (s, 3H), 2.80 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 166.30, 160.42, 152.02, 147.50, 137.09, 133.58, 131.44, 130.13, 124.71, 124.67, 123.25, 118.96, 117.95, 117.16, 52.22, 22.55; EI-MS *m/z* (%) 268 (M^+, 71), 237 (100), 181 (31), 152 (28), 118 (11); HRMS [EI-(+)] calcd for $C_{16}H_{12}O_4$ 268.0736, found 268.0738.

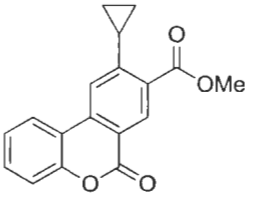
9-Phenyl-6*H*-dibenzo[*b*,*d*]pyran-6-one-8-carboxylic acid methyl ester (38)[1]



Salicylaldehyde (**5**) (0.50 g, 4.1 mmol), dimethyl glutaconate (**6**) (1.29 g, 8.16 mmol), acetophenone (**37**) (1.47 g, 12.3 mmol) and pyrrolidine (0.72 g, 10 mmol) in 1,4-dioxane (10 mL) afforded DBP **38** (0.49 g, 36%) as a colorless solid. R_f = 0.40 (30% ethyl

acetate / hexanes); mp 195-196 °C; IR (nujol) ν = 1738 (s), 1719 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ = 8.89 (s, 1H), 8.09–8.07 (m, 2H), 7.56–7.53 (m, 1H), 7.50–7.46 (m, 3H), 7.42–7.40 (m, 3H), 7.37–7.34 (m, 1H), 3.74 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 167.26, 160.52, 152.24, 149.08, 140.21, 137.00, 133.12, 131.80, 131.49, 128.57, 128.38, 125.03, 124.54, 123.56, 120.11, 118.26, 117.46, 52.59; GC-MS *m/z* (%) 330 (M^+, 81), 299 (100), 271 (11), 255 (25), 226 (40), 213 (24); Anal. calcd for $C_{21}H_{14}O_4$; C, 76.36; H, 4.27. Found C, 76.20; H, 4.10.

9-Cyclopropyl-6*H*-dibenzo[*b,d*]pyran-6-one-8-carboxylic acid methyl ester (40)

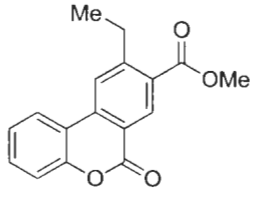


Salicylaldehyde (**5**) (0.50 g, 4.1 mmol), dimethyl glutaconate (**6**) (1.29 g, 8.16 mmol), cyclopropyl methyl ketone (**39**) (1.03 g, 12.3 mmol) and pyrrolidine (0.72 g, 10 mmol) in 1,4-dioxane (10 mL) afforded DBP **40** (0.55 g, 45%) as a colorless solid.[2] R_f = 0.50 (30% ethyl acetate / hexanes); mp 190–192 °C; IR (neat) ν = 1711 (s), 1608 (s), 1225 (s), 1187 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ = 8.84 (s, 1H), 8.03 (d, J = 8.1 Hz, 1H), 7.65 (s, 1H), 7.53–7.50 (m, 1H), 7.36–7.33 (m, 2H), 3.97 (s, 3H), 2.95–2.90 (m, 1H), 1.24–1.20 (m, 2H), 0.93–0.89 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 167.19, 160.80, 152.93, 152.35, 137.48, 133.51, 131.97, 131.77, 125.03, 123.48, 118.67, 118.54, 118.38,

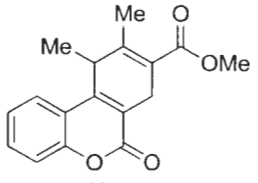
[2] The product obtained from chromatography was triturated with hexanes (3 × 5 mL) instead of diethyl ether.

117.68, 52.76, 14.57, 10.79; APCI-(+)-MS *m/z*(%) 296 (20), 295 ([M + 1]$^+$, 100), 263 (8); HRMS [EI-(+)] calcd for $C_{18}H_{14}O_4$ 294.0892, found 294.0888.

9-Ethyl-6*H*-dibenzo[*b,d*]pyran-6-one-8-carboxylic acid methyl ester (42) and 7,10-dihydro-9,10-dimethyl-6*H*-dibenzo[*b,d*]pyran-6-one-8-carboxylic acid methyl ester (43)



42

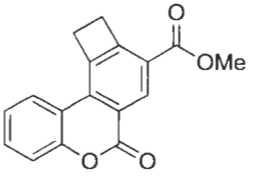


43

Salicylaldehyde (**5**) (0.50 g, 4.1 mmol), dimethyl glutaconate (**6**) (1.29 g, 8.16 mmol), butanone (**41**) (1.47 g, 20.4 mmol) and pyrrolidine (0.72 g, 10 mmol) in 1,4-dioxane (10 mL) afforded (prior to trituration) a mixture of DBP **42** and dihydro-DBP **43** as a colorless solid. Trituration of the product obtained from chromatography with diethyl ether (3 × 5 mL) afforded DBP **42** (0.44 g, 39%) as a colorless solid. The ether washes were concentrated under reduced pressure and subjected to column chromatography (dichloromethane) to give dihydro-DBP **43** (0.14 g, 12%) as a colorless solid. **42**: R_f = 0.60 (30% ethyl acetate / hexanes); mp 196–197 °C ; IR (neat) ν = 1715 (s), 1608 (m), 1297 (w), 1251 (m), 1228 (s), 1282 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 8.90 (s, 1H), 8.10–8.08 (m, 1H), 7.98 (s, 1H), 7.53–7.50 (m, 1H), 7.37–7.34 (m, 2H), 3.94 (s, 3H), 3.19 (q, J = 7.5 Hz, 2H), 1.34 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 166.40, 160.50, 153.29, 152.04, 137.29, 133.75, 131.44, 130.02, 124.73, 123.29, 123.27,

118.95, 118.01, 117.33, 52.33, 28.22, 15.59; APCI-(+)-MS *m/z* (%) 284 (20), 283 ([M + 1]$^+$, 100), 253 (6); HRMS [EI-(+)] calcd for $C_{17}H_{14}O_4$ 282.0892, found 282.0895. **43**: R_f = 0.55 (30% ethyl acetate / hexanes); mp 129–130 °C; IR (neat) ν = 1708 (s), 1655 (w), 1289 (w), 1206 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 7.61 (d, J = 7.2 Hz, 1H), 7.52–7.49 (m, 1H), 7.37–7.36 (m, 1H), 7.34–7.30 (m, 1H), 3.82–3.77 (m, 1H), 3.80 (s, 3H), 3.71–3.69 (m, 1H), 3.27–3.21 (m, 1H), 2.31 (s, 3H), 1.40 (d, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 167.48, 160.70, 153.10, 148.38, 147.55, 130.81, 124.33, 123.29, 121.67, 120.50, 117.76, 117.40, 51.58, 38.97, 26.64, 19.96, 19.55; APCI-(+)-MS *m/z* (%) 286 (17), 285 ([M + 1]$^+$, 87), 254 (19), 253 (100); HRMS [EI-(+)] calcd for $C_{17}H_{16}O_4$ 284.1049, found 284.1044.

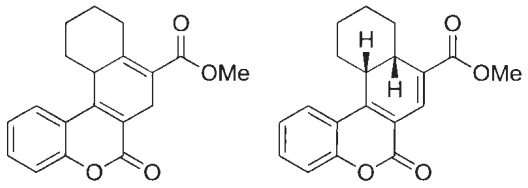
Dibenzopyranone 45[1]



Salicylaldehyde (**5**) (0.50 g, 4.1 mmol), dimethyl glutaconate (**6**) (1.29 g, 8.16 mmol), cyclobutanone (**44**) (0.86 g, 12 mmol) and pyrrolidine (0.72 g, 10 mmol) in 1,4-dioxane (10 mL) afforded DBP **45** (0.40 g, 35%) as a colorless solid. R_f = 0.60 (30% ethyl acetate / hexanes); mp 245–246 °C; IR (neat) ν = 1726 (s), 1612 (m), 1237 (s), 1210 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 8.83 (s, 1H), 7.83 (d, J = 7.1 Hz, 1H), 7.50 (t, J = 7.2 Hz, 1H), 7.34–7.31 (m, 2H), 3.94 (s, 3H), 3.59 (s, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 165.00, 161.02, 155.32, 151.89, 140.84, 132.97, 131.63, 131.30, 125.84, 125.31,

124.67, 119.87, 117.53, 117.31, 52.16, 32.16, 31.05; EI-MS *m/z* (%) 280 (M^+, 100), 279 (73), 249 (17), 221 (14), 165 (36), 139 (9); HRMS [EI-(+)] calcd for $C_{17}H_{12}O_4$ 280.0736, found 280.0735.

Benzo[*b*]-3,5,6,7,8,8a-hexahydronaphthaleno[2,1-*d*]-6*H*-pyran-6-one-8-carboxylic acid methyl ester (47)[1] and (8a*S,12a*R**)-benzo[*b*]-4a,5,6,7,8,8a-hexahydronaphthaleno[2,1-*d*]-6*H*-pyran-6-one-8-carboxylic acid methyl ester (48)[1]**

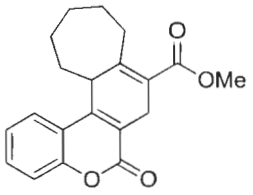


47 **48**

Salicylaldehyde (**5**) (0.50 g, 4.1 mmol), dimethyl glutaconate (**6**) (1.29 g, 8.16 mmol), cyclohexanone (**46**) (1.03 g, 12.2 mmol) and pyrrolidine (0.72 g, 10 mmol) in 1,4-dioxane (10 mL) afforded a mixture of dihydro-DBPs **47** and **48** as a colorless solid.[2] Column chromatography afforded a pure sample of **47** (0.23 g, 18%) and a 12.5 : 1 mixture (^{1}H NMR analysis) of **47** and **48** (0.53 g, 42%). Combined yield = 0.76 g (60%); **47**:**48** = 57:3. **47**: R_f = 0.50 (30% ethyl acetate / hexanes); mp 168–170 °C; IR (neat) ν = 1703 (s), 1607 (w), 1222 (m), 1207 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 7.58 (d, J = 8.0 Hz, 1H), 7.51–7.48 (m, 1H), 7.37–7.35 (m, 1H), 7.32–7.29 (m, 1H), 3.80 (s, 3H), 3.80–3.76 (m, 1H), 3.64–3.59 (m, 2H), 3.40 (dd, J = 23.9, 6.0 Hz, 1H), 2.43–2.39 (m, 1H), 2.09–2.06 (m, 1H), 1.96–1.94 (m, 2H), 1.83–1.80 (m, 1H), 1.61–1.43 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 167.83, 160.72, 152.99, 148.72, 145.36, 130.62,

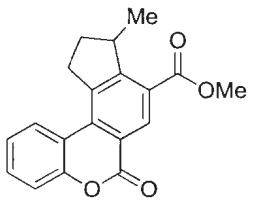
124.15, 123.62, 120.02, 118.43, 117.80, 117.40, 51.59, 42.53, 36.70, 32.03, 29.32, 27.05, 26.94; EI-MS *m/z* (%) 310 (M^+, 59), 279 (78), 251 (100), 223 (15), 209 (15), 181 (22), 165 (35); HRMS [EI-(+)] calcd for $C_{19}H_{18}O_4$ 310.1205, found 310.1199.

Dihydrodibenzopyranone 50[1]



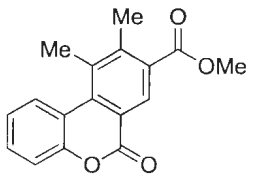
Salicylaldehyde (**5**) (0.50 g, 4.1 mmol), dimethyl glutaconate (**6**) (1.29 g, 8.16 mmol), cycloheptanone (**49**) (1.37 g, 12.2 mmol) and pyrrolidine (0.72 g, 10 mmol) in 1,4-dioxane (10 mL) afforded dihydro-DBP **50** (0.64 g, 48%) as a colorless solid.[2] R_f = 0.50 (30% ethyl acetate / hexanes); mp 135–136 °C; IR (neat) ν = 1701 (s), 1606 (m), 1290 (m), 1262 (w), 1225(s), 1210 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ = 7.60–7.58 (m, 1H), 7.53–7.49 (m, 1H), 7.38–7.36 (m, 1H), 7.35–7.31 (m, 1H), 3.87–3.82 (m, 2H), 3.80 (s, 3H), 3.56–3.50 (m, 1H), 3.27–3.22 (m, 1H), 2.39–2.34 (m, 1H), 2.10–2.08 (m, 1H), 1.98–1.97 (m, 1H), 1.86–1.80 (m, 3H), 1.70–1.68 (m, 1H), 1.45–1.35 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 167.38, 160.73, 153.13, 150.82, 148.88, 130.74, 124.29, 123.16, 122.23, 120.26, 117.87, 117.35, 51.53, 42.44, 35.44, 33.51, 28.32, 27.20, 26.79, 25.53; EI-MS *m/z* (%) 324 (M^+, 84), 293 (100), 281 (81), 268 (70), 249 (55), 209 (43), 181 (44), 165 (41), 152 (47); HRMS [EI-(+)] calcd for $C_{20}H_{20}O_4$ 324.1362, found 324.1358.

9-Methylbenzo[*b*]-2,3-dihydro-1*H*-indeno[5,4-*d*]-6*H*-pyran-6-one-8-carboxylic acid methyl ester (52)[1]



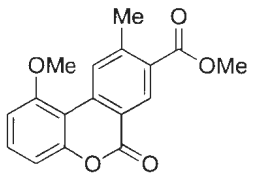
Salicylaldehyde (**5**) (0.50 g, 4.1 mmol), dimethyl glutaconate (**6**) (1.29 g, 8.16 mmol), 2-methylcyclopentanone (**51**) (1.03 g, 12.2 mmol) and pyrrolidine (0.72 g, 10 mmol) in 1,4-dioxane (10 mL) afforded DBP **52** (0.44 g, 36%) as a colorless solid. R_f = 0.50 (30% ethyl acetate / hexanes); mp 206–207 °C; IR (neat) ν = 1714 (s), 1558 (w), 1230 (s), 1200 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ = 8.95 (s, 1H), 8.24 (d, J = 8.0 Hz, 1H), 7.53–7.50 (m, 1H), 7.39–7.34 (m, 2H), 4.14–4.08 (m, 1H), 3.58–3.39 (m, 2H), 2.37–2.27 (m, 1H), 2.11–2.07 (m, 1H), 1.29 (d, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 165.94, 161.20, 160.49, 152.14, 141.01, 135.00, 132.81, 130.96, 127.17, 126.42, 124.56, 120.72, 119.08, 118.13, 52.37, 39.18, 33.57, 33.31, 20.47; EI-MS *m/z* (%) 308 (M^+, 100), 293 (54), 275 (31), 205 (21), 189 (17), 138 (10); HRMS [EI-(+)] calcd for $C_{19}H_{16}O_4$ 308.1049, found 308.1049.

9,10-Dimethyl-6*H*-dibenzo[*b,d*]pyran-6-one-8-carboxylic acid methyl ester (53)



To a solution of **43** (50 mg, 0.18 mmol) in benzene (10 mL) was added DDQ (60 mg, 0.26 mmol) in one portion and the resulting mixture was heated at reflux for 24 h. The reaction mixture was then cooled to room temperature and gravity filtered. The filtrate was concentrated under reduced pressure and the residue was subjected to column chromatography ($CHCl_3$) to afford DBP **53** (42 mg, 85%) as a colorless solid. R_f = 0.60 (30 % ethyl acetate / hexanes); mp 141–143 °C; IR (neat) ν 1717 (s), 1595 (w), 1228 (m), 1206 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ = 8.70 (s, 1H), 8.16 (d, J = 7.9 Hz, 1H), 7.49 (t, J = 7.2 Hz, 1H), 7.39 (d, J = 7.8 Hz, 1H), 7.33 (t, J = 7.3 Hz, 1H), 3.95 (s, 3H), 2.78 (s, 3H), 2.68 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 167.62, 161.13, 151.76, 145.88, 136.45, 135.23, 131.34, 130.39, 129.99, 128.11, 123.84, 120.10, 118.86, 118.02, 52.41, 20.62, 18.36; APCI-(+)-MS *m/z* (%) 284 (19), 283 ($[M + 1]^+$, 100); HRMS [EI-(+)] calcd for $C_{17}H_{14}O_4$ 282.0892, found 282.0897.

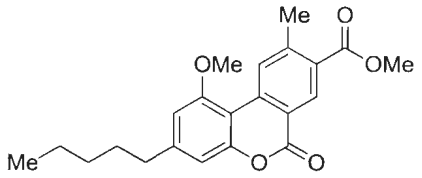
1-Methoxy-9-methyl-6*H*-dibenzo[*b*,*d*]pyran-6-one-8-carboxylic acid methyl ester (54)



Salicylaldehyde **21** (0.10 g, 0.66 mmol), dimethyl glutaconate (**6**) (0.21 g, 1.3 mmol), anhydrous acetone (**35**) (0.38 g, 6.6 mmol) and pyrrolidine (0.12 g, 1.7 mmol) in 1,4-dioxane (2 mL) afforded DBP **54** (0.092 g, 47%) as a colorless solid.[2] R_f = 0.40 (30 % ethyl acetate / hexanes); mp 189–191 °C; IR (neat) ν = 1720 (s), 1607 (m), 1213 (s), 1079

(s) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ = 9.00 (s, 1H), 8.92 (s, 1H), 7.47 (t, J = 8.3 Hz, 1H), 7.10 (dd, J = 8.2, 1.1 Hz, 1H), 6.92 (d, J = 8.4 Hz, 1H), 4.11 (s, 3H), 3.97 (s, 3H), 2.83 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 166.52, 160.73, 158.70, 153.27, 147.22, 137.08, 132.98, 130.95, 130.46, 128.98, 118.71, 110.54, 107.57, 106.97, 56.08, 52.13, 22.87; APCI-(+)-MS *m/z* (%) 300 (15), 299 ([M + 1]$^+$, 100); HRMS [EI-(+)] calcd for $C_{17}H_{14}O_5$ 298.0841, found 298.0847.

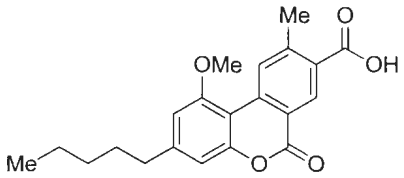
1-Methoxy-9-methyl-3-pentyl-6*H*-dibenzo[*b,d*]pyran-6-one-8-carboxylic acid methyl ester (60)



Salicylaldehyde **59** (1.19 g, 5.36 mmol), dimethyl glutaconate (**6**) (1.70 g, 10.7 mmol), anhydrous acetone (**35**) (3.11 g, 53.5 mmol) and pyrrolidine (0.95 g, 13.4 mmol) in 1,4-dioxane (24 mL) afforded DBP **60** (0.94 g, 48%) as a colorless solid.[2] R_f = 0.50 (20% ethyl acetate / hexanes); mp 130–133 °C; lR (neat) ν = 1721 (s), 1608 (w), 1214 (s), 1079 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ = 8.95 (s, 1H), 8.83 (s, 1H), 6.84 (d, J = 1.5 Hz, 1H), 6.68 (d, J = 1.5 Hz, 1H), 4.05 (s, 3H), 3.92 (s, 3H), 2.78 (s, 3H), 2.67 (t, J = 7.8 Hz, 2H), 1.66 (quint, J = 7.4 Hz, 2H), 1.37–1.34 (m, 4H), 0.90 (t, J = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 166.58, 160.95, 158.46, 153.18, 147.13, 137.33, 132.99, 129.99, 128.45, 118.34, 110.09, 107.39, 105.21, 55.96, 52.06, 36.14, 31.42, 30.53, 22.87, 22.51,

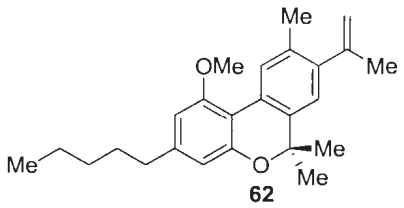
14.01; APCI-(+)-MS *m/z* (%) 370 (20), 369 ([M + 1]$^+$, 100); HRMS [EI-(+)] calcd for $C_{22}H_{24}O_5$ 368.1624, found 368.1632.

1-Methoxy-9-methyl-3-pentyl-6*H*-dibenzo[*b*,*d*]pyran-6-one-8-carboxylic acid (61)

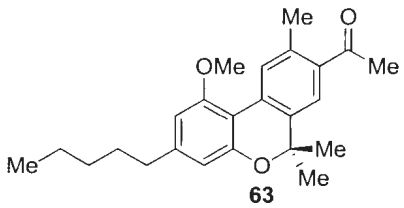


A solution of **60** (0.50 g, 1.36 mmol) in 10% KOH / methanol (10 mL) was heated at reflux for 6 h. The reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure. To the residue was added water (5 mL) and the pH was adjusted to 2 using concentrated HCl. A precipitate formed and the mixture was suction filtered. The solids were vaccum dried for an hour and then dried under air in an oven at 100 °C for 12 h to afford **61** (0.43 g, 90%) as a cream colored solid. R_f = 0.20 (30% ethyl acetate / hexanes); mp 272–275 °C; IR (neat) ν = 3158–2465 (br s), 1733 (s), 1699 (m), 1579 (s) cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz) δ = 8.80 (s, 1H), 8.66 (s, 1H), 6.94 (s, 1H), 6.87 (s, 1H), 4.05 (s, 3H), 2.72 (s, 3H), 2.68 (t, J = 7.7 Hz, 3H), 1.65 (quint, J = 7.4 Hz, 2H), 1.37–1.30 (m, 4H), 0.89 (t, J = 6.8 Hz, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ = 167.32, 159.90, 158.17, 152.45, 147.10, 146.36, 136.32, 131.85, 129.50, 117.85, 109.26, 107.99, 104.28, 56.28, 35.26, 31.01, 30.00, 22.57, 22.03, 14.01; APCI-(+)-MS *m/z* (%) 356 (20), 355 [M + 1]$^+$, 100); HRMS [EI-(+)] calcd for $C_{21}H_{22}O_5$ 354.1467, found 354.1466.

8-(2-Propenyl)-1-methoxy-6,6,9-trimethyl-3-pentyl-6*H*-dibenzo[*b*,*d*]pyran (62) and 8-acetyl-1-methoxy-6,6,9-trimethyl-3-pentyl-6*H*-dibenzo[*b*,*d*]pyran (63)



62

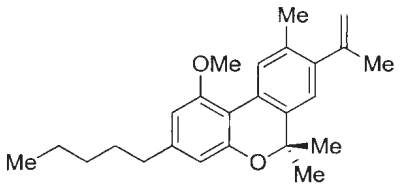


63

To a –78 °C suspension of carboxylic acid **61** (250 mg, 0.71 mmol) in THF (5 mL) was added methyllithium (1.28 M in diethyl ether, 4.40 mL, 5.64 mmol) and the mixture was stirred for 10 min. The reaction mixture was brought to room temperature and stirred for a period of 2 h. The reaction mixture was cooled to –78 °C and quenched with satd. NH_4Cl (10 mL) and then warmed to room temperature.The resulting mixture was extracted with chloroform (3 × 10 mL), dried over Na_2SO_4 and the solvent was removed under reduced pressure. To the residue was added benzene (7 mL) and *p*-TsOH (20 mg), and the mixture was heated at 70 °C for 30 min. The reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure. The residue was dissolved in diethyl ether (20 mL), washed with saturated aqueous $NaHCO_3$ solution (10 mL), dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was subjected to column chromatography (5% ethyl acetate / hexanes) to afford **62** (37 mg, 14 %) and **63** (110 mg, 42%) as pale yellow oils. **62**: R_f = 0.80 (30% ethyl acetate / hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.19 = (s, 1H), 6.97 (s, 1H), 6.47 (d, J = 1.5 Hz, 1H), 6.43 (d, J = 1.5 Hz, 1H), 5.20–5.19 (m, 1H), 4.48–4.87 (m, 1H), 3.93 (s, 3H), 2.57 (t, J = 7.8 Hz, 3H), 2.34 (s, 3H), 2.05 (s, 3H), 1.63 (quint, J = 7.6 Hz, 2H), 1.59 (s, 6H), 1.35–1.33 (m, 4H), 0.90 (t, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ =

157.21, 154.27, 145.96, 144.22, 142.24, 137.05, 133.09, 128.08, 126.32, 121.85, 114.71, 110.89, 109.72, 104.98, 77.21, 55.56, 36.17, 31.56, 30.64, 27.05, 24.31, 22.56, 20.07, 14.05; APCI-(+)-MS *m/z* (%) 366 (31), 365 ([M + 1]$^+$, 100), 349 (8); HRMS [CI-(+)] calcd for $C_{25}H_{33}O_2$ 365.2481, found 365.2487. **63**: R_f = 0.50 (30% ethyl acetate / hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 8.26 (s, 1H), 7.52 (s, 1H), 6.47 (d, J = 1.5 Hz, 1H), 6.43 (d, J = 1.5 Hz, 1H), 3.93 (s, 3H), 2.58 (s, 3H), 2.57–2.54 (m, 2H), 2.56 (s, 3H), 1.64–1.61 (m, 2H), 1.62 (s, 6H), 1.34–1.32 (m, 4H), 0.89 (t, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 200.91, 157.76, 154.89, 145.94, 137.41, 136.78, 135.42, 131.18, 129.84, 123.72, 110.96, 108.98, 105.10, 77.21, 55.60, 36.26, 31.53, 30.59, 29.49, 26.99, 22.55, 22.12, 14.04; APCI-(+)-MS *m/z* (%) 368 (27), 367 ([M + 1]$^+$, 100); HRMS [CI-(+)] calcd for $C_{24}H_{31}O_3$ 367.2273, found 367.2265.

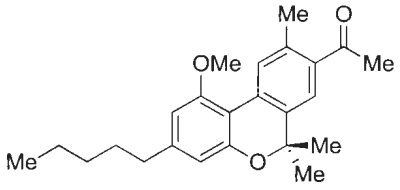
8-(2-Propenyl)-1-methoxy-6,6,9-trimethyl-3-pentyl-6*H*-dibenzo[*b*,*d*]pyran (62)



To a solution of **60** (102 mg, 0.28 mmol) in THF (5 mL) was added methylmagnesium bromide (3.0 M in diethyl ether, 1.8 mL, 5.39 mmol) at 0 °C over 5 min. The resulting mixture was heated at 70 °C for 16 h and then cooled to 0 °C before the addition of saturated aqueous NH_4Cl solution (10 mL). The reaction mixture was extracted with chloroform (3 × 10 mL), dried over Na_2SO_4 and the solvent was removed under reduced pressure. To the residue was toluene (5 mL) and *p*-TsOH (20 mg) and the resulting

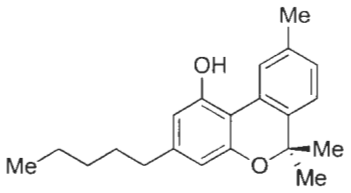
mixture was heated at 70 °C for 1 h. The reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate (15 mL), washed with staurated aqueous $NaHCO_3$ solution (10 mL), dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was subjected to column chromatography (2% ethyl acetate / hexanes) to afford **62** (88 mg, 87%) as a pale yellow oil. See above for characterization data.

8-Acetyl-1-methoxy-6,6,9-trimethyl-3-pentyl-6*H*-dibenzo[*b*,*d*]pyran (63)



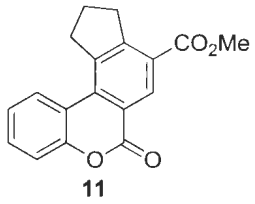
To a solution of **62** (80 mg, 0.22 mmol) in a 6:4 mixture of dry THF / deionized H_2O (2 mL) was added 4% OsO_4 in water (100 μL). The resulting mixture was stirred at room temperature for 20 min and $NaIO_4$ (190 mg, 0.89 mmol) was then added in several portions. The reaction mixture was stirred at room temperature for 16 h and then quenched by the addition of saturated aqueous Na_2SO_3 solution (5 mL). The resulting mixture was extracted with ethyl acetate (2 × 10 mL) and the combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (5 mL), dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was subjected to column chromatography (7% ethyl acetate / hexanes) to obtain **63** (46 mg, 57%) as a pale yellow oil. See above for characterization data.

Cannabinol (1-hydroxy-6,6,9-trimethyl-3-pentyl-6*H*-dibenzo[*b*,*d*]pyran) (1)



A mixture of **63** (25 mg, 0.071 mmol), acetic anhydride (0.3 mL) and 66% HI (0.3 mL) was heated at 120 °C for 4 h. The reaction mixture was then cooled to room temperature and extracted with diethyl ether (2 × 10 mL). The combined organic layers were washed with saturated aqueous Na_2SO_3 solution (10 mL), washed with aqueous saturated $NaHCO_3$ solution (10 mL), dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was subjected to column chromatography (10% ethyl acetate / hexanes) to afford **1** (20 mg, 95%) as a colorless oil. R_f = 0.50 (20% ethyl acetate / hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 8.15 (s, 1H), 7.14 (d, J = 7.8 Hz, 1H), 7.08–7.66 (m, 1H), 6.44 (d, J = 1.6 Hz, 1H), 6.29 (d, J = 1.6 Hz, 1H), 5.10 (s, 1H), 2.51 (t, J = 7.7 Hz, 3H), 2.38 (s, 3H), 1.63–1.57 (m, 2H), 1.59 (s, 6H), 1.33–1.31 (m, 4H), 0.89 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 154.65, 152.95, 144.54, 136.90, 136.87, 127.59, 127.49, 126.32, 122.63, 110.82, 109.83, 108.67, 77.29, 35.60, 31.47, 30.46, 27.10, 22.54, 21.53, 14.03; APCI-(+)-MS *m/z* (%) 312 (24), 311 ($[M + 1]^+$, 100); HRMS [EI-(+)] calcd for $C_{21}H_{26}O_2$ 310.1933, found 310.1938.

3.6 Selected ^{1}H and ^{13}C NMR spectra for Chapter 3



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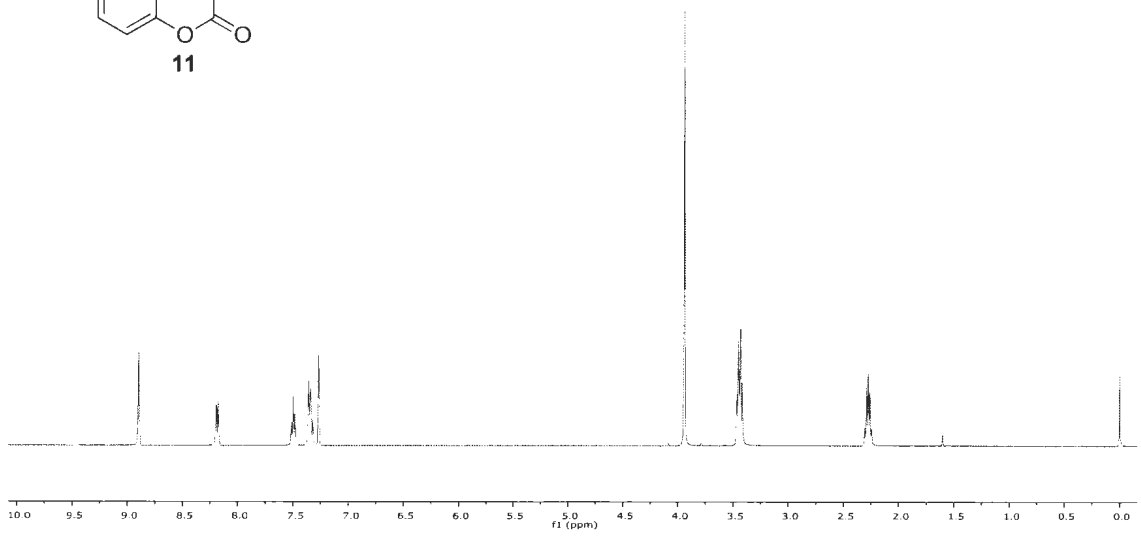

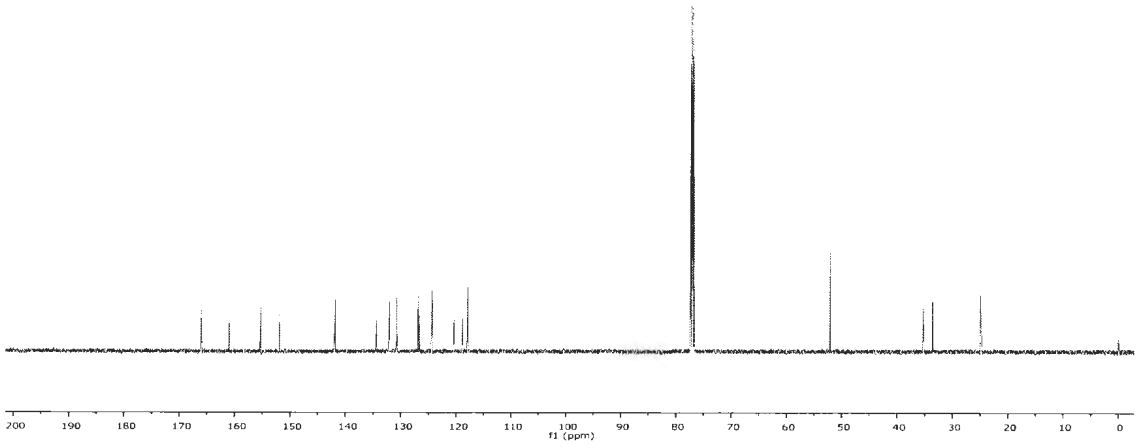

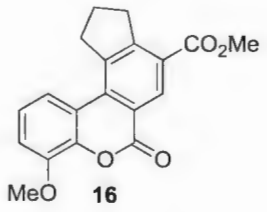
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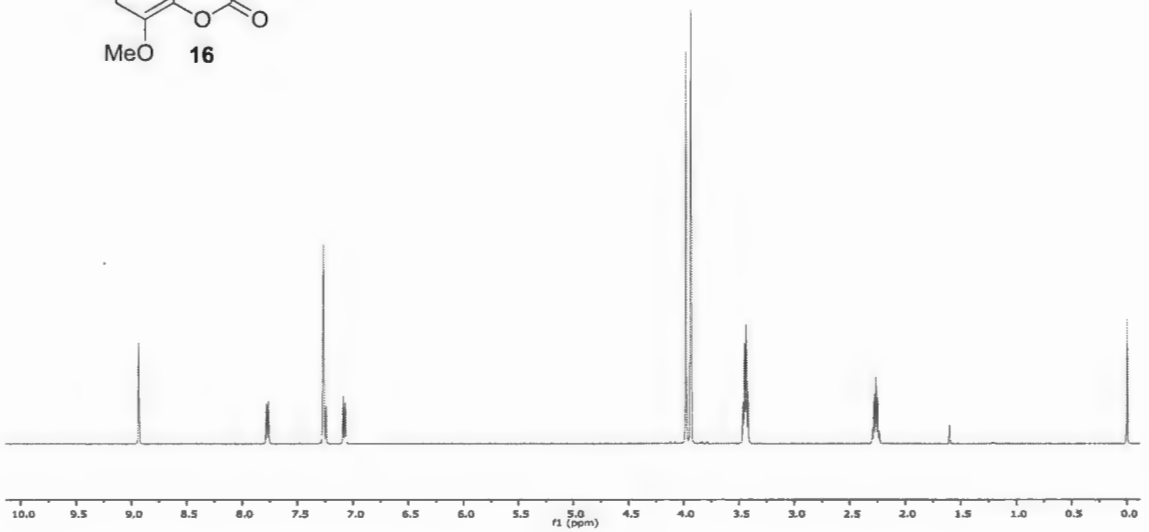
MeO

16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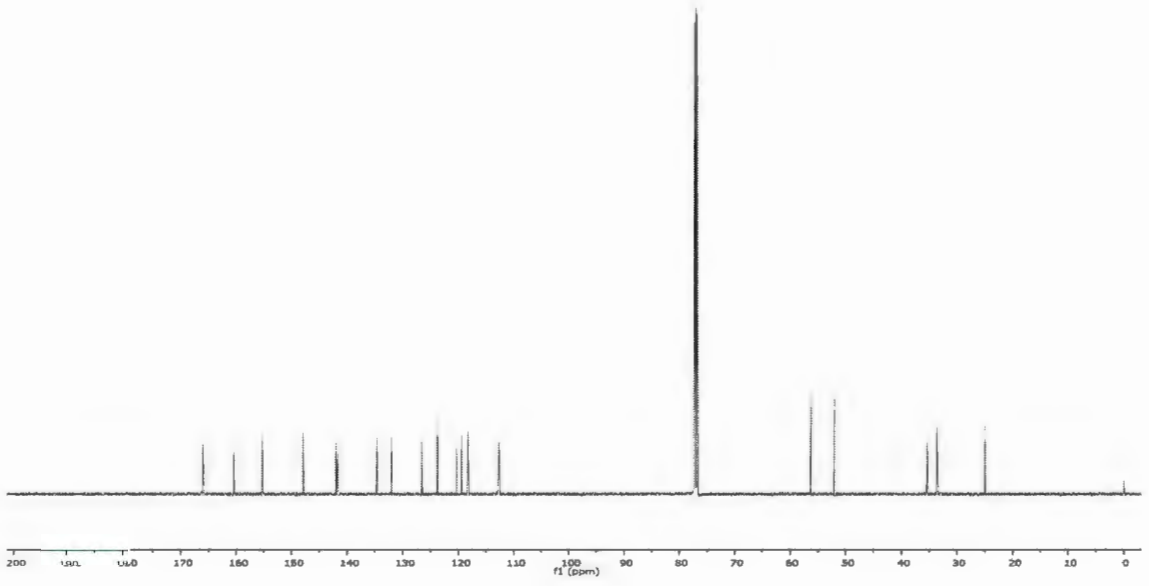
f1 (ppm)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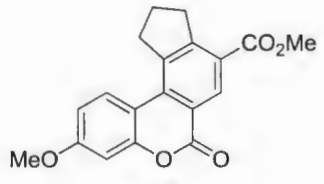
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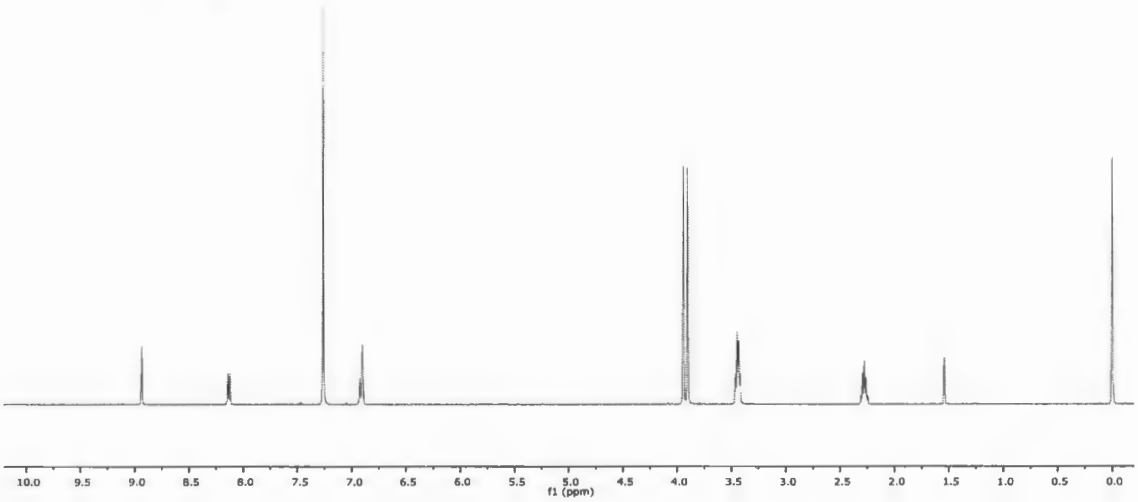
O
O

18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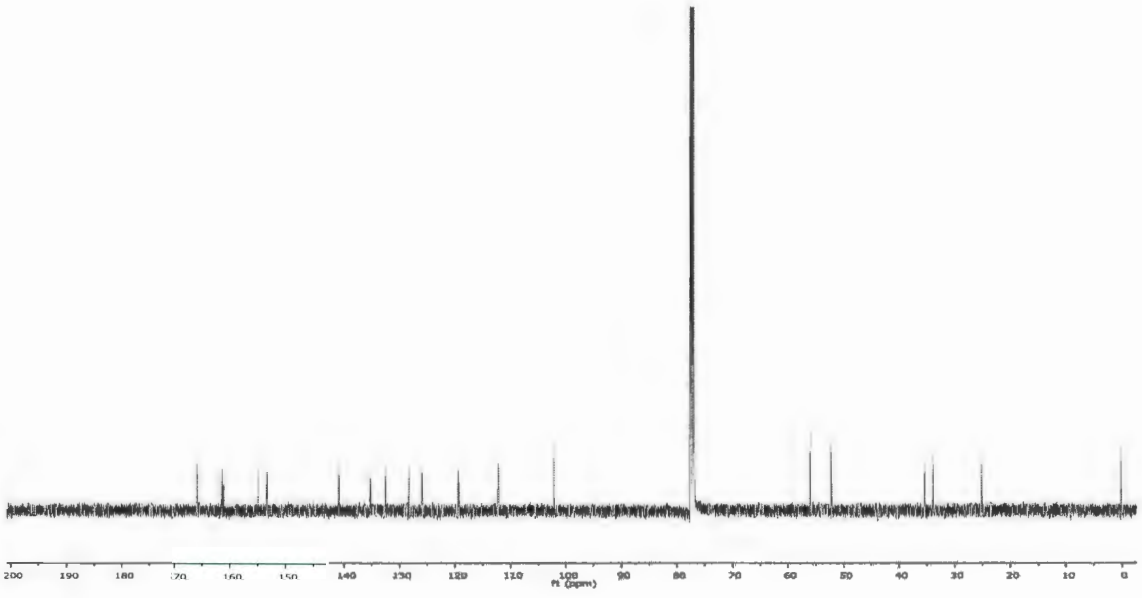
f1 (ppm)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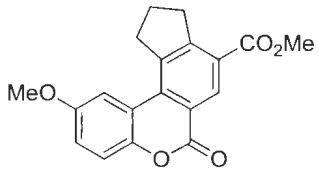
f1 (ppm)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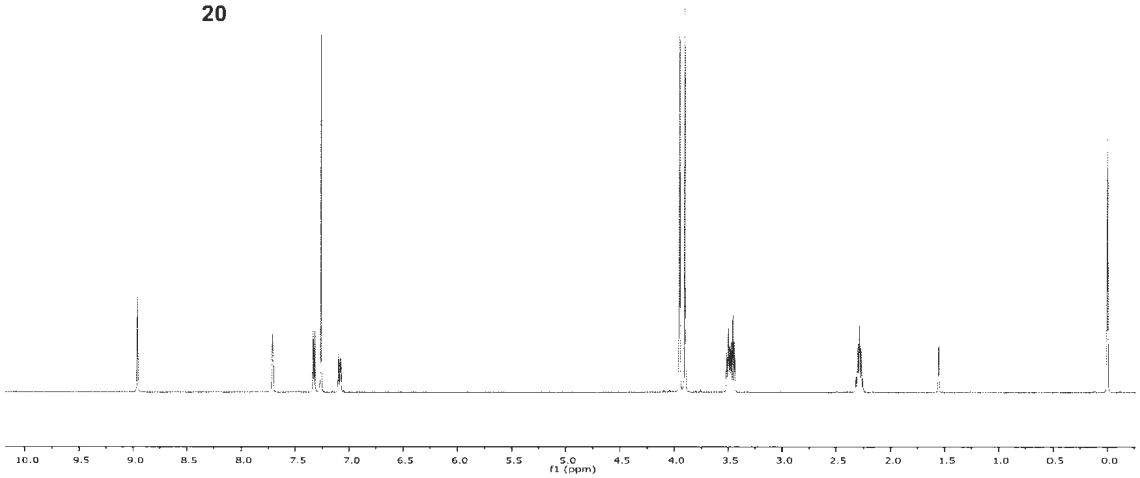
MeO
O
O

20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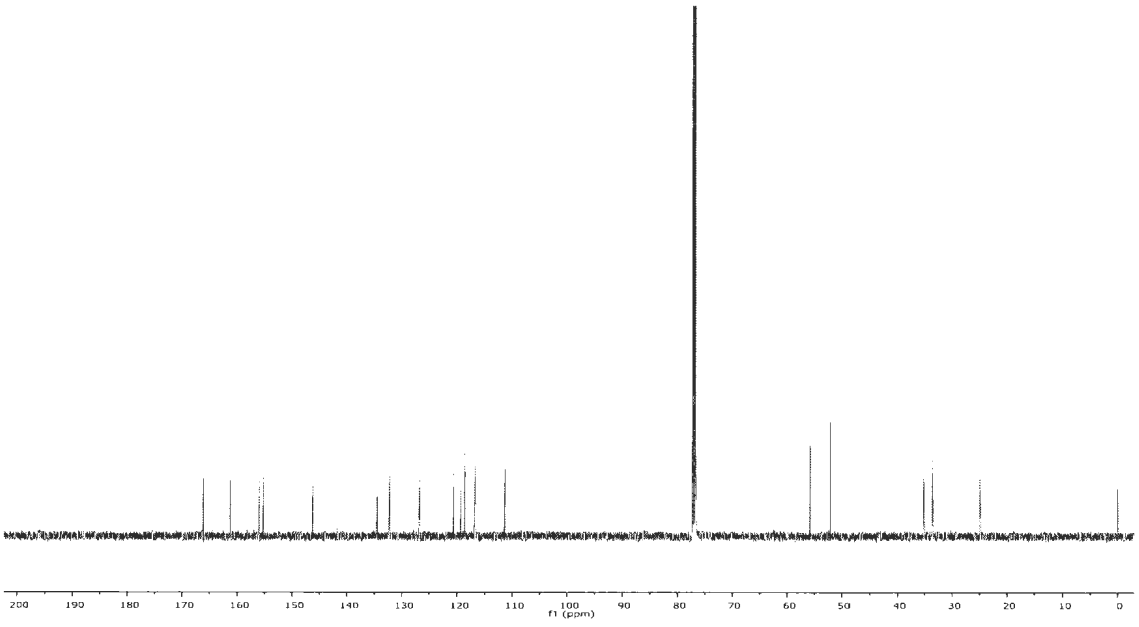
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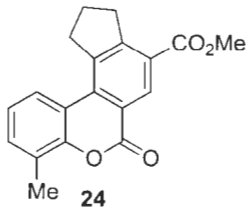
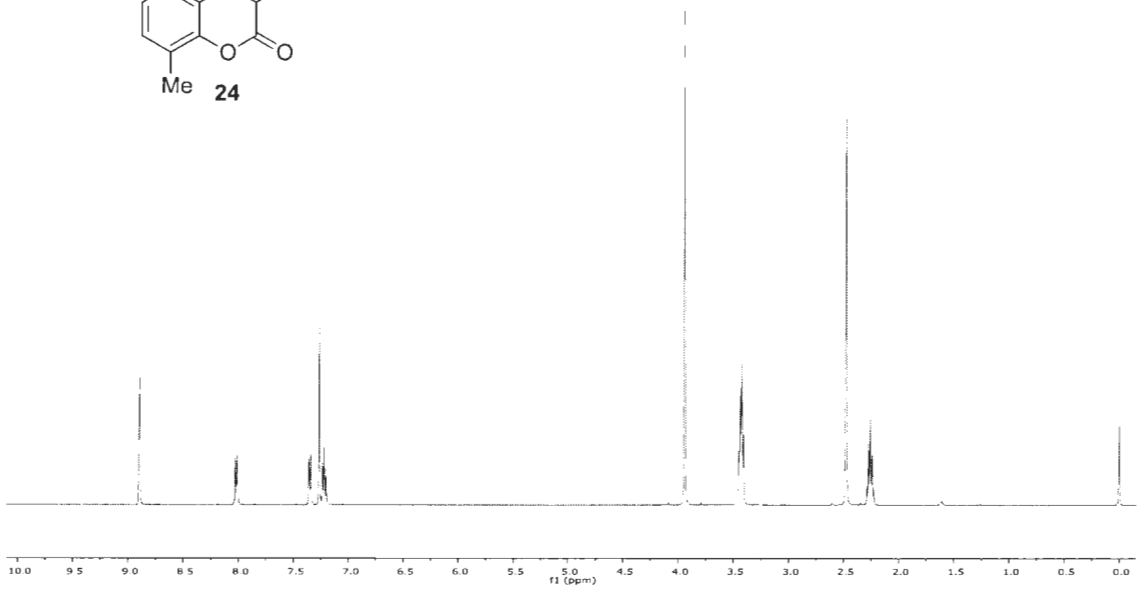

CO2Me
O
O
Me

24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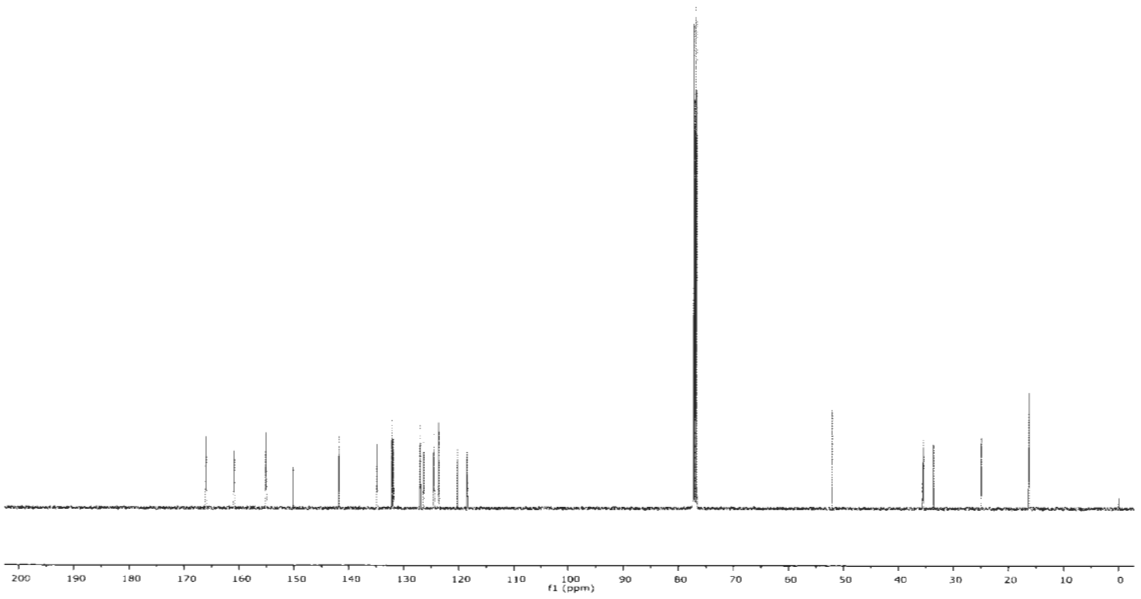
f1 (ppm)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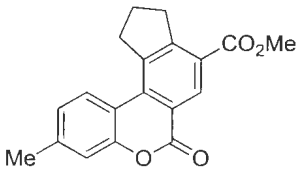
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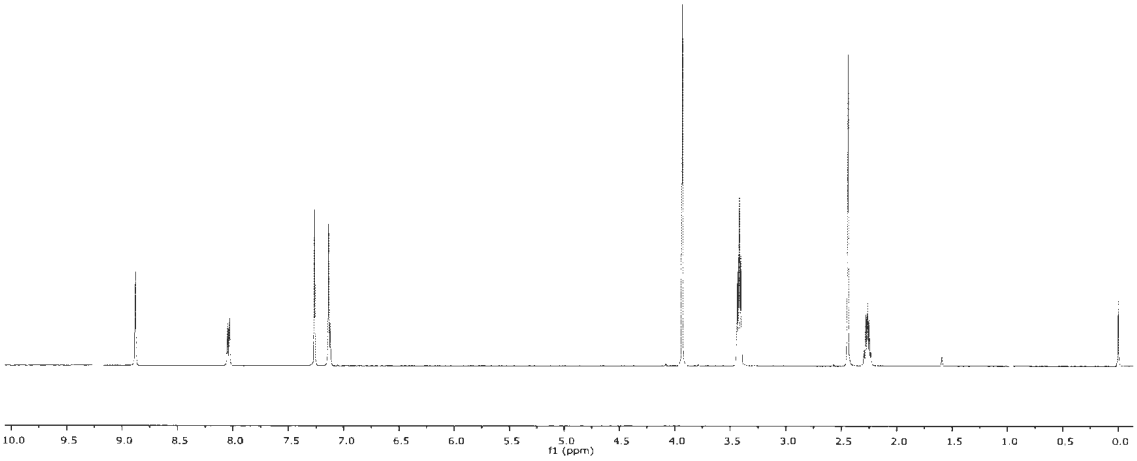
Me
O
O

26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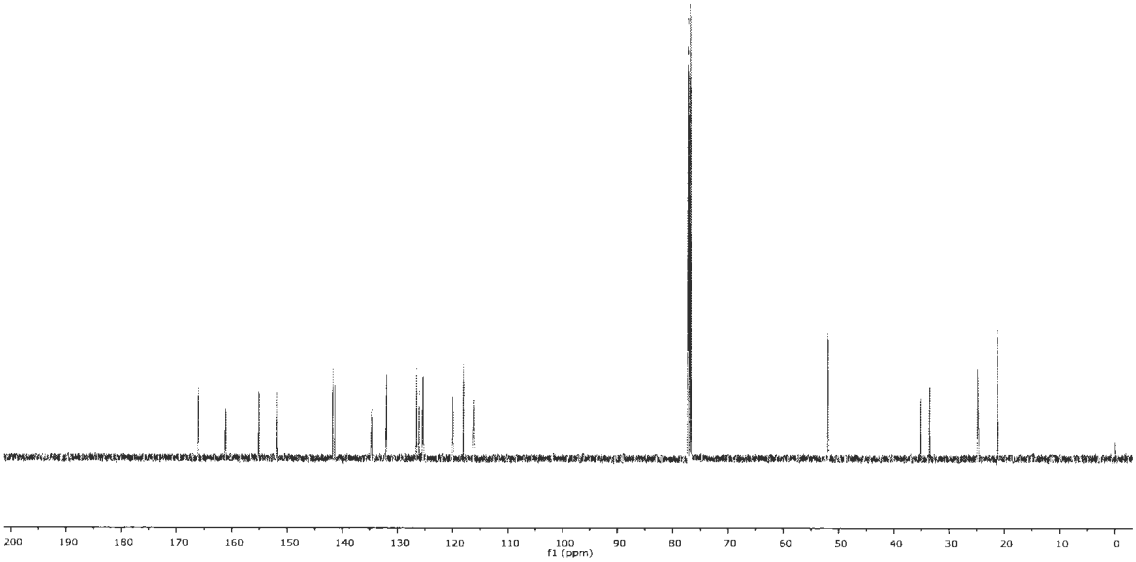
f1 (ppm)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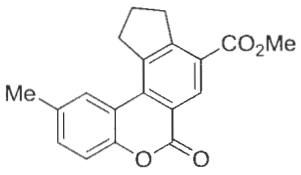
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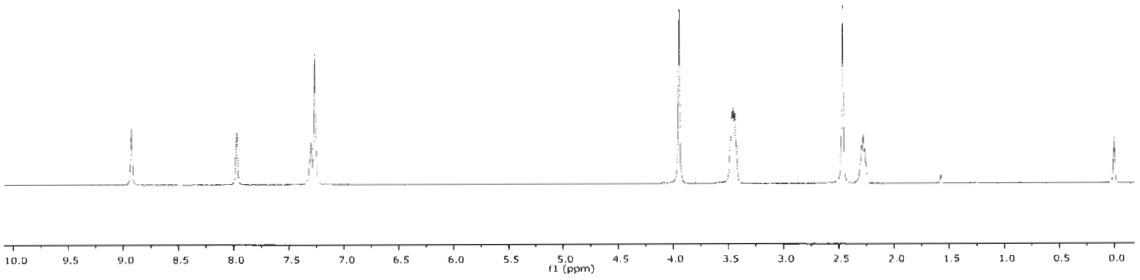
O

28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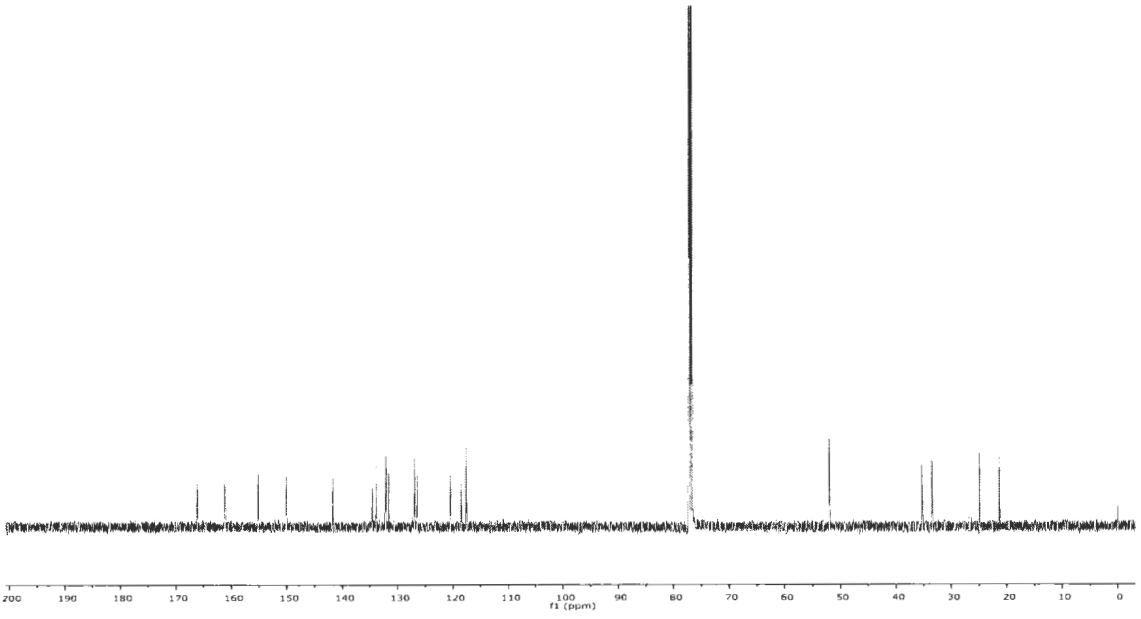
f1 (ppm)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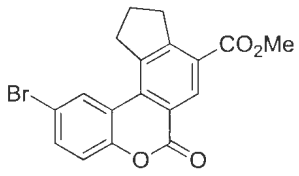
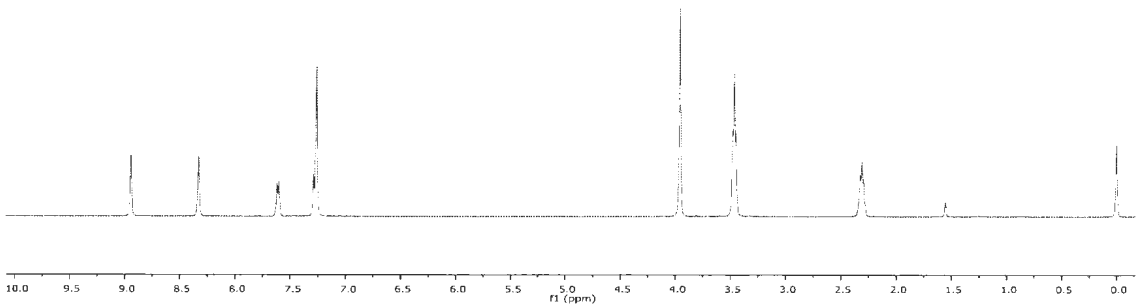

CO2Me
Br
O
O

30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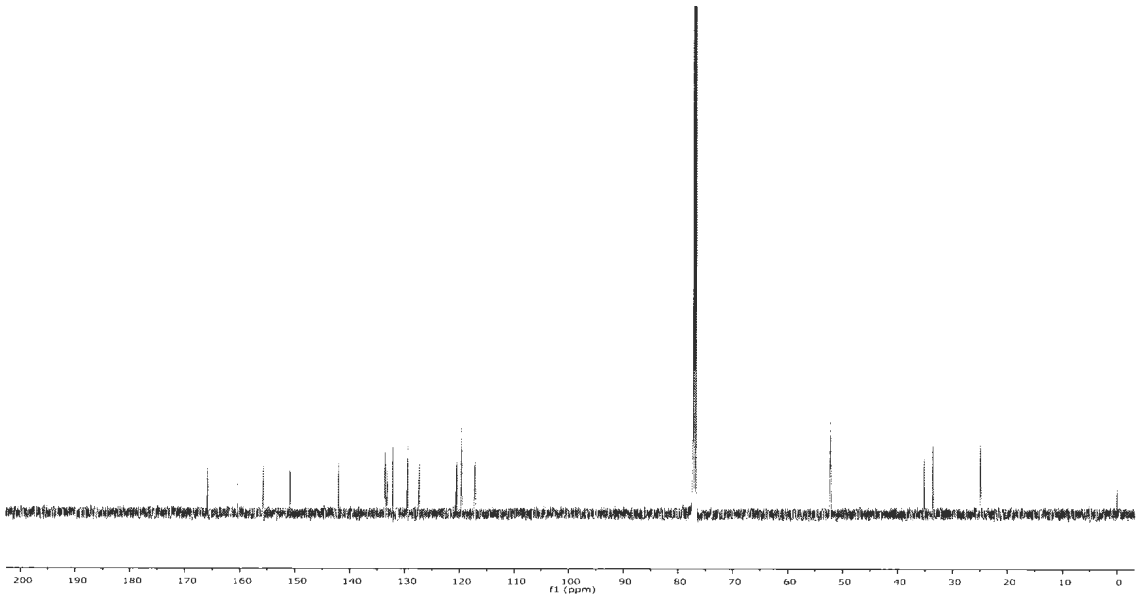
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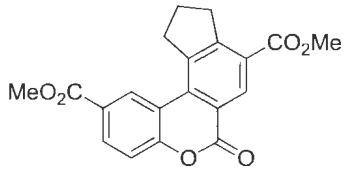
f1 (ppm)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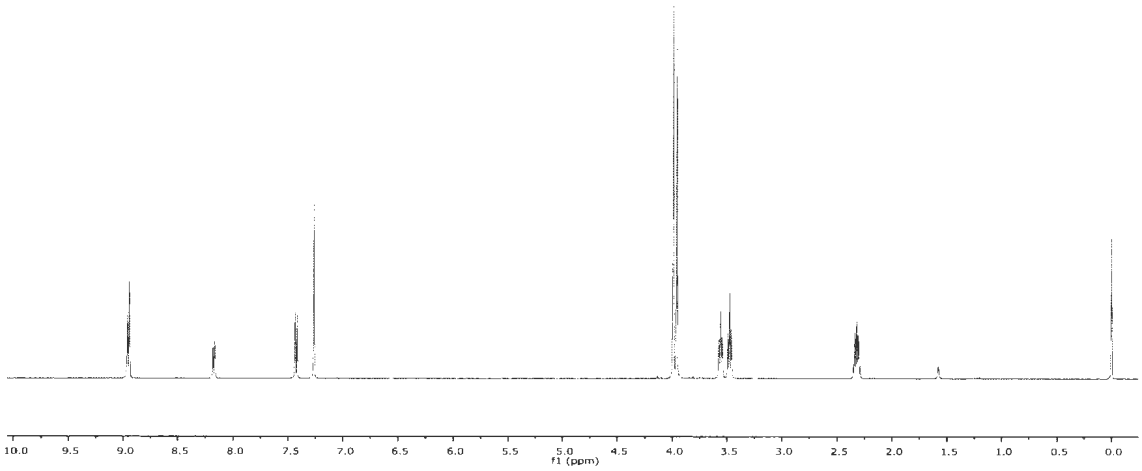
MeO2C
O
O

32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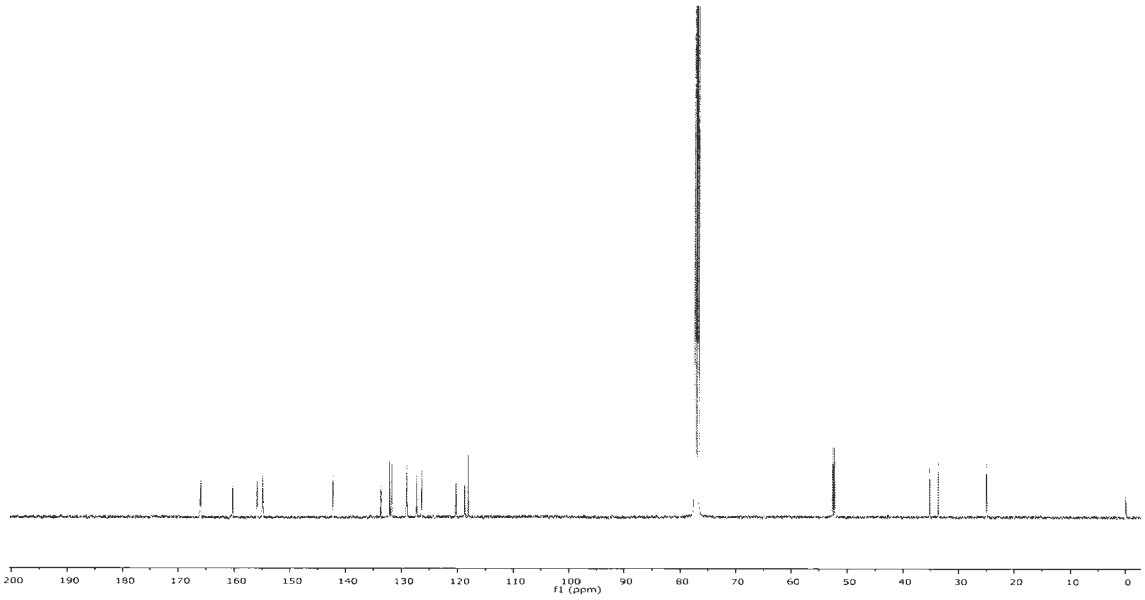
f1 (ppm)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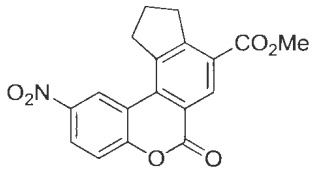
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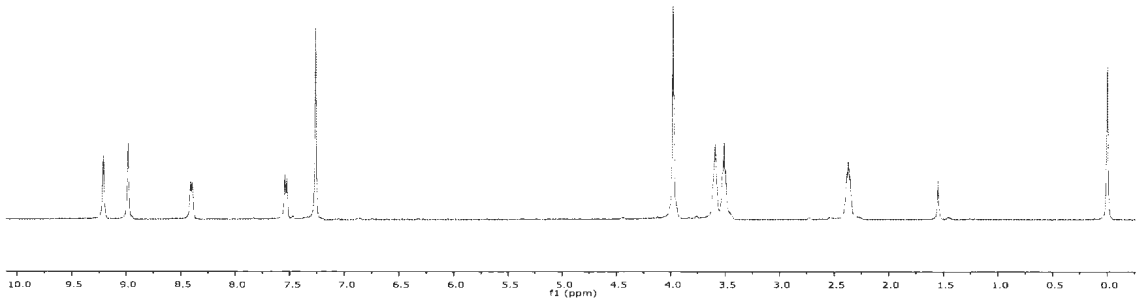
O_2N
O
O

34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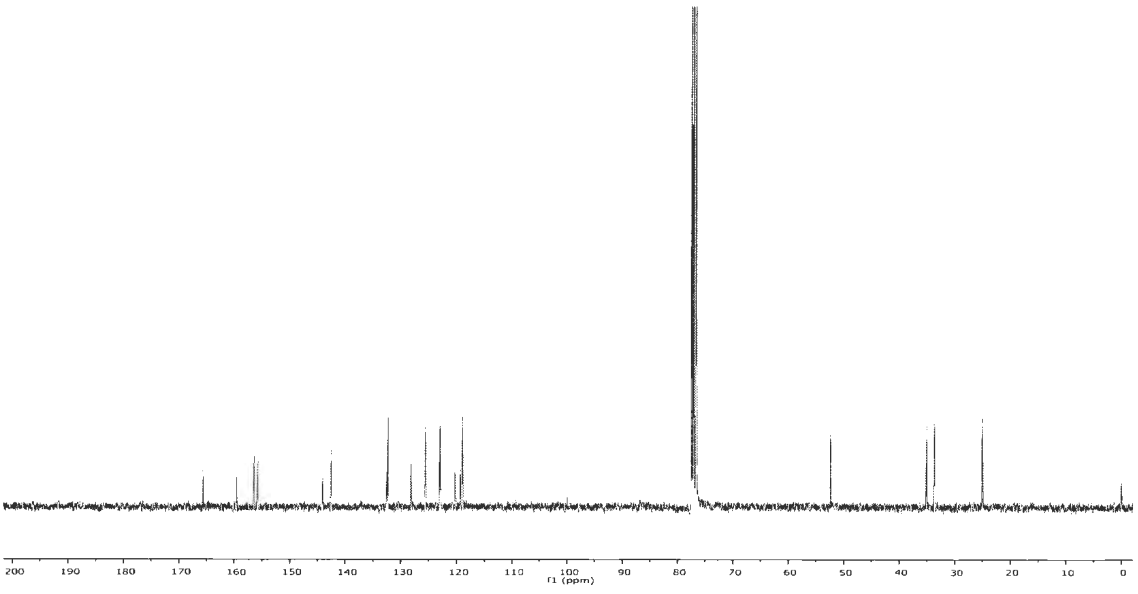
f1 (ppm)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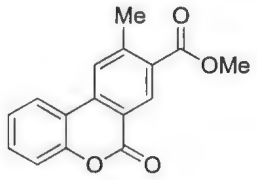
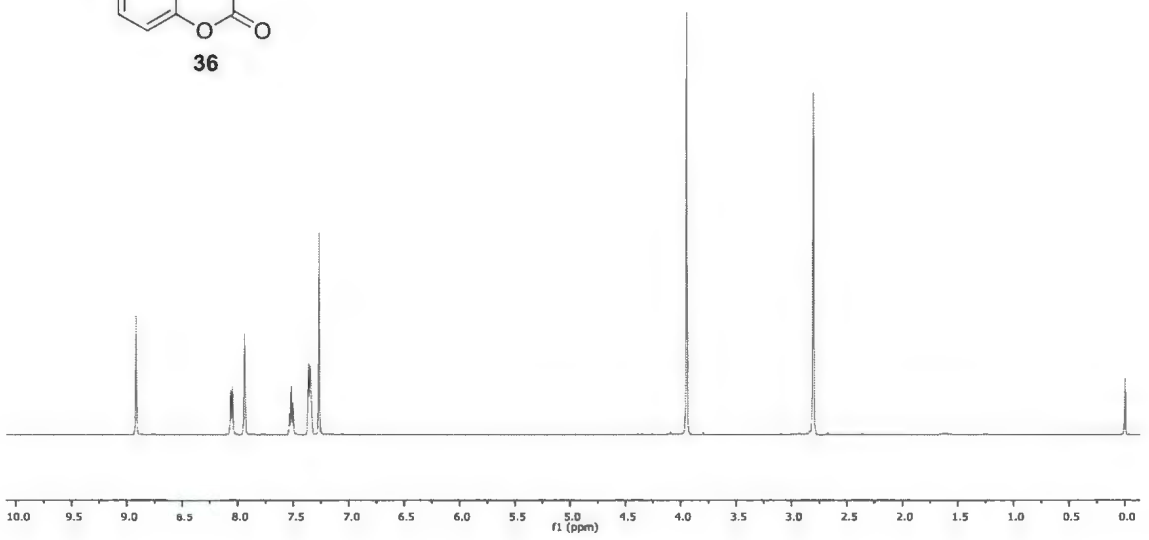
f1 (ppm)


Me
O
OMe
O
O

36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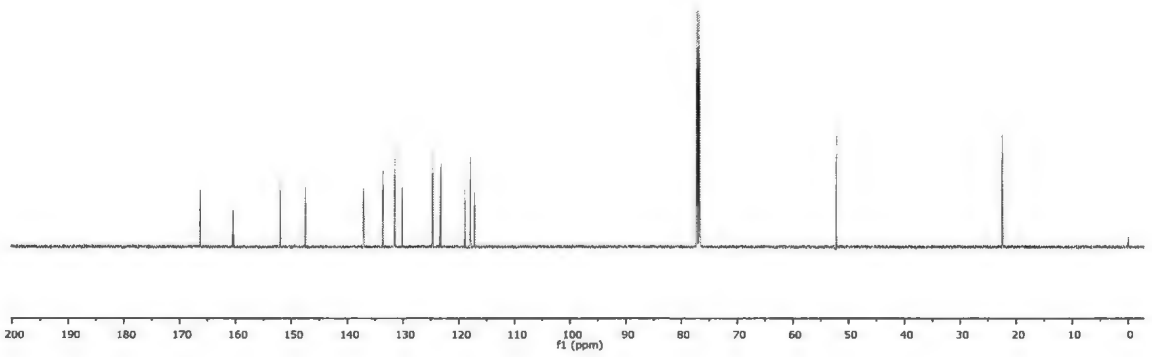
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


200
190
180
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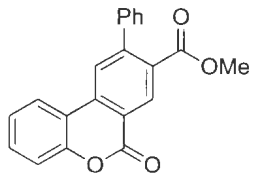
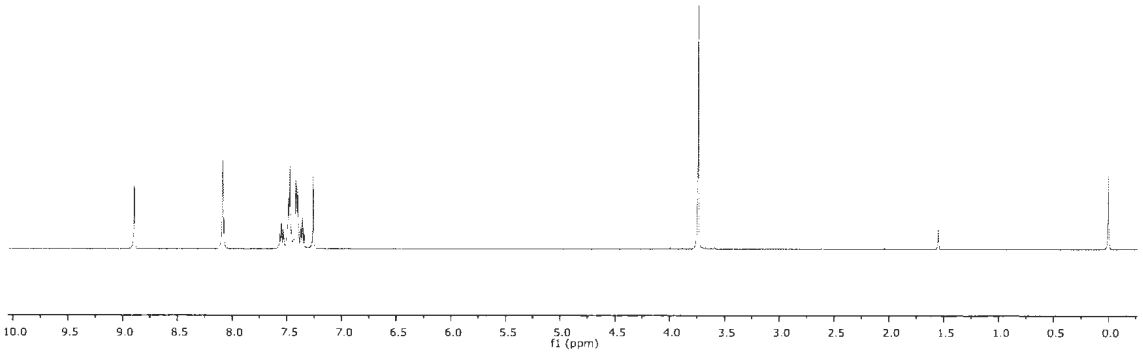
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


Ph
O
OMe
O
O

38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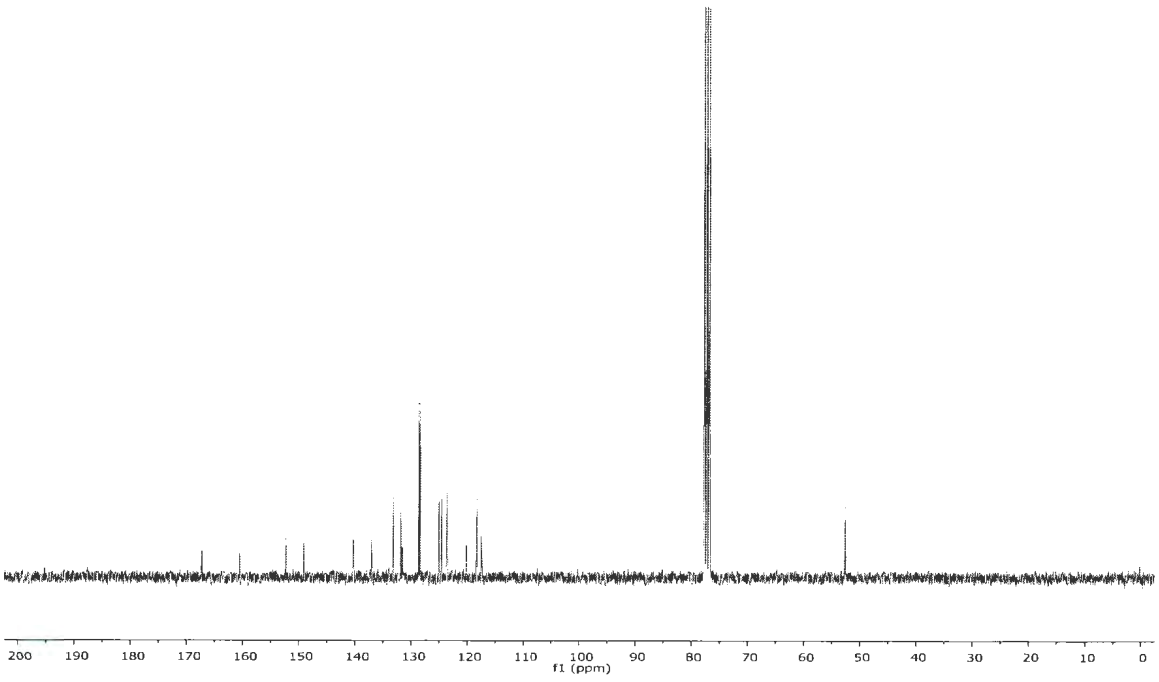
f1 (ppm)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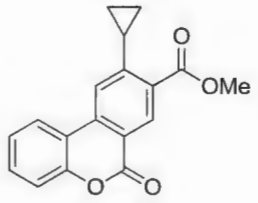
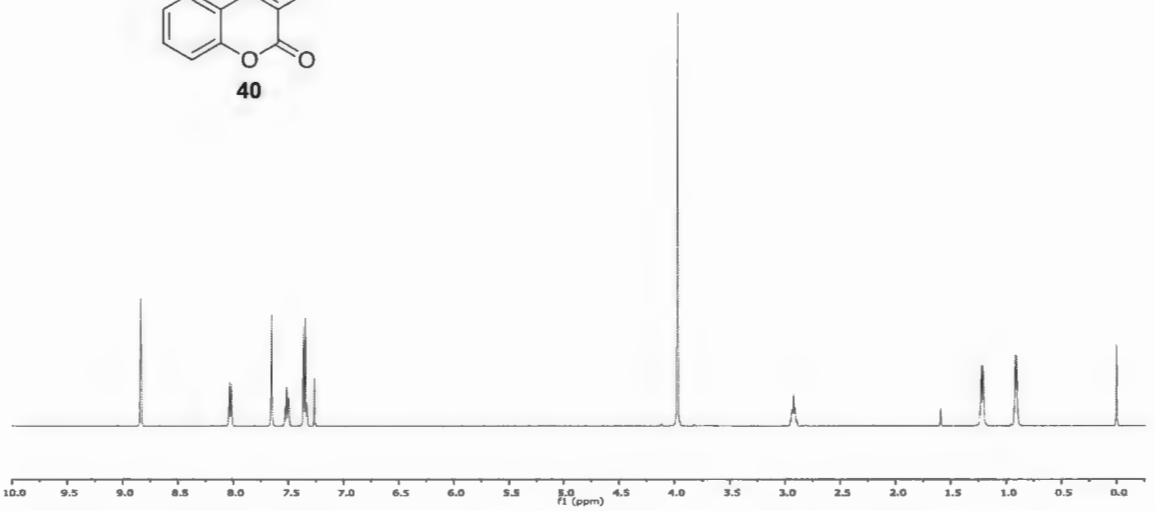
f1 (ppm)


O
OMe
O
O

40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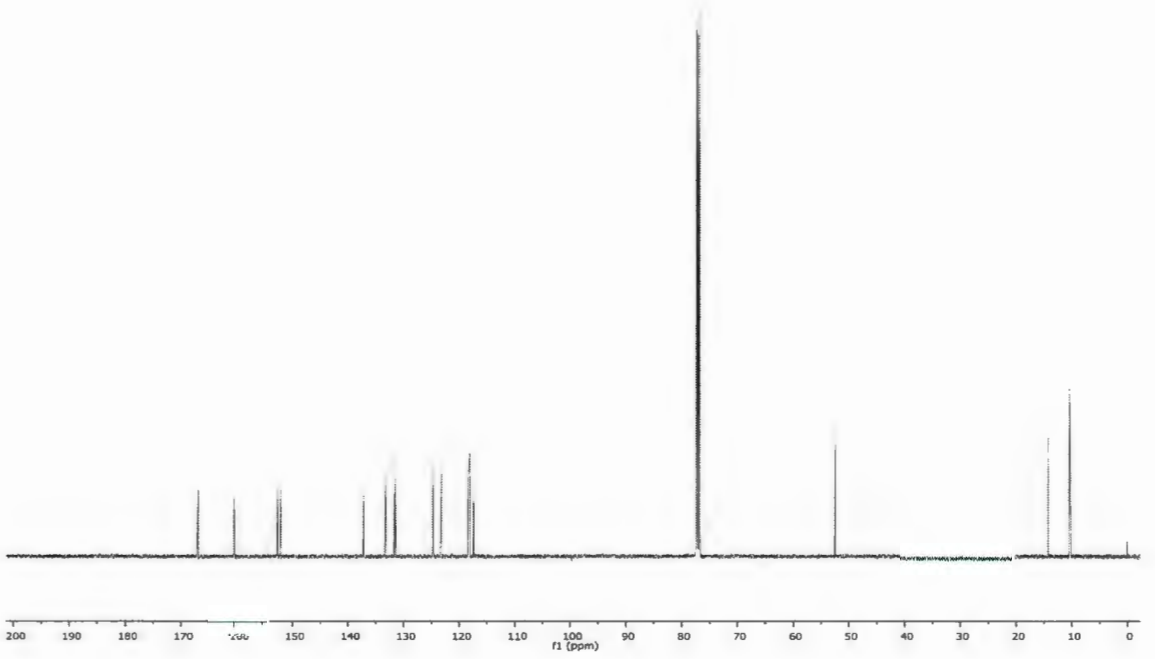
f1 (ppm)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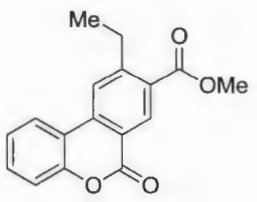
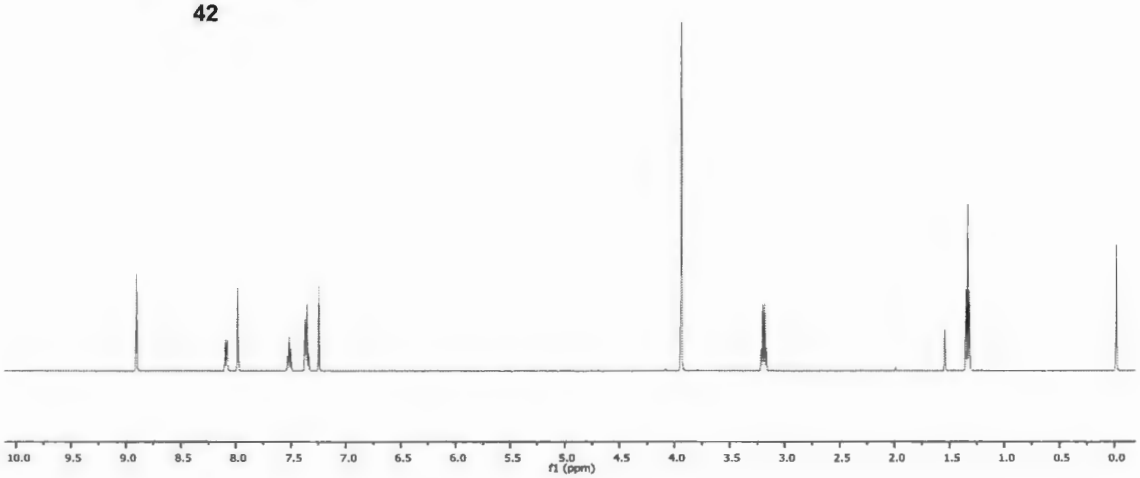
f1 (ppm)


Me
O
OMe
O
O

42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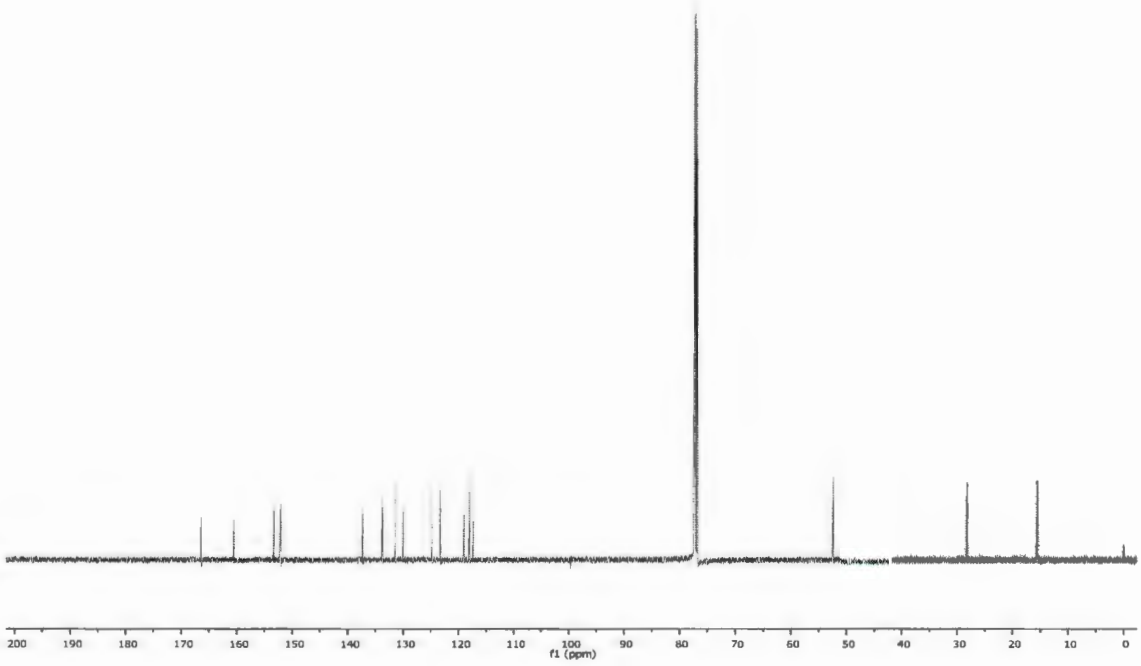
f1 (ppm)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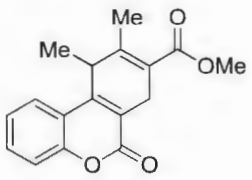
f1 (ppm)


Me
O
Me
OMe
O
O

43

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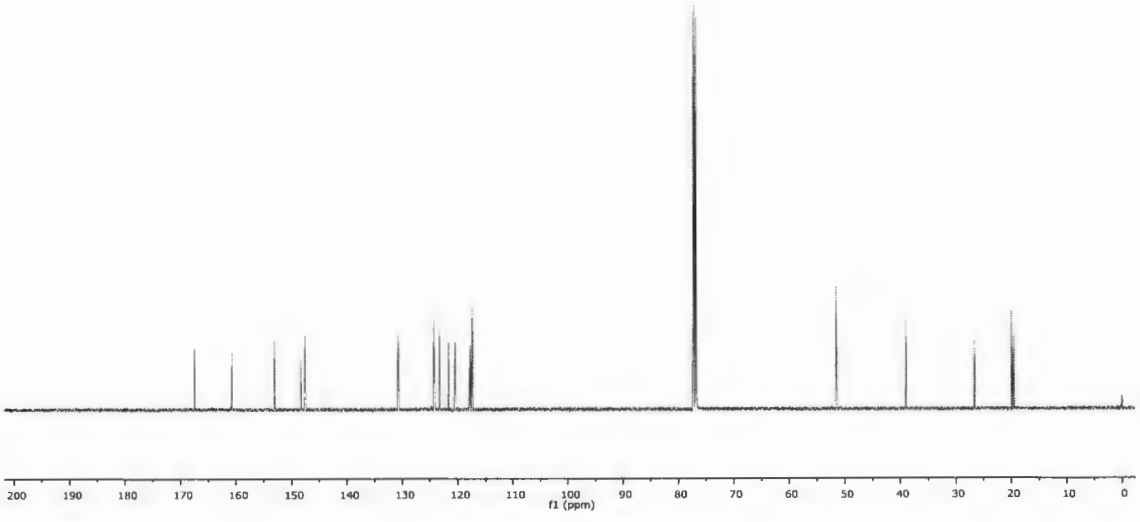
f1 (ppm)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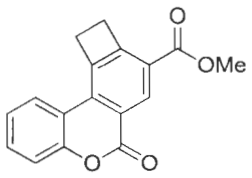
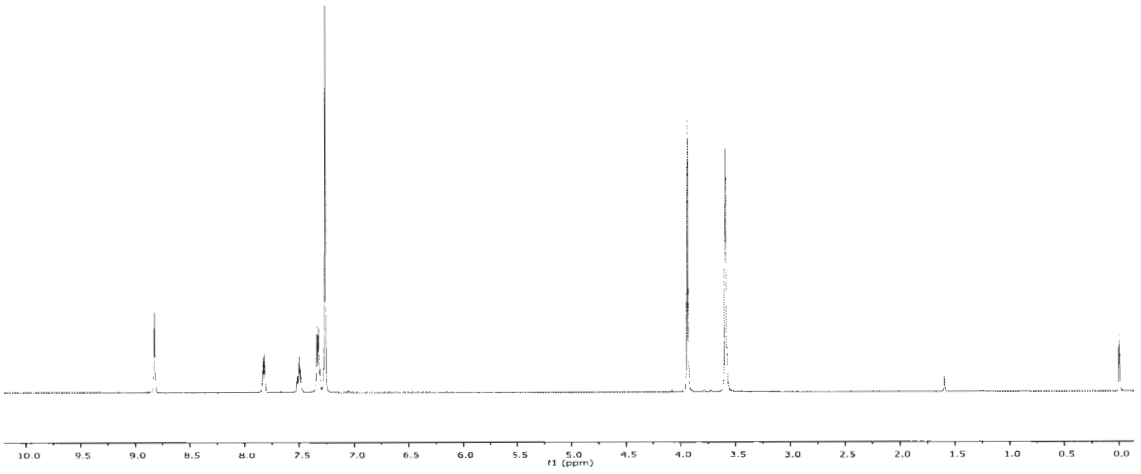
f1 (ppm)


O
OMe
O
O

45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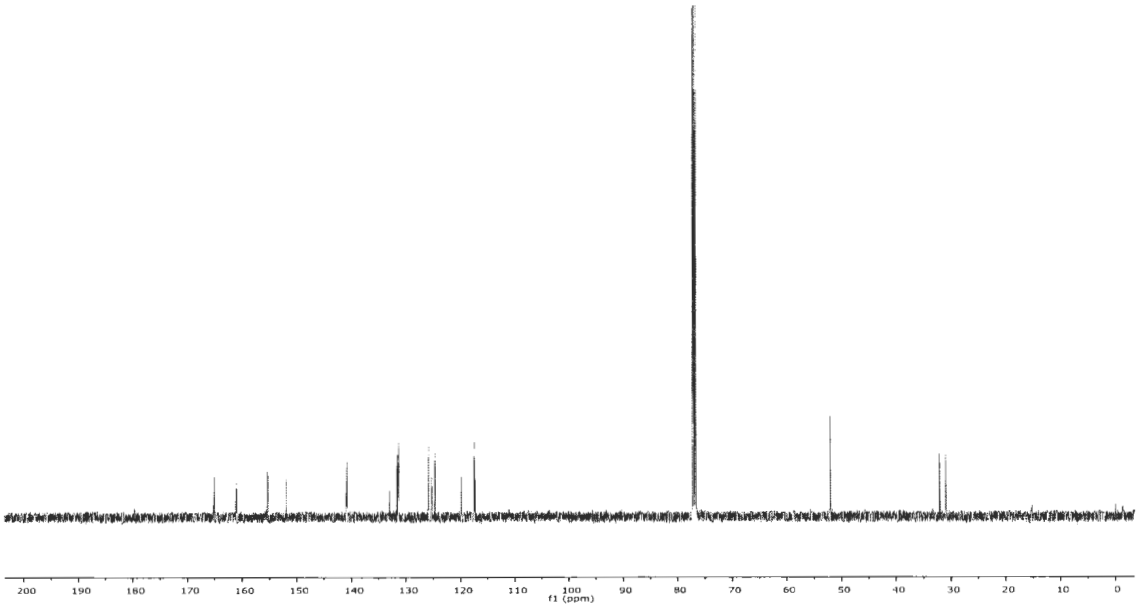
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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190
180
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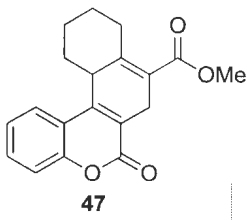
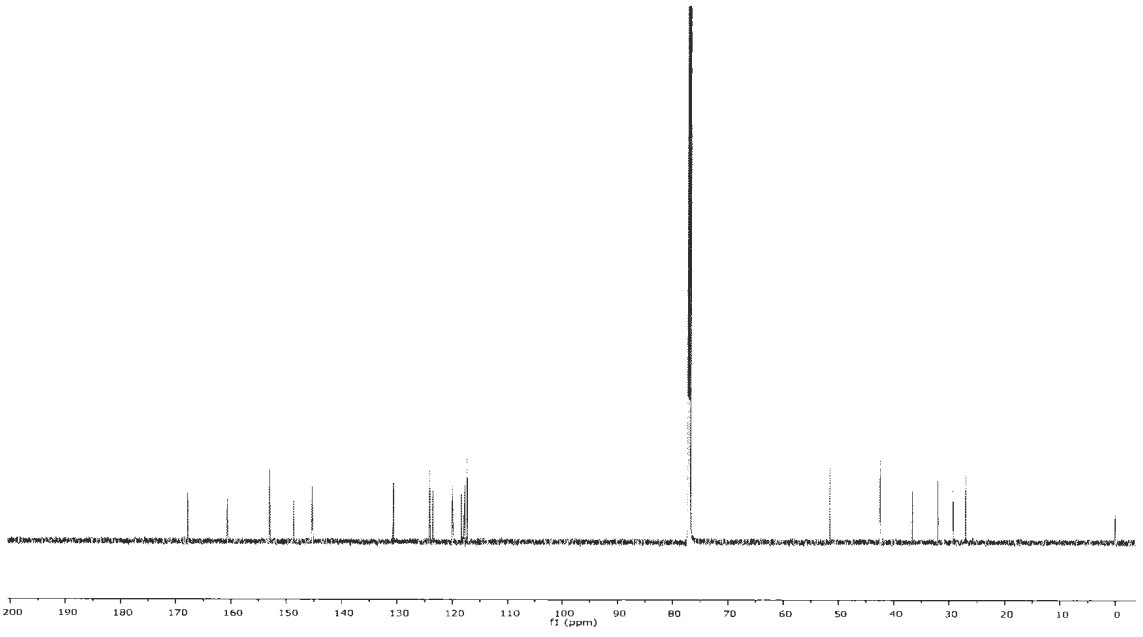
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


O
OMe
O
O

47

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
f1 (ppm)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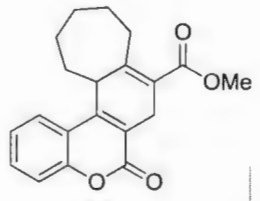
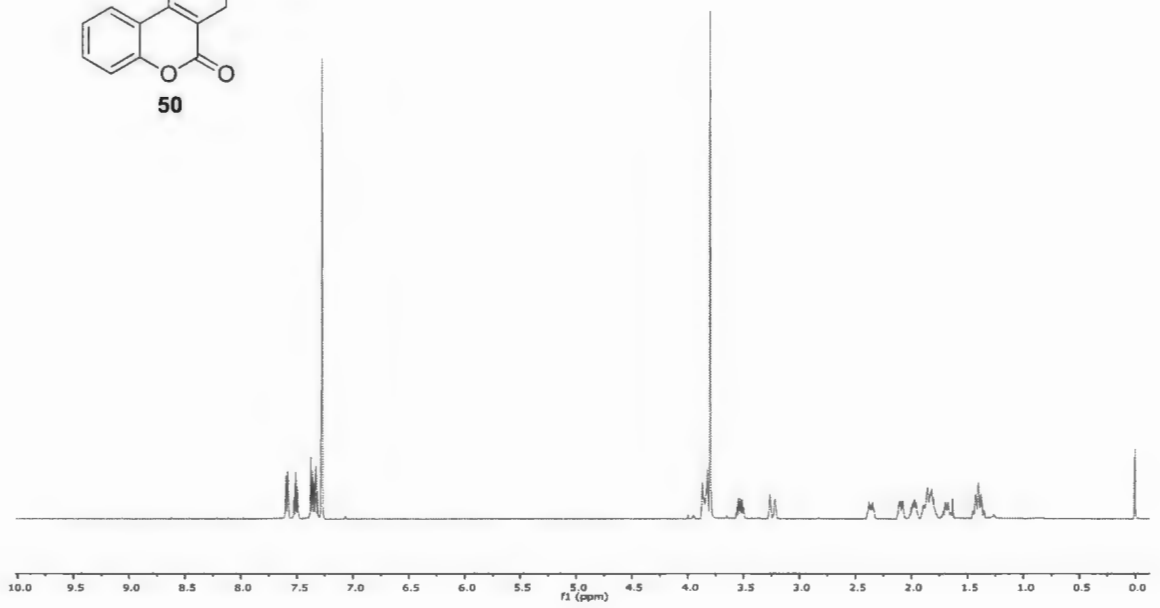
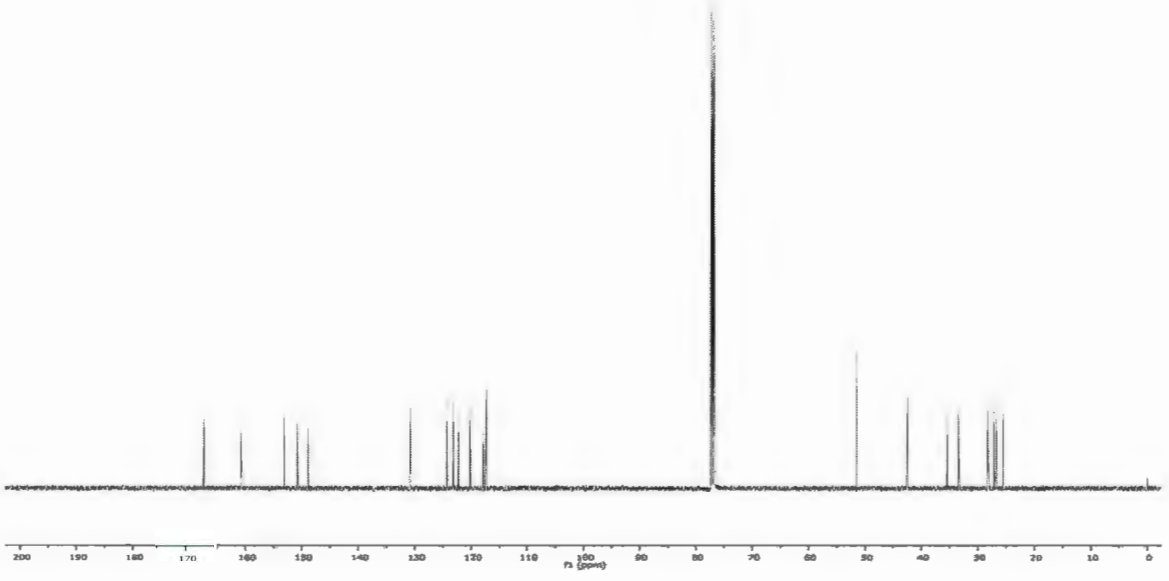
f1 (ppm)


O
OMe
O
O

50


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
f1 (ppm)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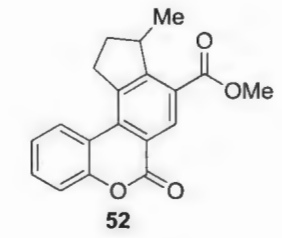
f1 (ppm)


Me
O
OMe
O
O

52

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
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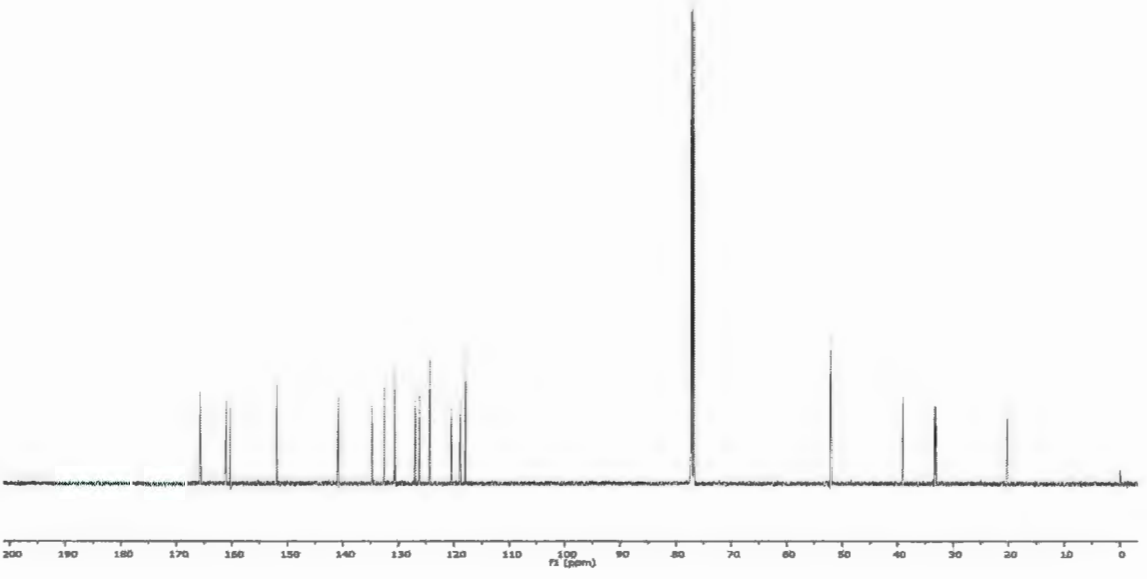
0.0
f1 (ppm)


200
190
180
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150
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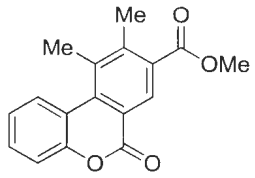
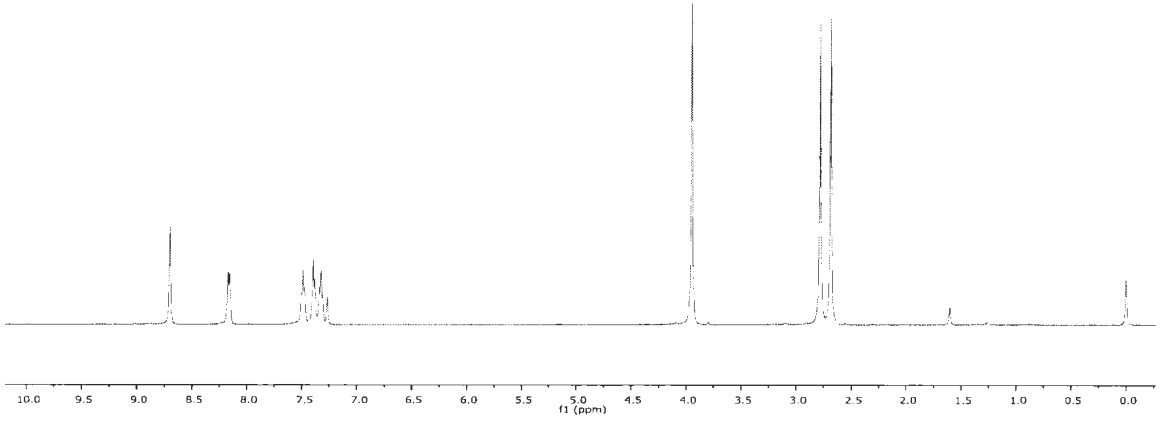
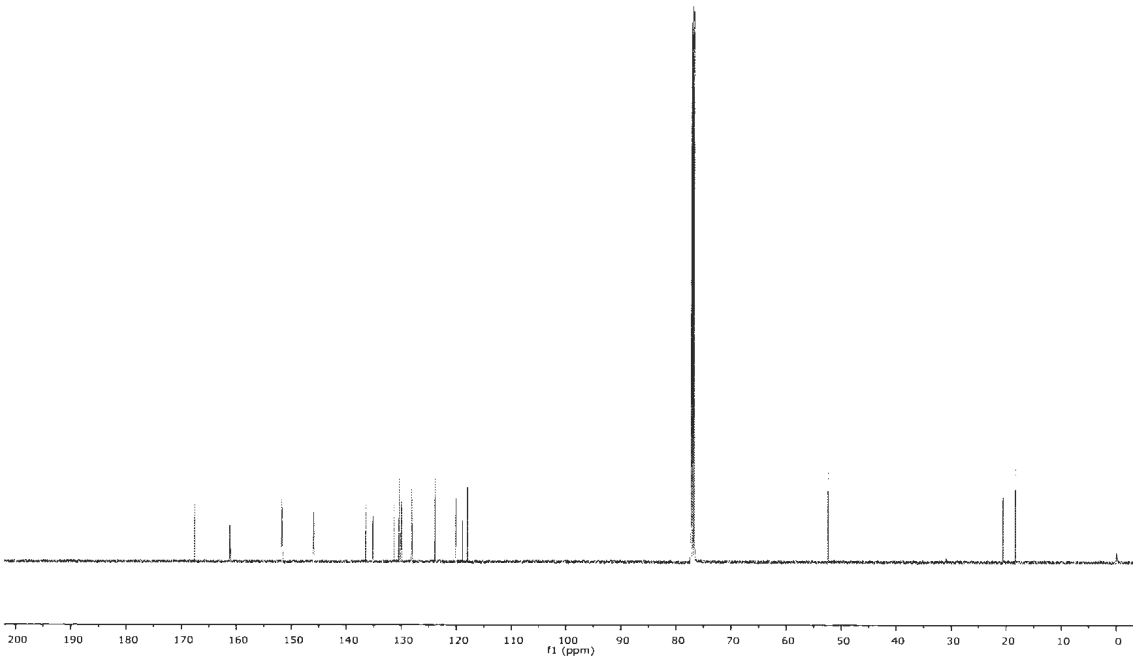
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


Me
O
Me
OMe
O
O

53


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
f1 (ppm)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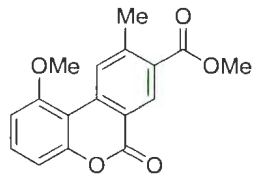
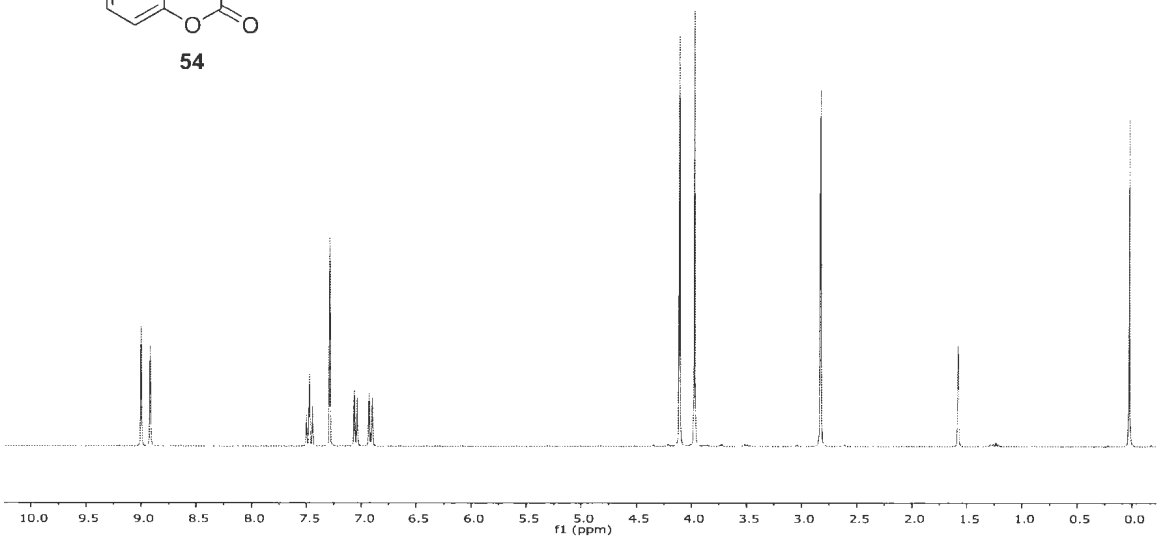
f1 (ppm)


Me
O
OMe
OMe
O
O

54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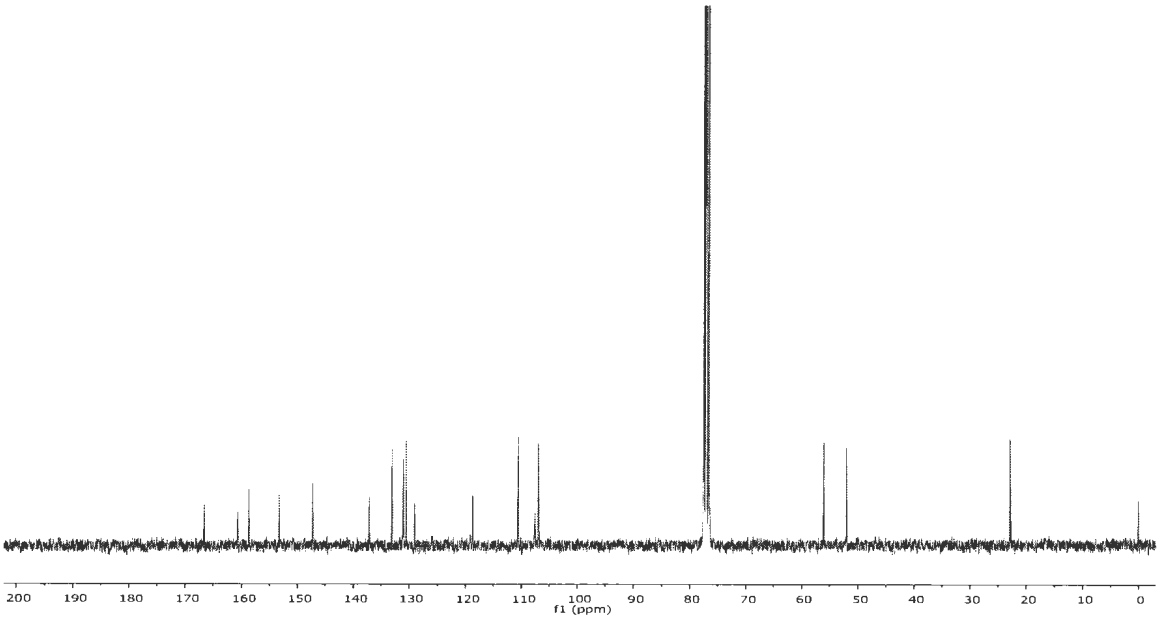
f1 (ppm)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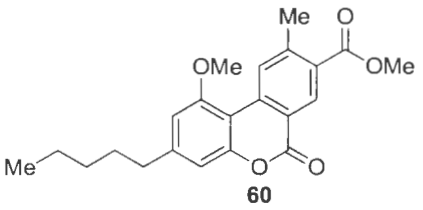
f1 (ppm)


Me
O
OMe
OMe
Me
O
O

60

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9.5
9.0
8.5
8.0
7.5
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6.5
6.0
5.5
5.0
4.5
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3.5
3.0
2.5
2.0
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1.0
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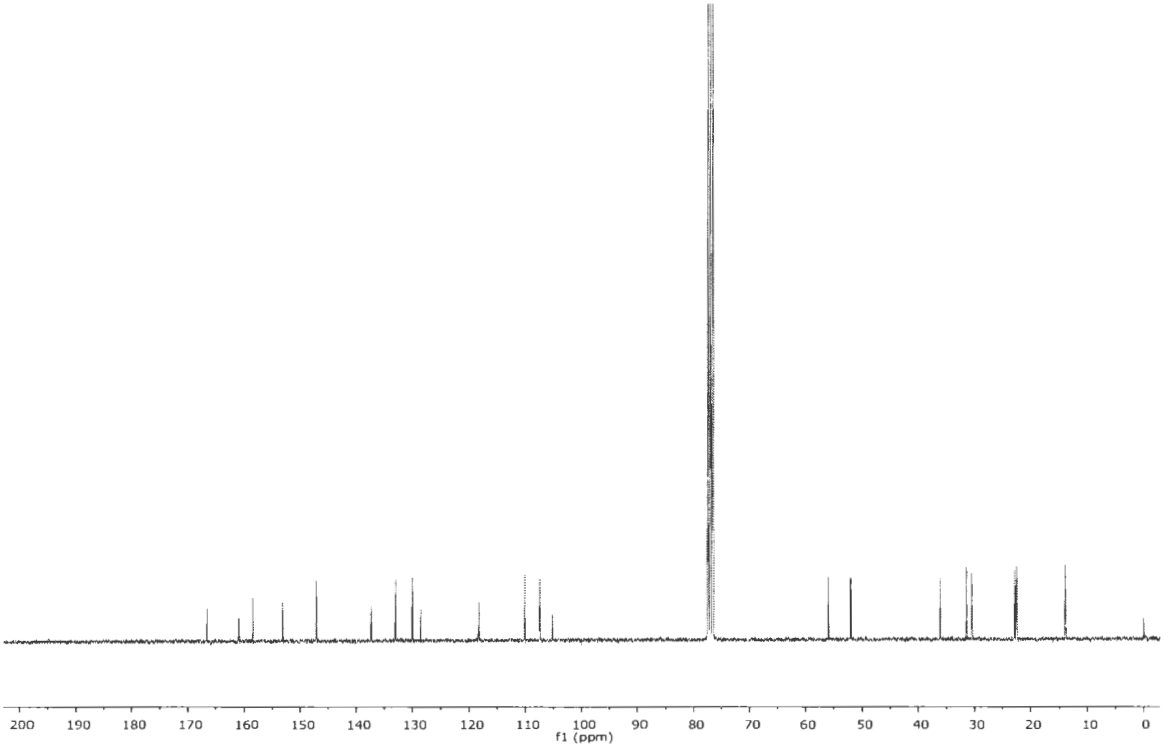
0.0
f1 (ppm)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190
180
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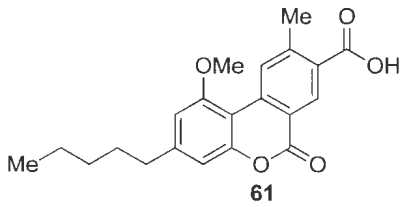
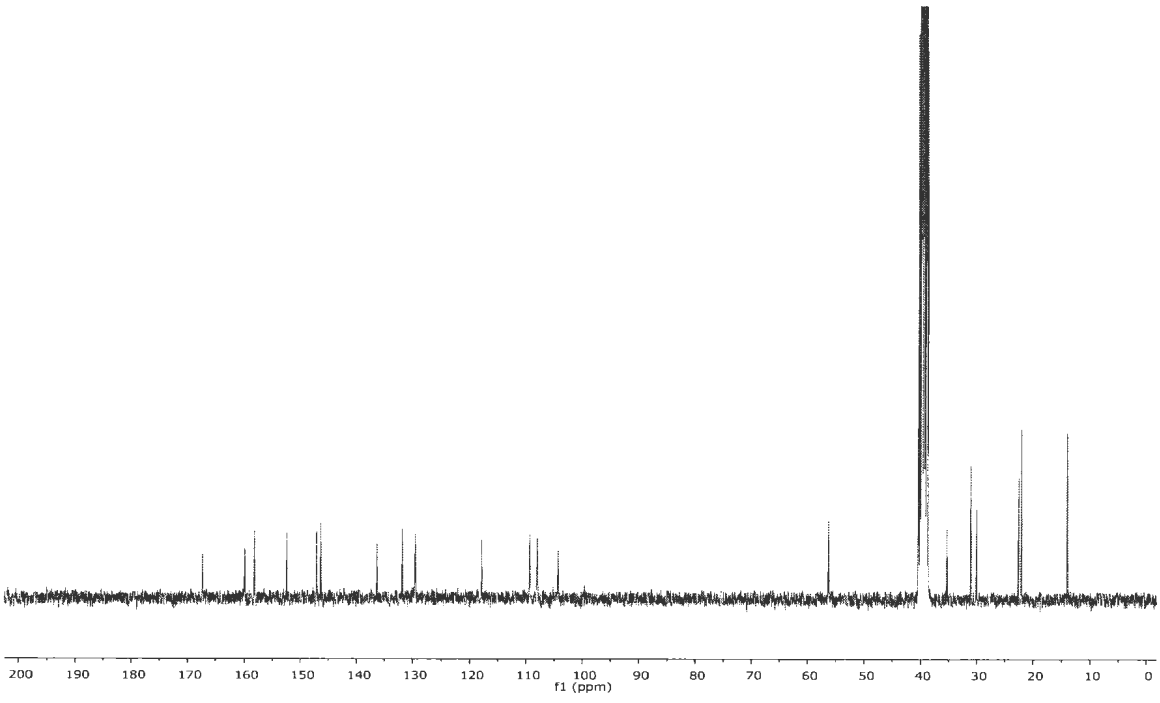
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


Me
O
OMe
OH
Me
O
O

61

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
f1 (ppm)


200
190
180
170
160
150
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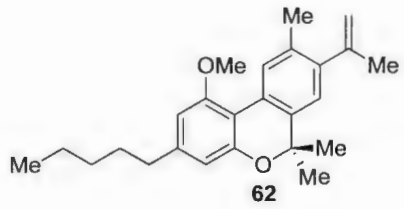
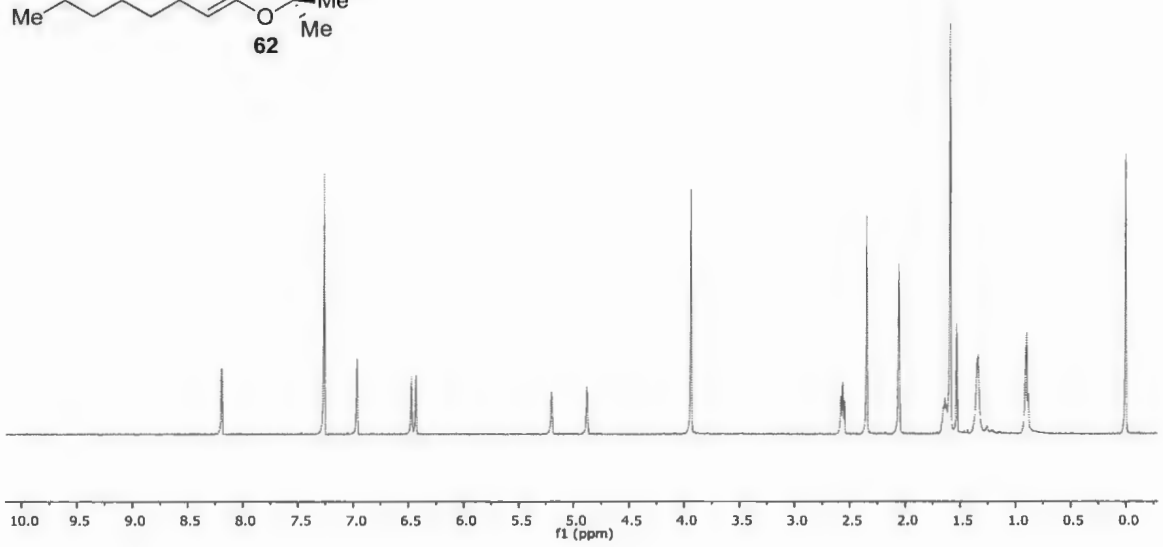
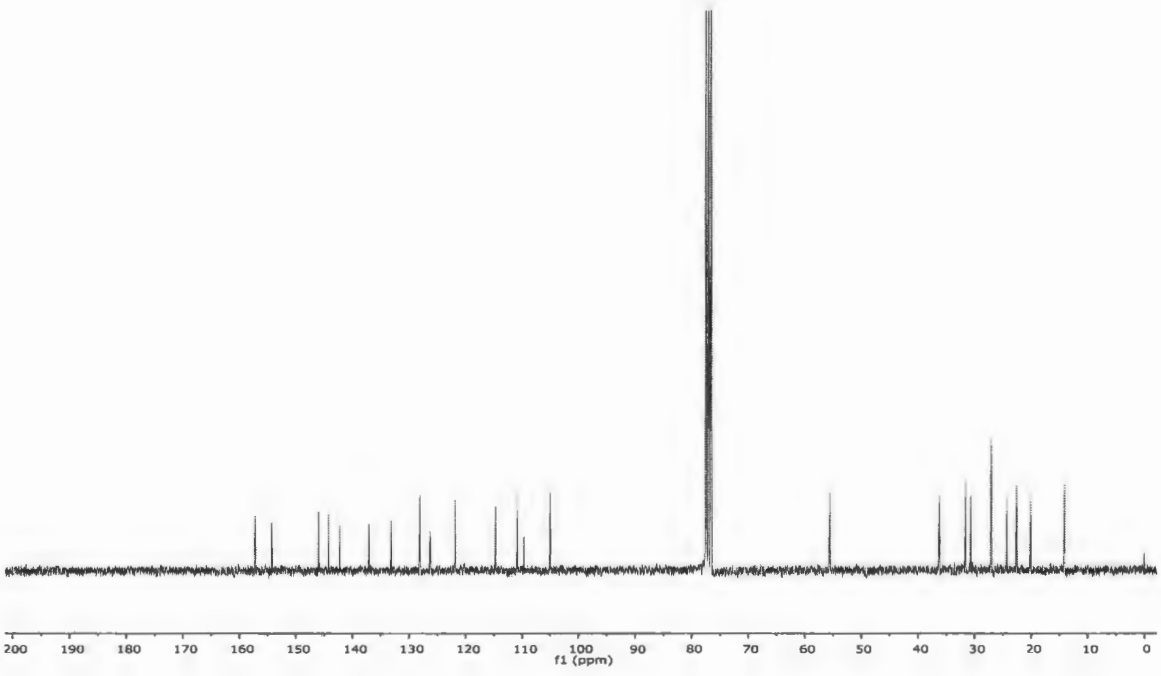
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


Me
OMe
Me
Me
Me
O
Me

62


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
f1 (ppm)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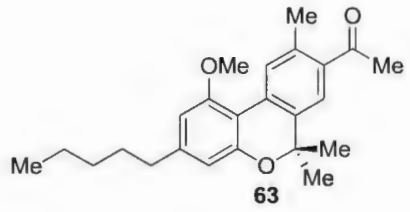
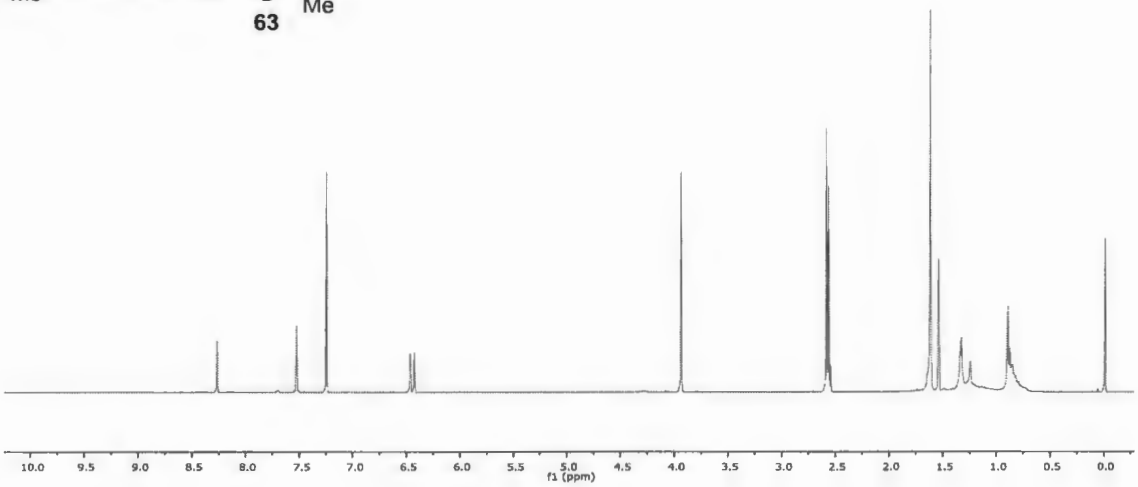
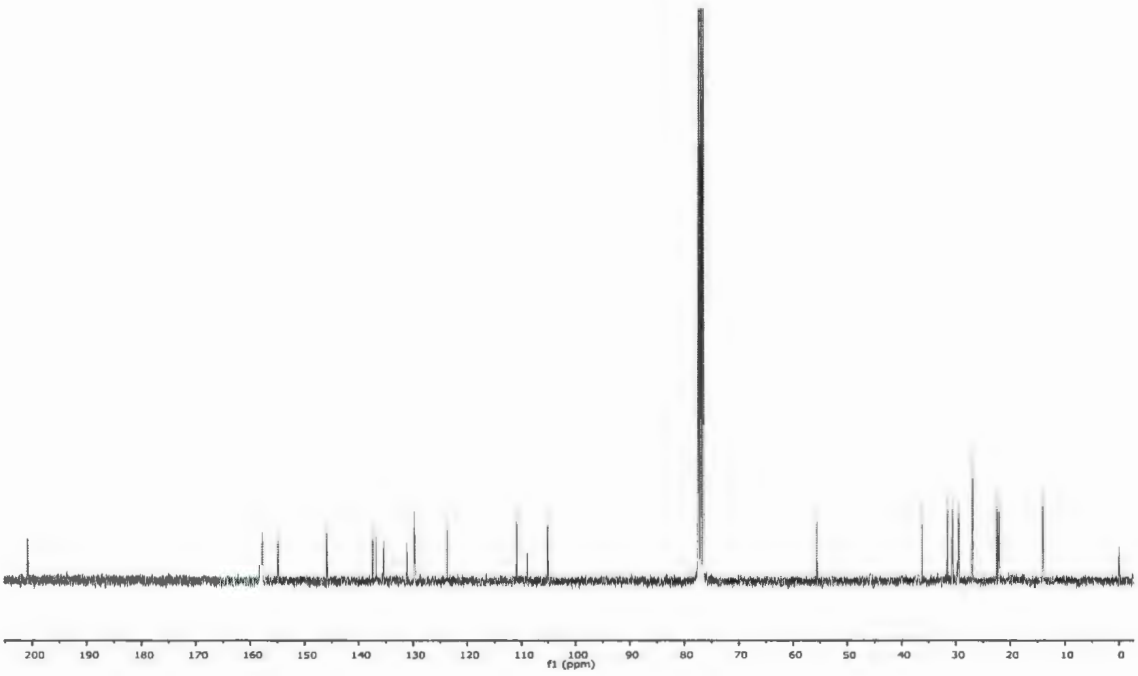
f1 (ppm)


Me
O
OMe
Me
Me
Me
O
Me

63


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
f1 (ppm)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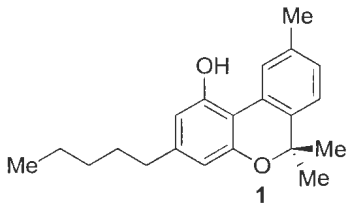
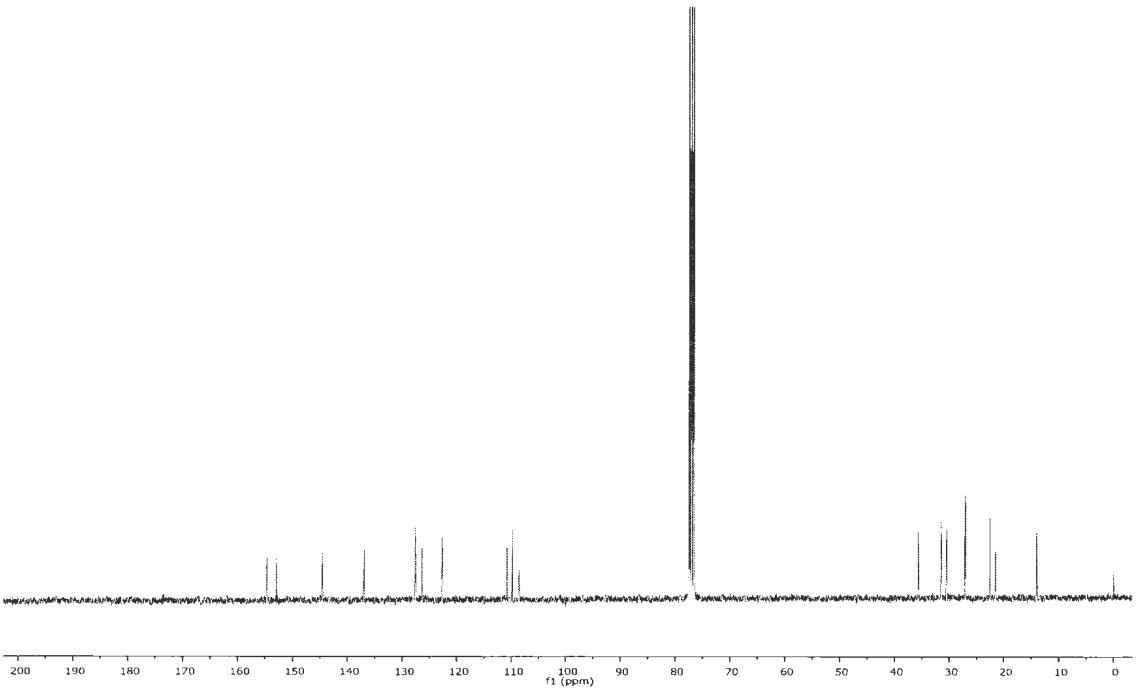
f1 (ppm)


Me
OH
Me
Me
O
Me

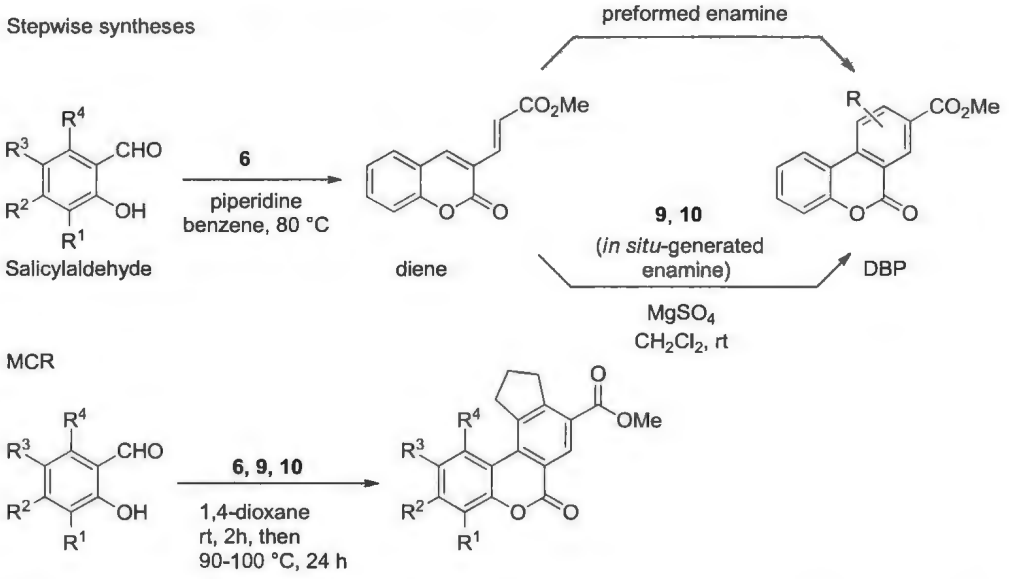
1

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
f1 (ppm)


200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

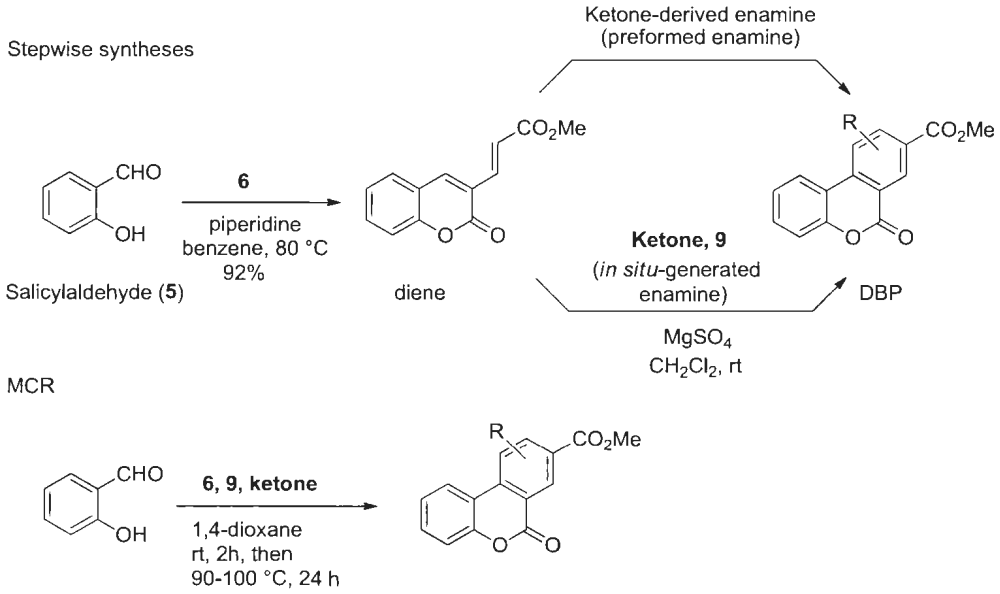
3.7 Table of yields for stepwise and multicomponent DBPs syntheses

Table S1. Comparison of yields between the MCR and the corresponding stepwise syntheses of A-ring substituted DBPs using both preformed and in situ-generated enamines.



Entry	Salycyl-lalde	Substit-tuent	DBP	diene	DBP from diene (preformed enamine)	DBP from diene (*in situ*- generated enamine)	DBP overall (preformed enamine)	DBP overall (*in situ*- generated enamine)	DBP (MCR)	Improve-ment over stepwise syntheses (%)	
1	**5**	none	**11**	92	43	74	40	68	69	29	1
2	**15**	R^1 = OMe	**16**	–	–	–	–	–	57	–	–
3	**17**	R^2 = OMe	**18**	–	–	–	–	–	64	–	–
4	**19**	R^3 = OMe	**20**	71	51	64	36	45	79	43	34
5	**21**	R^4 = OMe	**22**	–	–	–	–	–	0	–	–
6	**23**	R^1 = Me	**24**	72	48	54	35	39	48	13	9
7	**25**	R^2 = Me	**26**	80	51	57	41	46	62	21	16
8	**27**	R^3 = Me	**28**	78	47	50	37	39	68	31	29
9	**29**	R^3 = Br	**30**	65	51	35	33	23	67	34	44
10	**31**	R^3 = CO_2Me	**32**	66	41	34	27	22	51	24	29
11	**33**	R^3 = NO_2	**34**	26	24	22	6	6	10	4	4

Table S2. Comparison of yields between the MCR and the corresponding stepwise syntheses of C-ring substituted DBPs using both preformed and in situ-generated enamines.



Entry	Ketone	DBP	diene	DBP from diene (preformed enamine)	DBP from diene (*in situ*- generated enamine)	DBP overall (preformed enamine)	DBP overall (*in situ*- generated enamine)	DBP (MCR)	Improvement over stepwise syntheses (%)	
1	**35**	**36**	92	–	66	–	61	71	–	1
2	**37**	**38**	92	64	74	59	68	36	–23	–33
3	**39**	**40**	92	–	–	–	–	45	–	–
4	**41**	**42+43**	92	–	–	–	–	51	–	–
5	**44**	**45**	92	–	26	–	24	35	–	11
6	**46**	**47+48**	92	86	82	79	75	60	–19	–15
7	**49**	**50**	92	80	46	74	43	48	–26	5
8	**51**	**52**	92	–	17	–	16	36	–	16

Chapter 4

Concise, Aromatization-based Approach to Elaborate C_2-Symmetric Pyrenophanes

This chapter is partly based upon the following publication:

Nandaluru, P. R.; Dongare, P.; Kraml, C. M.; Pascal Jr., R. A.; Dawe, L. N.; Thompson, D. W.; Bodwell, G. J. *Chem. Commun.* **2012**, 48, 7747–7749.

Contributions of authors

G. J. Bodwell: research supervisor, manuscript preparation.

P. R. Nandaluru: synthetic experimental work, manuscript preparation.

P. Dongare, D. W. Thompson: measurement of photophysical properties.

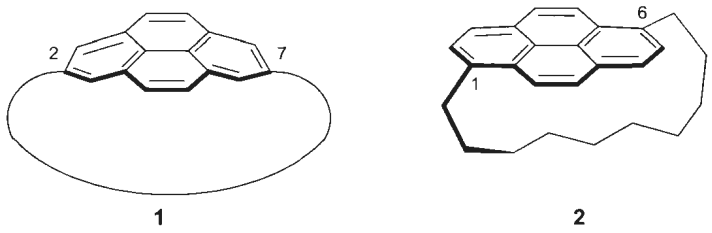
L. N. Dawe: X-ray crystallographic studies.

C. M. Kraml: resolution of chiral pyrenophanes.

R. A. Pascal Jr.: measurement of CD spectra and optical rotations.

4.1 Introduction

For the [*n*]cyclophanes, *i.e.* those composed of one aromatic system and one bridge, pyrene is the largest aromatic system to have been used frequently. All but one of the known [*n*]pyrenophanes are [*n*](2,7)pyrenophanes (**1**),[1] which have C_{2v} symmetry and are thus inherently achiral systems.[2] The exception is [10](1,6)pyrenophane (**2**),[3] which is C_2-symmetric and thus an inherently chiral cyclophane.[4]



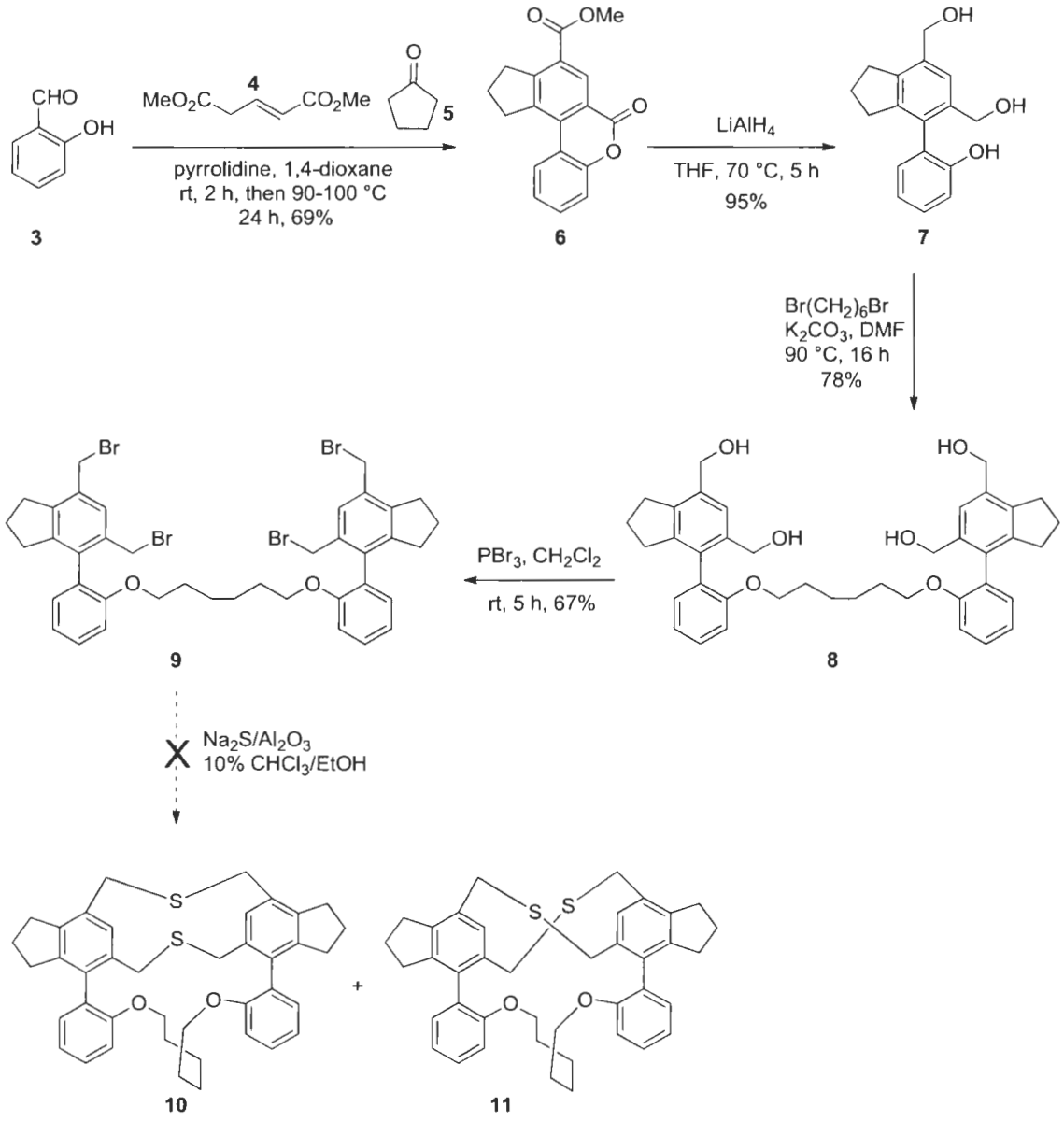
Scheme 4.1. C_{2v} (**1**, achiral) and C_2 (**2**, chiral) symmetric pyrenophanes.

The synthesis of **2** was modeled on the general synthetic approach to the [*n*](2,7)pyrenophanes (**1**),[1] but proved to be highly problematic.[3] As a result, work aimed at the development of an improved synthetic approach to [*n*](1,6)pyrenophanes was initiated. The initial results of this work are presented in this chapter.

4.2 Results and Discussion

Inspiration for a new synthetic approach to [n](1,6)pyrenophanes came from a recently reported multicomponent reaction (MCR) that affords 6*H*-dibenzo[*b,d*]pyran-6-ones (DBPs)[5] described in the previous chapter. In one example of this reaction, salicylaldehyde (**3**) reacted with dimethyl glutaconate (**4**) and cyclopentanone (**5**) in the presence of pyrrolidine to afford DBP **6** in 69% yield (Scheme 4.2). Within **6** can be

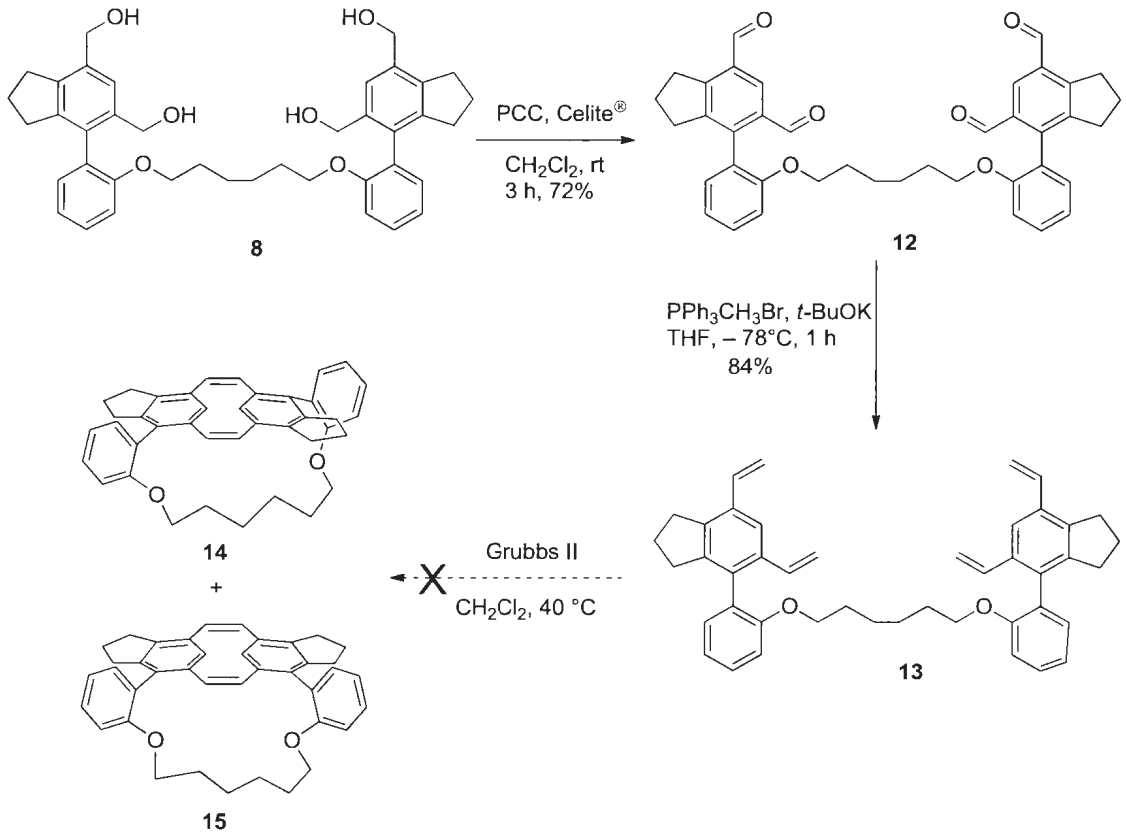
seen the elements of a 4-substituted isophthalate, which corresponds to the type of starting material used for the synthesis of **2**.[3] Reduction of **6** with $LiAlH_4$ afforded triol **7** (95%). The difference in acidity of the different types of OH groups (benzylic and phenolic) enabled two units of **7** to be tethered by way of a highly chemoselective *O*-alkylation reaction with 1,6-dibromohexane, which afforded tetraol **8** (78%). Tetraol **8** contains two elements of axial chirality, which means that two diastereomers exist. Tlc analysis showed a single spot under various conditions and the ^1H NMR spectrum, although quite complex, did not exhibit any signals that could definitively be assigned to the respective diastereomers. Evidence for the presence of both diastereomers was obtained at a later stage (vide infra). Tetraol **8** was converted into the corresponding tetrabromide **9** by reacting it with PBr_3 and this set the stage for application of the thiacyclophane route, a standard approach used in the Bodwell group for the synthesis of pyrenophanes.[1,3] Unfortunately, all attempts to generate the expected isomeric dithiacyclophanes **10** and **11** upon treatment of **9** with Na_2S/Al_2O_3 were unsuccessful. If successful, this method would have involved conversion of the dithiacyclophane into a cyclophanediene (*e.g.* **14**, Scheme 4.3) and a valence isomerization / dehydrogenation (VID) reaction to afford the pyrenophane (*e.g.* **16**, Scheme 4.4) (7 steps overall from **8**).



Scheme 4.2. Failed approach to (1,6)pyrenophane **16** via the thiacyclophane route.

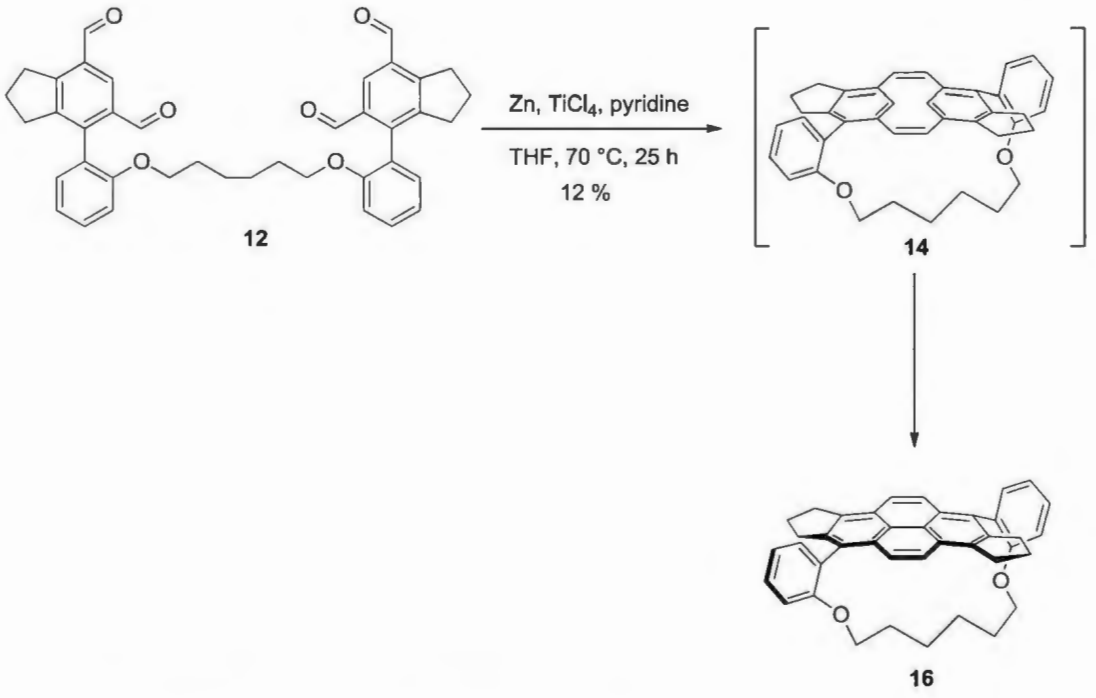
With the failure of this reaction, alternative ways for the construction of the pyrenophane **16** were sought. In this regard, tetraol **8** was oxidized with PCC/Celite® to

afford tetraaldehyde **12** (72%) as a mixture of diastereomers (1:1.2 mixture, ^{1}H NMR analysis) and this mixture was subjected to a four-fold Wittig reaction to furnish the corresponding tetraalkene **13** (85%), in preparation for a ring-closing metathesis (RCM) reaction (Scheme 4.3). Tetraalkene **13** was subjected to RCM conditions using Grubbs II catalyst with the intention of forming the cyclophanediene **14** (along with an isomeric cyclophanediene **15**). Unfortunately, this reaction produced a complex mixture of products (as shown by tlc analysis), from which no identifiable product could be isolated using column chromatography. However, the failure of this reaction was not very surprising as no example of RCM having been used for the synthesis of [2.2]metacyclophane systems (**14** is also a [2.2]metacyclophane) is known.[6]



Scheme 4.3. Failed approach to (1,6)pyrenophane **16** via an RCM based route.

Finally, as an alternative aimed at forming cyclophanediene **14** (along with an isomeric cyclophanediene **15**), compound **12** was subjected to McMurry reaction conditions (Scheme 4.4).[7] Gratifyingly, in this event, the only compound isolated from this reaction was [12](1,6)pyrenophane derivative **16** (12%).



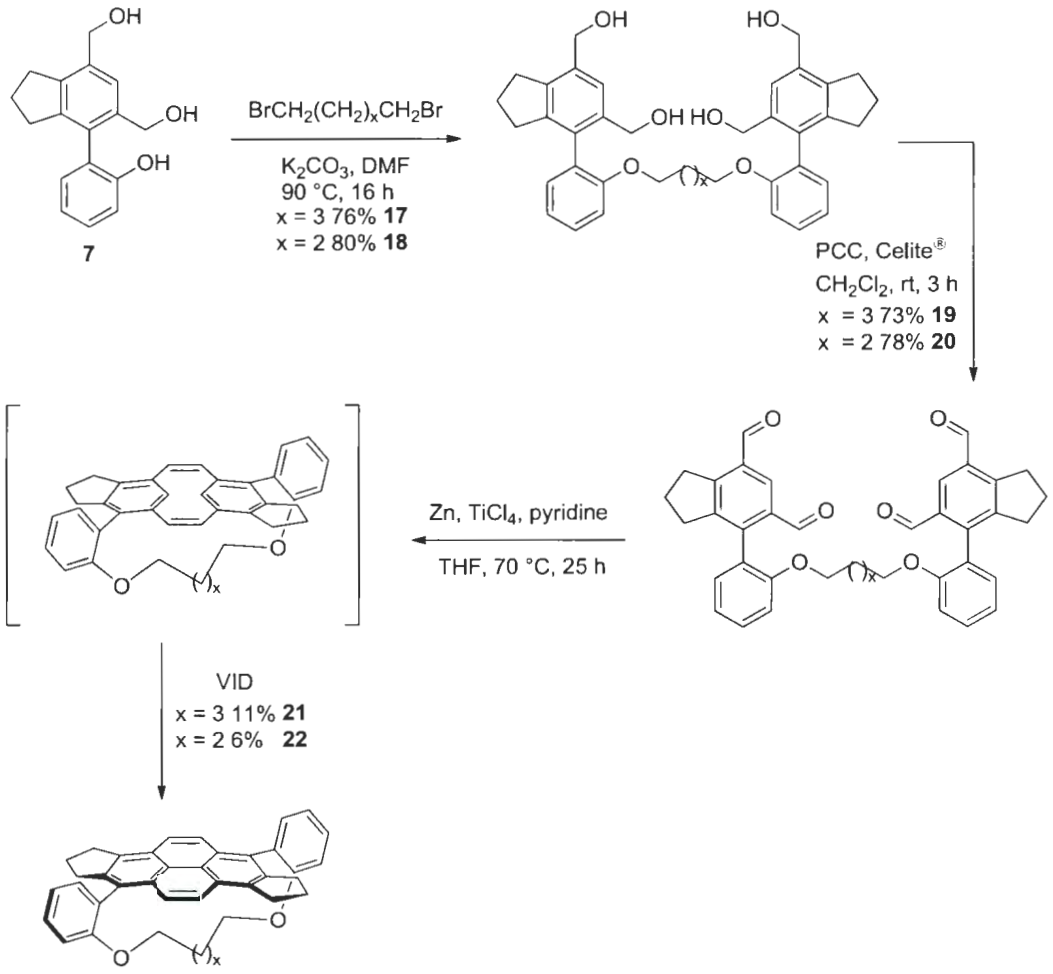
Scheme 4.4. Synthesis of [12](1,6)pyrenophane **16**.

The (1,6) bridging motif in **16** was evident from its ^{1}H NMR spectrum, which contained an AB system (δ 7.89 and 7.69 ppm, J = 9.2 Hz) for the protons attached to the pyrene system and high field signals for some of the bridge protons (2H multiplets centered at δ 0.36, 0.14, –0.39 and –0.51 ppm), which lie across the face of the pyrene system. The (1,8) isomer of **16** would have exhibited two singlets for the pyrenyl protons and is not expected to exhibit aliphatic signals at such high field.[3]

Although the yield of **16** is low, the result is noteworthy for several reasons. First, the reaction delivers the target pyrenophane directly, thereby replacing a 7-step sequence with a 2-step sequence. The reaction is also very productive, as it leads to the formation of three new carbon-carbon bonds and two new aromatic rings. A likely order of events

is two successive intramolecular McMurry reactions leading to metacyclophanediene **14** followed by a VID reaction. The observation of dehydrogenation under reductive (McMurry) conditions is not without precedent when it results in the formation of an aromatic system.[7] In the present case, the high aromatic stabilization energy of pyrene (74.6 kcal/mol)[8] provides ample driving force for dehydrogenation. Assuming that the reaction indeed proceeds through metacyclophanediene **14**, it is a very rare example of a McMurry reaction leading to a [2.2]metacyclophane[6,9] and the first example of the McMurry reaction being used to form *both* bridges of a [2.2]metacyclophanediene. The presence of a tether between the two isophthalaldehyde units in **12** is presumably advantageous in this regard. Finally, it is interesting to note that (1,6)pyrenophane **16** was formed to the exclusion of its (1,8) isomer. This is in contrast to the dithiacyclophane-derived [10](1,6)pyrenophane (**2**), which was formed as the minor component of a 4:7 mixture with [10](1,8)pyrenophane.[3]

By following the same set of reactions that were employed for the synthesis of [12](1,6)pyrenophane (**16**) from the intermediate triol **7**, two of its lower homologues were synthesized. In this event, *O*-alkylation of **7** with dibromopentane and dibromobutane afforded tetraols **17** (76%) and **18** (80%), respectively, and subsequent oxidation of these compounds using PCC produced the corresponding tetraaldehydes **19** (73%) and **20** (78%) as an inseparable mixture of diastereomers (1:1.3 mixture, ^{1}H NMR analysis) (Scheme 4.5). To complete the syntheses, these tetraaldehydes were subjected to a McMurry reaction, which afforded the targeted [11](1,6)pyrenophane **21** (11%) and [10](1,6)pyrenophane **22** (6%), respectively.



Scheme 4.5. Synthesis of [11](1,6)pyrenophane **21** and [10](1,6)pyrenophane **22**.

Pyrenophane **16** is a rather elaborate derivative of [12](1,6)pyrenophane, which means that the pyrene system would be expected to be less distorted from planarity than that of [10](1,6)pyrenophane (**2**). Indeed, the solid-state structure of **16** revealed a pyrene system that is less twisted than the one in **2**. The twist in the pyrene system can be assessed using the torsion angles through its middle bonds (C6-C7-C26-C27-C28-C16-

C17-C29). For **16**, the five angles range from 160.1 to 174.1° and the average deviation from 180° (the value for a planar pyrene system) is 10.8° (Table 4.1). This compares to a range of 159.9 to 170.5° and an average deviation from 180° of 14.1° in **2**.[3] The bend in the pyrene system of **16** (as indicated by the smallest angle formed by C8-C7-C26 and C18-C17-C16) is 17.4°, which is also smaller than the corresponding value in **2** (27.3°).[3,10] Relatively long intramolecular C(sp^3)–H···π interactions[11] (3.30 Å) between protons attached to C37 and C38 and the apical rings of the pyrene system are also observed. The unit cell (space group $P\bar{1}$, SI-Figure 3) consists of two enantiomeric molecules in a face-to-face arrangement with a closest π···π contact of 3.47 Å.[12]

In the case of [10](1,6)pyrenophane **22**, the solid-state structure showed a pyrene unit that has more twist than that of **2** and obviously much more when compared to its higher homologue **16**. For **22**, the average deviation from the five angles (range from 148.9 to 164.4) is 22.1°. Though the X-ray crystal structure for [11](1,6)pyrenophane **21** couldn't be obtained, its structure was calculated at the B3LYP/6-31G(D) level of theory.[13] The predicted average deviation from planarity for **21** was 15.5°. The structures of **16** and **22** were also calculated at the same level of theory and the predicted average deviations from planarity (21.4° for **22**; 10.9° for **16**) were in excellent agreement with the experimentally determined values (22.1° for **22**; 10.8° for **16**). Thus, the predicted value for **21** can be viewed with a reasonable degree of confidence.

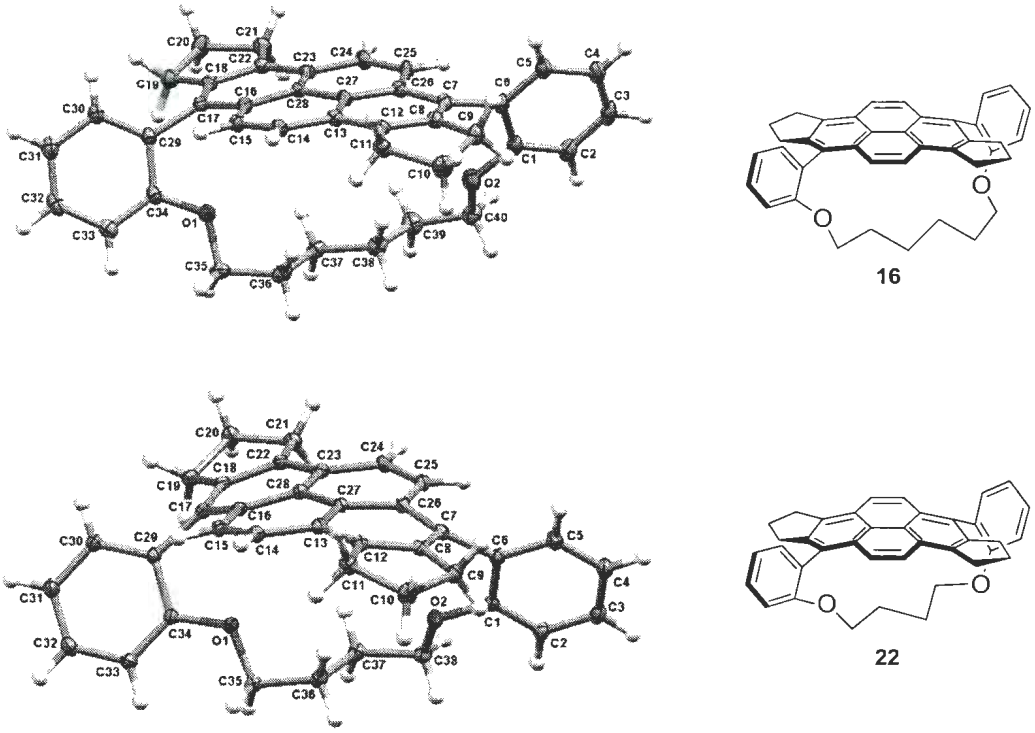
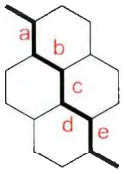
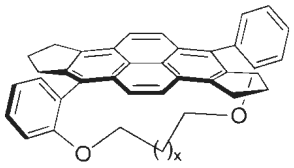


Figure 4.1. X-ray crystal structures of pyrenophanes**16** and **22**.





16, **21** and **22**

Bond	$-O(CH_2)_4O-$ (calcd)	$-O(CH_2)_4O-$ (X-ray)	$-O(CH_2)_5O-$ (calcd)	$-O(CH_2)_6O-$ (calcd)	$-O(CH_2)_6O-$ (X-ray)
a	151.3	151.9	161.4	166.1	168.6
b	−162.2	−164.4	−164.8	−170.2	−174.1
c	161.3	161.4	166.7	171.0	172.0
d	−163.1	−162.8	−166.7	−170.9	−171.7
e	155.1	148.9	162.7	167.5	160.1
average deviation	21.4	22.1	15.5	10.9	10.8

average deviation: average deviation from 180°.

Table 4.1. Calculated (B3LYP/6-31G(D)) and measured (X-ray) torsion angles in the pyrene system.

Photophysical properties of 16, 21 and 22

The absorption spectrum for **16** (Fig. 4.2, top left) exhibits significant complexity in the low energy absorption band envelope with bands λ_{max} (ε, M^{-1} cm^{-1}) at 392 (1.4×10^4), 373 (3.2×10^4), 365 (3.0×10^4), 355 (2.5×10^4), 295 (3.9×10^4) and 283 (2.5×10^4) nm, whereas its emission spectrum shows bands λ_{max} at 400 and 419 nm. The absorption features at 392 nm and the barely resolved band at 365 nm are not apparent in the emission profile. As a result, the mirror image symmetry between the absorption and emission spectra expected for a 2-state system is absent. These observations imply that

the lowest energy absorption band envelope is comprised of two overlapping transitions and their vibronic components, one of which leads to emission and the other to non-radiative decay. The fluorescence quantum yield (Φ) for **16** is 0.40 and the fluorescence lifetime (τ_f) is 1.7 ns. This compares to $\Phi = 0.64$ and $\tau_f = 480$ ns for pyrene.[14]

The absorption and emission spectra for **21** (Fig. 4.2, top right) are similar to those of **16**. In the case of **21**, absorption bands λ_{max} (ε, M^{-1} cm^{-1}) are observed at 395 (8.5×10^4), 377 (1.8×10^4), 362 (1.8×10^4), 297 (2.9×10^4) and 285 (2.2×10^4) nm and emission bands are observed at λ_{max} at 404 and 422 nm. The only significant difference between the spectral features of **21** from those of **16** is that the low energy absorption band at 395 nm is nearly merged with the neighbouring band at 377 nm. The fluorescence quantum yield (Φ) for **21** (0.44) is slightly higher than that of **16** (0.40), but its fluorescence lifetime (τ_f) (1.5 ns) is slightly shorter than that of **16** (1.7 ns).

The absorption and emission spectra for **22** (Fig. 4.2, bottom) are somewhat different in appearance from those of its two higher homologs, **16** and **21**. Its absorption bands appear at λ_{max} (ε, M^{-1} cm^{-1}) at 385 (3.9×10^4), 373 (4.2×10^4), 353 (2.1×10^4), 300 (4.9×10^4) and 290 (3.3×10^4) nm and emission bands at 417 and 436 nm. The low energy absorption band that was observed for **16** (392 nm) and **21** (395 nm) is now (presumably) buried underneath the band at 385 nm. Furthermore, a decrease in fluorescence lifetime (τ_f = 1.2 ns) and a pronounced increase in fluorescence quantum yield ($\Phi = 0.80$) was observed.

By this preliminary study, it can be inferred that the fluorescence lifetime (τ_f = 1.7, 1.5 and 1.2 ns) for these pyrenophanes (**16**, **21** and **22**) decreases as the pyrene becomes more twisted, whereas the quantum yield (Φ = 0.40, 0.46 and 0.80) increases. The origin of this intriguing trend is being investigated in collaboration with Prof. David W. Thompson's group.

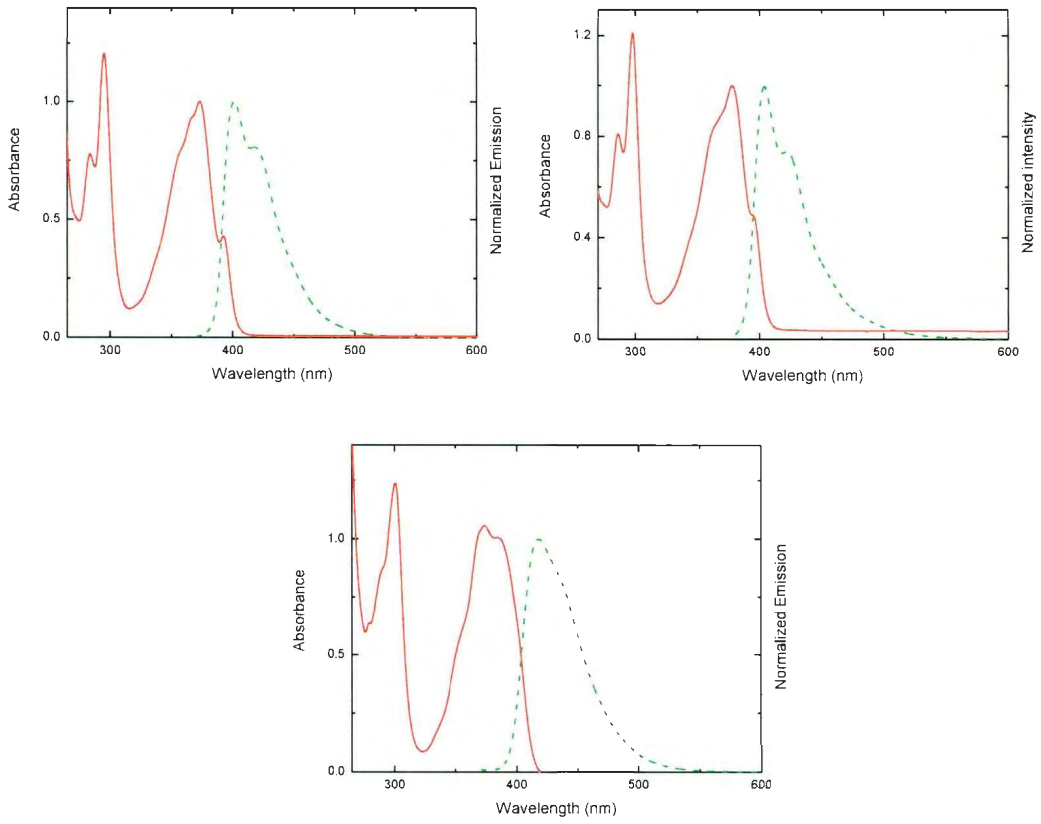


Figure 4.2. Normalized absorption (solid line) and emission spectra (dashed line) for **16** (top left), **21** (top right) and **22** (bottom) in $CHCl_3$ (1 atm N_2) at 298 ± 3 K.

Chiroptical Properties of 16, 21 and 22

Small samples (*ca.* 10 mg) of (+)-**16** (>99% *ee* by HPLC) and (–)-**16** (>99% *ee* by HPLC) were obtained by preparative chiral phase HPLC (Chiralpak OD-H column: 40% ethanol (0.1% diethylamine) / CO_2, 100 bar). The CD spectra (Fig. 4.3, top left) of the two enantiomers are nearly perfect mirror images and the specific rotations ($[\alpha]_D^{23} = +130° \pm 20°$ ($c = 0.13$, $CHCl_3$) and $[\alpha]_D^{23} = -120° \pm 20°$ ($c = 0.14$, $CHCl_3$)) agree well. The low precision is due to the small quantities of the pure enantiomers.

Although the CD spectra of the enantiomers of **21** (Fig. 4.3, top right) show mirror images of one another, their specific rotations couldn't be determined because of the turbid nature of their solutions even at low concentrations. In the case of **22** (Fig. 4.3, bottom), the CD spectra again show a mirror image relationship and the specific rotations of its enantiomers are $[\alpha]_D^{24} = +290° \pm 20°$ and $[\alpha]_D^{24} = -230° \pm 30°$ ($c = 0.12$ in $CHCl_3$).

Unfortunately, specific rotation values of enantiomers of **21** are not available to draw a more accurate comparison of chiroptical properties among pyrenophanes, **16**, **21** and **22**. However, when comparison is made between **16** and **22**, *i.e.* the longest and the shortest tethered pyrenophanes of the three homologs, it appears that the specific rotation value increases as the twist in the pyrene system increases.

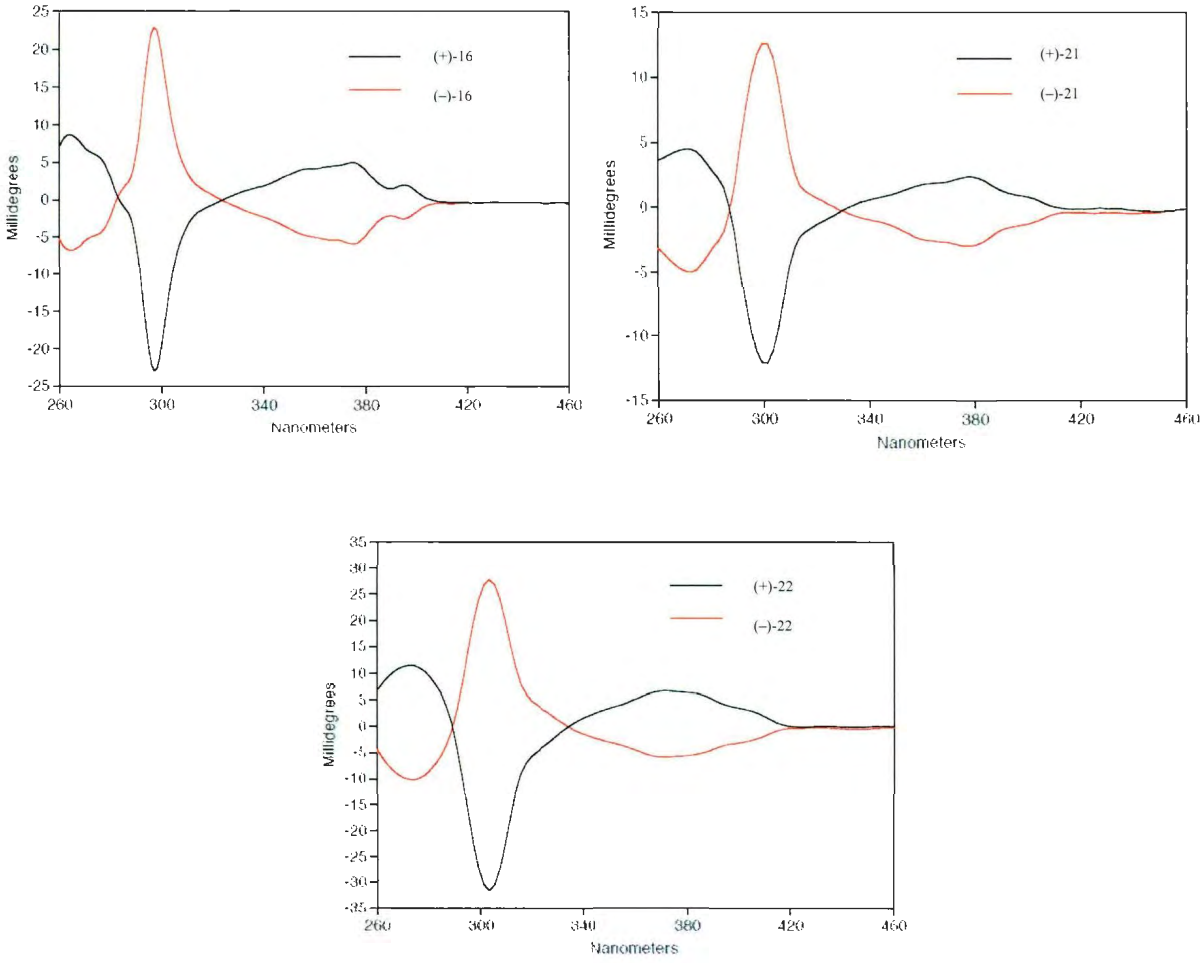
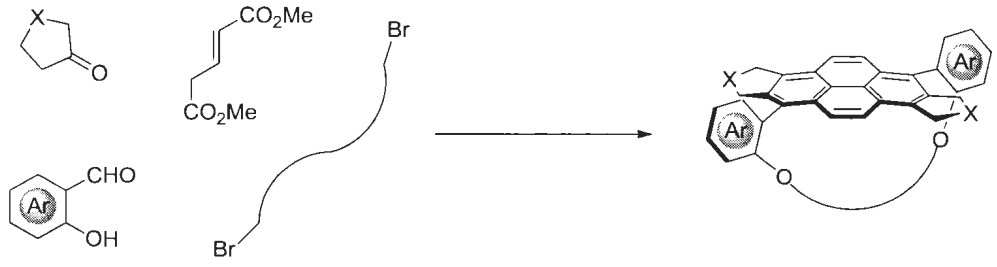


Figure 4.3. CD spectra for (+)-**16**, **21** and **22** (black line) and (−)-**16, 21 and 22** (red line).

4.3 Conclusions

In summary, (1,6)pyrenophanes **16**, **21**, **22** were synthesized by a route that both starts and ends with a highly productive reaction. The initial multicomponent reaction not only brought together most of the atoms required for these pyrenophanes, but also

generated a new aromatic ring that ultimately manifested itself as the two apical rings in the pyrene system. The synthesis culminated in a very unusual twofold intramolecular McMurry / VID reaction, which generated the two central aromatic rings of the pyrene system. As such, all four of the rings in the pyrene unit were created during the synthesis. Looking forward, the multicomponent reaction holds promise for the synthesis of related pyrenophanes through variation of the ketone and salicylaldehyde components of the MCR. There is also potential to vary the length of the bridge (and thus the degree of deformation of the pyrene system) by varying the length of the dihalide used in the *O*-alkylation reaction. Enantioselective syntheses of these inherently chiral cyclophanes are also conceivable.[15]



Scheme 4.6. Points of diversity for future (1,6)pyrenophane syntheses.

4.4 References

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2) The C_{2v} symmetry arises upon time averaging of two degenerate bridge conformers.

3) Yang, Y.; Mannion, M. R.; Dawe, L. N.; Kraml, C. M.; Pascal Jr., R. A.; Bodwell, G. J. *J. Org. Chem.* **2012**, *77*, 57.

4) The term "inherently chiral cyclophane" is used here to denote a cyclophane that is chiral in its parent form (the bare bones assembly of arene(s) and bridge(s)), and not by virtue of the presence of substituents on an otherwise achiral cyclophane.

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9) (a) Merner, B. L.; Dawe, L. N.; Bodwell, G. J. *Angew. Chem. Int. Ed.* **2009**, *48*, 5487. (b) Yamato, T.; Miyamoto, S.; Saisyo, T. Manabe, T.; Okuyama, J. *Chem. Res.* **2003**. 63.

10) The evaluation of bend using this metric requires the torsion angle for C8-C26-C18-C16 to be close to 180°. For **11**, the angle is 175.1°, which is comparable to 174.5° in **2** (ref. 3).

11) The C–H···centroid angles are 157.6° and 159.8°, which qualifies these interactions as meaningful, according to: Arunan, E.; Desiraju, G. R.; Klein R. A.; Sadlej, J.; Scheiner, S.; Alkorta, I.; Clary, D. C.; Crabtree, R. H.; Dannenberg, J. J.; Hobza, P.; Kjaergaard, H. G.; Legon, A. C.; Mennucci, B.; Nesbitt, D. J.; *Pure Appl. Chem.*, 2012, **83**, 1619. Slightly longer C(sp^3)–H···π interactions (3.39–3.51 Å) between protons on C36 and C39 and the two central rings of the pyrene system are not meaningful because the C–H···centroid angles are less than 130° (128.1–128.5°). For discussions of the C–H···π hydrogen bond, see: Desiraju, G. R. *Angew. Chem. Int. Ed.*, 2011, **50**, 52, and references cited therein.

12) While this distance may evoke thoughs of nascent π stacking, it is important to bear in mind that the pyrene systems are twisted and bent away from one another. Thus, the 3.47 Å distance applies only to the closest contact and not the full pyrene surfaces.

13) Dr. Zhao, Department of Chemistry, Memorial University is gratefully acknowledged for his help with B3LYP/6-31G(D) calculated structures.

14) Tran-Thi, T.-H., Prayer, C.; Uznanski, P.; Hynes, J. T. *J. Phys. Chem. A*, 2002, **106**, 2244.

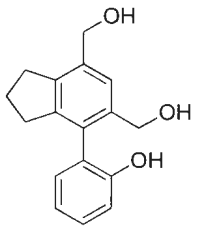
15) Bringmann, G.; Mortimer, A. J. P.; Keller, P. A.; Gresser, M. J.; Garner, J.; Breuning, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 5384.

4.5 Experimental procedures and characterization data

General I: The general experimental can be found on page 47.

General II: DMF was vacuum distilled from CaH_2.

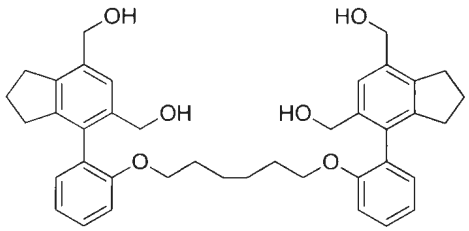
2,3-Dihydro-5,7-bis(hydroxymethyl)-4-(2-hydroxyphenyl)-1*H*-indene (7)



To a 0 °C slurry of $LiAlH_4$ (1.55 g, 40.8 mmol) in THF (45 mL) was added dibenzopyranone **6** (3.00 g, 10.2 mmol) in several portions and the resulting mixture was heated at 70 °C for 5 h. After cooling to 0 °C, water (20 mL) was added carefully over a period of 20 min. The reaction mixture was diluted with aqueous 1.0 M HCl solution (100 mL) and extracted with $CHCl_3$ (3 × 200 mL). The combined organic layers were dried over Na_2SO_4, gravity filtered and the solvent was removed under reduced pressure. The residue was triturated with ether (2 × 15 mL) to afford **7** (2.59 g, 95%) as a colorless solid. R_f = 0.60 (ethyl acetate); mp 148–150 °C; IR (neat) ν 3482 (w), 3265 (m), 3067 (m), 2928 (m), 2361 (w), 1447 (m), 1058 (s) cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ 9.23 (br s, 1H), 7.36 (s, 1H); 7.15 (td, J = 7.7, 1.7 Hz, 1H), 6.95 (dd, J = 7.5, 1.7 Hz, 1H), 6.90 (d, J = 8.1 Hz, 1H), 6.82 (t, J = 7.4 Hz, 1H), 5.06 (t, J = 5.5 Hz, 1H), 4.86 (br s, 1H), 4.49 (d, J = 5.2 Hz, 2H), 4.25 (d, J = 13.5, 1H), 4.17 (d, J = 13.4 Hz, 1H), 2.85 (t, J = 7.5 Hz, 2H), 2.51–2.47 (m, 2H), 1.97–1.89 (m, 2H); ^{13}C NMR (DMSO-d_6, 500 MHz) δ 154.10, 142.36, 138.70, 137.90, 135.79, 131.36, 130.39, 128.10, 125.84, 123.09, 118.70,

115.36, 61.36, 60.74, 31.54, 30.16, 24.25; ESI-(+)-MS *m/z* (%) 294 (19), 293 ($[M + Na]^+$, 100), 253 (7), 223(5), 217 (8).

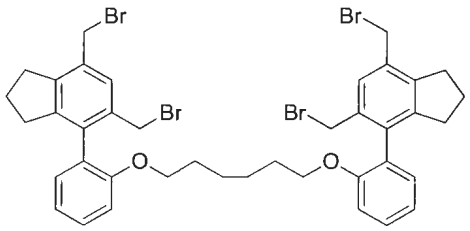
1,6-Bis(2-(2,3-dihydro-5,7-bis(hydroxymethyl)-1*H*-inden-4-yl)phenoxy)hexane (8)



To a suspension of triol **7** (1.00 g, 3.70 mmol) and K_2CO_3 (1.53 g, 11.1 mmol) in DMF (15 mL) was added 1,6-dibromohexane (0.49 g, 2.0 mmol). The resulting mixture was stirred vigorously at 90 °C for 16 h and then cooled to room temperature. Water (30 mL) was added and the resulting mixture was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with water (50 mL), dried over Na_2SO_4, gravity filtered and the solvent was removed under reduced pressure. The residue was subjected to column chromatography (5% MeOH / $CHCl_3$) to obtain tetraol **8** (0.90 g, 78%) as a colorless solid. R_f = 0.40 (ethyl acetate); mp 131–133 °C; IR (neat) ν 3450–3100 (br, m), 2941 (w), 2860 (w), 2364 (w), 2328 (w), 1444 (s), 1233 (s) cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ 7.36 (s, 1H), 7.32–7.28 (m, 1H), 7.04–7.02 (m, 1H), 7.01 (dd, J = 7.4, 1.9 Hz, 1H), 6.97–6.94 (m, 1H), 5.04 (t, J = 5.5 Hz, 1H), 4.82 (t, J = 5.3 Hz, 1H), 4.47 (d, J = 5.5 Hz, 2H), 4.16 (dd, J = 14.0, 5.8 Hz, 1H), 4.12 (dd, J = 14.0, 5.7 Hz, 1H), 3.87–3.78 (m, 2H), 2.84–2.75 (m, 2H), 2.48–2.36 (m, 2H), 1.93–1.82 (m, 2H), 1.42–1.39 (m, 2H), 1.10–1.07 (m, 2H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 155.33, 142.13, 138.53, 137.73,

135.87, 131.00, 130.40, 128.39, 127.81, 123.11, 120.11, 112.21, 67.29, 61.31, 60.68, 31.51, 30.12, 28.35, 24.78, 24.26; ESI-(+)-MS *m/z* (%) 647 (11), 646 (48), 645 ([M + Na]$^+$, 100), 569 (9), 551 (7), 359 (8), 305 (7); MALDI-TOF MS cald for $C_{40}H_{46}O_6Na$ 645.3192, found 645.3194.

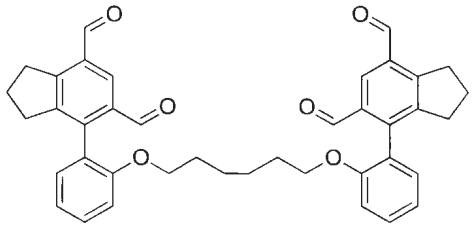
1,6-Bis(2-(2,3-dihydro-5,7-bis(bromomethyl)-1*H*-inden-4-yl)phenoxy)hexane (9)



To a 0 °C solution of **8** (0.20g, 0.32 mmol) in CH_2Cl_2 (20 mL) was added phosphorous tribromide (0.26 g, 0.96 mmol) and the resulting mixture was stirred at room temperature for 5 h. The reaction mixture was diluted with CH_2Cl_2 (20 mL), washed with 10% $NaHCO_3$ solution (15 mL) and then with water (10 mL). The organic layer was dried over Na_2SO_4, gravity filtered and the solvent was removed under reduced pressure. The residue was subjected to column chromatography (50% CH_2Cl_2 / hexanes) to obtain **9** (0.20 g, 67%) as a colorless solid. R_f = 0.50 (10% ethyl acetate / hexanes); mp 153-156 °C; lR (neat) v = 2940 (w), 2845 (w), 2364 (w), 1437 (m), 1235 (s), 1203 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.35–7.31 (m, 1H), 7.28 (d, J = 1.8 Hz, 1H), 7.16 (dd, J = 7.4, 1.8 Hz, 1H), 7.00 (td, J = 7.5, 1.0 Hz, 1H), 6.91 (dd, J = 8.3, 1.1 Hz, 1H), 4.47–4.33 (m, 2H), 4.34 (dd, J = 10.0, 1.6 Hz, 1H), 4.18 (d, J = 10.0 Hz, 1H), 3.84–3.77 (m, 2H), 3.00–2.89 (m, 2H), 2.59–2.47 (m, 2H), 2.07–1.94 (m, 2H), 1.47–1.44 (m, 2H), 1.08–1.05 (m,

2H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 155.69, 145.46, 143.64, 135.62, 134.58, 132.30, 130.53, 129.10, 129.07 127.08, 120.43, 112.01, 67.89, 32.39, 32.33, 31.93, 31.14, 28.78, 25.38, 24.52.

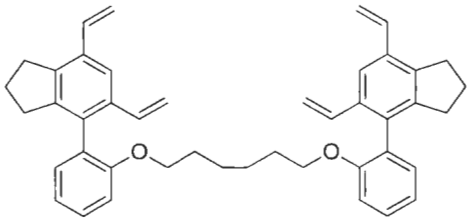
1,6-Bis(2-(5,7-diformyl-2,3-dihydro-1*H*-inden-4-yl)phenoxy)hexane (12)



To a solution of tetraol **8** (0.90 g, 1.5 mmol) in CH_2Cl_2 (45 mL) was added Celite® (2.70 g) in one portion. To this suspension was added PCC (3.74 g, 17.4 mmol) in several portions and the resulting mixture was stirred at room temperature for 3 h. The reaction mixture was vacuum filtered through a plug of Celite® and the cake was washed thoroughly with $CHCl_3$ (3 × 50 mL). The filtrate was removed under reduced pressure and the residue was subjected to column chromatography (30% ethyl acetate / hexanes) to afford tetraaldehyde **12** (0.63 g, 72%, *ca.* 1.2:1 mixture of diastereomers by ^{1}H NMR analysis) as a colorless solid. R_f = 0.30 (30% ethyl acetate / hexanes); mp 168–171 °C; IR (neat) ν 2944 (w), 2857 (w), 2364 (w), 2329 (w), 1691 (s), 1590 (m), 1241 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 10.17 (s, 1H), 10.16 (s, 1H), 9.71 (s, 1H), 9.70 (s, 1H), 8.27 (s, 1H), 8.27 (s, 1H), 7.44–7.40 (m, 2H), 7.17–7.15 (m, 2H), 7.07 (t, J = 7.4 Hz, 1H), 7.06 (t, J = 7.3 Hz, 1H), 6.99–6.96 (m, 2H), 3.85–3.82 (m, 4H), 3.45–3.31 (m, 4H), 2.80–2.71 (m, 2H), 2.64–2.54 (m, 2H), 2.18–2.00 (m, 4H), 1.48–1.43 (m, 4H), 1.08–1.05 (m, 4H);

^{13}C NMR ($CDCl_3$, 75 MHz) δ 192.32, 191.70 (191.68), 155.83, 151.74 (151.69), 147.26 (147.23), 143.41, 133.36, 131.43, 130.75, 130.32, 129.82 (129.78), 124.42, 120.69, 111.94, 68.00 (67.96), 33.10, 31.27, 28.75, 25.41 (25.36), 24.91 (24.88); APCI-(+)-MS *m/z* (%) 617 (11), 616 (43), 615 ($[M + H]^+$, 100). HRMS [(EI-(+)] calcd for $C_{40}H_{38}O_6$ 614.2668, found 614.2670.

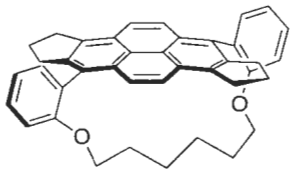
1,6-Bis(2-(5,7-divinyl-2,3-dihydro-1*H*-inden-4-yl)phenoxy)hexane (13)



To PPh_3MeBr (1.00 g, 2.80 mmol) in THF (6 mL) was added *t*-BuOK (0.38 g, 3.39 mmol) in three portions and the resulting mixture was stirred at room temperature over a period of 2 h. The reaction mixture was then cooled to – 78 °C, a solution of **12** (0.30 g, 0.72 mmol) in THF(20 mL, boiling was required for complete dissolution of **12**) was added drop wise for a period of 15 min and the mixture was stirred at this temperature for 1 h. The reaction mixture was warmed to room temperature and quenching with water (5 mL). Organic layer was separated and the aqueous layer was washed with ethyl acetate (2 × 10 mL). The combined organic layers were dried over Na_2SO_4, gravity filtered and the solvent was removed under reduced pressure. The residue was subjected to column chromatography (5-10 % ethyl acetate / hexanes) to obtain **13** (0.25 g, 84%) as an off-white solid. R_f = 0.60 (10% ethyl acetate / hexanes); mp 107-110 °C; IR (neat) ν 2930

(w), 2364 (w), 1588 (w), 1448 (m), 1230 (s), 1036 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.60 (s, 1H), 7.33–7.27 (m, 1H), 7.05 (dd, J = 7.4, 1.9 Hz, 1H), 6.99 (d, J = 7.3 Hz, 1H), 6.97–6.91 (m, 1H), 6.81 (dd, J = 17.7, 11.0 Hz, 1H), 6.43 (dd, J = 17.6, 11.0 Hz, 1H), 5.73 (d, J = 17.5, 1H), 5.58 (d, J = 17.5 Hz, 1H), 5.29 (d, J = 11.2 Hz, 1H), 4.99 (d, J = 11.0 Hz, 1H), 3.79 (t, J = 6.4 Hz, 2H), 2.97 (t, J = 8.1 Hz, 2H), 2.56 (t, J = 7.4 Hz, 2H), 2.02–1.92 (m, 2H), 1.48–1.44 (m, 2H), 1.12–1.07 (m, 2H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 156.14, 144.37, 141.23, 135.84, 135.21, 134.74, 133.67, 132.38, 131.31, 128.74, 128.47, 120.33, 119.61, 114.49, 113.05, 112.41, 68.19, 32.32, 31.97, 28.94, 25.47, 24.71; APCI-(+)-MS *m/z* (%) 609 (13), 608 (49), 607 ($[M+1]^+$, 100), 605 (4); HRMS [(EI-(+)] calcd for $C_{44}H_{46}O_2$ 606.3498, found 606.3491.

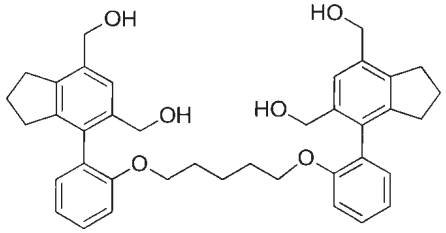
Pyrenophane 16



To a 0 °C suspension of Zn (<10 micron, 1.06 g, 17.1 mmol) in THF (35 mL) was added $TiCl_4$ (1.0 M in CH_2Cl_2, 13.0 mL, 13 mmol) over a period of 15 min and the resulting mixture was heated at 70 °C for 1 h. Pyridine (0.13 mL, 1.67 mmol) was added to the hot reaction mixture and heating was continued for 15 min. A solution of tetraaldehyde **12** (0.50 g, 0.81 mmol) in THF (30 mL, boiling was required for complete dissolution of **12**) was added over a period of 30 min and heating was continued for 24 h. The reaction mixture was cooled to room temperature and 10% aqueous NaOH solution (20 mL) was

added. The precipitate that formed was removed by vacuum filtered through a plug of Celite®, which was then washed with $CHCl_3$ (3 × 35 mL). The filtrate was washed with H_2O (2 × 50 mL), dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was subjected to column chromatography using neutral Al_2O_3 (5–10% ethyl acetate / hexanes) and the product was triturated with diethyl ether (2 × 1 mL) to give pyrenophane **16** (53 mg, 12 %) as an off-white solid. R_f = 0.50 (10% ethyl acetate / hexanes); mp 185-188 °C; ^{1}H NMR (CD_2Cl_2, 500 MHz) δ 7.89 (d, J = 9.2 Hz, 1H), 7.73 (d, J = 6.8 Hz, 1H), 7.69 (d, J = 9.2 Hz, 1H), 7.42 (t, J = 8.3 Hz, 1H), 7.26 (t, J = 7.4 Hz, 1H), 6.98 (d, J = 8.0 Hz, 1H), 3.55 (t, J = 7.4 Hz, 2H), 3.32-3.26 (m, 2H), 3.20-3.16 (m, 1H), 2.85-2.79 (m, 1H), 2.35-2.24 (m, 2H), 0.38-0.33 (m, 1H), 0.17-0.11 (m, 1H), −0.35 - –0.43 (m, 1H), −0.47 - –0.55 (m, 1H); ^{13}C NMR (CD_2Cl_2, 75 MHz) δ 158.48, 141.83, 138.73, 130.91, 129.87, 129.39, 126.21, 125.10, 123.18, 122.09, 116.96, 70.96, 33.71, 32.40, 30.66, 26.03, 25.62; APCI-(+)-MS *m/z* (%) 551 (10), 550 (43), 549 ($[M + H]^+$, 100), 547 (4); HRMS [(EI-(+)] calcd for $C_{40}H_{36}O_2$ 548.2715, found 548.2718.

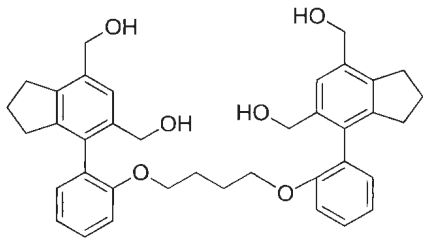
1,6-Bis(2-(2,3-dihydro-5,7-bis(hydroxymethyl)-1*H*-inden-4-yl)phenoxy)pentane (17)



To a suspension of triol **7** (1.00 g, 3.7 mmol) and K_2CO_3 (1.53 g, 11.1 mmol) in DMF (15 mL) was added 1,5-dibromopentane (0.47 g, 2.1 mmol). The resulting mixture was

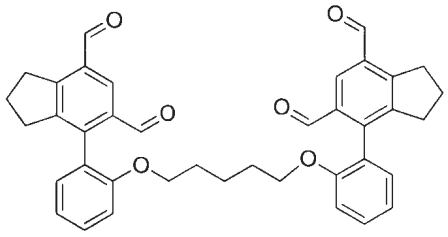
stirred vigorously at 90 °C for 16 h and then cooled to room temperature. Water (30 mL) was added and the resulting mixture was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with water (50 mL), dried over Na_2SO_4, gravity filtered and the solvent was removed under reduced pressure. The residue was subjected to column chromatography (5% MeOH / $CHCl_3$) to obtain tetraol **17** (0.86 g, 76%) as a colorless solid. R_f = 0.30 (ethyl acetate); mp 63-65 °C; IR (neat) ν = 3450-3100 (br, w), 2926 (w), 2861 (w), 2364 (w), 1444 (m), 1229 (s), 1017 (s) cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ 7.37 (s, 1H), 7.33–7.29 (m, 1H), 7.03–7.01 (m, 2H), 6.98–6.95 (m, 1H), 5.06 (t, J = 5.4 Hz, 1H), 4.85–4.82 (m, 1H), 4.49 (d, J = 5.4 Hz, 2H), 4.17 (dd, J = 13.4, 5.4 Hz, 1H), 4.13 (dd, J = 13.4, 5.2 Hz, 1H), 3.83–3.71 (m, 2H), 2.82 (t, J = 7.5 Hz, 2H), 2.48–2.36 (m, 2H), 1.93–1.83 (m, 2H), 1.44–1.37 (m, 2H), 1.13–1.09 (m, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 155.47, 142.24, 138.68, 137.88, 136.00, 131.09, 130.52, 128.53, 127.97, 123.20, 120.29, 112.40, 67.50 (67.46), 61.44, 60.79, 31.64, 30.26, 27.87 (27.84), 24.38, 21.71 (21.65); ESI-(+)-MS *m/z* (%) 633 (10), 632 (41), 631 ($[M + Na]^+$, 100), 218 (4); MALDI-TOF MS cald for $C_{39}H_{44}O_6Na$ 631.3036, found 631.3021.

1,6-Bis(2-(2,3-dihydro-5,7-bis(hydroxymethyl)-1*H*-inden-4-yl)phenoxy)butane (18)



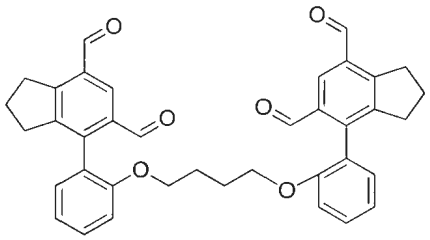
To a suspension of triol **7** (1.00 g, 3.70 mmol) and K_2CO_3 (1.53 g, 11.1 mmol) in DMF (15 mL) was added 1,4-dibromobutane (0.44 g, 2.0 mmol). The resulting mixture was stirred vigorously at 90 °C for 16 h and then cooled to room temperature. Water (30 mL) was added and the resulting mixture was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with water (50 mL), dried over Na_2SO_4, gravity filtered and the solvent was removed under reduced pressure. The residue was subjected to column chromatography (5% MeOH / $CHCl_3$) to obtain tetraol **18** (0.88 g, 80%) as a colorless solid. IR (neat) v = 3450-3100 (br m), 2947 (w), 2871 (w), 2835 (w), 2364 (w), 2328 (w), 1445 (m), 1229 (s), 1015 (s) cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ 7.37 (s, 1H), 7.30–7.27 (m, 2H), 7.00 (dd, J = 7.4, 1.9 Hz, 1H), 6.98–6.94 (m, 2H), 5.05 (t, J = 5.5 Hz, 1H), 4.82 (t, J = 5.3 Hz, 1H), 4.48 (d, J = 5.4 Hz, 1H), 4.15 (dd, J = 13.3, 5.3 Hz, 1H), 4.11 (dd, J = 13.3, 5.2 Hz, 1H), 3.80–3.77 (m, 2H), 2.83–2.72 (m, 2H), 2.45–2.35 (m, 2H), 1.90–1.80 (m, 2H), 1.46–1.43 (m, 2H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 155.25, 142.11 (142.08), 138.60, 137.68, 135.88, 130.95, 130.40, 128.37, 127.78, 123.14, 120.14, 112.21, 67.10 (67.05), 61.31, 60.67, 31.52, 30.11, 24.96, 24.41; ESI-(+)-MS *m/z* (%) 619 (9), 618 (41), 617 ($[M + Na]^+$, 100), 218 (4); MALDI-TOF MS cald for $C_{38}H_{42}O_6Na$ 617.2879, found 617.2877.

1,6-Bis(2-(5,7-diformyl-2,3-dihydro-1*H*-inden-4-yl)phenoxy)pentane (19)



To a solution of tetraol **17** (0.86 g, 1.40 mmol) in CH_2Cl_2 (45 mL) was added Celite® (2.56 g) in one portion. To this suspension was added PCC (3.62 g, 16.8 mmol) in several portions and the resulting mixture was stirred at room temperature for 3 h. The reaction mixture was vacuum filtered through a plug of Celite® and the cake was washed thoroughly with $CHCl_3$ (3 × 50 mL). The filtrate was removed under reduced pressure and the residue was subjected to column chromatography (30% ethyl acetate / hexanes) to afford tetraaldehyde **19** (0.61 g, 73%, *ca.* 1.3:1 mixture of diastereomers by ^{1}H NMR analysis) as a colorless solid. R_f = 0.40 (30% ethyl acetate / hexanes); mp 146-149 °C; IR (neat) ν 2957 (w), 2871 (w), 2364 (w), 1690 (s), 1589 (m), 1239 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 10.19 (s, 1H), 10.19 (s, 1H), 9.71 (s, 1H), 9.69 (s, 1H), 8.28 (s, 2H), 7.42 (t, J = 8.1 Hz, 2H), 7.17 (dd, J = 7.4, 1.8 Hz, 2H), 7.08–7.05 (m, 2H), 6.95 (t, J = 7.4 Hz, 2H), 3.85–3.74 (m, 4H), 3.46–3.33 (m, 4H), 2.81–2.73 (m, 2H), 2.63–2.54 (m, 2H), 2.17–1.98 (m, 4H), 1.48–1.42 (m, 4H), 1.12–1.08 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 192.28, 191.68, 155.68, 151.77 (151.69), 147.22 (147.15), 143.31 (143.29), 133.26, 131.35, 130.69, 130.31, 129.77 (129.69), 124.28, 120.70, 111.87 (111.84), 67.87 (67.84), 33.05, 31.22, 28.23, 24.87 (24.84), 22.18; APCI-(+)-MS *m/z* (%) 603 (11), 602 (42), 601 ([M+1]$^+$, 100); HRMS [(EI-(+)] calcd for $C_{39}H_{36}O_6$ 600.2512, found 600.2513.

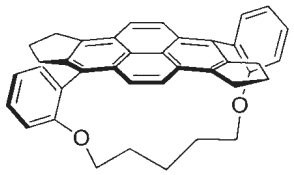
1,6-Bis(2-(5,7-diformyl-2,3-dihydro-1*H*-inden-4-yl)phenoxy)butane (20)



To a solution of tetraol **18** (0.90 g, 1.5 mmol) in CH_2Cl_2 (45 mL) was added Celite® (2.70 g) in one portion. To this suspension was added PCC (3.92 g, 18.2 mmol) in several portions and the resulting mixture was stirred at room temperature for 3 h. The reaction mixture was vacuum filtered through a plug of Celite® and the cake was washed thoroughly with $CHCl_3$ (3 × 50 mL). The filtrate was removed under reduced pressure and the residue was subjected to column chromatography (30% ethyl acetate / hexanes) to afford tetraaldehyde **20** (0.70 g, 78%, *ca.* 1.3:1 mixture of diastereomers by ^{1}H NMR analysis) as a colorless solid. R_f = 0.30 (30% ethyl acetate / hexanes); mp 191-193 °C; IR (neat) v 2949 (w), 2842 (w), 2712 (w), 2364 (w), 1691 (s), 1590 (m), 1241 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 10.19 (s, 1H), 10.18 (s, 1H), 9.69 (s, 1H), 9.65 (s, 1H), 8.27 (s, 1H), 8.25 (s, 1H), 7.41–7.36 (s, 2H), 7.16 (dd, J = 7.5, 1.8 Hz, 2H), 7.06 (td, J = 7.4, 1.0 Hz, 1H), 6.88–6.84 (m, 2H), 3.81–3.74 (m, 4H), 3.43–3.29 (m, 4H), 2.79–2.71 (m, 2H), 2.62–2.52 (m, 2H), 2.19–1.95 (m, 4H), 1.48–1.45 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 192.28 (192.25), 191.63 (191.61), 155.51, 151.83 (151.73), 147.18 (147.10), 143.19 (143.18), 133.22 (133.18), 131.34, 130.69, 130.30, (130.28), 129.83 (129.68), 124.24 (124.20), 120.76, 111.69 (111.68), 67.63 (67.53), 33.02, 31.21 (31.18), 25.53

(25.44), 24.86 (24.81); APCI-(+)-MS *m/z* (%) 589 (10), 588 (44), 587 ($[M+1]^+$, 100), 569 (6); HRMS [(EI-(+)] calcd for $C_{38}H_{34}O_6$ 586.2355, found 586.2350.

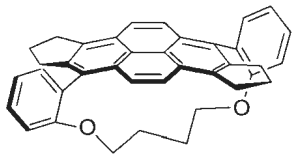
Pyrenophane 21



To a 0 °C suspension of Zn (<10 micron, 1.09 g, 17.1 mmol) in THF (35 mL) was added $TiCl_4$ (1.0 M in CH_2Cl_2, 13.3 mL, 13.3 mmol) over a period of 15 min and the resulting mixture was heated at 70 °C for 1 h. Pyridine (0.13 mL, 1.67 mmol) was added to the hot reaction mixture and heating was continued for 15 min. A solution of tetraaldehyde **19** (0.50 g, 0.81 mmol) in THF (30 mL, boiling was required for complete dissolution of **19**) was added over a period of 30 min and heating was continued for 24 h. The reaction mixture was cooled to room temperature and 10% aqueous NaOH solution (20 mL) was added. The precipitate that formed was removed by vacuum filtered through a plug of Celite®, which was then washed with $CHCl_3$ (3 × 35 mL). The filtrate was washed with H_2O (2 × 50 mL), dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was subjected to column chromatography using neutral Al_2O_3 (5–10% ethyl acetate / hexanes) and the product was triturated with diethyl ether (2 × 1 mL) to give pyrenophane **21** (49 mg, 11 %) as an off-white solid. R_f = 0.40 (10% ethyl acetate / hexanes); mp 206-209 °C; ^{1}H NMR (CD_2Cl_2, 500 MHz) δ 7.89 (d, J = 9.0, 1H), 7.84 (d, J = 7.2 Hz, 1H), 7.64 (d, J = 9.4 Hz, 1H), 7.40 (t, J = 7.1 Hz, 1H), 7.33 (t, J = 7.4 Hz,

1H), 6.99 (d, J = 8.0 Hz, 1H), 3.55 (t, J = 7.8 Hz, 1H), 3.42-3.36 (m, 1H), 2.87-2.85 (m, 1H), 2.78-2.72 (m, 1H), 2.78-2.72 (m, 1H), 2.40-2.38 (m, 1H), 2.34-2.27 (m, 2H), 0.59-0.50 (m, 1H), 0.24-0.15 (m, 1H), −1.20 - −1.27 (m, 1H); ^{13}C NMR (CD_2Cl_2, 75 MHz) δ 158.91, 141.95, 138.91, 133.15, 130.67, 130.25, 129.54, 129.51, 126.70, 126.40, 125.46, 123.28, 123.16, 120.32, 72.03, 33.44, 32.30, 31.33, 25.62, 22.45; APCI-(+)-MS *m/z* (%) 537 (10), 536 (44), 535 ($[M+1]^+$, 100), 533 (3); HRMS [(EI-(+)] calcd for $C_{39}H_{34}O_2$ 534.2559, found 534.2558.

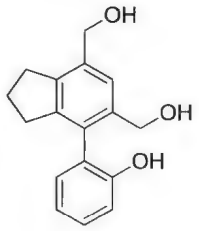
Pyrenophane 22



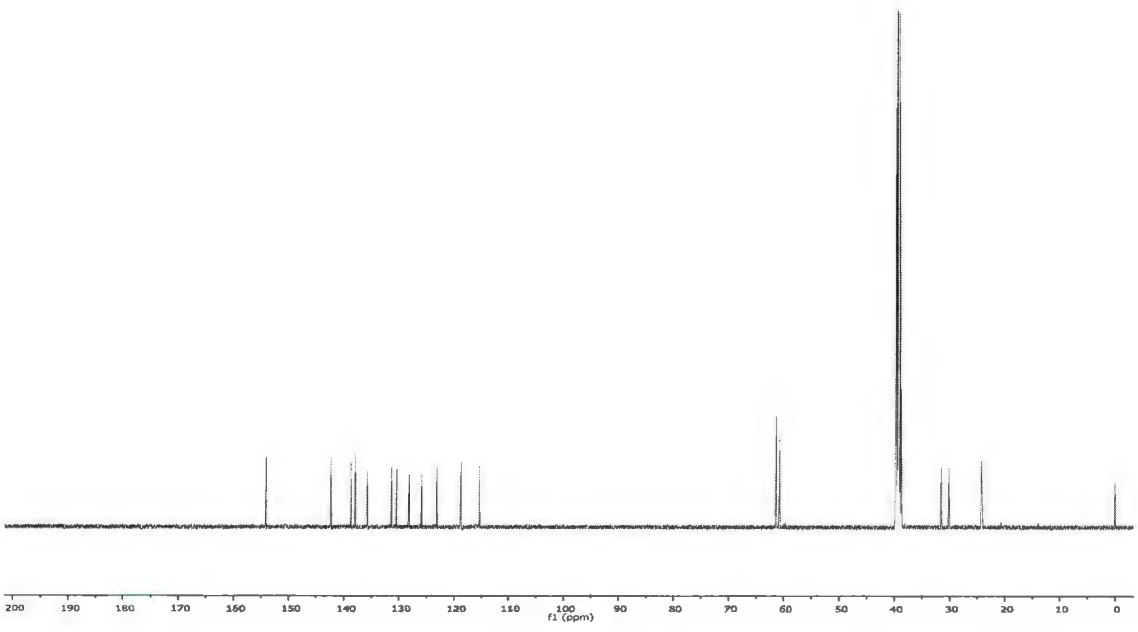
To a 0 °C suspension of Zn (<10 micron, 1.12 g, 16.7 mmol) in THF (35 mL) was added $TiCl_4$ (1.0 M in CH_2Cl_2, 13.7 mL, 13.0 mmol) over a period of 15 min and the resulting mixture was heated at 70 °C for 1 h. Pyridine (0.13 mL, 1.67 mmol) was added to the hot reaction mixture and heating was continued for 15 min. A solution of tetraaldehyde **20** (0.50 g, 0.81 mmol) in THF (30 mL, boiling was required for complete dissolution of **20**) was added over a period of 30 min and heating was continued for 24 h. The reaction mixture was cooled to room temperature and 10% aqueous NaOH solution (20 mL) was added. The precipitate that formed was removed by vacuum filtered through a plug of Celite®, which was then washed with $CHCl_3$ (3 × 35 mL). The filtrate was washed with H_2O (2 × 50 mL), dried over Na_2SO_4 and the solvent was removed under reduced

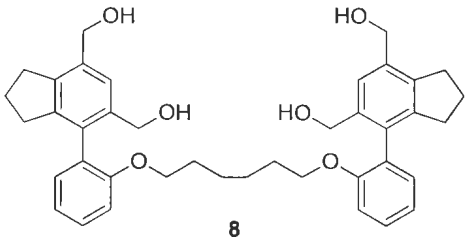
pressure. The residue was subjected to column chromatography using neutral Al_2O_3 (5–10% ethyl acetate / hexanes) and the product was triturated with diethyl ether (2 × 1 mL) to give pyrenophane **22** (26 mg, 6 %) as an off-white solid. R_f = 0.30 (10% ethyl acetate / hexanes); mp 195-198 °C; ^{1}H NMR (CD_2Cl_2, 500 MHz) δ 7.90 (dd, J = 7.3, 1.9 Hz, 1H), 7.86 (d, J = 9.1 Hz, 1H), 7.67 (d, J = 9.1 Hz, 1H), 7.33 (td, J = 7.7, 1.9 Hz, 1H), 7.28 (td, J = 7.4, 1.3 Hz, 1H), 6.81 (dd, J = 7.8, 1.3 Hz, 1H), 3.53-3.50 (m, 2H), 3.43 (ddd, J = 16.0, 8.5, 5.0 Hz, 1H), 2.74-2.70 (m, 1H), 2.66-2.61 (m, 1H), 2.37-2.22 (m, 2H), 1.95-1.92 (m, 1H), −0.19 - −0.28 (m, 1H), − 0.72-0.81 (m, 1H); ^{13}C NMR (CD_2Cl_2, 75 MHz) δ 157.66, 142.42, 139.10, 132.50, 130.90, 130.11, 129.36, 129.31, 126.85, 126.68, 125.96, 122.97, 122.54, 118.58, 70.25, 33.22, 32.22, 25.87, 25.55; APCI-(+)-MS *m/z* (%) 523 (10), 522 (44), 521 ($[M+1]^+$, 100), 519 (3); HRMS [(EI-(+)] calcd for $C_{38}H_{32}O_2$ 520.2402, found 520.2403.

4.6 Selected ^{1}H and ^{13}C NMR spectra for Chapter 4



7

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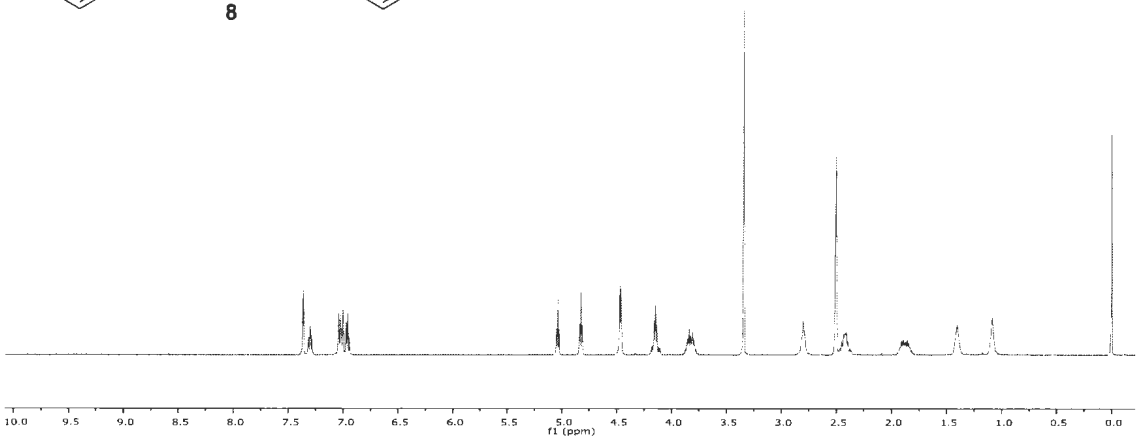
O
O

8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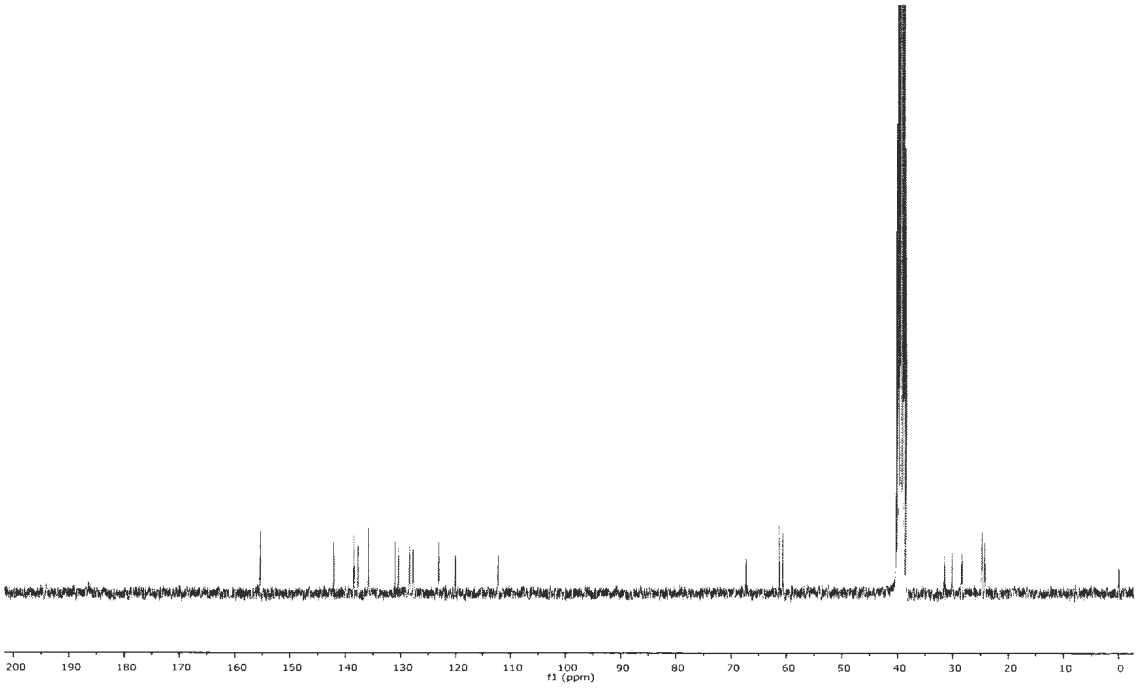
f1 (ppm)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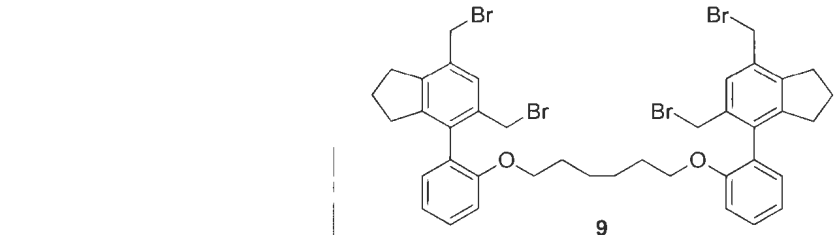
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Br
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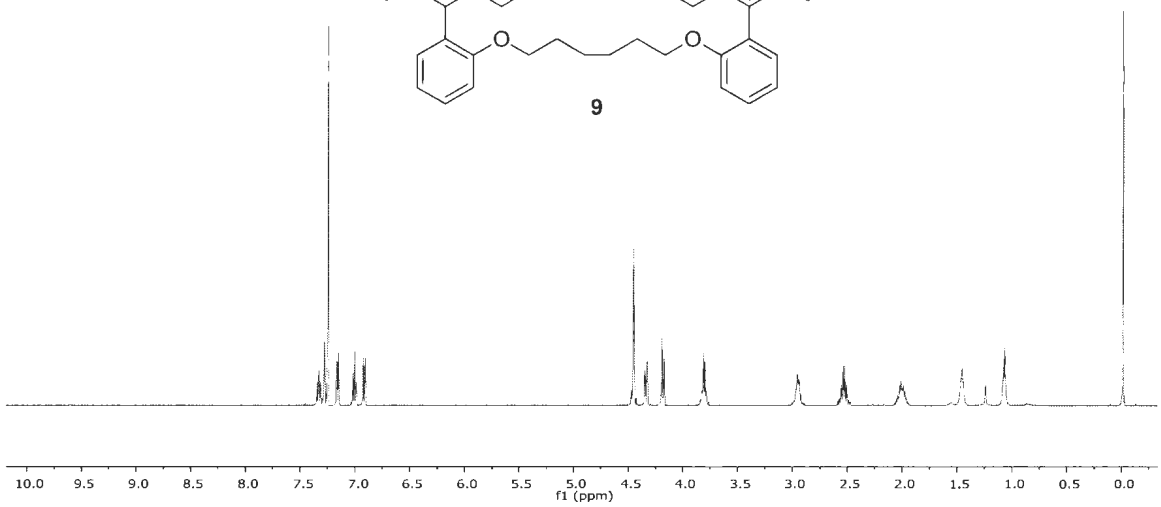
O

9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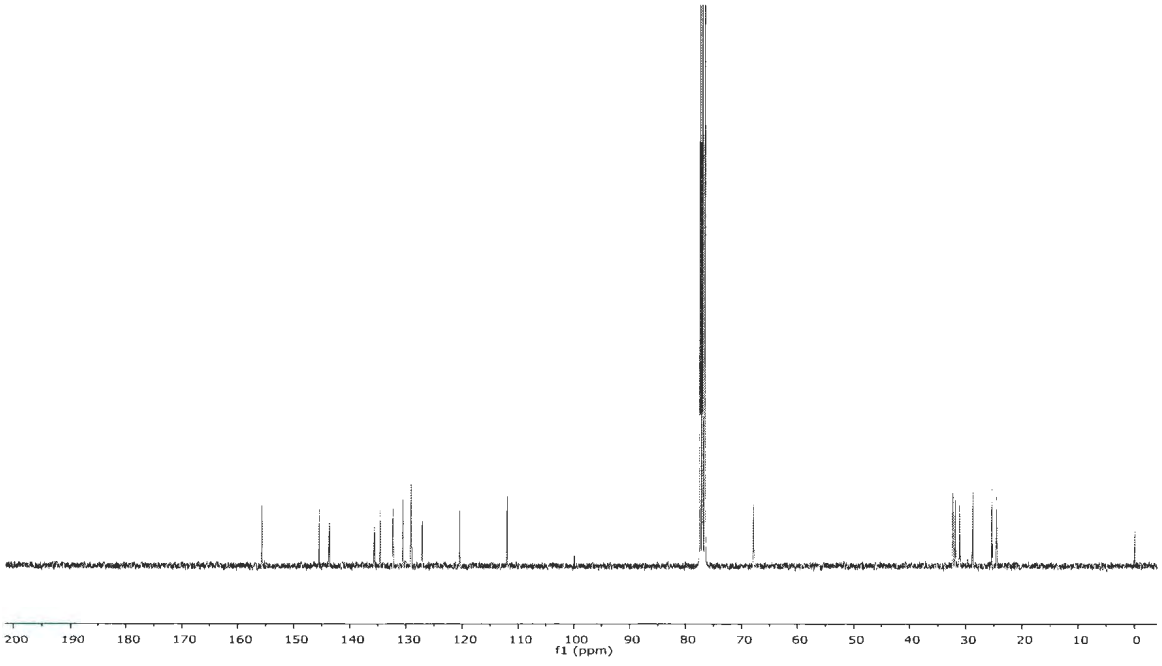
f1 (ppm)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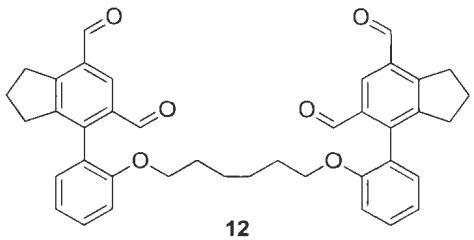
f1 (ppm)



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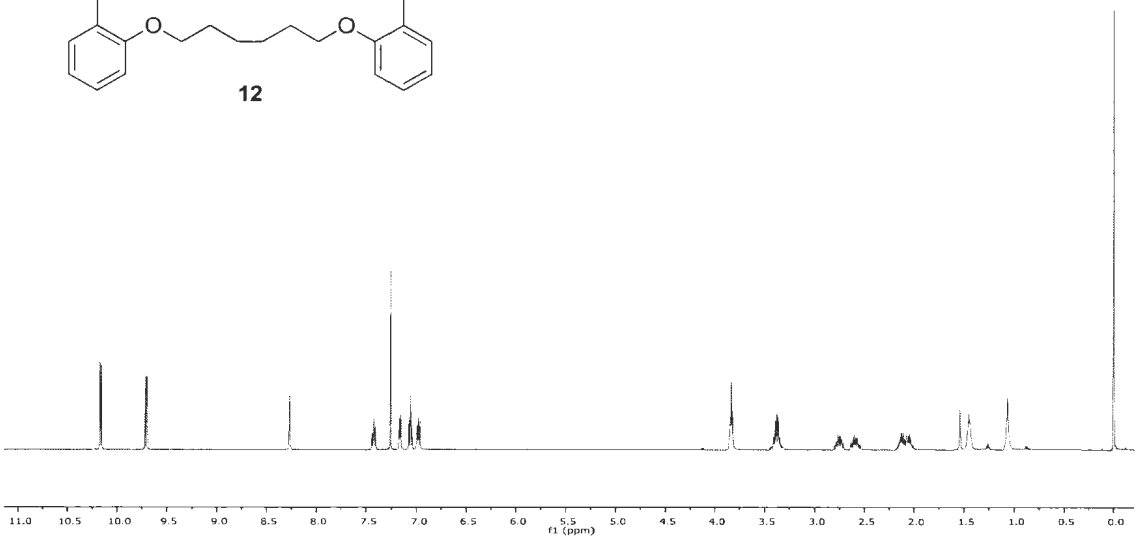
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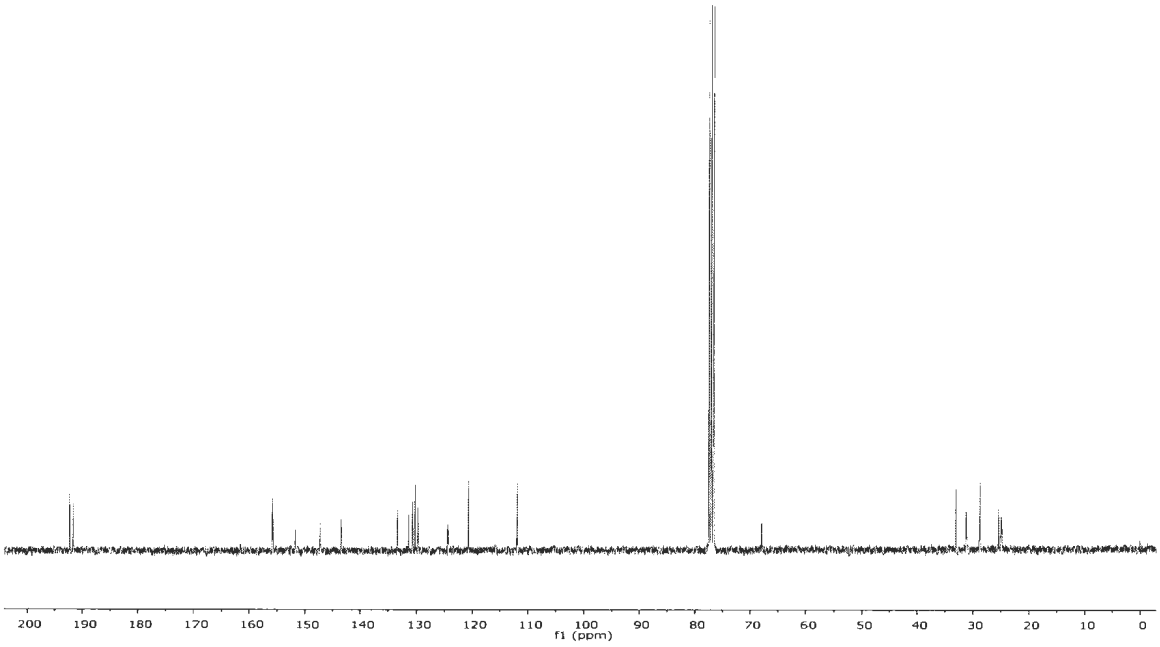
f1 (ppm)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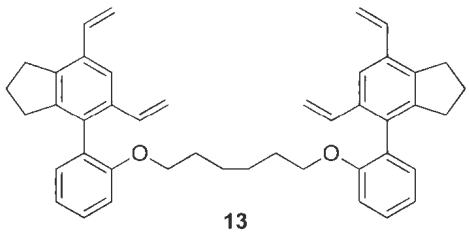

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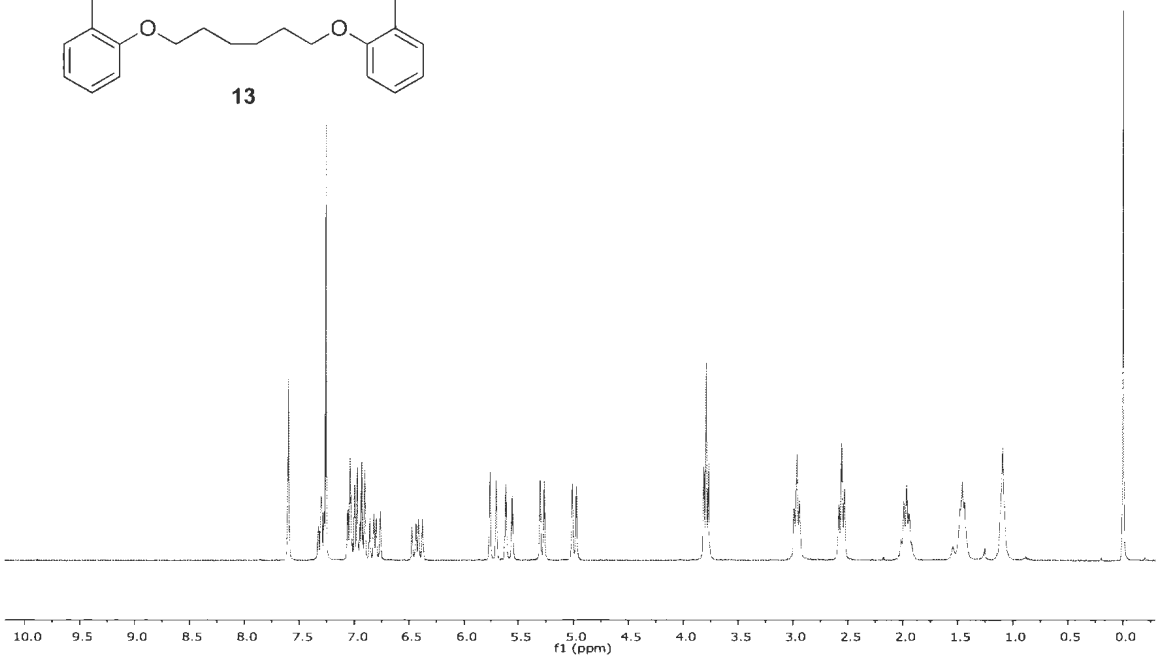
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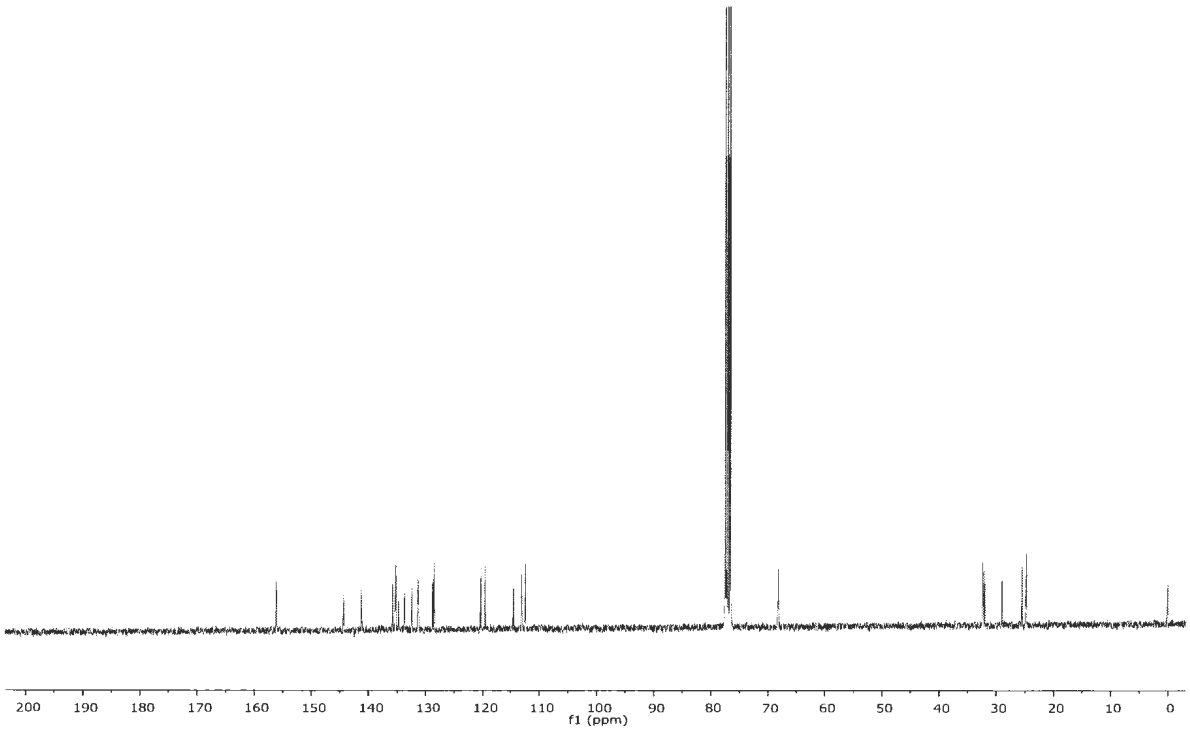
f1 (ppm)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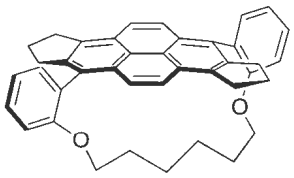
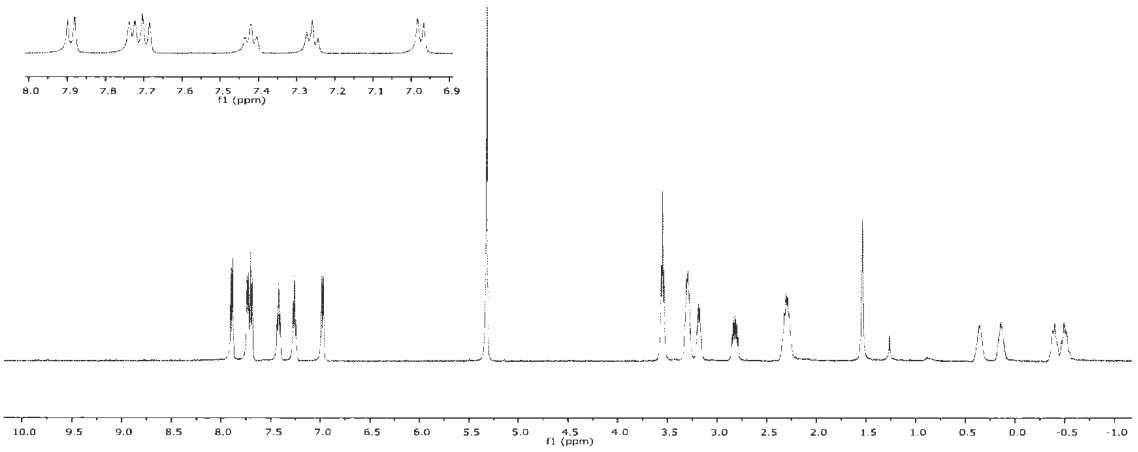
f1 (ppm)



16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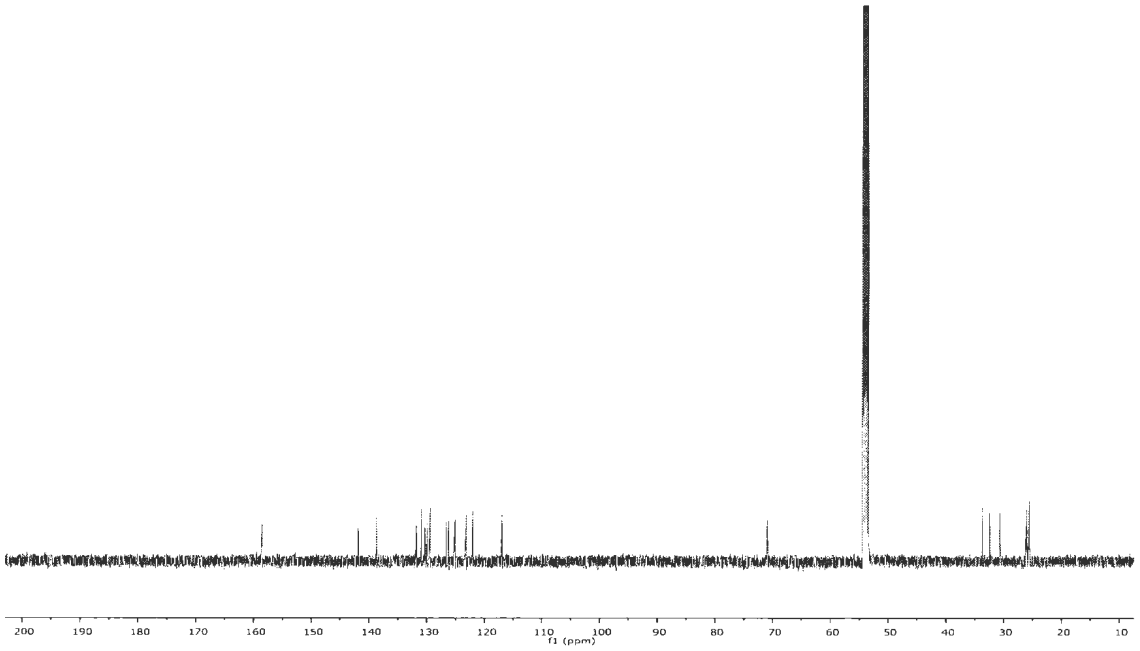
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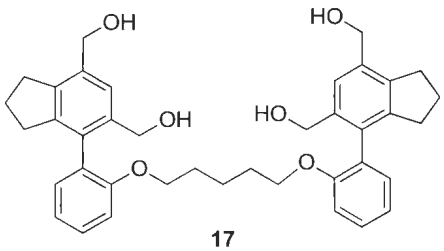
f1 (ppm)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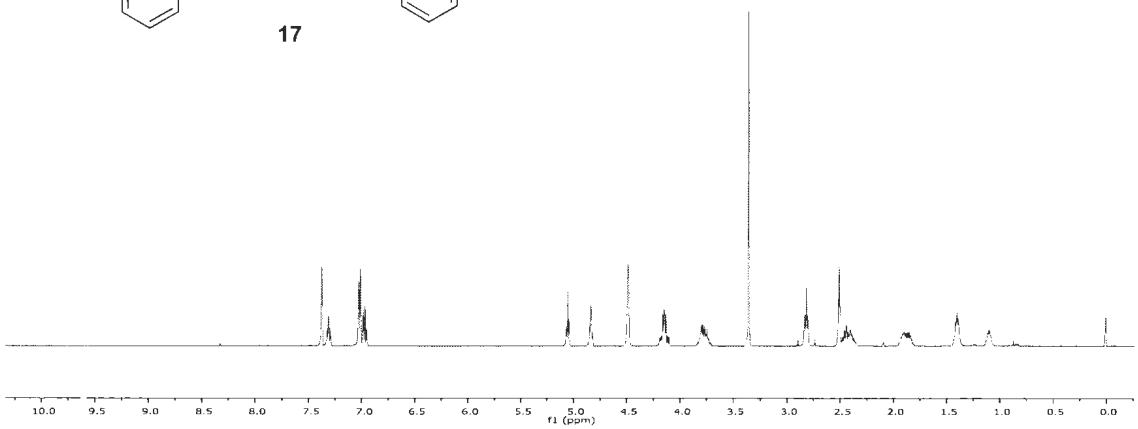
O

17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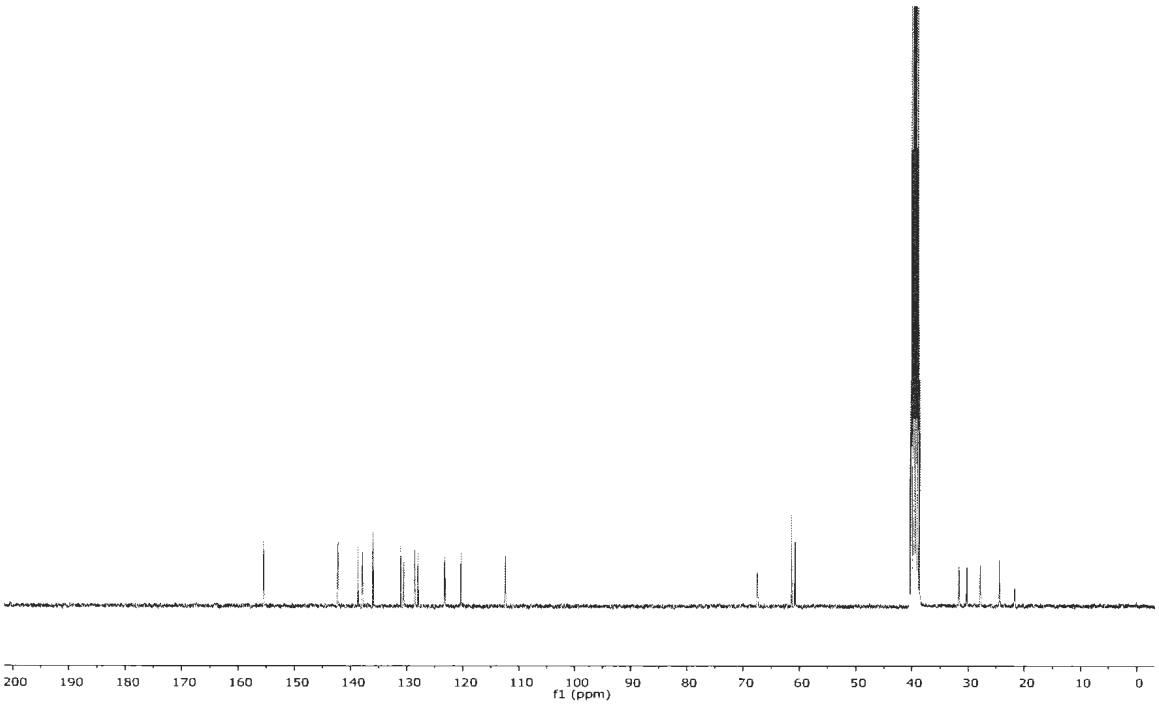
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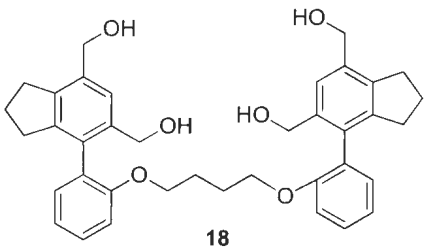
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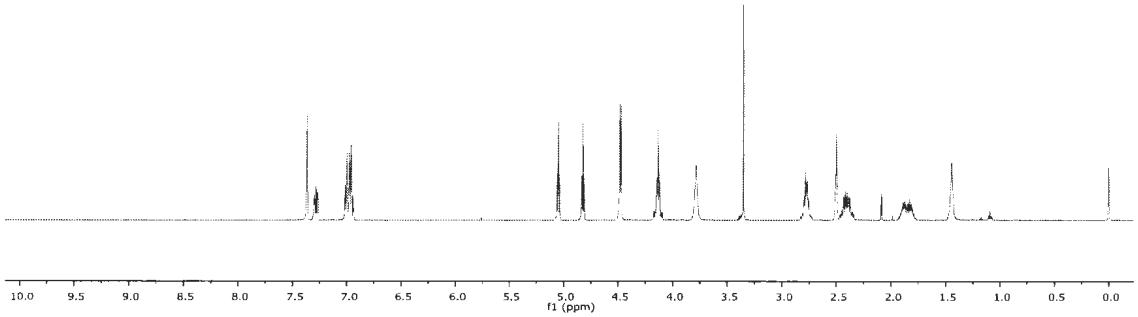
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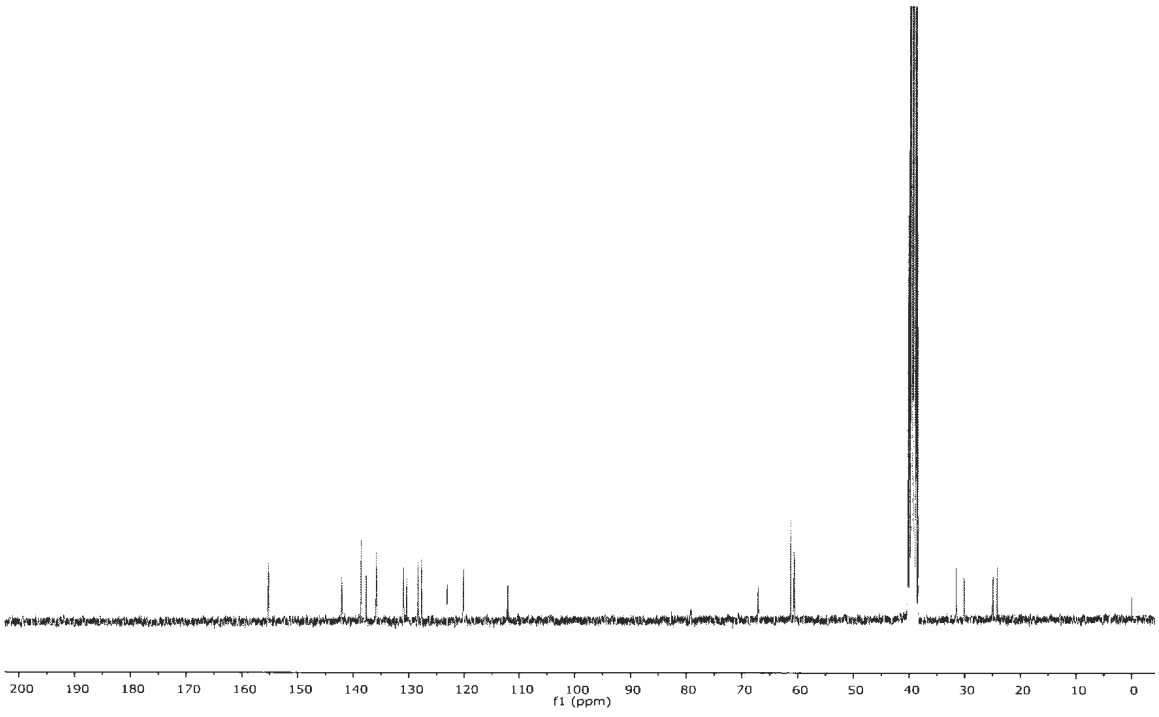
f1 (ppm)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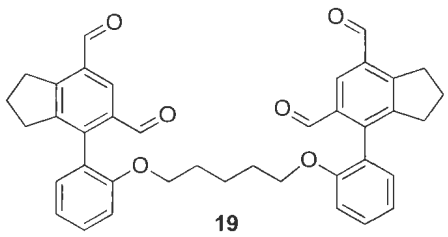

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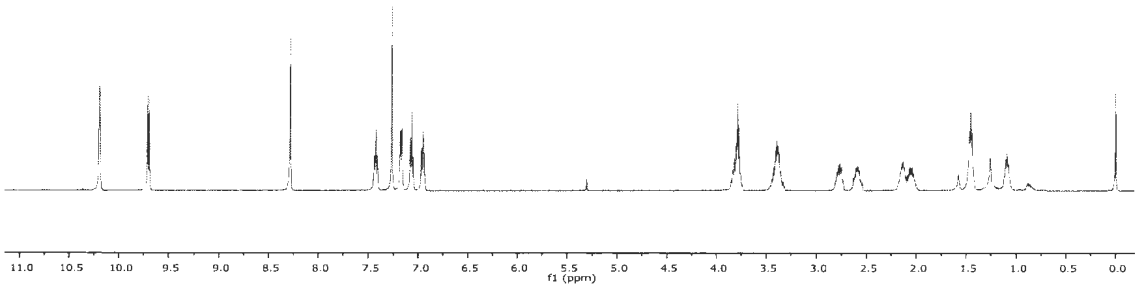
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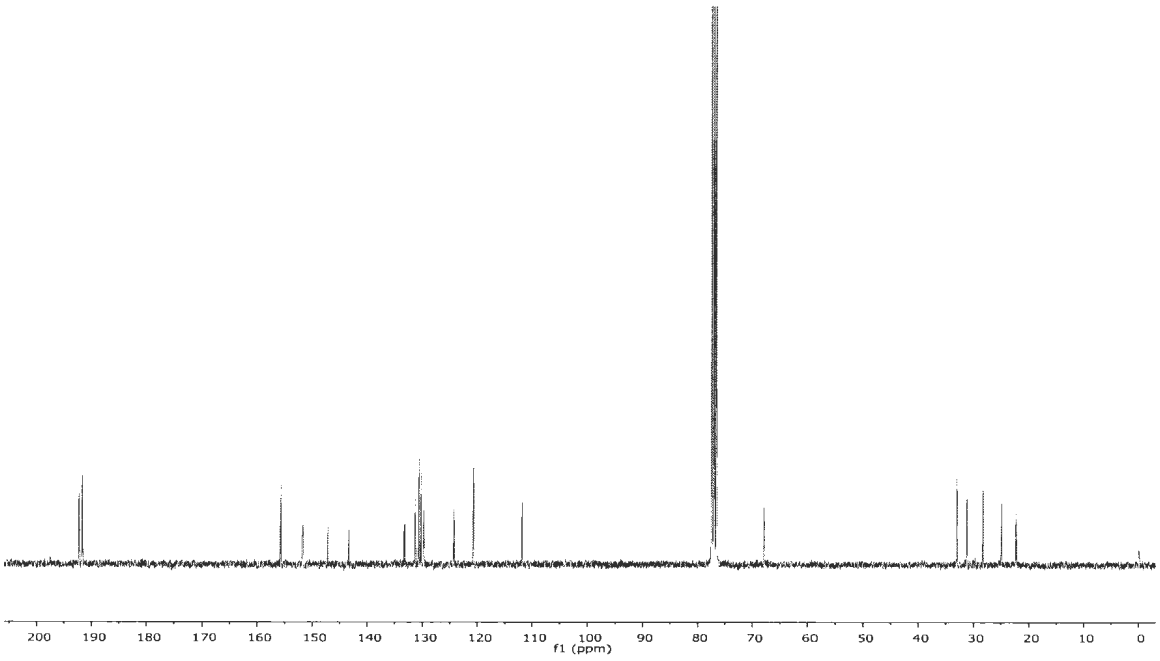
f1 (ppm)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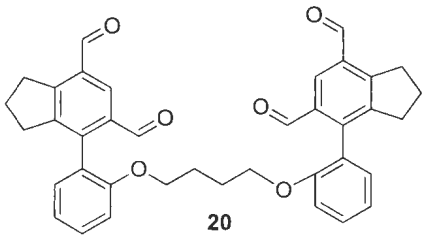
f1 (ppm)



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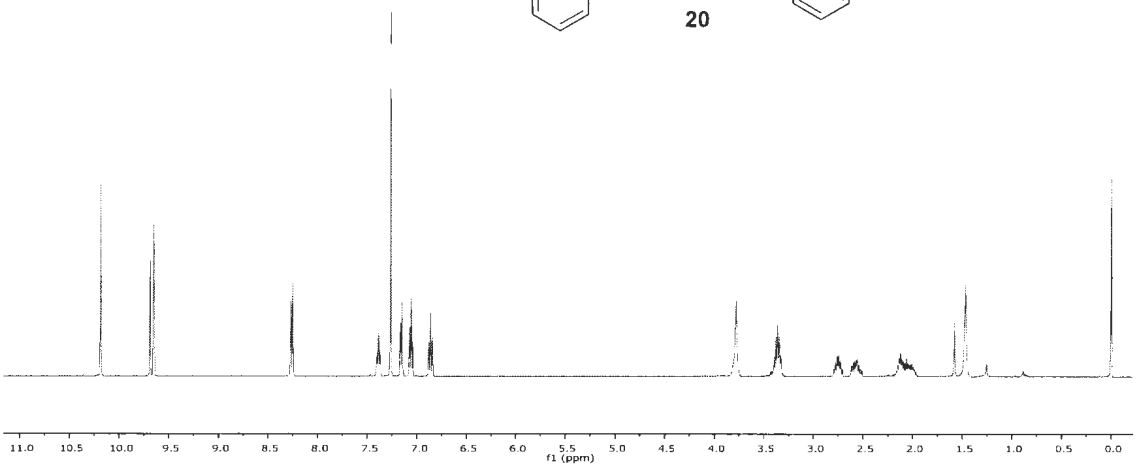
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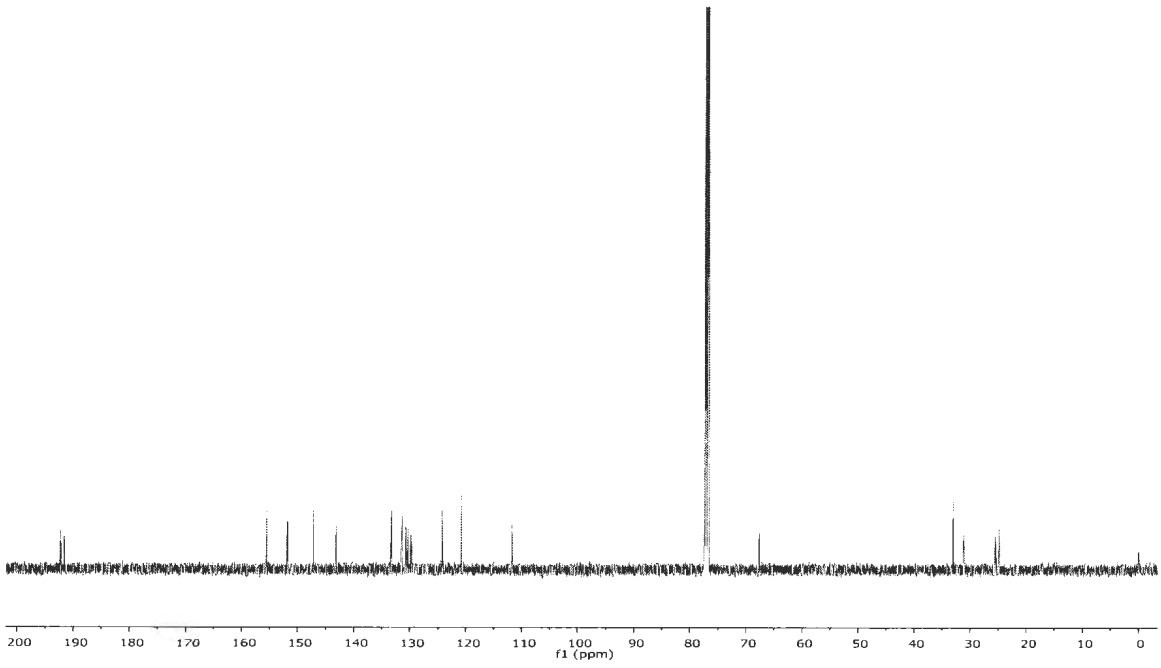
f1 (ppm)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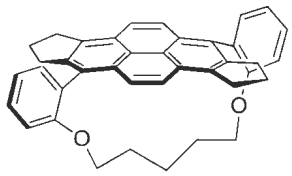
f1 (ppm)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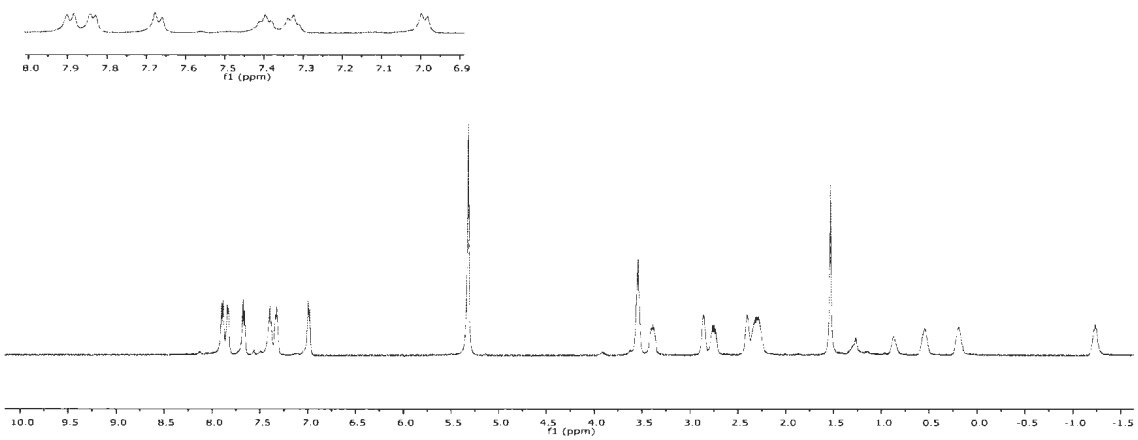
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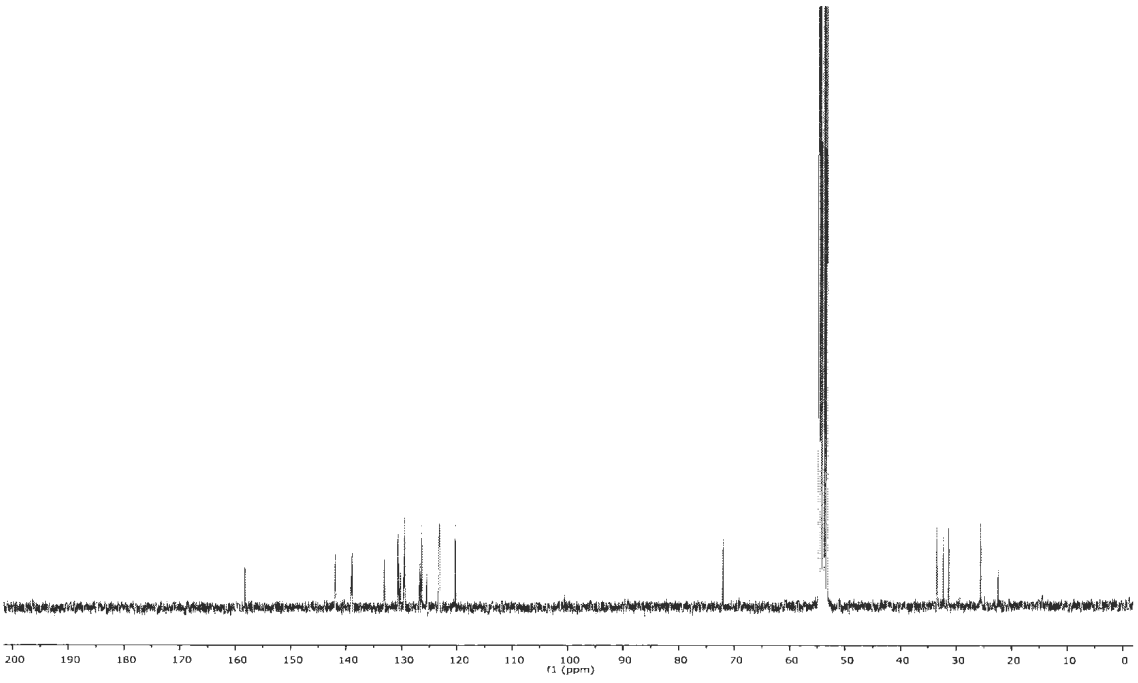
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.5
f1 (ppm)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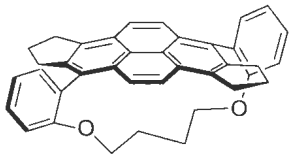
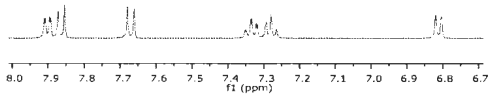


22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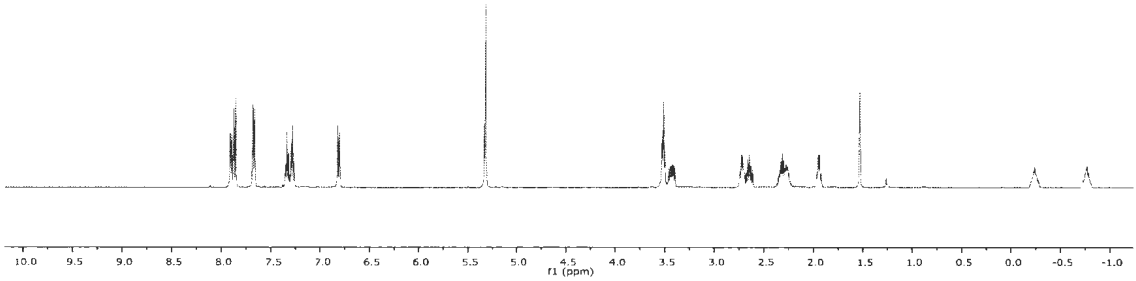
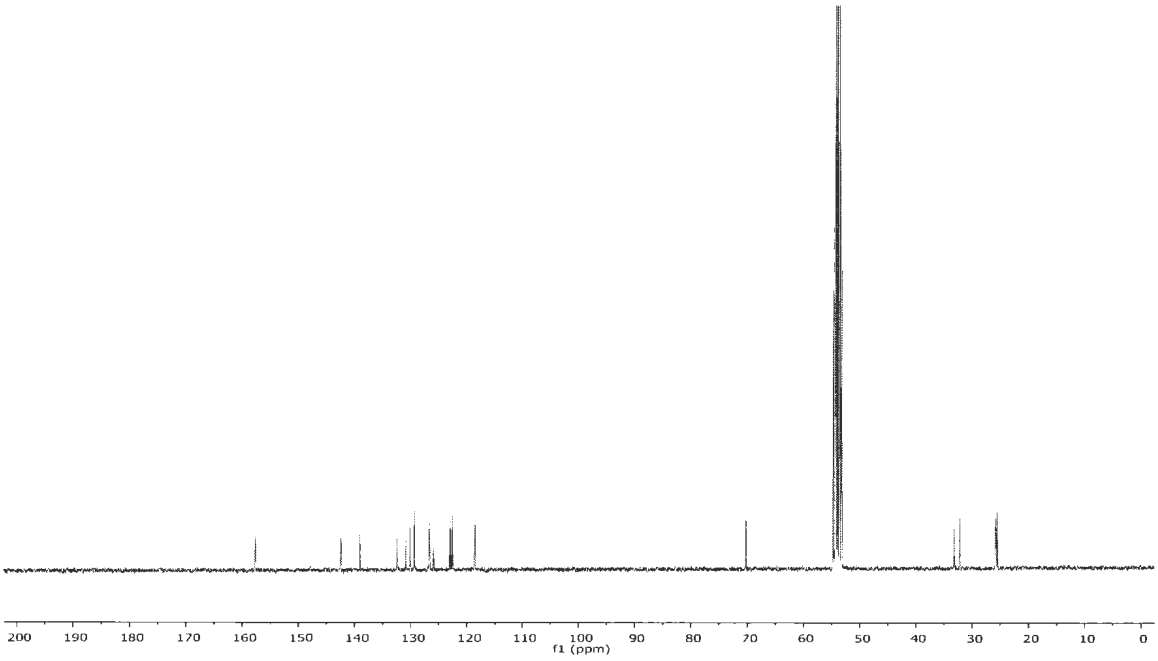
f1 (ppm)


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 -0.5 -1.0
f1 (ppm)


200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

Details of the Resolution of 16

Requestor: Graham Bodwell Sample ID: **16**

Amount received: 20 mg Quote #:

Analysis Summary:

The following SFC separation yielded 9 mg of peak-1 (chemical purity >99%, ee >99%) and 10 mg of peak-2 (chemical purity >99%, ee >99%). Chromatograms are included in this report.

Preparative Method:

OD-H (20 x 2 cm)

40% ethanol(0.1% DEA)/CO_2, 100 bar

100 bar

60 mL/min, 254 nm.

Analytical Method:

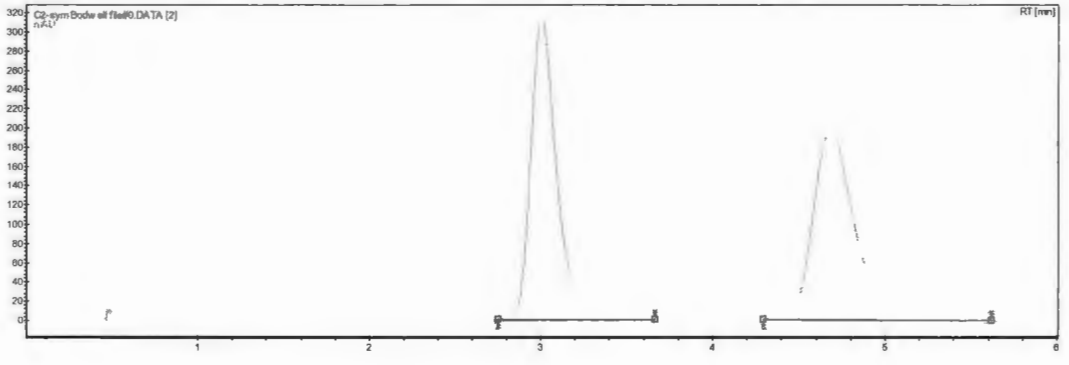
OD-H (15 x 0.46 cm)

40% methanol(0.1% DEA)/CO_2, 100 bar

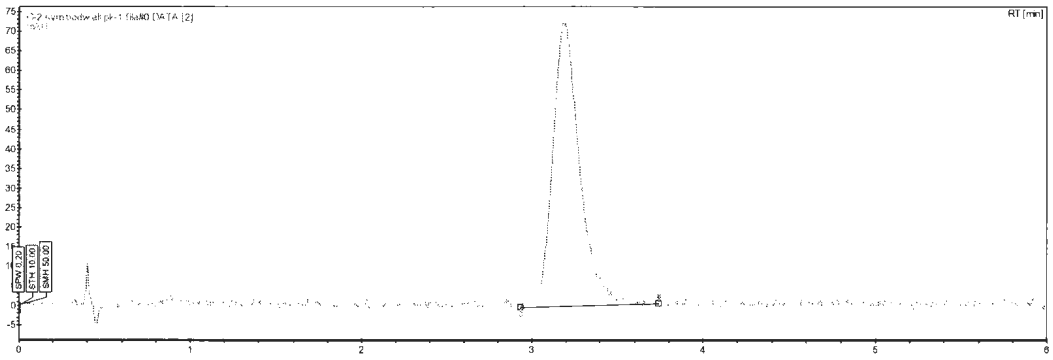
3 mL/min, 220 and 254 nm

inj vol.: 5 mL, 0.75 mg/mL 1:1:1 ethanol:DCM:DMSO

Sample: 16

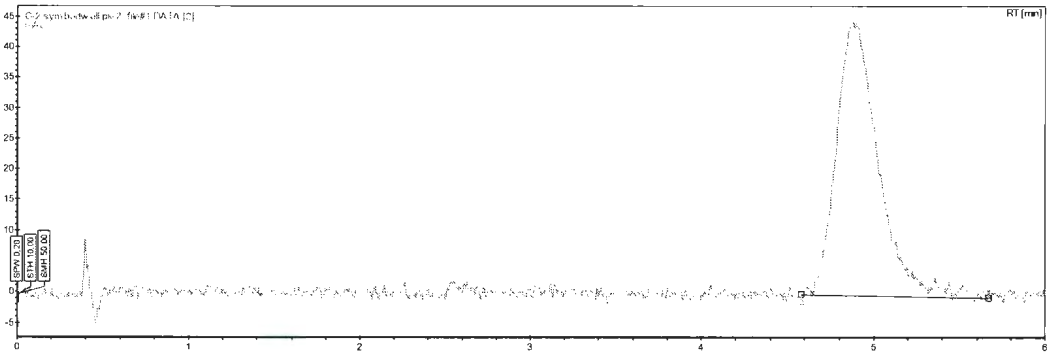


Sample: 16 peak-1



Index	Time (min)	Area (%)
Peak-1	3.19	100.00
Peak-2		
Total		100.00

Sample: 16 peak-2



Index	Time (min)	Area (%)
Peak-1		
Peak-2	4.88	100.00
Total		100.00

4.7 Supplementary crystallographic information for pyrenophanes 16 and 22

Single crystal X-ray diffraction studies. A crystal of **16** and **22** was mounted on a low temperature diffraction loop and measured on a Rigaku Saturn CCD area detector with graphite monochromated Mo-Kα radiation. The structure was solved by direct methods[S1] and expanded using Fourier techniques.[S2] Neutral atom scattering factors were taken from Cromer and Waber.[S3] Anomalous dispersion effects were included in Fcalc;[S4] the values for Δf' and Δf'' were those of Creagh and McAuley.[S5] The values for the mass attenuation coefficients are those of Creagh and Hubbell.[S6] All calculations and visualizations were performed using CrystalStructure[S7,S8] and Mercury[S9] crystallographic software packages, except for refinement, which was performed using SHELXL-97.[S1] Non-hydrogen atoms were refined anisotropically, while hydrogen atoms were introduced in calculated positions and refined on a riding model. Crystallographic details of **16** are summarized in Table 1 and crystallographic details of **22** are presented in Table 5.

Pyrenophane **16** crystallized in the triclinic space group $P\bar{1}$ with Z = 2. Figure 1 shows the asymmetric unit, while the alternate view in Figure 2 highlights the numerous intramolecular (methylene) C–H···π interactions (3.30 – 3.51 Å; Table 2). Note that the longer (methylene)C–H···π interactions are considered insignificant due to the small Donor – Hydrogen ... Acceptor (D – H ··· A) bond angles (these deviate significantly from linearity).[S4-S10] The torsion angle for C8-C26-C18-C16 is 175.1°, while the bend angle between the planes defined by C7-C8-C26 and C17-C18-C16 is 17.4°. The twist in the pyrene system can be assessed based on the torsion angles through the middle of the pyrene system (C6-C7-C26-C27-C28-C16-C17-C29; Table 3); each angle would measure 180° in a planar system, however, here, the five angles range from 160.0 – 174.1°. Further intermolecular π···π interactions (3.47 Å; Figure 3) are present between adjacent molecules in the packed unit cell, as calculated from closest mean plane contacts.

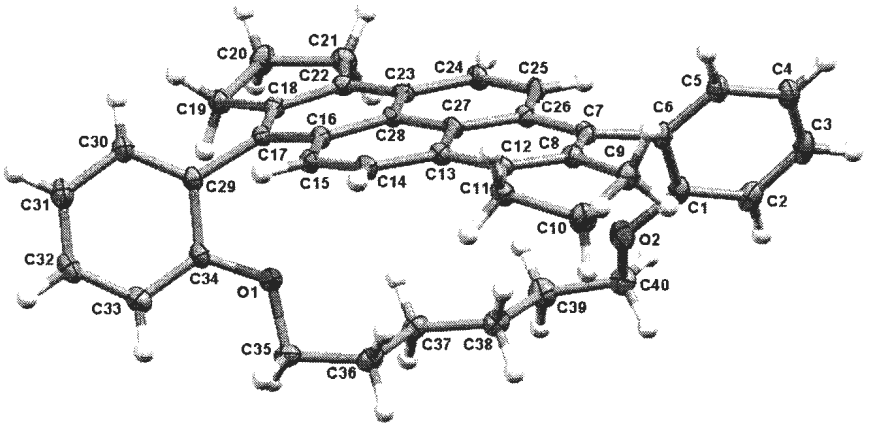


Figure 1: Asymmetric unit for **16** with 30% probability ellipsoids; H-atom labels omitted for clarity.

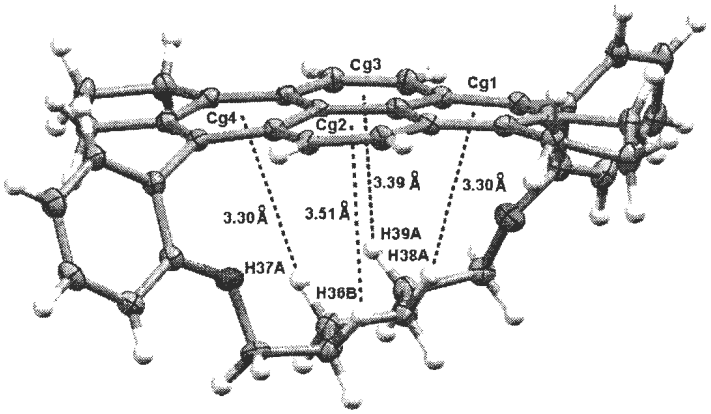


Figure 2: Alternate view of the asymmetric unit of **16**, with (sp^3)C–H to π contacts indicated by dashed lines.

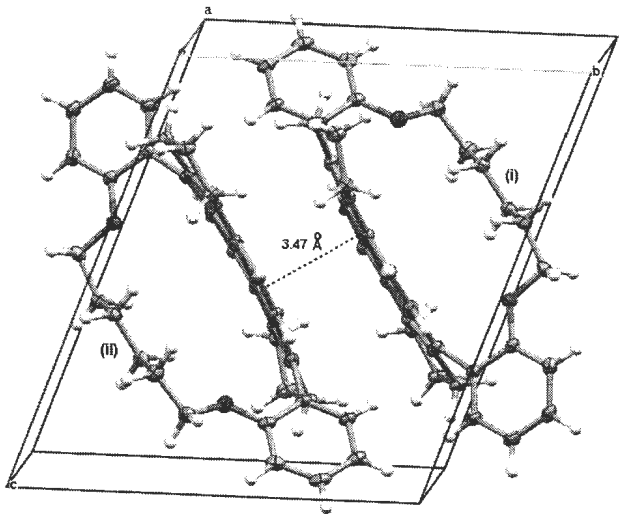


Figure 3: Packed unit cell for **16**. Separation between the planes formed by the atoms C13, C16, C23, C26, C27 and C28, and their symmetry equivalent, inversion related, counterparts generated by the operation (ii) 1-x, 1-y, 1-z indicated by a dashed line.

Table 1 Summary of X-ray Data

Compound reference	**16**
Chemical formula	$C_{40}H_{36}O_2$
Formula Mass	548.69
Crystal system	Triclinic
a/Å	9.395(5)
b/Å	12.771(6)
c/Å	13.799(7)
α/°	104.045(8)
β/°	107.143(4)
γ/°	106.279(6)
Unit cell volume/Å^3	1419.9(12)
Temperature/K	153(2)
Space group	$P\bar{1}$
No. of formula units per unit cell, *Z*	2
Radiation type	MoKα
Absorption coefficient, μ/mm^{-1}	0.077
No. of reflections measured	13837
No. of independent reflections	5859
R_{int}	0.0590
Final R_1 values ($I > 2\sigma(I)$)	0.0884
Final $wR(F^2)$ values (all data)	0.1924
Goodness of fit on F^2	1.150

$R1 = \Sigma \, ||Fo| - |Fc|| \, / \, \Sigma \, |Fo|, \; I > 2\sigma(I)$

$wR2 = [\Sigma \, (w \, (Fo^2 - Fc^2)^2) / \Sigma \, w(Fo^2)^2]^{1/2}$, all data

Table 2: Intramolecular (methylene)C-H…π interactions for **16**

D – H ··· A	**D – H**	**H ··· A**	**D – H ··· A**
C38 – H38A ... Cg1	0.99 Å	3.30 Å	159.8°
C36 – H36B ... Cg2	0.99 Å	3.51 Å	128.1°
C39 – H39A ... Cg3	0.99 Å	3.39 Å	128.5°
C37 – H37A ... Cg4	0.99 Å	3.30 Å	157.6°

For Table 2:

Cg1 is the centroid of C7, C8, C12, C13, C26, C27

Cg2 is the centroid of C13-C15, C27, C28

Cg3 is the centroid of C23-C28

Cg4 is the centroid of C16-C18, C22, C23, C28

Table 3: Torsion angles through the middle of the pyrene system (°)

C6 – C7 – C26 – C27	168.5(2)
C7 – C26 – C27 – C28	–174.1(2)
C26 – C27 – C28 – C16	172.0(2)
C17 – C16 – C28 – C27	–171.5(2)
C28 – C16 – C17 – C29	160.1(2)

Pyrenophane **22** crystallized in the triclinic space group $P\bar{1}$ with Z = 2 (crystallographic details summarized in Table 4). Figure 4 shows the asymmetric unit, while the alternate view in Figure 5 highlights the numerous possible intramolecular (methylene)C-H...π interactions (3.12 – 3.48 Å; Table 5), however, these are likely to be considered insignificant due to the small Donor – Hydrogen ... Acceptor (D – H ... A) bond angles (these deviate significantly from linearity.)[S10] A more likely real, but weak, intermolecular (phenyl)C-H...π interaction (3.35 Å; Figure 6) is present between adjacent molecules in the packed unit cell.

The torsion angle for C8-C26-C18-C16 is 166.2° while the bend angle between the planes defined by C7-C8-C26 and C17-C18-C16 is 44.3°. The twist in the pyrene system can be

assessed based on the torsion angles through the middle of the pyrene system (C6-C7-C26-C27-C28-C16-C17-C29; Table 6); each angle would measure 180° in a planar system, however, here, the five angles range from 148.9 – 164.4°.

Table 4 Summary of X-ray data

Compound reference	**22**
Chemical formula	$C_{38}H_{32}O_2$
Formula Mass	520.64
Crystal system	Triclinic
a/Å	9.143(5)
b/Å	11.785(6)
c/Å	13.878(7)
α/°	109.572(3)
β/°	97.451(4)
γ/°	105.330(6)
Unit cell volume/Å^3	1319.1(12)
Temperature/K	163(2)
Space group	$P\bar{1}$
No. of formula units per unit cell, *Z*	2
Radiation type	MoKα
Absorption coefficient, μ/mm^{-1}	0.079
No. of reflections measured	11569
No. of independent reflections	5876
R_{int}	0.0301
Final R_1 values ($I > 2\sigma(I)$)	0.0529
Final $wR(F^2)$ values (all data)	0.1491
Goodness of fit on F^2	1.103

$R1 = \Sigma \, ||Fo| - |Fc|| \, / \, \Sigma \, |Fo|, \, I > 2\sigma(I)$
$wR2 = [\Sigma \, (w \, (Fo^2 - Fc^2)^2) / \Sigma \, w(Fo^2)^2]^{1/2}$, all data

Table 5: Possible (methylene)C-H…π interactions for **22**

D – H ... A	**D – H**	**H ... A**	**D – H ... A**	
C36 – H36B ... Cg1	0.99 Å	3.48 Å	150.2°	Intramolecular
C36 – H36B ... Cg2	0.99 Å	3.34 Å	132.7°	Intramolecular
C37– H37B ... Cg3	0.99 Å	3.12 Å	139.0°	Intramolecular

C37 – H37B ... Cg4	0.99 Å	3.36 Å	155.6°	Intramolecular
C30 – H30 ... Cg4^{iv}	0.95 Å	3.35 Å	167.2°	Intermolecular

For Table 5:

Cg1 is the centroid of C7, C8, C12, C13, C26, C27

Cg2 is the centroid of C13-C15, C27, C28

Cg3 is the centroid of C23-C28

Cg4 is the centroid of C16-C18, C22, C23, C28

Symmetry operator (iv) 2-x, 1-y, 1-z

Table 6: Torsion angles through the middle of the pyrene system for **22** (°)

C6 – C7 – C26 – C27	151.92(11)
C7 – C26 – C27 – C28	-164.40(13)
C26 – C27 – C28 – C16	161.40(13)
C17 – C16 – C28 – C27	-162.83(13)
C28 – C16 – C17 – C29	148.90(13)

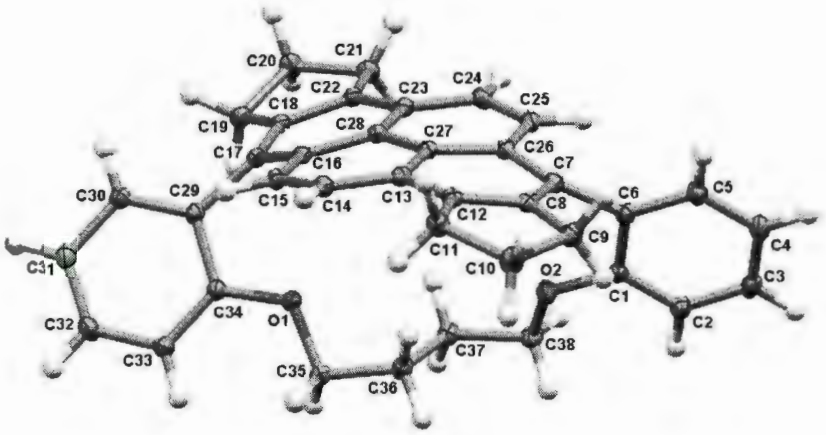


Figure 4: Asymmetric unit for **22** with 30% probability ellipsoids; H-atom labels omitted for clarity.

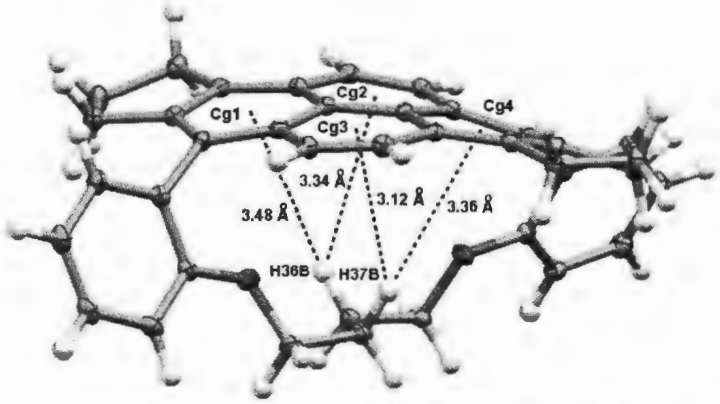


Figure 5: Alternate view of the asymmetric unit of **22**, with short methylene-H to π contacts indicated by dashed lines.

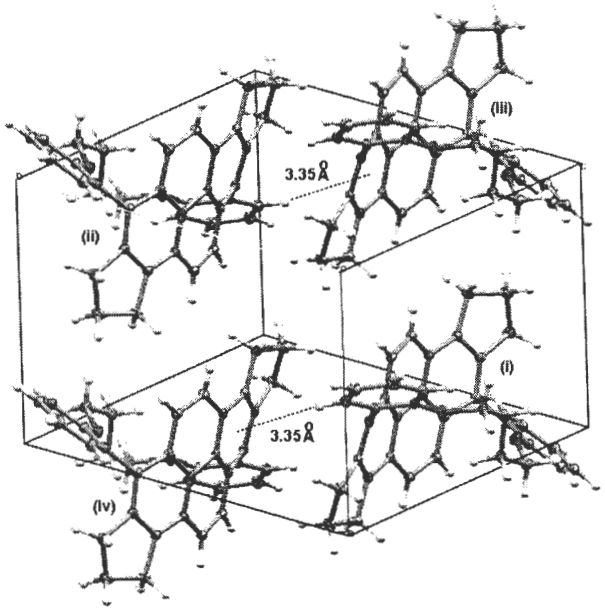


Figure6: Expanded, packed unit cell for **22**. Separation between the centroid of [C16-C17, C22, C23, C28] and the atom H30 of an adjacent, terminal benzene ring indicated by a dashed line. (i) x,y,z (ii) 1-x, 1-y, 1-z (iii) -1+x, y, z (iv) 2-x, 1-y, 1-z.

References for crystallographic information:

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S2. *DIRDIF99*: Beurskens, P. T.; Admiraal, G.; Beurskens, G.; Bosman, W. P.; de Gelder, R.; Israel, R.; Smits, J. M. M. (1999). The DIRDIF-99 program system, Technical Report of the Crystallography Laboratory, University of Nijmegen, The Netherlands.

S3. Cromer, D. T.; Waber, J. T. "International Tables for X-ray Crystallography", Vol. IV, The Kynoch Press, Birmingham, England, Table 2.2 A (1974).

S4. Ibers, J. A.; Hamilton, W. C. *Acta Cryst.*, 1964, **17**, 781.

S5. Creagh, D. C.; McAuley, W. J. "International Tables for Crystallography", Vol C, (A.J.C. Wilson, ed.), Kluwer Academic Publishers, Boston, Table 4.2.6.8, pages 219-222 (1992).

S6. Creagh, D. C.; Hubbell, J. H. "International Tables for Crystallography", Vol C, (A.J.C. Wilson, ed.), Kluwer Academic Publishers, Boston, Table 4.2.4.3, pages 200-206 (1992).

S7. CrystalStructure 3.7.0: Crystal Structure Analysis Package, Rigaku and Rigaku/MSC (2000-2005). 9009 New Trails Dr. The Woodlands TX 77381 USA.

S8. CRYSTALS Issue 10: Watkin, D. J.; Prout, C. K.; Carruthers, J. R.; Betteridge, P.W. Chemical Crystallography Laboratory, Oxford, UK. (1996)

S9. Mercury 3.0: C. F. Macrae, P. R. Edgington, P. McCabe, E. Pidcock, G. P. Shields, R. Taylor, M. Towler and J. van de Streek, *J. Appl. Cryst.*, 2006, **39**, 453.

S10. Arunan, E.; Desiraju, G. R.; Klein, R. A.; Sadlej, J.; Scheiner, S.; Alkorta, I.; Clary, D. C.; Crabtree, R. H.; Dannenberg, J. J.; Hobza, P.; Kjaergaard, H. G.; Legon, A. C.; Mennucci, B.; Nesbitt, D. J. *Pure Appl. Chem.*, 2012, **83**, 1619.

4.8 Experimental details of the absorption and emission spectra

Sample preparation. Samples were dissolved 2.5 mL of $CHCl_3$ (Fisher, Spectral grade) in a 1.0 cm path-length screw-top quartz cuvettes received from Starna. UV-Vis and fluorescence spectra of solvent were routinely recorded prior to addition of the sample to ensure that the solvent did not contain absorbing or emitting impurities. Extinction coefficients were determined by gravimetric methods with typical concentrations of between 10^{-5} to 10^{-6} M.

Electronic spectra. UV-vis spectra were obtained using an Agilent 8453A Diode Array UV-visible spectrophotometer. Manipulation of the UV-visible spectroscopic data were conducted using ChemStation software provided by Agilent or by exporting the data and utilizing Microcal Origin 8.0 analysis software.

Luminescence measurements were performed using a Photon Technology International (PTI) Quantamaster 6000 photon counting spectrofluorometer equipped with a 75 W Ushio Xenon arc lamp as the excitation source. The emitted light was collected 90° to the excitation beam and detected by a Hammamatsu R-928 photomultiplier tube (PMT) housed in Products for Research water-cooled PMT housing. Emission spectra were corrected for instrument response and light loss using correction factors supplied by manufacturer. Excitation spectra were corrected in real time using correction factors supplied by the manufacturers.

Emission quantum yields were measured on optically dilute (Abs < 0.2 with λ_{exc} = 350 nm, 1 atm N_2) $CHCl_3$ solutions at 295 ± 3 K by relative actinometry using a standard quinine bisulfate in 0.1 M aqueous sulfuric acid (Φ_{std} = 0.52 at λ_{exc} = 350 nm). Quantum yields were determined using:

$$\phi_{em} = \phi_{std}\left(\frac{A_{std}}{A_{un}}\right)\left(\frac{I_{un}}{I_{std}}\right)\left(\frac{n_{un}}{n_{std}}\right)^2 \qquad [S5\text{-}1]$$

Where A is a solution absorbance, I the emission intensity, n the refraction index of the solvent and the subscripts *un* and *std* refer to the unknown and standard, respectively.

Time Resolved Emission Measurements. Lifetimes were obtained using PTI LaserStrobe TM-3 fluorescence lifetime spectrofluorometer. Sample excitation was afforded by a PTI GL-3300 nitrogen laser coupled to the high-resolution PTI GL-302 dye laser. Instrument response functions (IRF) were obtained using a scattering solution

(milk or coffee powder in H_2O). The extraction of lifetimes from experimental data was performed using by curve fitting procedures based on Marquardt minimization algorithm provided by PTI or the data was exported and data analysis was accomplished using Microcal Origin 8.0 software.

Chapter 5

An Inverse Electron Demand Diels-Alder- Based Total Synthesis of Defucogilvocarcin V and some C-8 Analogues

This Chapter is based on the following publication:

Nandaluru, P.R.; Bodwell, G. J. *J. Org. Chem.* **2012**, *77*, 8028.

Contributions of authors

G. J. Bodwell: research supervisor, manuscript preparation.

P. R. Nandaluru: experimental work, manuscript preparation.

5.1 Introduction

A class of aryl *C*-glycoside-containing natural products, comprised of the gilvocarcins,[1-4] ravidomycin (**2**),[5-6] the chrysomycins (**3**)[7-8] and polycarcin (**4**),[9] has been isolated from different species of *Streptomyces*. These compounds exhibit impressive biological properties, including antibacterial[2,10] and strong antitumor activity.[11-14] Structurally, they share a common tetracyclic aromatic core (6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-one), to which a sugar is attached at C-4. Individual gilvocarcins are distinguished by variation of the R group at C-8, by which they were named as gilvocarcin M (R = methyl), gilvocarcin E (R = ethyl) and gilvocarcin V (R = vinyl). Furthermore, the aglycon of one of them, defucogilvocarcin V (**5c**), was isolated from the fermentation broth of *Streptomyces arenae* 2064 by Mishra and co-workers.[15] Studies suggested that the antitumor activity of defucogilvocarcin V (**5c**), on activation by light, is similar to that of the parent gilvocarcin V (**1c**).[15,16] This implies that the role of sugar moiety in the anticancer activity may be of minor importance.

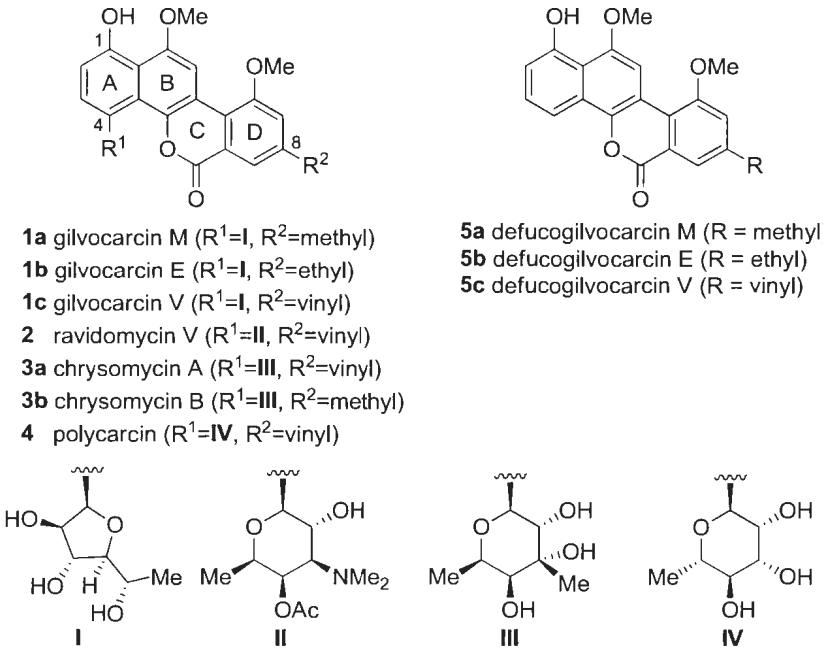


Figure 5.1. The gilvocarcin family of natural products.

The gilvocarcins (**1**) and their aglycons (defucogilvocarcins, **5**) have been targets of the synthetic community because of their impressive biological profiles. Whereas only a handful of total syntheses of gilvocarcins have been accomplished,[17–20] a relatively large number of defucogilvocarcin syntheses has been reported. The strategies used to approach the defucogilvocarcins can be sorted into three categories according to the ring(s) generated during the key step(s): 1) formation of the C ring using a) Suzuki coupling followed by lactonization,[21–23] b) esterification / intramolecular biaryl bond formation,[24] c) nucleophilic aromatic substitution / lactonization,[25–26] d) Pechmann condensation[27] and e) conjugate addition / lactonization;[28] 2) formation of the A and C rings using f) Diels-Alder reaction (A ring) / Meerwein coupling / lactonization (C

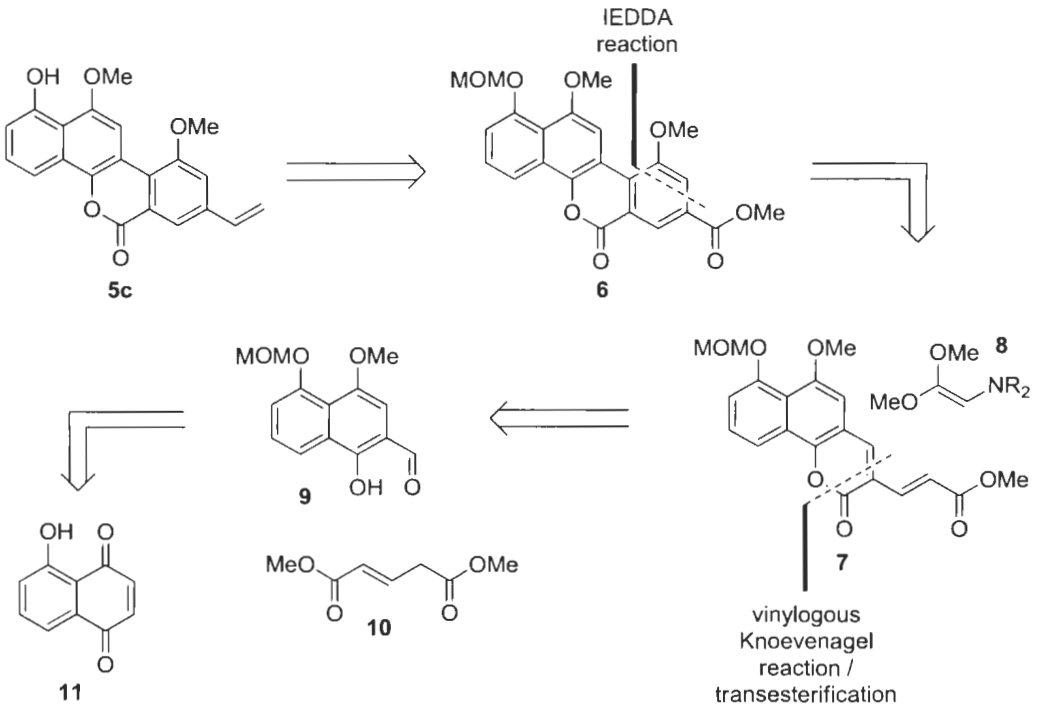
ring);[29–31] and 3) formation of the B and C rings using g) a Dötz chromium carbene benzannulation / lactonization,[32] h) a [2+2] cycloaddition / pericyclic ring opening – ring closing / lactonization[33] and i) a condensation reaction between a styryl sulfone and a phthalide.[34] More recently, a one-pot enzymatic synthesis of defucogilvacarcin M starting from acetyl-CoA and malonyl-CoA using fifteen enzymes has been reported.[35] Notably, none of the non-enzymatic synthetic approaches to the defucogilvocarcins involves the formation of the D-ring, which is where variations at C-8 of natural products are present.

5.2 Results and Discussion

In connection with ongoing work aimed at the development and application of the inverse electron demand Diels-Alder (IEDDA) reaction,[36] our group has reported the synthesis of a variety of electron deficient dienes.[37–44] The common structural feature of these systems is the presence of two electron withdrawing groups on the diene unit with a 1,3-relationship. This motif allows the two electron-withdrawing groups to electronically bias the diene in a co-operative fashion, which results in completely regioselective cycloaddition upon reaction with electron rich dienophiles. This chemistry has provided access to several different classes of compounds, including 2-hydroxybenzophenones,[38] isophthalates,[39] xanthones,[40] pyrido[2,3-*c*]coumarins[41] and 6*H*-dibenzo[*b,d*]pyran-6-ones (DBPs).[42-44] Additionally, the methodology developed for the synthesis of DBPs has been exploited in total syntheses of cannabinol[44] and urolithin M7,[45] as well as in the synthesis of an elaborate chiral cyclophane.[46] To further demonstrate the value of this methodology, defucogilvocarcins were identified as attractive synthetic targets. Reported

herein are details of the total synthesis of defucogilvocarcin V (**5c**) and some of its C-8 analogues.

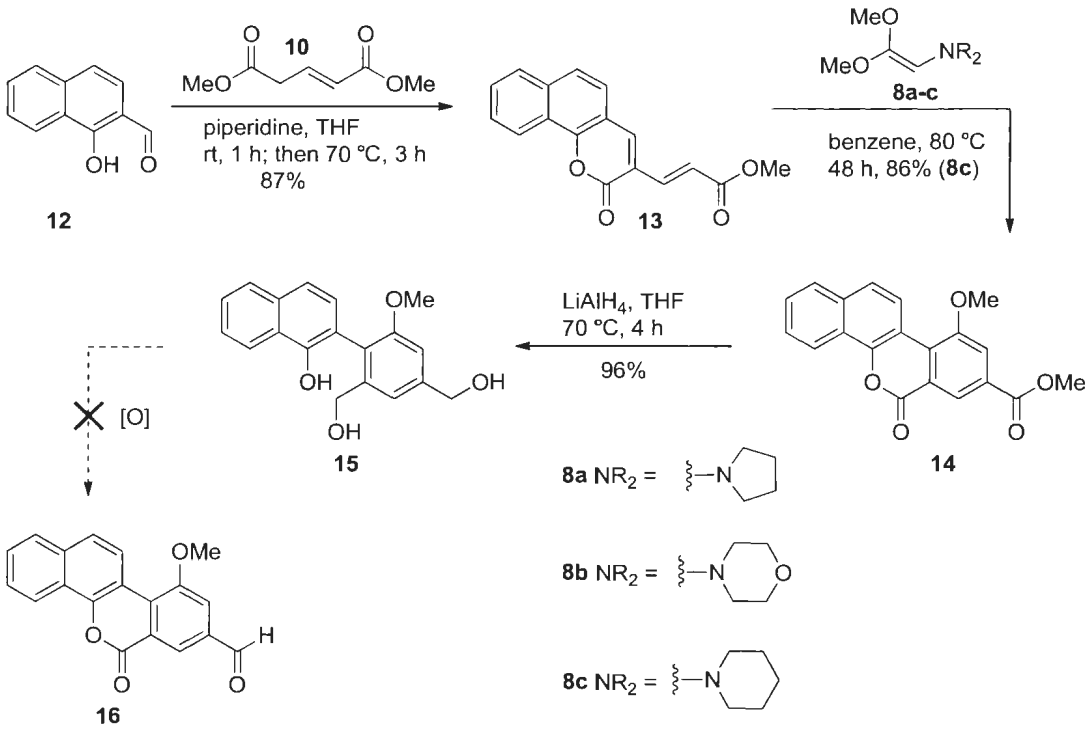
The retrosynthetic analysis of **5c** based on our DBP-forming methodology commences with functional group interconversion to provide 6*H*-benzo[*d*]naphtho[1,2-*b*]benzopyran-6-one (**6**) (Scheme 5.1). The D-ring and C-ring are then opened successively using an IEDDA-driven domino transform,[42,43,45] (giving naphthalene-derived diene **7** and electron rich dienophile **8**) and a vinylogous Knoevenagel condensation / transesterification transform to afford 1-hydroxy-2-naphthaldehyde **9** and dimethyl glutaconate (**10**). The differentially *O*-protected 1-hydroxy-2-naphthaldehyde **9** leads back to commercially available juglone (**11**).



Scheme 5.1. Retrosynthetic analysis of defucogilvocarcin V (**5C**).

Before initiating work on the synthesis of **9**, a model study starting from more abundantly and inexpensively available 1-hydroxy-2-naphthaldehyde (**12**) was conducted to test the viability of the key steps (Scheme 5.2). The reaction of **12** with dimethyl glutaconate (**10**) afforded diene **13** in high yield (87%). Diene **13** was then subjected to the key IEDDA reaction with a series of enamines derived from dimethoxyacetaldehyde, i.e. **8a–c**, whereby it was found that the nature of the secondary amine used to generate the enamine played a critical role in the reaction. While the use of the pyrrolidine-derived enamine **8a** resulted in the consumption of the starting diene, no identifiable product was obtained from the reaction. On the other hand, the morpholine-derived enamine **8b** did not undergo reaction with **13** under the same conditions. After some experimentation, it was found that diene **13** reacted smoothly with the piperidine-derived enamine **8c** to afford **14** (86%). In this case, more concentrated solutions were required to drive the reaction to completion. The reasons for differences in reactivity between the various enamines **8a-c** are not immediately obvious. In any event, the IEDDA reaction involving **8c** proceeded with complete regioselectivity, in line with previous observations.[37–45] Consequently, the newly-generated D-ring was endowed with correctly placed methoxy and methoxycarbonyl groups, the latter of which was poised for conversion to the required vinyl functionality. Both the ester and lactone functionalities present in **14** were reduced with $LiAlH_4$ to give triol **15** (96%). It was envisaged that oxidation of **15** would afford lactone-aldehyde **16** (via a hemiacetal), but all attempts to accomplish this transformation using various oxidizing agents (PCC, MnO_2, IBX and Fétizon's reagent) failed. In all cases, the starting material was consumed to give a

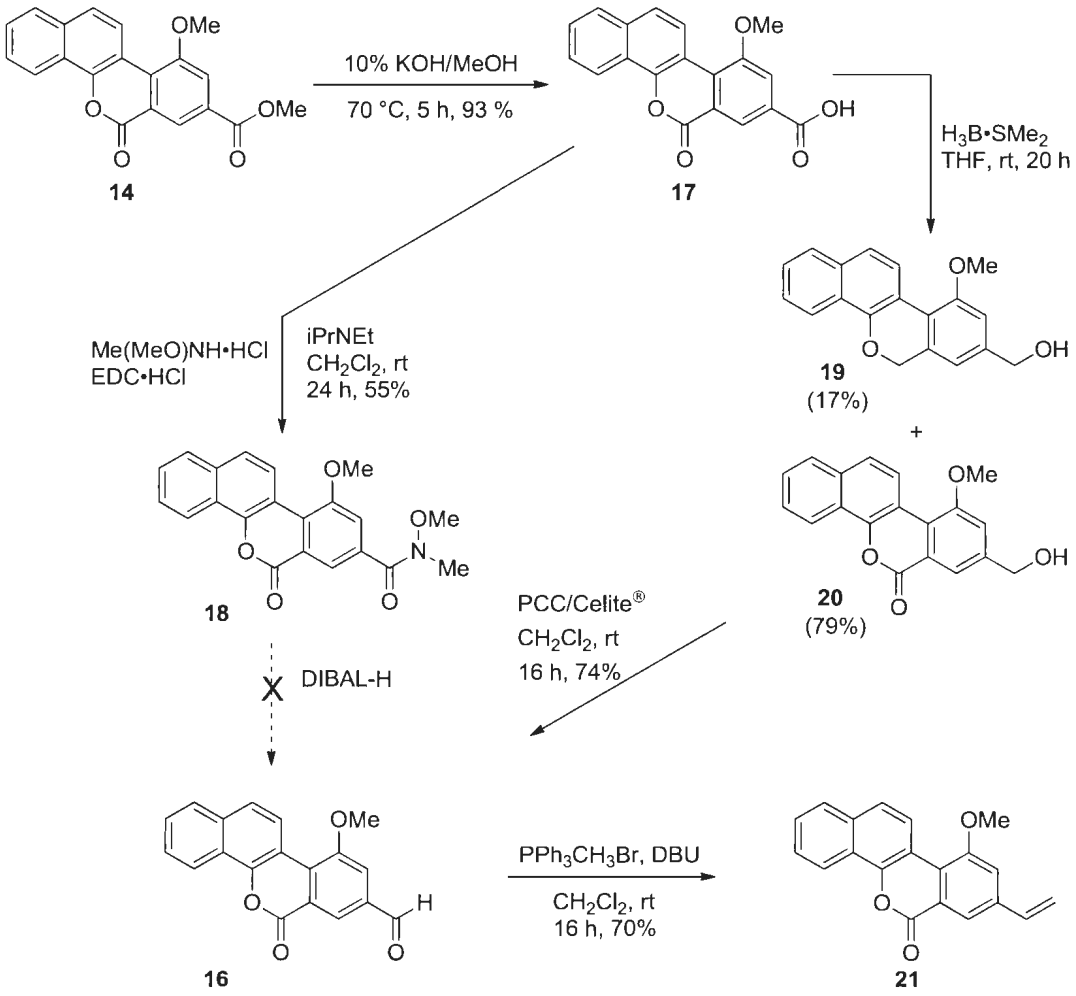
deeply colored reaction mixture, from which no identifiable product was isolated. Quinone formation may compete with the desired transformation.



Scheme 5.2. Attempted synthesis of a defucogilvocarcin V model.

Although the viability of the two key steps had been established, an alternative approach to functional group management was required. Accordingly, methods for achieving the chemoselective reduction of the ester over the lactone were investigated. To this end, hydrolysis of **14** afforded carboxylic acid **17** (93%) (Scheme 5.3). In this reaction, both the ester and lactone were presumably hydrolyzed and the lactone reformed during the acidic workup. Weinreb amide **18** was then prepared in a moderate

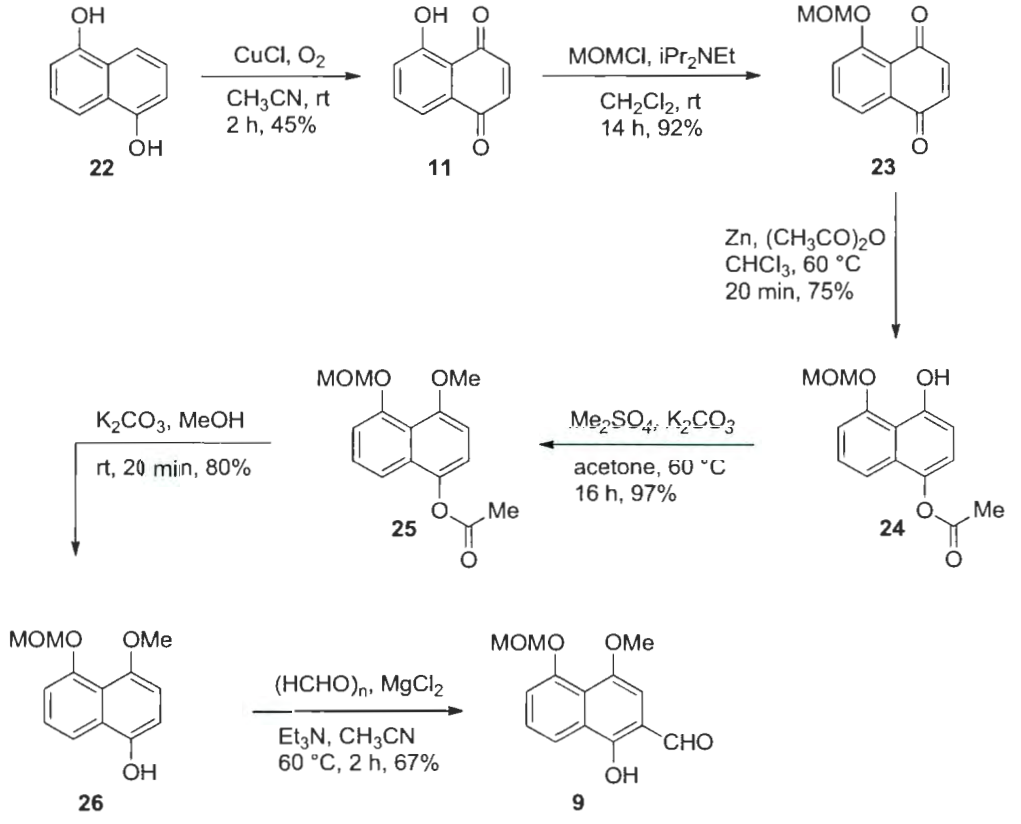
yield (55%) in preparation for a chemoselective reduction with DIBAL-H, which was intended to result in the formation of aldehyde **16**. Unfortunately, this reaction showed no evidence of progress at −78 °C, the temperature typically used for this transformation.[47] Upon warming the reaction mixture to room temperature and stirring at this temperature for 12 h, the starting material was consumed, but a complex mixture of products was produced (TLC and ^{1}H NMR analysis). However, a chemoselective reduction of acid **17** was achieved using $Me_2S{\cdot}BH_3$. This afforded benzylic alcohol **20** (79%) along with a minor, but still significant, amount of the overreduced benzylic alcohol **19** (17%). Oxidation of **20** was achieved using PCC / Celite® to give aldehyde **16** (73%). Finally, a Wittig reaction under mild conditions[48] using DBU as the base was employed to obtain the olefin **21** (70%), thereby completing the model study. Model compound **21** was synthesized in six steps from commercially available 1-hydroxy-2-naphthaldehyde (**12**) in 28% overall yield.



Scheme 5.3. Completion of the defucogilvocarcin V model study.

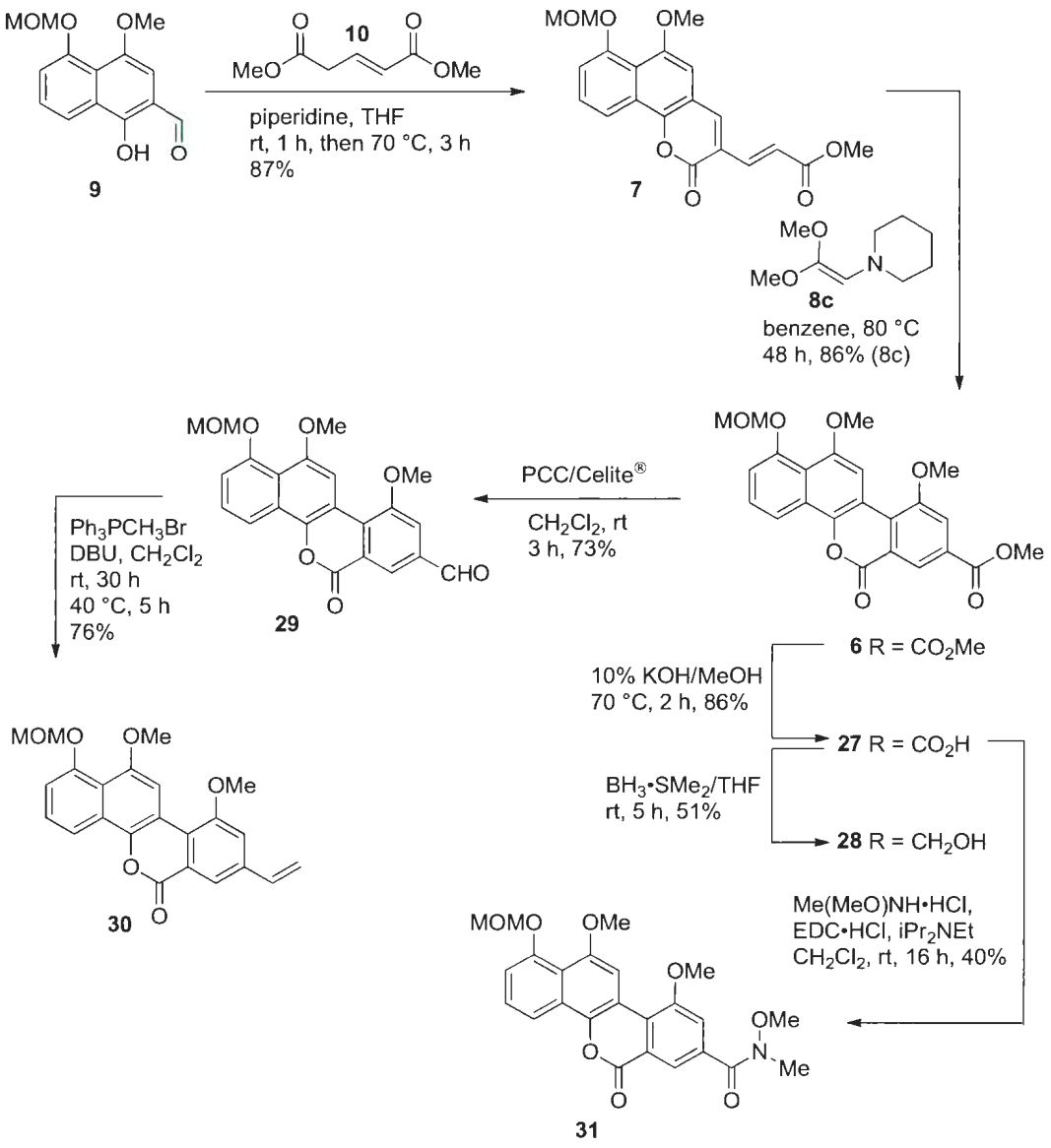
Upon successful completion of the model study, attention was turned to applying the approach to the synthesis of defucogilvocarin V (**5c**). The synthesis began from juglone (**11**), which is commercially available or readily accessible from 1,5-dihydroxynaphthalene (**22**).[49] The hydroxyl group of juglone (**11**) was MOM-protected[50] and the resulting 1,4-naphthoquinone **23** (92%) was subjected to a reductive acylation /

methylation protocol, which was based upon procedures described for the *O*-methyl analog of **23** (Scheme 5.4).[51] This involved reduction of the naphthoquinone **23** with Zn and selective *O*-acetylation at the less sterically hindered site. The monoacylated product **24** (75%) was then *O*-methylated upon treatment with dimethyl sulfate to give **25** (97%). The acetyl group was removed using K_2CO_3 in MeOH to afford naphthol **26** (80%), which was regioselectively formylated using the Skattebøl *ortho*-formylation[52] to provide the required hydroxynaphthaldehyde **9** (63%).



Scheme 5.4. Synthesis of hydroxynaphthaldehyde **9**.

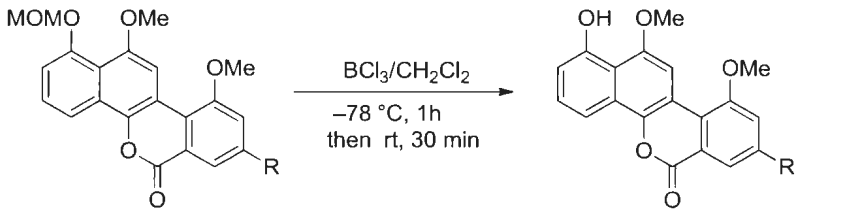
With **9** in hand, a vinylogous Knoevenagel reaction was carried out with dimethyl glutaconate (**10**) to generate the corresponding electron deficient diene **7** (87%) (Scheme 5.5). Reaction of **7** with enamine **8c** resulted in the formation of ester **6** (89%), which differs from the natural product only in the nature of the C-8 substituent and the presence of the protective group at C-1. Hydrolysis of the ester provided carboxylic acid **27** (86%), which was then reduced to afford benzylic alcohol **28** (51%). Oxidation of **28** gave aldehyde **29** (74%), which was subjected to a Wittig reaction to furnish olefin **30** (76%). To mirror the model study, carboxylic acid **27** was converted into the corresponding Weinreb amide **31** (40%).



Scheme 5.5. Synthesis of MOM-protected defucogilvocarcin V (**30**).

Finally, compounds **6**, **29**, **30** and **31** were deprotected using BCl_3 (Scheme 5.6). This reaction smoothly afforded defucogilvocarcin V (**5c**) (83%) along with three C-8

analogues, **32** (87%), **33** (82%) and **34** (63%). The total synthesis of defucogilvocarcin V (**5c**) was accomplished in 12 steps from juglone in 5.3% overall yield.



6 R = CO_2Me
29 R = CHO
30 R = $CH=CH_2$
31 R = C(O)NMe(OMe)

32 R = CO_2Me (87%)
33 R = CHO (83)
5c R = $CH=CH_2$ (82%)
34 R = C(O)NMe(OMe) (63%)

Scheme 5.6. Synthesis of defucogilvocarcin V (**5C**) and C–8 analogs **32–34**.

5.3 Conclusions

The approach to defucogilvocarcin V (**5c**) described here differs from all previously reported approaches in that it involves construction of the D-ring. Not only is the D-ring formed with the required C-10 methoxy group, but it also bears an ester at C-8, which is where differences in the natural defucogilvocarcins and gilvocarcins occur. Synthetic manipulation of the ester group led to the natural product defucogilvocarcin V (**5c**) as well as three C-8 analogues, which all offer opportunities for further elaboration.

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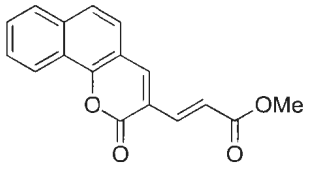
5.5 Experimental procedures and characterization data

General I: The general experimental can be found in page 47.

General II: Acetone was distilled over K_2CO_3. Acetonitrile and triethylamine were distilled over CaH_2.

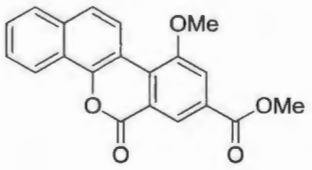
Methyl (*E*)-3-(6*H*-naphtho[1,2-*b*]pyran-6-on-5-yl)acrylate (13).



To a solution of 1-hydroxy-2-naphthaldehyde (**12**) (2.00 g, 11.6 mmol) and dimethyl glutaconate (**10**) (2.76 g, 17.5 mmol) in THF (40 mL) was added piperidine (0.99 g, 12 mmol) and the resulting mixture was stirred at room temperature for 1 h and then at 70 °C for 3 h. The reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure. The residue was dissolved in $CHCl_3$ (600 mL) and the resulting solution was washed with aqueous 1.0 M HCl solution (1×). The layers were separated and the organic layer was dried over Na_2SO_4 and gravity filtered. The solvent was removed under reduced pressure and diethyl ether (15 mL) was added to the residue. The resulting mixture was stirred for 10 min and vacuum filtered. On repetition of this process (ether addition to the solids, stirring and filtration), **13** (2.83 g, 87%) was obtained as a yellow solid. R_f = 0.30 (30% ethyl acetate / hexanes); mp 191–193 °C; IR (neat) ν = 1708 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.57–8.55 (m, 1H), 7.98 (s, 1H), 7.89–7.87 (m, 1H), 7.70 (d, J = 8.5 Hz, 1H), 7.69–7.66 (m, 2H), 7.63 (d, J = 15.9 Hz,

1H), 7.49 (d, J = 8.5 Hz, 1H), 7.17 (d, J = 15.8 Hz, 1H), 3.83 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.72, 159.28, 151.40, 144.68, 138.50, 135.55, 129.59, 128.17, 127.71, 125.14, 123.90, 123.08, 122.94, 122.86, 121.74, 114.71, 52.10; ESI-(+)-MS *m/z* (%) 303 (100, $[M+Na]^+$); HRMS [EI-(+)] calcd for $C_{17}H_{12}O_4$ 280.0736, found 280.0732.

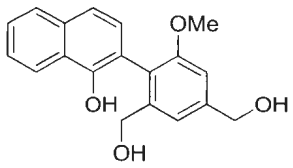
10-Methoxy-6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-one-8-carboxylic acid methyl ester (14).



A mixture of dimethoxyacetaldehyde (1.86 g, 10.7 mmol, 60% solution in water) and piperidine (0.73 g, 8.6 mmol) in benzene (35 mL) was heated at reflux for 1 h using a Dean-Stark apparatus. Solvent (~30 mL) was removed from the reaction flask through the Dean-Stark condenser. The reaction mixture was cooled to room temperature and **13** (0.30 g, 1.1 mmol) was added in one portion. The resulting mixture was then heated at reflux for 48 h (note: the low dilution is critical for the complete consumption of the starting material). The reaction was monitored by ^{1}H NMR analysis (an aliquot was taken from the reaction using a pipette, ether (0.5 mL) was added, the supernatant was decanted and the residue was dried under vacuum; ^{1}H NMR was performed after every 12 h, starting from 24 h). The reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure. The residue was dissolved in $CHCl_3$ (70 mL) and washed with aqueous 1.0 M HCl solution (2×). The layers were separated and

the organic layer dried over Na_2SO_4 and gravity filtered. The solvent was removed under reduced pressure and the residue was subjected column chromatography ($CHCl_3$). The product obtained from chromatography was triturated with ether (2×7 mL) to give **14** (0.30 g, 86%) as a pale yellow solid. R_f = 0.30 (30% ethyl acetate / hexanes); mp 247–250 °C; IR (neat) ν = 1715 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.96 (d, J = 9.2 Hz, 1H), 8.75 (d, J = 1.7 Hz, 1H), 8.61–8.57 (m, 1H), 7.93 (d, J = 1.7 Hz, 1H), 7.85–7.82 (m, 1H), 7.68 (d, J = 9.1 Hz, 1H), 7.63–7.59 (m, 2H), 4.14 (s, 3H), 3.99 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.87, 160.74, 157.64, 147.70, 134.33, 130.58, 128.67, 128.45, 127.44, 126.97, 124.73, 124.33, 124.03, 123.53, 123.10, 122.80, 116.82, 112.81, 56.58, 52.82; APCI-(+)-MS m/z (%) 335 ($[M+H]^+$, 100); HRMS [CI-(+)] calcd for $C_{20}H_{15}O_5$ 335.0919, found 335.0930.

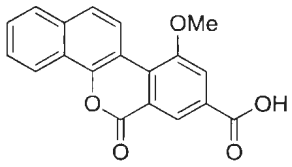
2-(2,4-Bis(hydroxymethyl)-6-methoxy)-1-naphthol (15).



To a 0 °C slurry of $LiAlH_4$ (0.18 g, 4.7 mmol) in THF (20 mL) was added **14** (0.40 g, 1.2 mmol) in several portions and the reaction mixture was heated at reflux for 4 h. After cooling to 0 °C, the reaction was quenched by the careful addition of aqueous 1.0 M HCl solution (20 mL). The resulting mixture was vacuum filtered and the filtrate was washed thoroughly with $CHCl_3$ (4×). The layers were separated and the aqueous layer was washed with $CHCl_3$ (1×). The combined organic layers were dried over Na_2SO_4 and

gravity filtered. The solvent was removed under reduced pressure and the residue was triturated with ether (2×3 mL) to afford **15** (0.39 g, 96%) as a colorless solid. R_f = 0.20 (50% ethyl acetate / hexanes); mp 197–200 °C; IR (neat) ν = 3389 (w) cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ 8.18–8.17 (m, 1H), 7.82–7.80 (m, 1H), 7.48–7.42 (m, 2H), 7.37 (d, J = 8.3 Hz, 1H), 7.16 (d, J = 1.6 Hz, 1H), 7.01 (d, J = 8.3 Hz, 1H), 6.93 (d, J = 1.6 Hz, 1H), 5.20 (t, J = 5.8 Hz, 1H), 4.56 (d, J = 4.7 Hz, 2H), 4.18 (d, J = 13.9 Hz, 1H), 4.10 (d, J = 13.8 Hz, 1H), 3.29 (s, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 156.75, 149.36, 142.76, 141.86, 133.72, 129.64, 127.37, 125.74, 125.33, 124.69, 122.83, 122.23, 118.65, 117.66, 116.70, 107.55, 63.27, 60.86, 55.30; APCI-(−)-MS *m/z* (%) 309 (100, $[M-H]^-$); HRMS [EI-(+)] calcd for $C_{19}H_{18}O_4$ 310.1205, found 310.1208.

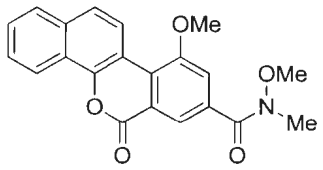
10-Methoxy-6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-one-8-carboxylic acid (17).



A suspension of **14** (0.60 g, 1.8 mmol) in 10% KOH / methanol (30 mL) was heated at reflux for 5 h. The reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure. To the residue was added water (10 mL) and the pH was adjusted to ~ 2.0 using aqueous 5.0 M HCl solution. The resulting mixture was suction filtered. The solids were vacuum dried for 1 h and then air dried in an oven at 90–100 °C for 12 h to afford **17** (0.53 g, 93%) as a pale yellow solid. R_f = 0.60 (ethyl acetate); mp 266–269 °C; IR (neat) ν = 3200–2700 (br, w), 1734 (s) cm^{-1}; ^1H NMR

(DMSO-d_6, 500 MHz) δ 8.99 (d, J = 9.1 Hz, 1H), 8.46 (d, J = 1.6 Hz, 1H), 8.42–8.38 (m, 1H), 8.03–7.99 (m, 1H), 7.95 (d, J = 1.7 Hz, 1H), 7.85 (d, J = 9.1 Hz, 1H), 7.72–7.68 (m, 2H), 4.15 (s, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 165.77, 159.47, 157.06, 146.46, 133.40, 131.34, 128.18, 127.32, 126.95, 126.76, 124.15, 123.55, 122.50, 122.39, 122.30, 121.49, 116.66, 112.18, 56.36; APCI-(−)-MS *m/z* (%) 319 (100, $[M-H]^-$); HRMS [EI-(+)] calcd for $C_{19}H_{12}O_5$ 320.0685, found 320.0687.

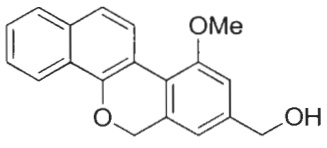
_N_,10-dimethoxy-_N_-methyl-6_H_-benzo[_d_]naphtho[1,2-_b_]pyran-6-one-8-carboxamide (18).



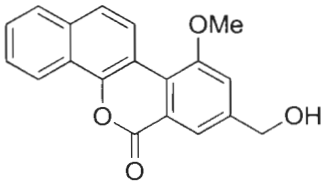
To a mixture of **17** (0.18 mg, 0.55 mmol) and EDCI·HCl (0.20 g, 1.0 mmol) in CH_2Cl_2 (3.0 mL) was added iPr_2NEt (0.28 g, 2.2 mmol) and the resulting mixture was stirred at room temperature for 1 h. To the resulting mixture was added *N,O*-dimethylhydroxylamine hydrochloride (0.13 g, 1.3 mmol) in one portion and the mixture was stirred at room temperature for a further 24 h. Water (20 mL) was then added followed by the aqueous 1.0 M HCl solution (15 mL). The layers were separated and the aqueous layer was washed with $CHCl_3$ (2×). The combined organic layers were dried over Na_2SO_4 and gravity filtered. The solvent was removed under reduced pressure and the residue was subjected to column chromatography (3% methanol / $CHCl_3$) and the product was triturated with ether (2×1 mL) to afford **18** (0.11 g, 55%) as a colorless solid.

R_f = 0.50 (50% ethyl acetate / hexanes); mp 164–167 °C; IR (neat) ν = 1718 (s), 1633 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 9.03 (d, J = 9.1 Hz, 1H), 8.64–8.62 (m, 1H), 8.53 (d, J = 1.6 Hz, 1H), 7.89–7.87 (m, 1H), 7.75–7.73 (m, 2H), 7.65–7.61 (m, 2H), 4.15 (s, 3H), 3.67 (s, 3H), 3.44 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.14, 160.98, 157.50, 147.46, 134.51, 134.21, 128.30, 127.46, 126.96, 124.82, 124.01, 123.65, 122.81, 122.79, 122.70, 117.09, 113.02, 61.67, 56.58, 34.04; APCI-(+)-MS *m/z* (%) 364 (100, $[M+H]^+$); HRMS [EI-(+)] calcd for $C_{21}H_{17}NO_5$ 363.1107, found 363.1111.

8-(Hydroxymethyl)-10-methoxy-6*H*-benzo[*d*]naphtho[1,2-*b*]pyran (19) and 8-(hydroxymethyl)-10-methoxy-6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-one (20).



19

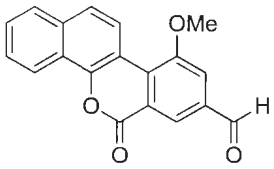


20

To a 0 °C suspension of **17** (0.20 g, 0.63 mmol) in THF (20 mL) was added $H_3B{\cdot}SMe_2$ (1.8 mL, 3.7 mmol) dropwise over a period of 5 min and the resulting mixture was stirred at room temperature for 20 h. The reaction mixture was cooled to 0 °C and methanol (3.0 mL) was added dropwise. The solvent was removed under reduced pressure and the residue was dissolved in $CHCl_3$ (200 mL). The resulting solution was washed with aqueous 1.0 M HCl solution (1×) and then with saturated aqueous $NaHCO_3$ solution (1×). The layers were separated and the organic layer was dried over Na_2SO_4, gravity filtered and the solvent was removed under reduced pressure. The residue was triturated with

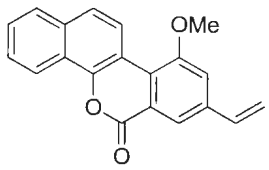
ether (3×3 mL) to afford **20** (153 mg, 79%) as a colorless solid. The ether layer was concentrated under reduced pressure and the residue was subjected to column chromatography (40% ethyl acetate / hexanes) to afford **19** (30 mg, 17%) as a colorless solid. **19**: R_f = 0.80 (ethyl acetate); mp 122–125 °C; IR (neat) v = 3400–3100 (br, w) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.49 (d, J = 8.8 Hz, 1H), 8.28-8.26 (m, 1H), 7.81-7.78 (m, 1H), 7.50 (d, J = 8.8 Hz, 1H), 7.48-7.44 (m, 2H), 7.00 (d, J = 1.5 Hz, 1H), 6.86 (d, J = 1.4 Hz, 1H), 5.16 (s, 2H), 4.73 (s, 2H), 3.97 (s, 3H), 1.73 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.54, 150.78, 141.36, 134.19, 133.75, 127.30, 126.43, 125.88, 125.32, 124.99, 122.20, 120.43, 118.75, 116.96, 115.63, 110.13, 69.29, 65.11, 55.72; APCI-(+)-MS *m/z* (%) $[M+H]^+$ not observed, 291 (11), 275 (100); HRMS [EI-(+)] calcd for $C_{19}H_{16}O_3$ 292.1099, found 292.1116. **20**: R_f = 0.70 (ethyl acetate); mp 231–234 °C; IR (neat) v = 3433 (m), 1692 (s) cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ 9.02 (d, J = 9.1 Hz, 1H), 8.43–8.41 (m, 1H), 8.02–8.00 (m, 1H), 7.99 (d, J = 1.5 Hz, 1H), 7.86 (d, J = 9.1 Hz, 1H), 7.72–7.66 (m, 2H), 7.60 (d, J = 1.6 Hz, 1H), 5.54 (t, J = 5.6 Hz, 1H), 4.70 (d, J = 3.5 Hz, H), 4.11 (s, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 160.20, 157.10, 145.47, 145.13, 132.93, 127.70, 127.46, 126.97, 124.36, 123.53, 122.69, 122.09, 121.84, 121.36, 118.88, 115.81, 113.02, 62.17, 56.37; ESI-(+)-MS *m/z* (%) 307 (100, $[M+H]^+$); HRMS [EI-(+)] calcd for $C_{19}H_{14}O_4$ 306.0892, found 306.0901.

10-Methoxy-6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-one-8-carbaldehyde (16).



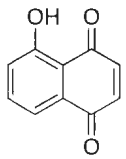
To a mixture of **20** (0.19 g, 0.62 mmol) and Celite® (0.20 g) in CH_2Cl_2 (10 mL) was added PCC (0.33 g, 1.5 mmol) in several portions and the resulting mixture was stirred at room temperature for 20 h. The reaction mixture was gravity filtered and the filter cake was washed repeatedly with $CHCl_3$ (3×). The solvent was removed under reduced pressure and the residue was subjected to column chromatography (4% methanol / $CHCl_3$). The product was triturated with ether (3×1 mL) to afford **16** (0.14 g, 74%) as a pale yellow solid. R_f = 0.30 (30% ethyl acetate / hexanes); mp 238–241 °C; IR (neat) ν = 1722 (m), 1688 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 10.11 (s, 1H), 9.03 (d, J = 9.1 Hz, 1H), 8.64–8.62 (m, 1H), 8.59 (s, 1H), 7.89–7.88 (m, 1H), 7.83 (s, 1H), 7.74 (d, J = 9.1 Hz, 1H), 7.66–7.64 (m, 2H), 4.18 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 190.39, 160.33, 158.12, 148.00, 136.16, 134.38, 130.29, 128.60, 127.30, 127.11, 126.94, 124.52, 124.03, 123.33, 123.31, 122.69, 112.77, 112.56, 56.45; ESI-(+)-MS *m/z* (%) 305 (7, $[M+H]^+$), 102 (100); HRMS [EI-(+)] calcd for $C_{19}H_{12}O_4$ 304.0736, found 304.0725.

10-Methoxy-8-vinyl-6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-one (21).



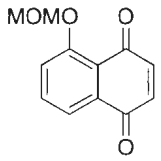
A mixture of PPh_3MeBr (0.59 g, 1.7 mmol) and DBU (0.30 g, 2.0 mmol) in CH_2Cl_2 (8.0 mL) was heated at reflux for 1 h. The reaction mixture was cooled to room temperature and **16** (0.10g, 0.32 mmol) was added in one portion. The resulting mixture was stirred at room temperature for 16 h. The reaction mixture was diluted with $CHCl_3$ (50 mL) and washed with aqueous 1.0 M HCl solution (1×). The organic layer was dried over Na_2SO_4 and gravity filtered. The solvent was removed under reduced pressure and the residue was subjected to column chromatography (CH_2Cl_2) to afford **21** (70 mg, 70%) as a colorless solid. R_f = 0.50 (30% ethyl acetate / hexanes); mp 202–205 °C; IR (neat) ν = 1718 (s), 1599 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.96 (d, J = 9.1 Hz, 1H), 8.60 (dd, J = 7.1, 2.2 Hz, 1H), 8.16 (d, J = 1.7 Hz, 1H), 7.85 (dd, J = 6.8, 2.3 Hz, 1H), 7.69 (d, J = 9.0 Hz, 1H), 7.62–7.57 (m, 2H), 7.36 (d, J = 1.7 Hz, 1H), 6.81 (dd, J = 17.5, 10.8 Hz, 1H), 5.95 (d, J = 17.5 Hz, 1H), 5.44 (d, J = 10.8 Hz, 1H), 4.11 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.49, 157.79, 146.67, 138.71, 135.61, 133.77, 127.84, 127.40, 126.77, 124.71, 124.35, 123.83, 123.67, 123.35, 122.61, 120.74, 116.54, 114.23, 113.45, 56.27; APCI-(+)-MS *m/z* (%) 303 (100, $[M+H]^+$); HRMS [EI-(+)] calcd for $C_{20}H_{14}O_3$ 302.0943, found 302.0934.

5-Hydroxy-1,4-naphthoquinone (juglone) (11).



This compound was both purchased and synthesized using the following procedure, which is a modified version of a literature procedure.[49] To a mechanically stirred suspension of 1,5-dihydroxynaphthalene (**22**, 17.5 g, 109 mmol) in acetonitrile (260 mL) was added freshly prepared CuCl[53] (6.50 g, 65.7 mmol) and a strong current of O_2 gas was bubbled through the reaction mixture for 2 h. The reaction mixture was vacuum filtered through a plug of Celite® and the filter cake was washed thoroughly with $CHCl_3$ (500 mL). The filtrate was concentrated under reduced pressure and the residue was subjected to column chromatography ($CHCl_3$) to afford **11** (8.51 g, 45%) as an orange solid. R_f = 0.60 (30% ethyl acetate / hexanes); mp 147–152 °C (lit. mp[49] 154-161 °C); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 11.90 (s, 1H), 7.66-7.61 (m, 2H), 7.29 (dd, J = 7.8, 1.9 Hz, 1H), 6.96 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 190.29, 184.25, 161.45, 139.59, 138.65, 136.57, 131.76, 124.50, 119.16, 114.97; HRMS [EI-(+)] calcd for $C_{10}H_6O_3$ 174.0317, found 174.0320.

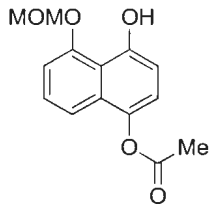
5-(Methoxymethoxy)-1,4-naphthoquinone (23).



To 0 °C solution of **11** (5.00 g, 28.7 mmol) and MOMCl (5.78 g, 71.8 mmol) in CH_2Cl_2 (80 mL) was added iPr_2NEt (7.43 g, 57.5 mmol) dropwise over 15 min and the reaction mixture was stirred at room temperature for 14 h. To this mixture was added saturated aqueous NH_4Cl solution (50 mL) and the layers were separated. The aqueous layer was

extracted with CH_2Cl_2 (1×) and the combined organic layers were dried over Na_2SO_4 and gravity filtered. The solvent was removed under reduced pressure and the residue was subjected to column chromatography (25% ethyl acetate / hexanes). The product was triturated with hexanes (2×15 mL) to afford **23** (5.80 g, 92%). R_f = 0.30 (30% ethyl acetate / hexanes); mp 98–101 °C (lit. mp[50] 102.5–103 °C); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.80 (dd, J = 7.6, 1.2 Hz, 1H), 7.67 (dd, J = 8.5, 7.5 Hz, 1H), 7.54 (d, J = 8.4, 1.2 Hz, 1H), 6.89 (d, J = 10.3 Hz, 1H), 6.86 (d, J = 10.3 Hz, 1H), 5.36 (s, 2H), 3.55 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 185.04, 184.17, 157.11, 140.80, 136.37, 134.73, 133.99, 122.33, 120.68, 120.53, 95.10, 56.64; HRMS [EI-(+)] calcd for $C_{12}H_{10}O_4$ 218.0579, found 218.0582.

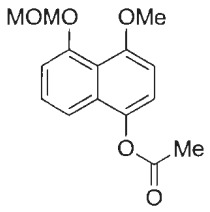
4-Acetoxy-8-(methoxymethoxy)-1-naphthol (24).



To a mixture of **23** (1.00 g, 4.59 mmol) and zinc (3.00 g, 45.9 mmol) in $CHCl_3$ (30 mL) was added acetic anhydride (0.93 g, 9.1 mmol) and pyridine (0.89 g, 11 mmol). The resulting mixture was heated at gentle reflux for 20 min. The reaction mixture was cooled to room temperature, diluted with $CHCl_3$ (60 mL) and washed with cold aqueous 1.0 M HCl solution (1×). The layers were separated and the organic layer was dried over Na_2SO_4 and gravity filtered. The solvent was removed under reduced pressure and the

residue was subjected to column chromatography (20% ethyl acetate / hexanes) to afford **24** (0.90 g, 75%) as an off-white solid. R_f = 0.40 (30% ethyl acetate / hexanes); mp 92–93 °C; IR (neat) ν = 1753 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 9.26 (s, 1H), 7.44 (d, J = 8.5 Hz, 1H), 7.35 (t, J = 8.1 Hz, 1H), 7.13 (d, J = 8.4 Hz, 1H), 7.10 (d, J = 7.7 Hz, 1H), 6.85 (d, J = 8.4 Hz, 1H), 5.45 (s, 2H), 3.58 (s, 3H), 2.42 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.91, 153.83, 152.28, 138.69, 129.30, 126.57, 119.98, 115.92, 115.73, 109.51, 108.38, 95.75, 56.87, 20.94; APCI-(−)-MS *m/z* (%) 261 (100, $[M–H]^-$); HRMS [EI-(+)] calcd for $C_{14}H_{14}O_5$ 262.0841, found 262.0844.

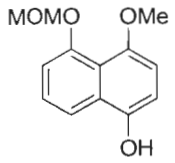
1-Acetoxy-4-methoxy-5-(methoxymethoxy)naphthalene (25).



To a solution of **24** (1.00 g, 3.82 mmol) in acetone (20 mL) was added K_2CO_3 (2.63 g, 19.0 mmol) and Me_2SO_4 (3.85 g, 30.5 mmol) and the mixture was heated at reflux for 16 h. The reaction mixture was cooled to room temperature and gravity filtered. The solvent was removed under reduced pressure and the residue was subjected to column chromatography (10% ethyl acetate / hexanes to remove excess dimethyl sulfate, then 25% ethyl acetate / hexanes to elute the product) and the product was triturated with hexanes (2×5 mL) to afford **25** (1.02 g, 97%) as a colorless solid. R_f = 0.35 (30% ethyl acetate / hexanes); mp 55–57 °C; IR (neat) ν = 1748 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 500

MHz) δ 7.49 (d, J = 8.4 Hz, 1H), 7.40 (t, J = 8.0 Hz, 1H), 7.14 (d, J = 8.8 Hz, 1H), 7.12 (d, J = 8.8 Hz, 1H), 6.81 (d, J = 8.4 Hz, 1H), 5.26 (s, 2H), 3.96 (s, 3H), 3.60 (s, 3H), 2.43 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.86, 154.82, 154.23, 140.02, 130.14, 127.08, 119.37, 118.35, 115.61, 114.11, 105.25, 96.82, 56.59, 56.42, 20.99; ESI-(+)-MS *m/z* (%) 299 (100, $[M+Na]^+$); HRMS [EI-(+)] calcd for $C_{15}H_{16}O_5$ 276.1008, found 276.0995.

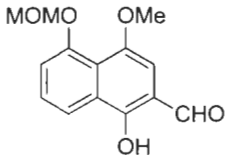
4-Methoxy-5-(methoxymethoxy)-1-naphthol (26).



A 0 °C solution of **25** (2.20 g, 7.97 mmol) in methanol (25 mL) was purged with nitrogen for 15 min and then K_2CO_3 (1.21 g, 8.75 mmol) was added in one portion. The resulting mixture was stirred at room temperature for 20 min and the solvent was removed under reduced pressure. Cold deionized water (50 mL) was added slowly to the residue and the resulting mixture was extracted with ethyl acetate (3×). The combined organic layers were dried over Na_2SO_4 and gravity filtered. The solvent was removed under reduced pressure and the residue was subjected to column chromatography (25 % ethyl acetate / hexanes) to afford **26** (1.50 g, 80%) as an off-white solid. R_f = 0.30 (30% ethyl acetate / hexanes); mp 108–111 °C; IR (neat) ν = 3413 (br, s) cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.86 (d, J = 8.4 Hz, 1H), 7.40 (t, J = 8.0 Hz, 1H), 7.14 (d, J = 7.6 Hz, 1H), 6.75 (d, J = 8.2 Hz, 1H), 6.72 (d, J = 8.3 Hz, 1H), 5.26 (s, 2H), 4.94 (s, 1H), 3.91 (s, 3H), 3.61 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.70, 150.80, 145.40, 127.83, 125.90, 119.63,

116.47, 114.47, 108.63, 107.20, 96.99, 57.38, 56.44; APCI-(−)-MS *m/z* (%) 233 (100, $[M-H]^-$); HRMS [EI-(+)] calcd for $C_{13}H_{14}O_4$ 234.0892, found 234.0887.

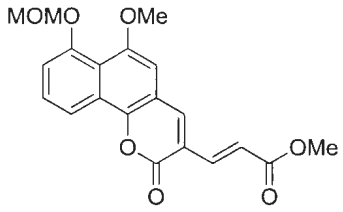
1-Hydroxy-4-methoxy-5-(methoxymethoxy)-2-naphthaldehyde (9).



Acetonitrile (21 mL) was purged with nitrogen for a period of 15 min and then **26** (0.70 g, 3.0 mmol) was added, followed by paraformaldehyde (0.62 g, 21 mmol) and triethylamine (1.50 g, 14.9 mmol). The resulting mixture was heated at 60 °C for 2 h with vigorous stirring. The reaction mixture was cooled to 0 °C and diluted with cold ethyl acetate (30 mL). To the resulting mixture was added slowly cold saturated aqueous NH_4Cl solution (20 mL), followed by cold aqueous 1.0 M HCl solution (10 mL). The layers were separated and the aqueous layer was washed with ethyl acetate (2×). The combined organic layers were dried over Na_2SO_4 and gravity filtered. The solvent was removed under reduced pressure and the residue was subjected to column chromatography (30% ethyl acetate / hexanes). The product was triturated with hexanes (2×3 mL) to afford **9** (0.49 g, 63%) as a yellow solid. R_f = 0.40 (30% ethyl acetate / hexanes); mp 91–94 °C, IR (neat) ν = 1646 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 12.24 (s, 1H), 9.93 (s, 1H), 8.19 (dd, J = 8.4, 1.2 Hz, 1H), 7.49 (t, J = 8.0 Hz, 1H), 7.35 (dd, J = 7.7, 1.2 Hz, 1H), 6.83 (s, 1H), 5.26 (s, 2H), 3.96 (s, 3H), 3.61 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 195.85, 156.16, 153.80, 149.75, 128.12, 127.00, 123.14, 119.09,

119.05, 113.24, 105.10, 97.05, 57.11, 56.51; APCI-(−)-MS *m/z* (%) 261 (100, $[M-1]^-$); HRMS [EI-(+)] calcd for $C_{14}H_{14}O_5$ 262.0841, found 262.0844.

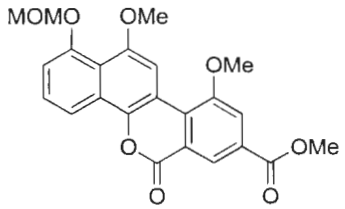
Methyl (*E*)-4-methoxy-5-(methoxymethoxy)-3-(6*H*-naphtho[1,2-*b*]pyran-6-on-5-yl)acrylate (7).



To a solution of **9** (0.78 g, 3.0 mmol) and dimethyl glutaconate (**10**) (0.94 g, 5.9 mmol) in THF (15 mL) was added piperidine (0.26 g, 3.0 mmol) and the resulting mixture was stirred at room temperature for 1 h and then heated at 70 °C for 3 h. The reaction mixture was cooled to room temperature, diluted with $CHCl_3$ (350 mL) and washed with cold aqueous 1.0 M HCl solution (1×). The layers were separated and the organic layer was dried over Na_2SO_4 and gravity filtered. The solvent was removed under reduced pressure and the residue was slurried with diethyl ether (20 mL), stirred for 10 min and vacuum filtered. This process (ether addition, stirring and filtration) was repeated to afford **7** (0.96 g, 87%) as a yellow solid. R_f = 0.30 (50% ethyl acetate / hexanes); mp 184–187 °C; IR (neat) ν = 1714 (m), 1697 (s), 998 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.26 (d, J = 8.3 Hz, 1H), 7.90 (s, 1H), 7.62 (d, J = 15.9 Hz, 1H), 7.57 (t, J = 8.1 Hz, 1H), 7.30 (d, J = 7.5 Hz, 1H), 7.17 (d, J = 15.8 Hz, 1H), 6.74 (s, 1H), 5.29 (s, 2H), 4.01 (s, 3H), 3.83 (s. 3H), 3.61 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.56, 159.17, 154.30, 153.93, 145.76,

143.95, 138.30, 128.28, 126.23, 122.88, 122.16, 120.47, 117.17, 117.08, 114.52, 101.41, 96.80, 56.62, 56.55, 51.88; APCI-(+)-MS *m/z* (%) 371 (50, $[M+H]^+$, 50), 339 (100); HRMS [CI-(+)] calcd for $C_{20}H_{19}O_7$ 371.1131, found 371.1136.

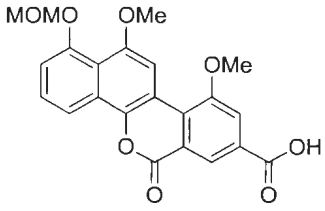
10,12-Dimethoxy-1-(methoxymethoxy)-6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-one-8-carboxylic acid methyl ester (6).



A mixture of dimethoxyacetaldehyde (2.35 g, 13.5 mmol, 60% solution in water) and piperidine (0.92 g, 11 mmol) in benzene (40 mL) was heated at reflux for 1 h using a Dean-Stark apparatus. Approximately 30 mL of solvent was removed from the reaction flask through the Dean-Stark apparatus. The reaction mixture was cooled to room temperature and **7** (0.50 g, 1.4 mmol) was added in one portion. The resulting mixture was then heated at reflux for 48 h. The reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure. The residue was dissolved in $CHCl_3$ (400 mL) and washed with water (1×). The organic layer was dried over Na_2SO_4 and gravity filtered. The solvent was removed under reduced pressure and the residue was subjected to column chromatography (5% methanol / $CHCl_3$). Diethyl ether (20 mL) was added to the residue and the mixture was stirred well for 10 min and vacuum filtered. This process (ether addition to the solids, stirring and filtration) was repeated to afford **6**

(0.51 g, 89%) as an orange solid. R_f = 0.30 (50% ethyl acetate / hexanes); mp 222–225 °C; IR (neat) ν = 1735 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.76 (d, J = 1.7 Hz, 1H), 8.41 (s, 1H), 8.30 (d, J = 8.4 Hz, 1H), 7.94 (d, J = 1.7 Hz, 1H), 7.52 (t, J = 8.1 Hz, 1H), 7.26–7.24 (m, 1H), 5.30 (s, 2H), 4.15 (s, 3H), 4.03 (s, 3H), 3.99 (s, 3H), 3.63 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.86, 160.76, 157.56, 153.88, 152.87, 142.18, 130.71, 128.43, 127.63, 126.83, 124.48, 123.53, 119.64, 117.28, 116.87, 116.10, 112.96, 104.32, 97.09, 56.80, 56.76, 56.74, 52.82; APCI-(+)-MS *m/z* (%) 425 (58, $[M+H]^+$), 393 (100); HRMS [CI-(+)] calcd for $C_{23}H_{21}O_8$ 425.1236, found 425.1248.

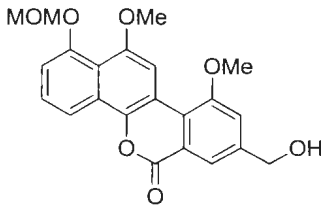
10,12-Dimethoxy-1-(methoxymethoxy)-6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-one-8-carboxylic acid (27).



A suspension of **6** (0.11 g, 0.26 mmol) in 10% KOH / methanol (3.0 mL) was heated at reflux for 2 h. The reaction mixture was cooled to room temperature and the majority of the solvent was removed under reduced pressure. The residue was cooled to 0 °C and cold water (1 mL) was added dropwise to dissolve the residue. The pH was adjusted to ~ 4.0 using cold aqueous 1.0 M HCl solution. The yellow precipitate that formed was isolated by suction filtration. The solids were vacuum dried for 2 h and then dried under air in an oven at 90–100 °C for 12 h to afford **27** (91 mg, 86%) as a pale yellow solid. R_f

= 0.20 (ethyl acetate); mp 197–200 °C; IR (neat) ν = 3300–2400 (br, w), 1733 (m), 1689 (s) cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ 8.41 (d, J = 1.6 Hz, 1H), 8.34 (s, 1H), 8.01 (d, J = 8.4 Hz, 1H), 7.90 (d, J = 1.7 Hz, 1H), 7.57 (t, J = 8.1 Hz, 1H), 7.24 (d, J = 7.7 Hz, 1H), 5.29 (s, 2H), 4.14 (s, 3H), 3.95 (s, 3H), 3.52 (s, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 165.85, 159.60, 157.12, 153.46, 152.18, 140.65, 131.68, 127.72, 126.53, 125.74, 122.66, 118.19, 116.81, 115.39, 114.68, 112.46, 103.22, 95.92, 56.61, 56.06, 56.01; ESI-(−)-MS *m/z* (%) 409 (100, $[M-H]^-$); MALDI-TOF HRMS calcd for $C_{22}H_{18}O_8$ 410.1002, found 410.0991.

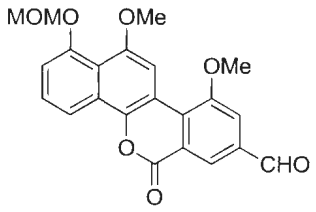
8-(Hydroxymethyl)-10,12-dimethoxy-1-(methoxymethoxy)-6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-one-8-carboxylic acid (28).



To a 0 °C suspension of **27** (80 mg, 0.20 mmol) in THF (8.0 mL) was added $H_3B{\cdot}SMe_2$ (0.60 mL, 1.2 mmol) dropwise over a period of 5 min and the resulting mixture was stirred at room temperature for 5 h. The reaction mixture was cooled to 0 °C, methanol (1 mL) was added dropwise and the solvent was removed under reduced pressure. The residue was dissolved in $CHCl_3$ (20 mL) and the resulting solution was washed with aqueous $NaHCO_3$ solution (1×), dried over Na_2SO_4 and gravity filtered. The solvent was removed under reduced pressure and the residue was subjected to column

chromatography (2% methanol / $CHCl_3$). The product was triturated with ether (2×1 mL) to afford **28** (40 mg, 51%) as a pale yellow solid. R_f = 0.50 (ethyl acetate); mp 165–168 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.24 (d, J = 8.7 Hz, 1H), 8.10 (s, 1H), 7.88 (s, 1H), 7.50 (t, J = 8.1 Hz, 1H), 7.21 (d, J = 7.8 Hz, 1H), 7.06 (s, 1H), 5.30 (s, 2H), 4.69 (s, 2H), 3.94 (s, 3H), 3.89 (s, 3H), 3.67 (s, 3H), 2.55 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.06, 157.09, 153.35, 151.84, 142.78, 140.45, 126.91, 126.48, 122.92, 122.84, 119.53, 118.56, 117.08, 115.96, 114.47, 113.26, 103.79, 97.22, 64.35, 56.61, 56.07, 55.93; APCI-(+)-MS *m/z* (%) 397 (95, $[M+H]^+$), 214 (100); HRMS [EI-(+)] calcd for $C_{22}H_{20}O_7$ 396.1209, found 396.1222.

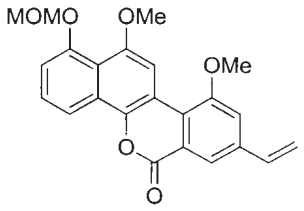
10,12-Dimethoxy-1-(methoxymethoxy)-6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-one-8-carbaldehyde (29).



To a mixture of **28** (60 mg, 0.15 mmol) and Celite® (100 mg) in CH_2Cl_2 (8.0 mL) was added PCC (65 mg, 0.30 mmol) in three portions and the resulting mixture was stirred at room temperature for 3 h. The reaction mixture was gravity filtered and the filter cake was washed throughly with $CHCl_3$. The solvent was removed under reduced pressure and the residue was subjected to column chromatography (2% methanol / $CHCl_3$). The residue was triturated with diethyl ether (2×1 mL) to afford **29** (44 mg, 73%) as a yellow

solid. R_f = 0.40 (50% ethyl acetate / hexanes); mp 200–203 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 10.10 (s, 1H), 8.59 (d, J = 1.6 Hz, 1H), 8.44 (s, 1H), 8.33 (d, J = 8.9 Hz, 1H), 7.81 (d, J = 1.8 Hz, 1H), 7.55 (t, J = 8.5 Hz, 1H), 7.29–7.28 (m, 1H), 5.31 (s, 2H), 4.18 (s, 3H), 4.05 (s, 3H), 3.63 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 190.27, 160.23, 157.87, 153.59, 152.66, 142.29, 136.10, 129.80, 127.48, 127.09, 126.45, 123.57, 119.51, 116.98, 116.04, 112.59, 103.75, 96.72, 56.51, 56.45, 56.40; APCI-(+)-MS *m/z* (%) 395 (52, $[M+H]^+$), 394 (100), 363 (99); HRMS [EI-(+)] calcd for $C_{22}H_{18}O_7$ 394.1053, found 394.1067.

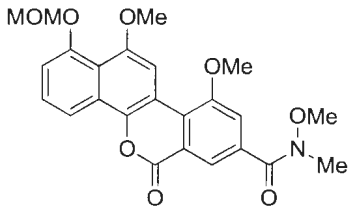
10,12-Dimethoxy-1-(methoxymethoxy)-8-vinyl-6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-one (30).



A mixture of PPh_3MeBr (135 mg, 0.38 mmol) and DBU (68 mg, 0.45 mmol) in CH_2Cl_2 (2.5 mL) was heated at reflux for 1 h. The reaction mixture was cooled to room temperature and **29** (25 mg, 0.06 mmol) was added in one portion. The resulting mixture was stirred at room temperature for 16 h and then heated at reflux for 2 h. The reaction mixture was cooled to room temperature and diluted with $CHCl_3$ (20 mL). The resulting mixture was washed with aqueous 1.0 M HCl solution (1×) and the layers were separated. The organic layer was dried over Na_2SO_4 and gravity filtered. The solvent was removed

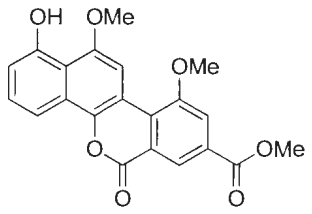
under reduced pressure and the residue was triturated with ether (2×0.5 mL). ^{1}H NMR analysis of the residue showed the presence of starting material (*ca.* 10%), so the material was resubjected to the original reaction conditions using freshly prepared ylide. This time, the reaction mixture was refluxed first for 3 h and then stirred at room temperature for 12 h. The workup was performed as before. The residue was subjected to column chromatography (2% methanol / $CHCl_3$) and the product was triturated with ether (2×1 mL) to afford **30** (19 mg, 76%) as a yellow solid. R_f = 0.60 (50% ethyl acetate / hexanes); mp 184–187 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.44 (s, 1H), 8.33 (d, J = 8.4 Hz, 1H), 8.18 (s, 1H), 7.52 (t, J = 7.8 Hz, 1H), 7.38 (s, 1H), 7.25–7.22 (m, 1H), 6.82 (dd, J = 17.6, 11.1 Hz, 1H), 5.96 (d, J = 18.4 Hz, 1H), 5.45 (d, J = 11.0 Hz, 1H), 5.31 (s, 2H), 4.13 (s, 3H), 4.04 (s, 3H), 3.63 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.29, 157.49, 153.57, 152.48, 140.96, 138.62, 135.38, 127.20, 126.73, 123.86, 123.52, 120.69, 118.84, 116.95, 116.41, 115.45, 114.07, 113.36, 104.34, 96.93, 56.61, 56.51, 56.29; APCI-(+)-MS *m/z* (%) 394 (26), 393 (100, $[M+H]^+$), 392 (29), 363 (8), 362 (23), 361 (87), 346 (4), 279 (9), 217 (8), 215 (8), 214 (56); HRMS [EI-(+)] calcd for $C_{23}H_{20}O_6$ 392.1260, found 392.1272.

_N_,10,12-Trimethoxy-1-(methoxymethoxy)-_N_-methyl-6_H_-benzo[_d_]naphtho[1,2-_b_]pyran-6-one-8-carboxamide (31).



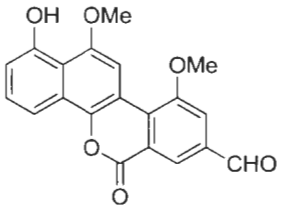
To a solution of EDCI·HCl (23 mg, 0.12 mmol) in CH_2Cl_2 (1.5 mL) was added DIPEA (47 mg, 0.36 mmol) and the resulting mixture was stirred at room temperature for 15 min. Carboxylic acid **27** (25 mg, 0.061 mmol) was added and the resulting mixture was stirred for 30 min. *N*,*O*-Dimethylhydroxylamine hydrochloride (18 mg, 0.18 mmol) was then added in three portions and the reaction mixture was stirred for a further 16 h. The reaction mixture was diluted with $CHCl_3$ (15 mL) and washed with aqueous 1.0 M HCl solution (1×). The layers were separated and the aqueous layer was washed with $CHCl_3$ (2×). The combined organic layers were dried over Na_2SO_4 and gravity filtered. The solvent was removed under reduced pressure and the residue was subjected to column chromatography (1% methanol / $CHCl_3$). The product was triturated with ether (2×0.5 mL) to afford **31** (11 mg, 40%) as a pale yellow solid. R_f = 0.40 (ethyl acetate); mp 134–137 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.52 (d, J = 1.7 Hz, 1H), 8.47 (s, 1H), 8.34 (dd, J = 8.5, 1.1 Hz, 1H), 7.74 (d, J = 1.7 Hz, 1H), 7.53 (t, J = 8.1 Hz, 1H), 7.27–7.24 (m, 1H), 5.31 (s, 2H), 4.15 (s, 3H), 4.05 (s, 3H), 3.66 (s, 3H), 3.63 (s, 3H), 3.44 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.88, 160.76, 157.16, 153.62, 152.62, 141.67, 134.37, 127.36, 126.68, 126.45, 122.97, 122.62, 119.24, 117.04, 116.88, 115.73, 112.89, 104.29, 96.88, 61.45, 56.63, 56.55, 56.52, 33.82; APCI-(+)-MS *m/z* (%) 454 (96, $[M+H]^+$), 422 (100); HRMS [EI-(+)] calcd for $C_{24}H_{23}NO_8$ 453.1424, found 453.1421.

1-Hydroxy-10,12-dimethoxy-6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-one-8-carboxylic acid methyl ester (32).



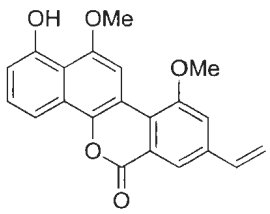
To a –78 °C solution of **6** (100 mg, 0.24 mmol) in CH_2Cl_2 (20 mL) was added BCl_3 (1.0 M solution in CH_2Cl_2, 1.2 mL, 1.2 mmol) dropwise and the resulting mixture was stirred at this temperature for 1 h. The reaction mixture was warmed to room temperature and stirred for an additional 30 min. To this mixture was added cold water (15 mL) and then $CHCl_3$ (25 mL). The layers were separated and the aqueous layer was extracted with $CHCl_3$ (2×). The combined organic layers were dried over Na_2SO_4 and gravity filtered. The solvent was removed under reduced pressure and the residue was subjected to column chromatography (2% methanol / $CHCl_3$). The product was triturated with ether (2×2 mL) to afford **32** (81 mg, 87%) as a yellow solid. R_f = 0.30 (50% ethyl acetate / hexanes); mp 258–261 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.28 (s, 1H), 8.69 (d, J = 1.6 Hz, 1H), 8.26 (s, 1H), 8.03 (d, J = 8.5 Hz, 1H), 7.84 (s, 1H), 7.50 (t, J = 8.0 Hz, 1H), 7.02 (d, J = 7.7 Hz, 1H), 4.12 (s, 3H), 4.11 (s, 3H), 4.00 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.53, 160.40, 157.11, 154.20, 151.96, 142.66, 130.49, 128.76, 127.93, 125.95, 124.20, 123.13, 116.57, 115.32, 113.67, 113.43, 112.10, 101.41, 56.56, 56.05, 52.64; APCI-(+)-MS *m/z* (%) 381 (70, $[M+H]^+$), 214 (100); HRMS [EI-(+)] calcd for $C_{21}H_{16}O_7$ 380.0896, found 380.0905.

1-Hydroxy-10,12-dimethoxy-6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-one-8-carboxaldehyde (33).



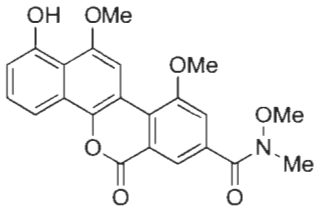
To a –78 °C solution of **29** (11 mg, 0.028 mmol) in CH_2Cl_2 (3.0 mL) was added BCl_3 (1.0 M solution in CH_2Cl_2, 0.25 mL, 0.25 mmol) dropwise and the resulting mixture was stirred at this temperature for 1 h. The reaction mixture was warmed to room temperature and stirred for an additional period of 30 min. To this mixture was added cold water (10 mL) and then $CHCl_3$ (15 mL). The layers were separated and the aqueous layer was extracted with $CHCl_3$ (2×). The combined organic layers were dried over Na_2SO_4 and gravity filtered. The solvent was removed under reduced pressure and the residue was subjected to column chromatography (2% methanol / $CHCl_3$) and the product was triturated with ether (2×1 mL) to afford **33** (8 mg, 82%) as a yellow solid. R_f = 0.45 (50% ethyl acetate / hexanes); mp 269–271 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.11 (s, 1H), 9.35 (s, 1H), 8.61 (s, 1H), 8.41 (s, 1H), 8.12 (d, J = 8.4 Hz, 1H), 7.83 (s, 1H), 7.55 (d, J = 8.1 Hz, 1H), 7.08 (d, J = 7.6 Hz, 1H), 4.19 (s, 3H), 4.17 (s, 3H); APCI-(+)-MS *m/z* (%) 351 (16, $[M+H]^+$), 214 (100); HRMS [EI-(+)] calcd for $C_{20}H_{14}O_6$ 350.0790, found 350.0799.

1-Hydroxy-10,12-dimethoxy-8-vinyl-6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-one (defucogilvocarcin V) (5c).



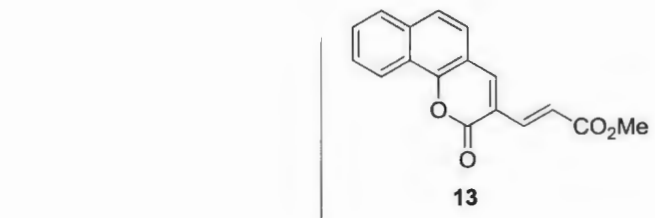
To a –78 °C solution of **30** (14 mg, 0.035 mmol) in CH_2Cl_2 (4.0 mL) was added BCl_3 (1.0 M solution in CH_2Cl_2, 0.30 mL, 0.30 mmol) dropwise and the resulting mixture was stirred at this temperature for 1 h. The reaction mixture was warmed to room temperature and stirred for an additional min. To this mixture was added cold water (10 mL) and then $CHCl_3$ (15 mL). The layers were separated and the aqueous layer was extracted with $CHCl_3$ (2×). The combined organic layers were dried over Na_2SO_4 and gravity filtered. The solvent was removed under reduced pressure and the residue was subjected to column chromatography (2% methanol / $CHCl_3$). The product was triturated with ether (2×1 mL) to afford **5c** (10 mg, 83%) as a yellow solid. R_f = 0.65 (50% ethyl acetate / hexanes); mp 240–245 °C (lit. mp[15] 253–257 °C); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.30 (s, 1H), 8.22 (s, 1H), 8.08 (s, 1H), 8.03 (d, J = 8.4 Hz, 1H), 7.47 (t, J = 7.9 Hz, 1H), 7.27 (s, 1H), 6.78 (d, J = 7.9 Hz, 1H), 6.76 (dd, J = 17.7, 10.7 Hz, 1H), 5.92 (d, J = 17.5 Hz, 1H), 5.43 (d, J = 10.9 Hz, 1H), 4.07 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.08, 157.15, 154.16, 151.75, 141.47, 138.57, 135.29, 128.46, 126.03, 123.46, 123.22, 120.51, 116.44, 114.71, 113.85, 113.36, 112.68, 101.42, 56.13, 55.89; APCI-(+)-MS *m/z* (%) 349 (100, $[M+H]^+$); HRMS [EI-(+)] calcd for $C_{21}H_{16}O_5$ 348.0998, found 348.1013.

1-Hydroxy-*N*,10,12-trimethoxy-*N*-methyl-6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-one-8-carboxamide (34).

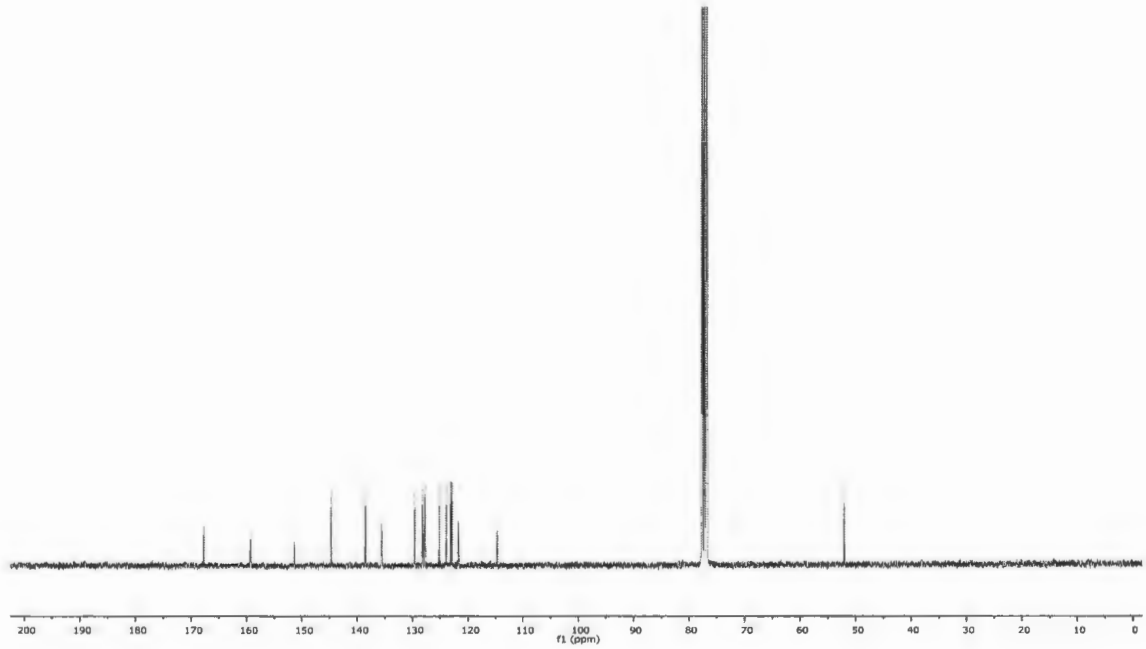


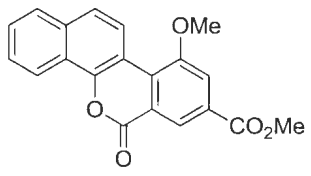
To a –78 °C solution of **31** (9 mg, 0.02 mmol) in CH_2Cl_2 (2.0 mL) was added BCl_3 (1.0 M solution in CH_2Cl_2, 0.20 mL, 0.20 mmol) dropwise and the resulting mixture was stirred at this temperature for 1 h. The reaction mixture was cooled to room temperature and stirred for an additional 30 min. To this mixture was added cold water (10 mL) and then $CHCl_3$ (15 mL). The layers were separated and the aqueous layer was extracted with $CHCl_3$ (2×). The combined organic layers were dried over Na_2SO_4 and gravity filtered. The solvent was removed under reduced pressure and the residue was subjected to column chromatography (1% methanol / $CHCl_3$). The product was triturated with hexanes (2×1 mL) to afford **34** (5 mg, 63%) as a pale yellow solid. R_f = 0.40 (ethyl acetate); mp 178–181 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.35 (s, 1H), 8.51 (d, J = 1.7 Hz, 1H), 8.38 (s, 1H), 8.09 (d, J = 8.4 Hz, 1H), 7.73 (d, J = 1.7 Hz, 1H), 7.52 (t, J = 8.1 Hz, 1H), 7.04 (d, J = 7.8 Hz, 1H), 4.15 (s, 3H), 3.67 (s, 3H), 3.44 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.81, 160.61, 156.99, 154.18, 152.02, 142.44, 134.41, 128.73, 126.31, 126.09, 122.88, 122.68, 116.91, 115.23, 113.70, 113.23, 112.29, 101.64, 99.97, 61.46, 56.55, 56.13, 33.82; APCI-(+)-MS *m/z* (%) 410 (100, $[M+H]^+$); HRMS [EI-(+)] calcd for $C_{22}H_{19}NO_7$ 409.1162, found 409.1153.

5.6 Selected ^{1}H and ^{13}C NMR spectra for Chapter 5



13

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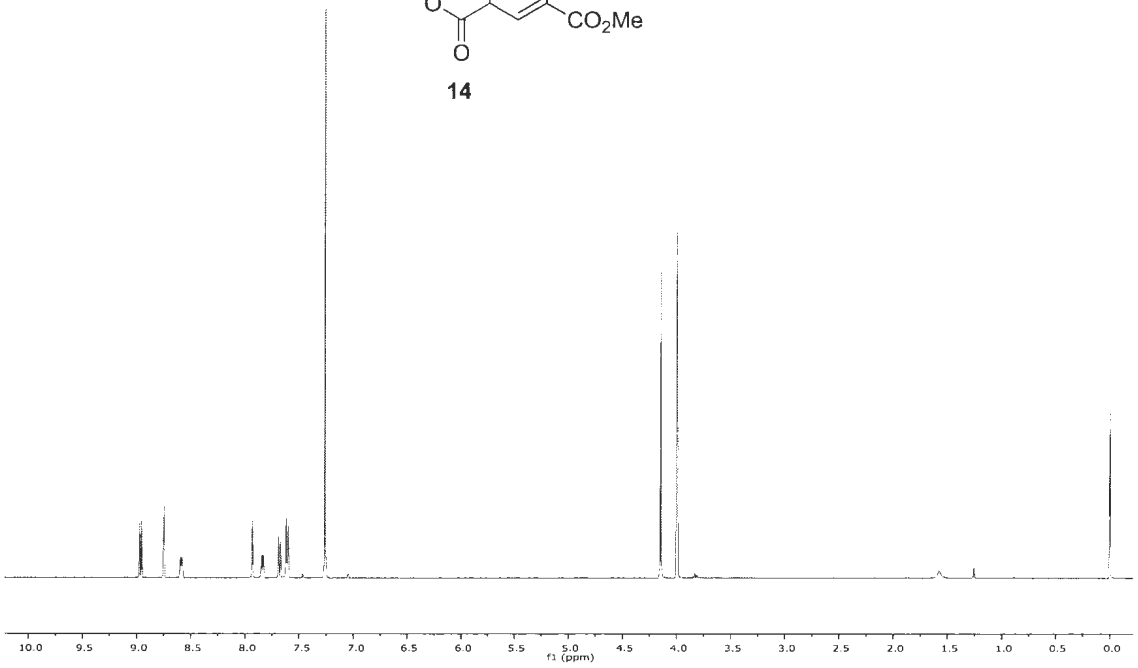
O
O
CO2Me

14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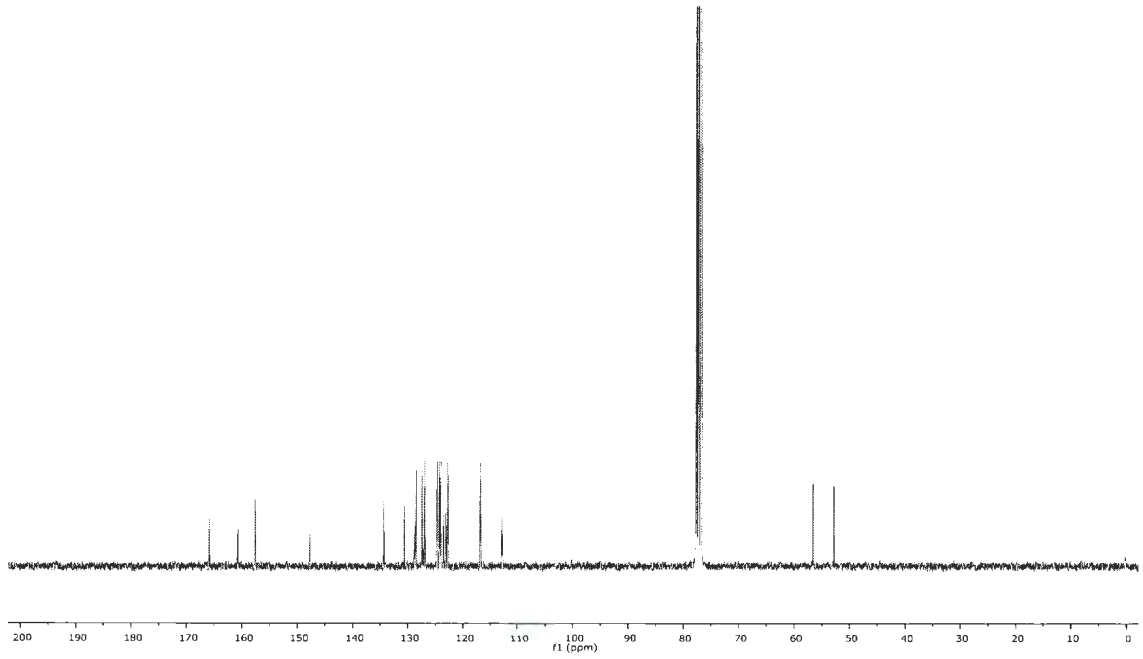
f1 (ppm)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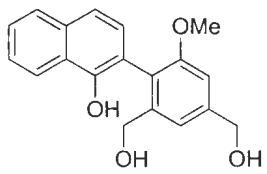
f1 (ppm)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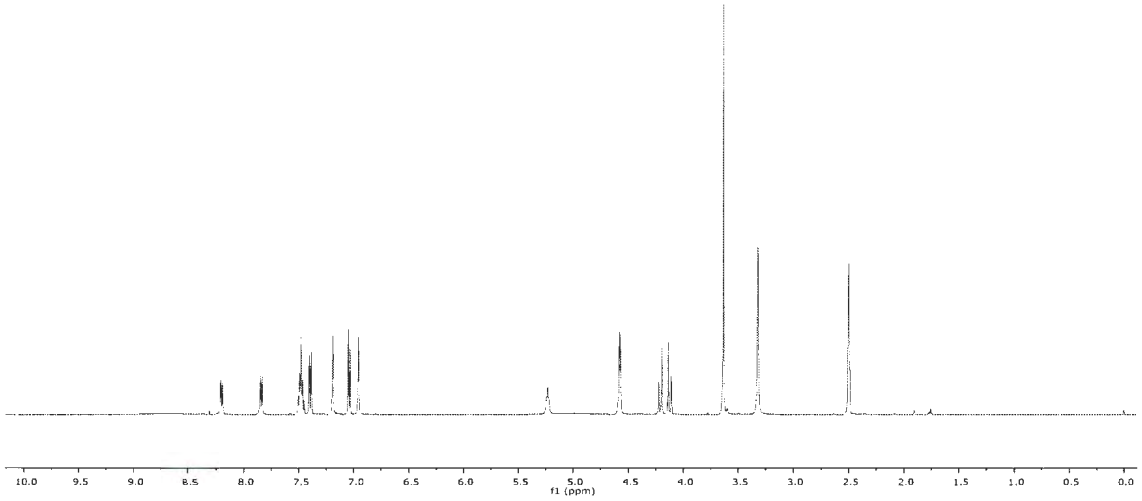
OH
OH
OH

15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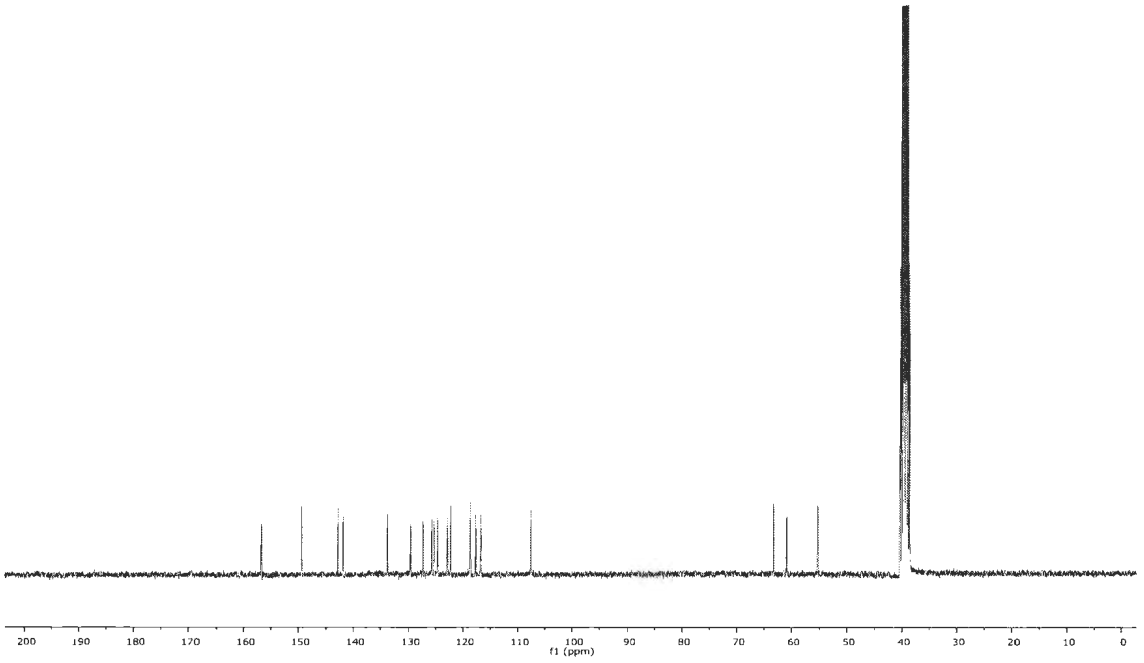
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


200
190
180
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160
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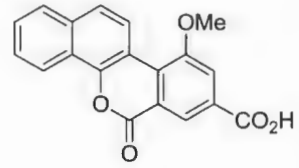
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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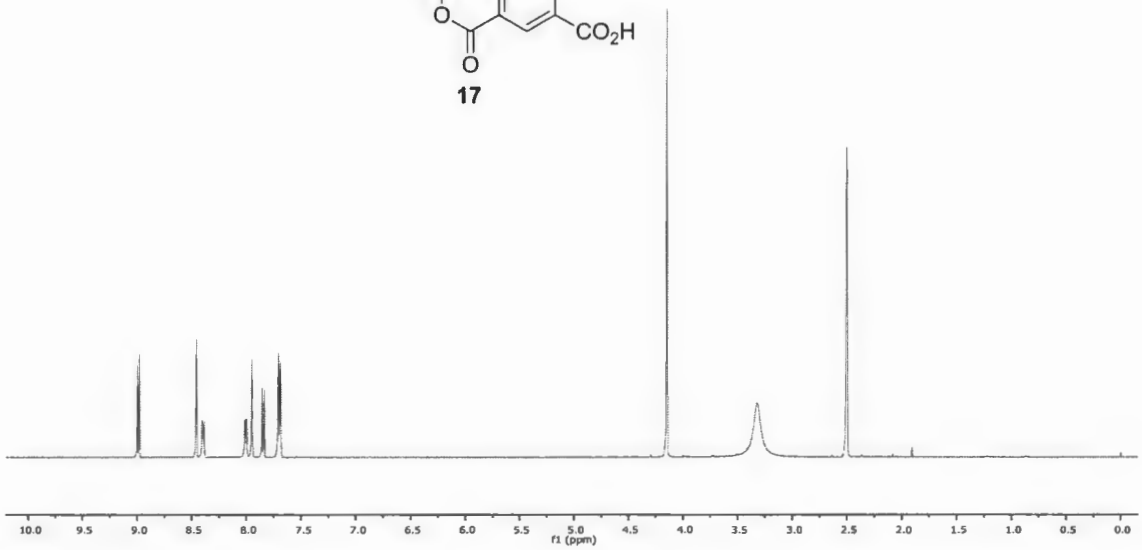
O
O
CO2H

17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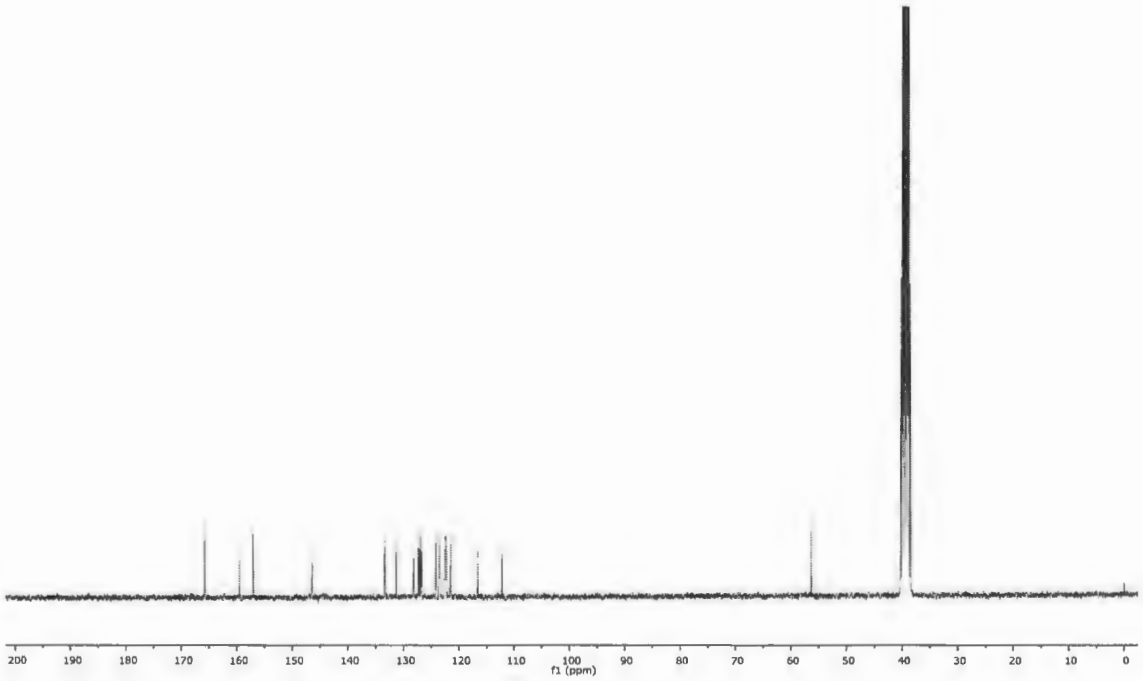
f1 (ppm)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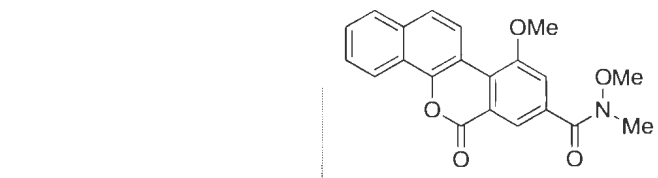
f1 (ppm)


OMe
OMe
N
Me
O
O
O

18

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6.5
6.0
5.5
5.0
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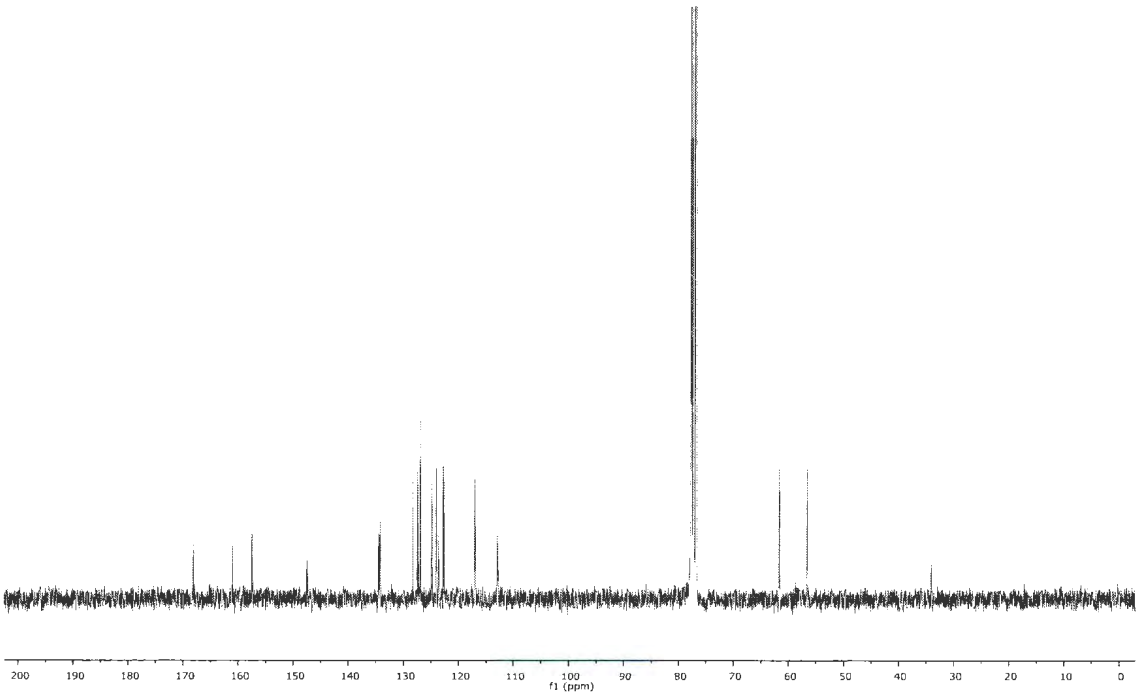
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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100
90
80
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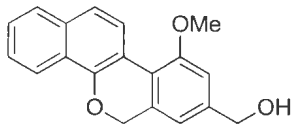
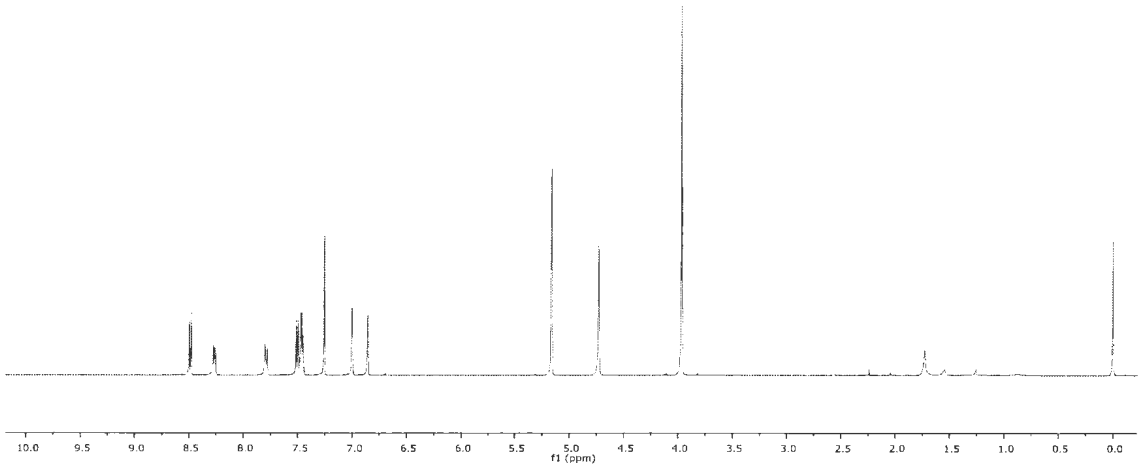
50
40
30
20
10
0
f1 (ppm)


OMe
O
OH

19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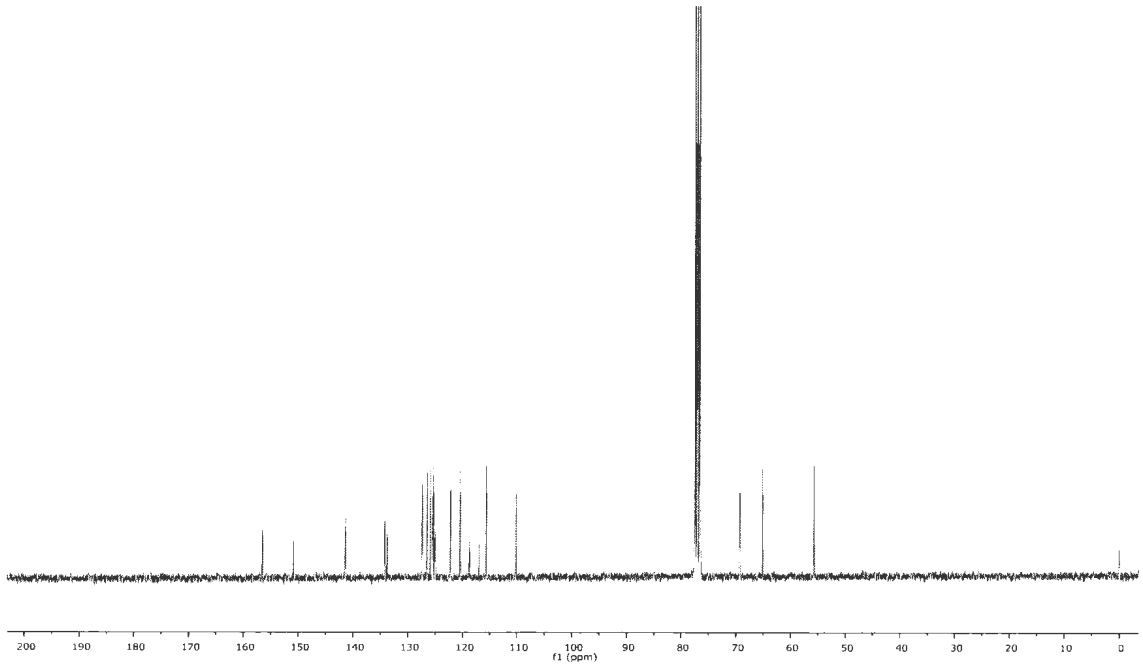
f1 (ppm)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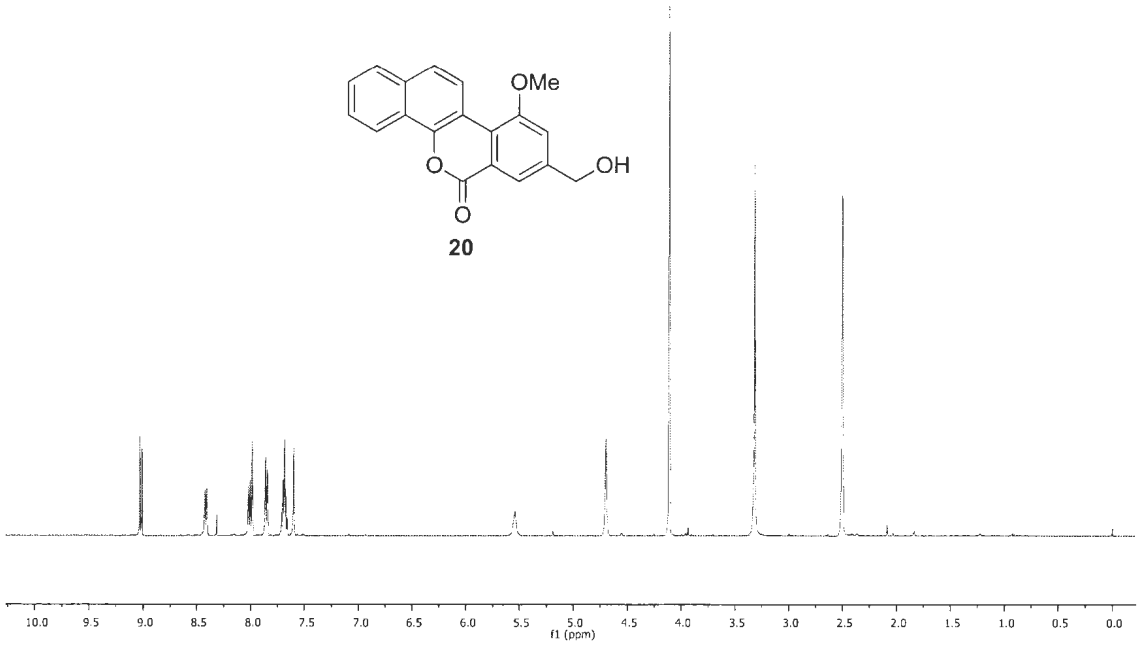
f1 (ppm)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O
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7.5
7.0
6.5
6.0
5.5
5.0
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4.0
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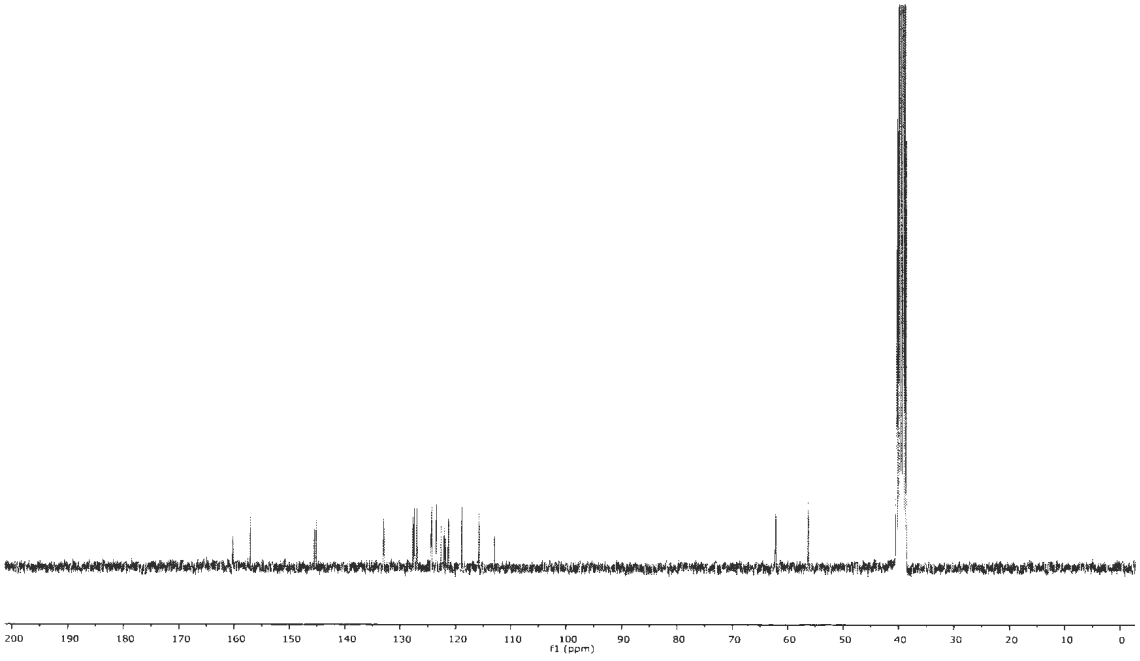
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

20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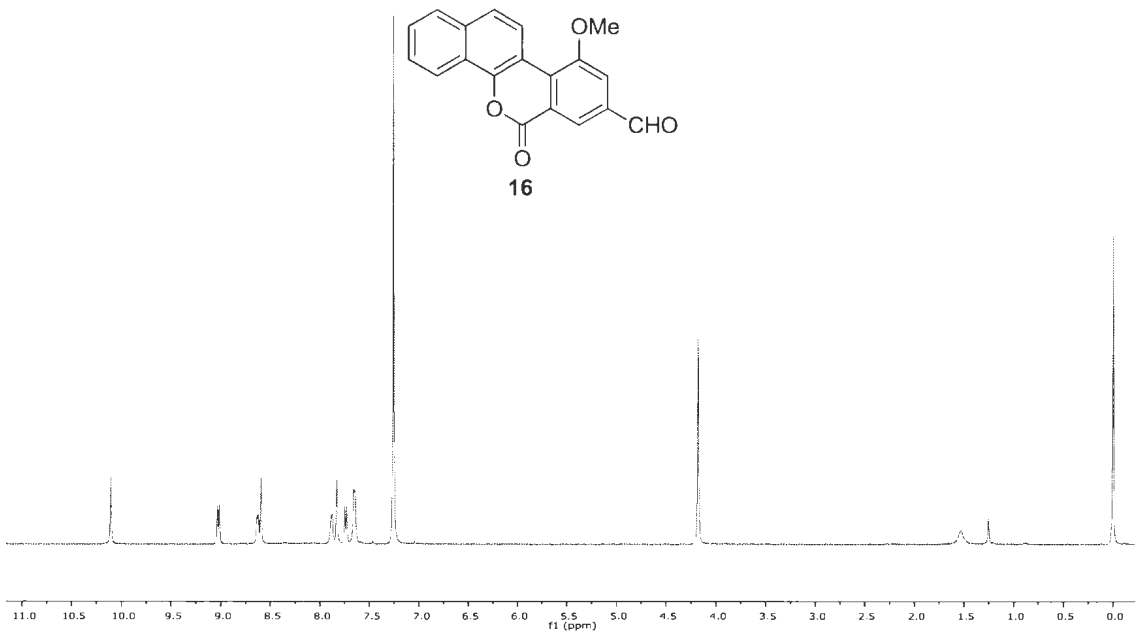
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CHO
O
O
16
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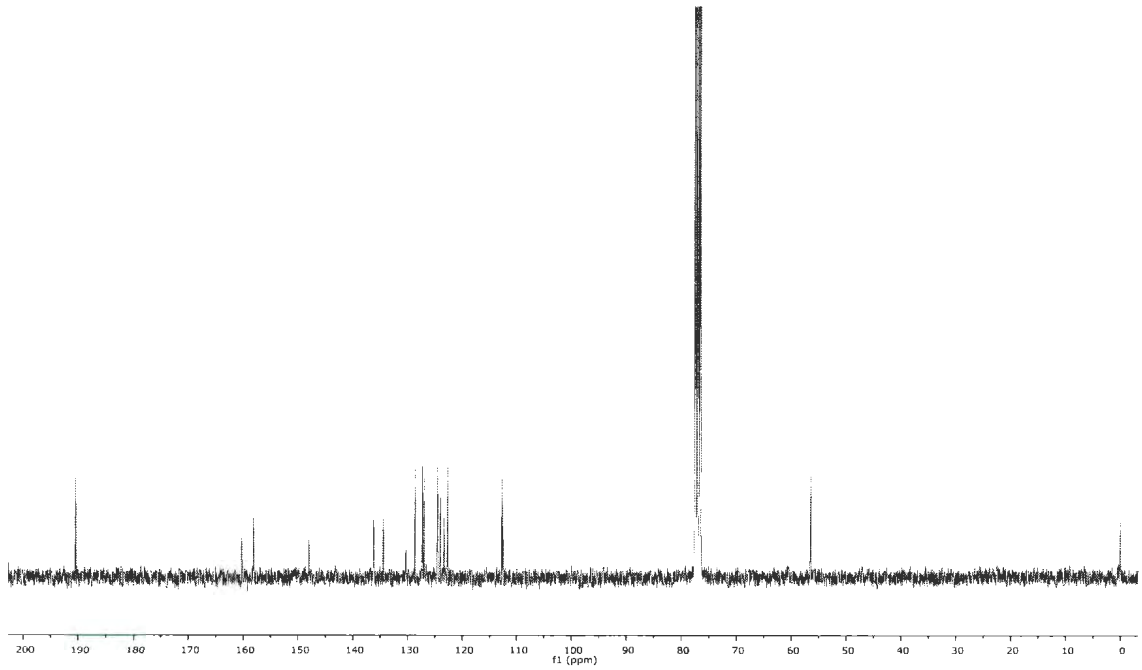
f1 (ppm)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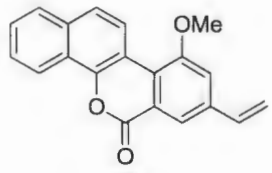
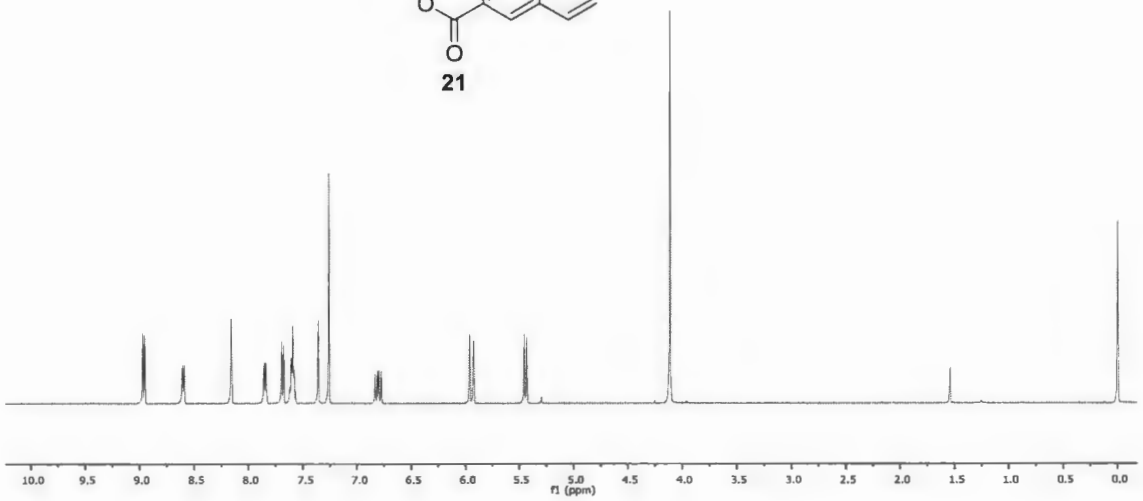
f1 (ppm)


OMe
O
O

21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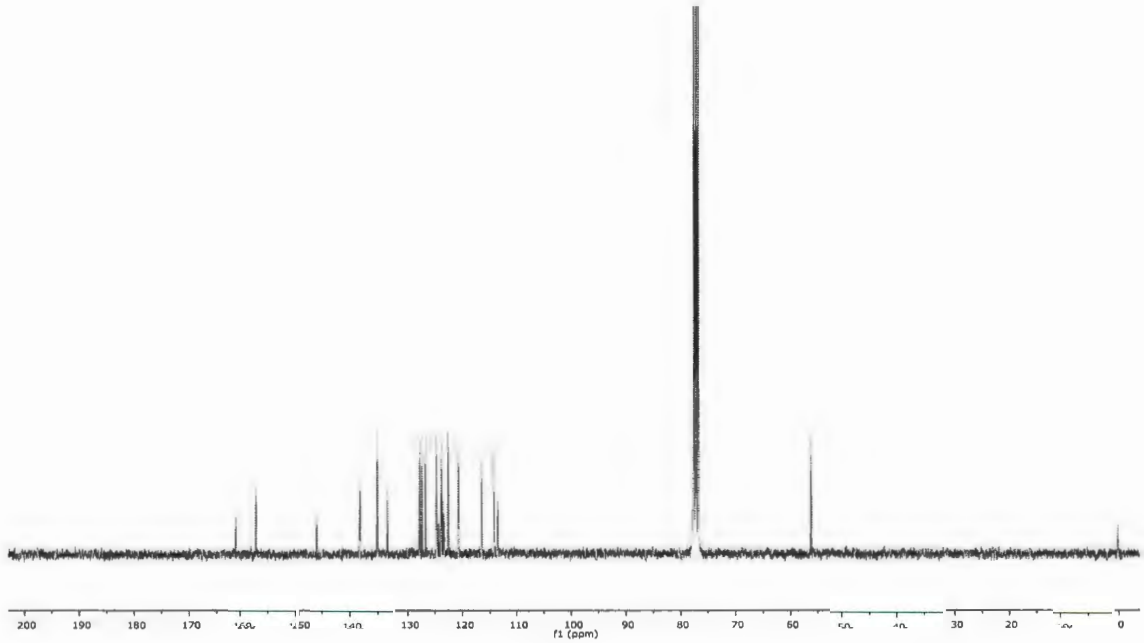
0.0
f1 (ppm)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20
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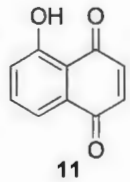
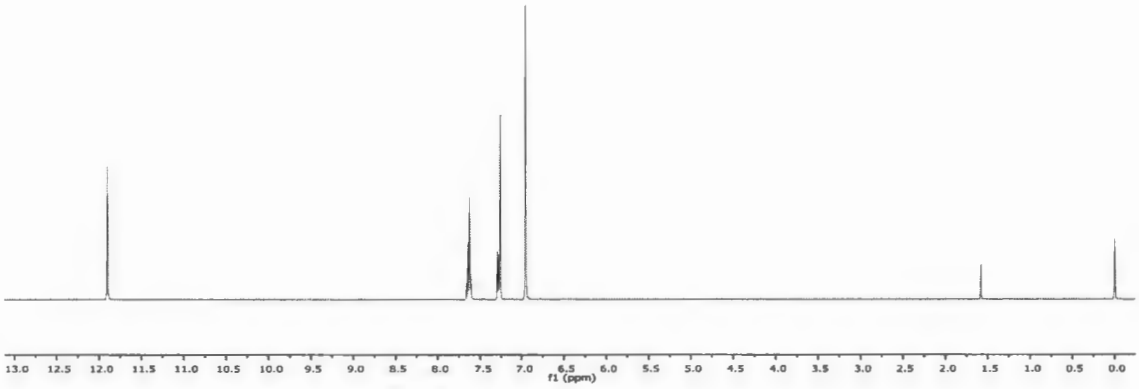
f1 (ppm)


OH
O
O

11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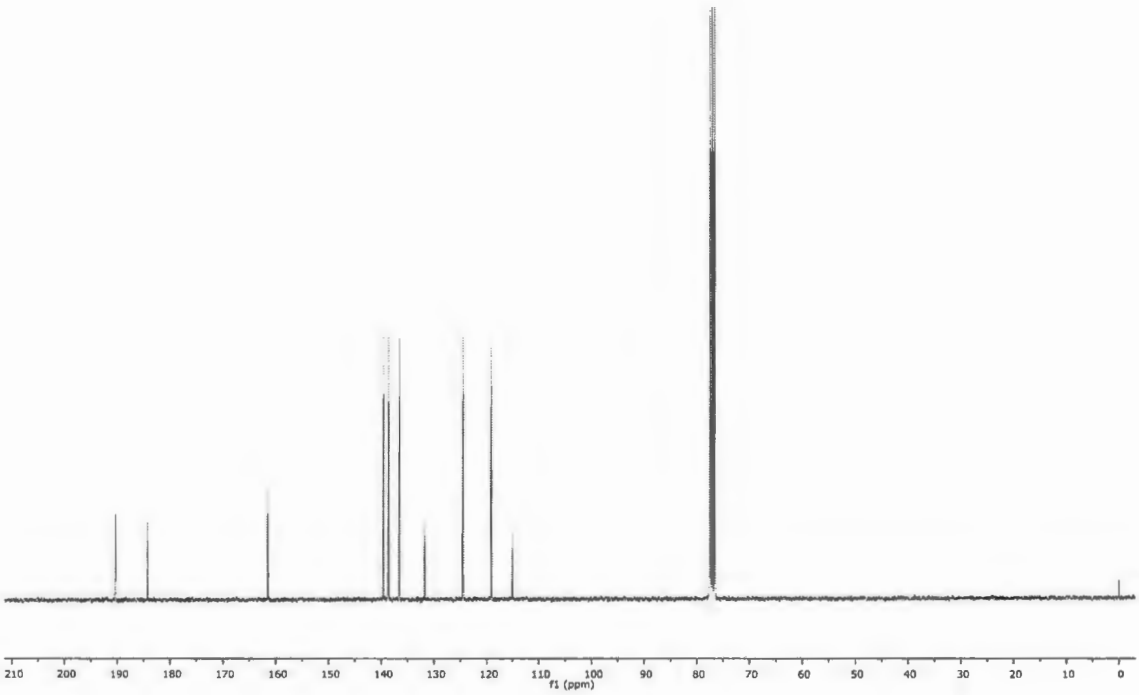
f1 (ppm)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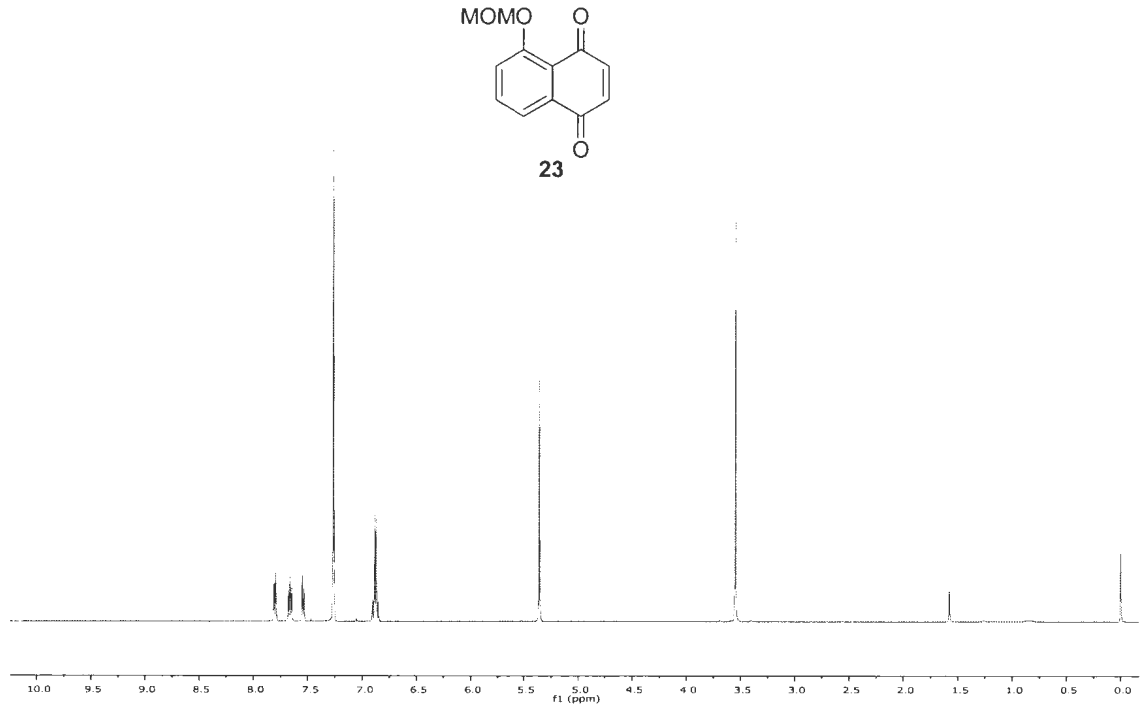
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O
O

23

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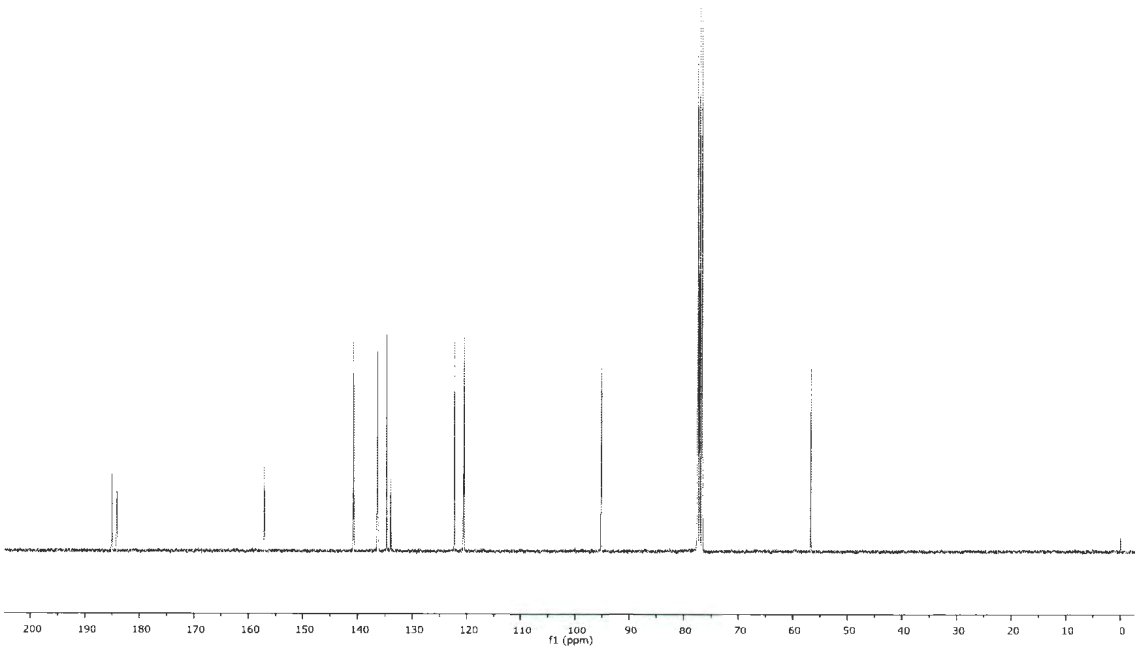
f1 (ppm)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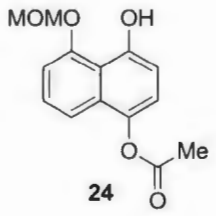
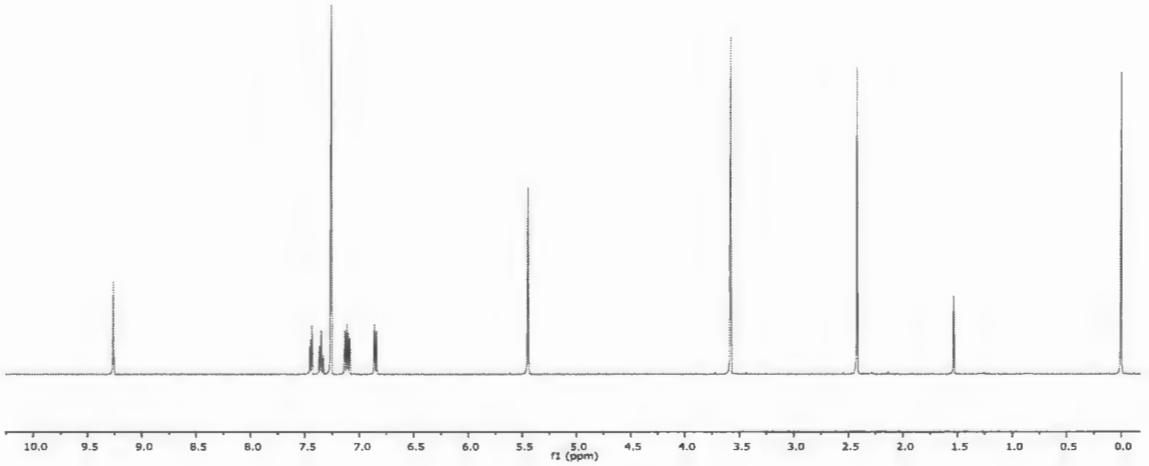

MOMO
OH
O
Me
O

24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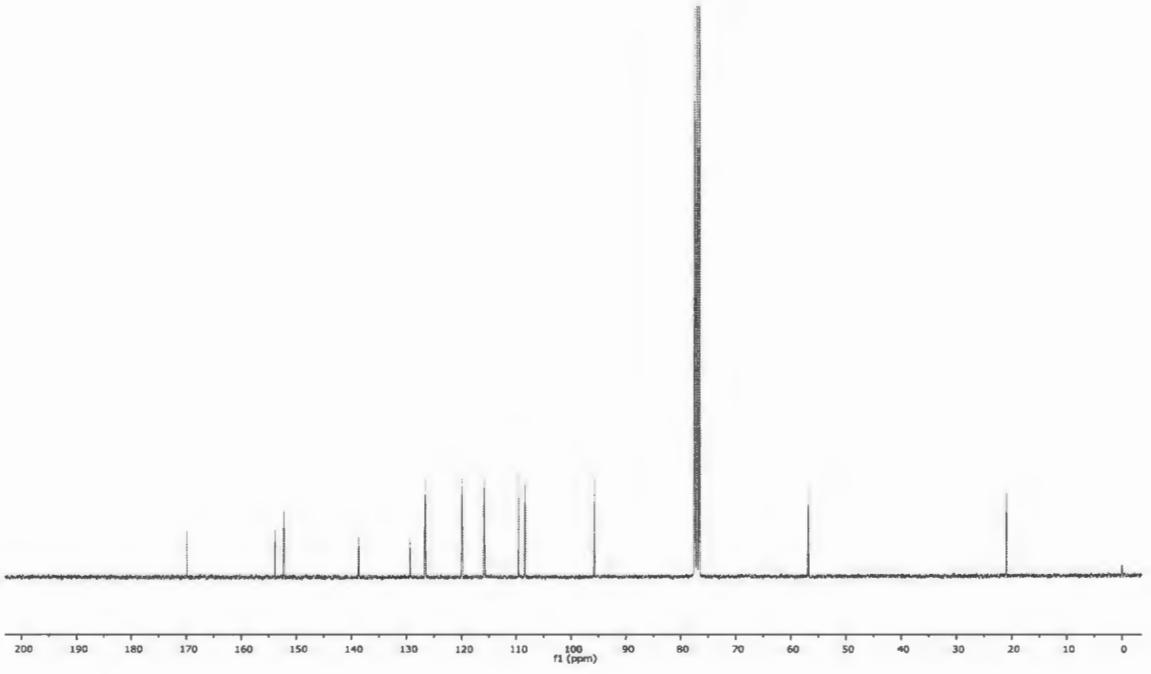
0.0
f1 (ppm)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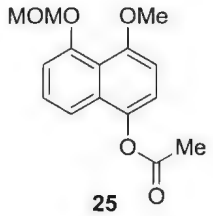
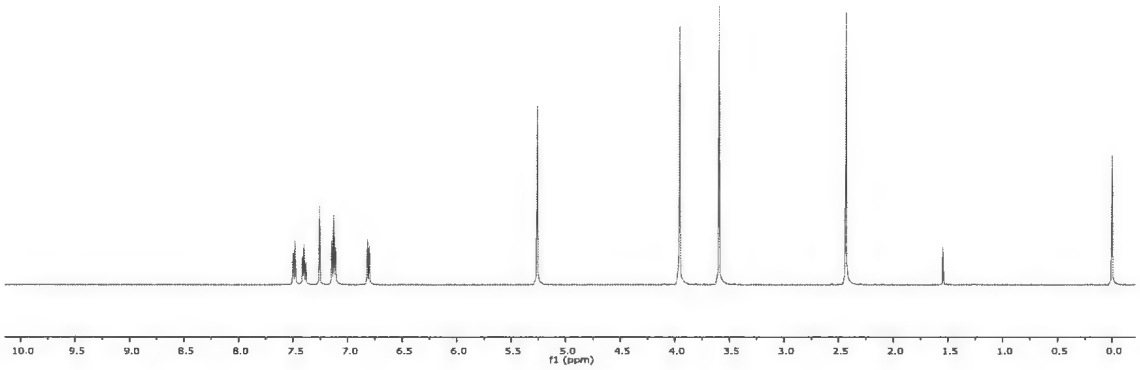
f1 (ppm)


MOMO
OMe
O
Me
O

25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3.0
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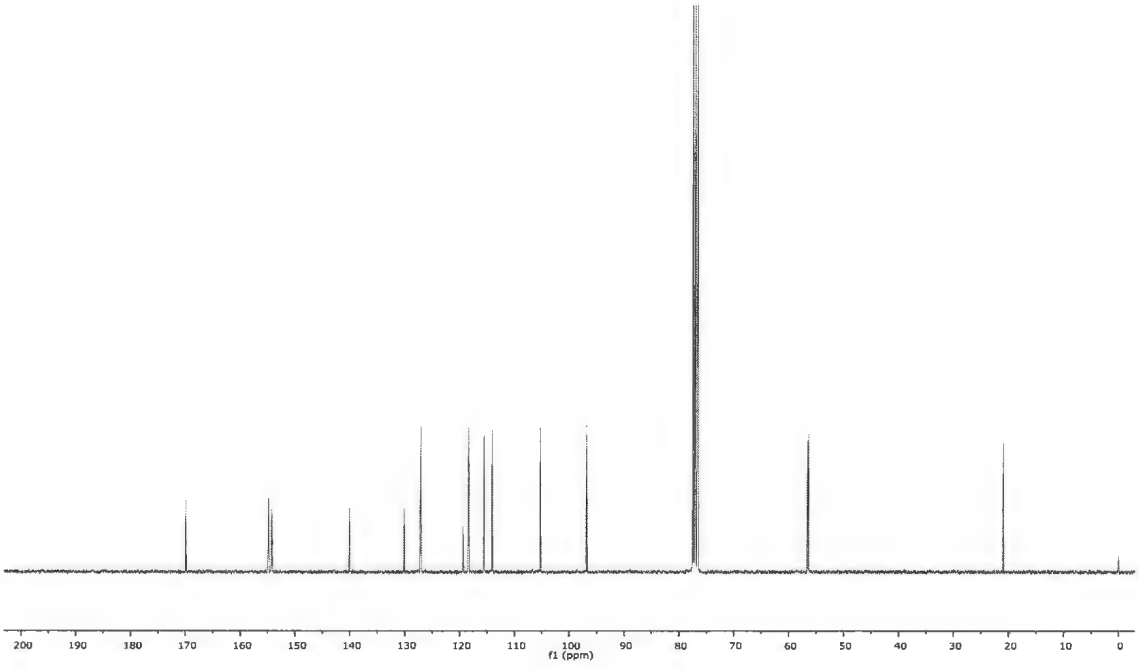
1.0
0.5
0.0
f1 (ppm)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80
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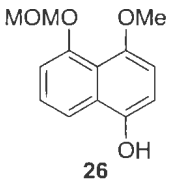
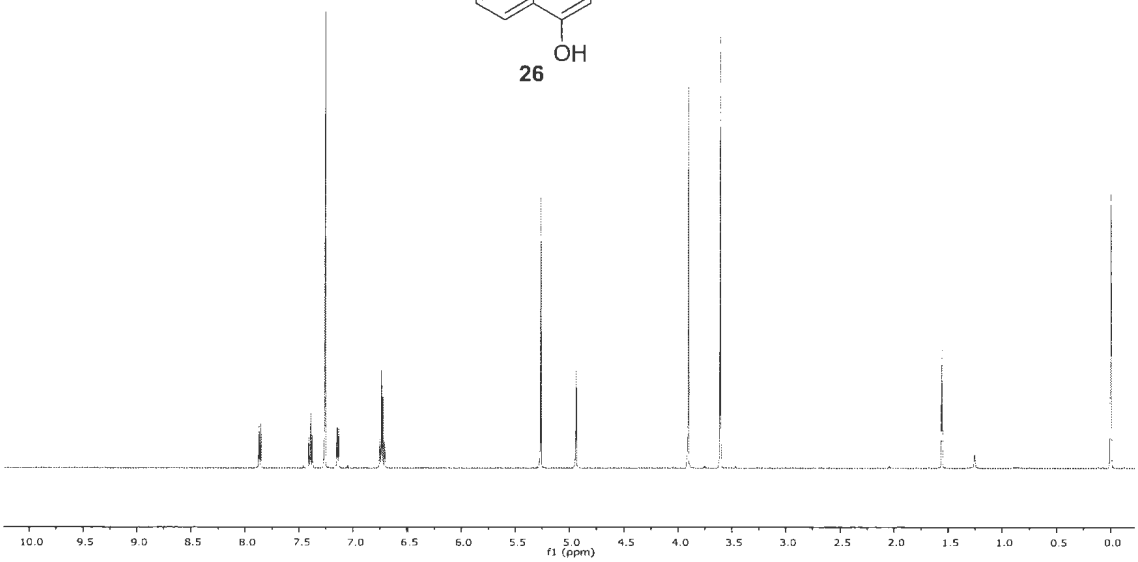
50
40
30
20
10
0
f1 (ppm)


MOMO
OMe
OH

26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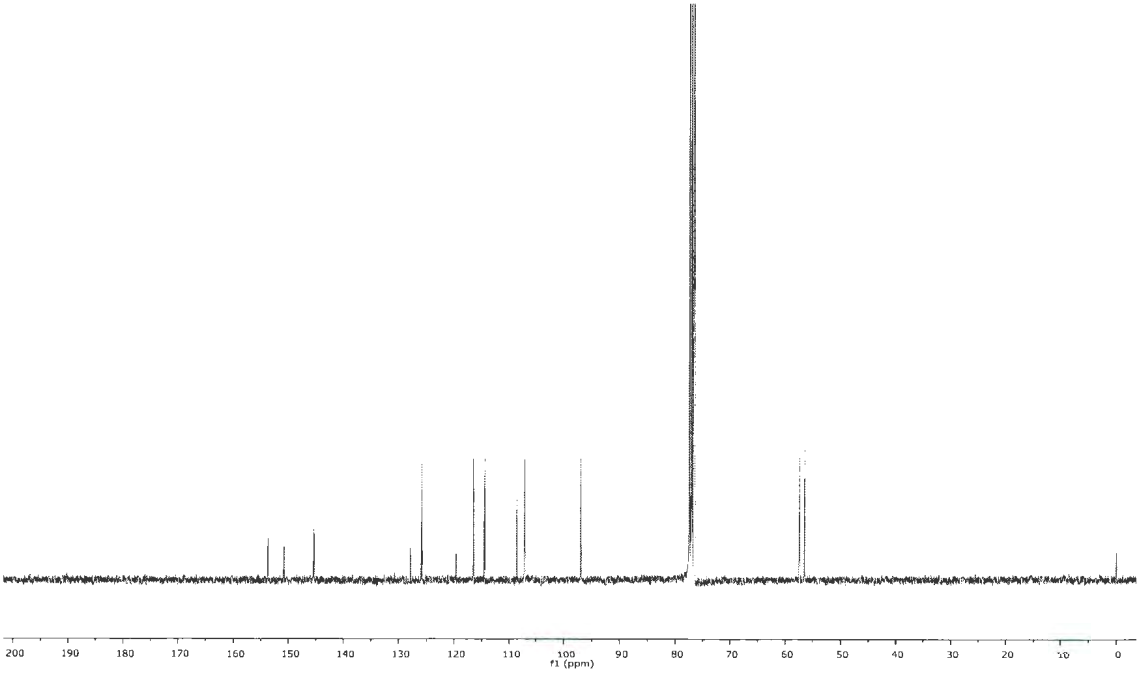
f1 (ppm)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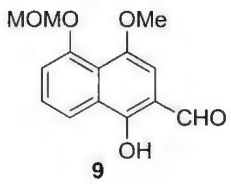
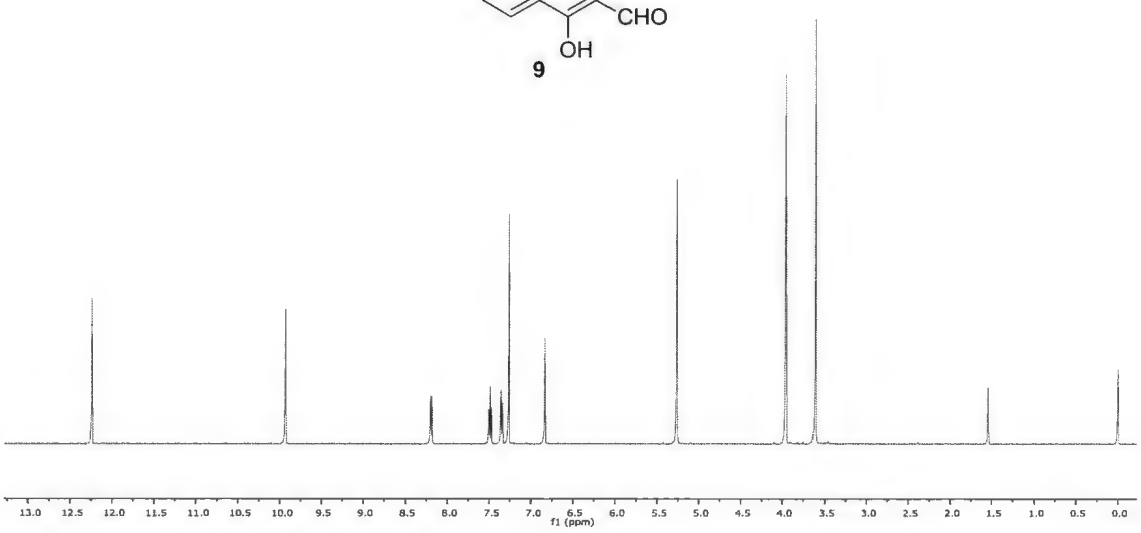
f1 (ppm)


MOMO
OMe
CHO
OH

9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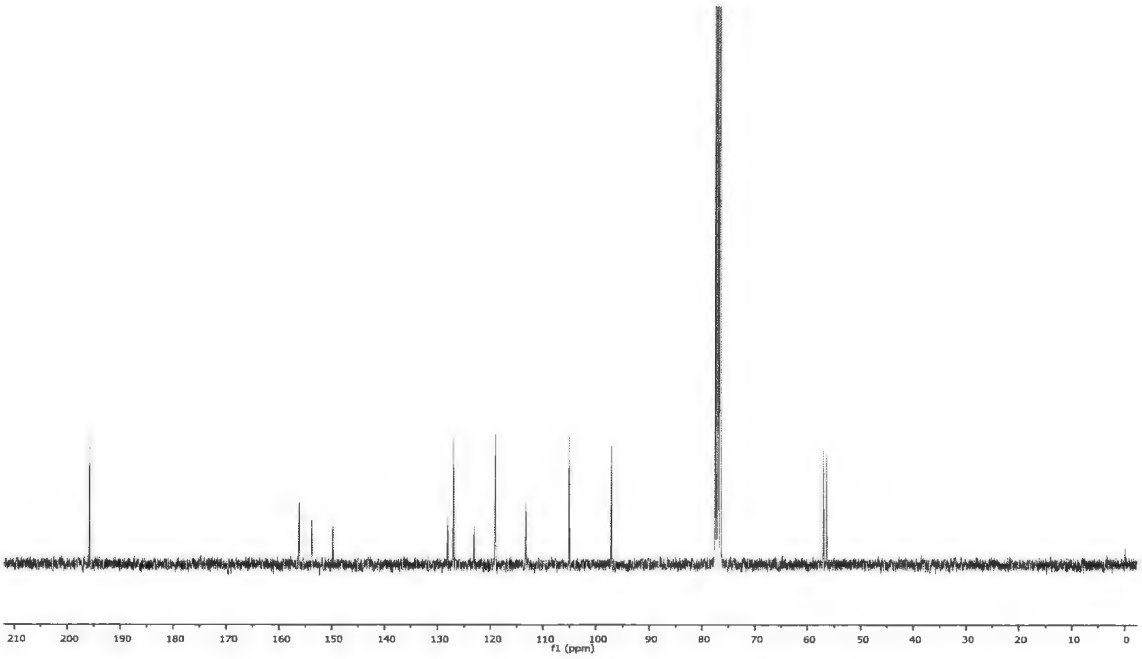
f1 (ppm)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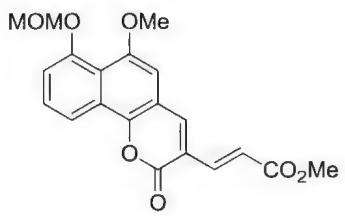
f1 (ppm)


MOMO
OMe
O
O
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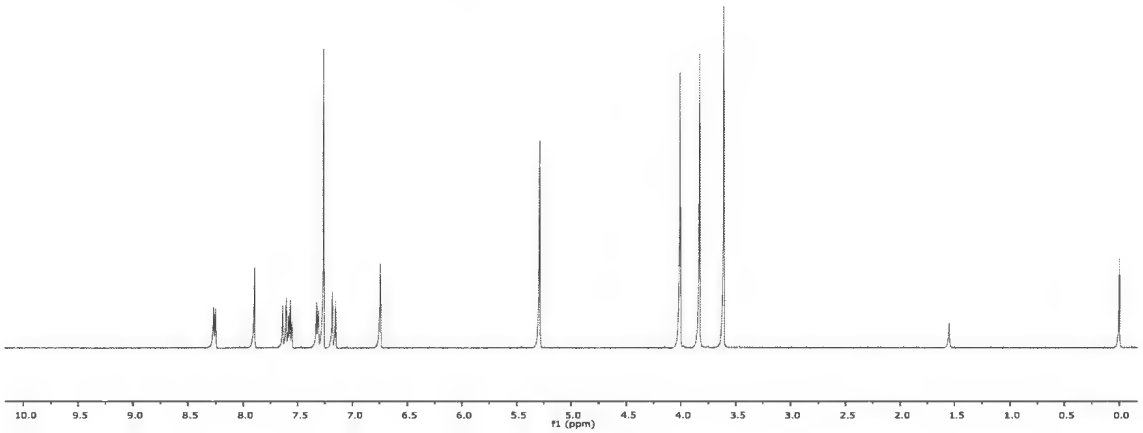
7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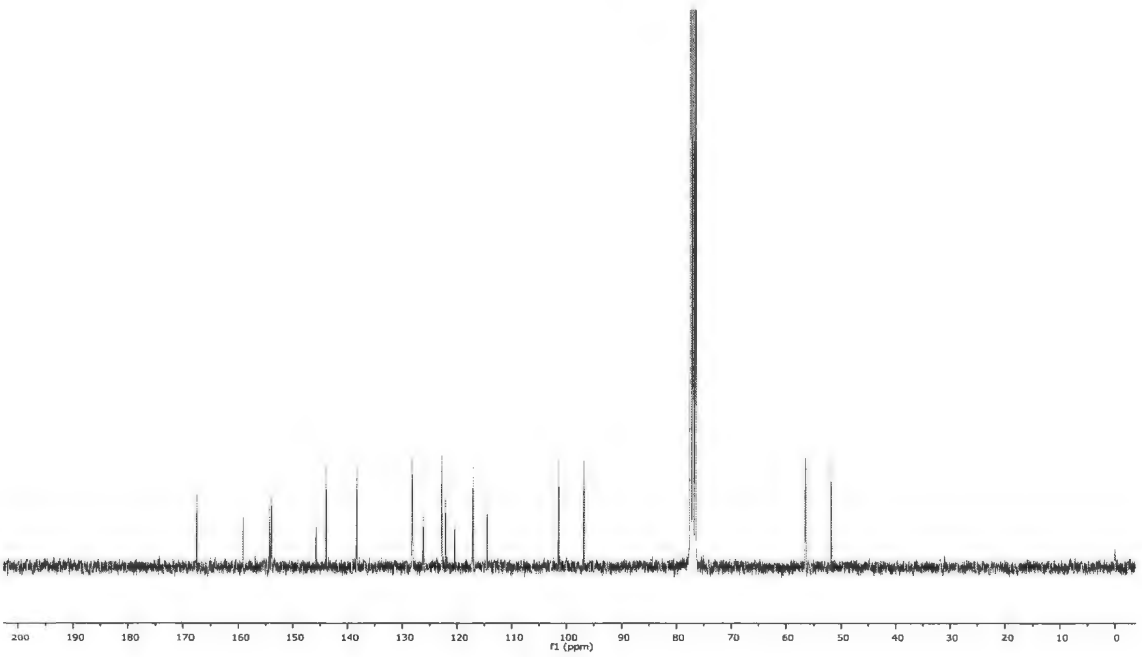
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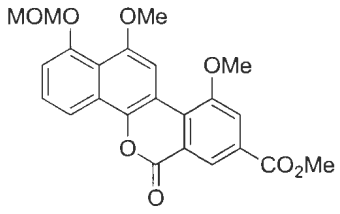
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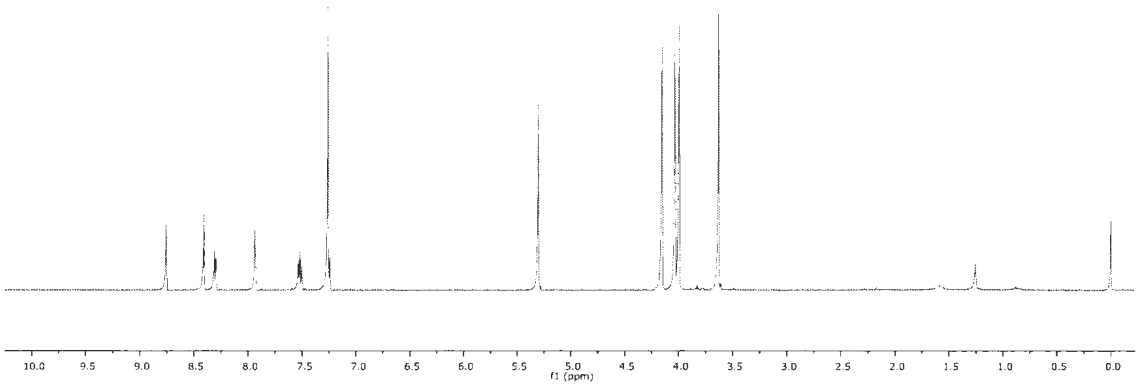
O
CO2Me

6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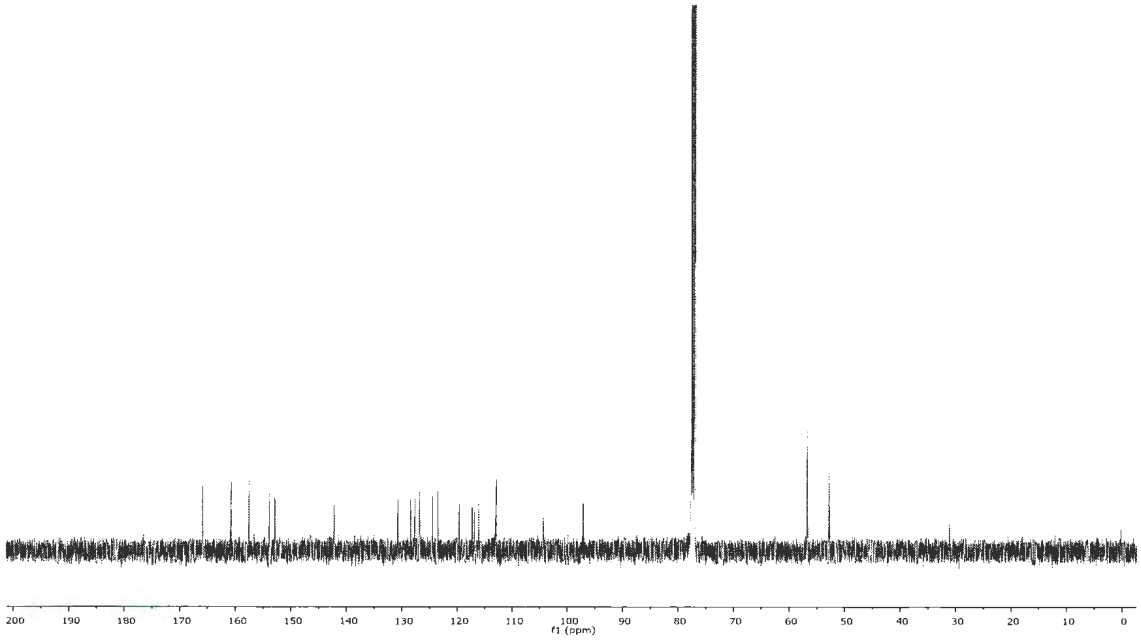
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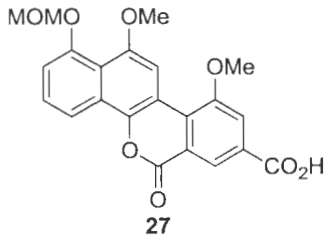
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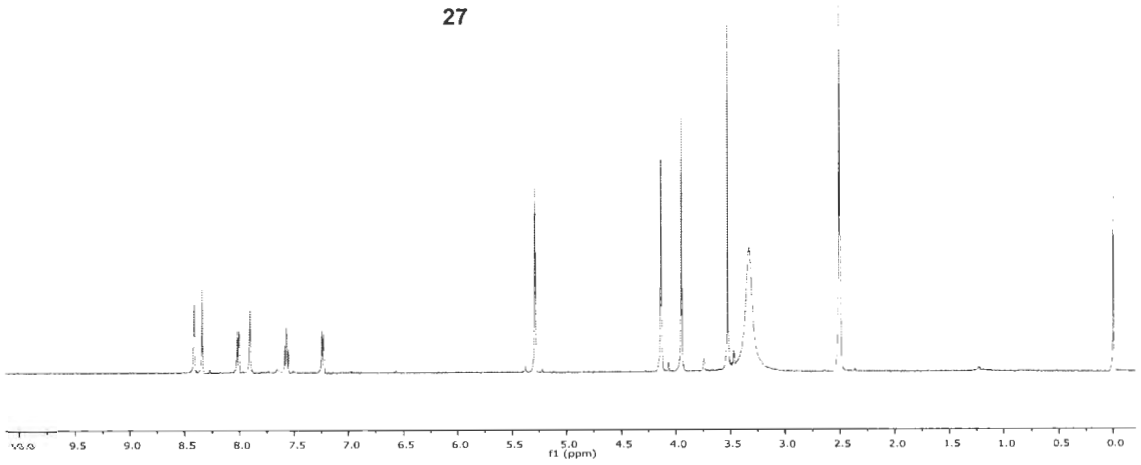
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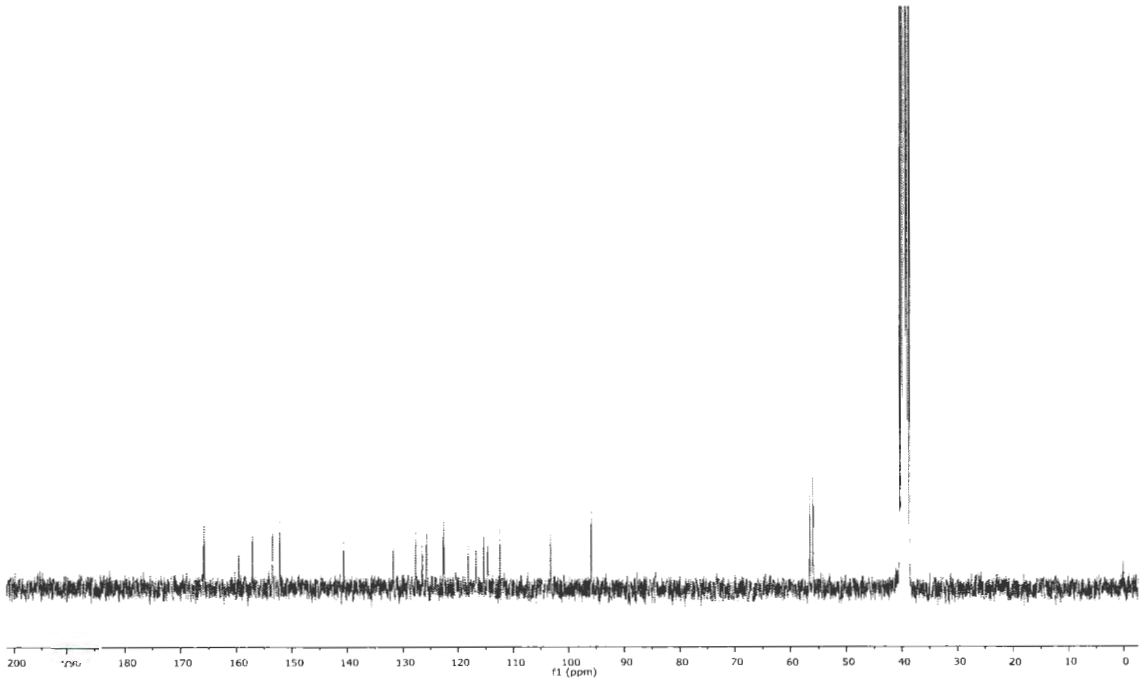
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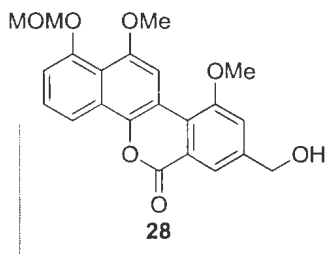
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O

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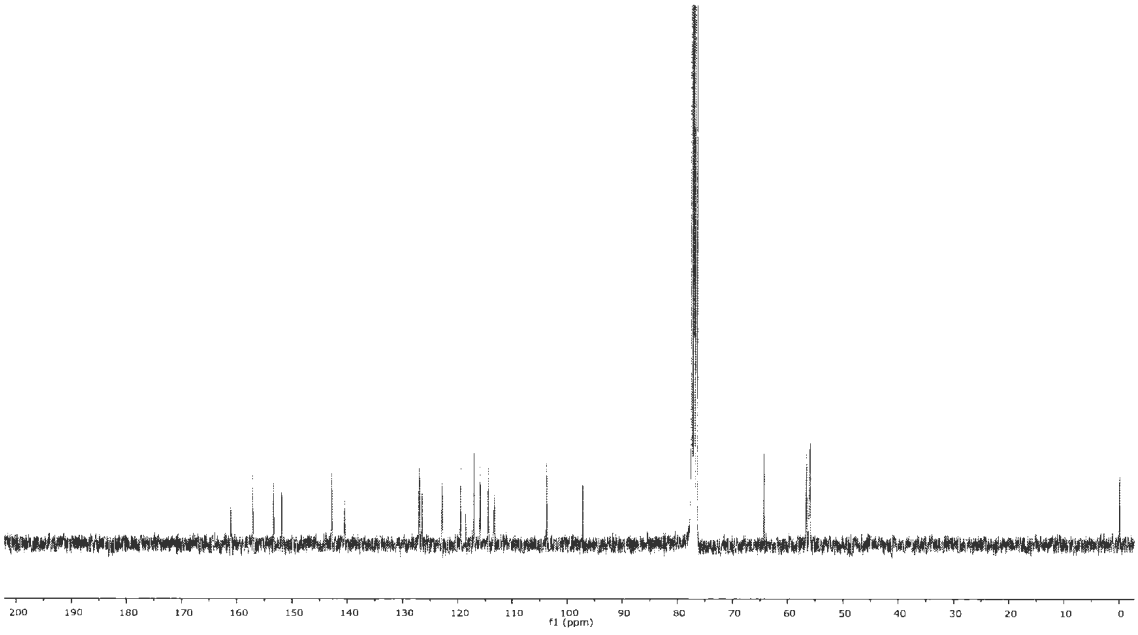
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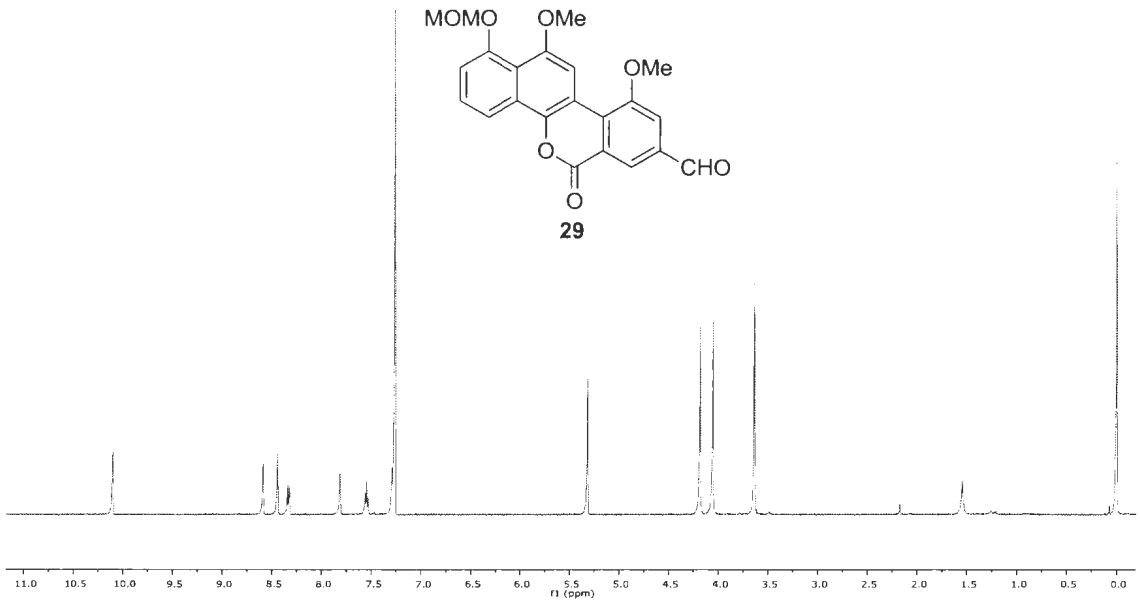
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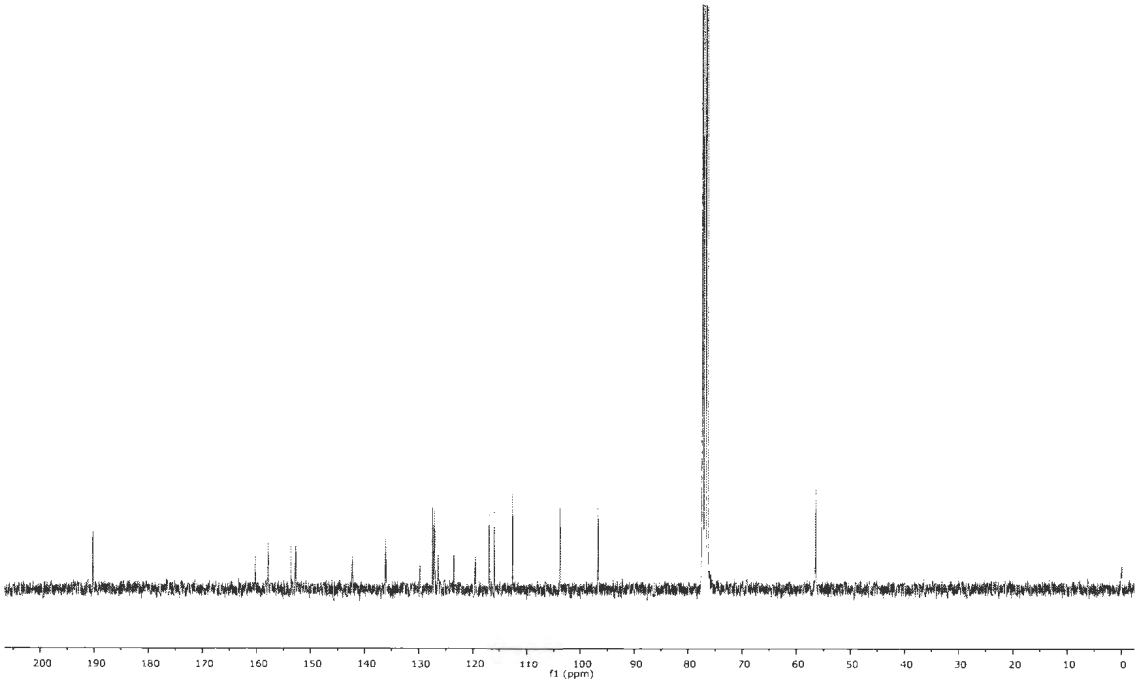
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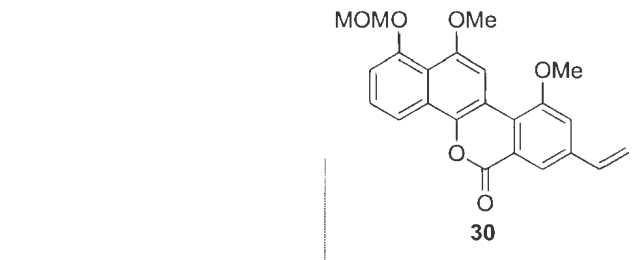
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O

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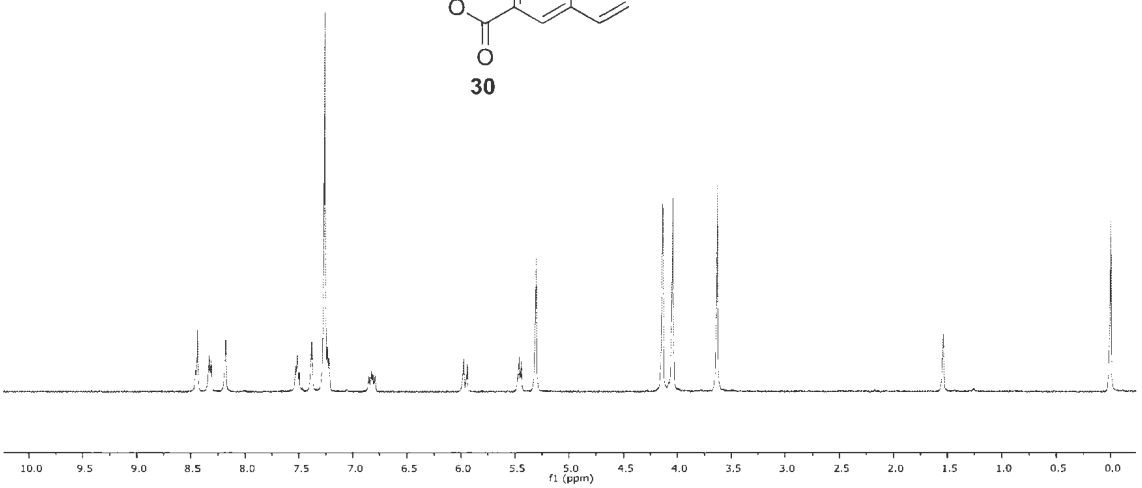
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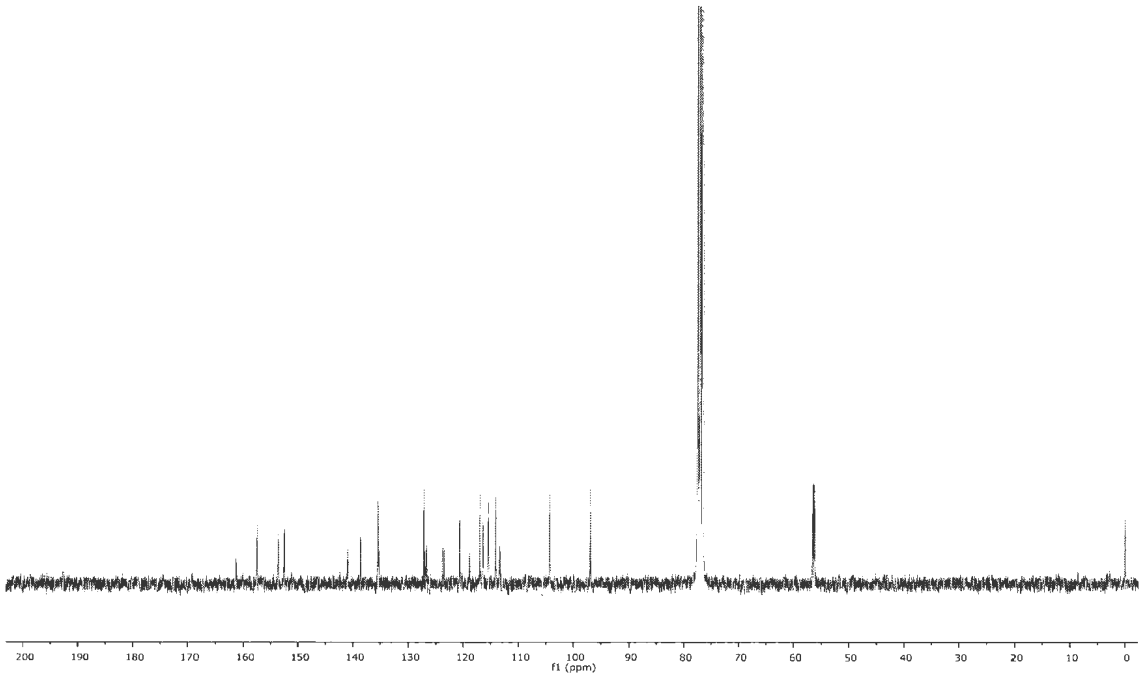
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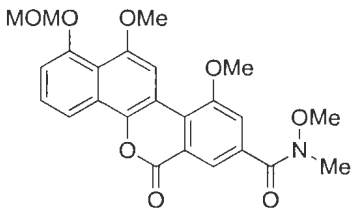
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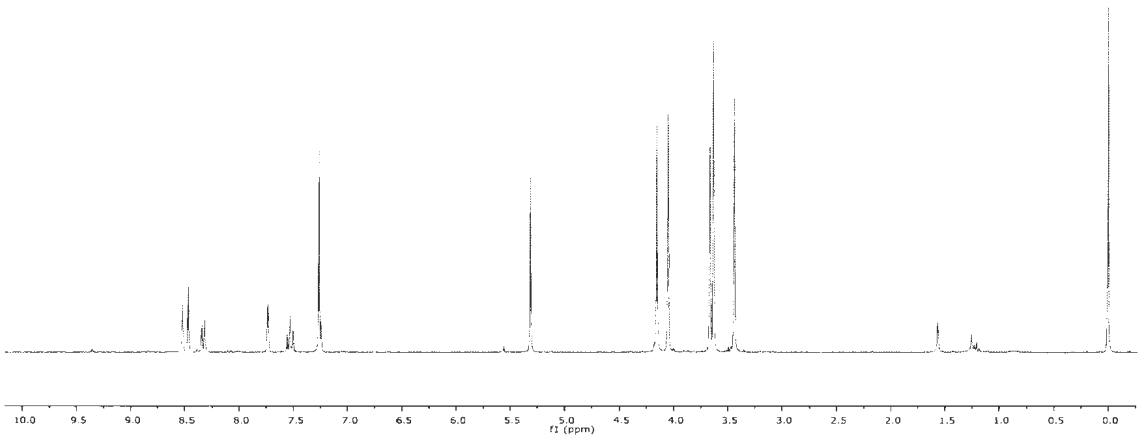
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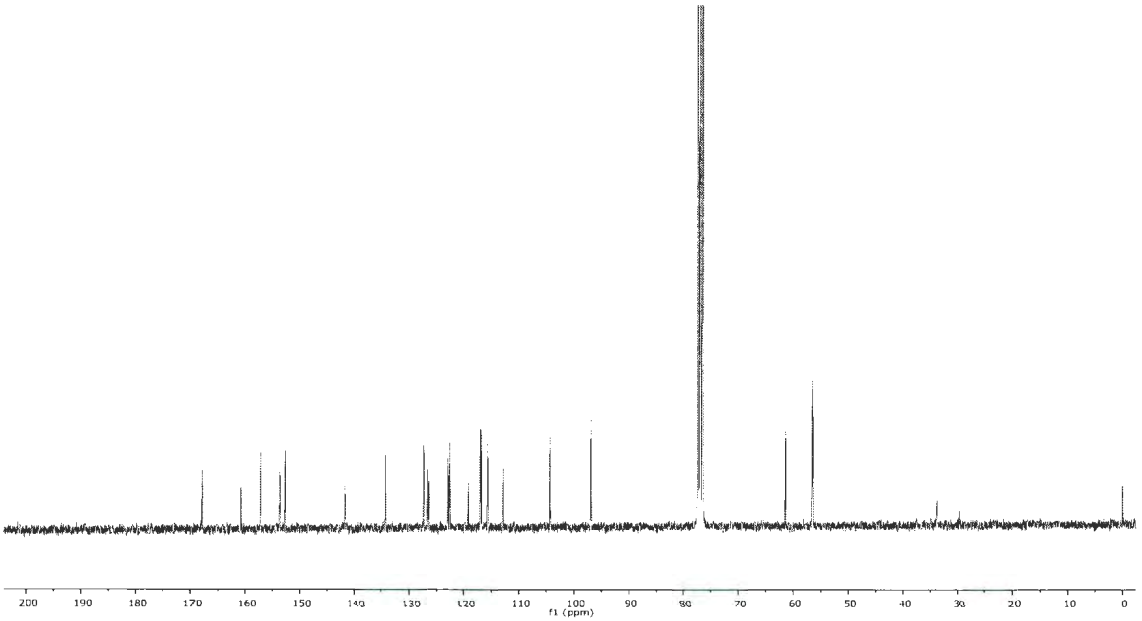
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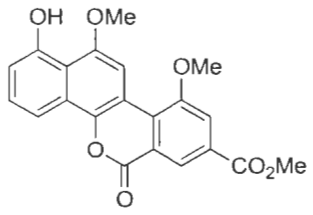
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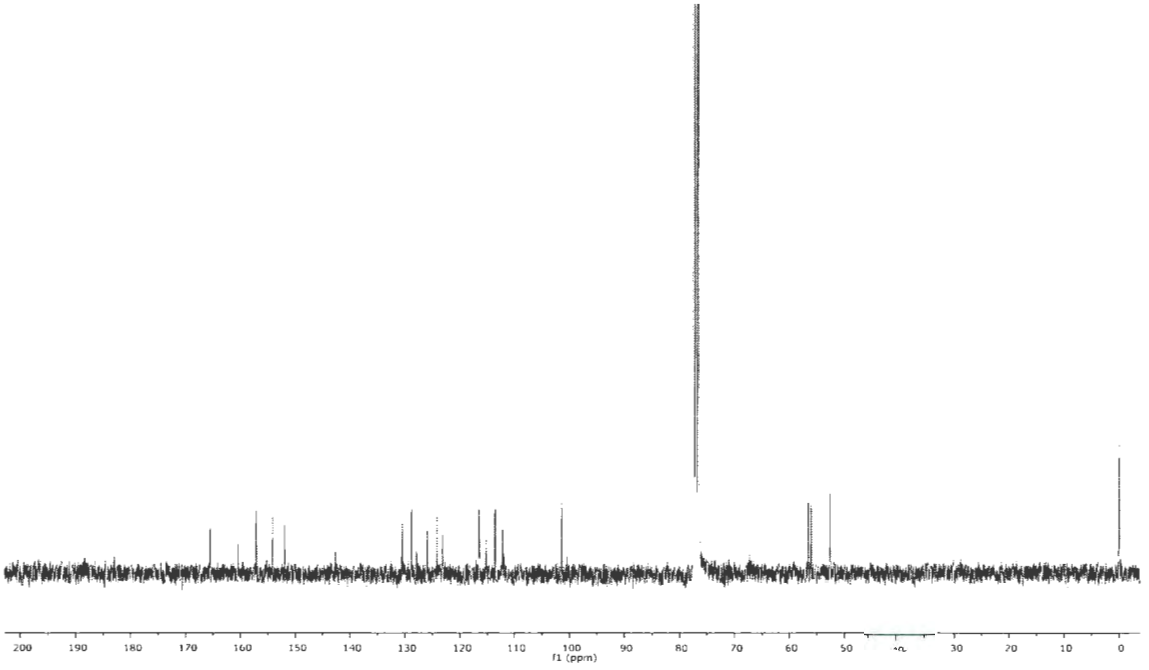
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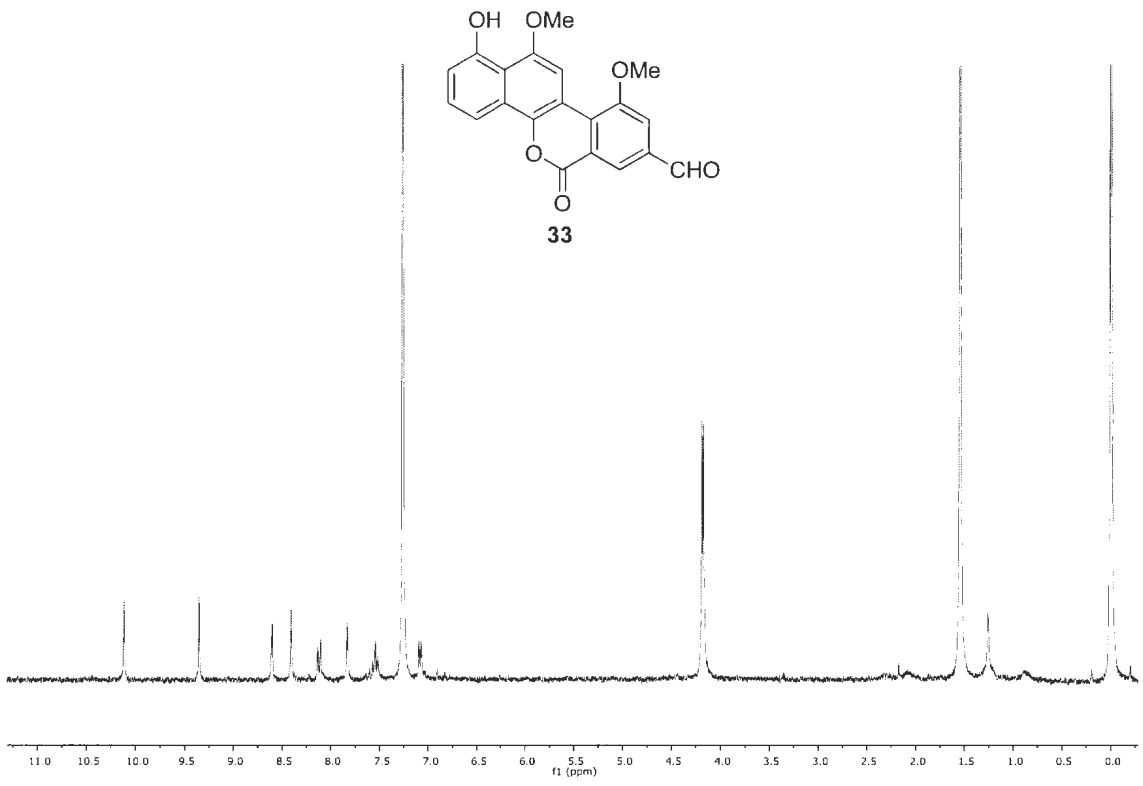
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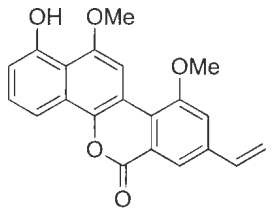
33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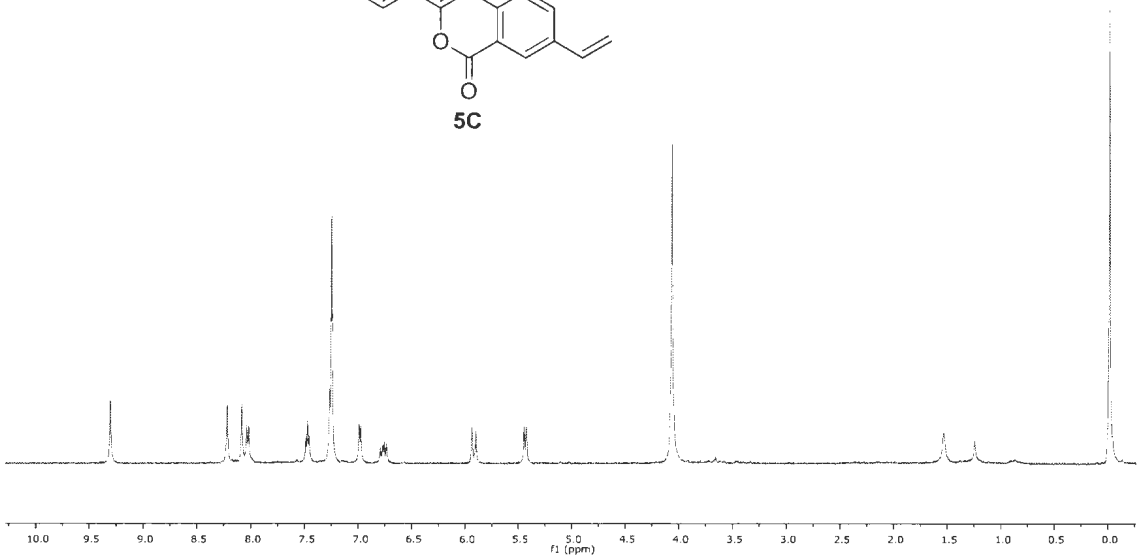
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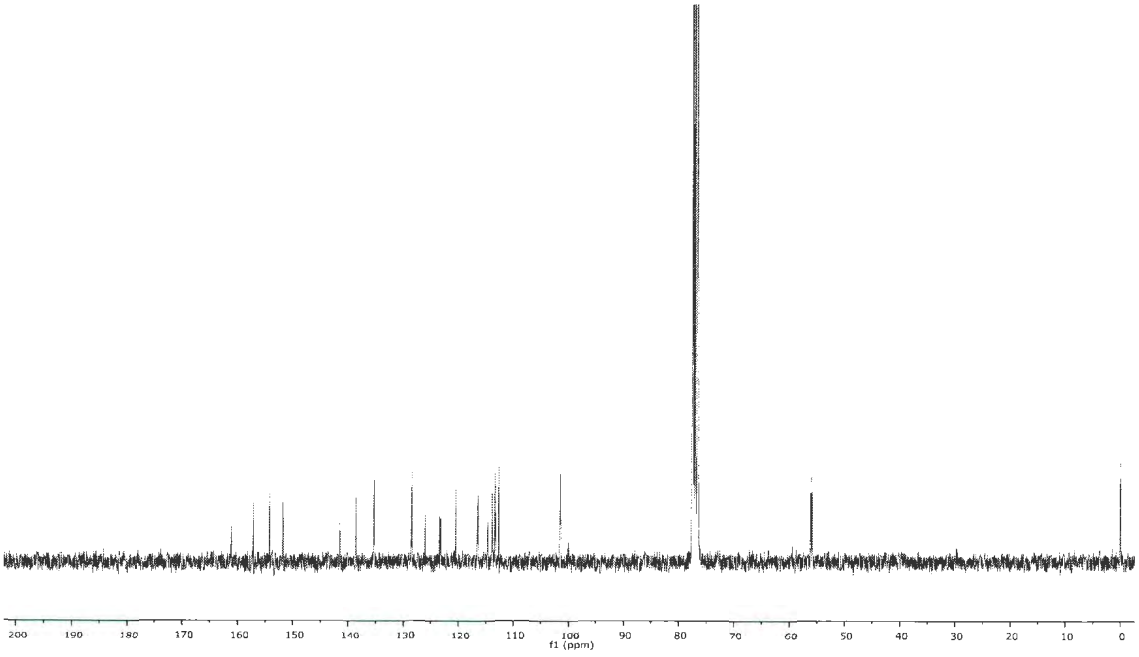
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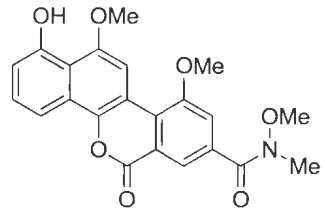
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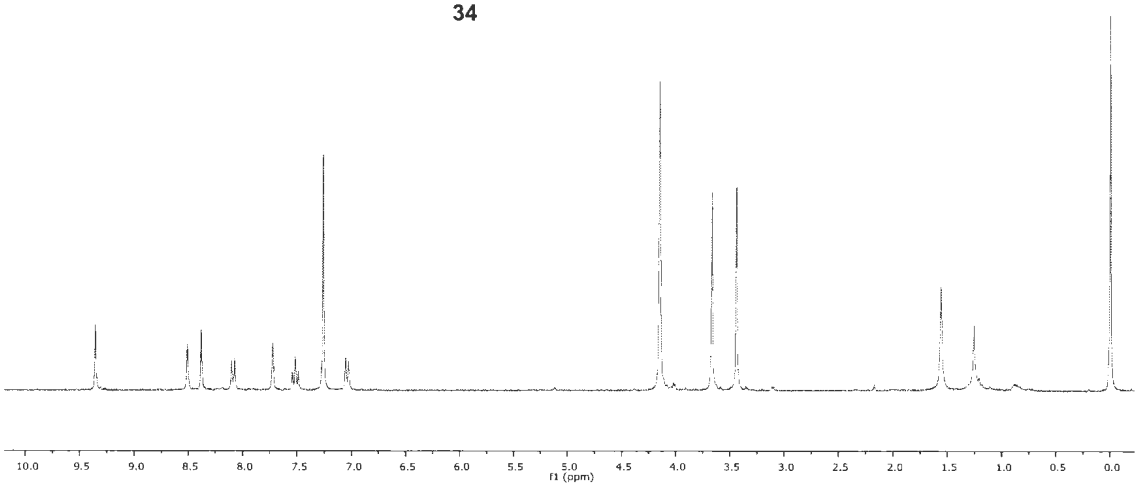
34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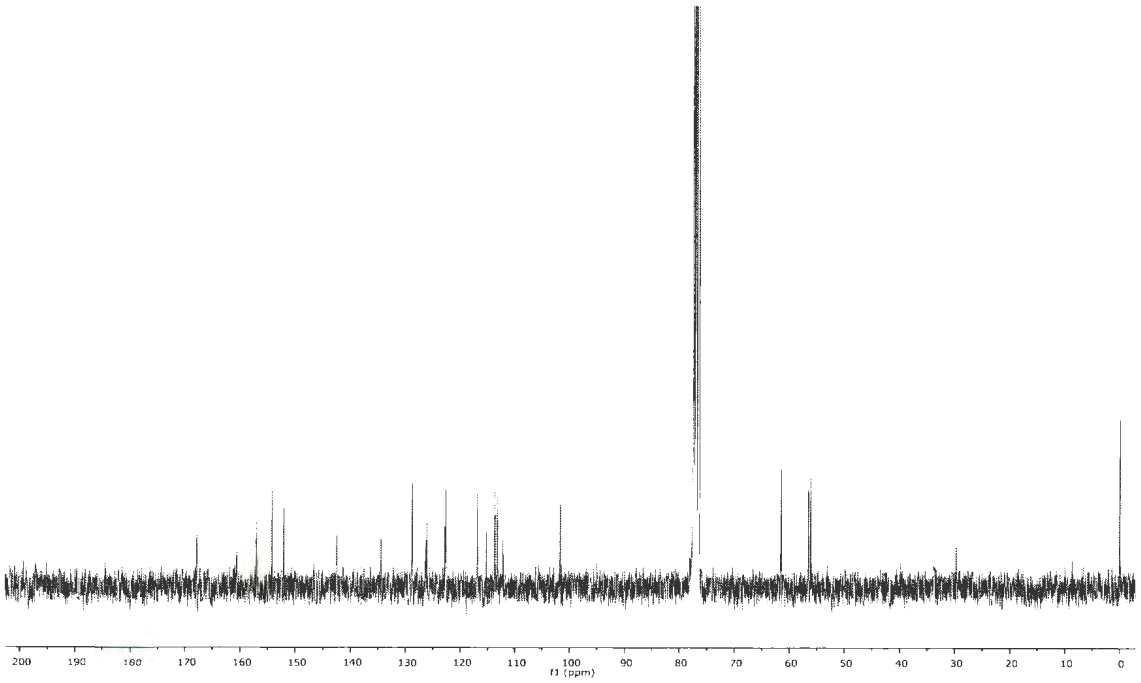
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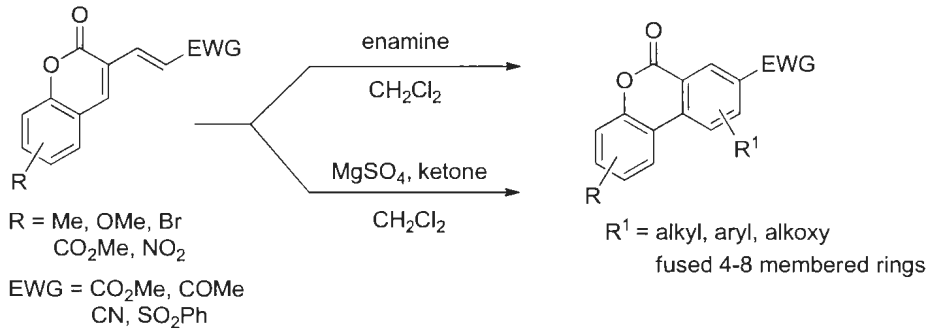
Chapter 6

Conclusions

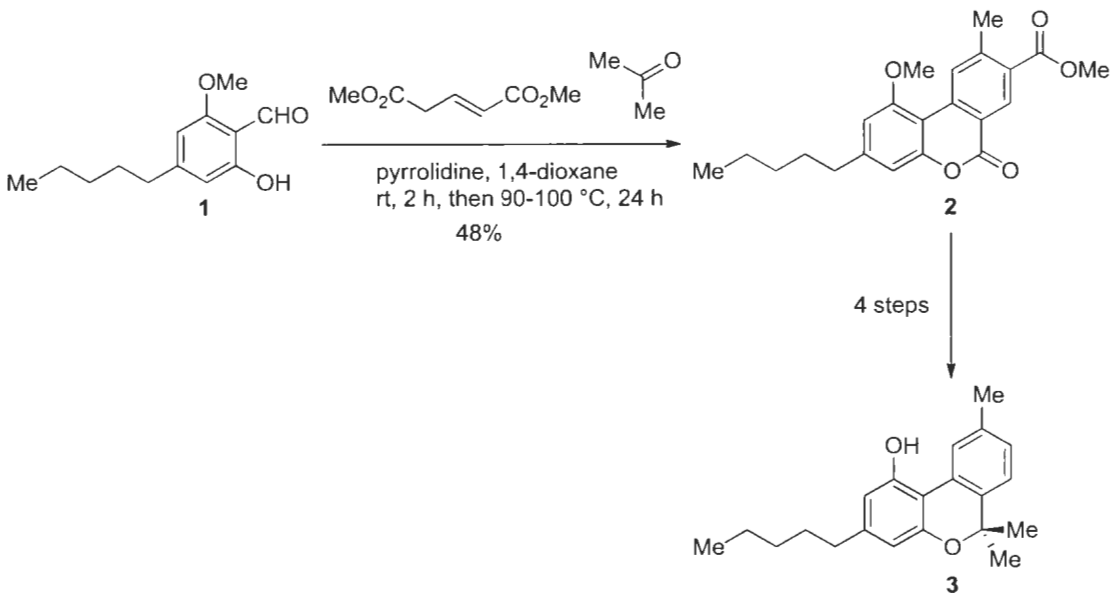
The initial investigations of the synthesis of 6*H*-dibenzo[*b*,*d*]pyran-6-ones using inverse electron demand Diels-Alder (IEDDA)-based strategies were carried out by I. R. Pottie, a former graduate student in the Bodwell group. This project involved the synthesis of coumarin-fused electron-deficient dienes and the study of their IEDDA reactions using electron-rich dienophiles. In this regard, a set of coumarin-fused dienes, was synthesized, in which the electron-withdrawing group at the terminus of the diene unit and the nature and position of the "R" group on the diene were varied. These dienes were found to react with the preformed enamine derived from cyclopentanone and pyrrolidine to afford DBPs. Subsequently, *in situ* enamine generation conditions were developed and this significantly simplified the synthesis of DBPs, by offering the advantage of not having to synthesize the enamine. Using a coumarin-fused diene (EWG = CO_2Me, R = H), both preformed and *in situ* methods were thoroughly investigated by employing a variety of enamines (preformed method) or ketones (*in situ* method) to afford the corresponding DBPs (Scheme 6.1). In one example, where the dienophile was a ketene acetal, the initial cycloadduct was isolated and its structure is consistent with a concerted cycloaddition. P. R. Nandaluru's contributions to this project were 1) to repeat a number of I. R. Pottie's experiments to conform yields, provide material for full characterization and provide material to expand the scope of this methodology, and 2) to expand and solidify the scope of the methodology. Only the synthetic work leading to new compounds or ones using the *in situ* method is presented in Chapter 2. P. R.

Nandaluru is also heavily involved in the writing and preparation of the manuscript for publication.



Scheme 6.1. Preformed and *in situ* methods for the synthesis of DBPS.

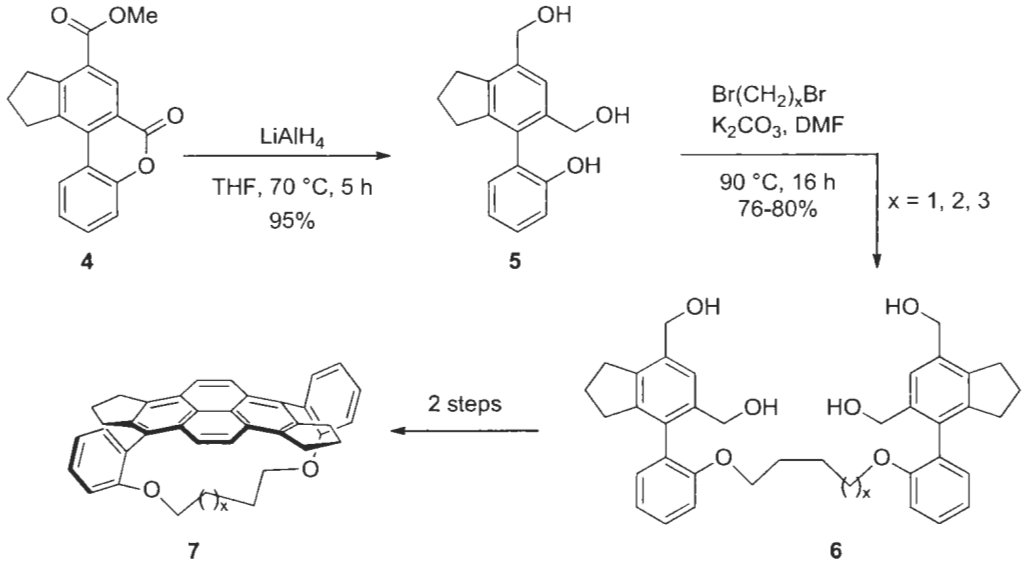
Based on the observation that a secondary amine played a catalytic role in the formation of *both* the diene (piperidine in the Knoevenagel condensation) and the dienophile (pyrrolidine in enamine formation) components in stepwise methods, a multicomponent reaction (MCR) was developed. In this MCR, the overall transformation involved six reactions in one pot to give rapid access to a broad range of DBPs. Using this methodology, a variety of A- and C-ring substituted DBPs were synthesized and in most cases, where comparisons can be made, the yields are higher than stepwise methods. One of the DBPs (**2**) generated using this MCR served as a precursor for a concise synthesis of cannabinol (**3**), a prominent member of the cannabinoid class of natural products. The results of this work are presented in Chapter 3. P. R. Nandaluru contributed all of the synthetic work and was heavily involved in the writing and preparation of the manuscript for publication.



Scheme 6.2. MCR leading to a key intermediate **2** in the cannabinol synthesis.

To further demonstrate the value of the MCR, pyrenophanes were considered to be attractive targets, as synthesis of structurally diverse pyrenophanes that contain nonplanar pyrene systems is another major area of interest in the Bodwell group. In this project, the very productive MCR provided an efficient entry into pyrenophane precursors. One of the DBPs (**4**) generated using the MCR was used for a very concise synthesis (5 steps) of elaborate C_2-symmetric pyrenophanes (Scheme 6.3). The synthesis relied upon two very productive events: 1) the MCR and 2) a double McMurry / valence isomerization / dehydrogenation reaction, and provided novel (1,6)-pyenophanes exclusively over their (1,8)-pyrenophanes. This approach to pyrenophanes has great potential for structural modifications of pyrenophanes because of the broad scope of the MCR. The results of this work are presented in Chapter 4. P. R. Nandaluru contributed all of the synthetic

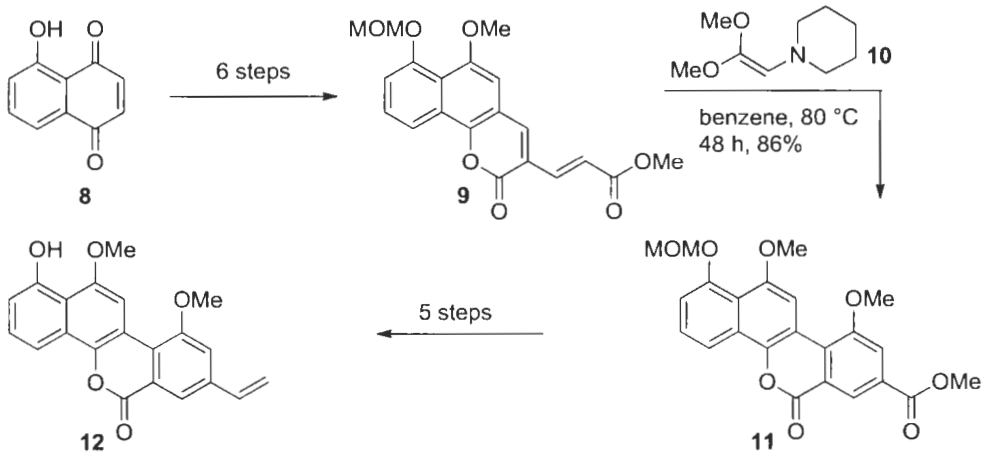
work and was heavily involved in the writing and preparation of the manuscript for publication.



Scheme 6.3. Synthesis of C_2-symmetric pyrenophanes using DBP **4**.

In the last project, the IEDDA-based step wise method was employed in the total synthesis of defucogilvocarcin V, an antitumor compound. The synthesis of the natural product was accomplished in 12 steps from the commercially available juglone (**8**) in 5.2% overall yield. The key step of the approach was the IEDDA reaction of diene **9** and the enamine **10** derived from dimethoxyacetaldehyde to afford the tetracyclic aromatic motif **11**. The ester functionality present in **11** was subjected to functional group interconversions to afford the natural product as well as, three new C-8 analogues. The results of this work are presented in Chapter 5. P. R. Nandaluru contributed all of the

synthetic work and was heavily involved in the writing and preparation of the manuscript for publication.



Scheme 6.4. IEDDA reaction in the synthesis of defucogilvocarcin V.

In summary, both step-wise and MCR methodologies were developed for the synthesis of DBPs and these methods were used effectively in the synthesis of both natural and non-natural products.