EXPLORATION OF THE INVERSE-ELECTRON-DEMAND DIELS-ALDER (IEDDA) REACTION. RAPID ACCESS TO BENZOCOUMARINS VIA IEDDA-DRIVEN DOMINO REACTIONS OF COUMARIN-FUSED ELECTRON-DEFICIENT DIENES WITH ELECTRON-RICH DIENOPHILES

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Exploration of the Inverse-Electron-Demand Diels-Alder (IEDDA) Reaction. Rapid Access to Benzocoumarins via IEDDA-Driven Domino Reactions of Coumarin-Fused Electron-Deficient Dienes With Electron-Rich Dienophiles

by

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Abstract

Chapter 1 overviews the general concepts of the Diels-Alder reaction, and particular attention is given to the inverse-electron-demand Diels-Alder reaction (IEDDA). Examples of all-carbon diene systems that contain electron-withdrawing groups at their 1- and 3-positions and their IEDDA reactivity are described.

Chapter 2 presents the synthesis of a coumarin-fused diene that was produced in a single step. An oxidative cleavage of this diene produces 3-formylcoumarin, which can be used in the Horner-Wadsworth-Emmons reaction or the Knoevenagel condensation to afford other coumarin-fused dienes.

Chapter 3 presents the IEDDA reactivity of methyl (*E*)-3-(2-oxo-*2H*-chromen-3-yl)acrylate with electron-rich dienophiles. Enamines undergo an IEDDA-driven domino reaction to produce benzocoumarins. The reaction procedure can be simplified by generating the dienophile *in situ*.

Chapter 4 details the methodology development of the IEDDA-driven domino reactions. The methodology was used to synthesize a subunit of a new heterokekulene and efficiently generate benzocoumarins from the appropriate phenols. Preliminary results for producing azabenzcoumarins are also discussed.

Chapter 5 contains details of a concise, high yielding total synthesis of a naturally occurring benzocoumarin by applying the methodology developed in Chapter 4. An IEDDA-driven domino reaction constitutes the key step of the synthesis.

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List of Abbreviations

Δ	heat
Φ	biaryl bond torsion angle
δ	chemical shift
ε	extinction coefficient
°C	degrees Celsius
Ac	Acetyl
AM1	Austin model 1
Anal	analysis
AO	atomic orbital
BINOL	binaphthol
Bn	benzyl
bp	boiling point
calcd	calculated
d	day(s)
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
EI-MS	electron impact mass spectroscopy
Et	ethyl
EDG	electron-donating group

EWG	electron-withdrawing group
eV	electron volt(s)
equiv	equivalent
FMO	frontier molecular orbital
GC-MS	gas chromatography mass spectrometry
h	hour(s)
hfc	3-(heptafluoropropylhydroxymethylene)-*d*-Camphorate
HOMO	highest occupied molecular orbital
HRMS	high-resolution mass spectrometry
HWE	Horner-Wadsworth-Emmons
Hz	hertz
IEDDA	inverse electron demand Diels-Alder
IR	infrared (spectroscopy)
kcal	kilocalorie(s)
LDA	lithium diisopropylamide
LUMO	lowest unoccupied molecular orbital
M^+	molecular ion peak
m-CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
min	minute(s)
mol	mole(s)
mp	melting point

MO	molecular orbital
NMR	nuclear magnetic resonance (spectroscopy)
NOE	nuclear overhauser enhancement
ORTEP	Oak Ridge thermal ellipsoid plot
Ph	phenyl
PMA	phosphomolybdic acid
ppm	parts per million
quint	quintet
rt	room temperature
P(*o*-tolyl)$_3$	tri-*o*-tolylphosphine
SEM	silylethoxymethyl
TADDOL	1,1,4,4-Tetraphenyl-2,3-O-Isopropylidene-*l*-Threitol
TBS	*tert*-butyldimethylsilyl
TFA	trifluoroacetic acid
tfc	3-(trifluoromethylhydroxymethylene)-*d*-Camphorate
THF	tetrahydrofuran
tlc	thin layer chromatography
TMS	trimethylsilyl
p-TSA	*p*-toluenesulfonic acid
UV	ultraviolet (spectroscopy)
Vis	visible (light)

Chapter 1.

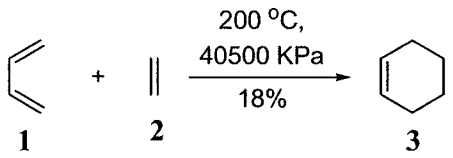
Introduction

1 Introduction

1.1 Diels-Alder Reaction

In 1906, Albrecht reported "a 'dimeric complex' which formed upon a thermal reaction of cyclopentadiene and *p*-benzoquinone."[1] This dimeric complex is now known to be a [4π + 2π] cycloadduct. Starting in 1928, Otto Diels and Kurt Alder published a series of papers that focused on an in-depth investigation of this transformation.[2] They reported the formation of several [4π + 2π] cycloadducts from various 1,3-dienes and alkenes. Since these initial reports, the Diels-Alder cycloaddition has become the most important synthetic operation for producing highly substituted six membered rings. For their pioneering investigations of this reaction, Diels and Alder were awarded the Nobel Prize in Chemistry in 1950. This reaction is illustrated by the parent reaction between 1,3-butadiene **1** (the diene) with ethene **2** (the dienophile) to give cyclohexene **3** (Scheme 1.1).[3]

The Diels-Alder reaction is described as a [4π + 2π] pericyclic reaction that



Scheme 1.1: The parent Diels-Alder cycloaddition.

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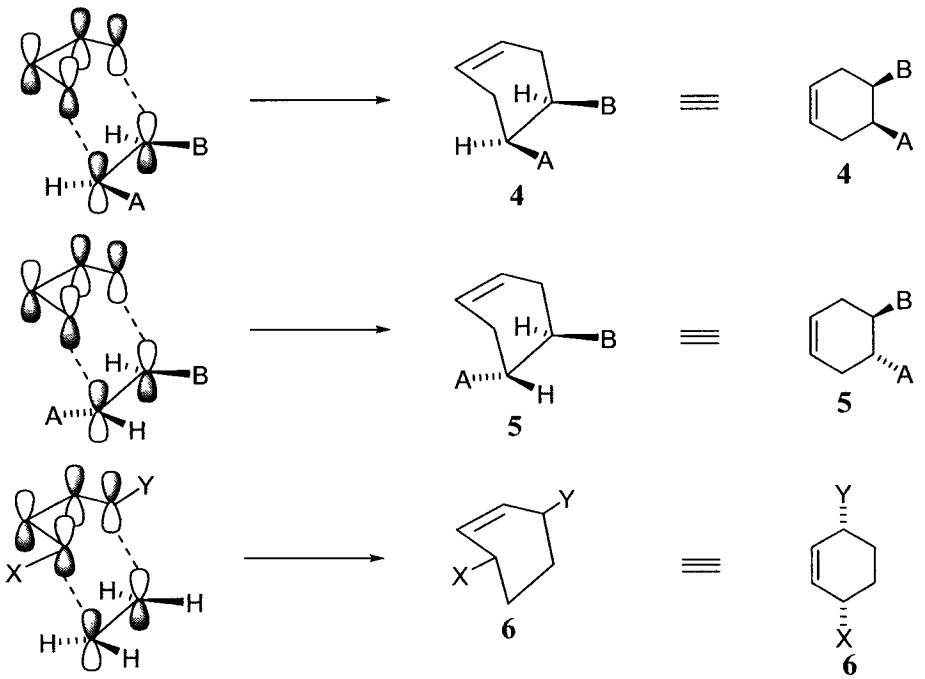
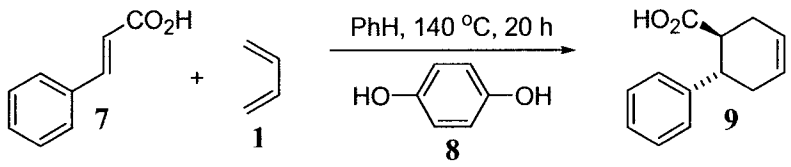
[1] Albrecht, W. *Justus Liebigs Ann. Chem.* **1906**, *348*, 31–49.
[2](a) Diels, O.; Alder, K. *Justus Liebigs Ann. Chem.* **1928**, *460*, 98–122. (b) Diels, O; Alder, K.; Lübbert, W.; Naujoks, E.; Qyerberitz, F.; Röhl, K.; Segeberg, H. *Justus Liebigs Ann. Chem.* **1929**, *470*, 62–103. (c) Diels, O.; Alder, K. *Ber.* **1929**, *62*, 2081–2087. (d) Diels, O.; Alder, K. *Ber.* **1929**, *62*, 2087–2090.
[3] Joshel, L. M.; Butz, L. W. *J. Am. Chem. Soc.* **1941**, *63*, 3350–3351.



Scheme 1.2: Suprafacial addition and conservation of relative stereochemistry of the diene and the dienophile in the cycloadduct.

proceeds by suprafacial addition in both components (Scheme 1.2). According to this description, it is a concerted, cyclic reorganization of the π electrons between the reacting partners, rather than a non-concerted, stepwise bond formation and bond cleavage process. Woodward and Hoffmann have defined suprafacial addition as "a process in which bonds made or broken lie on the same face of the system undergoing reaction".[4] This mode of addition is responsible for the retention of the relative stereochemistry of the diene and dienophile within the Diels-Alder reaction. Alder *et al.* had disclosed an example of this stereospecificity in 1929 when (*E*)-cinnamic acid **7** was heated with 1,3-

[4] Woodward, R. B.; Hoffmann, R. *The Conservation of Orbital Symmetry* Verlag-Chemie/Academic: Weinheim, 1971, p. 65.



Scheme 1.3: Example of the suprafacial addition of the Diels-Alder reaction preserving the stereochemistry of the reactant.

butadiene **1** in the presence of the radical scavenger hydroquinone **8** to produce the substituted cyclohexene **9** (Scheme 1.3).[5]

The issue of concertedness has been debated thoroughly. Stepwise mechanisms involving ionic intermediates (Scheme 1.4) or diradical intermediates are possible.[6] In the ionic case, a Michael-like addition of the dienophile to the diene would afford a zwitterion intermediate **10**. If the zwitterion **10** is short lived, i.e. the rate of the intramolecular reaction is quicker than rotation along C1-C2 sigma bond; the kinetic product **4** is produced. However, if the lifetime of zwitterion **10** is long enough and can allow for rotation along C1-C2 sigma bond to achieve equilibrium with **11**, formation of either the kinetic product **4** or thermodynamic product **5** can occur.

It is believed that the majority of Diels-Alder reactions are concerted processes and theoretical analyses agree with this view.[7] Concerted, by definition, means "achieved or performed together". However, this definition does not take into account

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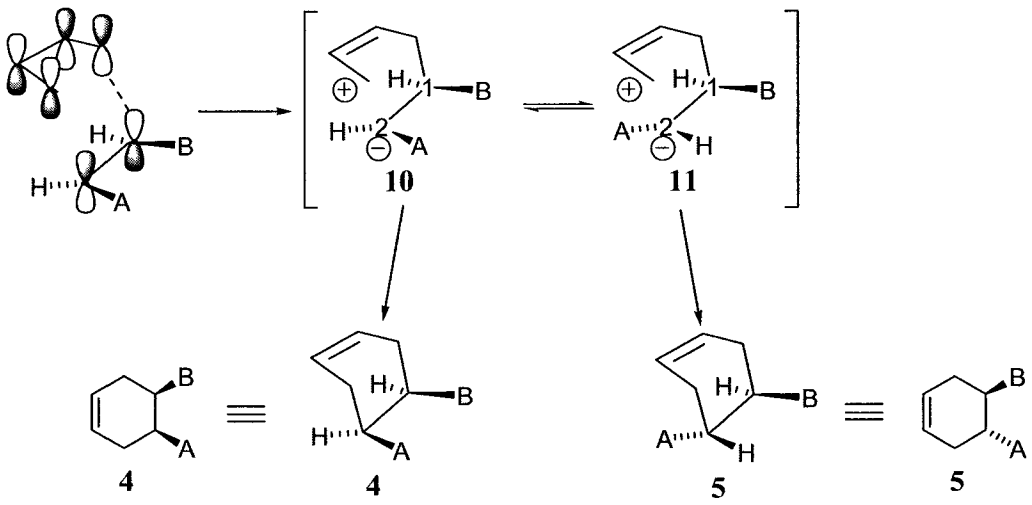
[5] Alder, K.; Vagt, H.;Vogt, W. *Justus Liebigs Ann. Chem.* **1949**, *565*, 135–148.

[6] (a) Dewar, M. J. S.; Olivella, S.; Stewart, J. P. *J. Am. Chem. Soc.* **1986**, *108*, 5771–5779. (b) For a review of this topic, see: Sauer, J.; Sustmann, R. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 779–807.

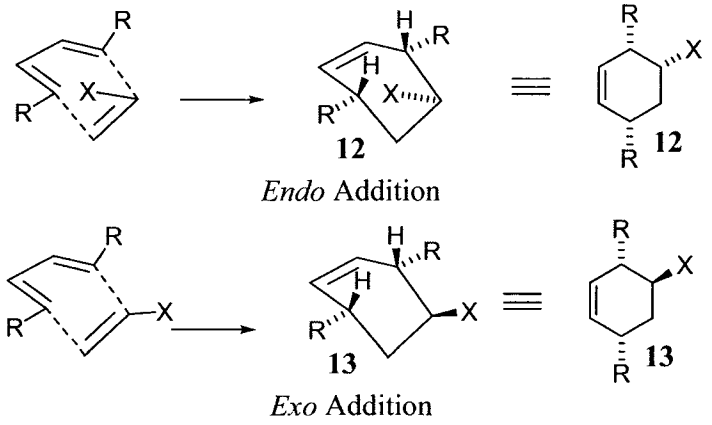
[7] (a) Gajewski, J. J.; Peterson, K. B.; Kagel, J. R. *J. Am. Chem. Soc.* **1987**, *109*, 5545–5546. (b) Houk, K. N.; Lin, Y. T.; Brown, F. K. *J. Am. Chem. Soc.* **1986**, *108*, 554–556.



Scheme 1.4: Example of a non-concerted mechanism that produces a mixture of diastereomers.

the rate at which each bond is being formed and broken as the reaction proceeds. If the extent of bond breakage and formation at one terminus of the diene is the same as the bond-breakage and formation at the other terminus at the transition state, the mechanism is considered to be synchronous. This rate of bond-breaking and bond-forming can occur at differing degrees depending on the substituent pattern and polarity of the reacting diene and dienophile. That is, the more polarized the reactants the more divergent these rates are. This process can be described as asynchronous.[8] Mechanistically, the Diels-Alder reaction can be considered as lying on a continuum between synchronous, with equal rates of new σ-bond formation at the transition state, and stepwise. Between these two extremes on the continuum, the mechanistic pathway proceeds via an asynchronous process.

[8] (a) Woodward, R. B.; Katz, T. J. *Tetrahedron* **1959**, *5*, 70–89. (b) Dewar, M. J. S.; Pierini, A. B. *J. Am. Chem. Soc.* **1984**, *106*, 203–208.

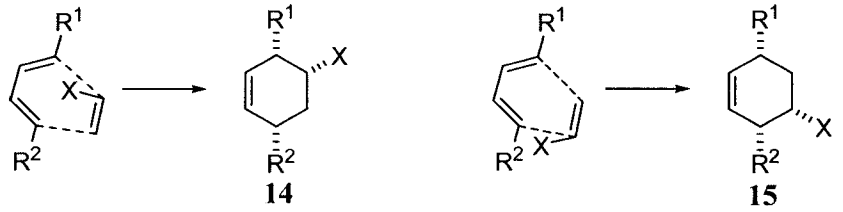


Scheme 1.5: The Diels-Alder transition states.

Another stereochemical feature of the Diels-Alder reaction is *endo*/*exo* selectivity. This has to do with whether a substituent (or substiuents) on the dienophile is situated toward (*endo*) or away from (*exo*) the diene π system at the transition state (Scheme 1.5). These two transition states are diastereomeric (unless rendered degenerate by symmetry) and lead to diastereomeric products. The general preference for *endo* addition, especially for unsaturated substituents, is known as the "Alder rule".[9]

Examples shown above utilize symmetrical dienes and either symmetrical or unsymmetrical dienophiles in the Diels-Alder reaction. A cycloaddition between an unsymmetrical diene and an unsymmetrical dienophile, via only an *endo* transition state, can afford two regioisomers (Scheme 1.6). In this example, the regiochemical outcome is determined by whether the substituent on the dienophile is closer to the substituent R^1 or

[9] (a) Alder, K.; Stein, G.; von Budedenbrock, F.; Eckardt, W.; Frercks, W.; Schneider, S. *Justus Liebigs Ann. Chem.* **1934**, *514*, 1–33. (b) Alder, K.; Stein, G.; Liebmann, M.; Rolland, E. *Justus Liebigs Ann. Chem.* **1934**, *514*, 197–211. (c) Alder, K.; Stein, G.; Rolland, E.; Schulze, G. *Justus Liebigs Ann. Chem.* **1934**, *514*, 211–227.



Scheme 1.6: Possible regiochemical outcome of the Diels-Alder reaction when R^1 is not equal to R^2.

R^2 on the diene when the bond forming process begins to generate either cyclohexene **14** or cyclohexene **15**. Usually, introductory organic chemistry lecturers use valence bond theory to rationalize the observed regiochemistry of the cycloadducts.

Carey and Sundberg have quoted this empirical description as "writing as many plausible Lewis structures as possible which correspond to the correct molecular connectivity."[10] For a monosubstituted 1,3-butadiene, i.e., dienes **16** and **18**, resonance contributors can be envisioned by placing increased electron density on a specific terminal carbon atom (Scheme 1.7). Dienophile **20**, on the other hand, contains one electropositive carbon atom. When butadiene **16** and dienophile **20** undergo a cycloaddition reaction, the electron-rich carbon atom of **16** begins the bonding process with the electropositive carbon atom of **20** to afford *ortho*-substituted cyclohexene **22**. Alternately, diene **18** generates the *para*-substituted cyclohexene **23** from the Diels-Alder reaction with dienophile **20**. Typically, when a monosubstituted butadiene reacts with an electronically biased dienophile the outcome of the Diels-Alder reaction will be a single regioisomer.

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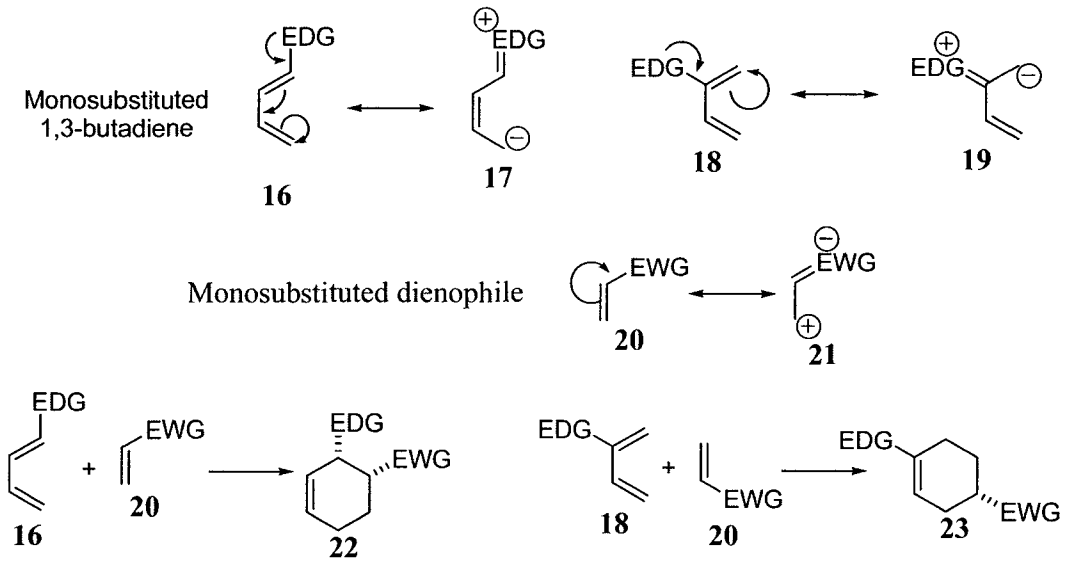
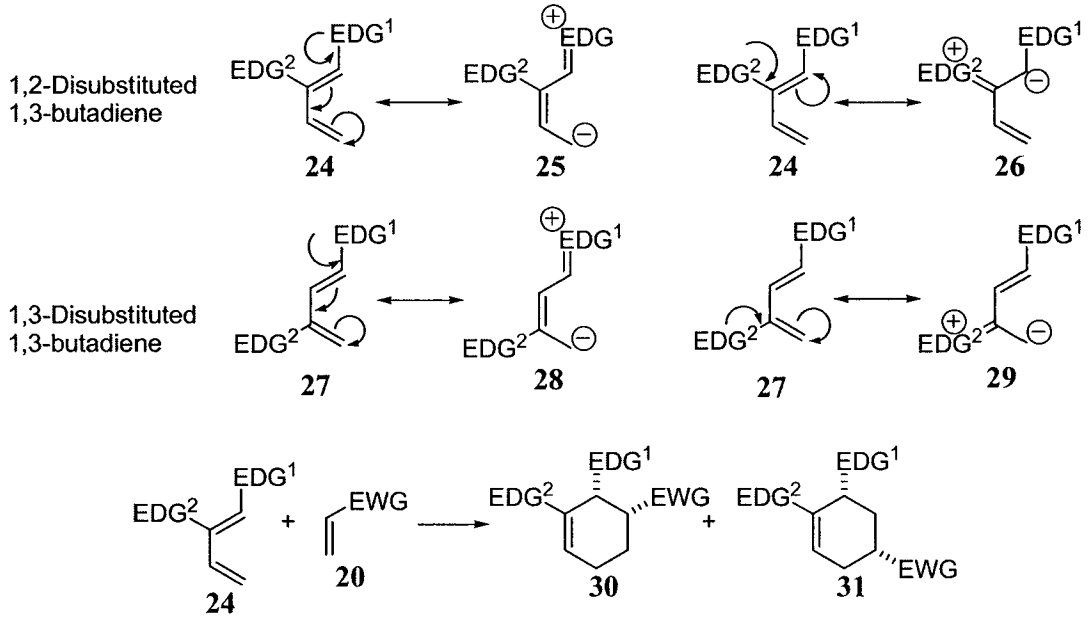
[10] Carey, F. A.; Sundberg, R. J. In *Advanced Organic Chemistry Part A: Structure and Mechanisms* Plenum Press: New York 1990, 3rd ed., p. 3.



Scheme 1.7: Valence bond explanation of the regiochemical outcome of the Diels-Alder reaction with monosubstituted dienes.

Dienes can bear more than one substituent. These substituents, depending on their substitution pattern on the diene, can enhance or deter the regiochemical outcome of a cycloaddition with an electronically biased dienophile (Scheme 1.8). With electron-donating groups at the 1- and 2-positions of the diene, i.e., structure **24**, there is an increase of electron density on two terminal carbon atoms as shown in (valence-bond) resonance structures **25** and **26**. This can lead to both regiochemical isomers, i.e. **30** and **31**, being generated from a cycloaddition with the electronically biased dienophile **20**. However, with the inclusion of electron-donating groups at the 1- and 3-position of the diene, as in e.g. diene **27**, both substituents donate electron density to the same terminal carbon atom. The result of this cooperation is enhanced regioselectivity and reactivity towards electronically biased dienophiles, e.g. alkene **20**. These dienes, for example



Scheme 1.8: Valence bond explanation of the regiochemical outcome of the Diels-Alder reaction with disubstituted dienes.

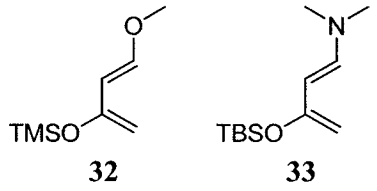


Figure 1.1: Danishefsky's diene **32** and Rawal's diene **33**.

Danishefsky's diene **32**[11] and more recently Rawal's diene **33** (Figure 1.1),[12] have enjoyed widespread use,[13] especially in the synthesis of natural products.[13c-13f]

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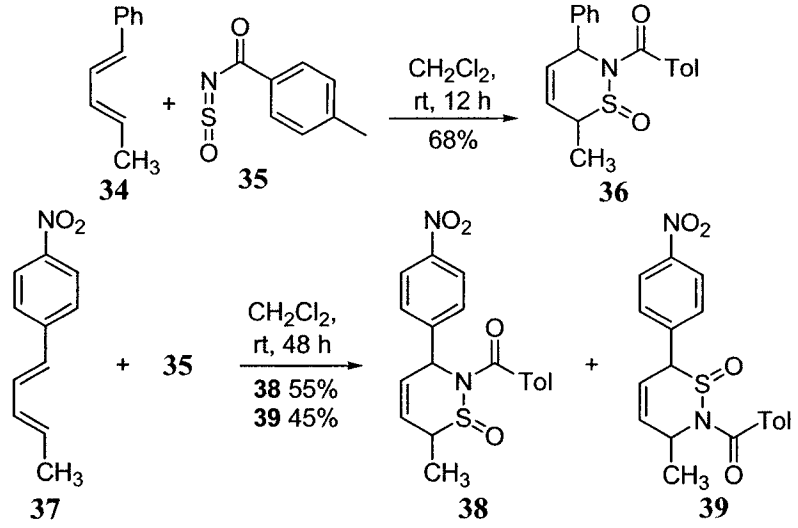
[11] Danishefsky, S.; Kitahara, T. *J. Am. Chem. Soc.* **1974**, *96*, 7807–7808.

[12] Kozmin, S. A.; Janey, J. M.; Rawal, V. H. *J. Org. Chem.* **1999**, *64*, 3039–3052.

[13] (a) Fringuelli, F.; Taticchi, A. *Dienes in the Diels-Alder Reaction*; John Wiley and Sons: New York, 1990. For reviews on the subject, see: (b) Corey, E. J. *Angew. Chem. Int. Ed.* **2002**, *41*, 1650–1667. (c) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1668–1698. (d) Danishefsky, S. *Acc. Chem. Res.* **1981**, *14*, 400–406. (e) Danishefsky, S. J.; DeNinno, M. P. *Angew. Chem., Int. Ed. Engl.* **1987**, 15-23. (f) Danisheksky, S. *Chemtracts: Org. Chem.* **1989**, *2*, 273–286.

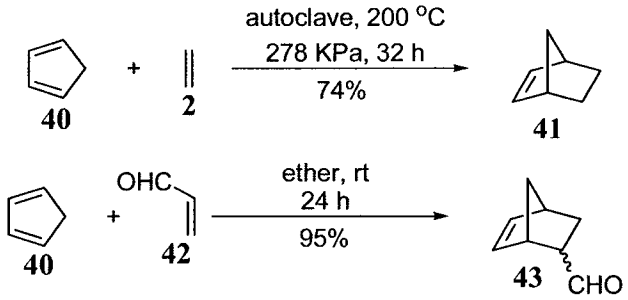
Carpanelli and Gaiani reported several cycloadditions, two of which are shown in Scheme 1.9,[14] that reveal a problem when using valence bond theory to predict the regiochemical outcome of the Diels-Alder reaction. The disubstituted diene **34** underwent a reaction with *N*-sulphinyl-*p*-toluamide **35** to produce cycloadduct **36** as the only regiochemical product isolated.[15] The regiochemical outcome of the cycloaddition was altered by the inclusion of a *p*-nitrobenzene substituent instead of the phenyl group on the diene. Diene **37** affords a 55:45 mixture of cycloadducts **38** and **39** when it undergoes reaction with dienophile **35**.[15] If the Carey and Sundberg definition of valence bond theory was applied to rationalize the outcome of these reactions, the explanation would not explain why the regiochemical outcome was altered and the reaction rate was notably slower. Carpanelli and Gaiani used Frontier Molecular Orbital (FMO) theory to



Scheme 1.9: Examples demonstrating the regiochemical outcome of the Diels-Alder reaction.

[14] Carpanelli, C; Gaiani, G. *Gazz. Chim. Ital.* **1982**, *112*, 191–194.

[15] The authors did not comment on the stereochemical outcome of the cycloaddition, i.e., whether the product was obtained from an *endo* or *exo* transition state because they can't tell.



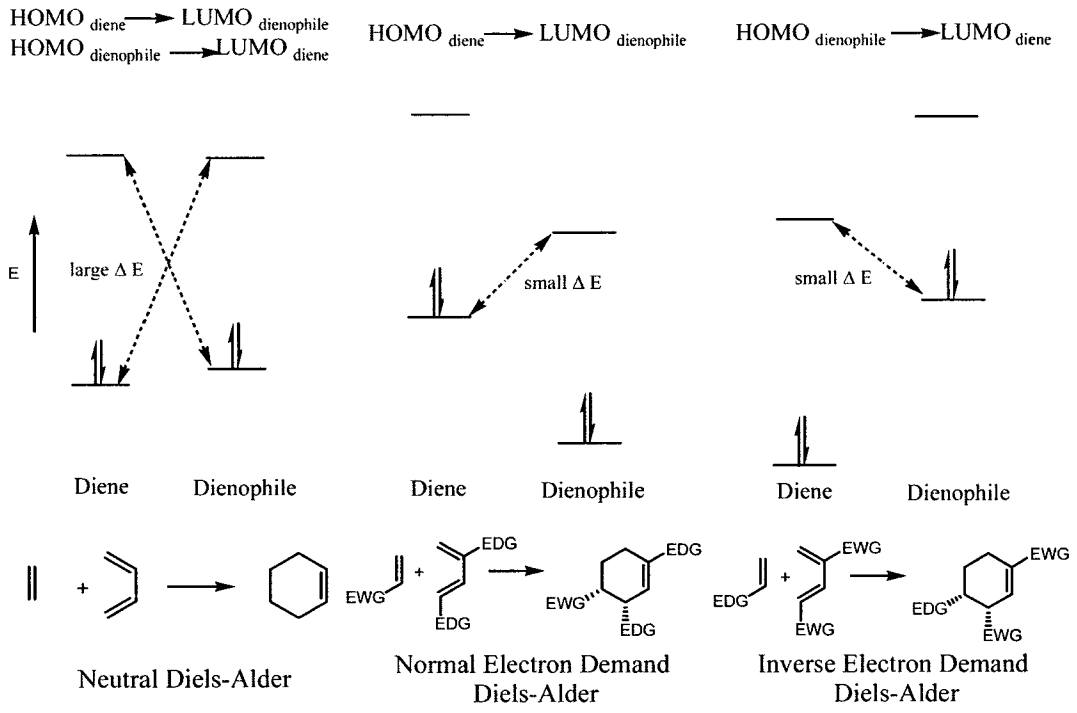
Scheme 1.10: Demonstration of substituent effects on the reacting partners of the Diels-Alder reaction.

rationalize the regiochemical outcome of the Diels-Alder reactions they reported.

FMO theory is a qualitative approach commonly used to explain the reactivity and selectivity of the Diels-Alder reaction.[16] The cycloaddition of cyclopentadiene **40** with ethene **2** occurs under harsh conditions; i.e. 200 °C, 278 KPa over 32 h, to produce norbornene **41** (74%, Scheme 1.10).[17] Placing substituents, either electron-donating or electron-withdrawing, on the diene and/or dienophile can greatly influence the progress of the reaction. For example, acrolein **42** was reacted with cyclopentadiene **40** to afford the bicyclic aldehyde **43** as a mixture of *endo* and *exo* cycloadducts under mild conditions, i.e., ether as the solvent and at room temperature for 24 h. This difference in reactivity, by the addition of an aldehyde group to the dienophile, was attributed to the change in the difference in energy between the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) of the reacting species. The basis for concentrating attention on these two molecular orbitals is they are closest in

[16] (a) Woodward, R. B.; Hoffman, R. *J. Am. Chem. Soc.* **1965**, *87*, 395–397. (b) Sustmann, R.; Schubert, R. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 840. (c) Houk, K. N. *J. Am. Chem. Soc.* **1973**, *95*, 4092–4094. (d) Houk, K. N. *Acc. Chem. Res.* **1975**, *8*, 361–369.

[17] Diels, O.; Alder, K. *Justus Liebigs Ann. Chem.* **1928**, *460*, 98–122.



Scheme 1.11: Representation of the FMO interactions for the three types of Diels-Alder reactions

energy to each other and the extent of their interaction is inversely proportional to their energy of separation and can be correlated to the rate of the reaction.[18]

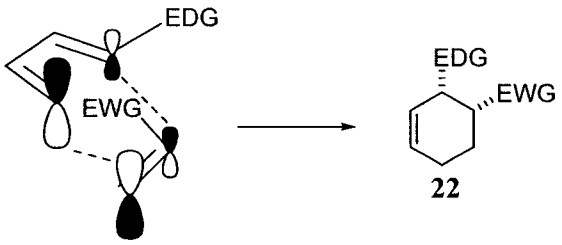
There are three classifications of the Diels-Alder reaction: the neutral Diels-Alder reaction, normal (electron-demand) Diels-Alder reaction, and the inverse-electron-demand Diels-Alder (IEDDA). Each of these utilizes the interaction or mixing of frontier molecular orbitals as shown in Scheme 1.11, which allows the pericyclic reaction to proceed. The neutral Diels-Alder reaction takes place between a diene and dienophile that do not bear electron-donating or electron-withdrawing substituents. Of the three reaction types, this one typically has the largest energy difference between the HOMO

[18] Sauer, J.; Sustmann, R. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 779–807.

and LUMO of the reacting species and thus usually proceeds only under severe conditions.

The normal Diels-Alder reaction has enjoyed widespread use within the synthetic community.[13] The inclusion of electron-donating substituents on the diene results in the energy of its frontier molecular orbitals to be raised compared to the parent diene, 1,3-butadiene **1**. Addition of electron-withdrawing groups on the dienophile results in a lowering the energy of its frontier molecular orbitals compared to the parent dienophile, ethene **2**. These energy changes to the FMOs of the reacting species create a smaller energy difference between the $HOMO_{diene}$ and the $LUMO_{dienophile}$. The reduction of this energy barrier results in substantial increase in the rate of the reaction and thus the normal Diels-Alder reaction can be carried out under far milder conditions than required for the neutral Diels-Alder, e.g. Scheme 1.10.

The IEDDA reaction has the opposite FMO interaction to that of the normal Diels-Alder reaction. The inclusion of an electron-withdrawing group on the diene lowers the energy of its frontier molecular orbitals whereas the dienophile bears an electron-donating group, which raises the energy of its frontier molecular orbitals. Again, the overall effect of the electronically complementary substituents on the diene and dienophile is to lower the energy difference between the $HOMO_{dienophile}$ and the $LUMO_{diene}$ compared to the same frontier molecular orbitals of the neutral Diels-Alder reaction. In a similar fashion to the normal Diels-Alder reaction, the reduction of this energy barrier results in substantial increase in the rate of the reaction and thus the



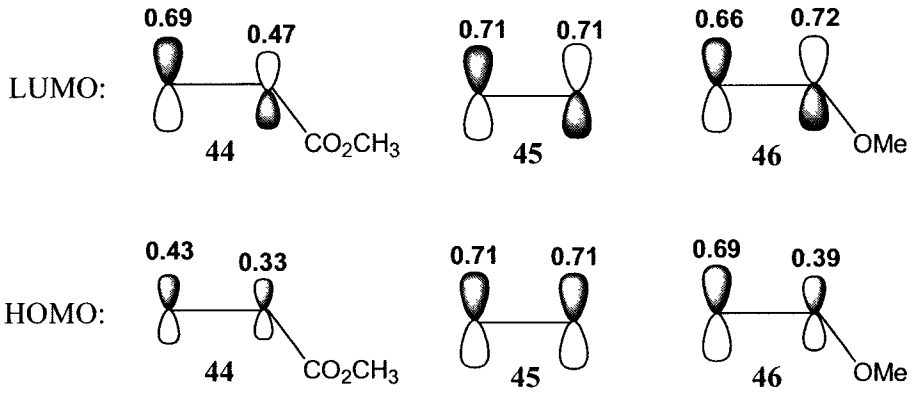
Scheme 1.12: Regiochemical outcome of the Diels-Alder reaction using FMO theory.

IEDDA reaction can be carried out under far milder conditions than required for the neutral Diels-Alder.

The regioselectivity can be explained using valence bond theory, as discussed above, but is perhaps explained better using FMO theory. This involves the examination of the (molecular) orbital coefficients of the HOMO and LUMO of the reacting partners. The diene and dienophile will orient in such a way as to allow the terminal carbon atom of one reacting species that has the largest orbital coefficient to begin bond formation with the corresponding carbon atom of the other reacting species (Scheme 1.12). This interaction determines the regiochemical outcome of the cycloaddition.

Orbital coefficients shown in Scheme 1.13 are representative of the perturbations to the molecular orbitals of ethene when electron-donating and electron-withdrawing groups are placed on the molecule.[19] The numbers located above the orbitals represent the magnitude of the coefficient of that orbital. For the following discussion it has arbitrarily been chosen that the darkened portion of the orbital represents a positive or in-phase symmetry while the light portion of the orbital represents a negative or out-of-

[19] Houk, K. N. In *Pericyclic Reactions* Marchand, A. P.; Lehr, R. E., eds.; Academic: New York, 1977, vol. II, pp. 203–205.



Scheme 1.13: Orbital coefficients for a range of dienophiles.

phase symmetry.[20] When *p* orbitals next to one another have similar symmetry, both in-phase or both out-of-phase, a bonding interaction occurs, e.g. HOMO **44**. If both *p* orbitals have different symmetries, one in-phase and one out-of-phase, an antibonding interaction occurs, e.g. LUMO **44**.

Orbital coefficients for the HOMO of ethene **45** and the LUMO of ethene **45** are identical. When substituents, either electron-donating or electron-withdrawing, are placed on ethene the magnitudes of the orbitals coefficients are influenced significantly.[21] The LUMO of methyl acrylate interacts with the HOMO of an electron-rich diene to

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[20] See ref. 19, pg. 203.

[21] (a) Kahn, S. D.; Pau, C. F.; Overman, L. E.; Hehre, W. J. *J. Am. Chem. Soc.* **1986**, *108*, 7381–7396. (b) Jordon, K. D.; Michejda, J. A.; Burrow, P. D. *Chem. Phys. Lett.* **1976**, *42*, 227–231. (c) Kadifachi, S. *Chem. Phys. Lett.* **1984**, *108*, 233–236. (d) Sauer, J.; Wiest, H.; Mielert, A. *Chem. Ber.* **1964**, *97*, 3183–3207. (e) Pearson, R. G. *J. Org. Chem.* **1989**, *54*, 1423–1430. (f) Dougherty, D.; Brint, P.; McGlynn, S. P. *J. Am. Chem. Soc.* **1978**, *100*, 5597–5603. (g) Heinis, T.; Chowdury, S.; Scott, S. L.; Kebarle, P. *J. Am. Chem. Soc.* **1988**, *110*, 400–407. (h) Dinur, U.; Honig, B. *J. Am. Chem. Soc.* **1979**, *101*, 4453–4460. (i) Dewar, M. J. S.; Rzepa, H. S. *J. Am. Chem. Soc.* **1978**, *100*, 784–790. (j) Ng, L.; Jordan, K. D.; Krebs, A.; Rüger, W. *J. Am. Chem. Soc.* **1982**, *104*, 7414–7416. (k) El-Basil, S.; Said, M. *Ind. J. Chem.* **1980**, *19B*, 1071–1073. (l) Bihlmaier, W.; Huisgen, R.; Reissig, H.-U.; Voss, S. *Tetrahedron Lett.* **1979**, 2621–2624. (m) Houk, K. N. *Acc. Chem. Res* **1975**, *8*, 361–369. (n) Michl, J.; Becker, R. J. *J. Chem. Phys.* **1967**, *46*, 3889–3894.

allow the pericyclic reaction to occur. The orbital with the larger coefficient, i.e., 0.69, of the acrylate will bond with the terminal carbon atom of the diene that has the larger orbital coefficient. The similar process occurs with the reaction between methyl vinyl ether and an electron-deficient diene. The carbon atom that bears the larger orbital coefficient, i.e., 0.69, of the $HOMO_{dienophile}$ and the terminal carbon atom of the $LUMO_{diene}$ react with one another.

When discussing the orbital coefficients for a diene, only the orbitals that are located on terminal carbons have any significance with the Diels-Alder reaction. These orbitals are involved in the primary bonding process. The published data on the magnitude of orbital coefficients for dienes concentrate on electron-rich dienes and the following discussion will only deal with such systems.[21a,21b,21d,21m,22]

The magnitude of the orbital coefficients on each terminal carbon atom of the HOMO **49** and the LUMO **49** of 1,3-butadiene are the same (Scheme 1.14). Addition of an electron-donating group, e.g. a methoxy substituent, at C-1 of 1,3-butadiene results in a perturbation of the FMOs of 1,3-butadiene. In particular for the HOMO, which is involved in the bonding process of the normal Diels-Alder reaction, the magnitude of the orbital coefficient at C-4 is larger than the orbital coefficient at C-1. Again, this difference in orbital coefficients plays a role in determining the regiochemical outcome of

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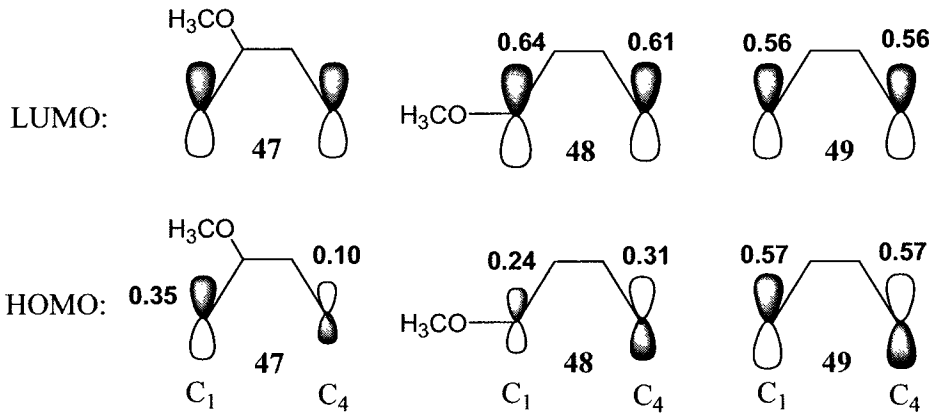
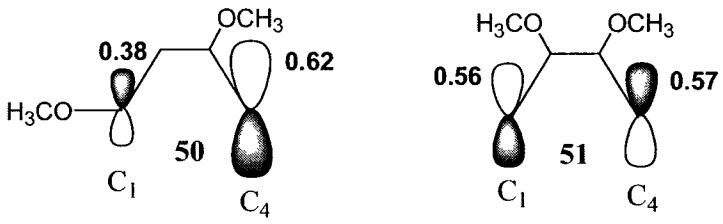
[22] (a) Sustmann, R.; Schubert, R. *Tetrahedron Lett.* **1972**, 2739–2742. (b) Kakushima, M. *Can. J. Chem.* **1979**, *57*, 2564–2568. (c) Kroner, J.; Bock, H. *Theor. Chim. Acta* **1968**, *12*, 214–228. (d) Alston, P. V.; Ottenbrite, R. M.; Shillady, D. D. *J. Org. Chem.* **1973**, *38*, 4075–4077. (e) Alston, P. V.; Ottenbrite, R. M. *J. Org. Chem.* **1975**, *40*, 1111–1116. (f) Jordan, K. D.; Burrow, P. D. *Chem. Phys. Lett.* **1975**, *36*, 594–598. (g) Giordan, J. C.; McMillan, M. R.; Moore, J. H.; Staley, S. W. *J. Am. Chem. Soc.* **1980**, *102*, 4870–4872. (h) Jordan, K. D.; Burrow, P. D. *Acc. Chem. Res.* **1978**, *11*, 341–348. (i) Van Veen, E. H. *Chem. Phys. Lett.* **1976**, *41*, 535–539. (j) Lazzaroni, R.; Boutique, J. P.; Riga, J.; Verbist, J. J.; Fripiat, J. G.; Delhalle, J. *J. Chem. Soc. Perkin Trans. II* **1985**, 97–102.



Scheme 1.14: Comparison of orbital coefficients for two electron-rich dienes and 1,3-butadiene.

a reaction between this diene and an electron-poor dienophile. When the methoxy group is placed on the C_2 carbon, only the data for the HOMO have been reported.[22a] Yet again, the inclusion of an electron-donating group, i.e., methoxy substituent, at C-2 results in perturbation of the FMOs of 1,3-butadiene. The orbital coefficient at C-1 is larger than the corresponding orbital coefficient at C-4. Once more, this difference in orbital coefficients helps direct the regiochemical outcome in the normal Diels-Alder reaction.

When two substituents are placed on the diene, the effect can either work cooperatively or against one another with regard to the development of regiochemistry. When substituents of the same electronic nature, i.e. electron-donating or -withdrawing, are placed at the 1- and 3-positions, e.g. adduct **50** (Scheme 1.15), they cooperate to favor the same regiochemical outcome of the Diels-Alder reaction. If the substituents are at the 2- and 3-positions, e.g. **51**, they work against one another and the orbital coefficients



Scheme 1.15: Cooperative and uncooperative effect of two substituents on 1,3-butadiene.

reflect this. There are many substitution patterns of 1,3-butadiene when more than one substituent is bonded to this moiety. These effects must be taken into account for predicting the regiochemical outcome of the Diels-Alder reaction.

1.2 The Inverse-Electron-Demand Diels-Alder Reaction

Of the three electronic types of Diels-Alder reactions, the normal Diels-Alder is by far the most studied and frequently used. This is not to say that the IEDDA reaction has received little attention. To the contrary, there is a substantial body of literature on the IEDDA reaction, the major aspects of which are discussed below.

1.2.1 Azadienes

IEDDA dienes need low-lying LUMOs to allow interactions with the HOMOs of electron-rich dienophiles and permit the cycloadditions to occur. Azadienes have a nitrogen atom in the diene moiety. Replacing a carbon atom with a more electronegative

element, e.g. nitrogen, lowers the LUMO energy of that diene making it more receptive to react with an electron-rich dienophile. This atom replacement acts in the same manner as placing electron-withdrawing groups onto the diene. The more heteroatoms that are present in the diene the lower the LUMO becomes, resulting in the diene becoming more reactive towards electron-rich dienophiles.

The 1- and 2-aza-1,3-butadiene systems have been studied,[25] but more commonly the azadiene is embedded within an aromatic unit and generally referred to as a heteroaromatic diene. These electron-deficient dienes and their IEDDA reactions have been reviewed.[23] Several total syntheses of natural products have been disclosed using these dienes.[24] The utilization of an electron-deficient pyridine as a diene in the IEDDA reaction is rare.[25] Pyridazines **52**,[26] also called 1,2-diazines, substituted with electron-withdrawing substituents undergo IEDDA reactions. After the initial reaction with an electron-rich alkene, the bicyclic intermediate **54** is formed (Scheme 1.16). This intermediate undergoes a retro-Diels-Alder reaction extruding N_2 to generate another electron-deficient diene **55**. Typically, the electron-donating group that was present in the dienophile can participate in an elimination reaction after the retro-Diels-Alder reaction in order to produce the aromatic product **56**.

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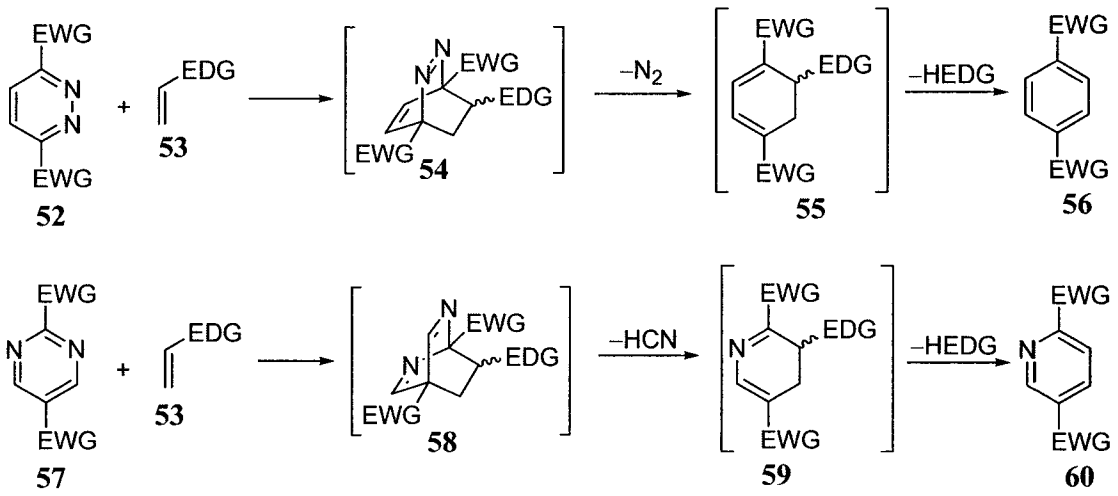
[23] (a) Boger, D. L.; Weinreb, S. M. In *Hetero Diels-Alder Methodology in Organic Synthesis*; Academic Press, Inc.: San Diego, 1987. (b) Fringuelli, F.; Taticchi, A. In *Dienes in the Diels-Alder Reaction*; Wiley Interscience: New York, 1990. (c) Weinreb, S. M.; Staib, R. R. *Tetrahedron* **1982**, *38*, 3087–3128. (d) Boger, D. L. *Tetrahedron* **1983**, *39*, 2869–2939.

[24] Boger, D. L. *Chem. Rev.* **1986**, 781–793.

[25] (a) Neunhoeffer, H.; Lehmann, B. *Liebigs Ann. Chem.* **1975**, 1113–1119. (b) Gompper, R.; Heinemann, U. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 216.

[26] For reviews of 1,2-diazine IEDDA chemistry see: (a) Tisler, M.; Stanovnik, B. In *Advances in Heterocyclic Chemistry*; Academic Press, Inc.: New York, 1979; Vol. 24, pp. 363–456. (b) Tisler, M.; Stanovnik, B. In *Comprehensive Heterocyclic Chemistry*; Pergamon: Oxford, 1984; Vol. 3, pp. 1–56.



Scheme 1.16: General synthetic pathway for heteroazadiene IEDDA reaction.

Recently, Bodwell and Li[27] have reported the concise synthesis of indolophane **61** and its transannular[28] inverse-electron-demand Diels-Alder reaction to produce the pentacyclic indoloid sytem **63** (Scheme 1.17). Indolophane **61** was produced in three steps with a sequential hydroboration/Suzuki-Miyaura cross-coupling reaction[29] as the key step. When heated, the transannular IEDDA reaction gives intermediate **62**, which then loses N_2 via a retro-Diels-Alder reaction to afford the pentacyclic indoloid system **63** (90%). This methodology has recently been applied to a formal total synthesis of (±)-strychnine **64** (Figure 1.2).[30]

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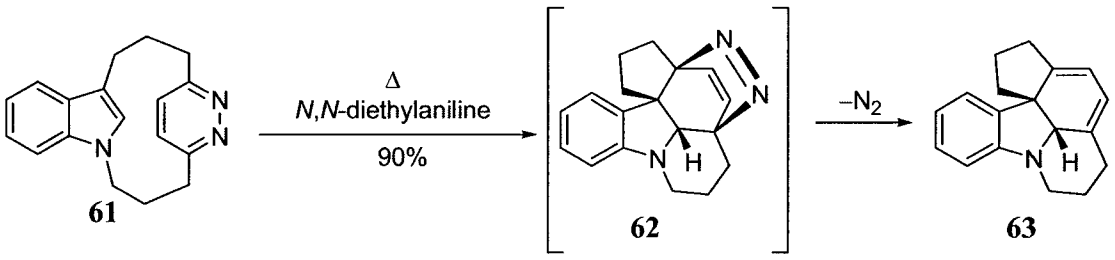
[27] Bodwell, G. J.; Li, J. *Org. Lett.* **2002**, *4*, 127–130.

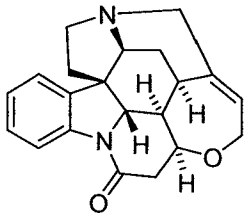
[28] For an example of a transannular Diels-Alder reaction, see: Marsualt, E.; Toró, A.; Nowak, P.; Deslongchamps, P. *Tetrahedron* **2001**, *57*, 4243–4260.

[29] (a) Chemler, S. R.; Danishefsky, S. J. *Org. Lett.* **2000**, *2*, 2695–2698. (b) Oh-e, T.; Miyaura, N. Suzuki, A. *J. Org. Chem.* **1993**, *58*, 2201–2208. (c) Miyaura, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Satoh, M.; Suzuki, A. *J. Am. Chem. Soc.* **1989**, *111*, 314–321.

[30] Bodwell, G. J.; Li, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 3261–3262.



Scheme 1.17: A transannular inverse electron demand Diels-Alder to give access to a pentacyclic indoloid system.



64

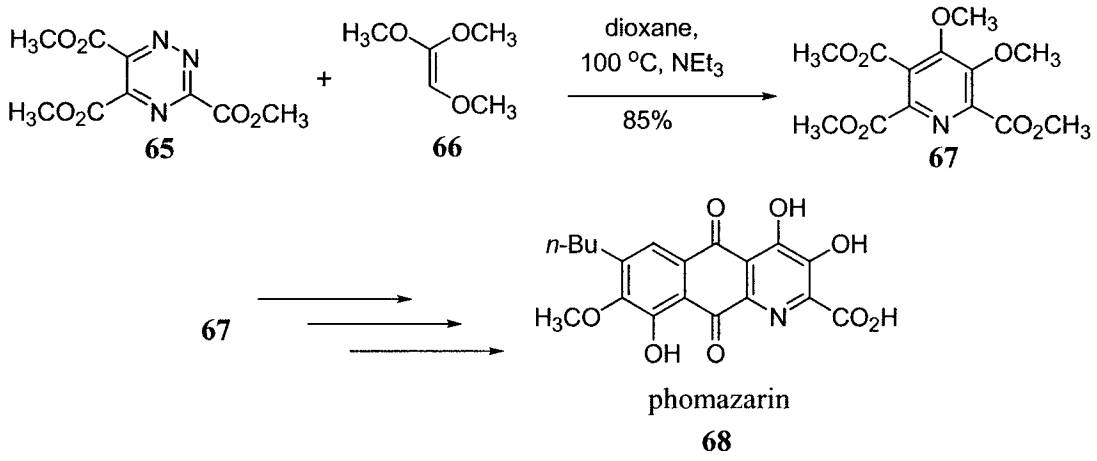
Figure 1.2: Strychnine

Pyrimidines **57**, or 1,3-diazine, bearing strongly electron-withdrawing substituents will take part in IEDDA reactions as well. The reaction proceeds by a mechanism analogous to that of pyridazines **52**, with one major difference. The bicyclic intermediate **58** that is produced from the initial IEDDA reaction undergoes a retro-Diels-Alder reaction to extrude hydrogen cyanide instead of N_2. Substituted pyridines **60** are obtained when the dienophile contains a group that can take part easily in an elimination reaction.

The most thoroughly investigated heteroaromatic azadiene is the 1,2,4-triazine system.[31] Recently, Boger reported the synthesis of the naturally occurring azaanthraquinone phomazarin **68** (Scheme 1.18).[32] The electron-poor heteroarene **65** was heated with the electron-rich alkene **66** to obtain the highly substituted pyridine **67**

[31] For reviews of 1,2,4-triazine IEDDA chemistry see: (a) Neunhoeffuer, A.; Wiley, P.F. In *Chemistry of Heterocyclic Compounds* Weissberger, A.; Taylor, E. C., Eds; Wiley: New York, 1978, Vol. 33, pp. 226–228. (b) Neunhoeffuer, A. In *Comprehensive Heterocyclic Chemistry* Boulton, A. J.; McKillop, A., Eds.; Pergamon: London, 1984, Vol. 3, pp. 421–429. (c) see ref. 23(d), pp. 2912–2922. (d) Boger, D. L. *Chem. Rev.* **1986**, *86*, 781–793.

[32] Boger, D. L.; Hong, J.; Hikota, M.; Ishida, M. *J. Am. Chem. Soc.* **1999**, *121*, 2471–2477.



Scheme 1.18: Synthesis of phomazarin **68** using an IEDDA of 1,2,4-triazine molecule.

through the domino IEDDA/retro-Diels-Alder/elimination sequence. Pyridine **67** was then transformed into phomazarin **68** in several steps.

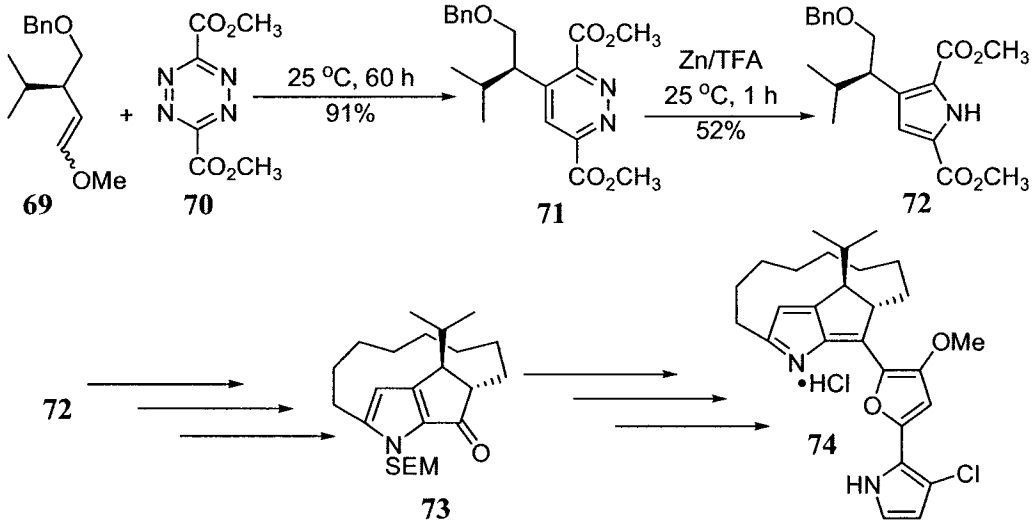
The even more electron-deficient 1,2,4,5-tetrazines have also been the subjects of broad interest. Extensive investigations have defined the scope and potential of 1,2,4,5,-tetrazine participation within the inverse-electron-demand Diels-Alder reaction.[33] Although very reactive towards electron-rich dienophiles, Boger and Weinreb point out that only a limited number of symmetrical 1,2,4,5,-tetrazines have been reported, which suggests some difficulties might be associated with the preparation of this type of electron-deficient heteroarene.[34] A lack of synthetic methods to afford nonsymmetrical 1,2,4,5-tetrazines has limited the use of these in the IEDDA reaction. The IEDDA

[33] For reviews of 1,2,4,5-tetrazine chemistry see: (a) Neunhoeffuer, A. In *Comprehensive Heterocyclic Chemistry* Pergamon: London 1984, Vol. 3, pp. 550–555. (b) Neunhoeffuer, A.; Wiley, P. F. In *Chemistry of Hetrocyclic Compounds* Weissberger, A.; Taylor, E. C., Eds.; Wiley: New York, 1978, Vol. 33, pp. 1095–1097.

[34] Boger, D. L.; Weinreb, S. M. In *Hetero Diels-Alder Methodology in Organic Synthesis*; Academic Press, Inc.: San Diego, 1987, pg. 335.

reaction mechanism resembles the pathway for pyridazine. Typically, the product isolated from this IEDDA reaction is a substituted pyridazine when the electron-donating group can participate in an elimination reaction to afford the heteroarene. The pyridazine can then undergo a second IEDDA reaction, usually under more forcing conditions, to produce a highly substituted benzene ring in two synthetic operations.

Boger and Houng recently disclosed the total synthesis of *ent*-(−)-roseophilin hydrochloride **74**, which featured a key IEDDA reaction between 1,2,4,5-tetrazine **70** and enantiomerically pure vinyl ethers **69** to produce pyridazine **71** (90%, Scheme 1.19).[35] The pyridazine was then subjected to a reductive ring contraction in the presence of zinc and trifluoroacetic acid to afford pyrrole **72** (52%). The pyrrole was transformed into **73** and then finally into *ent*-(−)-roseophilin·HCl **74**.

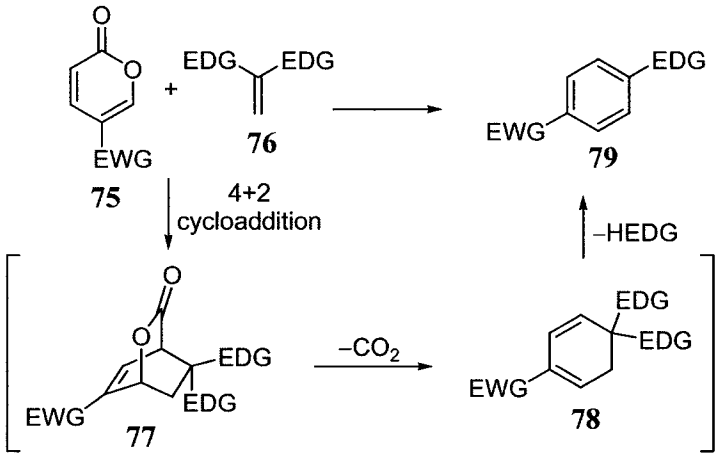


Scheme 1.19: Synthesis of *ent*-(−)-roseophilin·HCl **74** using an IEDDA reaction of 1,2,4,5-tetrazine **70** with dienophile **69**.

[35] Boger, D. L.; Hong, J. *J. Am. Chem. Soc.* **2001**, *123*, 8515–8519.

1.2.2 All-Carbon Electron-Deficient Dienes Within 6-Membered Rings

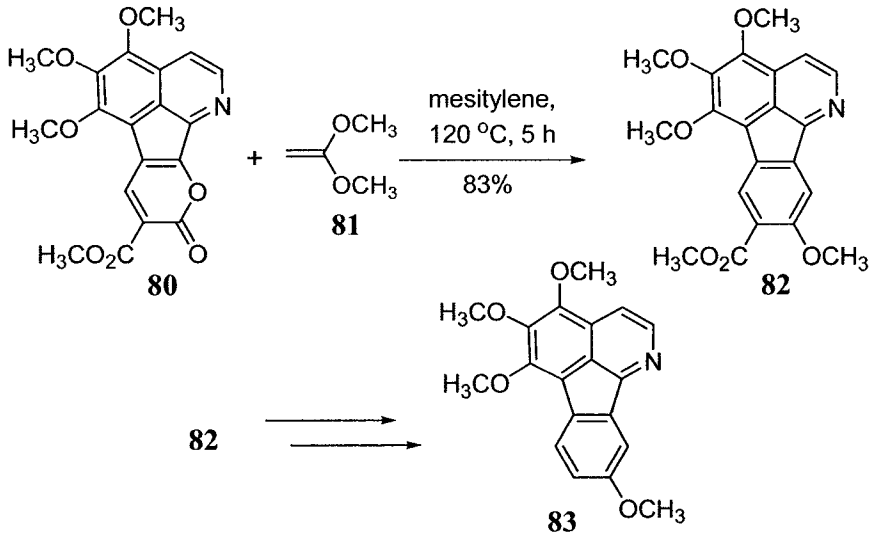
2-Pyrones are by far the most investigated and reported[36] of the all-carbon electron-poor dienes that have been utilized for IEDDA chemistry. Mechanistically, the reaction of these dienes, e.g. 5-substituted-2-pyrones (Scheme 1.20), is analogous to the heteroaromatic azadiene system discussed above. The initial Diels-Alder reaction produces a bicyclic lactone **77**. Under appropriate reaction conditions this species will produce CO_2 via a retro-Diels-Alder reaction to give diene **78**. When the dienophile used in this reaction contains a group that can be easily eliminated, e.g. as HEDG, the product obtained is arene **79**.



Scheme 1.20: General reaction mechanism for an IEDDA reaction of 5-substituted 2-pyrone with an electron-rich alkene.

[36] (a) Cho, C.-G.; Kim, Y.-W; Lim, Y.-W.; Park, J.-S. Lee, H.; Koo, S. *J. Org. Chem.* **2002**, *67*, 290–293. (b) Chen, C.-H.; Liao, C.-C. *Org. Lett.* **2000**, *2*, 2049–2052. For reviews of 2-pyrone chemistry see: (c) Posner, G. H.; Bull, D. S. *Recent Res. Devel. in Org. Chem.* **1997**, *1*, 259–271. (d) Afarinkia, K.; Vinader, V.; Nelson, T. D.; Posner, G. H. *Tetrahedron* **1992**, *48*, 9111–9171. (e) Kalinin, V. N.; Shilova, O. S. *Russ. Chem. Rev.* **1994**, *63*, 661–666. (f) Markò, I. E.; Evans, G. R.; Seres, P.; Chelle, I.; Janousek, Z. *Pure Appl. Chem.* **1996**, *68*, 113–122.

The majority of cycloadditions using 2-pyrones as the diene proceed under thermal conditions, but it has been demonstrated that Lewis acids can facilitate these reactions.[37] 2-Pyrones have been reacted with a wide variety of dienophiles such as vinyl ethers,[38] ketene acetals,[39] ynamines,[40] and enamines.[41] Reaction conditions may be modified to obtain the bicyclic lactones **77** or products that have lost CO_2, i.e. **78**. This methodology has produced several natural products like sendaverine,[42] 6,7-benzomorphans,[43] juncosol,[44] rufescine **83** (Scheme 1.21),[45] and imeluteine.[45]



Scheme 1.21: Key IEDDA reaction within the rufescine **83** total synthesis.

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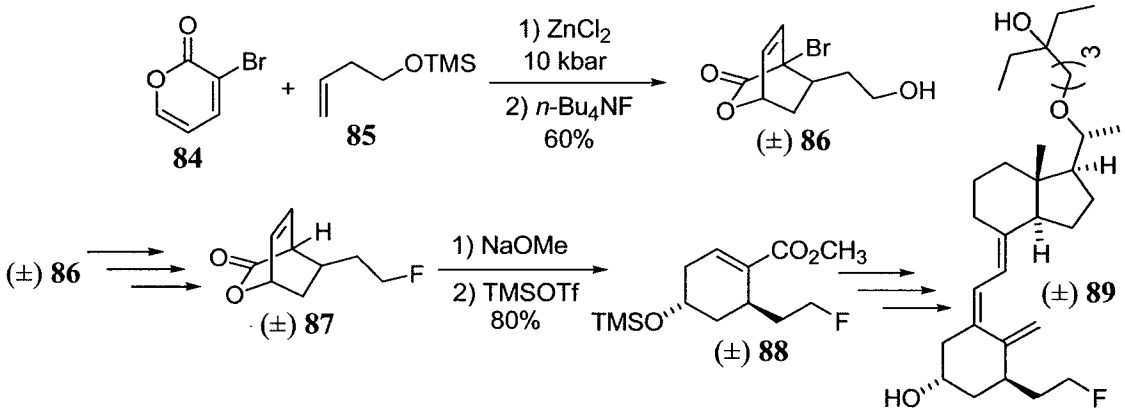
[37] Posner, G. H.; Dai, H.; Bull, D. S.; Lee, J.-K.; Eydoux, F.; Ishihara, Y.; Welsh, W.; Pryor, N.; Petr Jr., S. *J. Org. Chem.* **1996**, *61*, 671–676.
[38] Posner, G. H.; Wettlaufer, D. G. *Tetrahedron Lett.* **1986**, *27*, 667–670.
[39] Jung, M. E.; Hagenah, J. A. *J. Org. Chem.* **1987**, *52*, 1889–1902.
[40] Bryson, T. A.; Donelson, D. M. *J. Org. Chem.* **1977**, *42*, 2930–2931.
[41] Gingrich, H. L.; Roush, D. M.; Van Saun, W. A. *J. Org. Chem.* **1983**, *48*, 4869–4873.
[42] Boger, D. L.; Mullican, M. D. *J. Org. Chem.* **1984**, *49*, 4033–4044.
[43] Boger, D. L.; Patel, M.; Mullican, M. D. *Tetrahedron Lett.* **1982**, *23*, 4559–4562.
[44] Boger, D. L.; Mullican, M. D. *Tetrahedron Lett.* **1982**, *23*, 4555–4558.; Boger, D. L.; Mullican, M. D. *J. Org. Chem.* **1984**, *49*, 4045–4050.
[45] Boger, D. L.; Brotherton, C. E. *J. Org. Chem.* **1984**, *49*, 4050–4055.

More recently, this methodology has been used to set up the relative stereochemistry around a cyclohexene ring within analogs of the hormone 1α,25-dihydroxyvitamin D_3 **89** (Scheme 1.22).[46] A high pressure/Lewis acid catalyzed IEDDA reaction occurs between 3-bromo-2-pyrone and the terminal alkene to give the desired cycloadduct **86** with complete regioselectivity, complete *endo*-selectivity and in moderate yield. Through a series of functional group interconversions, this product was transformed into fluoride **87**. This bicyclic lactone was then opened through basic methanolysis of the ester function to afford cyclohexene **88**. Double bond migration, which ruled out the reverse reaction, presumably occurred following the opening of the lactone. Ester **88** was then transformed into analogs of 1α,25-dihydroxyvitamin D_3 **89**.

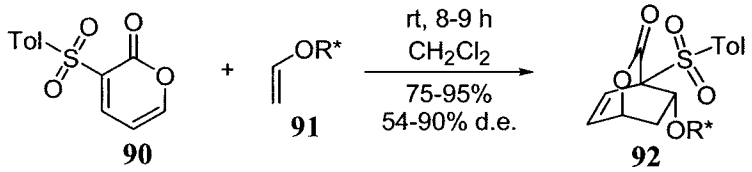
A key feature of this approach is that it is highly diastereoselective. Early attempts to achieve this goal investigated the use of 3-(4-tolylsulfinyl)pyran-2-one as a



Scheme 1.22: Key IEDDA reaction within the total synthesis of a desired analog of 1α,25-dihydroxyvitamin D3.

[46] Posner, G. H.; Lee, J. K.; White, C.; Hutchings, R. H.; Dai, H.; Kachinski, J. L.; Dolan, P.; Kensler, T. W. *J. Org. Chem.* **1997**, *62*, 3299–3314.

diene and achieved moderate diasteroselectivity.[47] Posner quickly followed this report by reacting chiral alkyl vinyl ethers **91** with 3-(4-tolylsulfonyl)pyran-2-one **90** to afford bicyclic lactones **92** with moderate to high diastereoselectivities (Scheme 1.23).[48] This idea remained dormant for several years until reports surfaced discussing the use of chiral Lewis acids such as, $Eu(hfc)_3$,[49] (+)-$Yb(tfc)_3$,[50] and (−)-$Pr(hfc)_3$.[51] Unfortunately, these catalysts gave disappointingly low enantioselectivities.[50] Shortly after these reports, modest to high enantioselectivities, i.e. 57% - >95%, were published using a TADDOL-titanium species,[52] BINOL-titanium species,[53] and a Binol-$Yb(OTf)_3$ species.[54]



90 **91** **92**

Scheme 1.23: IEDDA reaction of 2-pyrone **96** with a chiral vinyl ether.

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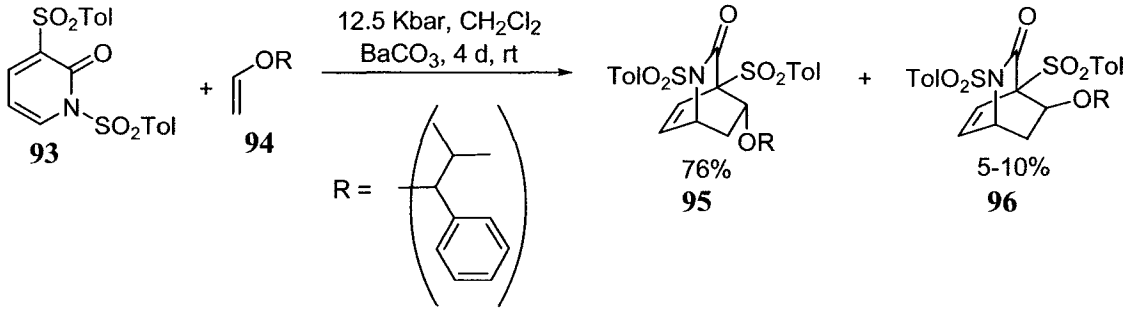
[47] Posner, G. H.; Harrison, W. *J. Chem. Soc., Chem. Commun.* **1985**, 1786–1787.
[48] Posner, G. H.; Wettlaufer, D. G. *Tetrahedron Lett.* **1986**, *27*, 667–670.
[49] Markó, I. E.; Evans, G. R. *Synlett* **1994**, 431–433.
[50] Posner, G. H.; Ishihara, Y. *Tetrahedron Lett.* **1994**, *35*, 7545–7548.
[51] Posner, G. H.; Carry, J.-C.; Anjeh, T. E. N.; French, A. N. *J. Org. Chem.* **1992**, *57*, 7012–7014.
[52] Posner, G. H.; Carry, J.-C.; Lee, J. K.; Bull, D. S.; Dai, H. *Tetrahedron Lett.* **1994**, *35*, 1321–1324.
[53] (a) Posner, G. H.; Eydoux, F.; Lee, J. K.; Bull, D. S. *Tetrahedron Lett.* **1994**, *35*, 7541–7544. (b) Posner, G. H.; Dai, H.; Bull, D. S.; Lee, J.-K.; Eydoux, F.; Ishihara, Y.; Welsh, W.; Pryor, N.; Petr Jr., S. *J. Org. Chem.* **1996**, *61*, 671–676.
[54] (a) Markó, I. E.; Evans, G. R.; Declercq, J.-P. *Tetrahedron* **1994**, *50*, 4557–4574. (b) Markó, I. E.;Chellé-Regnaut, I.; Leroy, B.; Warriner, S. L. *Tetrahedron Lett.* **1997**, *38*, 4269–4272. (c) Markó, I. E.; Evans, G. R.; Declercq, J.-P.; Tinant, Bernard, T.; Feneau-Dupont, J. *Acros Org. Acta* **1995**, *1*, 63–64.

There are other dienes which are similar to 2-pyrone, but these have not attracted as much attention over the years. One of these systems is 2-pyridone. This system readily undergoes normal Diels-Alder reactions.[55] There are only a few reports of this diene undergoing an IEDDA reaction.[56] One example involves the reaction of 2-pyridone **93** with vinyl ethers **94** under high-pressure conditions (Scheme 1.24). Electron-withdrawing groups were placed on the 2-pyridone structure to (presumably) lower its LUMO and render it a more reactive IEDDA diene.

Recently, another system has appeared in the literature and it has gathered some attention. Liao *et al.* accidentally discovered that a masked *o*-benzoquinone underwent an IEDDA reaction with furan (Scheme 1.25).[57] Methyl 4-hydroxy-3-methoxybenzoate **97** when stirred in the presence of (diacetoxy)iodobenzene (DAIB) in methanol forms the masked *o*-benzoquinone **98**. It reacts with furan **99** under very mild conditions to



Scheme 1.24: An IEDDA reaction using a substituted 2-pyridone with a vinyl ether.

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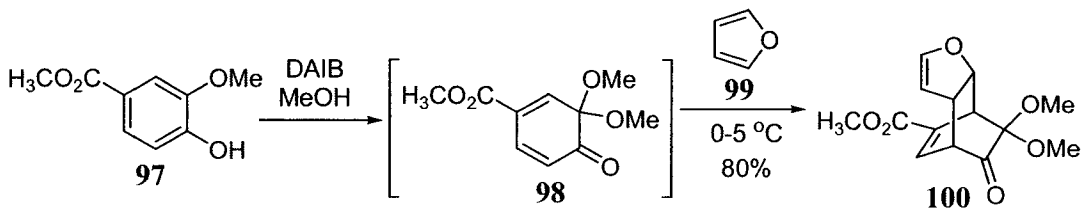
[55] (a) Afarinkia, K.; Vinader, V.; Nelson, T. D.; Posner, G. H. *Tetrahedron* **1992**, *48*, 9111–9171. (b) Posner, G. H.; Vinader, V.; Afarinkia, K. *J. Org. Chem.* **1992**, *57*, 4088–4097.

[56] (a) Hazai, L.; Deák, G.; Tóth, G.; Schnitta, A.; Szôllôsy, Á.; Tamás, J. *Acta Chim. Hung.* **1983**, *113*, 237–241. (b) Hazai, L.; Schnitta, A.; Deák, G.; Tóth, G.; Szôllôsy, Á. *Acta Chim. Hung.* **1984**, *117*, 99–116. (c) Hazai, L.; Schnitta, A.; Deák, G.; Tamás, J. *Acta Chim. Hung.* **1985**, *120*, 271–274. (d) Posner, G. H.; Switzer, C. *J. Org. Chem.* **1987**, *52*, 1644–1646.

[57] Chen, C.-H.; Rao, P. D.; Liao, C.-C. *J. Am. Chem. Soc.* **1998**, *120*, 13254–13255.

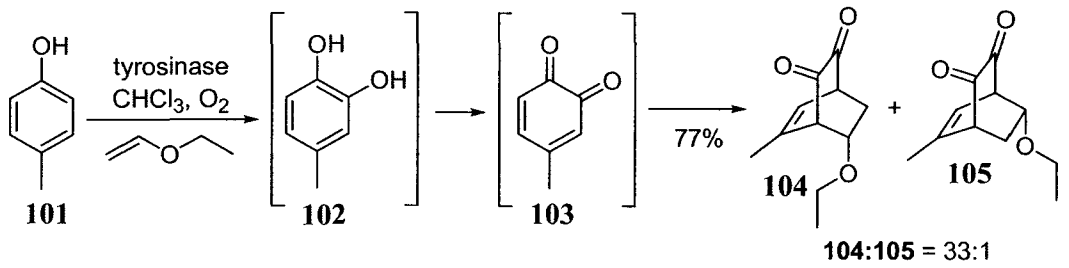


Scheme 1.25: Inverse electron demand Diels-Alder reactivity of a masked *o*-benzoquinone with furan.

produce the cycloadduct **100** (80%). Liao *et al.* demonstrated that the reactivity of this diene with a series of substituted furans afforded the cycloadducts in high yields via *endo* transition states. Since this initial report, this masked *o*-benzoquinone has been reacted with other dienophiles, such as enol/thioenol ethers,[58] thiophenes, [59] and pyrroles.[60] Rodrigo and co-workers have recently reported an intramolecular version of this reaction to afford the natural product halenaquinone.[61]

Around the same time, Waldmann *et al.*[62] reported the generation of *o*-benzoquinones from substituted phenols through an enzymatic hydroxylation/oxidation process using a tyrosinase/O_2 mixture, e.g. Scheme 1.26. A series of dienophiles was found to react with these *o*-benzoquinones, when generated *in situ*, to produce bicyclic 1,2-diketones, e.g. **104**, in very variable yields (19-85%). For example, phenol **101** was oxidized to the catechol **102** by tyrosinase, which was further oxidized by the O_2 present to generate the *o*-benzoquinone **103**. Ethyl vinyl ether reacted as a dienophile to give a

[58] (a) Arjona, O.; Medel, R.; Plumet, J. *Tetrahedron Lett.* **1999**, *40*, 8431–8433. (b) Gao, S.-Y; Ko, S.; Lin, Y.-L.; Peddinti, R. K.; Liao, C.-C. *Tetrahedron* **2001**, *57*, 297–308.
[59] Lai, C.-H.; Ko, S.; Roa, P. D.; Liao, C.-C. *Tetrahedron Lett.* **2001**, *42*, 7851–7854.
[60] Hsich, M.-F.; Peddinti, R. K.; Liao, C.-C. *Tetrahedron Lett.* **2001**, *42*, 5481–5484.
[61] Sutherland, H. S.; Souza, F. E. S.; Rodrigo, R. G. A. *J. Org. Chem.* **2001**, *66*, 3639–3641.
[62] Muller, G. H.; Lang, A.; Seithel, D. R.; Waldmann, H. *Chem. Eur. J.* **1998**, *4*, 2513–2522.

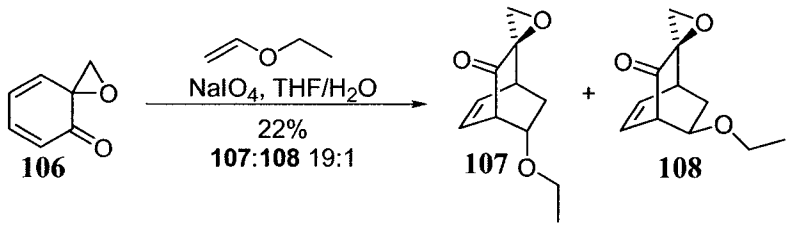


Scheme 1.26: Inverse-electron-demand Diels-Alder reactivity of an *in situ* generated *o*-benzoquinone with ethyl vinyl ether.

mixture afforded the mixture of cycloadducts **104** and **105** in 77% yield in a 33:1 ratio via an IEDDA reaction. Typically, these diene systems lack regiochemical control in pericyclic processes.[63] This makes the observed ratio of regioisomers produced from this example to be astonishing due to the fact that the inclusion of one methyl group, a very weak electron-donating group, dictates the regiochemical outcome of the cycloaddition.

In 1993, Gesson *et al.*[64] discovered that 6-spiroepoxycyclohexadienones **106**, obtained from salicyl alcohols by Alder-Becker oxidation with $NaIO_4$, in the presence of excess ethyl vinyl ether would produce a mixture of cycloadducts **107** and **108** in 22% yield. This initial report was followed by an in-depth examination of the IEDDA reactivity with various dienophiles with 4-bromo-6-spiroepoxycyclohexa-2,4-dienone.[65] It was observed that the reactions occurred in good yields with complete regioselectivity and facial selectivity with all dienophiles adding *syn* to the epoxide oxygen. The

[63] Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem. Int. Ed.* **2002**, *41*, 1668–1698. More specifically, refer to pp. 1687–1688.
[64] Gesson, J.-P.; Hervaud, L.; Mondon, M. *Tetrahedron Lett.* **1993**, *34*, 2941–2944.
[65] (a) Bonnarme, V.; Bachmann, C.; Cousson, A.; Mondon, M.; Gesson, J.-P. *Tetrahedron* **1999**, *55*, 433–448. (b) Mondon, M.; Boeker, N.; Gesson, J.-P. *J. Chem. Research (S)* **1999**, 484–485.



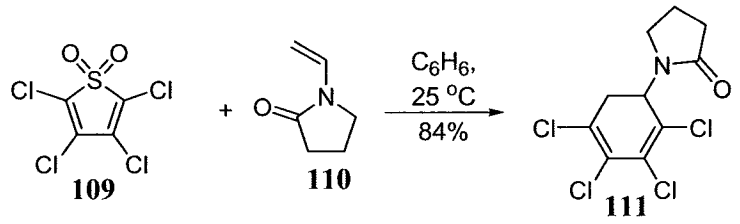
Scheme 1.27: Inverse-electron-demand Diels-Alder reactivity of an *in situ* generated spiroepoxydiene **106** with ethyl vinyl ether.

endo:*exo* selectivity varied from poor with vinyl acetate (1:2), to excellent with ethyl vinyl ether (19:1) (Scheme 1.27).

1.2.3 All-Carbon Electron-Deficient Dienes Within 5-Membered Rings

These systems have received much less attention than those discussed above. Raasch reported an in-depth study of the reactivity of tetrachlorothiophene 1,1-dioxide **109** with electron-poor, neutral and electron-rich dienophiles.[66] Diene **109** was prepared by oxidation of tetrachlorothiophene with *m*-CPBA. In general, reactions with electron-poor dienophiles needed elevated temperatures to promote the cycloaddition. However, electron-rich dienophiles such as *N*-vinylpyrrolidinone (Scheme 1.28), would react with the diene **109** at room temperature, indicating a favorable HOMO/LUMO interaction as compared to the reaction of electron-poor dienophiles, to afford tetrachlorocyclohexadiene **111** (84%). It was somewhat surprising, that aromatization via the elimination of 2-pyrrolidinone did not occur under these conditions.

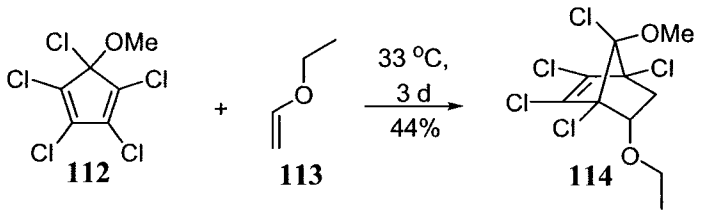
[66] Raasch, M. S. *J. Org. Chem.* **1980**, *45*, 856–867.



Scheme 1.28: Inverse-electron-demand Diels-Alder reaction of tetrachlorothiophene 1,1-dioxide **109** with *N*-vinylpyrrolidinone **110.**

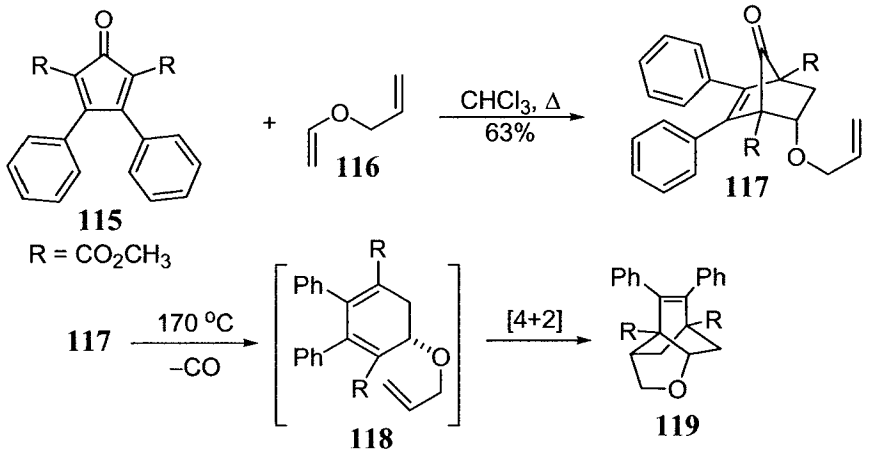
Cyclopentadiene **112** was synthesized as part of a project aimed at studying facial selectivity of the Diels-Alder reactivity of 5-substituted 1,3-cyclopentadienes.[67] Electron-poor, neutral and electron-rich dienophiles were all reacted with this diene. All the dienophiles, for example ethyl vinyl ether **113**, added *syn* to the methoxy group of the diene and via an *endo* transition state (Scheme 1.29). The authors of this study concluded that the data "suggests that the stabilization, and hence facial selectivity, in all cyclopentadiene derivatives is due mainly to steric or torsional considerations".

Cyclopentadienone **115** was reported to react with allyl vinyl ether **116** to produce bicyclic ketone **117** in 63% yield via an *endo* transition state (Scheme 1.30).[68]



Scheme 1.29: IEDDA reaction of diene **112** with ethyl vinyl ether **113** to only afford endo adduct **114.**

[67] Burry, L. C.; Bridson, J. N.; Burnell, D. J. *J. Org. Chem.* **1995**, *60*, 5931–5934.
[68] Harano, K.; Uchida, K.; Izuma, M.; Aoki, T.; Eto, M.; Hisano, T. *Chem. Pharm. Bull.* **1988**, *36*, 2312–2322.



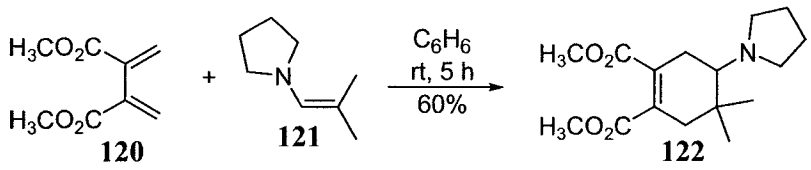
Scheme 1.30: IEDDA reactivity of cyclopentadienone **115** with allyl vinyl ether **116** to afford **119**.

Subsequent loss of carbon monoxide followed by an intramolecular [4+2] afforded cage compound **119** (92%). However, the instability of simple cyclopentadienones required the incorporation of numerous and bulky stabilizing substituents, i.e. phenyl,[69] to enable the desired cycloadditions to occur. All of the dienes discussed within this section appear to have low synthetic utility.

1.2.4 Acyclic Electron-Deficient Dienes

This group of electron-deficient dienes is not a prominent one, but has been receiving increasing levels of attention over the past decade. The first diene to be investigated for its IEDDA reactivity was dimethyl 2,3-dimethylenebutanedioate **120**.[70] A two-step synthesis was employed to produce **120** in 50% overall yield, which was a

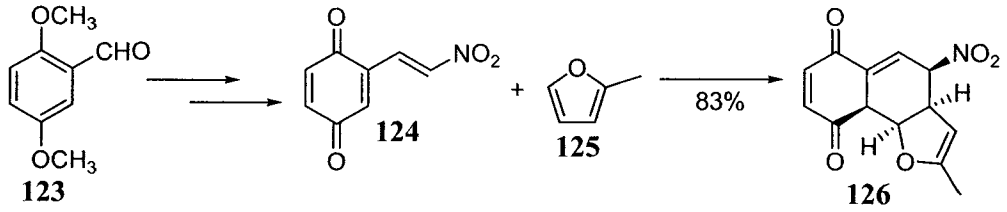
[69] Harano, K.; Yasuda, M.; Ban, T.; Kanematsu, K. *J. Org. Chem.* **1980**, *45*, 4455–4462.
[70] Grundke, C.; Hoffman, H. M. R. *Chem. Ber.* **1987**, *120*, 1461–1462.



Scheme 1.31: IEDDA reactivity of dimethyl 2,3-dimethylenebutanedioate **120** with enamine **121**.

marked improvement from the previously reported synthesis.[71] Unfortunately, diene **120** was reacted with only a single electron-rich dienophile, enamine **121**, to afford cycloadduct **122** in 60% yield (Scheme 1.31).

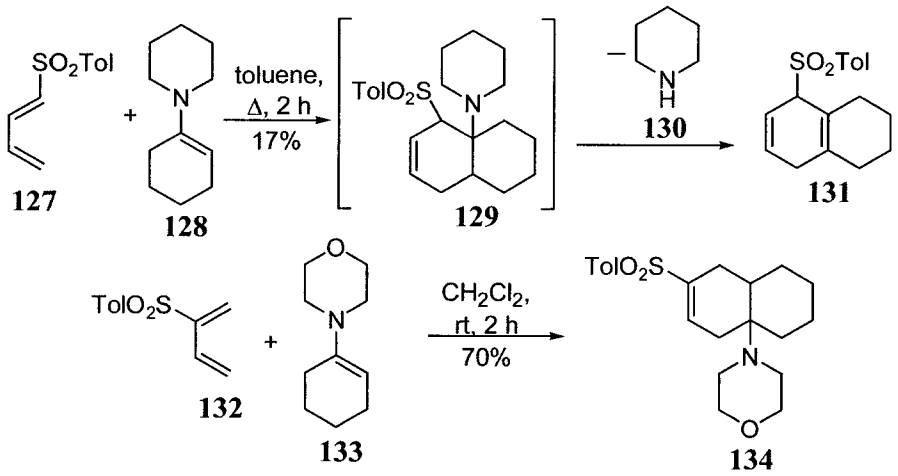
More recently, Noland and Kedrowskia disclosed the synthesis of 2-(2-nitrovinyl)-1,4-benzoquinone **124**.[72] The electron-poor diene **124** was generated in a three-step procedure starting from 2,5-dimethoxybenzaldehyde **123**. The diene was reacted with several electron-rich dienophiles, e.g. **125** (Scheme 1.32), to produce a series of cycloadducts similar to **126** in low to high yields (14-95%). It should be noted that the cycloadducts were obtained as a single regioisomer via an *endo* transition state.



Scheme 1.32: IEDDA reactivity of diene **124** with furan **125**.

[71] (a) Bailey, W. J.; Hudson, R. L.; Yates, E. T. *J. Org. Chem.* **1963**, *28*, 828–831. (b) Bellus, D.; Weis, C. D. *Tetrahedron Lett.* **1973**, *14*, 999–1000.
[72] Noland, W. E.; Kedrowski, B. L. *J. Org. Chem.* **1999**, *64*, 596–603.

Electron-poor dienes that contain sulfonyl groups seem to be the most investigated within this group of dienes. An in-depth review was disclosed on the chemistry of these compounds, which includes the small number of reports of IEDDA chemistry.[73] Dienes with sulfonyl groups at the 1-position[74] and 2-position[75] have been shown to react with electron-rich olefins (Scheme 1.33), for example, sulfonyl diene **127** reacts with enamine **128** to generate intermediate cycloadduct **129**, followed by an elimination of piperidine **130** to give **131** (17%). Surprisingly, a 1,4-elimination of toluene sulfinate does not occur to aromatize the product. A second example involves the reaction of sulfonyl diene **132** with electron-rich olefin **133** to give rise **134** in much better yield (70%). This higher yield for the second example demonstrates Spino's



Scheme 1.33: Two examples of the IEDDA reactivity of monosubtituted sulfonyl dienes.

[73] Bäckvall, J.-E.; Chinchilla, R.; Nájera, C.; Yus, M. *Chem. Rev.* **1998**, *98*, 2291–2312.
[74] (a) Flitsch, W.; Lubisch, W.; Rosche, J. *Liebigs Ann. Chem.* **1987**, 655–659.

hypothesis[76] that a monosubstitiuted diene reacts better in a [4 + 2] mechanism when the diene contains an unsaturated substituent at the 2-position rather than the 1-position.

There are a very few published examples of the synthesis of electron-poor all-carbon dienes bearing substituents at the 1- and 3-positions. The electron-rich counterparts, e.g. Danishefsky's diene **32**[11] and Rawal's diene **33**[12] have enjoyed widespread use, especially in the synthesis of natural products.[13c-13f] The attractiveness of these dienes is the high reactivity in the normal Diels-Alder and the predictable nature of the regiochemical outcome (see section 1.1 Diels-Alder Reaction). Dienes that are electronically complementary to Danishefsky's and Rawal's diene, i.e., **135** – **139** (Figure 1.3), would be expected to exhibit the same predictable regiochemistry in the inverse-electron-demand Diels-Alder reaction.

Ahn and Hall reported the synthesis of dienes **135-138** in 1981 by a retro-Diels-Alder approach (Scheme 1.34).[77] Cyclopentadiene **40** was reacted with acrylonitrile (X =

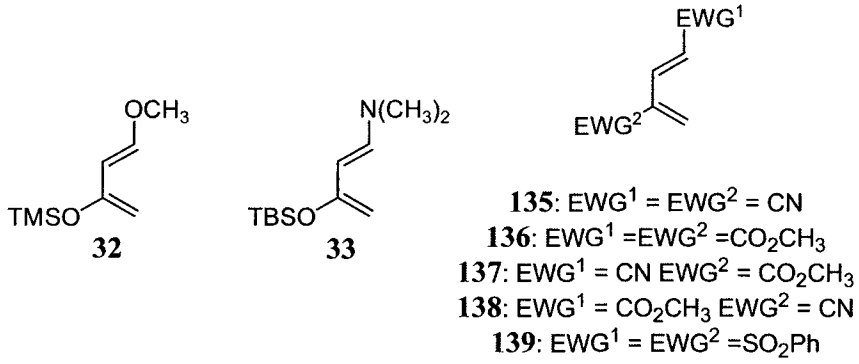


Figure 1.3: Electronic complements of electron-rich 1,3-disubstituted butadienes.

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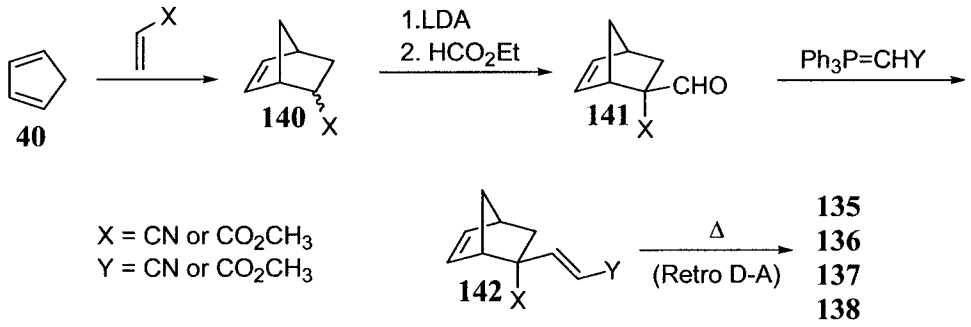
[75] (a) Bäckvall, J.-E.; Juntinen, S. K.; *J. Am. Chem. Soc.* **1987**, *109*, 6396–6403. (b) Chou, T.; Hung, S.-C.; Tso, H.-H. *J. Org. Chem.* **1987**, *52*, 3394–3399. (c) Bäckvall, J.-E.; Rise, F. *Tetrahedron Lett.* **1989**, *30*, 5347–5348.

[76] Spino, C.; Pesant, M.; Dory, Y. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 3262–3265.

[77] Ahn, K.-D.; Hall, H. K. *J. Polym. Sci., Polym. Chem. Ed.* **1981**, *19*, 629–644.

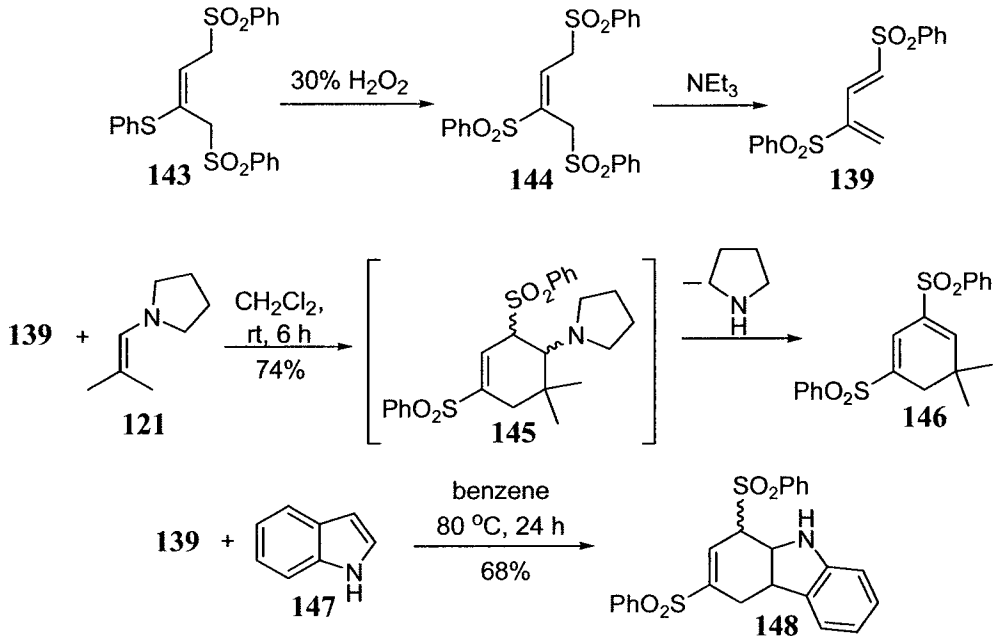


Scheme 1.34: Ahn and Hall's synthetic strategy for producing electron poor dienes.

CN) or methyl acrylate (X = CO_2CH_3) to produce bicyclic alkenes **140**. Treatment with lithium diisopropylamide and quenching the resulting anion with ethyl formate generated aldehyde **141**. Wittig reactions with the appropriate phosphoranes afforded vinylnorbornenes **142**, which were subjected to a thermally driven retro-Diels-Alder reaction to generate the desired electron-deficient dienes. It was discovered that these dienes readily polymerized in a 1,4 sense.

Some time after this initial report, Padwa *et al.*[78] accidentally observed diene **139** when investigating the IEDDA reactivity of 2,3-sulfonyl-1,3-butadiene. A more concise route to **139** was then published (Scheme 1.35).[79] Unfortunately, it was observed to dimerize readily when purified. To combat this problem, the diene was generated *in situ* with variety of electron-rich olefins, e.g enamine **121** (Scheme 1.35), and the diene was trapped as the cycloadduct. All observed products such as **146** were reported to have the expected regiochemistry. Even the much weaker dienophile indole **147** reacted with **139** to form **148**, although a longer reaction time and higher reaction temperature were

[78] Padwa, A.; Harrison, B.; Norman, B. H. *J. Org. Chem.* **1991**, *56*, 2713–2720.
[79] Padwa, A.; Gareau, Y.; Harrison, B.; Rodriguez, A. *J. Org. Chem.* **1992**, *57*, 3540–3545.



Scheme 1.35: Synthesis of Padwa's diene **139** and examples of it's IEDDA reactivity

required. Again, the regioselective control was complete. Since this time, no further work in the area of IEDDA chemistry has been reported.

1.2.5 IEDDA Research in the Bodwell Group

The Bodwell group first became involved in research into the IEDDA reaction in the early 1990s. The impetus for this work was the possibility of discovering a new route to isophthalates, which are important precursors to cyclophanes. Thus, electron-deficient 1,3-disubstituted dienes were the primary subjects of investigation. With the knowledge that **135-138** are not very stable, attention turned towards annulated systems, e.g. **149-152** (Figure 1.4). It was envisaged that annulation would stabilize the diene kinetically, and

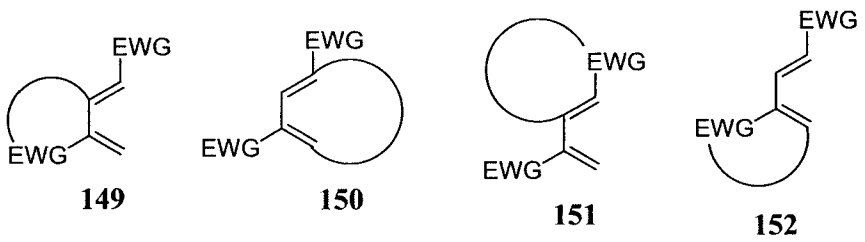


Figure 1.4: Modes of annulating the electron poor diene.

possibly also thermodynamically. However, striking the proper balance between stability and reactivity was an important consideration. System **152** was selected for initial investigation. The synthesis of this type of electron-deficient diene and its IEDDA reactivity will be presented and discussed in the following chapters, ending with a total synthesis of a natural product that utilizes the methodology that was developed.

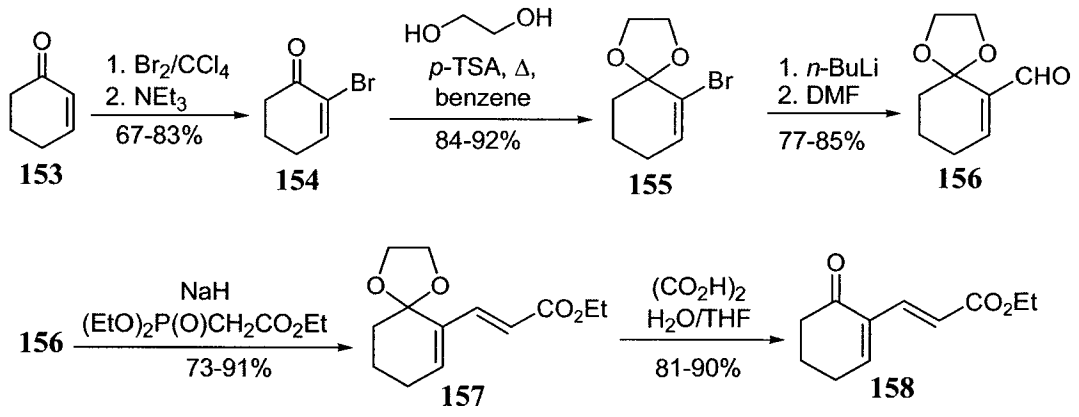
Chapter 2.

Preparation of New Electron-Deficient Dienes

2.0 Preparation of New Electron-Deficient Dienes

2.1 Introduction

The first report of a cycloalkane-annulated diene **158** prepared in the Bodwell group, appeared in 1997 (Scheme 2.1).[82] The synthesis began with cyclohexenone **153**, which was subjected to a bromination/dehydrobromination sequence to give bromoketone **154** in moderate to good yields. Immediate protection of the ketone as a cyclic acetal afforded **155** in high yield. A halogen-metal exchange was performed by treatment of **155** with *n*-butyllithium and this was followed by the addition of dry DMF to afford aldehyde **156** in high yields. Horner-Wadsworth-Emmons (HWE) olefination[83] of **156** gave diene **157**, exclusively with the *E* geometry at the newly formed double bond. Removal of the cyclic acetal protecting group afforded electron-deficient diene



Scheme 2.1: Synthesis of cycloalkane annulated diene **158**.

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[82] Bodwell, G. J.; Pi, Z. *Tetrahedron Lett.* **1997**, *38*, 309–312.

[83] For reviews of the Horner-Wadsworth-Emmons olefination, see: (a) Minami, T.; Okauchi, T.; Kouno, R. *Synthesis* **2001**, 349–357. (b) Boutagy, J.; Thomas, R. *Chem. Rev.* **1974**, *74*, 87–99. (c) Wadsworth, W. S. *Org. React.* **1977**, *25*, 73–253. (d) Grob, H.; Keitels, I. *Z. Chem.* **1982**, *22*, 117–126.

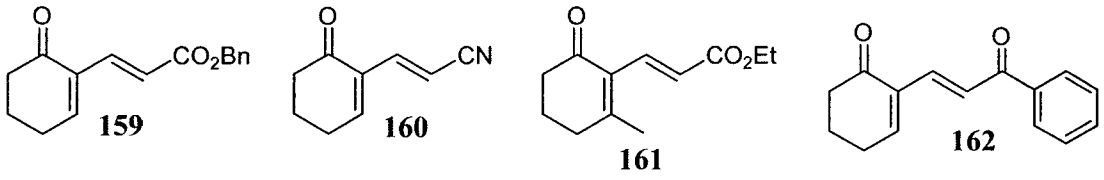

Figure 2.1: Dienes produced through the HWE olefination strategy.

158. It was gratifying that **158** was, it was found to be sufficiently stable to be isolated and characterized. If stored at room temperature, it began to show signs of decomposition immediately, but it was observed to be stable for several weeks at –20 °C under an atmosphere of N_2.

Using this approach, a series of related electron-deficient dienes, i.e. **159-162** (Figure 2.1),[84] were prepared and their IEDDA chemistry was investigated. Some of this chemistry will be discussed in Chapter 3.1. All of these dienes were reported to be stable for several weeks at –20 °C under an atmosphere of N_2, similar to **158**.

[84] (a) Pi, Z. *M.Sc. Thesis* **1996**, Memorial University of Newfoundland. (b) Langille, J. D. *M.Sc. Thesis* **1999**, Memorial University of Newfoundland.

2.2 Results and Discussion

2.2.1 Synthesis of a Coumarin-Fused Diene

Two key aspects of practical syntheses of complex molecules in organic chemistry are the brevity of execution and the incorporation of new technology.[85] From this perspective the synthetic strategy used to produce diene **158** led to the achievement of the initial goal of generating an electron-deficient diene that was substituted with electron-withdrawing groups at the 1 and 3 positions but the five step sequence can hardly be called brief. The annulation strategy was also successful in sufficiently stabilizing the diene to enable it to be isolated and to be used in further reactions with electron-rich dienophiles without the need for special handling (see Section 3.1).

A more expedient synthetic route was desired for production of electron-deficient dienes. In this vein, it was envisaged that dimethyl glutaconate **163** (a vinylogue of dimethyl malonate) would undergo vinylogous Knoevenagel condensations with aldehydes **164a-c**, respectively to afford dienes **165a-165c** (Scheme 2.2). Isomerically pure diene **165c** had been previously synthesized through a tin-mediated palladium-catalyzed cross-coupling reaction.[86] The stability of this diene was not discussed, but it was reportedly purified by column chromatography on silica gel, which gave cause for optimism. However, reactions of aldehydes **164a**, **164b**, and **164c** with dimethyl glutaconate **163** resulted in the consumption of the reactants and the formation of

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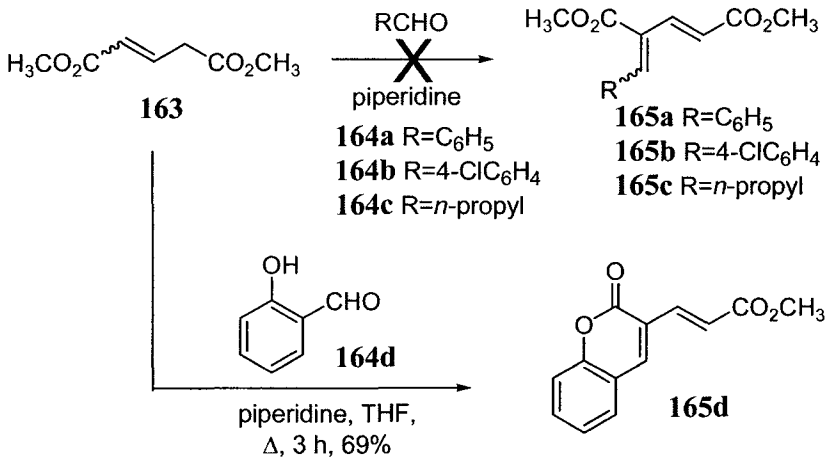
[85] Hudlicky, T. *Chem. Rev.* **1996**, *96*, 3–30.

[86] (a) Rossi, R.; Carpita, A.; Bellina, F.; Cossi, P. *J. Organomet. Chem.* **1993**, *451*, 33–43. (b) Bellina, F.; Carpita, A.; Santis, M.; Rossia, R. *Tetrahedron* **1994**, *50*, 12029–12046.

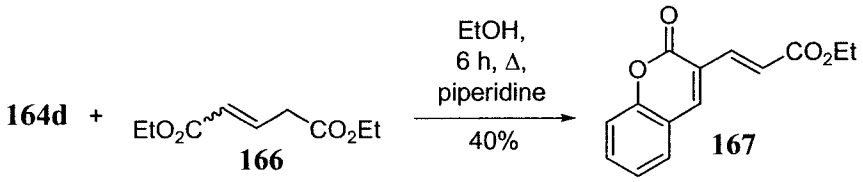


Scheme 2.2: Vinylogous Knoevenagel condensations of dimethyl glutaconate with aldehydes.

intractable products. With the knowledge of the reported instability of the parent dienes **135-139**[79,81] (see Figure 1.3), it may well be that the desired products **165a**, **165b**, and **165c** did indeed form, but reacted further under the conditions of their formation.

The failure of these reactions led to an investigation of the Knoevenagel condensation between salicylaldehyde **164d** and dimethyl glutaconate **163**. The reaction between diethyl malonate and salicylaldehyde is known to afford 3-carbethoxy-coumarin[87] and it was anticipated that the reaction between **164d** and **163** would occur in an analogous manner to give **165d**. This process worked well, giving the coumarin-fused diene **165d** in 69% yield as well as some intractable material. The stability of diene **165d** (>6 months in air) was far greater than the previous dienes **158-162** (several weeks at –20 °C under N_2) produced by the Bodwell research group. This was most likely a

[87] Horning, E. C.; Horning, M. G.; Dimmig, D. A. *Org. Synth., Coll. Vol. III* **1955**, 165–167.



Scheme 2.3: Triggle *et al.* synthesis of the ethyl ester coumarin-fused diene **167**.

consequence of the partial aromatic character of the 2-pyrone moiety. Changing the solvent from THF to benzene increased the yield of **165d** from 69% to 92%. The geometry about the acrylate double bond was assigned as the (*E*)-isomer by virtue of the 15.3 Hz coupling constant between C2-H and C3-H of the acrylate moiety.

The analogous reaction with diethyl glutaconate **166** had been reported using ethanol as the solvent (Scheme 2.3).[88] The product, compound **167**, was prepared for the purpose of investigating its photochemical properties and not the investigation of its IEDDA chemistry. Comparing the physical properties of the solvent used for the formation of the coumarin-fused dienes, **165d** and **167**, the yield of the product appeared to be related to the dielectric constant of the solvent (Table 2.1), i.e. as the dielectric constant of the solvent became smaller the yield for the diene became larger. It was difficult to make any conclusions about this relationship because the reaction was completed only in three different solvent systems. Performing the reaction in a variety of solvents with different dielectric constants would create better data to help make a proper conclusion. In fact, there may not be any relationship between the two at all. In 1937, Cope reported that the removal of water from the reaction mixture would significantly

[88] Padmanabhan, S.; Peri, R.; Triggle, D. J. *Synth. Commun.* **1996**, *26*, 827-831.

improve the yield of Knoevenagel condensation[89] and this might be the reason why the yield of diene **165d** was the highest when the reaction was completed in benzene.

Table 2.1: Comparison of solvent dielectric constant versus the yield of coumarin-fused diene **165d**.

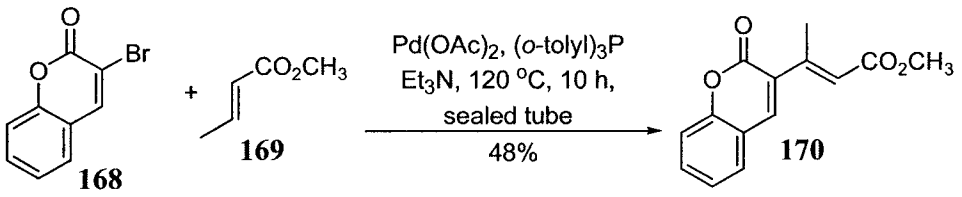
Entry	Solvent	Yield	Dielectric Constant[90]
1	EtOH	40%	24.55
2	THF	68%	7.58
3	Benzene	92%	2.28

2.2.2 Modification of the Coumarin-Fused Diene

2.2.2.1 The Heck Reaction

The vinylogous Knoevenagel condensation was successful in generating an electron-deficient coumarin-fused diene that was substituted with electron-withdrawing groups at the 1 and 3 positions in only one synthetic operation. Attention was now turned to an investigation of both the generality of this approach (see Section 4.2) and the viability of other concise routes to related dienes. The syntheses of a number of electron-deficient dienes by palladium-catalyzed cross coupling reactions have been

[89] Cope, A. C. *J. Am. Chem. Soc.* **1937**, *59*, 2327–2330.
[90] Values taken from: Smith, M. B. In *Organic Synthesis*, McGraw Hill, Inc: New York, 1994, pg. 125.



Scheme 2.4: Mitra *et al.* synthesis of coumarin-fused diene **170**.

explored recently.[86,91] A communication from Mitra *et al.*[92] reported the palladium-catalyzed coupling reaction of several olefins with 3-bromocoumarin **168**. In one example, the electron-poor olefin methyl (*E*)-crotonate **169** was used to prepare coumarin-fused diene **170** (48%, Scheme 2.4). This prompted the initiation of an investigation into the use of the Heck reaction[93] as a general approach to construct coumarin-fused diene systems **171a-171d** (Scheme 2.5).

The reaction conditions described by Mitra *et al.* included the use of a sealed tube, which is unsuitable for the production of the desired dienes in multigram quantities. Consequently, attention was turned to finding reaction conditions that would allow this and related transformations to proceed satisfactorily without the need for a sealed tube.

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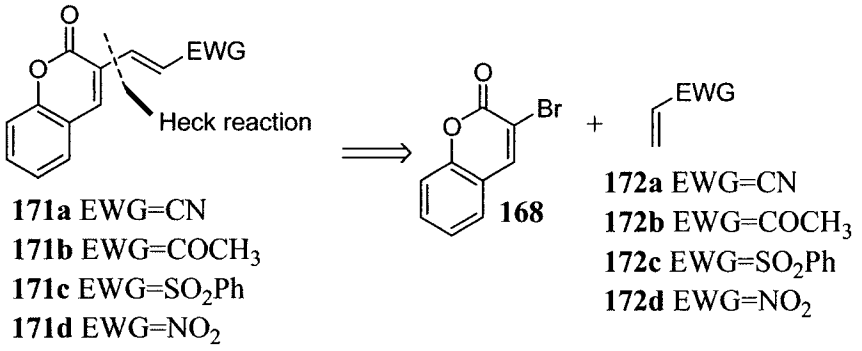
[91] (a) Houpis, I. N.; DiMechele, L.; Molina, A. *Synlett* **1993**, 365–366. (b) Jeges, G.; Skoda-Földes, R.; Kollár, L.; Horváth, J.; Tuba, Z. *Tetrahedron* **1998**, *54*, 6767–6780. (c) Kim, H.-O.; Ogbu, C. O.; Nelson, S.; Kahn, M. *Synlett* **1998**, 1059–1060.

[92] Mitra, A. K.; Nilay, A. D.; Karchaudhuri, N.; Mitra, J. *J. Chem. Research (S)* **1998**, 766–767.

[93] (a) Heck, R. F. *J. Am. Chem. Soc.* **1968**, *90*, 5518–5526. (b) Heck, R. F. *Acc. Chem. Res.* **1979**, *12*, 146–151. For recent reviews, see: (c) Bohlm, C.; Hildebrand, J. P.; Muniz, K.; Hermanns, N. *Angew Chem., Int. Ed. Engl.* **2001**, *40*, 3285–3308. (d) deVries, J. G. *Can. J. Chem.* **2001**, *79*, 1086–1092. (e) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009–3066. (f) Franzen, R. *Can. J. Chem.* **2000**, *78*, 957–962. (g) Brase, S.; deMeijere, A. In *Palladium-Catalysed Coupling of Organyl Halides to Alkenes – The Heck Reaction*; Diederich, F.; Stang, P. J., Eds.; Wiley-VCH, Inc.: New York, 1998; pp. 99–166. (h) Crisp, G. T. *Chem. Soc. Rev.* **1998**, *27*, 427–436. (i) Cabri, W.; Gibson, S. E.; Middleton, R. J. *Cont. Org. Syn.* **1996**, *3*, 447–471. (j) Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2–7. (k) de Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379–2441.



171a EWG=CN
171b EWG=$COCH_3$
171c EWG=SO_2Ph
171d EWG=NO_2

172a EWG=CN
172b EWG=$COCH_3$
172c EWG=SO_2Ph
172d EWG=NO_2

Scheme 2.5: Retrosynthetic cut to produce a varitety of electron-poor all-carbon dienes.

3-Bromocoumarin **168**[94] was easily produced in multigram quantities using a bromination/dehydrobromination procedure[95] and then subjected to a series of Heck reactions under varying conditions. Results of this investigation are listed in Table 2.2.

The reaction of **168** with ethyl acrylate **173** (Entry 1) gave the desired diene **167** in 50% yield. This result was very encouraging. The reaction was repeated at a higher concentration (Entry 2), but this required in a significantly longer reaction time and resulted in a slightly lower yield (44%). Furthermore, the starting 3-bromocoumarin **168** was not totally consumed (28% recovered). Increasing the number of equivalents of the alkene at these concentrations resulted in a 33% yield of the diene (Entry 3). Again, the starting material was not completely consumed (12% recovered).

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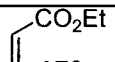
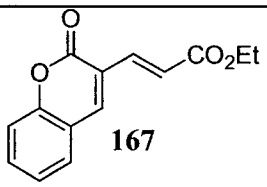
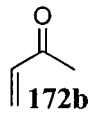
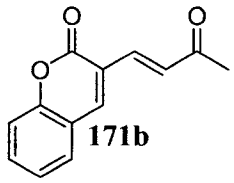
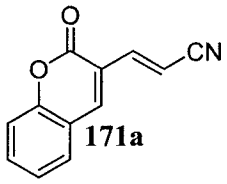
[94] (a) Thapliyal, P. C.; Singh, P. K.; Khanna, R. N. *Synth. Commun.* **1993**, *23*, 2821–2826. (b) Bansal, V.; Kanodia, S.; Thapliyal, P. C.; Khanna, R. N. *Synth. Commun.* **1996**, *26*, 887–891.

[95] (a) Bordwell, F. C.; Wellman, K. M. *J. Org. Chem.* **1963**, *28*, 2544–2550. (b) Smith, A. B.; Branca, S. J.; Pilla, N. N.; Guaciaro, M. A. *J. Org. Chem.* **1982**, *47*, 1855–1869.

Table 2.2: Investigation to produce coumarin-fused dienes by utilizing the Heck reaction with **168**.

Entry	[**168**]	Alkene	Conditions	Product	Yield
1.	0.1 M	 **173** 0.15 M	C_6H_6, NEt_3 (0.72 M), $Pd(OAc)_2$ (2.3×10^{-3} M), PPh_3 (2.8×10^{-3} M), 80 °C, 3 h	 **167**	50%
2.	0.44 M	**173** 0.66 M	C_6H_6, NEt_3 (3.2 M), $Pd(OAc)_2$ (1.0×10^{-2} M), PPh_3 (1.2×10^{-2} M), 80 °C, 119 h	**167**	44%
3.	0.44 M	**173** 4.4 M	C_6H_6, NEt_3 (3.2 M), $Pd(OAc)_2$ (1.0×10^{-2} M), PPh_3 (1.2×10^{-2} M), 80 °C, 119 h	**167**	33%
4.	0.44 M	**173** 0.66 M	C_6H_6, NEt_3 (3.2 M), $Pd(OAc)_2$ (1.0×10^{-2} M), P(*o*-tolyl)$_3$(1.2×10^{-2} M), 80 °C, 164 h	**167**	37%
5.	0.44 M	**173** 0.66 M	C_6H_6, K_2CO_3 (3.2 M), $Pd(OAc)_2$ (1.0×10^{-2} M), PPh_3 (1.2×10^{-2} M), 80 °C, 164 h	**167**	11%
6.	0.44 M	**173** 0.66 M	C_6H_6, NEt_3 (3.2 M), $Pd(OAc)_2$ (1.0×10^{-2} M), PPh_3 (1.2×10^{-2} M), CuI (1.1×10^{-2} M), 80 °C, 24 h	**167**	67%

7.	0.44 M	**173** 0.66 M	C_6H_6, NEt_3 (3.2 M), $Pd(OAc)_2$ (1.0×10^{-2} M), P(*o*-tolyl)$_3$(1.2×10^{-2} M), CuI (1.1×10^{-2} M), 80 °C, 6.5 h	**167**	85%
8.	0.44 M	 **172b** 0.66 M	C_6H_6, NEt_3 (3.2 M), $Pd(OAc)_2$ (1.0×10^{-2} M), P(*o*-tolyl)$_3$(1.2×10^{-2} M), CuI (1.1×10^{-2} M), 80 °C, 30.5 h	 **171b**	4%
9.	0.44 M	 **172a** 0.66 M	C_6H_6, NEt_3 (3.2 M), $Pd(OAc)_2$ (1.0×10^{-2} M), P(*o*-tolyl)$_3$(1.2×10^{-2} M), CuI (1.1×10^{-2} M), 80 °C, 23.5 h	 **171a**	13%
10.	0.44 M	**172a** 0.66 M	C_6H_6, NEt_3 (3.2 M), $Pd(OAc)_2$ (1.0×10^{-2} M), P(*o*-tolyl)$_3$(1.2×10^{-2} M), CuI (7.8×10^{-2} M), 80 °C, 20.5 h	**171a**	8%
11.	0.44 M	**172a** 4.4 M	C_6H_6, NEt_3 (3.2 M), $Pd(OAc)_2$ (1.0×10^{-2} M), P(*o*-tolyl)$_3$(1.2×10^{-2} M), CuI (7.8×10^{-2} M), 80 °C, 18.5 h	**171a**	5%

Thoughts were then turned to modifying the catalyst being used for the Heck reaction. A more sterically hindered phosphine, P(*o*-tolyl)$_3$, was used instead of triphenylphosphine, similar to the original paper by Mitra *et al.* Unfortunately, this modification to the reaction conditions did not significantly change the end result of the Heck reaction (Entry 4). Potassium carbonate has also been used frequently as an inorganic base in the Heck reaction. Changing the base from NEt_3 to potassium carbonate had the effect of significantly decreasing the rate of the reaction (Entry 5). After 164 h, TLC analysis revealed that **168** was still the major component in the reaction mixture. After workup and purification, diene **167** was isolated in only 11% yield with a 50% recovery of the starting compound **168**.

Up to this point, none of the reaction conditions employed led to the production of significant amounts of the desired coumarin-fused diene. It was not until the accidental addition of CuI to the reaction mixture that the yield of the coumarin-fused diene rose to synthetically acceptable levels (Entry 6). Changing the phosphine used in the reaction from triphenylphosphine to the more sterically demanding P(*o*-tolyl)$_3$, raised the yield of diene **167** to 85% and the time of the reaction also improved considerably (from 24 h to 6.5 h).

Initial optimism about this methodology evaporated following the very poor yields that were obtained from the use of methyl vinyl ketone **172b** (4%) and acrylonitrile **172a** (13%) under analogous conditions (Entry 8 and 9). The number of equivalents of CuI was increased in the reaction with acrylonitrile, but there was no increase in the rate and a slightly lower yield of the product was obtained (Entry 10). Suspecting that the

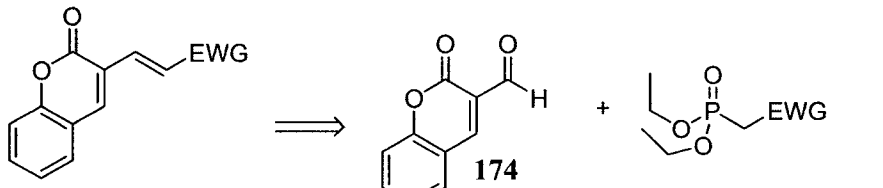
alkene might be undergoing polymerization before it could react, dropwise addition was attempted (Entry 11), but no apparent improvement was observed.

This approach would seemingly need an in-depth study to fully understand and optimize the chemistry, which would require significant time. During this same time, other avenues that could produce the coumarin-fused dienes were being investigated. It was decided to stop pursuing the Heck reaction and the time was devoted to chemistry that was achieving results. In the future, the Heck reaction investigation will be reopened because there are many questions left unanswered, which include the role of CuI. This methodology may well be useful for the production of a variety of electron-poor dienes if the proper reaction conditions can be found.

2.2.2.2 The Horner-Wadsworth-Emmons Reaction

Previous diene syntheses from the Bodwell group[96] demonstrated that the diene unit could be effectively produced using a Horner-Wadsworth-Emmons[83] reaction of aldehyde **156** (Scheme 2.1). It was therefore envisaged that application of this strategy to 3-formylcoumarin **174** and phosphonates **175a-d**, might provide access to multigram quantities of a variety of electron-poor dienes related to **165d** (Scheme 2.6). The initial approach to **174** was to reduce chemoselectively the methyl ester of 3-carbomethoxycoumarin **176** to an aldehyde using DIBAL. However, the only product isolated from this reaction was **177**, which was derived from the hydride being delivered

[96] (a) Ref. 84(a), pp 22–45. (b) Ref. 84(b), pp 36–57.



171a EWG=CN
171b EWG=$COCH_3$
171c EWG=SO_2Ph
171d EWG=NO_2

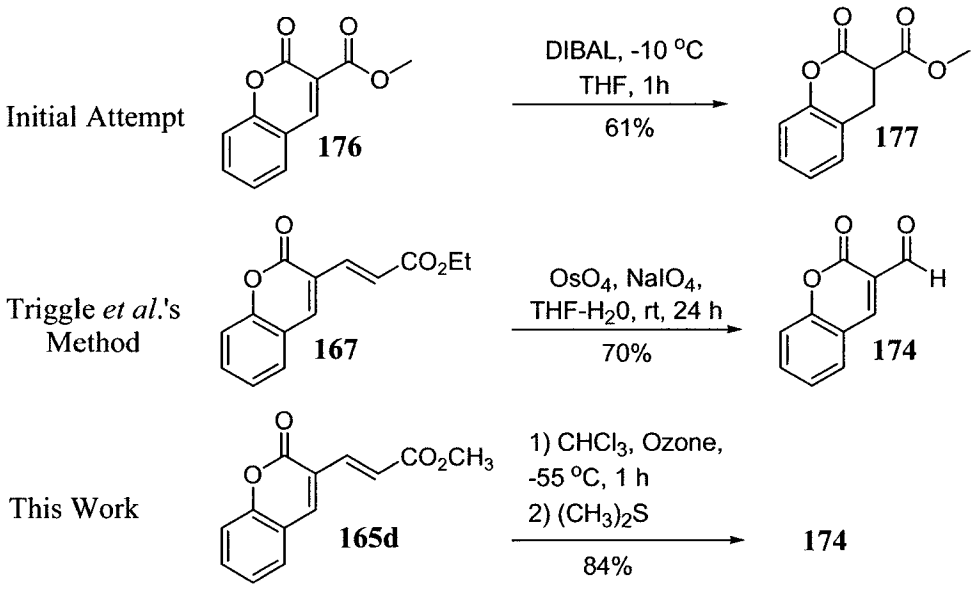
175a EWG=CN
175b EWG=$COCH_3$
175c EWG=SO_2Ph
175d EWG=NO_2

Scheme 2.6: Retrosynthetic cut using Horner-Wadsworth-Emmons methodology.

in a 1,4-fashion instead of the desired 1,2-fashion (initial attempt, Scheme 2.7). Oxidative cleavage of the acrylate double bond of **165d** was then investigated. This idea was not atom economical,[97] but the starting materials used to produce **165d** are cheap and the synthesis of 3-formylcoumarin would only be two steps long.

Triggle *et al.* reported the synthesis of 3-formylcoumarin **174** when they disclosed the synthesis of diene **167** (Scheme 2.7).[88] Treatment of **167** with sodium periodate and catalytic amounts of osmium tetroxide, caused selective oxidative cleavage of the acrylate double bond to give 3-formylcoumarin **174** in 70% yield. In order to avoid the use of the very toxic and expensive $OsO_4/NaIO_4$ method, an analogous oxidative cleavage using ozone was attempted with diene **165d**, which afforded **174** in good yield. After some experimentation, it was discovered that the reaction temperature should be maintained between –55 °C and –60 °C for optimum results (84% yield). If the reaction temperature was any cooler, a precipitate (presumably **165d**) would form and the reaction would not proceed. If the reaction temperature was warmer, the substrate would be

[97] For general discussion of atom economy in organic synthesis, see: (a) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259–281. (b) Trost, B. M. *Angew. Chem.* **1995**, *107*, 285–307. (c) Trost, B. M. *Science* **1991**, *254*, 1471–1477.

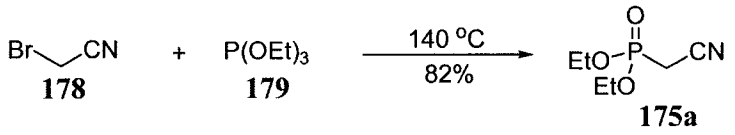


Scheme 2.7: Synthesis of 3-formylcoumarin **174**.

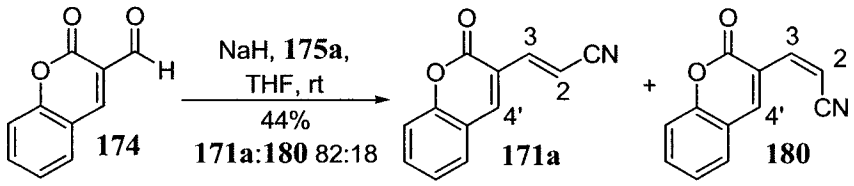
transformed exclusively into baseline material according to TLC analysis. Normally, three gram quantities of 3-formylcoumarin **174** was prepared in a single reaction.

With the ability to produce quickly multigram quantities of 3-formylcoumarin **174**, sights were set on producing some new electron-deficient dienes via the Horner-Wadsworth-Emmons reaction. For the preparation of **171a**, phosphonate **175a** was required (Scheme 2.6). This phosphonate is commercially available, but is very expensive. It was therefore decided to synthesize it via a Michaelis-Arbuzov reaction[98] between bromoacetonitrile **178** and triethyl phosphite **179**, which proceeded in 82% yield (Scheme 2.8).

[98] For a review of the Michaelis-Arbuzov reaction, see: Bhattacharya, A. K.; Thyagarajan, G. *Chem. Rev.* **1981**, *81*, 415–430.



Scheme 2.8: Synthesis of diethyl (cyanomethyl)phosphonate **175a**.

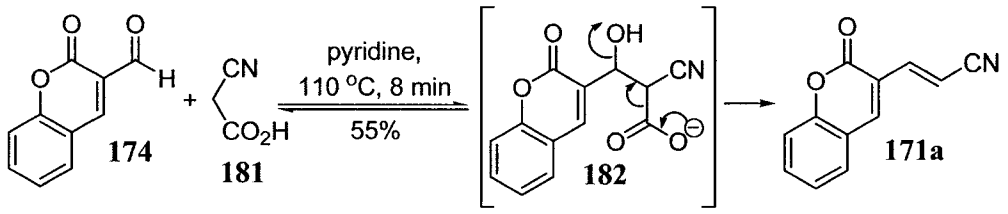


Scheme 2.9: Synthesis of diene isomers **171a** and **180** via Horner-Wadsworth-Emmons olefination reaction.

Horner-Wadsworth-Emmons olefination reaction between 3-formylcoumarin **174** and phosphonate **175a** gave an inseparable mixture of dienes **171a** and **180** (Scheme 2.9) in 44% combined yield with a ratio of 82:18, as determined by integration of the respective C2-H signals in the ^{1}H NMR spectrum of the mixture. The major isomer **171a** was assigned as the *E* isomer by virtue of the 15.7 Hz coupling constant between C2-H and C3-H. The corresponding coupling constant of 12.2 Hz in **180** was used to assign it as the *Z* isomer. A striking difference between the ^{1}H NMR spectra of **171a** and **180** is the chemical shift of C4'-H: δ 7.83 for **171a** and δ 8.68 for **180**. This large difference (0.85 ppm) is also consistent with the latter compound being the *Z* isomer. The proximity of the cyano group to C4'-H would be expected to deshield this proton anisotropically and/or sterically. Interestingly, the 82/18 *E/Z* ratio obtained from this reaction was almost identical with the ratio obtained (83/17) when phosphonate **175a** was reacted with

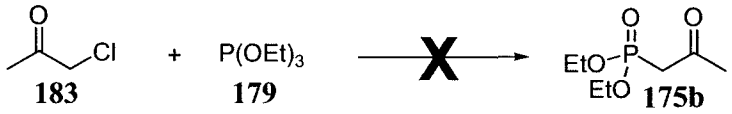
156 by a previous member of the Bodwell Group.[99] It has been documented that phosphonate anions stabilized by a cyano group are more disposed to the formation of isomer mixtures than the corresponding ester-stabilized phosphonate anions.[100]

With an eye toward developing synthetic strategies to produce only a single isomer, a procedure reported by Nohara was attempted.[101] Cyanoacetic acid **181** and **174** were heated in the presence of pyridine. A Knoevenagel condensation occurred to give only the cyano diene **171a** (55%, Scheme 2.10). As the reaction proceeds, presumably intermediate **182** was present as four diastereomers. Since diene **171a** was the only product isolated, the *Z* isomer was not isolated, only the diastereomer(s) leading to the formation of **171a** would eliminate CO_2 and hydroxide via an E_2 mechanism. Presumably this reaction pathway(s) has a significantly lower free energy of activation at the rate-determining step in the mechanism. The product isolated had a 16.4 Hz coupling constant between C2-H and the C3-H, which suggests the *E* geometry.



Scheme 2.10: Synthesis of **171a** with cyanoacetic acid **181** and **174**.

[99] Ref. 84(a), pp 24–25.
[100] Jones, G.; Maisey, R. F. *J. Chem. Soc., Chem. Commun.* **1968**, 543–555.
[101] Nohara, A.; Kuriki, H.; Saijo, T.; Sugihara, H.; Kanno, M; Sanno, Y. *J. Med. Chem.* **1977**, *20*, 141–145.



Scheme 2.11: Failed attempt to produce **175b** via the Michaelis-Arbuzov reaction.

The synthesis of diene **171b** using the Horner-Wadsworth-Emmons approach was then investigated (Scheme 2.6). Initial attempts to synthesize phosphonate **175b** via the Michaelis-Arbuzov reaction shown in Scheme 2.11 were not successful. The product from this reaction exhibited signals in its ^{1}H NMR spectrum that were inconsistent with the expected product.[102] A literature search revealed that Allen and Johnson disclosed this reaction almost a half a century ago to produce phosphate ester **184** (Figure 2.2).[103] One year later, it was revealed that α-haloketones could react via two different mechanisms depending on which halogen was bonded to the ketone.[104]

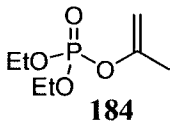
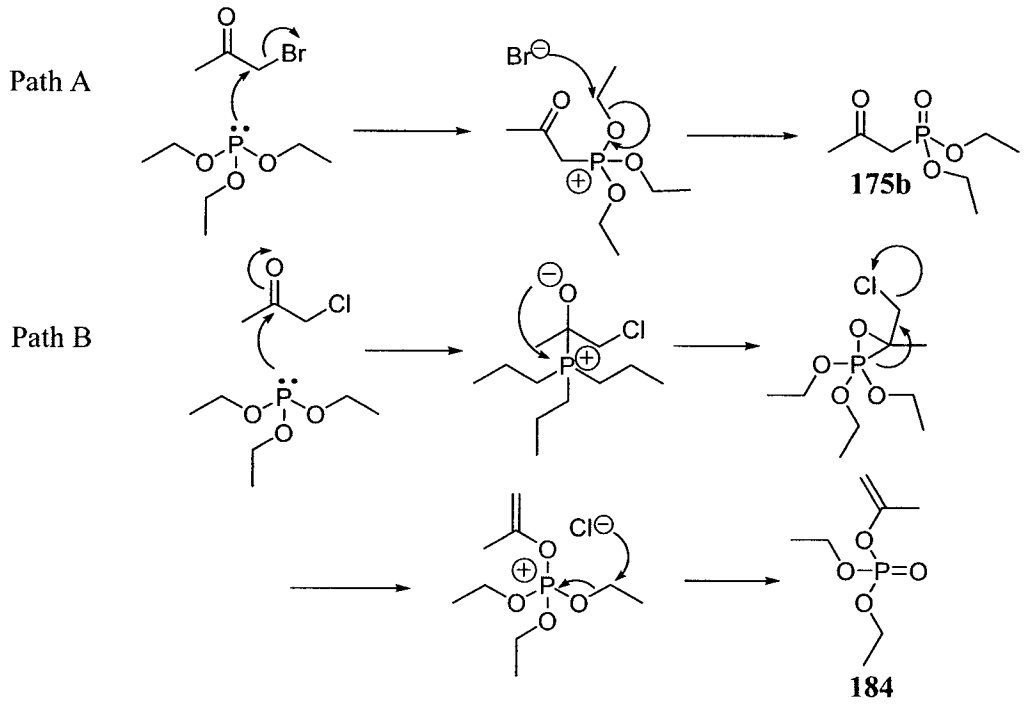


Figure 2.2: Phosphate **184**

Trialkyl phosphite **179** can attack chloroacetone **183** at two different sites to produce either the phosphonate **175b** or the phosphate ester **184** (Scheme 2.12). If the halogen was bromide or iodide, the initial attack occurs on the carbon bonded to the halogen (Path A), the reaction mechanism was that of Michaelis-Arbuzov, and phosphonate **175b** was produced. If the halogen was chloride, the initial attack was on

[102] NMR data published by Aldrich chemical company at http://www.sigmaaldrich.com.
[103] Allen, J. F.; Johnson, O. H. *J. Am. Chem. Soc.* **1955**, *77*, 2871–2875.
[104] (a) Pudovic, A. N.; Aver'yanova, V. P. *Zhur. Obshcheĭ. Khim.* **1956**, *26*, 1426–1431. (b) Hudson, R. F. In *Structure and Mechanism in Organo-Phosphorus Chemistry*; Wiberg, K. B.; ed.; Academic Press: London, 1965, Vol. 5, pp. 131–163.

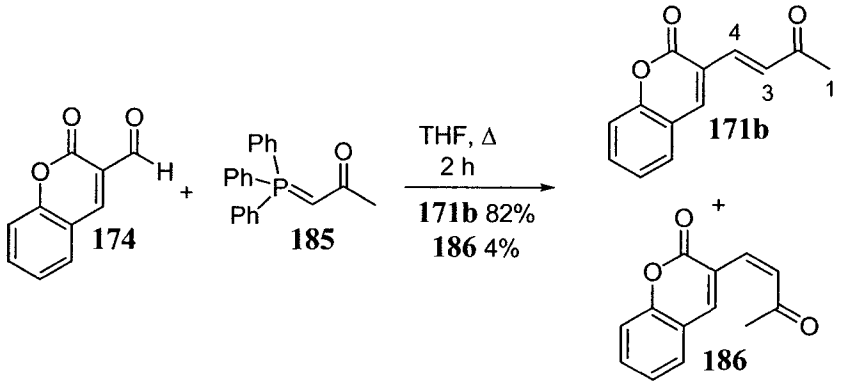


Scheme 2.12: Mechanistic pathways available to triethyl phoshite with reaction of α-haloketone.

the carbonyl carbon (Path B), the mechanism goes through a P(V) intermediate which gave phosphate vinyl ether **184**.

With the failure to produce phosphonate **175b** via Michaelis-Arbuzov reaction using chloroacetone **183** and triethyl phosphite **179**, another route was needed. Bromoacetone and iodoacetone were not commercially available so attention turned to the use of the Wittig[105] reaction. Stabilized ylid **185** was easily prepared,[106] and it reacted

[105] For recent reviews, see: (a) Nicolaou, K. C.; Härter, M. W.; Gunzner, J. L.; Nadin, A. *Liebigs Ann.* **1997**, 1283–1301. (b) Waschbüsch, R.; Carran, J.; Marinetti, A.; Savignac, P. *Synthesis* **1997**, 727–743. (c) Heron, B. M. *Heterocycles* **1995**, *41*, 2357–2386. (d) Vedejs, E.; Peterson, M. J. In *Topics in Stereochemistry*; Eliel, E. L.; Wilen, S. H., eds.; 1994, Vol. 21, pp. 1–157. (e) Murphy, P. J. *Chem. Soc. Rev.* **1988**, *17*, 1–30.

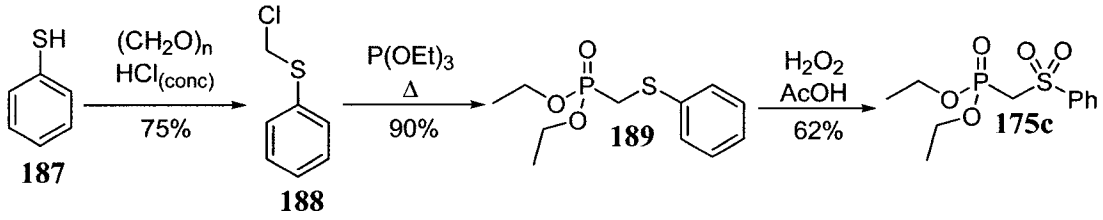


Scheme 2.13: Synthesis of diene **171b** and **186** via a Wittig reaction.

smoothly with **174** to afford diene **171b** as the major product in 82% yield (Scheme 2.13) after purification by column chromatography. A large coupling constant of 15.9 Hz between C3-H and C4-H suggested an *E* geometry about the double bond. The minor product, **186,** was isolated as a mixture (total yield of mixture: 4%) with a small amount of **171b** present (10% of the mixture was **171b**). The yield for **171b** within the mixture was calculated from the ratio of the integrals for the C1-H signals from the ^{1}H NMR spectrum.

Attention was then turned to the synthesis of the sulfonyl diene **171c**. In order to apply the Horner-Wadsworth-Emmons approach, phosphonate **175c** was required (Scheme 2.6). Neither it nor an appropriate α-halosulfone precursor was commercially available, so a recently reported three step procedure was employed (Scheme 2.14).[107] Thiophenol **187** and paraformaldehyde in the presence of aqueous concentrated HCl produced chloromethyl phenyl sulfide **188** with an unknown minor impurity (*ca.* 10%)

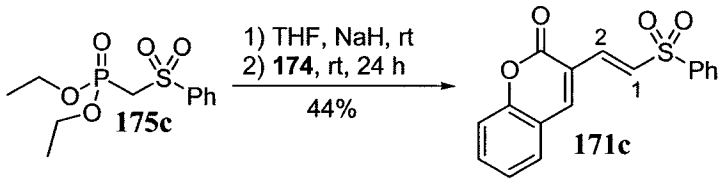
[106] (a) Ramirez, F.; Dershowitz, S. *J. Org. Chem.* **1957**, *22*, 41–45. (b) Dominguez, C.; Csákÿ, A. G.; Magano, J.; Plumet, J. *Synthesis* **1989**, 172–175.
[107] Enders, D.; von Berg, S.; Jandeleit, B. *Org. Syn.* **2000**, *78*, 169–175.



Scheme 2.14: Three-step synthesis of phosphonate **175c**.

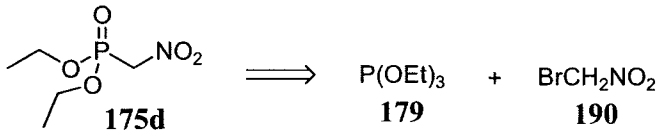
after vacuum distillation in 75% yield. The synthesis was continued with the minor impurity present. This mixture was reacted with triethyl phosphite **179** to afford the phosphonate **189** in 90% yield after vacuum distillation. The ^{1}H NMR spectrum of the product revealed that the previous impurity had not reacted during the Michaelis-Arbuzov reaction. Oxidation of **189** with H_2O_2/acetic acid gave analytically pure sulfone **175c** in 62% yield after purification by column chromatography.

With desired phosphonate **175c** in hand, the Horner-Wadsworth-Emmons reaction with **174** was attempted. Sulfone diene **171c** was generated in 44% yield after column chromatography (Scheme 2.15). By virtue of the large coupling constant of 14.9 Hz between C1-H and C2-H, the *E* stereochemistry was assigned to the newly formed double bond.

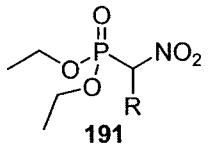


Scheme 2.15: Horner-Wadsworth-Emmons reaction to afford diene **171c**.

To prepare nitrodiene **171d** by the previously successful Horner-Wadsworth-Emmons approach, phosphonate **175d** was required (Scheme 2.16). However, the expense of the direct precursor bromonitromethane **190** and the lack of any reported examples of the use of **175d** to form nitroethene prompted the investigation of a more common method for the production of nitroalkenes, namely the Henry reaction.[108] However, examples of phosphonate **191**[109] (Figure 2.3) were discovered, reactions using this phosphonate were not examined.



Scheme 2.16: Retrosynthetic analysis of phosphonate **175d**.



191

R = Alkyl

Figure 2.3: Phosphonate **191**.

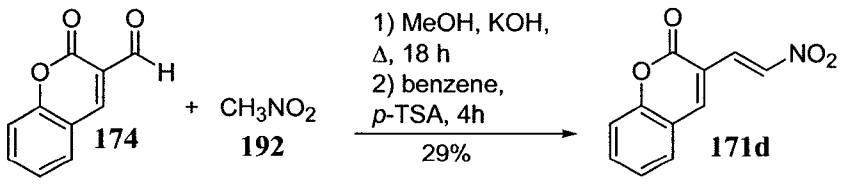
[108] For recent reviews dealing with the Henry reaction, see: (a) Luzzio, F. A. *Tetrahedron* **2001**, *57*, 915–945. (b) Rosini, G. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1999, Vol. 2, pp 321–394. (c) Pinnick, H. W. In *Organic Reactions*; Paquette, L. A., ed.; Wiley: New York, 1990, Vol. 38, Ch. 3. (d) Rosini, G.; Ballini, R. *Synthesis* **1988**, 833–847.

[109] (a) Franklin, A. S. *Synlett* **2000**, 1154–1156. (b) Kandil, A. A.; Porter, T. M.; Slessor, K. N. *Synthesis* **1987**, 411–413. (c) Zoń, J. *Synthesis* **1984**, 661–663.

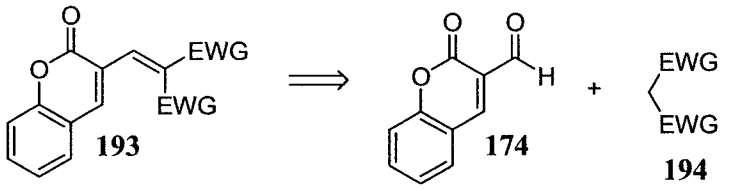
2.2.2.3 Condensation Reactions of 3-Formylcoumarin

Initial attempts to react 3-formylcoumarin **174** with nitromethane **192** under Henry reaction conditions failed. However, a two-step procedure (Scheme 2.17) was successful in producing the desired diene, but in only 29% yield. Unfortunately, attempts to repeat this reaction failed miserably. Diene **171d**, when stored at room temperature, was transformed into insoluble material within seven days. The strongly electron-withdrawing nitro group presumably lowered the FMOs of this molecule to the point that some sort of self-reaction or polymerization process occurred comparatively easily. This example underscored the powerful electron-withdrawing capabilities of the nitro group. If conditions can be found to successfully repeat the Henry reaction for the production of **171d**, it would have to be stored at low temperature or in a benzene matrix.

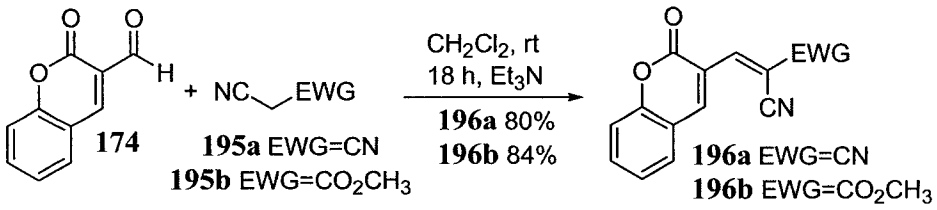
Focus shifted to placing a third electron-withdrawing group on the coumarin-fused diene. Keeping in mind that strongly electronically-biased dienes were desired, the only position to place a third group was at position 1 of the diene, as in **193**. Retrosynthetic analysis of this molecule led to 3-formylcoumarin and a reactive disubstituted methane, e.g. **194**, as starting materials (Scheme 2.18).



Scheme 2.17: Use of the Henry reaction to afford nitro diene **171d**.



Scheme 2.18: Retrosynthetic analysis of diene **193**.



Scheme 2.19: Synthesis of dienes bearing three EWGs.

Malononitrile **195a** was selected first to attempt a condensation with **174**. Stirring them together in the presence of catalytic amounts of triethylamine afforded the desired diene **196a** (80%, Scheme 2.19). This diene showed remarkable stability even though it bears three electron-withdrawing groups. It has so far been stored for over one year under air at room temperature without observable decomposition.

Methyl cyanoacetate **195b** was then employed under the same reaction conditions and a single geometric isomer, **196b**, was obtained (84%). Saturation of the C4'-H resonance gave no NOE enhancement to support this assignment. However, AM1 calculations using the CambridgeSoft Chem 3D package of software indicated that **196b** is 4.2 kcal/mol lower in energy than the other geometric isomer. A single crystal x-ray structure determination would give an unambiguous answer to the stereochemical issue.

2.3 Conclusions and Future Directions

Coumarin-fused diene **165d** was synthesized in high yield on a multigram scale from readily available and inexpensive salicylaldehyde **164d** and dimethyl glutaconate **163**. The incorporation of an electron-deficient diene unit into a partially aromatic system rendered it indefinitely stable under ambient conditions. No diene previously prepared by the Bodwell group has displayed this level of stability. Ozonolysis of **165d** afforded 3-formylcoumarin **174** in good yield, which allowed related dienes to be synthesized using a Horner-Wadsworth-Emmons reaction or a condensation reaction. This chemistry enables a variety of electron-withdrawing groups to be placed at the 1-position of the diene moiety. All of the dienes produced could be stored for long periods of time under ambient conditions with the exception of the nitro diene **171d**.

Cursory studies on the applicability of the Heck reaction as means of producing coumarin-fused dienes were conducted and some promising results were obtained. Further work in this area is warranted, as this was not an exhaustive investigation and leaves many unanswered questions. The Stille coupling could also provide access to these dienes and should be included in future investigations.

2.4 Experimental

2.4.1 General Experimental Procedure

All reactions were performed under an atmosphere of N_2 unless otherwise noted. Except where stated, commercial reagents and all solvents were used as received. THF was distilled immediately prior to use from sodium/benzophenone. Melting points (mp) were measured with a Fisher-Johns melting point apparatus and are uncorrected.

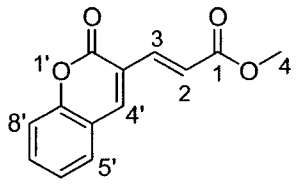
Thin layer chromatography (TLC) was performed using Macherey-Nagel Polygram® SIL G/UV_{254} precoated silica plates. TLC plates were visualized using a short wave (254 nm) UV lamp or a PMA solution. Flash chromatography was carried out using Silica Gel 60 (E. Merck, 230-400 mesh) with the mobile phase indicated in the experimental sections.

^{1}H NMR spectra were obtained from $CDCl_3$ solutions, except when noted, using a General Electric 300 NB instrument operating at 300.1 MHz or a Bruker Avance 500 instrument operating at 500.1 MHz. Chemical shifts are relative to internal Me_4Si standard. Coupling constants are reported in Hz. Reported multiplicities are apparent. ^{13}C NMR spectra are recorded at 75.47 and 125.8 MHz. Chemical shifts are reported relative to the solvent (δ 77.0 for $CDCl_3$, δ 39.5 for DMSO-d_6) and the number of attached protons, as determined by an attached proton experiment are given in parentheses. Assignments, where given, were established using HMQC, HMBC, and COSY experiments.

Infrared (IR) spectra (cm^{-1}) were recorded on a Mattson Polaris FT-IR spectrophotometer using neat samples or as Nujol mulls in NaCl cells. Low resolution mass spectroscometric (ms) data were obtained on a V.G. Micromass 7070HS instrument operating at 70 eV. High-resolution mass spectroscometric data were performed by the University of Ottawa Mass Spectrometry Centre. Combustion analyses were obtained at the MicroAnalytical Service Laboratory at the University of Alberta and Canadian Microanalytical Service, Ltd. UV-VIS spectra were obtained on a Cary 5e spectrophotometer.

2.4.2 Experimental Procedures

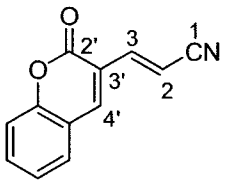
Methyl (*E*)-3-(2-oxo-*2H*-chromen-3-yl)acrylate (165d)



To a magnetically stirred solution of salicylaldehyde (0.44 mL, 4.1 mmol) and dimethyl glutaconate (0.57 mL, 4.1 mmol) in benzene (25 mL) was added piperidine (0.20 mL, 2.0 mmol) in one portion and the resulting mixture was heated at reflux with azeotropic removal of water for 4 h. Upon cooling to room temperature, a white precipitate formed, which was isolated by suction filtration. The filter cake was washed with cool benzene (25 mL) to afford **165d** (0.58 g, 62%) as a white solid. The filtrate was concentrated under reduced pressure and purified by flash chromatography on silica gel (3% ethyl

acetate/CH_2Cl_2) to afford a second batch of **165d** (0.29, 30%, total=0.87 g, 92%)): mp 176-178 °C, IR (nujol) 1727 (s) cm^{-1}; UV/vis (MeOH) λ_{max} (log ε) 315 (3.62), 290 (3.63) nm; ^1H NMR ($CDCl_3$, 500.1 MHz) δ 7.88 (s, 1H, C4'-H), 7.59-7.55 (m, 3H, C5'-H + C7'-H + C3-H), 7.35-7.30 (m, 2H, C6'-H + C8'-H), 7.10 (d, *J*= 15.3 Hz, 1H, C2-H), 3.82 (s, 3H, C4-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.2 (0), 159.0 (0), 153.5 (0), 143.5 (1), 138.0 (1), 132.8 (1), 128.5 (1), 124.8 (1), 123.2 (1), 122.2 (0), 118.9 (0), 116.6 (1), 51.8 (3); EI-MS *m/z* (%) 230 (M^+, 16), 199 (12), 171 (100), 143 (6), 115 (24); Anal. calcd for $C_{13}H_{10}O_4$: C, 67.82; H, 4.38. Found C, 67.71; H, 4.27.

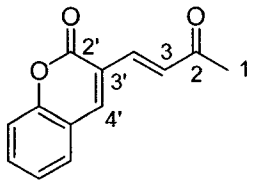
(*E*)-3-(2-Oxo-2*H*-chromen-3-yl)acrylonitrile (171a)



3-Formylcoumarin **174** (264 mg, 1.51 mmol) and cyanoacetic acid (141 mg, 1.66 mmol) were heated on an oil bath (bath temperature 110 °C) and then pyridine (4.0 mL) was added dropwise over 30 s. The stirred mixture was heated at 110 °C for 8 min and then cooled to room temperature. The crude mixture was dissolved in CH_2Cl_2 (20 mL), washed with aqueous 1 M HCl solution (3×20 mL), dried over $MgSO_4$, gravity filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel (CH_2Cl_2) to afford **171a** (164 mg, 55%) as a light yellow solid: mp 170-172 °C; IR (nujol) 2215 (m), 1724 (s), 1606 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.85 (s, 1H, C4'-H), 7.66-7.62 (m, 1H, C7'-H), 7.59 (d, *J*=7.7 Hz, 1H, C5'-

H), 7.39-7.35 (m, 2H, C6'-H + C8'-H), 7.20 (d, *J*=16.4 Hz, 1H, C3-H), 6.86 (d, *J*=16.4 Hz, 1H, C2-H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 158.6 (0, C2'), 153.5 (0, C8'a), 144.8 (1, C4'), 143.9 (1, C3), 133.7 (1, C7'), 128.8 (1, C5'), 125.1 (1, C6'), 121.0 (0, C3'), 118.5 (0, C4'a), 118.0 (0, C1), 116.7 (1, C8'), 102.8 (1, C2); GC-MS *m/z* (%) 197 (M^+, 100), 170 (29), 169 (59), 140 (28), 114 (20); HRMS (EI) calcd for $C_{12}H_7NO_2$: 197.0476, found 197.0493.

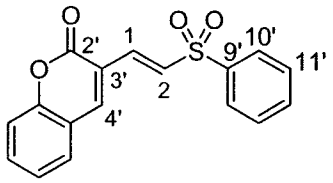
(*E*)-2-Oxo-1-(2-oxo-2*H*-chromen-3-yl)butene (171b)



To a magnetically stirred solution of 3-formylcoumarin **174** (2.59 g, 14.9 mmol) in THF (75 mL) was added ylid **43**[108] (4.73 g, 14.9 mmol) in one portion and the resulting mixture was heated at reflux for 2 h. The reaction was cooled to room temperature and then concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel (3% ethyl acetate/CH_2Cl_2) to afford **171b** (2.61 g, 82%) as a white solid: mp 157-158 °C; IR (nujol) 1704 (s), 1661 (s), 1603 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.94 (s, 1H, C4'-H), 7.61-7.57 (m, 2H, C5'-H + C7'-H), 7.47 (d, *J*=15.9 Hz, 1H, C4-H), 7.36 (d, *J*=8.3 Hz, 1H, C8'-H), 7.33 (t, *J*=8.1 Hz, 1H, C6'-H), 7.29 (d, *J*=15.9 Hz, 1H, C3-H), 2.40 (s, 3H, C1-H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 198.3 (0, C2), 159.3 (0, C2'), 153.6 (0, C8a'), 143.3 (1, C4'), 135.9 (1, C4), 133.0 (1, C7), 130.8 (1, C3), 128.5 (1, C5'), 124.9 (1, C6'), 122.5 (0, C3'), 119.0 (0, C4a'), 116.7 (1, C8'), 28.6 (3,

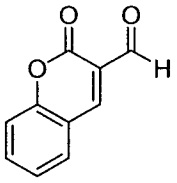
C1); GC-MS *m/z* (%) 214 (M^+, 4), 199 (6), 172 (13), 171 (100), 143 (3), 127 (2), 115 (18); HRMS (EI) calcd for $C_{13}H_{10}O_3$: 214.0629, found 214.0607.

(*E*)-2-(Phenylsulfonyl)-1-(2-oxo-2*H*-chromen-3-yl)ethene (171c)



To a 0 °C slurry of 60% sodium hydride (0.449 g, 11.2 mmol) in anhydrous THF (50 mL) was added dropwise a solution of diethyl phosphonomethylbenzenesulfonate[110] (3.11 g, 11.2 mmol) in anhydrous THF (10 mL) and the resulting clear solution was stirred for 15 min at 0 °C. Then a solution of 3-formylcoumarin **174** (1.63 g, 9.35 mmol) in anhydrous THF (50 mL) was added dropwise. The reaction was allowed to stir at 0 °C for 30 min then the temperature was raised to room temperature and allowed to stir for 24 h. After this time the solvent was removed under reduced pressure and the crude material was purified by column chromatography on silica gel (CH_2Cl_2) to afford **171c** (1.20 g, 41%) as a white solid: mp 205-206 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.96-7.94 (m, 3H, C4'-H + C10'-H), 7.79 (d, *J*=15.1 Hz, 1H, C1-H), 7.65-7.56 (m, 5H, C5'-H + C7'-H + C11'-H + C12'-H), 7.51 (d, *J*=14.7 Hz, 1H, C2-H), 7.36-7.33 (m, 2H, C6'-H + C8'-H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 158.6 (0, C2'), 153.7 (0, C8'), 146.5 (1, C4'), 140.2 (0, C9'), 135.4 (1, C1), 133.7 (1), 133.5 (1), 133.0 (1, C2), 129.4 (1, C11'), 128.8 (1, C5'), 127.8 (1, C10'), 125.1 (1, C6'), 120.4 (0, C3'), 118.7 (0, C4a'), 116.7 (1, C8'); EI-MS *m/z* (%) 312 (M^+, 2), 172 (12), 171 (100), 142 (3), 115 (14).

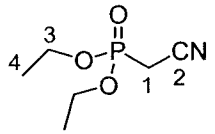
3-Formylcoumarin (174)



Methyl (2*E*)-3-(2'-oxo-*2'H*-chromen-3'-yl) acrylate **165d** (3.00 g, 13.0 mmol) was dissolved in chloroform (350 mL). The reaction vessel was placed in a Dry Ice/acetone bath and the temperature was lowered to –55 °C. The cooling bath was maintained at this temperature and ozone was bubbled through the solution for 50 min at which time the color became a dark blue. Nitrogen gas was bubbled through the solution for 30 min to remove any residual ozone present and then the Dry Ice/acetone bath temperature was allowed to rise to –30 °C. Dimethyl sulfide (3.5 mL, 47.6 mmol) was added in one portion to the magnetically stirred solution and the temperature of the resulting mixture was allowed to slowly rise to room temperature and was stirred for 16 h. It was concentrated under reduced pressure and the crude material was purified by flash chromatography on silica gel (2.5% ethyl acetate/CH_2Cl_2) to afford **174** (1.90 g, 84%) as a white solid: mp 132-134 °C (lit. mp: 131-132 °C[110]); IR (nujol) 1737 (s), 1692 (s), 1609 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 10.27 (s, 1H), 8.43 (s, 1H), 7.72-7.68 (m, 2H), 7.42-7.37 (m, 2H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 187.7, 160.1, 155.5, 145.6, 135.0, 130.8, 125.3, 121.8, 118.2, 117.1; EI-MS *m/z* (%) 174 (M^+, 21), 146 (100), 118 (78), 90 (40), 89 (46), 63 (38).

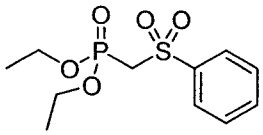
[110] Boehm, T.; Schumann, G.; Hansen, H. *Arch. Pharm.* **1933**, *271*, 490-???.

Diethyl (cyanomethyl)phosphonate (175a)



A magnetically stirred solution of bromoacetonitrile (5.81 mL, 83.4 mmol) and triethyl phosphite (14.3 mL, 83.4 mmol) in a 50 mL round bottom flask equipped with a Dean-Stark trap, was heated slowly until the reaction mixture began to boil vigorously and a clear colorless liquid began to collect in the Dean-Stark trap. The reaction temperature was then carefully heated to 140 °C and maintained at this temperature for 60 min. The reaction mixture was cooled to room temperature and the crude material was purified by vacuum distillation to afford **192** (12.17 g, 82%) as a clear colorless liquid: bp 98-106 °C/ 1 mm Hg (lit bp: 101-102 °C/ 0.4 mm Hg[111]); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.31-4.21 (m, 4H, C3-H), 2.88 (d, *J*=20.9 Hz, 2H, C1-H), 1.43-1.38 (m, 6H, C4-H).

Diethyl [(phenylsulfonyl)methyl]phosphonate (175c)[107]

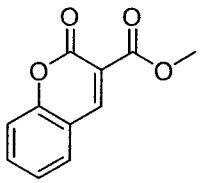


Diethyl [(phenylthio)methyl]phosphonate **189** (90.2 g, 0.368 mol) and acetic acid (350 mL) in a 1 L three neck RBF fitted with a thermometer and a condenser at 50 °C was

[111] Aldrich Chemical Company *Aldrich Handbook of Fine Chemicals and Laboratory Equipment* 2000-2001, pg. 576.

added 30% hydrogen peroxide (114 mL, 1.10 mol) at a rate such that the internal temperature did not rise above 80 °C. Once the addition was finished the reaction temperature was raised to 85 °C for 3 h then cooled to room temperature. The reaction mixture was transferred to an Erlenmeyer flask and neutralized with 10 M NaOH. The neutral aqueous material was extracted with CH_2Cl_2 (5×200 mL). The combined organic layers were washed with aqueous saturated $NaHSO_3$ solution (2×50 mL), dried over $MgSO_4$, gravity filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography using gradient elution techniques (1:1 diethyl ether/hexanes then ethyl acetate) to afford **175c** (63.3 g, 62%) as a clear colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.01 (d, J = 7.8 Hz, 2H), 7.69 (t, J = 7.3 Hz, 1H), 7.59 (t, J=7.6 Hz, 2H), 4.20-4.11 (m, 4H), 3.78 (d, J=16.3 Hz, 2H), 1.30 (t, J=7.0 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 140.0, 134.0, 129.0, 128.3, 63.3, 53.7 (d, $J_{C,P}$=38 Hz), 16.1.

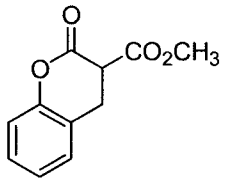
2-Oxo-*2H*-chromene-3-carboxylic acid methyl ester (176)



To a solution of salicylaldehyde (4.4 mL, 41 mmol) and dimethyl malonate (5.2 mL, 45 mmol) in benzene (50 mL) was added piperidine (0.86 mL, 20 mmol) in one portion and the resulting mixture was heated at reflux with azeotropic removal of water for 1 h. Upon cooling to room temperature, a white precipitate formed, which was isolated by suction filtration. The filter cake was washed with cool benzene (25 mL) to afford **176**

(0.63 g, 8%) as a white solid. The filtrate was concentrated under reduced pressure. The crude material was recrystalized from ethanol to afford a second batch of **176** (3.7 g, 44%, total=4.3 g, 52%): mp 115.5-116.5 °C; IR (nujol) 1744 (s), 1728 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 300.1 MHz) δ 8.58 (s, 1H), 7.70-7.61 (m, 2H), 7.39-7.32 (m, 2H), 3.97 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 163.5, 156.6, 155.1, 149.1, 134.4, 129.5, 124.8, 117.7, 116.7, 52.8; EI-MS *m/z* (%) 204 (M^+, 52), 173 (100), 146 (35), 101 (17).

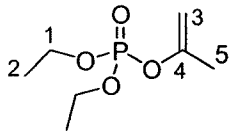
2-Oxochroman-3-carboxylic acid methyl ester (177)



To a solution of 3-carbomethoxycoumarin (2.00 g, 9.80 mmol) in THF (70 mL) at –10 °C was added a 1M solution DIBAL in THF of (19.6 mL, 19.6 mmol) dropwise over 1 h maintaining the temperature at –10 °C. The reaction was allowed to warm to room temperature and stirred for 30 min. The reaction was carefully quenched with H_2O (10 mL) and the lithium salts that were produced were removed by suction filtration. The layers in the filtrate were separated and the organic layer was dried over $MgSO_4$, gravity filtered and concentrated under reduced pressure to afford **177** (1.23 g, 61%) as a white solid: mp 95-97 °C, IR (nujol) 1777 (s), 1737 (s), 1610 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 300.1 MHz) δ 7.41-7.35 (m, 1H), 7.32 (d, *J*=7.6 Hz, 1H), 7.25-7.19 (m, 1H), 7.16 (d, *J*=8.1 Hz, 1H), 3.90-3.85 (m, 4H), 3.52 (dd, *J*=16.0, 9.0 Hz, 1H), 3.27 (dd, *J*=16.0, 6.2 Hz, 1H); ^{13}C

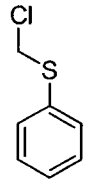
NMR ($CDCl_3$, 75.47 MHz) δ 167.9, 164.7, 151.2, 128.6, 128.2, 124.8, 120.6, 116.7, 53.0, 46.0, 27.1; EI-MS *m/z* (%) 206 (M^+, 13), 173 (14), 147 (100), 118 (34), 106 (26).

Diethyl isopropenyl phosphate (184)



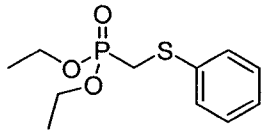
A magnetically stirred solution of chloroacetone (12.9 mL, 0.162 mol) and triethyl phosphite (27.8 mL, 0.162 mol) in a 50 mL round bottom flask equipped with a Dean-Stark trap, was heated slowly until the reaction mixture began to boil vigorously and a clear colorless liquid began to collect in the Dean-Stark trap. The reaction temperature was then carefully heated to 160 °C and maintained at this temperature for 60 min. The reaction mixture was cooled to room temperature and the crude material was purified by vacuum distillation to afford **184** (25.8 g, 82%) as a clear colorless liquid: bp 62-68 °C/ 1 mm Hg (lit bp: 72-73 °C/ 1 mm Hg[105]); ^1H NMR ($CDCl_3$, 300 MHz) δ 4.78-4.76 (m, 1H), 4.51-4.50 (m, 1H), 4.22-4.12 (m, 4H), 1.95 (s, 3H), 1.39-1.34 (m, 6H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 152.1, 98.0, 64.2, 20.7, 16.0; GC-MS *m/z* (%) 194 (M^+, 10), 155 (23), 137 (2), 127 (52), 99 (100).

Chloromethyl phenyl sulfide (188)[107]



To a solution of paraformaldehyde (18.9 g, 0.629 mol) in toluene (120 mL) and $HCl_{(conc)}$ (500 mL) at 50 °C was added thiophenol (51.3 mL, 0.500 mol) in toluene (120 mL) via a pressure equalizing dropping funnel over 1 h. Once the addition was complete, the reaction was cooled to room temperature and stirred for 16 h. The reaction mixture was transferred to a separatory funnel and the layers were separated. The aqueous layer was extracted with toluene (3×50 mL). The combined organic layers were washed with aqueous saturated NaCl solution (100 mL), dried over $MgSO_4$, gravity filtered and concentrated under reduced pressure. The crude material was purified by vacuum distillation to afford **188** (59.8 g, 75%) as a clear colorless liquid: bp 119-120 °C at 18 mm Hg (lit bp: 106-107 °C at 11 mm Hg); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.53-7.50 (m, 2H), 7.40-7.33 (m, 3H), 4.96 (s, 2H).

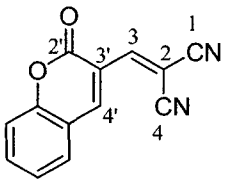
Diethyl [(phenylthio)methyl]phosphonate (189)[109]



Triethyl phosphite (139 mL, 0.812 mol) at 130 °C in a three-necked 1 L round bottom flask fitted with a thermometer and condenser connected to a safety bottle charged with

ethanol, was added chloromethyl phenyl sulfide **188** (64.9 g, 0.406 mol) via a pressure equalization dropping funnel over 40 min. After this addition the temperature was raised to 150 °C to allow the reaction mixture to reflux for 15 h. The excess triethyl phosphite was removed via a short path distillation apparatus at 1 mm Hg to leave **189** (90.6 g, 91%) as a clear colorless liquid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.45-7.43 (m, 2H), 7.34-7.28 (m, 2H), 4.17-4.11 (m, 4H), 3.20 (d, *J*=13.9 Hz, 2H), 1.30 (t, *J*=7.0 Hz, 6H).

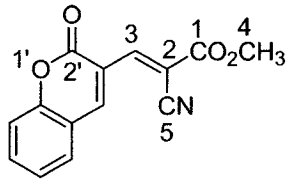
2-(2-Oxo-2*H*-chromen-3-ylmethylene)malononitrile (196a)



To a solution of 3-formylcoumarin (0.85 g, 4.9 mmol) and malononitrile (0.35 g, 5.4 mmol) in CH_2Cl_2 (20 mL) was added triethylamine (0.30 ml, 2.2 mmol) in one portion and the resulting solution was stirred for 18 h. As the reaction proceeded a yellow precipitate formed. Dichloromethane was added until the solid dissolved. This solution was washed with aqueous saturated $NaHCO_3$ solution (2×20 mL), a portion of aqueous saturated $NaHSO_3$ solution (20 mL) and then a portion of aqueous 1 M HCl solution (20 mL). The organic layer was dried over $MgSO_4$, gravity filtered and concentrated under reduced pressure to afford **196a** (0.86 g, 80%) as a yellow solid: mp 190-191 °C; IR (nujol) 2231 (m), 1714 (s), 1612 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$, 500.1 MHz) δ 8.87 (s, 1H, C4'-H), 8.17 (s, 1H, C3-H), 7.76-7.73 (m, 1H, C7'-H), 7.70 (dd, *J*=7.5, 1.6 Hz, 1H, C5'-H), 7.44-7.40 (m, 2H, C6'-H + C8'-H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 158.7 (0, C2'),

154.9 (0, C8'a), 151.9 (1, C3), 145.3 (1, C4'), 135.9 (1, C7'), 130.5 (1, C5'), 125.8 (1, C6'), 119.3 (0, C3'), 118.0 (0, C4'a), 117.2 (1, C8'), 112.7 (0), 112.0 (0), 85.7 (0, C2); EI-MS *m/z* (%) 222 (M^+, 100),194 (63), 165 (17), 139 (31), 88 (12); Anal. calcd for $C_{13}H_6N_2O_2$: C, 70.27; H, 2.72. Found C, 70.06; H, 2.48.

2-Cyano-3-(2-oxo-2*H*-chromen-3-yl)acrylic acid methyl ester (196b)



To a solution of 3-formylcoumarin (1.00 g, 5.74 mmol) and methyl cyanoacetate (0.63 g, 6.3 mmol) in CH_2Cl_2 (25 mL) was added triethylamine (0.30 ml, 2.2 mmol) in one portion and the resulting solution was stirred for 24 h. As the reaction proceeds a yellow precipitate forms. Dichloromethane was added until the solid dissolved. This solution was washed with aqueous saturated $NaHCO_3$ solution (2×20 mL), a portion of aqueous saturated $NaSO_3$ solution (20 mL) and then a portion of aqueous 1 M HCl solution (20 mL). The organic layer was dried over $MgSO_4$, gravity filtered and concentrated under reduced pressure to afford **196b** (1.24 g, 84%) as a yellow solid: mp 176-178 °C; IR (nujol) 2221 (m), 1727 (s), 1714 (s), 1589 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 500.1 MHz) δ 8.93 (s, 1H, C4'-H), 8.56 (s, 1H, C3-H), 7.70 (m, 2H, C5'-H + C7'-H), 7.40-7.38 (m, 2H, C6'-H + C8'-H), 3.96 (s, 3H, C4-H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 161.7 (0, C1), 159.3 (0, C2'), 154.5 (0, C8'a), 146.9 (1, C3), 144.6 (1, C4'), 134.8 (1, C7'), 130.1 (1, C5'), 125.4 (1, C6'), 119.7 (0, C3'), 118.3 (0, C4'a), 117.0 (1, C8'), 114.9 (0), 105.8 (0), 53.6 (3, C4);

EI-MS *m/z* (%) 255 (M^+, 33), 224 (13), 196 (100), 189 (24), 140 (14), 113 (7); Anal. calcd for $C_{14}H_9NO_4$: C, 65.88; H, 3.55; N, 5.48. Found C, 65.64; H, 3.36; N, 5.39.

Chapter 3.

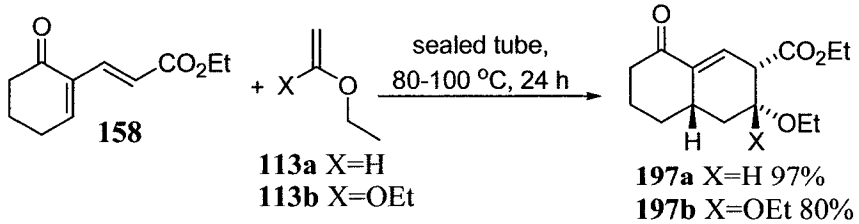
Inverse-Electron-Demand Diels-Alder Reaction

3.0 Inverse-Electron-Demand Diels-Alder Reaction

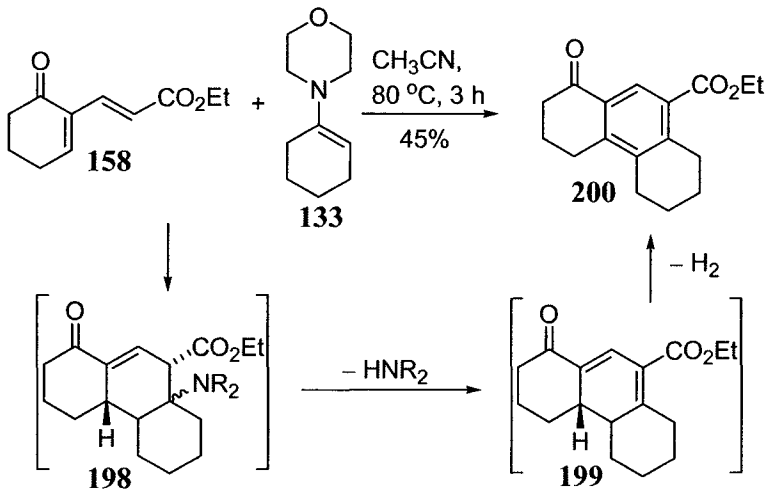
3.1 Previous Investigations

Electron-deficient dienes that have been synthesized in the Bodwell laboratory, e.g. **158-162**, have been the subject of previous investigations of their IEDDA reactivity.[84] For example, when diene **158** was heated with ethyl vinyl ether **113a** in a sealed tube, bicyclic ester **197a** was produced in 97% yield (Scheme 3.1). This Diels-Alder reaction occurs with complete regioselectivity and proceeded exclusively through an *endo* transition state. The product contains three stereogenic centers as well as functionality, i.e., an α,β-unsaturated ketone, might potentially be exploited in subsequent synthetic work. Reaction between **158** and 1,1-diethoxyethene **113b**, a ketene acetal, produced cycloadduct **197b** in good yield, with complete regioselectivity being again observed.

Diene **158** also reacted readily with enamine **133** in hot acetonitrile to afford the arene **200** (Scheme 3.2). Under these reaction conditions, neither the expected cycloadduct **198** nor the presumed intermediate diene **199**, which would be the product of



Scheme 3.1: IEDDA reaction between diene **158** and two dienophiles.



Scheme 3.2: IEDDA driven domino reaction of diene **158** with enamine **133**.

the elimination of morpholine from **198**, was observed. By some process, the nature of which was not established, an apparently facile dehydrogenation took place to produce the aromatic ring. Disproportionation was ruled out as the mechanism of aromatization by the absence of any reduced tricyclic products. Danishefsky had observed a similar dehydrogenation in a related system.[113]

A common feature of all IEDDA reactions that had been preformed in the Bodwell research group at the commencement of this work was that they proceed with complete regioselectivity. In those cases where the cycloadduct was isolated from the reaction mixture, i.e., no subsequent reactions occurred, the *endo* transition state was favored.

[113] Danishefsky, S.; Cunningham, R. *J. Org. Chem.* **1965**, *30*, 3676–3678.

3.2 IEDDA Reactions of Coumarin-Fused Dienes

3.2.1 Initial Investigations

With multigram quantities of diene **165d** in hand, an investigation of its IEDDA reactivity was initiated. Ethyl vinyl ether **113** was selected as the first electron-rich dienophile to be tested, since this dienophile reacted with all of the dienes previously synthesized in the Bodwell laboratory to give a single adduct in high yield. Unfortunately, this dienophile proved to be unreactive under the conditions used for diene **158** (Scheme 3.1). Attempts to promote this reaction by increasing the reaction temperature (up to 120 °C), increasing the reaction time (up to 4 d), or through Lewis acid catalysis by $Yb(OTf)_3$,[114] $Eu(hfc)_3$,[114] or silica gel[115] failed to produce the desired results. The partial aromatic character of the 2-pyrone moiety likely contributed heavily to the greater stability (> 6 months in air) and lower IEDDA reactivity of **165d** compared to **158** (a few days in air). More specifically, the participation of **165d** in an IEDDA reaction involves disruption of the aromatic character of its 2-pyrone unit and this translates into an energetic disincentive to reaction.

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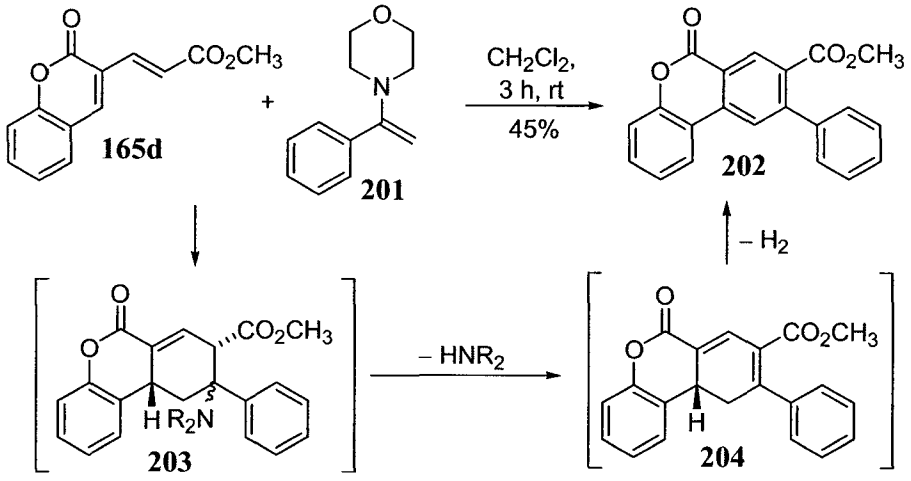
[114] See ref. 54.

[115] Posner, G. H.; Carry, J.-C.; Lee, J. K.; Bull, D. S.; Dai, H. *Tetrahedron Lett.* **1994**, *35*, 1321–1324.

Following the failure of the reaction between **165d** and **113**, attention was turned to enamine **201**. AM1 calculations using the Cambridgesoft Chem 3D package indicated that the HOMO of the enamine lies 0.61 eV higher in energy than that of ethyl vinyl ether **113**. Indeed, this increase in HOMO energy was sufficient to allow the reaction of **201** and **165d**, which led to the formation of benzocoumarin **202** (Scheme 3.3). No intermediates were isolated from the reaction mixture or observed upon monitoring the reaction by TLC analysis. As with diene **158**, the product presumably arises from a domino process that consists of an IEDDA reaction, elimination of the secondary amine used to generate the enamine (morpholine in this case), and an apparent dehydrogenation. Not having isolated or observed any reaction intermediates and the destruction of all stereogenic centres in the presumed adduct **203** by the subsequent elimination and dehydrogenation reactions made it impossible to formulate detailed conclusions about the

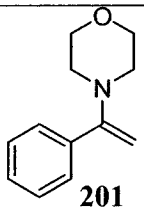
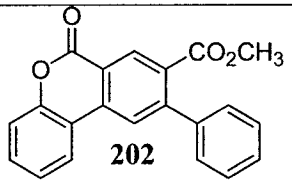
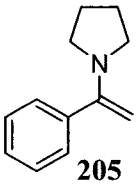
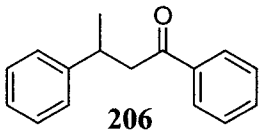


Scheme 3.3: IEDDA driven domino reaction between **165d** and enamine **201**.

reaction mechanism. What can be stated with confidence was that the product **202** was derived from a sequence beginning with an IEDDA reaction with the expected regiochemistry. No products arising from an IEDDA reaction with the opposite regiochemistry were observed in this, or any subsequent case.

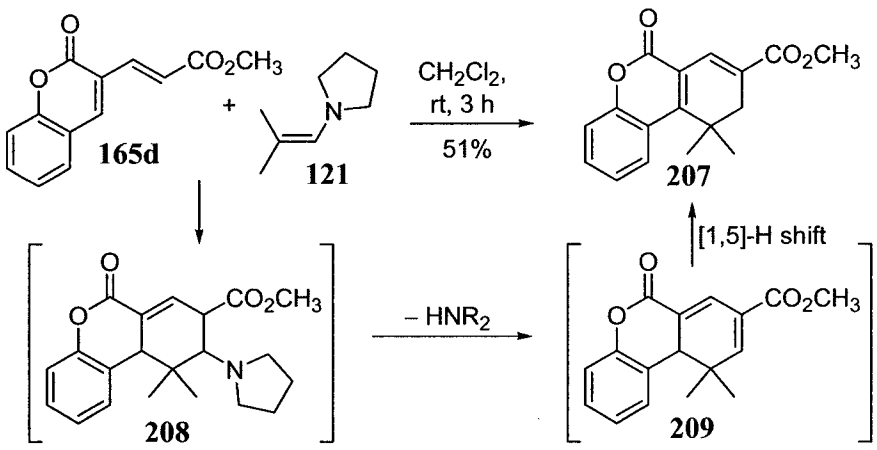
After some experimentation with the reaction conditions (Entries 2-6, Table 3.1), it was found that the same yield could be obtained from reactions run in CH_2Cl_2 at room temperature after just 1 h. The greater solubility of **165d** in CH_2Cl_2 allowed the reaction to be run at higher concentration than the analogous reaction performed in CH_3CN. Changing the amine portion of the enamine from morpholine to pyrrolidine, i.e. enamine **205**, led to a significant increase in yield of the isolated product **202** (64%, Entry 5). Again dichloromethane was found to be a better solvent than acetonitrile. A small amount of a by-product, **206,** was isolated from this reaction. That this was the hydrogenated self-condensation product of acetophenone provided the first clue as to the nature of the dehydrogenation step in the domino process. At this point, the room temperature reaction in CH_2Cl_2 (Entry 6) was chosen as the standard condition to evaluate the reactivity of diene **165d** with a variety of enamines.

Table 3.1:

Entry	Enamine	Conditions	Products	Yield
1.	 **201**	CH_3CN, 80 °C, 3 h, 0.022 M	 **202**	45%
2.	**201**	CH_3CN, r.t., 10 d, 0.022 M	**202**	37%
3.	**201**	CH_2Cl_2, r.t., 1 h, 0.17 M	**202**	46%
4.	**201**	CH_2Cl_2, r.t., 14 d, 0.17 M	**202**	24%
5.	 **205**	CH_2Cl_2, r.t., 3 h, 0.17 M	**202**	64%
6.	**205**	CH_3CN, r.t., 3 h, 0.17 M	**202**	48%
			 **206**	10%

Based on the previous results, the reaction between **165d** and enamine **121**,[116] having geminal methyl groups would be expected to produce the non-aromatized product **209** via an IEEDA reaction followed by the elimination of pyrrolidine. However, the only product isolated from this reaction was the tricyclic system **207** (Scheme 3.4). Its

[116] Chan, Y.; Epstein, W. W. *Org. Synth., Coll. Vol. VI* **1988**, 496–498.

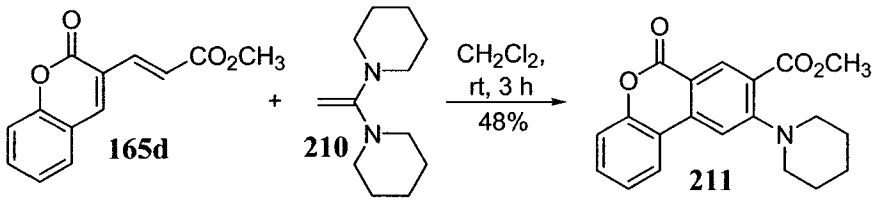


Scheme 3.4: Reaction of diene **165d** with enamine **121**.

formation can be explained by the formation of **209** by the expected sequence followed by a [1,5]-hydrogen shift. More extended conjugation and a lesser degree of steric congestion, as can be seen upon examination of molecular models, between one of the geminal methyl groups and the nearby aryl-H atom in **207** may well be responsible for the readiness with which the [1,5]-hydrogen shift occurs. AM1 calculations using the Spartan package of software indicated that **207** was 7.9 kcal/mol lower in energy than **209**.

In light of this result, ketene aminal **210**[117] was chosen as an electron-rich dienophile and subjected to reaction with **165d** under standard conditions (Scheme 3.5). In this case it was envisaged that a domino reaction consisting of an IEDDA reaction, elimination of piperidine, a [1,5]-hydrogen shift, and then a second elimination of piperidine, would take place to afford benzocoumarin **212** (Figure 3.1). In fact,

[117] Baganz, H.; Domaschke, L. *Chem. Ber.* **1962**, *95*, 2095–2096.



Scheme 3.5: Reaction of diene **165d** with ketene aminal **211**.

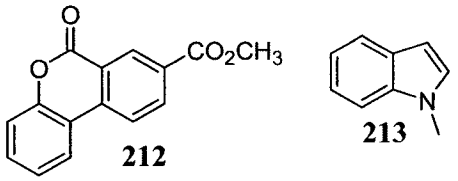


Figure 3.1: Benzocoumarin **212** and *N*-methylindole **213**.

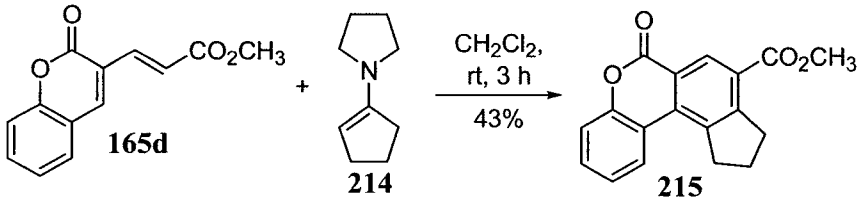
benzocoumarin **212** was not isolated, but rather **211** (48%). This suggested that the dehydrogenation reaction of the direct precursor to **211** (*cf.* **204**) occurs more quickly than a [1,5]-hydrogen shift.

Indoles have been reported to participate as dienophiles in IEDDA reactions.[118] The $HOMO_{dienophile}$-$LUMO_{diene}$ energy difference, calculated using CambridgeSoft Chem 3D software package, between *N*-methylindole **213** (Figure 3.1) and diene **165d** is 0.1 eV smaller than the difference between enamine **205** and **165d**. According to Sustmann and Sauer, the smaller energy difference would allow for a faster reaction.[16] However, no reaction between *N*-methylindole and **165d** occurred under the standard conditions or at elevated temperature, i.e. acetonitrile at reflux temperature. Even though the difference in the $HOMO_{dienophile}$ and $LUMO_{diene}$ is small enough to indicate a favorable outcome for

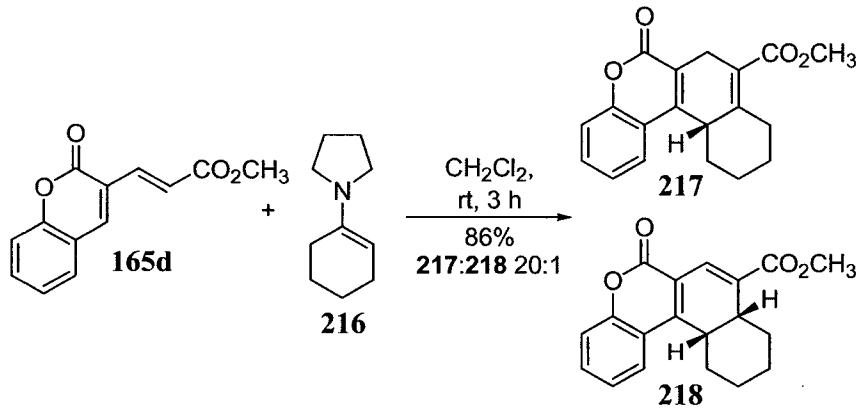
[118] Wan, Z.-K.; Snyder, J. K. *Tetrahedron Lett.* **1998**, *39*, 2487–2490.

the Diels-Alder reaction, the destruction of two aromatic entities would be expected to present a considerable energetic impediment to reaction.

Diene **165d** was then reacted with a series of enamines derived from cycloalkanones. Due to the cost of commercially-available cyclobutanone, this enamine was not synthesized. However, the enamine derived from cyclopentanone and pyrrolidine, **214**, was generated and it was reacted with diene **165d** under standard conditions to give benzocoumarin **215** (43%) (Scheme 3.6). As before, the newly-formed six-membered ring of the product was aromatic. Reaction of enamine **216** with **165d** afforded a 20:1 mixture of **217** and **218** in 86% combined yield (Scheme 3.7). Since all of the previous reactions of enamines, except **121**, with diene **165d** had resulted in the



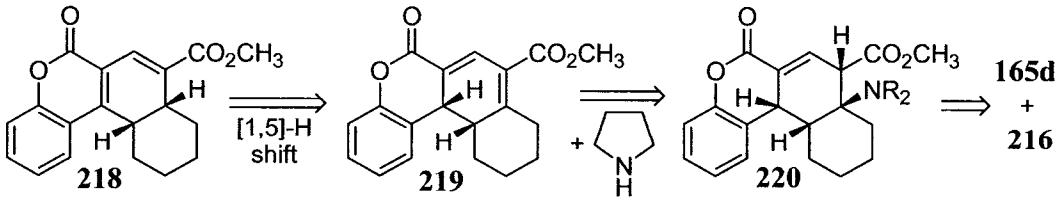
Scheme 3.6: IEDDA-driven-domino reaction of diene **165d** with enamine **214**.



Scheme 3.7: Reaction of diene **165d** with enamine **216**.

formation of aromatic products, the exclusive isolation of products that had not suffered dehydrogenation was surprising.

Initial structural assignments of **217** and **218** were accomplished by interpreting the results from 2D NMR experiments, and these were confirmed by single crystal x-ray diffraction experiment (Figures 3.2, and 3.3). The data for the minor product **218** revealed a *cis* ring juncture. A retrosynthetic analysis of **218** (Scheme 3.8) demonstrated that, if the domino reaction commenced with a concerted (asynchronous) Diels-Alder reaction, the cycloaddition would have had to go through an "N"-*exo* transition state with the pyrrolidinyl moiety *exo* to the diene. With only one stereogenic center, an analogous analysis cannot be applied to the major product **217**. Indeed, no conclusion can be drawn regarding the overall *endo*/*exo* selectivity of the reaction or whether **217** and **218** arise from the same precursor, distinct precursors, or both. Attempts to correlate the product ratio to the calculated heats of formation for all possible diene products, at the AM1 and PM3 levels of theory, gave inconclusive results (see Appendix 1). It seems as though both methods place little importance on the aromatic character of the 2-pyrone moiety. The mechanism at this point can still only be speculated upon.



Scheme 3.8: Retrosynthetic analysis of compound **218**.

Figure 3.2: ORTEP representation of **217** in the crystal.

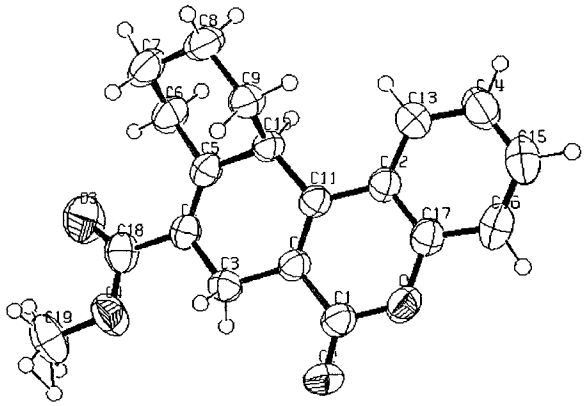
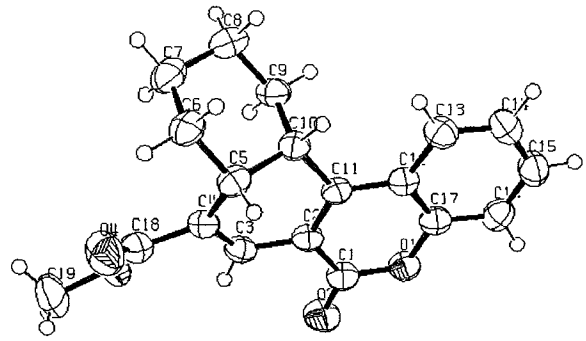
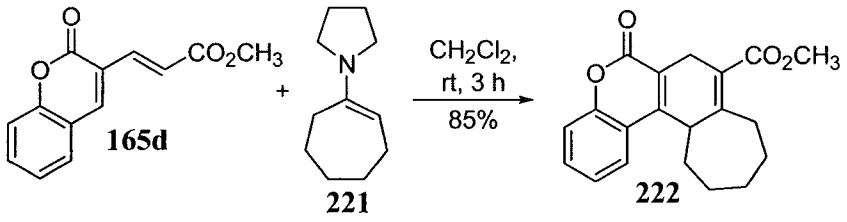
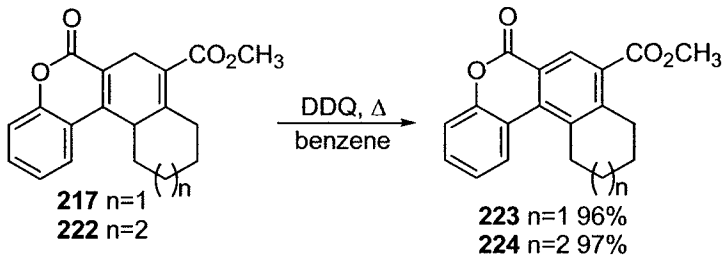


Figure 3.3: ORTEP representation of **218** in the crystal.





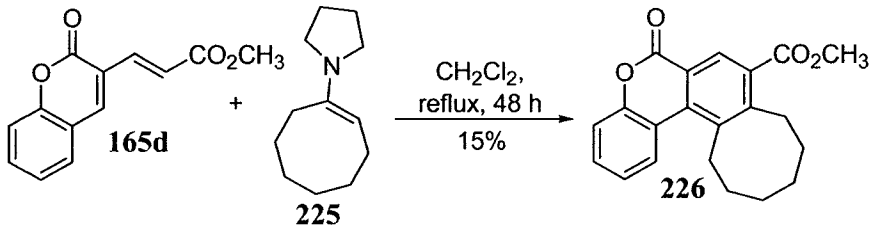
Scheme 3.9: Reaction of diene **165d** with enamine **221**.



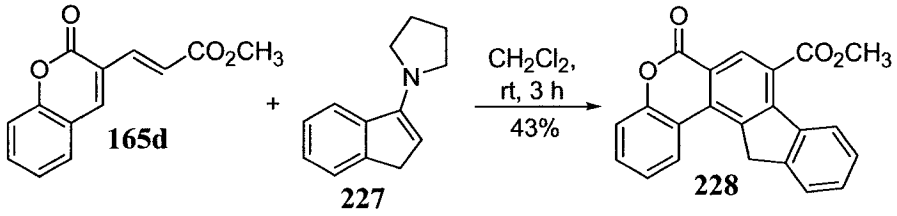
Scheme 3.10: Dehydrogenation reaction of **217** and **222**.

Reaction of **165d** with enamine **221** gave cyclic diene **222** as the only isolated product (85%) (Scheme 3.9). Again, the dehydrogenation of the proposed IEDDA-driven domino sequence did not occur. However, both **217** and **222** could be smoothly transformed into benzocoumarins **223** (96%) and **224** (97%) respectively by a dehydrogenation reaction with DDQ (Scheme 3.10).

The enamine from cyclooctanone **225** was then prepared. It was surprisingly that the reaction of diene **165d** with **225** did not occur under the standard reaction conditions. In order to induce reaction, the mixture had to be heated to reflux temperature (Scheme 3.11). A reaction time of 48 h was required for the complete consumption of the starting material according to tlc analysis. Only 15% of the aromatic product **226** was isolated and no "nonaromatized" products were produced. The increased reaction temperature



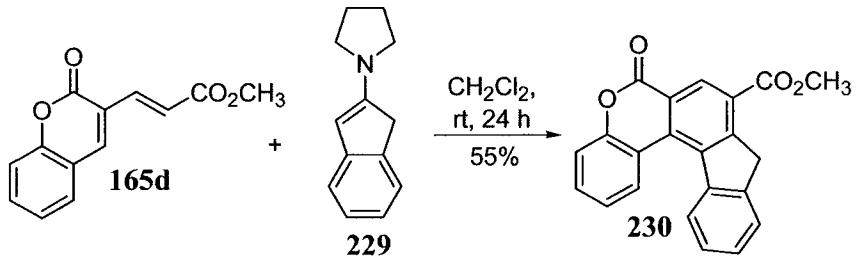
Scheme 3.11: Reaction of diene **165d** with enamine **225**.



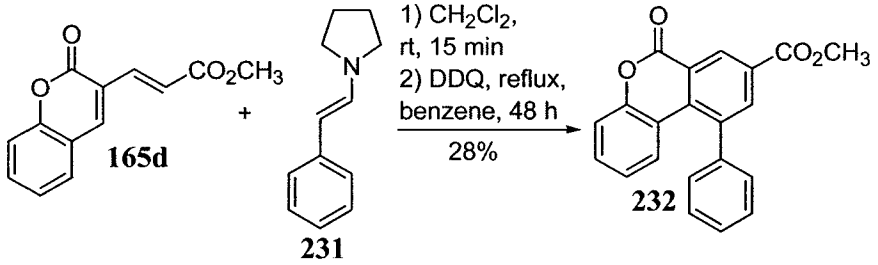
Scheme 3.12: IEDDA driven domino reaction of diene **165d** with enamine **227**.

presumably allowed the dehydrogenation step to take place. The remaining material was removed from the column packing with methanol but could not be identified.

The enamine derived from 1-indanone and pyrrolidine, **227**, was then produced. It reacted with **165d** under the standard reaction conditions to give benzocoumarin **228** in 43% yield (Scheme 3.12). This reaction produced only the "aromatized" product and the expected regiochemistry in the IEDDA reaction could again be inferred. Enamine **229**, derived from 2-indanone and pyrrolidine, reacted with **165d** to afford benzocoumarin **230** in 55% yield (Scheme 3.13). No other material was isolated. At this point, it was unclear whether a particular reaction with an enamine would produce a benzocoumarin or "nonaromatized" products.



Scheme 3.13: IEDDA driven domino reaction of diene **165d** with enamine **229**.



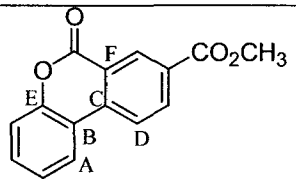
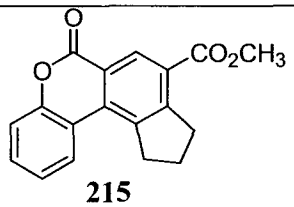
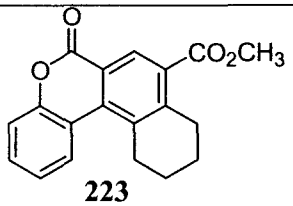
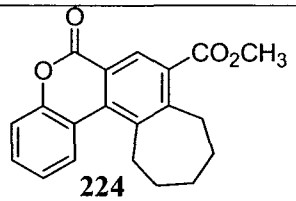
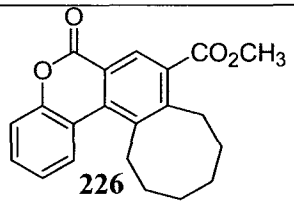
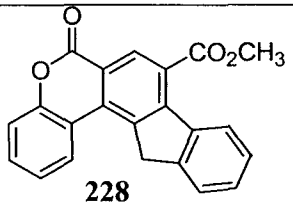
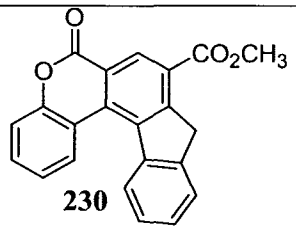
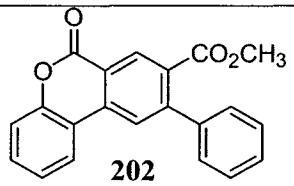
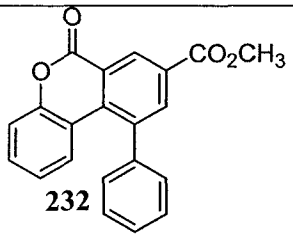
Scheme 3.14: Reaction of diene **165d** with enamine **231**.

Diene **165d** reacted with enamine **231** to afford what was tentatively assigned to be a mixture of "nonaromatized" products on the basis of the ^{1}H NMR spectrum of the crude reaction product. The spectrum revealed three methyl ester signals and a number of signals that had coupling patterns consistent with an *ortho* substituted aromatic ring. Attempts to separate the mixture by column chromatography failed. With the success of the previous reactions with DDQ, the mixture of compounds was reacted with DDQ in refluxing benzene. Unfortunately, this reaction produced only a 28% yield, based on the starting diene **165d**, of benzocoumarin **232** as the only isolated material (Scheme 3.14).

Bringmann[119] has reported that the benzocoumarin framework can easily twist out of planarity to reduce any intramolecular interactions when they exist. It was therefore decided to calculate and compare the torsion angles along the biaryl bond in the aromatized products to see if there was any correlation with the dehydrogenation reaction (Table 3.2). The benzocoumarin compounds that were calculated to be planar or very close to planar (average calculated torsion angle of the biaryl bond (Φ_{calc}) <4 °), i.e. **215**, **228**, and **202**, all easily underwent dehydrogenation during the reaction. When the Φ_{calc} was significant (>20 °), the dehydrogenation process did not occur and the products isolated from the reaction mixture were "nonaromatized" with one exception, **230**. Φ_{calc} for **230** was 20.9 °, but it was the only product isolated from the reaction of **165d** and enamine **229** (Scheme 3.13). The Φ_{calc} for the diene intermediates, the direct precursors to the final benzocoumarin compounds, were all very similar and no trend emerged from the data. These data seems to indicate that the presence of developing strain at the transition state of the dehydrogenation step is enough to block effectively this step under the conditions employed.

[119] (a) Bringmann, G.; Stefan, T. *Tetrahedron* **2001**, *57*, 331–344. For recent reviews discussing the twisting of benzocoumarin moiety, see: (b) Bringmann, G.; Menche, D. *Acc. Chem. Res.* **2001**, *34*, 615–624. (c) Bringmann, G.; Breuning, M.; Tasler, S. *Synthesis* **1999**, 525–558.

Table 3.2:

 General numbering used in this Table. Φ_{calc} is the relative average torsion angle of the carbon atoms indicated above	 **215** ABCD: 0 ° EBCF: 0 ° EBCD: 180 °(0 °) ABCF: 180 °(0 °) Φ_{calc}: **0 °**	 **223** ABCD: 24.0 ° EBCF: 17.7 ° EBCD: 161 °(19.0 °) ABCF: 155.3 °(24.7 °) Φ_{calc}: **21.4 °**
 **224** ABCD: 27.7 ° EBCF: 19.3 ° EBCD: 153.6 °(26.4 °) ABCF: 159.4 °(20.6 °) Φ_{calc}: **23.5 °**	 **226** ABCD: 24.5 ° EBCF: 17.9 ° EBCD: 162.7 °(17.3 °) ABCF: 154.9 °(25.1 °) Φ_{calc}: **21.2 °**	 **228** ABCD: 4.2 ° EBCF: 2.2 ° EBCD: 176.7 °(3.3 °) ABCF: 176.9 °(3.1 °) Φ_{calc}: **3.2 °**
 **230** ABCD: 23.2 ° EBCF: 18.5 ° EBCD: 164.1 °(15.9 °) ABCF: 154.1 °(25.9 °) Φ_{calc}: **20.9 °**	 **202** ABCD: 3.8 ° EBCF: 1.7 ° EBCD: 177.2 °(2.8 °) ABCF: 177.3 °(2.7 °) Φ_{calc}: **2.8 °**	 **232** ABCD: 20.7 ° EBCF: 16.6 ° EBCD: 164.3 °(15.7 °) ABCF: 158.4 °(21.6 °) Φ_{calc}: **20.9 °**

3.2.2 *In Situ* Generation of Enamines

It has been demonstrated that enamines can be hydrolyzed readily in alkaline, neutral, or acidic environments.[120] Therefore, the synthesis and purification of enamines is normally carried out in an anhydrous environment. Purification is typically achieved by vacuum distillation. However, as the molar mass of the enamine becomes increasingly large, the purification of these compounds becomes significantly more difficult due to the concomitant increase in the boiling point of the enamine. With the higher temperature required for vacuum distillation, thermal decomposition can start to compete with the distillation.

This being the case, attention was turned to the possibility of generating enamines for the reaction with **165d** *in situ*. If this were to be successful, the following advantages would be realized: 1) enamines that are not easily isolated could be used in the IEDDA-driven domino reaction; 2) the need to synthesize and purify the enamine before using it would be obviated; 3) a choice of procedures, i.e. "preformed" or "*in situ*", would be available for various enamines.

Cyclopentanone **233** was chosen as the first ketone for this investigation. Since the second step of the domino process is the elimination of the amine used to generate the enamine (Scheme 3.3), it was reasoned that a sub-stoichiometric amount of the amine

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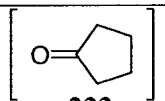
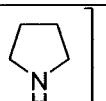
[120] Cook, A. G. In *Enamines Synthesis, Structure, and Reactions 2nd Edition, Revised and Expanded* Cook, A. G., ed.; Marcel Dekker, Inc.: New York, 1988, Ch. 3.

could be employed. The concentrations of the other reactants were based on the work summarized earlier in Table 3.1.

Upon mixing this ketone, pyrrolidine and **165d** with 4Å Molecular Sieves, in CH_2Cl_2, benzocoumarin **215** (63%) was generated as the only tlc-mobile spot using CH_2Cl_2 as eluent (Table 3.3, Entry 1). It was gratifying that the first attempt, which involved the use of 20 mol% of pyrrolidine, produced a higher yield of benzocoumarin **215** (63%) than by the preformed method (43%). This result also confirmed that the amine could be used catalytically. Reducing the proportion of pyrrolidine to only 5 mol% still led to the production of **215** (Entry 2), but tlc analysis indicated that the reaction stopped after about 1.5 h. The solution continued to stir for 24 h, but the tlc trace did not change. A mixture of **215** and the starting diene **165d** was obtained, for which conversions of 37% (**215**) and 59% (**165d**) were calculated from integration of the ^1H NMR spectrum of the mixture.

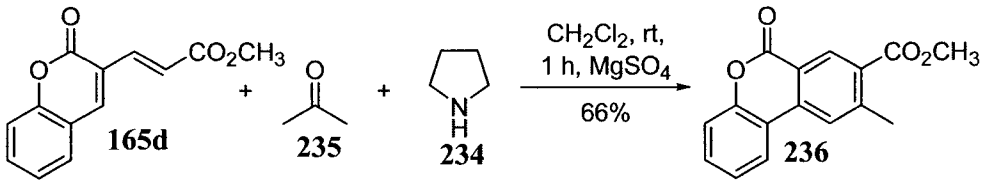
Table 3.3: Initial investigation for producing **215** using an *in situ* generated enamine.

Entry	**[165d]**	 **233**	 **234**	Conditions and drying agent[a]	Yield of **215**
1.	0.2 M	0.3 M	0.04 M	CH_2Cl_2, rt, 45 min, 4Å Molecular Sieves	63%
2.	0.2 M	0.3 M	0.01 M	CH_2Cl_2, rt, 24 h, 4Å Molecular Sieves	37%[b]
3.	0.2 M	0.4 M	0.04 M	CH_2Cl_2, rt, 20 min, 4Å Molecular Sieves	42%
4.	0.2 M	0.4 M	0.1 M	CH_2Cl_2, rt, 15 min, 4Å Molecular Sieves	56%
5.	0.2 M	1 M	0.1 M	CH_2Cl_2, rt, 15 min, 4Å Molecular Sieves	66%
6.	0.2 M	1 M	0.1 M	CH_2Cl_2, 0 °C, 45 min, 4Å Molecular Sieves	59%
7.	0.2 M	1 M	0.1 M	CH_2Cl_2, 40 °C, 15 min, 4Å Molecular Sieves	61%
8.	0.2 M	1 M	0.1 M	CH_2Cl_2, rt, 15 min, $MgSO_4$	74%

[a] Reaction times correspond to the approximate time required for the consumption of starting material, according to tlc analysis. [b] Obtained as a 27:73 mixture with **165d** in a combined yield of 96%.

The concentration of pyrrolidine was then increased to 20 mol% and the ketone concentration was increased slightly (Entry 3). This resulted in a 42% yield of **215**, but the reaction time decreased from 45 min to 20 min. Although the decrease in yield was disappointing, the increase in rate was promising. The concentration of pyrrolidine was then increased to 50 mol% (Entry 4), which resulted in the consumption of the starting diene after 15 min and a 56% yield of **215**. Increasing the concentration of the ketone resulted in a slight increase in yield of **215** (66%, Entry 5). Changing the reaction temperature did not significantly affect the yield of the benzocoumarin (Entries 6 and 7). However, as expected, performing the reaction at 0 °C required an increase in the time of the reaction. Substitution of the 4Å Molecular Sieves by $MgSO_4$ brought about a further improvement in the yield of the benzocoumarin **215** (74%, Entry 8), and also eliminated the need to activate molecular sieves before each reaction. The reaction conditions described in Entry 8 became the standard conditions for generating enamines *in situ* and will be referred to as the "standard *in situ* procedure" for the remainder of this dissertation. The previous procedure, described in Chapter 3.1, will be referred to as the "standard preformed enamine procedure".

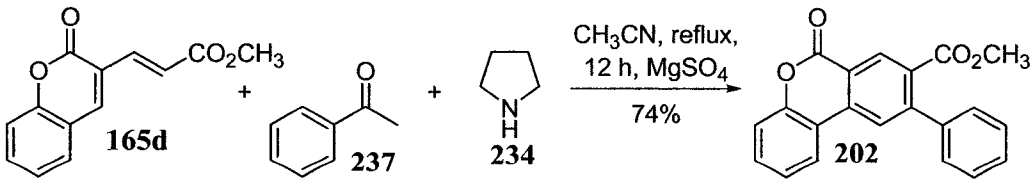
The synthesis and isolation of the enamine derived from acetone and pyrrolidine has not been reported in the literature. Attempts to convert acetone into its pyrrolidine-derived enamine failed, thus making this ketone a good candidate for the standard *in situ* procedure. The reaction proceeded smoothly to produce benzocoumarin **236** in 66% yield as the only TLC-mobile (CH_2Cl_2) product (Scheme 3.15). No unaromatized



Scheme 3.15: Reaction of **165d** with an *in situ* generation of the enamine from acetone **235**.

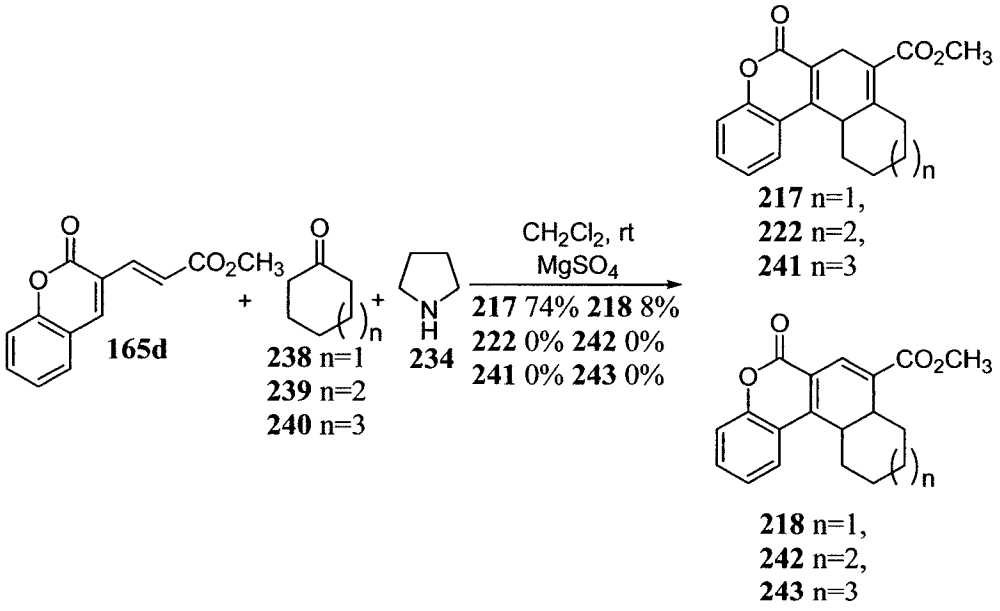
products were observed, which is consistent with the calculated (method) average torsion angle along the biaryl bond in **236** being 0 ° (*vide supra*).

Sights were then set on comparing the two methods to determine if one was generally superior to the other. Acetophenone was subjected to the conditions of the standard *in situ* procedure, and only acetophenone was recovered from the reaction mixture (92%). After some experimentation, it was discovered that the reaction required elevated temperatures to proceed. Changing from CH_2Cl_2 at reflux temperature (22%) to acetonitrile at reflux temperature produced benzocoumarin **202** in 74% yield (Scheme 3.16). This yield was slightly higher than the corresponding reaction using the standard preformed enamine procedure (66%) but the reaction time (12 h) was significantly longer, 12 h versus 3 h. However, the synthesis of the enamine **205**, which was problematic, did not have to be completed prior to the reaction.



Scheme 3.16: Reaction of **165d** with an *in situ* generation of the enamine from acetophenone **237**.

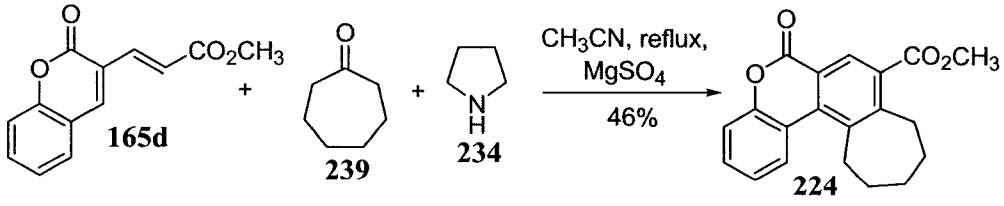
Attention was then turned to the *in situ* generation of a series of enamines derived from cycloalkanones. Cyclopentanone had been used for the initial investigations of the *in situ* procedure (Table 3.3). It was found that the reaction to afford benzocoumarin **215** was much quicker, 15 min instead of 3 h, and the yield was much better, 74% versus 43%, then when the preformed enamine **214** was used. Reaction with cyclohexanone under the standard *in situ* conditions gave a mixture of cyclic diene **217** and **218** in 82% combined yield (Scheme 3.17), which was similar to the combined yield obtained for the standard preformed enamine procedure (86%). However, the ratio of isomers changed slightly, preformed procedure: **217**:**218** 20:1; *in situ* procedure: **217**:**218** 9:1. The major difference between the two reactions was the significant change in the reaction times, 5 d (*in situ*) compared to 3 h (preformed).



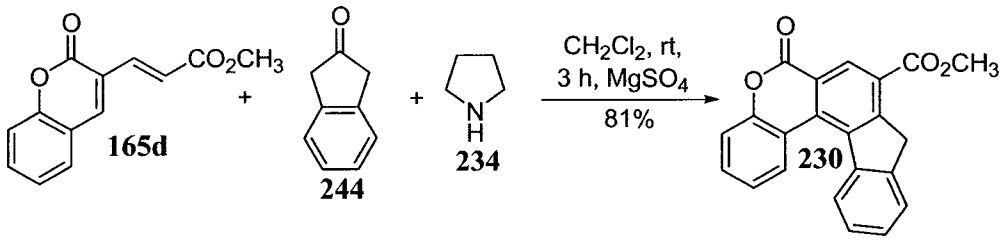
Scheme 3.17: Reaction with enamines generated *in situ* from cycloalkanones with diene **165d**.

It was surprising that cycloheptanone **239** and cyclooctanone **240** did not react under the conditions of the standard *in situ* procedure. When the reaction solvent was changed to acetonitrile and the reaction temperature was raised to reflux temperature, cyclooctanone still did not react. However, cycloheptanone **239** did react under these conditions, generating only the aromatized product **224** in 46% yield (Scheme 3.18). By comparison, the enamine **221** derived from cycloheptanone gave lactone **222** in high yield (85%) under the standard preformed enamine conditions, whereas the enamine derived from cyclooctanone, **225**, gave a low yield (15%) of the corresponding benzocoumarin **226** at an elevated reaction temperature. It is a mystery why the apparent rate of reaction becomes slower with increasing ring size of the cycloalkanes.

Reaction of diene **165d** with the *in situ*-generated enamine of 2-indanone afforded benzocoumarin **230** in good yield (81%) (Scheme 3.19), which was significantly higher than that obtained using the preformed enamine method (55%). The reaction time was approximately the same. When the ketone was changed to 1-indanone, no reaction was observed with diene **165d**. Nevertheless, the results so far suggest that when the *in situ* procedure is successful, the yield of the product is usually higher than that obtained using the preformed enamine procedure.

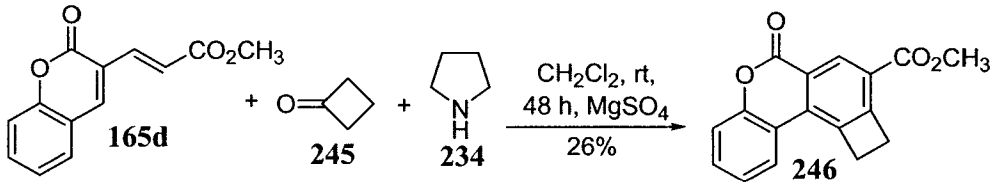


Scheme 3.18: Reaction of **165d** with an *in situ* generated enamine from cycloheptanone **239**.



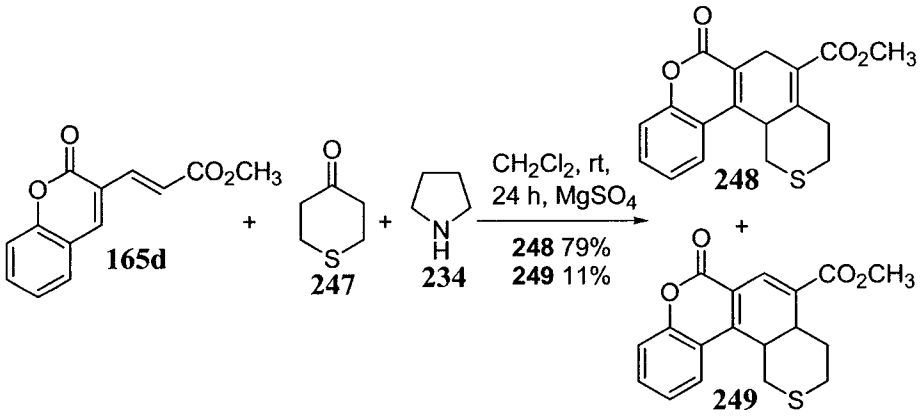
Scheme 3.19: Reaction of **165d** with an *in situ* generated enamine from 2-indanone **244**.

Several comparatively expensive ketones, the conversion of which into enamines under normal conditions would be very uneconomical, were then selected for study using the *in situ* procedure. To minimize the waste of these ketones, the number of equivalents of the ketone used in the standard procedure was lowered (5 equivalents to 1.5 equivalents). The first ketone to receive attention using this slightly modified procedure was cyclobutanone **245** (Scheme 3.20). This reaction produced benzocoumarin **246** in 26% yield, and the reaction time was 48 h. The relatively slow rate might be a consequence of the lower concentration, or the inherent strain in cyclobutenes, or both. The Φ_{calc} in the product was 0 °, so the observation of only an aromatized product was not surprising. Cyclopropanone was not employed because the enamine reportedly does not form, but rather an aminal is generated.[121]

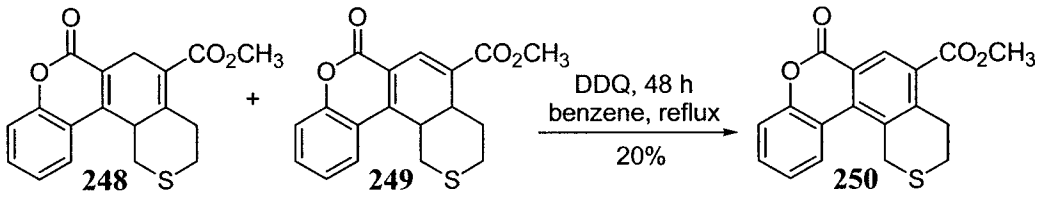


Scheme 3.20: Synthesis of benzocoumarin **246**.

[121] Wasserman, H. H.; Baird, M. S. *Tetrahedron Lett.* **1970**, 1729-1733.



Scheme 3.21: Reaction of an *in situ* generated enamine of ketone **247** with **165d**.



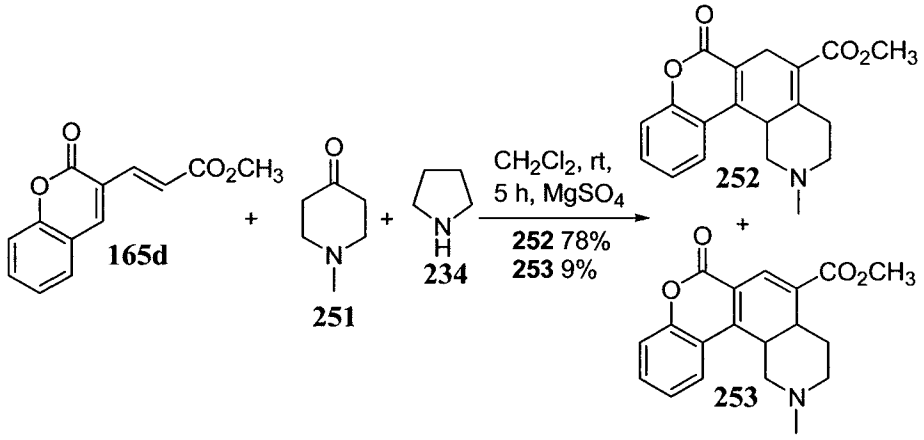
Scheme 3.22: Dehydrogenation of the mixture **248** and **249**.

Tetrahydrothiopyran-4-one **247** was then reacted with diene **165d** under the conditions used for the reaction with cyclobutanone. As in the case of cyclohexanone, this afforded a mixture of nonaromatized products **248** (79%) and **249** (11%)(Scheme 3.21). Heating the mixture **248/249** in the presence of DDQ generated **250**, but only in a disappointing 20% yield (Scheme 3.22). The sensitivity of the sulfur atom towards oxidation may have been the cause for the poor yield. Other methods for the oxidation of **244** (and **245**), such as Pd/C in refluxing xylene,[122] which is reported to be compatible with heteroatoms, may well prove to be more successful. The average torsion angle of

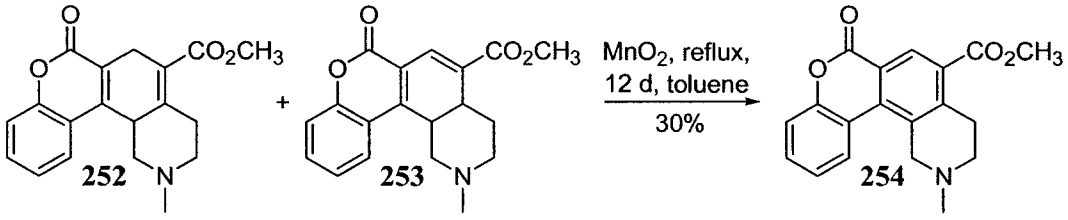
[122] Mekouar, K.; Genisson, Y.; Leue, S.; Greene, A. E. *J. Org. Chem.* **2000**, *65*, 5212–5215.

the biaryl bond in **250** was calculated to be 22 °, which is consistent with the observation of no dehydrogenation step.

With the success of the reaction with ketone **247**, diene **165d** was then reacted under the same reaction conditions with the nitrogen analogue, 1-methyl-4-piperidone **251**. The IEDDA-driven domino reaction proceeded smoothly to afford a mixture of nonaromatized products **252** (78%) and **253** (9%) (Scheme 3.23).[123] Attempts to aromatize the mixture to generate benzocoumarin **254** via a dehydrogenation reaction with DDQ failed. However, benzocoumarin **254** (Φ_{calc}=18 °) was obtained in modest



Scheme 3.23: Reaction of an *in situ* generated enamine of ketone **251** with **165d**.

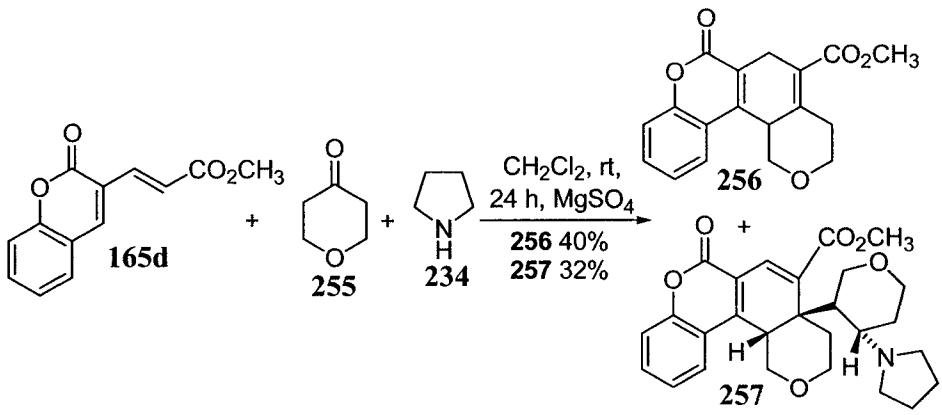


Scheme 3.24: Dehydrogenation reaction of the mixture **252** and **253** using MnO_2.

[123] Yields calculated from ^{1}H NMR spectrum.

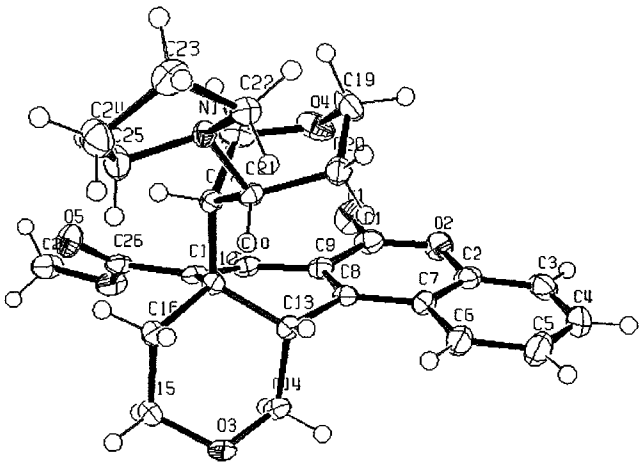
yield (30%) when **252** and **253** were reacted with MnO_2 in toluene for 12 days (Scheme 3.24). As before, other methods may ultimately prove to be effective.

The final ketone in this series to receive attention was tetrahydropyran-4-one **255**. The reaction involving **255** (Scheme 3.25) was stirred for 24 h, although the results from TLC analysis did not change after 3 h. The reaction was allowed to continue because TLC results indicated the presence of the starting diene **165d**. In the previous two examples, i.e. reactions with ketones **247** and **251**, diene **165d** was totally consumed. Separation of the reaction mixture by column chromatography afforded 18% of diene **165d**, a single nonaromatized product, cyclic diene **256** (40%), and a new compound that was assigned to structure **257** (32%) on the basis of a single crystal X-ray diffraction experiment (Figure 3.4).

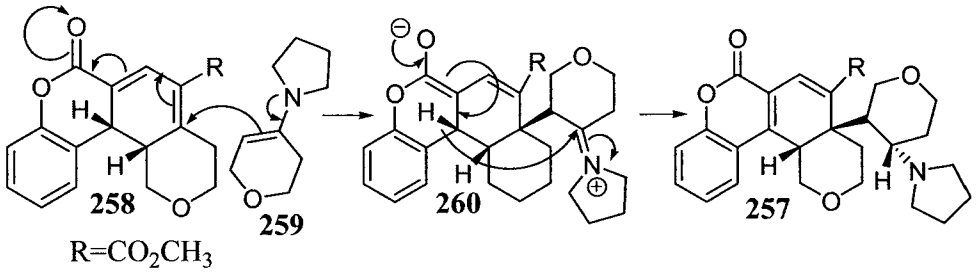


Scheme 3.25: Reaction of **165d** and an *in situ* generated enamine of ketone **255**.

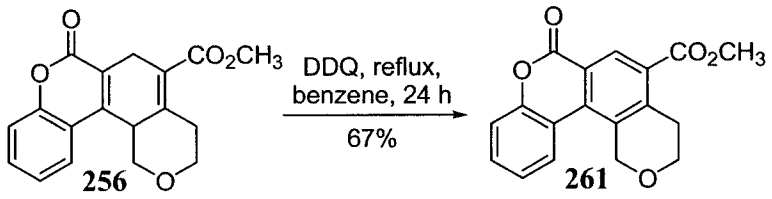
Figure 3.4: ORTEP representation of **257** in the crystal.



The formation of **257** in this reaction was very puzzling, considering that analogous compounds were not isolated from any of the other reactions. A proposed mechanism for the formation of **257** is shown in Scheme 3.26. Akin to previous reactions, IEDDA reaction followed by the elimination of pyrrolidine would afford **258**. Conjugate addition of a second equivalent of enamine **259** to the less sterically hindered face of **258** would afford zwitterion **260**. The resulting extended enolate is poised to undergo an intramolecular hydride transfer to the imminium ion via a six-membered transition state. The stereochemical outcome of this step is fully consistent with the observed stereochemistry in **257** (see C21 in Figure 3.4).



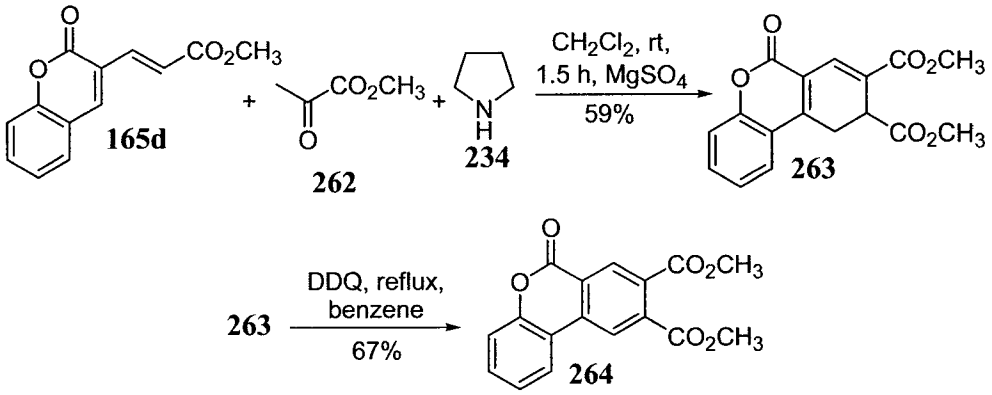
Scheme 3.26: Proposed mechanism for the formation of **257.**



Scheme 3.27: Reaction of **256** with DDQ.

Reaction of **256** with DDQ proceeded smoothly to afford benzocoumarin **261** in 67% yield (Scheme 3.27). The calculated torsion angle about the biaryl bond was 16.5 °. As in the previous cases, the dehydrogenation reaction does not occur at room temperature.

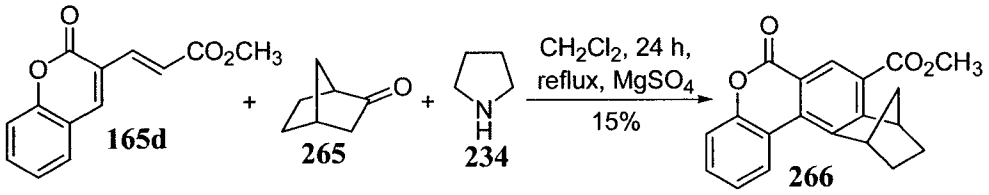
Sights were set on other ketones that could be used to generate enamines *in situ.* The first was methyl pyruvate **262.** Using the standard *in situ* procedure, no reaction occurred. However, cyclic diene **263** was produced in reasonable yield (59%) when a large excess of ketone **262** (10 equivalents) and pyrrolidine (9 equivalents) **234** were used (Scheme 3.28). Analysis by TLC revealed that the reaction was probably finished after approximately 5 min, but it was not stopped until 1.5 h had elapsed. The IEDDA-driven domino reaction had still occurred in this case, which suggested that the HOMO/LUMO



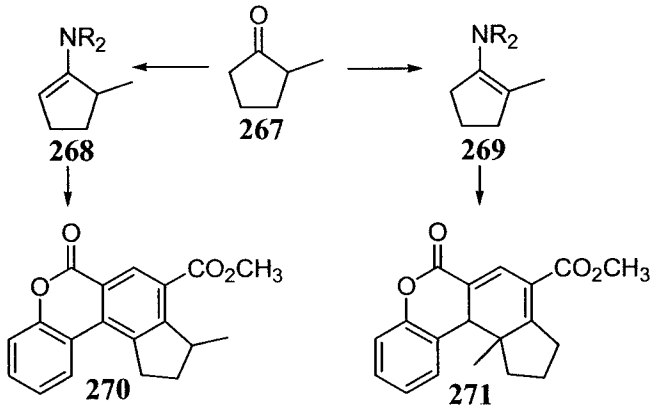
Scheme 3.28: Synthesis of benzocoumarin **264**.

gap was still sufficiently small when an electron-withdrawing group, a methyl ester, was bonded to the double bond of the enamine. In fact, the calculated HOMO of the pyrrolidine-derived enamine of **262** using the Cambridgesoft Chem 3D package of software was –8.73 eV, which is only slightly higher energy than that of 1-(2-methyl-propenyl)pyrrolidine **121** (–8.91 eV). The product isolated from the reaction mixture was "nonaromatized," that is the dehydrogenation reaction did not occur, even though the Φ_{calc}= 0.4 °. The presence of the methyl ester must play a role in hindering the progress of the dehydrogenation reaction. Cyclic diene **263** was easily transformed into benzocoumarin **264** (67%) upon reaction with DDQ.

Because of its expense, norcamphor **265** was reacted using the reaction conditions for cyclobutanone. When the reaction was conducted at room temperature, TLC analysis showed only starting materials were present after 24 h. When the reaction was carried out in CH_2Cl_2 at reflux, it resulted in the production of benzocoumarin **266** (Φ_{calc}= 2.5 °) in 15% yield (Scheme 3.29). The starting diene was also recovered in 28% yield.



Scheme 3.29: Synthesis of benzocoumarin **266**.



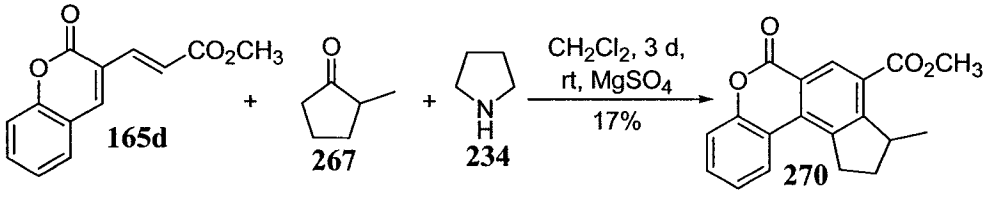
Scheme 3.30: Possible products of an *in situ* generated enamine derived from **267**.

2-Methylcyclopentanone **267** was investigated next. This ketone can potentially form two different enamines **268** and **269** (Scheme 3.30). It has been reported that the ratio between enamines **268** and **269** can be manipulated depending on the amine used to synthesize the enamine.[124] Gurowitz and Joseph[125] reported that when pyrrolidine was used as the secondary amine, the ratio of the enamines (**268**:**269**) was 90:10. Reaction between **267**, pyrrolidine **234** and **165d** afforded only benzocoumarin **270** (Φ_{calc}= 12.5 °) in 17% yield (Scheme 3.31). Neither compound **271**, which would result from enamine **269** (when NR_2=pyrrolidine), nor any follow-on product thereof was isolated.

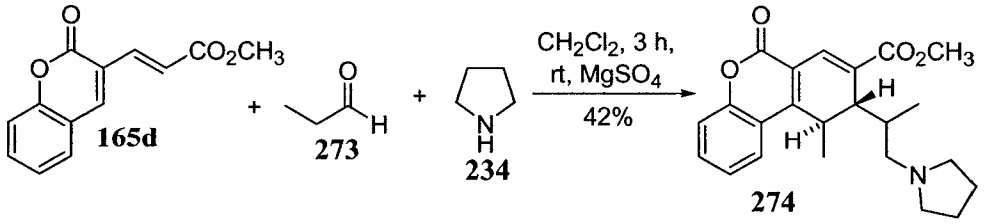
[124] Ref. 120, p. 40.
[125] Gurowitz, W. D.; Joseph, M. A. *Tetrahedron Lett.* **1967**, 4433–4437.

Gurowitz's report suggests this enamine was present. Considering only 17% of the mass recovered was identified, it is difficult to comment on the selectivity of the diene towards reaction with the two enamines, **268** and **269**. However, with enamine **268** being a trisubstituted dienophile, its rate of reaction with diene **165d** was probably slower than the tetrasubstituted dienophile **269**.

Attempts to prepare the enamine from propionaldehyde and pyrrolidine were unsuccessful as was an attempt to generate this enamine using the standard *in situ* procedure. However, when the procedure was modified slightly by increasing the equivalents of the aldehyde (3 equiv.) and amine (4 equiv.), a reaction occurred over 3 h. The expected IEDDA-elimination-dehydrogenation reaction to afford the appropriate benzocoumarin did not occur. Instead, coumarin **274** was isolated from the reaction mixture in 42% yield (Scheme 3.32). The structure was assigned using the results from 2D NMR experiments while the relative stereochemistry was tentatively assigned.



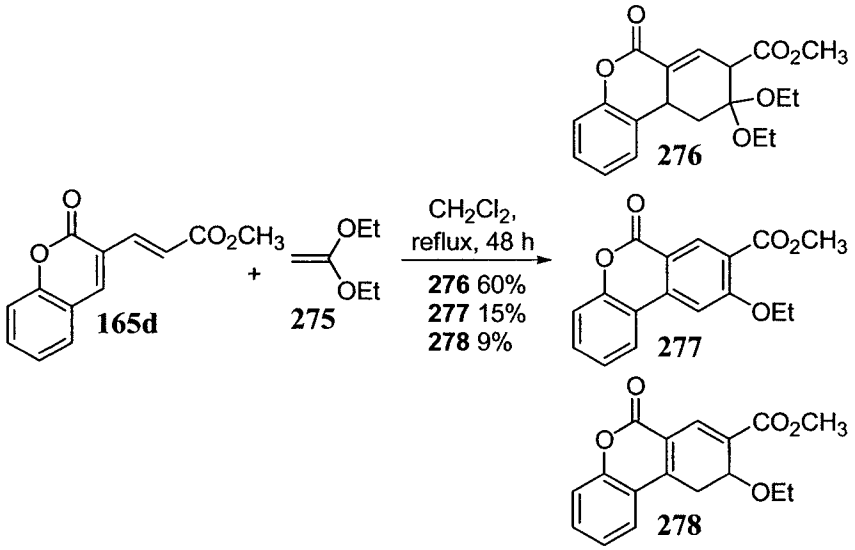
Scheme 3.31: Synthesis of benzocoumarin **270**.



Scheme 3.32: Synthesis of coumarin **274**.

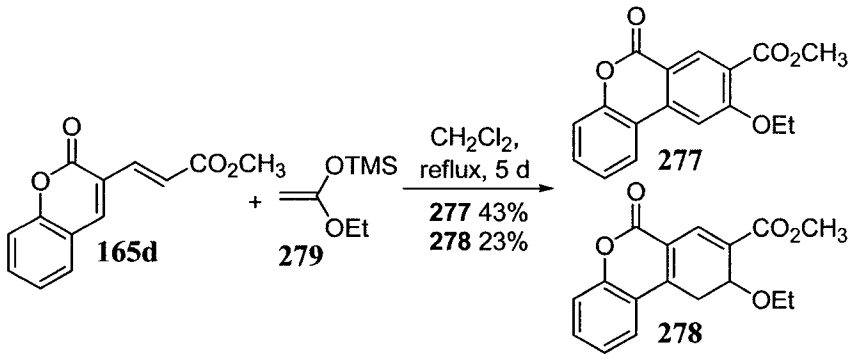
3.2.3 Reactions with Ketene Acetals

Ethyl vinyl ether **113** was found to be unreactive toward diene **165d** under quite forcing conditions. However, ketene acetal **275** reacted with diene **165d** in CH_2Cl_2 at reflux to afford three products (Scheme 3.33). The direct cycloadduct **276** (60%) was the major product. Benzocoumarin **277**, which is the product of the previous observed IEDDA-driven domino reaction, was obtained in 15% yield. Finally, cyclic diene **278** was isolated in 9% yield. This product is the result of a domino IEDDA/elimination/[1,5]-H shift process. It was surprising that **278** did not undergo elimination of ethanol to afford a new aromatic ring. In fact, this compound showed remarkable stability, surviving storage under air for a long period (> 3 years) without any discernable decomposition. As in the reactions with enamines, all of the isolated products had the expected regiochemistry.



Scheme 3.33: Reaction of diene **165d** with ketene acetal **269**.

Ketene acetal **279**[126] was synthesized by reacting ethyl acetate with LDA to generate the enolate. The resulting anion was quenched with TMSCl to afford a mixture of *O*- and *C*-alkylated products (70:30, respectively) in 20% overall yield. The ratio was determined from the ^{1}H NMR spectrum of the mixture. The reaction of this mixture with **165d** afforded two products (Scheme 3.34): benzocoumarin **277** (43%) from an IEDDA/elimination/dehydrogenation sequence and cyclic diene **278** (23%) from an IEDDA/elimination/[1,5]-H shift process. Neither of these products contained an OTMS group. Thus, HOTMS was a much better leaving group than HOEt, possibly due to the fact that this selective elimination of HOTMS would relieve more steric congestion upon its elimination.



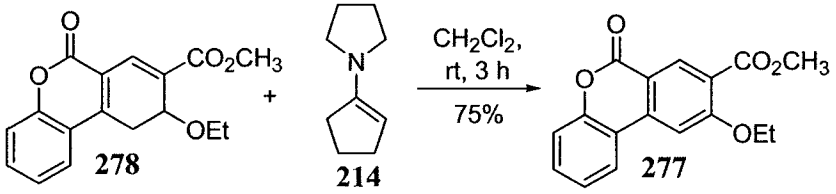
Scheme 3.34: Reaction of diene **165d** with ketene acetal **279**.

[126] Colvin, E. W. In *Silicon Reagents in Organic Synthesis*; Academic Press: San Diego, 1988, pp. 99–119.

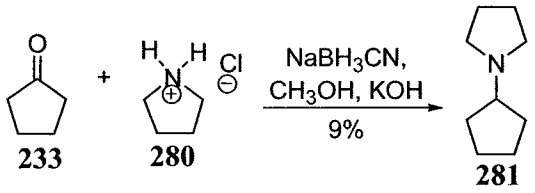
3.2.3 Dehydrogenation Reaction

The dehydrogenation that occurred during many of the domino processes described above is not well-understood. Disproportionation could be ruled out immediately by virtue of the yields of some of the IEDDA-elimination-dehydrogenation reactions, which were above 50%. Furthermore, the corresponding reduced products were never observed. Spontaneous loss of molecular hydrogen at room temperature seemed unreasonable because the evolution of gas was not observed during the progress of the reactions and was ruled out as a possibility in these cases. Oxidation by the presence of atmospheric oxygen to form the new aromatic ring was also difficult to accept because the reactions were all performed under an atmosphere of nitrogen. If the oxidation occurred during the workup, the TLC results would presumably have changed from before the work-up procedure to after the work-up procedure. This was found not to be the case. Moreover, dienes **278**, **217**, and **222** were all isolated from the reaction mixture and then purified by column chromatography in the presence of oxygen and these compounds did not oxidize to the corresponding aromatic products, especially **278,** the dehydrogenation product of which has an average torsion angle of 0.9 ^{o} along the biaryl bond.

An attempt to react **278**, which is also an electron-deficient diene having electron-withdrawing groups at the 1- and 3-positions of the diene, with enamine **214** did not produce any of the IEDDA cycloadduct, but rather only benzocoumarin **277** in 75% yield (Scheme 3.35). This clearly indicated that the enamine is involved in the



Scheme 3.35: Unexpected aromatization of **278** to afford **277**.



Scheme 3.36: Synthesis of amine **281**.

dehydrogenation process. Although no hydrogenated enamine, e.g. amine **281**, had been observed in any of the reactions of **165d** with an enamine, no particular effort had been made to look for the presence of such products. The IEDDA-driven domino reaction using enamine **214** (Scheme 3.6) was then repeated. Following consumption of the starting material, the reaction mixture was washed with 1M aqueous HCl solution to remove any basic compounds. The aqueous layer from the acid wash was neutralized then extracted with CH_2Cl_2. Amine **281** was then synthesized separately in only 9% yield via a reductive amination using $NaBH_3CN$ with cyclopentanone and pyrrolidine hydrochloride **280** (Scheme 3.35).[127] Using amine **281** as a standard, GC/MS analysis of the extract from the neutralized acid wash of the reaction between **214** and **165d** was consistent with the presence of amine **281** in that extract.

[127] Procedure taken from: Borch, R. F. *Org. Synth., Coll. Vol. VI* **1988**, 499-501.

The notion of the enamine being the hydrogen acceptor is suitable but it is not true for every reaction. For example, the reaction between diene **165d**, cyclopentanone **233**, and pyrrolidine **234** for the initial investigation of the *in situ* method, when the concentration of the amine was 5 mol% (Table 3.3, Entry 2), produced the aromatized product, benzocoumarin **215**, in 37% yield. If the enamine were the only molecule to accept hydrogen then the yield for this reaction should have been only 5%. This was not the case. Clearly, the driving force for this process, formation of an aromatic sextet, is very powerful and allows hydrogen to be transferred to any molecule in the reaction medium that can accept the hydrogen.

3.2.4 Inverse Addition

Unexpected results from the reaction of diene **278** with enamine **214** raised some questions that needed to be investigated. If the enamine was playing a role in the dehydrogenation reaction, perhaps increasing its concentration could enhance the yield of the IEDDA-driven domino reaction. It was therefore decided to increase the number of molar equivalents of enamine from 1.5 (initial investigation) to 5, as well as to add the diene to the enamine. The solvent used for these reactions was CH_2Cl_2.

Under these reaction conditions, enamine **205** reacted with diene **165d** to afford benzocoumarin **202** in 71% yield, which was slightly better than the yield obtained using the standard preformed conditions (64%) (Table 3.1). Also, the reaction time decreased to 1.5 h. This was a promising result, so ketene aminal **210** was subjected to reaction

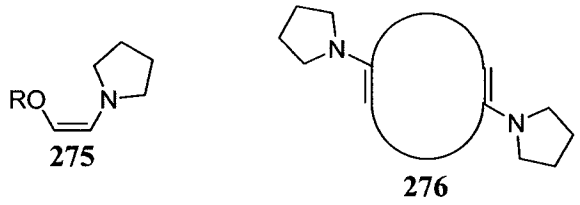
with **165d** using the same reaction conditions. This reaction only produced 41% of benzocoumarin **211**, which was slightly lower yield than the initial investigation (48%) (Scheme 3.5). However, 35% of the starting diene was recovered from the reaction mixture. Since the ketene aminal used for this reaction was not freshly prepared, it may well be that it had suffered some decomposition. This reaction should be repeated in the future with freshly prepared ketene aminal **210**.

Enamine **214** was then reacted with diene **165d** under the inverse addition conditions. A single product spot appeared by TLC analysis but the R_f value was different from that of the desired benzocoumarin **215**. The time required for this conversion (15 min) was much shorter than the reaction under standard conditions. Both the ^{1}H and ^{13}C NMR spectra of this product were extremely complex. The low-resolution mass spectrum indicated a M^{+} peak of 433 mass units, which would correspond to a product derived from an IEDDA reaction, elimination of pyrrolidine, [1,5]-H shift followed by another IEDDA reaction with a second equivalent of the enamine. This product would generate 27 carbon signals in the ^{13}C NMR spectrum. However, the ^{13}C NMR spectrum of the isolated product generated 51 signals. This implies that the material isolated from the reaction was a mixture of diastereomers that contain some carbon atoms that are chemically equivalent. To date, suitable crystals for an x-ray diffraction experiment have not been obtained. Due to the inconsistency of the results using the inverse addition procedure, it was not investigated further.

3.3 Conclusions and Future Directions

Diene **165d** has been reacted with a variety of enamines to produce benzocoumarins and related systems by an IEDDA-driven domino process. It has been demonstrated that the enamine can either be prepared prior to the reaction with **165d** or generated *in situ*. Some insight into the nature of the loss of hydrogen to afford the benzocoumarin moiety was gained. Ketene acetals and ketene aminals both react smoothly with **165d**.

In the future, the use of dienophiles that contain more than one group that can take part in elimination reactions, e.g. **275**, should be investigated. These dienophiles will provide a means other than dehydrogenation for the aromatization to occur. This may lead to the direct formation of benzocoumarins in cases where the dehydrogenation reaction did not occur and possibly give fewer side products. Dienophiles that contain two reactive sites, e.g. **276**, could also be used for the production of new and interesting cyclophanes.



275 **276**

Figure 3.5: Future dienophiles.

3.4 Experimental

3.4.1 General Experimental Procedures

The general experimental procedures can be found in Section 2.4.1, located on page 65. Two general experimental procedures for the reactions of diene **165d** with electron rich dienophiles are shown below. For compounds prepared according to either or both of these procedures the data specific to that reaction are listed in the following order: Compound number, which procedure, physical appearance of the product (quantity isolated, yield, reaction time): characterization data. If the compound was synthesized by more than one procedure, the physical appearance and characterization data will only be listed for the first procedure reported.

Standard preformed enamine procedure:

To a magnetically stirred, room temperature solution of **165d** (1.00 g, 4.34 mmol) in CH_2Cl_2 (25 mL) was added neat enamine (6.51 mmol) 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 (4% EtOAc/CH_2Cl_2, unless otherwise stated) to afford the reaction product(s).

Standard *in situ* procedure:

To a magnetically stirred, room temperature solution of **165d** (1.00 g, 4.34 mmol), the ketone (21.7 mmol, or 6.5 mmol for expensive ketones), and $MgSO_4$ (1.00 g, 83 mmol) in CH_2Cl_2 (25 mL) was added neat pyrrolidine (0.18 mL, 2.17 mmol). The mixture was stirred at room temperature and the disappearance of starting material was monitored by TLC. The $MgSO_4$ was removed by gravity filtration. The filtrate was washed with aqueous 1M HCl solution (3×25 mL), dried over $MgSO_4$, gravity filtered, and then concentrated under reduced pressure. The residue was subjected to flash chromatography on silica gel to afford the reaction product(s).

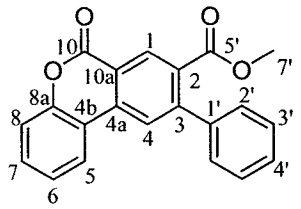
Standard procedure for generating enamines:[127]

To a magnetically stirred solution of the ketone (0.1 mol) was added neat pyrrolidine (0.15 mol) in benzene (200 mL) and the resulting mixture was heated at reflux with azeotropic removal of water until the appropriate volume of water was removed from the reaction mixture. The reaction mixture was cooled to room temperature and then concentrated under reduced pressure. The residue was subjected to vacuum distillation to afford the enamine.

[127] If the ketone was an aryl ketone the number of molar equivalents of pyrrolidine was increased to 15 instead of 1.5.

3.4.2 Experimental Procedures

3-Phenyl-9,10-dihydro-9-oxaphenanthren-10-one-2-carboxylic acid methyl ester (202)

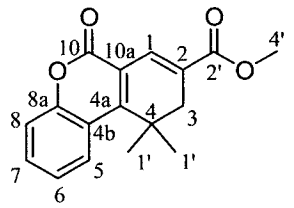


202, standard preformed enamine procedure, white solid (0.90 g, 64%, 3 h): mp 195-196 °C; IR (nujol) 1738 (s), 1719 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.81 (s, 1H, C1-H), 8.03-8.01 (m, 2H), 7.56-7.31 (m, 8H), 3.74 (s, 3H, C7'); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.9 (0), 160.0 (0), 151.8 (0), 148.7 (0), 139.8 (0), 136.5 (0), 132.7 (1), 131.4 (1), 131.1 (0), 128.2 (1), 128.1 (1), 124.7 (1), 124.2 (1), 123.2 (1), 119.6 (0), 117.8 (1), 117.1 (0), 52.3 (3, C6'); 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.

Modified *in situ* procedure: To a solution of **165d** (1.00 g, 4.34 mmol), acetophenone (2.53 mL, 21.7 mmol), and $MgSO_4$ (1.00 g, 83 mmol) in CH_3CN (25 mL) was added neat pyrrolidine (0.18 mL, 2.17 mmol) dropwise and heated at reflux for 12 h. The mixture was cooled to room temperature and $MgSO_4$ was removed by gravity filtration. The filtrate was washed with aqueous 1M HCl solution (3 x 25 mL), dried over $MgSO_4$, gravity filtered, and then concentrated by reduced pressure to leave an oily solid. Hexanes (2 mL) was added to this material and after manual agitation for 5 min, the hexane solution was decanted into another flask. The solid residue that was left behind in

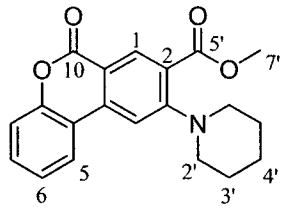
the round bottom flask was purified by flash chromatography on silica gel (4% EtOAc/CH_2Cl_2) to afford **202** (1.06, 74%).

4,4-Dimethyl-3,4,9,10-tetrahydro-9-oxaphenanthren-10-one-2-carboxylic acid methyl ester (207)



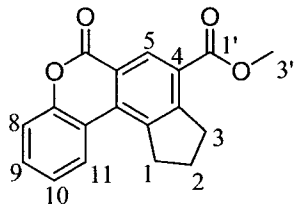
207, standard preformed enamine procedure, white solid (0.69 g, 56%, 3 h): mp 139-141 °C; IR (nujol) 1717 (s) cm^{-1}; UV λ_{max} (log ε) (MeOH) 308 (3.29), 288 (3.35) nm; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.04 (d, *J*=8.3 Hz, 1H, C5-H), 7.48-7.45 (m, 1H, C7-H), 7.37 (dd, *J*=8.2, 1.1 Hz, 1H, C8-H), 7.31-7.26 (m, 1H, C6-H), 6.72 (t, *J*=1.7 Hz, 1H, C1-H), 3.82 (s, 3H, C4'-H), 3.47 (d, *J*=1.6 Hz, 2H, C3-H), 1.73 (s, 6H, C1'-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.7 (0), 160.7 (0), 152.7 (0), 149.5 (0), 145.3 (1, C1), 130.2 (1, C7), 126.7 (1, C5), 123.4 (1, C6), 122.0 (0), 120.7 (0), 117.8 (1, C8), 117.6 (0), 51.8 (3, C3'), 37.8 (0), 28.26 (3, C1'), 25.5 (2, C3); EI-MS *m/z* (%) 284 (M^+, 6), 269 (100), 225 (27), 166 (23), 165 (21); Anal. calcd for $C_{17}H_{16}O_4$: C, 71.82; H, 5.67. Found C, 71.82; H, 5.74.

3-(1-Piperidinyl)-9,10-dihydro-9-oxaphenanthren-10-one-2-carboxylic acid methyl ester (211)



211, standard preformed enamine procedure, yellow solid (0.71 g, 48%, 18 h): mp 130-131 °C; IR (nujol) 1718 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.68 (s, 1H, C1-H), 7.99 (d, *J*=6.9 Hz, 1H, C5-H), 7.48 (t, *J* = 8.5 Hz, 1H, C7-H), 7.47 (s, 1H, C4-H), 7.30-7.34 (m, 2H, C6-H + C8-H), 3.93 (s, 3H, C7'-H), 3.26-3.28 (m, 4H, C2'-H), 1.76-1.81 (m, 4H, C3'-H), 1.66-1.71 (m, 2H, C4'-H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 167.3 (0, C5'), 160.6 (0, C10), 156.6 (0, C3), 152.1 (0, C8a), 138.1 (0, C4a), 135.6 (1, C1), 131.1 (1, C7), 124.3 (1, C6), 122.9 (1, C5), 122.7 (0), 117.9 (1, C8), 117.7 (0), 111.7 (0), 108.6 (1, C4), 52.8 (2, C2'), 52.3 (3, C7'), 25.6 (2, C3'), 24.0 (2, C4'); EI-MS *m/z* (%) 337 (M^+, 44), 322 (100), 304 (51), 376 (46), 250 (14), 223 (12), 139 (27), 84 (37); HRMS (EI) calcd for $C_{20}H_{19}NO_4$: 337.1313, found 337.1314.

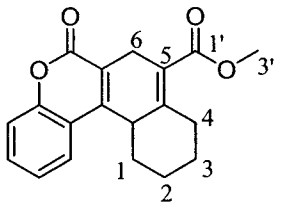
2,3,6,7-Tetrahydro-*1H*-7-oxacyclopenta[c]phenanthren-6-one-4-carboxylic acid methyl ester (215)



215, standard preformed enamine procedure, white solid (0.65 g, 43%, 3 h): mp 231-232 °C; IR (nujol) 1721 (s), 1600 (m) cm^{-1}; UV λ_{max} (log ε) (MeOH) 335 (3.85), 322 (3.84), 303 (3.92), 285 (4.14), 276 (4.08) nm; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.91 (s, 1H, C5-H), 8.20 (d, *J*=7.9 Hz, 1H, C11-H), 7.52-7.49 (m, 1H, C9-H), 7.37-7.32 (m, 2H, C10-H + C8-H), 3.94 (s, 3H, C3'-H), 3.48-3.43 (m, 4H, C1-H + C3-H), 2.28 (quint, *J*=7.7 Hz, 2H, C2-H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 166.0 (0, C1'), 160.9 (0, C6), 155.3 (0, C3a), 151.9 (0, C7a), 141.8 (0, C11c), 134.4 (0, C11b), 132.0 (1, C5), 130.7 (1, C9), 126.8 (1, C11), 126.6 (0), 124.3 (1, C10), 120.4 (0), 118.8 (0, C11a), 117.9 (1, C8), 52.1 (3, C3'), 35.3 (2), 33.6 (2), 24.9 (2, C2); EI-MS *m/z* (%) 294 (M^+, 100), 279 (22), 263 (40), 262 (30), 191 (23), 178 (21), 152 (11); Anal. calcd for $C_{18}H_{14}O_4$: C, 73.46; H, 4.79. Found C, 73.19; H, 4.67.

215, standard *in situ* prodcedure, (0.95 g, 74%, 15 min)

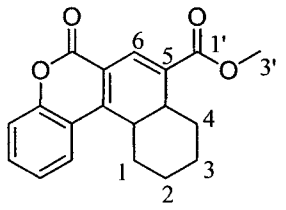
1,2,3,4,6,7,8,12c-Octahydro-8-oxabenzo[c]phenanthren-7-one-5-carboxylic acid methyl ester (217)



217, standard preformed enamine procedure, white solid (1.09, 82%, 3 h): mp 168.5-170 °C; IR (nujol) 1711 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.55 (d, J = 7.6 Hz, 1H, C12-H), 7.49-7.44 (m, 1H, C10-H), 7.35-7.25 (m, 2H, C11-H + C9-H), 3.79 (s, 3H, C3'-H), 3.79-3.75 (m, 1H, C4-H), 3.59-3.48 (m, 2H, C6-H + C12c-H), 3.32 (dd, J=23.4, 5.3 Hz, 1H, C6-H), 2.40-2.35 (m, 1H, C2-H), 2.08-1.79 (m, 4H, C2-H + C2-H + C3-H + C4-H), 1.59-1.40 (m, 2H, C2-H + C3-H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 167.4 (0), 160.3 (0), 152.5 (0), 148.6 (0), 145.0 (0), 130.3 (1, C10), 123.9 (1, C11), 123.4 (1, C12), 119.5 (0), 117.9 (0), 117.4 (0), 116.9 (1, C9), 51.2 (3, C3'-H), 42.1 (1, C12c), 36.4 (2, C1), 31.7 (2, C4), 29.0 (2, C3), 26.7 (2, C6), 26.5 (2, C2); EI-MS *m/z* (%) 310 (M^+, 59), 279 (78), 251 (100), 223 (15), 209 (15), 181 (22), 165 (35), 115 (10), 75 (11); Anal. calcd for $C_{19}H_{18}O_4$: C, 73.53; H, 5.85. Found C, 73.36; H, 6.04.

217, standard *in situ* procedure, (0.99 g, 74%, 5 d)

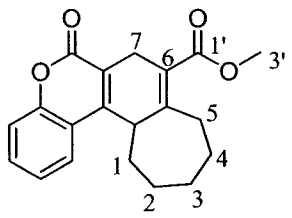
1,2,3,4,4a,7,8,12c-Octahydro-8-oxabenzo[c]phenanthren-7-one-5-carboxylic acid methyl ester (218)



218, standard preformed enamine procedure, white solid (0.05 g, 4%, 3 h): mp 209.5-211 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.70 (dd, *J*=8.7, 2.7 Hz, 1H, C12-H), 7.63 (d, *J*=3.1 Hz, 1H, C6-H), 7.58-7.52 (m, 1H, C10-H), 7.37-7.31 (m, 2H, C11-H + C9-H), 3.83 (s, 3H, C3'-H), 3.24-3.18 (m, 1H), 3.08-3.05 (m, 1H), 2.29-2.86 (m, 1H), 1.78-1.70 (m, 2H), 1.60-1.37 (m, 4H), 1.28-1.19 (m, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 167.4 (0), 159.5 (0), 153.9 (0), 152.8 (0), 132.6 (0), 132.1 (1, C10), 130.0 (1, C6), 124.6 (1, C11), 124.2 (1, C12), 120.3 (0), 117.8 (0), 117.5 (1, C9), 51.8 (3, C3'), 37.1 (1), 34.4 (1), 25.6 (2), 24.9 (2), 22.4 (2); EI-MS *m/z* (%) 310 (M^+, 54), 279 (27), 251 (100), 223 (43), 165 (21), 139 (18), 62 (24); Anal. calcd for $C_{19}H_{18}O_4$: C, 73.53; H, 5.85. Found C, 73.47; H, 5.76.

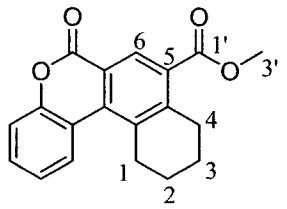
218, standard *in situ* procedure, (0.11 g, 8%, 5 d).

2,3,4,5,7,8,9,13c-Octahydro-*1H*-9-oxacyclopenta[c]phenanthren-8-one-6-carboxylic acid methyl ester (222)



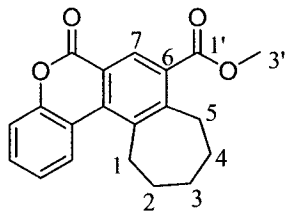
222, standard preformed enamine procedure, white solid (1.13 g, 80%, 3 h): mp 135-136 °C; IR (nujol) 1703 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.58 (dd, *J*=8.4, 1.2 Hz, 1H, C13-H), 7.52-7.49 (m, 1H, C11-H), 7.35 (dd, *J*=8.2, 1.3 Hz, 1H, C10-H), 7.34-7.30 (m, 1H, C12-H), 3.86-3.81 (m, 2H, C7-H + C13c-H), 3.79 (s, 3H, C3'-H), 3.58-3.52 (m, 1H, C5-H), 3.21-3.26 (m, 1H, C7-H), 2.34-2.37 (m, 1H, C5-H), 2.07-2.11 (m, 1H, C1-H), 1.95-1.99 (m, 1H, C4-H), 1.79-1.88 (m, 3H, C2-H + C3-H + C4-H), 1.66-1.69 (m, 1H, C2-H), 1.36-1.42 (m, 2H, C1-H + C3-H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 167.3 (0, C1'), 160.7 (0, C8), 153.1 (0, C9a), 150.7 (0, C5a), 148.8 (0, C13b), 130.7 (1, C11), 124.2 (1, C12), 123.1 (1, C13), 122.2 (0, C6), 120.2 (0, C7a), 117.8 (0, C13a), 117.3 (1, C10), 51.5 (3, C3'), 42.4 (1, C13c), 35.4 (2, C1), 33.5 (2, C5), 28.3 (2, C2), 27.2 (2, C3), 26.7 (2, C7), 25.5 (2, C4); EI-MS *m/z* (%) 324 (M^+, 84), 293 (100), 281 (81), 268 (70), 249 (55), 209 (43), 181 (44), 165 (41), 152 (47); Anal. calcd for $C_{20}H_{20}O_4$: C, 74.06; H, 6.21. Found C, 73.80; H, 6.27.

1,2,3,4,7,8-Hexahydro-8-oxabenzo[c]phenanthren-7-one-5-carboxylic acid methyl ester (223)



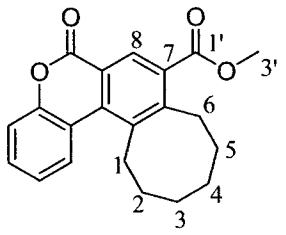
To a magnetically stirred solution of **217** (0.62 g, 2.0 mmol) in benzene (100 mL) was added DDQ (0.50 g, 2.2 mmol) in one portion and the resulting mixture was heated at reflux for 24 h. The reaction mixture was then cooled to room temperature and gravity filtered. The filtrate was concentrated under reduced pressure. The residue was subjected to flash chromatography on silica gel (2% ethyl acetate/CH_2Cl_2) to afford **223** (0.59 g, 96%) as a white solid: mp 163-164 °C; IR (nujol) 1721 (s) cm^{-1}; UV λ_{max} (log ε) (MeOH) 334 (3.36), 322 (3.42), 283 (3.85) nm; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.71 (s, 1H, C6-H), 8.27 (d, *J*=8.2 Hz, 1H, C12-H), 7.52-7.46 (m, 1H, C10-H), 7.39-7.28 (m, 2H, C11-H + C9-H), 3.93 (s, 3H, C3'-H), 3.31-3.27 (m, 4H, C1-H + C4-H), 1.92-1.66 (m, 4H, C2-H + C3-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.0 (0), 160.9 (0), 151.6 (0), 145.9 (0), 136.9 (0), 136.3 (0), 130.7 (0), 130.2 (1, C10), 129.9 (1, C6), 128.3 (1, C12), 123.6 (1, C11), 119.6 (0), 118.5 (0), 117.8 (1, C9), 52.2 (3), 32.6 (2), 28.5 (2), 22.6 (2), 21.7 (2); EI-MS *m/z* (%) 308 (M^+, 100), 276 (70), 249 (24), 205 (17), 165 (19), 95 (11); Anal. calcd for $C_{19}H_{16}O_4$: C, 74.01; H, 5.23. Found C, 73.98; H, 5.08.

2,3,4,5,8,9-Hexahydro-*1H*-9-oxacyclohepta[c]phenanthren-8-one-6-carboxylic acid methyl ester (224)



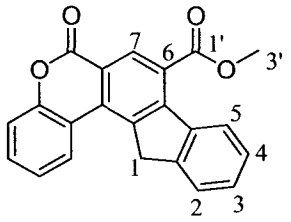
To a magnetically stirred solution of **222** (0.50 g, 1.54 mmol) in benzene (25 mL) was added DDQ (0.35 g, 1.54 mmol) in one portion and the resulting mixture was heated at reflux for 72 h. The reaction mixture was cooled to room temperature and the tan precipitate was removed by suction filtration. The filtrate was concentrated under reduced pressure and the residue was subjected to flash chromatography on silica gel (3% ethyl acetate/CH_2Cl_2) to afford **224** (0.48 g, 97%) as a white solid: mp 151-152 °C, IR (nujol) 1720 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.61 (s, 1H, C7-H), 7.96 (dd, *J*=7.7, 1.3 Hz, 1H, C13-H), 7.50-7.47 (m, 1H, C11-H), 7.39 (dd, *J*=8.4, 1.2 Hz, 1H, C10-H), 7.32-7.29 (m, 1H, C12-1H), 3.94 (s, 3H, C3'-H), 3.36-3.34 (m, 2H, C1-H), 3.28-3.26 (m, 2H, C5-H), 1.98-1.97 (m, 4H, C2-H + C3-H), 1.86-1.84 (m, 2H, C4-H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 168.0 (0, C1'), 161.1 (0, C8), 151.8 (0), 151.6 (0), 141.8 (0), 135.5 (0), 131.3 (1, C12), 130.3 (0), 129.6 (0), 127.6 (1, C13), 123.9 (1, C11), 120.2 (0), 118.8 (0), 118.0 (1, C10), 52.4 (3, C3'), 31.5 (2, C1), 31.0 (2+2, C5), 26.7 (2, C4), 26.3 (2); EI-MS *m/z* (%) 322 (M^+, 100), 308 (21), 291 (22), 263 (22), 205 (15), 165 (18), 152 (12); Anal. calcd for $C_{20}H_{28}O_4$: C, 74.52; H, 5.63. Found C, 74.37; H, 5.60.

1,2,3,4,5,6,9,10-Octahydro-10-oxacycloocta[c]phenanthren-9-one-7-carboxylic acid methyl ester (226)



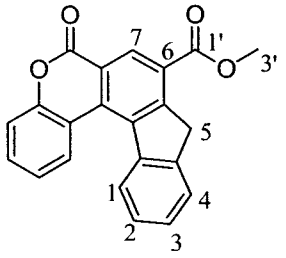
To a magnetically stirred solution of **165d** (500 mg, 2.17 mmol) in CH_2Cl_2 (25 mL) was added neat 1-(1-pyrolidinyl)cyclooctene (1.12 g, 6.51 mmol) dropwise and the resulting solution was heated at reflux for 48 h. The reaction mixture cooled to room temperature and the solvent was then removed under reduced pressure. The residue was subjected to flash chromatography on silica gel (CH_2Cl_2) to afford **226** (108 mg, 15%) as a white solid: mp 153-155 °C; IR (nujol) 1733 (s), 1719 (s), 1606 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz, 333 °K) δ 8.76 (s, 1H), 8.27 (dd, *J*=8.4, 1.1 Hz, 1H), 7.51-7.47 (m, 1H), 7.38 (dd, *J*=8.5, 1.2 Hz, 1H), 7.34-7.31 (m, 1H), 3.94 (s, 3H), 3.39-3.34 (m, 2H), 3.29-3.24 (m, 2H), 2.07-2.02 (m, 2H), 1.98-1.93 (m, 2H), 1.70-1.65 (m, 2H), 1.47-1.40 (m, 2H); ^{13}C NMR ($CDCl_3$, 125.8 MHz, 333 °K) δ 167.8, 161.0, 152.0, 149.5, 140.3, 135.6, 132.2, 130.7, 130.3, 127.8, 124.0, 121.1, 118.9, 118.4, 52.2, 31.4, 31.1, 29.4, 28.9, 27.2, 26.0; EI-MS *m/z* (%) 336 (M^+, 100), 305 (57), 279 (22), 268 (47), 237 (13), 189 (15); HRMS (EI) calcd for $C_{21}H_{20}O_4$: 336.1360, found 336.1368.

8,9-Dihydro-9-oxa-1*H*-indeno[3,2-c]phenanthren-8-one-6-carboxylic acid methyl ester (228)



228, standard preformed enamine procedure, white solid (635 mg, 43%, 3 h): mp 256.5-257 °C; IR (nujol) 1741 (s), 1720 (s), 1599 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.89 (s, 1H, C7-H), 8.42 (d, J = 7.3 Hz, 1H, C13-H), 8.32 (d, J = 7.0 Hz, 1H, C5-H), 7.70 (d, J = 7.7 Hz, 1H, C2-H), 7.60-7.59 (m, 1H, C11-H), 7.49-7.43 (m, 4H, C12-H + C10-H + C3-H + C4-H), 4.39 (s, 2H, C1-H), 4.08 (s, 3H, C3'-H); ^{13}C-NMR ($CDCl_3$, 125.8 MHz) δ 167.6 (0, C1'), 160.9 (0, C8), 152.0 (0, C9a), 147.3 (0, C5b), 144.8 (0, C1a), 140.0 (0), 137.8 (0, C5a), 133.5 (0, C13b), 132.4 (1, C7), 130.9 (1, C11), 129.3 (1, C3), 127.4 (1, C4); 127.1 (0), 126.6 (1, C13), 125.4 (1, C5), 124.7 (1, C12), 124.5 (1, C2), 119.5 (0), 118.6 (0), 118.3 (1, C10), 52.8 (3, C3'), 39.8 (2, C1); EI-MS *m/z* (%) 342 (M^+, 98), 283 (100), 255 (29), 226 (32), 171 (17), 127 (18), 113 (42); HRMS (EI) calcd for $C_{22}H_{14}O_4$: 342.0891, found 342.0903.

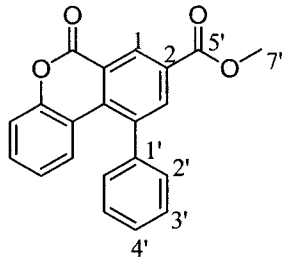
6-Methoxycarbonyl-8,9-dihydro-9-oxa-5*H*-indeno[2,3-c]phenanthren-8-one (230)



230, standard preformed enamine procedure, white solid (0.82 g, 55%, 24 h): mp 206-208 °C; IR (nujol) 1745 (s), 1720 (s), 1607 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.87 (s, 1H, C7-H), 8.51-8.49 (m, 1H, C13-H), 8.17 (d, *J*=8.2 Hz, 1H, C1-H), 7.60 (d, *J*=7.4 Hz, 1H, C4-H), 7.54-7.50 (m, 1H, C11-H), 7.40-7.35 (m, 2H, C10-H +C3-H), 7.28-7.23 (m, 2H, C12-H + C2-H), 4.34 (s, 2H, C5-H), 3.99 (s, 3H, C3'-H); ^{13}C-NMR ($CDCl_3$, 125.8 MHz) δ 165.5 (0, C1'), 160.8 (0, C8), 153.4 (0), 151.2 (0, C9a), 144.7 (0), 139.2 (0), 138.8 (0), 134.1 (0), 131.5 (1, C11), 130.5 (1, C7), 128.2 (1, C3), 127.2 (1, C13), 126.3 (0), 126.0 (1, C2), 125.1 (1, C4), 123.3 (1, C12 + C1), 121.9 (0), 117.7 (1, C10), 117.6 (0, C13a), 52.2 (3, C3'), 39.2 (2, C5); EI-MS *m/z* (%) 342 (M^+, 100), 283 (27), 255 (19), 239 (14), 226 (31), 113 (26); HRMS (EI) calcd for $C_{22}H_{14}O_4$: 342.0891, found 342.0902.

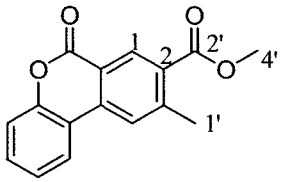
230, standard *in situ* procedure, (1.21 g, 81%, 3 h).

4-Phenyl-9,10-dihydro-9-oxaphenanthren-10-one-2-carboxylic acid methyl ester (232)



To a magnetically stirred solution of **165d** (1.00 g, 4.34 mmol) in CH_2Cl_2 (25 mL) was added neat 2-phenyl-1-(1-pyrrolidinyl)ethene (1.62 g, 8.68 mmol) dropwise and the resulting solution was stirred at room temperature for 15 min. It was washed with aqueous 1 M HCl solution (3×10 mL), dried over $MgSO_4$, gravity filtered, and concentrated under reduced pressure. To a solution of the crude reaction mixture in benzene (50 mL) was added DDQ (536 mg, 2.36 mmol) and the resulting mixture refluxed for 48 h. This mixture was concentrated under reduced pressure and the residue was subjected to flash chromatography on silica gel (5% ethyl acetate/CH_2Cl_2) to afford **232** (408 mg, 28%) as a white solid: mp 188-189 °C; IR (nujol) 1740 (s), 1728 (s), 1603 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 9.12 (d, *J*=2.1 Hz, 1H, C1-H), 8.27 (d, *J*=2.1 Hz, 1H, C3-H), 7.53-7.50 (m, 3H), 7.39-7.33 (m, 4H), 7.13-7.11 (m, 1H), 6.87-6.84 (m, 1H), 3.98 (s, 3H, C7'-H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 165.4 (0, C5'), 160.8 (0, C10), 151.9 (0, C8a), 141.2 (0), 140.3 (0), 138.4 (1, C3), 136.1 (0), 131.5 (1, C1), 131.0 (1), 129.6 (0), 129.4 (1), 128.7 (1), 128.4 (1), 128.1, (1), 123.6 (1), 123.0 (0), 117.9 (1), 117.7 (0), 52.6 (3, C7'); EI-MS *m/z* (%) 330 (M^+, 100), 270 (30), 214 (50), 183 (49), 156 (29), 127 (21), 77 (9); Anal. calcd for $C_{21}H_{14}O_4$: C, 76.36; H, 4.27. Found C, 76.01; H, 4.20.

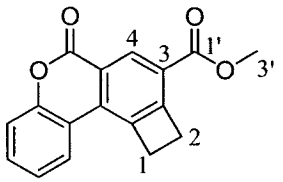
3-Methyl-9,10-dihydro-9-oxaphenanthren-10-one-2-carboxylic acid methyl ester (236)



236, standard *in situ* procedure,[128] white solid (0.769 g, 66%, 1 h): mp 216-217 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.09 (s, 1H, C1-H), 8.05 (dd, *J*=6.3, 2.4 Hz, 1H, C5-H), 7.93 (s, 1H, C4-H), 7.54-7.49 (m, 1H, C7-H), 7.37-7.33 (m, 2H, C6-H + C8-H), 3.95 (s, 3H, C4'-H), 2.78 (s, 3H, C1'-H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 166.2 (0), 160.4 (0), 151.9 (0), 147.5 (0), 137.0 (0), 133.5 (1, C1), 131.4 (1, C7), 130.0 (0), 124.7 (1, C6), 124.6 (1, C1'), 123.2 (1, C5), 118.9 (0), 117.9 (1, C8), 117.0 (0), 52.2 (3, C4'), 22.5 (3, C1'); EI-MS *m/z* (%) 268 (M^+, 71), 237 (100), 181 (31), 152 (28), 118 (11), 76 (22); Anal. calcd for $C_{16}H_{12}O_4$: C, 71.64; H, 4.51. Found C, 71.58; H, 4.40.

[128] Anhydrous acetone must be used to achieve this result. If drum acetone was used, the yield was significantly lower, i.e. 45-51%.

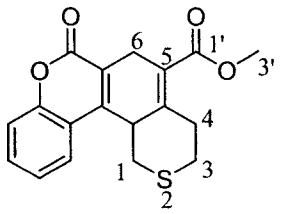
1,2,5,6-Tetrahydro-6-oxacyclobuta[c]phenanthren-5-one-3-carboxylic acid methyl ester (246)[129]



246, standard *in situ* procedure for expensive ketones, white solid (0.16 g, 26%, 48 h): mp 245-246 °C; IR (nujol) 1723 (s), 1611 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.84 (s, 1H, C4-H), 7.84 (d, *J*=7.5 Hz, 1H, C10-H), 7.52-7.49 (m, 1H, C8-H), 7.35-7.31 (m, 2H, C9-H, C7-H), 3.94 (s, 3H, C3'-H), 3.60 (s, 4H, C1-H, C2-H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 165.0 (0, C1'), 161.0 (0, C5), 155.3 (0, C2a), 151.9 (0, C6a), 140.8 (0, C10c), 133.0 (0, C10b), 131.6 (1, C4), 131.3 (1, C8), 125.8 (1, C10), 125.3 (0), 124.6 (1, C9), 119.9 (0), 117.5 (1, C7), 117.3 (O, C10a), 52.1 (3, C3'), 32.1 (2), 31.0 (2); EI-MS *m/z* (%) 280 (100, M^+), 279 (73), 249 (17), 221 (14), 165 (36), 139 (9); HRMS (EI) calcd for $C_{17}H_{12}O_4$: 280.0735, found 280.0736.

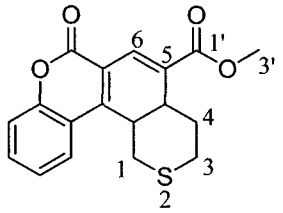
[129] Reaction was scaled down by a factor of 2.

3,4,6,7,8,12c-Hexahydro-*1H*-8-oxa-2-thiabenzo[c]phenanthren-7-one-5-carboxylic acid methyl ester (248)



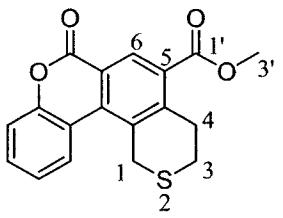
248, standard *in situ* procedure for expensive ketones, white solid (1.13 g, 79%, 24 h): mp 212-214.5 °C; IR (nujol) 1706 (s), 1605 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.63 (d, *J*=7.2 Hz, 1H, C12-H), 7.53 (t, *J*=7.7 Hz, 1H, C10-H), 7.38 (d, *J*=9.0 Hz, 1H, C9-H), 7.35 (t, *J*=8.1 Hz, 1H, C11-1H), 4.10-4.04 (m, 2H, C3-H, C12c-H), 3.81 (s, 3H, C3'), 3.72-3.67 (m, 1H, C6-H), 3.39-3.33 (m, 1H, C6-H), 3.08-3.01 (m, 2H, C4-H, C1-H), 2.90-2.87 (m, 1H, C4-H), 2.80-2.75 (m, 1H, C1-H), 2.40-2.35 (m, 1H, C3-H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 167.3 (0, C1'), 160.4 (0, C7), 153.0 (0, C8a), 145.5 (0, C4a), 143.3 (0, C12b), 131.0 (1, C10), 124.6 (1, C11), 123.4 (1, C12), 121.2 (0), 120.2 (0), 117.5 (1, C9), 117.3 (0, C12a), 51.8 (3, C3'), 44.5 (1, C12c), 37.2 (2, C1), 34.4 (2, C3), 32.0 (2, C4), 27.0 (2, C6); EI-MS *m/z* (%) 328 (M^+, 26), 280 (44), 269 (93), 223 (27), 178 (27), 61 (100); HRMS (EI) calcd for $C_{18}H_{16}O_4S$: 328.0768, found 328.0750.

3,4,4a,7,8,12c-Hexahydro-*1H*-8-oxa-2-thiabenzo[c]phenanthren-7-one-5-carboxylic acid methyl ester (249)



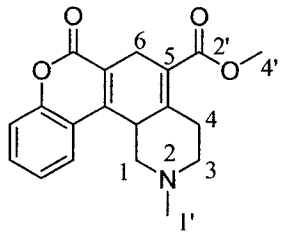
249, standard *in situ* procedure for expensive ketones, white solid (0.16 g, 11%, 24 h): mp 199-200 °C; IR (nujol) 1719 (s), 1708 (s), 1608 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.74 (dd, *J*=8.2, 1.1 Hz, 1H, C12-H), 7.70 (d, *J*=2.6 Hz, 1H, C6-H), 7.60-7.57 (m, 1H, C10-H), 7.39-7.36 (m, 2H, C11-H + C9-H), 3.84 (s, 3H, C3'-H), 3.59-3.54 (m, 1H, C12c-H), 3.31-3.27 (m, 1H, C3-H), 3.22-3.20 (m, 1H, C4a-H), 2.89 (t, *J* = 12.7 Hz, 1H, C1-H), 2.68 (td, *J* = 13.4, 2.3 Hz, 1H, C4-H), 2.49-2.46 (m, 1H, C4-H), 2.25-2.22 (m, 1H, C1-H), 2.07-2.01 (m, 1H, C3-H); ^{13}C-NMR ($CDCl_3$, 125.8 MHz) δ 166.8 (0, C1'), 159.1 (0, C7), 154.0 (0, C8a), 150.4 (0, C12b), 132.6 (1, C10), 131.4 (0), 131.1 (1, C6), 124.9 (1, C11), 124.1 (1, C12), 117.8 (0), 117.6 (1, C9), 117.2 (0), 52.0 (3, C3'), 38.1 (1, C12c), 34.1 (1, C4a), 26.4 (2, C3), 25.0 (2, C1), 24.3 (2, C4); EI-MS *m/z* (%) 328 (M^+, 68), 280 (38), 254 (59), 223 (85), 179 (11), 139 (30), 74 (23), 61 (100); HRMS (EI) calcd for $C_{18}H_{16}O_4S$: 328.0768, found 328.0767.

3,4,7,8-Tetrahydro-*1H*-8-oxa-2-thiabenzo[c]phenanthren-7-one-5-carboxylic acid methyl ester (250)



To a magnetically stirred solution of **248** (200 mg, 0.61 mmol) in benzene (10 mL) was added DDQ (140 mg, 0.61 mmol) in one portion and the resulting mixture was heated at reflux for 48 h. The reaction was cooled to room temperature and the solvent was removed under reduced pressure. The residue was subjected to flash chromatography (5% ethyl acetate/CH_2Cl_2) on silica gel to afford **250** (39 mg, 20%) as a white solid: mp 150-152 °C; IR (nujol) 1721 (s), 1607 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.85 (s, 1H, C6-H), 8.00 (d, *J*=8.1 Hz, 1H, C12-H), 7.55-7.52 (m, 1H, C10-H), 7.44 (dd, *J*=8.2, 1.4, 1H, C9-H), 7.37-7.34 (m, 1H, C11-H), 4.26 (s, 2H, C1-H), 3.97 (s, 3H, C3'-H), 3.60 (t, *J*=6.2 Hz, 2H, C4-H), 3.01 (t, *J*=6.7 Hz, 2H, C3-H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 166.8 (0, C1'), 160.8 (0, C7), 151.8 (0, C8a), 147.4 (0, C4a), 136.9 (0, C12c), 134.6 (0, C12b), 131.0 (1, C10), 130.9 (1, C6), 129.9 (0, C5), 128.0 (1, C12), 124.3 (1, C11), 120.3 (0, C6a), 118.3 (1, C9), 117.8 (0, C12a), 52.6 (3, C3'), 27.5 (2, C1), 26.6 (2, C4), 25.8 (2, C3); EI-MS *m/z* (%) 326 (M^+, 74), 311 (100), 293 (21), 279 (26), 267 (41), 165 (21); Anal. calcd for $C_{18}H_{14}SO_4$: C, 66.25; H, 4.32. Found C, 65.70; H, 4.25.

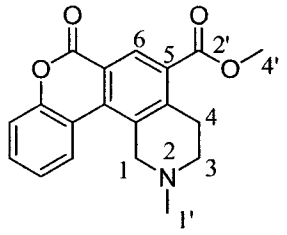
***N*-Methyl-3,4,6,7,8,12c-hexahydro-*1H*-8-oxa-2-azabenzo[c]phenanthren-7-one-5-carboxylic acid methyl ester (252)**



252, standard *in situ* procedure for expensive ketones,[130] yellow solid (1.13 g, 80%, 5 h): mp 122-123 °C, IR (nujol) 1713 (s), 1668 (m), 1607 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.71 (dd, *J*=7.5, 1.3 Hz, 1H, C12-H), 7.52-7.49 (m, 1H, C10-H), 7.36 (d, *J*=7.7 Hz, 1H, C9-H), 7.33 (t, *J*=7.7 Hz, 1H, C11-H), 3.99 (m, 1H, C12c-H), 3.81 (s, 3H, C4'-H), 3.79-3.75 (m, 1H, C6-H), 3.61-3.48 (m, 2H, C4-H), 3.44-3.41 (m, 1H, C1-H), 3.17-3.14 (m, 1H, C3-H), 2.35 (s, 3H, C1'-H), 2.34-2.31 (m, 1H, C6-H), 2.23-2.18 (m, 1H, C3-H), 2.06 (t, *J*=11.0 Hz, 1H, C1-H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 167.4 (0, C2'), 160.4 (0, C7), 152.8 (0, C8a), 145.7 (0, C4a), 142.4 (0, C12b), 130.8 (1, C10), 124.3 (1, C11), 123.7 (1, C12), 121.0 (0), 119.3 (0), 117.6 (0, C12a), 117.4 (1, C9), 62.7 (2, C1), 57.9 (2, C3), 51.7 (3, C4'), 45.2 (3, C1'), 41.3 (1, C12c), 31.0 (2, C6), 27.1 (2, C4); EI-MS *m/z* (%) 325 (M^+, 52), 324 (45), 281 (100), 266 (42), 249 (45), 178 (16), 152 (12), 58 (94); HRMS (EI) calcd for $C_{19}H_{19}O_4N$ 325.1313, found 325.1315.

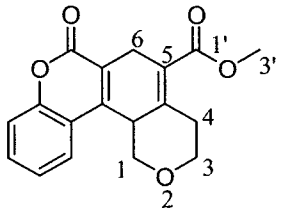
[130] Eluent for column chromatography was 5% MeOH/CH_2Cl_2.

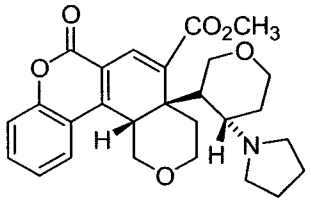
***N*-Methyl-3,4,7,8-tetrahydro-*1H*-2-aza-8-oxabenzo[c]phenanthren-7-one-5-carboxylic acid methyl ester (254)**



To a magnetically stirred solution of **252** and **253** (220 mg, 0.68 mmol) in toluene (25 mL) was added manganese dioxide (62.3 mg, 0.72 mmol) in one portion and the resulting mixture was heated at reflux for 12 h. The reaction mixture was cooled to room temperature then filtered through a plug of celite. The filtrate was concentrated under reduced pressure and the residue was subjected to flash chromatography (5% $MeOH/CH_2Cl_2$) on silica gel to afford **254** (68.3 mg, 31%) as a yellow solid: mp 165-168 °C, IR (nujol) 1720 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.89 (s, 1H, C6-H), 8.02 (d, *J*=8.3 Hz, 1H, C12-H), 7.55-7.52 (m, 1H, C10-H), 7.43 (dd, *J*=6.7, 1.2 Hz, 1H, C9-H), 7.38-7.35 (m, 1H, C11-H), 4.07 (s, 2H, C1-H), 3.93 (s, 3H, C4'-H), 3.50 (t, *J*=6.3 Hz, 2H, C4-H), 2.81 (t, *J*=6.4 Hz, 2H, C3-H), 2.58 (s, 3H, C1'-H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 166.5 (0, C2'), 160.9 (0, C7), 151.9 (0, C8a), 143.7 (0, C4a), 135.6 (0, C12b), 134.4 (0), 131.3 (1, C6), 130.7 (1, C10), 130.0 (0), 128.2 (1, C12), 124.1 (1, C11), 120.0 (0), 118.3 (1, C9), 118.2 (0, C12a), 60.6 (2, C1), 52.3 (3, C4'), 51.8 (2, C3), 46.3 (3, C1'), 29.3 (2, C4); EI-MS *m/z* (%) 323 (M^+, 18), 322 (25), 293 (96), 250 (57), 222 (100), 194 (14), 152 (11); Anal. calcd for $C_{19}H_{17}NO_4$: C, 70.58; H, 5.30; N, 4.33. Found C, 70.39; H, 5.62; N, 4.38.

3,4,6,7,8,12c-Hexahydro-*1H*-2,8-dioxabenzo[c]phenanthren-7-one-5-carboxylic acid methyl ester (256) and 4a-(*cis*-(1-pyrrolidinyl)tetrapyran-3-yl)-3,4,4a,12c-hexaahydro-*1H*-2,8-dioxabenzo[c]phenanthren-7-one-5-carboxylic acid methyl ester (257)

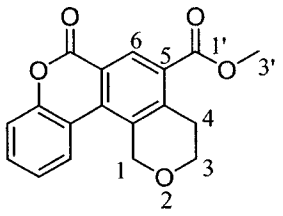




256, standard *in situ* procedure for expensive ketones, white solid (0.43 g, 40%, 24 h): mp 188-189.5 °C; IR (nujol) 1712 (s), 1608 (m) cm^{-1}, ^1H NMR ($CDCl_3$, 500 MHz) δ 7.72 (dd, *J*=7.3, 1.3 Hz, 1H, C12-H), 7.53-7.50 (m, 1H, C10-H), 7.36 (dd, *J*=8.3, 1.3 Hz, 1H, C11-H), 7.35-7.32 (m, 1H, C9-H), 4.52 (dd, *J*=10.8, 3.9 Hz, 1H, C1-H), 4.27-4.24 (m, 1H, C3-H), 3.98-3.95 (m, 1H, C12c-H), 3.84-3.81 (m, 1H, C4-H), 3.81 (s, 3H, C3'-H), 3.64-3.48 (m, 3H, C3-H + C6-H), 3.34 (t, *J*=10.2 Hz, 1H, C1-H), 2.42-2.39 (m, 1H, C4-H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 167.2 (0, C1'), 160.3 (0, C7), 152.7 (0, C8a), 144.7 (0, C4a), 140.3 (0, C12b), 131.0 (1, C10), 124.4 (1, C11), 123.6 (1, C12), 121.5 (0, C6a), 119.3 (0, C5), 117.5 (0, C12a), 117.4 (1, C9), 73.9 (2, C1), 70.9 (2, C3), 51.7 (3, C3'), 43.1 (1, C12c), 33.0 (2, C4), 27.1 (2, C6); EI-MS *m/z* (%) 312 (M^+, 33), 282 (49), 281 (72), 267 (62), 253 (100), 223 (80), 178 (52), 139 (24); HRMS (EI) calcd for $C_{18}H_{16}O_5$: 312.0997, found 312.1006.

257: mp 286-287 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.85 (s, 1H), 7.77 (d, *J*=7.4 Hz, 1H), 7.71-7.67 (m, 1H), 7.46-7.67 (m, 2H), 4.51 (dd, *J*=14.2, 3.8 Hz, 1H), 4.29 (t, *J*=12.2 Hz, 1H), 4.01-3.95 (m, 2H), 3.87 (s, 3H), 3.85-3.76 (m, 4H), 3.53-3.47 (m, 2H), 3.36 (t, *J*=10.9 Hz, 1H), 3.29 (t, *J*=11.9 Hz, 1H), 2.77-2.73 (m, 1H), 2.68 (d, *J*=14.1 Hz, 1H), 2.48-2.23 (m, 5H), 2.02-1.84 (m, 4H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 167.9 (0), 158.3 (0), 154.3 (0), 149.1 (0), 134.2 (1), 132.8 (0), 132.6 (1), 125.8 (1), 124.1 (1), 118.1 (1), 117.7 (0), 117.4 (0), 65.4 (2), 65.3 (2), 62.8 (1), 62.3 (2), 62.0 (2), 53.9 (2), 53.6 (2), 52.7 (3), 42.3 (0), 40.7 (1), 38.6 (1), 28.7 (2), 26.4 (2), 23.4 (2), 23.3 (2); EI-MS *m/z* (%) 465 (M^+, 5), 464 (6), 347 (2), 252 (3), 223 (3), 154 (46), 153 (47), 110 (44), 97 (100).

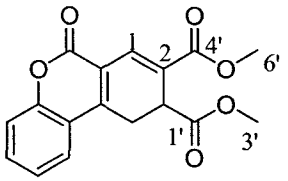
3,4,7,8-Tetrahydro-*1H*-2,8-dioxabenzo[c]phenanthren-7-one-5-carboxylic acid methyl ester (261)



To a magnetically stirred solution of **256** (151 mg, 0.48 mmol) in benzene (50 mL) was added DDQ (109 mg, 0.48 mmol) in one portion and the resulting mixture was heated at reflux for 24 h. The reaction mixture was then cooled to room temperature, diluted with benzene (25 mL) and gravity filtered to remove the light brown precipitate. The filtrate was concentrated under reduced pressure. The residue was then subjected to flash chromatography on silica gel (5% ethyl acetate/CH_2Cl_2,) to afford **261** (101 mg, 67%) as a white solid: mp 216-217 °C, IR (nujol) 1723 (s), 1705 (s), 1598 (m) cm^{-1}; ^{1}H NMR

($CDCl_3$, 500 MHz) δ 8.94 (s, 1H, C6-H), 7.78 (d, *J*=7.7 Hz, 1H, C12-H), 7.57-7.53 (m, 1H, C10-H), 7.44 (d, *J*=7.9, 1H, C9-H), 7.38-7.35 (m, 1H, C11-H), 5.28 (s, 2H, C1-H), 4.08 (t, *J*=6.1 Hz, 2H, C3-H), 3.95 (s, 3H, C3'-H), 3.47 (t, *J*=6.0 Hz, 2H, C4-H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 166.2 (0, C1'), 160.7 (0, C7), 151.9 (0, C8a), 142.8 (0, C4a), 135.1 (0), 134.8 (0), 131.6 (1, C6), 131.0 (1, C10), 129.9 (0), 128.0 (1, C12), 124.4 (1, C11), 120.1 (0), 118.4 (1, C9), 117.9 (0, C12a), 70.0 (2, C1), 64.5 (2, C3), 52.3 (3, C3'), 28.3 (2, C4); EI-MS *m/z* (%) 310 (M^+, 84), 279 (30), 251 (100), 223 (43), 165 (37); Anal. calcd for $C_{18}H_{14}O_5$: C, 69.67; H, 4.55. Found C, 69.54; H, 4.75.

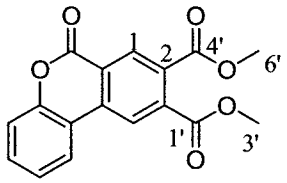
3,4,9,10-Tetrahydro-9-oxaphenanthren-10-one-2,3-dicarboxylic acid dimethyl ester (263)



To a magnetically stirred solution of **165d** (502 mg, 2.18 mmol), methyl pyruvate (2.00 mL, 22.1 mmol), and $MgSO_4$ (500 mg, 4.15 mmol) in CH_2Cl_2 (12.5 mL) was added neat pyrrolidine (1.63 mL, 19.5 mmol) dropwise and the resulting mixture was stirred at room temperature for 1.5 h. It was diluted with CH_2Cl_2 (25 mL), washed with aqueous 1M HCl solution (3×15 mL), dried over $MgSO_4$, gravity filtered, and concentrated under reduced pressure. The crude yellow oil was then subjected to flash chromatography on silica gel (5% ethyl acetate/CH_2Cl_2) to afford **263** (400 mg, 59%) as a yellow solid: mp 130-134 °C; IR (nujol) 1728 (s), 1712 (s), 1605 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.87 (s, 1H, C1-H), 7.78-7.76 (m, 1H, C5-H), 7.60-7.56 (m, 1H, C7-H), 7.38-7.33 (m,

2H, C6-H + C8-H), 4.08 (dd, *J*=10.1, 2.6 Hz, 1H, C3-H), 3.89-3.83 (m, 4H, C4-H + C6'-H), 3.65 (s, 3H, C3'-H), 3.05 (dd, *J*=18.0, 7.7 Hz, 1H, C3-H; ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 171.9 (0, C1'), 166.0 (0, C4'), 158.8 (0, C10), 153.4 (0, C8a), 147.7 (0, C4a), 132.7 (1, C7), 130.4 (1, C1), 126.9 (0, C2), 124.7 (1, C6), 124.7 (1, C5), 118.6 (0, C10a), 118.3 (0, C4b), 117.2 (1, C8), 52.6 (3, C3'), 52.2 (3, C2'), 36.3 (1, C3), 26.0 (2, C4); EI-MS *m/z* (%) 314 (M^+, 8), 255 (100), 223 (46), 211 (59), 168 (19), 139 (33); HRMS (EI) calcd for $C_{17}H_{14}O_6$: 314.0789, found 314.0801.

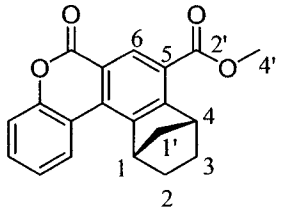
9,10-Dihydro-9-oxaphenanthren-10-one-2,3-dicarboxylic acid dimethyl ester (264)



To a magnetically stirred solution of **263** (60 mg, 0.19 mmol) in benzene (5.0 mL) was added DDQ (44 mg, 0.19 mmol) in one portion and the resulting mixture was heated at reflux for 48 h. The reaction mixture was cooled to room temperature, filtered through a plug of celite, and concentrated under reduced pressure. The residue was then subjected to flash chromatography on silica gel (5% ethyl acetate/CH_2Cl_2,) to afford **264** (40 mg, 67%) as a white solid: mp 151-152 °C; IR (nujol) 1728 (s), 1714 (s), 1612 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.83 (s, 1H, C1-H), 8.33 (s, 1H, C4-H), 8.08 (d, *J*=7.5 Hz, 1H, C5-H), 7.59-7.55 (m, 1H, C7-H), 7.40-7.37 (m, 2H, C6-H + C8-H), 4.00 (s, 3H, C3'-H), 3.97 (s, 3H, C6'-H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 167.5 (0, C1'), 165.7 (0, C4'), 159.6 (0, C10), 151.9 (0, C8a), 138.6 (0, C3), 137.4 (0, C4a), 132.2 (1, C6), 132.1 (1,

C1), 130.4 (0), 125.0 (1, C7), 123.4 (1, C5), 122.4 (1, C4), 122.3 (0), 118.0 (1, C8), 116.6 (0, C4b), 53.2 (3, C3'), 52.9 (3, C6'); EI-MS *m/z* (%) 312 (M^+, 80), 281 (100), 194 (10), 139 (19), 126 (7); Anal. calcd for $C_{17}H_{12}O_6$: C, 65.39; H, 3.87. Found C, 65.13; H, 3.93.

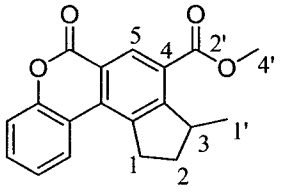
1,4-Methano-1,2,3,4,7,8-hexahydro-8-oxabenzo[c]phenanthren-7-one-5-carboxylic acid methyl ester (266)



266, standard *in situ* procedure for expensive ketones,[128,131] white solid (107 mg, 15 %, 24 h): mp 230-231 °C; IR (nujol) 1727 (s), 1715 (s), 1598 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.87 (s, 1H, C6-H), 8.30 (d, *J*=7.9 Hz, 1H, C12-H), 7.53-7.50 (m, 1H, C10-H), 7.40-7.36 (m, 2H, C11-H + C9-H), 4.43 (m, 1H, C4-H), 4.27 (m, 1H, C1-H), 3.97 (s, 3H, C4'-H), 2.25-2.17 (m, 2H, C2-H + C3-H), 1.78-1.75 (m, 1H, C1'-H), 1.68-1.66 (m, 1H, C1'-H), 1.48-1.44 (m, 1H, C2-H), 1.38-1.34 (m, 1H, C3-H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 166.1 (0, C2'), 161.1 (0, C7), 158.4 (0, C4a), 151.7 (0, C8a), 144.6 (0, C12c), 131.5 (0, C12b), 131.0 (1, C6), 130.7 (1, C10), 126.4 (1, C12), 124.5 (1, C11), 123.9 (0), 119.4 (0), 118.6 (0, C12a), 118.0 (1, C9), 52.1 (3, C4'), 48.6 (2, C1'), 43.9 (1, C4), 42.9 (1, C1), 25.8 (2, C2), 25.0 (2, C3); EI-MS *m/z* (%) 320 (M^+, 51), 292 (100), 262 (21), 260 (30), 233 (26), 205 (24), 176 (17), 130 (11); HRMS (EI) calcd for $C_{20}H_{16}O_4$: 320.1048, found 320.1063.

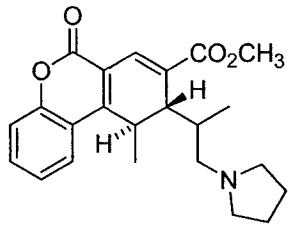
[131] Reaction temperature was at the reflux temperature of dichloromethane.

3-Methyl-2,3,6,7-tetrahydro-*1H*-7-oxacyclopenta[c]phenanthren-6-one-carboxylic acid methyl ester (270)



266, standard *in situ* procedure for expensive ketones,[128] white solid (114 mg, 17%, 3 h): mp 206-207 °C; IR (nujol) 1726 (s), 1716 (s), 1606 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.99 (s, 1H, C5-H), 8.26 (d, *J*=8.3 Hz, 1H, C11-H), 7.55-7.52 (m, 1H, C9-H), 7.41 (dd, *J*=8.3, 1.1 Hz, 1H, C8-H), 7.37 (t, *J*=7.7 Hz, 1H, C10-H), 4.14-4.11 (m, 1H, C3-H), 3.96 (s, 3H, C4'-H), 3.58-3.40 (m, 2H), 2.35-2.90 (m, 1H), 2.11-2.07 (m, 1H), 1.29 (d, *J*=7.1 Hz, 3H, C1'-H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 165.8 (0, C2'), 161.0 (0, C6), 160.3 (0, C3a), 152.0 (0, C7a), 140.8 (0, C11c), 134.8 (0, C11b), 132.6 (1, C5), 130.8 (1, C11), 127.0 (1, C9), 125.3 (0), 124.3 (1, C10), 120.6 (0), 118.9 (0, C11b), 118.0 (1, C8), 52.1 (3, C4'), 39.0 (1, C3), 33.4 (2), 33.1 (2), 20.3 (3, C1'); EI-MS *m/z* (%) 308 (M^+, 100), 293 (54), 275 (31), 205 (21), 189 (17), 138 (10), 76 (10); HRMS (EI) calcd for $C_{19}H_{16}O_4$: 308.1048, found 308.1034; Anal. calcd for $C_{19}H_{16}O_4$: C, 74.01; H, 5.23. Found C, 73.28; H, 5.27.

***trans*-4-methyl-3-(1-(pyrrolidin-1-yl)prop-2-yl)-3,4,9,10-Tetrahydro-9-oxaphenanthren-10-one-2-carboxylic acid methyl ester (274)**



274: mp 63-67 °C, IR (nujol) 1716 (s), 1615 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) 7.81 (s, 1H), 7.61 (d, *J*=8.2 Hz, 1H), 7.56 (t, *J*=7.6 Hz, 1H), 7.37-7.35 (m, 2H), 3.82 (s, 3H), 3.44-3.41 (m, 1H), 3.08-3.07 (d, *J*=3.6 Hz, 1H), 2.80-2.46 (m, 5H), 2.40-2.26 (m, 1H), 2.03-1.93 (m, 1H), 1.87-1.70 (m, 4H), 1.23 (d, *J*=6.4 Hz, 3H), 0.73 (d, *J*=7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 167.7 (0), 160.0 (0), 154.3 (0), 132.7 (1), 130.6 (0), 128.5 (1), 125.3 (1), 124.8 (1), 118.4 (0), 118.2 (0), 117.9 (1), 117.3 (0), 60.0 (2), 54.3 (2), 52.4 (3), 41.0 (1), 35.5 (1), 29.4 (1), 23.8 (2), 19.6 (3), 15.7 (3); EI-MS *m/z* (%) 381 (M^+, 1), 268 (5), 237 (5), 152 (3), 111 (6), 84 (100); HRMS (EI) calcd for $C_{23}H_{27}NO_4$: 381.1960, found 381.1945.

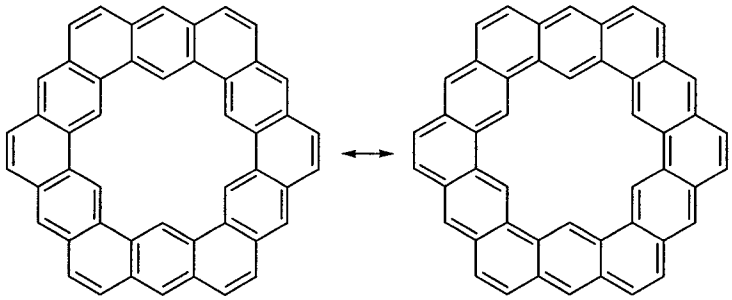
Chapter 4.

Extension of the Methodology

4.1 A Hetero Kekulene Derivative

4.1.1 Introduction

Diederich and Staab[127] first synthesized kekulene **284a** (Figure 4.1) in 1978 as the first member of a series of compounds designated as cycloarenes or coronaphenes. The synthesis of **284a** was a challenging problem and to date only four structures are found in this family of compounds.[127,128] Before this synthesis, the electronic structure of **284a** was the subject of considerable theoretical debate.[129] The debate centered on the π electronic structure of **284a**. Specifically, the relative importance of the two resonance structures **284a** and **284b** was at the heart of the discussion. In **284b**, there are two concentric annulene perimeters connected by radial single bonds. The outer annulene ring is a [30]annulene, while the inner ring is an [18]annulene. Both of these annulenes



284a **284b**

Figure 4.1: Kekulene.

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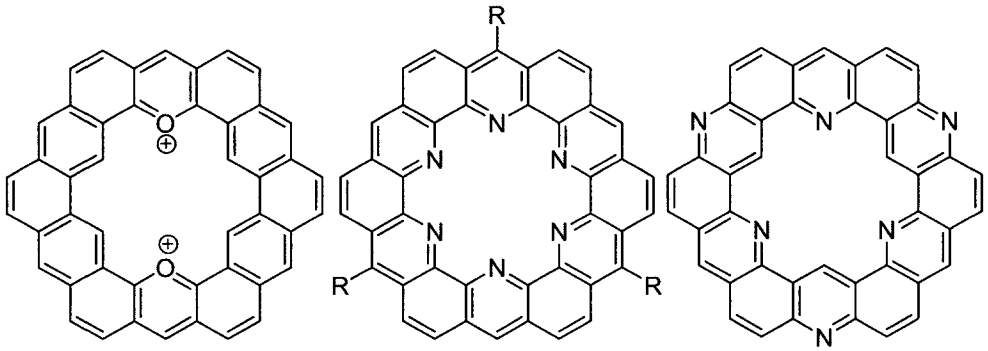
[127] Diederich, F.; Staab, H. A. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 372–374.

[128] (a) Katritzky, A. R.; Marson, C. M. *J. Am. Chem. Soc.* **1983**, *105*, 3279–3283. (b) Ransohoff, J. E. B.; Staab, H. A. *Tetrahedron Lett.* **1985**, *26*, 6179–6182. (c) Bell, T. W.; Firestone, A. *J. Am. Chem. Soc.* **1986**, *108*, 8109–8111. (d) Tutobouët, A.; Hancock, R.; Demeismynck, M.; Lhomme, J. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1190–1191.

[129] (a) Ege, G.; Fischer, H. *Tetrahedron* **1967**, *23*, 149–157. (b) Ege, G.; Vogler, H. *Theor. Chim. Acta* **1972**, *26*, 55-65. (c) Aihara, J. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 1429–1430.

are of the [4n+2]-type. The first resonance structure, i.e. **284a**, consists of a series of localized aromatic sextets[130] that are linked by a double bond and a single bond (*cf.* phenanthrene) in such a fashion to create a macrocyclic structure. The localized aromatic sextet leads to structure **284a** being an important or dominating canonical form.[131] However, the exact nature of kekulene has still remained controversial.[132]

Dodecahydro-18,21-dioxoniakekulene **285**,[128a] dodecahydrohexaazakekulene **286**,[128b,128c] 3,9,15,19,21,23-hexaazakekulene **287**[128d] (Figure 4.2) are the other three compounds in this family. Having established that the IEDDA-driven domino reactions of diene **165d** could provide access to benzocoumarins, it was envisaged that this



285 **286** R=*n*-butyl **287**

Figure 4.2: Heteroaromatic analogues of kekulene.

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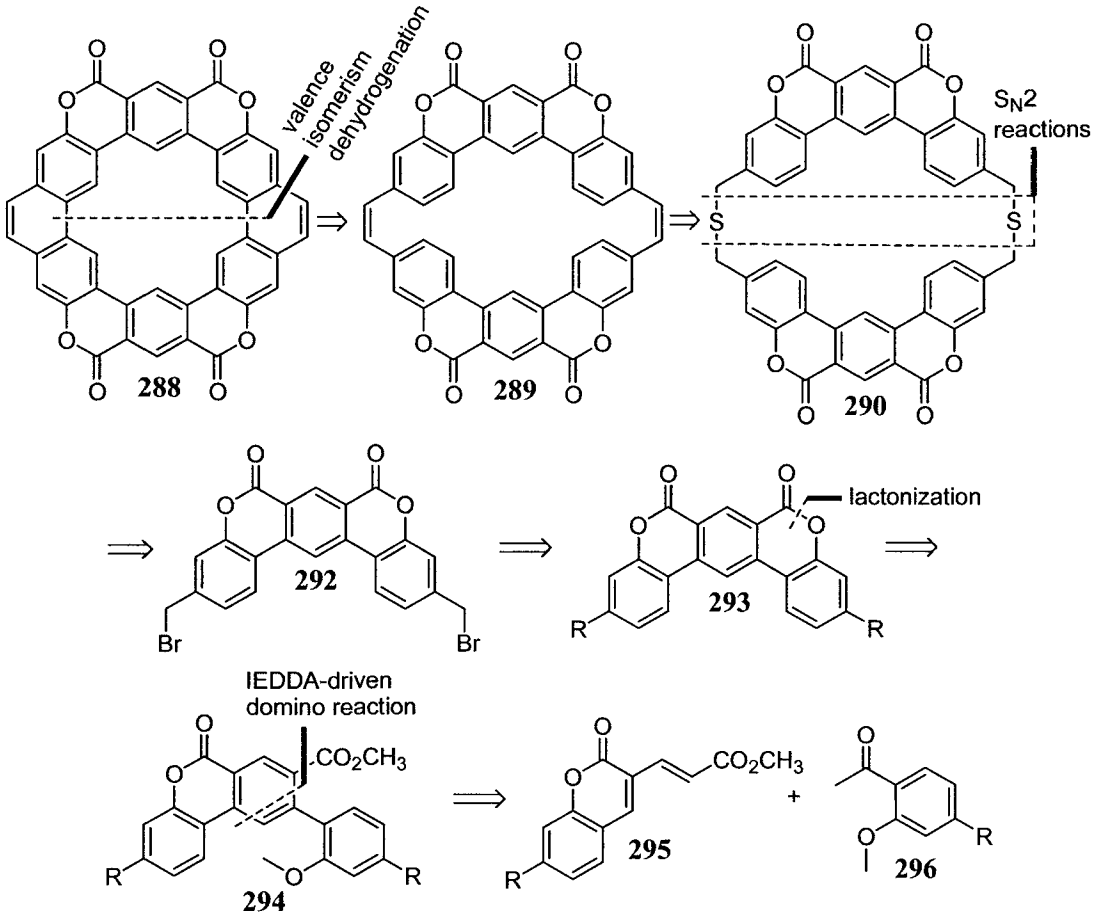
[130] Clar., E. In *The Aromatic Sextet*, John Wiley and Sons: London, 1972.

[131] (a) Krieger, C.; Diederich, F.; Scheitzer, D.; Staab, H. A. *Angew. Chem., Int. Ed. Engl.* **1979**, *16*, 699–701. (b) Staab, H. A.; Diederich, F.; Krieger, C.; Scheitzer, D. *Chem. Ber.* **1983**, *116*, 3504–3512. (c) Scheitzer, D.; Houser, K. H.; Vogler, H.; Diederich, F.; Staab, H. A. *Mol. Physics* **1982**, *46*, 1141–1153. (d) Jiao, H.; Schleyer, P. v. R. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2383–2386.

[132] (a) Randic, M. *Pure Appl. Chem.* **1983**, 55, 347. (b) Vogler, H. *J. Mol. Struct. (Theochem)* **1985**, *122*, 333–341. (c) Lahti, P. M. *J. Org. Chem.* **1988**, *53*, 4590–4593. (d) Allinger, N. L.; Li, F.; Yan, L.; Tai, J. C. *J. Comput. Chem.* **1990**, *11*, 868–895. (e) Cioslowski, J.; O'Connor, P. B.; Fleischmann, E. D. *J. Am. Chem. Soc.* **1991**, *113*, 1086–1089. (f) Zhou, Z. *J. Phys. Org. Chem.* **1995**, *8*, 103–107. (g) Aihara, J. *J. Am. Chem. Soc.* **1992**, *114*, 865–868.



Scheme 4.1: Retrosynthetic analysis of heterokekulene **288**.

methodology could be utilized to produce another heteroaromatic analogue of kekulene **288**.

A retrosynthetic analysis of **288** is shown in Scheme 4.1. Target **288** was taken back to cyclophanediene **289** by a *cis*-stilbene to phenanthrene-type valence isomerization/dehydrogenation transform. This was then taken back to **290** according to standard cyclophane chemistry, for which a wealth of experience exists in the Bodwell

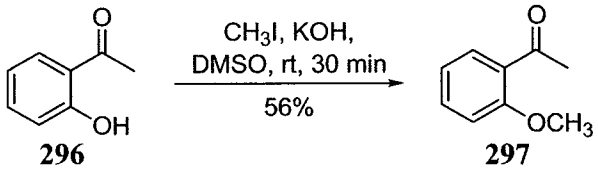
group.[133] Dithiacyclophane **290** was envisaged as coming from the action of Na_2S/Al_2O_3[134] on dibromide **291**, which contains two benzocoumarin moieties. The transform of an appropriate substituted analogue of **292** into benzocoumarin **293** via lactonization, afforded a target that was structurally similar to **202**, which was prepared earier (see Section 3.2) using an IEDDA-driven domino reaction. According to this methodology, diene **294** and ketone **295** were identified as the potentially direct precursors of **293**.

4.1.2 Results and Discussion

Initial work on this project involved the use of diene **165d**, which corresponds to **295**, where R=H. The parent system was selected because a) it was readily available, b) it could be used as a model system to test the feasibility of the synthetic plan and optimize conditions, and c) it would lead synthetically to **295** (R=H), which is a sizable fragment of **288**. The acetophenone derivative **297**[135] was synthesized in 56% yield upon alkylation of 2-hydroxyacetophenone **296** with methyl iodide (Scheme 4.2).[136] Attempts to produce the enamine from **297** failed, so the possibility of generating it *in situ* was investigated. The first attempt at the IEDDA reaction between **297** and diene **165d** was

---

[133] (a) Mannion, M. *Ph.D. Thesis* **1999**, Memorial University of Newfoundland. (b) Houghton, T. *Ph.D. Thesis* **1999**, Memorial University of Newfoundland. (c) Bodwell, G. J.; Miller, D. O.; Vermeij, R. J. *Org. Lett.* **2001**, *3*, 2093–2096. (d) Bodwell, G. J.; Fleming, J. J.; Miller, D. O. *Tetrahedron* **2001**, *57*, 3577–3587. (e) Bodwell, G. J.; Fleming, J. J.; Mannion, M. R.; Miller, D. O. *J. Org. Chem.* **2000**, *65*, 5360–5371. (f) Bodwell, G. J.; Houghton, T. J.; Miller, D. *Tetrahedron Lett.* **1998**, *39*, 2231–2234. (g) Bodwell, G. J.; Bridson, J. N.; Houghton, T. J.; Yarlagadda, B. *Tetrahedron Lett.* **1997**, *38*, 7475–7478.
[134] Bodwell, G. J.; Houghton, T. J.; Koury, H. E.; Yarlagadda, B. *Synlett* **1995**, 751–752.
[135] This compound was commercially available but to save time it was quickly synthesized.

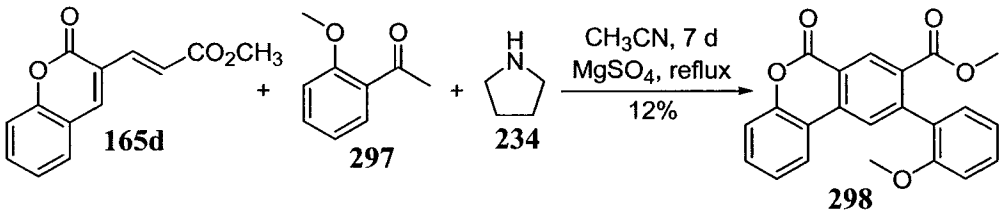


296 **297**

Scheme 4.2: Synthesis of 2'-methoxyacetophenone **297**.

conducted at room temperature. No reaction took place. Increasing the reaction temperature to the reflux temperature of dichloromethane led to the production of several compounds after 12 h of reaction according to TLC analysis. No further reaction appeared to occur over the ensuing 12 h, at which point the reaction was terminated. The desired compound **298** was obtained in only 11% yield. The starting diene **165d** was still present in the reaction mixture, but could not be isolated in a sufficiently pure form to establish the percent recovery. No other pure compound was isolated.

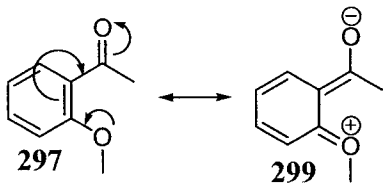
The reaction solvent was changed to acetonitrile and the reaction was repeated. It was heated at reflux temperature until all of the starting diene was consumed, which took 7 days. Under these conditions only 12% of **298** was obtained (Scheme 4.3). As in the previous case, a number of other compounds were generated but no other pure



165d **297** **234** **298**

Scheme 4.3: Synthesis of **298**.

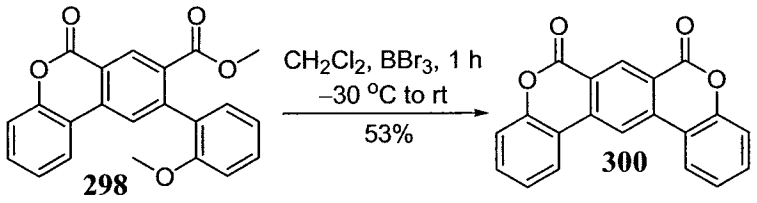
[136] Procedure was taken from: Johnstone, R. A. W.; Rose, M. E. *Tetrahedron* **1979**, *35*, 2169–2173.



Scheme 4.4: A resonance contributor of 2'-methoxyacetophenone **297**.

compounds could be isolated from the reaction mixture. It is worthy of note that the analogous reaction of **165d** with acetophenone only required 1 d for the starting mixture to be consumed. The sluggishness of this reaction is most likely a consequence of the presence of the electron-donating methoxy group (Scheme 4.4). Although it would be expected to render the resulting enamine a more reactive dienophile than the enamine derived from acetophenone, it also renders the carbonyl group in **297** less electrophilic than that of acetophenone. Since enamine formation commences with a nucleophilic attack of a secondary amine on a carbonyl group the rate of enamine formation from **297** and pyrrolidine **234** would be expected to be significantly slower than the analogous reaction with acetophenone. With the enamine formation being slow, other reaction pathways leading to unwanted product may compete significantly.

With small amounts of **298** on hand, attention turned to generating a subunit of the desired heterokekulene **288**. Reaction of **298** with BBr_3 followed by an acid workup afforded **300** (53%) presumably via a de-*O*-methylation/lactonization sequence (Scheme 4.5). Attempts to obtain ^1H NMR data for the product using $CDCl_3$, CD_2Cl_2, and CD_3OH solutions failed because the material was not sufficiently soluble in these solvents. A weak ^1H NMR spectrum was obtained from a DMSO-d_6 solution. Because of the low



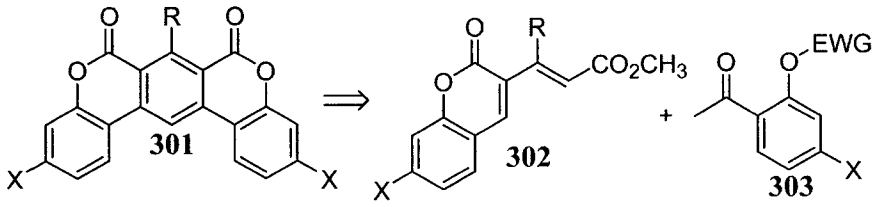
Scheme 4.5: Synthesis of a portion of the desired heterokekulene **288**.

solubility of **300**, no other NMR data could be obtained. The low-resolution mass spectrum exhibited the correct molecular ion peak at 314 mass units.

4.1.3 Conclusions and Future Directions

A substructure of a proposed new heterokekulene was synthesized using an IEDDA-driven domino reaction as the key bond-forming step in the synthesis. The individual yields of the synthetic route were disappointing and future work will have to address these shortcomings. Nevertheless, the route is short and the methodology could conceivably be applied to a total synthesis of heterokekulene **288**, which would be the fifth known molecule of this family.

In order to realize this goal, the Diels-Alder reaction must obviously be improved. The addition of an electron withdrawing protecting group to the hydroxy group, i.e. **303** when X=H, would presumably lower the electron donating ability of the oxygen atom and thus improve the rate of enamine formation. As well, one or more solubilizing groups need to be added to the system to enable further synthetic elaboration. For



Scheme 4.6: Future directions for producing a heterokekulene.

example, dienes **302** would lead to the formation of heterokekulene subunits **301**. Of course, a study of the synthesis and reactivity of such dienes will be required first.

4.2 Benzocoumarins

4.2.1 Introduction

The benzocoumarin moiety **304** (Figure 4.3) is present in a small group of oxygenated natural products (Figure 4.4) consisting of **305a** (isolated from the scent gland of the Canadian beaver *Castor fiber*),[137] alternariol **305b** (*Dematiaceae* molds),[138] autumnariol **305c** (*Eucomis autumnalis*),[139] autumnariniol **305d** (*Eucomis autumnalis*),[15] **305e** (*Tamarix nilotica*),[140] altenuisol **305f** (*Alternaria tenius*),[141] and **305g** (*trogopterus xanthipes*).[142]

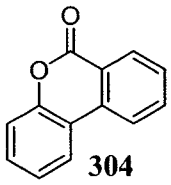
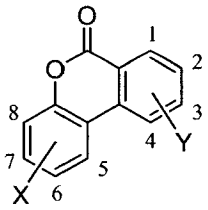


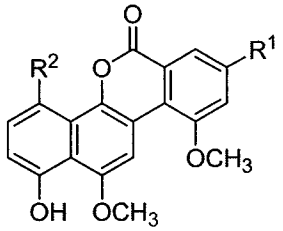
Figure 4.3: Benzocoumarin **304**.

[137] Lederer, E. *Bull. Soc. Chim. Biol.* **1942**, *24*, 1115–1121.
[138] Raistrick, H.; Stilkings, C. E.; Thomas, R. *Biochemistry* **1953**, *55*, 421–433.
[139] Sidwell, W. T. L.; Fritz, H.; Tamm, C. *Helv. Chim. Acta* **1971**, *54*, 207–215.
[140] Nawwar, M. A. M.; Souleman, A. M. A. *Phytochemistry* **1984**, *23*, 2966–2967.
[141] Pero, R. W.; Harvan, D.; Blois, M. C. *Tetrahedron Lett.* **1973**, 945–948.
[142] Jeong, S.-J.; Kim, N.-Y.; Kim, D.-H.; Kang, T.-H.; Ahn, N.-H.; Miyamoto, T.; Higuchi, R.; Kim, Y.-C. *Planta Medica* **2000**, *66*, 76–77.

This moiety was also found as an aggregate in a common ring system of a group of antibiotics isolated from various strains of *Streptomyces*.[143] Some of the members of this group **309**, known as the gilvocarcin family, exhibit remarkable antitumor activity with exceptionally low toxicity, e.g. gilvocarcin V **306a**.[144]



305a: X= 7-OH; Y= 2-OH
305b: X= 5-CH_3,7-OH; Y= 1,3$(OH)_2$ (alternariol)
305c: X= 5-CH_3,7-OH; Y= 1-OH (autumnariol)
305d: X= 5-CH_3,7-OH,8-OCH_3; Y= 1-OH (autumnariniol)
305e: X= 7,8-$(OH)_2$; Y= 2,3,4-$(OH)_3$
305f: X= 6-OH,7-OCH_3; Y= 1,3-$(OH)_2$ (altenuisol)
305g: X= 7-OH; Y= 2,4-$(OH)_2$



306a: R^1= $CH{=}CH_2$; R^2= glycoside
306b: R^1= CH_3; R^2= glycoside
306c: R^1= CH_2CH_3; R^2= glycoside

Figure 4.4: Natural products containing the benzocoumarin unit.

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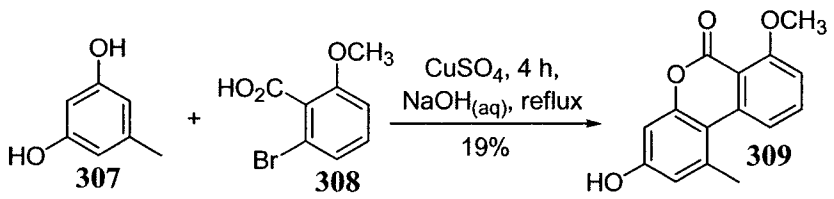
[143] Isolation and structure determination of the gilvocarcins, see: (a) Hatano, K.; Higashide, E.; Shibata, M.; Kameda, Y.; Horii, S.; Mizuno, K. *Agric. Biol. Chem.* **1980**, *44*, 1157–1163. (b) Horii, S.; Fukase, H.; Mizuta, E.; Hatano, K.; Mizuno, K. *Chem. Pharm. Bull.* **1980**, *28*, 3601–3611. (c) Nakano, H.; Matsuda, Y.; Ito, K.; Ohkubo, S.; Morimoto, M.; Tomita, F. *J. Antibiot.* **1981**, *34*, 266–270. (d) Takahashi, K.; Yoshida, M.; Tomita, F.; Shirahata, K. *J. Antibiot.* **1981**, *34*, 271–275. (e) Hirayama, N.; Takahashi, K.; Shirahata, K.; Ohashi, Y.; Sasada, Y. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1338–1342. (f) Balitz, D. M.; O'Herron, F. A.; Bush, J.; Vyas, D. M.; Nettleton, D. E.; Grulich, R. E.; Bradner, W. T.; Doyle, T. W.; Arnold, E.; Clardy, J. *J. Antibiot* **1981**, *34*, 1544–1555. (g) Jain, T. C.; Simolike, G. C.; Jackman, L. M. *Tetrahedron* **1983**, *39*, 599–605. (h) Frolova, V. I.; Kuzovkov, A. D.; Chernyshev, A. I. *Antiobiotiki (Moscow)* **1984**, *29*, 329–332.

[144] Most recent studies on the biological activity of the gilvocarcins, see: (a) Arai, M.; Tomoda, H.; Matsumoto, A.; Takahashi, Y.; Woodruff, B. H.; Ishiguro, N.; Kobayashi, S.; Omura, S. *J. Antibiot.* **2001**, *54*, 554–561. (b) Matsumoto, A.; Hanawalt, P. C. *Cancer Res.* **2000**, *60*, 3921–3926. (c) Arce, R.; Oyola, R.; Alegria, A. E. *Photochem. Photobiol.* **1998**, *68*, 25–31. (d) Towers, G. H. N.; Page, J. E.; Hudson, J. B. *Curr. Org. Chem.* **1997**, *1*, 395–414. (e) Kikuchi, O.; Eguchi, T.; Kakinuma, K.; Koezuka, Y.; Shindo, K.; Otake, N. *J. Antibiot.* **1993**, *46*, 985–991. (f) Knobler, R. M.; Radlwimmer, F. B.; Lane, M. J. *Nucleic Acid Res.* **1992**, *20*, 4553–4557. (g) Eguchi, T.; Li, H.-Y.; Kazami, J.; Kakinuma, K.; Otake, N. *J. Antibiot.* **1990**, *43*, 1077–1081.



Scheme 4.7: Synthesis of **309** using the Hurtley reaction, a precursor to Autumnariol.

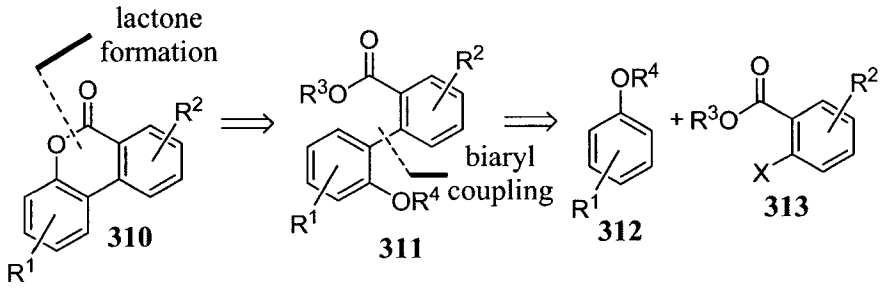
Early synthetic work aimed at the production of the benzocoumarin motif used the Hurtley reaction,[145] which consists of the condensation of an electron rich phenol with an *o*-halobenzoic acid in alkaline medium in the presence of catalytic copper sulfate (Scheme 4.7). Benzocoumarin **305a**,[146] alternariol **305b**,[147] autumnariol **305c**,[148] and autumnariniol **305d**,[148] have all been synthesized using the Hurtley reaction. Typically, the yields for this reaction are low and consequently the Hurtley reaction is not ideal synthetically, despite the significant increase in molecular complexity in it products.

Since these initial reports, alternative routes to the benzocoumarin motif have been published. For example the intramolecular reaction of biphenyl-2-carboxylic acids[149] or benzoic acid phenyl ester;[150] the intramolecular reaction between benzoquinones and phenol,[151] and a normal Diels-Alder reaction followed by an

[145] (a) Hurtley, W. R. H. *J. Chem. Soc.* **1929**, 1870–1873. For a mechanistic study of the Hurtley reaction, see (b) Bruggnik, A.; McKillop, A. *Tetrahedron* **1975**, *31*, 2607–2619.
[146] (a) Lederer, E.; Polonsky, J. *Bull. Soc. Chim. Fr.* **1948**, 831–834. (b) Lederer, E. *J. Chem. Soc.* **1949**, 2115–2125.
[147] Sóti, F.; Incze, M.; Kajtár-Peredy, M.; Baitz-Gács, E.; Imre, L.; Farkas, L. *Chem. Ber.* **1977**, *110*, 979–984.
[148] Farkas, L.; Sóti, F.; Incze, M.; Nógradádi, M. *Chem. Ber.* **1974**, *107*, 3874–3877.
[149] Migachev, G. I. *Zh. Org. Khim.* **1979**, *15*, 503–508.
[150] Heacock, R. A.; Hey, D. H. *J. Chem. Soc* **1954**, 2481–2484.
[151] Müller, v.-P.; Venakis, T.; Euguster, C. H. *Helv. Chem. Acta* **1979**, *62*, 2833–2840.

intramolecular esterification[152] were reported prior to 1980. These methodologies all lack generality and efficiency.

The isolation of the gilvocarcins, **306a–306c**, led to a surge of research into generating this structural subunit.[153] Several successful approaches were reported, the key step of which involves or requires palladium-catalyzed biaryl coupling,[154] Meerwein arylation,[155] nucleophilic aromatic substitution of a Grignard reagent,[156] Dötz chromium carbene benzannulation,[157] and an organoaluminum coupling.[158] However, all of these approaches shared the same retrosynthetic analysis (Scheme 4.8). In the synthetic direction, this consists of biaryl formation followed by a lactonization. The only



Scheme 4.8: Typical retrosynthetic cut for benzocoumarin **310**.

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[152] Bartl, K.; Kraatz, U.; Korte, F. *Liebigs Ann. Chem.* **1976**, 407–411.

[153] For a review on the synthesis of the gilvocarcins, see: Hua, D. H.; Saha, S. *Recl. Trav. Chim. Pays-Bas* **1995**, *114*, 341–355.

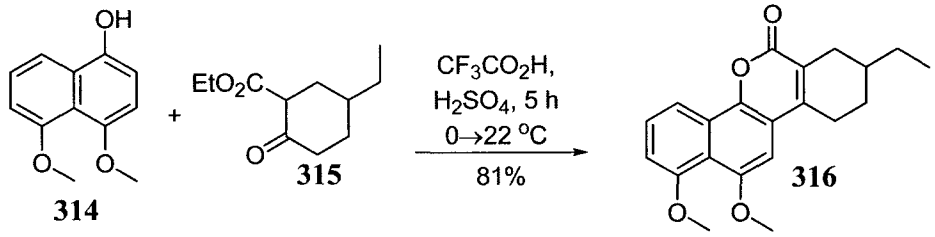
[154] (a) Matsumoto, T.; Hosoya, T.; Suzuki, K. *J. Am. Chem. Soc.* **1992**, *114*, 3568–3570. (b) Hosoya, T.; Takashiro, E.; Matsumoto, T.; Suzuki, K. *J. Am. Chem. Soc.* **1994**, *116*, 1004–1015. (c) Deshpande, P. P.; Martin, O. R. *Tetrahedron Lett.* **1990**, *31*, 6313–6316. (d) Jung, M. E.; Jung, Y. H. *Tetrahedron Lett.* **1988**, *29*, 2517–2520. (e) Alo, B. I.; Kandil, A.; Patil, P. A.; Sharp, M. J.; Siddiqui, M. A.; Snieckus, V. *J. Org. Chem.* **1991**, *56*, 3763–3768.

[155] McKenzie, T. C.; Hassen, W.; Macdonald, S. J. F. *Tetrahedron Lett.* **1987**, *28*, 5435–5436. MacDonald, S. J. F.; McKenzie, T. C.; Hassen, W. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1528–1530.

[156] Findlay, J. A.; Daljeet, A.; Murray, P. J.; Rej, R. N. *Can. J. Chem.* **1987**, *65*, 427-431. Patten, A. D.; Nguyen, N. H.; Danishefsky, S. J. *J. Org, Chem.* **1988**, *53*, 1003–1007.

[157] Parker, K. A.; Coburn, C. A. *J. Org. Chem.* **1991**, *56*, 1666–1668.

[158] Hart, D. J.; Merriman, G. H. *Tetrahedron Lett.* **1989**, *30*, 5093–5096.



Scheme 4.9: Synthesis of **316** via the Pechmann condensation.

approach not to use this sequence of events took advantage of the Pechman condensation.[159] For example, 4,5-dimethoxy-1-naphthol **314** was reacted with β-keto ester **315** to afford lactone **316** in 81% yield (Scheme 4.9).[159b] The reaction proceeds via a transesterification followed by an intramolecular cyclization to afford **316**.

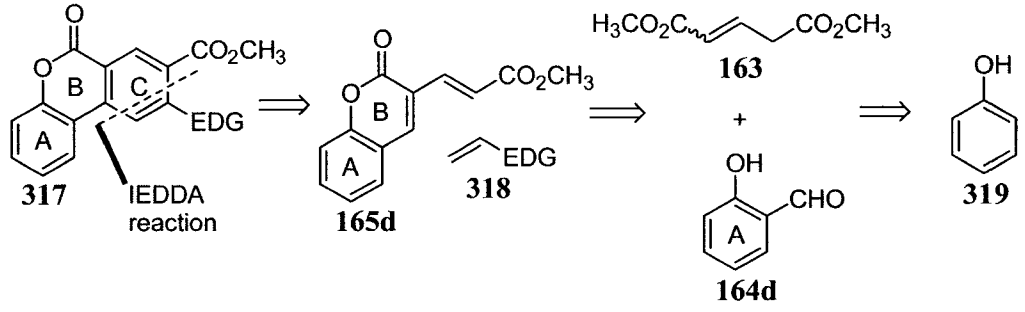
The methodology of choice seems to be the use of a palladium-catalyzed reaction to generate the biaryl bond. This has been achieved both intra- and intermolecularly. The palladium-catalyzed reactions are reported to proceed in moderate to high yields. With this approach being the most general and efficient, it suffers from the drawback that it is dependant on an increasingly expensive transition metal. It would therefore seem that there is a need for an alternative route that is concise, general, efficient, and does not require the use of expensive reagents and/or catalysts.

[159] (a) McGee, L. R.; Confalone, P. N. *J. Org. Chem.* **1988**, *53*, 3695–3701. (b) Hua, D. H.; Saha, S.; Roche, D.; Maeng, J. C.; Iguchi, S.; Baldwin, C. *J. Org. Chem.* **1992**, *57*, 399–403.

4.2.2 Results and Discussion

Examination of the retrosynthetic analysis of benzocoumarin **317** using the IEDDA-driven domino reaction (Scheme 4.10) reveals that the substituents on two carbon atoms in the C ring of **317** have their origin in the dienophile **318**. Thus, the nature of these substituents on **317** will be limited to those compatible with enamine formation. Further analysis suggests every position of the A ring could conceivably be substituted through the use of an appropriately substituted salicylaldehyde. There are very few salicylaldehydes commercially available. This lack of availability created the need for quick and efficient methods of preparing salicylaldehydes and *ortho*-formylation immediately sprung to mind.

Ortho-Formylation of phenols using traditional methods, such as the Reimer-Tiemann[160] or the Duff reaction,[161] produces the desired salicylaldehyde in low yields, and this was indeed found to be the case for a number of phenols. However, the use of



Scheme 4.10: Retrosynthetic analysis of the parent benzocoumarin **320**.

[160] For reviews on this subject, see: (a) Wynberg, H. In *Comprehensive Organic Synthesis* Trost, B. M.; Flemming, I., Eds.; Pergamon Press: Oxford, 1991, Vol. 2, pp. 769–775 (b) Wynberg, H.; Meijer, E. W. *Org. React.* **1982**, *28*, 1–36.

[161] (a) Duff, C. J. *J. Chem. Soc.* **1941**, 547. For a recent example on this subject, see: (b) Lindoy, L. F.; Meehan, G. V.; Svenstrup, N. *Synthesis* **1998**, 1029–1032.

Skattebøl's[162] method for the *ortho*-Fomylation of phenols, i.e., paraformaldehyde in the presence of triethylamine/$MgCl_2$, afforded the necessary salicylaldehydes for this investigation in good yield (Table 4.1, Entries 1-5). These yields were comparable to the results reported by Skattebøl. However, Skattebøl reported that this method was not efficient when the phenol was electron deficient (Entries 6-7). Consequently, methyl 4-hydroxybenzoate was *ortho*-formylated in 48% yield and 4-nitrophenol was formylated in 26% yield using Duff reaction conditions instead. Attempts to generate 6-methylsalicylaldehyde failed.

Table 4.1: Synthesis of Salicylaldehydes

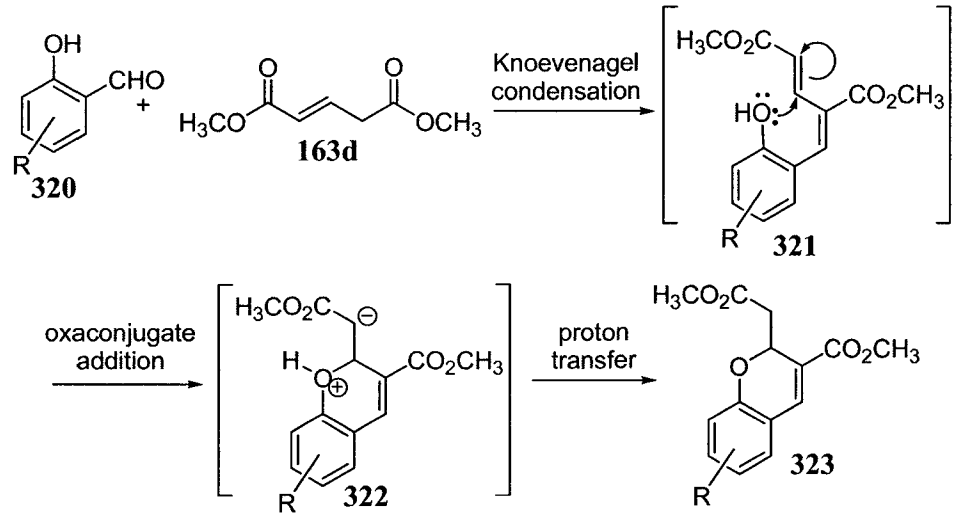
Entry	Phenol	Aldehyde	Yield[a]	Yield[b]
1.	4-methylphenol	5-methylsalicylaldehyde	21%[161b]	85%
2.	3-methylphenol	4-methylsalicylaldehyde	14%[c,163]	61%[d]
3.	2-methylphenol	3-methylsalicylaldehyde	11%[163]	94%
4.	4-methoxyphenol	5-methoxysalicylaldehyde	18%[161b]	96%
5.	4-bromophenol	5-bromosalicylaldehyde	29%[161b]	71%
6.	methyl 4-hydroxybenzoate	methyl 3-formyl-4-hydroxybenzoate	48%[164]	
7.	4-nitrophenol	5-nitrosalicylaldehyde	26%[164]	

[a] Duff reaction conditions. [b] Skattebøl *et al.* reaction conditions.[162]
[c] Isolated as a 1:1 mixture with 6-methylsalicylaldehyde.
[d] recrystallized from hexanes to remove the minor product 6-methylsalicylaldehyde.

[162] Hofsløkken, N. U.; Skattebøl, L. *Acta Chem. Scand.* **1999**, *53*, 258–262.
[163] Russel, A.; Lockhart, L. B. *Org. Synth., Coll. Vol. III* **1955**, 463–464.
[164] Suzuki, Y.; Takahashi, H. *Chem. Pharm. Bull.* **1983**, *31*, 1751–1753.

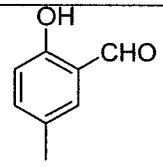
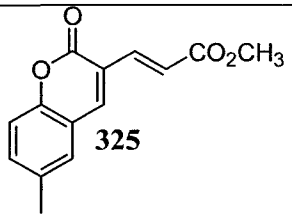
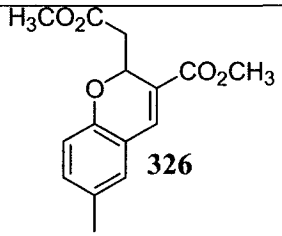
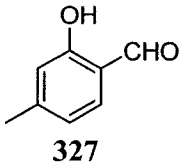
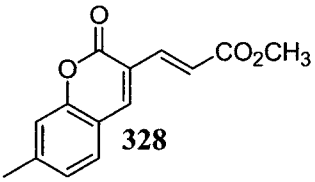
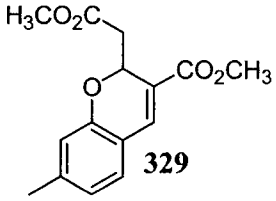
With these salicylaldehydes in hand, a series of vinylogous Knoevenagel condensations were performed. The reaction conditions used were those used to generate the parent diene **165d**. The results from these condensations with dimethyl glutaconate are shown in Table 4.2. Salicylaldehydes **324** (Entry 1), **327** (Entry 2), and **330** (Entry 3) were smoothly converted into coumarin dienes **325** (72%), **328** (80%) and **331** (78%). However, reactions involving the remaining salicylaldehydes (Entries 4-7) led to the isolation of the desired coumarin diene, but also an unexpected *2H*-chromene products, **335**, **338**, **341**, and **344**.

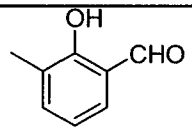
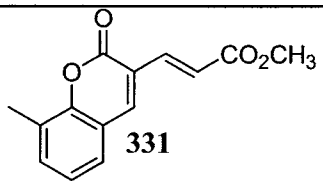
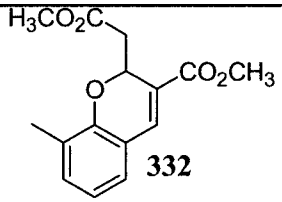
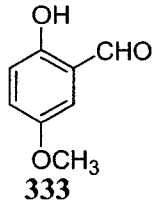
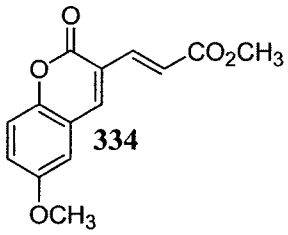
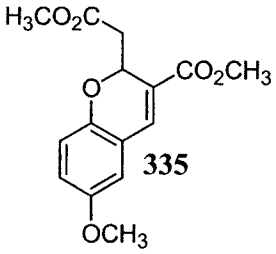
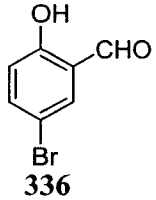
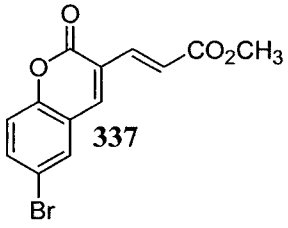
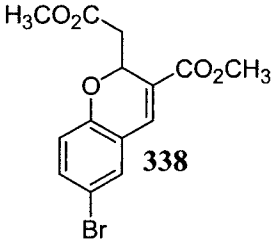
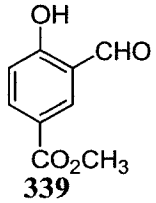
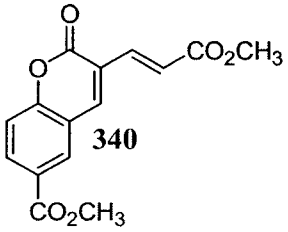
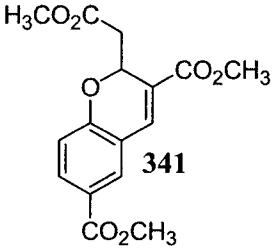
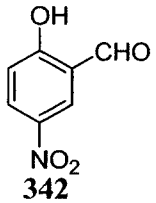
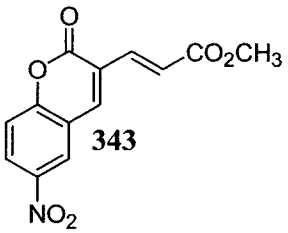
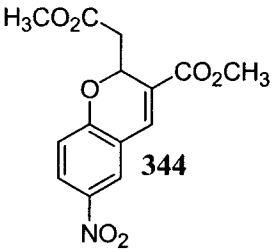
The isolation of the chromene product does not correlate with the electronic nature of the substituent. The chromene product were generated when the substituent bonded on the salicylaldehyde was either electron-poor or electron-rich. In the case of the 5-nitrosalicylaldehyde **342**, the *2H*-chromene **344** was the major product. When the substituent was an alkyl group, the reaction produced only the coumarin diene and none of the chromene product. Without the isolation of any reaction intermediates, it is difficult to make a sound conclusion about a possible mechanism for the formation of either product. However, one possible mechanism for the formation of these chromene products is shown in Scheme 4.11. It seems at some point during the mechanism an oxaconjugate addition occurs between the phenol and the α,β-unsaturated ester. All of the coumarin dienes synthesized were assigned as the (*E*)-isomer by the virtue of the large coupling constant (15-16 Hz) between C2-H and C3-H of the acrylate moiety. The (*Z*)-isomer was not observed in any case.



Scheme 4.11: A possible mechanism for the formation of chromene **323**.

Table 4.2: Reaction of the salicylaldehydes with dimethyl glutaconate.

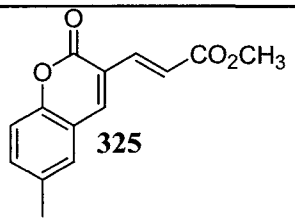
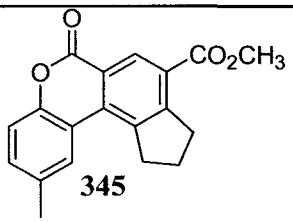
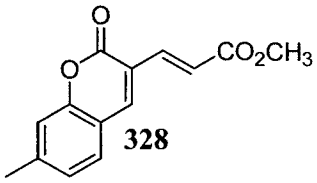
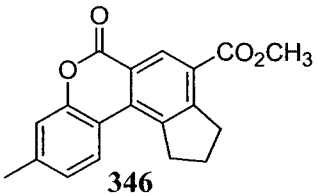
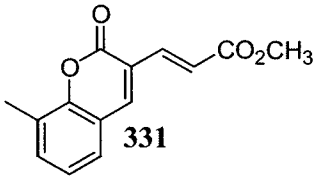
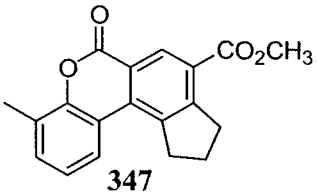
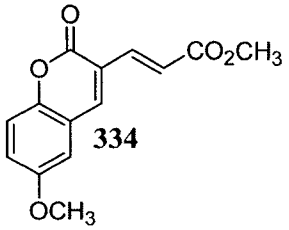
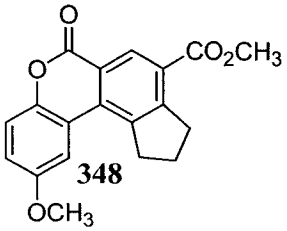
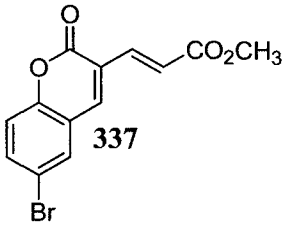
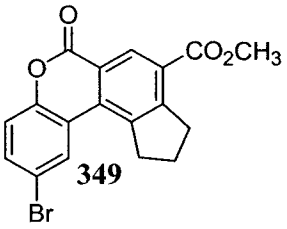
Entry	Aldehyde	Diene Product	Yield	2*H*-Chromene Product	Yield
1.	 **324**	 **325**	72%	 **326**	0%
2.	 **327**	 **328**	80%	 **329**	0%

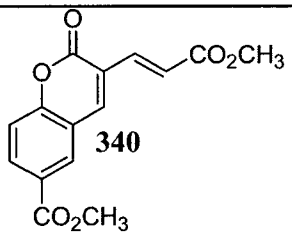
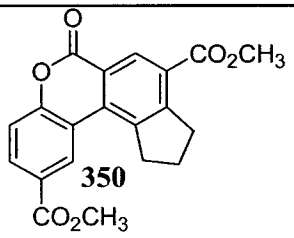
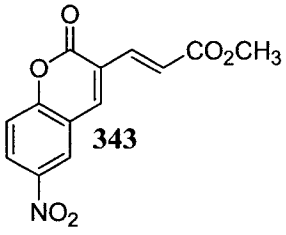
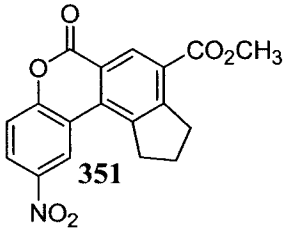
3.	 **330**	 **331**	78%	 **332**	0%
4.	 **333**	 **334**	71%	 **335**	19%
5.	 **336**	 **337**	65%	 **338**	25%
6.	 **339**	 **340**	66%	 **341**	15%
7.	 **342**	 **343**	26%	 **344**	72%

With these coumarin dienes in hand, the IEDDA-driven domino reactions were attempted. The results are shown in Table 4.3. All of these reactions were performed with the enamine derived from cyclopentanone and pyrrolidine, **214**, using the standard preformed conditions. They all proceeded smoothly to afford the desired benzocoumarin in moderate yields, except for the product derived from the nitro diene **343**. This reaction only produced 24% of desired product **351**. The low yield may well be related to the low solubility of **351** in organic solvents and the need to purify this compound by flash chromatography. For each reaction, the only mobile product (3% ethyl acetate/CH_2Cl_2) was assigned as the aromatized product, which was expected due to the fact that Φ_{calc} was $< 1\ ^{o}$ (Table 4.3) in each case. The remaining material from each reaction could be removed from the column packing by significantly increasing the polarity of the eluent solvent to 5% MeOH/CH_2Cl_2. However, the ^{1}H NMR spectrum of this product was far too complex to assign structures.

The time of the reaction was reported as the time it took for the starting coumarin diene to be consumed according to TLC analysis. The reaction times were mostly 3 h, with the exception of two cases. Diene **328** (Entry 2) had a slightly longer reaction time (4 h). The apparent decrease in rate can be attributed to the presence of the weakly donating methyl group that is in conjugation with the diene unit. The substituents bonded to the A ring on all of the other dienes were not in conjugation with the diene unit. On the other hand, diene **343** (Entry 7) was consumed in only 1.5 h. Even though the nitro group is not in conjugation with the diene, the very strong electron withdrawing nature of this substituent may nevertheless serve to activate the diene through induction.

Table 4.3: IEDDA-driven domino reactions of the dienes with enamine **214**.

Entry	Diene	Product	Time	Φ_{calc}	Yield
1.	 **325**	 **345**	3 h	0.3 °	47%
2.	 **328**	 **346**	4 h	0.3 °	51%
3.	 **331**	 **347**	3 h	0.5 °	48%
4.	 **334**	 **348**	3 h	0.9 °	51%
5.	 **337**	 **349**	3 h	0.4 °	51%

6.	 **340**	 **350**	3 h	0.7 °	41%
7.	 **343**	 **351**	1.5 h	0.0 °	24%

The reactions discussed above demonstrate the ease with which substituents can be placed on the A ring of the benzocoumarin framework by starting from the appropriate phenol. As discussed earlier, choosing an appropriate enamine can then lead to the introduction of substituents on the C ring of the benzocoumarin. Up to this point, substituents have been placed on five of the possible 7 carbon atoms of benzocoumarin (indicated by *) as shown in Figure 4.5.

To place substituents at carbon atom "a" in the benzocoumarin structure in Figure

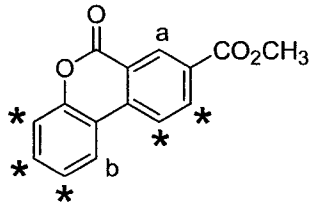
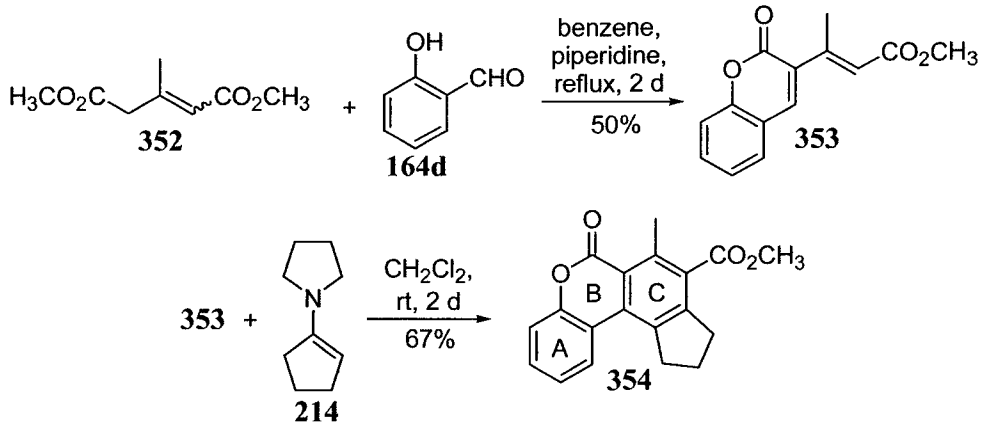


Figure 4.5: Carbon atoms that can have substituents on benzocoumarin

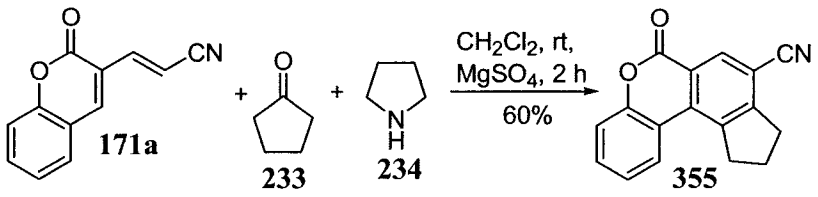


Scheme 4.12: Synthesis of benzocoumarin **354**.

4.5, the necessary group would need to be included on the corresponding carbon atom in the glutaconate starting material. Although the synthetic methods for the production of glutaconate esters are known,[165] the commercial availability of substituted glutaconate **352** led to its selection for study. It reacted with salicylaldehyde **164d** to afford coumarin diene **353** in 50% yield after 2 d of reaction (Scheme 4.12), which was longer than the corresponding reaction of **164d** with dimethyl glutaconate **163** (3 h). The structure of **353** was tentatively assigned as the *E* isomer. The AM1 calculation using the CambridgeSoft Chem 3D package of software indicated that the calculated heat of formation of **353** was 8.8 kcal/mol lower in energy than the other geometric isomer.

The subsequent IEDDA-driven domino reaction of **353** with enamine **214** afforded benzocoumarin **354** in moderate yield (67%, Φ_{calc}=1.3 °) over 2 d. It is not surprising that this IEDDA reaction takes longer than the IEDDA reaction discussed

[165] For a review of this subject, see: Vlad, P. F.; Krimer, M. Z. *Org. Prep. Proced. Int.* **1998**, *30*, 657–697.

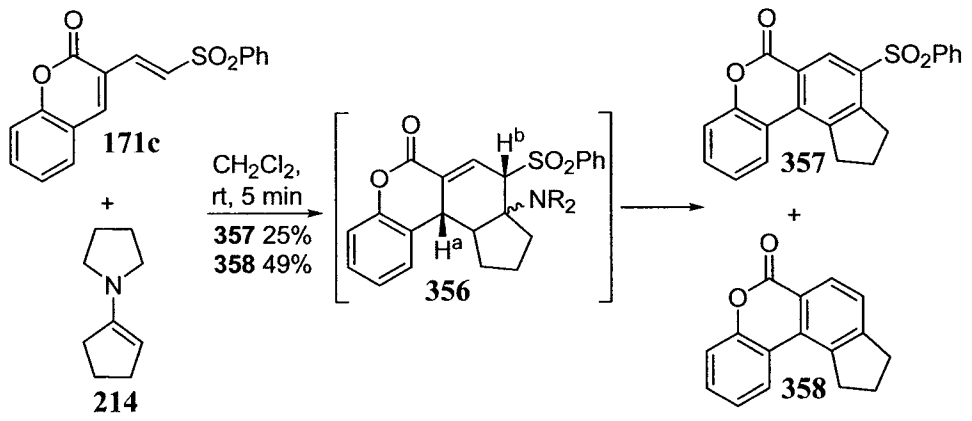


Scheme 4.13: Synthesis of benzocoumarin **355**.

above. The inclusion of the methyl group raises the calculated energy of the LUMO of diene **353** (−1.237 eV) by 0.156 eV from that of diene **165d** (−1.393 eV). This results in a larger HOMO-LUMO gap between the diene and dienophile, which renders the interaction between these FMOs less favorable resulting in a slower rate of reaction.[18] The addition of the methyl group may also cause the diene to favor an *s-trans* geometry instead of the desired *s-cis* geometry, which was needed for the pericyclic reaction to occur.

Finally, dienes containing electron-withdrawing groups other than the methyl ester, for example diene **171a**, will alter the functionality at position 2 of the benzocoumarin unit. Diene **171a** was reacted with cyclopentanone **233** and pyrrolidine **234** using the standard *in situ* procedure to produce the expected benzocoumarin **353** (Φ_{calc}=0.4 °) in 60% yield (Scheme 4.13).

Reaction of **171c** with enamine **214** under the standard preformed conditions afforded benzocoumarin **357** (25%) and **358** (49%) (Scheme 4.14). Benzocoumarin **357** (Φ_{calc}=0.3 °) is the expected product and presumably arises by the usual IEDDA/elimination/dehydrogenation process. Assuming an initial IEDDA reaction afforded adduct **356**, the formation of benzocoumarin **358** could be accounted for by a



Scheme 4.14: Reaction of sulfone diene **171c** with enamine **214**.

1,4 elimination of H^a and the phenyl sulfone group to produce benzene sulfinic acid, followed by the elimination of pyrrolidine **234**. Considering that the phenyl sulfone group is a far superior leaving group to both the cyano and, especially, the methoxycarbonyl group, the formation of **358** cannot be viewed as particularly surprising.

4.2.3 Conclusions and Future Directions

The reactions described above demonstrate that the IEDDA-driven domino reaction is a relatively general and efficient method for the rapid construction for substituted benzocoumarins. Compared to the previously reported methodologies, the approach described here uses readily available, cheap starting materials and does not require the use of palladium.

In the future, methods to afford 6-substituted salicylaldehydes quickly and efficiently need to be investigated. Other electron-poor dienes, besides the examples discussed above, should have their IEDDA reactivity explored.

4.3 Azabenzocoumarins

4.3.1 Introduction

Having successfully applied the IEDDA-driven domino reaction to produce quickly the benzocoumarin skeleton, an investigation into the feasibility of incorporating nitrogen atoms into the benzocoumarin skeleton by an analogous approach was initiated. Only five such compounds, **359**,[154e] **360**,[166] **361**,[167] **362**,[168] **363**,[167] have been reported, and three of them do not have fully aromatic C rings (Figure 4.6). In fact, it has been

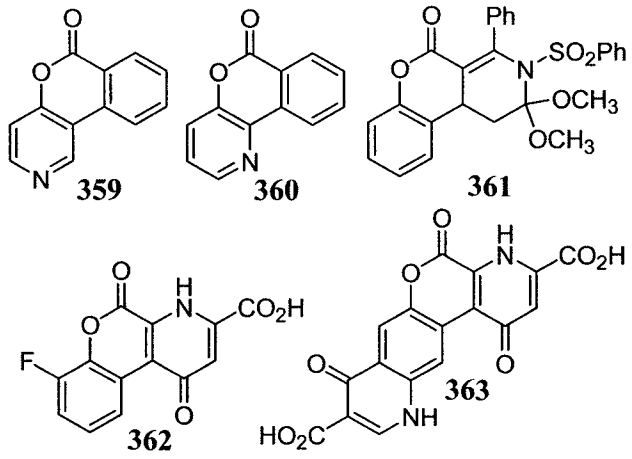


Figure 4.6: Previously synthesized 3,4-azabenzocoumarins

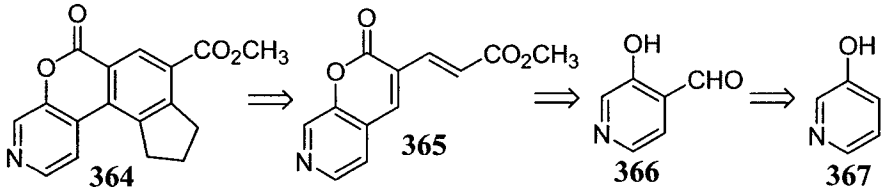
[166] (a) Zhang, W.; Pugh, G. *Tetrahedron Lett.* **2001**, *42*, 5613–5615. (b) Dennis, N.; Katrizky, A. R.; Parton, S. K. *J. Chem. Soc., Perkin Trans. 1* **1974**, 750–754.
[167] Boder, D.; Kasper, A. M. *J. Am. Chem. Soc.* **1989**, *111*, 1517–1519.
[168] Trkovnik, M.; Ivezic, Z. J. *Heterocyclic Chem.* **2000**, *37*, 137–141.

said, "azacoumarins are difficult to synthesize and their biological and pharmacological activities have been little investigated".[169]

4.3.2 Results and Discussion

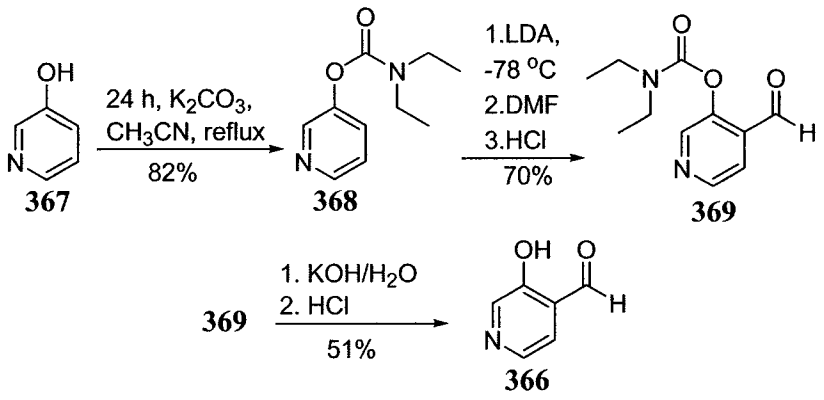
Benzocoumarin **364** was selected as the first target. The retrosynthetic analysis of this compound shown in Scheme 4.14 leads back to suggest 3-hydroxypyridine **367** as the starting material. Skattebøl reported the $MgCl_2$/triethylamine/paraformaldehyde procedure would produce poor results when the phenol contained electron-withdrawing substituents, so this method was not attempted. Duff conditions were employed, but this method was unsuccessful in generating the pyridine carboxaldehyde. In 1985 Snieckus and Miah reported the synthesis of pyridine carboxaldehyde **366** via an *ortho* lithiation reaction using a carbamate group as a director.[170] 3-Hydroxypyridine **367** was reacted with *N*,*N*-diethylcarbamoyl chloride and K_2CO_3 to afford the *O*-carbamate **368** in 82% yield (Scheme 4.16).

Attempts to produce the pyridine carboxaldehyde **366** using the reaction



Scheme 4.15: Retrosynthetic analysis of azabenzocoumarin **364**.

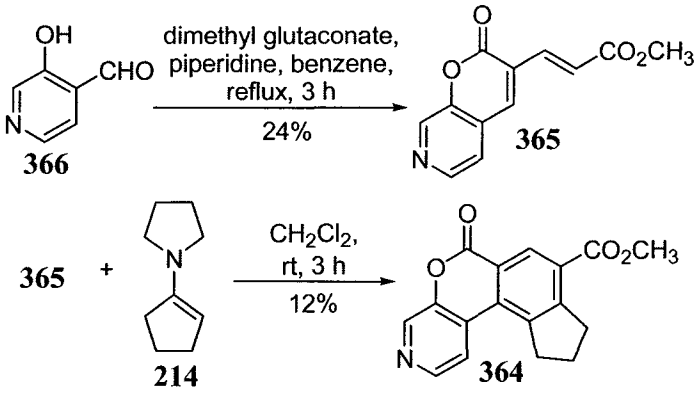
[169] Brufola, G.; Fringuelli, F.; Piermatti, O.; Pizza, F. *Heterocycles* **1997**, *45*, 1715–1721.
[170] Miah, M. A. J.; Snieckus, V. *J. Org. Chem.* **1985**, *50*, 5436–5438.



Scheme 4.16: Synthesis of pyridine carbaldehyde **366**.

conditions reported by Miah and Snieckus failed. After some experimentation, it was found that the use of LDA at –78 °C to generate the lithiated arene followed by quenching with DMF afforded **369** in 70% yield. No evidence for the formation of the regioisomeric pyridine-2-carboxaldehyde was obtained. Removal of the carbamate directing group was achieved by reaction with aqueous KOH, which afforded **366** in 51% yield.

With the necessary aldehyde in hand, reaction with dimethyl glutaconate using conditions for the formation of **165d** produced the azadiene **365**, but in only 24% yield (Scheme 4.17). The reason for the unexpectedly low yield was not immediately obvious. The large coupling constant (15.7 Hz) between C2-H and C3-H in the ^{1}H NMR spectrum suggested the *E* geometry about the double bond. Reaction of **365** with enamine **214** afforded the azabenzocoumarin **364** (Φ_{calc}=0.5 °) in only 12% yield. The low yield of **364** was also disappointing and somewhat puzzling. The presence of the nitrogen atom



Scheme 4.17: Synthesis of azabenzocoumarin **364**.

in **365** did not appear to have any effect on the rate of the reaction. As in the case of the reaction of **165d** and **214**, it took 3 h for the starting material to be consumed.

4.3.3 Conclusions and Future Directions

Described above is a preliminary investigation of the feasibility of quickly generating the azabenzocoumarin motif using the methodology developed in Chapter 4.2. Although the methodology was successful in producing a new azabenzocoumarin **364**, the low yields mean that there is plenty of room for optimization.

Furthermore, more efficient routes for producing the required pyridine carboxaldehyde need to be developed. If this can be accomplished, a series of azacoumarins, **370-372**, and their derivatives should become readily accessible.

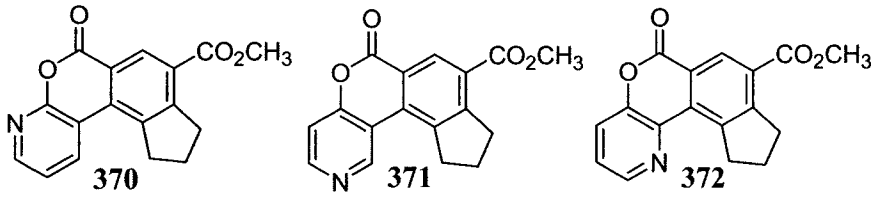


Figure 4.7: Future azacoumarin targets.

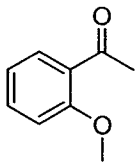
4.4 Experimental

4.4.1 General Experimental Procedures

The general experimental procedures can be found in Section 2.4.1, located on page 65.

4.4.2 Experimental Procedures for Chapter 4.1

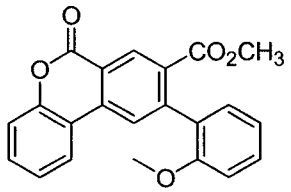
2'-Methoxyacetophenone (297)



To a solution of freshly powdered KOH (45.0 g, 1.24 mol) and 2'-hydroxyacetophenone (24.1 mL, 0.200 mol) in DMSO (400 mL) was added CH_3I (25.0 mL, 0.400 mol) dropwise and the resulting mixture was stirred at room temperature for 30 min. The reaction mixture was poured into water (4 L) and then extracted with CH_2Cl_2 (3×150 mL). The combined organic layers were dried over $MgSO_4$, gravity filtered and then concentrated under reduced pressure. The resulting clear yellow liquid was purified by vacuum distillation to afford **297** (16.9 g, 56%) as a clear colorless liquid: bp: 96-98 °C at 5mm Hg (lit[172] bp: 131 °C at 18mm Hg); ^{1}H NMR (300.1 MHz, $CDCl_3$) δ 7.74 (dd, *J*=7.5, 1.6 Hz, 1H), 7.50-7.44 (m,1H), 7.02-6.96 (m, 2H), 3.92 (s, 3H), 2.62 (s, 3H).

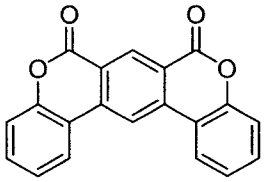
[172] Aldrich Handbook of Fine Chemicals and Laboratory Equipment 2000-2001.

3-(2-methoxyphenyl)-9-oxa-9,10-dihydrophenanthren-10-one-2-carboxylic acid methyl ester (298)



To a magnetically stirred solution of diene **165d** (1.00 g, 4.34 mmol), **297** (3.0 mL, 22 mmol) and $MgSO_4$ (1.00 g, 8.31 mmol) in acetonitrile (25 mL) was added neat pyrrolidine (0.36 mL, 4.3 mmol) in one portion and the resulting mixture was heated at reflux for 7 d. The reaction mixture was cooled to room temperature then concentrated under reduced pressure. The residue was taken up in CH_2Cl_2 (100 mL) and washed with aqueous 1M HCl solution (3×50mL), dried over $MgSO_4$, gravity filtered, and concentrated under reduced pressure. The crude material was subjected to flash chromatography on silica gel (3% ethyl acetate/CH_2Cl_2) to afford **298** as a white solid: mp 195-196 °C; IR (nujol) 1730 (s), 1614 (s) cm^{-1}; ^1H NMR (300.1 MHz, $CDCl_3$) δ 8.90 (s, 1H), 8.08-8.05 (m, 2H), 7.56-7.51 (m, 1H), 7.47-7.32 (m, 4H), 7.12 (t, *J*=7.6 Hz, 1H), 6.96 (d, *J*=8.5 Hz, 1H), 3.76 (s, 3H), 3.75 (s, 3H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 166.7 (0), 160.4 (0), 155.9 (0), 151.9 (0), 145.5 (0), 137.0 (0), 132.2 (0), 132.1 (1), 131.4 (1), 130.0 (1), 129.6 (1), 129.1 (0), 124.8 (1), 124.7 (1), 123.3 (1), 121.0 (1), 119.7 (0), 117.9 (1), 117.3 (0), 110.3 (1), 55.2 (3), 52.1 (3); EI-MS *m/z* (%) 360 (M^+, 41), 329 (100), 267 (14), 202 (6), 172 (4); HRMS (EI) calcd for $C_{22}H_{16}O_5$: 360.0998, found 360.0875.

2,7-Dioxa-1,2,7,8-tetrahydrodibenzo[c,h]anthracene-1,8-dione (300)



To a magnetically stirred, –30 °C solution of **298** (102 mg, 0.277 mmol) in CH_2Cl_2 (5 mL) was added BBr_3 (0.039 mL, 0.416 mmol) dropwise and the resulting mixture was allowed to warm slowly to room temperature over 1 h. Carefully, aqueous 1 M HCl solution (10 mL) was added and a white precipitate was produced. This solid was isolated by suction filtration to afford **300** (46.1 mg, 53%) as a white solid: mp > 300 °C, ^{1}H NMR (500.1 MHz, DMSO-*d6*) δ 9.38 (s, 1H), 9.03 (s, 1H), 8.89 (d, *J*=8.0 Hz, 2H), 7.74-7.70 (m, 2H), 7.56-7.51 (m, 4H); ^{13}C NMR[173] ($CDCl_3$, 125.8 MHz) δ 160.4, 152.5, 140.1, 133.2, 126.3, 121.8, 118.5, 118.0, 117.7; EI-MS *m/z* (%) 314 (M^+, 100), 286 (18), 258 (23), 229 (21), 202 (20), 176 (9).

4.4.3 Experimental Procedures for Chapter 4.2

General formylation procedure:

To a magnetically stirred solution of the phenol derivative (20 mmol), anhydrous magnesium (II) chloride (30 mmol) and anhydrous triethylamine (75 mmol) in anhydrous acetonitrile (100 mL) was added anhydrous paraformaldehyde (135 mmol) in one portion and the resulting mixture was heated at reflux until the TLC trace indicated that the starting phenol was consumed. The mixture was cooled to room temperature, aqueous 1M HCl solution (50 mL) was added, and then the mixture was extracted with diethyl

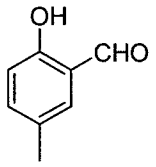
[173] Due to the low solubility only a partial ^{13}C spectrum data can be reported.

ether (3×50 mL). The combined organic layers were dried over $MgSO_4$, gravity filtered and concentrated under reduced pressure. The residue was subjected to flash chromatography to afford the salicylaldehyde. The data for each salicylaldehyde are reported as: compound number, (eluent for chromatography) physical appearance (yield): spectroscopic data.

General IEDDA-driven domino reaction procedure:

To a magnetically stirred solution of the coumarin diene (4.34 mmol) in CH_2Cl_2 (25 mL) was added neat enamine (6.5 mmol) dropwise and the resulting mixture was stirred at room temperature for the time indicated in Table 4.3. The solvent was removed under reduced pressure and the residue was subjected to flash chromatography on silica gel (4% ethyl acetate/CH_2Cl_2) to afford the benzocoumarin.

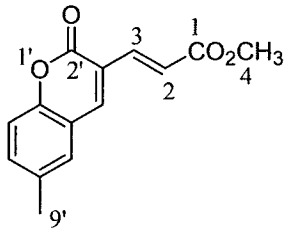
5-Methylsalicylaldehyde (324)[174]



(1:1 pet. ether/ CH_2Cl_2) 85%: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.84 (s, 1H), 9.84 (s, 1H), 7.34-7.32 (m, 2H), 6.89 (d, *J*=9.7 Hz, 1H), 2.33 (s, 3H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 196.5, 159.5, 138.0, 133.4, 129.1, 120.3, 117.3, 20.2.

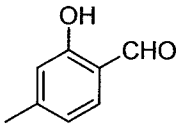
[174] Nonhebel, D. C. *Tetrahedron* **1968**, *24*, 1869–1874.

Methyl (*E*)-3-(6-methyl-2-oxo-*2H*-chromen-3-yl)acrylate (325)



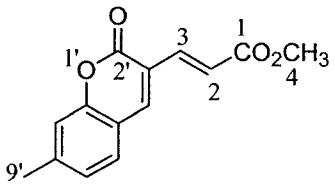
To a magnetically stirred solution of **324** (5.40 g, 40.0 mmol) and **163** (5.58 mL, 40.0 mmol) in benzene (50 mL) was added piperidine (1.96 mL, 20.0 mmol) dropwise and the resulting mixture was heated at reflux with azeotropic removal of water for 1 h. The mixture was cooled to room temperature, whereupon a white precipitate formed. This solid was collected by suction filtration to afford **325** (6.78 g, 70%) as a white solid. The filtrate was concentrated under reduced pressure, and the residue was taken up in CH_2Cl_2 (100 mL), washed with aqueous 1 M HCl solution (2×50 mL) and water (50 mL). The organic layer was dried over $MgSO_4$, gravity filtered and concentrated under reduced pressure. The residue was recrystallized from 95% EtOH to afford another batch of **325** (0.78 g, 8%) (total yield: 7.56 g, 78%): mp 176-177 °C; IR (nujol) 1723 (s), 1710 (s), 1603 (m), 1196 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.81 (s, 1H, C4'-H), 7.55 (d, *J*=16.3 Hz, 1H, C3-H), 7.38 (dd, *J*=8.4, 1.9 Hz, 1H, C7'-H), 7.32 (s, 1H, C5'-H), 7.23 (d, *J*=9.0 Hz, 1H, C8'-H), 7.09 (d, *J*=15.7 Hz, 1H, C2-H), 3.81 (s, 3H, C4'), 2.42 (s, 3H, C9'-H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 167.3 (0, C1), 159.2 (0, C2'), 151.7 (0, C4'a), 143.5 (1, C4'), 138.2 (1, C3), 134.5 (0, C6'), 134.0 (1, C7'), 128.2 (1, C5'), 123.0 (1, C2), 122.0 (0, C3'), 118.7 (0, C4'a), 116.3 (1, C8'), 51.8 (3, C4), 20.7 (3, C9'); EI-MS *m/z* (%) 244 (M^+, 21), 213 (11), 185 (100), 128 (10); Anal. calcd for $C_{14}H_{12}O_4$: C, 68.85; H, 4.95. Found C, 68.67; H, 4.83.

4-Methylsalicylaldehyde (327)[175]



(1:1 pet. ether/ CH_2Cl_2) then a recrystallization from hexanes to afford **327** (61%): ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 11.05 (s, 1H), 9.82 (s, 1H), 7.42 (d, *J*=7.2 Hz, 1H), 6.84-6.79 (m, 2H), 2.38 (s, 3H).

Methyl (*E*)-3-(7-methyl-2-oxo-*2H*-chromen-3-yl)acrylate (327)

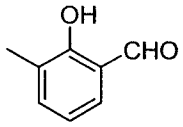


To a magnetically stirred solution of **327** (1.29 g, 10.8 mmol) and **163** (1.51 mL, 10.8 mmol) in benzene (16 mL) was added neat piperidine (0.53 mL, 5.4 mmol) dropwise and the resulting mixture was heated at reflux with azeotropic removal of water for 1 h. The reaction was cooled to room temperature, whereupon a white precipitate formed. This solid was collected by suction filtration to afford **328** (1.86 g, 71%). The filtrate was concentrated under reduced pressure. The residue was taken up in CH_2Cl_2 (100 mL), washed with aqueous 1 M HCl solution (2×50 mL) and water (50 mL). The organic layer was dried over $MgSO_4$, gravity filtered and then concentrated under reduced pressure. The residue was subjected to flash chromatography on silica gel (4% ethyl acetate/CH_2Cl_2) to afford a second batch of **328** (0.23 g, 9%) (total yield: 2.09 g, 80%):

[175] Aldred, R.; Johnston, R.; Levin, D.; Neilan, J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1823–1831.

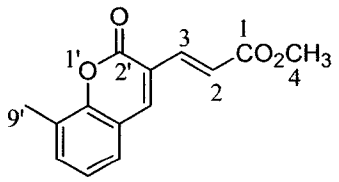
mp 222-223 °C; IR (nujol) 1713 (s), 1616 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.84 (s, 1H, C4'-H), 7.56 (d, *J*=16.3 Hz, 1H, C3-H), 7.43 (d, *J*=8.3 Hz, 1H, C5'-H), 7.16-7.12 (m, 2H, C6'-H + C8'-H), 7.08 (d, *J*=15.7 Hz, 1H, C2-H), 3.81 (s, 3H, C4-H), 2.48 (s, 3H, C9'-H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 167.5 (0, C1), 159.3 (0, C10'), 153.7 (0, C8'a), 144.6 (0, C7'), 143.6 (1, C4'), 138.3 (1, C3), 128.2 (1, C5'), 126.1 (1, C6'), 122.6 (1, C2), 121.1 (0, C3'), 116.8 (1, C8'), 116.6 (0, C4'a), 51.8 (3, C4), 22.0 (3, C9'); GC-MS *m/z* (%) 244 (M^+, 20), 213 (12), 203 (3), 186 (13), 185 (100), 157 (3), 128 (12); HRMS (EI) calcd for $C_{14}H_{12}O_4$: 244.0735, found: 244.0735.

3-Methylsalicylaldehyde (330)[172]



(1:1 pet ether/CH_2Cl_2), 94%: IR (nujol) 3057 (m), 1659 (s), 1617 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 11.26 (s, 1H), 9.88 (s, 1H), 7.40-7.38 (m, 2H), 6.93 (t, *J*=7.5, 1H), 2.27 (s, 3H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 196.7, 160.0, 137.8, 131.3, 128.8, 120.0, 119.3, 15.0; EI-MS *m/z* (%) 136 (M^+, 100), 135 (83), 118 (9), 107 (21).

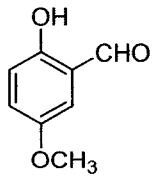
Methyl (*E*)-3-(8-methyl-2-oxo-*2H*-chromen-3-yl)acrylate (331)



To a magnetically stirred solution of **330** (2.71 g, 19.8 mmol), and **163** (3.5 mL, 19.8 mmol) in benzene (30 mL) was added piperidine (1.0 mL, 9.9 mmol) dropwise and the

resulting mixture was heated at reflux with azeotropic removal of water for 1 h. The reaction mixture was cooled to room temperature, whereupon a white precipitate formed. The precipitate was isolated by suction filtration to afford **331** (0.54 g, 11%) as a white solid. The filtrate was concentrated under reduced pressure. The residue was taken up in CH_2Cl_2 (50 mL), washed with aqueous 1M HCl solution (2×50 mL) and water (50 mL). The organic layer was dried over $MgSO_4$, gravity filtered, and concentrated under reduced pressure. The residue was subjected to flash chromatography on silica gel (CH_2Cl_2) to afford a second batch of **331** (2.95 g, 61%) (total yield: 3.49 g, 72%): mp 131-132 °C; IR (nujol) 1725 (s), 1712 (s), 1600 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.85 (s, 1H, C4'-H), 7.55 (d, *J*=16.0 Hz, 1H, C3-H), 7.41 (d, *J*=6.9 Hz, 1H, C7'-H), 7.38 (d, *J*=7.8 Hz, 1H, C5'-H), 7.20 (t, *J*=7.9 Hz, 1H, C6'-H), 7.08 (d, *J*=15.5 Hz, 1H, C2-H), 3.81 (s, 3H, C4-H), 2.44 (s, 3H, C9'-H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 167.2 (0, C1), 159.0 (0, C2'), 151.8 (0, C8'a), 143.9 (1, C4'), 138.1 (1, C3), 134.1 (1, C7'), 126.2 (1, C5'), 126.0 (0, C8'), 124.3 (1, C6'), 122.8 (1, C2), 121.7 (0, C3'), 118.5 (0, C4'a), 51.7 (3, C4), 15.2 (3, C9'); EI-MS *m/z* (%) 244 (M^+, 16), 186 (11), 185 (100), 128 (6), 115 (3), 102 (2); Anal. calcd for $C_{14}H_{12}O_4$: C, 68.85; H, 4.95. Found C, 68.39; H, 4.91.

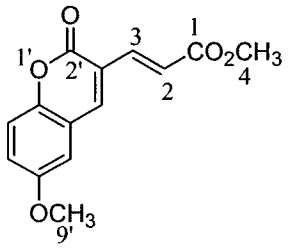
5-Methoxysalicylaldehyde (333)[172]

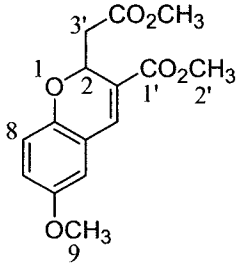


(1:1 Et_2O/ CH_2Cl_2) yellow oil: IR (neat) 3249 (m), 2838 (s), 2739 (m), 1660 (s), 1623 (s); ^1H NMR ($CDCl_3$, 300 MHz) δ 10.66 (s, 1H), 9.86 (s, 1H), 7.15 (dd, *J*=8.6, 2.8 Hz, 1H),

7.00 (d, *J*=2.3 Hz, 1H), 6.93 (d, *J*=9.8 Hz, 1H), 3.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 196.1, 156.0, 152.7, 125.2, 120.0, 118.7, 115.1, 55.9; EI-MS *m/z* (%) 152 (100), 137 (53), 109 (19), 81 (25), 63 (12); Anal. calcd for $C_8H_8O_3$: C, 63.15; H, 5.30. Found C, 62.69; H, 5.33.

Methyl (*E*)-3-(6-methoxy-2-oxo-*2H*-chromen-3-yl)acrylate (334) and 6-methoxy-2-methoxycarbonylmethyl-*2H*-chromene-3-carboxylic acid methyl ester (335)





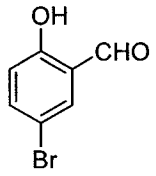
To a magnetically stirred solution of **333** (4.00 g, 26.3 mmol) and **163** (3.7 mL, 26 mmol) in benzene (75 mL) was added neat piperidine (1.3 mL, 13 mmol) dropwise and the resulting mixture was heated at reflux with azeotropic removal of water for 2 h. The reaction mixture was cooled to room temperature, whereupon a yellow precipitate formed. This solid was isolated by suction filtration and the filter cake was washed with cold benzene (2×40 mL), to afford **334** (4.89 g, 71%). The filtrate was then concentrated under reduced pressure and then the residue was subjected to flash chromatography on silica gel (5% ethyl acetate/CH_2Cl_2) to afford **335** (1.32 g, 19%) as a yellow solid.

334: mp 202-203 °C; IR (nujol) 1729 (s), 1713 (s), 1634 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.82 (s, 1H, C4'-H), 7.57 (d, *J*=15.7 Hz, 1H, C3-H), 7.28 (d, *J*=8.8 Hz, 1H, C8'-H), 7.17-7.09 (m, 2H, C7'-H + C2-H), 6.95 (d, *J*=2.8 Hz, 1H, C5'-H), 3.87 (s, 3H, C9'-

H), 3.82 (s, 3H, C4-H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 167.4 (0, C1), 159.2 (0, C2'), 156.3 (0, C6'), 148.1 (0, C8'a), 143.3 (1, C4'), 138.1 (1, C3), 123.3 (1, C2), 122.6 (0, C3'), 121.0 (1, C7'), 119.3 (0, C4'a), 117.7 (1, C8'), 110.0 (1, C5'), 55.9 (3, C9'), 51.9 (3, C4); EI-MS *m/z* (%) 260 (M^+, 39), 229 (16), 201 (100), 158 (8), 102 (9), 76 (8), HRMS (EI) *m/z* calcd for $C_{14}H_{12}O_5$: 260.0684, found 260.0709.

335: mp 66-67 °C; IR (nujol) 1745 (s), 1699 (s), 1640 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.46 (s, 1H, C4-H), 6.84 (dd, *J*=9.0, 3.0 Hz, 1H, C7-H), 6.80 (d, *J*=8.8 Hz, 1H, C8-H), 6.70 (d, *J*=3.1 Hz, 1H, C5-H), 5.67 (dd, *J*=10.5, 3.4 Hz, 1H, C2-H), 3.82 (s, 3H, C2'-H), 3.77 (s, 3H, C9-H), 3.71 (s, 3H, C5'-H), 2.78 (dd, *J*=15.1, 9.9 Hz, 1H, C3'-H), 2.54 (dd, *J*=14.9, 3.2 Hz, 1H, C3'-H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 170.2 (0, C4'), 164.7 (0, C1'), 154.4 (0, C6), 146.3 (0, C8a), 133.5 (1, C4), 124.8 (0, C3), 120.4 (0, C4a), 118.3 (1, C7), 117.9 (1, C8), 112.8 (1, C5), 70.5 (1, C1), 55.7 (3, C9), 52.0 (3, C2'), 51.8 (3, C5'), 38.1 (2, C3'); EI-MS *m/z* (%) 292 (M^+, 9), 232 (23), 219 (100), 176 (9), 174 (8), 103 (4); HRMS (EI) *m/z* calcd for $C_{15}H_{16}O_6$: 292.0946, found 292.0975.

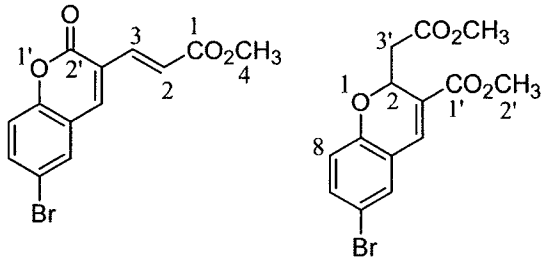
5-Bromosalicylaldehyde (336)



(1:1 Et_2O/ CH_2Cl_2) yellow solid: mp 99-100.5 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 10.94 (s, 1H), 9.85 (s, 1H), 7.68 (d, *J*=3.3 Hz, 1H), 7.60 (dd, *J*=8.8 Hz, 1.8, 1H), 6.91 (d, *J*=1.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 195.4, 160.5, 139.7, 135.6, 121.7, 119.8, 111.3;

EI-MS *m/z* (%) 202 (M^+ ^{81}Br, 93), 200 (M^+ ^{79}Br, 95), 184 (12), 182 (13), 143 (21); HRMS (EI) calcd for $C_7H_5O_2Br$: 199.9472, found 199.9477.

Methyl (*E*)-3-(6-bromo-2-oxo-*2H*-chromen-3-yl)acrylate (337) and 6-bromo-2-methoxycarbonylmethyl-*2H*-chromene-3-carboxylic acid methyl ester (338)



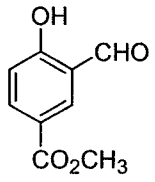
To a magnetically stirred solution of **336** (2.50 g, 12.4 mmol), and **163** (1.75 mL, 12.4 mmol) in benzene (20 mL) was added neat piperidine (0.61 mL, 6.2 mmol) dropwise and the resulting mixture was heated at reflux with azeotropic removal of water for 1 h. The reaction mixture was cooled to room temperature, whereupon a white solid precipitated. This solid was isolated by suction filtration and the filter cake was washed with cold benzene (2×25 mL), to afford **337** (2.12 g, 55%). The filtrate was concentrated under reduced pressure and then the residue was subjected to flash chromatography on silica gel (5% ethyl acetate/CH_2Cl_2) to afford a second batch of **337** (0.38 g, 10%) (total yield: 2.50 g, 65%) and **338** (1.32 g, 25%) each as a white solid.

337: mp 210-211 °C; IR (nujol) 1740 (s), 1707 (s), 1630 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.78 (s, 1H, C4'-H), 7.68 (d, *J*=1.4 Hz, 1H, C5'-H), 7.66 (dd, *J*=8.7, 2.5 Hz, 1H, C7'-H), 7.55 (d, *J*=15.9 Hz, 1H, C3-H), 7.24 (d, *J*=9.4 Hz, 1H, C8'-H), 7.12 (d, *J*=15.8 Hz, 1H, C2-H), 3.82 (s, 3H, C4-H); ^{13}C-NMR ($CDCl_3$, 125.8 MHz) δ 167.1 (0, C1),

158.3 (0, C10'), 152.3 (0, C8'a), 141.9 (1, C4'), 137.5 (1, C3), 135.5 (1, C7'), 130.6 (1, C5'), 124.2 (1, C2), 123.5 (0, C3'), 120.4 (0, C4'a), 118.4 (1, C8'), 117.4 (0, C6'), 51.9 (3, C4); GC-MS *m/z* (%) 310 (M^{+} ^{81}Br, 16), 308 (M^{+} ^{79}Br, 16), 279 (9), 277 (9), 251 (99), 249 (100), 142 (30), 114 (15); HRMS (EI) calcd for $C_{13}H_9O_4Br$: 307.9683, found 307.9671.

338: mp 77-79 °C; IR (nujol) 1727 (s), 1693 (s), 1632 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.40 (s, 1H, C4-H), 7.34 (dd, *J*=8.5, 2.3 Hz, 1H, C7-H), 7.28 (d, *J*=3.0 Hz, 1H, C5-H), 6.76 (d, *J*=8.9 Hz, 1H, C8-H), 5.72 (dd, *J*=9.7, 3.2 Hz, 1H, C2-H), 3.83 (s, 3H, C2'-H), 3.71 (s, 3H, C5'-H), 2.77 (dd, *J*=15.6, 9.6 Hz, 1H, C2'-H), 2.59 (dd, *J*=15.5, 3.2 Hz, 1H, C3'-H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 169.9 (0, C4'), 164.3 (0, C1'), 151.7 (0, C8a), 134.9 (1, C7), 132.1 (1, C4), 131.0 (1, C5), 125.3 (0, C3), 121.7 (0, C4a), 118.9 (1, C8), 113.9 (0, C6), 70.9 (1, C2), 52.1 (3, C2'), 51.9 (3, C5'), 38.5 (2, C3'); EI-MS *m/z* (%) 342 (M^{+2}, 6), 340 (M^{+}, 6), 282 (57), 280 (58), 269 (96), 267 (100), 224 (19), 222 (16), 115 (21); HRMS (EI) calcd for $C_{14}H_{13}O_5Br$: 339.9945, found 339.9916.

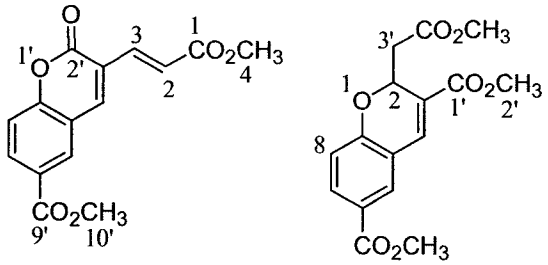
Methyl 3-formyl-4-hydroxybenzoate (339)[162]



To a mechanically stirred solution of methyl 4-hydroxybenzoate (3.04 g, 20.0 mmol) in 75% polyphosphoric acid (20 mL) was added hexamethylenetetraamine (2.80 g, 20.0 mmol) in 4 portions (5 min intervals) at 100 °C and the resulting mixture was stirred for 50 min at this temperature. The heat source was removed and while still hot, cold water

(80 mL) was added carefully. The resulting mixture was then cooled to room temperature. The white precipitate which formed was isolated by suction filtration to afford **339** (1.73 g, 48%) as a white solid: mp 82-84 °C (lit mp[162] 82-83 °C); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 11.39 (s, 1H), 9.96 (s, 1H), 8.33 (d, *J*=2.4 Hz, 1H), 8.20 (dd, *J*=8.8, 1.6 Hz, 1H), 7.04 (d, *J*=8.8 Hz, 1H), 3.94 (s, 3H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 196.3, 165.6, 165.0, 137.8, 136.1, 122.3, 120.1, 118.0, 52.2; GC-MS *m/z* (%) 180 (M^+, 47), 179 (7), 150 (9), 149 (100), 93 (9).

Methyl (*E*)-3-(6-methoxycarbonyl-2-oxo-*2H*-chromen-3-yl)acrylate (340) and 2-methoxycarbonylmethyl-*2H*-chromene-3,6-dicarboxylic acid methyl ester (341)

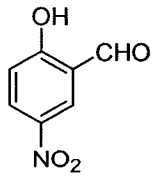


To a magnetically stirred solution of **339** (508 mg, 2.8 mmol) and **163** (0.39 mL, 2.8 mmol) in benzene (10 mL) was added piperidine (0.14 mL, 1.4 mmol) dropwise and the resulting mixture was heated at reflux with azeotropic removal of water for 2 h. The reaction mixture was cooled to room temperature, whereupon a white precipitate formed. This solid was isolated by suction filtration and the filter cake was washed with cold benzene (2×10 mL) to afford **340** (0.22 g, 28%). The filtrate was concentrated under reduced pressure and then the residue was subjected to flash chromatography on silica gel (5% ethyl acetate/CH_2Cl_2) to afford a second batch of **340** (0.31 g, 38%) (total yield: 0.53 g, 66%) and **331** (0.13 g, 15%) each as a white solid.

340: mp 233-234 °C; IR (nujol) 1748 (s), 1720 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.27 (d, *J*=2.0 Hz, 1H, C5'-H), 8.23 (dd, *J*=9.4, 2.0 Hz, 1H, C7'-H), 7.90 (s, 1H, C4'-H), 7.57 (d, *J*=15.6 Hz, 1H, C3-H), 7.40 (d, *J*=9.3 Hz, 1H, C8'-H), 7.13 (d, *J*=15.7 Hz, 1H, C2-H), 3.97 (s, 3H, C10'-H), 3.83 (s, 3H, C4-H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 167.1 (0, C1), 165.4 (0, C9'), 158.3 (0, C10'), 156.2 (0, C8'a), 142.9 (1, C4'), 137.5 (1, C3), 133.6 (1, C7'), 130.5 (1, C5'), 127.0 (0, C6'), 124.1 (1, C2), 123.2 (0, C3'), 118.7 (0, C4'a), 116.9 (1, C8'), 52.6 (3, C10'), 52.0 (3, C4); EI-MS *m/z* (%) 288 (M^+, 14), 257 (17), 230 (15), 229 (100), 170 (4), 99 (5); HRMS (EI) calcd for $C_{15}H_{12}O_6$: 288.0633, found 288.0616.

341: mp 126-127 °C; IR (nujol) 1737 (s), 1692 (s), 1609 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.95 (dd, *J*=8.3, 2.0 Hz, 1H), 7.91 (s, 1H), 7.87 (d, *J*=2.0 Hz, 1H), 6.90 (d, *J*=8.8 Hz, 1H), 5.79 (dd, *J*=9.6, 3.3 Hz, 1H), 3.90 (s, 3H), 3.84 (s, 3H), 3.71 (s, 3H), 2.79 (dd, *J*=15.5, 9.6 Hz, 1H), 2.65 (dd, *J*=14.7, 3.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 169.9 (0), 166.1 (0), 164.4 (0), 156.6 (0), 133.9 (1), 132.8 (1), 130.6 (1), 124.6 (0), 124.0 (0), 119.5 (0), 117.1 (1), 71.5 (1), 52.2 (3), 52.1 (3), 51.9 (3), 39.1 (2); GC-MS *m/z* (%) 320 (M^+, 5), 260 (63), 247 (100), 229 (5), 202 (15), 171 (8), 115 (8).

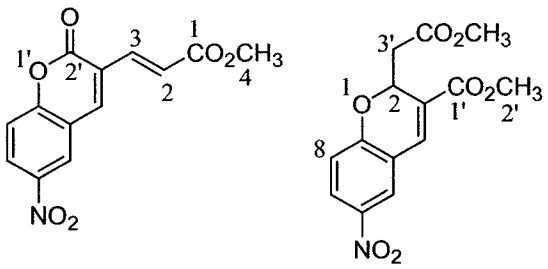
5-Nitrosalicylaldehyde (342)



To a magnetically stirred solution of 4-nitrophenol (10.0 g, 71.9 mmol) in trifluoroacetic acid (75 mL) was added hexamethylenetetraamine (10.1 g, 71.9 mmol) carefully in one

portion and the resulting mixture was heated at reflux for 84 h. The mixture was cooled to room temperature then poured into aqueous 6 M HCl solution (600 mL) and stirred for 30 min. The mixture was extracted with CH_2Cl_2 (4×100 mL), dried over $MgSO_4$, gravity filtered, and concentrated under reduced pressure. The residue was subjected to flash chromatography on silica gel (CH_2Cl_2) to afford **342** (3.09 g, 26%) as a yellow solid: mp 130-132 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 11.63 (s, 1H), 10.03 (s, 1H), 8.59 (d, J = 1.9 Hz, 1H), 8.42 (dd, J = 9.4, 2.4 Hz, 1H), 7.14 (d, J = 8.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 195.5, 166.1, 140.5, 131.6, 129.7, 119.3, 118.9.

Methyl (*E*)-3-(6-nitro-2-oxo-*2H*-chromen-3-yl)acrylate (343) and 6-nitro-2-methoxycarbonylmethyl-*2H*-chromene-3-carboxylic acid methyl ester (344)



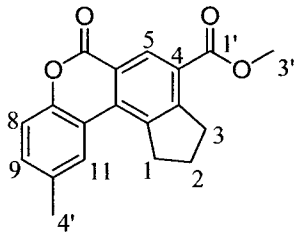
To a magnetically stirred solution of **342**(2.85 g, 17.0 mmol) and **163** (2.40 mL, 17.0 mmol) in benzene (60 mL) was added neat piperidine (0.84 mL, 8.5 mmol) dropwise and the resulting mixture was heated at reflux with azeotropic removal of water for 30 min. During this time a white solid formed in the reaction mixture. The reaction mixture was cooled to room temperature, suction filtered and the filter cake was washed with cold benzene (2×25 mL) to afford **343** (1.22 g, 26%). The filtrate was concentrated under

reduced pressure and then the residue was subjected to flash chromatography on silica gel (5% ethyl acetate/CH_2Cl_2) to give **344** (3.83 g, 72%) as a white solid.

343: mp 210-211 °C; IR (nujol) 1768 (s), 1697 (s), 1611 (m), 1208 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.68-8.67 (m, 2H, C4'-H + C5'-H), 8.47 (dd, *J*=9.5, 3.1 Hz, 1H, C7'-H), 7.68 (d, *J*=9.2 Hz, 1H, C8'-H), 7.54 (d, *J*=15.9 Hz, 1H, C3-H), 6.97 (d, *J*=16.0 Hz, 1H, C2-H), 3.76 (s, 3H, C4-H); ^{13}C-NMR ($CDCl_3$, 125.8 MHz) δ 166.2 (0, C1), 158.0 (0, C2'), 156.6 (0, C8'a), 143.7 (0, C6'), 143.2 (1, C4'), 137.6 (1, C3), 127.4 (1, C7'), 124.8 (1, C5'), 123.0 (0, C3'), 122.7 (1, C2), 119.2 (0, C4'a), 117.8 (1, C8'), 51.9 (3, C4); EI-MS *m/z* (%) 275 (M^+, 14), 216 (100), 170 (39), 114 (10), 88 (7);

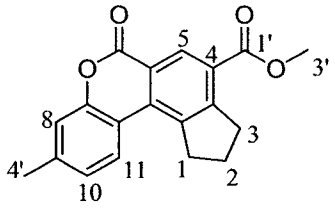
344: mp 143-144 °C; IR (nujol) 1729 (s), 1697 (s), 1612 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.16 (dd, *J*=9.0, 2.5 Hz, 1H, C7-H), 8.09 (d, *J*=2.5 Hz, 1H, C5-H), 7.52 (s, 1H, C4-H), 6.96 (d, *J*=9.0 Hz, 1H, C8-H), 5.85 (dd, *J*=9.6, 3.2 Hz, 1H, C2-H), 3.86 (s, 3H, C2'-H), 3.72 (s, 3H, C5'-H), 2.80 (dd, *J*=15.4, 10.0 Hz, 1H, C3'-H), 2.71 (dd, *J*=15.4, 3.8 Hz, 1H, C3'-H); ^{13}C-NMR ($CDCl_3$, 125.8 MHz) δ 169.5 (0, C4'), 163.9 (0, C1'), 158.0 (0, C8a), 142.3 (0, C6), 131.6 (1, C4), 127.8 (1, C7), 126.0 (0, C2), 124.3 (1, C5), 119.7 (0, C4a), 117.5 (1, C8), 72.2 (1, C1), 52.4 (3, C2'), 52.0 (3, C5'), 39.3 (2, C3'); EI-MS *m/z* (%) 307 (M^+, 5), 247 (100), 234 (67), 188 (60), 115 (9); HRMS (EI) calcd for $C_{14}H_{13}NO_7$: 307.0691, found 307.0677.

10-Methyl-2,3,6,7-tetrahydro-*1H*-7-oxacyclopenta[c]phenanthren-6-one-4-carboxylic acid methyl ester (345)



345, white solid (0.63 g, 47%): mp 258-260 °C; IR (nujol) 1724 (s), 1715 (s), 1209 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.94 (s, 1H, C5-H), 7.99 (s, 1H, C11-H), 7.31 (d, *J*=8.3 Hz, 1H, C9-H), 7.27 (d, *J*=7.6 Hz, 1H, C8-H), 3.95 (s, 3H, C3'-H), 3.49-3.43 (m, 4H, C1-H + C3-H), 2.47 (s, 3H, C4'-H), 2.28 (quint, *J*=7.6 Hz, 2H, C2-H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 166.1 (0, C1'), 161.2 (0, C6), 155.2 (0, C3a), 150.0 (0, C7a), 141.7 (0, C11c), 134.6 (0, C11b), 133.8 (0, C10), 132.1 (1, C5), 131.6 (1, C9), 126.9 (1, C11), 126.5 (0), 120.5 (0), 118.5 (0, C11a), 117.6 (1, C8), 52.1 (3, C3'), 35.4 (2), 33.6 (2), 25.0 (2, C2), 21.4 (3, C4'); EI-MS *m/z* (%) 308 (M^+, 100), 277 (29), 249 (14), 205 (14), 189 (11), 109 (5); HRMS (EI) calcd. for $C_{19}H_{16}O_4$: 308.1048, found 308.1034.

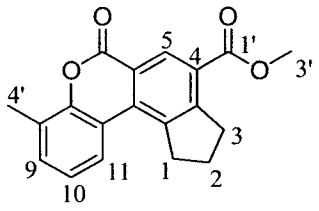
9-Methyl-2,3,6,7-tetrahydro-*1H*-7-oxacyclopenta[c]phenanthren-6-one-4-carboxylic acid methyl ester (346)



346, white solid (0.68, 51%): mp 268-269 °C; IR (nujol) 1720 (s), 1623 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.90 (s, 1H, C5-H), 8.06 (d, *J*=8.1 Hz, 1H, C11-H), 7.16-7.13

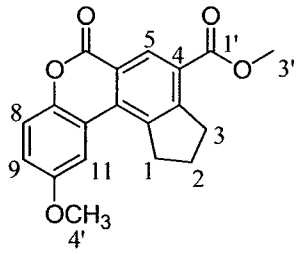
(m, 2H, C10-H + C8-H), 3.94 (s, 3H, C3'-H), 3.43 (t, *J*=7.7 Hz, 4H, C1-H +C3-H), 2.45 (s, 3H, C4'-H), 2.27 (quint, *J*=7.7 Hz, 2H, C2-H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 166.1 (0, C1'), 161.2 (0, C6), 155.1 (0, C3a), 151.9 (0, C7a), 141.7 (0, C9), 141.3 (0, C11c), 134.6 (0, C11b), 132.0 (1, C5), 126.6 (1, C11), 126.2 (0), 125.4 (1, C10), 120.0 (0), 118.0 (1, C8), 116.2 (0, C11a), 52.0 (3, C1'), 35.2 (2), 33.6 (2), 24.9 (2, C2), 21.3 (3, C4'); GC-MS *m/z* (%) 308 (M^+, 100), 293 (14), 277 (37), 249 (15), 205 (16), 189 (25), 165 (12); HRMS (EI) *m/z* calcd for $C_{19}H_{16}O_4$: 308.1048, found 308.1064.

8-Methyl-2,3,6,7-tetrahydro-*1H*-7-oxacyclopenta[c]phenanthren-6-one-4-carboxylic acid methyl ester (347)



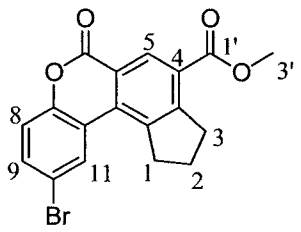
347, white solid (0.65 g, 48%): mp 228-229 °C; IR (nujol), 1718 (s), 1193 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.82 (s, 1H, C5-H), 7.97 (d, *J*=7.9 Hz, 1H, C11-H), 7.32 (d, *J*=7.6 Hz, 1H, C9-H), 7.19 (t, *J*=7.8 Hz, 1H, C10-H), 3.93 (s, 3H, C3'-H), 3.39 (t, *J*=7.6 Hz, 4H, C1-H + C3-H), 2.44 (s, 3H, C4'-H), 2.24 (quint, *J*=7.7 Hz, 2H, C2-H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 165.9 (0, C1'), 160.8 (0, C6), 155.0 (0, C3a), 150.0 (0, C7a), 141.7 (0, C11c), 134.7 (0, C11b), 132.1 (1, C9), 131.8 (1, C5), 126.9 (0, C8), 126.3 (0), 124.5 (1, C11), 123.6 (1, C10), 120.1 (0), 118.3 (0, C11a), 52.0 (3, C3'), 35.4 (2), 33.5(2), 24.8 (2, C2), 16.2 (3, C4'); GC-MS *m/z* (%) 308 (M^+, 100), 293 (16), 277 (34), 248 (15), 205 (17), 189 (25), 165 (13).

10-Methoxy-2,3,6,7-tetrahydro-*1H*-7-oxacyclopenta[c]phenanthren-6-one-4-carboxylic acid methyl ester (348)



348, light orange solid (0.72 g, 51%): mp 244-245 °C; IR (nujol) 1719 (s), 1703 (s), 1600 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.86 (s, 1H, C5-H), 7.71 (d, *J*=2.9 Hz, 1H, C11-H), 7.34 (d, *J*=9.0 Hz, 1H, C8-H), 7.09 (dd, *J*=9.0, 2.0 Hz, 1H, C9-H), 3.95 (s, 3H, C3'-H), 3.90 (s, 3H, C4'-H), 3.51-3.44 (m, 4H, C1-H + C3-H), 2.29 (quint, *J*=7.55 Hz, 2H, C2-H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 166.1 (0, C1'), 161.2 (0, C6), 155.9 (0, C10), 155.2 (0, C3a), 146.2 (0, C7a), 141.7 (0, C11c), 134.4 (0, C11a), 132.2 (1, C5), 126.8 (0), 120.6 (0), 119.3 (0, C11b), 118.6 (1. C9), 116.8 (1, C8), 111.3 (1, C11), 55.8 (3, C4'), 52.1 (3, C3'), 35.2 (2), 33.6 (2), 25.0 (2, C2); GC-MS *m/z* (%) 324 (M^+, 100), 293 (14), 221 (8), 165 (22), 139 (10); HRMS (EI) calcd for $C_{19}H_{16}O_5$: 324.0997, found 324.1024.

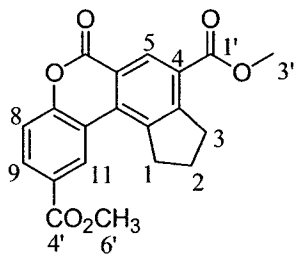
10-Bromo-2,3,6,7-tetrahydro-*1H*-7-oxacyclopenta[c]phenanthren-6-one-4-carboxylic acid methyl ester (349)[176]



349, white solid (0.410 g, 51%): mp 262-263 °C; IR (nujol) 1731 (s), 1716 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.95 (s, 1H, C5-H), 8.33 (d, *J*=1.5 Hz, 1H, C11-H), 7.61 (dd, *J*=8.6, 2.2 Hz, 1H, C9-H), 7.29 (d, *J*=8.6 Hz, 1H, C8-1H), 3.96 (s, 3H, C3'-H), 3.47 (t, *J*=7.7 Hz, 4H, C1-H + C3-H), 2.31 (quint, *J*=7.8 Hz, 2H, C2-H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 166.3 (0, C1'), 160.8 (0, C6), 156.1 (0, C3a), 151.3 (0, C7a), 142.4 (0, C11c), 133.9 (1, C9), 133.6 (0, 11b), 132.6 (1, C5), 129.9 (1, C11), 127.8 (0), 121.0 (0), 120.8 (0), 120.0 (1, C8), 117.6 (0, C11a), 52.7 (3, C3'), 35.6 (2), 34.0 (2), 25.4 (2, C2); EI-MS *m/z* (%) 374 (M^+ ^{81}Br, 97), 372 (M^+ ^{79}Br, 100), 343 (29), 341 (33), 178 (14), 176 (20), 88 (28), 76 (17); Anal. calcd for $C_{18}H_{13}O_4Br$: C, 57.53; H, 3.50. Found C, 57.93; H, 3.51; HRMS (EI) calcd for $C_{18}H_{13}O_4Br$: 371.9996, found 371.9991.

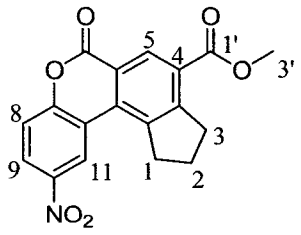
[176] Reaction was scaled down from the general procedure by a factor of 2.

2,3,6,7-tetrahydro-*1H*-7-oxacyclopenta[c]phenanthren-6-one-4,10-dicarboxylic acid methyl ester (350)



350, white solid (0.62 g, 41%): mp >300 °C; IR (nujol) 1731 (s), 1706 (s), 1666 (s), 1586 (m) ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.00-8.99 (m, 2H, C5-H + C11-H), 8.19 (dd, *J*=8.2, 2.2 Hz, 1H, C9-H), 7.46 (d, *J*=7.9 Hz, 1H, C8-H), 4.00 (s, 3H, C6'-H), 3.97 (s, 3H, C3'-H), 3.59 (t, *J*= 7.4 Hz, 2H, C1-H), 3.49 (t, *J*=7.9 Hz, 2H, C3-H), 2.33 (quint, *J*=7.3 Hz, 2H, C2-H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 166.1 (0, C4'), 166.0 (0, C1'), 160.4 (0, C6), 155.8 (0, C3a), 154.9 (0, C7a), 142.2 (0, C11c), 133.7 (0, C11b), 132.2 (1, C5), 131.7 (1, C9), 129.1 (1, C11), 127.3 (0, C4), 126.4 (0, C10), 120.3 (0, C5a), 118.8 (0, C11a), 118.1 (1, C8), 52.5 (3, C6'), 52.2 (3, C3'), 35.2 (2, C1), 33.7 (2, C3), 25.0 (2, C2); GC-MS *m/z* (%) 352 (M^+, 100), 321 (57), 293 (22), 189 (21), 176 (30), 144 (9118).

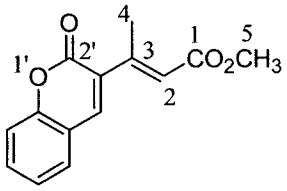
10-Nitro-2,3,6,7-tetrahydro-*1H*-7-oxacyclopenta[c]phenanthren-6-one-4-carboxylic acid methyl ester (351)[175]



351, white solid (0.19 g, 24%): mp 272-273 °C; IR (nujol) 1753 (s), 1729 (s), 1599 (m), 1529 (s), 1354 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.22 (d, *J*=2.8 Hz, 1H, C11-H),

9.00 (s, 1H, C5-H), 8.41 (dd, *J*=8.9, 2.7 Hz, 1H, C9-H), 7.54 (d, *J*=9.0 Hz, 1H, C8-H), 3.98 (s, 3H, C3'-H), 3.60 (t, *J*=7.3 Hz, 2H), 3.52 (t, *J*=8.2 Hz, 2H), 2.37 (quint, *J*=7.7 Hz, 2H, C2-H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 165.7 (0, C1'), 159.6 (0, C6), 156.4 (0, C3a), 155.7 (0, C7a), 144.1 (0, C10), 142.5 (0), 132.5 (0, C11b), 132.3 (1, C5), 128.2 (0), 125.6 (1, C9), 122.9 (1, C11), 120.3 (0), 119.3 (0, C11a), 119.0 (1, C8), 52.4 (3, C3'), 35.1 (2), 33.7 (2), 25.0 (2, C2); EI-MS *m/z* (%) 339 (M^+, 100), 307 (48), 280 (22), 234 (13), 176 (16), 88 (10); Anal. calcd for $C_{18}H_{13}NO_6$: C, 63.72; H, 3.86; N, 4.13. Found C, 63.37; H, 3.72; N, 4.05.

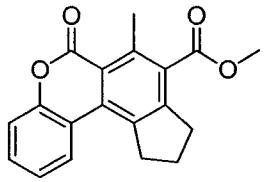
(*E*)-3-(2-Oxo-*2H*-chromen-3-yl)but-2-enoic acid methyl ester (353)



To a magnetically stirred solution of salicylaldehyde **164d** (1.24 mL, 11.6 mmol) and dimethyl 3-methylglutaconate **352** (1.83 mL, 11.6 mmol) in benzene (43 mL) was added piperidine (0.57 mL, 5.8 mmol) dropwise and the resulting mixture was heated at reflux for 45 h. The mixture was cooled to room temperature, whereupon a white precipitate formed. This solid was isolated by suction filtration and the filter cake was washed with cold 95% ethanol (25 mL) to afford **353** as a white solid: mp 163-164.5 °C; IR (nujol) 1699 (s), 1609 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.74 (s, 1H, C4'-H), 7.57-7.52 (m, 2H, C5'-H + C7'-H), 7.35-7.29 (m, 2H, C6'-H +C8'-H), 6.44 (d, *J*=1.2 Hz, 1H, C2-H), 3.77 (s, 3H, C5-H), 2.53 (d, *J*=1.5 Hz, 3H, C4-H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 166.7 (0, C1), 159.1 (0, C2'), 153.6 (0, C8a), 150.1 (0, C3), 140.1 (1, C4'), 132.2 (1, C7'),

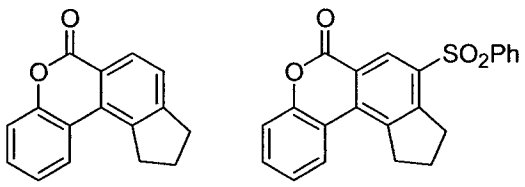
129.8 (0), 128.2 (1, C5'), 124.6 (1, C6'), 120.8 (1, C2), 118.8 (0), 116.5 (1, C8'), 51.3 (3, C5), 17.7 (3, C4); GC-MS *m/z* (%) 244 (M^+, 23), 213 (11), 212 (14), 185 (100), 184 (48), 128 (24), 127 (10); HRMS (EI) calcd for $C_{14}H_{12}O_4$: 244.0735, found 244.0750.

5-Methyl-2,3,6,7-tetrahydro-*1H*-7-oxacyclopenta[c]phenanthren-6-one-4-carboxylic acid methyl ester (354)[176]



354, white solid (0.45 g, 67%): mp 174-175 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.15 (d, *J*=8.2 Hz, 1H), 7.48-7.45 (m, 1H), 7.34 (dd, *J*=8.3, 1.3 Hz, 1H), 7.29 (t, *J*=7.4 Hz, 1H), 3.97 (s, 3H), 3.47 (t, *J*=7.1, 2H), 3.03 (t, *J*=7.7 Hz, 2H), 2.81 (s, 3H), 2.22 (quint, *J*=7.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 169.3 (0), 160.3 (0), 151.5 (0), 149.8 (0), 140.1 (0), 138.0 (0), 134.3 (0), 132.8 (0), 130.1 (1), 126.7 (1), 123.8 (1), 119.3 (0), 119.2 (0), 117.2 (1), 52.4 (3), 36.1 (2), 32.3 (2), 25.1 (2), 20.7 (3); GC-MS *m/z* (%) 308 (M^+, 100), 293 (90), 277 (39), 248 (61), 205 (20) 189 (26); HRMS (EI) calcd for $C_{19}H_{16}O_4$: 308.1048, found 308.1039.

4-Phenylsulfonyl-2,3,6,7-tetrahydro-*1H*-7-oxacyclopenta[c]phenanthren-6-one (357) and 2,3,6,7-tetrahydro-*1H*-7-oxacyclopenta[c]phenanthren-6-one (358)



To a magnetically stirred solution of **171c** (312 mg, 1.00 mmol) in CH_2Cl_2 (5.75 mL) was added neat **214** (206 mg, 1.50 mmol) dropwise and the resulting mixture was stirred for 5 min at room temperature. The mixture was diluted with CH_2Cl_2 (20 mL), washed with aqueous 1M HCl solution (20 mL), dried over $MgSO_4$, gravity filtered, and then concentrated under reduced pressure. The residue was subjected to flash chromatography (CH_2Cl_2) to afford **357** (92.3 mg, 25%) and **358** (116 mg, 49%) each as a white solid:

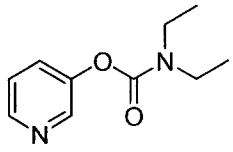
357: mp 285-286 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.04 (s, 1H), 8.18 (d, *J*=8.7 Hz, 1H), 7.98 (d, *J*=8.0 Hz, 2H), 7.62 (t, *J*=7.4 Hz, 1H), 7.57-7.53 (m, 3H), 7.42 (d, *J*=8.6 Hz, 1H), 7.36 (t, *J*=7.5 Hz, 1H), 3.46 (t, *J*=7.5 Hz, 2H), 3.28 (t, *J*=7.8 Hz, 2H), 2.26 (quint, *J*=7.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 160.3 (0), 152.1 (0), 151.4 (0), 143.3 (0), 140.4 (0), 137.5 (0), 135.7 (0), 133.6 (1), 131.4 (1), 130.4 (1), 129.3 (1), 128.1 (1), 126.9 (1), 124.5 (1), 121.2 (0), 118.3 (0), 118.1 (1), 35.4 (2), 32.2 (2), 25.0 (2).

358: mp 165-166 °C; IR (nujol) 1723 (s), 1712 (s), 1598 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.30 (d, *J*=7.3 Hz, 1H), 8.17 (d, *J*=7.1 Hz, 1H), 7.48-7.45 (m, 2H), 7.38 (d, *J*=7.4 Hz, 1H), 7.34-7.30 (m, 1H), 3.46 (t, *J*=7.4 Hz, 2H), 3.08 (t, *J*=7.8 Hz, 2H), 2.36-2.24 (m, 2H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 161.8 (0), 153.7 (0), 151.4 (0), 139.5 (0), 131.7 (0), 129.7 (1), 129.6 (1), 126.4 (1), 125.1 (1), 124.1 (1), 120.2 (0), 119.6 (0), 117.7 (1),

35.4 (2), 33.0 (2), 25.1 (2); EI-MS *m/z* (%) 236 (M^+, 100), 207 (36), 191 (13), 178 (11), 165 (9), 152(9); HRMS (EI) calcd for $C_{16}H_{12}O_2$: 236.0837, found 236.0835.

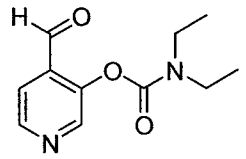
4.4.4 Experimental procedures for Chapter 4.3

_N,N_-Diethylcarbamic acid pyridin-3-yl ester (368)[170]



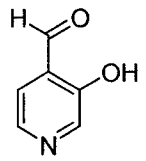
To a magnetically stirred mixture of 3-hydroxypyridine **367** (5.00 g, 52.6 mmol) and *N,N*-diethylcarbamoyl chloride (7.32 mL, 57.9 mmol) in acetonitrile (150 mL) was added K_2CO_3 (7.99 g, 57.9 mmol) in one portion and the resulting mixture was heated at reflux for 3 h. The mixture was cooled to room temperature and suction filtered. The filtrate was concentrated under reduced pressure and the residue was subjected to vacuum distillation to afford **368** (8.37 g, 82%) as a clear colourless liquid: bp 155-158 °C at 0.8 mm of Hg; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.45-8.43 (m, 2H), 7.54-7.51 (m, 1H), 7.30 (dd, *J*=8.4, 4.7 Hz, 1H), 3.48-3.38 (m, 4H), 1.28-1.20 (m, 6H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 153.4 (0), 148.1 (0), 146.1 (1), 143.6 (1), 129.3 (1), 123.6 (1), 42.4 (2), 42.0 (2), 14.1 (3), 13.2 (3); EI-MS *m/z* (%) 194 (M^+, 2), 101 (6), 100 (100), 78 (5), 72 (71).

***N,N*-Diethylcarbamic acid 4-formylpyridin-3-yl ester (369)**



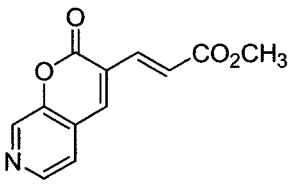
To a magnetically stirred solution diisopropylamine (0.79 mL, 5.6 mmol) in THF (21 mL) at –78 °C (dry ice/acetone) was added 1.35 M *n*-butyllithium in hexanes (4.2 mL, 5.6 mmol) dropwise and the resulting mixture was stirred at –78 °C for 20 min. A solution of **368** (1.00 g, 5.15 mmol) in THF (1 mL) was added dropwise to the freshly generated LDA solution at –78 °C and the resulting solution was stirred for 10 min, whereupon a white precipitate had formed. Neat anhydrous DMF (0.45 mL, 5.6 mmol) was added dropwise to the stirring mixture at –78 °C and the resulting mixture was stirred for 10 min at this temperature then allowed to slowly warm to room temperature. During the addition of DMF, the white precipitate dissolved. Once at room temperature, the reaction was quenched by the addition of aqueous saturated ammonium chloride solution (10 mL). The aqueous layer was extracted with Et_2O (2×10 mL) and the combined organic layers were dried over $MgSO_4$, gravity filtered, and concentrated under reduced pressure. The residue was subjected to flash chromatography on silica gel (5% MeOH/CH_2Cl_2) to afford **369** (0.80 g, 70%) as a white solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 10.21 (s, 1H), 8.67-8.66 (m, 2H), 7.70 (d, *J*=4.9 Hz, 1H), 3.53 (q, *J*=7.2 Hz, 2H), 3.42 (q, *J*=7.1 Hz, 2H), 1.32 (t, *J*=7.0 Hz, 3H), 1.24 (t, *J*=7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 187.8 (1), 153.0 (0), 147.32 (1), 147.27 (0), 146.4 (1), 133.6 (0), 121.1 (1), 42.7 (2), 42.2 (2), 14.3 (3), 13.2 (3).

4-Formyl-3-hydroxypyridine (366)



To a magnetically stirred solution of **369** (294 mg, 1.32 mmol) in water (6 mL) was added NaOH (191 mg, 4.78 mmol) in one portion and the resulting mixture was stirred at room temperature for 30 min. The reaction was quenched with aqueous saturated ammonium chloride (10 mL) and the resulting mixture was extracted with CH_2Cl_2 (3×10 mL). Aqueous 1M HCl solution was added to the aqueous layer until the pH was approximately 5 and the resulting mixture was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were dried over $MgSO_4$, gravity filtered, and concentrated under reduced pressure to afford **366** (83.7 mg, 50%) of a yellow solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 10.35 (brs, 1H), 10.04 (s, 1H), 8.56 (s, 1H), 8.41 (d, *J*=5.3 Hz, 1H), 7.44 (d, *J*=5.4 Hz, 1H).

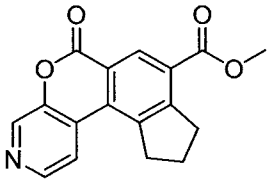
Methyl (*E*)-3-(7-aza-2-oxo-*2H*-chromen-3'-yl)acrylate (365)



To a magnetically stirred solution of **366** (83.7 mg, 0.679 mmol) and **163** (0.10 mL, 0.711 mmol) in benzene (3 mL) was added neat piperidine (0.03 mL, 0.340 mmol) dropwise and the reaction was heated at reflux with azeotropic removal of water for 45 min. The mixture was cooled to room temperature, upon which a white precipitate

formed. This solid was isolated by suction filtration to afford **365** (38 mg, 24%) as a white solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.78 (s, 1H), 8.58 (d, *J*=5.1 Hz, 1H), 7.84 (s, 1H), 7.58 (d, *J*=16.4 Hz, 1H), 7.43 (d, *J*=5.3 Hz, 1H), 7.17 (d, *J*=16.3 Hz, 1H), 3.84 (s, 3H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 166.8 (0), 157.6 (0), 148.4 (0), 145.4 (1), 140.4 (1), 139.5 (1), 136.8 (1), 127.7 (0), 125.8 (1), 123.9 (0), 120.3 (1), 52.1 (3).

2,3,6,7-Tetrahydro-*1H*-7-oxacyclopenta[c]phenanthren-6-one-4-carboxylic acid m ethyl ester (364)



To a magnetically stirred solution of **365** (31.1 mg, 0.135 mmol) in CH_2Cl_2 (2 mL) was added neat enamine (28.3 mg, 0.203 mmol) dropwise and the resulting mixture was stirred at room temperature for 3 h. The solvent was removed under reduced pressure and the residue was subjected to flash chromatography on silica gel (25% ethyl acetate/CH_2Cl_2) to afford **364** (4.9 mg, 12%) as a white solid.

Chapter 5.

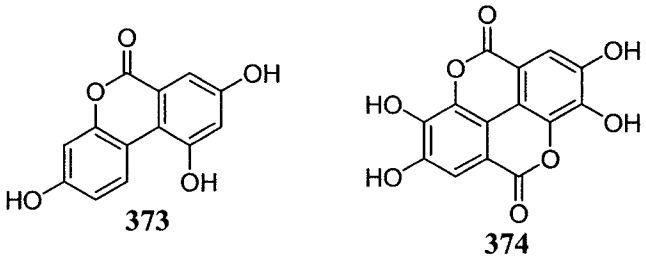
Application of the Methodology

to the Total Synthesis of a Natural Product

5.1 Synthesis of a Naturally Occurring Benzocoumarin

5.1.1 Introduction

Recently, a group from Korea reported the isolation of benzocoumarin **373** from the feces of *Trogopterus xanthipes* (Pteropi Faeces).[142] **373** is believed to be a metabolite of ellagic acid **374**. Pteropi Faeces has been prescribed for the treatment of angiostasis and dysmenorrhea in Chinese traditional medicine.[177] It was desired to demonstrate the versatility of the benzocoumarin-forming methodology developed above by applying it to the synthesis of benzocoumarin **373**.

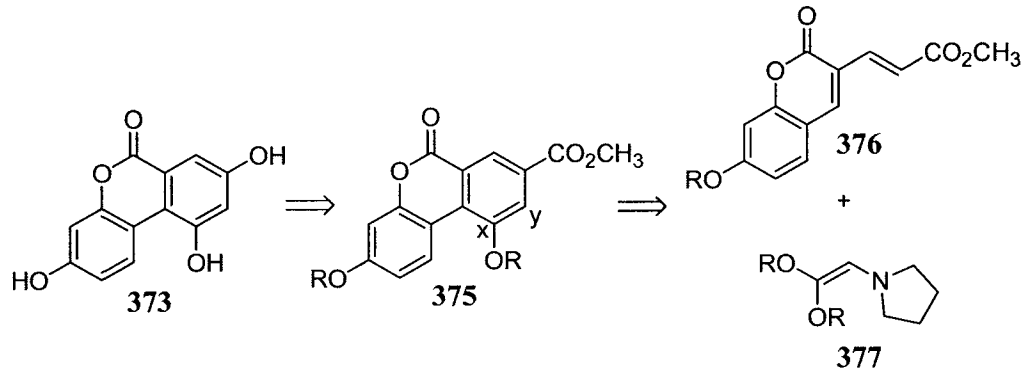


373 **374**

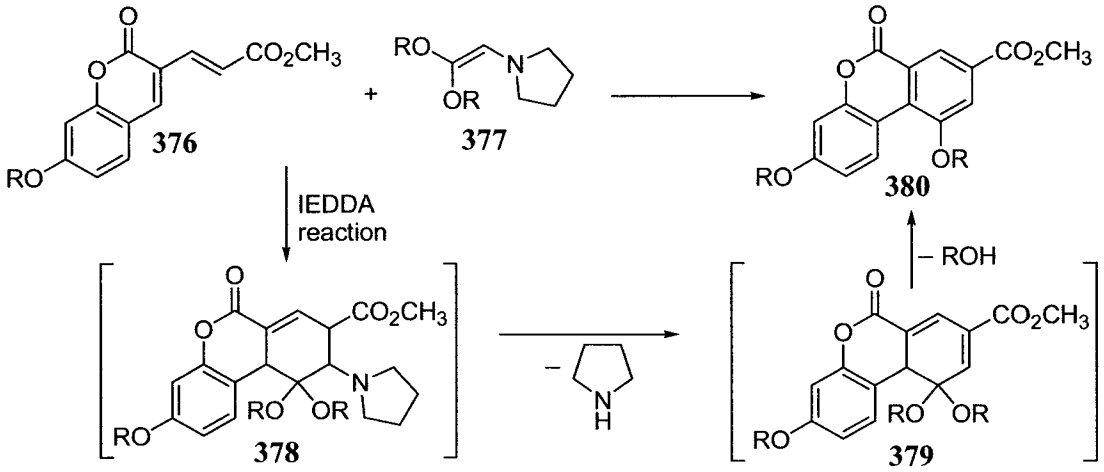
Figure 5.1: Benzocoumarin **373** and Ellagic Acid **374**.

5.2 Results and Discussion:

A retrosynthetic analysis of **373** (Scheme 5.1) suggested that there were two synthetic challenges in generating this benzocoumarin. First, a dienophile was needed that would result in the placement of an appropriate substituent at the x position of **375**, while leaving no substituent at the adjacent y position. After some deliberation,



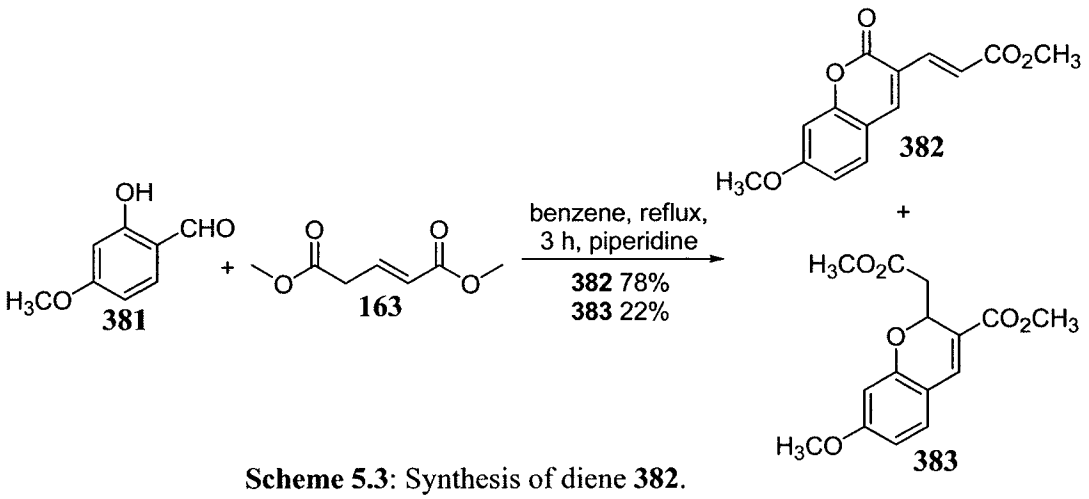
Scheme 5.1: Retrosynthetic analysis of **373**.



Scheme 5.2: Anticipated reaction sequence of diene **376** with dienophile **377**.

dienophiles of the general structure **377** were identified as promising candidates. Since enamines had already shown themselves to be more reactive dienophiles then ketene acetals, it was anticipated that the single amino group would overpower the two alkoxy groups in determining the regiochemistry of the IEDDA reaction. Furthermore, the resulting adduct would be in a position to aromatize via two eliminations (pyrrolidine and

[177] The Dictionary of Chinese drugs. Shanghai Science and Technologic Publisher: pp. 875–877, Shougakukan, Tokyo 1985.

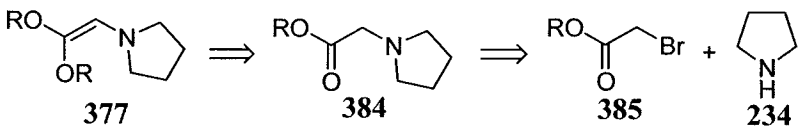


Scheme 5.3: Synthesis of diene **382**.

an alcohol) (Scheme 5.2) rather than by elimination and dehydrogenation. Second, the functional group interconversion of the methyl ester into a hydroxy group would need to be accomplished without destroying the 2-pyrone moiety in the molecule.

Reaction between commercially available salicylaldehyde **381** and dimethyl glutaconate **163** produced coumarin-fused diene **382** (78%) and chromene **383** (22%) (Scheme 5.3). As with other examples discussed in this dissertation, the large coupling constant between C2-H and C3-H (15.9 Hz) suggested the *E* isomer. With gram quantities of the required diene on hand, the challenge of generating dienophile **377** was initiated.

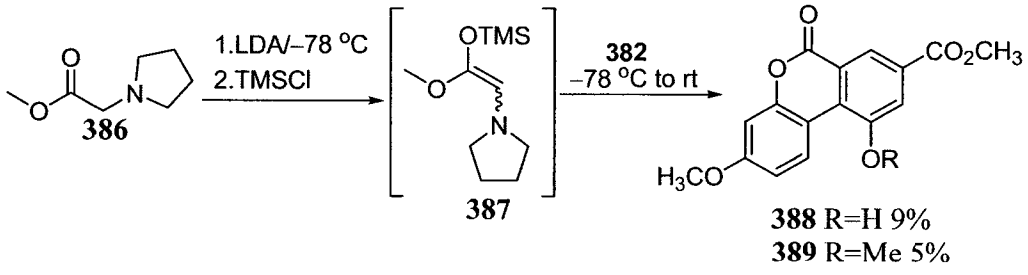
This dienophile can be viewed as a combination of an enamine and ketene acetal. Using reported methods of generating ketene acetals,[178] initial attempts to synthesize dienophile **377** would exploit this chemistry. Retrosynthetic analysis of the dienophile (Scheme 5.4) put forward a two-step route for generating the dienophile.



Scheme 5.4: Retrosynthetic analysis of dienophile **377**.

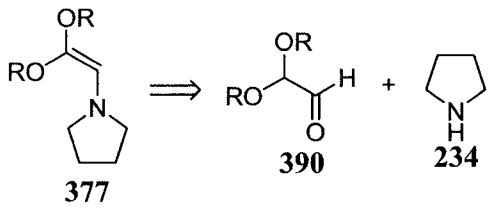
Methyl bromoacetate and pyrrolidine **234** reacted to afford pyrrolidin-1-ylacetic acid methyl ester **386** in 74% yield. Generating the enolate from this product using LDA and then quenching it with TMSCl proved to be problematic. All attempts to isolate the desired dienophile failed. A one-pot procedure was then adopted. The previous reaction was repeated and instead of attempting to isolate the dienophile, a solution of diene **382** was then transferred into the crude dienophile mixture via cannula. The resulting reaction produced two compounds, **388** (9%) and **389** (5%) (Scheme 5.5). In line with expectations, both of these products arose from IEDDA reactions in which the pyrrolidine group dictated the regiochemistry. However, the low recovery made it difficult to say if this regioselectivity was exclusive or not.

The disappointing yield led to an investigation of a second route to the desired dienophile **377** (Scheme 5.6). This retrosynthetic analysis suggested the dienophile could



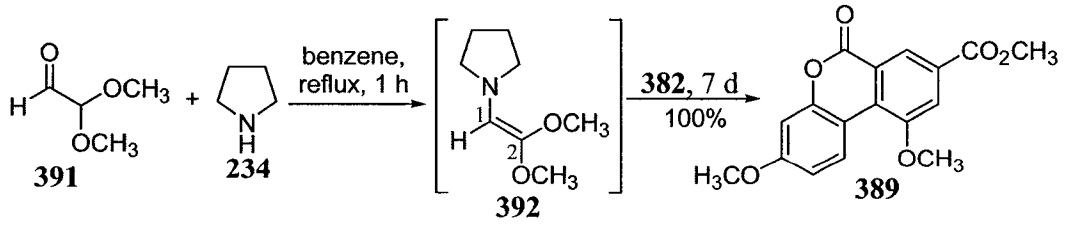
Scheme 5.5: Generation of dienophile from **386**.

[178] Colvin, E. W. In *Silicon Reagents in Organic Synthesis*, Acedemic Press: Toronto, 1988.



Scheme 5.6: A second retrosynthetic analysis of **377**.

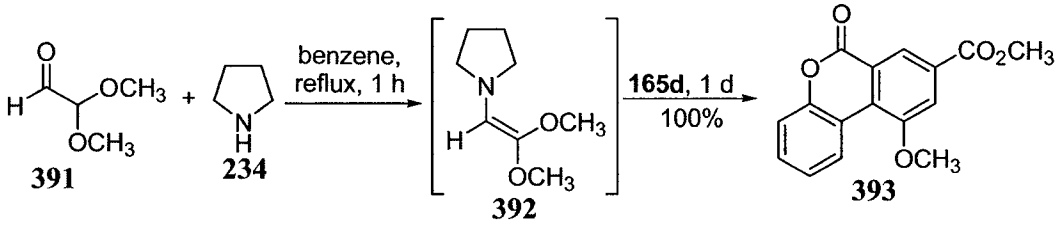
be generated from aldehyde **390** and pyrrolidine **234**. Attempts to generate and isolate the dienophile by applying a reported procedure used previously to produce the enamine derived from isobutyraldehyde and pyrrolidine[116] failed. However, reacting aldehyde **391** with pyrrolidine **234** while removing water azeotropically for 1 h and then adding the diene **382** as a solid afforded **389** quantitatively after 7 d of reaction (Scheme 5.7). This result demonstrated that this particular dienophile adds to the diene **382** in a completely regioselective manner and suggests that a single dialkylamino group is a more effective π-donor than two alkoxy groups bonded to the same carbon atom. In other words, this suggests that enamines are more nucleophilic than ketene acetals. AM1 calculations, using the CambridgeSoft Chem 3D package, agree with this conclusion. The orbital coefficient at C1 in **392** (0.38) was calculated to be significantly smaller than that of C2 (0.52).



Scheme 5.7: Synthesis of benzocoumarin **389**.

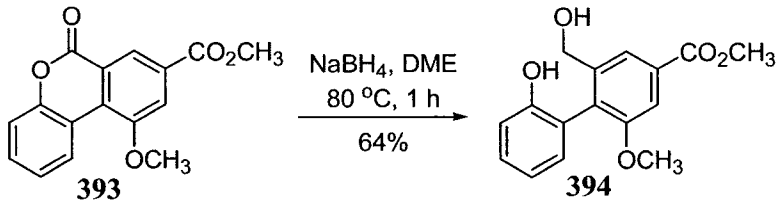
With the spectacular success of this IEDDA reaction, attention was then turned to solving the synthetic challenge of the functional group interconversion of the methyl ester to a hydroxy group while leaving the 2-pyrone moiety intact. For initial work aimed at determining appropriate reaction conditions for achieving this transformation effectively, a slightly simpler and more abundantly available model compound **393** was employed. This was prepared in quantitative yield by the reaction of **392** with diene **165d** (Scheme 5.8). In this case, the reaction required only 1 d to go to completion, and the pyrrolidine group again dictated the regiochemistry. That the reaction time with diene **382** was considerably longer than that with **165d** can be attributed to the presence of the electron donating methoxy group in conjugation with the diene moiety. This would be expected to affect strongly the HOMO/LUMO separation between the diene and dienophile and thus the reaction rate.

Initially it was decided to reduce the methyl ester to an aldehyde and subject this to a Dakin oxidation[179] to generate the necessary phenol. Unfortunately, reaction between **393** and DIBAL at –78 °C, typical conditions to transform a methyl ester into the



Scheme 5.8: Synthesis of benzocoumarin **393**.

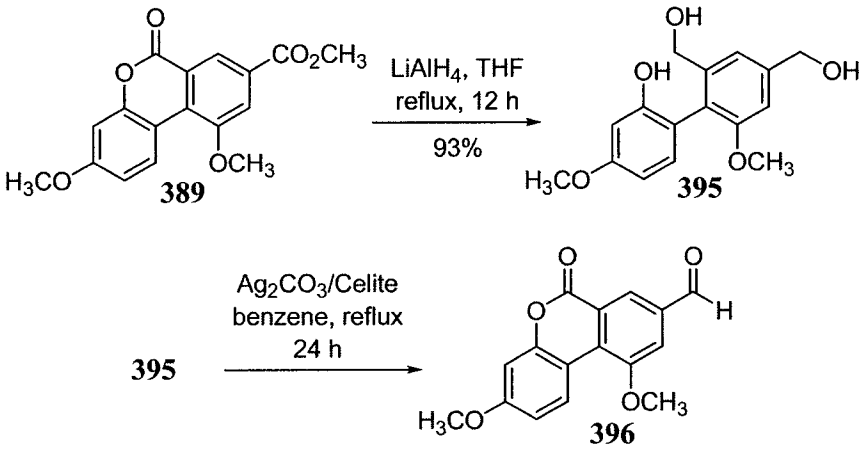
[179] Examples of the Dakin reaction, see: (a) Schönberg, A.; Badran, N.; Starowsky, N. A. *J. Chem. Soc.* **1955**, 1019–1021. (b) Kabalka, G. W.; Reddy, N. K.; Narayana, C. *Tetrahedron Lett.* **1992**, *33*, 865–866. (c) Varma, R. S.; Naicker, K. P. *Org. Lett.* **1999**, *2*, 189–191.



Scheme 5.9: Synthesis of benzocoumarin **394**.

aldehyde, failed. Warming the reaction to –50 °C resulted in the appearance of several spots on the TLC trace. The ^{1}H NMR spectrum of the crude reaction mixture indicated that this reaction produced a mixture of several compounds. The use of $NaBH_4$ in DME, which was reported to reduce specifically aromatic esters to alcohols, was then employed.[180] This procedure did not touch the methyl ester but rather only resulted in the reduction of the 2-pyrone moiety to afford the biaryl **394** in 64% yield (Scheme 5.9). This result served notice that the 2-pyrone was more electrophilic than the methyl ester. Under this scenario, it was decided to reduce the 2-pyrone moiety along with the methyl ester and then regenerate the 2-pyrone unit at a later stage.

Reaction of **389** with excess $LiAlH_4$ produced the biaryl **395** in 93% yield (Scheme 5.10). Oxidation of **395** with MnO_2 over 24 h produced a complex mixture of compounds by TLC analysis. Changing the oxidant to PCC afforded aldehyde **396** in 81% yield. Subsequently, it was discovered that Fétizon's reagent[181] (Ag_2CO_3 on Celite) afforded **396** in 99% yield. The oxidation reaction regenerates the 2-pyrone moiety, presumably via oxidation of the benzylic alcohol near the phenolic OH group, formation of a hemiacetal and its oxidation to an ester. The other benzylic alcohol is simply



Scheme 5.10: Synthesis of benzocoumarin **396**.

oxidized to an aldehyde group, which is set to be oxidized under Dakin oxidation conditions to give the necessary hydroxy group. Unfortunately, all attempts to oxidize the aldehyde to the corresponding phenol failed. This was not particulary surprising since the Dakin oxidation conditions require a hydroxy group *ortho* or *para* to the aldehyde slated for oxidation. De-methylation by reaction with BBr_3 (52%) was then performed. It was envisaged that the OH substituent in extended conjugation with the aldehyde would enable the Dakin oxidation to proceed. However, attempted Dakin oxidation of the resulting benzocoumarin also failed (Scheme 5.11).

Following the failure of the aldehyde to undergo oxidation to the phenol, sights were set on producing the corresponding methyl ketone. Grey[182] reported the transformation of an acid chloride to methyl ketone under mild condition using

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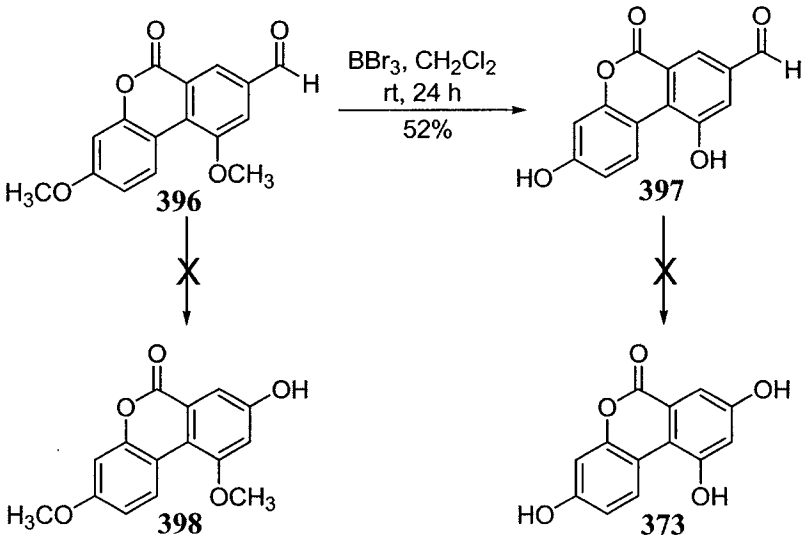
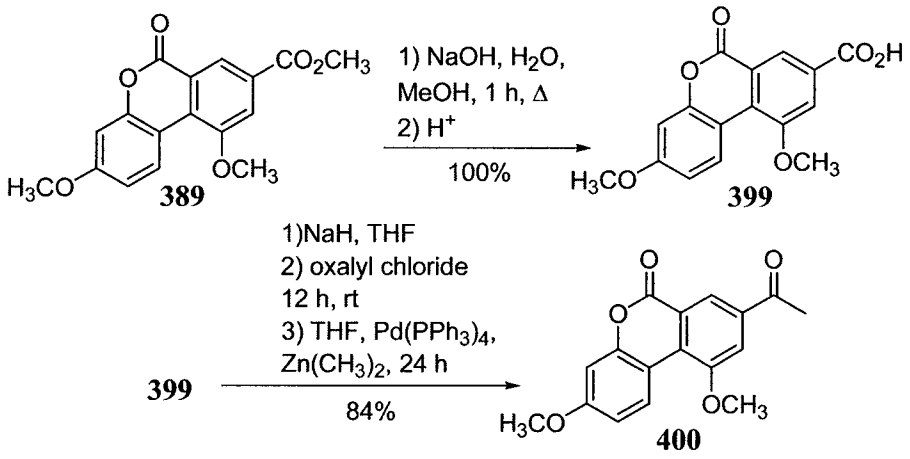
[180] Zanka, A.; Ohmori, H.; Okamoto, T. *Synlett* **1999**, 1636–1638.
[181] Fétizon, M.; Golfier, M.; Louis, J.-M. *Tetrahedron* **1975**, *31*, 171–176.
[182] Grey, R. A. *J. Org. Chem.* **1984**, *49*, 2288–2289.



Scheme 5:11: Failure of the Dakin oxidation route.

dimethylzinc and a palladium catalyst. Dimethylzinc has been reported not to react with the ester functionality, so this method was chosen as the next synthetic route.

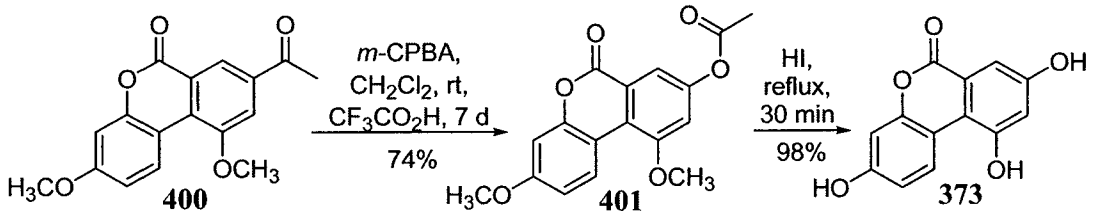
Synthesis of benzocoumarin **399** by hydrolysis of the methyl ester of benzocoumarin **389** was easily achieved in quantitative yield upon basic hydrolysis followed by an acidic workup. The carboxylic acid **399** was treated with oxalyl chloride at reflux temperature and the resulting crude acid chloride was reacted with excess dimethylzinc in the presence of $Pd(PPh_3)_4$ to afford benzocoumarin **400** in good yield (84%) (Scheme 5.12).



Scheme 5.12: Two-step synthesis of benzocoumarin **400** from **389**.

Baeyer-Villager oxidation[183] of benzocoumarin **400** using *m*-CPBA in trifluoroacetic acid at room temperature proceeded smoothly to afford benzocoumarin **401** in 74% yield (Scheme 5.13). This product is a protected form of the target natural product. Deprotection of all three phenolic OH groups was achieved upon heating benzocoumarin **401** in aqueous concentrated HI solution for 30 min to afford the natural product **373** in 98% yield. The overall yield of **373** from the commercially available salicylaldehyde **381** was 48%. The ^{1}H and ^{13}C NMR spectra of **373** matched the reported ^{13}C spectrum data from the original isolation paper.[142]

[183] Examples of the Baeyer Villager reaction, see: (a) Suginome, H.; Yamada, S. *J. Org. Chem.* **1985**, *50*, 2489–2494. (b) de Azevedo, M. B. M.; Murta, M. M.; Greene, A. E. *J. Org. Chem.* **1992**, *57*, 4567–4569. (c) Kametani, T.; Kotoh, T.; Fujio, J.; Nogiwa, I.; Tsubuki, M.; Honda, T. *J. Org. Chem.* **1988**, *53*, 1982–1991. (d) Syper, L. *Synthesis* **1989**, 167–172. (e) Smissman, E. E.; Li, J. P.; Israili, Z. H. *J. Org. Chem.* **1968**, *33*, 4231–4236.



Scheme 5.13: Synthesis of benzocoumarin **373** from benzocoumarin **400**.

5.3 Conclusion and Future Directions

A concise, high yielding total synthesis has been completed for the naturally occurring benzocoumarin **373**. An IEDDA-driven domino reaction based on the methodology discussed in previous chapters constituted the key step of the synthesis. The application of this methodology to the total synthesis of more formidable natural products such as members of the gilvocarcin family **306a-c** would now appear to be a worthwhile endeavor.

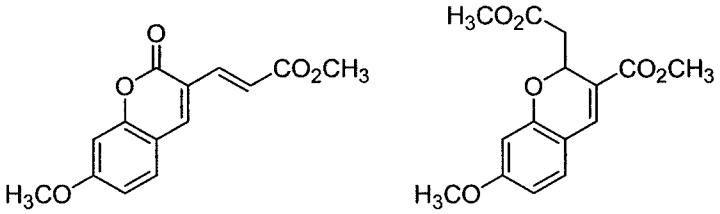
5.4 Experimental

5.4.1 General Experimental Procedures

The general experimental procedures can be found in Section 2.4.1, located on page 65.

5.4.2 Experimental Procedures

Methyl (*E*)-3-(7-methoxy-2-oxo-*2H*-chromen-3-yl) acrylate (382) and 3-methoxycarbonyl-2-methoxycarbonylmethyl-7-methoxy-*2H*-chromene (383)



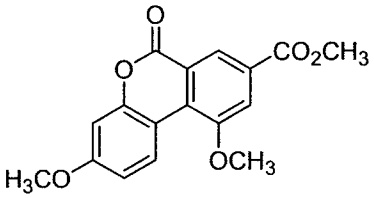
To a magnetically stirred solution of 2-hydroxy-4-methoxybenzaldehyde **381** (5.00 g, 32.9 mmol) and **163** (4.86 mL, 34.5 mmol) in benzene (100 mL) was added piperidine (1.63 mL, 16.5 mmol) dropwise and the resulting mixture was heated at reflux with azeotropic removal of water for 3 h. The reaction mixture was cooled to room temperature, whereupon a white precipitate formed. The mixture was further cooled in an ice/water bath and the precipitate was isolated by suction filtration and the filter cake was washed with cool benzene (50 mL) to afford **382** (6.69 g, 78%). The filtrate was concentrated under reduced pressure and the residue was subjected to flash

chromatography on silica gel (5% ethyl acetate/CH_2Cl_2) to afford **383** (2.13 g, 22%) as a yellow oil.

382: mp 207-208 °C; IR (nujol) 1719 (s), 1604 (s), 1190 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.81 (s, 1H, C4-H), 7.55 (d, *J*=16.2 Hz, 1H, C1'-H), 7.44 (d, *J*=7.8 Hz, 1H, C5-H), 7.05 (d, *J*=15.5 Hz, 1H, C2'-H), 6.88 (dd, *J*=9.0, 2.5 Hz, 1H, C6-H), 6.83 (d, *J*=1.6 Hz, 1H, C8-H), 3.90 (s, 3H, C5'-H), 3.80 (s, 3H, C4'-H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 167.6 (0, C3'), 163.9 (0, C7), 159.3 (0, C2), 155.6 (0, C8a), 143.9 (1, C4), 138.6 (1, C1'), 129.6 (1, C5), 121.8 (1, C2'), 118.8 (0, C3), 113.4 (1, C6), 112.7 (0, C4a), 100.5 (1, C8), 55.9 (3, C5'), 51.8 (3, C4'); EI-MS *m/z* (%) 260 (M^+, 47), 229 (24), 201 (100), 173 (6), 102 (10); Anal. calcd for $C_{14}H_{12}O_5$: C, 64.61; H, 4.65. Found C, 64.23; H, 4.78.

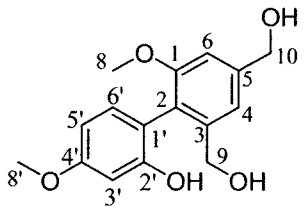
383: IR (neat) 3003 (m), 2953 (s), 2842 (m), 1738 (s), 1706 (s), 1612 (s); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.47 (s, 1H, C4-H), 7.07 (d, *J*=8.2 Hz, 1H, C5-H), 6.51 (dd, *J*=8.3, 2.7 Hz, 1H, C6-H), 6.42 (d, *J*=2.6 Hz, 1H, C8-H), 5.71 (dd, *J*=10.1, 3.3 Hz, 1H, C1-H), 3.81 (s, 3H, C2'-H), 3.79 (s, 3H, C6'-H), 3.72 (s, 3H, C5'-H), 2.80 (dd, *J*=15.2, 9.9 Hz, 1H, C3'-H), 2.57 (dd, *J*=15.7, 3.2 Hz, 1H, C3'-H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 170.3 (0, C4'), 165.0 (0, C1'), 163.4 (0, C7), 154.4 (0, C8a), 133.6 (1, C4), 129.9 (1, C5), 120.7 (0, C3), 113.2 (0, C4a), 108.7 (1, C6), 102.3 (1,C8), 71.0 (1, C2), 55.5 (3, C6'), 52.8 (3, C2' + C5'), 39.6 (2, C3'); EI-MS *m/z* (%) 292 (M^+, 12), 232 (21), 219 (100), 174 (11), 126 (12), 99 (15), 59 (27); HRMS (EI) calcd for $C_{15}H_{16}O_6$: 292.0946, found 292.0958.

4,7-Dimethoxy-9,10-dihydro-9-oxaphenanthren-10-one-2-carboxylic acid methyl ester (389)



A solution of dimethoxyacetaldehyde (60 wt. % solution in water) (19.6 mL, 0.130 mol) and pyrrolidine (9.76 mL, 0.117 mol) in benzene (150 mL) was heated at reflux with azeotropic removal of water for 1 h. The resulting mixture was allowed to cool for 10 min and solid **382** (3.38 g, 13.0 mmol) was added in one portion. The resulting mixture was heated at reflux for 7 d. The reaction mixture was cooled to room temperature then concentrated under reduced pressure. The residue was taken up in CH_2Cl_2 (150 mL) and washed with aqueous 1 M HCl solution (5×50 mL), dried over $MgSO_4$, gravity filtered and, concentrated under reduced pressure to afford **389** (4.08 g, 100%) as a tan solid: mp 195-196 °C; IR (nujol) 1735 (s), 1715 (s), 1607 (m), 1121 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.76 (d, *J*=9.3 Hz, 1H, C5-H), 8.57 (d, *J*=1.1 Hz, 1H, C1-H), 7.80 (d, *J*=1.0 Hz, 1H, C3-H), 6.81 (dd, *J*=9.6, 3.0 Hz, 1H, C6-H), 6.76 (d, *J*=2.6 Hz, 1H, C8-H), 4.08 (s, 3H, C2'-H), 3.96 (s, 3H, C4'-H), 3.87 (s, 3H, C1'-H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 165.6 (0, C3'), 161.3 (0, C7), 160.7 (0, C10), 156.4 (0, C4), 152.7 (0, C8a), 130.0 (1, C5), 129.1 (0), 128.0 (0, C8c), 124.0 (1, C1), 121.3 (0), 116.1 (1, C3), 111.7 (1, C6), 110.0 (0, C8b), 101.3 (1, C8), 56.1 (3, C2'), 55.3 (3, C1'), 52.4 (3, C4'); EI-MS *m/z* (%) 314 (M^+, 100), 299 (53), 283 (13), 212 (4), 157 (4), 77 (2); Anal. calcd for $C_{17}H_{14}O_6$: C, 64.97; H, 4.49. Found C, 65.03; H, 4.61.

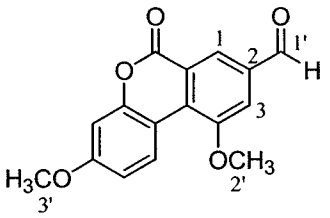
3',6'-Bis-(hydroxymethyl)-4,1'-dimethoxybiphen-2-ol (395)



To a 0 °C slurry of $LiAlH_4$ (1.77 g, 46.6 mmol) in THF (10 mL) was added a solution of **389** (2.32 g, 7.37 mmol) in THF (150 mL) dropwise. The ice/water bath was then removed and the resulting mixture was heated at reflux for 5 h. After cooling to room temperature water (1.7 mL) was added carefully and stirring was continued for 10 min. Aqueous 15% NaOH solution (1.7 mL) was then added and stirring was continued for 10 min. Another portion of water (5.1 mL) was added and stirring was continued for 30 min. The mixture was diluted with aqueous 1 M HCl solution (100 mL) and extracted with EtOAc (3×50 mL). The combined organic layers were dried over $MgSO_4$, gravity filtered and concentrated under reduced pressure to afford **395** (2.01 g, 94%) as a white solid: mp 147.5-148 °C; IR (nujol) 3408 (brs), 1611 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 9.08 (brs, 1H, C2'-OH), 7.11 (s, 1H, C4), 6.85 (s, 1H, C6-H), 6.78 (d, *J*=8.3 Hz, 1H, C6'-H), 6.44 (d, *J*=2.5 Hz, 1H, C3'-H), 6.39 (dd, *J*=8.3, 2.4 Hz, 1H, C5'-H), 5.15 (t, *J*=5.7 Hz, 1H, C10-OH), 4.85 (brs, 1H, C9-OH), 4.52 (d, *J*=5.3 Hz, 2H, C10-H), 4.19 (d, *J*=13.5 Hz, 1H, C9-H), 4.10 (d, *J*=14.3 Hz, 1H, C9-H), 3.72 (s, 3H, C8'-H), 3.61 (s, 3H, C8-H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 159.3 (0, C4'), 156.6 (0, C1), 155.6 (0, C2'), 142.02 (0), 142.00 (0), 131.8 (1, C6'), 123.2 (0, C2), 116.3 (1, C4), 115.6 (0, C1'), 107.4 (1, C6), 104.2 (1, C5'), 101.2 (1, C3'), 63.3 (2, C10), 60.7 (2, C9), 55.3 (3, C8), 54.8 (3,

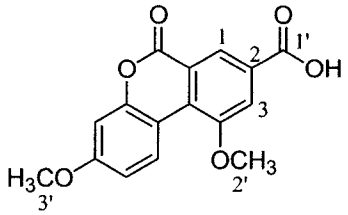
C8); EI-MS *m/z* (%) 290 (M^+, 29), 272 (100), 257 (50), 241 (21), 227 (5), 128 (8); HRMS (EI) calcd for $C_{16}H_{18}O_5$: 290.1153, found 290.1152.

2-Formyl-4,7-dimethoxy-9,10-dihydro-9-oxaphenanthren-10-one (396)



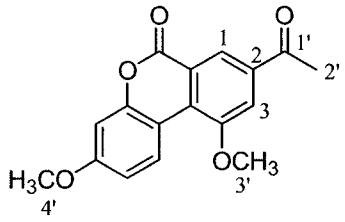
To a magnetically stirred solution of **395** (241 mg, 0.831 mmol) in benzene (50 mL) was added freshly made Fétizon reagent (8.55 g, 12.5 mmol) in one portion and the resulting mixture was heated at reflux for 24 h. The mixture was cooled to room temperature then suction filtered to remove the excess Fétizon reagent.[181] The filtrate was concentrated under reduced pressure and the residue was subjected to flash chromatography on silica gel (4% ethyl acetate/CH_2Cl_2) to afford **396** (0.234 g, 99%) as a white solid: mp 225-227 °C; IR (nujol) 1731 (s), 1699 (s), 1622 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 10.07 (s, 1H, C3'-H), 8.93 (d, *J*=8.8 Hz, 1H, C5-H), 8.51 (d, *J*=1.7 Hz, 1H, C1-H), 7.78 (d, *J*=1.6 Hz, 1H, C3-H), 6.93-6.89 (m, 2H, C6-H + C8-H), 4.14 (s, 3H, C2'-H), 3.91 (s, 3H, C1'-H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 190.5 (1, C3'), 161.9 (0, C7), 160.7 (0, C10), 157.3 (0, C4), 153.3 (0, C8a), 135.3 (0), 130.5 (1, C5), 130.2 (0, C4a), 127.4 (1, C1), 121.9 (0), 112.9 (0), 112.4 (1, C3), 112.2 (1, C6), 101.5 (1, C8), 56.3 (3, C2'), 55.7 (3, C1'); EI-MS *m/z* (%) 284 (M^+, 100), 269 (56), 254 (7), 198 (6), 142 (9), 114 (6); HRMS (EI) calcd for $C_{16}H_{12}O_5$: 284.0684, found 284.0685.

4,7-Dimethoxy-9,10-dihydro-9-oxaphenanthren-10-one-2-carboxylic acid (399)



A solution of **389** (1.22 g, 3.89 mmol) in 9:1 1M NaOH/EtOH (100 mL) was heated at reflux for 1 h. The heat source was removed and the pH of the reaction was immediately made acidic using aqueous concentrated HCl while the mixture was still hot. Once acidic, a white precipitate formed. The mixture was cooled to room temperature and the precipitate was isolated by suction filtration to afford **399** (1.17 g, 100 %) as a white solid: mp > 300 °C; IR (nujol) 3158-2465 (brs), 1737 (s), 1690 (s), 1610 (s) cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ 13.44 (brs, 1H, -CO_2H), 8.77 (d, *J*=8.5 Hz, 1H, C5-H), 8.32 (d, *J*=1.5 Hz, 1H, C1-H), 7.83 (d, *J*=1.7 Hz, 1H, C3-H), 6.95 (d, *J*=2.5 Hz, 1H, C8-H), 6.92 (dd, *J*=9.6, 2.8 Hz, 1H, C6-H), 4.08 (s, 3H, C2'-H), 3.86 (s, 3H, C3'-H); ^{13}C NMR (DMSO-d_6, 125.8 MHz) δ 165.9 (0, C1'), 161.0 (0, C7), 159.9 (0, C10), 156.3 (0, C4), 152.3 (0, C8a), 130.2 (0), 129.6 (1, C5), 126.9 (0, C4a), 122.7 (1, C1), 120.9 (0), 116.4 (1, C3), 111.8 (0, C6), 109.5 (0, 4b), 101.3 (1, C8), 56.3 (3, C2'), 55.7 (3, C3'); EI-MS *m/z* (%) 300 (M^+, 100), 285 (57), 214 (6), 150 (4), 113 (4); Anal. calcd for $C_{16}H_{12}O_6$: C, 64.00; H, 4.03. Found C, 63.88; H, 4.00.

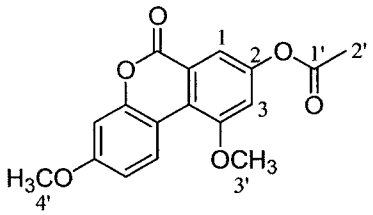
4,7-Dimethoxy-2-(1-oxoethyl)-9,10-dihydro-9-oxaphenanthren-10-one (400)



To a slurry of **399** (2.00 g, 6.66 mmol) in THF (80 mL) at 0 °C (ice/water bath) was added NaH (60% dispersion in mineral oil) (0.296 g, 7.33 mmol) slowly and the resulting mixture was allowed to stir and warm to room temperature for 1 h. The mixture was concentrated under reduced pressure and freshly distilled oxalyl chloride (70 mL) was added to the residue. The resulting mixture was then heated at reflux for 12 h, cooled to room temperature and concentrated under reduced pressure. THF (80 mL) was added to the residue and the mixture was cooled to 0 °C (ice/water bath). A 2 M solution of $Zn(CH_3)_2$ in hexanes (1.3 mL, 20 mmol) was added dropwise followed by $Pd(PPh_3)_4$ (80 mg, 0.15 mmol) in one portion and the mixture was stirred at room temperature for 4 d. The reaction was quenched with aqueous saturated ammonium chloride solution (50 mL) and stirred at room temperature for 30 min. The THF was removed under reduced pressure. To the remaining aqueous mixture was added CH_2Cl_2 (500 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2×50 mL) and the combined organic layers were dried over $MgSO_4$, gravity filtered and concentrated under reduced pressure. The residue was then subjected to flash chromatography on silica gel (5% ethyl acetate/CH_2Cl_2) to afford **400** (1.67 g, 84%) as a white solid: mp 249-250 °C; IR (nujol) 1731 (s), 1676 (s), 1629 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.91 (d,

J=9.0 Hz, 1H, C5-H), 8.58 (d, *J*=1.3 Hz, 1H, C1-H), 7.91 (d, *J*=1.8 Hz, 1H, C3-H), 6.92-6.88 (m, 2H, C6-H + C8-H), 4.12 (s, 3H, C3'-H), 3.90 (s, 3H, C4'-H), 2.71 (s, 3H, C2'-H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 196.5 (0, C1'), 161.7 (0, C7), 161.0 (0, C10), 157.0 (0, C4), 153.0 (C8a), 136.0 (0, C2), 130.3 (1, C5), 128.9 (0, C4a), 123.8 (1, C1), 121.5 (0, C10a), 114.1 (1, C3), 112.1 (1, C6), 110.2 (0, C4b), 101.5 (1, C8), 56.2 (3, C3'), 55.7 (3, C4'), 26.5 (3, C2'); GC-MS *m/z* (%) 298 (M^+, 100), 283 (98), 255 (16), 212 (16), 141 (9), 113 (9); HRMS (EI) calcd for $C_{17}H_{14}O_5$: 298.0840, found 298.0862.

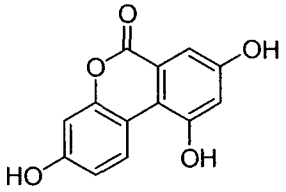
2-Acetoxy-4,7-dimethoxy-9,10-dihydro-9-oxaphenanthren-10-one (401)



To a magnetically stirred solution of **400** (114 mg, 0.382 mmol) and *m*-CPBA (0.503 g, 1.91 mmol) in CH_2Cl_2 (5 mL) was added trifluoroacetic acid (0.03 mL, 0.4 mmol) dropwise and the resulting mixture was stirred for 4 d at room temperature. The reaction was diluted with CH_2Cl_2 (25 mL) and then concentrated under reduced pressure onto silica gel. The residue was immediately subjected to flash chromatography on silica gel (4% ethyl acetate/ CH_2Cl_2) to afford **401** (88.9 mg, 74%) as a white solid: mp 207-208 °C; IR (nujol) 1769 (s), 1726 (s), 1621 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.80 (d, *J*=9.6 Hz, 1H, C5-H), 7.70 (d, *J*=3.1 Hz, 1H, C1-H), 7.08 (d, *J*=2.8 Hz, 1H, C3-H), 6.88-6.86 (m, 2H, C6-H + C8-H), 4.04 (s, 3H, C3'-H), 3.88 (s, 3H, C4'-H), 2.36 (s, 3H, C2'-

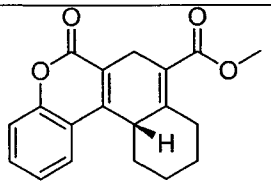
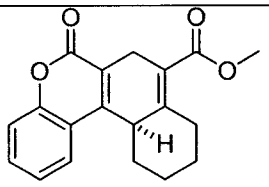
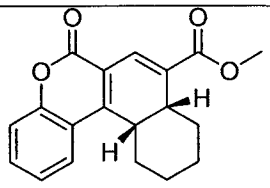
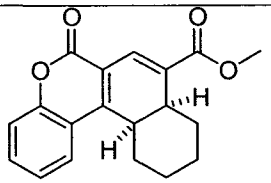
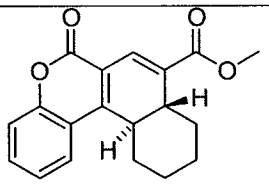
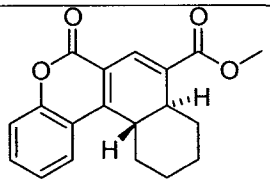
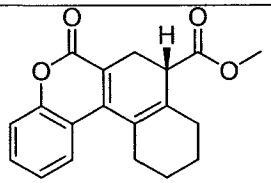
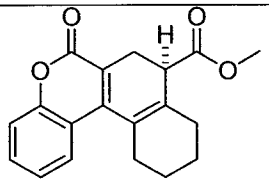
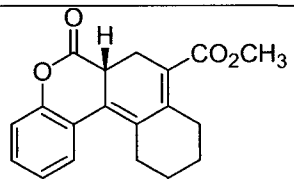
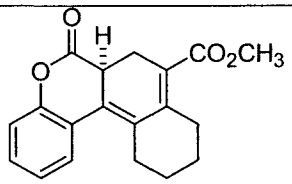
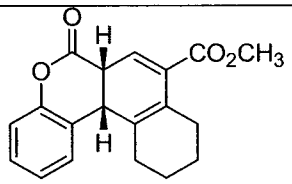
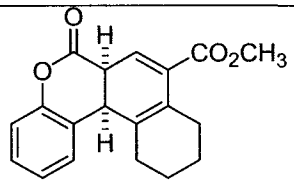
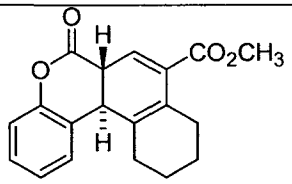
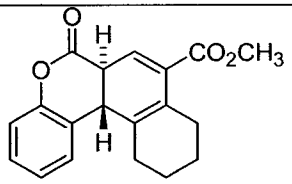
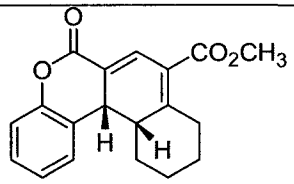
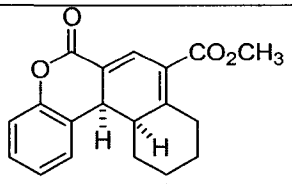
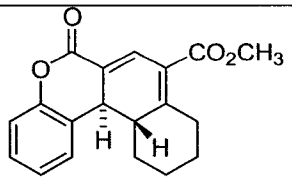
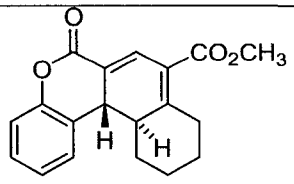
H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 169.0 (0, C1'), 160.8 (0, C10), 160.5 (0, C7), 157.6 (0, C4), 152.0 (0, C8a), 149.9 (0, C2), 129.1 (1, C5), 122.7 (0, C4a), 122.3 (0, C10a), 114.7 (1, C1), 111.8 (1, C6), 111.1 (1, C3), 110.4 (0, C4b), 101.4 (1, C8), 56.2 (3, C3'), 55.5 (3, C4'), 21.1 (3, C2'); GC-MS *m/z* (%) 314 (M^+, 16), 272 (100), 257 (43), 228 (8), 185 (6), 115 (3); HRMS (EI) calcd for $C_{17}H_{14}O_6$: 314.0789, found 314.0773.

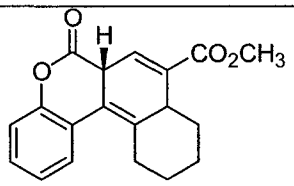
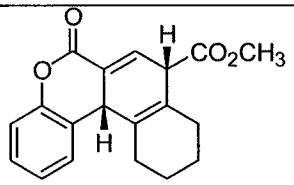
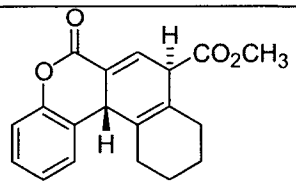
2,4,7-Trihydroxy-9,10-dihydro-9-oxaphenanthren-10-one (373)



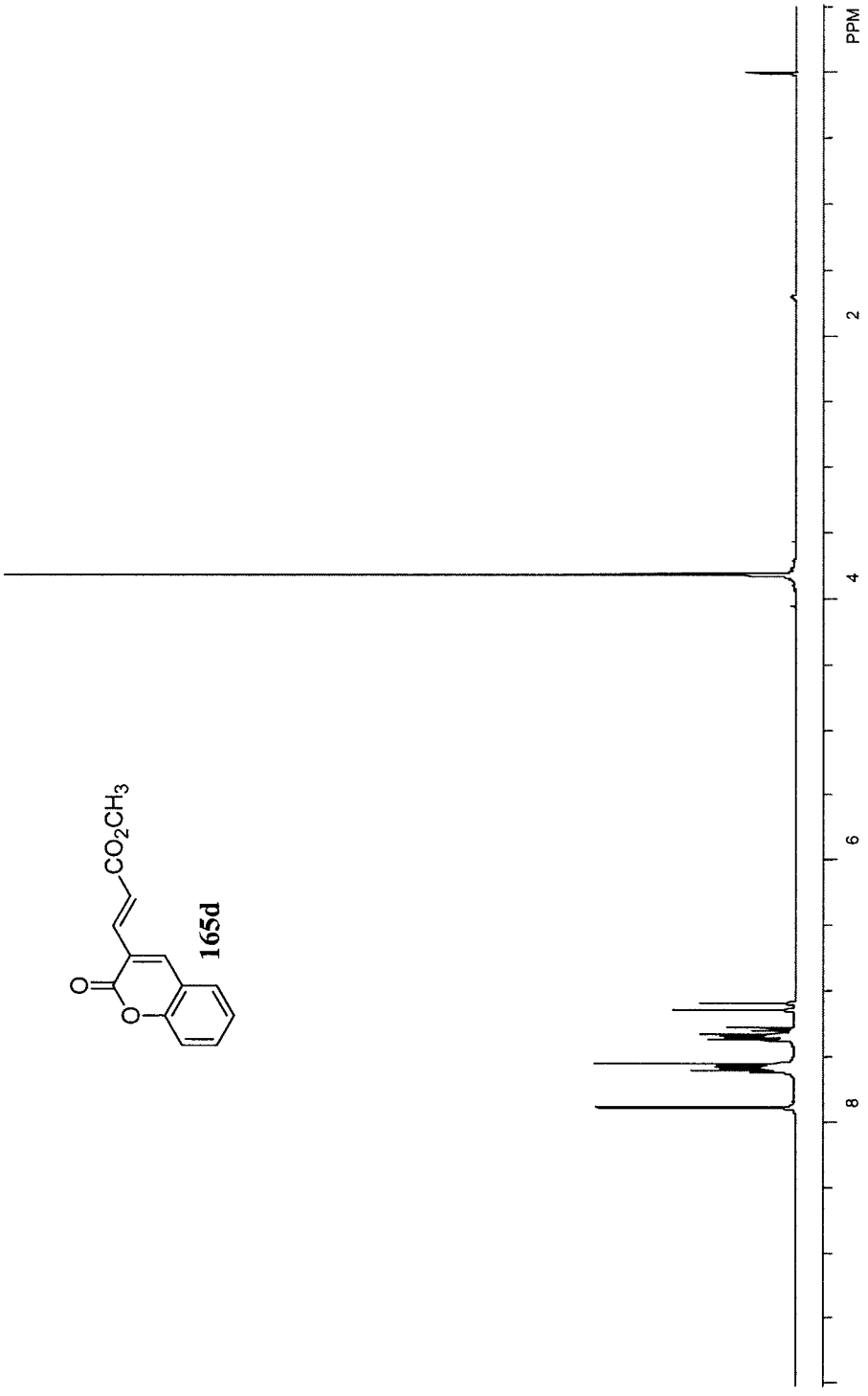
To **401** (20.1 mg, 0.0639 mmol) was added aqueous 65% HI solution (5 mL) and the resulting mixture was heated at reflux for 30 min. The reaction was cooled to room temperature and the solid was isolated by suction filtration using a sintered glass funnel. The solid was washed with cold water (5 mL) and allowed to dry under reduced pressure in a dessicator for 24 h to afford **373** (15.3 mg, 98%) as a white solid: mp >300 °C (lit. mp[177] >300 °C), IR (nujol) 3418 (m), 1700 (s), 1617 (m) cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 10.76 (s, 1H), 10.01 (s, 1H), 9.97 (s, 1H), 8.74 (d, *J*=9.0 Hz, 1H), 7.12 (d, *J*=2.8 Hz, 1H); 6.85 (d, *J*=2.0 Hz, 1H), 6.69 (dd, *J*=8.8, 2.5 Hz, 1H); ^{13}C NMR (DMSO-d_6, 125.8 MHz) δ 160.7, 157.2, 157.0, 156.0, 150.2, 127.9, 121.6, 114.7, 112.3, 109.91, 109.86, 105.9, 102.6; EI-MS *m/z* (%) 244 (M^+, 3).

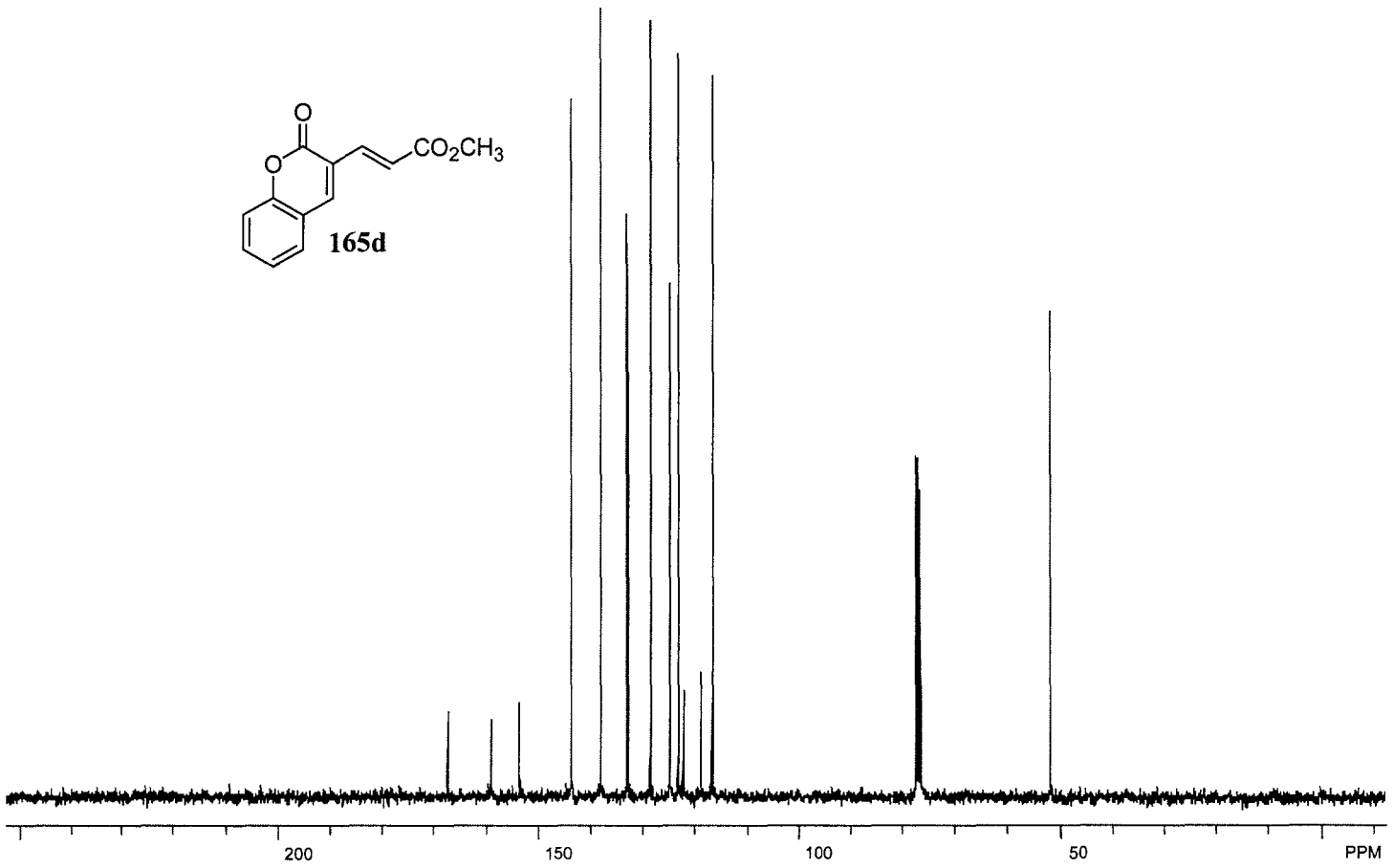
Appendix 1: Heats of formation of possible products from the reaction of diene **165d** and enamine **216** (units = kcal/mol).

 AM1: –103.97 PM3: –107.85	 AM1: –103.89 PM3: –107.78	 AM1: –99.01 PM3: –103.94
 AM1: –99.15 PM3: –104.05	 AM1: –98.39 PM3: –101.85	 AM1: –98.10 PM3: –100.59
 AM1: –104.97 PM3: –109.26	 AM1: –103.42 PM3: –109.11	 AM1: –116.16 PM3: –106.82
 AM1: –116.40 PM3: –107.03	 AM1: –96.02 PM3: –116.87	 AM1: –94.28 PM3: –116.95
 AM1: –97.20 PM3: –110.49	 AM1: –99.10 PM3: –111.86	 AM1: –97.41 PM3: –105.60
 AM1: –97.75 PM3: –101.09	 AM1: –96.16 PM3: –98.03	 AM1: –96.32 PM3: –98.14

 AM1: –114.61 PM3: –117.88	 AM1: –99.77 PM3: –105.19	 AM1: –111.49 PM3: –112.86

Appendix 2: Selected NMR Spectra

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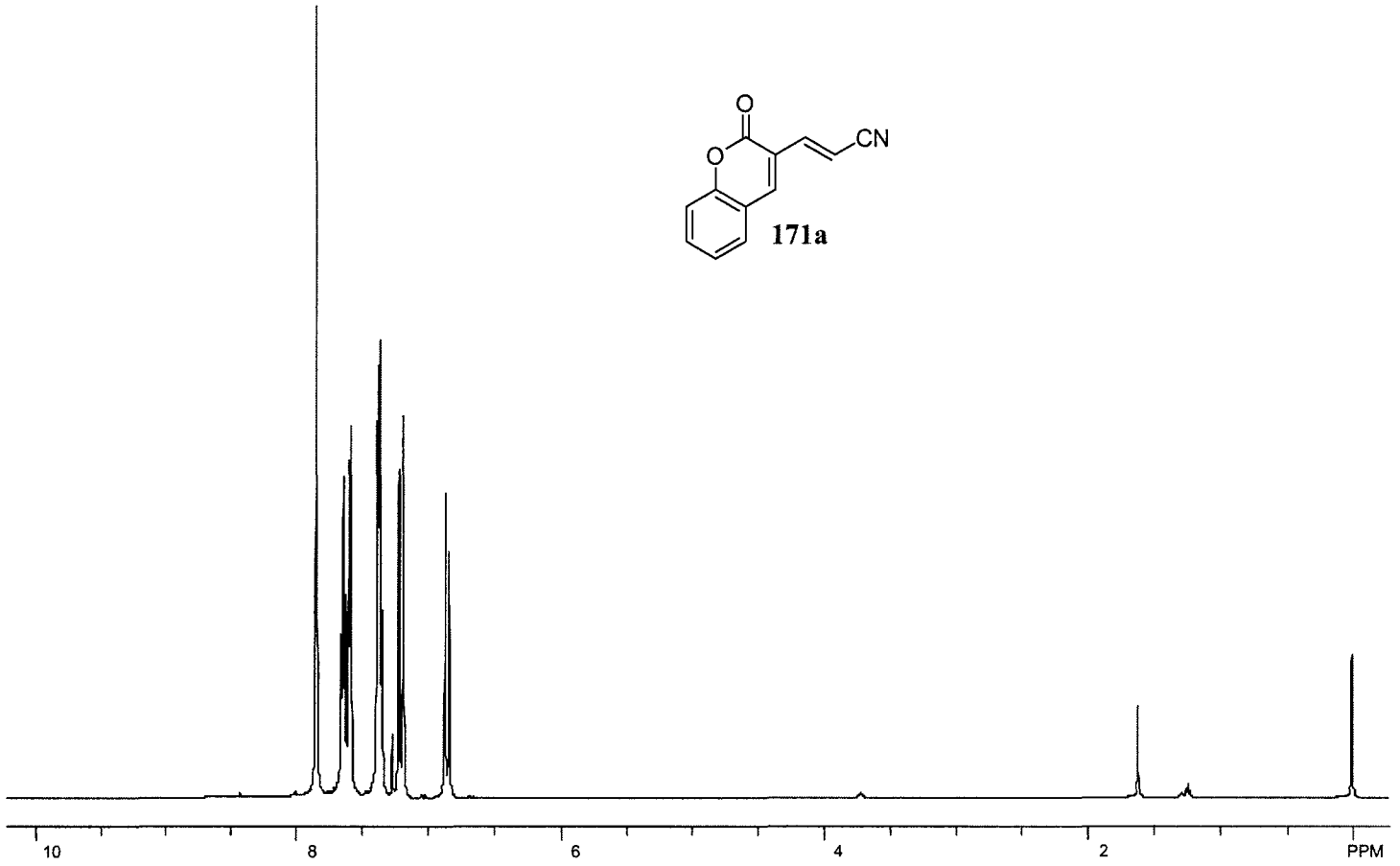
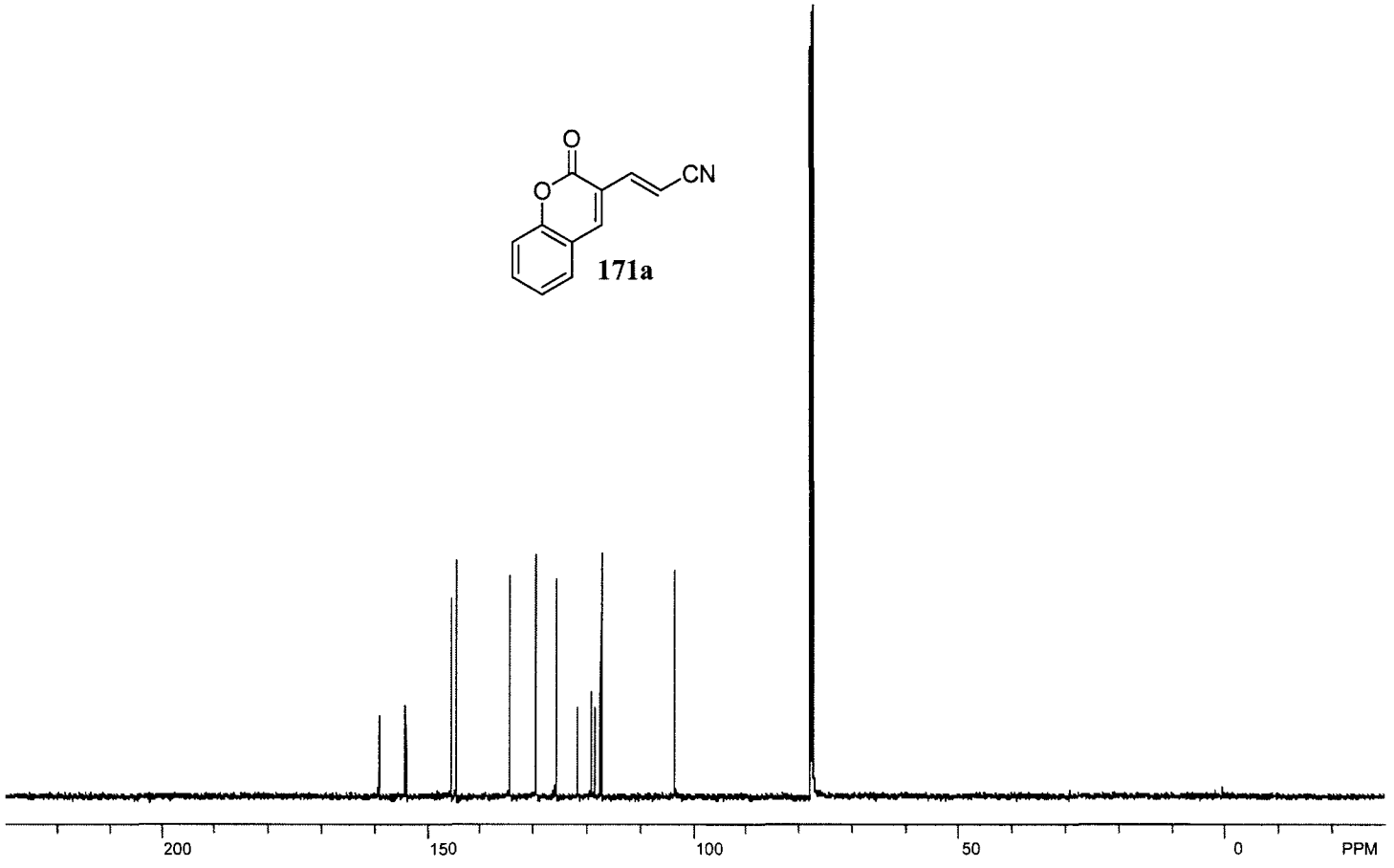
O
CO_2CH_3
165d
200
150
100
50
PPM


O
O
CN
171a
10
8
6
4
2
PPM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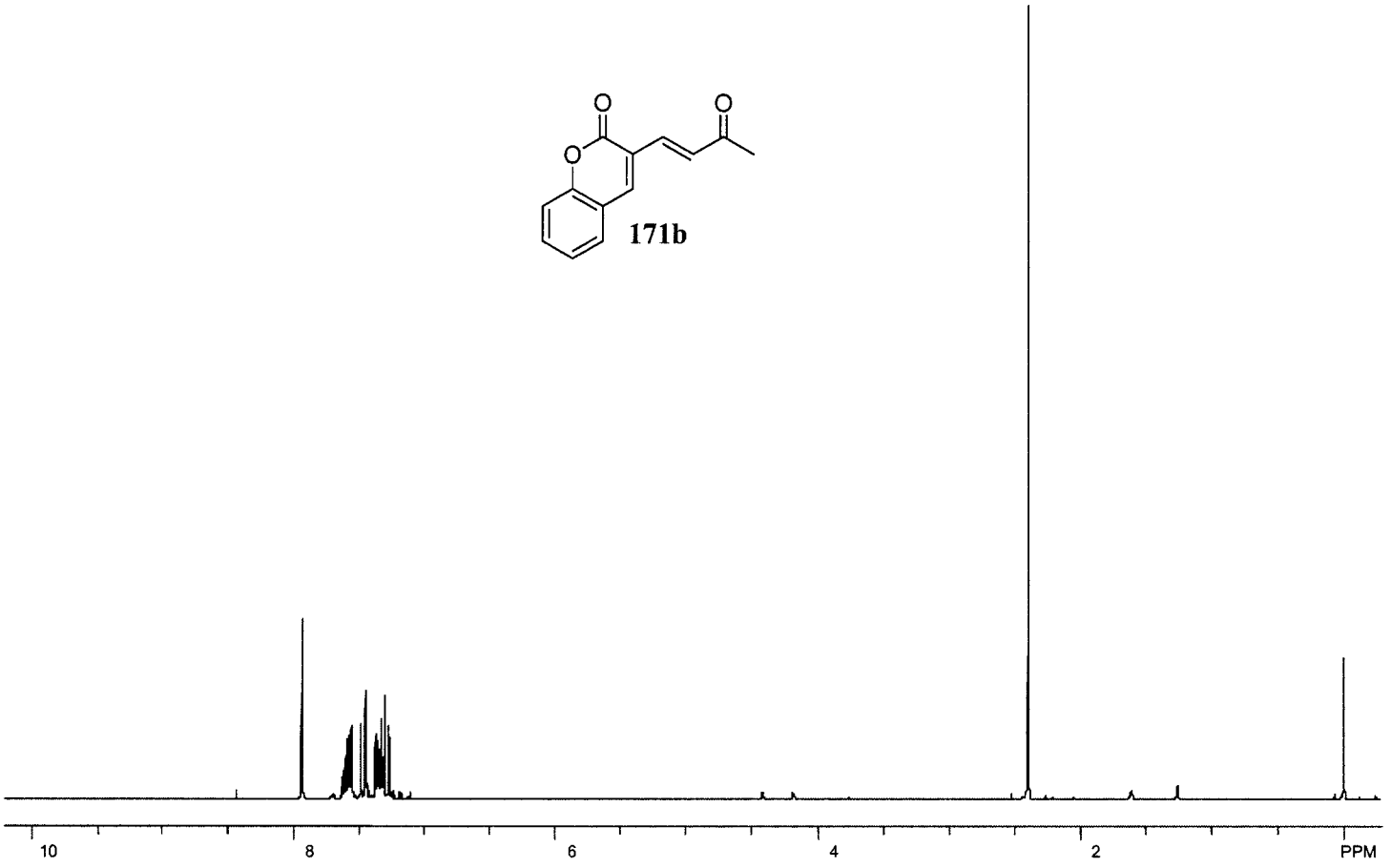
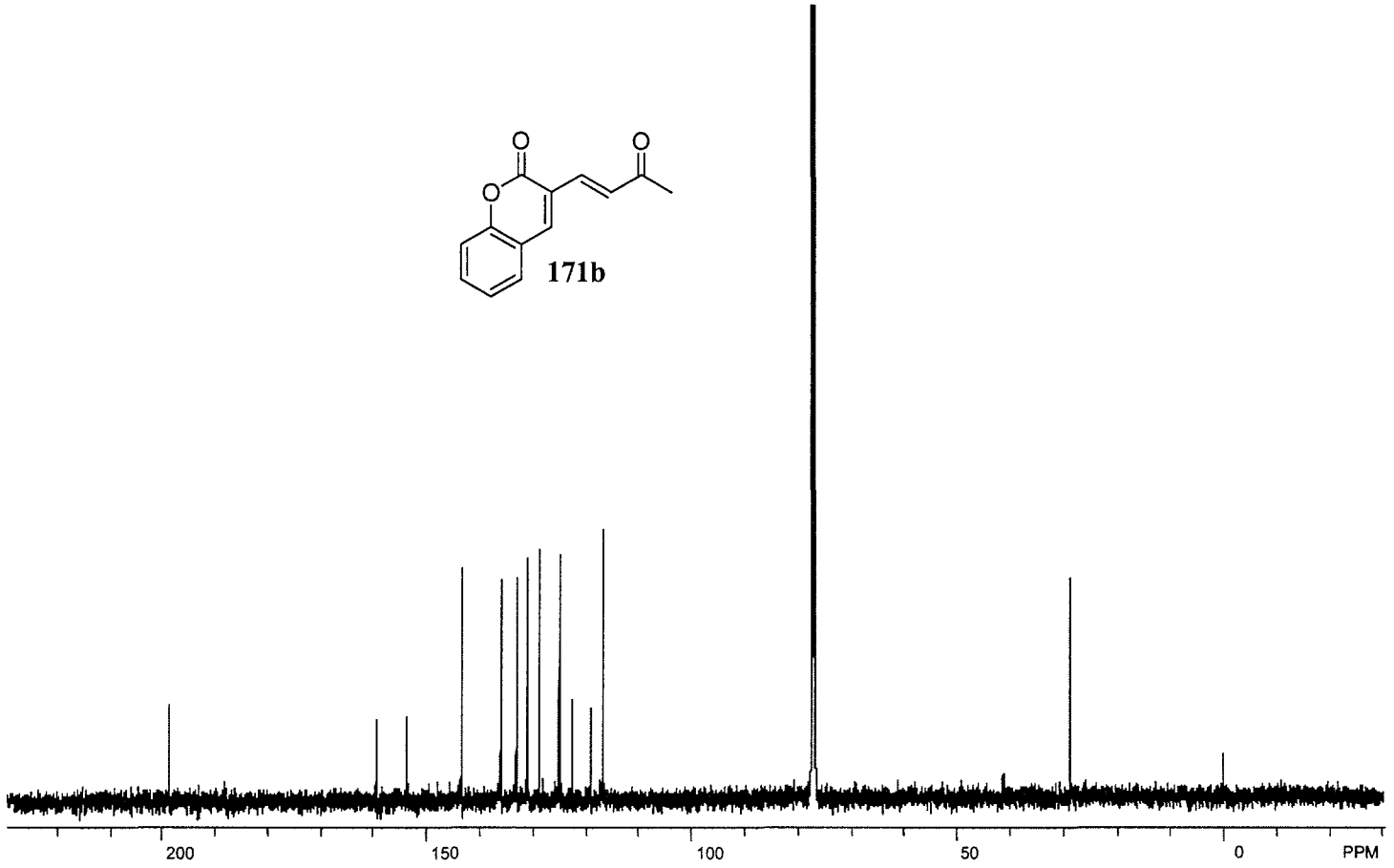
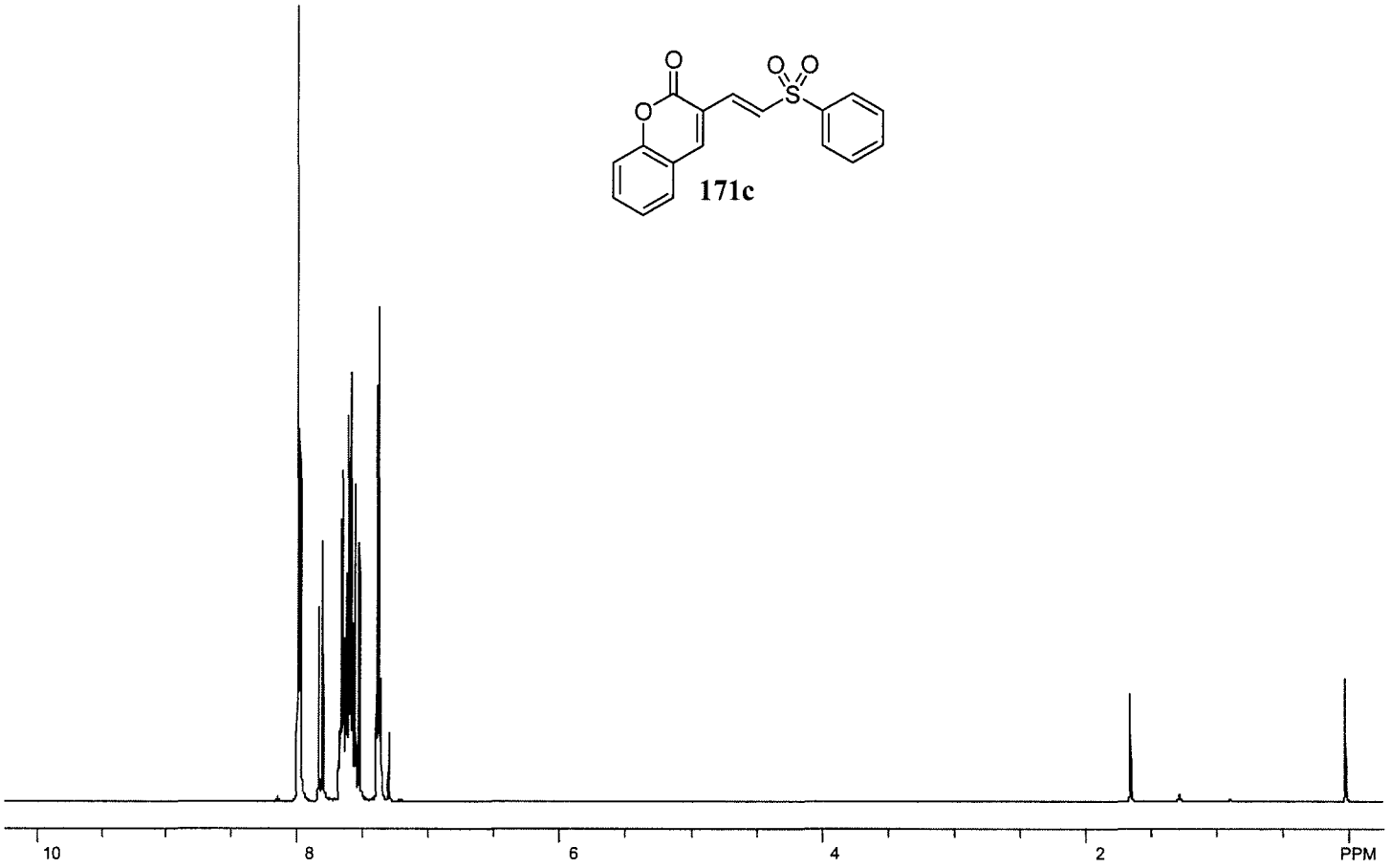
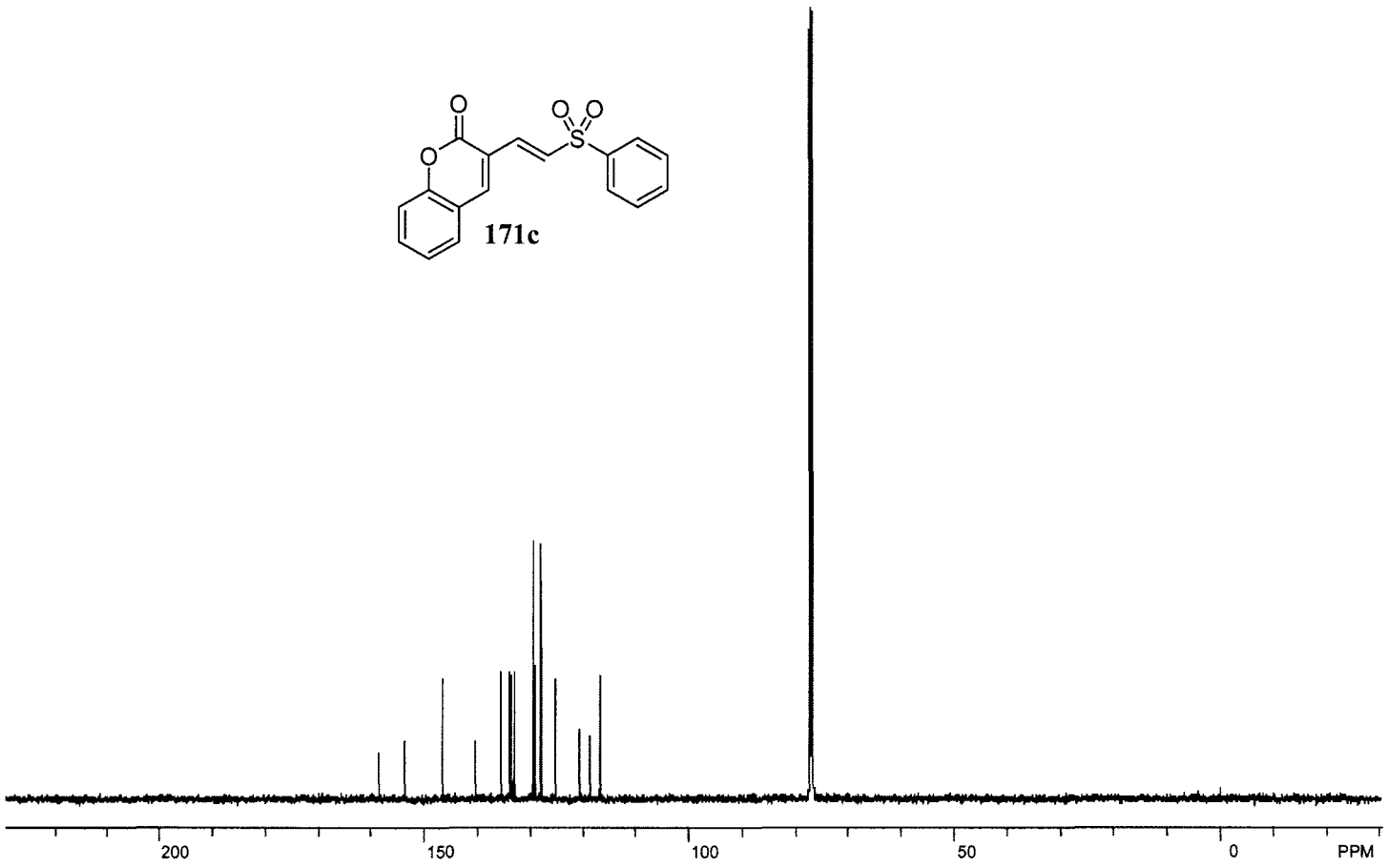
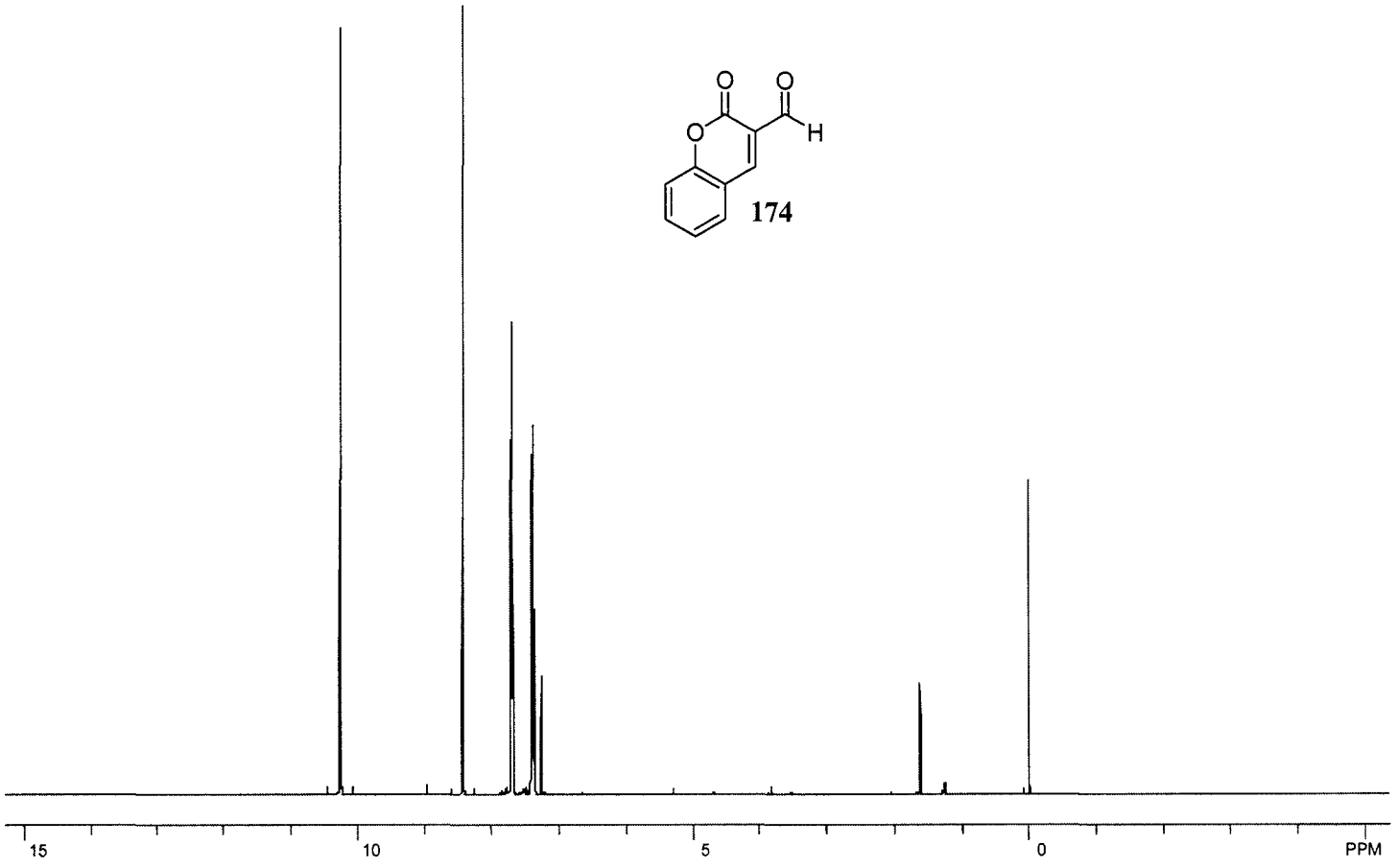
O
CN
171a
200
150
100
50
0
PPM


171b
10
8
6
4
2
PPM


171b
200
150
100
50
0
PPM


171c
10
8
6
4
2
PPM


171c
200
150
100
50
0
PPM



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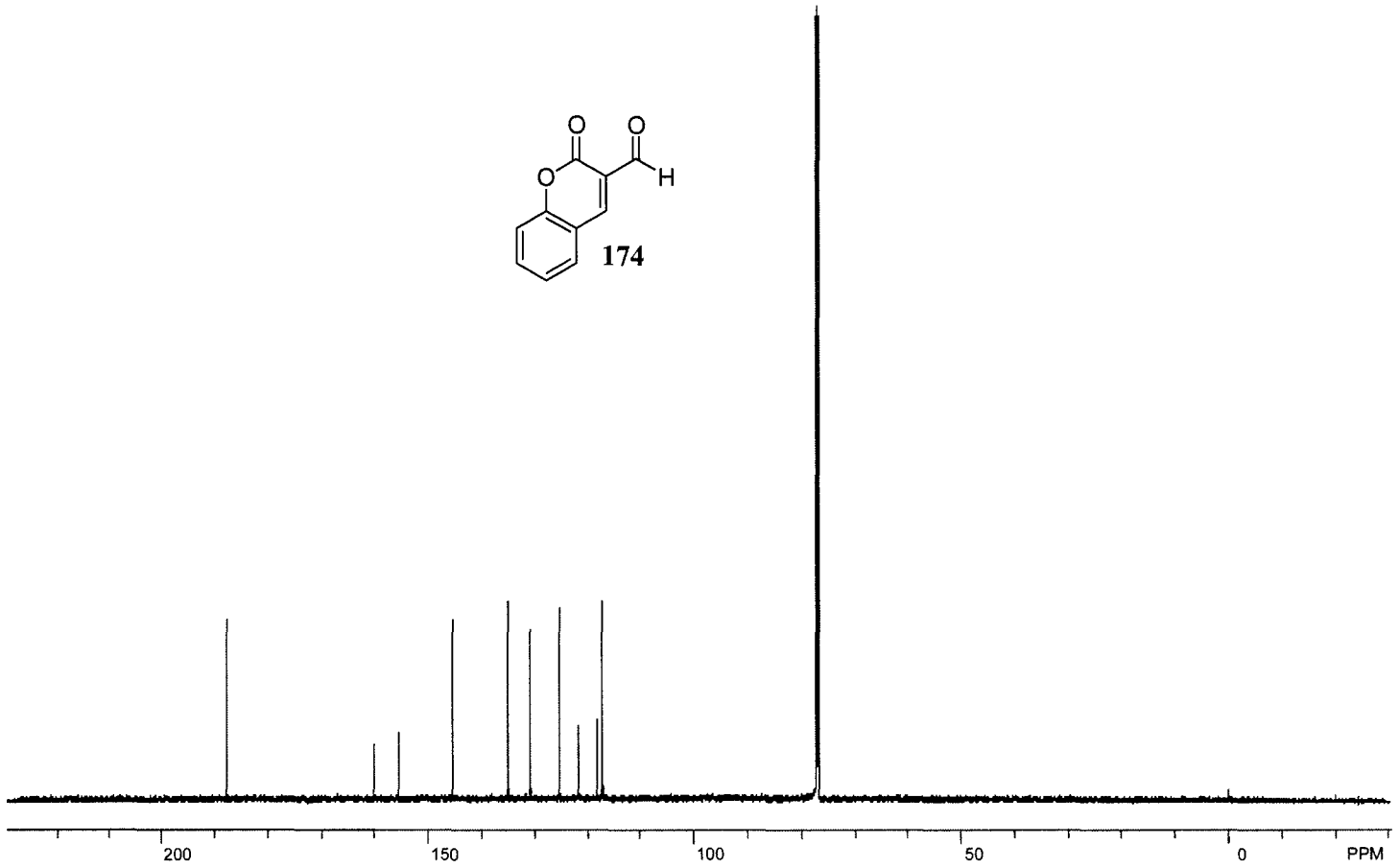

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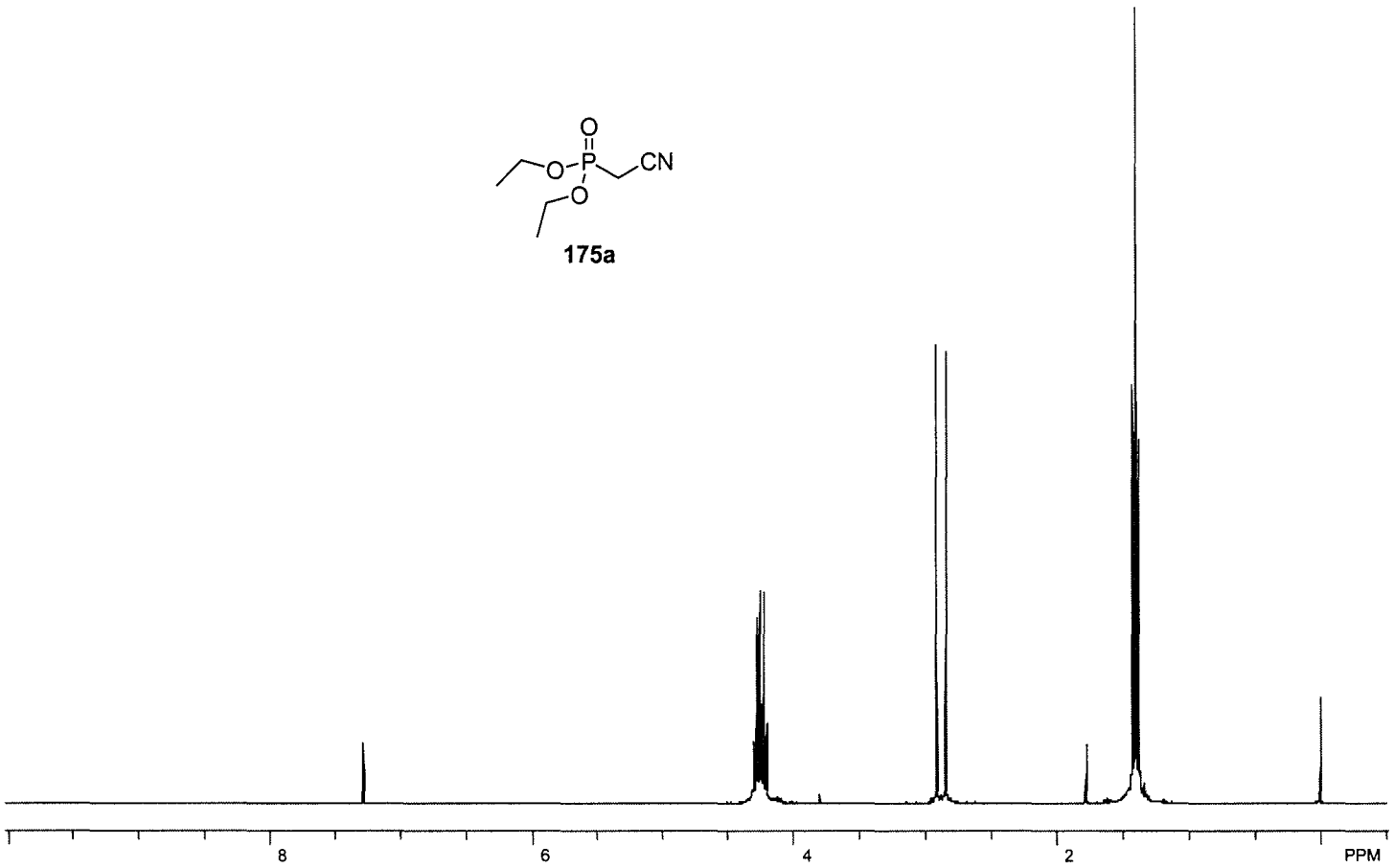

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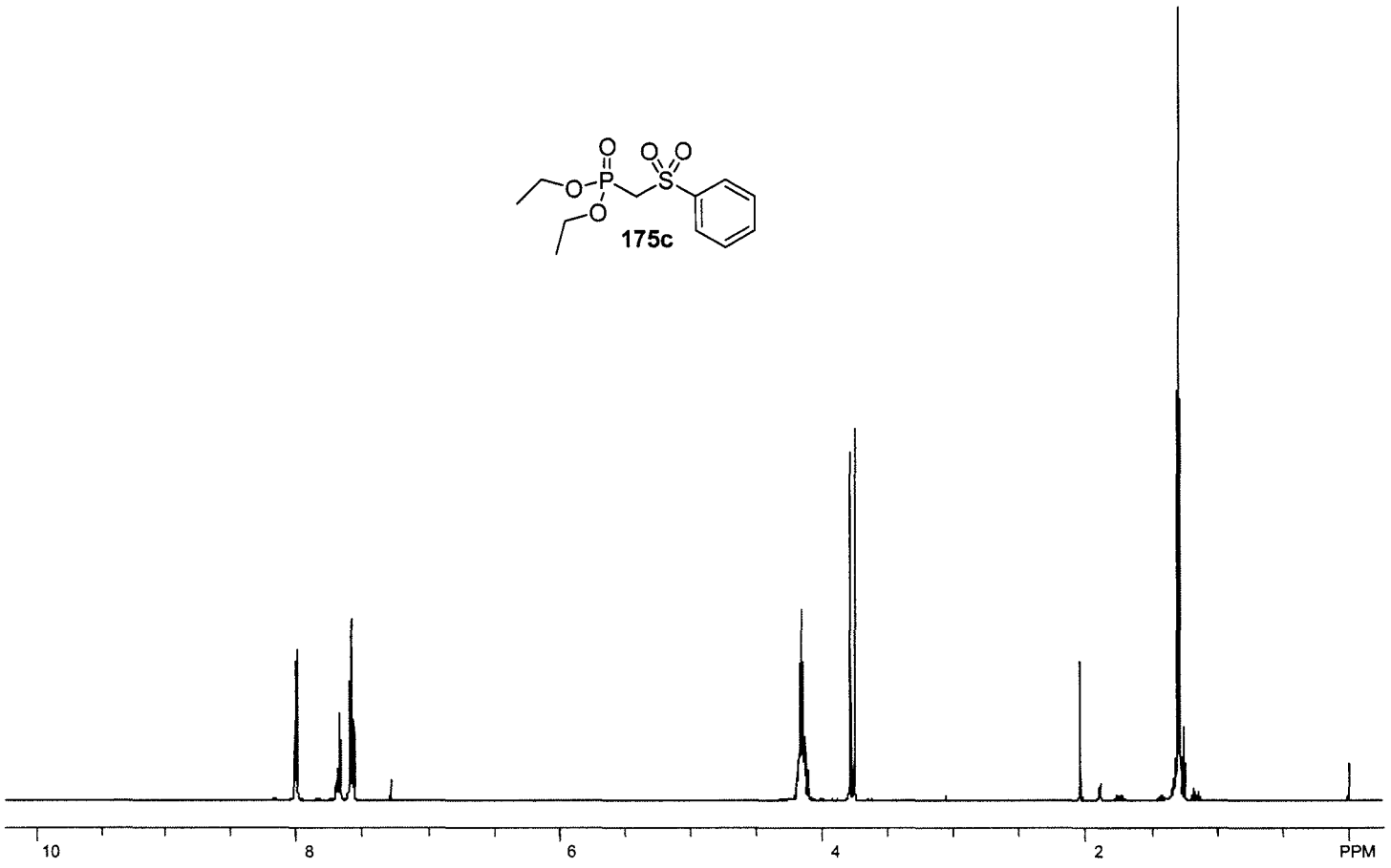
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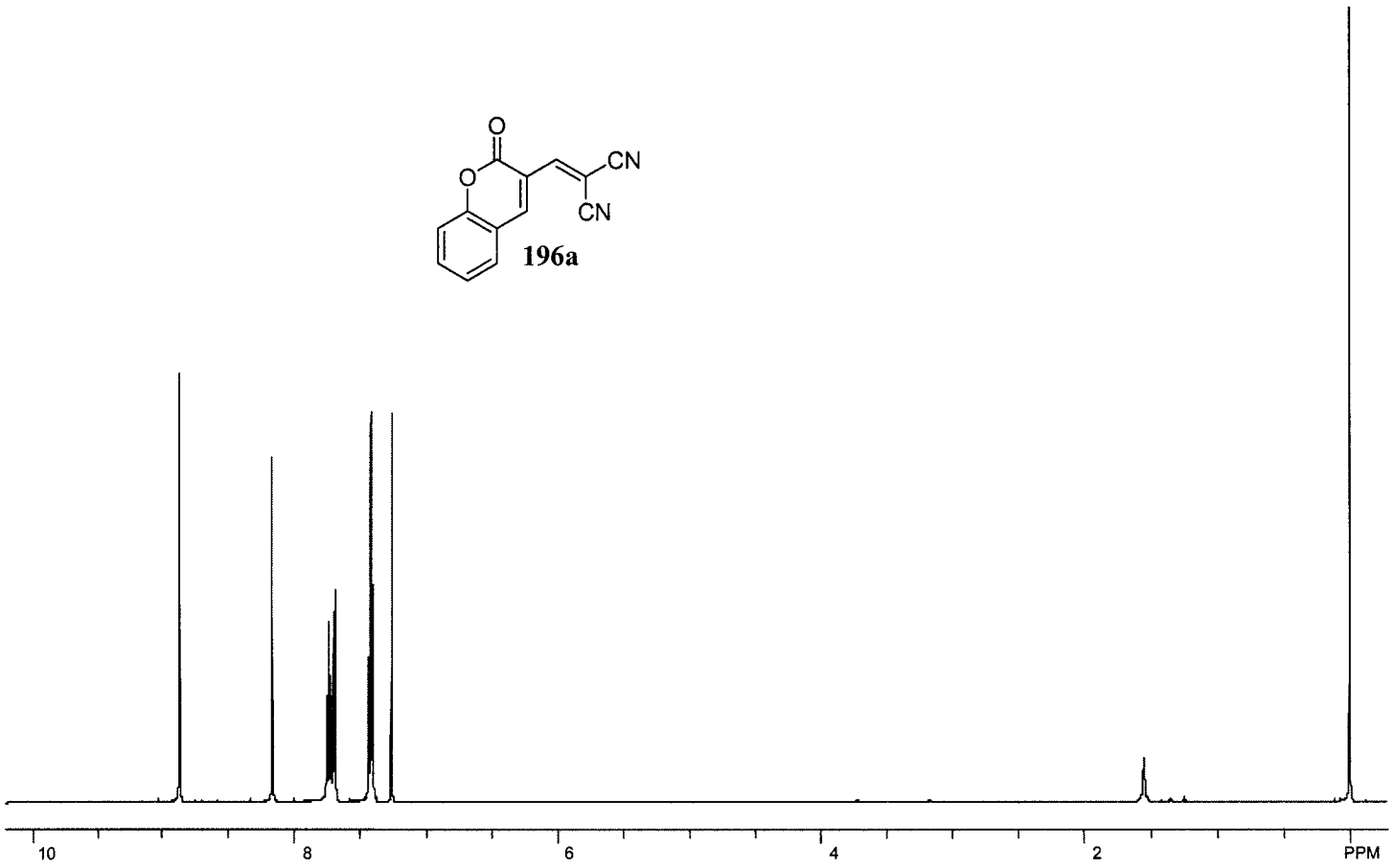

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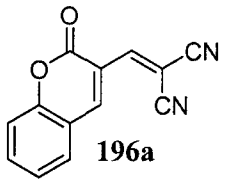

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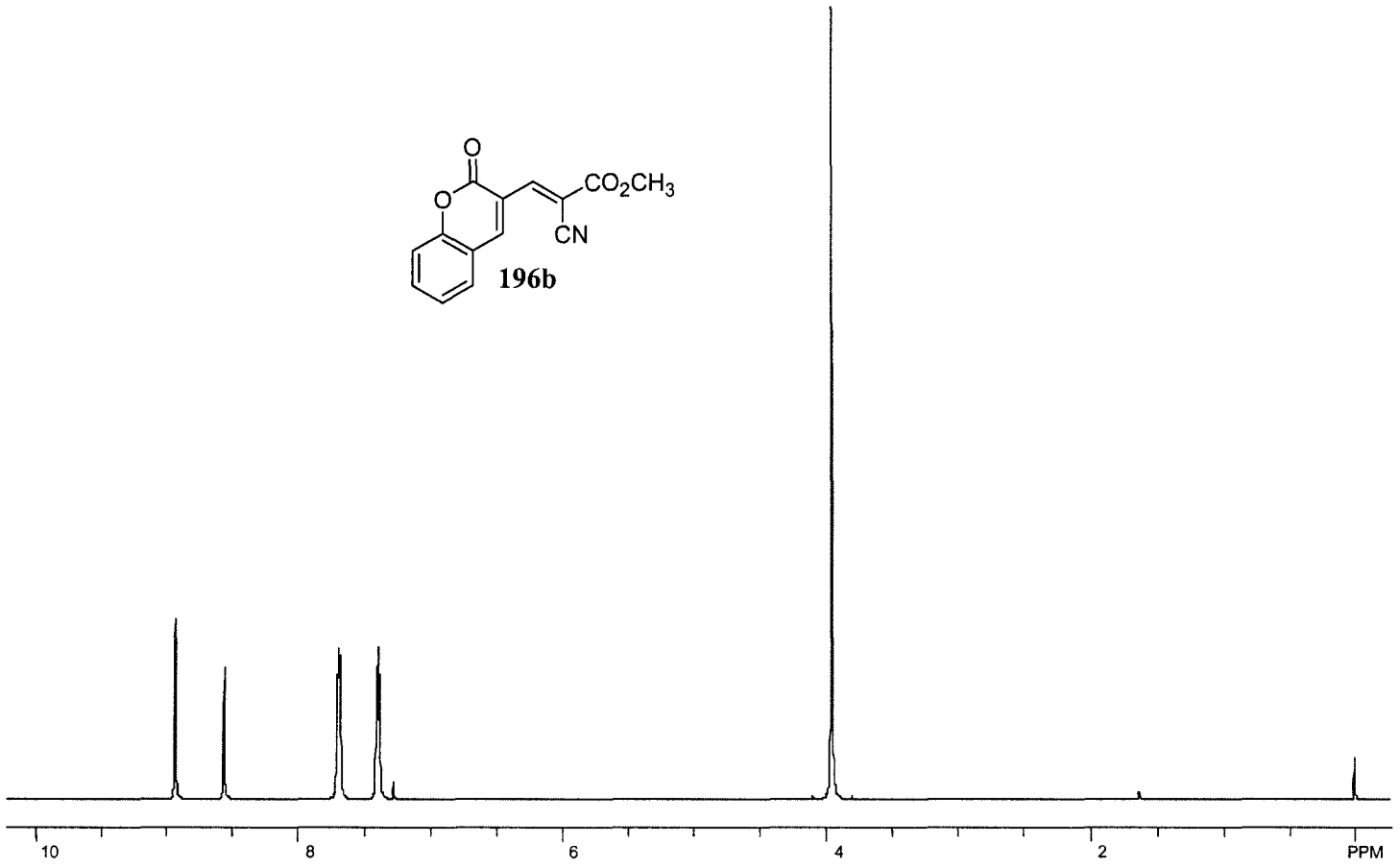
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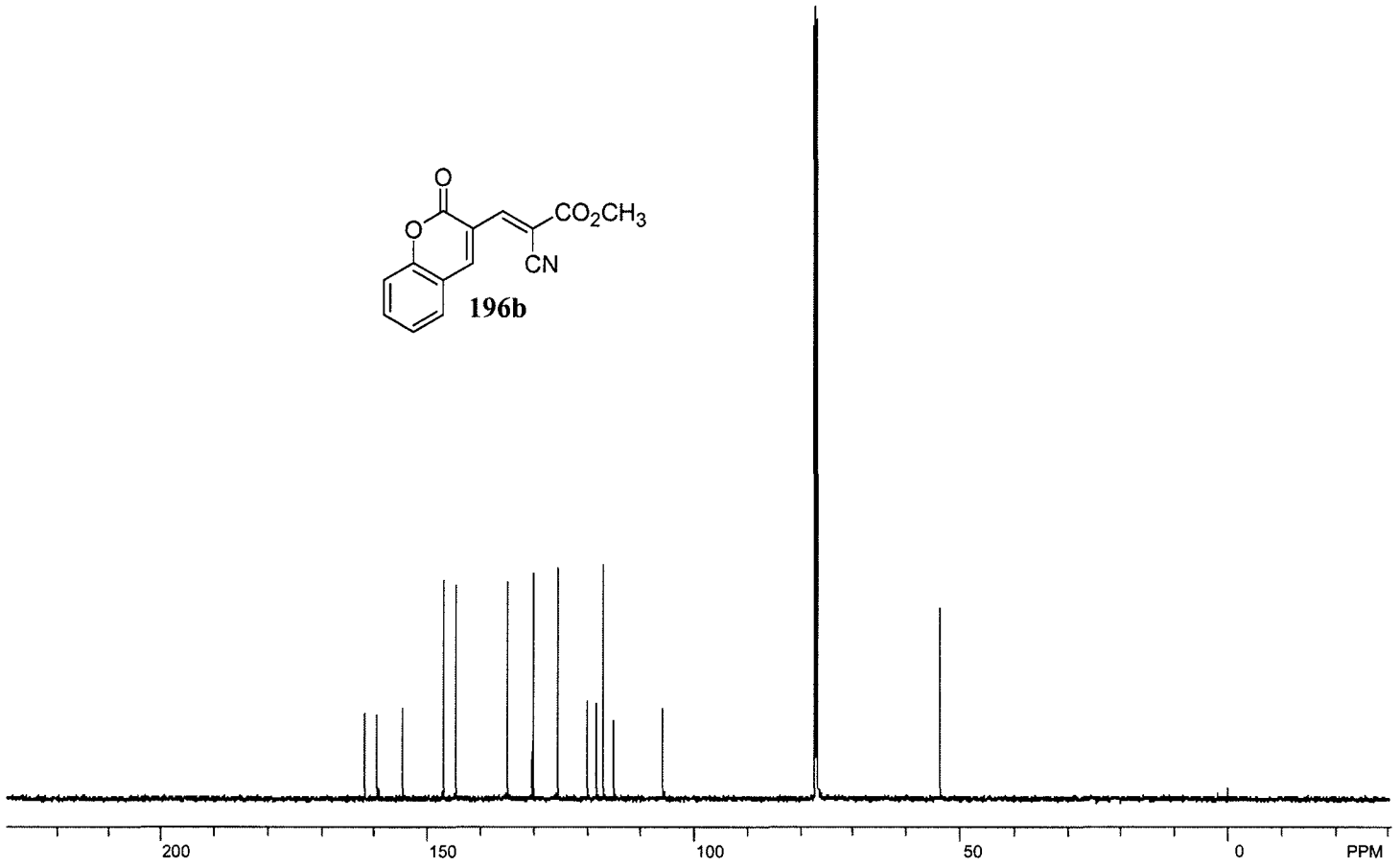
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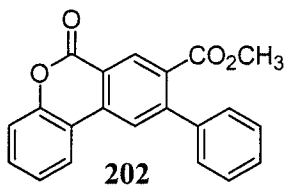

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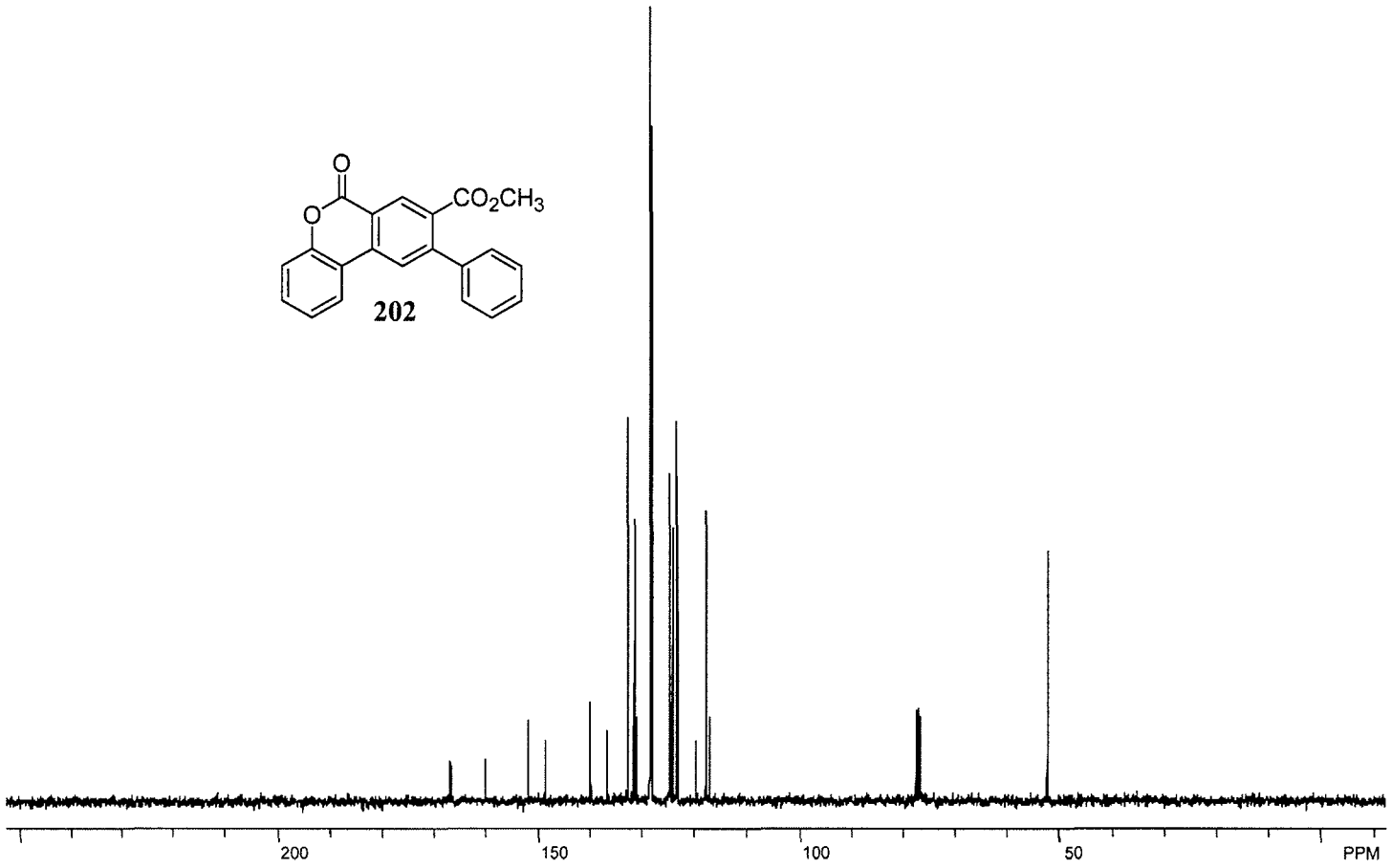

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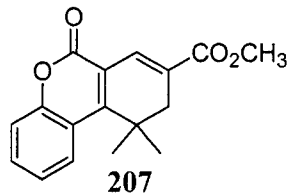

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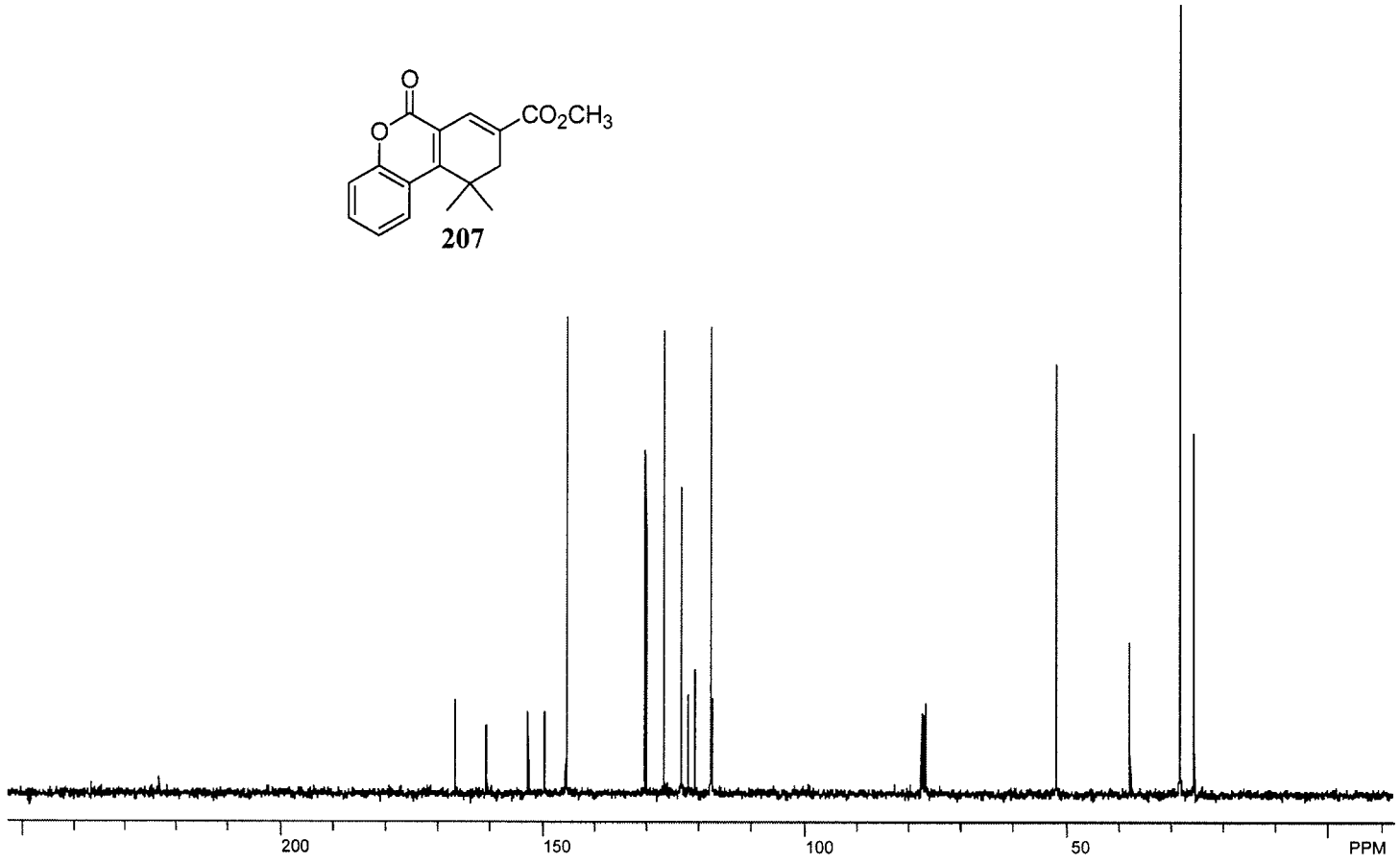

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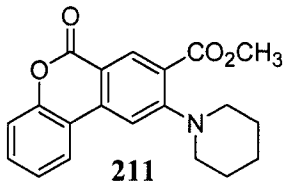

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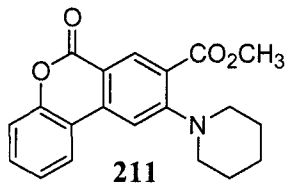

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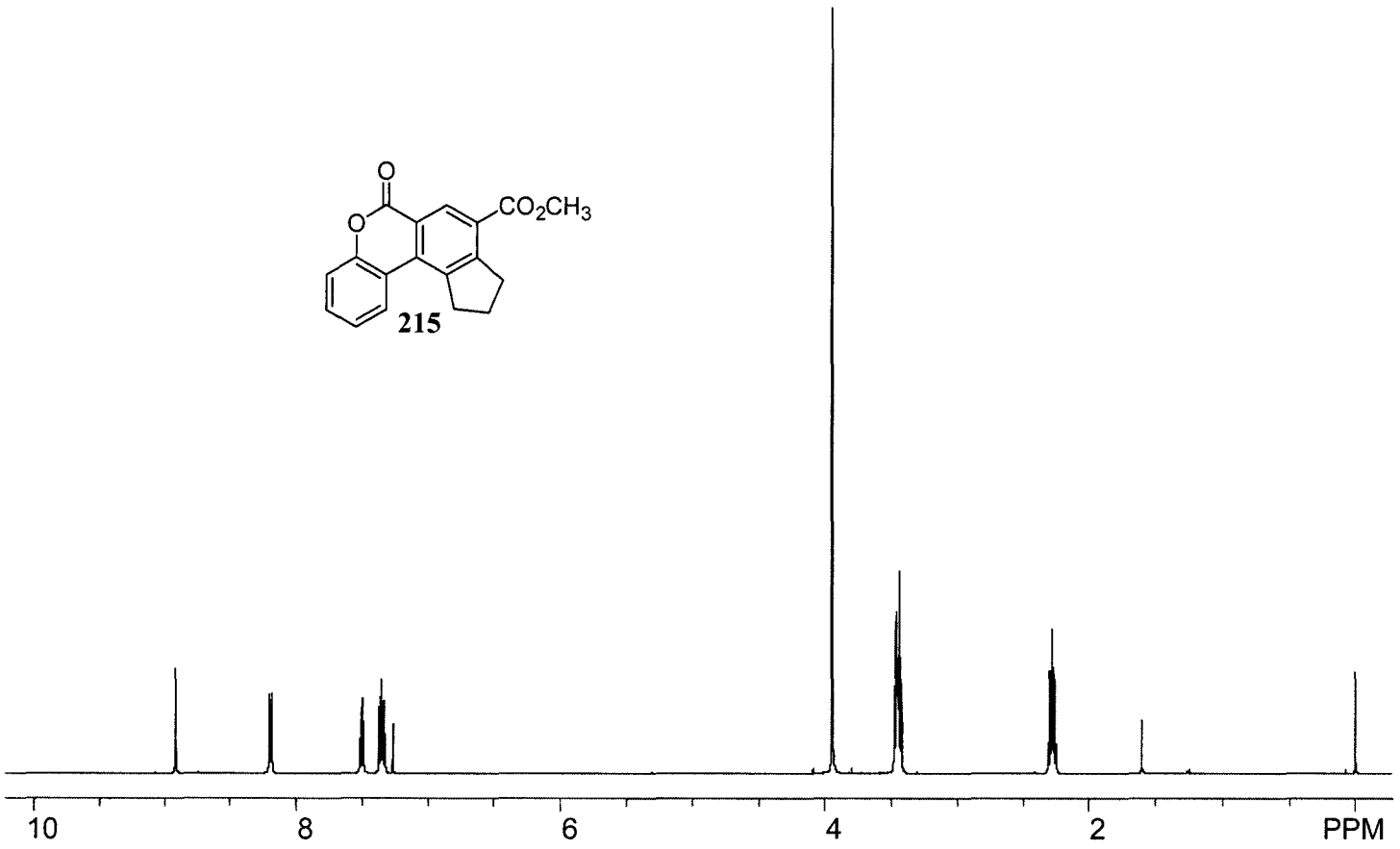

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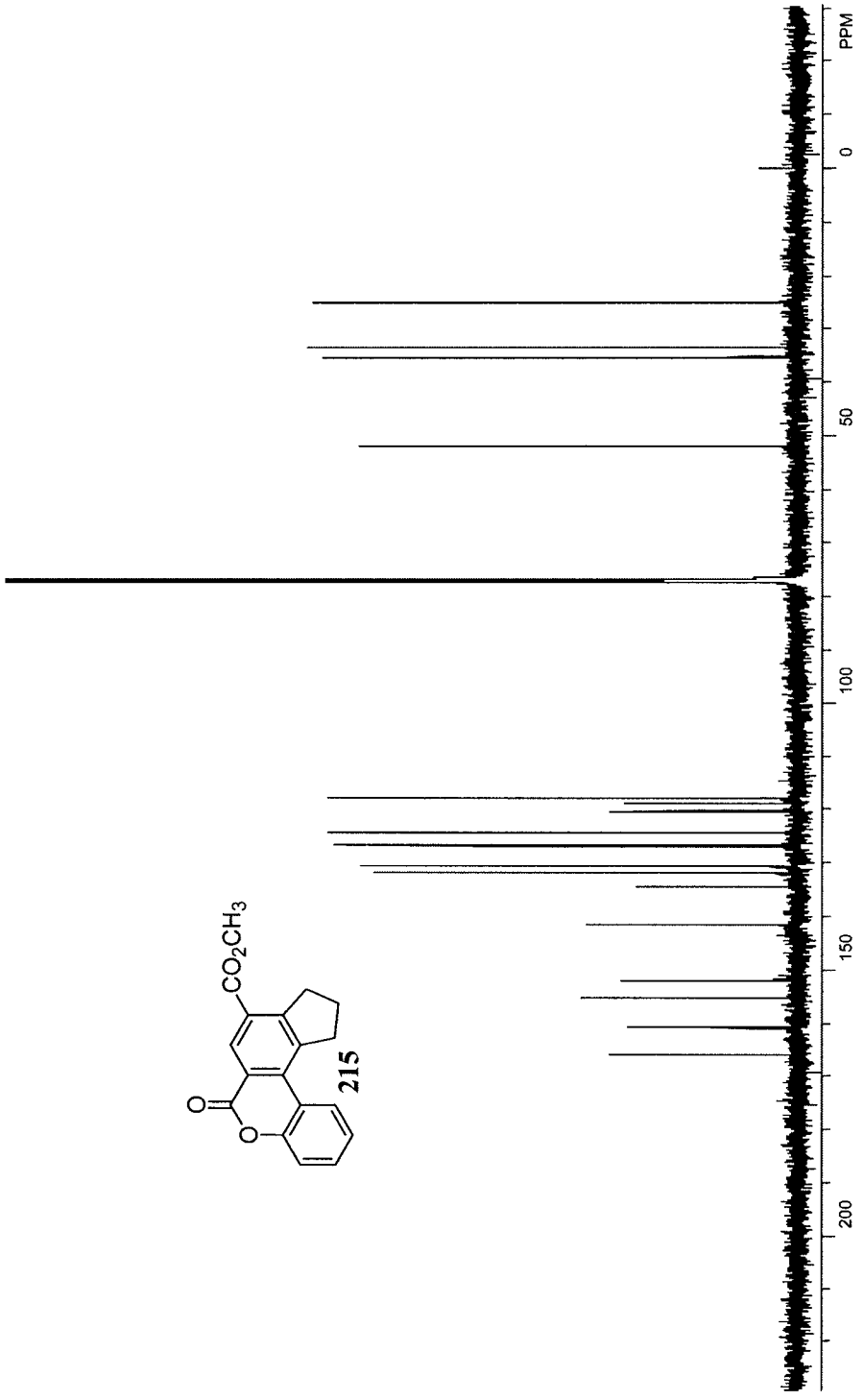

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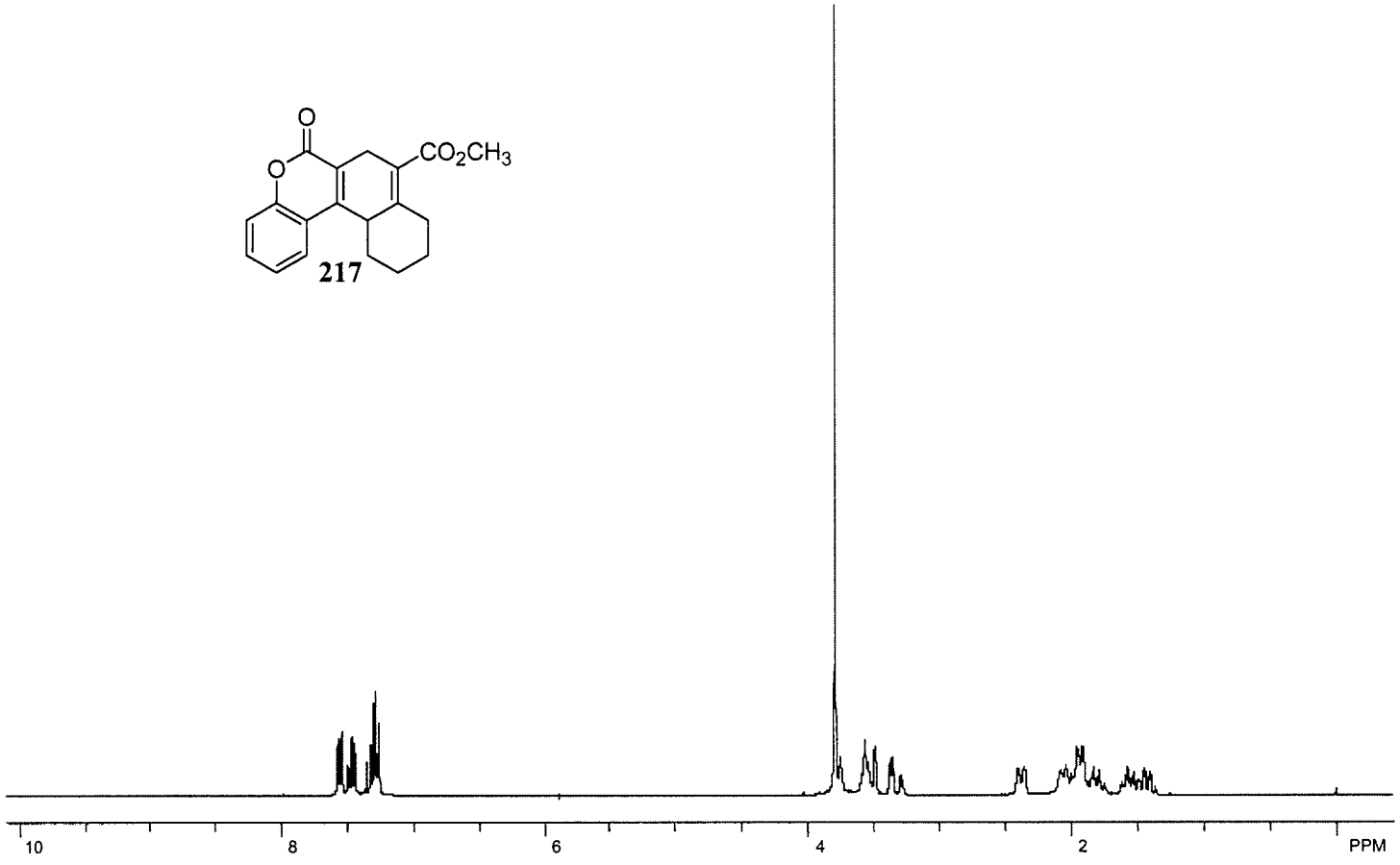

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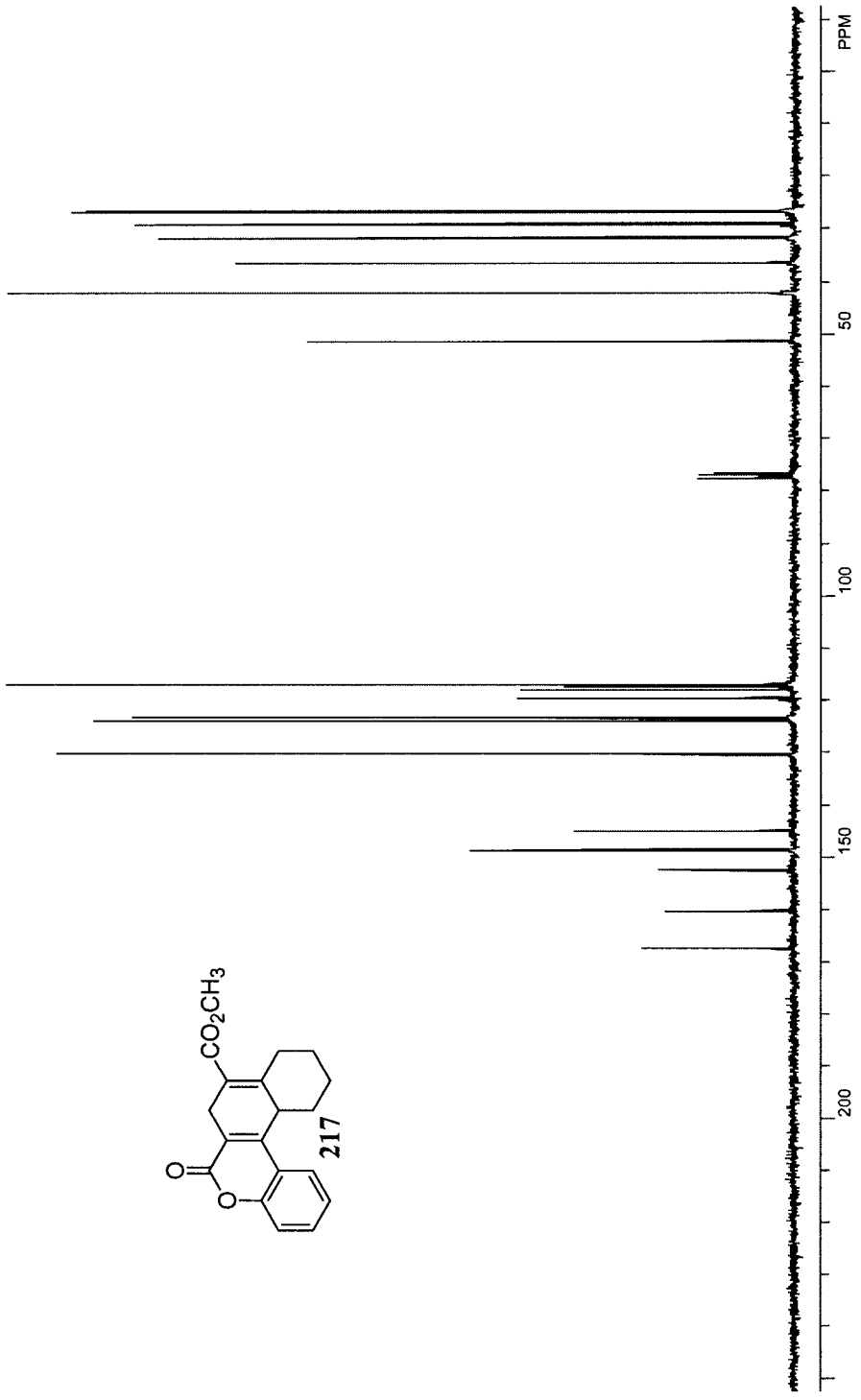

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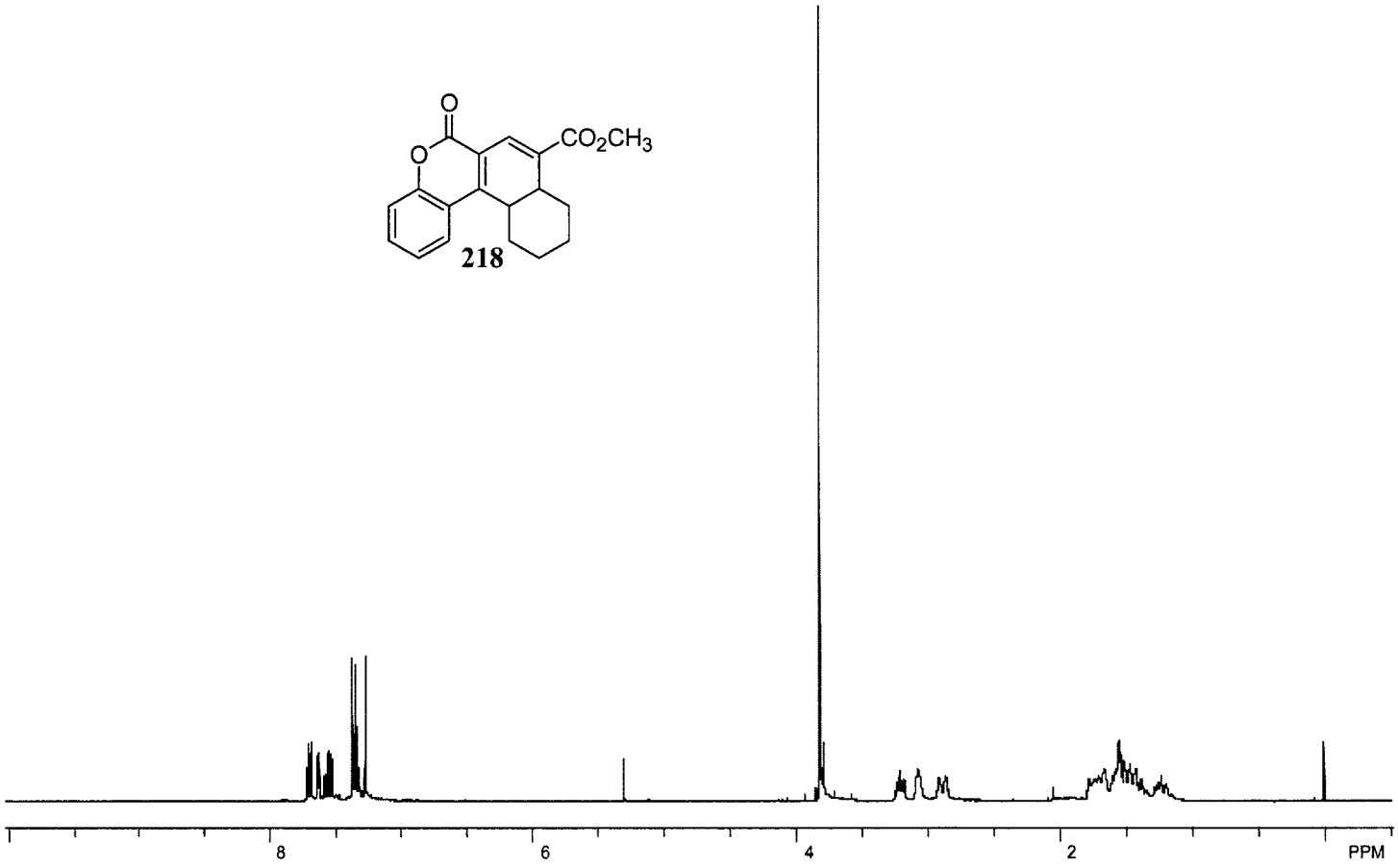

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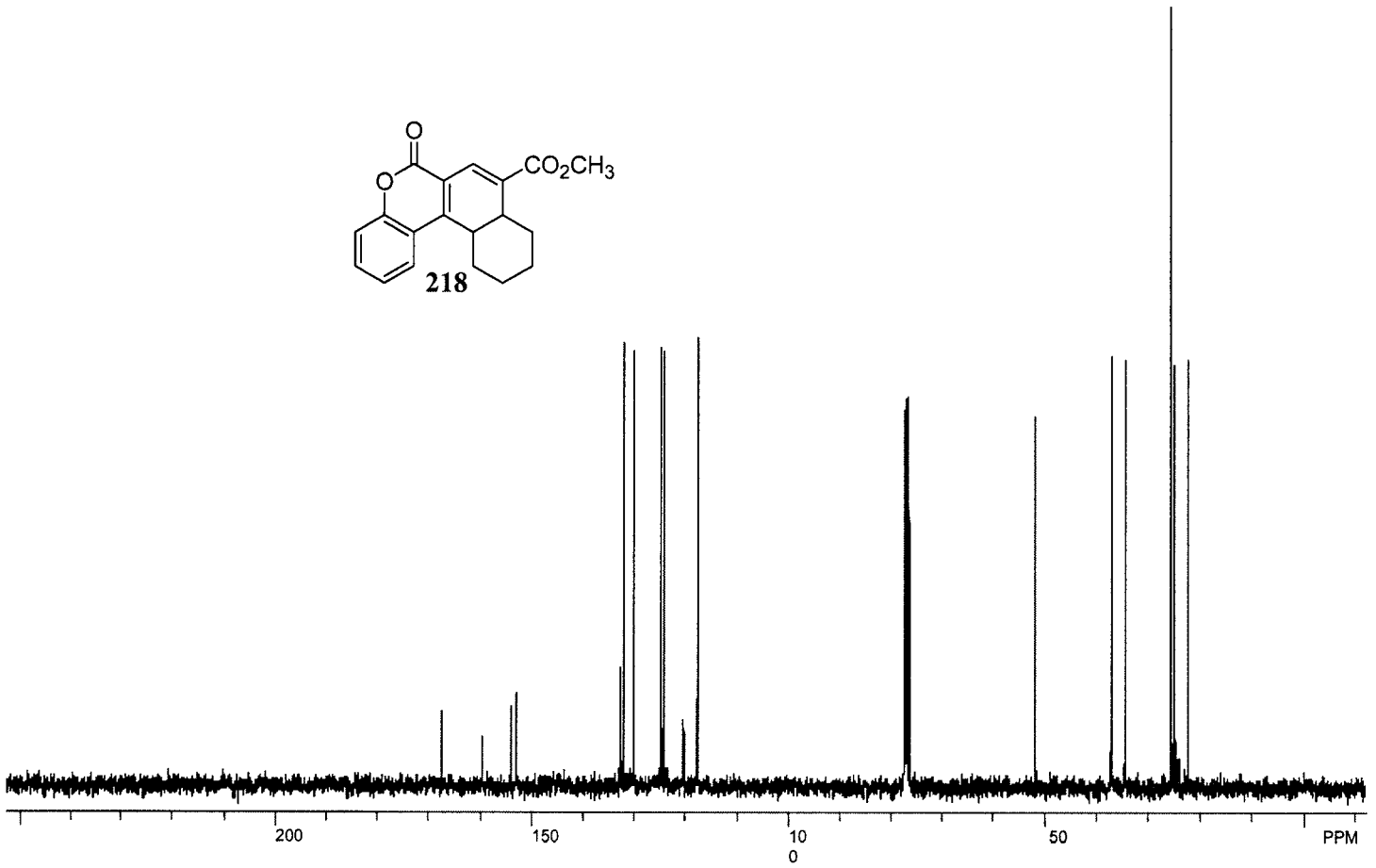

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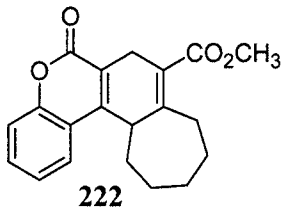

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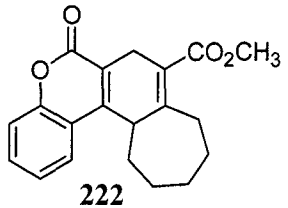

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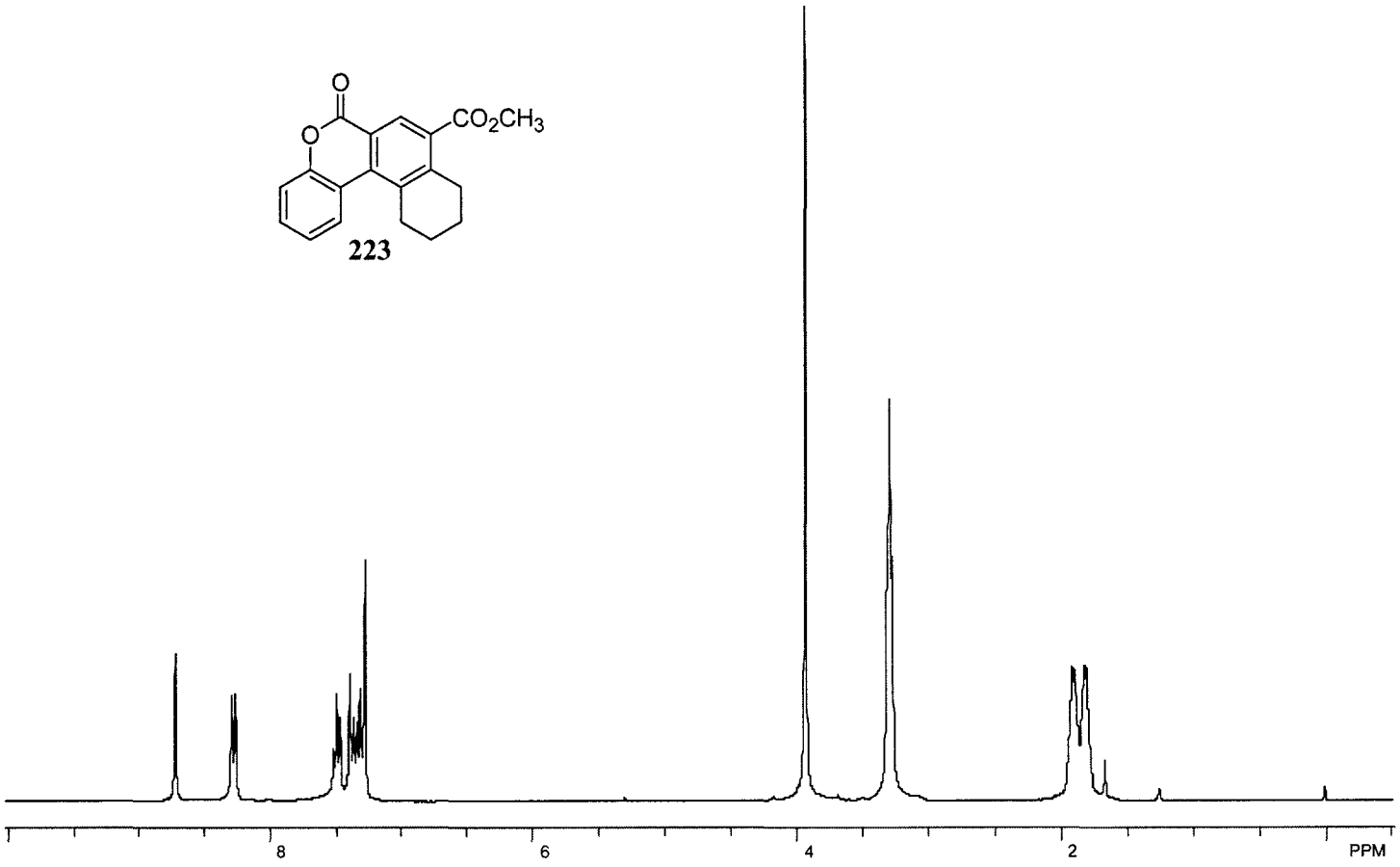

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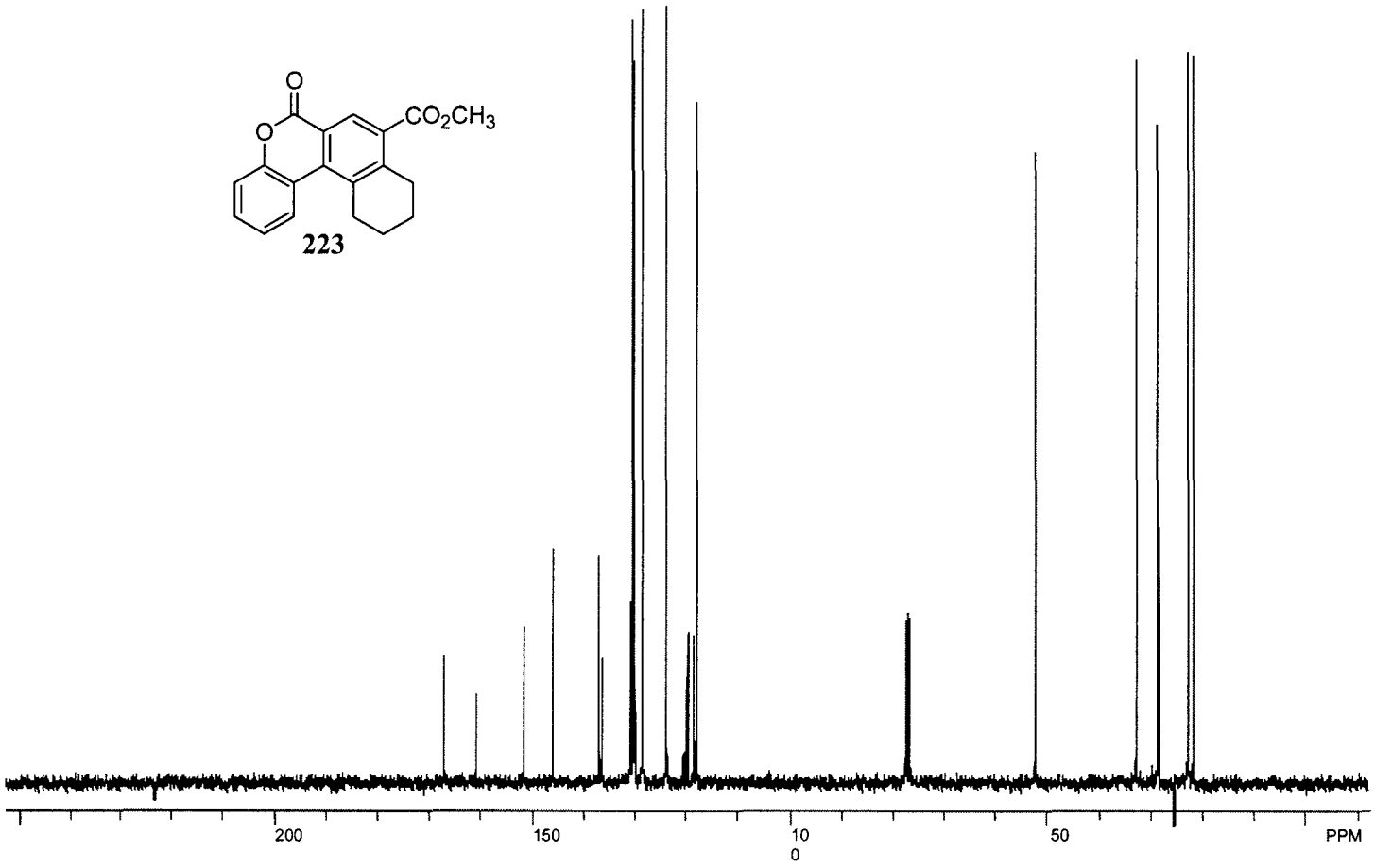
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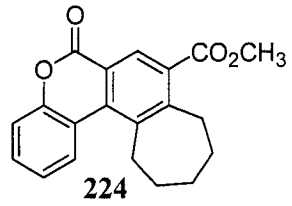

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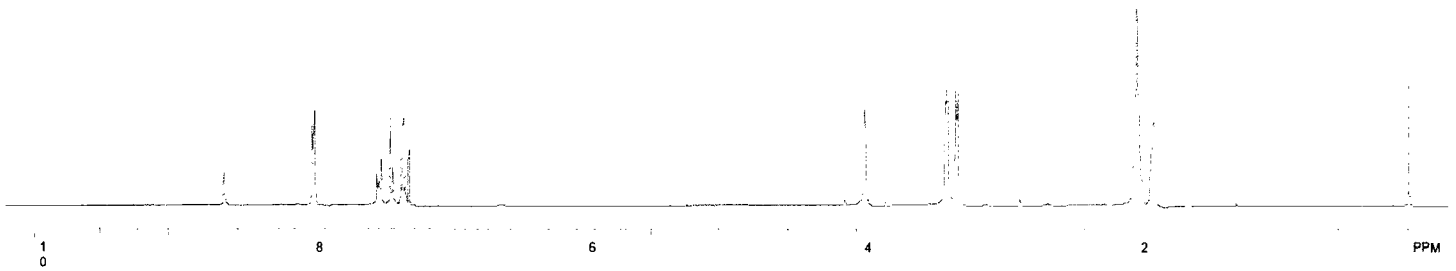

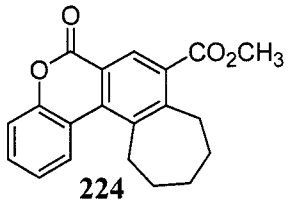

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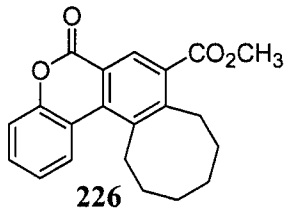

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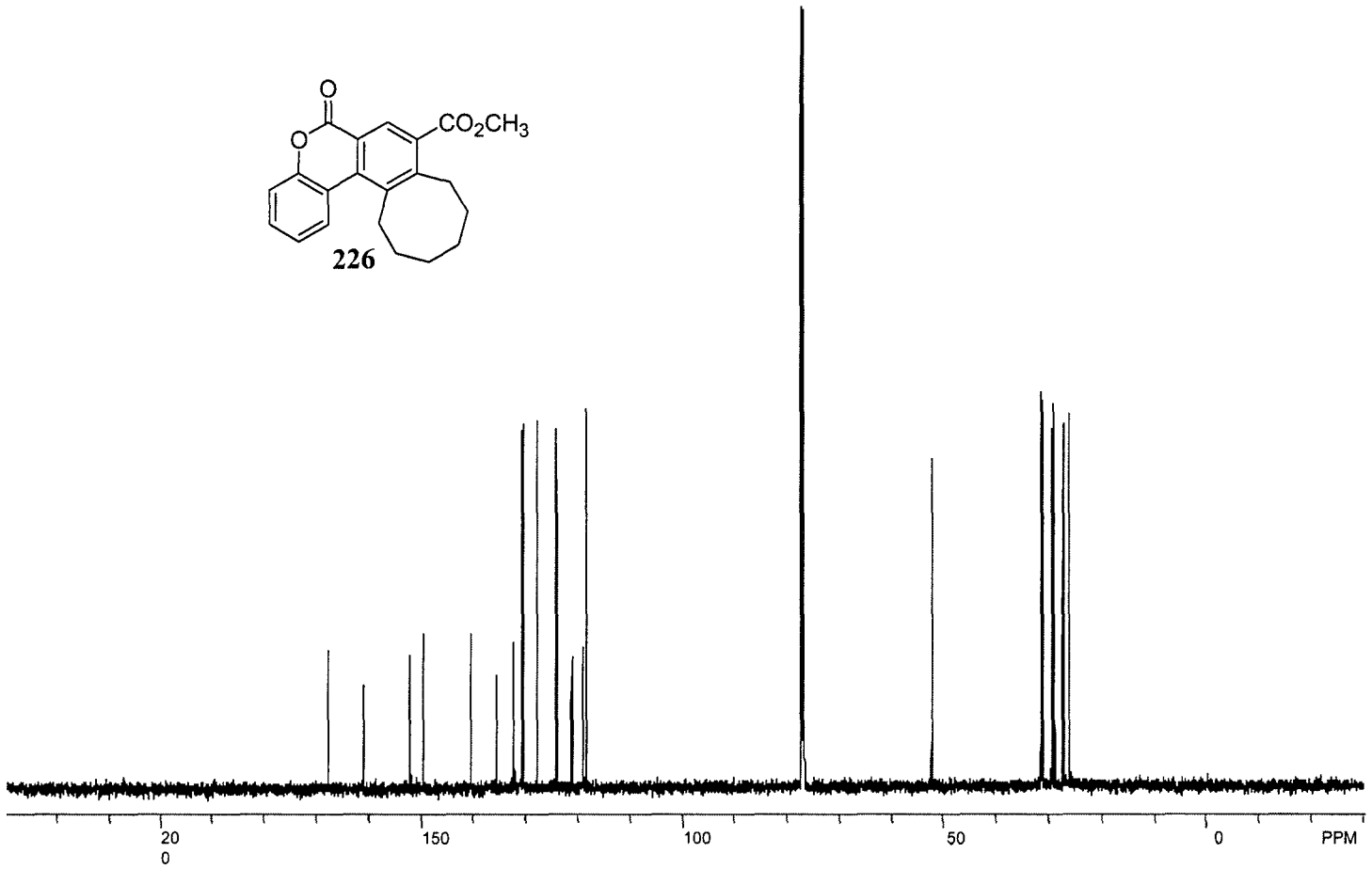
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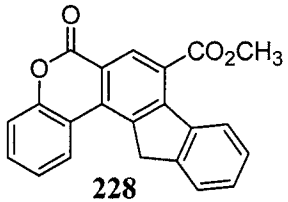

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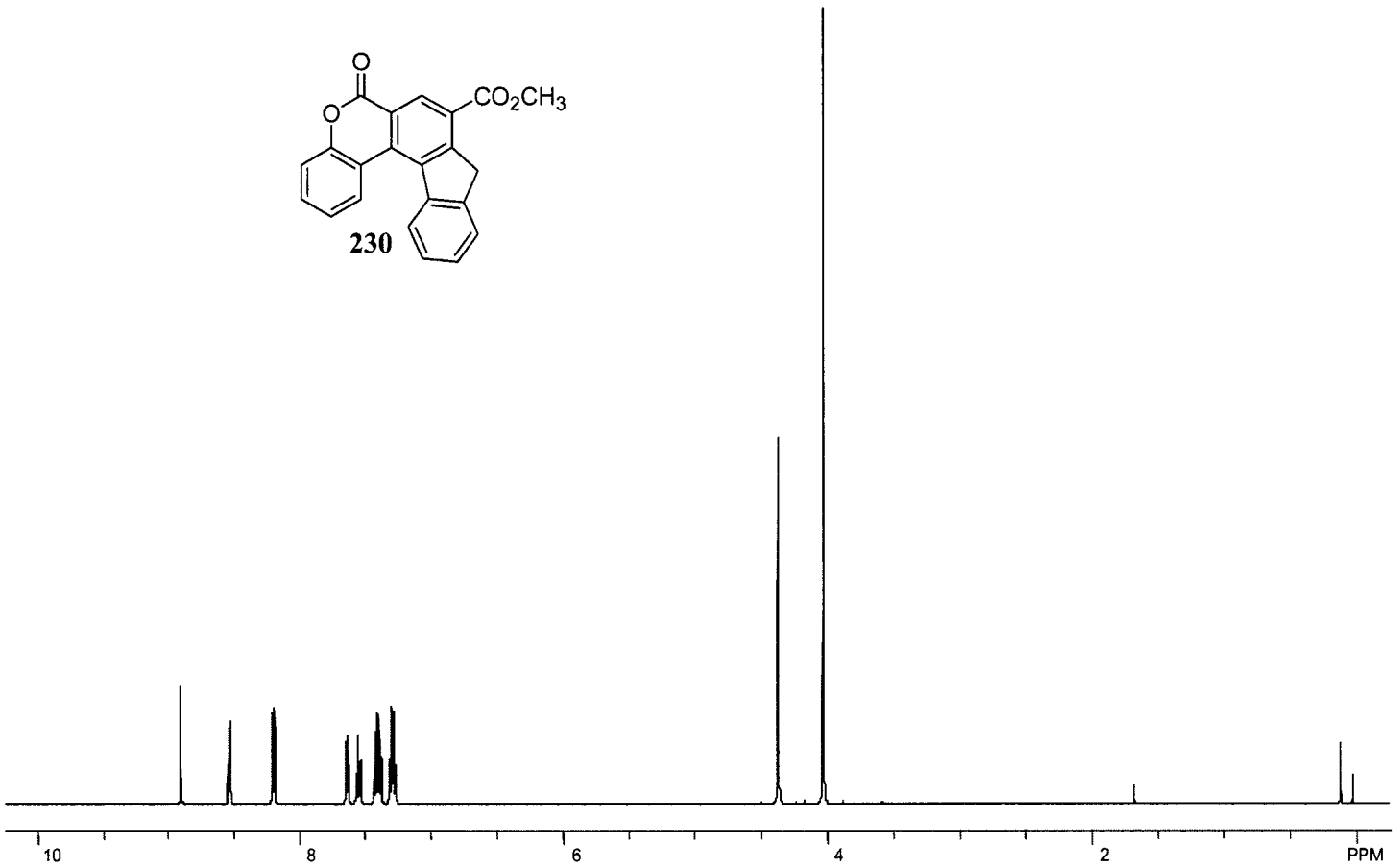

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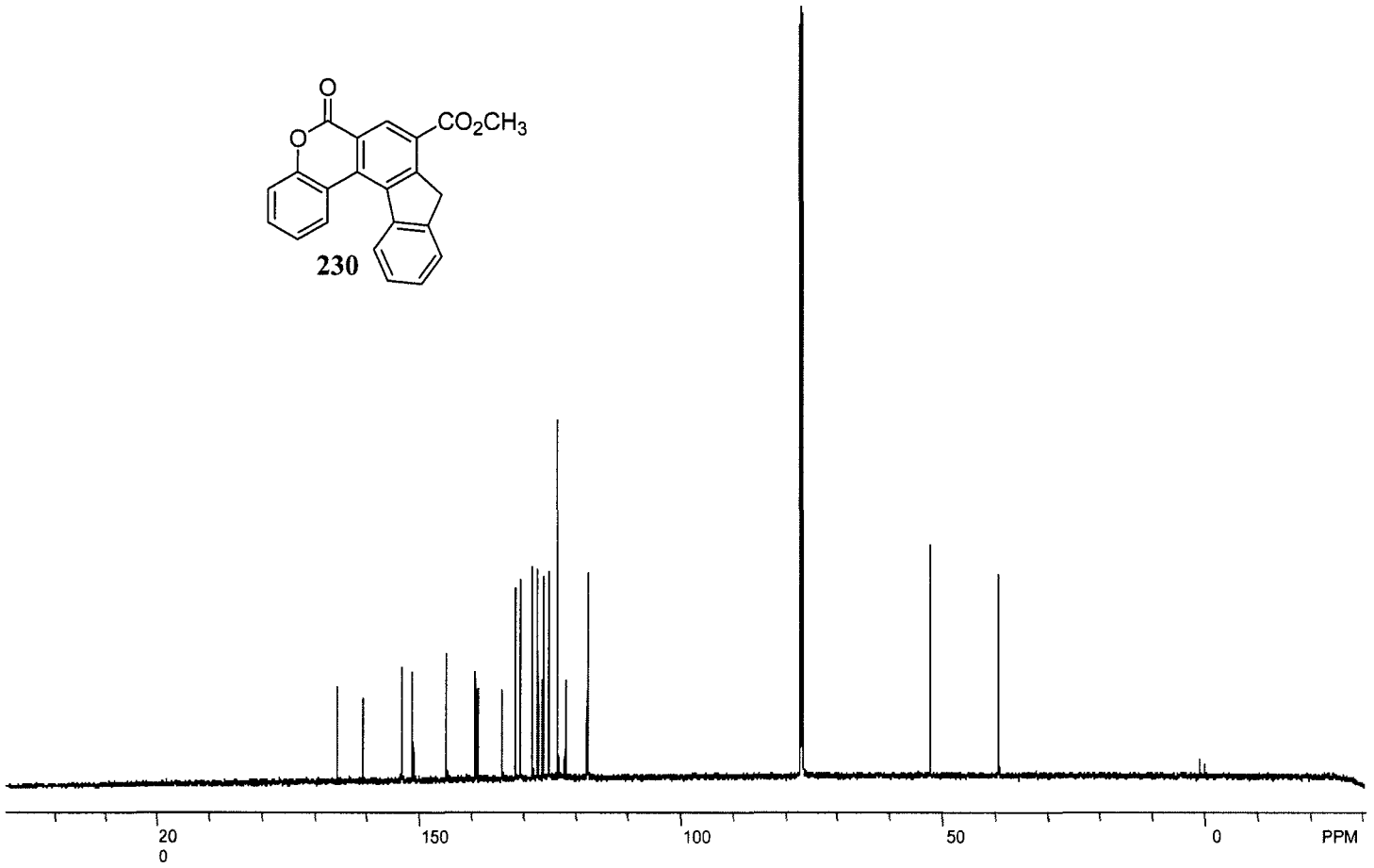
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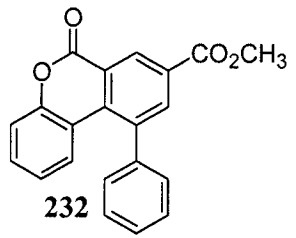

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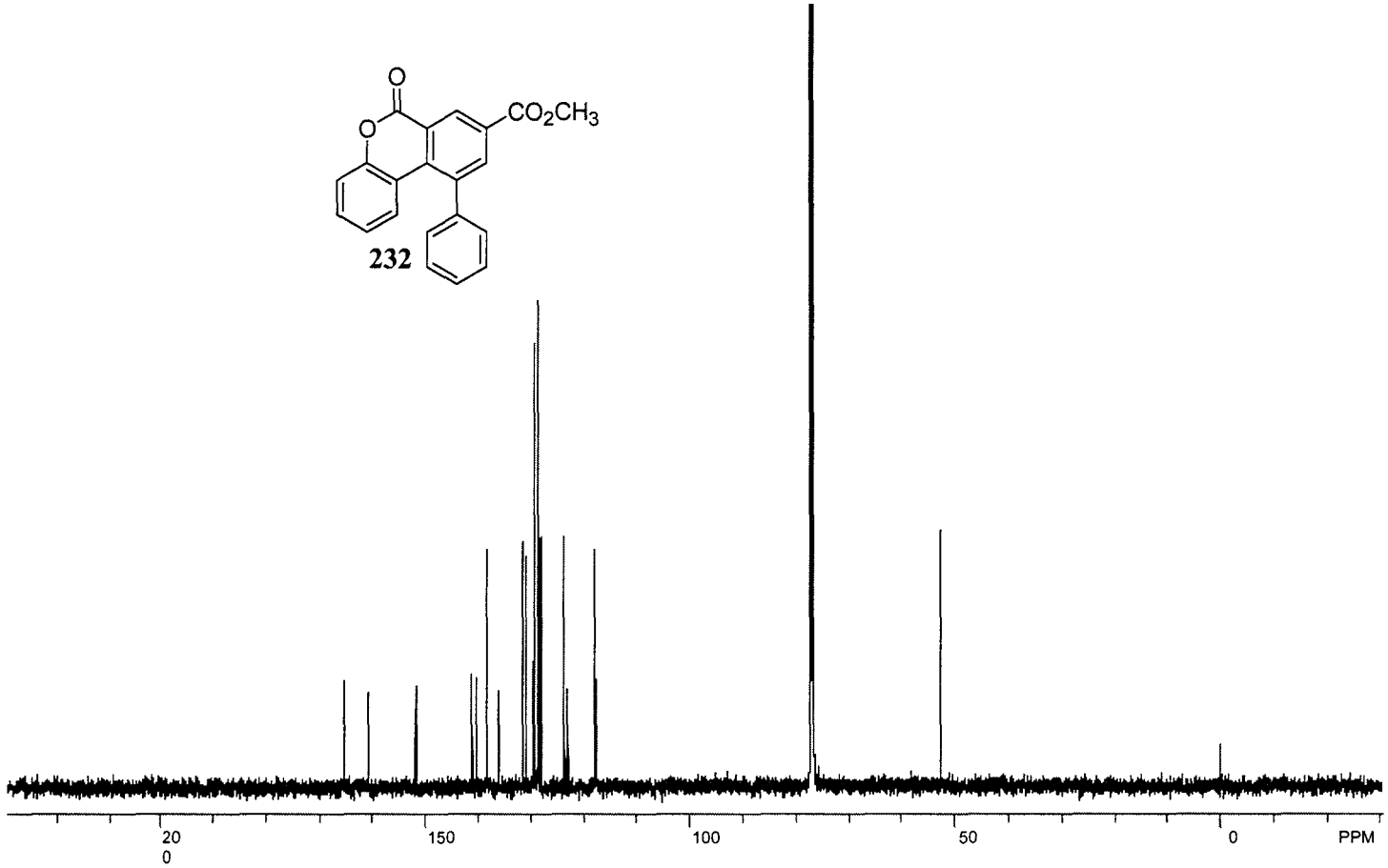
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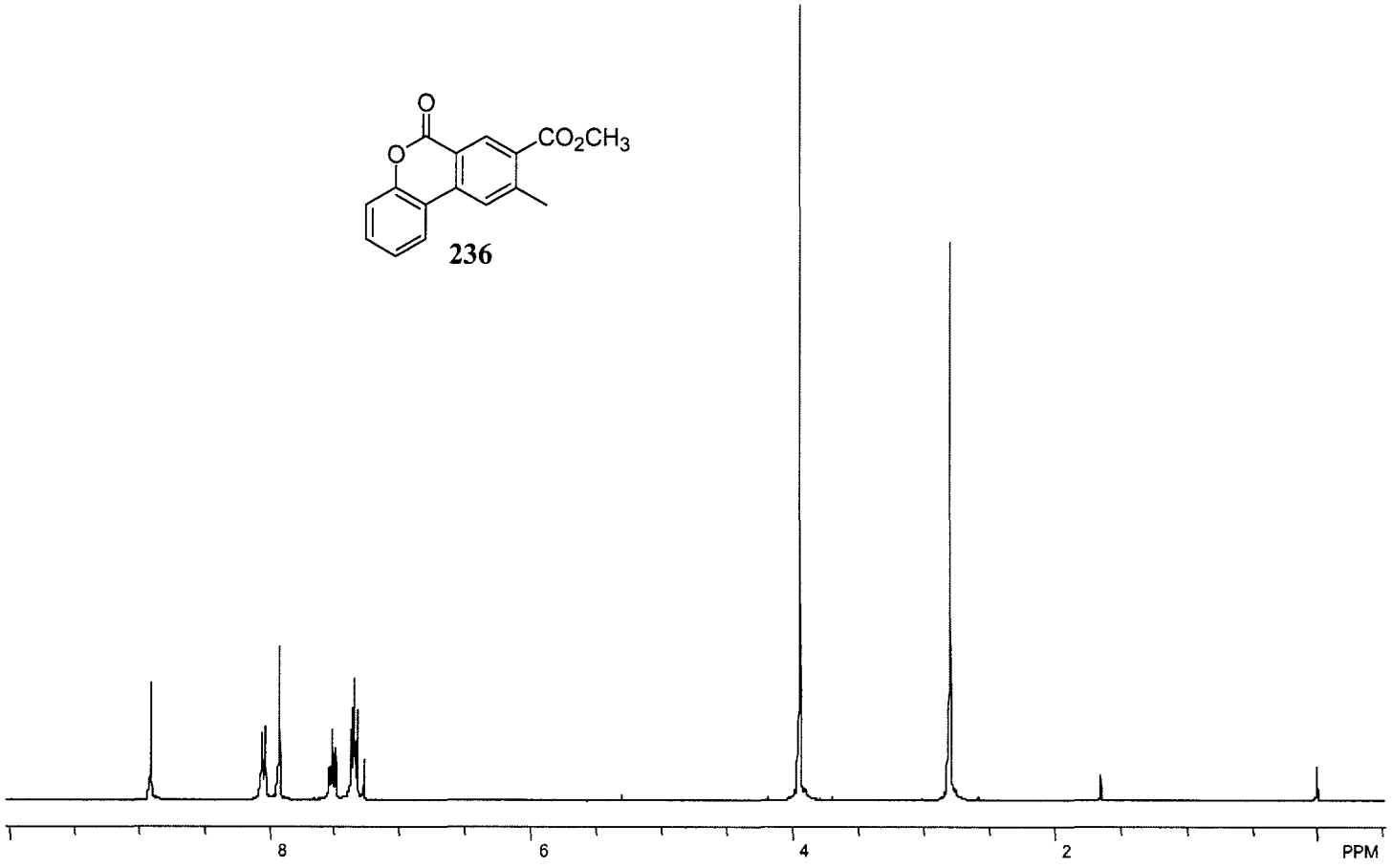

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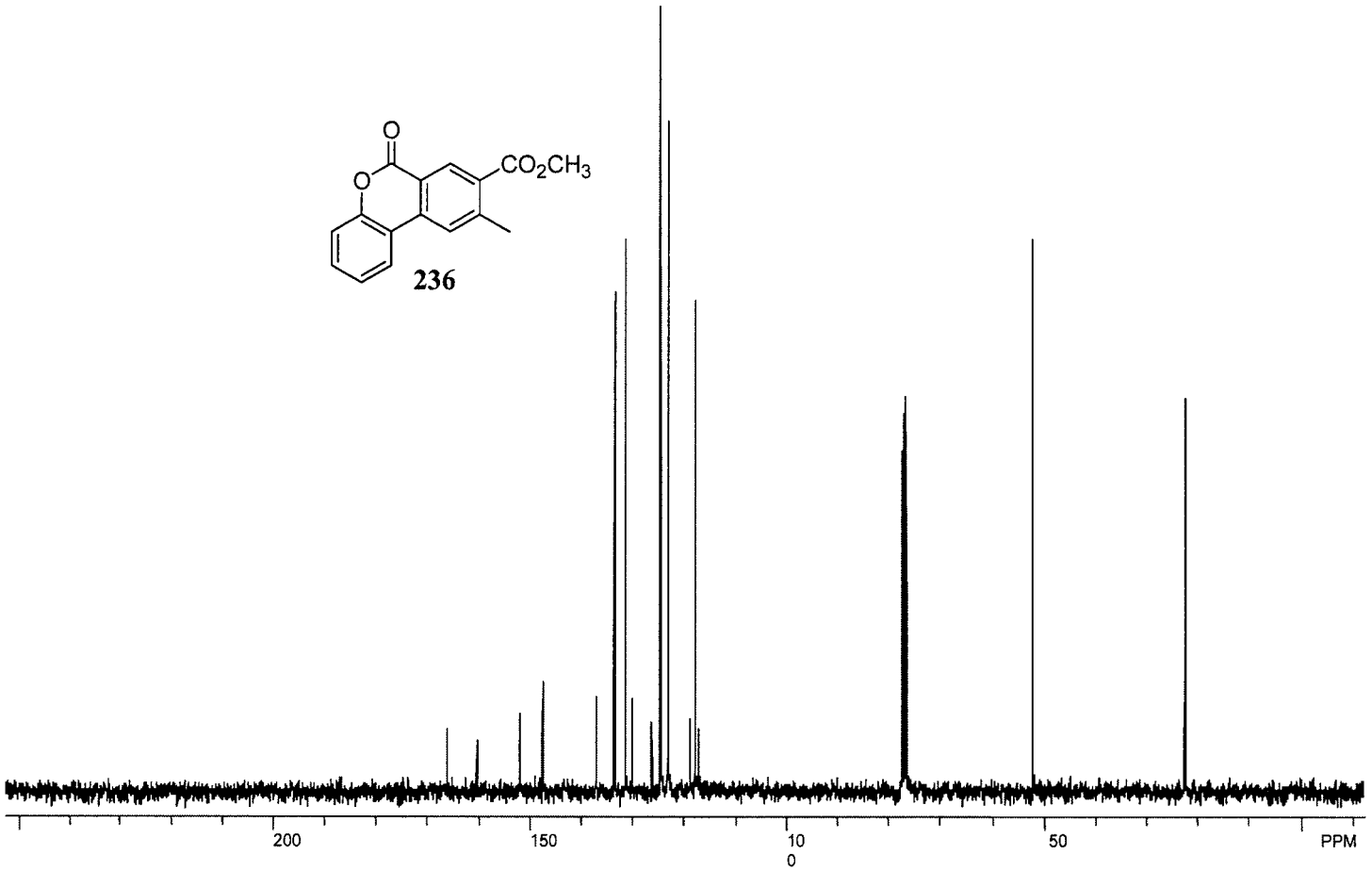

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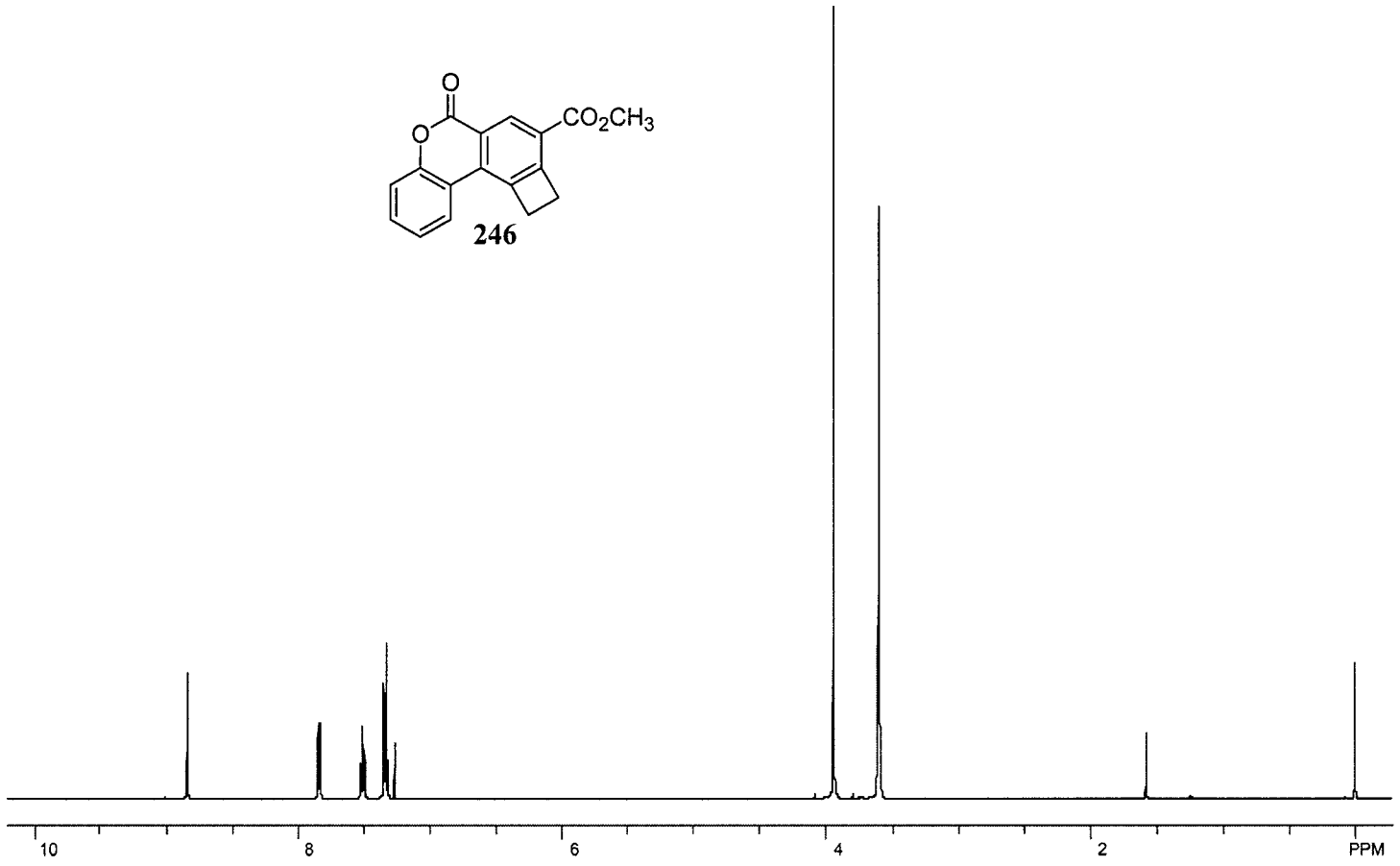

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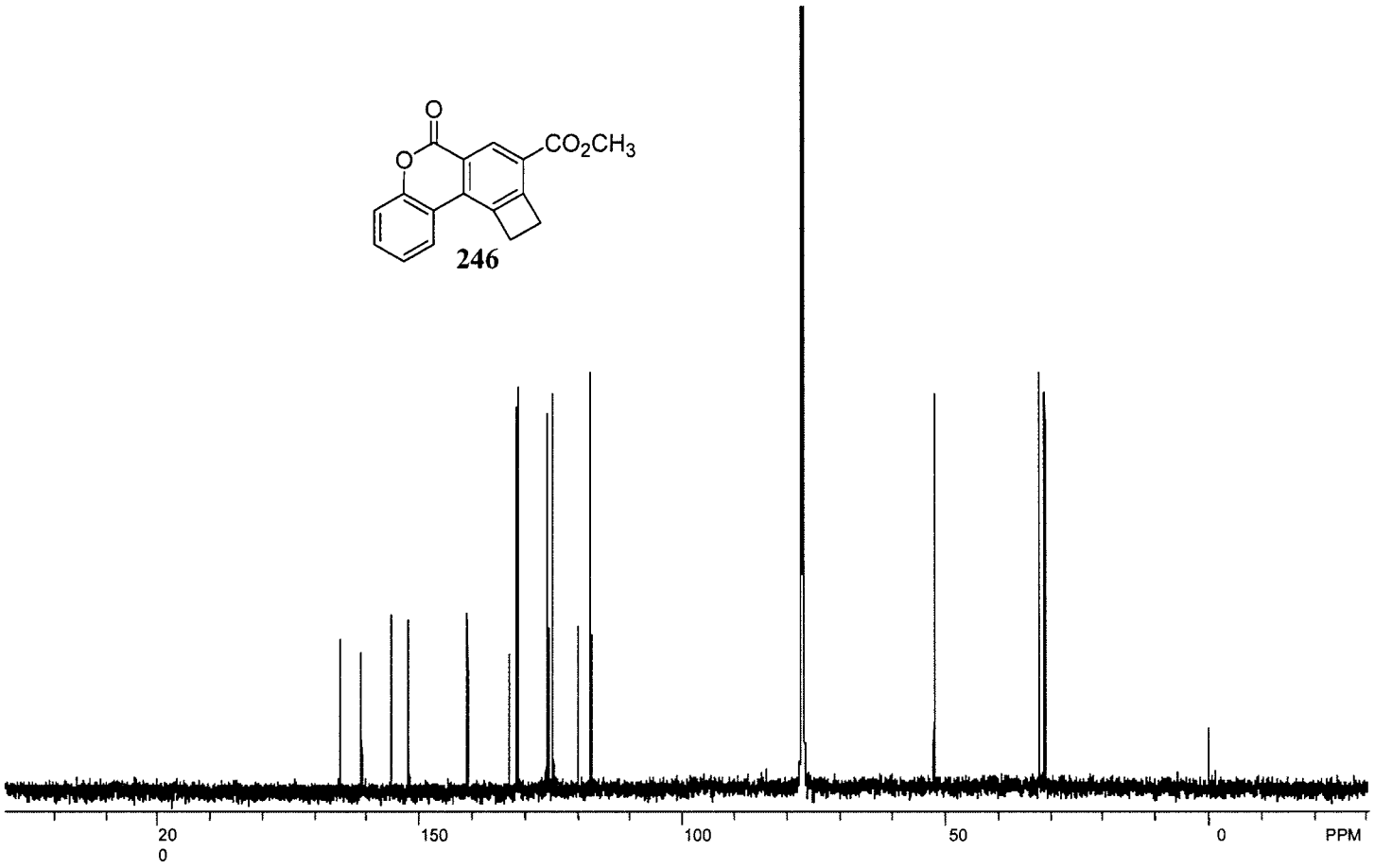
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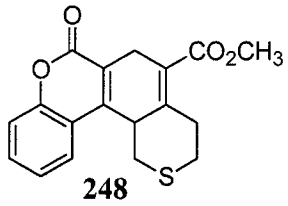

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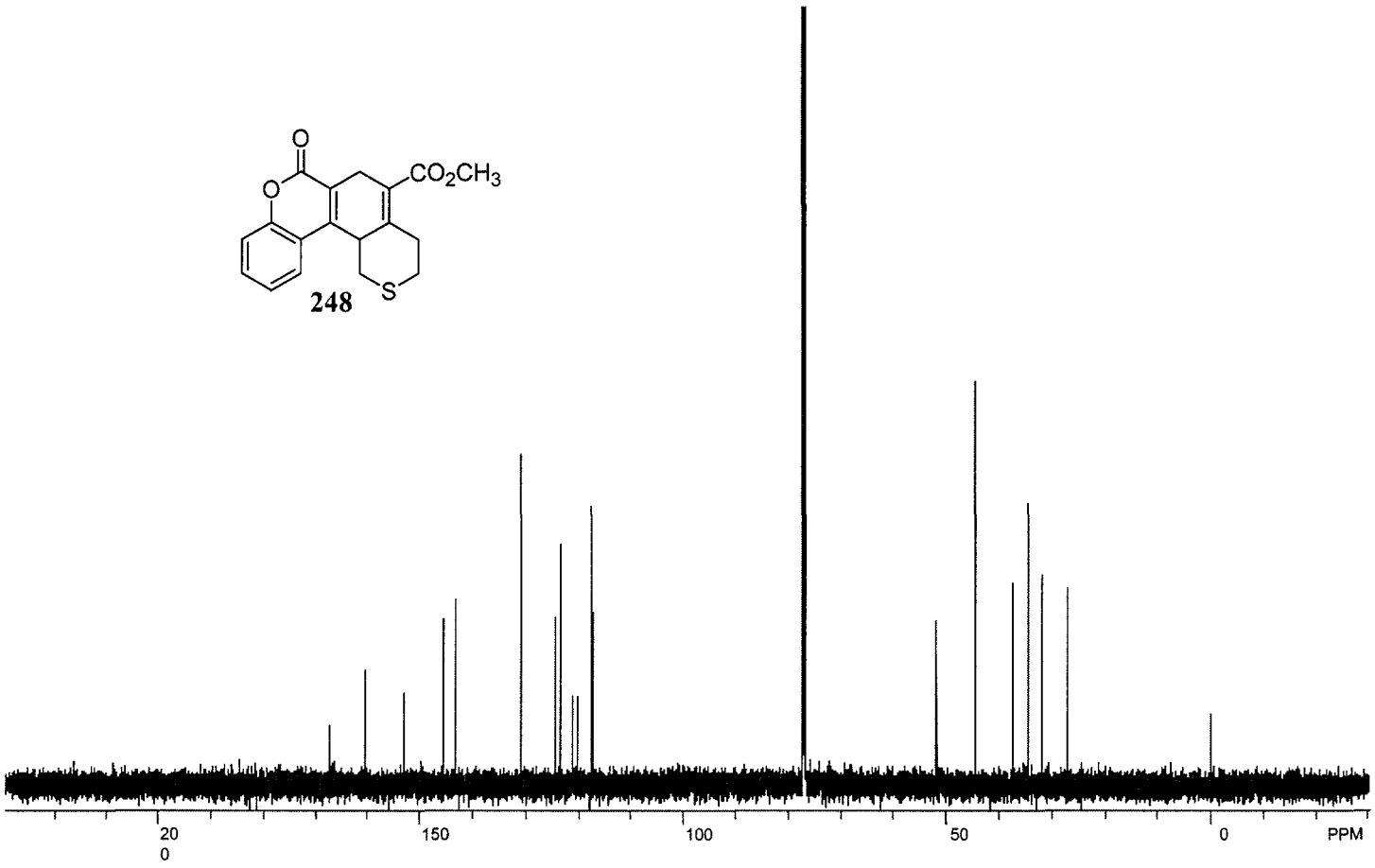
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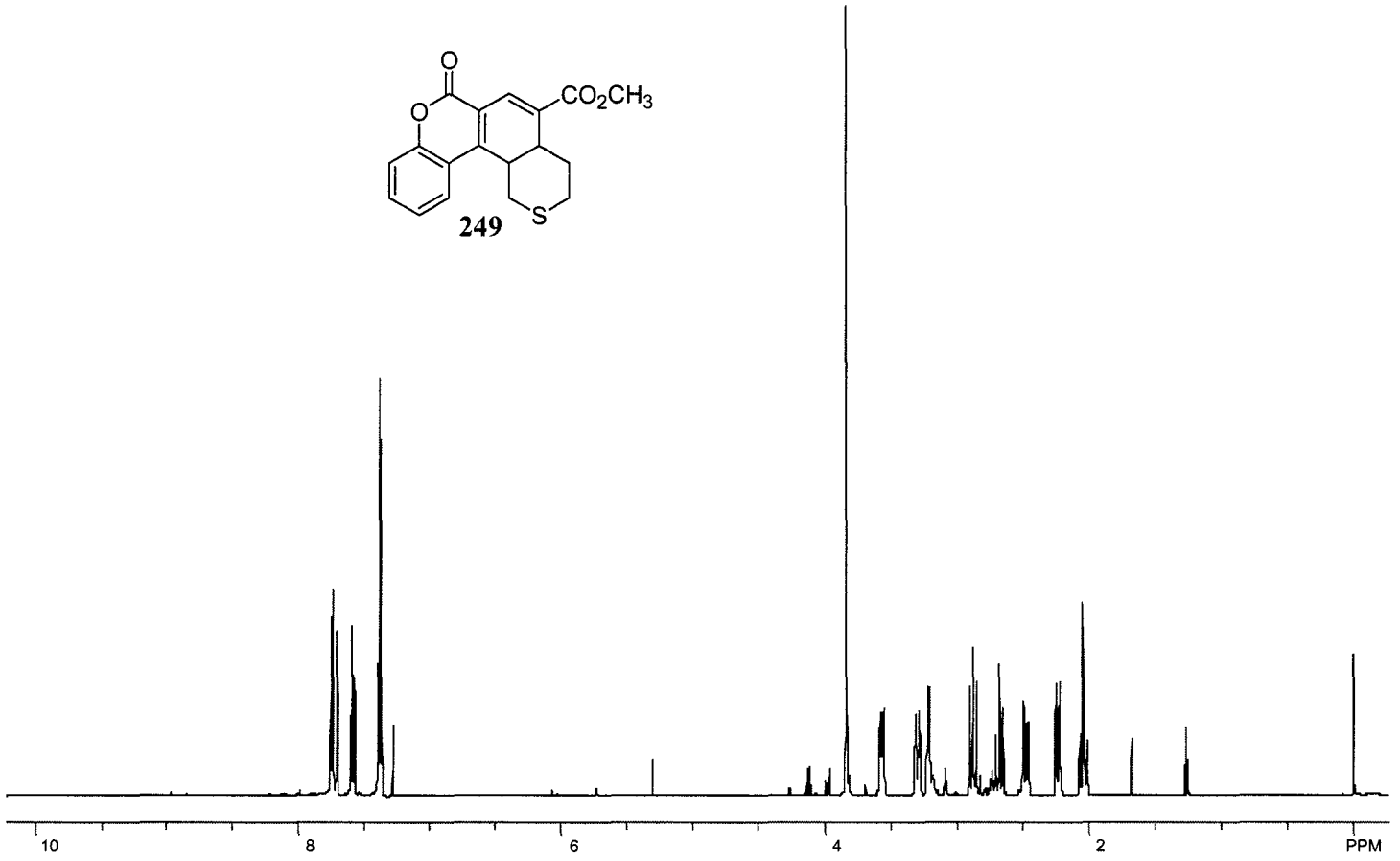
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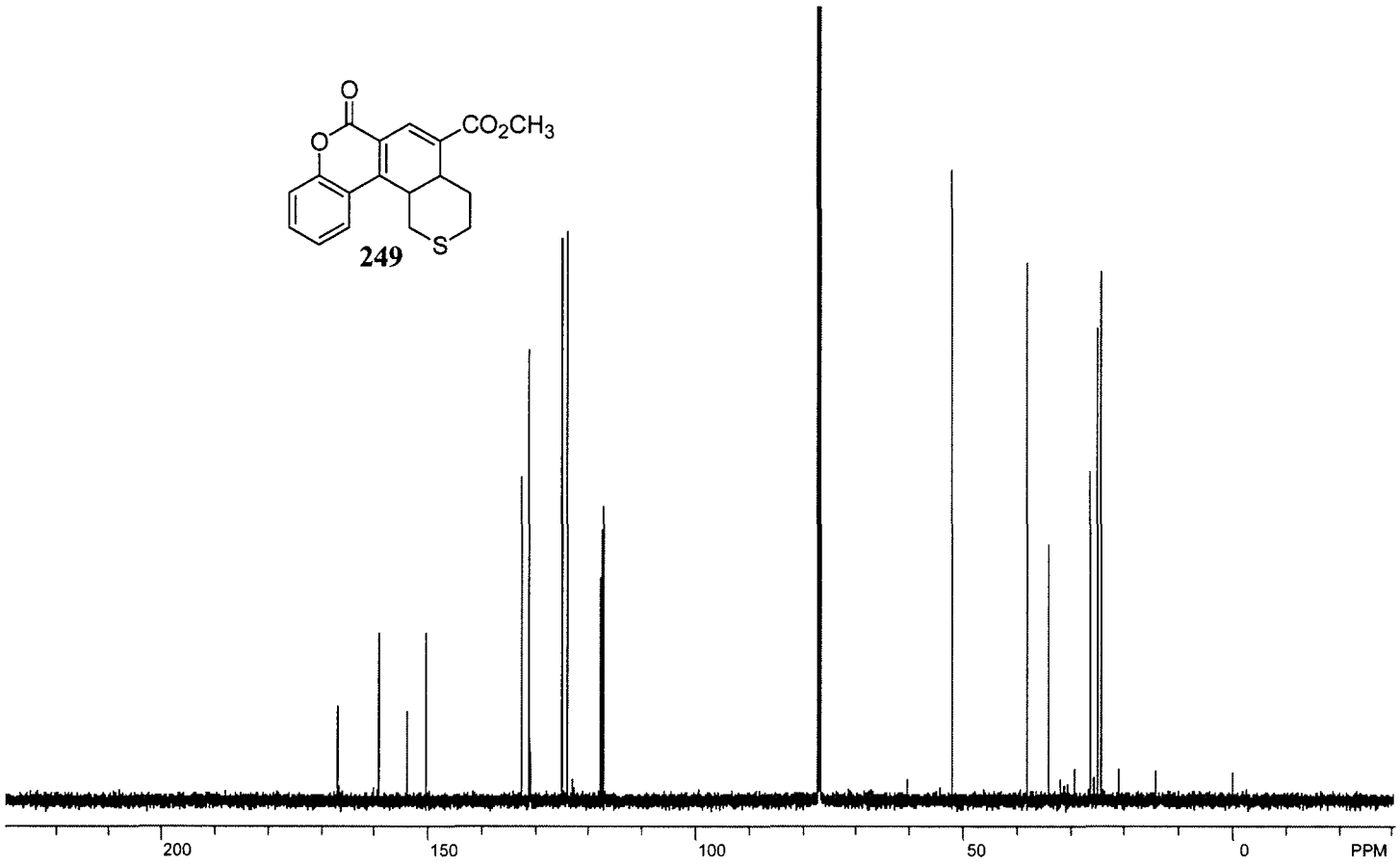
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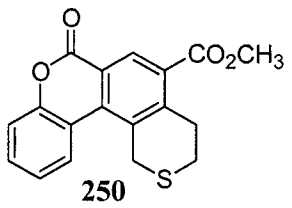

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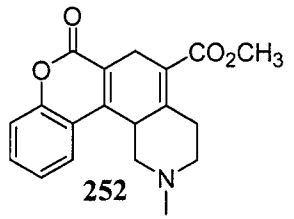

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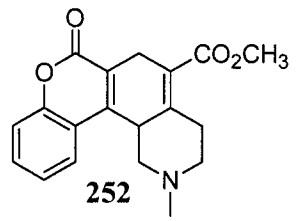

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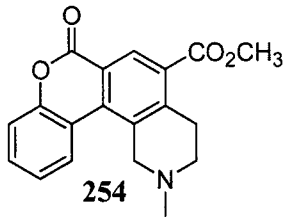

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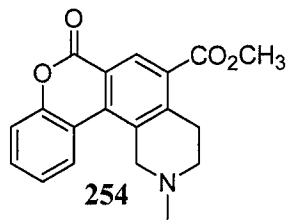

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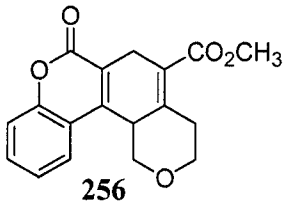

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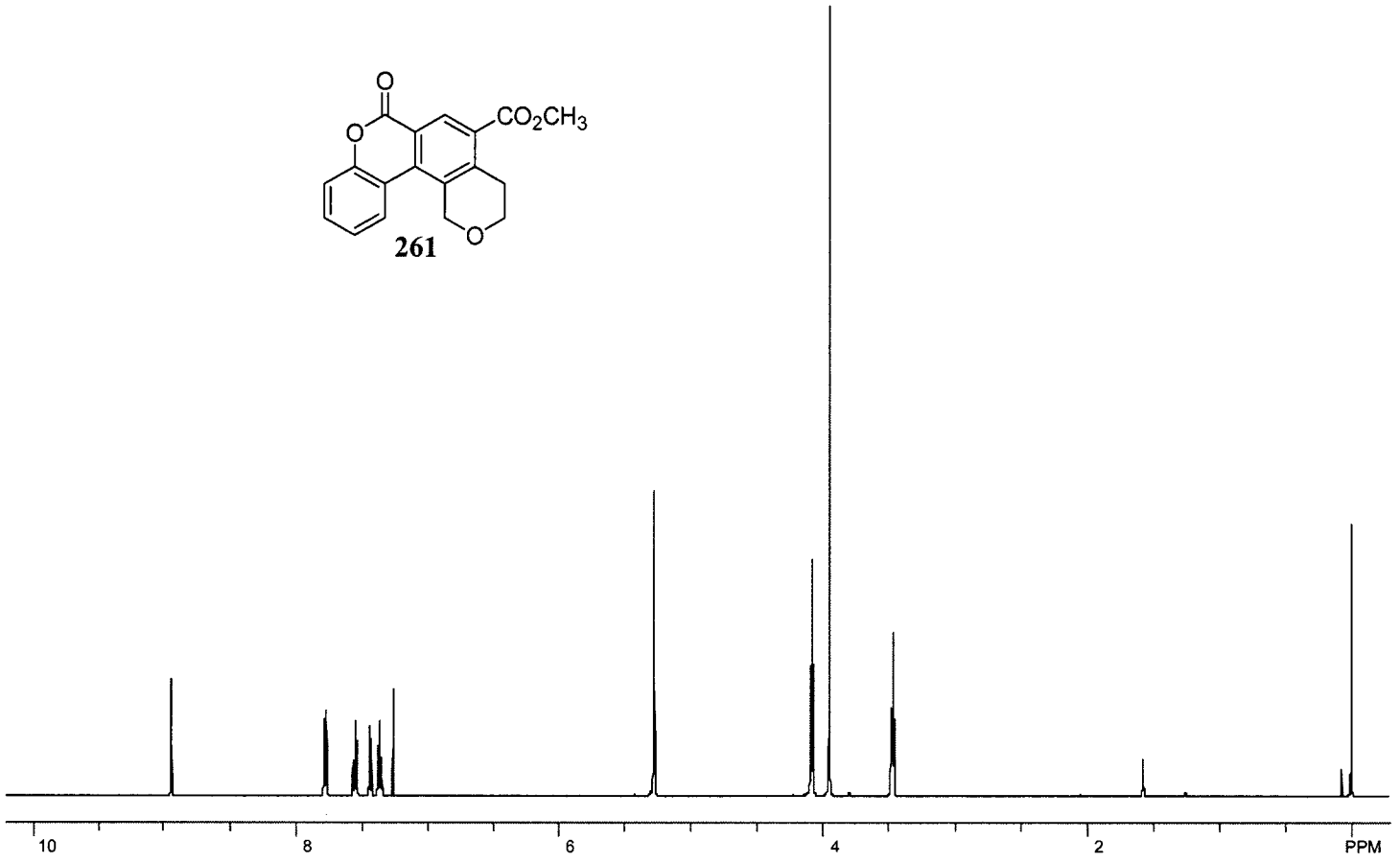

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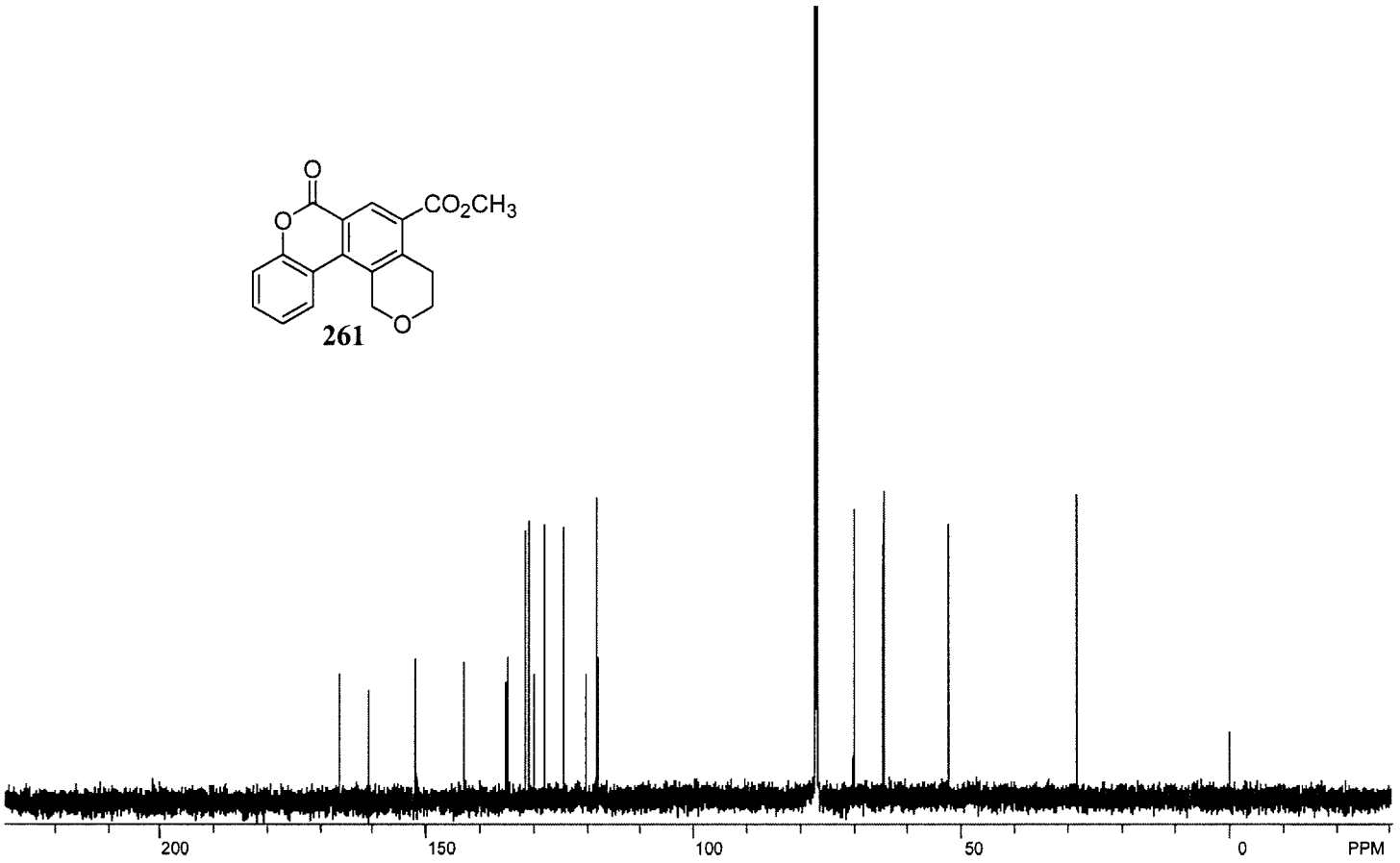

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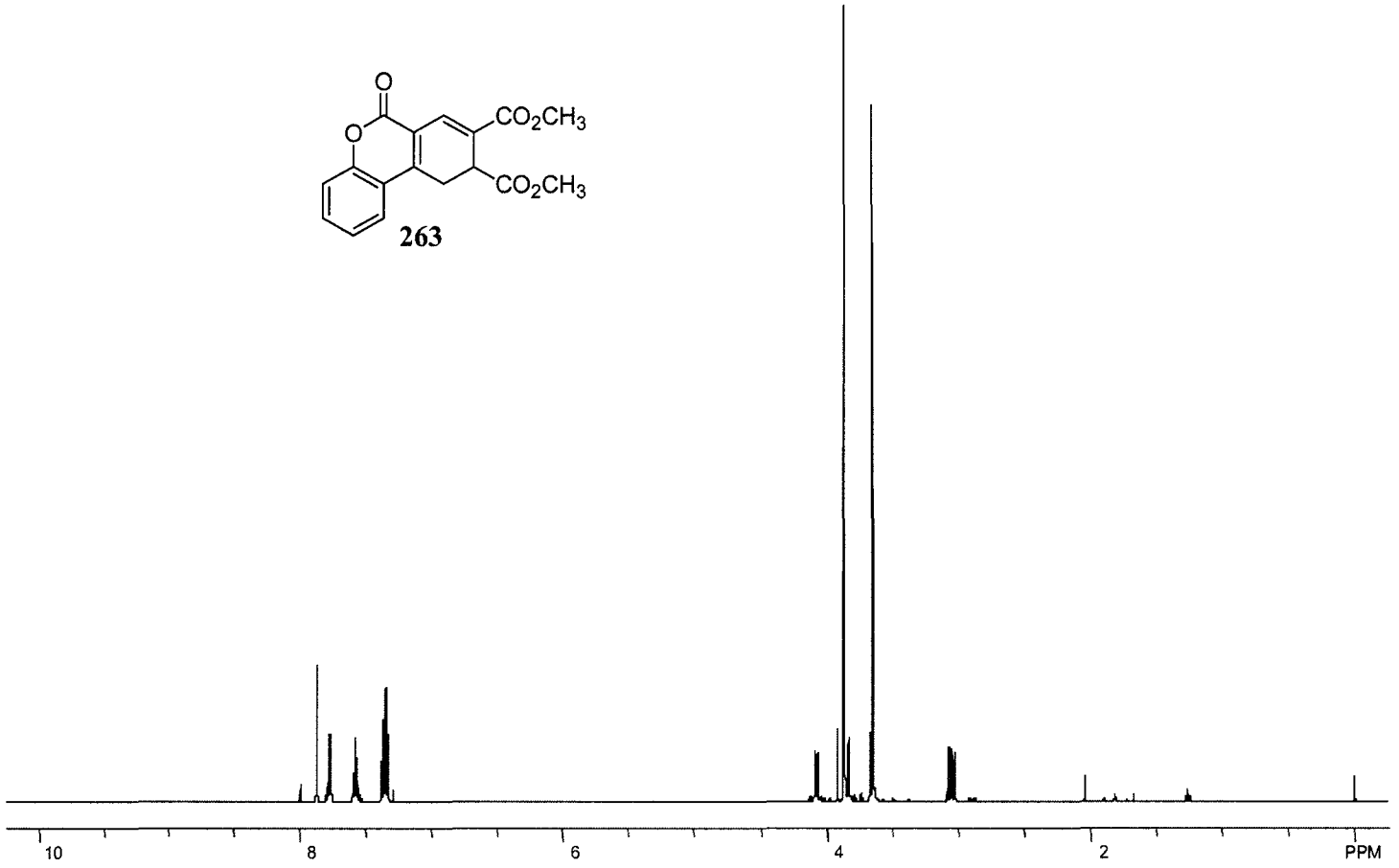
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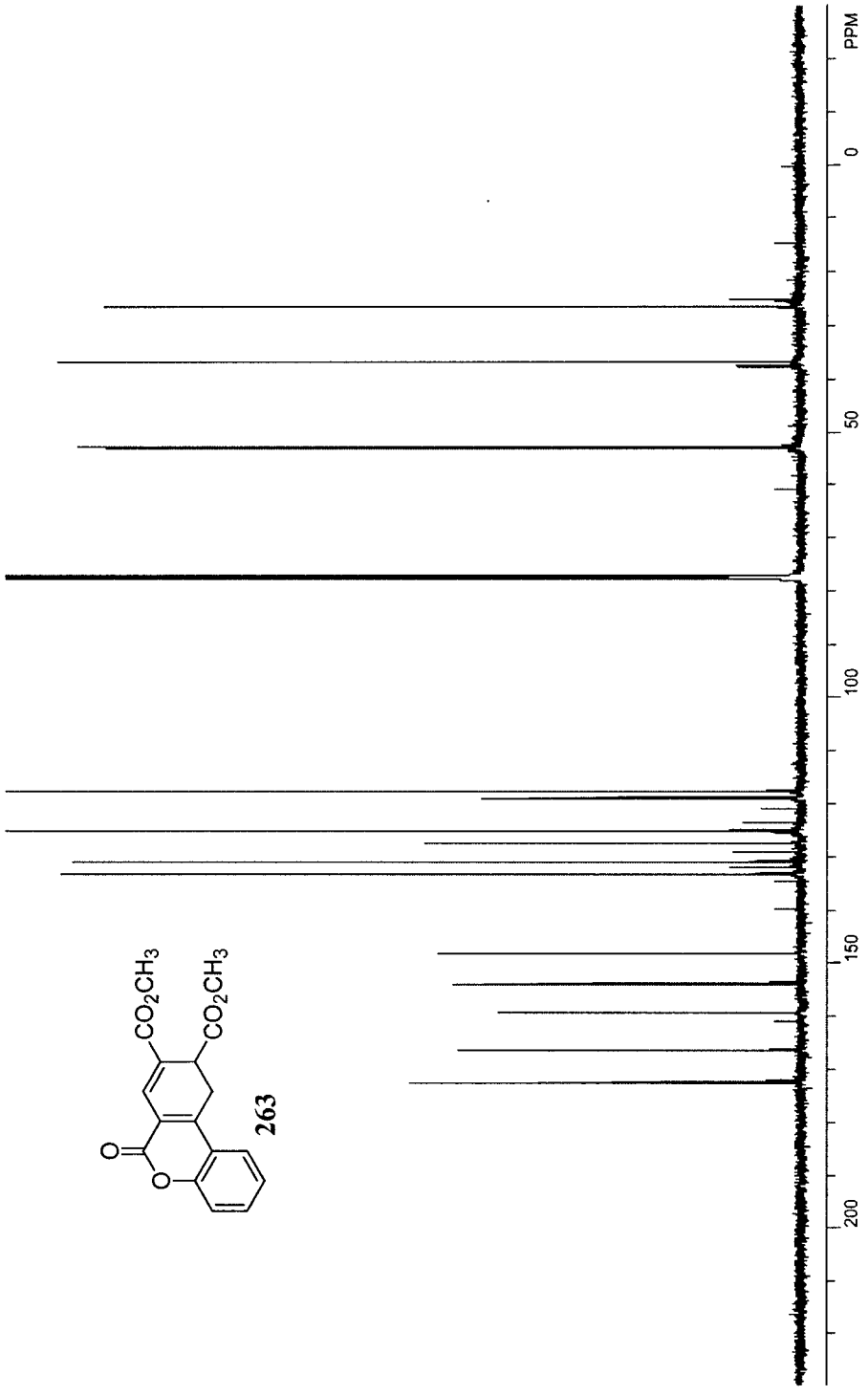

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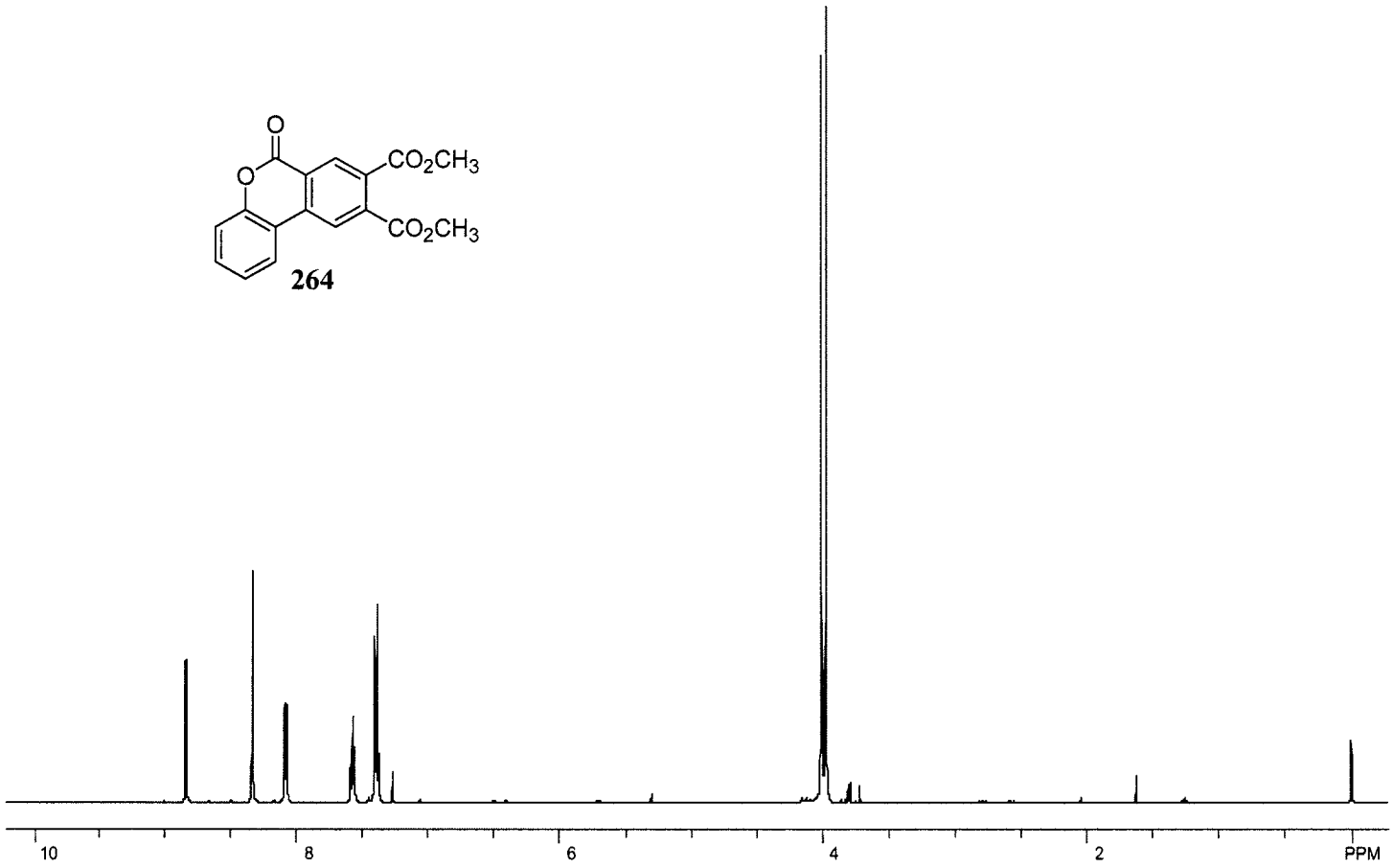

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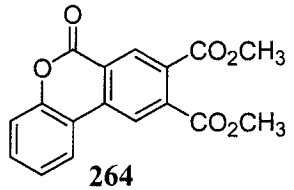

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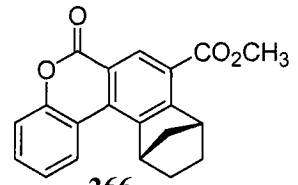

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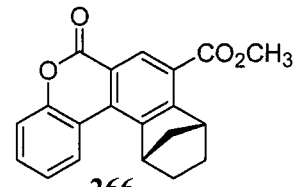

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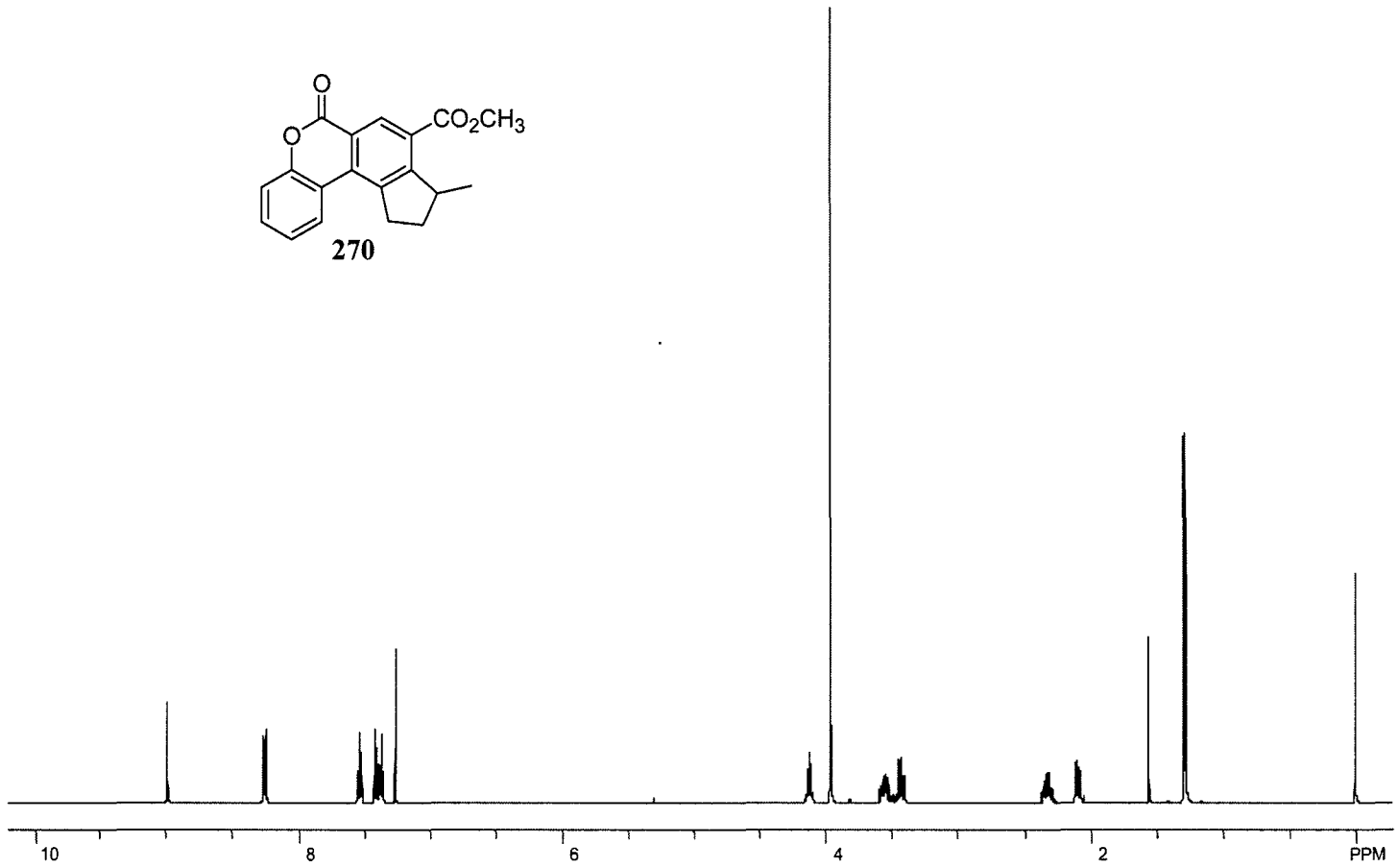

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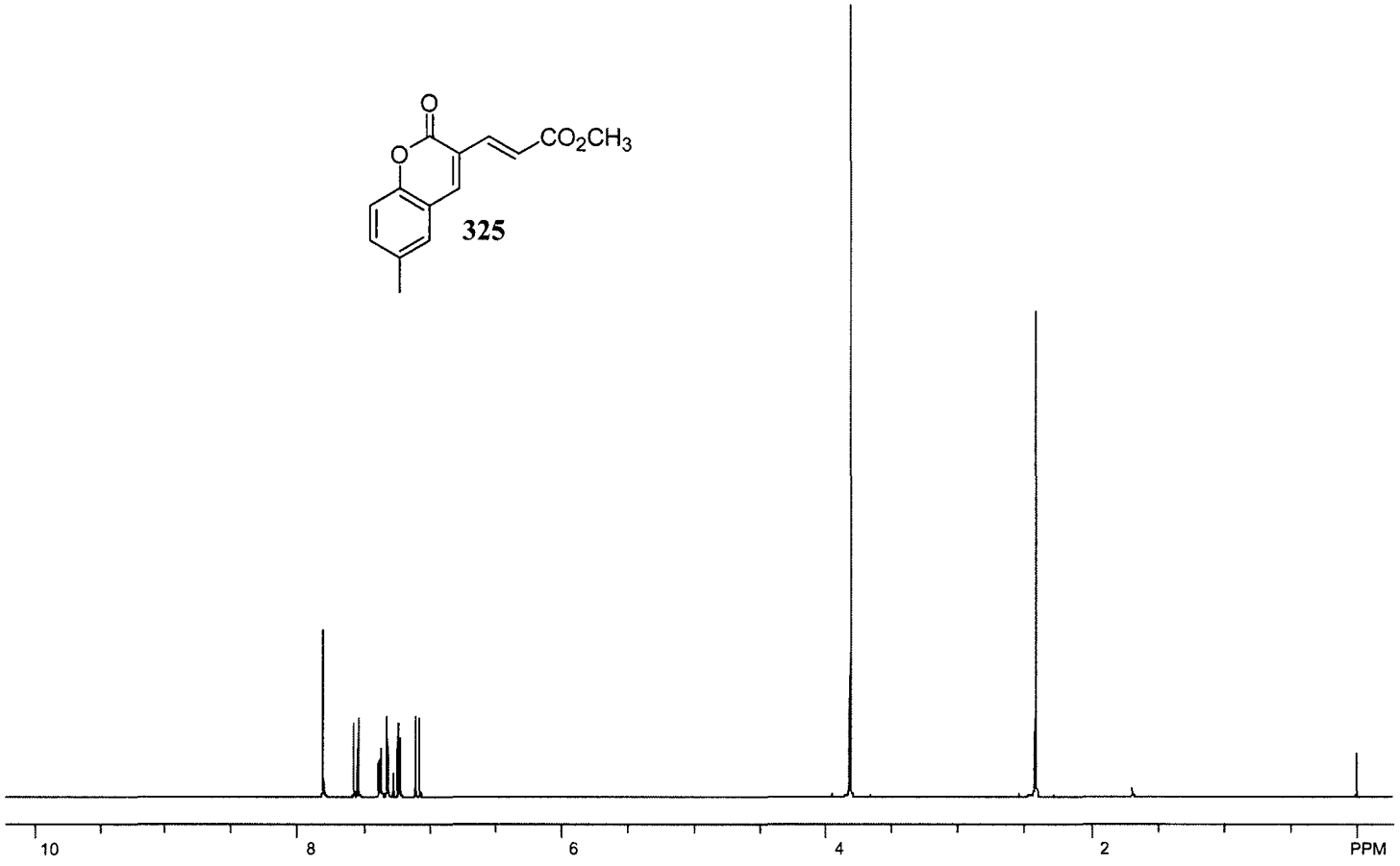
298



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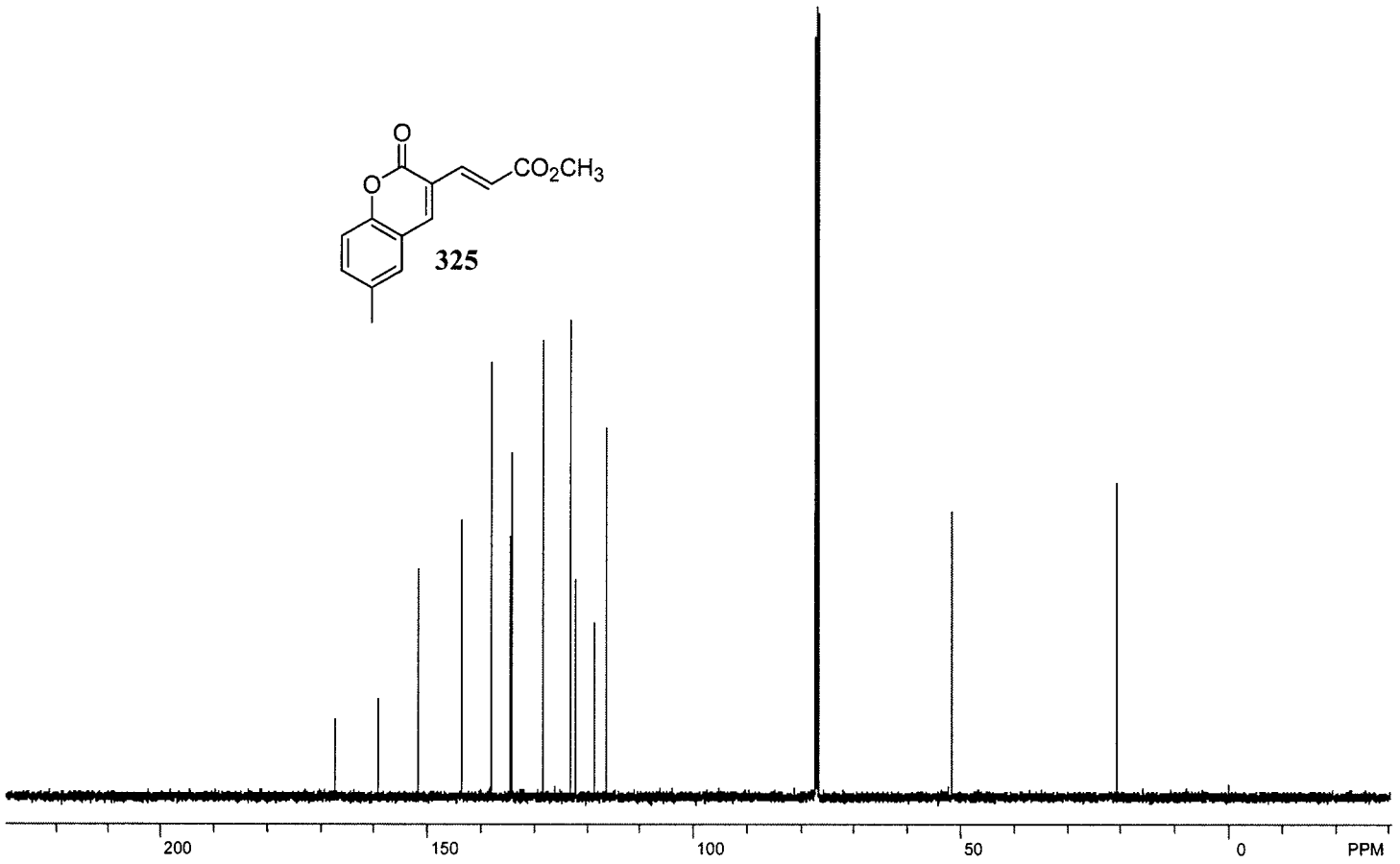
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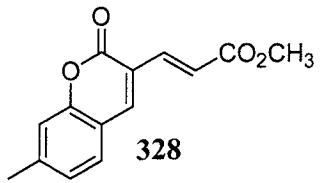

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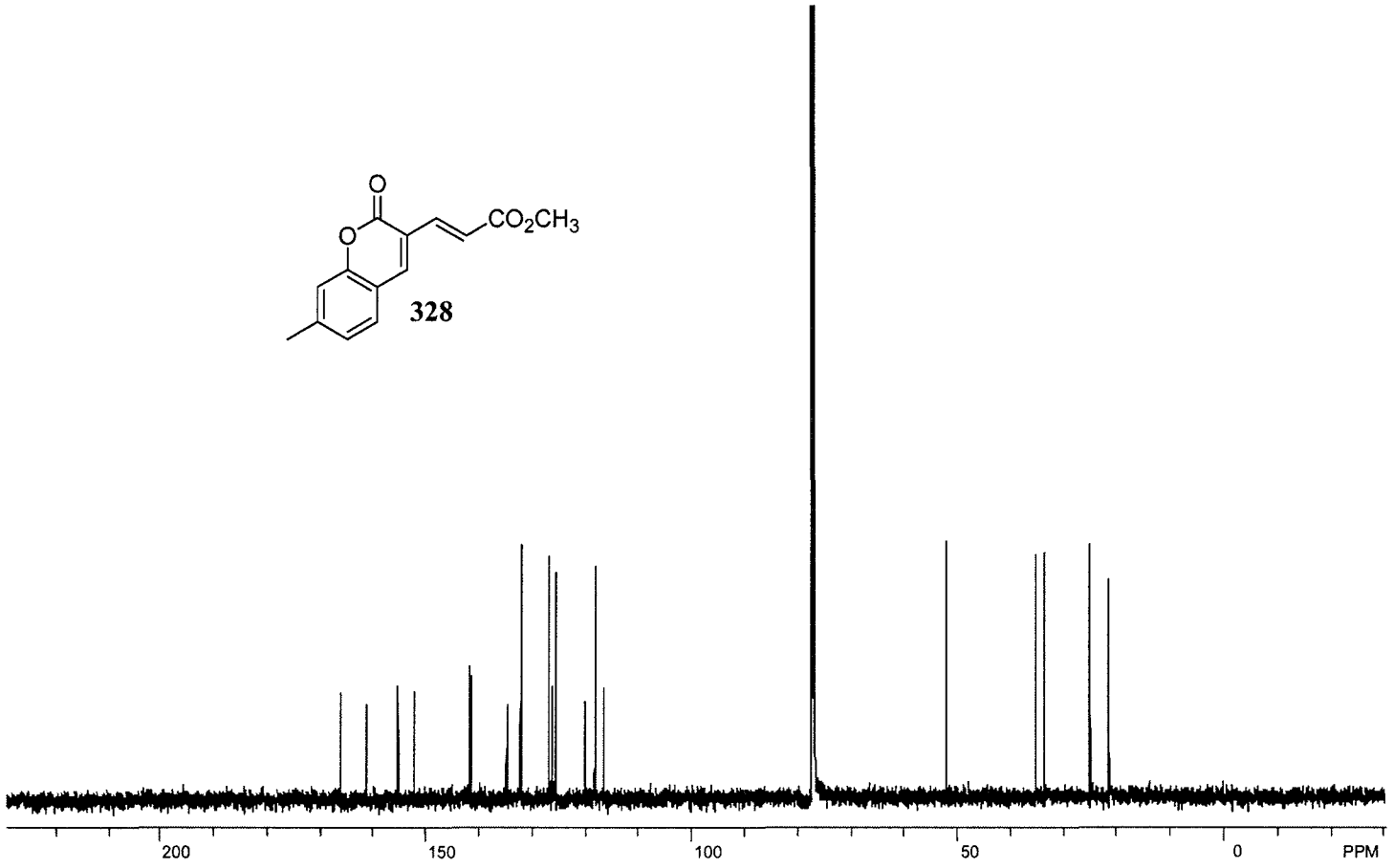
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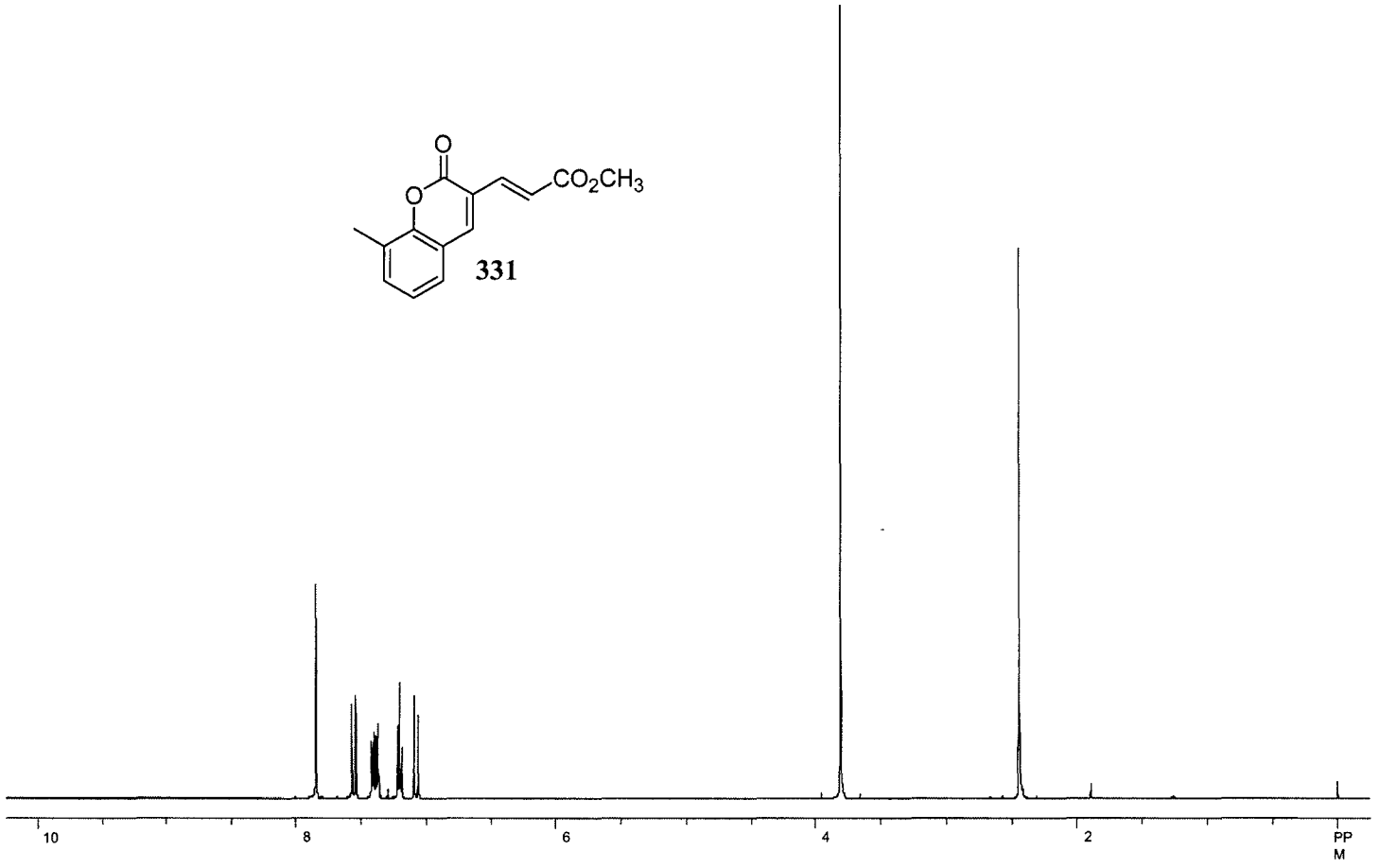
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PP
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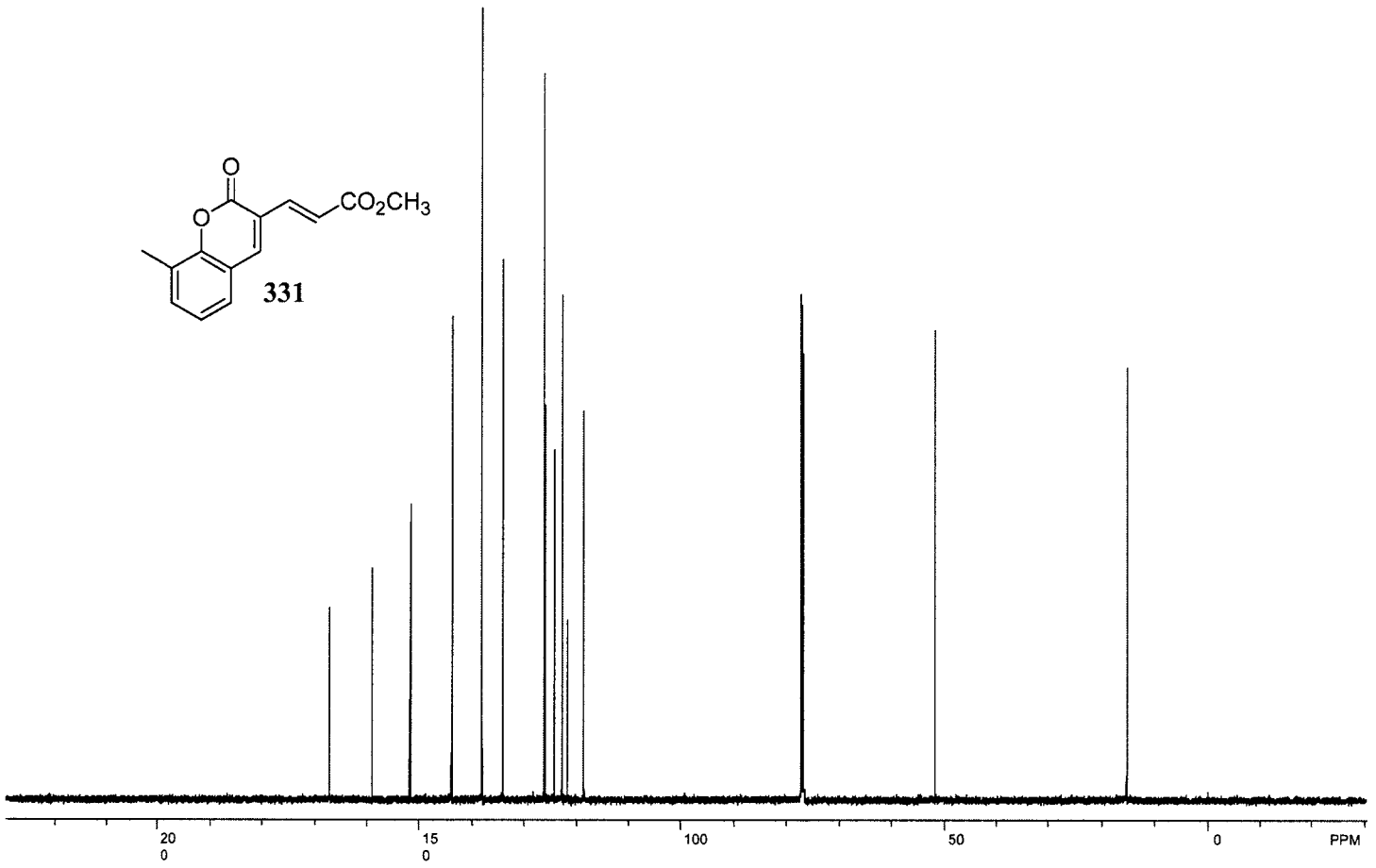
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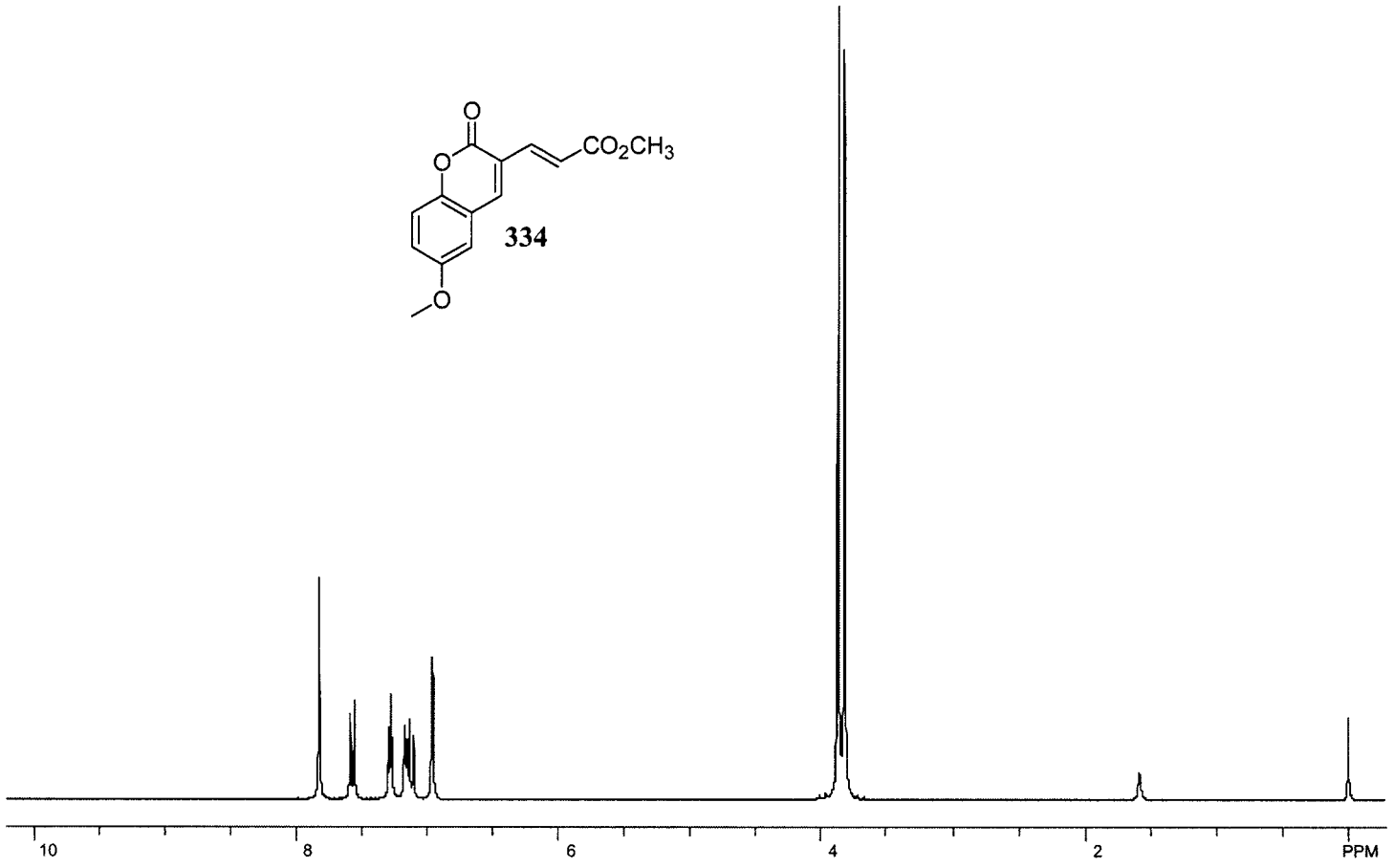

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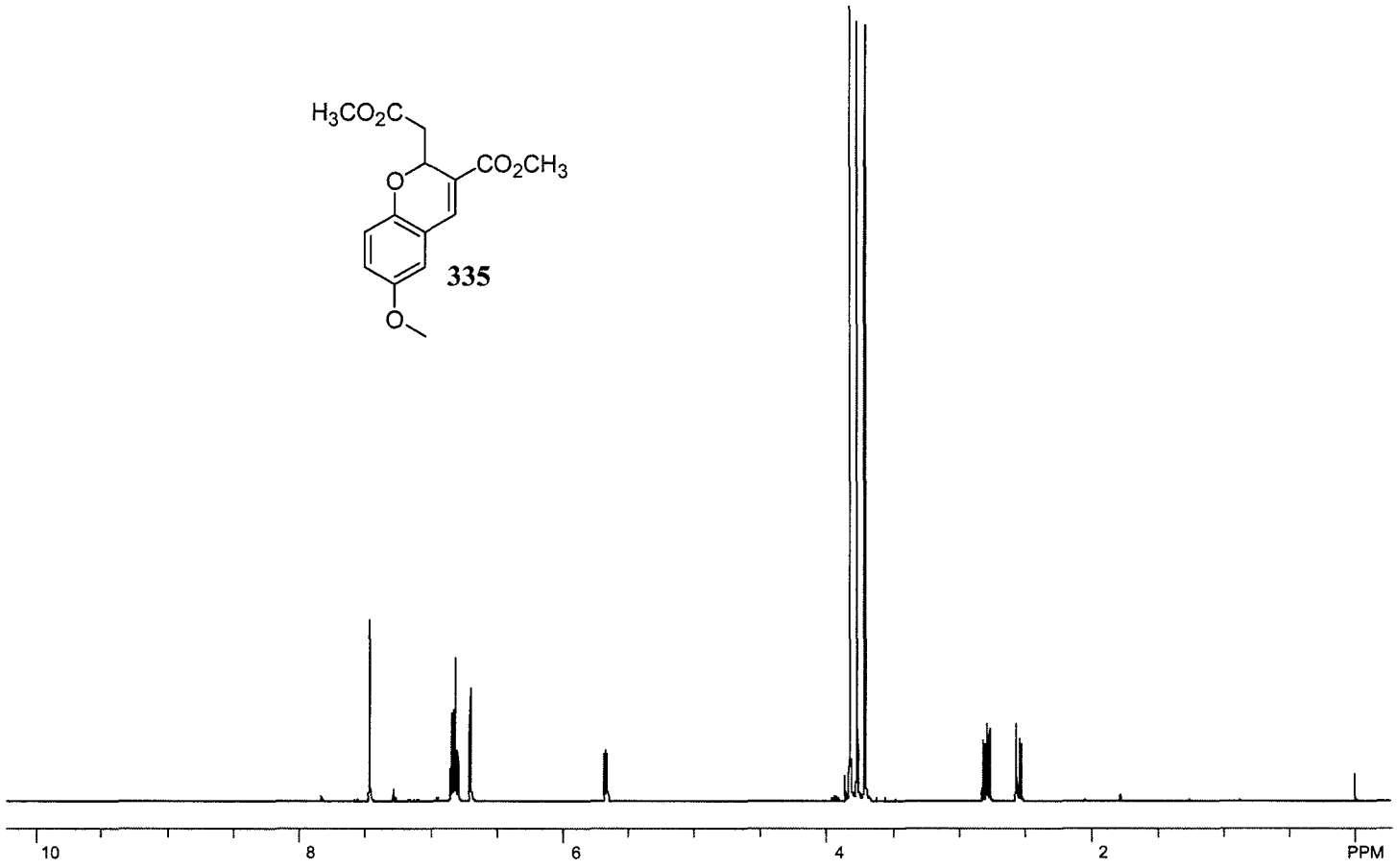
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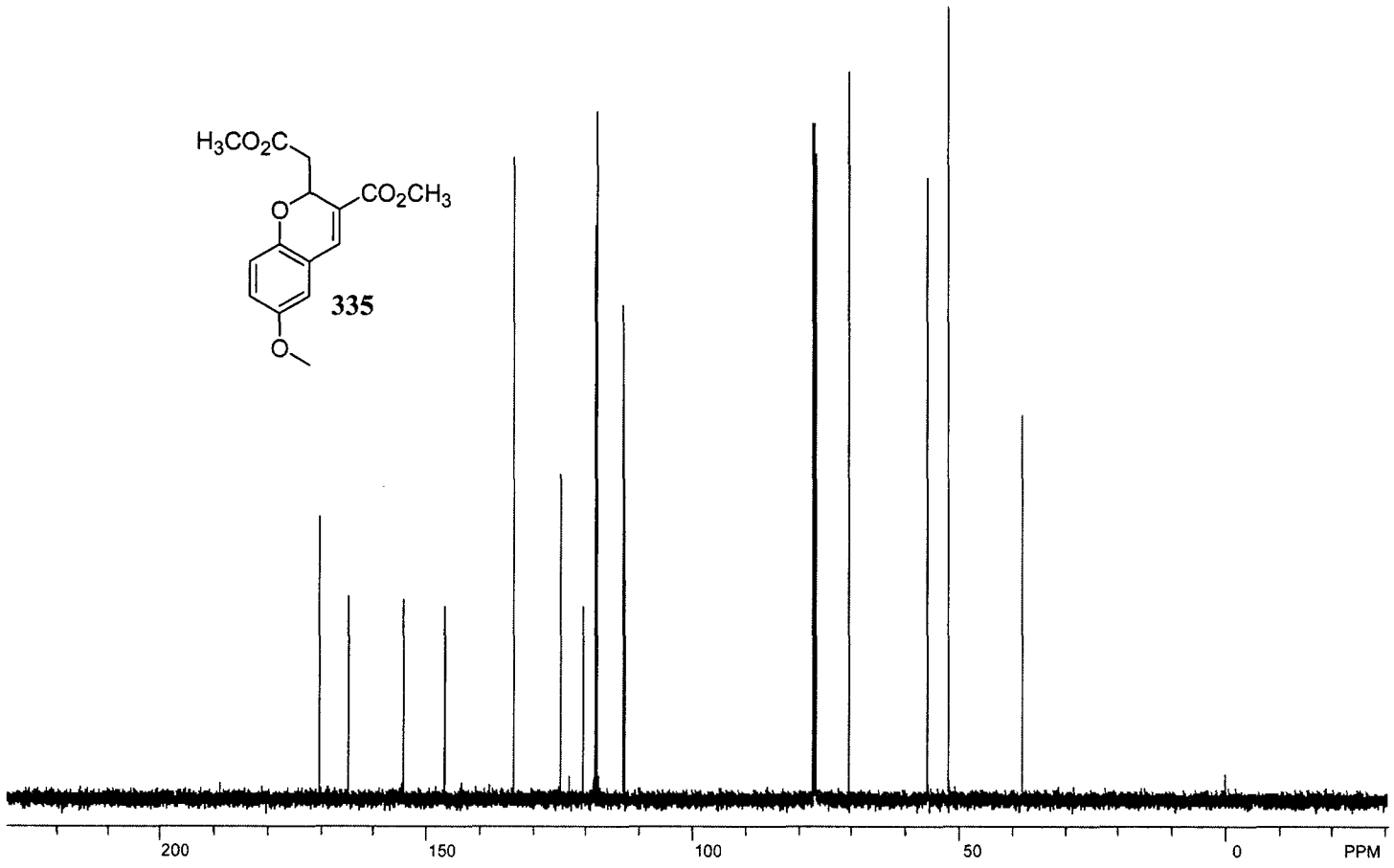
PPM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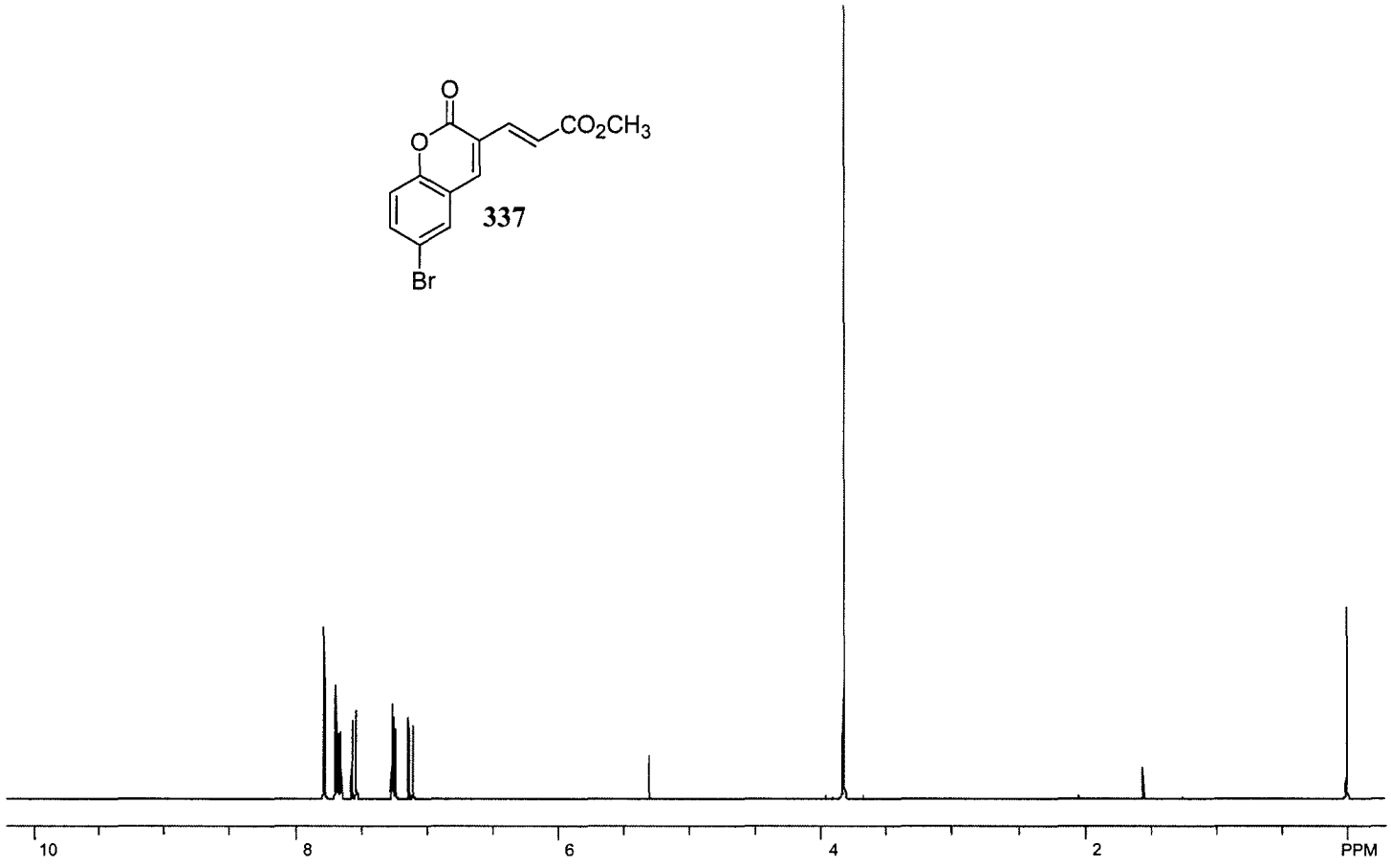
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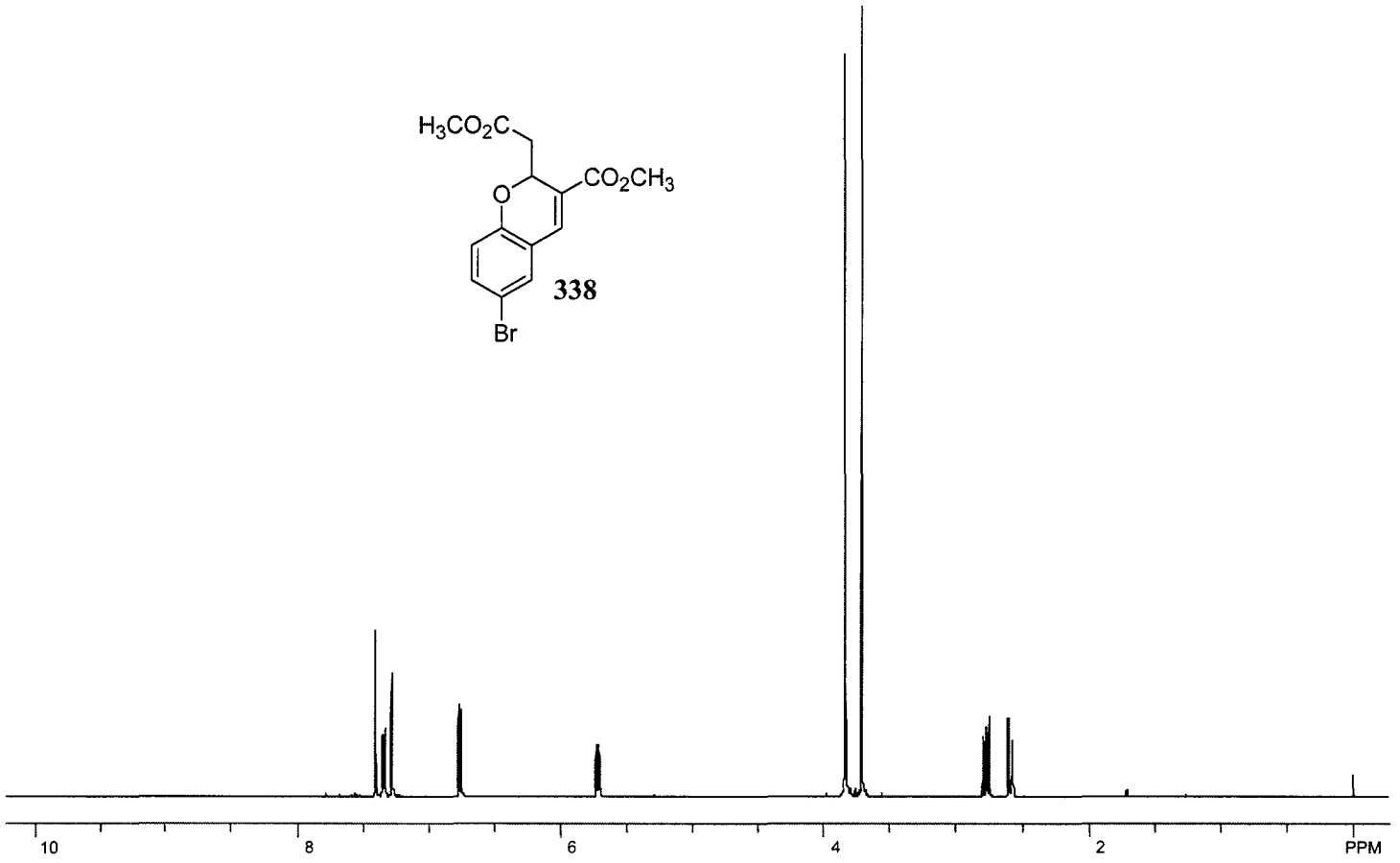
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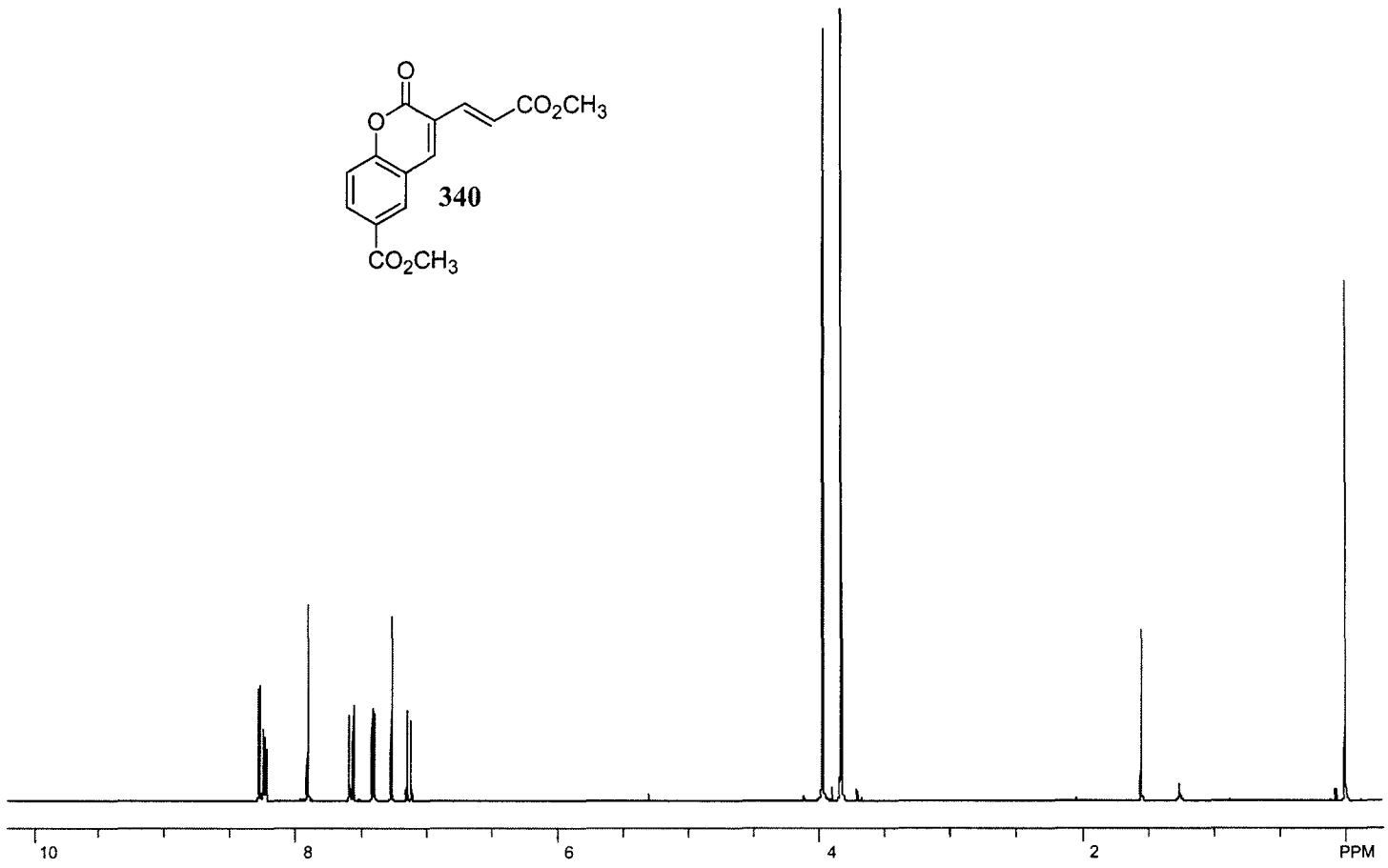
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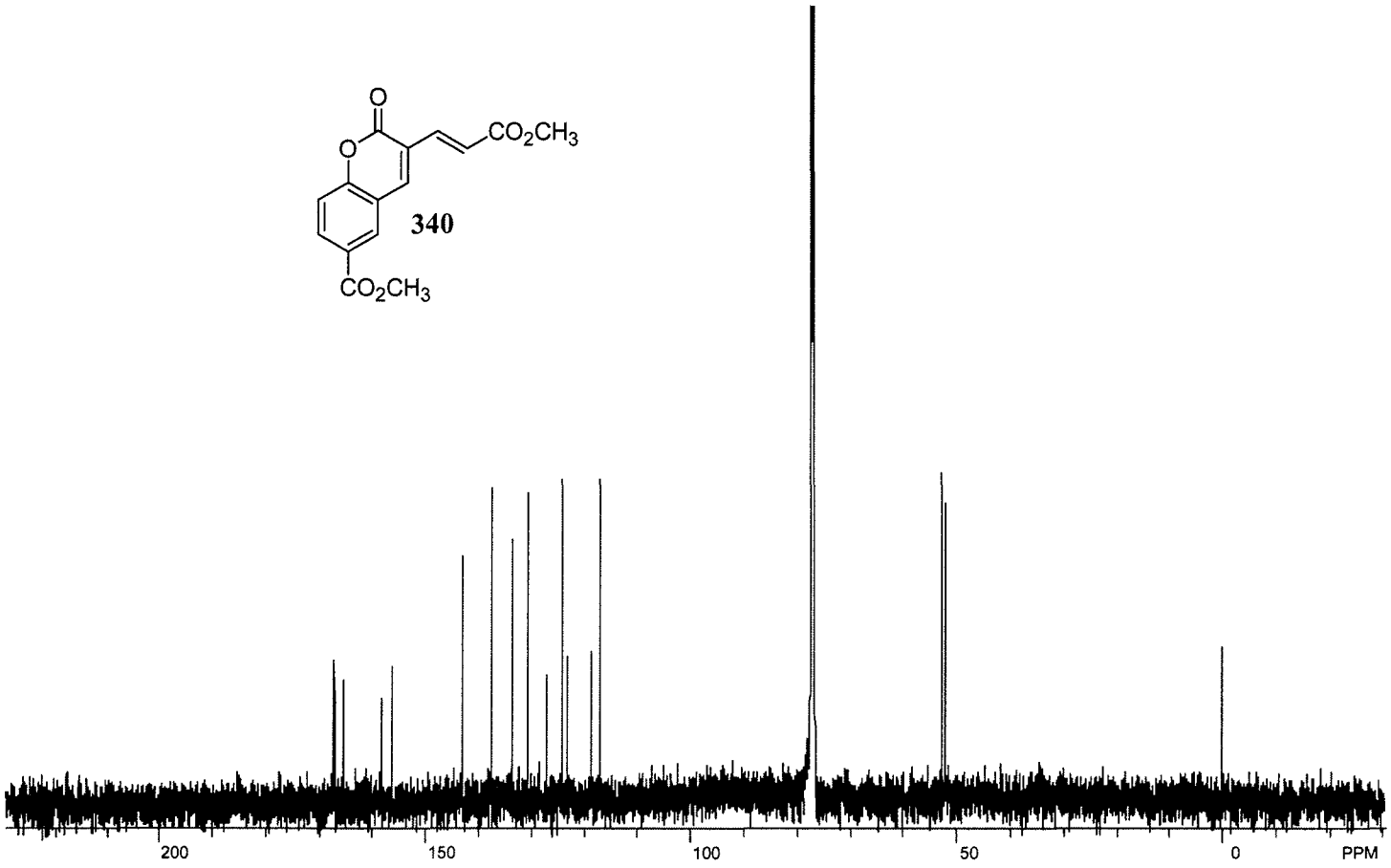

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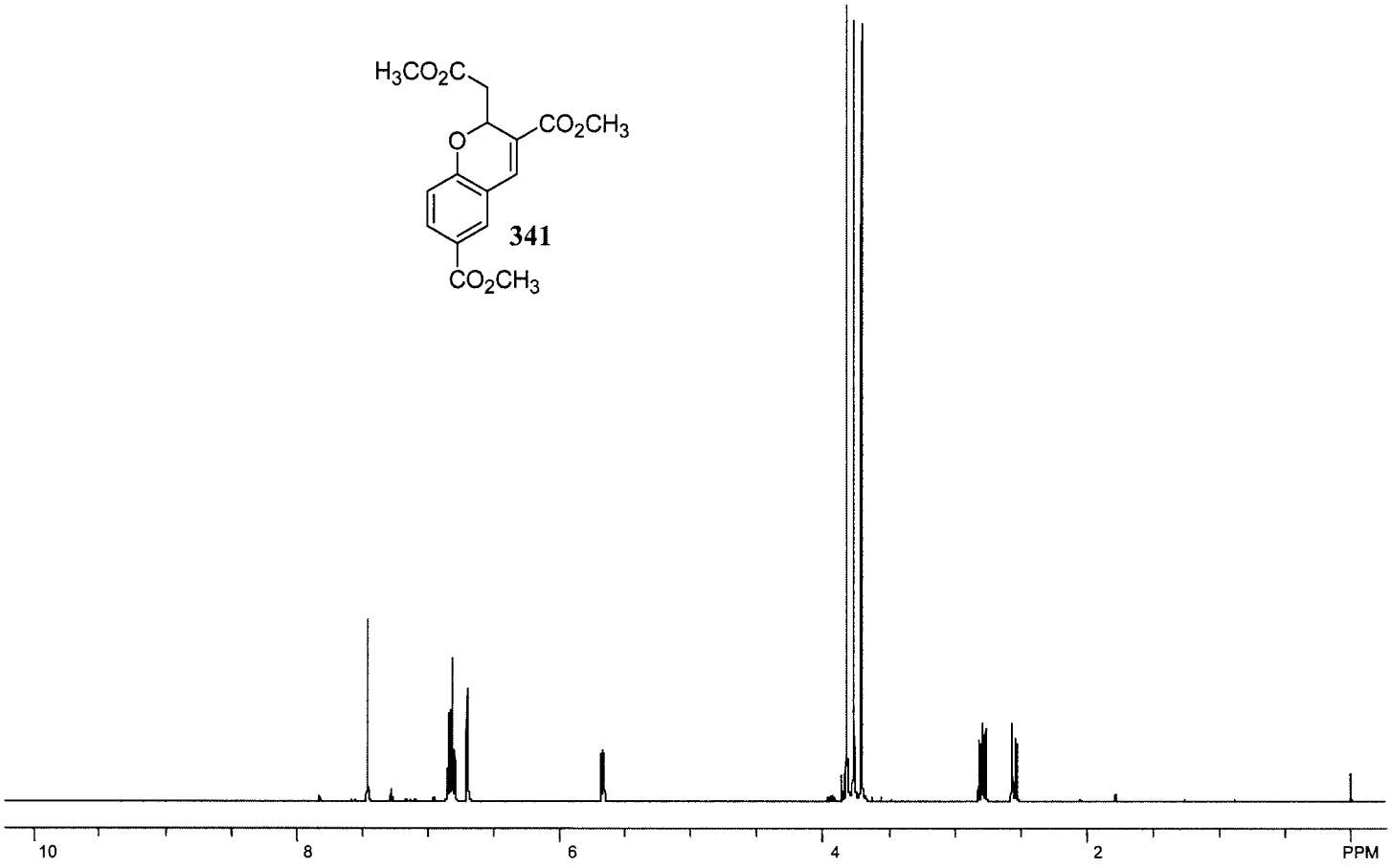

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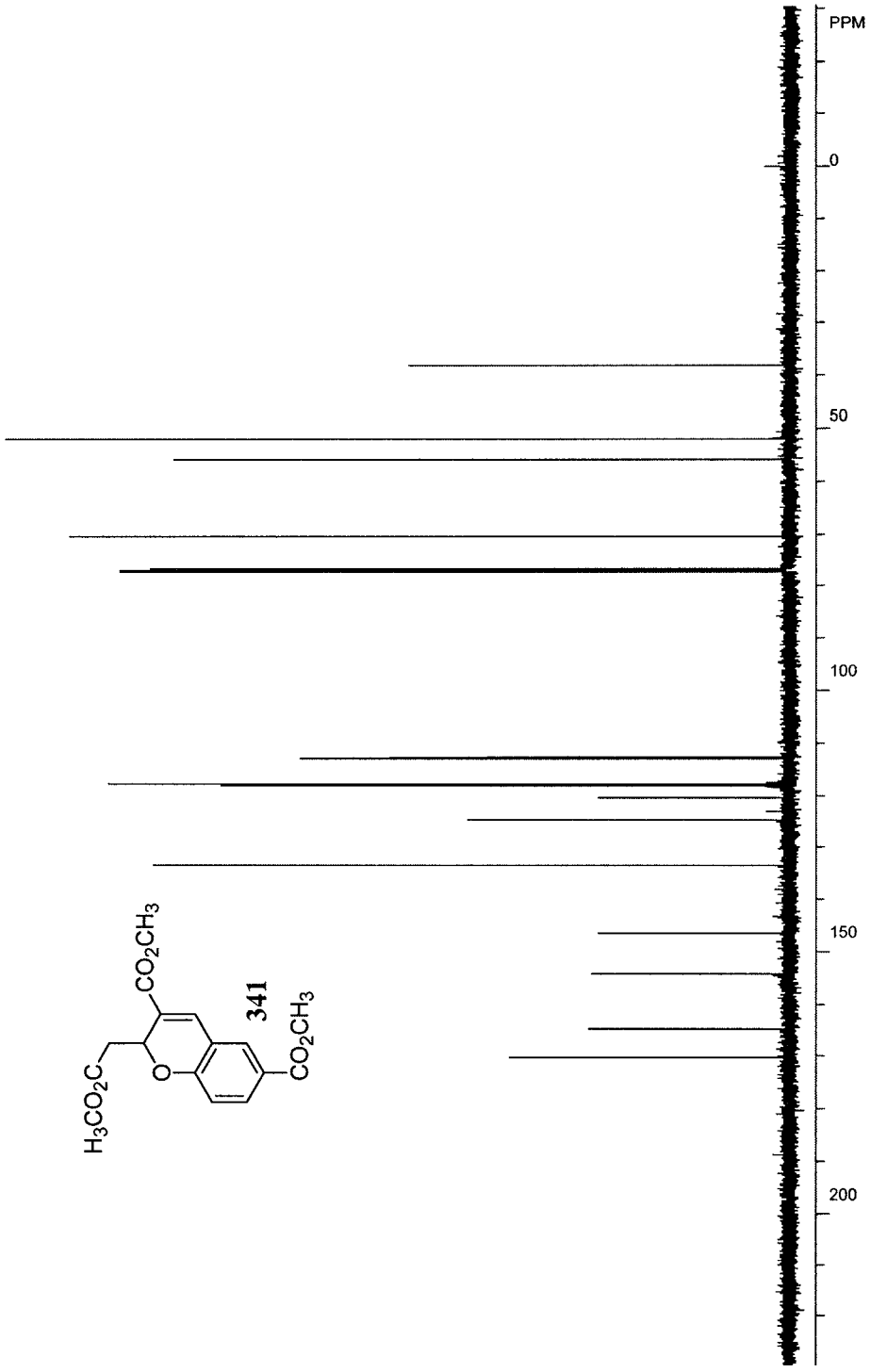
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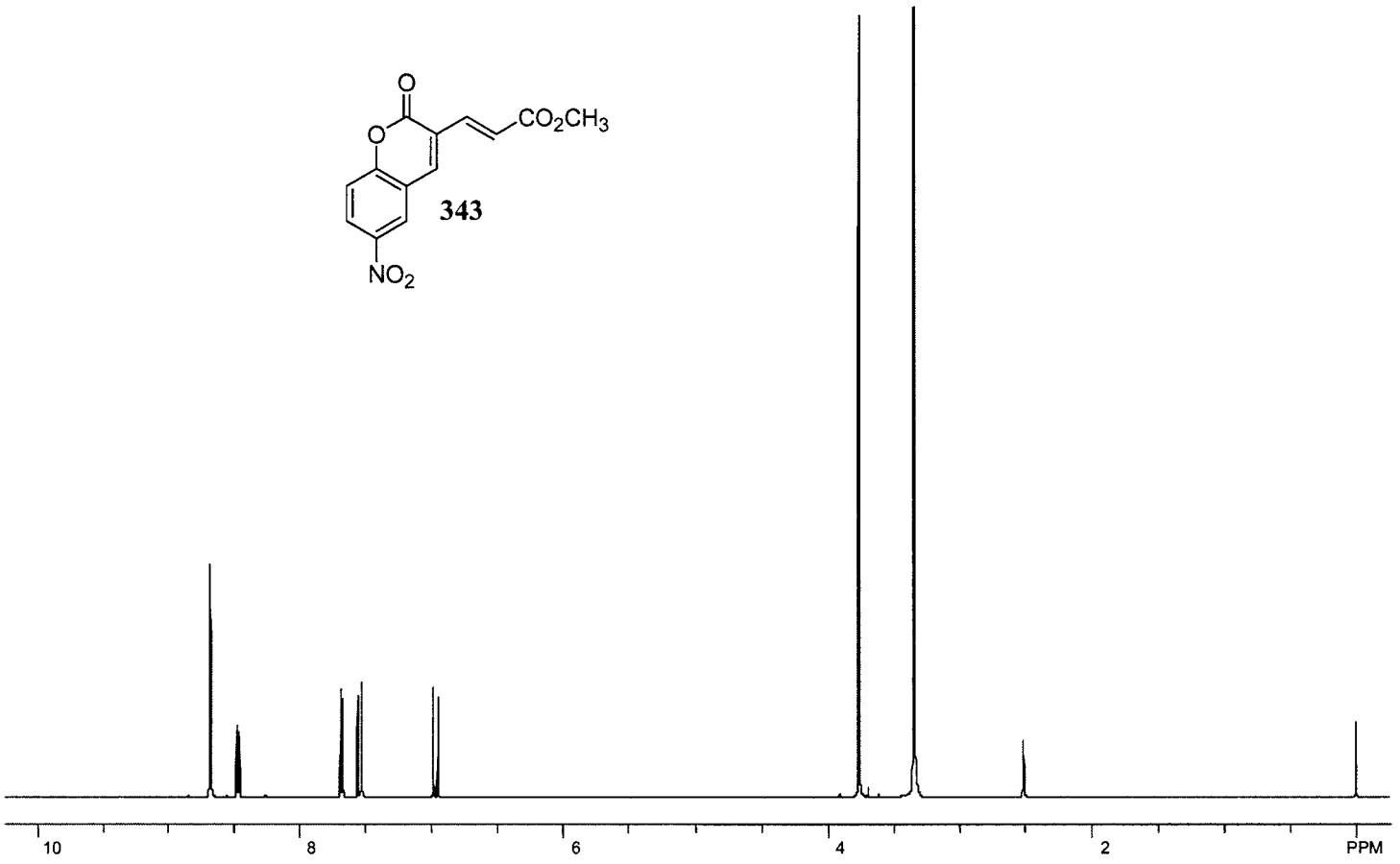
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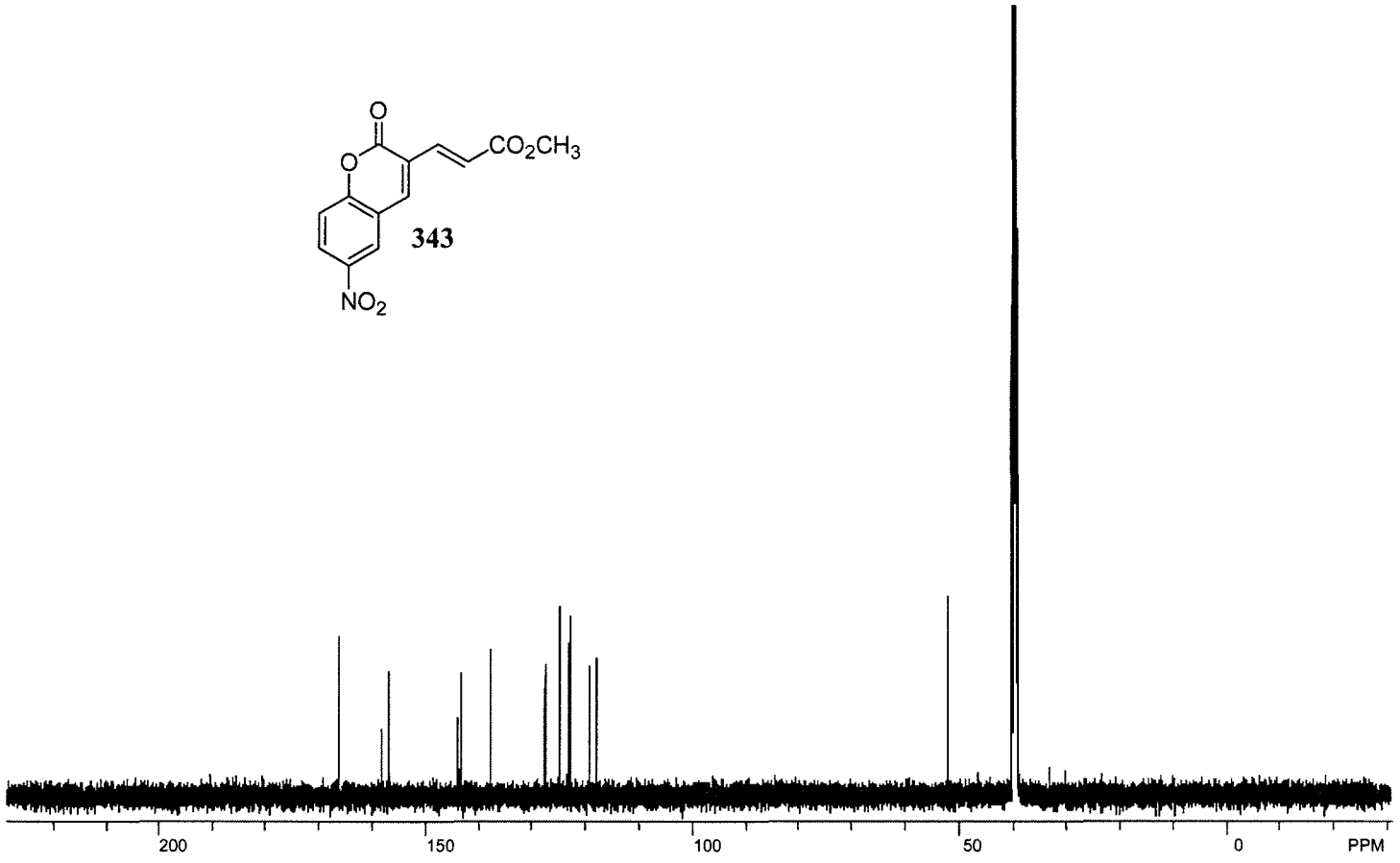

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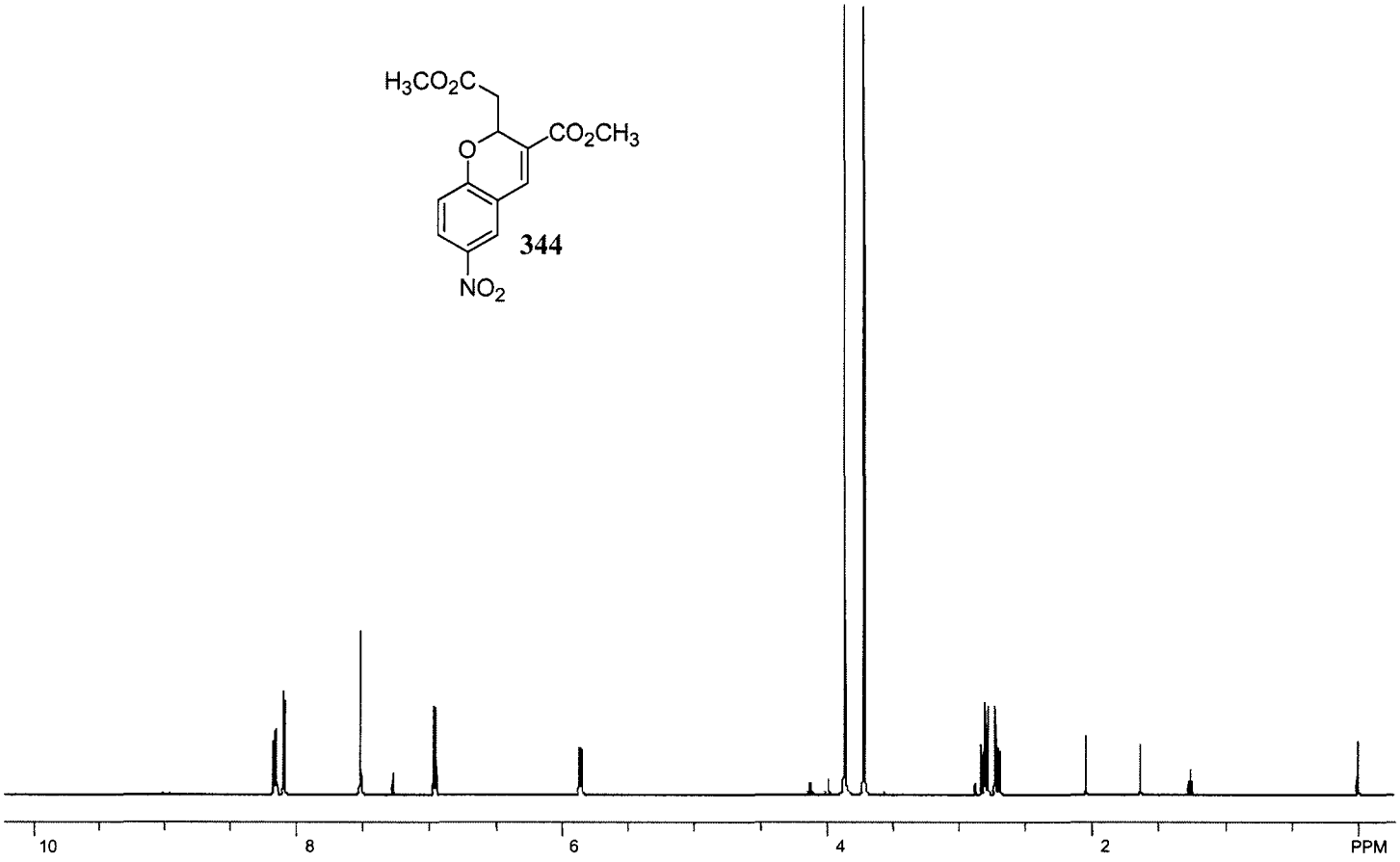
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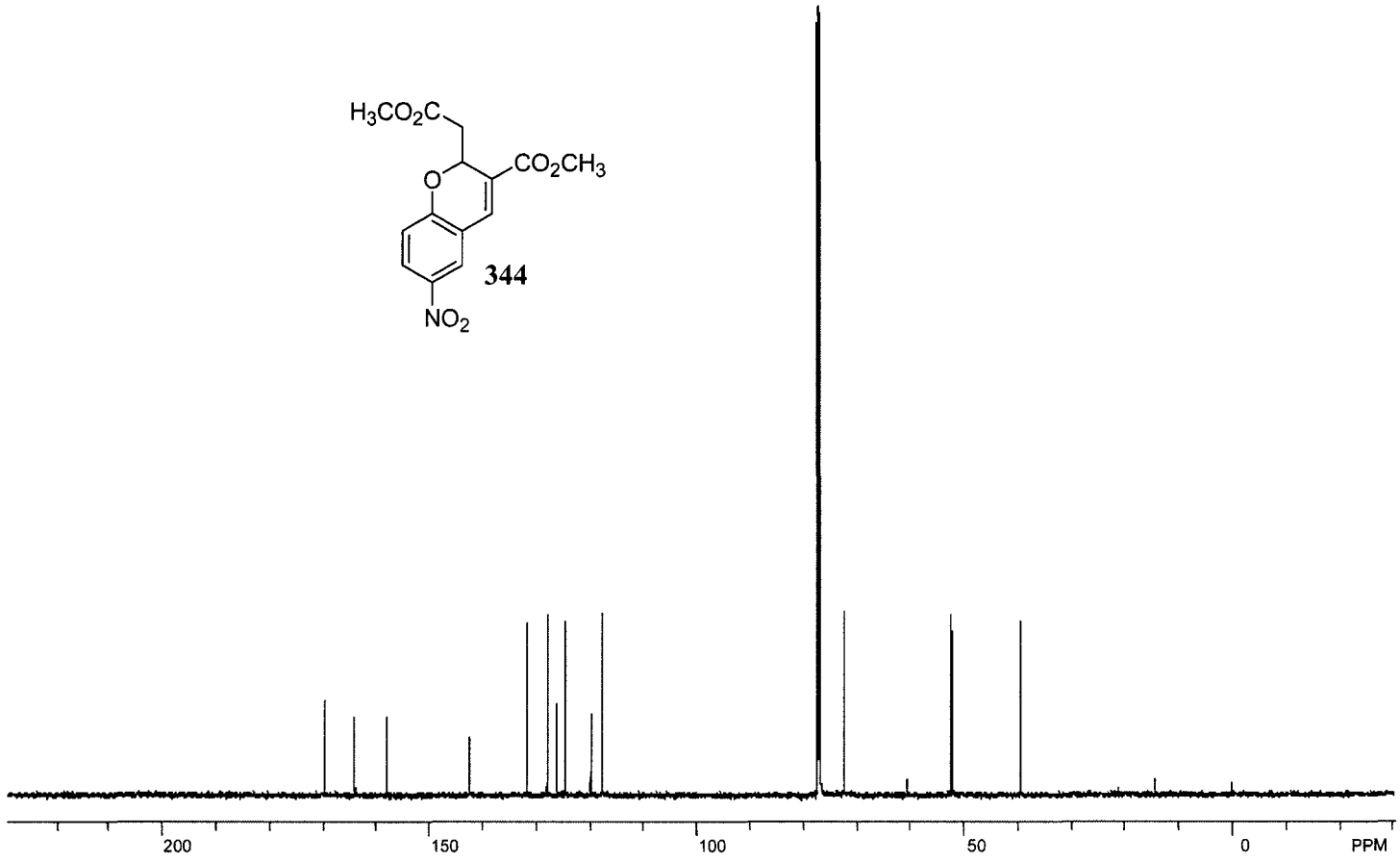
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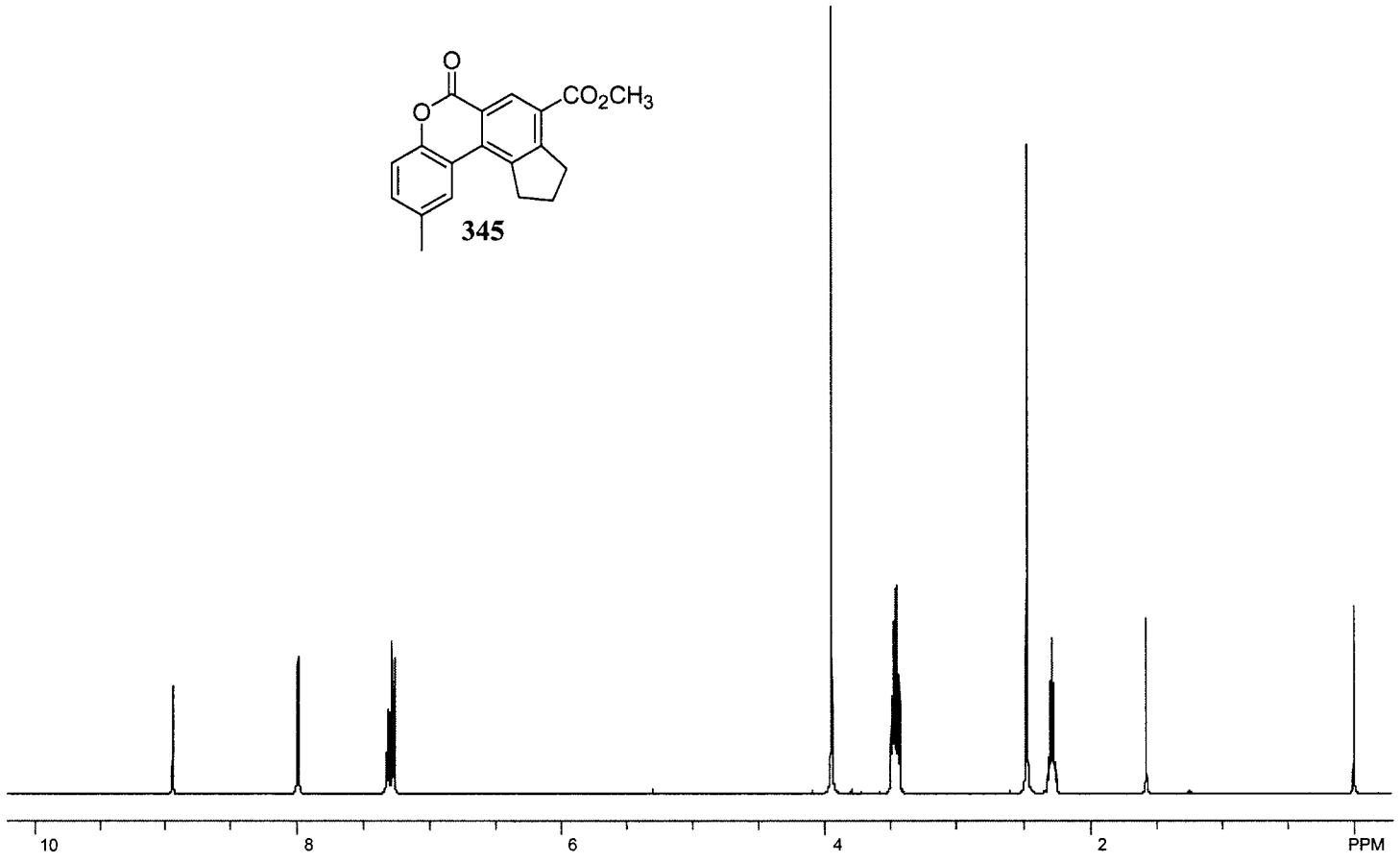

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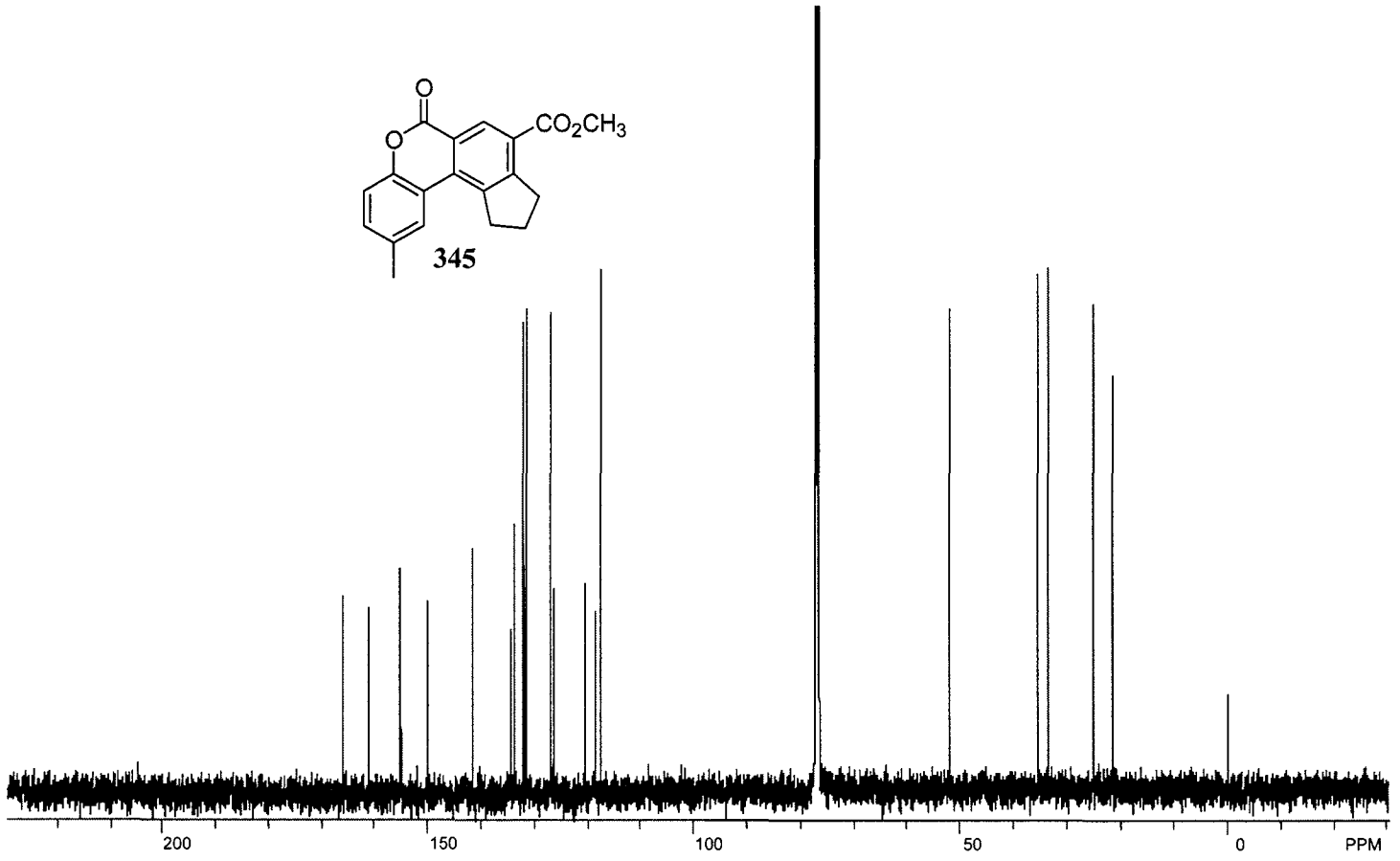
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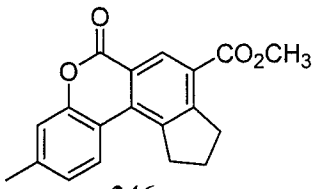

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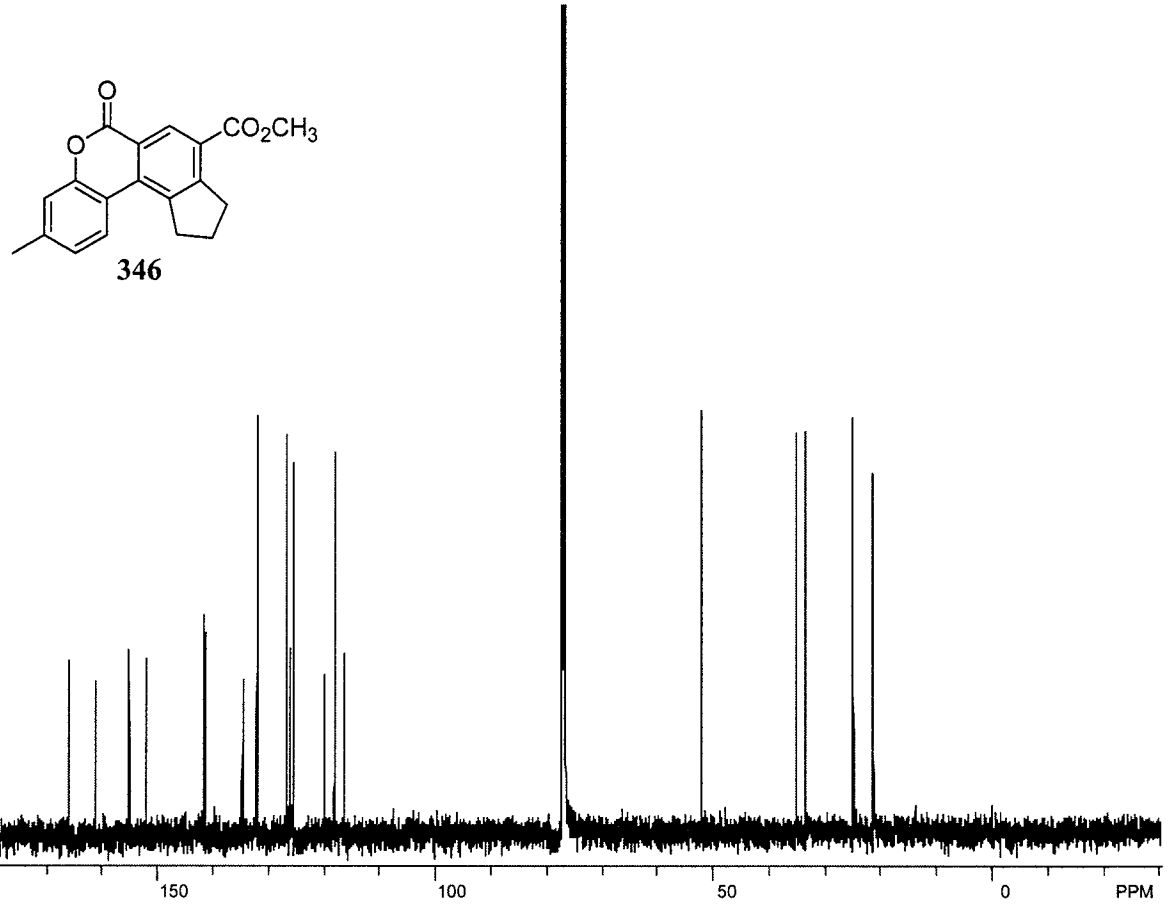

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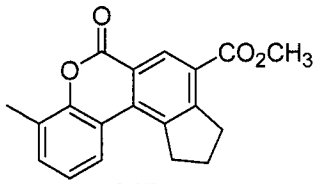

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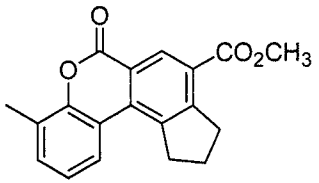

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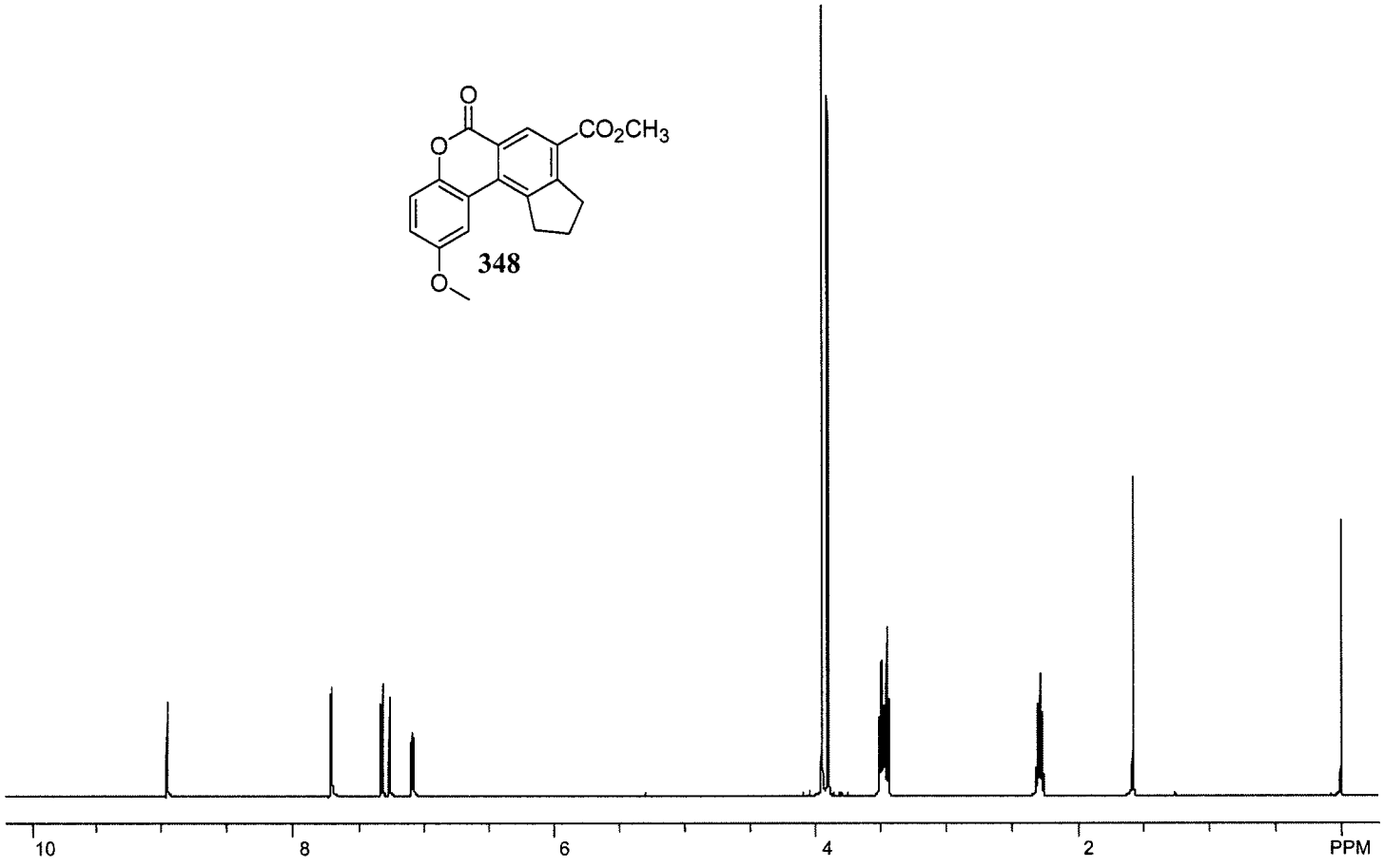
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PPM

PPM
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200
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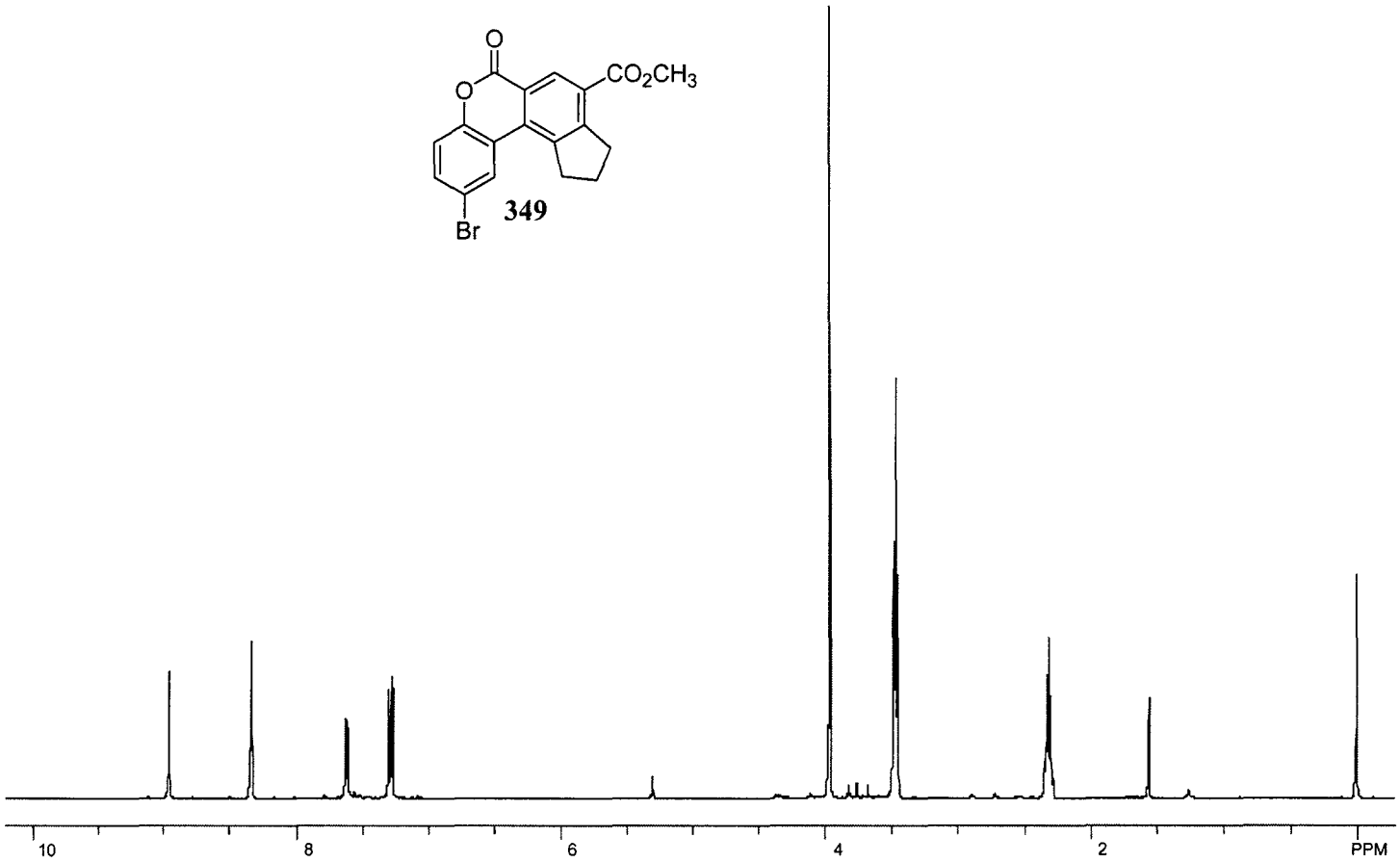
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PPM

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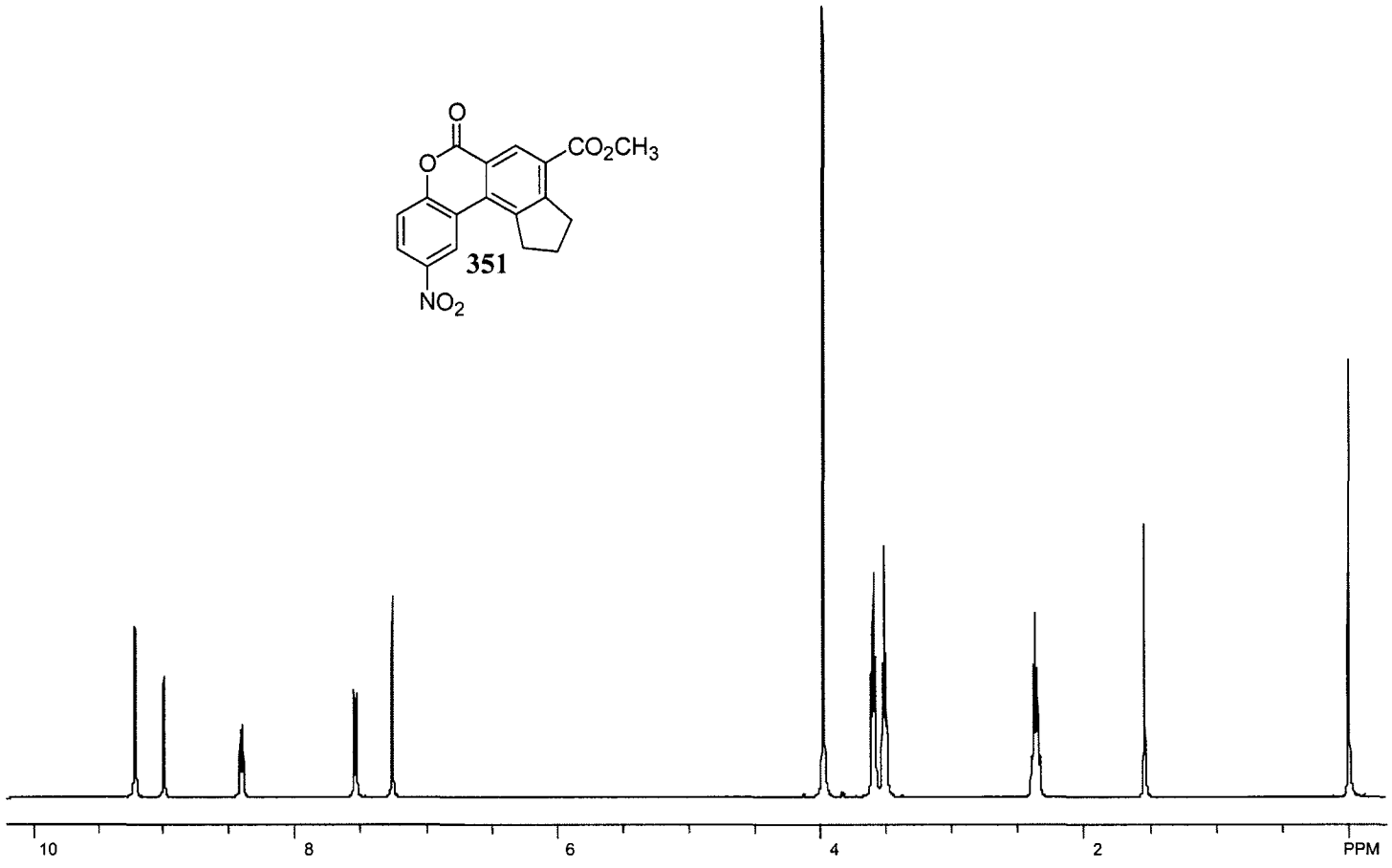
350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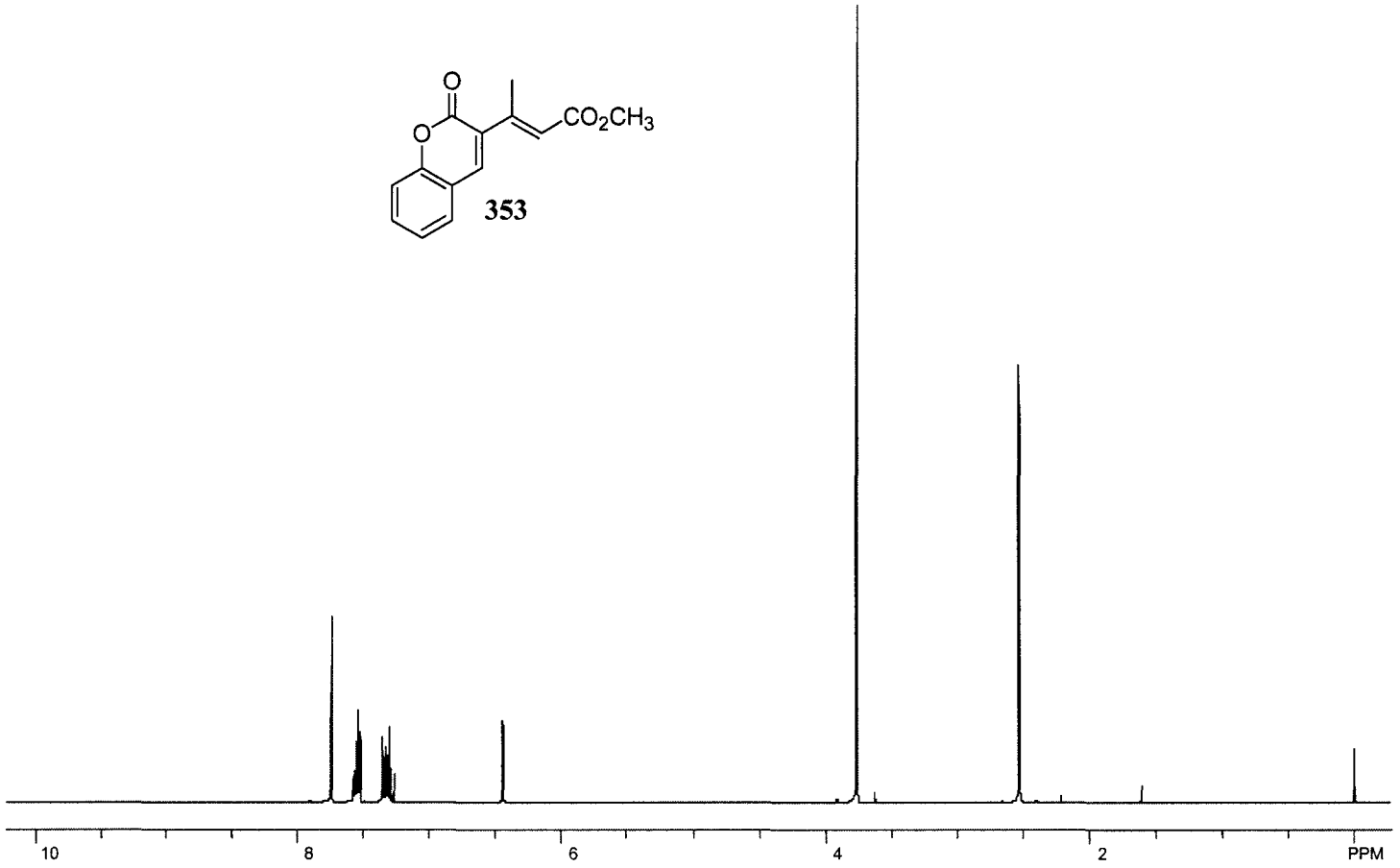
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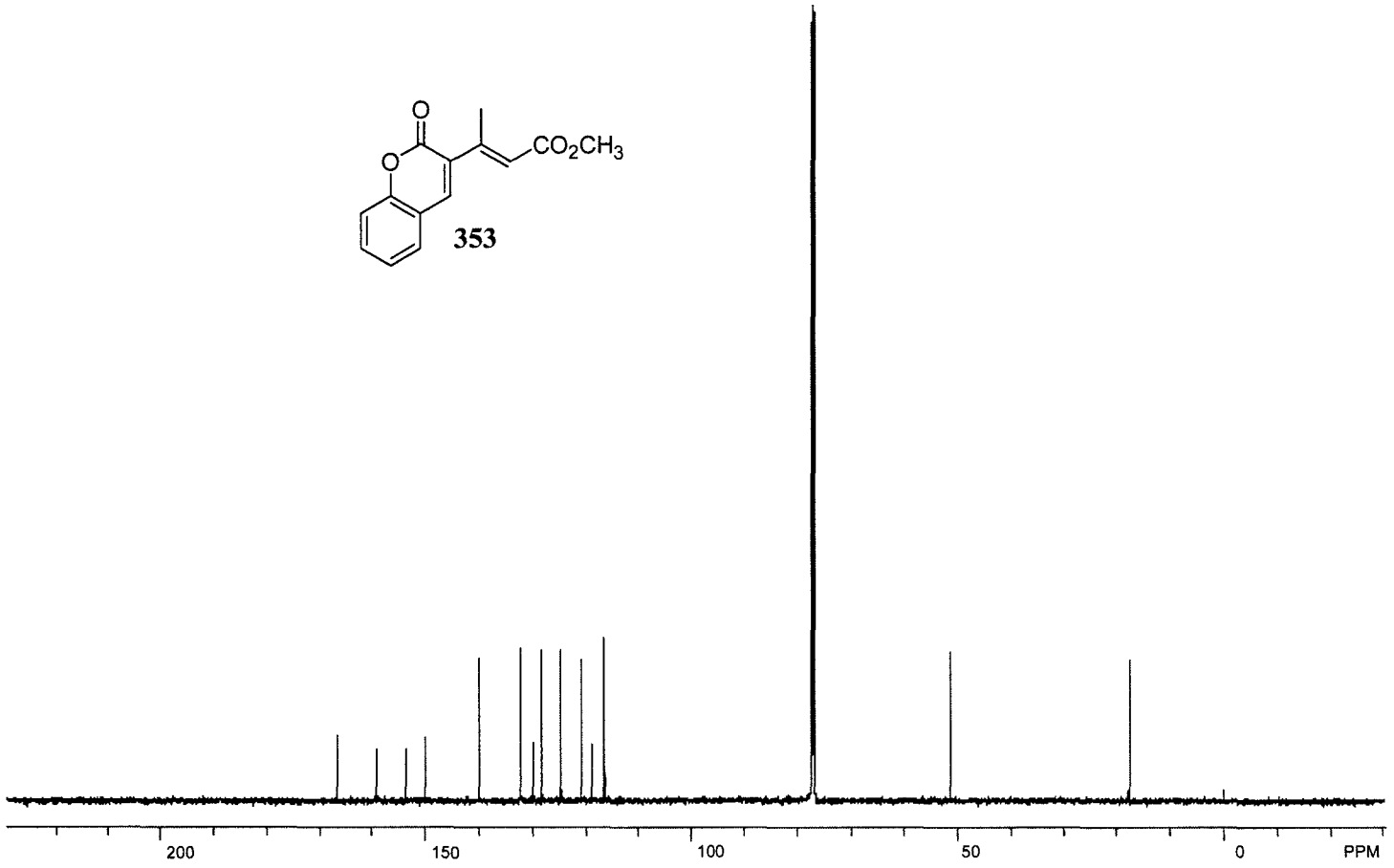

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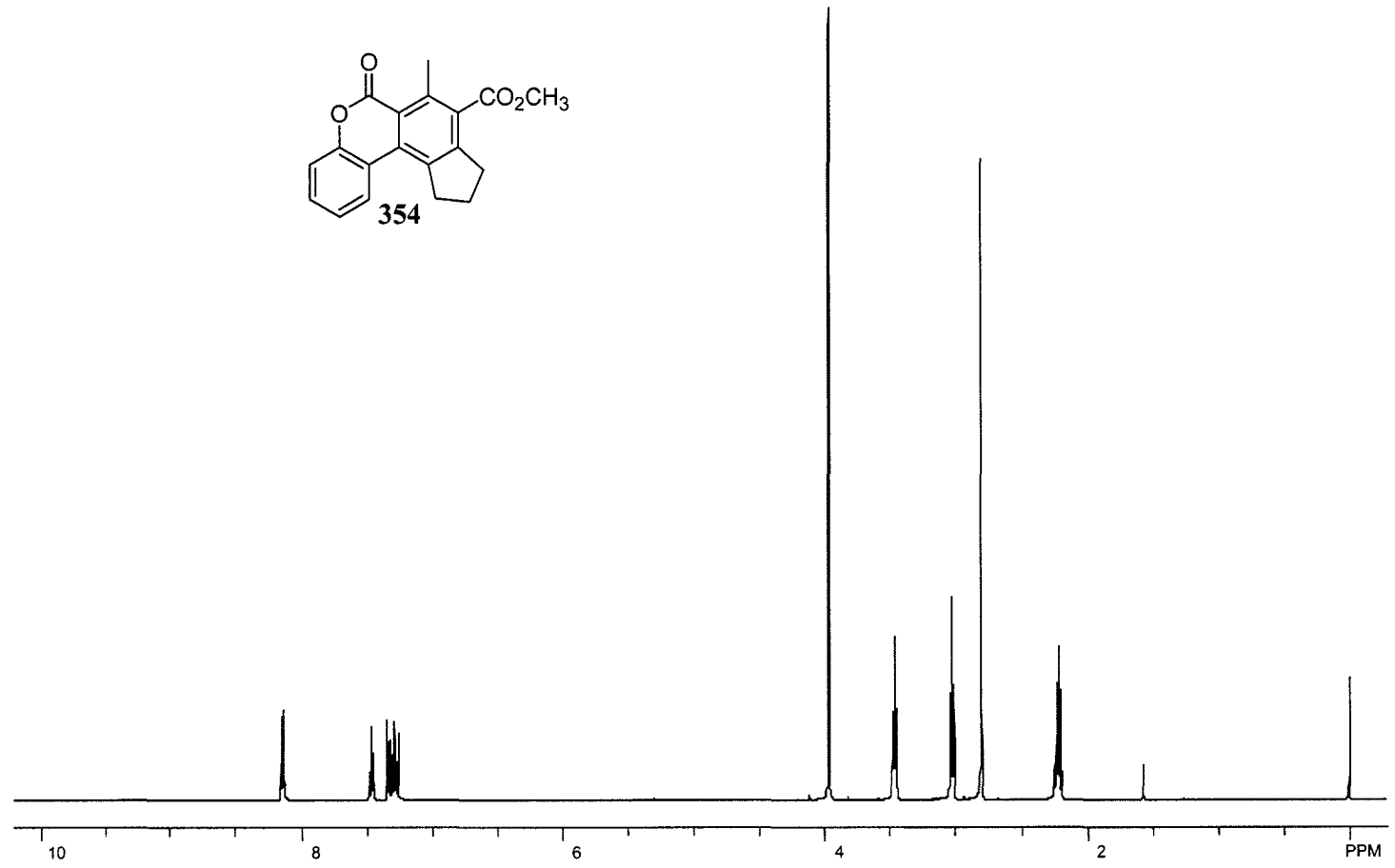

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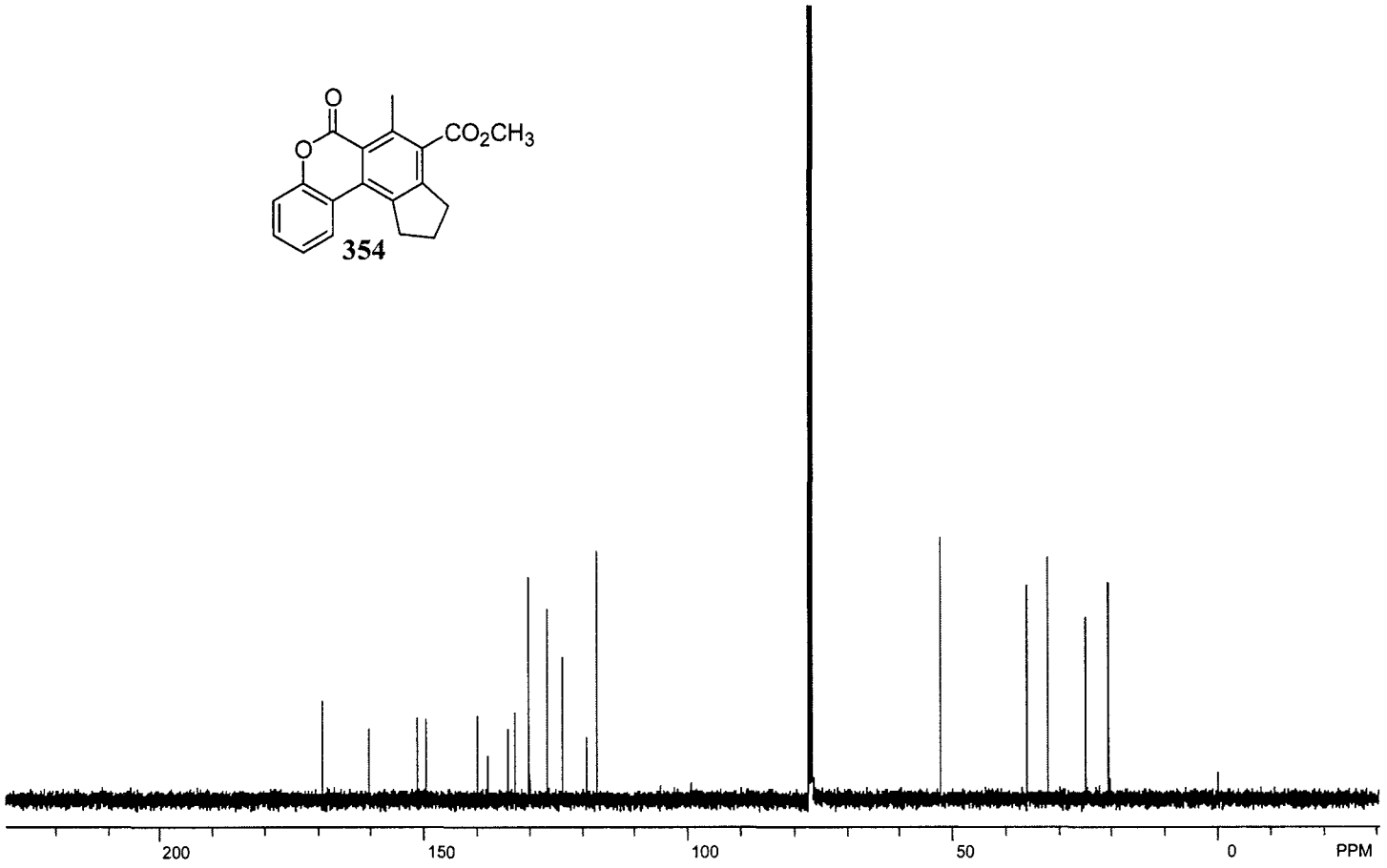

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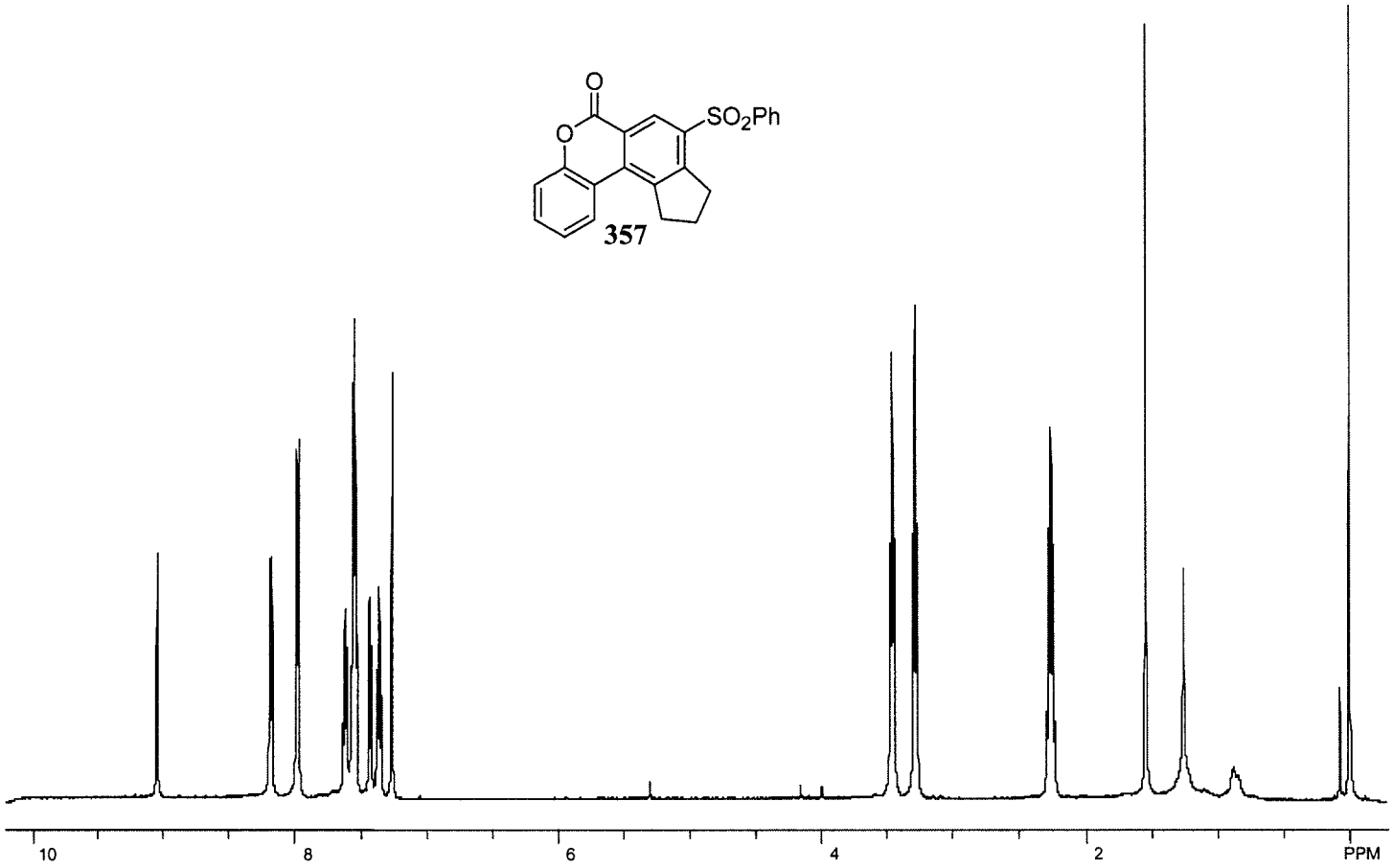
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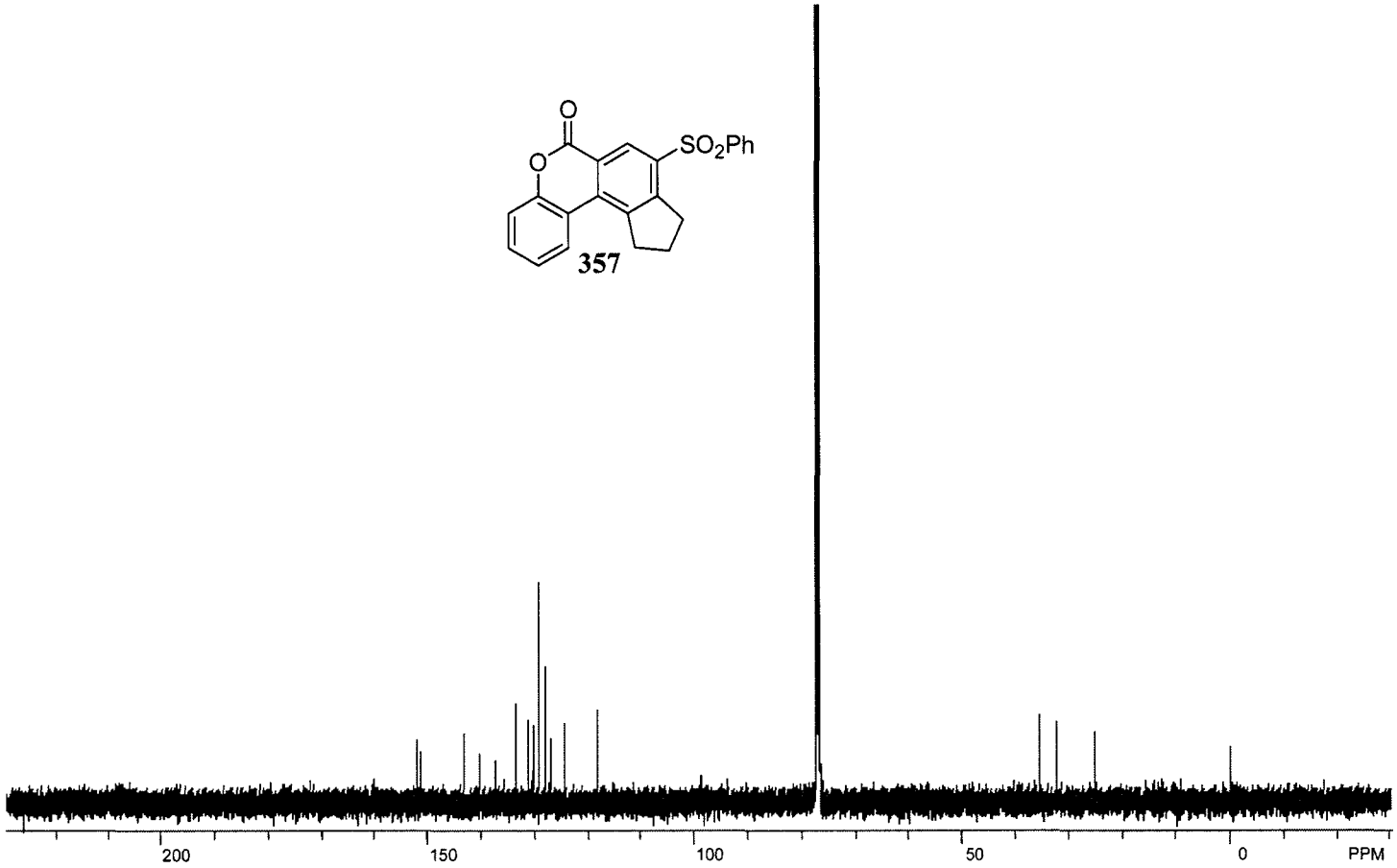
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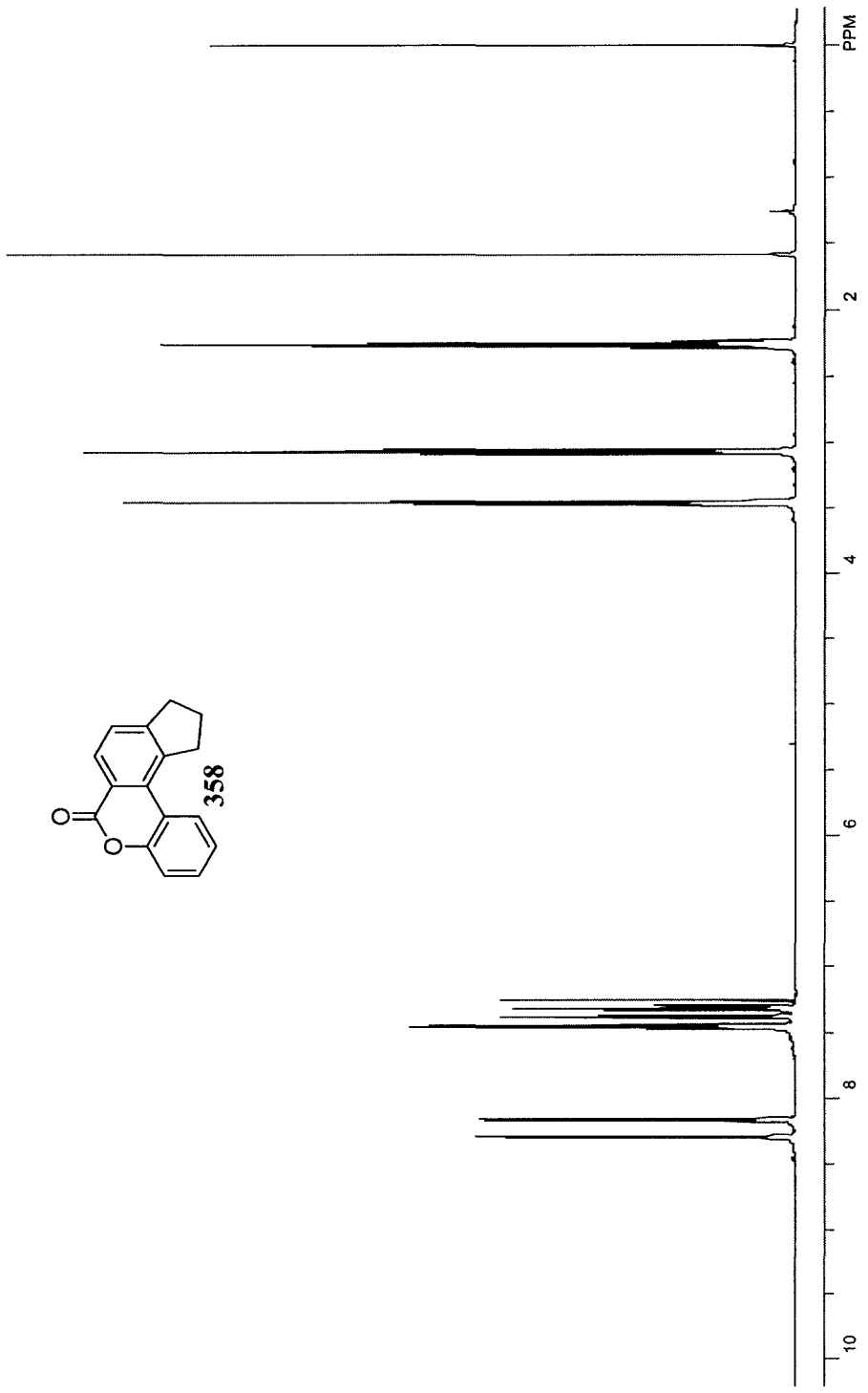
358
PPM
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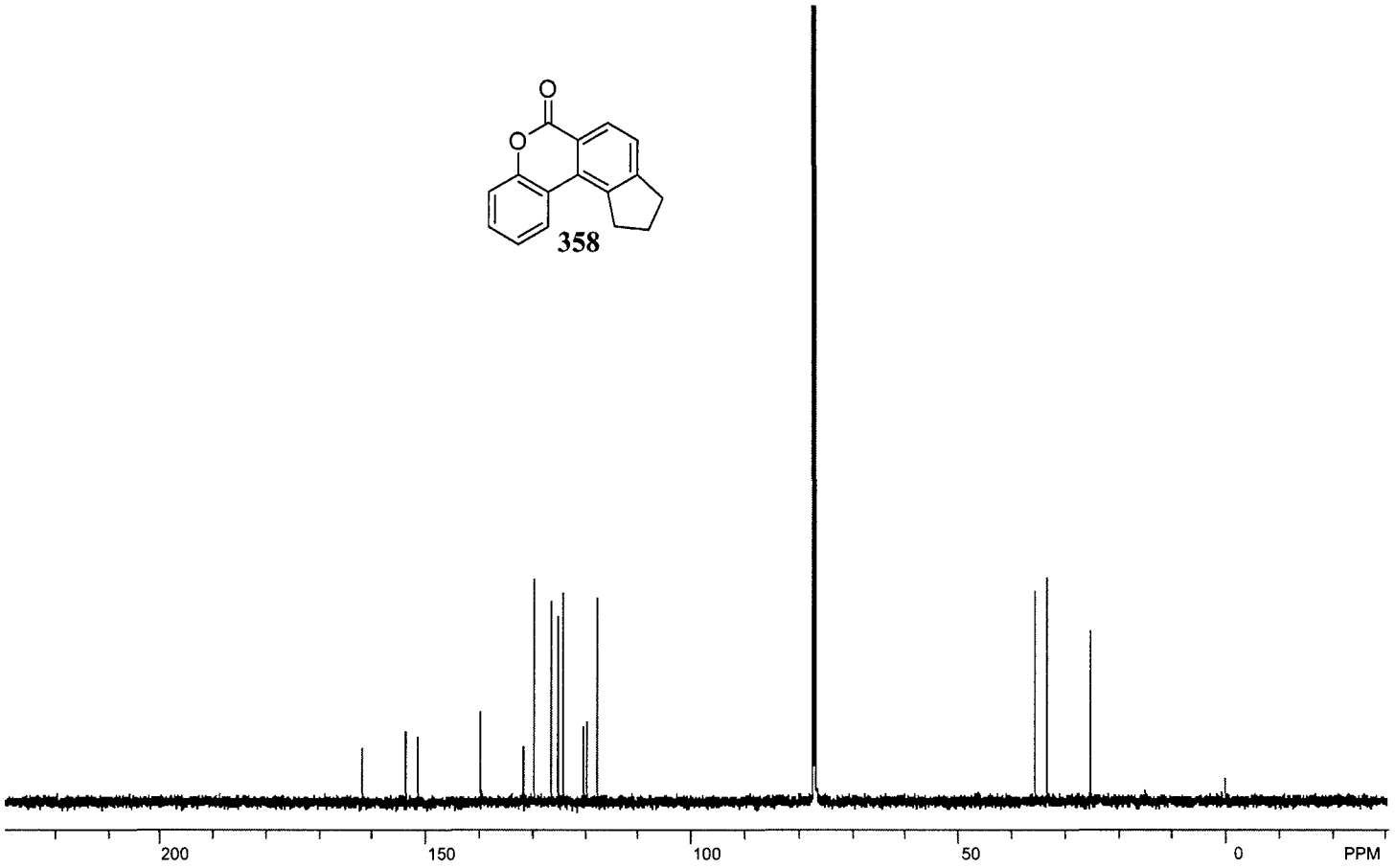
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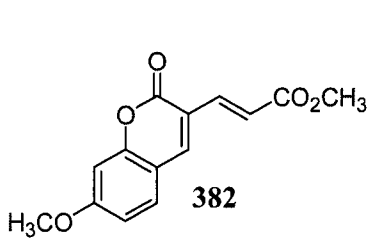
PPM



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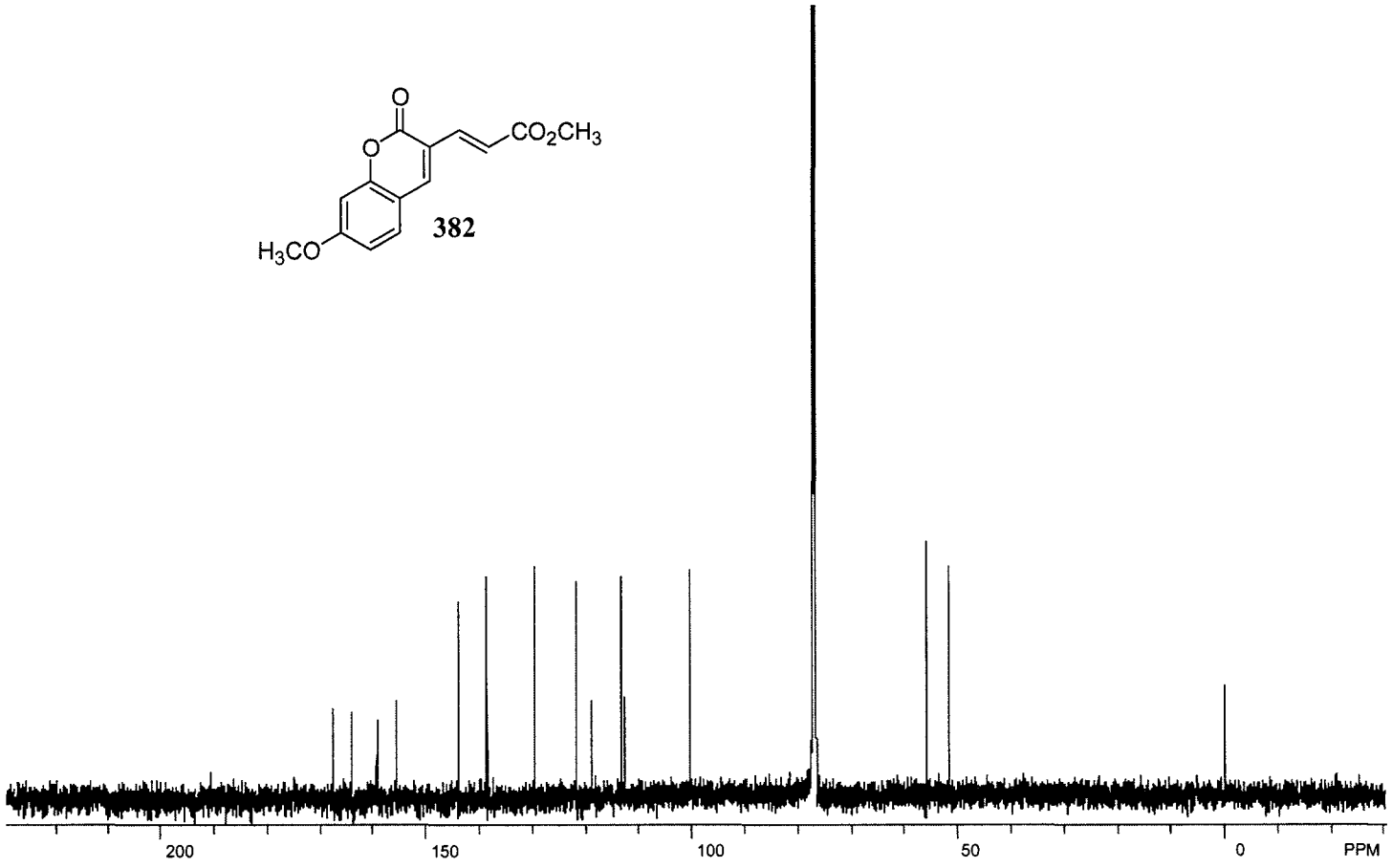
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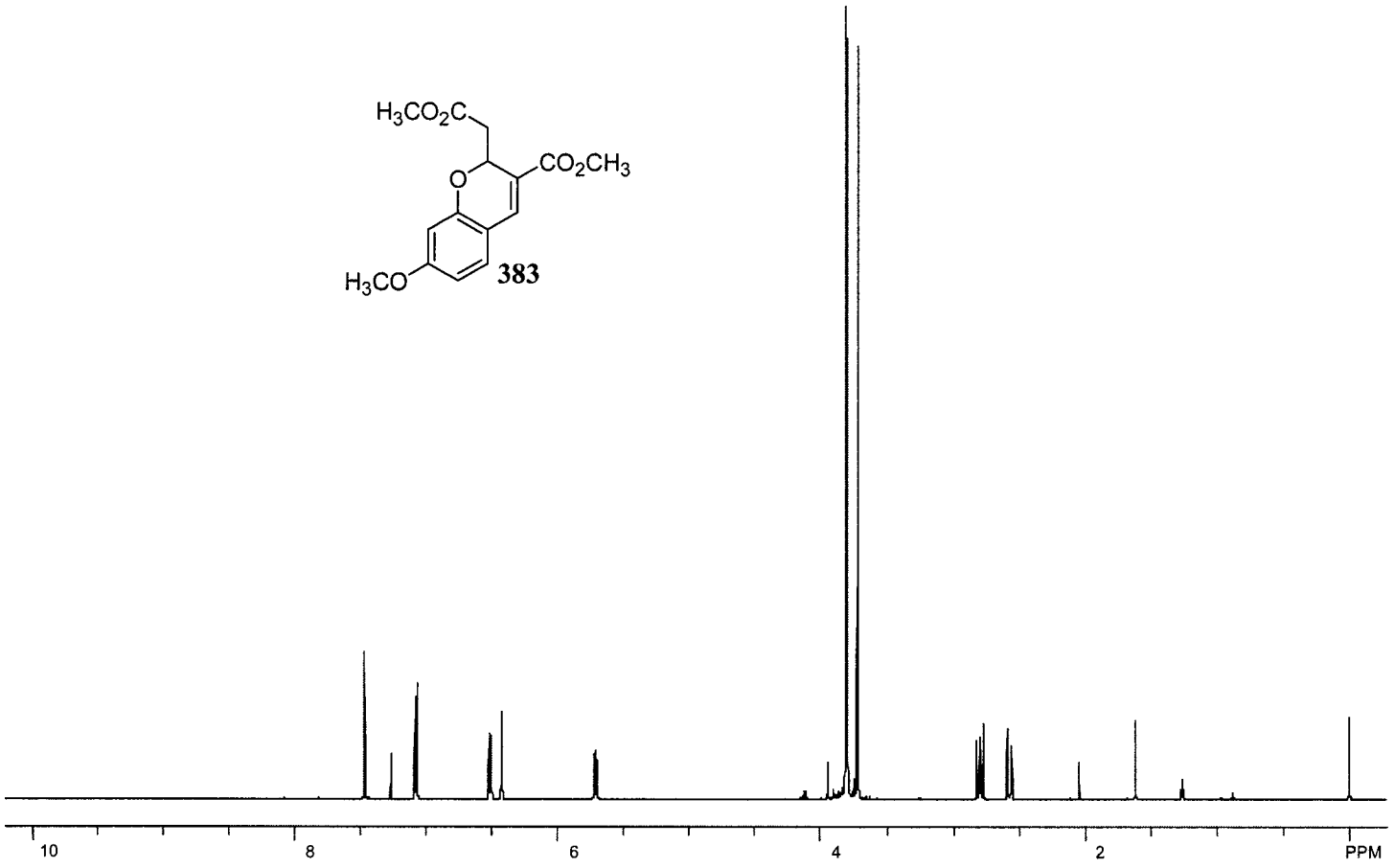
0
PPM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2
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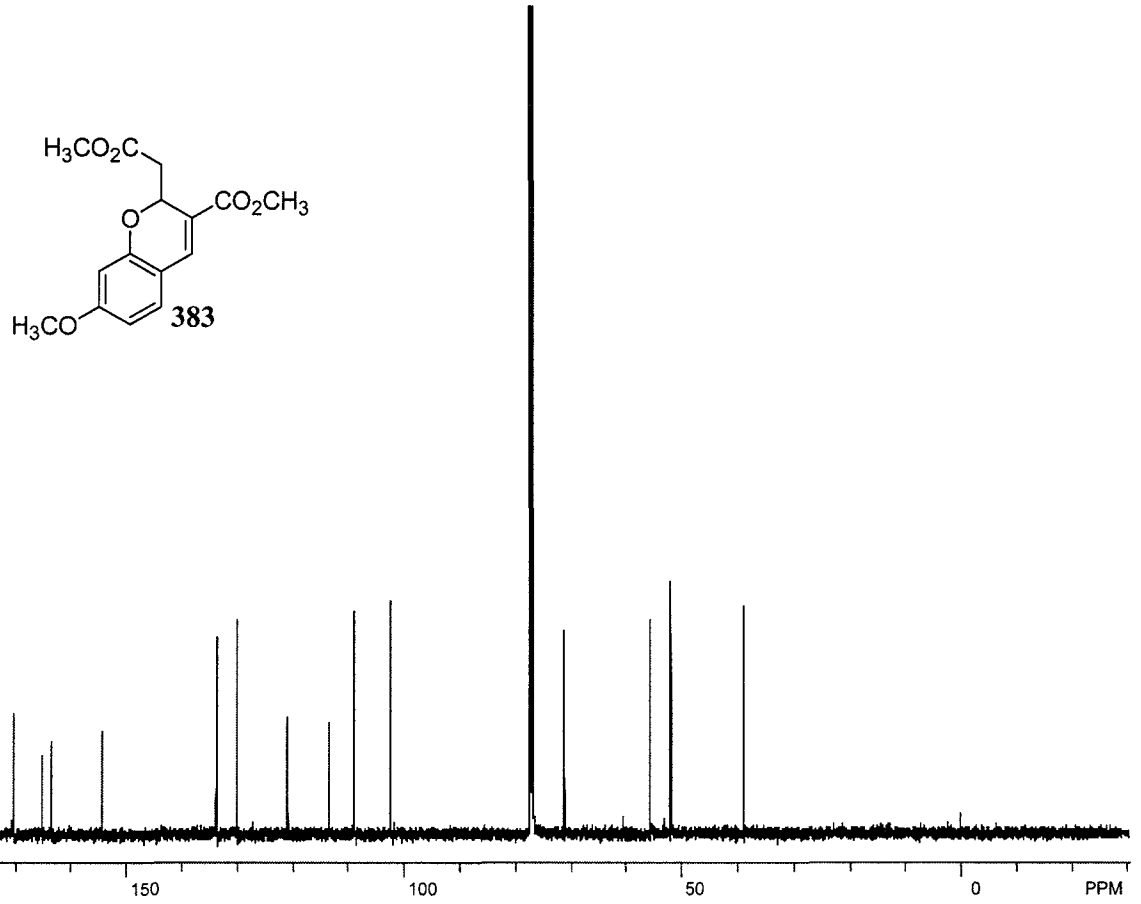
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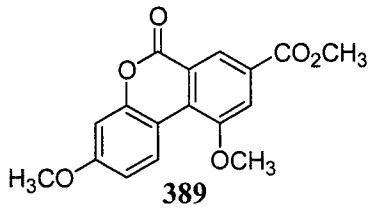

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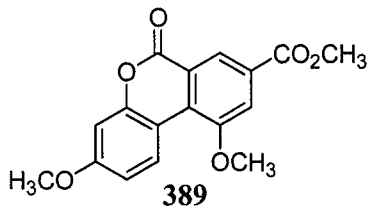

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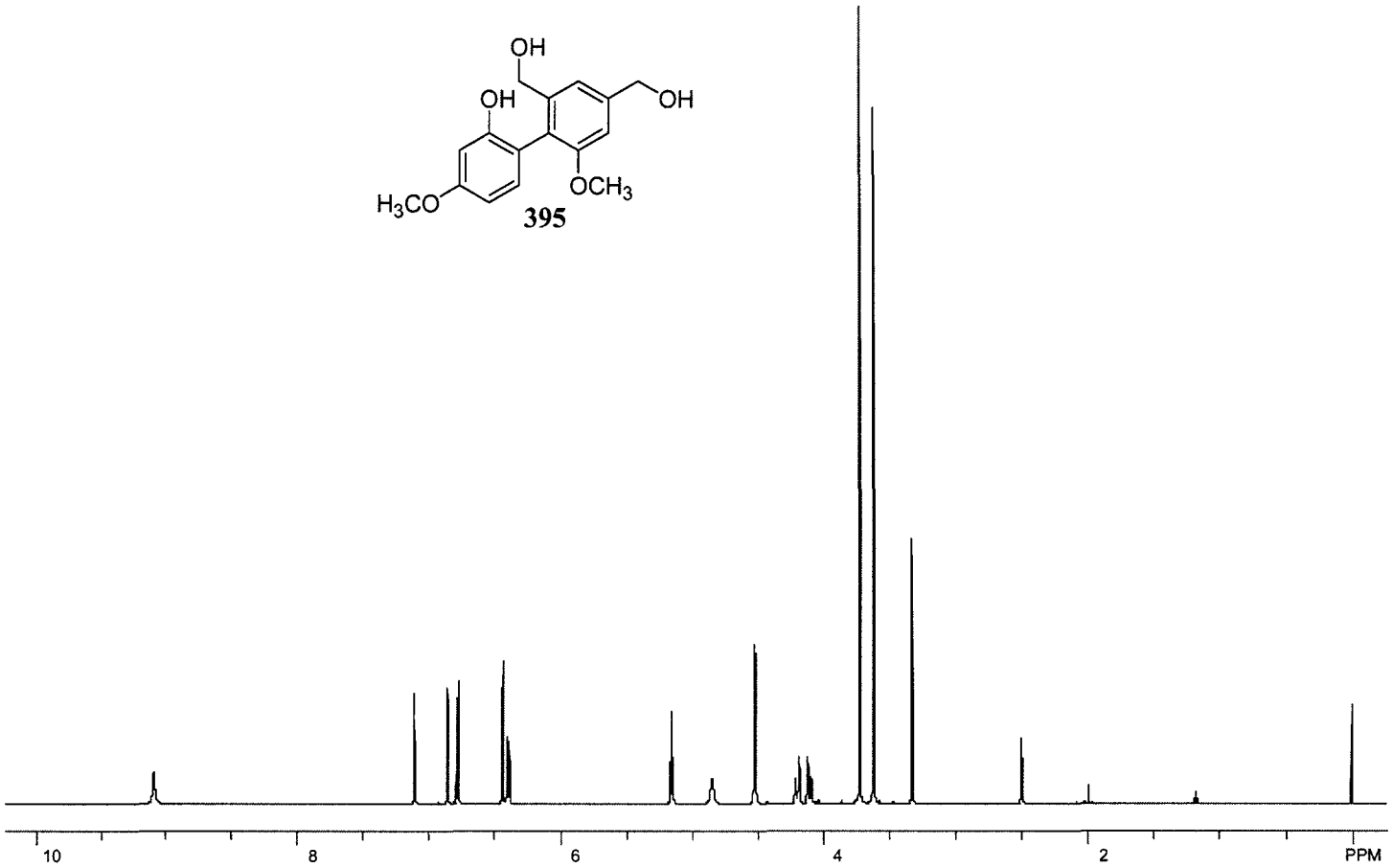
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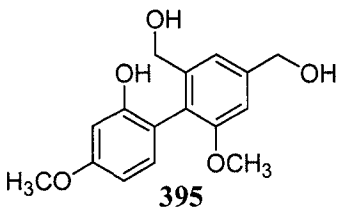

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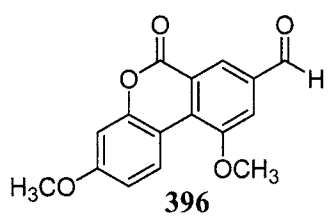

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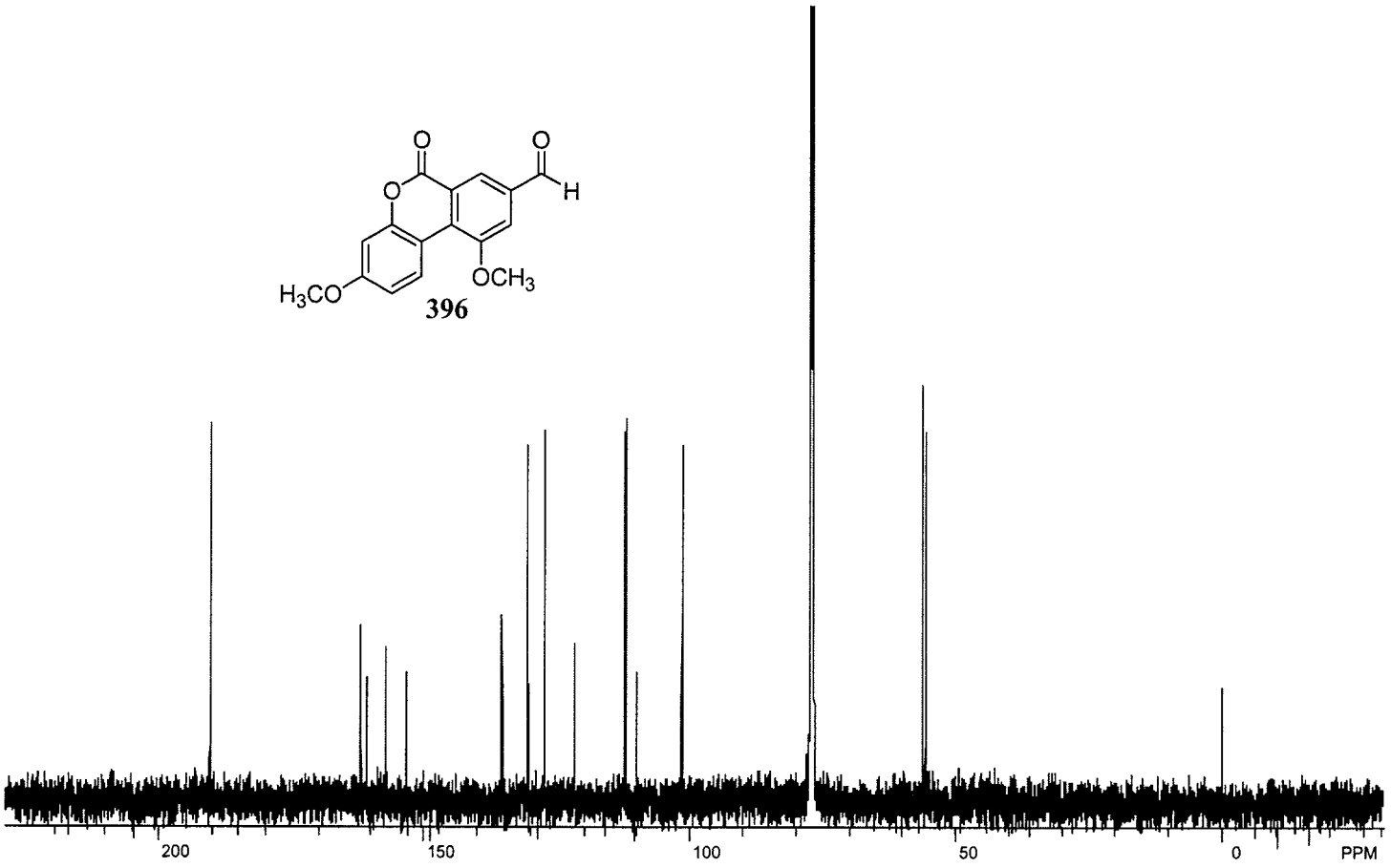

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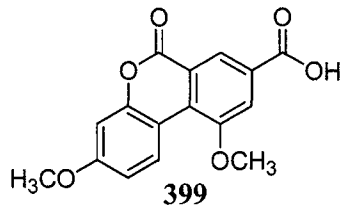

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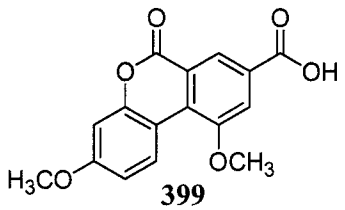

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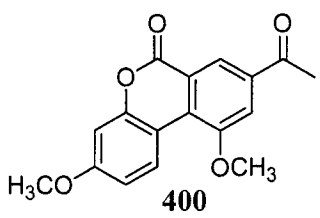

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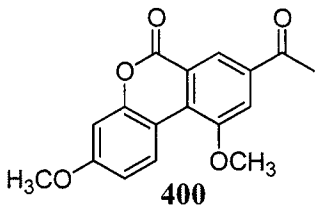

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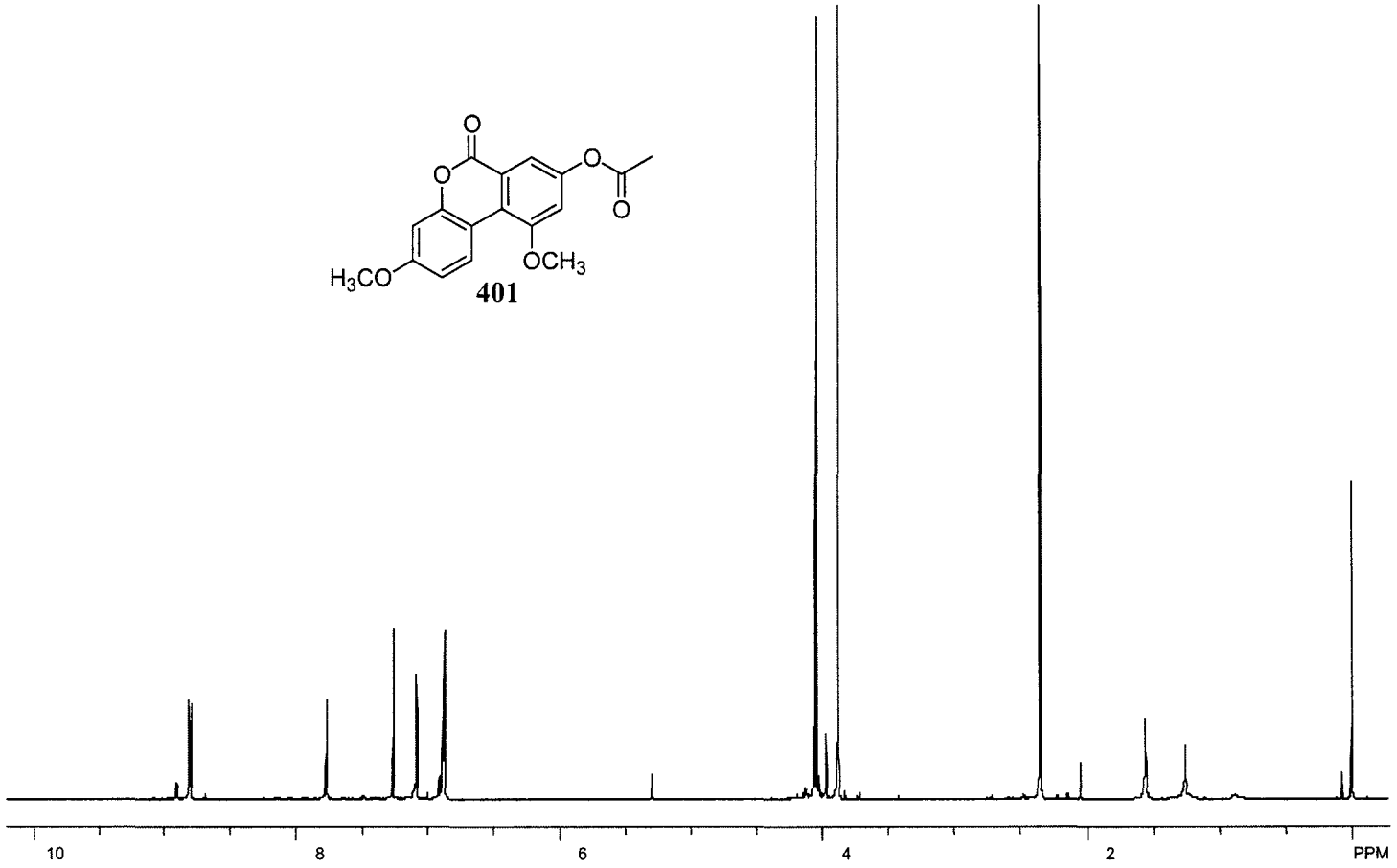

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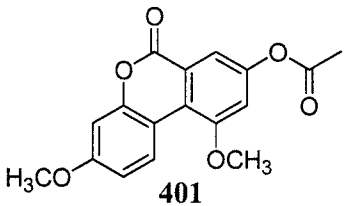

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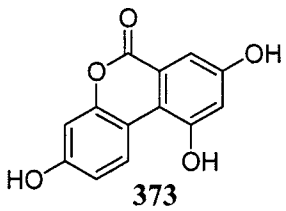

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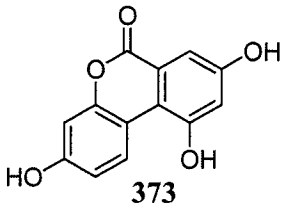

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Appendix 3:

App. 3.1 X-ray crystallography data for compound **217**:

Experimental

Data Collection

A pale yellow plate crystal of $C_{19}H_{18}O_4$ having approximate dimensions of 0.40 x 0.10 x 0.40 mm was mounted on a glass fiber. All measurements were made on a Rigaku AFC6S diffractometer with graphite monochromated Cu-Kα radiation.

Cell constants and an orientation matrix for data collection, obtained from a least-squares refinement using the setting angles of 24 carefully centered reflections in the range $58.50 < 2\theta < 59.76^{o}$ corresponded to a primitive monoclinic cell with dimensions:

a = 9.772(2) Å
b = 8.0060(9) Å β = 99.929(8)°
c = 19.773(1) Å
V = 1523.8(3) Å^3

For Z = 4 and F.W. = 310.35, the calculated density is 1.35 g/cm^3. The systematic absences of:

h0l: h+l ± 2n
0k0: k ± 2n

uniquely determine the space group to be:

$P2_1/n$ (#14)

The data were collected at a temperature of 26 ± 1°C using the ω-2θ scan technique to a maximum 2θ value of 120.1°. Omega scans of several intense reflections, made prior to data collection, had an average width at half-height of 0.29° with a take-off angle of 6.0°. Scans of $(1.78 + 0.14 \tan \theta)^{o}$ were made at a speed of 4.0°/min (in ω). The weak reflections ($I < 10.0\sigma(I)$) were rescanned (maximum of 10 scans) and the counts were accumulated to ensure good counting statistics. Stationary background counts were recorded on each side of the reflection. The ratio of peak counting time to background

counting time was 2:1. The diameter of the incident beam collimator was 1.0 mm, the crystal to detector distance was 400 mm, and the detector aperture was 6.0 x 3.0 mm (horizontal x vertical).

Data Reduction

Of the 2602 reflections which were collected, 2444 were unique (R_{int} = 0.014). The intensities of three representative reflections were measured after every 150 reflections. No decay correction was applied.

The linear absorption coefficient, μ, for Cu-Kα radiation is 7.7 cm^{-1}. An empirical absorption correction based on azimuthal scans of several reflections was applied which resulted in transmission factors ranging from 0.82 to 1.00. The data were corrected for Lorentz and polarization effects. A correction for secondary extinction was applied (coefficient = 5.69273e-006).

Structure Solution and Refinement

The structure was solved by direct methods[1] and expanded using Fourier techniques[2]. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. The final cycle of full-matrix least-squares refinement[3] on F was based on 1835 observed reflections ($I > 2.00\sigma(I)$) and 209 variable parameters and converged (largest parameter shift was 0.00 times its esd) with unweighted and weighted agreement factors of:

$$R = \Sigma \, ||Fo| - |Fc|| \, / \, \Sigma \, |Fo| = 0.035$$

$$R_w = [\, \Sigma \, w \, (|Fo| - |Fc|)^2 \, / \, \Sigma \, w \, Fo^2]^{1/2} = 0.036$$

The standard deviation of an observation of unit weight[4] was 2.83. The weighting scheme was based on counting statistics and included a factor (p = 0.008) to downweight the intense reflections. Plots of $\Sigma \, w \, (|Fo| - |Fc|)^2$ versus |Fo|, reflection order in data collection, sin θ/λ and various classes of indices showed no unusual trends. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.14

and -0.10 $e^-/Å^3$, respectively.

Neutral atom scattering factors were taken from Cromer and Waber[5]. Anomalous dispersion effects were included in Fcalc[6]; the values for $\Delta f'$ and $\Delta f''$ were those of Creagh and McAuley[7]. The values for the mass attenuation coefficients are those of Creagh and Hubbell[8]. All calculations were performed using the teXsan[9] crystallographic software package of Molecular Structure Corporation.

References

(1) SIR92: Altomare, A., Cascarano, M., Giacovazzo, C., Guagliardi, A. (1993). J. Appl. Cryst., 26, 343.

(2) DIRDIF94: Beurskens, P.T., Admiraal, G., Beurskens, G., Bosman, W.P., de Gelder, R., Israel, R. and Smits, J.M.M.(1994). The DIRDIF-94 program system, Technical Report of the Crystallography Laboratory, University of Nijmegen, The Netherlands.

(3) Least Squares function minimized:

$$\Sigma w(|F_o|-|F_c|)^2 \text{ where}$$

$$w = 1/[\sigma^2(Fo)] = [\sigma^2_c(Fo) + p^2Fo^2/4]^{-1}$$

$\sigma_c(Fo)$ = e.s.d. based on counting statistics

p = p-factor

(4) Standard deviation of an observation of unit weight:

$$[\Sigma w(|F_o|-|F_c|)^2/(N_o-N_v)]^{1/2}$$

where N_o = number of observations

N_v = number of variables

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

(6) Ibers, J. A. & Hamilton, W. C.; Acta Crystallogr., 17, 781 (1964).

(7) 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).

(8) 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).

(9) teXsan for Windows: Crystal Structure Analysis Package, Molecular Structure Corporation (1997).

EXPERIMENTAL DETAILS

A. Crystal Data

Empirical Formula	$C_{19}H_{18}O_4$
Formula Weight	310.35
Crystal Color, Habit	pale yellow, plate
Crystal Dimensions	0.40 X 0.10 X 0.40 mm
Crystal System	monoclinic
Lattice Type	Primitive
No. of Reflections Used for Unit Cell Determination (2θ range)	24 (58.5 - 59.8°)
Omega Scan Peak Width at Half-height	0.29°

Lattice Parameters	a = 9.772(2) Å b = 8.0060(9) Å c = 19.773(1) Å β = 99.929(8) ° V = 1523.8(3) Å^3
Space Group	$P2_1/n$ (#14)
Z value	4
D_{calc}	1.353 g/cm^3
F_{000}	656.00
μ(CuKα)	7.72 cm^{-1}

B. Intensity Measurements

Diffractometer	Rigaku AFC6S
Radiation	CuKα (λ = 1.54178 Å) graphite monochromated
Take-off Angle	6.0°
Detector Aperture	6.0 mm horizontal 3.0 mm vertical
Crystal to Detector Distance	400 mm
Voltage, Current	50kV, 27.5mA

Temperature	26.0°C
Scan Type	ω-2θ
Scan Rate	4.0°/min (in ω) (up to 10 scans)
Scan Width	$(1.78 + 0.14 \tan \theta)^{\circ}$
$2\theta_{max}$	120.1°
No. of Reflections Measured	Total: 2602
Corrections	Unique: 2444 (R_{int} = 0.014) Lorentz-polarization Absorption (trans. factors: 0.8168 - 1.0000) Secondary Extinction (coefficient: 5.69273e-006)

C. Structure Solution and Refinement

Structure Solution	Direct Methods (SIR92)
Refinement	Full-matrix least-squares on F
Function Minimized	$\Sigma w (\|Fo\| - \|Fc\|)^2$
Least Squares Weights	$1/\sigma^2(Fo) = 4Fo^2/\sigma^2(Fo^2)$
p-factor	0.0080
Anomalous Dispersion	All non-hydrogen atoms

No. Observations (I>2.00σ(I))	1835
No. Variables	209
Reflection/Parameter Ratio	8.78
Residuals: R; Rw	0.035 ; 0.036
Goodness of Fit Indicator	2.83
Max Shift/Error in Final Cycle	0.00
Maximum peak in Final Diff. Map	0.14 $e^-/Å^3$
Minimum peak in Final Diff. Map	-0.10 $e^-/Å^3$

App. 3.2 X-ray crystallography data for compound **218**:

Experimental

Data Collection

A pale yellow irregular crystal of $C_{19}H_{18}O_4$ having approximate dimensions of 0.20 x 0.20 x 0.40 mm was mounted on a glass fiber. All measurements were made on a Rigaku AFC6S diffractometer with graphite monochromated Cu-Kα radiation.

Cell constants and an orientation matrix for data collection, obtained from a least-squares refinement using the setting angles of 25 carefully centered reflections in the range $58.07 < 2\theta < 59.46^o$ corresponded to a primitive monoclinic cell with dimensions:

a = 7.846(1) Å
b = 23.6535(9) Å β = 97.932(9)°
c = 8.3161(6) Å
V = 1528.6(2) $Å^3$

For Z = 4 and F.W. = 310.35, the calculated density is 1.35 g/cm^3. The systematic

absences of:

h0l: $l \pm 2n$
0k0: $k \pm 2n$

uniquely determine the space group to be:

$P2_1/c$ (#14)

The data were collected at a temperature of $26 \pm 1^{o}C$ using the ω-2θ scan technique to a maximum 2θ value of 120.1^{o}. Omega scans of several intense reflections, made prior to data collection, had an average width at half-height of 0.31^{o} with a take-off angle of 6.0^{o}. Scans of $(1.78 + 0.14 \tan \theta)^{o}$ were made at a speed of 4.0^{o}/min (in ω). The weak reflections ($I < 10.0\sigma(I)$) were rescanned (maximum of 10 scans) and the counts were accumulated to ensure good counting statistics. Stationary background counts were recorded on each side of the reflection. The ratio of peak counting time to background counting time was 2:1. The diameter of the incident beam collimator was 1.0 mm, the crystal to detector distance was 400 mm, and the detector aperture was 6.0 x 6.0 mm (horizontal x vertical).

Data Reduction

Of the 2533 reflections which were collected, 2347 were unique ($R_{int} = 0.014$). The intensities of three representative reflections were measured after every 150 reflections. No decay correction was applied.

The linear absorption coefficient, μ, for Cu-Kα radiation is 7.7 cm^{-1}. An empirical absorption correction based on azimuthal scans of several reflections was applied which resulted in transmission factors ranging from 0.96 to 1.00. The data were corrected for Lorentz and polarization effects. A correction for secondary extinction was applied (coefficient = 4.58118e-006).

Structure Solution and Refinement

The structure was solved by direct methods[1] and expanded using Fourier techniques[2]. The non-hydrogen atoms were refined anisotropically. The hydrogen atom coordinates were refined but their isotropic B's were held fixed The final cycle of full-matrix least-squares refinement[3] on F was based on 1535 observed reflections ($I > 2.00\sigma(I)$) and 263 variable parameters and converged (largest parameter shift was 0.00 times its esd) with unweighted and weighted agreement factors of:

$$R = \Sigma \, ||Fo| - |Fc|| \, / \, \Sigma \, |Fo| = 0.037$$

$$R_w = [\Sigma \, w \, (|Fo| - |Fc|)^2 \, / \, \Sigma \, w \, Fo^2]^{1/2} = 0.037$$

The standard deviation of an observation of unit weight[4] was 1.88. The weighting scheme was based on counting statistics and included a factor ($p = 0.013$) to downweight the intense reflections. Plots of $\Sigma \, w \, (|Fo| - |Fc|)^2$ versus $|Fo|$, reflection order in data collection, $\sin \theta/\lambda$ and various classes of indices showed no unusual trends. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.19 and -0.13 $e^-/Å^3$, respectively.

Neutral atom scattering factors were taken from Cromer and Waber[5]. Anomalous dispersion effects were included in Fcalc[6]; the values for $\Delta f'$ and $\Delta f''$ were those of Creagh and McAuley[7]. The values for the mass attenuation coefficients are those of Creagh and Hubbell[8]. All calculations were performed using the teXsan[9] crystallographic software package of Molecular Structure Corporation.

References

(1) SIR92: Altomare, A., Cascarano, M., Giacovazzo, C., Guagliardi, A. (1993). J. Appl. Cryst., 26, 343.

(2) DIRDIF94: Beurskens, P.T., Admiraal, G., Beurskens, G., Bosman, W.P., de Gelder, R., Israel, R. and Smits, J.M.M.(1994). The DIRDIF-94 program system, Technical Report of the Crystallography Laboratory, University of Nijmegen, The Netherlands.

(3) Least Squares function minimized:

$\Sigma w(|F_o|-|F_c|)^2$ where

$w = 1/[\sigma^2(Fo)] = [\sigma^2_c(Fo) + p^2Fo^2/4]^{-1}$
$\sigma_c(Fo)$ = e.s.d. based on counting statistics
p = p-factor

(4) Standard deviation of an observation of unit weight:

$[\Sigma w(|F_o|-|F_c|)^2/(N_o-N_v)]^{1/2}$

where N_o = number of observations
N_v = number of variables

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

(6) Ibers, J. A. & Hamilton, W. C.; Acta Crystallogr., 17, 781 (1964).

(7) 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).

(8) 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).

(9) teXsan for Windows: Crystal Structure Analysis Package, Molecular Structure Corporation (1997).

EXPERIMENTAL DETAILS

A. Crystal Data

Empirical Formula	$C_{19}H_{18}O_4$
Formula Weight	310.35
Crystal Color, Habit	pale yellow, irregular
Crystal Dimensions	0.20 X 0.20 X 0.40 mm
Crystal System	monoclinic
Lattice Type	Primitive
No. of Reflections Used for Unit Cell Determination (2θ range)	25 (58.1 - 59.5°)
Omega Scan Peak Width at Half-height	0.31°
Lattice Parameters	a = 7.846(1) Å b = 23.6535(9) Å c = 8.3161(6) Å β = 97.932(9) ° V = 1528.6(2) Å^3
Space Group	$P2_1/c$ (#14)
Z value	4
D_{calc}	1.348 g/cm^3
F_{000}	656.00
μ(CuKα)	7.70 cm^{-1}

B. Intensity Measurements

Diffractometer	Rigaku AFC6S
Radiation	CuKα (λ = 1.54178 Å) graphite monochromated
Take-off Angle	6.0°
Detector Aperture	6.0 mm horizontal 6.0 mm vertical
Crystal to Detector Distance	400 mm
Voltage, Current	50kV, 27.5mA
Temperature	26.0°C
Scan Type	ω-2θ
Scan Rate	4.0°/min (in ω) (up to 10 scans)
Scan Width	$(1.78 + 0.14 \tan \theta)^{\circ}$
$2\theta_{max}$	120.1°
No. of Reflections Measured	Total: 2533 Unique: 2347 (R_{int} = 0.014)
Corrections	Lorentz-polarization Absorption (trans. factors: 0.9590 - 1.0000) Secondary Extinction (coefficient: 4.58118e-006)

C. Structure Solution and Refinement

Structure Solution	Direct Methods (SIR92)
Refinement	Full-matrix least-squares on F
Function Minimized	Σ w (|Fo| - |Fc|)^2
Least Squares Weights	$1/\sigma^2(Fo) = 4Fo^2/\sigma^2(Fo^2)$
p-factor	0.0130
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (I>2.00σ(I))	1535
No. Variables	263
Reflection/Parameter Ratio	5.84
Residuals: R; Rw	0.037 ; 0.037
Goodness of Fit Indicator	1.88
Max Shift/Error in Final Cycle	0.00
Maximum peak in Final Diff. Map	0.19 $e^-/Å^3$
Minimum peak in Final Diff. Map	-0.13 $e^-/Å^3$

App 3.3 X-ray crystallography data for compound **257**:

Experimental

Data Collection

A colourless needle crystal of $C_{28}H_{34}NO_6Cl_3$ having approximate dimensions of 0.53 x 0.12 x 0.08 mm was mounted on a glass fiber. All measurements were made on a Bruker P4/CCD system with graphite monochromated Mo-Kα radiation and a rotating anode generator.

Cell constants and an orientation matrix for data collection corresponded to a C-centered monoclinic cell with dimensions:

a = 35.794(3) Å
b = 6.9906(5) Å β = 108.969(1)°
c = 22.866(2) Å
V = 5410.8(6) Å^3

For Z = 8 and F.W. = 586.94, the calculated density is 1.44 g/cm^3. Based on the systematic absences of:

hkl: h+k ± 2n
h0l: l ± 2n

packing considerations, a statistical analysis of intensity distribution, and the successful solution and refinement of the structure, the space group was determined to be:

C2/c (#15)

The data were collected at a temperature of -80 ± 1°C.. The full hemisphere of data was collected with 30 sec., 0.3 deg., frames to a maximum 2θ value of 52.8°.

Data Reduction

Of the 16870 reflections which were collected, 5518 were unique (R_{int} = 0.059). The linear absorption coefficient, μ, for Mo-Kα radiation is 3.8 cm^{-1}. The Siemens area detector absorption routine (SADABS) was used to correct the data with maximum and minimum effective transmissions of 0.9700 and 0.8227 respectively. The data were corrected for Lorentz and polarization effects.

Structure Solution and Refinement

The structure was solved by direct methods[2] and expanded using Fourier techniques[3]. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included and positionally refined. The final cycle of full-matrix least-squares refinement[4] on F^2 was based on 3697 observed reflections and 445 variable parameters and converged (largest parameter shift was 0.00 times its esd) with unweighted and weighted agreement factors of:

$$R1 = \Sigma \, ||Fo| - |Fc|| \, / \, \Sigma \, |Fo| = 0.052$$

$$wR2 = [\Sigma (w (Fo^2 - Fc^2)^2) / \Sigma \, w(Fo^2)^2]^{1/2} = 0.128$$

The standard deviation of an observation of unit weight[5] was 1.02. The weighting scheme was based on counting statistics. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.73 and -0.40 $e^-/Å^3$, respectively.

Neutral atom scattering factors were taken from Cromer and Waber[6]. Anomalous dispersion effects were included in Fcalc[7]; the values for Δf' and Δf" were those of Creagh and McAuley[8]. The values for the mass attenuation coefficients are those of Creagh and Hubbell[9]. All calculations were performed using the teXsan[10] crystallographic software package of Molecular Structure Corporation except for refinement, which was performed using SHELXL-97[11].

References

(1) CrystalClear: Rigaku Corporation, 1999.

(2) SHELX97: Sheldrick, G.M. (1997).

(3) DIRDIF94: Beurskens, P.T., Admiraal, G., Beurskens, G., Bosman, W.P., de Gelder, R., Israel, R. and Smits, J.M.M.(1994). The DIRDIF-94 program system, Technical Report of the Crystallography Laboratory, University of Nijmegen, The Netherlands.

(4) Least Squares function minimized: (SHELXL97)

$$\Sigma w(F_o^2-F_c^2)^2 \text{ where}$$

$$w = 1/[\,\sigma^2(Fo^2) + (0.0569 \cdot P)^2 + 6.0736 \cdot P\,]$$
$$P = (\text{Max}(Fo^2,0) + 2Fc^2)/3$$

(5) Standard deviation of an observation of unit weight:

$$[\Sigma w(F_o^2-F_c^2)^2/(N_o-N_v)]^{1/2}$$

where: N_o = number of observations
N_v = number of variables

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

(7) Ibers, J. A. & Hamilton, W. C.; Acta Crystallogr., 17, 781 (1964).

(8) 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).

(9) 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).

(10) teXsan for Windows version 1.06: Crystal Structure Analysis Package, Molecular Structure Corporation (1997-9).

(11) SHELX97: Sheldrick, G.M. (1997).

EXPERIMENTAL DETAILS

A. Crystal Data

Empirical Formula	$C_{28}H_{34}NO_6Cl_3$
Formula Weight	586.94
Crystal Color, Habit	colourless, needle
Crystal Dimensions	0.53 X 0.12 X 0.08 mm
Crystal System	monoclinic
Lattice Type	C-centered
Lattice Parameters	a = 35.794(3) Å b = 6.9906(5) Å c = 22.866(2) Å β = 108.969(1) ° V = 5410.8(6) Å^3
Space Group	C2/c (#15)
Z value	8
D_{calc}	1.441 g/cm^3
F_{000}	2464.00
μ(MoKα)	3.83 cm^{-1}

B. Intensity Measurements

Diffractometer	Bruker P4/ CCD
Radiation	MoKα (λ = 0.71073 Å) graphite monochromated
Temp	-80 $\pm$ 1°C.
Scan Rate	30s, 0.3 deg. frames
$2\theta_{max}$	52.8°
No. of Reflections Measured	Total: 16870 Unique: 5518 (R_{int} = 0.059)
Corrections	Lorentz-polarization SADABS correction (trans. Factors: 0.9700 – 0.8227)

C. Structure Solution and Refinement

Structure Solution	Direct Methods (SHELX97)
Refinement	Full-matrix least-squares on F^2
Function Minimized	Σ w $(Fo^2 - Fc^2)^2$
Least Squares Weights	$w = 1/ [\sigma^2(Fo^2) + (0.0569 \cdot P)^2 + 6.0736 \cdot P]$ where $P = (Max(Fo^2,0) + 2Fc^2)/3$
Anomalous Dispersion	All non-hydrogen atoms
No. Observations ($I>2.00\sigma(I)$)	3697
No. Variables	445

Reflection/Parameter Ratio	8.31
Residuals: R1; wR2	0.052 ; 0.128
Goodness of Fit Indicator	1.02
Max Shift/Error in Final Cycle	0.00
Maximum peak in Final Diff. Map	0.73 $e^-/Å^3$
Minimum peak in Final Diff. Map	-0.40 $e^-/Å^3$